

Diastereodivergent Synthesis of Fused Ring Systems

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Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2011 and March 2015. The dissertation is a result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Emily Kiss

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Abbreviations

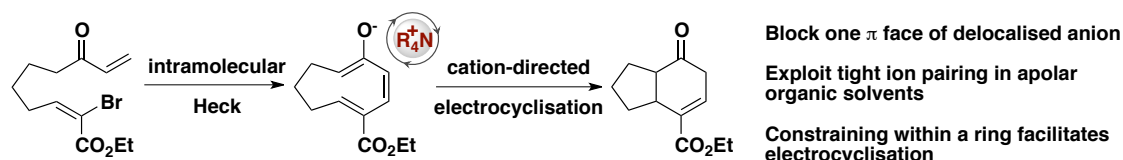
Ar	Aromatic
br	Broad
C	Celsius
COSY	Correlation spectroscopy
CLIP-HSQMBC	Clean in-phase multiplets-heteronuclear single quantum multiple bond correlation
d	Doublet
DEPT	Distortionless enhancement by polarization transfer
DIPM	Diisopropyl malonate
DMF	<i>N, N</i> - Dimethylformamide
DMP	Dess-Martin Periodinane
<i>dr</i>	Diastereomeric ratio
<i>ee</i>	Enantiomeric excess
ESI	Electrospray ionization
EWG	Electron withdrawing group
FTIR	Fourier-transform infrared
g	Grams
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
hr	Hour
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear multiple-quantum correlation
Hz	Hertz
IR	Infra-red
IPA	<i>Isopropanol</i>
L	Litres
LDA	Lithium diisopropylamine
LRMS	Low resolution mass spectrometry
λ	Wavelength

m	Milli-
M	Molar
mins	Minutes
mol	Moles
MS	Mass spectrometry
MS	Molecular sieves
NMR	Nuclear magnetic resonance
Ph	phenyl
ppm	Parts per million
PTC	Phase transfer catalysis
q	Quartet
quin.	Quintet
R	Generic substituent
RT	Room temperature
s	Singlet
Sept	Septet
sec	Second
SM	Starting material
t	Temperature
TBABS	Tetrabutylammonium bisulfate
TBME	<i>Tert</i> -butyl methyl ether
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
UV	Ultra violet
°	Degrees

Abstract

Introduction

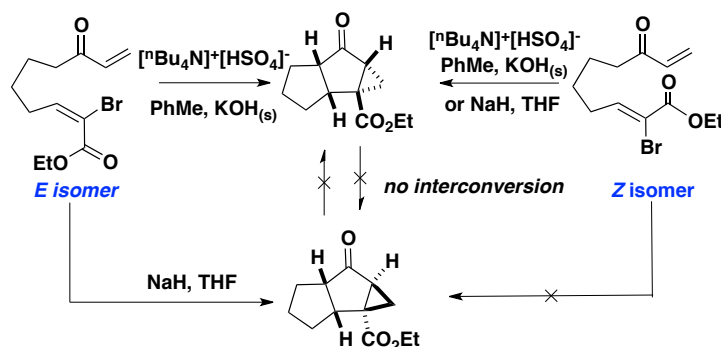
We envisioned using phase transfer catalysis (PTC) to develop asymmetric carba-6 π -electrocyclisations. We believed that the configurational lability of 6 π systems could be reduced by constraining them within a ring system.



Scheme 1: Proposed work, using PTC to perform a transannular electrocycloisatation reaction

Results and Discussion

En route to the synthesis of a starting material for the transannular electrocycloisatation reaction, we noticed that a 5-5-3 fused ring system had formed, in one step, from a linear precursor and as a single diastereomer. We synthesised both geometric isomers of the starting materials, and unexpectedly, the *E* or *Z* isomers cyclised to form different products under different reaction conditions. We further investigated the 5-5-3 system, generating substrate scope and computationally and experimentally exploring the mechanism.



Scheme 2: Cyclisation of *E* and *Z* isomers under two different reaction conditions

Conclusion

In one step we have constructed three carbon-carbon bonds, up to five contiguous stereogenic centres and all as a single diastereomer. We have synthesised 15 examples and have probed the mechanism experimentally and computationally. We have also investigated asymmetric examples of this reaction.

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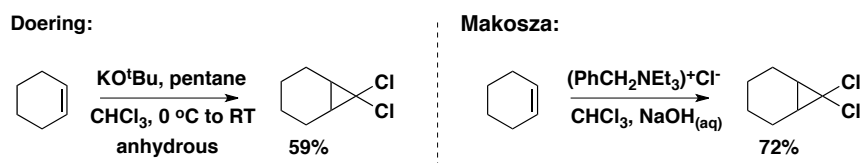
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1. Introduction

1.1 Historical Context of Phase-Transfer Catalysis

Today, phase-transfer catalysis is a well-established method in synthetic organic chemistry and has found extensive use, particularly as a mild method for alkylation reactions.¹ The origins of phase-transfer catalysis can be traced back to the mid 20th century. In 1954, Doering synthesised dichlorocyclopropanes by addition of dichlorocarbene to olefins. He stressed that anhydrous conditions were necessary for this transformation, as dichlorocarbene is rapidly hydrolysed in the presence of water.² In a seminal paper, Makosza later noticed that in the presence of a phase-transfer catalyst (triethylbenzylammonium chloride), this reaction could be undertaken using 50% aqueous NaOH as the base.³



Scheme 1: Synthesis of dichlorocyclopropanes by Doering and Makosza

He hypothesised that the triethylbenzylammonium chloride was able to solubilise hydroxide in the organic phase, where it reacts with chloroform to form the trichloromethyl anion, which associates with the triethylbenzylammonium cation. This is then transformed into the dichlorocarbene, which reacts rapidly with the olefin, forming the product, reforming the quaternary ammonium chloride catalyst that can re-enter the catalytic cycle.

Following this, Starks coined the phrase phase-transfer catalysis, describing the catalyst as “an agent which transfers one reactant across the interface into the other phase so that reaction can proceed.”⁴

1.2 Mechanisms of Phase-Transfer Catalysis

Both Mąkosza and Starks have since proposed mechanisms to describe phase-transfer catalysis. In the early stages of the development of phase-transfer catalysis, Starks proposed a mechanistic picture, which has come to be known as the “extractive” mechanism.⁴ In this simple model, the phase-transfer catalyst (Q^+X^-) can move between the organic and aqueous phases and is therefore able to equilibrate with the base in the aqueous phase. The resulting lipophilic ion pair can then be extracted into the organic phase. The quaternary ammonium hydroxide (Q^+HO^-) can deprotonate an acidic substrate (RH) to give a reactive Q^+R^- species, which reacts in the organic phase.

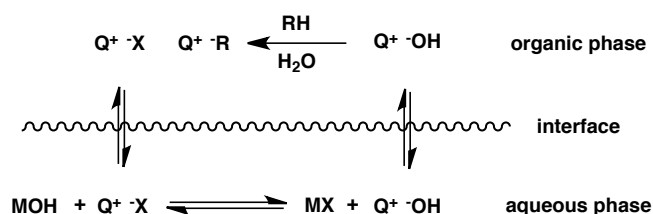


Figure 1: Stark's extractive mechanism

Following this work, some phase-transfer catalysed processes were encountered which could not be explained by a simple extractive mechanism, for example, the phase-transfer catalysed alkylation of phenylacetonitrile with BuI in 50% aqueous NaOH.⁵ In cases such as this, Mąkosza has proposed an alternative “interfacial” mechanism to be operative.⁶ The substrate is now deprotonated at the interface to form a metal

carbanion, and following counterion exchange with the catalyst, this forms the reactive Q^+R^- species. This ion pair is then extracted from the interface into the organic phase where it can undergo reaction.

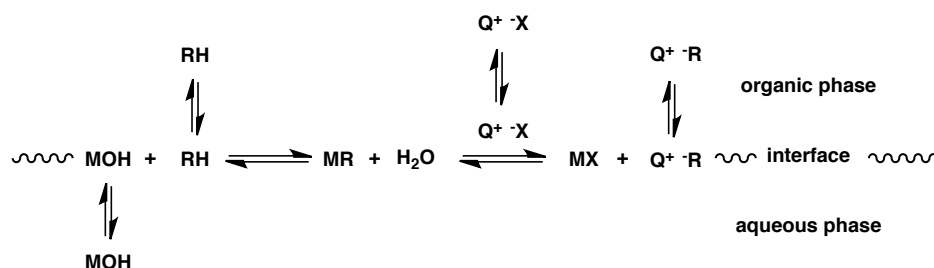


Figure 2: Makosza's interfacial mechanism

1.3 Predicting the Mechanism of a Phase-Transfer Reaction

Usually the most significant factors governing which mechanism will be operative are the substrate and catalyst. Generally, substrates with moderate acidity (pK_a 16-23) will react according to an interfacial mechanism, whereas those with a very low acidity (pK_a 23-37) will react *via* an extractive mechanism. If the catalyst used is particularly lipophilic, then this will also favour the extractive process, since it will be more effective at extraction of hydroxide.⁷

There are several experimental means that can be used in order to suggest which mechanism is at play. An extractive process will display a simple kinetic profile, usually with a first order dependence upon both substrate and catalyst. In the case of an interfacial mechanism, the kinetics will be more complex, usually displaying a fractional order with respect to reagents and catalyst. The stirring speed can also be used as a means to probe the reaction mechanism, since the rate of an interfacial process will exhibit a strong dependence upon stirring speed whereas an extractive

mechanism will operate with a rate independent on the stirring speed (above a certain threshold ca. 300 rpm).⁷

Interfacial	Extractive
Substrate pKa 16-23	Substrate pKa (< 16 or 23-37)
Less lipophilic catalyst	Highly lipophilic catalyst
Strong dependence on stirring speed	Independent of stirring speed
Complex kinetics	Simple kinetics

Table 1: Summary of the features determining whether a reaction proceeds *via* an interfacial or extractive mechanism

1.4 Asymmetric Phase-Transfer Reactions

Phase-transfer catalysis relies on tight ion pairing between an anion and catalyst, allowing otherwise insoluble anions to enter an organic environment. The tight ion pairing necessary for a phase-transfer reaction to occur has been exploited by utilising chiral cations, which associate strongly with the reactive species, inducing asymmetry in the resulting reaction. Maruoka has published several review articles that describe the detailed applications of this method.⁸

Several different architectures of chiral phase-transfer catalyst have been disclosed.

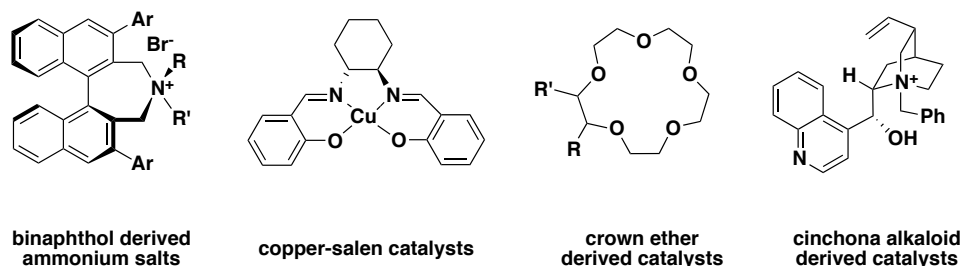


Figure 3: Different phase-transfer catalyst architectures

Binaphthyl quaternary ammonium salts are valuable phase-transfer catalysts, and can be synthesised in ~6 steps from commercially available binol.⁹ In some cases, copper salen complexes and crown ethers have also been successfully employed as phase-transfer catalysts.^{1b}

Catalysts based on the cinchona scaffold have been used extensively in the literature for a number of reasons: a) both pseudo enantiomers of the alkaloids are commercially available and inexpensive, b) they are easily modified at the olefin and hydroxyl functional groups, and c) they can be readily quaternised to form a wide range of ammonium salts in a single step using various commercially available alkyl halides.

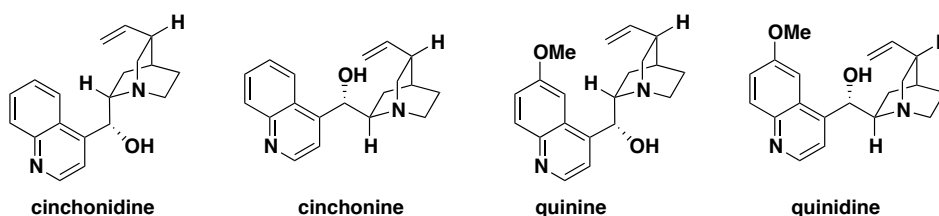
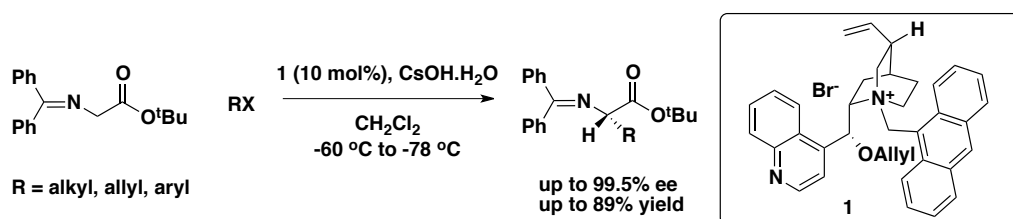


Figure 4: The four cinchona catalyst scaffolds used by the Smith group

The Smith group has extensively used cinchona alkaloid-derived catalysts based on these four scaffolds.

Many asymmetric phase-transfer reactions are performed at low temperatures to increase the enantioselectivity of the reaction. Often, the degree of cooling can be problematic since the reaction mixture could not be cooled to temperatures lower than the freezing point of the aqueous base. In 1997, Corey overcame this problem by performing the first asymmetric solid-liquid phase-transfer reaction, which allowed the reaction mixture to be cooled to $-78\text{ }^{\circ}\text{C}$, affording products in up to 99.5% ee.¹⁰



Scheme 2: First asymmetric solid-liquid phase-transfer reaction

1.5 Summary

Phase-transfer catalysis has been used extensively since its discovery, due to the mild reaction conditions, inexpensive reagents and simple experimental setups required to perform the reaction. The extension to asymmetric methodology has rendered phase-transfer catalysis a useful and inexpensive way to synthesise enantioenriched products. We wanted to utilise asymmetric phase-transfer catalysis to develop methodology for the asymmetric hexatriene electrocyclisation reaction, a topic that has very little literature precedent.

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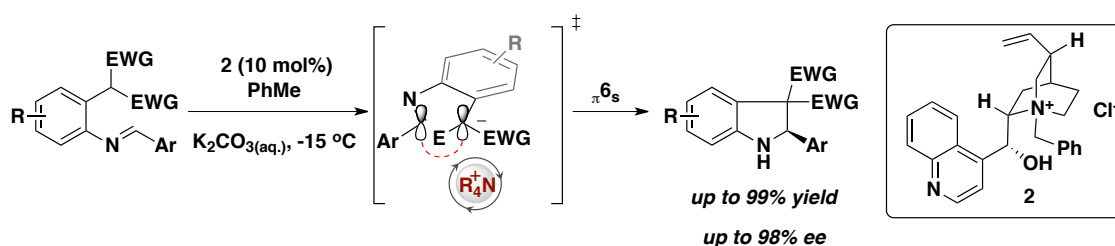
2. Transannular Electrocyclisation Reactions

2.1 Introduction

2.1.1 Asymmetric [1-5] 6π Electrocyclisation Reactions

Work in the Smith group has extensively investigated the relatively unexplored asymmetric 6π electrocyclisation reaction. Despite the utility of this powerful carbon-carbon bond forming reaction, there still remain a limited number of examples in the literature.¹

Our research group has developed methodology for 6π electrocyclisation reactions using a phase-transfer catalyst to induce asymmetry in the products.²



Scheme 3: Smith group methodology for the formation of indolines

In this reaction, the substrate is deprotonated to form a delocalised anion, which undergoes counterion exchange with the chiral phase-transfer catalyst. The chiral catalyst binds preferentially to one π -face of the delocalised anion, forming a tight ion pair in the non-polar organic solvent. This tight ion pairing can control the absolute sense of orbital rotation in the following disrotatory 6π electrocyclisation.³

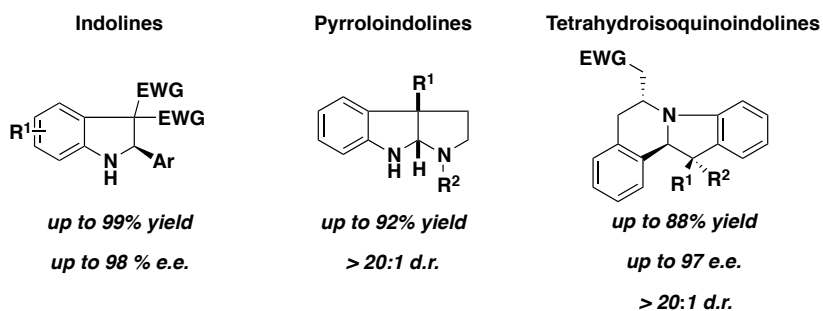
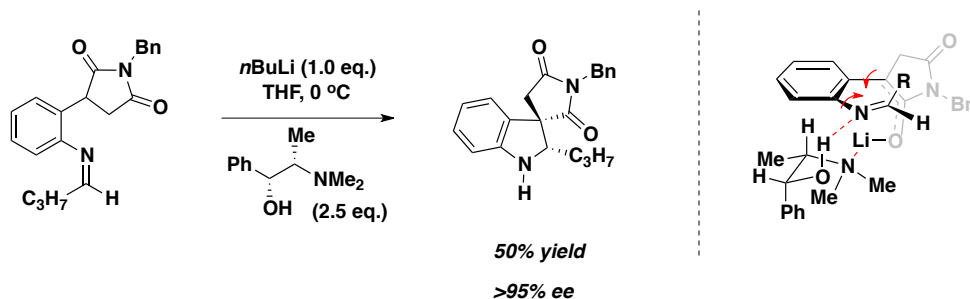


Figure 5: Different scaffolds synthesised using the Smith group methodology

This methodology has been used to synthesise indolines, pyrroloindolines and tetrahydroisoquinoindolines, amongst others, with excellent levels of stereocontrol and in very good yields.⁴

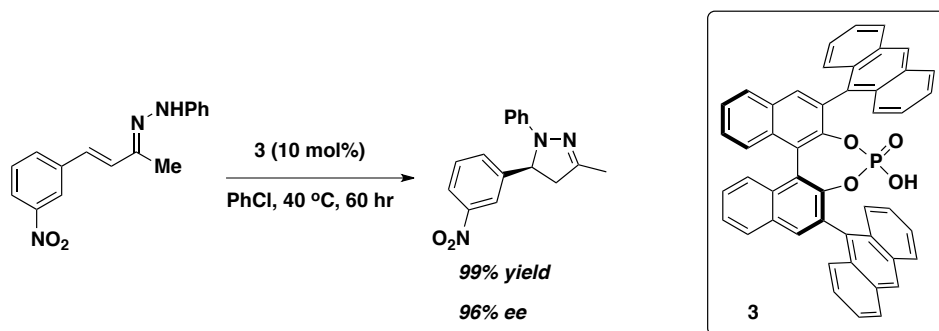
Veenstra and Speckamp have performed base-promoted 6π electrocyclisation reactions of azapentadienyl anions using *N*-methylephedrine as a super-stoichiometric additive to induce enantioselectivity.⁵



Scheme 4: 6π electrocyclisation reactions of azapentadienyl anions

The binding mode proposed by the authors relies on hydrogen bonding and chelation between the deprotonated substrate and *N*-methylephedrine to transfer stereochemical information. Although this reaction has afforded high ee in certain substrates, it does display significant substrate specificity; replacing the propyl group with a butyl group reduces the ee to 38%.

Müller and List have shown that chiral Brønsted acids can be used to synthesise substituted pyrazoline rings in high enantiomeric excesses.⁶



Scheme 5: Synthesis of pyrazoline rings with high stereoselectivity

The proposed method of asymmetric induction relies on the tight ion pair formed between the chiral phosphoric acid and the protonated imine, and allows access to products with excellent levels of yield and ee.

All three of these approaches have utilized pentadienyl anions for the electrocyclisation reaction. We wanted to expand this methodology to the catalytic asymmetric electrocyclisation of hexatriene scaffolds, a subject that has not been explored extensively in the literature. Indeed, only one example has been reported to date.⁷

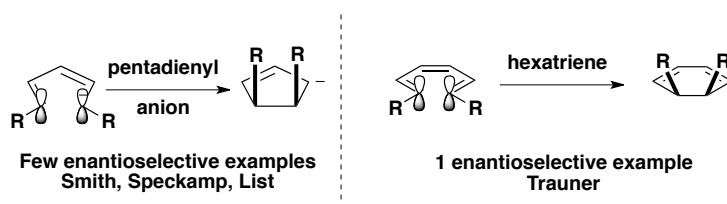
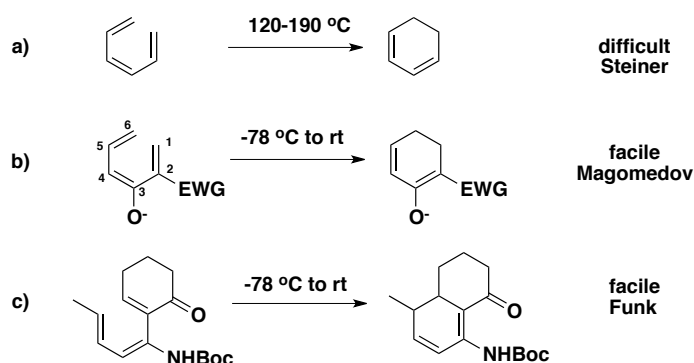


Figure 6: Pentadienyl anion *vs* hexatriene electrocyclisations

2.1.2 [1-6] 6 π Electrocyclisation Reactions

Hexatrienes constitute the archetypal substrates for electrocyclisation reactions. However, in their simplest form they require high temperatures and long reaction times to proceed (Scheme 6a).⁸ It is perhaps this feature that renders these processes not suitable for transformation using catalytic asymmetric methods.

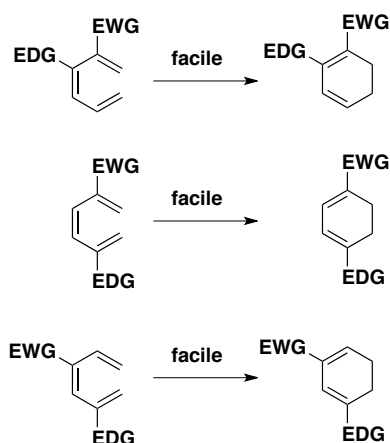
Magomedov noticed that the presence of an electron withdrawing group at C2 of a 3-oxido hexatriene system (Scheme 6b) lowers the activation energy for cyclisation substantially, allowing the reaction to proceed under mild conditions.⁹



Scheme 6: Hexatriene electrocyclisation reactions. Reaction rates can be accelerated by addition of directing groups

Funk also observed that a hexatriene electrocyclisation could be performed under mild conditions using amidotrienes (Scheme 6c). He proposed that the coexistence of amido and carbonyl groups “electronically activated” the thermal 6 π -cyclisation.¹⁰ In both of these cases, the careful incorporation of electron withdrawing and donating groups has lowered the activation energy for cyclisation.

Intrigued by the mild reaction conditions employed by Magomedov and Funk, Fu modelled the electrocyclisation of hexatriene scaffolds computationally, and demonstrated that substitution at certain positions on the hexatriene can have a considerable impact on the rate of electrocyclisation.¹¹

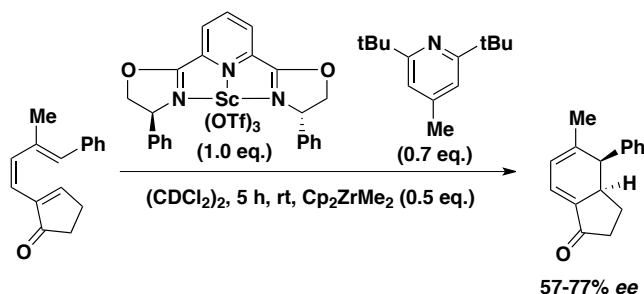


Scheme 7: Combinations of electron withdrawing and donating groups that aid the hexatriene electrocyclisation reaction

This computational work has demonstrated that a synergistic combination of electron withdrawing and donating groups can reduce the barrier to electrocyclisation by up to 10 kcal mol⁻¹. However, synthesising compounds that are so reactive to electrocyclisation may prove difficult. A number of solutions to this are possible: 1) synthesise a reactive hexatriene *in situ*, 2) rely on removing protecting groups to reveal more powerful electron-donating groups, or 3) to use Lewis or Brønsted acids to convert modest electron-withdrawing groups into stronger ones.¹¹

These captodative effects have been exploited in several hexatriene electrocyclisations in the racemic sense,¹² but only one example of an enantioselective hexatriene

electrocyclisation reaction has been disclosed to date. In this seminal work, Trauner used a chiral scandium PyBOX complex to mediate the enantioselectivity of a hexatriene electrocyclisation reaction.¹³



Scheme 8: The first and only asymmetric hexatriene electrocyclisation reaction

The moderate to high enantioselectivity for this reaction is likely a result of interaction of the chiral Lewis acid with the carbonyl group in the starting material, a feature that lowers the energy of activation for the electrocyclisation reaction.

Interestingly, under analogous conditions the *des*-methyl starting material is inert and does not cyclise until heated to 100 °C. The authors attributed the low rate of cyclisation of this substrate to be a consequence of the reluctance of the starting material to adopt the requisite *s*-cis conformation. The synergistic effects of the electron donating methyl group and electron withdrawing ketone also lower the electrocyclisation energy barrier. Without the methyl substituent present, the *s*-trans conformation is more populated, which disfavours electrocyclisation, allowing other pathways to proceed.

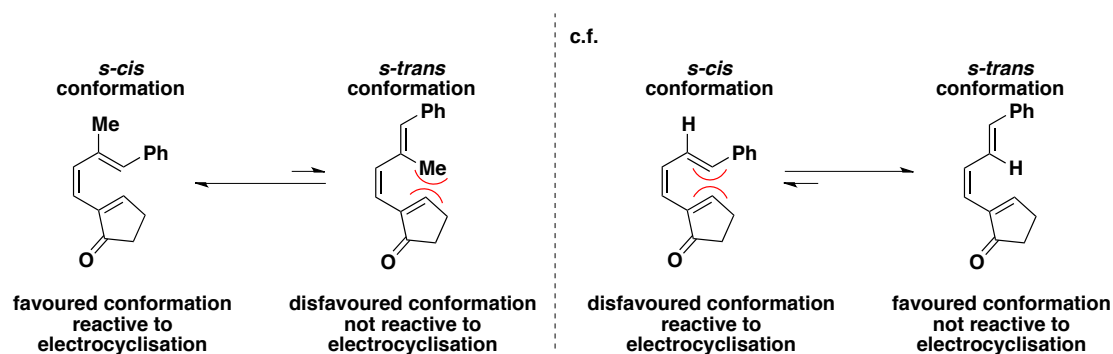


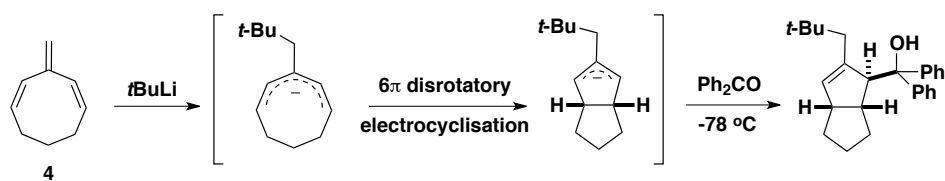
Figure 7: The favoured and disfavoured conformations for the methylated substrate and the *des*-methyl version. Only the *s-cis* conformation is reactive to electrocyclication

Although the substrate scope of this process is limited to a single example, it still remains the only reported example of an asymmetric [1-6] 6π electrocyclication reaction.

2.1.3 Transannular Electrocyclication Reactions

Another way of reducing the barrier to electrocyclication is to constrain the system within a ring, reducing the entropic contribution to cyclisation. There are very few examples of transannular electrocyclic processes in the literature and those that have been reported are based on the racemic cyclisation of pentadienyl anions.

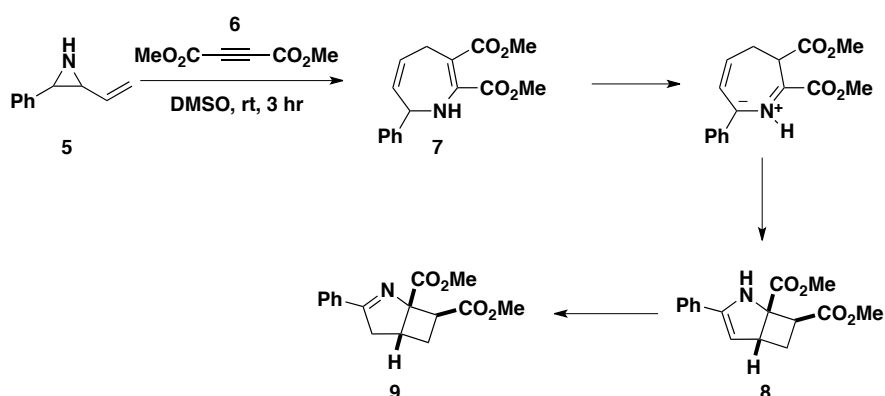
Williams formed cyclooctadienyl anions *in situ*, and observed that they undergo efficient thermal disrotatory electrocyclication.^{14,15}



Scheme 9: Transannular electrocycloisatlon reaction

The organolithium reagent was added to a solution of triene **4** at -78 °C, and warming to 22 °C resulted in carbolithiation and electrocyclic ring closure. The resulting anion was then quenched with an electrophile to afford the product.

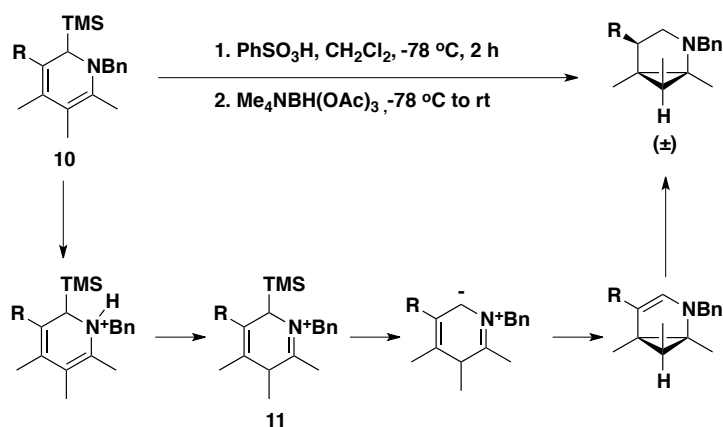
Yudin utilised a transannular electrocycloisatlon reaction for the synthesis of aminocyclobutanes.¹⁶



Scheme 10: Transannular electrocycloisatlon reaction for the synthesis of aminocyclobutanes

The vinyl aziridine **5** undergoes nucleophilic attack onto the acetylene **6**, followed by a Cope rearrangement to form an azepine **7**. The azepine is deprotonated at the benzylic position and a 6 π electron system is generated. This participates in a disrotatory electrocycloisatlon leading to an intermediate aminocyclobutane **8**, which can then tautomerise to give the imine product **9**.

Ellman noticed an unexpected reaction when he submitted one of his compounds to acidic conditions.¹⁷



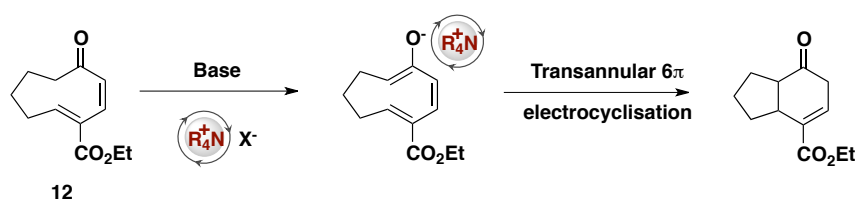
Scheme 11: Unexpected reaction noticed by Ellman

He proposed that the dihydropyridine **10** is *N*-protonated under the acidic conditions, and then proton transfer results in the formation of ketiminium **11**. Desilylation then occurs, which results in the formation of a 6 π system, which can then undergo a torquoselective disrotatory electrocycisation to form an enamine and subsequent reduction of the enamine forms the product.

The transannular nature of all three of these examples reduces the activation energy for electrocycisation, allowing them to be performed at low temperatures.

2.2 Concept and Aims

We wanted to expand the Smith group methodology to explore hexatriene electrocyclisation reactions. We thought that we might be able to reduce the entropic bias towards electrocyclisation by undertaking a transannular hexatriene electrocyclisation.



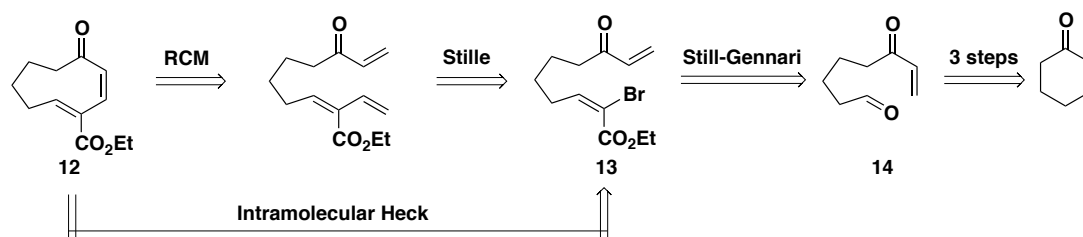
Scheme 12: Proposed system to investigate an asymmetric hexatriene electrocyclisation reaction

With this in mind, we aimed to prepare a simple transannular precursor **12**, which, in the presence of a base and chiral counterion, we hoped would undergo an asymmetric carba- 6π -electrocyclisation.

2.3 Results and Discussion

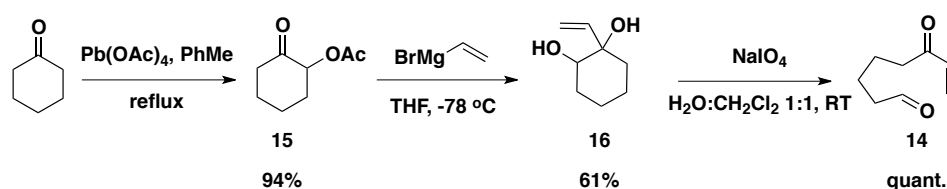
2.3.1 Synthesis of the Transannular Precursor

We envisioned that the transannular precursor **12** could be synthesised using either an intramolecular Heck reaction or Stille coupling followed by a ring closing metathesis (RCM). This meant that we required bromo-olefin **13**, which we hoped could be synthesised from the Still-Gennari reaction of aldehyde **14**. This compound could be in turn synthesised in three steps from cyclohexanone using known literature procedures.



Scheme 13: Retrosynthetic analysis for transannular electrocyclisation precursor **12**

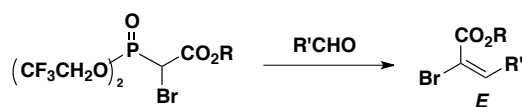
In the forward sense, we began with an α -acetylation reaction of cyclohexanone with $\text{Pb}(\text{OAc})_4$. This was followed by a Grignard addition and deacylation, and then a periodate cleavage of the diol to form compound **14** in 57% yield over three steps.



Scheme 14: Formation of the key aldehyde intermediate **14**

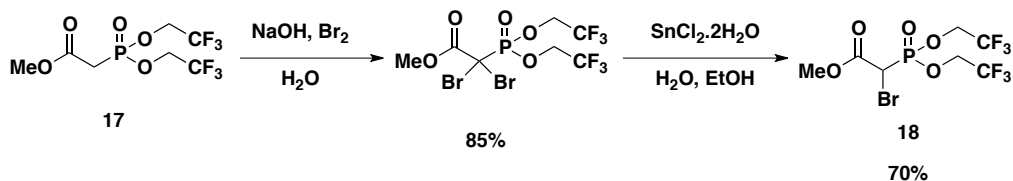
With **14** in hand, we aimed to synthesise the Still-Gennari reagent in order to introduce the α -bromoacrylate with *E* double bond selectivity.

There are very few methods for the synthesis of (*E*)- α -bromoacrylates in the literature, the majority of which require long reaction times, multiple steps or have limited substrate scope.¹⁸ In 2000, Kogen prepared a novel brominated Still-Gennari reagent, which was used to efficiently synthesise a wide range of α -bromoacrylates with high stereoselectivity in a single step from the parent aldehyde.¹⁹



Scheme 15: Facile synthesis of *E* bromoacrylates by Kogen

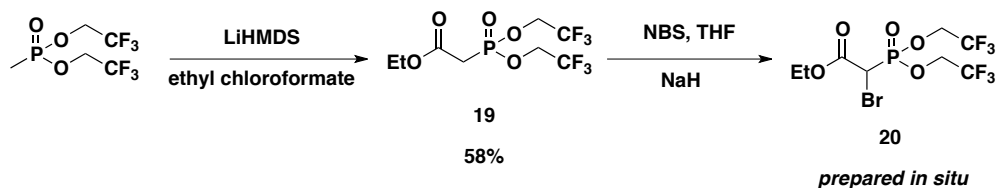
Kogen prepared bromophosphonoacetate **18** in two steps from the Still-Gennari reagent **17**, which could itself be prepared a single step from a commercially available starting material. Freshly prepared sodium bromide afforded the dibromide, which was subsequently reduced by 1 eq. of SnCl_2 and purified by distillation to afford **18**.



Scheme 16: Kogen's synthesis of the Still-Gennari precursor

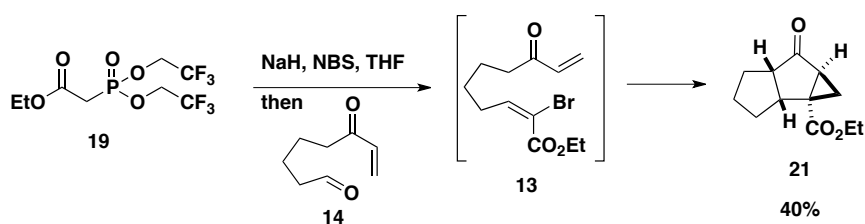
However, in our hands, this synthesis of bromophosphonoacetate **20** resulted in an inseparable mixture of recovered starting material, along with mono-, and di-brominated phosphononacetate, which could not be subsequently carried through to the next reaction. There have been a number of reports following Kogen's original publication that also concluded that such bromophosphonoacetates are difficult to synthesise.^{20, 21}

We decided to change the route for the synthesis of this Still-Gennari reagent and followed a different literature procedure, which formed the brominated Still-Gennari reagent **20** *in situ* and used it immediately.²²



Scheme 17: Synthesis we employed for the formation of the Still-Gennari reagent

Accordingly, we treated the Still-Gennari reagent **19** with sodium hydride and NBS and then added aldehyde **14**. Under these conditions, we were surprised to find that instead of the expected bromo-olefin **13**, we observed a complex product **21** containing a 5-5-3-fused ring system. Moreover, this reaction proceeded with essentially perfect diastereocontrol over the four newly formed stereocentres. This unexpected result forms the basis of Chapter 3.

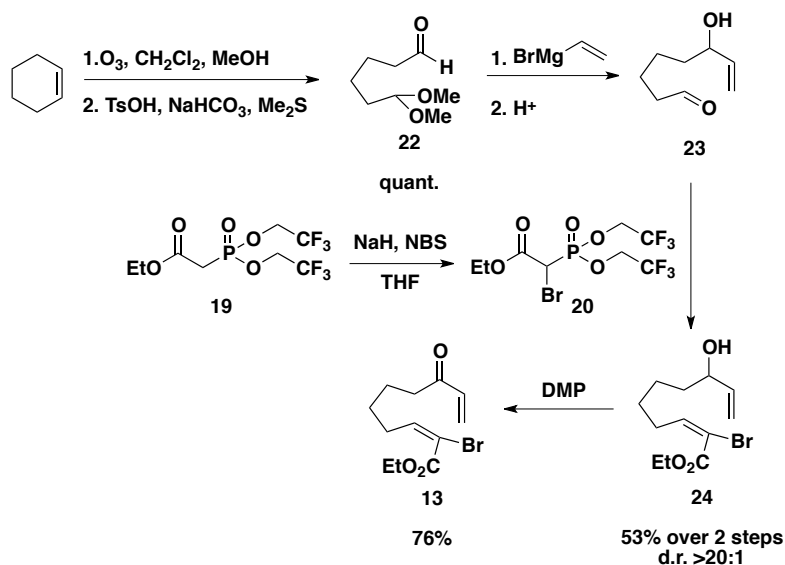


Scheme 18: Unexpected formation of a 5-5-3 fused tricyclic product **21**

2.3.2 Changing the Route

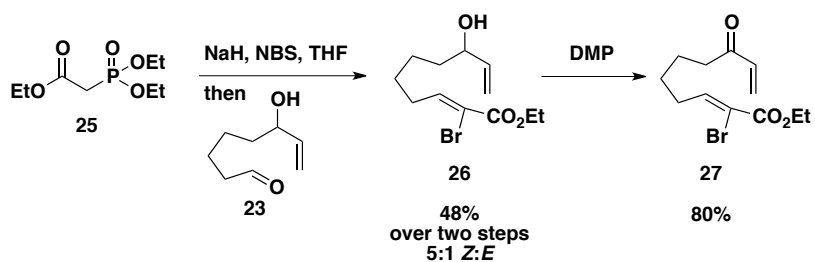
The synthetic route was altered so that **13** could be synthesised and isolated. We carried out ozonolysis and selective mono-protection of cyclohexene as described in the literature,²³ and then successfully performed a Grignard reaction with the unprotected aldehyde. Finally, deprotection of the acetal to yield aldehyde **23** was accomplished under standard conditions. With aldehyde **23** in hand, a Still-Gennari reaction was performed, where the Still-Gennari reagent was prepared *in situ* as described previously, to afford **24**. Oxidation was accomplished under non-basic and

mild conditions using Dess-Martin periodinane (DMP) to afford the desired product **13** in 76% yield.



Scheme 19: Synthesis of the *E* brominated olefin **13**

Utilising an analogous route (Scheme 20), it was also possible to synthesise the other geometric isomer **26** by employing the brominated Horner-Wadsworth-Emmons reagent (prepared *in situ* from commercially available HWE reagent **25**). It is noteworthy that **25** is much less expensive than the Still-Gennari reagent.



Scheme 20: Synthesis of *Z* bromo olefin **27** using an analogous method

The yield for the formation of the *Z* isomer was comparable to that of the *E* (55% over two steps *vs.* 53%).

2.3.3 Confirmation of Double Bond Geometry

After synthesising **13** and **27**, we wanted to confirm that the double bond geometry that we had assigned to each compound was correct. Our initial tentative assignment was based on two factors: 1) the olefin hydrogen trans to the ester (*H*5 of compound **13** in our case) usually appears further upfield in the ^1H NMR spectrum than when the ester is cis to the hydrogen (*H*5 of compound **27** in our case);²⁴ 2) it is preceded that Still-Gennari reactions of bromophosphonoacetates such as **20** usually lead to the *E* isomer, whereas the Horner-Wadsworth-Emmons reaction tend to give the *Z* isomer. Given that both of these observations matched our assignment, we were reasonably confident that we had assigned the double bond geometry correctly. However, we decided to confirm our assignments using NMR.

Standard nOe and nOeSY analysis proved inconclusive for the determination of the double bond geometry so we resorted to a CLIP-HSQMBC experiment.^a This is a 2D experiment that can measure long-range proton-carbon coupling constants.²⁵ It is important to point out that the magnitude of the coupling constant in a CLIP-HSQMBC experiment can be interpreted in a similar fashion to the coupling constants in ^1H NMR spectrum, i.e., protons trans to each other across a double bond exhibit a larger coupling constant to ones which are cis to each other.

^a Thanks to Prof. Tim Claridge for performing these experiments

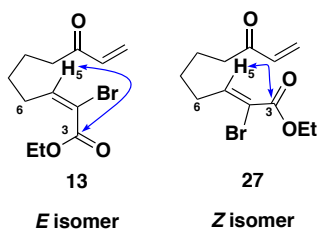


Figure 8: The arrows highlight the coupling investigated for H_5 to confirm the double bond geometry

A sample containing both isomers was examined and a 1D cross section focussing on the interaction of H_5 to the carbonyl carbon (C_3) was observed (Figure 9). The *E* isomer **13** displayed a doublet of triplets (Figure 9b), consistent with the coupling of C_3 - H_5 (doublet) and H_5 - H_6 (triplet). Similarly, the *Z* isomer **27** displayed a triplet of doublets (Figure 9c). The *E* and *Z* isomers give different C_3 - H_5 doublet splittings, indicative of whether H_5 is oriented cis or trans to the carbonyl (C_3).

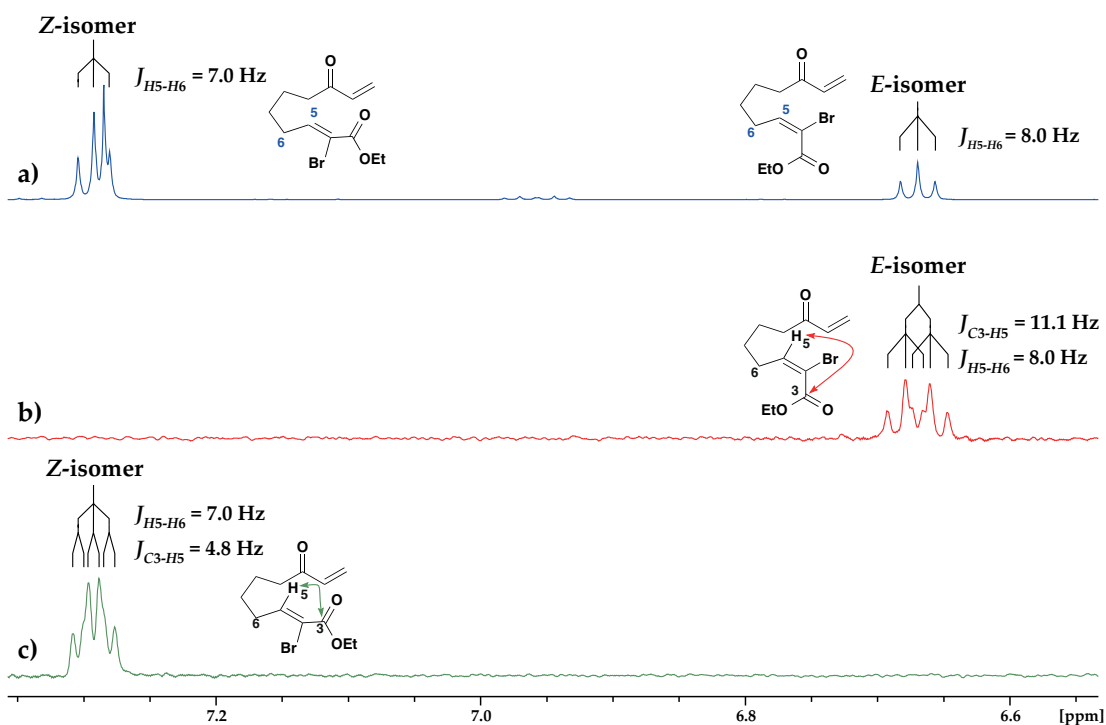
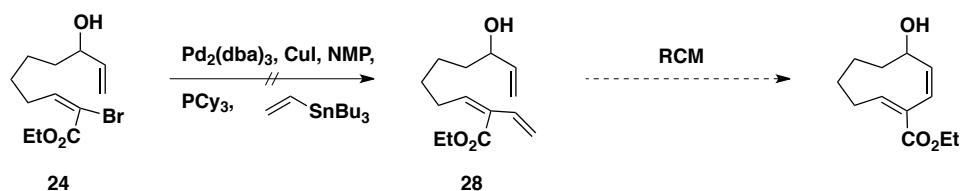


Figure 9: a) ^1H NMR spectrum of the mixture of the *E* and *Z* isomers, b) 1D representation of CLIP-HSQC, focussing on H_5 in the *E* isomer, c) 1D representation of CLIP-HSQC, focussing on H_5 in the *Z* isomer

For the *E* isomer (**13**), where *H*5 is trans to the carbonyl, $J_{C3-H5} = 11.1$ Hz, and for the *Z* isomer (**27**), where *H*5 is cis to the carbonyl, $J_{C3-H5} = 4.8$ Hz. These results are in good agreement with the literature and confirm our assignment of *E/Z* stereochemistry of **13** and **27**.

2.3.4 Ring Closing Metathesis Approach

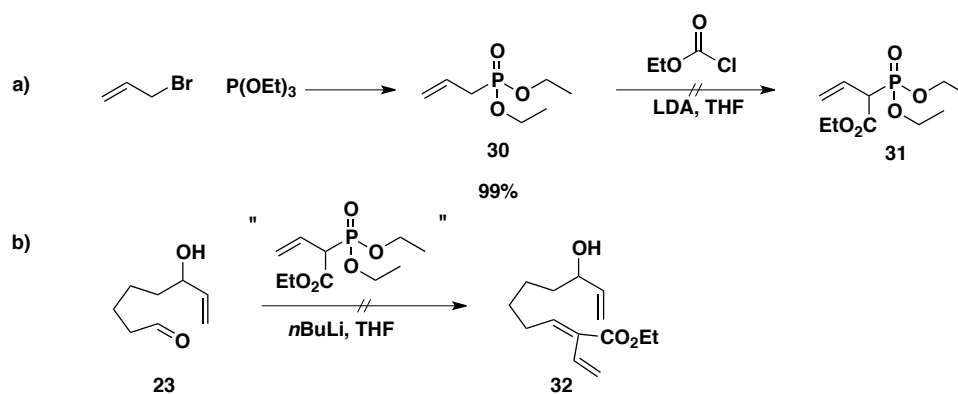
With **24** in hand, we decided to first attempt a Stille reaction to form the RCM precursor **28**.



Scheme 21: Attempted Stille reaction with *E* bromo-olefin **24**

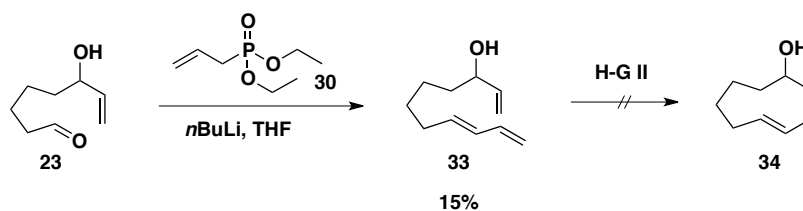
Unfortunately, under standard conditions, we did not observe any of the desired product in the crude ^1H NMR, even after heating to 100 °C for three days. By mass spec, we were only able to identify peaks that corresponded to the starting material and the product corresponding to proto-debromination. This reaction was also attempted on the *Z* double bond isomer of **24**, and the same result was observed.

We next decided to change the route and introduce the double bond using a Horner-Wadsworth-Emmons reagent that already contains the appropriate functionality.



Scheme 22: a) Attempted synthesis and isolation of HWE reagent **31**, b) Attempts at synthesising the HWE reagent *in situ* and using it immediately

Following a literature procedure, the Arbuzov reaction between triethylphosphite and allyl bromide took place in 99% yield. However, we were unable to acylate this material. We tried to form **31** *in situ*, but this approach proved unsuccessful. Formation of this reagent is challenging, with very little literature precedence,²⁶ so we decided to use the simplified HWE reagent **30** to see if we could make the key bond. It is possible that the reduction in entropic cost in rendering a system transannular might even enable this reaction to take place without the electron withdrawing group.

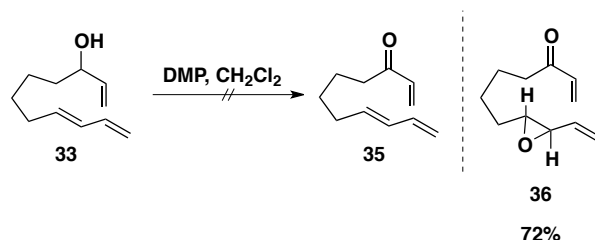


Scheme 23: Synthesis of the triene **33**, followed by unsuccessful RCM

Pleasingly, the HWE reaction did form the desired product, albeit in 15% yield. There are very few examples of using allylic phosphonates as Horner-Wadsworth-Emmons reagents in the literature, and those that do usually employ HMPA as a co-solvent.²⁷ We tried adding DMPU, which is known to be a less toxic alternative to HMPA, but unfortunately the yield did not improve.²⁸ We also attempted a ring closing

metathesis (RCM) using Hoveyda-Grubbs 2nd generation catalyst. Unfortunately the RCM gave a complex mixture of products, which we thought may be due to the alcohol complexing with the catalyst. We decided that we should oxidise the alcohol and attempt the RCM of the resulting ketone.

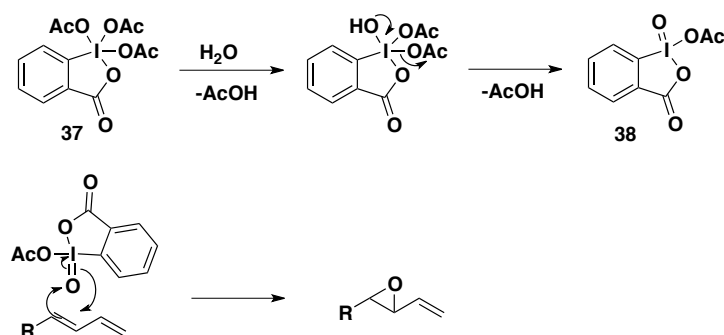
Submitting the alcohol to standard oxidation conditions using DMP, we noticed that the NMR of the product did not match that of what we were expecting. After careful assignment, we realised that the DMP conditions had epoxidised the internal alkene.



Scheme 24: Unexpected epoxide formation after attempted oxidation of alcohol 33

The epoxide geometry was assigned as trans by *J* coupling analysis of the two epoxide hydrogens. This oxidation is not without precedent; the Nicolaou group have reported a related process in the synthesis of Epoxyquinomycin B.²⁹

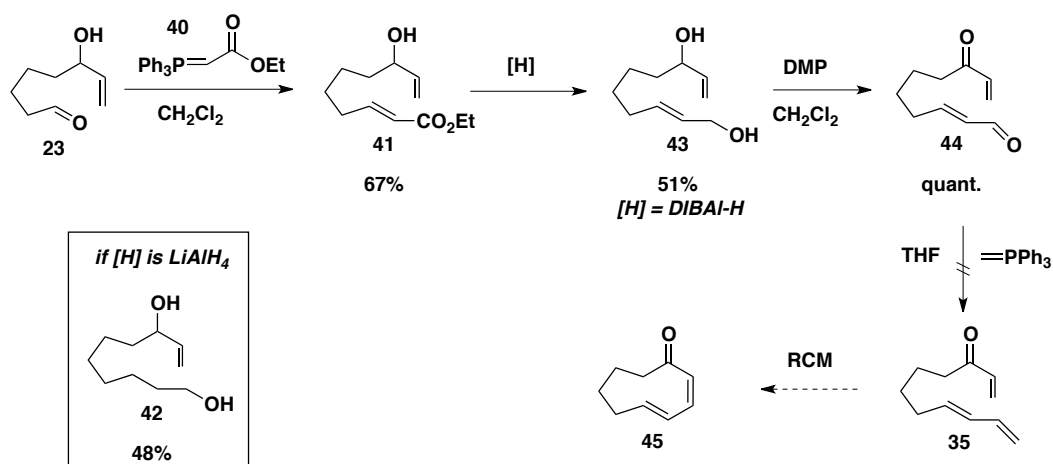
A possible mechanism for the formation of this epoxide is shown in Scheme 25.



Scheme 25: Possible mechanism for the formation of the unexpected epoxide 36

It has been shown that DMP oxidations are accelerated by the presence of water.³⁰ We postulate that the DMP **37** is activated by adventitious water present in the reaction mixture, leading to **38**, which is attacked by the most electron rich alkene to form the corresponding epoxide. Two equivalents of DMP were added to the reaction mixture, and the alcohol was also oxidised.

This method towards the synthesis of the RCM precursor was proving difficult so we decided to alter the route to try to circumvent the low yielding HWE reaction, and to avoid the need for an oxidation, eliminating the possibility of the unwanted epoxidation reaction. The altered synthesis started with a Wittig reaction to install the ester, which proceeded cleanly in 67% yield. We then attempted a reduction to generate diol **43** using LiAlH₄. Under these conditions, the α,β -unsaturated ester was fully reduced to the aliphatic alcohol **42**, but we were pleased to find that employing DIBAL-H as a less reactive reducing agent led to allylic alcohol **43** in 51% yield. The resulting diol was then oxidised to aldehyde **44** using DMP in quantitative yield. Fortunately, we did not observe any epoxidation of this substrate under these oxidation conditions. A Wittig reaction was then attempted on aldehyde **44**. The Wittig reagent was prepared *in situ* using *n*BuLi, but unfortunately the Wittig reaction was unsuccessful and resulted in a complex mixture.



Scheme 26: Alternative synthetic route for the formation of the transannular electrocyclisation precursor

We felt that the intramolecular Heck might prove a more straightforward method to assemble the key starting material and therefore turned our attention towards this approach.

2.3.5 Intramolecular Heck Approach

The Heck reaction is a palladium catalysed C-C bond forming reaction, in which an aryl or allenyl halide or triflate is coupled with an alkene. The catalytic cycle is similar to other palladium catalysed cross coupling reactions.

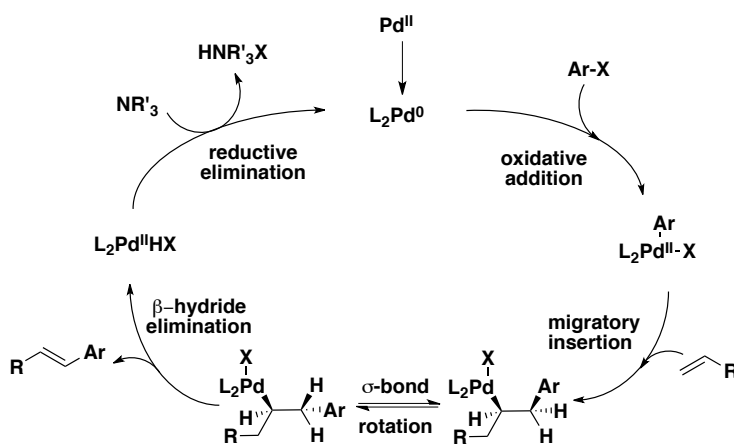


Figure 10: Catalytic cycle for the Heck reaction

Pd(0) is the reactive species, which can either be added to the reaction mixture directly or formed *in situ* from reduction of a Pd(II) pre-catalyst. The reactive Pd(0) undergoes oxidative addition into the Ar-X bond. The Pd then forms a π -complex with the alkene, which subsequently inserts into Pd in a syn migratory insertion step. The resulting complex then undergoes a σ -bond rotation which allows β -hydride elimination to occur. In the presence of a base, Pd(0) is then regenerated by reductive elimination of Pd(II), ready to enter another catalytic cycle.

Regioselectivity in the migratory insertion of the intramolecular Heck reactions is usually determined by sterics.³¹ The ring closure is highly *exo* selective for the formation of five, six, and seven- membered rings.

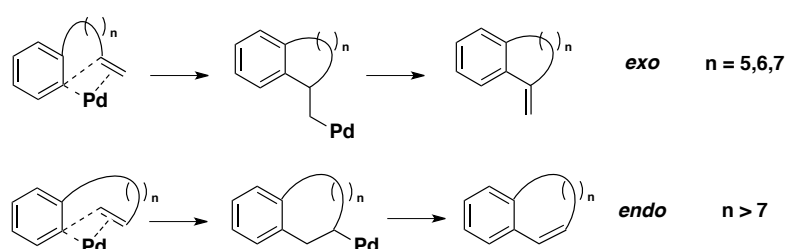
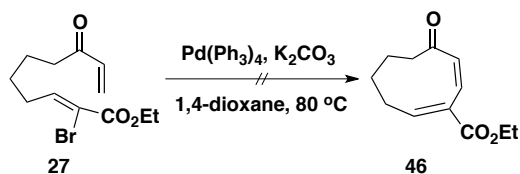


Figure 11: Regioselectivity for the intramolecular Heck reaction

When the chain length is increased, the tether is much longer and more flexible, which can enable *endo* insertion to take place. The longer the tether, the higher the yield for the *endo*-cyclisation.³²

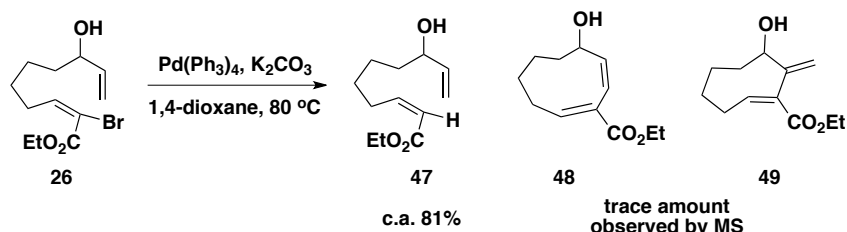
An intramolecular Heck reaction was attempted with **27**. Unfortunately, under the reaction conditions, the starting material decomposed to form a complex mixture of

products. With hindsight, this may be due to the basic conditions promoting a Diels-Alder type reaction (see Chapter 3).



Scheme 27: First attempt at the intramolecular Heck reaction

To try and circumvent this problem, we decided to use the alcohol **26**, which would not be sensitive to the basic reaction conditions, and hopefully would not undergo any undesired side reactions.

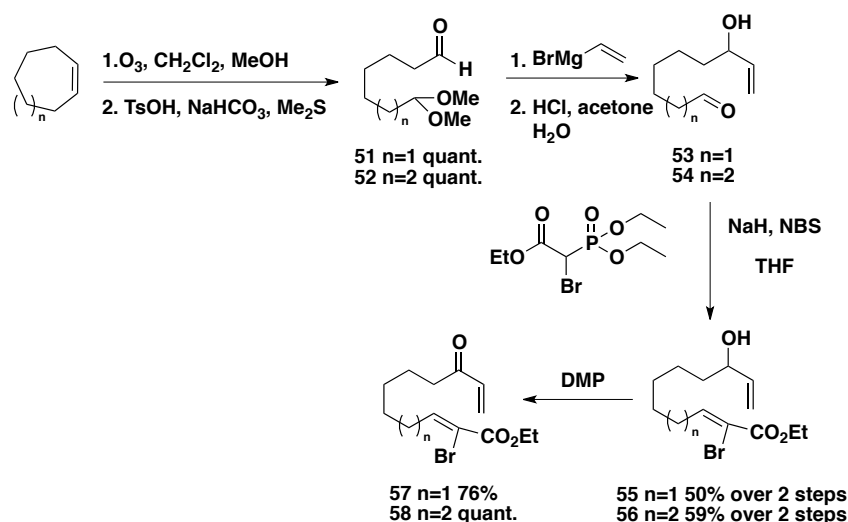


Scheme 28: Intramolecular Heck reaction on the alcohol. Formation of some product is observed in the mass spec

Under standard reaction conditions, we observed mainly protodebromination to form **47**, rather than the desired intramolecular Heck reaction. By mass spec there was a peak that corresponded to the mass of product **48** or **49**, but we were unable to isolate this material by column chromatography.

We thought that the formation of a nine membered ring with two double bonds may be unfavourable due to the high ring strain of the product. We therefore decided to synthesise two alternative precursors, with one or two additional carbons in the

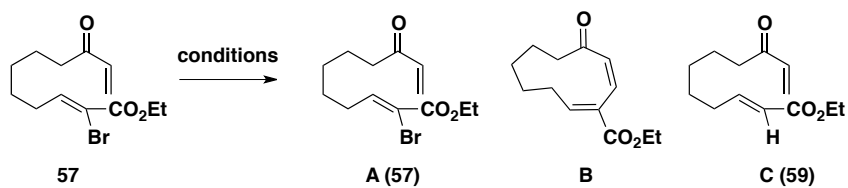
backbone, thereby forming ten or 11 membered rings respectively. We hoped that the increase in tether length would relieve some of the strain and make it possible for the intramolecular Heck reaction to occur. The synthesis of the two larger intramolecular Heck precursors was performed analogously to that of the formation of 27.



Scheme 29: Synthesis of the longer tethered starting materials using an analogous method to that used for shorter tether lengths

We were able to isolate the monoprotected dialdehydes **51** and **52** from the ozonolysis of cycloheptene and cyclooctene in quantitative yield, which is in accordance to the literature for these reactions.³³ The Grignard addition, deprotection, Horner-Wadsworth Emmons and oxidation all took place in good yields for both tether lengths.

The intramolecular Heck reaction was then attempted with **57**. Unfortunately, under both conditions attempted, the desired product was not observed.



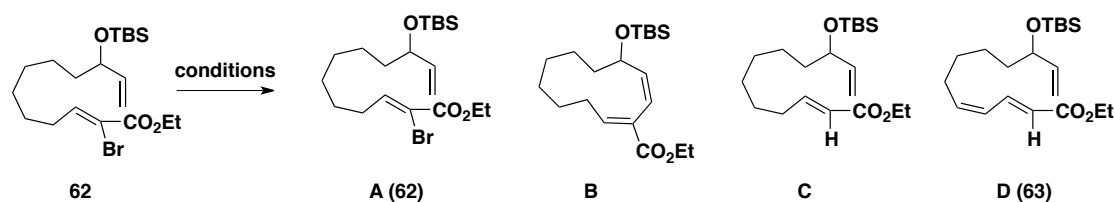
Conditions	A	B	C
Pd(PPh ₃) ₄ , K ₂ CO ₃ , 1,4-dioxane, 80 °C	2	0	1
Pd(OAc) ₂ , NaHCO ₃ , TBACl, DMF, 90 °C	1.2	0	1

Table 2: Intramolecular Heck conditions attempted and the products formed are shown as ratios relative to each other

Using either a Pd(II) pre-catalyst or Pd(0) directly, apart from recovered starting material, the main product observed was that of protodebromination. There was also some evidence of degradation of the starting material.^b

The reaction was then attempted with **56**, in the hope that the longer tether would lead to reduced protodebromination and favour the intramolecular Heck reaction.

