

The Synthesis of *ortho*-Fused Cycloocta-2,5-dien-1-one Cores and Their Derivatisation

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Abstract

Eight-membered rings are notoriously difficult to synthesise due to unfavourable transannular and conformational strain within the ring system. That being said, there are many biologically active natural products that contain such ring systems. For instance, potent anti-cancer compound Taxol®, has an eight-membered ring at its core. Many contemporary synthetic routes to 8-membered rings require the use of complex cyclisation precursors, due to the difficulties associated with the formation of 8-membered rings. The synthesis of such precursors commonly include multiple steps, with each step consuming researcher time, effort and resources.

Described herein is new methodology that can be used to synthesise eight-membered carbocyclic cores, in a one-pot, single step synthesis from easily attainable starting materials. A novel Cannizzaro triggered cascade allowed swift formation of eight-membered rings from three components without the need to synthesise, purify and characterise unwanted intermediates. The key step in the cascade is a Cannizzaro-like 1,5-hydride transfer that simultaneously forms a carbanion and powerfully Michael accepting ynone. Annulation is achieved through the reaction of these centres.

Application of this methodology led to the synthesis of 30 novel *ortho*-fused eight-membered carbocycles, in up to 81% yield. Utilisation of a 'temperature switch', based on competition of kinetic and thermodynamic pathways, enabled the synthesis of 7 novel 1,2-dihydronaphthalen-1-ol or naphthalene cores. The mechanisms of the aforementioned transformations have also been probed both experimentally and computationally to support our proposed mechanism.

With the aim of synthesising a diverse library of 8-membered ring derivatives, the Cannizzaro cascade was extended to enable trapping of a reactive intermediate with electrophiles. A Diversity Oriented Synthetic project was undertaken using the products of the 3- and 4-component cascade reaction as starting points to build molecular diversity.

In a maximum of three-steps, from commercial bromo-aldehydes, we have been able to develop a library of compounds that contain; four-, five-, six-, eight- and nine-membered ring systems; nitrogen, sulfur and oxygen containing heteroaromatics; bicyclic and tricyclic fused-ring systems; and functional groups including a carboxylic acid, amides, lactams, alcohols, ketones, halogens, nitriles, esters, oximes, alkenes, alkynes, enones and a pyrazalone ring.

Representative examples from this library have been through a limited number of biological screening assays and have shown biological activity in two different areas. It was found that some compounds in this library are able to stimulate the secretion of Glucagon-like Peptide-1, a possible target for the treatment of type II diabetes.

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Abbreviations

Approx.	Approximately
BBN	9-Borabicyclo[3.3.1]nonane
CAS	Chemical Abstracts Service
CO-ADD	Community for Open Antimicrobial Drug Discovery
COD	1,5-Cyclooctadiene
DCE	1,2-Dichloroethane
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DOS	Diversity Oriented Synthesis
dppf	1,1'- <i>Bis</i> (diphenylphosphino)ferrocene
EC ₅₀	Effective Concentration
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>e.e.</i>	Enantiomeric Excess
EM _T	Thermodynamic Effective Molarity
Equiv.	Equivalents
EWG	Electron Withdrawing Group
FDA	Food and Drug Administration
GLP-1	Glucagon-like Peptide-1
HHT	Homoharringtonine
HOBt	Hydroxybenzotriazole
HOMO	Highest Occupied Molecular Orbital
KHMDS	Potassium hexamethyldisilazide
Mol.	Molecular
NCS	<i>N</i> -Chlorosuccinimide
NBD	Norbornadiene
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
OIDD	Open Innovation Drug Discovery
pg	Protecting Group
ppm	Parts Per Million
RCM	Ring Closing Metathesis

SIMes	1,3- <i>Bis</i> (2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TOS	Target Oriented Synthesis
μw	Microwave

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Chapter 1: Cannizzaro Cascade Synthesis of Fused 8-Membered Ring Systems

1.1 Introduction

1.1.1 Difficulties associated with 8-membered ring synthesis

Medium-sized carbocycles, particularly cyclooctanoids, have proven to be difficult substrates to synthesise from acyclic precursors due to the significant transannular and conformational strain present in their ring structure.¹ The saturated cyclooctane ring system has been extensively studied and at room temperature >94%² of its population exists in a boat-chair conformation to minimise transannular interactions (Figure 1).

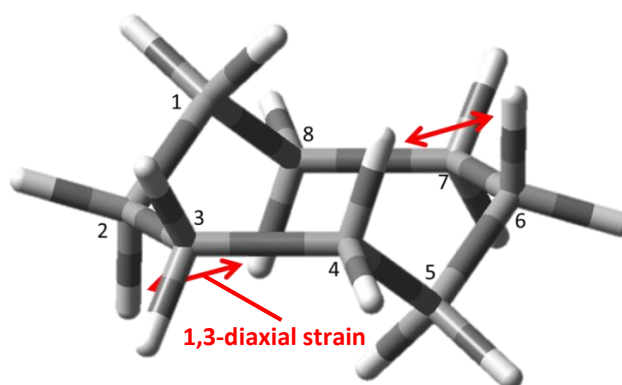


Figure 1 Boat-chair conformation of cyclooctane showing transannular interactions

Although this boat-chair conformation has the lowest energy, transannular interactions are still significant as 1,3-diaxial hydrogens are positioned close together in space (1.8 Å). Baeyer ring strain^{3,4} can be observed with a simple Hartree-Fock optimisation of cyclooctane using the 3-21G basis set.⁵ This computational model predicts that the bond angle of C1-C2-C3 is 116.5°, C2-C3-C4 is 117.0° and C4-C5-C6 is 113.0°. These three bond angles are therefore forced away from the ideal 109.5° angle adopted by a carbon sp³ centre. The dihedral angles of the ring are also far removed from the ideal geometries that can be achieved by an acyclic carbon chain. The boat-chair cyclooctane ring possesses dihedral angles of 41.9° and 91.5° showing significant destabilising gauche interactions.

The difficulty in forming 8-membered rings was highlighted by work carried out by Grubbs *et al.*⁶ Having developed metathesis methodology that successfully formed 5- to 7-membered carbocycles,^{7,8} he found this methodology could not be applied directly to cyclooctanoid derivatives. It was suggested that this could be due to the inherent strain of 8-membered rings, or kinetic factors that control the ring closing event. Such kinetic factors are directly related to the length of the carbon chain; as chain length increases, the two reactive sites in an acyclic precursor have a decreased chance of gaining the required

proximity for a successful reaction. There is also significant entropic loss as cyclisation brings loss of rotational freedom about seven C–C bond rotors.⁹

A study by Hillier *et al.*¹⁰ set out to quantify the difficulties in forming medium sized ring systems using a model based on ring closing metathesis (RCM). Thermodynamic effective molarities (EM_T) were calculated for the cyclisation of α,ω -dienes (**1**) to cycloalkenes (**2**). Thermodynamic effective molarity is a measure of a compound's resistance to cyclisation. It is calculated from the intramolecular cyclisation equilibrium constant and the intermolecular dimerization equilibrium constant. In real terms, effective molarity is the reaction concentration needed for cyclisation to out-compete dimerisation. Hence an increase in effective molarity signifies a more favourable cyclisation.

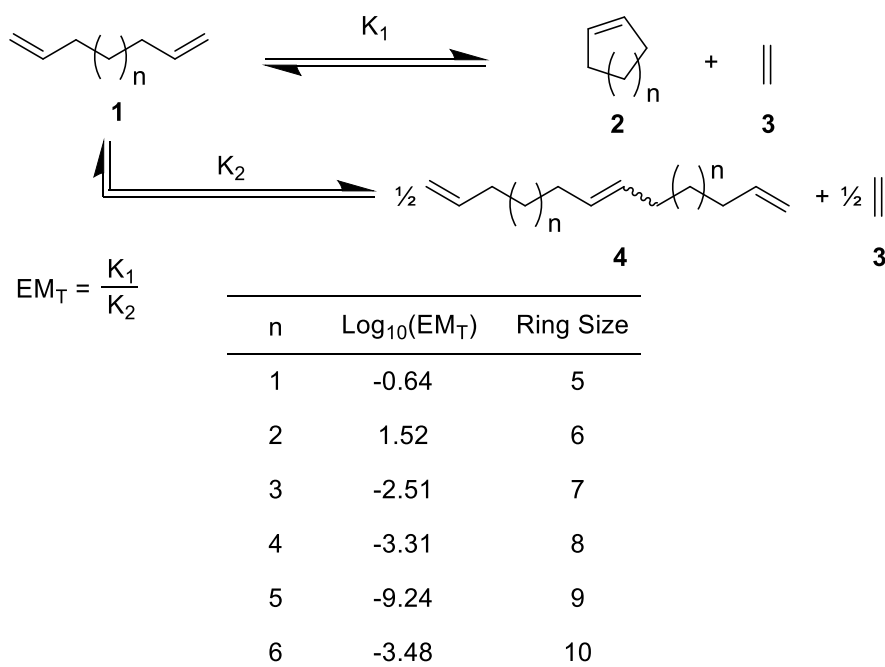
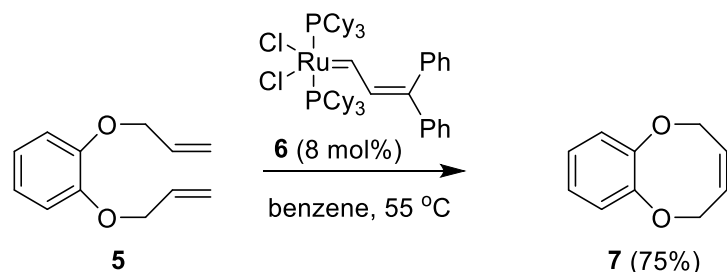


Table 1 Hillier *et al.* RCM model and calculated thermodynamic effective molarity

Table 1 shows that the calculated thermodynamic effective molarity for RCM to cyclohexene ($n = 2$) is far greater than any other ring system. Formation of an 8-membered ring ($n = 4$) has an effective molarity close to 5 orders of magnitude less than the formation of the analogous 6-membered ring. This calculation predicts that for an 8-membered RCM to have the same ring to dimer ratio as a 1 mL 6-membered RCM reaction, it would need to be diluted to a volume of 100 L. The lowest thermodynamic effective molarity calculated was for the formation of 9-membered rings. When ring size is increased to a 10-membered ring, ring strain decreases meaning RCM of this system is comparable to that of 8-membered rings.

To overcome this issue, Grubbs introduced conformational constraint into the carbon chain in the form of a fused ring (**5**). This constraint prevented rotation about a bond rotor in the middle of a chain. Not only did this lessen the impact of entropic loss due to cyclisation, but also templated the reactive centres closer together in space (Scheme 1).⁶



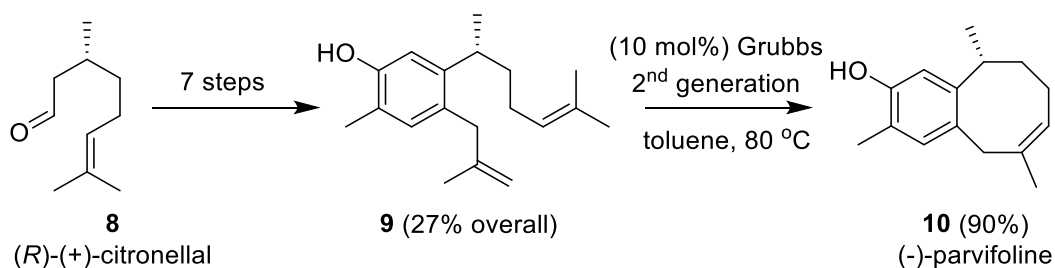
Scheme 1 Grubbs' use of conformational constraint

This alteration resulted in an increased chance of proximity and therefore a viable metathesis route. This strategy of conformational constraint is widely applied to enable the synthesis of medium sized rings and usually results in fused ring systems or unsaturation. That being said, Grubbs ring closing metathesis has become a very popular method for forming 8-membered rings.^{11,12}

1.1.2 Synthesis of 8-membered Rings in Target Oriented Synthesis

There are many biologically active natural products containing 8-membered rings;^{13,14,2} interestingly, many of these compounds also contain fused ring systems that may increase cyclisation capability of the acyclic precursor by positioning reactive centres in closer proximity.

A relatively simple natural product is that of (-)-parvifoline **10**. Chavan *et al.* utilised Grubbs ring closing metathesis methodology to form this benzo-fused cyclooctene¹⁵ (Scheme 2).

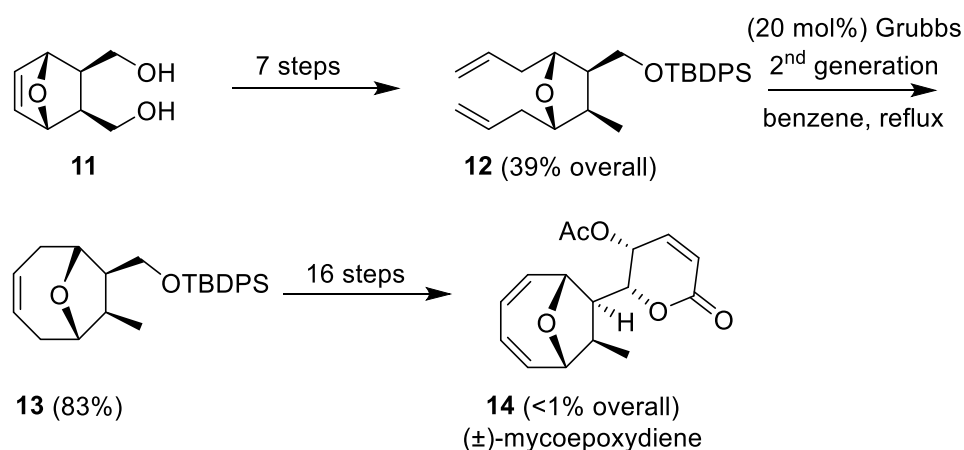


Scheme 2 Chavan *et al.* synthesis of (-)-parvifoline

(-)-Parvifoline **10** was synthesised from optically pure citronellal **8**, avoiding a potentially difficult enantioselective step. The high yielding RCM of **9** to form the 8-membered ring was aided by the rigid benzene ring in the carbon skeleton. Even with this constraint, high

catalyst loading and relatively high temperatures are still needed to successfully form the 8-membered ring.

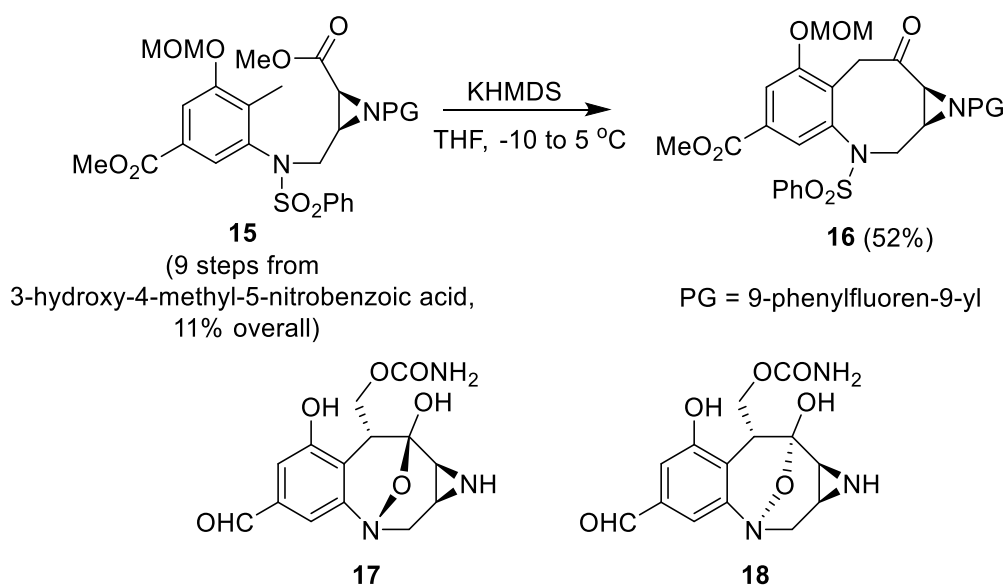
A second example showing the importance of 8-membered rings is shown in the structure of biologically active mycoepoxydiene **14** (Scheme 3) which has shown promise as an anti-tumour agent.¹⁶ Tadano *et al.* exploited Grubbs RCM to cyclise a constrained 1,9-diene (**12**) in high yield.¹⁷ This natural product contains a 1,4-oxygen bridged cyclooctadiene and it is the presence of this bridging unit which constrains the carbon chain, facilitating ring closing metathesis.



Scheme 3 Tadano *et al.* synthesis of ($\pm$)-mycoepoxydiene

Although RCM is a very useful and powerful tool in the synthesis of cyclooctanoids, the examples shown highlight some undesirable features that are common among other RCM routes to 8-membered rings. These include high loadings of an expensive catalyst (10 – 20 mol%), step intensive formation of the required dienes (which reduces overall yield) and the need for a constrained precursor in order to direct the reactive centres together.

Moving away from ring closing metathesis there are numerous other ways to close 8-membered rings. A particularly good example was shown by Rapoport and Jones in their efforts towards the synthesis of potent anti-cancer compounds **17** and **18**.¹⁸ By carefully choosing their cyclisation precursor (**15**), they were able to form the required nitrogen containing 8-membered ring **16**, via a simple condensation reaction, in 52% yield (Scheme 4).¹⁹



Scheme 4 Rapoport and Jones efforts towards anti-cancer agents

The key to the success of this ring closing reaction is twofold. In order to diminish the barrier to forming the fused cyclooctane ring, the reactive centres in **15** are held in quite a rigid conformation due to the combined effect of the fused benzene and aziridine rings. Secondly, the tolyl-aromatic ring substituents, particularly the *para*-ester group, play an important role in increasing tolyl-proton acidity. The base used to deprotonate the tolyl-protons was bulky and non-nucleophilic potassium hexamethyldisilazide, which has a pK_{aH} of 26 in THF.²⁰ Without the activating substituents, a stronger base would have been required, which may have led to deprotonation of the carbonyl α -proton.

Taxol (**19**) (Figure 2) is an important compound that contains an 8-membered ring and is perhaps the most widely studied natural product with this ring size. It has proven to be a very effective drug for ovarian, breast and lung cancers²¹ among a broad range of other antitumor activity.²² Arguably one of the most challenging aspects of a Taxol total synthesis is the closure of the 8-membered B-ring, referred to by Nicolaou as '*one of the most daunting problems of the entire [Taxol] campaign*'.²³ A review by Nicolaou *et al.*²⁴ also showed that in the mission to synthesise Taxol, several interesting syntheses of 8-membered rings have been accomplished.

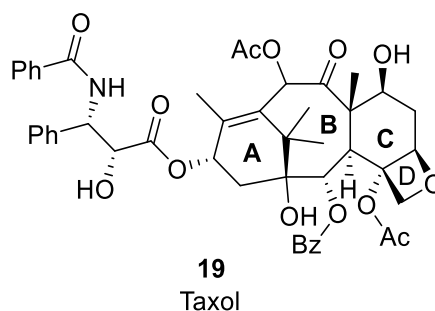
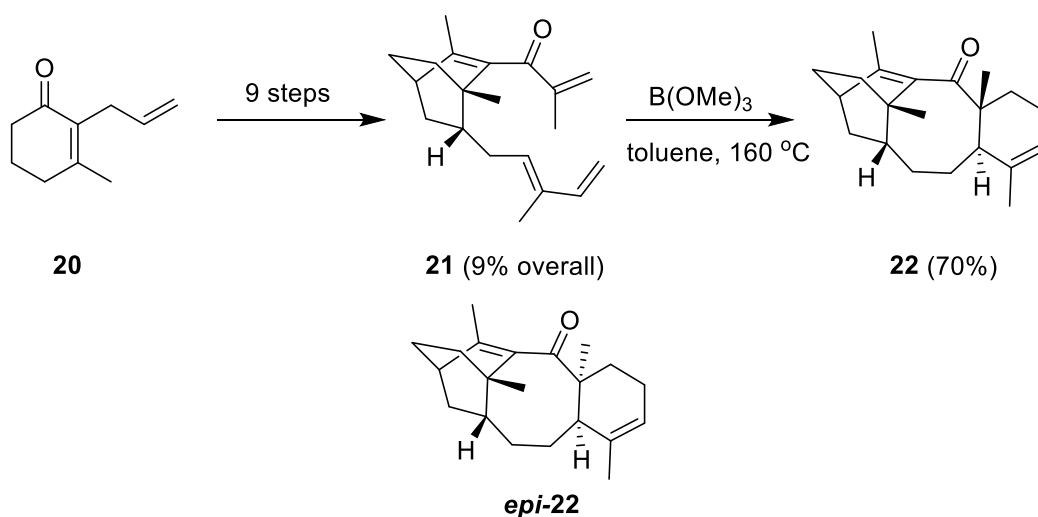


Figure 2 Taxol

An impressive contribution to the formation of the Taxol skeleton by Sakan and Craven included an intramolecular Diels-Alder approach to forming 8-membered ring **22** (Scheme 5).²⁵

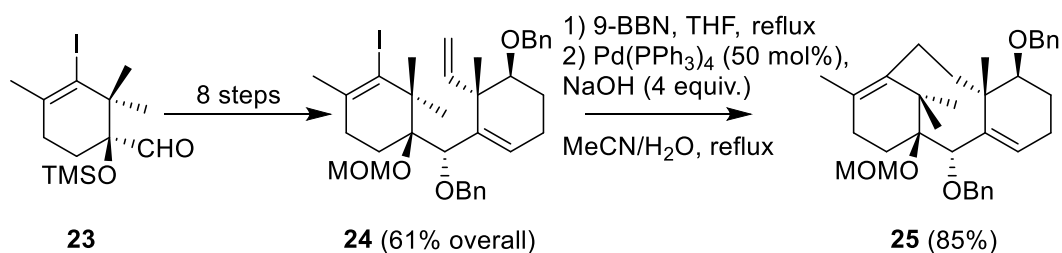


Scheme 5 Sakan and Craven Diels-Alder approach to Taxol skeleton

The choice of Lewis acid was crucial to ensure the desired isomer was formed. The use of dimethyl aluminium chloride in place of trimethyl borate resulted in the formation of the epimer *epi-22* shown in Scheme 5. Interestingly, the catalyst-free thermally induced reaction of **21** to **22** proceeded with good conversion, but appreciable amounts of uncharacterised by-products were formed, which hindered isolation. This example of cyclisation is particularly impressive as two stereocentres were formed in a controlled manner. As seen with previous examples, entropic assistance was sought by utilising a fused ring system to increase the proximity of reaction centres.

A common reaction type that has also been applied to Taxol 8-ring syntheses are palladium-catalysed coupling reactions.^{26,27} A good example of this was shown by Nakada

*et al.*²⁸ who used a *B*-alkyl Suzuki-Miyaura cross-coupling^{29,30} to make tricycle **25** (Scheme 6).



Scheme 6 Nakada *et al.* palladium cross-coupling to synthesise Taxol 8-membered ring

After an 8-step synthesis with impressive overall yield, iodo-alkene **24** was firstly heated to reflux in THF with 9-borobicyclo[3.3.1]nonane to give the hydroboration product. This alkyl borane then underwent intramolecular palladium-catalysed cross-coupling with the vinyl halide to give carbocycle **25**, forming the Taxol 6-8-6-ring system in high yield. However, an undesirable palladium loading of 50 mol% was required.

There are a number of lignan derived natural products with a related cyclooctanoid skeleton (**26**). These highly oxygenated natural products also contain biaryl axial chirality (Figure 3).

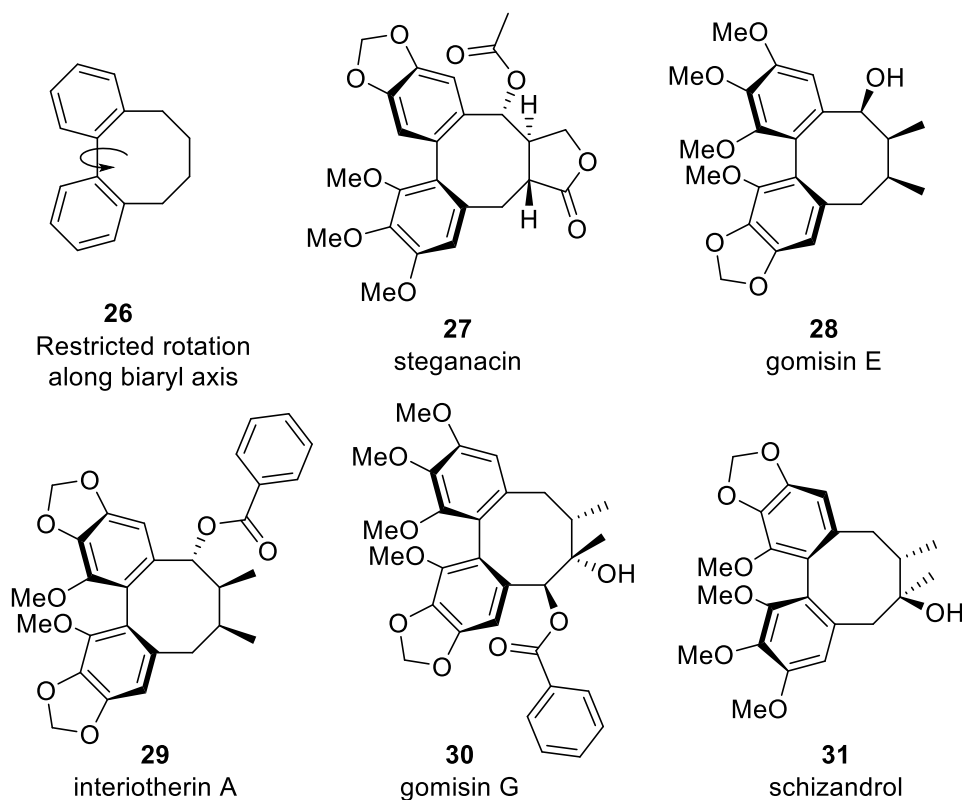
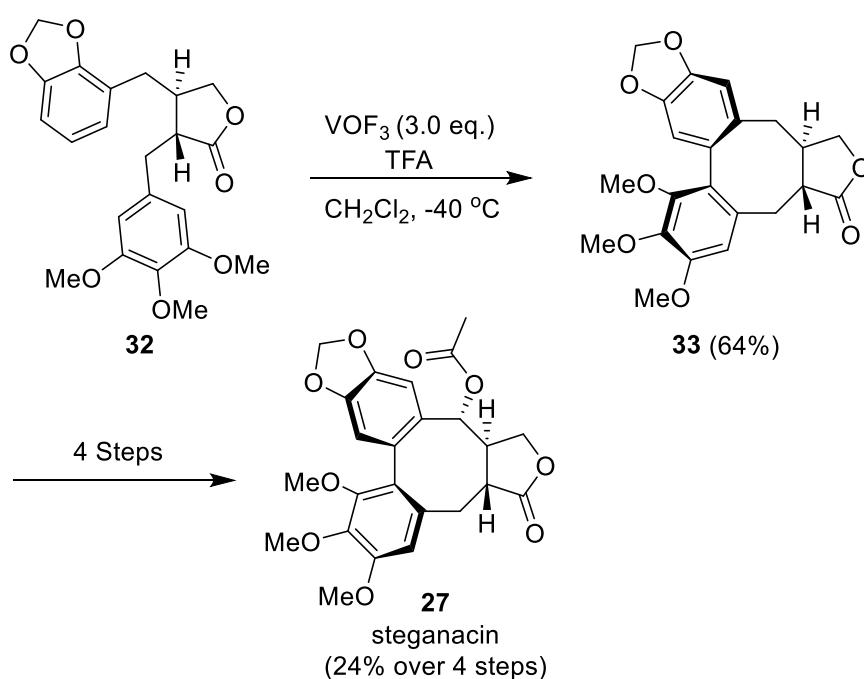


Figure 3 Related lignin derived natural products with biaryl chirality

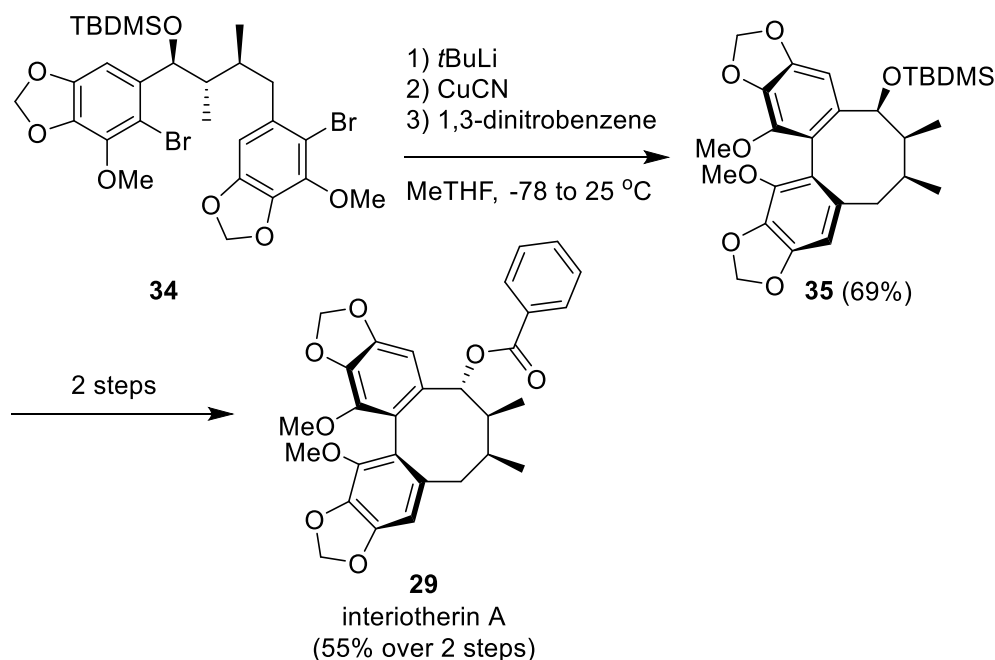
There is a wide range of biological activity that has been linked to this type of structure, including: anti-HIV properties for gomisin E (**28**) and interiotherin A (**29**),³¹ anti-tumour and anti-leukemic properties for steganacin (**27**),^{32,33} and anti-Alzheimer's applications for schizandrol (**31**).³⁴ The most common synthetic method used to form the 8-membered ring in these compounds is an aromatic oxidative coupling.^{35,36} The first asymmetric total synthesis of steganacin by Koga *et al.* utilised a vanadium mediated oxidative coupling to form 8-membered ring **33** (Scheme 7).³⁵ Electron rich aromatic oxidative couplings of this kind are thought to proceed via radical intermediates after electron transfers with transition metals.³⁶ General applicability of this type of cyclisation is low due to the highly electron rich aromatic substrates required.



Scheme 7 Koga *et al.* synthesis of steganacin

Steganacin (**27**) was accessed after a further 4 steps from lactone **33**, including a thermal atropisomerisation step.

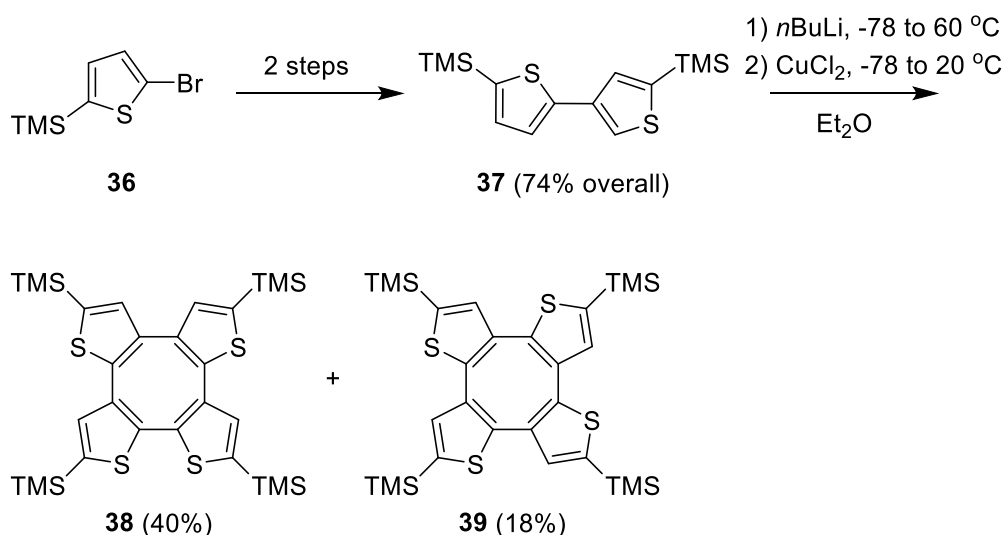
A different approach to the oxidative coupling of this biaryl system was reported by Coleman *et al.*³⁷ who were able to use cyanocuprate chemistry³⁸ to furnish the desired biaryl **35** *en route* to synthesising interiotherin A **29** (Scheme 8).



Scheme 8 Coleman *et al.* synthesis of interiotherin A

Halogen lithium exchange of dihalide **34** with *tert*-butyllithium followed by biarylcuprate formation and subsequent oxidation gave silylated **35** in 69% yield. The use of highly pyrophoric *tert*-butyllithium and the potential risk of cyanide exposure can make this synthetic route less desirable. The final interiotherin A product (**29**) was furnished by desilylation and subsequent Mitsunobu inversion of 8-membered ring **35**.

As well as having a great significance in medicinal and natural product chemistry, it is also important to note the other uses of 8-membered rings, such as in organic electronics.^{39,40} A good illustration of this was reported by Wang *et al.* who developed methodology to synthesise antiaromatic thiophene-fused cyclooctatetraenes **38** and **39** (Scheme 9).⁴¹ The dimerisation of thiophene **37** was brought about by selective deprotonation and subsequent copper mediated oxidative coupling. The reaction gave rise to 2 product isomers, **38** and **39** in 40 and 18% yields, respectively. Although regioselectivity is not high, the authors reported that the isomers were separable by flash column chromatography.



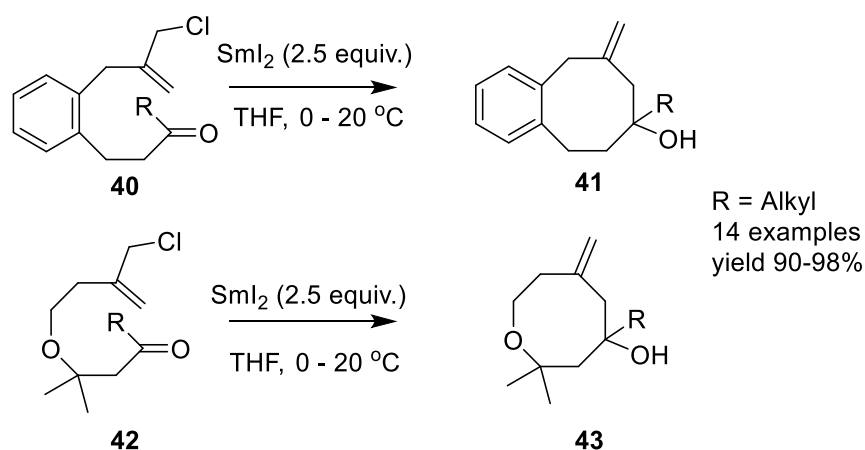
Scheme 9 Wang *et al.* synthesis of cyclooctatetraenes

Analysing target syntheses that involve 8-membered ring formation highlights their overall difficulty. Generally, a high catalyst loading is required often with harsher than expected conditions. Although this is inherent in the nature of target synthesis, it is also worth noting that attaining the cyclisation precursors usually takes a lot of time and effort. As the required cyclisations are difficult to accomplish, designing and synthesising the right precursor can become very difficult and drastically reduce the overall yield. In an age where chemists are focusing increasingly on step and atom efficient processes, this shows the need for new methodologies that can deliver a range of 8-membered rings in a quick and efficient manner.

1.1.3 Contemporary Methodologies Aimed at Synthesis of 8-Membered Rings

Medium sized rings represent well-known challenging targets to synthesise quickly and sustainably. Of all the 3 to 10-membered carbocycles on the Reaxys database only 3.5%⁴² belong to the cyclooctanoid cohort, indicating the need for new methodologies to fill this global research gap.

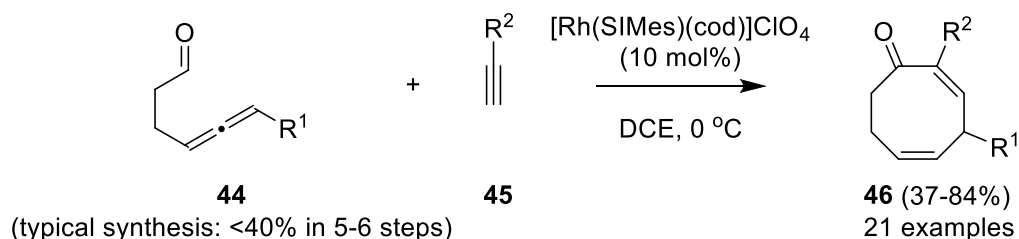
Matsuda *et al.* have developed a method of producing a range of 8- and 9-membered rings using a samarium mediated Barbier-type coupling approach (Scheme 10).⁴³ However, no synthetic route to the cyclisation precursor was discussed making it difficult to comment on its overall efficiency. Despite the lack of information concerning the synthesis of the precursor compounds, the 8-membered ring formations proceeded in very high yields. The cyclisation gave carbocycles (**41**), or oxygen containing heterocycles (**43**), in very impressive yields (90-98%) (Scheme 10).



Scheme 10 Matsuda *et al.* samarium mediated Barbier type couplings

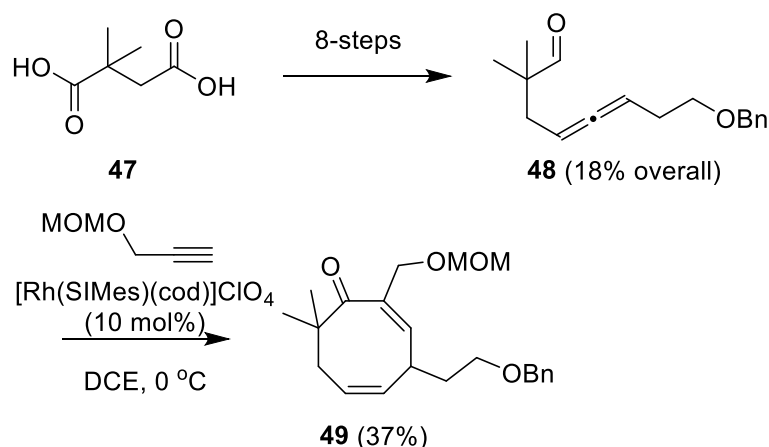
From the reported examples the limitations of this methodology seem quite severe. There is limited room for substrate scope as there are only two types of variation possible; heterocycle (**43**) vs. carbocycle (**41**) and the ketone substituent. Only aliphatic ketones of type **40** and **42** have been reported and it seems that functional group tolerance on this alkyl chain has not been explored. The absence of a templating fused ring that positions reactive centres in a favourable geometry is noteworthy in ether **42**, although the addition of *geminal*-dimethyl substitution induces the rate enhancing Thorpe-Ingold effect⁴⁴ for the closure.

A popular approach to cyclooctanoid formation is to exploit metal-catalysed cycloadditions.^{45,46} This type of approach has become increasingly popular in medium ring synthesis as it lends itself well to the formation of unsaturated rings. This unsaturation is commonplace in 8-membered rings as it reduces transannular strain. Sato *et al.* have reported rhodium-catalysed [6+2] cycloadditions to yield cyclooctadienones (**46**) in a range of yields (37-84%) (Scheme 11).⁴⁷ This work showed that a range of alkyl acetylenes (**45**) were tolerated: esters, alcohols and nitrogen containing derivatives all gave yields over 60%. Acetylene gas was also used effectively to give high yielding products. Whilst alkyl and phenyl allenals (**44**) were also shown to work well, the yields decreased when steric bulk was added. Conversely, if the steric bulk of R¹ or R² was too small, the usually excellent regioselectivity of the cycloaddition suffered.



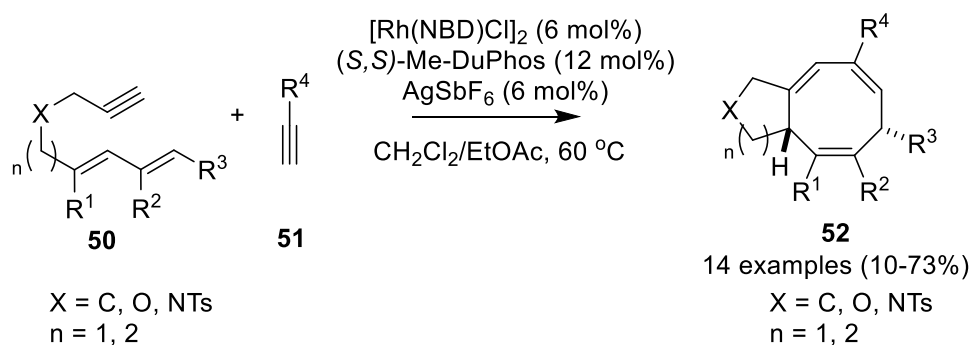
Scheme 11 Sato *et al.* rhodium-catalysed [6+2] cycloaddition

It is evident from this chemistry that while the ring closing event is impressive, the overall attractiveness of the route may be reduced by the protracted synthesis of the required allenals. One of the more challenging allenals, *geminal* dimethyl **48**, was synthesised over 8-steps with an overall yield of 18% (Scheme 12).⁴⁸ The effect of this *geminal* dimethyl substitution made the cyclisation into the analogous 8-membered carbocycle **49** more challenging, decreasing the yield to 37%. The overall compound yield of 8-membered ring **49** was 7%.



Scheme 12 Protracted synthesis of carbocycle **49** by Sato *et al.*

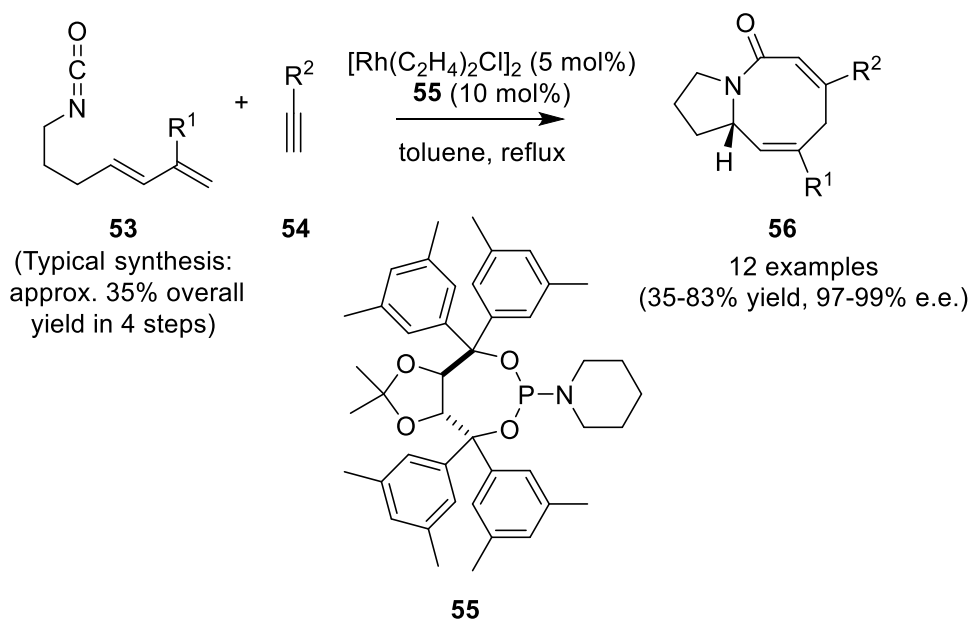
A different type of cycloaddition was reported by Gilbertson and DeBoef who utilised a [4+2+2] cycloaddition between a diene tethered to an alkyne (**50**) and an acetylene (**51**) (Scheme 13).^{49,50} This cycloaddition was also mediated via rhodium catalysis. With 14 examples, this reaction was shown to have significant scope. Alkyne **51** typically contained a propargyl ether although acetylene gas was shown to be tolerated reasonably well. When the diene was terminated with a methyl in the R³ position, single diastereoisomers of cyclooctatriene **52** were observed, but when R³ was a proton, regioselectivity of acetylene addition became problematic leading to a maximum of 3:1 diastereoselectivity.



Scheme 13 Gilbertson and DeBoef [4+2+2] cycloaddition to form cyclooctatrienes

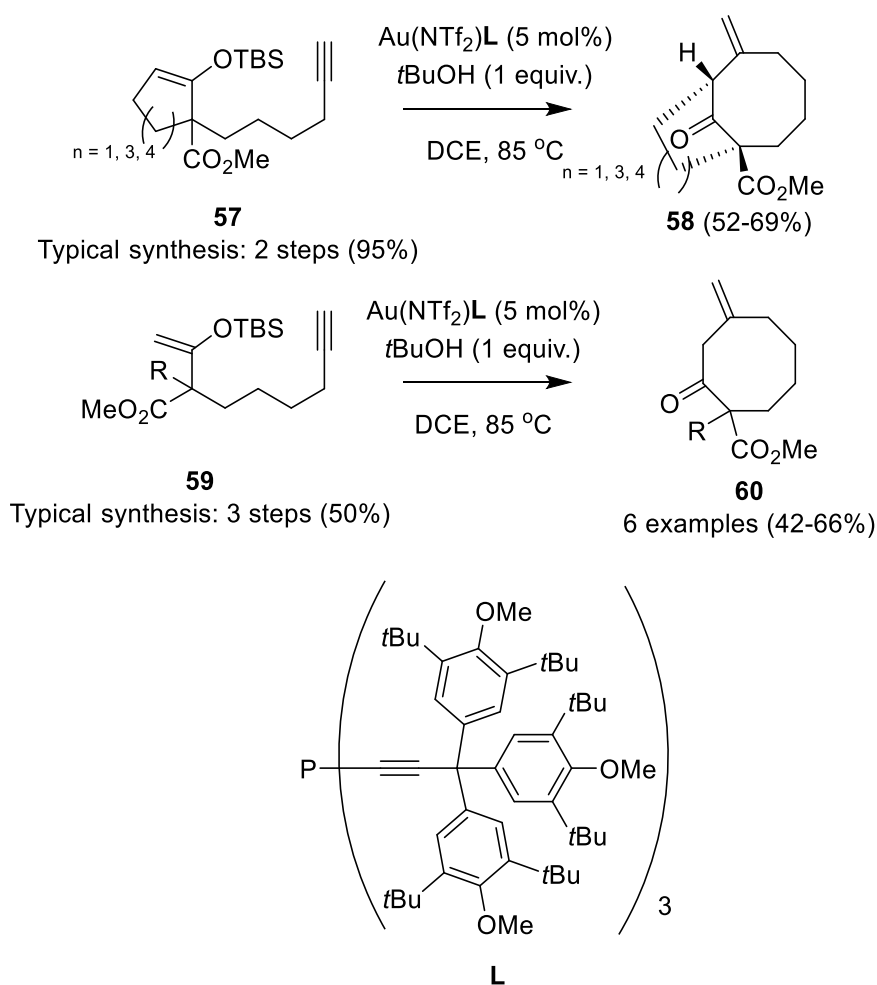
The substituents R^1 and R^2 were only reported to be a proton or a methyl group. Three and four atom tethers were effective at yielding 5- and 6- membered rings fused to the 8- ring target. The highest yields were achieved when the tether contained an ether or sulfonamide. The active catalytic species was pre-formed by reaction of a 1:2:1 mixture of $[\text{Rh}(\text{NBD})\text{Cl}]_2$: (S,S) -Me-DuPhos: AgSbF_6 , but the exact nature of the catalyst system was unknown to the authors and all attempts to characterise it were inconclusive. A further publication by Gilbertson⁵¹ reported the use of a different chiral ligand to carry-out a similar [4+2+2] cycloaddition. In this more recent work, the active catalytic species is discussed and it is postulated that the active catalytic species are similar in nature in both publications. Unfavourable aspects to this chemistry include the elaborate catalytic system and the need to synthesise the initial tethered diene/alkyne (**50**), which is not reported in detail. The use of an expensive chiral ligand is also undesirable as the author only reports the enantioselectivity of a single example, giving 40% *e.e.*

There are two reported, rhodium-catalysed, enantioselective [4+2+2] cycloadditions to make 8-membered rings.^{52,53} The most impressive of these is the synthesis of azocines by Rovis *et al.* in which a chiral phosphoramidite (**55**) was used to form the asymmetric cycloadduct of a tethered dienyl isocyanate (**53**) with a terminal alkyne (Scheme 14). This reaction was shown to synthesise a variety of azocines in a very high enantioselectivity of 97-99% *e.e.* and in moderate yields of typically 65%. A range of aliphatic, aromatic and functionalised acetylenes were tolerated along with methyl substituted dienes. As has been the common theme among cycloadditions, the unsaturated starting materials are not commercially available. The tethered dienyl isocyanates (**53**) can be synthesised in 4 steps from methyl hex-5-ynoate⁵⁴ in a typical overall yield of 35%.



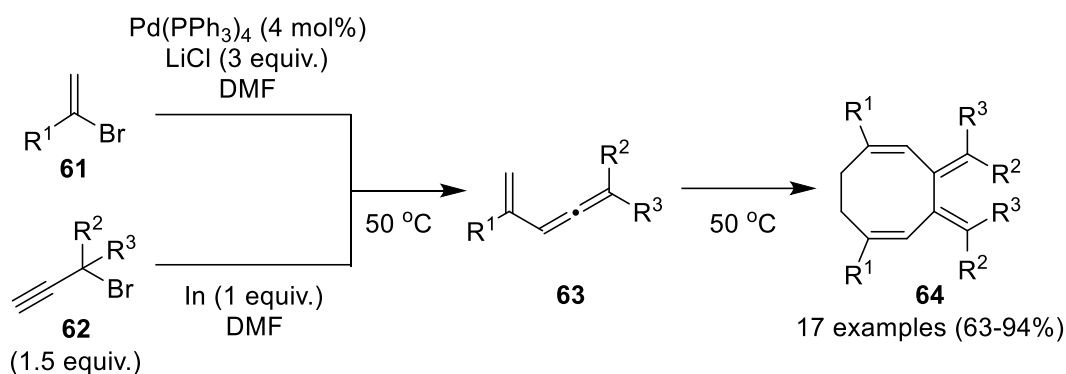
Scheme 14 Rovis *et al.* asymmetric synthesis of azocines

An entirely different kind of metal-catalysed cyclisation to 8-membered rings was reported by Sawamura *et al.*⁵⁵ In this publication Sawamura described how gold catalysis can be used along with a large, cavity containing ligand to promote the cyclisation of a range of 8-membered rings (Scheme 15). Sawamura was successful in synthesising bicycles (**58**) and technically more challenging, non-fused, cyclooctanones (**60**). Clever ligand design allowed the formation of non-fused rings, overcoming the entropic problem others had failed to solve. In other examples, the acyclic precursor requires some type of constraint in its skeleton; Sawamura circumvents this by using a metal-ligand system which forms a cone-shaped cavity containing structures, forcing the reactive centres closer together. As with other examples, the tolerance to R group variation on silyl enol ether **59** is relatively low, with all but one example involving a substituted benzyl group. A further complication one would encounter when repeating these experiments would be obtaining the catalyst ligand, which has to be synthesised in three steps.

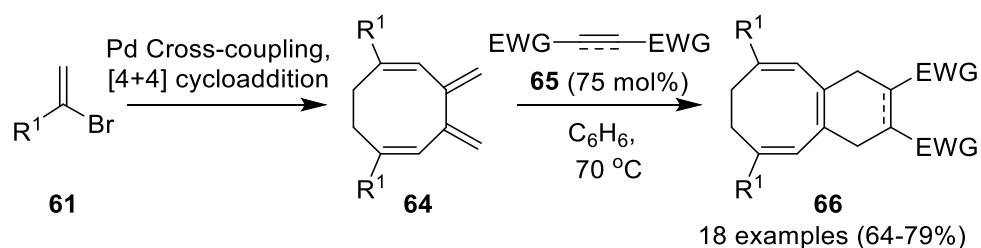


Scheme 15 Sawamura et al. gold-catalysed synthesis of cyclooctanones

A very common theme in the synthesis of 8-membered rings is the need to synthesise an elaborate cyclisation precursor/catalyst to enable annulation. A one-pot procedure that allows the synthesis of a range of cyclooctanoids would be a desirable tool. To our knowledge the only reported one-pot, multi-component, procedure capable of synthesising a range of 8-membered rings was produced by Kang *et al.*⁵⁶ In this work the author describes a palladium-catalysed cascade to form cyclooctadienes via a tandem cross-coupling and homo [4+4] cycloaddition (Scheme 16). This is very powerful methodology as the author started with simple, easily attained starting materials such as α -bromostyrene (**61**, $R^1 = \text{Ph}$) and propargyl bromide (**62**, $R^2 = R^3 = \text{H}$), and rapidly accessed the analogous ring system **64** in 94% yield.

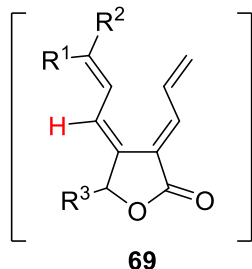
Scheme 16 Kang *et al.* one-pot synthesis of cyclooctadienes

The scope of this reaction was reasonable with only moderate limitations. A wide range of substituted aryl R^1 groups were tolerated, with only one example below 70% yield, whilst alkyl R^1 groups promoted a different reaction pathway to form a related cyclohexene. Very little variation at positions R^2 and R^3 was accepted, allowing just proton or methyl groups. Substitution of bromine for other halides was tolerated on both **61** and **62** with only a minor drop in yield. Impressively, Kang also reported an extension of this cascade to include the initial cross-coupling, homo [4+4] cycloaddition and then a further [4+2] cycloaddition using the exocyclic diene moiety (Scheme 17). Only unsubstituted exocyclic dienes derived from propargyl bromide were tolerated but a wide range of substituted α -bromostyrenes were used successfully to give yields of typically ~70%. Dienophiles included electron poor alkenes, alkynes, aldehydes and (cyclic)enones.



Scheme 17 Extension of palladium-catalysed cascade reaction

A synthetic methodology paper that proposed an interesting mechanism for the formation of 8-membered rings was published by Ma and Gu.⁵⁷ The authors suggest the thermal rearrangement of 1,2,4Z,7-tetraenes (**67**) to form fused cyclooctanoids (**68**) via intermediate **69**, in an interesting 1,5-hydrogen migration followed by electrocyclic rearrangement (Scheme 18).



Scheme 18 Ma and Gu's thermal rearrangement of 1,2,4Z,7-tetraenes

This reaction was shown to tolerate aliphatic, aromatic and spirocyclic R¹/R² variation whilst R³ can contain substituted aromatic or alkyl groups. There was also an example using a cyclohexanone ring in place of the lactone. A particular strength of this methodology is the elegant catalyst and reagent-free conditions. The synthesis of annulation precursors **67** however, are not so simple. The exact procedures were not published but comparison to similar substrates⁵⁸ showed synthesis would be possible in 6-steps with consolidated yields of approximately 30%. Ma and Gu report compelling evidence to support the theorised 1,5-hydrogen migration but the exact mechanism of this migration is not discussed. Figure 4 shows three possible mechanisms that would lead to bis-diene **69**. Deprotonation by the solvent triggering alkene rearrangement and reprotonation from the solvent at the allenic centre, or direct deprotonation by the allene to initiate isomerisation are two possible pathways. A third possibility could be a 1,5-hydride migration in which a formal hydride adds into the centre of the allene, triggering the rearrangement. Initially the third case would seem least likely, but it should not be entirely discounted.

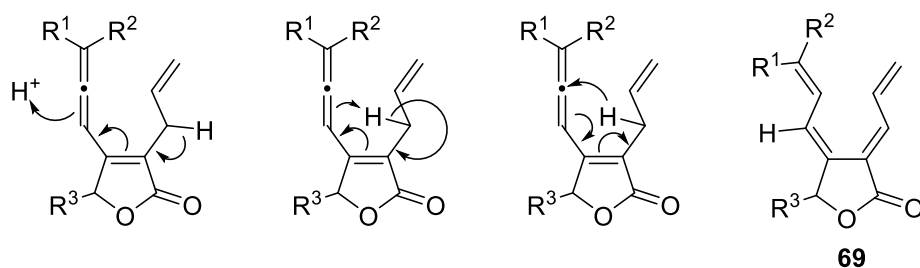
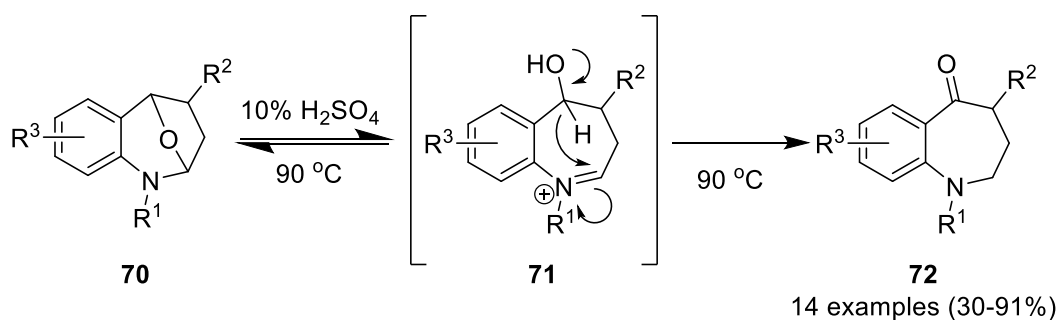


Figure 4 1,5-hydrogen migration to form bis-diene **69**

Bai *et al.* recently published an article in which they suggest the possibility of a 1,5-hydride transfer from a benzylic alcohol (**71**) into an electron deficient iminium in the synthesis of 7-membered rings (Scheme 19).⁵⁹ This type of internal redox process is well reported in the literature for the synthesis of 5- to 7-membered ring systems,⁶⁰ but to our knowledge no general synthetic procedure has been developed to form 8-membered rings.

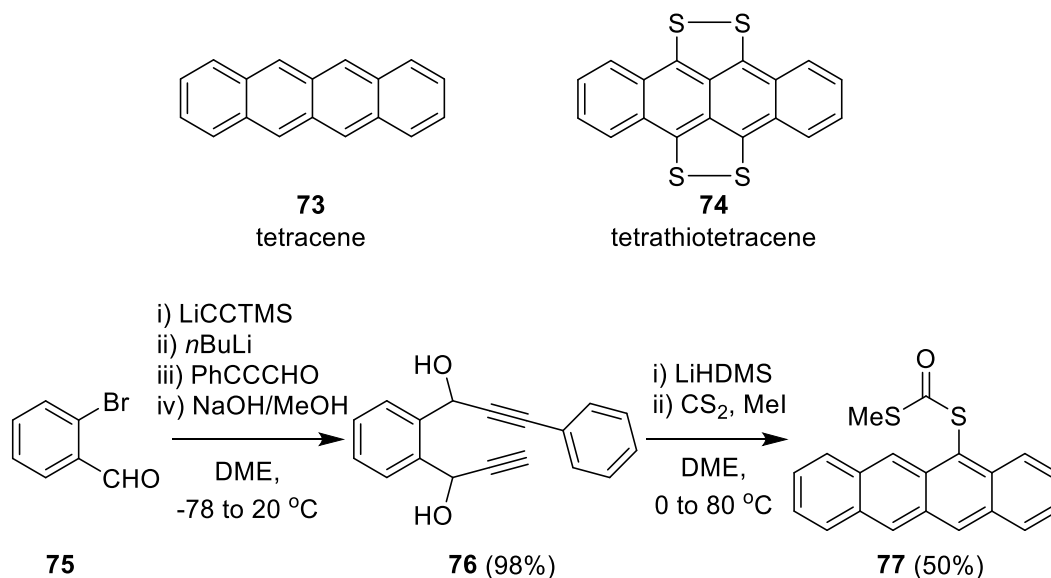


Scheme 19 Bai *et al.* 1,5-hydride shift

1.2 Results and Discussion

1.2.1 Previous Work of the Woodward Group

In recent years the Woodward Group has been interested in the synthesis of tetracene (**73**) and its derivatives, such as tetrathiotetracene (**74**), for applications in organic electronics.^{61,62} During this research, a multi-step reaction was developed to synthesise *bis*-propargylic alcohols such as **76**, a precursor to tetrathiotetracene and other tetracene derivatives via **77** (Scheme 20).

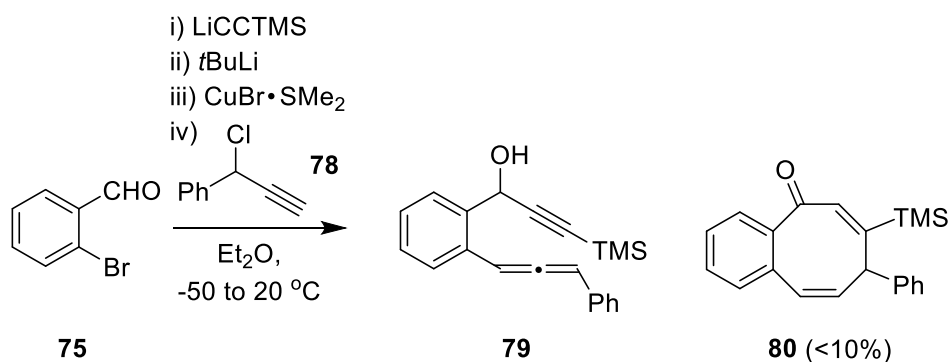


Scheme 20 Woodward Group synthesis of tetracene derivatives

Synthesis of *bis*-propargylic alcohol **76** was achieved in one pot from low-cost, readily available starting materials.⁶¹ This installed the necessary carbon skeleton to allow for an electrocyclic cascade, delivering substituted tetracene **77** in 50% yield.

Complementary to this procedure, a related one-pot reaction was to synthesise allene **79**, a direct precursor to the challenging unsubstituted tetracene target **73** (Scheme 21). Firstly, lithiated TMS-acetylide would be formed *in situ* from trimethylsilylacetylene and *n*-butyllithium. Aldehyde **75** would next be added to give the 1,2-addition product. Lithium-halogen exchange followed by transmetalation with copper(I) bromide dimethyl sulfide would then form an organocopper species, after which propargylic chloride **78** would be added to the reaction mixture. It was hoped that S_N2' addition into the terminal acetylene would yield allene **79**. Once isolated, it was thought that desilylation of allene **79** followed by bis-allene formation (via [3,3]-sigmatropic rearrangement of the propargylic alcohol), and finally an electrocyclic cascade followed by elimination would lead to tetracene **73**. This theory could never be tested as allene **79** could not be isolated;

a low yield (less than 10%) of 8-membered ring **80** was isolated in its place, with the remainder of the reaction leading to intractable mixtures. It was soon realised that this unexpected product was novel and if the methodology could be developed into a general synthesis of 8-membered rings, this would be a significant discovery.



Scheme 21 Attempted synthesis of allene **79**

A crystal structure was sought to confirm the product's structure and connectivity. Recrystallisation from pentane afforded crystals of diffractable quality (Figure 5).⁶³

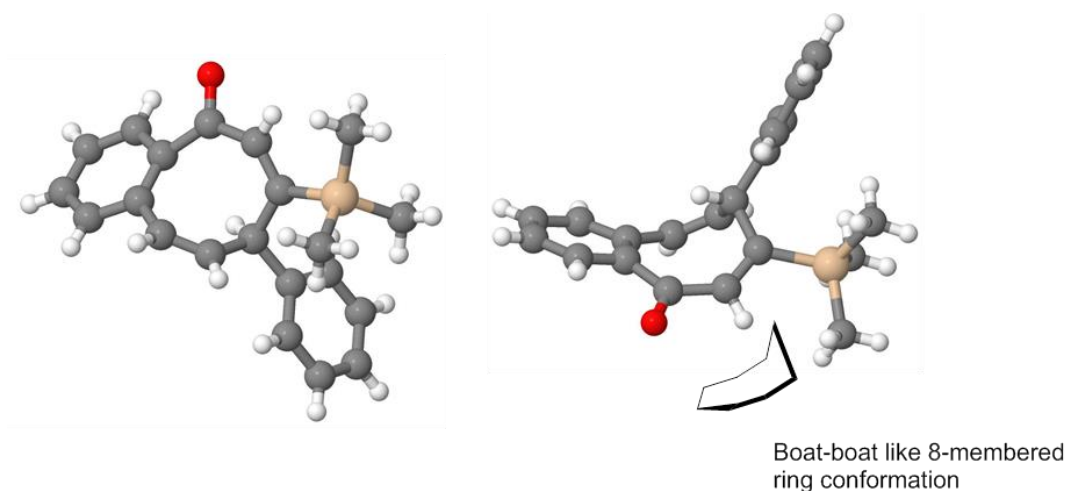
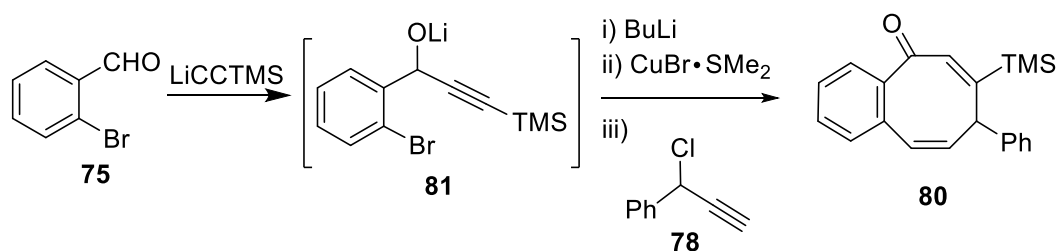


Figure 5 X-ray crystal structure confirming geometry of **80**

The ring conformation shown in Figure 5 is similar to a boat-boat, but one apex is significantly more planar than the other due to its bicyclic nature. It is also interesting to note the lack of 1,3-transannular interactions due to the unsaturation present in the bicycle.

Due to the structural elements of cyclooctanoid **80**, it was likely derived from the proposed allene **79** but the exact mechanism was initially unclear as it seemed the benzylic alcohol had been oxidised. To gain a better understanding of this reaction, the conditions were optimised (Table 2).⁶³ The initial reaction described in Scheme 21 is summarised in run 1

yielding <10% of ring **80**. Pleasingly, exchanging highly pyrophoric *tert*-butyllithium for the milder *n*-butyllithium saw an improved yield (Run 2). The stoichiometry of copper(I) bromide dimethyl sulfide and propargylic chloride **78** were also reduced to match the formation of a homo-cuprate. Organometallics derived from lithium alkoxide **81** were observed to be poorly soluble in diethyl ether so the reaction solvent was switched to tetrahydrofuran (run 3). This led to an improved reaction that enabled identification of the cyclisation occurring upon warm-up of the reaction to between -20 and -10 °C.



Run	Solvent	i) Conditions	ii) Conditions	iii) Conditions	Yield of 80 (%)
1	Et_2O	<i>t</i> BuLi (2 equiv.) 20 min -50 °C	1 equiv. 20 min -50 °C	1 equiv. 5 h -50 to 20 °C	<10
2	Et_2O	<i>n</i> BuLi (1 equiv.) 10 min 0 °C	0.5 equiv. 5 min -50 °C	0.5 equiv. 1 h -50 to 10 °C	14
3	THF	<i>n</i> BuLi (1 equiv.) 15 min -50 °C	0.5 equiv. 10 min -50 °C	0.5 equiv. 1 h -50 to 10 °C	53
4	THF	<i>n</i> BuLi (1 equiv.) 15 min -50 °C	0.5 equiv. 1 h -50 °C	0.5 equiv. 1.5 h -50 to -10 °C	70
5	THF	<i>n</i> BuLi (1 equiv.) 15 min -50 °C	0.5 equiv. 1 h -50 °C	0.5 equiv. 3.5 h -50 to -10 °C	35

Carried out on: **72** (0.71 mmol), trimethylsilylacetylene (0.77 mmol)/*n*BuLi (0.72 mmol), $\text{CuBr} \cdot \text{SMe}_2$ (0.36-0.71 mmol), **75** (0.35-0.70 mmol) in Et_2O or THF (1.0 mL). Yields of **80** were determined by GC (Factor-4 column, T_i 50 °C, T_Δ 3 °C/min, T_f 250 °C) against genuine samples and an internal standard (1-methyl naphthalene, 50 μL).

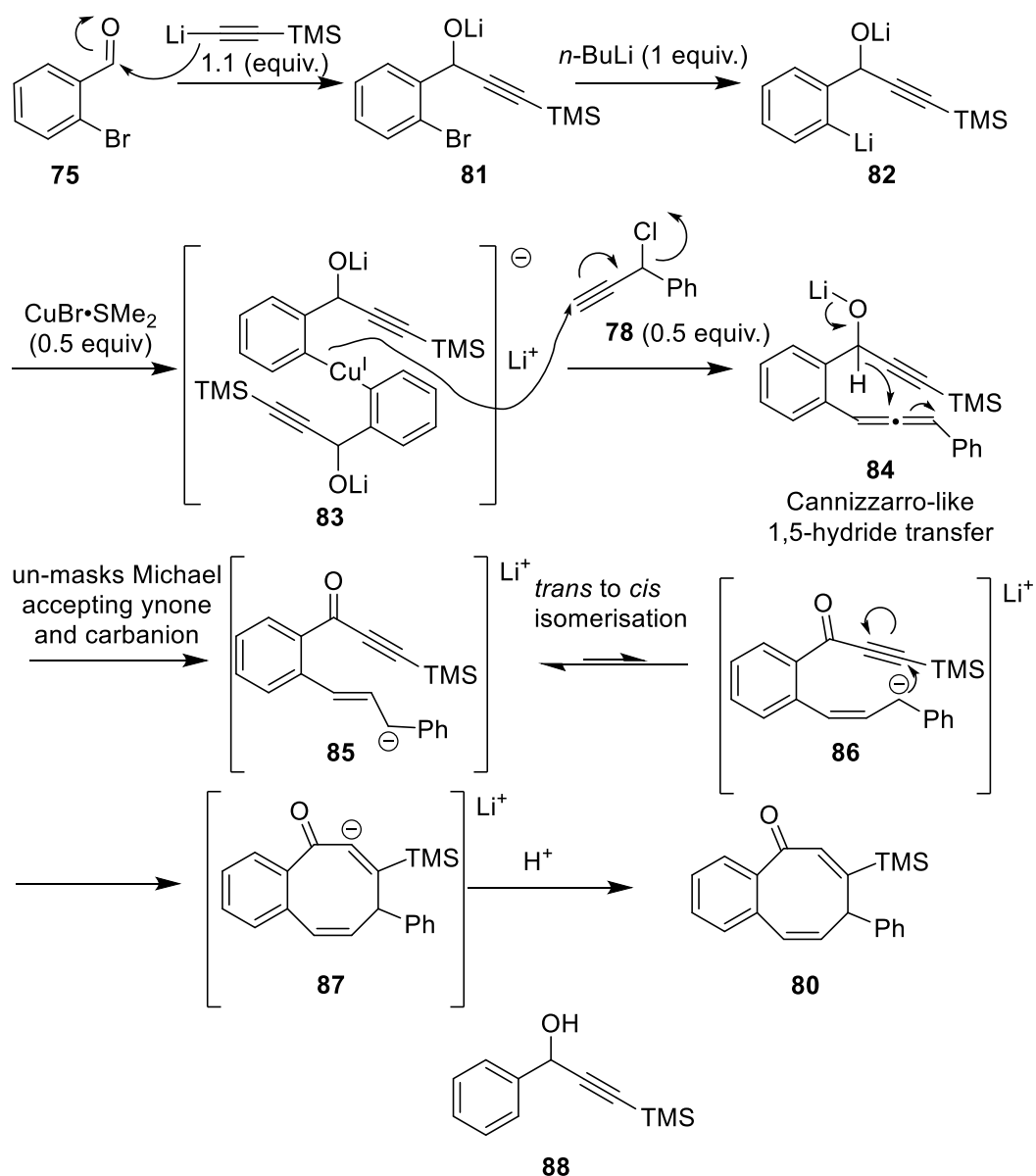
Table 2 Optimisation of cascade reaction forming 8-membered ring **80**

Independent treatment of tetrahydrofuran solutions containing lithium alkoxide **81** with *n*-butyllithium followed by deuterium oxide quench confirmed complete lithium/halogen

exchange was realised within 15 minutes at $-50\text{ }^{\circ}\text{C}$ and that the resulting organolithium was significantly stable at these temperatures. However, above *ca.* $-15\text{ }^{\circ}\text{C}$ the same species began to decompose rapidly. Thus, $-50\text{ }^{\circ}\text{C}$ was selected as the temperature for optimisation of the transmetalation. When the diorganocuprate was prepared under the conditions of run 3 ($-50\text{ }^{\circ}\text{C}$, 10 min from the aryllithium with copper(I) bromide dimethyl sulfide) then treated with methylvinyl ketone, very poor conversions to the 1,4-addition product were attained. This strongly suggested that transmetalation to copper is rather slow in this system. Gratifyingly, extending the time for CLi/CCu exchange to 1 h (run 4) significantly increased the quantity of 8-membered ring **80**. The addition of propargylic chloride **78** was found to be most effective if it was added at $-50\text{ }^{\circ}\text{C}$ and the reaction allowed to warm to $-10\text{ }^{\circ}\text{C}$ over 30 minutes (run 4). After holding the temperature at $-10\text{ }^{\circ}\text{C}$ for 1 hour the reaction could be quenched to give the product. Further extending the $\text{S}_{\text{N}}2'$ addition hold time to 3 hours had a detrimental effect on the yield of carbocycle **80** (run 5). Having obtained the optimised procedure (run 4) a reaction was carried out on a 1.6 mmol scale. This reaction yielded 8-membered carbocycle **80** in a very pleasing 70% isolated yield.

Using what was learnt during reaction optimisation a possible mechanism was suggested that included a novel, Cannizzaro-like, 1,5-hydride transfer that triggers the cyclisation cascade. This internal redox event can show how benzylic alcohol **81** can be oxidised as part of an overall mechanism to give the connectivity shown in Figure 5.

Our proposed mechanism is described in Scheme 22. At $-50\text{ }^{\circ}\text{C}$ trimethylsilylacetylene is lithiated using *n*-butyllithium; this produces the acetylide nucleophile that can then form the 1,2-addition product **81** with 2-bromobenzaldehyde **75**. Lithium-halogen exchange with *n*-butyllithium converts lithium alkoxide **81** into aryl-lithium **82**. Homo-cuprate **85** is then formed via transmetalation with copper(I) bromide dimethyl sulfide. An $\text{S}_{\text{N}}2'$ addition between the soft cuprate nucleophile and propargylic chloride **78** leads to allene **84**.



Scheme 22 Proposed mechanism to account for the formation of carbocycle **80**

On warming to -10 °C the ring closing cascade is then initiated by the novel, Cannizzaro-like, 1,5-hydride shift to form *trans* carbanion **85**. *Trans* to *cis* isomerisation brings the Michael accepting ynone and nucleophilic anion into a geometry that allows annulation to bicycle **87**. This carbocyclic anion is then quenched at -10 °C with aqueous ammonium chloride solution to give the final 8-membered ring **80**. The desired product is formed in a 1:1 ratio with alcohol **88** which is an unavoidable byproduct derived from homo-cuprate **83**.

Having discovered a new reaction, optimised it and proposed a plausible mechanism, the next steps were to attempt to generalise this novel synthesis of 8-membered rings and explore reaction scope. It was at this point I took control of the project.

1.2.2 Effects of Aldehyde Variation

A range of *ortho*-bromo aldehydes were trialled in the 3-component reaction sequence. Where possible, commercially available substrates were tested but in one case a short synthesis was carried out to form a suitable heteroaromatic system (**98**). The optimal conditions found for the synthesis of **80** (Table 2, run 4) were applied to all cascade reactions.

Table 3 shows how varying aldehyde structures affect the yield of the associated cyclooctanoid derivative. Electronically neutral and sterically undemanding **75** (entry 1) was the highest yielding substrate of the benzene derived aldehydes (entries 1-9). Substitution of this aldehyde was tolerated in all positions; however, when comparing entry 2 to entry 3, it was evident that substitution in the 6 position of the aldehyde led to significantly reduced yields (5-fluoro vs 6-fluoro 55 and 27% respectively). Entries 8 and 9 show how substitution in the 3 position resulted in lower yields of 8-membered rings **106** and **107**. It is thought the drop in yield associated with substitution in the 3 position can be rationalised by thinking about homo-cuprate reactivity (Figure 6). As two aldehyde derived units combine to form the cuprate, any additional steric bulk on the aldehyde has a twofold effect on the steric clash around the cuprate. Comparing the availability of organometallic bonds in **111** and **112** demonstrates the crowded nature of organometallic **112**. Due to its proximity to the organometallic bond, substitution in the 3 position has a detrimental effect in congesting this area.

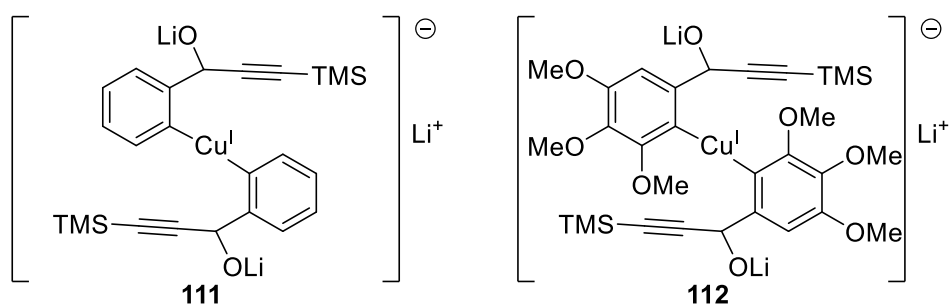


Figure 6 Representation of metal bound species derived from **75** and **95**

75, 89-99			80, 100-110		
Entry	Aldehyde	Product Yield ^a (%)	Entry	Aldehyde	Product Yield ^a (%)
1		77 70	7		105 52
2		100 55	8		106 trace ^b
3		101 27	9		107 26
4		102 62	10		108 72
5		103 62	11		109 21
6		104 37	12		110 0

a) isolated yield; b) Isolated in ~5% yield with significant impurities.

Table 3 Table showing effect of aldehyde variation on yield

Electron withdrawing and electron donating groups were tolerated with good yields (entries 2 and 5). The varied yields from aldehydes **92-95** (entries 5-8) suggested that poly-substitution caused issues for the reaction. It is thought that the decrease in yield arises from steric factors rather than electronic effects. The importance of aldehyde steric profile can be demonstrated by comparing how aldehyde **94** (entry 7) leads to a significantly higher yield of tricycle **105** (52%) than the electronically similar aldehyde **93** (entry 6) and bicycle **104** (37%). The freely rotating methoxy groups in **93** increase its steric profile which leads to decreased reaction yield. Overall the highest yielding aldehyde was thiophene **97** (entry 10). This electron rich thiophene was used to synthesise 8-membered ring **108** in 72% yield. Although *N*-methylindole **98** did not lead to a high yield of carbocycle **109**, it did lead to a product with a more drug-like structure.

It was discovered that characteristic ^1H NMR signals were present in the spectra of the crude mixtures. The desired 8-membered rings commonly displayed a doublet with approximately 9.5 Hz coupling at around 5.0 ppm (Figure 7). This signal originates from the benzylic CH highlighted in Figure 7. The benzylic alcohol by-product on the other hand had a signal further downfield at around 5.5 ppm. Comparison of these peaks in crude ^1H spectra data provided good estimates into the yield to be expected on isolation.

