Approaches to the Synthesis of Highly Substituted Aromatic and Fused Rings: The Metal Catalyzed Cyclisation Versus the Thermal Cyclisation

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Dedicated to Dr. Alfred Bader on the occasion of his 93rd birthday and in memory of Oxana Bennett

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Abstract A domino reaction has been used for the construction of lactonamycin derivatives. This research led to a comparison study between palladium mediated cascade cyclisations and thermal alkyne [2+2+2] cyclisations. A palladium mediated cyclisation of alkenyl bromides with alkynes and furans has been shown to furnish highly substituted aromatic rings. Penta and hexasubstituted aromatic rings have been also been prepared by the thermolysis of suitably substituted alkynes under microwave conditions. Tetrasubstituted pyridines can also be prepared using nitriles instead of alkynes. This work will provide a new and interesting array of drug templates; mechanistic details are discussed for both reaction series.

Key words alkynes, aromatic rings, cyclisation, thermolysis, palladium

Over the years domino reactions have been developed as powerful methods for the efficient synthesis of complex molecules, often of biological interest.¹ Domino reactions entail at least two consecutive bond forming or bond rearrangement reactions where each following reaction relies on the chemistry involved in the preceding step.² These time resolved sequences³ can be designed by carefully evaluating the functional group reactivity in the starting materials and as such they can be initiated using a variety of techniques, including photochemistry,⁴ radical chemistry,⁵ metal catalysis,⁶ organocatalysis,⁷ and thermal cyclisations.^{8,9} Given the importance of aromatic polyfunctional arrays in the chemical industries, we sought to develop new domino processes for the preparation of the aforementioned ring systems. This paper is concerned with the evaluation of the scope and limitations of our domino process for the preparation of polysubstituted aromatic rings. A palladium mediated cyclisation together with a thermal approach for the formation of functionalized aromatic rings are compared.

In 2006, model studies were developed that could be applied to the synthesis of lactonamycin (Figure 1). Other interesting fused heterocyclic and carbocyclic fused ring systems could also be formed under the cyclisation conditions.¹⁰

Figure 1 The structure of the antibiotic lactonamycin

Initially, a tin mediated radical cyclisation had been envisioned to convert amide **2** to the tetracycle **3**. Early investigations however led to the unexpected tetracycle **4** in 14% yield when the alkenyl bromide **2** was treated with tin hydride and AIBN in refluxing benzene (Scheme 1).

Scheme 1 An unexpected thermal cyclisation during studies on the synthesis of lactonamycin

Thermal degradation studies were undertaken to determine the stability of the alkenyl bromide **2**. It was found that in the absence of tin hydride the substrate **2** provided the lactam **4** in improved yields for almost all of the investigated solvents (Table 1).

Table 1 Decomposition studies

Entry	Solvent	Reaction Time (hr)	Yield (%)
1	Benzene	48	26
2	THF	144	35
3	Toluene	2	41
4	DMF	0.5	63
5	Diglyme	0.5	23
6	DMSO	0.25	decomposition

The significant difference between the yields for DMF and toluene was attributed to the known decomposition of DMF to dimethylamine and carbon monoxide. It was hypothesized that the dimethylamine produced during the decomposition of DMF scavenged hydrobromic acid produced during the reaction. Based upon this hypothesis and Corey's work on gibberellic acid,¹¹ we decided to investigate the use of an acid trap. When 1,2-epoxyhexane was added to the reaction mixture, the tetracyclic product **4** was isolated in an improved yield of 76% (Scheme 2).

Scheme 2 Unexpected cyclisation to provide **4**

We have since shown that the core of the antibiotic lactonamycin can be constructed in one synthetic operation in 73% yield from the amide **8** using this strategy (Scheme 3).¹² Of key importance in the synthesis of the cyclisation substrate is the use of the Knochel-Hauser base¹³ which provided **8** in 60% yield from the aldehyde **6**. The use of *tert*-butyl bromide, a neutral proton source, in the workup was also important to the success of this reaction; other proton sources had adverse effects on the yield.

Scheme 3 Thermal cyclisation to form the core of lactonamycin

Further investigations to extend our original findings were carried out (Scheme 4).^{9,14} It was found that both the amide **10** and ester **11** cyclisation precursors cyclized to their respective furan products **12** and **13**. There is however a significant difference in the rate of reaction between the two substrates. The difference in rate of reaction can be rationalized by considering the relative populations of the reactive conformers: there is a lower population of the cisoid conformer for the ester than for the amide.

Scheme 4 The synthesis of annulated furans from acyclic precursors

Thus far, we have used ester and amide substrates for the cyclisation reaction. In view of the importance of fused all carbon rings in chemical research, we examined the possibility of using our cascade sequence for the formation of functionalized steroid mimics; for this purpose the ketone substrate **18** was prepared (Scheme 5). Conversion of the known alcohol **14** to the ether **15** proceeded smoothly with sodium hydride and 2,3-dibromopropene. The silyl protecting group was removed with TBAF and the resulting alcohol **16** was oxidized under Swern conditions to provide the aldehyde **17**. Addition of lithium trimethylsilylacetylide to **17** formed, after work up, a propargylic alcohol, which was then oxidized with Dess–Martin periodinane to form the ketone **18**.

Scheme 5 Synthesis of the thermal cyclisation precursor **18**

In boiling toluene, the ketone precursor **18** cyclized over four days to form the cyclopentenone **19** in 62% yield (Scheme 6). The alkyne **20** was also formed in 11% yield during the reaction through protodesilylation of the starting material due to the prolonged heating.

Scheme 6 Synthesis of the annulated furan **19**

To suppress the formation of the alkyne **20**, microwave heating was investigated. As expected, the shorter reaction time suppressed the formation of the alkyne for all solvents investigated. The reaction duration in toluene was substantially reduced from 96 hours to 2 hours for a comparable yield (Entry 3, Table 2). DMF, acetonitrile, and DCE all provided the product **19** in a marginally lower yield than toluene. In line with our previous results (Entry 6, Table 1), DMSO caused complete decomposition of the cyclisation substrate. Given DCE's more favourable volatility and microwave absorption properties when compared to toluene,¹⁵ a higher temperature run was conducted. Cyclisation of the ketone substrate **18** at 200 °C provided the expected product **28** in an improved 81% yield (Entry 8, Table 2).

Table 2 Microwave synthesis of **19**

Entry	Solvent	Temperature (°C)	Duration (hr)	Yield (%) ^a
1	Toluene	150	4	26
2	Toluene	175	4	59
3	Toluene	185	2	72
4	DMF	185	2	68
5	Acetonitrile	185	2	66
6	DMSO	185	2	decomposition
7	DCE	185	2	65
8	DCE	200	2	81

^a For all entries, the alkyne **20** was not observed

We had previously prepared the homologue of the cyclisation substrate **21** from 5-hexyn-1-ol using the chemistry described in scheme 5. Unfortunately after 4 days in boiling toluene, there was no evidence of the cyclized product **22** by ¹H NMR. With microwave conditions in hand, the cyclisation of **21** was reinvestigated at the higher temperature of 200 °C with no success (Scheme 7). This result can be rationalised by considering the increase in the degrees of freedom of ketone **21** relative to the successful substrate **18**. Notably, the dioxolane **23**, prepared by protection of **18**, was also unsuccessful under both conventional and microwave heating.

Scheme 7 Unsuccessful cyclisations of derivatives of **18**

With optimised microwave conditions in hand for the synthesis of the annulated furan **19**, the synthesis of pyrrole and thiophene analogues was investigated. The previously prepared alcohol **14** was chosen as a convenient point to form the amine and sulphide examples. The alcohol **14** was converted to the

free amine **26** through a modified Gabriel amine synthesis. Allylation of the primary amine **26**, followed by tosyl protection gave intermediate **28** (Scheme 8).

Scheme 8 Preparation of nitrogen **28** derivative of the ether **15**

The sulphide **30** was prepared using a two step sequence. A Mitsunobu reaction provided the thioester **29**, which was deprotected and then allylated *in situ* to give **30** (Scheme 9).

Scheme 9 Preparation of sulfur **30** derivative of the ether **15**

The synthetic sequence for **14** to **18** (Scheme 5) was used to provide the cyclisation precursors **31** and **32** from the protected alcohols **28** and **30**. When the substrates were heated in a microwave reactor, the expected pyrrole **33** and thiophene **34** products were formed in 61% and 58% yields respectively (Scheme 10).

Scheme 10 Microwave synthesis of annulated pyrrole **33** and thiophene **34**

Multiple pathways have been proposed to account for this transformation (Scheme 11).⁹ The first step of the mechanistic proposal can be divided into either concerted or stepwise pathways. In the concerted pathway, the labelled precursor **35** proceeds directly in one step via a propargylic ene reaction to the alkenyl allene **36**, which can then undergo a Diels-Alder cyclisation to provide the observed product **37**. A stepwise mechanism may also account for the formation of alkenyl allene **36**, proceeding via the diradical **38**. The diradical **38** abstracts a deuteron to give the vicinal diradical **39**. Further rearrangement of this intermediate, followed by cyclisation and radical-radical recombination would provide the product **37**.