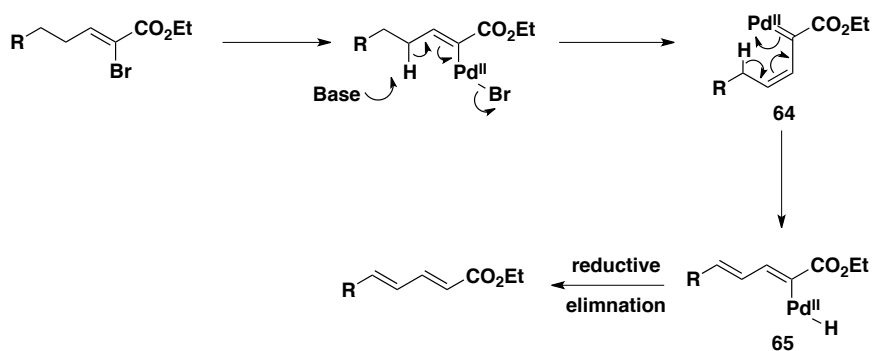
^b The ratios of these products were calculated from integration of the ¹H NMR of the crude, and are relative to each other



Conditions	A	B	C	D
Pd(PPh ₃) ₄ , K ₂ CO ₃ , MeCN, 80 °C	1	0	0	0
Pd(OAc) ₂ , NaHCO ₃ , TBACl, DMF, 90 °C	3	0	0	1

Table 4: Intramolecular Heck conditions attempted and the products formed are shown as ratios relative to each other

Unfortunately, under both conditions attempted, the desired product was not observed.^d Depending on the palladium source used, the main products recovered were starting material A (62) and triene D (63). The proto-debromination product was not observed for this system.



Scheme 30: Possible mechanism for the formation of triene D (63)

^d The ratios of these products were calculated from integration of the ¹H NMR of the crude, and are relative to each other

We postulated that the palladium inserted into the carbon-bromine bond, and then the base deprotonated the substrate, forming **64**, which then formed a palladium-hydride species **65** that reductively eliminated to form the product.

2.4 Conclusion

We concluded that the synthesis of a transannular precursor was non-trivial. Since we had noticed the formation of an interesting 5-5-3 fused ring system (see page 20), we decided to turn our attention to investigating the mechanism and examining the substrate scope for this unexpected reaction.

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3. Investigating the Mechanism for the 5-5-3 Systems

3.1 Introduction

3.1.1 Intramolecular Diels-Alder Reactions

Over the last 80 years, the Diels-Alder reaction has been employed extensively as a powerful method for the construction of complex molecular architectures bearing numerous stereocentres from simple precursors. If the process is rendered intramolecular by tethering the diene to the dienophile, complex polycyclic products can be obtained in a single step, often with excellent levels of diastereoselectivity.

More recently, methods for the control of the absolute stereochemistry of this important transformation have been disclosed. Metal and organo-based catalysts have been extensively utilised to perform enantioselective IMDA reactions. These modes of activation rely upon reducing the energy gap between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile through lowering of the LUMO. MacMillan,¹ Corey² and Evans,³ amongst others⁴ have pioneered this field, synthesising trans-indanyl and decalin systems in high enantioselectivities and diastereoselectivities.

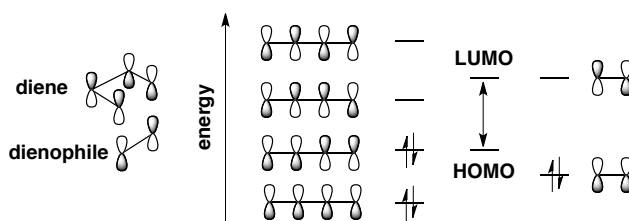
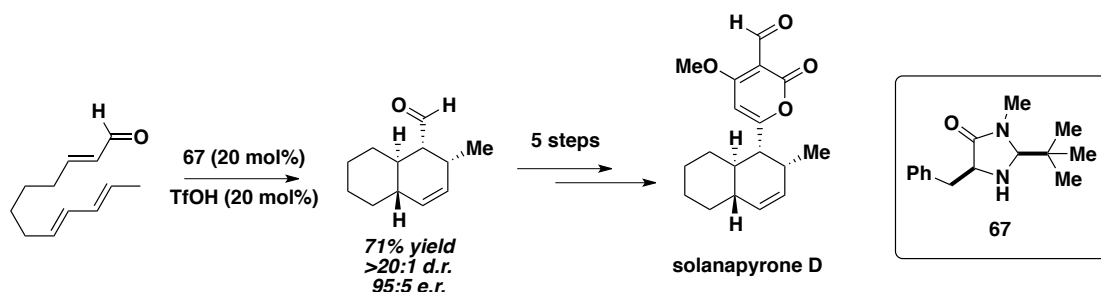


Figure 12: Energy level diagram for the Diels-Alder reaction

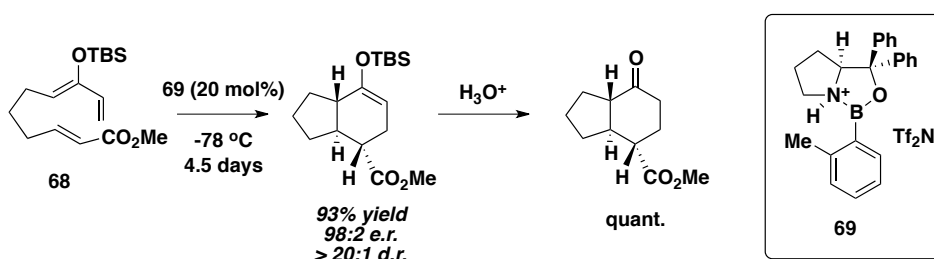
MacMillan has developed a LUMO-lowering strategy for asymmetric IMDA reactions.¹

This asymmetric methodology has been employed as the key step in the enantioselective total synthesis of solanapyrone D.



Scheme 31: Macmillan's LUMO lowering strategy using iminium catalysis

In 2003, Corey *et al.* used a related LUMO-lowering strategy, employing an *N*-protonated oxazaborolidine to catalyse the IMDA reaction of **68**.²

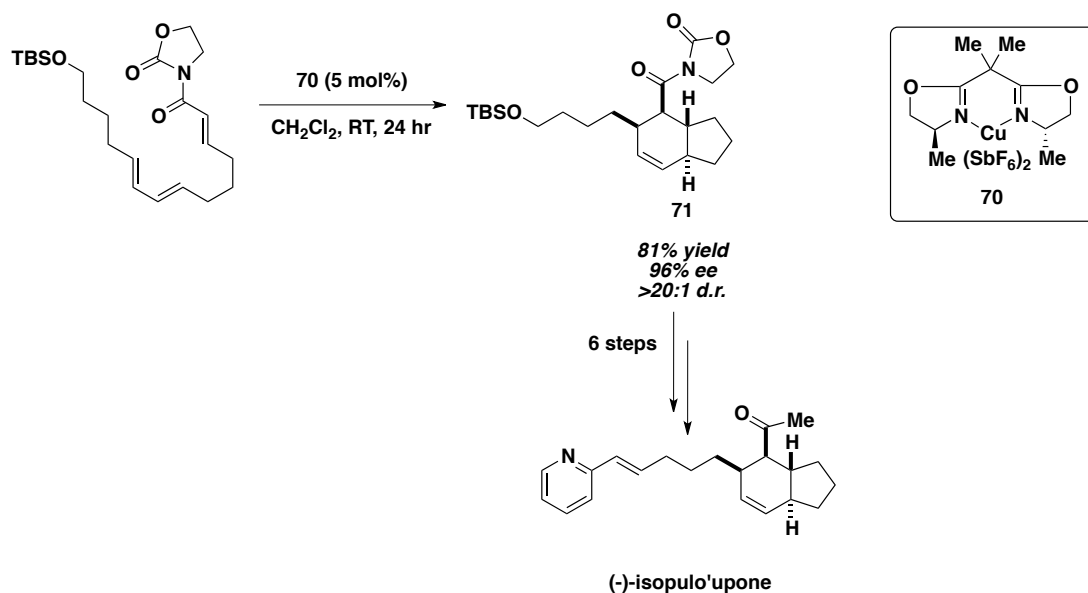


Scheme 32: Corey's LUMO lowering strategy using *N*-protonated oxazaborolidine catalysis

A total of nine IMDA reactions were carried out in excellent yields and enantioselectivities. Furthermore, the chiral ligand could easily be recovered following the reaction.

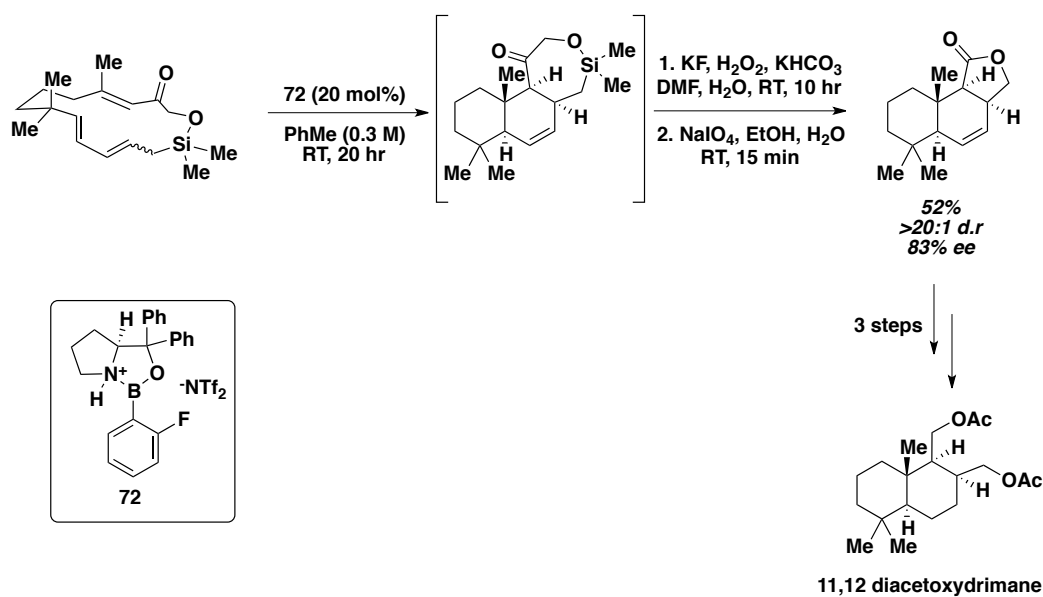
Evans has used a chiral metal complex **70** to catalyse an IMDA reaction, leading to cyclised products such as **71** in excellent yield, enantioselectivity and

diastereoselectivity.³ This enantioenriched material was then used as an intermediate in the asymmetric total synthesis of (-)-isopulo'upone.



Scheme 33: Evan's LUMO-lowering strategy used for the total synthesis of (-)-isopulo'upone

Jacobsen disclosed an impressive example of an asymmetric transannular Diels-Alder reaction in 2007, and used the methodology that they had developed to synthesise 11,12-diacetoxymethane.⁵



Scheme 34: Jacobsen's asymmetric transannular Diels-Alder reaction used in the synthesis of 11,12 diacetoxydrimane

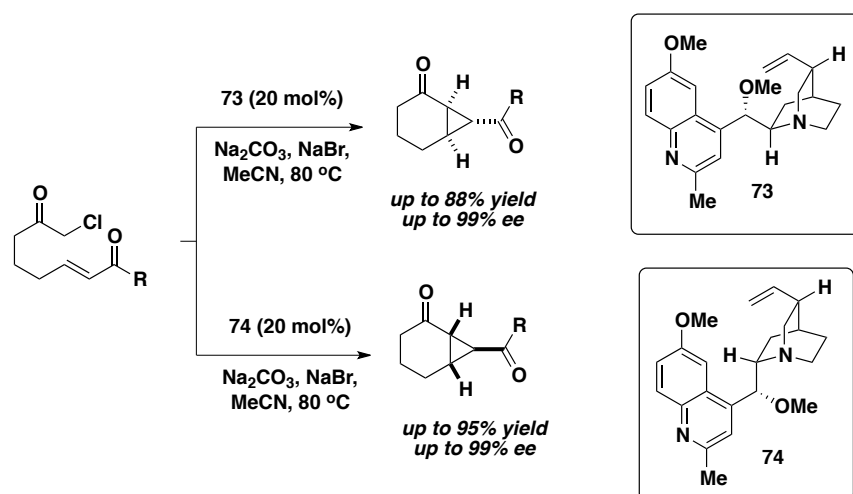
The *N*-protonated oxazaborolidine catalyst used proved to be remarkably general, tolerating a broad range of macrocyclic substrates, affording high yields, diastereoselectivities and enantioselectivities.

These systems all demonstrate very high degrees of stereocontrol, affording complex bicyclic products with multiple stereocentres in excellent yields.

3.1.2 Cyclopropanation Reactions

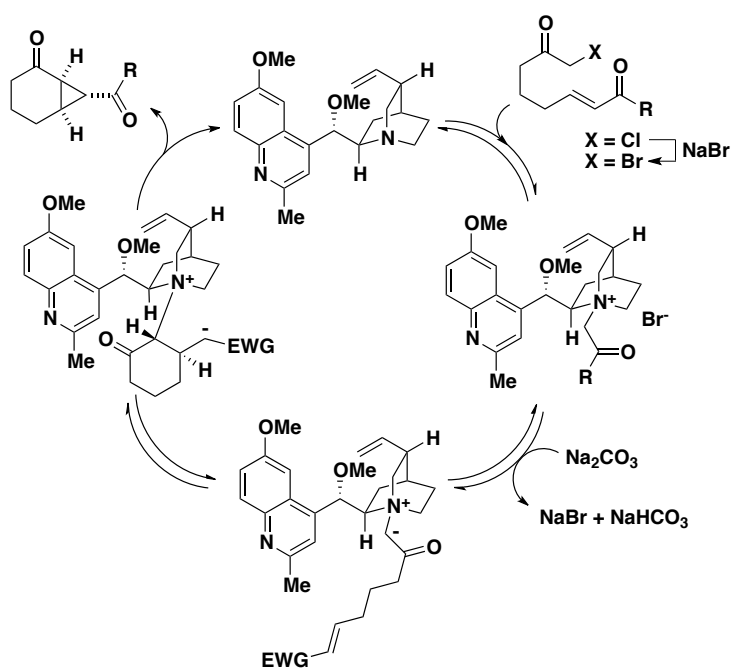
Cyclopropane derivatives are important motifs as synthetic intermediates and appear in numerous natural products⁶ and pharmaceutically active compounds.⁷ Fused cyclopropane containing systems have also been subject to substantial attention for their pharmaceutical significance.⁸

Gaunt has shown that 6-3 fused ring systems can be synthesised enantioselectively using quininium and quinidinium derived catalysts.⁹



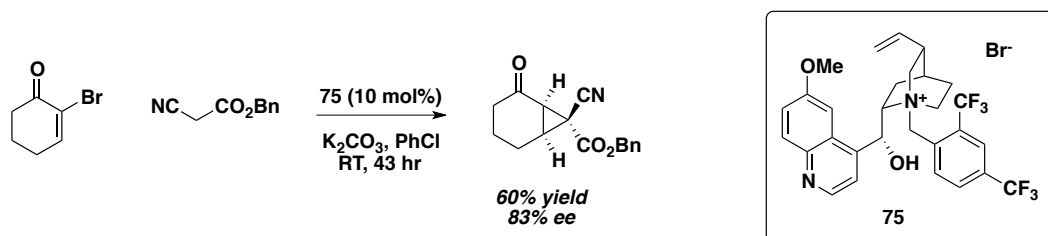
Scheme 35: Gaunt's cyclopropanation reaction

The substrate is initially activated *via* a Finklestein substitution with NaBr, and the resulting bromide undergoes a substitution reaction with the quinuclidine nitrogen, forming a quaternary ammonium salt. This undergoes deprotonation with Na_2CO_3 , followed by an intramolecular conjugate addition to form the cyclohexane. The resulting enolate then undergoes an intramolecular displacement to form the cyclopropane ring, expelling the catalyst to restart the catalytic cycle.



Scheme 36: Catalytic cycle for Gaunt's cyclopropanation reaction

Shioiri has utilised phase-transfer catalysis to form 6-3 fused ring systems in high enantiomeric excesses and yields.¹⁰

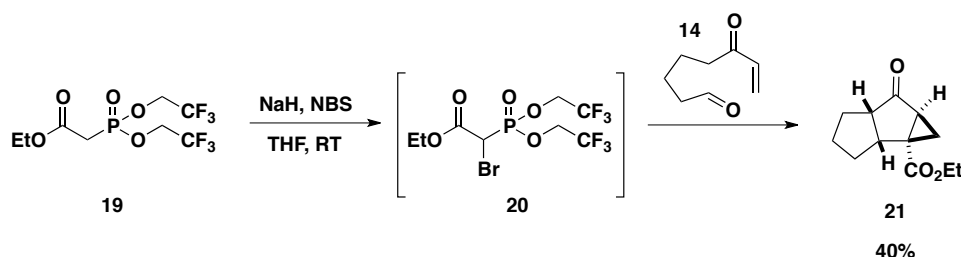


Scheme 37: Cyclopropanation reaction by Shioiri

The benzylcyanoacetate undergoes deprotonation followed by a Michael addition to form the brominated cyclohexanone. A proton exchange takes place, which enables an intramolecular displacement of the bromide ion, forming the cyclopropane ring.

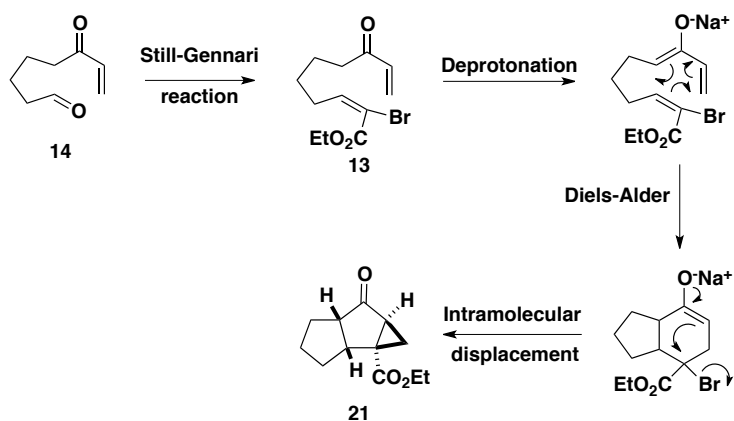
3.2 Concept and Aims

As mentioned in Chapter 2, we observed the following unexpected product **21** in an attempted Still-Gennari reaction. This led to the formation of three rings and four new stereogenic centres with complete control of diastereoselectivity. We were therefore interested in investigating this reaction further.



Scheme 38: Unexpected formation of a 5-5-3 fused ring system

In this reaction we carried out bromination of the Still-Gennari reagent *in situ*. The aldehyde **14** was subsequently added to the reaction mixture, and we noticed conversion to the 5-5-3 fused ring system **21**. Our initial hypothesis as to how product **21** had formed is shown in Scheme 39. We speculated that the desired Still-Gennari reaction had taken place. However, under the basic reaction conditions, the product had become deprotonated and undergone a Diels-Alder reaction, followed by an intramolecular displacement to form the three membered ring.

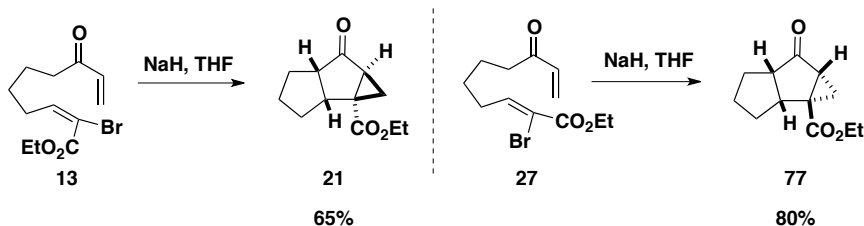


Scheme 39: Possible explanation for the formation of 5-5-3 product **21**

3.3 Results and Discussion

3.3.1 Proving the Hypothesis

We wanted to gain experimental evidence to prove that **13** was an intermediate in the formation of the 5-5-3 fused ring system. The synthetic route was therefore altered so that **13** could be synthesised and isolated. Fortunately, we had already synthesised both geometric isomers **13** and **27** (see page 21), and these were each subjected to the NaH/THF conditions believed to have caused the cyclisation in our initial observation.

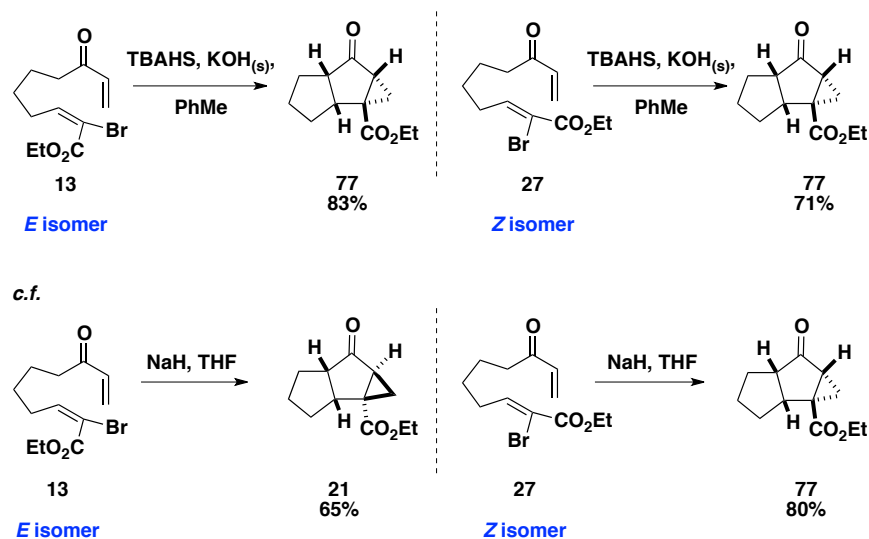


Scheme 40: Cyclisation of both geometric isomers under NaH/THF conditions

We were delighted to find that **13** cyclised to form **21** in 65% yield. The product was formed as a single diastereomer, which was the same as observed in the initial reaction, strongly implying that it is an intermediate in the formation of the novel

product **21**. Interestingly, isomer **27** cyclised to form a different diastereomer, which implies that the cyclisation is dependent on the geometry of the starting material.

We next set out to see if this cyclisation could be promoted under phase-transfer conditions.



Scheme 41: Cyclisation of both geometric isomers under two different reaction conditions

Surprisingly, under phase-transfer conditions both *E* and *Z* isomers **13** and **27** cyclised cleanly to form the same diastereomer of the product (the same as that observed in the cyclisation of the *Z* isomer under monophasic conditions).

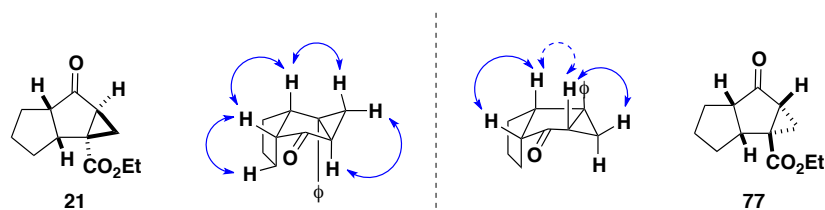
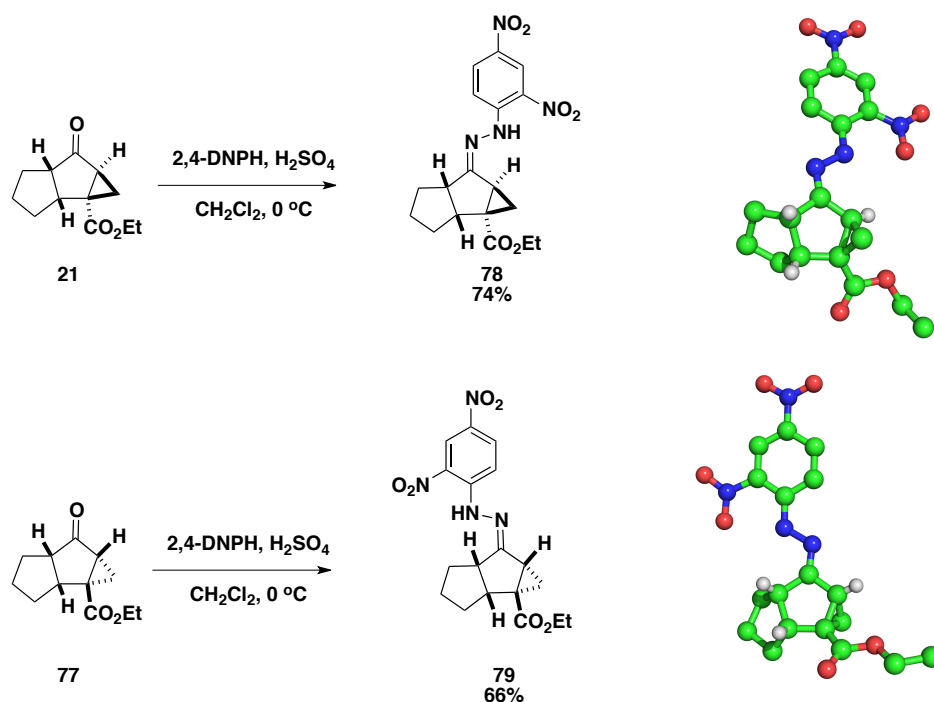


Figure 12: Relative stereochemistry was confirmed by nOe. Key interactions are highlighted with blue arrows. $\Phi = \text{CO}_2\text{Et}$ for clarity

The two different diastereomers were assigned by performing nOe experiments. The key nOe interactions are highlighted with blue arrows. The relative stereochemistry of both diastereomers was confirmed by single-crystal X-ray diffraction of 2,4-dinitrophenylhydrazine derivatives. The crystals were grown using vapour diffusion.^a



Scheme 42: Both diastereomers were derivatised with 2,4-dinitrophenylhydrazine and crystals grown using vapour diffusion

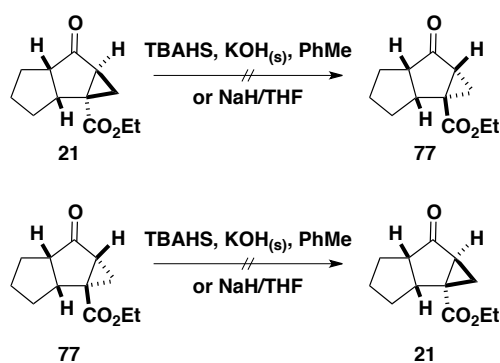
The crystal structures were in good agreement with our nOe analysis, showing that the 5-5 and 5-3 fused ring systems in both diastereomers adopt a cis conformation.

^a Thanks to Dr Russell Driver and Dr Amber Thompson for running the crystal structures

3.3.2 Explaining the Unusual Diastereodivergence

We were interested in the unusual diastereodivergence observed in these reactions.

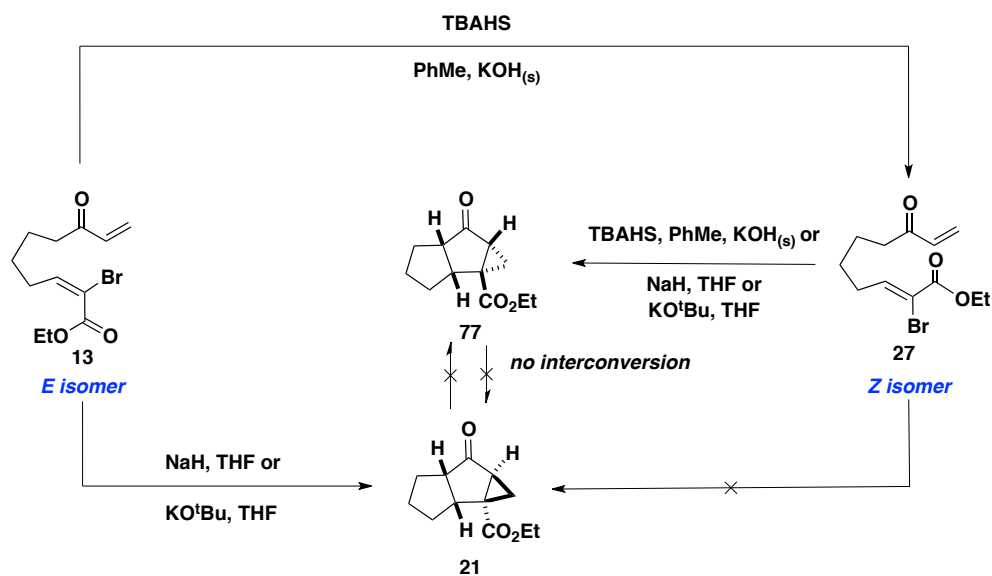
We set out by subjecting each 5-5-3 diastereomer to both sets of reaction conditions to eliminate the possibility of isomerisation of the two products.



Scheme 43: Both products were subjected to both sets of reaction conditions to see if they could interconvert

Neither diastereomer was interconverted under phase-transfer or NaH/THF conditions, ruling out simple equilibration of the product to a thermodynamic diastereomer.

We hypothesised that under PTC conditions there may be isomerisation of the *E* isomer 13 of the starting material to the *Z* isomer 27, followed by a cyclisation to form 77.



Scheme 44: A possible explanation for the unusual diastereodivergence observed in this reaction

We performed NMR time course experiments to monitor the reactions under phase-transfer conditions. We initially performed the cyclisation of the *E* isomer **13** using three different phase-transfer catalysts.

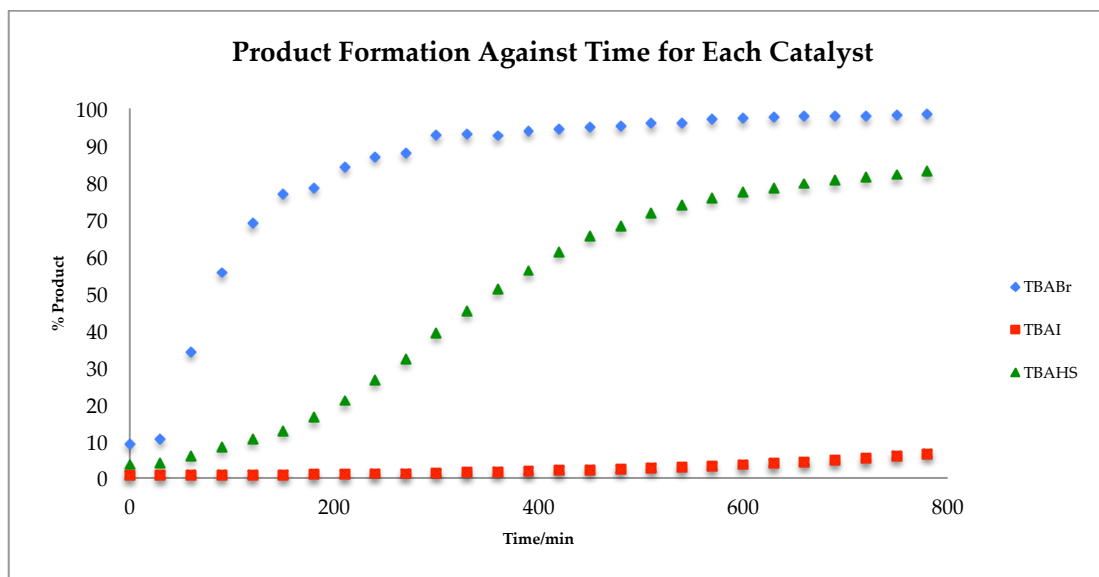
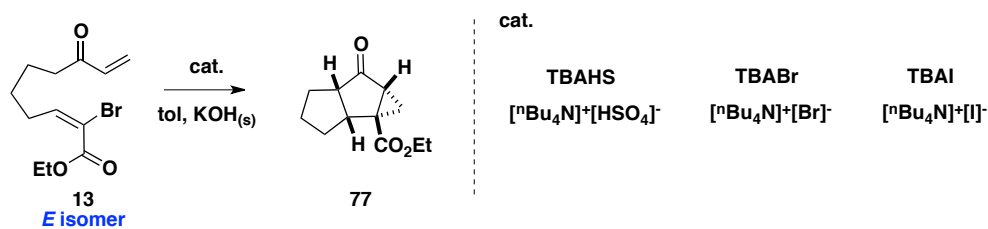


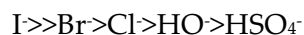
Figure 13: Graph of the formation of product against time for three different phase-transfer catalysts

Examining the cascade process for the (*E*)-bromoacrylate isomer **13** with TBAHS, we observed a strongly sinusoidal plot of conversion *vs* time, indicative of an activation step. Variation of the tetrabutylammonium salt employed illustrated that the counterion has a strong effect on the rate of reaction, with the bromide salt (TBABr) markedly accelerating conversion and the iodide salt (TBAI) proving inhibitory.

The slow reaction rate observed with the iodide salt was expected, as iodide is known to be an inhibitor in phase-transfer reactions. Mąkosza has demonstrated that this is due to iodide anions accumulating at the interface in a liquid-liquid system, decreasing the activity of the hydroxide anions towards deprotonation of the starting material.¹¹ A

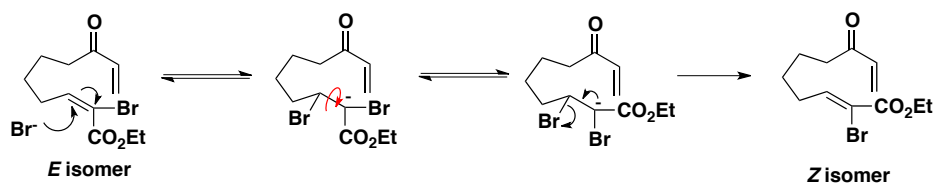
similar argument could be made to explain the results observed for the solid-liquid system used in this case, where the iodide anions compete with the hydroxyl anions, so deprotonation of the starting material is slow, and therefore the reaction is sluggish with TBAI.

Dehmlow has shown that under solid-liquid phase-transfer reactions, such as those shown in the graph above, the extractability of anions by the quaternary ammonium cation (i.e., the affinity of association of the anion with the quaternary ammonium cation) is in the order:¹²



The TBAHS more readily dissociates, which aids the association of the resulting quaternary ammonium salt with the substrate anion, and therefore the reaction rate. Thus, TBAHS is a superior phase-transfer catalyst to TBABr, which in turn is better than TBAI.¹³ However, this does not completely agree with the data obtained from the timecourse NMR experiments, since we would expect the TBAHS catalysed reaction to have a faster reaction rate than the reaction catalysed by TBABr. From this observation we speculated that the bromide ion could be involved in the isomerisation of the *E* isomer, and by facilitating the isomerisation, increasing the reaction rate.

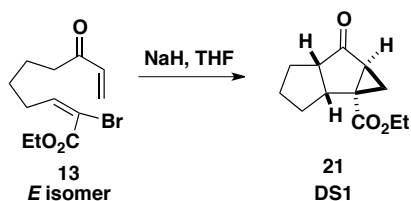
We hypothesised that bromide ions might carry out reversible 1,4-addition to the electron poor olefin, enabling bond rotation to occur, which could isomerise the double bond.



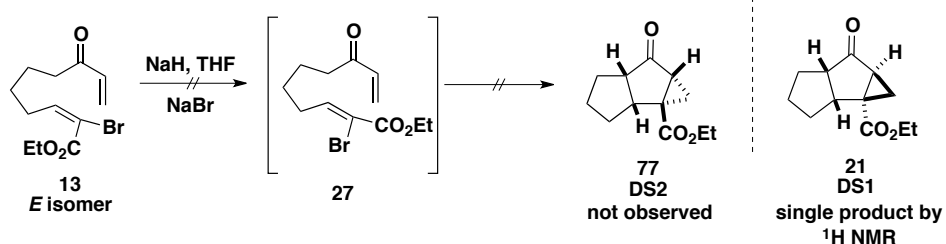
Scheme 45: Possible mechanism for the isomerisation of the *E* isomer to the *Z* isomer

We decided to perform reactions on the *E* isomer **13** to try and probe whether such a mechanism is viable. Firstly, we carried out the cyclisation of the *E* isomer **13** under NaH/THF conditions, but this time in the presence of excess NaBr. We hoped that if bromide could isomerise the double bond, we might begin to observe DS2 (**77**).

a) Standard cyclisation conditions:



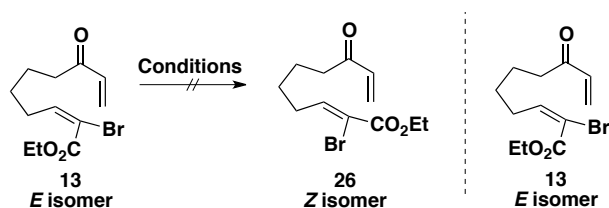
b) Cyclisation in the presence of excess NaBr:



Scheme 46: a) Cyclisation of the *E* isomer **13** under standard conditions afforded DS1 (**21**), b) Cyclisation of the *E* isomer **13** in the presence of excess NaBr afforded DS1(**21**) as the sole product

Adding excess bromide did not change the diastereoselectivity of the reaction and only DS1 (**21**) was observed.

We then submitted the *E* isomer **13** to a range of conditions that we speculated might trigger bromide catalysed isomerisation of the *E* isomer **13**. We initially tried using NaBr in the presence of 15-crown-5 or 2.2.1 cryptand, substances known to sequester Na⁺ ions (Table 5, entries 1 and 2).¹⁴ Under these conditions, no isomerisation was observed. Trying to solubilise NaBr by using DMSO also did not result in isomerisation of the *E* double bond geometry (Table 5, entry 3). Finally, we tried to mimic the phase-transfer conditions, firstly using stoichiometric amounts of TBABr in PhMe, and then using 10 mol% TBAHS and KBr (Table 5, entries 4 and 5). In both cases we recovered only unisomerised starting material.



Entry	Conditions	Outcome
1	15-crown-5 (1 eq.), NaBr (1 eq.), THF	No isomerisation
2	2.2.1 cryptand (1 eq.), NaBr (1 eq.), THF	No isomerisation
3	NaBr (1 eq.), DMSO	No isomerisation
4	TBABr (1 eq.), PhMe	No isomerisation
5	TBAHS (10 mol%), KBr (1 eq.), PhMe	No isomerisation

Table 5: Submitting the *E* isomer **13** to various conditions did not cause isomerisation of the double bond geometry

We did not observe isomerisation under any of these conditions, which strongly indicates that the bromide ion is not responsible for the isomerisation of the *E* isomer **13**. There must be another reason that the rate of reaction appears to be dependant on the nature of the counterion.

An NMR timecourse experiment was also carried out on the *Z* isomer **26**, by way of comparison of reaction rates, and to see if the unusual rate enhancement for the TBABr catalysed reaction was also observed in this system.

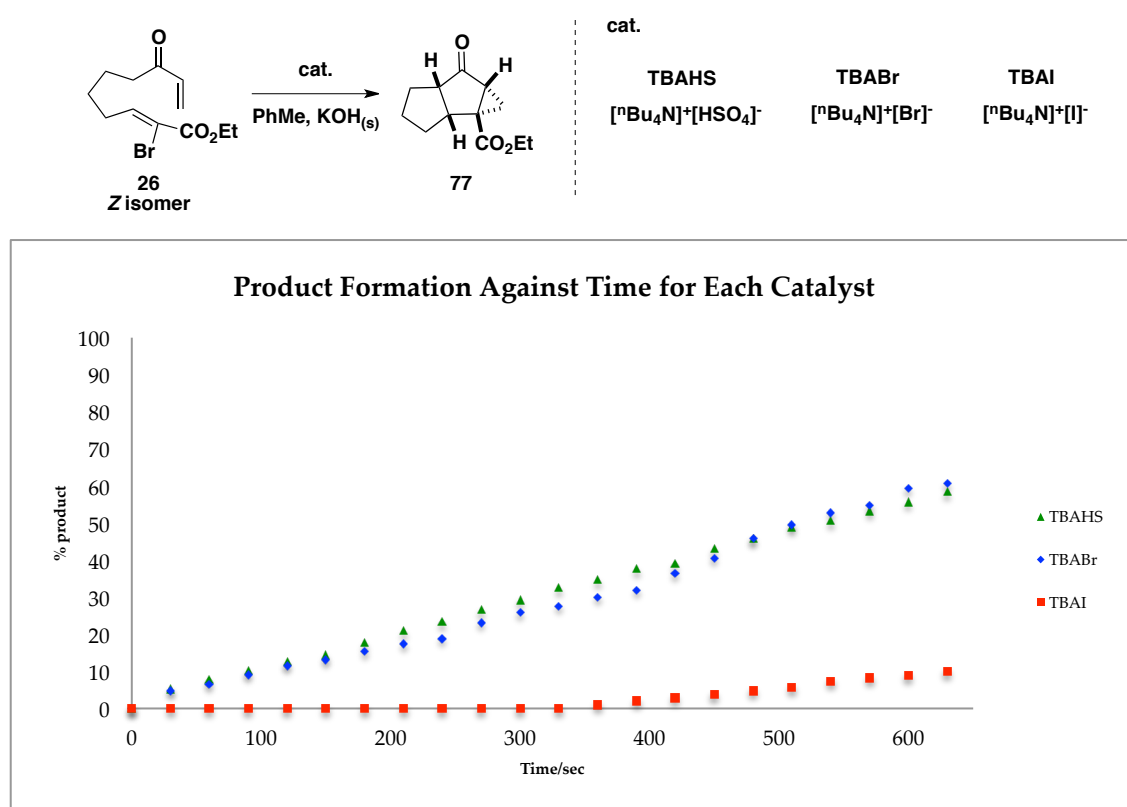


Figure 14: Graph of the formation of product against time for three different phase-transfer catalysts

Examining the cascade process for the (*Z*)-bromoacrylate isomer **26**, we observed a near linear plot of conversion *vs* time, in contrast to the sinusoidal plot observed for

the (*E*)- bromoacrylate isomer **13**. Varying the counterion from hydrogen sulfate to bromide in this instance made very little difference to the rate of reaction, but the iodide salt remained inhibitory. The linear increase of product concentration with time implies that no pre-equilibration of the catalyst or reagents is required before the reaction can proceed (i.e., there is no activation step for this reaction).

Finally, we closely examined our NMR timecourse experiments to see if we could observe any isomerisation of the (*E*)-bromoacrylate isomer **13** to the (*Z*)-bromoacrylate isomer **27** under the phase-transfer conditions.

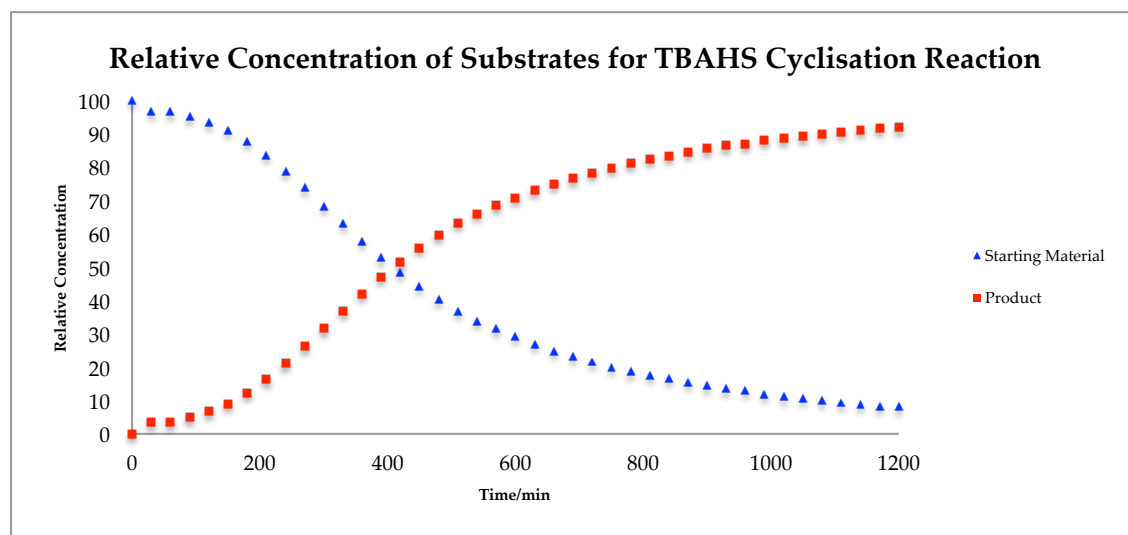
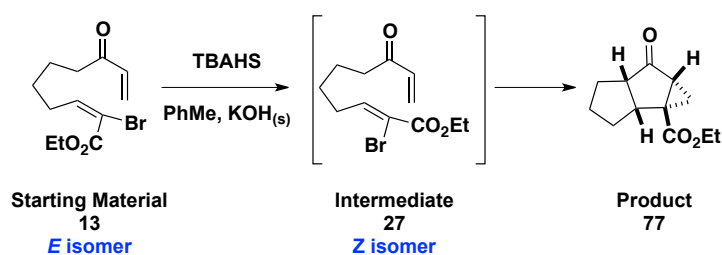
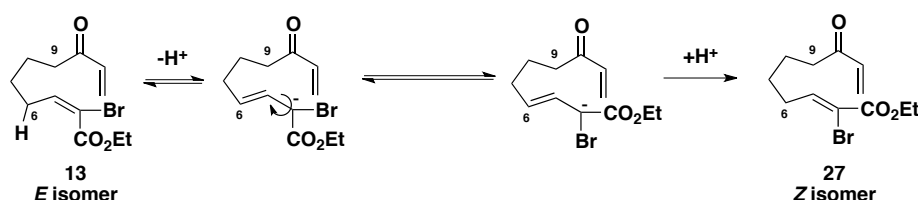


Figure 15: Graph of the formation of product over time

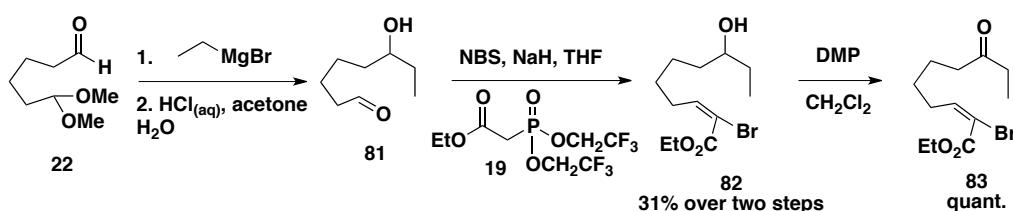
We did not observe any build up of the *Z* isomer **27** by NMR under the reaction conditions. This could be for two reasons: firstly, there is no isomerisation of the *E* isomer **13**, or secondly, there is isomerisation and the *Z* isomer **27** cyclises faster than the *E* isomer **13**, so the concentration of *E* isomer **13** never builds up.^b

We speculated that another possible explanation for the observed diastereodivergence could be isomerisation to the *Z* isomer **27** by deprotonation at the 6 position, as shown in Scheme 47.



Scheme 47: Possible explanation for the isomerisation of the *E* isomer **13** to the *Z* isomer **27**

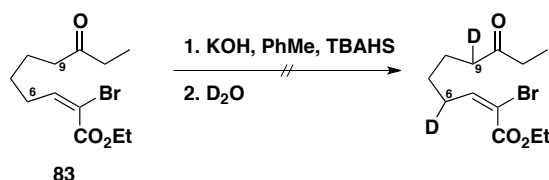
In order to probe this hypothesis, we decided to synthesise the starting material lacking the alkene acceptor, so we could observe isomerisation without the reaction going to completion.



Scheme 48: Synthesis of the starting material lacking the alkene acceptor **83**

^b It is not possible to stir the reaction in an NMR tube, and phase-transfer reactions are dependent on the stirring rate, so the NMR experiments do not completely mimic the reaction conditions in the lab

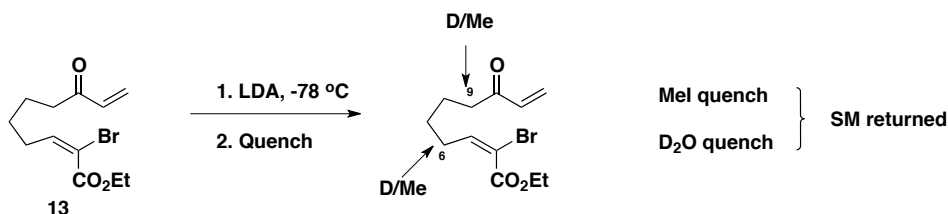
The synthesis of the required material went smoothly, and with **83** in hand, we were able to submit the *E* isomer **83** to the reaction conditions to see whether we could gain any evidence of deprotonation at the 6 position.



Scheme 49: Attempted cyclisation of **83** under phase-transfer conditions

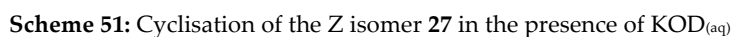
We performed the reaction under our standard conditions and quenched it with D₂O to see if there was any deuterium incorporation at the 6 position. Unfortunately, the starting material was not stable to the reaction conditions, and a complex mixture of products was formed.

As changing the starting material had not provided any insight into the reaction mechanism, we decided to submit the original starting material to basic conditions at a low temperature. We hoped that this would slow down the reaction, so a subsequent quench with D₂O or MeI may give us an idea of where deprotonation occurs.



Scheme 50: Attempted deprotonation and quench of the starting material

We knew that deprotonation of the starting material at room temperature afforded the cyclised product, so we thought that we could attempt the cyclisation under deuterated conditions to see if any deuterium incorporation is observed.



This reaction was less efficient with aqueous base, but the product that we were able to isolate did not contain any deuterium incorporation at the 6 position. This rules out this mechanism of isomerisation.

3.3.3 Computational Analysis of the Mechanism

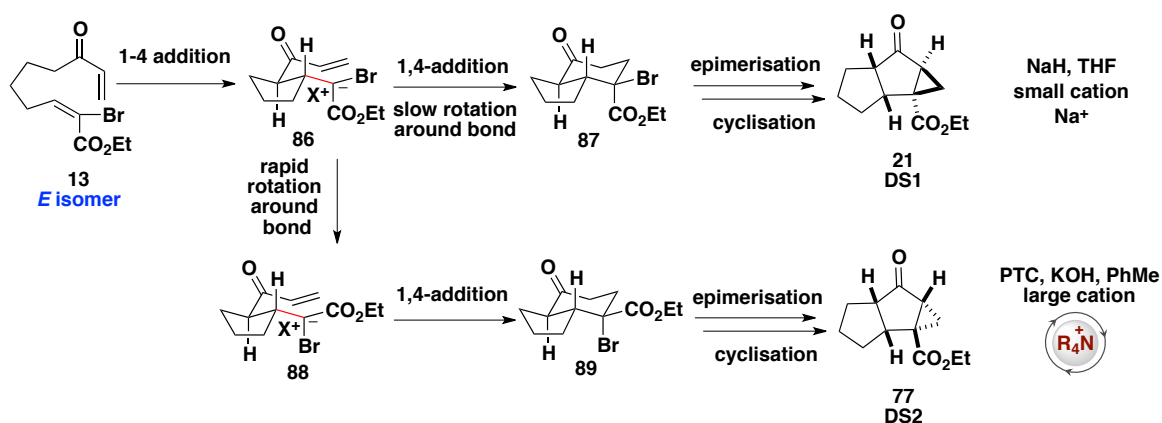
After attempting to elucidate the mechanism of this reaction by experimental techniques, we decided to collaborate with the Paton group, who are computational chemists capable of modelling this system and explaining our observations. Prof. Sergiy Okovytyy, Tetiana Sergeieva and Prof. Rob Paton modelled our system and the conclusions that they made are as follows:

- (1) The reaction proceeds by a double Michael reaction, not a Diels-Alder.
- (2) The first Michael addition is highly trans selective, and as a result the product of the second Michael addition is obtained as a 5-6 trans fused bicycle. The 5-6 trans ring junction has to epimerise to this cis before the cyclopropanation reaction can occur.
- (3) The size and coordination of the counterion plays a key role in the diastereodivergence. The counterion plays a crucial role in restricting rotation about a bond, a feature that explains the diastereodivergence we observe. When the counterion is Na^+ , it is small enough to bind closely to the anionic centre, restricting rotation. When the counterion is larger ($^+\text{NR}_4$), it can no longer bind closely to the anionic centre and cannot restrict rotation (see Scheme 53).

3.3.4 Experimental Evidence to Support Computational Work

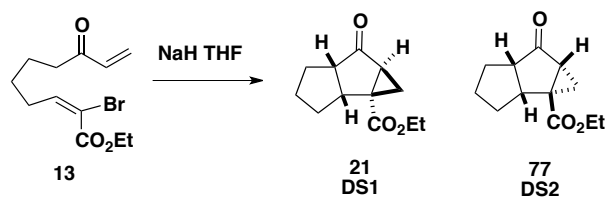
Using the information gained from the computational work, we have postulated a mechanism to explain the diastereodivergence. When the *E* isomer **13** is submitted to NaH/THF conditions, it undergoes a 1,4-addition to form **86**, with a trans ring junction. The sodium cation can bind closely to the resulting anion, causing rotation around the

highlighted bond to occur more slowly than the second 1,4-addition. The resulting 5-6 fused bicycle **87** has a trans ring junction, which must epimerise to the cis ring junction before an intramolecular displacement can occur to generate the three membered ring. When the *E* isomer **13** is submitted to the phase-transfer conditions, the first 1,4-addition occurs to form the same product, **86**. Under the phase-transfer conditions, the counterion is now much larger ($^+NR_4$), and it cannot bind closely to the substrate anion. Rotation around the highlighted bond is now much faster than 1,4-addition, forming **88**. This can now undergo a similar second 1,4-addition-epimerisation-cyclisation cascade to form DS2 (**77**).



Scheme 53: Computational explanation for the observed diastereodivergence

We wanted to gain experimental evidence to support the hypothesis that the sodium cation plays an important role in restricting rotation about a bond. In the presence of the sodium cation, rotation around the highlighted bond is slower than the 1,4-addition, affording DS1 (**21**) as the sole product. We thought that if we sequester the sodium cation, we may cause the bond rotation to be faster than the 1,4-addition, which would begin to favour DS2 (**77**). We therefore carried out the cyclisation in the presence of a crown ether.



Conditions	DS1 (21)	DS2 (77)
0 eq. 15-crown-5	1	0
1 eq. 15-crown-5	1	0.4
2 eq. 15-crown-5	1	0.67

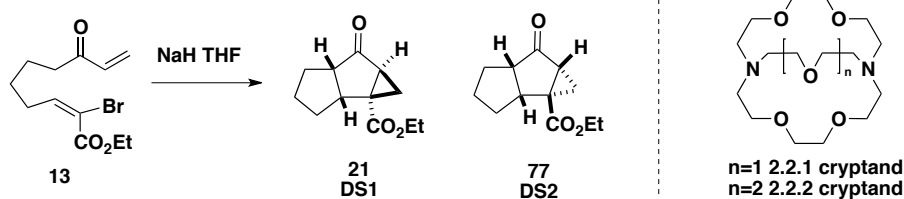
Table 6: Cyclisation of the *E* isomer **13** in the presence of 15-crown-5. Data given as a ratio calculated from the crude ^1H NMR

As increased crown ether was added to the reaction mixture, DS2 (**77**) began to be observed, which supports the computational hypothesis. The more crown ether added, the larger the quantity of DS2 (**77**) formed.^c

It has been shown that 15-crown-5 is not 100% effective at sequestering the Na^+ ,¹⁵ so we thought that we would also investigate the effect a cryptand has on the diastereoselectivity. Cryptands have been shown to be up to 10^4 times more effective at sequestering cations than crown ethers.^{d,16}

^c Two experimental methods were tried: 1) All components of the reaction were combined in one go and 2) the sodium hydride was pre-stirred with the crown ether. In both cases, the diastereoselectivity was calculated from ^1H NMR and exactly the same diastereoselectivity was observed

^d 2.2.2 Cryptand is specific for potassium cations and 2.2.1 cryptands are specific for sodium cations



Conditions	DS1 (21)	DS2 (77)
0 eq. 2.2.1 cryptand	1	0
1 eq. 2.2.1 cryptand	0	1

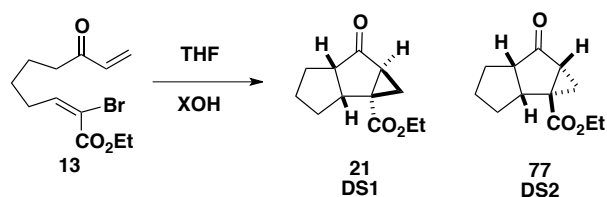
Table 7: Cyclisation of the *E* isomer **13** in the presence of 2.2.1 cryptand. Data given as a ratio calculated from the crude ^1H NMR

We observed a complete switch of diastereoselectivity in the presence of the cryptand.^e

This is consistent with the sodium cation playing a crucial role in the formation of DS1 (**21**).

We thought that we could gain further evidence to support this hypothesis by increasing the size of the counterion. It was assumed that a larger counterion would associate less strongly with the anion and therefore be less able to restrict rotation around the bond.

^e Two experimental methods were tried: 1) All components of the reaction were combined in one go and 2) the sodium hydride was pre-stirred with the cryptand. In both cases, the diastereoselectivity was calculated from ^1H NMR and exactly the same diastereoselectivity was observed



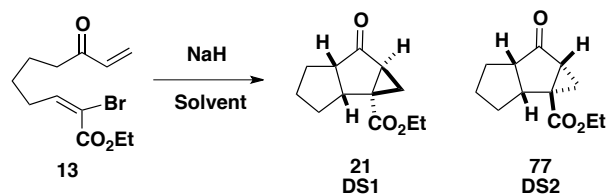
Base	DS1 (21)	DS2 (77)
NaOH	1	0
KOH	1	0
RbOH. <i>x</i> H ₂ O	1	0
CsOH.H ₂ O	1	0.63

Table 8: Cyclisation of the *E* isomer **13** in the presence of increasingly larger counterions. Data given as a ratio calculated from the crude ¹H NMR

In the presence of sodium, potassium and rubidium cations, we observed only DS1 (**21**), but increasing the size of the counterion to caesium began to permit formation of DS2 (**77**).^f

Finally, we wanted to observe the diastereomeric ratio of the product in the presence of different solvents. We proposed that the more polar the solvent, the larger the ratio of DS2 (**77**), as the polar solvent will disrupt the tight ion-pair between the substrate anion and sodium cation.

^f The hydroxide bases were examined as the carbonate bases did not promote cyclisation, even after stirring for five days



Solvent	DS1	DS2
THF	1	0
MeCN	1	1.5
DMF	0	1
DMSO	0	1

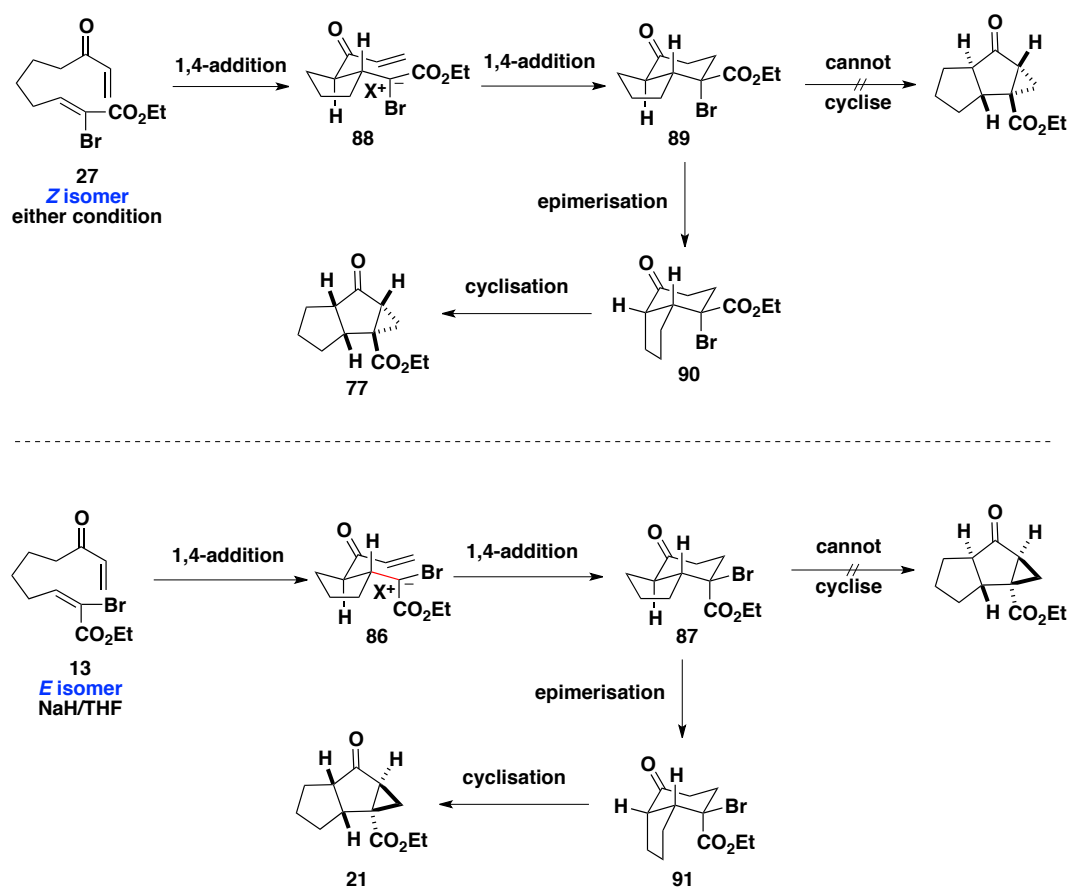
Table 9: Cyclisation of the *E* isomer **13** in the presence of increasingly polar solvents.[§] Data given as a ratio calculated from the crude ¹H NMR

As the solvent polarity was increased, the proportion of DS2 (**77**) increased. This is as expected if the computational hypothesis is correct. The three reactions: adding crown ether/cryptand, changing the size of the counterion and changing the solvent have all supported the computational hypothesis.

[§] PhMe and CH₂Cl₂ did not afford any product after five days

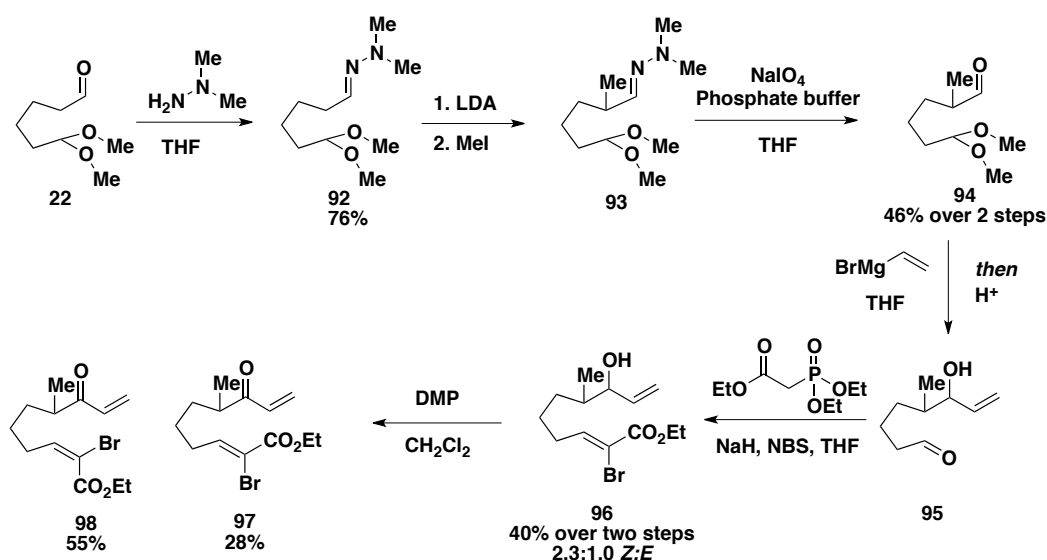
3.3.5 Probing the Epimerisation

Computational work suggested that the first Michael reaction results in *trans* hydrogen geometry across the cyclopentane ring, and epimerisation does not occur until after the second Michael addition has taken place. We wanted to see if we could probe this epimerisation step experimentally.



Scheme 54: Computational mechanism for the cyclisation of both *Z* and *E* isomers 27 and 13

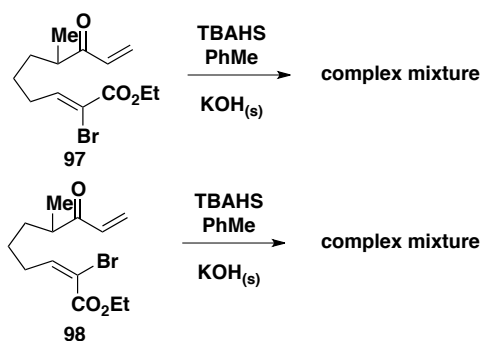
We hypothesised that if we could block the position α - to the ketone carbonyl with a methyl group so epimerisation could not occur, we may be able to stop the reaction going to completion, and observe a 5-6 trans fused ring system.



Scheme 55: Synthesis of the methyl substituted starting materials

Aldehyde **94** was synthesised *via* a modified literature route involving condensation with dimethylhydrazine followed by alkylation and deprotection.¹⁷ This aldehyde was then subjected to our usual sequence of Grignard addition, HWE olefination and oxidation to give a 2.3:1.0 mixture of double bond isomers, which could be fully separated by column chromatography.

We then submitted both isomers to the phase-transfer reaction conditions.



Scheme 56: Attempted cyclisation of the methyl substituted starting material under phase-transfer conditions

Under our usual phase-transfer conditions, we observed a complex mixture of products. This is consistent with the hypothesis that enolisation of this position plays an important role in the mechanism of formation of **21** and **77**.

3.4 References

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4. Investigating the Scope

4.1 Results and Discussion

After exploring the mechanism of the reaction both experimentally and computationally, we decided to investigate a variety of substrates with differing chain lengths, alternative electron-withdrawing groups and heteroatom substitutions, as well as systems with no leaving group.

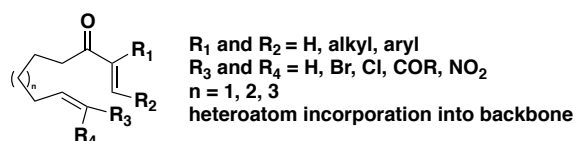
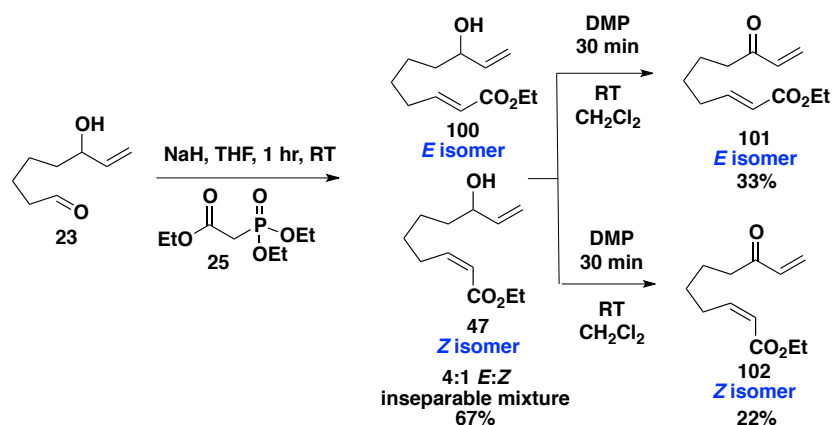


Figure 16: Potential substrate scope for the reaction

4.1.1 Non-Brominated Substrate

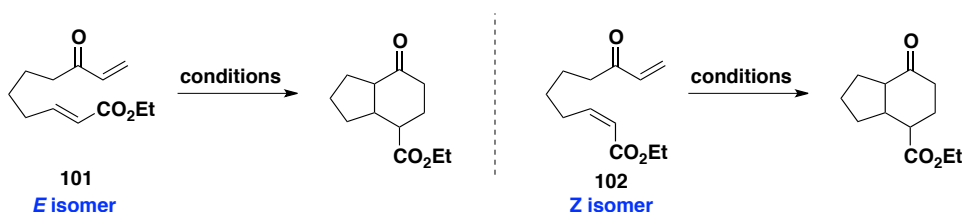
We began by investigating the cyclisation of the substrate analogous to that used previously, but lacking the bromine. The starting material was prepared similarly to compounds **13** and **27**.



