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FACULTY OF ENGINEERING AND PHYSICAL SCIENCES

SCHOOL OF CHEMISTRY

REAGENTLESS PHOTOCHEMICAL TRANSFORMATIONS OF DIHYDROFUROPYRIDINONES TO AZOCINES

by

MORGAN ANN MANNING

Thesis for the degree of Doctor of Philosophy

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Abstract

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Herein, the thermal and photochemical reactions of dihydrofuropyridinones will be described. Thermal rearrangements of alkynylcyclobutenones are well established routes to benzoquinones, cyclopentediones and furanones; all of which are found in several natural products. Recently, the Harrowven group reported a short synthesis of dihydrofuropyridinones *via* the reagentless thermolysis of alkynylcyclobutenones.

Following less successful thermal reactions of dihydrofuropyridinones, we are pleased to report that their photochemical rearrangements were found to exclusively give 8-membered nitrogen-containing rings, known as azocines. 8-Membered rings are particularly difficult to synthesise; however, we report the synthesis of azocines in high yields without the need for high dilution or catalysis techniques. Azocines are found in many natural products and are highly desirable within medicinal chemistry.

Optimisation of the photochemical rearrangement and the photochemical set up will be detailed in this thesis. A library of 22 azocines with various substituents has been created, including the addition of heterocycles and non-aromatic groups.

Finally, both the thermal and photochemical processes were linked under continuous flow to give a reagentless daisy chain sequence to azocines. This joint venture with Dr. Wei Sun resulted in higher yields of the azocines when compared to the step-wise procedures.

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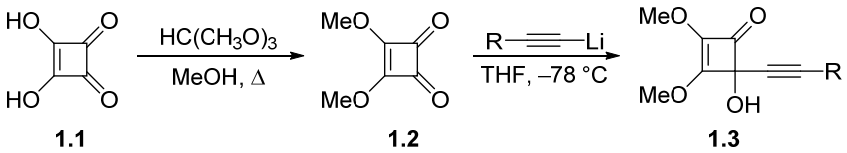
Abbreviations

Ac	acetyl	NBS	*N*-bromosuccinimide
BOC	di-*tert*-butyl dicarbonate	NMR	nuclear magnetic resonance
Bn	benzyl	OTBDMS	*tert*-butyldimethylsilyl ether
Bu	butyl	OTBDPS	*tert*-butyldiphenylsilyl ether
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene	OTf	trifluoromethanesulfonate
DCM	dichloromethane	PCC	pyridinium chlorochromate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	Ph	phenyl
DFT	density functional theory	ppm	parts per million
DIPEA	*N*,*N*-di*iso*propylethylamine	Pr	propyl
DMF	dimethylformamide	R	organyl
DMSO	dimethylsulfoxide	RCM	Ring closing metathesis
Et	ethyl	RT	room temperature
ESI	electron-spray ionisation	TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
equiv	equivalents	TFA	trifluoroacetic acid
h	hour	TFAA	trifluoroacetic anhydride
HFIP	hexafluoro*iso*propanol	THF	tetrahydrofuran
HRMS	high resolution mass spectrometry	TIPS	tri*iso*propylsilyl
IR	infra-red	TLC	thin-layer chromatography
J	coupling constant	TMS	trimethylsilyl
LDA	lithium di*iso*propylamide	UV	ultraviolet
LRMS	low resolution mass spectrometry		UVA: 315 – 400 nm
Me	methyl		UVB: 280 – 315 nm
min	minute		UVC: 100 – 280 nm
mmol	millimole	δ	chemical shift
mol	mole	ν	frequency / cm^{-1}
m.p.	melting point		

Chapter 1 Review of Alkynylcyclobutenone Rearrangements

Alkynylcyclobutenones such as **1.3**, are important cyclic precursors that are readily prepared from squaric acid **1.1**.[1–3] Pioneering work by Moore[2,4–10] and Liebeskind[3,11,12] on their rearrangement chemistry has led to many investigations into the thermal and photo-reactivity of alkynylcyclobutenones. In this chapter, the synthesis and rearrangements of alkynylcyclobutenones will be discussed; in addition to their synthetic utility and applications in target synthesis.



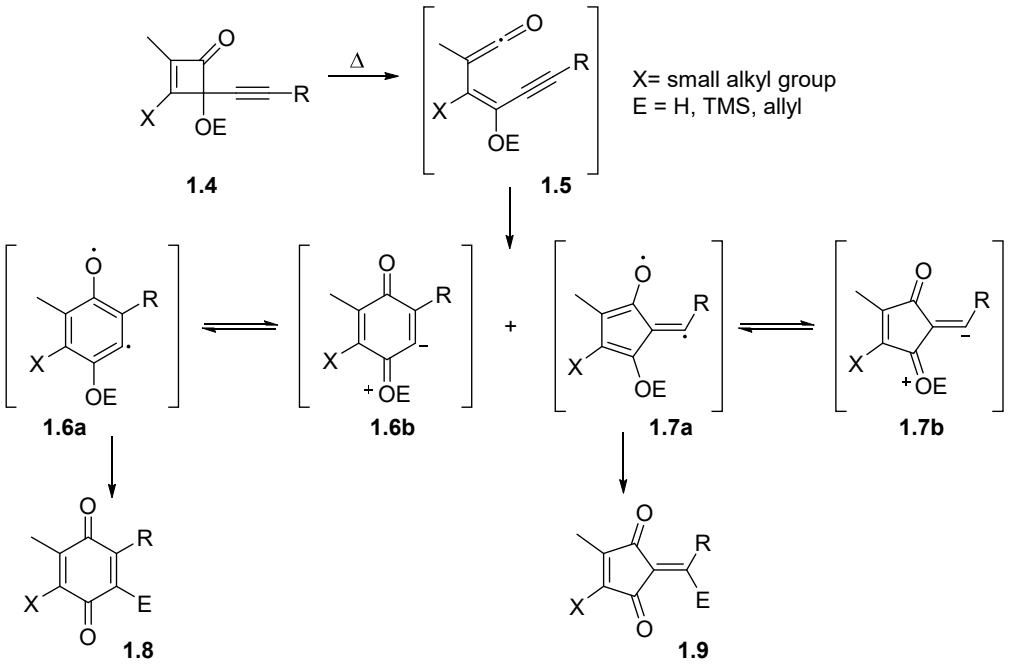
1.1 **1.2** **1.3**

Scheme 1.0. Preparation of alkynylcyclobutenone **1.3** from squaric acid **1.1**.

1.1 Mechanism of rearrangements - an historic overview

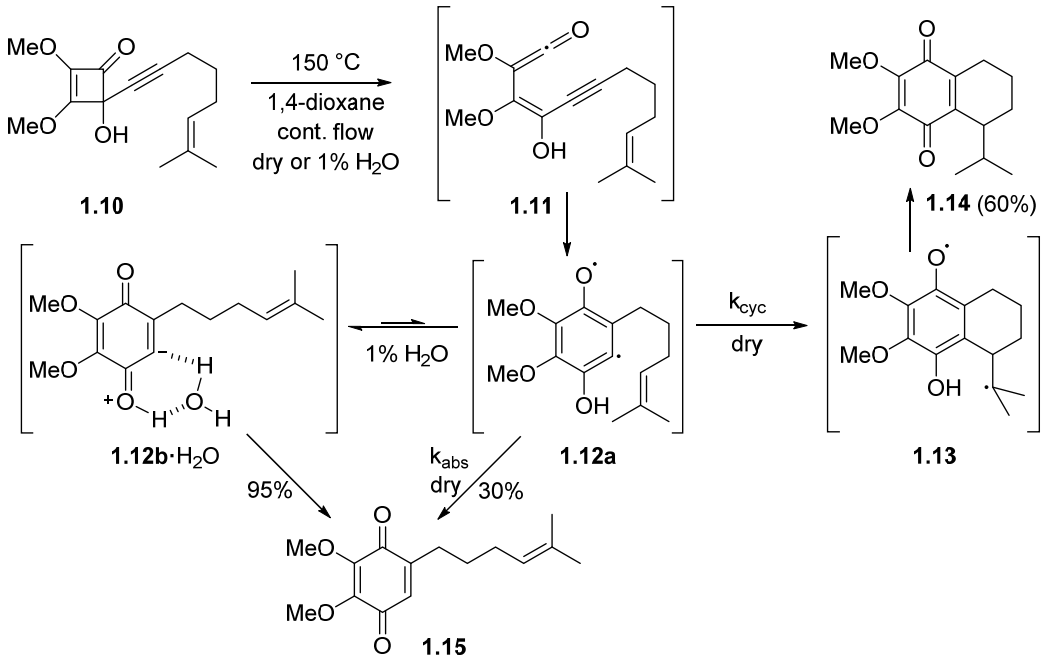
1.1.1 The Moore rearrangement of alkynylcyclobutenones

In 1985, Moore *et al*. described the electrocyclic ring opening of alkynylcyclobutenones under thermolysis to form benzoquinones or cyclopentenediones.[2] It was proposed that on heating in *p*-xylene, alkynlcyclobutenone **1.4** can undergo a 4π-electrocyclic ring opening to vinylketene **1.5**.[2,4] Ring closure of ketene **1.5**, next gave zwitterion intermediates **1.6b** & **1.7b** or diradical intermediates **1.6a** & **1.7a**, leading to the formation of the corresponding benzoquinone **1.8** or cyclopentedione **1.9** respectively (**Scheme 1.1.1**).[2,4] Moore *et al.* were interested in whether migration of the oxygen substituent, E, was an intra- or inter-molecular process. Their mechanistic studies, including deuterium doping, indicated that it migrates in an intramolecular fashion from oxygen to carbon.[4,13]



Scheme 1.1.1. The classical Moore rearrangement of alkynylcyclobutenones *via* vinylketene **1.5**. [4]

Further work by Moore *et al*. determined that the key intermediates of the rearrangement were diradicals rather than zwitterions.[4] Recent mechanistic studies by Harrowven *et al.* have shown that the zwitterion and diradical intermediates exist in equilibrium.[14] They have corroborated that their reactions can proceed *via* diradical species, following an investigation of the rearrangement of alkynylcyclobutenone **1.10** to the bicyclic quinone **1.14** (**Scheme 1.1.2**). Thus, thermolysis of alkynylcyclobutenone **1.10** in 1,4-dioxane at 150 °C gave a mixture of bicyclic quinone **1.14**, *via* radical cyclisation to **1.13** and quinone **1.15**, following hydrogen abstraction from the proximal phenol. The group postulated that doping the reaction with D_2O should favour cyclisation to **1.14** if this mechanism is correct, as the rate of deuterium-atom abstraction to quinone **1.15** would be slowed. In the event, the radical cyclisation pathway was shut down and the reaction gave deuterated quinone **1.15** exclusively. Moreover, protonated quinone **1.15** was obtained when water was added. Calculations showed that the availability of the two hydrogen bonds between water and **1.12a** induced an orbital isomer switch from the diradical intermediate to zwitterion.[14]

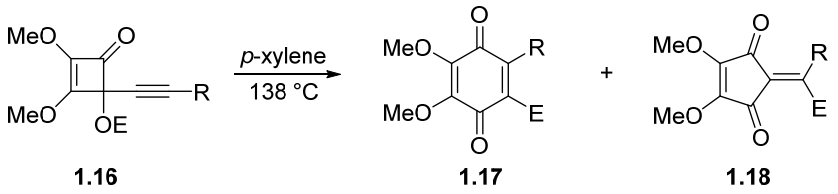


Scheme 1.1.2. An orbital isomer switch promoted by water gave quinone **1.15** as the major product .[14]

Moore initially postulated that the course of the reaction was determined by the nature of the alkyne substituent, R, with electron-withdrawing groups favouring cyclopentedione **1.18** formation, whereas electron-donating groups favoured quinone **1.17**.[2] Further work has shown that radical stabilising groups promote cyclopentedione formation (**Table 1.1.1**). This is because aromatic stabilisation of diradical intermediate **1.6a** competes with direct radical stabilisation by the alkyne substituent when forming **1.7a**.[4]

Moore *et al.* were able to produce highly substituted 1,4-benzoquinones from various 4-alkynylcyclobutenones following this method; the scope of the rearrangement is shown in **Table 1.1.2**. Addition of trialkylorthoformate to a refluxing solution of squaric acid **1.1** in the corresponding alcohol produces dialkoxysquarate **1.19** (**Scheme 1.0**).[8] Treatment of alkoxysquarate **1.19** with the appropriate alkyllithium in THF at -78 °C, followed by TFAA gave alkylcyclobutenone **1.20**. Next, addition of the corresponding lithium acetylide at -78 °C and subsequent quenching with trimethylsilyl chloride or ammonium chloride produced 4-alkynylcyclobutenone **1.21**. Finally, thermolysis of alkynylcyclobutenone **1.21** in *p*-xylene at 138 °C gave the corresponding quinone **1.22**.[4] If the cyclobutenedione **1.20** is unsymmetrical, the alkyne adds regioselectively to the more electrophilic carbonyl group, resulting in alkynylcyclobutenones such as **1.21**.[6]

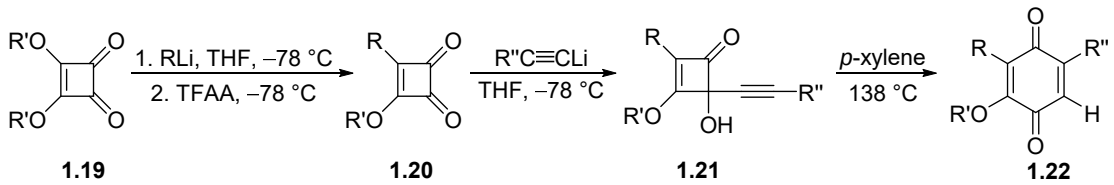
Table 1.1.1. The reaction outcome is determined by R; radical stabilising R groups result in the cyclopentenedione **1.18**.[4]



1.16 **1.17** **1.18**

Entry	R	E	Yield **1.17**%	Yield **1.18**%
a	C_6H_5	H	21	46
b	C_6H_5	TMS	52	13
c	OC_2H_5	H	25	50
d	OC_2H_5	TMS	23	55
e	TMS	H	41	5
f	$CO_2C_2H_5$	H	0	66
g	$CO_2C_2H_5$	TMS	0	33
h	$CH{=}CHOCH_3$	H	0	49

Table 1.1.2. Scope of the Moore rearrangement, formation of quinones **1.22** from dialkoxy squarates **1.19**.[4]



1.19 **1.20** **1.21** **1.22**

Entry	R	R’	R’’	Yield **1.22**%
a	C_6H_5	CH_3	$^nC_4H_9$	57
b	$C{\equiv}CC_6H_5$	CH_3	$^nC_4H_9$	57
c	C_6H_5	CH_2CH_3	$CH_2C_6H_5$	46
d	$^nC_4H_9$	CH_2CH_3	$CH_2C_6H_5$	47
e	$C_{10}H_7$	CH_2CH_3	$CH_2C_6H_5$	65
f	$^nC_4H_9$	CH_3	$CH_2C_6H_5$	84*
g	$C{\equiv}CC_6H_5$	CH_3	$CH_2C_6H_5$	50*

*yield obtained from a “one pot” sequence.

Notably, computational studies of the electrocyclic ring opening of cyclobutene reported by Houk *et al.*, found that π-donor substituents at C3 or C4, including hydroxyl groups, *e.g.* **1.23**, preferred outward rotation to **1.24a** (**Figure 1.1.1**).[15,16] This contrasted with π-acceptor substituents which favoured inward rotation to give the corresponding *Z*-diene.[17]

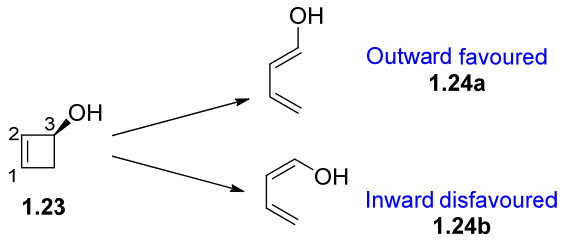


Figure 1.1.1. Conrotatory electrocyclic ring opening of cyclobutene in an outward and inward fashion.[15]

Houk *et al.* have also studied the ring opening of alkynylcyclobutenones such as **1.3**.[18] As expected, outward rotation of the hydroxyl group is preferred to give ketene intermediate **1.25a** (**Figure 1.1.2**).

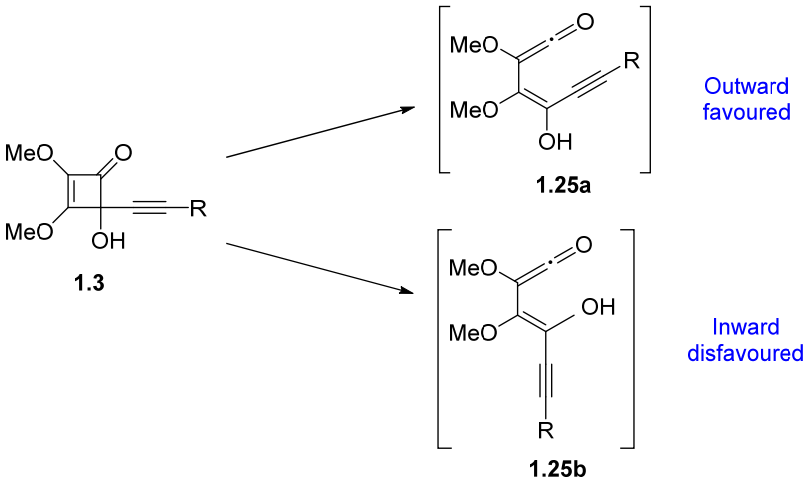


Figure 1.1.2. Electrocyclic ring opening of cyclobutenone in an outward and inward fashion.[18]

1.1.1.1 The Moore rearrangement to Quinones

Moore *et al.* have also reported the synthesis of annelated spiroepoxides **1.31** and annelated quinones **1.41** upon thermolysis of alkynylcyclobutenones in toluene. Thermolysis of 4-methoxy-4-alkynylcyclobutenone **1.26** gave diradical **1.28**, *via* ketene intermediate **1.27**, which could then undergo a 5-*exo*-*dig* cyclisation to diradical **1.29**. The vinyl radical of **1.29** could then abstract a hydrogen from the adjacent methoxy group to form diradical **1.30**, which then underwent a 3-*exo*-*trig* cyclisation to spiroepoxide **1.31** (**Scheme 1.1.3**).[9]

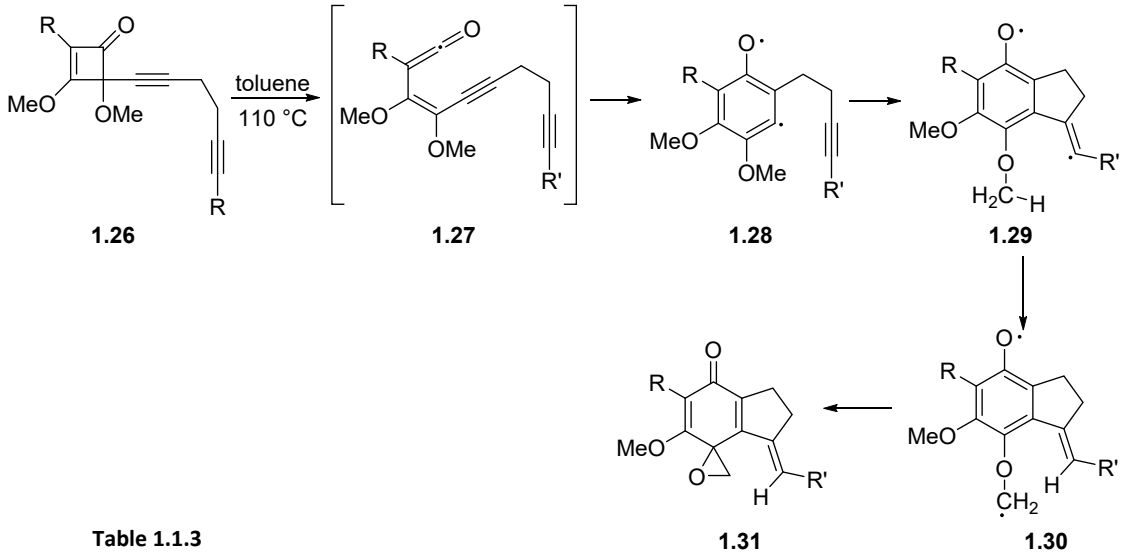


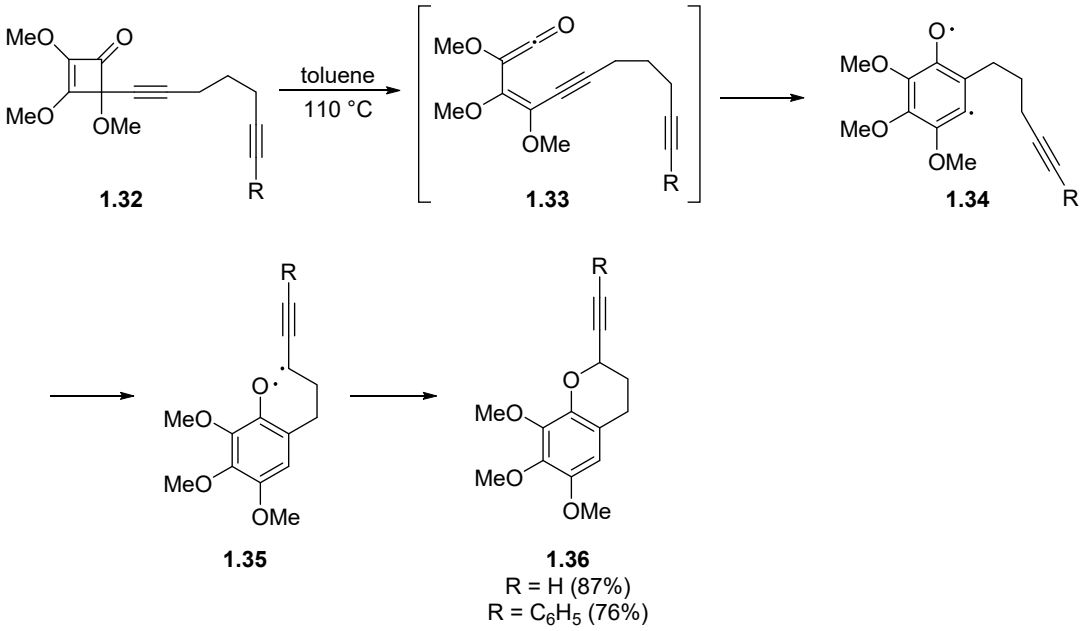
Table 1.1.3

Entry	R	R’	Yield **1.31**%
a	OCH_3	H	54
b	OCH_3	C_4H_8	87
c	OCH_3	$C(CH_3)_2OBn$	62
d	C_6H_5	C_6H_5	71
e	OCH_3	C_6H_5	91
f	OCH_3	$(CH_2)_3CH{=}CH_2$	70

Scheme 1.1.3. Formation of spiroepoxides **1.31** following thermolysis of protected alkynylcyclobutenones **1.26** in toluene.[9]

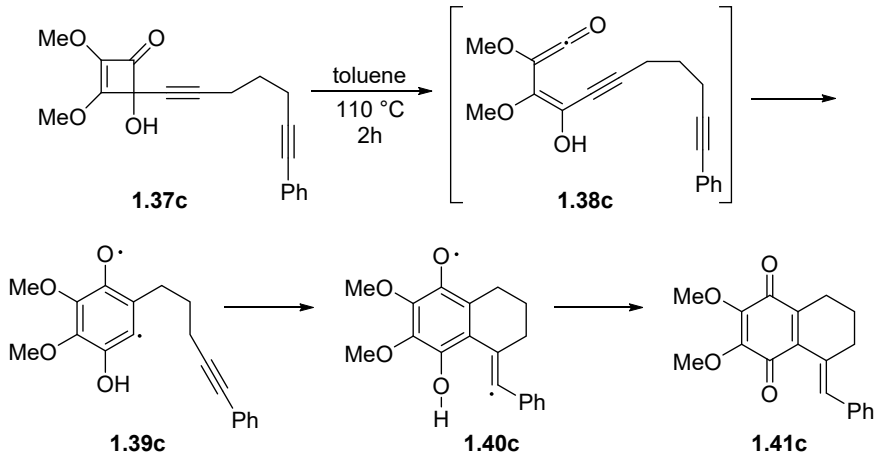
The outcome of the reaction is dependent on the distance between the two alkynyl groups in the alkynylcyclobutenone. For example, when the alkynyl groups are further apart, such as in alkynylcyclobutenone **1.32**, thermolysis in toluene results in diradical **1.34**. The aryl radical of **1.34**

can then partake in a 1,5-H transfer to propargyl radical **1.35**, which could then ring close to chromane **1.36** (**Scheme 1.1.4**).[9]



Scheme 1.1.4. A greater distance between alkynyl groups in alkynylcyclobutenone **1.32** results in chromanes **1.36**.[9]

Thermolysis of analogous 4-alkynyl-4-hydroxycyclobutenones **1.37c**, by contrast, resulted in quinones **1.41c** (**Scheme 1.1.5**). Moore *et al.* reported that in this case there was a kinetic preference for 6-*exo* addition of the aryl radical to the alkyne, instead of a 1,5-H transfer from the propargylic position; as that pathway is no longer blocked on steric grounds, or instead is reversible.[9] Interestingly, the reaction was found to be concentration dependent, with a mixture of annelated quinones **1.41** and quinones **1.42** formed under various concentrations (**Scheme 1.1.6**). At higher concentrations of alkynylcyclobutenone **1.37**, the unstable diradical **1.39** leads to quinone **1.42** *via* an intermolecular hydrogen transfer. At low concentration diradical **1.39** instead favours cyclisation to diradical **1.40**, which goes on to form annelated quinone **1.41** following a hydrogen atom abstraction from the hydroxyl group.[9]



Scheme 1.1.5. Alkynylcyclobutenone **1.37c** with a greater distance between alkynyl groups resulted in quinone **1.41c** following thermolysis in toluene.[9]

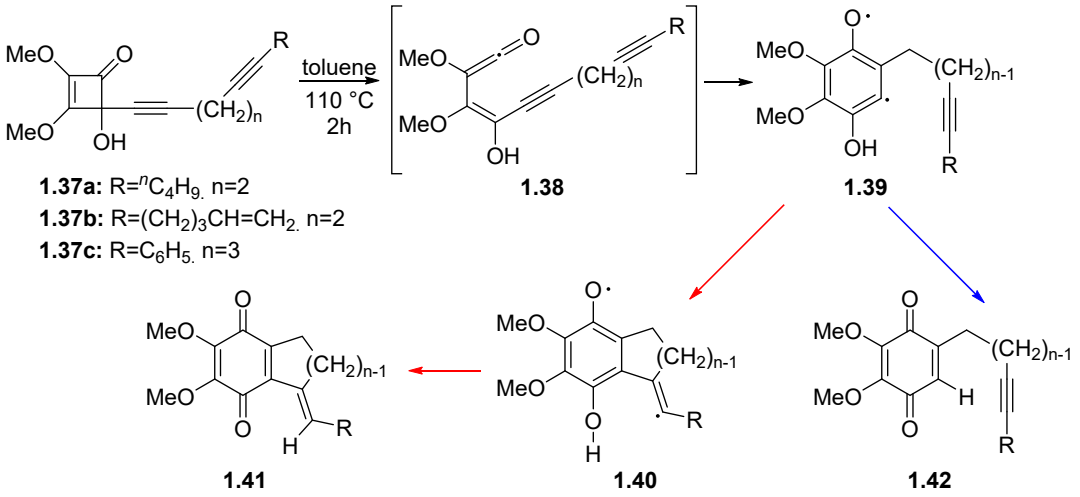
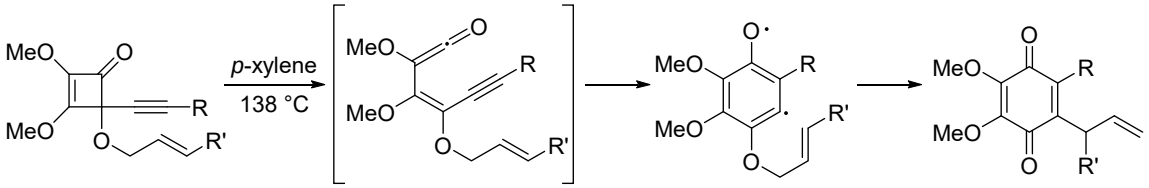


Table 1.1.4.

Cyclobutenone	Concentration (M)	Ratio **1.41**:**1.42**	Yield **1.41**%	Yield **1.42**%
1.37a	2.86×10^{-3}	23:1	80	/
1.37a	1.20	1:7	8	62
1.37b	2.43×10^{-3}	**1.41** observed	57	/
1.37b	0.1	1:1	77 combined	
1.37c	2.15×10^{-3}	**1.41** observed	63	/
1.37c	0.7	1:12	4.2	66

Scheme 1.1.6. Formation of annelated quinones **1.41** and quinones **1.42** following thermolysis of alkynylcyclobutenes **1.37** in toluene at different concentrations.[9]

In a related study, thermolysis of 4-alkynyl-4-(propargyloxy)cyclobutenones **1.43** produced alkoxybenzoquinones **1.46** displaying a 2,3-dialkylated pattern. In this case diradical **1.45** undergoes intramolecular radical addition to the proximal alkene which causes an allyl group migration to quinone **1.46**. Notably, thermolysis of **1.43c**, where R' is a methyl group, led to transposition of the allyl group on rearrangement, providing further evidence for this pathway.[19]



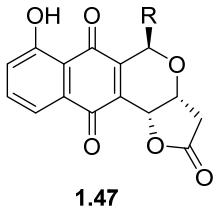
1.43 **1.44** **1.45** **1.46**

Table 1.1.5

Entry	R	R'	Yield **1.46**%
a	H	H	60
b	$CH_2C_6H_5$	H	76
c	$CH_2C_6H_5$	CH_3	54

Scheme 1.1.7. Thermolysis of alkynylcyclobutenones **1.43** gave quinones **1.46** in yields of 54−76%.[4]

Moore *et al.* extended the scope of these thermolyses by introducing heteroatoms into the alkynyl group of the alkynylcyclobutenone.[10] For example, as per **Scheme 1.1.8**, thermolyses of alkynylcyclobutenones such as **1.49**, resulted in pyranoquinones **1.50**; which are often found in natural products, such as frenolicin B and kalafungin **1.47** (**Figure 1.1.3**). The reactions were carried out in refluxing toluene at a concentration of 10^{-3} M and resulted in excellent yields. This paved the way for thermolyses of more complex alkynylcyclobutenones, to synthesise highly substituted pyranoquinones, including the total synthesis of pyranoquinone natural products. However, following thermolysis of **1.49a** at a higher concentration of 10^{-1} M, formation of quinone **1.51** was observed in 70% yield, with a mere 9% yield of pyranoquinone **1.50a**.[10]



frenolicin B (R = Pr)
kalafungin (R = Me)

1.47

Figure 1.1.3. Frenolicin B and kalafungin are pyranoquinones.

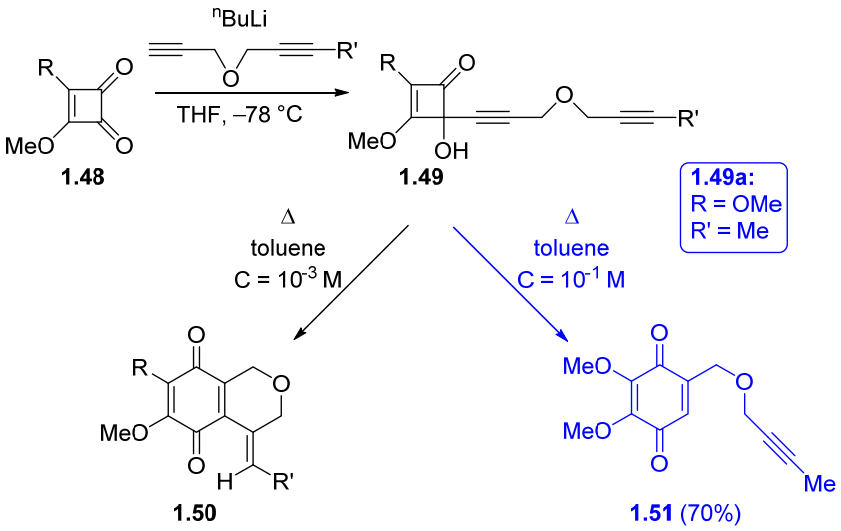


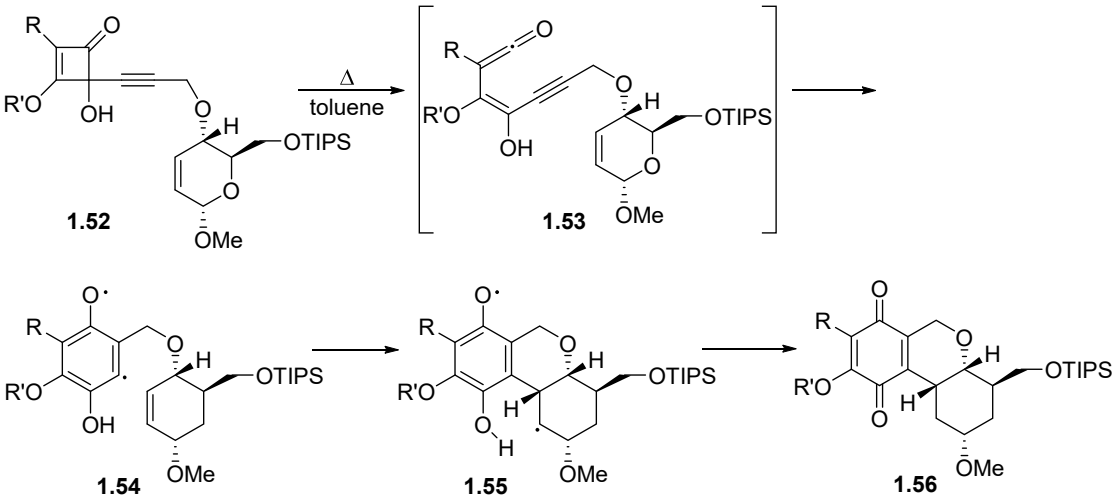
Table 1.1.6.

Entry	R	R'	Yield **1.50**%
a	OCH_3	CH_3	61
b	OCH_3	$^nC_4H_9$	67
c	OCH_3	C_6H_5	75
d	$^nC_4H_9$	C_6H_5	52

Scheme 1.1.8. Low concentration thermolyses of hetero-substituted alkynylcyclobutenones **1.49** in refluxing toluene gave pyranoquinones **1.50**.[10]

In a related study, thermolysis of alkynylcyclobutenone **1.52a** in refluxing toluene for 90 minutes gave pyranoquinone **1.56a** in 54% yield as a single diastereoisomer (**Scheme 1.1.9**). Once again, the reaction had a high tolerance for different substituents. ^{1}H NMR and NOE (nuclear Overhauser effect) analysis of pyranoquinone **1.56a** indicated a *cis*- ring junction stereochemistry, which was established through deuterium labelling studies (**1.57**). The reaction follows the course of the

previous examples, with ring opening of cyclobutenone **1.52** leading to ketene intermediate **1.53** then diradical **1.54**. A 6-*exo-trig* cyclisation to diradical **1.55** followed by abstraction of a hydrogen from the adjacent hydroxyl group forms pyranoquinone **1.56**.[10]



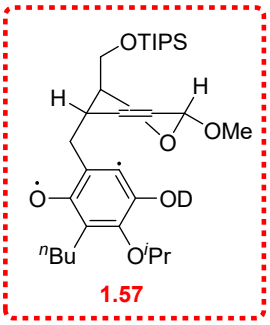


Table 1.1.7.

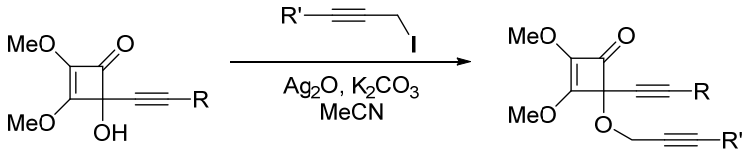
Entry	R	R'	Yield **1.56**%
a	OCH_3	CH_3	54
b	$^nC_4H_9$	$^iC_3H_7$	55
c	C_6H_5	CH_3	63
d	$CH{=}CH_2$	CH_3	51
e	$C{\equiv}CC_6H_5$	CH_3	42

Scheme 1.1.9. Thermolyses of alkynylcyclobutenones **1.52** in toluene gave pyranoquinones **1.56**.[10]

Moore *et al.* have further extended the chemistry to include propargyloxy substituents on the cyclobutenone which give highly substituted benzofurans upon thermolysis.[20] A large number of 4-alkynyl-4-(propargyloxy)cyclobutenones **1.59** were prepared by treating alkynylcyclobutenones **1.58** with propargyl iodides in the presence of silver(I) oxide and potassium carbonate at room temperature in acetonitrile (MeCN) (**Table 1.1.8**). Thermolysis of alkynylcyclobutenone **1.59a** in refluxing *p*-xylene gave methylenebenzofuran **1.64a** in 73% yield (**Scheme 1.1.10**). In this case, ring opening of alkynylcyclobutenone **1.59a** to vinylketene **1.60a** gave diradical **1.61a**, which upon 5-

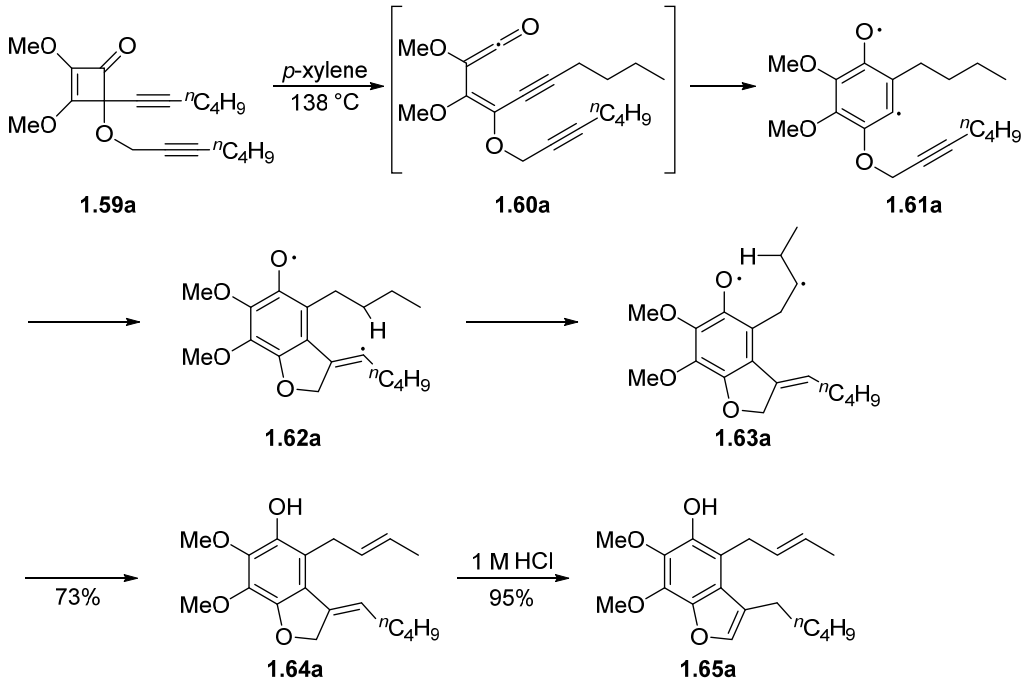
exo-dig cyclisation produced diradical **1.62a**. The resulting vinyl radical **1.62a** abstracted a hydrogen atom from the butyl side chain to give diradical **1.63a**. Transfer of a hydrogen atom to the phenoxy radical then gave methylenebenzofuran **1.64a**. Methylenebenzofuran **1.64a** was then converted to benzofuran **1.65a** in 95% yield upon mild acid treatment. Thermolysis of **1.59b**, with a shorter propargyl chain, gave methylenebenzofuran **1.64b** in 75% yield, whilst reducing the chain length of both the propargyl and alkynyl chains, as in **1.59c**, resulted in a 69% yield of methylenebenzofuran **1.64c** (**Scheme 1.1.11**).[20]

Table 1.1.8. Preparation of 4-alkynyl-4-(propargyloxy)cyclobutenones **1.59** by treating alkynylcyclobutenones **1.58** with propargyl iodides.[20]

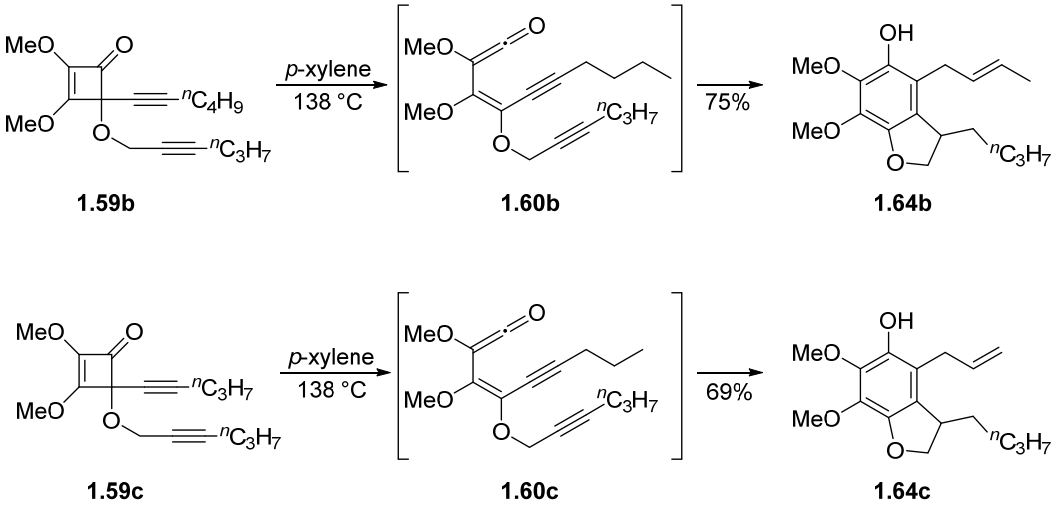


1.58 **1.59**

Entry	R	R’	Yield **1.59**%
a	$^{n}C_4H_9$	$^{n}C_4H_9$	76
b	$^{n}C_4H_9$	$^{n}C_3H_7$	85
c	$^{n}C_3H_7$	$^{n}C_3H_7$	88
d	C_2H_5	$^{n}C_3H_7$	81
e	CH_3	$^{n}C_3H_7$	73
f	$CH_2OC_6H_5$	$^{n}C_3H_7$	66
g	$CH_2C_6H_5$	$^{n}C_3H_7$	65
h	$C(CH_3)=CH_2$	$^{n}C_3H_7$	68

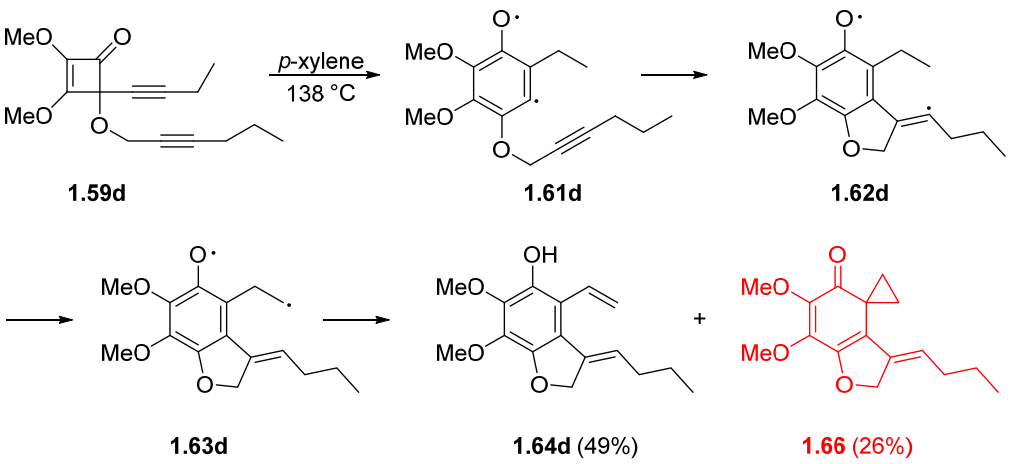


Scheme 1.1.10. Thermolysis of alkynylcyclobutenone **1.59a** to methylenebenzofuran **1.64a**.[20]



Scheme 1.1.11. Thermolyses of alkynylcyclobutenones **1.59b** and **1.59c** to the corresponding methlenebenzofurans **1.64b** and **1.64c**.[20]

Furthermore, thermolysis of alkynylcyclobutenone **1.59d**, with a propynyl residue at C4, resulted in methylenebenzofuran **1.64d** in 49% yield and spirocyclohexadienone **1.66** in 26% yield as corroborated by ^{1}H NMR. The group postulate that diradical **1.63d** could either follow hydrogen atom abstraction by the phenoxide radical to 4-vinylbenzofuran **1.64d** or undergo intramolecular radical recombination to spirocycle **1.66** (**Scheme 1.1.12**). They postulated that formation of the spiro compound **1.66** could be explained by the increased reactivity of the primary alkyl radical **1.63d** or steric effects of the smaller ethyl chain.[20]



Scheme 1.1.12. Thermolysis of 4-alkynyl-4-(propargyloxy)cyclobutenone **1.59d** produced methlenebenzofuran **1.64d** and spiro cyclohezadienone **1.66**.[20]

Moore *et al.* have extended the chemistry to synthesise *N*-heterocyclic ring systems such as piperidinoquinones **1.74** and phenathridines **1.77**, which are found in several natural products, including renierol **1.67** and *N*-formyl-1,2-dihydrorenierone **1.68** (**Figure 1.1.4**).[21] Thermolysis of alkynylcyclobutenones **1.70** in refluxing toluene gave piperidinoquinones **1.74** in 40 - 60% overall yields *via* the diradical intermediates **1.72** and **1.73** (**Scheme 1.1.13**).[10]

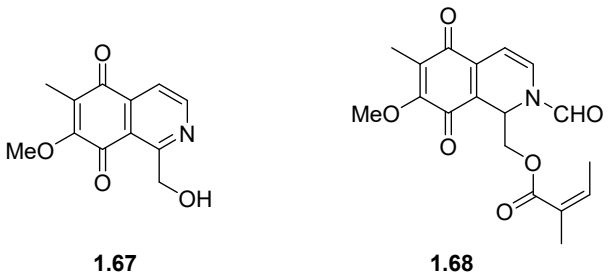


Figure 1.1.4. Natural product piperidinoquinones, renierol **1.67** and *N*-formyl-1,2-dihydrorenieron **1.68**.

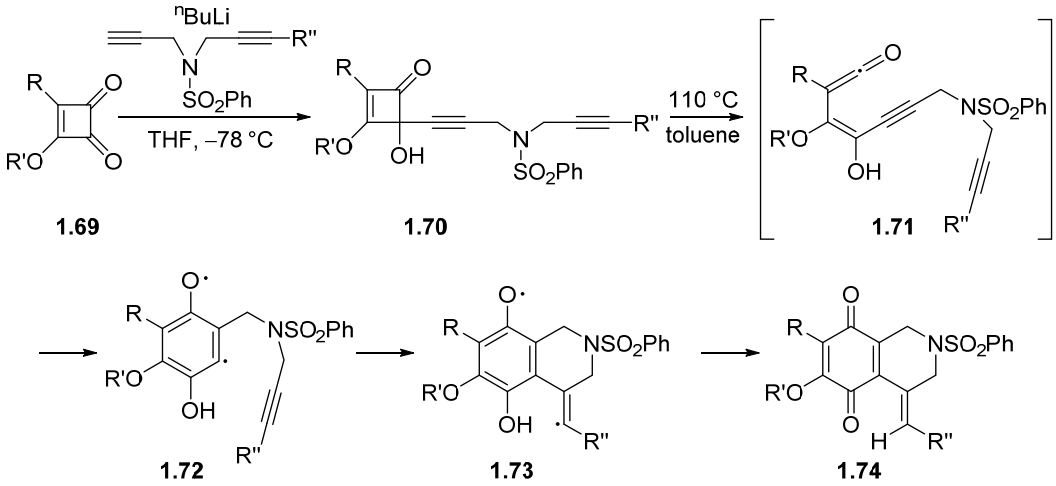
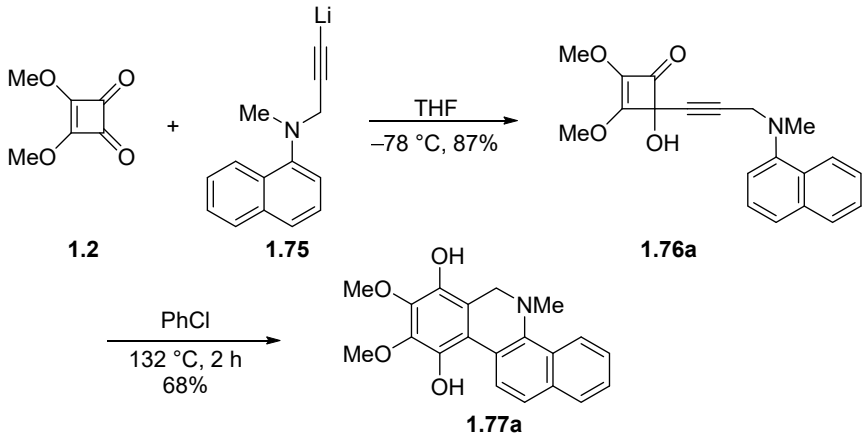


Table 1.1.9.

Entry	R	R’	R’’	Yield **1.74**%
a	C_6H_5	$^{i}C_3H_7$	TMS	44
b	OCH_3	CH_3	TMS	40
c	$^{n}C_4H_9$	$^{i}C_3H_7$	TMS	60
d	OCH_3	CH_3	$(CH_3)_2COH$	50
e	OCH_3	CH_3	C_6H_5	55
f	$^{n}C_4H_9$	$^{i}C_3H_7$	C_6H_5	57

Scheme 1.1.13 Thermolysis of alkynylcyclobutenones **1.70** in refluxing toluene gave piperidinoquinones **1.74**.[22]

Another example, involving addition of lithiated *N*-methyl-*N*-propargyl-1-napthylamine **1.75** to dimethoxy squarate **1.2** in THF at −78 °C gave alkynylcyclobutenone **1.76a**. Thermolysis of **1.76a** in chlorobenzene at 132 °C for 2 hours resulted in benzophenanthridine **1.77a** in 68% yield (**Scheme 1.1.14**).[22]

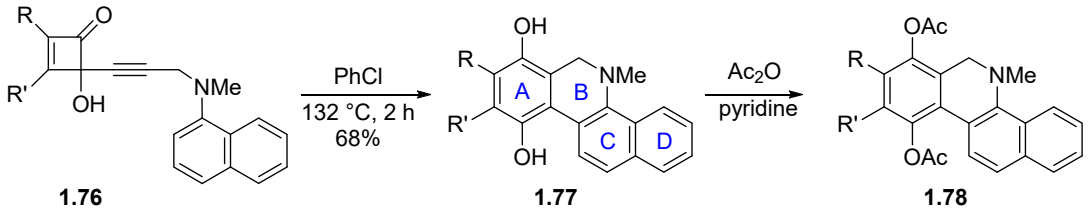


Scheme 1.1.14. Synthesis of benzophenanthridine **1.77a** from dimethoxy squarate **1.2** .[22]

A few years later, Moore *et al.* expanded the scope of benzophenanthridine synthesis, including a modification to the squarate-derived ring A (**Table 1.1.10**). Notably, alkoxy- and hydroxyl-ring A analogues of benzophenanthridinium salts have shown potential anti-tumour activity. Benzophenanthridines **1.77** were generally unstable and readily oxidised to the quinhydrone, this was visualised by a colour change from colourless to purple and supported by mass spectrometry. Conversion of benzophenanthridines **1.77** to the more stable acylated derivatives **1.78,** using acetic anhydride in pyridine solved this problem.[23]

Moore *et al.* extended this method to synthesise biologically important benzophenanthridinium ions. Benzophenanthridine alkaloids such as those shown in **Figure 1.1.5**, are biologically active compounds isolated from *Papaveraceae*, *Fumariaceae* and *Rutaceae* families. The most common from the group: chelerythrine (CHE) **1.82** and sanguinarine (SA) **1.80**, are anti-microbial, antifungal and anti-inflammatory agents; they have also been added to dental products to reduce plaque. Furthermore, benzophenanthridines have been shown to exhibit antiproliferatice activity and induce cytoxicity by apoptosis.[24]

Table 1.1.10. Further modification to the A ring of benzophenanthridine **1.78** and acylation to **1.79**.[22,23]



1.76 **1.77** **1.78**

Entry	R	R'	Yield **1.77%**	Yield **1.77%**	Yield **1.78%**
a	OCH_3	OCH_3	87	68	/
b	OCH_3	CH_3	70	66	45
c	$O^iC_3H_7$	$^iC_3H_7$	85	71	53
d	$^nC_4H_9$	$^iC_3H_7$	35	61	31
e	C_6H_5	$^iC_3H_7$	/	42	/

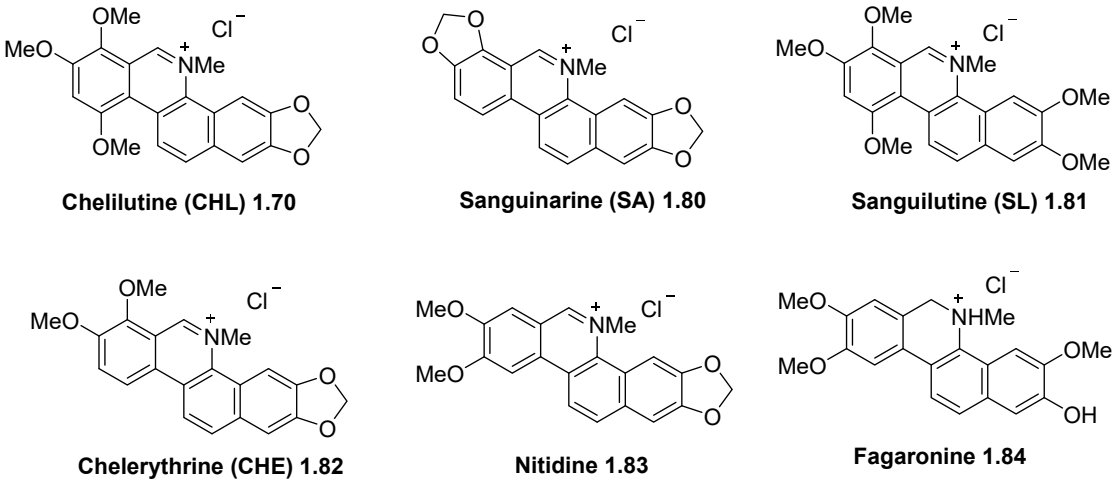
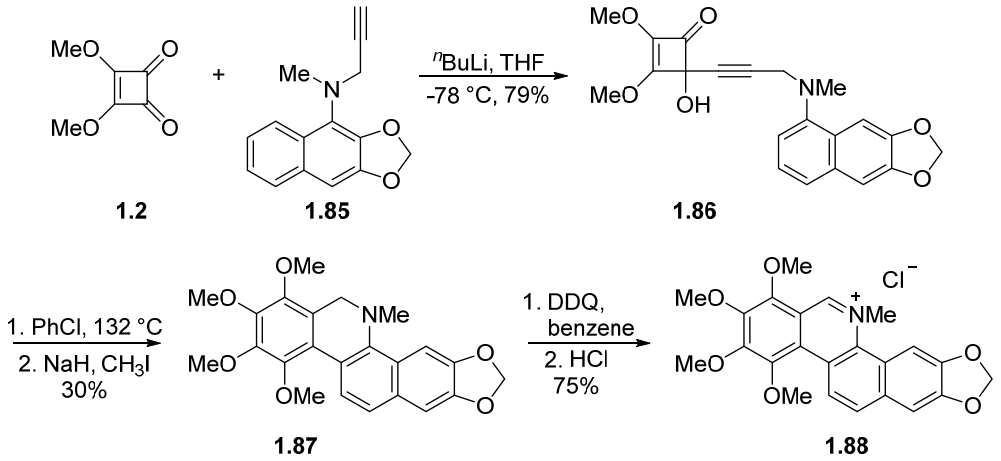


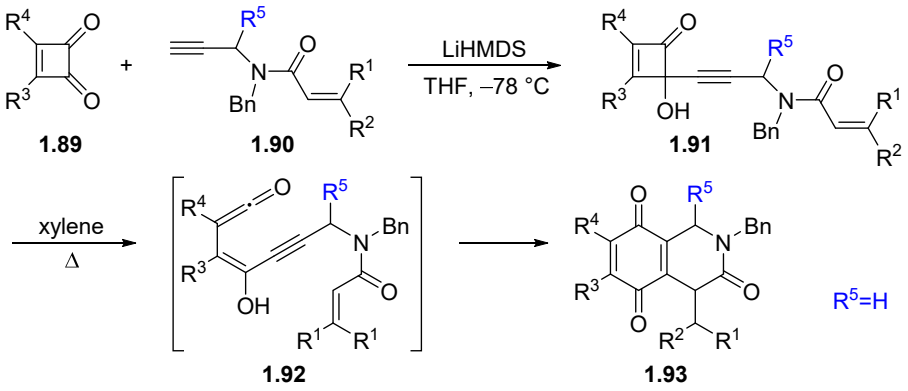
Figure 1.1.5. Natural product alkaloids containing a benzophenanthridinium ion core.

Firstly, as shown in **Scheme 1.1.15**, addition of lithiated propargylamine **1.85** to dimethyl squarate **1.2** gave alkynylcyclobutenone **1.86**. Thermolysis of **1.86** in refluxing chlorobenzene, followed by conversion of the hydroxyl groups to methoxy groups using sodium hydride and methyl iodide, gave tetramethoxybenzophenanthridine **1.87**. Oxidation of **1.87** with DDQ in benzene, followed by treatment with aqueous hydrochloric acid, gave the benzophenanthridinium ion **1.88** in 75% yield.[23]



Scheme 1.1.15. Synthesis of benzophenanthridinium ion **1.88**, a structure found in many natural products.[23]

Wipf *et al.* have developed the Moore rearrangement to synthesise isoquinoline-containing natural products, in particular isoquinoline-3,5,8-trione ring systems such as **1.93** (**Scheme 1.1.16**). Addition of lithiated *N*-benzylated α,β-unsaturated amides **1.90** to cyclobutenones **1.89** gave alkynylcyclobutenones **1.91**. Thermolysis of alkynylcyclobutenones **1.91** in degassed xylene at concentrations between 0.01 − 0.02 M resulted in the isoquinoline-3,5,8-triones **1.93**. BOC, benzhydryl and *tert*-butyl protecting groups were all tolerated well.[25]



1.89 **1.90** **1.91** **1.92** **1.93**

Table 1.1.11.

Entry	R^1	R^2	R^3	R^4	Yield **1.93**%
1	CH_3	CH_3	OCH_3	OCH_3	54
2	H	C_6H_5	$O^iC_3H_7$	CH_3	51
3	H	*p*-$OCH_3C_6H_4$	$O^iC_3H_7$	$O^iC_3H_7$	55
4	H	*p*-$CH_3C_6H_4$	CH_3	CH_3	51
5	H	*p*-$CH_3C_6H_4$	OCH_2CH_3	OCH_2CH_3	33
6	CH_3	CH_3	$O^iC_3H_7$	CH_3	45

Scheme 1.1.16. Wipf *et al.* have reported the thermolysis of alkynylcyclobutenones **1.91** to isoquinolin-3,5,8-triones **1.93** *via* ketene intermediate **1.92**.[25]

However, a related study by the group found that when a substituent was added to the CH_2 α to nitrogen, R^5, thermolysis resulted in decomposition instead of trione formation. The group postulated that this was due to formation of amide rotamers of the diradical intermediate, trans-**1.94** and cis-**1.94** (**Figure 1.1.6**). The trans rotamer is favoured where the R^5 and styrene moieties are trans to each other. This configuration of diradical trans-**1.94** is energetically disfavoured and inhibits annulation to trione **1.93**.[25]

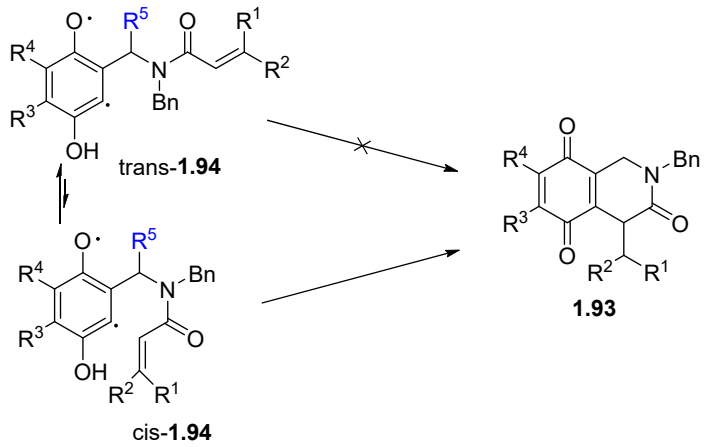
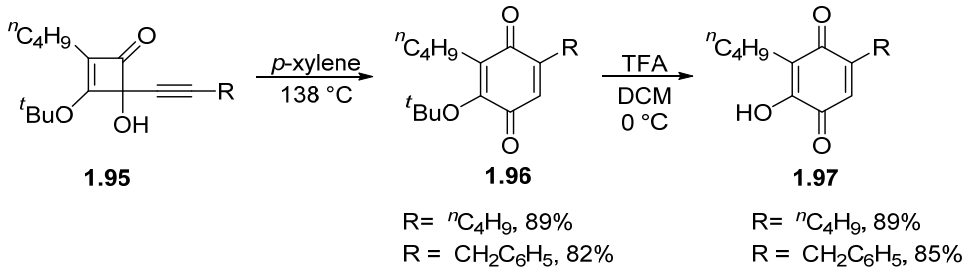


Figure 1.1.6. Formation of trione **1.93** is disfavoured when there is a substituent α to nitrogen, as the favoured trans diradical cannot annulate.[25]

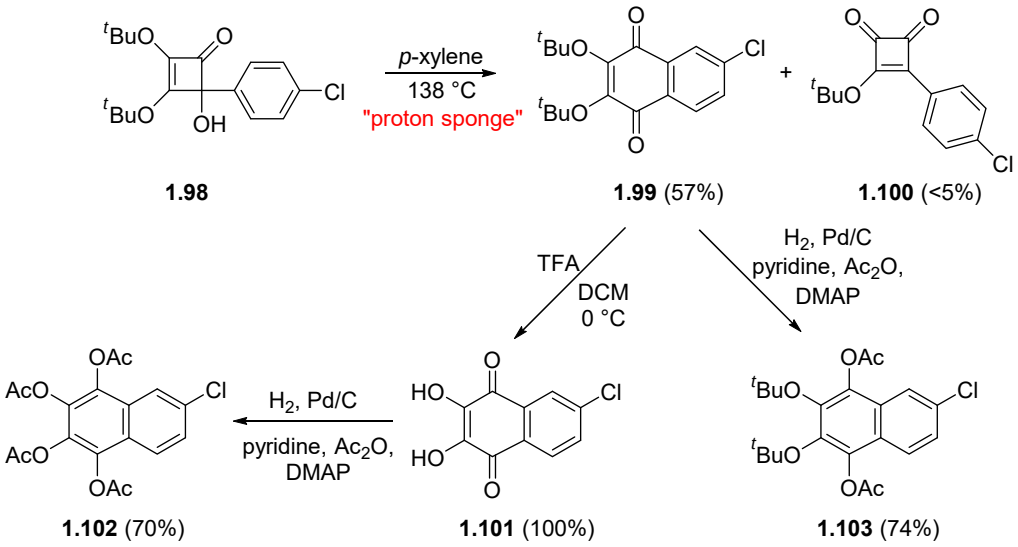
In 1990, Moore *et al.* reported the synthesis of hydroxyquinones from cyclobutenones. Thus, thermolysis of 4-alkynyl-3-*tert*-butoxycyclobutenones **1.95** in refluxing *p*-xylene gave *tert*-butoxyquinones **1.96**. Subsequent hydrolysis of the *tert*-butyl group with TFA at 0 °C resulted in hydroxyquinone **1.97** (**Scheme 1.1.17**). Removal of the *tert*-butyl group from *tert*-butoxycyclobutenone **1.95** was carried out under mild conditions; whereas hydrolysis of different alkoxyquinones required strong acidic or basic conditions.[26]



Scheme 1.1.17. Thermolyses of *tert*-butoxycyclobutenones **1.95** to *tert*-butoxyquinone **1.96** and subsequent hydrolysis to hydroxyquinone **1.97**.[26]

Moore *et al.* have also shown how this chemistry could be applied to synthesise hydroxynapthoquinone **1.101** and acylated quinone **1.102** (**Scheme 1.1.18**). Thermolysis of alkynylcyclobutenone **1.98** in *p*-xylene at 138 °C with a "proton sponge" (1,8-bis(dimethylamino)napthalene) gave quinone **1.99** and a small amount of the hydrolysis product

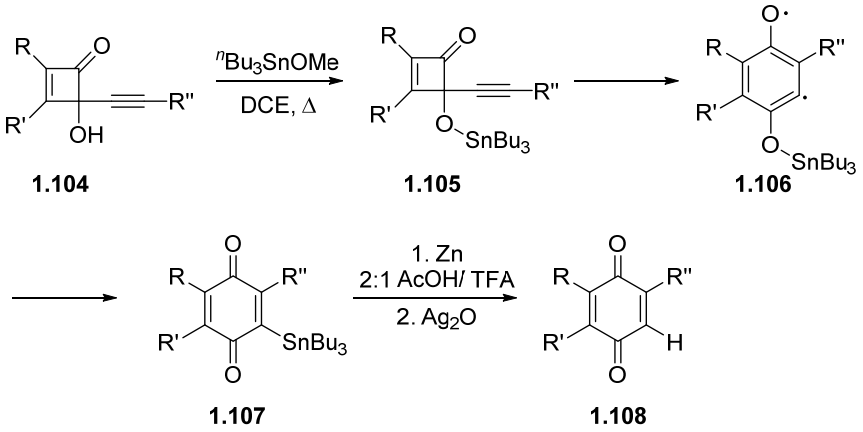
1.100. Treatment of quinone **1.99** with TFA gave dihydroxyquinone **1.101** quantitatively and then quinone **1.102** in 70% yield upon reduction and acylation. Alternatively, direct reductive acylation of quinone **1.99** produced quinone **1.103** in 74% yield, which is the *tert*-butoxy homologue of lonapalene, a drug used to treat psoriasis.[26]



Scheme 1.1.18. Hydroxynapthoquinone **1.101**, acylated napthoquinone **1.102** and quinone **1.103** can all be synthesised from the thermolysis of *tert*-butoxycyclobutenone **1.98**.[26]

Liebeskind *et al*. have demonstrated that alkynylcyclobutenones can be transformed into stannylquinones upon thermolysis with tributyltin methoxide. Thermolysis of alkynylcyclobutenones **1.104** in dichloroethane in the presence of 1.05 equiv. of tributyltin methoxide gave stannylquinones **1.107** after 10 − 15 minutes (**Table 1.1.12**). Destannylation of **1.107** upon treatment with zinc in acetic acid and TFA, followed by silver oxide, gave 1,4-benzoquinone **1.108**. This thermolysis reaction is a variant of the Moore rearrangement; as without tributyltin methoxide, the expected 1,4-benzoquinone **1.108** is formed. A point of interest is the decreased reaction time of thermolysis with tributyltin. Indeed, 4-stannyloxycyclobutenone **1.104** is more activated toward electrocyclic ring opening than an alkynylcyclobutenone without the $SnBu_3$ substituent.[27]

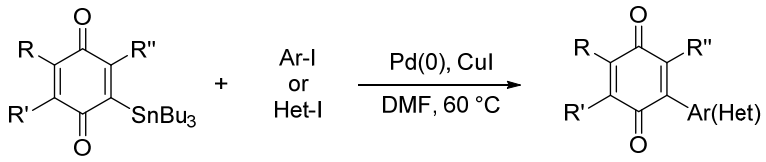
Table 1.1.12. Preparation of stannylquinones **1.107** from alkynylcyclobutenones **1.104**.[27]



Entry	R	R'	R''	Yield **1.107**%
a	CH_3	CH_3	H	78
b	CH_3	CH_3	$SiCH_3$	67
c	CH_3	CH_3	CH_3	78
d	CH_3	CH_3	$^nC_4H_9$	90
e	CH_3	OCH_3	H	20
f	CH_3	OCH_3	$^nC_4H_9$	45
g	CH_3	$O^iC_3H_7$	$^nC_4H_9$	64
h	CH_3	$O^iC_3H_7$	H	61
i	$O^iC_3H_7$	$O^iC_3H_7$	$^nC_4H_9$	46
j	OCH_3	OCH_3	$^nC_4H_9$	32
k	C_6H_5	C_6H_5	$^nC_4H_9$	59
l	C_6H_5	C_6H_5	CH_3	79
m	C_6H_5	C_6H_5	$SiCH_3$	76

Notably, a Stille cross-coupling with organic halides could be used to form highly functionalised quinones from the stannylated quinones (**Table 1.1.13**). Liebeskind *et al*. published details of the palladium catalysed cross-coupling of stannylquinones **1.107** with various vinyl-, aryl- and heteroaryl iodides to quinones **1.109**. They found that a copper(I) iodide cocatalyst was required and the reaction was performed in DMF at 60 °C.[27,28]

Table 1.1.13. Stille cross-coupling of stannylquinones **1.107** with aryl- and heteroaryl iodides .[28]



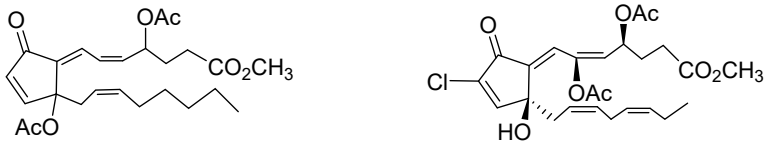
1.107 **1.109**

Entry	R	R'	R''	Ar-I/Het-I	Conditions	Yield **1.109**%
a	CH_3	CH_3	CH_3	1-iodo-4-nitrobenzene	$Pd_2(dba)_3$	85
b	CH_3	CH_3	CH_3	1-iodo-2-nitrobenzene	$Pd_2(dba)_3$, Ph_3As, N_2	82
c	CH_3	CH_3	CH_3	1-iodo-3-nitrobenzene	$Pd_2(dba)_3$, Ph_3As, N_2	80
d	CH_3	CH_3	CH_3	5-iodopyrimidine	$Pd_2(dba)_3$, Ph_3As, N_2	91
e	CH_3	OCH_3	$^nC_4H_9$	1-iodo-4-methoxybenzene	$Pd_2(dba)_3$, air	69
f	CH_3	OCH_3	$^nC_4H_9$	1-iodo-3-nitrobenzene	$Pd_2(dba)_3$, air	88
g	C_6H_5		C_6H_5	1-iodo-4-nitrobenzene	$Pd_2(dba)_3$, air	76
h	C_6H_5		$SiCH_3$	5-iodopyrimidine	$Pd_2(dba)_3$, air	49

It was found that increasing the amount of cocatalyst increased the rate of cross-coupling. An advantage of using a Stille reaction is the formation carbon-carbon bonds under mild conditions, without the need to use organolithiums at the cyclobutenedione stage.[27,28]

1.1.1.2 The synthesis of cyclopentediones from alkynylcyclobutenenones

Cyclopentenone cores have been found in a number of natural products including clavulones **1.110**[29] and punaglandins **1.111**[30] (**Figure 1.1.7**). Cyclopentenediones have displayed cytoxicity and anti-tumour activity in *in vitro* studies.[12,31,32]



clavulone I **1.110** punaglandin III **1.111**

Figure 1.1.7. Natural products clavulone I and punaglandin III with a cyclopentenone core.

Liebeskind *et al.* have reported the highly stereoselective palladium-catalysed synthesis of 4-oxygenated 5-alkylidenecyclopentenones **1.115** from alkynylcyclobutenones **1.112**. The palladium induced ring expansion proceeds *via* palladium intermediate **1.113** which rearranges to form intermediate **1.114** and HX (**Scheme 1.1.19**).[11] Introduction of AB, which can take the form of HX, C=CHCH$_2$Br or NBS, results in 5-alkylidenecyclopentenones **1.115** and regeneration of the palladium(II) catalyst. The reaction proved highly selective and forms the (*E*)-alkylidene as the major stereoisomer, suggesting trans addition of palladium across the alkyne, triggering exocyclic double bond formation.[12]

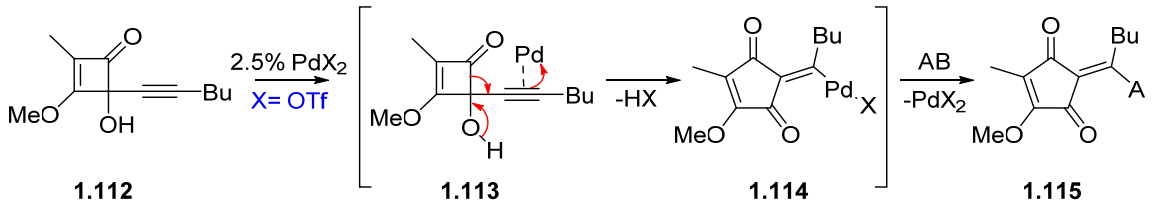
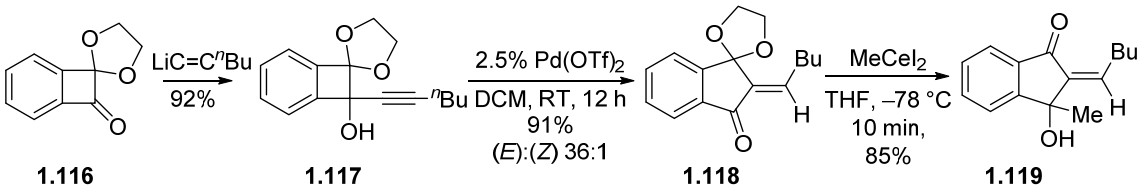


Table 1.1.14.

Entry	AB	A	Yield **1.115**%	(*E*):(*Z*)
a	HX	H	45	12:1
b	CH=CHCH$_2$Br	CH$_2$CH=CH$_2$	73	>20:1
c	NBS	Br	77	13:1

Scheme 1.1.19. Alkynylcyclobutenones **1.112** can be converted directly to cyclopentendiones **1.115** using a palladium(II) catalyst.[11]

This method can also be applied to the synthesis of alkylidene indandiones from benzocyclobutenediones. Thus, reaction of monoketal benzocyclobutenedione **1.116** with lithiated 1-hexyne gave alkyne adduct **1.117**, which upon treatment with 2.5% Pd(OTf)$_2$ in DCM at room temperature gave monoketal alkylidene indandione **1.118**, in 91% yield with excellent diastereochemistry. Monoketal benzocyclobutenedione was required due to the instability of the indandione product without the carbonyl protecting group. Removal of the ketal group *via* a 1,2-addition of a carbon nucleophile using an organocerium derivative, followed by mild acid hydrolysis gave alkylidene indandione **1.119** in 85% yield.[12]



Scheme 1.1.20. Synthesis of alkylidene indandiones **1.118** and **1.119** from benzocyclobutenedione **1.116**.[11,12]

1.1.1.3 Photolyses of Cyclobutenones

Further work by Moore *et al.* detailed the photochemical reaction of alkynylcyclobutenones to (5*H*)-furanones. They suggested that the photolytic ring opening of cyclobutenones is a stereoselective process, with the C4 hydroxyl group rotating inwards, in contrast to thermolysis in which the hydroxyl rotates outwards to form quinones.[5] The photolyses of alkynylcyclobutenones **1.3** results in ketenes **1.25b**, *via* inward rotation of the hydroxyl group. The intermediate ketene **1.25b** can then ring close to furanones **1.120**. The reactions were performed using a quartz 450 W Hanovia lamp in anhydrous THF at 0 °C; none of the corresponding quinones were oberserved.[4,5]

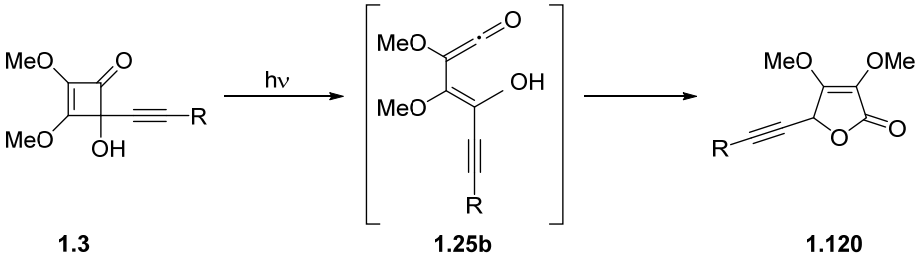


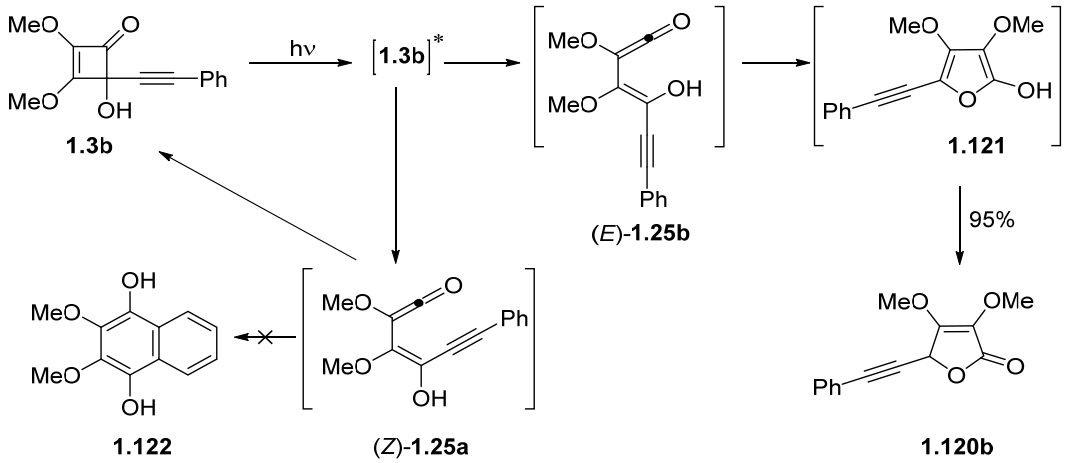
Table 1.1.15

Entry	R	Time (h)	Yield **1.120**%
a	$CH_2C_6H_5$	2	52
b	C_6H_5	4	28
c	$^nC_4H_9$	2.5	50

Scheme 1.1.21. Photolyses of alkynylcyclobutenone **1.3** resulted in furanone **1.120** *via* inward rotation of the hydroxyl group to form ketene **1.25b**.[4,5]

S. Eguchi *et al*. have also investigated the rearrangement and found that photolysis of cyclobutenones resulted in the formation of (5*H*)-furanones instead of the expected quinone. This was due to a change in the direction of twisting of the breaking bond, known as torquoselectivity.[33] In 1996, Houk *et al.* postulated that substituents with a lone pair rotate inward upon photolysis to stabilise the carbonyl radical centre in the diradical.[18] MINDO/3-CI calculations on excited state reactions of cyclobutenones were performed by Kikuchi, in which the perpendicular diradicals were formed instead of the zwitterion.[34]

It is worth noting that Harrowven *et al*. reported an increased yield of furanone **1.120b** from 28% to 95% following the photolysis of alkynylcyclobutenone **1.3b**. Alkynylcyclobutenone **1.3b** was irradiated under continuous flow in acetonitrile using a 9 W broad-spectrum UVB lamp (280 – 370 nm) for a residence time of 90 min (**Scheme 1.1.22**).[35] It was shown that cyclobutenone **1.3b** when excited photochemically, would open to both the (*E*)- and (*Z*)- vinylketenes **1.25** and that this was not a torquoselective process as had previously been thought.[36] The activation energy for the formation of vinylketene (*E*)-**1.25b** was higher than that for (*Z*)-**1.25a**, but the latter reverted back to cyclobutenone **1.3b** via a 4π-electrocyclisation. However, it was found that vinylketene (*E*)- **1.25b** favoured cyclisation to furanone **1.120b**.[35]

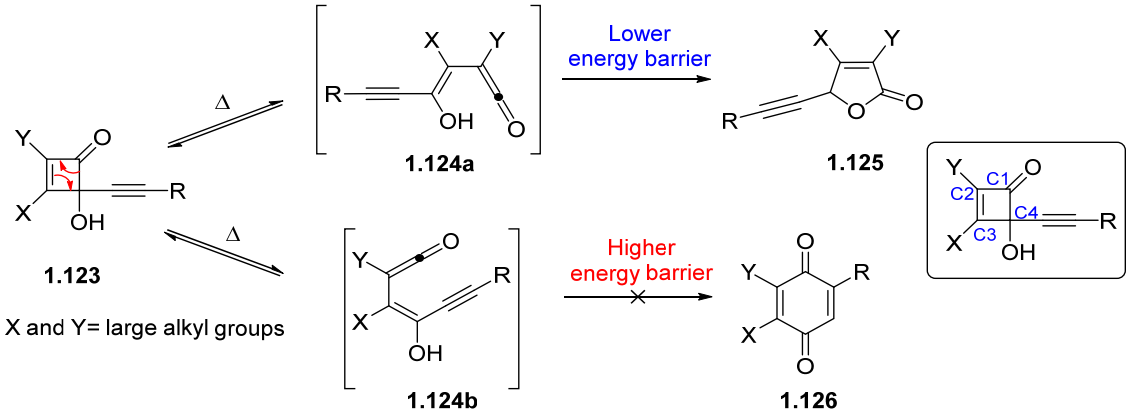


Scheme 1.1.22. Photolysis of cyclobutenone **1.3b** using a broad-spectrum UVB lamp under continuous flow gave the (5*H*)-furanone **1.120b**.