Scheme 11 Proposed mechanism for the observed cyclisation of the deuterium labelled thermolysis precursor **35**

The two distinct pathways leading to either **36** or **38** were proposed after comparing the mechanism of our transformation to the ene reaction. For a number of decades it has been suggested that the ene reaction exists on the interface between concerted and stepwise mechanisms, with specific examples to support both proposals.¹⁶ Recent computational experiments on the ene reaction however have provided evidence for a one step asynchronous mechanism, where the carbon-carbon bond formation is more advanced than the hydrogen transfer, for a range of substrates.¹⁷ Studies on the related Schmitt cyclisation¹⁸ also provides some insight to the mechanism of our transformation. Early computational studies by Engels suggested that the Schmitt cyclisation may follow either a concerted or stepwise pathway depending on the substrate.¹⁹ Singleton also showed that the mechanism of the cyclisation was substrate dependent, but his studies pointed to a more complex mechanistic phenomenon.²⁰ Instead of dividing the mechanism into concerted and stepwise pathways, Singleton demonstrated that there is a single transition state that leads to either the concerted product or the diradical intermediate, giving rise to a bifurcating reaction pathway.²¹ After early kinetic isotope experimental observations supporting a stepwise mechanism,²² Schmitt later supported this concept with his own computational experiments.²³ We propose that our transformation may exhibit the complex mechanistic behavior seen for both the ene reaction and Schmitt cyclisations, based upon our own previously reported observations. In a previous publication, it was shown that the replacement of the protons with deuterium led to a threefold decrease in the rate of reaction.⁹ Furthermore, the introduction of radical traps did not lead to the expected trapped products. These observations are consistent with the concerted mechanism suggested by other groups working in this area.^{24,25} As a counterpoint to these observations, the unusual formation of the compound **42** in a 30% yield from the ketone **41**, and the isolation of the by-product **44** from the cyclisation of **45** have been attributed to radical mechanisms (Scheme 12).⁹

Scheme 12 The unusual cyclisations of ketone **41** and alkyne **43**

Concurrent with our studies on the synthesis of lactonamycin and related compounds, a palladium assisted cascade cyclisation of substituted furans was also being investigated (Scheme 13). We have previously shown that carbon centered radicals can add to furans to provide substituted cyclopentenones through a fragmentation sequence. For example, the alkenyl bromide **48** was heated in toluene in the presence of tri-*n*-butyltin hydride and AIBN to give the bicycle **49** in 51% yield.²⁶ This mechanism involves a radical fragmentation of the furan ring before a [2+2+2] electrocycloaddition provides the aromatic ring. In later work, we demonstrated that the sulfone **50** can also undergo a radical mediated cyclisation with concomitant furan fragmentation to afford the tricycle **51**, albeit in a reduced yield of 11%.²⁷

Scheme 13 The palladium-mediated cascade and previous work on tin mediated cascades

In an effort to improve the yield of this process, we prepared the ether **46** for a palladium mediated cyclisation (Scheme 14). The aldehyde **53** was prepared by an acid catalyzed Michael addition with acrolein. Treatment of the aldehyde with ethynylmagnesium bromide and protection of the resultant alcohol gave the alkyne **54**. The propargyl alcohol **55** was formed and then allylated with 2,3-dibromopropene to furnish the cyclisation precursor **46** for the palladium studies.

Scheme 14 Preparation of the palladium cyclisation precursor **46**

The alkenyl bromide **46** was heated in the presence of palladium (II), providing the tricyclic ketone **47** in 28% yield (Scheme 15). This finding was remarkable as the precedent for a palladium mediated fragmentation of furan was limited. The only example at the time of this research was completed by Grimaud, who showed that a palladium mediated fragmentation was a convenient means of tandem ring closure and formation α,β -unsaturated aldehydes.²⁸ In contrast to Grimaud's work, which featured a single ring closure, we were able to form three rings in one pot. Further examples of palladium mediated cyclisation and concomitant furan fragmentation have since been disclosed.²⁹ Notably, the yield, 28%, for the palladium mediated domino reaction was an improvement previously investigated tin radical procedure.

Scheme 15 The palladium-mediated cascade of **46**

Additional examples were prepared from the alcohol **55** following the chemistry outlined for the thermal cyclisation precursors **31** and **32** disclosed earlier in this publication. With the precursors in hand, the palladium cyclisation fragmentation sequence was completed forming the expected aromatic products **59** and **60** from the diester **56** and amine **57** respectively (Scheme 16). The sulfide **58** however unexpectedly yielded the cyclopentadiene derivative **61** as the sole product. In this case, it is also notable that the sulfide oxidized under reaction conditions to provide the sulfone.

Scheme 16 Other examples of palladium mediated reactions

In the case of the ether precursor **46**, initial analysis of the reaction mixture showed two major products, but on continued heating under reflux one product diminished and the ketone **47** was isolated as the sole product. Based on our observations, it is proposed that all examples proceed via a cyclopentadiene intermediate, isolated as the sole product for the sulfide **58**. The cyclopentadiene **65** will then undergo ring expansion and aromatization to give the *bis*-annulated products (Scheme 17). In the case of the sulfide, further ring expansion was prevented due to increased ring strain induced by the presence of the sulfone moiety.

Scheme 17 A proposed mechanistic pathway for the formation of polysubstituted benzene rings

In order to avoid the use of metallic reagents in our cyclisation reactions and to attempt to improve the yields of the cyclized products, we investigated the thermal chemistry of these substrates. Heating the substrate **46** in the absence of palladium unfortunately yielded only starting material after two hours (Scheme 18). The transformation was also attempted at 200 °C in a microwave reactor, without success.

Scheme 18 Thermal cyclisation of the propargyl ether derivative **46**

Given our successful use of diyne systems in our approach to lactonamycin (Scheme 3), we decided to replace the bromoalkene with an alkyne to provide the new cyclisation substrate **68** (Scheme 19). This was accomplished in good yield from the previously synthesized propargyl alcohol **55**. In this new approach, the furan ring will be acting as the dienophile before the fragmentation sequence to give the tricyclic product **69**.

Scheme 19 Proposal for the thermal fragmentation of furan **68**

Gratifyingly, when the alkyne **68** was heated in DMF under microwave irradiation, the pentasubstituted benzene derivative **69** was isolated in 45% yield (Scheme 20).³⁰ We proposed that the mechanism for this cyclisation follows the same pathway as for the earlier thermal cyclisations (Scheme 11) to give an alkenyl allene intermediate **70**, which then undergoes a Diels-Alder cycloaddition with furan. Fragmentation of **71**, followed by oxidation, leads to the pentasubstituted benzene core of **69** (Scheme 21).

Scheme 20 Thermal cyclisation of the propargyl ether derivative **68** Scheme 21 Mechanism for the formation of the tricycle **69**

Early investigations on this theme explored the effect of substitution on the furan ring (Scheme 22). It was found that it was possible to prepare the aldehyde **76** from the mono substituted furan **73** or the ethyl ketone **77** from the ethyl substituted furan **74**. The yield for the aldehyde **76** was notably lower than both the parent compound and ethyl derivative due to the instability of the phenyl acetaldehyde **76**. Unsurprisingly, methyl substitution at the propargylic position, to give the precursor **75**, leads to an increased cyclisation yield over the unsubstituted parent compound **68**.

Scheme 22 Structural variations of the thermal cyclisation precursor **68**

Alcohol **55** (Scheme 14) was coupled with propiolic acid to give the ester **79**, which in turn cyclized to give the lactone **81** in 62% yield (Scheme 23). Similarly, the carboxylic acid may be formed from the alkyne **54** (Scheme 14) and esterified with propargyl alcohol to give the isomeric ester **80**. Cyclisation of this material under the usual conditions provided the lactone **82** also in 62% yield.

Scheme 23 Thermal cyclisations of ester derivatives **79** and **80**

It was proposed that substitution of this side chain would provide hexasubstituted aromatic rings. Methyl substitution was accomplished by the reaction of the alcohol **55** (Scheme 14) with 1-bromo-2-butyne to give the substrate **83**. Under standard conditions, **83** cyclized to give the hexasubstituted benzene core of **86** (Scheme 24). Alcohol **56** was also coupled with both phenylpropionic acid and naphthylpropionic acid to give **84** and **85** respectively. Cyclisation of these materials provided the lactones **87** and **88** with the aromatic rings positioned orthogonally to the tricycle, as shown by x-ray crystallography.