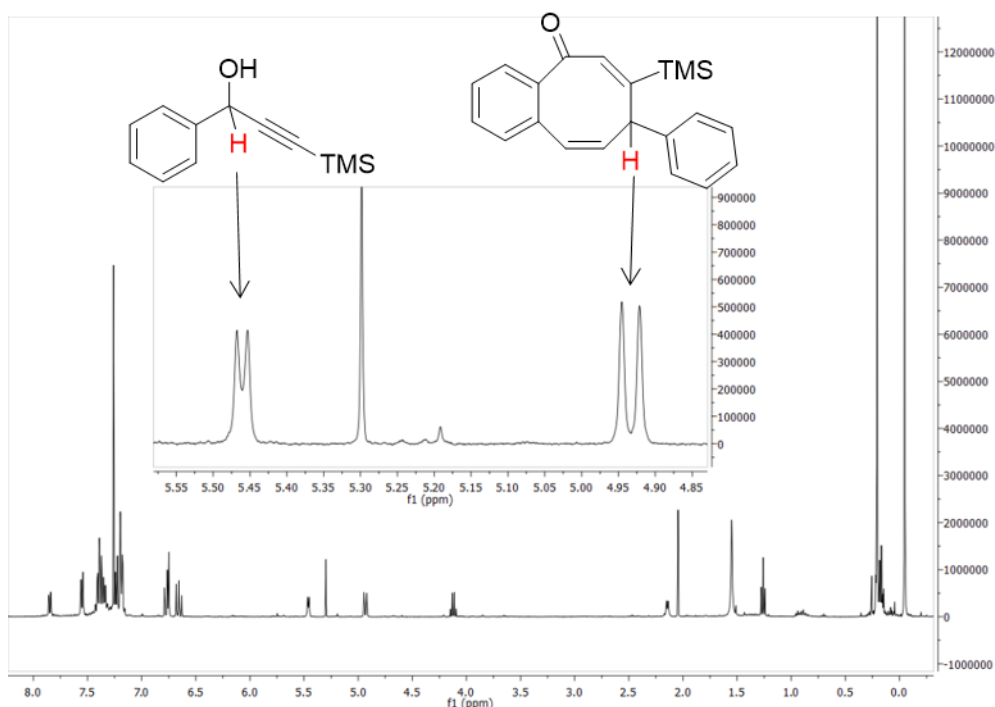
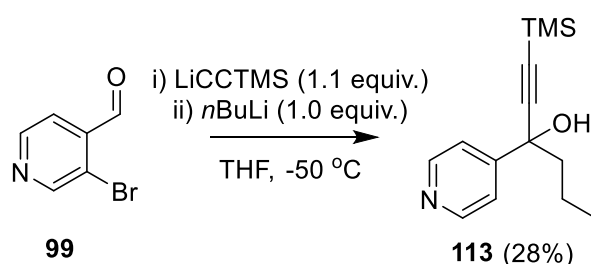


Figure 7 Representative crude ^1H NMR spectrum showing characteristic signals

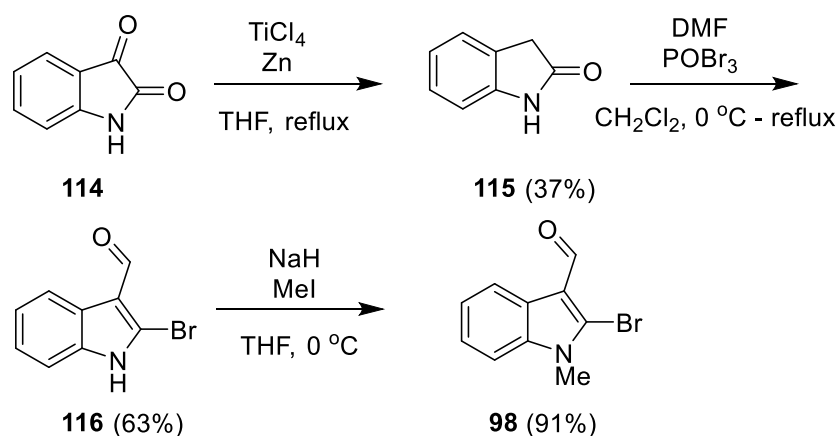
Entry 12 attempted to access pyridyl fused 8-membered ring **110** but was unsuccessful. Analysis of the crude mixture showed no sign of the characteristic ^1H NMR shift at around

5.0 ppm, but indicated the presence of a short aliphatic chain. Among other compounds a significant product from this reaction was found to be tertiary alcohol **113**. This alcohol can be reproducibly synthesised from the addition of lithium TMS-acetylide into aldehyde **99** followed by addition of *n*-butyllithium (Scheme 23). The mechanism for formation of this product is unclear, but addition of the lithium acetylide alone leads to the expected brominated secondary alcohol (analogous to **81**, Scheme 22). Subsequent addition of one equivalent of *n*-butyllithium presumably triggers halogen exchange and alcohol oxidation followed by nucleophilic addition of an *n*-butyllithium derived anion. It is possible the oxidation event is related to the Cannizzaro-like hydride transfer we rely upon for our cascade synthesis.



Scheme 23 Formation of tertiary alcohol **113**

For this study on aldehyde variation, indole **98** was not commercially available. It was therefore synthesised in 3-steps from isatin **114** (Scheme 24). Isatin **114** was reduced to amide **115**⁶⁴ before Vilsmeier-Haack formylation gave aldehyde **116**⁶⁵ in 63% yield. *N*-methylindole **98** was produced by methylation of indole **116**.



Scheme 24 Synthesis of *N*-methylindole **98**

1.2.3 Effects of Alkyne variation

To fully map the scope of this one-pot reaction, all components need to be varied to identify any limitations. To this end, a variety of aromatic and non-aromatic lithium acetylides were trialed in the newly discovered cascade (Table 4).

i) LiCCR (1.1 equiv.)
 ii) *n*BuLi (1.0 equiv.)
 iii) CuBr•SMe₂ (0.5 equiv.)
 iv)

75

78 (0.5 equiv.)

THF, -50 to -10 °C

80, 127-135

Entry Alkyne Product Yield^a (%)

1 **117** **80** 70

2 **118** **127** 61

3 **119** **128** 33

4 **120** **129** 50

5 **121** **130** 57

Entry Alkyne Product Yield^a (%)

6 **122** **131** 50

7 **123** **132** 37

8 **124** **133** 6

9 **125** **134** 0

10 **126** **135** 0

a) Isolated yield

Table 4 Table showing the effect of alkyne variation on reaction yield

Considering the non-aromatic cohort (entries 1-5) it seemed that the best yields are obtained by short, branched groups (entries 1 and 2, 70 and 61%, respectively). When comparing *tert*-butyl alkyne **118** (entry 2) to linear 1-pentyne **119** (entry 3) we can see a significant drop in yield, from 61 to 33%, respectively. Considering the proposed mechanism, it seems most likely that reactive differences caused by alkyne variation would manifest themselves in the annulation event in **86** (Scheme 22). As the electronic effects of a *tert*-butyl or *n*-propyl substituent on the alkyne are similar, it seems most plausible that a conformational difference is responsible for the discrepancy in yield. It is possible that a larger, more rigid, alkyne substituent could be conducive to a lower energy transition state when compared to a longer, more flexible substituent (Figure 8). The *tert*-butyl group is able to rotate (**136-137**) whilst the much more flexible *n*-propyl group is able to adopt many conformations, some of which are shown in Figure 8 (**138-140**).

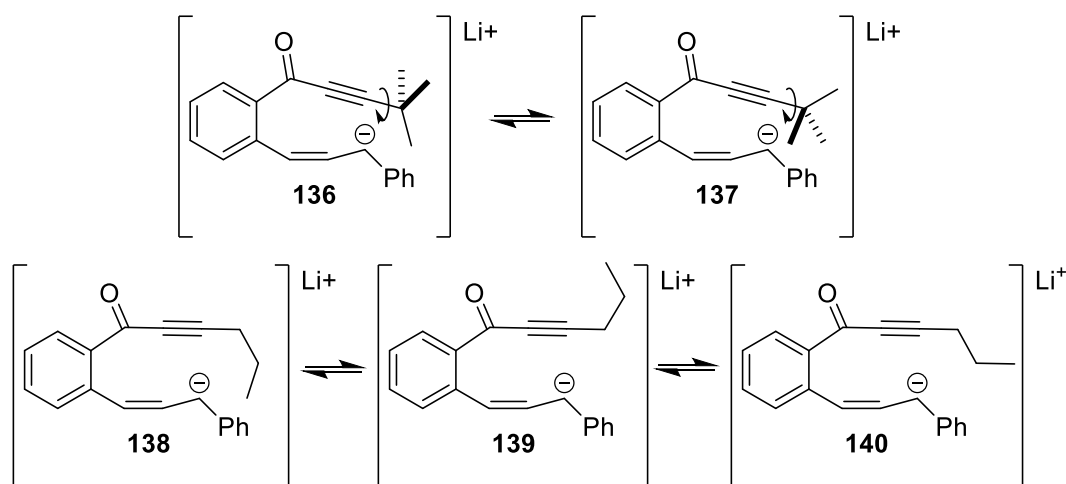


Figure 8 Rigidty of *tert*-butyl group versus flexibility of *n*-propyl group

Generally, non-aromatic alkynes performed better than aromatic alkynes; substituted aromatic alkynes (entries 7-10) could be tolerated but their yield was significantly diminished. Disubstituted aromatic alkyne **124** (entry 8) gave a yield of only 6% of 8-membered ring **134**. It is unclear whether this was caused by the electron withdrawing effects of the ring substituents or the steric influence of 3,5-disubstitution. If substitution was not a concern, one might expect alkyne **124** to outperform **122** due to its increased electron withdrawing nature (Figure 9). Electron deficient alkyne **142** would be more electrophilic than **141** so faster annulation would be expected. Although, as we are unsure of the exact nature of annulation, it is possible that cyclisation is copper mediated (**143**). If this is true, the electronic requirements for successful annulation may not be as straightforward.

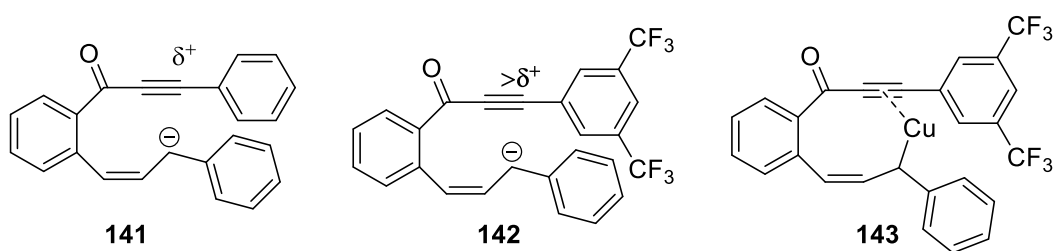
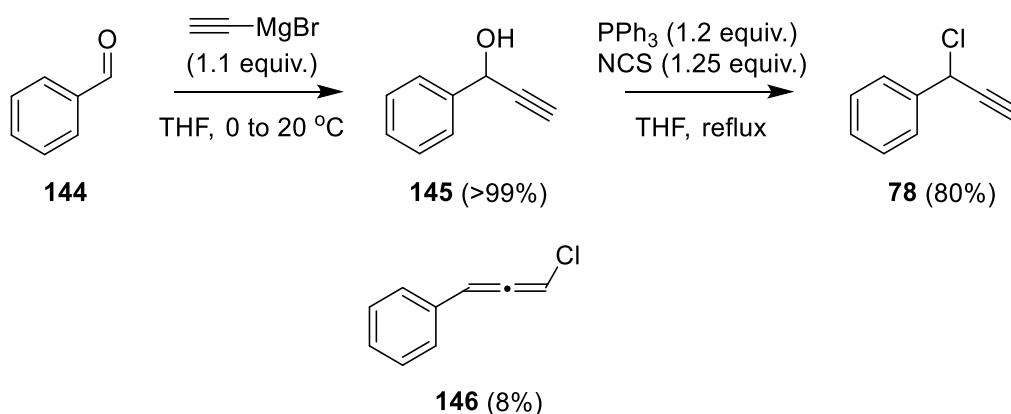


Figure 9 Possible electronic effects of alkyne

3,5-Disubstituted alkyne **125** (entry 9) does not lead to the expected 8-membered ring **134** and analysis of the crude reaction mixture shows a complete lack of formation of 8-membered ring. It seems that in this case it may be due to electronic effects as 4-methoxyphenyl **126** (entry 10) also performs poorly. Analysis of the crude reaction mixture by ^1H NMR spectroscopy shows a 10:1 ratio of benzylic alcohol (by-product):8-membered ring **135** (based on characteristic doublet at 5 ppm). Although low conversion was suggested, the 8-membered ring could not be isolated after column chromatography. The poor reactivity of the more electron rich aromatic groups could be explained by considering the decreased electrophilicity of the alkyne prior to annulation.

1.2.4 Synthesis of Propargylic Chlorides

The final reagent involved in the cascade reaction is a propargylic chloride. Unfortunately, the propargylic chlorides required for study were not commercially available, and in most cases, were novel compounds. A synthetic route had to be found to access these compounds whilst still maintaining our main goal of an overall step efficient synthesis of 8-membered rings.

Scheme 25 Synthesis of propargylic chloride **78**

The initial propargylic chloride used in this study (**78**) had been synthesised from benzaldehyde via a Grignard addition followed by an Appel reaction (Scheme 25). The

addition of commercially available ethynylmagnesium bromide onto benzaldehyde gave propargylic alcohol **145** in quantitative yield. The desired propargylic chloride **78** was synthesised as 10:1 mixture of S_N2 (**78**) and S_N2' (**146**) products. To increase overall efficiency and eliminate a purification step the alkyne/allene mixture was used crude in the one-pot synthesis of 8-membered rings.

As an effective way of accessing propargylic chlorides had been found, the next task was to synthesise a variety of propargylic alcohols. Table 5 shows the synthesis of propargylic alcohols **145** and **147 – 161**.

145, 147 - 161

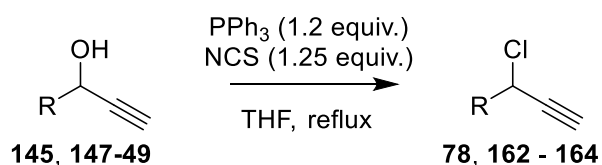
Entry	R	Product	Yield ^a (%)	Entry	R	Product	Yield ^a (%)
1	Ph	145	>99	9	4-CF ₃ Ph	154	98
2	4-MePh	147	>99	10	3-CNPh	155	92
3	4-ClPh	148	80	11	3-thiophenyl	156	96
4	<i>n</i> -pentyl	149	89	12	2-pyridyl	157	95
5	4- <i>t</i> BuPh	150	95	13	2-naphthyl	158	99
6 ^b	4-MeO ₂ CPh	151	91	14	1-naphthyl	159	89
7 ^b	4-MeOPh	152	97	15	2-furyl	160	>99
8 ^c	3-MeOPh	153	>99	16	5- <i>N</i> -methylpyrazolyl	161	80

a) isolated yield. b) Grignard addition at -50 °C. c) Grignard addition at -35 °C.

Table 5 Synthesis of propargylic alcohols

A range of propargylic alcohols were synthesised, in high to excellent yields (80 to >99%). Crude products were of a high enough purity to allow direct use without a costly purification step.

With a range of alcohols in hand, chlorination was the next step. Table 6 shows the high yielding synthesis of four propargylic chlorides, **78** and **153 - 155**.

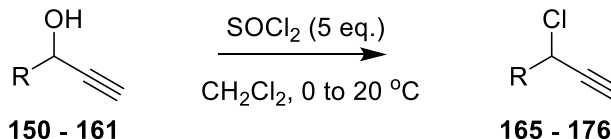


Entry	R	Product	Yield ^a (%)
1	Ph	78	80
2	4-MePh	162	81
3	4-ClPh	163	97
4	<i>n</i> -pentyl	164	>99

a) Yielded as a mixture of S_N2 and S_N2' addition products

Table 6 Synthesis of propargyl chlorides using Appel reaction

Due to the excess waste (triphenylphosphine oxide) generated by the Appel reaction, an alternative chlorination procedure was sought. It was found that the use of thionyl chloride increased the simplicity of the reaction whilst also removing the sometimes tedious step of separating triphenylphosphine oxide from the crude mixture. The rest of the required chlorinations were therefore carried out with thionyl chloride and are shown in Table 7.



Entry	R	Product	Yield ^a (%)	Entry	R	Product	Yield ^a (%)
1	4- <i>t</i> BuPh	165	89	7	3-thiophenyl	171	92
2	4-MeO ₂ CPh	166	90	8	2-pyridyl	172	0
3	4-MeOPh	167	0	9	2-naphthyl	173	86
4	3-MeOPh	168	>99	10	1-naphthyl	174	75
5	4-CF ₃ Ph	169	87	11	2-furyl	175	0
6	3-CNPh	170	83	12	5- <i>N</i> -methylpyrazolyl	176	99

a) Yielded as a mixture of S_N2 and S_N2' addition products

Table 7 Synthesis of propargylic chlorides using thionyl chloride

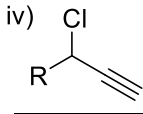
The propargylic alcohol substrates fit into two distinct categories, chlorination was either successful in a high yield (over 75%), or suffered complete failure (entries 3, 8 and 11). In the latter cases, no appreciable products were isolated and crude ^1H NMR spectra showed wide ranging mixtures of poorly resolved peaks. The common theme that links the ring systems that are not amenable to this chemistry (4-methoxyphenyl, pyridyl and furanyl), is the presence of a heteroaromatic ring that is often electron rich. It is thought that the desired propargylic chloride was initially formed, but these systems soon facilitated polymerisation, presumably by stabilisation of an $\text{S}_{\text{N}}1$ type cationic intermediate.

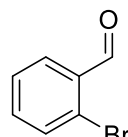
1.2.5 Effects of Propargylic Chloride Variation

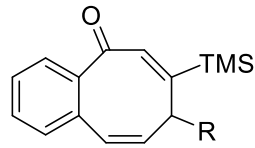
The synthesis of a range of propargylic chlorides was successful in high yields and without the need for costly purification steps. The effects these compounds had on the yield of 8-membered rings are outlined in Table 8.

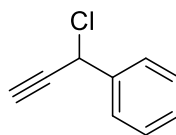
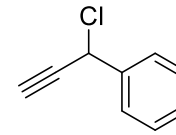
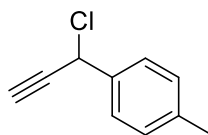
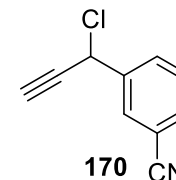
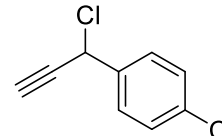
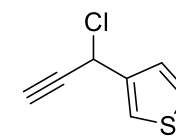
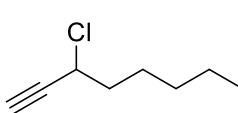
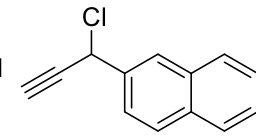
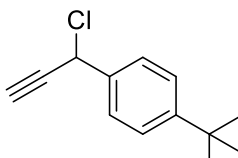
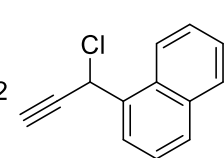
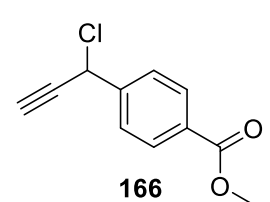
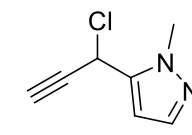
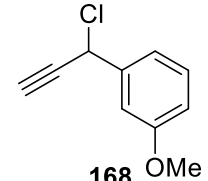
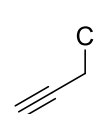
Electronically neutral *para*-substituted phenyl groups (entries 2, 3 and 5) gave moderate yields over 50%. Comparing the yield of *para*-methyl **178** (entry 2, 54%) and *para*-*t*-butyl **181** (entry 5, 52%) show that the size of the *para*-substituted group has little bearing on the yield of 8-membered ring. The electronic effect of substitution in this position has a drastic affect with electron withdrawing *para*-methyl ester **182** (entry 6) not forming at all. In general, electron withdrawing aromatic substituents make for bad substrates under the reaction conditions. Challenging substrates, *para*-methyl ester **182**, *para*-trifluoromethyl **184** and *meta*-cyano **185** have Hammett parameters of +0.45, +0.54 and +0.56 respectively⁶⁶ and show little to no conversion to the desired 8-membered ring. All other substituted phenyl derivatives have a Hammett parameter less than +0.23 (*para*-chloro).⁶⁶ A possible reason for decreased reactivity could be due to a stabilising effect on the reactive carbanion. Figure 10 shows mesomeric carbanion stabilisation by an aromatic ring substituted with methyl ester (**191**). Stabilisation of this anion reduces nucleophilicity and may cause reduced yields.

Heteroatoms were readily incorporated as thiophene **186** and nitrogen containing pyrazole derivative **189** gave good yields of 52 and 42%, respectively. Naphthalenes **173** and **174** (entries 11 and 12) are both tolerated but the 2-naphthyl **187** (48% yield) significantly outperformed 1-naphthyl **188** (24%) yield. The stark difference between naphthalenes can be attributed to substitution pattern as their steric profile and Hammett parameter are very similar.

i) LiCCTMS (1.1 equiv.)
 ii) *n*BuLi (1.0 equiv.)
 iii) CuBr•SMe₂ (0.5 equiv.)
 iv)  **78, 162-177**
 (0.5 equiv.)
 THF, -50 to -10 °C


75


80, 178 - 190

Entry	Propargyl Chloride	Product	Yield ^a (%)	Entry	Propargyl Chloride	Product	Yield ^a (%)
1	 78	80	70	8	 169	184	trace ^b
2	 162	178	54	9	 170	185	trace ^b
3	 163	179	54	10	 171	186	52
4	 164	180	0	11	 173	187	48
5	 165	181	52	12	 174	188	24
6	 166	182	0	13	 176	189	42
7	 168	183	42	14	 177	190	0

a) isolated yield b) trace product in crude ¹H NMR spectrum but not isolated

Table 8 Effects of propargylic chloride variation

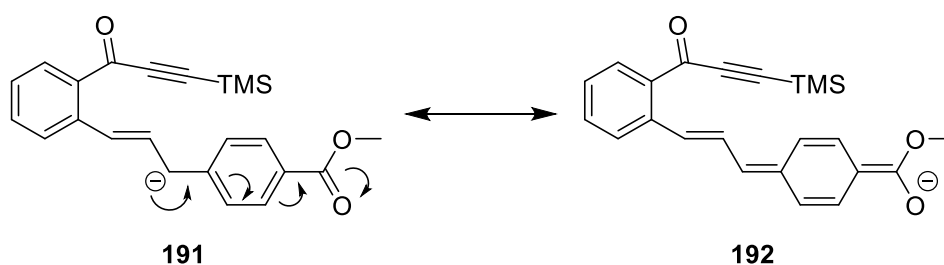


Figure 10 Mesomeric stabilisation of carbanion

Non aromatic propargylic chlorides **164** and commercially available **177** are not tolerated under these conditions.

There were three main propargylic chloride limitations identified in this study; non-aromatic groups were not tolerated, electron withdrawing groups were not tolerated and due to the instability of electron rich propargylic chloride's we could not assess their suitability. We next focussed on solving these issues.

1.2.6 The Synthesis and Use of Alternate Propargylic Systems

The use of propargylic chlorides had been successful and convenient up to this point, but due to the instability of electron rich substrates we wanted to explore the possibility of utilising different leaving groups. Figure 11 shows possible routes by which an electron rich aromatic group, such as furan, could facilitate the polymerisation of a propargylic chloride.

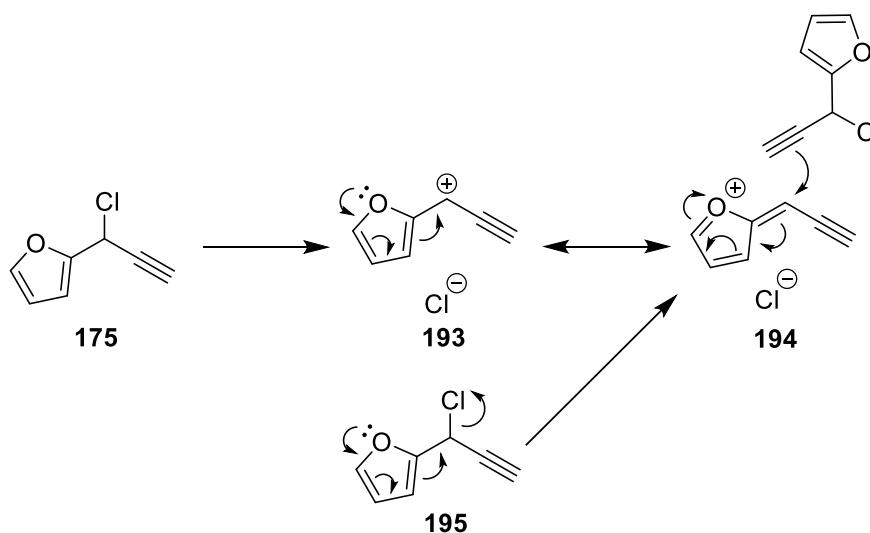
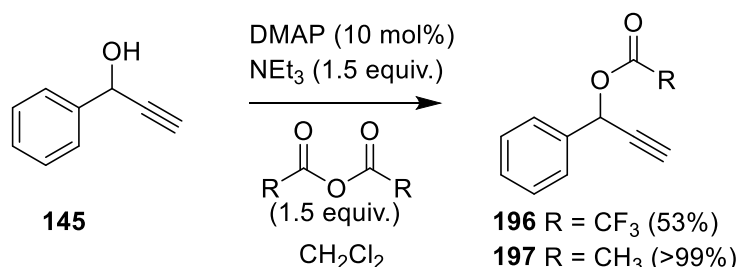


Figure 11 Possible routes of polymerisation

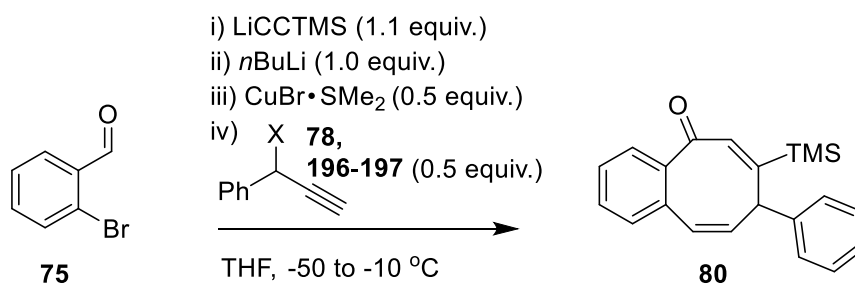
An S_N1 type chloride elimination could occur to give cation **193**, this cation can be stabilised by resonance to give oxonium **194** which can dimerise to start a polymerisation cycle. It is also possible that resonance structures such as **195** can directly trigger the elimination of the chloride anion. This process is governed not only by the electron donating capability of the aromatic, but also by the stability of the anion formed. We hoped by increasing the pK_{aH} of the anionic leaving group we would be able to synthesise a stable, electron rich, propargylic system. Initially we needed to know if the reaction could tolerate the use of non-chloride leaving groups.

Trifluoroacetate **196** and acetate **197** were synthesised from the corresponding propargylic alcohol in 53 and 99% yields, respectively (Scheme 26).



Scheme 26 Synthesis of alternate propargylic systems

The propargylic trifluoroacetate **196** and propargylic acetate **197** were subjected to the reaction conditions. Both systems were tolerated and synthesised carbocycle **80** in varying yields.



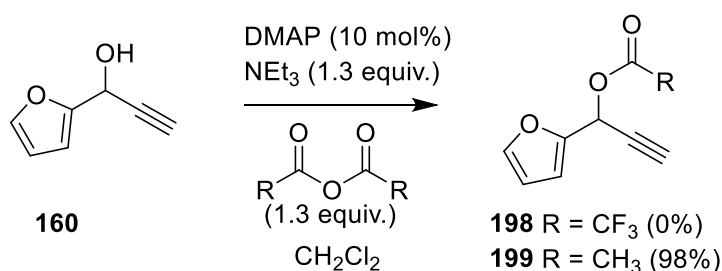
Entry	X (pK_{aH}) ^a	Yield (%)
1	Cl (-8.0)	70
2	OCOCF ₃ (-0.3)	58
3	OCOCH ₃ (4.8)	19

a) X⁻ pK_{aH} value in water ⁶⁷

Table 9 Effect of propargylic system on the cascade reaction

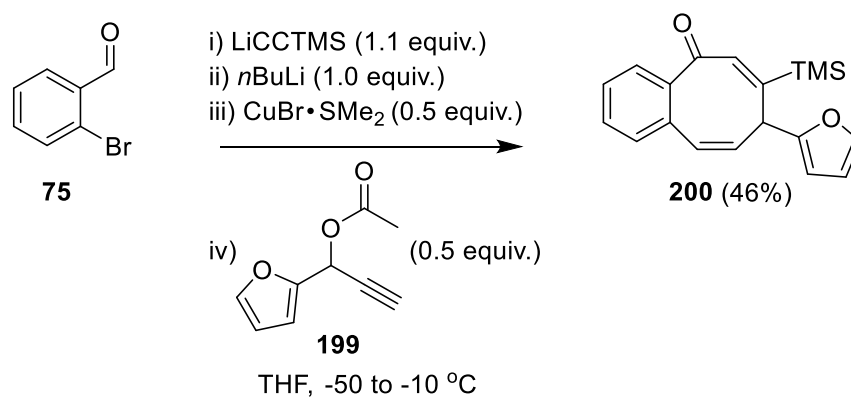
Table 9 shows that as the pK_{aH} of the leaving group increases, the yield of reaction decreases. This is presumably due to the reduced stability of the anion formed during S_N2' addition of the cuprate species into the alkyne (Scheme 22, **83**).

To complete the goal of synthesising an 8-membered ring system with an electron rich substituent, furyl propargylic acetate **199** was synthesised from propargylic alcohol **160** in 98% yield. The attempted synthesis of trifluoroacetate **198** resulted in a mixture of broad, presumably polymerised, crude ^1H NMR signals in its spectrum.



Scheme 27 Synthesis of furyl propargylic acetate **199**

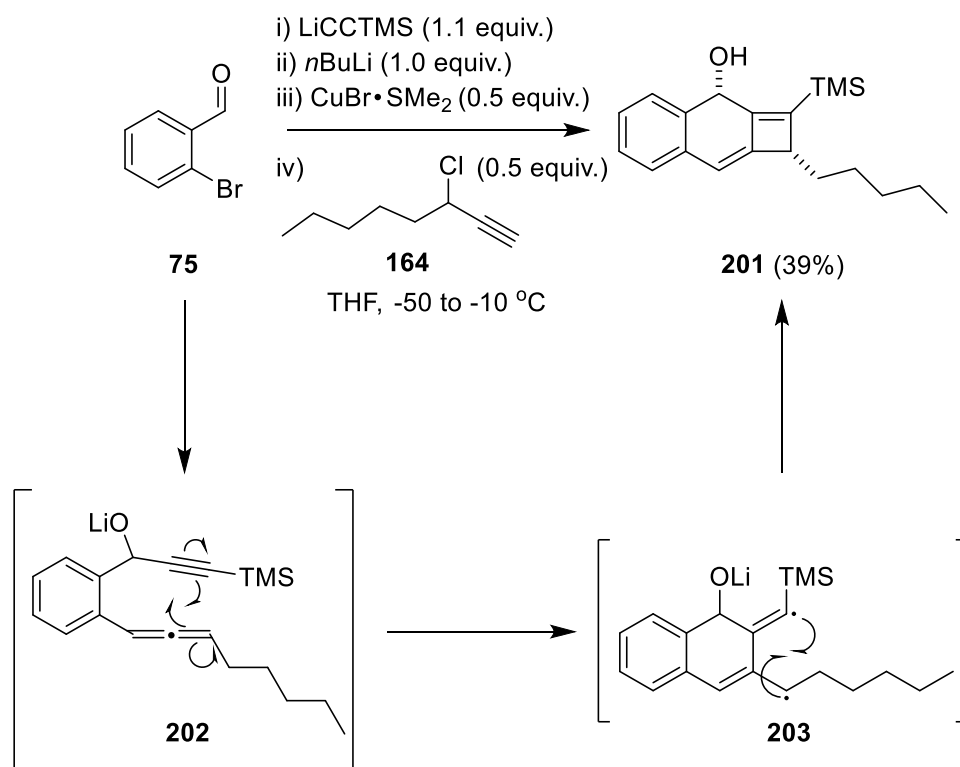
Pleasingly, the furyl containing 8-membered ring **200** was synthesised in 46% yield (Scheme 28). Comparatively, the result from using the furyl acetate was significantly better than the phenyl acetate (Table 9, 19%). This could be due to the same resonance structures shown in Figure 11 weakening the carbon to acetate bond, hence promoting S_N2' cuprate addition.



Scheme 28 Synthesis of 8-membered ring **200**

1.2.7 Cascade Reaction Chemoselectivity

Although alkyl propargylic chloride **164** and electron withdrawing aromatics **167**, **169-170** (Table 8) did not lead to the desired 8-membered ring, the products obtained were still of interest. Under the conditions described in Table 8 a novel cyclobutene ring system **201** was synthesised from alkyl propargylic chloride **164**.



Scheme 29 Synthesis of cyclobutene **192** via Myers-Saito cyclisation

Cyclobutene **201** was isolated in 39% yield as a single diastereoisomer using identical conditions to the reactions forming the intended 8-membered rings. The structure of this fused cyclobutene ring system was confirmed via X-ray crystallography (Figure 12). It is thought that this species is formed via a radical Myers-Saito⁶⁸ type cyclisation from intermediate **202** (Scheme 29).⁶⁹

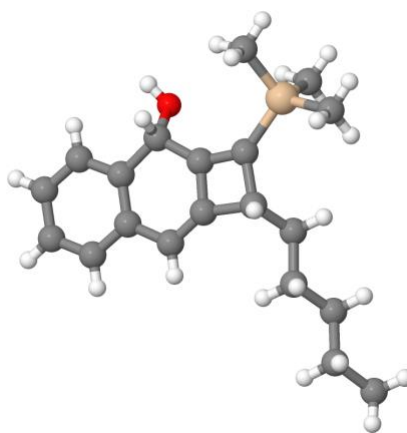
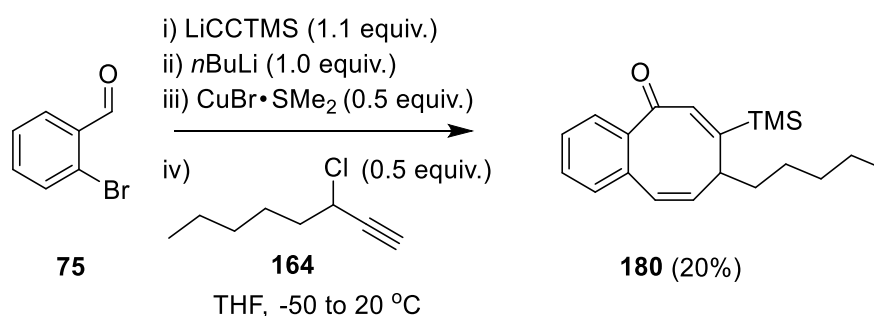


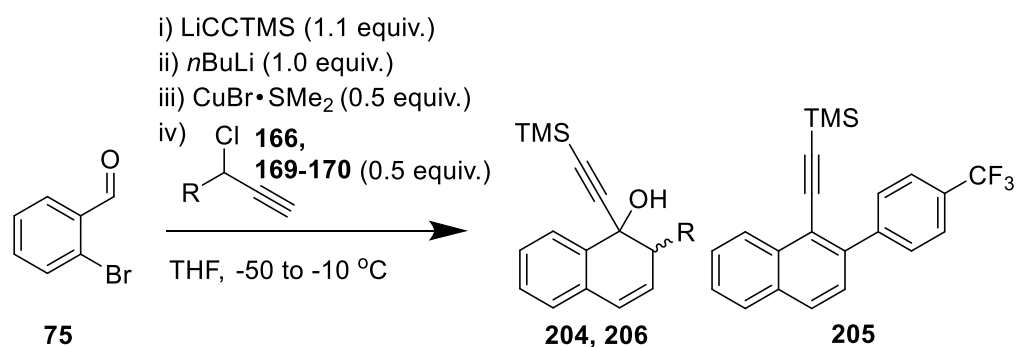
Figure 12 X-ray crystal structure of **201**

It seems that the 1,5-hydride transfer that triggers the usual annulation cascade to form an 8-membered ring did not occur. This could be due to the lack of anion stabilisation offered by the alkyl group compared to an aromatic counterpart. In an effort to encourage this Cannizzarro-like hydride transfer the reaction conditions were modified. The usual procedure calls for the addition of the propargylic chloride at -50 °C and then gradual warming to -10 °C where, after a hold period, the reaction is quenched. When the reaction was allowed to warm to room temperature (20 °C) instead of -10 °C the formation of the desired alkyl substituted 8-membered ring **180** was observed and isolated in a yield of 20%. It is thought that the hydride transfer is viable at this temperature as more energy is available to the system. A lower yield was however observed, possibly due to the instability of organometallics at this increased temperature and the competing Myers-Saito reaction.



Scheme 30 Synthesis of alkyl substituted 8-membered ring **171**

When using electron withdrawing aromatic propargylic chlorides **166** and **169-170**, instead of getting the expected 8-membered ring, novel 1,2-dihydronaphthalen-1-ols were synthesised in good yields (Table 10). The 1,2-dihydronaphthalen-1-ol derived from *para*-trifluoromethyl **169** could not be isolated cleanly due to difficulties separating it from the propargylic alcohol by-product (analogous to **88**, Scheme 22). It was found that by stirring the crude mixture with Amberlyst® 15 solid supported acid and 3 Å molecular sieves, it was possible to isolate the compound as its dehydrated naphthalene analogue **205**.



Entry	Propargyl Chloride	Product	Yield (%) ^a
1	 166	204	65 ^b
2	 169	205	48 ^c
3	 170	206	48 ^d

a) Isolated yield; b) isolated as a mixture of diastereoisomers; c) isolated as naphthalene **205** after stirring with Amberlyst® 15 and 3 Å mol. sieves; d) isolated as separate diastereoisomers in 36 and 12% yield

Table 10 Synthesis of novel 6-membered rings

The general 6-membered ring structure was confirmed via X-ray crystallography of **204** (Figure 13). The yields of these 6-membered rings were easily comparable to those observed in 8-membered ring synthesis with identical reaction conditions.

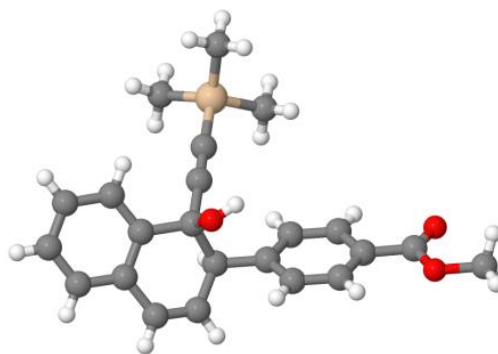


Figure 13 X-ray crystal structure of **204**

It is thought that benzo fused 6-membered rings, such as **204**, and benzo fused 8-membered rings, such as **80** share a common reaction intermediate. Anion **208** can perform a 1,4-addition into the ynone group to achieve annulation into an 8-membered ring (**209**), or alternatively, perform a 1,2-addition directly into the carbonyl to furnish a 6-membered alkoxide (**207**).

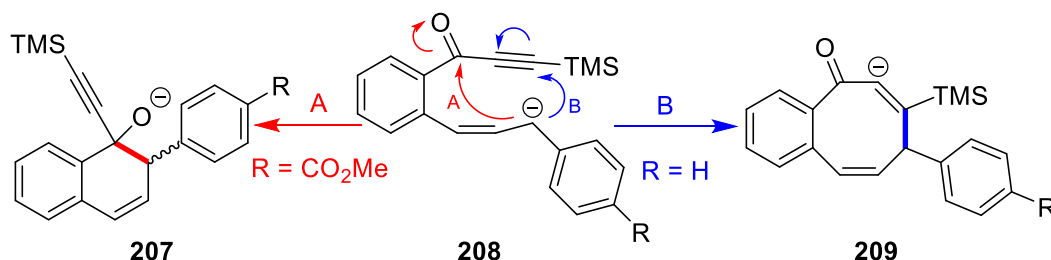
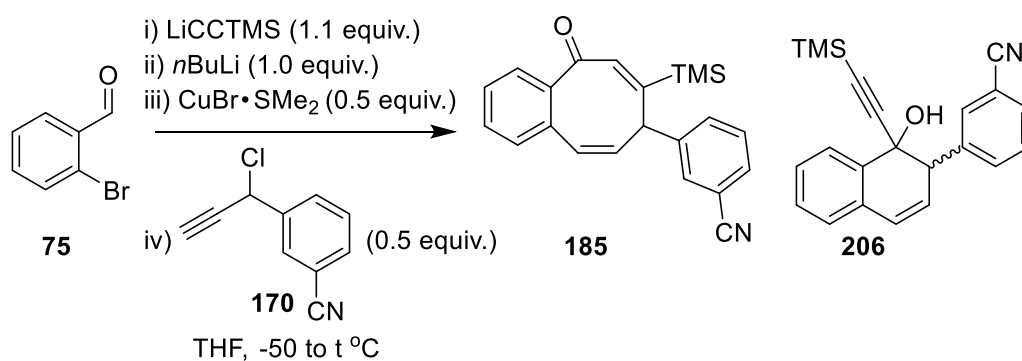


Figure 14 Alternate annulation pathways

When the *para*-substituent in Figure 14 is an electron withdrawing methyl ester group, the mesomeric stabilisation shown in Figure 10 causes a switch in chemoselectivity to favour the synthesis of a fused 6,6-ring system instead of 6,8-ring system.

When *meta*-nitrile and *para*-trifluoromethyl propargylic chlorides (**170** and **169** respectively) were used to synthesise naphthalene derivatives **206** and **205**, the crude ^1H NMR spectra suggested trace amounts of competing 8-membered ring product were also present (observation of characteristic doublet, approx. 9.5 Hz at 5.0 ppm, Figure 7). This showed that synthesis of the initially desired 8-membered ring was possible and encouraged us to investigate promoting this reaction pathway for these systems. The original optimisation of cyclooctanoid **80** showed that addition of the propargylic chloride at $-50\text{ }^\circ\text{C}$ and subsequent warming to $-10\text{ }^\circ\text{C}$, before a hold period, were the optimal conditions for 8-membered ring formation. A small temperature study was carried out using *meta*-nitrile **170** to ascertain if cyclisation temperature could influence chemoselectivity (Table 11). In this study, nitrile **170** was added at the usual $-50\text{ }^\circ\text{C}$ but the hold temperature was varied.



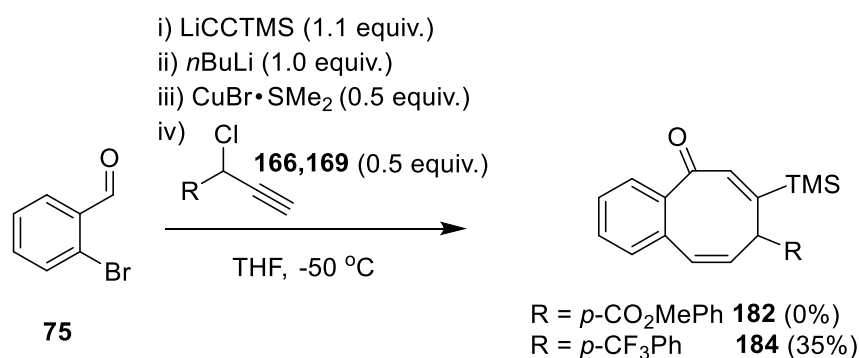
Entry	Hold temperature (°C)	Hold time (h)	Ratio of 185:206 ^a
1	-10	1	1:15
2	-20	1	1:7
3	-50	16	2:1 (42%) ^b

a) Ratio derived from integration of crude ¹H NMR peaks; b) Isolated yield of **185**

Table 11 Effect of temperature on the synthesis of **185**

It was very pleasing to see that variation of reaction temperature could influence chemoselectivity. At a hold temperature of -10 °C for 1 hour, formation of 6-membered ring **206** was favoured over the 8-membered ring **185** by a ratio of 15:1. If the reaction was kept at a constant -50 °C for 16 hours, the formation of desired 8-membered ring **185** could be favoured in a 2:1 (**185:206**) ratio with an isolated yield of 42% (entry 3). It is probable that even colder temperatures would increase this ratio further, but prolonged reaction times made this impractical.

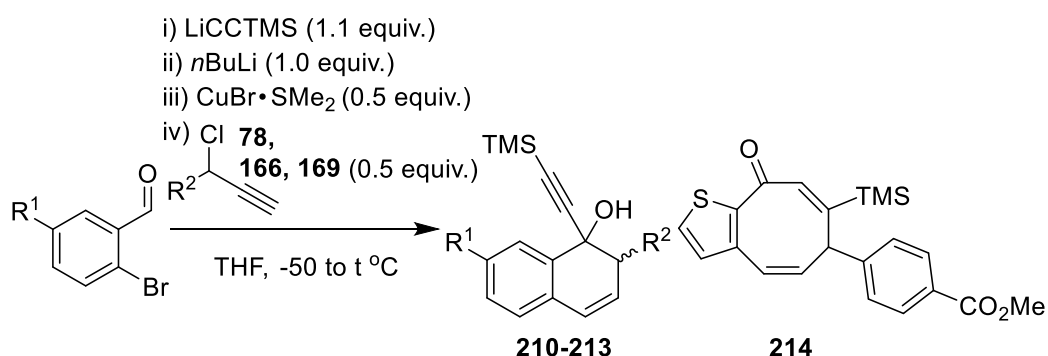
We had observed a ‘temperature switch’ that could be used to reverse the chemoselectivity of a reaction by only changing a single variable. To see if this temperature switch was a general feature of this reaction we re-attempted the synthesis of 8-membered rings **182** and **184** (derived from other electron withdrawing propargylic chlorides), at the cooler hold temperature of -50 °C.

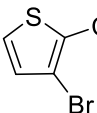


Scheme 31 Attempted synthesis of carbocycles **182** and **184**

We attained mixed results from this study, it showed that *para*-trifluoromethyl substituted propargylic chloride **169** was tolerated for the synthesis of 8-membered ring **184** (35% yield, 1:1 ratio of 8-ring:6-ring by crude ^1H NMR spectra analysis), whilst the *para*-methyl ester derivative exclusively synthesised dihydronaphthalene **204** only.

A small library of naphthalene derivatives **210-213** were synthesised in order to assess the scope of naphthalene formation (Table 12).



Entry	R ¹	R ²	Hold Temperature (°C)	Ratio of 6:8-ring ^a	Product	Yield (%) ^b
1	OMe	<i>para</i> -CO ₂ MePh	0	>50:1	210	52 ^c
2	OMe	<i>para</i> -CF ₃ Ph	0	3:1	211	42 ^d
3	F	<i>para</i> -CF ₃ Ph	0	5:1	212	49 ^d
4	H	Ph	20	4:1	213	48 ^d
5		<i>para</i> -CO ₂ MePh	0	1:>50	214	27

a) Derived via analysis of crude ^1H NMR spectroscopy; b) isolated yield; c) isolated as a mixture of diastereoisomers; d) isolated as dehydrated naphthalene after stirring with Amberlyst® 15 and 3 Å mol. sieves

Table 12 Synthesis of substituted naphthalenes

Comparison of entries 2 and 3 shows that mildly electron rich and electron withdrawing aromatic aldehydes are tolerated with moderate yields and similar chemoselectivity. The increased yield of naphthalene **210** over **211** (52 vs. 42%) displays the increased tendency of propargylic chloride **166** (methyl ester) to favour formation of the 6-membered ring over 8-membered ring. As lower temperatures were found to enhance the formation of 8-membered rings, entry 4 shows how increased cyclisation temperatures enhance the 6-membered ring pathway. In a previous cascade reaction, 2-bromobenzaldehyde and electronically neutral propargylic chloride **78** formed 8-membered ring **80** in 70% yield. In that reaction, 6-membered ring formation was not observed at -10 °C. Table 12 shows the

same reagents reacted at room temperature (20 °C) to favour formation of dihydronaphthalene **213** in a 4:1 ratio.

Conversely, 3-bromothiophene-2-carbaldehyde (entry 5) triggered the exclusive formation of cyclooctanoid **214**. This was surprising as all other reactions containing the *para*-methyl ester **166** heavily favoured 6-ring formation. A possible reason for this contrary behaviour was found by using DFT analysis.^{70,71} Calculations at the B3LYP/6-31G+(d) level of theory showed that in the ground state, a model thiophene anion has a geometrical predisposition for 8-ring formation (Figure 15). The templating effect of the 5-membered ring positions the reactive centres in an orientation favouring annulation to an eight-membered ring. Carbons B and C (cyclise to form 8-membered ring) are predicted to be 0.34 Å closer together than carbons B and A. The opposite is true for a benzene derived structure during the same calculation, carbons E and D (cyclise to form 6-membered ring) are 0.33 Å closer than E and F.

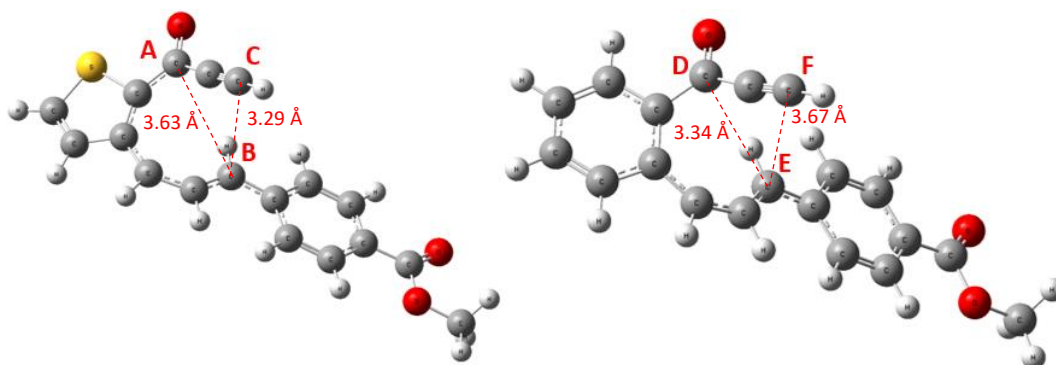
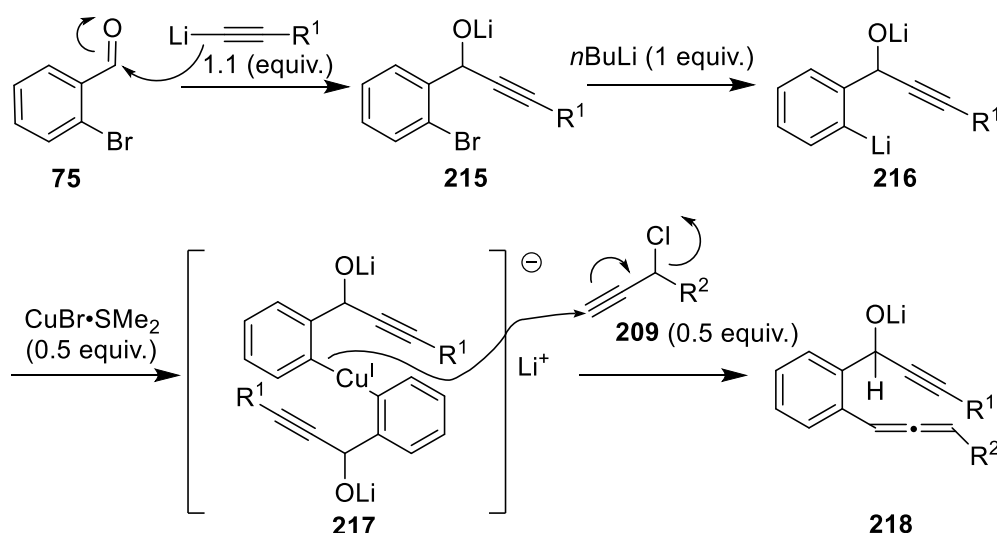


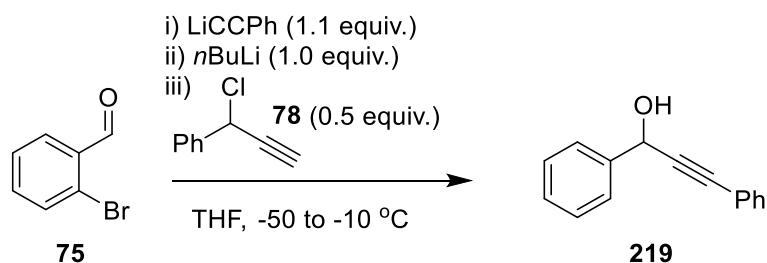
Figure 15 B3LYP/6-31G+(d) model to predict ground state geometry of cyclisation precursors

1.2.8 Mechanistic Insight

In Scheme 22 a plausible mechanistic pathway was proposed for the one-pot synthesis of 8-membered rings such as **80**. During our subsequent research we have not observed any results that can discount the present mechanism. However, we have observed points at which alternate reaction pathways diverge from the initially described route. We have therefore added to our mechanistic understanding by addressing the formation of alternate carbocycles such as cyclobutene **201** and 1,2-dihydronaphthalen-1-ol **204**.

Scheme 32 Formation of allene **218**

The proposed mechanism from aldehyde **75** to allene **218** (Scheme 32) is consistent with all products formed from the one-pot reaction. It is believed that allene **218** is a common intermediate for the formation of cyclooctanoids, dihydronaphthalenes and cyclobutene alike. In order to verify the importance of an organocopper/cuprate species (**217**), a reaction was carried out without the addition of copper(I) bromide dimethyl sulfide (Scheme 33).

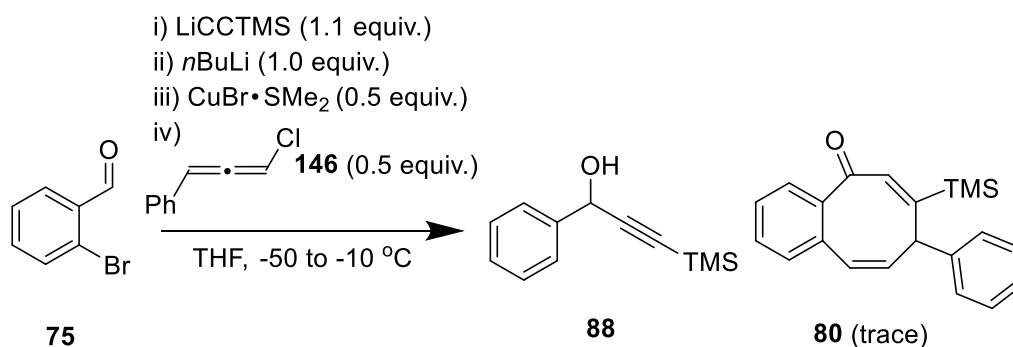


Scheme 33 Control reaction without addition of copper(I) bromide dimethyl sulfide

Without the addition of copper(I) bromide dimethyl sulfide, the only observed product was benzyl alcohol **219**. No evidence of allene formation or annulation could be seen in the crude ^1H NMR spectra. This would lead one to believe that cuprate formation, or at least the presence of copper, is essential for the reaction mechanism. Formation of **219** also supports the formation of dilithiated **216** (Scheme 32) as a reaction intermediate.

Propargylic chlorides were synthesised as a mixture with their $\text{S}_{\text{N}}2'$ derived allene analogues (Scheme 25). It was therefore important to ascertain if the allene impurity could partake in the reaction. In particular, we wanted to know if a chloro-allene such as **146** could react with a cuprate species such as **217** to give allene **218**. Allene **146** was isolated

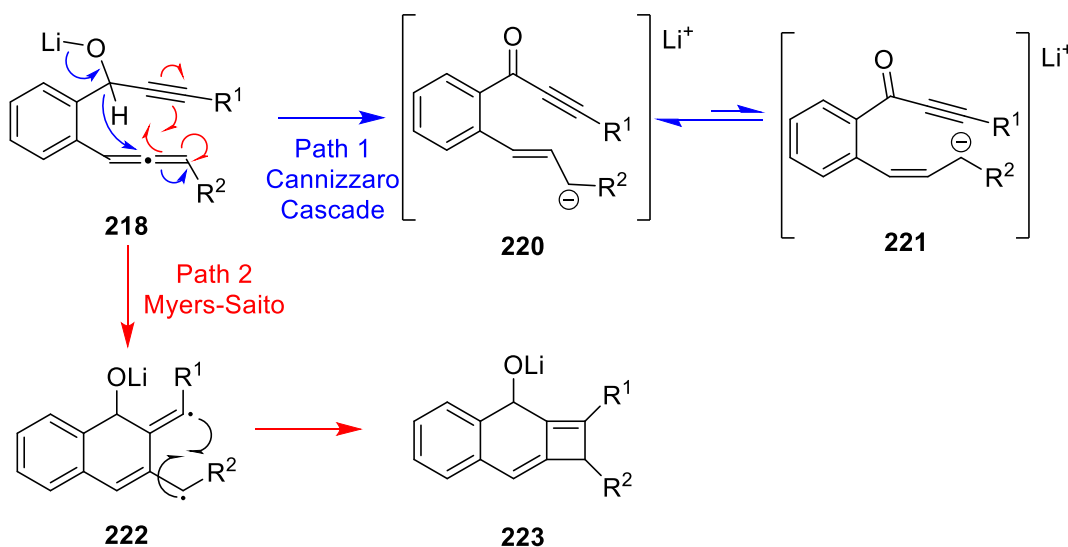
by column chromatography before a reaction was carried out using the allene (**146**) in place of propargylic chloride **78** (Scheme 34).



Scheme 34 Attempted synthesis without propargylic chloride

The major product was alcohol **88** but ¹H NMR analysis of the crude reaction mixture showed traces of carbocycle **780** (3%) along with some other small peaks of unknown origin. It is unknown whether the formation of 8-membered ring **80** was due to a reaction with a small amount of residual propargylic chloride **78** or direct consumption of allene **146**. Either way, as such a small amount of the ring system was found it is thought that any potential pathway including allenes such as **146** can be excluded.

The possibility of two reaction pathways from allene **218** have been touched on already. If R² is sufficiently electron withdrawing and can help stabilise carbanion formation, path 1 is taken (Scheme 35). This pathway involves a Cannizzaro-like 1,5-hydride shift to give ynone **220** followed by *trans* to *cis* isomerisation to give carbanion **221**.



Scheme 35 Possible reaction pathways from allene **218**

The proposed *trans* to *cis* isomerisation is possible via the mechanism shown in Figure 16. In Figure 16, intermediate **224** is represented with a covalent like bond to the lithium atom instead of a carbanion with lithium counter cation. This then isomerises via π -allyl complex **225** to give **226**. A simple bond rotation places the initially *trans* protons in a *syn* orientation (**227**). Alkene isomerisation, again via a π -allyl intermediate gives *cis* alkene **229**. As far as is known, all reactions that have had aromatic R² substituents have followed this hydride transfer and *trans* to *cis* isomerisation pathway.

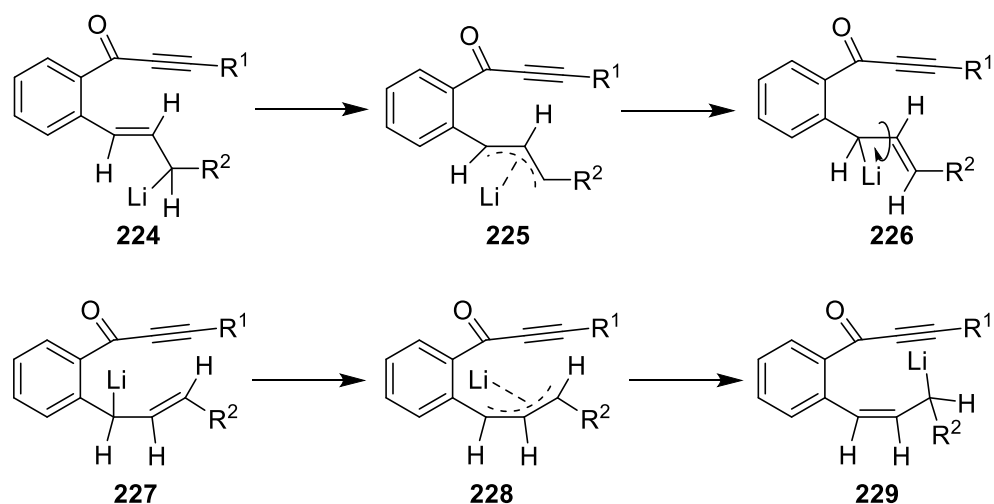
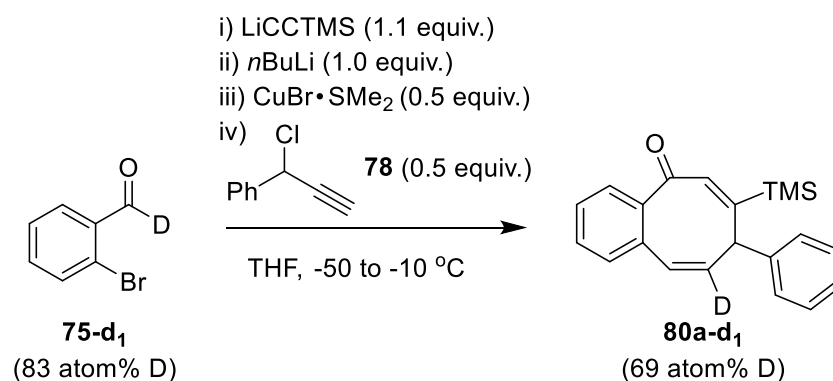


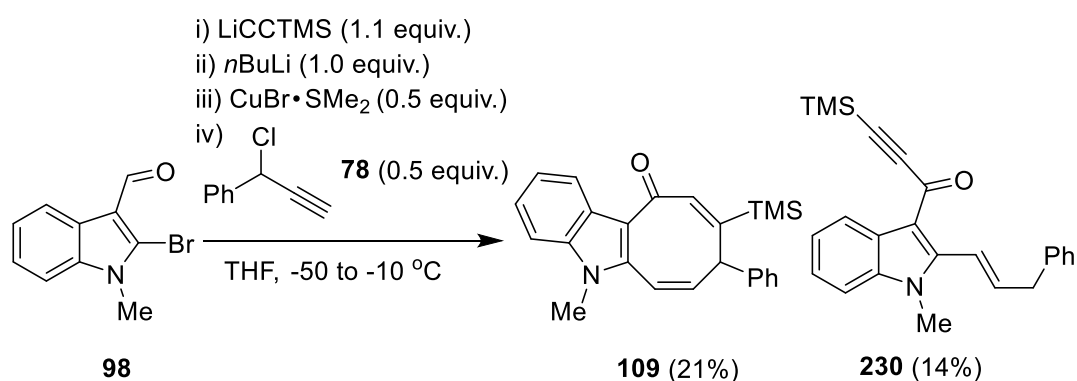
Figure 16 Alkene isomerisation of **224**

It is thought that if R² cannot sufficiently stabilise a carbanion, the Cannizzaro cascade cannot be accessed without increased temperatures. In the absence of a hydride transfer we have observed a Myers-Saito type radical cyclisation forming a cyclobutene system such as **223** (Scheme 35). It seems that when R² is aliphatic, Myers-Saito (path 2) is preferred at colder temperatures (-10 °C) but at room temperature (20 °C) the energy barrier to the Cannizzaro cascade can be overcome and the hydride transfer can occur.

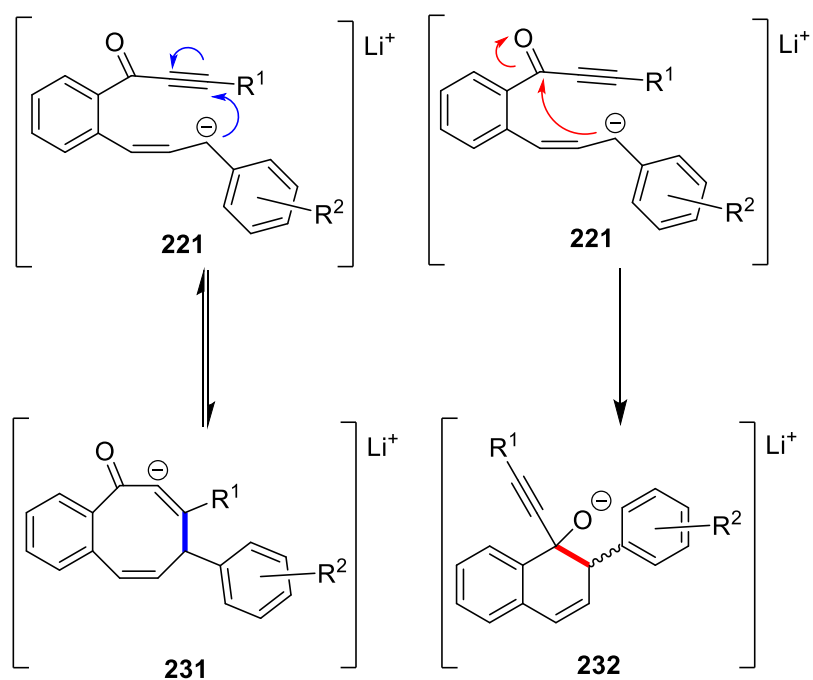
Further evidence to support a Cannizzaro-like 1,5-hydride transfer was obtained via a deuterium labelling experiment. Aldehyde **75-d₁** was synthesised and used to obtain 8-membered ring **80a-d₁** (Scheme 36).^{70,63} A high level of deuterium retention was observed and ¹H NMR analysis showed the loss of a double doublet at 6.66 ppm that corresponded to the alkene position shown in Scheme 36.

Scheme 36 Synthesis of deuterium labelled **80a-d₁**

It was found that cyclooctanoid **109** (Table 3) was formed more slowly than other substrates, leading to the isolation of alkene **230** in 14% yield (Scheme 37). The formation of ynone **230** reinforces the idea that annulation of 8-membered rings occurs via an ynone intermediate such as **220**. If a carbanion such as **220** was quenched before complete annulation an ynone such as **230** would be the expected product. The isolated alkene was shown to be the *trans*-alkene due to a characteristic 16.1 Hz coupling constant between the olefinic protons.

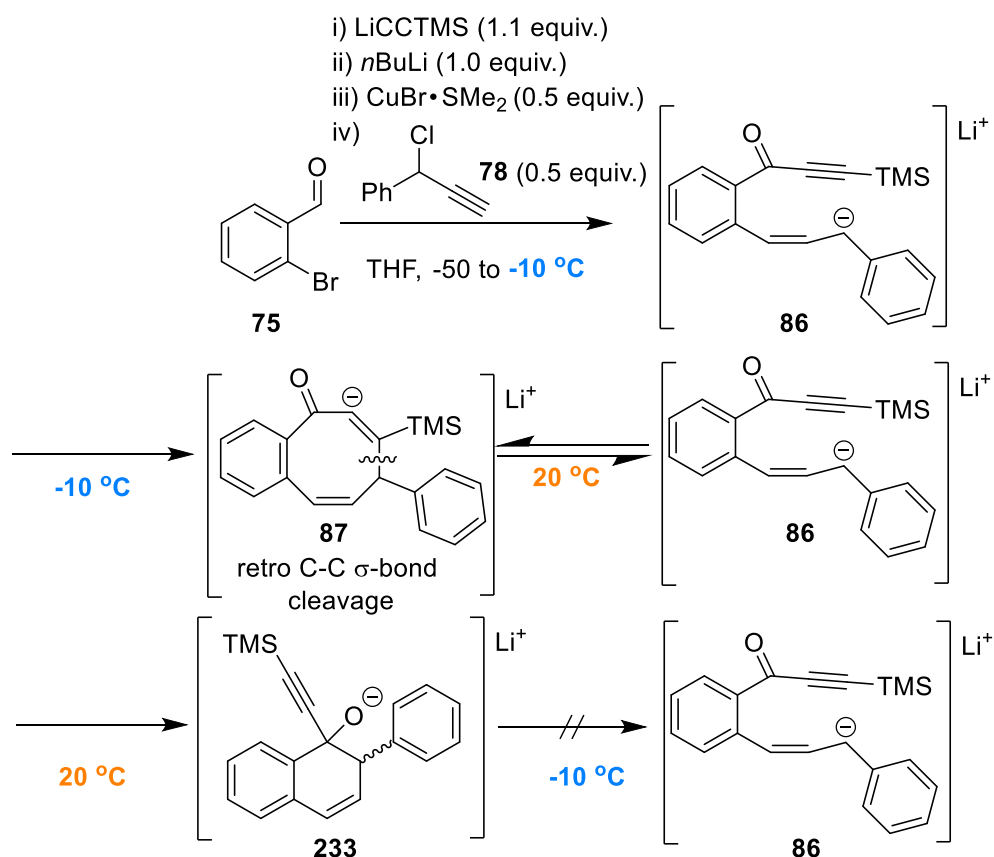
Scheme 37 Synthesis of N-methylindole **214**

As previously discussed, it was possible for carbanion **221** to cyclise via two different pathways. Nucleophilic 1,4-addition into the alkyne gave rise to an 8-membered ring (**231**) whilst 1,2-addition into the ketone yielded a 6-membered ring (Scheme 38).



Scheme 38 Formation of 8- and 6-membered carbocycles

Experimental results showed that when R^2 was particularly electron withdrawing, causing stabilisation of the anion, the formation of 6-membered ring **232** became favoured (Table 10). It was also found that increasing the temperature favoured formation of this dihydronaphthalene product (Table 11). This observation suggested the 6-membered ring to be the thermodynamically favoured product. If this is true, it follows that the formation of an 8-membered ring is the kinetic pathway that is favoured at lower temperatures. We therefore have competition between a kinetic and thermodynamic annulation pathway. Scheme 39 shows how the competing pathways are affected by reaction temperature.



Scheme 39 Effect of temperature on annulation pathway

We propose that under the standard reaction conditions (warming to $-10\text{ }^{\circ}\text{C}$ and holding for 1 hour) the reagents in Scheme 39 lead to the formation of cyclooctanion **87** via anion **86**. Assuming this is the kinetic product, carbocycle **87** is formed preferentially as the energetic barrier to its formation can be overcome at this temperature. The reaction mixture was then allowed to warm to $20\text{ }^{\circ}\text{C}$ and held for a further 1 hour. During this time, a temperature switch occurred and 6-membered ring **233** was favoured in a ratio of $>4:1$. The formation of this ring system suggests that annulation to the initial 8-membered **87** is in fact reversible at the higher temperature. Cleavage of the newly formed C–C σ -bond leads back to anion **86**. At the higher temperature of $20\text{ }^{\circ}\text{C}$ both reaction pathways are possible as the anion has enough energy to overcome the larger energetic barrier. Assuming 6-membered **233** is the thermodynamically more stable product, it is expected that it would now be favoured. The reaction mixture was finally re-cooled to $-10\text{ }^{\circ}\text{C}$ and held for a further 1 hour. Conversion from alkoxide **233** back to 8-membered **87** was not observed with the 6-membered ring still favoured in a ratio of $>4:1$. This would suggest that retro C–C σ -bond cleavage of alkoxide **233** is not possible at $-10\text{ }^{\circ}\text{C}$ and once the

synthesis of 6-membered rings has been triggered, it is not possible to 're-select' synthesis of the 8-membered ring.

The apparent effect of the electron withdrawing nature of R^2 (Scheme 38) on annulation chemoselectivity can be represented by considering the energies of anion **221**, rings **231/232** (from Scheme 38) and their respective transition states (Figure 17).

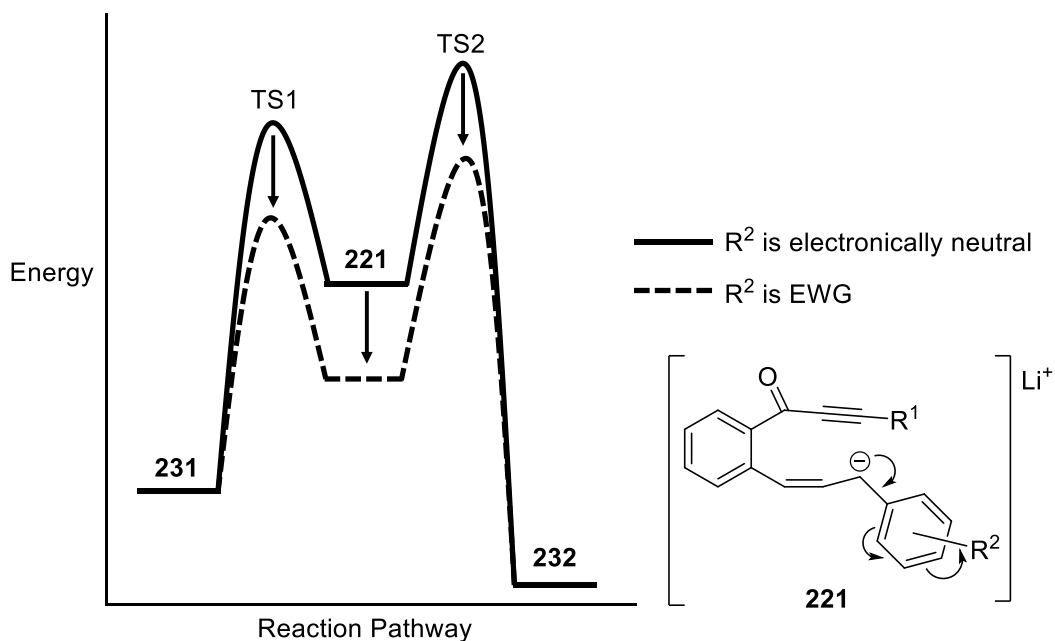


Figure 17 Effect of electron withdrawing group on energy profile

An electron withdrawing R^2 group (eg. CO_2Me) can act to stabilise anion **221**, relative to the parent system (with no phenyl substitution), by helping to spread the negative charge over a number of atoms. This stabilising effect gives anion **221** and its possible transition states a lower energy, as illustrated by the energetic pathways shown in Figure 17. Even though the activation energies needed to access rings **231/232** may not change significantly, the absolute energy required to overcome the transition state will be less. It is possible that this change in absolute energy could impact the temperature at which each pathway becomes available. Experimentally, this effect can be observed when electron withdrawing R^2 groups make the kinetically disfavoured route to a 6-membered ring viable at lower temperatures. In rings **231/232** the negative charge is localised to an area that R^2 cannot directly influence electronically so it is probable their energies would be affected by a much smaller degree.

Parallel to the experimental results gathered, proposed reaction pathways have also been modelled at the multi-component CBS-QB3 level of theory.^{5,70,72} To minimise

computational effort, a simplified model reaction pathway was calculated. In this model an unsubstituted acetylene was used to decrease atom count and, as the exact nature of the organometallics involved are not known, the reaction path was initially modelled on the 'naked ion' system shown below (Figure 18). As the cascade has been modelled in a metal free system its results should to be treated with caution, but may still provide a fair indication of the reaction landscape.

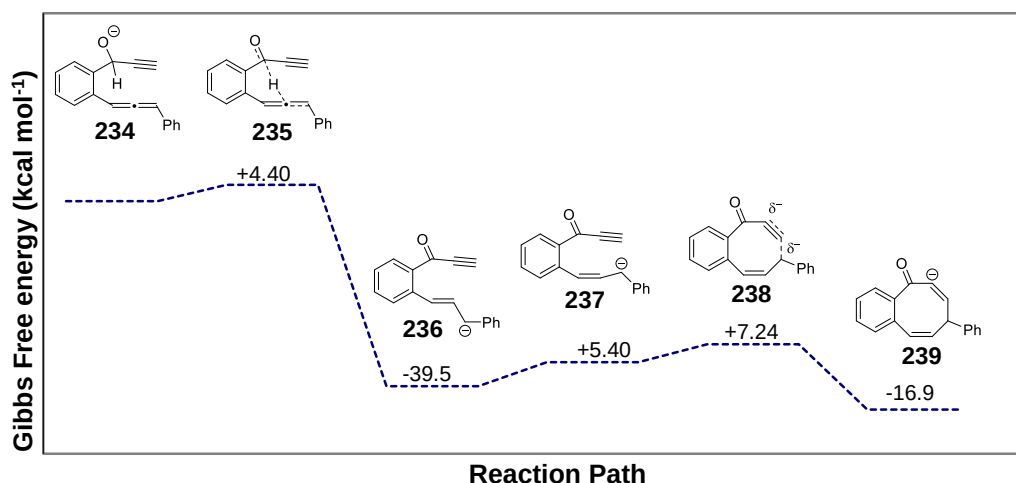


Figure 18 Reaction pathway of 8-membered ring modelled with multi-component CBS-QB3 method

Figure 18 shows a computed reaction pathway from allene **234**, through the hydride transfer transition state **235**, to carbanion **236**. *Trans* to *cis* isomerisation (**236** to **237**) occurs, followed by annulation to give 8-membered ring **223**. The calculations predict that the barrier to the hydride transfer (4.40 kcal mol⁻¹) is the smallest energetic barrier in the pathway. Alkene *trans* to *cis* isomerisation (5.40 kcal mol⁻¹) and annulation (7.24 kcal mol⁻¹) both have slightly higher energetic barriers. All transition states were characterised by a single negative vibrational frequency along the reaction coordinate⁷³ whilst optimised ground states possessed exclusively positive vibrational frequencies.

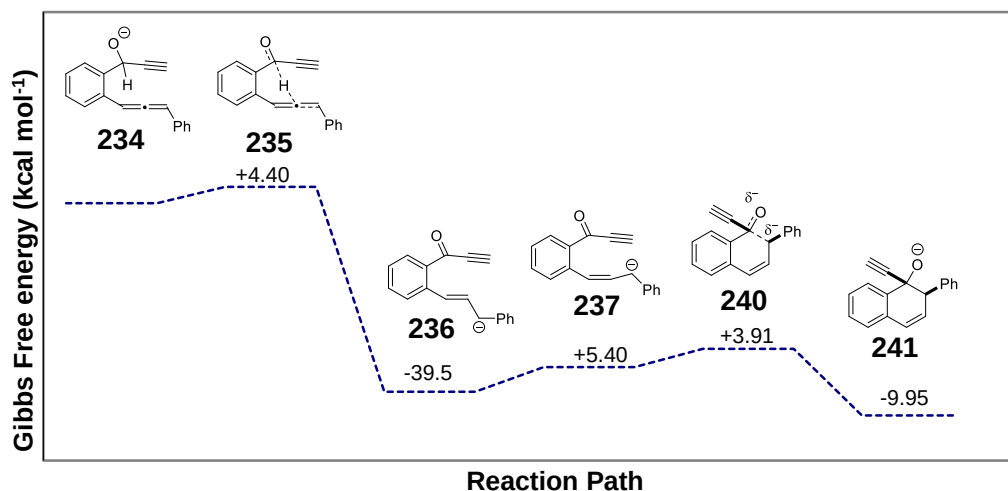


Figure 19 Reaction pathway of 6-membered ring modelled with multi-component CBS-QB3 method

Figure 19 shows the analogous calculated reaction pathway for 6-membered ring formation. The reaction pathway for 8 and 6-membered rings are identical until common intermediate **237**, where 1,2-addition into the carbonyl brings about 6-membered ring formation. Contrary to what experimental results suggest, 'naked ion' models at the CBS-QB3 level of theory predict that formation of 6-membered ring **241** has a lower activation energy (3.91 kcal mol⁻¹ vs 7.24 kcal mol⁻¹) and the product is thermodynamically less stable (by 3.32 kcal mol⁻¹) than 8-membered ring **239**. The computational model predicts the exact opposite to what experimental results tell us. The CBS-QB3 method aims to be accurate to approximately 1-2 kcal mol⁻¹ ⁷⁴ so it is possible that the already small energy differences between pathways could in fact be even closer. If anion **241** was predicted to be 2 kcal mol⁻¹ lower in energy (in line with approximate error limit) and 8-membered ring **239** was predicted to be 2 kcal mol⁻¹ higher in energy, the model would show formation of the 6-membered ring to be thermodynamically favoured. It is clear however that the calculations predict 6- and 8-ring reaction pathways to be viable and close in energy, such that they may be biased by experimental conditions.