1.2 Synthetic utility

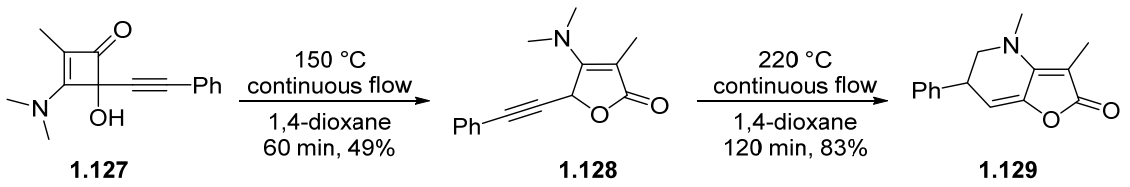
1.2.1 A new thermal rearrangement of alkynylcyclobutenones to (5*H*)-furanones and dihydrofuropyridinones

Recently, Harrowven *et al.* have shown that alkynylcyclobutenones with bulky residues at C2 and C3 produce 5(*H*)-furanones **1.125** on thermolysis, instead of the classically formed quinones **1.126**. In such cases, ring closure of ketene **1.124b** to quinone **1.126** is thermodynamically unfavoured with a high energy barrier (**Scheme 1.2.1**). As a result, the reaction reverses to alkynylcyclobutenone **1.123** and facilitates formation of ketene **1.124a**, which can easily ring close to furanone **1.125**.[37]



Scheme 1.2.1. Ring opening *via* vinyl ketene **1.124** to furanone **1.125** when X and Y are large alkyl groups.

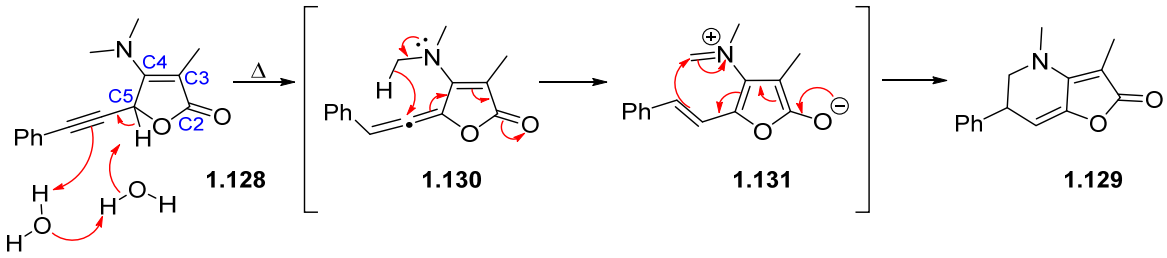
Dihydrofuropyridinones are fused heterocycles that are comprised of a furanone ring and a dihydropyridine ring. The Harrowven group have reported a novel synthesis of dihydrofuropyridinones involving two sequential thermal rearrangements of a 4-alkynyl-3-aminocyclobutenone **1.127** under continuous flow (**Scheme 1.2.2**). 4-Alkynyl-3-aminocyclobutenone **1.127** was heated to 150 °C in flow to give furanone **1.128** in 49% yield. During optimisation, Wei Sun from the Harrowven group found that at a temperature of 220 °C, dihydrofuropyridinone **1.129** was produced in 83% yield. [38]



Scheme 1.2.2. Thermal rearrangements of alkynylcyclobutenone **1.127** to furanone **1.128** and subsequently dihydrofuropyridinone **1.129**.

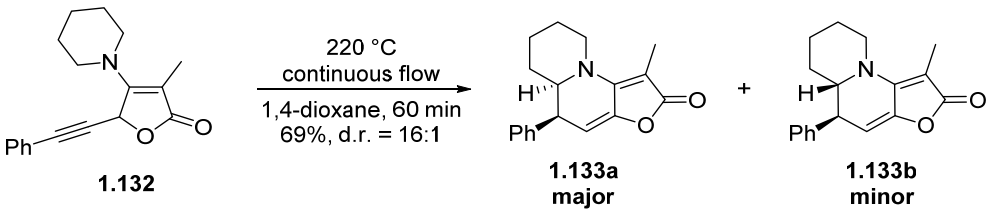
The group used an R4/R2$^+$ Vapourtec system which can comfortably heat reactions to 220 °C. Furthermore, an in-line back pressure regulator (BPR) ensures that solvents remain liquid above their boiling point. Performing these reactions under continuous flow enabled more common laboratory solvents to be used, such as 1,4-dioxane. The recent surge in the use of flow reactors in organic chemistry can be attributed to the many advantages the technique offers compared to batch reactions; including excellent heat/mass transfer, controlled mixing and improved scalability.[39,40] Optimisation can also be easier using flow as there is tight control over the temperature of the reaction and the flow rate can be adjusted to optimal reaction times.[41] Furthermore, flow processes are considered to be safer than batch processes, as the reaction is contained in a sealed system and the pressure is controlled by back pressure regulators. An attraction for us was the potential to daisy chain several flow reactions together to produce new compounds quickly and efficiently.[42,43]

The thermal rearrangement of furanone **1.128** to dihydrofuropyridinone **1.129** is believed to be catalysed by water as shown in **Scheme 1.2.3**. Computational studies indicated that the proton at C5 of furanone **1.128** undergoes a water catalysed 1,3-hydride shift *via* an 8-membered ring transition state to form allene **1.130**. Hydride transfer from allene **1.130** to alkene **1.131**, has a high energy barrier, making it the rate-determining step and the reason why the reaction has to be performed at 220 °C. A conformational change in **1.131** then brings into close proximity the enolate and iminium ion to facilitate ring closure to dihydrofuropyridinone **1.129**.[38]



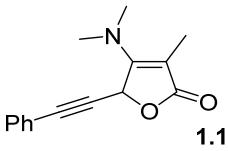
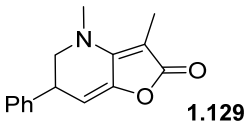
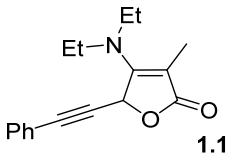
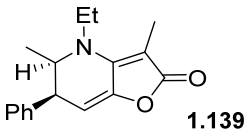
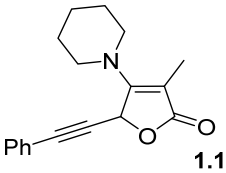
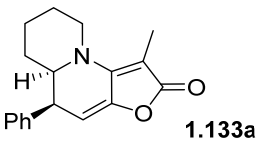
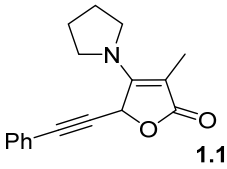
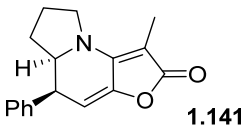
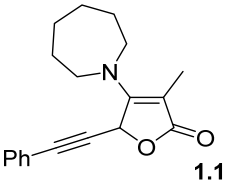
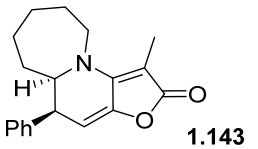
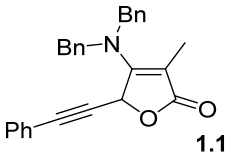
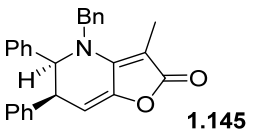
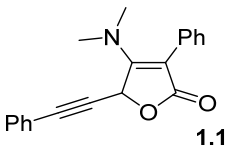
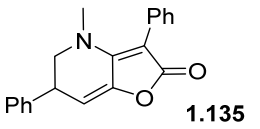
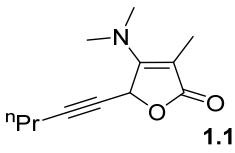
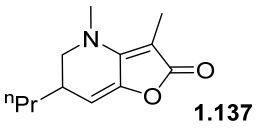
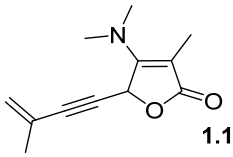
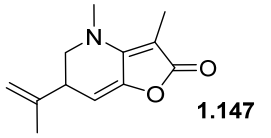
Scheme 1.2.3. The mechanism for the rearrangement of furanone **1.128** to dihydrofuropyridinone **1.129.**

Thermolyses of a variety of 5-alkynylfuranones with different substituents at C3 and C4 were carried out to test the scope of this new rearrangement. Different amine groups on the alkynylcyclobutenones, such as piperidine **1.132**, were successfully converted to dihydrofuropyridinones in good yields and with high diastereoselectivity (**Table 1.2.1**). X-ray diffraction and ^{1}H NMR analysis found the major diastereoisomer is the endo-dihydrofuropyridinone **1.133a** (**Scheme 1.2.4**).[38] The stereochemical course of the reaction was determined by a disrotatory 6π-electrocyclic ring closure of the zwitterion intermediate akin to **1.131** which followed the Woodward-Hoffman rules.[44] Furanone **1.134**, with a phenyl substituent at C3, was successfully thermolysed to the corresponding dihydrofuropyridinone **1.135** (**Table 1.2.1, entry g**).[38] Also worth noting, thermolysis of furanone **1.136** gave dihydrofuropyridinone **1.137** as the only product in 67% yield (**Table 1.2.1, entry h**).

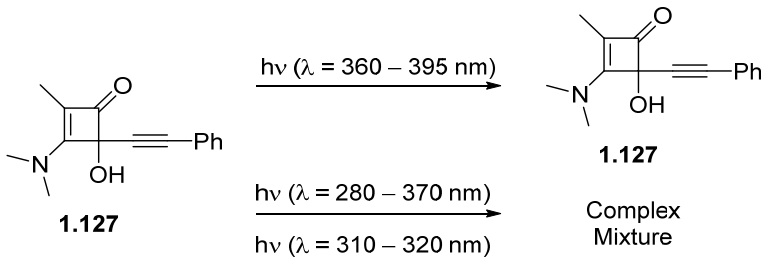


Scheme 1.2.4. Thermolysis of furanone **1.132** gave endo-dihydrofuropyridinone **1.133a** as the major product.

Table 1.2.1. Thermolyses of furanones to give the corresponding dihydrofuropyridinones.[38]

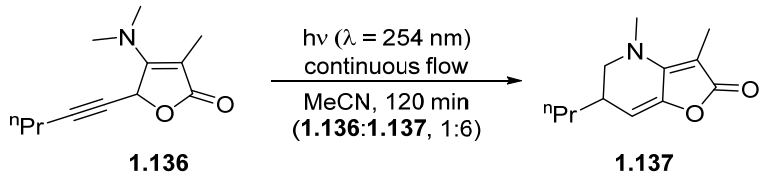
Entry	Furanone	Dihydrofuropyridinone	Reaction conditions	Yield (%)
a	 **1.128**	 **1.129**	220 °C, 120 min Continuous flow	83
b	 **1.138**	 **1.139**	220 °C, 120 min Continuous flow	80 *d.r.* = 4:1
c	 **1.132**	 **1.133a**	220 °C, 60 min Continuous flow	69 *d.r.* 16:1
d	 **1.140**	 **1.141**	220 °C, 60 min Continuous flow	86 *d.r.* = 25:1
e	 **1.142**	 **1.143**	220 °C, 60 min Continuous flow	79 *d.r.* = 7:1
f	 **1.144**	 **1.145**	220 °C, 60 min Continuous flow	76 *d.r.* = 6:1
g	 **1.134**	 **1.135**	220 °C, 60 min Continuous flow	76
h	 **1.136**	 **1.137**	220 °C, 240 min (2 x 2 h) Continuous flow	67
i	 **1.146**	 **1.147**	220 °C, 120 min Continuous flow	76

Previous work has detailed the photochemical rearrangement of alkynylcyclobutenones to (5*H*)-furanones (**Section 1.1.1.3**), so the photoreactivity of 4-alkynyl-3-aminocyclobutenone **1.127** was explored. The photolysis of 4-alkynyl-3-aminocyclobutenone **1.127** under continuous flow returned only starting material on irradiation with UVA, while irradiation with UVB or UVC gave a complex mixture of products that could not be separated readily by column chromatography.[38]



Scheme 1.2.5. Irradiation of alkynylcyclobutenone **1.127** using UVA, UVB and UVC light.

Wei Sun then irradiated furanone **1.136** under continuous flow and found that UVB and UVC irradiation both induced rearrangement to dihydrofuropyridinone **1.137** but only as a minor component in a complex product mixture (*cf*. **Table 1.2.1, entry h**). He concluded that the photolysis of furanones did not provide a useful method for effecting these rearrangements.[38]

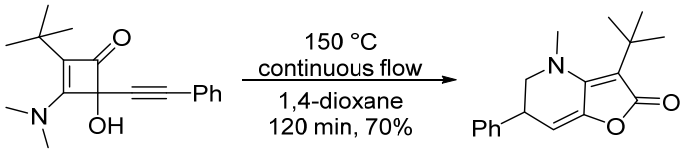


Scheme 1.2.6. Photolysis of furanone **1.136** with UVC irradiation gave the dihydrofuropyridinone **1.137** in a complex mixture. [38]

1.2.1.1 Introduction of a tert-butyl group

It has been reported that yields of dihydrofuropyridinones are generally higher when there is a *tert*-butyl group at C2 rather than a methyl residue (**Scheme 1.2.7**).[44] Once again, this is due to the steric buttressing effect of the *tert*-butyl residue. The energy barriers of each transition state are lowered,

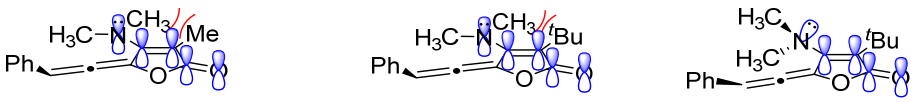
resulting in significantly reduced thermolysis temperatures. Indeed, alkynylcyclobutenone **1.148** can be converted directly to dihydrofuropyridinone **1.149** at 150 °C without isolation of the furanone intermediate **1.150**.[38]



1.148 **1.149**

Scheme 1.2.7. Thermolysis of *tert*-butylalkynylcyclobutenone **1.148** directly to dihydrofuropyridinone **1.149**.[38]

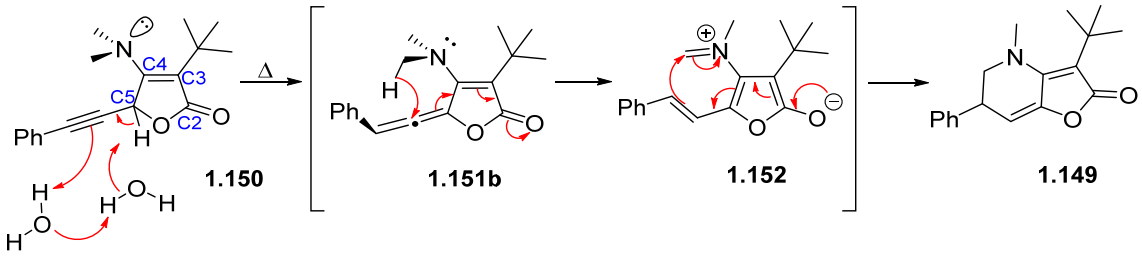
The large *tert*-butyl group leads to greater steric buttressing between the C3 and C4 residues in the allene intermediate **1.151a**; thus forcing the amino group at C4 to rotate out of conjugation with the furanone and adopt a tetrahedral sp^3 configuration as allene **1.151b** (**Figure 1.2.1).** The nitrogen lone pair is no longer conjugated to the unsaturated lactone, therefore, the energy barrier for the hydride transfer is lowered (**Scheme 1.2.8**).[38]



1.131 **1.151a** **1.151b**

Figure 1.2.1. The amino residue of methyl substituted allene **1.131** is sp^2 hybridised; sp^3 hybridised amino residue **1.151b** is favoured due to a steric interaction with the *tert*-butyl residue.

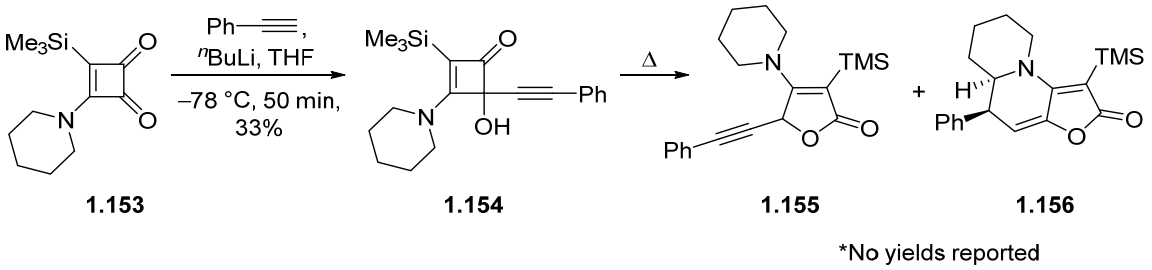
The rate-determining step of the thermolysis is conversion of the alkyne in furanone **1.150** to the corresponding allene **1.151b**. The *tert*-butyl residue increases the acidity of the C5 hydrogen in furanone **1.150**, making it more electrophilic. This is due to the loss of conjugation between the amino group and the lactone functionality. Additionally, the nitrogen lone pair of intermediate **1.151b** can donate electron density to the C-H σ* orbital; this is turn enables a hydride transfer to the electron poor allene forming zwitterion intermediate **1.152**.



Scheme 1.2.8. The nitrogen lone pair is not conjugated to the furanone moiety in **1.150** resulting in a more acidic C5 hydrogen. The NC-H bond of **1.151b** is weakened by the *tert*-butyl residue promoting formation of alkene **1.152**.

1.2.1.2 Introduction of silyl groups to cyclobutenedione

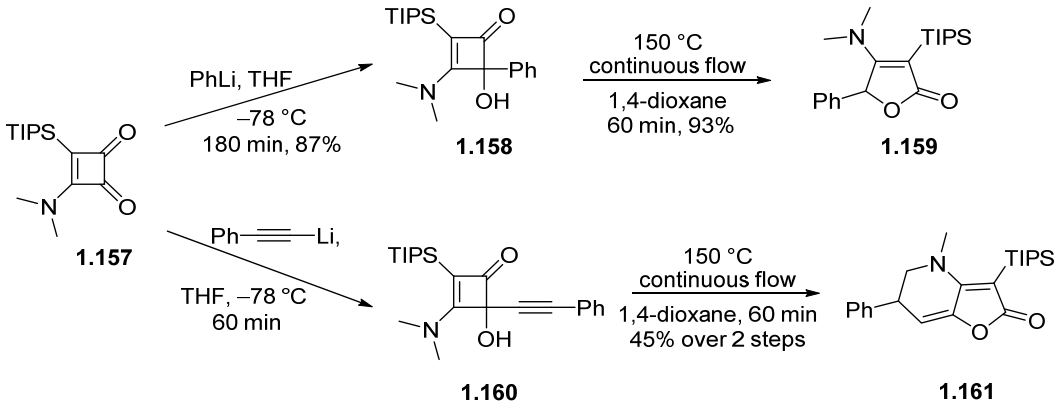
As part of his PhD studies, Dharyl Wilson explored the effect of introducing various silyl groups onto cyclobutenediones to further exploit the steric buttressing effect.[45] As silyl groups can be removed easily, it was hoped that this would enable the syntheses of dihydrofuropyridinones without a substituent at C3; potentially unlocking further transformations at the sp^2 hybridised carbon. Thermolysis of alkynylcyclobutenedione **1.154** with a trimethylsilyl (TMS) group at C2 did give the corresponding dihydrofuropyridinone **1.156**, in presumably low yields. Stability issues with alkynylcyclobutenone **1.154** prompted a survey of other silyl groups in the hope of finding one with greater promise (**Scheme 1.2.9**).[45]



Scheme 1.2.9. Formation of dihydrofuropyridinone **1.156** with a TMS substituent.[45]

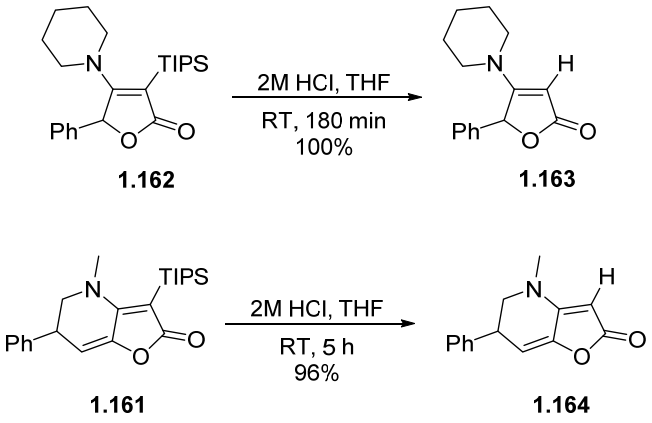
Attention was therefore directed to systems with the bulkier tri*iso*propylsilyl (TIPS) group, which led to more stable cyclobutenone intermediates. TIPS substituted phenylcyclobutenone **1.158** underwent thermolysis to provide the corresponding furanone **1.159** in 93% yield (**Scheme 1.2.10**). Addition of lithiated phenylacetylene to TIPS cyclobutenedione **1.157** proved less facile than phenyl addition, as it produced an unstable alkynylcyclobutenone **1.160** that had to be thermolysed

immediately. The resulting dihydrofuropyridinone **1.161** was formed in 45% yield over the two steps without isolation of the intermediate furanone.[45]



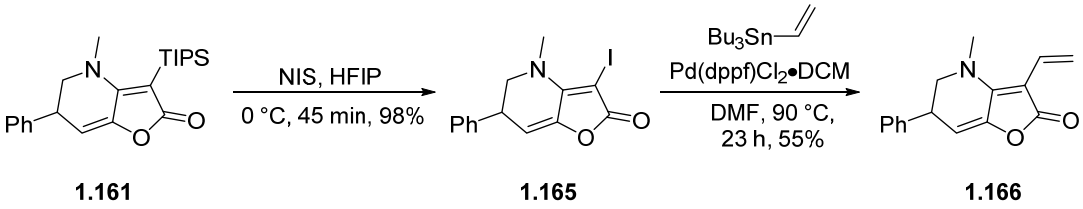
Scheme 1.2.10. Reactions of TIPS substituted cyclobutenone **1.157.**[45]

It was hoped that the TIPS group could be removed to give dihydrofuropyridinones without a substituent at C3. Firstly, TIPS substituted furanone **1.162** was desilylated using 2M HCl in THF to produce furanone **1.163** in quantitative yield. The same reaction conditions were applied to dihydrofuropyridinone **1.161** to give the desilylated product **1.164** in 96% yield after 5 hours (**Scheme 1.2.11**).[45]



Scheme 1.2.11. Desilylation of furanone **1.162** and dihydrofuropyridinone **1.161** in quantitative and near-quantitative yields.[45]

Alternatively, the silyl group of dihydrofuropyridinone **1.161** could be substitued for a halogen *via* iodination with NIS (**Scheme 1.2.12**). This modification to form dihydrofuropyridinone **1.165** introduced the possibility of effecting a palladium catalysed cross-coupling to further functionalise the ring system. Indeed, an example of a Stille cross-coupling with vinyltributylstannane was demonstrated giving dihydrofuropyridinone **1.166** in 55% yield.[45]



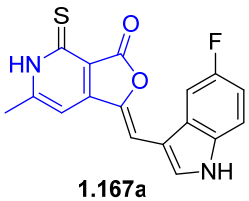
1.161 **1.165** **1.166**

Scheme 1.2.12. Iodination of dihydrofuropyridinone **1.161** and subsequent Stille cross-coupling to give the C3-vinyl substituted dihydrofuropyridinone **1.166**.[45]

1.3 Applications of dihydrofuropyridinones in target synthesis

1.3.1 Dihydrofuropyridinones in medicinal chemistry

In a 2014 study on anti-influenza virus activity, Jang *et al.* reported over 50% virus growth inhibition following treatment with dihydrofuropyridinone compounds. At 20 µM, (*Z*)-1-((5-fluoro-1*H*-indol-3-yl)methylene)-6-methyl-4-thioxo-4,5-dihydrofuro[3,4-*c*]pyridine-3(1*H*)-one **1.167a** was found to inhibit three isolates of the influenza virus. The main mode of action is the inhibition of viral neuraminidase activity by occupying the enzyme active site. Neuraminidase is required for cleavage of neuraminic acid moieties from cellular receptors and glycoproteins of influenza virions.[46]



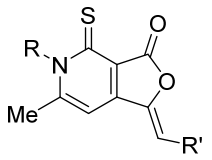
1.167a

Figure 1.3.1. Structure of dihydrofuropyridinone **1.167a** found to inhibit influenza virus growth.[46]

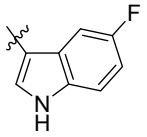
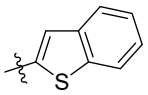
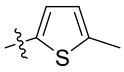
Jang *et al.* investigated the structure-activity relationship (SARs) of dihydrofuropyridinone derivatives **1.167**. A cell culture-based screening system was established for both influenza A and B viruses: A/Puerto Rico/8/34 (H1N1, PR8), A/Hong Kong/8/68 (H3N2) and B/Lee/40. Both the 50% effective concentration (EC_{50}) and the cytotoxic concentration (CC_{50}) were calculated using GradPad Prism 6 software. The group conducted several studies of these dihydrofuropyridinones; seven were found to consistently exhibit significant antiviral activity with a selectivity index (SI) of over 50 (**Table 1.3.1**). The selectivity index represents CC_{50}/EC_{50} and is over 900 in all cases, it is shown in brackets.[46]

Incorporating a bicyclic substituent at R' gave mixed results, with only two out of the nine tested compounds showing antiviral activity. When R' is an indole, a fluoride substituent is required, however, the indole can be replaced with a benzothiophen-2-yl substituent as in **1.167b**. An increased number of derivatives displaying antiviral activity was found when R' was monocyclic. For example, dihydrofuropyridinone **1.167c** with a thiophen-3-yl substituent at R', had a three-time higher antiviral activity compared with **1.167a**. Dihydrofuropyridinone **1.167d** with a thiophen-2-yl substituent at R', showed similar results to the bicyclic derivative **1.167b**. This led to the synthesis of derivatives with modifications to the thiophene ring; and pleasingly, addition of a methyl at positions 3 and 5 of the thiophene showed antiviral activity comparable to that of **1.167d**. Finally, the antiviral activity of dihydrofuropyridinone **1.167g**, is not inhibited when R is a methyl substituent.[46]

Table 1.3.1. Derivatives of dihydrofuropyridinone **1.167** that displayed antiviral activity.[46]



1.167

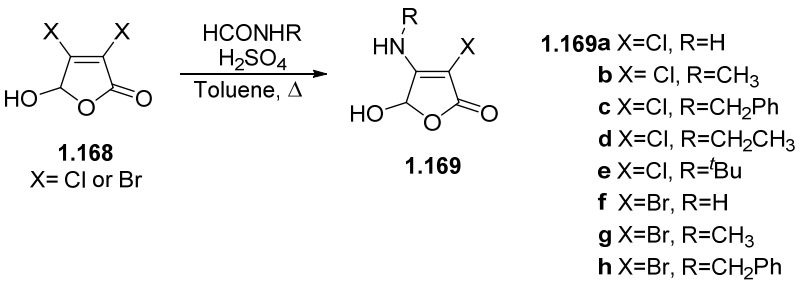
Compound	R	R'	EC_{50} (SI) A/Puerto Rico/8/34	A/Hong Kong/8/68	B/Lee/40
1.167a	-H		17.8±10.6 (>50.6)	17,4±6.3 (>51.7)	21.2±9.73 (>42.7)
1.167b	-H		16.1±6.0 (>55.9)	10.5±5.0 (>85.7)	18.4±12.8 (>48.9)
1.167c	-H		5.0±1.0 (>180.0)	6.2±3.1 (>145.2)	5.9±2.0 (>152.5)
1.167d	-H		7.5±3.2 (>120.0)	6.8±1.3 (>132.4)	7.0±3.8 (>128.6)
1.167e	-H		17.6±11.0 (>51.1)	12.7±8.2 (>70.9)	14.0±7.4 (>64.3)
1.167f	-H		8.0±3.6 (>112.5)	12.2±2.9 (>73.8)	9.6±3.5 (>93.8)
1.167g	-CH_3		12.1±9.5 (>74.4)	11.7±2.7 (>76.9)	8.0±3.6 (>112.5)

1.3.2 **(5*H*)-Furanones in medicinal chemistry**

There is an abundance of (5*H*)-furanones in nature, synthetic drugs, food and perfumes.[47] Natural products containing a (5*H*)-furanone have displayed cytotoxicity and antitumour activity.[48–50] Moreover, the (5*H*)-furanone moiety itself has exhibited antifungal, antibacterial and anti-

inflammatory properties.[51,52] Furanones can react readily with cysteine, in addition to enzymes and bacteria containing thiol groups. The C=C double bond interacts with the thiol groups, therefore inhibiting bacterial growth.[53] Decades of research on the syntheses and biological properties of (5*H*)-furanones has enabled extensive literature to be published, a few of these studies will be reported in this chapter.

A 2005 study by Lattmann *et al*. detailed the antibacterial activity of a series of 4-amino-5-hydroxy-2(5*H*)-furanones. Treatment of mucochloric acid **1.168** with various amides and sulfuric acid in refluxing toluene overnight gave the 2(5*H*)-furanones **1.169** (**Scheme 1.3.1**). Although not all of the yields have been reported, the authors note that higher yields were obtained when R was an alkyl group. Initial screening measured the zone of inhibition 2(5*H*)-furanones **1.169** displayed on bacterial agar plates. The furanones exhibited a broad activity against *Staphylococcus*, *Escherichia coli* and *Pseudomonas aeruginosa* bacteria (**Table 1.3.2**).[54] A further study investigated the minimum inhibitory concentration (MIC) and the minimum bacteriostatic concentration (MBC) of a variety of bacterials, including the three studied previously. It was found that furanone **1.169a** showed broad antibacterial activity, whilst alkylating the amine resulted in higher antibacterial activities.[54]

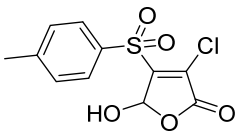


Scheme 1.3.1. Synthesis of 4-amino-5-hydroxy-2(5*H*)-furanones **1.169** from mucochloric acid **1.168**.[54]

Table 1.3.2. The effect of 2(5*H*)-furanones **1.169** on the zone of inhibition of bacterial agar plates.[54]

Entry	X	R	Yield **1.169**%	Zone of inhibition (mm)		
				S. aureus	*E. coli*	*P. aeruginosa*
1.169a	Cl	H	38	16	8	8
1.169b	Cl	CH_3	74	10	11	8
1.169c	Cl	$CH_2C_6H_5$	17	16	6	6
1.169g	Br	CH_3	53	16	9	7

A new study by Sharafutdinov *et al*. reports the significant antifungal activity of (5*H*)-furanone **1.170** against resistant *C. albicans* isolates in combination with fluconazole or terbinafine. Previous work has shown that furanones can quench the bacterial quorum-sensing pathways in some bacteria. Furthermore, some 2(5*H*)-furanone derivatives have been shown to exhibit biocidal activity against biofilm-embedded bacteria, including *Staphylococcus aureus.*[55]



1.170

Figure 1.3.2. 2(5*H*)-Furanone **1.170** has shown antifungal activity against *C.albicans*.[55]

Sharafutdinov *et al*. have shown that even though furanone **1.170** only exhibited moderate antimycotic activity, it lowered the MIC of fluconazole and terbinafine four-fold. Furthermore, furanone **1.170** rapidly penetrated into *C. albicans* biofilm allowing access of antifungals. They speculated that furanone **1.170** targets intracellular proteins instead of the membrane, with antifungal activity caused by direct protein damage. A limitation of furanone **1.170** is that it has shown high toxicity, though this could be offset by using lower concentrations which greatly increased the efficacy of fluconazole and terbinafine against resistant *C. albicans* strains.[55]

1.3.2.1 5(H)-Furanones in natural products

A brief glimpse of some of the natural products containing a (5*H*)-furanone is shown in **Figure 1.3.3**. For example, the (5*H*)-furanone moiety is found in vitamin C **1.171**; an antioxidant that is essential for enzyme function. 4,5-Dimethyl-3-hydroxy-2(5*H*)-furanone, known as sotolon **1.173**, is a powerful aroma compound with low odour thresholds, it is produced from the amino acid threonine. At high concentration sotolon emits fenugreek and curry aromas, whereas at lower concentrations, caramel or burnt sugar aromas are released. As a result, sotolon is found in many food products including rum, coffee and wine.[47,56] Another natural product with a (5*H*)-furanone moiety is umbelactone **1.174**, which was isolated from *Memycelon Umbelatum* Burm in the 1980s. Umbelactone has exhibited antiviral activity against Ranikhet disease, in addition to displaying spasmolytic and antiamphetamine activity.[48]

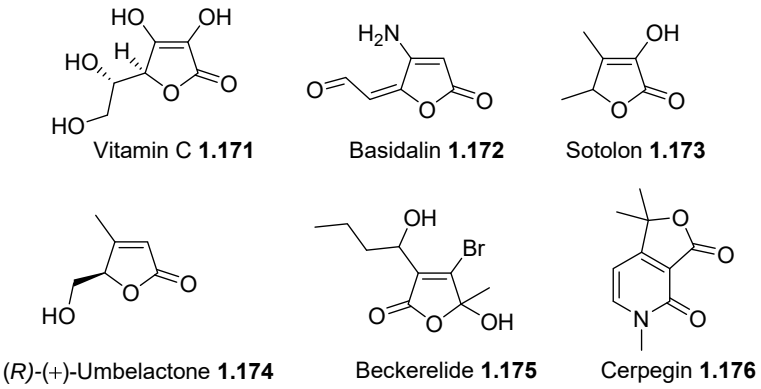
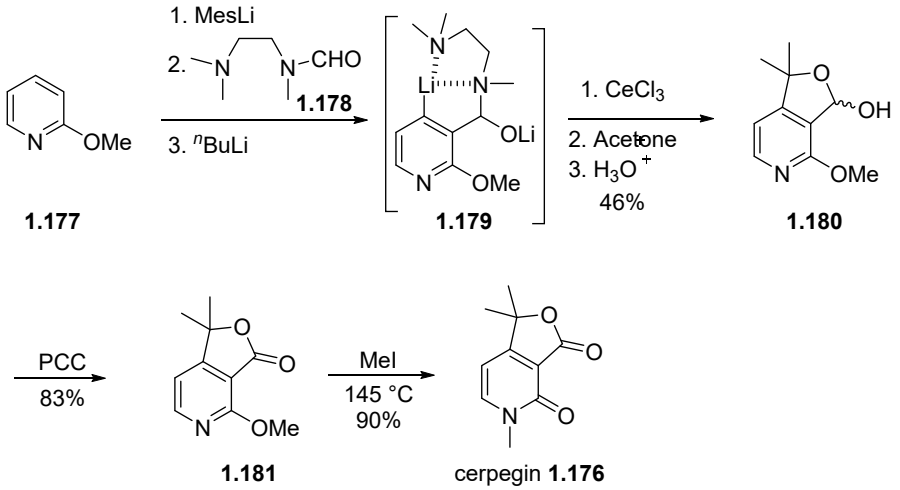


Figure 1.3.3. Examples of natural products containing a (5*H*)-furanone moiety.[57,58]

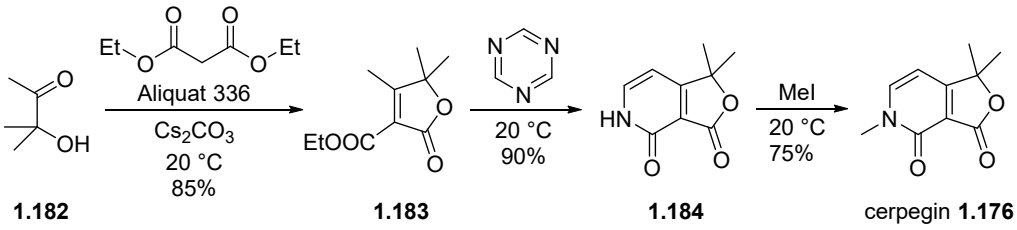
Another natural product containing the (5*H*)-furanone moiety is the alkaloid cerpegin **1.176**. Cerpegin was first isolated in the early 1990s from *Ceropegia juncea*, which itself is reported to exhibit analgesic, antiulcer, anti-inflammatory and tranquilising properties.[59,60] Cerpegin, (1,1,5-trimethylfuro[3,4-*c*]pyridine-3,4-dione) has been shown to inhibit the proteasome enzyme responsible for breaking damaged proteins and peptide bonds. Several multi-step syntheses of cerpegin have been reported, with total yields varying from 15 – 28%.[61–63]

In 1996, Hong and Comins reported the synthesis of cerpegin **1.176** from 2-methoxypyridine **1.177** (**Scheme 1.3.2**).[64] Lithiation of 2-methoxypyridine **1.177** was achieved at C3 using mesityllithium.[65,66] Addition of *N*-formyl-*N*,*N'*,*N'*-trimethylenediamine **1.178** formed an *in situ* α-amino alkoxide which upon treatment with ^{n}BuLi gave dianion **1.179**. Addition of dianion **1.179** to anhydrous $CeCl_3$ in THF, followed by treatment with acetone gave lactol **1.180** in 46% yield. Oxidation of **1.180** using PCC gave furanone **1.181** in 83% yield, which upon heating in methyl iodide gave cerpegin **1.176** in 90% yield, with an overall yield of 34%.[64]



Scheme 1.3.2. Hong and Comin's synthesis of cerpegin **1.176** in an overall yield of 34%.[64]

Later in 1996, Villemin and Liao reported the one-pot, three step synthesis of cerpegin **1.176** in an overall yield of 75%. Treatment of 3-hydroxy-3-methyl-2-butanone **1.182** with diethyl malonate and caesium carbonate at room temperature gave furanone **1.183** in 85% yield. The reaction was carried out with Aliquat 336 (Stark's catalyst) *via* phase transfer catalysis (PTC) in basic media. Furanone **1.183** can then react with *s*-triazine to form lactam **1.184** in 90% yield, with alkylation to cerpegin **1.176** achieved using methyl iodide (**Scheme 1.3.3**).[67]



Scheme 1.3.3. Villemin and Liao have reported a one pot synthesis of cerpegin **1.176**.[67]

Another family of natural products containing a (5*H*)-furanone moiety are the rubrolides **1.185**, over 19 of which have been discovered to date (**Figure 1.3.4**). They are marine tunicates isolated from *Ritterella rubra* and *Synoicum blochmanni* and were first discovered in the 1990s. Rubrolides have demonstrated *in vitro* antibiotic activities and selective inhibition of protein phosphatases.[68]

Rubrolides have also been shown to possess antibiotic, anti-inflammatory, cytotoxic and phytotoxic activities and can inhibit bacterial biofilm formation and photosynthesis.[69]

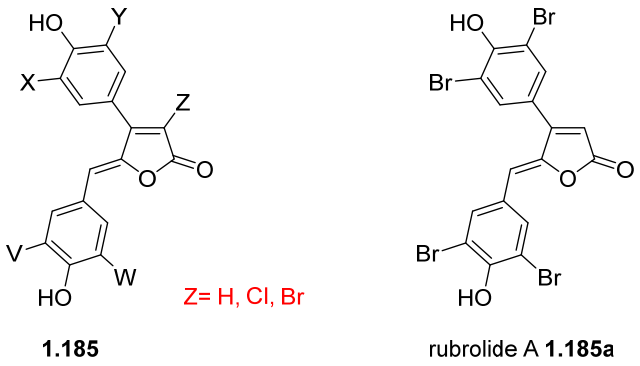


Figure 1.3.4. General structure of rubrolides on the left and rubrolide A on the right.

Syntheses of rubrolides A, C, D and E diacetates were first reported by Negishi and Kotora *via* a palladium catalysed cross-coupling. The precursors, **1.186a** and **1.186b** were synthesised by direct ethynylation of the corresponding aryl iodides while the requisite (*Z*)-β-halocinnamic acids **1.187a** and **1.187b** were synthesised from 4-iodophenol in multiple steps. The palladium catalysed coupling reactions of the two terminal alkynes **1.186** with the two (*Z*)-β-halocinnamic acids **1.187** afforded rubrolide diacetates A, C, D, and E (**1.188**) in isolated yields varying from 38 − 54% (**Scheme 1.3.4**). In each case, the *Z*:*E* ratio was ≥ 50:1 with ≤ 2 − 3% of byproduct **1.189.**[70] A related study found that $Pd(PPh_3)_4$ was superior to $Cl_2Pd(PPh_3)_2$ for the tandem cross-coupling-lactonisation reaction between phenylethyne **1.186** and (*Z*)-β-halocinnamic acid **1.187**.[70] Conversion of the diacetate **1.188c** into rubrolide C (**1.185c**) was achieved upon treatment with K_2CO_3 in a 1:1 mixture of MeOH/THF.

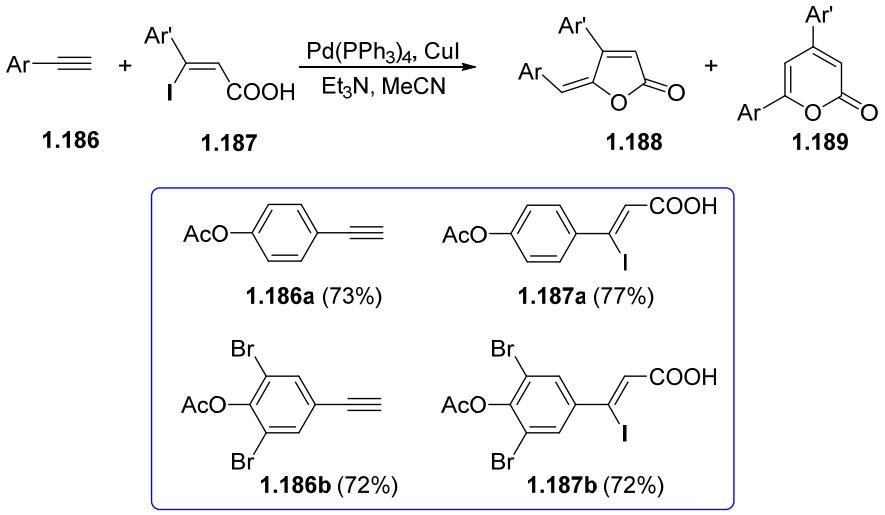


Table 1.3.3.

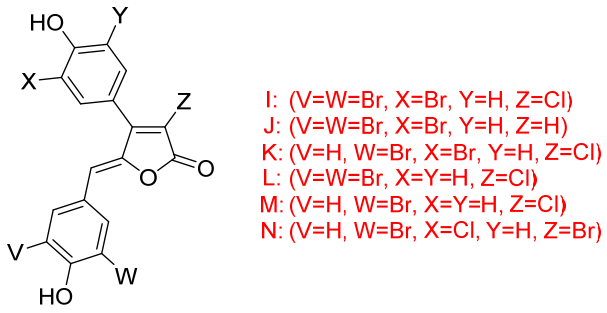
Phenylethyne **1.186**	(*Z*)-β-halocinnamic acid **1.187**	Rubrolide diacetate (Isolated yield **1.188**%)
1.186b	**1.187b**	A (38)
1.186b	**1.187a**	C (54)
1.186a	**1.187b**	D (54)
1.186a	**1.187a**	E (50)

Scheme 1.3.4. Palladium catalysed cross-couplings to afford rubrolide diacetates A, C, D and E **1.188**.[70]

In 2000, Ortega *et al*. discovered rubrolides I-N (**Figure 1.3.5**) and tested some of these against four tumour cell lines: P-388 suspension culture of mouse lymphoid neoplasm; monolayer cultures of human lung carcinoma (A-549); human colon carcinoma (HT-29) and human melanoma (MEL-28). The results are shown in **Table 1.3.4**, with rubrolides B, K and L each displaying significant cytotoxicity. Rubrolide M was the most active against all four tumour lines with the lowest median effective dose, ED_{50} = 1.2 μg/mL.[71]

Table 1.3.4. Median effective doses are rubrolides B, I, K, L and M against four cell lines.[71]

Rubrolide **1.185**	ED_{50}			
	P-388	A-549	HT-29	MEL-28
B	5	5	5	5
I	/	/	5	/
K	2.5	2.5	1.2	5
L	5	5	2.5	5
M	1.2	1.2	1.2	1.2

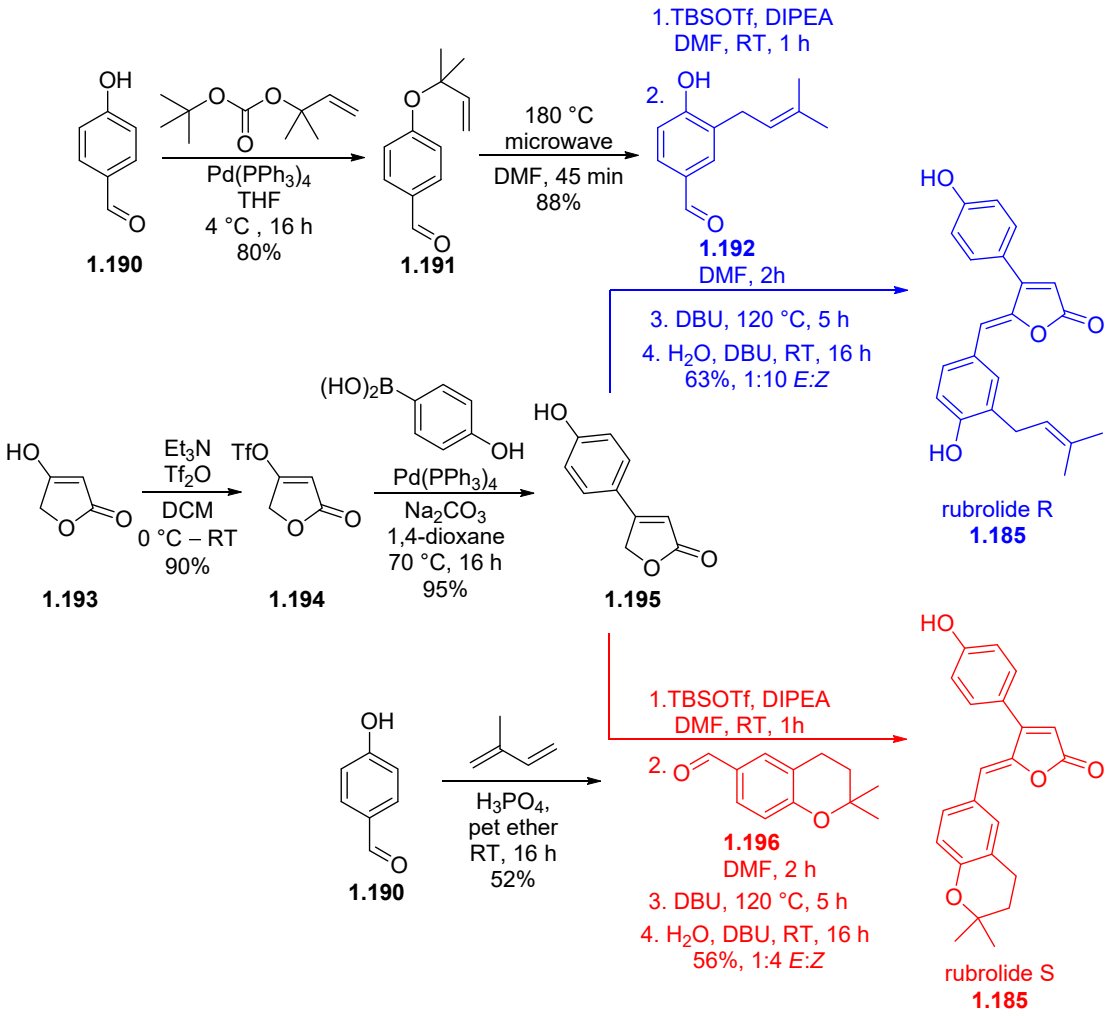


rubrolide **1.185**

Figure 1.3.5. Structure of rubrolides I-N **1.185**.[71]

In 2017, Schacht *et al*. reported the synthesis of rubrolides R and S utilising a Suzuki-Miyaura cross-coupling. Commercially available tetronic acid **1.193** can be converted to triflate **1.194** in 90% yield using triflic anhydride and triethylamine in DCM at 0 °C. A Suzuki-Miyaura cross-coupling between triflate **1.194** and 4-hydroxyphenylboronic acid in the presence of a palladium catalyst and sodium carbonate at 70 °C gave furanone **1.195**. Following optimisation of this cross-coupling it was found that higher yields and shorter reaction times were obtained using $Pd(PPh_3)_4$ instead of $PdCl_2(PPh_3)_2$. For example, 0.5 mol% $Pd(PPh_3)_4$ gave **1.195** in 95% yield after 16 hours.

Conversion of 4-hydroxybenzaldehyde **1.190** to 1,1-dimethylallyl ether **1.191** can be achieved using *tert*-butyl-(2-methylbut-3-en-2-yl) carbonate and $Pd(PPh_3)_4$ at 4 °C in THF. The Claisen rearrangement of ether **1.191** to benzaldehyde **1.192** was achieved in 88% yield *via* a 45 minute microwave reaction at 180 °C in DMF. The same precursor, 4-hydroxybenzaldehyde **1.190**, can be used to synthesise substituted benzaldehyde **1.196** in 52% yield using isoprene and phosphoric acid.[72] An aldol condensation between furanone **1.195** and benzaldehyde **1.192** gave rubrolide R in 54% yield as a 1:10 *E*:*Z* mixture. Analogously, the aldol coupling of furanone **1.195** and benzaldehyde **1.196** gave rubrolide S in 56% yield as a 1:4 *E*:*Z* mixture.[73,74]



Scheme 1.3.5. Schacht *et al*. have reported the synthesis of rubrolides R and S **1.185**, from tetronic acid **1.193**.[73]

In summary, the Moore rearrangement of alkynylcyclobutenones to quinones and cyclopentenediones has been instrumental in creating complex ring systems from four-membered rings. More recently, Harrowven *et al*. optimised these reactions using flow chemistry and

determined the mechanistic detail. The outward rotation of alkynylcyclobutenones during thermolysis has resulted in furanones and subsequently dihydrofuropyridinones. Further exploitation of these reactions could open up exciting opportunities to create more fused ring systems, which have been used extensively in medicinal chemistry and can be found in several natural products.

1.4 Aims & Objectives

This project is centred on the derivatisation of dihydrofuropyridinones akin to **1.129** *via* cycloaddition reactions to create more diverse polycyclic systems. The first objective is to scale up the synthesis of dihydrofuropyridinone **1.129** enabling thermal, photochemical and high-pressure transformations to be performed consecutively as detailed in **Figure 1.4.1**. Ultimately, the goal is to develop daisy chain sequences using reagentless techniques to create new and complex 3D scaffolds that will potentially have biological applications. Another aim is to synthesise a variety of dihydrofuropyridinones **1.202** from alkynylcyclobutenones **1.201**, with different alkyl residues at C2, different amines at C3 and alternative alkynyl groups at C4. This would enable a large number of scaffolds to be made in an efficient and cost effective manner.

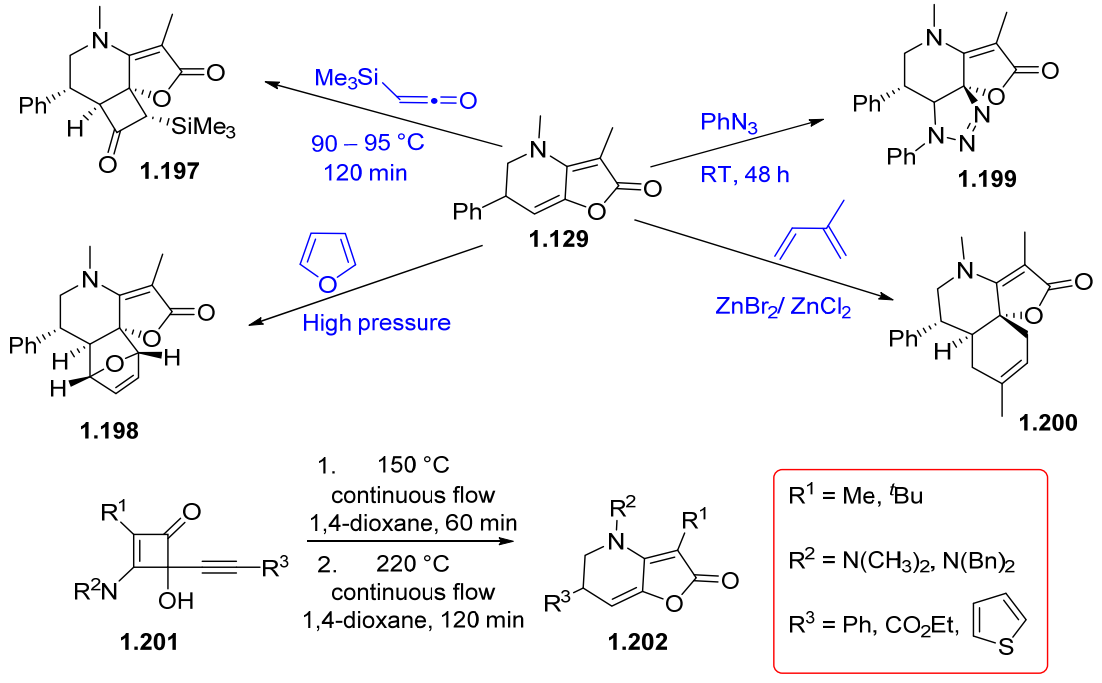


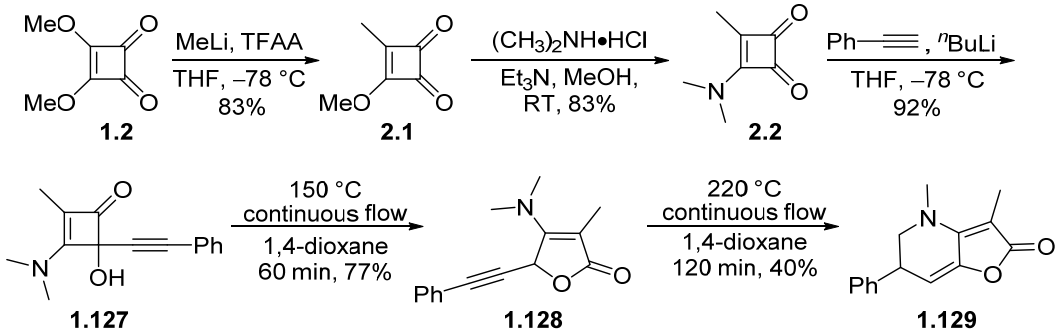
Figure 1.4.1. Potential reagentless transformations of dihydrofuropyridinone **1.129** and alkynylcyclobutenones **1.201**.

Chapter 2 Synthesis & Thermal Reactivity of Dihydrofuropyridinones

2.1 Synthesis of dihydrofuropyridinones

Initially, the objective was to scale up the synthesis of dihydrofuropyridinone **1.129** under flow, using the R4/R2^{+} Vapourtec system. The thermal rearrangements were previously carried out on small scales and afforded furanone **1.128** in 49% yield and dihydrofuropyridinone **1.129** in 83% yield (see **Introduction Scheme 1.2.2**).

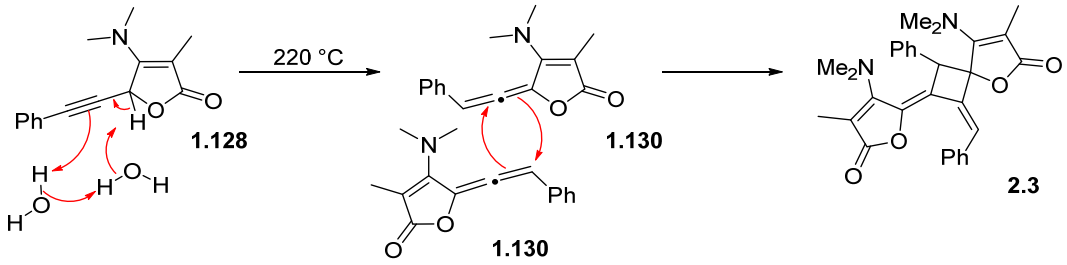
Firstly, dimethoxycyclobutenone **1.2** was treated with methyllithium in THF, followed by addition of TFAA to give cyclobutenone **2.1** in 83% yield. Amination with dimethylamine hydrochloride and triethylamine in methanol resulted in aminocyclobutenone **2.2** also in 83% yield. Addition of phenylacetylene was next effected by its deprotonation with ^{n}BuLi at –78 °C and reaction with aminocyclobutenone **2.2**, to alkynylcyclobutenenone **1.127** in 92% yield. Thermolysis of alkynylcyclobutenone **1.127** under continuous flow at 150 °C gave furanone **1.128** in 77% yield, while its thermal rearrangement to dihydrofuropyridinone **1.129** in 1,4-dioxane under continuous flow at 220 °C proceeded in 40% yield (**Scheme 2.1.1**).



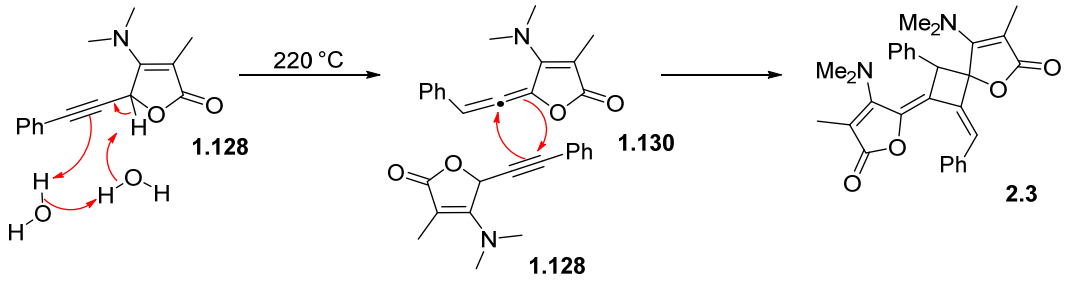
Scheme 2.1.1. Thermolysis of alkynylcyclobutenone **1.127** under continuous flow first at 150 °C and then 220 °C.

The second thermolysis to dihydrofuropyridinone **1.129** was plagued with issues and it is with regret that we were unable to repeat the yield of 83% reported by Wei Sun.[38] This was primarily due to reactor fouling even under conditions of higher dilutions. Additionally, at high concentrations under thermolysis, furanone **1.128** formed dimer **2.3** in appreciable yield. We

believe two possible mechanisms could have given this result; alkyne isomerisation to allene **1.130** and a [2+2] cycloaddition with further allene **1.130** (**Scheme 2.1.2**). Alternatively, alkyne isomerisation to allene **1.130** and a [2+2] cycloaddition with alkyne **1.128** (**Scheme 2.1.3**). Due to the consistently low yields when using the Vapourtec flow reactor and our inability to prevent reactor fouling and blocking, it was decided that large scale syntheses would be conducted in batch until these matters could be resolved.

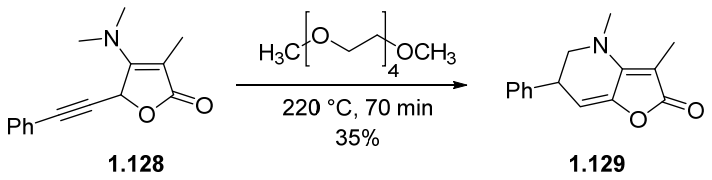


Scheme 2.1.2. A possible mechanism for the formation of dimer **2.3** *via* allene **1.130**.



Scheme 2.1.3. Another possible mechanism for the formation of dimer **2.3** *via* allene **1.130** and alkyne **1.128**.

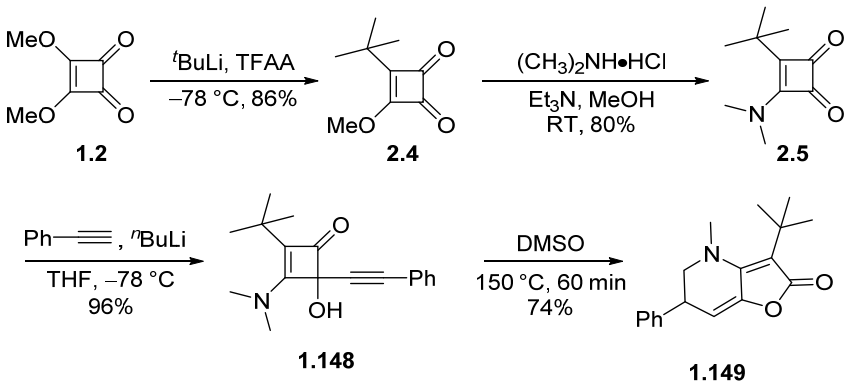
Thermolyses carried out under batch conditions were not ideal, a high boiling point solvent was required to enable the rearrangement of allene **1.130** to alkene **1.131** (see **Introduction Scheme 1.2.4**). Nevertheless, when a 0.041 mM solution of furanone **1.128** in tetraethylene glycol dimethyl ether was heated to 220 °C for 70 minutes, dihydrofuropyridinone **1.129** was given in 35% yield. The yield is slightly lower in batch than the 40% achieved when a 0.084 mM solution of furanone **1.128** was thermolysed under continuous flow. However, batch thermolysis produced almost twice the amount of material and bypassed concerns over reactor fouling and blockages.



Scheme 2.1.4. Batch thermolysis of furanone **1.128** to dihydrofuropyridinone **1.129**.

Simultaneously, focus was placed upon the synthesis of dihydrofuropyridinone **1.149** with a *tert*-butyl substituent at C2. As mentioned in **Section 1.2.1.1**, the *tert*-butyl group causes steric buttressing between the C2 and C3 residues in alkynylcyclobutenone **1.148**, which lowers the activation energy for formation of the corresponding dihydrofuropyridinone **1.149**. Indeed, it is produced directly by thermolysis of alkynylcyclobutenone **1.148** as the furanone intermediate rearranges at a lower temperature.

Thus, treatment of 3,4-dimethoxycyclobutenedione **1.2** with *tert*-butyllithium in THF, followed by TFAA, gave 3-*tert*-butyl-4-methoxycyclobutenedione **2.4** in 86% yield. Subsequent amination with dimethylamine hydrochloride and triethylamine afforded aminocyclobutenone **2.5** in 80% yield. Addition of lithiated phenylacetylene then gave alkynylcyclobutenone **1.148**, which was thermolysed under batch conditions at 150 °C to produce dihydrofuropyridinone **1.149** in 74% yield after 60 min (**Scheme 2.1.5**). Once again, thermolysis under batch conditions can be scaled up due to the lower concentration of alkynylcyclobutenone, this results in a much smaller chance of dimer formation. In this case, alkynylcyclobutenone **1.148** at a concentration of 0.018 M, gave dihydrofuropyridinone **1.149** in 74% yield.

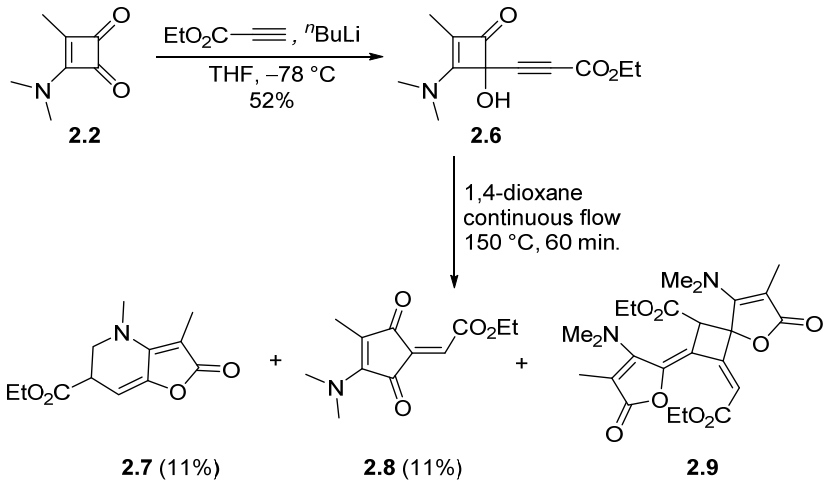


Scheme 2.1.5. Synthesis of dihydrofuropyridinone **1.149** from dimethoxycyclobutenone **1.2**.

2.2 Introduction of an alkynyl ester group

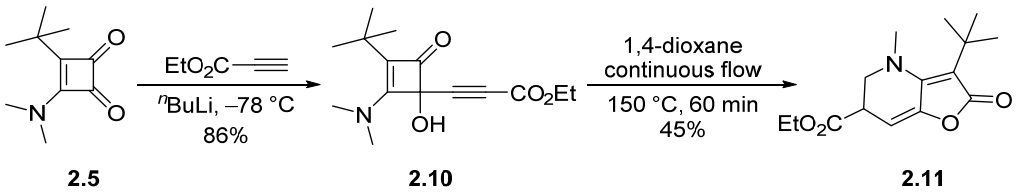
The Harrowven group have also reported the synthesis of cyclobutenones with alkynyl ester substituents instead of a phenylacetylene. To that end, cyclobutenone **2.2** was added to a solution of lithiated ethyl propiolate in THF at –78 °C, to give alkynylcyclobutenone **2.6** in 52% yield. Previous work by Wei Sun had shown that alkynylcyclobutenone **2.6** could be converted into dihydrofuropyridinone **2.7** in 34% yield, directly at lower temperatures and using shorter residence times. This is due to the lower energy barriers for each transition state when compared to the phenyl substituted furanone **1.128**. However, Wei Sun also noted that cyclopentenedione **2.8** was formed as a significant byproduct.[38]

Indeed, on repeating the thermolysis of alkynylcyclobutenone **2.6** in 1,4-dioxane at 150 °C under continuous flow, we were only able to produce dihydrofuropyridinone **2.7** in 11% yield. The reaction also yielded cyclopentedione **2.8** in 11% yield, with baseline material accounting for around half of the mass (**Scheme 2.1.6**). Analysis by mass spectrometry suggested that the baseline material corresponded to dimer **2.9** as evidenced by a peak at *m/z* 475 $[2M+H]^+$.



Scheme 2.1.6. Thermolysis of alkynylcyclobutenone **2.6** under continuous flow at 150 °C gave dihydrofuropyridinone **2.7** as a minor product together with cyclopentenedione **2.8** and dimer **2.9**.

Knowing that replacing the C2 methyl group for a *tert*-butyl substituent would lower the activation barriers of the rearrangement, we decided to try the same tactic with the alkynyl ester moiety. To that end, treatment of cyclobutenone **2.5** with lithiated ethyl propiolate in THF at –78 °C, resulted in an 86% yield of alkynylcyclobutenone **2.10**; which we hoped could be thermolysed directly to dihydrofuropyridinone **2.11**. The reaction was previously carried out by Wei Sun under continuous flow, at a concentration of 0.076 M and dihydrofuropyridinone **2.11** was formed in 70% yield as the only isolated product. When the reaction was repeated at a slightly higher concentration of 0.11 M, without changing any of the other conditions, dihydrofuropyridinone **2.11** was formed in only 45% yield (**Scheme 2.1.7**).



Scheme 2.1.7. Synthesis of *tert*-butyl dihydrofuropyridinone **2.11** from cyclobutenone **2.5**.

2.3 Thermal reactions of dihydrofuropyridinones and furanones

2.3.1 Diels-Alder cycloadditions

It was hoped that the distal alkene of dihydrofuropyridinones **1.129** and **1.149** could react in a thermal [4+2] Diels-Alder cycloaddition with 2,3-dimethylbuta-1,3-diene **2.12** (**Figure 2.1**). DFT calculations suggest that the furanone ring of dihydrofuropyridinone **1.149** is the more electron withdrawing alkene, therefore, the *tert*-butyl group makes the distal alkene a better dienophile.[38]

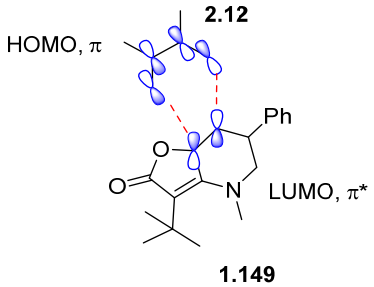
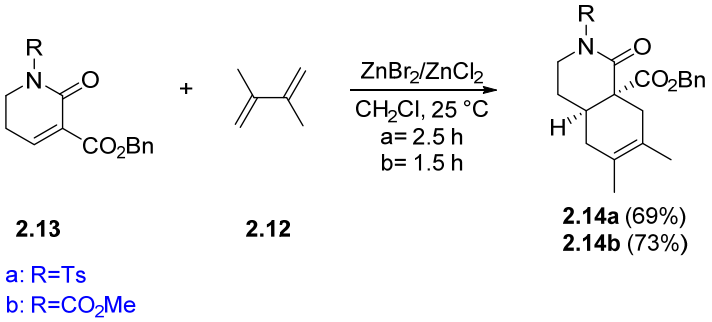


Figure 2.1. The bonding interaction between diene **2.12** HOMO and dihydrofuropyridinone **1.149** LUMO.

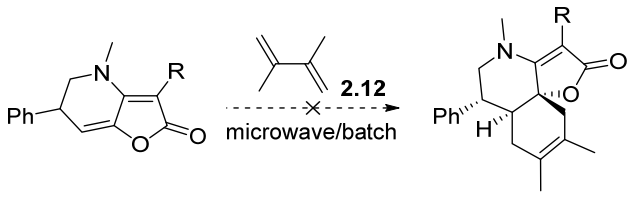
Diene **2.12** was chosen due to its increased electron density and record of successfully participating in Diels-Alder reactions. Casamitjana *et al*. have reported Diels-Alder reactions of 2,3-dimethylbuta-1,3-diene **2.12**, with dihydropyridones **2.13**, a structure similar to dihydrofuropyrdinone **1.129**. The reactions proceeded in considerably higher yields at room temperature in the presence of $ZnBr_2$ or $ZnCl_2$, compared to under thermal conditions. Diels-Alder adducts **2.14** were produced in yields of around 70% (**Scheme 2.1.8**).[75]



Scheme 2.1.8. Casamitjana *et al*. have reported Diels-Alder reactions of dihydropyridones **2.13** with dimethylbuta-1,3-diene **2.12**.[75]

Several Diels-Alder reactions were attempted on both dihydrofuropyridinones **1.129** and **1.149**. Unfortunately, batch reactions in various solvents at temperatures ranging from 25 – 100 °C, with and without the Lewis acid catalyst ($AlCl_3$), only resulted in recovered starting material. We then used microwave irradiation in an attempt to drive the reaction using high temperatures and pressures. Solvents used included toluene, methanol and 1,4-dioxane and temperatures ranged from 100 – 140 °C. Toluene proved to be a poor solvent for this purpose due to its low polarity and low dielectric constant.[76] Conversely, methanol with its high polarity heated up rapidly to 100 °C with a ramp time of only 30 seconds. 1,4-Dioxane was also examined as it was hoped that the synthesis and cycloaddition of dihydrofuropyridinones could be daisy chained together using the same solvent. However, all of these microwave reactions returned only starting material. (**Table 2.1**).

Table 2.1. Different conditions used for Diels-Alder cycloadditions of dihydrofuropyridinones **1.129** and **1.149** with 2,3-dimethylbuta-1,3-diene **2.12**. Unfortunately, these did not form the proposed adducts **2.15** or **2.16**.



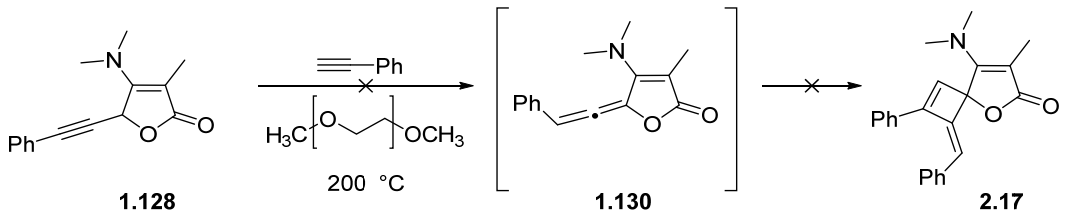
1.129 R = Me
1.149 R = ^{t}Bu

2.15 R = Me
2.16 R = ^{t}Bu

Entry	R	Solvent	T (°C)	Lewis Acid Catalyst	Method
1	*tert*-butyl	toluene	25	$AlCl_3$	batch
2	*tert*-butyl	toluene	80	$AlCl_3$	batch
3	*tert*-butyl	toluene:water 10:1	120	/	microwave
4	*tert*-butyl	1,4-dioxane	120	/	microwave
5	*tert*-butyl	methanol	100	/	microwave
6	methyl	methanol	100	/	microwave
7	methyl	1,4-dioxane	125	/	microwave
8	methyl	toluene	140	/	microwave

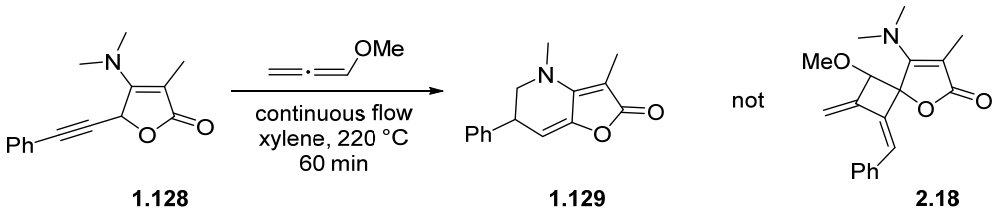
2.3.2 Formation of spiro-compounds

We hypothesised that the formation of furanone dimer **2.3** (See **Scheme 2.1.2**), could potentially be used to our advantage by adapting the chemistry to form heterocyclic spirocycles such as **2.17**. It was proposed that furanone **1.128** could undergo a thermal [2+2] cycloaddition with phenylacetylene to give spirolactone **2.17** (**Scheme 2.1.9**). The reactions were carried out in batch at 200 °C using the high boiling point solvent tetraethylene glycol dimethyl ether, or by microwave irradiation in 2-propanol. Unfortunately, in all cases only starting material was recovered with poor mass balance.



Scheme 2.1.9. The planned thermal [2+2] cycloaddition of furanone **1.128** with phenylacetylene did not lead to spirocycle **2.17**.

This suggested that the cycloaddition reaction proceeded *via* allene dimerisation rather than a [2+2] cycloaddition between an alkyne and allene. To test this hypothesis, we then attempted the reaction of furanone **1.128** with an electron rich allene to see if we could form the desired spirocycle **2.18**. Methoxyallene was added to a solution of furanone **1.128** in xylene and heated to 220 °C under continuous flow for 60 min. Dihydrofuropyridinone **1.129** was recovered, but unfortunately, there was no evidence of spirocycle **2.18** (**Scheme 2.1.10**).



Scheme 2.1.10. The [2+2] thermal cycloaddition of methoxyallene and furanone **1.128** did not yield spirocycle **2.18** and instead gave a small amount of dihydrofuropyridinone **1.129**.

To summarise, dihydrofuropyridinones **1.129** and **1.149** were synthesised in reasonable yields under continuous flow on the vapourtec system; however, problems such as reactor fouling and blockages arose during scale up. As a result, future syntheses were carried out under batch conditions at much lower concentrations. Furthermore, dihydrofuropyridinones **1.129** and **1.149** were thermally unreactive and did not undergo Diels-Alder reactions with dimethylbuta-1,3-diene **2.12**. Thermal cycloadditions of furanone **1.128** with phenylactylene and methoxyallene, did not form spirocycles; either the furanone was recovered or the corresponding dihydrofuropyridinone was obtained instead.