Scheme 57: Synthesis of the non-brominated *E* and *Z* isomers

A HWE reaction with aldehyde **23** (prepared as described previously) afforded a 4:1 ratio of *E*:*Z* isomers, which were inseparable from one another using silica gel

chromatography. DMP oxidation of the isomeric mixture afforded the now separable *E* and *Z* isomers **101** and **102** in 33% yield and 22% yield respectively. The two double bond isomers were individually subjected to a variety of basic conditions in an attempt to induce cyclisation.



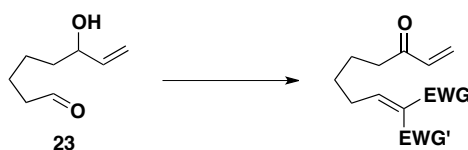
Conditions	<i>E</i> isomer cyclisation	<i>Z</i> isomer cyclisation
NaH, THF	Degraded SM	Degraded SM
KO ^t Bu, THF	Degraded SM	Degraded SM
KOH _(s) , PhMe, TBAHS	Degraded SM	Degraded SM
NaOH _(s) , PhMe, TBAHS	Degraded SM	Degraded SM
K ₂ CO _{3(s)} , PhMe, TBAHS	Degraded SM	Degraded SM
CsOH.H ₂ O _(s) , PhMe, TBAHS	Degraded SM	Degraded SM
LDA, THF	Degraded SM	Degraded SM
KHMDS, THF	Degraded SM	Degraded SM
LiHMDS, THF	Degraded SM	Degraded SM
Pyrrolidine, MeCN	Starting material	Starting Material
NaOEt, EtOH	Degraded SM	Degraded SM
DBU, THF	Starting material	Starting material

Table 10: Conditions used to attempt to induce cyclisation for the *E* and *Z* isomers

Unfortunately none of the conditions examined resulted in cyclisation, and only starting material (SM) or decomposition of the starting material were observed. In all cases a significant colour change was observed upon addition of the base, implying that the starting material was being deprotonated. We reasoned that the lack of reactivity was due to the ester group alone not being a powerful enough electron-withdrawing group for the double Michael reaction to proceed. At this point we decided to consider alternative systems with stronger electron withdrawing groups.

4.1.2 Incorporating Stronger Electron Withdrawing Groups

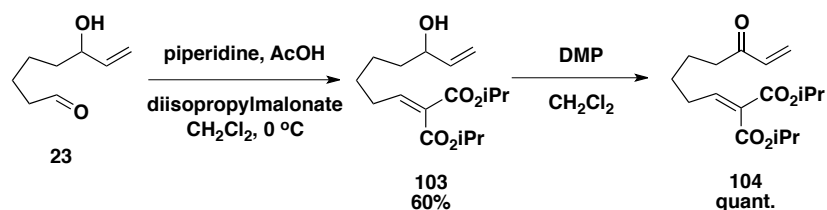
We thought that we could use aldehyde **23** as a common intermediate for the synthesis of starting materials with stronger electron withdrawing groups.



Scheme 58: Aldehyde **23** can be used as a common precursor for the synthesis of a variety of starting materials

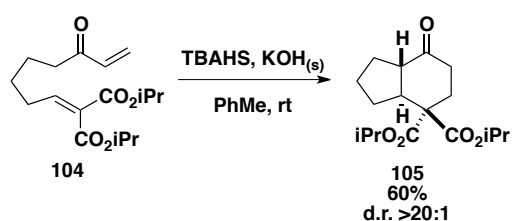
We commenced this investigation by carrying out a Knoevenagel reaction with diisopropylmalonate.^a Under standard conditions, aldehyde **23** reacted smoothly to form olefin **103**, which was easily oxidised using DMP in quantitative yield.

^a We chose this as we thought that the isopropyl groups would be much more stable to hydrolysis under the phase-transfer conditions, and we wanted to reduce the number of possible double bond isomers by using a symmetrical malonate



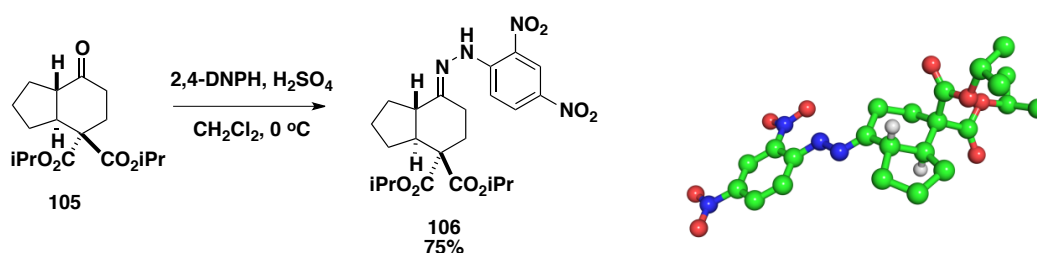
Scheme 59: Synthesis of malonate system **104**

The cyclisation of this malonate system was then attempted, and pleasingly, the substrate formed the 5-6 fused system as a single diastereomer.



Scheme 60: Cyclisation of the malonate system forms **105** as a single diastereomer^b

The relative stereochemistry of the bicyclic malonate was deduced using nOe data, and confirmed by single crystal X-ray crystallography of the product derived from the condensation of the malonate with 2,4-dinitrophenylhydrazine.^c



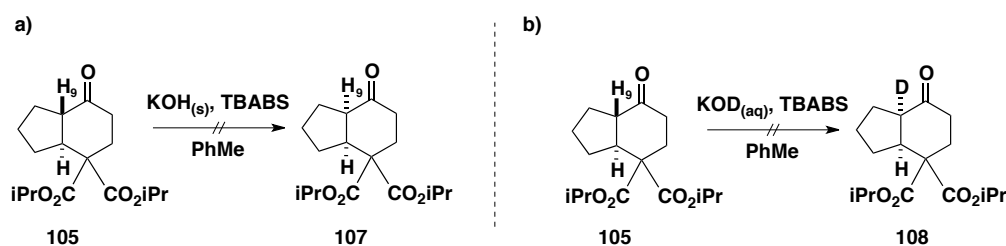
Scheme 61: Derivatisation of malonate system **105** with 2,4-dinitrophenyl hydrazine formed a crystalline solid, which allowed us to obtain a crystal structure

We wanted to explore whether it was possible to carry out an epimerisation that would give the corresponding *cis* 5-6 ring junction. We started by resubmitting the

^b The reaction proceeds cleanly, but the yield does not completely reflect this. We believe some of the starting material may polymerise under the reaction conditions

^c Thanks to Dr Russell Driver and Dr Amber Thompson for running the crystal structure

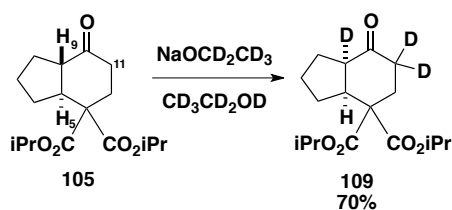
starting material to the reaction conditions, to see if an extended reaction time would have any effect, but no reaction was observed.



Scheme 62: a) Resubmitting the product to the reaction conditions did not epimerise the ring junction, b) deuterated conditions did not incorporate any deuterium, implying that no deprotonation was occurring

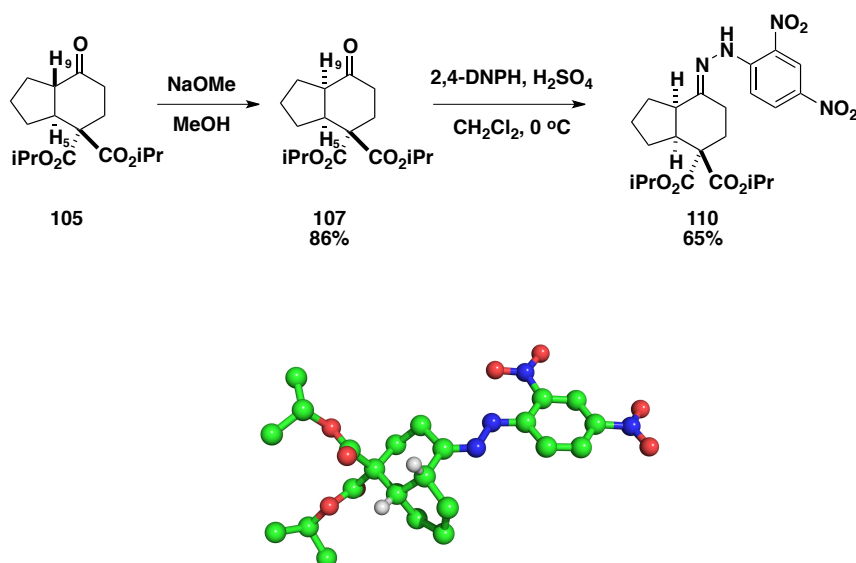
We attempted the reaction using KOD, to investigate whether *H*9 was deprotonated under these conditions. Again, no epimerisation was observed, and we saw no deuterium incorporation at *H*9, so we concluded that the *H*9 position was not being deprotonated under the conditions.

Agosta has reported that the ring junctions in substrates bearing a similar 5-6 scaffold can be epimerised using freshly prepared sodium ethoxide in ethanol.¹ We subjected **105** to these conditions and were pleased to see that the *H*9 and *H*11 positions had both undergone hydrogen-deuterium exchange.



Scheme 63: Sodium ethoxide was successfully employed to epimerise the ring junction from trans to cis

Furthermore, the NMR of the fused ring system had changed, which implied that the ring junction had epimerised from trans to cis. In order to confirm the identity of this compound, we carried out the reaction under protic conditions. In the presence of sodium ethoxide in ethanol, it was possible to convert the trans 5-6 ring geometry to the cis.

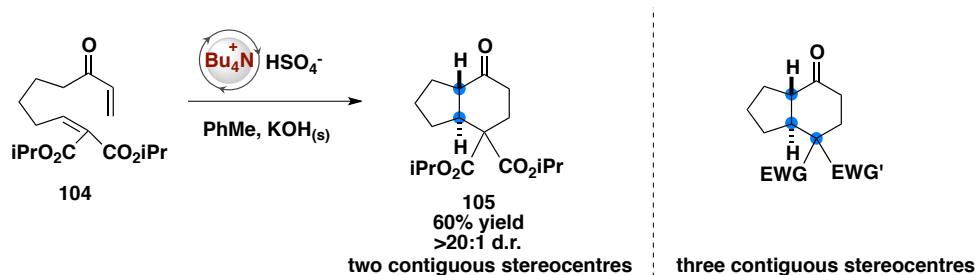


Scheme 64: The trans ring junction was successfully epimerised to the cis and then the product was derivatised with 2,4-dinitrophenylhydrazine so a crystal structure could be determined

The two protons on the *H5-H9* ring junction overlapped in all of the NMR solvents we tried (benzene-*d*₆, PhMe-*d*₈, CDCl₃, CD₂Cl₂, THF-*d*₈, acetone-*d*₆, MeOD, CD₃CN, DMSO-*d*₆), so it was not possible to carry out nOe analysis. Fortunately, we were able to derivatise the product and obtain another crystal structure that confirmed the relative stereochemistry between *H9* and *H5* to be cis.^d

^d Thanks to Mr John Joliffe and Dr Amber Thompson for running the crystal structure

We next set out to extend this methodology to form three contiguous stereocentres, of which one would be all carbon and quaternary.



Scheme 65: We wanted to extend the methodology to form products with three contiguous stereocentres

In order to achieve this, we thought that we could synthesise a range of substrates bearing two different electron withdrawing groups. We started the synthesis in the same fashion as for the synthesis of malonate **104**.

From common intermediate **23**, we attempted a Knoevenagel reaction with two different carbon acids.



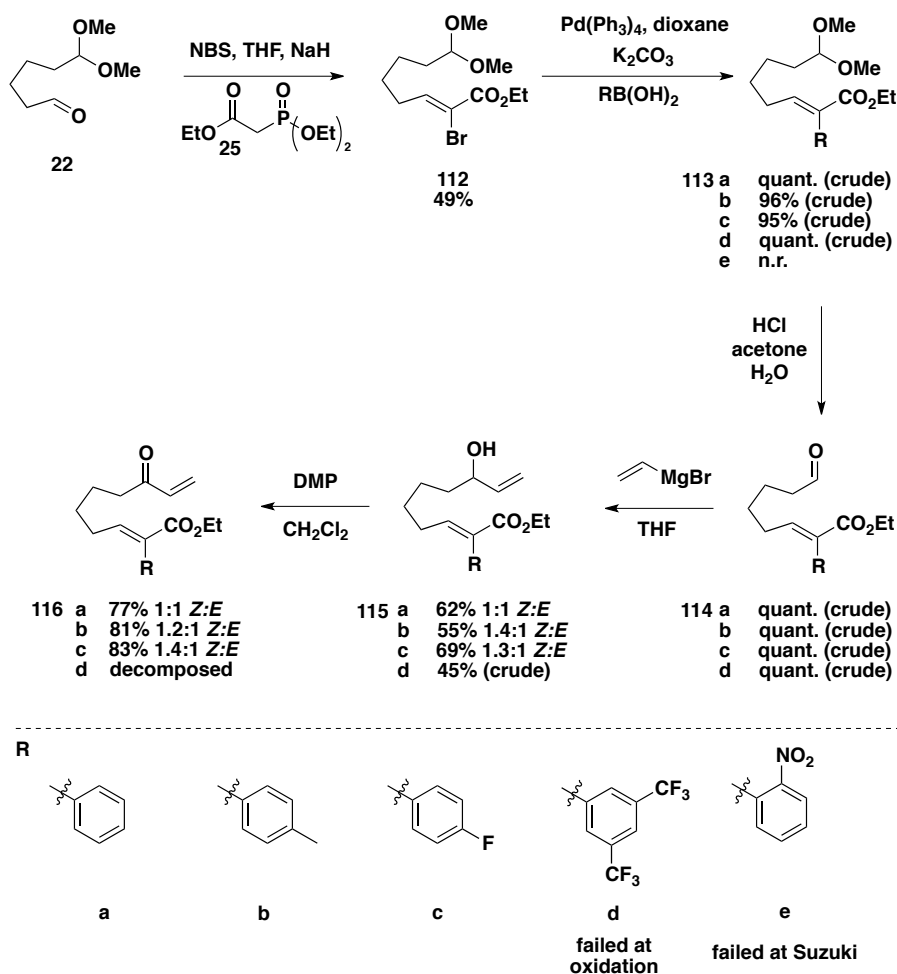
Conditions	Carbon acid	Outcome
Piperidine, AcOH, 4 Å MS	Ethylcyanoacetate	Mixture of products
Piperidine, AcOH, 4 Å MS	Ethyltrifluoroacetate	Degraded SM
TiCl_4 , CCl_4 , THF, pyridine	Ethyltrifluoroacetate	Degraded SM

Table 11: Conditions used to try two different Knoevenagel reactions

Unfortunately, under these conditions we observed extensive decomposition of the starting material and we were unable to isolate any of the desired products.

We hoped that a range of substrates with an aryl substituent could be synthesised with a Suzuki reaction from a parent bromide, using a similar reaction sequence to that used in the formation of the 5-5-3 cyclisation precursor.

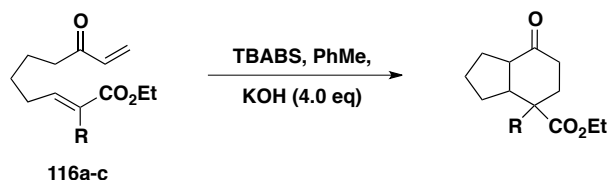
Accordingly, we began with the synthesis of bromo-olefin **112** in 49% yield. Purification was achieved *via* a quick column due to the instability of this material on silica. A Suzuki reaction was then performed, which worked well for four of the five aryl boronic acids tried. The acetals were unstable, so were immediately deprotected to form aldehydes, which were reacted with vinyl magnesium bromide and oxidised to form the corresponding ketones.



Scheme 66: A range of aryl-substituted substrates were synthesised by a Suzuki reaction from a parent bromide using a similar reaction sequence to that used in the formation of the 5-5-3 precursor

Using this method, it was possible to cleanly isolate three of the alcohols. The bis-trifluoromethylated compound proved difficult to purify after the Grignard reaction, so was taken through to the oxidation contaminated with ~15% of an unknown impurity. We were not able to cleanly isolate any of the product after the oxidation, which we believe may be due to the starting alcohol being contaminated with unknown impurities.

The cyclisation reactions were then attempted with these arylated starting materials. It was not possible to separate the double bond isomers at any stage of the synthesis of the starting materials, so the cyclisations were attempted using mixtures of *E*:*Z* isomers.



Entry	R	Outcome
1	Ph	Decomposed
2	<i>p</i> Me-Ph	Decomposed
3	<i>p</i> F-Ph	Decomposed

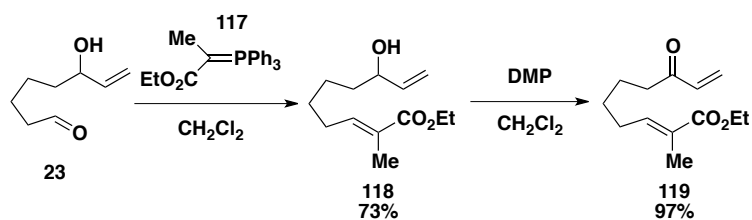
Table 12: Attempted cyclisation of the arylated substrates

Unfortunately, under these conditions we were unable to isolate any of the desired products.^e This reaction was complicated by the starting materials being mixtures of *E* and *Z* isomers, but the overall reaction was not smooth, and we decided not to pursue these substrates.

We then chose to explore different cyclisation precursors synthesised from commercially available Wittig reagents. The first step of the synthesis employed (carbethoxyethylidene)-triphenylphosphorane **117**, leading to **118** in 73% yield as a

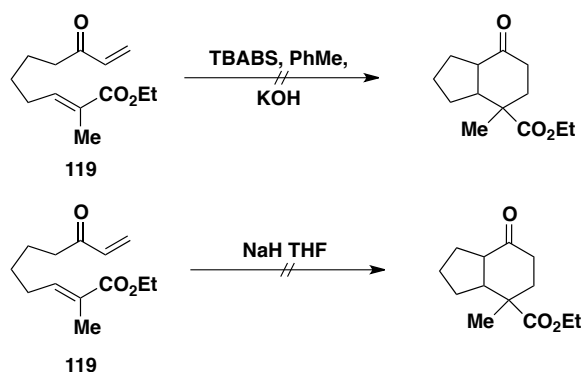
^e Unfortunately, these cyclisations were not successful, each affording two main products, but the ¹H NMR of the crude and columned material gave a complex mixture of products and the conversion was very poor

single double bond isomer. The allylic alcohol was oxidised in near quantitative yield to afford **119**.



Scheme 67: Synthesis of the methyl-substituted substrate

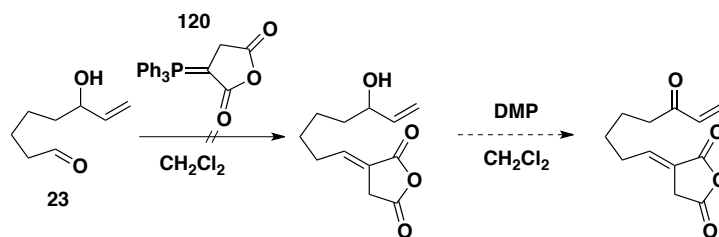
With **119** in hand, we attempted the cyclisation reaction under both the phase-transfer and NaH/THF conditions.



Scheme 68: Attempted cyclisation of the methyl substituted starting material

Unfortunately, for both reactions we did not observe any formation of the product. The starting material was consumed in both cases, but the reaction formed an inseparable mixture of compounds that could not be identified.

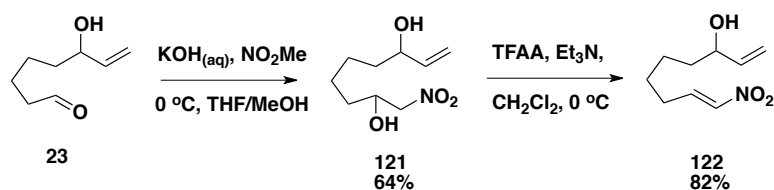
We then decided to use 2-(triphenylphosphoranylidene)succinic anhydride **120** as the Wittig reagent to see if we could synthesise a spiro-fused product. We hoped that the stronger electron withdrawing ability of the succinate moiety compared to the methyl group might favour cyclisation over polymerisation or degradation.



Scheme 69: Attempted synthesis of a substrate with an exocyclic Michael acceptor

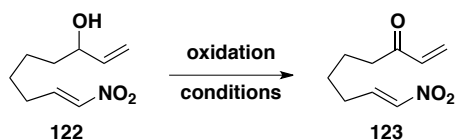
The Wittig reaction was unsuccessful in this case, so this substrate was not pursued any further. The substrates that we had synthesised with two different electron withdrawing groups did not cyclise smoothly, so we decided to concentrate on increasing the electron withdrawing ability of the alkene acceptor in a different way. We thought that utilising one stronger electron withdrawing group (i.e., ketone or nitro group, as opposed to the ester) may still allow us to synthesise products with three contiguous stereocentres.

Initially, we decided to attempt a Henry reaction. Aldehyde **23** was subjected to nitromethane under basic conditions and **121** was formed in 64% yield



Scheme 70: The Henry reaction and dehydration was successful, affording the nitro-olefin **122** in 82% yield

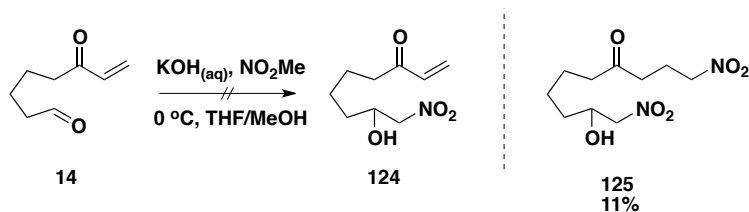
This material was then dehydrated using trifluoroacetic anhydride, which afforded nitro-olefin **122** in 82% yield. It now only remained to oxidise the allylic alcohol to the enone, a reaction which we did not envisage to be problematic.



Oxidation Conditions	Product
PCC/CH ₂ Cl ₂	SM
MnO ₂ /DCM	SM
TPAP/NMO/CH ₂ Cl ₂	SM
DMP/CH ₂ Cl ₂	SM
TEMPO/NaOCl	SM

Table 13: Conditions attempted to oxidise allylic alcohol **122** to enone **123**

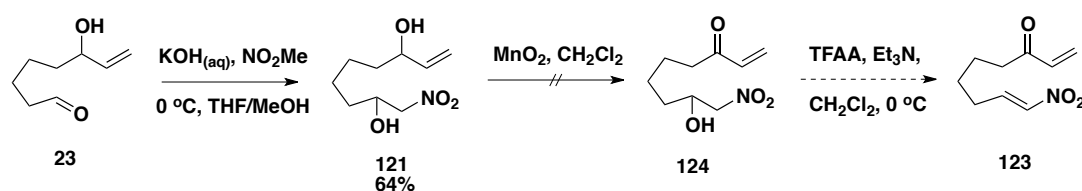
We were therefore surprised to find that under a range of oxidation conditions, only the starting material was recovered. We thought that we might be able to start with the ketone in place and attempt the Henry reaction, so as to avoid the oxidation in the final step.



Scheme 71: Henry reaction afforded **125** in 11% yield

Submitting ketone **14** to the reaction conditions afforded a mixture of products, but we did not observe **124**. We were able to isolate **125** in 11% yield, where the nitromethane had carried out a 1,4-addition to the α,β -unsaturated ketone as well as a 1,2-addition to the aldehyde.

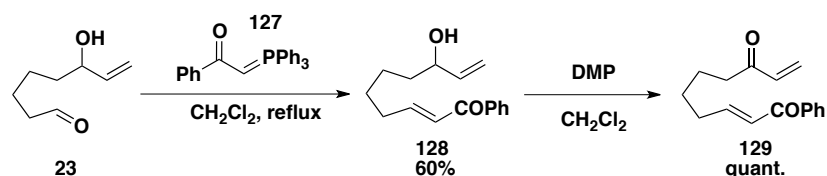
Finally, we thought that we may be able to do a selective oxidation of the α,β -unsaturated alcohol before carrying out an elimination to form the nitro alkene.



Scheme 72: Henry reaction worked well, but attempted selective oxidation of **121** did not afford any product

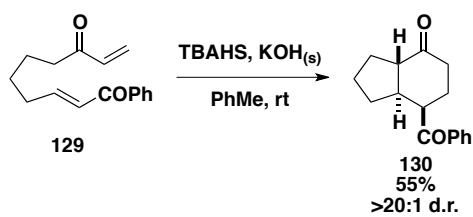
The Henry reaction was successful, as we had observed previously, but unfortunately oxidation using MnO_2 did not afford any product. We isolated mainly starting material after stirring for three days, along with some evidence of degradation. This reaction was not pursued further.

We thought that we could increase the electron withdrawing ability of the alkene acceptor by introducing a ketone, which is more electron withdrawing than the ester we tried initially. We wanted to choose a ketone which has no enolisable positions to avoid any unwanted side reactions under the basic conditions, so we selected a phenyl ketone.



Scheme 73: Wittig reaction with the aldehyde afforded alkene **128**, which was oxidised to form enone **129**

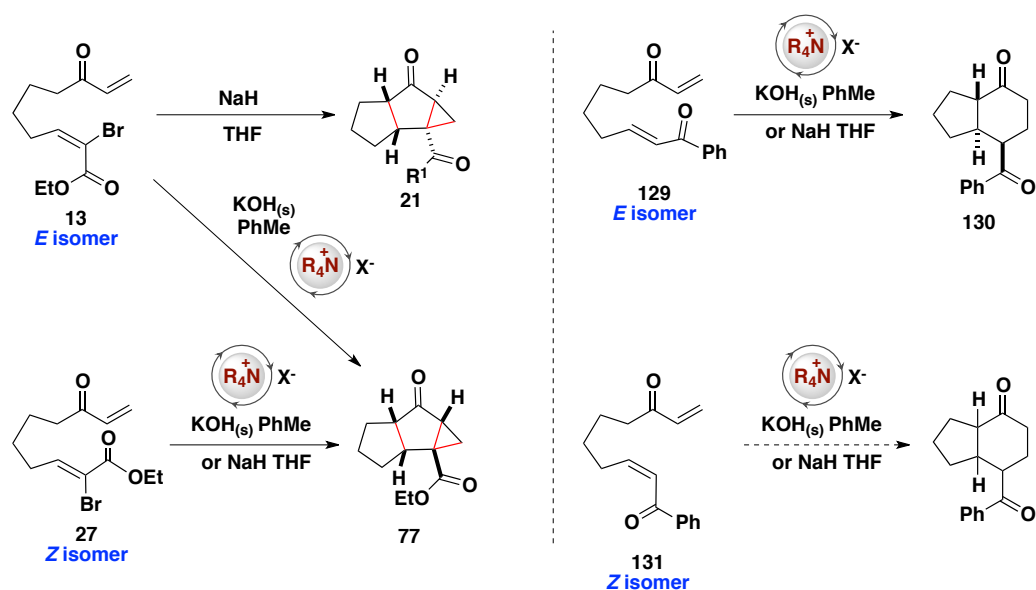
Wittig reagent **127** was synthesised in a single step from 2-bromoacetophenone, and we subsequently used this to install the phenyl ketone functional group, forming **128** as a single double bond isomer. The alcohol underwent oxidation to the corresponding ketone in quantitative yield to afford the starting material for the cyclisation reaction.



Scheme 74: Cyclisation of phenyl ketone **129** afforded bicycle **130** in 55% yield

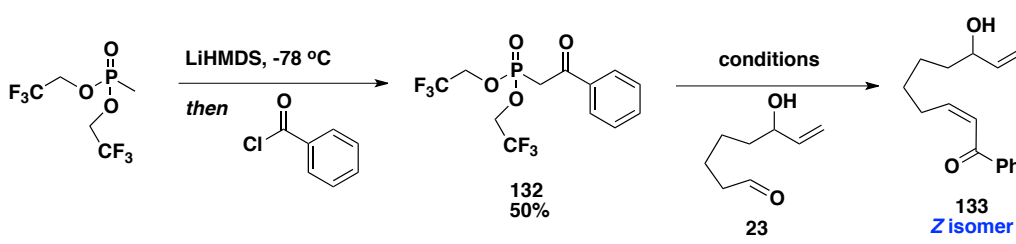
Upon subjection of this material to our standard cyclisation conditions, we were pleased to observe the product of the desired cyclisation reaction. We isolated bicycle **130** in 55% yield as a single diastereomer.

Because the *E* and *Z* isomers of the 5-5-3 precursors had formed different diastereomers under the same reaction conditions, we were interested in synthesising the *Z* isomer of the phenyl ketone and see if it would cyclise to form a different diastereomer of **130**.



Scheme 75: *E* and *Z* isomers of the bromoacrylate afforded different products under different reaction conditions. We wanted to see if a similar phenomenon would occur in the phenyl ketone system

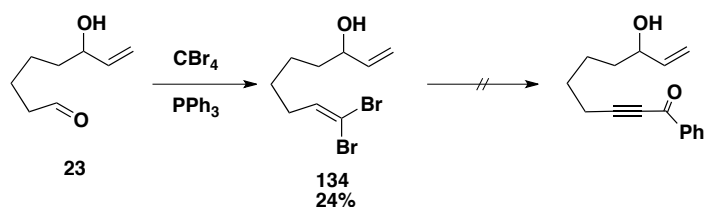
We hoped to be able to synthesise the *Z* isomer by using the Still-Gennari reagent in an analogous manner to that described previously (page 21). The Still-Gennari reagent was synthesised in a single step from commercially available starting materials, and then a number of conditions were used to try and synthesise the *Z* isomer.



Conditions	Product	<i>E</i> : <i>Z</i> ratio	Yield
NaH, THF, RT	<i>E</i> isomer	>20:1	65%
NaH, THF, -78 °C	<i>E</i> isomer	>20:1	63%
LiBr, Et ₃ N, THF, RT	<i>E</i> isomer	>20:1	56%
LiBr, Et ₃ N, THF, 0 °C	<i>E</i> isomer	>20:1	54%
K ₂ CO ₃ , 18-crown-6, PhMe, MeCN, -20 °C	<i>E</i> isomer	>20:1	61%

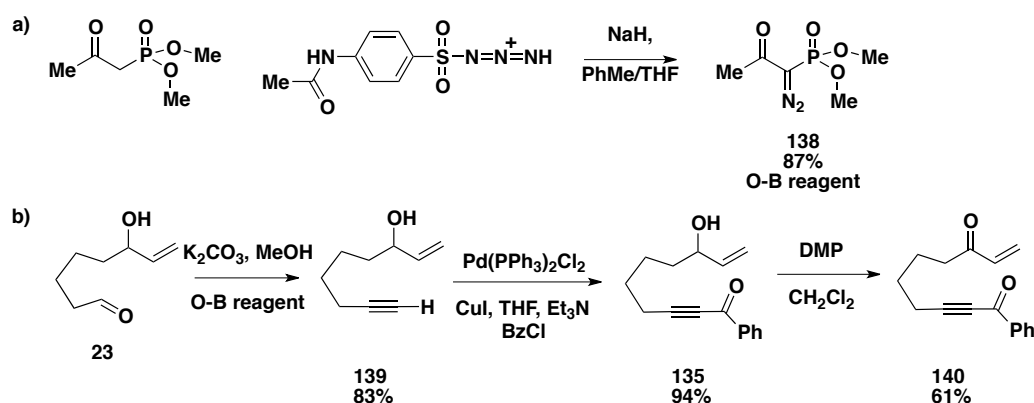
Table 14: Conditions used to try and synthesise the *Z* phenyl ketone 133

Unfortunately, under all of the conditions tried, we could only isolate the *E* isomer; even cooling the reaction mixture to cryogenic temperatures did not help favour formation of the *Z* isomer. We decided to change the route, and see if we could synthesise the alkyne and reduce it with Lindlar's catalyst to obtain the *Z* isomer. Our first attempt at synthesising the appropriate aldehyde involved a Corey-Fuchs reaction.



Scheme 76: Formation of the dibromide was successful, but we were unable to form the alkyne using *n*BuLi

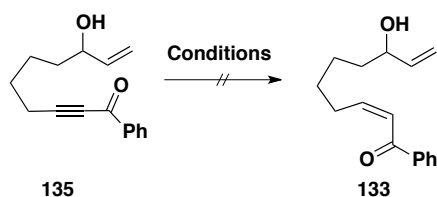
The Ramirez olefination was successful, leading to **134** in 24% yield. However, upon subjection of this dibromide to standard Corey-Fuchs conditions using *n*BuLi, the desired product was not observed. We decided to instead employ an Ohira-Bestmann (O-B) reaction to install the alkyne.



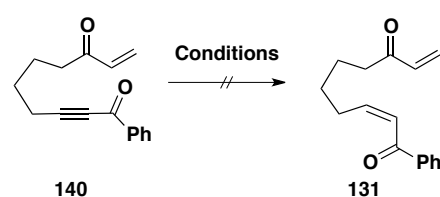
Scheme 77: a) Formation of the Ohira-Bestmann reagent, b) Use of the Ohira-Bestmann reagent to form the desired alkyne, which was then converted into the desired phenyl ketone substituted alkyne

The Ohira-Bestmann reagent was synthesised in 87% yield, and used to install the terminal olefin of **139**. A Sonogashira reaction then successfully installed the phenyl ketone portion, to afford **135** in 78% yield over two steps. We were also able to oxidise alcohol **135** to the corresponding ketone **140**.

Alcohol reaction:



Ketone reaction:



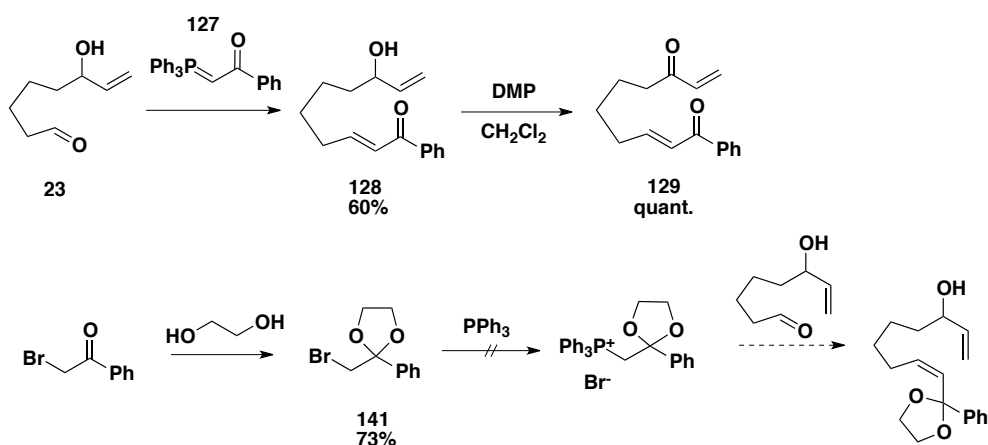
Conditions	Alcohol Reaction (135)	Ketone Reaction (140)
Lindlar, quinoline, H ₂ (2 balloons)	SM	SM
Lindlar, quinoline, H ₂ (5 balloons)	SM	SM
Pd/C/H ₂ , quinoline (2 balloons)	-	Fully reduced
Lindlar, H ₂ (2 balloons)	-	Fully reduced
Pd/BaSO ₄ , H ₂ (2 balloons)	-	Reduced alkene, alkyne untouched
Pd(PPh ₃) ₄ , SnBu ₃ H then TFA	<i>E</i> isomer	Reduced alkene, alkyne untouched
Pd ₂ (dba) ₃ , dppb, dioxane, formic acid	Complex mixture	-

Table 15: Conditions used to try and synthesise the *Z* isomer **133** or **131**

Unfortunately, we were not able to synthesise the *Z* isomer under any of the conditions tried. Attempted reduction with Lindlar's catalyst resulted in re-isolation of the starting material, even after increasing the pressure of H₂. Removing the quinoline resulted in over reduction, so we were convinced that the catalyst was active. Changing the catalyst to Pd/C also resulted in over reduction. Under homogeneous conditions using SnBu₃H and Pd(PPh₃)₄ we observed the *E* isomer for the alcohol

series, and interestingly, when the ketone was used as the substrate, the alkene was selectively reduced.

We then decided to change tactics and set out to synthesise the phenyl ketone using a Wittig reaction. We knew that stabilised ylids are usually selective for the *E* isomer, so we hoped that if we synthesised an unstabilised ylid, we may be able to bias the reaction enough to form the *Z* isomer.

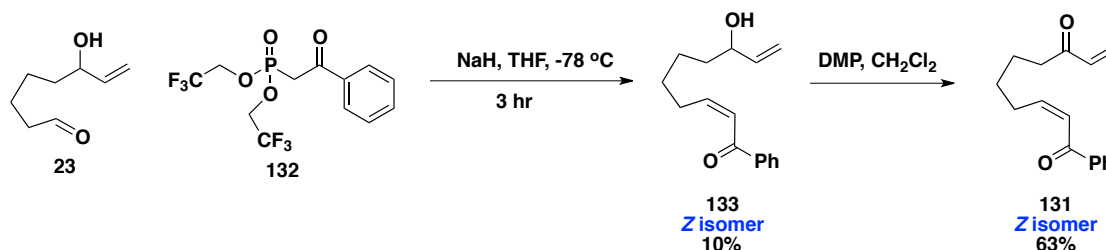


Scheme 78: Attempted synthesis of an unstabilised ylid

It was possible to synthesise the protected ketone **141** in 73% yield, but unfortunately we could not form the unstabilised ylid necessary to attempt the Wittig reaction. With hindsight this is perhaps not so surprising since triphenyl phosphite is required to carry out a sterically challenging S_N2 reaction.

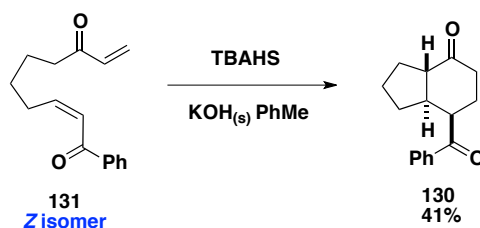
We then decided to revisit the Still-Gennari reaction to see if we could investigate why we were not producing any of the *Z* isomer. By carefully monitoring the NaH/THF reaction at $-78\text{ }^{\circ}\text{C}$, we detected small quantities of the *Z* alkene, which then isomerised

the *E* alkene over time. We therefore decided to stop the reaction after three hours, where the ratio of SM:*E*:*Z* was 1:2:1, and we managed to isolate the *Z* isomer **133** in 10% yield after purification.



Scheme 79: Still-Gennari reaction formed the *Z* isomer in 10% yield

Cis alkene **133** was successfully oxidised to the corresponding ketone **131** in 63% yield. We were pleased to see that no isomerisation of the cis double bond took place under our oxidative conditions. With **131** in hand, we attempted the cyclisation to see if the *Z* isomer would form a different diastereomer to the *E* isomer under the cyclisation conditions.



Scheme 80: Cyclisation of the *Z* isomer under phase-transfer conditions

Submitting the *Z* isomer **131** to the reaction conditions afforded mainly the *E* isomer. After 2 hr, there was no *Z* isomer **131** left in the reaction mixture, but we did see the appearance of the *E* isomer **129** by TLC. After the starting material had been fully consumed, we were only able to identify one product, the same diastereomer that we

had observed when we cyclised the *E* isomer **129**. The reaction was not spot to spot, and we think that the *Z* isomer **131** may have been cyclising to form another diastereomer, but we were unable to unambiguously identify this product. Ultimately, it appeared that the competing pathway of isomerisation to the *E* isomer **129** was favoured.

4.1.3 Increasing the Chain Length

We wanted to investigate whether it was possible to increase the chain length of the system, and see if the reaction would cyclise to form 6-5-3 or 7-5-3 ring systems.

Fortunately, we had already developed a synthetic route to the desired starting materials **57** and **58** in our work on transannular electrocyclicisation (page 31).

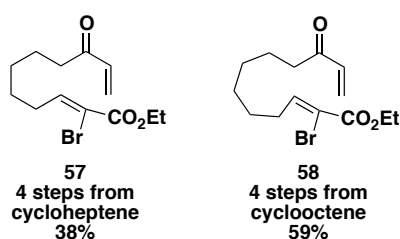
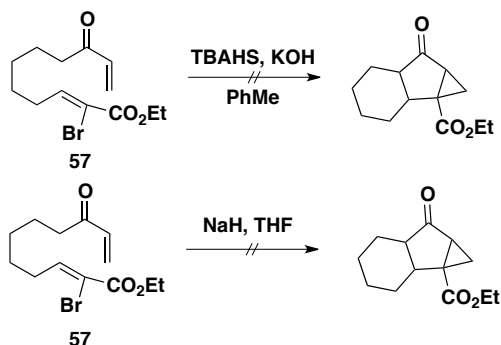


Figure 17: The two cyclisation precursors **57** and **58** were synthesised in good yield over four steps

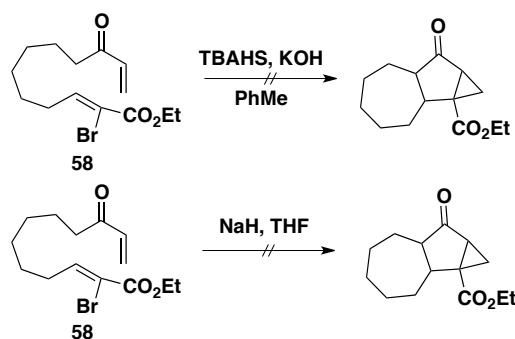
Initially the smaller chain length, **57** was examined using the two different cyclisation conditions.



Scheme 81: Attempted cyclisation of **57** under both phase-transfer and NaH conditions

Under both sets of reaction conditions, the starting material was consumed. The ^1H NMR of the crude and columned material showed appearance of new product-like peaks, but the spectra were complex and we were not able to assign the compound fully. However, the products obtained did have a mass that corresponded to the cyclised product. We tentatively speculate that this reaction gave an inseparable mixture of diastereomers. Perhaps this is not so surprising, as there is much more flexibility in a 6-5 system, where both the trans and cis ring junction geometries can form, whereas in a 5-5 system, the cis ring junction is strongly favoured.

We thought that a system with one more carbon in the backbone may cyclise to form a single diastereomer, as a trans ring junction is favoured in a 7-5 fused ring more than in a 6-5 fused system.²



Scheme 82: Attempted cyclisation of **58** under both phase-transfer and NaH conditions

Unfortunately, in both cases we did not observe the desired product. The mass recovery after the work up was only 60%, and we thought that this might be because some of the starting material had polymerised under the reaction conditions.

These results fit well with the literature relating to the stability of 6-5 and 7-5 fused ring systems. In 2005, Gordon and Hudlicky calculated the difference in energies for cis and trans 5-5, 6-5 and 7-5 fused ring systems.² From this, the thermodynamic ratio of cis/trans isomers was calculated for each ring system (Figure 18).

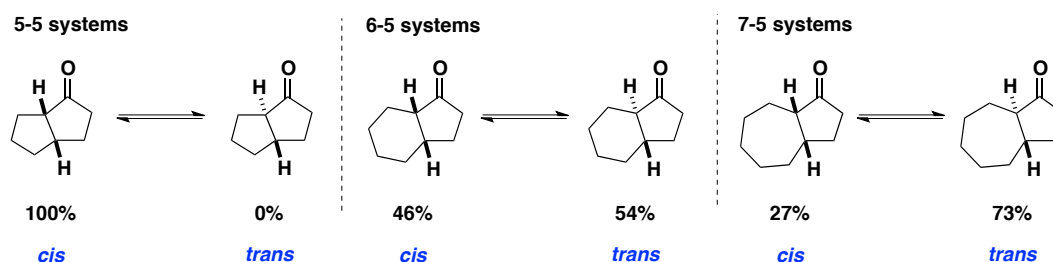


Figure 18: Thermodynamic ratio of cis/trans isomers calculated for three fused ring systems calculated by Gordon and Hudlicky

For the 5-5 fused system, the abundance of the trans system is 0%, which explains why in the example forming the 5-5-3 fused ring system, we only see the formation of the cis 5-5 fused ring system. As you increase the ring size from 5 to 6 to 7, the percentage abundance of the trans isomer increases, but never becomes exclusively favoured. This could explain why we do not see clean conversion to a single isomer for the larger chain lengths. We decided to concentrate our efforts on the synthesis of derivatives maintaining the chain same length to avoid the formation of other diastereomers.

4.1.4 Substituting on the Alkene Acceptor

We then returned to our successful 5-5-3 reaction and investigated whether the cyclisation would tolerate substitution in the α - or β - position of the enone.

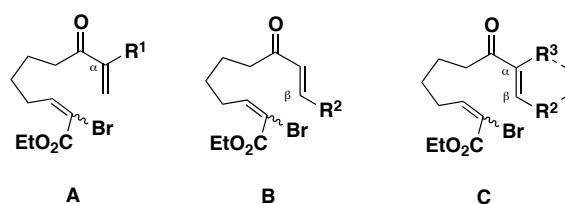
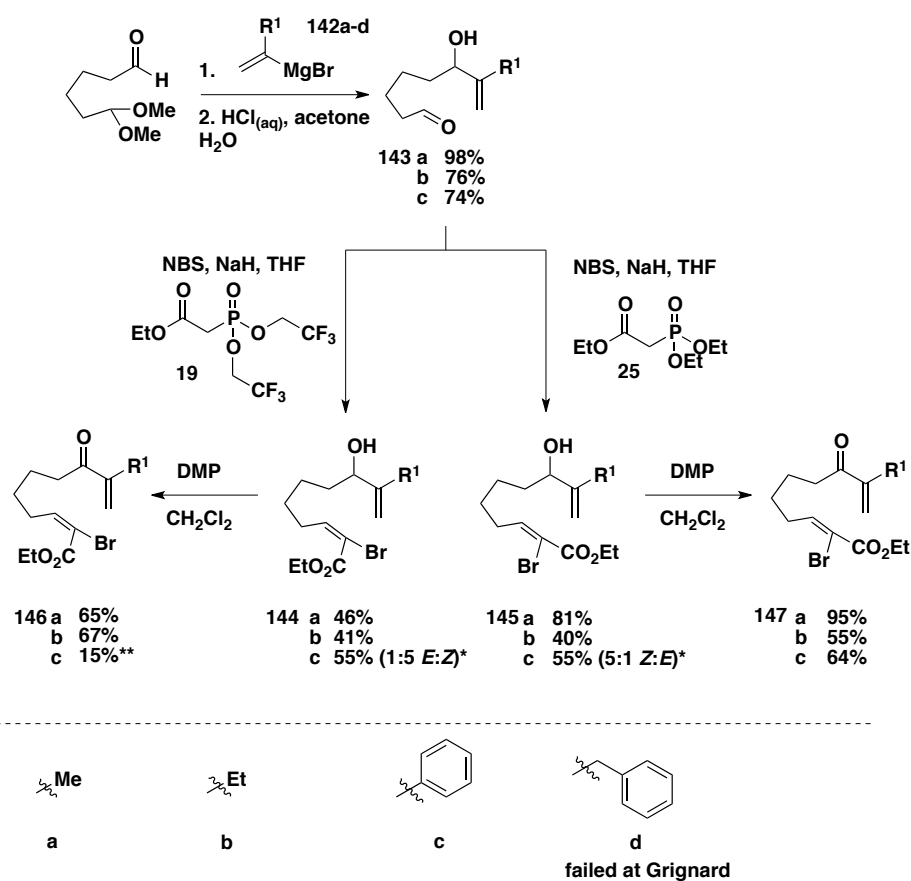


Figure 19: Three different scaffolds that we wanted to synthesise

We initially targeted α -substituted starting materials (e.g., A in Figure 19). Starting from aldehyde-acetal **22**, we used a number of Grignard reagents to synthesise a small library of compounds. The Grignard reagents were either commercially available or made *in situ* and used immediately.



* HWE reaction was performed on this substrate to afford an inseparable 1:5 mixture of *E:Z* isomers. This was taken onto the oxidation, where the isomers were separated. No SG reaction was performed on this substrate

**Yield is low due to it being based on the mass of the 1:5 mixture of *E:Z* isomers in the starting material, and this is the clean isolated *E* isomer

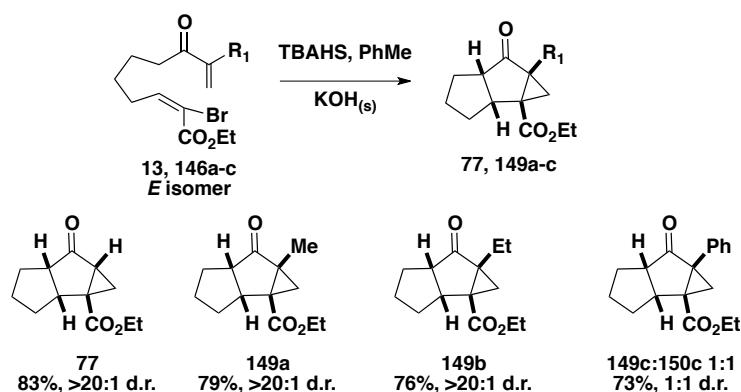
Scheme 83: Synthesis of α -substituted starting materials

The Grignard additions worked well, and the acetal products were deprotected to afford the corresponding aldehydes. We synthesised (3-phenylprop-1-en-2-yl) magnesium bromide (**142d**), but unfortunately this reagent did not form the substituted alkene. To confirm that we had synthesised the correct Grignard reagent, we conducted a test reaction with benzaldehyde. The corresponding secondary alcohol was observed in 90% yield. We chose to continue with the three substrates that we had synthesised and take them through the rest of the synthesis.

The intermediate aldehydes produced from the deprotection of the acetals were then either reacted under HWE or SG conditions to afford the *Z* or *E* alkenes respectively. The HWE reaction afforded a mixture of *E* and *Z* isomers, but they were fully separable by column chromatography either at this stage of the synthesis or after the subsequent oxidation. The SG reaction was much more selective for the *E* isomer, with the reactions affording at least 10:1 *E*:*Z* ratio in all cases. The alcohols synthesised under these conditions were then be oxidised to the ketones to afford the cyclisation precursors.^f

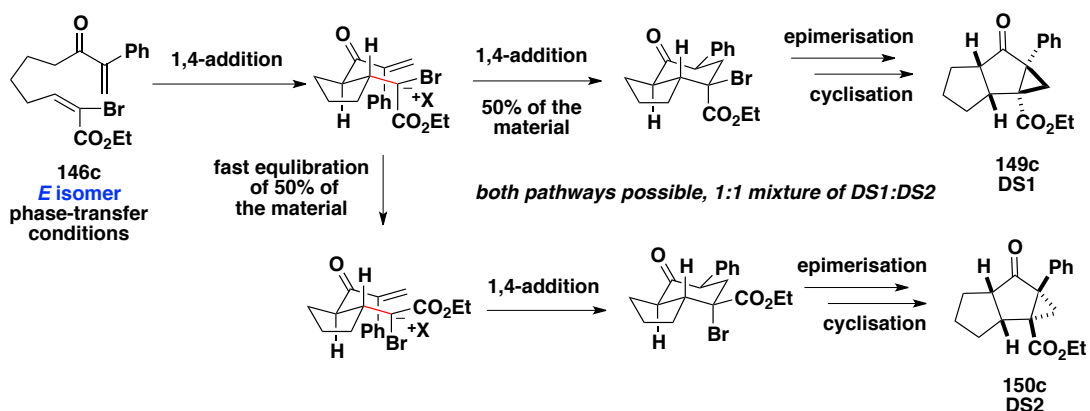
With a small library of α -substituted cyclisation precursors in hand, we attempted the cyclisation of the *E* isomers under phase-transfer conditions.

^f For the phenyl substituent **145c**, it was not necessary to perform the SG reaction, as we were able to isolate sufficient quantities of the *E* isomer from the separation of the 5:1 *Z*:*E* mixture after oxidation of the HWE reaction



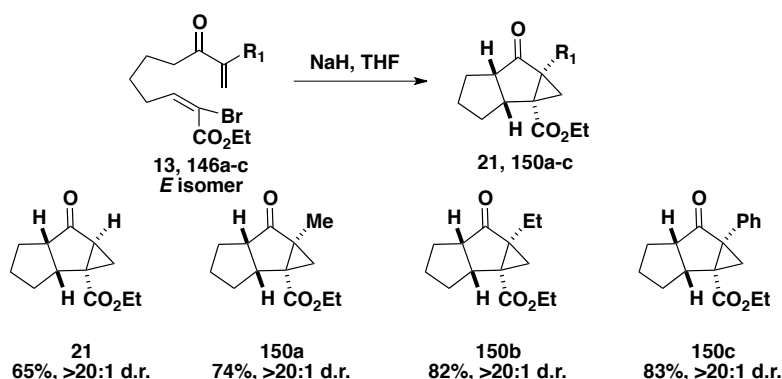
Scheme 84: Cyclisation of *E* isomers under phase-transfer conditions

All of these substrates cleanly cyclised under our optimised conditions leading to the products in high yields. In all but one case, the same diastereomer as was observed for the unsubstituted system, **77**. Interestingly, phenyl substituted **146c** cyclised to give a 1:1 mixture of diastereomers. Perhaps in this case, the slight activating effect of the phenyl group increases the rate of the second 1,4-addition reaction, such that it becomes able to compete with bond rotation.



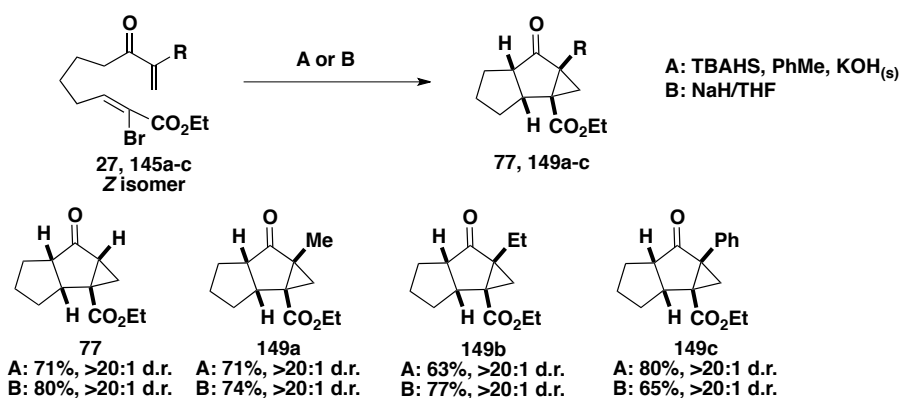
Scheme 85: Possible mechanism to explain the mixture of diastereomers obtained for the phenyl ketone system

We then submitted the *E* isomers to the NaH conditions, to see whether we would observe the same diastereodivergence as we had seen previously.



Scheme 86: Cyclisation of *E* isomers under NaH conditions

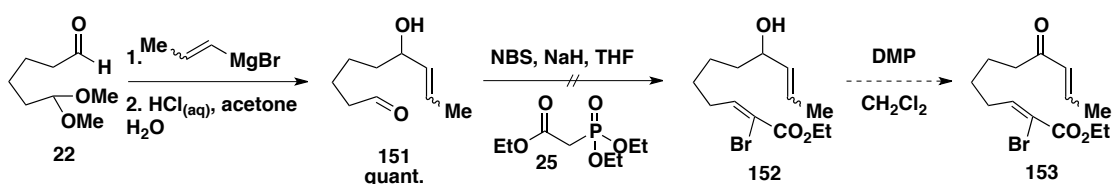
All of the reactions proceeded smoothly, affording a single diastereomer in high yield. From careful nOe analysis, we concluded that this product was the same diastereomer as the one that had been observed in the unsubstituted series. Finally, we submitted the *Z* isomer to the two different cyclisation conditions.



Scheme 87: Cyclisation of the *Z* isomers under both phase-transfer and NaH conditions

As with the unsubstituted case, the Z isomers cyclised to form the same diastereomer irrespective of the reaction conditions.

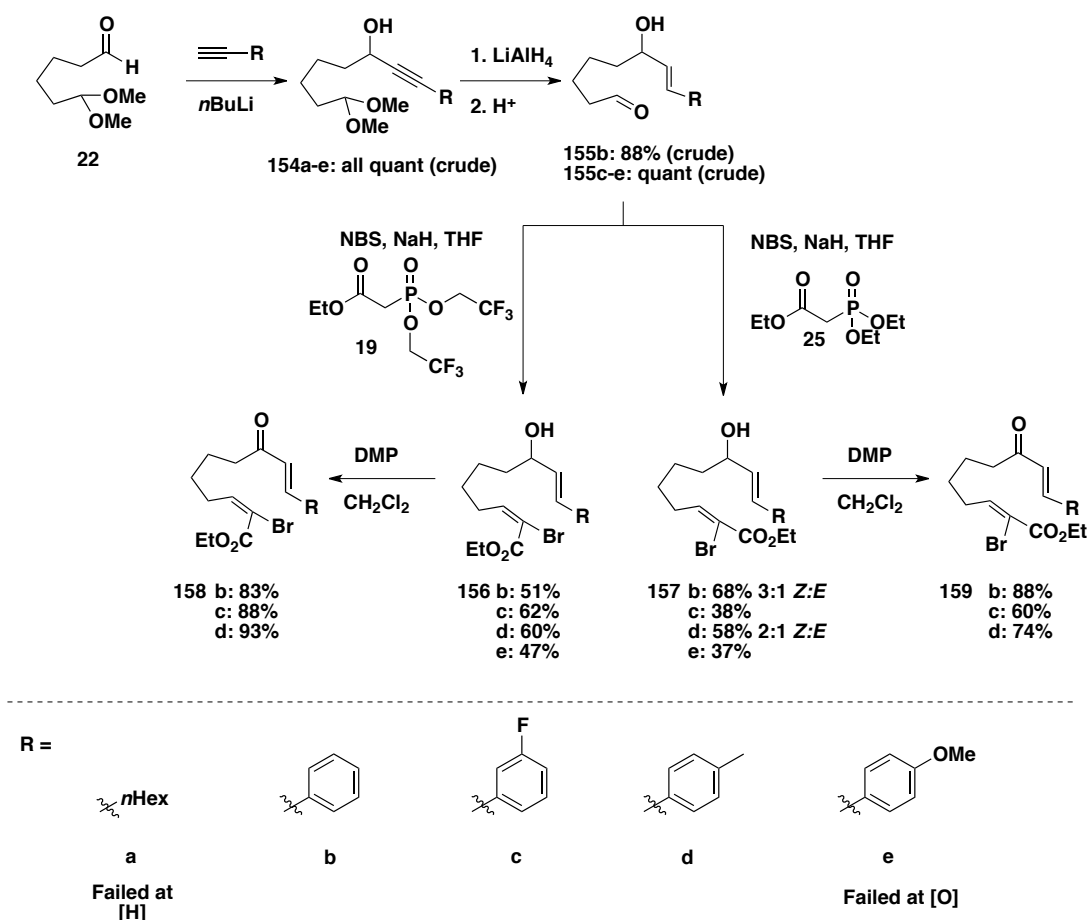
We then turned our attention to the synthesis of β -substituted compounds. Our initial target was the simple methyl substituted cyclisation precursor **153**.



Scheme 88: Attempted synthesis of the methyl substituted alkene

Utilising commercially available 1-propenyl magnesium bromide solution, the first step worked well, affording a 1:1 mixture of double bond isomers, which we did not attempt to separate at this stage due to the instability of the aldehyde. Unfortunately, the HWE step was not successful, affording a complicated mixture of isomeric compounds, which could not be separated from each other.

As an alternative strategy, we decided to add commercially available acetylenes to aldehyde **22** and then reduce the alkyne to the corresponding β -substituted alkene with LiAlH_4 . We then carried out the usual deprotection-HWE/SG-oxidation sequence to afford the cyclisation precursors.



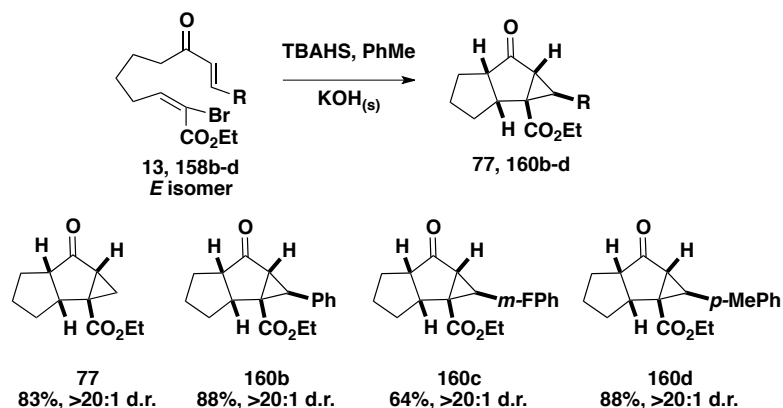
Scheme 89: Synthesis of β -substituted starting materials

This sequence of steps was successful for the synthesis of the phenyl, 3-F-phenyl and 4-Me-phenyl substituents, where both *E* and *Z* isomers of the bromo-olefin were separately prepared.

In two cases, we were unable to access the desired substrate: an aliphatic hexyl chain and 4-methoxyphenyl group. We were unable to reduce hexyl substituted **154a** with LiAlH_4 , recovering only starting material, even after extended reaction times and higher temperatures. The reduction of aliphatic alkynes has been shown to be challenging by other members of the group. The 4-OMe phenyl substituent (**158e** and

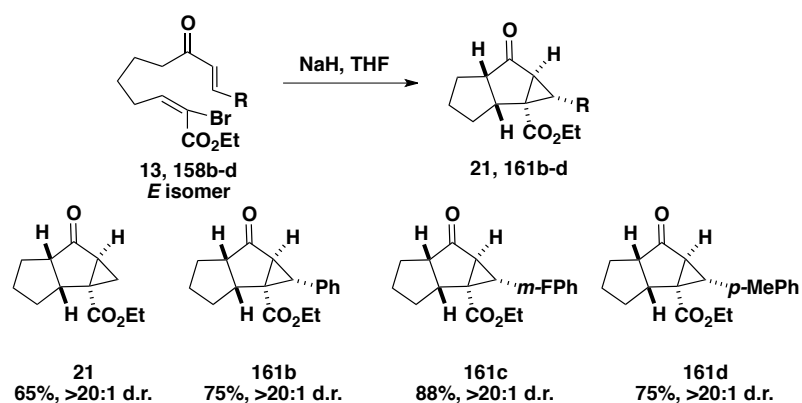
159e) also proved difficult to synthesise. We were able to make alcohols **156e** and **157e**, but attempts to oxidise these compounds to the ketone led to decomposition.

With three new substrates in hand, we subjected them to the cyclisation conditions. We started with the *E* isomer under phase-transfer conditions.



Scheme 90: Cyclisation of the *E* isomer under phase-transfer conditions

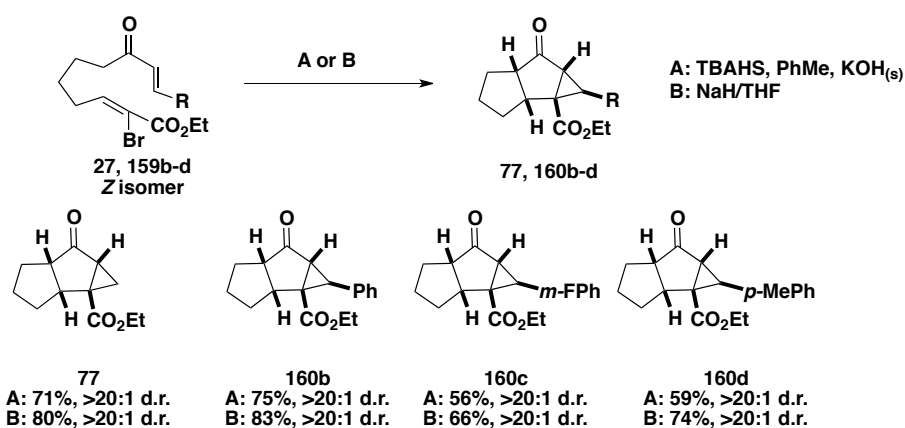
Under phase-transfer conditions, all three substrates cyclised smoothly in good yields. As we had seen with the unsubstituted case, we observed complete control over the four stereogenic centres at the ring junctions. Moreover, we were pleased to find that the new stereocentre on the cyclopropane was also formed with high diastereocontrol and all three products, which contain five new contiguous stereocentres, were all formed as a single diastereomer. We then decided to submit the *E*-bromo-acrylates to the NaH/THF conditions to see if we observe the same diastereodivergence as we had seen in the unsubstituted system.



Scheme 91: Cyclisation of the *E* isomer under NaH conditions

These substrates cyclised much more slowly than those with substituents at the α position. We think that this is because the groups may be sterically hindering the final cyclisation to form the three membered ring. Nevertheless, the cyclisation proceeded in high yields, again with complete diastereocontrol.^g

Finally, we submitted the *Z* isomer to both reaction conditions.

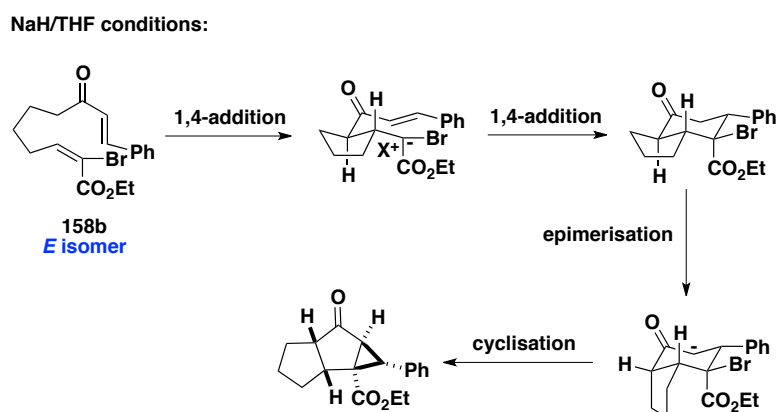


Scheme 92: Cyclisation of the *Z* isomer under both phase-transfer and NaH conditions

^g When the reaction was stopped early we observed some of the 5-6 intermediate product. Resubmitting this isolated material to the reaction conditions gave the 5-5-3 product

All three substrates cyclised to form the same diastereomer under both reaction conditions attempted. This result is analogous to the simple system with no substitution (**77**). These products were all obtained in good to excellent yields.