The apparent failure of the computational model may be caused by the absence of solvent and metal ligation. The inclusion of a lithium counter cation would probably favour the stabilisation of alkoxide **241** and it is likely that an alkyne-copper complex would work to favour 1,4-addition over 1,2-addition. If the exact nature of the organometallic was known, solvent effects were incorporated and access to increased computational power was possible, perhaps the entire system could be effectively modelled computationally.

The failure of the computational model to correctly identify the kinetic and thermodynamic products could be evidence to suggest that annulation may be brought about via copper mediation. Copper is known to readily form alkyne complexes and their interactions have been widely studied,⁷⁵ such an alkyne complex could facilitate the 1,4-addition involved in 8-membered ring annulations. Computational analysis of copper(I) has shown that copper alkyne complexes have a closely balanced mixture of electrostatic and covalent interactions (53% electrostatic versus 47% covalent) and that the largest covalent contribution is from ligand-to-metal σ donation (Figure 20).⁷⁶ Attempts to incorporate metallic centres into the computational model were made, but progress was limited due to difficulties in finding viable transition state geometries.

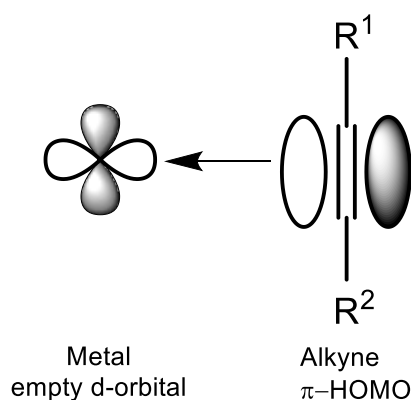


Figure 20 Ligand-to-metal σ donation from ligand π -orbital to empty metal d-orbital

In an effort to experimentally probe the possible copper-alkyne interaction during the annulation event, a scalemic synthesis of 8-membered carbocycle **131** was attempted. It was hoped that if copper was involved in the annulation event, chirality could be transferred from a chiral copper ligand to the resultant 8-membered ring (Figure 21).

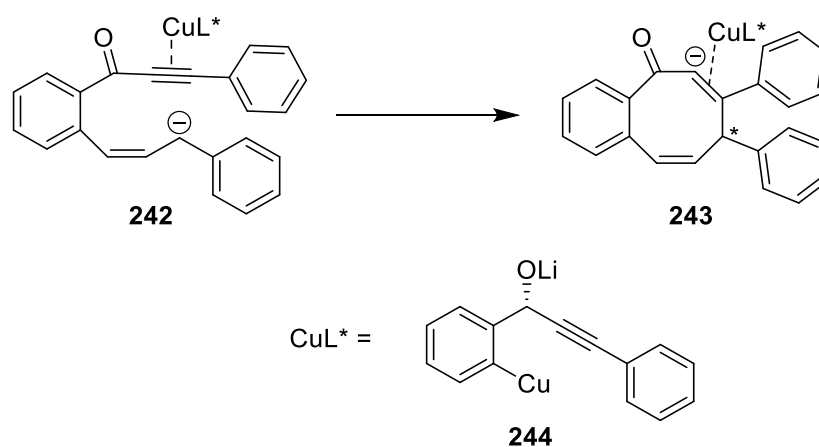
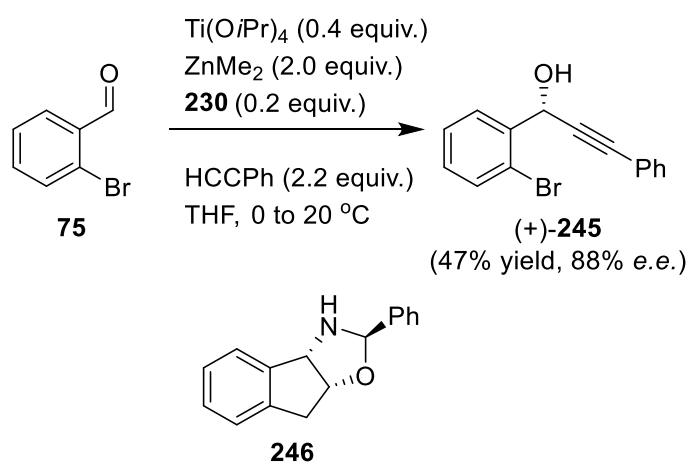


Figure 21 Potential chirality transfer stemming from copper-alkyne interaction

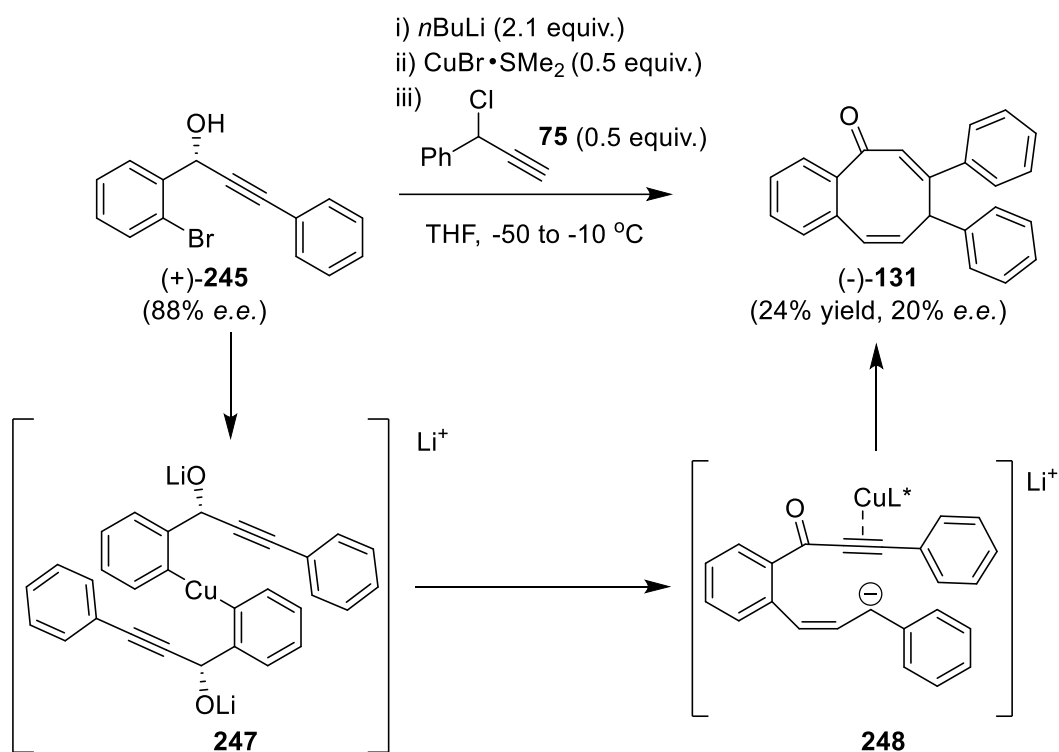
Due to the nature of homo-cuprate in the reaction sequence, we theorised that the non-transferred copper-aryl group (**244**) would be an ideal source of copper bound chirality. In order to produce this chiral species, we firstly needed to adapt the one-pot synthesis into a two-pot synthesis that involved the initial formation of enantioenriched propargylic alcohol **245** (Scheme 40).



Scheme 40 Synthesis of propargylic alcohol **(+)-245**

Chemistry by Zhang *et al.*⁷⁷ was reproduced to firstly synthesise ligand **246** from (1*S*, 2*R*)-(-)-*cis*-1-amino-2-indanol before organo-zinc chemistry was utilised to form the desired chiral propargylic alcohol **245**. Chiral HPLC techniques were used to analyse enantiopurity, where the product was found to have an enantiomeric excess of 88%.

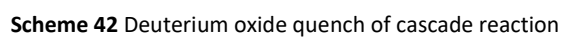
Alcohol **(+)-229** was used as a starting material in a modified cascade synthesis of scalemic 8-membered ring **131** (Scheme 41). Two equivalents of *n*-butyllithium were added to deprotonate the alcohol and also achieve lithium halogen exchange. The addition of copper(I) bromide dimethyl sulfide formed chiral homo-cuprate **247**, which then transferred one aryl unit to react with propargylic chloride **78**. The transferred aryl unit underwent a Cannizzaro-like 1,5-hydride transfer, simultaneously destroying its chiral centre and forming ynone **248**. This annulation precursor led to the synthesis of carbocycle **(-)-131** in 20% enantiomeric excess. The overall two-pot synthesis of ring system **131** was significantly lower than its one-pot predecessor (11 vs 50% yield). This is in part due to the significant increase in cascade reaction by-products. One mayor by-product was thought to be the butyl addition product, analogous to what was found in Scheme 23.



Scheme 41 Scalemic synthesis of cyclooctanoid (-)-131

It is proposed that this partial chirality transfer from **245** (88% e.e.) to **128** (20% e.e.) is evidence of a copper species being present in the annulation event. It is thought that the retained chiral unit from the homo-cuprate acts as a chiral ligand in a structure similar to intermediate **248**. It is not inconceivable that homo-cuprate **247** could directly act to influence annulation geometry, but this would still fit with our overall hypothesis that 8-membered ring annulation is copper mediated. We cannot however discount kinetic resolution of propargylic chloride **78** by a match/mismatch relationship with cuprate **247**.⁷⁸ That being said, the chiral centre on this propargylic chloride is itself destroyed in the formation of the resultant allene which leads to anion **248** (with free rotation at the centre in question). A 'memory of chirality effect' could explain partial asymmetric induction but this is seen as less likely.⁷⁹

The final experimental evidence to support the proposed mechanism is the formation of **80b-d₁**. To support the formation of an anionic intermediate such as **249** a reaction was carried out and quenched by the addition of deuterium oxide (Scheme 42). A high level of deuterium incorporation was encountered and ¹H NMR analysis showed the loss of a doublet at 6.75 ppm that corresponded to the alkene position shown in Scheme 42.



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1.3 Conclusions

Using newly developed one-pot cascade strategies, novel substituted *ortho*-fused cycloocta-2,5-dien-1-ones were synthesised in a range of yields up to 72%. The cascade reaction can tolerate a wide variety of (hetero)aromatic 2-bromo aldehydes (10 examples) and also a range of aromatic and non-aromatic terminal alkynes (7 examples). The only non-commercial starting material was the propargylic chloride which could be synthesised in two steps without the need for costly purification steps. A library of propargylic chlorides was prepared and are, for the most part, tolerated in this synthetic process (8 examples). The initial substrate scope investigation revealed the synthesis of 25 novel cyclooctanoids with an average cascade reaction yield of 46%. Initial limitations included the use of alkyl propargylic chlorides, electron withdrawing propargylic chlorides and the synthesis of electron rich propargylic chlorides. Methodology was then developed to directly address each initial limitation, leading to the synthesis of five additional novel substrates.

In a classical stepwise synthesis, the molecular transformations of the cascade reaction would be completed in four discrete steps: formation of a bromo propargyl alcohol, formation of allenyl alcohol, oxidation to form an ynone and finally annulation to the 8-membered ring. Each step would have its own set of reaction conditions, solvents, and purification procedures all of which expend both time and resources. For a four-step process to achieve a compounded yield of 46%, each step would have to average 82% isolated yield. Thus demonstrating the overall efficiency of this one-pot process.

This cascade reaction can also be applied to the synthesis of other novel ring systems including 6-membered 1,2-dihydronaphthalen-1-ol/naphthalene cores (7 examples in an average yield of 50%) and 4-membered 1,3-dihydrocyclobuta[*b*]naphthalen-3-ol cores (1 example, 39%). A 'temperature switch' that reversed chemoselectivity enabled the selective synthesis of either 8 or 6-membered rings from identical reagents.

A range of experimental results, including a scalemic 8-membered ring synthesis, coupled with high level computational modelling, have also led to increased confidence in the proposed 1,5-hydride transfer mechanism.

Chapter 2: Diversification of *ortho*-Fused Cycloocta-2,5-dien-1-ones for Potential Use in Diverse Molecular Libraries

2.1 Introduction

2.1.1 Common Methods of Drug Discovery

For many years the most successful method of drug discovery has been via natural product isolation and synthesis. Of all the U.S. Food and Drug Administration (FDA) approved small molecules for the treatment of cancer, 49% are either natural products or direct derivatives.⁸⁰ This approach to drug design, based around natural product synthesis, can be described as Target Oriented Synthesis (TOS). Such TOS projects usually begin with the isolation and characterisation of a natural product with an interesting structure or property. If the natural feedstock is rare, or extraction is low yielding, the desired molecule can become a target for synthetic chemists who wish to find a more attractive route. A prime example of this would be the isolation of marine natural product discodermolide **250** (Figure 22). Extraction chemists were only able to obtain discodermolide in 0.002% yield (by weight)⁸¹ from a rare, deep-water sponge found exclusively in the Caribbean.⁸² It was found to have anti-cancer properties,⁸¹ prompting synthetic chemists to find a more effective synthetic route.⁸³ Once a synthetic route to a target compound has been discovered, it is then possible to synthesise derivatives which can increase biological potency or help to ascertain its mode of action.

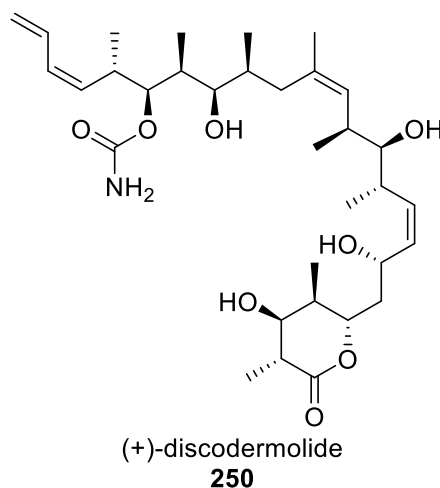
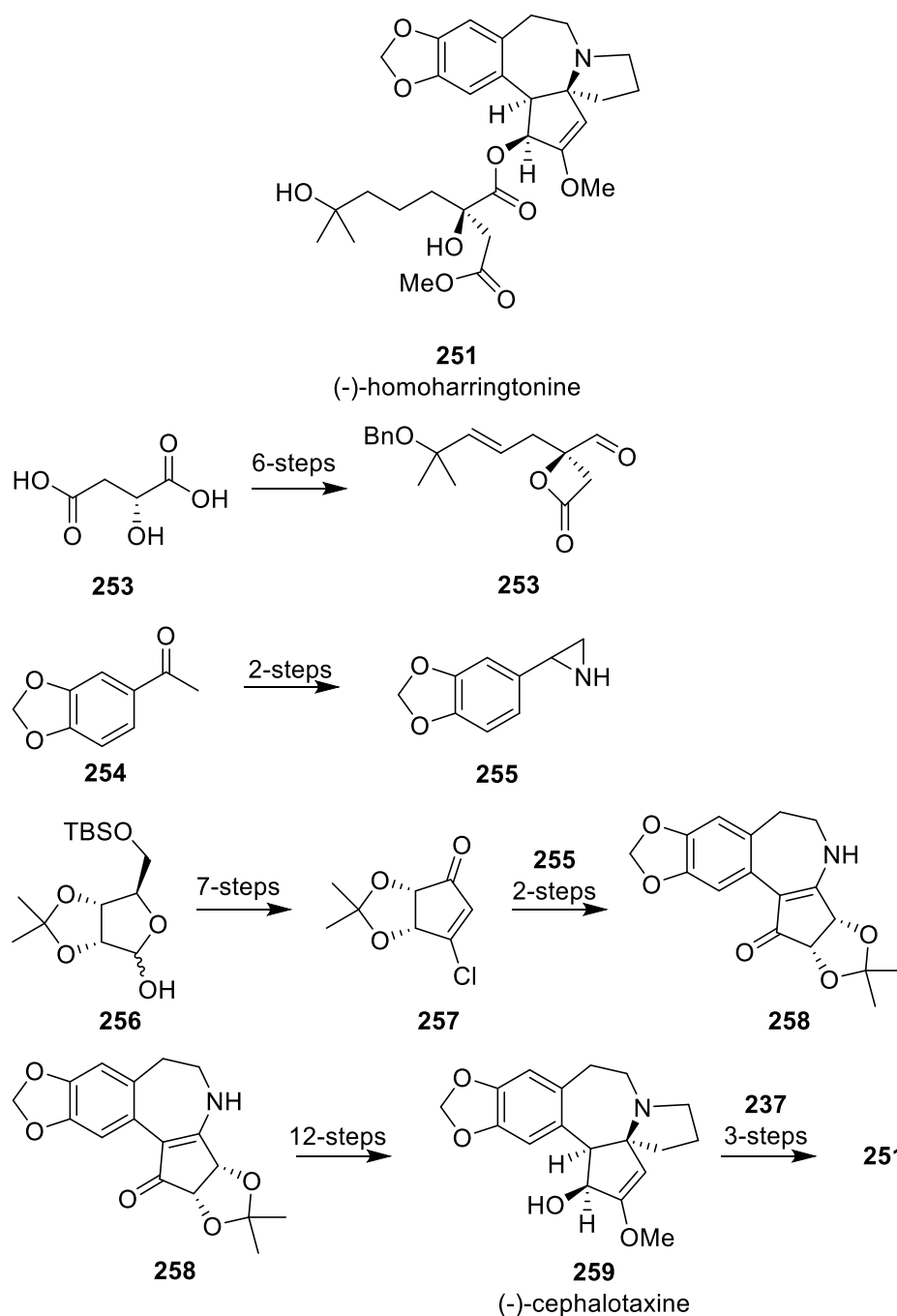


Figure 22 Rare marine natural product (+)-discodermolide.

A recent example of a natural product gaining FDA drug approval,⁸⁴ is homoharringtonine (HHT) **251**.⁸⁵ In 2012 the FDA approved its use for the treatment of chronic myeloid leukemia under the trade name Synribo™. Homoharringtonine was first isolated in 1970 from the Japanese plum-yew (*cephalotaxus harringtonii*)⁸⁶ and was widely studied for its anti-leukemic properties.⁸⁷ As natural extraction did not provide a reliable source for testing, TOS were employed to find synthetic routes.

A total synthesis of HHT was reported by Eckelbarger *et al.* who completed the synthesis in 32 steps with an overall yield of 0.07% (Scheme 43).⁸⁸

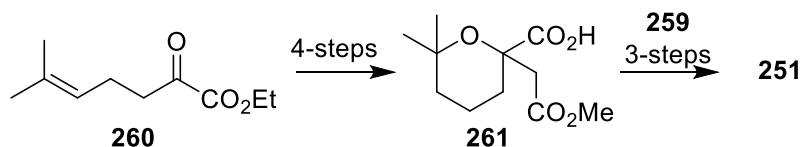


Scheme 43 Eckelbarger *et al.* total synthesis of (-)-homoharringtonine

Scheme 43 shows the synthesis of HHT via the combining of fragments **253**, **255** and **257**. Aziridine **255** and cyclopentenone **257** combine before a rearrangement leads to benzazepine **258**. Twelve linear steps, including stereoselective spirocycle formation, bring about the synthesis of related natural product (-)-cephalotaxine **259**. Esterification with lactone **253** leads to the desired anti-leukemic (-)-homoharringtonine. To complete a

32-step synthesis, considerable time and effort has to be injected into the project. It is therefore important to be sure of some type of reward. An advantage of this type of approach is the certainty of biological results if the target synthesis is successful. In this particular case, the extraction chemists had briefly assessed its biological activity,⁸⁶ making it an attractive synthetic target. Disadvantages of this type of approach include the likelihood of a step-intensive process, the potential of numerous failed routes and the unexpected problems such a large synthetic target can provide.

Perhaps a more attractive TOS route of HHT is reported by Robin *et al.* who employed a semi-synthesis.⁸⁹ Enantiopure (-)-cephalotaxine **259** can be extracted from the Japanese plum-yew in much greater quantities than its ester derivative making it a viable extraction product. Using this, Robin reported the semi-synthesis of (-)-homoharringtonine **251** in seven steps with an overall yield of 28%.



Scheme 44 Robin *et al.* semi-synthesis of (-)-homoharringtonine

Starting from keto ester **260**, racemic carboxylic acid **261** could be synthesised in 4 steps. A dicyclohexylcarbodiimide mediated esterification using an excess of acid **261** allowed partial kinetic resolution to provide the intermediate with the desired stereochemistry. The unwanted epimer could be removed via chromatography before ring-opening and hydrolysis yielded (-)-homoharringtonine. Although this semi-synthesis is considerably shorter than the total synthesis, leading to an increased yield, it does rely on the availability of a complex natural product precursor. The commercial Synribo™ drug is produced in a similar manner via direct esterification of (-)-cephalotaxine.⁹⁰

An alternative method of drug discovery is based on combinatorial chemistry.^{91,92} Using this method, it is possible to develop very large compound libraries in a short amount of time. These compound libraries are then used in high throughput screens to test for biological activity. A common type of combinatorial approach relies on a solid supported split-mix procedure. This method is based on work by Lam *et al.* (1991) in which a library of over 1 million unique pentapeptides were synthesised and screened for biological activity.⁹³ The mechanics of this process are highlighted in Figure 23.

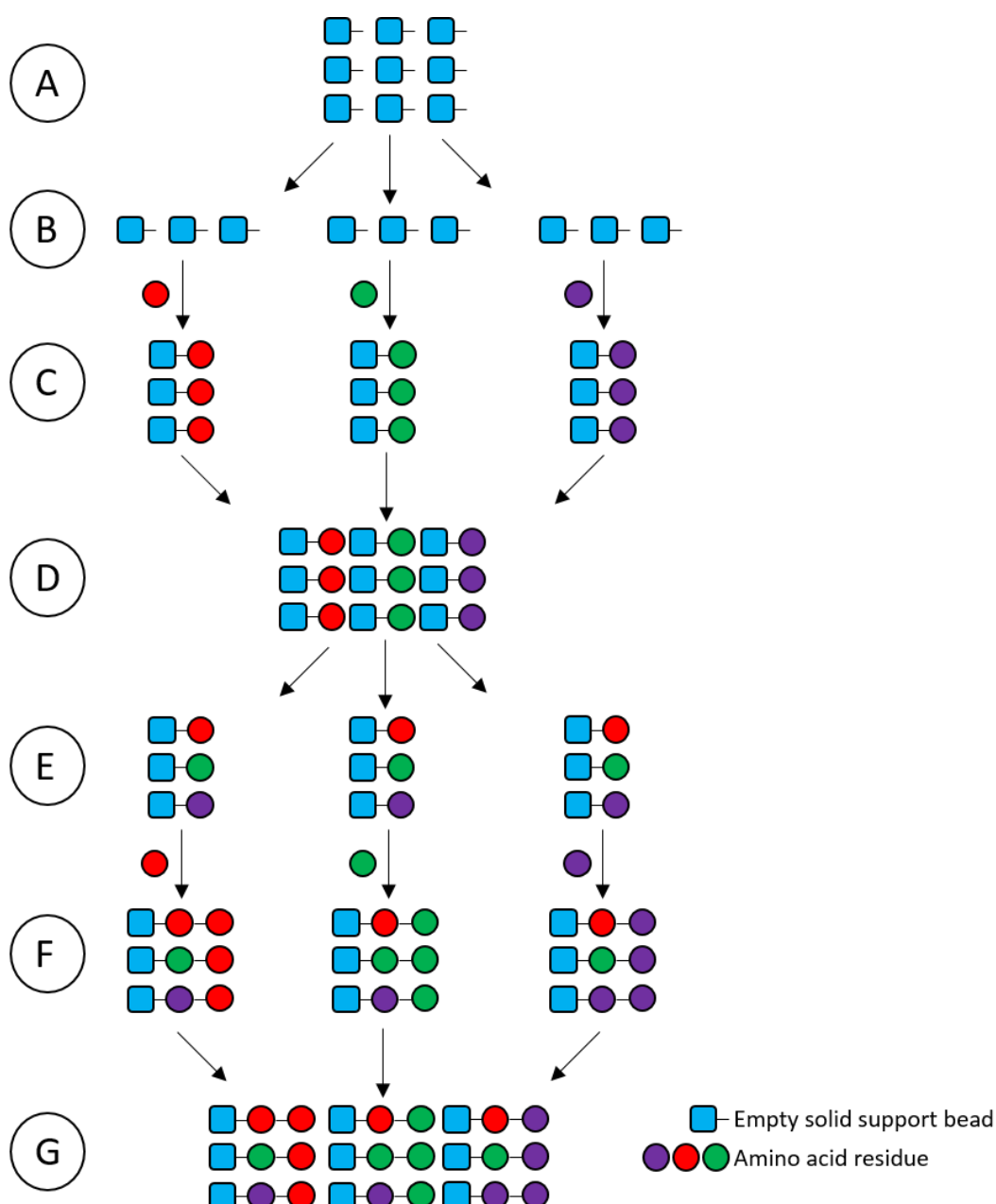
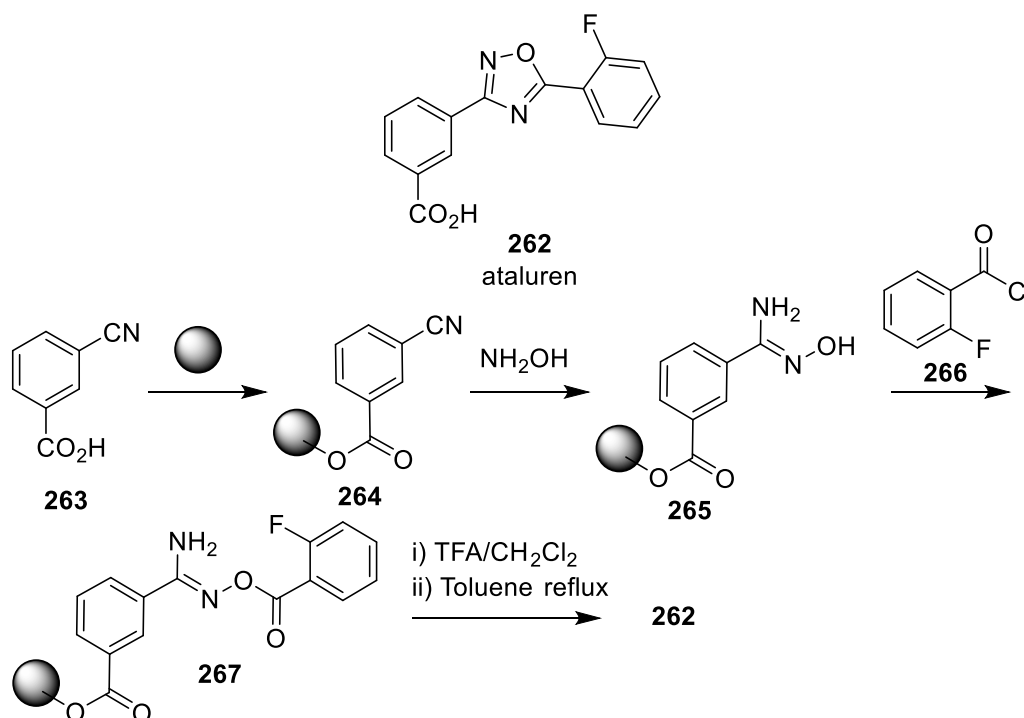


Figure 23 Simplified representation of solid supported split-mix procedure

A number of empty solid support beads are split into the desired number of portions (**B**); Lam used nineteen amino acids but for simplicity Figure 23 depicts a process with just three amino acid residues. Each portion is then attached to a residue (**C**), before being pooled back together to form the bulk material once again (**D**). After efficient mixing, the beads are again separated into the desired number of portions (**E**). In the case of the simplified representation, considerable luck would be needed to coincidentally amass three identical portions containing one of each residue. If each block represented one hundred beads however, one could imagine how a statistical distribution would be achieved. The process of attaching a second residue and pooling is completed to give the complete set

of possible dipeptide combinations (**G**). After every split-mix iteration the library size increases exponentially, meaning that theoretically, using 19 residues and making pentapeptides, Lam would be able to produce up to 2,476,099 (19^5) unique residues. This method leads to each bead containing a single peptide entity so each bead can be mechanically isolated and treated as an independent compound. High throughput screening was carried out on the solid supported residue and isolation/characterisation of the residue was only carried out if its biological activity made it worthwhile. A disadvantage of this system is that at the time of testing, the molecule associated with each bead is unknown. The exact sequence can only be identified once purified from the biological testing residues and cleaved from the solid supporting scaffold. Unfortunately, it is common for only very small amounts of material to be available at this stage.

A drug discovery example that derived from a combinatorial method is that of ataluren **262**. In 2014 ataluren, under the trade name Translarna™, gained European Medicines Agency approval to be administered for the treatment of Duchenne muscular dystrophy.⁹⁴ As ataluren targets so called nonsense mutations⁹⁵ it may also find clinical use against other genetic disorders, with clinical trials underway to treat cystic fibrosis⁹⁶. Ataluren was first reported by Welch *et al.*⁹⁷ as part of a screen of a molecular library of 800,000 small molecules. Details about the synthetic route are limited (Scheme 45), but it is reported that 3-cyanobenzoic acid is treated with a resin to form solid supported **264**.



Scheme 45 Welch *et al.* solid supported synthesis of ataluren **262**

This is reacted with hydroxylamine to form hydroxyamidide **265** before addition of acid chloride **26** gives intermediate **267**. Cleavage with trifluoroacetic acid gives the free carboxylic acid before azeotropic removal of water in refluxing toluene yields ataluren (**262**). Figure 24 shows the general structure of a possible library of small molecules that could be quickly synthesised using the procedure developed by Welch *et al.*

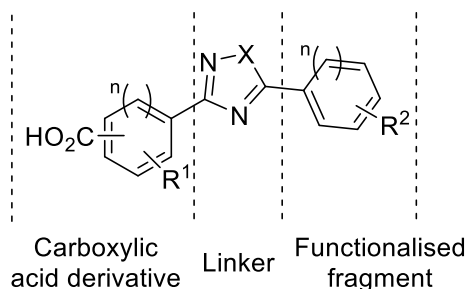


Figure 24 Generalised structure of potential small molecule library

Critics of this type of drug discovery method would say that although a large compound library can be built very quickly, true molecular diversity is still lacking. That is, as the molecular backbone of substrates can still be very similar. In the case of Welch *et al.* we can see that the short solid supported synthesis of ataluren will always yield products with the same three fragments; a carboxylic acid, a linker and a second functionalised fragment.

The aim of synthesising substrate libraries with as much molecular diversity as possible is known as Diversity-Oriented Synthesis (DOS). This is a modern technique coined by Schreiber in 2000.⁹⁸ In a seminal introductory paper to DOS, he went on to eloquently describe its goals '*...diversity-oriented synthesis (DOS) populates chemical space broadly with small molecules having diverse structures. The goals of DOS include the development of pathways leading to the efficient (three- to five-step) synthesis of collections of small molecules having skeletal and stereochemical diversity with defined coordinates in chemical space*'.⁹⁹ Another pioneer of DOS is Spring^{100,101} who argues that the size of a screening library does not necessarily predict its quality and that molecular diversity is in fact crucial.¹⁰² It is common for biological systems to be 'challenged' with small molecule screens,^{103,104} but when the precise nature of the target is unknown it is not logical to use a large library of structurally similar molecules. A more diverse library spread over chemical space should elicit more meaningful information about the target.

The need for novel methodologies to occupy and screen unexplored chemical space can be highlighted by a study of the CAS registry by Lipkus *et al.* By statistically analysing all known cyclic organic compounds in the CAS registry (24 million entries – in 2008), Lipkus

attempted to quantify the diversity of the known chemical universe.¹⁰⁵ It was found that 0.25% of all known molecular frameworks can account for 50% of the total compound database. Lipkus also suggests that the distribution conforms to a power law: that is that the more often a framework has been synthesised, the more likely it will be used in the future. Known synthetic pathways are less likely to fail and are therefore more attractive. It is accepted that some areas of chemical space have increased biological activity,¹⁰⁶ but it also follows that the most commonly synthesised frameworks will have undergone broader biological screening. Any biological hits would then work to further increase the popularity of a particular scaffold. It can be argued that efficient DOS approaches to drug discovery can work to fight against such historical biasing.¹⁰⁷

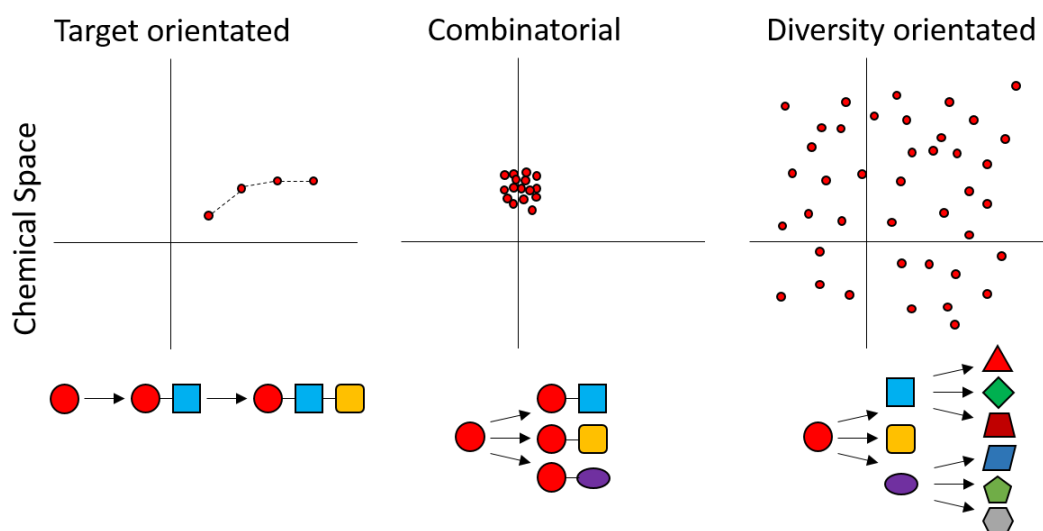
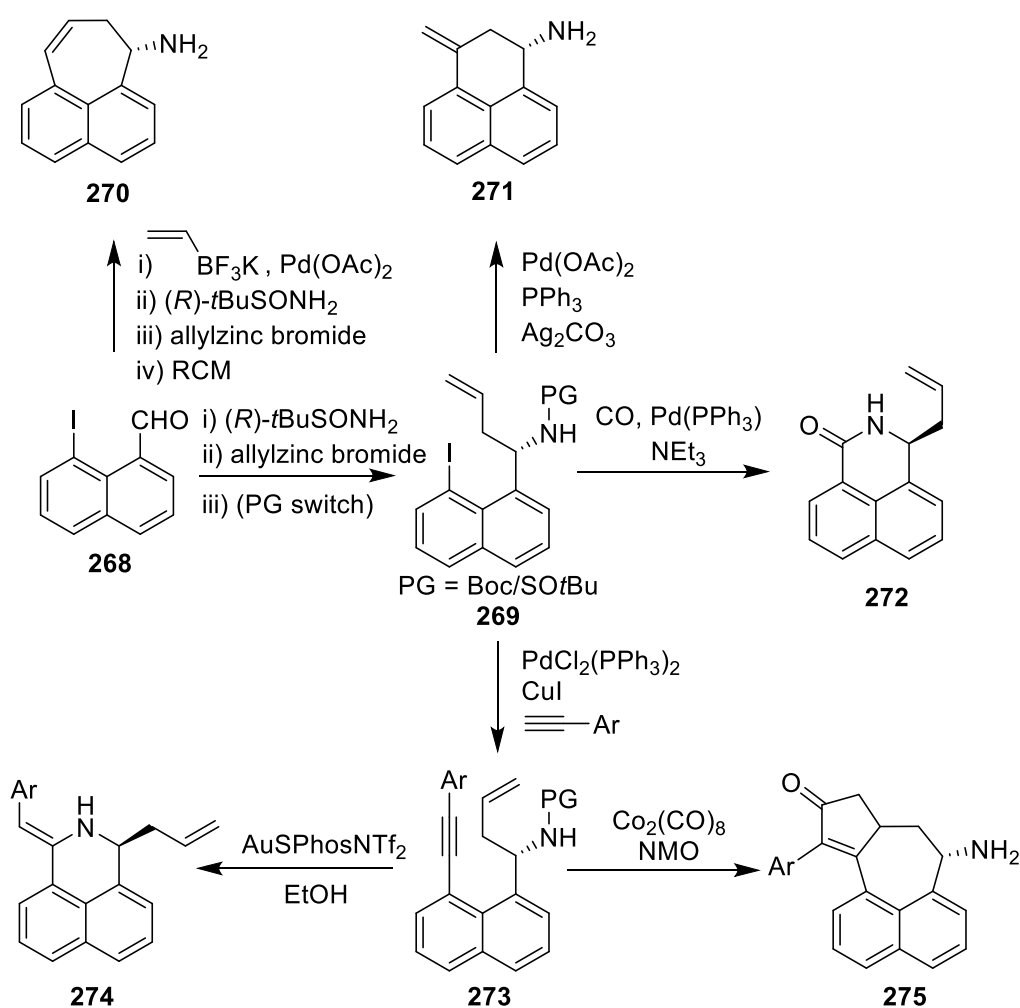


Figure 25 Representatin of TOS, Combinatorial Synthesis and DOS.

Figure 25 shows a schematic representation of how TOS, combinatorial chemistry and DOS exist in chemical space and how each is achieved. Target-oriented synthesis links one substrate to the next with a series of chemical reactions until it reaches its target; which may or may not have biological activity. This method explores a very low percentage of known chemical space. Combinatorial chemistry provides a library of related compounds using similar starting materials and procedures. It is capable of detailed mapping of a limited area of chemical space. The ultimate goal of DOS libraries is to reach as large a coverage of chemical space as possible. This would be achieved via a short series of diversity enabling reactions that allow rapid access to structurally varied entities. Whereas a TOS chemist would use retrosynthesis as a tool to achieve their goal, DOS chemists need to consider forward synthetic planning.⁹⁹

This is the means by which a reaction product can become a substrate in a subsequent transformation that is capable of drastically altering its molecular skeleton/properties. In an ideal DOS strategy using forward synthetic planning, each time a substrate is manipulated, a new reactive centre is added or uncovered. This reactive centre should then be capable of adding another iteration of diversity via increasing the number of stereochemical orientations, addition of appendages or through skeletal modifications.

A recent example of a DOS approach to library design was reported by Fustero *et al.* who were able to synthesise a range of diverse scaffolds from 8-iodonaphthalene-1-carbaldehyde **268** (Scheme 46, middle left) in 2-5 steps.¹⁰⁸



Scheme 46 Fustero *et al.* DOS approach to library design (product structures assume deprotection)

Seven membered amine **270** was directly synthesised from the iodoaldehyde via Suzuki cross coupling followed by one-pot condensation, allylation and ring closing metathesis. Forward synthetic planning was utilised to synthesise naphthalenes **269** and **273** as they both act as points of diversion for the synthetic route. Iodonaphthalene **269** was

synthesised via condensation with Ellman's sulfinamide and subsequent stereoselective allylation with allylzinc bromide. In some reactions a *tert*-butoxycarbonyl protecting group was desired, in which case the sulfinamide was cleaved with hydrochloric acid before installing the new protecting group. Iodonaphthalene **269** could perform an intramolecular Heck reaction to synthesise tricycle **271** or an aminocarbonylation to give lactam **272**. Sonogashira cross coupling led to alkyne **273** which could subsequently be exposed to hydroamination conditions to yield diene **274** or a Pauson-Khand reaction to give cyclopentenone **275**.

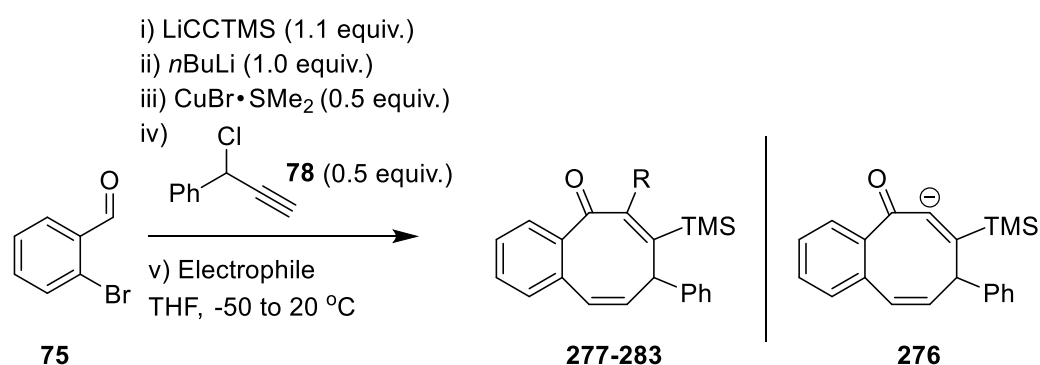
This short synthetic route delivers a range of varied and enantioenriched products containing five different cyclic molecular scaffolds, ring sizes between five and seven atoms, as well as bicycles, tricycles and tetracycles. The ultimate goal of a DOS project such as Fustero's would be its incorporation into a much larger and diverse library that can be used screen known chemical space against a range of targets.

2.2 Results and Discussion

Due to the swift formation of molecular complexity brought about by our Cannizzaro cascade, we decided that the parent (6*E*,9*Z*)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one core was an ideal candidate for a short Diversity Oriented Synthesis project. Initial areas of diversification could be based upon carbonyl chemistry, silyl group manipulation, ring expansions/contractions and the extension of the cascade to trap onto electrophilic species.

2.2.1 Utilisation of Cyclic Non-classical Enolate to Add Molecular Diversity

In the previous chapter we discovered that addition of deuterium oxide to quench the reaction, in place of aqueous ammonium chloride, led to the formation of **80b-d₁** (entry 1, Table 13). This was achieved via the electrophilic trapping of non-classical enolate **276**.



Entry	Electrophile	Equiv.	R	Product	Yield (%) ^a
1	D ₂ O	10	D	80b-d₁	64
2	MeI	10	Me	277	44
3	I ₂	5	I	278	58
4 ^b	CO _{2(s)}	30	CO ₂ H	279	49
5	Allyl bromide	5	CH ₂ CH=CH ₂	280	61
6	DMF	10	CHO	281	0
7	Ac ₂ O	10	COMe	282	0
8	Bu ₃ SnCl	2	SnBu ₃	283	0

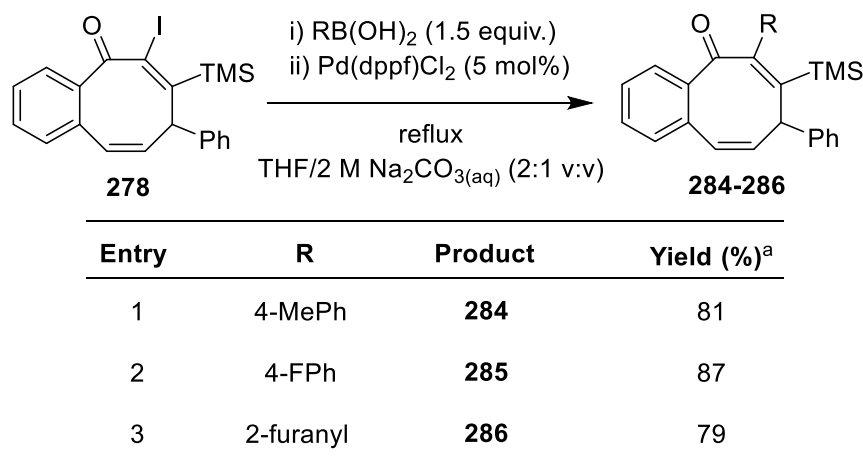
a) Isolated yield; b) solid CO₂ added directly to the reaction in small portions

Table 13 Electrophilic trapping of reactive non-classical enolate species

Expanding upon this, we were able to extend the 3-component reaction into a 4-component, one-pot, procedure. After the initial 3-component process the reactive anion was trapped with a variety of electrophiles before an aqueous quench (Table 13). In line

with our DOS approach we employed forward synthetic planning to choose electrophiles that, once installed, can act as reactive handles in further diversification steps. The only exception to this was iodomethane addition (entry 2), which was employed to show that direct alkylation was tolerated at this position, yielding methyl substituted **261** in 44% yield. Formation of iodo **278** (58%), carboxylic acid **279** (49%) and allyl **280** (61%) were all formed in good overall yields. The attempted quenches with *N,N*-dimethylformamide, acetic anhydride and tributyltin chloride were unsuccessful and after an aqueous work up, yielded mixtures of parent 8-ring **80** and its competing 6-membered analogue. As the anionic site on the 8-membered ring is already reasonably congested (adjacent to a TMS group), it is thought that larger electrophiles (entry 8) were not tolerated due to increased steric demand. However, it is possible that stannane **283** was initially formed before being hydrolysed, although it is unlikely an aqueous work up would have degraded aldehyde **281** or ketone **282**.

Iodo-substituted ring **278** was considered to be an ideal candidate for Suzuki-Miyaura¹⁰⁹ cross-coupling reactions to further add molecular diversity. A small study was carried out with aryl boronic acids to assess suitability for palladium-catalysed cross couplings (Table 14).



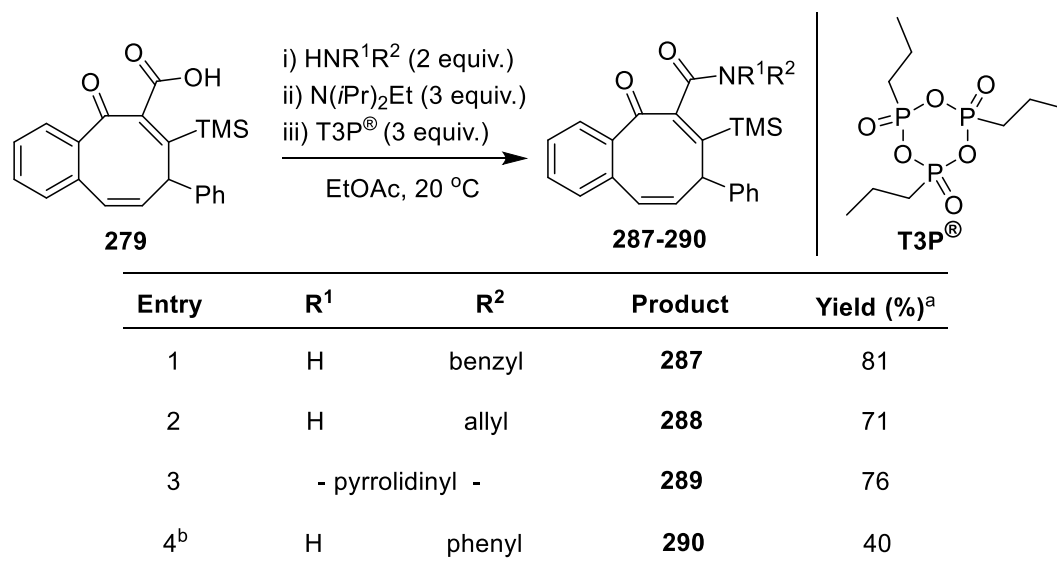
a) Isolated yield; b) 1.05 equiv. of boronic acid used

Table 14 Suzuki-Miyaura cross-coupling reactions of iodo 8-membered ring **278**

The reaction conditions included refluxing the substrate in a mixture of THF and 2 molar aqueous sodium carbonate solution (2:1 v:v) in the presence of the required boronic acid and Pd(dppf)Cl_2 catalyst.¹¹⁰ Aryl-substituted rings **284-286** were synthesised in good yields (79-87%) and showed tolerance of an electron rich furan moiety. The degassing of both

THF and aqueous sodium carbonate solution was required to achieve a high yielding cross-coupling procedure.

Carboxylic acid **279** was selected to undergo a second round of derivatisation to further increase our compound library. Amide couplings were a relatively simple way of adding diversity to this scaffold.



a) isolated yield; b) reaction carried out using aniline (1 equiv.), *N,N'*-dicyclohexylcarbodiimide (1 equiv.), hydroxybenzotriazole (1 equiv.), diisopropylethylamine (1.3 equiv.) in THF

Table 15 Amide coupling reactions of carboxylic acid **263**

Amide couplings were achieved using T3P[®] and Hünigs base (with one exception, entry 4), at room temperature in ethyl acetate. Cyclic phosphonic anhydride T3P[®] was chosen as the amide coupling reagent due to its ease of work up (both reagent and reaction by-product are water soluble) and relatively low cost. Table 15 shows a range of successful amide couplings in 40-81% yield. Primary and secondary amines (entry 3) were tolerated in high yields whilst aromatic amine **290** possessed a lower yield (entry 4). Direct comparison may not be possible due to the different conditions (amide **290** was synthesised before T3P[®] became available to us), but a lower yield may be expected due to the reduced nucleophilicity of the aniline nitrogen. The synthesis of allyl amide **288** demonstrated that with the correct choice of substrate, another reactive handle could be installed for a third round of derivatisation.

An X-ray crystal analysis of benzyl amide **287** (Figure 26) confirmed amide formation and showed a weak¹¹¹ intramolecular hydrogen bond (2.3 Å) between the amide proton and ketone carbonyl.

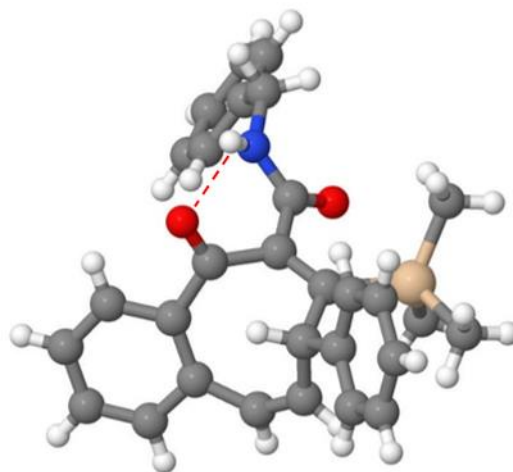
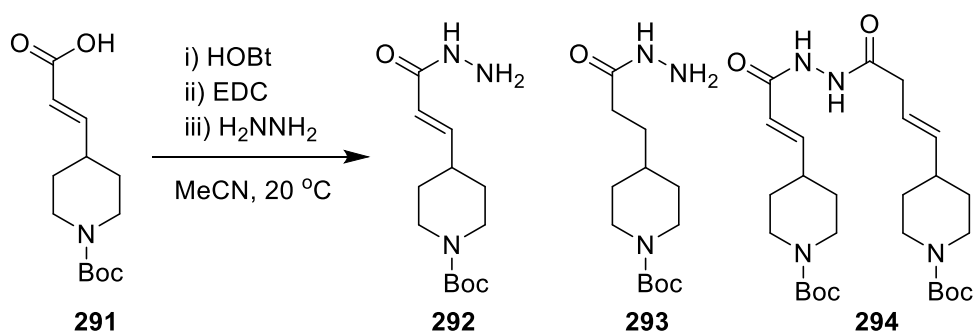


Figure 26 X-ray crystal structure of benzyl amide **287** showing weak hydrogen-bond interaction

Work by Zhang *et al.* identified an efficient way of adding hydrazine to α,β -unsaturated carboxylic acids.¹¹² Initially Zhang found clean formation of the desired hydrazide (**292**) to be difficult due to the formation of *bis*-coupled hydrazide dimer **294** and reduced derivatives such as **293** (Scheme 47).

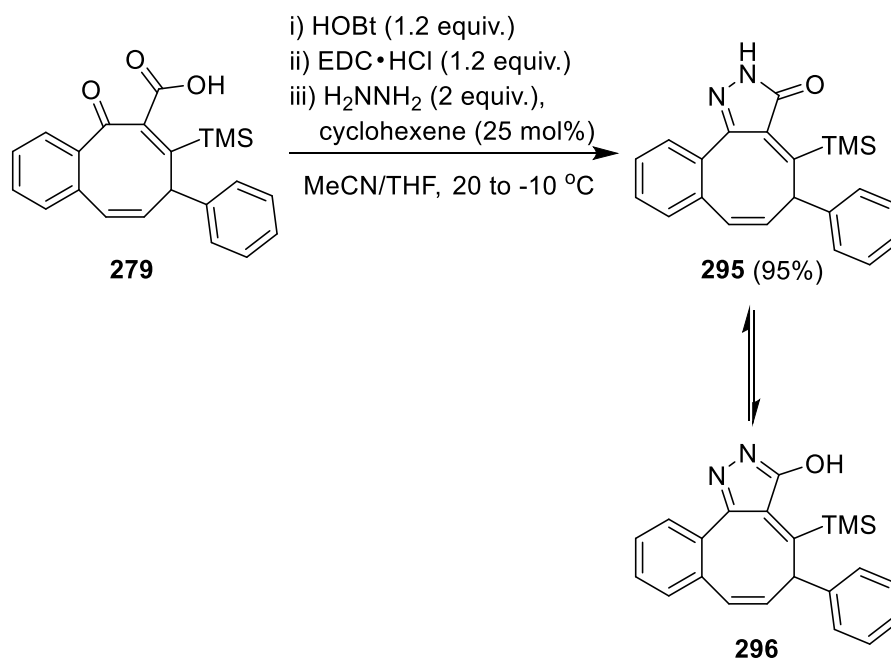


Scheme 47 Zhang *et al.* synthesis of hydrazide **292**

It was proposed that small amounts of diimide present in commercial hydrazine can act to reduce double bonds in the α,β -position. To alleviate this problem, cyclohexene was added to the hydrazine solution prior to reaction to scavenge any residual diimide.¹¹³ It is believed that cyclohexene is not active in the subsequent amine coupling and is removed *in vacuo* during the work-up. Dimer formation was controlled by careful consideration of the reaction procedure, namely the inverse addition of the pre-formed reactive acid intermediate to a solution containing hydrazine.

Zhang's procedure was adapted to couple 8-membered carboxylic acid **279** with hydrazine to form pyrazolone **295** in excellent yield (Scheme 48). It seems that amide formation and

subsequent condensation both run to completion as there was no evidence to suggest the existence of the intermediate hydrazone in crude ^1H NMR spectrum.



Scheme 48 Amide coupling of carboxylic acid **279** with hydrazine, to form pyrazolone **295**

Proton NMR spectroscopy showed that in a solution of deuterated chloroform the amide coupling product existed between two interchanging species. X-ray crystal analysis showed that in the solid state the product exists as pyrazolone **295** (Figure 27). Tautomerisation of pyrazolones is a well-studied phenomenon,¹¹⁴ it is thought that exchange between species **295/296** is responsible for the observed exchange phenomenon in the NMR spectra.

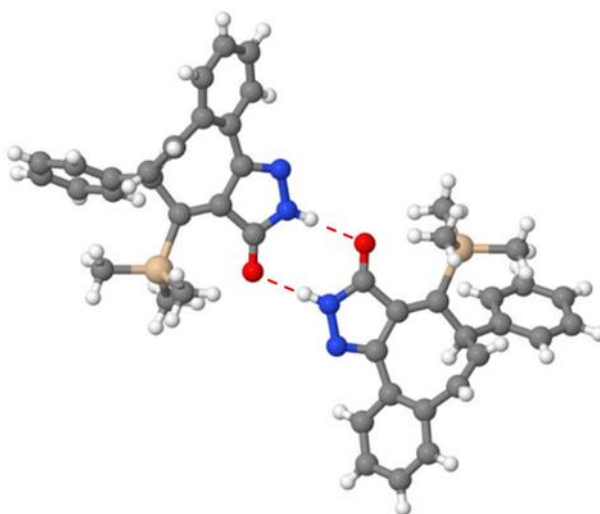
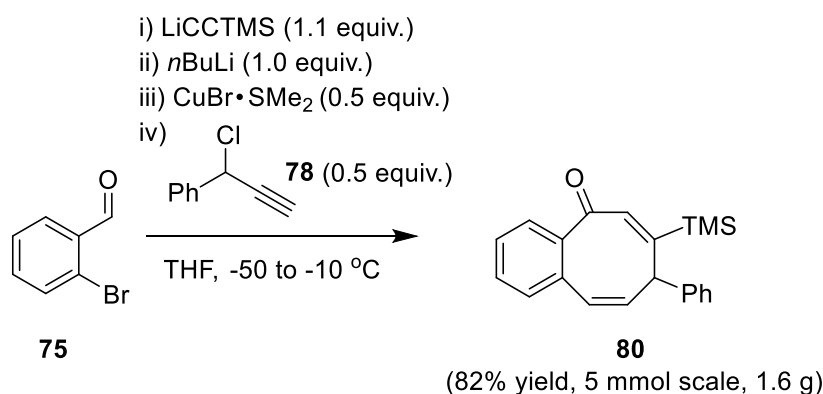


Figure 27 X-ray crystal structure of pyrazolone **295** showing hydrogen-bond interactions

It is evident from X-ray analysis that intermolecular hydrogen bonded dimers are formed with bond lengths of 2.0 Å. Hydrogen bonds of this length are considered to be of moderate strength and consist of mainly electrostatic interactions.¹¹¹ It is also noteworthy that a bicyclic axis has been formed during this step, with enough steric mass to slow exchange, atropisomerism could be observed.

2.2.2 Diversification of (6*E*,9*Z*)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one and (6*E*,9*Z*)-7-(*tert*-butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one

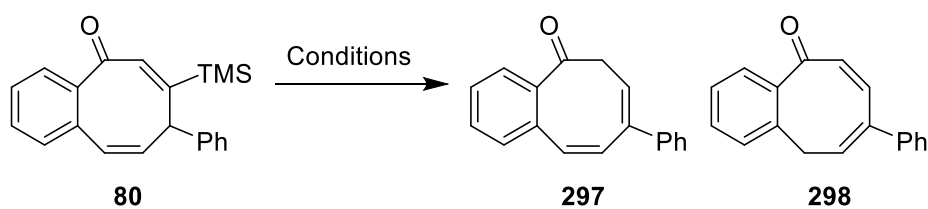
Diversification of the parent scaffold (6*E*,9*Z*)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one **80** was sought, meaning a larger scale synthesis was required. The reaction was scaled up to 5 mmol, where the desired ring system could be made in gram quantities (Scheme 49).



Scheme 49 Synthesis of parent 8-membered ring **80** in gram quantities

The yield increased from 70% (0.8 mmol scale) to 82% (5 mmol scale) on scale-up. This moderate increase in yield is thought to originate from a more efficient isolation. On larger scale, crystallisation of the crude residue yielded an initial crop of clean product, allowing a much smaller/efficient flash-column to recover a second crop.

In order to remove the trimethylsilyl group from silyl-substituted ring **80**, it was subjected to the desilylating conditions shown in Table 16. Fluoride and acidic conditions both successfully desilylated the molecule, but interestingly they both led to different and unexpected products. It seems that on removal of the trimethylsilyl group, alkene isomerisation occurs, but the nature of the isomerisation depends on the desilylation method.



Entry	Conditions	Product	Yield (%) ^a
1	TBAF (2 equiv.) THF, 0 °C	297	84
2	TFA (neat), 20 °C	298	92

a) Isolated yield

Table 16 Desilylation of parent ring system **80**

Exposure to tetrabutylammonium fluoride (TBAF) solution produced desilylated diene **297** in 84% yield. Stirring in neat trifluoroacetic acid (TFA) led to the formation of enone **298** in 92% yield. Loss of the trimethylsilyl ^1H NMR signal (~ 0.0 ppm) and the appearance of a methylene unit in ^{13}C NMR (dept 90 analysis, 45.3 ppm vs. 46.3 ppm) led to the proposed isomeric structures **297/298**, but it was initially unclear which set of conditions led to each isomer. Heteronuclear multiple bond correlation NMR experiments revealed that the methylene unit derived from the TBAF reaction showed a strong correlation to the carbonyl at peak at ~ 195 ppm, suggesting structure **297**. Examination of the carbonyl stretching frequencies (1720 vs. 1580 cm^{-1}) via infrared analysis was also found to be diagnostic in the identification of the isomers. The product derived from entry 2 (TFA) has a very low carbonyl stretch of 1580 cm^{-1} which is in accord with similar cyclic $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyls.¹¹⁵

It is proposed that diene **297** is formed via the process shown in Figure 28. A fluoride anion adds into the silicon atom to form pentavalent silicon intermediate¹¹⁶ **299** before fluorosilane cleavage gives anionic ring **300**. Tautomerisation to give 1,3-diene **301** is favoured as the anionic charge in this species is in conjugation with both aromatic rings, leading to enhanced stabilisation. Tautomerisation is also aided by the acidity of the migrating proton in **300** which is both benzylic and doubly allylic. An aqueous work-up then furnishes diene **297**.

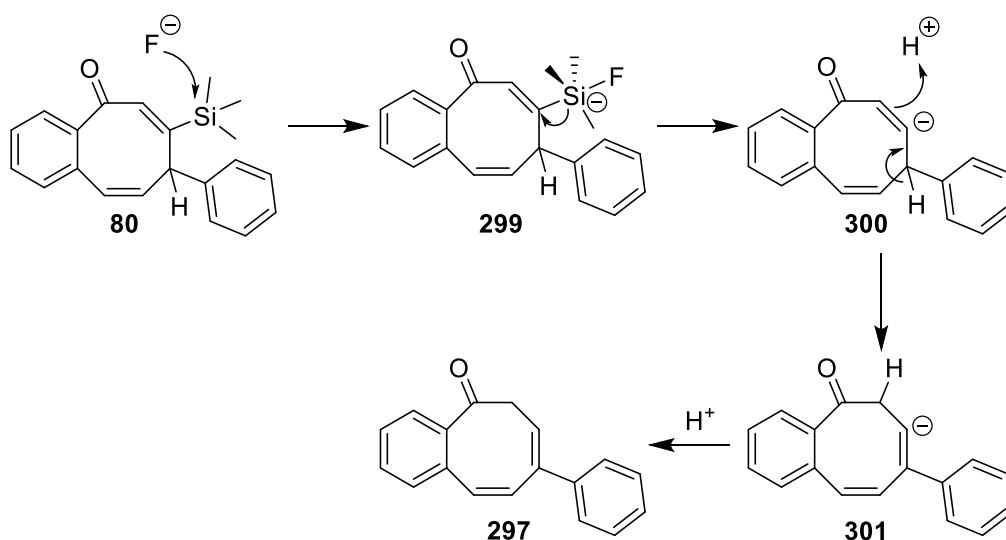


Figure 28 Proposed mechanism for the formation of diene **297**

In contrast to this, a proposed mechanism for the formation of $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **298** under acidic conditions is shown in Figure 29. It is thought that protonation of the carbonyl in neat TFA promotes tautomerisation to enol **303** via migration of the activated benzylic and doubly allylic proton.

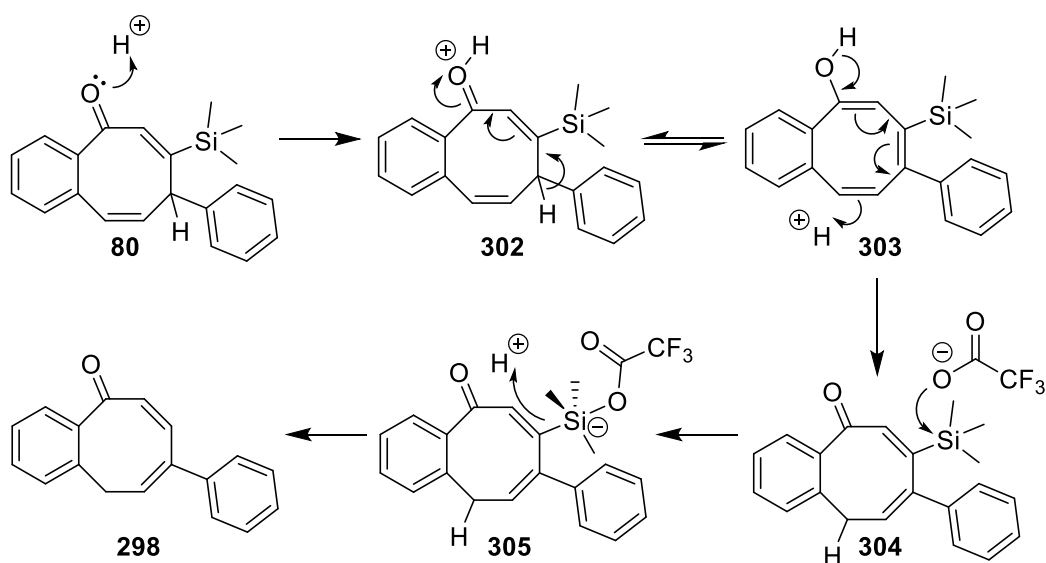
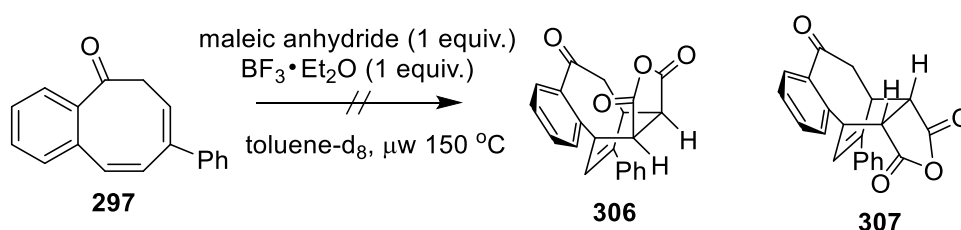


Figure 29 Proposed mechanism for the formation of $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **282**

Even though benzocyclooctatetraenes are known,¹¹⁷ it is proposed that the anti-aromaticity (12 π -electrons) of fused-ring **303** will lead to instability and reversible tautomerisation. If enol **303** tautomerises to enone **304** through its extended π -system, it may drop into an energy well. This is as the migrating proton is less activated in its new position. Carboxylate addition into the silyl group of enone **304** would lead to anion **305**

and subsequent protonation into $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **298**. As this reaction was carried out in neat TFA, it is considered that anion **305** would be protonated instantaneously as the silicon group eliminates, making isomerisation to the more stable **301** unnecessary. It was also found that if a sample of diene **297** was subjected to neat TFA, isomerisation did not occur and starting material was recovered. Further studies, particularly DFT computational approaches, will be necessary to fully validate the proposals of Figure 28 and Figure 29.

With diene **297** in hand, our thoughts moved toward the potential use of Diels-Alder reactions to add further molecular complexity. Scheme 50 shows an attempted Diels-Alder reaction between maleic anhydride and diene **297** using boron trifluoride diethyl etherate as a Lewis acid.



Scheme 50 Attempted Diels-Alder reaction between diene **297** and maleic anhydride

The formation of a Diels-Alder adduct such as **306/307** was not observed, but the complete consumption of the starting material into an unknown product was successful. Conversely, crude ^1H NMR analysis also showed that maleic anhydride had not been consumed. As mass spectroscopy suggested the unknown product had identical mass to the starting material, a rearrangement was considered. Photochemical 4π electrocyclisations of cyclooctadienes are known to form *cis*-fused cyclobutene systems¹¹⁸ (**309**, Figure 30). The *cis*-fused product is the photochemically allowed, disrotatory electrocycloisatation product.¹¹⁹

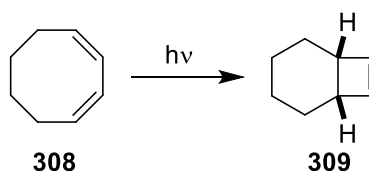
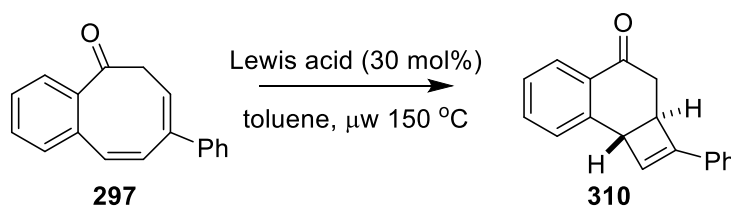


Figure 30 4π electrocycloisatation of cyclooctadiene

With a similar thermally promoted, conrotatory electrocycloisatation a distinct possibility under our reactions conditions, further experimentation was carried out (Table 17).



Entry	Lewis acid	Yield (%) ^a
1	BF ₃ •Et ₂ O	82
2	FeCl ₃	trace ^b
3	-	0

a) Isolated yield; b) Some evidence of formation in crude ¹H NMR

Table 17 Formation of fused cyclobutene **310**

It was found that microwave irradiation at 150 °C for one hour, in the presence of 30 mol% boron trifluoride diethyl etherate, could furnish cyclobutene **295** as a single stereoisomer in 82% yield. A control experiment without the addition of a Lewis acid led to recovery of starting material (entry 3), whilst using iron(III) chloride revealed traces of cyclobutene **310** (via crude ¹H NMR analysis, large amounts of polymeric aromatic by-products were also present). All of our analytical results, including 2D NMR techniques, were consistent with the formation of cyclobutene **310**. Stereochemical assignment however took a little more thought.

It is proposed that *trans*-cyclobutene **310** is synthesised from **297** and is based on the assumption that the enclosed microwave is 'dark' and therefore any photochemical electrocyclisation pathway is discounted. If the transformation is in fact a 4π electrocyclisation, the two possible products from the diene HOMO are shown in Figure 31. The lower energy *cis,cis*-8-membered ring **311** could thermally cyclise in a conrotatory manner to give *trans*-**310**, whereas the *cis,trans*-8-membered ring **312** could thermally cyclise to *cis*-**310**. Although the existence of *cis,trans*-1,3-cyclooctadiene is known,¹²⁰ the possibility of alkene isomerisation between dienes **311** and **312** is thought to be highly disfavoured as the presence of seven consecutive sp² centres would make *cis,trans*-diene **312** an unlikely structure.

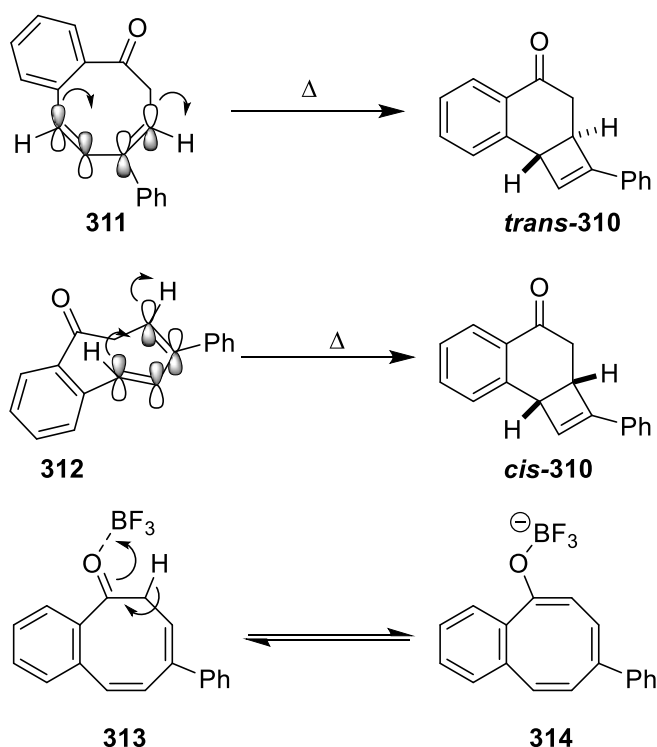


Figure 31 4π electrocyclisations to form *cis/trans*-**310**

It is evident from Table 17 that the presence of a Lewis acid is crucial to the formation of the tricyclic ring system. As the diene is linked via conjugation to the carbonyl, any oxygen coordination to a Lewis acid would have an electronic effect on the diene and its reactivity. The presence of the Lewis acid could act to enolise the 8-membered ring, forming an anti-aromatic system (**314**). In turn, the instability that arises from this anti-aromaticity could encourage the proposed electrocyclisation.

There is of course the possibility that the formation of cyclobutene **310** is not an electrocyclisation, in which case the stereochemical outcome would be harder to predict. A stepwise mechanism (Figure 32) includes the formation of an ionic intermediate such as boronate **315**. This is considered unlikely as in order to form the carbocation, the aromaticity of the benzene system is disturbed, losing $\sim 36 \text{ kcal mol}^{-1}$ of stabilisation energy.¹²¹ As carbocation **315** is relatively flat, (all but 2 carbons are sp^2 hybridised) one may also expect competing formation of both stereoisomers, whereas we observe the formation of exclusively one stereoisomer.

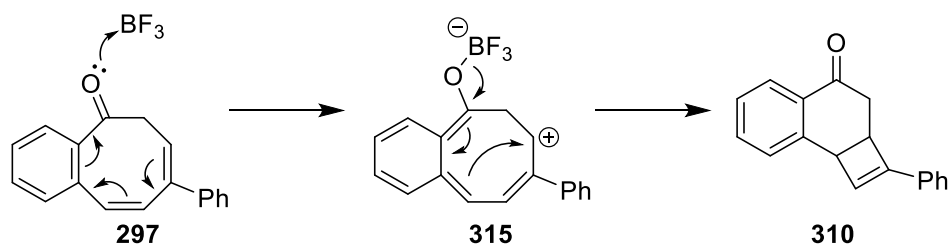
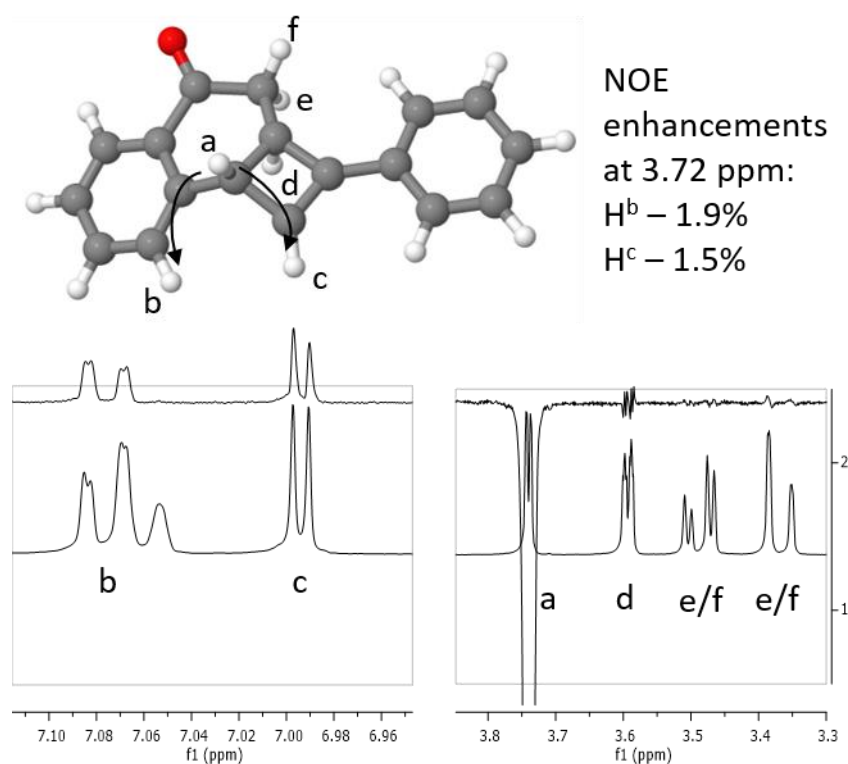


Figure 32 Ionic mechanism forming cyclobutene **310**

Although *trans*-fused-cyclobutenes are uncommon, there is literature precedent.¹²² Structurally similar, saturated, *trans*-fused-cyclobutanes are a lot more common.^{123,124} Nuclear Overhauser effect ¹H NMR analysis also supports the formation of *trans*-**310** (Figure 33). Irradiation of H^a (at 3.72 ppm) showed NOE enhancements of 1.9 and 1.5% for protons H^b and H^c, respectively, without enhancement of H^d.



a) 'Noisy' baseline at ~3.6 ppm is due to its proximity (ppm) to the irradiated signal and is not thought to be an NOE enhancement.

Figure 33 DFT model of *trans*-**310** (B3LYP/6-31G (d,p)) showing proposed NOE enhancements.

If H^a and H^d were on the same face of the molecule, one would expect an NOE enhancement in the above experiment. DFT analysis (B3LYP/6-31g (d, p)) predicts that in *cis*-**310**, H^a – H^d would be 2.4 Å apart, which is significantly less than the predicted H^a – H^b distance of 3.0 Å. Therefore, it is unlikely that H^b would see an NOE enhancement without H^d.

Scheme 51 Attempted synthesis of cyclobutene **316**

80 R = TMS
127 R = *t*Bu

NH₂·HCl (20 equiv.)
 NaOAc (20 equiv.)
 EtOH, reflux

317 R = TMS (83%)
E/Z 1.7:1
318 R = *t*Bu (98%)
E/Z 1.5:1

Scheme 52 Synthesis of oximes **317-318**

It is thought that in a cyclic *E*-oxime, the oxygen interacts with the α -CH in such a way as to partially occupy the C-H σ^* orbital. This acts to weaken the bond and increase its

polarity, giving the carbon a slightly negative charge and the hydrogen a slightly positive charge.

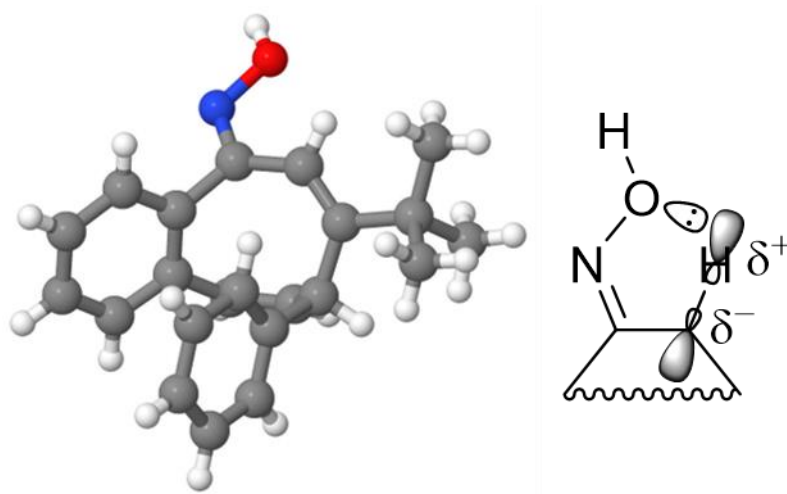


Figure 34 X-ray crystal structure of oxime **E-318** and interaction of oxime with α -CH

This has a significant effect on the ^1H and ^{13}C NMR spectrum of the α -CH, the proton becomes less shielded and shifts downfield whilst the carbon has increased shielding and moves upfield. This effect is evident in the NMR spectra of oxime **318** (Figure 35); the major isomer α -CH has a proton peak at 7.35 ppm and the corresponding carbon at 118 ppm. The minor isomer α -CH has a higher field proton signal (6.75 ppm) and a lower field carbon signal (124 ppm), which is consistent with the stereochemical assignment in Scheme 52.