Chapter 3 Photochemical Transformations of Dihydrofuropyridinones

3.1 Azocines in medicinal chemistry

3.1.1 Synthesis of medium-sized rings

Medium-sized rings, in particular, 8-membered rings are known to be challenging to synthesise, predominately due to transannular strain and the loss of entropy upon ring closure. [77–82] Traditional end-to-end cyclisations are often aided with inconvenient high or pseudo dilution techniques and are prone to competing intramolecular reactions. [83–86] There are many techniques used to synthesise medium-sized rings, including RCM,[87–90] ring expansions [91–97] and microwave synthesis.[98]

Azocines are 8-membered nitrogen heterocycles and are present in many natural products, making them highly desirable within medicinal chemistry.[99–105] In 1986, Thorsett *et al.* found that the 8-membered lactam **3.1** was a potent inhibitor of angiotensin converting enzyme (ACE).[106] Inhibitors of ACE such as enalaprilat **3.2**, are used for cardiovascular treatment to lower blood pressure. The group have shown that these 8-membered lactams can be a useful replacement of the alanylproline **3.3** portion of the potent ACE inhibitor enalaprilat **3.2**.

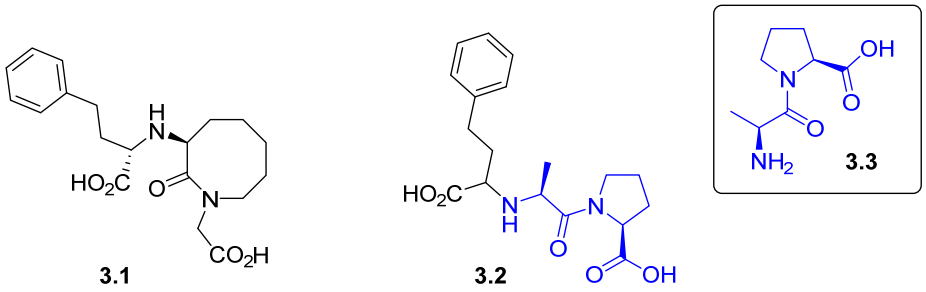
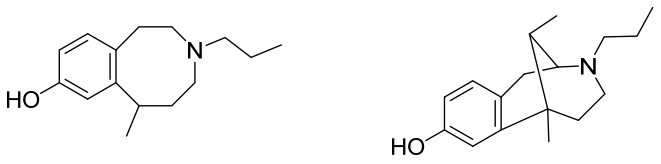


Figure 3.1.1. The 8-membered lactam **3.1** can be used to replace the alanylproline component of the drug enalaprilat **3.2**.[106]

Furthermore, in the 1970s, May and co-workers tested benzoazocines and benzomorphans for analgesic properties. It was found that benzoazocines interacted with the opiate receptor of rat brain homogenates receptors more weakly than the corresponding benzomorphans. However, the benzoazocines followed a correlation between receptor affinity and analgetic activity, with benzoazocine **3.4a** having the highest analgesic effect of the series.[107,108]



3.4a **3.4b**

Figure 3.1.2. *N*-alkylbenzoazocine **3.4a** and the corresponding benzomorphan **3.4b** showed promising analgetic effects.[107,108]

3.1.2 Azocines in natural products

A few examples of natural products containing an azocine ring are shown in **Figure 3.1.3**. The most prominent example is manzamine A **3.5**, which is a natural product discovered in 1986 from an Okinawan marine sponge found in Japan. It was found to inhibit the growth of P388 mouse leukaemia cells and has proven a popular target for total synthesis.[109]

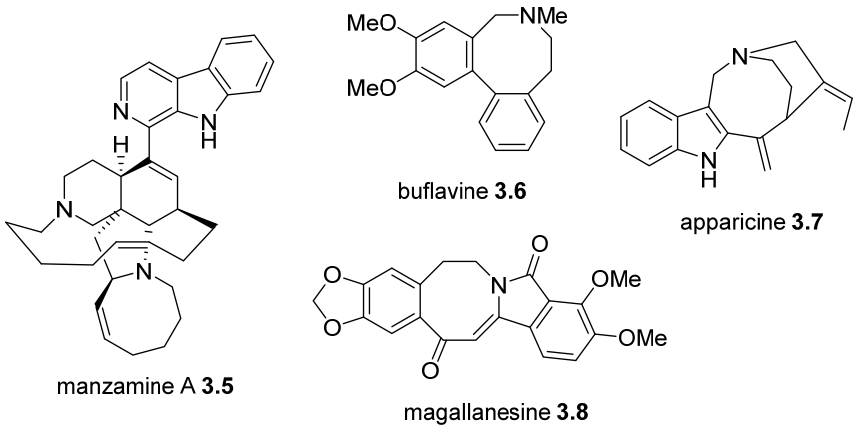
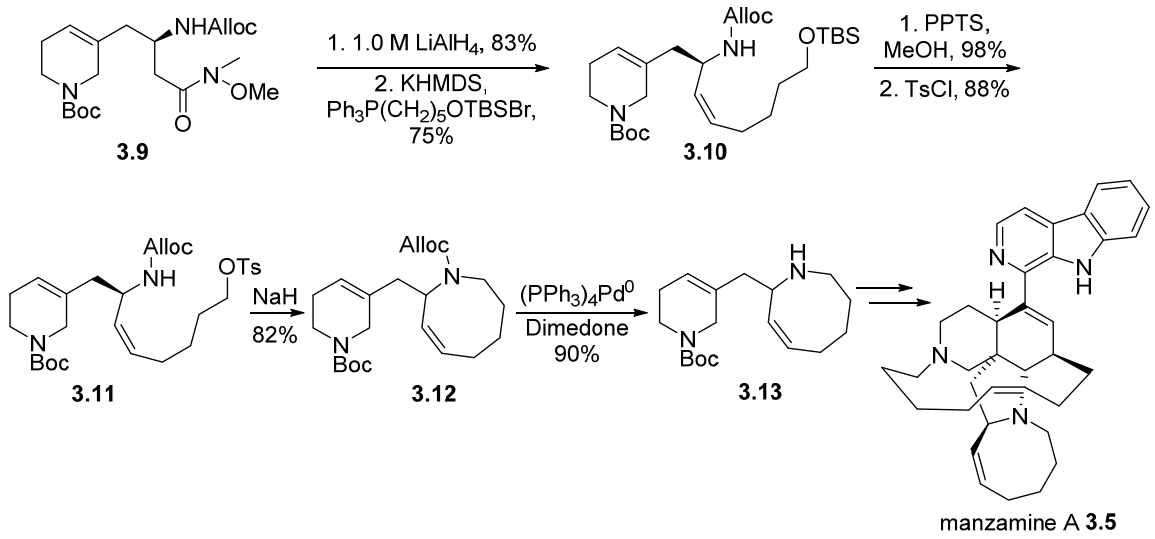


Figure 3.1.3. Examples of natural products containing an azocine motif.

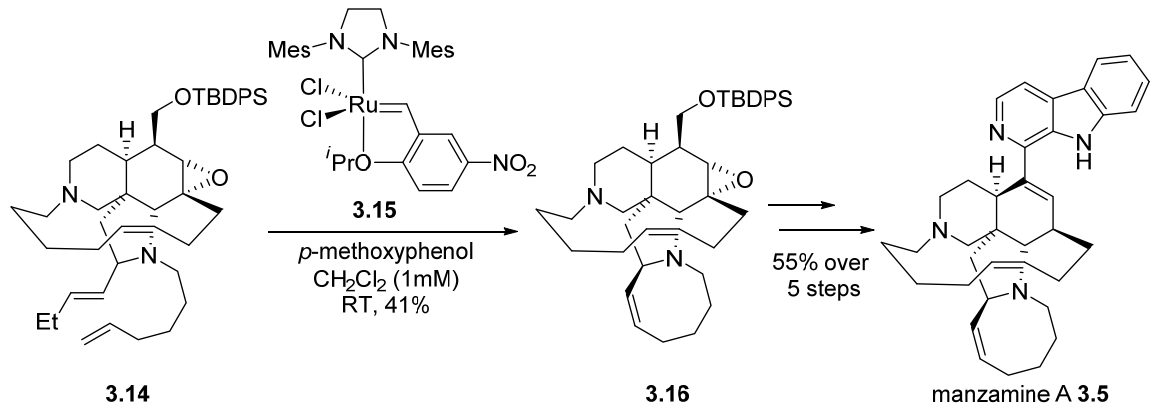
The first total synthesis of manzamine A was published in 1998 by Winkler and Axten.[110] It had a convergent synthesis with a linear sequence of 17 steps from the azocine precursor **3.13**.[111] Thus, Weinreb amide **3.9** was reduced with lithium aluminium hydride to the corresponding aldehyde in 83% yield, which then underwent a Wittig alkenylation to the *cis*-alkene **3.10** in 75% yield. Conversion of the silyl ether of **3.10** to a tosylate group using pyridinium *p*-toluenesulfonate and then *p*-toluenesulfonyl chloride gave tosylate **3.11**. Tosylate **3.11** was added by syringe pump to a solution of sodium hydride under high dilution, to give the 8-membered ring **3.12** in 82% yield.

Removal of the Alloc protecting group using tetrakis(triphenylphosphine)palladium(0)[112] in the presence of dimedone produced azocine **3.13** (**Scheme 3.1.1**).[111]



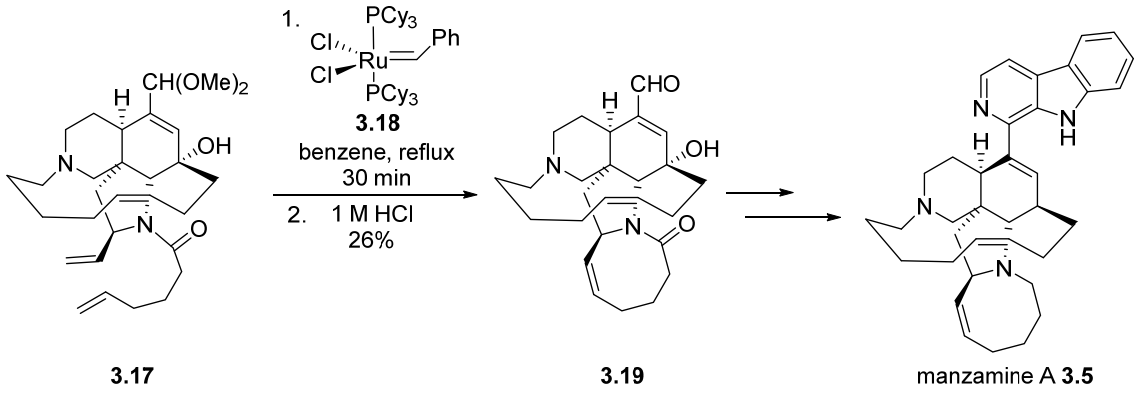
Scheme 3.1.1. Winkler and Axten synthesis of the azocine unit of manzamine A **3.5**.[111]

There have been many more reported total syntheses of manzamine A **3.5** [113–118], including several approaches to the tetracyclic core. [119,120] Fukuyama *et al*.'s total synthesis, in which the azocine was formed at the latter stages, was based on a RCM. Thus, the RCM of diamine **3.14** in DCM at high dilution, in the presence of ruthenium catalyst **3.15** and *p*-methoxyphenol, gave azocine **3.16** in 41% yield (**Scheme 3.1.2**). Azocine **3.16** was advanced to manzamine A **3.5**, in a further 5 steps in 55% yield.[113]

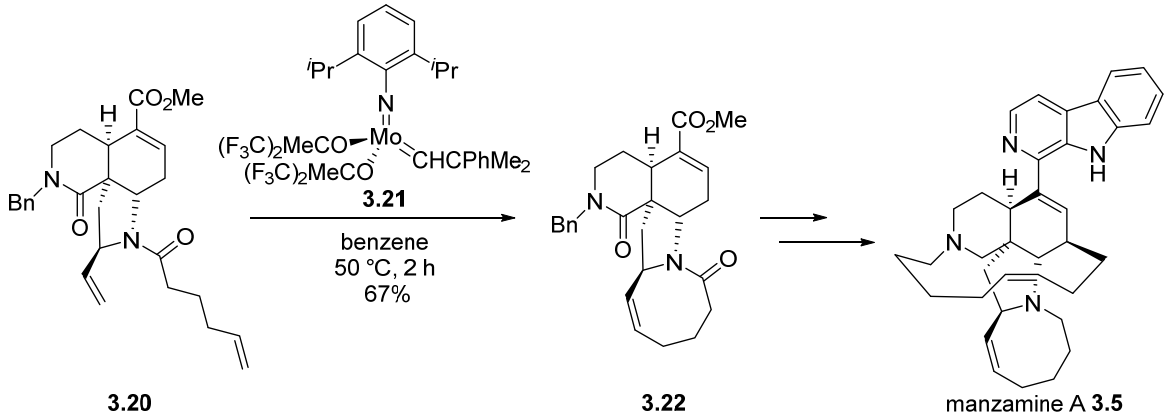


Scheme 3.1.2. Fukuyama *et al*. synthesis of the azocine unit of manzamine A **3.5**.[113]

Martin *et al*. also utilised a ring closing metathesis. Treatment of diene **3.17** with Grubbs ruthenium catalyst **3.18**, under high dilution, directly followed by an aqueous acid work up to remove the dimethyl acetal, gave azocine **3.19** in 26% yield (**Scheme 3.1.3**).[116] A later paper by the group detailed a higher yielding RCM of diene **3.20** with molybdenum catalyst **3.21** under high dilution, to give azocine **3.22** in 67% yield (**Scheme 3.1.4**).[114]

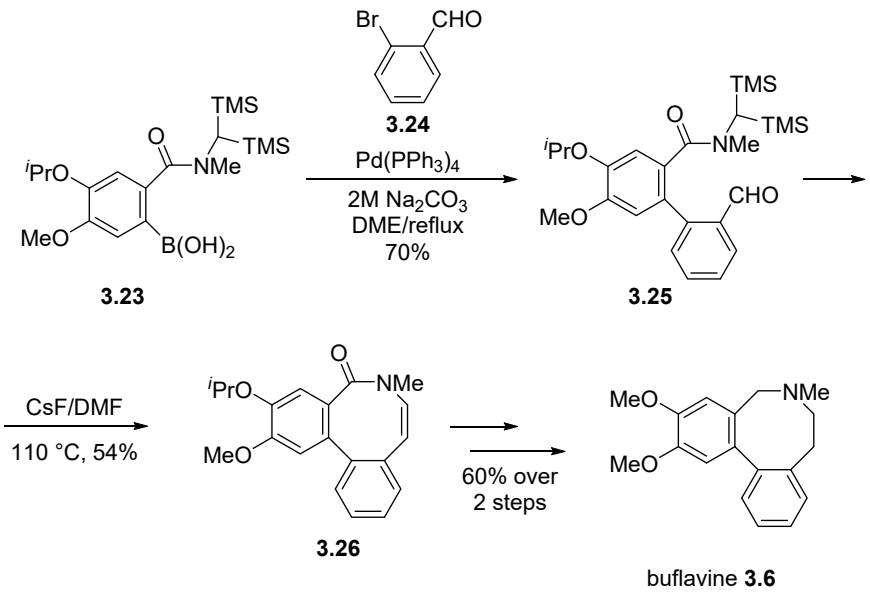


Scheme 3.1.3. Martin *et al*. synthesis of the azocine ring of manzamine A **3.5** in 26% yield.[116]



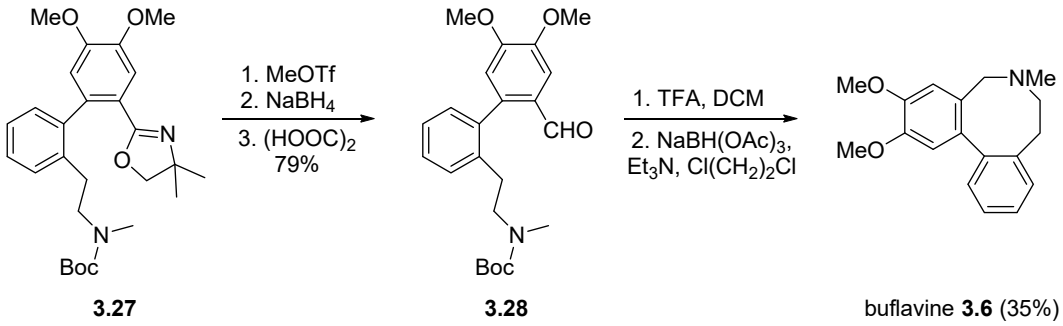
Scheme 3.1.4. A more recent synthesis of the azocine ring of manzamine A **3.5** in 67% yield from Martin *et al*.[114]

Buflavine **3.6** is an *Amaryllidaceae* alkaloid isolated from Boophane flava bulbs[121], it has possible α-adrenolytic and anti-serotonin activities.[122,123] The first total synthesis by Patil and Snieckus in 1997, detailed a convergent preparation of buflavine **3.6** *via* a Suzuki-Miyaura cross-coupling and an intramolecular Peterson Olefination under high dilution (**Scheme 3.1.5**). Buflavine **3.6** was produced from azocine **3.26** in a further 2 steps in 60% yield.[124]



Scheme 3.1.5. Patil and Snieckus synthesis of the azocine ring found in buflavine **3.6**.[124]

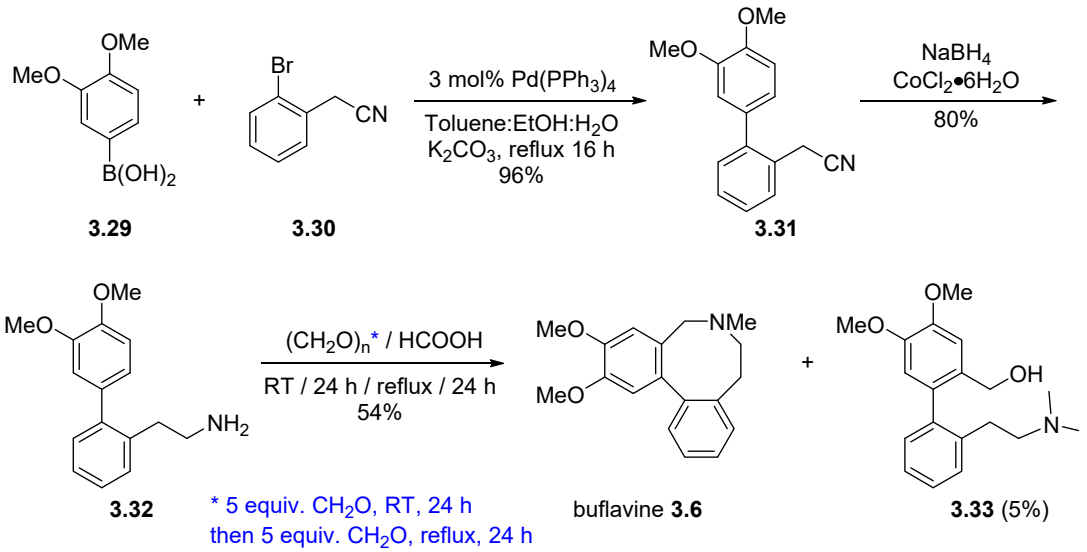
Grandclaudon *et al.* have reported a 7-step synthesis of buflavine **3.6**, with azocine formation as the last step. Reductive cleavage of the oxazoline ring of biarylalkylamine **3.27** resulted in benzaldehyde derivative **3.28.** *N*-Deprotection of **3.28** under high dilution, followed by reductive amination gave buflavine **3.6** in a yield of 35% (**Scheme 3.1.6**).[125]



Scheme 3.1.6. The final steps of Grandclaudon *et al.*'s synthesis of buflavine **3.6**.[125]

An even shorter 3-step synthesis reported by Sahakitpichan and Ruchirawat in 2003, employed a Suzuki-Miyaura cross-coupling of commercially available boronic acid **3.29** and 2-bromophenylacetonitrile **3.30** to biaryl **3.31** (**Scheme 3.1.7**). This was followed by reduction of the nitrile group to amine **3.32** in 80% yield, in the presence of sodium borohydride and cobalt chloride

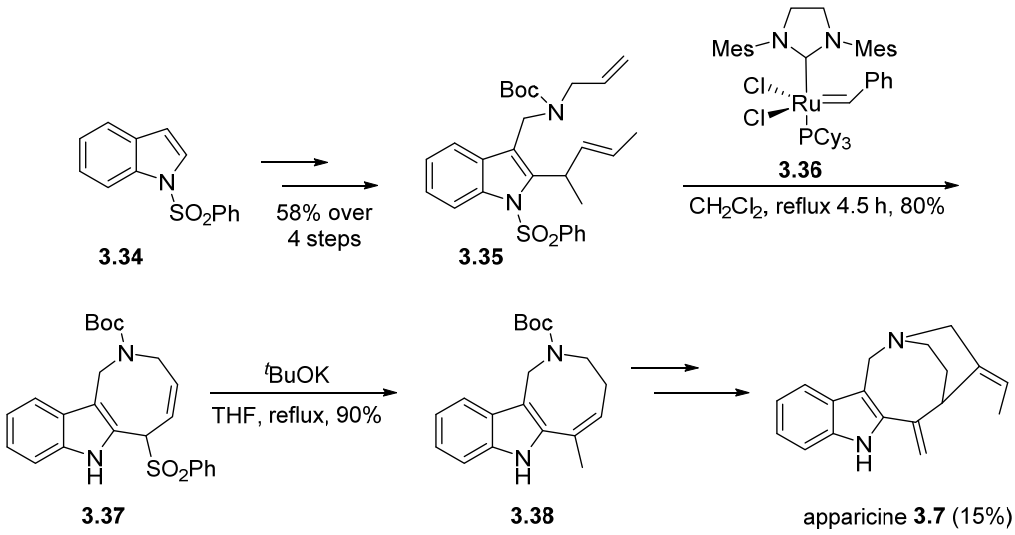
hexahydrate. A Pictet-Spengler cascade to the azocine, followed by *N*-methylation, gave buflavine **3.6** in 54% yield, without the need for high dilution. However, byproduct biarylalcoholamine **3.33**, was formed in 5% yield, most likely from an electrophilic substitution of the aryl ring with paraformaldehyde.[126]



Scheme 3.1.7. Sahakitpichan and Ruchirawat's synthesis of buflavine **3.6**, *via* a Suzuki-Miyaura coupling followed by a Pictet-Spengler cascade and *N*-methylation.[126]

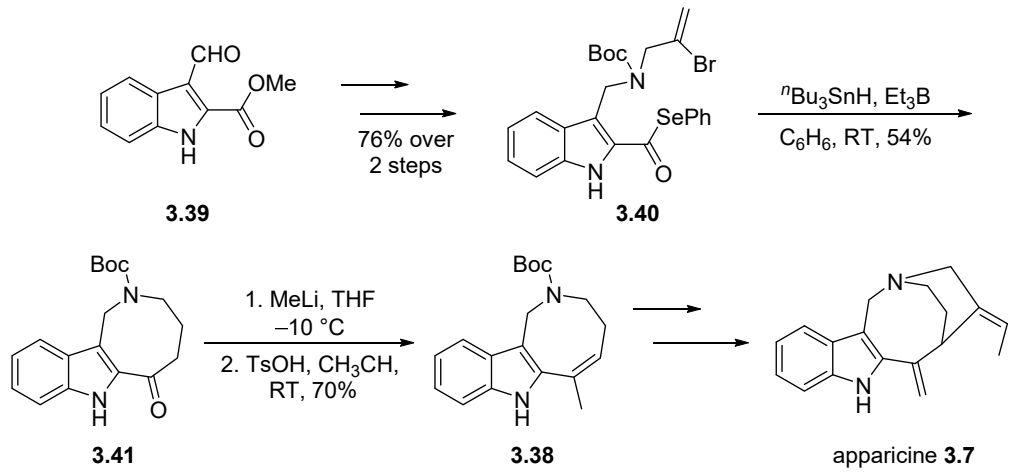
Bennasar *et al.* have published several papers detailing the synthesis of apparicine **3.7**, which is an indole alkaloid isolated from *Aspidosperma dasycarpon*.[127] The group have reported the first total synthesis of apparicine; with two procedures to synthesise the azocinoindole intermediate **3.38**. The first, an indole-templated RCM and the second an acyl radical cyclisation.

Thus, 1-(phenylsulfonyl)indole **3.34** was converted to diene **3.35** in 4 steps in a 58% overall yield. Treatment of diene **3.35** with Grubbs second generation catalyst **3.36** in refluxing DCM under high dilution, afforded azocine **3.37** in 80% yield. This was followed by a base-induced isomerisation using potassium *tert*-butoxide, to give the key azocinolindole **3.38** in 90% yield. Apparicine **3.7** was formed in a further 3 steps in an overall yield of 15% (**Scheme 3.1.8**).[127,128]



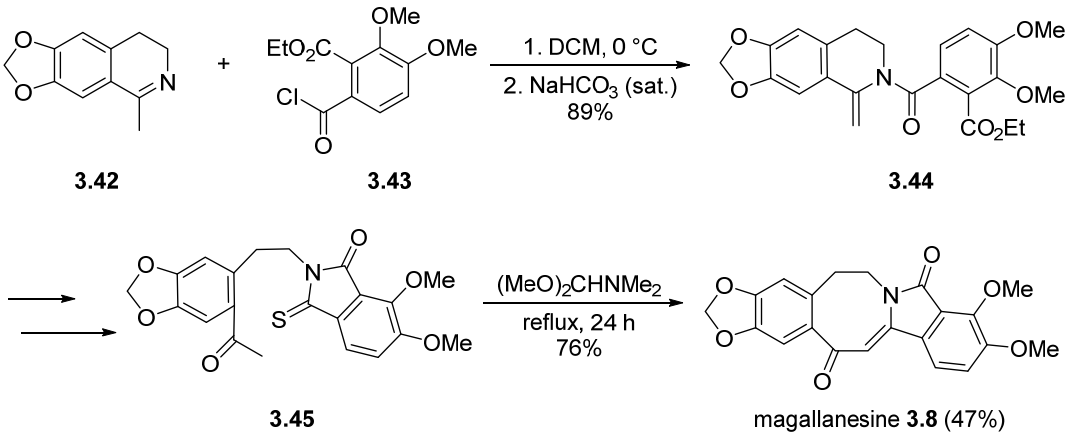
Scheme 3.1.8. Bennasar *et al.* used an RCM to azocine **3.37**, followed by alkene isomerisation to the key azocinoindole intermediate **3.38**.[127–129]

The second route to azocinoindole **3.38,** was an acyl radical cyclisation, followed by functional group interconversion of a ketone to an allene (**Scheme 3.1.9**).[129] Selenoester **3.40** was formed in 2 steps from aldehyde **3.39** in 76% yield. Treatment of selenoester **3.40** with radical mediator ^{n}BuSnH and initiator Et_3B, promoted an 8-*endo* cyclisation to azocine **3.41** in 54% yield, without the need for high dilution. Addition of methyllithium to azocine **3.41**, followed by dehydration under mildly acidic conditions gave the key azocinoindole intermediate **3.38** in 70% yield.[127,129]



Scheme 3.1.9. Bennasar *et al.* synthesis of the key intermediate azocinoindole **3.38** *via* an acyl radical cyclisation.[129]

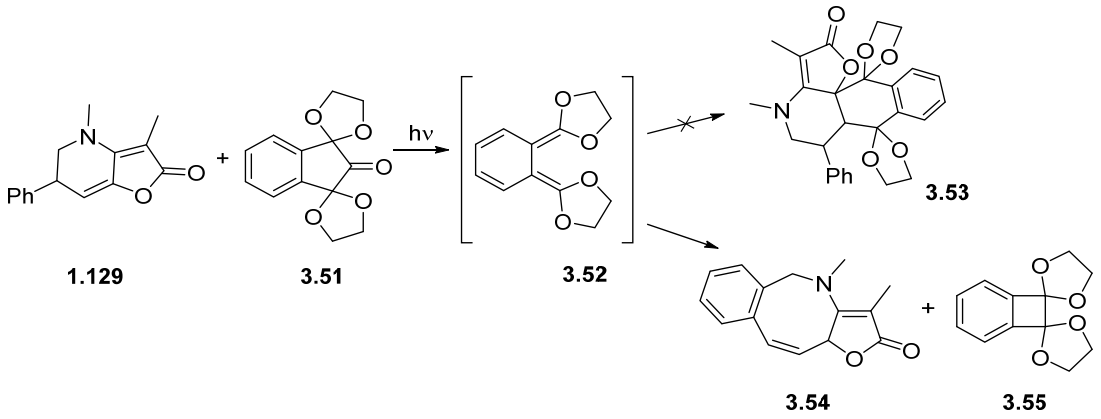
Magallanesine **3.8** is an alkaloid obtained from *Berberis Darwiniim*, located in Chile.[130] In 1989, Danishefsky *et al.* reported the first total synthesis of magallanesine **3.8** in 47% overall yield. The azocine core was formed in the final step of the synthesis *via* an intramolecular cyclisation of thio-activated imide **3.45**.[131]



Scheme 3.1.10. Danishefsky *et al.* synthesis of magallanesine **3.8** from activated imide **3.45**.[131]

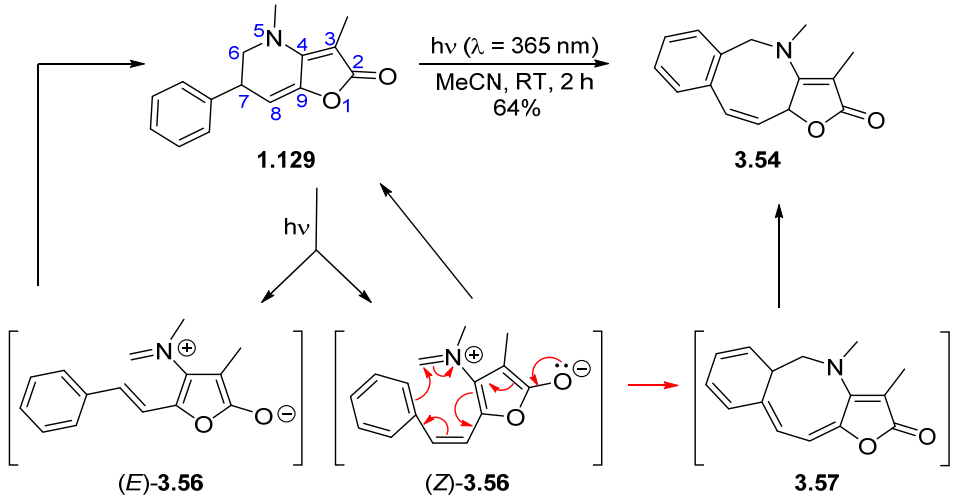
3.2 Initial photochemical studies

Next, we decided to explore the photochemical potential of dihydrofuropyridinones. Work in the group demonstrated the *in-situ* formation of intermediate **3.52** following UVA irradiation of 2-indanone **3.51**. It was hoped that dihydrofuropyridinone **1.129** would undergo a [4+2] cycloaddition with intermediate **3.52**, to form adduct **3.53**. The reaction was conducted on a 36 W UVA flow reactor at a flow rate of 0.83 mL min^{-1} and a residence time of 2 h. Two compounds were identified in the reaction mixture and could not be separated by column chromatography; these were identified by ^{1}H NMR as benzoazocine **3.54** and benzocyclobutane **3.55**, none of the expected adduct **3.53** was observed (**Scheme 3.2.1**).



Scheme 3.2.1. Photochemical reaction of dihydrofuropyridinone **1.129** formed a mixture of ring products **3.54** and **3.55** instead of the expected [4+2] adduct **3.53**.

This prompted us to irradiate dihydrofuropyridinone **1.129** alone with UVA and pleasingly, after 2 h in acetonitrile, benzoazocine **3.54** was given in 64% yield (**Scheme 3.2.2**). A characteristic signal from the ^{1}H NMR spectrum of dihydrofuropyridinone **1.129**, is a 1H doublet at 5.64 ppm corresponding to the alkene C**H**. The ^{1}H NMR spectrum of benzoazocine **3.54**, has 1H doublet of doublets at 6.71 ppm and 5.84 ppm which correspond to the alkene protons, in addition to a 1H doublet of doublet at 5.23 ppm corresponding to the OC**H** proton (**Figure 3.2.1**).



Scheme 3.2.2. Initial mechanism following UVA irradiation of dihydrofuropyridinone **1.129** to benzoazocine **3.54**.

We postulated that the piperidine ring of dihydrofuropyridinone **1.129**, first opened to form a mixture of intermediates (*E*)- and (*Z*)-**3.56**. Both intermediates **3.56** could reclose *via* a 6π-electrocyclisation to return dihydrofuropyridinone **1.129**. However, (*Z*)-**3.56** could also close to form the 8-membered ring **3.57**, which upon re-aromatisation, gave the observed benzoazocine **3.54** (**Scheme 3.2.2**).

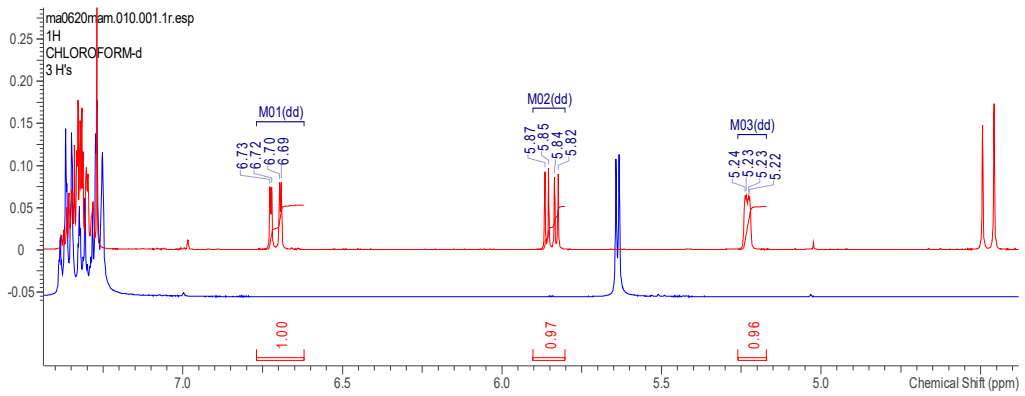


Figure **3.2.1**. Part of the ^{1}H NMR spectra of dihydrofuropyridinone **1.126** (blue) and benzoazocine **3.54** (red). See **Chapter 5** for full spectra.

However, an alternative mechanism appears more likely, based on DFT calculations carried out by Dr. Wei Sun. Upon UVA irradiation, the singlet excited state of dihydrofuropyridinone ^{1}[**1.129**]* relaxes directly to benzoazocine intermediate **3.57** *via* a [1,3]-sigmatropic shift (**Figure 3.2.2**). Intermediate **3.57** then undergoes a thermal [1,5]-hydride shift to benzoazocine **3.54** at ambient temperature with an estimated activation energy of 16.1 kcal/mol. Both processes obey the Woodward-Hoffman selection rules for pericyclic reactions.[132,133]

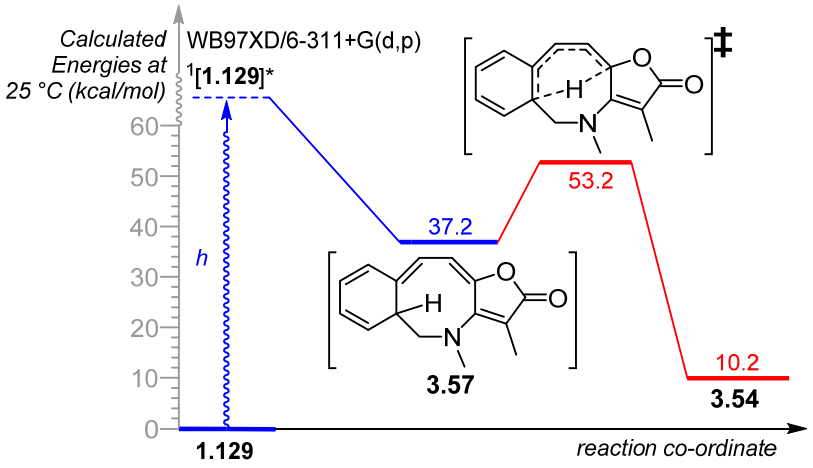
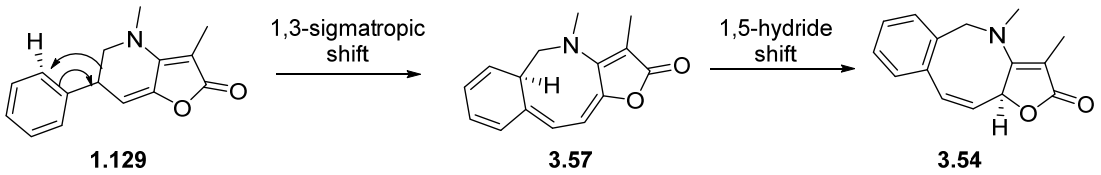
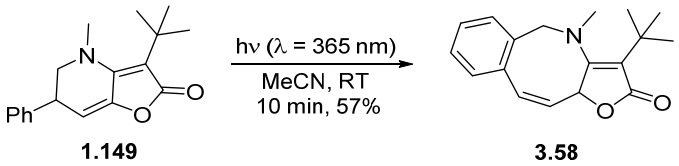


Figure 3.2.2. Calculated free energy barriers for the rearrangement of dihydrofuropyridinone **1.129**.

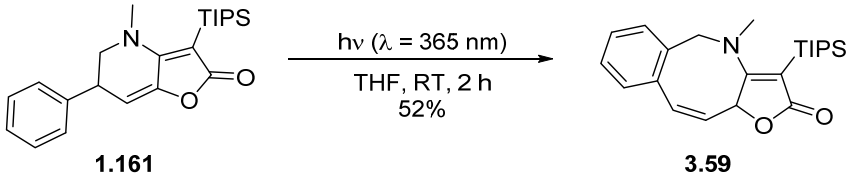


Scheme 3.2.3. The new proposed mechanism of dihydrofuropyridinone **1.129** to benzoazocine **3.54**.

Next, dihydrofuropyridinone **1.149** with a *tert*-butyl group at C3 was irradiated with UVA using a 10 W LED reactor under continuous flow in acetonitrile, and pleasingly, it gave benzoazocine **3.58** in 57% yield after 10 min (**Scheme 3.2.4**). Following these promising results, we decided to irradiate TIPS-substituted dihydrofuropyridinone **1.161**, made by Dharyl Wilson during his PhD studies.[45] Azocine **3.59** was formed in 52% yield following irradiation with UVA for 2 h in dry THF (**Scheme 3.2.5**).



Scheme 3.2.4. Photochemical transformation of dihydrofuropyridinone **1.149** to benzoazocine **3.58** using UVA.



Scheme 3.2.5. UVA irradiation of TIPS-substituted dihydrofuropyridinone **1.161** gave benzoazocine **3.59**.

3.3 Optimisation studies of dihydrofuropyridinones to benzoazocines

Over the course of the project several reactors were used, including a reactor equipped with a 36 W Hg lamp for larger scale syntheses (**Figure 3.3.1**). FEP (fluorinated ethylene propylene) tubing is wrapped around a quartz cylinder encapsulating the lamp, which can produce around 9 W of UVA radiation. An outside water jacket cools the reactor and a peristaltic pump is used to continuously pump the reaction mixture.

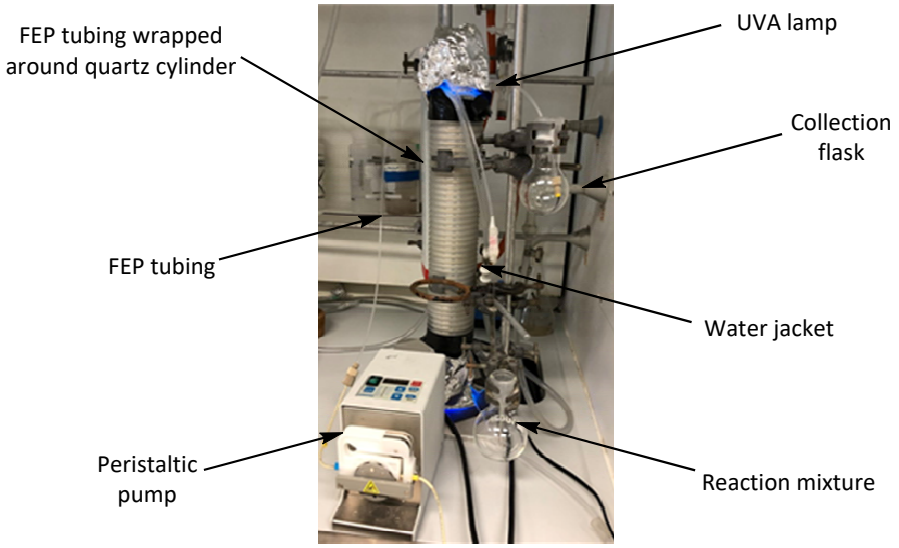


Figure 3.3.1. The 36 W photoreactor under continuous flow, using a set-up akin to that described by Booker-Milburn and Berry et al.[134]

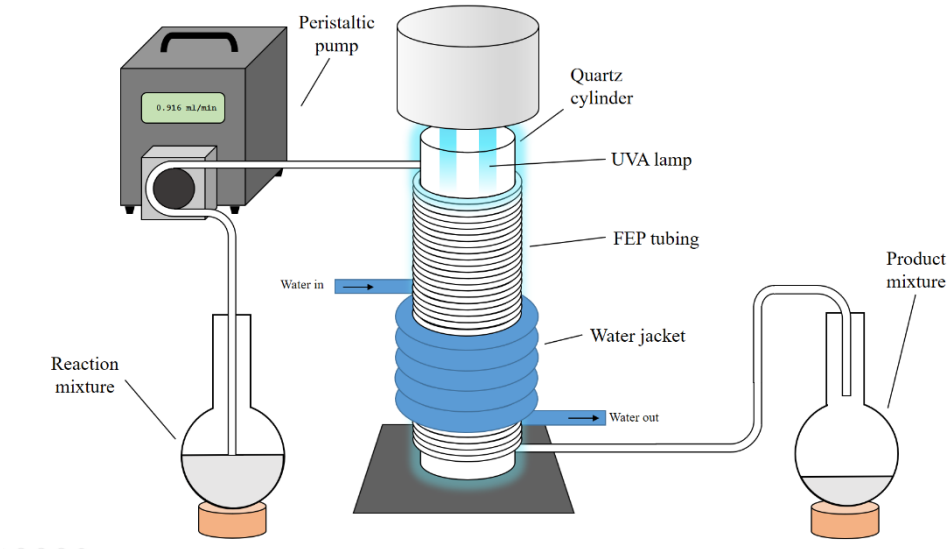


Figure 3.3.2. Schematic of the 36 W photoreactor set-up under continuous flow.

Another reactor used was a smaller 10 mL reactor, with a 9 W Hg lamp, which when brand new is able to produce 3 W of UVA radiation (**Figure 3.3.3**).[35] The set-up is similar to the 36 W reactor, with the FEP tubing wrapped around a quartz cylinder. Unlike the 36 W reactor, it is not used under continuous flow, rather the reaction mixture was manually injected into the centre of the reactor (2 mL in total) to ensure the sample was uniformly irradiated. After the reaction, solvent was injected through the reactor to obtain the product.

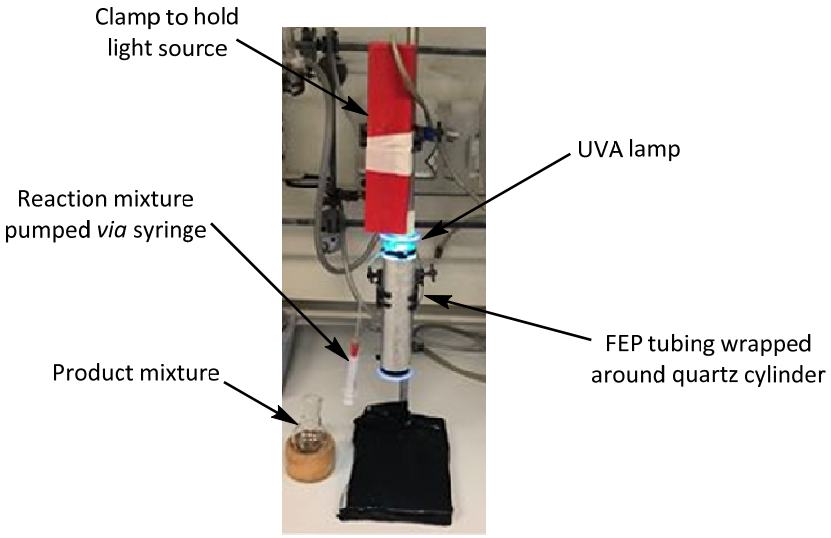


Figure 3.3.3. 9 W UVA photoreactor, the reactor is not under flow, the reagent has to be injected manually.

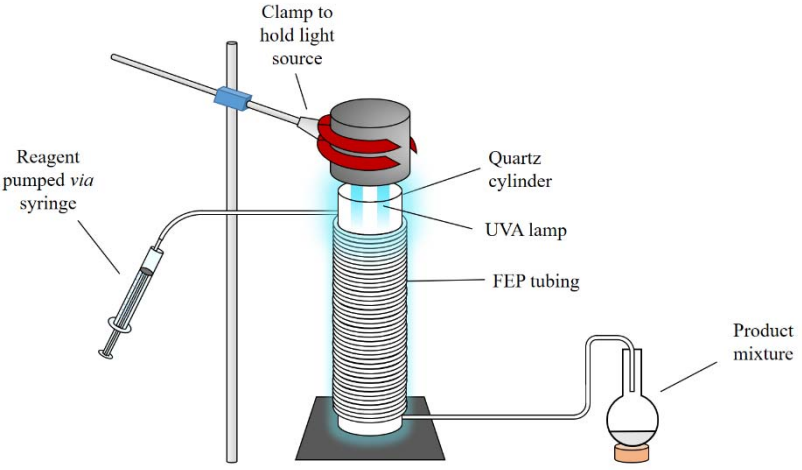


Figure 3.3.4. Schematic of the 9 W photoreactor with manual injection of the reagent.

The final reactor was a 10 W LED UVA reactor, 6 x 1.7 W LEDs are attached to a unit topped with a fan which cools the reactor (**Figure 3.3.5**). The photochemical unit is placed above a board mounted with spiral FEP tubing totaling 6 mL, a peristaltic pump is used to pump the reaction mixture through the reactor. A protective cover is used to contain the UVA radiation when the LED reactor is switched on.

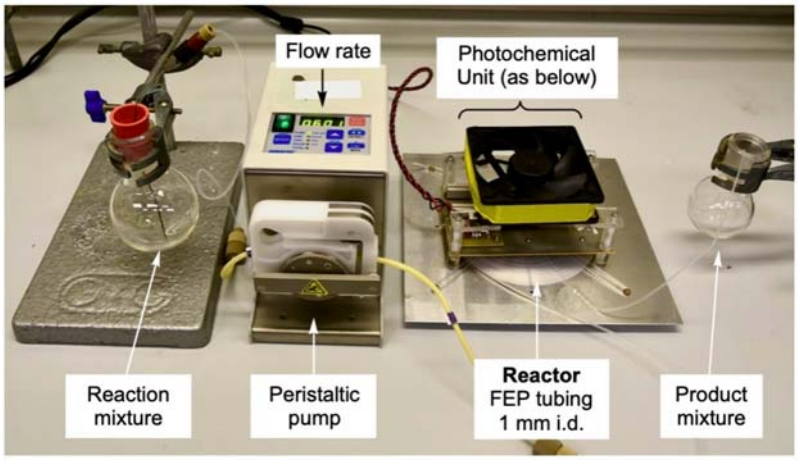


Figure 3.3.5. 10 W LED photoreactor as designed by the Harrowven group.

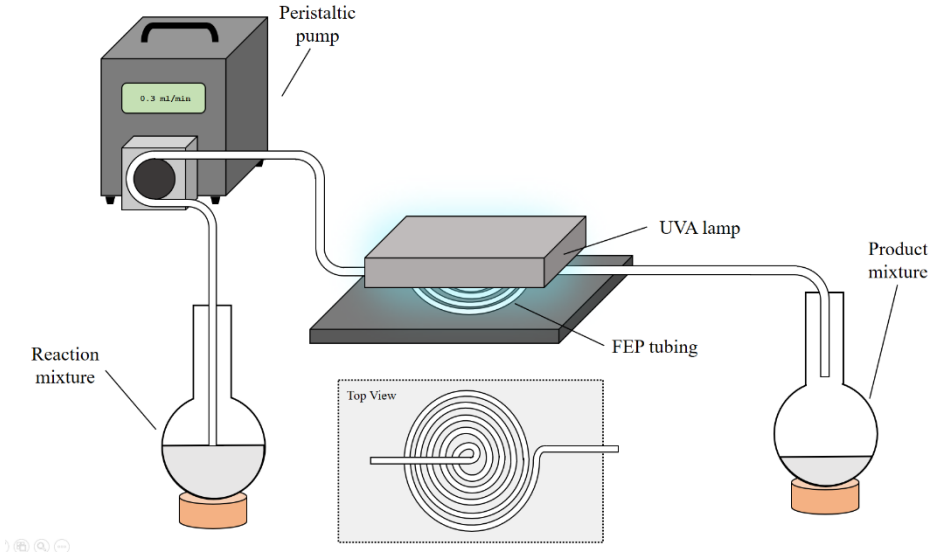
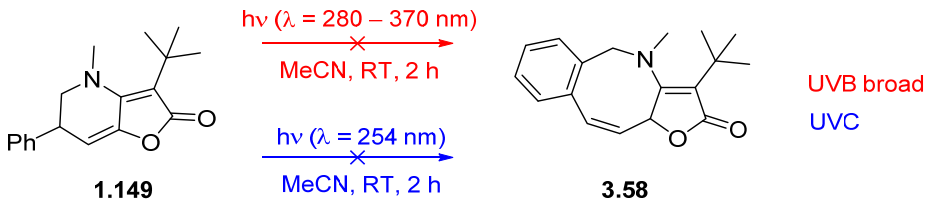


Figure 3.3.6. Schematic of the 10 W LED photoreactor set-up under continuous flow, top view of spiral tubing shown.

3.3.1 Alternative light wavelengths

The above photochemical reactions were all performed using UVA irradiation. Naturally we were curious as to the effect of wavelength on the course of the reaction. *tert*-Butyl dihydrofuropyridinone **1.149** was chosen as the substrate for these optimisation reactions due to the relative ease with which it can be synthesised from dimethoxycyclobutenone **1.2** (See **Scheme 2.1.5**). Notably when dihydrofuropyridinone **1.149** was exposed to UVC irradiation for 2 h, crude ^{1}H NMR showed destruction of starting material and no benzoazocine **3.58** was formed. UVB broadband was then used to irradiate dihydrofuropyridinone **1.149** for 2 h. Crude ^{1}H NMR showed recovery of starting material in addition to degradation to polymeric material. We have therefore concluded that both UVB and UVC irradiation is ineffective at forming benzoazocine **3.58**. Detailed UV spectral studies have been performed using 3 UV lamps, it is with regret that UV-VIS spectra of the dihydrofuropyridinones were not recorded.



Scheme 3.3.1. Photochemical transformation of dihydrofuropyridinone **1.149** using UVB and UVC irradiation did not produce benzoazocine **3.58**.

3.3.2 Residence time

We next focused our attention on optimising the reaction with UVA. Initial studies were performed on the large 36 W reactor at concentrations between 0.03 − 0.04 M. We found that the residence time of the reaction could be reduced from 2 h to 1 h without altering the yield. However, we were concerned that the modest yields were due to over-irradiation of the dihydrofuropyridinone with the 36 W lamp. Therefore, we utilised the less powerful 9 W UVA reactor to irradiate dihydrofuropyridinone **1.149** for various residence times. All of the dihydrofuropyridinone had reacted after 20 min in acetonitrile and pleasingly, no polymeric material was observed. This would suggest that we were indeed over-irradiating the dihydrofuropyridinone and considerably less time is needed to promote the rearrangement.

3.3.3 Concentration

Concentration was also probed, as we were aware that photochemical reactions are highly concentration dependent. Our preliminary work conducted on the small 9 W reactor was highly concentration dependent since it had a maximum solvent volume of 2 mL. **Table 3.1** shows the results of changing both the concentration, residence time and light source on the photochemical rearrangement. The highest yields of benzoazocine **3.58**, were obtained with the 10W LED lamp at concentrations between 0.03 − 0.04 M, following irradiation for around 10 min. We also carried out photochemical reactions at different temperatures as detailed in **Table 3.1**, **Entries 17 and 18**. We found that preheating/cooling the reaction mixtures had little effect on the yield of benzoazocine. We were also aware that the temperature was not maintained inside the reactor and therefore discontinued these temperature studies.

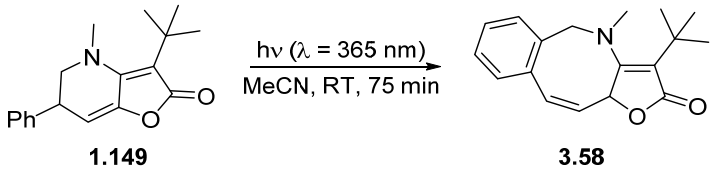
3.3.4 Benzoazocine stability

Crude ^{1}H NMR spectra were very clean and showed the benzoazocine without contamination or polymeric material. However, benzoazocine **3.58** was not stable in chloroform solution, as observed by the degradation of NMR samples which turned green in a matter of hours. We suspected that benzoazocines were acid sensitive and hypothesised that during purification, prewashing the column with triethylamine would neutralise the acidic silica and prevent degradation, resulting in a higher yield. Unfortunately, this was to the detriment of purity, as new peaks appeared in the ^{1}H NMR spectra, including two doublet of doublets at around 6.0 ppm which have *J* values consistent with a *trans*-alkene (**Figure 3.3.7**). Consequently, the yields of these reactions appear higher due to the impurities, as shown in **Table 3.1, Entries 9, 10 and 11**. Future reactions did not involve purification with triethylamine and instead, rapid column chromatography was performed.

3.3.5 Reaction solvent

Finally, various solvents were tested and it was found that acetonitrile, DMSO and 1,4-dioxane all provided benzoazocine **3.58** in high yields. In this example with benzoazocine **3.58**, using THF as the reaction solvent resulted in degradation. However, as described later, THF was used for photoreactions of other dihydrofuropyridinones with success, in particular when solubility in acetonitrile was low.

Table 3.1. The effect of concentration, residence time and light source on the photoreaction of dihydrofuropyridinone **1.149** to benzoazocine **3.58**.



1.149 **3.58**

Entry	Lamp	Concentration (M)	Residence time (min)	Yield of benzoazocine **3.58**%
1	9 W	0.092	20	43
2	9 W	0.21	25	17
3	36 W	0.00091	75	52
4	36 W	0.0065	60	39
5	36 W	0.019	60	50
6	36 W	0.036	20	18
7	36 W	0.036	120	50
8	36 W	0.065	60	32
9	10 W LED	0.036	7	~ 52 *
10	10 W LED	0.036	7	~ 87 *
11	10 W LED	0.067	7	~ 60 *
12	10 W LED	0.037	10	46
13	10 W LED	0.041	20	54
14	10 W LED	0.041	10	57
15	10 W LED	0.043	12	55
16	10 W LED	0.046	7	42
17	10 W LED	0.037	7	51▪1
18	10 W LED	0.042	7	41▪2

* Impurities in sample due to prewashing the column with triethylamine (**Figure 3.3.4**)

▪ 1 Temperature study, 51% yield when starting material heated to 50 °C.

▪2 Temperature study, 41% yield when starting material cooled to −10 °C.

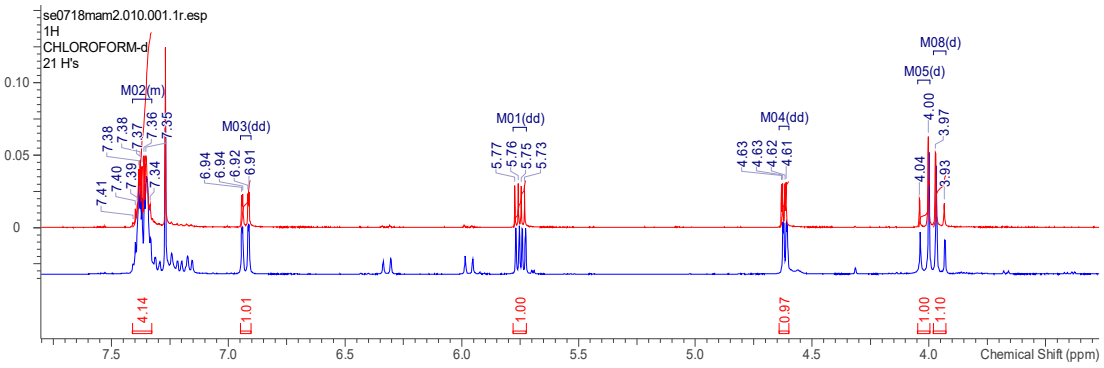
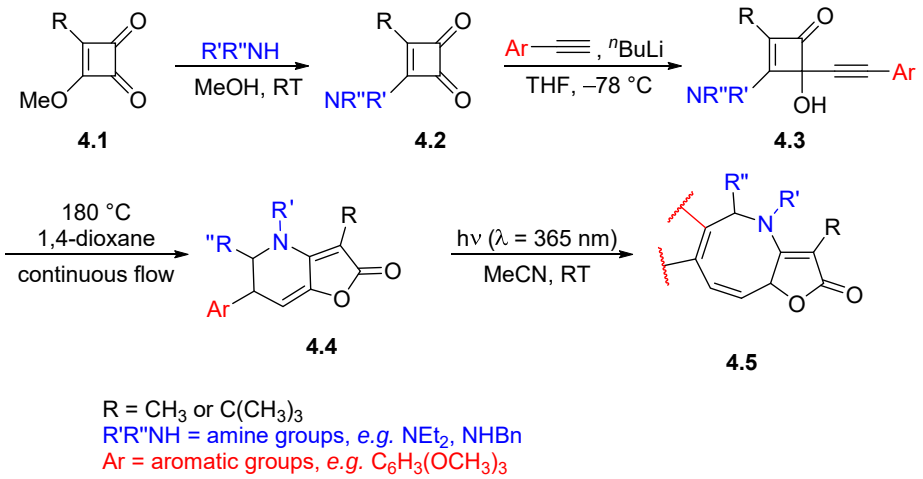


Figure 3.3.7. Part of the ^{1}H NMR spectra of benzoazocine **3.58** with impurity peaks (blue) and without (red). See **Chapter 5** for full spectrum.

Chapter 4 Photochemical Reactions of Dihydrofuropyridinone Analogues

Following the discovery of the photochemical rearrangement of dihydrofuropyridinone **1.149** to benzoazocine **3.58**, we decided to probe the reaction further to create a library of azocine compounds. **Scheme 4.0** details the planned sequence using various amines, including unsymmetrical amines, as well as alternative aromatic groups. The effect of changing the amine and/or the phenyl ring will be described herein.



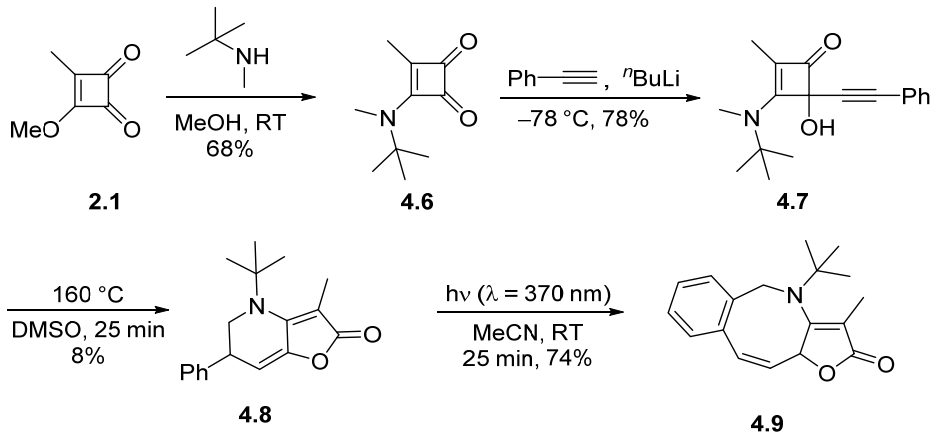
Scheme 4.0. Planned synthesis of azocines **4.5** with various amine and aromatic substituents.

4.1 Alternative amine groups

4.1.1 *N-tert*-Butylmethylamine

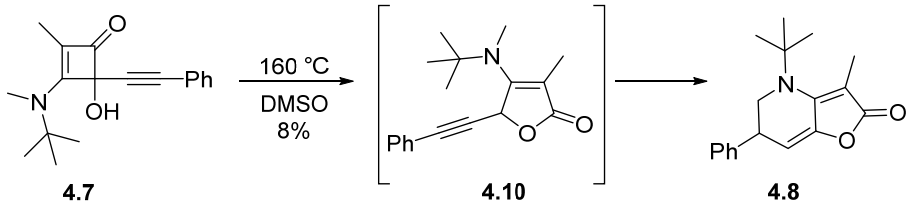
Firstly, we considered changing the position of the bulky *tert*-butyl group from C3 to the amine. We hoped this would have the effect of enabling the rearrangement of alkynylcyclobutenone to dihydrofuropyridinone to proceed at a lower temperature. Of course, we were also curious as to whether *N*-substitution with such a bulky group would inhibit the photochemical rearrangement to the azocine. To that end, *N-tert*-butylmethylamine was added to a solution of cyclobutenone **2.1** in methanol to give aminocyclobutenone **4.6** in 68% yield after 75 min. The coupling of phenylacetylene to aminocyclobutenone **4.6** using ^{n}BuLi at –78 °C, afforded alkynylcyclobutenone **4.7** in 78% yield. Subsequent thermolysis of alkynylcyclobutenone **4.7**, in DMSO at 160 °C gave

dihydrofuropyridinone **4.8** in 8% yield. We tried multiple times to improve the yield of this thermolysis in both batch conditions and under continuous flow, unfortunately, to no avail. Dihydrofuropyridinone **4.8** was then irradiated with a 9 W UVA lamp and after 25 min, benzoazocine **4.9** was isolated in 74% yield (**Scheme 4.1.1**).



Scheme 4.1.1. Synthesis of benzoazocine **4.9** in 74% yield from cyclobutenone **2.1**.

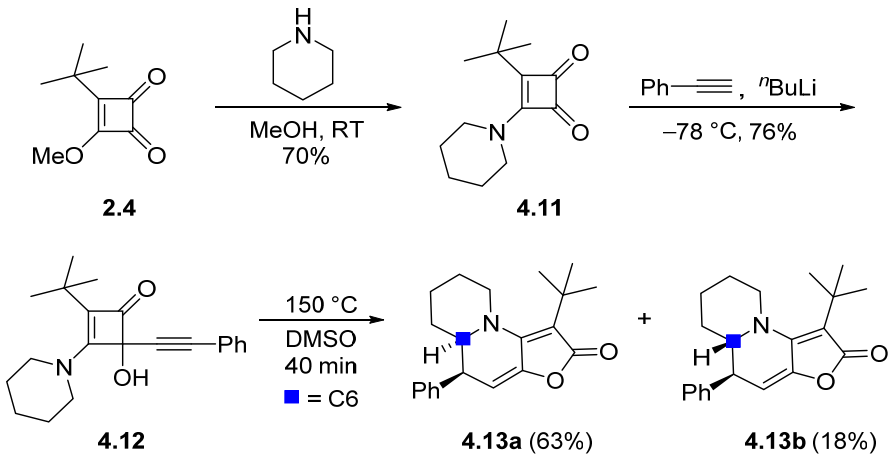
This result was encouraging, as it showed that incorporating a bulky substituent on the nitrogen does not impede the rearrangement to the azocine. However, the yield of the thermolysis step was very low at 8% and as the remaining mass was baseline material, it allowed no clues as to how the yield might be improved. We suspect that in the furanone intermediate **4.10**, the bulky *tert*-butyl group rotates away from the C3 methyl residue which results in a much slower rearrangement to the dihydrofuropyridinone **4.8** (**Scheme 4.1.2**).



Scheme 4.1.2. The nitrogen *tert*-butyl residue of furanone **4.10** rotates away from the methyl at C3.

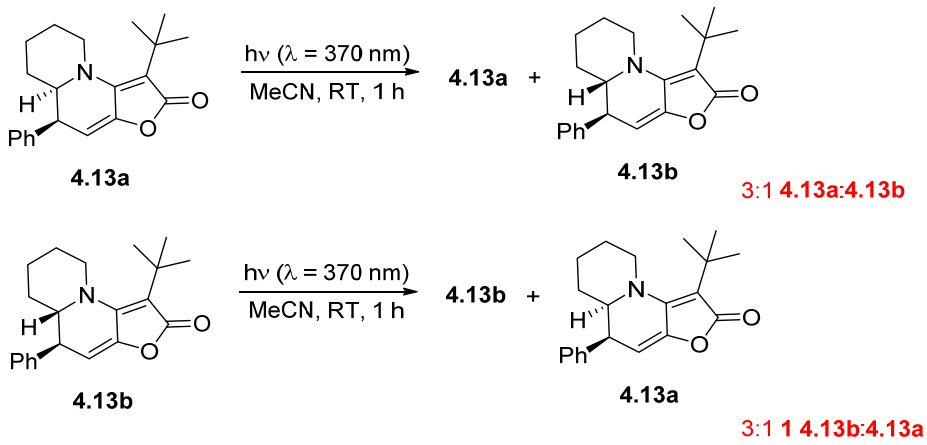
4.1.2 Piperidine

Next, we focused our attention on synthesising azocines with two stereocentres in order to confirm the relative stereochemistry. We were, however, mindful that the formation of a new stereogenic centre at C6 (blue square, **Scheme 4.1.3**) would result in a mixture of diastereoisomers of the dihydrofuropyridinone as shown in **Scheme 1.2.4**. Amination of cyclobutenone **2.4** at C3 with piperidine gave cyclobutenone **4.11** in 70% yield, then addition of lithiated phenylacetylene gave alkynylcyclobutenone **4.12** in 76% yield. Thermolysis of alkynylcyclobutenone **4.12** at 150 °C in DMSO, produced dihydrofuropyridinone **4.13a** in 63% yield and the minor diastereoisomer **4.13b** in 18% yield (**Scheme 4.1.3**).



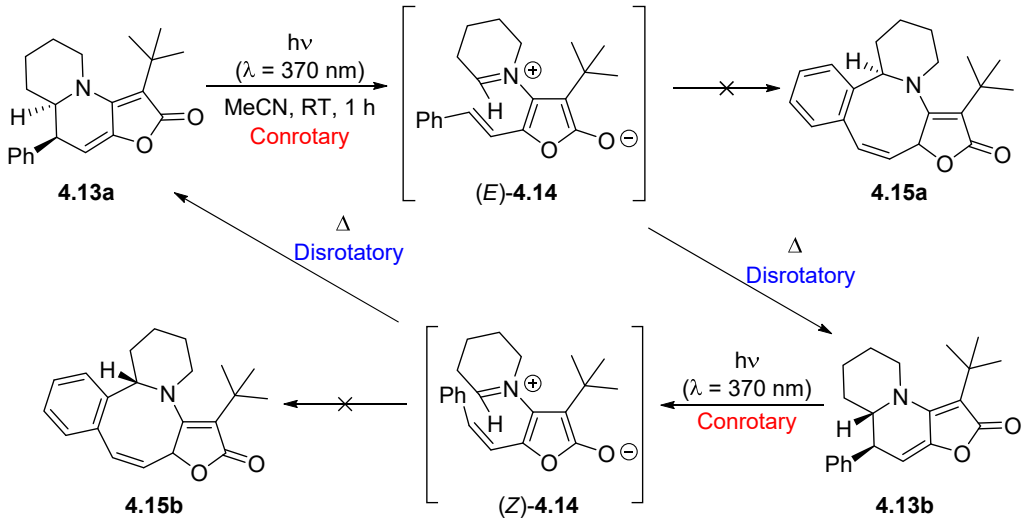
Scheme 4.1.3. Thermolysis of alkynylcyclobutenone **4.12** gave dihydrofuropyridinones **4.13a** and **4.13b**.

Irradiation of the major diastereoisomer **4.13a** with UVA for 1 h, unexpectedly led to the minor diastereoisomer **4.13b** (**Scheme 4.1.4**). Conversely, irradiation of the minor isomer **4.13b**, with UVA for 1 h also resulted in an isomerisation to the major isomer **4.13a**. The crude ^{1}H NMR spectra for each photolysis confirmed that mostly starting material was recovered in a ratio of 3:1 with the isomerised product. Unfortunately, neither UVA nor UVB irradiation produced the desired azocine **4.15**.



Scheme 4.1.4. Irradiation of **4.13a** and **4.13b** with UVA resulted in isomerisation to the other isomer.

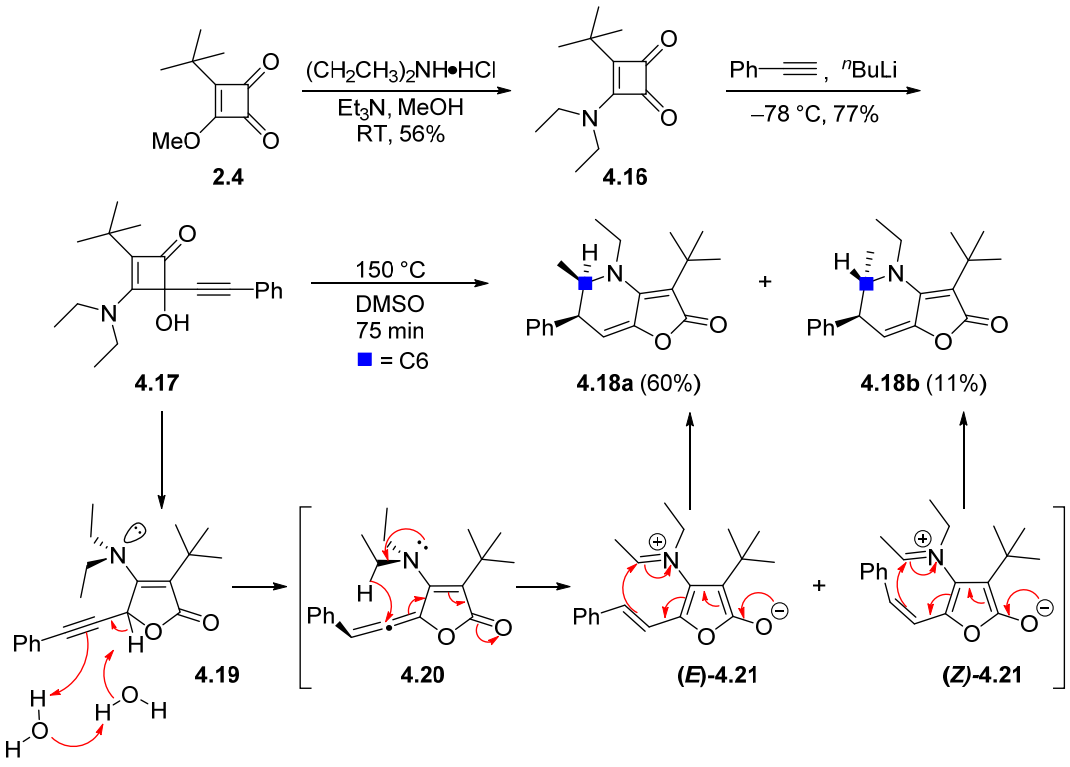
These results suggest that the 6-membered ring of the dihydrofuropyridinones **4.13** are photochemically ring-opened in a 6π conrotatory manner, followed by a thermal 6π disrotatory ring closure to the other diastereoisomer (**Scheme 4.1.5**).



Scheme 4.1.5. Suggested mechanism for the photochemical isomerism of dihydrofuropyridinone **4.13a**.

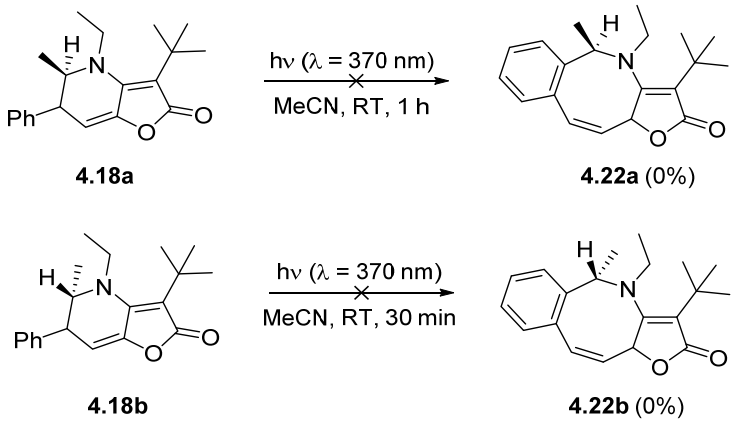
4.1.3 Diethylamine

We wanted to further explore the effect of C6 substitution on the photochemical rearrangement of dihydrofuropyridinones, with dihydrofuropyridinone **4.18**. To cyclobutenone **2.4** in methanol was added diethylamine hydrochloride and trimethylamine to give aminocyclobutenone **4.16** in 56% yield. Addition of lithiated phenylacetylene in THF at –78 °C, gave alkynylcyclobutenone **4.17** in 77% yield. Subsequent thermolysis in DMSO at 150 °C provided dihydrofuropyridinone **4.18a** in 60% yield and its minor diastereoisomeric partner **4.18b**, in 11% yield (**Scheme 4.1.6**). Intermediate allene **4.20** can form both (*E*)- and (*Z*)- iminium alkenes **4.21**, which ring close to **4.18a** and **4.18b** respectively.



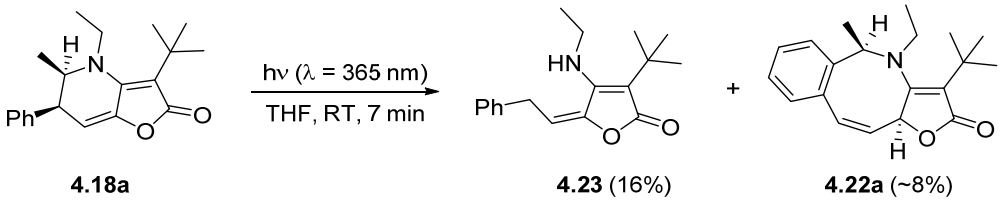
Scheme 4.1.6. Thermolysis of alkynylcyclobutenone **4.17** resulted in dihydrofuropyridinones **4.18a** and **4.18b**.

Exposure of the major dihydrofuropyridinone **4.18a** to UVA irradiation for 1 h did not provide the desired benzoazocine **4.22a** (**Scheme 4.1.7**). The ^{1}H NMR spectrum of the crude material showed that all of the starting material had been consumed. Unfortunately, most of the mass was lost and only 7 mg of new material was recovered; which was insufficient for further analysis. A similar result was obtained following UVA irradiation of minor dihydrofuropyridinone **4.18b** for 30 min with only 3 mg of new material isolated.



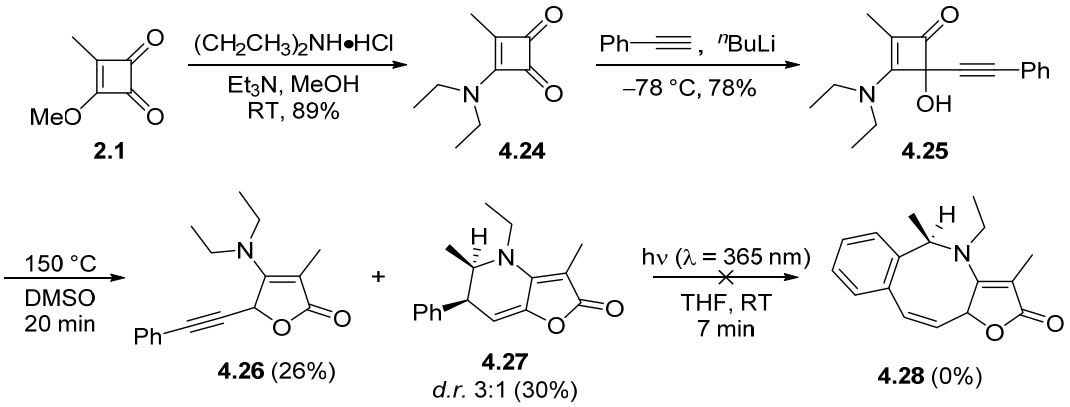
Scheme 4.1.7. UVA irradiation of dihydrofuropyridinones **4.18a/b** did not yield the desired benzoazocines.

A new batch of dihydrofuropyridinone **4.18a** was synthesised and then irradiated with UVA in dry THF on the 10 W LED reactor. The result yielded around 8% of the expected benzoazocine **4.22a**, however, 16% of the hydrolysis product **4.23** was also formed (**Scheme 4.1.8**). The presence of the hydrolysis product **4.23** was confirmed by mass spectrometry as well as ^{1}H NMR. Upon repeating for a third time, in dry acetonitrile at the same concentration, a complex mixture was given. Furthermore, irradiating the minor dihydrofuropyridinone **4.18b** with UVA under dry conditions gave inconclusive results.



Scheme 4.1.8. UVA irradiation of dihydrofuropyridinone **4.18a** gave the hydrolysis product **4.23** as well as a small amount of benzoazocine **4.22a**.

We were then curious as to whether the *tert*-butyl group at C3 of the dihydrofuropyridinone had any effect on the photochemical rearrangement. Thus, to cyclobutenone **2.1** was added diethylamine hydrochloride and trimethylamine giving aminocyclobutenone **4.24** in 89% yield (**Scheme 4.1.9**). Addition of lithiated phenylacetylene then gave alkynylcyclobutenone **4.25** in 78% yield. Subsequent thermolysis in DMSO at 150 °C provided dihydrofuropyridinone **4.27** in 30% yield, as a 3:1 mixture of diastereoisomers, in addition to furanone **4.26** in 26% yield. Irradiation of the diastereotopic mixture of **4.27**, with UVA in THF on the 10W LED reactor, unfortunately resulted in recovery of starting material.

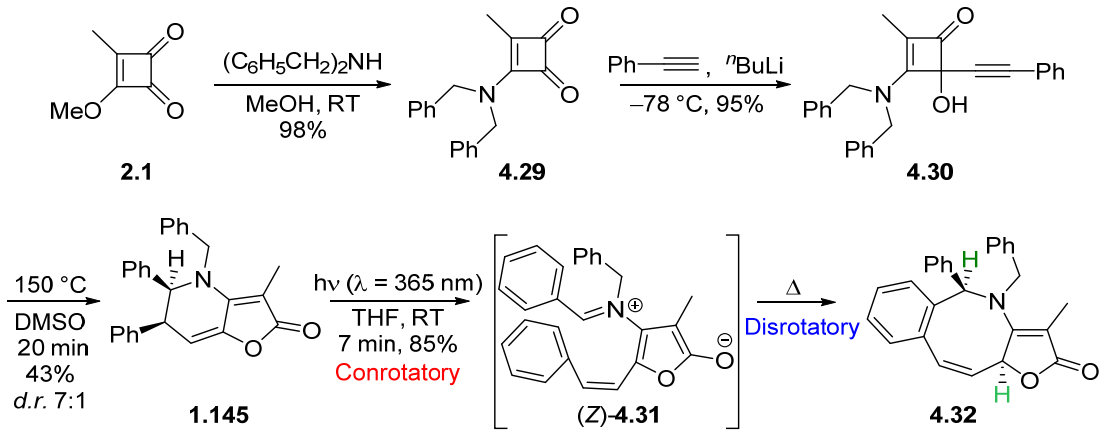


Scheme 4.1.9. Synthesis of dihydrofuropyridinone **4.27** as a 3:1 ratio of diastereoisomers, subsequent irradiation with UVA did not yield benzoazocine **4.28**.