Scheme 24 Variation of the alkyne side chain to form hexasubstituted aromatic rings

In order to compare these results to the palladium methods, the diester **89**, amine **90**, and sulfide **91** cyclisation precursors were also prepared (Scheme 25). The diester **92** and amine **93** cyclisation substrates formed the expected products in a lower yield than the ether example. The yields were however comparable to the yields for the palladium cyclisation (Scheme 16). In contrast to the palladium methods, the sulfide **94**, featuring a benzene core was accessible using the thermal approach.

Scheme 25 Cyclisation of diester, nitrogen, and sulfur linked diynes

In addition, we demonstrated that the cyclic ether **100** could also be formed (Scheme 26). The alcohol **96** was deprotonated and reacted with propargyl bromide to give the alkyne **97**. The propargyl alcohol **98** was formed and the ether **99** synthesized. Cyclisation in acetonitrile furnished the tricycle **100**.

Scheme 26 Cyclisation to form the annulated furan **100** and preparation of the precursor **99**

It was proposed that the cyclisation and fragmentation sequence could be performed in an intermolecular fashion using the diyne **102** (Scheme 27). We have previously investigated a similar intermolecular reaction with a number of dienophiles.³¹ In this example, thermolysis of the diyne **104** forms the corresponding alkenyl allene **105** which forms the bicycle upon reaction with allyl alcohol. The adduct is then trapped by the pendant alcohol to provide tricyclic product **106**. Danheiser has also reported intra-intermolecular examples.²⁵

For these studies, the diyne **102** was prepared from butyn-2-ol through a three step sequence (Scheme 28). The alcohol was first protected as the silyl ether **108** before deprotonation and reaction with *para*-formaldehyde to give the propargyl alcohol **109**.³² Treatment of the propargyl alcohol with propargyl bromide in the presence of sodium hydride gave the ether **102**.

Heating the ether **102** in acetonitrile under microwave conditions did not form the intermolecular aromatic product **103** (Scheme 29). Spectral analysis of the crude material however revealed a complex reaction profile that merited further investigation.

In the absence of the furan component, it was possible to isolate two new products from this reaction. The furan **110** was isolated in a 40% yield, along with the enone **111** (Scheme 30).

To account for the product distribution, the following mechanism was proposed (Scheme 31). The alkenyl allene **112** is formed following the previously discussed mechanism. Protonation of **112** forms the two regioisomers **113** and **114**. The *Z*-alkene **113** aromatizes and the silyl enol ether **115** is hydrolyzed to give the furan product **110**. The cyclic ketone **111** is formed through electrocyclicisation of the triene **116**. The resultant diene **117** is hydrolyzed to form the unsaturated ketone **111**.

The sulfide **119** was also prepared and this cyclized under identical conditions (Scheme 32). The previously prepared alcohol was converted to thio acetate **118** under Mitsunobu conditions. The thio acetate was cleaved and reacted with propargyl bromide to give the sulfur precursor **119**. Thermolysis of the diyne **119** over six hours gave the expected products **120** and **121** in a reduced yield compared to ether variant **102**.

The amine **124** was prepared from the diyne **122** (Scheme 33). Deprotonation and reaction with acetaldehyde, followed by protection of the alcohol, gave the precursor **124**. When heated in acetonitrile, a subtly different product profile was observed. The pyrrole **125** and enone **126** were isolated in 41% and 16% yield respectively, as well as the previously unobserved tetrasubstituted alkene **127** in 14% yield.

Scheme 33 Thermolysis of diyne substrates in the absence of an alkene

We were also able to apply this chemistry to the synthesis of substituted pyridines by installing a nitrile group in the precursor (Scheme 34). The alcohol **56** was alkylated to give the nitrile **128**; cyclisation of the nitrile provided the pyridine **129** in 42% yield.

Scheme 34 Thermolysis of nitrile **128**

After the initial success in the formation of a pyridine ring, we prepared the cyclisation precursor **130** (Scheme 35). We proposed that the nitrile ester **130** would cyclize to provide the pyridine product **131**. However, when **130** was heated in acetonitrile at 200 °C in the presence of water, the amine **132** was formed unexpectedly in 62% isolated yield. If the nitrile ester **130** was allowed to stand at room temperature, the Diels-Alder product **133** was formed quantitatively. When the adduct **133** was heated for four hours at 200 °C, the amine **132** was formed together with the starting material **130** proceeding via a retro-Diels-Alder reaction.

Scheme 35 Unexpected formation of **132** and **133**

We rationalized the formation of **132** as due to the carbonyl-carbonyl steric compression in structure **131** versus the relief of steric compression in **132**. The proposed mechanism of this transformation is shown in scheme 36. The furan **130** was presumed to undergo an intramolecular cyano-ene reaction to form the allene **134**.²⁵ An intramolecular aza-Diels-Alder then was assumed to furnish the unstable lactone **135**. This

intermediate then underwent ring opening and cleavage of the carbon nitrogen bond to give the less strained intermediate **132**, upon tautomerization. This intriguing reaction is now the subject of further research.

Scheme 36 Proposed mechanism for the formation of the amine **132**.

This paper is concerned with our findings on the metal catalyzed versus metal free domino cyclisation reactions of a range of alkene and alkyne containing substrates. We report our extension of existing work on the formation of annulated heteroaromatic compounds, based on earlier work conducted on the synthesis of lactonamycin. We also discuss our findings on the one pot formation of highly substituted benzene rings and the relationship to our investigations on palladium mediated fragmentation of furans.

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

Commercially available chemicals and reagents were used as supplied unless otherwise stated. Toluene, DCE, and acetonitrile were distilled from calcium hydride. All solvents for high temperature reactions (>100 °C) were first deoxygenated by sparging for at least 1 hour with nitrogen or argon gas. Reactions were monitored by crude NMR of the RM or by TLC using Merck glass backed TLC plates coated with a 0.25 mm layer of 60 F254 silica gel. Visualisation was achieved using 254 nm UV radiation and potassium permanganate, phosphomolybdic acid or vanillin stains as deemed appropriate. Column chromatography was carried out using Merck Kieselgel 60 or Fluorochem (40 – 63 µm). NMR spectroscopy was performed using either Varian NMR System-600 MHz (600 MHz for ¹H and 151 MHz for ¹³C), Varian NMR System-500 MHz (500 MHz for ¹H and 126 MHz for ¹³C), or a Bruker AV-400 (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR), and referenced relative to the residual non-deuterated solvent peak. Chemical shifts are reported in parts per million. Spectral peaks are assigned as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad), and combinations thereof. Coupling constants (J) are reported to the nearest 0.5 Hz. Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Coherence (HMBC), Correlation Spectroscopy (COSY) and Hydrogen-Deuterium exchange (H-D) experiments were also run where necessary to allow for the full elucidation of structures. Mass spectrometry was performed using a Fisons Instrument VG Autospec and a Bruker Daltonics Apex III. Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform instrument with an ATR attachment. Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

Procedures

5-(Trimethylsilyl)-7,8-dihydro-4H-indeno[4,5-c]furan-6(5H)-one (19)

8-(2-Bromoallyloxy)-1-(trimethylsilyl)octa-1,6-diyn-3-one (300 mg, 0.9 mmol) and epoxyhexene in DCE (2 mL) were heated to 185 °C using a microwave reactor. After 2 hours, the volatiles were removed under vacuum to give a crystalline solid. The crude material was then purified by column chromatography (50% ethyl acetate in hexane) to provide the title compound as a white crystalline solid (180 mg, 0.73 mmol, 81%).

R_f = 0.30 (25% ethyl acetate in hexane)

Melting Point: 107.1 °C – 110.4 °C (CHCl₃)

IR (neat): 3134, 2948, 1680, 1619, 1435, 1403, 1108, 1025, 831, 813, 755 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.62 – 7.49 (m, 1H), 7.19 (t, *J* = 2.0 Hz, 1H), 2.91–2.67 (m, 4H), 2.53 (t, *J* = 5.0 Hz, 2H), 2.34–2.29 (m, 1H), -0.14 (s, 9H).

¹³C NMR (CDCl₃, 100 MHz): δ = 206.8, 156.4, 140.3, 138.5, 137.7, 122.4, 121.4, 35.0, 25.6, 21.8, 19.4, -2.2.

HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₉O₂Si: 247.1154; found: 247.1165.

2-Tosyl-5-(trimethylsilyl)-4,5,7,8-tetrahydrocyclopenta[e]isoindol-6(2H)-one (33)

(*N*-(2-Bromoallyl)-*N*-(6-oxo-8-(trimethylsilyl)octa-2,7-diynyl)-4-methylbenzenesulfonamide (60 mg, 0.12 mmol) and 1,2-epoxyhexane (0.14 mL, 1.2 mmol) in DCE (1.2 mL) were heated to 200 °C for 2 hours using a microwave reactor. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography (30% EtOAc in hexane) to furnish the title compound as a pale yellow gum (29 mg, 0.073 mmol, 61%).