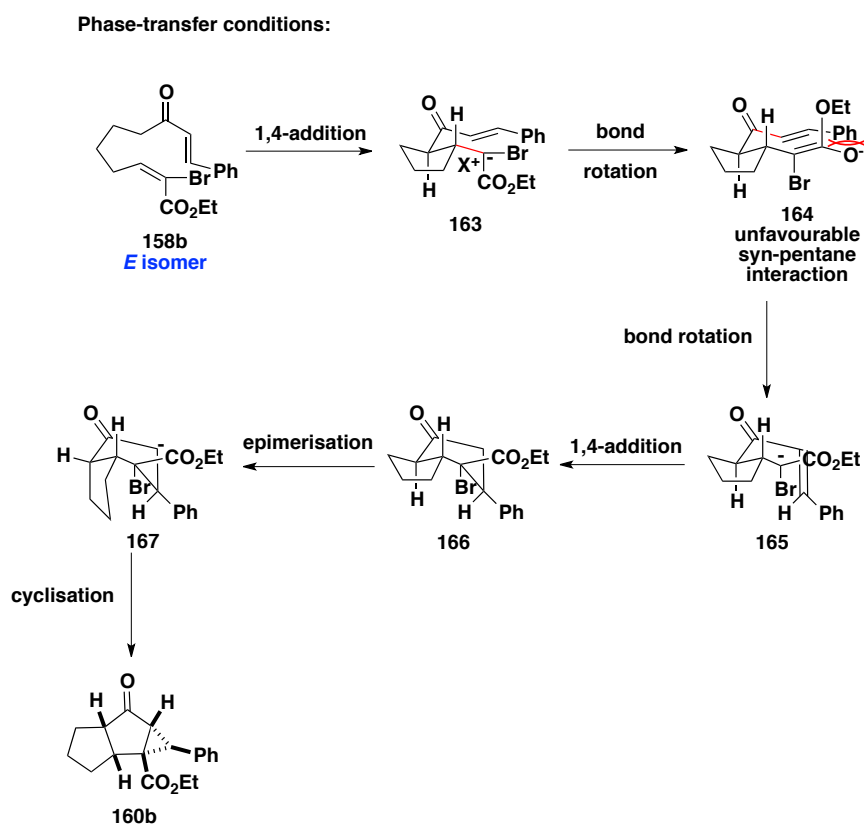
Submitting the *E* isomer **158b** to NaH/THF conditions results in the formation of product **161b**. We speculate that the mechanism goes through a chair-like configuration, where the phenyl group is equatorial after the first 1,4-addition. The product of the second 1,4-addition retains the equatorial position for the bulky phenyl group, and epimerisation of the proton α - to the carbonyl affords the 5-6 *cis* ring geometry, which can then undergo an intramolecular bromide displacement to form the product.



Scheme 93: Possible mechanism for the cyclisation of the *E* isomer **158b** under NaH/THF conditions

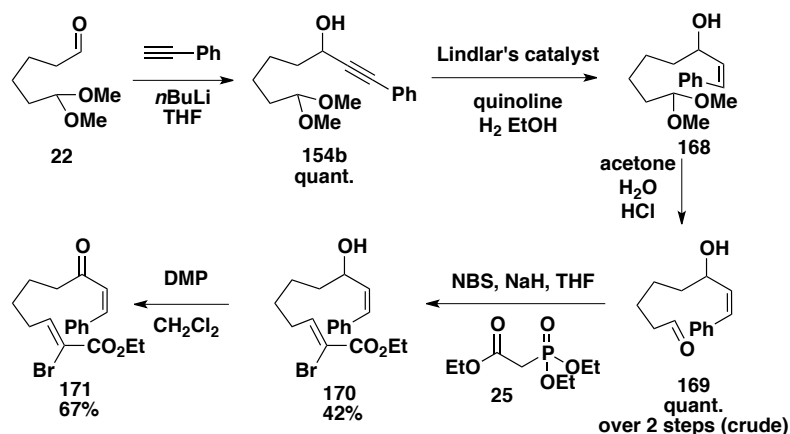
Interestingly, in the case of the phase-transfer cyclisation, the stereochemistry of the apical position of the cyclopropane has the opposite configuration to **161b** (relative to the stereogenic centres at the 5,5- ring junction).

We speculate that the product of the first 1,4-addition and bond rotation takes place as seen in the unsubstituted case (page 59, Scheme 53), but that now in intermediate **164**, there is an unfavourable syn-pentane interaction. Bond rotation about the highlighted bond alleviates this steric clash, resulting in a boat-like configuration **165**. The second 1,4-addition then produces **166** where the bulky phenyl group is pseudo-equatorial. Epimerisation to the cis 5-5-ring junction, followed by intramolecular bromide displacement would form **160b**.



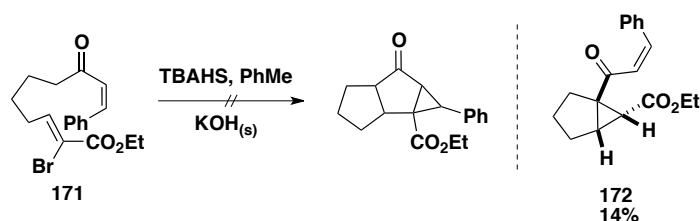
Scheme 94: Possible mechanism for the cyclisation of the *E* isomer under phase-transfer conditions

We had investigated the scope of the reaction using a trans alkene, so we were interested to see what diastereoisomer we could obtain from the cyclisation of a cis alkene.



Scheme 95: Synthesis of the cis alkene, achieved by submitting the alkyne to Lindlar's catalyst

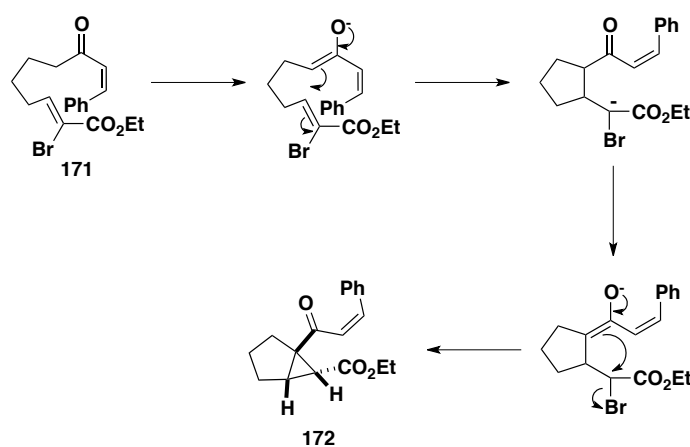
Fortunately, we were able to obtain the cis alkene in excellent yield by reduction of **154b** with Lindlar's catalyst. This material was taken through the remainder of the synthesis without any isomerisation of the cis double bond. With the starting material in hand, we attempted the cyclisation under phase-transfer conditions.



Scheme 96: Cyclisation of the cis alkene afforded a 5-3 fused ring system

Surprisingly, the cyclisation did not form the 5-5-3 fused ring system, with the main product of the reaction being the 5-3 fused system **172** depicted in Scheme 96. We

postulate that the *cis* alkene was too hindered for the second 1,4-addition to occur, so a proton transfer, followed by intramolecular displacement can occur to form **172**.

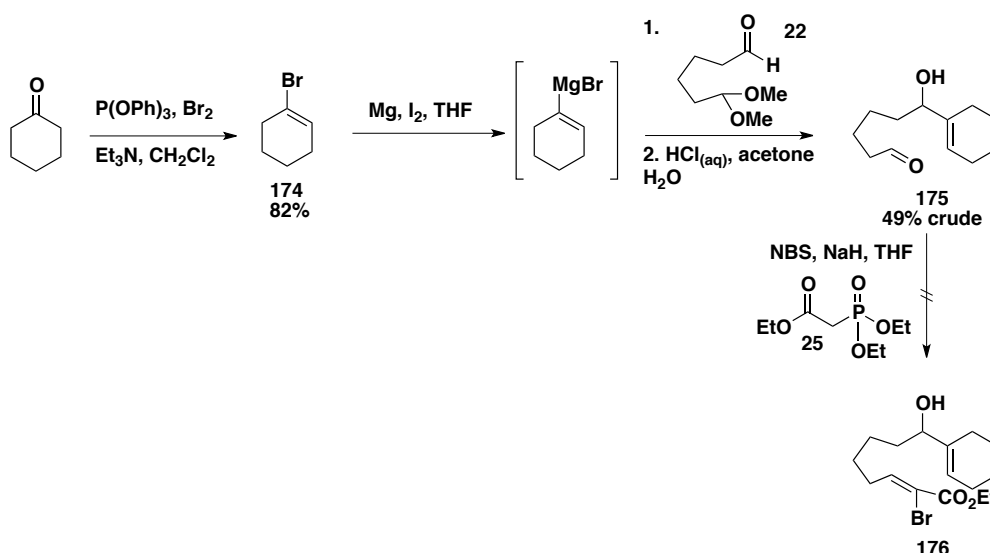


Scheme 97: Possible mechanism for the formation of the 5-3 fused ring system **172**

Whilst this was not the product we were expecting, **172** was formed as a single diastereomer and future work will probe the efficiency of this alternative cyclisation reaction.

We were also interested in substrates containing a cyclic alkene, such as **C** in Figure 19.

Firstly, we synthesised bromocyclohexene **174** using a known literature procedure.³



Scheme 98: Attempted synthesis of cyclic alkene **176**

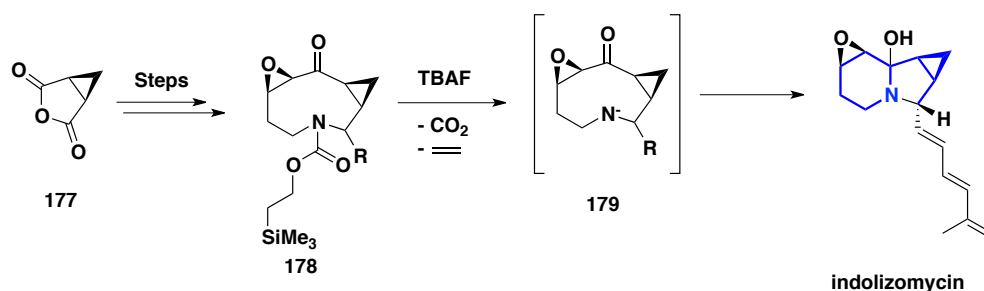
With **174** in hand, we formed the Grignard reagent and reacted it with aldehyde **22** and deprotected the acetal to form aldehyde **175**. With aldehyde **175** in hand, we attempted the HWE reaction. Unfortunately, we were unable to isolate any of the desired product.^h

4.1.5 Adding Heteroatoms into the Backbone

We aimed to increase the scope of our reaction by introducing heteroatoms into the backbone of the simple system. We thought that our method of synthesising fused rings could be expanded to build up the 6-5-3 fused ring system of indolizomycin.

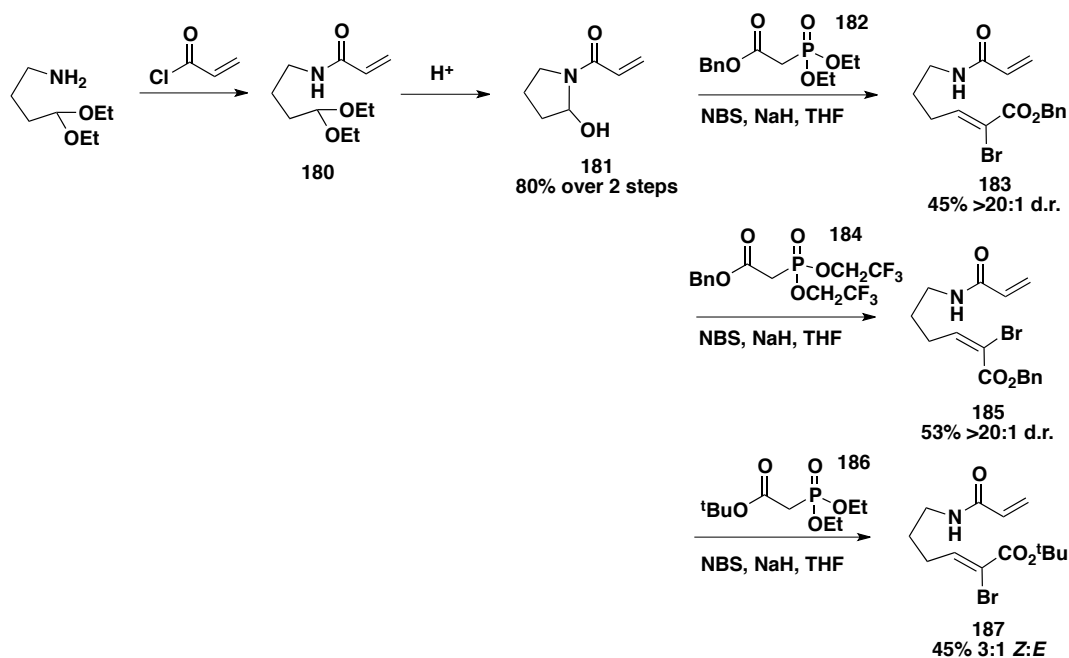
Indolizomycin was first synthesised racemically by Danishefsky in 1993.⁴ Danishefsky started with an anhydride **177**, which was converted to the *N*-protected macrocycle **178**. Removal of the *N*-protecting group allowed the resulting azininone to cyclise to the natural product.

^h The reaction was very messy, and after columnning, we isolated three separate compounds, and none of them resembled the desired product or showed the product in the mass spec



Scheme 99: Danishefsky's synthesis of indolizomycin

Inspired by this synthesis, we set out to synthesise an aza-5-5-3 core. We found that the starting materials could be easily synthesised in three steps from commercially available starting materials by amide formation followed by deprotection. The resulting aldehyde exclusively formed the hemiaminol **181**, but we found that this compound could be reacted with Still-Gennari or Horner-Wadsworth-Emmons reagents to form cyclisation precursors **183**, **185** and **187**.



Scheme 100: Synthesis of three starting materials with an amide in the backbone

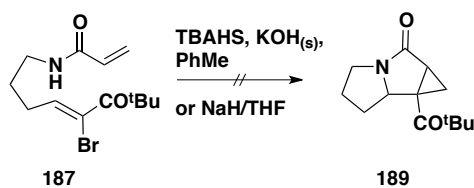
We submitted the benzyl ester starting material **183** to phase-transfer conditions (TBAHS, KOH_(s), PhMe). After the work up, we noticed that there was a loss of mass, but the ¹H NMR of the crude mixture looked promising, and a 2D TLC showed that the product was not degrading on silica. However, after columnning the crude mixture, we could not isolate any product. A small screen of reaction conditions did not lead to any improvement, either resulting in decomposition or low mass recovery following chromatography.



Conditions	Purification Method	Result
TBAHS, KOH _(s) , PhMe	Work up and column	No product isolated
TBAHS, KOH _(s) , PhMe	No work up, column	No product isolated
TBAHS, KOH _(s) , PhMe	Work up, Et ₃ N doped column	No product isolated
NaH/THF	Work up and column	Complex mixutre
KOtBu/THF	Work up and column	Complex mixture
Et ₃ N/CHCl ₃	Work up and column	No product isolated

Table 16: Attempted cyclisation and purification conditions for amide substrate **183**

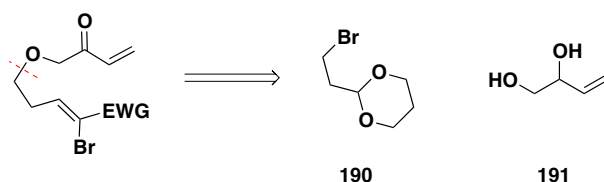
Similarly, attempting the cyclisation on the *tert*-butyl ester substrate afforded no product.



Scheme 101: Attempting the cyclisation of the *tert*-butyl ester substrate **187**

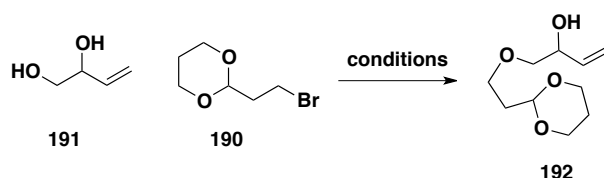
In Danishefsky's total synthesis of indolizomycin it was mentioned that indolizomycin was unstable, and his synthesis delayed the installation of the 6-5-3 ring system until a very late stage.⁴ If the product of our cyclisation is unstable, this could explain why we could not isolate **188** or **189**.

We decided to investigate adding other heteroatoms into the backbone. We thought that we could synthesise the core of the oxygen-containing starting material from two commercially available starting synthons.



Scheme 102: Retrosynthetic analysis of the substrate containing oxygen in the backbone

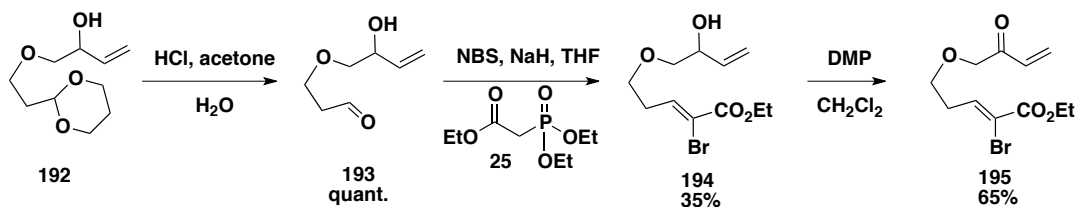
We relied on the less hindered primary alcohol reacting faster than the secondary, and evaluated several sets of conditions.



Entry	Conditions	Outcome
1	NaH, THF	Insoluble
2	NaH, THF:DMF 1:1	5% yield, soluble
3	NaH, DMF, NaI	20% yield, soluble
4	NaH, DMF, TBAI, DMPU	70% yield, soluble

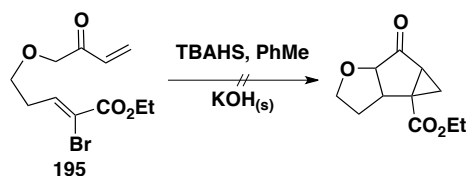
Table 17: Conditions used to alkylate diol **191**

Using NaH in THF did not afford any product as the starting material and products were insoluble. Adding some DMF solubilised the reactants, but only led to the product in 5% yield. Adding NaI and heating the reaction resulted in a slightly a higher yield. Adding TBAI and DMPU was most successful, affording the product in 70% yield.



Scheme 103: Synthesis of oxygen-containing substrate **195**

With **192** in hand, we were able to deprotect the acetal, obtaining aldehyde **193** in quantitative yield. Following HWE reaction and oxidation with DMP, we were able to obtain the desired oxygenated cyclisation precursor **193**.ⁱ



Scheme 104: Attempted cyclisation of the oxygen-containing substrate **195**

Disappointingly, cyclisation of this material did not afford any product. We think that the starting material may be unstable, leading to a mixture of products under the reaction conditions.^j

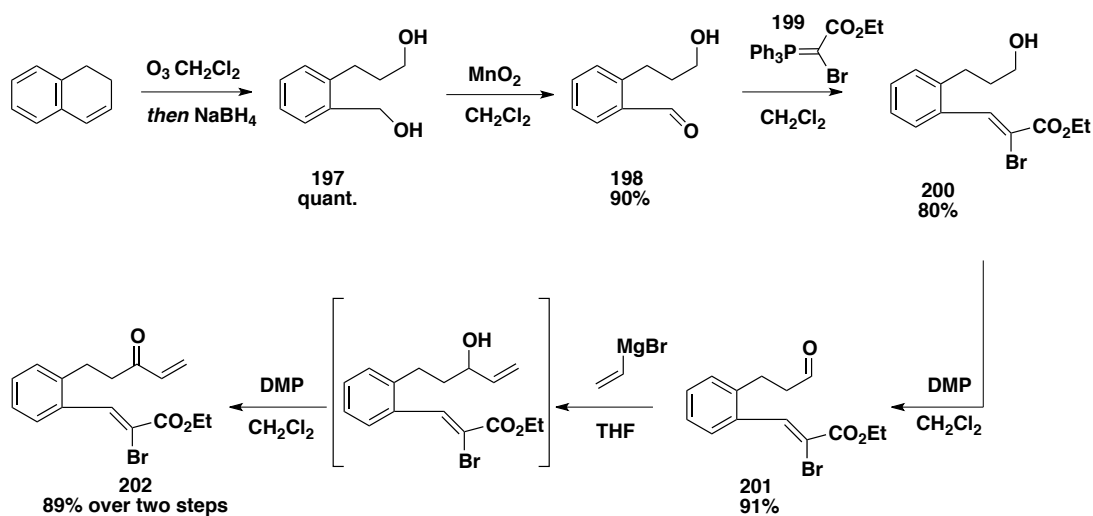
Unfortunately, the heteroatom-containing backbones appeared to be too unstable, so we decided to determine whether it would be possible to introduce an aromatic ring into the backbone.

We started by performing an ozonolysis on the 1,2 hydronaphthalene, and we quenched the reaction with sodium borohydride to afford the diol **197**. We then used MnO₂ to selectively oxidise the benzylic alcohol to the aldehyde **198**, which was then reacted with the brominated Wittig reagent **199** to afford bromo-olefin **200**. This alcohol was

ⁱ Both alcohol **194** and ketone **195** were contaminated with ~10% of an unknown impurity, which could not be identified, and could not be separated from the desired products

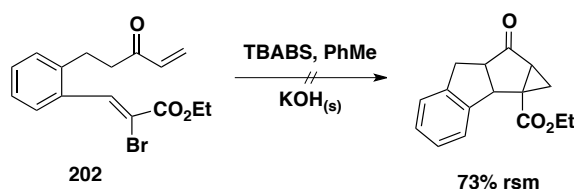
^j We noticed that the ¹H NMR of the crude material was not the same as the starting material, but it did still have some alkene peaks present, so we are confident that it is not the 5-5-3 fused product, but we could not isolate anything that we could identify

oxidised to aldehyde **201**, which was subsequently reacted with vinyl magnesium bromide and oxidised to the ketone to afford cyclisation precursor **202**.



Scheme 105: Synthesis of substrate **202** with a phenyl group in the backbone

With the cyclisation precursor in hand, we attempted the cyclisation.

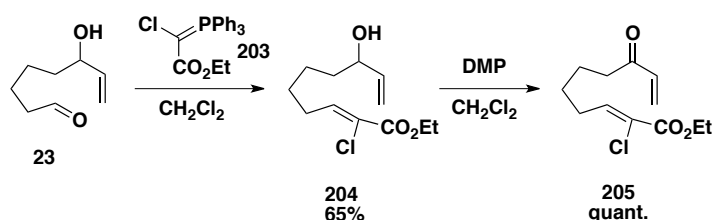


Scheme 106: Attempted cyclisation of substrate **202** containing a phenyl group in the backbone

Under the reaction conditions the starting material did not react. We re-isolated the starting material after stirring for 5 days at RT, in 73% yield. The energy barrier for cyclisation in this case must be too high to allow any reaction.

4.1.6 Changing the Acceptor

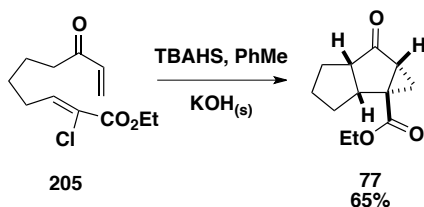
We were interested to see whether chlorinated alkenes were also viable substrates for the cyclisation reaction.



Scheme 107: Synthesis of the chlorinated substrate **205**

The Wittig reaction proceeded smoothly, affording **204** as a single geometric isomer. Subsequent oxidation afforded the starting material in 65% over the two steps.^k

Submission of the starting material to phase-transfer conditions afforded the 5-5-3 fused product **77** as the same diastereomer as observed for the brominated reaction, and in a comparable yield.



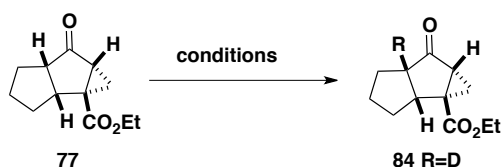
Scheme 108: Cyclisation of the chlorinated starting material **77** under phase-transfer conditions

4.1.7 Derivatisations

To demonstrate the synthetic utility of the cyclised products, we aimed to functionalise the 5-5-3 ring systems that we had synthesised. We first investigated deprotonating the α -position and then trapping it with various electrophiles.

^k Wittig reagent **203** was synthesised in one step from commercially available ethyl 2-(triphenylphosphoranylidene)acetate

We initially employed LDA or KHMDS as a base and then added MeI or allyl bromide as reactive alkylating agents. In all cases we observed only recovered starting material. To test whether deprotonation or alkylation was the problem, we quenched the reaction with D₂O. No deuteration was observed, which indicates that deprotonation had not taken place. Using ethoxide in deuterated ethanol led to complete deuteration indicating that the desired anion had been formed, although under analogous conditions we were unable to carry out alkylation with MeI.

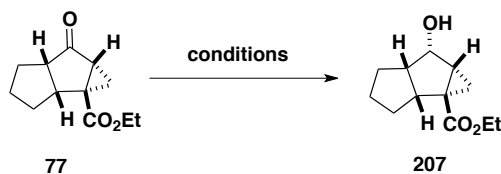


R	Conditions	Outcome
Me	LDA, THF then MeI	SM
Me	KHMDS, THF then MeI	SM
Allyl	LDA, THF then allylbromide	SM
D	LDA, THF then D ₂ O	SM
D	EtOD, EtONa then D ₂ O	R=D, 92% yield
Me	EtOH, EtONa then MeI	SM

Table 18: Conditions used to try to deprotonate and alkylate the α -position

We then wanted to see if we could reduce the ketone to the alcohol diastereoselectively. Reduction with sodium borohydride afforded a 2.5:1.0 mixture of diastereomers. Leuche modified conditions gave a slight improvement on the d.r. to

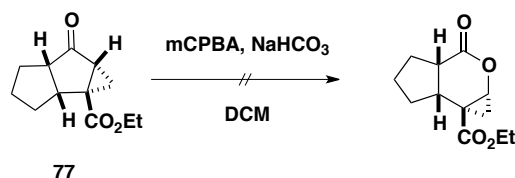
2.8:1.0. Pleasingly, utilising a bulky reducing agent, L-selectride, it was possible to reduce the ketone to a single diastereomer of the alcohol **207** in excellent yield.



Conditions	d.r.	Yield
NaBH ₄ , MeOH, RT	2.5:1.0	98%
NaBH ₄ , CeCl ₃ , MeOH, RT	2.8:1.0	94%
L-Selectride, RT	>20:1	95%

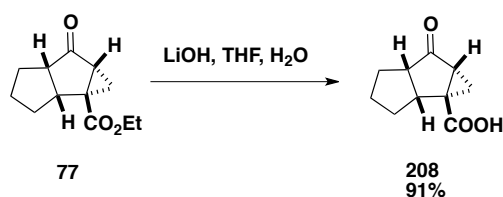
Table 19: Conditions used to reduce the ketone

We then tried to perform a Bayer-Villiger oxidation of the ketone to see if we could synthesise the ring expanded product, but unfortunately, we did not observe any of the desired product, only recovering the starting material. This is a challenging reaction, and to the best of our knowledge, has only been carried out twice on 5-3 fused ring systems.⁵



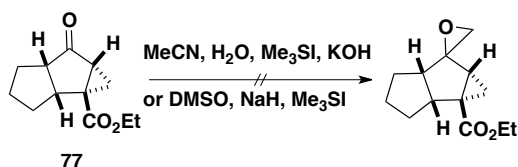
Scheme 109: Attempted Bayer-Villiger oxidation of the ketone

We saponified the ester to make the acid, which worked very well, affording the acid in 91% yield. This acid represents a useful handle for further functionalisation.



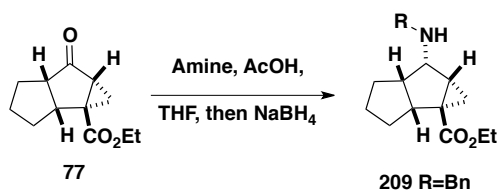
Scheme 110: Saponification of the ester

We also attempted a Corey-Chaykovsky reaction, to see whether we could form the epoxide. Two sets of reaction conditions were evaluated, but in both cases, none of the desired product was formed.



Scheme 111: Attempted Corey-Chaykovsky reaction

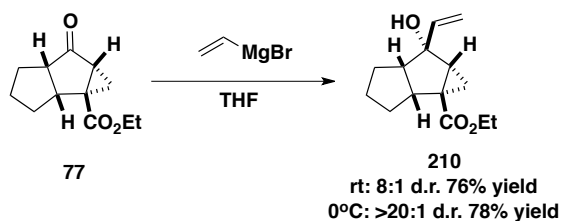
A reductive amination was then attempted. Using methylamine, we did not observe the desired imine. This may be due to the high volatility of this amine. With isopropylamine we also observed no condensation. Benzylamine proved more effective, and following reduction with NaBH_4 , the desired product was formed. In order to aid separation of the product from residual benzylamine, we carried out the reaction with 0.8 eq. of benzylamine, which led to the desired amine **209** in 75% yield (based on benzylamine) as a single diastereomer.



Amine	Outcome
Me	SM
iPr	SM
Bn	Product inseparable from BnNH ₂
Bn (0.8 eq.)	Product (R=Bn) 75% yield

Table 20: Conditions used to perform a reductive amination reaction

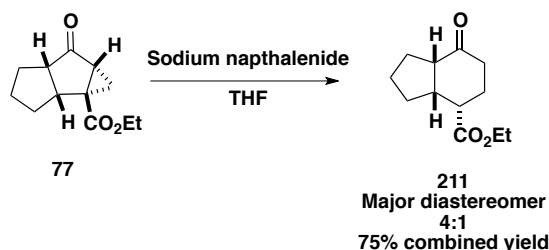
It was also possible to attack the ketone with a Grignard reagent, and cooling the temperature to 0 °C enabled isolation of the product as a single diastereomer in 78% yield.



Scheme 112: Grignard reaction on the ketone. Cooling the reaction to 0 °C afforded the product as a single diastereomer

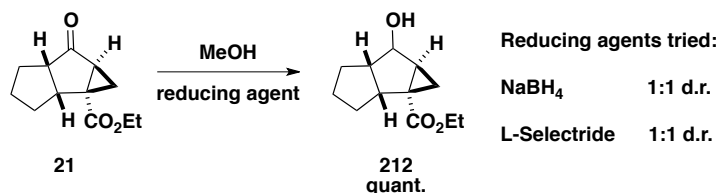
We also wanted to see if we could open the three membered ring to allow access to the 5-6 fused ring system. We therefore synthesised sodium naphthalenide *in situ* and

reacted it immediately with the 5-5-3 starting material. We were pleased to be able to form the 5-6 cis fused ring system in a 4:1 d.r. and in 75% yield.¹



Scheme 113: Formation of the 5-6 fused ring system by reduction with sodium naphthalenide

Finally, we investigated whether the other diastereomer of the product would be able to undergo derivatisations with similar levels of diastereoselectivity.



Scheme 114: Reduction of 5-5-3 fused ring system **21** under optimised reduction conditions of 5-5-3 fused ring system **77**

Under the optimised conditions from the reduction of the other diastereomer (L-selectride, MeOH), the reaction afforded a 1:1 mixture of diastereomers. This is most likely down to the shape of the starting material. This diastereomer is “s” shaped, whereas the other diastereomer is concave, which gives a face that is more vulnerable to attack by the nucleophile.

¹ It was not possible to identify the relative stereochemistry of the minor diastereomer as the key ¹H peaks we coincident in all NMR solvents attempted

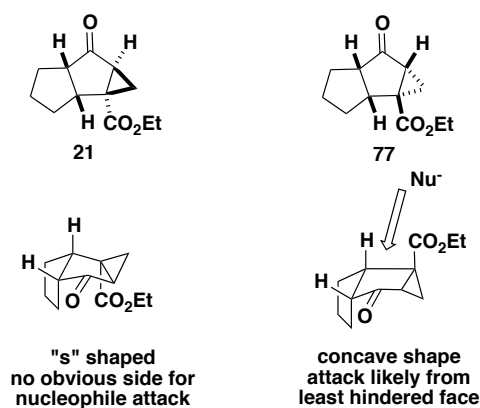


Figure 20: Possible explanation for the diastereoselectivity observed for the nucleophilic attack onto 5-5-3 ring system 77

In summary, we have demonstrated that it is possible to derivatise the 5-5-3 products. The diastereoselectivity of the attack by nucleophiles is dependant on the shape of the compound, with the concave diastereomer affording higher levels of diastereoselectivities than the "s" shaped one.

4.2 References

- ¹ A. R. Matlin and W. C. Agosta, *J. Chem. Soc. Perkin Trans. I*, **1987**, 365
- ² H. L. Gordon, S. Freeman and T. Hudlicky, *Synlett*, **2005**, 2911
- ³ F. Zhan and G. Liang, *Angew. Chem. Int. Ed.*, **2013**, 52, 1266
- ⁴ G. Kim, M. Y. Chu-Moyer, S. J. Danishefsky and G. K. Schulte, *J. Am. Chem. Soc.*, **1993**, 115, 30
- ⁵ (a) R. Gniłka and C. Wawrzeńczyk, *Aust. J. Chem.*, **2013**, 66, 1399 (b) P. A. Parziale and J. A. Berson, *J. Am. Chem. Soc.*, **1991**, 113, 4595

5. Enantioselective Cyclisation Reactions

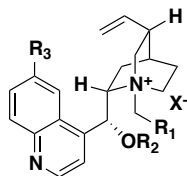
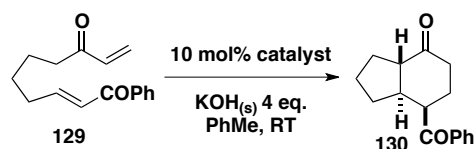
5.1 Concept and Aims

As discussed previously, phase transfer catalysis constitutes an attractive method to control the asymmetry of bond forming processes. We hoped that by employing a chiral quaternary ammonium salt we might be able to control the absolute stereochemistry of the transformations discussed in Chapter 4.

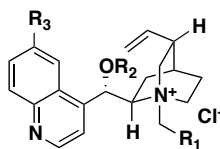
5.2 Results and Discussion

5.2.1 Reaction Optimisation on Phenyl Ketone System

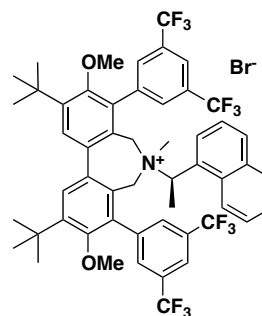
We began this investigation for the straightforward cyclisation of phenyl ketone **129**. In the presence of commercially available phase-transfer catalyst **2** we obtained cyclised product **130** in a promising 10% ee (Table 21, entry 1). Increasing the steric bulk of the *N*-pendant group led to an increase in ee (Table 21, entry 2), but incorporation of an electron-withdrawing group at this position resulted in a reduction in ee (Table 21, entry 3). Changing the catalyst to the pseudo enantiomer, *N*-benzyl cinchoninium chloride afforded the product in comparable enantioselectivity, but with the opposite absolute stereochemistry (Table 21, entry 4). Interestingly, incorporating an electron withdrawing group on the *N*-pendant group for this catalyst scaffold afforded an increase in enantioselectivity (Table 21, entry 5). Protection of the C9 hydroxy group did not afford any improvement on the enantioselectivity (Table 21, entries 6 and 7). Using a quininium based catalyst (Table 21, entry 8), resulted in a significant increase in enantioselectivity, to 37% ee. Lygo's catalyst **221** did not offer any improvement, so we decided to continue our screening employing the quininium based catalyst **218**.



- 2** $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{H}$, $X = \text{Cl}$
214 $R_1 = 9\text{-anthracenyl}$, $R_2 = \text{H}$, $R_3 = \text{H}$, $X = \text{Cl}$
215 $R_1 = (4\text{-CF}_3)\text{C}_6\text{H}_4$, $R_2 = \text{H}$, $R_3 = \text{H}$, $X = \text{Br}$
216 $R_1 = 9\text{-anthracenyl}$, $R_2 = \text{allyl}$, $R_3 = \text{H}$, $X = \text{Br}$
217 $R_1 = \text{Ph}$, $R_2 = \text{allyl}$, $R_3 = \text{H}$, $X = \text{Br}$
218 $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{OMe}$, $X = \text{Cl}$



- 219** $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{H}$
220 $R_1 = (4\text{-CF}_3)\text{C}_6\text{H}_4$, $R_2 = \text{H}$, $R_3 = \text{H}$



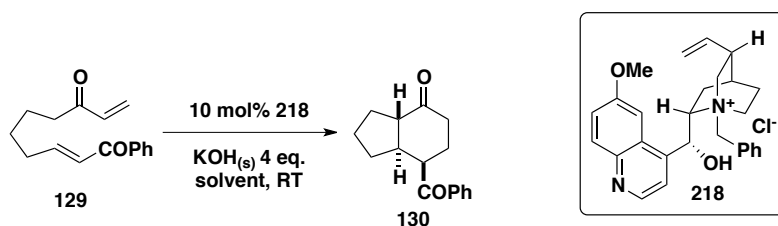
221

Entry	Catalyst	ee (%)
1	2	(+) 10
2	214	(+) 20
3	215	(+) 5
4	219	(-) 10
5	220	(-) 17
6	216	(+) 5
7	217	(+) 10
8	218	(+) 37
9	221	(-) 30

Table 21: Catalyst screen for the cyclisation of phenyl ketone **129**

Next we investigated the impact of the reaction solvent. A variety of polar and non-polar solvents were explored whilst utilising catalyst **218**. Use of chlorobenzene

showed a minor increase in enantioselectivity compared to toluene (Table 22, entry 2). Hexane afforded a slightly lower selectivity, but the yield for this reaction was greatly reduced, possibly due to insolubility of the starting material. MeCN and CH₂Cl₂ both afforded a reduction in enantioselectivity compared to toluene. Interestingly, the results show that the use of a mildly polar solvent (Et₂O) is beneficial, whilst in a strongly polar solvent (MeOH), no product was observed.

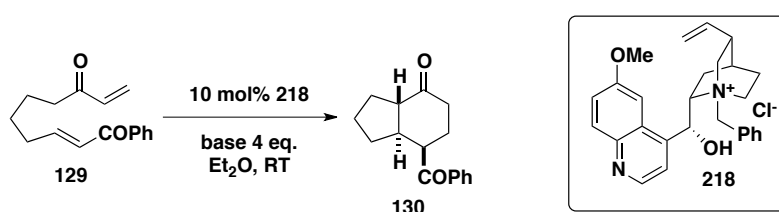


Entry	Solvent	ee (%)
1	PhMe	(+) 37
2	C ₆ H ₅ Cl	(+) 39
3	Hexane	(+) 30
4	MeCN	(+) 25
5	CH ₂ Cl ₂	(+) 30
6	Et ₂ O	(+) 45
7	MeOH	No product

Table 22: Solvent screen for the cyclisation of phenyl ketone **129**

Encouraged by this result, we decided to use Et₂O as the solvent and investigate the effect of the nature of the base on the enantioselectivity. Attempting the reaction with

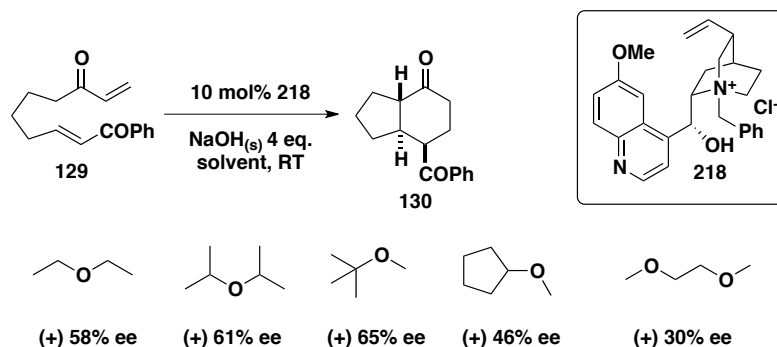
aqueous KOH afforded a significant reduction in enantioselectivity and the reaction was much less clean; the product was formed but a multitude of decomposition products were also present and they could not be identified. Changing the counterion from potassium to cesium resulted in a slight decrease in enantioselectivity (Table 23, entry 4), but changing the cation to sodium resulted in a significant increase in enantioselectivity. Weaker bases took much longer to induce cyclisation, and this did not result in enhanced enantioselectivity (Table 23, entries 5 and 6). With the weakest base, KH_2PO_4 no reaction was observed after 96 hr.



Entry	Base	ee (%)	Reaction time
1	$\text{KOH}_{(\text{s})}$	(+) 45	2 hr
2	$\text{KOH}_{(\text{aq})}$	(+) 18	4 hr
3	$\text{NaOH}_{(\text{s})}$	(+) 58	2 hr
4	$\text{CsOH} \cdot \text{H}_2\text{O}_{(\text{s})}$	(+) 41	2 hr
5	$\text{K}_2\text{CO}_{3(\text{s})}$	(+) 45	22 hr
6	$\text{Cs}_2\text{CO}_{3(\text{s})}$	(+) 48	22 hr
7	$\text{KH}_2\text{PO}_{4(\text{s})}$	No product	96 hr

Table 23: Base screen for the cyclisation of phenyl ketone **129**

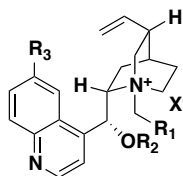
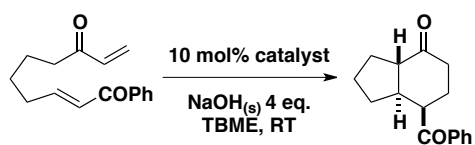
After performing a short catalyst screen, and determining the optimal base for the reaction, we decided to revisit solvent optimisation and investigate more hindered ethers. Increasing the steric bulk of the ether increased the enantioselectivity further, with *tert*-butyl methyl ether (TBME) resulting in a further rise in ee to 65%. Cyclopentyl methyl ether and dimethoxyethene resulted in diminished selectivity.



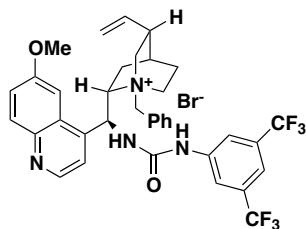
Scheme 115: Solvent screen of various ethers for cyclisation of phenyl ketone **129**

Using our optimal solvent and base combination, we returned to catalyst optimisation. We saw previously that the quinine derived catalyst afforded the best yield, so we focussed our screen around this scaffold. A more bulky C6'-isopropyl substituted catalyst resulted in comparable enantioselectivity to the methyl group (Table 24, entry 2). Protection of the C9 hydroxy group led to a completely racemic product (Table 24, entry 3 and 4). This implies that this group places an important role in substrate binding. We therefore introduced hydrogen bond donor groups either at the C9 position or the C6' position, all of which resulted in reduced enantioselectivity (Table 24, entries 5-8).^a

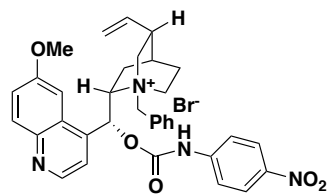
^a For details on all the catalysts screened, see Experimental, page 358



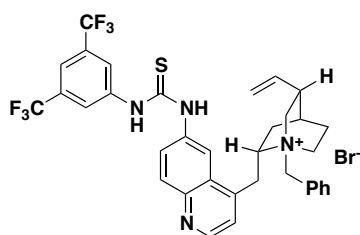
218 $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{OMe}$, $X = \text{Cl}$
 223 $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{O}i\text{Pr}$, $X = \text{Br}$
 224 $R_1 = \text{Ph}$, $R_2 = \text{Bn}$, $R_3 = \text{OH}$, $X = \text{Br}$
 225 $R_1 = \text{Ph}$, $R_2 = \text{allyl}$, $R_3 = \text{OMe}$, $X = \text{Br}$



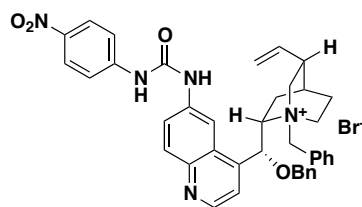
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227



228

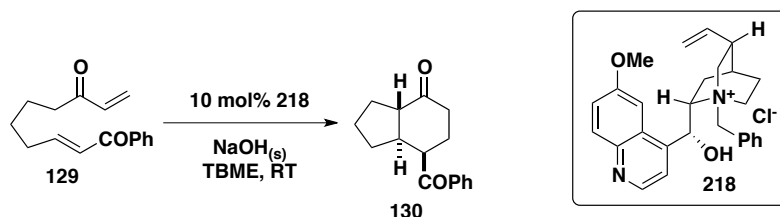


229

Entry	Catalyst	ee (%)
1	218	(+) 65
2	223	(+) 62
3	224	0
4	225	0
5	226	(-) 7
6	227	(+) 10
7	228	0
8	229	(+) 10

Table 24: Catalyst screen for cyclisation of phenyl ketone **129**

We then investigated the effect of base stoichiometry. We tried four different loadings, varying from substoichiometric to 10 equivalents. Substoichiometric quantities of base resulted in a decrease in ee, but the enantioselectivity increased as more base was used. However, adding a large excess of base did not increase the enantioselectivity any further.



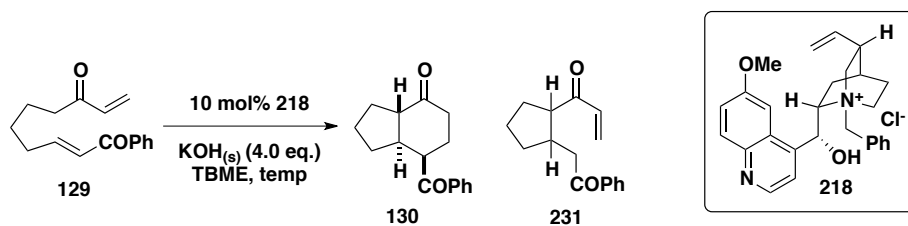
Entry	Equivalents $\text{NaOH}_{(s)}$	ee (%)
1	0.1	53
2	1	56
3	4	65
4	10	64

Table 25: Investigating the effect of equivalents of base on the cyclisation of phenyl ketone **129**

Utilising solid bases has the benefit of allowing the reaction to be carried out at cryogenic temperatures.^b We investigated what effect temperature has on the enantioselectivity. At -30 °C, we did not observe the formation of any product, and we were able to reisolate the starting material. Performing the reaction at -15 °C did result in consumption of the starting material, but we were only able to isolate the product of

^b The lower limit for systems involving aqueous bases is -15 °C due to the freezing of the aqueous layer

the first 1,4-addition, **231** in 40% yield.^c Interestingly, at 0 °C the enantioselectivity was slightly lower than the corresponding reaction at room temperature.



Entry	Temperature (°C)	Product	ee (%)
1	-30	n.r. after 3 days	-
2	-15	231	-
3	0	130	(+) 60
4	rt	130	(+) 65

Table 26: Investigating the effect of temperature on the cyclisation of phenyl ketone **129**

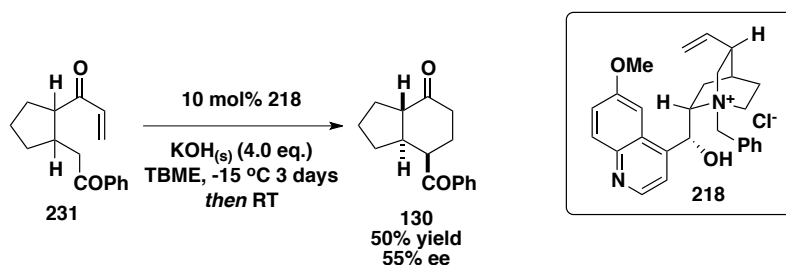
We decided to investigate the product of the first 1,4-addition, to see if we could determine the stereochemistry of the ring junction and also investigate if it would go on to form the product if resubjected to the reaction conditions.^d

Re-submitting **231** to the reaction conditions at -15 °C and then warming to room temperature resulted in conversion to **130**. This material was isolated in 50% yield and

^c This product was isolated in 40% yield, with the rest of the reaction mixture assumed to have polymerised as the mass recovery after work up was only 55%

^d The peaks corresponding to the hydrogens on the ring junction were not separable in the NMR solvents tried (benzene-d₆, PhMe-d₈, CDCl₃, CD₂Cl₂, THF-d₈, acetone-d₆, MeOD, CD₃CN, DMSO-d₆), and we were unable to derivatise the product with 2,4-dinitrophenylhydrazine

(+) 55% ee. This drop in enantioselectivity is consistent with the observation we made previously that cooling the reaction results in a lower enantioselectivity.



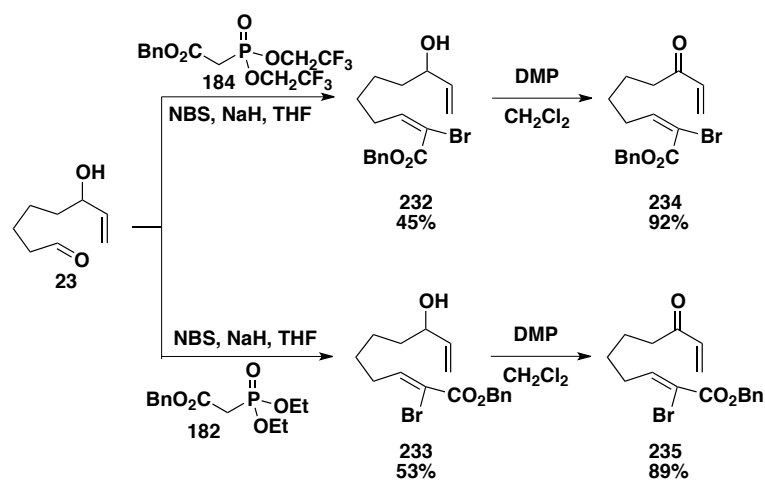
Scheme 116: Submitting the intermediate to the reaction conditions afforded the product in 55% ee

The final optimised conditions used 4.0 eq. of $\text{NaOH}_{(s)}$, 10 mol% of quinuclidine catalyst **218** and TBME as the solvent at room temperature.^e

5.2.2 Reaction Optimisation on 5-5-3 Systems

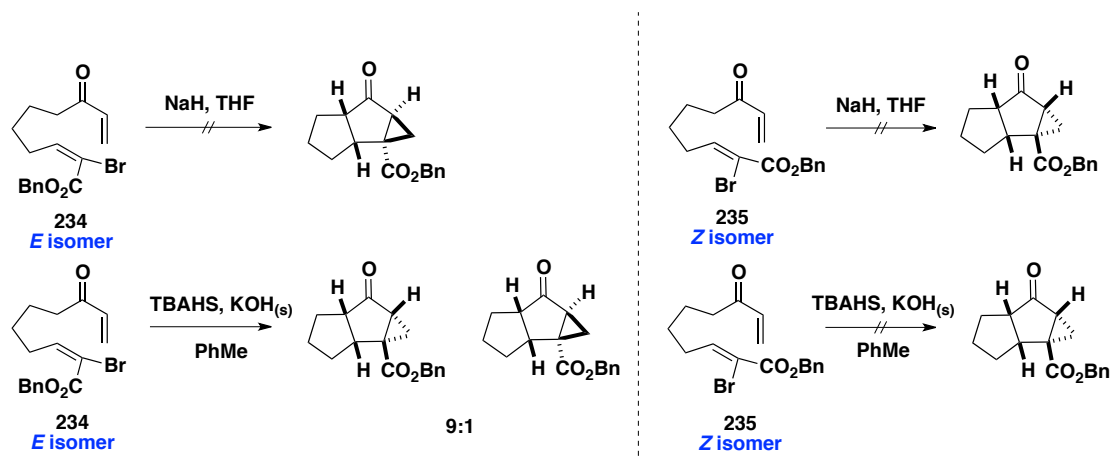
We then wanted to see if we could use these conditions to induce enantioselectivity in the more complex 5-5-3 series. We were immediately confronted by a hurdle, in that the complete lack of UV absorption of the 5-5-3 products prevented us from carrying out analysis by chiral HPLC. We hoped to synthesise a derivative of **13** or **27** containing a UV chromophore and settled upon **234** or **235**, containing a benzyl ester. This substrate was readily assembled using an analogous route to that synthesised previously. Both double bond isomers were synthesised in good yields.

^e We attempted the cyclisation of the malonate system **104** under these conditions, but unfortunately, we did not observe any formation of the product. For details on the cyclisation conditions used, see Experimental, page 362



Scheme 117: Synthesis of the benzyl ester substrates

We now tested the cyclisation cascade under phase-transfer and NaH conditions. We were surprised to find that in all four cases, the reaction was significantly slower than in the ethyl ester case. Moreover, the diastereodivergence was not perfect, and a small quantity of the minor diastereomer was observed upon cyclisation of the *E* isomer under phase transfer conditions. It is remarkable that the subtle variation of this remote ester functionality can have such a significant impact upon the cyclisation reaction.



Scheme 118: Attempted cyclisation of the *E* and *Z* isomers of the benzyl ester substrate

We decided to employ an alternative approach to visualise the products. We carried out the cyclisation reaction of **27** and then derivatised the products with a UV active nucleophile. Addition of phenylmagnesium bromide did not introduce a sufficiently strong chromophore, however, changing to biphenylmagnesium bromide enabled clear visualisation of the peaks.

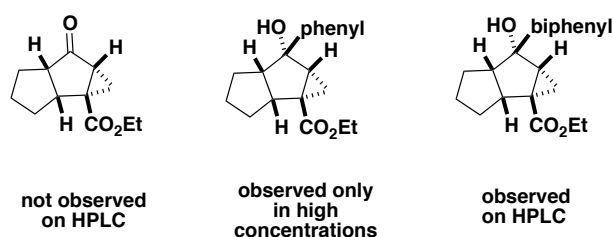


Figure 21: Derivatising the product to increase the UV activity for visualisation on the HPLC

We initially applied the optimised conditions from the 5-6 system **129** to the cyclisation of **27**, but did not observe any product, we speculated that this was due to the insolubility of the starting material in TBME.

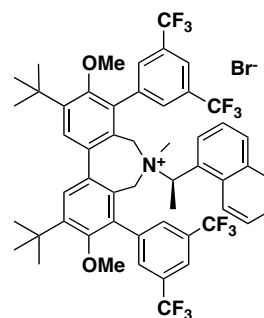
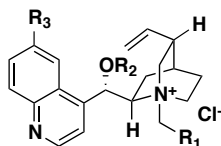
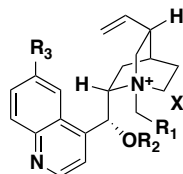
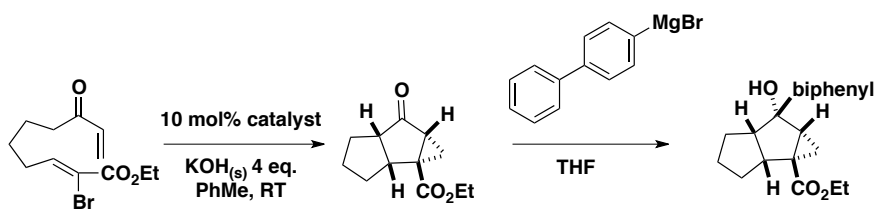
Upon switching the solvent to PhMe, we observed the cyclised product (following derivatisation) in 3% ee. We decided to undergo a short catalyst, base and solvent screen to determine whether we could obtain high enantioselectivities in this reaction. For these reactions we noticed that the reaction was no longer completely diastereoselective. After addition of biphenylmagnesium bromide, two major diastereomers were observed. Although these were separable, the HPLC spectra were not completely pure, so these results must be interpreted with some caution.

Nevertheless, we set about varying the catalyst and investigating the ee of the major diastereomer (which was the same in all cases).^f

The enantioselectivities for this reaction were much lower than those observed for the phenyl ketone 5-6 system. As observed previously, pseudoenantiomeric catalysts afforded enantioenriched material with the opposite absolute configuration (Table 27, entries 1-4). Interestingly, protection of the C9 hydroxy group actually increased the enantioselectivity of the reaction, to 8% ee. Incorporation of electron withdrawing groups on the *N*-pendant group afforded small, seemingly non-systematic variations in ee (Table 27, entries 6-9). Use of the Lygo catalyst **221** also did not result in any increase in enantioselectivity. We used the cinconine derived catalyst for the solvent and base screen.^g

^f The minor isomer was not obtained in a large enough mass for it to be UV active enough for visualisation on the HPLC

^g For full details on the solvent and base screen, see experimental, page 367-369



2 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{H}, X = \text{Cl}$
 218 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{OMe}, X = \text{Cl}$
 217 $R_1 = \text{Ph}, R_2 = \text{allyl}, R_3 = \text{H}, X = \text{Br}$
 236 $R_1 = 1,2,3\text{-FPh}, R_2 = \text{H}, R_3 = \text{H}, X = \text{Br}$

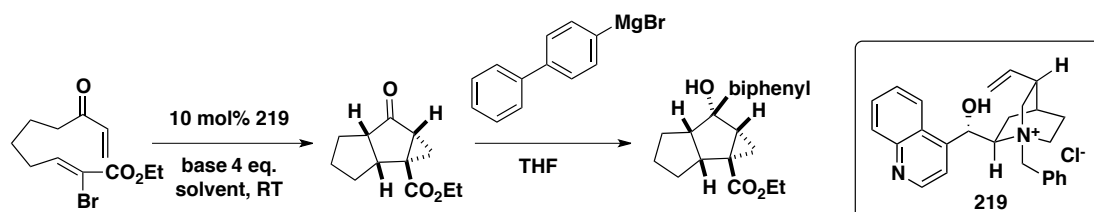
219 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{H}$
 237 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{OMe}$
 238 $R_1 = 4\text{-CF}_3\text{Ph}, R_2 = \text{H}, R_3 = \text{OMe}$
 239 $R_1 = 3,5\text{-CF}_3\text{Ph}, R_2 = \text{H}, R_3 = \text{H}$
 240 $R_1 = \text{C}_6\text{F}_5, R_2 = \text{H}, R_3 = \text{OMe}$

221

Entry	Catalyst	ee(%)
1	2	(+) 3
2	219	(-) 8
3	218	(+) 4
4	237	(-) 2
5	217	(+) 8
6	236	(+) 4
7	238	(-) 6
8	239	(-) 1
9	240	(-) 6
10	221	(-) 4

Table 27: Catalyst screen for the cyclisation of the Z bromo acrylate 27

Altering the solvent did not have much of an effect on the enantioselectivity. Aromatic solvents (Table 28, entries 1-3) proved optimal for this reaction. Aqueous base decomposed the starting material, and weak bases did not afford any cyclised product (Table 28, entry 7).

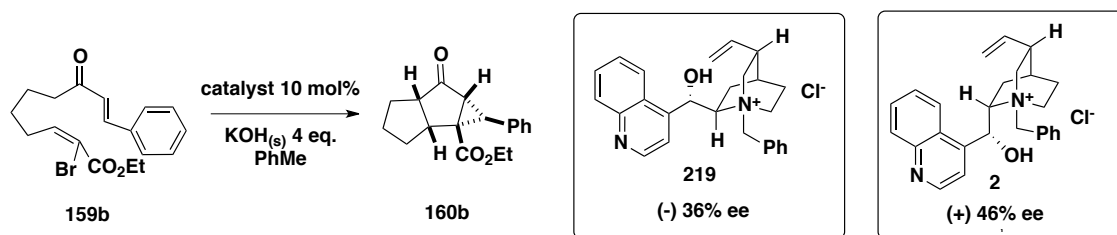


Entry	Solvent	Base	ee (%)
1	PhMe	KOH _(s)	(-) 8
2	PhH	KOH _(s)	(-) 8
3	Xylenes	KOH _(s)	(-) 10
4	DMF	KOH _(s)	decomposed
5	MeOH	KOH _(s)	decomposed
6	PhMe	KOH _(aq)	decomposed
7	PhMe	Cs ₂ CO ₃	n.r.
8	PhMe	CsOH.H ₂ O _(s)	(-) 7
9	PhMe	NaOH _(s)	(-) 8

Table 28: Solvent and base screen for the cyclisation of the *Z* bromo acrylate **27**

Before abandoning this asymmetric reaction, we applied our optimised conditions to another 5-5-3 precursor. We chose the phenyl system so that we did not have to

derivatise the product, as this example was weakly UV active, and we could obtain a reliable HPLC trace.



Scheme 119: Applying the previously optimised conditions to the cyclisation of the phenyl substrate **159b**.

Further optimisation on this system afforded the product in 46% ee

The optimised conditions from the simple 5-5-3 system afforded the product in (-) 36% ee, which was much more promising than the (-) 8% ee for the simple system. We then performed a catalyst, base and solvent screen, and determined that the best conditions for this system are using *N*-benzyl cinchonidinium chloride as the catalyst, toluene as the solvent and 4.0 eq. KOH_(s) as the base. These conditions afforded the product in (+) 46% ee.^h

5.3 Conclusion

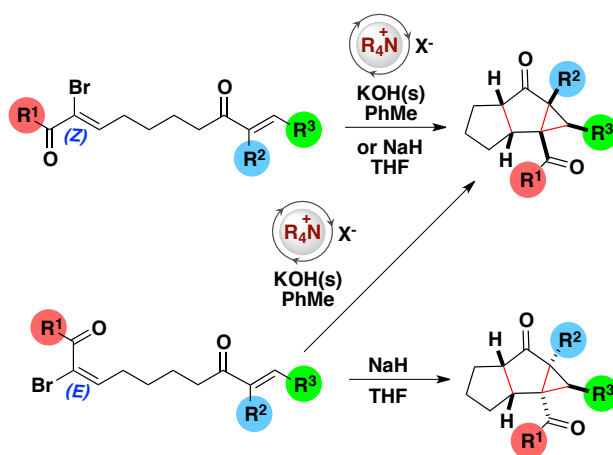
Through the extensive reaction optimisation, it has been possible to optimise the phenyl ketone system so we can synthesise the product in 65% ee. We have made some progress in developing an asymmetric route to 5-5-3 fused ring systems and have been able to obtain material in up to 40% ee. In the future, if we want to achieve more promising enantioselectivities, it may be best to pursue catalysts that bind directly to the substrate.

^h For full details on the catalyst, solvent and base screen, see experimental, page 370-372

6. Conclusions and Future Work

We started our investigations by attempting to synthesise transannular precursors. En route to their synthesis, we noticed that we had performed an unexpected reaction, synthesising three rings and up to five contiguous stereocentres in a single operation with complete diastereocontrol. After attempting various other methods for the synthesis of the transannular precursor, we concluded that the synthesis was non-trivial. Since we had noticed the formation of an interesting 5-5-3 fused ring system, we decided to turn our attention to investigating the mechanism and examining the substrate scope for this unexpected reaction.

When we further investigated the formation of this 5-5-3 fused ring system, we also noticed that the reaction exhibits unusual diastereodivergence, depending on the reaction conditions used. The mechanism for this unusual diastereodivergence has been studied both experimentally and computationally.



Scheme 120: Cyclisation of *E* and *Z* bromoacrylates under phase-transfer and NaH conditions

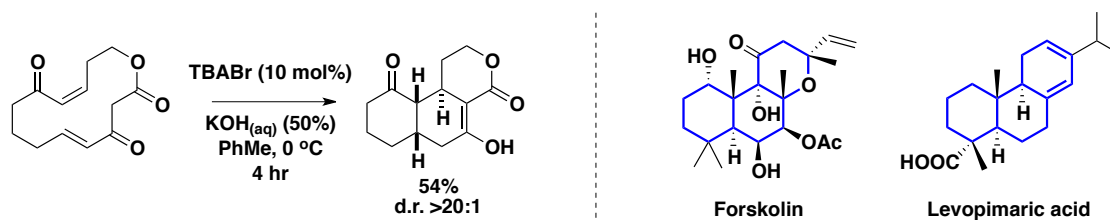
We have also synthesised a number of examples, probing the steric and electronic requirements of the cyclisation. We discovered that the reaction is specific to the 5-5-3 ring core; extension into larger ring sizes or introducing heteroatoms into the backbone

have proved difficult and result in substrates that do not cyclise smoothly. We have been able to synthesise analogues of the 5-5-3 core, introducing functional groups at the alpha and beta positions. It was also possible to derivatise the products. We have been able to functionalise the ketone, saponify the ester and open the three membered ring. The diastereoselectivity of the attack by nucleophiles is dependant on the shape of the compound, with the concave diastereomer affording higher levels of diastereoselectivities than the “s” shaped one.

This reaction has also been extended to substrates lacking the bromine, and it has been shown that these can cyclise in a similar fashion, to afford 5-6 fused ring systems.

Through extensive reaction optimisation, it has been possible to optimise the reaction conditions so that we can synthesise 5-6 fused ring systems in 65% ee. We have made some progress in developing an asymmetric route to 5-5-3 fused ring systems and have been able to obtain material in up to 40% ee. In the future, if we want to achieve more promising enantioselectivities, it may be best to pursue catalysts that bind directly to the substrate.

Looking forward, work is underway in the lab on extending this methodology to the synthesis of natural product like scaffolds.



Scheme 121: Transannular cyclisation and natural product scaffolds bearing a similar structure

7. Experimental

7.1 Methods

7.1.1 Naming and Numbering

Compounds have been named according to IUPAC recommendations. The atomic numbering system for compounds does not correspond to the IUPAC names but was chosen to allow for simplistic and consistent assignment of spectra.

7.1.2 General Experimental

All reactions were carried out under an argon atmosphere in washed and oven-dried glassware. Reactions were stirred using a magnetic Teflon® stirrer bar and a stirrer hot plate. When used, anhydrous DMF was fitted with a Sure Seal™ cap and supplied from Sigma Aldrich. Anhydrous CH₂Cl₂, Et₂O, toluene and methanol were purified by filtration through activated alumina columns employing the method of Grubbs *et al.*¹ Other solvents were used as supplied (analytical or HPLC grade) without prior purification. Petrol 40-60 refers to the fraction of petroleum ether which boils in the range 40-60 °C. Where mixtures of solvents are specified, the stated ratios are volume:volume. Triethylamine was distilled over CaH₂ and stored over KOH under an inert argon atmosphere. Unless otherwise indicated, all aqueous solutions used were saturated. Removal of solvents under reduced pressure was achieved using a Büchi rotary evaporator with bath temperatures of up to 50 °C.

7.1.3 Reagents

Reagents were used directly as supplied by major chemical suppliers, or following purification according to procedures described by Perrin and Armarego.²

7.1.4 Chromatography

TLC was performed using commercially available Merck Kieselgel 60F₂₅₄ 0.25 mm precoated aluminium backed plates. Visualisation was with UV fluorescence (254 nm), vanillin or potassium permanganate solution and heat.

Flash column chromatography was performed using commercially available VWR silica gel: 230-400 mesh (40-63 μm).

Analytical HPLC was carried out using a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler and TCC-3000SD column compartment, and a Daicel Chiralpak IA or AD-H column (0.46 cm x 25 cm), equipped with the appropriate guard column (0.4 cm x 1 cm).