4.1.4 Dibenzylamine

Having shown that *N*-substituted dihydrofuropyridinones can rearrange to the corresponding benzoazocines, it was disappointing to find that the reaction did not extend to substrates where both positions were functionalised. To probe this further, we decided to incorporate an amine that could stabilise the photochemical transition state. Previous work within our group by Wei Sun has shown that cyclobutenediones with a dibenzylamino substituent at C4, gave *syn* conformation upon thermolysis (**Table 1.2.1**).

To that end, dibenzylamine was added to a solution cyclobutenone **2.1** in methanol to give aminocyclobutenone **4.29** in 98% yield. Addition of lithiated phenylacetylene then formed alkynylcyclobutenone **4.30** in 95% yield and subsequent thermolysis in DMSO at 150 °C provided dihydrofuropyridinone **1.145** in 43% yield as an inseparable 7:1 mixture of diastereoisomers (**Scheme 4.1.10**). UVA irradiation of the diastereotopic mixture **1.145**, on the 10 W LED reactor in THF, resulted in an 85% yield of benzoazocine **4.32**. We believe that this is due to the increased stability of the iminium ion (*Z*)-**4.31**, due to conjugation with the phenyl ring (**Scheme 4.1.10**). Furthermore, the steric effect between the phenyl ring and the C3 methyl is small, enabling ring closure to benzoazocine **4.32**. X-ray analysis of dibenzyl azocine **4.32** has shown that the hydrogens at C6 (NC**H**Ph) and C15 (OC**H**) are on the same face (See **Appendix A**)

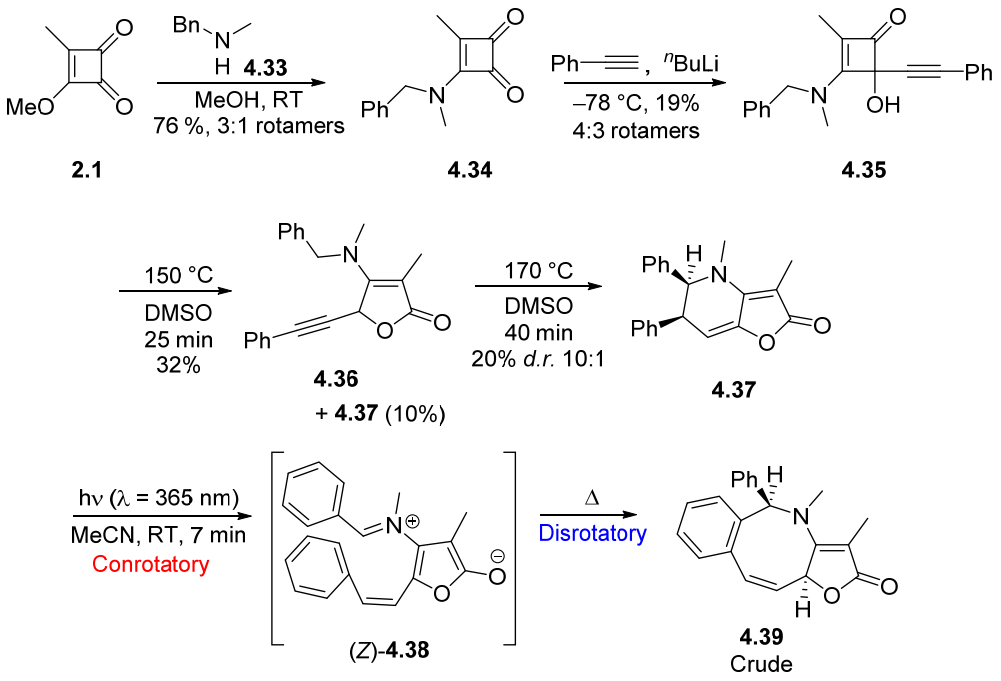


Scheme 4.1.10. Thermolysis of alkynylcyclobutenone **4.30** to dihydrofuropyridinone **1.145** and subsequent UVA irradiation to benzoazocine **4.32**.

4.1.5 Benzylmethylamine

Following this success, we next decided to probe the reaction further by incorporating a benzylmethylamino group into the cyclobutenone, *e.g.* **4.34**. The corresponding dihydrofuropyridinone **4.37**, would then have both *N*- and C6-substitution and the iminium ion intermediate (*Z*-**4.38**) would be stabilised by conjugation with the phenyl group as in the aforementioned dibenzylamine example (*Z*)-**4.31**.

A solution of cyclobutenone **2.1** in methanol at room temperature was treated with *N*-benzylmethylamine **4.33** to form cyclobutenone **4.34** in 76% yield as a 3:1 mixture of rotamers (**Scheme 4.1.11**). Addition of lithiated phenylacetylene to cyclobutenone **4.34** in THF at –78 °C, produced alkynylcyclobutenone **4.35** in 19% yield as a 4:3 mixture of rotamers. Subsequent thermolysis of alkynylcyclobutenone **4.35** in DMSO at 150 °C, gave mostly furanone **4.36**, in 32% yield and dihydrofuropyridinone **4.37** in 10% yield. Unlike the dibenzylamine example (**Scheme 4.1.10**), the reaction did not proceed directly to the dihydrofuropyridinone. Thermolysis of furanone **4.36** in DMSO at 170 °C for 40 min, resulted in only a 20% yield of dihydrofuropyridinone **4.37**, as a 10:1 mixture of diastereoisomers.



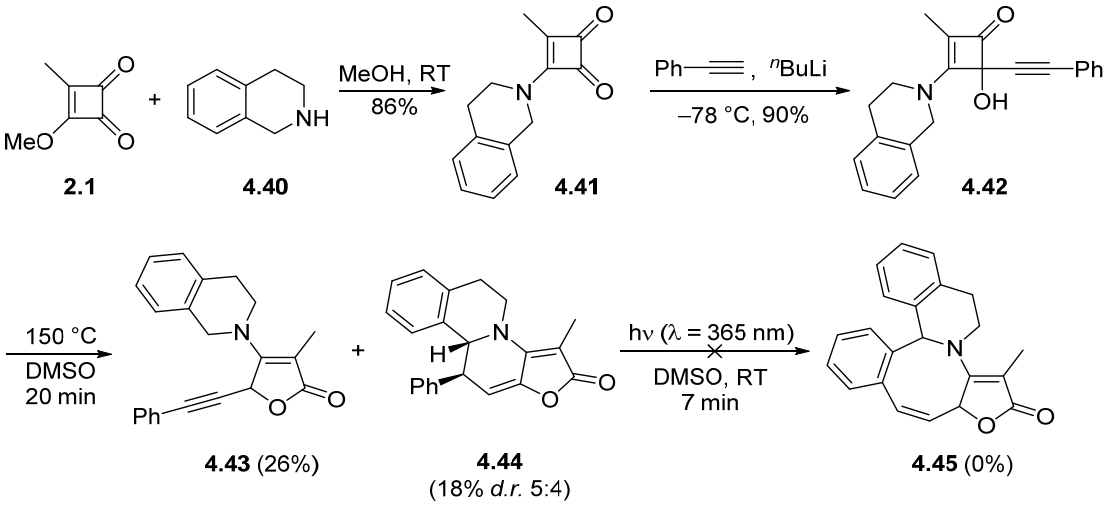
Scheme 4.1.11. Synthesis of dihydrofuropyridinone **4.37** and irradiation with UVA to benzoazocine **4.39**.

Irradiation of dihydrofuropyridinone **4.37** with UVA radiation for 7 min in acetonitrile, gave a clean crude ^{1}H NMR spectrum. Unfortunately, the crude material was not purified at the time, as the reaction was carried out on a small 50 mg scale. Regrettably, further analysis of the product was not performed and because the reaction sequence was plagued with low yields and rotameric mixtures, no further work was carried out on this example. It is highly likely that repeating this reaction under optimum conditions will produce benzoazocine **4.39** in high yields, the crude ^{1}H NMR spectrum is provided in **Appendix C**.

4.1.6 Tetrahydroisoquinoline

Next, we hoped that incorporating a tetrahydroisoquinoline residue would produce a benzoazocine with 5 fused ring systems such as benzoazocine **4.45**. To test this, a solution of cyclobutenone **2.1** in methanol was treated with 1,2,3,4-tetrahydroisoquinoline **4.40** to give aminocyclobutenone **4.41** in 86% yield (**Scheme 4.1.12**). Addition of lithiated phenylacetylene then gave alkynylcyclobutenone **4.42** in 90% yield. Subsequent thermolysis in DMSO at 150 °C, gave dihydrofuropyridinone **4.44** in 18% yield as a 5:4 ratio of diastereoisomers together with furanone

4.43 in 26% yield. Regrettably, irradiation of dihydrofuropyridinone **4.44** with UVA in DMSO, only returned starting material. DMSO was used as the solvent due to its low solubility in THF and acetonitrile. Importantly, a test photochemical reaction of dihydrofuropyridinone **1.149** in DMSO gave benzoazocine **3.8** in good yield, confirming that DMSO was a suitable solvent for the reaction.

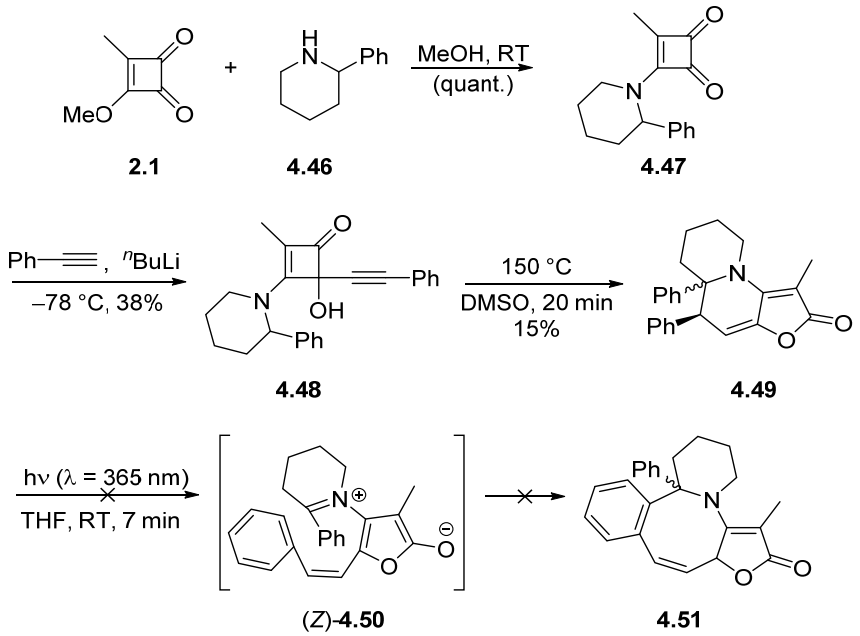


Scheme 4.1.12. Synthesis of dihydrofuropyridinone **4.44** as a 5:4 ratio of diastereoisomers, irradiation with UVA did not yield benzoazocine **4.45**.

4.1.7 2-Phenylpiperidine

Finally, we sought to prove the impact of C6 substitution further by adding a 2-phenylpiperidine ring to the cyclobutenedione, *e.g.* **4.47**. This was based on the theory that the phenyl ring could stabilise the iminium ion intermediate (*Z*)-**4.50** by conjugation and promote its rearrangement to benzoazocine **4.51**.

To that end, 2-phenylpiperidine **4.46** was added to a solution cyclobutenone **2.1** in methanol to give aminocyclobutenone **4.47** in quantitative yield (**Scheme 4.1.13**). Purification proved challenging as 2-phenylpiperidine **4.46** was still present after two column chromatographic purifications and a basic work up. Addition of lithiated phenylacetylene to aminocyclobutenone **4.47** in THF at –78 °C, produced alkynylcyclobutenone **4.48** in 38% yield. Thermolysis in DMSO at 150 °C then gave dihydrofuropyridinone **4.49** in a low yield of 15%. Unfortunately, when irradiated with UVA on the 10W LED reactor in dry THF, only starting material was recovered.



Scheme 4.1.13. Synthesis of dihydrofuropyridinone **4.49**, UVA irradiation did not yield benzoazocine **4.51**.

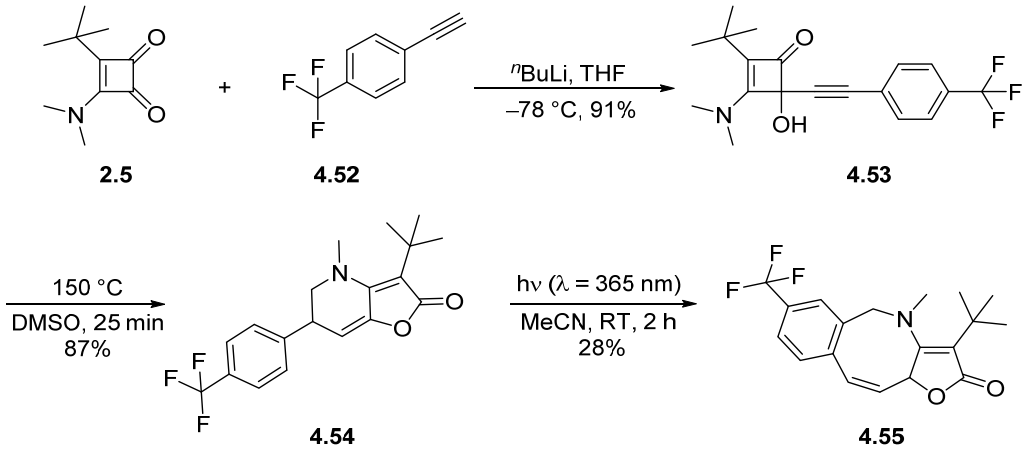
In summary, the lack of success irradiating piperidine, 2-phenylpiperidine and tetrahydroisoquinoline substituents suggested that the photochemical reaction does not tolerate cyclic amines, even when they lead to stabilised iminium ion intermediates. At this juncture, the amines tolerated were dimethylamine, dibenzylamine and to a certain degree *tert*-butylmethylamine.

4.2 Substituted phenyl groups

4.2.1. Trifluoromethylphenyl

We next wanted to see how electron donating and withdrawing groups on the phenyl ring of the dihydrofuropyridinone would effect the rearrangement to the corresponding benzoazocine. To that end, commercially available 4-trifluoromethylphenylacetylene **4.52** was deprotonated with ^{n}BuLi in THF at –78 °C and added *via* cannula to a solution of aminocyclobutenone **2.5** in THF at –78 °C, alkynylcyclobutenone **4.53** was formed in 91% yield. Subsequent thermolysis in DMSO at 150 °C gave dihydrofuropyridinone **4.54** in 87% yield, whilst irradiation with UVA on the 36 W reactor gave benzoazocine **4.55** in 28% yield after 2 h. We repeated the photochemical rearrangement 5 times

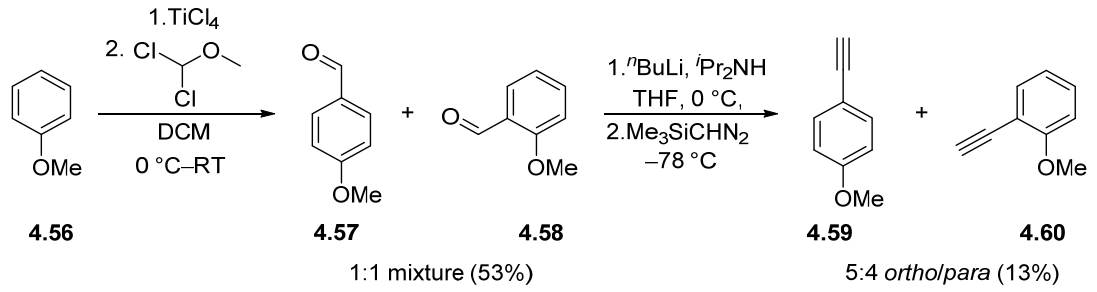
and found that the yields were consistently low, between 17 – 28%, with the remaining mass being polymeric material.



Scheme 4.2.1. Synthesis and photochemical rearrangement of dihydrofuropyridinone **4.54** to azocine **4.55**.

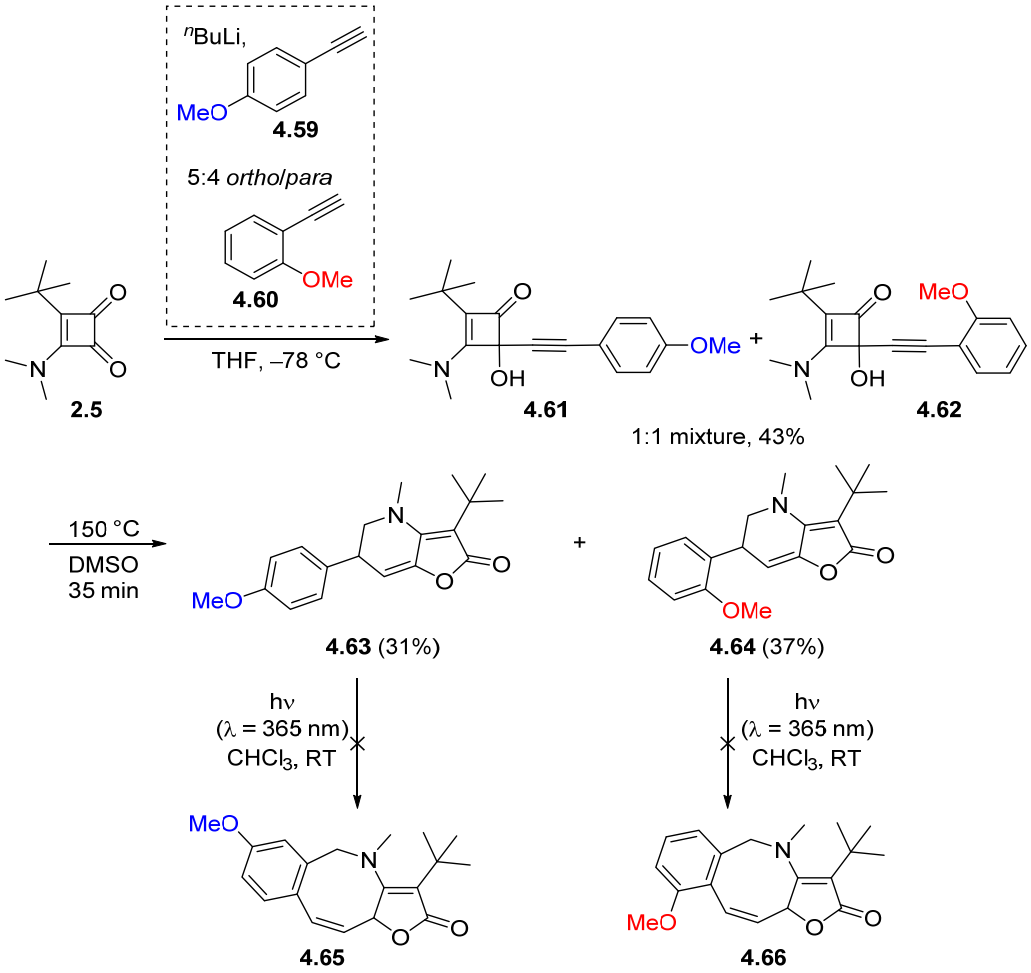
4.2.2 Methoxyphenyl

We next turned our attention to phenylacetylene analogues with an electron donating methoxy substituent. *para*-Anisaldehyde **4.57** could be synthesised from anisole **4.56** using titanium tetrachloride and dichloromethyl methyl ether following a literature procedure reported by Chen *et al.*[135] However, in our hands it gave an inseparable 1:1 mixture of *ortho* (**4.58**) and *para*-anisaldehyde **4.57**. This mixture was then used to synthesise the corresponding alkynes following a procedure reported by Mamane *et al.*[136] Firstly, LDA was prepared *in situ* following deprotonation of di*iso*propylamine with ^{n}BuLi. Trimethylsilyldiazomethane was then deprotonated and added to the anisaldehyde mixture to give an inseparable 5:4 mixture of 4- and 2-methoxyphenylacetylene **4.59** and **4.60** respectively (**Scheme 4.2.2**).



Scheme 4.2.2. Synthesis of 4- and 2-methoxyphenylacetylene **4.59** and **4.60** as an inseparable 5:4 mixture.

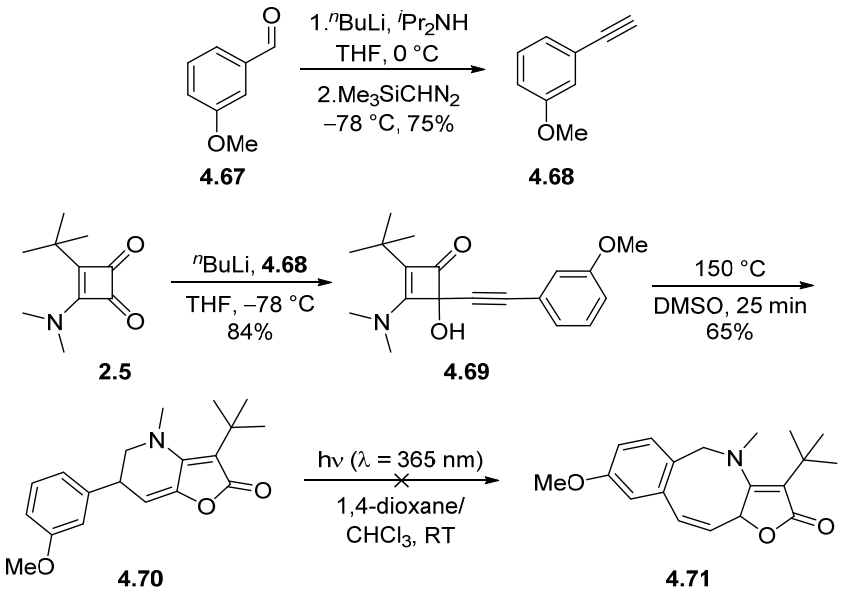
Next, the mixture of 2- and 4-methoxyphenylacetylene **4.60** and **4.59**, was deprotonated and added to a solution of aminocyclobutenone **2.5** in THF at –78 °C, to give the alkynylcyclobutenones **4.61** and **4.62** as an inseparable 1:1 mixture in 43% yield (**Scheme 4.2.3**). Pleasingly, thermolysis of these adducts at 150 °C in DMSO produced 4-methoxyphenyldihydrofuropyridinone **4.63** in 31% yield and 2-methoxyphenyldihydrofuropyridinone **4.64** in 37% yield and these were separable by column chromatography. Alas, UVA irradiation of both dihydrofuropyridinones in chloroform failed to give the desired benzoazocines. Chloroform was used due to their poor solubility in acetonitrile and THF, upon reflection it is most likely that chloroform was not tolerated well under UVA. This must be due to the UV cut off of chloroform, this is the wavelength in which the solvent absorbs light; which could be the same wavelength that the reagent absorbs.



Scheme 4.2.3. UVA irradiation of 2- and 4-methoxydihydrofuropyridinones **4.64** and **4.63** did not yield the corresponding benzoazocines.

We hypothesised that the failure of the photochemical reaction could be due to the positioning of the electron donating methoxy groups. This led us to synthesise 3-methoxyphenylacetylene **4.68** from *meta*-anisaldehyde **4.67** following the procedure reported by Mamane *et al*.[136] Addition of lithiated 3-methoxyphenylacetylene **4.68** to aminocyclobutenone **2.5** in THF at –78 °C formed alkynylcyclobutenone **4.69** in 84% yield. Subsequent thermolysis at 150 °C in DMSO gave 3-methoxydihydrofuropyridinone **4.70** in 65% yield. Unfortunately, its photochemical rearrangement using UVA irradiation in chloroform did not give the expected benzoazocine **4.71** (**Scheme 4.2.4**).

It was at this point that we suspected the photochemical reactions were compromised by our choice of solvent. The photoreaction of dihydrofuropyridinone **4.70** was repeated in 1,4-dioxane, which is known to be compatible with UVA. Regrettably, as evidenced by the ^{1}H NMR spectrum, the starting material remained and benzoazocine **4.71** was not formed. As a result, we decided to move away from this substrate and focus on more substituted benzaldehydes.

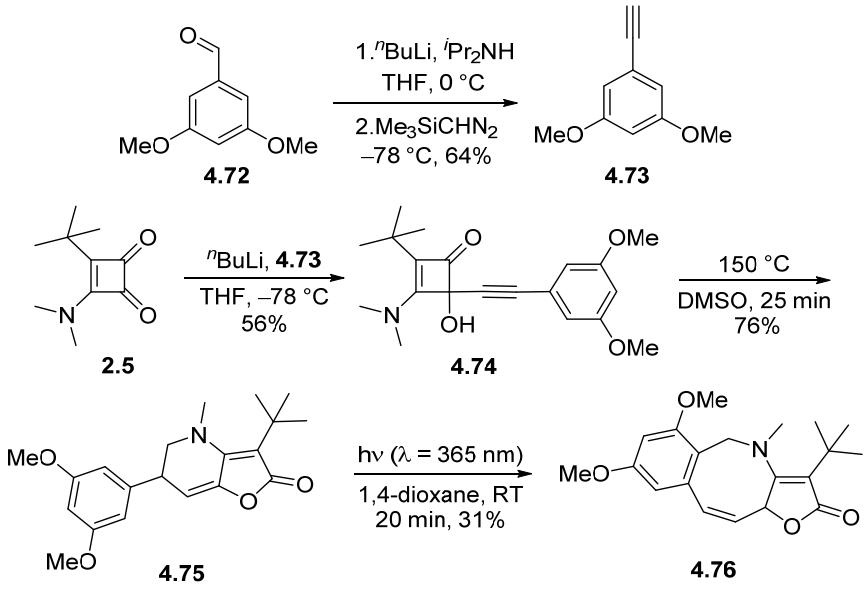


Scheme 4.2.4. Synthesis of dihydrofuropyridinone **4.70** and its irradiation with UVA.

4.2.2.1 3,5-Dimethoxyphenyl

Next, we incorporated two methoxy groups in the 3- and 5- positions of the phenyl ring to increase its electron density and hopefully its reactivity. To achieve this, 3,5-dimethoxybenzaldehyde **4.72** was transformed into 1-ethynyl-3,5-dimethoxybenzene **4.73** in 64% yield.[136] Deprotonation of the resulting alkyne **4.73** with ^{n}BuLi in THF at –78 °C and subsequent coupling to aminocyclobutenone

2.5 gave alkynylcyclobutenone **4.74** in 56% yield (**Scheme 4.2.5**). Thermolysis of alkynylcyclobutenone **4.74** at 150 °C in DMSO produced dihydrofuropyridinone **4.75** in 76% yield. Pleasingly, UVA irradiation of dihydrofuropyridinone **4.75** in 1,4-dioxane using a 9W UVA lamp gave benzoazocine **4.76** in 31% yield after 20 min.

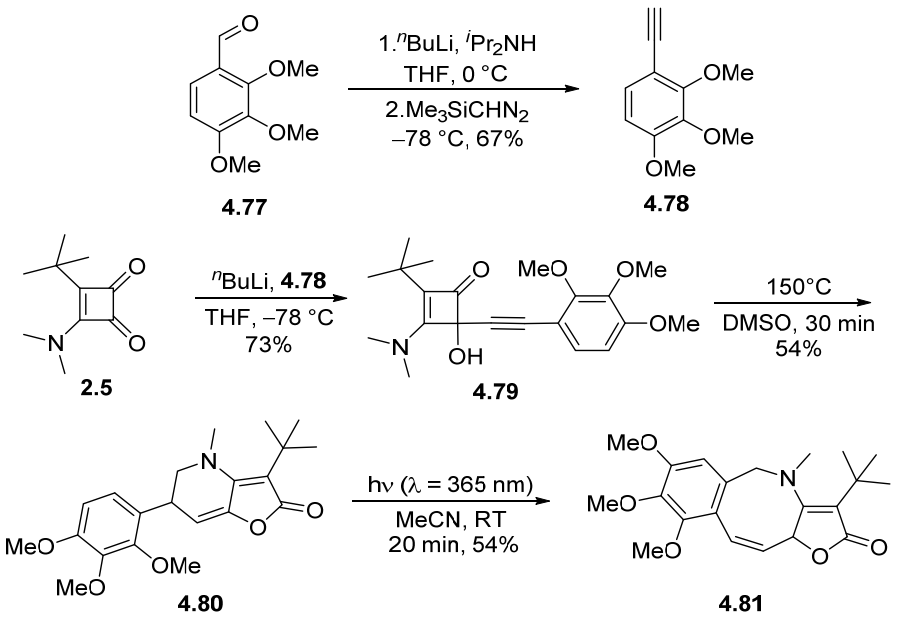


Scheme 4.2.5. Synthesis of dihydrofuropyridinone **4.75** and its irradiation with UVA to benzoazocine **4.76**.

4.2.2.2 Trimethoxyphenyl

2,3,4-Trimethoxyphenyl

We hoped that substituting the phenyl ring with three methoxy groups would further enhance its reactivity due to the large increase in electron density in the phenyl ring. Repeating the synthetic sequence with 1-ethynyl-2,3,4-trimethoxybenzene **4.78**, resulted in the formation of dihydrofuropyridinone **4.80** in 54% yield. We were then pleased to find its irradiation in 1,4-dioxane using the 9 W UVA lamp, successfully gave benzoazocine **4.81** in 54% yield after 20 min (**Scheme 4.2.6**).



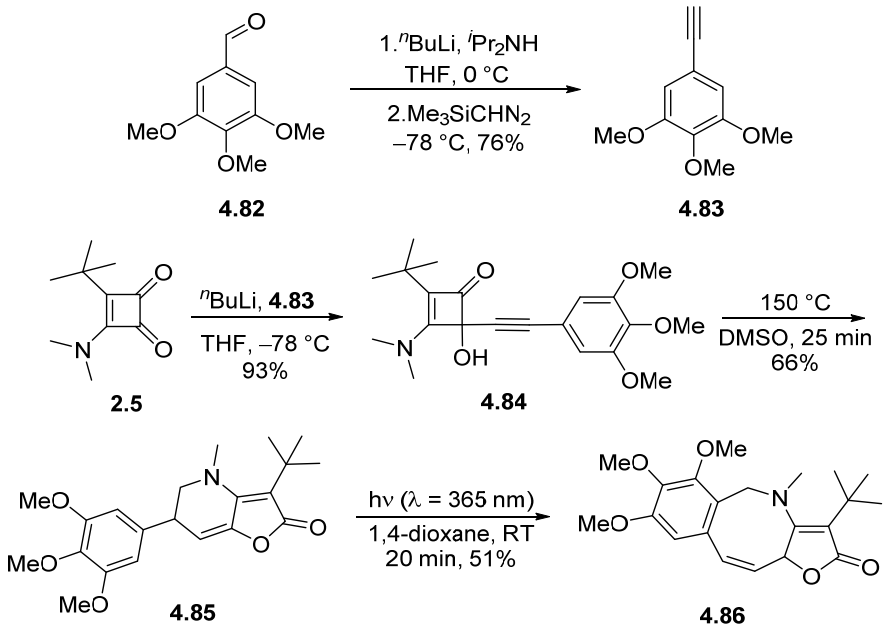
Scheme 4.2.6. Synthesis of dihydrofuropyridinone **4.80** and its irradiation with UVA to benzoazocine **4.81**.

3,4,5-Trimethoxyphenyl

Following this result, we decided to extend the reaction using 1-ethynyl-3,4,5-trimethoxybenzene **4.83**. Applying the aforementioned sequence gave dihydrofuropyridinone **4.85** in 66% yield and its irradiation in 1,4-dioxane produced benzoazocine **4.86** in 44% yield (**Scheme 4.2.7**). The photoreaction of dihydrofuropyridinone **4.85** to benzoazocine **4.86** was performed 4 times, each under different conditions (**Table 4.1**). The highest yield of benzoazocine **4.86** (51%), was achieved on the 10 W LED reactor using a 0.03 M concentration of dihydrofuropyridinone **4.85**.

Table 4.1. The different conditions used to irradiate dihydrofuropyridinone **4.85** under continuous flow with UVA to form benzoazocine **4.86** (See **Scheme 4.2.7**).

Entry	Lamp	Concentration (M)	Residence time (min)	Yield of benzoazocine **4.86** (%)
1	9 W	0.0702	20	44
2	9 W	0.159	20	33
3	10 W	0.0332	7	51
4	10 W	0.0516	7	43



Scheme 4.2.7. Synthesis of dihydrofuropyridinone **4.85** and its irradiation with UVA to benzoazocine **4.86**.

4.3 Heterocyclic substituents

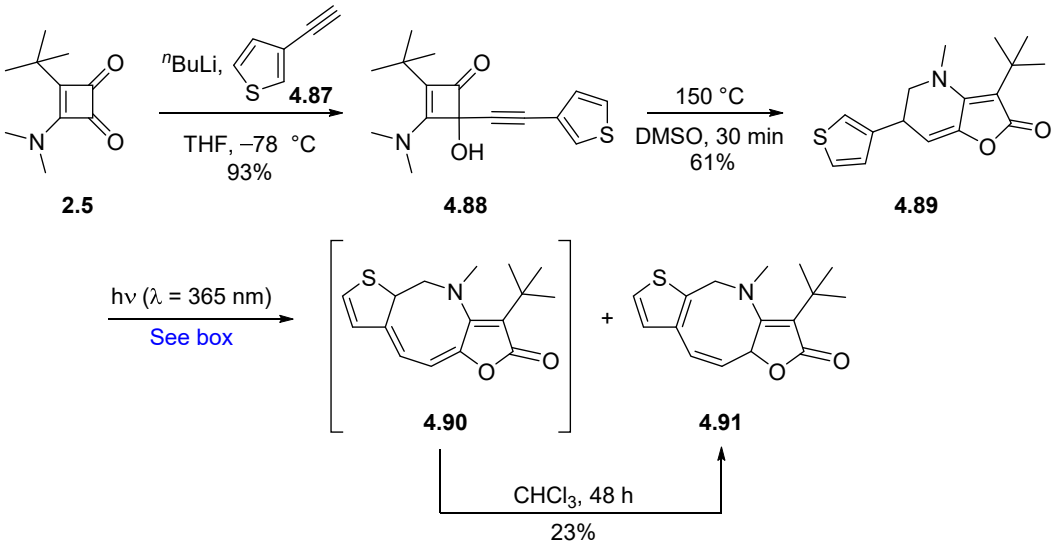
4.3.1 3-Ethynylthiophene

We were curious to see if other aromatic groups could facilitate the photoreaction to azocines. To that end, commercially available 3-ethynylthiophene **4.87** was deprotonated with ^{n}BuLi in THF at –78 °C and coupled to aminocyclobutenone **2.5** to give alkynylcyclobutenone **4.88** in 93% yield. Subsequent thermolysis in DMSO at 150 °C formed dihydrofuropyridinone **4.89** in 61% yield (**Scheme 4.3.1**). The photochemical reaction of dihydrofuropyridinone **4.89** with UVA irradiation resulted in a mixture of azocine **4.91** and intermediate tetraene **4.90**. This was the first time that an intermediate tetraene was observed in any ^{1}H NMR spectra. Indeed, we found that upon standing in chloroform for 48 h, intermediate **4.90** was transformed into the desired azocine **4.91** in 23% yield.

In order to coax intermediate **4.90** to azocine **4.91**, a small amount of triethylamine was added to dihydrofuropyridinone **4.89** before irradiation on the 9W UVA reactor. Furthermore, during purification a 1% triethylamine: petroleum ether solution was used to prewash the column in an attempt to push the rearrangement to azocine **4.91**, but unfortunately, intermediate tetraene **4.90**

was still present. We then hoped the rearrangement would be catalysed by irradiating dihydrofuropyridinone **4.89** with acetic acid. Following purification, tetraene intermediate **4.90** was once again isolated with azocine **4.91**.

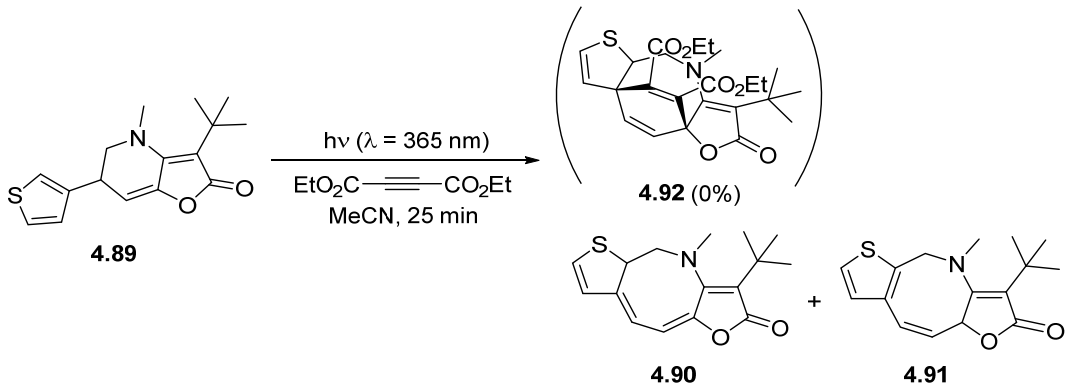
We suspected that the rearrangement of tetraene **4.90** to azocine **4.91** was catalysed by heat and sought to heat the product mixture after the photoreaction. Thus, dihydrofuropyridinone **4.89** in acetonitrile was irradiated using the 10 W LED reactor, for 20 min under argon and the resulting mixture heated to 60 °C for 2 h. Azocine **4.91** was formed as a mixture with starting material and other impurities, resulting in an unreportable yield. However, irradiation of dihydrofuropyridinone **4.89** in THF, on the 10 W LED reactor for 20 min under argon, gave a mixture of tetraene **4.90** and azocine **4.91** in 28% yield. Furthermore, a 3:2 mixture of starting material **4.89** and azocine **4.91** was recovered in 69% yield; this equates to a total yield of 46% of azocine **4.91**.



Scheme 4.3.1. Synthesis of dihydrofuropyridinone **4.89** and its irradiation with UVA to give an inseparable mixture of azocine **4.91** and intermediate tetraene **4.90**.

We then wanted to see if intermediate tetraene **4.90** would react with a strong dienophile such as diethyl acetylenedicarbonate, in a Diels-Alder cycloaddition to form adduct **4.92**. To that end, a solution of dihydrofuropyridinone **4.89** and diethyl acetylenedicarbonate in acetonitrile was irradiated with the 10 W LED reactor for 25 min. Unfortunately, neither the crude ^{1}H NMR or mass

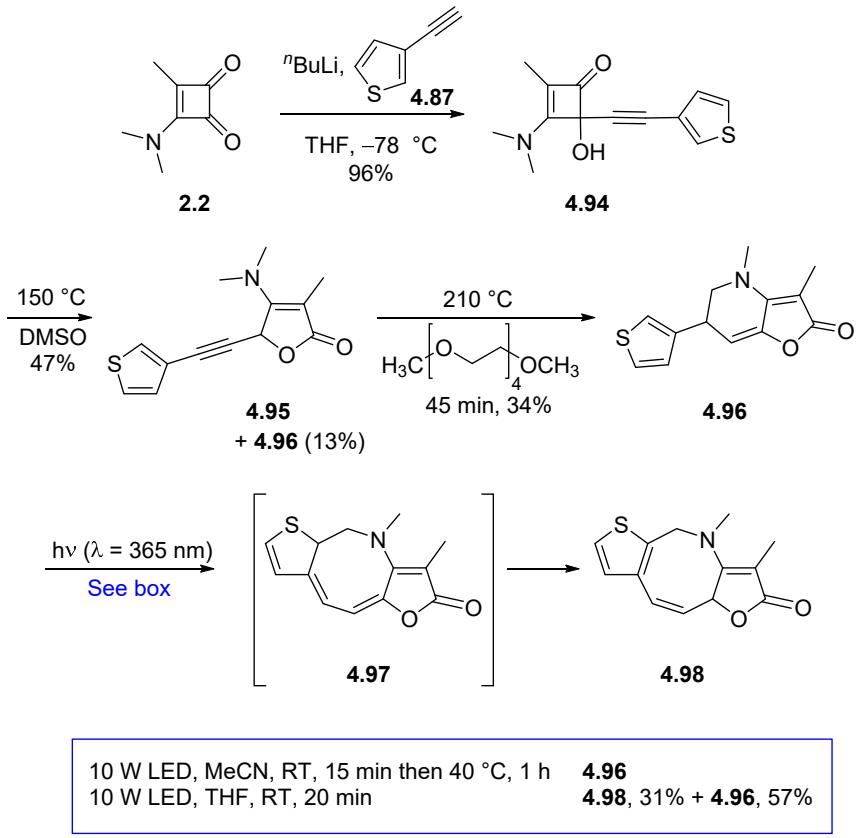
spectrum indicated the presence of the Diels-Alder adduct **4.92**; intermediate tetraene **4.90** and azocine **4.91** were observed but purification was not performed (**Scheme 4.3.2**).



Scheme 4.3.2. Irradiation of dihydrofuropyridinone **4.89** with diethyl acetylenedicarbonate did not form adduct **4.92.**

We wanted to see if the *tert*-butyl substituent had a significant effect on the thermal and photochemical rearrangements with a thiophene substituent. Thus, addition of a solution of lithiated 3-ethynylthiophene **4.87** to aminocyclobutenone **2.2** in THF at –78 °C, gave alkynylcyclobutenone **4.94** in 96% yield. Subsequent thermolysis in DMSO at 150 °C formed furanone **4.95** in 47% yield and dihydrofuropyridinone **4.96** in 13% yield. Further thermolysis of furanone **4.95** in tetraethylene glycol dimethyl ether at 210 °C, produced dihydrofuropyridinone **4.96** in 34% yield after 45 min (**Scheme 4.3.3**).

The first photochemical reaction of dihydrofuropyridinone **4.96** in acetonitrile, was performed on the 10 W LED reactor for 15 min under an argon atmosphere. Once the reaction was completed, the mixture was concentrated *in vacuo*, diluted in chloroform and heated to 40 °C for 1 h. We hoped that any conjugated tetraene **4.97** would be converted to azocine **4.98**, but unfortunately, only crude starting material **4.96** was recovered. The photoreaction was repeated on the 10 W LED reactor in THF for 20 min, once again under an argon atmosphere. Azocine **4.98** was formed in 31% yield, with a 57% yield of recovered starting material and a 12% yield of unidentified mass (**Scheme 4.3.3**). None of the conjugated tetraene **4.97** was observed in the crude ^{1}H NMR spectrum.



Scheme 4.3.3. Synthesis of dihydrofuropyridinone **4.96**, its irradiation with UVA in THF gave azocine **4.98**.

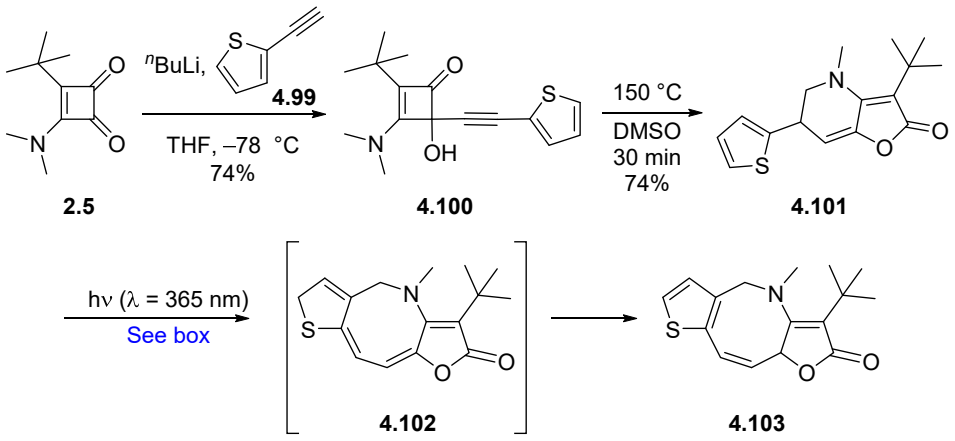
4.3.2 2-Ethynylthiophene

We were very curious to see if the conjugated diene would be observed with the 2-ethynylthiophene analogue. To that end, addition of lithiated 2-ethynylthiophene **4.99** to aminocyclobutenone **2.5** at –78 °C in THF, gave alkynylcyclobutenone **4.100** in 74% yield (**Scheme 4.3.4**). Subsequent thermolysis in DMSO at 150 °C for 30 min, resulted in dihydrofuropyridinone **4.101** also in 74% yield.

Initially, we irradiated dihydrofuropyridinone **4.101** in acetonitrile on the 10 W LED reactor for 10 min. Akin to the 3-thiophene analogue, a mixture of conjugated tetraene **4.102** and azocine **4.103** were obtained in 21% yield and once again, on standing in chloroform, all of the conjugated tetraene **4.102** had converted to azocine **4.103** after 48 h. We decided to repeat the reaction and then heat the crude mixture to catalyse the diene rearrangement. Dihydrofuropyridinone **4.101** in acetonitrile, was irradiated for 15 min under an argon atmosphere on the 10 W LED reactor and then heated to 60 °C for 2 h. An inseparable 2:1 mixture of starting material **4.101** and azocine **4.103** was obtained in a 65% yield, corresponding to an approximated yield of azocine **4.103** of 22%.

It was around this time that we found success with the 3-thiophene analogue using THF as the photochemical solvent. Thus, dihydrofuropyridinone **4.101** in THF was irradiated with UVA on the 10 W LED reactor for 20 min under argon and the crude mixture then heated for 2 h at 50 °C. Unfortunately, once again, an inseparable 1:1 mixture of starting material **4.101** and azocine **4.103**, was obtained in 70% yield. In this case, using THF as the reaction solvent had no effect on the reaction. Furthermore, we concluded that heating the crude product mixture was detrimental, as we were unable to isolate the azocine cleanly without the dihydrofuropyridinone.

Finally, we decided to repeat the initial conditions using acetonitrile without heating, but under an argon atmosphere. Thus, dihydrofuropyridinone **4.101** in acetonitrile, was irradiated for 20 min on the 10 W LED reactor under argon, resulting in a mixture of tetraene **4.102** and azocine **4.103** in 27% yield. All of the tetraene **4.102** was converted to azocine **4.103** after standing in chloroform for 72 h. Furthermore, a 4:1 mixture of azocine **4.103** and starting material **4.101** was also obtained in 35% yield, resulting in a total yield of azocine **4.103** of 55% (**Scheme 4.3.4**).

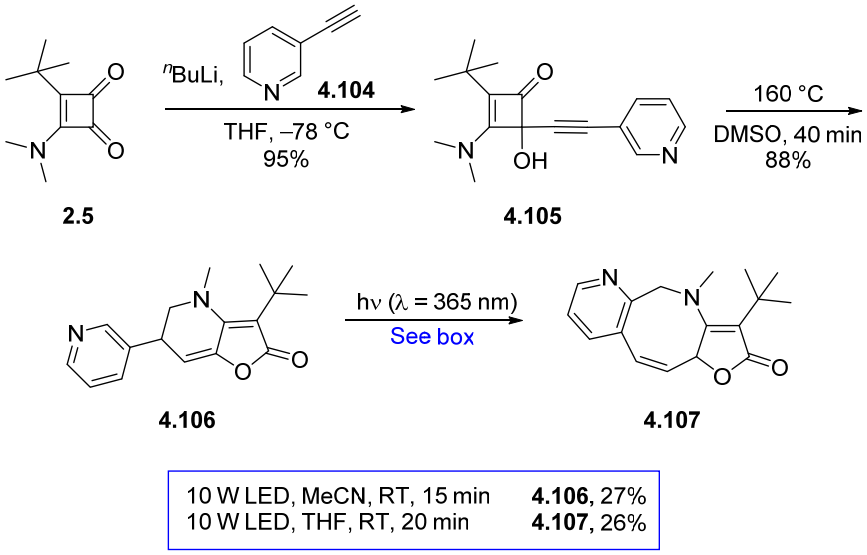


Scheme 4.3.4. Synthesis and subsequent photoreaction of dihydrofuropyridinone **4.101** gave tetraene **4.102** and then azocine **4.103**.

4.3.3 Pyridine

Subsequently, we wanted to try an electron poor heteroaromatic, such as pyridine. To that end, commercially available 3-ethynylpyridine **4.104** in THF at –78 °C, was deprotonated using ^{n}BuLi then coupled to aminocyclobutenone **2.5** to give alkynylcyclobutenone **4.105** in 95% yield. Subsequent thermolysis in DMSO at 160 °C for 40 min under an argon atmosphere produced dihydrofuropyridinone **4.106** in 88% yield (**Scheme 4.3.5**).

The first photochemical reaction of dihydrofuropyridinone **4.106** was performed on the 10 W LED reactor in acetonitrile for 15 min, under an argon atmosphere. The crude ^{1}H NMR spectrum showed only starting material **4.106**, which was recovered in 27% yield with significant mass loss during purification (**Scheme 4.3.5**). However, irradiating dihydrofuropyridinone **4.106** in THF on the 10 W LED reactor for 20 min under an argon atmosphere gave azocine **4.107** in 26% yield, the remaining mass was unidentifiable. We found that a residence time of 20 min, at a concentration of 0.03 M were the optimum conditions, although yields were consistent and ranged between 22 – 26%.

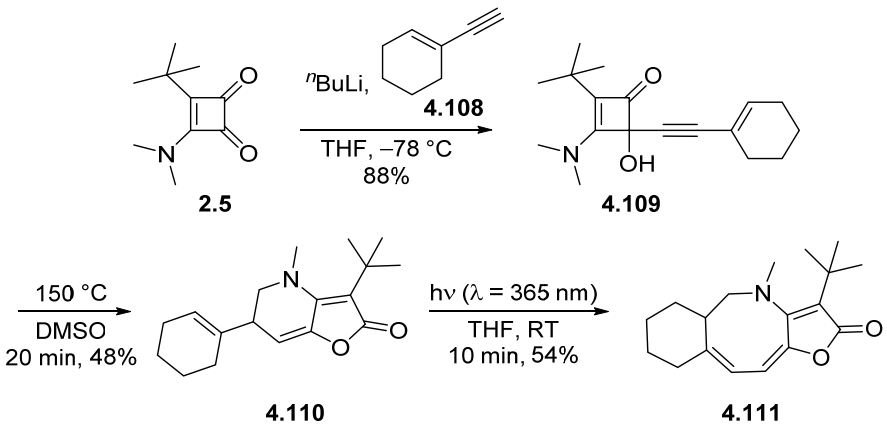


Scheme 4.3.5. Synthesis of dihydrofuropyridinone **4.106** and subsequent irradiation with UVA to azocine **4.107**.

4.4 Non-aromatic substituents

4.4.1 1-Ethenylcyclohexene

The photochemical rearrangement proved compatible with various aromatic substituents, we were curious to see if it would also proceed with alkenes. A point of saturation was required to enable closure to the 8-membered ring during the photochemical rearrangement. Thus, 1-ethenylcyclohexene was chosen due to its availability from commercial sources. Deprotonation of 1-ethenylcyclohexene **4.108** was achieved using ^{n}BuLi in THF at –78 °C. The resulting organolithium was then coupled to aminocyclobutenone **2.5** to give alkynylcyclobutenone **4.109** in 88% yield. Subsequent thermolysis in DMSO at 150 °C gave dihydrofuropyridinone **4.110** in 48% yield. Pleasingly, irradiation of dihydrofuropyridinone **4.110** in THF on the 10 W LED photoreactor produced azocine **4.111** in 54% yield, in addition to starting material (which was not recovered during purification). Notably, azocine **4.111** was formed as the conjugated triene, in contrast to the skipped diene azocines previously observed.

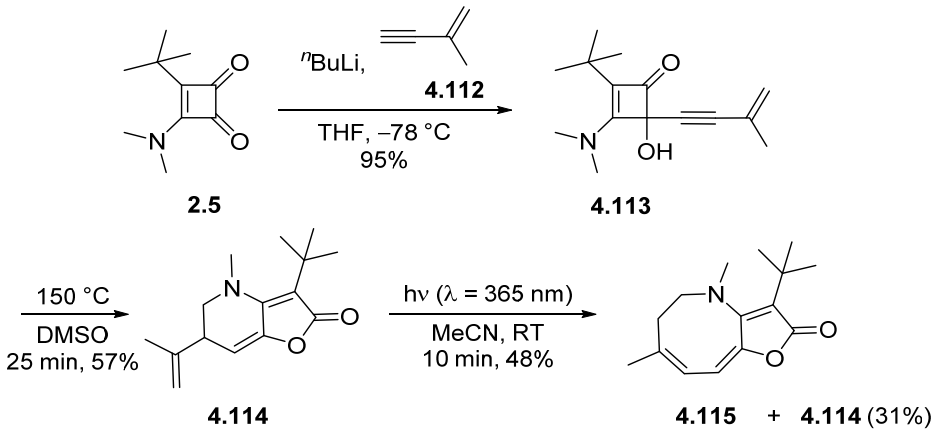


Scheme 4.4.1. Synthesis and irradiation of dihydrofuropyridinone **4.110** to conjugated azocine **4.111**.

4.4.2 2-Methyl-1-buten-3-yne

The aforementioned result opened up the possibility of using an aliphatic alkene instead of a cyclic alkene or aromatic system. To that end, 2-methyl-1-but-3-yne **4.112** was deprotonated with ^{n}BuLi in THF at –78 °C and coupled to cyclobutenone **2.5** to give a 95% yield of alkynylcyclobutenone **4.113**. Thermolysis of **4.113** in DMSO at 150 °C, gave dihydrofuropyridinone **4.114** bearing an isopropene substituent in 57% yield. Irradiation of dihydrofuropyridinone **4.114** in THF on the 10 W

LED reactor for 7 min, resulted in azocine **4.115** in 34% yield and recovered starting material in 57% yield. The reaction was repeated for a longer residence time of 10 min in acetonitrile and pleasingly, azocine **1.115** was given in 48% yield and only 31% of starting material was recovered. Once again, the conjugated triene azocine was formed.

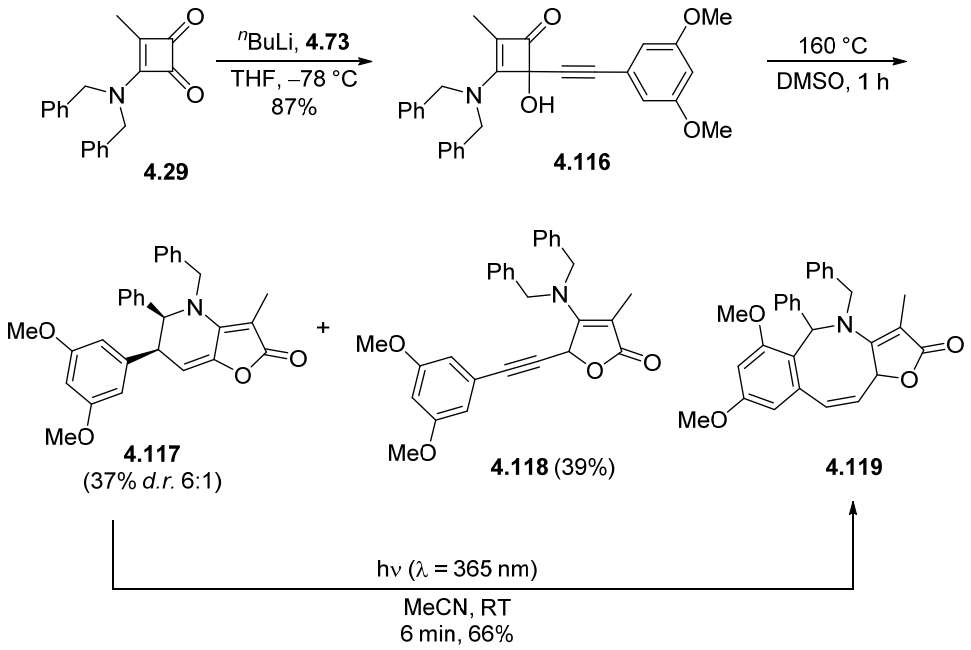


Scheme 4.4.2. Synthesis and irradiation of dihydrofuropyridinone **4.114** to azocine **4.115**.

4.5 Reactions with substituted amines and aryl/vinyl groups

4.5.1 3,5-Dimethoxyphenyl

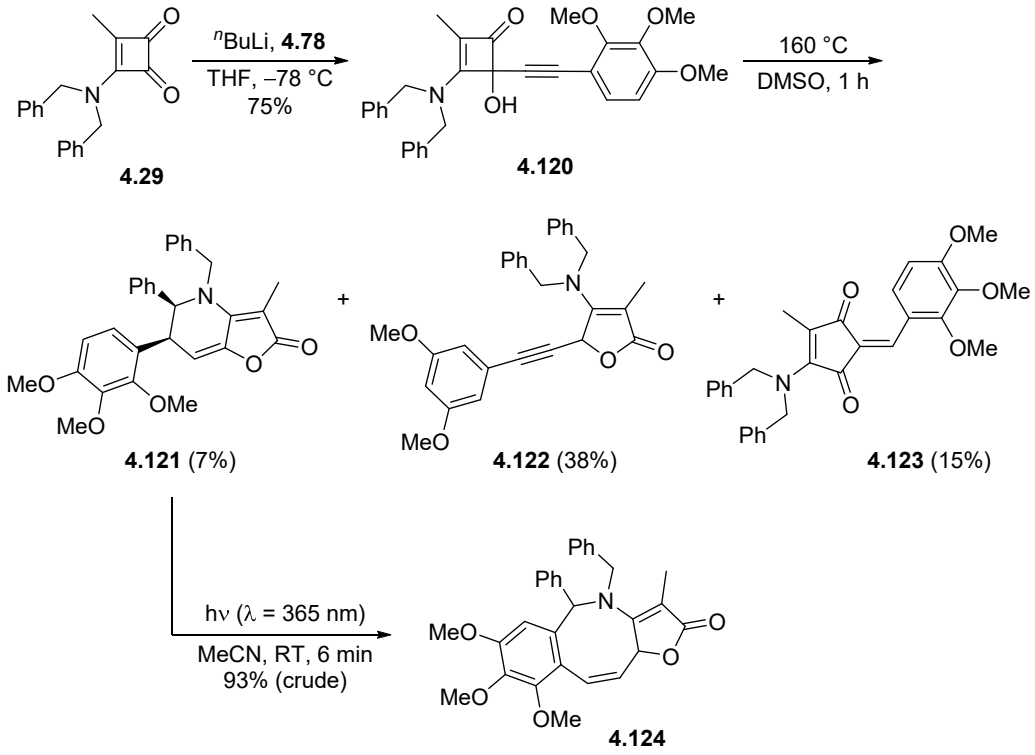
We next wanted to see how arene substituents on dibenzylamino and benzylmethylamino cyclobutenones would effect the course of the reactions. To that end, dihydrofuropyridinone **4.117** bearing a 3,5-dimethoxyphenyl group was synthesised in 37% yield and irradiated in acetonitrile on the 10 W LED reactor to give benzoazocine **4.119** in 66% yield (**Scheme 4.5.1**).



Scheme 4.5.1. Synthesis and photochemical reaction of dihydrofuropyridinone **4.117** to azocine **4.119**.

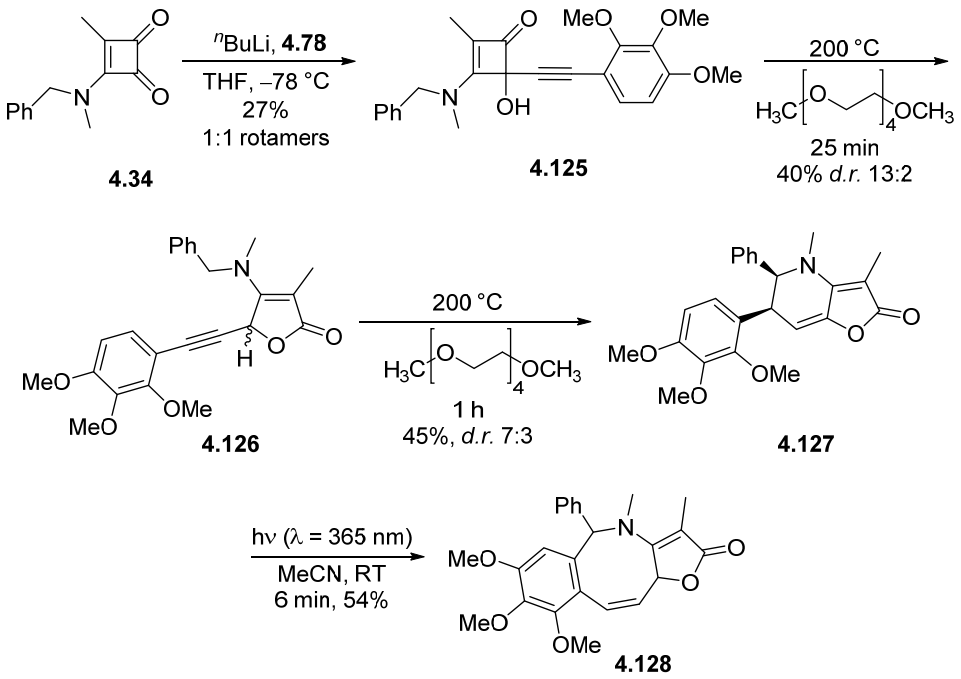
4.5.2 2,3,4-Trimethoxyphenyl

The dibenzylamino and benzylmethylamino cyclobutenones were then used with the trimethoxyphenyl substituents. Lithiated 2,3,4-trimethoxyphenyl **4.78** was coupled to cyclobutenone **4.29** to give alkynylcyclobutenone **4.120** in 75% yield. Thermolysis of alkynylcyclobutenone **4.120** in DMSO at 160 °C under an argon atmosphere, resulted in a mixture of products, including furanone **4.122**, isolated in 38% yield (**Scheme 4.5.2**). Following purification, dihydrofuropyridinone **4.121** was initially isolated as a mixture with byproduct **4.123**, which itself was a mixture of *E*- and *Z*- isomers. Separation of this mixture was achieved by HPLC (high performance liquid chromatography) to give dihydrofuropyridinone **4.121** in 7% yield and byproducts **4.123** in 12% and 3% yields as the *E*- and *Z*- isomers. Irradiation of dihydrofuropyridinone **4.121** in acetonitrile on the 10 W LED reactor for 6 min, resulted in benzoazocine **4.124** in 93% crude yield. Purification was not necessary as the crude ^{1}H NMR spectrum showed no impurities or solvent peaks. The reaction was not repeated due to the problems encountered with the previous thermolysis step.



Scheme 4.5.2. Synthesis of dihydrofuropyridinone **4.121** and irradiation with UVA to benzoazocine **4.124**.

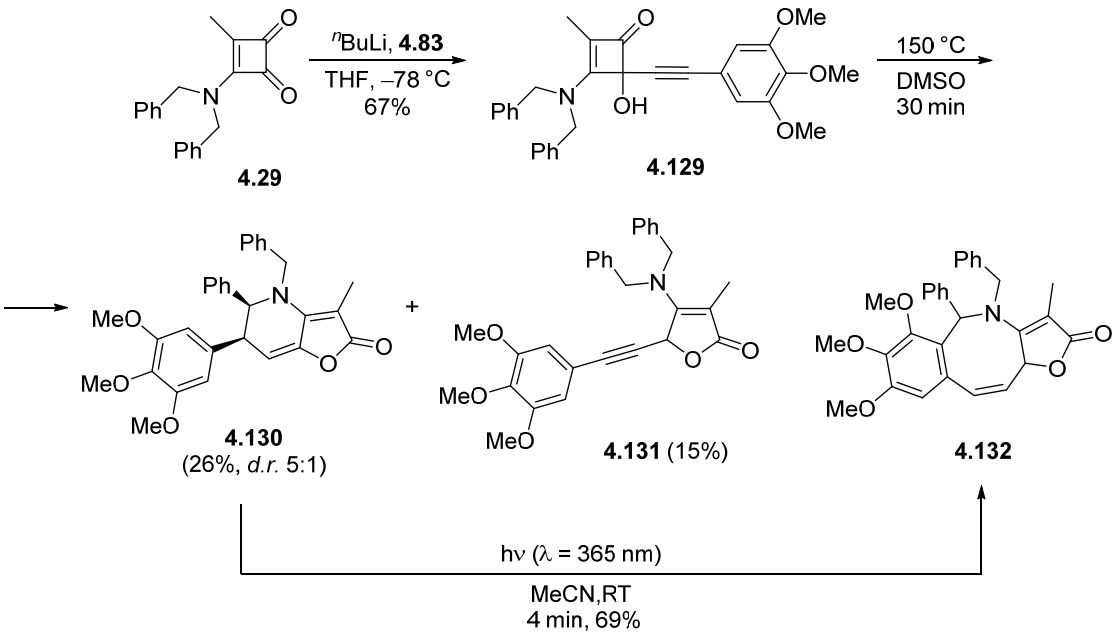
The coupling of lithiated 2,3,4-dimethoxyphenyl **4.78** to benzylmethylamino cyclobutenone **4.34** gave a 27% yield of alkynylcyclobutenone **4.125** as a 1:1 mixture of rotamers (**Scheme 4.5.3**). Thermolysis of alkynylcyclobutenone **4.125** in tetraethylene glycol dimethyl ether at 200 °C resulted in furanone **4.126** in 40% yield as a 13:2 rotameric mixture after 25 min. This was then thermolysed in tetraethylene glycol dimethyl ether at 200 °C for 1 h under an argon atmosphere to give dihydrofuropyridinone **4.127** in 45% yield as a 7:3 mixture of diastereoisomers. Irradiation of the diastereotopic mixture of dihydrofuropyridinone **4.127** in acetonitrile on the 10 W LED reactor, gave benzoazocine **4.128** in 54% yield after 6 min.



Scheme 4.5.3. Synthesis of dihydrofuropyridinone **4.127** and irradiation with UVA to benzoazocine **4.128**.

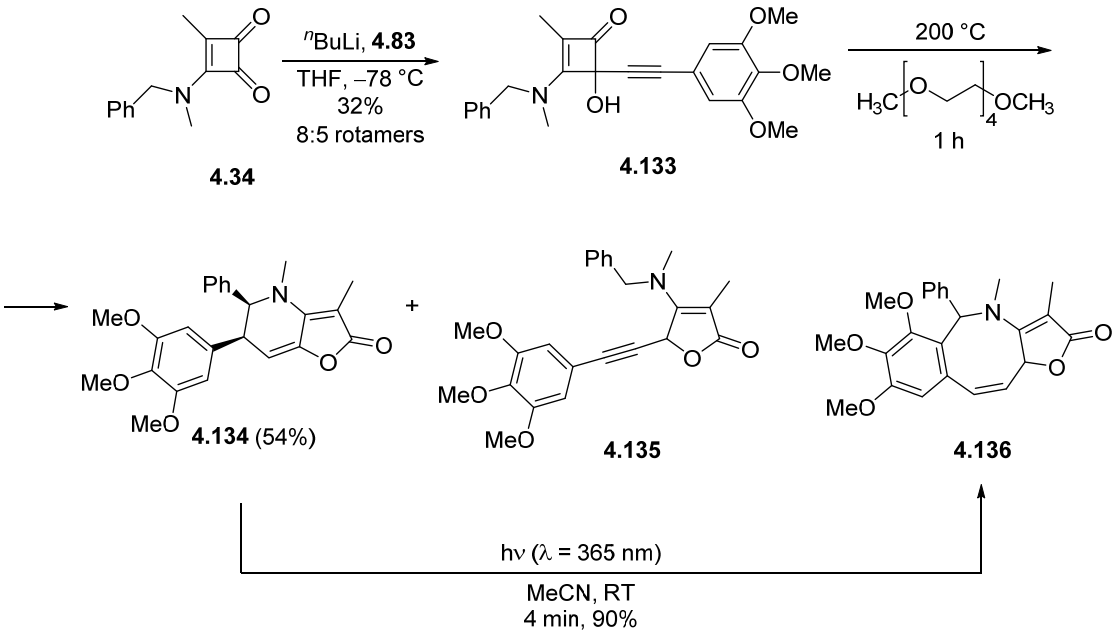
4.5.3 3,4,5-Trimethoxyphenyl

Thermolysis of alkynylcyclobutenone **4.129** in DMSO at 150 °C under an argon atmosphere, gave dihydrofuropyridinone **4.130** in 26% yield as a 5:1 mixture of diastereoisomers and furanone **4.131** in 15% yield. Irradiation of dihydrofuropyridinone **4.130** in acetonitrile for 4 min on the 10 W LED reactor, gave benzoazocine **4.132** in 69% yield (**Scheme 4.5.4**). The lower residence time was due to user error as the peristaltic pump not being calibrated properly. We suspect that repeating the reaction for 6 or 7 minutes will result in a higher yield of benzoazocine.



Scheme 4.5.4. Synthesis and irradiation of dihydrofuropyridinone **4.130** with UVA gave benzoazocine **4.132**.

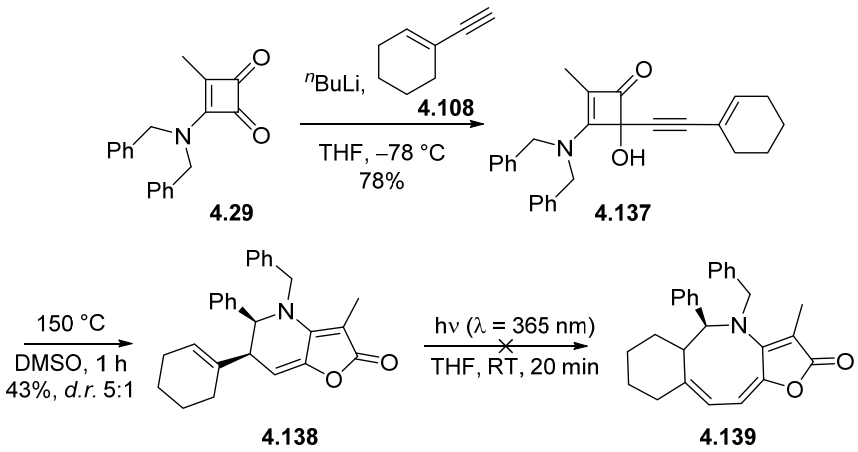
Finally, addition of lithiated 3,4,5-trimethoxyphenylacetylene **4.83** to cyclobutenone **4.34** gave alkynylcyclobutenone **4.133** as an 8:5 mixture of rotamers (**Scheme 4.5.5**). Thermolysis of alkynylcyclobutenone **4.133** in tetraethylene glycol dimethyl ether at 200 °C gave dihydrofuropyridinone **4.134** in 54% yield as a single diastereoisomer following purification by column chromatography. A further fraction suggested that furanone **4.135** and the trans-diastereoisomer of **4.134** were byproducts of the reaction, though neither could be isolated cleanly. UVA irradiation of dihydrofuropyridinone **4.134** in acetonitrile on the 10 W LED reactor for a residence time of 4 min, gave benzoazocine **4.136** in 90% yield.



Scheme 4.5.5. Synthesis and UVA irradiation of dihydrofuropyridinone **4.134** to benzoazocine **4.136**.

4.5.4 1-Ethenylcyclohexene

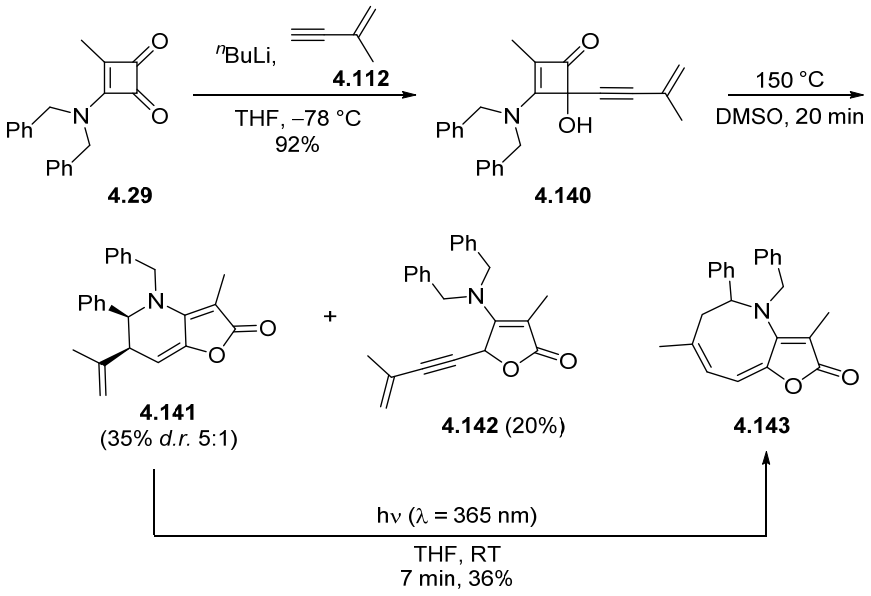
Extending the methodology further; lithiated 1-ethenylcyclohexene **4.108** was added to aminocyclobutenone **4.29** to give alkynylcyclobutenone **4.137** in 78% yield. Subsequent thermolysis in DMSO at 150 °C gave dihydrofuropyridinone **4.138** in 43% yield as a 5:1 mixture of diastereoisomers (**Scheme 4.5.6**). Unfortunately, irradiation of dihydrofuropyridinone **4.138** on the 10 W LED photoreactor did not yield azocine **4.139** and instead returned starting material with the trans-diastereoisomer of **4.138** present in trace amounts. The reaction was repeated with different solvents including THF, 1,4-dioxane and acetonitrile and irradiated for various residence times, but the azocine was not produced on any occasion. This result could be due to the steric clash of the two phenyl groups with the cyclohexane ring making 8-ring closure less viable than 6-ring closure.



Scheme 4.5.6. Synthesis of dihydrofuropyridinone **4.138**, irradiation with UVA did not give azocine **4.139**.

4.5.5 2-Methyl-1-buten-3-yne

Lithiated 2-methyl-1-buten-3-yne **4.112** was then coupled to cyclobutenone **4.29** to give alkynylcyclobutenone **4.140** in 92% yield (**Scheme 4.5.7**). Subsequent thermolysis at 150 °C in DMSO gave a 35% yield of the corresponding dihydrofuropyridinone **4.141** as an inseparable 5:1 mixture of diastereoisomers, in addition to byproduct furanone **4.142** in 20% yield. UVA irradiation of the diastereotopic mixture of dihydrofuropyridinone **4.141** in THF using the 10 W LED lamp produced azocine **4.142** in 36% yield as the conjugated triene. A full list of the azocines made to date is provided in **Figure 4.5.1**.



Scheme 4.5.7. Synthesis of dihydrofuropyridinone **4.141** and irradiation with UVA to azocine **4.143**.

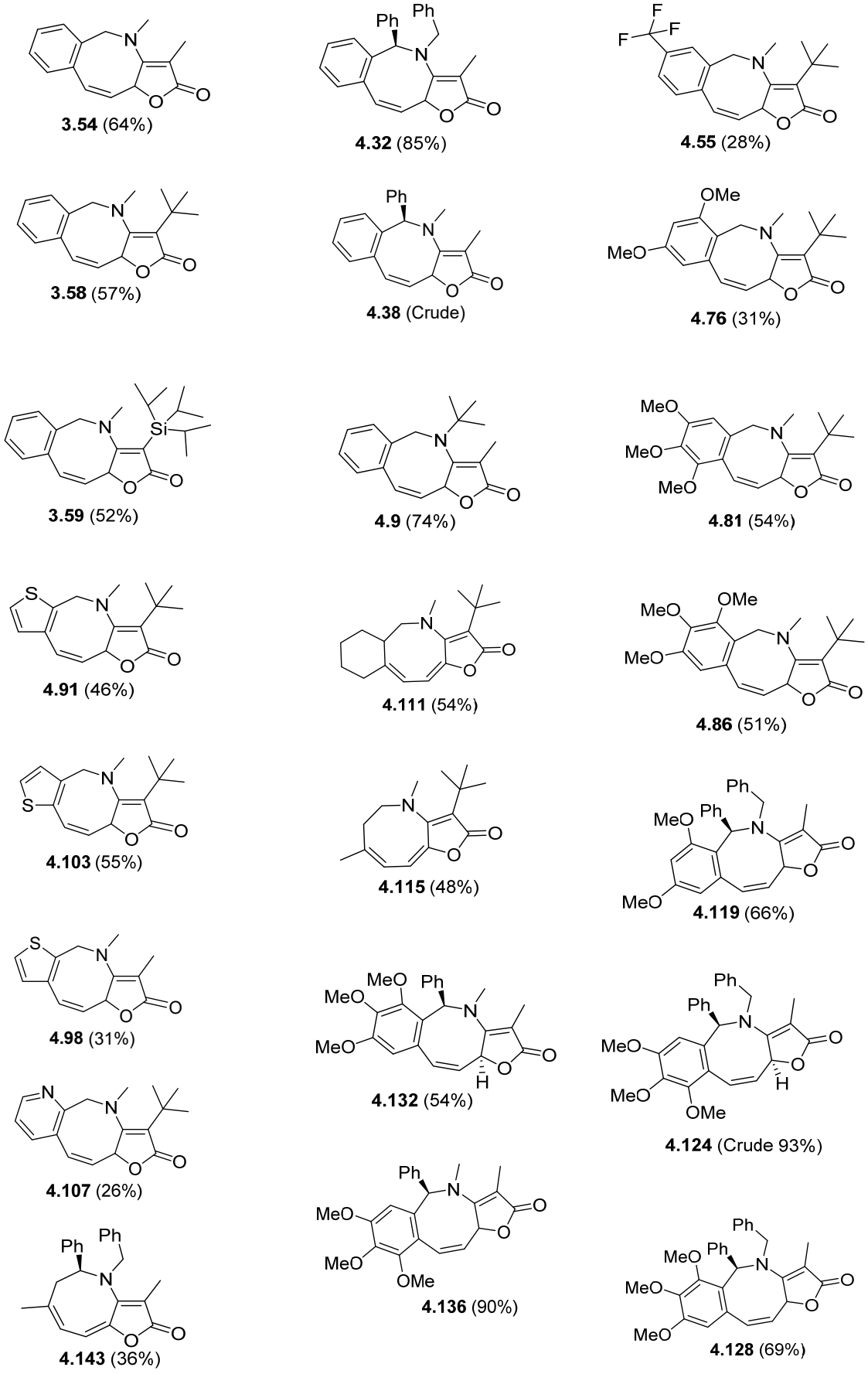
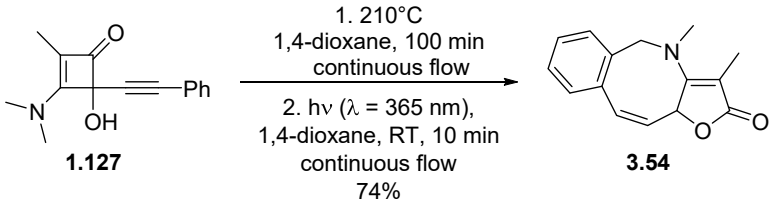


Figure 4.5.1. Isolated yields of the azocines synthesised to date. *See Chapter 5 for experimentals details.