R_f = 0.36 (30% ethyl acetate in hexane)

IR (neat) 2953, 2924, 2852, 1685, 1615, 1535, 1370, 1286, 1171, 1054, 841, 675 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.77 – 7.68 (m, 2H), 7.30 – 7.26 (m, 2H), 7.22 (d, *J* = 2.0 Hz, 1H), 6.88 (dt, *J* = 2.0, 1.0 Hz, 1H), 2.85 – 2.62 (m, 4H), 2.51 (t, *J* = 5.0 Hz, 2H), 2.39 (s, 3H), 2.30 – 2.22 (m, 1H), -0.26 (s, 9H).

¹³C NMR (CDCl₃, 100 MHz): δ = 206.7, 157.3, 145.3, 140.5, 136.0, 130.1, 126.9, 126.3, 124.9, 116.7, 116.6, 35.0, 25.3, 21.7, 21.6, 21.2, -2.3.

HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₂₁H₂₆NO₃Si: 400.1403; found: 400.1400.

5-(Trimethylsilyl)-7,8-dihydro-4*H*-indenol[5,4-*c*]thiophen-6(5*H*)-one (34)

8-(2-Bromoallylthio)-1-(trimethylsilyl)octa-1,6-diyn-3-one (15 mg, 0.043 mmol) and 1,2-epoxyhexane (0.05 mL, 0.4 mmol) in DCE (0.4 mL) were heated to 200 °C for 2 hours using a microwave reactor. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography (15% ethyl acetate in hexane) to furnish the title compound as a pale yellow gum (6.5 mg, 0.025 mmol, 58%).

R_f = 0.15 (15% ethyl acetate in hexane)

IR (neat) 2958, 2924, 1686, 1603, 1350, 1250, 848 cm⁻¹

¹H NMR (CDCl₃, 500 MHz) δ = 7.35 (d, *J* = 2.5 Hz, 1H), 6.93 (ddd, *J* = 2.5, 2, 0.5 Hz, 1H), 3.08 – 2.90 (m, 3H), 2.81 – 2.74 (m, 1H), 2.57 (t, *J* = 5.0 Hz, 2H), 2.33 (ddt, *J* = 8.0, 2.5, 1 Hz, 1H), -0.17 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz) δ = 207.4, 159.2, 140.3, 138.8, 136.7, 121.6, 119.4, 35.2, 26.1, 25.3, 22.2, -2.3.

HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₈OSSi: 262.0848; found: 262.0846.

1-(8-(*tert*-Butyldimethylsilyloxy)-3,6,7,8-tetrahydro-1*H*-indenol[4,5-*c*]furan-5-yl)propan-2-one (47)

To a stirred solution of triphenylphosphine (180 mg, 0.68 mmol), potassium carbonate (630 mg, 4.50 mmol) and (6-(2-bromoallyloxy)-1-(5-methylfuran-2-yl)hex-4-yn-3-yloxy)(*tert*-butyl)dimethylsilane (1.0 g, 2.3 mmol) in acetonitrile (20 mL) was added palladium (II) acetate (50

mg, 0.23 mmol). The resulting mixture was heated at 80 °C for 5 hours and quenched with water (40 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic fractions were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (10% diethyl ether in hexane) to yield the title compound as a orange/green viscous oil (230 mg, 0.65 mmol, 28%).

IR (neat): 3403, 2928, 2854, 1709, 1412, 1358 cm⁻¹

¹H NMR (CDCl₃, 500 MHz): δ = 6.94 (s, 1H), 5.35–5.25 (m, 2H), 5.10 – 5.02 (m, 3H), 3.68 (m, 2H), 2.90 (ddd, *J* = 15.5, 9, 2, 1H), 2.69–2.61 (m, 1H), 2.52–2.46 (m, 1H), 2.16 (s, 3H), 1.93 (dtd, *J* = 12.5, 9, 7.5, 1H), 0.93 (s, 9H), 0.16 (d, *J* = 10.5, 6H).

¹³C NMR (CDCl₃, 126 MHz): δ = 205.7, 140.8, 139.0, 134.6, 129.6, 121.4, 76.4, 72.9, 72.4, 48.4, 36.4, 29.3, 28.5, 25.8, 18.0, -4.2, -4.8.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₂₀H₃₀O₃SiNa: 369.1862; found: 369.1860.

Dimethyl 8-(*tert*-butyldimethylsilyloxy)-5-(2-oxopropyl)-3,6,7,8-tetrahydroas-indacene-2,2(1*H*)-dicarboxylate (59)

Dimethyl 2-(2-bromoallyl)-2-(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)malonate (400 mg, 0.74 mmol), DPPE (60 mg, 0.15 mmol), palladium (II) acetate (17 mg, 0.074 mmol), potassium carbonate (200 mg, 1.5 mmol) was heated to 120 °C in DMF (50 mL) for 25 minutes. The reaction mixture was then diluted with water (500 mL) and extracted with diethyl ether (3 x 250 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (40% diethyl ether in hexane) to yield the title compound as a colourless oil (110 mg, 0.24 mmol, 32%).

IR (neat) 2954, 2856, 1734, 1472 cm⁻¹

¹H NMR (CDCl₃, 500 MHz): δ = 6.92 (s, 1H), 5.34 (t, *J* = 6.5 Hz, 1H), 3.76 (m, 7H), 3.67–3.45 (m, 5H), 2.88 (ddd, *J* = 15.5, 9.0, 3.0 Hz, 1H), 2.60 (dt, *J* = 16, 8, 1H), 2.48–2.39 (m, 1H), 2.14 (s, 3H), 1.93 (dtd, *J* = 13.0, 8.5, 6.5 Hz, 1H), 0.94 (s, 9H), 0.18 (d, *J* = 22, 6H).

¹³C NMR (CDCl₃, 126 MHz): δ = 206.1, 172.4, 172.1, 141.0, 140.9, 139.7, 135.6, 129.2, 124.8, 76.3, 60.5, 52.9, 52.8, 48.6, 40.1, 38.8, 36.1, 29.3, 25.9, 18.0, -4.1, -4.7.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₂₅H₃₆NaO₆Si: 483.2179; found: 483.2200.

tert-Butyl 8-(*tert*-butyldimethylsilyloxy)-5-(2-oxopropyl)-3,6,7,8-tetrahydrocyclopenta[e]isoindole-2(1*H*)-carboxylate (60)

To a stirring solution of *tert*-butyl 2-bromoallyl(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)carbamate (500 mg, 0.95 mmol), dppe (75 mg, 0.19 mmol), potassium carbonate (260 mg, 1.9 mmol) in DMF (25 mL) was added palladium (II) acetate (22 mg, 0.095 mmol) in one lot. The reaction mixture was heated to 87 °C for 4 hours and diluted with water (250 mL) whereupon it was then extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (20% diethyl ether in hexane) to yield the title compound as a white solid (150 mg, 0.34 mmol, 35%).

MP: 112–115 °C

IR (neat): 2929, 2857, 1697, 1472, 1399 cm⁻¹

¹H NMR (CDCl₃, 500 MHz): δ = 6.95 (d, *J* = 24.5 Hz, 1H), 5.34 (t, *J* = 7.5 Hz, 1H), 4.84 (dd, *J* = 23.0, 15.0 Hz, 1H), 4.69–4.99 (m, 3H), 3.67 (d, *J* = 2.5 Hz, 2H), 2.96–2.82 (m, 1H), 2.69–2.58 (m, 1H), 2.55–2.43 (m, 1H), 2.16 (s, 3H), 1.93 (ddt, *J* = 17.5, 12.5, 9.0 Hz, 1H), 1.52 (d, *J* = 3.0 Hz, 9H), 0.95 (d, *J* = 9.5 Hz, 9H), 0.18 (d, *J* = 21.5 Hz, 6H).

¹³C-NMR (CDCl₃, 126 MHz): δ = 205.6, 154.6, 140.7, 140.0, 136.7, 132.9, 129.8, 123.2, 79.5, 76.6, 51.3, 51.3, 48.4, 36.4, 29.3, 28.6, 28.5, 28.4, 25.9, 25.9, 18.0, -4.1, -5.0.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₂₅H₃₉NNaO₄Si: 468.2546; found: 468.2541.

(E)-4-(4-(*tert*-Butyldimethylsilyloxy)-1,3,4,5,6,6a-hexahydropentaleno[1,2-c]thiophen-6a-yl-1,1-dioxide)but-3-en-2-one (61)

To a solution of (6-(2-bromoallylthio)-1-(5-methylfuran-2-yl)hex-4-yn-3-yloxy)(*tert*-butyl)dimethylsilane (1.0 g, 2.3 mmol), dppe (180 mg, 0.45 mmol), potassium carbonate (620 mg, 4.5 mmol) in DMF (40 mL) was added palladium (II) acetate (50 mg, 0.23 mmol). The reaction mixture was heated to 120 °C for 30 minutes and then diluted down with water (400 mL). The mixture was then extracted with diethyl ether (3 x 200 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography (0-50% diethyl ether in hexane) to give the title compound as a bright yellow viscous oil (360 mg, 0.90 mmol, 40 %).