7.1.5 NMR

All final compounds were characterised using NMR spectroscopy. ¹H and ¹³C spectra were run using either a Bruker AVC500 (500 MHz), AVF400 (400 MHz), DPX400 (400 MHz) or DPX200 (200 MHz) spectrometer at ambient temperature, with chemical shifts (δ) quoted in parts per million (ppm), measured relative to SiMe₄ (TMS) or appropriate solvent peaks. Coupling constants (*J*) are quoted to the nearest 0.5 Hz. Assignment was aided by the use of COSY, HMQC or HSQC spectra. Common

abbreviations used are: br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sept. (septet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets), and m (multiplet).

7.1.6 Mass Spectrometry

Mass spectra were determined using electrospray ionisation (ESI⁺), performed on a Micromass LCT Premier spectrometer. Accurate masses (HRMS) were recorded on Bruker MicroTOF and Micromass GCT spectrometers under conditions of electrospray ionization (ESI) and field ionization (FI) respectively. Values are reported as a ratio of mass to charge in Daltons.

7.1.7 IR Spectroscopy

Infra red spectroscopy was performed on a Bruker Tensor 27 FTIR spectrometer, and analysed as thin films on NaCl plates. Only structurally important IR absorbances are quoted in wavenumbers (cm⁻¹) with the abbreviation br. (broad) if necessary.

7.1.8 Melting point

Melting points were determined using a Reichert melting point apparatus and are uncorrected.

7.1.9 X-ray crystallography

X-ray crystallography was performed by Dr Amber Thompson, Dr Russell Driver or Mr John Jolliffe at the CRL Chemical Crystallography X-ray facility or Diamond Light Source.

7.2 General Procedures

General Procedure 1:

Commercially available Grignard reagents were used directly. When the Grignard reagent was not commercially available, the following procedure was adopted:

Magnesium (1 eq.) was flame dried in an oven-dried flask under vacuum for 5 min. The flask was allowed to cool to RT, and I₂ (1 crystal) and THF (1 mL/mmol) were added. Appropriate bromo-olefin (1 eq.) was added dropwise to maintain a gentle reflux. Once the magnesium was consumed, the Grignard reagent was used immediately.

Grignard reagent (1.2 eq.) was added dropwise to a solution of appropriate aldehyde (1 eq.) in THF (8 mL/ mmol) at -78 °C and the resulting solution was stirred at this temperature for 3 hr. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. Acetone (8 mL/mmol), H₂O (1.5 mL/mmol) and HCl (1.0 M aq., 0.5 mL/mmol) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined organic extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound that was unstable to further purification. The crude aldehyde was either used immediately or stored under Ar at -20 °C.

General Procedure 2:

HWE **25** or SG reagent **19** (1 eq.) was dissolved in THF (5 mL/mmol). NaH (60% dispersion in mineral oil, 2 eq.) and NBS (1 eq.) were added and the resulting suspension was stirred for 1 hr. Appropriate aldehyde (1 eq.) was dissolved in THF (2 mL/mmol) and added to the reaction mixture, and the resulting suspension was stirred overnight. The reaction mixture was quenched with NH₄Cl (sat. aq.), the layers separated and the aqueous layer extracted with EtOAc (x 2). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2) (unless otherwise stated)) to afford the title compound.

General Procedure 3

DMP (1.5 eq.) was added to a solution of appropriate alcohol (1 eq.) in CH₂Cl₂ (4 mL/mmol), and the resulting suspension was stirred at RT overnight. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1) (unless otherwise stated)) to afford the title compound.

General Procedure 4

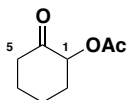
Phase-transfer catalyst (PTC) (10 mol%) was added to a solution of the cyclisation precursor (1 eq.) in toluene (~2-4 mL/mmol), and the resulting solution was cooled to the appropriate temperature. Powdered KOH (4 eq.) was added and the resulting solution stirred until the reaction was complete (determined by TLC). The mixture was quenched with NH₄Cl (sat. aq.) and allowed to warm to RT if appropriate. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2) (unless otherwise stated)) to afford the cyclised product.

General Procedure 5

NaH (60% dispersion in mineral oil, 2 eq.) was added to a solution of the cyclisation precursor (1 eq.) in THF (~2-4 mL/mmol), and the resulting solution was stirred until the reaction was complete (determined by TLC). The solution was quenched with NH₄Cl (sat. aq.) and allowed to warm to RT if appropriate. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2) (unless otherwise stated)) to afford the cyclised product.

7.3 Experimental

Preparation of 2-acetoxycyclohexanone **15**

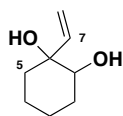


According to a literature procedure,³ cyclohexanone (2.14 mL, 20.4 mmol) was dissolved in PhMe (40 mL), $\text{Pb}(\text{OAc})_4$ (10.8 g, 12.2 mmol) was added and the solution heated to reflux for 2 hr. The reaction mixture was allowed to cool to RT, diluted with Et_2O and washed with HCl (1.0 M aq., x 3). The organic extract was dried over Na_2SO_4 , filtered, and the filtrate concentrated under reduced pressure to afford compound **15** (3.00 g, 94%) as a yellow oil, which required no further purification.

^1H NMR (400 MHz, CDCl_3) δ_{H} 5.14 (dd, $J = 6.5, 11.0$ Hz, 1 H, H_1), 2.54-2.46 (m, 1 H, H_5), 2.45-2.23 (m, 2 H, H_2, H_5'), 2.16 (s, 3 H, COOCH_3), 2.12-2.04 (m, 1 H, H_2'), 2.00-1.91 (m, 1 H, H_4), 1.88-1.56 (m, 3 H, H_4', H_3, H_3'); **^{13}C NMR (101 MHz, CDCl_3)** δ_{C} 204.6 (C_6), 170.0 (CH_3CO_2), 76.7 (C_1), 40.6 (C_5), 32.8 (C_2), 27.0 (C_4), 23.7 (C_3), 20.9 (CH_3CO_2); **LRMS m/z (ESI $^+$)** 157 ($[\text{M}+\text{H}]^+$ 11%), 179 ($[\text{M}+\text{Na}]^+$ 46%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.⁴

Preparation of 1-vinylcyclohexane-1,2-diol, **16**

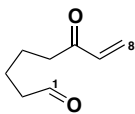


According to a literature procedure,¹¹ ketone **15** (2.6 g, 17 mmol) was stirred in THF (20 mL) at -78 °C for 15 min. Vinylmagnesium bromide (1.0 M in THF, 50 mL, 50 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 1 hr. The reaction mixture was allowed to warm to RT and stirred for 1 hr, cooled to 0 °C, and quenched with H₂O. The mixture was then diluted with EtOAc, washed with NH₄Cl (sat. aq.) and brine (x 2), dried over K₂CO₃, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil with 1:3 *dr* (crude ¹H NMR). The crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (1:1)) to afford compound **16** (1.4 g, 61%, 1:3 *dr*) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ_H 5.90 (dd, *J* = 10.5, 17.5 Hz, 1 H, *H*7), 5.41 (dd, *J* = 1.5, 17.5 Hz, 1 H, *H*8), 5.21 (dd, *J* = 1.5, 10.5 Hz, 1 H, *H*8'), 3.51 (d, *J* = 10.0 Hz, 1 H, *H*1), 2.21 (s, 1 H, OH), 1.85-1.14 (m, 9 H, *H*2, *H*3, *H*4, *H*5, OH); ¹³C NMR (101 MHz, CDCl₃) δ_C 143.5 (*C*7), 116.2 (*C*8), 74.2 (*C*6), 73.2 (*C*1), 35.5 (*C*5), 28.9 (*C*2), 22.6 (*C*4), 20.6 (*C*3); LRMS *m/z* (ESI⁺) 142 ([*M*+Na]⁺ 100%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.³

Preparation of 6-oxooct-7-enal **14**



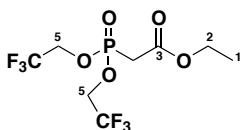
According to a literature procedure,³ Pb(OAc)₄ (640 mg, 1.46 mmol) was added to a solution of diol **16** (200 mg, 1.46 mmol) in MeCN (10 mL) and the resulting solution was stirred at RT for 10 min. The solution was diluted with EtOAc and washed with HCl (1.0 M aq., x 3). The combined extracts were dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford compound **14** (190 mg, 97%) as a colourless oil, which was unstable to further purification, so was used crude in the next reaction.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at 9.81 (s, 1 H, H1), 6.35 (dd, *J* = 17.5, 9.5 Hz, 1 H, H7), 6.21 (dd, *J* = 17.5, 1.5 Hz, 1 H, H8), 5.84 (dd, *J* = 9.5, 1.5 Hz, 1 H, H8').

Alternative preparation:

A solution of diol **16** (200 mg, 1.46 mmol) in CH₂Cl₂ (10 mL) was added to a solution of sodium (meta)periodate (600 mg, 2.82 mmol) in H₂O (10 mL). The resulting biphasic mixture was vigorously stirred for 2 hr. The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (x 3). The combined extracts were washed with H₂O and brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford compound **14** (204 mg, quant.) as a colourless oil, which was unstable to further purification, so was used crude in the next reaction, with the same characteristic peaks as previously reported.

Preparation of ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate **19**



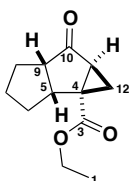
According to a literature procedure,⁵ HMDS (1.86 mL, 8.80 mmol) in THF (7 mL) was added dropwise to a solution of *n*-BuLi (1.6 M in hexanes, 5.00 mL, 8.00 mmol) at -20 °C, and the resulting solution was cooled to -78 °C. Bis(2,2,2-trifluoroethyl) methylphosphonate (1.00 g, 3.85 mmol) and ethyl chloroformate (0.400 mL, 4.00 mmol) were dissolved in THF (17 mL) and added dropwise to the reaction mixture. The resulting solution was kept in the -78 °C bath overnight, allowing to gradually warm, and was then treated with HCl (1.0 M) until acidic. The aqueous layer was extracted with CH₂Cl₂ (x 3) and the combined extracts were dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was purified by flash column chromatography (SiO₂, pet 40-60: Et₂O (1:1)) to afford compound **19** (700 mg, 58%) as a yellow oil.

N.B. Yields of this reaction vary. Leaving the reaction mixture below -20 °C overnight generally affords the best yields.

¹H NMR (200 MHz, CDCl₃) δ_H 4.46 (quin., *J* = 8.0 Hz, 4 H, *H*5), 4.23 (q, *J* = 7.0 Hz, 2 H, *H*2), 3.17 (d, *J* = 21.0 Hz, 2 H, *H*4), 1.30 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_C 165.6 (C3), 123.7 (q, *J* = 227 Hz, C6), 62.5 (q, *J* = 38 Hz, C5), 34.6 (C2), 33.2 (C4), 14.4 (C1); **¹⁹F NMR (376 MHz, CDCl₃)** δ_F -75.5; **LRMS *m/z* (ESI⁺)** 355 ([*M*+*H*]⁺ 100%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.⁵

Preparation of (1aR*, 1bR*, 4aS*, 5aS*)-ethyl 5-oxooctahydro-1H-cyclopropa[a]pentalene-1a-carboxylate **21**



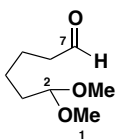
According to a modified literature procedure,⁶ NaH (60% dispersion in mineral oil, 112 mg, 2.80 mmol) was added to a solution of S-G reagent **19** (474 mg, 1.43 mmol) in THF (10 mL) and the reaction mixture was stirred for 5 min. NBS (255 mg, 1.43 mmol) was added and the resulting solution stirred for 1 hr. A solution of aldehyde **14** (200 mg, 1.43 mmol) in THF (3 mL) was added dropwise to the reaction mixture, and allowed to stir at RT for 16 hr. The reaction was quenched by the addition of NH₄Cl (sat. aq.), and extracted with Et₂O (x 3). The combined organic extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil with >20:1 d.r. (crude ¹H NMR). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **21** (117 mg, 40%, >20:1 d.r.) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 4.16 (q, *J* = 7.0 Hz, 2 H, *H*₂), 2.90 (q, *J* = 7.5 Hz, 1 H, *H*₅), 2.56 (q, *J* = 7.5 Hz, 1 H, *H*₉), 2.42 (dd, *J* = 9.5, 4.5 Hz, 1 H, *H*₁₁), 2.23 (ddd, *J* = 13.5, 7.5, 4.0 Hz, 1 H, *H*₈), 1.82 (dt, *J* = 7.5, 2.0 Hz, 2 H, *H*₆), 1.76 (dd, *J* = 4.5, 1.0 Hz, 1 H, *H*₁₂), 1.71-1.63 (m, 1 H, *H*₇), 1.55-1.46 (m, 1 H, *H*_{7'}), 1.38 (t, *J* = 4.5 Hz, 1 H, *H*_{12'}), 1.31-1.29 (m, 1 H, *H*_{8'}), 1.26 (t, *J* = 7.0 Hz, 3 H, *H*₁); **¹³C NMR (126 MHz, CDCl₃)** δ_C 214.0 (C₁₀), 171.0 (C₃), 60.9 (C₂), 48.6 (C₅), 43.0 (C₉), 36.7 (C₄), 34.8 (C₁₁), 31.9 (C₈), 26.6 (C₇, C₆), 22.7 (C₁₂), 14.2 (C₁); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₂H₁₆NaO₃ 231.0992,

found 231.0986; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2929 (C-H), 2855 (C-H), 1730 (C=O), 1670 (C=O ketone), 1471, 1251, 833.

Stereochemistry determined by nOe experiments.

Preparation of 6,6-dimethoxyhexanal **22**

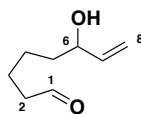


According to a literature procedure,¹³ MeOH (13 mL) was added to a solution of cyclohexene (1.90 mL, 18.0 mmol) in CH₂Cl₂ (60 mL) at -78 °C. Ozone was bubbled through the solution until the solution turned blue, after which ozone addition was stopped and oxygen was passed through the solution until the blue colour was discharged. The cold bath was removed and *p*-toluenesulfonic acid (300 mg, 1.60 mmol) was added. The solution was allowed to warm to RT and was stirred for 90 min. Anhydrous NaHCO₃ (535 mg, 6.4 mmol) was added, the mixture stirred for 15 min, and dimethylsulfide (3.00 mL, 36.0 mmol) was added. This was allowed to stir at RT for 12 hr; the solution was then concentrated under reduced pressure to ~12 mL. CH₂Cl₂ was added, the mixture washed with H₂O and the aqueous layer extracted with CH₂Cl₂ (x 2). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford compound **22** (3.60 g, quant.) as a colourless oil, which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_H 9.73 (t, *J* = 1.5 Hz, 1 H, *H*7), 4.31 (t, *J* = 5.5 Hz, 1 H, *H*2), 3.27 (s, 6 H, *H*1), 2.41 (td, *J* = 7.0, 1.5 Hz, 2 H, *H*6), 1.71-1.49 (m, 4 H, *H*3, *H*5), 1.45-1.25 (m, 2 H, *H*4); ¹³C NMR (101 MHz, CDCl₃) δ_C 202.4 (*C*7), 104.3 (*C*2), 52.6 (*C*1), 43.5 (*C*6), 32.2 (*C*3), 24.4 (*C*5), 21.4 (*C*4); LRMS (ESI⁺) 183 ([*M*+Na]⁺ 30%), 343 ([2*M*+Na]⁺ 70%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.⁷

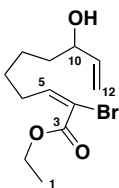
Preparation of 6-hydroxyoct-7-enal **23**



Following **General Procedure 1**, using vinyl magnesium bromide (1.0 M in THF, 12.0 mL, 12.0 mmol) and aldehyde **22** (1.60 g, 10.0 mmol) in THF (80 mL) afforded compound **23** (1.00 g, 71%) as a yellow oil, which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_{H} 9.75 (s, 1 H, *H*1), 5.84 (ddd, *J* = 17.5, 10.5, 6.5 Hz, 1 H, *H*7), 5.18 (dd, *J* = 17.5, 1.5 Hz, 1 H, *H*8), 5.09 (dd, *J* = 10.5, 1.5 Hz, 1 H, *H*8'), 4.20-4.02 (m, 1 H, *H*6), 3.49 (br. s, 1 H, OH), 2.44 (td, *J* = 7.0, 1.5 Hz, 2 H, *H*2), 1.80-1.20 (m, 6 H, *H*3, *H*4, *H*5); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 202.7 (*C*1), 141.2 (*C*7), 114.8 (*C*8), 73.0 (*C*6), 43.7 (*C*2), 36.9 (*C*5), 24.6 (*C*3), 21.9 (*C*4); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₈H₁₄NaO₂ 165.0886, found 165.0890; **IR ν_{max} /cm⁻¹ (thin film)** 3420 (br., OH), 2934 (C-H), 2861 (C-H), 1720 (C=O), 1390 (C=C), 992, 920.

Preparation of (*E*)-ethyl 2-bromo-8-hydroxydeca-2,9-dienoate, **24**



Following **General Procedure 2**, using SG reagent **19** (2.3 g, 7.0 mmol), NaH (560 mg, 14.0 mmol), NBS (1.2 g, 7.0 mmol) and aldehyde **23** (1.0 g, 7.0 mmol) afforded the title compound **24** (533 mg, 53% over two steps).

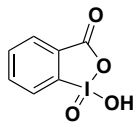
¹H NMR (400 MHz, CDCl₃) δ_{H} 6.59 (t, J = 7.5 Hz, 1 H, *H*5) 5.79 (ddd, J = 17.0, 10.5, 6.0 Hz, 1 H, *H*11), 5.15 (dt, J = 17.0, 1.5 Hz, 1 H, *H*12), 5.04 (dt, J = 10.5, 1.5 Hz, 1 H, *H*12'), 4.20 (q, J = 7.0 Hz, 2 H, *H*2), 4.03 (q, J = 6.0 Hz, 1 H, *H*10), 2.44 (q, J = 7.5 Hz, 2 H, *H*6), 1.58 (br. s, 1 H, OH), 1.51-1.35 (m, 6 H, *H*7, *H*8, *H*9), 1.27 (t, J = 7.0 Hz, 3 H, *H*1);

¹³C NMR (101 MHz, CDCl₃) δ_{C} 163.0 (C3), 148.3 (C5), 141.1 (C11), 114.7 (C12), 111.3 (C4), 73.1 (C10), 62.4 (C2), 36.6 (C7/8/9), 31.3 (C6), 27.5 (C7/8/9), 25.0 (C7/8/9), 14.1 (C1);

HRMS (ESI⁺) m/z calculated for [M+Na]⁺ C₁₂H₁₉BrNaO₃ 313.0410, found 313.0412;

IR ν_{max} /cm⁻¹ (thin film) 3401 (OH), 2934 (C-C), 1715 (C=O), 1370, 1226, 1027.

Preparation of IBX



N.B. Care must be taken. IBX is explosive and the synthesis is heavily dependant on the internal temperature of the reaction. This method has proven to work most consistently in our hands.

Following a literature procedure,⁸ oxone (182 g, 260 mmol) was placed in a 1 L, 2-necked rbf with an overhead stirrer attached through the main arm. H₂O (650 mL) was added carefully through the side arm and the side arm was then wiped dry. Iodobenzoic acid (50 g, 200 mmol) was added through the side arm *via* a powder funnel, and the side arm wiped so no iodobenzoic acid was present in the joint. A guard tube, filled with only cotton wool was placed in the side arm and the reaction mixture was stirred on a medium-stirring rate using the overhead stirrer. A blast shield was placed around the reaction set up, and the reaction mixture was heated so the internal temperature was 70 °C (monitored through the side arm). Once the reaction mixture reached an internal temperature of 70 °C, the reaction was stirred for 3 hr. After this time, the reaction mixture was a clear solution, with no residue or undissolved reagents. The heat was turned off, the stirring speed slowed down, and the reaction mixture was let cool slowly to RT (in our case, we left the reaction mixture in the dry syn, with no extra insulation required). When the reaction mixture reached RT, it was cooled to 5 °C using a cyclohexane-dry ice bath (temperature of the bath was monitored, not the internal temperature). Care must be taken to add no more than the minimum amount of dry ice required to cool the cyclohexane to 5 °C. Adding

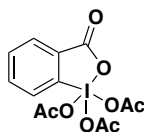
too much dry ice will stick to the flask and make it difficult to remove without disturbing the (explosive) contents of the flask. After stirring slowly at this temperature for 1.5 hr, the product crashed out of solution. The reaction mixture was then filtered under reduced pressure, washing with H₂O (6 x 80 mL), and then acetone (2 x 80 mL), taking care to agitate the solid after each wash, to ensure any oxone was dissolved in the solvent. The solid was then transferred into a 100 mL rbf and dried under high vacuum overnight, behind a blast shield, to afford the IBX (48 g, 85%).

¹H NMR (400 MHz, DMSO-d₆) δ_H 8.16 (d, *J* = 7.5 Hz, 1 H, *ArH*), 8.05 (dd, *J* = 7.5, 1.0 Hz, 1 H, *ArH*), 8.01 (dd, *J* = 8.0, 1.5 Hz, 1 H, *ArH*), 7.86 (td, *J* = 7.5, 1.0 Hz, 1 H, *ArH*);^a **¹³C NMR (101 MHz, DMSO-d₆)** δ_C 168.7 (C=O), 147.0 (CAr), 133.9 (CAr), 133.5 (CAr), 131.8 (CAr), 131.6 (CAr), 125.4 (CAr); **Mpt:** 220-230 °C (not recommended, as IBX is explosive at high temperatures). Spectroscopic data are consistent with those reported in the literature.⁸

N.B. IBX is soluble in DMSO, but insoluble in CDCl₃

^a OH was not observed in the ¹H NMR

Preparation of DMP 37



N.B. Care must be taken. DMP is explosive and the synthesis is heavily dependant on the internal temperature of the reaction. This method has proven to work most consistently in our hands.

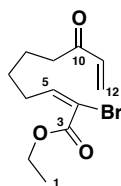
According to a literature procedure,⁹ Ac₂O (178 mL, 1186 mmol) was added to a 500 mL, 2-necked rbf with an internal stirrer bar. TsOH.H₂O (227 mg, 1.2 mmol) was added to the reaction mixture and then IBX (48 g, 171 mmol) was added. The necks of the flask were all wiped clean to ensure no residue was present. The main neck was equipped with a guard tube containing only cotton wool, and the side arm was stoppered with a glass stopper. The reaction mixture was stirred on a medium stirring rate, a blast shield was placed around the reaction set up, and the reaction mixture was heated so the internal temperature was 80 °C (monitored through the side arm). Once the reaction mixture reached an internal temperature of 80 °C, the reaction was stirred at this temperature for 2 hr. After this time, the reaction mixture was a clear solution, with no residue or undissolved reagents. The heat and stirrer was turned off, and the reaction mixture is let cool slowly to RT (in our case, we left the reaction mixture in the dry syn, with no extra insulation required). When the reaction mixture reached RT, it was cooled to 0 °C using an ice bath (temperature of the bath was monitored, not the internal temperature). After leaving the reaction mixture at this temperature for 1.5 hr, the product crashed out of solution. The reaction mixture was then filtered under reduced pressure, washing with Et₂O (5 x 20 mL), taking care to agitate the solid after

each wash. The solid was then transferred into a 100 mL rbf, and dried under high vacuum overnight, behind a blast shield, to afford DMP **37** (60 g, 83%).

¹H NMR (400 MHz, CDCl₃) δ_H 8.36-8.30 (m, 2 H, ArH), 8.10 (td, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.93 (td, *J* = 7.5, 1.0 Hz, 1 H ArH), 2.35 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.03 (s, 3 H, OAc); **¹³C NMR (101 MHz, CDCl₃)** δ_C 175.8 (C=O), 174.9 (C=O), 175.7 (C=O), 142.3 (CAr), 135.8 (CAr), 133.8 (CAr), 131.8 (CAr), 129.1 (CAr), 126.5 (CAr), 20.7 (OAc), 20.4 (OAc), 20.3 (OAc);^b **Mpt:** 128-130 °C (not recommended as DMP has been shown to be explosive at high temperatures). Spectroscopic data are consistent with those reported in the literature.¹⁰

^b One C=O was not observed in the ¹³C NMR

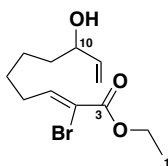
Preparation of (E)-ethyl 2-bromo-8-oxodeca-2,9-dienoate **13**



Following **General Procedure 3**, using DMP (1.17 g, 2.76 mmol) and alcohol **24** (533 mg, 1.85 mmol) afforded the title compound **13** (395 mg, 76%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.66 (t, J = 7.5 Hz, 1 H, H_5), 6.35 (dd, J = 17.5, 10.5 Hz, 1 H, H_{11}), 6.22 (dd, J = 17.5, 1.5 Hz, 1 H, H_{12}), 5.83 (dd, J = 10.5, 1.5 Hz, 1 H, $H_{12'}$), 4.27 (q, J = 7.5 Hz, 2 H, H_2), 2.61 (t, J = 7.5 Hz, 2 H, H_9), 2.52 (q, J = 7.5 Hz, 2 H, H_6), 1.73-1.62 (m, 2 H, H_8), 1.58-1.45 (m, 2 H, H_7), 1.34 (t, J = 7.5 Hz, 3H, H_1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.4 (C10), 162.9 (C3), 148.0 (C5), 136.5 (C11), 128.1 (C12), 111.5 (C4), 62.1 (C2), 39.1 (C9), 31.3 (C6), 28.3 (C7), 23.4 (C8), 14.1 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₂H₁₇NaO₃Br 311.0253, found 311.0249; **IR ν_{max} /cm⁻¹ (thin film)** 2937 (C-H), 1715 (C=O), 1682 (C=O), 1615 (C=C).

Preparation of (*E*)-ethyl 8-hydroxydeca-2,9-dienoate **26**

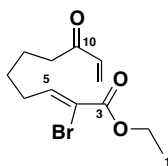


Following **General Procedure 2**, using HWE reagent **25** (1.6 g, 7.00 mmol), NaH (560 mg, 14.0 mmol), NBS (1.2 g, 7.00 mmol) and aldehyde **23** (1.0 g, 7.00 mmol) afforded the title compound **26** (500 mg, 48% over two steps) as a 5:1 (*Z*:*E*) mixture of isomers.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.28 (t, J = 7.0 Hz, 1 H, *H*5), 5.86 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H, *H*11), 5.23 (dd, J = 17.0, 1.5 Hz, 1 H, *H*12), 5.11 (dd, J = 10.5, 1.5 Hz, 1 H, *H*12'), 4.27 (q, J = 7.0 Hz, 2 H, *H*2), 4.15-4.05 (m, 1 H, *H*10), 2.36 (q, J = 7.0 Hz, 2 H, *H*6), 1.65-1.40 (m, 7 H, *H*7, *H*8, *H*9, OH), 1.33 (t, J = 7.0 Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 162.5 (*C*3), 148.3 (*C*5), 145.9 (*C*11), 141.1 (*C*4), 116.5 (*C*12), 73.0 (*C*10), 62.4 (*C*2), 36.6 (*C*9), 32.0 (*C*6), 28.6 (*C*7), 25.1 (*C*8), 14.2 (*C*1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₂H₂₀NaO₃Br 313.0410, found 313.0400; **IR** ν_{max} /cm⁻¹ (**thin film**) 3402 (br., OH), 2934 (C-H), 1714 (C=O), 1624 (C=C).

E isomer data omitted for clarity.

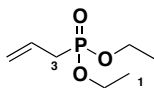
Preparation of (Z)-ethyl 2-bromo-8-oxodeca-2,9-dienoate **27**



Following **General Procedure 3**, using DMP (1.0 g, 2.6 mmol) and alcohol **26** (500 mg, 1.7 mmol) afforded the title compound **27** (390 mg, 80%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.27 (t, $J = 7.5$ Hz, 1 H, H_5), 6.35 (dd, $J = 18.0, 10.5$ Hz, 1 H, H_{11}), 6.22 (dd, $J = 18.0, 2.5$ Hz, 1 H, H_{12}), 5.83 (dd, $J = 10.5, 2.5$ Hz, 1 H, $H_{12'}$), 4.26 (q, $J = 7.5$ Hz, 2 H, H_2), 2.62 (t, $J = 7.5$ Hz, 2 H, H_9), 2.36 (q, $J = 7.5$ Hz, 2 H, H_6), 1.69 (quin, $J = 7.5$ Hz, 2 H, H_8), 1.53 (quin, $J = 7.5$ Hz, 2 H, H_7), 1.32 (t, $J = 7.5$ Hz, 3 H, H_1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.4 (C10), 162.3 (C3), 145.5 (C5), 136.5 (C11), 128.2 (C12), 116.8 (C4), 62.4 (C2), 39.1 (C9), 31.9 (C6), 27.0 (C7), 23.4 (C8), 14.5 (C1); **HRMS (ESI⁺)** m/z calculated for $[M+Na]^+$ C₁₂H₁₇NaO₃Br 311.0253, found 311.0248; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2937 (C-H), 1722 (C=O), 1681 (C=O), 1620 (C=C).

Preparation of diethyl allylphosphonate **30**

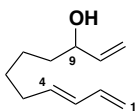


According to a literature procedure,¹¹ allyl bromide (2.9 mL, 33 mmol) was dissolved in triethylphosphite (5.2 mL, 30 mmol) and the resulting solution stirred at 140 °C for 4 hr. The reaction mixture was concentrated under reduced pressure to afford the crude product **30** (5.3 g, 99%) as a colourless oil which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_{H} 5.79-5.65 (m, 1 H, *H*₄) 5.19-5.10 (m, 2 H, *H*₅), 4.07-3.98 (m, 4 H, *H*₂), 2.58-2.49 (m, 2 H, *H*₃), 1.27-1.22 (m, 6 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 127.5 (*C*₄), 119.9 (*C*₅), 63.5 (*C*₂), 31.5 (d, *J* = 140.0 Hz, *C*₃), 16.4 (*C*₁); **LRMS *m/z* (ESI⁺)** 179.1 ([*M*+*H*]⁺ 100%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.¹¹

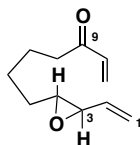
Preparation of (E)-undeca-1,8,10-trien-3-ol **33**



HWE reagent **30** (2.2 g, 12.7 mmol) was dissolved in THF (50 mL) and cooled to -78 °C. *n*BuLi (1.6 M in hexanes, 8 mL, 12.7 mmol) was added and the reaction mixture stirred for 10 min. Aldehyde **23** (1.5 g, 10.6 mmol) was dissolved in THF (8 mL) and DMPU (2.6 mL, 21.2 mmol) was added. This mixture was added dropwise to the HWE/*n*BuLi mixture at -78 °C and the resulting reaction mixture stirred at this temperature for 2 hr. The reaction mixture was allowed to warm to RT, and was quenched by the addition of NH₄Cl (sat. aq.). The layers were separated and the aqueous layer extracted with Et₂O (x 3). The combined extracts were washed with brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **33** (260 mg, 15%).

¹H NMR (400 MHz, CDCl₃) δ_H 6.19 (dt, *J* = 17.0, 10.5 Hz, 1 H, *H*₂) 5.92 (dd, *J* = 15.0, 10.5 Hz, 1 H, *H*₃), 5.74 (ddd, *J* = 16.5, 10.5, 6.5, 1 H, *H*₁₀), 5.57 (dt, *J* = 15.0, 8.0 Hz, 1 H, *H*₄), 5.09 (d, *J* = 17.0 Hz, 1 H, *H*₁₁), 4.99-4.94 (m, 2 H, *H*_{11'}, *H*₁), 4.83 (d, *J* = 10.0 Hz, 1 H, *H*_{1'}), 3.97 (q, *J* = 6.5 Hz, 1 H, *H*₉), 1.98 (q, *J* = 6.5 Hz, 2 H, *H*₅), 1.45-1.38 (m, 2 H, *H*₈), 1.32-1.26 (m, 5 H, *H*₆, *H*₇, OH); **¹³C NMR (101 MHz, CDCl₃)** δ_C 141.2 (C₁₀), 137.3 (C₂), 135.2 (C₄), 131.1 (C₃), 114.8 (C₁, C₁₁), 73.2 (C₉), 36.9 (C₈), 32.5 (C₅), 29.1 (C_{6/7}), 24.9 (C_{6/7}); **HRMS (FI⁺)** *m/z* calculated for [M+H]⁺ C₁₁H₁₈O 166.1358, found 166.1355; **IR** ν_{max}/cm⁻¹ (thin film) 3356 (OH), 2930 (C-H), 2857 (C-H), 1651 (C=C), 1424, 1002, 950, 920, 897, 732.

Preparation of 7-(3-vinyloxiran-2-yl)hept-1-en-3-one **36**

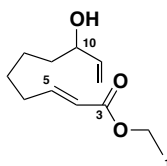


Following **General Procedure 3**, using DMP (103 mg, 0.24 mmol) and alcohol **33** (20 mg, 0.12 mmol) afforded the title compound **36** (14 mg, 72%) as a colourless oil, contaminated with ~5% of an unknown impurity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.28 (dd, $J = 17.5, 10.5$ Hz, 1 H, H_{10}), 6.15 (dd, $J = 17.5, 1.0$ Hz, 1 H, H_{11}), 5.76 (dd, $J = 10.5, 1.0$ Hz, 1 H, $H_{11'}$), 5.50 (ddd, $J = 17.5, 10.5, 7.5$ Hz, 1 H, H_2), 5.38 (dd, $J = 10.5, 1.5$ Hz, 1 H, H_1), 5.19 (dd, $J = 10.0, 1.5$ Hz, 1 H, $H_{1'}$), 3.03 (dd, $J = 7.5, 2.0$ Hz, 1 H, H_3), 2.76 (ddd, $J = 6.0, 5.0, 2.0$ Hz, 1 H, H_4), 2.54 (t, $J = 7.0$ Hz, 2 H, H_8), 1.65-1.55 (m, 2 H, H_7), 1.55-1.35 (m, 4 H, H_5, H_6); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.6 (C_9), 136.5 (C_{10}), 135.8 (C_2), 128.1 (C_{11}), 119.1 (C_1), 60.2 (C_4), 58.7 (C_3), 39.3 (C_8), 31.8 (C_5), 25.5 (C_6), 23.6 (C_7); **HRMS (ESI⁺)** m/z calculated for $[M+Na]^+$ C₁₁H₁₆NaO₂ 203.1043, found 203.1044; **IR ν_{max} /cm⁻¹ (thin film)** 2936 (C-H), 2861 (C-H), 1699 (C=O), 1680, 1642, 1615, 1458, 1403, 1368, 1282.

Stereochemistry across epoxide determined by coupling constant (2.0 Hz, indicating trans-hydrogens)

Preparation of (*E*)-ethyl 8-hydroxydeca-2,9-dienoate **41**

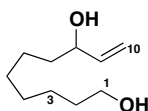


Wittig reagent **40** (3.00 g, 8.4 mmol) was added to a solution of aldehyde **23** (1.00 g, 7.00 mmol) in CH₂Cl₂ (80 mL), and the reaction mixture brought to reflux for 24 hr. The reaction mixture was then allowed to cool to RT and concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, hex:Et₂O (7:3)) to afford compound **41** (1.00 g, 67% as an inseparable 4:1 mixture of *E*:*Z* isomers) as a colourless oil.

Z isomer omitted for clarity

¹H NMR (400 MHz, CDCl₃) δ_H 6.95 (dt, *J* = 15.5, 7.0 Hz, 1 H, *H*5), 5.85 (ddd, *J* = 17.5, 10.5, 6.5 Hz, 1 H, *H*11), 5.81 (d, *J* = 15.5 Hz, 1 H, *H*4), 5.22 (d, *J* = 17.5 Hz, 1 H, *H*12), 5.10 (d, *J* = 10.5 Hz, 1 H, *H*12'), 4.18 (q, *J* = 7.0 Hz, 2 H, *H*2), 3.55-3.45 (m, 1 H, *H*10), 2.30-2.15 (m, 2 H, *H*6), 1.79-1.00 (m, 10 H, *H*7, *H*8, *H*9, OH, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_C 166.7 (C3), 150.2 (C5), 141.1 (C11), 121.4 (C4), 114.7 (C12), 73.0 (C10), 60.2 (C2), 36.7 (C9), 32.1 (C6), 28.8 (C7), 24.9 (C8), 14.3 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₂H₂₀NaO₃ 235.1310, found 235.1303; **IR ν_{max}/cm⁻¹ (thin film)** 3237 (br., OH), 2934 (C-H), 2860 (C-H), 1715 (C=O), 1652 (C=C), 1367, 1269, 1185.

Preparation of dec-9-ene-1,8-diol **42**

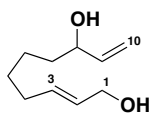


Ester **41** (500 g, 2.4 mmol) was dissolved in Et₂O (20 mL) and the resulting solution was cooled to -78 °C. LiAlH₄ (2.0 M in Et₂O, 2.4 mL, 4.7 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 1 hr. The reaction mixture was then let warm to 0 °C, and H₂O (0.712 mL) and NaOH (15% aq., 0.178 mL) were added cautiously. The reaction mixture was allowed to warm to RT and was stirred rapidly for 1 hr. The reaction was diluted with Et₂O and the reaction mixture was filtered, washed with Et₂O and the filtrate dried over Na₂SO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. This crude product was purified by flash column chromatography (SiO₂, Et₂O) to afford compound **42** (200 mg, 48%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 5.83 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H, *H*₉), 5.18 (d, *J* = 17.0 Hz, 1 H, *H*₁₀), 5.06 (d, *J* = 10.5 Hz, 1 H, *H*_{10'}), 4.05 (q, *J* = 6.5 Hz, 1 H, *H*₈), 3.57 (t, *J* = 6.5 Hz, 2 H, *H*₁), 2.56 (br. s, 1 H, OH), 1.55- 1.45 (m, 4 H, *H*₂/*H*₃/*H*₄/*H*₅/*H*₆/*H*₇), 1.35-1.25 (m, 8 H, *H*₂/*H*₃/*H*₄/*H*₅/*H*₆/*H*₇); **¹³C NMR (126 MHz, CDCl₃)** δ_C 141.3 (C₉), 114.4 (C₁₀), 73.1 (C₈), 60.4 (C₁), 36.8 (C₂/3/4/5/6/7), 32.5 (C₂/3/4/5/6/7), 30.3 (C₂/3/4/5/6/7), 29.5 (C₂/3/4/5/6/7), 28.9 (C₂/3/4/5/6/7), 28.2 (C₂/3/4/5/6/7); **LRMS (ESI⁺)** *m/z* [M+Na]⁺ 195.13.

Spectroscopic properties of this compound are consistent with the data reported in the literature.¹²

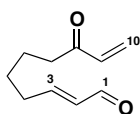
Preparation of (E)-deca-2,9-diene-1,8-diol **43**



Ester **41** (500 g, 2.4 mmol) was dissolved in THF (20 mL) and the resulting solution was cooled to -78 °C. DIBALH (1.0 M in Et₂O, 7 mL, 7.0 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 1 hr. The reaction mixture was then let warm to 0 °C and NH₄Cl (sat. aq.) was added cautiously. The reaction mixture was allowed to warm to RT was diluted with Et₂O and the reaction mixture was filtered, washed with Et₂O and the filtrate dried over Na₂SO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (2:8)) to afford compound **43** (210 mg, 51%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_H 5.90- 5.80 (m, 1 H, *H*9), 5.70-5.55 (m, 2 H, *H*2, *H*3), 5.21 (d, *J* = 17.0 Hz, 1H, *H*10), 5.09 (d, *J* = 10.0 Hz, 1 H, *H*10'), 5.06 (br. s, 1 H, *H*8), 2.50-2.20 (m, 3 H, *H*1, OH), 2.05 (d, *J* = 5.0 Hz, 2 H, *H*4), 1.66-1.45 (m, 2 H, *H*7), 1.40-1.25 (m, 4 H, *H*5, *H*6); **¹³C NMR (101 MHz, CDCl₃)** δ_C 141.3 (*C*9), 132.9 (*C*2), 129.1 (*C*3), 114.5 (*C*10), 73.6 (*C*8), 63.5 (*C*1), 36.8 (*C*7), 32.5 (*C*4), 27.1 (*C*5/6), 24.8 (*C*5/6); **HRMS (ESI⁺) *m/z*** calculated for [M+Na]⁺ C₁₀H₁₈NaO₂ 193.1199, found 193.1206; **IR ν_{max}/cm⁻¹ (thin film)** 3324 (OH), 2929 (C-H), 2856 (C-H), 1425, 1088, 990, 968, 919.

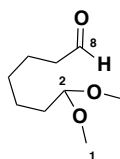
Preparation of (*E*)-8-oxodeca-2,9-dienal **44**



According to a modified literature procedure,¹³ DMP (1.5 g, 3.5 mmol) was added to a solution of alcohol **43** (200 mg, 1.2 mmol) in CH₂Cl₂ (20 mL), and the resulting suspension was stirred at RT overnight. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a white solid. The crude product was adsorbed onto silica and purified quickly by flash column chromatography (SiO₂, pet 40-60:Et₂O (1:1)) to afford compound **44** (200 mg, quant.) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 9.56 (sd, $J = 7.5, 1.0$ Hz, 1 H, *H*1), 6.86 (dt, $J = 15.5, 7.0$ Hz, 1 H, *H*3), 6.37 (ddd, $J = 17.5, 10.5, 1.0$ Hz, 1 H, *H*9) 6.24 (d, $J = 17.5$ Hz, 1 H, *H*10), 6.14 (qq, $J = 7.5, 1.5$ Hz, 1 H, *H*2), 5.86 (d, $J = 10.5$ Hz, 1 H, *H*10'), 2.64 (t, $J = 7.0$ Hz, 2 H, *H*7), 2.39 (q, $J = 7.0$ Hz, 2 H, *H*4), 1.71 (quin., $J = 7.0$ Hz, 2 H, *H*6), 1.56 (quin, $J = 7.0$ Hz, 2 H, *H*5); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.3 (C8), 194.0 (C1), 158.1 (C3), 136.5 (C9), 133.2 (C2), 128.2 (C10), 39.1 (C7), 32.5 (C4), 27.4 (C5), 23.3 (C6); **HRMS (ESI⁺) m/z** calculated for [M+Na]⁺ C₁₀H₁₄NaO₂ 189.0886, found 189.0890; **IR ν_{max} /cm⁻¹ (thin film)** 2970 (C-H), 1739 (C=O), 1638 (C=O), 1366, 1229, 1217, 974.

Preparation of 7,7-dimethoxyheptanal **51**

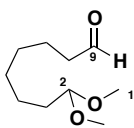


According to a literature procedure,¹⁴ MeOH (15 mL) was added to a solution of cycloheptene (2.4 mL, 20.8 mmol) in CH₂Cl₂ (80 mL) at -78 °C. Ozone was bubbled through the solution until the solution turned blue, after which ozone addition was stopped and oxygen was passed through the solution until the blue colour was discharged. The cold bath was removed and *p*-toluenesulfonic acid (360 mg, 1.9 mmol) was added. The solution was allowed to warm to RT and was stirred for 90 min. Anhydrous NaHCO₃ (700 mg, 8.3 mmol) was added, the mixture stirred for 15 min, and dimethylsulfide (3 mL, 41.6 mmol) was added. This was allowed to stir at RT for 12 hr; the solution was then concentrated under reduced pressure to ~15 mL. CH₂Cl₂ was added, the mixture washed with H₂O and the aqueous layer extracted with CH₂Cl₂ (x 2). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford compound **51** (3.6 g, quant.) as a colourless oil, which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_H 9.76 (s, 1 H, *H*8), 4.36 (t, *J* = 6.0 Hz, 1 H, *H*2), 3.21 (s, 6 H, *H*1), 2.44 (td, *J* = 7.5, 2.0 Hz, 2 H, *H*7), 1.70-1.55 (m, 4 H, *H*6, *H*3), 1.40-1.32 (m, 4 H, *H*4, *H*5); **¹³C NMR (101 MHz, CDCl₃)** δ_C 202.7 (C8), 104.5 (C2), 52.6 (C1), 43.6 (C7), 32.3 (C6 or C3), 29.2 (C5 or C4), 24.5 (C5 or C4), 21.7 (C6 or C3); **LRMS (ESI⁺)** 197.1 ([*M*+Na]⁺ 100%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.¹⁴

Preparation of 8,8-dimethoxyoctanal 52

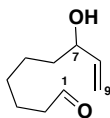


According to a literature procedure,¹⁵ MeOH (30 mL) was added to a solution of cyclooctene (3.3 mL, 30 mmol) in CH₂Cl₂ (70 mL) at -78 °C. Ozone was bubbled through the solution until the solution turned blue, after which ozone addition was stopped and oxygen was passed through the solution until the blue colour was discharged. The cold bath was removed and *p*-toluenesulfonic acid (561 mg, 3 mmol) was added. The solution was allowed to warm to RT and was stirred for 90 min. Anhydrous NaHCO₃ (833 mg, 7.8 mmol) was added, the mixture stirred for 15 min, and dimethylsulfide (5 mL, 66 mmol) was added. This was allowed to stir at RT for 12 hr; the solution was then concentrated under reduced pressure to ~15 mL. CH₂Cl₂ was added, the mixture washed with H₂O and the aqueous layer extracted with CH₂Cl₂ (x 2). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford compound **52** (5.6 g, quant.) as a colourless oil, which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_H 9.77 (t, *J* = 1.5 Hz, 1 H, *H*₉), 4.36 (t, *J* = 6.0 Hz, 1 H, *H*₂), 3.31 (s, 6 H, *H*₁), 2.43 (td, *J* = 7.5, 2.0 Hz, 2 H, *H*₈), 1.66-1.55 (m, 4 H, *H*₇, *H*₃), 1.38-1.28 (m, 6 H, *H*₄, *H*₅, *H*₆); **¹³C NMR (101 MHz, CDCl₃)** δ_C 202.8 (*C*₉), 107.9 (*C*₂), 50.8 (*C*₁), 43.8 (*C*₈), 32.4 (*C*₇/*C*₃), 29.4, 29.2, 24.8 (*C*₄, *C*₅, *C*₆), 21.7 (*C*₇/*C*₃); **LRMS (ESI⁺)** 211.1 ([*M*+*Na*]⁺ 100%).

Spectroscopic properties of this compound are consistent with the data reported in the literature.¹⁵

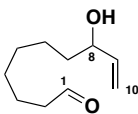
Preparation of 7-hydroxynon-8-enal **53**



Following **General Procedure 1**, using vinyl magnesium bromide (1.0 M in THF, 16 mL, 16 mmol) and aldehyde **51** (2.3 g, 13 mmol) in THF (30 mL) afforded compound **53** (1.5 g, 75%) as a yellow oil, which was unstable to further purification.

¹H NMR (400 MHz, CDCl₃) δ_{H} 9.71 (s, 1 H, *H*1), 5.82 (dd, *J* = 16.0, 10.5 Hz, 1 H, *H*8), 5.18 (dd, *J* = 16.0, 1.0 Hz, 1 H, *H*9), 5.05 (dd, *J* = 10.5, 1.0 Hz, 1 H, *H*9'), 4.10-4.00 (m, 1 H, *H*7), 2.41 (td, *J* = 7.0, 2.0 Hz, 2 H, *H*2), 2.29 (br. s, 1 H, OH), 1.7-1.6 (m, 2 H, *H*3), 1.55-1.45 (m, 2 H, *H*6), 1.35-1.20 (m, 4 H, *H*4, *H*5); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 202.9 (*C*1), 141.3 (*C*8), 114.4 (*C*9), 78.5 (*C*7), 43.7 (*C*2), 36.9, 30.3, 28.5, 21.9 (*C*3, *C*4, *C*5, *C*6); **HRMS (ESI⁺)** *m/z* calculated for [*M*+Na]⁺ C₉H₁₆NaO₂ 179.1043, found 179.1048; **IR** ν_{max} /cm⁻¹ (**thin film**) 3419 (br., OH), 2933 (C-H), 2859 (C-H), 1721 (C=O), 1410, 991, 920.

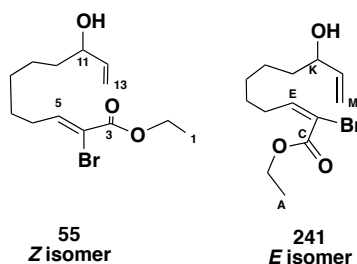
Preparation of 8-hydroxydec-9-enal **54**



Following **General Procedure 1**, using vinyl magnesium bromide (1.0 M in THF, 19 mL, 16 mmol) and aldehyde **52** (3.0 g, 19 mmol) in THF (40 mL) afforded compound **54** (2.6 g, 96%) as a yellow oil, which was unstable to further purification.

¹H NMR (400 MHz, CDCl₃) δ_{H} 9.76 (t, $J = 1.5$ Hz, 1 H, *H*1), 5.87 (ddd, $J = 17.0, 10.5, 6.5$ Hz, 1 H, *H*9), 5.22 (dt, $J = 17.0, 1.5$ Hz, 1 H, *H*10), 5.10 (dt, $J = 10.5, 1.5$ Hz, 1 H, *H*10'), 4.09 (q, $J = 6.5$ Hz, 1 H, *H*8), 2.47-2.39 (m, 2 H, *H*2), 1.86 (br. s, 1 H, OH), 1.68-1.59 (m, 1 H, *H*3), 1.55-1.48 (m, 4 H, *H*7, *H*5), 1.45-1.27 (m, 4 H, *H*6, *H*4); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 202.9 (*C*1), 141.3 (*C*9), 114.4 (*C*10), 73.2 (*C*8), 43.8 (*C*2), 36.9 (*C*7), 29.5 (*C*6), 29.0 (*C*5), 25.3 (*C*4), 21.8 (*C*3); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₀H₁₈NaO₂ 193.1199, found 193.1199; **IR** ν_{max} /cm⁻¹ (thin film) 3429 (br., OH), 2930 (C-H), 2856 (C-H), 1721 (C=O), 1409, 991, 921.

Preparation of (Z and E)-ethyl 2-bromo-9-hydroxyundeca-2,10-dienoate **55**

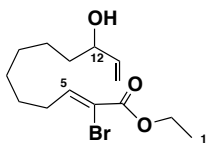


Following **General Procedure 2**, using Horner-Wadsworth-Emmons reagent **25** (500 mg, 1.5 mmol), THF (10 mL), NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol), NBS (117 mg, 1.5 mmol) and aldehyde **53** (253 mg, 1.5 mmol) afforded an inseparable 2.5:1 mixture of compound **55:241** (300 mg, 66%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_H 7.28 (t, *J* = 7.5 Hz, 2.5 H, *H*5), 6.66 (t, *J* = 8.0 Hz, 1 H, *H*E), 5.91-5.79 (m, 3.5 H, *H*12, *H*L), 5.23 (dd, *J* = 17.0, 1.0 Hz, 3.5 H, *H*13, *H*M), 5.11 (dd, *J* = 10.5, 1.5 Hz, 3.5 H, *H*13', *H*M'), 4.31-4.25 (m, 5 H, *H*2), 4.26-4.14 (m, 2 H, *H*B), 4.13-4.07 (m, 3.5 H, *H*11, *H*K), 2.50 (q, *J* = 7.5 Hz, 2 H, *H*F), 2.35 (q, *J* = 7.5 Hz, 5 H, *H*6), 1.61-1.45 (m, 7 H, *H*7, *H*G), 1.45-1.34 (m, 21 H, *H*8, *H*H, *H*9, *H*I, *H*10, *H*J), 1.29 (t, *J* = 7.5 Hz, 10.5 H, *H*1, *H*A); ¹³C NMR (101 MHz, CDCl₃) δ_C 166.8 (CC), 162.5 (C3), 149.2 (CE), 146.1 (C5), 141.2 (C12), 121.3 (CL), 116.4 (C4), 114.7 (C13), 114.6 (CM), 111.4 (CD), 73.1 (C11), 62.4 (C2), 60.1 (CB), 36.8 (C7/8/9/10/G/H/I/J), 32.0 (C6), 29.1 (CF), 27.4 (C7/8/9/10/G/H/I/J), 25.0 (C7/8/9/10/G/H/I/J), 14.2 (C1), 14.1 (CA);^c HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₁₃H₂₁BrNaO₃ 327.0566, found 327.0561; IR ν_{max}/cm⁻¹ (thin film) 3413 (OH), 2931 (C-C), 1715 (C=O), 1624 (C=O), 1463, 1368, 1257.

^c Not all ¹³C peaks were found for the minor isomer

Preparation of (Z)-ethyl 2-bromo-10-hydroxydodeca-2,11-dienoate **56**

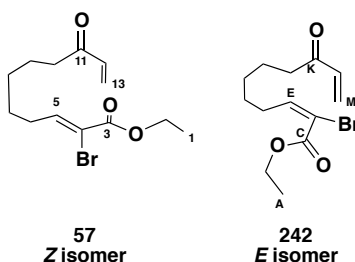


Following **General Procedure 2**, using Horner-Wadsworth-Emmons reagent **25** (1.97 g, 8.8 mmol), THF (20 mL), NaH (60% dispersion in mineral oil, 700 mg, 17.6 mmol), NBS (1.57 mg, 8.8 mmol) and aldehyde **54** (1.50 g, 8.8 mmol) afforded compound **56** (1.71 g, 61%, as an inseparable 5:1 *Z:E* mixture).

Some *E* isomer peaks are omitted for clarity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.30 (t, $J = 7.0$ Hz, 1 H, *H*5), 5.85 (t, $J = 7.5$ Hz, 0.2 H, *H*5 (*E* isomer)), 5.91-5.82 (ddd, $J = 17.5, 10.5, 7.0$ Hz, 1 H, *H*13), 5.24 (dt, $J = 17.5, 1.5$ Hz, 1 H, *H*14), 5.13 (dt, $J = 10.5, 1.5$ Hz, 1 H, *H*14'), 4.29 (q, $J = 7.0$ Hz, 2 H, *H*2), 4.28 (q, $J = 7.0$ Hz, 1 H, *H*12), 2.50 (q, 0.4 H, *H*6 (*E* isomer)), 2.36 (q, $J = 7.5$ Hz, 2 H, *H*6), 1.63 (br. s, 1 H, OH), 1.59-1.45 (m, 10 H, *H*7, *H*8, *H*9, *H*10, *H*11), 1.36 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 162.6 (C3), 148.7 (C5 (*E* isomer)), 146.2 (C5), 141.3 (C13), 116.4 (C4), 114.7 (C14), 73.2 (C2), 62.4 (C12), 36.9 (C11), 32.0 (C6), 31.4, 29.2, 29.1, 25.2 (C7, C8, C9, C10), 14.2 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₄H₂₃BrNaO₃ 341.0723, found 341.0732; **IR ν_{max} /cm⁻¹ (thin film)** 3408 (OH), 2929 (C-C), 1714 (C=O), 1624 (C=O), 1463, 1368, 1254.

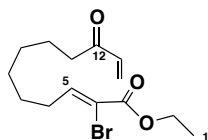
Preparation of (Z and E)-ethyl 2-bromo-9-oxoundeca-2,10-dienoate 57



Following **General Procedure 3**, using DMP (5.51 g, 13.2 mmol), alcohol **55** (2.0 g, 6.6 mmol) and CH_2Cl_2 (80 mL) afforded compound **57** (1.52 g, 76%, 4:1 Z:E isomers) as a colourless oil.

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.29 (t, $J = 7.5$ Hz, 4 H, *H*5), 6.96 (dt, $J = 16.0, 7.0$ Hz, 1 H, *HL*), 6.67 (t, $J = 7.5$ Hz, 1 H, *HE*), 6.39 (dd, $J = 17.5, 10.5$ Hz, 4 H, *H*12), 6.35 (dd, $J = 10.5, 1.5$, 4 H, *H*13), 6.23 (dd, $J = 17.5, 1.5$, 4 H, *H*13'), 5.87-5.82 (m, 2 H, *HM*, *HM'*), 4.32-4.25 (m, 8 H, *H*2), 4.20, (q, $J = 7.0$ Hz, 2 H, *HB*), 2.65-2.58 (m, 8 H, *H*10), 2.51 (q, $J = 7.5$ Hz, 2 H, *HJ*), 2.37 (q, $J = 7.5$ Hz, 8 H, *H*6), 2.22 (qd, $J = 7.5, 1.5$ Hz, 2 H, *HF*), 1.73-1.61 (m, 10 H, *H*9, *HI*), 1.58-1.47 (m, 10 H, *H*7, *HG*), 1.44-1.27 (m, 25 H, *H*8, *HH*, *H*1, *HA*); **^{13}C NMR (126 MHz, CDCl_3)** δ_{C} 200.7 (*C*11), 290.0 (*CK*), 166.7 (*CC*), 162.5 (*C*3), 149.0 (*CL*), 148.3 (*CE*), 145.8 (*C*5), 136.6 (*C*12), 128.0 (*C*13), 121.5 (*CM*), 116.6 (*C*4), 111.3 (*CD*), 62.4 (*C*2), 60.2 (*CB*), 39.4 (*C*10), 31.9 (*C*6), 31.8 (*CF*), 31.2 (*CJ*), 31.1, 28.9, 28.7, 28.6, 27.8, 27.4 (*C*7, *C*8, *C*9, *CG*, *CH*, *CI*), 14.3 (*C*1), 14.2 (*CA*); **HRMS (ESI⁺)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{19}\text{BrNaO}_3$ 325.0410, found 325.0405; **IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film)** 2934 (C-H), 1716 (C=O), 1681 (C=O), 1617, 1401, 1367.

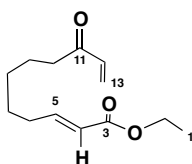
Preparation of (Z)-ethyl 2-bromo-10-oxododeca-2,11-dienoate **58**



Following **General Procedure 3**, using DMP (400 mg, 0.94 mmol), alcohol **56** (200 mg, 0.63 mmol) and CH₂Cl₂ (10 mL) afforded compound **58** (200 mg, quant.) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.21 (t, J = 7.0 Hz, 1 H, *H*5), 6.28 (dd, J = 17.5, 10.5 Hz, 1 H, *H*13), 6.15 (dd, J = 17.5, 1.0 Hz, 1 H, *H*14), 5.75 (dd, J = 10.5, 1.0 Hz, 1 H, *H*14'), 4.20 (q, J = 7.0 Hz, 2 H, *H*2), 2.52 (t, J = 7.0 Hz, 2 H, *H*11), 2.27 (q, J = 7.0 Hz, 2 H, *H*6), 1.60-1.52 (m, 2 H, *H*10), 1.46-1.39 (m, 4 H, *H*7, *H*8/9), 1.39-1.24 (m, 2 H, *H*8/9), 1.26 (t, J = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 201.0 (C12), 162.9 (C3), 148.5 (C5), 136.6 (C13), 128.0 (C14), 116.4 (C4), 62.4 (C2), 39.5 (C11), 32.0 (C6), 29.0 (C8/9), 28.9 (C8/9), 27.4 (C7), 23.8 (C10), 14.2 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₄H₂₂BrO₃ 317.0747, found 317.0751; **IR ν_{max} /cm⁻¹ (thin film)** 2929 (C-H), 1726 (C=O), 1682 (C=O), 1400, 1367, 1253, 1037.

Preparation of (*E*)-ethyl 9-oxoundeca-2,10-dienoate **59**



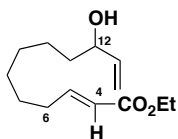
Bromo-olefin **57** (50 mg, 0.17 mmol) was dissolved in 1,4-dioxane (3 mL) under an Ar atmosphere and Pd(PPh₃)₄ (10 mg, 0.008 mmol) and K₂CO₃ (70 mg, 0.51 mmol) were added. The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product (2:1 SM:**59**). This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **59** (10 mg, 26%) and recovered starting material **57** (30 mg, 58%).

¹H NMR (400 MHz, CDCl₃) δ_H 6.97 (dt, *J* = 15.5, 7.5 Hz, 1 H, *H*5), 6.37 (dd, *J* = 17.5, 10.5 Hz, 1 H, *H*12), 6.24 (dd, *J* = 17.5, 1.5 Hz, 1 H, *H*13), 5.85 (dd, *J* = 10.5, 1.5 Hz, 1 H, *H*13'), 5.83 (dt, *J* = 15.5, 1.5, 1 H, *H*4), 4.20 (q, *J* = 7.0 Hz, 2 H, *H*2), 2.61 (t, *J* = 7.5 Hz, 2 H, *H*10), 2.23 (qd, *J* = 7.5, 1.5 Hz, 2 H, *H*6), 1.66 (quin, *J* = 7.5 Hz, 2 H, *H*9), 1.51 (quin, *J* = 7.5 Hz, 2 H, *H*7), 1.40-1.33 (m, 2 H, *H*8), 1.31 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_C 200.7 (C11), 166.8 (C3), 149.0 (C5), 136.6 (C12), 128.0 (C13), 121.5 (C4), 65.9 (C2), 39.4 (C10), 31.9 (C6), 28.7 (C8), 27.8 (C7), 23.6 (C9), 14.3 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₃H₂₀NaO₃ 247.1305, found 247.1302; **IR ν_{max}/cm⁻¹ (thin film)** 2934 (C-H), 1716 (C=O), 1681 (C=O), 1653, 1402, 1367, 1263, 1181, 1043.

Alternative preparation:

Bromo-olefin **57** (50 mg, 0.17 mmol) was dissolved in DMF (3 mL) under an Ar atmosphere and Pd(OAc)₂ (3.8 mg, 0.008 mmol), TBACl (39 mg, 0.17 mmol) and NaHCO₃ (43 mg, 0.51 mmol) were added. The reaction mixture was heated to 90 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product (1.2:1 SM:**57**). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **59** (12 mg, 26%) and recovered starting material **57** (15 mg, 29%). Compound **59** had identical data to that seen previously.

Preparation of (E)-ethyl 10-hydroxydodeca-2,11-dienoate **60**



Bromo-olefin **56** (50 mg, 0.16 mmol) was dissolved in 1,4-dioxane (5 mL) under an Ar atmosphere and Pd(PPh₃)₄ (10 mg, 0.008 mmol) and K₂CO₃ (66 mg, 0.48 mmol) were added. The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product (1:1.1, **60**:SM). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **60** (13 mg, 34% 1:1.1 mixture of **60**:SM (yield based on **60**)).

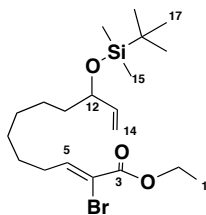
SM omitted for clarity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.98 (dt, J = 15.5, 7.0 Hz, 1 H, H_5), 5.89 (dddd, J = 17.5, 10.0, 6.0, 1.0 Hz, 1 H, H_{13}), 5.83 (dt, J = 15.5, 1.5 Hz, 1 H, H_4), 5.24 (dt, J = 17.5, 1.5 Hz, 1 H, H_{14}), 5.13 (dt, J = 10.5, 1.5 Hz, 1 H, H_{14}'), 4.21 (q, J = 7.0 Hz, 2 H, H_2), 4.14 (quin, J = 7.0 Hz, 1 H, H_{12}), 4.12 (br. s, 1 H, OH), 2.24-2.18 (m, 2 H, H_6), 1.58-1.45 (m, 10 H, H_7 , H_8 , H_9 , H_{10} , H_{11}), 1.36 (t, J = 7.0 Hz, 3 H, H_1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 166.8 (C3), 149.4 (C5), 141.3 (C13), 121.3 (C4), 114.7 (C14), 73.2 (C2), 60.2 (C12), 36.9 (C11), 32.1 (C6), 29.2, 28.2, 27.4, 25.2 (C7, C8, C9, C10), 14.3 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₄H₂₄NaO₃ 263.1629, found 263.1618; **IR ν_{max} /cm⁻¹ (thin film)** 3416 (OH), 2986 (C-C), 1715 (C=O), 1529, 1445, 1257, 1184, 1041.

Alternative preparation:

Bromo-olefin **56** (50 mg, 0.16 mmol) was dissolved in DMF (5 mL) under an Ar atmosphere and Pd(OAc)₂ (3.8 mg, 0.008 mmol), TBACl (44 mg, 0.16 mmol) and NaHCO₃ (40 mg, 0.48 mmol) were added. The reaction mixture was heated to 90 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc and the filtrate dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product (1.2:1 SM:**60**). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **60** (15 mg, 39% 1:2.1 mixture of **60**:SM (yield based on **60**)). Compound **60** had identical data to that seen previously.

Preparation of (Z)-ethyl 2-bromo-10-((*tert*-butyldimethylsilyl)oxy)dodeca-2,11-dienoate **62**



Alcohol **56** (500 mg, 1.57 mmol) was dissolved in CH₂Cl₂ (15 mL) and the resulting solution cooled to 0 °C. Imidazole (534 mg, 7.85 mmol) and TBSCl (474 mg, 3.14 mmol) were added and the resulting solution was let warm to RT. The reaction mixture was stirred for 2 hr, and then diluted with CH₂Cl₂. Brine was added to the reaction mixture, the layers separated and the aqueous layer extracted with CH₂Cl₂ (x 2). The combined extracts were dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (99:1)) to afford compound **62** (621 mg, 92%).

¹H NMR (400 MHz, CDCl₃) δ_H 7.25 (t, *J* = 7.5 Hz, 1 H, *H*₅), 5.76 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1 H, *H*₁₃), 5.09 (dt, *J* = 17.0, 1.5 Hz, 1 H, *H*₁₄), 4.98 (dt, *J* = 10.5, 1.5 Hz, 1 H, *H*_{14'}), 4.24 (q, *J* = 7.0 Hz, 2 H, *H*₂), 4.04 (q, *J* = 6.0 Hz, 1 H, *H*₁₂), 2.30 (q, *J* = 7.5 Hz, 2 H, *H*₆), 1.48-1.39 (m, 4 H, *H*₇, *H*_{8/9/10/11}), 1.32-1.28 (m, 4 H, *H*_{8/9/10/11}), 1.30 (t, *J* = 7.0 Hz, 3 H, *H*₁), 0.86 (m, 11 H, *H*₁₇, *H*_{8/9/10/11}), 0.02 (s, 3 H, *H*₁₅) 0.00 (s, 3 H, *H*_{15'}); ¹³C NMR (101 MHz, CDCl₃) δ_C 162.6 (C3), 146.3 (C5), 141.9 (C13), 116.3 (C4), 113.5 (C14), 73.8 (C12), 62.4 (C2), 38.0 (C7/8/9/10/11), 32.1 (C6), 29.3 (C7/8/9/10/11), 29.3 (C7/8/9/10/11),

25.9 (C17), 25.0 (C7/8/9/10/11), 18.3 (C7/8/9/10/11), 14.2 (C1), -4.4 (C15), -4.8 (C15');^d

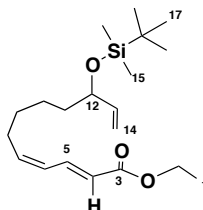
HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₂₀H₃₇BrNaSiO₃ 455.1588, found 455.1578;

IR $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2929 (C-C), 2856 (C-C), 1717 (C=O), 1625, 1463, 1366, 1251, 1040, 920.