4.6 Daisy Chains

One of our key objectives was to daisy chain two processes together (See **Section 1.4**). With that in mind, we decided to try to sequence the thermolysis and photochemical steps. This project was carried out with Dr. Wei Sun using the R4/R2^{+} Vapourtec system linked to a 6 x 1.7 W LED reactor as shown in **Figure 4.6.1**.

Work by Dr. Wei Sun has shown that the thermolysis product, (*e.g.* dihydrofuropyridinone **1.129**, See **Scheme 1.2.2**) did not need to be isolated and purified before photolysis to the azocine, *e.g.* **3.54**, regardless of whether the furanone byproduct, *e.g.* **1.128** was present (**Scheme 4.6.1**). The furanone was inert to UVA irradiation and did not affect the rearrangement of the dihydrofuropyridinone to the azocine. The crude ^{1}H NMR spectrum of a daisy chain reaction performed by Dr. Wei Sun has shown that furanone was present in low quantities in the product mixture which was easily separated from the azocine during purification.



Scheme 4.6.1. A daisy chain sequence to benzoazocine **3.54** under continuous flow performed by Dr. Wei Sun.

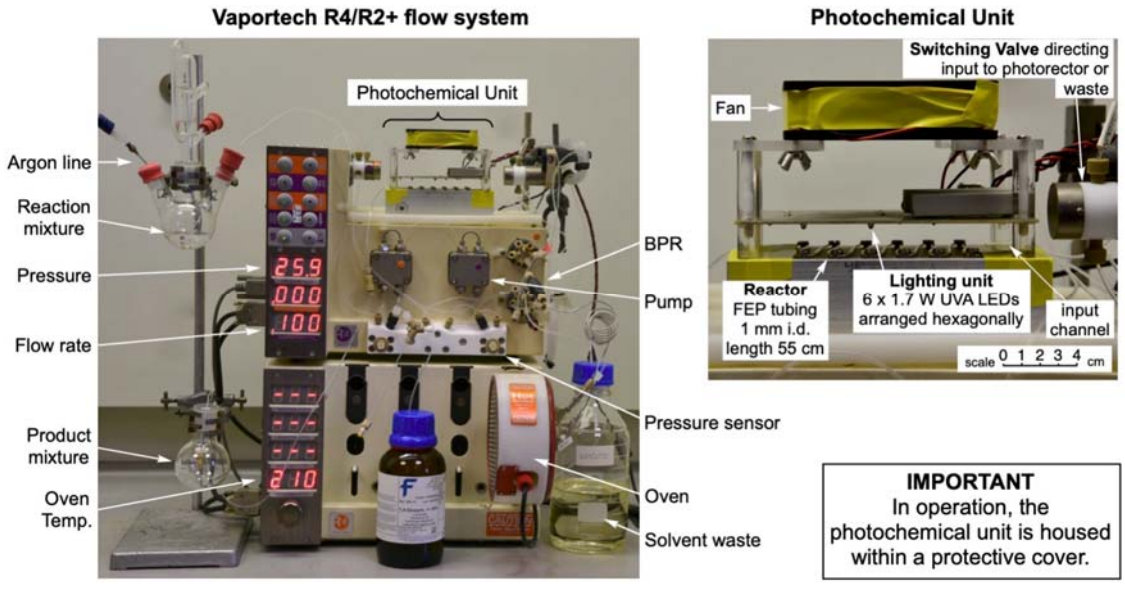
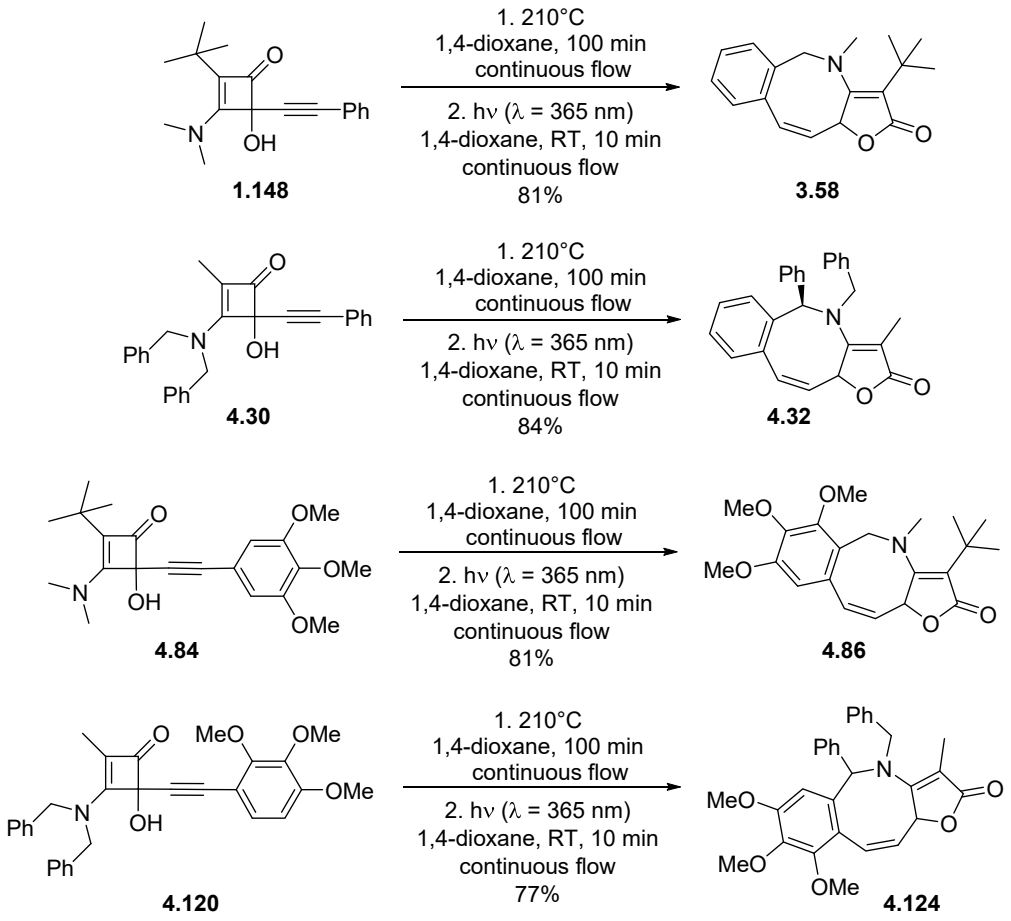


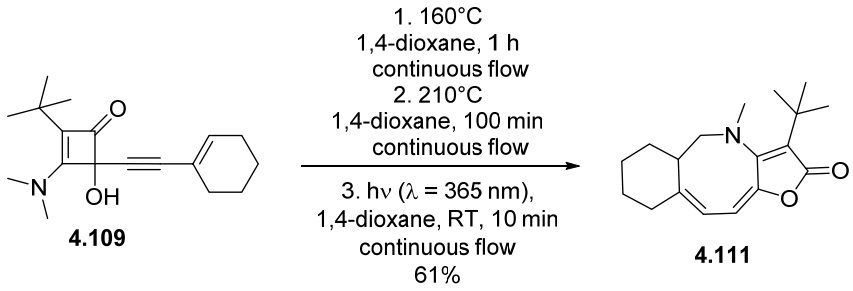
Figure 4.6.1. The R4/R2^{+} Vapourtec and 10 W LED reactor set up for daisy chain reactions.

As the two processes were linked, the reaction solvent needed to be the same. We used 1,4-dioxane as this was the solvent of choice in the thermolyses under continuous flow. Furthermore, our optimisation studies had shown that it can be tolerated in the photoreactor. The process was limited by the flow rate of the thermolysis, therefore a smaller length of reactor tubing was required in the photoreactor so as not to over irradiate the dihydrofuropyridinone.

The following examples were carried out by Dr. Wei Sun using the set up shown in **Figure 4.6.1**. For example, alkynylcyclobutenone **1.148** was heated to 210 °C under continuous flow for a residence time of 100 min, then irradiated with UVA light from 6 x 1.7 W LEDs for 10 min to give benzoazocine **3.58** in 81% yield (**Scheme 4.6.1**). In the case of the ethenylcyclohexane example **4.109**, the thermolysis step was repeated due to the poor conversion to dihydrofuropyridinone **4.110**. Firstly, alkynylcyclobutenone **4.109** was heated to 160 °C for 1 h and then at 210 °C for a further 100 min, before being irradiated with UVA to give azocine **4.111** in 61% yield. These preliminary results show that the yields of azocines produced following daisy chain syntheses were substantially higher than those attained using stepwise procedures.

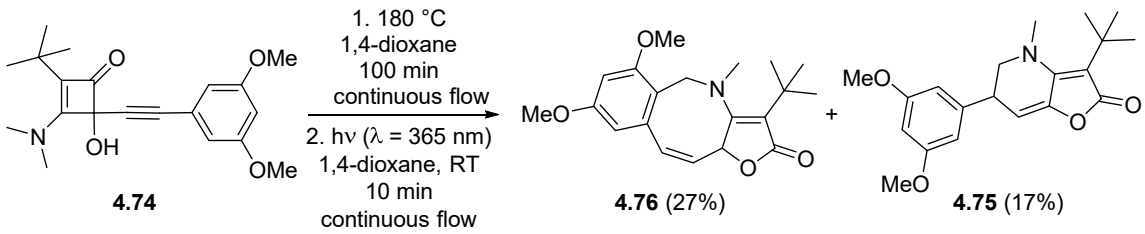


Scheme 4.6.2. Daisy chain reactions to azocines performed by Dr. Wei Sun.



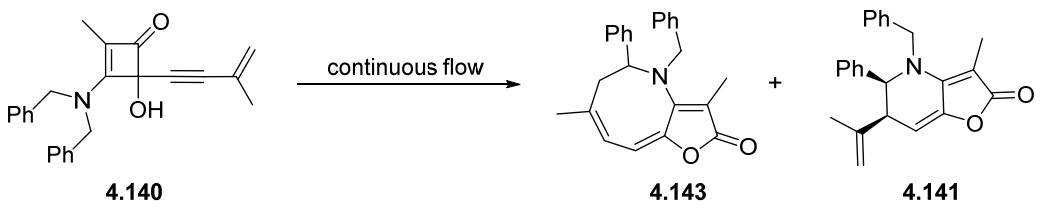
Scheme 4.6.3. Alkynylcyclobutenone **4.108** required 2 thermolyses to synthesise dihydrofuropyridinone **4.109**, prior to UVA irradiation to give azocine **4.110**.

Following Dr. Wei Sun's work, we attempted a daisy chain sequence to form 3,5-dimethoxy benzoazocine **4.76**. The stepwise procedure gave a low yield of 31% of **4.76** and we hoped that daisy chaining the thermal and photo processes would give an improvement. Unfortunately, the first daisy chain attempt, in which we heated alkynylcyclobutenone **4.74** to 220 °C for 100 min before irradiation with UVA, resulted in recovery of dihydrofuropyridinone **4.75** and isolation of a small amount of impure benzoazocine **4.76**. Comparatively, in the stepwise reactions, alkynylcyclobutenone **4.74** was only heated to 150 °C to form the dihydrofuropyridinone **4.75**. This would suggest that we over heated alkynylcyclobutenone **4.74**, resulting in decomposition. The daisy chain reaction was then repeated at a lower thermolysis temperature of 180 °C for 100 min before irradiation with UVA (6 x 1.7 W) under continuous flow. Once again, dihydrofuropyridinone **4.75** was isolated in 18% yield, but this time the major product was benzoazocine **4.76**, given in 27% yield (**Scheme 4.6.4**). We have concluded that the photoreaction to benzoazocine **4.76** was low yielding and ceased further work on this substrate.



Scheme 4.6.4. Daisy chain reaction of alkynylcyclobutenone **4.74** to benzoazocine **4.76** in a lower 27% yield.

Next, we focused on the daisy chain reaction to synthesise azocine **4.143** in an attempt to improve the yield from 36%. Alkynylcyclobutenone **4.140** was heated to 210 °C for 100 min in 1,4-dioxane and then irradiated with UVA for 10 min under continuous flow. Unfortunately, azocine **1.143** was isolated in only 27% yield and dihydrofuropyridinone **4.141** was given in 36% yield (**Scheme 4.6.5**). We suspected that the yield would be increased by performing the thermolysis twice as per the ethenylcyclohexene example in **Scheme 4.6.3**, as there was no aromatic group to drive the reaction. To that end, alkynylcyclobutenone **4.140** was first heated to 150 °C for 1 h under continuous flow and the resulting solution concentrated *in vacuo* and stored under argon overnight. The crude mixture was further heated to 210 °C for 100 min under continuous flow and then immediately irradiated with UVA for 10 min. It is with regret that the yield of azocine **1.143** was not improved, with only 20% isolated, whilst dihydrofuropyridinone **1.141** was given in 24% yield. It would seem that the additional thermolysis step impeded the reaction and further optimisation work is needed.



1. 210 °C, 1,4-dioxane, 100 min
2. hν (λ = 365 nm), 1,4-dioxane, RT, 10 min

4.143, 27% + **4.141,** 36%

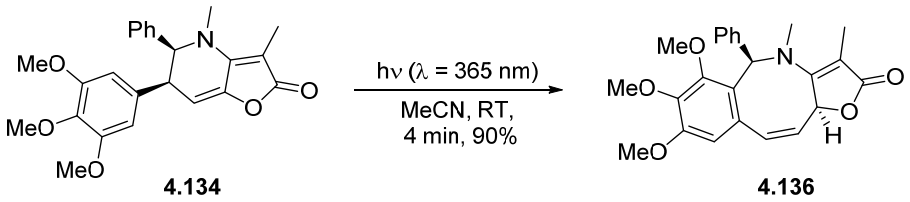
1. 160 °C, 1,4-dioxane, 1 h
2. 210 °C, 1,4-dioxane, 100 min
3. hν (λ = 365 nm), 1,4-dioxane, RT, 10 min

4.143, 20% + **4.141**, 24%

Scheme 4.6.5. Daisy chain reactions of alkynylcyclobutenone **4.140** to azocine **4.143**.

4.7 Conclusions and Future Work

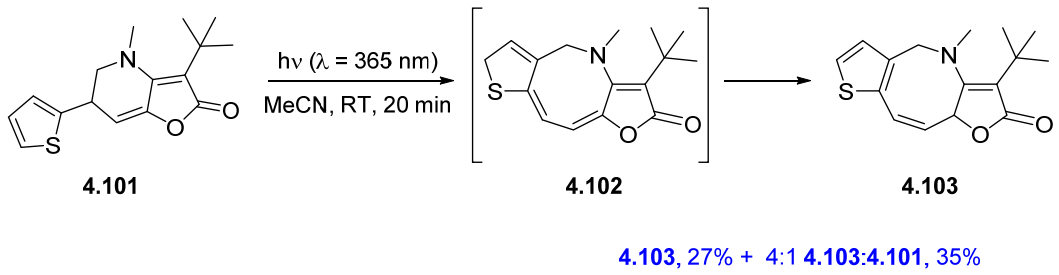
In summary, we have synthesised 22 azocines in yields varying from 21 – 90%, following the irradiation of dihydrofuropyridinones with UVA light. We have incorporated different substituents on the nitrogen, the C3 carbon and the phenyl ring and have also reported examples of azocines with heterocyclic and vinyl substituents. The highest yielding photoreaction was benzoazocine **4.136** from dihydrofuropyridinone **4.134** with *N*-methyl, 6-phenyl and 7-(3,4,5-trimethoxyphenyl) residues (**Scheme 4.7.1**).



Scheme 4.7.1. Irradiation of dihydrofuropyridinone **4.134** with UVA gave benzoazocine **4.136** in 90% yield.

A recurring pattern was the high yields attained for benzoazocines derived from dihydrofuropyridinones with aryl substituents at C6 and C7. Notably, these resulted in diastereomeric mixtures of products, often with a very high *d.r.* favouring the rel-5*R*,10*Z*,11a*S* diastereoisomer, *e.g.* **4.136**. Alas, routes to the dihydrofuropyridinone precursors were in many cases plagued with low yields due to incomplete thermolysis and almost always produced a mixture of diasteroisomers that were difficult to separate and analyse due to rotamers.

Notably, we successfully incorporated heterocyclic substituents into the dihydrofuropyridinone precursors to enable the synthesis of azocines with fused thiophene and pyridine rings, such as azocine **4.103** (**Scheme 4.7.2**). In most cases, these reactions followed the usual course to give products with a skipped diene unit. However, for some of these examples, rearomatisation of the heterocycle was slowed such that the initially formed azocine **4.102**, with a tetraene conjugation to the carbonyl, could be isolated as a product of the reaction. The conjugated azocine was also formed as the only product in examples without an aromatic substituent *e.g.* **4.111** (**Figure 4.5.1**).



Scheme 4.7.2. Irradiation of dihydrofuropyridinone **4.101** with UVA gave a mixture of tetraene **4.102** and skipped diene azocine **4.103**.

Future work would be to extend these azocine syntheses to systems without the furanone moiety, allowing for a more generalised approach to 8-membered ring synthesis. Emphasis should be placed on daisy chain sequences as these one-pot reactions are higher yielding. The photochemical rearrangement could potentially be used on similar systems to synthesise high value compounds with importance in medicinal chemistry. Due to the disruption caused by the Covid-19 pandemic, we were not able to demonstrate the value of sequencing the thermal and photochemical rearrangements in all of the 22 cases developed. With further optimisation, the efficiency and value of the method as a means to prepare azocines and benzoazocines would be properly demonstrated.

Chapter 5 Experimentals

5.1 General experimental techniques

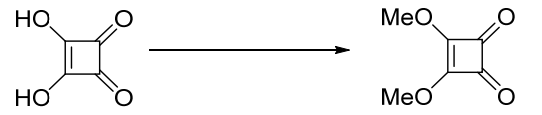
Reagents that were commercially available were purchased and used without further purification unless stated otherwise. THF was distilled from sodium benzophenone ketyl under argon. All air and water sensitive reactions were carried out under argon using flame dried glassware. Purification by column chromatography was carried out under a slight positive pressure using silica (Sigma-Aldrich, technical grade 60 Å pore size, 230-400 mesh particle size and 40-63 µm particle size). Thin layer chromatography (TLC) was carried out on Merck Silica Gel 60 Å F 254 0.2 mm plates, which were visualised under UV (254 nm) followed by staining with 1% aqueous $KMnO_4$. Melting points were measured on a microscopic Electrothermal IA9100 Digital Melt Point Apparatus and are uncorrected. Infrared spectra (IR) were recorded in solution using a Nicolet iS5 Laboratory FT-IR spectrometer. Absorptions are described as s (strong), m (medium), w (weak) or br (broad) and are reported in cm^{-1}.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIIIHD 400 (400/100 MHz) at 298 K unless stated otherwise. NMR analyses were carried out in deuterated chloroform ($CDCl_3$), supplied by Sigma Aldrich. Chemical shifts were reported in parts per million (ppm) using residual solvent as a reference and assignments were made on the basis of chemical shifts, coupling constants (*J*), DEPT-135, HSQC, COSY, HMBC and comparison with literature values where available. Resonances are depicted as s (singlet), d (doublet), t (triplet), q (quartet), sxt (sextet), sept (septet), m (multiplet), br (broad) and app (apparent). Coupling constants (*J*) given in Hz are rounded to the nearest 0.1 Hz.

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 prepared in MeOH and introduced to the mass spectrometer *via* a Dionex Ultimate 3000 autosampler and uHPLC pump over 5 minutes at a flow rate of 0.6 mL/min using a gradient 20% MeCN (0.2% formic acid) to 100% MeCN (0.2% formic acid). 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 analyzed and 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. Spectra were recorded over a mass range of *m/z* 40-500 at 70 eV and *m/z* values were reported with their respective abundances.

5.2 Experimental procedures for the synthesis of dihydrofuropyridinones

3,4-Dimethoxycyclobut-3-ene-1,2-dione (1.2)



1.1
$C_4H_2O_4$
Mol Wt: 114.06

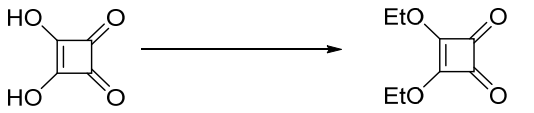
1.2
$C_6H_6O_4$
Mol Wt: 142.11

To a solution of 3,4-dihydroxycyclobut-3-ene-1,2-dione **1.1** (17.9 g, 157 mmol) in methanol (200 mL) was added trimethylorthoformate (35 mL, 320 mmol). The mixture was heated at reflux for 15 h then cooled to RT and concentrated *in vacuo.* The crude product was dissolved in DCM (150 mL) and $NaHCO_3$ (70 mL) was added slowly. The aqueous phase was separated and extracted with DCM (3 x 50 mL) and the combined organic phases washed with water (2 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by recrystallization (ethyl acetate/ cyclohexane) afforded the title compound **1.2** (18.0 g, 126 mmol, 81%) as fine white crystals.

Data is consistent with literature values.[137]

MP (DCM)	48 – 50 °C
FT-IR (ν_{max}/cm^{-1}, DCM)	2964 (w), 1811 (m), 1724 (m), 1588 (s), 1477 (m), 1351 (s), 1083 (s), 1032 (m).
δ_H (400 MHz, $CDCl_3$)	4.35 (6H, s, 2×OC**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	189.1 (2×**C**), 184.4 (2×**C**), 60.9 (2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	143 ([M+H]$^+$, 100%).

3,4-Diethoxycyclobut-3-ene-1,2-dione (5.1)



1.1
$C_4H_2O_4$
Mol Wt: 114.06

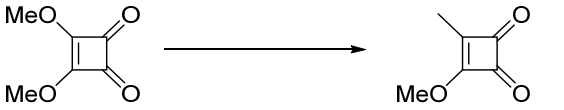
5.1
$C_8H_{10}O_4$
Mol Wt: 170.16

To a solution of 3,4-dihydroxycyclobut-3-ene-1,2-dione **1.1** (4.90 g, 43.0 mmol) in ethanol (55 mL) was added triethylorthoformate (20 mL, 120 mmol). The mixture was heated at reflux for 60 h then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10 – 20% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **5.1** (5.86 g, 34.5 mmol, 79%) as a yellow oil.

Data is consistent with literature values.[138]

FT-IR (ν_{max}/cm^{-1}, DCM)	2985 (w), 1811 (m), 1729 (s), 1593 (s), 1482 (m), 1421 (s), 1381 (m), 1330 (s), 1023 (s).
δ_H (400 MHz, $CDCl_3$)	4.69 (4H, q, *J* = 7.1 Hz, 2×OC**H**$_2$) 1.43 (6H, t, *J* = 7.1 Hz, 2×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	189.1 (2×**C**), 184.1 (2×**C**), 70.4 (2×**C**H$_2$), 15.4 (2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	193 ([M+Na]$^+$, 21%), 171 ([M+H]$^+$, 100%).

3-Methoxy-4-methylcyclobut-3-ene-1,2-dione (2.1)



1.2
$C_6H_6O_4$
Mol Wt: 142.11

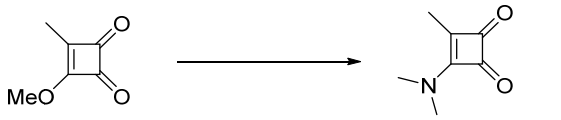
2.1
$C_6H_6O_3$
Mol Wt: 126.1

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.2** (3.53 g, 24.8 mmol) in THF (100 mL) at –78 °C was added a solution methyllithium (1.6 M in Et_2O, 17.1 mL, 27.3 mmol) in THF (100 mL) *via* cannula. After 40 min, TFAA (3.85 mL, 27.3 mmol) was added slowly. After a further 60 min sat. NH_4Cl (30 mL) was added and the reaction mixture warmed to RT and diluted with water (100 mL). The aqueous phase was separated and extracted with DCM (2 x 100 mL) then the combined organic phases were dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound **2.1** (2.49 g, 19.8 mmol, 83%) solid.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, DCM)	2960 (w), 1803 (m), 1787 (m), 1751 (s), 1593 (vs), 1457 (w), 1383 (m), 1343 (s), 1072 (m).
δ_H (400 MHz, $CDCl_3$)	4.38 (3H, s, OC**H**$_3$) 2.18 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	199.1 (**C**), 195.5 (**C**), 193.7 (**C**), 180.2 (**C**), 60.9 (**C**H$_3$), 9.5 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	127 ([M+H]$^+$, 100%).

3-(Dimethylamino)-4-methylcyclobut-3-ene-1,2-dione (2.2)



2.1
$C_6H_6O_3$
Mol W: 126.11

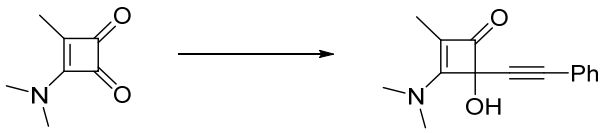
2.2
$C_7H_9NO_2$
Mol Wt: 139.15

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **2.1** (1.80 g, 14.3 mmol) in methanol (100 mL) was added dimethylamine hydrochloride (1.51 g, 18.6 mmol) and triethylamine (2.59 mL, 18.6 mmol). After 45 min at RT, the reaction was concentrated *in vacuo* and purified by column chromatography (60 – 100% ethyl acetate/petroleum ether 40 – 60 °C) to give the title compound **2.2** (1.66 g, 11.9 mmol, 83%) as a white solid.

Data is consistent with literature values.[38]

MP (DCM)	130 – 133 °C
FT-IR (ν_{max}/cm^{-1}, DCM)	2942 (br), 1778 (s), 1726 (m), 1616 (vs), 1411 (m), 1236 (w), 1067 (s).
δ_H (400 MHz, $CDCl_3$)	3.41 (3H, s, NC**H$_3$**) 3.21 (3H, s, NC**H$_3$**) 2.31 (3H, s, C**H$_3$**) ppm.
δ_C (100 MHz, $CDCl_3$)	192.8 (**C**), 191.7 (**C**), 183.4 (**C**), 166.3 (**C**), 39.8 (**C**H$_3$), 39.1 (**C**H$_3$), 10.5 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	162 ([M+Na]$^+$, 100%).

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (1.127)



2.2
$C_7H_9NO_2$
Mol Wt: 139.15

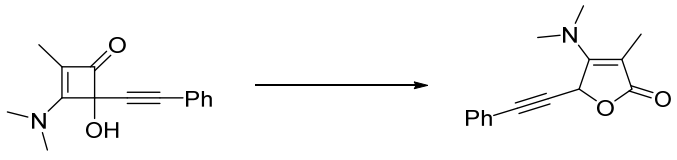
1.127
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

To a solution of phenylacetylene (1.6 mL, 14.6 mmol) in THF (50 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 6.0 mL, 15.0 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.2** (1.58 g, 11.4 mmol) in THF (80 mL) at –78 °C. After 100 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT. The reaction was diluted with water (60 mL) and the aqueous phase separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (15 – 20% acetone/DCM) afforded the title compound **1.127** (2.53 g, 10.5 mmol, 92%) as an off-white solid.

Data is consistent with literature values.[38]

MP (DCM)	163 – 164 °C
FT-IR (ν_{max}/cm^{-1}, DCM)	3237 (br), 1750 (w), 1588 (vs), 1413 (m), 1269 (m), 1139 (m), 1083 (m), 1024 (m), 759 (m).
δ_H (400 MHz, $CDCl_3$)	7.43 – 7.41 (2H, m, 2×Ar**H**) 7.29 – 7.23 (3H, m, 3×Ar**H**) 4.89 (1H, br s, O**H**) 3.29 (3H, s, NC**H$_3$**) 3.17 (3H, s, NC**H$_3$**) 1.77 (3H, s, C**H$_3$**) ppm.
δ_C (100 MHz, $CDCl_3$)	184.5 (**C**), 169.9 (**C**), 131.8 (2×**C**H), 128.5 (**C**H), 128.1 (2×**C**H), 122.3 (**C**), 114.7 (**C**), 88.1 (**C**), 84.9 (**C**), 81.7 (**C**), 40.1 (**C**H_3), 39.5 (**C**H_3), 7.7 (**C**H_3) ppm.
LRMS (ESI $^+$)	264 ([M+Na]$^+$, 9%), 242 ([M+H]$^+$, 100%).

4-(Dimethylamino)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (1.128)



1.127
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

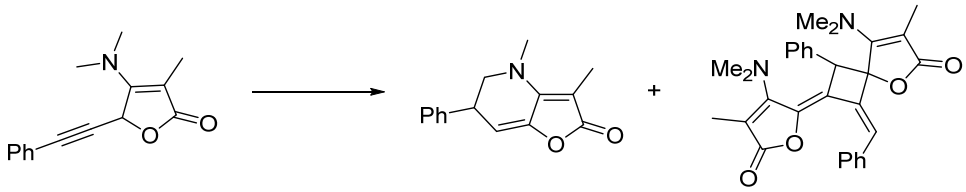
1.128
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

Alkynylcyclobutenone **1.127** (481 mg, 1.99 mmol) in 1,4-dioxane (30 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 60 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (50% ethyl acetate/petroleum ether 40 – 60 °C) to afford the title compound **1.128** (371 mg, 0.481 mmol, 77%) as a yellow oil.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, DCM)	2921 (w), 1740 (m), 1623 (s), 1408 (m), 1373 (w), 1299 (w), 1032 (m).
δ_H (400 MHz, $CDCl_3$)	7.44 – 7.42 (2H, m, 2×Ar**H**) 7.35 – 7.29 (3H, m, 3×Ar**H**) 5.48 (1H, s, C**H**) 3.18 (6H, s, 2×NC**H**$_3$) 1.99 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.2 (**C**), 161.7 (**C**), 131.8 (2×**C**H), 129.1 (**C**H), 128.4 (2×**C**H), 121.5 (**C**), 89.0 (**C**), 87.3 (**C**), 82.0 (**C**), 67.0 (**C**H), 40.9 (2×**C**H$_3$), 9.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	264 ([M+Na]$^+$, 29%), 242 ([M+H]$^+$, 100%).

3,4-Dimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (1.129)



1.128
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

1.129
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

2.3
$C_{30}H_{30}N_2O_4$
Mol Wt: 482.58

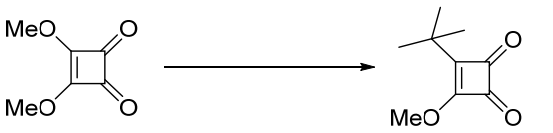
Furanone **1.128** (202 mg, 0.841 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 120 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (10 – 40% diethyl ether/petroleum ether 40 – 60 °C) to afford the title compound **1.129** (62.4 mg, 0.259 mmol, 31%) as a dark yellow oil and a fraction containing dimer **2.3** (506 mg, 1.05 mmol, 40%) as a brown gel.

Alternatively, furanone **1.128** (491 mg, 2.03 mmol) in tetraethylene glycol dimethyl ether (50 mL) was heated at 220 °C. After 70 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (30 – 60% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **1.129** (173mg, 0.717 mmol, 35%) as a yellow oil.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, DCM)	2922 (w), 1744 (s), 1616 (s), 1318 (m), 1293 (m), 1030 (m), 848 (w), 753 (m), 701 (m).
δ_H (400 MHz, $CDCl_3$)	7.39 – 7.25 (5H, m, 5×Ar**H**) 5.64 (1H, d, *J* = 3.9 Hz, C=C**H**) 3.90 (1H, ddd, *J* = 9.1, 6.0, 4.0 Hz, PhC**H**) 3.45 (1H, dd, *J* = 11.9, 6.0 Hz, NC**H**H) 3.19 (1H, dd, *J* = 11.9, 8.6 Hz, NCH**H**) 3.15 (3H, s, NC**H$_3$**) 2.05 (3H, s, C**H$_3$**) ppm.
δ_C (100 MHz, $CDCl_3$)	172.0 (**C**), 151.3 (**C**), 145.5 (**C**), 140.9 (**C**), 128.8 (2×**C**H), 127.7 (2×**C**H), 127.5 (**C**H), 104.1 (**C**H), 90.5 (**C**), 58.0 (**C**H$_2$), 39.8 (**C**H$_3$), 39.1 (**C**H), 8.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	264 ([M+Na]$^+$, 9%), 242 ([M+H]$^+$, 100%).
HRMS (ESI$^+$)	Found: 242.1175. $C_{15}H_{16}NO_2$ [M+H]$^+$ requires 242.1176.

3-(*tert*-Butyl)-4-methoxycyclobut-3-ene-1,2-dione (2.4)



1.2
$C_6H_6O_4$
Mol Wt: 142.11

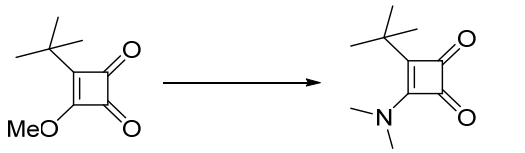
2.4
$C_9H_{12}O_3$
Mol Wt: 168.19

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.2** (22.0 g, 155 mmol) in THF (500 mL) at –78 °C was added ^{t}BuLi (1.6 M in Et_2O, 100 mL, 170 mmol). After 75 min, TFAA (26.1 mL, 186 mmol) was added dropwise and after a further 70 min sat. NH_4Cl (100 mL) was added then warmed to RT. The reaction mixture was diluted with water (100 mL). The aqueous phase was separated and extracted with DCM (400 mL and then 2 x 100 mL), the organic phases were combined, dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (5 – 20% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **2.4** (22.3 g, 132 mmol, 86%) as an orange oil.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, DCM)	2970 (m), 1791 (m), 1761 (s), 1737 (s), 1602 (m), 1587 (s), 1483 (m), 1360 (s), 1276 (w), 1225 (w), 1142 (w), 1052 (w).
δ_H (400 MHz, $CDCl_3$)	4.41 (3H, s, OC**H**$_3$) 1.30 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	197.3 (**C**), 195.0 (**C**), 194.2 (**C**), 190.8 (**C**), 61.1 (**C**H$_3$), 34.4 (**C**), 27.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	169 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (2.5)



2.4
$C_9H_{12}O_3$
Mol Wt: 168.19

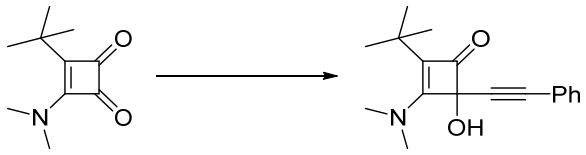
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

A solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **2.4** (637 mg, 3.79 mmol), dimethylamine hydrochloride (401 mg, 4.93 mmol) and triethylamine (1.10 mL, 7.58 mmol) in methanol (50 mL) was stirred at RT for 80 min then concentrated *in vacuo.* Purification by column chromatography (50 – 60% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **2.5** (547 mg, 3.02 mmol, 80%) as an off-white solid.

Data is consistent with literature values.[38]

MP (DCM)	82 – 83 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	2972 (w), 2933 (w), 1772 (m), 1720 (s), 1584 (s), 1462 (w), 1426 (m), 1405 (m), 1366 (m), 1250 (m), 1167 (s), 1113 (s), 1063 (m).
δ_H (400 MHz, $CDCl_3$)	3.37 (6H, br s, N(C**H**$_3$)$_2$) 1.42 (9H, s, C(C**H$_3$**)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	194.4 (**C**), 190.3 (**C**), 181.9 (**C**), 177.5 (**C**), 43.3 (br s, **C**H$_3$), 40.0 (br s, **C**H$_3$), 33.8 (**C**), 30.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	204 ([M+Na]$^+$, 55%), 182 ([M+H]$^+$, 100%).

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-(phenylethynyl)cyclobut-2-en-1-one (1.148)



2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

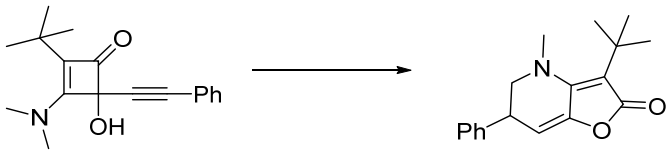
1.148
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

To a solution of phenylacetylene (5 mL, 45.5 mmol) in THF (150 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 17.2 mL, 43.1 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (6.51 g, 35.9 mmol) in THF (250 mL) at –78 °C. After 70 min, sat. NH_4Cl (50 mL) was added, the solution was warmed to RT and diluted with water (100 mL). The aqueous phase was separated and extracted with DCM (300 mL) and then (2 x 100 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 100% ethyl acetate/petroleum ether 40 – 60 °C) to afford the title compound **1.148** (9.76 g, 34.4 mmol, 96%) as a yellow solid.

Data is consistent with literature values.[38]

MP (DCM)	Degraded above 150 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	3239 (w), 2959 (w), 1732 (m), 1572 (s), 1489 (w), 1406 (m), 1364 (w), 1256 (m), 1142 (w), 1079 (w), 758 (m).
δ_H (400 MHz, $CDCl_3$)	7.46 – 7.44 (2H, m, 2×Ar**H**) 7.30 – 7.27 (3H, m, 3×Ar**H**) 4.45 (1H, br s, O**H**) 3.32 (6H, br s, N(C**H**$_3$)$_2$) 1.30 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.7 (**C**), 168.0 (**C**), 131.9 (2×**C**H), 128.5 (**C**H), 128.1 (2×**C**H), 127.1 (**C**), 122.4 (**C**), 88.0 (**C**), 85.4 (**C**), 81.7 (**C**), 42.0 (br s, 2×**C**H$_3$), 31.0 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	306 ([M+Na]$^+$, 30%), 284 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-4-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (1.149)



1.148
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

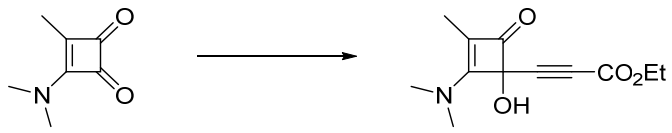
1.149
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

Alkynylcyclobutenone **1.148** (522 mg, 1.84 mmol) in DMSO (100 mL) was heated at 150 °C. After 60 min, the reaction was cooled to RT and diluted with water (100 mL). The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic phases washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 25% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **1.149** (386 mg, 1.36 mmol, 74%) as an orange solid.

Data is consistent with literature values.[38]

MP (DCM)	97 – 98 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	2959 (m), 1749 (s), 1682 (w), 1587 (s), 1453 (w), 1406 (w), 1289 (w), 1066 (w), 1046 (m), 701 (m).
δ_H (400 MHz, $CDCl_3$)	7.38 – 7.24 (5H, m, 5×Ar**H**) 5.70 (1H, d, *J* = 3.7 Hz, C=C**H**) 3.86 (1H, ddd, *J* = 8.8, 5.1, 3.8 Hz, PhC**H**) 3.40 (1H, dd, *J* = 13.0, 5.3 Hz, NC**H**H) 3.20 (1H, dd, *J* = 13.0, 8.8 Hz, NCH**H**) 3.07 (3H, s, NC$\mathbf{H_3}$) 1.41 (9H, s, C(C$\mathbf{H_3}$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.7 (**C**), 152.8 (**C**), 146.4 (**C**), 141.1 (**C**), 128.9 (2×**C**H), 127.8 (2×**C**H), 127.4 (**C**H), 109.4 (**C**), 105.1 (**C**H), 58.8 (**C**H_2), 45.2 (**C**H), 38.0 (**C**H_3), 31.2 (**C**), 30.6 (3×**C**H_3) ppm.
LRMS (ESI $^+$)	284 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 284.1652. $C_{18}H_{22}NO_2$ [M+H]$^+$ requires 284.1645.

Ethyl 3-(2-(dimethylamino)-1-hydroxy-3-methyl-4-oxocyclobut-2-en-1-yl)propiolate (2.6)



2.2
$C_7H_9NO_2$
Mol Wt: 139.15

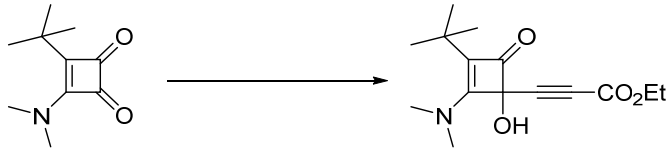
2.6
$C_{12}H_{15}NO_4$
Mol Wt: 237.26

To a solution of ethyl propiolate (1.25 mL, 12.3 mmol) in THF (50 mL) was added ^{n}BuLi (2.5 M in hexanes, 5.0 mL, 12.5 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.2** (1.32 g, 9.46 mmol) in THF (90 mL) at –78 °C. After 120 min sat. NH_4Cl (25 mL) was added and the solution warmed to RT. The reaction was diluted with water (100 mL) and the aqueous phase separated and extracted with DCM (4 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (0 – 30% acetone/DCM) to afford the title compound **2.6** (1.17 g, 9.46 mmol, 52%) as an off-white solid.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3220 (w), 2936 (w), 2231 (w), 1754 (w), 1709 (m), 1587 (s), 1413 (m), 1247 (m), 1022 (w).
δ_H (400 MHz, $CDCl_3$)	5.34 (1H, br s, O**H**) 4.23 (2H, q, *J* = 7.2 Hz, OC**H**$_2$) 3.24 (3H, s, NC**H**$_3$) 3.19 (3H, s, NC**H**$_3$) 1.77 (3H, s, C**H**$_3$) 1.30 (3H, t, *J* = 7.2, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	181.8 (**C**), 168.3 (**C**), 153.2 (**C**), 115.7 (**C**), 82.8 (**C**), 81.1 (**C**), 79.2 (**C**), 62.2 (**C**H$_2$), 40.4 (**C**H$_3$), 39.5 (**C**H$_3$), 14.0 (**C**H$_3$), 7.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	475 ([2M+H]$^+$, 75%), 238 ([M+H]$^+$, 100%).

Ethyl 3-(3-(*tert*-butyl)-2-(dimethylamino)-1-hydroxy-4-oxocyclobut-2-en-1-yl)propiolate (2.10)



2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

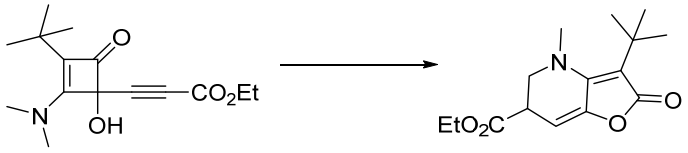
2.10
$C_{15}H_{21}NO_4$
Mol Wt: 279.34

To a solution of ethyl propiolate (0.60 mL, 5.93 mmol) in THF (50 mL) was added ^{n}BuLi (2.5 M in hexanes, 2.37 mL, 5.93 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution cyclobutenedione **2.5** (716 mg, 3.95 mmol) in THF (50 mL) at –78 °C. After 70 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT. The reaction was diluted with water (50 mL) and the aqueous phase separated and extracted with DCM (4 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (1 – 10% acetone/DCM) to afford the title compound **2.10** (949 mg, 3.40 mmol, 86%) as a yellow solid.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2963 (w), 1734 (w), 1712 (m), 1584 (s), 1407 (w), 1366 (w), 1247 (m), 1026 (w).
δ_H (400 MHz, $CDCl_3$)	4.23 (2H, q, *J* = 7.1 Hz, OC**H**$_2$) 5.25 (1H, br s, O**H**) 3.27 (6H, s, N(C**H**$_3$)$_2$) 1.30 (3H, t, *J* = 7.2, C**H**$_3$) 1.28 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	180.3 (**C**), 166.6 (**C**), 153.3 (**C**), 128.0 (**C**), 83.3 (**C**), 80.9 (**C**), 79.0 (**C**), 62.1 (**C**H$_2$), 42.1 (br, 2x**C**H$_3$), 31.1 (**C**), 30.8 (3×**C**H$_3$), 14.0 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	280 ([M+H]$^+$, 100 %).

Ethyl 3-(*tert*-butyl)-4-methyl-2-oxo-2,4,5,6-tetrahydrofuro[3,2-b]pyridine-6-carboxylate (2.11)



2.10
$C_{15}H_{21}NO_4$
Mol Wt: 279.34

2.11
$C_{15}H_{21}NO_4$
Mol Wt: 279.34

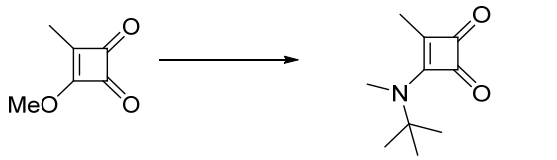
Alkynylcyclobutenone **2.10** (315 mg, 1.13 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 60 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (20 – 50% diethyl ether/petroleum ether 40 – 60 °C) to afford the title compound **2.11** (142 mg, 0.508 mmol, 45%) as an orange oil.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2959 (w), 1731 (s), 1685 (w), 1591 (m), 1457 (w), 1301 (m), 1188 (m), 1068 (w), 1027 (w), 983 (m).
δ_H (400 MHz, $CDCl_3$)	5.70 (1H, d, *J* = 4.2 Hz, C=C**H**) 4.20 (2H, m, OC**H**$_2$) 3.53 – 3.42 (3H, m, C**H** + C**H**$_2$) 3.12 (3H, s, NC**H**$_3$) 1.36 (9H, s, C(C**H**$_3$)$_3$) 1.28 (3H, t, *J* = 7.2 Hz, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	170.9 (**C**), 169.1 (**C**), 152.0 (**C**), 146.0 (**C**), 109.9 (**C**), 99.3 (**C**H), 61.3 (**C**H$_2$), 51.6 (**C**H$_2$), 44.9 (**C**H$_3$), 37.1 (**C**H), 31.0 (**C**), 30.2 (3×**C**H$_3$), 13.9 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	280 ([M+H]$^+$, 100%).

5.3 Experimental procedures to dihydrofuropyridinones with alternative amine groups

3-(*tert*-Butyl(methyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.6)



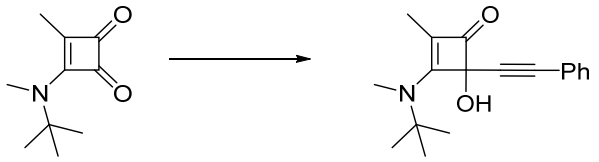
2.1
$C_6H_6O_3$
Mol Wt:126.11

4.6
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

A solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **2.1** (879 mg, 6.97 mmol) and *N*-*tert*-butylmethylamine (1.25 mL, 10.5 mmol) in methanol (100 mL) was stirred at RT for 17 h then concentrated *in vacuo.* Purification by column chromatography (60 – 80% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.6** (857 mg, 4.73 mmol, 68%) as an off-white solid.

MP (Et_2O)	94 – 95 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	2962 (w), 1772 (m), 1726 (m), 1557 (s), 1399 (w), 1172 (w), 1053 (m).
δ_H (400 MHz, $CDCl_3$)	3.31 (3H, br s, NC**H**$_3$) 2.36 (3H, s, C**H**$_3$) 1.48 (9H, s, C(C**H**$_3$)$_3$ ppm.
δ_C (125 MHz, $CDCl_3$)	192.5 (2×**C**), 182.7 (**C**), 168.2 (**C**), 59.4 (**C**H$_3$), 35.4 (**C**), 29.3 (3×**C**H$_3$), 12.1 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	183 ([M+H]$^+$, 100%).

3-(*tert*-Butyl(methyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (4.7)



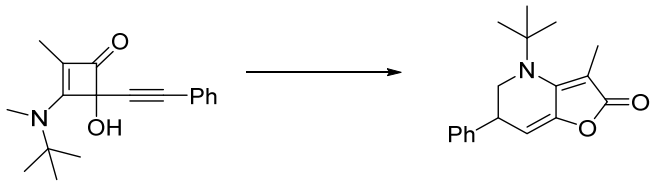
4.6
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.7
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

To a solution of phenylacetylene (0.470 mL, 4.28 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.71 mL, 4.28 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.6** (646 mg, 3.56 mmol) in THF (50 mL) at –78 °C. After 80 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT and diluted with water (40 mL). The aqueous phase separated and extracted with DCM (3 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (80 – 100% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.7** (791 mg, 2.79 mmol, 78%) as a white solid.

MP (Et_2O)	Decomposed after 160 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	3248 (w), 2981 (m), 1734 (m), 1556 (vs), 1394 (m), 1170 (w), 1144 (w), 1080 (w), 758 (w), 693 (w).
δ_H (400 MHz, $CDCl_3$)	7.44 – 7.41 (2H, m, 2×Ar**H**) 7.29 – 7.25 (3H, m, 3×Ar**H**) 4.46 (1H, s, O**H**) 3.34 (3H, s, NC**H$_3$**) 1.86 (3H, s, C**H$_3$**) 1.46 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	185.5 (**C**), 169.5 (**C**), 131.8 (2×**C**H), 128.5 (**C**H), 128.1 (2×**C**H), 122.4 (**C**), 115.6 (**C**), 88.2 (**C**), 85.7 (**C**), 83.7 (**C**), 57.9 (**C**), 35.7 (**C**H$_3$), 29.3 (3×**C**H$_3$), 11.0 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	284 ([M+H]$^+$, 100%

4-(*tert*-Butyl)-3-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.8)



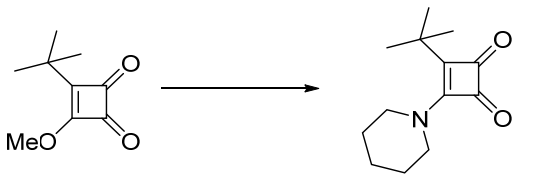
4.7
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

4.8
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

Alkynylcyclobutenone **4.7** (237 mg, 0.835 mmol) in DMSO (50 mL) was heated at 150 °C. After 25 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.8** (18.6 mg, 0.066 mmol, 8%) as a yellow oil.

FT-IR (ν_{max}/cm^{-1}, DCM)	2919 (m), 2850 (w), 1754 (vs), 1684 (w), 1591 (vs), 1453 (w), 1288 (m), 1221 (w), 1032 (w), 756 (w), 701 (w).
δ_H (400 MHz, $CDCl_3$)	7.37 – 7.28 (3H, m, 3×Ar**H**) 7.25 – 7.22 (2H, m, 2×Ar**H**) 5.72 (1H, d, *J* = 4.4 Hz, C=C**H**) 3.70 (1H, m, PhC**H**) 3.64 (1H, dd, *J* = 12.2, 4.8 Hz, C**H**H) 3.38 (1H, dd, *J* = 12.2, 6.7 Hz, CH**H**) 2.10 (3H, s, C**H**$_3$) 1.26 (9H, s, NC(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	172.7 (**C**), 150.6 (**C**), 148.1 (**C**), 140.0 (**C**), 128.6 (2×**C**H), 127.9 (2×**C**H), 127.4 (**C**H), 104.8 (**C**H), 93.2 (**C**), 55.9 (**C**), 51.9 (**C**H$_2$), 39.9 (**C**H), 29.9 (3×**C**H$_3$), 14.0 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	284 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 284.1646. $C_{18}H_{22}NO_2$ [M+H]$^+$ requires 284.1645.

3-(*tert*-Butyl)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione (4.11)



2.4
$C_9H_{12}O_3$
Mol Wt: 168.19

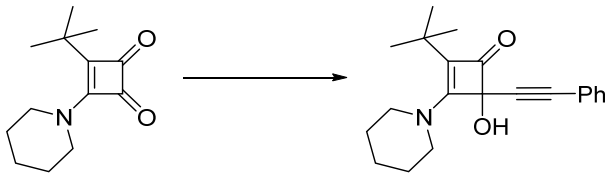
4.11
$C_{13}H_{19}NO_2$
Mol Wt: 221.30

A solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **2.4** (1.98 g, 11.8 mmol) and piperidine (1.20 mL, 11.8 mmol) in methanol (100 mL) was stirred at RT for 80 min then concentrated *in vacuo.* Purification by column chromatography (50 – 100 % ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.11** (1.83 g, 8.27 mmol, 70%) as a yellow solid.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2937 (w), 2863 (w), 1772 (m), 1723 (m), 1581 (s), 1452 (w), 1286 (m), 1192 (m).
δ_H (400 MHz, $CDCl_3$)	3.83 (4H, br m, 2×NC**H**$_2$) 1.74 – 1.72 (6H, br m, 3×C**H**$_2$) 1.40 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	194.8 (**C**), 189.9 (**C**), 179.8 (**C**), 176.4 (**C**), 51.0 (br s, C**H**$_2$), 49.7 (br s, C**H**$_2$), 33.8 (**C**), 29.5 (3×**C**H$_3$), 26.1 (**C**H$_2$), 23.5 (2×C**H**$_2$) ppm.
LRMS (ESI $^+$)	443 ([2M+H]$^+$, 94%), 222 ([M+H]$^+$, 100%).

2-(*tert*-Butyl)-4-hydroxy-4-(phenylethynyl)-3-(piperidin-1-yl)cyclobut-2-en-1-one (4.12)



4.11
$C_{13}H_{19}NO_2$
Mol Wt: 221.30

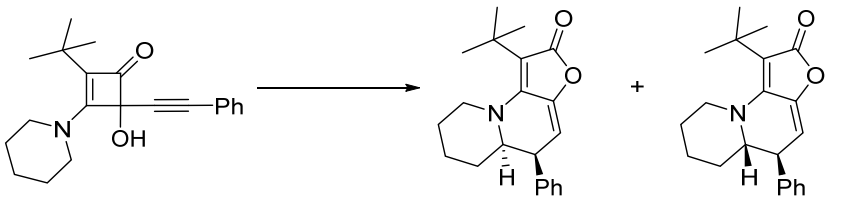
4.12
$C_{21}H_{25}NO_2$
Mol Wt: 323.44

To a solution of phenylacetylene (0.91 mL, 8.25 mmol) in THF (50 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 3.3 mL, 8.25 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.11** (1.52 g, 6.88 mmol) in THF (80 mL) at –78 °C. After 90 min, sat. NH_4Cl (30 mL) was added, the solution was warmed to RT and diluted with water (100 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (20 – 50% ethyl acetate/petroleum ether 40 – 60 °C) to afford the title compound **4.12** (1.68 g, 5.19 mmol, 76%) as a white solid.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3232 (w), 2939 (w), 2862 (w), 1730 (w), 1558 (s), 1443 (w), 1283 (m), 575 (w).
δ_H (400 MHz, $CDCl_3$)	7.45 – 7.43 (2H, m, 2×Ar**H**) 7.31 – 7.26 (3H, m, 3×Ar**H**) 4.35 (1H, br s, O**H**) 3.72 (4H, br s, 2×NC**H**$_2$) 1.78 – 1.76 (6H, m, 3×C**H**$_2$) 1.29 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.1 (**C**), 166.2 (**C**), 131.9 (2×**C**H), 128.4 (**C**H), 128.1 (2×**C**H), 125.6 (**C**), 122.5 (**C**), 87.6 (**C**), 85.6 (**C**), 81.5 (**C**), 51.0 (2×**C**H$_2$), 31.0 (**C**), 30.5 (3×**C**H$_3$), 25.9 (2×C**H**$_2$), 23.7 (C**H**$_2$) ppm.
LRMS (ESI $^+$)	324 ([M+H]$^+$, 100%).

rel-(5*S*,5a*R*) and rel-(5*R*,5a*R*)-1-(*tert*-Butyl)-5-phenyl-5,5a,6,7,8,9- hexahydro-2*H*-furo[2,3-c]quinolizin-2-one (4.13)



4.12
$C_{21}H_{25}NO_2$
Mol Wt: 323.44

4.13a
$C_{21}H_{25}NO_2$
Mol Wt: 323.43

4.13b
$C_{21}H_{25}NO_2$
Mol Wt: 323.43

Alkynylcyclobutenone **4.12** (1.66 g, 5.14 mmol) in DMSO (70 mL) was heated at 150 °C for 40 min, then cooled to RT and diluted with water (70 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases were washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (5 – 20% ethyl acetate/petroleum ether 40 – 60 °C) afforded the major diastereoisomer **4.13a** (1.05 g, 3.24 mmol, 63%) as an orange solid and the minor diastereoisomer **4.13b** (301 mg, 0.932 mmol, 18%) as an orange oil.

Data is consistent with literature values.[38]

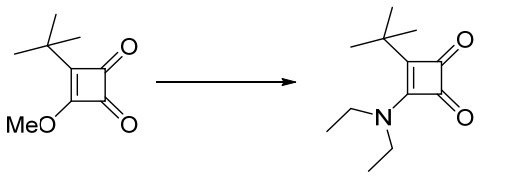
rel-(5*S*,5a*R*)-1-(*tert*-Butyl)-5-phenyl-5,5a,6,7,8,9-hexahydro-2*H*-furo[2,3-c]quinolizin-2-one (4.13a):

MP (DCM)	158 – 159 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	2938 (m), 2864 (w), 1747 (s), 1685 (w), 1572 (m), 991 (m), 732 (m).
δ_H (400 MHz, $CDCl_3$)	7.34 – 7.25 (3H, m, 3×Ar**H**) 7.15 – 7.12 (2H, m, 2×Ar**H**) 5.70 (1H, d, *J* = 5.6 Hz, C=C**H**) 4.07 (1H, m, NC**H**H) 3.68 (1H, app t, *J* = 5.6 Hz, PhC**H**) 3.30 (1H, ddd, *J* = 11.5, 5.4, 2.3 Hz, NC**H**) 2.88 (1H, ddd, *J* = 13.2, 11.7, 2.6 Hz, NCH**H**) 1.75 – 1.44 (6H, m, (3H, m, 3×C**H**$_2$) 1.42 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.7 (**C**), 153.8 (**C**), 145.2 (**C**), 141.6 (**C**), 128.8 (2×**C**H), 128.4 (2×**C**H), 127.3 (**C**H), 111.6 (**C**), 106.5 (**C**H), 63.7 (**C**H), 52.8 (**C**H$_2$), 42.1 (**C**H), 31.5 (**C**), 29.6 (3×**C**H$_3$), 28.3 (**C**H$_2$), 25.1 (**C**H$_2$), 22.1 (**C**H$_2$) ppm.
LRMS (ESI $^+$)	324 ([M+H]$^+$, 100%).

rel-(5*R*,5a*R*)-1-(*tert*-Butyl)-5-phenyl-5,5a,6,7,8,9-hexahydro-2*H*-furo[2,3-c]quinolizin-2-one (4.13b):

FT-IR (ν_{max}/cm^{-1}, DCM)	2936 (m), 2864 (w), 1754 (s), 1688 (w), 1614 (w), 1569 (m), 992 (m), 702 (m).
δ_H (400 MHz, $CDCl_3$)	7.37 – 7.31 (3H, m, 3×Ar**H**) 7.22 – 7.20 (2H, m, 2×Ar**H**) 5.56 (1H, d, *J* = 2.9 Hz, C=C**H**) 3.72 (1H, dd, *J* = 9.9. 2.9 Hz, PhC**H**) 3.64 (1H, m, NC**H**H) 3.14 (1H, ddd, *J* = 10.1, 6.7, 3.8 Hz, NC**H**) 2.93 (1H, m, NCH**H**) 1.75 – 1.46 (6H, m, (3H, m, 3×C**H**$_2$) 1.39 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.6 (**C**), 153.1 (**C**), 144.9 (**C**), 138.6 (**C**), 129.0 (2×**C**H), 128.5 (2×**C**H), 127.3 (**C**H), 106.3 (**C**), 104.9 (**C**H), 62.0 (**C**H), 54.8 (**C**H$_2$), 44.6 (**C**H), 31.0 (**C**), 30.2 (3×**C**H$_3$), 28.2 (**C**H$_2$), 24.5 (**C**H$_2$), 23.8 (**C**H$_2$) ppm.
LRMS (ESI $^+$)	324 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-4-(diethylamino)cyclobut-3-ene-1,2-dione (4.16)



2.4
$C_9H_{12}O_3$
Mol Wt:168.19

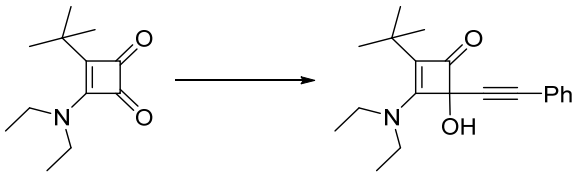
4.16
$C_{12}H_{19}NO_2$
Mol Wt: 209.29

A solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **2.4** (704 mg, 4.19 mmol), diethylamine hydrochloride (919 mg, 8.39 mmol) and triethylamine (1.75 mL, 12.6 mmol) in methanol (50 mL) was stirred at 35 °C for 22.5 h then concentrated *in vacuo.* Purification by column chromatography (30 – 60% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.16** (592 mg, 2.83 mmol, 68%) as a yellow solid.

Data is consistent with literature values.[38]

MP (DCM)	58 – 59 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2973 (m), 1770 (s), 1724 (s), 1572 (s), 1449 (m), 1364 (w), 1300 (m), 1162 (m), 1056 (m).
δ_H (400 MHz, $CDCl_3$)	3.72 (4H, br s, 2×NC**H**$_2$) 1.41 (9H, s, C(C**H**$_3$)$_3$ 1.28 (6H, t, *J* = 7.1 Hz, 2×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	194.5 (**C**), 190.2 (**C**), 180.7 (**C**), 177.0 (**C**), 46.2 (br m, 2×C**H**$_2$), 34.1 (**C**), 29.5 (3×**C**H$_3$), 14.1 (br m, 2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	443 ([2M+H]$^+$, 94%), 210 ([M+H]$^+$, 100%).

2-(*tert*-Butyl)-3-(diethylamino)-4-hydroxy-4-(phenylethynyl)cyclobut-2-en-1-one (4.17)



4.16
$C_{12}H_{19}NO_2$
Mol Wt: 209.29

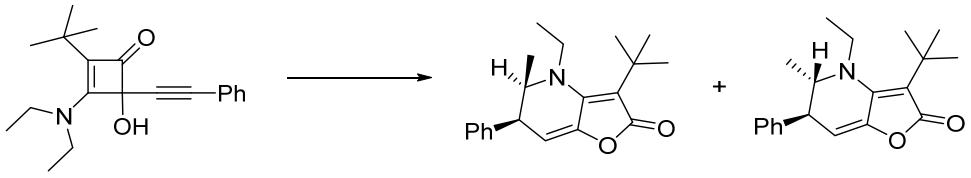
4.17
$C_{20}H_{25}NO_2$
Mol Wt: 311.43

To a solution of phenylacetylene (0.23 mL, 2.11 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 0.84 mL, 2.11 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.16** (368 mg, 1.76 mmol) in THF (60 mL) at –78 °C. After 100 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (30 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 100% ethyl acetate/hexane) afforded the title compound **4.17** (423 mg, 1.36 mmol, 77%) as an off-white solid.

Data is consistent with literature values.[38]

MP (DCM)	Decomposed over 90 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3250 (w), 2973 (w), 1727 (m), 1560 (s), 1298 (m), 1142 (w), 1077 (w), 758 (w).
δ_H (400 MHz, $CDCl_3$)	7.46 – 7.44 (2H, m, 2×Ar**H**) 7.33 – 7.28 (3H, m, 3×Ar**H**) 3.76 (1H, m, NC**H**) 3.63 – 3.55 (3H, m, 3×NC**H**) 1.66 (1H, s, O**H**) 1.34 (6H, t, *J* = 7.1 Hz, 2×C**H**$_3$) 1.31 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.0 (**C**), 167.0 (**C**), 131.8 (2×**C**H), 128.6 (**C**H), 128.2 (2×**C**H), 126.4 (**C**), 122.4 (**C**), 87.7 (**C**), 85.5 (**C**), 81.7 (**C**), 44.2 (2×**C**H$_2$), 31.3 (**C**), 30.5 (3×**C**H$_3$), 13.2 (2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	312 ([M+H]$^+$, 100%).

(5*R*,6*S*)-3-(*tert*-Butyl)-4-ethyl-5-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.18)



4.17
$C_{20}H_{25}NO_2$
Mol Wt: 311.43

4.18a
$C_{20}H_{25}NO_2$
Mol Wt: 311.43

4.18b
$C_{20}H_{25}NO_2$
Mol Wt: 311.43

Alkynylcyclobutenone **4.17** (661 mg, 2.12 mmol) in DMSO (70 mL) was heated at 150 °C for 30 min, then cooled to RT and diluted with water (70 mL). The mixture was extracted with ethyl acetate (3 x 70 mL) then the combined organic phases were washed with water (3 x 210 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (5 – 20% ethyl acetate/petroleum ether 40 – 60 °C) afforded the major diastereoisomer **4.18a** (531 mg, 1.71 mmol, 80%) as a yellow solid and the minor diastereoisomer **4.18b** (101 mg, 0.323 mmol, 15%) as a yellow oil.

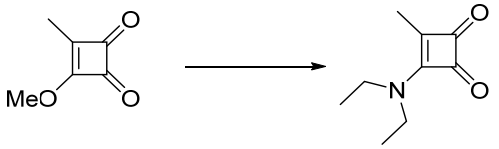
(5*R*,6*S*)-3-(*tert*-Butyl)-4-ethyl-5-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.18a):

MP (DCM)	86 – 87 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2973 (m), 1750 (s), 1685 (m), 1572 (s), 1292 (m), 1234 (w), 989 (m), 947 (m), 767 (m).
δ_H (400 MHz, $CDCl_3$)	7.35 – 7.33 (2H, m, 2×Ar**H**) 7.26 (1H, m, Ar**H**) 7.20 – 7.18 (2H, m, 2×Ar**H**) 5.53 (1H, dd, *J* = 5.9, 0.79 Hz, C=C**H**) 3.47 (1H, br d, *J* = 6.0 Hz, C**H**Ph) 3.41 (2H, m, NC**H**H + C**H**(CH_3)) 3.06 (1H, dq, *J* = 14.2, 7.1 Hz, NCH**H**) 1.41 (3H, d, *J* = 6.9 Hz, C**H**$_3$) 1.38 (9H, s, C(C**H**$_3$)$_3$) 0.71 (3H, t, *J* = 7.1 Hz, NCH_2C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	170.0 (**C**), 149.8 (**C**), 145.9 (**C**), 141.8 (**C**), 128.6 (2×**C**H), 128.0 (2×**C**H), 127.3 (**C**H), 106.5 (**C**), 99.8 (**C**H), 59.2 (**C**H), 49.1 (**C**H_2), 43.7 (**C**H), 30.9 (**C**), 30.7 (3×**C**H_3), 21.3 (**C**H_3), 13.3 (**C**H_3) ppm.
LRMS (ESI $^+$)	312 ($[M+H]^+$, 100%).

(5*S*,6*S*)-3-(*tert*-Butyl)-4-ethyl-5-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.18b):

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2969 (m), 1753 (s), 1681 (w), 1573 (s), 1452 (m), 1288 (m), 1217 (m), 988 (m), 701 (m).
δ_H (400 MHz, $CDCl_3$)	7.38 – 7.34 (2H, m, 2×Ar**H**) 7.31 – 7.28 (1H, m, Ar**H**) 7.23 – 7.21 (2H, m, 2×Ar**H**) 5.63 (1H, dd, *J* = 2.5, 1.0 Hz, C=C**H**) 4.29 (1H, dd, *J* = 5.4, 2.6 Hz, PhC**H**) 3.68 (1H, dq, *J* = 14.1, 7.0 Hz, NC**H**H) 3.44 (1H, m, C**H**) 3.18 (1H, dq, *J* = 14.1, 7.2 Hz, NCH**H**) 1.38 (9H, s, C(C**H**$_3$)$_3$) 1.33 (3H, t, *J* = 7.1 Hz, NCH$_2$C**H**$_3$) 0.89 (3H, d, *J* = 6.9 Hz, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.8 (**C**), 151.2 (**C**), 146.2 (**C**), 140.2 (**C**), 128.7 (2×**C**H), 128.2 (2×**C**H), 127.1 (**C**H), 113.5 (**C**), 102.5 (**C**H), 56.3 (**C**H), 49.4 (**C**H$_2$), 41.6 (**C**H), 31.4 (**C**), 29.8 (3×**C**H$_3$), 14.7 (**C**H$_3$), 14.2 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	312 ([M+H]$^+$, 100%).

3-(Diethylamino)-4-methylcyclobut-3-ene-1,2-dione (4.24)



2.1
$C_6H_6O_3$
Mol Wt: 126.11

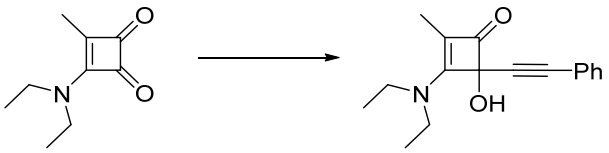
4.24
$C_9H_{13}NO_2$
Mol Wt: 167.21

A solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **2.1** (502 mg, 3.98 mmol), diethylamine hydrochloride (660 mg, 6.02 mmol) and triethylamine (0.83 mL, 5.97 mmol) in methanol (40 mL) was stirred at RT for 80 min then concentrated *in vacuo.* Purification by column chromatography (50 – 80% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.24** (596 mg, 3.57 mmol, 89%) as a pale yellow oil.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2975 (w), 2937 (w), 2880 (w), 1775 (m), 1730 (s), 1584 (vs), 1466 (m), 1441 (s), 1384 (w), 1365 (w), 1297 (m), 1211 (m), 1157 (w), 1062 (m).
δ_H (400 MHz, $CDCl_3$)	3.74 (2H, q, *J* = 7.2 Hz, NC**H**$_2$) 3.43 (2H, q, *J* = 7.3 Hz, NC**H**$_2$) 2.24 (3H, s, C**H**$_3$) 1.25 (6H, dt, *J* = 15.7, 7.2 Hz, NCH$_2$C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	193.0 (**C**), 191.6 (**C**), 182.3 (**C**), 165.9 (**C**), 44.6 (**C**H$_2$), 44.3 (**C**H$_2$), 14.6 (CH$_2$**C**H$_3$), 14.3 (CH$_2$**C**H$_3$), 10.4 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	190 ([M+Na]$^+$, 33%, 168 ([M+H]$^+$, 100%).

3-(Diethylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (4.25)



4.24
$C_9H_{13}NO_2$
Mol Wt: 167.21

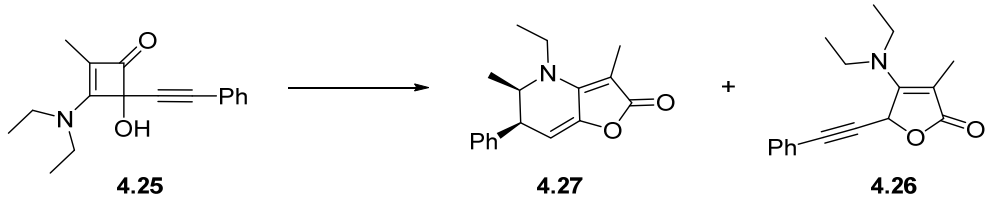
4.25
$C_{17}H_{19}NO_2$
Mol Wt: 269.34

To a solution of phenylacetylene (0.48 mL, 4.37 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.70 mL, 4.25 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.24** (547 mg, 3.27 mmol) in THF (40 mL) at –78 °C. After 120 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (40 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 30% acetone/ DCM) to afford the title compound **4.25** (686 mg, 2.55 mmol, 78%) as a yellow solid.

Data is consistent with literature values.[38]

MP (DCM)	136 – 137 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3234 (w), 2976 (w), 1745 (m), 1569 (vs), 1490 (w), 1444 (m), 1382 (w), 1364 (w), 1297 (m), 1160 (w), 1140 (m), 1080 (m).
δ_H (400 MHz, $CDCl_3$)	7.43 – 7.41 (2H, m, 2×Ar**H**) 7.29 – 7.23 (3H, m, 3×Ar**H**) 4.79 (1H, br s, O**H**) 3.77 (1H, dq, *J* = 14.3, 7.2 Hz, NC**H**H) 3.59 (1H, dq, *J* = 14.2, 7.1 Hz, NCH**H**) 3.48 – 3.38 (2H, m, NC**H**$_2$) 1.76 (3H, s, C**H**$_3$) 1.35 (3H, t, *J* = 7.2 Hz, $CH_2C\mathbf{H}_3$) 1.29 (3H, t, *J* = 7.2 Hz, $CH_2C\mathbf{H}_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.4 (**C**), 169.3 (**C**), 131.8 (2×**C**H), 128.5 (**C**H), 128.1 (2×**C**H), 122.4 (**C**), 113.9 (**C**), 87.9 (**C**), 85.2 (**C**), 81.9 (**C**), 45.4 (**C**H_2), 43.4 (**C**H_2), 14.3 (**C**H_3), 14.0 (**C**H_3), 7.7 (**C**H_3) ppm.
LRMS (ESI $^+$)	270 ([M+H]$^+$, 100%).

(5*R*,6*S*)-4-Ethyl-3,5-dimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.27)



4.25
$C_{17}H_{19}NO_2$
Mol Wt: 269.34

4.27
$C_{17}H_{19}NO_2$
Mol Wt: 269.34

4.26
$C_{17}H_{19}NO_2$
Mol Wt: 269.34

Alkynylcyclobutenone **4.25** (659 mg, 2.45 mmol) in DMSO (50 mL) was heated at 150 °C. After 20 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 50% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.27** (199 mg, 0.737 mmol, 30%, *d.r* 3:1) as an orange gel and byproduct furanone **4.26** (168 mg, 0.624 mmol, 26%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

2972 (w), 2930 (w), 1747 (s), 1693 (w), 1612 (vs), 1492 (w), 1450 (m), 1379 (w), 1353 (m), 1280 (w), 1236 (w), 1218 (w), 1199 (w), 1074 (w), 1034 (m).

δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.38 – 7.15 (5H, m, 5×Ar**H**)
5.51 (1H, d, *J* = 6.0 Hz, C=C**H**)
3.65 (1H, m, NC**H**H + *minor* C**H**CH_3)
3.49 (1H, dd, *J* = 6.0, 1.7 Hz, C**H**Ph)
3.33 (1H, qdd, *J* = 6.6, 1.7, 0.6 Hz, C**H**CH_3)
3.05 (1H, dq, *J* = 14.5, 7.2 Hz, NCH**H**)
1.99 (3H, s, C**H**$_3$)
1.40 (3H, d, *J* = 6.6 Hz, CHC**H**$_3$)
0.93 (3H, t, *J* = 7.2 Hz, CH_2C**H**$_3$)

Signals attributed to the minor diastereoisomer:
7.38 – 7.15 (5H, m, 5×Ar**H**)
5.63 (1H, d, *J* = 3.4 Hz, C=C**H**)
4.05 (1H, dd, *J* = 5.6, 3.5 Hz, C**H**Ph)
3.74 (1H, m, NC**H**H)
3.21 (1H, dq, *J* = 14.5, 7.2 Hz, NCH**H**)
2.02 (3H, s, C**H**$_3$)
1.29 (3H, t, *J* = 7.2 Hz, CH_2C**H**$_3$)
0.91 (3H, d, *J* = 6.6 Hz, CHC**H**$_3$)

δ_C (100 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
172.5 (**C**), 148.6 (**C**), 145.0 (**C**), 141.2 (**C**), 128.7 (2×**C**H), 127.6 (2×**C**H), 127.4 (**C**H), 100.4 (**C**H), 88.0 (**C**), 60.5 (**C**H), 45.3 (**C**H), 43.9 (**C**H_2), 19.8 (**C**H_3), 14.4 (**C**H_3), 8.9 (**C**H_3) ppm.

Signals attributed to the minor diastereoisomer:
172.5 (**C**), 149.7 (**C**), 145.5 (**C**), 138.7 (**C**), 128.6 (3×**C**H), 127.4 (2×**C**H), 102.6 (**C**H), 89.2 (**C**), 57.5 (**C**H), 45.0 (**C**H), 42.9 (**C**H_2), 15.0 (**C**H_3), 13.4 (**C**H_3), 9.0 (**C**H_3) ppm

LRMS (ESI $^+$)

270 ($[M+H]^+$, 100%).

HRMS (ESI $^+$)

Found: 270.1492. $C_{17}H_{20}NO_2$ $[M+H]^+$ requires 270.1489.

4-(Diethylamino)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (4.26):

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

2977 (w), 2932 (w), 1732 (s), 1609 (vs), 1490 (w), 1441 (m), 1380 (w), 1321 (w), 1289 (m), 1211 (w), 1150 (w), 1092 (m), 1072 (m), 1032 (s).

δ_H (400 MHz, $CDCl_3$)

7.46 – 7.43 (2H, m, 2×Ar**H**)
7.36 – 7.30 (3H, m, 3×Ar**H**)
5.51 (1H, s, C**H**)
3.53 (2H, m, NC**H**$_2$)
3.42 (2H, m, NC**H**$_2$)
1.98 (3H, s, C**H**$_3$)
1.26 (6H, t, *J* = 7.1 Hz, 2×C**H**$_3$) ppm.

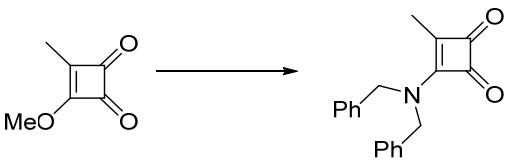
δ_C (100 MHz, $CDCl_3$)

175.4 (**C**), 160.6 (**C**), 131.8 (2×**C**H), 129.1 (**C**H), 128.4 (2×**C**H), 121.5 (**C**), 87.9 (**C**), 87.0 (**C**), 82.6 (**C**), 66.9 (**C**H), 44.1 (2×**C**H_2), 14.2 (2×**C**H_3), 9.2 (**C**H_3) ppm.

LRMS (ESI $^+$)

292 $[M+Na]^+$, 41%, 270 ($[M+H]^+$, 100%).

3-(Dibenzylamino)-4-methylcyclobut-3-ene-1,2-dione (4.29)



2.1
$C_6H_6O_3$
Mol Wt:126.11

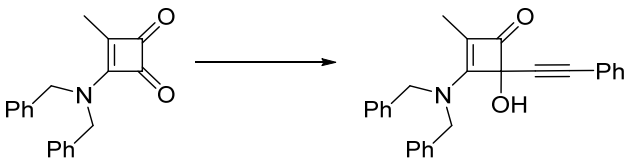
4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

A solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **2.1** (537 mg, 4.26 mmol) and dibenzylamine (1.25 mL, 6.38 mmol) in methanol (100 mL) was stirred at RT for 130 min then concentrated *in vacuo.* Purification by column chromatography (30 – 40% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.29** (1.21g, 4.15 mmol, 98%) as a yellow solid.