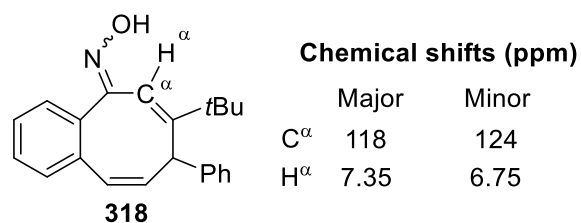
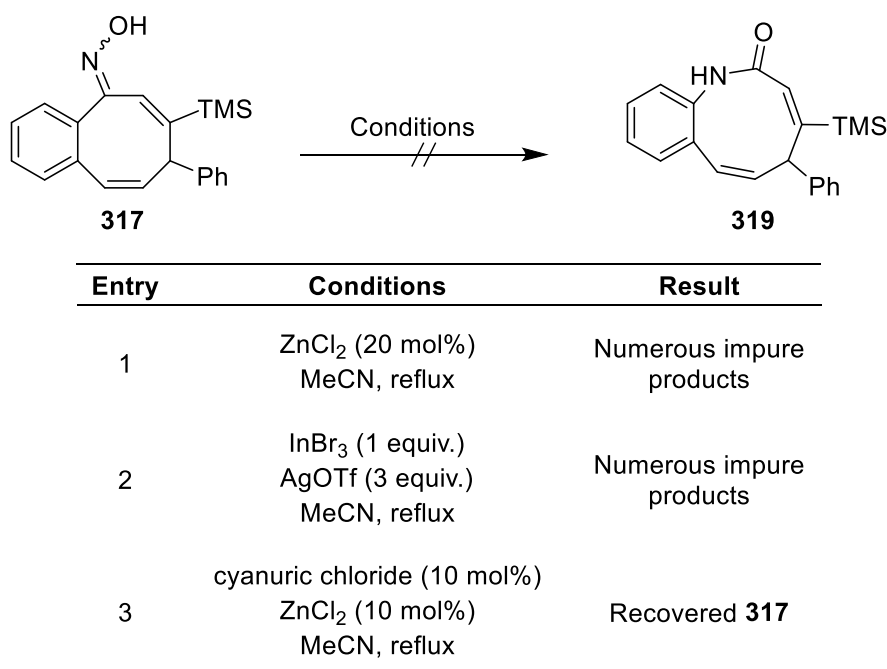
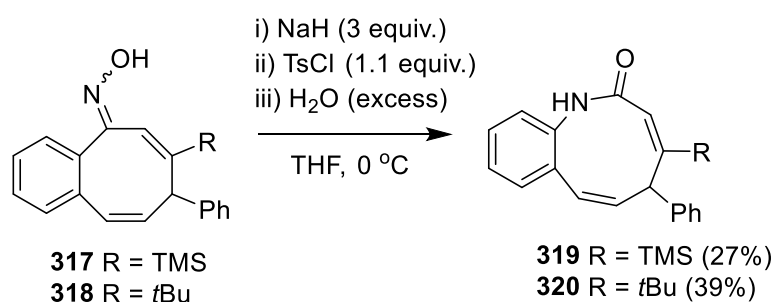


Figure 35 Proton and carbon NMR shifts for the α -CH in oxime **318**

Ring expansion of oxime **317** via a Beckmann rearrangement was explored, with results shown in (Table 18). Literature conditions,^{127,128} including the use of Lewis acids and cyanuric chloride, failed to cleanly promote the desired rearrangement to lactam **319**.

**Table 18** Attempted synthesis of lactam **319**

Such rearrangements generating medium sized rings are known to be challenging,¹²⁹ it was feared that the trialled conditions had failed to promote the initial expulsion of water from the oxime. As Beckmann rearrangements from tosylated oximes are known in the literature,¹³⁰ tosylation of oximes **317-318** was attempted in order to introduce a more favourable leaving group. Gratifyingly, it was found that upon tosylation and subsequent aqueous work up, the synthesis of 9-membered lactams **319-320** was realised.

**Scheme 53** Synthesis of lactams **319-320** under tosylating conditions

It is thought that tosylation of the oxime causes spontaneous aryl migration and tosylate expulsion. Aqueous work up then hydrolyses the intermediate imine into an amide. The regioselectivity of the rearrangement was confirmed via X-ray analysis of silyl lactam **319** (Figure 36). Although the yields of the rearrangements themselves are moderate (27 and 39%), the overall 3-step processes from 2-bromobenzaldehyde, (**319**-18% **320**-23%) are

better than other literature examples of 9-membered lactam syntheses (7-steps, 24% and 6-steps, 43%).¹³¹

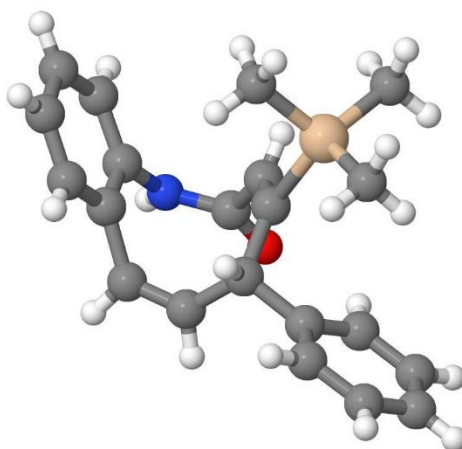


Figure 36 X-ray crystal structure of lactam **319**

It has been suggested that *anti*-Beckmann rearrangements are favoured over their *syn* counterparts.¹³⁰ This is due to the advantageous molecular orbital alignment that leads to N–O bond cleavage. Computational mechanistic analysis¹³² suggests that N–O bond cleavage and bond migration occur simultaneously. One way to describe this this would be to consider the N–O antibonding orbital being filled with the electron density from the migrating bond. As shown in Figure 37, this process has a much better orbital alignment for an *anti*-Beckmann rearrangement. The observed moderate yields in Scheme 53 could in part be due to the mixture of *E/Z* oximes utilised as starting materials (**317** 1.7:1, **318** 1.5:1). The favoured *E*-oximes would be expected to lead to the observed lactams **319-320**, whilst the *Z*-oximes could have reacted to form an isomeric lactam, if the Beckmann rearrangement occurred at all. Computational analysis has also shown that aryl migration is favoured over alkyl migration (Ph TS=+16 kcal mol⁻¹ vs. Me TS=+19.2 kcal mol⁻¹)¹³² so some energetic differentiation between the formation of isomeric lactams would be expected.

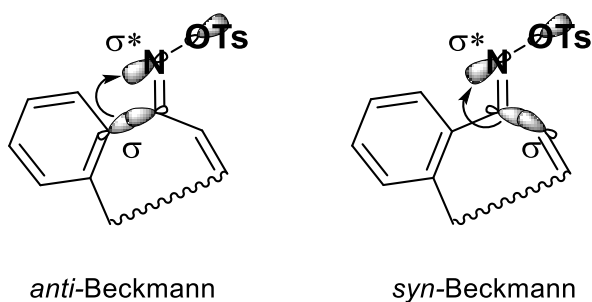


Figure 37 Orbital overlap in *anti*- vs. *syn*-Beckmann rearrangements

Grignard additions into 8-membered enones **80** and **127** were explored with the use of commercially available methylmagnesium bromide and allylmagnesium bromide (Table 19). All these Grignard reactions were high yielding with both substrates showing comparable reactivity, there was a slight bias to the addition of methylmagnesium bromide, assumedly due to the size of the nucleophile.

80 $R^1 = \text{TMS}$
127 $R^1 = t\text{Bu}$

321-324

Entry	R^1	R^2	Product	<i>syn:anti</i> ^b	Yield (%) ^a
1	TMS	Me	321	1:7	97
2	TMS	CH_2CHCH_2	322	1:3	82
3	<i>t</i> Bu	Me	323	>40:1	95
4	<i>t</i> Bu	CH_2CHCH_2	324	>40:1	88

a) Isolated yield; b) Ascertained via ^1H NMR analysis, diastereomeric assignment relates to the orientation of the OH in respect to the phenyl group

Table 19 Grignard additions into enones **80** and **127**

The diastereoselectivity of the addition to the different substrates however, was markedly different. Silyl-substituted **80** produced methyl and allyl Grignard adducts in 1:7 and 1:3 *syn:anti* ratios respectively, whereas *tert*-butyl **127** produced only the *syn*-diastereoisomers (diastereomeric assignment relates to the orientation of the OH in respect to the phenyl group in all cases). The substrates differ by a single atom (silicon vs. carbon) yet the favoured diastereoisomer is reversed and the magnitude of selectivity is greatly increased. The favoured diastereoisomers of methyl Grignard additions were confirmed via X-ray crystal analysis of Grignard adducts **321** and **323** (Figure 38). The ^1H NMR chemical shift of the CHPh proton is also indicative of the diastereoisomer formed, with a higher frequency signal (~ 4.6 ppm) indicating *anti*-diastereoisomer formation (vs. ~ 4.4 ppm for the equivalent *syn*-signal). On that basis, the diastereoselectivities of allyl Grignard additions were assigned, which also showed drastic selectivity differences.

Conformational bias in the starting enones (**80** and **127**) is the source of this diastereoselective reversal. X-ray crystal structures of the starting materials (Figure 38) show that in TMS substituted **80**, the phenyl group is pseudo equatorial. This places the CHPh proton endocyclic, presumably to minimise transannular strain. In the X-ray

structure of *tert*-butyl **127**, the shorter =C–CMe₃ vs. =C–SiMe₃ bond (1.53 compared to 1.90 Å) leads to significant increase in allylic A_{1,2} strain,¹³³ destabilising the pseudo equatorial phenyl placement seen in **80**. A subsequent conformational change results in endocyclic placement of the phenyl group, directly obscuring one of the diastereotopic faces of the carbonyl. Figure 38 shows that for *tert*-butyl **127**, blocking of the Burgi-Dunitz¹³⁴ approach angle leads to Grignard additions occurring on the bottom face only, forming almost exclusively *syn*-**323**. Both diastereofaces of TMS substituted **80** are more open so *anti* selectivity is not as good, leading to **321** in a 1:7 *syn:anti* ratio.

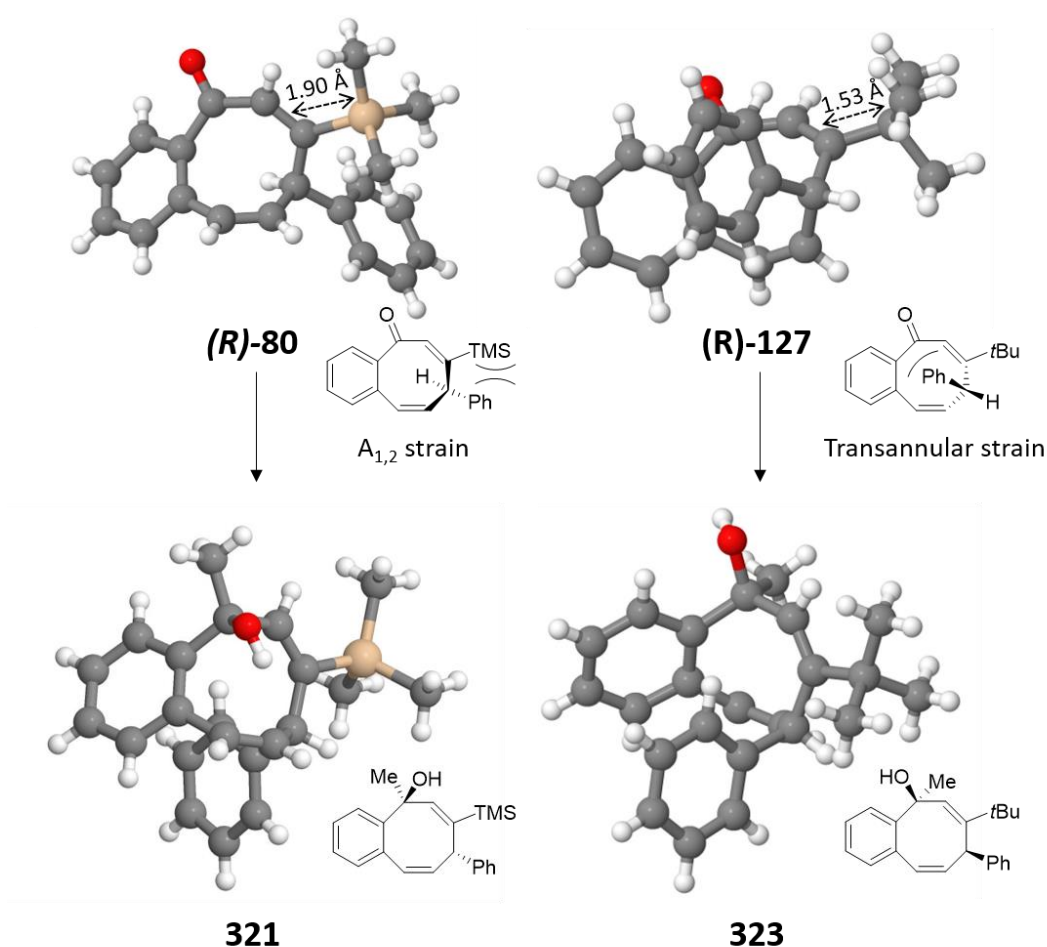
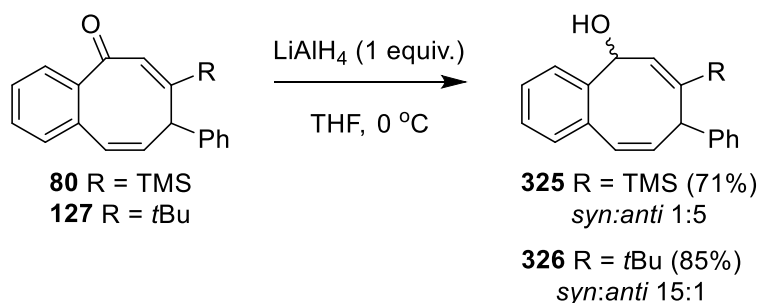


Figure 38 X-ray crystal structures of **80**, **127**, **321** and **323**

In a forward synthetic plan that aims to generate diversity, the ability to select reaction stereoselectivity based upon the induction of A_{1,2} strain is synthetically useful. In further derivatisation steps, allyl groups from Grignard reactions can be exploited along with the alcohol groups formed during the addition.

Reduction of ketones **80** and **127** to their corresponding alcohols was also carried out, as shown in Scheme 54.

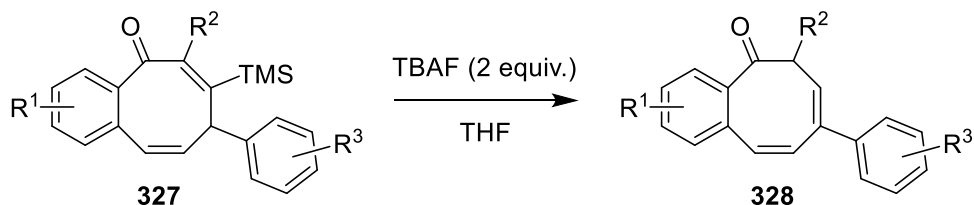


Scheme 54 Formation of alcohols **325-326**. Diastereomeric ratios ascertained via ^1H NMR analysis, diastereomeric assignment relates to the orientation of the OH in respect to the phenyl group

Lithium aluminium hydride was used to synthesise TMS substituted **325** and *tert*-butyl substituted **326** in 71 and 85% yields respectively, both were synthesised as a mixture of *syn* and *anti* diastereoisomers. Following the pattern of the Grignard additions (**321-324**) and the known confirmations of the starting ketones it is thought that the major isomer of **325** is the *anti*-isomer whilst alcohol **326** favours *syn* addition (diastereomeric assignment relates to the orientation of the OH in respect to the phenyl group in all cases).

2.2.3 Key Results from Biological Screening Assays

A key aspect involved in DOS projects is the screening of novel compounds against a variety of therapeutic targets. An attractive option open to us in this regard, was the use of the Lilly Open Innovation Drug Discovery (OIDD) program.¹³⁵ This screening program is continually evolving with different therapeutic targets being added or removed with the development of Lilly's interests. A small library of 8-membered rings was sent to OIDD to assess possible biological activity against a range of targets. To make our compound library fit with OIDD regulations, silicon groups were removed (Scheme 55).



Scheme 55 Desilylation of OIDD substrates

As less than 5 mg of each substrate was required, reactions were carried out in a suitably small scale. For this reason, it was concluded that meaningful yield calculations could not

be extracted. The synthesised substrates for Lilly OIDD screening are shown in (Figure 39). Amide **289** resisted tetrabutylammonium fluoride promoted desilylation so screening was carried out on the original TMS derivative.

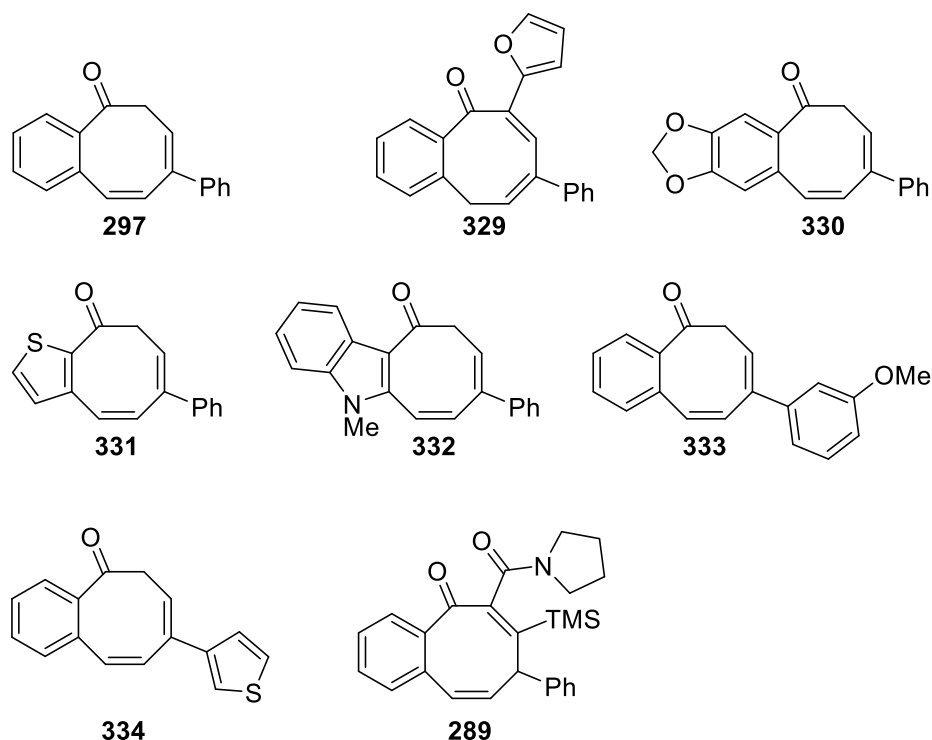


Figure 39 Substrates screened in Lilly OIDD program

The most promising results obtained from OIDD screening showed that a range of compounds were active in the stimulation of Glucagon-like Peptide 1 (GLP-1) secretion. This peptide, produced in the small intestine, stimulates the secretion of insulin from pancreatic islets.¹³⁶ Global occurrence of type II diabetes is swiftly increasing as lifestyle habits have evolved to include more sugar-rich foods, a greater caloric consumption and less exercise.¹³⁷ The secretion of GLP-1 is decreased as a result of type II diabetes, making stimulation of its secretion a possible target for novel therapeutic treatments. Table 20 shows the results gained from OIDD screening for GLP-1 secretion stimulation.

Entry	Substrate	GLP-1 Secretion (%Stim. at 20 μ mol) ^a	EC ₅₀ (μ mol) ^a
1	297	48	16.4
2	329	44	24.8
3	330	42	20.8
4	331	112	10.7
5	332	127	2.9
6	333	73	12.3
7	334	148	5.7
8	289	94	12.2

a) Analysis carried out using mSTC-1 cell line taken from a mouse intestinal tumour.

Table 20 GLP-1 stimulation results obtained from Lilly OIDD screening

As the substrates in entries 1 to 8 were considered to be ‘active hits’ in the initial 20 μ mol screen, they were carried forward to a secondary screen consisting of a concentration response curve. From this secondary screen it was then possible to calculate the effective concentration (EC₅₀) of each substrate. The EC₅₀ is the dose required to attain 50% of its maximum effectiveness. In this case, it is the concentration that elicits 50% of the maximum stimulation for each substrate. We can see that indole **332** (entry 5) and thiophene **334** (entry 7) were the most successful substrates in this study giving 127 and 148% stimulation at 20 μ mol with effective concentrations of 2.9 and 5.7 μ mol respectively. In general, it can be seen that substrates containing a thiophene or nitrogen containing ring are more successful GLP-1 secretion agonists.

Screening of these substrates with human colorectal cells (hNCI-H716 cell line) showed reduced effectiveness to the point where EC₅₀ values were all above 40 μ mol. To be considered for further GLP-1 screening, the OIDD program targeted substrates with an EC₅₀ below 1 μ mol. Even though the Lilly OIDD program has completed its screening of this library against GLP-1 stimulation, further screens are still on-going to find hits in different therapeutic areas.

A second compound library was assessed for possible antimicrobial activity by the Community for Open Antimicrobial Drug Discovery (CO-ADD). In a search for novel antibiotics, CO-ADD aims to combat drug-resistant infections by collaborating with synthetic chemists to screen novel compounds for antimicrobial activity.¹³⁸ Figure 40 shows the small library screened for antimicrobial activity by CO-ADD.

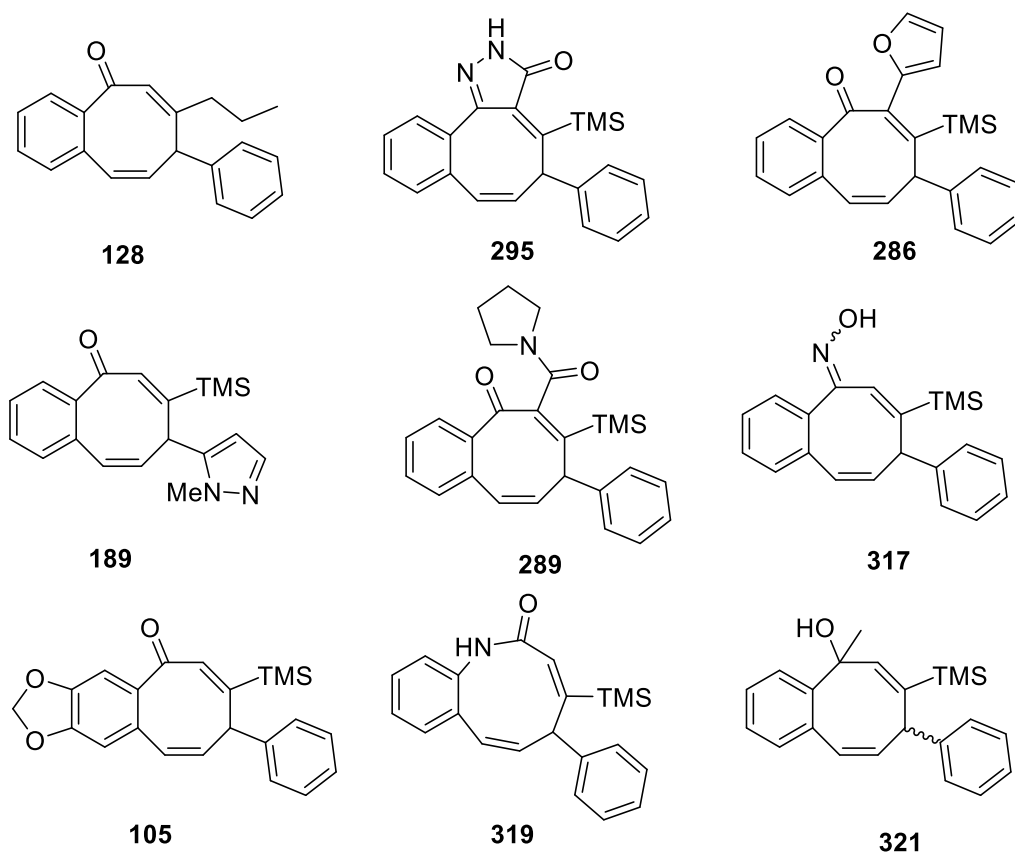


Figure 40 Small compound library supplied to CO-ADD for antimicrobial screening

The substrates in Figure 40 were all screened against the growth of five bacterial strains: *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*; and two fungi: *Candida albicans* and *Cryptococcus neoformans*. It was found that furan **286** inhibited the growth of *A. baumannii* by 50%, which the CO-ADD considered to be a successful 'hit'. The bacteria *A. baumannii* is multidrug resistant and is frequently found in hospital environments. It is most commonly attributed to ventilator associated pneumonia and bloodstream infections.¹³⁹ In all other cases, CO-ADD classified the substrates as inactive in all screens.

2.3 Conclusions

Addition of a small electrophile at the end of the cascade sequence extended the original three-component, one-pot, cascade into a four-component reaction capable of the synthesis of diverse 8-membered rings. Forward synthetic planning was employed with careful consideration of the chosen electrophile ensuring the installation of new reactive handles. The exploitation of these reactive handles led to a range of Suzuki-Miyaura cross couplings as well as amide couplings.

It was found that representative 8-membered ring scaffolds could be used as starting materials for further transformations aimed towards a DOS project. Ring-contractions, ring-expansions, oxime formations, desilylations, carbonyl reductions and stereoselective Grignard additions were all successfully accomplished.

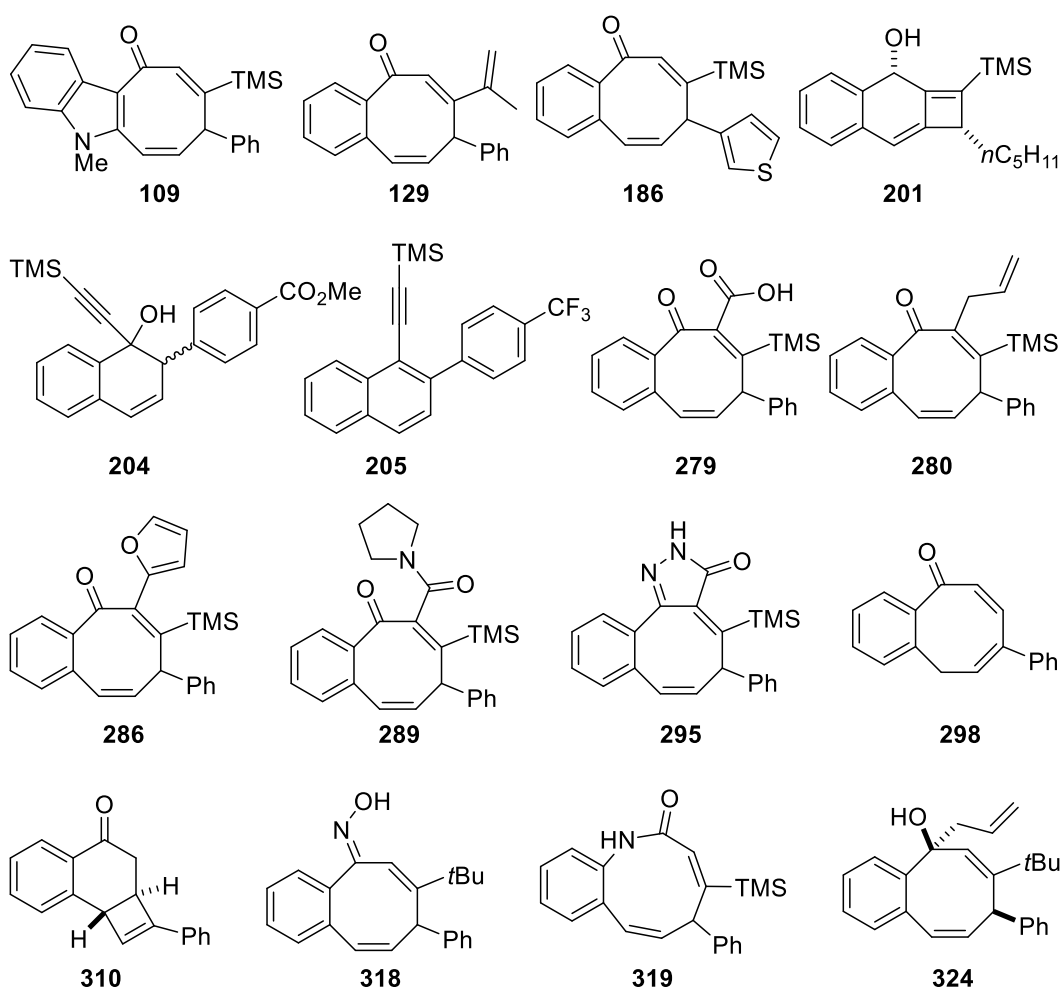


Figure 41 Representative sample of diverse molecular library

Using our cascade procedure, we have been able to develop products containing a wide range of molecular diversity. In a maximum of three-steps, from commercial bromo-

aldehydes, we have been able to develop a library of compounds with a representative sample shown in Figure 41 .

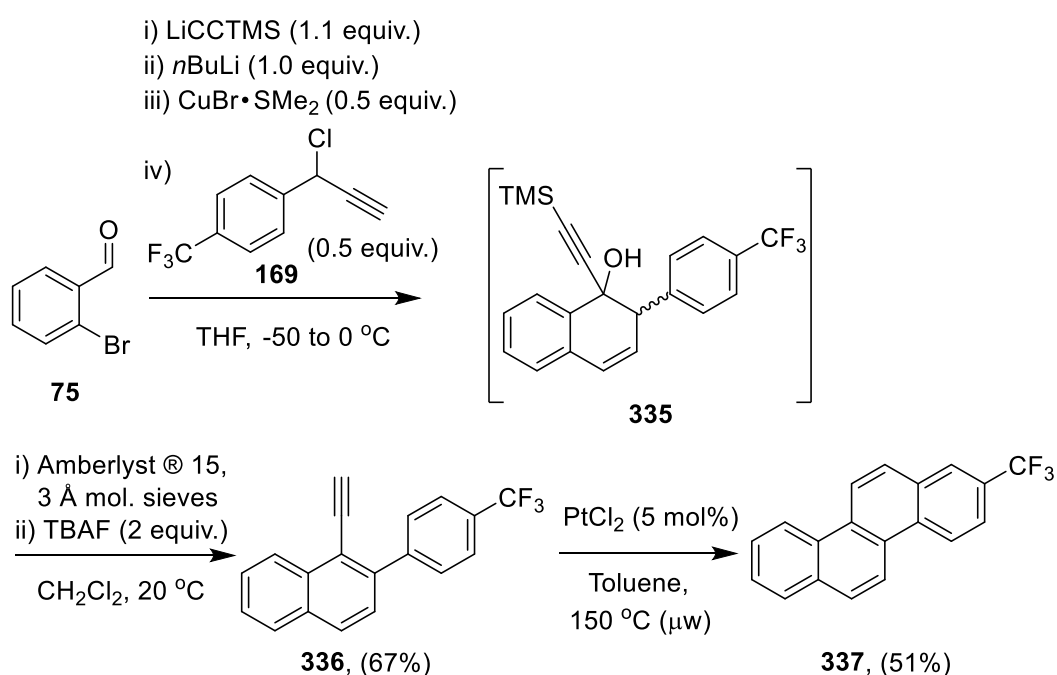
The total library includes: four-, five-, six-, eight- and nine-membered ring systems; nitrogen, sulfur and oxygen containing heteroaromatics; bicyclic and tricyclic fused-ring systems; and functional groups including a carboxylic acid, amides, lactams, alcohols, ketones, halogens, nitriles, esters, oximes, alkenes, alkynes, enones and a pyrazalone ring.

Limited biological screening has been completed on a selection of substrates with positive results in two areas. A range of desilylated substrates showed activity for promoting the secretion of GLP-1, a peptide linked to the treatment of type II diabetes. Anti-microbial activity was also displayed by furanyl **286** inhibiting the growth of multidrug resistant bacteria *Acinetobacter baumannii*.

2.4 Future Work and Ongoing Research

2.4.1 Ongoing research

Research aimed at identifying novel routes to synthesise tetracyclic polyaromatic hydrocarbons, such as tetracene, prompted the initial discovery of the Cannizzaro triggered cascade synthesis. The project has circled back with ongoing research exploring a step efficient route to substituted tetracyclic polyaromatic chrysenes. Although chrysenes are carcinogenic and mutagenic,¹⁴⁰ it has also been reported that some substituted chrysenes, due to their DNA intercalating nature, have been shown to act as anticancer agents.¹⁴¹ Scheme 56 shows some preliminary work that highlights a new, efficient route to substituted chrysenes.



Scheme 56 Step efficient synthesis of 2-(trifluoromethyl)chrysene **337**

This synthetic route was telescoped from 2-bromobenzaldehyde to reach terminal alkyne **336** in one synthetic session, without the need to isolate, purify and characterise intermediates. The Cannizzaro triggered cascade was employed with an electron withdrawing propargylic chloride to favour formation of dihydronaphthalene **335**. The crude mixture was then subjected to dehydrating conditions before the addition of tetrabutylammonium fluoride removed the trimethylsilyl group to give **336** in an overall isolated yield of 67%. Sealed microwave heating of the terminal alkyne in the presence of platinum(II) chloride¹⁴² furnished chrysene **337** in 51% yield. Research is ongoing to generalise this synthetic route and it is hoped that publication will follow in due course.

2.4.2 Future Work

Due to the nature of a diversity oriented synthetic project, it is almost impossible to fully explore every avenue of diversification. For this reason, one could argue that such a project is never truly completed. In this project for example, without considering any 'new' chemistry, there are a large number of diverse molecules that could be synthesised using different combinations of reactions/reagents that have already been noted. Some additional compounds that could be synthesised using this crossover approach are shown in Figure 42.

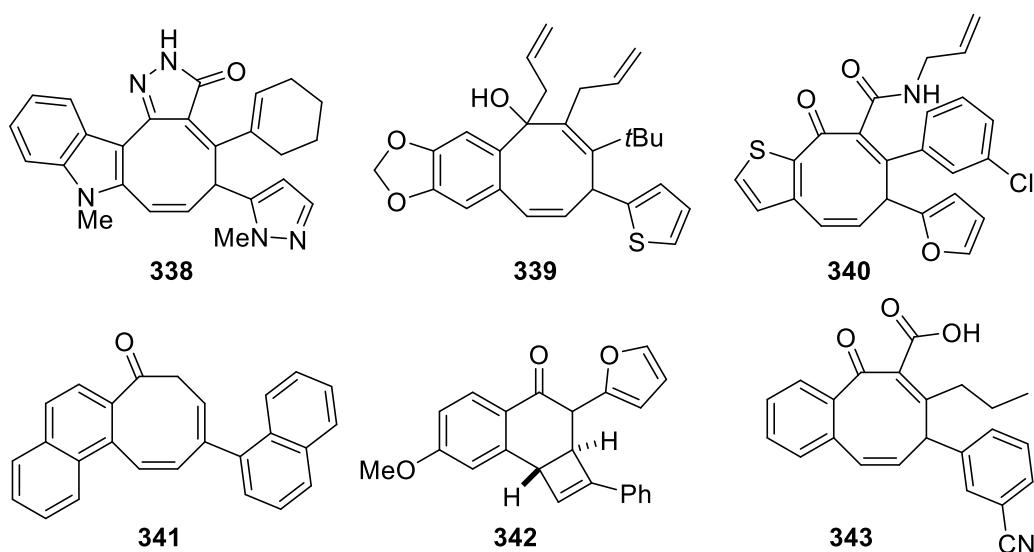


Figure 42 Representative sample of potential products formed via a crossover of known techniques

Although this approach is in some ways similar to combinatorial chemistry, it may be beneficial to develop each known area of diversity via a crossover with another reaction type. This way, a larger compound library can be accessed quickly whilst still growing its diversity. For example, methylindole **338** could be synthesised via the coupling of hydrazine to a novel carboxylic acid, prepared from a unique combination of cascade starting materials. Similarly, a second potential crossover is displayed as allyl **339** could be formed via a different combination of cascade starting materials followed by allyl Grignard addition into the carbonyl. Each substrate in Figure 42 could potentially be synthesised via new combinations of already known reagents/techniques.

Forward synthetic planning can be considered to ensure that further transformations can be performed with crossover substrates. Figure 43 shows how allyl **339** may be able to undergo ring closing metathesis, dehydration and DDQ oxidation¹⁴³ to reach a core biaryl scaffold found in many natural products.

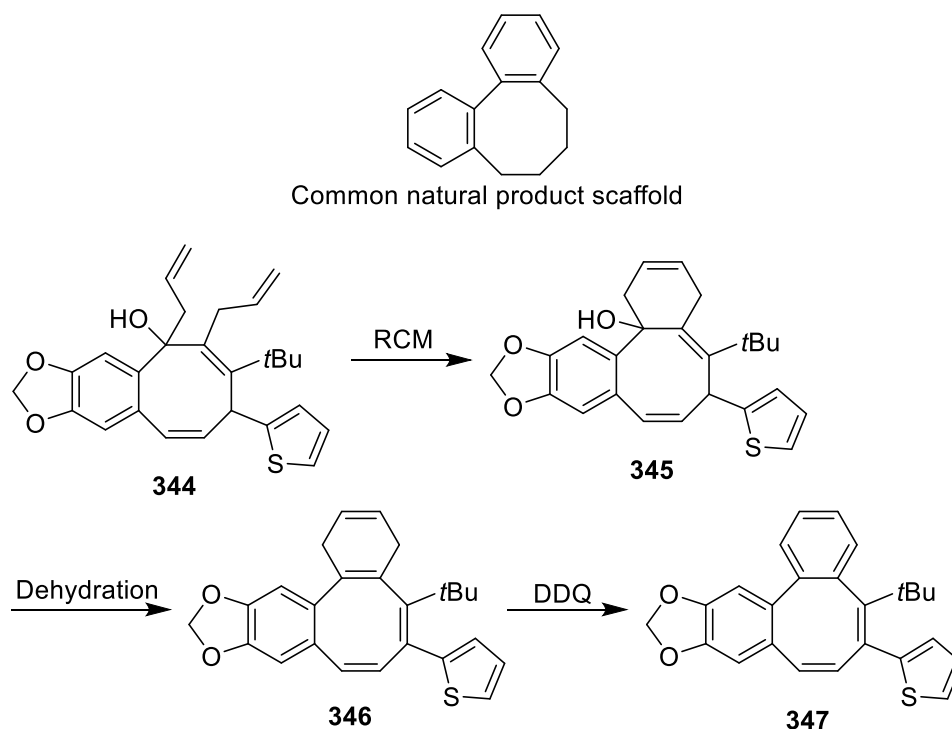


Figure 43 Potential synthesis of common biaryl scaffold

A potential diversity enhancing step originating from hypothetical crossover substrate **340** is shown in Figure 44. An intramolecular Heck reaction could lead to nine-membered lactam **348**.

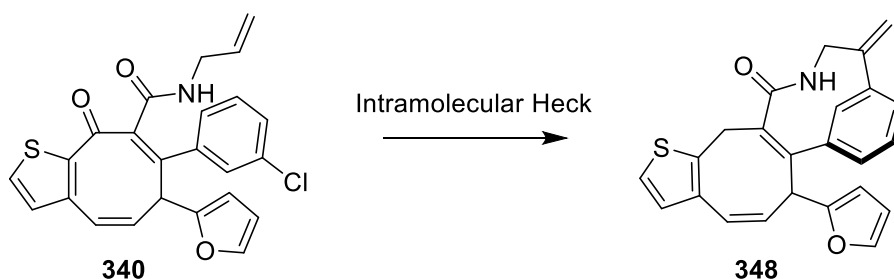


Figure 44 Potential synthesis of nine-membered lactam **348**

There are also reactive handles that have stayed untouched throughout this investigation. It could be possible to exploit these groups in any future research. An example of this would be to reduce the nitrile group in ring system **185** with lithium borohydride¹⁴⁴ to expose a primary amine (Figure 45). It is also possible that lithium borohydride could reduce the ketone in carbocycle **185**. As this proposed route is primarily a diversity creating step, carbonyl reduction could even be considered beneficial. With an amine such as **349** in hand, amide coupling methodology could enable the synthesis of dual 8-membered ring systems such as **350**.

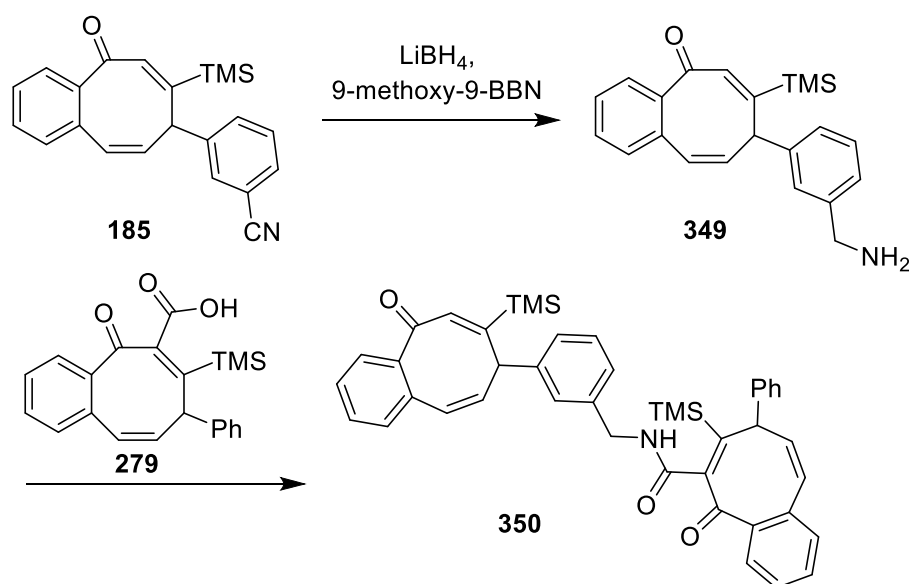


Figure 45 Potential amide coupling to form bis 8-membered ring **350**

It is clear that future work in this area should aim to increase the size and diversity of the compound library. That way, future biological screening assays can benefit from a wider and more detailed coverage of this small section of chemical space.

3.0 Experimental

3.1 General Experimental

All reactions were carried out under an atmosphere of argon using flame-dried Schlenk tubes or in sealed microwave tubes. Dichloromethane was used distilled from calcium hydride; tetrahydrofuran was distilled from sodium/benzophenone ketyl under argon. Aldehydes were purchased from Sigma-Aldrich and were used as received. Alkynes were purchased from Sigma-Aldrich and were distilled before use. Organometallics were from Sigma-Aldrich and titrated before use. Cooling was achieved using a Haake DC50-K75 refrigerated circulator or a Huber TC50E immersion cooler. All temperatures are referred to the temperatures of the cooling baths used. Microwave heating was carried out using a CEM Discover™ Microwave System running at 250W. Thin layer chromatography was performed on foil-backed plates coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light and basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase used was silica gel 60 (220–240 mesh) supplied by Fluorochem. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer with a platinum ATR attachment or a Bruker Tensor 27 FT-IR spectrometer using NaCl plates. Nuclear magnetic resonance spectra were recorded on a Bruker DPX-400 (400.2 MHz), Bruker AV400 (400.1 MHz), Bruker AV(III)400 (400.1 MHz), Bruker AV(III)400hd (400.1 MHz) or a Bruker AV(III)500 (500.1 MHz) spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm for ^1H NMR data; chloroform-d, 77.16 ppm for ^{13}C NMR data; dimethyl sulfoxide-d₆, 2.50 ppm for ^1H NMR data; dimethyl sulfoxide-d₆, 39.52 ppm for ^{13}C NMR data.¹⁴⁵ Coupling constants (J) are quoted in Hertz and carbon multiplicities were assigned using DEPT procedures. Mass spectrometry was performed using a VG Micromass AutoSpec spectrometer (EI) or Bruker MicroTOF (ESI) as noted.

3.2 General Procedures

General procedure A – Cannizzaro Cascade reaction.

The terminal acetylene (1.62 – 1.70 mmol) was dissolved in tetrahydrofuran (2.3 mL) under argon and cooled to -50 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 1.62 – 1.79 mmol) was then added and the mixture stirred for 20 minutes. Neat bromoaldehyde (1.62 mmol) was added to the reaction mixture. Thin-layer chromatography was used to

confirm consumption of the aldehyde. After 60 minutes additional *n*-butyllithium (1.6 M in hexanes, 1.62 – 1.70 mmol) was added forming yellow, orange or dark coloured solutions. After 15 minutes solid copper(I) bromide dimethyl sulfide (167 mg, 0.81 mmol) was then added under a cushion of argon, normally forming tan suspensions/dark solutions at -50 °C. After a further 1 hour neat propargylic chloride (0.79 mmol) was added to the reaction mixture, which was then allowed to warm slowly to -10 °C (unless otherwise stated) over a period of 30 minutes and kept there for 1 hour or a specified time. The reaction was then quenched with pH = 7 ammonia buffered saturated aqueous ammonium chloride solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography of the crude extract afforded the title compound.

General Procedure B – Synthesis of propargylic alcohols

An appropriate benzaldehyde (ca. 1-2 g) was dissolved in tetrahydrofuran under argon to make a 2 M solution and cooled to 0 °C. Ethynylmagnesium bromide (0.5 M in tetrahydrofuran, 1.1 molar equivalents) was added, turning the solution orange from colourless. After completion of the addition the reaction mixture was warmed to room temperature. After 3 hours the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product in near quantitative yield that could be used directly in the next step.

General Procedure C – Propargylic chloride synthesis using Appel reaction

Parent alcohol was dissolved in tetrahydrofuran under argon to make a 1.1 M solution. Triphenylphosphine (1.20 molar equivalents) was then added and the solution cooled to 0 °C. *N*-Chlorosuccinimide (1.25 molar equivalents) was next dissolved in tetrahydrofuran under argon to give a 0.6 M solution, and this solution added dropwise over 15 minutes to the reaction mixture. After completion of the addition the reaction mixture was heated to reflux for 18 hours, after which time the solution was cooled to room temperature and pentane added. The reaction mixture was then filtered and the filtrate concentrated to provide the crude product.

General Procedure D – Propargylic chloride synthesis using thionyl chloride

Crude parent alcohol was dissolved in dichloromethane under argon to make a 0.35 M solution. This was cooled to 0 °C before thionyl chloride (5 molar equivalents) was added dropwise to the reaction mixture over 10 minutes. After stirring for 2 hours the reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour. The reaction mixture was then concentrated *in vacuo* to afford the crude product which could be used as attained. Propargylic chlorides of this type are thermally sensitive (especially those containing electron rich aryl unit); they should all be either used as prepared or stored at -20 °C for less than 2 weeks.

General procedure E – Synthesis of amides using T3P®

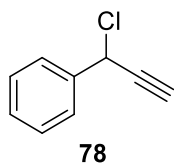
To a suspension of (6Z, 9Z)-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxylic acid (**279**) (75 mg, 0.21 mmol) in ethyl acetate (0.22 mL) was added amine (0.42 mmol) followed by *N,N*-diisopropylethylamine (0.11 mL, 0.62 mmol) and T3P® in ethyl acetate (50% wt., 0.25 mL, 0.42 mmol). After stirring for 3 hours 0.5 M hydrogen chloride solution (1 mL) was added and the mixture extracted with ethyl acetate (3 x 1 mL). Organic residues were dried over magnesium sulfate and concentrated *in vacuo* to give crude product. Purification was achieved via flash column chromatography.

General procedure F – Desilylation using TBAF

Silylated substrate was dissolved in THF under argon and the resulting solution was cooled to 0 °C. Tetrabutylammonium fluoride (2 equiv.) was added and the solution was stirred for 1 hour. The reaction was quenched by the addition of water and extracted with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound.

3.3 Experimental Data

(1-Chloroprop-2-yn-1-yl)benzene

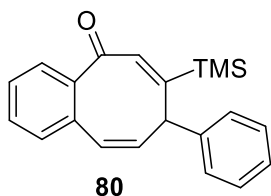
(78)

General thionyl chloride procedure. Afforded the title compound as an inseparable 17:1 mixture of $S_N2:S_N2'$ products (1-chloroprop-2-yn-1-yl)benzene and (3-chloroprop-1,2-dien-1-yl)benzene. Providing (1-chloroprop-2-yn-1-yl)benzene (**78**) in 86% yield as a pale yellow oil. **R_f** (pentane): 0.72; **IR** (NaCl, film): $\nu_{\max}$ 3295, 2126, 1647, 1494, 1455, 1270, 1193 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl_3): δ 7.60 – 7.57 (m, 2H, ArH), 7.42 – 7.34 (m, 3H, ArH), 5.66 (d, J = 2.4 Hz, 1H, ArCHCl), 2.86 (d, J = 2.4 Hz, 1H, CCH); **¹³C NMR** (100.6 MHz, CDCl_3): δ 138.1 (C), 129.3 (CH), 129.0

(CH), 127.7 (CH), 80.7 (C), 77.0 (CH), 49.2 (CH); **MS** (EI+): m/z 115 $[M-Cl]^+$; HRMS: found 115.0554 $C_9H_7^+$ requires 115.0542 Compound characterisation data was found to be in agreement with literature values.¹⁴⁶

(6E,9Z)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one

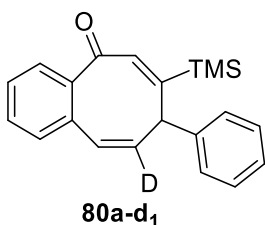
(80)



Synthesised from: trimethylsilylacetylene (229 μ L, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.58 M in hexanes, 1.62 mmol), 2-bromobenzaldehyde (**75**) (189 μ L, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.58 M in hexanes, 1.62 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (20:1 pentane:diethyl ether) afforded the title compound (6E,9Z)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**80**) (177 mg, 0.55 mmol) in 70% yield as a pale yellow crystalline solid. **Rf** (10:1 pentane:diethyl ether): 0.56; **Mp**: 104–107 °C; **IR** (NaCl, film): $\nu_{\max}$ 3753, 3452, 3063, 3030, 2955, 2897, 2099, 1996, 1634, 1496, 1477, 1450, 1277, 1249 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.86 – 7.84 (m, 1H, ArH), 7.43 – 7.35 (m, 2H, ArH), 7.26 – 7.16 (m, 6H, ArH), 6.78 (d, J = 10.7 Hz, 1H, CCHCH), 6.75 (d, J = 1.1 Hz, 1H, OCCH), 6.66 (dd, J = 10.7 Hz, 9.7 Hz, 1H, CCHCH), 4.94 (d, J = 9.7 Hz, 1H, CHPh), -0.03 – -0.05 (m, 9H, Si(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃): δ 195.3 (C), 165.1 (C), 141.8 (CH), 140.3 (C), 139.8 (C), 136.1 (CH), 135.0 (C), 131.0 (CH), 130.8 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.0 (CH), 46.0 (CH), -0.1 (CH₃); **MS** (ESI+): m/z 319 $[M+H]^+$; HRMS: found 319.1504 $C_{21}H_{23}OSi$ requires 319.1513; **CHN** Anal. calcd. for $C_{21}H_{22}OSi$ C: 79.20, H: 6.96%; found C: 79.15, H: 6.84%. Preparation of **80** on a 5 mmol scale gave 1.6 g (81%).

(6E,9Z)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one-9-d₁

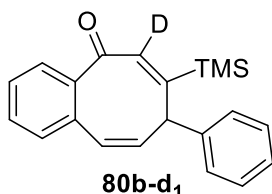
(80a-d₁)¹⁴⁷



Synthesised from: trimethylsilylacetylene (229 μ L, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.60 M in hexanes, 1.6 mmol), 2-bromobenzaldehyde-d₁ (301 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.01 mL, 1.60 mol dm⁻³, 1.62 mmol), CuBr·SMe₂ (167 mg, 0.810 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.790 mmol) using the general procedure. Flash column chromatography (20:1 pentane:diethyl ether) afforded the title compound (6E,9Z)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one-d₁ (**80a-d₁**) (148 mg, 0.463 mmol, 69 atom% D) in 59% yield as a pale yellow crystalline solid. **Rf** (10:1 pentane:diethyl ether):

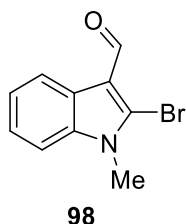
0.55; **Mp**: 97-100 °C; **IR** (NaCl, film): $\nu_{\max}$ 3441, 3061, 3028, 2956, 2897, 2361, 1945, 1883, 1633, 1611, 1496, 1476, 1449, 1410, 1277, 1250, 1210, 1120, 1093, 1079, 1050, 1008 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.92 – 7.80 (m, 1H, ArH), 7.46 – 7.33 (m, 2H, ArH), 7.31 – 7.14 (m, 6H, ArH), 6.78 (d, J = 10.6 Hz, 0.31H, CCHCH), 6.78 (s, 0.69H, CCHCD), 6.76 (d, J = 1.1 Hz, 1H, OCCH), 6.66 (dd, J = 10.6, 9.7 Hz, 0.31H, CCHCH), 4.94 (d, J = 7.0 Hz, 1H, CHPh), -0.02 – -0.09 (m, 9H, $\text{Si}(\text{CH}_3)_3$); **^2H NMR** (61.4 MHz, CHCl_3): δ 6.72 (s); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 195.2 (C), 165.2 (C), 141.8 (CH), 140.3 (C), 139.8 (C), 136.1 (CH, residual non-D), 135.8 (t, J = 24.5 Hz, CD), 135.0 (C), 131.0 (CH), 130.8 (CH), 129.3 (CH), 128.8 (CH, residual non-D), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.0 (CH), 45.9 (CH), -0.1 (CH_3); **MS** (ESI+): m/z 320 $[\text{M}+\text{H}]^+$; HRMS: found 320.1570 $\text{C}_{21}\text{H}_{22}\text{DOSi}$ requires 320.1575.

(6E,9Z)-6-Deuterio-(-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (80b-d₁)¹⁴⁸

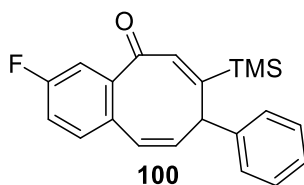


Synthesised from: trimethylsilylacetylene (229 μL , 1.62 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.0 mL, 1.58 M in hexanes, 1.62 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol), $n\text{BuLi}$ for bromine exchange (1.0 mL, 1.58 M in hexanes, 1.62 mmol),

$\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Treatment with D_2O (158 μL , 7.9 mmol) for 30 mins at -10 °C followed by usual extraction and flash column chromatography (20:1 pentane:diethyl ether) afforded the title compound (6E,9Z)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one-6-d₁ (**80b-d₁**) (161 mg, 0.50 mmol) in 64% yield as a pale yellow microcrystalline solid. (91% deuterium incorporation). **Rf** (10:1 pentane:diethyl ether): 0.56; **Mp**: 104-107 °C; **IR** (NaCl, film): $\nu_{\max}$ 3753, 3452, 3063, 3030, 2955, 2897, 2099, 1996, 1634, 1496, 1477, 1450, 1277, 1249 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.86 – 7.84 (m, 1H, ArH), 7.43 – 7.35 (m, 2H, ArH), 7.26 – 7.16 (m, 6H, ArH), 6.78 (d, J = 10.7 Hz, 1H, CCHCH), 6.66 (dd, J = 10.7 Hz, 9.7 Hz, 1H, CCHCH), 4.94 (d, J = 9.7 Hz, 1H, CHPh), -0.03 – -0.05 (m, 9H, $\text{Si}(\text{CH}_3)_3$), based on the integral of the residual CH signal at 6.75 ppm the sample was >90% **80a-d₁**; **^{13}C NMR** (100.6 MHz, CDCl_3): δ 195.3 (C), 165.1 (C), 141.6 (J_{CD} ~ 26 Hz, CD, low intensity), 140.3 (C), 139.8 (C), 136.1 (CH), 135.0 (C), 131.0 (CH), 130.8 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.0 (CH), 46.0 (CH), -0.1 (CH_3), due to poor signal intensity the J_{CD} coupling could not be accurately determined.

2-Bromo-1-methyl-1H-indole-3-carbaldehyde**(98)**

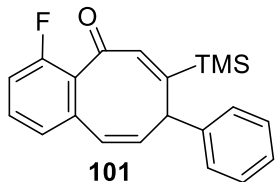
2-bromoindole-3-carbaldehyde (680 mg, 3.03 mmol) was dissolved in THF (27 mL) and cooled to 0 °C under an atmosphere of argon. Sodium hydride (60% in mineral oil, 363 mg, 9.09 mmol) was washed with pentane and cooled to 0 °C before the aldehyde solution was added. This was stirred for 30 minutes before iodomethane (0.6 mL, 9.1 mmol) was added. After a further 30 minutes water (10 mL) was added and the reaction mixture extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford 2-bromo-1-methyl-1H-indole-3-carbaldehyde (**98**) (658 mg, 2.76 mmol) in 91% yield as a pale brown solid. **Rf** (1:1 pentane:diethyl ether): 0.32; **Mp**: 114-116 °C [lit. 111-112 °C]^[511]; **IR** (NaCl, film): $\nu_{\max}$ 3059, 2923, 1653, 1499, 1469, 1386, 1375, 1036, 797, 744 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl_3): δ 10.04 (s, 1H, CHO), 8.37 – 8.28 (m, 1H, ArH), 7.38 – 7.28 (m, 3H, ArH), 3.85 (s, 3H, NCH₃); **¹³C NMR** (100.6 MHz, CDCl_3): δ 185.5 (CH), 137.5 (C), 126.5 (C), 125.4 (C), 124.2 (CH), 123.5 (CH), 121.4 (CH), 115.5 (C), 109.8 (CH), 31.9 (CH₃); **MS** (ESI+): m/z 238 [M+H]⁺; HRMS: found 237.9865 C₁₀H₉BrNO⁺ requires 237.9862. Compound characterisation data was found to be in agreement with literature values.¹⁴⁹

(6E,9Z)-3-Fluoro-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one**(100)**¹⁴⁷

Synthesised from: trimethylsilylacetylene (229 μL , 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.60 M in hexanes, 1.62 mmol), 2-bromo-5-fluorobenzaldehyde (329 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.60 M in hexanes, 1.62 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (25:1 pentane:diethyl ether) afforded the title compound (6E,9Z)-3-fluoro-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**100**) (146 mg, 0.435 mmol) in 55% yield as a yellow crystalline solid. **Rf** (20:1 pentane:diethyl ether): 0.56; **Mp**: 90-92 °C; **IR** (NaCl, film): $\nu_{\max}$ 3064, 3032, 2957, 2897, 1601, 1568, 1488, 1451, 1408, 1384, 1328, 1307, 1270, 1250, 1234, 1201, 1121, 1087, 1071, 1034 cm^{-1} ; **¹H NMR** (500.1 MHz, CDCl_3): δ 7.58 – 7.51 (m, 1H, ArH), 7.26 – 7.21 (m, 2H ArH), 7.21 – 7.14 (m, 4H ArH), 7.14 – 7.06 (m, 1H ArH), 6.74 (d, J = 10.7 Hz, 1H, CCHCH), 6.72 (d, J = 1.1 Hz, 1H, OCCH), 6.64 (dd, J = 10.7, 9.7 Hz, 1H, CCHCH), 4.89 (d, J = 9.7 Hz, 1H, CHPh), 0.00 – -0.07 (m, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl_3): δ 193.6 (d, J = 1.4 Hz, C), 165.8 (s, C), 162.3 (d, J = 248 Hz, C), 141.8 (d, J = 6.4 Hz, C), 140.9 (s, CH), 139.5 (s, C), 136.1 (s, CH), 131.6 (d, J = 7.6 Hz, CH),

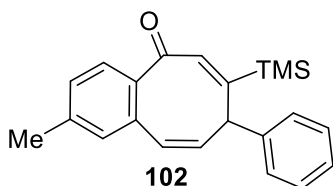
131.4 (d, $J = 3.2$ Hz, C), 128.5 (s, CH), 128.2 (s, CH), 128.0 (s, CH), 127.1 (s, CH), 118.6 (d, $J = 22.0$ Hz, CH), 117.0 (d, $J = 22.9$ Hz, CH), 46.0 (s, CH), -0.2 (s, CH₃); **MS** (ESI⁺): m/z 337 [M+H]⁺; HRMS: found 337.1399 C₂₁H₂₂FOSi requires 337.1418.

(6*E*,9*Z*)-4-Fluoro-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (101)



Synthesised from: trimethylsilylacetylene (229 μ L, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.60 M in hexanes, 1.62 mmol), 2-bromo-5-fluorobenzaldehyde (329 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.60 M in hexanes, 1.62 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (20:1 pentane:diethyl ether) afforded the title compound (6*E*,9*Z*)-4-fluoro-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**101**) (72 mg, 0.214 mmol) in 27% yield as a yellow crystalline solid. **R_f** (20:1 pentane:diethyl ether): 0.23; **Mp**: 104-106 °C; **IR** (NaCl, film): $\nu_{\max}$ 3062, 3028, 2956, 2898, 1633, 1607, 1571, 1494, 1448, 1251, 1016, 904, 841 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.16 – 7.02 (m, 6H, Ar*H*), 6.96 – 6.91 (m, 1H Ar*H*), 6.90 (d, $J = 1.1$ Hz, 1H, OCCH), 6.73 (d, $J = 10.5$ Hz, 1H, CCHCH), 6.69 (d, $J = 7.6$ Hz, 1H, Ar*H*) 6.43 (dd, $J = 10.5, 9.7$ Hz, 1H, CCHCH), 4.90 (d, $J = 9.7$ Hz, 1H, CHPh), 0.01 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.05 MHz, CDCl₃): δ 192.7 (s, C), 165.1 (s, C), 159.2 (d, $J = 249.9$ Hz, C), 142.5 (s, CH), 139.7 (s, C), 137.1 (s, CH), 135.8 (d, $J = 3.0$ Hz, C), 130.0 (d, $J = 8.4$ Hz, CH), 129.3 (d, $J = 16.1$ Hz, C), 128.3 (s, CH), 128.1 (s, CH), 127.5 (d, $J = 2.3$, CH), 126.6 (s, CH), 122.6 (d, $J = 3.1$, CH), 114.7 (d, $J = 21.5$, CH), 46.2 (s, CH), -0.9 (s, CH₃); **MS** (ESI⁺): m/z 359 [M+Na]⁺; HRMS: found 359.1236 C₂₁H₂₁FNaOSi requires 359.1238.

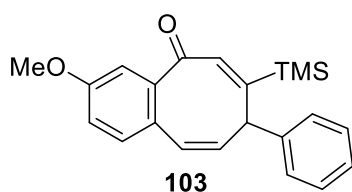
(6*E*,9*Z*)-2-Methyl-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (102)



Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromo-4-methylbenzaldehyde (322 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (neat pentane to 20:1 pentane:diethyl ether gradient elution) afforded the title compound (6*E*,9*Z*)-2-methyl-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**102**) (162 mg, 0.49 mmol) in 62% yield as colourless solid. **R_f** (9:1 pentane:diethyl ether): 0.49; **Mp**: 125-127 °C; **IR** (NaCl, film): $\nu_{\max}$ 3028, 2954, 2896, 1599, 1496, 1278, 1250, 913, 902, 840, 753, 699 cm⁻¹; **¹H NMR** (400.1 MHz, CDCl₃): δ 7.87 (d, $J = 8.2$ Hz, 1H,

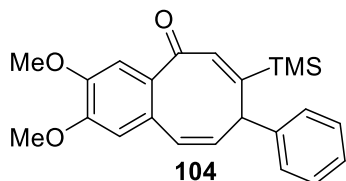
ArH), 7.30 – 7.15 (m, 6H, ArH), 7.05 – 7.00 (m, 1H, ArH), 6.73 (d, $J = 10.8$ Hz, 1H, CCHCH), 6.70 (d, $J = 1.2$ Hz, 1H, OCCH), 6.67 (dd, $J = 10.8, 9.2$ Hz, 1H, CCHCH), 4.94 (d, $J = 9.2$ Hz, 1H, CHPh), 2.36 (s, 3H, ArCH₃), -0.06 (s, 9H, Si(CH₃)₃); ¹³C NMR (125.8 MHz, CDCl₃): δ 194.8 (C), 164.4 (C), 141.7 (C), 141.6 (CH), 139.9 (C), 137.6 (C), 136.0 (CH), 135.4 (C), 131.3 (CH), 130.1 (CH), 129.0 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 46.0 (CH), 21.4 (CH₃), 0.1 (CH₃); **MS** (ESI+): m/z 355 [M+Na]⁺; HRMS: found 355.1486 C₂₂H₂₄NaOSi⁺ requires 355.1489; **CHN** Anal. calcd. for C₂₂H₂₄OSi C: 79.47, H: 7.29%; found C: 79.37, H: 7.31%.

(6E,9Z)-3-Methoxy-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (103)¹⁴⁷



Synthesised from: trimethylsilylacetylene (229 μL, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.60 M in hexanes, 1.62 mmol), 2-bromo-5-methoxybenzaldehyde (348 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.60 M in hexanes, 1.62 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (20:1 pentane:diethyl ether) afforded the title compound **(6E,9Z)-3-methoxy-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (103)** (171 mg, 0.49 mmol) in 62% yield as a pale yellow crystalline solid. **Rf** (20:1 pentane:diethyl ether): 0.33; **Mp**: 91–93 °C; **IR** (NaCl, film): $\nu_{\max}$ 3451, 3022, 2400, 2095, 1640, 1499, 1336, 1281, 1216 cm⁻¹; ¹H NMR (400.2 MHz, CDCl₃): δ 7.47 – 7.47 (m, 1H, ArH), 7.30 – 7.14 (m, 6H, ArH), 7.04 – 7.01 (m, 1H, ArH), 6.74 (d, $J = 10.7$ Hz, 1H, CCHCH), 6.66 (d, $J = 1.0$ Hz, 1H, OCCH), 6.61 (dd, $J = 10.7, 9.6$ Hz, 1H, CCHCH), 4.84 (d, $J = 9.6$ Hz, 1H, CHPh), 3.87 (s, 3H, CH₃O), -0.05 (s, 9H, Si(CH₃)₃); ¹³C NMR (125.8 MHz, CDCl₃): δ 195.0 (C), 164.2 (C), 159.2 (C), 140.8 (C), 140.5 (CH), 139.9 (C), 134.8 (CH), 131.8 (CH), 128.8 (CH), 128.7 (C), 128.4 (CH), 128.2 (CH), 127.0 (CH), 119.3 (CH), 113.8 (CH), 55.6 (CH₃), 46.2 (CH), 0.1 (CH₃); **MS** (ESI+): m/z 349 [M+H]⁺; HRMS: found 349.1623.

(6E,9Z)-2,3-Dimethoxy-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (104)

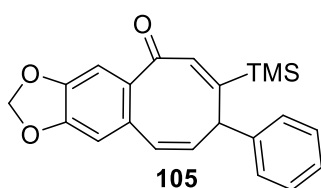


Synthesised from: trimethylsilylacetylene (229 μL, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.60 M in hexanes, 1.62 mmol), 6-bromoveratraldehyde (397 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.60 M in hexanes, 1.62 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (5:2 pentane:diethyl ether) afforded the title compound **(6E,9Z)-2,3-dimethoxy-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (104)** (110mg, 0.291

mmol) in 37% yield as a colourless solid. **Rf** (5:2 pentane:diethyl ether): 0.27; **Mp**: 145-147 °C; **IR** (NaCl, film): $\nu_{\max}$ 3006, 2957, 1583, 1515, 1463, 1368, 1260, 1225, 1090, 841 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): 7.68 (s, 1H, ArH), 7.38 – 7.16 (m, 5H, ArH), 6.75 – 6.64 (m, 3H, ArH, CCHCH, CCHCH), 6.61 (d, J = 0.8 Hz, 1H, OCCH), 4.82 (d, J = 7.2 Hz, 1H, CHPh), 3.97 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), -0.06 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.05 MHz, CDCl_3): δ 193.6 (C), 162.6 (C), 151.8 (C), 148.8 (C), 140.3 (CH), 139.8 (C), 135.5 (CH), 132.7 (C), 131.0 (C), 129.0 (CH), 128.5 (CH), 128.1 (CH), 127.02 (CH), 113.2 (CH), 112.1 (CH), 56.2 ($2 \times \text{CH}_3$), 46.2 (CH), 0.29 (CH_3) **MS** (ESI+): m/z 401 $[\text{M}+\text{Na}]^+$; HRMS: found 401.1528 $\text{C}_{23}\text{H}_{26}\text{NaO}_3\text{Si}$ requires 401.1543.

(6E,9Z)-8-Phenyl-7-(trimethylsilyl)cycloocta[4,5]benzo[1,2-*d*][1,3]dioxol-5(8H)-one

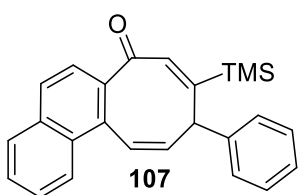
(105)



Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 6-bromo-1,3-benzodioxole-5-carboxaldehyde (371 mg, 1.62 mmol), $n\text{BuLi}$ for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (19:1 pentane:diethyl ether) afforded the title compound (6E,9Z)-8-phenyl-7-(trimethylsilyl)cycloocta[4,5]benzo[1,2-*d*][1,3]dioxol-5(8H)-one (**105**) (150 mg, 0.41 mmol) in 52% yield as colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.24; **Mp**: 155-157 °C; **IR** (NaCl, film): $\nu_{\max}$ 3028, 2954, 2898, 1590, 1504, 1483, 1378, 1248, 1037, 839, 754, 700 cm^{-1} ; **^1H NMR** (400.1 MHz, CDCl_3): δ 7.48 (s, 1H, ArH), 7.30 – 7.24 (m, 2H, ArH), 7.23 – 7.17 (m, 3H, ArH), 6.66 (d, J = 1.1 Hz, 1H, OCCH), 6.64 – 6.58 (m, 3H, CCHCH, CCHCH, ArH), 6.02 (d, J = 1.3 Hz, 1H, $\text{OCH}_a\text{H}_b\text{O}$), 6.00 (d, J = 1.3 Hz, 1H, $\text{OCH}_b\text{H}_a\text{O}$), 4.93 – 4.84 (m, 1H, CHPh), -0.06 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (125.8 MHz, CDCl_3): δ 193.0 (C), 163.9 (C), 150.4 (C), 148.0 (C), 141.0 (CH), 139.8 (C), 135.6 (CH), 134.9 (C), 132.3 (C), 128.5 ($2 \times \text{CH}$), 128.2 (CH), 127.0 (CH), 110.3 (CH), 108.6 (CH), 102.0 (CH_2), 46.1 (CH), 0.1 (CH_3); **MS** (ESI+): m/z 363 $[\text{M}+\text{H}]^+$; HRMS: found 363.1416 $\text{C}_{22}\text{H}_{23}\text{O}_3\text{Si}^+$ requires 363.1411. **CHN** Anal. calcd. for $\text{C}_{22}\text{H}_{22}\text{O}_3\text{Si}$ C: 72.89, H: 6.12%; found C: 72.75, H: 6.20%.

(8E,11Z)-10-Phenyl-9-(trimethylsilyl)cycloocta[α]naphthalen-7(10H)-one

(107)

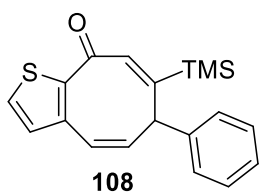


Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 1-bromo-2-naphthaldehyde (381 mg, 1.62 mmol), $n\text{BuLi}$ for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70

mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (15:1 to 5:1 pentane:diethyl ether gradient elution) afforded the title compound (8*E*,11*Z*)-10-phenyl-9-(trimethylsilyl)cycloocta[*a*]naphthalen-7(10*H*)-one (**107**) (77 mg, 0.21 mmol) in 26% yield as colourless solid. **Rf** (5:1 pentane:diethyl ether): 0.42; **Mp**: 142-144 °C; **IR** (NaCl, film): $\nu_{\max}$ 3025, 2954, 1694, 1614, 1458, 1274, 1258, 1075, 890, 840 cm⁻¹; **¹H NMR** (400.1 MHz, CDCl₃): δ 8.30 – 8.24 (m, 1H, Ar*H*), 7.96 (dd, *J* = 7.2, 1.1 Hz, 1H, Ar*H*), 7.93 – 7.86 (m, 2H, Ar*H*), 7.71 – 7.56 (m, 2H, Ar*H*), 7.31 – 7.19 (m, 5H, Ar*H*), 7.18 (d, *J* = 1.7 Hz, 1H, OCCH), 6.68 (dd, *J* = 15.9, 1.1 Hz, 1H, CCHCH), 6.26 (dd, *J* = 15.9, 8.4 Hz, 1H, CCHCH), 5.18 (ddd, *J* = 8.4, 1.1, 1.1 Hz, 1H, CHPh), 0.28 (s, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl₃): δ 192.2 (C), 153.1 (C), 152.6 (C), 137.5 (C), 137.0 (CH), 136.7 (C), 135.0 (C), 132.4 (CH), 130.2 (CH), 130.1 (C), 129.8 (CH), 129.5 (CH), 129.2 (CH), 128.8 (CH), 127.8 (CH), 127.3 (CH), 126.4 (CH), 125.5 (CH), 120.4 (CH), 45.9 (CH), -0.3 (CH₃); **MS** (ESI⁺): *m/z* 369 [M+H]⁺; HRMS: found 369.1667 C₂₅H₂₅OSi⁺ requires 369.1669.

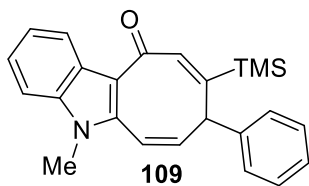
(4*Z*,7*E*)-6-Phenyl-7-(trimethylsilyl)cycloocta[*b*]thiophen-9(6*H*)-one

(108)¹⁴⁷

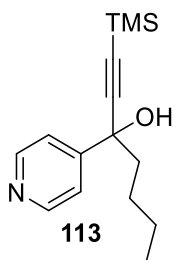


Synthesised from: trimethylsilylacetylene (229 μ L, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.62 M in hexanes, 1.62 mmol), 3-bromothiophene-2-carboxaldehyde (316 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.62 M in hexanes,

1.62 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (20:1 to 9:1 pentane:diethyl ether gradient) afforded the title compound (4*Z*,7*E*)-6-phenyl-7-(trimethylsilyl)cycloocta[*b*]thiophen-9(6*H*)-one (**108**) (185 mg, 0.570 mmol) in 72% yield as a pale yellow crystalline solid. **Rf** (15:1 pentane:diethyl ether): 0.38; **Mp**: 112-115 °C; **IR** (NaCl, film): $\nu_{\max}$ 3089, 3063, 3013, 2955, 2897, 1597, 1567, 1513, 1497, 1451, 1409, 1355, 1280, 1249, 1216, 1088, 1069, 1031, 1009 cm⁻¹; **¹H NMR** (400.1 MHz, CDCl₃): δ 7.64 (d, *J* = 5.2 Hz, 1H, CHSC), 7.37 – 7.19 (m, 5H, Ar*H*), 7.12 (d, *J* = 5.2 Hz, 1H, CHCHS), 6.92 (d, *J* = 10.7 Hz, 1H, CCHCH), 6.79 (dd, *J* = 10.7, 9.2 Hz, 1H, CCHCH), 6.47 (s, 1H, OCCH), 4.49 (d, *J* = 9.2 Hz, 1H, CHPh), -0.08 – -0.09 (m, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl₃): δ 188.0 (C), 159.7 (C), 145.8 (C), 139.9 (C), 139.4 (C), 136.3 (CH), 136.2 (CH), 133.6 (CH), 132.0 (CH), 128.6 (CH), 127.6 (CH), 127.2 (CH), 125.4 (CH), 47.1 (CH), 0.4 (CH₃); **MS** (ESI⁺): *m/z* 325 [M+H]⁺; HRMS: found 325.1061 C₁₉H₂₁OSSi requires 325.1077.

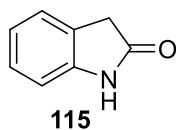
(8*E*,11*Z*)-10-Phenyl-9-(trimethylsilyl)cycloocta[*a*]naphthalen-7(10*H*)-one (109)

Synthesised from: trimethylsilylacetylene (203 μ L, 1.44 mmol), *n*BuLi for acetylene deprotonation (0.9 mL, 1.60 M in hexanes, 1.51 mmol), 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde (**98**) (294 mg, 1.23 mmol), *n*BuLi for bromine exchange (0.8 mL, 1.60 M in hexanes, 1.29 mmol), CuBr·SMe₂ (127 mg, 0.62 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (90 mg, 0.60 mmol) using general procedure A. Flash column chromatography (17:3 to 7:3 pentane:diethyl ether gradient elution) afforded the title compound (8*E*,11*Z*)-10-phenyl-9-(trimethylsilyl)cycloocta[*a*]naphthalen-7(10*H*)-one (**109**) (45 mg, 0.16 mmol) in 20% yield as colourless solid. **R_f** (1:1 pentane:diethyl ether): 0.41; **Mp**: 213–215 °C decom. °C; **IR** (NaCl, film): ν_{max} 3055, 2953, 2896, 1583, 1565, 1496, 1465, 1417, 1375, 1334, 1248, 1054, 840, 749, 700 cm⁻¹; **¹H NMR** (400.1 MHz, CDCl₃): δ 8.93 – 8.82 (m, 1H, Ar*H*), 7.46 – 7.18 (m, 8H, Ar*H*), 7.10 (dd, *J* = 11.0, 9.7 Hz, 1H, CCHCH), 6.84 (d, *J* = 11.0 Hz, 1H, CCHCH), 6.55 (s, 1H, OCCH), 4.76 (d, *J* = 9.7 Hz, 1H, CHPh), 3.81 (s, 3H, NCH₃), -0.07 (s, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl₃): δ 189.7 (C), 155.7 (C), 141.1 (C), 140.2 (CH), 140.1 (CH), 139.6 (C), 137.5 (C), 128.6 (CH), 127.8 (CH), 127.6 (C), 127.1 (CH), 124.9 (CH), 124.7 (CH), 123.2 (CH), 119.9 (C), 117.5 (CH), 109.1 (CH), 46.8 (CH), 30.8 (CH₃), 0.5 (CH₃); **MS** (ESI⁺): *m/z* 372 [M+H]⁺; HRMS: found 372.1781 C₂₄H₂₆NOSi⁺ requires 372.1778.

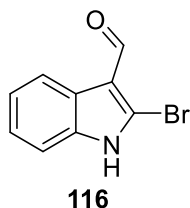
3-(Pyridin-4-yl)-1-(trimethylsilyl)hept-1-yn-3-ol (113)

Trimethylsilylacetylene (1.62 mmol) was dissolved in tetrahydrofuran (2.3 mL) under argon and cooled to -50 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 1.79 mmol) was then added and the mixture stirred for 20 minutes. 3-Bromo-4-carboxaldehyde (1.47 mmol) was added to the reaction mixture. Thin-layer chromatography was used to confirm consumption of the aldehyde. After 60 minutes additional *n*-butyllithium (1.6 M in hexanes, 1.47 mmol) was added. After 15 minutes the reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with ethyl acetate (3 x 5 mL) to give 3-(Pyridin-4-yl)-1-(trimethylsilyl)hept-1-yn-3-ol (**113**). **IR** (NaCl, film): ν_{max} 3132, 2958, 2864, 2360, 2166, 1602, 1416, 1250, 843 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 8.58 – 8.43 (m, 2H, Ar*H*), 7.54 – 7.47 (m, 2H, Ar*H*), 3.87 (br s, 1H, OH), 1.95 – 1.74 (m, 2H, HOCCH₂), 1.46 – 1.19 (m, 4H, CH₂CH₂CH₂CH₃), 0.86 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 0.19 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃): δ 154.2 (C), 149.5 (CH), 120.8 (CH), 107.0 (C), 91.1

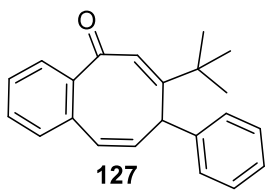
(C), 72.5 (C), 45.0 (CH₂), 26.6 (CH₂), 22.7 (CH₂), 14.0 (CH₃), 0.0 (CH₃); **MS** (ESI⁺): *m/z* 262 [M+H]⁺; HRMS: found 262.1644 C₁₅H₂₄NOSi⁺ requires 262.1622.