IR (neat): 3405, 2927, 2855, 1666, 1590, 1462, 1252 cm⁻¹

¹H NMR (CDCl₃, 500 MHz): δ = 7.23 (d, *J* = 16.0 Hz, 1H), 6.51 (s, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 4.97 (dd, *J* = 4.5, 2.5 Hz, 1H), 4.96-4.92 (m, 1H), 4.76 (t, *J* = 3 Hz, 1H), 4.10 (t, *J* = 3.0 Hz, 2H), 2.74-2.65 (m, 1H), 2.45-2.37 (m, 1H), 2.37-2.29 (m, 1H), 2.27 (s, 3H), 1.85-1.77 (m, 1H), 0.87 (s, 9H), 0.03 (d, 6H).

¹³C NMR (CDCl₃, 126 MHz): δ = 198.8, 150.8, 146.9, 138.9, 137.9, 135.5, 131.3, 129.3, 105.7, 79.1, 37.2, 33.0, 29.4, 27.1, 25.8, 18.1, -4.8, -4.8.

HRMS (ESI+): *m/z* [M+Na]⁺ calcd for C₂₀H₃₀NaO₄SSi: 417.1532; found: 417.1548.

5-(2-Oxopropyl)-6,7-dihydro-1*H*-indeno[4,5-*c*]furan-8(3*H*)-one (69)

tert-Butyldimethyl(1-(5-methylfuran-2-yl)-6-(prop-2-ynyloxy)hex-4-yn-3-yloxy)silane (50 mg, 0.14 mmol) was dissolved in dimethylformamide (5.0 mL) and heated to 200 °C for 3 hours in a microwave. The reaction mixture was decanted into water, stirred for 10 minutes, and the organics extracted with diethyl ether. The organic layer was then washed with brine, dried with magnesium sulfate and concentrated to give the title compound as a white to pale yellow solid (15 mg, 0.065, 47%).

Rf = 0.20 (50% ethyl acetate in petroleum ether).

IR (neat): 2923, 1708, 1463, 1108 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ = 7.26 (s, 1H), 5.37 (s, 2H), 5.10 (s, 2H), 3.83 (s, 2H), 3.03 (t, *J* = 5.5 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.27 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz) δ = 206.8, 204.9, 153.8, 140.1, 136.5, 131.9, 131.7, 128.1, 73.0, 72.6, 47.3, 36.3, 29.9, 25.3.

HRMS (EI+): *m/z* [M]⁺ calcd for C₁₄H₁₄O₃: 230.0943; found: 230.0943.

2-(8-Oxo-3,6,7,8-tetrahydro-1*H*-indeno[4,5-*c*]furan-5-yl)acetaldehyde (76)

tert-Butyl(1-(furan-2-yl)-6-(prop-2-ynyloxy)hex-4-yn-3-yloxy)dimethylsilane (50 mg, 0.15 mmol) was dissolved in DMF (5 mL) in a microwave vial, and purged with nitrogen. The vial was then heated at 200 °C for 4 hours in the microwave. The reaction mixture was then diluted into water (20 mL), extracted with diethyl ether, the organic layer washed with brine and then dried with magnesium sulfate. The solvent was removed and the crude purified using column chromatography (0-50% ethyl acetate in petroleum ether) to yield a highly viscous yellow oil (10 mg, 0.046 mmol, 31%).

Rf = 0.25 (40% ethyl acetate in petroleum ether).

IR (neat): 2925, 1698, 1588, 1077 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 9.82 (t, *J* = 1.5 Hz, 1H), 7.31 (s, 1H), 5.38 (t, *J* = 2.5 Hz, 2H), 5.10 (s, 2H), 3.85 (d, *J* = 1.5 Hz, 2H), 3.05 (m, 2H), 2.72 (m, 2H).

¹³C NMR (CDCl₃, 125 MHz): δ = 206.6, 197.7, 153.9, 140.3, 136.9, 132.1, 129.4, 128.2, 73.0, 72.6, 47.3, 36.3, 25.3.

HRMS (EI-): *m/z* [M-H]⁻ calcd for C₁₃H₁₁O₃: 215.0708; found: 215.0692.

5-(2-Oxobutyl)-6,7-dihydro-1*H*-indeno[4,5-*c*]furan-8(3*H*)-one (77)

A microwave vial was charged with *tert*-butyldimethyl(1-(5-ethylfuran-2-yl)-6-(prop-2-ynyloxy)hex-4-yn-3-yloxy)silane (32 mg, 0.09 mmol)

and acetonitrile (4.9 mL). A single drop of water was then added. The vial was placed in a microwave reactor for 5 hours at 200 °C. The resultant solution was concentrated under reduced pressure and the crude material was then purified via column chromatography (50% ethyl acetate in pentane) to afford the title compound as an off white-solid (14 mg, 0.06 mmol, 63%).

Rf: 0.57 (50 % ethyl acetate in pentane)

IR (neat): 2935, 2857, 2361, 1703, 1624, 1592, 1108, 1041 cm⁻¹.

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.28 (s, 1H), 5.30 (t, *J* = 2.5 Hz, 2H), 5.07 (m, 2H), 3.82 (s, 2H), 3.02 (m, 2H), 2.66 (m, 2H), 2.56 (q, *J* = 7 Hz, 2H), 1.07 (t, *J* = 7 Hz, 3H).

¹³C NMR (CD₂Cl₂, 125 MHz): δ = 207.4, 206.4, 153.7, 139.8, 135.9, 132.2, 131.6, 127.8, 72.6, 72.3, 45.6, 36.1, 25.1, 7.6.

HRMS No mass found by EI or CI

1,1-Dimethyl-5-(2-oxopropyl)-1*H*,3*H*,6*H*,7*H*,8*H*-indeno[4,5-*c*]furan-8-one (78)

A microwave vial charged with *tert*-butyldimethyl{[6-methyl-1-(5-methylfuran-2-yl)-6-(prop-2-yn-1-yloxy)hept-4-yn-3-yl]oxy} silane (50 mg, 0.13 mmol), acetonitrile (4.9 mL) and water (0.05 mL) was heated to 200 °C for 2 hours under microwave conditions. The solution was concentrated under reduced pressure, and the crude material was purified by column chromatography (0-60% ethyl acetate in petroleum ether) to give the title compound as a colourless oil (21 mg, 0.081 mmol, 61%).

Rf = 0.25 (50% ethyl acetate in petroleum ether).

IR (neat): 2927, 1703, 1588, 1357, 1277, 1155, 1103 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.20 (s, 1H), 5.10 (s, 2H), 3.80 (s, 2H), 2.99 (m, 2H), 2.69 (m, 2H), 2.26 (s, 1H), 1.67 (s, 6H).

¹³C NMR (CDCl₃, 100 MHz): δ = 206.1, 204.9, 155.0, 144.5, 139.7, 131.8, 131.2, 128.3, 87.7, 70.9, 47.3, 36.7, 30.0, 26.8, 25.0.

HRMS (EI+): *m/z* [M+H]⁺ calcd for C₁₆H₁₉O₃: 259.1334; found: 259.1334.

5-(2-Oxopropyl)-1*H*,3*H*,6*H*,7*H*,8*H*-indeno[4,5-*c*]furan-3,8-dione (81)

A microwave vial charged with 4-[(*tert*-butyldimethylsilyl)oxy]-6-(5-methylfuran-2-yl)hex-2-yn-1-yl prop-2-ynoate (50 mg, 0.14 mmol), acetonitrile (4.9 mL) and water (0.05 mL) was heated to 200 °C for 2 hours under microwave conditions. The solution was concentrated under reduced pressure, and the crude material was purified by column chromatography (0 to 50% ethyl acetate in DCM) to give the title compound as an off-white crystalline solid (21 mg, 0.086 mmol, 62%).

Rf = 0.35 (50% ethyl acetate in DCM)

IR (neat): 2928, 1763, 1709, 1600, 1335, 1166, 1104, 1013 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.87 (s, 1H), 5.57 (s, 2H), 3.94 (s, 2H), 3.15 (m, 2H), 2.79 (m, 1H), 2.32 (s, 1H).

¹³C NMR (CDCl₃, 100 MHz): δ = 205.4, 203.7, 170.0, 161.2, 143.6, 134.4, 132.6, 131.8, 126.3, 69.8, 47.1, 36.3, 30.1, 26.3.