Data is consistent with literature values.[38]

MP (CH_3Cl)	90 – 91 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3063 (w), 3029 (w), 1783 (m), 1732 (m), 1596 (vs), 1581 (s), 1496 (w), 1443 (m), 1364 (w), 1254 (w), 1068 (m).
δ_H (400 MHz, $CDCl_3$)	7.45 – 7.34 (6H, m, 6×Ar**H**) 7.26 – 7.24 (2H, m, 2×Ar**H**) 7.17 (2H, br d, *J* = 6.9 Hz, 2×Ar**H**) 4.88 (2H, s, NC**H**$_2$) 4.49 (2H, s, NC**H**$_2$) 2.23 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	192.9 (**C**), 191.8 (**C**), 183.7 (**C**), 167.1 (**C**), 134.7 (**C**), 134.5 (**C**), 129.4 (2×**C**H), 129.1 (2×**C**H), 128.7 (2×**C**H), 128.6 (2×**C**H), 127.0 (2×**C**H), 52.1 (2×**C**H$_2$), 10.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	314 ([M+Na]$^+$, 57%), 292 ([M+H]$^+$, 100%).

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (4.30)



4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

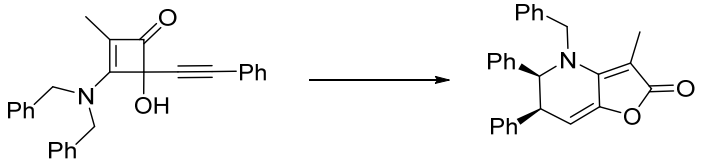
4.30
$C_{27}H_{23}NO_2$
Mol Wt: 393.49

To a solution of phenylacetylene (0.30 mL, 2.76 mmol) in THF (25 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.2 mL, 2.99 mmol) dropwise. After 15 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.29** (672 mg, 2.30 mmol) in THF (65 mL) at –78 °C. After 70 min, sat. NH_4Cl (30 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 50% ethyl acetate/ petroleum ether 40 – 60 °C) afforded the title compound **4.30** (862 mg, 2.19 mmol, 95%) as an off-white solid.

Data is consistent with literature values.[38]

MP (DCM)	162 – 163 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3227 (w), 1748 (m), 1590 (s), 1570 (vs), 1490 (w), 1442 (m), 1175 (w), 1082 (w), 1022 (w), 736 (m), 757 (m), 695 (m).
δ_H (400 MHz, $CDCl_3$)	7.43 – 7.24 (15H, m, 15×Ar**H**) 4.82 (1H, d, *J* = 15.3 Hz, NC**H**H) 4.76 (1H, d, *J* = 15.0 Hz, NCH**H**) 4.50 (1H, d, *J* = 16.1 Hz, NC**H**H) 4.41 (1H, d, *J* = 16.0 Hz, NCH**H**) 3.83 (1H, br s, O**H**) 1.75 (3H, s C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.5 (**C**), 170.4 (**C**), 135.5 (**C**), 135.1 (**C**), 131.9 (2×**C**H), 129.2 (2×**C**H), 128.8 (2×**C**H), 128.7 (2×**C**H), 128.6 (**C**H), 128.1 (3×**C**H), 128.1 (**C**H), 126.9 (2×**C**H), 122.1 (**C**), 115.0 (**C**), 88.9 (**C**), 84.9 (**C**), 82.3 (**C**), 53.8 (**C**H$_2$), 51.0 (**C**H$_2$), 7.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	416 ([M+Na]$^+$, 46%), 394 ([M+H]$^+$, 100%).

rel-(5*S*,6*S*)-4-Benzyl-3-methyl-5,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (1.145)



4.30
$C_{27}H_{23}NO_2$
Mol Wt: 393.49

1.145
$C_{27}H_{23}NO_2$
Mol Wt: 393.49

Alkynylcyclobutenone **4.30** (279 mg, 0.779 mmol) in DMSO (40 mL) was heated at 150 °C. After 20 min, the reaction was cooled to RT and diluted with water (40 mL). The mixture was extracted with ethyl acetate (3 x 40 mL) then the combined organic phases washed were with water (3 x 120 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 30% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **1.145** (134 mg, 0.341 mmol, 48%, *d.r.* 7:1) as a yellow foam.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

3061 (w), 3028 (w), 1755 (s), 1694 (w), 1618 (vs), 1584 (w), 1494 (w), 1451 (w), 1296 (w), 1158 (w).

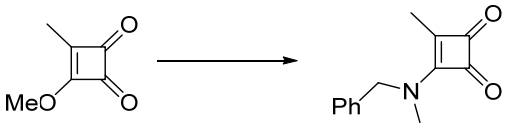
δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.44 – 7.29 (6H, m, 6×Ar**H**)
7.24 – 7.09 (7H, m, 7×Ar**H**)
6.84 (2H, d, *J* = 7.2 Hz, 2×Ar**H**)
5.53 (1H, d, *J* = 5.8 Hz, C=C**H**)
5.02 (1H, d, *J* = 16.0, NC**H**H)
4.31 (1H, d, *J* = 2.3 Hz, NCPh**H**)
3.97 (1H, d, *J* = 16.0 Hz, NCH**H**)
3.88 (1H, dd, *J* = 5.9, 2.5 Hz, PhC**H**)
2.02 (3H, s, C**H**$_3$) ppm.

Signals attributed to the minor diastereoisomer:
7.44 – 7.29 (5H, m, 5×Ar**H**)
7.24 – 7.09 (6H, m, 6×Ar**H**)
6.75 (2H, dd, *J* = 8.0, 1.4 Hz, 2×Ar**H**)
6.64 (2H, d, *J* = 7.2 Hz, 2×Ar**H**)
5.62 (1H, d, *J* = 2.7 Hz, C=C**H**)
4.92 (1H, s, NC**H**H)
4.48 (1H, dd, *J* = 6.8, 2.9 Hz, PhC**H**)
4.40 (1H, d, *J* = 7.0 Hz, NCPh**H**)
3.98 (1H, d, *J* = 16.1 Hz, NCH**H**)
2.00 (3H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the major diastereoisomer:* 172.3 (**C**), 150.4 (**C**), 145.5 (**C**), 141.1 (**C**), 140.2 (**C**), 136.2 (**C**), 129.0 (2×**C**H), 128.7 (2×**C**H), 128.6 (2×**C**H), 128.2 (**C**H), 127.9 (2×**C**H), 127.6 (2×**C**H), 126.9 (2×**C**H), 126.5 (2×**C**H), 100.2 (**C**H), 89.2 (**C**), 67.8 (**C**H), 52.6 (**C**H_2), 47.3 (**C**H), 9.2 (**C**H_3) ppm. *Available signals attributed to the minor diastereoisomer:* 102.6 (**C**H), 66.7 (**C**H), 53.2 (**C**H_2), 45.7 (**C**H) ppm.
LRMS (ESI $^+$)	394 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 394.1806. $C_{27}H_{24}NO_2$ $[M+H]^+$ requires 394.1802. Found: 416.1626. $C_{27}H_{23}NNaO_2$ $[M+Na]^+$ requires 416.1621.

3-(Benzyl(methyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.34)



2.1
$C_6H_6O_3$
Mol Wt:126.11

4.31
$C_{13}H_{13}NO_2$
Mol Wt: 215.25

A solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **2.1** (601 mg, 4.76 mmol) and *N*-benzylmethylamine (0.922 mL, 7.15 mmol) in methanol (50 mL) was stirred at RT for 90 min then concentrated *in vacuo.* The reaction was diluted with EtOAc (50 mL) and washed with 2M HCl (aq) (30 mL) and neutralized with $NaHCO_3$ (60 mL). The aqueous phase was separated and extracted with EtOAc (2×30 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (60 – 80% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.31** (777.3 mg, 3.61 mmol, 76%) as a 3:1 mixture of rotamers as an orange gel and 10% recovered *N*-benzylmethylamine.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)
2924 (w), 1781 (m), 1727 (m), 1596 (vs), 1496 (w), 1447 (m), 1414 (m), 1264 (w), 1060 (m), 740 (m), 701 (m).

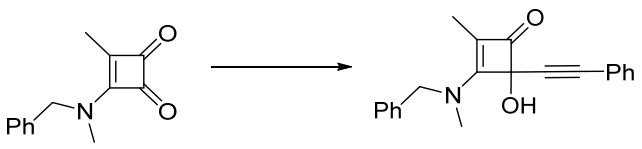
δ_H (400 MHz, $CDCl_3$)
Signals attributed to the major rotamer:
7.44 – 7.34 (3H, m, 3×Ar**H**)
7.27 (1H, m, Ar**H**)
7.20 (1H, m, Ar**H**)
4.89 (2H, s, NC**H**$_2$)
3.10 (3H, s, NC**H**$_3$)
2.31 (3H, s, C**H**$_3$) ppm.

Signals attributed to the minor rotamer:
7.44 – 7.34 (3H, m, 3×Ar**H**)
7.27 (1H, m, Ar**H**)
7.20 (1H, m, Ar**H**)
4.59 (2H, s, NC**H**$_2$)
3.35 (3H, s, NC**H**$_3$)
2.23 (3H, s, C**H**$_3$) ppm

δ_C (100 MHz, $CDCl_3$)
Signals attributed to the major rotamer:
192.9 (**C**), 191.6 (**C**), 183.3 (**C**), 167.0 (**C**), 134.7 (**C**), 129.0 (2×**C**H), 128.5 (**C**H), 128.4 (2×**C**H), 55.2 (**C**H$_2$), 36.8 (**C**H$_3$), 10.6 (**C**H$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the minor rotamer:* 192.7 (**C**), 191.8 (**C**), 183.6 (**C**), 166.5 (**C**), 134.3 (**C**), 129.3 (2×**C**H), 128.6 (**C**H), 126.9 (2×**C**H), 56.3 (**C**H_2), 36.8 (**C**H_3), 10.6 (**C**H_3) ppm.
LRMS (ESI $^+$)	238 ($[M+Na]^+$, 86%), 216 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 216.1022. $C_{13}H_{14}NO_2$ $[M+H]^+$ requires 216.1019. Found: 238.0840. $C_{13}H_{13}NNaO_2$ $[M+Na]^+$ requires 238.0838.

3-(Benzyl(methyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (4.35)



4.34
$C_{13}H_{13}NO_2$
Mol Wt: 215.25

4.35
$C_{21}H_{19}NO_2$
Mol Wt: 317.39

To a solution of phenylacetylene (0.71 mL, 6.48 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 2.6 mL, 6.48 mmol) dropwise. After 30 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.34** (1.16 g, 5.40 mmol) in THF (80 mL) at –78 °C. After 120 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (60 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (60 – 80% ethyl acetate/ petroleum ether 40 – 60 °C) afforded the title compound **4.35** (331 mg, 1.04 mmol, 19%) as a 4:3 mixture of rotamers as a brown gum.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)
3235 (w), 1748 (m), 1590 (vs), 1573 (vs), 1443 (m), 1413 (m), 1267 (m), 1148 (w), 1082 (m), 758 (m), 731 (m), 692 (m).

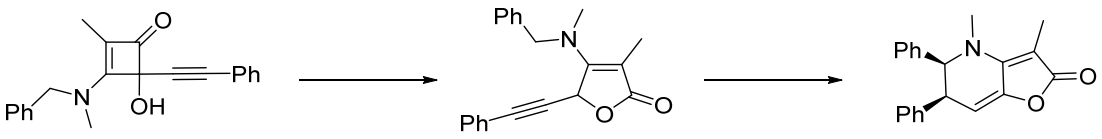
δ_H (400 MHz, $CDCl_3$)
Signals attributed to the major rotamer:
7.46 – 7.22 (10H, m, 10×Ar**H**)
4.88 (1H, d, *J* = 15.2 Hz, NC**H**H)
4.72 (1H, d, *J* = 15.2 Hz, NCH**H**)
4.35 (1H, br s, O**H**)
3.04 (3H, s, NC**H**$_3$)
1.85 (3H, s C**H**$_3$) ppm.

Signals attributed to the minor rotamer:
7.46 – 7.22 (10H, m, 10×Ar**H**)
4.62 (1H, d, *J* = 15.9 Hz, NC**H**H)
4.59 (1H, d, *J* = 16.0 Hz, NCH**H**)
4.35 (1H, br s, O**H**)
3.28 (3H, s, NC**H**$_3$)
1.74 (3H, s C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)
Signals attributed to the major rotamer:
184.2 (**C**), 169.8 (**C**), 135.1 (**C**), 131.9 (4×**C**H), 128.8 (2×**C**H), 128.4 (2×**C**H), 128.1 (2×**C**H), 122.1 (**C**), 115.0 (**C**), 88.8 (**C**), 84.82 (**C**), 82.1 (**C**), 57.0 (**C**H$_2$), 36.2 (**C**H$_3$), 7.9 (**C**H$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the minor rotamer*: 184.4 (**C**), 170.1 (**C**), 135.1 (**C**), 129.2 (2×**C**H), 128.7 (**C**H), 128.6 (**C**H), 128.2 (3×**C**H), 126.9 (3×**C**H), 122.2 (**C**), 115.1 (**C**), 88.6 (**C**), 84.79 (**C**), 82.2 (**C**), 55.7 (**C**H_2), 37.8 (**C**H_3), 7.7 (**C**H_3) ppm.
LRMS (ESI $^+$)	318 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 318.1488. $C_{21}H_{20}NO_2$ $[M+H]^+$ requires 318.1489. Found: 340.1306. $C_{21}H_{19}NNaO_2$ $[M+Na]^+$ requires 340.1308.

3,4-Dimethyl-5,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.37)



4.35
$C_{21}H_{19}NO_2$
Mol Wt: 317.39

4.36
$C_{21}H_{19}NO_2$
Mol Wt: 317.39

4.37
$C_{21}H_{19}NO_2$
Mol Wt: 317.39

Alkynylcyclobutenone **4.35** (322 mg, 1.01 mmol) in DMSO (50 mL) was heated at 150 °C under an argon atmosphere. After 25 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the furanone **4.36** (103 g, 0.326 mmol, 32%) as a brown oil. The intermediate furanone **4.36** in DMSO (20 mL) was heated to 170 °C under an argon atmosphere, cooled to RT after 40 minutes and diluted with water (20 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 20 mL) then the combined organic phases washed were with water (3 x 60 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 60% diethyl ether/petroleum ether 40 – 60 °C) afforded the dihydrofuropyridinone **4.37** (20.5 mg, 0.065 mmol, 20%) as a yellow solid.

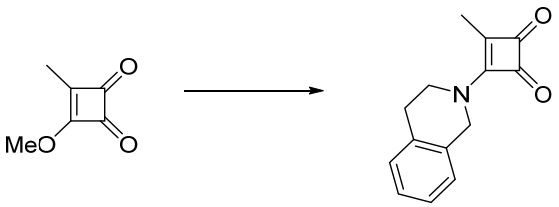
MP (DCM)	Decomposed after 144 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3061 (w), 3027 (w), 2925 (w), 1754 (m), 1619 (vs), 1578 (m), 1492 (w), 1451 (m), 1416 (w), 1315 (w), 1293 (m), 1028 (m).
δ_H (400 MHz, $CDCl_3$)	7.45 – 7.31 (6H, m, 6×Ar**H**) 7.24 – 7.20 (4H, m, 4×Ar**H**) 5.48 (1H, d, *J* = 5.6 Hz, C=C**H**) 4.26 (1H, d, *J* = 3.0 Hz, NC**H**Ph) 3.83 (1H, dd, *J* = 5.6, 3.1 Hz, C**H**Ph) 3.05 (3H, s, NC**H**$_3$) 2.12 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	172.3 (**C**), 150.6 (**C**), 144.8 (**C**), 141.7 (**C**), 140.2 (**C**), 129.0 (2×**C**H), 128.9 (2×**C**H), 128.1 (**C**H), 127.6 (2×**C**H), 127.6 (**C**H), 126.3 (2×**C**H), 100.9 (**C**H), 89.8 (**C**), 71.0 (**C**H), 47.8 (**C**H), 38.3 (**C**H$_3$), 9.1 (**C**H$_3$) ppm.

LRMS (ESI $^+$)	340 $[M+Na]^+$, 32%, 318 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 318.1491. $C_{21}H_{20}NO_2$ $[M+H]^+$ requires 318.1489. Found: 340.1310. $C_{21}H_{19}NNaO_2$ $[M+Na]^+$ requires 340.1308.

4-(Benzyl(methyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (4.36):

δ_H (400 MHz, $CDCl_3$)	7.45 – 7.26 (10H, m, 10×Ar**H**) 5.61 (1H, apparent d, *J* = 0.7 Hz, C**H**) 4.77 (1H, d, *J* = 16.3 Hz, NC**H**H) 4.61 (1H, d, *J* = 16.2 Hz, NCH**H**) 3.16 (3H, s, NC$\mathbf{H}_3$) 1.98 (3H, s, C$\mathbf{H}_3$) ppm.

3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-4-methylcyclobut-3-ene-1,2-dione (4.41)



2.1
$C_6H_6O_3$
Mol Wt: 126.11

4.41
$C_{14}H_{13}NO_2$
Mol Wt: 227.26

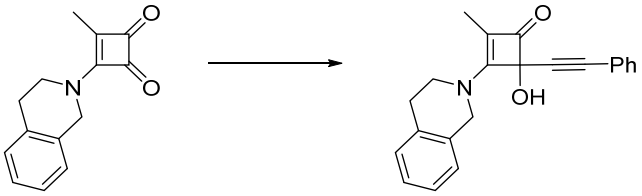
A solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **2.1** (428 mg, 3.39 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.42 mL, 3.39 mmol) in methanol (50 mL) was stirred at RT for 90 min then concentrated *in vacuo.* Purification by column chromatography (50 – 80% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.41** (660 mg, 2.90 mmol, 86%) as a yellow solid.

Data is consistent with literature values. [38]

MP (DCM)	168 – 170 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2918 (w), 1780 (m), 1726 (m), 1596 (vs), 1580 (s), 1497 (w), 1443 (br), 1379 (w), 1284 (w), 1262 (m), 1075 (m), 759 (m).
δ_H (400 MHz, $CDCl_3$)	*Signals attributed to the major rotamer*: 7.27 – 7.24 (4H, m, 4×Ar**H**) 4.80 (2H, s, NC**H**$_2$) 4.22 (2H, t, *J* = 5.9 Hz, NC**H**$_2$CH$_2$) 3.01 (2H, t, *J* = 5.9 Hz, NCH$_2$C**H**$_2$) 2.38 (3H, s, C**H**$_3$) *Signals attributed to the minor rotamer*: 7.21 – 7.11 (4H, m, 4×Ar**H**) 5.12 (2H, s, NC**H**$_2$) 3.87 (2H, t, *J* = 6.2 Hz, NC**H**$_2$CH$_2$) 3.06 (2H, t, *J* = 6.1 Hz, NCH$_2$C**H**$_2$) 2.35 (3H, s, C**H**$_3$)
δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the major rotamer*: 192.9 (**C**), 191.7 (**C**), 182.0 (**C**), 166.8 (**C**), 133.3 (**C**), 130.1 (**C**), 129.3 (**C**H), 127.5 (**C**H), 126.9 (**C**H), 126.9 (**C**H), 49.1 (**C**H$_2$), 44.5 (**C**H$_2$), 29.0 (**C**H$_2$), 11.0 (**C**H$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the minor rotamer*: 192.9 (**C**), 191.6 (**C**), 182.0 (**C**), 166.1 (**C**), 132.6 (**C**), 132.0 (**C**), 128.7 (**C**H), 127.5 (**C**H), 127.1 (**C**H), 126.2 (**C**H), 48.1 (**C**H_2), 46.0 (**C**H_2), 28.5 (**C**H_2), 10.9 (**C**H_3) ppm.
LRMS (ESI $^+$)	250 $[M+Na]^+$, 56%, 228 $[M+H]^+$, 100%).

3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (4.42)



4.41
$C_{14}H_{13}NO_2$
Mol Wt: 227.26

4.42
$C_{22}H_{19}NO_2$
Mol Wt: 329.40

To a solution of phenylacetylene (0.33 mL, 2.99 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.20 mL, 2.99 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.41** (567 mg, 2.49 mmol) in THF (70 mL) at –78 °C. After 100 min, sat. NH_4Cl (20 mL) was added then the solution was warmed to RT and diluted with water (30 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 30% acetone/ DCM) afforded the title compound **4.42** (742 mg, 2.25mmol, 90%) as an off-white foam.

Data is consistent with literature values. [38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$) 3233 (w), 1749 (m), 1590 (s), 11570 (vs), 1490 (w), 1452 (m), 1299 (w), 1265 (m), 1215 (w), 1175 (w), 1084 (w), 905 (m).

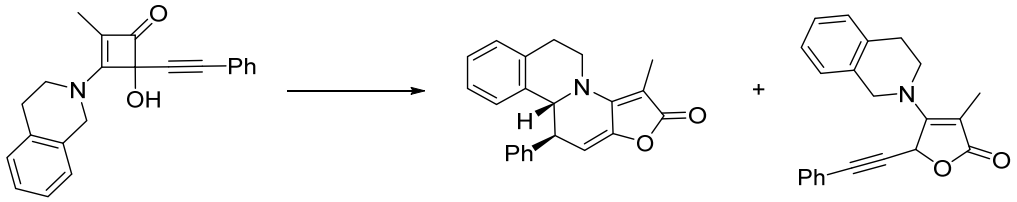
δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major rotamer:
7.45 (2H, dd, *J* = 7.6, 1.7 Hz, 2×Ar**H**)
7.36 – 7.12 (7H, m, 7×Ar**H**)
4.83 (1H, d, *J* = 16.5 Hz, NC**H**H)
4.80 (1H, d, *J* = 16.5 Hz, NCH**H**)
4.32 (1H, s, O**H**)
4.11 – 3.94 (2H, m, NC**H**$_2$CH$_2$)
3.14 – 3.02 (2H, m, NCH$_2$C**H**$_2$)
1.88 (3H, s, C**H**$_3$)

Signals attributed to the minor rotamer:
7.36 – 7.12 (9H, m, 9×Ar**H**)
4.99 (1H, d, *J* = 16.3 Hz, NC**H**H)
4.95 (1H, d, *J* = 16.4 Hz, NCH**H**)
4.24 (1H, s, O**H**)
3.92 – 3.81 (2H, m, NC**H**$_2$CH$_2$)
3.14 – 3.02 (2H, m, NCH$_2$C**H**$_2$)
1.86 (3H, s, C**H**$_3$)

δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the major rotamer*: 184.2 (**C**), 168.4 (**C**), 133.9 (**C**), 131.8 (2×**C**H), 131.2 (**C**), 128.6 (2×**C**H), 128.2 (2×**C**H), 127.2 (**C**H), 126.7 (**C**H), 126.0 (**C**H), 122.2 (**C**), 114.9 (**C**), 88.3 (**C**), 84.8 (**C**), 81.9 (**C**), 49.0 (**C**H_2), 46.1 (**C**H_2), 29.0 (**C**H_2), 8.0 (**C**H_3) ppm. *Signals attributed to the minor rotamer*: 184.3 (**C**), 168.3 (**C**), 133.2 (**C**), 132.5 (**C**), 131.8 (2×**C**H), 129.2 (2×**C**H), 128.1 (**C**H), 127.2 (2×**C**H), 126.9 (**C**H), 126.2 (**C**H), 122.1 (**C**), 114.8 (**C**), 88.7 (**C**), 84.7 (**C**), 82.0 (**C**), 49.2 (**C**H_2), 45.4 (**C**H_2), 28.7 (**C**H_2), 8.0 (**C**H_3) ppm.
LRMS (ESI $^+$)	352 $[M+Na]^+$, 31%, 330 $[M+H]^+$, 100%).

(11*S*)-3-Methyl-11-phenyl-5,6,10b,11-tetrahydro-2H-furo[2',3':5,6]pyrido[2,1-a]isoquinolin-2-one (4.44)



4.42
$C_{22}H_{19}NO_2$
Mol Wt: 329.40

4.44
$C_{22}H_{19}NO_2$
Mol Wt: 329.40

4.43
$C_{22}H_{19}NO_2$
Mol Wt: 329.40

Alkynylcyclobutenone **4.42** (650 mg, 1.97 mmol) in DMSO (60 mL) was heated at 150 °C. After 20 min, the reaction was cooled to RT and diluted with water (60 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) then the combined organic phases washed were with water (3 x 180 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (30 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.44** (119 mg, 0.360 mmol, 18%, *d.r.* 5:4) as a yellow solid and byproduct **4.43** (203 mg, 0.617 mmol, 31%) as a brown foam.

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)
3061 (w), 2925 (w), 2866 (w), 1749 (s), 1692 (w), 1618 (vs), 1492 (w), 1448 (m), 1373 (w), 1335 (w), 1302 (m).

δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.35 – 7.29 (2H, m, 2×Ar**H**)
7.20 – 6.98 (5H, m, 5×Ar**H**)
6.76 (1H, m, Ar**H**)
6.59 (1H, d, *J* = 8.0 Hz, Ar**H**)
5.62 (1H, d, *J* = 4.3 Hz, C=C**H**)
4.71 (1H, d, *J* = 6.7 Hz, NC**H**)
4.21 (1H, ddd, *J* = 12.7, 5.6, 2.6 Hz, NC**H**H)
4.04 (1H, dd, *J* = 6.7, 4.3 Hz, NC**H**Ph)
3.42 (1H, m, NCH**H**)
3.19 (1H, m, C**H**H)
2.83 (1H, dt, *J* = 15.6, 3.0 Hz, CH**H**)
2.06 (3H, s, C**H**$_3$)

Signals attributed to the minor diastereoisomer:
7.35 – 7.29 (2H, m, 2×Ar**H**)
7.20 – 6.98 (6H, m, 6×Ar**H**)
6.86 (1H, d, *J* = 7.6 Hz, Ar**H**)
5.85 (1H, d, *J* = 6.4 Hz, C=C**H**)
5.15 (1H, d, *J* = 4.2 Hz, NC**H**)
4.09 (1H, m, NC**H**H)

δ_H (400 MHz, $CDCl_3$)	3.88 (1H, dd, *J* = 6.2, 4.3 Hz, C**H**Ph) 3.42 (1H, m, NCH**H**) 2.41 (1H, dt, *J* = 15.4, 2.3 Hz, C**H**H) 2.13 (1H, m, CH**H**) 2.10 (3H, s, C**H**$_3$)
δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the major diastereoisomer:* 172.2 (**C**), 151.0 (**C**), 145.1 (**C**), 140.6 (**C**), 135.0 (**C**), 133.0 (**C**), 129.2 (2×**C**H), 128.8 (2×**C**H), 128.2 (**C**H), 127.6 (**C**H), 127.4 (**C**H), 126.5 (**C**H), 125.9 (**C**H), 104.3 (**C**H), 91.8 (**C**), 64.4 (**C**H), 46.2 (**C**H_2), 45.0 (**C**H), 29.5 (**C**H_2), 9.0 (**C**H_3) ppm. *Signals attributed to the minor diastereoisomer:* 172.2 (**C**), 151.8 (**C**), 146.0 (**C**), 135.0 (**C**), 134.8 (**C**), 134.1 (**C**), 129.0 (2×**C**H), 128.7 (2×**C**H), 127.7 (**C**H), 127.3 (**C**H), 126.9 (**C**H), 126.7 (**C**H), 126.6 (**C**H), 105.7 (**C**H), 90.4 (**C**), 61.1 (**C**H), 46.4 (**C**H), 43.7 (**C**H_2), 28.9 (**C**H_2), 9.0 (**C**H_3) ppm.
LRMS (ESI $^+$)	330 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 330.1491. $C_{22}H_{20}NO_2$ $[M+Na]^+$ requires 330.1489.

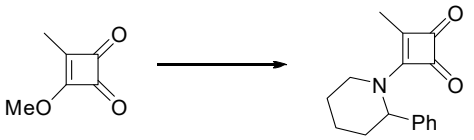
4-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (4.43):

Data is consistent with literature values.[38]

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3060 (w), 3023 (w), 2927 (w), 2241 (w), 1735 (s), 1619 (vs), 1584 (m), 1490 (m), 1442 (m), 1321 (w), 1290 (m), 1271 (m), 1247 (w), 1076 (m), 1033 (m).
δ_H (400 MHz, $CDCl_3$)	7.37 – 7.28 (5H, m, 5×Ar**H**) 7.23 – 7.11 (4H, m, 4×Ar**H**) 5.64 (1H, s, C**H**) 4.86 (1H, d, *J* = 16.0 Hz, NC**H**H) 4.78 (1H, d, *J* = 16.0 Hz, NCH**H**) 3.93 (1H, dt, *J* = 13.2, 5.5 Hz, NC**H**HCH_2) 3.76 (1H, ddd, *J* = 13.0, 8.1, 4.6 Hz, NCH**H**CH_2) 3.07 (1H, m, C**H**H) 2.96 (1H, dt, *J* = 16.1, 5.3 Hz, CH**H**) 2.08 (3H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	175.1 (**C**), 160.5 (**C**), 133.7 (**C**), 132.4 (**C**), 131.8 (2×**C**H), 129.1 (**C**H), 128.9 (**C**H), 128.3 (2×**C**H), 127.1 (**C**H), 126.6 (**C**H), 126.0 (**C**H), 121.3 (**C**), 89.7 (**C**), 87.5 (**C**), 82.1 (**C**), 66.7 (**C**H), 50.0 (**C**H_2), 46.0 (**C**H_2), 28.9 (**C**H_2), 10.3 (**C**H_3) ppm.
LRMS (ESI $^+$)	330 ($[M+H]^+$, 100%).

3-Methyl-4-(2-phenylpiperidin-1-yl)cyclobut-3-ene-1,2-dione (4.47)



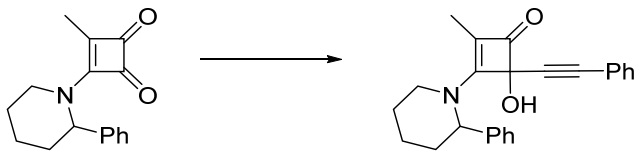
2.1
$C_6H_6O_3$
Mol Wt: 126.11

4.47
$C_{16}H_{17}NO_2$
Mol Wt: 255.32

A solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **2.1** (521 mg, 4.13 mmol) and 2-phenylpiperidine (1.0 mL, 6.30 mmol) in methanol (50 mL) was stirred at RT for 180 min then concentrated *in vacuo.* Purification by column chromatography (30 – 50% ethyl acetate/petroleum ether 40 – 60 °C) gave the title compound **4.47** (1.13 g, 4.42 mmol, quant. with ca. 8% inseparable amine) as an orange oil.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2945 (w), 1779 (m), 1731 (m), 1593 (vs), 1496 (w), 1447 (br), 1280 (w), 1260 (w), 1230 (w), 1204 (w), 1056 (w), 1015 (m).
δ_H (400 MHz, $CDCl_3$)	*Mixture of rotamers ca. 6:5. Complex spectrum, see Appendix B.*
δ_C (100 MHz, $CDCl_3$)	*Signals attributed to the major rotamer:* 193.0 (**C**), 182.9 (**C**), 166.3 (**C**), 137.2 (**C**), 129.3 (2×**C**H), 127.7 (**C**H), 125.8 (2×**C**H), 58.4 (**C**H), 43.8 (**C**H_2), 28.3 (**C**H_2), 25.5 (**C**H_2), 18.4 (**C**H_2), 10.6 (**C**H_3) ppm, with one C coincident or obscured. *Signals attributed to the minor rotamer:* 191.7 (**C**), 182.6 (**C**), 165.8 (**C**), 137.4 (**C**), 129.0 (2×**C**H), 127.4 (**C**H), 126.3 (2×**C**H), 56.6 (**C**H), 44.8 (**C**H_2), 27.8 (**C**H_2), 25.8 (**C**H_2), 18.6 (**C**H_2), 11.0 (**C**H_3) ppm, with one C coincident or obscured.
LRMS (ESI $^+$)	278 $[M+Na]^+$, 55%, 256 $[M+H]^+$, 100%).

4-Hydroxy-2-methyl-4-(phenylethynyl)-3-(2-phenylpiperidin-1-yl)cyclobut-2-en-1-one (4.48)



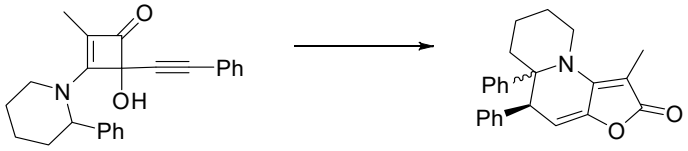
4.47
$C_{16}H_{17}NO_2$
Mol Wt: 255.32

4.48
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

To a solution of phenylacetylene (0.57 mL, 5.15 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 2.10 mL, 5.25 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.47** (1.01 g, 3.96 mmol) in THF (60 mL) at –78 °C. After 70 min, sat. NH_4Cl solution (20 mL) was added, the solution was warmed to RT and diluted with water (60 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 60% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.48** (543 mg, 1.52 mmol, 38%) as a brown foam.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3241 (w), 2943 (w), 2864 (w), 1746 (m), 1586 (s), 1568 (vs), 1490 (w), 1448 (m), 1281 (m), 1156 (w), 1084 (w), 1015 (m).
δ_H (400 MHz, $CDCl_3$)	*Mixture of rotamers and diastereoisomers. Complex spectrum, see Appendix B.*
δ_C (100 MHz, $CDCl_3$)	*Complex spectrum, see Appendix B*
LRMS (ESI $^+$)	380 $[M+Na]^+$, 16%, 358 $[M+H]^+$, 100%).

(5*S*)-1-Methyl-5,5a-diphenyl-5,5a,6,7,8,9-hexahydro-2H-furo[2,3-c]quinolizin-2-one (4.49)



4.48
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

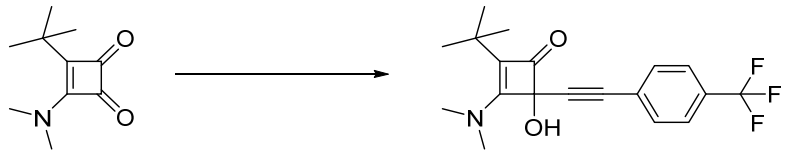
4.49
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

Alkynylcyclobutenone **4.48** (466 mg, 1.30 mmol) in DMSO (60 mL) was heated at 150 °C for 20 min then cooled to RT and diluted with water (60 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) then the combined organic phases were washed with water (3 x 180 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 50% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.49** (69.6 mg, 0.195 mmol, 15%) as a yellow solid.

MP (DCM)	Decomposed after 146 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2935 (w), 2865 (w), 1754 (s), 1698 (m), 1600 (vs), 1493 (w), 1445 (m), 1372 (w), 1329 (m), 1288 (m), 1239 (m), 1193 (w), 1137 (w), 1074 (w), 1041 (m).
δ_H (400 MHz, $CDCl_3$)	7.39 – 7.35 (2H, m, 2×Ar**H**) 7.33 – 7.28 (3H, m, 3×Ar**H**) 7.26 – 7.24 (3H, m, 3×Ar**H**) 6.97 (2H, m, 2×Ar**H**) 5.45 (1H, d, *J* = 5.0 Hz, C=C**H**) 4.07 (1H, m, NC**H**H) 3.87 (1H, d, *J* = 4.9 Hz, C**H**Ph) 3.34 (1H, m, NCH**H**) 2.17 (3H, s, C**H**$_3$) 1.96 (1H, m, *J* = 13.6 Hz, C**H**H) 1.67 (1H, td, *J* = 13.7, 3.4 Hz, CH**H**) 1.53 – 1.48 (4H, m, 2×C**H**$_2$)
δ_C (100 MHz, $CDCl_3$)	172.5 (**C**), 152.0 (**C**), 144.2 (**C**), 142.5 (**C**), 138.2 (**C**), 129.9 (2×**C**H), 128.6 (2×**C**H), 128.2 (2×**C**H), 127.6 (**C**H), 127.3 (2×**C**H), 127.2 (**C**H), 103.6 (**C**H), 91.0 (**C**), 67.8 (**C**), 53.7 (**C**H), 45.7 (**C**H$_2$), 31.6 (**C**H$_2$), 24.1 (**C**H$_2$), 19.4 (**C**H$_2$), 10.3 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	380 $[M+Na]^+$, 21%, 358 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 358.1798. $C_{24}H_{24}NO_2$ $[M+H]^+$ requires 358.1802.

5.4 Experimental procedures to dihydrofuropyridinones with substituted phenyl groups

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-((4-(trifluoromethyl)phenyl)ethynyl)cyclobut-2-en-1-one (4.53)



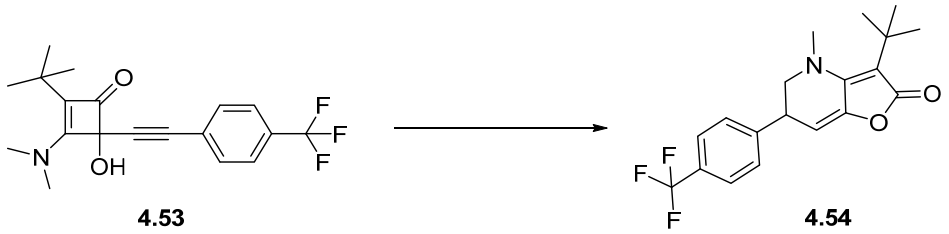
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.53
$C_{19}H_{20}F_3NO_2$
Mol Wt: 351.37

To a solution of 4-(trifluoromethyl)phenylacetylene (0.6 mL, 3.71 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.5 mL, 3.71 mmol) dropwise. After 15 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (560 mg, 3.09 mmol) in THF (60 mL) at –78 °C. After 80 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (25 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (50 – 70% ethyl acetate/petroleum ether 40 – 60 °C) to afford the title compound **4.53** (992 mg, 2.82 mmol, 91%) as a white solid.

MP (DCM)	Decomposed after 150 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	3235 (w), 2962 (w), 1733 (w), 1577 (s), 1407 (m) 1322 (s), 1167 (m), 1126 (m), 1106 (s), 1063 (m), 844 (w).
δ_H (400 MHz, $CDCl_3$)	7.55 – 7.50 (4H, m, 4×Ar**H**) 4.89 (1H, s, O**H**) 3.33 (6H, br s, N(C**H**$_3$)$_2$) 1.31 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	183.0 (**C**), 168.1 (**C**), 132.0 (2×**C**H), 130.1 (**C**, q, J_{C-F} = 32.8 Hz), 127.0 (**C**), 126.3 (**C**), 125.0 (2×**C**H, q, J = 3.7 Hz), 88.3 (**C**), 123.8 (**C**F$_3$, q, J_{C-F} = 272 Hz), 88.3 (**C**), 86.4 (**C**), 81.3 (**C**), 42.0 (br s, 2×**C**H$_3$), 31.0 (**C**), 30.9 (3×**C**H$_3$).
$\delta_{F\{1H\}}$ (376 MHz, $CDCl_3$)	-63.1 (s, CF_3) ppm
LRMS (ESI $^+$)	352 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 352.1525. $C_{19}H_{20}F_3NO_2$ [M+H]$^+$ requires 352.1519.

3-(*tert*-Butyl)-4-methyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.54)



4.53
$C_{19}H_{20}F_3NO_2$
Mol Wt: 351.37

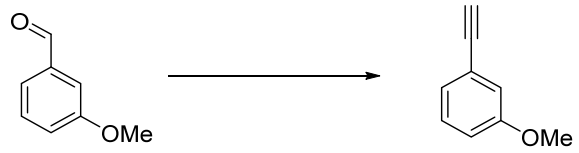
4.54
$C_{19}H_{20}F_3NO_2$
Mol Wt: 351.37

Alkynylcyclobutenone **4.53** (955 mg, 2.72 mmol) in DMSO (100 mL) was heated at 150 °C. After 25 min, the reaction was cooled to RT and diluted with water (100 mL). The mixture was extracted with ethyl acetate (3 x 100 mL) then the combined organic phases were washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 50% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.54** (834 mg, 2.37 mmol, 87%) as a yellow solid.

Data is consistent with literature values.[38]

MP (DCM)	94 – 95 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	2960 (w), 1750 (m), 1682 (w), 1588 (m), 1324 (s), 1124 (m), 1067 (m), 838 (w).
δ_H (400 MHz, $CDCl_3$)	7.62 (2H, d, *J* = 8.1 Hz, 2×Ar**H**) 7.37 (2H, d, *J* = 8.2 Hz, 2×Ar**H**) 5.66 (1H, d, *J* = 3.4 Hz, C=C**H**) 3.93 (1H, ddd, *J* = 8.4, 5.0, 3.6 Hz, PhC**H**) 3.43 (1H, dd, *J* = 13.0, 5.2 Hz, NC**H**H) 3.20 (1H, dd, *J* = 13.1, 8.4 Hz, NCH**H**) 3.07 (3H, s, NC**H**$_3$) 1.40 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.4 (**C**), 152.4 (**C**), 146.8 (**C**), 145.2 (**C**), 140.0 (**C**H), 133.4 (**C**H), 129.8 (**C**, q, J_{C-F} = 32.8 Hz), 125.8 (2×**C**H, q, *J* = 4.2 Hz), 124.0 (**C**F$_3$, q, J_{C-F} = 272 Hz), 110.2 (**C**), 103.9 (**C**H), 58.4 (**C**H$_2$), 45.2 (**C**H$_3$), 37.8 (**C**H), 31.3 (**C**), 30.5 (3×**C**H$_3$).
LRMS (ESI $^+$)	352 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 352.1519. $C_{19}H_{20}F_3NO_2$ [M+H]$^+$ requires 352.1519

1-Ethynyl-3-methoxybenzene (4.68)



4.67
$C_8H_8O_2$
Mol Wt: 136.15

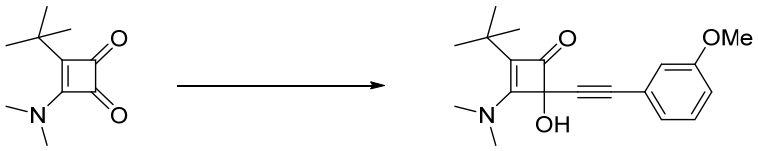
4.68
C_9H_8O
Mol Wt: 132.16

Following a literature procedure,[136] to a solution of di*iso*propylamine (0.74 mL, 5.25 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 2.0 mL, 4.85 mmol) dropwise. After 10 min, the reaction was cooled to –78 °C and trimethylsilyldiazomethane (2.0 M in diethyl ether, 2.4 mL, 4.85 mmol) was added dropwise. After 30 min a solution of *meta*-anisaldehyde **4.67** (0.49 mL, 4.04 mmol) in THF (20 mL) was added dropwise. The reaction was allowed to warm to RT and after 16 h water (20 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with water (3 x 30 mL) and brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 20% diethyl ether/ petroleum ether 40 – 60 °C) afforded the title compound **4.68** (399 mg, 3.02 mmol, 75%) as a colourless oil.

Data is consistent with literature values. [139]

δ_H (400 MHz, $CDCl_3$)	7.31 (1H, m, Ar**H**) 7.17 (1H, dt, *J* = 7.6, 1.2 Hz, Ar**H**) 7.10 (1H, dd, *J* = 2.6, 1.4 Hz, Ar**H**) 6.98 (1H, ddd, *J* = 8.3, 2.6, 0.9 Hz, Ar**H**) 3.90 (3H, s, OC**H**$_3$) 3.14 (1H, s, C**H**) ppm.
δ_C (100 MHz, $CDCl_3$)	159.3 (**C**), 129.4 (**C**H), 124.6 (**C**H), 123.1 (**C**), 117.0 (**C**H), 115.4 (**C**H), 83.6 (**C**), 76.9 (**C**H), 55.3 (**C**H$_3$) ppm.

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-((3-methoxyphenyl)ethynylcyclobut-2-en-1-one (4.69)



2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

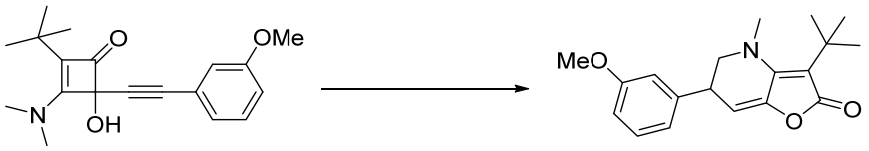
4.69
$C_{19}H_{23}NO_3$
Mol Wt: 313.40

To a solution of 1-ethynyl-3-methoxybenzene **4.68** (297 mg, 2.25 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 0.9 mL, 2.25 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (340 mg, 1.87 mmol) in THF (35 mL) at –78 °C. After 65 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (3 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (60 – 70% ethyl acetate/petroleum ether 40 – 60 °C) to afford the title compound **4.69** (492 mg, 1.57 mmol, 84%) as a pale yellow solid.

Data is consistent with literature values.[38]

MP (Et_2O)	Decomposed after 145 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	3236 (w), 2959 (w), 1732 (w), 1572 (vs), 1406 (m), 1364 (w), 1257 (w), 1207 (w), 1140 (w), 1042 (w).
δ_H (400 MHz, $CDCl_3$)	7.18 (1H, m, Ar**H**) 7.04 (1H, dt, *J* = 7.6, 1.2 Hz, Ar**H**) 6.98 (1H, dd, *J* = 2.5, 1.4 Hz, Ar**H**) 6.86 (1H, ddd, *J* = 8.3, 2.6. 1.0 Hz, Ar**H**) 4.40 (1H, br s, O**H**) 3.78 (3H, s, OC**H**$_3$) 3.32 (6H, s, N(C**H**$_3$)$_2$) 1.30 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.6 (**C**), 168.0 (**C**), 159.2 (**C**), 129.2 (**C**H), 127.2 (**C**), 124.4 (**C**H), 123.4 (**C**), 116.6 (**C**H), 115.3 (**C**H), 87.9 (**C**), 85.2 (**C**), 81.7 (**C**), 55.3 (**C**H$_3$), 42.1 (br s, 2×**C**H$_3$), 31.0 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	314 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-6-(3-methoxyphenyl)-4-methyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.70)



4.69
$C_{19}H_{23}NO_3$
Mol Wt: 313.40

4.70
$C_{19}H_{23}NO_3$
Mol Wt: 313.40

Alkynylcyclobutenone **4.69** (365 mg, 1.17 mmol) in DMSO (50 mL) was heated at 150 °C. After 25 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases were washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 30% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.70** (239 mg, 0.763 mmol, 65%) as a dark yellow gel.

FT-IR (ν_{max}/cm^{-1}, DCM)	2957 (w), 2916 (m), 2949 (w), 1749 (s), 1681 (w), 1585 (vs), 1457 (w), 1291 (m), 1049 (w), 983 (m).
δ_H (400 MHz, $CDCl_3$)	6.85 – 6.82 (2H, m, 2×Ar**H**) 6.78 – 6.77 (2H, m, 2×Ar**H**) 5.69 (1H, d, *J* = 3.3 Hz, C=C**H**) 3.84 (1H, m, PhC**H**) 3.81 (3H, s, OC**H**$_3$) 3.39 (1H, dd, *J* = 13.0, 5.3 Hz, C**H**H) 3.21 (1H, dd, *J* = 13.0, 8.8 Hz, CH**H**) 3.07 (3H, s, NC**H**$_3$) 1.40 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.6 (**C**), 160.0 (**C**), 152.8 (**C**), 146.3 (**C**), 142.7 (**C**), 130.0 (**C**H), 120.1 (**C**H), 113.6 (**C**H), 112.6 (**C**H), 109.5 (**C**), 105.0 (**C**H), 58.7 (**C**H$_2$), 55.2 (**C**H$_3$), 45.2 (**C**H$_3$), 38.0 (**C**H), 31.2 (**C**), 30.6 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	314 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 314.1753. $C_{19}H_{24}NO_3$ [M+H]$^+$ requires 314.1751.

1-Ethynyl-3,5-dimethoxybenzene (4.73)

4.72
$C_9H_{10}O_3$
Mol Wt: 166.18

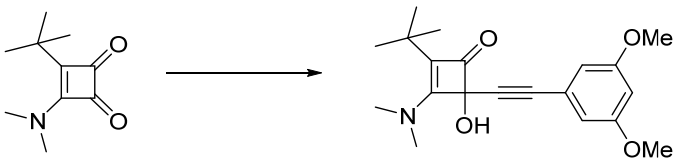
4.73
$C_{10}H_{10}O_2$
Mol Wt: 162.19

Following a literature procedure,[136] to a solution of di*iso*propylamine (0.60 mL, 4.25 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 1.6 mL, 4.00 mmol) dropwise. After 10 min, the reaction was cooled to –78 °C and trimethylsilyldiazomethane (2.0 M in diethyl ether, 2.0 mL, 4.00 mmol) was added dropwise. After 30 min a solution of 3,5-dimethoxybenzaldehyde **4.72** (524 mg, 3.15 mmol) in THF (20 mL) was added *via* cannula. The reaction was allowed to warm to RT and after 16 h water (20 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with water (3 x 30 mL) and then brine (40 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 20% diethyl ether/ petroleum ether 40 – 60 °C) afforded the title compound **4.73** (326 mg, 2.01 mmol, 64%) as a colourless oil.

Data is consistent with literature values.[140]

δ_H (400 MHz, $CDCl_3$)	6.66 (2H, d, *J* = 2.3 Hz, 2×Ar**H**) 6.48 (1H, t, *J* = 2.3 Hz, Ar**H**) 3.79 (6H, s, 2×OC**H**$_3$) 3.06 (1H, s, C**H**) ppm.
δ_C (100 MHz, $CDCl_3$)	160.5 (2×**C**), 123.3 (**C**), 109.9 (2×**C**H), 102.2 (**C**H), 83.6 (**C**), 76.7 (**C**H), 55.3 (2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	163 ([M+H]$^+$, 100%).

2-(t*ert*-Butyl)-4-((3,5-dimethoxyphenyl)ethynyl)-3-(dimethylamino)-4-hydroxycyclobut-2-en-1-one (4.74)



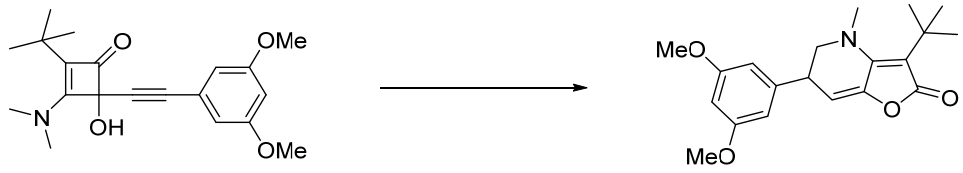
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.74
$C_{20}H_{25}NO_4$
Mol Wt: 343.42

To a solution of 1-ethynyl-3,5-dimethoxybenzene **4.73** (438 mg, 2.75 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.20 mL, 3.00 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (415 mg, 2.29 mmol) in THF (50 mL) at –78 °C. After 105 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT and diluted with water (60 mL). The aqueous phase was separated and extracted with DCM (3 x 60 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.74** (652 mg, 1.82 mmol, 80%) as an off-white solid.

MP (DCM)	Decomposed after 140 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3227 (w), 2961 (w), 1732 (w), 1580 (vs), 1457 (w), 1420 (w), 1406 (w), 1364 (w), 1256 (w), 1205 (m), 1156 (m).
δ_H (400 MHz, $CDCl_3$)	6.61 (2H, d, *J* = 2.3 Hz, 2×Ar**H**) 6.44 (1H, t, *J* = 2.3 Hz, Ar**H**) 3.77 (6H, s, 2×OC**H**$_3$) 3.32 (6H, s, 2×NC**H**$_3$) 1.31 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.2 (**C**), 167.6 (**C**), 160.4 (2×**C**), 127.5 (**C**), 123.5 (**C**), 109.6 (2×**C**H), 102.2 (**C**H), 88.1 (**C**), 84.7 (**C**), 81.8 (**C**), 55.4 (2×**C**H$_3$), 42.1 (br s, 2×**C**H$_3$), 31.1 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	344 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-6-(3,5-dimethoxyphenyl)-4-methyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.75)



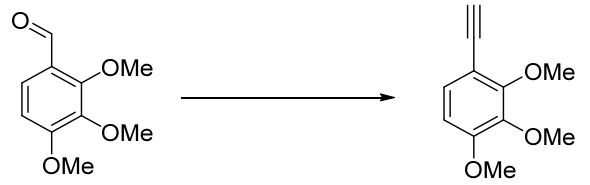
4.74
$C_{20}H_{25}NO_4$
Mol Wt: 343.42

4.75
$C_{20}H_{25}NO_4$
Mol Wt: 343.42

Alkynylcyclobutenone **4.74** (125 mg, 0.363 mmol) in DMSO (50 mL) was heated at 150 °C. After 25 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases were washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 30% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.75** (94.7 mg, 0.276 mmol, 76%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, DCM)	2956 (w), 1747 (s), 1682 (w), 1594 (vs), 1459 (m), 1429 (w), 1407 (w), 1334 (w), 1294 (w), 1203 (m), 1155 (s), 1066 (m).
δ_H (400 MHz, $CDCl_3$)	6.38 (3H, s, 3×Ar**H**) 5.66 (1H, d, *J* = 3.7 Hz, C=C**H**) 3.81– 3.76 (1H, m, obscured, PhC**H**) 3.78 (6H, s, 2×OC**H**$_3$) 3.37 (1H, dd, *J* = 13.0, 5.3 Hz, C**H**H) 3.21 (1H, dd, *J* = 13.0, 8.8 Hz, CH**H**) 3.07 (3H, s, NC**H**$_3$) 1.39 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.6 (**C**), 161.1 (2×**C**), 152.7 (**C**), 146.2 (**C**), 143.5 (**C**), 109.3 (**C**), 105.8 (2×**C**H), 104.9 (**C**H), 99.0 (**C**H), 58.5 (**C**H$_2$), 55.3 (2×**C**H$_3$), 45.1 (**C**H$_3$), 38.2 (**C**H), 31.1 (**C**), 30.5 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	344 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 366.1675. $C_{20}H_{25}NNaO_4$ [M+Na]$^+$ requires 366.1676.

Ethynyl-2,3,4-trimethoxybenzene (4.78)



4.77
$C_{10}H_{12}O_4$
Mol Wt: 196.20

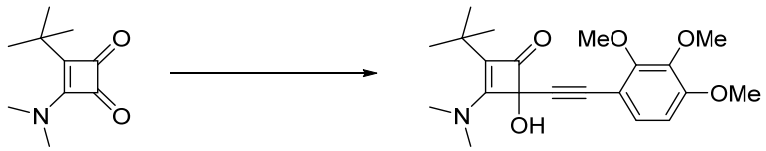
4.78
$C_{11}H_{12}O_3$
Mol Wt: 192.21

Following a literature procedure,[136] to a solution of di*iso*propylamine (1.07 mL, 7.56 mmol) in THF (60 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 2.79 mL, 6.98 mmol) dropwise. After 25 min, the reaction was cooled to –78 °C and trimethylsilyldiazomethane (2.0 M in diethyl ether, 3.49 mL, 6.98 mmol) was added dropwise. After 30 min a solution of 2,3,4-trimethoxybenzaldehyde **4.77** (1.14 g, 5.82 mmol) in THF (40 mL) was added *via* cannula. The reaction was allowed to warm to RT and after 18 h water (40 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with water (2 x 60 mL) and brine (60 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 30% diethyl ether/ petroleum ether 40 – 60 °C) afforded the title compound **4.78** (892 mg, 4.64 mmol, 80%) as an off-white gel.

Data is consistent with literature values.[141]

δ_H (400 MHz, $CDCl_3$)	7.17 (1H, d *J* = 8.7 Hz, Ar**H**) 7.13 (1H, d, *J* = 8.7 Hz, Ar**H**) 3.99 (3H, s, OC**H**$_3$) 3.87 (6H, s, 2×OC**H**$_3$) 3.20 (1H, s, C**H**) ppm.
δ_C (100 MHz, $CDCl_3$)	155.4 (**C**), 154.7 (**C**), 142.1 (**C**), 128.6 (**C**H), 109.2 (**C**), 107.3 (**C**H), 79.8 (**C**), 79.7 (**C**H), 61.3 (**C**H$_3$), 61.0 (**C**H$_3$), 56.0 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	193 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 193.0857. $C_{11}H_{13}O_3$ [M+H]$^+$, requires 193.0859.

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-((4-(trifluoromethyl)phenyl)ethynyl)cyclobut-2-en-1-one (4.79)



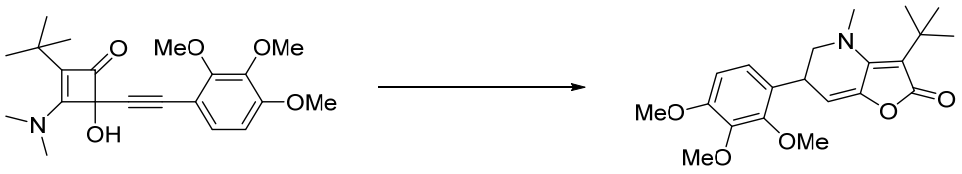
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.79
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

To a solution of 1-ethynyl-2,3,4-trimethoxybenzene **4.78** (935 mg, 4.81 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 2.00 mL, 5.00 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (702 mg, 3.87 mmol) in THF (60 mL) at –78 °C. After 75 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (50 – 100% ethyl acetate/petroleum ether 40 – 60 °C) to afford the title compound **4.79** (1.28 g, 3.44 mmol, 89%) as a white foam.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3253 (w), 2960 (w), 1733 (w), 1580 (vs), 1493 (m), 1466 (w), 1410 (m), 1300 (w), 1208 (w), 1090 (m).
δ_H (400 MHz, $CDCl_3$)	7.13 (1H, d, *J* = 8.6 Hz, Ar**H**) 6.58 (1H, d, *J* = 8.7 Hz, Ar**H**) 4.08 (1H, br s, O**H**) 3.94 (3H, s, OC**H**$_3$) 3.86 (3H, s, OC**H**$_3$) 3.86 (3H, s, OC**H**$_3$) 3.32 (6H, br s, N(C**H**$_3$)$_2$) 1.29 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.5 (**C**), 167.9 (**C**), 155.0 (**C**), 154.6 (**C**), 142.0 (**C**), 128.4 (**C**H), 127.1 (**C**), 109.4 (**C**), 107.2 (**C**H), 88.0 (**C**), 84.2 (**C**), 81.9 (**C**), 61.3 (**C**H$_3$), 61.1 (**C**H$_3$), 56.0 (**C**H$_3$), 42.0 (br s, 2×**C**H$_3$), 31.0 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	374 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-4-methyl-6-(2,3,4-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.80)



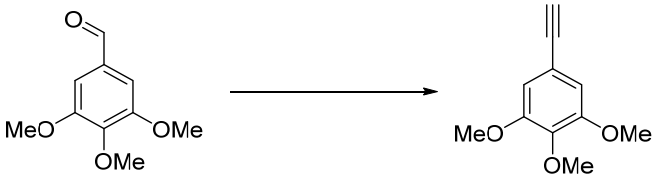
4.79
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

4.80
$C_{21}H_{27}NO_5$
373.45

Alkynylcyclobutenone **4.79** (310 mg, 0.830 mmol) in DMSO (50 mL) was heated at 150 °C. After 30 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases were washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 40% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.80** (161 mg, 0.432 mmol, 54%) as a yellow oil.

FT-IR (ν_{max}/cm^{-1}, DCM)	2955 (br), 1745 (s), 1681 (w), 1583 (s), 1493 (s), 1463 (s), 1417 (m), 1365 (w), 1281 (m), 1093 (vs), 1064 (m), 1045 (m).
δ_H (400 MHz, $CDCl_3$)	6.82 (1H, d, *J* = 8.7 Hz, Ar**H**) 6.64 (1H, d, *J* = 8.7 Hz, Ar**H**) 5.60 (1H, d, *J* = 3.9 Hz, C=C**H**) 4.13 (1H, m, PhC**H**) 3.92 (3H, s, OC**H**$_3$) 3.87 (3H, s, OC**H**$_3$) 3.84 (3H, s, OC**H**$_3$) 3.39 (1H, dd, *J* = 12.8, 5.3 Hz, C**H**H) 3.11 (1H, dd, *J* = 12.8, 8.0 Hz, CH**H**) 3.04 (3H, s, NC**H**$_3$) 1.38 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.7 (**C**), 153.0 (**C**), 152.9 (**C**), 151.3 (**C**), 146.2 (**C**), 142.1 (**C**), 126.4 (**C**), 122.6 (2×**C**H), 108.5 (**C**), 107.2 (**C**H), 105.4 (**C**H), 61.2 (**C**H$_3$), 60.7 (**C**H$_3$), 57.6 (**C**H$_2$), 55.9 (**C**H$_3$), 45.2 (**C**H$_3$), 31.1 (**C**H$_3$), 31.0 (**C**), 30.6 (2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	374 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 374.1968. $C_{21}H_{28}NO_5$ [M+H]$^+$ requires 374.1962. Found 396.1788. $C_{21}H_{27}NNaO_5$ [M+Na]$^+$ requires 396.1781.

5-Ethynyl-1,2,3-trimethoxybenzene (4.83)



4.82
$C_{10}H_{12}O_4$
Mol Wt: 196.20

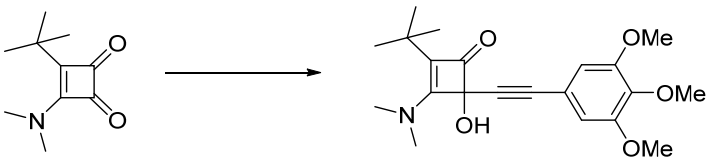
4.83
$C_{11}H_{12}O_3$
Mol Wt: 192.21

Following a literature procedure,[136] to a solution of di*iso*propylamine (0.52 mL, 3.72 mmol) in THF (30 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 1.4 mL, 3.43 mmol) dropwise. After 10 min, the reaction was cooled to –78 °C and trimethylsilyldiazomethane (2.0 M in diethyl ether, 1.9 mL, 3.43 mmol) was added dropwise. After 30 min a solution of 3,4,5-trimethoxybenzaldehyde **4.82** (561 mg, 2.86 mmol) in THF (20 mL) was added *via* cannula. The reaction was allowed to warm to RT and after 16 h water (20 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with water (3 x 30 mL) and then brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 20% diethyl ether/ petroleum ether 40 – 60 °C) afforded the title compound **4.83** (420 mg, 2.19 mmol, 76%) as an off-white solid.

Data is consistent with literature values.[142]

MP (DCM)	75 – 77 °C.
δ_H (400 MHz, $CDCl_3$)	6.74 (2H, s, 2×Ar**H**) 3.86 (9H, m, 3×OC**H**$_3$) 3.04 (1H, s, C**H**) ppm.
δ_C (100 MHz, $CDCl_3$)	153.0 (2×**C**), 139.3 (**C**), 117.0 (**C**), 109.3 (2×**C**H), 83.7 (**C**), 76.2 (**C**H), 60.9 (**C**H$_3$), 56.1 (2×**C**H$_3$) ppm.
LRMS (ESI $^+$)	193 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 193.0859. $C_{11}H_{13}O_3$ [M+H]$^+$, requires 193.0859.

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-((3,4,5-trimethoxyphenyl)ethynyl)cyclobut-2-en-1-one (4.84)



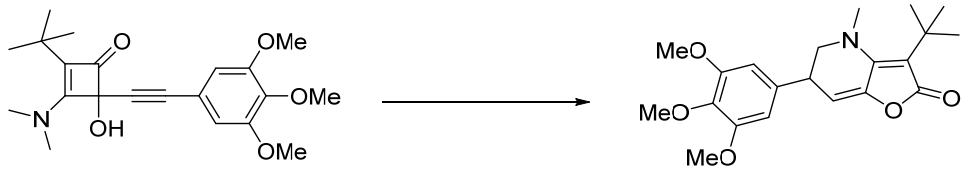
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.84
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

To a solution of 5-ethynyl-1,2,3-trimethoxybenzene **4.83** (362 mg, 1.88 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 0.75 mL, 1.88 mmol) dropwise. After 15 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (284 mg, 1.57 mmol) in THF (30 mL) at –78 °C. After 100 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT. The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (60 – 100% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.84** (544 mg, 1.46 mmol, 93%) as a yellow solid.

MP (DCM)	Decomposed after 130 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3225 (w), 2959 (w), 1732 (w), 1575 (vs), 1503 (m), 1463 (w), 1408 (m), 1364 (w), 1236 (m), 1126 (s).
δ_H (400 MHz, $CDCl_3$)	6.69 (2H, s, 2×Ar**H**) 3.85 (3H, s, OC**H**$_3$) 3.84 (6H, s, 2×OC**H**$_3$) 3.82 (1H, br s, O**H**) 3.33 (6H, s, 2×NC**H**$_3$) 1.31 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.3 (**C**), 167.7 (**C**), 152.9 (2×**C**), 139.1 (**C**), 127.4 (**C**), 117.2 (**C**), 109.2 (2×**C**H), 88.2 (**C**), 84.2 (**C**), 81.8 (**C**), 60.9 (**C**H$_3$), 56.2 (2×**C**H$_3$), 42.1 (br s, 2×**C**H$_3$), 31.1 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	396 ([M+Na]$^+$, 23%), 374 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-4-methyl-6-(3,4,5-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.85)



4.84
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

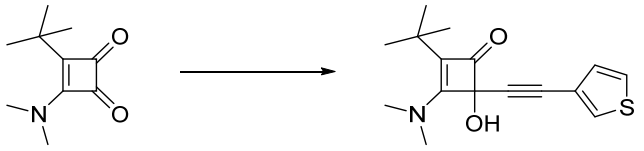
4.85
$C_{21}H_{27}NO_5$
373.45

Alkynylcyclobutenone **4.84** (260 mg, 0.697 mmol) in DMSO (60 mL) was heated at 150 °C. After 25 min, the reaction was cooled to RT and diluted with water (60 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) then the combined organic phases were washed with water (3 x 180 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 60% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.85** (171 mg, 0.458 mmol, 66%) as an orange gel.

FT-IR (ν_{max}/cm^{-1}, DCM)	2956 (br), 1745 (s), 1681 (w), 1588 (s), 1507 (m), 1458 (m), 1421 (w), 1337 (m), 1235 (m), 1125 (vs), 1065 (w).
δ_H (400 MHz, $CDCl_3$)	6.44 (2H, s, 2×Ar**H**) 5.68 (1H, d, *J* = 3.6 Hz, C=C**H**) 3.86 (6H, s, 2×OC**H**$_3$) 3.84 (3H, s, OC**H**$_3$) 3.81 (1H, ddd, *J* = 9.1, 5.3, 3.6 Hz, PhC**H**) 3.37 (1H, dd, *J* = 13.1, 5.1 Hz, C**H**H) 3.21 (1H, dd, *J* = 13.0, 9.2 Hz, CH**H**) 3.10 (3H, s, NC**H**$_3$) 1.41 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.6 (**C**), 153.5 (2×**C**), 152.7 (**C**), 146.3 (**C**), 137.2 (**C**), 136.8 (**C**), 109.4 (**C**), 105.1 (**C**H), 104.6 (2×**C**H), 60.9 (**C**H$_3$), 58.8 (**C**H$_2$), 56.1 (2×**C**H$_3$), 45.1 (**C**H$_3$), 38.4 (**C**H), 31.2 (**C**), 30.6 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	374 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 374.1961. $C_{21}H_{28}NO_5$ [M+H]$^+$, requires 374.1962.

5.5 Experimental procedures to dihydrofuropyridinones with heteroaromatic or non-aromatic substituents

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-(thiophen-3-ylethynyl)cyclobut-2-en-1-one (4.88)



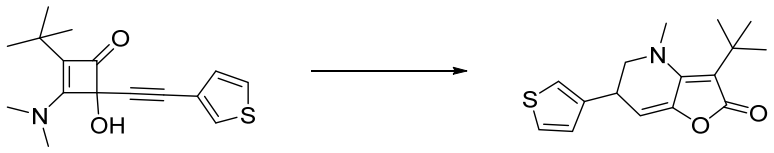
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.88
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

To a solution of 3-ethynylthiophene (0.17 mL, 1.68 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 0.6 mL, 1.46 mmol) dropwise. After 30 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (203 mg, 1.12 mmol) in THF (30 mL) at –78 °C. After 65 min, sat. NH_4Cl (15 mL) was added, the solution warmed to RT and diluted with water (20 mL). The aqueous phase was separated and extracted with DCM (3 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (5 – 10% acetone/DCM) to afford the title compound **4.88** (300 mg, 1.04 mmol, 93%) as a white solid.

MP ($CHCl_3$)	Decomposed after 150 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3240 (w), 2959 (w), 1732 (w), 1577 (vs), 1407 (m), 1364 (w), 1258 (w), 1183 (w), 1140 (w), 1072 (w).
δ_H (400 MHz, $CDCl_3$)	7.47 (1H, dd, *J* = 2.9, 1.1 Hz, Ar**H**) 7.24 (1H, dd, *J* = 5.0, 3.1 Hz, Ar**H**) 7.12 (1H, dd, *J* = 5.0, 1.2 Hz, Ar**H**) 4.03 (1H, br s, O**H**) 3.31 (6H, s, 2×NC**H**$_3$) 1.30 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.4 (**C**), 167.8 (**C**), 130.0 (**C**H), 129.5 (**C**H), 127.3 (**C**), 125.1 (**C**H), 121.4 (**C**), 84.9 (**C**), 83.3 (**C**), 81.8 (**C**), 42.0 (br s, 2×**C**H$_3$), 31.0 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	601 ([2M+Na]$^+$, 48%), 312 ([M+Na]$^+$, 25%), 290 [M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 290.1214. $C_{16}H_{20}NO_2S$ [M+H]$^+$ requires 290.1209.

3-(*tert*-Butyl)-4-methyl-6-(thiophen-3-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.89)



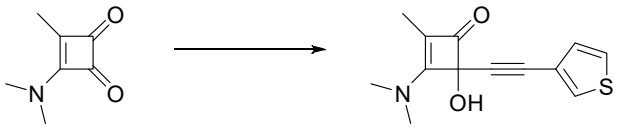
4.88
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

4.89
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

Alkynylcyclobutenone **4.88** (415 mg, 1.43 mmol) in DMSO (100 mL) was heated at 150 °C. After 30 min, the reaction was cooled to RT and diluted with water (100 mL). The mixture was extracted with ethyl acetate (3 x 100 mL) then the combined organic phases were washed with water (3 x 300 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (5 – 10% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.89** (252 mg, 0.872 mmol, 61%, ca. 90% pure) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	2956 (w), 2924 (m), 1745 (vs), 1681 (w), 1585 (s), 1458 (w), 1407 (w), 1365 (w), 1333 (w), 1393 (w), 1064 (w).
δ_H (400 MHz, $CDCl_3$)	7.33 (1H, dd, *J* = 4.7, 3.0 Hz, Ar**H**) 7.07 (1H, br s, Ar**H**) 6.98 (1H, br d, *J* = 4.8 Hz, Ar**H**) 5.71 (1H, d, *J* = 3.9 Hz, C=C**H**) 3.93 (1H, m, PhC**H**) 3.45 (1H, dd, *J* = 13.0, 5.0 Hz, C**H**H) 3.22 (1H, dd, *J* = 12.9, 7.8 Hz, CH**H**) 3.05 (3H, s, NC$\mathbf{H_3}$) 1.39 (9H, s, C(C$\mathbf{H_3}$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.6 (**C**), 152.7 (**C**), 146.0 (**C**), 141.5 (**C**), 126.8 (**C**H), 126.5 (**C**H), 121.7 (**C**H), 109.1 (**C**), 104.8 (**C**H), 57.7 (**C**H_2), 45.3 (**C**H_3), 33.3 (**C**H), 31.1 (**C**), 30.5 (3×**C**H_3) ppm.
LRMS (ESI $^+$)	290 ($[M+H]^+$, 100%)
HRMS (ESI $^+$)	Found 290.1210. $C_{16}H_{20}NO_2S$ $[M+H]^+$ requires 290.1209.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(thiophen-3-ylethynyl)cyclobut-2-en-1-one (4.94)



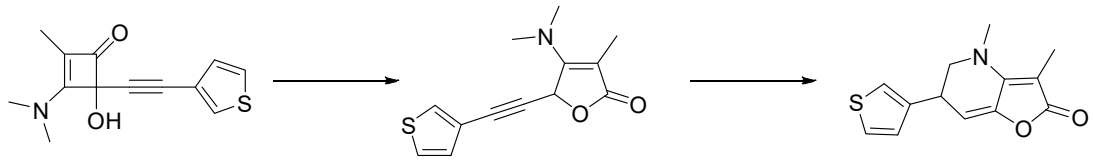
2.2
$C_7H_9NO_2$
Mol Wt: 139.15

4.94
$C_{13}H_{13}NO_2S$
Mol Wt: 247.31

To a solution of 3-ethynylthiophene (0.28 mL, 2.84 mmol) in THF (25 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.3 mL, 3.25 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.2** (346 mg, 2.49 mmol) in THF (50 mL) at –78 °C. After 2 h, sat. NH_4Cl (20 mL) was added then the solution was warmed to RT and diluted with water (20 mL). The aqueous phase was separated and extracted with DCM (3 x 60 mL)., then the organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 30% acetone/DCM) to afford the title compound **4.94** (588 mg, 2.38 mmol, 96%) as a white foam.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3237 (br, w), 3104 (w), 1750 (w), 1584 (vs), 1411 (m), 1270 (w), 1138 (w), 1023 (w), 786 (w).
δ_H (400 MHz, $CDCl_3$)	7.46 (1H, dd, *J* = 3.0, 1.2 Hz, Ar**H**) 7.23 (1H, dd, *J* = 5.0, 3.1 Hz, Ar**H**) 7.10 (1H, dd, *J* = 5.0, 1.2 Hz, Ar**H**) 4.42 (1H, br s, O**H**) 3.29 (3H, s, NC**H**$_3$) 3.19 (3H, s, NC**H**$_3$) 1.79 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.1 (**C**), 169.6 (**C**), 129.9 (**C**H), 129.5 (**C**H), 125.2 (**C**H), 121.3 (**C**), 114.9 (**C**), 84.4 (**C**), 83.5 (**C**), 81.8 (**C**), 40.2 (**C**H$_3$), 39.5 (**C**H$_3$), 7.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	495 ([2M+H]$^+$, 25%), 248 [M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 270.0553. $C_{13}H_{13}NNaO_2S$ [M+Na]$^+$ requires 270.0559. Found: 248.0733. $C_{13}H_{14}NO_2S$ [M+H]$^+$ requires 248.0740.

3,4-Dimethyl-6-(thiophen-3-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.96)



4.94
$C_{13}H_{13}NO_2S$
Mol Wt: 247.31

4.95
$C_{13}H_{13}NO_2S$
Mol Wt: 247.31

4.96
$C_{13}H_{13}NO_2S$
Mol Wt: 247.31

A solution of alkynylcyclobutenone **4.94** (328 mg, 1.33 mmol) in DMSO (40 mL) was degassed then heated at 160 °C for 45 min. The reaction was then cooled to RT and diluted with water (40 mL). The mixture was extracted with ethyl acetate (3 x 40 mL) then the combined organic phases were washed with water (3 x 120 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (30 – 70% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.96** (43.8 mg, 0.177 mmol, 13%) as a yellow gel and furanone **4.95** (155 mg, 0.625 mmol, 47%, ca. 90% pure) as an orange gel.

A solution of furanone **4.95** (76 mg, 0.307 mmol) in tetraglyme (20 mL), was heated at 210 °C under argon for 45 min then cooled to RT and diluted with water (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL) then the combined organic phases were washed with water (3 x 60 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.96** (26.1 mg, 0.106 mmol, 34%, ca. 90% pure) as a yellow gel.

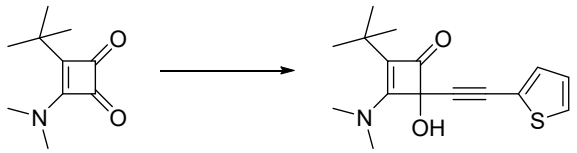
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	2924 (w), 1749 (m), 1620 (s), 1450 (w), 1321 (w), 1297 (m), 1090 (m), 1031 (m), 907 (s), 728 (vs), 646 (m).
δ_H (400 MHz, $CDCl_3$)	7.32 (1H, dd, *J* = 5.0, 2.9 Hz, Ar**H**) 7.09 (1H, m, Ar**H**) 6.99 (1H, dd, *J* = 5.0, 1.3 Hz, Ar**H**) 5.65 (1H, d, *J* = 4.2 Hz, C=C**H**) 3.97 (1H, m, ArC**H**) 3.46 (1H, dd, *J* = 11.8, 5.8 Hz, C**H**H) 3.19 (1H, dd, *J* = 11.8, 7.6 Hz, CH**H**) 3.15 (3H, s, NC**H**$_3$) 2.02 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	172.0 (**C**), 151.2 (**C**), 145.2 (**C**), 141.3 (**C**), 126.8 (**C**H), 126.4 (**C**H), 121.7 (**C**H), 103.8 (**C**H), 90.5 (**C**), 57.2 (**C**H$_2$), 39.1 (**C**H), 34.9 (**C**H$_3$), 8.8 (**C**H$_3$) ppm.

LRMS (ESI $^+$)	248 ($[M+H]^+$, 100%)
HRMS (ESI $^+$)	Found: 248.0740. $C_{13}H_{14}NO_2S$ $[M+H]^+$ requires 248.0740.

4-(Dimethylamino)-3-methyl-5-(thiophen-3-ylethynyl)furan-2(5*H*)-one (4.95):

δ_H (400 MHz, $CDCl_3$)	7.51 (1H, dd, *J* = 2.9, 1.1 Hz, Ar**H**) 7.28 (1H, dd, *J* = 5.1, 3.0 Hz, Ar**H**) 7.12 (1H, dd, *J* = 5.0, 1.2 Hz, Ar**H**) 5.47 (1H, s, C**H**) 3.18 (6H, s, 2×NC**H**$_3$) 2.01 (3H, s, C**H$_3$**) ppm.

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-(thiophen-2-ylethynyl)cyclobut-2-en-1-one (4.100)



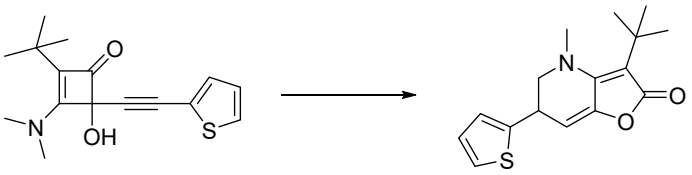
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.100
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

To a solution of 2-ethynylthiophene (0.50 mL, 5.27 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 2.2 mL, 5.50 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (759 mg, 4.19 mmol) in THF (60 mL) at –78 °C. After 95 min, sat. NH_4Cl (30 mL) was added, the solution warmed to RT and diluted with water (70 mL). The aqueous phase was separated and extracted with DCM (3 x 70 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 40% acetone/DCM) to afford the title compound **4.100** (894 mg, 3.09 mmol, 74%) as a brown foam.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3225 (br w), 2959 (w), 1731 (m), 1569 (vs), 1436 (w), 1406 (s), 1364 (m), 1257 (m), 1202 (w), 1186 (m), 1137 (m).
δ_H (400 MHz, $CDCl_3$)	7.25 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**) 7.22 (1H, dd, *J* = 3.6, 1.2 Hz, Ar**H**) 6.95 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**) 4.44 (1H, br s, O**H**) 3.31 (6H, s, 2×NC**H**$_3$) 1.30 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.3 (**C**), 167.8 (**C**), 132.7 (**C**H), 127.5 (**C**H), 127.3 (**C**), 126.8 (**C**H), 122.3 (**C**), 89.2 (**C**), 81.8 (**C**), 81.3 (**C**), 42.0 (br s, 2×**C**H$_3$), 31.0 (**C**), 31.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	579 ([2M+H]$^+$, 15%), 290 [M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found 290.1217. $C_{16}H_{20}NO_2S$ [M+H]$^+$ requires 290.1209.