Indolin-2-one**(115)**

Following the procedure of Lin *et al.*⁶⁴ the title compound indolin-2-one was afforded in 37% yield as a white solid. **Rf** (neat diethyl ether): 0.35; **Mp** 116-118 °C [lit. 126-127 °C]⁶⁴; **IR** (NaCl, film): ν_{max} 3140, 3084, 3026, 1736, 1683, 1621, 1476, 1335, 1305, 1234, 1203, 946, 742, 677 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 8.93 (br s, 1H, NH), 7.25 – 7.18 (m, 2H, ArH), 7.05 – 6.98 (m, 1H, ArH), 6.90 (d, *J* = 7.7 Hz, 1H, ArH), 3.55 (s, 2H, ArCH₂); **¹³C NMR** (100.6 MHz, CDCl₃): δ 178.0 (C), 142.7 (C), 128.1 (CH), 125.4 (C), 124.7 (CH), 122.4 (CH) 109.9 (CH), 36.4 (CH₂); **MS** (ESI⁺): *m/z* 156 [M+Na]⁺; HRMS: found 156.0423 C₈H₇NNaO⁺ requires 156.0420. Compound characterisation data was found to be in agreement with literature values.¹⁵⁰

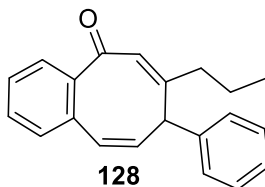
2-Bromoindole-3-carbaldehyde**(116)**

Adapted from a procedure by Gilchrist *et al.*⁶⁵ A solution of *N,N*-dimethylformamide (1.19 mL, 15.4 mmol) in dichloromethane (6 mL) was cooled to 0 °C under an atmosphere of argon. A solution of phosphorus oxybromide (3.55 g, 12.4 mmol) in dichloromethane (10 mL) was added dropwise over 10 minutes. This thick cloudy mixture was heated to reflux for 15 minutes before heating was stopped and indolin-2-one (660 mg, 4.96 mmol) was added in portions over 2 minutes. Refluxing was then resumed for 2.5 hours before it was cooled and ice (10 g) was added. The aqueous layer was separated and the organic phase further extracted with water (10 mL). The combined aqueous washings were basified with solid potassium carbonate to form a white precipitate. To complete hydrolysis this was filtered and the precipitate was then added to a mixture of ethanol (20 mL) and 2M aqueous sodium hydroxide solution (8 mL). After stirring for 1 hour the mixture was acidified with 2M hydrochloric acid and filtered to afford the title compound 2-bromoindole-3-carbaldehyde (**116**) (702 mg, 3.13 mmol) in 63% yield as a pale brown solid. **Mp** 212-214 °C decom. [lit. 196-198 °C]⁶⁵; **IR** (ATR): ν_{max} 3103, 2912, 2835, 1639, 1619, 1583, 1492, 1417, 1369, 1342, 1091, 833, 735 cm⁻¹; **¹H NMR** (400.2 MHz, (CD₃)₂SO): δ 13.08 (br s, 1H, NH), 9.90 (s, 1H, CHO), 8.07 (dd, *J* = 6.7, 1.4 Hz, 1H, ArH), 7.47 – 7.40 (m, 1H, ArH), 7.32 – 7.18 (m, 2H, ArH); **¹³C NMR** (100.6 MHz, (CD₃)₂SO): δ 184.5 (CH), 136.4 (C), 124.8 (C), 123.8 (CH), 123.3 (C), 122.7 (CH), 119.7 (CH), 114.3 (C), 111.7 (CH); **MS** (ESI⁺): *m/z* 226 [M+H]⁺; HRMS: found 225.9691 C₉H₇BrNO⁺ requires 225.9685. Compound characterisation data was found to be in agreement with literature values.⁶⁵

(6E,9Z)-7-(tert-Butyl)-8-phenylbenzo[8]annulen-5(8H)-one**(127)**

Synthesised from: 3,3-dimethyl-1-butyne (209 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.52 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.52 M in hexanes, 1.70 mmol),

CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (20:1 pentane:diethyl ether) of the crude extract afforded the title compound (6E,9Z)-7-(tert-butyl)-8-phenylbenzo[8]annulen-5(8H)-one (**127**) (144 mg, 0.48 mmol) in 61% yield as a colourless crystalline solid. **Rf** (10:1 pentane:diethyl ether): 0.25; **Mp**: 100 - 102 °C; **IR** (NaCl, film): ν_{max} 3059, 3023, 2966, 1623, 1608, 1592, 1298, 1237, 778, 736 cm^{-1} ; **¹H NMR** (500.1 MHz, CDCl₃): δ 7.18 – 7.10 (m, 1H, ArH), 7.04 – 6.95 (m, 2H, ArH), 6.92 – 6.78 (m, 5H, ArH), 6.77 – 6.71 (m, 3H, CCHCH, OCCH, ArH) 6.42 (dd, *J* = 10.9 Hz, 9.1 Hz, 1H, CCHCH), 4.76 (d, *J* = 9.1 Hz, 1H, CHPh), 1.25 (s, 9H, C(CH₃)₃); **¹³C NMR** (125.03 MHz, CDCl₃): δ 197.5 (C), 168.8 (C), 140.9 (C), 139.2 (C), 137.5 (CH), 134.0 (C), 130.5 (CH), 130.2 (CH), 129.3 (CH), 128.9 (CH), 127.6 (CH), 127.4 (CH), 127.4 (CH), 127.1 (CH), 125.6 (CH), 45.3 (CH), 39.1 (C), 29.0 (CH₃); **MS** (ESI⁺): *m/z* 325 [M+Na]⁺; HRMS: found 325.1556 C₂₂H₂₂NaO requires 323.1563; **CHN** Anal. calcd. for C₂₂H₂₂O C: 87.38, H: 7.33%; found C: 87.27, H: 7.27%.

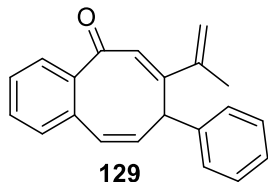
(6Z,9Z)-8-Phenyl-7-propylbenzo[8]annulen-5(8H)-one**(128)**

Synthesised from: 1-pentyne (168 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂

(167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (50:1 to 20:1 pentane:diethyl ether gradient elution) of the crude extract afforded the title compound (6Z,9Z)-8-Phenyl-7-propylbenzo[8]annulen-5(8H)-one (**128**) (76 mg, 0.26 mmol) in 33% yield as a colourless crystalline solid. **Rf** (9:1 pentane:diethyl ether): 0.59; **Mp** 73 - 75 °C; **IR** (NaCl, film): ν_{max} 3059, 3028, 2961, 2872, 1607, 1588, 1294, 1251, 1028, 783, 748, 701 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.81 – 7.75 (m, 1H, ArH), 7.45 – 7.37 (m, 2H, ArH), 7.34 – 7.28 (m, 2H, ArH), 7.26 – 7.14 (m, 4H, ArH), 6.78 (d, *J* = 10.4 Hz, 1H, CCHCH), 6.62 (dd, *J* = 10.4, 9.8 Hz, 1H, CCHCH), 6.47 (dd, *J* = 2.3, 1.3 Hz, 1H, OCCH), 4.88 (d, *J* = 9.8 Hz, 1H, CHPh), 2.19 – 2.15 (m, 2H, CCH₂CH₂), 1.51 – 1.24 (m, 2H, CH₂CH₂CH₃), 0.80 (t, *J* = 7.3 Hz, 3H, CH₂CH₂CH₃); **¹³C NMR** (100.05 MHz, CDCl₃): δ 194.5 (C), 165.8 (C), 141.4 (C), 138.4 (C), 135.6 (CH), 134.3 (C), 131.9

(CH), 130.7 (CH), 130.4 (CH), 128.6 (2 x CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 45.9 (CH), 38.2 (CH₂), 21.4 (CH₂), 13.9 (CH₃); **MS** (ESI⁺): *m/z* 289 [M+H]⁺; HRMS: found 289.1565 C₂₁H₂₁O⁺ requires 289.1587.

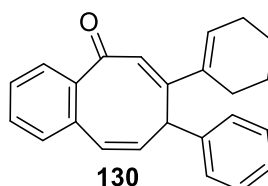
(6*E*,9*Z*)-8-Phenyl-7-(prop-1-en-2-yl)benzo[8]annulen-5(8*H*)-one (129)



Synthesised from: 2-methyl-1-buten-3-yne (162 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.48 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.48 M in hexanes, 1.70 mmol),

CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (gradient elution: 19:1 to 9:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-8-phenyl-7-(prop-1-en-2-yl)benzo[8]annulen-5(8*H*)-one (**129**) (113 mg, 0.39 mmol) in 50% yield as a colourless crystalline solid. **R_f** (9:1 pentane:diethyl ether): 0.32; **Mp**: 85 - 87 °C; **IR** (NaCl, film): ν_{max} 3028, 2921, 1608, 1588, 1496, 1445, 1288, 1251, 1122, 1023, 899, 786 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.80 – 7.72 (m, 1H, Ar*H*), 7.43 – 7.31 (m, 2H, Ar*H*), 7.24 – 7.08 (m, 6H, Ar*H*), 6.85 (d, *J* = 10.5 Hz, 1H, CCH*H*), 6.64 (dd, *J* = 10.5 Hz, 9.4 Hz, 1H, CCH*H*), 6.64 (s, 1H, OCCH), 5.11 (s, 1H, CCH_aH_b), 5.03 – 5.01 (m, 1H, CCH_aH_b), 5.02 (d, *J* = 9.4 Hz, 1H, CCH*H*), 1.69 (s, 3H, CCH₃); **¹³C NMR** (100.05 MHz, CDCl₃): δ 195.3 (C), 163.0 (C), 144.3 (C), 141.0 (C), 139.2 (C), 136.6 (CH), 134.5 (C), 132.5 (CH), 130.7 (CH), 130.6 (CH), 129.7 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 126.6 (CH), 118.1 (CH₂), 44.3 (CH), 22.1 (CH₃); **MS** (ESI⁺): *m/z* 309 [M+Na]⁺; HRMS: found 309.1258 C₂₁H₁₈NaO⁺ requires 309.1250.

(6*E*,9*Z*)-7-(Cyclohex-1-en-1-yl)-8-phenylbenzo[8]annulen-5(8*H*)-one (130)



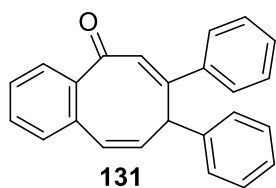
Synthesised from: 1-ethynylcyclohexene (199 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.52 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.52 M in hexanes, 1.70 mmol),

CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (9:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-7-(cyclohex-1-en-1-yl)-8-phenylbenzo[8]annulen-5(8*H*)-one (**130**) (147 mg, 0.45 mmol) in 57% yield as a yellow crystalline solid. **R_f** (9:1 pentane:diethyl ether): 0.23; **Mp**: 90 - 92 °C; **IR** (NaCl, film): ν_{max} 3059, 3027, 2929, 1604, 1587, 1496, 1448, 1285, 1116, 781, 744, 699 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.77 – 7.67 (m, 1H, Ar*H*), 7.41 – 7.30 (m, 2H, Ar*H*), 7.23 – 7.07 (m, 6H, Ar*H*),

6.83 (d, $J = 10.5$ Hz, 1H, CCHCH), 6.58 (dd, $J = 10.5$ Hz, 9.7 Hz, 1H, CCHCH), 6.58 (s, 1H, OCCH), 5.92 (m, 1H, CCHCH₂), 4.99 (d, $J = 9.7$ Hz, 1H, CHPh), 2.12 – 1.72 (m, 4H, CCHCH₂, CCH₂), 1.54 – 1.18 (m, 4H, 2 × CH₂CH₂CH₂); ¹³C NMR (100.05 MHz, CDCl₃): δ 195.3 (C), 164.7 (C), 141.4 (C), 139.5 (C), 138.0 (C), 136.8 (CH), 134.4 (C), 131.6 (CH), 130.6 (CH), 130.3 (CH), 130.0 (CH), 129.3 (CH), 128.3 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 126.4 (CH), 44.4 (CH), 27.8 (CH₂), 25.8 (CH₂), 22.4 (CH₂), 21.7 (CH₂); **MS** (ESI+): m/z 327 [M+H]⁺; HRMS: found 327.1745 C₂₄H₂₃O requires 327.1743; **CHN** Anal. calcd. for C₂₄H₂₂O C: 88.31, H: 6.79%; found C: 88.12, H: 6.84%.

(6*E*,9*Z*)-7,8-Diphenylbenzo[8]annulen-5(8*H*)-one

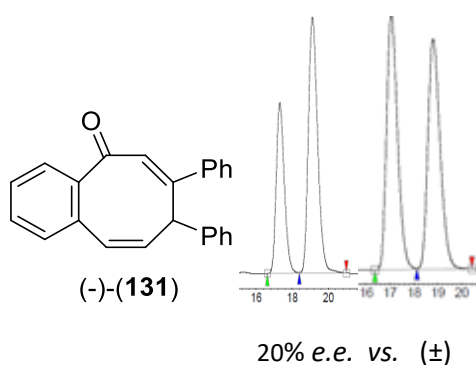
(131)



131

Method A: Synthesised from: phenylacetylene (187 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.52 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.52 M in hexanes,

1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (gradient elution: 19:1 to 9:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-7,8-diphenylbenzo[8]annulen-5(8*H*)-one (**131**) (128 mg, 0.40 mmol) in 50% yield as a colourless crystalline solid. **R_f** (9:1 pentane:diethyl ether): 0.24; **Mp**: 138–140 °C; **IR** (NaCl, film): ν_{max} 3059, 3028, 1607, 1587, 1494, 1443, 1291, 1249, 1117, 1031, 787, 697 cm⁻¹; ¹H NMR (400.2 MHz, CDCl₃): δ 7.82 – 7.74 (m, 1H, ArH), 7.45 – 7.34 (m, 2H, ArH), 7.25 – 7.14 (m, 6H, ArH), 7.12 – 6.95 (m, 5H, ArH), 6.91 (d, $J = 10.4$ Hz, 1H, CCHCH), 6.82 – 6.74 (m, 2H, OCCH, CCHCH), 5.25 (d, $J = 9.6$ Hz, 1H, CHPh); ¹³C NMR (100.05 MHz, CDCl₃): δ 194.9 (C), 161.8 (C), 141.2 (C), 139.9 (C), 139.0 (C), 137.0 (CH), 134.9 (CH), 134.5 (C), 130.6 (CH), 130.6 (CH), 129.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (2 × CH), 128.1 (CH), 128.0 (CH), 126.4 (CH), 45.9 (CH); **MS** (ESI+): m/z 323 [M+H]⁺; HRMS: found 323.1433 C₂₄H₁₉O requires 323.1430; **CHN** Anal. calcd. for C₂₄H₁₈O C: 89.41, H: 5.63%; found C: 89.09, H: 5.63%.

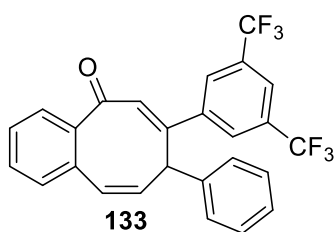


Method B: To a solution of (*R*)-1-(2-bromophenyl)-3-phenylprop-2-yn-1-ol (**245**) (295 mg, 1.03 mmol) in THF (1.5 mL) under argon at -50 °C was added *n*butyllithium (1.6 M in hexanes, 0.64 mL, 1.03 mmol). After 20 minutes a second portion of *n*butyllithium (1.6 M in hexanes, 0.71 mL, 1.14 mmol) was added.

After 15 minutes solid copper(I) bromide dimethyl sulfide (107 mg, 0.52 mmol) was then added under a cushion of argon forming a brown solution. After a further 1 hour (1-chloroprop-2-yn-1-yl)benzene (**78**) (0.50 mmol) was added to the reaction mixture, which was then allowed to warm slowly to -10 °C over a period of 30 minutes and kept there for 1 hour. The reaction was then quenched with pH = 7 ammonia buffered saturated aqueous ammonium chloride solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography (19:1 to 9:1 pentane:diethyl ether gradient elution) of the crude extract afforded the title compound (-)-(6*E*,9*Z*)-7,8-diphenylbenzo[8]annulen-5(8*H*)-one (**131**) (40 mg, 0.12 mmol) in 24% yield as a colourless solid. **HPLC:** Chiralcel OD-H; mobile phase, hexane:2-propanol (9:1 v/v); flow rate, 0.5 mL/min; retention times, 17.0 min (40%), 19.0 min (60%), 20% e.e.; $[\alpha]_D^{20}$: -83.8 (*c* = 0.6 in CHCl₃).

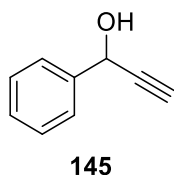
(6*E*,9*Z*)-7,8-Diphenylbenzo[8]annulen-5(8*H*)-one

(133)



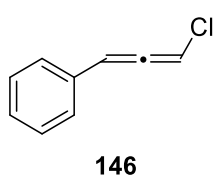
Synthesised from: 1-Ethynyl-3,5-bis(trifluoromethyl)benzene (302 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.3 mL, 1.37 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL, 1.62 mmol) *n*BuLi for bromine exchange (1.2 mL, 1.37 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A. Flash column chromatography (gradient elution: 19:1 to 9:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-7-(3,5-bis(trifluoromethyl)phenyl)-8-phenylbenzo[8]annulen-5(8*H*)-one (**133**) (21 mg, 0.05 mmol) in 6% yield as an orange oil. **R_f** (9:1 pentane:diethyl ether): 0.33; **IR** (NaCl, film): ν_{max} 3031, 2961, 1616, 1380, 1279, 1178, 1135, 907, 702 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.87 – 7.79 (m, 1H, ArH), 7.67 (s, 1H, ArH), 7.54 – 7.43 (m, 4H, ArH),

7.30 – 7.24 (m, 1H, ArH), 7.19 – 7.06 (m, 3H, ArH) 7.00 – 6.91 (m, 3H, ArH, CCHCH), 6.80 – 6.71 (m, 2H, OCCH, CCHCH), 5.21 (d, $J = 9.6$ Hz, 1H, CHPh); ^{13}C NMR (100.05 MHz, CDCl_3): δ 194.3 (C), 158.6 (C), 141.7 (C), 140.6 (C), 137.6 (C), 136.1 (CH), 136.0 (CH), 134.4 (C), 131.3 (q, $J = 33.6$ Hz, C), 131.2 (CH), 130.8 (CH), 129.8 (CH), 128.8 (2 $\times$ CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.3 (CH), 123.1 (q, $J = 272.9$ Hz, C), 121.8 (m, CH), 45.8 (CH); **MS** (ESI+): m/z 459 $[\text{M}+\text{H}]^+$; HRMS: found 459.1188 $\text{C}_{26}\text{H}_{17}\text{F}_6\text{O}^+$ requires 459.1178.

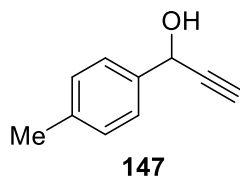
1-Phenylprop-2-yn-1-ol**(145)**

Following general procedure B the title compound 1-phenylprop-2-yn-1-ol (**145**) was afforded in >99% yield as a brown oil. **Rf** (9:1 pentane:diethyl ether): 0.47; **IR** (CHCl_3 , solution): ν_{max} 3592, 3306, 2121, 1494, 1454, 1017, 942, 649 cm^{-1} ; ^1H NMR (400.2 MHz, CDCl_3): δ 7.60 –

7.52 (m, 2H, ArH), 7.44 – 7.31 (m, 3H, ArH), 5.48 (d, $J = 2.2$ Hz, 1H, ArCHOH), 2.68 (d, $J = 2.2$ Hz, 1H, CCH), 2.06 (br s, 1H, ArCHOH); ^{13}C NMR (100.6 MHz, CDCl_3): δ 140.1 (C), 128.7 (CH), 128.5 (CH), 126.7 (CH), 83.6 (C), 74.9 (CH), 64.3 (CH); **MS** (ESI+): m/z 132 $[\text{M}]$; HRMS: found 132.0572 $\text{C}_9\text{H}_8\text{O}$ requires 132.0575. Compound characterisation data was found to be in agreement with literature values¹⁵¹ and was found to be identical to the reagent as purchased from Sigma-Aldrich (Cat. No. 226610-1G, CAS Number: 4187-87-5).

(3-Chloropropa-1,2-dien-1-yl)benzene**(146)**

Synthesised using general procedure C. Flash column chromatography (neat pentane) of the crude extract afforded the title compound (3-chloropropa-1,2-dien-1-yl)benzene (**146**). ^1H NMR (400.2 MHz, CDCl_3): δ 7.40 – 7.28 (m, 5H, ArH), 6.57 (d, $J = 5.8$ Hz, 1H, PhCH), 6.43 (d, $J = 5.8$ Hz, 1H, CHCl); ^1H NMR data found to be in agreement with literature values.¹⁵²

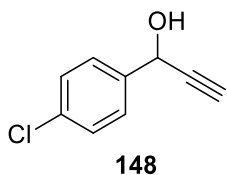
1-(p-Tolyl)prop-2-yn-1-ol**(147)**

Following general procedure B the title compound 1-(p-tolyl)prop-2-yn-1-ol (**147**) was afforded in >99% yield as a brown oil. **IR** (NaCl, film): ν_{max} 3530, 3364, 3290, 2117, 1614, 1513, 1179, 1016, 947, 817 cm^{-1} ; ^1H NMR (400.2 MHz, CDCl_3): δ 7.44 (d, $J = 7.9$ Hz, 2H, ArH),

7.20 (d, $J = 7.9$ Hz, 2H, ArH), 5.44 (dd, $J = 6.2, 2.1$ Hz, 1H, ArCHOH), 2.66 (d, $J = 2.1$ Hz, 1H, CCH), 2.36 (s, 3H, ArCH₃), 2.11 (d, $J = 6.2$ Hz, 1H, OH); ^{13}C NMR (100.6 MHz, CDCl_3): 128.5 (C), 137.2 (C), 129.4 (CH), 126.6 (CH), 83.7 (C), 74.7 (CH), 64.3 (CH), 21.2 (CH₃); **MS** (ESI+):

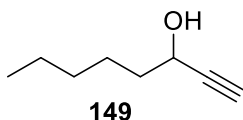
m/z 169 $[M+Na]^+$; HRMS: found 169.0626 $C_{10}H_{10}NaO^+$ requires 169.0624. Compound characterisation data was found to be in agreement with literature values.¹⁵¹

1-(4-Chlorophenyl)prop-2-yn-1-ol (148)



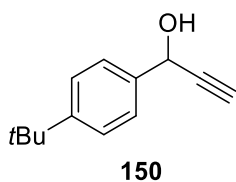
Following general procedure B the title compound 1-(4-chlorophenyl)prop-2-yn-1-ol (**148**) was afforded in 80% yield as a brown oil. **IR** (NaCl, film): $\nu_{\max}$ 3550, 3346, 3297, 2120, 1597, 1491, 1406, 1092, 1015, 950, 835, 792 cm^{-1} ; **^1H NMR** (400.2 MHz, $CDCl_3$): δ 7.53 – 7.47 (m, 2H, ArH), 7.39 – 7.34 (m, 2H, ArH), 5.49 – 5.42 (m, 1H, ArCHOH), 2.69 (d, J = 2.2 Hz, 1H, CCH), 2.21 (br d, J = 5.5 Hz, 1H, OH); **^{13}C NMR** (100.6 MHz, $CDCl_3$): 138.6 (C), 134.5 (C), 128.9 (CH), 128.1 (CH), 83.2 (C), 75.3 (CH), 63.8 (CH); **MS** (EI): m/z 166 $[M]$; HRMS: found 166.0185 C_9H_7ClO requires 166.0185 Compound characterisation data was found to be in agreement with literature values.¹⁵³

Oct-1-yn-3-ol (149)

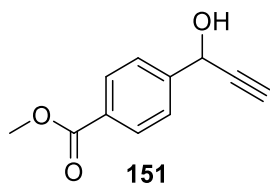


Following general procedure B the title compound oct-1-yn-3-ol (**149**) was afforded in 89% yield as a dark oil. **Rf** (4:1 pentane:diethyl ether): 0.34; **IR** (NaCl, film): $\nu_{\max}$ 3365, 3311, 2956, 2931, 2861, 1458, 1028, 654, 628 cm^{-1} ; **^1H NMR** (400.2 MHz, $CDCl_3$): δ 4.37 (td, J = 6.5, 2.0 Hz, 1H, CHOH), 2.46 (d, J = 2.0 Hz, 1H, CCH), 1.95 (br s, 1H, CHOH), 1.81 – 1.64 (m, 2H, CHOHCH₂), 1.55 – 1.19 (m, 6H, CH₂CH₂CH₂CH₃), 1.00 – 0.77 (m, 3H, CH₂CH₃); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 85.2 (C), 72.9 (CH), 62.4 (CH), 37.8 (CH₂), 31.6 (CH₂), 24.8 (CH₂), 22.7 (CH₂), 14.1 (CH₃). Data was found to be in agreement with literature values.¹⁵⁴

1-(4-(tert-Butyl)phenyl)prop-2-yn-1-ol (150)

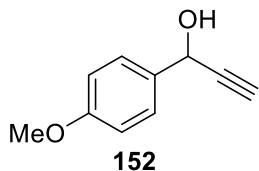


Following general procedure B the title compound 1-(4-(tert-butyl)phenyl)prop-2-yn-1-ol (**150**) was afforded in 95% yield as an orange oil. **Rf** 9:1 pentane:diethyl ether): 0.24; **IR** (NaCl, film) $\nu_{\max}$ 3292, 2964, 2904, 2869, 2118, 1613, 1511, 1410, 1364, 1269, 1017, 948, 839, cm^{-1} ; **^1H NMR** (400.2 MHz, $CDCl_3$): 7.54 – 7.47 (m, 2H, ArH), 7.45 – 7.39 (m, 2H, ArH), 5.45 (d, J = 2.2 Hz, 1H, ArCHOH), 2.67 (d, J = 2.2 Hz, 1H, CCH), 1.99 (s, 9H, C(CH₃)₃); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 151.8 (C), 137.3 (C), 126.5 (CH), 125.8 (CH), 83.8 (C), 74.8 (CH), 64.4 (CH), 34.8 (C), 31.4 (CH₃); **MS** (ESI+): m/z 211 $[M+Na]^+$; HRMS: found 211.1099 $C_{13}H_{16}NaO^+$ requires 211.1093. ^1H NMR data was found to be in agreement with literature values.¹⁵⁵

Methyl 4-(1-hydroxyprop-2-yn-1-yl)benzoate**(151)****151**

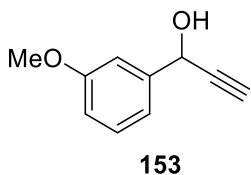
Following general procedure B the title compound methyl 4-(1-hydroxyprop-2-yn-1-yl)benzoate (**151**) was afforded in 91% yield as an orange oil. **Rf** (1:1 pentane:diethyl ether): 0.46; **IR** (NaCl, film): $\nu_{\max}$ 3428, 3291, 2954, 2118, 1717, 1612, 1437, 1413, 1312,

1285, 1192, 1114, 1019, 755, 708 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.07 – 8.02 (m, 2H, ArH), 7.65 – 7.59 (m, 2H ArH), 5.52 (dd, J = 6.1, 2.3 Hz, 1H, CHOH), 3.92 (s, 3H, OCH_3), 2.69 (d, J = 2.3 Hz, 1H CCH), 2.48 (d, J = 6.1 Hz, 1H CHOH); **^{13}C NMR** (100.6 MHz, CDCl_3): 166.9 (C), 144.9 (C), 130.3 (C), 130.1 (CH), 126.6 (CH), 83.1 (C), 75.5 (CH), 64.0 (CH), 52.4 (CH_3); **MS** (ESI+): m/z 213 [$\text{M}+\text{Na}$] $^+$; HRMS: found 213.0535 $\text{C}_{11}\text{H}_{10}\text{NaO}_3^+$ requires 213.0522.

1-(4-Methoxyphenyl)prop-2-yn-1-ol**(152)****152**

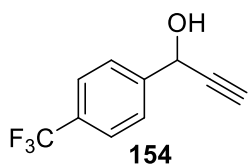
Following general procedure B the title compound 1-(4-methoxyphenyl)prop-2-yn-1-ol (**152**) was afforded in 97% yield as a brown oil. **Rf** (1:1 pentane:diethyl ether): 0.36; **IR** (NaCl, film): $\nu_{\max}$ 3286, 1610, 1511, 1248, 1174, 1111, 1030, 948 cm^{-1} ; **^1H NMR**

(400.2 MHz, CDCl_3): 7.51 – 7.45 (m, 2H, ArH), 6.95 – 6.89 (m, 2H, ArH), 5.42 (dd, J = 6.1, 2.2 Hz, 1H, CHOH), 3.82 (s, 3H, OCH_3), 2.66 (d, J = 2.2 Hz, 1H, CCH), 2.13 (d, J = 6.1 Hz, 1H, CHOH); **^{13}C NMR** (100.6 MHz, CDCl_3): 160.0 (C), 132.5 (C), 128.2 (CH), 114.2 (CH), 83.8 (C), 74.8 (CH), 64.2 (CH), 55.5 (CH_3); **MS** (ESI+): m/z 145 [$\text{M}+\text{OH}$] $^+$; HRMS: found 145.0638 $\text{C}_{10}\text{H}_9\text{O}^+$ requires 145.0648. Compound characterisation data was found to be in agreement with literature values.¹⁵⁶

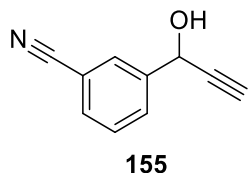
1-(3-Methoxyphenyl)prop-2-yn-1-ol**(153)****153**

Following general procedure B where addition of Grignard was carried out at -35°C , warmed to room temperature and stirred for 17 hours. The title compound 1-(3-methoxyphenyl)prop-2-yn-1-ol (**153**) was afforded in >99% yield as a brown oil. **Rf** (1:1

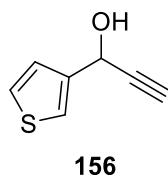
pentane:diethyl ether): 0.48; **IR** (NaCl, film) $\nu_{\max}$ 3394, 3287, 3004, 2942, 1601, 1588, 1488, 1261, 1037 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.31 (ddd, J = 8.2, 7.4, 0.6 Hz, 1H, ArH), 7.16 – 7.09 (m, 2H, ArH), 6.89 (ddd, J = 8.2, 2.5, 1.1 Hz, 1H, ArH), 5.45 (dd, J = 6.1, 2.2 Hz, 1H, ArCHOH), 3.83 (s, 3H, OCH_3), 2.67 (d, J = 2.2 Hz, 1H CCH), 2.20 (d, J = 6.1 Hz, 1H, OH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 160.0 (C), 141.7 (C), 129.9 (CH), 119.0 (CH), 114.4 (CH), 112.1 (CH), 83.5 (C), 74.9 (CH), 64.5 (CH), 55.4 (CH_3); **MS** (ESI+): m/z 145 [$\text{M}+\text{OH}$] $^+$; HRMS: found 145.0633 $\text{C}_{10}\text{H}_9\text{O}^+$ requires 145.0648. Compound characterisation data was found to be in agreement with literature values.¹⁵⁷

1-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (154)

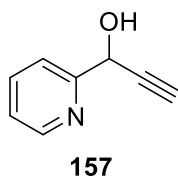
Following general procedure B the title compound 1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (**154**) was afforded in 98% yield as a dark oil. **Rf** (9:1 pentane:diethyl ether): 0.12; **IR** (NaCl, film): $\nu_{\max}$ 3308, 2123, 1621, 1418, 1327, 1166, 1126, 1068, 1018, 948, 848, 668 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.71 – 7.63 (m, 4H, ArH), 5.53 (br s, 1H, CHOH), 2.71 (d, J = 2.3 Hz, 1H, CCH), 2.37 (br s, 1H, CHOH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 143.8 (C), 130.8 (q, J = 32.5 Hz, C), 127.0 (CH), 125.8 (q, J = 3.8 Hz, CH), 124.1 (q, J = 272.1, C), 82.9 (C), 75.7 (CH), 63.9 (CH); **^{19}F NMR** (376.5 MHz, CDCl_3): δ -62.63 (s); **MS** (EI+): m/z 200 $[\text{M}]^+$; HRMS: found 200.0440 $\text{C}_{10}\text{H}_7\text{F}_3\text{O}^+$ requires 200.0449.

3-(1-Hydroxyprop-2-yn-1-yl)benzonitrile (155)

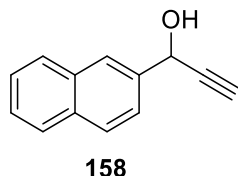
Following general procedure B where addition of Grignard was carried out at -40 °C. The title compound 3-(1-hydroxyprop-2-yn-1-yl)benzonitrile (**155**) was afforded in 92% yield as a brown oil. **Rf** (1:1 pentane:diethyl ether): 0.39; **IR** (NaCl, film): $\nu_{\max}$ 3400, 3291, 2233, 2119, 1482, 1434, 1146, 1028, 804, 737, 689 cm^{-1} ; **^1H NMR** (500.1 MHz, CDCl_3): δ 7.90 – 7.87 (m, 1H, ArH), 7.82 – 7.78 (m, 1H, ArH), 7.64 (dt, J = 7.7, 1.5 Hz, 1H, ArH), 7.51 (td, J = 7.7, 0.6 Hz, 1H, ArH), 5.51 (dd, J = 5.8, 2.2 Hz, 1H, ArCHOH), 2.73 (d, J = 2.2 Hz, 1H, CCH), 2.37 (d, J = 5.8 Hz, 1H, OH); **^{13}C NMR** (125.8 MHz, CDCl_3): δ 141.5 (C), 132.2 (CH), 131.2 (CH), 130.4 (CH), 129.6 (CH), 118.7 (C), 112.9 (C), 82.5 (C), 76.1 (CH), 63.5 (CH); **MS** (ESI+): m/z 158 $[\text{M}+\text{H}]^+$; HRMS: found 158.0604 $\text{C}_{10}\text{H}_8\text{NO}^+$ requires 158.0600.

1-(Thiophen-3-yl)prop-2-yn-1-ol (156)

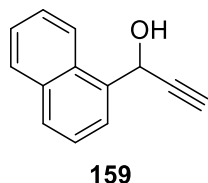
Following general procedure B the title compound 1-(thiophen-3-yl)prop-2-yn-1-ol (**156**) was afforded in 96% yield as an orange solid. **Rf** (10:1 pentane:diethyl ether): 0.05; **Mp**: 59-61 °C [lit. 57-59 °C];¹⁵⁸ **IR** (NaCl, film): $\nu_{\max}$ 3290, 2119, 1420, 1294, 1150, 1017, 973, 904, 835, 793, 731, 652 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.45 – 7.41 (m, 1H, ArH), 7.33 (dd, J = 5.0, 3.0 Hz, 1H, ArH), 7.21 (dd, J = 5.0, 1.3 Hz, 1H, ArH), 5.50 (dd, J = 6.8, 2.1 Hz, 1H, ArCHOH), 2.65 (d, J = 2.1 Hz, 1H, CCH), 2.31 (d, J = 6.8 Hz, 1H, OH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 141.5 (C), 126.8 (CH), 126.4 (CH), 123.0 (CH), 83.4 (C), 74.2 (CH), 60.5 (CH). Compound characterisation data was found to be in agreement with literature values.¹⁵⁸

1-(Pyridin-2-yl)prop-2-yn-1-ol**(157)**

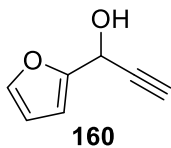
Following general procedure B the title compound 1-(pyridin-2-yl)prop-2-yn-1-ol (**157**) was afforded in 95% yield as a brown solid. **Mp**: 67-69 °C; **IR** (NaCl, film): $\nu_{\max}$ 3290, 2844, 2115, 1595, 1573, 1474, 1438, 1048, 1005, 950, 761, 666, cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.56 (ddd, J = 5.0, 1.8, 1.0 Hz, 1H, ArH), 7.75 (ddd, 7.7, 7.7, 1.8 Hz, 1H, ArH), 7.54 (app dq, J = 7.9, 1.0 Hz, 1H, ArH), 7.30 – 7.25 (m, 1H, ArH), 5.50 (d, J = 2.3 Hz, 1H CHOH), 4.92 (br s, 1H, CHOH), 2.57 (d, J = 2.3 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 157.6 (C), 148.4 (CH), 137.5 (CH), 123.4 (CH), 121.0 (CH), 83.4 (C), 73.9 (CH), 63.5 (CH); **MS** (ESI+): m/z 134 $[\text{M}+\text{H}]^+$; HRMS: found 134.0578 $\text{C}_8\text{H}_8\text{NO}^+$ requires 134.0600.

1-(Naphthalen-2-yl)prop-2-yn-1-ol**(158)**

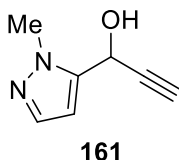
Following general procedure B the title compound 1-(naphthalen-2-yl)prop-2-yn-1-ol (**158**) was afforded in 99% yield as a brown solid. **Rf** 9:1 pentane:diethyl ether): 0.06; **Mp**: 53 - 55 °C [lit. 53.8-54.5 °C];¹⁵⁹ **IR** (NaCl, film): $\nu_{\max}$ 3289, 3055, 2116, 1600, 1017, 820 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.02 – 7.99 (m, 1H, ArH), 7.90 – 7.82 (m, 3H, ArH), 7.66 (dd, J = 8.5, 1.8 Hz, 1H, ArH), 7.54 – 7.48 (m, 2H, ArH), 5.64 (d, J = 2.2 Hz, 1H, ArCHOH), 2.74 (d, J = 2.2 Hz, 1H, CCH), 2.38 (br s, 1H, OH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 137.4 (C), 133.4 (C), 133.3 (C), 128.8 (CH), 128.4 (CH), 127.8 (CH), 126.6 (CH), 126.5 (CH), 125.6 (CH), 124.6 (CH), 83.6 (C), 75.3 (CH), 64.7 (CH); **MS** (ESI+): m/z 165 $[\text{M}-\text{OH}]^+$; HRMS: found 165.0701 $\text{C}_{13}\text{H}_9^+$ requires 165.0699. ^1H NMR data was found to be in agreement with literature values.¹⁵⁹

1-(Naphthalen-1-yl)prop-2-yn-1-ol**(159)**

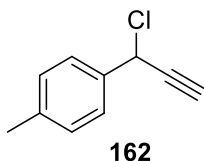
Following general procedure B, then flash column chromatography (17:3 pentane:diethyl ether) of the crude extract afforded the title compound 1-(naphthalen-1-yl)prop-2-yn-1-ol (**159**) in 89% yield as a pale yellow solid. **Rf** (7:3 pentane:diethyl ether): 0.33; **Mp**: 62-64 °C [lit. 61-63 °C];¹⁶⁰ **IR** (NaCl, film): $\nu_{\max}$ 3290, 3050, 2118, 1559, 1510, 1005, 936, 802, 780 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.31 – 8.26 (m, 1H, ArH), 7.92 – 7.83 (m, 3H, ArH), 7.612 – 7.45 (m, 3H, ArH), 6.14 (d, J = 2.2 Hz, 1H, ArCHOH), 2.75 (d, J = 2.2 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 135.1 (C), 134.2 (C), 130.6 (C), 129.7 (CH), 128.9 (CH), 126.7 (CH), 126.1 (CH), 125.4 (CH), 124.8 (CH), 123.9 (CH), 83.3 (C), 75.7 (CH), 62.9 (CH); **MS** (ESI+): m/z 205 $[\text{M}+\text{Na}]^+$; HRMS: found 205.0629 $\text{C}_{13}\text{H}_{10}\text{NaO}^+$ requires 205.0624. Compound characterisation data was found to be in agreement with literature values.¹⁵⁵

1-(Furan-2-yl)prop-2-yn-1-ol**(160)**

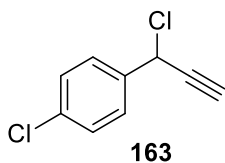
Following general procedure B the title compound 1-(furan-2-yl)prop-2-yn-1-ol (**160**) was afforded in >99% yield as a dark oil. **Rf** (3:2 pentane:diethyl ether): 0.34; **IR** (ATR): $\nu_{\max}$ 3358, 3290, 2923, 2118, 1187, 1145, 1073, 1009, 964, 745 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.42 (dd, J = 1.8, 0.9 Hz, 1H, ArH), 6.47 (ddd, J = 3.3, 0.9, 0.9 Hz, 1H, ArH), 6.36 (dd, J = 3.3, 1.8 Hz, 1H, ArH), 5.50 (app br s, 1H, HOCH), 2.62 (d, J = 2.3 Hz, 1H, CCH), 2.53 (br s, 1H, HOCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 152.5 (C), 143.3 (CH), 110.6 (CH), 108.1 (CH), 81.1 (C), 74.2 (CH), 58.1 (CH); **MS** (EI+): m/z 122 $[\text{M}]^+$; HRMS: found 122.0358 $\text{C}_7\text{H}_6\text{O}_2^+$ requires 122.0368. Compound characterisation data was found to be in agreement with literature values.¹⁶¹

1-(1-Methyl-1H-pyrazol-5-yl)prop-2-yn-1-ol**(161)**

Following general procedure B the title compound 1-(1-methyl-1H-pyrazol-5-yl)prop-2-yn-1-ol (**161**) was afforded in 80% yield as a yellow solid. **Mp**: 109 - 111 $^{\circ}\text{C}$; **Rf** (3:2 pentane:diethyl ether): 0.08; **IR** (NaCl, film): $\nu_{\max}$ 3286, 2950, 2851, 2119, 1488, 1430, 1398, 1285, 1201, 1033, 950, 782, 651 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.36 (d, J = 1.8 Hz, 1H, ArH), 6.35 (d, J = 1.8 Hz, 1H, ArH), 5.53 (dd, J = 6.1, 2.1 Hz, 1H, HOCH), 3.93 (s, 3H, NCH_3), 3.26 (br d, J = 6.1 Hz, 1H, OHCH), 2.66 (d, J = 2.1 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 140.6 (C), 138.0 (CH), 105.9 (CH), 81.3 (C), 74.7 (CH), 56.5 (CH), 37.2 (CH_3); **MS** (ESI+): m/z 137 $[\text{M}+\text{H}]^+$; HRMS: found 137.0716 $\text{C}_7\text{H}_9\text{N}_2\text{O}^+$ requires 137.0709.

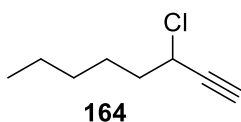
1-(1-Chloroprop-2-yn-1-yl)-4-methylbenzene**(162)**

General procedure C afforded the title compound as an inseparable 7:1 mixture of $\text{S}_{\text{N}}2$: $\text{S}_{\text{N}}2'$ products 1-(1-chloroprop-2-yn-1-yl)-4-methylbenzene and 1-(1-chloropropa-1,2-dien-1-yl)-4-methylbenzene. Providing 1-(1-chloroprop-2-yn-1-yl)-4-methylbenzene (**162**) in 81% yield as a pale yellow oil. **IR** (NaCl, film): $\nu_{\max}$ 3295, 3029, 2865, 1614, 1512, 1198, 1181, 837, 820, 726 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.47 (d, J = 8.0 Hz, 2H, ArH), 7.20 (d, J = 8.0 Hz, 2H, ArH), 5.64 (d, J = 2.3 Hz, 1H, ArCHCl), 2.84 (d, J = 2.3 Hz, 1H, CCH), 2.37 (s, 3H, ArCH_3); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 139.4 (C), 136.3 (C), 129.7 (CH), 127.6 (CH), 80.9 (C), 76.7 (CH), 49.2 (CH), 21.4 (CH_3); **MS** (EI+): m/z 129 $[\text{M}-\text{Cl}]^+$; HRMS: found 129.0745 $\text{C}_{10}\text{H}_9^+$ requires 129.0699.

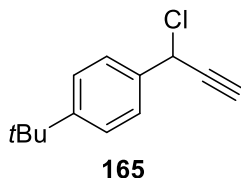
1-Chloro-4-(1-chloroprop-2-yn-1-yl)benzene**(163)**

General procedure C afforded the title compound as an inseparable 32:1 mixture of $S_N2:S_N2'$ products 1-chloro-4-(1-chloroprop-2-yn-1-yl)benzene and 1-chloro-4-(1-chloropropa-1,2-dien-1-yl)benzene.

Providing 1-chloro-4-(1-chloroprop-2-yn-1-yl)benzene (**163**) in 97% yield as a pale yellow oil. **IR** (NaCl, film): $\nu_{\max}$ 3297, 2955, 2127, 1597, 1491, 1408, 1195, 1093, 1016, 989, 835, 822, 729, 687 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.55 – 7.49 (m, 2H, ArH), 7.40 – 7.34 (m, 2H, ArH), 5.62 (d, $J = 2.4$ Hz, 1H, ArCHCl), 2.89 (d, $J = 2.4$ Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 136.6 (C), 135.3 (C), 129.2 (CH), 129.1 (CH), 80.2 (C), 77.3 (CH), 48.3 (CH); **MS** (EI+): m/z 149 $[\text{M}-\text{Cl}]^+$; HRMS: found 149.0178 $\text{C}_9\text{H}_6\text{Cl}^+$ requires 149.0153.

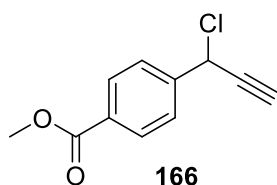
3-Chlorooct-1-yne**(164)**

General procedure C afford the title compound 3-chlorooct-1-yne (**164**) in >99% yield as a dark oil. **IR** (NaCl, film): $\nu_{\max}$ 2957, 2931, 2861, 1734, 1458, 1377, 1171, 1119, 722 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 4.50 (dt, $J = 6.7, 2.3$ Hz, 1H, CH_2CHCl), 2.59 (d, $J = 2.3$ Hz, 1H, CCH), 2.00 – 1.90 (m, 2H, CH_2CHCl), 1.61 – 1.48 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 1.42 – 1.22 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.96 – 0.85 (m, 3H, CH_2CH_3); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 82.2 (C), 74.3 (CH), 48.1 (CH), 39.1 (CH₂), 31.1 (CH₂), 25.9 (CH₂), 22.6 (CH₂), 14.1 (CH₃). Data was found to be in agreement with literature values.¹⁶²

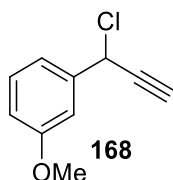
1-(*tert*-Butyl)-4-(1-chloroprop-2-yn-1-yl)benzene**(165)**

General procedure D afforded the title compound as an inseparable 11:1 mixture of $S_N2:S_N2'$ products 1-(*tert*-butyl)-4-(1-chloroprop-2-yn-1-yl)benzene and 1-(*tert*-butyl)-4-(3-chloropropa-1,2-dien-1-yl)benzene. Providing 1-(*tert*-butyl)-4-(1-chloroprop-2-

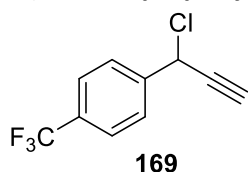
yn-1-yl)benzene (**165**) in 89% yield as a brown oil. **IR** (NaCl, film): $\nu_{\max}$ 3295, 2964, 2904, 2869, 2126, 1509, 1461, 1270, 1364, 839, 817, 691 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.55 – 7.48 (m, 2H, ArH), 7.45 – 7.39 (m, 2H, ArH), 5.65 (d, $J = 2.4$ Hz, 1H, ArCHCl), 2.85 (d, $J = 2.4$ Hz, CCH), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 152.6 (C), 153.1 (C), 127.4 (CH), 126.0 (CH), 80.9 (C), 76.7 (CH), 49.1 (CH), 34.9 (C), 31.4 (CH₃); **MS** (ESI+): m/z 171 $[\text{M}-\text{Cl}]^+$; HRMS: found 171.1083 $\text{C}_{13}\text{H}_{15}^+$ requires 171.1168.

Methyl 4-(1-chloroprop-2-yn-1-yl)benzoate**(166)**

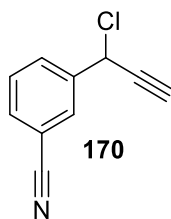
General procedure D afforded the title compound as an inseparable 11:1 mixture of $S_N2:S_N2'$ products methyl 4-(1-chloroprop-2-yn-1-yl)benzoate and methyl 4-(1-chloroprop-1,2-dien-1-yl)benzoate. Yielding 4-(1-chloroprop-2-yn-1-yl)benzoate (**166**) in 90% yield as a dark solid. **Mp**: 86 - 88 °C; **IR** (NaCl, film): $\nu_{\max}$ 3256, 2952, 2126, 1719, 1415, 1288, 1115, 710 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.09 – 8.04 (m, 2H, ArH), 7.68 – 7.63 (m, 2H, ArH), 5.67 (d, J = 2.4 Hz, 1H, CHOH), 3.93 (s, 3H, OCH_3), 2.88 (d, J = 2.4 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 166.5 (C), 142.6 (C), 131.0 (C), 130.3 (CH), 127.7 (CH), 80.0 (C), 77.5 (CH), 52.4 (CH_3), 48.3 (CH); **MS** (ESI+): m/z 173 [$\text{M}-\text{Cl}$] $^+$; HRMS: found 173.0606 $\text{C}_{11}\text{H}_9\text{O}_2^+$ requires 173.0597.

1-(1-Chloroprop-2-yn-1-yl)-3-methoxybenzene**(168)**

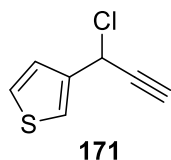
General procedure D afforded the title compound 1-(1-chloroprop-2-yn-1-yl)-3-methoxybenzene (**168**) in quantitative yield as a brown oil. **IR** (NaCl, film): $\nu_{\max}$ 3291, 3004, 2960, 2837, 2124, 1602, 1587, 1491, 1466, 1455, 1435, 1318, 1282, 1265, 1160, 1042, 715 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.34 – 7.28 (m, 1H, ArH), 7.18 – 7.12 (m, 2H, ArH), 6.90 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H, ArH), 5.62 (d, J = 2.5 Hz, 1H, ArCHCl), 3.84 (s, 3H, OCH_3), 2.85 (d, J = 2.5 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 160.0 (C), 139.5 (C), 130.0 (CH), 120.0 (CH), 115.0 (CH), 113.2 (CH), 80.6 (C), 76.9 (CH), 55.5 (CH_3), 49.1 (CH); **MS** (EI+): m/z 145 [$\text{M}-\text{Cl}$] $^+$; HRMS: found 145.0631 $\text{C}_{10}\text{H}_9\text{O}^+$ requires 145.0648.

1-(1-Chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene**(169)**

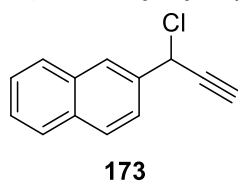
General procedure D afforded the title compound as an inseparable 6:1 mixture of $S_N2:S_N2'$ products 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene and 1-(3-chloroprop-1,2-dien-1-yl)-4-(trifluoromethyl)benzene. Providing 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**169**) in 87% yield as a dark oil. **IR** (NaCl, film): $\nu_{\max}$ 3306, 2129, 1620, 1420, 1326, 1168, 1127, 1068, 1020, 992, 849, 828 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.74 – 7.63 (m, 4H, ArH), 5.67 (d, J = 2.4 Hz, 1H, CHCl), 2.89 (d, J = 2.4 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 141.8 (C), 131.4 (q, J = 32.7 Hz, C), 128.1 (CH), 126.1 (q, J = 3.7 Hz, CH), 123.9 (q, J = 272.3 Hz, C), 79.9 (C), 77.7 (CH), 48.1 (CH); **^{19}F NMR** (376.5 MHz, CDCl_3): δ -62.80 (s); **MS** (EI+): m/z 218 [M] $^+$; HRMS: found 218.0105 $\text{C}_{10}\text{H}_6^{35}\text{ClF}_3^+$ requires 218.0110.

3-(1-Chloroprop-2-yn-1-yl)benzonitrile**(170)****170**

General procedure D afforded the title compound as an inseparable 6:1 mixture of $S_N2:S_N2'$ products 3-(1-chloroprop-2-yn-1-yl)benzonitrile and 3-(1-chloropropa-1,2-dien-1-yl)benzonitrile. Providing 3-(1-chloroprop-2-yn-1-yl)benzonitrile (**170**) in 83% yield as a brown oil. **IR** (NaCl, film): $\nu_{\max}$ 3293, 3065, 2232, 1481, 1434, 1269, 1147, 804, 714, 681 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.92 – 7.89 (m, 1H, ArH), 7.85 – 7.78 (m, 1H, ArH), 7.69 – 7.64 (m, 1H, ArH), 7.53 (app t, J = 7.9 Hz, 1H, ArH), 5.65 (d, J = 2.3 Hz, 1H, ArCHCl), 2.92 (d, J = 2.3 Hz, 1H, CCH); **^{13}C NMR** (125.0 MHz, CDCl_3): δ 139.6 (C), 132.8 (CH), 132.1 (CH), 131.3 (CH), 129.9 (CH), 118.2 (C), 113.2 (C), 74.9 (C), 78.1 (CH), 47.6 (CH); **MS** (EI+): m/z 373 [$2\text{M}+\text{Na}$] $^+$; HRMS: found 373.0266 $\text{C}_{20}\text{H}_{12}\text{Cl}_2\text{N}_2\text{Na}^+$ requires 373.0270.

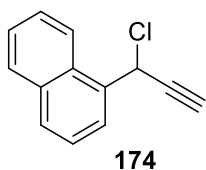
3-(1-Chloroprop-2-yn-1-yl)thiophene**(171)****171**

General procedure D afforded the title compound as an inseparable 11:1 mixture of $S_N2:S_N2'$ products 3-(1-chloroprop-2-yn-1-yl)thiophene and 3-(1-chloropropa-1,2-dien-1-yl)thiophene. Providing 3-(1-chloroprop-2-yn-1-yl)thiophene (**171**) in 92% yield as a brown oil. **IR** (NaCl, film): $\nu_{\max}$ 3292, 3105, 1671, 1419, 1290, 824, 782, 744, 704 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.51 – 7.48 (m, 1H, ArH), 7.34 (dd, J = 5.1, 3.0 Hz, 1H, ArH), 7.23 (dd, J = 5.1, 1.1 Hz, 1H, ArH), 5.73 (d, J = 2.4 Hz, 1H, ArCHCl), 2.82 (d, J = 2.4 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 138.7 (C), 127.2 (CH), 126.8 (CH), 124.5 (CH), 80.6 (C), 75.9 (CH), 44.2 (CH); **MS** (EI): m/z 155 [M]; HRMS: found 155.9803 $\text{C}_7\text{H}_5\text{ClS}$ requires 155.9800.

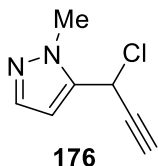
2-(1-Chloroprop-2-yn-1-yl)naphthalene**(173)****173**

General procedure D afforded the title compound as an inseparable 13:1 mixture of $S_N2:S_N2'$ products 2-(1-chloroprop-2-yn-1-yl)naphthalene and 2-(3-chloropropa-1,2-dien-1-yl)naphthalene.

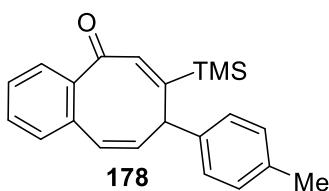
Providing 2-(1-chloroprop-2-yn-1-yl)naphthalene (**173**) in 86% yield as a brown solid. **Mp**: 62–64 $^{\circ}\text{C}$; **IR** (NaCl, film): $\nu_{\max}$ 3293, 3058, 1600, 1508, 860, 818, 751, 705 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.03 (d, J = 1.2 Hz, 1H, ArH), 7.92 – 7.78 (m, 3H, ArH), 7.68 (dd, J = 8.6, 1.9 Hz, 1H, ArH), 7.57 – 7.47 (m, 2H, ArH), 5.83 (d, J = 2.4 Hz, 1H, ArCHCl), 2.93 (d, J = 2.4 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 135.3 (C), 133.6 (C), 133.1 (C), 129.2 (CH), 128.5 (CH), 127.9 (CH), 127.1 (CH), 126.8 (2 x CH), 125.1 (CH), 80.7 (C), 77.3 (CH), 49.5 (CH); **MS** (ESI+): m/z 165 [$\text{M}-\text{Cl}$] $^+$; HRMS: found 165.0707 C_{13}H_9 requires 165.0699.

1-(1-Chloroprop-2-yn-1-yl)naphthalene (174)

General thionyl chloride procedure afforded the title compound as an inseparable 4:1 mixture of $S_N2:S_N2'$ products 1-(1-chloroprop-2-yn-1-yl)naphthalene and 1-(3-chloroprop-1,2-dien-1-yl)naphthalene. Providing 1-(1-chloroprop-2-yn-1-yl)naphthalene (**174**) in 75% yield as a brown oil. **IR** (NaCl, film): $\nu_{\max}$ 3293, 3054, 1597, 1511, 966, 800, 779 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.29 – 8.24 (m, 1H, ArH), 8.01 – 7.83 (m, 3H, ArH), 7.68 – 7.45 (m, 3H, ArH), 6.35 (d, J = 2.4 Hz, 1H, ArCHCl), 2.95 (d, J = 2.4 Hz, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 134.2 (C), 132.9 (C), 130.6 (CH), 130.0 (C), 129.2 (CH), 127.0 (CH), 126.5 (CH), 126.4 (CH), 125.3 (CH), 123.4 (CH), 80.6 (C), 71.3 (CH), 47.2 (CH); **MS** (ESI+): m/z 165 $[\text{M}-\text{Cl}]^+$; HRMS: found 165.0700 $\text{C}_{13}\text{H}_9^-$ requires 165.0699.

5-(1-Chloroprop-2-yn-1-yl)-1-methyl-1H-pyrazole (176)

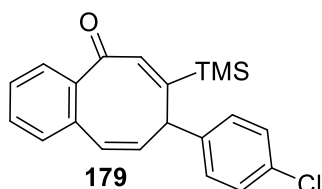
Using general procedure D but stirred at room temperature for 17 hours afforded the title compound 5-(1-chloroprop-2-yn-1-yl)-1-methyl-1H-pyrazole (**176**) in 99% yield as a yellow solid. **Mp**: 112 – 114 °C; **IR** (NaCl, film): $\nu_{\max}$ 3294, 2952, 2124, 1400, 1202, 795, 750, 722, 673, 650 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.69 (d, J = 2.3 Hz, 1H, ArH), 6.62 (d, J = 2.3 Hz, 1H, ArH), 5.75 (d, J = 2.5 Hz, 1H, ArCHCl), 4.23 (s, 3H, NCH_3), 2.93 (d, J = 2.5 Hz, 1H, CCH); **^{13}C NMR** (125.6 MHz, CDCl_3): δ 139.9 (C), 135.9 (CH), 107.3 (CH), 77.7 (CH), 77.1 (C), 38.6 (CH), 37.1 (CH_3); **MS** (ESI+): m/z 151 $[\text{M}-\text{Cl}+\text{MeOH}]^+$; HRMS: found 151.0873 $\text{C}_8\text{H}_{11}\text{N}_2\text{O}^+$ requires 151.0866.

(6E,9Z)-8-(p-Tolyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (178)

Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) $n\text{BuLi}$ for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol) 1-(1-chloroprop-2-yn-1-yl)-4-methylbenzene (**162**) (130 mg, 0.79 mmol) using general procedure A. Flash column chromatography (20:1 pentane:diethyl ether) of the crude extract afforded the title compound (6E,9Z)-8-(p-tolyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**178**) (142 mg, 0.43 mmol) in 54% yield as a colourless crystalline solid. **Rf** (10:1 pentane:diethyl ether): 0.39; **Mp**: 100–102 °C; **IR** (NaCl, film): $\nu_{\max}$ 3024, 2953, 1611, 1590, 1515, 1276, 1249, 1008, 913, 841, 781, 760 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.87 (dd, J = 7.6 Hz, 1.7 Hz, 1H, ArH), 7.45 – 7.34 (m, 2H, ArH), 7.19 (dd, J = 7.3 Hz, 1.7 Hz, 1H, ArH), 7.11 – 7.03 (m, 4H, ArH), 6.76 (d, J = 10.7, 1H, CCHCH), 6.73 (d, J = 1.2 Hz, 1H, OCCH), 6.65 (dd, J = 10.7 Hz, 9.7

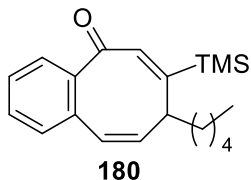
Hz, 1H, CCHCH), 4.89 (d, J = 9.7 Hz, 1H, CHAr), 2.29 (s, 3H, ArCH₃), -0.05 (s, 9H, Si(CH₃)₃); ¹³C NMR (100.05 MHz, CDCl₃): δ 195.3 (C), 165.6 (C), 141.7 (CH), 140.3 (C), 136.7 (C), 136.6 (C), 136.4 (CH), 135.1 (C), 131.0 (CH), 130.8 (CH), 129.4 (CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 45.7 (CH), 21.1 (CH₃), 0.07 (CH₃); **MS** (ESI+): m/z 333 [M+H]⁺; HRMS: found 333.1674 C₂₂H₂₅OSi⁺ requires 333.1669.

(6E,9Z)-8-(4-Chlorophenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (179)



Synthesised from: trimethylsilylacetylene (235 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) and 1-chloro-4-(1-chloroprop-2-yn-1-yl)benzene (**163**) (130 mg, 0.79 mmol) using general procedure A. Flash column chromatography (50:1 to 20:1 pentane:diethyl ether gradient elution) of the crude extract afforded the title compound (6E,9Z)-8-(4-chlorophenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**179**) (152 mg, 0.43 mmol) in 54% yield as a colourless crystalline solid. **Rf** (10:1 pentane:diethyl ether): 0.22; **Mp**: 121 - 123 °C; **IR** (NaCl, film): $\nu_{\max}$ 3026, 2954, 1611, 1591, 1492, 1276, 1250, 1093, 1014, 912, 841, 783 cm⁻¹; ¹H NMR (400.2 MHz, CDCl₃): δ 7.84 – 7.76 (m, 1H, ArH), 7.44 – 7.32 (m, 2H, ArH), 7.22 – 7.13 (m, 3H, ArH), 7.12 – 7.06 (m, 2H, ArH), 6.78 (d, J = 10.6 Hz, 1H, CCHCH), 6.75 (d, J = 0.9 Hz, 1H, OCCH), 6.57 (dd, J = 10.6 Hz, 9.7 Hz, 1H, CCHCH), 4.86 (d, J = 9.7 Hz, 1H, CHAr), 0.01 (s, 9H, Si(CH₃)₃); ¹³C NMR (100.05 MHz, CDCl₃): δ 195.4 (C), 163.9 (C), 142.0 (CH), 140.1 (C), 138.4 (C), 135.7 (CH), 134.8 (C), 132.7 (C), 131.0 (CH), 130.6 (CH), 129.5 (CH), 129.3 (CH), 129.3 (CH), 128.4 (CH), 128.1 (CH), 45.44 (CH), 0.1 (CH₃); **MS** (ESI+): m/z 353 [M+H]⁺; HRMS: found 353.1120 C₂₁H₂₁ClOSi⁺ requires 353.1123.

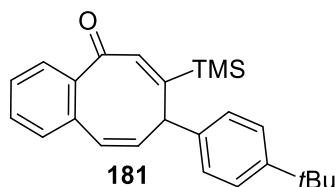
(6E,9Z)-8-Pentyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (180)



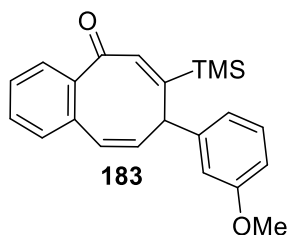
Synthesised from: trimethylsilylacetylene (235 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), 3-chlorooct-1-yne (**164**) (114 mg, 0.79 mmol) and warmed directly to ambient temperature before stirring for 1 hour using general procedure A. Flash column chromatography (neat pentane to 19:1 pentane:diethyl ether gradient elution) afforded the title compound (6E,9Z)-8-pentyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**180**) (50 mg, 0.16 mmol) in 20% yield as a

lightly coloured oil. **Rf** (9:1 pentane:diethyl ether): 0.53; **IR** (ATR): $\nu_{\max}$ 2954, 2927, 2857, 1611, 1590, 1457, 1275, 1248, 1007, 836, 779, 757 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.87 – 7.78 (m, 1H, ArH), 7.46 (ddd, $J = 7.5, 7.5, 1.5$ Hz, 1H, ArH), 7.39 (ddd, $J = 7.5, 7.5, 1.5$ Hz, 1H, ArH), 7.25 – 7.20 (m, 1H, ArH), 6.60 (d, $J = 10.7$ Hz, 1H CCHCH), 6.56 (d, $J = 1.2$ Hz, 1H, OCCH), 5.92 (dd, $J = 10.7, 9.3$ Hz, 1H, CCHCH), 3.36 (ddd, $J = 9.3, 9.3, 5.9$ Hz, 1H, CHCH_2H_b), 1.69 – 1.56 (m, 2H, CHCH_2CH_2), 1.30 – 0.93 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.80 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 0.26 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.1 MHz, CDCl_3): δ 196.5 (C), 164.5 (C), 140.7 (CH), 140.5 (CH), 140.1 (C), 135.4 (C), 130.9 (CH), 130.7 (CH), 129.5 (CH), 128.3 (CH), 127.7 (CH), 42.8 (CH), 32.7 (CH_2), 31.7 (CH_2), 28.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 0.6 (CH_3); **MS** (ESI+): m/z 335 $[\text{M}+\text{Na}]^+$; HRMS: found 335.1797 $\text{C}_{20}\text{H}_{28}\text{NaOSi}^+$ requires 335.1802.

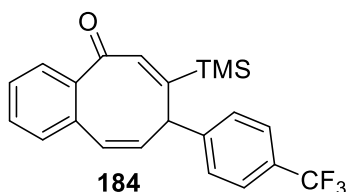
(6E,9Z)-8-(4-(tert-Butyl)phenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (181)



Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) $n\text{BuLi}$ for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol) 1-(tert-butyl)-4-(1-chloroprop-2-yn-1-yl)benzene (**165**) (163 mg, 0.79 mmol) using general procedure A. Flash column chromatography (gradient elution, neat pentane to 33:1 pentane:diethyl ether) of the crude extract afforded the title compound (6E,9Z)-8-(4-(tert-butyl)phenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**181**) (154 mg, 0.41 mmol) in 52% yield as a yellow crystalline solid. **Rf** (9:1 pentane:diethyl ether): 0.59; **Mp**: 95 – 97 $^\circ\text{C}$; **IR** (NaCl, film): $\nu_{\max}$ 3057, 3027, 2961, 2901, 2868, 1611, 1592, 1510, 1275, 1249, 915, 841, 783, 763 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): 7.86 – 7.79 (m, 1H, ArH), 7.43 – 7.33 (m, 2H, ArH), 7.30 – 7.24 (m, 2H, ArH), 7.17 (dd, $J = 7.1, 1.9$ Hz, 1H, ArH), 7.15 – 7.10 (m, 2H, ArH), 6.77 (d, $J = 10.7$ Hz, 1H, CCHCH), 6.77 (d, $J = 1.2$ Hz, 1H, OCCH), 6.66 (dd, $J = 10.6, 9.7$ Hz, 1H, CCHCH), 4.93 (d, $J = 9.7$ Hz, 1H, CHAr), 1.28 (s, 9H, $\text{C}(\text{CH}_3)_3$), -0.04 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.05 MHz, CDCl_3): δ 195.2 (C), 166.0 (C), 150.1 (C), 141.8 (CH), 140.4 (C), 136.7 (C), 136.3 (CH), 135.0 (C), 130.8 (CH), 130.7 (CH), 129.1 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 125.2 (CH), 45.6 (CH), 34.5 (C), 31.4 (CH_3), -0.1 (CH_3); **MS** (ESI+): m/z 375 $[\text{M}+\text{H}]^+$; HRMS: found 375.2996 $\text{C}_{25}\text{H}_{31}\text{OSi}^+$ requires 375.2139; **CHN** Anal. calcd. for $\text{C}_{25}\text{H}_{30}\text{OSi}$ C: 80.16, H: 8.07%; found C: 80.21, H: 8.19%.

(6E,9Z)-8-(3-Methoxyphenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (183)

Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 1-(1-chloroprop-2-yn-1-yl)-3-methoxybenzene (**168**) (143 mg, 0.79 mmol) using general procedure A. Flash column chromatography (40:1 to 9:1 pentane:ethyl acetate gradient elution) of the crude extract afforded the title compound (6E,9Z)-8-(3-methoxyphenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**183**) (116 mg, 0.33 mmol) in 42% yield as a colourless crystalline solid. **Rf** (19:1 pentane:ethyl acetate): 0.22; **Mp**: 84 - 86 °C; **IR** (NaCl, film): $\nu_{\max}$ 3026, 2954, 1609, 1588, 1490, 1276, 1249, 1158, 1052, 841, 783 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.86 (dd, *J* = 7.6, 1.8 Hz, 1H, ArH), 7.47 – 7.33 (m, 2H, ArH), 7.23 – 7.12 (m, 2H, ArH), 6.84 – 6.68 (m, 5H, 3ArH, CCHCH, OCCH), 6.63 (dd, *J* = 10.7, 9.7 Hz, 1H, CCHCH), 4.90 (d, *J* = 9.7 Hz, 1H, CHAr), 3.76 (s, 3H, OCH₃), -0.02 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.05 MHz, CDCl₃): δ 195.2 (C), 165.0 (C), 159.7 (C), 141.9 (CH), 141.4 (C), 140.2 (C), 136.0 (CH), 135.0 (C), 131.0 (CH), 130.8 (CH), 129.4 (CH), 129.4 (CH), 128.8 (CH), 128.0 (CH), 120.6 (CH), 114.3 (CH), 112.4 (CH), 55.4 (CH₃), 45.9 (CH), 0.0 (CH₃); **MS** (ESI⁺): *m/z* 349 [M+H]⁺; HRMS: found 349.1612 C₂₂H₂₅O₂Si⁺ requires 349.1618; **CHN** Anal. calcd. for C₂₂H₂₄O₂Si C: 75.82, H: 6.94%; found C: 75.76, H: 7.00%.

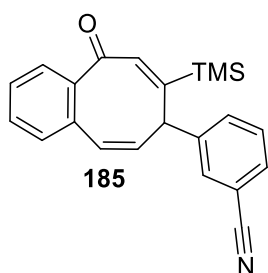
(6E,9Z)-8-(4-(Trifluoromethyl)phenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (184)

Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**169**) (173 mg, 0.79 mmol) and held at -50 °C for 16 hours using a modification of general procedure A. Flash column chromatography (49:1 to 9:1 pentane:diethyl ether gradient elution) afforded the title compound (6E,9Z)-8-(4-(trifluoromethyl)phenyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**184**) (107 mg, 0.28 mmol) in 35% yield as a colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.31; **Mp**: 114-116 °C; **IR** (NaCl, film): $\nu_{\max}$ 3060, 2957, 2899, 2360, 1613, 1591, 1413, 1327, 1277, 1251, 1164, 1123, 1070, 1018, 840 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.77 – 7.70 (m, 1H, ArH), 7.43 (d, *J* = 8.1 Hz, 2H, ArH),

7.38 – 7.30 (m, 2H, ArH), 7.25 (d, $J = 8.1$ Hz, 2H, ArH), 7.13 – 7.07 (m, 1H, ArH), 6.80 (d, $J = 10.7$ Hz, 1H, CCHCH), 6.80 (d, $J = 0.9$ Hz, 1H, OCCH), 6.59 (dd, $J = 10.7, 9.5$ Hz, 1H, CCHCH), 4.93 (d, $J = 9.5$ Hz, 1H, CHAr), 0.00 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃): δ 195.5 (C), 163.1 (C), 144.0 (C), 142.3 (CH), 140.1 (C), 135.4 (CH), 134.6 (C), 130.9 (CH), 130.4 (CH), 129.7 (CH), 129.1 (q, $J = 32.4$ Hz, C), 129.1 (CH), 128.4 (CH), 128.1 (CH), 125.1 (q, $J = 3.7$ Hz, CH), 124.2 (q, $J = 272.0$ Hz, C), 45.8 (CH), -0.4 (CH₃); **¹⁹F NMR** (376.5 MHz, CDCl₃): δ -62.54 (s); **MS** (ESI⁺): m/z 409 [M+Na]⁺; HRMS: found 409.1216 C₂₂H₂₁F₃NaOSi⁺ requires 409.1206.

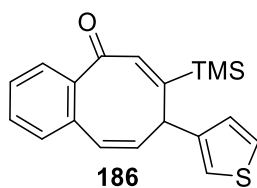
3-((5Z,8E)-10-Oxo-8-(trimethylsilyl)-7,10-dihydrobenzo[8]annulen-7-yl)benzonitrile

(185)

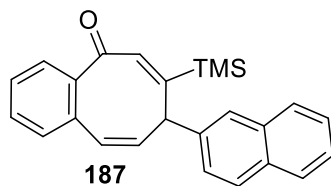


Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 3-(1-chloroprop-2-yn-1-yl)benzonitrile (**170**) (138 mg, 0.79 mmol) using general procedure A with one exception.

After the addition of 3-(1-chloroprop-2-yn-1-yl)benzonitrile (**170**) the reaction temperature was left at -50 °C for 16 hours before quenching with pH = 7 ammonia buffered saturated aqueous ammonium chloride solution. Flash column chromatography (gradient elution: 9:1 to 4:1 pentane:diethyl ether) of the crude extract afforded the title compound 3-((5Z,8E)-10-oxo-8-(trimethylsilyl)-7,10-dihydrobenzo[8]annulen-7-yl)benzonitrile (**185**) (113 mg, 0.33 mmol) in 42% yield as a colourless crystalline solid. **R_f** (4:1 pentane:diethyl ether): 0.18; **Mp**: 155 - 157 °C; **IR** (NaCl, film): ν_{max} 3061, 2955, 2897, 2229, 1611, 1589, 1480, 1277, 1250, 1010, 901, 841, 747 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.69 – 7.60 (m, 1H, ArH), 7.41 – 7.22 (m, 6H, ArH), 7.09 – 7.01 (m, 1H, ArH), 6.82 (d, $J = 0.6$ Hz, 1H, OCCH), 6.81 (d, $J = 10.8$ Hz, 1H, CCHCH), 6.51 (dd, $J = 10.8, 9.4$ Hz, 1H, CCHCH), 4.87 (d, $J = 9.4$ Hz, 1H, CHAr), 0.04 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.05 MHz, CDCl₃): δ 195.6 (C), 162.1 (C), 142.6 (CH), 141.4 (C), 140.1 (C), 134.9 (CH), 134.3 (C), 132.6 (CH), 131.4 (CH), 130.8 (CH), 130.4 (CH), 130.2 (CH), 130.0 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 118.8 (C), 112.2 (C), 45.5 (CH), 0.7 (CH₃); **MS** (ESI⁺): m/z 344 [M+H]⁺; HRMS: found 344.1462 C₂₂H₂₂NOSi⁺ requires 344.1465.

(6E,9Z)-8-(Thiophen-3-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (186)

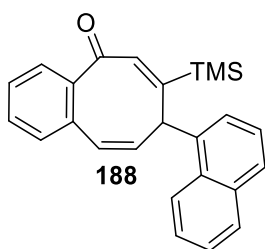
Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 3-(1-chloroprop-2-yn-1-yl)thiophene (**171**) (124 mg, 0.79 mmol) using general procedure A. Flash column chromatography (19:1 pentane:diethyl ether) of the crude extract afforded the title compound (6E,9Z)-8-(thiophen-3-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**186**) (134 mg, 0.41 mmol) in 52% yield as a colourless crystalline solid. **Rf** (9:1 pentane:diethyl ether): 0.31; **Mp**: 111 - 113 °C; **IR** (NaCl, film): ν_{max} 3104, 3025, 2953, 2896, 1610, 1589, 1277, 1249, 1008, 845, 785, 743, 691 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.83 (dd, *J* = 7.6, 1.7 Hz, 1H, ArH), 7.46 – 7.34 (m, 2H, ArH), 7.23 – 7.16 (m, 2H, ArH ArH-thiophene), 7.00 – 6.95 (m, 1H, ArH-thiophene), 6.87 (dd, *J* = 4.9, 1.2 Hz, 1H, ArH-thiophene), 6.74 (d, *J* = 10.7 Hz, 1H, CCHCH), 6.71 (d, *J* = 1.2 Hz, 1H, OCCH), 6.56 (dd, *J* = 10.7, 9.6 Hz, 1H, CCHCH), 4.86 (d, *J* = 9.6 Hz, 1H, CHAr), 0.00 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.05 MHz, CDCl₃): δ 195.1 (C), 164.5 (C), 141.3 (CH), 140.5 (C), 140.0 (C), 136.5 (CH), 134.7 (C), 130.9 (CH), 130.7 (CH), 129.2 (CH), 128.5 (2 x CH), 127.9 (CH), 125.6 (CH), 121.4 (CH), 42.4 (CH), 0.4 (CH₃); **MS** (ESI+): *m/z* 325 [M+H]⁺; HRMS: found 325.1079 C₁₉H₂₁OSSi⁺ requires 325.1077; **CHN** Anal. calcd. for C₁₉H₂₀OSSi C: 70.32, H: 6.21%; found C: 70.31, H: 6.20%.

(6E,9Z)-8-(Naphthalen-2-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (187)

Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 2-(1-chloroprop-2-yn-1-yl)naphthalene (**173**) (159 mg, 0.79 mmol) using general procedure A. Flash column chromatography (gradient elution, neat pentane to 19:1 pentane:diethyl ether) of the crude extract afforded the title compound (6E,9Z)-8-(naphthalen-2-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**187**) (140 mg, 0.38 mmol) in 48% yield as a yellow crystalline solid. **Rf** (9:1 pentane:diethyl ether): 0.33; **Mp**: 111 - 113 °C; **IR** (NaCl, film): ν_{max} 3056, 2954, 2896, 1609, 1591, 1507, 1277, 1249, 1010, 841, 750 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.90 – 7.84 (m, 1H, ArH), 7.81 – 7.69 (m, 3H, ArH), 7.64 (s, 1H, ArH), 7.47 – 7.40 (m, 2H, ArH), 7.39 – 7.31 (m, 2H, ArH), 7.28 (dd, *J* = 8.5, 1.7 Hz, 1H, ArH), 7.22

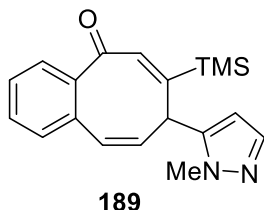
– 7.16 (m, 1H, ArH), 6.84 (d, $J = 10.7$ Hz, 1H, CCHCH), 6.81 (d, $J = 1.1$ Hz, 1H, OCCH), 6.78 (dd, $J = 10.7, 9.0$ Hz, 1H, CCHCH), 5.08 (d, $J = 9.0$ Hz, 1H, CHAr), -0.05 (s, 9H, Si(CH₃)₃); ¹³C NMR (100.05 MHz, CDCl₃): δ 195.4 (C), 164.7 (C), 141.9 (CH), 140.2 (C), 137.3 (C), 136.1 (CH), 135.0 (C), 133.2 (C), 132.4 (C), 131.0 (CH), 130.7 (CH), 129.4 (CH), 129.1 (CH), 128.0 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 126.3 (CH), 126.3 (CH), 125.9 (CH), 46.2 (CH), 0.0 (CH₃); MS (ESI+): m/z 391 [M+Na]⁺; HRMS: found 391.1484 C₂₅H₂₄NaOSi⁺ requires 391.1489.