^d C16 was not observed in the ¹³C spectrum

Preparation of (2*E*,4*Z*)-ethyl 10-((*tert*-butyldimethylsilyl)oxy)dodeca-2,4,11-trienoate

63



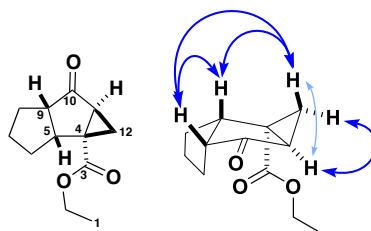
Bromo-olefin **62** (100 mg, 0.23 mmol) was dissolved in DMF (10 mL) under an Ar atmosphere and Pd(OAc)₂ (5.2 mg, 0.023 mmol), TBACl (52 mg, 0.23 mmol) and NaHCO₃ (39 mg, 0.46 mmol) were added. The reaction mixture was heated to 90 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product (3:1 SM:**63**). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **63** (20 mg, 25%) and recovered starting material (60 mg, 60%).

¹H NMR (500 MHz, CDCl₃) δ_H 7.22 (dd, *J* = 15.5, 10.0 Hz, 1 H, *H*5), 8.16-6.05 (m, 2 H, *H*6, *H*7), 5.77-5.70 (m, 2 H, *H*4, *H*13), 5.10 (dt, *J* = 17.0, 1.5 Hz, 1 H, *H*14), 4.99 (dt, *J* = 10.0, 1.5 Hz, 1 H, *H*14'), 4.17 (q, *J* = 7.0, 2 H, *H*2), 4.04 (q, *J* = 6.0 Hz, 1 H, *H*12), 2.14 (q, *J* = 7.0 Hz, 2 H, *H*8), 1.48-1.38 (m, 4 H, *H*9, *H*11), 1.26 (t, *J* = 7.0 Hz, 3 H, *H*1), 0.87-0.83 (m, 2 H, *H*10), 0.86 (s, 9 H, *H*17), 0.01 (s, 3 H, *H*15), 0.00 (s, 3 H, *H*15'); **¹³C NMR (126 MHz, CDCl₃)** δ_C 167.3 (C3), 145.1 (C5), 144.5 (C6/7), 141.7 (C13), 128.5 (C6/7), 119.2 (C4), 113.6 (C14), 73.7 (C12), 60.2 (C2), 37.8 (C9/11), 32.9 (C8), 28.7 (C9/11), 25.9 (C17), 24.7 (C10), 14.3 (C1), -4.4 (C15), -4.8 (C15');^e **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺

^e C16 was not observed in the ¹³C spectrum

$\text{C}_{20}\text{H}_{36}\text{NaSiO}_3$ 375.2326, found 375.2317; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2930 (C-H), 2857 (C-H), 1715 (C=O), 1643, 1618, 1463, 1367, 1303, 1253, 1136.

Preparation of (1aR*, 1bR*, 4aS*, 5aS*)-ethyl 5-oxooctahydro-1H-cyclopropa[a]pentalene-1a-carboxylate **21**

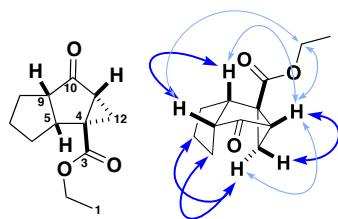


Following **General Procedure 5**, using cyclisation precursor **13** (*E* isomer) (50 mg, 0.17 mmol), THF (4 mL), NaH (7 mg, 0.17 mmol) afforded compound **21** (23 mg, 65%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 4.16 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.90 (q, $J = 7.5$ Hz, 1 H, *H*5), 2.56 (q, $J = 7.5$ Hz, 1 H, *H*9), 2.42 (dd, $J = 9.5, 4.5$ Hz, 1 H, *H*11), 2.23 (ddd, $J = 13.5, 7.5, 4.0$ Hz, 1 H, *H*8), 1.82 (dt, $J = 7.5, 2.0$ Hz, 2 H, *H*6), 1.76 (dd, $J = 4.5, 1.0$ Hz, 1 H, *H*12), 1.71-1.63 (m, 1 H, *H*7), 1.55-1.46 (m, 1 H, *H*7'), 1.38 (t, $J = 4.5$ Hz, 1 H, *H*12'), 1.31-1.29 (m, 1 H, *H*8'), 1.26 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 214.0 (C10), 171.0 (C3), 60.9 (C2), 48.6 (C5), 43.0 (C9), 36.7 (C4), 34.8 (C11), 31.9 (C8), 26.6 (C7, C6), 22.7 (C12), 14.2 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₂H₁₆NaO₃ 231.0992, found 231.0986; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2929 (C-H), 2855 (C-H), 1730 (C=O), 1670 (C=O), 1471, 1251, 833.

N.B. Key nOe interactions are highlighted. Bold dark blue indicate a strong correlation and light blue indicate a weak correlation.

Preparation of (1a*S, 1b*R**, 4a*S**, 5a*R**)-ethyl 5-oxooctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **77****



Following **General Procedure 4**, using cyclisation precursor **27** (*Z* isomer) (50 mg, 0.17 mmol), toluene (4 mL), KOH (39 mg, 0.68 mmol), tetrabutylammonium bisulfate (6 mg, 0.02 mmol) at RT afforded compound **77** (25 mg, 71%).

Following **General Procedure 4**, using cyclisation precursor **13** (*E* isomer) (50 mg, 0.17 mmol), toluene (4 mL), KOH (39 mg, 0.68 mmol), tetrabutylammonium bisulfate (6 mg, 0.02 mmol) at RT afforded compound **77** (29 mg, 83%).

Following **General Procedure 5**, using cyclisation precursor, **13** (*Z* isomer) (50 mg, 0.17 mmol), THF (4 mL), NaH (7 mg, 0.17 mmol) afforded compound **77** (28 mg, 80%).

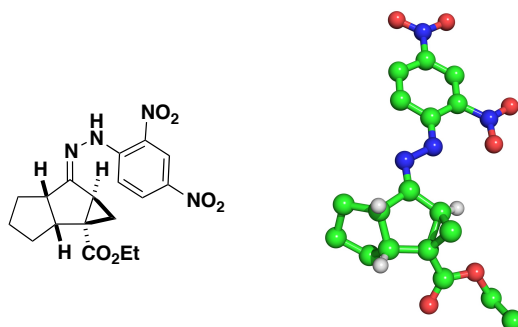
¹H NMR (500 MHz, CDCl₃) δ_H 4.17 (q, *J* = 7.0 Hz, 2 H, *H*2), 3.60-3.50 (m, 1 H, *H*5), 2.87 (dd, *J* = 10.5, 9.5 Hz, 1 H, *H*9), 2.44 (ddd, *J* = 10.5, 4.5, 1.0 Hz, 1 H, *H*11), 2.10-2.05 (m, 1 H, *H*8), 1.92-1.73 (m, 3 H, *H*7, *H*6, *H*12), 1.67-1.57 (m, 2 H, *H*8', *H*7'), 1.51-1.42 (m, 1 H, *H*6'), 1.39 (t, *J* = 4.5 Hz, 1 H, *H*12'), 1.26 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_C 213.2 (C10), 172.1 (C3), 61.1 (C2), 54.0 (C5), 40.2 (C9), 37.7 (C11), 30.9 (C8), 30.2 (C6), 29.5 (C7), 18.5 (C12), 14.2 (C1)^f; **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺

^f C4 not observed in ¹³C spectrum

$\text{C}_{12}\text{H}_{16}\text{NaO}_3$ 231.0992, found 231.0986; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2929 (C-C), 2855 (C-C), 1730 (C=O), 1670 (C=O).

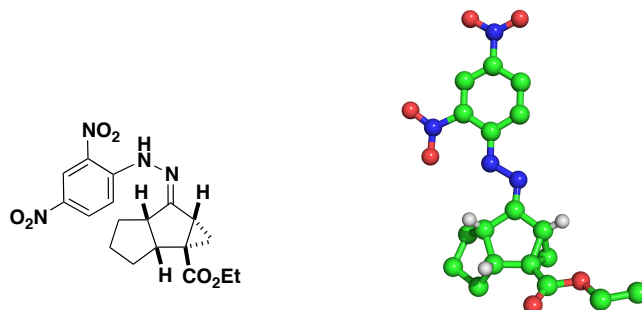
N.B. Key nOe interactions are highlighted. Bold dark blue indicate a strong correlation and light blue indicate a weak correlation.

Preparation of (1a*R,1b*R**,4a*S**,5a*S**,*Z*)-ethyl 5-(2-(2,4-dinitrophenyl)hydrazono)octahydro-1*H*-cyclopropa[*a*]pentalene-1a-carboxylate **78****



Ketone **21** (20 mg, 0.096 mmol) was dissolved in MeOH (5 mL) and the solution cooled to 0 °C. 2,4-Dinitrophenylhydrazine (190 mg, 50% in H₂O, 0.48 mmol) and H₂SO₄ (0.01 mL) were added and the reaction mixture was stirred at 0 °C for 30 min. After this time, the reaction mixture was let warm to RT, and stirred at this temperature for 90 min. The reaction mixture was diluted with Et₂O and passed through a small plug of silica, eluting with Et₂O. The reaction mixture was concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **78** (28 mg, 74%). X-ray diffraction quality crystals were grown by vapour diffusion from EtOAc and pentanes. An X-ray crystal structure confirmed the identity of this product.

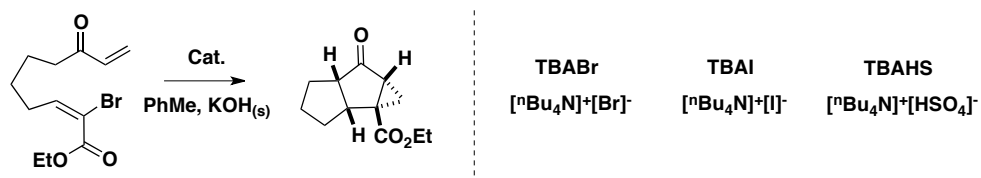
Preparation of (1a*S,1b*R**,4a*S**,5a*R**,*E*)-ethyl 5-(2-(2,4-dinitrophenyl)hydrazono)octahydro-1*H*-cyclopropa[*a*]pentalene-1a-carboxylate **79****



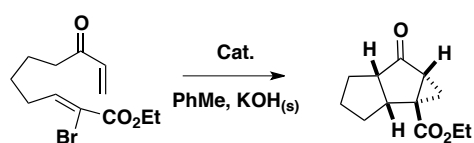
Ketone **77** (20 mg, 0.096 mmol) was dissolved in MeOH (5 mL) and the solution cooled to 0 °C. 2,4-Dinitrophenylhydrazine (190 mg, 50% in H₂O, 0.48 mmol) and H₂SO₄ (0.01 mL) were added and the reaction mixture was stirred at 0 °C for 30 min, After this time, the reaction mixture was let warm to RT, and stirred at this temperature for 90 min. The reaction mixture was diluted with Et₂O and passed through a small plug of silica, eluting with Et₂O. The reaction mixture was concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **79** (25 mg, 66%). X-ray diffraction quality crystals were grown by vapour diffusion from EtOAc and pentanes. An X-ray crystal structure confirmed the identity of this product.

NMR experiments

KOH_(s) (7 mg, 0.12 mmol) and phase-transfer catalyst (0.003 mmol) were placed in an NMR tube and starting material (*E* or *Z* isomer, 10 mg, 0.034 mmol) dissolved in toluene-d₈ (0.5 mL) was added. The NMR tube was then placed in the NMR machine, the sample is shimmed, locked and then a ¹H NMR was taken every 30 mins for up to 16 hr. The data was then analysed on TOPSPIN by integration of characteristic peaks in the starting material, intermediate (if necessary) and product, and graphs are generated.



Time/min	TBABr [product]	TBAI [product]	TBAHS [product]
0	9.09	0.745	3.656
30	10.526	0.745	3.891
60	34.013	0.782	6.018
90	55.505	0.819	8.41
120	68.858	0.865	10.471
150	76.864	0.892	12.789
180	78.431	0.959	16.444
210	84.099	1.034	20.966
240	86.879	1.137	26.459
270	88	1.235	32.247
300	92.8	1.371	39.33
330	92.905	1.492	45.24
360	93	1.634	51.151
390	93.855	1.802	56.077
420	94.406	2	61.115
450	94.962	2.187	65.376
480	95.202	2.436	68.192
510	95.848	2.677	71.637
540	96.178	2.944	73.99
570	97.129	3.247	75.84
600	97.2912	3.572	77.331
630	97.623	3.983	78.491
660	97.767	4.369	79.593
690	97.836	4.825	80.453
720	97.899	5.36	81.363
750	98.1685	5.993	82.088
780	98.493	6.536	83.023
810	100	7.209	82.484
840	100	8.058	83.475



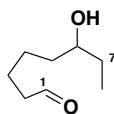
TBABr
[ⁿBu₄N]⁺[Br]⁻

TBAI
[ⁿBu₄N]⁺[I]⁻

TBAHS
[ⁿBu₄N]⁺[HSO₄]⁻

Time/min	TBAHS [product]	TBABr [product]	TBAI [product]
0	0	0	0
30	5.213	4.762	0
60	7.834	6.542	0
90	10.314	9.091	0
120	12.664	11.504	0
150	14.53	13.043	0
180	17.695	15.254	0
210	20.949	17.355	0
240	23.372	18.699	0
270	26.74	23.077	0
300	29.329	25.926	0
330	32.66	27.536	0
360	34.853	30.07	0.99
390	37.695	31.973	1.96
420	39.21	36.306	2.9
450	43.182	40.476	3.8
480	45.799	45.946	4.7
510	48.98	49.495	5.6
540	50.739	52.83	7.4
570	53.271	54.751	8.3
600	55.752	59.35	9
630	58.42	60.784	9.9

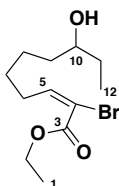
Preparation of 6-hydroxyoctanal **81**



Following **General Procedure 1**, using ethyl magnesium bromide (1.0 M in THF, 9.4 mL, 9.4 mmol), aldehyde **22** (1.0 g, 6.245 mmol) in THF (20 mL) afforded compound **XX** (900 mg, 67%) as a yellow oil, which was unstable to further purification.

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.70 (t, $J = 1.5$ Hz, 1 H, H_1), 4.05 (t, $J = 7.0$ Hz, 1 H, H_6).

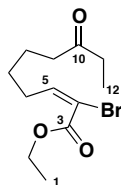
Preparation of (*E*)-ethyl 2-bromo-8-hydroxydec-2-enoate **82**



Following **General Procedure 2**, using SG reagent **19** (1.2 g, 3.5 mmol), NaH (280 mg, 7.0 mmol), NBS (618 mg, 3.5 mmol) and aldehyde **81** (500 g, 3.5 mmol) afforded the title compound **82** (400 mg, 31% over two steps).

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.67 (t, $J = 7.5$ Hz, 1 H, *H*5) 4.27 (q, $J = 7.0$ Hz, 2 H, *H*2), 3.55-3.50 (m, 1 H, *H*10), 2.51 (q, $J = 7.5$ Hz, 2 H, *H*6), 1.65 (br. s, 1 H, OH), 1.52-1.45 (m, 6 H, *H*7, *H*8, *H*9), 1.45-1.35 (m, 2 H, *H*11), 1.34 (t, $J = 7.0$ Hz, 3 H, *H*1), 0.94 (t, $J = 7.5$ Hz, 3 H, *H*12); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 162.9 (C3), 150.9 (C5), 116.5 (C4), 73.1 (C10), 62.6 (C2), 36.6 (C7/8/9/11), 34.3 (C6), 31.4 (C7/8/9/11), 30.2 (C7/8/9/11), 28.8 (C7/8/9/11), 14.2 (C1), 9.9 (C12); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₂H₂₁BrNaO₃ 315.0566, found 315.0573; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3401 (OH), 2932 (C-H), 1713 (C=C), 1461, 1369, 1222, 1095, 1026.

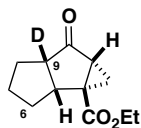
Preparation of (E)-ethyl 2-bromo-8-oxodec-2-enoate **83**



Following **General Procedure 3**, using DMP (580 mg, 1.37 mmol) and alcohol **82** (200 mg, 0.68 mmol) afforded compound **83** (200 mg, quant.) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.67 (t, J = 7.5 Hz, 1 H, H_5) 4.29 (q, J = 7.0 Hz, 2 H, H_2), 2.53 (q, J = 7.5 Hz, 2 H, H_6), 2.47-2.41 (m, 4 H, H_9 , H_{11}), 1.67-1.60 (m, 2 H, H_8), 1.52-1.45 (m, 2 H, H_7), 1.36 (t, J = 7.0 Hz, 3 H, H_1), 1.07 (t, J = 7.5 Hz, 3 H, H_{12}); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 211.3 (C10), 162.9 (C3), 148.1 (C5), 111.5 (C4), 62.4 (C2), 41.9 (C9/11), 35.9 (C9/11), 31.9 (C6), 28.3 (C7), 23.4 (C8), 14.1 (C1), 7.8 (C12); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₂H₁₉BrNaO₃ 313.0410, found 313.0408; **IR ν_{max} /cm⁻¹ (thin film)** 2938 (C-H), 1712 (C=C), 1459, 1369, 1221, 1115, 1025.

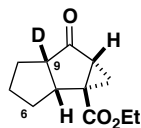
Preparation of (1aS*, 1bR*, 4aS*, 5aR*)-ethyl 5-oxooctahydro-1H-cyclopropa[a]pentalene-1a-carboxylate-4a-d 84



Tetrabutylammonium bisulfate (6 mg, 0.02 mmol) was added to a solution of the cyclisation precursor **27** (Z isomer) (50 mg, 0.17 mmol) in toluene (4 mL). KOD_(aq) (40% solution in D₂O, 1.7 mL, 0.68 mmol) was added and the resulting solution stirred until the reaction was complete (determined by TLC). The mixture was quenched with D₂O, the layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2) to afford compound **84** (28 mg, 79%).

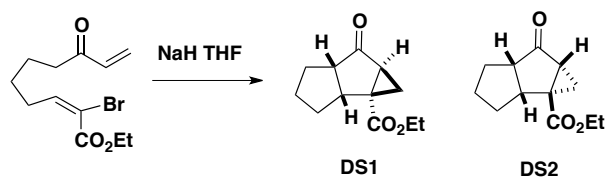
¹H NMR (500 MHz, CDCl₃) δ_H 4.09 (q, *J* = 7.0 Hz, 2 H, *H*₂), 3.51-3.46 (m, 1 H, *H*₅), 2.36 (dd, *J* = 10.0, 4.5 Hz, 1 H, *H*₁₁), 2.02-1.94 (m, 1 H, *H*₆), 1.83-1.67 (m, 3 H, *H*₇, *H*₈, *H*₁₂), 1.59-1.51 (m, 2 H, *H*_{6'}, *H*_{7'}), 1.43-1.37 (m, 1 H, *H*_{8'}), 1.32 (t, *J* = 4.5 Hz, 1 H, *H*_{12'}), 1.19 (t, *J* = 7.0 Hz, 3 H, *H*₁); ¹³C NMR (126 MHz, CDCl₃) δ_C 213.2 (C₁₀), 172.1 (C₃), 61.1 (C₂), {53.8, 53.6, 53.4, 1:1:1 t, *J*_{C-D} = 20.5 Hz, (C₉)}, 40.2 (C₅/11), 40.1 (C₅/11), 37.7 (C₄), 30.9 (C₆), 30.1 (C₈), 29.5 (C₇), 22.7 (C₁₂), 14.2 (C₁); HRMS (ESI⁺) *m/z* calculated for [M+H]⁺ C₁₂H₁₆²HO₃ 210.1235, found 210.1236; IR ν_{max}/cm⁻¹ (thin film) 2957 (C-C), 1720 (C=O), 1451, 1380, 1247, 1202, 1132.

Preparation of (1a*S**, 1b*R**, 4a*S**, 5a*R**)-ethyl 5-oxooctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate-4*a-d* **84**



Tetrabutylammonium bisulfate (6 mg, 0.02 mmol) was added to a solution of the cyclisation precursor **13** (*E* isomer) (50 mg, 0.17 mmol) in toluene (4 mL). KOD_(aq) (40% solution in D₂O, 1.7 mL, 0.68 mmol) was added and the resulting solution stirred until the reaction was complete (determined by TLC). The mixture was quenched with D₂O, the layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2) to afford compound **84** (23 mg, 65%) with identical spectroscopic properties as observed previously.

Sequestering the cation:



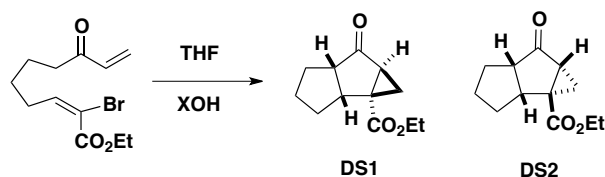
NaH (2.8 mg, 0.07 mmol) was dissolved in THF (0.5 mL) and the Na⁺ sequestering agent was added. The resulting solution was stirred for one hr. After this time, cyclisation precursor **13** (*E* isomer) (10 mg, 0.034 mmol) was dissolved in THF (0.5 mL) and this was added to the reaction mixture. The resulting solution was stirred until TLC showed complete consumption of starting material. The crude reaction mixture was filtered through a small plug of silica, eluting with Et₂O. The filtrate was concentrated under reduced pressure and the subsequent ¹H NMR was used to determine the diastereomeric ratio.

Alternative method:

Cyclisation precursor **13** (*E* isomer) (10 mg, 0.034 mmol) was dissolved in THF (1 mL) and NaH (2.8 mg, 0.07 mmol) and the Na⁺ sequestering agent were added. The resulting solution was stirred until TLC showed complete consumption of starting material. The crude reaction mixture was filtered through a small plug of silica, eluting with Et₂O. The filtrate was concentrated under reduced pressure and the subsequent ¹H NMR was used to determine the diastereomeric ratio (which was exactly the same to the previous method in all cases).

Sequestering agent	Equivalents wrt NaH	DS1	DS2
15-crown-5	0	1	0
15-crown-5	1	1	0.4
15-crown-5	2	1	0.67
2.2.1 cryptand	1	0	1

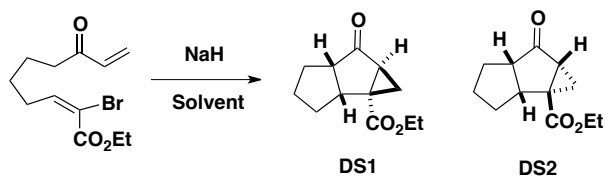
Altering the size of the cation:



Cyclisation precursor **13** (*E* isomer) (10 mg, 0.034 mmol) was dissolved in THF (1 mL) and XOH (0.07 mmol) was added. The reaction mixture was stirred until TLC showed complete consumption of starting material. The crude reaction mixture was filtered through a small plug of silica, eluting with Et₂O. The filtrate was concentrated under reduced pressure and the subsequent ¹H NMR was used to determine the diastereomeric ratio.

Base	DS1	DS2
NaOH	1	0
KOH	1	0
RbOH.xH ₂ O	1	0
CsOH.H ₂ O	1.0	0.63

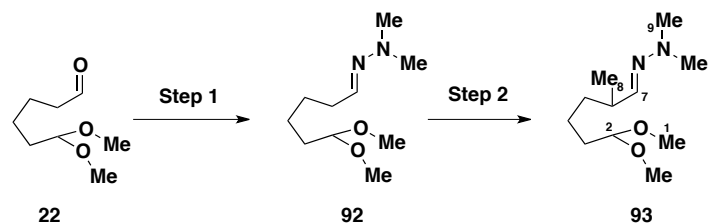
Changing the solvent:



Cyclisation precursor **13** (*E* isomer) (10 mg, 0.034 mmol) was dissolved in solvent (1 mL) and NaH (2.8 mg, 0.07 mmol) was added. The reaction mixture was stirred until TLC showed complete consumption of starting material. The crude reaction mixture was filtered through a small plug of silica, eluting with Et₂O. The filtrate was concentrated under reduced pressure and the subsequent ¹H NMR was used to determine the diastereomeric ratio.

Solvent	DS1	DS2
THF	1	0
MeCN	1	1.5
DMF	0	1
DMSO	0	1

Preparation of (*E*)-2-(6,6-dimethoxy-2-methylhexylidene)-1,1-dimethylhydrazine **93**



Step 1:

According to a modified literature procedure,¹⁶ aldehyde **22** (2.30 g, 14.4 mmol) was cooled to 0 °C and *N,N*-dimethyl hydrazine (1.31 mL, 17.3 mmol) was added. The reaction mixture was stirred for 30 min. Et₂O and H₂O were added to the reaction mixture, the layers separated and the organic layer dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford compound **92** (2.20 g, 76%) as a clear oil.

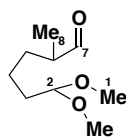
Step 2:

Diisopropylamine (2.6 mL, 18.5 mmol) was dissolved in THF (19 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M in hexanes, 11.6 mL 18.5 mmol) was added and the reaction mixture allowed to warm to 0 °C. After 15 min at this temperature, the reaction mixture was cooled back down to -78 °C. **92** from step 1 (2.20 g, 10.7 mmol) was dissolved in THF (19 mL) and added dropwise to the solution of LDA at -78 °C. The resulting solution was allowed to warm to 0 °C and stirred at this temperature for 2 hr. The solution was then cooled to -78 °C, and MeI (1 mL, 16.4 mmol) was added. The reaction mixture was stirred at -78 °C for one hr and then RT for one hr. The reaction mixture was then poured onto H₂O:CH₂Cl₂ (2:1, 45 mL:22.5 mL). NaHCO₃ (sat. aq.) was then added and the layers separated. The aqueous layer was washed with

CH₂Cl₂ (x 2), dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford crude **93** (3.00 g, 127%).

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 4.39-4.32 (m, 1 H, *H*2), 3.79-3.72 (m, 1 H, *H*7), 3.32 (s, 6 H, *H*1), 2.71 (s, 3 H, *H*9), 2.46 (s, 3 H, *H*9'), 1.46 (d, *J* = 6.5 Hz, 3 H, *H*8).

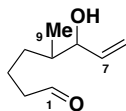
Preparation of 6,6-dimethoxy-2-methylhexanal **94**



Acetal **93** (3.00 g, 13.9 mmol) was dissolved in THF (200 mL) and phosphate buffer (pH 7, 200 mL) was added. Sodium periodate (16 g, 75 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was diluted with Et₂O and the layers separated. The aqueous layer was extracted with Et₂O (x 2), dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. The crude product quickly purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2) to afford compound **94** (1.10 g, 46%) which was unstable to further purification.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 9.62 (d, *J* = 2.0 Hz), 4.36 (t, *J* = 5.5 Hz, 1 H, *H*₆), 3.32 (s, 6 H, *H*₁), 1.10 (d, *J* = 7.0 Hz, 3 H, *H*₈).

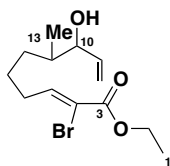
Preparation of 6-hydroxy-5-methyloct-7-enal **95**



Following **General Procedure 1**, using vinyl magnesium bromide (1.0 M in THF, 9.5 mL, 9.5 mmol), aldehyde **94** (1.1 g, 6.3 mmol) in THF (30 mL) afforded compound **95** (400 mg, 41%) as a yellow oil, which was unstable to further purification.

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.76 (s, 1 H, H_1), 5.95-5.75 (m, 1 H, H_7), 5.24 (d, $J = 17.0$ Hz, 1 H, H_8), 5.16 (d, $J = 10.0$ Hz, 1 H, H_8'), 4.07-3.96 (m, 1 H, H_6), 0.91 (dd, $J = 6.5, 2.0$ Hz, 3 H, H_9).

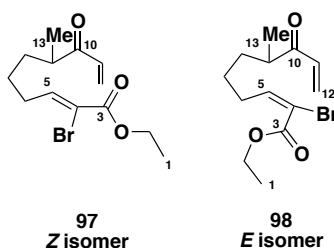
Preparation of (Z)-ethyl 2-bromo-8-hydroxy-7-methyldeca-2,9-dienoate **96**



Following **General Procedure 2**, using HWE reagent **25** (574 g, 2.56 mmol), NaH (205 mg, 5.12 mmol), NBS (456 mg, 2.56 mmol) and aldehyde **95** (400 mg, 2.56 mmol) afforded the title compound **96** (240 mg, 40% over two steps) as a 2.3:1.0 (Z:E) mixture of isomers.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.22 (t, $J = 7.0$ Hz, 1 H, *H*5), 6.60 (t, $J = 7.5$ Hz, 0.4 H, *H*5 (*E* isomer)), 5.84-5.74 (m, 1.4 H, *H*11, *H*11 (*E* isomer)), 5.16 (dt, $J = 17.0, 1.5$ Hz, 1.4 H, *H*12, *H*12 (*E* isomer)), 5.10 (dt, $J = 10.5, 1.5$ Hz, 1.4 H, *H*12', *H*12' (*E* isomer)), 4.20 (q, $J = 7.0$ Hz, 2 H, *H*2), 4.19 (q, $J = 7.0$ Hz, 0.8 H, *H*2 (*E* isomer)) 3.95-3.90 (m, 1 H, *H*10), 3.90-3.85 (m, 0.4 H, *H*10 (*E* isomer)), 2.42 (q, $J = 7.0$, 0.8 H, *H*6 (*E* isomer)), 2.31-2.24 (m, 2 H, *H*6), 1.57-1.40 (m, 7 H, *H*7/*H*8/*H*9/*OH* (both isomers)), 1.27 (t, $J = 7.0$ Hz, 1.2 H *H*1 (*E* isomer)), 1.26 (t, $J = 7.0$ Hz, 3 H, *H*1), 1.21-1.03 (m, 2.8 H, *H*7/*H*8/*H*9/*OH* (both isomers)), 0.85-0.80 (m, 4.2 H, *H*13, *H*13 (*E* isomer)); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (*C*3 *E* isomer), 162.5 (*C*3), 148.5 (*C*5 *E* isomer), 146.5 (*C*5), 139.6 (*C*11), 139.11 (*C*11 *E* isomer), 116.5 (*C*4), 116.0 (*C*4 *E* isomer), 115.9 (*C*12), 111.2 (*C*12 *E* isomer), 76.6 (*C*10 both isomers), 62.4 (*C*2), 62.1 (*C*10 *E* isomer), 38.3 (*C*7/*C*8/*C*9 both isomers), 32.4 (*C*6 both isomers), 31.8 (*C*7/*C*8/*C*9 both isomers), 26.5 (*C*7/*C*8/*C*9 both isomers), 25.2 (*C*1 both isomers), 14.1 (*C*13 both isomers); **HRMS (FI⁺)** m/z calculated for [*M*+Na]⁺ C₁₃H₂₁BrO₃ 304.0674, found 304.0673; **IR ν_{max} /cm⁻¹ (thin film)** 3546 (OH), 2963 (C-H), 2933 (C-H), 2873 (C-H), 1713 (C=O), 1624, 1461, 1425, 1368, 1343, 1252.

Preparation of (*Z* and *E*)-ethyl 2-bromo-7-methyl-8-oxodeca-2,9-dienoate **97** and **98**



Following **General Procedure 3**, using DMP (418 mg, 0.99 mmol) and alcohol **96** (200 mg, 0.66 mmol, 2.3:1.0 (*Z*:*E*) mixture of isomers) afforded compound **98** (*E* isomer, 30 mg, 80% based on *E* SM) and compound **97** (*Z* isomer, 130 mg, 94% based on *Z* SM), both as colourless oils.

***E* isomer 98:**

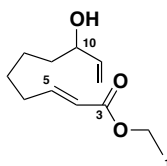
¹H NMR (400 MHz, CDCl₃) δ_{H} 6.57 (t, $J = 7.5$ Hz, 1 H, *H*5), 6.36 (dd, $J = 17.5, 10.5$ Hz, 1 H, *H*11), 6.21 (dd, $J = 17.5, 1.5$ Hz, 1 H, *H*12), 5.73 (dd, $J = 10.5, 1.5$ Hz, 1 H, *H*12'), 4.19 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.80-2.70 (m, 1 H, *H*9), 2.45-2.36 (m, 2 H, *H*6), 1.69-1.60 (m, 1 H, *H*8), 1.40-1.34 (m, 3 H, *H*8', *H*7), 1.27 (t, $J = 7.0$ Hz, 3 H, *H*1), 1.04 (d, $J = 7.0$ Hz, 3 H, *H*13); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 203.8 (*C*10), 162.9 (*C*3), 147.9 (*C*5), 135.1 (*C*11), 128.3 (*C*12), 111.5 (*C*4), 62.5 (*C*2), 43.1 (*C*9), 32.4 (*C*6), 31.4 (*C*8), 26.4 (*C*7), 16.6 (*C*13), 14.1 (*C*1); **HRMS (FI⁺)** m/z calculated for [*M*+Na]⁺ C₁₃H₁₉O₃Br 302.0518, found 302.0520; **IR ν_{max} /cm⁻¹ (thin film)** 2935 (C-H), 1715 (C=O), 1677 (C=O), 1612, 1459, 1402, 1369, 1344, 1221.

***Z* isomer 97:**

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.25 (t, $J = 7.0$ Hz, 1 H, *H*5), 6.43 (dd, $J = 17.5, 10.5$ Hz, 1 H, *H*11), 6.28 (dd, $J = 17.5, 1.5$ Hz, 1 H, *H*12), 5.80 (dd, $J = 10.5, 1.5$ Hz, 1 H, *H*12'), 4.26 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.89-2.79 (m, 1 H, *H*9), 2.34 (q, $J = 7.0$ Hz, 2 H, *H*6), 1.79-1.70 (m,

1 H, *H*8), 1.52-1.40 (m, 3 H, *H*8', *H*7), 1.33 (t, *J* = 7.0 Hz, 3 H, *H*1), 1.11 (d, *J* = 7.0 Hz, 3 H, *H*13); **¹³C NMR (101 MHz, CDCl₃)** δ_c 203.7 (C10), 162.9 (C3), 145.4 (C5), 135.2 (C11), 128.3 (C12), 116.8 (C4), 62.4 (C2), 43.1 (C9), 32.4 (C6), 31.3 (C8), 25.2 (C7), 16.6 (C13), 14.2 (C1); **HRMS (FI⁺)** *m/z* calculated for [M+Na]⁺ C₁₃H₁₉O₃Br 302.0518, found 302.0514; **IR ν_{max}/cm⁻¹ (thin film)** 2935 (C-H), 17235 (C=O), 1676 (C=O), 1612, 1459, 1402, 1368, 1250, 1036.

Preparation of (*E*)-ethyl 8-hydroxydeca-2,9-dienoate **100**

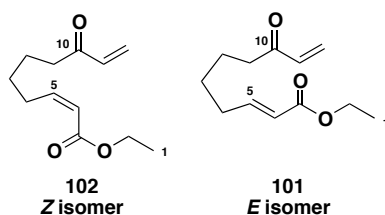


Wittig reagent **40** (3.00 g, 8.4 mmol) was added to a solution of aldehyde **23** (1.00 g, 7.00 mmol) in CH₂Cl₂ (80 mL), and the reaction mixture brought to reflux for 24 hr. The reaction mixture was then allowed to cool to RT and concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, hex:Et₂O (7:3)) to afford compound **100** (1.00 g, 67% as an inseparable 4:1 mixture of *E*:*Z* isomers) as a colourless oil.

Z isomer omitted for clarity

¹H NMR (400 MHz, CDCl₃) δ_H 6.95 (dt, *J* = 15.5, 7.0 Hz, 1 H, *H*5), 5.85 (ddd, *J* = 17.5, 10.5, 6.5 Hz, 1 H, *H*11), 5.81 (d, *J* = 15.5 Hz, 1 H, *H*4), 5.22 (d, *J* = 17.5 Hz, 1 H, *H*12), 5.10 (d, *J* = 10.5 Hz, 1 H, *H*12'), 4.18 (q, *J* = 7.0 Hz, 2 H, *H*2), 3.55-3.45 (m, 1 H, *H*10), 2.30-2.15 (m, 2 H, *H*6), 1.79-1.00 (m, 10 H, *H*7, *H*8, *H*9, OH, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_C 166.7 (C3), 150.2 (C5), 141.1 (C11), 121.4 (C4), 114.7 (C12), 73.0 (C10), 60.2 (C2), 36.7 (C9), 32.1 (C6), 28.8 (C7), 24.9 (C8), 14.3 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₂H₂₀NaO₃ 235.1310, found 235.1303; **IR** ν_{max}/cm⁻¹ (**thin film**) 3237 (br., OH), 2934 (C-H), 2860 (C-H), 1715 (C=O), 1652 (C=C), 1367, 1269, 1185.

Preparation of (*E*)- and (*Z*)-ethyl 8-oxodeca-2,9-dienoate **101** and **102**



Following **General Procedure 3**, using DMP (1.83 g, 4.32 mmol), alcohol **100** (458 mg, 2.16 mmol) and CH₂Cl₂ (30 mL) afforded the separated isomeric olefins (1.0:1.5 *E*:*Z*), **101** (150 mg, 33%) and **102** (100 mg, 22%), both as yellow oils.

Z isomer 102:

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.35 (dd, $J = 4.0, 17.5$ Hz, 1 H, *H*₁₁), 6.25-6.15 (m, 2 H, *H*₅, *H*₁₂), 5.85-5.73 (m, 2 H, *H*₄, *H*_{12'}), 4.16 (q, $J = 7.0$ Hz, 2 H, *H*₂), 2.72-2.57 (m, 4 H, *H*₆, *H*₉), 1.72-1.62 (m, 2 H, *H*₈), 1.55-1.40 (m, 2 H, *H*₇), 1.28 (t, $J = 7.0$ Hz, 3 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.7 (*C*₁₀), 166.4 (*C*₃), 149.8 (*C*₅), 136.5 (*C*₁₁), 128.0 (*C*₁₂), 120.1 (*C*₄), 59.8 (*C*₂), 39.2 (*C*₉), 28.6 (*C*₆), 28.4 (*C*₇), 23.4 (*C*₈), 15.3 (*C*₁); **HRMS (ESI⁺)** m/z calculated for [*M*+Na]⁺ C₁₂H₁₈NaO₃ 233.1148, found 233.1152; **IR** ν_{max} /cm⁻¹ (thin film) 2934 (C-H), 1717 (C=O), 1692 (C=O), 1644 (C=C), 1643 (C=C), 1413, 1158, 1033.

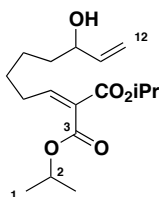
E isomer 101:

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.94 (dt, $J = 15.5, 7.0$ Hz, 1 H, *H*₅), 6.35 (dd, $J = 17.5, 10.5$ Hz, 1 H, *H*₁₁), 6.21 (dd, $J = 17.5, 1.5$ Hz, 1 H, *H*₁₂), 5.85-5.79 (m, 2 H, *H*_{12'}, *H*₄), 4.17 (q, $J = 7.0$ Hz, 2 H, *H*₂), 2.60 (t, $J = 7.0$ Hz, 2 H, *H*₉), 2.22 (dt, $J = 7.0, 1.5$ Hz, 2 H, *H*₆), 1.72-1.61 (m, 2 H, *H*₈), 1.53-1.45 (m, 2 H, *H*₇), 1.28 (t, $J = 7.0$ Hz, 3 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.4 (*C*₁₀), 166.6 (*C*₃), 148.6 (*C*₅), 136.5 (*C*₁₁), 128.0 (*C*₁₂), 121.6 (*C*₄), 60.2 (*C*₂), 39.2 (*C*₉), 31.9 (*C*₆), 27.5 (*C*₇), 23.3 (*C*₈), 14.3 (*C*₁); **HRMS (ESI⁺)** m/z

calculated for $[M+Na]^+$ $C_{12}H_{18}NaO_3$ 233.1148, found 233.1147; **IR** ν_{max}/cm^{-1} (**thin film**)

2937 (C-H), 1716 (C=O), 1681 (C=O), 1654 (C=C), 1616 (C=C) 1401, 1367, 1266.

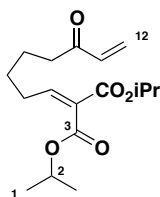
Preparation of diisopropyl 2-(6-hydroxyoct-7-en-1-ylidene)malonate **103**



According to a modified literature procedure,¹⁷ piperidine (70 μ L, 7.0 μ mol) and AcOH (40 μ L, 7.0 μ mol) were added to a solution of aldehyde **23** (50 mg, 0.35 mmol) and diisopropyl malonate (70 μ L, 0.40 mmol) in CH_2Cl_2 (5 mL) and the reaction mixture stirred at 0 $^\circ\text{C}$ for 45 min. 4 $\text{\AA}$ MS were added, and the reaction mixture was allowed to warm to RT over 15 min. The solution was diluted with Et_2O , washed with H_2O , and the combined aqueous layers extracted with Et_2O (x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was purified by flash column chromatography (SiO_2 , pet 40-60: Et_2O (7:3)) to afford compound **103** (60 mg, 60%) as a colourless oil.

^1H NMR (400 MHz, CDCl_3) δ_{H} 6.91 (t, J = 7.5 Hz, 1 H, H_5), 5.84 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H, H_{11}), 5.20 (dd, J = 17.0, 1.5 Hz, 1 H, H_{12}), 5.11 (dd, J = 10.5, 1.5 Hz, 1 H, H_{12}'), 5.08 (sept., J = 6.5 Hz, 1 H, H_2), 5.06 (sept., J = 6.5 Hz, 1 H, H_{2}'), 4.06 (t, J = 6.5 Hz, 1 H, H_{10}), 2.30 (q, J = 7.5 Hz, 2 H, H_6), 1.60-1.42 (m, 7 H, H_7 , H_8 , H_9 , OH), 1.23 (d, J = 6.5 Hz, 6 H, H_1), 1.22 (d, J = 6.5 Hz, 6 H, H_{1}'); **^{13}C NMR (101 MHz, CDCl_3)** δ_{C} 166.3 (C_3), 164.6 (C_3'), 149.2 (C_5), 142.0 (C_{11}), 130.3 (C_4), 115.4 (C_{12}), 73.4 (C_{10}), 69.2 (C_2 , C_2'), 36.8 (C_9), 29.6 (C_6), 28.3 (C_7), 25.1 (C_8), 21.8 (C_1 , C_1'); **HRMS (ESI $^+$)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{17}\text{H}_{28}\text{NaO}_5$ 335.1829, found 335.1819; **IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film)** 3402 (br., OH), 2981 (C-H), 2936 (C-H), 1717 (C=O), 1646 (C=C), 1374, 1225, 1104.

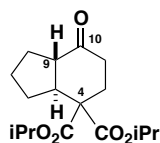
Preparation of diisopropyl 2-(6-oxooct-7-en-1-ylidene)malonate **104**



Following **General Procedure 3**, using DMP (116 mg, 0.270 mmol), alcohol **103** (50 mg, 0.160 mmol) and CH₂Cl₂ (3 mL) afforded compound **104** (50 mg, quant.) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.91 (t, J = 7.5 Hz, 1 H, H_5), 6.33 (dd, J = 17.0, 10.5 Hz, 1 H, H_{11}), 6.20 (d, J = 17.0 Hz, 1 H, H_{12}), 5.81 (d, J = 10.5 Hz, 1 H, $H_{12'}$), 5.16 (sept., J = 6.5 Hz, 1 H, H_2), 5.07 (sept., J = 6.5 Hz, 1 H, $H_{2'}$), 2.59 (t, J = 7.5 Hz, 2 H, H_9), 2.29 (q, J = 7.5 Hz, 2 H, H_6), 1.65 (quin., J = 7.5 Hz, 2 H, H_8), 1.50 (quin., J = 7.5 Hz, 2 H, H_7), 1.29 (d, J = 6.5 Hz, 6 H, H_1), 1.25 (d, J = 6.5 Hz, 6 H, $H_{1'}$); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.3 (C10), 165.1 (C3), 163.5 (C3'), 147.6 (C5), 136.4 (C11), 129.7 (C4), 128.0 (C12), 68.8 (C2, C2'), 39.0 (C9), 29.3 (C6), 27.8 (C7), 23.4 (C8), 21.7 (C1, C1'); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₇H₂₆NaO₅ 333.1672, found 333.1667; **IR** ν_{max} /cm⁻¹ (thin film) 2982 (C-H), 1720 (C=O), 1680 (C=O), 1646 (C=C), 1375, 1258, 1226.

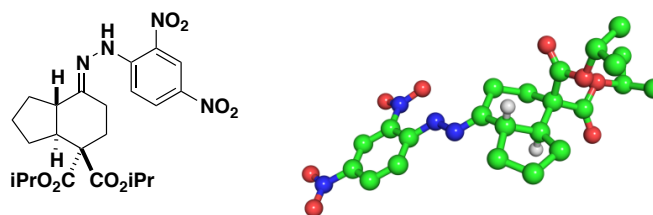
Preparation of (3aS*,7aS*)-diisopropyl 7-oxohexahydro-1H-indene-4,4(2H)-dicarboxylate **105**



Following **General Procedure 4**, using cyclisation precursor **104** (100 mg, 0.380 mmol), toluene (10 mL), KOH (74 mg, 1.32 mmol), tetrabutylammonium bisulfate (35 mg, 0.080 mmol) at RT afforded compound **105** (60 mg, 60%, >20:1 d.r.) as a colourless oil.

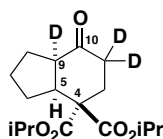
¹H NMR (500 MHz, CDCl₃) δ_{H} 5.15 (sept., J = 6.5 Hz, 1 H, H_2), 5.07 (sept., J = 6.5 Hz, 1 H, H_2'), 2.74-2.59 (m, 3 H, H_9 , H_{11} , H_{12}), 2.41-2.31 (m, 1 H, H_{11}'), 2.20-2.07 (m, 1 H, H_5), 2.06-1.99 (m, 1 H, H_{12}'), 1.98-1.90 (m, 2 H, H_6), 1.80-1.72 (m, 2 H, H_8), 1.69-1.57 (m, 2 H, H_7), 1.31-1.22 (m, 12 H, H_1 , H_1'); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 209.9 (C_{10}), 170.7 (C_3), 168.9 (C_3'), 69.2 (C_2), 69.0 (C_2'), 56.5 (C_4), 51.7 (C_9), 50.7 (C_5), 38.6 (C_{11}), 34.2 (C_{12}), 27.8 (C_6), 22.4 (C_7), 21.6 (C_1 , C_1'), 21.4 (C_8); **HRMS (ESI⁺)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{17}\text{H}_{26}\text{NaO}_5$ 333.1672, found 333.1663; **IR ν_{max} /cm⁻¹ (thin film)** 2979 (C-H), 1717 (C=O), 1707 (C=O), 1455, 1375, 1233.

Preparation of (3a*S**,7a*S**,*E*)-diisopropyl 7-(2-(2,4-dinitrophenyl)hydrazono)hexahydro-1*H*-indene-4,4(2*H*)-dicarboxylate **106**



Ketone **105** (20 mg, 0.06 mmol) was dissolved in MeOH (3 mL) and the solution cooled to 0 °C. 2,4-Dinitrophenylhydrazine (119 mg, 50% in H₂O, 0.3 mmol) and H₂SO₄ (0.01 mL) were added and the reaction mixture was stirred at 0 °C for 30 min. After this time, the reaction mixture was let warm to RT, and stirred at this temperature for 90 min. The reaction mixture was diluted with Et₂O and passed through a small plug of silica, eluting with Et₂O. The reaction mixture was concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **106** (22 mg, 75%). X-ray diffraction quality crystals were grown by vapour diffusion from EtOAc and pentanes. An X-ray crystal structure confirmed the identity of this product.

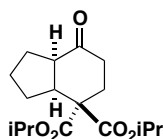
Preparation of (3a*S,7a*R**)-diisopropyl 6,6,7a trideutero-7-oxohexahydro-1*H*-indene-4,4(2*H*)-dicarboxylate **109****



According to a modified literature procedure,¹⁸ sodium (4 mg, 0.16 mmol) was dissolved in ethanol-*d*₆ (1.5 mL) and the reaction mixture stirred until the sodium was fully dissolved. Ketone **105** (50 mg, 0.16 mmol) was dissolved in ethanol-*d*₆ (1.5 mL) and added dropwise into the solution of sodium ethoxide in ethanol-*d*₆. The resulting solution was stirred for 24 hr, quenched with D₂O and extracted with Et₂O (x 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **109** (35 mg, 70%).

¹H NMR (500 MHz, CDCl₃) δ_H 5.07 (quin., *J* = 6.5 Hz, 1 H, *H*₂), 4.98 (quin., *J* = 6.5 Hz, 1 H, *H*₂'), 2.96-2.92 (m, 1 H, *H*₅), 2.32 (dd, *J* = 14.5, 2.0 Hz, 1 H, *H*₁₂) 2.26-2.21 (m, 2 H, *H*₈, *H*₁₂'), 1.62-1.50 (m, 2 H, *H*₈', *H*₇), 1.49-1.39 (m, 2 H, *H*₇', *H*₆), 1.20-1.17 (m, 1 H, *H*₆'), 1.20 (t, *J* = 6.5 Hz, 6 H, *H*₁), 1.16 (t, *J* = 6.5 Hz, 6 H, *H*₁'); **¹³C NMR (126 MHz, CDCl₃)** δ_C 210.7 (C₁₀), 170.8 (C₃), 169.7 (C₃'), 69.2 (C₂, C₂'), 55.7 (C₄), {50.4, 50.3, 50.1, 1:1:1 t, *J*_{C-D} = 20.0 Hz (C₉)}, 45.9 (C₅), {36.9, 36.7, 36.6, 36.4, 36.3, 1:1:1:1:1 quin., *J*_{C-D} = 20.0 Hz (C₁₁)}, 26.7 (C₆), 26.6 (C₁₂), 24.7 (C₈), 21.7 (C₇), 21.6 (C₁), 21.5 (C₁'); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₇H₂₄D₃O₅ 314.2041, found 314.2036; **IR** ν_{max}/cm⁻¹ (thin film) 2980 (C-H), 1723 (C=O), 1456, 1375, 1253, 1227, 1181, 1145, 1194.

Preparation of (3aS*,7aR*)-diisopropyl 7-oxohexahydro-1H-indene-4,4(2H)-dicarboxylate **107**

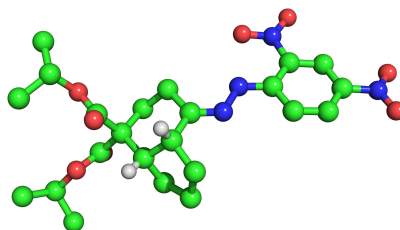
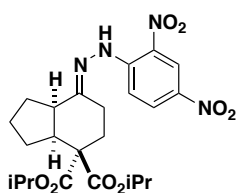


Sodium (4 mg, 0.16 mmol) was dissolved in ethanol (2 mL) and the reaction mixture stirred until the sodium was fully dissolved. Ketone **105** (50 mg, 0.16 mmol) was dissolved in ethanol (2 mL) and added dropwise into the solution of sodium ethoxide in ethanol. The resulting solution was stirred for 24 hr, quenched with H₂O and extracted with Et₂O (x 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **107** (43 mg, 86%).

Ring junction geometry could not be confirmed by nOe analysis.

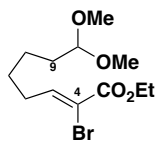
¹H NMR (500 MHz, CDCl₃) δ_H 5.07 (quin., *J* = 6.5 Hz, 1 H, *H*₂), 4.98 (quin., *J* = 6.5 Hz, 1 H, *H*₂'), 3.03-2.99 (m, 1 H, *H*₉), 2.97-2.92 (m, 1 H, *H*₅) 2.37-2.33 (m, 1 H, *H*₁₂) 2.32-2.29 (m, 2 H, *H*₈, *H*₁₁), 2.28-2.22 (m, 1 H, *H*₁₂'), 2.14-2.06 (m, 1 H, *H*₁₁'), 1.61-1.50 (m, 2 H, *H*₈', *H*₇), 1.49-1.40 (m, 2 H, *H*₇', *H*₆), 1.20-1.17 (m, 1 H, *H*₆'), 1.20 (t, *J* = 6.5 Hz, 6 H, *H*₁), 1.16 (dd, *J* = 6.5, 4.5 Hz, 6 H, *H*₁'); **¹³C NMR (126 MHz, CDCl₃)** δ_C 210.7 (C₁₀), 170.8 (C₃), 169.7 (C₃'), 69.2 (C₂, C₂'), 55.7 (C₄), 50.7 (C₉), 45.9 (C₅), 37.2 (C₁₁), 26.7 (C₆), 26.6 (C₁₂), 24.9 (C₈), 21.7 (C₇), 21.6 (C₁), 21.5 (C₁'); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₇H₂₆NaO₅ 333.1673, found 333.1667; **IR** ν_{max}/cm⁻¹ (**thin film**) 2979 (C-H), 1722 (C=O), 1456, 1374, 1243, 1179, 1102, 907.

Preparation of (3a*S**,7a*R**,*E*)-diisopropyl 7-(2-(2,4-dinitrophenyl)hydrazono)hexahydro-1*H*-indene-4,4(2*H*)-dicarboxylate **110**



Ketone **107** (20 mg, 0.06 mmol) was dissolved in MeOH (3 mL) and the solution cooled to 0 °C. 2,4-Dinitrophenylhydrazine (119 mg, 50% in H₂O, 0.3 mmol) and H₂SO₄ (0.01 mL) were added and the reaction mixture was stirred at 0 °C for 30 min. After this time, the reaction mixture was let warm to RT, and stirred at this temperature for 90 min. The reaction mixture was diluted with Et₂O and passed through a small plug of silica, eluting with Et₂O. The reaction mixture was concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **110** (19 mg, 65%). X-ray diffraction quality crystals were grown by vapour diffusion from EtOAc and pentanes. An X-ray crystal structure confirmed the identity of this product.

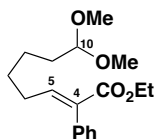
Preparation of (Z)-ethyl 2-bromo-8,8-dimethoxyoct-2-enoate **112**



Following **General Procedure 2**, using HWE reagent **25** (2.8 g, 12.5 mmol), NaH (1.0 g, 25.0 mmol), NBS (2.2 g, 12.5 mmol) and aldehyde **22** (2.0 g, 12.5 mmol) afforded the title compound **112** (1.9 g, 49% over two steps).

^1H NMR (500 MHz, CDCl_3) showed characteristic peaks at δ_{H} 7.31 (q, $J = 7.0$ Hz, 1 H, H_5), 3.21 (s, 6 H, H_{11}); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 162.1 (C3), 145.8 (C5), 116.6 (C4), 104.4 (C10), 52.8 (C11); HRMS (ESI^+) m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{21}\text{BrNaO}_4$ 331.0515, found 331.0515; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2939 (C-C), 1723 (C=O), 1625, 1367, 1254, 1127, 1043.

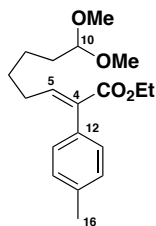
Preparation of (*E*)-ethyl 8,8-dimethoxy-2-phenyloct-2-enoate **113a**



Bromo-olefin **112** (200 mg, 0.65 mmol) was dissolved in 1,4-dioxane (3 mL) under an Ar atmosphere and Pd(PPh₃)₄ (38 mg, 0.03 mmol), phenylboronic acid (87 mg, 0.72 mmol) and K₂CO₃ (269 mg, 1.95 mmol) were added. The reaction mixture was heated to 85 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product **113a** (200 mg, quant), which was not purified any further due to instability of the acetal on silica.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 7.72-7.55 (m, 2 H, H5/Ar), 7.55-7.30 (m, 2 H, H5/Ar), 7.30-7.20 (m, 2 H, H5/Ar), 3.73 (s, 6 H, H11).

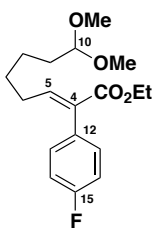
Preparation of (*E*)-ethyl 8,8-dimethoxy-2-(*p*-tolyl)oct-2-enoate **113b**



Bromo-olefin **112** (200 mg, 0.65 mmol) was dissolved in 1,4-dioxane (3 mL) under an Ar atmosphere and Pd(PPh₃)₄ (38 mg, 0.03 mmol), *p*-methylphenylboronic acid (99 mg, 0.72 mmol) and K₂CO₃ (269 mg, 1.95 mmol) were added. The reaction mixture was heated to 85 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product **113b** (200 mg, 96%), which was not purified any further due to instability of the acetal on silica.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 7.74-7.60 (m, 2 H, *H*5/Ar), 7.55-7.45 (m, 1 H, *H*5/Ar), 7.20-7.10 (m, 2 H, *H*5/Ar), 3.71 (s, 6 H, *H*11), 3.32 (s, 3 H, *H*16).

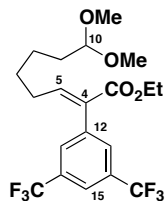
Preparation of (*E*)-ethyl 2-(4-fluorophenyl)-8,8-dimethoxyoct-2-enoate **113c**



Bromo-olefin **112** (200 mg, 0.65 mmol) was dissolved in 1,4-dioxane (3 mL) under an Ar atmosphere and Pd(PPh₃)₄ (38 mg, 0.03 mmol), *p*-fluorophenylboronic acid (101 mg, 0.72 mmol) and K₂CO₃ (269 mg, 1.95 mmol) were added. The reaction mixture was heated to 85 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product **113c** (200 mg, 95%), which was not purified any further due to instability of the acetal on silica.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 7.74-7.60 (m, 2 H, *H*5/*Ar*), 7.50-7.40 (m, 2 H, *H*5/*Ar*), 7.10-6.95 (m, 1 H, *H*5/*Ar*), 3.71 (s, 6 H, *H*11).

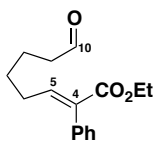
Preparation of (E)-ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-8,8-dimethoxyoct-2-enoate **113d**



Bromo-olefin **112** (200 mg, 0.65 mmol) was dissolved in 1,4-dioxane (3 mL) under an Ar atmosphere and Pd(PPh₃)₄ (38 mg, 0.03 mmol), *m*-CF₃phenylboronic acid (186 mg, 0.72 mmol) and K₂CO₃ (269 mg, 1.95 mmol) were added. The reaction mixture was heated to 85 °C and stirred at this temperature overnight. The reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product **113d** (300 mg, quant.), which was not purified any further due to instability of the acetal on silica.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 7.83-7.60 (m, 2 H, *H*5/Ar), 7.55-7.45 (m, 1 H, *H*5/Ar), 7.25-7.15 (m, 1 H, *H*5/Ar), 3.71 (s, 6 H, *H*11).

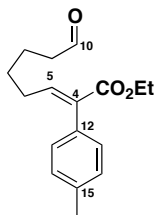
Preparation of (*E*)-ethyl 8-oxo-2-phenyloct-2-enoate **114a**



Acetal **113a** (200 mg, 0.65 mmol) was dissolved in acetone (10 mL), H₂O (5 mL) and HCl (1.0 M, aq., 5 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **114a** (130 mg, quant.) that was unstable to further purification.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_{H} 9.78 (t, J = 1.5 Hz, 1 H, *H*₁₀), 6.14 (t, J = 7.5 Hz, 1 H, *H*₅).

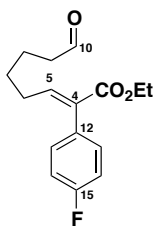
Preparation of (*E*)-ethyl 8-oxo-2-(*p*-tolyl)oct-2-enoate **114b**



Acetal **113b** (200 mg 0.63 mmol) was dissolved in acetone (10 mL), H₂O (5 mL) and HCl (1.0 M, aq., 5 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **114b** (170 mg, quant.) that was unstable to further purification.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 9.78 (s, 1 H, *H*10), 6.11 (t, *J* = 7.5 Hz, 1 H, *H*5), 2.33 (d, *J* = 1.5 Hz, 3 H, *H*16).

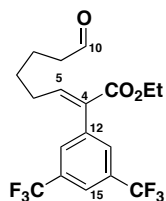
Preparation of (*E*)-ethyl 2-(4-fluorophenyl)-8-oxooct-2-enoate **114c**



Acetal **113c** (200 mg 0.62 mmol) was dissolved in acetone (10 mL), H₂O (5 mL) and HCl (1.0 M, aq., 5 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **114c** (172 mg, quant.) that was unstable to further purification.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 9.73 (t, *J* = 1.5 Hz, 1 H, *H*₁₀), 6.10 (t, *J* = 7.5 Hz, 1 H, *H*₅).

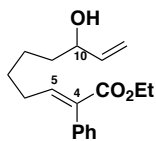
Preparation of (*E*)-ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-8-oxooct-2-enoate **114d**



Acetal **113d** (200 mg 0.45 mmol) was dissolved in acetone (10 mL), H₂O (5 mL) and HCl (1.0 M, aq., 5 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **114d** (179 mg, quant.) that was unstable to further purification.

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 9.75 (s, 1 H, *H*10), 7.19 (t, *J* = 7.0 Hz, 1 H, *H*5).

Preparation of (*E*)-ethyl 8-hydroxy-2-phenyldeca-2,9-dienoate **115a**



Vinyl magnesium bromide (1.0 M in THF, 0.98 mL, 0.98 mmol) was added dropwise to a solution of aldehyde **114a** (130 mg, 0.65 mmol) in THF (8 mL) at -78 °C, and the resulting solution was stirred at this temperature for 3 hr. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **115a** (1:1 mixture of *E* and *Z* isomers, 116 mg, 62%) as a colourless oil.

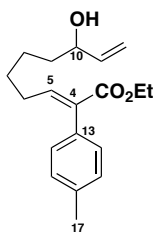
¹H NMR (500 MHz, CDCl₃) δ_H 7.28 (t, *J* = 7.5 Hz, 4 H, Ar*H*, Ar*H*'), 7.25-7.20 (m, 4 H, Ar*H*, Ar*H*'), 7.08 (d, *J* = 7.0 Hz, 2 H, Ar*H*, Ar*H*'), 6.97 (t, *J* = 7.5 Hz, 1 H, *H*5'), 6.08 (t, *J* = 7.5 Hz, 1 H, *H*5), 5.82-5.70 (m, 2 H, *H*11, *H*11'), 5.12 (dd, *J* = 22.0, 17.5 Hz, 2 H, *H*12, *H*12'), 5.02 (t, *J* = 11.0 Hz, 2 H, *H*12, *H*12'), 4.22 (q, *J* = 7.0 Hz, 2 H, *H*2), 4.13 (q, *J* = 7.0 Hz, 2 H, *H*2'), 4.05-4.01 (m, 1 H, *H*10), 3.98-3.95 (m, 1 H, *H*10'), 2.36 (q, *J* = 7.5 Hz, 2 H, *H*6), 2.02 (q, *J* = 7.5 Hz, 2 H, *H*6'), 1.56-1.44 (m, 7 H, *H*8/8', *H*7/7', OH/*H*', *H*9), 1.44-1.35 (m, 7 H, *H*8/8', *H*7/7', OH/*H*', *H*9'), 1.24 (t, *J* = 7.0 Hz, 3 H, *H*1), 1.18 (t, *J* = 7.0 Hz, 3 H, *H*1');
¹³C NMR (127 MHz, CDCl₃) δ_C 167.3 (*C*3), 166.3 (*C*3'), 143.7 (*C*5'), 140.1 (*C*11, *C*11'), 138.1 (*C*5), 134.4 (*C*4, *C*4'), 133.1 (*C*Ar, *C*Ar'), 128.7 (*C*Ar, *C*Ar'), 126.9 (*C*Ar, *C*Ar'), 126.0 (*C*Ar, *C*Ar'), 113.6 (*C*12, *C*12'), 72.0 (*C*10, *C*10'), 59.7 (*C*2, *C*2'), 35.7 (*C*7/8/9, *C*7'/8'/9'),

28.2 (C6), 28.3 (C6'), 28.4 (C7/8/9, C7'/8'/9'), 23.9 (C7/8/9, C7'/8'/9'), 13.2 (C1, C1');

HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₁₈H₂₄NaO₃ 311.1618, found 311.1620;

IR $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 3500 (OH), 2933 (C-H), 1713 (C=O), 1635, 1494, 1444, 1371, 1255, 1198.

Preparation of (*E*)-ethyl 8-hydroxy-2-(*p*-tolyl)deca-2,9-dienoate **115b**

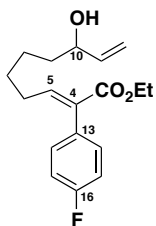


Vinyl magnesium bromide (1.0 M in THF, 0.98 mL, 0.98 mmol) was added dropwise to a solution of aldehyde **114b** (170 mg, 0.63 mmol) in THF (8 mL) at -78 °C, and the resulting solution was stirred at this temperature for 3 hr. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **115b** (1:1.4 mixture of *Z*:*E* isomers, 105 mg, 55%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.23 (d, *J* = 8.0 Hz, 2.8 H, Ar*H*), 7.18 (d, *J* = 7.5 Hz, 2 H, Ar*H*'), 7.15 (d, *J* = 7.5 Hz, 2 H, Ar*H*'), 7.00 (d, *J* = 8.0 Hz, 2.8 H, Ar*H*), 7.03 (t, *J* = 7.5 Hz, 1 H, *H*5'), 6.14 (t, *J* = 7.5 Hz, 1.4 H, *H*5), 5.92-5.82 (m, 2.4 H, *H*11, *H*11'), 5.23 (dd, *J* = 18.5, 17.5 Hz, 2.4 H, *H*12, *H*12'), 5.12 (t, *J* = 10.5 Hz, 2.4 H, *H*12, *H*12'), 4.31 (q, *J* = 7.0 Hz, 2.8 H, *H*2), 4.22 (q, *J* = 7.0 Hz, 2 H, *H*2'), 4.14-4.11 (m, 1.4 H, *H*10), 4.08-4.05 (m, 1 H, *H*10'), 2.44 (q, *J* = 7.5 Hz, 2.8 H, *H*6), 2.39 (s, 4.2 H, *H*17), 2.36 (s, 3 H, *H*17'), 2.12 (q, *J* = 7.5 Hz, 2 H, *H*6'), 1.66 (br. s, 2.4 H, OH, OH'), 1.61-1.53 (m, 7.6 H, *H*8/8', *H*7/7', *H*9), 1.53-1.45 (m, 6.8 H, *H*8/8', *H*7/7', *H*9'), 1.33 (t, *J* = 7.0 Hz, 4.2 H, *H*1), 1.28 (t, *J* = 7.0 Hz, 3 H, *H*1'); **¹³C NMR (127 MHz, CDCl₃)** δ_C 168.5 (C3), 167.5 (C3'), 149.1 (C5'), 144.4 (C11,

C11'), 141.2 (C5), 138.2 (C4, C4'), 137.3 (CAr, CAr'), 129.6 (CAr, CAr'), 129.0 (CAr, CAr'), 126.9 (CAr, CAr'), 114.8 (C12, C12'), 73.1 (C10, C10'), 60.7 (C2, C2'), 36.8 (C7/8/9, C7'/8'/9'), 29.9 (C6), 29.2 (C6'), 28.7 (C7/8/9, C7'/8'/9'), 25.0 (C7/8/9, C7'/8'/9'), 21.1 (C17, C17'), 14.3 (C1, C1'); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₉H₂₆NaO₃ 325.1774, found 325.1775; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 3490 (OH), 2931 (C-H), 1779 (C=O), 1514, 1369, 1279, 1095, 991.