3-(*tert*-Butyl)-4-methyl-6-(thiophen-2-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.101)



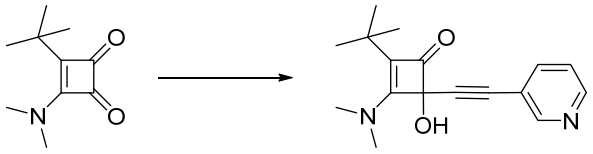
4.100
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

4.101
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

Alkynylcyclobutenone **4.100** (429 mg, 1.48 mmol) in DMSO (50 mL) was heated at 150 °C. After 30 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases were washed with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (5 – 10% acetone/DCM) afforded the title compound **4.101** (316 mg, 1.09 mmol, 74%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	2959 (w), 2906 (w), 2016 (w), 1979 (w), 1749 (vs), 1683 (w), 1587 (s), 1457 (w), 1406 (w), 1365 (w), 1329 (w), 1290 (w).
δ_H (400 MHz, $CDCl_3$)	7.22 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**) 6.97 (1H, dd, 5.1, 3.5 Hz, Ar**H**) 6.90 (1H, dt, *J* = 3.5, 1.0 Hz, Ar**H**) 5.72 (1H, d, *J* = 4.3 Hz, C=C**H**) 4.09 (1H, m, ArC**H**) 3.53 (1H, dd, *J* = 13.0, 5.0 Hz, C**H**H) 3.28 (1H, dd, *J* = 13.0, 7.0 Hz, CH**H**) 3.08 (3H, s, NC**H**$_3$) 1.39 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.5 (**C**), 152.4 (**C**), 146.1 (**C**), 144.3 (**C**), 127.0 (**C**H), 124.9 (**C**H), 124.6 (**C**H), 109.4 (**C**), 104.5 (**C**H), 58.6 (**C**H$_2$), 45.4 (**C**H$_3$), 33.2 (**C**H), 31.2 (**C**), 30.6 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	290 ([M+H]$^+$, 100%)
HRMS (ESI $^+$)	Found 290.1214. $C_{16}H_{20}NO_2S$ [M+H]$^+$ requires 290.1209.

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-(pyridin-3-ylethynyl)cyclobut-2-en-1-one (4.105)



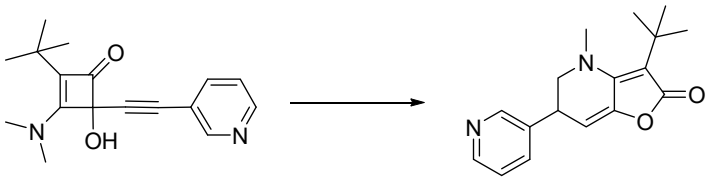
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.105
$C_{17}H_{20}N_2O_2$
Mol Wt: 284.36

To a solution of 3-ethynylpyridine (759 mg, 7.36 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 3.1 mL, 7.75 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (1.12 g, 6.19 mmol) in THF (70 mL) at –78 °C. After 160 min, sat. NH_4Cl (30 mL) was added, the solution warmed to RT and diluted with water (80 mL). The aqueous phase was separated and extracted with DCM (3 x 100 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 70% acetone/DCM) to afford the title compound **4.105** (1.68 g, 5.91 mmol, 95%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	2959 (br m), 2868 (w), 1733 (m), 1574 (vs), 1476 (w), 1405 (s), 1364 (m), 1255 (m), 1185 (m), 1140 (m).
δ_H (400 MHz, $CDCl_3$)	8.62 (1H, br d, *J* = 1.3 Hz, Ar**H**) 8.46 (1H, dd, *J* = 5.0, 1.7 Hz, Ar**H**) 7.68 (1H, app dt, *J* = 8.1, 1.8 Hz, Ar**H**) 7.17 (1H, ddd, 7.9, 5.0, 1.0 Hz, Ar**H**) 3.29 (6H, s, 2×NC**H**$_3$) 1.25 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	183.1 (**C**), 168.3 (**C**), 151.9 (**C**H), 148.3 (**C**H), 138.9 (**C**H), 126.8 (**C**), 122.9 (**C**H), 119.8 (**C**), 89.7 (**C**), 83.9 (**C**), 81.2 (**C**), 42.0 (br s, 2×**C**H$_3$), 30.9 (**C**), 30.9 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	285 $[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 285.1602. $C_{17}H_{21}N_2O_2$ $[M+H]^+$ requires 285.1598.

3-(*tert*-Butyl)-4-methyl-6-(pyridin-3-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.106)



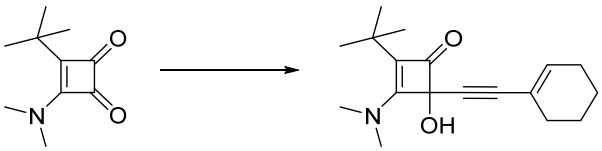
4.105
$C_{17}H_{20}N_2O_2$
Mol Wt: 284.36

4.106
$C_{17}H_{20}N_2O_2$
Mol Wt: 284.36

Alkynylcyclobutenone **4.105** (630 mg, 2.22 mmol) in DMSO (70 mL) was heated at 160 °C. After 40 min, the reaction was cooled to RT and diluted with water (70 mL). The mixture was extracted with ethyl acetate (3 x 70 mL) then the combined organic phases were washed with water (3 x 210 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 100% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.106** (556 mg, 1.96 mmol, 88%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	2958 (m), 2906 (w), 1745 (vs), 1683 (w), 1584 (vs), 1479 (w), 1425 (m), 1406 (m), 1365 (w), 1299 (m), 1285 (w).
δ_H (400 MHz, $CDCl_3$)	8.53 – 8.51 (2H, m, Ar**H**) 7.55 (1H, dt, *J* = 7.9, 1.9 Hz, Ar**H**) 7.27 (1H, ddd, 8.0, 4.9, 0.7 Hz, Ar**H**) 5.62 (1H, d, *J* = 3.8 Hz, C=C**H**) 3.88 (1H, ddd, *J* = 8.3, 4.9, 3.9 Hz, ArC**H**) 3.43 (1H, dd, *J* = 13.1, 4.8 Hz, C**H**H) 3.18 (1H, dd, *J* = 13.1, 8.2 Hz, CH**H**) 3.06 (3H, s, NC$\mathbf{H_3}$) 1.38 (9H, s, C(C$\mathbf{H_3}$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.3 (**C**), 152.3 (**C**), 149.3 (**C**H), 148.8 (**C**H), 146.7 (**C**), 136.5 (**C**), 135.1 (**C**H), 123.7 (**C**H), 109.7 (**C**), 103.5 (**C**H), 58.3 (**C**H$_2$), 45.1 (**C**H$_3$), 35.5 (**C**H), 31.1 (**C**), 30.5 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	285([M+H]$^+$, 100%)
HRMS (ESI $^+$)	Found: 285.1605. $C_{17}H_{21}N_2O_2$ [M+H]$^+$ requires 285.1598.

2-(*tert*-Butyl)-4-(cyclohex-1-en-1-ylethynyl)-3-(dimethylamino)-4-hydroxycyclobut-2-en-1-one (4.109)



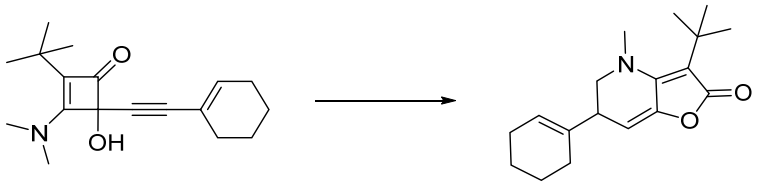
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.109
$C_{18}H_{25}NO_2$
Mol Wt: 287.40

To a solution of 1-ethenylcyclohexene (0.718 mL, 6.10 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 2.44 mL, 6.25 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (852 mg, 4.70 mmol) in THF (70 mL) at –78 °C. After 105 min, sat. NH_4Cl (20 mL) was added, the solution warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 20% acetone/DCM) to afford the title compound **4.109** (1.33 g, 4.64 mmol, 99%) as an off-white gel.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3252 (w), 2930 (m), 2861 (w), 1732 (m), 1577 (vs), 1436 (w), 1406 (m), 1364 (w), 1258 (w), 1186 (w), 1137 (m), 1067 (w).
δ_H (400 MHz, $CDCl_3$)	6.15 (1H, tt, *J* = 3.9, 1.8 Hz, C=C**H**) 3.66 (1H, br s, O**H**) 3.27 (6H, s, 2×NC**H**$_3$) 2.14 – 2.06 (4H, m, 2×C**H**$_2$) 1.65 – 1.54 (4H, m, 2×C**H**$_2$) 1.28 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.7 (**C**), 167.9 (**C**), 136.0 (**C**H), 127.0 (**C**), 120.0 (**C**), 90.0 (**C**), 82.4 (**C**), 81.8 (**C**), 41.9 (br s, 2×**C**H$_3$), 31.0 (**C**), 31.0 (3×**C**H$_3$), 28.9 (**C**H$_2$), 25.6 (**C**H$_2$), 22.2 (**C**H$_2$), 21.4 (**C**H$_2$) ppm.
LRMS (ESI $^+$)	310 ([M+Na]$^+$, 34%), 288 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-6-(cyclohex-1-en-1-yl)-4-methyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.110)



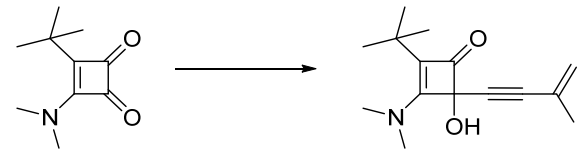
4.109
$C_{18}H_{25}NO_2$
Mol Wt: 287.40

4.110
$C_{18}H_{25}NO_2$
Mol Wt: 287.40

Alkynylcyclobutenone **4.109** (729 mg, 2.54 mmol) in DMSO (60 mL) was heated at 150 °C. After 20 min, the reaction was cooled to RT and diluted with water (60 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) then the combined organic phases were washed with water (3 x 180 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 50% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.110** (384 mg, 1.34 mmol, 48%) as an orange solid.

MP ($CHCl_3$)	84 – 86 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	2927 (br), 2859 (m), 1746 (vs), 1682 (w), 1584 (s), 1481 (w), 1457 (w), 1365 (w), 1332 (w), 1294 (m), 1218 (w), 1063 (w),
δ_H (400 MHz, $CDCl_3$)	5.54 (1H, m, C=C**H**) 5.52 (1H, d, *J* = 3.8 Hz, C=C**H**) 3.24 (1H, dd, *J* = 12.6, 5.1 Hz, NC**H**H) 3.13 – 3.02 (2H, m, NCH**H** + =CHC**H**) 3.09 (3H, s, NC$\mathbf{H_3}$) 2.06 – 1.99 (2H, m, C$\mathbf{H_2}$) 1.70 – 1.53 (4H, m, 2×C$\mathbf{H_2}$) 1.38 (9H, s, C(C$\mathbf{H_3}$)$_3$) 1.34 – 1.31 (2H, m, C$\mathbf{H_2}$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.9 (**C**), 153.0 (**C**), 145.7 (**C**), 136.8 (**C**), 124.8 (**C**H), 108.4 (**C**), 105.3 (**C**H), 55.5 (**C**H$_2$), 45.3 (**C**H$_3$), 39.2 (**C**H), 31.1 (**C**), 30.6 (3×**C**H$_3$), 27.2 (**C**H$_2$), 25.3 (**C**H$_2$), 22.9 (**C**H$_2$), 22.3 (**C**H$_2$) ppm.
LRMS (ESI $^+$)	288 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 288.1964. $C_{18}H_{26}NO_2$ [M+H]$^+$ requires 288.1958.

2-(*tert*-Butyl)-3-(dimethylamino)-4-hydroxy-4-(3-methylbut-3-en-1-yn-1-yl)cyclobut-2-en-1-one (4.113)



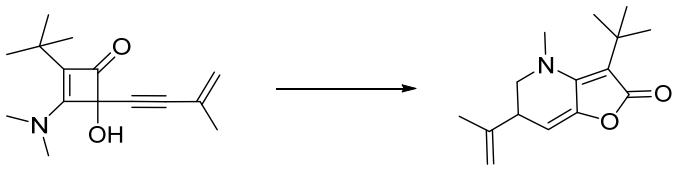
2.5
$C_{10}H_{15}NO_2$
Mol Wt: 181.24

4.113
$C_{15}H_{21}NO_2$
Mol Wt: 247.34

To a solution of 2-methyl-1-buten-3-yne (0.42 mL, 4.43 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.8 mL, 4.50 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.5** (669 mg, 3.69 mmol) in THF (60 mL) at –78 °C. After 70 min, sat. NH_4Cl (30 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (10 – 30% acetone/DCM) to afford the title compound **4.113** (871 mg, 3.52 mmol, 95%) as an off-white solid.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3243 (w), 2957 (w), 2868 (w), 1732 (m), 1569 (vs), 1436 (w), 1405 (m), 1364 (m), 1255 (m), 1188 (m), 1150 (m), 1111 (m).
δ_H (400 MHz, $CDCl_3$)	5.52 (1H. br s, O**H**) 5.27 (1H, dq, *J* = 2.0, 1.0 Hz, C=C**H**H) 5.18 (1H, dq, *J* = 2.0, 1.6 Hz, C=CH**H**) 3.24 (6H, s, NC**H**$_3$) 1.84 (3H, app t, *J* = 1.3 Hz, C**H**$_3$) 1.23 (9H, s 3×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	182.5 (**C**), 168.6 (**C**), 126.3 (**C**), 126.2 (**C**), 122.3 (**C**H$_2$), 88.6 (**C**), 84.6 (**C**), 81.1 (**C**), 41.9 (br s, 2×**C**H$_3$), 30.8 (3×**C**H$_3$), 30.8 (**C**), 23.1 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	270 ([M+Na]$^+$, 54%), 248 ([M+H]$^+$, 100%).

3-(*tert*-Butyl)-4-methyl-6-(prop-1-en-2-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.114)



4.113
$C_{15}H_{21}NO_2$
Mol Wt: 247.34

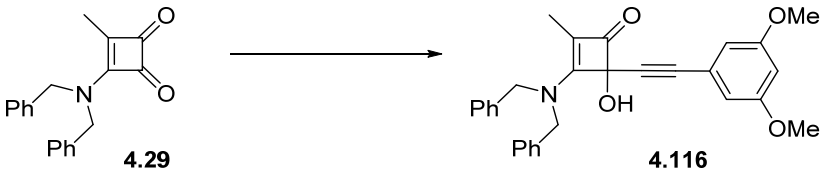
4.114
$C_{15}H_{21}NO_2$
Mol Wt: 247.34

Alkynylcyclobutenone **4.113** (505 mg, 2.04 mmol) in DMSO (60 mL) was heated at 150 °C. After 25 min, the reaction was cooled to RT and diluted with water (60 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) then the combined organic phases washed were with water (3 x 180 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 20% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.114** as an orange solid (290 mg, 1.17 mmol, 57%).

MP (DCM)	62 – 63 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2959 (w), 2912 (w), 1749 (vs), 1683 (w), 1585 (s), 1456 (w), 1405 (w), 1365 (w), 1289 (w), 1218 (w), 1066 (w), 983 (m).
δ_H (400 MHz, $CDCl_3$)	5.54 (1H, m, C=C**H**) 4.93 (1H, m, C=C**H**H) 4.86 (1H, s, C=CH**H**) 3.28 (1H, m, NC**H**H) 3.20 – 3.15 (2H, m, NCH**H** + C**H**) 3.11 (3H, s, NC**H**$_3$) 1.80 (3H, s, C**H**$_3$) 1.38 (9H, s, 3×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.7 (**C**), 152.8 (**C**), 145.9 (**C**), 144.4 (**C**), 113.6 (**C**H$_2$), 108.9 (**C**), 104.7 (**C**H), 55.3 (**C**H$_2$), 45.2 (**C**H$_3$), 39.0 (**C**H), 31.0 (**C**), 30.6 (3×**C**H$_3$), 21.1 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	248 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 270.1467. $C_{15}H_{21}NNaO_2$ [M+Na]$^+$ requires 270.1465.

5.6 Experimental procedures to dihydrofuropyridinones with both substituted amines and aryl/vinyl groups

3-(Dibenzylamino)-4-((3,5-dimethoxyphenyl)ethynyl)-4-hydroxy-2-methylcyclobut-2-en-1-one (4.116)



4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

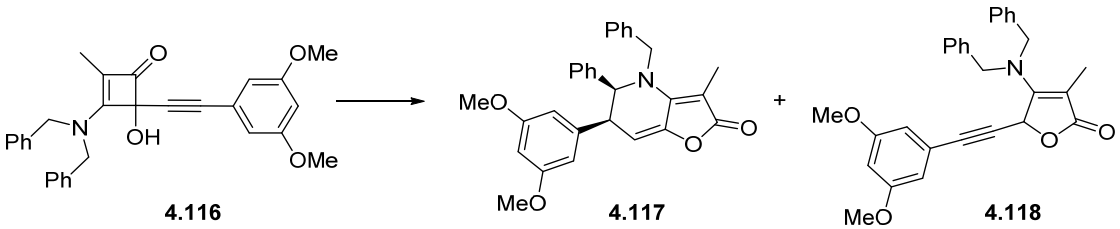
4.116
$C_{29}H_{27}NO_4$
Mol Wt: 453.54

To a solution of 1-ethynyl-3,5-dimethoxybenzene **4.73** (316 mg, 1.95 mmol) in THF (25 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 0.80 mL, 1.97 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.29** (442 mg, 1.52 mmol) in THF (50 mL) at –78 °C. After 65 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 70% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.116** (600 mg, 1.32 mmol, 87%) as a white foam.

FT-IR (ν_{max}/cm^{-1}, DCM)	3233 (w), 1747 (w), 1590 (vs), 1577 (vs), 1495 (w), 1441 (m), 1420 (w), 1259 (w), 1204 (m), 1155 (s), 1082 (w), 1062 (w),
δ_H (400 MHz, $CDCl_3$)	7.43 – 7.32 (8H, m, 8×Ar**H**) 7.25 – 7.23 (2H, m, 2×Ar**H**) 6.52 (2H, d, *J* = 2.3 Hz, 2×Ar**H**) 6.42 (1H, app t, *J* = 2.3 Hz, Ar**H**) 4.92 (1H, br s, O**H**) 4.84 (1H, d, *J* = 15.0 Hz, NC**H**H) 4.73 (1H, d, *J* = 15.2 Hz, NCH**H**) 4.50 (1H, d, *J* = 16.0 Hz, NC**H**H) 4.39 (1H, d, *J* = 16.0 Hz, NCH**H**) 3.71 (6H, s, 2×OC**H**$_3$) 1.75 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.7 (**C**), 170.5 (**C**), 160.3 (2×**C**), 135.4 (**C**), 135.0 (**C**), 129.2 (2×**C**H), 128.8 (3×**C**H), 128.2 (**C**H), 128.1 (**C**H), 127.0 (2×**C**H), 123.4 (**C**), 115.0 (**C**), 109.5 (3×**C**H), 102.4 (**C**H),

δ_C (100 MHz, $CDCl_3$)	88.8 (**C**), 84.5 (**C**), 82.3 (**C**), 55.4 (2×**C**H_3), 53.8 (**C**H_2), 51.0 (**C**H_2), 7.7 (**C**H_3) ppm.
LRMS (ESI $^+$)	476 ($[M+Na]^+$, 32%), 454 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 454.2019. $C_{29}H_{28}NO_4$ $[M+H]^+$, requires 454.2013. Found: 476.1833. $C_{29}H_{27}NNaO_4$ $[M+Na]^+$ requires 476.1832.

rel-(5*S*,6*S*)-4-Benzyl-6-(3,5-dimethoxyphenyl)-3-methyl-5-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.117)



4.116
$C_{29}H_{27}NO_4$
Mol Wt: 453.54

4.117
$C_{29}H_{27}NO_4$
Mol Wt: 453.54

4.118
$C_{29}H_{27}NO_4$
Mol Wt: 453.54

Alkynylcyclobutenone **4.116** (361 mg, 0.795 mmol) in DMSO (40 mL) was heated at 160 °C. After 60 min, the reaction was cooled to RT and diluted with water (40 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 40 mL) then the combined organic phases were washed with water (3 x 120 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (30 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.117** (134 mg, 0.296 mmol, 37%, *d.r.* 6:1) as a yellow gel and byproduct furanone (140 mg, 0.308 mmol, 39%) as a dark yellow oil.

FT-IR (ν_{max}/cm^{-1}, DCM)

2957 (w), 2925 (m), 1757 (s), 1618 (vs), 1453 (m), 1430 (w), 1296 (br), 1204 (m), 1157 (m), 1065 (w).

δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.45 – 7.32 (3H, m, 3×Ar**H**)
7.23 – 7.09 (5H, m, 5×Ar**H**)
6.92 – 6.90 (2H, m, 2×Ar**H**)
6.36 (1H, dd, *J* = 2.2 Hz, Ar**H**)
6.32 (2H, d, *J* = 2.2 Hz, 2×Ar**H**)
5.51 (1H, d, *J* = 5.6 Hz, C=C**H**)
5.00 (1H, d, *J* = 16.1 Hz, NC**H**H)
4.32 (1H, d, *J* = 2.5 Hz, NC**H**Ph)
3.98 (1H, d, *J* = 16.4 Hz, NCH**H**)
3.80 (1H, dd, *J* = 5.8, 2.6 Hz, C**H**Ph)
3.75 (6H, s, 2×OC**H**$_3$)
2.00 (3H, s, C**H**$_3$) ppm.

Signals attributed to the minor diastereoisomer:
7.45 – 7.32 (3H, m, 3×Ar**H**)
7.23 – 7.09 (5H, m, 5×Ar**H**)
6.73 – 6.71 (2H, m, 2×Ar**H**)
6.23 (1H, app t, *J* = 2.3 Hz, Ar**H**)
5.87 (2H, d, *J* = 2.2 Hz, 2×Ar**H**)
5.56 (1H, d, *J* = 2.6 Hz, C=C**H**)

δ_H (400 MHz, $CDCl_3$) 5.06 (1H, d, *J* = 16.1 Hz, NC**H**H)
4.40 (1H, dd, *J* = 7.2, 2.7 Hz, C**H**Ph)
4.36 (1H, d, *J* = 7.1 Hz, NC**H**Ph)
3.98 (1H, d, *J* = 16.1 Hz, NCH**H**)
3.88 (3H, s, OC**H**$_3$)
3.84 (3H, s, OC**H**$_3$)
2.00 (3H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) *Signals attributed to the major diastereoisomer:*
172.3 (**C**), 161.0 (2×**C**), 150.3 (**C**), 145.5 (**C**), 143.5 (**C**), 140.3 (**C**), 136.3 (**C**), 129.0 (2×**C**H), 128.6 (2×**C**H), 128.2 (**C**H), 127.6 (**C**H), 127.0 (2×**C**H), 126.5 (2×**C**H), 106.2 (2×**C**H), 100.1 (**C**H), 99.0 (**C**H), 89.3 (**C**), 67.8 (**C**H), 55.3 (2×**C**H$_3$), 52.6 (**C**H$_2$), 47.5 (**C**H), 9.2 (**C**H$_3$) ppm.

Signals attributed to the minor diastereoisomer:
172.2 (**C**), 160.4 (2×**C**), 150.6 (**C**), 145.7 (**C**), 140.7 (**C**), 137.1 (**C**), 136.0 (**C**), 129.1 (2×**C**H), 128.4 (2×**C**H), 128.0 (2×**C**H), 127.7 (**C**H), 127.2 (**C**H), 127.1 (2×**C**H), 110.8 (**C**H), 110.2 (**C**H), 107.0 (**C**H), 102.4 (**C**H), 99.5 (**C**H), 89.9 (**C**), 66.5 (**C**H), 55.2 (2×**C**H$_3$), 52.7 (**C**H$_2$), 45.8 (**C**H), 7.9 (**C**H$_3$) ppm.

LRMS (ESI $^+$) 454 ($[M+H]^+$, 100%).

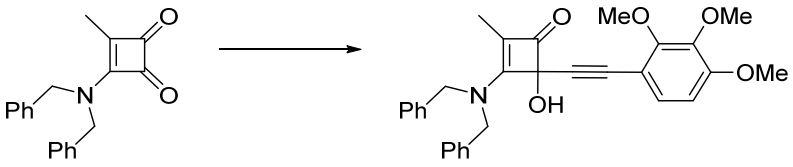
HRMS (ESI $^+$) Found: 454.2021. $C_{29}H_{28}NO_4$ $[M+H]^+$, requires 454.2013.
Found: 476.1838. $C_{29}H_{27}NNaO_4$ $[M+Na]^+$ requires 476.1832.

4-(Dibenzylamino)-5-((3,5-dimethoxyphenyl)ethynyl)-3-methylfuran-2(5*H*)-one (4.118):

δ_H (400 MHz, $CDCl_3$) 7.39 – 7.32 (6H, m, 6×Ar**H**)
7.26 – 7.24 (4H, m, 4×Ar**H**)
6.50 (2H, m, 2×Ar**H**)
6.48 (1H, m, Ar**H**)
5.63 (1H, app d, *J* = 0.7 Hz, C**H**)
4.83 (2H, d, *J* = 16.5 Hz, NC**H**$_2$)
4.49 (2H, d, *J* = 16.5 Hz, NC**H**$_2$)
3.76 (6H, s, 2×OC**H**$_3$)
1.95 (3H, app d, *J* = 0.6 Hz, C**H**$_3$).

LRMS (ESI $^+$) 454 ($[M+H]^+$, 100%).

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-((2,3,4-trimethoxyphenyl)ethynyl)cyclobut-2-en-1-one (4.120)



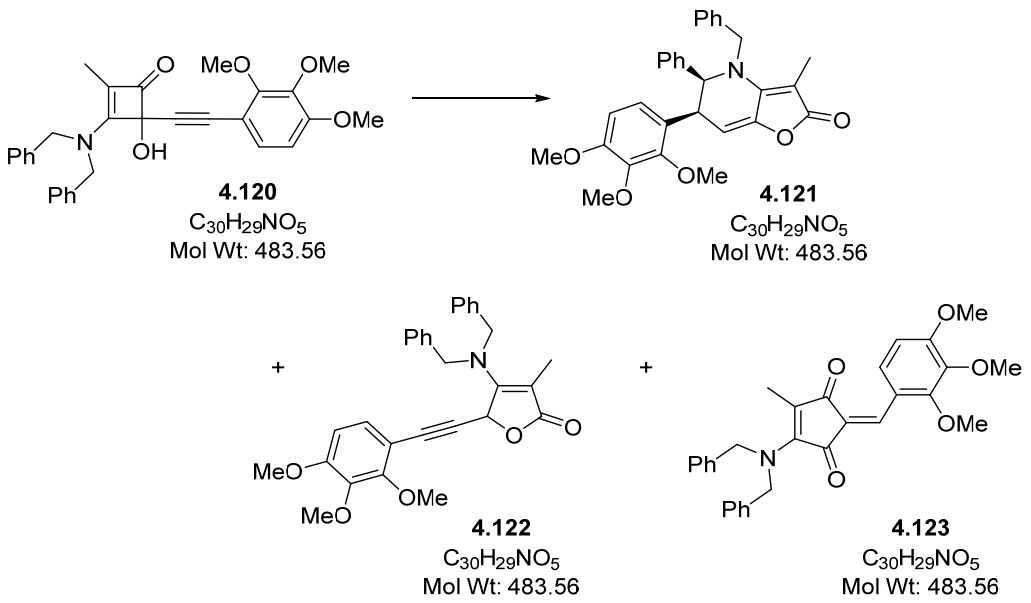
4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

4.120
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

To a solution of 2,3,4-trimethoxyphenylacetylene **4.78** (465 mg, 2.42 mmol) in THF (22 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.00 mL, 2.50 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.29** (541 mg, 1.86 mmol) in THF (50 mL) at –78 °C. After 70 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 70% ethyl acetate/ petroleum ether 40 – 60 °C) afforded the title compound **4.120** (676 mg, 1.40 mmol, 75%) as an orange foam.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3241 (w), 2938 (w), 1748 (m), 1591 (vs), 1574 (vs), 1466 (m), 1452 (m), 1442 (m), 1413 (m), 1290 (m), 1169 (w), 1092 (s), 1016 (m).
δ_H (400 MHz, $CDCl_3$)	7.43 – 7.32 (8H, m, 8×Ar**H**) 7.25 – 7.23 (2H, m, 2×Ar**H**) 7.05 (1H, d, *J* = 8.7 Hz, Ar**H**) 6.56 (1H, d, *J* = 8.7 Hz, Ar**H**) 4.91 (1H, d, *J* = 14.9 Hz, NC**H**H) 4.67 (1H, d, *J* = 15.0 Hz, NCH**H**) 4.46 (1H, d, *J* = 16.4 Hz, NC**H**H) 4.41 (1H, d, *J* = 16.1 Hz, NCH**H**) 3.86 (3H, s, OC**H**$_3$) 3.86 (3H, s, OC**H**$_3$) 3.84 (3H, s, OC**H**$_3$) 1.73 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.5 (**C**), 170.3 (**C**), 155.1 (**C**), 154.6 (**C**), 141.9 (**C**), 135.6 (**C**), 135.0 (**C**), 129.1 (2×**C**H), 128.9 (2×**C**H), 128.7 (2×**C**H), 128.5 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 126.9 (2×**C**H), 114.9 (**C**), 109.2 (**C**), 107.1 (**C**H), 87.5 (**C**), 85.3 (**C**), 82.5 (**C**), 61.2 (**C**H$_3$), 61.1 (**C**H$_3$), 53.8 (**C**H$_2$), 56.0 (**C**H$_3$), 50.9 (**C**H$_2$), 7.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	506 ([M+Na]$^+$, 67%), 484 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 484.2132. $C_{30}H_{30}NO_5$ [M+H]$^+$ requires 484.2118. Found: 506.1941. $C_{30}H_{29}NNaO_5$ [M+Na]$^+$ requires 506.1938.

rel-(5*S*,6*S*)-4-Benzyl-3-methyl-5-phenyl-6-(2,3,4-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.121)



Alkynylcyclobutenone **4.120** (650 mg, 1.34 mmol) in DMSO (50 mL) was heated at 160 °C under an argon atmosphere. After 60 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% diethyl ether/petrol) gave a mixed fraction (333 mg, 0.689 mmol, 51%) and byproduct furanone **4.122** (246 mg, 0.509 mmol, 38%, ca. 80% pure). Separation of the mixed fraction by HPLC (50% diethyl ether/petrol) afforded the dihydrofuropyridinone **4.121** (42.7 mg, 0.0883 mmol, 7%) as a yellow solid, and the *E*- and *Z*- isomers of byproduct **4.123** as **4.123a** (79.8 mg, 0.165 mmol, 12%) as a yellow gel and **4.123b** (21.3 mg, 0.044 mmol, 3%)

(5*S*,6*S*)-4-Benzyl-3-methyl-5-phenyl-6-(2,3,4-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.121):

MP (DCM)	Decomposed above 125 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2981 (m), 2971 (m), 1757 (s), 1631 (vs), 1493 (m), 1463 (m), 1417 (w), 1381 (w), 1273 (m), 1252 (w), 1163 (w), 1095 (s).
δ_H (400 MHz, $CDCl_3$)	7.42 – 7.31 (5H, m, 5×Ar**H**) 7.12 (1H, m, Ar**H**) 7.06 – 7.02 (2H, m, 2×Ar**H**) 6.87 (1H, d, *J* = 8.6 Hz, Ar**H**) 6.76 – 6.74 (2H, m, 2×Ar**H**)

δ_H (400 MHz, $CDCl_3$)	6.66 (1H, d, *J* = 8.6 Hz, Ar**H**) 5.38 (1H, d, *J* = 6.2 Hz, C=C**H**) 5.07 (1H, d, *J* = 15.7 Hz, NC**H**H) 4.30 (1H, s, NC**H**Ph) 4.13 (1H, d, *J* = 6.2 Hz, C**H**Ph) 3.93 (1H, d, *J* = 15.7 Hz, NCH**H**) 3.92 (3H, s, OC$\mathbf{H}_3$) 3.82 (3H, s, OC$\mathbf{H}_3$) 3.75 (3H, s, OC$\mathbf{H}_3$) 2.04 (3H, s, C$\mathbf{H}_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	172.4 (**C**), 153.5 (**C**), 151.1 (**C**), 150.1 (**C**), 146.2 (**C**), 142.3 (**C**), 140.5 (**C**), 136.3 (**C**), 128.8 (2×**C**H), 128.4 (2×**C**H), 127.8 (**C**H), 127.4 (**C**H), 127.0 (2×**C**H), 126.3 (2×**C**H), 126.1 (**C**), 123.2 (**C**H), 106.3 (**C**H), 99.3 (**C**H), 88.3 (**C**), 65.6 (**C**H), 60.7 (**C**H_3), 60.6 (**C**H_3), 56.1 (**C**H_3), 52.6 (**C**H_2), 40.5 (**C**H), 9.2 (**C**H_3) ppm.
LRMS (ESI $^+$)	506 ($[M+Na]^+$, 49%), 484 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 484.2125. $C_{30}H_{30}NO_5$ $[M+H]^+$ requires 484.2118. Found: 506.1941. $C_{30}H_{29}NNaO_5$ $[M+Na]^+$ requires 506.1938.

4-(Dibenzylamino)-3-methyl-5-((2,3,4-trimethoxyphenyl)ethynyl)furan-2(5*H*)-one (4.122):

δ_H (400 MHz, $CDCl_3$)	7.40 – 7.25 (10H, m, 10×Ar**H**) 7.05 (1H, d, *J* = 8.7 Hz, Ar**H**) 6.62 (1H, d, *J* = 8.8 Hz, Ar**H**) 5.63 (1H, s, C**H**) 4.99 (2H, d, *J* = 16.5 Hz, NC$\mathbf{H}_2$) 4.41 (2H, d, *J* = 16.6 Hz, NC$\mathbf{H}_2$) 3.89 (3H, s, OC$\mathbf{H}_3$) 3.88 (3H, s, OC$\mathbf{H}_3$) 3.87 (3H, s, OC$\mathbf{H}_3$) 1.96 (3H, s, C$\mathbf{H}_3$) ppm.
LRMS (ESI $^+$)	484 ($[M+H]^+$, 100%).

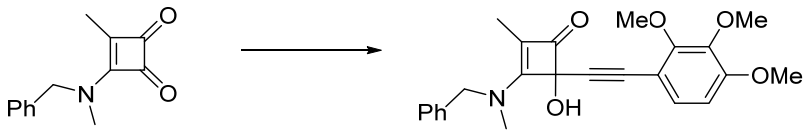
Byproduct 4.123a:

δ_H (400 MHz, $CDCl_3$)	8.78 (1H, d, *J* = 9.1 Hz, C=C**H**) 7.76 (1H, s, Ar**H**) 7.40 – 7.30 (6H, m, 6×Ar**H**) 7.24 – 7.22 (4H, m, 4×Ar**H**) 6.76 (1H, d, *J* = 9.1 Hz, Ar**H**) 4.94 (4H, s, 2×NC**H**$_2$) 3.96 (3H, s, OC**H**$_3$) 3.94 (3H, s, OC**H**$_3$) 3.87 (3H, s, OC**H**$_3$) 2.13 (3H, s, C**H**$_3$) ppm.
LRMS (ESI $^+$)	484 ($[M+H]^+$, 100%).

Byproduct 4.123b:

δ_H (400 MHz, $CDCl_3$)	8.41 (1H, d, *J* = 9.1 Hz, C=C**H**) 7.85 (1H, s, Ar**H**) 7.39 – 7.29 (6H, m, 6×Ar**H**) 7.23 – 7.21 (4H, m, 4×Ar**H**) 6.72 (1H, d, *J* = 9.1 Hz, Ar**H**) 4.89 (4H, s, 2×NC**H**$_2$) 3.97 (3H, s, OC**H**$_3$) 3.91 (3H, s, OC**H**$_3$) 3.87 (3H, s, OC**H**$_3$) 2.14 (3H, s, C**H**$_3$) ppm.
LRMS (ESI $^+$)	484 ($[M+H]^+$, 100%).

3-(Benzyl(methyl)amino)-4-hydroxy-2-methyl-4-((2,3,4-trimethoxyphenyl)ethynyl)cyclobut-2-en-1-one (4.125)



4.34
$C_{13}H_{13}NO_2$
Mol Wt: 215.25

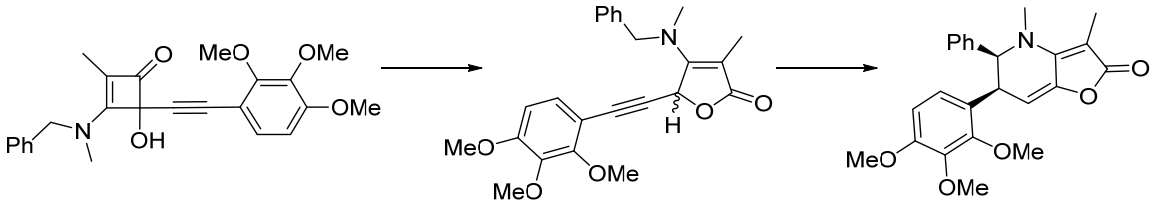
4.125
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

To a solution of 2,3,4-trimethoxyphenylacetylene **4.78** (613 mg, 3.19 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.50 mL, 3.75 mmol) dropwise. After 15 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.34** (734 mg, 3.41 mmol) in THF (70 mL) at –78 °C. After 60 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% ethyl acetate/ petroleum ether 40 – 60 °C) afforded the title compound **4.125** (376 mg, 0.922 mmol, 27%) as a 1:1 mixture or rotamers as a brown gum.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3241 (br), 2939 (w), 1749 (w), 1091 (vs), 1577 (vs), 1493 (m), 1458 (m), 1413 (s), 1298 (m), 1236 (w), 1091 (s), 1017 (m).
δ_H (400 MHz, $CDCl_3$)	7.46 – 7.28 (10H, m, 10×Ar**H**) 7.13 (1H, d, *J* = 8.7 Hz, Ar**H**) 7.01 (1H, d, *J* = 8.6 Hz, Ar**H**) 6.57 (1H, d, *J* = 8.7 Hz, Ar**H**) 6.53 (1H, d, *J* = 8.8 Hz, Ar**H**) 4.83 (1H, d, *J* = 14.9 Hz, NC**H**H) 4.77 (1H, d, *J* = 14.8 Hz, NCH**H**) 4.64 (2H, br d, *J* = 15.9 Hz, NC**H**H + O**H**) 4.54 (1H, d, *J* = 15.9 Hz, NCH**H**) 3.88 (6H, s, 2×OC**H**$_3$) 3.84 (12H, m, 4×OC**H**$_3$) 3.30 (3H, s, NC**H**$_3$) 3.00 (3H, s, NC**H**$_3$) 1.82 (3H, s C**H**$_3$) 1.72 (3H, s C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	184.6 + 184.4 (**C**), 170.2 + 170.0 (**C**), 155.0 + 155.0 (**C**), 154.6 + 154.5 (**C**), 142.0 + 141.9 (**C**), 135.5 + 135.1 (**C**), 129.1 + 128.7 (2×**C**H), 128.6 + 128.5 (2×**C**H), 128.1 + 128.1 (**C**H), 126.9 (**C**H), 114.8 + 114.7 (**C**), 109.3 + 109.2 (**C**), 107.2 + 107.0 (**C**H), 87.6 + 87.5 (**C**), 85.0 + 84.7 (**C**), 82.2 + 82.2 (**C**), 61.3 + 61.2 (**C**H_3), 61.0 + 56.0 (2×**C**H_3), 56.9 + 55.6 (**C**H_2), 37.7 + 36.0 (**C**H_3), 7.8 + 7.6 (**C**H_3) ppm.
LRMS (ESI $^+$)	430 $[M+Na]^+$, 50%, 408 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 408.1812. $C_{24}H_{26}NO_5$ $[M+H]^+$ requires 408.1805. Found: 430.1625. $C_{24}H_{25}NNaO_5$ $[M+Na]^+$ requires 430.1625.

rel-(5*S*,6*S*)-3,4-Dimethyl-5-phenyl-6-(2,3,4-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.127)



4.125
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

4.126
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

4.127
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

Alkynylcyclobutenone **4.125** (342 mg, 0.839 mmol) in tetraethylene glycol dimethyl ether (30 mL) was heated at 200 °C under an argon atmosphere. After 25 min, the reaction was cooled to RT and diluted with water (30 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) then the combined organic phases washed were with water (3 x 90 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the furanone **4.126** (138 mg, 0.338 mmol, 40%, *d.r*. 13:2). The intermediate furanone **4.126** in tetraethylene glycol dimethyl ether (20 mL) was heated to 200 °C under an argon atmosphere, then cooled to RT after 60 minutes and diluted with water (20 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 20 mL) and the combined organic phases washed were with water (3 x 60 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 30% diethyl ether/petroleum ether 40 – 60 °C) afforded the dihydrofuropyridinone **4.127** (41.3 mg, 0.101 mmol, 45%, *d.r.* 7:3) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)
2935 (w), 1754 (s), 1617 (vs), 1695 (w), 1493 (m), 1463 (m), 1416 (m), 1316 (w), 1287 (m), 1094 (s), 1037 (m).

δ_H (400 MHz, $CDCl_3$)
Signals attributed to the major diastereoisomer:
7.39 – 7.29 (3H, m, 3×Ar**H**)
7.04 (1H, m, Ar**H**)
6.85 (1H, d, *J* = 8.7 Hz, Ar**H**)
6.69 (1H, m, Ar**H**)
6.64 (1H, d, *J* = 8.7 Hz, Ar**H**)
5.32 (1H, d, *J* = 6.0 Hz, C=C**H**)
4.25 (1H, d, *J* = 1.7 Hz, NC**H**Ph)
4.16 (1H, dd, *J* = 6.0, 1.7 Hz, C**H**Ph)
3.96 (3H, s, OC**H**$_3$)
3.91 (3H, s, OC**H**$_3$)
3.86 (3H, s, OC**H**$_3$)

δ_H (400 MHz, $CDCl_3$) 3.37 (3H, s, NC**H**$_3$)
2.09 (3H, s, C**H**$_3$) ppm.

Signals attributed to the minor diastereoisomer:
7.39 – 7.29 (4H, m, 4×Ar**H**)
7.11 (1H, m, Ar**H**)
6.31 (1H, d, *J* = 8.7 Hz, Ar**H**)
6.16 (1H, d, *J* = 8.6 Hz, Ar**H**)
5.48 (1H, d, *J* = 3.1 Hz, C=C**H**)
4.79 (1H, dd, *J* = 7.0, 3.1 Hz, C**H**Ph)
4.49 (1H, d, *J* = 7.0 Hz, NC**H**Ph)
3.85 (3H, s, OC**H**$_3$)
3.84 (3H, s, OC**H**$_3$)
3.75 (3H, s, OC**H**$_3$)
3.38 (3H, s, NC**H**$_3$)
2.08 (3H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) *Signals attributed to the major diastereoisomer:*
172.4 (**C**), 153.3 (**C**), 150.9 (**C**), 150.8 (**C**), 145.3 (**C**), 142.2 (**C**), 140.7 (**C**), 128.8 (2×**C**H), 127.8 (**C**H), 126.7 (**C**), 126.1 (2×**C**H), 122.8 (**C**H), 106.9 (**C**H), 100.0 (**C**H), 89.0 (**C**), 70.0 (**C**H), 60.9 (**C**H$_3$), 60.8 (**C**H$_3$), 55.9 (**C**H$_3$), 40.3 (**C**H), 38.6 (**C**H$_3$), 9.0 (**C**H$_3$) ppm.

Signals attributed to the minor diastereoisomer:
172.3 (**C**), 152.9 (**C**), 151.4 (**C**), 151.3 (**C**), 145.3 (**C**), 141.6 (**C**), 136.5 (**C**), 127.8 (3×**C**H), 127.7 (2×**C**H), 124.0 (**C**), 123.9 (**C**H), 106.8 (**C**H), 102.8 (**C**H), 90.0 (**C**), 68.1 (**C**H), 61.1 (**C**H$_3$), 60.7 (**C**H$_3$), 55.9 (**C**H$_3$), 38.5 (**C**H), 38.2 (**C**H$_3$), 9.1 (**C**H$_3$) ppm.

LRMS (ESI $^+$) 408 ($[M+H]^+$, 100%).

4-(Benzyl(methyl)amino)-3-methyl-5-((2,3,4-trimethoxyphenyl)ethynyl)furan-2(5*H*)-one (4.126):

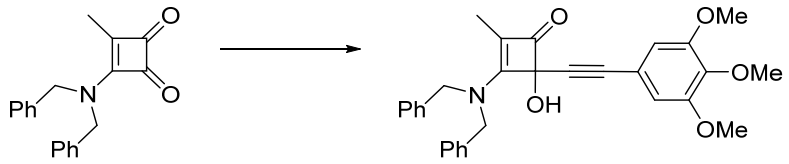
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$) 2937 (w), 2330 (w), 1733 (m), 1621 (vs), 1493 (m), 1466 (m), 1412 (s), 1291 (m), 1208 (w), 1106 (m), 1089 (s), 1053 (m).

δ_H (400 MHz, $CDCl_3$) 7.41 – 7.27 (5H, m, 5×Ar**H**)
7.08 (1H, d, *J* = 8.7 Hz, Ar**H**)
6.63 (1H, d, *J* = 8.7 Hz, Ar**H**)
5.64 (1H,d, *J* = 0.7 Hz, C**H**)

δ_H (400 MHz, $CDCl_3$) 4.85 (1H, d, *J* = 16.4 Hz, NC**H**H)
4.59 (1H, d, *J* = 16.3 Hz, NCH**H**)
3.91 (3H, s, OC**H**$_3$)
3.89 (3H, s, OC**H**$_3$)

δ_H (400 MHz, $CDCl_3$)	3.88 (3H, s, OC**H**$_3$) 3.19 (3H, s, NC**H**$_3$) 1.98 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.3 (**C**), 161.8 (**C**), 155.1 (**C**), 142.1 (**C**), 136.7 (2×**C**), 129.0 (3×**C**H), 128.3 (**C**H), 127.8 (**C**H), 126.7 (2×**C**H), 108.6 (**C**), 107.3 (**C**H), 89.4 (**C**), 84.5 (**C**), 84.1 (**C**), 67.4 (**C**H_3), 61.3 (**C**H_3), 61.1 (**C**H_3), 56.2 (**C**H_2), 38.8 (**C**H_3), 9.8 (**C**H_3) ppm.
LRMS (ESI $^+$)	430 $[M+Na]^+$, 48%, 408 ($[M+H]^+$, 100%).

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-((3,4,5-trimethoxyphenyl)ethynyl)cyclobut-2-en-1-one (4.129)



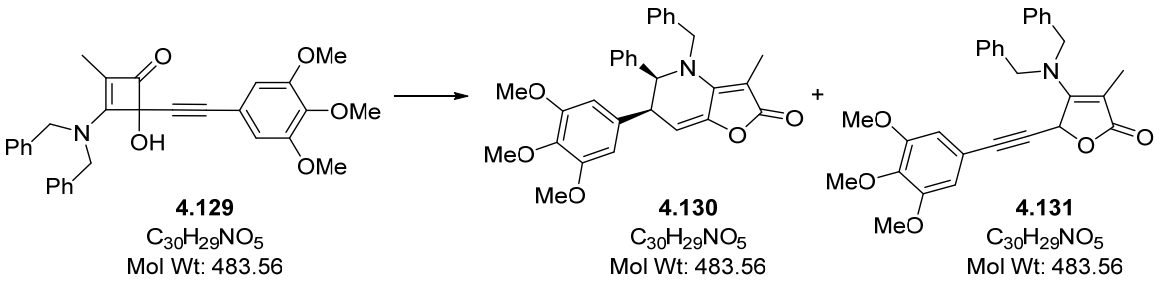
4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

4.129
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

To a solution of 3,4,5-trimethoxyphenylacetylene (511 mg, 2.66 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.10 mL, 2.75 mmol) dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.29** (692 mg, 2.37 mmol) in THF (60 mL) at –78 °C. After 70 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 80% ethyl acetate/ petroleum ether 40 – 60 °C) afforded the title compound **4.129** (772 mg, 1.60 mmol, 67%) as a pale brown solid.

MP (DCM)	63 – 64 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3246 (w), 2938 (w), 1747 (m), 1590 (s), 1569 (vs), 1442 (s), 1411 (m), 1345 (w), 1237 (s), 1125 (s), 1092 (m), 1002 (m).
δ_H (400 MHz, $CDCl_3$)	7.46 – 7.33 (8H, m, 8×Ar**H**) 7.27 – 7.23 (2H, m, 2×Ar**H**) 6.58 (2H, s, 2×Ar**H**) 4.90 (1H, d, *J* = 15.2 Hz, NC**H**H) 4.67 (1H, d, *J* = 15.3 Hz, NCH**H**) 4.55 (1H, d, *J* = 15.9 Hz, NC**H**H) 4.36 (1H, d, *J* = 16.0 Hz, NCH**H**) 3.83 (3H, s, OC**H**$_3$) 3.76 (6H, s, 2×OC**H**$_3$) 1.76 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.6 (**C**), 170.5 (**C**), 152.9 (2×**C**), 139.1 (**C**), 135.4 (**C**), 135.1 (**C**), 129.2 (2×**C**H), 128.8 (2×**C**H), 128.7 (2×**C**H), 128.1 (2×**C**H), 127.0 (2×**C**H), 117.0 (**C**), 115.0 (**C**), 109.1 (2×**C**H), 89.0 (**C**), 83.9 (**C**), 82.3 (**C**), 60.9 (**C**H$_3$), 56.1 (2×**C**H$_3$), 53.8 (**C**H$_2$), 51.1 (**C**H$_2$), 7.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	506 ([M+Na]$^+$, 27%), 484 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 484.2128. $C_{31}H_{29}NO_5$ [M+H]$^+$ requires 484.2118.

rel-(5*S*,6*S*)-4-Benzyl-3-methyl-5-phenyl-6-(3,4,5-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.130)



Alkynylcyclobutenone **4.129** (553 mg, 1.14 mmol) in DMSO (50 mL) was heated at 150 °C under an argon atmosphere. After 30 min, the reaction was cooled to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.130** (142 mg, 0.293 mmol, 26%, *d.r.* 5:1) as an orange gel and furanone byproduct **4.131** (81.5 mg, 0.169 mmol, 15%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

2938 (w), 2838 (w), 1756 (s), 1695 (w), 1618 (vs), 1505 (m), 1452 (m), 1421 (m), 1329 (w), 1295 (w), 1126 (s), 1002 (m).

δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.45 – 7.34 (4H, m, 4×Ar**H**)
7.22 – 7.14 (4H, m, 4×Ar**H**)
6.90 (2H, dd, *J* = 7.6, 1.7 Hz, 2×Ar**H**)
6.33 (2H, s, 2×Ar**H**)
5.54 (1H, m, *J* = 5.8 Hz, C=C**H**)
5.00 (1H, d, *J* = 16.0 Hz, NC**H**H)
4.31 (1H, d, *J* = 2.9 Hz, NC**H**Ph)
3.98 (1H, d, *J* = 16.0 Hz, NCH**H**)
3.84 (3H, s, OC**H**$_3$)
3.82 (1H, dd, *J* = 5.6, 3.0 Hz, C**H**Ph)
3.78 (6H, s, 2×OC**H**$_3$)
2.02 (3H, s, C**H**$_3$) ppm.

Signals attributed to the minor diastereoisomer:
7.45 – 7.34 (4H, m, 4×Ar**H**)
7.22 – 7.14 (4H, m, 4×Ar**H**)
6.70 – 6.68 (2H, m, 2×Ar**H**)
5.90 (2H, s, 2×Ar**H**)
5.54 (1H, obscured d, C=C**H**)
5.06 (1H, d, *J* = 16.4 Hz, NC**H**H)

δ_H (400 MHz, $CDCl_3$)

4.40 (1H, dd, *J* = 7.1, 2.6 Hz, C**H**Ph)
4.36 (1H, d, *J* = 7.1 Hz, NC**H**Ph)
4.00 (1H, d, *J* = 16.6 Hz, NCH**H**)
3.76 (3H, s, OC$\mathbf{H}_3$)
3.57 (6H, s, 2×OC$\mathbf{H}_3$)
1.99 (3H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer
172.3 (**C**), 153.3 (2×**C**), 150.3 (**C**), 145.5 (**C**), 140.1 (**C**), 137.5 (**C**), 136.7 (**C**), 136.3 (**C**), 129.0 (2×**C**H), 128.6 (2×**C**H), 128.2 (**C**H), 127.7 (**C**H), 127.0 (2×**C**H), 126.6 (2×**C**H), 105.0 (2×**C**H), 100.3 (**C**H), 89.4 (**C**), 68.1 (**C**H), 60.9 (**C**H_3), 56.2 (2×**C**H_3), 52.6 (**C**H_2), 47.6 (**C**H), 9.2 (**C**H_3) ppm.

Signals attributed to the minor diastereoisomer:
172.1 (**C**), 152.8 (2×**C**), 150.6 (**C**), 145.7 (**C**), 140.1 (**C**), 137.2 (**C**), 137.2 (**C**), 136.2 (**C**), 129.1 (**C**H), 128.9 (**C**H), 128.9 (**C**H), 128.3 (**C**H), 128.0 (2×**C**H), 127.9 (**C**H), 127.2 (**C**H), 126.9 (2×**C**H), 106.2 (2×**C**H), 102.5 (**C**H), 89.9 (**C**), 66.8 (**C**H), 60.8 (**C**H_3), 56.0 (2×**C**H_3), 52.8 (**C**H_2), 45.9 (**C**H), 9.1 (**C**H_3).

LRMS (ESI $^+$)

506 ($[M+Na]^+$, 54%), 484 ($[M+H]^+$, 100%).

HRMS (ESI $^+$)

Found: 484.2125. $C_{30}H_{30}NO_5$ $[M+H]^+$ requires 484.2118.
Found: 506.1938. $C_{30}H_{29}NNaO_5$ $[M+Na]^+$ requires 506.1938.

4-(Dibenzylamino)-3-methyl-5-((3,4,5-trimethoxyphenyl)ethynyl)furan-2(5*H*)-one (4.131):

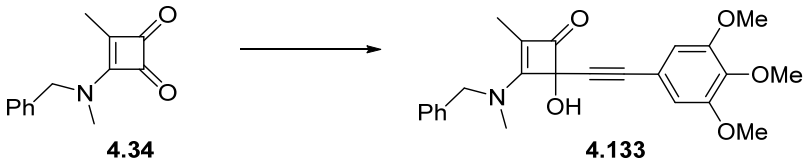
δ_H (400 MHz, $CDCl_3$)

7.39 – 7.31 (8H, m, 8×Ar**H**)
7.25 (2H, m, 2×Ar**H**)
6.56 (2H, s, 2×Ar**H**)
5.65 (1H, s, C**H**)
4.78 (2H, d, *J* = 16.4 Hz, NC$\mathbf{H}_2$)
4.54 (2H, d, *J* = 16.5 Hz, NC$\mathbf{H}_2$)
3.87 (3H, s, OC$\mathbf{H}_3$)
3.81 (6H, s, 2×OC$\mathbf{H}_3$)
1.96 (3H, s, C$\mathbf{H}_3$) ppm.

LRMS (ESI $^+$)

484 ($[M+H]^+$, 100%).

3-(Benzyl(methyl)amino)-4-hydroxy-2-methyl-4-((3,4,5-trimethoxyphenyl)ethynyl)cyclobut-2-en-1-one (4.133)



4.34
$C_{13}H_{13}NO_2$
Mol Wt: 215.25

4.133
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

To a solution of 3,4,5-trimethoxyphenylacetylene **4.83** (926 mg, 4.88 mmol) in THF (40 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.22 mL, 3.10 mmol) dropwise. After 10 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.34** (876 mg, 4.07 mmol) in THF (70 mL) at –78 °C. After 75 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (50 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (50 – 100% ethyl acetate/ petroleum ether 40 – 60 °C) afforded the title compound **4.133** (533 mg, 1.31 mmol, 32%) as an 8:5 mixture of rotamers as a brown foam.

MP (DCM)	80 – 83 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3257 (w), 2938 (w), 1749 (w), 1590 (s), 1574 (vs), 1503 (m), 1451 (m), 1411 (m), 1345 (w), 1237 (m), 1125 (s).
δ_H (400 MHz, $CDCl_3$)	*Signals attributed to the major rotamer:* 7.46 – 7.28 (5H, m, 5×Ar**H**) 6.55 (2H, s, 2×Ar**H**) 4.96 (1H, d, *J* = 15.2 Hz, NC**H**H) 4.65 (1H, d, *J* = 15.2 Hz, NCH**H**) 3.82 (3H, s, OC**H**$_3$) 3.75 (6H, s, 2×OC**H**$_3$) 3.04 (3H, s, NC**H**$_3$) 1.84 (3H, s C**H**$_3$) ppm. *Signals attributed to the minor rotamer:* 7.46 – 7.28 (5H, m, 5×Ar**H**) 6.69 (2H, s, 2×Ar**H**) 4.61 (2H, m, NC**H**$_2$) 3.84 (3H, s, OC**H**$_3$) 3.82 (6H, s, 2×OC**H**$_3$) 3.28 (3H, s, NC**H**$_3$) 1.74 (3H, s C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) *Signals attributed to the major rotamer:*
184.4 (**C**), 170.0 (**C**), 152.8 (2×**C**), 139.0 (**C**), 135.1 (**C**), 128.8 (2×**C**H), 128.3 (2×**C**H), 126.9 (**C**H), 117.0 (**C**), 114.9 (**C**), 109.1 (2×**C**H), 88.8 (**C**), 83.9 (**C**), 82.2 (**C**), 60.9 (**C**H_3), 56.9 (**C**H_2), 56.1 (2×**C**H_3), 36.2 (**C**H_3), 7.8 (**C**H_3) ppm.

δ_C (100 MHz, $CDCl_3$) *Signals attributed to the minor rotamer:*
184.6 (**C**), 170.2 (**C**), 152.9 (2×**C**), 139.1 (**C**), 135.4 (**C**), 129.2 (2×**C**H), 128.2 (**C**H), 128.1 (2×**C**H), 117.2 (**C**), 115.0 (**C**), 109.1 (2×**C**H), 88.6 (**C**), 83.9 (**C**), 82.2 (**C**), 60.9 (**C**H_3), 56.1 (2×**C**H_3), 55.7 (**C**H_2), 37.8 (**C**H_3), 7.7 (**C**H_3) ppm.

LRMS (ESI $^+$) 430 $[M+Na]^+$, 48%, 408 ($[M+H]^+$, 100%).

HRMS (ESI $^+$) Found: 408.1810. $C_{24}H_{26}NO_5$ $[M+H]^+$ requires 408.1805.
Found: 430.1628. $C_{24}H_{25}NNaO_5$ $[M+Na]^+$ requires 430.1625.

rel-(5*S*,6*S*)-3,4-Dimethyl-5-phenyl-6-(3,4,5-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.134)

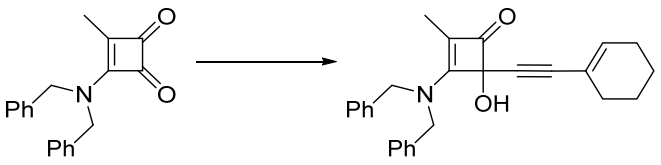
4.133
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

4.134
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

Alkynylcyclobutenone **4.133** (443 mg, 1.09 mmol) in tetraethylene glycol dimethyl ether (50 mL) was heated at 200 °C under an argon atmosphere. After 60 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 80% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.134** (240 mg, 0.588 mmol, 54%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2935 (w), 2838 (w), 1753 (s), 1618 (vs), 1590 (s), 1505 (m), 1452 (m), 1417 (m), 1313 (m), 1291 (m), 1235 (m), 1124 (vs), 1028 (m).
δ_H (400 MHz, $CDCl_3$)	7.39 – 7.33 (3H, m, 3×Ar**H**) 7.21 – 7.18 (2H, m, 2×Ar**H**) 6.33 (2H, s, 2×Ar**H**) 5.51 (1H, d, *J* = 5.1 Hz, C=C**H**) 4.22 (1H, d, *J* = 4.3 Hz, NC**H**Ph) 3.84 (3H, s, OC**H**$_3$) 3.80 (6H, s, 2×OC**H**$_3$) 3.77 (1H, dd, *J* = 5.1, 4.3 Hz, C**H**Ph) 3.03 (3H, s, NC**H**$_3$) 2.11 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	172.2 (**C**), 153.4 (**C**), 150.7 (2×**C**), 144.8 (**C**), 140.0 (**C**), 137.4 (**C**), 137.2 (**C**), 128.9 (2×**C**H), 128.2 (**C**H), 126.7 (2×**C**H), 104.8 (2×**C**H), 101.3 (**C**H), 90.2 (**C**), 71.3 (**C**H), 60.8 (**C**H$_3$), 56.2 (2×**C**H$_3$), 48.2 (**C**H), 38.1 (**C**H$_3$), 9.2 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	430 ([M+Na]$^+$, 58%), 408 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 408.1814. $C_{24}H_{26}NO_5$ [M+H]$^+$ requires 408.1805. Found: 430.1629. $C_{24}H_{25}NNaO_5$ [M+Na]$^+$ requires 430.1625.

4-(Cyclohex-1-en-1-ylethynyl)-3-(dibenzylamino)-4-hydroxy-2-methylcyclobut-2-en-1-one (4.137)



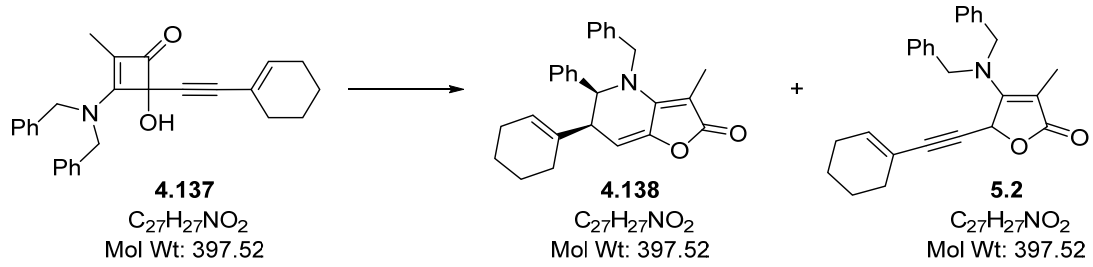
4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

4.137
$C_{27}H_{27}NO_2$
Mol Wt: 397.52

To a solution of 1-ethynylcyclohexene (0.54 mL, 4.59 mmol) in THF (30 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.8 mL, 5.49 mmol) dropwise. After 15 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.29** (1.01 g, 3.45 mmol) in THF (50 mL) at –78 °C. After 75 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (80 mL). The aqueous phase was separated and extracted with DCM (3 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (30 – 60% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **4.137** (1.07 g, 2.69 mmol, 78%) as a brown gel.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3240 (w), 2929 (w), 1747 (m), 1590 (s), 1570 (vs), 1496 (w), 1440 (m), 1364 (w), 1258 (m), 1169 (w), 1078 (w).
δ_H (400 MHz, $CDCl_3$)	7.41 – 7.32 (8H, m, 8×Ar**H**) 7.23 – 7.21 (2H, d, *J* = 7.2 Hz, 2×Ar**H**) 6.08 (1H, m, C=C**H**) 4.75 (1H, d, *J* = 15.2 Hz, NC**H**H) 4.69 (1H, d, *J* = 15.4 Hz, NCH**H**) 4.46 (1H, d, *J* = 15.9 Hz, NC**H**H) 4.37 (1H, d, *J* = 15.9 Hz, NCH**H**) 2.05 – 2.04 (4H, m 2×C**H**$_2$) 1.70 (3H, s C**H**$_3$) 1.62 – 1.52 (4H, m, 2×C**H**$_2$) ppm.
δ_C (100 MHz, $CDCl_3$)	185.2 (**C**), 170.7 (**C**), 136.2 (**C**H), 135.5 (**C**), 135.1 (**C**), 129.1 (2×**C**H), 128.8 (2×**C**H), 128.7 (2×**C**H), 128.1 (**C**H), 128.0 (**C**H), 126.9 (2×**C**H), 119.8 (**C**), 114.6 (**C**), 90.8 (**C**), 82.3 (**C**), 82.1 (**C**), 53.7 (**C**H$_2$), 50.9 (**C**H$_2$), 28.8 (**C**H$_2$), 25.6 (**C**H$_2$), 22.1 (**C**H$_2$), 21.4 (**C**H$_2$), 7.6 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	420 ([M+Na]$^+$, 79%), 398 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 398.2125. $C_{27}H_{28}NO_2$ [M+H]$^+$ requires 398.2115.

rel-(5*S*,6*S*)-4-Benzyl-6-(cyclohex-1-en-1-yl)-3-methyl-5-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.138)



4.137
$C_{27}H_{27}NO_2$
Mol Wt: 397.52

4.138
$C_{27}H_{27}NO_2$
Mol Wt: 397.52

5.2
$C_{27}H_{27}NO_2$
Mol Wt: 397.52

Alkynylcyclobutenone **4.137** (467 mg, 1.17 mmol) in DMSO (50 mL) was heated at 170 °C. After 60 min, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) then the combined organic phases washed were with water (3 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 100% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.138** (132 mg, 0.333 mmol, 28%, *d.r.* 5:1) as a brown gel and furanone byproduct **5.2** as a red oil (200 mg, 0.504 mmol, 43%, ca. 90% pure).

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

2925 (w), 2856 (w), 1753 (s), 1695 (w), 1662 (w), 1617 (vs), 1495 (w), 1450 (m), 1361 (w), 1295 (m), 1157 (w).

δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.41 – 7.30 (7H, m, 7×Ar**H**)
7.26 – 7.18 (3H, m, 3×Ar**H**)
5.55 (1H, m, C=C**H**CH_2)
5.39 (1H, d, *J* = 5.9 Hz, C=C**H**CH)
5.12 (1H, d, *J* = 15.9 Hz, NC**H**H)
4.23 (1H, br s, C**H**Ph)
3.96 (1H, d, *J* = 16.0 Hz, NCH**H**)
2.98 (1H, d, *J* = 5.9 Hz, C**H**)
2.60 (0.5H, m, C**H**H)
2.32 (0.5 H, m, C**H**H)
2.03 (3H, s, C**H**$_3$)
1.96 – 1.34 (7H, m, 3×C**H**$_2$ + CH**H**) ppm.

Signals attributed to the minor diastereoisomer:
7.41 – 7.30 (5H, m, 5×Ar**H**)
7.26 – 7.18 (2H, m, 2×Ar**H**)
7.07 (2H, dd, *J* = 7.6, 1.8 Hz, 2×Ar**H**)
7.00 (1H, s, Ar**H**)
5.46 (1H, d, *J* = 2.7 Hz, C=C**H**CH)
5.25 (1H, m, C=C**H**CH_2)
5.02 (1H, d, *J* = 16.1Hz, NC**H**H)
4.29 (1H, d, *J* = 7.1 Hz, C**H**Ph)

δ_H (400 MHz, $CDCl_3$)

4.03 (1H, d, *J* = 16.7 Hz, NCH**H**)
3.73 (1H, dd, *J* = 7.1, 2.7 Hz, C**H**)
2.52 (0.5H, m, C**H**H)
2.39 (0.5 H, C**H**H)
2.11 (3H, s, C$\mathbf{H}_3$)
1.96 – 1.34 (7H, m, 3×C$\mathbf{H}_2$ + CH**H**) ppm.

δ_C (100 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
172. 5 (**C**), 150.2 (**C**), 144.8 (**C**H), 141.0 (2×**C**), 136.7 (**C**), 136.0 (**C**), 128.9 (2×**C**H), 128.8 (2×**C**H), 127.8 (**C**H), 127.5 (2×**C**H), 126.2 (2×**C**H), 125.7 (**C**H), 99.9 (**C**H), 88.1 (**C**), 63.1 (**C**H), 52.5 (N**C**H_2), 48.5 (**C**H), 27.7 (**C**H_2), 25.3 (**C**H_2), 22.8 (**C**H_2), 22.1 (**C**H_2), 9.2 (**C**H_3) ppm.

Signals attributed to the minor diastereoisomer:
172.4 (**C**), 150.7 (**C**), 145.0 (**C**), 140.4 (**C**H), 137.3 (2×**C**), 129.0 (**C**H), 128.9 (2×**C**H), 128.3 (**C**H), 128.1 (**C**H), 127.6 (**C**H), 127.2 (2×**C**H), 127.1 (**C**H), 126.9 (**C**H), 102.8 (**C**H), 89.5 (**C**), 65.2 (**C**H), 53.2 (N**C**H_2), 46.3 (**C**H), 28.0 (**C**H_2), 27.4 (**C**H_2), 22.5 (**C**H_2), 21.4 (**C**H_2), 10.1 (**C**H_3) ppm.

LRMS (ESI $^+$)

398 ($[M+H]^+$, 100%).

HRMS (ESI $^+$)

Found: 398.2122. $C_{27}H_{28}NO_2$ $[M+H]^+$ requires 398.2115.
Found: 420.1939. $C_{27}H_{27}NaNO_2$ $[M+Na]^+$ requires 420.1934.

5-(Cyclohex-1-en-1-ylethynyl)-4-(dibenzylamino)-3-methylfuran-2(5*H*)-one (5.2):

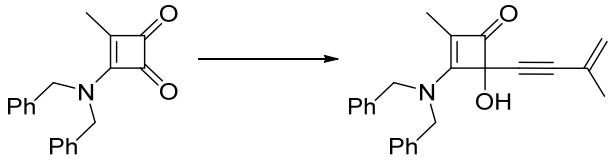
δ_H (400 MHz, $CDCl_3$)

7.41 – 7.32 (7H, m, 7×Ar**H**)
7.25 – 7.23 (3H, m, 3×Ar**H**)
6.11 (1H, m, C=C**H**)
5.53 (1H, s, C**H**)
4.83 (2H, d, *J* = 16.4 Hz, NC$\mathbf{H}_2$)
4.43 (2H, d, *J* = 16.5 Hz, NC$\mathbf{H}_2$),
2.13 – 2.05 (3H, m, C$\mathbf{H}_2$ + C**H**H)
1.93 (3H, app d, *J* = 0.7 Hz, C$\mathbf{H}_3$),
1.66 – 1.56 (3H, m, C$\mathbf{H}_2$ + CH**H**) ppm.

LRMS (ESI +)

398 ([M+H]+, 100%).

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-(3-methylbut-3-en-1-yn-1-yl)cyclobut-2-en-1-one (4.140)



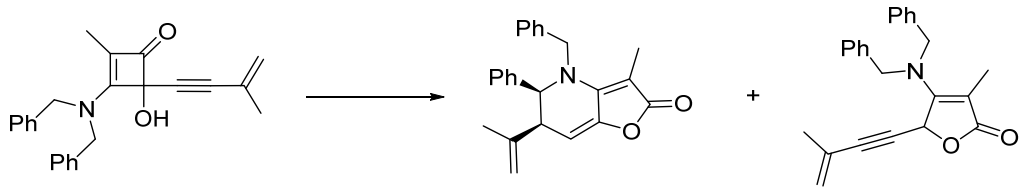
4.29
$C_{19}H_{17}NO_2$
Mol Wt: 291.35

4.140
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

To a solution of 2-methyl-1-buten-3-yne (0.18 mL, 1.94 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 0.90 mL, 2.25 mmol) dropwise. After 15 min, the solution was added *via* cannula to a solution of cyclobutenedione **4.29** (473 mg, 1.62 mmol) in THF (50 mL) at –78 °C. After 75 min, sat. NH_4Cl (20 mL) was added, the solution was warmed to RT and diluted with water (30 mL). The aqueous phase was separated and extracted with DCM (2 x 50 mL) and the combined organic phases dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (10 – 30% acetone/ DCM) afforded the title compound **4.140** (544 mg, 1.52 mmol, 94%) as an off-white solid.

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3242 (w), 2921 (w), 1748 (m), 1590 (s), 1572 (vs), 1496 (w), 1440 (m), 1365 (w), 1289 (w), 1258 (m), 1178 (w), 1118 (m).
δ_H (400 MHz, $CDCl_3$)	7.42 – 7.32 (8H, m, 8×Ar**H**) 7.22 (2H, d, *J* = 7.1 Hz, 2×Ar**H**) 5.28 (1H, dq, *J* = 1.8, 1.0 Hz, C=C**H**H) 5.24 (1H, dq, *J* = 1.8, 1.6 Hz, C=CH**H**) 4.76 (1H, d, *J* = 15.3 Hz, NC**H**H) 4.67 (1H, d, *J* = 15.2 Hz, NCH**H**) 4.48 (1H, d, *J* = 16.0 Hz, NC**H**H) 4.37 (1H, d, *J* = 16.0 Hz, NCH**H**) 1.84 (3H, t, *J* = 1.2 Hz, C**H**$_3$) 1.72 (3H, s C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	184.7 (**C**), 170.5 (**C**), 135.5 (**C**), 135.1 (**C**), 129.1 (2×**C**H), 128.8 (2×**C**H), 128.7 (2×**C**H), 128.1 (**C**H), 128.1 (**C**H), 126.9 (2×**C**H), 125.9 (**C**), 123.0 (**C**H$_2$), 114.8 (**C**), 88.9 (**C**), 83.9 (**C**), 82.2 (**C**), 53.7 (**C**H$_2$), 50.9 (**C**H$_2$), 23.0 (**C**H$_3$), 7.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	380 ([M+Na]$^+$, 40%), 358 ([M+H]$^+$, 100%).

rel-(5*S*,6*S*)-4-Benzyl-3-methyl-5-phenyl-6-(prop-1-en-2-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.141)



4.140
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

4.141
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

4.142
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

Alkynylcyclobutenone **4.140** (504 mg, 1.40 mmol) in DMSO (60 mL) was heated at 150 °C. After 20 min, the reaction was cooled to RT and diluted with water (60 mL). The mixture was extracted with ethyl acetate (3 x 60 mL) then the combined organic phases washed were with water (3 x 180 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (20 – 50% diethyl ether/petroleum ether 40 – 60 °C) afforded the title compound **4.141** (175 mg, 0.491 mmol, 35%, *d.r.* 5:1) as a yellow oil and furanone byproduct **4.142** as a brown oil (102 mg, 0.285 mmol, 20%).

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

3028 (w), 2924 (w), 1754 (s), 1696 (w), 1617 (vs), 1584 (w), 1495 (w), 1450 (m), 1359 (w), 1289 (br), 1158 (w), 1039 (w).

δ_H (400 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
7.37 – 7.31 (6H, m, 6×Ar**H**)
7.18 – 7.16 (4H, m, 4×Ar**H**)
5.33 (1H, d, *J* = 5.9 Hz, C=C**H**)
5.07 (1H, d, *J* = 15.8 Hz, NC**H**H)
4.92 (1H, m, C=C**H**H)
4.84 (1H, m, C=CH**H**)
4.26 (1H, d, *J* = 1.5 Hz, NC**H**Ph)
3.99 (1H, d, *J* = 15.9 Hz, NCH**H**)
3.11 (1H, d, *J* = 5.3 Hz, C**H**)
2.01 (3H, s, C**H**$_3$)
1.64 (3H, s, C**H**$_3$) ppm.

Signals attributed to the minor diastereoisomer:
7.37 – 7.31 (8H, m, 8×Ar**H**)
7.11 (2H, m, 2×Ar**H**)
5.48 (1H, d, *J* = 2.6 Hz, C=C**H**)
5.00 (1H, d, *J* = 16.3 Hz, NC**H**H)
4.77 (1H, m, C=C**H**H)
4.61 (1H, s, C=CH**H**)
4.30 (1H, d, *J* = 7.1 Hz, NC**H**Ph)

δ_H (400 MHz, $CDCl_3$)

4.00 (1H, d, *J* = 16.6 Hz, NCH**H**)
3.86 (1H, dd, *J* = 7.0, 2.6 Hz, C**H**)
1.94 (3H, s, C$\mathbf{H}_3$)
1.38 (3H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$)

Signals attributed to the major diastereoisomer:
172.4 (**C**), 150.1 (**C**), 144.9 (**C**), 143.9 (**C**), 140.7 (**C**), 136.5 (**C**), 128.9 (2×**C**H), 128.8 (2×**C**H), 128.0 (**C**H), 127.9 (**C**H), 127.5 (2×**C**H), 126.2 (2×**C**H), 114.4 (**C**H_2), 100.0 (**C**H), 88.6 (**C**), 62.8 (**C**H), 52.6 (**C**H_2), 48.5 (**C**H), 20.9 (**C**H_3), 9.2 (**C**H_3) ppm.

Signals attributed to the minor diastereoisomer:
172.3 (**C**), 150.4 (**C**), 144.1 (**C**), 142.2 (**C**), 137.1 (**C**), 136.7 (**C**), 129.0 (2×**C**H), 128.9 (**C**H), 128.3 (**C**H), 128.3 (2×**C**H), 128.3 (2×**C**H), 126.9 (2×**C**H), 115.6 (**C**H_2), 102.2 (**C**H), 89.9 (**C**), 64.7 (**C**H), 52.5 (**C**H_2), 46.3 (**C**H), 21.7 (**C**H_3), 9.1 (**C**H_3) ppm.

LRMS (ESI $^+$)

380 $[M+Na]^+$, 35%, 358 ($[M+H]^+$, 100%).

HRMS (ESI $^+$)

Found: 358.1799. $C_{24}H_{24}NO_2$ $[M+H]^+$ requires 358.1802.

4-(Dibenzylamino)-3-methyl-5-(3-methylbut-3-en-1-yn-1-yl)furan-2(5*H*)-one (4.142):

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)

3029 (w), 2922 (w), 1738 (s), 1619 (vs), 1495 (w), 1430 (m), 1354 (w), 1296 (m), 1165 (w), 1086 (m).