(6*E*,9*Z*)-8-(Naphthalen-1-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (188)



Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 1-(1-chloroprop-2-yn-1-yl)naphthalene (**174**) (159 mg, 0.79 mmol) using general procedure A. Flash column chromatography (neat pentane to 19:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-8-(naphthalen-1-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**188**) (69 mg, 0.19 mmol) in 24% yield as a colourless crystalline solid. R_f (9:1 pentane:diethyl ether): 0.38; Mp: 154 - 156 °C; IR (NaCl, film): ν_{max} 3052, 2954, 2895, 1609, 1590, 1278, 1248, 1011, 910, 840, 783 cm⁻¹; ¹H NMR (400.2 MHz, CDCl₃): δ 8.04 – 7.97 (m, 1H, ArH), 7.85 – 7.68 (m, 3H, ArH), 7.59 (d, $J = 7.2$ Hz, 1H, ArH), 7.47 – 7.38 (m, 5H, ArH), 7.22 – 7.14 (m, 1H, ArH), 6.95 (dd, $J = 10.7, 9.7$ Hz, 1H, CCHCH), 6.85 (d, $J = 1.1$ Hz, 1H, OCCH), 6.83 (d, $J = 10.7$ Hz, 1H, CCHCH), 5.60 (d, $J = 9.7$ Hz, 1H, ArCH), -0.33 (s, 9H, Si(CH₃)₃); ¹³C NMR (100.05 MHz, CDCl₃): δ 195.0 (C), 166.9 (C), 141.7 (CH), 140.5 (C), 135.6 (CH), 135.1 (2 x C), 134.0 (C), 132.9 (C), 131.2 (CH), 130.9 (CH), 129.3 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 125.9 (CH), 125.0 (CH), 124.2 (CH), 123.9 (CH), 43.0 (CH), -0.4 (CH₃); MS (ESI+): m/z 369 [M+H]⁺; HRMS: found 369.1664 C₂₅H₂₅OSi⁺ requires 369.1669.

(6*E*,9*Z*)-8-(1-Methyl-1*H*-pyrazol-5-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (189)

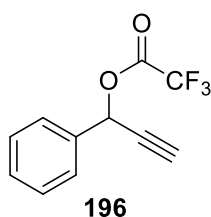


Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), 5-(1-chloroprop-2-yn-1-yl)-1-methyl-1*H*-pyrazole (**176**) (122 mg, 0.79 mmol) and held at -10 °C for 1 hour using general procedure A. Flash column

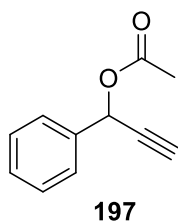
chromatography (1:1 pentane:diethyl ether) afforded the title compound (6*E*,9*Z*)-8-(1-methyl-1*H*-pyrazol-5-yl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**189**) (105 mg, 0.33 mmol) in 42% yield as a colourless solid. **Rf** (1:1 pentane:diethyl ether): 0.19; **Mp**: 116-118 °C; **IR** (NaCl, film): $\nu_{\max}$ 3058, 3034, 2953, 2897, 1613, 1591, 1476, 1278, 1250, 938, 842, 785 cm^{-1} ; **¹H NMR** (500.1 MHz, CDCl_3): δ 7.95 (d, J = 7.8 Hz, 1H, Ar*H*), 7.53 – 7.48 (m, 1H, Ar*H*), 7.47 – 7.41 (m, 1H, Ar*H*), 7.39 (d, J = 1.5 Hz, 1H, Ar*H*), 7.26 (d, J = 7.4 Hz, 1H, Ar*H*), 6.75 (d, J = 10.7 Hz, 1H, CCH*CH*), 6.66 (d, J = 1.2 Hz, 1H, COCH), 6.51 (dd, J = 10.7, 9.4 Hz, 1H, CCH*CH*), 6.25 (s, 1H, Ar*H*), 4.71 (d, J = 9.4 Hz, 1H, CHAr), 3.55 (s, 3H, NCH₃), -0.05 (s, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl_3): δ 195.7 (C), 160.3 (C), 141.1 (CH), 140.9 (C), 139.6 (C), 138.2 (CH), 135.1 (CH), 134.6 (C), 131.7 (CH), 131.7 (CH), 130.3 (CH), 129.2 (CH), 128.4 (CH), 104.5 (CH), 39.0 (CH), 36.6 (CH₃), -1.0 (CH₃); **MS** (ESI⁺): m/z 323 [M+H]⁺; HRMS: found 323.1592 C₁₉H₂₃N₂OSi⁺ requires 323.1574.

1-Phenylprop-2-yn-1-yl 2,2,2-trifluoroacetate

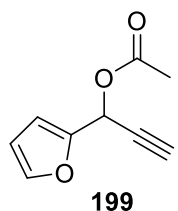
(**196**)



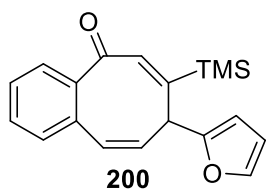
Neat 1-phenylprop-2-yn-1-ol (500 mg, 3.78 mmol) was dissolved in dichloromethane (6 mL) and cooled to 0 °C. Solid 4-(dimethylamino)pyridine (46 mg, 0.38 mmol) was added before trimethylamine (0.8 mL, 5.66 mmol). Trifluoroacetic anhydride (*CARE!*) (0.8 mL, 5.7 mmol) was added dropwise and the mixture was stirred for 90 minutes before water (5 mL) was added. The mixture was extracted with dichloromethane (3 x 5mL) and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography (49:1 pentane:diethyl ether) of the crude extract afforded the title compound 1-phenylprop-2-yn-1-yl 2,2,2-trifluoroacetate (**196**) (456 mg, 2.00 mmol) in 53% yield as a colourless oil. **Rf** (9:1 pentane:diethyl ether): 0.66; **IR** (NaCl, film): $\nu_{\max}$ 3301, 3040, 2133, 1790, 1372, 1226, 1173, 1147, 891, 696 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl_3): δ 7.62 – 7.57 (m, 2H, Ar*H*), 7.50 – 7.45 (m, 3H, Ar*H*), 6.57 (d, J = 2.3 Hz, 1H, PhCHO), 2.85 (d, J = 2.3 Hz, 1H, CCH), **¹³C NMR** (100.6 MHz, CDCl_3): δ 156.6 (q, J = 42.8 Hz, C), 134.3 (C), 130.2 (CH), 129.2 (CH), 128.1 (CH), 114.5 (q, J = 286.0 Hz, C), 78.1 (CH), 77.9 (C), 69.7 (CH); **MS** (ESI⁺): m/z 115 [M-CF₃COO]⁺; HRMS: found 115.0548 C₉H₇⁺ requires 115.0542. Compound characterisation data was found to be in agreement with literature values.¹⁶³

1-Phenylprop-2-yn-1-yl acetate**(197)**

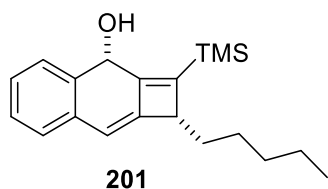
Neat 1-phenylprop-2-yn-1-ol (500 mg, 3.78 mmol) was dissolved in dichloromethane (6 mL) and cooled to 0 °C. Solid 4-(dimethylamino)pyridine (46 mg, 0.38 mmol) was added before trimethylamine (0.8 mL, 5.7 mmol). Acetic anhydride (0.55 mL, 5.66 mmol) was added dropwise and the mixture was stirred for 80 minutes before water (5 mL) was added. The mixture was extracted with dichloromethane (3 x 5 mL) and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the title compound 1-phenylprop-2-yn-1-yl acetate (**197**) (658 mg, 3.78 mmol) in >99% yield as a yellow oil. **Rf** (4:1 pentane:diethyl ether): 0.46; **IR** (NaCl, film): ν_{max} 3288, 3035, 2126, 1742, 1371, 1226, 1017, 698 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.60 – 7.55 (m, 2H, ArH), 7.47 – 7.37 (m, 3H, ArH), 6.49 (d, J = 2.3 Hz, 1H, PhCHO), 2.69 (d, J = 2.3 Hz, 1H, CCH), 2.15 (s, 3H, COCH_3); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 169.9 (C), 136.6 (C), 129.2 (CH), 128.9 (CH), 127.8 (CH), 80.4 (C), 75.5 (CH), 65.5 (CH), 21.2 (CH_3); **MS** (ESI+): m/z 197 $[\text{M}+\text{Na}]^+$; HRMS: found 197.0580 $\text{C}_{11}\text{H}_{10}\text{NaO}_2^+$ requires 197.0573. Compound characterisation data was found to be in agreement with literature values.¹⁶⁴

1-(Furan-2-yl)prop-2-yn-1-yl acetate**(199)**

Neat 1-(furan-2-yl)prop-2-yn-1-ol (500 mg, 4.09 mmol) was dissolved in dichloromethane (5 mL) before trimethylamine (0.74 mL, 5.32 mmol) and acetic anhydride (0.50 mL, 5.32 mmol) were added. Solid 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) was added and the mixture was stirred for four hours before water (5 mL) was added. The mixture was extracted with dichloromethane (3 x 5 mL) and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the title compound 1-(furan-2-yl)prop-2-yn-1-yl acetate (**199**) (655 mg, 3.99 mmol) in 98% yield as a dark oil. **Rf** (3:2 pentane:diethyl ether): 0.67; **IR** (NaCl, film): 3292, 2132, 1742, 1500, 1371, 1221, 1011, 748 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.44 (dd, J = 1.9, 0.9 Hz, 1H, ArH), 6.58 – 6.55 (m, 1H, ArH), 6.50 (d, J = 2.4 Hz, 1H, AcOCH), 6.38 (dd, J = 3.3, 1.9 Hz, 1H, ArH), 2.62 (d, J = 2.4 Hz, 1H, CCH), 2.12 (s, 3H, COCH_3); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 169.9 (C), 148.9 (C), 143.8 (CH), 110.7 (CH), 110.5 (CH), 77.8 (C), 74.8 (CH), 58.3 (CH), 21.0 (CH_3); **MS** (EI+): m/z 164 $[\text{M}]^+$; HRMS: found 164.0470 $\text{C}_9\text{H}_8\text{O}_3^+$ requires 164.0473. Proton NMR data was found to be in agreement with literature values.¹⁶⁵

(6*E*,9*Z*)-8-(2-Furanyl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (200)

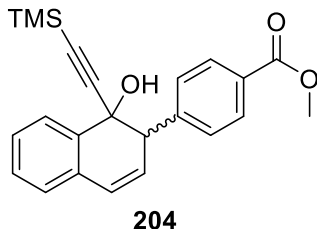
Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), 1-(furan-2-yl)prop-2-yn-1-yl acetate (**199**) (130 mg, 0.79 mmol) and held at -10 °C for 1.5 hours using general procedure A. Flash column chromatography (19:1 pentane:diethyl ether) afforded the title compound (6*E*,9*Z*)-8-(2-furanyl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**200**) (110 mg, 0.36 mmol) in 46% yield as a colourless solid. **Rf** (4:1 pentane:diethyl ether): 0.47; **Mp**: 127-129 °C; **IR** (ATR): ν_{max} 3113, 3033, 2961, 1598, 1584, 1505, 1278, 1249, 1009, 843, 749 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.79 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.50 – 7.37 (m, 2H, Ar*H*), 7.33 – 7.30 (m, 1H, Furanyl*H*), 7.23 – 7.18 (m, 1H, Ar*H*), 6.74 (d, *J* = 10.5 Hz, 1H, CCHCH), 6.73 (d, *J* = 1.6 Hz, 1H, OCCH), 6.42 (dd, *J* = 10.5, 9.7 Hz, 1H, CCHCH), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H, Furanyl*H*), 6.14 – 6.08 (m, 1H, Furanyl*H*), 4.84 (d, *J* = 9.7 Hz, 1H, CHAr) -0.02 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.1 MHz, CDCl₃): δ 194.6 (C), 164.3 (C), 153.6 (C), 142.0 (CH), 141.3 (CH), 140.4 (C), 134.6 (CH), 134.3 (C), 130.9 (CH), 130.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 110.9 (CH), 107.1 (CH), 40.7 (CH), -1.0 (CH₃); **MS** (ESI⁺): *m/z* 331 [M+Na]⁺; HRMS: found 331.1130 C₁₉H₂₀NaO₂Si⁺ requires 331.1125.

1-Pentyl-2-(trimethylsilyl)-1,3-dihydrocyclobuta[*b*]naphthalen-3-ol (201)

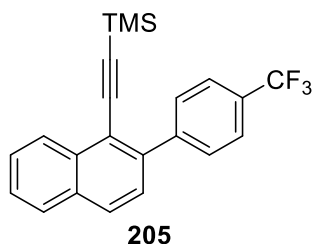
Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 3-chlorooct-1-yne (**164**) (114 mg, 0.79 mmol) using general procedure A. Flash column chromatography (9:1 to 4:1 pentane:diethyl ether) of the crude extract afforded the title compound 1-pentyl-2-(trimethylsilyl)-1,3-dihydrocyclobuta[*b*]naphthalen-3-ol (**201**) (97 mg, 0.31 mmol) in 39% yield as an oil. **Rf** (9:1 pentane:diethyl ether): 0.45; **IR** (NaCl, film): ν_{max} 3446, 2956, 2926, 2856, 1475, 1450, 1247, 1013, 912, 838, 751, 628 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.56 – 7.51 (m, 1H, Ar*H*), 7.24 – 7.13 (m, 2H, Ar*H*), 7.08 (dd, *J* = 7.3, 1.8 Hz, 1H, Ar*H*) 5.80 (s, 1H, CCHC), 5.31 (dd, *J* = 9.4, 2.7 Hz, 1H, CHOH), 3.62 – 3.55 (m, 1H, CHCH_aH_b), 1.81 (d, *J* = 9.4 Hz, 1H, CHOH), 1.78 – 1.68 (m, 1H, CHCH_aH_b), 1.56 – 1.40 (m, 3H, CHCH_aH_b, CH_aH_bCH₂) 1.38 – 1.27 (m, 4H, CH₂CH₂CH₃), 0.95 – 0.87 (m, 3H, CH₂CH₃) 0.23 (s, 9H, Si(CH₃)₃); **¹³C NMR**

(100.05 MHz, CDCl₃): δ 160.3 (C), 158.1 (C), 145.9 (C), 137.1 (C), 135.2 (C), 129.9 (CH), 128.4 (CH), 127.5 (CH), 126.2 (CH), 107.6 (CH), 63.8 (CH), 52.9 (CH), 33.3 (CH₂), 32.2 (CH₂), 28.6 (CH₂), 22.8 (CH₂), 14.3 (CH₃), -1.1 (CH₃); **MS** (ESI+): m/z 335 [M+Na]⁺; HRMS: found 335.1791 C₂₀H₂₈NaOSi⁺ requires 335.1802.

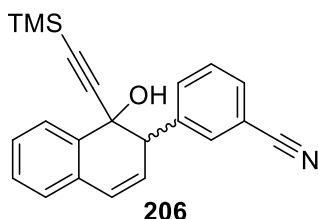
Methyl 4-(1-hydroxy-1-((trimethylsilyl)ethynyl)-1,2-dihydronaphthalen-2-yl)benzoate (204)



Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), methyl 4-(1-chloroprop-2-yn-1-yl)benzoate (**166**) (165 mg, 0.79 mmol) and held at -10 °C for 1 hour using general procedure A. Flash column chromatography (9:1 to 4:1 pentane:diethyl ether) of the crude extract afforded the title compound methyl 4-(1-hydroxy-1-((trimethylsilyl)ethynyl)-1,2-dihydronaphthalen-2-yl)benzoate (**204**) (194 mg, 0.51 mmol) in 65% yield as a colourless crystalline solid. **Rf** (4:1 pentane:diethyl ether): 0.15; **Mp**: 86–88 °C; **IR** (NaCl, film): $\nu_{\max}$ 3458, 2957, 2166, 1723, 1611, 1437, 1311, 1282, 1250, 1182, 1106, 844, 762 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃, Product obtained as a 5:1 ratio of *syn:anti* (OH to Ar); stereochemical assignment based on NMR correlation to **2b** (X-ray)): δ 8.07 – 8.02 (m, 2H, ArH, *syn*), 7.92 – 7.86 (m, 1.4H, 1ArH for *syn*, 2ArH for *anti*), 7.73 – 7.68 (0.2H, ArH, *anti*), 7.55 – 7.50 (m, 2H, ArH, *syn*), 7.40 – 7.16 (m, 4H, 3ArH for *syn*, 5ArH for *anti*), 6.74 (dd, J = 9.7, 2.9 Hz, 1.2H, CCHCH, *syn* and *anti*), 6.11 (dd, J = 9.7, 4.6 Hz, 0.2H, CCHCH, *anti*), 6.03 (dd, J = 9.7, 2.6 Hz, 1H, CCHCH, *syn*), 4.08 (dd, J = 2.9, 2.6 Hz, 1H, CHCHAr, *syn*), 4.01 (dd, J = 4.6, 1.6 Hz, 0.2H, CHCHAr, *anti*), 3.93 (s, 3H, OCH₃, *syn*), 3.89 (s, 0.6H, OCH₃, *anti*), 2.48 (s, 0.2H, OH, *anti*), 1.96 (s, 1H, OH, *syn*), 0.18 (s, 9H, Si(CH₃)₃, *syn*), 0.05 (s, 1.8H, Si(CH₃)₃, *anti*); **¹³C NMR** (100.05 MHz, CDCl₃): δ 167.2 (C, *syn*), 167.1 (C, *anti*), 143.9 (C, *syn*), 143.3 (C, *anti*), 135.5 (C, *anti*), 135.1 (C, *syn*), 132.0 (C, *anti*), 131.7 (C, *syn*), 130.9 (CH, *syn* and *anti*), 130.0 (CH, *anti*), 129.5 (C, *syn* and *anti*), 129.45 (CH, *syn*), 129.35 (CH, *anti*), 129.3 (CH, *syn*), 129.2 (CH, *anti*), 129.0 (CH, *syn*), 128.9 (CH, *anti*), 128.7 (CH, *anti*), 128.5 (CH, *syn*), 128.3 (CH, *syn*), 127.7 (CH, *anti*), 127.2 (2 x CH, *syn*), 126.3 (CH, *anti*), 106.1 (C, *syn*), 104.6 (C, *anti*), 93.9 (C, *anti*), 92.5 (C, *syn*), 72.8 (C, *anti*), 71.1 (C, *syn*), 53.8 (CH, *anti*), 52.9 (CH, *syn*), 52.25 (CH₃, *syn*), 52.2 (CH₃, *anti*), -0.1 (CH₃, *syn*), -0.2 (CH₃, *anti*); **MS** (ESI+): m/z 359 [M-OH]⁺; HRMS: found 359.1461 C₂₃H₂₃O₂Si⁺ requires 359.1462.

Trimethyl((2-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethynyl)silane (205)

Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**169**) (173 mg, 0.79 mmol), warmed to -10 °C and stirred for 1 hour using general procedure A. Reaction residue was then dissolved in dichloromethane (5 mL) before Amberlyst 15 ion exchange resin (345 mg, ground into powder) and 3 Å molecular sieves were added. After stirring for 2 hours the mixture was filtered and concentrated *in vacuo* to afford the crude product. Flash column chromatography (pentane, neat) afforded the title compound trimethyl((2-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethynyl)silane (**205**) (137 mg, 0.37 mmol) in 47% yield as a yellow oil. **R_f** (pentane, neat): 0.26; **IR** (NaCl, film): ν_{max} 3058, 2960, 2150, 1617, 1326, 1251, 1166, 1126, 1046, 886, 844, 817 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl₃): δ 8.50 – 8.43 (m, 1H, ArH), 7.92 – 7.85 (m, 2H, ArH), 7.84 – 7.79 (m, 2H, ArH), 7.73 – 7.68 (m, 2H, ArH), 7.64 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H, ArH), 7.56 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 0.20 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃): δ 144.7 (C), 141.6 (C), 133.8 (C), 132.5 (C), 130.3 (CH), 129.6 (q, *J* = 32.2 Hz, C), 129.1 (CH), 128.2 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 126.9 (CH), 124.9 (q, *J* = 3.7 Hz, CH), 124.5 (q, *J* = 271.8, C), 118.9 (C), 104.3 (C), 102.0 (C), -0.12 (CH₃); **¹⁹F NMR** (376.5 MHz, CDCl₃): δ -62.46 (s); **MS** (EI+): *m/z* 368 [M]⁺; HRMS: found 368.1200 C₂₂H₁₉F₃Si⁺ requires 368.1208.

3-(1-Hydroxy-1-((trimethylsilyl)ethynyl)-1,2-dihydronaphthalen-2-yl)benzonitrile (206)

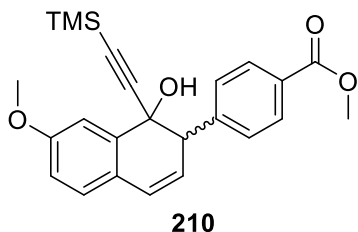
Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol) 3-(1-chloroprop-2-yn-1-yl)benzonitrile (**170**) (138 mg, 0.79 mmol) and held at -10 °C for 1 hour using general procedure A. Flash column chromatography (9:1 to 3:1 pentane:diethyl ether) of the crude extract afforded the title compound *syn*-3-(1-hydroxy-1-((trimethylsilyl)ethynyl)-1,2-dihydronaphthalen-2-yl)benzonitrile (**206**) (99 mg, 0.28 mmol) in 36% yield as an oil and *anti*-3-(1-hydroxy-1-((trimethylsilyl)ethynyl)-1,2-

dihydronaphthalen-2-yl)benzonitrile (32 mg, 0.09 mmol) in 12% yield as an oil. Stereochemical assignment (OH to Ar) based on NMR correlation to **204** (X-ray).

Syn data: **Rf** (4:1 pentane:diethyl ether): 0.26; **IR** (NaCl, film): $\nu_{\max}$ 3446, 3065, 2960, 2230, 2167, 1483, 1250, 1052, 911, 861, 843, 793, 760, 733 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.90 – 7.85 (m, 1H, ArH), 7.78 – 7.74 (m, 1H, ArH), 7.70 (dt, $J = 7.8, 1.5$ Hz, 1H, ArH), 7.64 (dt, $J = 7.8, 1.4$ Hz, 1H, ArH), 7.47 (dt, $J = 7.8, 0.6$ Hz, 1H, ArH), 7.41 – 7.31 (m, 2H, ArH), 7.23 – 7.18 (m, 1H, ArH), 6.75 (dd, $J = 9.5, 2.9$ Hz, 1H, CCHCH), 5.99 (dd, $J = 9.5, 2.5$ Hz, 1H, CCHCH), 4.03 (dd, $J = 2.9, 2.5$ Hz, 1H, CHCHAR), 1.92 (s, 1H, OH), 0.19 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.05 MHz, CDCl_3): δ 140.3 (C), 135.2 (CH), 135.1 (C), 134.6 (CH), 131.5 (C), 131.3 (CH), 129.7 (CH), 128.75 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 127.3 (CH), 127.0 (CH), 119.1 (C), 112.1 (C), 105.6 (C), 93.2 (C), 71.1 (C), 52.6 (CH), -0.1 (CH_3); **MS** (ESI+): m/z 366 $[\text{M}+\text{Na}]^+$; HRMS: found 366.1285 $\text{C}_{22}\text{H}_{21}\text{NNaOSi}^+$ requires 366.1285.

Anti data: **Rf** (4:1 pentane:diethyl ether): 0.16; **IR** (NaCl, film): $\nu_{\max}$ 3430, 3038, 2960, 2230, 2170, 1483, 1250, 1090, 912, 861, 844, 793, 760, 733 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.72 – 7.66 (m, 1H, ArH), 7.55 – 7.48 (m, 2H, ArH), 7.42 (dt, $J = 7.9, 1.6$ Hz, 1H, ArH), 7.40 – 7.34 (m, 1H, ArH), 7.34 – 7.29 (m, 2H, ArH), 7.23 (dd, $J = 7.2, 1.5$ Hz, 1H, ArH), 6.76 (dd, $J = 9.7, 1.5$ Hz, 1H, CCHCH), 6.08 (dd, $J = 9.7, 4.8$ Hz, 1H, CCHCH), 3.97 (dd, $J = 4.8, 1.5$ Hz, 1H, CHCHAR), 2.47 (s, 1H, OH), 0.07 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.05 MHz, CDCl_3): δ 139.4 (C), 134.9 (C), 134.4 (CH), 133.5 (CH), 131.7 (C), 131.1 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.95 (CH), 127.2 (CH), 126.4 (CH), 118.9 (C), 112.0 (C), 104.2 (C), 94.4 (C), 72.6 (C), 53.1 (CH), -0.3 (CH_3); **MS** (ESI+): m/z 366 $[\text{M}+\text{Na}]^+$; HRMS: found 366.1289 $\text{C}_{22}\text{H}_{21}\text{NNaOSi}^+$ requires 366.1285.

Methyl 4-(1-hydroxy-7-methoxy-1-((trimethylsilyl)ethynyl)-1,2-dihydronaphthalen-2-yl)benzoate (210)



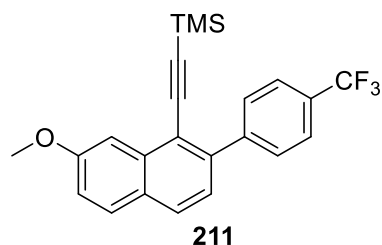
Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.2 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromo-5-methoxybenzaldehyde (348 mg, 1.62 mmol), $n\text{BuLi}$ for

bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol), methyl 4-(1-chloroprop-2-yn-1-yl)benzoate (**166**) (165 mg, 0.79 mmol) and held at -10°C for 1 hour before warming to 0°C and holding for 1 hour using general procedure A. Flash column chromatography (9:1 to 4:1 pentane:diethyl ether) of the crude extract

afforded the title compound methyl 4-(1-hydroxy-7-methoxy-1-((trimethylsilyl)ethynyl)-1,2-dihydronaphthalen-2-yl)benzoate (**2e**) (165 mg, 0.41 mmol) in 52% yield as an off white solid. **Rf** (4:1 pentane:diethyl ether): 0.15; **Mp**: 50-52 °C; **IR** (ATR): $\nu_{\max}$ 3458, 3037, 2955, 2164, 1718, 1608, 1494, 1435, 1276, 1245, 1105, 1034, 1021, 837 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl_3 , Product obtained as a 3:1 ratio of *syn:anti* (OH to Ar); stereochemical assignment based on NMR correlation to **2b** (X-ray)): δ 8.06 – 8.00 (m, 2H, ArH, *syn*), 7.92 – 7.86 (m, 0.66H, ArH, *anti*), 7.55 – 7.49 (m, 2H, ArH, *syn*), 7.46 (d, $J = 2.6$ Hz, 1H, ArH, *syn*), 7.32 – 7.27 (m, 0.99H, ArH, *anti*), 7.15 (d, $J = 8.3$ Hz, 0.33H, ArH, *anti*), 7.13 (d, $J = 8.3$ Hz, 1H, ArH, *syn*), 6.88 (dd, $J = 8.3, 2.6$ Hz, 1H, ArH, *syn*), 6.86 (dd, $J = 8.3, 2.6$ Hz, 0.33H, ArH, *anti*), 6.69 (dd, $J = 9.6, 2.7$ Hz, 1H, CCHCH, *syn*), 6.69 (dd, $J = 9.6, 1.5$ Hz, 0.33H, CCHCH, *anti*), 5.98 (dd, $J = 9.6, 4.6$ Hz, 0.33H, CCHCH, *anti*), 5.90 (dd, $J = 9.6, 2.7$ Hz, 1H, CCHCH, *syn*), 4.03 (dd, $J = 2.7, 2.7$ Hz, 1H, CHCHAr, *syn*), 3.97 (dd, $J = 4.6, 1.5$ Hz, 0.33H, CHCHAr, *anti*), 3.93 (s, 3H, CO_2CH_3 , *syn*), 2.89 (s, 0.99H, CO_2CH_3 , *anti*), 3.85 (s, 3H, OCH_3 , *syn*), 3.82 (s, 0.33H, OCH_3 , *anti*), 2.51 (s, 0.33H, OH, *anti*), 1.98 (s, 1H, OH, *syn*), 0.17 (s, 9H, $\text{Si}(\text{CH}_3)_3$, *syn*), 0.05 (s, 1.8H, $\text{Si}(\text{CH}_3)_3$, *anti*); **¹³C NMR** (100.05 MHz, CDCl_3): δ 167.2 (C, *syn*), 167.1 (C, *anti*), 159.9 (C, *anti*), 159.7 (C, *syn*), 144.0 (C, *syn*), 143.5 (C, *anti*), 137.2 (C, *anti*), 136.8 (C, *syn*), 130.8 (CH, *syn*), 129.0 (CH, *anti*), 129.5 (C, *syn*), 129.3 (CH, *syn*), 129.3 (CH, *anti*), 128.4 (CH, *syn*), 128.4 (CH, *anti*), 127.7 (CH, *syn*), 127.2 (CH, *anti*), 126.3 (CH, *syn*), 126.2 (CH, *anti*), 125.1 (C, *anti*), 124.8 (C, *syn*), 114.5 (CH, *syn*), 114.2 (CH, *anti*), 112.9 (CH, *syn*), 112.2 (CH, *anti*), 106.0 (C, *syn*), 104.5 (C, *anti*), 93.9 (C, *anti*), 92.5 (C, *syn*), 73.0 (C, *anti*), 71.4 (C, *syn*), 55.5 (CH_3 , *syn*), 55.4 (CH_3 , *anti*), 53.7 (CH, *anti*), 52.8 (CH, *syn*), 52.3 (CH_3 , *syn*), 52.2 (CH_3 , *anti*), -0.1 (CH_3 , *syn*), -0.2 (CH_3 , *anti*). One C signal from the *anti* diastereoisomer could not be observed, it is assumed this is due to overlap with stronger *syn* CH signal; **MS** (ESI+): m/z 429 $[\text{M}+\text{Na}]^+$; HRMS: found 429.1500 $\text{C}_{24}\text{H}_{26}\text{NaO}_4\text{Si}^+$ requires 429.1493.

((7-Methoxy-2-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethynyl)trimethylsilane

(211)

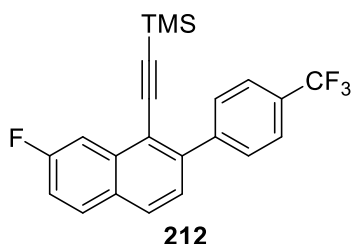


Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromo-5-methoxybenzaldehyde (348 mg, 1.62 mmol), *n*BuLi for

bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol), 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**169**) (173 mg, 0.79 mmol), warmed to -10 °C and stirred for 1 hour before warming to 0 °C and holding for 1 hour

using general procedure A. Reaction residue was then dissolved in dichloromethane (5 mL) before Amberlyst 15 ion exchange resin (345 mg, ground into powder) and 3 Å molecular sieves were added. After stirring for 1 hour the mixture was filtered and concentrated *in vacuo* to afford the crude product. Flash column chromatography (pentane, neat) afforded the title compound ((7-methoxy-2-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethynyl)trimethylsilane (**211**) (130 mg, 0.33 mmol) in 42% yield as a colourless solid, further purification can be achieved via recrystallisation in pentane. **Rf** (49:1 pentane:diethyl ether): 0.33; **Mp**: 115-117 °C **IR** (ATR): $\nu_{\max}$ 3004, 2962, 2934, 2150, 1621, 1505, 1458, 1325, 1221, 1110, 1017, 833, 761 cm^{-1} ; **^1H NMR** (500.1 MHz, CDCl_3): δ 7.84 – 7.80 (m, 3H, ArH), 7.79 (d, J = 2.5 Hz, 1H, ArH), 7.77 (d, J = 8.9 Hz, 1H, ArH), 7.72 – 7.68 (m, 2H, ArH), 7.35 (d, J = 8.4 Hz, 1H, ArH), 7.21 (dd, J = 8.9, 2.5 Hz, 1H, ArH), 3.98 (s, 3H, OCH_3), 0.21 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (125.8 MHz, CDCl_3): δ 159.2 (C), 144.8 (q, J = 1.4 Hz, C), 141.9 (C), 135.4 (C), 130.2 (CH), 129.8 (CH), 129.6 (q, J = 32.4, C), 128.8 (CH), 127.9 (C), 124.8 (q, J = 3.7 Hz, CH), 124.7 (CH), 124.5 (q, J = 271.9 Hz, C), 119.6 (CH), 117.5 (C), 105.2 (CH), 104.1 (C), 102.4 (C), 55.4 (CH_3), -0.1 (CH_3); **^{19}F NMR** (376.5 MHz, CDCl_3): δ -62.41 (s); **MS** (EI+): m/z 368 $[\text{M}+\text{H}]^+$; HRMS: found 399.1387 $\text{C}_{23}\text{H}_{22}\text{F}_3\text{OSi}^+$ requires 399.1392.

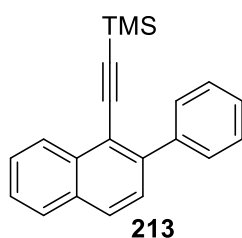
((7-Fluoro-2-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethynyl)trimethylsilane (212)



Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromo-5-fluorobenzaldehyde (329 mg, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol), 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**169**) (173 mg, 0.79 mmol), warmed to -10 °C and stirred for 1 hour before warming to 0 °C and holding for 1 hour using general procedure A. Reaction residue was then dissolved in dichloromethane (5 mL) before Amberlyst 15 ion exchange resin (345 mg, ground into powder) and 3 Å molecular sieves were added. After stirring for 1 hour the mixture was filtered and concentrated *in vacuo* to afford the crude product. Flash column chromatography (pentane, neat) afforded the title compound ((7-fluoro-2-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethynyl)trimethylsilane (**212**) (150 mg, 0.39 mmol) in 49% yield as a yellow solid. **Rf** (pentane neat): 0.35; **Mp**: 79-81 °C **IR** (ATR): $\nu_{\max}$ 2963, 2151, 1616, 1506, 1322, 1248, 1162, 1108, 1093, 1064, 832, 757 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 8.08 (dd, J = 10.7_{HF}, 2.5 Hz, 1H, ArH), 7.88 (d, J = 8.6 Hz, 1H, ArH), 7.87 (dd, J = 8.9, 5.6_{HF} Hz, 1H, ArH), 7.83 – 7.77 (m, 2H, ArH), 7.74 – 7.68 (m, 2H, ArH), 7.45 (d, J = 8.6 Hz, 1H, ArH), 7.34 (ddd, J = 8.9,

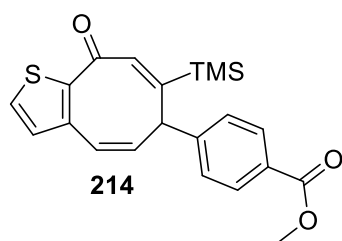
8.2_{HF}, 2.5 Hz, 1H, ArH), 0.20 (s, 9H, Si(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.0 (d, *J* = 247.6 Hz, C), 144.4 (C), 142.4 (C), 135.1 (d, *J* = 9.3 Hz, C), 130.7 (d, *J* = 9.2 Hz, CH), 130.2 (CH), 129.9 (q, *J* = 32.6 Hz, C), 129.5 (C), 128.9 (CH), 126.3 (d, *J* = 2.4 Hz, CH), 124.9 (q, *J* = 3.8 Hz, CH), 124.4 (q, *J* = 272.1 Hz, C), 118.5 (d, *J* = 5.6 Hz, C), 117.3 (d, *J* = 25.8 Hz, CH), 110.8 (d, *J* = 22.7 Hz, CH), 104.8 (C), 101.4 (C), -0.2 (CH₃); ¹⁹F NMR (376.5 MHz, CDCl₃): δ -62.47 (s, 3F, CF₃), -111.83 (ddd, *J* = 10.7, 8.2, 5.6 Hz, 1F, ArF); MS (EI⁺): *m/z* 386 [M]⁺; HRMS: found 386.1109 C₂₂H₁₈F₄Si⁺ requires 386.1114.

Trimethyl((2-phenylnaphthalen-1-yl)ethynyl)silane (213)



Synthesised from: trimethylsilylacetylene (235 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol), warmed to -10 °C and stirred for 1 hour before warming to room temperature and stirring for a further 1 hour using general procedure A. Reaction residue was then dissolved in dichloromethane (5 mL) before Amberlyst 15 ion exchange resin (345 mg, ground into powder) and 3 Å molecular sieves were added. After stirring for 1 hour the mixture was filtered and concentrated *in vacuo* to afford the crude product. Flash column chromatography (pentane, neat) afforded the title compound trimethyl((2-phenylnaphthalen-1-yl)ethynyl)silane (**213**) (114 mg, 0.38 mmol) in 48% yield as a yellow oil. Rf (pentane, neat): 0.17; IR (NaCl, film): ν_{max} 3057, 2858, 2151, 1494, 1249, 886, 843, 761, 699 cm⁻¹; ¹H NMR (400.2 MHz, CDCl₃): δ 8.54 – 8.49 (m, 1H, ArH), 7.90 (dd, *J* = 8.8, 2.0 Hz, 2H, ArH), 7.79 – 7.72 (m, 2H, ArH), 7.68 – 7.62 (m, 1H, ArH), 7.60 – 7.53 (m, 2H, ArH), 7.52 – 7.39 (m, 3H, ArH), 0.25 (s, 9H, Si(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃): δ 143.2 (C), 141.0 (C), 133.9 (C), 132.2 (C), 130.0 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 126.4 (CH), 118.4 (C), 103.5 (C), 102.6 (C), 0.0 (CH₃); MS (ESI⁺): *m/z* 301 [M+H]⁺; HRMS: found 301.1404 C₂₁H₂₁Si⁺ requires 301.1407.

Methyl 4-((4Z,7E)-9-oxo-7-(trimethylsilyl)-6,9-dihydrocycloocta[b]thiophen-6-yl)benzoate (214)

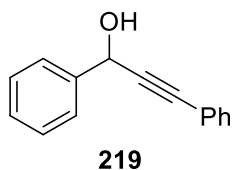


Synthesised from: trimethylsilylacetylene (235 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.50 M in hexanes, 1.79 mmol), 3-bromothiophene-2-carboxaldehyde (176 μL, 1.62 mmol), *n*BuLi for bromine exchange (1.1 mL, 1.50 M in hexanes, 1.70 mmol), CuBr·SMe₂ (167 mg, 0.81 mmol), methyl

4-(1-chloroprop-2-yn-1-yl)benzoate (**166**) (165 mg, 0.79 mmol) and held at -10 °C for 1 hour before warming to 0 °C and holding for 1 hr using a modification of general procedure A. Flash column chromatography (9:1 to 4:1 pentane:diethyl ether gradient elution) afforded the title compound methyl 4-((4*Z*,7*E*)-9-oxo-7-(trimethylsilyl)-6,9-dihydrocycloocta[*b*]thiophen-6-yl)benzoate (**214**) (79 mg, 0.21 mmol) in 27% yield as an off white solid. **Rf** (4:1 pentane:diethyl ether): 0.33; **Mp**: 129-131 °C; **IR** (ATR): $\nu_{\max}$ 3087, 2955, 1720, 1593, 1567, 1431, 1408, 1277, 1252, 1176, 1106, 835 cm^{-1} ; **¹H NMR** (500.1 MHz, CDCl_3): δ 8.03 – 7.98 (m, 2H, ArH), 7.67 (d, J = 5.2 Hz, 1H, ArH), 7.41 – 7.35 (m, 2H, ArH), 7.14 (d, J = 5.2 Hz, 1H, ArH), 6.95 (dd, J = 10.7, 1.0 Hz, 1H, CCHCH), 6.78 (dd, J = 10.7, 9.2 Hz, 1H, CCHCH), 6.49 (d, J = 0.8 Hz, 1H, OCCH), 4.53 (d, J = 9.2 Hz, 1H, CHAr), 3.91 (s, 3H, OCH₃), -0.08 (s, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl_3): δ 187.8 (C), 166.9 (C), 158.6 (C), 145.9 (C), 145.0 (C), 139.8 (C), 136.8 (CH), 135.4 (CH), 133.9 (CH), 132.0 (CH), 129.9 (CH), 129.1 (C), 127.7 (CH), 125.9 (CH), 52.3 (CH₃), 47.2 (CH), 0.5 (CH₃); **MS** (ESI⁺): m/z 405 [M+Na]⁺; HRMS: found 405.0958 C₂₁H₂₂NaO₃SSi⁺ requires 405.0951.

1,3-Diphenylprop-2-yn-1-ol

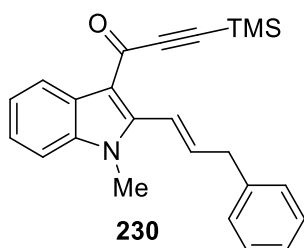
(219)



Synthesised from: phenylacetylene (187 μL , 1.70 mmol), *n*BuLi for acetylene deprotonation (1.2 mL, 1.52 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.52 M in hexanes, 1.70 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol) using general procedure A, but without addition of CuBr·SMe₂. **Rf** (4:1 pentane:diethyl ether): 0.13; **IR** (ATR): $\nu_{\max}$ 3331, 3060, 3032, 2922, 1598, 1489, 1453, 1443, 1188, 1029, 997, 959, 915, 755, 690 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl_3): δ 7.67 – 7.60 (m, 2H, ArH), 7.52 – 7.46 (m, 2H, ArH), 7.45 – 7.29 (m, 6H, ArH), 5.70 (d, J = 6.2 Hz, 1H, CHOH), 2.28 (d, J = 6.2 Hz, 1H, CHOH); **¹³C NMR** (100.6 MHz, CDCl_3): δ 140.8 (C), 131.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 126.9 (CH), 122.5 (C), 88.9 (C), 86.8 (C), 65.2 (CH); **MS** (EI⁺): m/z 208 [M]⁺; HRMS: found 208.0878 C₁₅H₁₂O⁺ requires 208.0888. Characterisation data in agreement with that already reported.⁷⁷

(*E*)-1-(1-Methyl-2-(3-phenylprop-1-en-1-yl)-1*H*-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-one

(230)

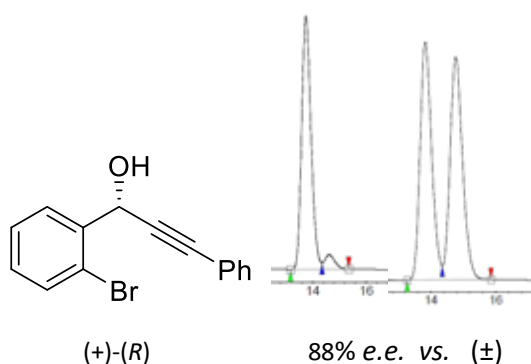


Synthesised from: trimethylsilylacetylene (203 μL , 1.44 mmol), *n*BuLi for acetylene deprotonation (0.9 mL, 1.60 M in hexanes, 1.51 mmol), 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde (**98**) (294 mg, 1.23 mmol), *n*BuLi for bromine

exchange (0.8 mL, 1.60 M in hexanes, 1.29 mmol), CuBr·SMe₂ (127 mg, 0.62 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (90 mg, 0.60 mmol) using general procedure A. Flash column chromatography (17:3 to 7:3 pentane:diethyl ether gradient elution) afforded the title compound (*E*)-1-(1-Methyl-2-(3-phenylprop-1-en-1-yl)-1*H*-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-one (**230**) (32 mg, 0.16 mmol) in 14% yield **IR** (NaCl, film): $\nu_{\max}$ 3028, 2958, 1590, 1575, 1507, 1471, 1404, 1251, 1086, 846, 746 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 8.58 – 8.51 (m, 1H, ArH), 7.36 – 7.27 (m, 7H, ArH), 7.24 – 7.18 (m, 1H, ArH), 6.42 (dd, *J* = 16.1, 1.2 Hz, 1H, ArCHCH), 6.34 (dt, *J* = 16.1, 5.8 Hz, 1H, CHCHCH₂), 4.35 (dd, *J* = 5.8, 1.2 Hz, 2H, CHCHCH₂), 3.76 (s, 3H, NCH₃), 0.30 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃): δ 171.4 (C), 147.6 (C), 137.0 (C), 136.9 (C), 132.2 (CH), 128.7 (CH), 127.7 (CH), 126.5 (C), 126.3 (CH), 124.8 (CH), 123.3 (CH), 122.9 (CH), 121.9 (CH), 114.5 (C), 109.6 (CH), 104.5 (C), 96.9 (C), 30.1 (CH₃), 29.3 (CH₂), -0.5 (CH₃); **MS** (ESI⁺): *m/z* 372 [M+H]⁺; HRMS: found 372.1775 C₂₄H₂₆NOSi⁺ requires 372.1778.

(*R*)-1-(2-Bromophenyl)-3-phenylprop-2-yn-1-ol

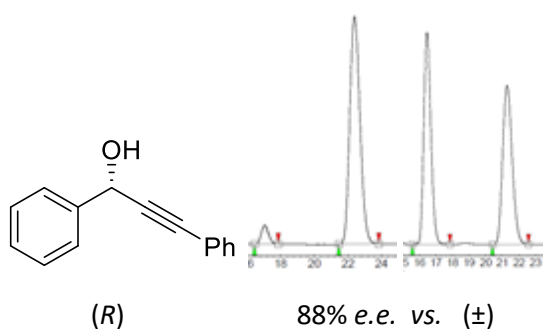
(245)



To a solution of (2*R*,3*aS*,8*aR*)-2-phenyl-3,3*a*,8,8*a*-tetrahydro-2*H*-indeno[1,2-*d*]oxazole (**246**) (119 mg, 0.50 mmol) in THF (10 mL) under argon was added titanium isopropoxide (296 μ L, 1.00 mmol) and a dimethyl zinc (1.6 M in toluene, 3.12 mL, 5.0 mmol). After 90 minutes

phenylacetylene (0.60 mL, 5.50 mmol) was added and then after a further 90 minutes the mixture was cooled to 0 °C and 2-bromobenzaldehyde (292 μ L, 2.50 mmol) was added. This was allowed to warm to room temperature and stirred for 15 hours before 1.5M hydrochloric acid (10 mL) was added. The mixture was extracted with ethyl acetate (3 x 10 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The crude product was purified by flash column chromatography (9:1 to 4:1 pentane:diethyl ether gradient elution) to afford the title compound (*R*)-1-(2-bromophenyl)-3-phenylprop-2-yn-1-ol (**245**) (340 mg, 1.18 mmol) in 47% yield as a yellow oil. **R_f** (4:1 pentane:diethyl ether): 0.21; **IR** (ATR): $\nu_{\max}$ 3310, 3060, 2922, 2851, 2231, 1597, 1569, 1489, 1467, 1438, 1189, 1021, 963, 815, 754, 742, 689 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.85 (dd, *J* = 7.7, 1.6 Hz, 1H, ArH), 7.62 – 7.57 (m, 1H, ArH), 7.52 – 7.45 (m, 2H, ArH), 7.42 – 7.36 (m, 1H, ArH), 7.35 – 7.28 (m, 3H, ArH), 7.22 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H, ArH), 6.02 (d, *J* = 5.5 Hz,

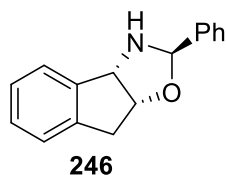
^1H , CHOH), 2.59 (d, $J = 5.5$ Hz, 1H, CHOH); ^{13}C NMR (100.6 MHz, CDCl_3): δ 139.5 (C), 133.1 (CH), 131.8 (CH), 130.0 (CH), 128.7 (2 x CH), 128.3 (CH), 127.9 (CH), 122.8 (C), 122.3 (C), 87.7 (C), 86.9 (C), 64.7 (CH); **MS** (ESI $^+$): m/z 309 $[\text{M}+\text{Na}]^+$; HRMS: found 308.9890 $\text{C}_{15}\text{H}_{11}\text{BrNaO}^+$ requires 308.9885; **HPLC**: Chiralcel OD-H; mobile phase, hexane:2-propanol (4:1 v/v); flow rate, 0.5 mL/min; retention times, 14.0 min (94%), 15.0 min (6%), 88% e.e.; $[\alpha]_{\text{D}}^{20}$: +60.3 ($c = 1.0$ in CHCl_3). Compound characterisation data was found to be in agreement with literature values.¹⁶⁶ An authentic racemic sample was attained by the addition of LiCCPh to 2-bromobenzaldehyde in THF.



To achieve clear baseline separation via chiral HPLC, dehalogenation of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-ol was required ($n\text{BuLi}$, then H_2O). To provide a comparison scalemic sample the same procedure was carried out using (*R*)-1-(2-

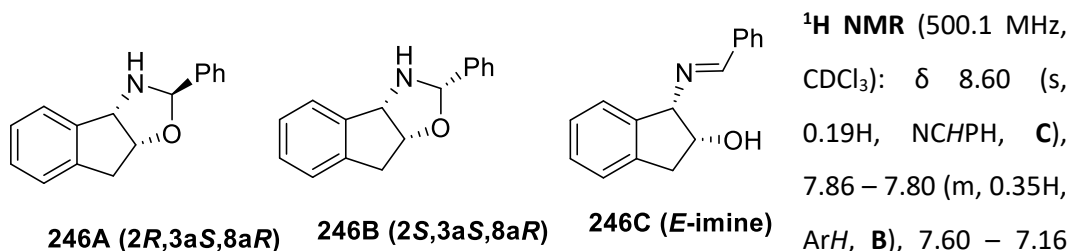
bromophenyl)-3-phenylprop-2-yn-1-ol. To a solution of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-ol (**245**) at -50 °C was added $n\text{butyllithium}$ (1.6 M in hexanes, 2 equiv.). This was stirred for 30 minutes before the addition of water and subsequent extraction with ethyl acetate gave (*R*)-1,3-diphenylprop-2-yn-1-ol (**219**). **HPLC**: Chiralcel OD-H; mobile phase, hexane:2-propanol (4:1 v/v); flow rate, 0.5 mL/min; retention times, 17.0 min (6%), 22.5 min (94%), 88% e.e. Compound characterisation data was identical to that reported for **219**.

(2*R*,3*aS*,8*aR*)-2-Phenyl-3,3*a*,8,8*a*-tetrahydro-2*H*-indeno[1,2-*d*]oxazole (**246**)



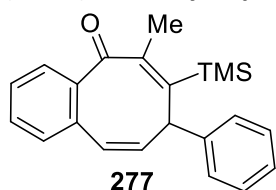
Commercial (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (1.49 g, 10.0 mmol) and benzaldehyde (1.01 mL, 10.0 mmol) were stirred in dichloromethane (20 mL) for 24 hours. The crude product was attained on evaporation of the solvent and purified via recrystallization (6:1 petroleum ether:*i*PrOH) to afford the title compound (2*R*,3*aS*,8*aR*)-2-phenyl-3,3*a*,8,8*a*-tetrahydro-2*H*-indeno[1,2-*d*]oxazole (**246**) (1.90 g, 8.0 mmol) in 80% yield as a colourless solid. **Rf** (4:1 pentane:diethyl ether): 0.18; **Mp**: 79–80 °C; **IR** (ATR): ν_{max} 3277, 3059, 3033, 2934, 2853, 1478, 1456, 1435, 1376, 1322, 1215, 1168, 1020, 895, 712 cm^{-1} ; **MS** (ESI $^+$): m/z 238 $[\text{M}+\text{H}]^+$; HRMS: found 238.1231 $\text{C}_{16}\text{H}_{16}\text{NO}^+$ requires 238.1226; $[\alpha]_{\text{D}}^{20}$: -85.3 ($c = 1.1$ in EtOH). In CDCl_3 solution **246A** is in equilibrium with forms **246B**

and **246C** in a 5.2:1.8:1.0 ratio whose full assignment is given below as it is absent in the primary literature.⁷⁷



(m, 13.32H, 9ArH for A, 8ArH for B, 8ArH for C), 7.08 (d, *J* = 7.4 Hz, 0.19H, ArH, C), 5.48 (s, 0.35H, NOCHPh, B), 5.12 (s, 1H, NOCHPh, A), 5.10 (d, *J* = 5.7 Hz, 1H, CHN, A), 4.97 – 4.90 (m, 1.70H, CHO for A, CHN and CHO for B), 4.83 (d, *J* = 4.9 Hz, 0.19H, CHN, C), 4.68 (ddd, *J* = 4.9, 4.9, 3.4 Hz, 0.19H, CHOH, C), 3.42 – 3.07 (m, 3.08H, PhCH_aH_b for A, PhCH_aH_b for B, PhCH_aH_b for C), 2.62 (br s, 1.54H, NH for A, NH for B, OH for C); ¹³C NMR (125.8 MHz, CDCl₃): δ 163.1 (CH, C), 142.6 (C, A), 141.8 (C, B), 141.6 (C, C), 141.5 (C, B), 141.3 (C, C), 141.2 (C, A), 138.8 (C, A), 138.2 (C, B), 135.7 (C, C), 131.5 (CH, C), 128.9 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH, A), 128.7 (CH), 128.6 (CH, A), 128.5 (CH, A), 128.5 (CH, B), 128.4 (CH, C), 127.4 (CH, B), 127.4 (CH, A), 126.8 (CH, C), 126.3 (CH, A), 126.2 (CH, B), 126.1 (CH, A), 128.8 (CH, B), 125.4 (CH, B), 124.9 (CH, A), 124.5 (CH, C), 93.6 (CH, B), 91.8 (CH, A), 81.0 (CH, B), 80.1 (CH, A), 75.7 (CH, C), 74.8 (CH, C), 69.2 (CH, B), 69.0 (CH, A), 40.1 (CH₂, C), 39.6 (CH₂, A), 38.6 (CH₂, B). Four CH peaks in the aromatic region could not confidently be assigned to B/C and one CH peak from B/C could not be observed most probably due to coincidental overlap. Compound characterisation data was found to be in agreement with literature values.⁷⁷

(6E,9Z)-6-Methyl-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (277)

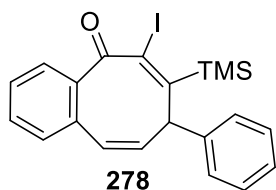


Synthesised from: trimethylsilylacetylene (235 μL, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol),

CuBr·SMe₂ (167 mg, 0.81 mmol) (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol), trapped with iodomethane (0.49 mL, 7.9 mmol) using general procedure A. Flash column chromatography (neat pentane to 50:1 pentane:diethyl ether gradient elution) of the crude extract afforded the title compound (6E,9Z)-6-methyl-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**277**) (123 mg, 0.37 mmol) in 47% yield as a colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.42; **Mp** 90 – 92 °C; **IR** (NaCl, film): *v*_{max}

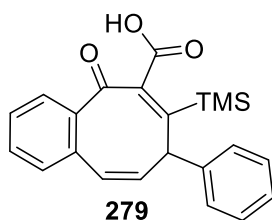
3027, 2953, 2897, 1653, 1593, 1495, 1277, 1262, 1250, 1156, 951, 840, 790, 723 cm^{-1} ; ^1H NMR (500.1 MHz, CDCl_3): δ 8.00 – 7.95 (m, 1H, ArH), 7.58 – 7.53 (m, 1H, ArH), 7.45 – 7.40 (m, 2H, ArH), 7.33 – 7.26 (m, 4H, ArH), 7.24 – 7.18 (m, 1H, ArH), 6.74 (d, J = 11.4 Hz, 1H, CCHCH), 6.67 (dd, J = 11.4, 8.5 Hz, 1H, CCHCH), 4.54 (d, J = 8.5 Hz, 1H, CHPh), 2.00 (s, 3H, CCH₃), -0.03 (s, 9H, Si(CH₃)₃); ^{13}C NMR (125.8 MHz, CDCl_3): δ 207.3 (C), 144.5 (C), 142.4 (C), 141.8 (C), 138.2 (C), 137.3 (CH), 135.7 (C), 134.1 (CH), 132.2 (CH), 131.7 (CH), 131.3 (CH), 128.4 (CH), 127.7 (CH), 127.0 (CH), 126.6 (CH), 48.1 (CH), 18.6 (CH₃), 1.5 (CH₃); **MS** (ESI+): m/z 355 $[\text{M}+\text{Na}]^+$; HRMS: found 355.1495 $\text{C}_{22}\text{H}_{24}\text{NaOSi}^+$ requires 355.1489.

(6Z,9Z)-6-Iodo-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (278)



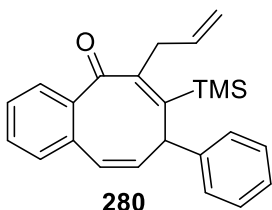
Synthesised from: trimethylsilylacetylene (235 μL , 1.70 mmol), $n\text{BuLi}$ for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μL , 1.62 mmol) $n\text{BuLi}$ for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol),

$\text{CuBr}\cdot\text{SMe}_2$ (167 mg, 0.81 mmol) (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol), trapped with a solution of iodine (1.00 g, 3.95 mmol) in diethyl ether (5 mL). Reaction was allowed to warm to room temperature and stirred for 45 minutes using general cascade reaction procedure A. Flash column chromatography (20:1 pentane:diethyl ether) of the crude extract afforded the title compound (6Z,9Z)-6-iodo-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**278**) (195 mg, 0.44 mmol) in 56% yield as a colourless solid. **Rf** (10:1 pentane:diethyl ether): 0.37; **Mp**: 146 - 148 $^\circ\text{C}$; **IR** (NaCl, film): ν_{max} 3027, 2953, 2896, 1658, 1591, 1566, 1495, 1249, 847, 790, 745, 699 cm^{-1} ; ^1H NMR (400.2 MHz, CDCl_3): δ 8.00 – 7.93 (m, 1H, ArH), 7.64 – 7.56 (m, 1H, ArH), 7.50 – 7.41 (m, 2H, ArH), 7.36 – 7.21 (m, 5H, ArH), 6.79 (dd, J = 11.4, 1.1 Hz, 1H, CCHCH), 6.59 (dd, J = 11.4, 8.7 Hz, 1H, CCHCH), 4.70 (ddd, J = 8.7, 1.1, 1.1 Hz, 1H, CHPh), 0.08 (s, 9H, Si(CH₃)₃); ^{13}C NMR (100.05 MHz, CDCl_3): δ 199.0 (C), 152.0 (C), 140.4 (C), 135.6 (C), 134.8 (CH), 134.7 (C), 134.5 (CH), 133.0 (CH), 132.7 (CH), 132.3 (CH), 128.7 (CH), 128.2 (CH), 127.1 (CH), 126.8 (CH), 100.0 (C), 50.6 (CH), 0.87 (CH₃); **MS** (ESI+): m/z 445 $[\text{M}+\text{H}]^+$; HRMS: found 445.0480 $\text{C}_{21}\text{H}_{22}\text{IOSi}^+$ requires 445.0479; **CHN**: Anal. calcd. for $\text{C}_{21}\text{H}_{21}\text{IOSi}$ C: 56.76, H: 4.76%; found C: 56.76, H: 4.69%.

(6Z,9Z)-5-Oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxylic acid**acid****(279)**

Synthesised from: trimethylsilylacetylene (235 μ L, 1.70 mmol), *n*BuLi for acetylene deprotonation (1.1 mL, 1.60 M in hexanes, 1.79 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol) *n*BuLi for bromine exchange (1.1 mL, 1.60 M in hexanes, 1.70 mmol),

CuBr·SMe₂ (167 mg, 0.81 mmol) (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol), trapped with solid carbon dioxide (approx. 1 g, 22.7 mmol) added in small portions as the reaction mixture warmed to room temperature using general procedure A. Elution through a small plug of silica (neat diethyl ether) following by trituration in diethyl ether afforded the title compound. A further crop of title compound was obtained by flash column chromatography (75:25:1 pentane:diethyl ether:acetic acid) of the trituration liquors to afford (6Z,9Z)-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxylic acid (**279**) (141 mg, 0.39 mmol) in 49% yield as a colourless solid. **Rf** (50:50:1 pentane:diethyl ether:acetic acid): 0.41; **Mp**: 200 – 202 °C; **IR** (ATR): ν_{max} 2952, 1686, 1660, 1566, 1412, 1287, 1253, 850 cm⁻¹; **¹H NMR** (400.2 MHz, (CD₃)₂SO): δ 13.13 (br s, 1H, COOH), 7.82 (dd, *J* = 7.8, 1.3 Hz, 1H, ArH), 7.69 (ddd, *J* = 7.8, 7.2, 1.5 Hz, 1H, ArH), 7.60 (dd, *J* = 8.2, 1.0 Hz, 1H, ArH), 7.58 – 7.51 (m, 1H, ArH), 7.42 – 7.36 (m, 2H, ArH), 7.32 – 7.26 (m, 1H, ArH), 7.24 – 7.18 (m, 2H, ArH), 6.94 (d, *J* = 11.3 Hz, 1H, CCHCH), 6.75 (dd, *J* = 11.3, 8.6 Hz, 1H, CCHCH), 4.49 (d, *J* = 8.6 Hz, 1H, CHPh), -0.05 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.05 MHz, (CD₃)₂SO): δ 201.6 (C), 166.2 (C), 158.9 (C), 141.4 (C), 140.5 (C), 139.3 (C), 135.2 (CH), 134.7 (CH), 134.6 (C), 133.0 (CH), 133.0 (CH), 131.6 (CH), 129.1 (CH), 128.8 (CH), 127.5 (CH), 127.0 (CH), 48.1 (CH), 2.0 (CH₃); **MS** (ESI⁺): *m/z* 385 [M+Na]⁺; **HRMS**: found 385.1062 C₂₂H₂₂NaO₃Si⁺ requires 385.1230.

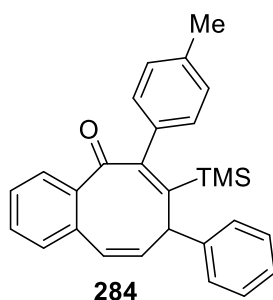
6-Allyl-(6E,9Z)-8-phenyl-7-(trimethylsilyl)benzo[8]annulene-5(8H)-one**(280)**

Synthesised from: trimethylsilylacetylene (229 μ L, 1.62 mmol), *n*BuLi for acetylene deprotonation (1.0 mL, 1.58 M in hexanes, 1.62 mmol), 2-bromobenzaldehyde (189 μ L, 1.62 mmol), *n*BuLi for bromine exchange (1.0 mL, 1.58 M in hexanes, 1.62 mmol),

CuBr·SMe₂ (167 mg, 0.81 mmol) and (1-chloroprop-2-yn-1-yl)benzene (**78**) (119 mg, 0.79 mmol), trapped with allyl bromide (3.43 μ L, 3.95 mmol) for 30 mins at -10 °C, allowing to warm to room temperature over 30 minutes and stirring for 30 minutes more using general procedure A. Flash column chromatography (gradient elution, neat pentane to 19:1 pentane:diethyl ether) afforded the title compound (6E,9Z)-6-allyl-8-phenyl-7-

(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**280**) (173 mg, 0.48 mmol) in 61% yield as colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.60; **Mp**: 88-90 °C; **IR** (NaCl, film): ν_{max} 3037, 3024, 3013, 1649, 1593, 1496, 1252, 963, 909, 843 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.90 – 7.86 (m, 1H, Ar*H*), 7.53 – 7.47 (m, 2H, Ar*H*), 7.30 – 7.23 (m, 4H, Ar*H*), 7.21 – 7.16 (m, 1H, Ar*H*), 6.74 (d, J = 11.3 Hz, 1H, CCHCH), 6.66 (dd, J = 11.3 Hz, 8.2 Hz, 1H, CCHCH), 5.48 (dddd, J = 17.1, 10.1, 7.4, 5.3 Hz, 1H, CH_2CH), 4.85 (app dq, J = 17.1, 1.4 Hz, 1H, =CH_{trans}), 4.77 (app dq, J = 10.1, 1.4 Hz, 1H, =CH_{cis}), 4.56 (d, J = 8.2 Hz, 1H, CHPh), 3.34 (app ddt, J = 15.3, 7.4, 1.4 Hz, 1H, $\text{CH}_{2\alpha}$), 3.11 (app ddt, J = 15.3, 5.3, 1.4 Hz, 1H, $\text{CH}_{2\beta}$), -0.04 (m, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 206.2 (C), 147.4 (C), 143.8 (C), 141.5 (C), 139.8 (C), 137.1 (CH), 135.4 (C), 134.6 (CH), 133.9 (CH), 131.9 (CH), 131.6 (CH), 131.5 (CH), 128.4 (CH), 127.9 (CH), 127.0 (CH), 126.6 (CH), 116.9 (CH_2), 48.1 (CH), 37.8 (CH_2), 1.8 (CH_3); **MS** (ESI⁺): m/z 381 [$\text{M}+\text{Na}$]⁺; HRMS: found 381.1648 $\text{C}_{24}\text{H}_{26}\text{NaOSi}^+$ requires 381.1645.

(6*E*,9*Z*)-8-Phenyl-6-(*p*-tolyl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (284)

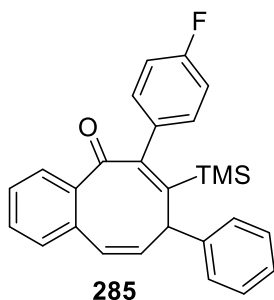


(6*Z*,9*Z*)-6-Iodo-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**278**) (50.0 mg, 0.112 mmol) was dissolved in THF (0.5 mL). *p*-Tolylboronic acid (16 mg, 0.117 mmol), $\text{PdCl}_2(\text{dppf})$ (3.0 mg, 4.1 μmol) and 2 M aqueous sodium carbonate solution (0.25 mL, 5.0 mmol) were added sequentially and the reaction mixture heated to reflux. After 16 hours the mixture was allowed to cool

and filtered through a plug of Celite® eluting with ethyl acetate (5 mL). The eluent was then washed with water (5 mL) before the aqueous washings were extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography (19:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-8-phenyl-6-(*p*-tolyl)-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**284**) (37.0 mg, 90.5 μmol) in 81% yield as a colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.51; **Mp**: 78 - 80 °C; **IR** (ATR): ν_{max} 3027, 2952, 1651, 1591, 1506, 1496, 1260, 1246, 1014, 904, 838, 792, 773, 763, 748, 699, 683 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.78 (dd, J = 7.9, 1.5 Hz, 1H, Ar*H*), 7.62 (m, 1H, Ar*H*), 7.51 – 7.46 (m, 1H, Ar*H*), 7.44 – 7.30 (m, 5H, Ar*H*), 7.27 – 7.21 (m, 1H, Ar*H*), 7.04 (d, J = 8.0 Hz, 2H, Ar*H*), 6.96 (d, J = 8.0 Hz, 2H, Ar*H*), 6.87 – 6.74 (m, 2H, CCHCH and CCHCH), 4.75 (d, J = 8.1 Hz, 1H, CHPh), 2.30 (s, 3H, PhCH_3), -0.32 (s, 9H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 205.1 (C), 150.7 (C), 144.9 (C), 141.0 (C), 138.8 (C), 137.7 (C), 137.2 (CH), 135.3 (C), 135.0 (C), 134.1 (CH), 132.2 (CH), 131.9 (CH), 131.3 (CH), 129.6 (CH), 128.8 (CH),

128.4 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 48.2 (CH), 21.4 (CH₃), 2.3 (CH₃); **MS** (ESI⁺): *m/z* 409 [M+H]⁺; HRMS: found 409.1988 C₂₈H₂₉OSi⁺ requires 409.1982.

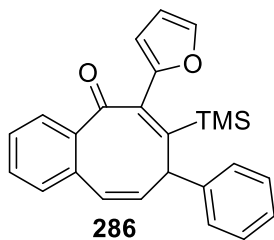
(6*E*,9*Z*)-6-(4-Fluorophenyl)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (285)



(6*Z*,9*Z*)-6-Iodo-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**278**) (50 mg, 0.112 mmol) was dissolved in THF (0.5 mL). 4-Fluorobenzeneboronic acid (24 mg, 0.168 mmol), PdCl₂(dppf) (4.0 mg, 5.5 μmol) and 2 M aqueous sodium carbonate solution (0.25 mL, 5.0 mmol) were added sequentially and the reaction mixture heated to reflux. After 4 hours the

mixture was allowed to cool and filtered through a plug of Celite® eluting with ethyl acetate (5 mL). The eluent was then washed with water (5 mL) before the aqueous washings were extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography (19:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-6-(4-fluorophenyl)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**285**) (40.0 mg, 97.0 μmol) in 87% yield as a colourless solid. **R_f** (9:1 pentane:diethyl ether): 0.44; **Mp**: 154 - 156 °C; **IR** (NaCl, film): $\nu_{\max}$ 3060, 3029, 2956, 2897, 2250, 1658, 1650, 1604, 1591, 1503, 1261, 1248, 1224, 1157, 1017, 907, 852, 840 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.79 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.62 – 7.56 (m, 1H, Ar*H*), 7.49 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 7.43 – 7.31 (m, 5H, Ar*H*), 7.28 – 7.22 (m, 1H, Ar*H*), 7.09 – 7.02 (m, 2H, Ar*H*), 6.97 – 6.89 (m, 2H, Ar*H*), 6.84 (d, *J* = 11.6 Hz, 1H, CCH*CH*), 6.78 (dd, *J* = 11.6, 8.3 Hz, 1H, CCH*CH*), 4.75 (d, *J* = 8.3 Hz, 1H, CH*Ph*), -0.32 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃): δ 204.5 (C), 162.7 (d, *J* = 247.1 Hz, C), 149.4 (C), 145.9 (C), 140.7 (C), 138.5 (C), 137.1 (CH), 135.4 (C), 134.2 (CH), 133.9 (d, *J* = 3.5 Hz, C), 132.4 (CH), 131.9 (CH), 131.5 (CH), 131.4 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 126.9 (CH), 115.1 (d, *J* = 21.4 Hz, CH), 48.2 (CH), 2.2 (CH₃); **MS** (ESI⁺): *m/z* 413 [M+H]⁺; HRMS: found 413.1730 C₂₇H₂₆FOSi⁺ requires 413.1731.

(6*E*,9*Z*)-6-(Furan-2-yl)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (286)

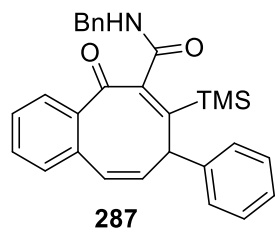


(6*Z*,9*Z*)-6-Iodo-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**278**) (50 mg, 0.112 mmol) was dissolved in THF (0.5 mL). 2-Furanylboronic acid (19 mg, 0.168 mmol), PdCl₂(dppf) (4.0 mg, 5.5 μmol) and 2 M aqueous sodium carbonate solution (0.25 mL, 5.0 mmol) were added sequentially and the reaction mixture

heated to reflux. After 4 hours the mixture was allowed to cool and filtered through a plug

of Celite® eluting with ethyl acetate (5 mL). The eluent was then washed with water (5 mL) before the aqueous washings were extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography (19:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*E*,9*Z*)-6-(furan-2-yl)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**286**) (34.0 mg, 88.4 μ mol) in 79% yield as a colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.47; **Mp**: 102 - 104 °C; **IR** (NaCl, film): $\nu_{\max}$ 3059, 3029, 2952, 1657, 1591, 1288, 1248, 853, 841, 747, 734 cm^{-1} ; **^1H NMR** (400.2 MHz, CDCl_3): δ 7.96 (dd, J = 7.8, 1.5 Hz, 1H, Ar*H*), 7.57 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, Ar*H*), 7.49 – 7.41 (m, 2H, Ar*H*), 7.36 (dd, J = 1.8, 0.7 Hz, 1H, Furanyl*H*), 7.35 – 7.30 (m, 4H, Ar*H*), 7.26 – 7.21 (m, 1H, Ar*H*), 6.78 (d, J = 11.5 Hz, 1H, CCH*H*), 6.70 (dd, J = 11.5, 8.3 Hz, 1H, CCH*H*), 6.35 (dd, J = 3.4, 1.8 Hz, 1H, Furanyl*H*) 6.10 (dd, J = 3.4, 0.7 Hz, 1H, Furanyl*H*), 4.80 (d, J = 8.3 Hz, 1H, CH*Ph*), -0.09 (s, 9H, Si(CH₃)₃); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 204.1 (C), 150.4 (C), 145.9 (C), 141.9 (CH), 141.3 (C), 139.4 (C), 138.7 (C), 136.6 (CH), 135.3 (C), 134.2 (CH), 132.4 (CH), 131.9 (CH), 131.6 (CH), 128.5 (CH), 128.1 (CH), 127.2 (CH), 126.8 (CH), 111.8 (CH), 110.5 (CH), 48.5 (CH), 2.00 (CH₃); **MS** (ESI+): m/z 385 [M+H]⁺; HRMS: found 385.1634 C₂₅H₂₅O₂Si⁺ requires 385.1618.

(6*Z*,9*Z*)-*N*-Benzyl-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-



carboxamide

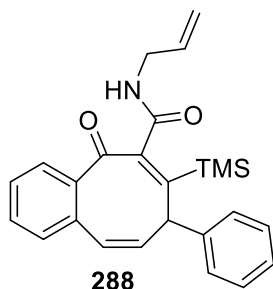
(287)

Following general procedure E with benzylamine, flash column chromatography (9:1 pentane:diethyl ether) of the crude extract afforded the title compound (6*Z*,9*Z*)-*N*-benzyl-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxamide

(287) (76 mg, 0.17 mmol) in 81% yield as a colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.14; **Mp**: 157-159 °C; **IR** (NaCl, film): $\nu_{\max}$ 3391, 3061, 3029, 2950, 2897, 2246, 1665, 1590, 1513, 1497, 1273, 1260, 1246, 910, 782, 733, 698 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3): δ 7.99 (dd, J = 7.9, 1.4 Hz, 1H, Ar*H*), 7.63 – 7.56 (m, 1H, Ar*H*), 7.50 – 7.40 (m, 2H, Ar*H*), 7.36 – 7.27 (m, 5H, Ar*H*), 7.29 – 7.19 (m, 5H, Ar*H*), 6.90 (d, J = 11.2 Hz, 1H, CCH*H*), 6.73 (dd, J = 11.2, 8.8 Hz, 1H, CCH*H*), 6.60 (br dd, J = 5.6, 5.6 Hz, 1H, NH), 4.57 (d, J = 8.8 Hz, 1H, CH*Ph*), 4.50 (dd, J = 14.9, 5.6 Hz, 1H, NHCH_aH_b), 4.40 (dd, J = 14.9, 5.6 Hz, 1H, NHCH_bH_a), 0.02 (s, 9H, Si(CH₃)₃); **^{13}C NMR** (400.2 MHz, CDCl_3): δ 203.3 (C), 164.0 (C), 156.6 (C), 142.4 (C), 140.4 (C), 139.1 (C), 137.9 (C), 135.8 (C), 135.5 (CH), 134.5 (CH), 133.2 (CH), 132.9 (CH), 131.6 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 127.0 (CH),

48.7 (CH), 44.0 (CH₂), 2.1 (CH₃); **MS** (ESI⁺): m/z 474 [M+Na]⁺; HRMS: found 474.1869 C₂₉H₂₉NNaO₂Si⁺ requires 474.1860.

(6Z,9Z)-N-Allyl-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-



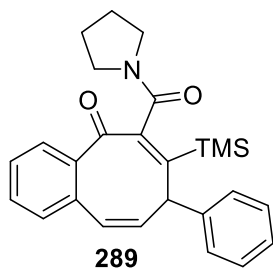
carboxamide (288)

Following general procedure E with allylamine, flash column chromatography (9:1 pentane:diethyl ether) of the crude extract afforded the title compound (6Z,9Z)-N-allyl-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxamide

(288) (62 mg, 0.15 mmol) in 71% yield as a colourless solid. **Rf**

(9:1 pentane:diethyl ether): 0.14; **Mp**: 134-136 °C; **IR** (NaCl, film): $\nu_{\max}$ 3395, 3029, 2951, 2898, 2246, 1667, 1645, 1590, 1476, 1274, 1260, 1246, 911, 846, 783, 743, 735, 700 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 8.05 – 8.00 (m, 1H, ArH), 7.62 – 7.56 (m, 1H, ArH), 7.49 – 7.42 (m, 2H, ArH), 7.33 – 7.27 (m, 2H, ArH), 7.25 – 7.19 (m, 3H, ArH), 6.89 (d, J = 11.2 Hz, 1H, CCHCH), 6.73 (dd, J = 11.2, 8.8 Hz, 1H, CCHCH), 6.42 (br dd, J = 5.1, 5.1 Hz, 1H, NH), 5.82 (dddd, J = 17.2, 10.2, 5.5, 5.5 Hz, 1H, CH₂CHCH₂), 5.21 – 5.09 (m, 2H, CH₂CHCH₂), 4.56 (d, J = 8.8 Hz, 1H, CHPh), 3.98 – 3.79 (m, 2H, NHCH₂CH₂CH), -0.02 (s, 9H, Si(CH₃)₃); **¹³C NMR** (400.2 MHz, CDCl₃): δ 203.4 (C), 163.9 (C), 156.4 (C), 142.3 (C), 140.4 (C), 139.0 (C), 135.8 (C), 135.5 (CH), 134.5 (CH), 133.8 (CH), 133.2 (CH), 132.9 (CH), 131.6 (CH), 129.6 (CH), 128.2 (CH), 127.0 (2 x CH), 116.5 (CH₂), 48.6 (CH), 42.2 (CH₂), 2.1 (CH₃); **MS** (ESI⁺): m/z 825 [2M+Na]⁺; HRMS: found 825.3541 C₅₀H₅₄N₂NaO₄Si⁺ requires 825.3514.

(6Z,9Z)-8-Phenyl-6-(pyrrolidine-1-carbonyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-



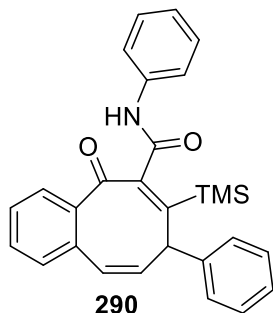
one (289)

Following general procedure E with pyrrolidine but stirred for 17 hours, flash column chromatography (1:1 pentane:diethyl ether) of the crude extract afforded the title compound (6Z,9Z)-8-phenyl-6-(pyrrolidine-1-carbonyl)-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one

(289) (67 mg, 0.16 mmol) in 76% yield as a colourless solid. **Rf** (3:2 diethyl ether:pentane): 0.27; **Mp**: 203-205 °C; **IR** (NaCl, film) $\nu_{\max}$ 3060, 3029, 2952, 2876, 2239, 1626, 1589, 1417, 1248, 912, 844, 787, 728, 701 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 8.19 – 8.12 (m, 1H, ArH), 7.57 – 7.50 (m, 1H, ArH), 7.46 – 7.35 (m, 2H, ArH), 7.32 – 7.17 (m, 5H, ArH), 6.87 (d, J = 11.2 Hz, 1H, CCHCH), 6.77 (dd, J = 11.2, 9.2 Hz, 1H, CCHCH), 4.76 (d, J = 9.2 Hz, 1H, CHPh), 3.51 – 3.36 (m, 2H, pyrrolidine), 3.31 (ddd, J = 10.6, 5.3, 5.3 Hz, 1H, pyrrolidine), 2.78 (ddd, J = 10.1, 7.6, 7.6 Hz, 1H, pyrrolidine), 1.94 – 1.67 (m, 4H, pyrrolidine), -0.01 (s, 9H, Si(CH₃)₃); **¹³C NMR** (400.2 MHz, CDCl₃): δ 197.3

(C), 166.0 (C), 153.8 (C), 148.6 (C), 139.8 (C), 138.5 (C), 137.0 (CH), 135.9 (C), 132.9 (CH), 132.5 (CH), 131.9 (CH), 131.4 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 47.6 (CH₂), 46.9 (CH), 45.7 (CH₂), 26.0 (CH₂), 24.4 (CH₂), 1.2 (CH₃); **MS** (ESI⁺): *m/z* 438 [M+Na]⁺; HRMS: found 438.1866 C₂₆H₂₉NNaO₂Si⁺ requires 438.1860.