Preparation of (*E*)-ethyl 2-(4-fluorophenyl)-8-hydroxydeca-2,9-dienoate **115c**

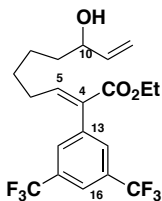


Vinyl magnesium bromide (1.0 M in THF, 0.98 mL, 0.98 mmol) was added dropwise to a solution of aldehyde **114c** (172 mg, 0.62 mmol) in THF (8 mL) at -78 °C, and the resulting solution was stirred at this temperature for 3 hr. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **115c** (1:1.3 mixture of *Z*:*E* isomers 131 mg, 69%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.31-7.29 (m, 4.6 H, ArH, ArH'), 7.15 (t, *J* = 7.0 Hz, 2.3 H, ArH, ArH'), 7.07 (t, *J* = 7.5 Hz, 1 H, H5'), 7.02 (t, *J* = 7.5 Hz, 2.3 H, ArH, ArH'), 6.13 (t, *J* = 7.5 Hz, 1.3 H, H5), 5.92-5.80 (m, 2.3 H, H11, H11'), 5.23 (t, *J* = 18.0 Hz, 2.3 H, H12, H12'), 5.12 (t, *J* = 10.0 Hz, 2.3 H, H12, H12'), 4.30 (q, *J* = 7.0 Hz, 2.6 H, H2), 4.22 (q, *J* = 7.0 Hz, 2 H, H2'), 4.14-4.10 (m, 1.3 H, H10), 4.10-4.05 (m, 1 H, H10'), 2.46 (q, *J* = 7.5 Hz, 2.6 H, H6), 2.10 (q, *J* = 7.5 Hz, 2 H, H6'), 1.61-1.52 (m, 8.2 H, H8/8', H7/7', OH/H', H9), 1.52-1.43 (m, 7.9 H, H8/8', H7/7', OH/H', H9'), 1.33 (t, *J* = 7.0 Hz, 3.9 H, H1), 1.28 (t, *J* = 7.0 Hz, 3 H, H1'); **¹³C NMR (127 MHz, CDCl₃)** δ_C 168.1 (C3), 167.1 (C3'), 162.0 (d, *J* = 246.5 Hz, C16), 162.3 (d, *J* = 247.5 Hz, C16'), 145.1 (C5'), 141.4 (C11, C11'), 139.8

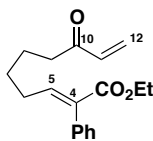
(C5), 134.0 (C4, C4'), 133.1 (C13, C13'), 131.4 (d, $J = 7.7$ Hz, C14), 128.9 (d, $J = 7.7$ Hz, C14'), 115.0 (d, $J = 28.6$ Hz, C15), 114.9 (C12, C12'), 114.7 (d, $J = 28.6$ Hz, C15'), 73.1 (C10, C10'), 60.9 (C2, C2'), 36.8 (C7/8/9, C7'/8'/9'), 29.9 (C6), 29.4 (C6'), 28.7 (C7/8/9, C7'/8'/9'), 25.0 (C7/8/9, C7'/8'/9'), 14.3 (C1, C1'); **^{19}F NMR (377 MHz, CDCl_3)** δ_{F} -114.9; **HRMS (ESI⁺)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{23}\text{NaFO}_3$ 329.1523, found 329.1525; **IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film)** 3502 (OH), 2933 (C-H), 1722 (C=O), 1500, 1369, 1220, 1193, 1159.

Preparation of (*E*)-ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-8-hydroxydeca-2,9-dienoate **115d**



Vinyl magnesium bromide (1.0 M in THF, 0.68 mL, 0.68 mmol) was added dropwise to a solution of aldehyde **114d** (179 mg, 0.45 mmol) in THF (8 mL) at -78 °C, and the resulting solution was stirred at this temperature for 3 hr. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **115d** (86 mg, 45%) as a colourless oil, which was contaminated with an unknown impurity, which could not be separated from the product, so the compound was taken on crude to the next step.

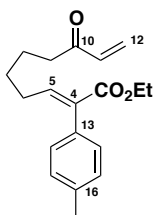
Preparation of (E)-ethyl 8-oxo-2-phenyldeca-2,9-dienoate **116a**



Following **General Procedure 3**, using DMP (258 mg, 0.61 mmol), alcohol **115a** (116 mg, 0.41 mmol) and CH₂Cl₂ (10 mL) afforded compound **116a** (1:1 *E:Z* mixture of isomers, 90 mg, 77%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.26 (d, *J* = 7.5 Hz, 4 H, ArH, ArH'), 7.22-7.20 (m, 4 H, ArH, ArH'), 7.05 (dd, *J* = 7.5, 1.5 Hz, 2 H, ArH, ArH'), 6.93 (t, *J* = 7.5 Hz, 1 H, H5'), 6.29-6.17 (m, 2 H, H11, H11'), 6.12 (dd, *J* = 17.5, 1.0, 2 H, H12, H12'), 6.08-6.03 (m, 1 H, H5), 5.72 (dd, *J* = 10.5, 1.0, 1 H, H12), 5.70 (dd, *J* = 10.5, 1.0, 1 H, H12'), 4.19 (q, *J* = 7.0 Hz, 2 H, H2), 4.10 (q, *J* = 7.0 Hz, 2 H, H2'), 2.53 (t, *J* = 7.5 Hz, 2 H, H9), 2.40 (t, *J* = 7.5 Hz, 2 H, H9'), 2.35 (q, *J* = 7.5 Hz, 2 H, H6), 2.01 (q, *J* = 7.5 Hz, 2 H, H6'), 1.61 (quin., *J* = 7.5 Hz, 2 H, H8), 1.50-1.44 (m, 4 H, H8', H7) 1.25-1.10 (m, 2 H, H7'), 1.24 (t, *J* = 7.0 Hz, 3 H, H1), 1.22 (t, *J* = 7.0 Hz, 3 H, H1'); **¹³C NMR (127 MHz, CDCl₃)** δ_C 200.7 (C10), 200.5 (C10'), 168.3 (C3), 167.3 (C3'), 144.3 (C5'), 138.9 (C5), 136.5 (C11, C11'), 135.4 (C4, C4'), 135.1 (CAr, CAr'), 129.7 (CAr, CAr'), 127.9 (CAr, CAr'), 127.1 (C12, C12'), 126.8 (CAr, CAr'), 60.8 (C2, C2'), 39.3 (C9, C9'), 34.1 (C7'), 28.9 (C6), 28.3 (C6'), 27.7 (C8'/7), 22.6 (C8/8'/7), 22.4 (C8/8'/7), 15.3 (C1), 14.1 (C1'); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₈H₂₂NaO₃ 309.1461, found 309.1460; **IR ν_{max}/cm⁻¹ (thin film)** 2980 (C-H), 2933 (C-H), 1711 (C=O), 1681, 1615, 1495, 1445, 1401, 1370, 1247.

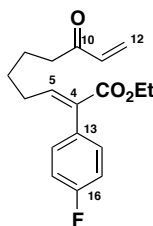
Preparation of (*E*)-ethyl 8-oxo-2-(*p*-tolyl)deca-2,9-dienoate **116b**



Following **General Procedure 3**, using DMP (221 mg, 0.52 mmol), alcohol **115b** (105 mg, 0.35 mmol) and CH₂Cl₂ (10 mL) afforded compound **116b** (1.2:1 *E*:*Z* mixture of isomers, 85 mg, 81%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.13 (d, *J* = 8.0 Hz, 2.2 H, Ar*H*, Ar*H*'), 7.09 (d, *J* = 8.0 Hz, 2.2 H, Ar*H*, Ar*H*'), 7.05 (d, *J* = 8.0 Hz, 2.2 H, Ar*H*, Ar*H*'), 6.67 (d, *J* = 8.0 Hz, 2.2 H, Ar*H*, Ar*H*'), 6.93 (t, *J* = 7.5 Hz, 1 H, *H*5'), 6.31-6.20 (m, 2.2 H, *H*11, *H*11'), 6.15 (dd, *J* = 17.0, 1.0, 1.2 H, *H*12), 6.09 (dd, *J* = 17.0, 1.0 Hz, 1 H, *H*12'), 6.04 (t, *J* = 7.5 Hz, 1.2 H, *H*5), 5.74 (dd, *J* = 10.0, 1.0, 1.2 H, *H*12), 5.72 (dd, *J* = 10.0, 1.0, 1 H, *H*12'), 4.22 (q, *J* = 7.5 Hz, 2.4 H, *H*2), 4.12 (q, *J* = 7.5 Hz, 2 H, *H*2'), 2.55 (t, *J* = 7.5 Hz, 2.4 H, *H*9), 2.43 (t, *J* = 7.5 Hz, 2 H, *H*9'), 2.36 (q, *J* = 7.5 Hz, 2.4 H, *H*6), 2.29 (s, 3 H, *H*17'), 2.27 (s, 3.6 H, *H*17), 2.04 (q, *J* = 7.5 Hz, 2 H, *H*6'), 1.63 (quin., *J* = 7.5 Hz, 2.4 H, *H*8), 1.55-1.43 (m, 4.4 H, *H*8', *H*7) 1.37 (quin., *J* = 7.5 Hz, 2 H, *H*7'), 1.24 (t, *J* = 7.5 Hz, 3.6 H, *H*1), 1.19 (t, *J* = 7.5 Hz, 3 H, *H*1'); **¹³C NMR (127 MHz, CDCl₃)** δ_C 200.7 (C10), 200.6 (C10'), 168.4 (C3), 167.4 (C3'), 143.9 (C5'), 137.9 (C5), 136.6 (C11, C11'), 134.9 (C4, C4'), 134.2 (CAr, CAr'), 128.6 (CAr, CAr'), 129.0 (CAr, CAr'), 127.2 (C12, C12'), 126.9 (CAr, CAr'), 60.8 (C2, C2'), 39.3 (C9), 39.1 (C9'), 29.8 (C6), 28.9 (C6'), 27.7 (C7/8'), 23.5 (C7'), 22.4 (C8), 20.5 (C7/8'), 21.1 (C17, C17'), 14.1 (C1, C1'); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₉H₂₄NaO₃ 323.1618, found 323.1617; **IR** ν_{max}/cm⁻¹ (thin film) 2928 (C-H), 1711 (C=O), 1681, 1615, 1513, 1461, 1401, 1370, 1247.

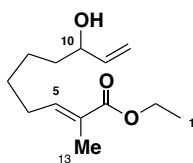
Preparation of (E)-ethyl 2-(4-fluorophenyl)-8-oxodeca-2,9-dienoate **116c**



Following **General Procedure 3**, using DMP (272 mg, 0.64 mmol), alcohol **115c** (131 mg, 0.43 mmol) and CH₂Cl₂ (10 mL) afforded compound **116c** (1:1.4 mixture of Z:E isomers, 109 mg, 83%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.22-7.19 (m, 2.4 H, ArH, ArH'), 7.05 (dd, J = 8.0, 5.0 Hz, 2.4 H, ArH, ArH'), 6.99-6.96 (m, 4.8 H, ArH, ArH'), 6.93 (t, J = 7.5 Hz, 1 H, H5'), 6.31-6.21 (m, 2.4 H, H11, H11'), 6.16 (dd, J = 17.5, 1.0, 1.4 H, H12), 6.10 (dd, J = 17.5, 1.0 Hz, 1 H, H12'), 6.04 (t, J = 7.5 Hz, 1.4 H, H5), 5.75 (t, J = 10.5, 1.4 H, H12), 5.76 (t, J = 10.5, 1 H, H12'), 4.21 (q, J = 7.0 Hz, 2.8 H, H2), 4.13 (q, J = 7.0 Hz, 2 H, H2'), 2.56 (t, J = 7.5 Hz, 2.8 H, H9), 2.44 (t, J = 7.5 Hz, 2 H, H9'), 2.39 (q, J = 7.5 Hz, 2.8 H, H6), 2.03 (q, J = 7.5 Hz, 2 H, H6'), 1.64 (quin., J = 7.5 Hz, 2.8 H, H8), 1.55-1.45 (m, 4.8 H, H8', H7) 1.38 (quin., J = 7.5 Hz, 2 H, H7'), 1.24 (t, J = 7.0 Hz, 4.2 H, H1), 1.19 (t, J = 7.5 Hz, 3 H, H1'); **¹³C NMR (127 MHz, CDCl₃)** δ_{C} 200.6 (C10), 200.4 (C10'), 167.9 (C3), 167.0 (C3'), 162.4 (d, J = 246.1 Hz, C16), 161.9 (d, J = 246.1 Hz, C16'), 144.6 (C5'), 139.6 (C5), 136.5 (C11, C11'), 133.1 (C4, C4'), 133.4 (CAr, CAr'), 131.4 (d, J = 8.6 Hz, C14), 129.0 (d, J = 8.6 Hz, C14'), 128.1 (C12, C12'), 115.2 (d, J = 21.0 Hz, C15), 114.9 (d, J = 21.0 Hz, C15'), 60.9 (C2, C2'), 39.3 (C9), 39.1 (C9'), 29.8 (C6), 26.3 (C6'), 29.0 (C7/8'), 23.5 (C7'), 22.4 (C8), 22.4 (C7/8'), 14.3 (C1, C1'); **¹⁹F NMR (377 MHz, CDCl₃)** δ_{F} -114.9; **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₁NaFO₃ 327.1367, found 327.1366; **IR ν_{max} /cm⁻¹ (thin film)** 2936 (C-H), 1710 (C=O), 1681, 1603, 1509, 1461, 1402, 1370, 1222.

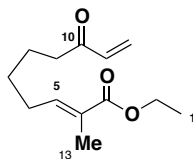
Preparation of (*E*)-ethyl 8-hydroxy-2-methyldeca-2,9-dienoate **118**



Wittig reagent **117** (1.9 g, 5.3 mmol) was added to a solution of aldehyde **23** (500 mg, 3.5 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture brought to reflux for 24 hr. The reaction mixture was then allowed to cool to RT and concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO_2 , pet 40-60:Et₂O (8:2)) to afford compound **118** (580 mg, 73%) as a colourless oil.

¹H NMR (400 MHz, CDCl_3) δ_{H} 6.68 (td, $J = 7.5, 1.5$ Hz, 1 H, *H*5), 5.80 (ddd, $J = 17.0, 10.0, 6.0$ Hz, 1 H, *H*11), 5.15 (dt, $J = 17.0, 1.5$ Hz, 1 H, *H*12), 5.04 (dt, $J = 10.0, 1.5$ Hz, 1 H, *H*12'), 4.12 (q, $J = 7.0$ Hz, 2 H, *H*2), 4.03 (q, $J = 6.0$ Hz, 1 H, *H*10), 2.11 (q, $J = 7.5$ Hz, 2 H, *H*6), 1.75 (s, 3 H, *H*13), 1.51-1.45 (m, 2 H, *H*9), 1.43-1.35 (m, 5 H, *H*7, *H*8, *OH*), 1.22 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl_3)** δ_{C} 168.3 (*C*3), 142.0 (*C*5), 141.2 (*C*11), 127.9 (*C*4), 114.7 (*C*12), 73.5 (*C*2), 60.4 (*C*10), 36.8 (*C*9), 28.6 (*C*6), 28.5 (*C*7/8), 25.1 (*C*7/8), 14.3 (*C*1), 12.4 (*C*13); **HRMS (ESI⁺)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{22}\text{NaO}_3$ 249.1451, found 249.1458; **IR ν_{max} /cm⁻¹ (thin film)** 3453 (br., *OH*), 2933 (*C-H*), 2860 (*C-H*), 1707 (*C=O*), 1647 (*C=C*), 1368, 1272, 1092, 991, 746.

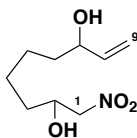
Preparation of (E)-ethyl 2-methyl-8-oxodeca-2,9-dienoate **119**



Following **General Procedure 3**, using DMP (562 mg, 1.30 mmol), alcohol **118** (200 mg, 0.88 mmol) and CH₂Cl₂ (10 mL) afforded compound **119** (191 mg, 97%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.67 (tq, $J = 7.5, 1.5$ Hz, 1 H, *H*5), 6.28 (dd, $J = 17.5, 10.5$ Hz, 1 H, *H*11), 6.15 (dd, $J = 17.5, 1.0$ Hz, 1 H, *H*12), 5.76 (dd, $J = 10.5, 1.0$ Hz, 1 H, *H*12'), 4.11 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.53 (t, $J = 7.5$ Hz, 2 H, *H*9), 2.13 (q, $J = 7.5$ Hz, 2 H, *H*6), 1.76 (s, 3H, *H*13), 1.63-1.56 (m, 2 H, *H*8), 1.44-1.37 (m, 2 H, *H*7), 1.22 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.6 (*C*10), 168.2 (*C*3), 141.5 (*C*4), 141.6 (*C*5), 136.5 (*C*11), 128.0 (*C*12), 60.4 (*C*2), 39.3 (*C*9), 28.5 (*C*6), 28.2 (*C*7), 23.6 (*C*8), 14.3 (*C*1), 12.4 (*C*13); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₃H₂₀NaO₃ 247.1305, found 247.1302; **IR ν_{max} /cm⁻¹ (thin film)** 2982 (C-H), 1718 (C=O), 1688 (C=O), 1467, 1374, 1256, 1225, 1181, 1145.

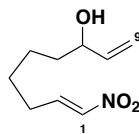
Preparation of 1-nitronon-8-ene-2,7-diol **121**



According to a modified literature procedure,¹⁹ a solution of KOH (62 mg, 1.10 mmol) in H₂O (0.4 mL) was added to a solution of aldehyde **23** (100 mg, 0.700 mmol) and nitromethane (0.12 mL, 2.10 mmol) in THF/MeOH (2 mL/1 mL) at 0 °C, and the reaction mixture stirred vigorously for 15 min. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (7:3)) to afford compound **121** (90 mg, 64%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 5.85 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H, *H*8), 5.21 (d, J = 17.0 Hz, 1 H, *H*9), 5.11 (d, J = 10.5 Hz, 1 H, *H*9'), 4.45-4.25 (m, 3 H, *H*1, *H*2), 4.26-4.15 (m, 1 H, *H*7), 2.71-2.45 (m, 2 H, 2 x OH), 1.60-1.32 (m, 8 H, *H*3, *H*4, *H*5, *H*6); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 141.9 (*C*8), 115.6 (*C*9), 81.2 (*C*1), 73.5 (*C*7), 68.9 (*C*2), 36.8 (*C*6), 33.8 (*C*3), 25.1 (*C*5), 25.0 (*C*4); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₉H₁₇NNaO₄ 226.1050, found 226.1051; **IR ν_{max} /cm⁻¹ (thin film)** 3402 (br., OH), 2981 (C-H), 2936 (C-H), 1646 (C=C), 1550 (NO₂), 1383 (NO₂), 992, 924.

Preparation of (*E*)-9-nitronona-1,8-dien-3-ol **122**

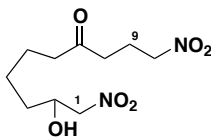


According to a modified literature procedure,²⁰ trifluoroacetic anhydride (400 μ L, 2.6 mmol) and Et₃N (700 μ L, 4.9 mmol) were added to a solution of diol **121** (500 mg, 2.46 mmol) in CH₂Cl₂ (20 mL) at 0 °C. The resulting solution was allowed to warm to RT and stirred for 1 hr. The solution was diluted with CH₂Cl₂, washed with H₂O, NH₄Cl (sat. aq.) and brine, and the combined aqueous layers extracted with CH₂Cl₂ (2 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **122** (300 mg, 82%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.25 (dt, J = 13.5, 7.0 Hz, 1 H, *H*₂), 6.98 (d, J = 13.5 Hz, 1 H, *H*₁), 5.80 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H, *H*₈), 5.45-5.30 (m, 3 H, *H*₉, *H*_{9'}, *H*₇), 2.29 (q, J = 7.0 Hz, 2 H, *H*₃), 1.91-1.70 (m, 2 H, *H*₆), 1.56 (q, J = 7.0 Hz, 2 H, *H*₄), 1.50-1.35 (m, 2 H, *H*₅);^g **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 142.7 (*C*₂), 140.7 (*C*₁), 134.6 (*C*₈), 120.3 (*C*₉), 79.8 (*C*₇), 33.5 (*C*₆), 28.3 (*C*₃), 27.4 (*C*₄), 24.4 (*C*₅); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₉H₁₅NNaO₃ 208.0944, found 208.0943; **IR ν_{max} /cm⁻¹ (thin film)** 3402 (br., OH), 1650 (C=C), 1524 (NO₂), 1352 (NO₂), 1218, 1151, 932.

^g OH was not observed in the ¹H NMR spectrum

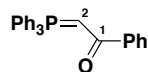
Preparation of 9-hydroxy-1,10-dinitrodecan-4-one **125**



According to a modified literature procedure,²¹ a solution of KOH (62 mg, 1.10 mmol) in H₂O (1.0 mL) was added to a solution of aldehyde **14** (100 mg, 0.71 mmol) and nitromethane (0.12 mL, 2.10 mmol) in 2:1 THF:MeOH (5.0 mL:2.5 mL) at 0 °C, and the reaction mixture was stirred vigorously for 15 min. The reaction mixture was then allowed to warm to RT and NH₄Cl (sat. aq.) was added. The layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **125** (20 mg, 11%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 4.39-4.30 (m, 5 H, *H*1, *H*2, *H*10), 2.51 (t, *J* = 7.0 Hz, 2 H, *H*8), 2.39 (t, *J* = 7.0 Hz, 2 H, *H*3), 2.19 (quin., *J* = 6.5 Hz, 2 H, *H*6), 1.60-1.30 (m, 7 H, *H*4, *H*5, *H*9, OH); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 208.7 (*C*7), 80.6 (*C*1/10), 74.6 (*C*1/10), 68.3 (*C*2), 42.4 (*C*3), 38.4 (*C*8), 33.3 (*C*6), 24.9 (*C*9), 23.0 (*C*4), 21.1 (*C*5); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₀H₁₈N₂NaO₆ 285.1063, found 285.1100; **IR ν_{max} /cm⁻¹ (thin film)** 3402 (br., OH), 2939 (C-H), 1707 (C=O), 1546 (NO₂), 1377 (NO₂), 1104, 912, 730.

Preparation of 1-phenyl-2-(triphenylphosphoranylidene)ethanone **127**



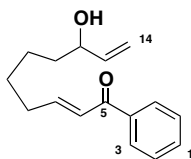
According to a literature procedure,²² bromoacetophenone (5.60 g, 27.8 mmol) and triphenylphosphine (7.31 g, 27.8 mmol) were dissolved in THF (250 mL) and the reaction mixture heated to reflux for 4 hr. The reaction mixture was allowed to cool to RT and the phosphonium salt precipitate was washed with Et₂O (× 3). This salt was dissolved in 1.5:1 H₂O:CH₂Cl₂ (50:33 mL) and NaOH (aq., 2 M, 14 mL) was added. The resulting mixture was stirred at RT overnight and then extracted with CH₂Cl₂ (3 × 100 mL). The combined organics were washed with brine (50 mL), dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford compound **127** (9.50 g, 95%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ_H 8.10-7.25 (m, 20 H, ArH), 4.44 (d, *J* = 24.5 Hz, 1 H, H₂);

¹³C NMR (101 MHz, CDCl₃) δ_C 186.0 (C1), 142.4 (CAr), 134.0 (CAr), 139.4 (CAr), 132.9 (CAr), 130.1 (CAr), 129.7 (CAr), 129.6 (CAr), 128.6 (CAr), 127.7 (CAr), 127.4 (CAr), 50.4 (C2); **Mpt** 180-181 °C (lit: 178-180 °C).²²

Spectroscopic properties of this compound were consistent with the data reported in the literature.

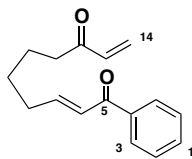
Preparation of (*E*)-8-hydroxy-1-phenyldeca-2,9-dien-1-one **128**



Wittig reagent **127** (1.60 g, 4.30 mmol) was added to a solution of aldehyde **23** (500 mg, 3.50 mmol) in CH₂Cl₂ (25 mL) and the reaction mixture brought to reflux for 24 hr. The reaction mixture was allowed to cool to RT and concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (7:3)) to afford compound **128** (500 mg, 60%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.91 (t, J = 7.5 Hz, 2 H, *H*3), 7.53 (t, J = 7.5 Hz, 1 H, *H*1), 7.44 (t, J = 7.5 Hz, 2 H, *H*2), 7.05 (dt, J = 15.5, 7.0 Hz, 1 H, *H*7), 6.87 (d, J = 15.5 Hz, 1 H, *H*6), 5.85 (ddd, J = 17.0, 10.5, 6.0 Hz, 1 H, *H*13), 5.20 (d, J = 17.0 Hz, 1 H, *H*14), 5.05 (d, J = 10.5 Hz, 1 H, *H*14'), 4.09 (dt, J = 7.0, 6.0 Hz, 1 H, *H*12), 2.31 (q, J = 7.0 Hz, 2 H, *H*8), 2.05 (br. s, 1 H, OH), 1.61-1.10 (m, 6 H, *H*9, *H*10, *H*11); **¹³C NMR (100 MHz, CDCl₃)** δ_{C} 190.8 (C5), 149.7 (C7), 138.5 (C4), 137.9 (C13), 132.9 (C1), 132.6 (C2), 128.4 (C3), 126.0 (C6), 114.0 (C14), 71.1 (C12), 36.0 (C11), 33.9 (C8), 28.8 (C9), 27.6 (C10); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₂₀NaO₂ 267.1356, found 267.1360; **IR** ν_{max} /cm⁻¹ (thin film) 3438 (br., OH), 2932 (C-H), 1666 (C=O), 1616 (C=C), 1578, 1447, 1285.

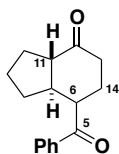
Preparation of (*E*)-1-phenyldeca-2,9-diene-1,8-dione **129**



Following **General Procedure 3**, using DMP (1.50 g, 3.50 mmol), alcohol **128** (500 mg, 2.10 mmol) and CH₂Cl₂ (30 mL), afforded compound **129** (500 mg, quant.) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.93 (d, J = 7.5 Hz, 2 H, *H*3), 7.56 (t, J = 7.5 Hz, 1 H, *H*1), 7.47 (t, J = 7.5 Hz, 2 H, *H*2), 7.05 (dt, J = 15.5, 7.0 Hz, 1 H, *H*7), 6.90 (d, J = 15.5 Hz, 1 H, *H*6), 6.36 (dd, J = 17.5, 10.5 Hz, 1 H, *H*13), 6.23 (dd, J = 17.5, 1.0 Hz, 1 H, *H*14), 4.84 (dd, J = 10.5, 1.0 Hz, 1 H, *H*14'), 2.64 (t, J = 7.0 Hz, 2 H, *H*11), 2.36 (q, J = 7.0 Hz, 2 H, *H*8), 1.71 (quin., J = 7.0 Hz, 2 H, *H*10), 1.57 (quin., J = 7.0 Hz, 2 H, *H*9); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.9 (*C*12), 191.4 (*C*5), 149.6 (*C*7), 138.5 (*C*4), 137.0 (*C*13), 133.0 (*C*1), 129.0 (*C*2, *C*3), 128.5 (*C*14), 126.7 (*C*6), 39.6 (*C*11), 33.0 (*C*8), 28.0 (*C*9), 23.9 (*C*10); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₈NaO₂ 265.1199, found 265.1194; **IR ν_{max} /cm⁻¹ (thin film)** 1698 (C=O), 1670 (C=O), 1650 (C=C), 1618 (C=C), 1345, 1039, 904.

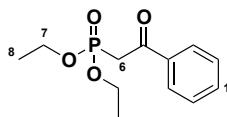
Preparation of (3aS*,7R*,7aS*)-7-benzoylhexahydro-1H-inden-4(2H)-one **130**



Following **General Procedure 4**, using cyclisation precursor **129** (100 mg, 0.410 mmol), toluene (10 mL), KOH (93 mg, 1.64 mmol), tetrabutylammonium bisulfate (12 mg, 0.040 mmol) at RT afforded compound **130** (55 mg, 55%, >20:1 d.r.) as a colourless oil.

¹H NMR (500 MHz, C₆D₆) δ_{H} 7.91 (d, $J = 7.5$ Hz, 1 H, ArH), 7.30-7.12 (m, 4 H, ArH), 3.05 (q, $J = 8.0$ Hz, 1 H, H₆), 2.82 (quin., $J = 8.0$ Hz, 1 H, H₇), 2.73 (q, $J = 8.0$ Hz, 1 H, H₁₁), 2.41-2.22 (m, 2 H, H₁₀, H₁₃), 2.21-2.09 (m, 1 H, H_{13'}), 1.85-1.68 (m, 2 H, H₁₄), 1.67-1.47 (m, 3 H, H_{10'}, H₉, H₈), 1.36-1.25 (m, 1 H, H_{9'}), 1.15-0.99 (m, 1 H, H_{8'}); **¹³C NMR (126 MHz, C₆D₆)** δ_{C} 211.8 (C₁₂), 202.8 (C₅), 137.7 (CAr), 133.7 (CAr), 129.8 (CAr), 129.6 (CAr), 51.0 (C₁₁), 45.4 (C₆), 44.3 (C₇), 37.8 (C₁₃), 32.0 (C₈), 27.1 (C₁₄), 26.2 (C₁₀), 23.8 (C₉); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₈NaO₂ 265.1199, found 265.1192; **IR ν_{max} /cm⁻¹ (thin film)** 2952 (C-H), 1705 (C=O), 1676 (C=O), 1596, 1579, 1447; Daicel CHIRALPAK IA, 4.6 mm x 250 mm, 5:95 2-propanol:hexane, 1.0 mL/min, retention times of enantiomers: 10.1 min, 11.8 min.

Preparation of diethyl (2-oxo-2-phenylethyl)phosphonate **243**

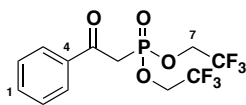


According to a literature procedure,²³ diethyl methylphosphonate (0.29 mL, 2.0 mmol) was dissolved in THF (15 mL), and the resulting solution cooled to -78 °C. *n*BuLi (2.5 mL, 1.6 M in hexanes, 4.0 mmol) was added slowly and the reaction mixture stirred at this temperature for 10 min. After which, methyl benzoate (0.32 mL, 2.2 mmol) was added slowly, and the reaction mixture stirred at -78 °C for 2 hr. The reaction mixture was allowed to warm to RT, and was quenched with NH₄Cl (sat. aq.). The layers were separated and the aqueous layer was extracted with CHCl₃ (× 3). The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. This crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (1:1)) to afford compound **243** (400 mg, 78%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_H 7.96 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.54 (t, *J* = 7.5 Hz, 1 H, Ar), 7.41 (t, *J* = 8.0 Hz, 2 H, Ar), 4.09 (dq, *J* = 7.5 Hz, 4 H, *H*7) 3.58 (d, *J* = 22.5 Hz, 2 H, *H*6), 1.22 (t, *J* = 7.5 Hz, 6 H, *H*8); **¹³C NMR (101 MHz, CDCl₃)** δ_C 192.0 (C5), 136.5 (C4), 133.7 (CAr), 129.0 (CAr), 128.5 (CAr), 62.7 (C7), 38.4 (d, *J* = 130 Hz, C6), 16.2 (C8); **LRMS m/z (ESI⁺)** 257 ([M+H]⁺ 63%), 279 ([M+Na]⁺ 100%).

Spectroscopic properties of this compound were consistent with the data reported in the literature.²³

Preparation of bis(2,2,2-trifluoroethyl) (2-oxo-2-phenylethyl)phosphonate **132**



According to a modified literature procedure,⁵ *n*BuLi (9.6 mL, 1.6 M in hexanes, 15 mmol) was cooled to -20 °C. HMDS (3.7 mL, 17 mmol) was dissolved in THF (14 mL) and added dropwise to the cooled *n*BuLi solution. The resulting solution was cooled to -78 °C, and a solution of bis(2,2,2-trifluoroethyl) methylphosphonate (2 g, 7.7 mmol) and benzoyl chloride (1.0 mL, 9.0 mmol) in THF (34 mL) was added dropwise. The resulting solution was kept in the -78 °C bath overnight, allowing to warm gradually, and was then treated with HCl (1.0 M) until acidic. The layers were separated, the aqueous layer extracted with Et₂O (x 2), and the combined organic extracts were washed with brine. The organic layer was then dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. This crude product was purified by flash column chromatography (SiO₂, pet 40-60: Et₂O (7:3)) to afford compound **132** (1.4 g, 50%) as a colourless oil.

N.B. Yields of this reaction vary. Leaving the reaction mixture below -20 °C overnight generally affords the best yields.

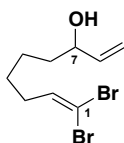
¹H NMR (400 MHz, CDCl₃) δ_H 7.95 (d, *J* = 8.0 Hz, 2 H, *H*₃), 7.65 (tt, *J* = 6.5, 1.5 Hz, 1 H, *H*₁), 7.50 (t, *J* = 8.0 Hz, 2 H, *H*₂), 4.61-4.44 (m, 4 H, *H*₇), 3.85 (d, *J* = 22.0 Hz, 2 H, *H*₆);

¹³C NMR (101 MHz, CDCl₃) δ_C 191.3 (C₅), 135.7 (C₄), 134.4 (C₁), 128.8 (C₃), 128.7 (C₂), 123.0 (qd, *J* = 277.0, 8.5 Hz, C₈), 62.8 (qd, *J* = 38.0, 5.5 Hz, C₇), 37.5 (d, *J* = 144.5 Hz, C₆)

¹⁹F NMR (377 MHz, CDCl₃) δ_F 75.4; HRMS (ESI⁺) *m/z* calculated for [M+H]⁺

$\text{C}_{12}\text{H}_{11}\text{F}_6\text{NaO}_4\text{P}$ 387.0191, found 387.0190; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2970 (C-H), 1738 (C=O), 1682 (C=O), 1598, 1450, 1371.

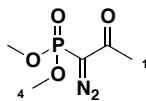
Preparation of 9,9-dibromonona-1,8-dien-3-ol **134**



According to a modified literature procedure,²⁴ aldehyde **23** (200 mg, 1.41 mmol) and CBr₄ (697 mg, 2.10 mmol) were dissolved in CH₂Cl₂ (15 mL) and cooled to 0 °C. Triisopropylphosphite (0.76 mL, 3.08 mmol) was dissolved in CH₂Cl₂ (5 mL) and added to the reaction mixture over 1 hr, and then the reaction mixture was stirred for a further hr. The reaction mixture was quenched by the addition of NaHCO₃ (sat. aq.), the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (x 3). The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **134** (100 mg, 24%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_H 6.40 (t, *J* = 7.0 Hz, 1 H, *H*₂), 5.87 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H, *H*₈), 5.23 (dt, *J* = 17.0, 1.5 Hz, 1 H, *H*₉), 5.12 (dt, *J* = 10.5, 1.5 Hz, 1 H, *H*_{9'}), 4.11 (q, *J* = 6.5 Hz, 1 H, *H*₇), 2.14-2.09 (m, 2 H, *H*₃), 1.58-1.50 (m, 3 H, *H*₆, OH), 1.56-1.50 (m, 4 H, *H*₄, *H*₅); ¹³C NMR (126 MHz, CDCl₃) δ_C 141.1 (C₈), 138.6 (C₂), 114.8 (C₉), 88.8 (C₁), 73.1 (C₇), 36.6 (C₆), 32.9 (C₃), 27.7 (C_{4/5}), 24.8 (C_{4/5}); HRMS (ESI⁺) *m/z* calculated for [M+H]⁺ C₉H₁₅Br₂O 296.9484, found 296.9400; IR ν_{max}/cm⁻¹ (thin film) 3423 (OH), 2935 (C-H), 1263, 1077, 988.

Preparation of dimethyl (1-diazo-2-oxopropyl)phosphonate 138

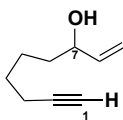


According to a literature procedure,²⁵ dimethyloxopropylphosphonate (0.17 mL, 1.21 mmol) was dissolved in 5:1 PhMe:THF (5 mL:1 mL) and the resulting solution cooled to 0 °C. NaH (60% dispersion in mineral oil, 53 mg, 1.30 mmol) was added over 10 min and the reaction mixture was stirred for 1 hr. Acetamidobenzenesulfonyl azide (317 mg, 1.30 mmol) was added, the mixture allowed to warm to RT, and stirred for 16 hr. The reaction mixture was then filtered through Celite, washed with PhMe (x 2), and EtOAc (x 2). The filtrate was concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was purified by flash column chromatography (SiO₂, pet 40-60:EtOAc (1:4)) to afford compound **138** (200 mg, 87%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 3.84 (d, J = 12.0 Hz, 6 H, H_4), 2.24 (s, 3 H, H_1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 189.6 (C2), 128.4 (C3), 53.6 (C1), 27.1 (C4); **LRMS m/z (ESI⁺)** 193 ([M+H]⁺ 100%), 215 ([M+Na]⁺ 90%).

Spectroscopic properties of this compound were consistent with the data reported in the literature.²⁵

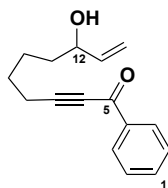
Preparation of non-1-en-8-yn-3-ol **139**



According to a modified literature procedure,²⁶ Ohira-Bestmann reagent **138** (150 mg, 0.78 mmol) was dissolved in MeOH (5 mL) and added to a solution of aldehyde **23** and K₂CO₃ (180 mg, 1.30 mmol) in MeOH (5 mL), and the resulting solution stirred for 90 min. The reaction mixture was diluted with Et₂O (10 mL), quenched with NaHCO₃ (5% aq., 15 mL), and the aqueous layer extracted with Et₂O (2 x 6 mL). The combined extracts were washed with brine (6 mL), dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **139** (75 mg, 83%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 5.80 (ddd, *J* = 17.5, 10.5, 6.5 Hz, 1 H, *H*₈), 5.16 (dt, *J* = 17.0, 1.5 Hz, 1 H, *H*₉), 5.05 (dt, *J* = 10.5, 1.5 Hz, 1 H, *H*_{9'}), 4.08-4.01 (m, 1 H, *H*₇), 2.14 (td, *J* = 7.0, 2.5 Hz, 2 H, *H*₃), 1.88 (t, *J* = 2.5 Hz, 1 H, *H*₁), 1.55-1.44 (m, 7 H, *H*₄, *H*₅, *H*₆, OH); ¹³C NMR (126 MHz, CDCl₃) δ_C 141.1 (C₈), 114.8 (C₉), 84.5 (C₂), 73.1 (C₇), 68.4 (C₁), 36.4 (C₆), 28.4 (C₄), 24.5 (C₅), 18.4 (C₃); HRMS (ESI⁺) *m/z* calculated for [M+H]⁺ C₉H₁₅O 139.1045, found 139.1084; IR ν_{max}/cm⁻¹ (thin film) 3301 (OH), 2939 (C-H), 2862 (C-H), 1121, 1069, 991.

Preparation of 8-hydroxy-1-phenyldec-9-en-2-yn-1-one **135**

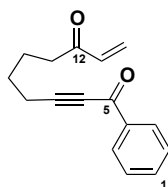


According to a modified literature procedure,²⁷ Pd(PPh₃)₂Cl₂ (56 mg, 0.08 mmol) and CuI (42 mg, 0.22 mmol) were suspended in THF (15 mL) and the resulting suspension stirred under Ar for 1 hr. NEt₃ (0.6 mL, 4.4 mmol), benzoyl chloride (0.5 mL, 4.4 mmol), and terminal alkyne **139** (600 mg, 4.4 mmol) dissolved in THF (10 mL) were added to the reaction mixture, and the resulting suspension stirred at RT for 2 hr. The reaction mixture was quenched by the addition of NH₄Cl (sat. aq.), the layers were separated and the aqueous layer was extracted with EtOAc (x 3). The combined organics were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (6:4)) to afford compound **135** (1.0 g, 94%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ_H 8.09-8.04 (m, 2 H, H₃), 7.53 (tt, *J* = 1.5, 6.5 Hz, 1 H, H₁), 7.40 (tt, *J* = 1.5, 8.0 Hz, 2 H, H₂), 5.80 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H, H₁₃), 5.17 (dt, *J* = 17.0, 1.5 Hz, 1 H, H₁₄), 5.05 (dt, *J* = 10.5, 1.5 Hz, 1 H, H₁₄'), 4.11-4.03 (m, 1 H, H₁₂), 2.45 (t, *J* = 7.0 Hz, 2 H, H₈), 1.69-1.60 (m, 3 H, H₁₀, H₉), 1.57-1.44 (m, 4 H, H₁₁, H₁₁', H₉', OH); ¹³C NMR (126 MHz, CDCl₃) δ_C 178.3 (C₅), 141.0 (C₁₃), 136.9 (C₄), 134.0 (C₁), 130.6 (C₃), 129.6 (C₂), 115.0 (C₁₄), 96.5 (C₆), 79.8 (C₇), 73.0 (C₁₂), 36.3 (C_{11/10}), 27.7 (C₉), 24.8 (C_{11/10}), 19.2 (C₈); HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₁₆H₁₈NaO₂

265.1199, found 265.1200; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 3420 (OH), 2937 (C-H), 2201 (alkyne), 1639 (C=O), 1264, 1069, 990.

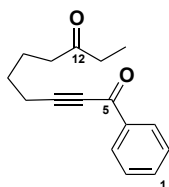
Preparation of 1-phenyldec-9-en-2-yne-1,8-dione **140**



Following **General Procedure 3**, using DMP (2.98 g, 7.0 mmol), alcohol **135** (1.0 g, 4.1 mmol) and CH₂Cl₂ (80 mL). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (7:3)) to afford compound **140** (600 mg, 61%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 8.13 (dd, J = 9.0, 1.0 Hz, 2 H, *H*3), 7.60 (tt, J = 1.0, 7.5 Hz, 1 H, *H*1), 7.48 (t, J = 7.5 Hz, 2 H, *H*2), 6.36 (dd, J = 17.0, 10.5 Hz, 1 H, *H*13), 6.23 (dd, J = 17.5, 1.0 Hz, 1 H, *H*14), 5.84 (dd, J = 10.5, 1.0 Hz, 1 H, *H*14'), 2.67 (t, J = 7.0 Hz, 2 H, *H*11), 2.53 (t, J = 7.0 Hz, 2 H, *H*8), 1.87-1.78 (m, 2 H, *H*9), 1.75-1.66 (m, 2 H, *H*10); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 200.1 (*C*12), 178.2 (*C*5), 136.8 (*C*13), 136.4 (*C*4), 134.0 (*C*1), 129.3 (*C*3), 128.7 (*C*2), 128.3 (*C*14), 96.0 (*C*7), 79.9 (*C*6), 38.7 (*C*11), 27.3 (*C*10), 23.0 (*C*9), 19.2 (*C*8); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₆NaO₂ 263.1043, found 263.1041; **IR ν_{max} /cm⁻¹ (thin film)** 2939 (C-H), 2231 (alkyne), 2199 (alkyne), 1679 (C=O), 1639 (C=O), 1579, 1449, 1263.

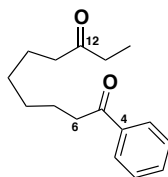
Preparation of 1-phenyldec-2-yne-1,8-dione **245**



According to a modified literature procedure,²⁸ alkyne **140** (100 mg, 0.42 mmol) was dissolved in THF (4 mL) and Pd(PPh₃)₄ (10 mg, 0.008 mmol) was added to the flask under an Ar atmosphere. Bu₃SnH (0.13 mL, 0.42 mmol) was dissolved in THF (3 mL) and added to the reaction mixture dropwise over 2 hr. The resulting suspension was stirred at RT for 1 hr and then the reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude product. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **245** (65 mg, 61%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 8.06 (d, J = 8.5 Hz, 2 H, H_3), 7.53 (t, J = 8.0 Hz, 1 H, H_1), 7.40 (t, J = 7.5 Hz, 2 H, H_2), 2.50 (q, J = 7.0 Hz, 2 H, H_{10}), 2.46 (t, J = 7.0 Hz, 2 H, H_8), 2.42 (q, J = 7.0 Hz, 2 H, H_{13}), 1.79-1.71 (m, 2 H, H_{11}), 1.69-1.66 (m, 2 H, H_9), 0.97 (t, 3 H, H_{14}); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 210.9 (C12), 178.2 (C5), 136.8 (C4), 133.9 (C1), 129.6 (C3), 128.5 (C2), 96.0 (C7), 79.9 (C6), 41.9 (C8), 35.9 (C13), 27.8 (C9), 23.4 (C11), 19.2 (C10), 7.8 (C14); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₈NaO₂ 265.1199, found 265.1192; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2937 (C-H), 2200 (alkyne), 1711 (C=O), 1640 (C=O), 1597, 1579, 1449, 1312, 1262.

Preparation of 1-phenyldecane-1,8-dione **246**



Alkyne **140** (100 mg, 0.42 mmol) was dissolved in EtOH (4 mL) and Pd/C (10 mg, 10 wt%) and quinolone (5.4 mg, 0.042 mmol) were added to the flask under a H₂ atmosphere. The resulting suspension was stirred at RT for 3 hr and then the reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure, and then the residue dissolved in Et₂O and extracted against HCl (1.0 M aq., x 3). The organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **246** (80 mg, 77%).

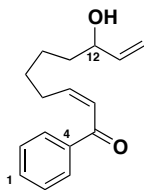
¹H NMR (400 MHz, CDCl₃) δ_{H} 8.27 (d, J = 4.0 Hz, 1 H, ArH), 7.19 (t, J = 7.5 Hz, 2 H, ArH), 7.10 (t, J = 7.5 Hz, 2 H, ArH), 2.52 (t, J = 8.0 Hz, 2 H, H₆), 2.36-2.25 (m, 4 H, H₁₁, H₁₃), 1.55-1.45 (m, 4 H, H₇, H_{9/10}), 1.27-1.21 (m, 4 H, H₈, H_{9/10}), 0.97 (t, J = 7.0 Hz, 3 H, H₁₄); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 210.9 (C₁₂), 171.2 (C₅), 144.9 (C₄), 128.4 (CAr), 128.3 (CAr), 125.9 (CAr), 42.4 (C₁₁), 42.4 (C₆), 42.0 (C₁₃), 39.1 (C₇), 29.3 (C_{8/9/10}), 29.2 (C_{8/9/10}), 23.9 (C_{9/10}), 7.9 (C₁₄); **HRMS (FI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₂₂O₂ 246.1620, found 246.1654; **IR ν_{max} /cm⁻¹ (thin film)** 3026 (C-H), 2929, 1712 (C=O), 1603, 1495, 1453, 1412, 1374, 1113.

N.B. This is a known compound, but previous literature data is not complete²⁹

Alternative procedure:

Alkyne **140** (100 mg, 0.42 mmol) was dissolved in EtOH (4 mL) and Lindlar's catalyst (10 mg, 10 wt%) was added to the flask under a H₂ atmosphere. The resulting suspension was stirred at RT for 2 hr and then the reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure to afford the title compound **246** (65 mg, 63%) with identical spectroscopic properties as previously reported.

Preparation of (Z)-8-hydroxy-1-phenyldeca-2,9-dien-1-one **133**



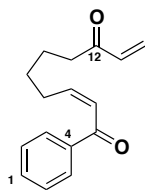
Still-Gennari reagent **132** (1.50 g, 4.12 mmol) was dissolved in THF (25 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 330 mg, 8.24 mmol) was added slowly and the reaction mixture stirred for 20 min at this temperature, and then cooled to -78 °C. Aldehyde **23** (585 mg, 4.12 mmol) was dissolved in THF (5 mL), and cooled to -78 °C. The solution of aldehyde **23** in THF was added to the reaction mixture and the resulting suspension stirred at -78 °C for 3 hr (TLC indicated a mixture of SM and product).^h The reaction mixture was quenched with ice water (20 mL), the layers separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (30 mL), dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. ¹H NMR showed a 1:2:1 mixture of SM:trans:cis. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (15:5)) to afford compound **133** (110 mg, 10%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_H 7.87 (d, *J* = 7.5 Hz, 2 H, *H*3), 7.48 (tt, *J* = 7.5, 1.5 Hz, 1 H, *H*1), 7.37 (t, *J* = 7.5 Hz, 2 H, *H*2), 7.09 (dt, *J* = 11.5, 1.5 Hz, 1 H, *H*6), 6.25 (dt, *J* = 11.5, 7.5 Hz, 1 H, *H*7), 5.78 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1 H, *H*13), 5.14 (dt, *J* = 17.0, 1.5 Hz, 1 H, *H*14), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1 H, *H*14'), 4.02 (q, *J* = 7.0 Hz, 1 H, *H*12), 2.57 (qd, *J* = 7.5, 1.5 Hz, 2 H, *H*8), 1.58-1.31 (m, 6 H, *H*9, *H*10, *H*11); ¹³C NMR (126 MHz,

^h The reaction was not allowed to go to completion as the cis product isomerised into the trans product

CDCl₃) δ_c 192.1 (C5), 149.3 (C7), 141.2 (C13), 138.5 (C4), 132.7 (C1), 128.5 (C3), 128.4 (C2), 124.5 (C6), 114.6 (C14), 73.1 (C12), 36.7 (C9/10/11), 29.7 (C8), 29.0 (C9/10/11), 25.0 (C9/10/11); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₂₀NaO₂ 267.1356, found 267.1357; **IR** $\nu_{\max}/\text{cm}^{-1}$ (**thin film**) 3435 (OH), 2931 (C-H), 2858 (C-H), 1664 (C=O), 1578, 1449, 1228.

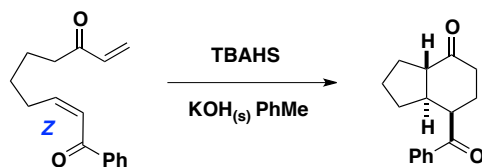
Preparation of (Z)-1-phenyldeca-2,9-diene-1,8-dione **131**



Following **General Procedure 3**, using DMP (340 mg, 0.80 mmol), alcohol **133** (100 mg, 0.40 mmol) and CH₂Cl₂ (20 mL). The crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **131** (60 mg, 63%) as a colourless oil.

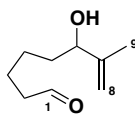
¹H NMR (400 MHz, CDCl₃) δ_{H} 7.94 (d, J = 7.5 Hz, 2 H, *H*3), 7.56 (tt, J = 2, 7.5 Hz, 1 H, *H*1), 7.47 (t, J = 7.5 Hz, 2 H, *H*2), 6.83 (dt, J = 11.5, 1.5 Hz, 1 H, *H*6), 6.34 (dt, J = 11.5, 7.5 Hz, 1 H, *H*7), 6.35 (dd, J = 17.0, 10.5 Hz, 1 H, *H*13), 6.22 (dd, J = 17.0, 1.0 Hz, 1 H, *H*14), 5.82 (dd, J = 10.5, 1.0 Hz, 1 H, *H*14'), 2.67 (qd, J = 7.5, 1.5 Hz, 2 H, *H*8), 2.62 (t, J = 7.5 Hz, 2 H, *H*11), 1.70 (quin., J = 7.5 Hz, 2 H, *H*10), 1.54 (quin., J = 7.5 Hz, 2 H, *H*9); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 200.8 (C12), 192.1 (C5), 148.9 (C7), 138.6 (C4), 136.8 (C13), 132.8 (C1), 128.6 (C3), 128.4 (C2), 128.1 (C14), 124.7 (C6), 39.2 (C11), 29.5 (C8), 28.7 (C9), 23.5 (C10); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₈NaO₂ 265.1199, found 265.1191; **IR** ν_{max} /cm⁻¹ (thin film) 2934 (C-H), 1665 (C=O), 1612 (C=O), 1449, 1403, 1228.

Preparation of (3aS*,7R*,7aS*)-7-benzoylhexahydro-1H-inden-4(2H)-one **130**



Following **General Procedure 4**, using cyclisation precursor **131** (50 mg, 0.20 mmol), toluene (5 mL), KOH (47 mg, 0.82 mmol), tetrabutylammonium bisulfate (6 mg, 0.020 mmol) at RT afforded compound **130** (20 mg, 41%, >20:1 d.r.) as a colourless oil, with identical spectroscopic properties to those reported previously.

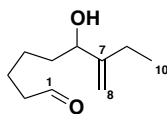
Preparation of 6-hydroxy-7-methyloct-7-enal **143a**



Following **General Procedure 1**, using 600 mg of aldehyde **22** and isopropenyl magnesium bromide (0.5 M in THF) afforded the title compound **143a** in 98% yield.

¹H NMR (400 MHz, CDCl₃) δ_{H} 9.77 (s, 1 H, *H*1), 4.94 (br. s, 1 H, *H*8), 4.84 (br. s, 1 H, *H*8'), 4.09 (t, *J* = 6.0 Hz, 1 H, *H*6), 2.45 (td, *J* = 7.0, 1.5 Hz, 2 H, *H*2), 1.72 (s, 3 H, *H*9), 1.70-1.40 (7 H, *H*3, *H*4, *H*5, OH); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 202.6 (*C*1), 147.4 (*C*7), 111.1 (*C*8), 75.6 (*C*6), 43.8 (*C*2), 34.5 (*C*5), 25.1 (*C*4), 21.9 (*C*3), 17.5 (*C*9); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₉H₁₆NaO₂ 179.1043, found 179.1043; **IR** ν_{max} /cm⁻¹ (**thin film**) 3413 (OH), 2937 (C-C), 2862 (C-C), 1720 (C=O), 1451, 1020, 911.

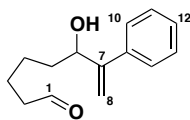
Preparation of 6-hydroxy-7-methylenenon-8-enal **143b**



Following **General Procedure 1**, using 2.0 g of aldehyde **22** and 2-bromo-1-butene afforded the title compound **143b** in 76% yield.

¹H NMR (400 MHz, CDCl₃) δ_{H} 9.78 (s, 1 H, *H*1), 5.02 (s, 1 H, *H*8), 4.86 (s, 1 H, *H*8'), 4.13 (dd, *J* = 7.0 Hz, 1 H, *H*6), 4.10 (br. s, 1 H, OH), 2.47 (td, *J* = 7.5, 1.5 Hz, 2 H, *H*2), 2.15-2.00 (m, 2 H, *H*9), 1.75-1.55 (m, 2 H, *H*3), 1.45-1.30 (m, 2 H, *H*4), 1.28 (t, *J* = 7.0 Hz, 2 H, *H*5), 1.08 (t, *J* = 7.0 Hz, 3 H, *H*10); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 202.7 (*C*1), 153.5 (*C*7), 108.5 (*C*8), 75.3 (*C*6), 43.9 (*C*2), 35.4 (*C*3), 25.3 (*C*4), 23.9 (*C*9), 14.2 (*C*5), 12.0 (*C*10); **HRMS (FI⁺)** *m/z* calculated for [M+H]⁺ C₁₀H₁₈O₂ 170.1307, found 170.1308; **IR** ν_{max} /cm⁻¹ (**thin film**) 3423 (br., OH), 2936 (C-H), 1721 (C=O), 1648, 1459, 1409.

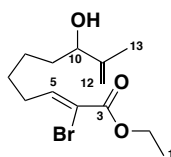
Preparation of 6-hydroxy-7-phenyloct-7-enal **143c**



Following **General Procedure 1**, using 2.0 g of aldehyde **22** and α -bromostyrene afforded the title compound **143c** in 74% yield.

^1H NMR (400 MHz, CDCl_3) δ_{H} 9.74 (t, J = 1.5 Hz, 1 H, H_1), 7.47-7.30 (m, 5 H, H_{10} , H_{11} , H_{12}), 5.37 (s, 1 H, H_8), 5.33 (s, 1 H, $H_{8'}$), 4.66 (dd, J = 7.0, 4.5 Hz, 1 H, H_6), 2.41 (td, J = 7.0, 1.5 Hz, 2 H, H_2), 1.75-1.40 (m, 7 H, H_3 , H_4 , H_5 , OH); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 202.7 (C1), 151.9 (C7), 139.8 (C9), 128.5 (CAr), 127.8 (CAr), 126.9 (CAr), 113.8 (C8), 73.6 (C6), 43.8 (C2), 35.8, 21.8, 21.1 (C3, C4, C5); HRMS (ESI $^+$) m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{18}\text{NaO}_2$ 241.1199, found 241.1197; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3421 (br, OH), 2937 (C-H), 1719 (C=O), 1493, 1443, 1390.

Preparation of (Z)-ethyl 2-bromo-8-hydroxy-9-methyldeca-2,9-dienoate **145a**



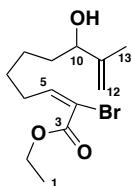
Following **General Procedure 2**, using HWE reagent **25** (1.4 g, 6.4 mmol), NaH (512 mg, 12.8 mmol), NBS (1.1 g, 6.4 mmol) and aldehyde **143a** (1.0 g, 6.4 mmol) afforded the title compound **145a** (803 mg, 81% over two steps) as a 1:5 (*E*:*Z*) mixture of isomers.

E isomer data omitted for clarity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.13 (t, $J = 7.0$ Hz, 1 H, *H*5) 4.80-4.77 (m, 1 H, *H*12) 4.70-4.67 (m, 1 H, *H*12'), 4.12 (q, $J = 7.0$ Hz, 2 H, *H*2), 3.90-3.82 (m, 1 H, *H*10), 2.20 (q, $J = 7.0$ Hz, 2 H, *H*6), 1.57 (s, 3 H, *H*13), 1.46-1.34 (m, 7 H, *H*7, *H*8, *H*9, OH), 1.18 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 162.5 (C3), 147.5 (C5), 116.5 (C4), 111.1 (C12), 75.8 (C10), 62.4 (C2), 34.5 (C7/8/9), 32.0 (C6), 27.5 (C7/8/9), 25.3 (C7/8/9), 17.5 (C13), 14.1 (C1);ⁱ **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₃H₂₁BrNaO₃ 327.0566, found 327.0561; **IR ν_{max} /cm⁻¹ (thin film)** 3411 (OH), 2936 (C-C), 1714 (C=O), 1624 (C=O), 1447, 1369, 1257.

ⁱC11 was not observed in the ¹³C spectra

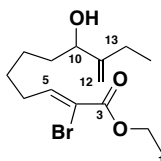
Preparation of (E)-ethyl 2-bromo-8-hydroxy-9-methyldeca-2,9-dienoate **144a**



Following **General Procedure 2**, using SG reagent **19** (2.1 g, 6.4 mmol), NaH (512 mg, 12.8 mmol), NBS (1.1 g, 6.4 mmol) and aldehyde **143a** (1.0 g, 6.4 mmol, prepared from isopropenylmagnesium bromide (0.5 M in THF)) afforded the title compound **144a** (461 mg, 46% over two steps).

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.67 (t, J = 7.0 Hz, 1 H, H_5), 4.93 (s, 1 H, H_{12}), 4.84 (s, 1 H, $H_{12'}$), 4.27 (qt, J = 7.0, 1.0 Hz, 2 H, H_2), 4.05 (t, J = 6.5 Hz, 1 H, H_{10}), 2.51 (q, J = 7.0 Hz, 2 H, H_6), 1.71 (br. s, 1 H, OH), 1.72 (s, 3 H, H_{13}), 1.60-1.40 (m, 6 H, H_7 , H_8 , H_9), 1.34 (tt, J = 7.0, 1.0 Hz, 3 H, H_1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C3), 148.4 (C5), 147.5 (C11), 146.0 (C4), 111.2 (C12), 75.7 (C10), 62.4 (C2), 34.5 (C7/8/9), 32.0 (C6), 27.5 (C7/8/9), 25.3 (C7/8/9), 17.5 (C13), 14.1 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₃H₂₁BrNaO₃ 327.0566, found 327.0577; **IR** ν_{max} /cm⁻¹ (thin film) 3415 (OH), 2936 (C-C), 1715 (C=O), 1447, 1370, 1224.

Preparation of (Z)-ethyl 2-bromo-8-hydroxy-9-ethyldeca-2,9-dienoate **145b**

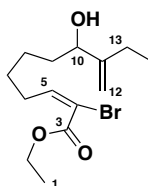


Following **General Procedure 2**, using HWE reagent **25** (1.3 g, 5.9 mmol), NaH (472 mg, 11.8 mmol), NBS (1.0 g, 5.9 mmol) and aldehyde **22** (1.0 g, 5.9 mmol, prepared from 2-bromo-1-butene) afforded the title compound **145b** (403 mg, 40% over two steps) as a 4:1 *Z:E* mixture of isomers.

E isomer data omitted for clarity

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.30 (t, *J* = 7.0 Hz, 1 H, *H*5), 5.03 (s, 1 H, *H*12), 4.86 (s, 1 H, *H*12'), 4.29 (q, *J* = 7.0 Hz, 2 H, *H*2), 4.12-4.09 (m, 1 H, *H*10), 2.37 (q, *J* = 7.5 Hz, 2 H, *H*6), 2.19-1.95 (m, 2 H, *H*13), 1.63-1.45 (m, 7 H, *H*7, *H*8, *H*9, OH), 1.34 (t, *J* = 7.0 Hz, 3 H, *H*1), 1.09 (t, *J* = 7.5 Hz, 3 H, *H*14); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C3), 153.5 (C11), 148.4 (C5), 116.5 (C4), 108.5 (C12), 75.4 (C10), 62.4 (C2), 35.1 (C7/8/9), 31.4 (C6), 27.5 (C7/8/9), 25.4 (C7/8/9), 23.9 (C13), 14.2 (C1), 12.2 (C14); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₄H₂₃BrNaO₃ 341.0723, found 341.0717; **IR** ν_{max} /cm⁻¹ (**thin film**) 3420 (OH), 2936 (C-C), 1715 (C=O), 1650, 1624, 1461.

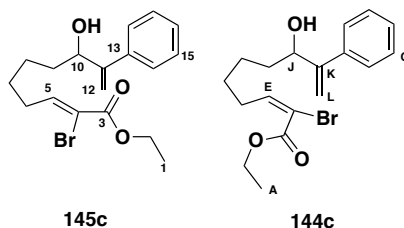
Preparation of (E)-ethyl 2-bromo-8-hydroxy-9-ethyldeca-2,9-dienoate **144b**



Following **General Procedure 2**, using SG reagent **19** (2.0 g, 5.9 mmol), NaH (472 mg, 11.8 mmol), NBS (1.0 g, 5.9 mmol) and aldehyde **22** (1.0 g, 5.9 mmol, prepared from 2-bromo-1-butene) afforded the title compound **144b** (410 mg, 41% over two steps).

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.59 (t, $J = 7.5$ Hz, 1 H, H_5), 4.94 (t, $J = 1.5$ Hz, 1 H, H_{12}), 4.78 (s, 1 H, $H_{12'}$), 4.20 (q, $J = 7.0$ Hz, 2 H, H_2), 4.04-4.00 (m, 1 H, H_{10}), 2.44 (q, $J = 7.5$ Hz, 2 H, H_6), 2.09-1.87 (m, 2 H, H_{13}), 1.52-1.35 (m, 7 H, H_7 , H_8 , H_9 , OH), 1.27 (t, $J = 7.0$ Hz, 3 H, H_1), 1.01 (t, $J = 7.5$ Hz, 3 H, H_{14}); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C3), 153.5 (C11), 148.4 (C5), 111.1 (C4), 108.5 (C12), 75.5 (C10), 62.9 (C2), 34.2 (C7/8/9), 31.4 (C6), 28.7 (C7/8/9), 25.2 (C7/8/9), 23.9 (C13), 14.1 (C1), 12.2 (C14); **HRMS (ESI⁺)** m/z calculated for $[\text{M}+\text{Na}]^+$ C₁₄H₂₃BrNaO₃ 341.0723, found 341.0718; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3409 (OH), 2936 (C-C), 1715 (C=O), 1461, 1369, 1224.

Preparation of (*Z* and *E*)-ethyl 2-bromo-8-hydroxy-9-phenyldeca-2,9-dienoate **144c and **145c****

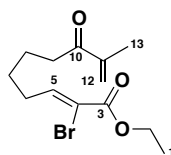


Following **General Procedure 2**, using HWE reagent **25** (1.1 g, 4.6 mmol), NaH (368 mg, 9.2 mmol), NBS (819 g, 4.6 mmol) and aldehyde **143c** (1.0 g, 4.6 mmol, prepared from α -bromostyrene) afforded the title compounds **144c** and **145c** (548 mg, 55% over two steps) as an inseparable 1:5 (*E*:*Z*) mixture of isomers.

N.B. The bromoacrylate geometric isomers were inseparable at this stage, but could be separated in sufficient quantities in the subsequent oxidation step.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.43-7.25 (m, 35 H, ArH, H5), 6.64 (t, J = 7.5 Hz, 1 H, HE), 5.81 (t, J = 1.5 Hz, 1 H, HL), 5.78 (t, J = 1.5 Hz, 1 H, HL'), 5.38 (s, 5 H, H12), 5.33 (s, 5 H, H12'), 4.66 (quin., J = 4.0 Hz, 5 H, H10), 4.29 (q, J = 7.0 Hz, 10 H, H2), 4.27 (q, J = 7.0 Hz, 2 H, HB), 4.20 (q, J = 7.0 Hz, 1 H, HJ), 2.48 (q, J = 7.5 Hz, 2 H, HF), 2.32 (q, J = 7.0 Hz, 10 H, H6), 1.80 (br. s, 6 H, OH), 1.68-1.39 (m, 36 H, H7, H8, H9, HG, HH, HI), 1.35 (t, J = 7.0 Hz, 15 H, H1), 1.31 (t, J = 7.0 Hz, 3 H, HA); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 166.8 (CC), 162.5 (C3), 152.0 (CE), 149.1 (C5), 148.4 (C11), 145.9 (CK), 128.4 (CAr), 127.7 (CAr), 126.9 (CAr), 121.4 (CL, C13), 116.5 (C4), 112.7 (C12), 111.3 (CD), 73.4 (C10, CJ), 62.4 (C2), 60.2 (CB), 35.7 (C7/8/9), 35.6 (CG/H/I), 32.0 (C6), 31.3 (CF), 28.5, 27.8, 27.4, 25.3, 25.2 (C7/8/9/G/H/I), 14.3 (C1), 14.1 (CA); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₃BrNaO₃ 389.0723, found 389.0721; **IR ν_{max} /cm⁻¹ (thin film)** 3436 (OH), 2936 (C-C), 1714 (C=O), 1625 (C=O), 1493, 1444, 1368.