HRMS No mass found by EI or CI;

5-(2-Oxopropyl)-1*H*,3*H*,6*H*,7*H*,8*H*-indeno[4,5-*c*]furan-1,8-dione (82)

A microwave vial was charged with prop-2-yn-1-yl 4-[(*tert*-butyldimethylsilyl)oxy]-6-(5-methylfuran-2-yl)hex-2-ynoate (50 mg, 0.11 mmol) and acetonitrile (4.9 mL) and water (0.05 mL) and was heated to 200 °C for 2 hours under microwave conditions. The solution was concentrated under reduced pressure yielding the crude material. The crude material was purified by flash column chromatography (0-2% methanol in DCM) to give the title compound as a yellow solid (21 mg, 0.086 mmol, 62%).

Rf = 0.28 (3% MeOH in DCM).

IR (neat): 2926, 1759, 1708, 1289, 1166, 1111, 1017 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.50 (s, 1H), 5.32 (s, 2H), 3.97 (s, 2H), 3.05 (m, 2H), 2.78 (m, 2H), 2.33 (s, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ = 203.5, 202.9, 167.5, 157.3, 148.5, 139.3, 135.3, 128.5, 121.9, 69.4, 47.2, 36.6, 30.4, 25.4.

HRMS (EI+): *m/z* [M+H]⁺ calcd for C₁₄H₁₃O₄: 245.0814; found: 245.0810.

4-Methyl-5-(2-oxopropyl)-1,3,6,7-tetrahydro-8H-indeno[4,5-c]furan-8-one (86)

A microwave vial charged with ((6-(but-2-yn-1-yloxy)-1-(5-methylfuran-2-yl)hex-4-yn-3-yl)oxy)(*tert*-butyl)dimethylsilane (50 mg, 0.14 mmol), acetonitrile (4.9 mL) and water (0.05 mL) was heated to 200 °C for 5 hours under microwave conditions. The solution was concentrated under reduced pressure and the crude material was purified by column chromatography (7.5% ethyl acetate in DCM) to give the title compound as a white solid (16 mg, 0.065 mmol, 48%).

R_f = 0.20 (10% ethyl acetate in DCM).

IR (neat): 2925, 2850, 1716, 1687, 1602, 1360, 1325, 1161, 1140 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.40 and 5.36 (t, *J* = 2.5 Hz, 2H), 5.09 (m, 2H), 3.85 and 3.82 (s, 2H), 3.01 (m, 2H), 2.69 (m, 2H), 2.27 and 2.26 (s, 3H), 2.18 (s, 3H). *Some peaks are doubled due to the presence of rotamers.*

¹³C NMR (100 MHz, CDCl₃): δ = 206.5, 204.8, 154.5, 139.6, 137.4, 135.8, 130.3, 128.1, 73.9, 73.1, 72.8, 72.6, 47.3, 43.8, 36.5, 36.3, 30.0, 29.8, 25.8, 25.3, 16.9. *Some peaks are doubled due to the presence of rotamers.*

HRMS (EI+): *m/z* [M]⁺ calcd for C₁₅H₁₆O₃: 244.1094; found: 244.1103.

5-(2-Oxopropyl)-4-phenyl-1H,3H,6H,7H,8H-indeno[4,5-c]furan-3,8-dione (87)

A microwave vial charged with 4-[(*tert*-butyldimethylsilyl)oxy]-6-(5-methylfuran-2-yl)hex-2-yn-1-yl 3-phenylprop-2-ynoate (50 mg, 0.11 mmol), acetonitrile (4.9 mL) and water (0.05 mL) was heated to 200 °C for 2 hours under microwave conditions. The solution was concentrated under reduced pressure. The crude material was purified by column chromatography (0-50% ethyl acetate in DCM) to yield the title compound as a colourless oil (24 mg, 0.075 mmol, 65%).

R_f = 0.52 (50% ethyl acetate in DCM).

IR (neat): 2921, 2851, 1760, 1714, 1615, 1359, 1159, 1093, 1014 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.46 (m, 3H), 7.13 (m, 2H), 5.55 (s, 2H), 3.71 (s, 2H), 3.12 (m, 2H), 2.81 (m, 2H), 2.07 (s, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ = 205.5, 204.7, 168.7, 161.2, 144.2, 134.7, 133.6, 131.2, 129.3, 128.8, 128.5, 127.5, 123.6, 68.3, 44.0, 36.3, 30.2, 26.7.

HRMS (EI+): *m/z* [M+H]⁺ calcd for C₂₀H₁₇O₄: 321.1127; found: 321.1133.

4-(Naphthalen-1-yl)-5-(2-oxopropyl)-6,7-dihydro-1H-indeno[4,5-c]furan-3,8-dione (88)

A microwave vial charged with 4-[(*tert*-butyldimethylsilyl)oxy]-6-(5-methylfuran-2-yl)hex-2-yn-1-yl 3-(naphthalen-1-yl) propiolate (65 mg, 0.13 mmol), acetonitrile (4.9 mL) and water (0.05 mL) was heated to 200 °C for 2 hours under microwave conditions. The solution was concentrated under reduced pressure and the crude material was purified by column chromatography (7.5% ethyl acetate in DCM) to yield the title compound as a white solid (23 mg, 0.062 mmol, 48%).

R_f = 0.37 (10% ethyl acetate in DCM).

IR (neat): 2924, 1763, 1706, 1609, 1358, 1101 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.96 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.55 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.49 (ddd, *J* = 8, 7, 1 Hz, 1H), 7.34 (ddd, *J* = 8, 7, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.13 (dd, *J* = 8.5, 1.0 Hz, 1H), 5.59 (d, *J* = 1.0 Hz, 2H), 3.61 (1H, d, *J* = 17.5 Hz), 3.46 (1H, d, *J* = 17.5 Hz), 3.17 (m, 2H), 2.85 (m, 2H), 1.81 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 205.6, 204.4, 168.3, 161.5, 145.5, 144.1, 134.8, 133.4, 132.5, 131.6, 131.4, 129.3, 128.8, 126.8, 126.6, 126.4, 125.3, 124.9, 124.7, 68.4, 43.8, 36.4, 30.2, 26.7.

HRMS (ESI+): *m/z* [M+H]⁺ calcd for C₂₄H₁₉O₄: 371.1283; found: 371.1281.

Dimethyl 8-oxo-5-(2-oxopropyl)-3,6,7,8-tetrahydroas-indacene-2,2(1H)-dicarboxylate (92)

Dimethyl 2-(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)-2-(prop-2-ynyl)malonate (50 mg, 0.11 mmol) was dissolved in dimethylformamide (2 mL) and heated to 200 °C for 3 hours in a microwave. The reaction mixture was decanted into water, stirred for 10 minutes, and the organics extracted with diethyl ether. The organic layer was then washed with brine, dried with magnesium sulfate and concentrated. The crude was then purified using flash column chromatography (20-60% ethyl acetate in petroleum ether) to give the title compound as a pale yellow gum (12 mg, 0.035 mmol, 32%).

R_f = 0.20 (60% ethyl acetate in petroleum ether).

IR (neat): 2850, 1730, 1710, 1425, 1255, 1140, 1065 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (s, 1H), 3.91 (s, 2H), 3.76 (s, 2H), 3.74 (s, 6H), 3.58 (s, 2H), 2.95 (m, 2H), 2.67 (m, 2H), 2.23 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 205.2, 172.1, 153.6, 141.0, 137.7, 133.4, 131.2, 131.2, 60.7, 53.2, 47.4, 39.9, 39.1, 36.5, 29.9, 24.9.

HRMS (EI+): *m/z* [M+H]⁺ calcd for C₁₉H₂₁O₆: 345.1338; found: 345.1344.

5-(2-oxopropyl)-2-tosyl-2,3,6,7-tetrahydrocyclopenta[e] isoidol-8(1H)-one (93)

N-(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)-4-methyl-N-(prop-2-ynyl)benzene sulfonamide (0.053 g, 0.11 mmol) was dissolved in acetonitrile (2 mL) in a microwave vial, subsequently adding a drop of water and purging with nitrogen. The mixture was then heated in the microwave at 195 °C for 1.5 hours. After removing the solvent, the crude material was purified by column chromatography (0-5% ethyl acetate in dichloromethane) to yield a white gum (13 mg, 0.034 mmol, 32%).

R_f = 0.20 (10% ethyl acetate in dichloromethane).

IR (neat): 2924, 1705, 1595, 1344, 1160, 1095 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.78 (m, 2H), 7.31 (m, 2H), 7.17 (s, 1H), 4.84 (t, *J* = 2.5 Hz, 2H), 4.61 (m, 2H), 3.79 (s, 2H), 2.95 (m, 2H), 2.66 (m, 2H), 2.39 (s, 3H), 2.25 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 206.1, 204.5, 154.1, 143.8, 136.7, 133.6, 133.3, 132.4, 132.2, 129.9, 129.3, 127.6, 52.8, 52.8, 46.9, 36.1, 29.9, 25.0, 21.5.

HRMS (EI+): *m/z* [M+H]⁺ calcd for C₂₁H₂₂NO₄S: 384.1270; found: 384.1279.