(6Z,9Z)-5-Oxo-N,8-diphenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-

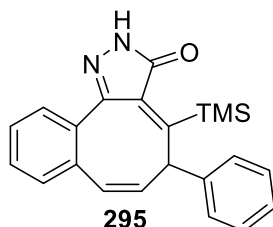


carboxamide

(290)

To a solution of (6Z, 9Z)-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxylic acid (**279**) in THF was added 1-hydroxybenzotriazole hydrate (1 equiv.), DCC (1 equiv.) and diisopropylethylamine (1.3 equiv.). Aniline (2 equiv.) was added and the reaction stirred for 18 hours. Water was added and the mixture extracted with ethyl acetate before the organics were washed with a saturated solution of sodium bicarbonate, dried over magnesium sulfate and concentrated *in vacuo*. Flash column chromatography of the crude extract afforded the title compound (6Z,9Z)-5-Oxo-N,8-diphenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxamide (**290**) in 40% yield. **Mp**: 175-177 °C; **IR** (NaCl, film): $\nu_{\max}$ 3335, 3059, 2953, 1678, 1618, 1599, 1531, 1498, 1440, 1314, 1249, 845, 749, 735 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 8.30 (br s, 1H, NH), 8.07 (dd, *J* = 8.1, 1.5 Hz, 1H, ArH), 7.64 – 7.58 (m, 1H, ArH), 7.55 – 7.40 (m, 4H, ArH), 7.35 – 7.28 (m, 4H, ArH), 7.26 – 7.20 (m, 3H, ArH), 7.10 (dd, *J* = 7.4, 7.4 Hz, 1H, ArH), 6.94 (d, *J* = 11.1 Hz, 1H, CCHCH), 6.75 (dd, *J* = 11.2, 8.9 Hz, 1H, CCHCH), 4.61 (d, *J* = 8.9 Hz, 1H, CHPh), 0.04 (s, 9H, Si(CH₃)₃); **¹³C NMR** (400.2 MHz, CDCl₃): δ 203.3 (C), 162.1 (C), 156.9 (C), 142.7 (C), 140.1 (C), 138.9 (C), 137.7 (C), 135.9 (C), 135.3 (CH), 134.4 (CH), 133.3 (CH), 133.0 (CH), 131.7 (CH), 129.0 (CH), 128.5 (CH), 128.1 (CH), 127.0 (2 x CH), 124.5 (CH), 120.0 (CH), 48.6 (CH), 1.9 (CH₃); **MS** (ESI⁺): *m/z* 460 [M+Na]⁺; HRMS: found 460.1701 C₂₈H₂₇NNaO₂Si⁺ requires 460.1703.

(3aZ,6Z)-5-Phenyl-4-(trimethylsilyl)-2,5-dihydro-3H-benzo[7,8]cycloocta[1,2-c]pyrazol-

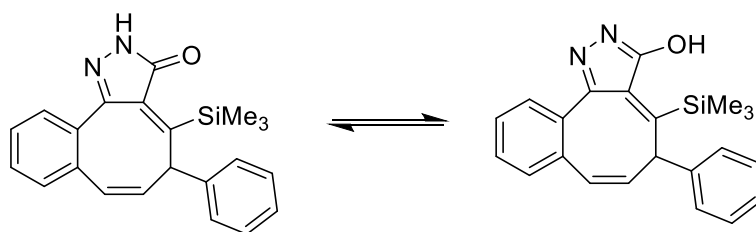


3-one

(295)

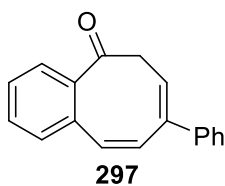
To a suspension of (6Z, 9Z)-5-oxo-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulene-6-carboxylic acid (**279**) (75 mg, 0.21 mmol) in acetonitrile (0.75 mL) was added 1-hydroxybenzotriazole hydrate (34 mg, 0.25 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (48 mg, 0.25 mmol). This was stirred for 3 hours before being added dropwise to a -10 °C, 1M hydrazine solution in THF (0.41 mL, 0.41 mmol) and cyclohexene (5 μ L, 0.05 mmol). The original vessel was rinsed

with acetonitrile (0.5 mL) and this was also added to the reaction to give a homogeneous yellow solution. After a further 1 hour at -10 °C water (2 mL) was added and the mixture extracted with ethyl acetate (7 mL) before the organics were washed with a saturated solution of sodium bicarbonate (3 x 2 mL), dried over magnesium sulfate and concentrated *in vacuo*. Flash column chromatography (4:1 pentane:diethyl ether) of the crude extract afforded the title compound (3aZ,6Z)-5-phenyl-4-(trimethylsilyl)-2,5-dihydro-3H-benzo[7,8]cycloocta[1,2-c]pyrazol-3-one (**295**) (70 mg, 0.20 mmol) in 95% yield as an orange solid. **Rf** (1:1 pentane:diethyl ether): 0.50; **Mp**: 155 – 157 °C decom.; **IR** (NaCl, film): ν_{max} 3215, 3062, 2950, 2897, 2245, 1687, 1570, 1495, 1247, 909, 849, 823, 735 cm^{-1} ; **MS** (ESI+): m/z 359 [M+H]⁺; HRMS: found 359.1572 C₂₇H₂₆FOSi⁺ requires 359.1574.

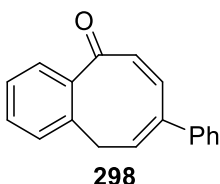


In NMR solution we have found tautomerisation occurs as a *major* and *minor* species is

present. The tautomerisation of pyrazolone rings is well studied.¹¹⁴ Proton NMR spectra indicates a 3.7:1 ratio of tautomers. X-ray crystal analysis shows that in the solid state the carbonyl species dominates. **¹H NMR** (400.2 MHz, CDCl₃): δ 8.81 (br s, 1H, NH, *major*), 8.75 (br s, 0.27H, OH, *minor*), 7.88 – 7.79 (m, 1H, ArH, *major*), 7.45 – 7.38 (m, 2H, ArH, *major*), 7.35 – 7.20 (m, 4.27H, 4 ArH for *major* and 1 ArH for *minor*), 7.17 – 7.09 (m, 2.27H, 2 ArH for *major* and 1 ArH for *minor*), 7.07 – 6.98 (m, 0.54H, ArH, *minor*), 6.95 (d, J = 10.4 Hz, 1H, CCHCH, *major*), 6.91 – 6.66 (m, 1.62H, 5 ArH and CCHCH, *minor*), 6.40 (dd, J = 10.3, 10.3 Hz, 1H, CCHCH, *major*), 6.27 (dd, J = 11.1, 8.7 Hz, 0.27H, CCHCH, *minor*), 5.34 (d, J = 10.3 Hz, 1H, CHPh, *major*), 5.28 (d, J = 8.7 Hz, 0.27H, CHPh, *minor*), 0.38 (s, 2.43H, Si(CH₃)₃, *minor*), 0.05 (s, 9H, Si(CH₃)₃, *major*); **¹³C NMR** (100.6 MHz, CDCl₃): δ 181.4 (C, *major*), 179.4 (C, *minor*), 166.9 (C, *minor*), 166.7 (C, *major*), 150.2 (C, *minor*), 149.8 (C, *major*), 141.3 (C, *major*), 140.8 (C, *minor*), 140.8 (C, *major*), 138.8 (C, *minor*), 136.4 (C, *minor*), 135.2 (CH, *minor*), 135.1 (C, *major*), 133.5 (C, *major*), 132.8 (C, *minor*), 132.2 (CH, *major*), 131.7 (CH, *major*), 130.9 (CH, *minor*), 129.9 (CH, *major*), 129.6 (CH, *minor*), 129.1 (CH, *major*), 129.1 (CH, *major*), 128.8 (CH, *major*), 128.7 (CH, *major*), 128.5 (CH, *minor*), 127.8 (CH, *minor*), 127.6 (CH, *minor*), 127.5 (CH, *minor*), 127.3 (CH, *major*), 127.1 (CH, *major*), 127.0 (CH, *minor*), 125.7 (CH, *minor*), 48.9 (CH, *major*), 48.8 (CH, *minor*), 0.83 (CH₃, *major*), -0.76 (CH₃, *minor*).

(7E,9Z)-8-Phenylbenzo[8]annulen-5(6H)-one**(297)**(6E,9Z)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**80**)

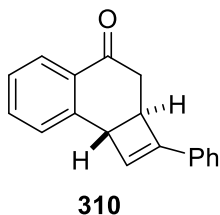
(100 mg, 0.31 mmol) was dissolved in THF (2.6 mL) under argon and the resulting solution was cooled to 0 °C. Tetrabutylammonium fluoride (0.60 mL, 1 M in THF, 0.63 mmol) was added and the solution was stirred for 1 hour. The reaction was quenched by the addition of water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound (7E,9Z)-8-phenylbenzo[8]annulen-5(6H)-one (**297**) (63.2 mg, 0.26 mmol) in 84% yield as a pale crystalline solid. **Rf** (4:1 pentane:diethyl ether): 0.46; **Mp**: 100-102 °C; **IR** (CHCl₃, solution): $\nu_{\max}$ 2962, 2932, 1720, 1464, 1291, 1130, 1075 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 8.38 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.59 – 7.52 (m, 1H, ArH), 7.49 – 7.43 (m, 1H, ArH), 7.41 – 7.22 (m, 6H, ArH), 7.12 (d, *J* = 12.6 Hz, 1H, CCHCH), 6.64 (d, *J* = 12.6 Hz, 1H, CCHCH), 6.20 (t, *J* = 8.3 Hz, 1H, OCCH₂CH), 3.63 (dd, *J* = 8.3, 0.6 Hz, 2H, OCCH₂CH); **¹³C NMR** (100.6 MHz, CDCl₃): δ 194.6 (C), 141.5 (C), 138.5 (C), 137.2 (C), 136.3 (C), 133.5 (CH), 133.2 (CH), 132.3 (CH), 130.8 (CH), 129.2 (CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 126.8 (CH), 123.8 (CH), 45.3 (CH₂); **MS** (ESI⁺): *m/z* 246 [M+Na]⁺; HRMS: found 269.0931 C₁₈H₁₄NaO⁺ requires 269.0937.

(6Z,8E)-8-Phenylbenzo[8]annulen-5(10H)-one**(298)**(6E,9Z)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**80**)

(75 mg, 0.24 mmol) was dissolved in trifluoroacetic acid (0.1 mL, 1.31 mmol). The resulting solution was stirred for 30 minutes before the reaction was quenched by the slow addition of saturated aqueous sodium bicarbonate solution (6 mL) and extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to furnish a brown oil. Residue was purified by flash column chromatography (neat dichloromethane) to afford the title compound (6Z,8E)-8-phenylbenzo[8]annulen-5(10H)-one (**298**) (55 mg, 0.322 mmol) as an orange solid in 92% yield. **Rf** (4:1, pentane: diethyl ether): 0.26; **Mp**: 84-86 °C; **IR** (CHCl₃, solution): $\nu_{\max}$ 3010, 1642, 1580, 1337, 1318 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 8.51 – 8.45 (m, 1H, ArH), 7.71-7.56 (m, 3H, ArH), 7.39 – 7.21 (m, 5H, ArH), 7.17 (dd, *J* = 11.9, 0.9 Hz, 1H, COCH), 6.94 (ddt, *J* = 1.9, 0.9, 0.9 Hz, 1H, CH_aH_bCH), 6.56 (dd, *J* = 11.9, 1.9 Hz, 1H, COCHCH), 3.84 (br s, 2H, CH_aH_bCH); **¹³C NMR** (100.6 MHz, CDCl₃): δ 187.8 (C), 148.8 (C), 139.0 (C), 138.4 (C), 138.1 (CH), 135.6 (C), 135.6 (CH), 133.7 (CH), 132.4 (CH), 130.9 (CH), 130.5 (CH), 129.9 (CH), 129.3 (CH), 128.9 (CH), 127.1

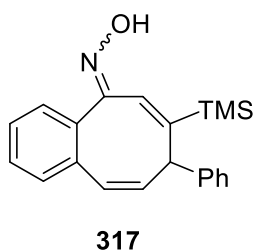
(CH), 46.3 (CH₂); **MS** (ESI+): m/z 247 [M+H]⁺; HRMS: found 247.1120 C₁₈H₁₅O⁺ requires 247.1117.

***trans*-2-Phenyl-2a,8b-dihydrocyclobuta[a]naphthalen-4(3*H*)-one (310)**



(7*E*,9*Z*)-8-Phenylbenzo[8]annulen-5(6*H*)-one (**297**) (100 mg, 0.41 mmol) was dissolved in toluene (2.3 mL) under argon. BF₃·Et₂O (15 μL, 0.12 mmol) was added and the resulting solution was exposed to microwave radiation at 150 °C, 290W for 30 minutes. The mixture was put through a silica plug eluting with diethyl ether before being concentrated *in vacuo* to give crude product. Residue was purified by flash column chromatography (19:1 pentane:diethyl ether) to afford the title compound 2-phenyl-2a,8b-dihydrocyclobuta[a]naphthalen-4(3*H*)-one (**310**) (79 mg, 0.32 mmol) in 79% yield as an off-white solid. **Rf** (9:1, pentane: diethyl ether): 0.15; **Mp**: 90-92 °C; **IR** (CHCl₃, solution): $\nu_{\max}$ 3069, 3011, 2966, 1768, 1732, 1481, 1448, 1240, 1134, 909 cm⁻¹; **¹H NMR** (400.2 MHz, CDCl₃): δ 7.49 – 7.42 (m, 2H, Ar*H*), 7.40 – 7.33 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 1H, Ar*H*), 7.18 (ddd, J = 7.4, 7.4, 1.7 Hz, 1H, Ar*H*), 7.15 – 7.10 (m, 1H, Ar*H*), 7.08 – 7.01 (m, 2H, Ar*H*), 6.97 (d, J = 3.3 Hz, 1H, CHCHCPh), 3.72 (dd, J = 3.3, 1.0 Hz, 1H, CHCHCPh), 3.58 (ddd, J = 5.0, 1.8, 1.0 Hz, 1H, OCCH_aH_bCH), 3.47 (dd, J = 16.8, 5.0 Hz, 1H, OCCH_aH_bCH), 3.35 (ddd, J = 16.8, 1.8, 0.9 Hz, 1H, COCH_bH_aCH); **¹³C NMR** (100.6 MHz, CDCl₃): δ 210.1 (C), 140.6 (C), 140.3 (C), 133.6 (C), 133.6 (C), 130.1 (2 × CH), 128.9 (CH), 128.4 (CH), 127.8 (CH), 127.2 (CH), 126.5 (CH), 125.4 (CH), 54.9 (CH), 48.8 (CH), 33.9 (CH₂); **MS** (ESI+): m/z 269 [M+Na]⁺; HRMS: found 269.0938 NaC₁₈H₁₄O⁺ requires 269.0937.

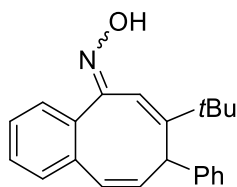
(6*E*,9*Z*)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one oxime (317)



To a solution of (6*E*,9*Z*)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**80**) (500 mg, 1.57 mmol) in ethanol (70 mL) was added hydroxylamine hydrochloride (2.20 g, 31.4 mmol) and anhydrous sodium acetate (2.60 g, 31.4 mmol). The reaction mixture was heated to reflux for 20 hours. After that, it was concentrated *in vacuo* before being dissolved in ethyl acetate (50 mL) and washed with water (25 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to obtain a yellow oil. The crude product was purified by flash column chromatography (5:1 pentane:diethyl ether) to give the title compound (6*E*,9*Z*)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one oxime (**317**) (434 mg, 1.30 mmol) in 83 % yield as a white solid. **Rf** (5:1 pentane:diethyl ether): 0.20; **Mp**: 120-122 °C; **IR** (NaCl, film): $\nu_{\max}$ 3229, 2954, 1599, 1492, 1447, 1248, 876, 757 cm⁻¹; **MS** (ESI+): m/z 334

[M+H]⁺; HRMS: found 334.1644 C₂₁H₂₄NOSi⁺ requires 334.1622. The product is obtained as a mixture of isomers in a 1.67:1 ratio favoring the *E*-oxime shown. Determination of individual isomer geometry was based on ¹H NMR shifts of oxime α-CH based on literature precedent. ¹H NMR (400 MHz, CDCl₃): δ 7.46 (d, *J* = 1.3 Hz, 1H, CNCH, *E*), 7.25-6.85 (m, 14H, 8 ArH for *E*, 9 ArH and CNCH for *Z*), 6.80 – 6.71 (m, 2.6H, ArH and CCHCH for *E*, CCHCH for *Z*), 6.29 (dd, *J* = 10.6, 9.4 Hz, 1H, CCHCH, *E*), 6.29 – 6.23 (m, 0.6H, CCHCH, *Z*), 4.69 (d, *J* = 9.4 Hz, 1H, CHPh, *E*) 4.67-4.62 (m, 0.6H, CHPh, *Z*) -0.02 (s, 14.4H, Si(CH₃)₃, *E* and *Z*). ¹³C NMR (400 MHz, CDCl₃): δ 159.2 (C, *Z*), 157.7 (C, *E*), 153.5 (C, *E*), 141.3 (C, *Z*), 141.2 (C, *E*), 137.4 (C, *E*), 135.8 (C, *Z*), 135.4 (CH, *E*), 134.6 (C, *E*), 131.3 (C, *Z*), 130.2 (CH, *E*), 129.7 (CH, *E*), 129.2 (CH, *E*), 128.5 (CH, *E*), 128.3 (CH, *E*), 127.7 (CH, *E*), 127.6 (CH, *Z*), 127.6 (CH, *Z*), 127.5 (CH, *E*), 127.1 (CH, *E*), 126.9 (CH, *Z*), 126.0 (CH, *E*), 46.8 (CH, *E*), 45.9 (CH, *Z*), -0.5 (CH₃, *E*). Nine signals from the *Z*-isomer could not be observed due to overlap with the stronger *E*-signals.

(6*E*,9*Z*)-7-(*tert*-Butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one oxime (318)



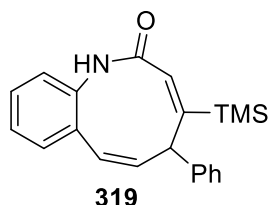
318

To a solution of (6*E*,9*Z*)-7-(*tert*-butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one (**127**) (500 mg, 1.65 mmol) in ethanol (60 mL) was added hydroxylamine hydrochloride (2.30 g, 33.0 mmol) and anhydrous sodium acetate (2.70 g, 33.0 mmol). The reaction mixture was heated to reflux for 19 hours. After that, it was concentrated *in vacuo* before being dissolved in ethyl acetate (50 mL) and washed with water (25 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (6*E*,9*Z*)-7-(*tert*-butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one oxime (**318**) (514 mg, 1.62 mmol) in 98% yield as a yellow solid. **R_f** (5:1 pentane:diethyl ether): 0.15; **Mp**:

166-168 °C; **IR** (NaCl, film): ν_{max} 3244, 2966, 2248, 1629, 1599, 1492, 1447, 1366, 911, 733 cm⁻¹; **MS** (ESI⁺): *m/z* 318 [M+H]⁺; HRMS: found 318.1874 C₂₂H₂₄NO⁺ requires 318.1852. The product was obtained as a mixture of isomers in a 1.54:1 ratio favoring the *E*-oxime isomer shown. Determination of isomers based on ¹H NMR, ¹³C NMR and 2D NMR analysis and the characteristic shifts of oxime α-CH. ¹H NMR (400 MHz, CDCl₃): δ 7.35 (s, 1H, CNCH, *E*), 7.14 – 6.66 (m, 15.5H, 8 ArH and CCHCH for *E*, 8 ArH CCHCH and CNCH for *Z*), 6.56 (d, *J* = 7.7 Hz, 0.65H, ArH, *Z*), 6.46 (d, *J* = 7.6 Hz, 1H, ArH, *E*) 6.28 (dd, *J* = 10.6, 9.1 Hz, 1H, CCHCH, *E*), 6.24 (dd, *J* = 10.5, 9.2 Hz, 0.65H, CCHCH, *Z*), 4.67 (d, *J* = 9.1 Hz, 1H, CHPh, *E*), 4.65 (d, *J* = 9.2 Hz, 0.65H, CHPh, *Z*), 1.16 (s, 9H, C(CH₃)₃, *E*), 1.13 (s, 5.85H, C(CH₃)₃, *Z*); ¹³C NMR (400 MHz, CDCl₃): δ 159.1 (C, *Z*), 157.6 (C, *E*), 156.5 (C, *E*), 154.6 (C, *Z*), 141.3 (C, *Z*), 141.2 (C, *E*), 137.6 (C, *E*), 136.6 (CH, *E* and *Z*), 135.9 (C, *Z*), 135.1 (C, *E*), 132.0 (C, *Z*), 131.2 (CH, *E*), 130.6

(CH, Z), 128.8 (CH, E), 128.3 (CH, Z), 127.7 (CH, E), 127.7 (CH, E), 127.6 (CH, Z), 127.2 (CH, Z), 126.9 (CH, E), 126.7 (CH, E), 126.5 (CH, Z), 126.4 (CH, E), 124.7 (CH, E), 124.7 (CH, Z), 124.4 (CH, Z), 118.0 (CH, E), 45.4 (CH, E), 45.2 (CH, Z), 39.0 (C, E), 38.4 (C, Z), 29.3 (CH₃, E), 29.2 (CH₃, Z). 2 CH signals from the Z-oxime could not be observed due to overlap with stronger E-oxime signals.

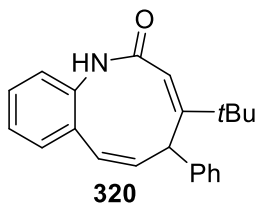
(3E,6Z)-5-Phenyl-4-(trimethylsilyl)-1,5-dihydro-2H-benzo[b]azonin-2-one (319)



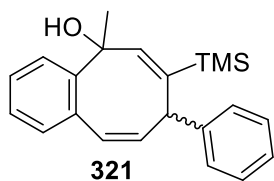
Sodium hydride (60% in oil, 180 mg, 4.50 mmol) was washed with pentane before a suspension was made in THF (10 mL) in an ice bath under argon. (6E,9Z)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one oxime (**317**) (500 mg,

1.5 mmol) was added and the mixture stirred at 0 °C for two hours. After this 4-toluenesulfonyl chloride (318 mg, 1.67 mmol) was added and stirred at the same temperature for a further two hours. Water was added (7 mL) and stirred for 5 minutes. The mixture was then diluted with water (30 mL) and extracted with dichloromethane (4 x 30 mL). The organic layer was washed with brine (40 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow solid. The crude product was purified by flash column chromatography (7:3 hexane:ethyl acetate) to afford the title compound (3E,6Z)-5-phenyl-4-(trimethylsilyl)-1,5-dihydro-2H-benzo[b]azonin-2-one (**319**) (138 mg, 0.37 mmol) in 27% yield as a colourless solid. **Rf** (7:3 hexane:ethyl acetate): 0.52; **Mp**: 111–113 °C; **IR** (NaCl, film): ν_{max} 3180, 3061, 3026, 2954, 2244, 1662, 1597, 1494, 1247, 913, 840, 752 cm⁻¹; **¹H NMR** (500.1 MHz, CDCl₃): δ 7.64 (d, *J* = 7.8 Hz, 1H, ArH), 7.42 – 7.03 (br m, 8H, ArH), 6.65 (s, 1H, COCH), 6.63 (d, *J* = 11.4 Hz, 1H, CCHCH), 6.51 (dd, *J* = 11.4, 11.4 Hz, 1H, CCHCH), 4.51 (d, *J* = 11.4 Hz, 1H, CHPh), -0.13 (s, 9H, Si(CH₃)₃); **¹³C NMR** (125.8 MHz, CDCl₃): δ 170.6 (C), 154.3 (C), 140.6 (C), 138.7 (CH), 134.3 (C), 133.2 (CH), 129.7 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 125.5 (CH), 125.5 (CH), 49.9 (CH), -0.1 (CH₃); **MS** (ESI+): *m/z* 334 [M+H]⁺; HRMS: found 334.1629 C₂₁H₂₄NOSi⁺ requires 334.1622.

In solution **319** shows three conformers. At room temperature one is stable and the other two exchange on the NMR timescale. In the ¹H NMR spectrum it was only possible to assign the signals for the non-exchanging conformer. In the ¹³C NMR spectrum it was not possible to distinguish which CH signals in the aromatic region belong to the more stable conformer. For this reason, all visible CH signals in the aromatic region are quoted above.

(3E,6Z)-4-(tert-Butyl)-5-phenyl-1H-benzo[b]azonin-2(5H)-one**(320)**

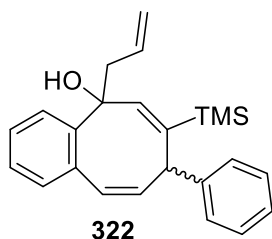
Sodium hydride (60% in oil, 113 mg, 2.83 mmol) was washed with pentane before a suspension was made in THF (9 mL) in an ice bath under argon. (6E,9Z)-7-(tert-Butyl)-8-phenylbenzo[8]annulen-5(8H)-one oxime (**318**) (300 mg, 0.95 mmol) was added and the mixture stirred at 0 °C for 100 minutes. After this 4-toluenesulfonyl chloride (200 mg, 1.05 mmol) was added and stirred at the same temperature for a further two hours. Water was added (5 mL) and stirred for 5 minutes. The mixture was then diluted with water (30 mL) and extracted with dichloromethane (4 x 30 mL). The organic layer was washed with brine (40 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow solid. The crude product was purified by flash column chromatography (7:3 hexane:ethyl acetate) to afford the title compound (3E,6Z)-4-(tert-butyl)-5-phenyl-1H-benzo[b]azonin-2(5H)-one (**320**) (117 mg, 0.37 mmol) in 39% yield as a colourless solid. **R_f** (7:3 hexane:ethyl acetate): 0.29; **Mp**: 148-150 °C; **IR** (NaCl, film): ν_{max} 3179, 3060, 2965, 2870, 2242, 1670, 1647, 1598, 1492, 1365, 910, 732 cm^{-1} ; **¹H NMR** (400.2 MHz, CDCl_3 , In NMR solution this molecule exists between two conformers in a 2:1 ratio): δ 7.53 – 7.45 (m, 2H, ArH, *major*), 7.40 – 7.14 (m, 9.5H, 5 ArH for *major*, 9 ArH for *minor*), 7.13 – 7.06 (m, 2H, ArH, *major*), 6.75 (br s, 1H, NH, *major*), 6.73 (dd, $J = 13.5$, 1.9 Hz, 0.5H, CCHCH, *minor*), 6.45 (dd, $J = 12.8$, 1.7 Hz, 1H, CCHCH, *major*), 6.02 (dd, $J = 12.8$, 4.5 Hz, 1H, CCHCH, *major*), 6.01 (dd, $J = 13.4$, 5.8 Hz, 0.5H, CCHCH, *minor*), 5.55 (s, 1H, COCH, *major*), 5.51 (d, $J = 1.3$ Hz, 0.5H, COCH, *minor*), 5.41 (br s, 0.5H, NH, *minor*), 4.52 – 4.46 (br m, 1H, CHPh, *major*), 4.41 (dd, $J = 5.8$, 1.9 Hz, 0.5H, CHPh, *minor*), 0.97 (s, 4.5H, $\text{C}(\text{CH}_3)_3$, *minor*), 0.80 (s, 9H, $\text{C}(\text{CH}_3)_3$, *major*); **¹³C NMR** (100.6 MHz, CDCl_3): δ 173.9 (C, *major*), 172.1 (C, *minor*), 156.0 (C, *major*), 152.2 (C, *minor*), 143.9 (C, *major*), 143.8 (C, *minor*), 137.0 (C, *major*), 136.2 (CH, *major* and *minor*), 135.9 (C, *minor*), 135.6 (C, *major*), 132.2 (C, *minor*), 129.6 (CH, *minor*), 129.5 (CH, *major*), 129.0 (2 x CH, *major*), 128.9 (CH, *minor*), 128.8 (CH, *minor*), 128.5 (CH, *major*), 128.4 (CH, *major*), 128.0 (CH, *major*), 127.9 (CH, *minor*), 127.8 (CH, *minor*), 127.7 (CH, *minor*), 127.4 (CH, *major*), 126.4 (CH, *major*), 126.3 (CH, *minor*), 124.6 (CH, *minor*), 123.0 (CH, *minor*), 121.0 (CH, *major*), 47.1 (CH, *major*), 45.9 (CH, *minor*), 37.3 (C, *minor*), 36.0 (C, *major*), 29.4 (CH_3 , *major*), 28.8 (CH_3 , *minor*); **MS** (ESI+): m/z 318 $[\text{M}+\text{H}]^+$; HRMS: found 318.1854 $\text{C}_{22}\text{H}_{24}\text{NO}^+$ requires 318.1852.

(6*E*,9*Z*)-5-Methyl-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulen-5-ol (321)(6*E*,9*Z*)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**80**)

(200 mg, 0.63 mmol) was dissolved in THF (5 mL) under argon at 0 °C and methylmagnesium bromide (0.45 mL, 1.64 M in diethyl ether, 0.75 mmol) was added before the mixture was stirred for 2

hours. A further portion of methylmagnesium bromide (0.2 mL, 1.64 M in diethyl ether, 0.33 mmol) was added to fully consume starting material. After a further 1 hour the reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (6*E*,9*Z*)-5-methyl-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulen-5-ol (**321**) (204 mg, 0.61 mmol) in 97% yield as a white solid. **R_f** (4:1 pentane:diethyl ether): 0.42; **Mp** 74–76 °C; **IR** (CHCl₃, solution): ν_{max} 3589, 3010, 1731, 1375, 1249, 1046, 838 cm⁻¹; **MS** (ESI⁺): *m/z* 357 [M+Na]⁺; HRMS: found 357.1643 NaC₂₂H₂₆OSi requires 357.1645.

Compound **321** is attained as a mixture of diastereoisomers in a 6.7:1 ratio. X-ray crystal analysis shows the major isomer to be *anti* (OH to Ph). **¹H NMR** (400.2 MHz, CDCl₃): δ 7.58 – 7.50 (m, 1.15H, 1 Ar*H* for *syn* and 1 Ar*H* for *anti*), 7.43 – 7.33 (m, 0.15H, Ar*H*, *syn*), 7.22–7.14 (m, 1H, Ar*H*, *anti*), 7.11 – 7.06 (m, 0.15H, Ar*H*, *syn*), 7.05 – 6.70 (m, 8.9H, 7 Ar*H* and CCHCH for *anti*, 5 Ar*H* and CCHCH for *syn*), 6.67 – 6.62 (m, 0.15H, Ar*H*, *syn*), 6.47 (d, *J* = 0.9 Hz, 0.15H, COHCH, *syn*), 6.41 (d, *J* = 1.1 Hz, 1H, COHCH, *anti*), 6.36 (dd, *J* = 10.5, 9.6 Hz, 1H, CCHCH, *anti*), 6.24 (dd, *J* = 10.7, 9.0 Hz, 0.15H, CCHCH, *syn*), 4.61 (dd, *J* = 9.6, 1.1 Hz, 1H, CHPh, *anti*), 4.43 (dd, *J* = 9.0, 0.9 Hz, 0.15H, CHPh, *syn*), 3.05 (s, 1H, OH, *anti*), 2.44 (s, 0.15H, OH, *syn*), 1.72 (s, 0.45H, CH₃, *syn*), 1.71 (s, 3H, CH₃, *anti*), -0.03 (s, 1.35H, Si(CH₃)₃, *syn*), -0.11 (s, 9H, Si(CH₃)₃, *anti*); **¹³C NMR** (100.6 MHz, CDCl₃): δ 150.3 (CH, *syn*), 149.6 (CH, *anti*), 143.9 (C, *syn*), 143.6 (C, *anti*), 143.5 (C, *anti*), 143.4 (C, *syn*), 141.8 (C, *syn*), 141.1 (C, *anti*), 140.3 (C, *syn*), 135.5 (C, *anti*), 135.0 (CH, *syn*), 134.9 (CH, *anti*), 132.2 (CH, *syn*), 131.9 (CH, *anti*), 128.3 (CH, *syn*), 128.2 (CH, *anti*), 128.0 (CH, *anti*), 127.9 (CH, *syn*), 127.6 (CH, *anti*), 127.4 (CH, *anti*), 127.2 (CH, *syn*), 127.1 (CH, *syn*), 126.2 (CH, *anti*), 126.0 (CH, *syn*), 125.8 (CH, *anti*), 125.5 (CH, *anti*), 125.2 (CH, *syn*), 125.2 (CH, *syn*), 76.7 (C, *syn*), 75.4 (C, *anti*), 45.3 (CH, *syn*), 44.8 (CH, *anti*), 31.1 (CH₃, *anti*), 30.2 (CH₃, *syn*), -0.4 (CH₃, *anti*), -0.9 (CH₃, *syn*).

(6E,9Z)-5-Allyl-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulen-5-ol (322)

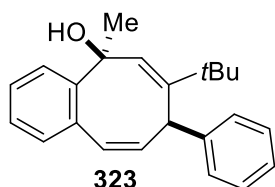
(6E,9Z)-8-Phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8H)-one (**80**)

(380 mg, 1.19 mmol) was dissolved in THF (10 mL) under argon at 0 °C and allylmagnesium bromide (2.3 mL, 0.61 M in diethyl ether, 1.43 mmol) was added before the mixture was stirred for 4 hours at this temperature. After this a further portion of allylmagnesium bromide (0.96 mL, 0.61 M in diethyl ether, 0.59 mmol) was added to fully consume starting material. After a further 1 hour the reaction was quenched with saturated ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 x 25 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The crude product was purified by flash column chromatography (3:2 pentane:diethyl ether) to give the title compound (6E,9Z)-5-Allyl-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulen-5-ol (**322**) (349 mg, 0.97 mmol) in 82% yield as a white solid. **R_f** (5:1 pentane:diethyl ether): 0.60; **Mp**: 79–81 °C; **IR** (NaCl, film): ν_{max} 3542, 2952, 2896, 1637, 1600, 1440, 1247, 1058, 877 cm^{-1} ; **MS** (ESI⁺): m/z 343 [M-OH]⁺; HRMS: found 343.1887 C₂₄H₂₇Si⁺ requires 343.1877.

Mixture of diastereoisomers formed. In analogy to MeMgBr Grignard addition, it is suggested that the *anti* isomer (OH to Ph) is the major isomer and *syn* isomer is the minor isomer (relationship 2.85:1) **¹H NMR** (400 MHz, CDCl₃): δ 7.72 (dd, J = 8.1, 1.2 Hz, 1H, ArH, *anti*), 7.56 (dd, J = 8.1, 1.2 Hz, 0.35H, ArH, *syn*), 7.34 – 7.27 (m, 1H, ArH, *anti*), 7.20 – 7.08 (m, 4H, ArH, *anti*), 7.08 – 7.00 (m, 2.4H, 1 ArH for *anti* and 4 ArH for *syn*), 7.00 – 6.95 (m, 1H, ArH, *anti*), 6.96 (d, J = 10.0 Hz, 1H, CCHCH, *anti*) 6.89 (d, J = 10.7 Hz, 0.35H, CCHCH, *syn*), 6.82 – 6.76 (m, 1H, ArH, *anti*), 6.71 (td, J = 7.4, 1.3 Hz, 0.35H, ArH, *syn*), 6.69 – 6.63 (m, 0.70H, 2ArH, *syn*), 6.53 – 6.48 (m, 0.70H, ArH and COHCH, *syn*), 6.36 (dd, J = 10.0, 10.0 Hz, 1H, CCHCH, *anti*), 6.28 (d, J = 1.9 Hz, 1H, COHCH, *anti*), 6.27 (dd, J = 10.7, 9.1 Hz, 0.35H, CCHCH, *syn*), 5.46 – 5.26 (m, 1.35H, CCH₂CHCH₂, *anti* and *syn*), 5.19 – 5.04 (m, 2.70H, CH₂CHCH_aH_b, *anti* and *syn*), 4.65 (dd, J = 10.0, 1.9 Hz, 1H, CHPh, *anti*), 4.55 (d, J = 9.1 Hz, 0.35H, CHPh, *syn*), 3.28 (dddd, J = 13.9, 5.7, 1.3, 1.3 Hz, 0.35H, CCH_aH_bCHCH₂, *syn*), 3.00 (dddd, J = 13.8, 5.8, 1.3, 1.3 Hz, 1H, CCH_aH_bCHCH₂, *anti*), 2.77 (s, 1H, OH, *anti*), 2.64 – 2.50 (m, 1.70H, CCH_aH_bCHCH₂ and OH for *syn* and CCH_aH_bCHCH₂ for *anti*), 0.04 (s, 3.15H, Si(CH₃)₃, *syn*), -0.15 (s, 9H, Si(CH₃)₃, *anti*); **¹³C NMR** (400 MHz, CDCl₃): δ 149.5 (CH, *syn*), 149.2 (CH, *anti*), 143.2 (C, *anti*), 141.7 (C, *syn*), 141.6 (C, *anti*), 141.3 (C, *anti*), 140.9 (C, *syn*), 139.4 (C, *syn*), 135.3 (C, *anti*), 135.1 (C, *syn*), 135.0 (CH, *syn*), 133.5 (CH, *anti*), 132.9 (CH, *syn*), 132.8 (CH, *anti*), 129.7 (CH, *anti*), 128.8 (CH, *anti*), 128.1 (CH, *anti*), 128.0 (CH,

anti), 127.6 (CH, *anti*), 127.5 (CH, *syn*), 127.0 (CH, *syn*), 126.8 (CH, *syn*), 126.6 (CH, *anti*), 126.4 (CH, *anti*), 126.4 (CH, *anti*), 126.2 (CH, *syn*), 125.9 (CH, *syn*), 124.7 (CH, *syn*), 120.0 (CH₂, *anti*), 119.9 (CH₂, *syn*), 78.1 (C, *syn*), 77.4 (C, *anti*), 45.4 (CH₂, *anti* and CH, *syn*), 44.4 (CH₂, *syn*), 43.8 (CH, *anti*), 0.4 (CH₃, *anti*), -1.4 (CH₃, *syn*). 2 CH signals from the *syn* isomer could not be observed due to overlap with stronger *anti* signals.

(6*E*,9*Z*)-7-(*tert*-Butyl)-5-methyl-8-phenyl-5,8-dihydrobenzo[8]annulen-5-ol (323)

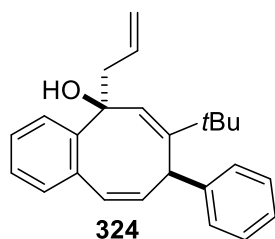


(6*E*,9*Z*)-7-(*tert*-Butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one (127)

(200 mg, 0.66 mmol) was dissolved in THF (5 mL) under argon at 0 °C and methylmagnesium bromide (0.48 mL, 1.64 M in diethyl ether, 0.79 mmol) was added before the mixture was stirred for 2

hours. A further portion of methylmagnesium bromide (0.2 mL, 1.64 M in diethyl ether, 0.33 mmol) was added to fully consume starting material. After a further 1 hour the reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (6*E*,9*Z*)-7-(*tert*-butyl)-5-methyl-8-phenyl-5,8-dihydrobenzo[8]annulen-5-ol (**323**) (201 mg, 0.63 mmol) in 95% yield as a white solid. **R_f** (5:1 pentane:diethyl ether): 0.40; **Mp**: 114-116 °C; **IR** (NaCl, film): ν_{max} 3439, 3058, 3012, 2964, 2869, 1492, 1465, 1364, 1219, 767, 758 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃): δ 7.51 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.00 – 6.92 (m, 1H, Ar*H*), 6.83 (d, *J* = 10.7 Hz, 1H, CCHCH), 6.74 (br s, 5H, Ar*H*), 6.67 (td, *J* = 7.4, 1.1 Hz, 1H, Ar*H*), 6.51 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.21 (dd, *J* = 10.7, 9.3 Hz, 1H, CCHCH), 6.14 (s, 1H, COHCH), 4.47 (d, *J* = 9.3 Hz, 1H, CHPh), 2.03 (br s, 1H, OH), 1.60 (s, 3H, CH₃), 1.08 (s, 9H, C(CH₃)₃); **¹³C NMR** (400.2 MHz, CDCl₃): δ 143.7 (C), 143.5 (C), 142.1 (C), 136.2 (CH), 135.4 (C), 134.7 (CH), 132.9 (CH), 128.3 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 125.7 (CH), 125.1 (CH), 124.5 (CH), 76.3 (C), 44.2 (CH), 38.1 (C), 29.7 (C), 29.5 (CH₃); **MS** (ESI⁺): *m/z* 301 [M-OH]⁺; HRMS: found 301.1964 C₂₃H₂₅⁺ requires 301.1951.

(6*E*,9*Z*)-5-Allyl-7-(*tert*-butyl)-8-phenyl-5,8-dihydrobenzo[8]annulen-5-ol (324)



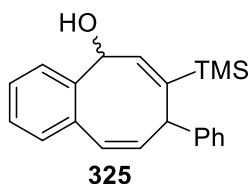
(6*E*,9*Z*)-7-(*tert*-Butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one (127)

(300 mg, 0.99 mmol) was dissolved in THF (6 mL) under argon at 0 °C and allylmagnesium bromide (2 mL, 0.6 M in diethyl ether, 1.19 mmol) was added before the mixture was stirred for 4 hours at this temperature. After this a further portion of allylmagnesium

bromide (0.31 mL, 0.6 M in diethyl ether, 0.19 mmol) was added to fully consume starting material. After a further 1 hour the reaction was quenched with saturated ammonium

chloride solution (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The crude product was purified by flash column chromatography (3:2 pentane:diethyl ether) to give the title compound (6*E*,9*Z*)-5-Allyl-7-(*tert*-butyl)-8-phenyl-5,8-dihydrobenzo[8]annulen-5-ol (**324**) (301 mg, 0.87 mmol) in 88% yield as a lightly yellow oil. **Rf** (5:1 pentane:diethyl ether): 0.53; **IR** (NaCl, film): $\nu_{\max}$ 3548, 3060, 3011, 2964, 2870, 1636, 1600, 1429, 1446, 1236, 1074, 1031, 729, 697 cm^{-1} ; **¹H NMR** (400 MHz, CDCl_3): δ 7.46 (dd, J = 8.1, 1.3 Hz, 1H, Ar*H*), 6.95 (dddd, J = 8.0, 7.3, 1.5, 0.6 Hz, 1H, Ar*H*), 6.87 (d, J = 10.6 Hz, 1H, CCHCH), 6.83-6.68 (m, 5H, Ar*H*), 6.66 (td, J = 7.4, 1.3 Hz, 1H, Ar*H*), 6.52 – 6.46 (m, 1H, Ar*H*), 6.25 (dd, J = 10.6, 9.3 Hz, 1H, CCHCH), 6.12 (s, 1H, COHCH), 5.24 (dddd, J = 17.1, 9.9, 9.0, 5.7 Hz, 1H, CCH₂CHCH₂), 5.08 (dddd, J = 17.1, 2.5, 1.4, 0.8 Hz, 1H, CCH₂CHCH_aH_b), 5.02 (dddd, J = 9.9, 2.5, 1.0, 0.8 Hz, 1H, CCH₂CHCH_aH_b), 4.51 (d, J = 9.3 Hz, 1H, CHPh), 3.16 (dddd, J = 13.8, 5.7, 1.4, 1.0 Hz, 1H, CCH_aH_bCHCH₂), 2.51 (dddd, J = 13.8, 9.0, 0.8, 0.8 Hz, 1H, CCH_bH_aCHCH₂), 2.43 (s, 1H, OH), 1.10 (s, 9H, C(CH₃)₃); **¹³C NMR** (400 MHz, CDCl_3): δ 144.3 (C), 142.2 (C), 141.5 (C), 135.4 (CH), 135.3 (C), 135.2 (CH), 133.7 (CH), 132.9 (CH), 128.0 (CH), 127.6 (CH), 127.0 (CH), 126.6 (CH), 126.4 (CH), 125.8 (CH), 124.4 (CH), 119.8 (CH₂), 77.1 (C), 44.5 (CH₂), 44.2 (CH), 38.3 (C), 29.6 (CH₃); **MS** (ESI⁺): m/z 327 [M-OH]⁺; HRMS: found 327.2117 C₂₅H₂₇⁺ requires 327.2107.

(6*E*,9*Z*)-8-Phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulen-5-ol (325)



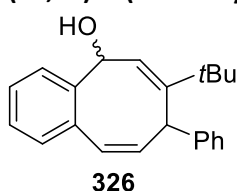
To a suspension of lithium aluminium hydride (12 mg, 0.31 mmol) in THF (0.5 mL) was added a solution of (6*E*,9*Z*)-8-phenyl-7-(trimethylsilyl)benzo[8]annulen-5(8*H*)-one (**80**) (100 mg, 0.31 mmol) in THF (2.5 mL) and the flask washed with THF (0.5 mL) at 0

°C under argon. The resulting solution was stirred at 0 °C for 1 h. The reaction was quenched by the addition of water (15 μL), followed by the addition of 10% aqueous sodium hydroxide solution (15 μL) and again water (45 μL). After filtration, ethyl acetate (5 mL) was added to the liquors and the solution washed with water (3 x 2 mL) before being dried over magnesium sulfate and concentrated *in vacuo*. Residue was purified by flash column chromatography (9:1 pentane:diethyl ether) to afford the title compound (6*E*, 9*Z*)-8-phenyl-7-(trimethylsilyl)-5,8-dihydrobenzo[8]annulen-5-ol (**325**) as a 4.8:1 inseparable mixture of diastereoisomers (71 mg, 0.22 mmol) in 71% yield as a colourless solid. **Rf** (9:1 pentane:diethyl ether): 0.26; **Mp**: 84-86 °C; **IR** (CHCl_3 , solution) $\nu_{\max}$ 3606, 3006, 2957, 1598, 1490, 1447, 1249, 1046, 838 cm^{-1} ; **MS** (ESI⁺): m/z 320 [M+Na]⁺; HRMS: found 343.1490 C₂₁H₂₄NaOSi⁺ requires 343.1489.

Compound **325** was attained as a mixture of diastereoisomers in a 4.8:1 ratio. In analogy to MeMgBr Grignard addition, it is suggested that the *anti* isomer (OH to Ph) is the major isomer and *syn* isomer is the minor isomer. **¹H NMR** (400.2 MHz, CDCl₃): δ 7.57 – 7.49 (m, 1.21H, 1 ArH for *anti* and 1ArH for *syn*), 7.44 – 7.38 (m, 2H, ArH, *anti*), 7.36 – 7.30 (m, 2H, ArH, *anti*), 7.29 – 7.12 (m, 4.21H, 4 ArH for *anti* and 1 ArH for *syn*), 6.88 – 6.76 (m, 0.84H, 4ArH, *syn*), 6.72 (d, *J* = 11.0 Hz, 0.21H, CCHCHCHPh, *syn*), 6.53 (dd, *J* = 13.2, 1.3 Hz, 1H, CHCHCHPh, *anti*), 6.50 (dd, *J* = 2.6, 0.8 Hz, 0.21H, ArH, *syn*), 6.48 – 6.42 (m, 0.63H, 2ArH and HOCHCH, *syn*), 6.27 (dd, *J* = 11.0, 9.0 Hz, 0.21H, CHCHCHPh, *syn*), 6.09 (dd, *J* = 13.2, 6.8 Hz, 1H, CHCHCHPh, *anti*), 6.08 (d, *J* = 7.5 Hz, 1H, HOCHCH, *anti*), 5.97 (dd, *J* = 7.5, 2.8 Hz, 1H, HOCH, *anti*), 5.75 (br dd, *J* = 3.0, 3.0 Hz, 0.21H, HOCH, *syn*), 4.55 (d, *J* = 9.0 Hz, 0.21H, CHCHCHPh, *syn*), 4.42 (d, *J* = 6.8 Hz, 1H, CHCHCHPh, *anti*), 2.01 (d, *J* = 3.0 Hz, 0.21H, OH, *syn*), 1.79 (d, *J* = 3.0 Hz, 1H, OH, *anti*), -0.03 (s, 9H, Si(CH₃)₃, *anti*), -0.08 (s, 1.89H, Si(CH₃)₃, *syn*); **¹³C NMR** (100.6 MHz, CDCl₃): δ 145.6 (CH, *syn*), 145.5 (CH, *anti*), 144.8 (C, *anti*), 143.2 (C, *anti*), 142.8 (C, *syn*), 140.7 (C, *syn*), 139.7 (C, *syn*), 138.7 (C, *anti*), 136.2 (CH, *anti*), 135.6 (C, *syn*), 135.2 (CH, *syn*), 133.1 (C, *anti*), 131.5 (CH, *anti*), 131.1 (CH, *syn*), 129.0 (CH, *anti*), 128.6 (CH, *anti*), 128.2 (CH, *anti*), 127.8 (CH, *syn*), 127.6 (CH, *anti*), 127.5 (CH, *syn*), 127.0 (CH, *syn*), 126.7 (CH, *syn*), 126.6 (CH, *anti*), 126.3 (CH, *anti*), 126.0 (CH, *syn*), 125.1 (CH, *syn*), 123.6 (CH, *syn*), 122.6 (CH, *anti*), 70.8 (CH, *syn*), 70.6 (CH, *anti*), 47.8 (CH, *anti*), 47.6 (CH, *syn*), -1.1 (CH₃, *syn*), -1.4 (CH₃, *anti*).

(6*E*,9*Z*)-7-(*tert*-Butyl)-8-phenyl-5,8-dihydrobenzo[8]annulen-5-ol

(326)



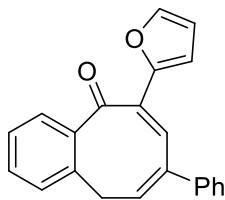
To a suspension of lithium aluminium hydride (13 mg, 0.33 mmol) in THF (0.5 mL) was added a solution of (6*E*,9*Z*)-7-(*tert*-butyl)-8-phenylbenzo[8]annulen-5(8*H*)-one (**127**) (100 mg, 0.33 mmol) in THF (2.5 mL) and the flask washed with THF (0.5 mL) at 0 °C under argon. The resulting solution was stirred at 0 °C for 1 h. The reaction was quenched by the addition of water (15 µL), followed by the addition of 10% aqueous sodium hydroxide solution (15 µL) and again water (45 µL). After filtration, ethyl acetate (5 mL) was added to the liquors and the solution washed with water (3 x 2 mL) before being dried over magnesium sulfate and concentrated *in vacuo*. Residue was purified by flash column chromatography (9:1 pentane:diethyl ether) to afford the title compound (6*E*,9*Z*)-7-(*tert*-Butyl)-8-phenyl-5,8-dihydrobenzo[8]annulen-5-ol (**326**) as a 14.9:1 inseparable mixture of diastereoisomers (84 mg, 0.28 mmol) in 85% yield as a colourless solid. **R_f** (9:1 pentane:diethyl ether): 0.24; **Mp**: 63 - 65 °C; **IR** (NaCl, film): ν_{max} 3341, 3022, 2964, 1507,

1448, 1364, 1239, 1041, 910, 737, 700 cm^{-1} ; **MS** (ESI+): m/z 327 $[\text{M}+\text{Na}]^+$; HRMS: found 327.1722 $\text{C}_{22}\text{H}_{24}\text{NaO}^+$ requires 327.1719.

Compound **326** was attained as a mixture of diastereoisomers in a 14.9:1 ratio. In analogy to MeMgBr Grignard addition, it is suggested that the *syn* isomer (OH to Ph) is the major isomer and *anti* isomer is the minor isomer. **^1H NMR** (400.2 MHz, CDCl_3): δ 7.58 – 7.48 (m, 0.21H, 3ArH, *anti*), 7.46 – 7.42 (m, 1H, ArH, *syn*), 7.41 – 7.31 (m, 0.21H, 3ArH, *anti*), 7.24 – 7.15 (m, 0.21H, 3ArH, *anti*), 7.14 – 7.06 (m, 1H, ArH, *syn*), 6.81 (d, J = 10.5 Hz, 1H, CHCHCHPh, *syn*), 6.80 – 6.37 (m, 5H, ArH, *syn*), 6.64 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, ArH, *syn*), 6.53 (dd, J = 14.0, 1.4 Hz, 0.07H, CHCHCHPh, *anti*), 6.33 (dd, J = 14.0, 7.9 Hz, 0.07H, CHCHCHPh, *anti*), 6.30 (d, J = 7.6 Hz, 1H, ArH, *syn*), 6.25 (d, J = 3.0 Hz, 1H, HOCHCH, *syn*), 6.24 (dd, J = 10.5, 9.4 Hz, 1H, CHCHCHPh, *syn*), 5.70 (dd, J = 9.0, 2.8 Hz, 0.07H, HOCH, *anti*), 5.62 (dd, J = 9.0, 1.1 Hz, 0.07H, HOCHCH, *anti*), 5.47 (br dd, J = 3.0, 3.0 Hz, 1H, HOCH, *syn*), 4.55 (d, J = 9.4 Hz, 1H, CHCHCHPh, *syn*), 4.49 (d, J = 7.9 Hz, 0.07H, CHCHCHPh, *anti*), 1.99 (d, J = 3.0 Hz, 1H, OH, *syn*), 1.67 (d, J = 2.8 Hz, 0.07H, OH, *anti*), 1.05 (s, 0.63H, $\text{C}(\text{CH}_3)_3$, *anti*), 1.03 (s, 9H, $\text{C}(\text{CH}_3)_3$, *syn*); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 143.6 (C), 143.4 (C), 140.9 (C), 136.1 (C), 134.7 (CH), 131.8 (CH), 131.4 (CH), 127.5 (CH), 127.3 (CH), 126.6 (CH), 126.1 (CH), 125.9 (CH), 124.4 (CH), 123.7 (CH), 70.5 (CH), 45.5 (CH), 37.7 (C), 29.9 (CH_3). Only the major *syn* diastereoisomer was visible in ^{13}C NMR.

(6Z,8E)-6-(Furan-2-yl)-8-phenylbenzo[8]annulen-5(10H)-one

(329)

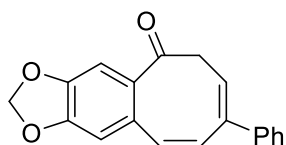


329

Following general procedure F. **^1H NMR** (400.2 MHz, CDCl_3): δ 7.92 – 7.83 (m, 2H, ArH), 7.72 – 7.66 (m, 1H, ArH), 7.64 (dd, J = 1.7, 0.7 Hz, 1H, furanyl-H), 7.63 – 7.59 (m, 2H, ArH), 7.55 – 7.50 (m, 1H, ArH), 7.47 – 7.40 (m, 3H, ArH), 7.29 (dd, J = 3.6, 0.7 Hz, 1H, furanyl-H), 7.26 – 7.25 (m, 1H, furanylCCH), 6.59 (dd, J = 3.6, 1.7 Hz, 1H, furanyl-H), 5.71 (dd, J = 9.1, 3.0 Hz, 1H, $\text{CCH}_a\text{H}_b\text{CH}$), 4.17 (ddd, J = 13.8, 3.0, 1.4 Hz, 1H, CCH_aH_b), 3.21 (dd, J = 13.8, 9.1 Hz, 1H, CCH_aH_b).

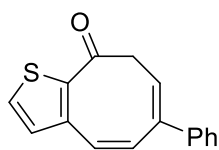
(7E,9Z)-8-Phenylcycloocta[4,5]benzo[1,2-d][1,3]dioxol-5(6H)-one

(330)

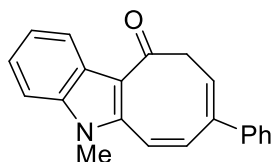


330

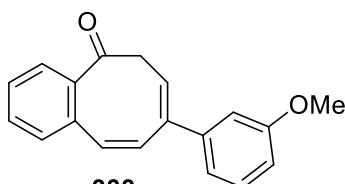
Following general procedure F. **^1H NMR** (400.2 MHz, CDCl_3): δ 7.83 (s, 1H, ArH), 7.36 – 7.25 (m, 5H, ArH), 6.99 (d, J = 12.5 Hz, 1H, CCHCH), 6.85 (s, 1H, ArH), 6.60 (d, J = 12.5 Hz, 1H, CCHCH), 6.18 (t, J = 8.3 Hz, 1H, CH_2CH), 6.03 (s, 2H, OCH_2O), 3.55 (d, J = 8.3 Hz, 2H, COCH_2).

(4Z,6E)-6-Phenylcycloocta[b]thiophen-9(8H)-one (331)**331**

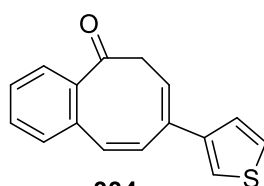
Following general procedure F. $^1\text{H NMR}$ (400.2 MHz, CDCl_3): δ 7.58 (d, $J = 5.2$ Hz, 1H, thiophenyl-*H*), 7.36 – 7.27 (m, 5H, *ArH*), 7.16 (d, $J = 5.2$ Hz, 1H, thiophenyl-*H*), 7.15 (d, $J = 12.4$ Hz, 1H, CCHCH), 6.75 (d, $J = 12.4$ Hz, 1H, CCHCH), 6.16 (dd, $J = 9.7, 7.4$ Hz, 1H, $\text{CH}_a\text{H}_b\text{CH}$), 3.55 (dd, $J = 10.8, 7.4$ Hz, 1H, COCH_aH_b), 3.16 (dd, 10.8, 9.7 Hz, 1H, COCH_aH_b).

(6Z,8E)-5-Methyl-8-phenyl-5,10-dihydro-11H-cycloocta[b]indol-11-one (332)**332**

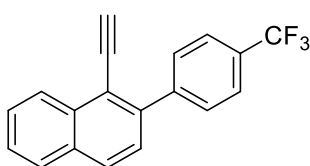
Following general procedure F. $^1\text{H NMR}$ (400.2 MHz, CDCl_3): δ 8.69 (ddd, $J = 7.7, 1.2, 1.2$ Hz, 1H, *ArH*), 7.42 – 7.23 (m, 8H, *ArH*), 7.10 (d, $J = 12.6$ Hz, 1H, CCHCH), 7.01 (d, $J = 12.6$ Hz, 1H, CCHCH), 6.32 (dd, $J = 9.7, 7.5$ Hz, 1H, $\text{CH}_a\text{H}_b\text{CH}$), 3.88 (s, 3H, NCH_3), 3.51 (dd, $J = 10.9, 7.5$ Hz, 1H, COCH_aH_b), 3.22 (dd, $J = 10.9, 9.7$ Hz, 1H, COCH_aH_b).

(7E,9Z)-8-(3-methoxyphenyl)benzo[8]annulen-5(6H)-one (333)**333**

Following general procedure F. $^1\text{H NMR}$ (400.2 MHz, CDCl_3): δ 8.37 (dd, $J = 8.0, 1.5$ Hz, 1H, *ArH*), 7.59 – 7.51 (m, 1H, *ArH*), 7.48 – 7.42 (m, 1H, *ArH*), 7.37 (ddd, $J = 8.4, 7.0, 1.5$ Hz, 1H, *ArH*), 7.26 – 7.18 (m, 1H, *ArH*), 7.11 (d, $J = 12.5$ Hz, 1H, CCHCH), 6.93 (ddd, $J = 7.7, 1.5, 1.0$ Hz, 1H, *ArH*), 6.88 – 6.77 (m, 2H, *ArH*), 6.63 (d, $J = 12.5$ Hz, 1H, CCHCH), 6.20 (t, $J = 8.3$ Hz, 1H, CH_2CH), 3.79 (s, 3H, OCH_3), 3.62 (d, $J = 8.3$ Hz, 2H, COCH_2).

(7E,9Z)-8-(thiophen-3-yl)benzo[8]annulen-5(6H)-one (334)**334**

Following general procedure F. $^1\text{H NMR}$ (400.2 MHz, CDCl_3): δ 8.40 (dd, $J = 8.0, 1.4$ Hz, 1H, *ArH*), 7.55 (ddd, $J = 8.0, 7.1, 1.5$ Hz, 1H, *ArH*), 7.48 – 7.44 (m, 1H, *ArH*), 7.40 (ddd, $J = 8.3, 7.1, 1.4$ Hz, 1H, *ArH*), 7.29 (dd, 5.1, 2.9 Hz, 1H, thiophenyl-*H*), 7.21 (dd, 5.1, 1.3 Hz, 1H, thiophenyl-*H*), 7.16 (dd, 2.9, 1.3 Hz, 1H, thiophenyl-*H*), 7.10 (d, $J = 12.6$ Hz, 1H, CCHCH), 6.71 (d, $J = 12.6$ Hz, 1H, CCHCH), 6.21 (t, $J = 8.3$ Hz, 1H, CH_2CH), 3.62 (d, $J = 8.3$ Hz, 2H, COCH_2).

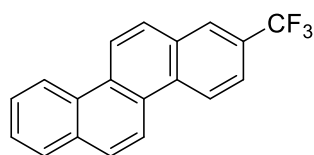
1-Ethynyl-2-(4-(trifluoromethyl)phenyl)naphthalene (336)**336**

Trimethylsilyl acetylene (470 μL , 3.40 mmol) was dissolved in tetrahydrofuran (4.6 mL) under argon and cooled to -50°C . A solution of *n*-butyllithium (1.55 M in hexanes, 2.3 mL, 3.6 mmol) was then added and the mixture stirred for 20

minutes. Neat 2-bromobenzaldehyde (378 μL , 3.24 mmol) was added to the reaction mixture. After 60 minutes additional *n*-butyllithium (1.55 M in hexanes, 2.2 mL, 3.40 mmol) was added forming yellow, orange or dark coloured solutions. After 15 minutes solid copper(I) bromide dimethyl sulfide (334 mg, 1.63 mmol) was then added under a cushion of argon, normally forming tan suspensions/dark solutions at $-50\text{ }^{\circ}\text{C}$. After a further 1 hour neat 1-(1-chloroprop-2-yn-1-yl)-4-(trifluoromethyl)benzene (**169**) (345 mg, 1.58 mmol) was added to the reaction mixture, which was then allowed to warm slowly to $-10\text{ }^{\circ}\text{C}$ over a period of 30 minutes and kept there for 45 mins before being warmed to $0\text{ }^{\circ}\text{C}$ and kept there for a further 45 minutes. The mixture was then quenched with pH = 7 ammonia buffered saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate ($3 \times 20\text{ mL}$). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The crude residue was then dissolved in dichloromethane (10 mL) before Amberlyst 15 ion exchange resin (700 mg, ground into powder) and 3 Å molecular sieves were added. After stirring for 1 hour the mixture was filtered before tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 6.5 mL, 6.5 mmol) was added and the reaction stirred for 30 minutes. The mixture was then washed with water ($3 \times 10\text{ mL}$) before the organic phase was dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product. Flash column chromatography (neat pentane) afforded the title compound 1-ethynyl-2-(4-(trifluoromethyl)phenyl)naphthalene (**336**) (313 mg, 1.06 mmol) in 67% yield as a yellow solid. **Rf** (9:1 pentane: diethyl ether): 0.63; **Mp**: $119\text{--}121\text{ }^{\circ}\text{C}$; **IR** (ATR): ν_{max} 3295, 3060, 1614, 1593, 1325, 1165, 1109, 1089, 1065, 1019, 816, 760, 660, 620 cm^{-1} ; **^1H NMR** (400.1 MHz, CDCl_3): δ 8.52 – 8.48 (m, 1H, ArH), 7.97 – 7.87 (m, 2H, ArH), 7.82 – 7.78 (m, 2H, ArH), 7.75 – 7.71 (m, 2H, ArH), 7.65 (ddd, $J = 8.4, 6.9, 1.4\text{ Hz}$, 1H, ArH), 7.58 (ddd, $J = 8.1, 6.9, 1.2\text{ Hz}$, 1H, ArH), 7.49 (d, $J = 8.5\text{ Hz}$, 1H, ArH), 3.48 (s, 1H, CCH); **^{13}C NMR** (100.6 MHz, CDCl_3): δ 144.5 (C), 142.0 (C), 134.1 (C), 132.5 (C), 130.2 (CH), 129.7 (q, $J = 32.5\text{ Hz}$, C), 129.4 (CH), 128.3 (CH), 127.8 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 125.1 (q, $J = 3.6\text{ Hz}$, CH), 124.4 (q, $J = 272.1\text{ Hz}$, C), 117.7 (C), 86.3 (CH), 80.6 (C); **^{19}F NMR** (376.4 MHz, CDCl_3): δ -62.41 (s, 3F, CF_3); **MS** (EI): m/z 296 [M]; HRMS: found 296.0798 $\text{C}_{19}\text{H}_{11}\text{F}_3$ requires 296.0813.

2-(Trifluoromethyl)chrysene

(**337**)



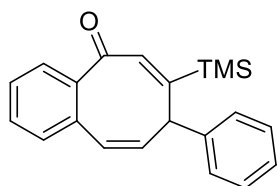
337

1-Ethynyl-2-(4-(trifluoromethyl)phenyl)naphthalene (**336**) (104 mg, 0.35 mmol) was mixed with platinum(II) chloride (5 mg, 17.5 μmol) in toluene (1.4 mL) inside a sealed microwave tube under a cushion of argon. The resulting mixture was

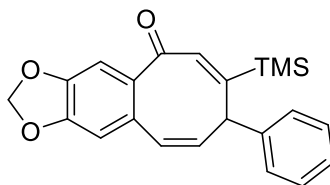
heated at 150 °C for 1 hour before being concentrated *in vacuo* to afford the crude product. Flash column chromatography (neat pentane to 49:1 pentane: diethyl ether gradient elution) afforded the title compound 2-(trifluoromethyl)chrysene (**337**) (52 mg, 0.18 mmol) in 51% yield as a colourless solid. **Rf** (neat pentane): 0.26; **Mp**: 275 -277 °C; **IR** (ATR): ν_{max} 3083, 1459, 1342, 1317, 1290, 1264, 1187, 1169, 1115, 1088, 1069, 902, 813, 753 cm^{-1} ; **^1H NMR** (400.1 MHz, $(\text{CD}_3)_2\text{SO}$): δ 9.18 (d, J = 8.8 Hz, 1H, ArH), 9.07 (d, J = 9.1 Hz, 1H, ArH), 9.01 (d, J = 8.3 Hz, 1H, ArH), 8.95 (d, J = 9.1 Hz, 1H, ArH), 8.60 (s, 1H, ArH), 8.33 (d, J = 9.1 Hz, 1H, ArH), 8.21 (d, J = 9.1 Hz, 1H, ArH), 8.15 (dd, J = 7.9, 1.3 Hz, 1H, ArH), 7.99 (dd, J = 8.8, 1.8 Hz, 1H, ArH), 7.80 (ddd, J = 8.3, 7.0, 1.8 Hz, 1H, ArH), 7.76 (ddd, J = 7.9, 7.0, 1.3 Hz, 1H, ArH); **^{13}C NMR** (100.6 MHz, $(\text{CD}_3)_2\text{SO}$): δ 132.2 (C), 132.0 (C), 131.1 (C), 129.8 (C), 129.1 (C), 128.6 (CH), 128.2 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.2 (C), 126.7 (q, J = 31.9 Hz, C), 126.1 (q, J = 4.3 Hz, CH), 125.2 (CH), 124.6 (q, J = 272.1 Hz, C), 123.8 (CH), 123.2 (CH), 122.2 (q, J = 3.2 Hz, CH), 121.6 (CH); **^{19}F NMR** (376.4 MHz, $(\text{CD}_3)_2\text{SO}$): δ -60.44 (s, 3F, CF_3); **MS** (EI): m/z 296 [M]; HRMS: found 296.0809 $\text{C}_{19}\text{H}_{11}\text{F}_3$ requires 296.0913.

3.4 Crystallographic Data

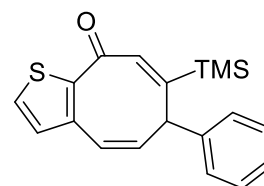
Data was collected by the School of Chemistry, University of Nottingham Crystallography Service using the standard methods described in the compound CIF files. The structures were solved and refined by standard methods. CIF files of the compounds analysed have been uploaded to the Cambridge Crystallographic Database (available from: www.ccdc.cam.ac.uk). The CCDC codes of the compounds uploaded and their structures are shown.