δ_H (400 MHz, $CDCl_3$)

7.40 – 7.31 (6H, m, 6×Ar**H**)
7.24 – 7.22 (4H, m, 4×Ar**H**)
5.53 (1H, s, C=C**H**)
5.31 – 5.20 (2H, m, C=C$\mathbf{H}_2$)
4.80 (2H, d, *J* = 16.4 Hz, C$\mathbf{H}_2$)
4.43 (2H, d, *J* = 16.5 Hz, C$\mathbf{H}_2$)
1.93 (3H, app d, *J* = 0.8 Hz, C$\mathbf{H}_3$),
1.84 (3H, app dd, *J* = 1.1, 0.4 Hz, C$\mathbf{H}_3$) ppm.

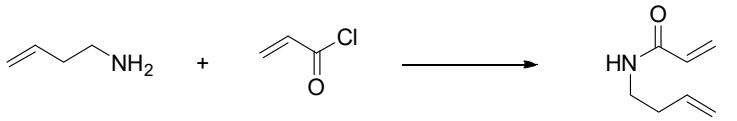
δ_C (100 MHz, $CDCl_3$)

175.1 (**C**), 161.5 (**C**), 136.5 (2×**C**), 129.0 (4×**C**H), 127.9 (2×**C**H), 126.8 (4×**C**H), 125.3 (**C**), 124.0 (**C**H_2), 90.1 (**C**), 89.1 (**C**), 81.1 (**C**), 67.2 (**C**H), 53.0 (2×**C**H_2), 22.8 (**C**H_3), 9.9 (**C**H_3) ppm.

LRMS (ESI $^+$)

380 $[M+Na]^+$, 64%, 358 $[M+H]^+$, 100%).

N-(But-3-en-1-yl)acrylamide (5.5)



5.3
C_4H_9N
Mol Wt: 71.12

5.4
C_3H_3ClO
Mol Wt: 90.51

5.5
$C_7H_{11}NO$
Mol Wt: 125.17

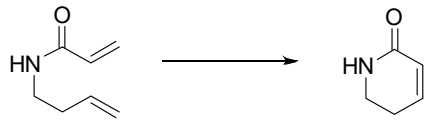
Following a literature procedure:[143]

To a solution of 3-buten-1-amine **5.3** (0.28 mL, 3.00 mmol) in DCM (10 mL) was added trimethylamine (0.5 mL, 3.59 mmol). The reaction was cooled to 0 °C, acryloyl chloride **5.4** (0.33 mL, 4.00 mmol) was added then the solution was warmed to RT. After 3 h, water (20 mL) was added then the aqueous phase was separated and extracted with DCM (2 x 20 mL). The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography (40 – 60% ethyl acetate/petroleum ether 40 – 60 °C) afforded the title compound **5.5** (432 mg, 3.45 mmol, quant.) as a colourless oil.

Data is consistent with literature values.[143–145]

FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3278 (br m), 3079 (w), 2932 (w), 1655 (vs), 1625 (m), 1547 (s), 1437 (w), 1408 (m), 1316 (w), 1244 (m), 1151 (w), 1066 (w), 986 (m), 956 (m), 916 (m).
δ_H (400 MHz, $CDCl_3$)	6.24 (1H, dd, *J* = 17.0, 1.6 Hz, COCH=C**H**H) 6.14 (1H, br s, N**H**) 6.11 (1H, dd, *J* = 17.1, 10.2 Hz, COC**H**) 5.76 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, CH_2C**H**=) 5.60 (1H, dd, *J* = 10.2, 1.6 Hz, COCH=CH**H**) 5.11 – 5.04 (2H, m, CH_2CH=C**H**$_2$) 3.38 (2H, td, *J* = 6.8, 5.9 Hz, NC**H**$_2$) 2.28 (2H, qt, *J* = 6.8, 1.3 Hz, C**H**$_2$CH=) ppm.
δ_C (100 MHz, $CDCl_3$)	165.6 (**C**), 135.1 (**C**H), 130.9 (**C**H), 126.1 (**C**H$_2$), 117.1 (**C**H$_2$), 38.5 (**C**H$_2$), 33.5 (**C**H$_2$) ppm.
LRMS (ESI $^+$)	126 ([M+H]$^+$, 100%).

5,6-Dihydropyridin-2(1*H*)-one (5.6)



5.5
$C_7H_{11}NO$
Mol Wt: 125.17

5.6
C_5H_7NO
Mol Wt: 97.12

Following a literature procedure[144]*:*

To a solution of *N*-(but-3-en-1-yl)acrylamide **5.5** (196 mg, 1.57 mmol) in anhydrous DCM (100 mL) was added 6 mol % Grubbs II catalyst (89.0 mg, 0.094 mmol). The reaction heated at reflux under argon for 5 h, then cooled to RT, filtered through celite and concentrated in vacuo. Purification by column chromatography (70 – 100% ethyl acetate/petroleum ether 40 – 60 °C followed by 100% acetone) afforded the title compound **5.6** (122 mg, 1.25 mmol, 80%) as a dark brown/green solid.

Data is consistent with literature values.[144]

MP (DCM)	61 – 63 °C.
FT-IR (ν_{max}/cm^{-1}, $CHCl_3$)	3277 (br w), 1674 (vs), 1606 (m), 1484 (m), 1457 (w), 1426 (w), 1340 (w), 1313 (w), 1147 (w), 1113 (w), 808 (m).
δ_H (400 MHz, $CDCl_3$)	6.65 (1H, dt, *J* = 10.0, 4.2 Hz, =C**H**CH_2) 6.32 (1H, br s, N**H**) 5.91 (1H, br d, *J* = 10.0 Hz, COC**H**) 3.43 (2H, t, *J* = 7.2 Hz, NC**H**$_2$) 2.36 (2H, tdd, *J* = 7.2, 4.3, 1.9 Hz, C**H**$_2$) ppm.
δ_C (100 MHz, $CDCl_3$)	166.5 (**C**), 141.5 (**C**H), 124.8 (**C**H), 39.6 (**C**H_2), 23.8 (**C**H_2) ppm.
LRMS (ESI $^+$)	98 ($[M+H]^+$, 100%).

5.7 Experimental procedures for the photochemical reactions of dihydrofuropyridinones to azocines

Set-Up A: Light source: 6 × 1.7W UVA (365 nm) LEDs. Reactor: Spiral wound FEP tubing with 6 mL capacity. **See Chapter 3 Figure 3.3.5** and **Figure 3.3.6**.

SAFETY NOTE: In operation, the photochemical unit is housed within a protective cover.

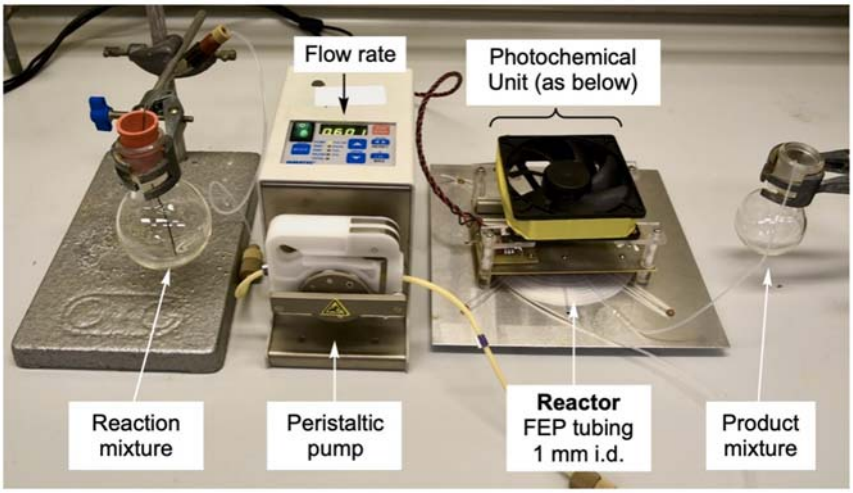
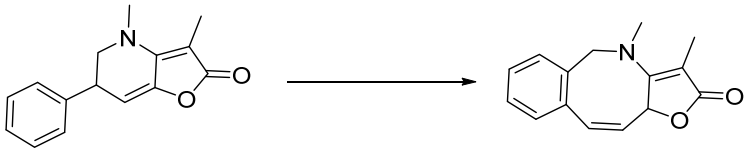


Figure 3.3.5. See Chapter 3.

Set-Up B: Light source: PL-L 36 W/10/4P. Reactor as detailed in *Angew. Chem. Int. Ed.* **2015**, *54*, 4531–4534.[14] **See Chapter 3 Figure 3.3.1** and **Figure 3.3.2**.

Set-Up C: Light source: PL-S/9W/10/2P. Reactor: FEP tubing wrapped around quartz cylinder with 2 mL capacity. Not under continuous flow. **See Chapter 3 Figure 3.3.3** and **Figure 3.3.4**.

(*Z*)-3,4-Dimethyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (3.54)



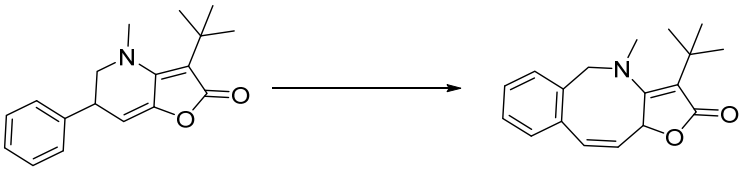
1.129
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

3.54
$C_{15}H_{15}NO_2$
Mol Wt: 241.29

A solution of dihydrofuropyridinone **1.129** (91.6 mg, 0.380 mmol) in dry acetonitrile (20 mL) was irradiated with UVA following set-up B for a residence time of 120 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30 – 70% ethyl acetate/ petroleum ether 40 – 60 °C) to give the title compound **3.54** (58.9 mg, 0.244 mmol, 64%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2928 (w), 1722 (s), 1611 (s), 1415 (m), 1316 (m), 1088 (m), 1025 (m).
δ_H (400 MHz, $CDCl_3$)	7.38 – 7.28 (4H, m, 4×Ar**H**) 6.71 (1H, dd, *J* = 12.1, 2.1 Hz, C=C**H**) 5.84 (1H, dd, *J* = 12.0, 4.6 Hz, HC=C**H**) 5.23 (1H, br dd, *J* = 4.6, 1.0 Hz, OC**H**) 4.48 (1H, d, *J* = 14.3 Hz, C**H**H) 4.05 (1H, d, *J* = 14.3 Hz, CH**H**) 3.32 (3H, s, NC**H**$_3$) 1.94 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.4 (**C**), 160.2 (**C**), 136.0 (**C**), 134.1 (**C**), 130.6 (**C**H), 130.3 (**C**H), 130.2 (**C**H), 128.5 (**C**H), 128.5 (**C**H), 128.3 (**C**H), 91.2 (**C**), 76.5 (**C**H), 56.5 (**C**H$_2$), 40.4 (**C**H$_3$), 9.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	242 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 242.1181. $C_{15}H_{16}NO_2$ [M+H]$^+$ requires 242.1103.

(*Z*)-3-(*tert*-Butyl)-4-methyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (3.58)



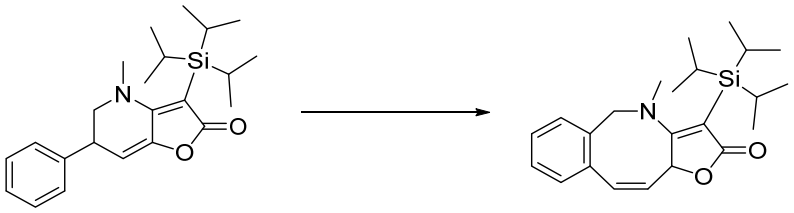
1.149
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

3.58
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

A solution of dihydrofuropyridinone **1.49** (129 mg, 0.455 mmol) in acetonitrile (11 mL) was irradiated with UVA following set-up A for a residence time of 10 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30 – 60% diethyl ether/ hexane) to give the title compound **3.58** (73.4 mg, 0.259 mmol, 57%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2958 (s), 2927 (m), 2870 (w), 1718 (s), 1639 (s), 1463 (m), 1366 (s).
δ_H (400 MHz, $CDCl_3$)	7.39 – 7.35 (4H, m, 4×Ar**H**) 6.93 (1H, dd, *J* = 10.8, 2.0 Hz, C=C**H**) 5.75 (1H, dd, *J* = 10.9, 6.0 Hz, HC=C**H**) 4.62 (1H, dd, *J* = 6.0, 1.8 Hz, OC**H**) 4.01 (1H, d, *J* = 14.8 Hz, C**H**H) 3.96 (1H, d, *J* = 14.9 Hz, CH**H**) 3.04 (3H, s, NC$\mathbf{H_3}$) 1.37 (9H, s, C(C$\mathbf{H_3}$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	173.4 (**C**), 161.5 (**C**), 136.6 (**C**), 132.7 (**C**), 131.3 (**C**H), 131.0 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 127.9 (**C**H), 127.9 (**C**H), 117.5 (**C**), 77.2 (**C**H), 53.9 (**C**H_2), 46.1 (**C**H_3), 32.1 (**C**), 28.6 (3×**C**H_3) ppm.
LRMS (ESI $^+$)	284 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 284.1643. $C_{18}H_{22}NO_2$ [M+H]$^+$ requires 284.1645.

(*Z*)-4-Methyl-3-(tri*iso*propylsilyl)-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (3.59)



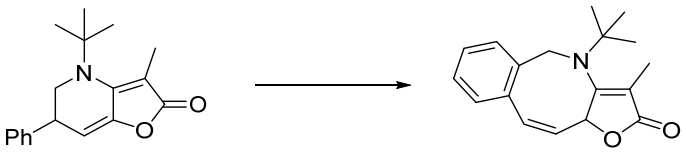
1.161
$C_{23}H_{33}NO_2Si$
Mol Wt: 383.61

3.59
$C_{23}H_{33}NO_2Si$
Mol Wt: 383.61

A solution of dihydrofuropyridinone **1.161** (104 mg, 0.272 mmol) in dry THF (20 mL) was irradiated with UVA following set-up B for a residence time of 120 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (10 – 50% ethyl acetate/ petroleum ether 40 – 60 °C) to give the title compound **3.59** (54 mg, 0.244 mmol, 52%) as a yellow solid.

MP (DCM)	147 – 148 °C.
FT-IR (ν_{max}/cm^{-1}, DCM)	2943 (m), 2864 (m), 1717 (m), 1568 (w), 1462 (w), 1160 (w).
δ_H (400 MHz, $CDCl_3$)	7.35 – 7.28 (4H, m , 4×Ar**H**) 6.72 (1H, dd, *J* = 11.9, 2.0 Hz, C=C**H**) 5.85 (1H, dd, *J* = 11.9, 4.5 Hz, HC=C**H**) 5.25 (1H, dd, *J* = 4.5, 2.1 Hz, OC**H**) 4.63 (1H, d, *J* = 14.6 Hz, C**H**H) 4.97 (1H, d, *J* = 14.7 Hz, CH**H**) 3.26 (3H, s, NC**H**$_3$) 1.51 (3H, sept, *J* = 7.6 Hz, 3×SiC**H)** 1.07 (9H, d, *J* = 7.5 Hz, 3×C**H**$_3$) 0.98 (9H, d, *J* = 7.6 Hz, 3×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	177.2 (**C**), 174.4 (**C**), 136.0 (**C**), 133.6 (**C**), 130.6 (**C**H), 130.1 (**C**H), 130.0 (**C**H), 129.1 (**C**H), 128.5 (2x**C**H), 87.4 (**C**), 78.4 (**C**H), 55.0 (**C**H$_2$), 44.6 (**C**H$_3$), 19.3 (3×**C**H$_3$), 18.9 (3×**C**H$_3$), 12.7 (3×**C**H) ppm.
LRMS (ESI $^+$)	384 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 384.2360. $C_{23}H_{34}NO_2Si$ [M+H]$^+$ requires 384.2353.

(*Z*)-4-(*tert*-Butyl)-3-methyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.9)



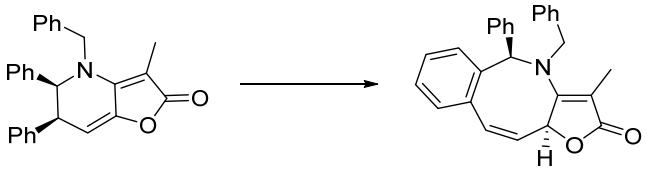
4.8
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

4.9
$C_{18}H_{21}NO_2$
Mol Wt: 283.37

A solution of dihydrofuropyridinone **4.8** (42.7 mg, 0.0151 mmol) in dry acetonitrile (2 mL) was irradiated with UVA following set-up C for a residence time of 25 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (10 – 40% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.9** (31.5 mg, 0.111 mmol, 74%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2957 (w), 2917 (s), 2849 (m), 1742 (s), 1634 (m), 1463 (w), 1407 (w), 1354 (w), 1198 (w), 1092 (w).
δ_H (400 MHz, $CDCl_3$)	7.25 – 7.22 (2H, m, 2×Ar**H**) 7.18 – 7.14 (2H, m, 2×Ar**H**) 6.58 (1H, dd, *J* = 11.9, 1.3 Hz, C=C**H**) 5.74 (1H, dd, *J* = 11.9, 6.1 Hz, HC=C**H**) 5.39 (1H, dd, *J* = 6.1, 0.9 Hz, OC**H**) 4.57 (1H, d, *J* = 16.3 Hz, C**H**H) 4.31 (1H, d, *J* = 16.3 Hz, CH**H**) 1.81 (3H, d, *J* = 1.2 Hz, C**H**$_3$) 1.28 (9H, s, NC(C**H**$_3$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	175.8 (**C**), 165.9 (**C**), 137.4 (**C**), 134.6 (**C**), 131.5 (**C**H), 130.8 (**C**H), 130.1 (**C**H), 128.7 (**C**H), 128.4 (**C**H), 127.1 (**C**H), 107.7 (**C**), 79.0 (**C**H) 57.5 (**C**), 52.1 (**C**H$_2$), 29.1 (3×**C**H$_3$), 12.2 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	284 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 284.1643. $C_{18}H_{22}NO_2$ [M+H]$^+$ requires 284.1645.

rel-(5*S*,11a*R*,10*Z*)-4-Benzyl-3-methyl-5-phenyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.32)



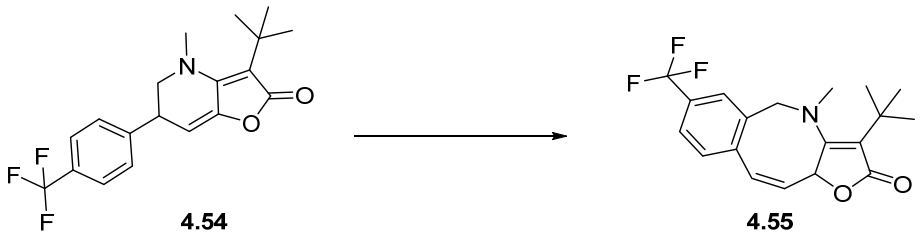
1.145
$C_{27}H_{23}NO_2$
Mol Wt: 393.49

4.32
$C_{27}H_{23}NO_2$
Mol Wt: 393.49

A solution of dihydrofuropyridinone **1.145** (161 mg, 0.410 mmol) in THF (10 mL) was irradiated with UVA following set-up A for a residence time of 7 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30 – 50% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.32** (137 mg, 0.349 mmol, 85%) as a white foam.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3059 (w), 3029 (w), 1731 (s), 1606 (vs), 1582 (m), 1494 (w), 1436 (m), 1340 (w), 1312 (m), 1181 (w), 1090 (m), 1056 (m).
δ_H (400 MHz, $CDCl_3$)	7.46 – 7.39 (2H, m, 2×Ar**H**) 7.35 – 7.20 (8H, m, 8×Ar**H**) 7.16 (1H, d, *J* = 7.2 Hz, Ar**H**) 6.91 (1H, dd, *J* = 7.6, 0.7 Hz, Ar**H**) 6.80 (2H, br d, *J* = 6.5 Hz, Ar**H**) 6.27 (1H, dd, *J* = 10.3, 1.1 Hz, C=C**H**) 5.75 (1H, s, C**H**Ph) 5.56 (1H, d, *J* = 16.3 Hz, NC**H**H) 5.40 (1H, dd, *J* = 10.5, 6.8 Hz, HC=C**H**) 5.04 (1H, d with fine splitting, *J* = 6.8 Hz, OC**H**) 4.28 (1H, d, *J* = 16.4 Hz, NCH**H**) 2.03 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.7 (**C**), 161.6 (**C**), 140.5 (**C**), 138.9 (**C**), 137.8 (**C**), 137.5 (**C**), 132.7 (**C**H), 132.5 (**C**H), 129.1 (2×**C**H), 128.7 (**C**H), 128.6 (2×**C**H), 128.4 (**C**H), 128.1 (2×**C**H), 128.1 (**C**H), 127.1 (2×**C**H), 126.8 (**C**H), 126.4 (2×**C**H), 90.6 (**C**), 76.0 (**C**H), 71.1 (**C**H), 56.8 (**C**H$_2$), 10.7 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	416 $[M+Na]^+$, 54%, 394 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 394.1804. $C_{27}H_{24}NO_2$ $[M+H]^+$ requires 394.1802. Found: 416.1622. $C_{27}H_{23}NNaO_2$ $[M+Na]^+$ requires 416.1621.

(*Z*)-3-(*tert*-Butyl)-4-methyl-7-(trifluoromethyl)-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.55)



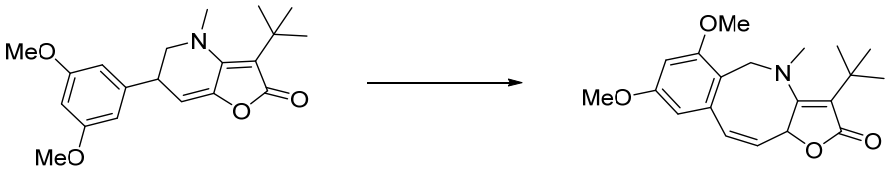
4.54
$C_{19}H_{20}F_3NO_2$
Mol Wt: 351.37

4.55
$C_{19}H_{20}F_3NO_2$
Mol Wt: 351.37

A solution of dihydrofuropyridinone **4.54** (304 mg, 0.866 mmol) in acetonitrile (120 mL) was irradiated with UVA following set-up B for a residence time of 90 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (5 – 10% ethyl acetate/ petroleum ether 40 – 60 °C) to give the title compound **4.55** (86.3 mg, 0.246 mmol, 28%) as a yellow solid.

MP (DCM)	127 – 128 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2971 (m), 1790 (s), 1761 (s), 1736 (m), 1636 (w), 1589 (vs), 1482 (w), 1453 (w), 1356 (s).
δ_H (400 MHz, $CDCl_3$)	7.63 – 7.61 (2H, m, 2×Ar**H**) 7.48 (1H, d, *J* = 8.0 Hz, Ar**H**) 6.93 (1H, d, *J* = 11.0 Hz, C=C**H**) 5.86 (1H, dd, *J* = 11.0, 5.9 Hz, HC=C**H**) 4.60 (1H, dd, *J* = 6.0, 1.8 Hz, OC**H**) 4.07 (1H, d, *J* = 15.4 Hz, C**H**H) 4.01 (1H, d, *J* = 15.3 Hz, CH**H**) 3.03 (3H, s, NC$\mathbf{H_3}$) 1.36 (9H, s, C(C$\mathbf{H_3}$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	173.0 (**C**), 160.6 (**C**), 140.0 (**C**), 133.4 (**C**), 130.4 (**C**, q, J_{C-F} = 33 Hz), 129.8 (**C**H), 128.6 (2×**C**H), 127.8 (**C**H, q, *J* = 3.7 Hz), 124.7 (**C**H, q, *J* = 3.7 Hz), 123.2 (**C**F$_3$, q, J_{C-F} = 272 Hz), 118.8 (**C**), 76.8 (**C**H), 53.7 (**C**H$_2$), 46.1 (**C**H$_3$), 32.2 (**C**), 28.5 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	352 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 352.1519. $C_{19}H_{21}F_3NO_2$ [M+H]$^+$ requires 352.1520.

(*Z*)-3-(*tert*-Butyl)-6,8-dimethoxy-4-methyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.76)



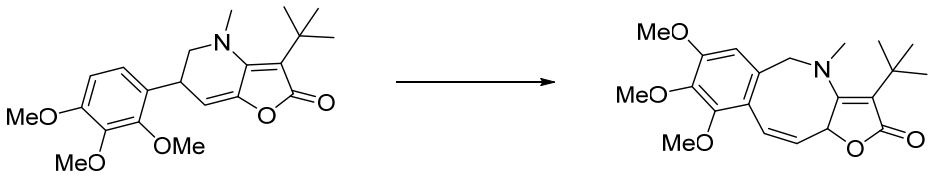
4.75
$C_{20}H_{25}NO_4$
Mol Wt: 343.42

4.76
$C_{20}H_{25}NO_4$
Mol Wt: 343.42

A solution of dihydrofuropyridinone **4.75** (83.3 mg, 0.223 mmol) in acetonitrile (7 mL) was degassed then irradiated with UVA following set-up A for a residence time of 15 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30 – 60% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.76** (50.9 mg, 0.136 mmol, 61%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2954 (w), 1735 (vs), 1598 (vs), 1458 (m), 1424 (w), 1398 (w), 1343 (w), 1308 (m), 1295 (m), 1216 (w), 1198 (m), 1147 (s), 1116 (w), 1072 (w), 1050 (s), 1035 (s).
δ_H (400 MHz, $CDCl_3$)	6.84 (1H, dd, *J* = 10.7, 1.5 Hz, C=C**H**) 6.49 (1H, d, *J* = 2.2 Hz, Ar**H**) 6.39 (1H, d, *J* = 2.3 Hz, Ar**H**) 5.69 (1H, dd, *J* = 10.6, 6.1 Hz, HC=C**H**) 4.68 (1H, dd, *J* = 6.1, 1.7 Hz, OC**H**) 4.35 (1H, d, *J* = 14.8 Hz, C**H**H) 3.86 (3H, s, OC**H**$_3$) 3.83 (3H, s, OC**H**$_3$) 3.63 (1H, d, *J* = 14.9 Hz, CH**H**) 3.12 (3H, s, NC**H**$_3$) 1.36 (9H, s, 3×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	173.7 (**C**), 161.4 (**C**), 159.7 (**C**), 159.6 (**C**), 139.3 (**C**), 131.1 (**C**H), 128.6 (**C**H), 116.0 (**C**), 113.3 (**C**), 102.3 (**C**H), 98.7 (**C**H), 77.2 (**C**H), 55.42 (**C**H$_3$), 55.41 (**C**H$_3$), 47.4 (**C**H$_3$), 47.1 (**C**H$_2$), 31.8 (**C**), 29.1 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	344 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 366.1670. $C_{20}H_{25}NNaO_4$ [M+Na]$^+$ requires 366.1676.

(*Z*)-3-(*tert*-Butyl)-7,8,9-trimethoxy-4-methyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.81)



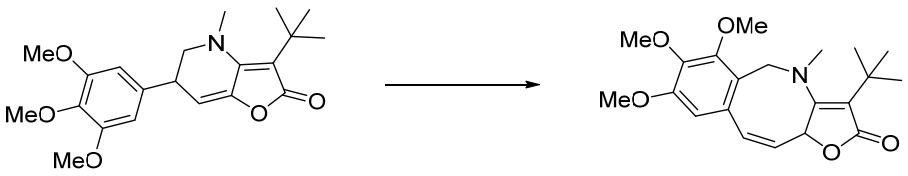
4.80
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

4.81
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

A solution of dihydrofuropyridinone **4.80** (122 mg, 0.326 mmol) in acetonitrile (8 mL) was irradiated with UVA following set-up A for a residence time of 10 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30 – 50% diethyl ether/ hexane to give the title compound **4.81** (89.7 mg, 0.240 mmol, 74%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2956 (w), 2917 (s), 2849 (m), 1741 (vs), 1616 (m), 1494 (m), 1458 (m), 1410 (w), 1376 (m), 1332 (m), 1279 (w), 1249 (w), 1195 (w), 1123 (s), 1051 (m), 1031 (m), 1003 (m).
δ_H (400 MHz, $CDCl_3$)	6.89 (1H, dd, *J* = 10.7, 1.8 Hz, C=C**H**) 6.64 (1H, s, Ar**H**) 5.70 (1H, dd, *J* = 10.6, 6.1 Hz, HC=C**H**) 4.66 (1H, dd, *J* = 6.1, 1.8 Hz, OC**H**) 3.92 – 3.84 (2H, m, C**H**$_2$) 3.91 (3H, s, OC**H**$_3$) 3.90 (3H, s, OC**H**$_3$) 3.87 (3H, s, OC**H**$_3$) 3.03 (3H, s, NC**H**$_3$) 1.36 (9H, s, C(C**H**$_3$)$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	173.4 (**C**), 161.3 (**C**), 153.7 (**C**), 151.0 (**C**), 141.7 (**C**), 128.6 (**C**), 127.8 (**C**H), 127.2 (**C**H), 124.2 (**C**), 117.3 (**C**), 110.0 (**C**H), 77.6 (**C**H) 61.1 (**C**H$_3$), 61.0 (**C**H$_3$), 56.1 (**C**H$_3$), 54.0 (**C**H$_2$), 46.2 (**C**H$_3$), 32.0 (**C**), 28.6 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	396 [M+ Na]$^+$, 61%; 374 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 374.1964. $C_{21}H_{28}NO_5$ [M+H]$^+$ requires 374.1962.

(*Z*)-3-(*tert*-Butyl)-6,7,8-trimethoxy-4-methyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.86)



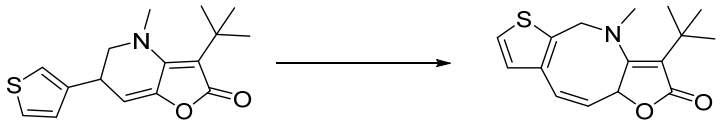
4.85
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

4.86
$C_{21}H_{27}NO_5$
Mol Wt: 373.45

A solution of dihydrofuropyridinone **4.85** (124 mg, 0.332 mmol) in 1,4-dioxane (10 mL) was irradiated with UVA following set-up A for a residence time of 7 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (20 – 70% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.86** (63.2 mg, 0.169 mmol, 51%) as a yellow oil.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2940 (m), 1739 (vs), 1608 (m), 1565 (w), 1490 (m), 1464 (w), 1383 (m), 1334 (m), 1244 (w), 1194 (w), 1120 (s), 1052 (m), 1031 (m).
δ_H (400 MHz, $CDCl_3$)	6.81 (1H, dd, *J* = 10.7, 1.4 Hz, C=C**H**) 6.57 (1H, s, Ar**H**) 5.69 (1H, dd, *J* = 10.7, 6.1 Hz, HC=C**H**) 4.68 (1H, dd, *J* = 6.1, 1.7 Hz, OC**H**) 4.26 (1H, d, *J* = 14.7 Hz, C**H**H) 3.96 (3H, s, OC**H**$_3$) 3.89 (3H, s, OC**H**$_3$) 3.88 (3H, s, OC**H**$_3$) 3.65 (1H, d, *J* = 14.7 Hz, CH**H**) 3.10 (3H, s, NC**H**$_3$) 1.36 (9H, s, C(C**H**$_3$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	173.6 (**C**), 161.5 (**C**), 152.9 (**C**), 152.7 (**C**), 142.1 (**C**), 133.0 (**C**), 130.8 (**C**H), 128.3 (**C**H), 120.7 (**C**), 114.3 (**C**), 105.6 (**C**H), 77.2 (**C**H), 60.8 (**C**H$_3$), 60.7 (**C**H$_3$), 56.0 (**C**H$_3$), 47.7 (**C**H$_2$), 47.1 (**C**H$_3$), 31.9 (**C**), 29.0 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	396 [M+ Na]$^+$, 40%; 374 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 374.1966. $C_{21}H_{28}NO_5$ [M+H]$^+$ requires 374.1962.

(*Z*)-4-(*tert*-Butyl)-3-methyl-5,10a-dihydrofuro[3,2-b]thieno[3,2-f]azocin-2(4*H*)-one (4.91)



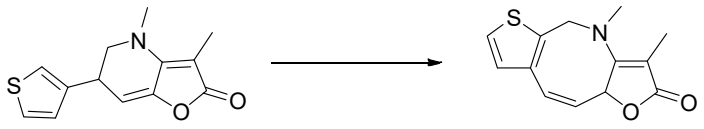
4.89
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

4.91
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

A solution of dihydrofuropyridinone **4.89** (139 mg, 0.479 mmol) in tetrahydrofuran (20 mL) was degassed then irradiated with UVA following set-up A for a residence time of 20 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (10 – 40% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.91** (38.6 mg, 0.133 mmol, 28%) as a yellow oil; followed by a 2:3 mixture of title compound **4.91** and dihydrofuropyridinone **4.89** (95.4 mg, 69%) as an orange oil, therefore in a combined **4.91** yield of 46%.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2955 (w), 2918 (m), 2850 (w), 1742 (vs), 1618 (m), 1463 (w), 1365 (w), 1345 (w), 1291 (w).
δ_H (400 MHz, $CDCl_3$)	7.27 (1H, d, *J* = 5.1 Hz, Ar**H**) 7.01 (1H, d, *J* = 5.1 Hz, Ar**H**) 6.74 (1H, dd, *J* = 10.5, 1.8 Hz, C=C**H**) 5.70 (1H, dd, *J* = 10.5, 5.8 Hz, HC=C**H**) 4.79 (1H, dd, *J* = 5.8, 1.8 Hz, OC**H**) 4.22 (1H, d, *J* = 16.0 Hz, C**H**H) 3.89 (1H, d, *J* = 16.0 Hz, CH**H**) 2.98 (3H, s, NC**H**$_3$) 1.37 (9H, s, C(C**H**$_3$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	173.2 (**C**), 162.2 (**C**), 137.9 (**C**), 132.9 (**C**), 128.6 (**C**H), 126.8 (**C**H), 126.2 (**C**H), 124.9 (**C**H), 119.0 (**C**), 77.8 (**C**H), 48.9 (**C**H$_2$), 45.7 (**C**H$_3$), 32.2 (**C**), 28.6 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	290 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 312.1023. $C_{16}H_{19}NNaO_2S$ [M+Na]$^+$ requires 312.1029.

(*Z*)-3,4-Dimethyl-5,10a-dihydrofuro[3,2-b]thieno[3,2-f]azocin-2(4*H*)-one (4.98)



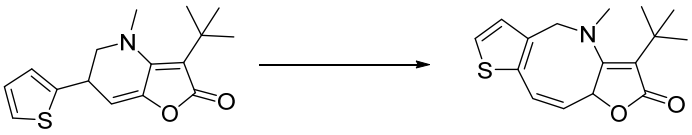
4.96
$C_{13}H_{13}NO_2S$
Mol Wt: 247.31

4.98
$C_{13}H_{13}NO_2S$
Mol Wt: 247.31

A solution of dihydrofuropyridinone **4.96** (42.9 mg, 0.173 mmol) in tetrahydrofuran (5 mL) was degassed then irradiated with UVA following set-up A for a residence time of 20 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (5 – 20% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.98** (13.4 mg, 0.054 mmol, 31%) as a yellow oil and a recovered dihydrofuropyridinone **4.96** (24.6 mg, 0.100 mmol, 57%).

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2921 (m), 2852 (w), 1724 (s), 1613 (vs), 1460 (w), 1407 (m), 1331 (w), 1310 (m), 1083 (m), 1039 (m), 757 (w).
δ_H (400 MHz, $CDCl_3$)	7.23 (1H, d, *J* = 5.1 Hz, Ar**H**) 6.97 (1H, d, *J* = 5.1 Hz, Ar**H**) 6.63 (1H, dd, *J* = 11.3, 2.0 Hz, C=C**H**) 5.78 (1H, dd, *J* = 11.3, 4.8 Hz, HC=C**H**) 5.25 (1H, ddd, *J* = 4.9, 2.0, 0.9 Hz, OC**H**) 4.51 (1H, d, *J* = 15.7 Hz, C**H**H) 4.11 (1H, d, *J* = 15.5 Hz, CH**H**) 3.32 (3H, s, NC**H**$_3$) 1.96 (3H, d, *J* = 0.7 Hz, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.3 (**C**), 160.6 (**C**), 137.9 (**C**), 134.2 (**C**), 128.4 (**C**H), 128.1 (**C**H), 125.5 (**C**H), 124.6 (**C**H), 93.4 (**C**), 77.2 (**C**H), 50.3 (**C**H$_2$), 41.1 (**C**H$_3$), 9.9 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	248 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 248.0736. $C_{13}H_{14}NO_2S$ [M+H]$^+$ requires 248.0740.

(*Z*)-3-(*tert*-Butyl)-4-methyl-5,10a-dihydrofuro[3,2-b]thieno[2,3-f]azocin-2(4*H*)-one (4.103)



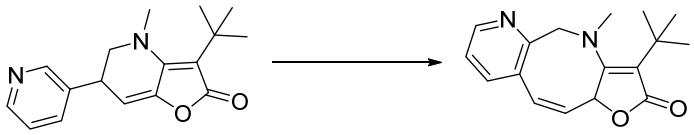
4.101
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

4.103
$C_{16}H_{19}NO_2S$
Mol Wt: 289.39

A solution of dihydrofuropyridinone **4.101** (68.4 mg, 0.236 mmol) in acetonitrile (8 mL) was degassed then irradiated with UVA following set-up A for a residence time of 20 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (5 – 20% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.103** (18.4 mg, 0.064 mmol, 27%) as a yellow oil; followed by a 4:1 mixture of title compound **4.103** and dihydrofuropyridinone **4.101** (24.1 mg, 35%) as yellow oil, therefore in a combined **4.103** yield of 55%.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2954 (m), 2867 (w), 1782 (w), 1736 (vs), 1615 (s), 1479 (w), 1438 (w), 1396 (w), 1289 (m), 1206 (m), 1095 (w), 1036 (s), 989 (m).
δ_H (400 MHz, $CDCl_3$)	7.36 (1H, d, *J* = 5.1 Hz, Ar**H**) 6.93 (1H, d, *J* = 5.0 Hz, Ar**H**) 6.69 (1H, dd, *J* = 10.8, 1.8 Hz, C=C**H**) 5.68 (1H, dd, *J* = 10.8, 5.6 Hz, HC=C**H**) 5.03 (1H, dd, *J* = 5.6, 2.0 Hz, OC**H**) 4.26 (1H, d, *J* = 16.0 Hz, C**H**H) 3.80 (1H, d, *J* = 16.0 Hz, CH**H**) 2.96 (3H, s, NC$\mathbf{H_3}$) 1.36 (9H, s, C(C$\mathbf{H_3}$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	173.4 (**C**), 163.4 (**C**), 136.8 (**C**), 134.8 (**C**), 129.7 (**C**H), 129.4 (**C**H), 126.7 (**C**H), 123.6 (**C**H), 118.2 (**C**), 77.4 (**C**H), 50.3 (**C**H$_2$), 45.5 (**C**H$_3$), 32.0 (**C**), 28.7 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	290 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 290.1211. $C_{16}H_{20}NO_2S$ [M+H]$^+$ requires 290.1209.

(*Z*)-3-(*tert*-Butyl)-4-methyl-5,11a-dihydrofuro[3,2-b]pyrido[3,2-f]azocin-2(4*H*)-one (4.107)



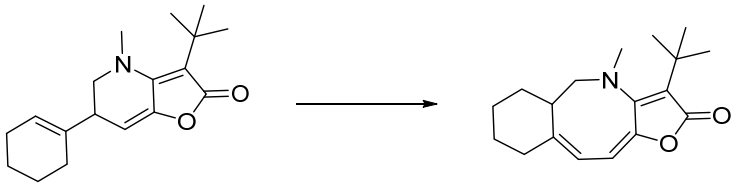
4.106
$C_{17}H_{20}N_2O_2$
Mol Wt: 284.36

4.107
$C_{17}H_{20}N_2O_2$
Mol Wt: 284.36

A solution of dihydrofuropyridinone **4.106** (93.7 mg, 0.330 mmol) in tetrahydrofuran (11 mL) was degassed then irradiated with UVA following set-up A for a residence time of 20 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (40 – 80% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.107** (23.0 mg, 0.081 mmol, 25%) as a yellow oil in addition to inseparable organic material.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2955 (w), 1740 (vs), 1613 (m), 1428 (w), 1365 (w), 1297 (w), 1202 (w), 1117 (w), 1051 (m), 1035 (m), 1001 (m).
δ_H (400 MHz, $CDCl_3$)	8.62 (1H, dd, *J* = 4.8, 1.7 Hz, Ar**H**) 7.66 (1H, dd, *J* = 7.8, 1.7 Hz, Ar**H**) 7.29 (1H, dd, *J* = 7.8, 4.7 Hz, Ar**H**) 6.90 (1H, dd, *J* = 10.9, 1.8 Hz, C=C**H**) 5.81 (1H, dd, *J* = 10.9, 6.0 Hz, HC=C**H**) 4.59 (1H, dd, *J* = 6.1, 1.9 Hz, OC**H**) 4.20 (1H, d, *J* = 14.6 Hz, C**H**H) 4.02 (1H, d, *J* = 14.8 Hz, CH**H**) 3.18 (3H, s, NC$\mathbf{H_3}$) 1.37 (9H, s, C(C$\mathbf{H_3}$)$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	173.1 (**C**), 160.9 (**C**), 152.1 (**C**), 149.4 (**C**H), 135.6 (**C**H), 131.4 (**C**), 129.8 (**C**H), 128.9 (**C**H), 122.5 (**C**H), 117.2 (**C**), 77.2 (**C**H), 55.7 (**C**H$_2$), 46.9 (**C**H$_3$), 32.1 (**C**), 28.7 (3×**C**H$_3$) ppm.
LRMS (ESI $^+$)	285 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 285.1597. $C_{17}H_{21}N_2O_2$ [M+H]$^+$ requires 285.1598.

(9aZ,11E)-3-(*tert*-Butyl)-4-methyl-5,5a,6,7,8,9-hexahydrobenzo[f]furo[3,2-b]azocin-2(4H)-one (4.111)



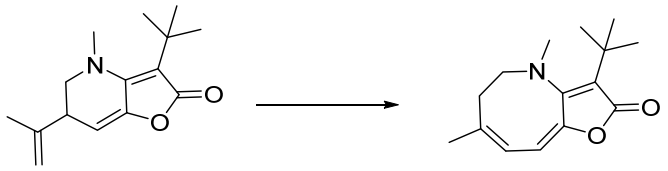
4.110
$C_{18}H_{25}NO_2$
Mol Wt: 287.40

4.111
$C_{18}H_{25}NO_2$
Mol Wt: 287.40

A solution of dihydrofuropyridinone **4.110** (208 mg, 0.724 mmol) in acetonitrile (20 mL) was irradiated with UVA following set-up A for a residence time of 10 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (10% ethyl acetate/ hexane) to give the title compound **4.111** (111 mg, 0.388 mmol, 54%) as a yellow solid.

MP ($CHCl_3$)	121 – 123 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2928 (m), 2857 (m), 1748 (vs), 1636 (w), 1591 (m), 1480 (w), 1451 (w), 1364 (w), 1320 (w), 1285 (w), 1251 (w), 1218 (w).
δ_H (400 MHz, $CDCl_3$)	5.81 (1H, dd, *J* = 6.0, 1.5 Hz, C=C**H**) 5.79 (1H, dd, *J* = 6.1, 1.8 Hz, HC=C**H**) 3.41 (1H, app t, *J* = 13.0 Hz, NC**H**H) 3.23 (1H, m, C**H**) 3.17 (1H, dd, *J* = 12.8, 4.9 Hz, NCH**H**) 2.77 (3H, s, NC**H**$_3$) 2.51 – 2.37 (2H, m, C**H**$_2$) 1.81 (1H, m, C**H**H) 1.60 (1H, m, CH**H**) 1.51 – 1.39 (4H, m, 2×C**H**$_2$) 1.34 (9H, s, 3×C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	169.9 (**C**), 156.4 (**C**), 149.4 (**C**), 144.4 (**C**), 136.9 (**C**), 119.8 (**C**H), 106.7 (**C**H), 63.8 (**C**H$_2$), 43.7 (**C**H$_3$), 36.4 (**C**H), 33.4 (**C**H$_2$), 33.3 (**C**), 28.8 (3×**C**H$_3$), 27.4 (**C**H$_2$), 26.4 (**C**H$_2$), 22.0 (**C**H$_2$) ppm.
LRMS (ESI $^+$)	288 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 288.1963. $C_{18}H_{26}NO_2$ [M+H]$^+$ requires 288.1958.

(7Z,9E)-3-(*tert*-Butyl)-4,7-dimethyl-5,6-dihydrofuro[3,2-b]azocin-2(4*H*)-one (4.115)



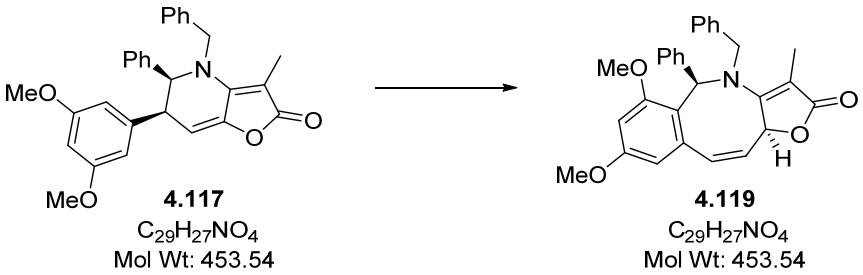
4.114
$C_{15}H_{21}NO_2$
Mol Wt: 247.34

4.115
$C_{15}H_{21}NO_2$
Mol Wt: 247.34

A solution of dihydrofuropyridinone **4.114** (241 mg, 0.972 mmol) in acetonitrile (20 mL) was irradiated with UVA following set-up A for a residence time of 10 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (10 – 30% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.115** (116 mg, 0.469 mmol, 48%) as a yellow solid.

MP ($CHCl_3$)	82 – 84 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2955 (w), 2926 (w), 2866 (w), 1743 (vs), 1641 (w), 1590 (m), 1481 (w), 1451 (m), 1388 (w), 1366 (m), 1315 (w), 1192 (s), 1113 (m).
δ_H (400 MHz, benzene-d6)	5.63 (1H, dq, *J* = 6.0, 1.5 Hz, C=C**H**) 5.37 (1H, dq, *J* = 6.1, 1.6 Hz, HC=C**H**) 2.83 (2H, m, NC$\mathbf{H}_2$) 2.38 (3H, s, NC$\mathbf{H}_3$) 1.91 (2H, m, C$\mathbf{H}_2$) 1.55 (3H, t, *J* = 1.5 Hz, C$\mathbf{H}_3$) 1.37 (9H, s, 3×C$\mathbf{H}_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	170.0 (**C**), 156.1 (**C**), 144.5 (**C**), 144.4 (**C**), 137.1 (**C**), 121.4 (**C**H), 107.4 (**C**H), 58.6 (**C**H_2), 44.3 (**C**H_3), 33.5 (**C**H_2), 33.3 (**C**), 28.8 (3×**C**H_3), 24.5 (**C**H_3) ppm.
LRMS (ESI $^+$)	248 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 248.1643. $C_{15}H_{22}NO_2$ $[M+H]^+$ requires 248.1645.

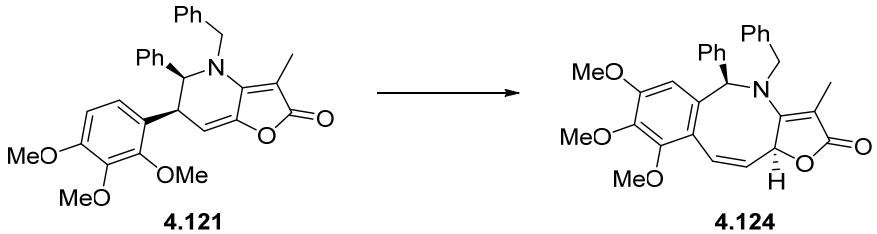
rel-(5*S*,11a*R*,10*Z*)-4-Benzyl-6,8-dimethoxy-3-methyl-5-phenyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.119)



A solution of dihydrofuropyridinone **4.117** (134 mg, 0.296 mmol) in acetonitrile (10 mL) was irradiated with UVA following set-up A for a residence time of 6 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30 – 100% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.119** (88.2 mg, 0.194 mmol, 66%) as a pale yellow solid.

MP (CH_2Cl_2)	Decomposed at 134 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2959 (w), 2926 (w), 1731 (s), 1598 (vs), 1580 (s), 1495 (w), 1452 (w), 1383 (w), 1316 (m).
δ_H (400 MHz, $CDCl_3$)	7. 39 – 7.29 (3H, m, 3×Ar**H**) 7.25 – 7.14 (5H, m, 5×Ar**H**) 6.77 (2H, br s, 2×Ar**H**) 6.41 (1H, d, *J* = 2.3 Hz, Ar**H**) 6.32 (1H, s NC**H**Ph) 6.24 (1H, d, *J* = 2.3 Hz, Ar**H**) 6.15 (1H, dd, *J* = 10.2, 1.5 Hz, C=C**H**) 5.55 (2H, d, *J* = 16.9 Hz, NC**H**H) 5.33 (1H, dd, *J* = 10.1, 6.9 Hz, HC=C**H**) 5.14 (1H, d with fine splitting, *J* = 7.0 Hz, OC**H**) 4.27 (1H, d, *J* = 16.9 Hz, NCH**H**) 3.81 (3H, s, OC**H**$_3$) 3.42 (3H, s, OC**H**$_3$) 1.98 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	176.0 (**C**), 161.7 (**C**), 160.2 (**C**), 159.6 (**C**), 142.3 (**C**), 140.4 (**C**), 138.3 (**C**), 132.6 (**C**H), 128.9 (**C**H), 128.4 (2×**C**H), 127.9 (2×**C**H), 127.3 (**C**H), 126.9 (2×**C**H), 126.5 (2×**C**H), 126.1 (**C**H), 120.8 (**C**), 103.4 (**C**H), 97.7 (**C**H), 89.7 (**C**), 76.0 (**C**H), 63.6 (**C**H), 57.5 (**C**H$_2$), 55.4 (**C**H$_3$), 55.0 (**C**H$_3$), 10.4 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	476 [M+Na]$^+$, 37%. 454 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 454.2022. $C_{29}H_{28}NO_4$ [M+H]$^+$ requires 454.2013. Found: 476.1838. $C_{29}H_{27}NNaO_4$ [M+Na]$^+$ requires 476.1832.

rel-(5*S*,11a*R*,10*Z*)-4-Benzyl-7,8,9-trimethoxy-3-methyl-5-phenyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.124)



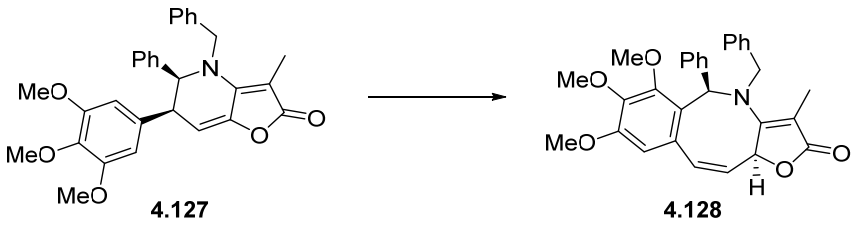
4.121
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

4.124
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

A solution of dihydrofuropyridinone **4.121** (42.7 mg, 0.0883 mmol) in acetonitrile (4 mL) was irradiated with UVA following set-up A for a residence time of 6 min. The resulting solution was concentrated *in vacuo* to give the title compound **4.124** (39.9 mg, 0.0825 mmol, 93%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2934 (w), 1729 (s), 1599 (vs), 1582 (s), 1494 (s), 1452 (m), 1436 (m), 1408 (m), 1325 (m), 1248 (w), 1194 (w), 1155 (w), 1124 (s), 1091 (m), 1057 (m), 1032 (m).
δ_H (400 MHz, $CDCl_3$)	7.45 – 7.31 (6H, m, 6×Ar**H**) 7.25 – 7.18 (3H, m, 3×Ar**H**) 6.81 (2H, br d, *J* = 6.6 Hz, 2×Ar**H**) 6.20 (1H, dd, *J* = 10.2, 1.3 Hz, C=C**H**) 6.01 (1H, s, Ar**H**) 5.63 (1H, s, C**H**Ph) 5.59 (1H, d, *J* = 15.8 Hz, NC**H**H) 5.26 (1H, dd, *J* = 10.2, 6.8 Hz, HC=C**H**) 5.08 (1H, d, *J* = 6.9 Hz, OC**H**) 4.23 (1H, d, *J* = 15.8 Hz, NCH**H**) 3.88 (3H, s, OC**H**$_3$) 3.76 (3H, s, OC**H**$_3$) 3.60 (3H, s, OC**H**$_3$) 2.10 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.8 (**C**), 161.5 (**C**), 153.4 (**C**), 151.1 (**C**), 142.1 (**C**), 140.4 (**C**), 138.1 (**C**), 134.3 (**C**), 129.0 (2×**C**H), 128.9 (**C**H), 128.2 (3×**C**H), 127.8 (2×**C**H), 127.6 (**C**H), 126.8 (**C**H), 125.9 (2×**C**H), 124.6 (**C**), 111.5 (**C**H), 90.7 (**C**), 76.6 (**C**H), 70.3 (**C**H), 61.0 (**C**H$_3$), 61.0 (**C**H$_3$), 56.9 (**C**H$_2$), 55.8 (**C**H$_3$), 10.9 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	484 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 484.2127. $C_{30}H_{30}NO_5$ [M+H]$^+$ requires 484.2118. Found: 506.1945. $C_{30}H_{29}NaNO_5$ [M+H]$^+$ requires 506.1951.

rel-(5*S*,11a*R*,10*Z*)-4-Benzyl-6,7,8-trimethoxy-3-methyl-5-phenyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.128)



4.127
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

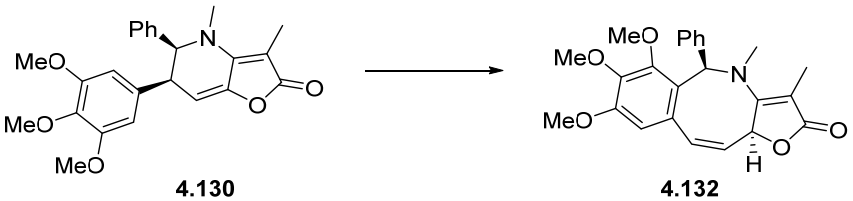
4.128
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

A solution of dihydrofuropyridinone **4.127** (107 mg, 0.220 mmol) in acetonitrile (6 mL) was irradiated with UVA following set-up A for a residence time of 4 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (60 – 100% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.128** (73.9 mg, 0.153 mmol, 69%) as a yellow solid.

MP (DCM)	75 – 78 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2934 (w), 1730 (s), 1600 (vs), 1581 (m), 1490 (m), 1446 (m), 1405 (w), 1347 (m), 1313 (m), 1238 (w), 1195 (w), 1153 (w), 1122 (s), 1069 (m).
δ_H (400 MHz, $CDCl_3$)	7.40 – 7.30 (5H, m, 5×Ar**H**) 7.23 – 7.14 (3H, m, 3×Ar**H**) 6.76 (2H, br s, 2×Ar**H**) 6.40 (1H, s, Ar**H**) 6.26 (1H, s, C**H**Ph) 6.14 (1H, dd, *J* = 10.1, 0.9 Hz, C=C**H**) 5.51 (1H, d, *J* = 16.6 Hz, NC**H**H) 5.35 (1H, dd, *J* = 10.0, 7.0 Hz, HC=C**H**) 5.15 (1H, d, *J* = 7.0 Hz, OC**H**) 4.26 (1H, d, *J* = 16.6 Hz, NCH**H**) 3.86 (3H, s, OC$\mathbf{H}_3$) 3.85 (3H, s, OC$\mathbf{H}_3$) 3.48 (3H, s, OC$\mathbf{H}_3$) 2.03 (3H, s, C$\mathbf{H}_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.9 (**C**), 161.8 (**C**), 153.4 (2×**C**), 142.1 (**C**), 141.2 (**C**), 138.0 (**C**), 134.1 (**C**), 132.3 (**C**H), 128.8 (**C**H), 128.7 (3×**C**H), 127.8 (**C**H), 127.6 (**C**H), 127.3 (2×**C**H), 126.7 (**C**H), 126.2 (2×**C**H), 125.7 (**C**), 106.3 (**C**H), 90.2 (**C**), 76.0 (**C**H), 63.8 (**C**H), 60.8 (**C**H_3), 60.8 (**C**H_3), 57.5 (**C**H_2), 55.9 (**C**H_3), 10.5 (**C**H_3) ppm.

LRMS (ESI $^+$)	506 $[M+Na]^+$, 59%, 484 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 484.2126. $C_{30}H_{30}NO_5$ $[M+H]^+$ requires 484.2118. Found: 506.1939. $C_{30}H_{29}NNaO_5$ $[M+Na]^+$ requires 506.1938.

rel-(5*S*,11a*R*,10*Z*)-(*Z*)-6,7,8-Trimethoxy-3,4-dimethyl-5-phenyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.132)



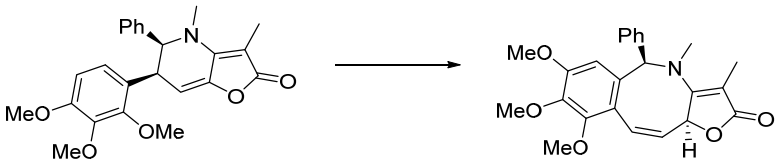
4.130
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

4.132
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

A solution of dihydrofuropyridinone **4.130** (86.3 mg, 0.212 mmol) in acetonitrile (6 mL) was irradiated with UVA following set-up A for a residence time of 4 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (70 – 100% diethyl ether/ petroleum ether 40 – 60 °C) to give the title compound **4.132** (77.9 mg, 0.191 mmol, 90%) as a white foam.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2934 (w), 1728 (s), 1607 (vs), 1491 (m), 1445 (m), 1404 (m), 1376 (m), 1321 (m), 1308 (m), 1237 (m), 1193 (w), 1124 (s), 1107 (m), 1081 (s), 1045 (s), 1017 (m).
δ_H (400 MHz, $CDCl_3$)	7.24 – 7.15 (3H, m, 3×Ar**H**) 6.75 (2H, br d, *J* = 7.3 Hz, 2×Ar**H**) 6.46 (1H, s, Ar**H**) 6.19 (1H, s, C**H**Ph) 6.11 (1H, dd, *J* = 10.2, 1.1 Hz, C=C**H**) 5.19 (1H, dd, *J* = 10.0, 6.7 Hz, HC=C**H**) 4.88 (1H, br d, *J* = 6.5 Hz, OC**H**) 4.04 (3H, s, OC**H**$_3$) 3.97 (3H, s, OC**H**$_3$) 3.89 (3H, s, OC**H**$_3$) 3.62 (3H, s, NC**H**$_3$) 2.19 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.9 (**C**), 161.2 (**C**), 153.3 (**C**), 153.2 (**C**), 141.9 (**C**), 141.6 (**C**), 133.3 (**C**), 131.6 (**C**H), 128.6 (**C**H), 128.1 (2×**C**H), 126.2 (**C**H), 126.1 (**C**), 125.6 (2×**C**H), 106.6 (**C**H), 91.3 (**C**), 76.4 (**C**H), 65.1 (br, **C**H$_3$ + **C**H), 61.7 (**C**H$_3$), 61.0 (**C**H$_3$), 55.9 (**C**H$_3$), 10.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	430 [M+Na]$^+$, 70%, 408 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 408.1815. $C_{24}H_{26}NO_5$ [M+H]$^+$ requires 408.1805.

rel-(5*S*,11a*R*,10*Z*)-7,8,9-Trimethoxy-3,4-dimethyl-5-phenyl-5,11a-dihydrobenzo[*f*]furo[3,2-b]azocin-2(4*H*)-one (4.136)



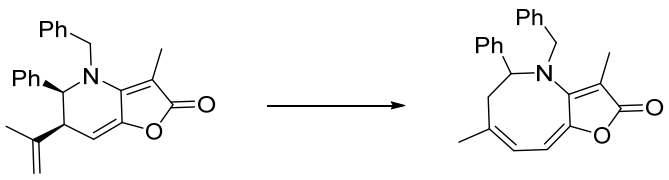
4.134
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

4.136
$C_{24}H_{25}NO_5$
Mol Wt: 407.47

A solution of dihydrofuropyridinone **4.134** (41.3 mg, 0.101 mmol) in acetonitrile (5 mL) was irradiated with UVA following set-up A for a residence time of 6 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (80 – 100% diethyl ether/ hexane) to give the title compound **4.136** (24.0 mg, 0.0589 mmol, 58%) as a yellow gel.

FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	2933 (w), 1731 (s) 1610 (vs), 1495 (m), 1447 (m), 1408 (m), 1396 (w), 1327 (s), 1247 (w), 1195 (w), 1125 (s), 1084 (m), 1024 (m).
δ_H (400 MHz, $CDCl_3$)	7.34 – 7.25 (3H, m, 3×Ar**H**) 7.05 (2H, d, *J* = 8.0 Hz, 2×Ar**H**) 6.64 (1H, s, Ar**H**) 6.45 (1H, dd, *J* = 11.7, 1.8 Hz, C=C**H**) 5.99 (1H, s, C**H**Ph) 5.60 (1H, dd, *J* = 11.8, 4.8 Hz, HC=C**H**) 5.28 (1H, br d, *J* = 4.7 Hz, OC**H**) 3.92 (3H, s, OC**H**$_3$) 3.86 (3H, s, OC**H**$_3$) 3.83 (3H, s, OC**H**$_3$) 3.28 (3H, s, NC**H**$_3$) 2.08 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	175.3 (**C**), 161.6 (**C**), 153.2 (**C**), 152.2 (**C**), 142.1 (**C**), 138.3 (**C**), 133.4 (**C**), 128.4 (2×**C**H), 127.9 (**C**H), 127.1 (**C**H), 126.8 (2×**C**H), 126.1 (**C**H), 123.5 (**C**), 109.7 (**C**H), 92.8 (**C**), 76.6 (2×**C**H), 61.2 (**C**H$_3$), 61.0 (**C**H$_3$), 56.2 (**C**H$_3$), 39.0 (br N**C**H$_3$), 10.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	430 $[M+Na]^+$, 80%, 408 ($[M+H]^+$, 100%).
HRMS (ESI $^+$)	Found: 408.1815. $C_{24}H_{26}NO_5$ $[M+H]^+$ requires 408.1805.

(7Z,9*E*)-4-Benzyl-3,7-dimethyl-5-phenyl-5,6-dihydrofuro[3,2-b]azocin-2(4*H*)-one (4.143)



4.141
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

4.143
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

A solution of dihydrofuropyridinone **4.141** (290 mg, 0.811 mmol) in acetonitrile (20 mL) was irradiated with UVA following set-up A for a residence time of 10 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography (30% diethyl ether/ hexane) to give the title compound **4.143** (135 mg, 0.378 mmol, 47%) as a white solid.

MP ($CHCl_3$)	163 – 164 °C.
FT-IR (ν_{max}/cm^{-1}, $CDCl_3$)	3027 (w), 2924 (w), 2854 (w), 1749 (vs), 1651 (w), 1597 (m), 1494 (w), 1420 (w), 1314 (m), 1178 (w), 1136 (m), 1061 (m).
δ_H (400 MHz, $CDCl_3$)	7.39 – 7.29 (8H, m, 8×Ar**H**) 7.16 (2H,m, 2×Ar**H**) 6.08 (1H, d, *J* = 6.0 Hz, C=C**H**) 6.03 (1H, d, *J* = 6.0 Hz, HC=C**H**) 4.19 (1H, dd, *J* = 13.6, 3.6 Hz, NC**H**Ph) 4.15 (1H, d, *J* = 13.9 Hz, NC**H**H) 4.12 (1H, d, *J* = 13.9 Hz, NCH**H**) 3.39 (1H, app t, *J* = 13.6, 13.3 Hz, C**H**H) 1.98 (1H, dd, *J* = 13.3, 3.5 Hz, CH**H**) 1.55 (3H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	171.2 (**C**), 155.6 (**C**), 147.0 (**C**), 144.0 (**C**), 140.5 (**C**), 137.8 (**C**), 128.6 (2×**C**H), 128.6 (2×**C**H), 128.3 (**C**H), 128.0 (2×**C**H), 127.7 (**C**H), 126.5 (2×**C**H), 121.0 (**C**H), 117.2 (**C**), 108.3 (**C**H), 67.3 (**C**H), 56.8 (**C**H$_2$), 37.6 (**C**H$_2$), 24.5 (**C**H$_3$), 9.8 (**C**H$_3$) ppm.
LRMS (ESI $^+$)	358 ([M+H]$^+$, 100%).
HRMS (ESI $^+$)	Found: 380.1625. $C_{24}H_{23}NNaO_2$ [M+Na]$^+$ requires 380.1621.

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Appendix A

Submitted by: **Morgan Manning**

Supervisor: **David Harrowven**

Solved by: **Mark Edward Light**

X-ray ID: **2020sot0013_R1_100K**

Crystal Data and Experimental (**4.128**)

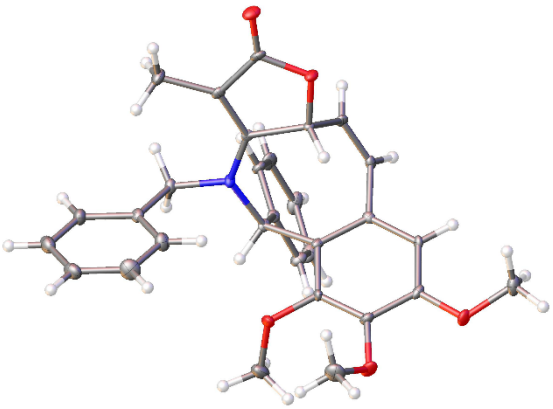


Figure 1: Thermal ellipsoids drawn at the 50% probability level. There are 4 molecules in the asymmetric unit.

Compound	**MM/8910/44**
Formula	$C_{30}H_{29}NO_5$
$D_{calc.}$/ g cm^{-3}	1.321
μ/mm^{-1}	0.090
Formula Weight	483.54
Colour	clear colourless
Shape	prism
Size/mm^3	0.24×0.17×0.06
T/K	100(2)
Crystal System	triclinic
Space Group	P-1
a/Å	8.7874(2)
b/Å	17.8436(4)
c/Å	31.3137(6)
α/°	97.518(2)
β/°	90.336(2)
γ/°	92.213(2)
V/Å^3	4863.82(18)
Z	8
Z'	4
Wavelength/Å	0.71073
Radiation type	MoK$_\alpha$
Θ_{min}/°	1.856
Θ_{max}/°	28.499
Measured Refl.	150262
Independent Refl.	24636
Reflections with I > 2(I)	18851
R_{int}	0.1015
Parameters	1313
Restraints	1164
Largest Peak	1.595
Deepest Hole	-0.433
GooF	1.136
wR_2 (all data)	0.3138
wR_2	0.2961
R_1 (all data)	0.1475
R_1	0.1215

Experimental. Single clear colourless prism-shaped crystals of **MM/8910/44** were recrystallised from a mixture of Et2O and petrol by slow evaporation. A suitable crystal 0.24×0.17×0.06 mm^3 was selected and mounted on a MITIGEN holder with silicon oil on an Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved with the ShelXT 2014/5 (Sheldrick, 2014) structure solution program using the direct phasing methods solution method and by using **Olex2** (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{30}H_{29}NO_5$, M_r = 483.54, triclinic, P-1 (No. 2), a = 8.7874(2) Å, b = 17.8436(4) Å, c = 31.3137(6) Å, α = 97.518(2)°, β = 90.336(2)°, γ = 92.213(2)°, V = 4863.82(18) Å^3, T = 100(2) K, Z = 8, Z' = 4, μ(MoK$_\alpha$) = 0.090, 150262 reflections measured, 24636 unique (R_{int} = 0.1015) which were used in all calculations. The final wR_2 was 0.3138 (all data) and R_1 was 0.1215 (I > 2(I)).

Submitted by: **Wei Sun**

Supervisor: **David Harrowven**

Solved by: **Mark Edward Light**

X-ray ID: **2019sot0030_K1_100K**

Crystal Data and Experimental (**4.32**)

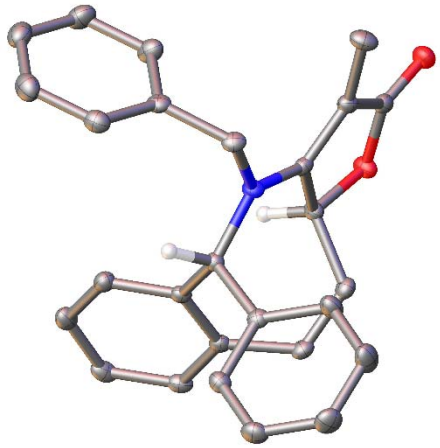


Figure 2: Thermal ellipsoids drawn at the 50% probability level. Selected hydrogens omitted for clarity.

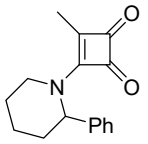
Compound	**SW/distero**
Formula	$C_{27}H_{23}NO_2$
$D_{calc.}$/ g cm^{-3}	1.265
μ/mm^{-1}	0.079
Formula Weight	393.46
Colour	clear colourless
Shape	prism
Size/mm^3	0.24×0.15×0.07
T/K	100.01(16)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	7.24960(10)
b/Å	16.9896(3)
c/Å	16.7783(3)
α/°	90
β/°	90.7420(10)
γ/°	90
V/Å^3	2066.37(6)
Z	4
Z'	1
Wavelength/Å	0.71073
Radiation type	MoK_α
Θ_{min}/°	3.055
Θ_{max}/°	28.500
Measured Refl.	21609
Independent Refl.	5231
Reflections with I > 2(I)	4743
R_{int}	0.0531
Parameters	272
Restraints	0
Largest Peak	0.444
Deepest Hole	-0.209
GooF	1.050
wR_2 (all data)	0.1110
wR_2	0.1074
R_1 (all data)	0.0511
R_1	0.0461

Experimental. Single clear colourless prism-shaped crystals of **SW/distero** were recrystallised from a mixture of Et2O and DCM by slow evaporation. A suitable crystal 0.24×0.15×0.07 mm^3 was selected and mounted on a MITIGEN holder with silicon oil on an XtaLAB AFC12 (RCD3): Kappa single diffractometer. The crystal was kept at a steady T = 100.01(16) K during data collection. The structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program using the Intrinsic Phasing solution method and by using **Olex2** (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

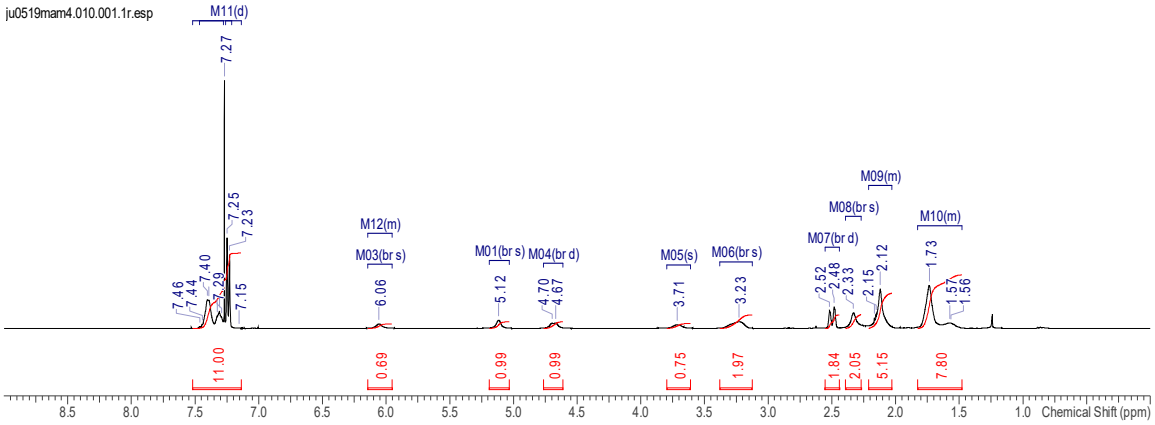
Crystal Data. $C_{27}H_{23}NO_2$, M_r = 393.46, monoclinic, $P2_1/c$ (No. 14), a = 7.24960(10) Å, b = 16.9896(3) Å, c = 16.7783(3) Å, β = 90.7420(10)°, α = γ = 90°, V = 2066.37(6) Å^3, T = 100.01(16) K, Z = 4, Z' = 1, μ(MoK_α) = 0.079, 21609 reflections measured, 5231 unique (R_{int} = 0.0531) which were used in all calculations. The final wR_2 was 0.1110 (all data) and R_1 was 0.0461 (I > 2(I)).

Appendix B

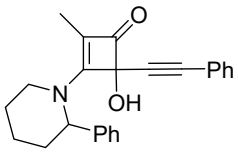
3-Methyl-4-(2-phenylpiperidin-1-yl)cyclobut-3-ene-1,2-dione (4.47)



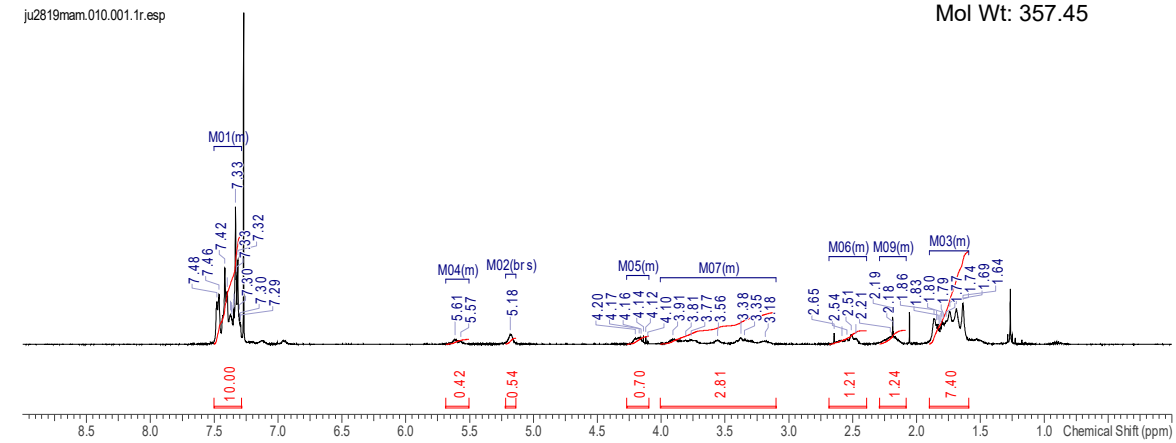
4.47
$C_{16}H_{17}NO_2$
Mol Wt: 255.32

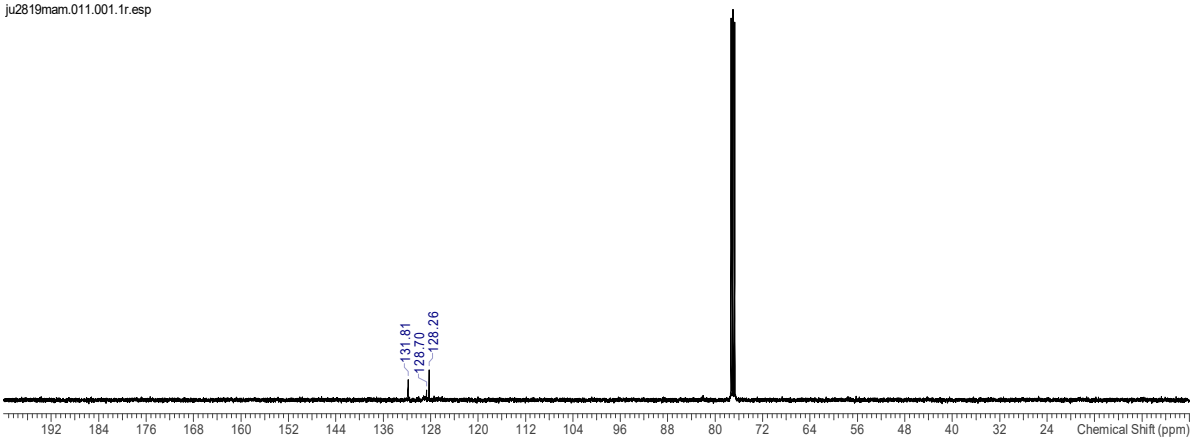


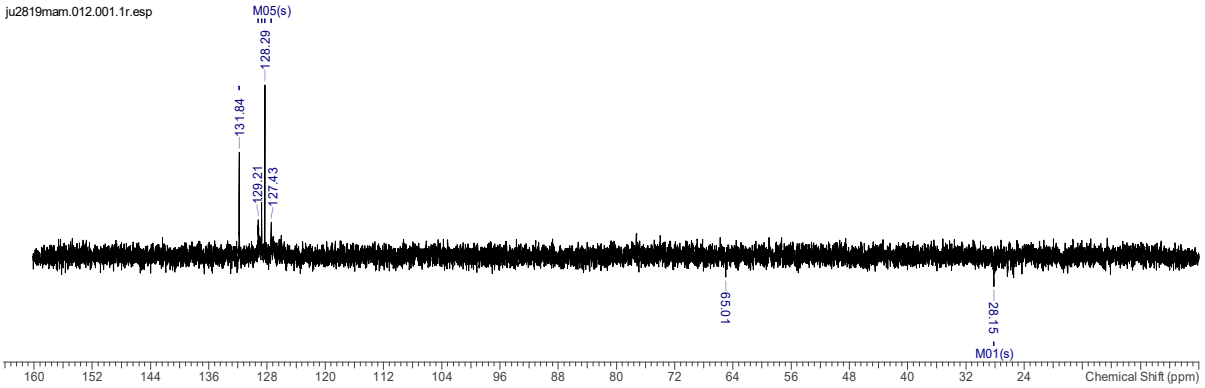
4-Hydroxy-2-methyl-4-(phenylethynyl)-3-(2-phenylpiperidin-1-yl)cyclobut-2-en-1-one (4.48)



4.48
$C_{24}H_{23}NO_2$
Mol Wt: 357.45

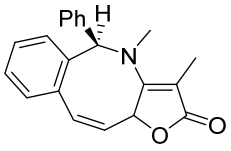






Appendix C

(5*R*,*Z*)-3,4-Dimethyl-5-phenyl-5,11a-dihydrobenzo[f]furo[3,2-b]azocin-2(4*H*)-one (4.38)



4.38

$C_{21}H_{19}NO_2$

Mol Wt: 317.39

δ_H (400 MHz, $CDCl_3$)

7.38 – 7.29 (7H, m, 7×Ar**H**)
7.11 –7.09 (2H, m, 2×Ar**H**)
6.44 (1H, dd, *J* = 12.2, 2.1 Hz, C=C**H**)
6.20 (1H, s, C**H**Ph)
5.74 (1H, dd, *J* = 12.2, 4.2 Hz, HC=C**H**)
5.38 (1H, br m, OC**H**)
3.20 (3H, s, NC**H**$_3$)
2.04 (3H, s, C**H**$_3$)