5-(2-Oxopropyl)-6,7-dihydro-1H-indeno[4,5-c]thiophen-8(3H)-one (94)

tert-Butyldimethyl(1-(5-methylfuran-2-yl)-6-(prop-2-ynylthio)hex-4-yn-3-yloxy)silane (0.05 g, 0.15 mmol) was dissolved in acetonitrile (2 mL), in a microwave vial; a drop of water was then added and the mixture purged with nitrogen. The vial was then heated at 200 °C for 6.5 hours in the microwave. The reaction mixture was then concentrated, and the crude mixture purified using column chromatography (0-50% ethyl acetate in petroleum ether) to yield a viscous yellow oil (10 mg, 0.041 mmol, 27%).

R_f = 0.35 (40% ethyl acetate in petroleum ether).

IR (neat): 2923, 1706, 1584, 1358, 1163 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.28 (s, 1H), 4.57 (t, *J* = 2.5 Hz, 2H), 4.22 (m, 2H), 3.79 (s, 2H), 2.98 (m, 2H), 2.69 (m, 2H), 2.25 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 206.9, 204.9, 153.6, 141.8, 138.2, 133.5, 131.7, 131.1, 47.1, 36.8, 36.6, 36.4, 29.9, 24.7.

HRMS No accurate mass found by EI+ or CI+.

1-(2,7-Dioxa-4,5,6,8-tetrahydro-as-indacen-4-yl)-2-propanone (100)

2-Methyl-5-((4-(prop-2-ynyloxy)but-2-ynyloxy)methyl)furan (0.010 g, 0.046 mmol) was dissolved in acetonitrile (0.5 mL) in a microwave vial. A drop of water was added, the vial purged with nitrogen, and heated in

the microwave at 200 °C for 1 hour. The solvent was removed to yield a yellow gum (10 mg, 0.046 mmol, 99%).

R_f = 0.35 (40% ethyl acetate in petroleum ether).

IR (neat): 2844, 1713, 1362, 1163, 1027 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.17 (s, 1H), 7.15 (t, *J* = 1.5 Hz, 1H), 4.81 (m, 2H), 4.65 (m, 2H), 3.48 (m, 1H), 2.81 (dd, *J* = 17.5, 7 Hz, 1H), 2.63 (dd, *J* = 17.5, 7 Hz, 1H), 2.54 (m, 1H), 2.15 (s, 3H), 2.03 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 207.3, 137.8, 134.9, 132.9, 124.4, 123.5, 117.2, 77.0, 74.1, 49.3, 30.7, 27.7, 26.1.

HRMS (CI+): *m/z* [M+H]⁺ calcd for C₁₃H₁₅O₃: 219.1021; found: 219.1020.

1-(4-Methylfuran-3-yl)propan-2-one (110)

tert-Butyldimethyl(5-(prop-2-ynyloxy)pent-3-yn-2-yloxy)silane³² (55 mg, 0.22 mmol) was dissolved in acetonitrile (2 mL) in a microwave vial; a drop of water was added and the vial purged with nitrogen. The mixture was heated at 190 °C in the microwave for 1 hour. After removal of the solvent, the crude mixture was purified using flash column chromatography (0-50% ethyl acetate in petrol) to yield the title compound 110 as a pale yellow oil (12 mg, 0.087 mmol, 40%) and 111 as a yellow oil (5 mg, 0.036 mmol, 15%).

R_f = 0.70 (50% ethyl acetate in petrol).

IR (neat): 2928 (C-H), 1716 (C=O), 1361, 1165, 1049 cm⁻¹.

¹H NMR (400 MHz): δ = 7.32-7.31 (m, 1H), 7.21-7.19 (m, 1H), 3.47 (s, 2H), 2.18 (s, 3H), 1.92-1.92 (d, *J* = 1 Hz, 3H).

¹³C NMR (125 MHz): δ = 206.0, 141.0, 140.1, 120.1, 118.4, 38.9, 29.2, 8.2.

HRMS (EI+): *m/z* [M] C₈H₁₀O₂ calcd for 138.0681; found: 138.0686.

1,6,7,7a-Tetrahydroisobenzofuran-5(3H)-one (111)

A yellow oil (5 mg, 0.036 mmol, 15%).

R_f = 0.15 (50% ethyl acetate in petrol)

IR (neat): 2941, 1677, 1667, 1373, 1194, 1051 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.94 (m, 1H), 4.69-4.64 (dt, *J* = 16.5, 1.5 Hz, 1H), 4.47-4.38 (dt, *J* = 16.5, 1.5 Hz, 1H), 4.33-4.29 (t, *J* = 8.5 Hz, 1H), 3.38-3.33 (dd, *J* = 10.5, 8.5 Hz, 1H), 3.02-2.93 (m, 1H), 2.57-2.52 (m, 1H), 2.42-2.33 (ddd, *J* = 17, 14.5, 5 Hz, 1H), 2.26-2.20 (ddd, *J* = 12, 5, 2.5 Hz, 1H), 1.75-1.64 (dddd, *J* = 14.5, 13, 11.5, 4.5 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 198.6, 168.8, 119.9, 73.2, 69.8, 41.7, 36.7, 25.6.

HRMS (EI+): *m/z* [M] calcd for C₈H₁₀O₂: 138.0681; found: 138.0686.

1-(4-Methylthiophen-3-yl)propan-2-one (120)

tert-Butyldimethyl(5-(prop-2-ynylthio)pent-3-yn-2-yloxy)silane (50 mg, 0.19 mmol) was dissolved in acetonitrile (2 mL) in a microwave vial. A drop of water was added, the vial purged with nitrogen, and the mixture heated in the microwave for 6 hours at 200 °C. The solvent was removed and the crude mixture purified by flash chromatography (20% ethyl acetate in petrol) to yield the title compound 120 as a yellow gum (6 mg, 0.039 mmol, 21%).

R_f = 0.40 (20% ethyl acetate in petrol).

IR (neat): 2927, 1709, 1356, 1158, 1100 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.07-7.06 (d, *J* = 3.5 Hz, 1H), 6.96-6.94 (m, 1H), 3.64 (s, 2H), 2.15 (s, 3H), 2.14-2.14 (d, *J* = 1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 206.0, 137.1, 134.1, 123.7, 122.0, 44.4, 29.3, 14.6.

HRMS (CI+): *m/z* [M+NH₄]⁺ calcd for C₈H₁₄NOS: 172.0796; found: 172.0799

8-Thiabicyclo[4.3.0]non-1-en-3-one (121)

tert-Butyldimethyl(5-(prop-2-ynylthio)pent-3-yn-2-yloxy)silane (0.20 g, 0.74 mmol) was dissolved in acetonitrile (4 mL) in a microwave vial. 2 drops of water were added, the vial purged with nitrogen, and the mixture heated in the microwave for 6 hours at 200 °C. The solvent was removed and the crude mixture purified by flash column

chromatography (10-20% ethyl acetate in petrol) to yield a pale yellow to yellow gum (13 mg, 0.084 mmol, 11%).

R_f = 0.15 (20% ethyl acetate in petrol).

IR (neat): 2926, 1664, 1321, 1251, 1194 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 6.00-5.99 (m, 1H), 3.85-3.70 (m, 2H), 3.17- 3.12 (dd, *J* = 11, 7.5 Hz, 1H), 3.06-2.97 (m, 1H), 2.69-2.63 (t, *J* = 10.5 Hz, 1H), 2.55-2.48 (m, 1H), 2.40-2.31 (m, 2H), 1.82- 1.71 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 198.9, 168.3, 123.6, 45.2, 36.8, 36.4, 35.8, 28.8.

HRMS (CI+): *m/z* [M+NH₄]⁺ calcd for C₈H₁₄NOS: 172.0796; found: 172.0794.

1-(4-Methyl-1-tosyl-1H-pyrrol-3-yl)propan-2-one (125)

N-(4-(*tert*-Butyldimethylsilyloxy)pent-2-ynyl)-4-methyl-*N*-(prop-2-ynyl) benzenesulfonamide (60 mg, 0.15 mmol) was dissolved in acetonitrile (2 mL) in a microwave vial. A drop of water was added, the vial purged with nitrogen, and then heated in the microwave at 200 °C for 1.5 hours. The solvent was removed and the crude mixture purified by flash column chromatography (5-50% ethyl acetate in petrol) to yield the title compound 125 as a white to yellow gum (18 mg, 0.062 mmol, 41%), along with 126 and 127.

R_f = 0.20 (20% ethyl acetate in petrol).

IR (neat): 2919, 1713, 1595, 1364, 1169, 1064 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.72-7.70 (m, 2H), 7.30-7.28 (m, 2H), 7.02-7.02 (d, *J* = 2 Hz, 1H), 6.89-6.88 (m, 1H), 3.41 (s, 2H), 2.39 (s, 3H), 2.11 (s, 3H), 1.90-1.89 (d, *J* = 1 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 205.9, 144.9, 136.3, 130.1, 126.9, 124.3, 121.8, 119.5, 118.5, 40.7, 29.2, 21.8, 10.4.