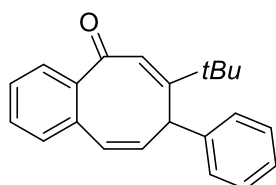
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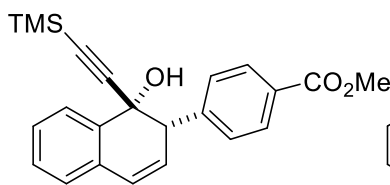
105
CCDC 1405854



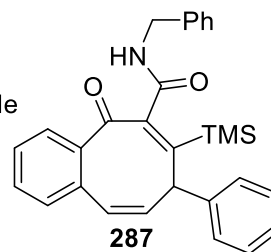
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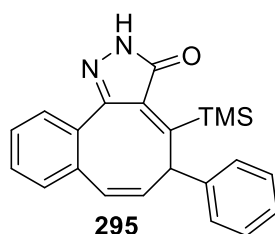
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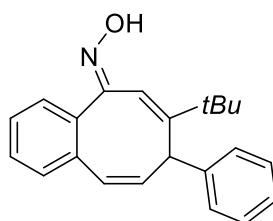
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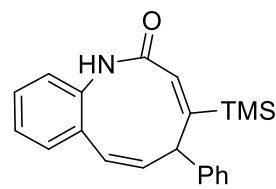
287
CCDC 1472247



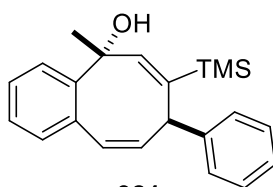
295
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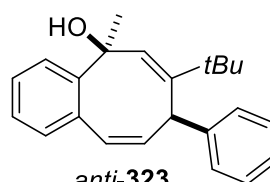
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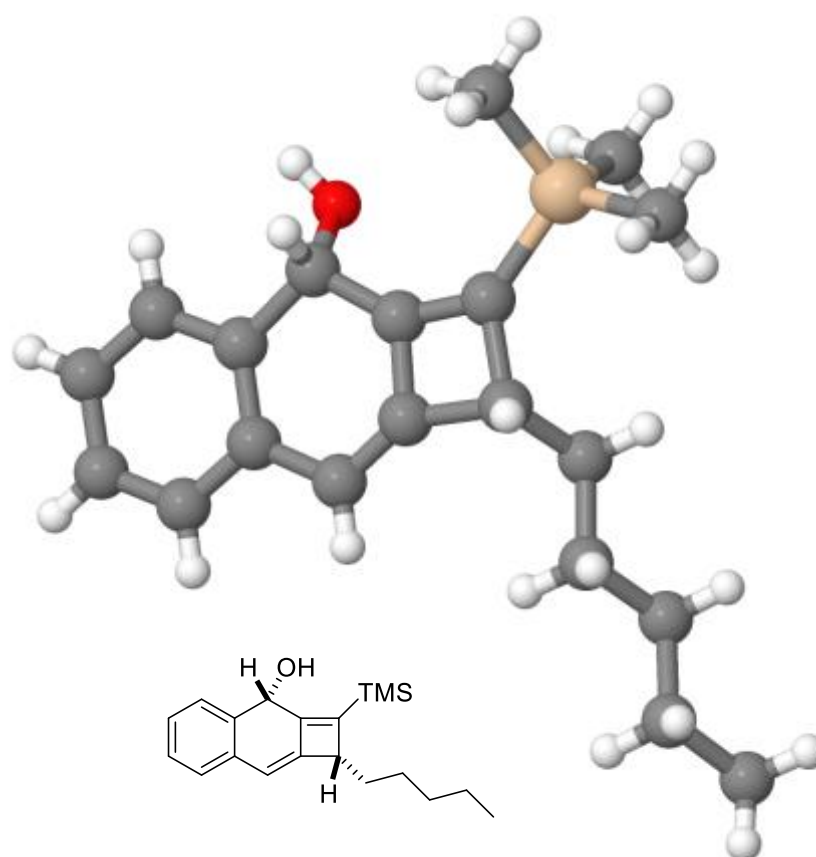
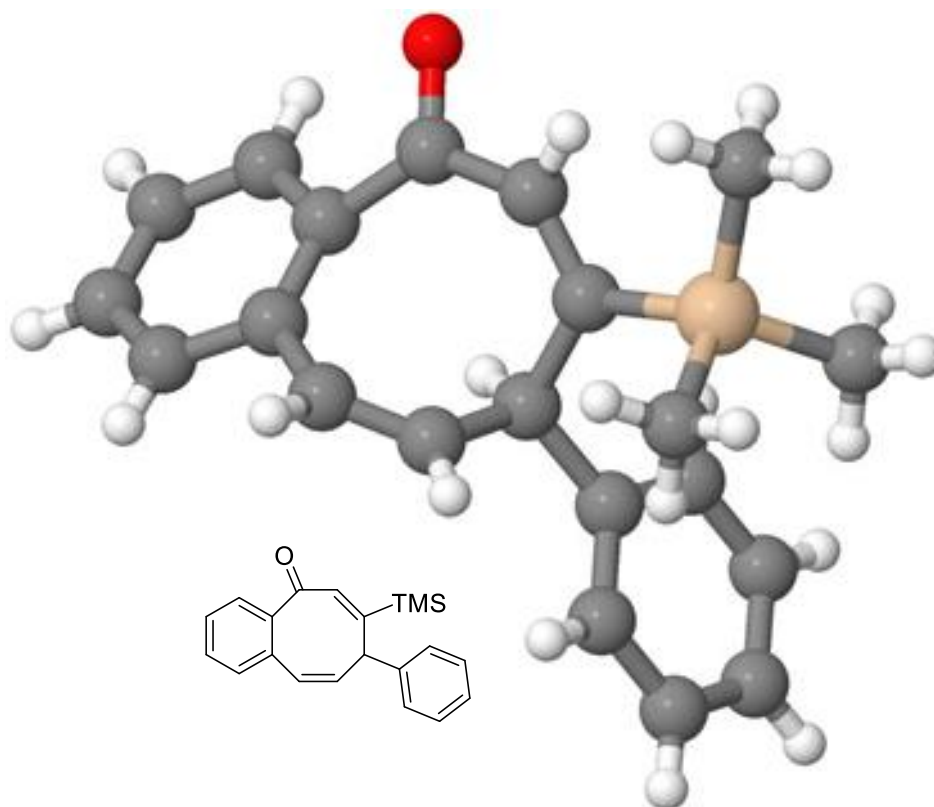
319
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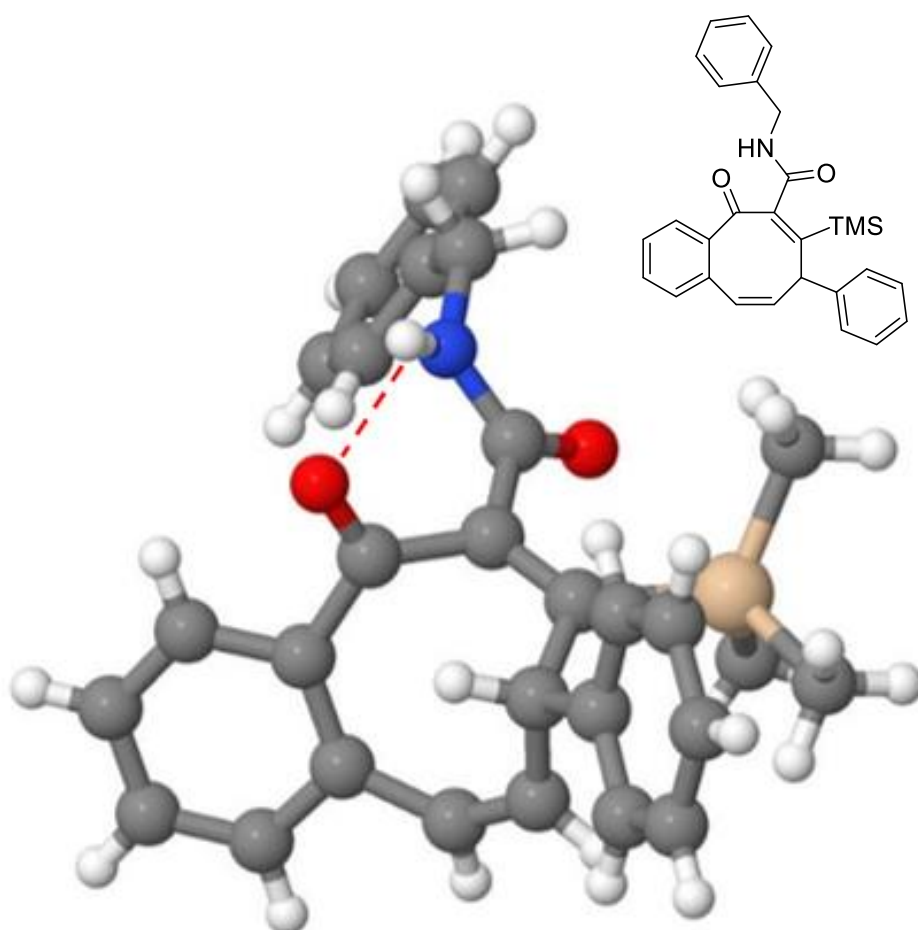
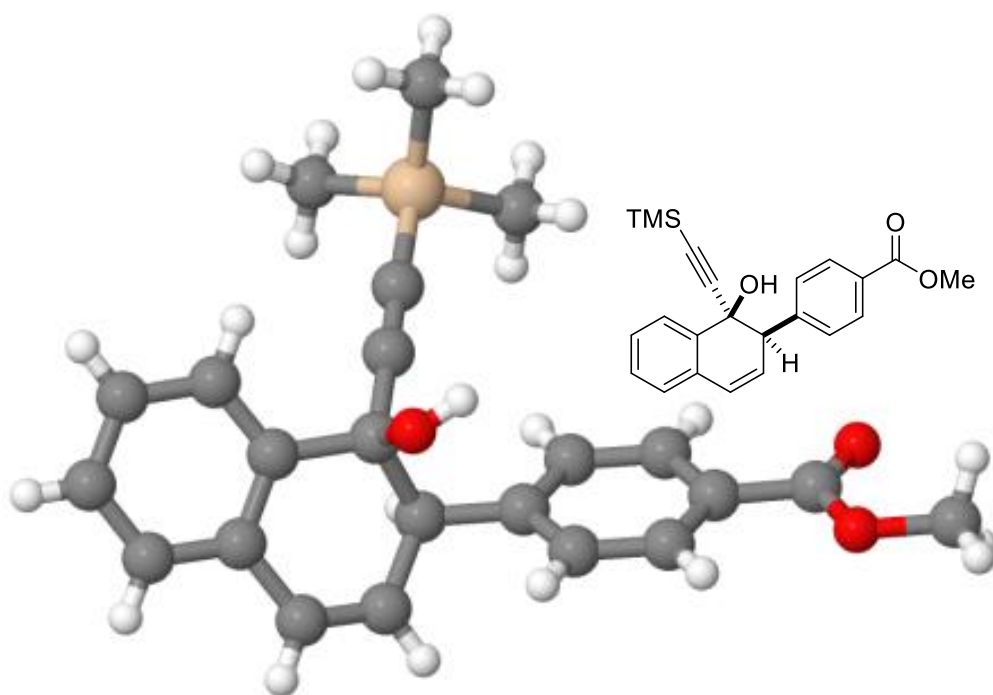


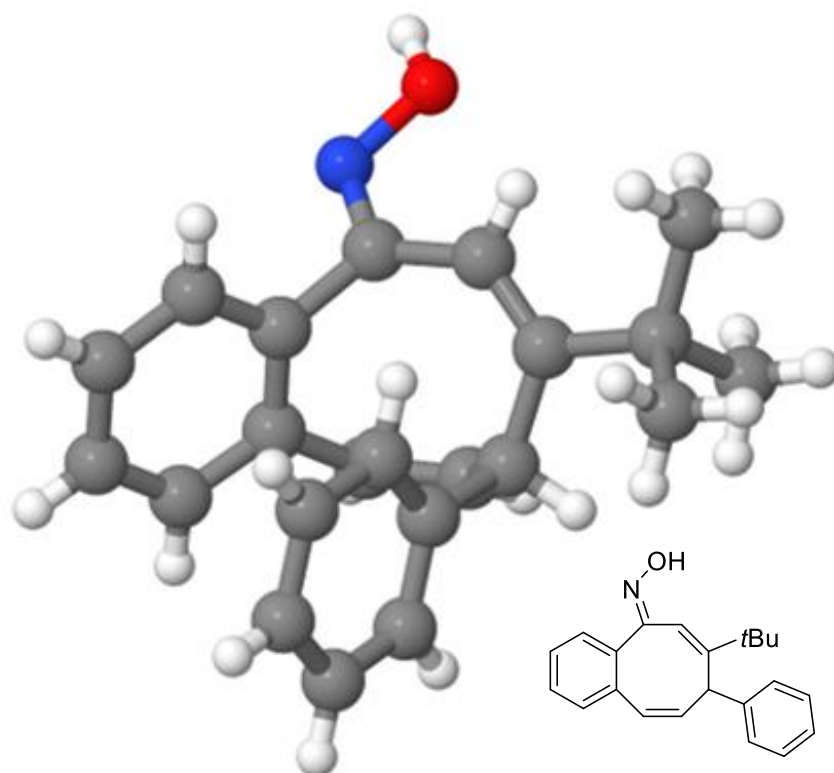
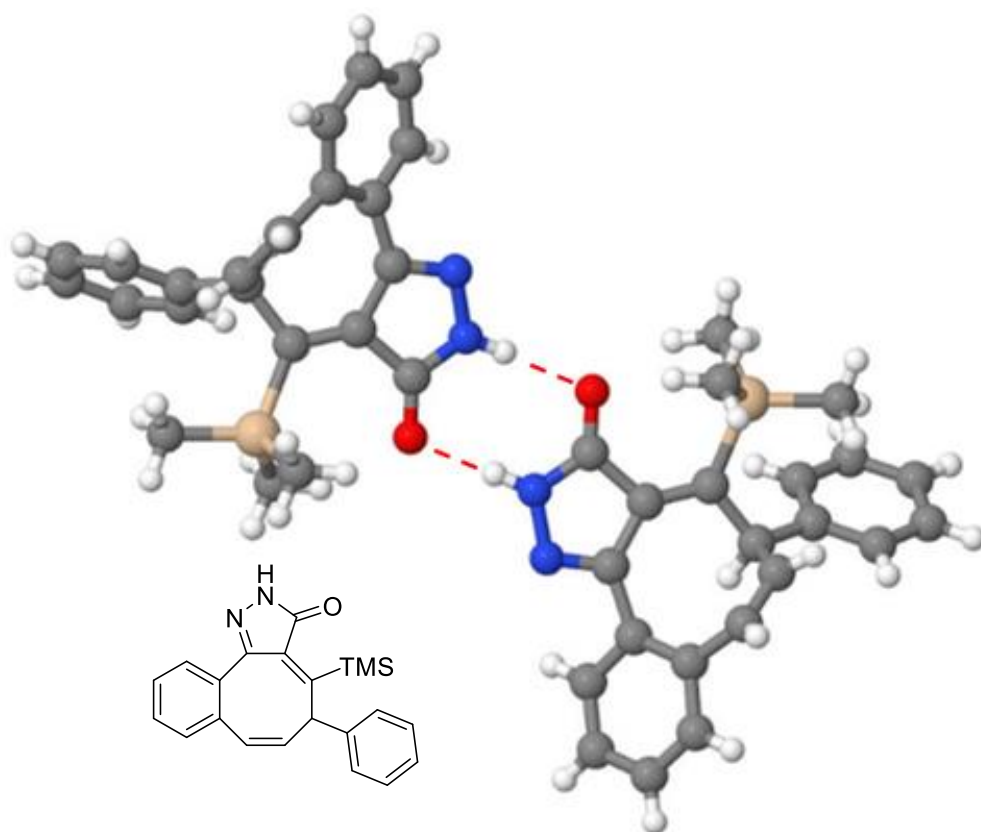
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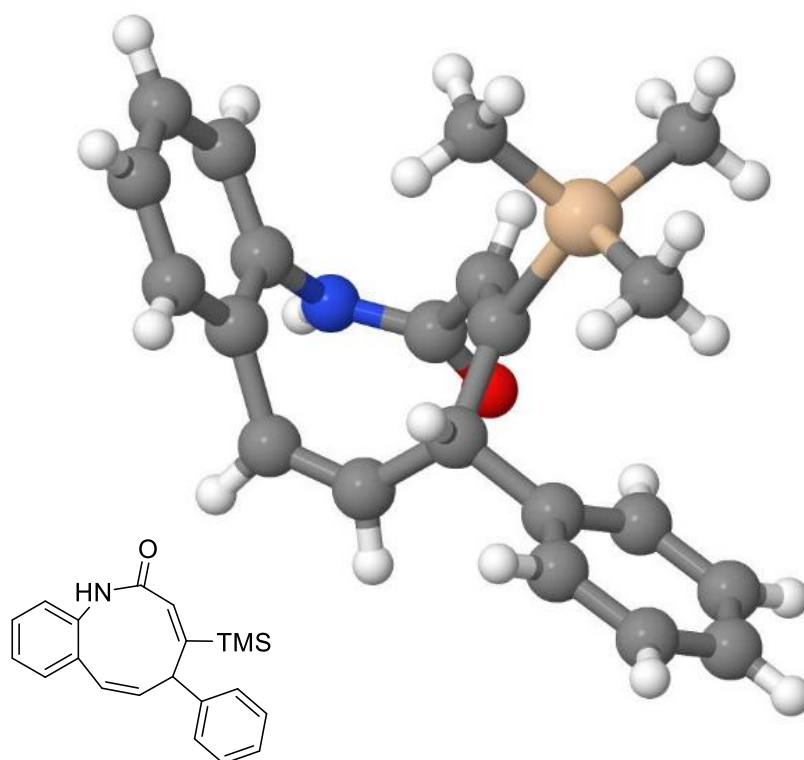


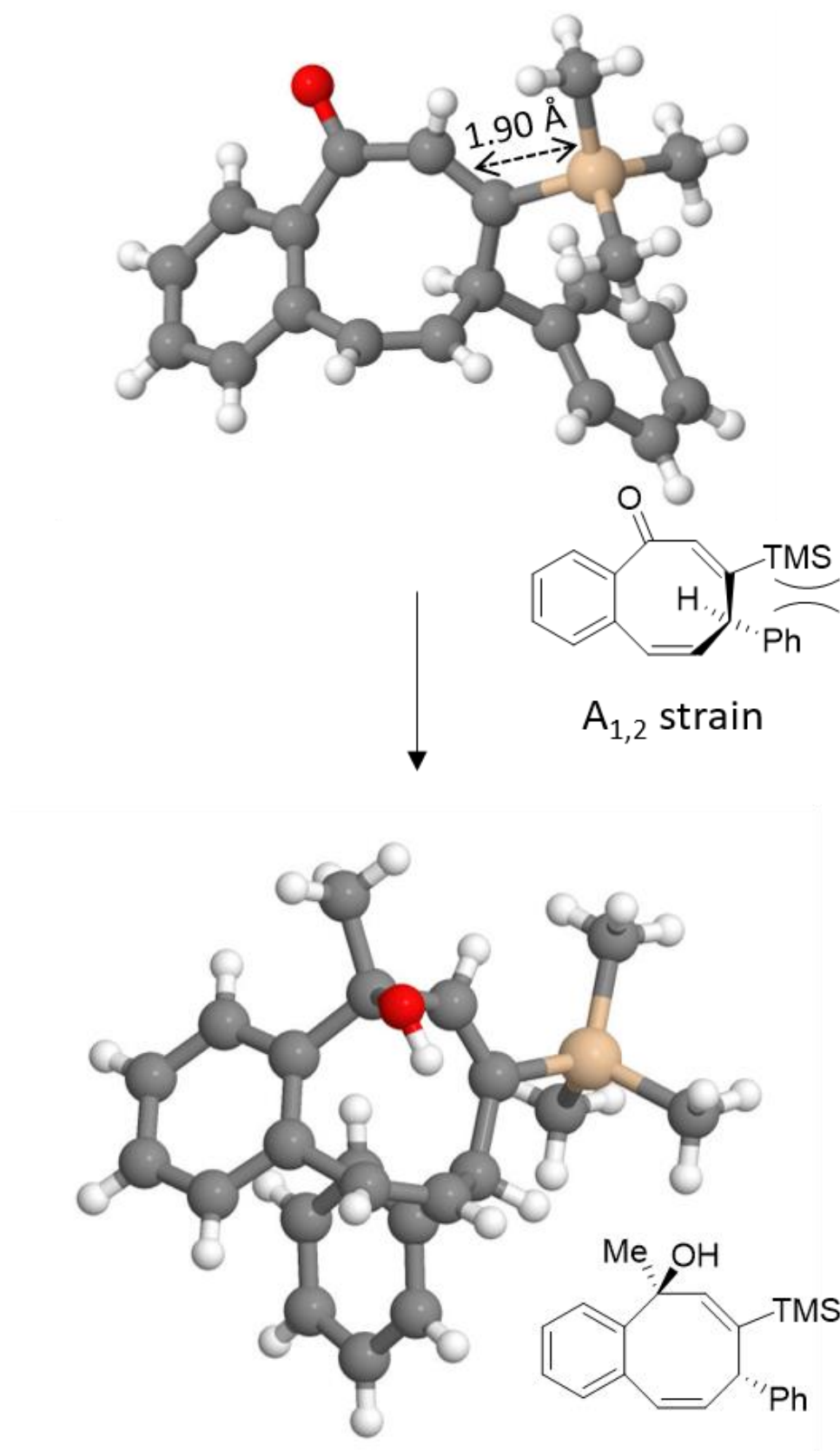
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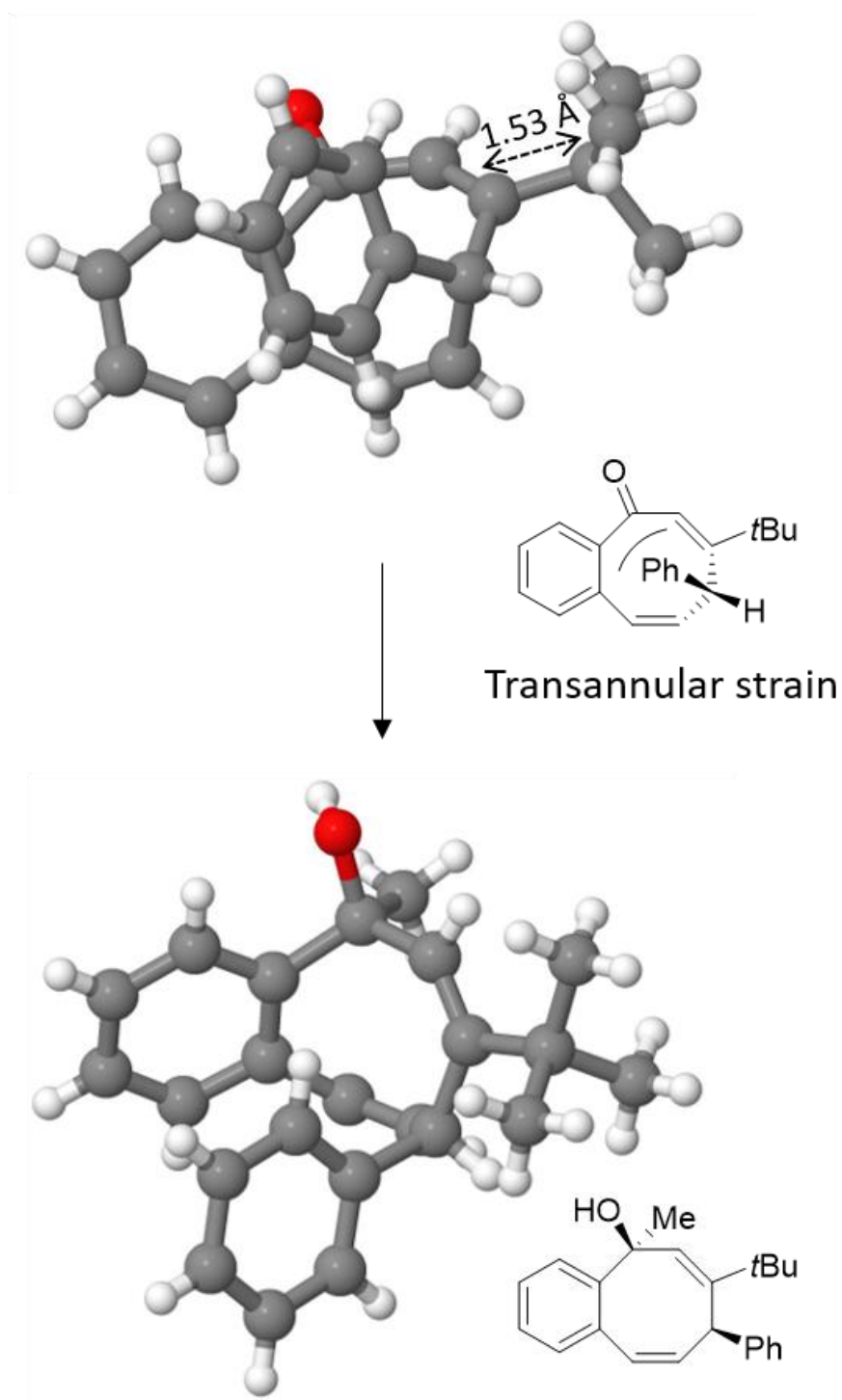


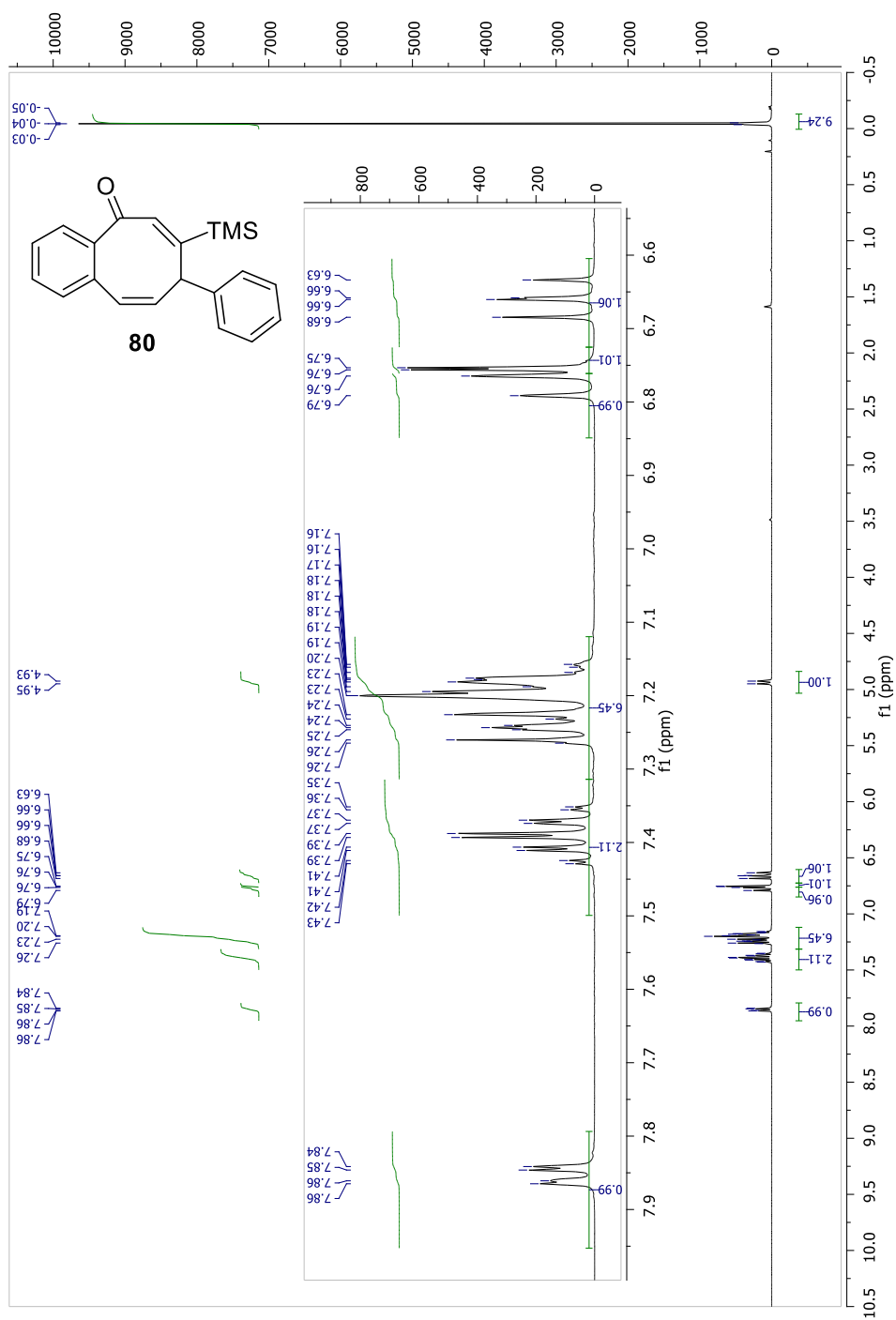


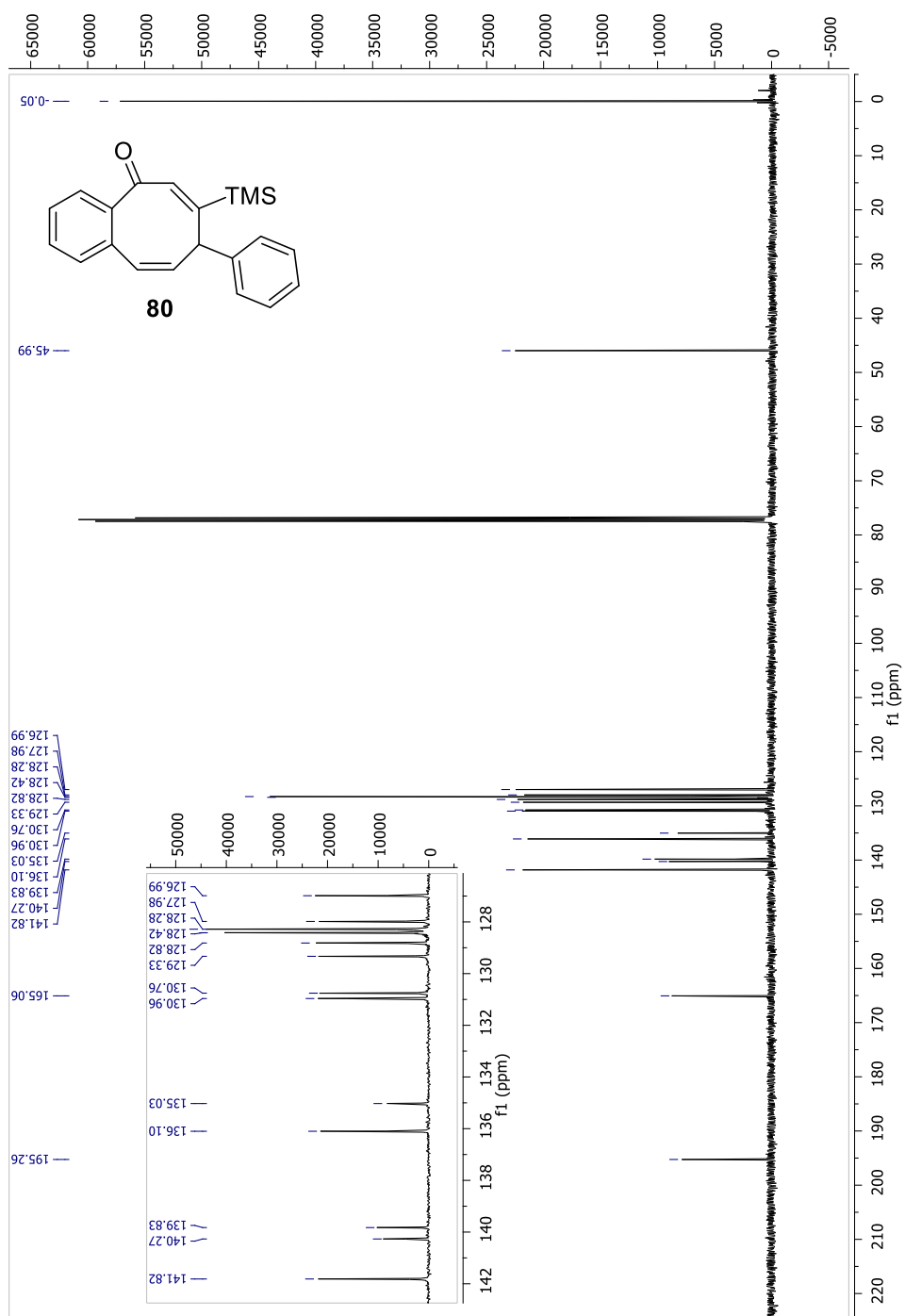








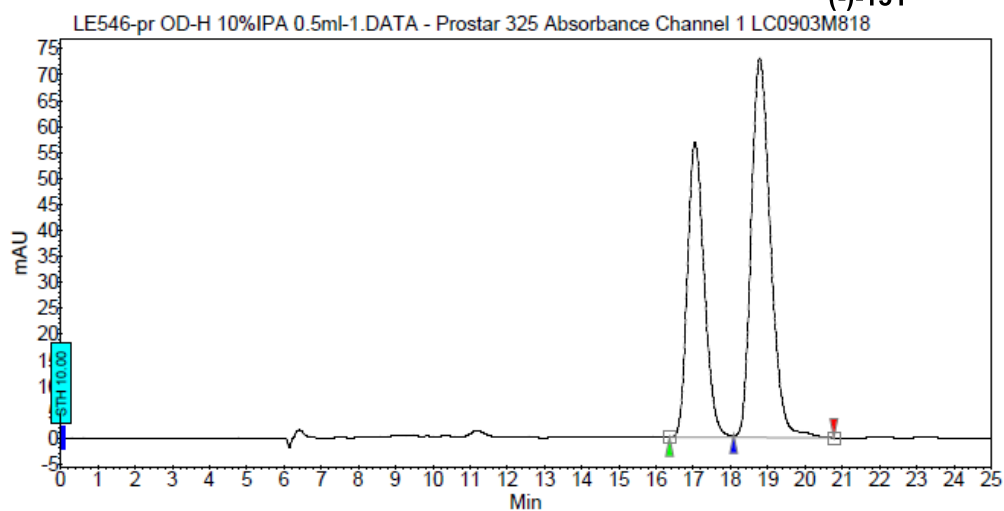
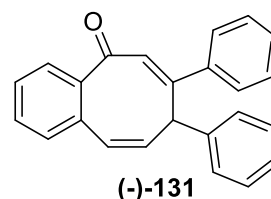
3.5 Representative ^1H NMR spectrum, ^{13}C NMR spectrum and HPLC Trace



**Chromatogram : LE546-pr OD-H 15%IPA
0.5ml-1_channel1**

System : PS325
Method : LE 10% IPA 0.5ML
User : User1

Acquired : 23/02/2016 14:12:58
Processed : 23/02/2016 14:39:17
Printed : 23/02/2016 18:09:17

**Peak results :**

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.05	40.41	56.7	29.7	40.409
2	UNKNOWN	18.79	59.59	73.1	43.9	59.591
Total			100.00	129.8	73.6	100.000

4.0 References

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- ⁵ All calculations were carried out using Gaussian 09, Rev D.01. We acknowledge support by the NSCCS and access to their slater service.
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One-Pot Cannizzaro Cascade Synthesis of *ortho*-Fused Cycloocta-2,5-dien-1-ones from 2-Bromo(hetero)aryl Aldehydes

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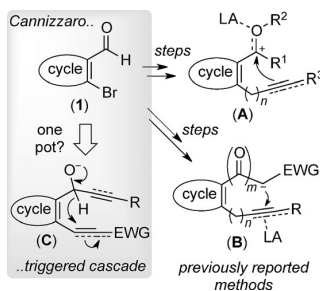
Abstract: An intramolecular Cannizzaro-type hydride transfer to an *in situ* prepared allene enables the synthesis of *ortho*-fused 4-substituted cycloocta-2,5-dien-1-ones with unprecedented technical ease for an eight-ring carboannulation. Various derivatives could be obtained from commercially available (hetero)aryl aldehydes, trimethylsilylacetylene, and simple propargyl chlorides in good yields.

Reasily (often commercially) available 2-bromo(hetero)aryl aldehydes (**1**, Scheme 1) constitute powerful and popular units for the construction of *ortho*-fused carbocyclic rings.^[1] Two strategies commonly employed in the multitudinous syntheses described in the literature involve 1) the derivatization of **1** to intermediates of type **A**, with a π -system attacking an electrophile that is ultimately derived from the aldehyde by functional-group manipulations (e.g., an alcohol, acetal, or even the aldehyde itself); or 2) formyl group homologation to an anion-stabilizing unit that attacks a suitably activated π -bond (**B**). Whereas many elegant catalytic systems that use intermediates **A** or **B** have already been described,^[2,3] the preparation of the suitable precursors is often step-intensive, raising questions on the overall process

efficiency in the “age of sustainability”.^[4] We speculated that a new annulation strategy, based on a Cannizzaro-type reaction via intermediate **C**, might be possible. As the hydride transfer simultaneously exposes a powerful Michael acceptor (ynone or equivalent) and a carbanion in close proximity, efficient annulation might be expected to occur (especially if **C** is directly attained *in situ*). Herein, we describe the use of such a strategy for the formation of eight-membered rings. The paucity of direct single-pot/step procedures to such medium rings attests to the known issues associated with their synthesis;^[5] they therefore provide a stringent test for strategy C. Although redox-based Cannizzaro reactions, including asymmetric and triggered C–C bond-forming versions, have recently been developed,^[6] to the best of our knowledge, they have not been employed for carboannulation reactions to medium rings. Genuine single-pot/step procedures to eight-membered rings are very limited—Reppé’s historical catalytic access to cyclooctatetraene^[7] and Murakami’s [4+2+2] approach^[8] being notable exceptions. Modern alternatives frequently describe catalytic cyclizations that proceed with exquisitely high yields (for the final step). Unfortunately, their overall synthetic efficiency is often compromised by the multistep syntheses required to obtain the cyclization precursors.^[9]

Initial investigation of our own proposal (C) centered on the combination of readily available 2-bromobenzaldehyde (**1a**), trimethylsilylacetylene (**2a**), and propargyl chloride **3a**. Encouragingly, even an initial run returned significant amounts of benzo[8]annulene derivative **4aaa** (Table 1, entry 1, ca. 7%) whose identity and regiochemistry was confirmed by X-ray crystallography (see the Supporting Information) as initial NMR data was not conclusive.^[10] Unfortunately, under the conditions of entry 1, multiple side products were also produced. Upon changing from an organocopper to an organocuprate formulation (entry 2), the reaction became much cleaner, but the yield of **4aaa** remained low. The recovered side products of entry 2 included significant amounts of the alcohols **5a** and **6a** together with unreacted **3a**. We could confirm that formation of **D** was almost quantitative in < 20 min under all conditions tried (Et₂O or THF, –78 to 0°C, based on recovered **5a** in independent reactions). We therefore suspected issues associated with both *n*BuLi–halogen exchange from **D** and the copper-promoted S_N2’ reaction leading to the progenitor for eight-ring formation. Further experiments were designed to probe these hypotheses (Table 1).

Organometallic compounds derived from **D** were poorly soluble in Et₂O so the reaction solvent was switched to THF (entry 3). This led to an improved reaction that enabled us to



Scheme 1. Proposed use of 2-bromo(hetero)aryl aldehydes in Cannizzaro-triggered annulation cascades compared to traditional approaches. EWG = electron-withdrawing group, LA = Lewis acid, R¹–R³ are generic groups, *n* and *m* are typically 0–1.

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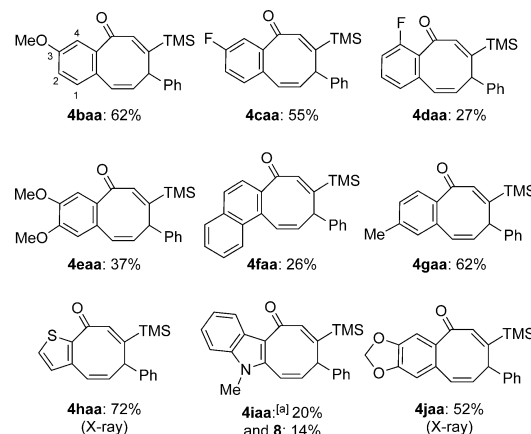
Table 1: Optimization of the Cannizzaro-triggered cascade reaction to eight-ring compound **4aaa**.^[a]

Entry	Solvent	Halogen exchange of intermediate D	Transmetalation with CuBr·SMe ₂	Addition of 3 a and cyclization	Yield 4aaa [%]
1	Et ₂ O	<i>t</i> BuLi (2 equiv), −50°C, 20 min	1 equiv, −50°C, 20 min	1 equiv, −50°C to RT over 5 h	< 10
2	Et ₂ O	<i>n</i> BuLi (1 equiv), 0°C, 10 min	0.5 equiv, −50°C, 5 min	0.5 equiv, −50°C to +10°C over 1.2 h	14 ^[b]
3	THF	<i>n</i> BuLi (1 equiv), −50°C, 15 min	0.5 equiv, −50°C, 10 min	0.5 equiv, −50°C to 10°C over 1.2 h	53
4	THF	<i>n</i> BuLi (1 equiv), −50°C, 15 min	0.5 equiv, −50°C, 1 h	0.5 equiv, −50°C to −10°C over 1.5 h; kept at −10°C for 1 h	70 (69) ^[c]
5	THF	<i>n</i> BuLi (1 equiv), −50°C, 15 min	0.5 equiv, −50°C, 1 h	0.5 equiv, −50°C to −10°C over 1.5 h; kept at −10°C for 2 h	35

[a] Reaction conditions: **1a** (0.71 mmol), **2a** (0.77 mmol)/*n*BuLi (0.72 mmol), CuBr·SMe₂ (0.36–0.71 mmol), **3a** (0.35–0.70 mmol) in Et₂O or THF (1.0 mL). The yields of **4aaa** were determined by GC analysis against genuine samples and an internal standard (1-methylnaphthalene, 50 µL). [b] The mass balance of the reaction included **3a**, **5a**, and **6a** in a 2.4:1.0:1.8 ratio. [c] The yield of isolated product for a reaction performed with 1.39 mmol of **3a** is shown in parentheses.

identify that the onset of the Cannizzaro-type cascade reaction occurs at −20 to −10°C for this substrate. Independent treatment of THF solutions containing **D** with *n*BuLi followed by quenching with D₂O confirmed that complete Br/Li exchange had occurred within 15 min at −40 to −60°C, and that the resulting organolithium species was rather stable at these temperatures. However, above approximately −15°C, the same species began to decompose rapidly. Thus, −40 to −50°C was selected as the temperature range for optimizing the transmetalation to CuBr·SMe₂. When the nominal diorganocuprate was prepared under the conditions of entry 3 (−50°C, 10 min, from the aryl lithium intermediate with CuBr·SMe₂) and then treated with methyl vinyl ketone, very poor conversions into the 1,4-addition product were attained. This strongly suggested that transmetalation to Cu^I is rather slow for this system. Gratifyingly, extending the time for Li/Cu exchange to one hour (entry 4) significantly increased the quantity of **4aaa** formed, and the GC yields were comparable to those attained through isolation (70% vs. 69%). Further extending the transmetalation time to two hours at −10°C had a detrimental effect on the yield of **4aaa** (entry 5).

With an optimized procedure for the preparation of parent compound **4aaa** in hand, we studied the scope of the reaction with respect to the 2-bromo(hetero)aryl aldehyde component **1**. Using the conditions of entry 4 (Table 1) and aldehydes **1b–1j**, the eight-ring compounds that are shown in Scheme 2 were attained. Substitution at the 3-position was better tolerated than at the 1- and 4-positions (products **4baa/4caa** vs. **4daa/4faa**). Monosubstitution at the 2-position was also tolerated. A comparison of the yields of **4baa–4gaa** indicates that steric factors are more important than electronic ones; for example, intramolecular OMe steric contacts increase the *ortho* steric profile of **4caa** versus **4jaa**. The yields of compounds **4haa–4jaa** also support this trend. Whereas the yields of **4aaa–4jaa** are modest, it should be borne in mind that they represent one-pot processes to analytically pure crystalline products on up to multigram scales, using only inexpensive commercial starting materials. The new process compares very favorably to the consolidated

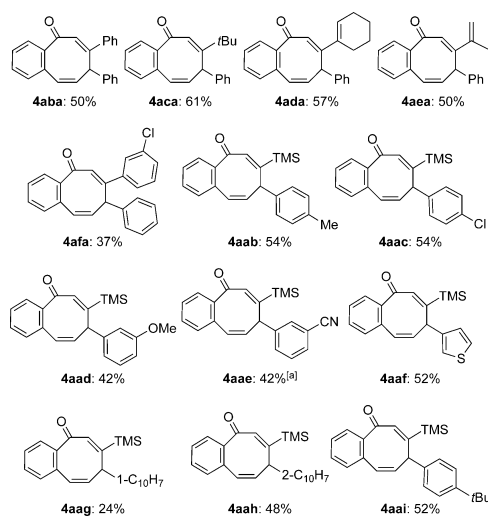


Scheme 2. Variation of the 2-bromo(hetero)aryl aldehyde; yields starting from the commercial aldehydes are given.^[9] [a] The precursor aldehyde was obtained from isatin (3 steps).

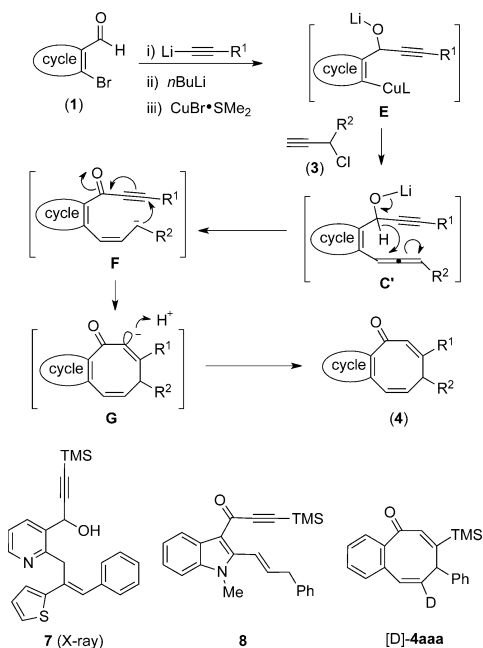
yields and time efficiencies of previously reported eight-ring syntheses.^[9]

By varying the acetylene component using the readily attained starting materials **2b–2f**, five further examples of eight-ring compounds **4** were synthesized (Scheme 3). The terminal alkyne substituent could encompass alkyl, vinyl, or aryl units, and the corresponding compounds were all obtained in acceptable yields. Finally, variation of the propargyl chloride was investigated using simple **3b–3i** (Scheme 3). The aryl moiety could accommodate both electron-donating and -withdrawing substituents and some functional groups (**4aae** and **4aaf**).

Whereas the full mechanistic features of our Cannizzaro-triggered cascade are still under investigation, a working hypothesis is shown in Scheme 4. Sequential 1,2-acetylide addition, halogen exchange, and transmetalation to copper affords intermediate **E**. This copper(I) species undergoes a γ -selective S_N2' addition to propargyl chloride **3** affording the non-isolable allene **C'**, which undergoes the Cannizzaro-type hydride shift proposed in Scheme 1. The resulting allyl anion

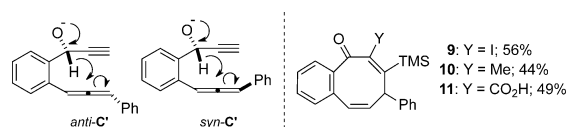


Scheme 3. Variation of the terminal acetylene and propargyl chloride. [a] Run at -50°C .



Scheme 4. Mechanistic proposal for the formation of eight-ring compounds **4**; L is indicative of the presence of a generic organocopper or -cuprate species.

is presumably placed in close proximity to the potent ynone Michael acceptor, which leads to efficient ring closure. The use of an aryl moiety as the R^2 substituent is apparently sufficient to stabilize the allyl anion and allow the necessary *trans* to *cis* isomerization. Protonation of the non-classical enolate **G** results in the formation of **4**. Several pieces of evidence support this chain of events. First, attempts to use 2-thienylcyanocuprates derived from a related aza substrate led to the isolation of **7** (X-ray structure) where the intermediate allene has been carbometalated rather than



Scheme 5. The computational models *anti-C'* and *syn-C'* and indirect evidence for the formation of **G**.

having accepted a hydride. For the formation of **4iaa**, we could isolate appreciable amounts of **8**, which is the expected product of a Cannizzaro-type hydride transfer without subsequent annulation. Use of the deuterated aldehyde 2-BrC₆H₄CDO ([D]-**1a**) led to the formation of the expected product [D]-**4aaa**, confirming the participation of the aldehyde in the Cannizzaro process.

The mechanistic proposal shown in Scheme 4 was also probed by DFT calculations at the M06-2X/6-31G(d) and CBS-QB3 levels of theory^[11] on the “metal-free” anions *anti-C'* and *syn-C'* (Scheme 5; see also the Supporting Information). Whereas the relationship of *anti-C'* and *syn-C'* to the reaction coordinate of the true organometallic species involved in the cascade process needs to be treated with caution, it does provide further evidence for the proposed mechanism. The calculated barriers for the Cannizzaro-type hydride transfer and the rearrangement of the allyl anion (the equivalent of the transformation of **C'** into **F** in Scheme 4) were approximately 5 and 7 kcal mol⁻¹, respectively. The calculations also indicate that non-classical enolates of type **G** are favored in the reaction over the equivalent allenolate structures. This idea was further reinforced by the observation that trapping of the reaction intermediates with iodine, iodomethane, or carbon dioxide, as opposed to a proton, leads to the formation of derivatives **9–11** (Scheme 5).

To the best of our knowledge, this Cannizzaro-triggered cascade process is unique. The nearest analogues that we could find are cyclizations reported by the Oonishi and Sato groups;^[9b,d] however, in these cases, the allene intermediate must be separately synthesized, and no Cannizzaro-type process is involved. Similarly, a single eight-ring side product (formed in 10% yield) was obtained by Alajarin and Vidal through a 1,5-hydride shift/8 π electrocyclization from a neutral 1,2-allenylacetal at 110 $^{\circ}\text{C}$.^[12] Again, no Cannizzaro-type trigger was proposed. Whereas Cannizzaro shifts have been used for oxidation-state manipulations in *ortho*-fused systems, in these processes, no annulation steps were involved.^[13] The most similar ynone eight-ring closure process that could be identified was developed by Schreiber and Kelly,^[14] but this transformation involves an alkoxide nucleophile.

In conclusion, we believe that this very simple formation of *ortho*-fused cycloocta-2,5-dien-1-one units demonstrates the potential of the developed method for rapid and efficient annulations. Investigations into extending the scope of both the present reaction and other variants are ongoing.

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Synthetic Methods

Diversification of *ortho*-Fused Cycloocta-2,5-dien-1-one Cores and Eight- to Six-Ring Conversion by σ Bond C–C CleavageLee Eccleshare, Leticia Lozada-Rodríguez, Philippa Cooper, Laurence Burroughs, John Ritchie, William Lewis, and Simon Woodward*^[a]

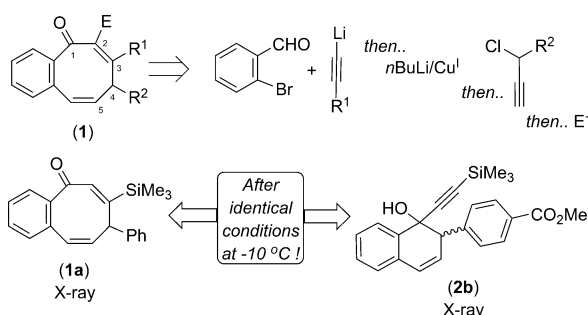
Abstract: Sequential treatment of 2-C₆H₄Br(CHO) with Li≡CR¹ (R¹=SiMe₃, *t*Bu), *n*BuLi, CuBr·SMe₂ and HC≡CCHClR² [R²=Ph, 4-CF₃Ph, 3-CNPh, 4-(MeO₂C)Ph] at –50 °C leads to formation of an intermediate carbanion (Z)-1,2-C₆H₄{C_A(=O)C≡CR¹}[CH=CH(CH)R²] (**4**). Low temperatures (–50 °C) favour attack at C₈ leading to kinetic formation of 6,8-bicyclics containing non-classical C-carbanion enolates (**5**). Higher temperatures (–10 °C to ambient) and electron-deficient R² favour retro σ -bond C–C cleavage regenerating **4**, which subsequently closes on C_A providing 6,6-bicyclic alkoxides (**6**). Computational modelling (CBS-QB3) indicated that both pathways are viable and of similar energies. Reaction of **6**

with H⁺ gave 1,2-dihydronaphthalen-1-ols, or under dehydrating conditions, 2-aryl-1-alkynyl naphthalenes. Enolates **5** react in situ with: H₂O, D₂O, I₂, allylbromide, S₂Me₂, CO₂ and lead to the expected C–E derivatives (E=H, D, I, allyl, SMe, CO₂H) in 49–64% yield directly from intermediate **5**. The parents (E=H; R¹=SiMe₃, *t*Bu; R²=Ph) are versatile starting materials for NaBH₄ and Grignard C=O additions, desilylation (when R¹=SiMe) and oxime formation. The latter allows formation of 6,9-bicyclics via Beckmann rearrangement. The 6,8-ring iodides are suitable Suzuki precursors for Pd-catalysed C–C coupling (81–87%), whereas the carboxylic acids readily form amides under T3P® conditions (71–95%).

Introduction

We recently described a new method for the synthesis of eight-membered rings^[1] that allows the preparation of gram quantities of cycloocta-2,5-dien-1-one cores (Scheme 1). When 2-bromobenzaldehydes were treated sequentially with acetylides, *n*BuLi, CuBr·SMe₂, propargylic chlorides and finally an

electrophile (typically, simple H⁺) the phenylene derivatives **1** were attained in moderate yields (25 examples at 26–72%, 14 above 50% yield). This ready access prompted us to consider the applicability of the chemistry to provide libraries of diversified cores of potential future use in medicinal chemistry.^[2] Specifically, we raised the questions: 1) What further diversity can be introduced into **1** via simple derivatisation; and 2) How far can the diversity of units R¹, R² and E⁺ units be extended. In fact, the group R² became of immediate initial importance, because one of our preliminary studies showed that this group could profoundly affect the reaction's chemoselectivity (Scheme 1, **1a** vs. formation of **2b** instead).



Scheme 1. Methodology for the preparation of eight-rings (**1a**) and initially unexplained competing six-ring (**2b**) when R² is 4-(MeO₂C)Ph.

Results and Discussion

Factors in eight- versus six-ring formation

Model reactions by using 2-bromobenzaldehyde, TMS-acetylene and various propargylic electrophiles were used to gain understanding of the effect of group R² on the reaction (Table 1). Under our standard conditions,^[1] highly chemoselective eight-ring formation was observed for **1a**, and this was isolated in good yield (70%). This chemoselectivity was not affected by the leaving group (Cl, O₂CCF₃, OAc), although the last of these gave lower yields of **1a** due to incomplete conversion. Decreasing the electron density within the aryl group was confirmed to promote specific formation of six-ring **2b**. X-ray studies (see the Supporting Information) confirmed a *syn* arrangement of the alcohol and aryl (R²) group in the major diastereomer of **2b**. In this *syn* isomer, the chemical shift and

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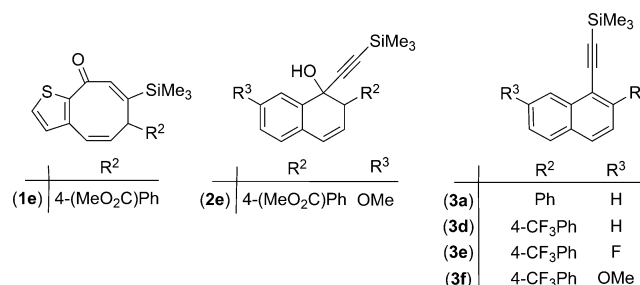
Table 1. Substituent and condition effects on the chemoselectivity of eight- versus six-ring formation.^[a]

R ²	X	Conditions prior to quench	(1)/(2) ^[b]	d.r. (2) ^[d]	Isolated product [%] ^[c]
Ph	Cl	warmed to −10 °C over 0.5 h and hold for 1 h (standard)	100:0	–	1a (70)
Ph	O ₂ CCF ₃	standard	100:0	–	1a (58)
Ph	OAc	standard	100:0	–	1a (19)
Ph	Cl	standard, then warm to rt over 0.5 h and hold for 1 h	1:4	2:1	3a ^[e,f] (48)
Ph	Cl	standard, then warm to rt over 0.5 h and hold for 1 h, then re-cool to −10 °C for 1 h	1:4	2:1	–
4-(MeO ₂ C)Ph	Cl	standard	0:100	5:1	2b (65)
4-(MeO ₂ C)Ph	Cl	kept at −50 °C for 16 h	0:100	5:1	–
3-CNPh	Cl	standard	1:9	2:1	2c (48)
3-CNPh	Cl	kept at −50 °C for 16 h	2:1	–	1c (42)
4-(CF ₃)Ph	Cl	standard	1:11	2:1	3d ^[e,f] (47)
4-(CF ₃)Ph	Cl	kept at −50 °C for 16 h	1:1	2:1	1d (35)
4-(MeO ₂ C)Ph	Cl	by using 2-bromo-5-methoxybenzaldehyde and warm to 0 °C (for 1 h)	0:100	3:1	2e ^[e] (52)
4-(CF ₃)Ph	Cl	by using 2-bromo-5-fluorobenzaldehyde warm to 0 °C and hold (for 1 h)	1:5	1:1	3e ^[e,f] (49)
4-(MeO ₂ C)Ph	Cl	by using 3-bromothiophene-2-carbaldehyde and warm to 0 °C (for 1 h)	100:0	–	1e ^[e] (27)
4-(CF ₃)Ph	Cl	by using 2-bromo-5-methoxybenzaldehyde and warm to 0 °C (for 1 h)	1:3	1:2	3f ^[e,f] (42)

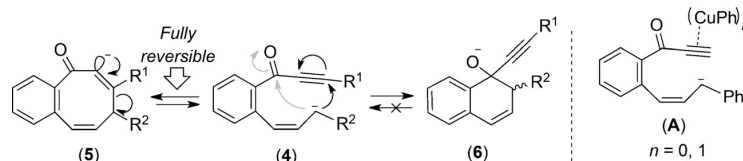
[a] Reagents: LiCCTMS (3.4 mL of 0.5 M THF/hexane solution) treated with 2-bromobenzaldehyde (1.62 mmol), followed by *n*BuLi (1.06 mL of 1.6 M hexane solution), CuBr·SMe₂ (0.81 mmol), propargylic electrophile (0.79 mmol) added at −50 °C. [b] From crude reaction mixture, determined by ¹H NMR spectroscopy. [c] Isolated. [d] *syn* (OH to R²)/*anti* ratio; stereochemical assignment is based on NMR correlation to **2b** (X-ray). [e] Structures of products **1e–3f** are shown below. [f] Isolated as naphthalene **3**; dehydration from **2** to **3** achieved with Amberlyst® 15 and 3 Å molecular sieves.

coupling constants of the CHR² proton (δ_{H} 4.08, J = 2.9, 2.6 Hz) are distinct from the same proton in the *anti* diastereomer (δ_{H} 4.01, J = 4.6, 1.6 Hz); the other derivatives had their relative stereochemistries assigned on this basis. For propargylic chlorides based on 3-CNPh substituents, the six- vs. eight-ring chemoselectivity is controlled by reaction temperature; reactions at −50 and −10 °C, prior to quenching, maximise the yields of **1c** and **2c**, respectively. The bis-trifluoromethyls **1d/2d** behaved analogously. When the parent (R¹ = SiMe₃, R² = Ph) reaction mixture was warmed to room temperature (over 30 min), **3a** (48%) was isolated upon protonation and dehydration. Conversely, the chemoselectivity in reactions using the 4-(CO₂Me)Ph substituted propargylic chloride could not be affected by changing the reaction temperature. Even at −50 °C (prior to quenching), no eight-ring formation was observed. The use of lower temperatures (to favour eight-ring formation) was considered, but deemed impractical, because the reactions become very slow below −50 °C. Use of both electron-rich and deficient substituted (MeO vs. F) 2-bromobenzaldehydes also resulted in product distributions showing increased six-ring formation at 0 °C (Table 1, **2e** and **3e–f**), when using electron-withdrawing R² groups in the propargylic chloride. However, use of 3-bromothiophene-2-carbaldehyde even with an electron-withdrawing R² group led to exclusive formation of only eight-ring **1e**, even under the highest temperature usable that did not induce competing extensive decomposition (0 °C).

The R² substituent and condition-dependant formation of mixtures of **1** and **2** is most in accord with interconversion of



a common intermediate (**4**) with both a non-classical C-enolate (**5**) and alkoxide (**6**) prior to final protonation (Scheme 2). A carbanion formulation for **5** was supported by our previous computational studies (formation of an eight-ring allenolate engenders too much ring strain).^[11] The antiperiplanar arrangement in **5** favours C–C σ -bond cleavage regenerating **4** (Scheme 2). Higher temperatures (−10 °C to ambient) resulted in thermodynamic capture of **4** forming alkoxide **6**. Formation of **6** is not reversible, because re-cooling solutions enriched with this anion did not result in the isolation of eight-ring products (see behaviour of **1a/2a** in Table 1). Formation of **6** is favoured by groups that stabilise the resultant benzyl anion. The behaviour of **4** has been computationally modelled by using simplified structure **A** ($n=0$) at the CBS-QB3 level of theory. To decrease computational cost in the model system (**A**), the atom count has been reduced by using R¹ = H, R² = phenyl and CuC₆H₄(2-CHOLiC≡CH) has been simplified to



Scheme 2. Mechanistic proposal for σ (C–C) cleavage processes in eight- versus six-ring formation.

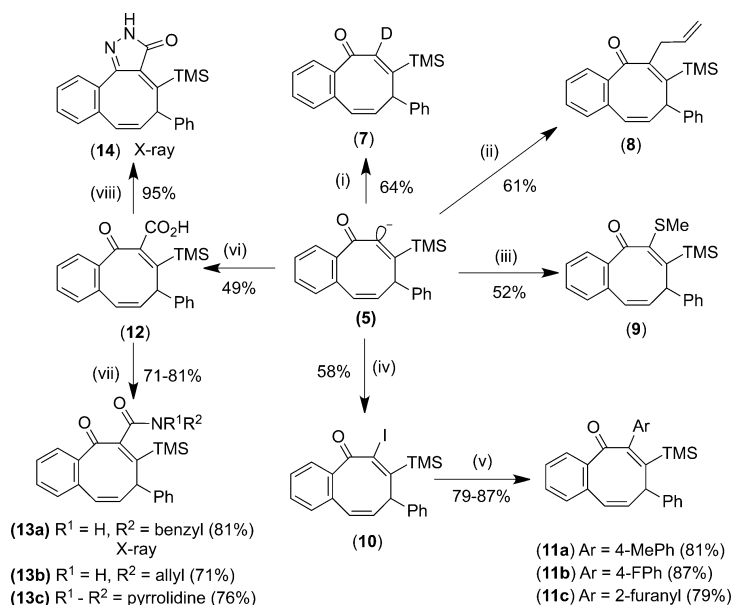
CuPh. Viable transition states for both eight- and six-rings (**B** and **C**, respectively, see the Supporting Information) could be identified with very similar energies. These simple (metal-free) models suggest that six-ring formation should be kinetically favoured, and that eight-ring products would be attained as the thermodynamic product—the opposite of what was actually observed. This failure of the computational model is apparently caused by the absence of metal ligation, in particular: 1) the absence of a strong Li–O bond ($112 \text{ kcal mol}^{-1}$)^[3] in the reaction coordinate approaching (**6**); and 2) the lack of Cu...alkyne coordination in events leading to (**5**) (see the Supporting Information). It is clear from Table 1 that the six- versus eight-ring reaction pathways are rather close in energy, such that they may be biased by experimental conditions in a useful manner. Support for Cu...alkyne coordination in events leading to **5** were provided by reaction of $\text{Li}[\text{Cu}(\text{C}_6\text{H}_4(2\text{-CHOLiC}\equiv\text{CPh}))_2]$ (formed from enantioenriched (*R*)-1,2- $\text{C}_6\text{H}_4\text{Br}(\text{CHOHC}\equiv\text{CPh})$, 88% *ee*) with ($\pm$)-PhCHClC $\equiv$ CH (see the Supporting Information). This resulted in the formation of (–)-**1j** with 20% *ee*. Thus, both chiral cuprate coordination to prochiral **4** and partial chirality transfer appear to be possible. The alternative possibility of kinetic resolution of ($\pm$)-PhCHClC $\equiv$ CH cannot be completely discounted; however, even if this was the case, the reaction manifold would still have to pass through **4** and a “memory of chirality” effect would be required to explain the observed enantiomeric excess (*ee*).^[4] This seems to be less likely than alkyne coordination, which was also favoured in preliminary computational studies by using **A** ($n=1$, see the Supporting Information). Conversion of **4** to **6** can be affected by polar co-solvents. The ^1H NMR spectrum of the crude reaction mixture containing **2a** (prior to conversion to **3a**) showed that addition of DMF (10 equiv compared to substrate) before warming to room temperature can increase the diastereoselectivity from 2:1 to 4:1. The facility of six-ring formation is more affected by geometrical factors than the electronic effects of the aldehyde. Both electron-rich and -poor substitution of the 1,2- C_6H_4 unit provides six-ring major products (**2e** and **3e** and **f**). However, replacement of the phenylene unit by a five ring 1,2-thiophenylene negates six-ring formation completely (**1e**). Calculations (B3LYP/6-31G+(d), vacuum, see Supporting Information) on the ground states of the model anions (*Z*)-1,2-Aryl($\text{C}_A(\text{=O})\text{C}\equiv\text{C}_B\text{H}$)[CH=CH(C_CH^-) $\text{C}_6\text{H}_4\text{CO}_2\text{Me}$] indicated that for Aryl= C_6H_4 , C_C is significantly closer to C_A ($\text{C}_A\text{--}\text{C}_C$ 3.34 Å, $\text{C}_B\text{--}\text{C}_C$ 3.67 Å). For Aryl= C_4S (thienyl), the opposite is true ($\text{C}_A\text{--}\text{C}_C$ 3.63 Å, $\text{C}_B\text{--}\text{C}_C$ 3.29 Å), in line with experimentally observed formation of **1e**. Finally, we note that cross-over from eight- to six-ring formation has been noted once before, but with alkoxide nucleophiles not carbanions.^[5]

Diversification by non-classical enolate

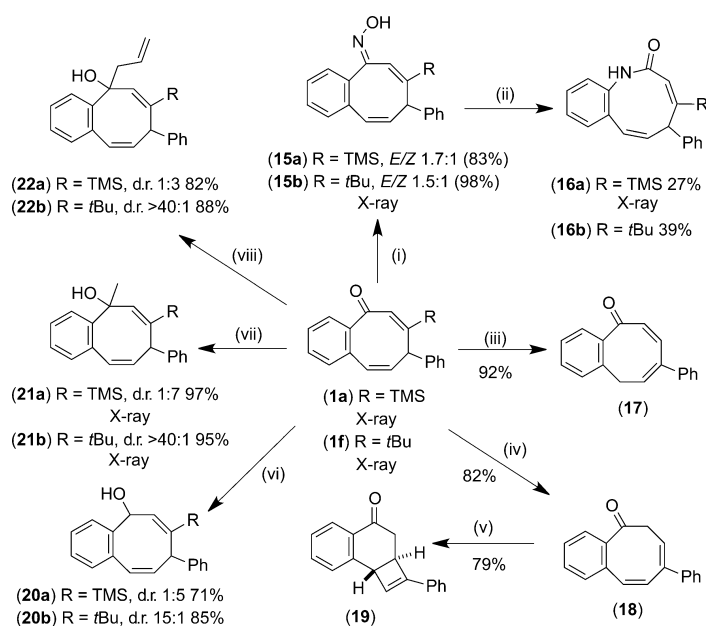
In many cases, the C-enolates (**5**) are stable at -10°C and thus offer an excellent point for rapid core diversification. We sought to extend the preliminary observations we had made in this area.^[1] It was found that a range of electrophiles can be added directly into the one-pot cascade sequence to give a wider variety of eight-ring derivatives or to install reactive handles (Scheme 3). Trapping enolate **5** with reactive deuterium oxide, allyl bromide, and dimethyl disulfide allowed preparation of functionalised ring systems **7–9** (52–64%). These procedures are not appropriate for lower reactivity electrophiles, for example, DEAD and tributyltin chloride resulted in the formation of the parent **1a** after aqueous work-up. Addition of elemental iodine led to the formation of **10**, in good yield, which lends itself well to further diversification by Suzuki–Miyaura cross-coupling reactions giving **11a–c** (79–87%) as representative examples. Amides **13a–c** and pyrazolone **14** can conveniently be synthesised from our previously described^[1] carboxylic acid **12** in 71–95% yield. The rapid synthesis of pyrazolone **14** (47% overall yield, 2 steps from 2-bromobenzaldehyde), amides **13a–c** (35–40% overall yield, 2 steps from 2-bromobenzaldehyde) and furyl **11c** (46% overall yield, 2 steps from 2-bromobenzaldehyde) showed how this methodology can swiftly incorporate heteroatoms and drug-like motifs into the core scaffold.

Diversification of eight-ring core structures

We have also explored the potential for representative eight-rings **1a** and **f** to provide additional derivatives through simple modification (Scheme 4). Ring expansions to nine-membered cyclic amides were achieved via the formation of oximes **15a–b**. These are attained in high yield in the presence of hydroxylamine hydrochloride and sodium acetate providing **15a** (83%, 1.7:1 *E:Z*) and **15b** (98%, 1.5:1 *E:Z*). Proton, ^{13}C and 2D NMR analysis of **15b** are in accord with the major isomer to be the *E*-oxime. Based on the X-ray structure of the parent carbonyl **1a** and **f**, we believe that proximity of the OH to the α -vinylic CH in the *E*-oxime causes characteristic shifts for this signal in ^1H and ^{13}C NMR spectrums, as has been observed before.^[6] In practice, the ^1H NMR *E*-oxime α -CH signal of **15b** resonates at $\delta=7.35$ ppm versus *Z*-oxime at approximately 6.75 ppm, whereas in the ^{13}C NMR spectra, the *E*-oxime α -CH showed $\delta_{\text{C}} \approx 118$ vs. $\delta_{\text{C}} \approx 124$ for the *Z*-oxime. The Beckmann rearrangement of oximes **15a–b** in the presence of toluenesulfonyl chloride gave nine-membered cyclic amides **16a–b** in moderate yields. Such rearrangements generating medium-sized rings



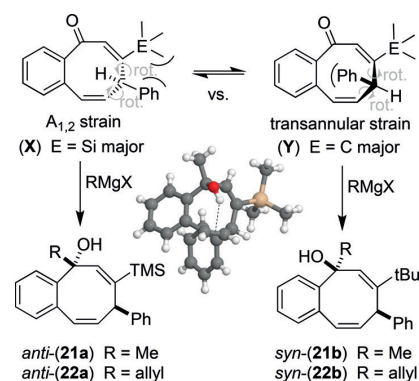
Scheme 3. Diversification via non-classical C-enolate (**5**, R¹ = SiMe₃, R² = Ph). Reagents and conditions: (i) D₂O (10 equiv), –10 °C; (ii) allyl bromide (5 equiv), –10 °C to ambient; (iii) dimethyl disulfide (5 equiv), –10 °C to ambient; (iv) I₂ (5.0 equiv), –10 °C to ambient; (v) arylboronic acid (1.05–1.50 equiv), [PdCl₂(dppf)] (3–5 mol%), sodium bicarbonate (5 equiv) in THF; (vi) solid CO₂ (ca. 20-fold excess), –10 °C to ambient; (vii) amine (2 equiv), NEt(*i*Pr)₂ (3 equiv), T3P® (2 equiv) in EtOAc; (viii) HOBT (1.2 equiv), EDC-HCl (1.2 equiv), hydrazine (2 equiv) in MeCN/THF.



Scheme 4. Diversification of eight-ring cores. Reagents and conditions: (i) hydroxylamine hydrochloride (20 equiv) and sodium acetate (20 equiv) in ethanol upon heating at reflux; (ii) sodium hydride (3 equiv) and toluenesulfonyl chloride (1.1 equiv) in THF; (iii) neat trifluoroacetic acid (5.5 equiv) from **1a** only; (iv) tetrabutylammonium fluoride (2 equiv) in THF from **1a** only; (v) boron trifluoride diethyl etherate (0.3 equiv) in toluene (μ w, 150 °C); (vi) lithium aluminium hydride (1 equiv) in THF; (vii) methylmagnesium bromide (1.7 equiv) in THF; (viii) allylmagnesium bromide (1.4–1.7 equiv) in THF.

are known to be challenging.^[7] However, it should be noted that the consolidated yields of nine-rings **16a–b** over the three-step sequence are competitive with current literature approaches to such systems.^[8] The regiochemistry of the rearrangements was confirmed by X-ray analysis of **16a**. Subjecting **1a** to neat trifluoroacetic anhydride cleaved the TMS group from the eight-membered ring and triggered alkene isomerisation to synthesise enone **17** in excellent yield. Conversely, removal of the TMS group with tetrabutylammonium fluoride triggered a different isomerisation that gave conjugated diene **18** in 82% yield. The reasons for differing isomerisation mechanisms are not completely understood, but **18** and **17** are not inter-convertible in the presence of trifluoroacetic acid. Fused cyclobutene **19** was synthesised in 79% yield from the intramolecular [2+2] cycloaddition of diene **18**. Microwave heating (150 °C) of the diene in the presence of boron trifluoride etherate gives the Woodward–Hoffmann thermally allowed *trans*-**19**, the stereochemistry of which was confirmed by NOE NMR experiments (see the Supporting Information).

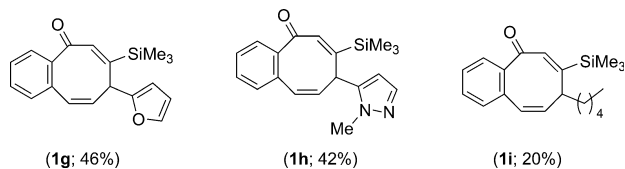
Reduction of the ketones **1a** and **f** with lithium aluminium hydride gave alcohols **20a** and **b** in 71 and 85% yield, respectively. Reduction of the carbonyl removes the Michael accepting enone moiety, potentially increasing its appeal for medicinal chemistry screening. Michael acceptor units are frequently excluded from initial screening protocols to avoid toxicological/suicide substrate issues.^[9] Interestingly, our own attempts at 1,4-conjugate additions into **1a** showed a complete resilience to nucleophilic attack at this position. Simple 1,2-addition of methylmagnesium bromide and allylmagnesium bromide into ketones **1a** and **f** proceeded with high yield of 82–97%. When analysing the stereo outcome of reactions, which involved direct 1,2-addition of Grignard reagents to the carbonyl, it became clear that opposite diastereoselectivity was attained from the two parent substrates **1a** ($R^1 = \text{SiMe}_3$) and **1f** ($R^1 = \text{tBu}$; $R^2 = \text{Ph}$ in both cases). Conformational bias in the *tert*-butyl (**1f**) versus TMS derivative (**1a**) starting materials is the source of this behaviour, based on analysis of their X-ray crystal structures (see the Supporting Information). For compound **1a**, conformation (**X**) is seen in the solid state (Scheme 5). The phenyl group is pseudo equatorial placing the *CHPh* proton endocyclic, presumably to minimise transannular strain. In the X-ray structure of **1f**, the shorter $\text{C}=\text{CMe}_3$ versus $\text{C}=\text{SiMe}_3$ bond (1.53 compared to 1.90 Å) leads to significant increase in allylic $A_{1,2}$ strain,^[10] destabilising conformer (**X**) and leading to the observation of (**Y**) in the solid state for **1f** (see the Supporting Information). The subsequent conformational change results in endocyclic placement of the phenyl group directly obscuring one of the diastereotopic faces of the carbonyl. The hypothesis that these solid-state observations also operate in solution is corroborated by the X-ray structures of the major diastereoisomers resulting from MeMgBr addition to **1a** and **f**. For *tert*-butyl (**1f**; conformer **Y**), addition to the bottom face is seen (see the Supporting Information) leading to *syn*-**21b** (diastereomeric assignment relates to the orientation of the OH in respect to the phenyl group in all cases, as shown in Scheme 5). Addition to the TMS derivative **1a** led to *anti*-**21a** as the major product. The ^1H NMR chemical shift of *CHPh*



Scheme 5. Conformational bias of eight-membered rings controls Grignard 1,2-addition diastereoselectivity and X-ray structural observation of $\text{H}\cdots\text{C}=\text{C}$ contact in *anti*-(**21a**) $\text{R} = \text{Me}$.

proton is indicative of the diastereoisomer formed, a higher frequency signal ($\delta_{\text{H}} \approx 4.6$ ppm) is indicative of *anti* diastereoisomer formation (vs. $\delta_{\text{H}} \approx 4.4$ ppm for the equivalent *syn* signal). On this basis, the diastereoselectivity of allyl Grignard additions were also assigned. Relative signal integrations were used to determine the *syn/anti* ratio in **21** and **22**. Blocking of the Bürgi–Dunitz^[11] (π^*) approach leads to excellent *syn* diastereoselectivity (>40:1) in the formation of **21b** and **22b**. The *anti* selectivity of **21a** and **22a** is not as good (7:1 and 3:1, respectively), because both diastereofaces of the carbonyl in **1a** are more open. There are hints that the distal *cis*- $\text{C}=\text{C}$ π bond might also act as a directing group ($\text{Mg}\cdots\pi$ bond in the Grignard addition), because product *anti*-(**21a**) showed an unusual, but potentially related, $\text{H}\cdots\pi$ -bond hydrogen bond (2.2 Å, structure in the centre of Scheme 5). However, this suggestion should be regarded as tentative. It seems that similar *syn/anti* control issues account for the stereochemical reversal seen in hydride addition to form **20a** and **b**. Due to the protection offered to the top diastereotopic face in conformation **1f**, it is tentatively assumed that hydride addition into carbonyl **1f** will also result in the formation of predominantly *syn*-(**20b**).

Finally, as the majority of our studies had involved the use of simple aryl groups in the R^2 position of structure **1**, we were very keen to extend the range of propargylic chlorides to include electron-rich (hetero)aromatics, electron-poor (hetero)aromatics and alkyl functionality. Although electron-rich aromatic propargylic chlorides proved too reactive to be used in the reaction (e.g., 2-furanyl $\text{CHClC}\equiv\text{CH}$ spontaneously decomposed at room temperature in our hands), the less reactive acetate allowed the one-pot synthesis of electron-rich **1g**. Conversely, electron-poor **1h** containing the pyrazolyl function could be prepared from the corresponding propargylic chloride (Scheme 6). By using 3-chlorooct-1-yne and a slightly modified procedure (see the Supporting information), we were also able to synthesise alkyl-chain-containing **1i**.



Scheme 6. Representative variation of substituent R^2 in compounds (1).

Conclusion

Due to the simplicity of their synthesis,^[1] bicyclic 6,8-ring systems containing the cycloocta-2,5-dien-1-one core are attractive starting materials for diversity chemistry potentially aimed at the development of biologically active libraries. Addition of $\text{LiC}\equiv\text{CR}^1$ to 2-bromobenzaldehyde, followed by subsequent cuprate formation and reaction with $\text{R}^2\text{CHClC}\equiv\text{CH}$ gave a non-classical C-enolate as the kinetic product at lower temperatures that can be trapped with a wide range of electrophiles to rapidly provide diverse libraries with little synthetic effort (1–3 steps total, consolidated yields > 25%). These products themselves are attractive starting points for ring expansion and diastereoselective addition reactions. If allowed to warm, the C-enolate rearranges via an unusual retro σ C–C bond cleavage to provide some 6,6-ring systems. In support of the assertion that the strategies presented herein are useful in biological activity discovery libraries, several of the compounds described herein have already revealed significant activity in open-innovation drug-discovery programmes.^[12]

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Keywords: annulation • C–C activation • medium-ring compounds • ring expansion • synthetic methods

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An efficient synthesis of substituted chrysenes



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ABSTRACT

Substituted chrysenes have been swiftly synthesised by the 6-*endo-dig* cyclisation of ethynylnaphthalenes using platinum(II) chloride. Cyclisation precursors were directly prepared from commercially available 2-bromoaldehydes in a telescoped synthetic procedure involving a Cannizzaro triggered cascade and subsequent dehydration and desilylation. This short synthetic procedure allows rapid access to derivatives of biologically active molecules with useful electronic properties.

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Introduction

Chrysene ($C_{18}H_{12}$) is a polycyclic aromatic hydrocarbon (PAH) that is formed during incomplete combustion of carbon rich fuels¹ and was the first PAH to be discovered in uncontaminated soil samples.² Whilst several studies have shown that chrysene and its metabolites,³ *trans*-1,2-dihydroxy-1,2-dihydrochrysene and *trans*-3,4-dihydroxy-3,4-dihydrochrysene (Scheme 1a) are carcinogenic and mutagenic,⁴ it has also been reported that some substituted chrysenes, due to their DNA intercalating nature, show anticancer activity.⁵ Due to their electronic properties chrysenes also have synthetic uses as single electron transfer mediators,⁶ mechanistic probes⁷ and have applications in the field of organic electronics.^{8,9} The two most common synthetic routes to chrysenes are the photochemical cyclisations of styrylnaphthalenes¹⁰ and metal catalysed cyclisations of aromatic acetylenes.^{8,11} Our efficient synthesis allows the rapid formation of substituted chrysenes, under simple, benign conditions from readily available commercial materials. As we are able to design chrysene substrates with substitution on both terminal rings and also access substitution patterns that are difficult to control with other synthetic methods¹⁰ (controlled substitution in the 2- and 4- positions), this work is perfectly complementary to that which has already been published.

Results and discussion

Recent work carried out within our group¹² highlighted how cascade reactions based around an unusual Cannizzaro like 1,5-

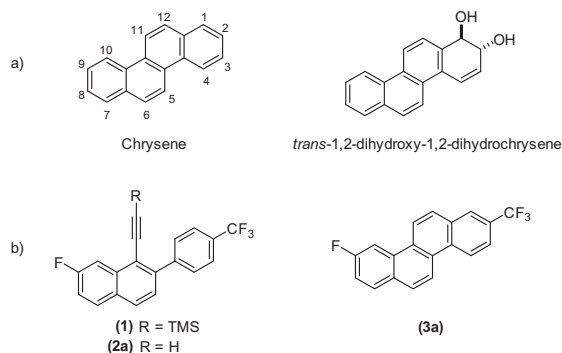
hydride transfer¹³ can be used to rapidly develop complex molecules, such as **1** (Scheme 1b), from commercially available 2-bromoaldehydes. We envisaged using a platinum(II) chloride catalysed, 6-*endo-dig* cyclisation^{8,11a} to attain a substituted chrysene from ethynylnaphthalene **1**. Under our initial conditions, heating to reflux with 5 mol% platinum(II) chloride in toluene, for a protracted reaction time of 65 h, we observed 58% conversion to the desilylated chrysene **3a** (Scheme 1b). Formation of the silylated chrysene was not observed. Unsatisfied with the long reaction times and incomplete conversion, more efficient reaction conditions were sought. The rate of reaction could be significantly increased by microwave heating to 150 °C in a sealed tube. As the formation of silyl-**3a** was not observed, it was considered that the sluggish annulation could be due to a slow desilylation of naphthalene **1** followed by the much faster annulation of the resultant terminal acetylene. When terminal acetylene **2a**, the desilylated derivative of **1**, was subjected to 150 °C microwave heating in the presence of 5 mol% platinum(II) chloride, complete consumption of the starting material was achieved within 1 h.

In order to generalise this new synthetic route to chrysenes as efficiently as possible, we telescoped the synthesis of ethynylnaphthalenes using our Cannizzaro cascade procedure (Scheme 2). The cascade procedure¹² affords crude 1,2-dihydronaphthalen-1-ol **7** which could be directly dehydrated using Amberlyst 15® to give silylated ethynylnaphthalene **8**. Subsequent addition of tetrabutylammonium fluoride solution to the reaction mixture followed by a single purification leads directly to ethynylnaphthalene **2** in up to 70% yield in a single synthetic session.

The scope of the telescoped route is shown in Table 1 by the synthesis of a range of ethynylnaphthalenes (**2a–f**). When the R² substituent is an electron withdrawing *p*-trifluoromethyl group (**2a–c**) the aromatic aldehyde can tolerate electron withdrawing,

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Scheme 1. (a) The numbering of chrysene and a carcinogenic metabolite; (b) Compounds from the preliminary investigation.

electron donating and electron neutral substitution and achieve yields of 45–67%. Functional groups are also tolerated in the R² position with *p*-methyl ester (**2d**) and *m*-nitrile (**2f**) substitution giving yields of 61% and 70%, respectively. Only when using a mildly electron withdrawing R² substituent, *o*-fluoro (**2e**), was a significant drop in yield observed. This is mainly due to a competing reaction pathway in which the Cannizzaro cascade forms a fused 8-membered ring in place of the 1,2-dihydronaphthalen-1-ol. This observation was not unexpected and is in line with our previous work.¹²

Substrates **2a–f** were used to assess the generality of the platinum(II) chloride catalysed synthesis of substituted chrysenes. Using the optimal conditions from our preliminary work, chrysenes **3a–f** were synthesised in 31–81% yield (Table 2). Substrates **2a–b**, with the *p*-trifluoro methyl R² substituent, perform well in

Table 1

Scope of the telescoped Cannizzaro cascade procedure.

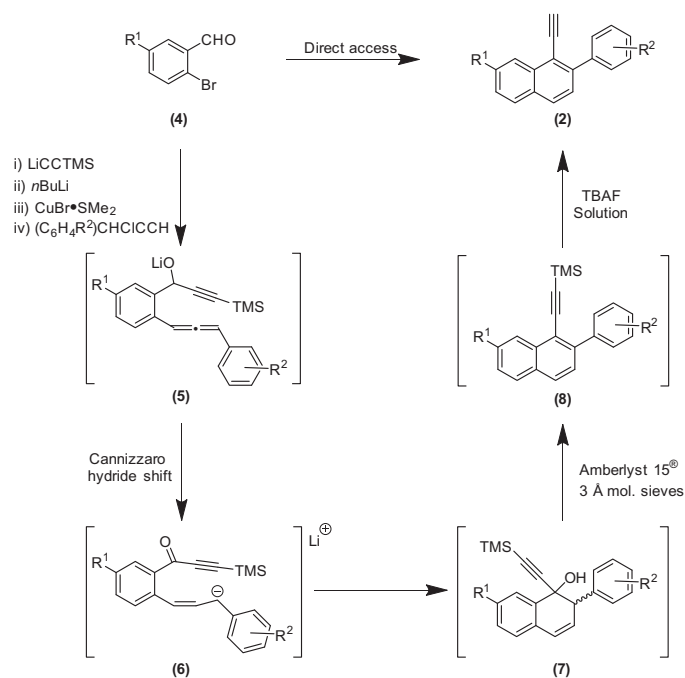
R ¹	R ²	Product	Yield (%) ^b
F	<i>p</i> -CF ₃	2a	58
OMe	<i>p</i> -CF ₃	2b	45
H	<i>p</i> -CF ₃	2c	67
H	<i>p</i> -CO ₂ Me	2d	61
H	<i>o</i> -F	2e	23
H	<i>m</i> -CN	2f	70

Reaction conditions: (i) LiC≡TMS (6.9 mL of 0.50 M THF-hexane solution) treated with 2-bromoaldehyde (3.24 mmol) at –50 °C; (ii) *n*BuLi (3.40 mmol); (iii) CuBr·SMe₂ (1.63 mmol); (iv) R²ArCClC≡CH, warmed to 0 °C; (v) Amberlyst 15[®] and 3 Å molecular sieves at room temperature; (vi) TBAF solution (1 M in THF, 6.5 mmol).

^a Full description of reaction conditions available in [Supplementary data](#).

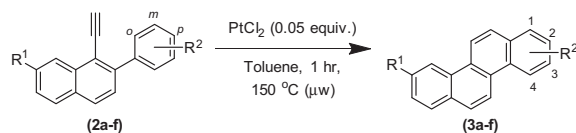
^b Isolated yield.

the cyclisation giving **3a–b** in 71% and 66% yields respectively. The closely related **3c** has a slightly lower yield of 51%, this could be in part due to its very poor solubility making purification challenging. Ester **3d** was synthesised in 65% yield, albeit with an extended reaction time of 2 h needed to achieve full consumption of the starting material. The highest yielding chrysene was 4-fluoro substituted **3e** attained in an impressive 83% yield.



Scheme 2. Telescoped synthesis of ethynynaphthalene **2**.

Table 2
Formation of substituted chrysenes **3a–f**.



R ¹	R ²	Product	Yield (%) ^a
F	<i>p</i> -CF ₃	3a	71
OMe	<i>p</i> -CF ₃	3b	66
H	<i>p</i> -CF ₃	3c	51
H	<i>p</i> -CO ₂ Me	3d	65 ^b
H	<i>o</i> -F	3e	83
H	<i>m</i> -CN	3f	31 ^c

^a Isolated yield.

^b Microwave heating was continued for a total of 2 h to achieve complete consumption of starting material.

^c Product was isolated as a 12:1 mixture of regioisomers favouring substitution at the 3 position versus the 1 position.

Substrate **2f** was chosen for this study to assess the regioselectivity of the cyclisation as both possible chrysene products have published ¹H NMR spectroscopic data.^{10a} Gratifyingly, inspection of our own sample showed that we obtained high regioselectivity with a 12:1 ratio favouring the formation of 3-nitrile substitution over 1-nitrile substitution. The lower yield of chrysene **3f** is thought to be caused by a competing polymerisation pathway involving the nitrile group.

Conclusion

We have developed a new, step efficient, synthetic route to substituted chrysenes. Application of a one-pot Cannizzaro cascade procedure followed by telescopic dehydration and desilylation gives swift access to ethynyl naphthalenes from very simple pre-

cursors. Formation of chrysenes can be achieved via platinum(II) chloride catalysed annulation under microwave heating. This overall synthetic sequence shows how one-pot reactions can be used to rapidly build up molecular complexity and access derivatives of valuable biologically active targets.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2016.12.004>.

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