HRMS (ES+): *m/z* [M+H]⁺ calcd for C₁₅H₁₈NO₃S: 292.1002; found: 292.1010.

2-Tosyl-1,2,3,6,7,7a-hexahydroisindol-5-one (126)

Pale yellow to yellow gum (7 mg, 0.024 mmol, 16%).

R_f = 0.25 (50% ethyl acetate in petrol).

IR (neat): 2933, 1670, 1595, 1345, 1162, 1094 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.73-7.71 (m, 2H), 7.37-7.35 (d, *J* = 8 Hz, 2H), 5.88-5.87 (m, 1H), 4.33-4.27 (dt, *J* = 17, 1.5 Hz, 1H), 3.94-3.90 (m, 1H), 3.83-3.79 (dt, *J* = 17, 2 Hz, 1H), 2.98-2.89 (m, 1H), 2.66-2.61 (dd, *J* = 11, 9.5 Hz, 1H), 2.49-2.45 (m, 1H), 2.45 (s, 3H), 2.34-2.25 (ddd, *J* = 17, 14.5, 5 Hz, 1H), 2.22-2.16 (ddd, *J* = 12.5, 5, 2.5 Hz, 1H), 1.64-1.53 (dddd, *J* = 14.5, 13, 11.5, 4.5 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 197.7, 164.0, 144.3, 132.8, 130.1, 127.9, 122.5, 53.2, 51.3, 40.5, 36.5, 26.7, 21.7.

2-Tosyl-2,3,6,7-tetrahydro-1H-isoidol-5(4H)-one (127)

Pale yellow to yellow gum (6 mg, 0.021 mmol, 14%).

R_f = 0.30 (50% ethyl acetate in petrol).

IR (neat): 2921, 1713, 1595, 1341, 1160, 1100 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.74-7.72 (m, 2H), 7.35-7.33 (d, *J* = 8 Hz, 2H), 4.08 (s, 2H), 4.04 (s, 2H), 2.77 (s, 2H), 2.52- 2.49 (t, *J* = 7 Hz, 2H), 2.44 (s, 3H), 2.40-2.36 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ = 207.4, 143.8, 134.3, 130.3, 130.0, 128.3, 127.6, 56.6, 56.5, 37.9, 23.1, 21.7.

6,7-Dihydro-1H-cyclopenta[d]furo[3,4-b]pyridin-8(3H)-one (129)

2-(4-(*tert*-Butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyloxy)acetoneitrile (42 mg, 0.12 mmol) was dissolved in acetonitrile (2 mL) in a microwave vial. A drop of water was added, and then the vial was purged with nitrogen. The mixture was heated at 200 °C in the microwave for 6 hours. The solvent was then removed and the crude mixture purified by flash chromatography (0-40% ethyl acetate in dichloromethane) to yield a pale yellow gum (8 mg, 0.046 mmol, 42%).

$R_f = 0.35$ (40% ethyl acetate in dichloromethane).

IR (neat): 2900, 1995, 1710, 1395, 1025 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): $\delta = 8.78$ (s, 1H), 5.40 (m, 2H), 5.10 (m, 2H), 3.27 (m, 2H), 2.76 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 206.9$, 160.7, 149.4, 146.4, 138.0, 128.0, 72.2, 71.7, 36.3, 24.3.

HRMS (ESI⁺): m/z [M+H]⁺ calcd for $\text{C}_{10}\text{H}_{10}\text{NO}_2$: 176.0712; found: 176.0718.

(E)-4-Amino-3-(5-oxo-2-(3-oxobut-1-en-1-yl)cyclopent-1-en-1-yl)furan-2(5H)-one (132)

A microwave vial charged with cyanomethyl 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynoate (50 mg, 0.14 mmol), acetonitrile (4.9 mL) and water (0.05 mL) was heated to 200 °C for 5 hours under microwave conditions. The solution was concentrated under reduced pressure and the crude material was purified by column chromatography (0-50% ethyl acetate in DCM) to give the title compound as a colourless oil (21 mg, 0.086 mmol, 62%).

$R_f = 0.27$ (5% MeOH in DCM).

IR (neat): 2918, 2850, 1724, 1263, 1098 cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 7.45$ (d, $J = 16.0$ Hz, 1H), 7.26 (br. s, 2H), 6.57 (d, $J = 16.0$ Hz, 1H), 4.73 (s, 2H), 2.77 (m, 2H), 2.47 (m, 2H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 206.6$, 198.1, 172.6, 167.1, 161.7, 137.8, 136.8, 130.8, 84.1, 66.6, 33.9, 27.8, 25.6.

HRMS (ESI[−]): m/z [M−H][−] calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_4$: 246.0766; found: 246.0771.

Cyanomethyl (syn-1-anti-3,6)-1-((*tert*-butyldimethylsilyl)oxy)-6-methyl-1,2,3,6-tetrahydro-3a,6-epoxyindene-7-carboxylate (133)

Cyanomethyl 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynoate (40 mg, 0.11 mmol) allowed to stand under N_2 for 10 days. The product was obtained as a white crystalline solid (40 mg, 0.11 mmol, 100%).

$R_f = 0.17$ (10% ethyl acetate in pentane).

MP = 87 – 90 °C; Decomposition.

IR (neat): 2930, 2238, 1720, 1253, 1087, 1057, 838 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): $\delta = 6.90$ (d, $J = 5.0$ Hz, 1H), 6.8 (d, $J = 5.0$ Hz, 1H), 5.0 (m, 1H), 4.8 (s, 2H), 2.5 (m, 1H), 2.2 (m, 2H), 2.0 (m, 1H), 1.9 (s, 3H), 0.8 (s, 9H), 0.1 (s, 3H), −0.1 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 181.1$, 161.8, 146.0, 145.1, 135.7, 114.4, 99.4, 95.6, 67.6, 48.2, 39.0, 25.7, 24.7, 18.2, 17.2, −4.7, −5.0.

HRMS (CI⁺): m/z [M+H]⁺ calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4\text{Si}$: 362.1788; found: 362.1782.

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Supporting Information

YES (this text will be updated with links prior to publication)YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)NO (this text will be deleted prior to publication)

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Biosketches

<p>Philip J. Parsons started his independent research career at the University of Southampton in 1979, after completing Post-Doctoral studies with Professor G Stork at Columbia University. While at the University of Southampton, he co-founded Cookson Chemicals Ltd., now Tocris Bioscience a brand of Bio-Techne, which won the Queen's Award for Industry for International Trade in 2002. In 1990, he was appointed Professor and Head of Organic Chemistry at the University of Reading. He later moved to the University of Sussex in 1995 where he was appointed Dean of the School of Chemistry, Physics, and Environmental Science. Recently, he was appointed Senior Research Investigator and now Professor at Imperial College London; he has recently founded Pareon Chemicals Ltd.</p>
<p>Lewis A. T. Allen completed his Masters Degree in chemistry at the University of Sussex where he was shortlisted for the 2011 MacQuitty Prize for outstanding performance at undergraduate level. He obtained his PhD from Imperial College London in 2015 after completing studies on the total synthesis of aphidicolin under the guidance of Professor Parsons. He has held a research position at Pareon Chemicals Ltd. and he is currently completing Post-Doctoral studies at Imperial College.</p>
<p>Daniel R. Jones completed his Masters Degree in chemistry at the University of York 2014, having spent a year in industry at RedX Pharma. After a short spell at Peakdale Molecular, he began his PhD studies at Imperial College London, working toward the synthesis of the potent antibiotic, lactonamycin under the supervision of Prof. Philip Parsons.</p>

<p>Alex C. Padgham studied chemistry at the University of Sussex, where he obtained his Masters Degree in 2011 and won the Alfred Bader Prize for his Masters dissertation. He is currently a PhD candidate at Imperial College London.</p>
<p>James A. Pryke studied chemistry at the University of Sussex, graduating in 2007 with a BSc Hons. He then completed his PhD studies with Prof Parsons, before becoming Head Brewer at Full Moon Brewery. In 2013, he began work at Johnson Matthey as a production chemist.</p>
<p>Joseph McKenna received his B.S. in Medicinal Chemistry from the University of Sussex in 2005, graduating with First Class Honors. He then joined the research group of Prof. P. J. Parsons where he focused on palladium and radical-mediated cascade reactions. Joseph joined Novartis in 2010, where he is currently a medicinal chemist in the field of oncology.</p>
<p>Daniel O'Reilly studied chemistry at Imperial College London after receiving the first place in Northern Ireland for A level Chemistry and A level Physics. He has completed summer projects for both Dr James Bull on amide containing cyclopropyl sulphides and later with Prof. Parsons on cascade cyclisations. After completing his masters project with Prof. Braddock, he has commenced his PhD studies at Imperial College London.</p>

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