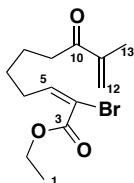
Preparation of (Z)-ethyl 2-bromo-9-methyl-8-oxodeca-2,9-dienoate **147a**



Following **General Procedure 3**, using DMP (1.68 g, 3.96 mmol) and alcohol **145a** (803 mg, 2.66 mmol) afforded the title compound **147a** (745 mg, 95%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.38 (t, $J = 7.0$ Hz, 1 H, *H*5), 5.96 (s, 1 H, *H*12), 5.78 (s, 1 H, *H*12'), 4.27 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.72 (t, $J = 7.0$ Hz, 2 H, *H*9), 2.37 (q, $J = 7.0$ Hz, 2 H, *H*6), 1.88 (s, 3 H, *H*13), 1.69 (quin., $J = 7.0$ Hz, 2 H, *H*8), 1.54 (quin., $J = 7.0$ Hz, 2 H, *H*7), 1.33 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 201.6 (C10), 162.4 (C3), 148.0 (C5), 144.5 (C11), 124.5 (C12), 116.7 (C4), 62.4 (C2), 36.9 (C9), 31.9 (C6), 27.2 (C7), 24.0 (C8), 17.6 (C13), 14.1 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₃H₁₉BrNaO₃ 325.0410, found 325.0409; **IR ν_{max} /cm⁻¹ (thin film)** 2931 (C-H), 1724 (C=O), 1676 (C=O), 1625, 1452, 1367.

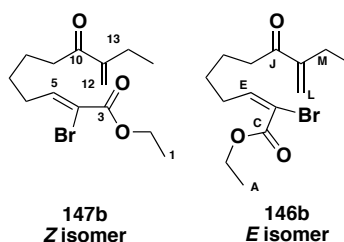
Preparation of (*E*)-ethyl 2-bromo-9-methyl-8-oxodeca-2,9-dienoate **146a**



Following **General Procedure 3**, using DMP (965 mg, 2.27 mmol) and alcohol **144a** (461 mg, 1.52 mmol) afforded the title compound **146a** (295 mg, 65%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.59 (t, $J = 7.5$ Hz, 1 H, *H*5), 5.90 (s, 1 H, *H*12), 5.71 (s, 1 H, *H*12'), 4.20 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.63 (t, $J = 7.5$ Hz, 2 H, *H*9), 2.45 (q, $J = 7.5$ Hz, 2 H, *H*6), 1.80 (s, 3 H, *H*13), 1.65-1.55 (m, 2 H, *H*8), 1.50-1.38 (m, 2 H, *H*7), 1.27 (t, $J = 7.0$ Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 201.7 (C10), 162.9 (C3), 148.1 (C5), 145.6 (C11), 124.5 (C12), 111.5 (C4), 62.4 (C2), 36.9 (C9), 31.9 (C6), 28.4 (C7), 24.0 (C8), 17.6 (C13), 14.1 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₃H₁₉BrNaO₃ 325.0410, found 325.0417; **IR ν_{max} /cm⁻¹ (thin film)** 2930 (C-H), 1715 (C=O), 1676 (C=O), 1629, 1452, 1369.

Preparation of (Z and E)-ethyl 2-bromo-9-ethyl-8-oxodeca-2,9-dienoate **146b and **147b****



Following **General Procedure 3**, using DMP (806 mg, 1.90 mmol) and alcohol **145b** (403 mg, 1.27 mmol), SiO₂ purification afforded the Z isomer **147b** (220 mg, 55%) as a colourless oil, and a 1:3 mixture of isomers **147b** and **146b** (36 mg, 9%).

Z isomer:

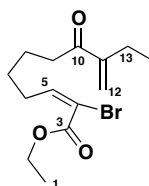
¹H NMR (400 MHz, CDCl₃) δ_H 7.30 (t, *J* = 7.5 Hz, 1 H, *H*5), 6.00 (s, 1 H, *H*12), 5.72 (s, 1 H, *H*12'), 4.26 (q, *J* = 7.5 Hz, 2 H, *H*2), 2.73 (t, *J* = 7.0 Hz, 2 H, *H*9), 2.39 (q, *J* = 7.5 Hz, 2 H, *H*6), 2.31 (q, *J* = 7.5 Hz, 2 H, *H*13), 1.74-1.64 (m, 2 H, *H*8), 1.59-1.47 (m, 2 H, *H*7), 1.36 (t, *J* = 7.5 Hz, 3 H, *H*1), 1.05 (t, *J* = 7.5 Hz, 3 H, *H*14); ¹³C NMR (126 MHz, CDCl₃) δ_C 201.7 (C10), 162.9 (C3), 150.4 (C11), 148.1 (C5), 145.6 (C4), 122.7 (C12), 62.4 (C2), 37.3 (C9), 31.9 (C6), 28.4 (C7), 23.9 (C8), 23.8 (C13), 14.1 (C1), 12.6 (C14); HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₁₄H₂₁BrNaO₃ 339.0566, found 339.0573; IR ν_{max}/cm⁻¹ (thin film) 2936 (C-H), 1724 (C=O), 1676 (C=O), 1625, 1459, 1368.

1:3 Z:E isomer, Z isomer omitted for clarity:

¹H NMR (400 MHz, CDCl₃) δ_H 6.59 (t, *J* = 7.5 Hz, 1 H, *H*E), 5.90 (s, 1 H, *H*L), 5.65 (s, 1 H, *H*L'), 4.20 (q, *J* = 7.0 Hz, 2 H, *H*B), 2.63 (t, *J* = 7.5 Hz, 2 H, *H*I), 2.45 (q, *J* = 7.5 Hz, 2 H, *H*F), 2.22 (q, *J* = 7.5 Hz, 2 H, *H*M), 1.62-1.54 (m, 2 H, *H*H), 1.46-1.39 (m, 2 H, *H*G), 1.27 (t, *J* = 7.0 Hz, 3 H, *H*A), 0.96 (t, *J* = 7.5 Hz, 3 H, *H*N); ¹³C NMR (126 MHz, CDCl₃) δ_C 201.7 (CJ), 162.9 (CC), 150.4 (CK), 148.1 (CE), 122.7 (CL), 111.5 (CD), 62.1 (CB), 37.4 (CI),

31.2 (CF), 28.4 (CG), 23.9 (CH), 23.8 (CM), 14.1 (CA), 12.6 (CN); **HRMS (ESI⁺)** *m/z*
calculated for [M+Na]⁺ C₁₄H₂₁BrNaO₃ 339.0566, found 339.0575; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**)
2935 (C-H), 1716 (C=O), 1676 (C=O), 1459, 1369, 1223.

Preparation of (E)-ethyl 2-bromo-9-ethyl-8-oxodeca-2,9-dienoate **146b**

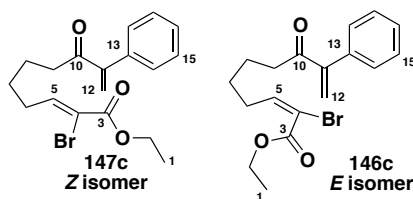


Following **General Procedure 3**, using DMP (820 mg, 1.93 mmol) and alcohol **144b** (410 mg, 1.29 mmol) afforded the title compound **146b** (275 mg, 67%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 6.59 (t, $J = 7.5$ Hz, 1 H, *H*5), 5.90 (s, 1 H, *H*12), 5.65 (s, 1 H, *H*12'), 4.20 (q, $J = 7.0$ Hz, 2 H, *H*2), 2.63 (t, $J = 7.5$ Hz, 2 H, *H*9), 2.45 (q, $J = 7.5$ Hz, 2 H, *H*6), 2.22 (q, $J = 7.5$ Hz, 2 H, *H*13), 1.62-1.54 (m, 2 H, *H*8), 1.46-1.39 (m, 2 H, *H*7), 1.27 (t, $J = 7.0$ Hz, 3 H, *H*1), 0.96 (t, $J = 7.5$ Hz, 3 H, *H*14); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 201.7 (C10), 162.9 (C3), 150.4 (C11), 148.1 (C5), 122.7 (C12), 111.5 (C4), 62.1 (C2), 37.4 (C9), 31.2 (C6), 28.4 (C7), 23.9 (C8), 23.8 (C13), 14.1 (C1), 12.6 (C14); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₄H₂₁BrNaO₃ 339.0566, found 339.0575; **IR ν_{max} /cm⁻¹ (thin film)** 2935 (C-H), 1716 (C=O), 1676 (C=O), 1459, 1369, 1223.

Preparation of (Z and E)-ethyl 2-bromo-8-oxo-9-phenyldeca-2,9-dienoate **146c** and

147c



Following **General Procedure 3**, using DMP (950 mg, 2.24 mmol) and alcohol **145c/144c** (548 mg, 1.50 mmol) afforded, separately upon chromatography, the *Z* isomer **147c** (350 mg, 64%) as a colourless oil, and the *E* isomer **146c** (80 mg, 15%) as a colourless oil.

Z isomer **147c**:

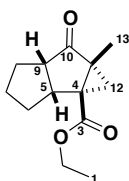
^1H NMR (400 MHz, CDCl_3) δ_{H} 7.41-7.36 (m, 3 H, ArH) 7.33-7.29 (m, 3 H, ArH, H5), 6.14 (s, 1 H, H12), 5.92 (s, 1 H, H12'), 4.30 (q, $J = 7.0$ Hz, 2 H, H2), 2.80 (t, $J = 7.0$ Hz, 2 H, H9), 2.39 (q, $J = 7.5$ Hz, 2 H, H6), 1.75 (quin, $J = 7.5$ Hz, 2 H, H8), 1.57 (quin., $J = 7.5$ Hz, 2 H, H7), 1.36 (t, $J = 7.0$ Hz, 3 H, H1); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 201.7 (C10), 162.5 (C3), 149.5 (C11), 145.5 (C5), 137.2 (C13), 128.3 (CAr), 128.2 (CAr), 128.1 (CAr), 124.4 (C12), 116.8 (C4), 62.4 (C2), 39.2 (C9), 31.9 (C6), 28.3 (C7), 23.9 (C8), 14.2 (C1); HRMS (ESI $^+$) m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{21}\text{BrNaO}_3$ 387.0566, found 387.0574; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2936 (C-H), 1721 (C=O), 1624 (C=O), 1494, 1445, 1367.

E isomer **146c**:

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.43-7.30 (m, 5 H, ArH), 6.68 (t, $J = 7.5$ Hz, 1 H, H5), 6.13 (s, 1 H, H12), 5.91 (s, 1 H, H12'), 4.29 (q, $J = 7.0$ Hz, 2 H, H2), 2.78 (t, $J = 7.5$ Hz, 2 H, H9), 2.55 (q, $J = 7.5$ Hz, 2 H, H6), 1.72 (quin., $J = 7.5$ Hz, 2 H, H8), 1.52 (quin., $J = 7.5$ Hz, 2 H, H7), 1.36 (t, $J = 7.0$ Hz, 3 H, H1); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 201.8 (C10), 162.9 (C3), 149.5 (C11), 148.4 (C5), 137.2 (C13), 128.3 (CAr), 128.2 (CAr), 128.1 (CAr), 124.3 (C12), 111.5 (C4), 62.1 (C2), 36.2 (C9), 31.9 (C6), 28.3 (C7), 23.9 (C8), 14.2 (C1); HRMS (ESI $^+$)

m/z calculated for $[M+Na]^+$ $C_{18}H_{21}BrNaO_3$ 387.0566, found 387.0572; **IR** $\nu_{\max}/\text{cm}^{-1}$ (**thin film**) 2937 (C-H), 1715 (C=O), 1612 (C=O), 1494, 1445, 1369.

Preparation of (1a*S,1b*R**,4a*S**,5a*R**)-ethyl 5a-methyl-5-oxooctahydro-1*H*-cyclopropa[*a*]-pentalene-1a-carboxylate **149a****



Following **General Procedure 4**, using cyclisation precursor **147a** (*Z* isomer) (50 mg, 0.17 mmol), toluene (4 mL), KOH (37 mg, 0.66 mmol), tetrabutylammonium bisulfate (6 mg, 0.02 mmol) at RT afforded compound **149a** (27 mg, 71%) as a colourless oil.

Following **General Procedure 4**, using cyclisation precursor **146a** (*E* isomer) (50 mg, 0.17 mmol), toluene (4 mL), KOH (37 mg, 0.66 mmol), tetrabutylammonium bisulfate (6 mg, 0.02 mmol) at RT afforded compound **149a** (30 mg, 79%) as a colourless oil.

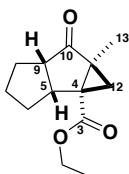
Following **General Procedure 5**, using cyclisation precursor **147a** (*Z* isomer) (50 mg, 0.17 mmol), THF (4 mL), NaH (7 mg, 0.17 mmol) afforded compound **149a** (28 mg, 74%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 4.26-4.15 (m, 2 H, *H*2), 3.62-3.55 (m, 1 H, *H*5), 2.82 (q, *J* = 9.5 Hz, 1 H, *H*9), 2.06-1.99 (m, 1 H, *H*6), 1.96-1.89 (m, 1 H, *H*8), 1.84-1.76 (m, 1 H, *H*7), 1.69 (dd, *J* = 5.0, 1.5 Hz, 1 H, *H*12), 1.61 (s, 1 H, *H*7'), 1.57-1.50 (m, 1 H, *H*6'), 1.47-1.41 (m, 1 H, *H*8'), 1.39 (d, 1 H, *J* = 5.0 Hz, 1 H, *H*12'), 1.36 (s, 3 H, *H*13), 1.29 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_C 214.9 (C10), 171.3 (C3), 61.0 (C2), 52.6 (C9), 45.9 (C11), 42.5 (C4), 39.9 (C5), 30.4 (C6), 30.2 (C8), 29.4 (C7), 23.5 (C12), 14.3

(C1), 11.7 (C13); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₃H₁₈NaO₃ 245.1148, found 245.1158; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2960 (C-H), 1719 (C=O), 1451, 1374, 1246.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (1aR*,1bR*,4aS*,5aS*)-ethyl 5a-methyl-5-oxooctahydro-1H-cyclopropa[*a*]-pentalene-1a-carboxylate **150a**

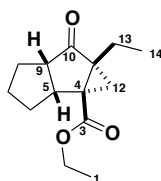


Following **General Procedure 5**, using cyclisation precursor **146a** (*E* isomer) (50 mg, 0.17 mmol), THF (4 mL), NaH (7 mg, 0.17 mmol) afforded compound **150a** (29 mg, 74%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 4.17-4.10 (m, 2 H, *H*₂), 2.76 (dd, *J* = 9.0, 7.5 Hz, 1 H, *H*₅), 2.49 (dd, *J* = 7.5, 6.5 Hz, 1 H, *H*₉), 2.19 (dtd, *J* = 13.0, 6.5, 3.5 Hz, 1 H, *H*₆), 1.78-1.74 (m, 2 H, *H*₈), 1.60-1.58 (m, 1 H, *H*₁₂), 1.55-1.45 (m, 2 H, *H*₇), 1.36 (d, *J* = 4.5 Hz, 1 H, *H*_{12'}), 1.37 (s, 3 H, *H*₁₃), 1.24 (t, *J* = 7.0 Hz, 3 H, *H*₁), 1.18-1.10 (m, 1 H, *H*_{6'}); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 215.4 (C10), 171.4 (C3), 60.8 (C2), 47.9 (C9), 43.8 (C5), 40.4 (C11), 40.6 (C4), 32.6 (C6), 26.7 (C12), 26.6 (C8), 26.5 (C7), 14.2 (C1), 11.2 (C13); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₃H₁₈NaO₃ 245.1148, found 245.1153; **IR** ν_{max} /cm⁻¹ (**thin film**) 2960 (C-H), 1724 (C=O), 1372, 1241, 1185.

N.B. Stereochemistry assigned by nOe analysis similar to compound **21**

Preparation of (1a*S,1b*R**,4a*S**,5a*R**)-ethyl 5a-ethyl-5-oxooctahydro-1*H*-cyclopropa[*a*]-pentalene-1a-carboxylate **149b****



Following **General Procedure 4**, using cyclisation precursor **147b** (*Z* isomer) (50 mg, 0.16 mmol), toluene (4 mL), KOH (35 mg, 0.63 mmol), tetrabutylammonium bisulfate (5 mg, 0.02 mmol) at RT afforded compound **149b** (25 mg, 63%) as a colourless oil.

Following **General Procedure 4**, using cyclisation precursor **146b** (*E* isomer) (50 mg, 0.16 mmol), toluene (4 mL), KOH (35 mg, 0.63 mmol), tetrabutylammonium bisulfate (5 mg, 0.02 mmol) at RT afforded compound **149b** (29 mg, 76%) as a colourless oil.

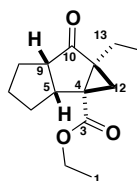
Following **General Procedure 5**, using cyclisation precursor **147b** (*Z* isomer) (50 mg, 0.16 mmol), THF (4 mL), NaH (6 mg, 0.16 mmol) afforded compound **149b** (30 mg, 77%) as a colourless oil.

¹H NMR (500 MHz, CHCl₃) δ_{H} 4.19-4.08 (m, 2 H, *H*2), 3.56-3.49 (m, 1 H, *H*5), 2.76-2.69 (m, 1 H, *H*9), 2.08 (sex, *J* = 7.5 Hz, 2 H, *H*13), 1.97-1.90 (m, 1 H, *H*6), 1.86-1.80 (m, 1 H, *H*8), 1.72-1.67 (m, 1 H, *H*7), 1.66 (dd, *J* = 5.0, 1.5 Hz, 1 H, *H*12), 1.58-1.50 (m, 1 H, *H*7'), 1.48-1.37 (m, 2 H, *H*6', *H*8'), 1.25 (d, *J* = 5.0 Hz, 1 H, *H*12'), 1.22 (t, *J* = 7.0 Hz, 3 H, *H*1), 0.77 (t, *J* = 7.5 Hz, 3 H, *H*14); **¹³C NMR (126 MHz, CHCl₃)** δ_{C} 214.8 (*C*10), 171.5 (*C*3), 61.1 (*C*2), 53.3 (*C*9), 52.10 (*C*11), 41.8 (*C*4), 39.9 (*C*5), 30.6 (*C*6), 30.2 (*C*8), 29.3 (*C*7), 22.9 (*C*12), 20.1 (*C*13), 14.3 (*C*1), 11.9 (*C*14); **HRMS (ESI⁺)** *m/z* calculated for [*M*+Na]⁺

$\text{C}_{14}\text{H}_{20}\text{NaO}_3$ 259.1305, found 259.1314; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2963 (C-H), 1720 (C=O), 1455, 1377, 1281.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (1aR*,1bR*,4aS*,5aS*)-ethyl 5a-ethyl-5-oxooctahydro-1H-cyclopropa[a]-pentalene-1a-carboxylate **150b**

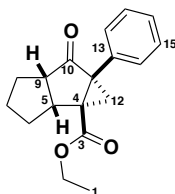


Following **General Procedure 5**, using cyclisation precursor **146b** (*E* isomer) (50 mg, 0.16 mmol), THF (4 mL), NaH (6 mg, 0.16 mmol) afforded compound **150b** (31 mg, 82%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 4.13 (qd, *J* = 7.0, 1.5 Hz, 2 H, *H*₂), 2.75 (dd, *J* = 8.5, 8.0 Hz, 1 H, *H*₅), 2.47-2.43 (m, 1 H, *H*₉), 2.25-2.19 (m, 1 H, *H*₆), 2.17 (q, *J* = 7.0 Hz, 1 H, *H*₁₃), 1.77-1.73 (m, 2 H, *H*₈), 1.64 (dd, *J* = 4.5, 1.5 Hz, 1 H, *H*₁₂), 1.56 (q, *J* = 7.0 Hz, 1 H, *H*_{13'}), 1.55-1.45 (m, 2 H, *H*₇), 1.31 (d, *J* = 4.5 Hz, 1 H, *H*_{12'}), 1.22 (t, *J* = 7.0 Hz, 3 H, *H*₁), 1.20-1.15 (m, 1 H, *H*_{6'}), 0.77 (t, *J* = 7.0 Hz, 3 H, *H*₁₄); **¹³C NMR (126 MHz, CDCl₃)** δ_C 214.9 (C₁₀), 171.5 (C₃), 60.8 (C₂), 48.2 (C₉), 46.7 (C₁₁), 43.5 (C₅), 40.1 (C₄), 32.6 (C₆), 28.5 (C₁₂), 26.7 (C₈), 26.5 (C₇), 18.8 (C₁₃), 14.2 (C₁), 11.9 (C₁₄); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₄H₂₀NaO₃ 259.1305, found 259.1313; **IR** ν_{max}/cm⁻¹ (**thin film**) 2962 (C-H), 1721 (C=O), 1449, 1374, 1286.

N.B. Stereochemistry assigned by nOe analysis similar to compound **21**

Preparation of (1a*S,1b*R**,4a*S**,5a*S**)-ethyl 5-oxo-5a-phenyloctahydro-1*H*-cyclopropa[*a*]-pentalene-1a-carboxylate **149c****



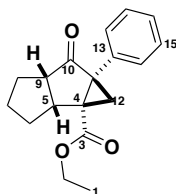
Following **General Procedure 4**, using cyclisation precursor, **147c** (*Z* isomer) (50 mg, 0.14 mmol), toluene (4 mL), KOH (31 mg, 0.55 mmol), tetrabutylammonium bisulfate (5 mg, 0.02 mmol) at RT afforded compound **149c** (32 mg, 80%) as a colourless oil.

Following **General Procedure 5**, using cyclisation precursor **147c** (*Z* isomer) (50 mg, 0.11 mmol), THF (4 mL), NaH (5 mg, 0.66 mmol) afforded compound **149c** (26 mg, 65%) as a colourless oil.

¹H NMR (500 MHz, PhMe) δ_{H} 7.15-7.03 (m, 5 H, ArH), 3.81-3.70 (m, 2 H, H5, H2), 3.63-3.57 (m, 1 H, H2'), 2.76-2.70 (m, 1 H, H9), 2.24 (dd, $J = 5.5, 1.5$ Hz, 1 H, H12), 1.84-1.76 (m, 1 H, H6), 1.68-1.61 (m, 1 H, H8), 1.48-1.29 (m, 4 H, H6', H8', H7), 1.26 (d, $J = 5.5$ Hz, 1 H, H12'), 0.56 (t, $J = 7.0$ Hz, 3 H, H1); **¹³C NMR (126 MHz, PhMe)** δ_{C} 210.3 (C10), 169.2 (C3), 137.1 (CAr), 134.5 (C13), 128.3 (CAr), 128.3 (CAr), 60.1 (C2), 54.2 (C11), 53.5 (C9), 44.2 (C4), 39.7 (C5), 30.5 (C6), 30.0 (C8), 29.0 (C7), 19.8 (C12), 13.3 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₀NaO₃ 307.1305, found 307.1311; **IR ν_{max} /cm⁻¹ (thin film)** 2958 (C-H), 1719 (C=O), 1447, 1375, 1256.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (1aR*,1bR*,4aS*,5aR*)-ethyl 5-oxo-5a-phenyloctahydro-1H-cyclopropa[a]-pentalene-1a-carboxylate **150c**



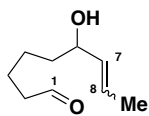
Following **General Procedure 4**, using cyclisation precursor **146c** (*E* isomer) (50 mg, 0.14 mmol), toluene (4 mL), KOH (31 mg, 0.55 mmol), tetrabutylammonium bisulfate (5 mg, 0.02 mmol) at RT afforded an inseparable 1:1 mixture of compound **149c** and compound **150c** (29 mg, 73%) as a colourless oil.

Following **General Procedure 5**, using cyclisation precursor **146c** (*E* isomer) (50 mg, 0.11 mmol), THF (4 mL), NaH (5 mg, 0.66 mmol) afforded compound **150c** (33 mg, 83%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.26-7.16 (m, 3 H, ArH), 7.08-7.04 (m, 2 H, ArH), 3.85-3.75 (m, 2 H, H₂), 2.89 (dd, *J* = 17.5, 7.5 Hz, 1 H, H₅), 2.68 (dd, *J* = 13.5, 7.5 Hz, 1 H, H₉), 2.42-2.37 (m, 1 H, H₆), 2.36 (dd, *J* = 5.0, 1.5 Hz, 1 H, H₁₂), 1.80 (dt, *J* = 8.5, 6.5 Hz, 2 H, H₈), 1.77-1.71 (m, 1 H, H₇), 1.70 (d, *J* = 5.0 Hz, 1 H, H_{12'}), 1.57-1.48 (m, 1 H, H_{7'}), 1.48-1.38 (m, 1 H, H_{6'}), 0.75 (m, *J* = 7.5 Hz, 3 H, H₁); **¹³C NMR (126 MHz, CDCl₃)** δ_C 213.5 (C₁₀), 169.9 (C₃), 133.4 (C₁₃), 130.4 (CAr), 130.0 (CAr), 128.3 (CAr), 60.5 (C₂), 49.9 (C₄), 48.9 (C₉), 43.7 (C₅), 43.1 (C₁₁), 32.8 (C₆), 26.8 (C₈), 26.7 (C₇), 25.7 (C₁₂), 13.6 (C₁); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₈H₂₀NaO₃ 307.1305, found 307.1313; **IR** ν_{max}/cm⁻¹ (thin film) 2958 (C-H), 1717 (C=O), 1500, 1447, 1371.

N.B. Stereochemistry assigned by nOe analysis similar to compound **21** and **77**

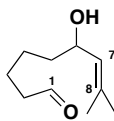
Preparation of 6-hydroxynon-7-enal **151**



Following **General Procedure 1**, using aldehyde **22** (500 mg, 3.14 mmol) and 1-propenyl magnesium bromide (0.5 M in THF, 7.5 mL, 3.8 mmol) afforded the title compound **151** (490 mg, quant.).

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.77 (s, 1 H, *H*1), 5.59-5.62 (m, 1 H, *H*7/8), 5.62-5.54 (m, 1 H, *H*7/8), 5.54-5.45 (m, 1 H, *H*7/8), 5.41-5.37 (m, 1 H, *H*7/8).

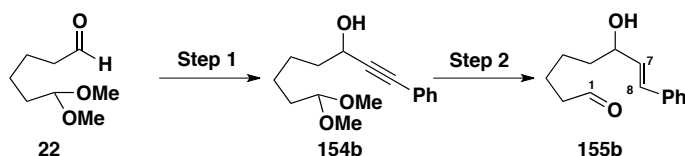
Preparation of 6-hydroxy-8-methylnon-7-enal **247**



Following **General Procedure 1**, using aldehyde **22** (1.5 g, 9.4 mmol) and 2-methyl-1-propenyl magnesium bromide (0.5 M in THF, 22.6 mL, 11.3 mmol) afforded the title compound **247** (1.3 g, 81%)

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.77 (t, $J = 1.5$ Hz, 1 H, H_1), 5.61 (t, $J = 7.5$ Hz, 1 H, H_7), 4.87-4.85 (m, 1 H, H_6), 1.30 (s, 6 H, H_9).

Preparation of (*E*)-6-hydroxy-8-phenyloct-7-enal **155b**



Step 1:

Phenyl acetylene (1.50 mL, 13.75 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M, 9 mL, 14.4 mmol) was added dropwise and the resulting solution stirred for 30 min. Aldehyde **22** (2.0 g, 12.5 mmol) was dissolved in THF (20 mL) and was added dropwise to the cooled solution. The reaction mixture was then let warm to RT, and then stirred for 1 hr at this temperature. The reaction mixture was quenched with H₂O and then the aqueous layer extracted with Et₂O (x 3). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford alkyne **154b** (3.3 g, quant.).

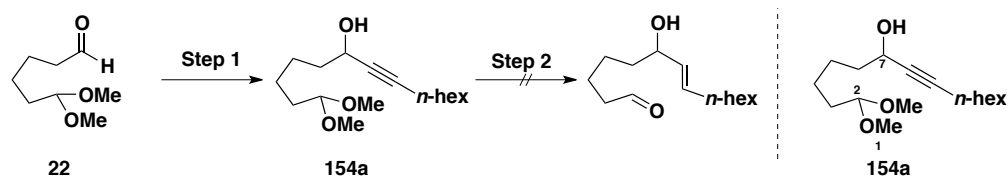
Step 2:

Alkyne **154b** (3.3 g, 12.6 mmol) was dissolved in THF (40 mL) and the resulting solution cooled to 0 °C. LiAlH₄ (6.90 mL, 13.75 mmol) was added dropwise and the reaction mixture stirred for 15 min. The reaction mixture was quenched with Rochelle's salt and the resulting mixture was stirred for 1 hr. Et₂O was added, the layers separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in acetone (50 mL), and HCl (1.0 M aq., 10 mL) and H₂O (10 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried

over MgSO_4 , filtered and the filtrate concentrated under reduced pressure to afford the title compound **155b** (2.4 g, 88%).

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.77 (t, $J = 1.5$ Hz, 1 H, $H1$), 6.58 (d, $J = 16.0$ Hz, 1 H, $H8$), 6.21 (dd, $J = 16.0, 7.0$ Hz, 1 H, $H7$), 4.29 (q, $J = 7.0$ Hz, 1 H, $H6$).

Preparation of 1,1-dimethoxytetradec-7-yn-6-ol **154a**



Step 1:

1-Octyne (2.0 mL, 13.75 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M, 9 mL, 14.4 mmol) was added dropwise and the resulting solution stirred for 30 min. Aldehyde **22** (2.0 g, 12.5 mmol) was dissolved in THF (20 mL) and was added dropwise to the cooled solution. The reaction mixture was then let warm to RT, and then stirred for 1 hr at this temperature. The reaction mixture was quenched with H₂O and then the aqueous layer extracted with Et₂O (x 3). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford alkyne **154a** (3.4 g, quant.).

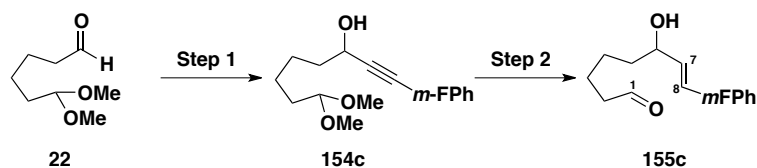
Step 2:

Alkyne **154a** (3.4 g, 12.5 mmol) was dissolved in THF (40 mL) and the resulting solution cooled to 0 °C. LiAlH₄ (6.9 mL, 13.75 mmol) was added dropwise and the reaction mixture stirred for 15 min. There was no evidence of product by TLC, so the reaction mixture was let warm to RT, and stirred at this temperature overnight. After this time, there was still no product by TLC, so the reaction mixture was heated to reflux overnight. The reaction mixture was let cool to RT, quenched with Rochelle's salt and the resulting mixture was stirred for 1 hr. Et₂O was added, the layers separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in acetone (50 mL), and HCl (1.0 M aq., 10 mL) and H₂O (10 mL) were added, and the resulting

solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the starting material **154a** (3.4 g, quant.).

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 4.39-4.34 (m, 1 H, *H*2/7), 3.78-3.74 (m, 1 H, *H*2/7), 3.33 (s, 6 H, *H*1).

Preparation of (*E*)-8-(3-fluorophenyl)-6-hydroxyoct-7-enal **155c**



Step 1:

m-Fluoro-phenyl acetylene (1.6 mL, 13.75 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M, 9 mL, 14.4 mmol) was added dropwise and the resulting solution stirred for 30 min. Aldehyde **22** (2.0 g, 12.5 mmol) was dissolved in THF (20 mL) and was added dropwise to the cooled solution. The reaction mixture was then let warm to RT, and then stirred for 1 hr at this temperature. The reaction mixture was quenched with H₂O and then the aqueous layer extracted with Et₂O (x 3). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford alkyne **154c** (3.5 g, quant.).

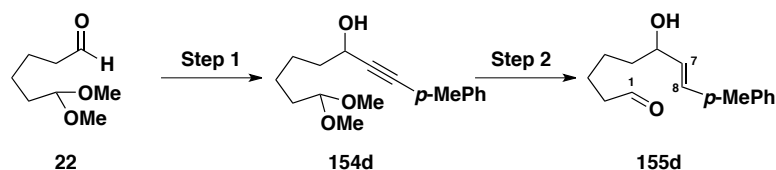
Step 2:

Alkyne **154c** (3.5 g, 12.5 mmol) was dissolved in THF (40 mL) and the resulting solution cooled to 0 °C. LiAlH₄ (6.9 mL, 13.75 mmol) was added dropwise and the reaction mixture stirred for 15 min. The reaction mixture was quenched with Rochelle's salt and the resulting mixture was stirred for 1 hr. Et₂O was added, the layers separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in acetone (50 mL), and HCl (1.0 M aq., 10 mL) and H₂O (10 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried

over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **155c** (2.9 g, quant.).

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 9.78 (s, 1 H, *H*1), 6.55 (d, *J* = 16.0 Hz, 1 H, *H*8), 6.22 (dd, *J* = 16.0, 6.5 Hz, 1 H, *H*7), 4.30 (q, *J* = 6.5 Hz, 1 H, *H*6).

Preparation of 6-hydroxy-8-(*p*-tolyl)oct-7-ynal **155d**



Step 1:

p-Me-acetylene (1.7 mL, 13.75 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M, 9 mL, 14.4 mmol) was added dropwise and the resulting solution stirred for 30 min. Aldehyde **22** (2.0 g, 12.5 mmol) was dissolved in THF (20 mL) and was added dropwise to the cooled solution. The reaction mixture was then let warm to RT, and then stirred for 1 hr at this temperature. The reaction mixture was quenched with H₂O and then the aqueous layer extracted with Et₂O (× 3). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford alkyne **154d** (3.4 g, quant.).

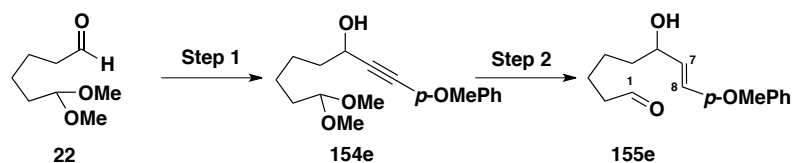
Step 2:

Alkyne **154d** (3.7 g, 12.5 mmol) was dissolved in THF (40 mL) and the resulting solution cooled to 0 °C. LiAlH₄ (6.9 mL, 13.75 mmol) was added dropwise and the reaction mixture stirred for 15 min. The reaction mixture was quenched with Rochelle's salt and the resulting mixture was stirred for 1 hr. Et₂O was added, the layers separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in acetone (50 mL), and HCl (1.0 M aq., 10 mL) and H₂O (10 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (× 3). The combined extracts were washed with H₂O and dried

over MgSO_4 , filtered and the filtrate concentrated under reduced pressure to afford the title compound **155d** (2.8 g, quant.).

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.77 (t, $J = 1.5$ Hz, 1 H, $H1$), 6.54 (d, $J = 16.0$ Hz, 1 H, $H8$), 6.16 (dd, $J = 16.0, 7.0$ Hz, 1 H, $H7$), 4.28 (q, $J = 7.0$ Hz, 1 H, $H6$), 2.31 (s, 3 H, Me).

Preparation of 6-hydroxy-8-(4-methoxyphenyl)oct-7-ynal 155e



Step 1:

p-Methoxy phenyl acetylene (1.8 mL, 13.75 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M, 9 mL, 14.4 mmol) was added dropwise and the resulting solution stirred for 30 min. Aldehyde **22** (2.0 g, 12.5 mmol) was dissolved in THF (20 mL) and was added dropwise to the cooled solution. The reaction mixture was then let warm to RT, and then stirred for 1 hr at this temperature. The reaction mixture was quenched with H₂O and then the aqueous layer extracted with Et₂O (x 3). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford alkyne **154e** (3.7 g, quant.).

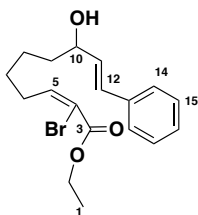
Step 2:

Alkyne **154e** (3.7 g, 12.5 mmol) was dissolved in THF (40 mL) and the resulting solution cooled to 0 °C. LiAlH₄ (6.9 mL, 13.75 mmol) was added dropwise and the reaction mixture stirred for 15 min. The reaction mixture was quenched with Rochelle's salt and the resulting mixture was stirred for 1 hr. Et₂O was added, the layers separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in acetone (50 mL), and HCl (1.0 M aq., 10 mL) and H₂O (10 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried

over MgSO_4 , filtered and the filtrate concentrated under reduced pressure to afford the title compound **155e** (3.7 g, quant.).

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.77 (t, $J = 1.5$ Hz, 1 H, $H1$), 6.51 (d, $J = 16.0$ Hz, 1 H, $H8$), 6.07 (dd, $J = 16.0, 7.0$ Hz, 1 H, $H7$), 4.26 (q, $J = 7.0$ Hz, 1 H, $H6$), 3.82 (s, 3 H, OMe).

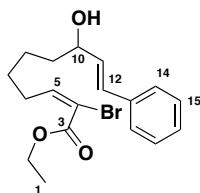
Preparation of (2Z,9E)-ethyl 2-bromo-8-hydroxy-10-phenyldeca-2,9-dienoate **157b**



Following **General Procedure 2**, using HWE reagent **25** (360 mg, 1.61 mmol), NaH (126 mg, 3.11 mmol), NBS (285 mg, 1.60 mmol) and aldehyde **155b** (350 mg, 1.57 mmol) afforded the title compound **157b** (400 mg, 68% over two steps) as a 3:1 (Z:E) mixture of isomers. Minor isomer not included for clarity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.41 (d, $J = 7.5$ Hz, 1 H, ArH), 7.36-7.30 (m, 3 H, H5, ArH), 7.30-7.25 (m, 2 H, ArH), 6.59 (d, $J = 16.0$ Hz, 1 H, H12), 6.24 (ddd, $J = 16.0, 7.0, 3.0$ Hz, 1 H, H11), 4.31-4.25 (m, 3 H, H2, H10), 2.54 (q, $J = 7.5$ Hz, 2 H, H6), 1.86 (br. s, 1 H, OH), 1.72-1.65 (m, 2 H, H9), 1.60-1.45 (m, 4 H, H7, H8), 1.35 (t, $J = 7.0$ Hz, 3 H, H1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C3), 148.3 (C5), 132.4 (C13), 130.4 (C11), 128.6 (C12), 128.4 (CAr), 127.7 (CAr), 126.5 (CAr), 116.6 (C4), 72.9 (C10), 62.4 (C2), 37.0 (C9), 32.0 (C6), 27.5 (C8), 25.2 (C7), 14.2 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₃BrNaO₃ 389.0723, found 389.0717; **IR ν_{max} /cm⁻¹ (thin film)** 3480 (OH), 2933 (C-H), 1712 (C=O), 1623, 1493, 1448, 1368.

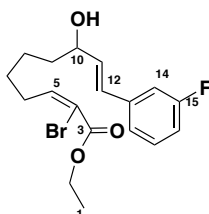
Preparation of (2E,9E)-ethyl 2-bromo-8-hydroxy-10-phenyldeca-2,9-dienoate **156b**



Following **General Procedure 2**, using SG reagent **19** (535 mg, 1.61 mmol), NaH (126 mg, 3.11 mmol), NBS (285 mg, 1.60 mmol) and aldehyde **155c** (350 mg, 1.57 mmol) afforded the title compound **156b** (300 mg, 51% over two steps) as a single isomer.

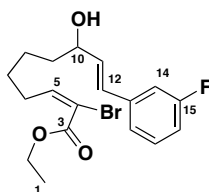
¹H NMR (400 MHz, CDCl₃) δ_{H} 7.40-7.38 (m, 2 H, ArH), 7.33 (t, $J = 8.0$ Hz, 2 H, ArH), 7.26-7.20 (m, 1 H, ArH), 6.67 (t, $J = 7.5$ Hz, 1 H, H5), 6.58 (d, $J = 16.0$ Hz, 1 H, H11), 6.22 (dd, $J = 16.0, 7.0$ Hz, 1 H, H12), 4.30-4.24 (m, 3 H, H2, H10), 2.52 (q, $J = 7.0$ Hz, 2 H, H6), 1.68-1.60 (m, 2 H, H9), 1.55-1.45 (m, 5 H, H7, H8, OH), 1.33 (t, $J = 7.0$ Hz, 3 H, H1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C3), 148.3 (C5), 136.6 (C13), 132.3 (C12), 130.5 (C11), 128.6 (CAr), 127.7 (CAr), 126.5 (CAr), 111.3 (C4), 72.9 (C10), 62.1 (C2), 37.0 (C9), 31.3 (C6), 28.7 (C7/8), 25.0 (C7/8), 14.1 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₃BrNaO₃ 389.0723, found 389.0717; **IR ν_{max} /cm⁻¹ (thin film)** 3470 (OH), 2934 (C-H), 1713 (C=O), 1494, 1448, 1369, 1342, 1224.

Preparation of (2Z,9E)-ethyl 2-bromo-10-(3-fluorophenyl)-8-hydroxydeca-2,9-dienoate **157c**



Following **General Procedure 2**, using HWE reagent **25** (631 mg, 2.82 mmol), NaH (224 mg, 5.64 mmol), NBS (498 mg, 2.80 mmol) and aldehyde **155c** (400 mg, 2.82 mmol) afforded the title compound **157c** (410 mg, 38% over three steps), which was inseparable from an unknown impurity, so was used crude in the next reaction.

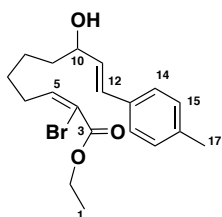
Preparation of (2*E*,9*E*)-ethyl 2-bromo-10-(3-fluorophenyl)-8-hydroxydeca-2,9-dienoate **156c**



Following **General Procedure 2**, using SG reagent **19** (700 mg, 2.10 mmol), NaH (170 mg, 2.10 mmol), NBS (378 mg, 2.10 mmol) and aldehyde **155c** (500 mg, 2.12 mmol) afforded the title compound **156c** (500 mg, 62% over three steps) as a single isomer.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.33-7.27 (m, 1 H, ArH), 7.16 (d, $J = 8.0$ Hz, 1 H, ArH), 7.10 (dt, $J = 10.0, 2.0$ Hz, 1 H, ArH), 7.00-6.92 (m, 1 H, ArH), 6.72-6.66 (m, 1 H, H₅), 6.57 (d, $J = 16.0$ Hz, 1 H, H₁₂), 6.25 (dd, $J = 16.0, 6.5$ Hz, 1 H, H₁₁), 4.33-4.25 (m, 3 H, H₁₀, H₂), 2.57-2.51 (m, 2 H, H₆), 1.72-1.63 (m, 2 H, H₉), 1.56-1.50 (m, 5 H, H₇, H₈, OH), 1.35 (t, $J = 7.0$ Hz, 1 H, H₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.5 (d, $J = 245.5$ Hz, C₁₅), 162.9 (C₃), 148.3 (C₅), 139.0 (C₁₃), 133.7 (C₁₁), 130.0 (CAr), 129.8 (C₁₂), 124.1 (CAr), 114.5 (d, $J = 21.5$ Hz, CAr), 112.9 (d, $J = 21.5$ Hz, CAr), 111.3 (C₄), 72.6 (C₁₀), 62.4 (C₂), 38.7 (C₉), 31.8 (C₆), 28.7 (C₈), 25.2 (C₇), 14.1 (C₁); **¹⁹F NMR (377 MHz, CDCl₃)** δ_{F} -113.5; **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₂BrFNaO₃ 407.0629, found 407.0622; **IR ν_{max} /cm⁻¹ (thin film)** 3470 (OH), 2934 (C-H), 1714 (C=O), 1611, 1584, 1488, 1446, 1369.

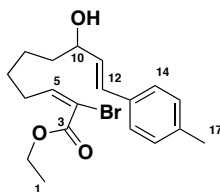
Preparation of (2Z,9E)-ethyl 2-bromo-8-hydroxy-10-(*p*-tolyl)deca-2,9-dienoate **157d**



Following **General Procedure 2**, using HWE reagent **25** (772 mg, 3.45 mmol), NaH (272 mg, 6.89 mmol), NBS (605 mg, 3.45 mmol) and aldehyde **155d** (800 mg, 3.45 mmol) afforded the title compound **157d** (760 mg, 58% over three steps) as a 2:1 mixture of brominated and non-brominated isomers. Minor isomer not included for clarity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.30-7.28 (m, 3 H, *H*₅, Ar*H*), 7.16-7.12 (m, 2 H, Ar*H*), 6.56 (d, *J* = 16.0 Hz, 1 H, *H*₁₂), 6.22-6.14 (m, 1 H, *H*₁₁), 4.32-4.25 (m, 1 H, *H*₁₀), 4.20 (q, *J* = 7.0 Hz, 2 H, *H*₂), 2.41-2.34 (m, 5 H, *H*₆, *H*₁₇), 1.76-1.60 (m, 3 H, *H*₉, OH), 1.55-1.40 (m, 4 H, *H*₇, *H*₈), 1.35 (t, *J* = 7.0 Hz, 3 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 166.7 (C3), 145.9 (C5), 137.6 (C13), 133.8 (C16), 131.3 (C11), 130.4 (C12), 129.3 (CAr), 129.1 (CAr), 116.6 (C4), 73.0 (C10), 60.2 (C2), 37.0 (C9), 31.6 (C6), 28.7 (C7/8), 25.2 (C7/8), 21.2 (C17), 14.1 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₉H₂₅BrNaO₃ 403.0879, found 403.0873; **IR** ν_{max} /cm⁻¹ (thin film) 3480 (OH), 2932 (C-H), 2859 (C-H), 1715 (C=O), 1652, 1513, 1446, 1367, 1258, 1040.

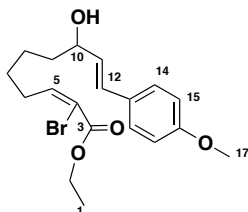
Preparation of (2E,9E)-ethyl 2-bromo-8-hydroxy-10-(p-tolyl)deca-2,9-dienoate **156d**



Following **General Procedure 2**, using SG reagent **19** (564 mg, 1.70 mmol), NaH (138 mg, 3.40 mmol), NBS (302 mg, 1.70 mmol) and aldehyde **155d** (400 mg, 1.70 mmol) afforded the title compound **156d** (390 mg, 60% over three steps) as a single isomer.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.31 (d, J = 8.0 Hz, 2 H, ArH), 7.16 (d, J = 8.0 Hz, 2 H, ArH), 6.69 (t, J = 7.5 Hz, 1 H, H₅), 6.56 (d, J = 16.0 Hz, 1 H, H₁₂), 6.18 (dd, J = 16.0, 7.0 Hz, 1 H, H₁₁), 4.31-4.26 (m, 3 H, H₁₀, H₂), 2.53 (q, J = 7.5 Hz, 2 H, H₆), 2.37 (s, 3 H, H₁₇), 1.70-1.63 (m, 3 H, H₉, OH), 1.56-1.46 (m, 4 H, H₇, H₈), 1.35 (t, J = 7.0 Hz, 3 H, H₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C₃), 148.5 (C₅), 137.6 (C₁₆), 133.8 (C₁₃), 131.3 (C₁₁), 130.4 (C₁₂), 129.3 (CAr), 126.4 (CAr), 111.3 (C₄), 73.0 (C₁₀), 62.1 (C₂), 36.9 (C₉), 31.4 (C₆), 28.8 (C_{7/8}), 25.0 (C_{7/8}), 21.2 (C₁₇), 14.1 (C₁); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₉H₂₅BrNaO₃ 403.0879, found 403.0876; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 3480 (OH), 2933 (C-H), 2859 (C-H), 1716 (C=O), 1513, 1369, 1224, 1027.

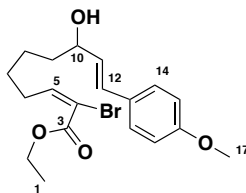
Preparation of (2Z,9E)-ethyl 2-bromo-8-hydroxy-10-(4-methoxyphenyl)deca-2,9-dienoate **157e**



Following **General Procedure 2**, using HWE reagent **25** (500 mg, 2.4 mmol), NaH (194 mg, 4.8 mmol), NBS (428 mg, 2.4 mmol) and aldehyde **155e** (600 mg, 2.4 mmol) afforded the title compound **157e** (350 mg, 37% over three steps).

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.36-7.28 (m, 3 H, *H*5, Ar*H*), 6.88 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.54 (d, *J* = 16.0 Hz, 1 H, *H*12), 6.10 (dd, *J* = 16.0, 7.0 Hz, 1 H, *H*11), 4.31-4.26 (m, 3 H, *H*2, *H*10), 3.84 (s, 3 H, *H*17), 2.39 (q, *J* = 7.0 Hz, 2 H, *H*6), 1.74-1.45 (m, 7 H, *H*7, *H*8, *H*9, OH), 1.35 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 162.5 (C3), 159.3 (C16), 145.9 (C5), 130.1 (C11, C12), 129.4 (C13), 127.6 (CAr), 116.6 (C4), 114.0 (CAr), 73.1 (C10), 62.4 (C2), 55.3 (C17), 37.0 (C9), 31.4 (C6), 28.7 (C7/8), 25.3 (C7/8), 14.2 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₉H₂₅BrNaO₄ 419.0828, found 419.0821; **IR** ν_{max} /cm⁻¹ (**thin film**) 3490 (OH), 2934 (C-H), 1714 (C=O), 1607, 1151, 1463, 1367, 1249, 1175, 1034.

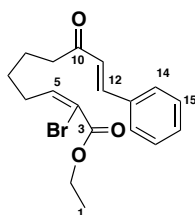
Preparation of (2*E*,9*E*)-ethyl 2-bromo-8-hydroxy-10-(4-methoxyphenyl)deca-2,9-dienoate **156e**



Following **General Procedure 2**, using SG reagent **19** (670 mg, 2.02 mmol), NaH (161 mg, 4.04 mmol), NBS (356 mg, 2.02 mmol) and aldehyde **155e** (500 mg, 2.02 mmol) afforded the title compound **156e** (375 mg, 47% over three steps).

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.34 (d, J = 8.5 Hz, 2 H, ArH), 6.88 (d, J = 8.5 Hz, 2 H, ArH), 6.69 (t, J = 8.0 Hz, 1 H, H₅), 6.54 (d, J = 16.0 Hz, 1 H, H₁₂), 6.06 (dd, J = 16.0, 7.0 Hz, 1 H, H₁₁), 4.31-4.24 (m, 3 H, H₁₀, H₂), 3.84 (s, 3 H, H₁₇), 2.54 (q, J = 7.5 Hz, 2 H, H₆), 1.70-1.60 (m, 2 H, H₉), 1.55-1.45 (m, 5 H, H₇, H₈, OH), 1.35 (t, J = 7.0 Hz, 3 H, H₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 163.0 (C₃), 169.3 (C₁₆), 148.4 (C₅), 130.1 (C₁₁, C₁₂), 129.4 (C₁₃), 129.3 (CAr), 113.9 (CAr), 111.3 (C₄), 73.1 (C₁₀), 62.1 (C₂), 55.3 (C₁₇), 37.2 (C₉), 32.1 (C₆), 28.7 (C_{7/8}), 25.1 (C_{7/8}), 14.1 (C₁); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₉H₂₅BrNaO₄ 419.0828, found 419.0823; **IR** ν_{max} /cm⁻¹ (thin film) 3490 (OH), 2933, 1713 (C=O), 1608, 1511, 1463, 1369, 1300, 1246, 1174.

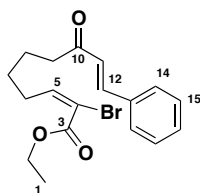
Preparation of (2Z,9E)-ethyl 2-bromo-8-oxo-10-phenyldeca-2,9-dienoate **159b**



Following **General Procedure 3**, using DMP (695 mg, 1.64 mmol) and alcohol **157b** (400 mg, 1.10 mmol) afforded the title compound **159b** (350 mg, 88%) as a 5:1 mixture of compound **159b** and the non-brominated substrate. Minor product not included for clarity.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.61-7.57 (m, 3 H, *H*₁₂, Ar*H*), 7.44-7.42 (m, 2 H, Ar*H*), 7.32 (m, 2 H, *H*₅, Ar*H*), 6.77 (d, *J* = 16.0 Hz, 1 H, *H*₁₁), 4.30 (q, *J* = 7.0 Hz, 2 H, *H*₂), 2.74 (t, *J* = 7.5 Hz, 2 H, *H*₉), 2.42 (q, *J* = 7.5 Hz, 2 H, *H*₆), 1.82-1.75 (m, 2 H, *H*₈), 1.65-1.59 (m, 2 H, *H*₇), 1.35 (t, *J* = 7.0 Hz, 3 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.0 (C₁₀), 162.5 (C₃), 145.6 (C₅), 142.6 (C₁₂), 134.5 (C₁₃), 130.5 (CAr), 128.9 (CAr), 128.3 (CAr), 126.1 (C₁₁), 116.8 (C₄), 62.4 (C₂), 40.5 (C₉), 32.0 (C₆), 28.3 (C₇), 23.8 (C₈), 14.3 (C₁); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₈H₂₁NaO₃Br 387.0566, found 387.0560; **IR** ν_{max} /cm⁻¹ (**thin film**) 2936 (C-H), 1718 (C=O), 1690 (C=O), 1662, 1611, 1576, 1495, 1449.

Preparation of (2*E*,9*E*)-ethyl 2-bromo-8-oxo-10-phenyldeca-2,9-dienoate **158b**

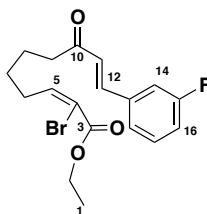


Following **General Procedure 3**, using DMP (524 mg, 1.24 mmol) and alcohol **156b** (300 mg, 0.82 mmol) afforded the title compound **158b** (250 mg, 83%) as a single isomer.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.60-7.55 (m, 3 H, *H*₁₂, *ArH*), 7.43-7.40 (m, 3 H, *ArH*), 6.77 (d, *J* = 16.0 Hz, 1 H, *H*₁₁), 6.70 (t, *J* = 7.5 Hz, 1 H, *H*₅), 4.29 (q, *J* = 7.0 Hz, 2 H, *H*₂), 2.72 (t, *J* = 7.0 Hz, 2 H, *H*₉), 2.57 (q, *J* = 7.5 Hz, 2 H, *H*₆), 1.79-1.72 (m, 2 H, *H*₈), 1.60-1.52 (m, 2 H, *H*₇), 1.36 (t, *J* = 7.0 Hz, 3 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.0 (*C*₁₀), 162.9 (*C*₃), 148.0 (*C*₅), 142.6 (*C*₁₂), 134.5 (*C*₁₃), 130.5 (*C*_{Ar}), 129.0 (*C*_{Ar}), 128.3 (*C*_{Ar}), 126.2 (*C*₁₁), 111.5 (*C*₄), 62.4 (*C*₂), 40.4 (*C*₉), 31.2 (*C*₆), 28.3 (*C*₇), 23.8 (*C*₈), 14.1 (*C*₁); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₈H₂₁NaO₃Br 387.0566, found 387.0560; **IR ν_{max} /cm⁻¹ (thin film)** 2937 (C-H), 1715 (C=O), 1663 (C=O), 1610, 1577, 1495, 1449, 1369.

Preparation of (2Z,9E)-ethyl 2-bromo-10-(3-fluorophenyl)-8-oxodeca-2,9-dienoate

159c

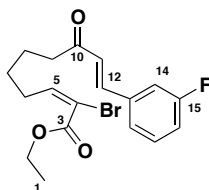


Following **General Procedure 3**, using DMP (331 mg, 0.78 mmol) and alcohol **157c** (200 mg, 0.52 mmol) afforded the title compound **159c** (120 mg, 60%), contaminated with ~5% of an unknown impurity.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.53 (d, J = 16.0 Hz, 1 H, H_{12}), 7.41-7.37 (m, 1 H, ArH), 7.35-7.30 (m, 2 H, ArH, H_5), 7.28-7.25 (m, 1 H, ArH), 7.12 (td, J = 8.0, 2.5 Hz, 1 H, ArH), 6.75 (d, J = 16.0 Hz, 1 H, H_{11}), 4.29 (q, J = 7.0 Hz, 2 H, H_2), 2.72 (t, J = 7.5 Hz, 2 H, H_9), 2.42 (q, J = 7.5 Hz, 2 H, H_6), 1.77 (quin., J = 7.5 Hz, 2 H, H_8), 1.64-1.57 (m, 2 H, H_7), 1.35 (t, J = 7.0 Hz, 3 H, H_1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 199.6 (C10), 162.9 (d, J = 247.0 Hz, C15), 162.5 (C3), 145.5 (C5), 141.1 (C12), 136.8 (C13), 130.5 (CAr), 127.1 (C11), 124.4 (CAr), 117.4 (d, J = 22.0 Hz, CAr), 116.8 (C4), 114.4 (d, J = 22.0, CAr), 62.5 (C2), 40.7 (C9), 31.9 (C6), 27.1 (C7), 23.7 (C8), 14.2 (C1); **¹⁹F NMR (377 MHz, CDCl₃)** δ_{F} -112.4; **HRMS (ESI⁺)** m/z calculated for [M+H]⁺ C₁₈H₂₁O₃BrFNa 405.0472, found 405.0465; **IR ν_{max} /cm⁻¹ (thin film)** 2938 (C-H), 1719 (C=O), 1667 (C=O), 1616, 1583, 1487, 1447, 1368, 1257.

Preparation of (2*E*,9*E*)-ethyl 2-bromo-10-(3-fluorophenyl)-8-oxodeca-2,9-dienoate

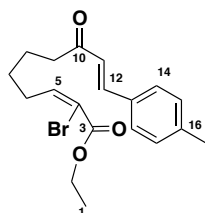
158c



Following **General Procedure 3**, using DMP (663 mg, 1.56 mmol) and alcohol **156c** (400 mg, 1.04 mmol) afforded the title compound **158c** (350 mg, 88%) as a single isomer.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.52 (d, $J = 16.0$ Hz, 1 H, *H*₁₂), 7.40-7.32 (m, 2 H, *ArH*), 7.30-7.25 (m, 1 H, *ArH*), 7.11 (tdd, $J = 8.0, 2.5, 1.0$ Hz, 1 H, *ArH*), 6.73 (d, $J = 16.0$ Hz, 1 H, *H*₁₁), 6.69 (t, $J = 7.5$ Hz, 1 H, *H*₅), 4.28 (q, $J = 7.0$ Hz, 2 H, *H*₂), 2.70 (t, $J = 7.0$ Hz, 2 H, *H*₉), 2.57 (q, $J = 7.5$ Hz, 2 H, *H*₆), 1.78-1.70 (m, 2 H, *H*₈), 1.59-1.50 (m, 2 H, *H*₇), 1.36 (t, $J = 7.0$ Hz, 3 H, *H*₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 199.6 (*C*₁₀), 162.9 (*C*₃), 163.1 (d, $J = 247.0$, *C*₁₅), 148.0 (*C*₅), 141.2 (*C*₁₂), 136.9 (*C*₁₃), 130.5 (*C*_{Ar}), 127.2 (*C*₁₁), 124.3 (*C*_{Ar}), 117.3 (d, $J = 20.0$ Hz, *C*_{Ar}), 114.2 (d, $J = 22.0$, *C*_{Ar}), 111.5 (*C*₄), 62.4 (*C*₂), 40.6 (*C*₉), 31.1 (*C*₆), 28.3 (*C*₇), 23.6 (*C*₈), 14.1 (*C*₁); **¹⁹F NMR (377 MHz, CDCl₃)** δ_{F} -112.4; **HRMS (ESI⁺)** m/z calculated for [*M*+*H*]⁺ C₁₈H₂₁O₃BrF 383.0653, found 383.0647; **IR ν_{max} /cm⁻¹ (thin film)** 2937 (C-H), 1714 (C=O), 1666 (C=O), 1613, 1582, 1485, 1447, 1369.

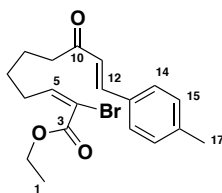
Preparation of (2Z,9E)-ethyl 2-bromo-8-oxo-10-(*p*-tolyl)deca-2,9-dienoate **159d**



Following **General Procedure 3**, using DMP (642 mg, 1.52 mmol) and alcohol **157d** (400 mg, 1.01 mmol) afforded the title compound **159d** (322 mg, 84%), contaminated with ~5% of an unknown impurity.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.56 (d, J = 16.0 Hz, 1 H, *H*12), 7.47 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.31 (t, 1 H, J = 7.5 Hz, *H*5), 7.23 (d, J = 8.0 Hz, 2 H, Ar*H*), 6.73 (d, J = 16.0 Hz, 1 H, *H*11), 4.29 (q, J = 7.0 Hz, 2 H, *H*2), 2.72 (t, J = 7.5 Hz, 2 H, *H*9), 2.42 (t, J = 7.5 Hz, 2 H, *H*6), 2.41 (s, 3 H, *H*17), 1.77 (quin., J = 7.5 Hz, 2 H, *H*8), 1.63-1.55 (m, 2 H, *H*7), 1.35 (t, J = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 200.1 (C10), 162.5 (C3), 145.6 (C5), 142.7 (C12), 141.0 (C16), 131.7 (C13), 129.7 (CAr), 128.3 (CAr), 125.2 (C11), 116.8 (C4), 62.4 (C2), 40.3 (C9), 31.9 (C6), 27.2 (C7), 23.9 (C8), 21.5 (C17), 14.2 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₉H₂₃NaO₃Br 401.0723, found 401.0718; **IR** ν_{max} /cm⁻¹ (**thin film**) 2936 (C-H), 1717 (C=O), 1655 (C=O), 1606, 1513, 1368, 1259, 1180, 1041.

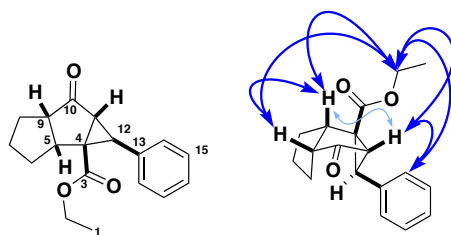
Preparation of (2*E*,9*E*)-ethyl 2-bromo-8-oxo-10-(*p*-tolyl)deca-2,9-dienoate **158d**



Following **General Procedure 3**, using DMP (321 mg, 0.75 mmol) and alcohol **156d** (200 mg, 0.51 mmol) afforded the title compound **158d** (180 mg, 93%) as a single isomer.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.56 (d, J = 16.0 Hz, 1 H, *H*12), 7.48 (d, J = 8.0 Hz, 2 H, *ArH*), 7.23 (d, J = 8.0 Hz, 2 H, *ArH*), 6.72 (d, J = 16.0 Hz, 1 H, *H*11), 6.70 (d, J = 8.0 Hz, 1 H, *H*5), 4.30 (q, J = 7.0 Hz, 2 H, *H*2), 2.71 (t, J = 7.0 Hz, 2 H, *H*9), 2.57 (q, J = 7.5 Hz, 2 H, *H*6), 2.41 (s, 3 H, *H*17), 1.79-1.70 (m, 2 H, *H*8), 1.60-1.52 (m, 2 H, *H*7), 1.37 (t, J = 7.0 Hz, 3 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 200.1 (*C*10), 162.9 (*C*3), 148.2 (*C*5), 142.6 (*C*12), 141.0 (*C*16), 131.7 (*C*13), 129.7 (*C*Ar), 128.3 (*C*Ar), 125.2 (*C*11), 111.5 (*C*4), 62.1 (*C*2), 40.3 (*C*9), 31.2 (*C*6), 28.4 (*C*7), 27.2 (*C*8), 21.5 (*C*17), 14.1 (*C*1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₉H₂₃NaO₃Br 401.0723, found 401.0715; **IR ν_{max} /cm⁻¹ (thin film)** 2935 (C-H), 1715 (C=O), 1658 (C=O), 1606, 1512, 1458, 1368, 1339, 1222, 1179, 1029.

Preparation of (1*S,1*aR**,1*bR**,4*aS**,5*aR**)-ethyl 5-oxo-1-phenyloctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **160b****



Following **General Procedure 4**, using cyclisation precursor **158b** (*E* isomer) (50 mg, 0.13 mmol), toluene (3 mL), KOH (30 mg, 0.53 mmol), tetrabutylammonium bisulfate (4 mg, 0.01 mmol) at RT afforded compound **160b** (34 mg, 88%) as a colourless oil.

Following **General Procedure 4**, using cyclisation precursor **159b** (*Z* isomer) (50 mg, 0.13 mmol), toluene (3 mL), KOH (30 mg, 0.53 mmol), tetrabutylammonium bisulfate (4 mg, 0.01 mmol) at RT afforded compound **160b** (29 mg, 75%) as a colourless oil.

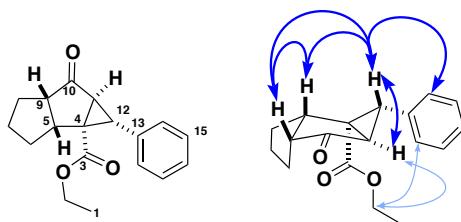
Following **General Procedure 5**, using cyclisation precursor **159b** (*Z* isomer) (50 mg, 0.13 mmol), THF (3 mL), NaH (10 mg, 0.26 mmol) afforded compound **160b** (32 mg, 83%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.32-7.28 (m, 3 H, Ar*H*), 7.26-7.20 (m, 2 H, Ar*H*), 3.88-3.79 (m, 2 H, *H*2), 3.52-3.45 (m, 1 H, *H*5), 3.06 (dd, *J* = 3.5, 1.5 Hz, 1 H, *H*11), 2.99-2.93 (m, 2 H, *H*12, *H*9), 2.34-2.28 (m, 1 H, *H*6), 2.01-1.88 (m, 3 H, *H*6', *H*7, *H*8), 1.78-1.70 (m, 1 H, *H*7'), 1.65-1.55 (m, 1 H, *H*8'), 0.83 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 212.7 (*C*10), 170.1 (*C*3), 134.0 (*C*13), 128.8 (*C*14/*C*15), 128.3 (*C*14/*C*15), 127.3 (*C*16), 60.7 (*C*2), 54.4 (*C*9), 44.5 (*C*4), 42.8 (*C*5), 42.1 (*C*11), 34.3 (*C*12), 31.8 (*C*6), 30.4 (*C*8),

29.7 (C7), 13.7 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₈H₂₀NaO₃ 307.1310, found 307.1303; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2950, 2870, 1703 (C=O), 1450, 1275, 1255, 1221, 1130.

N.B. Key nOe interactions are highlighted. Bold dark blue indicate a strong correlation and light blue indicate a weak correlation

Preparation of (1*R,1*aS**,1*bR**,4*aS**,5*aS**)-ethyl 5-oxo-1-phenyloctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **161b****

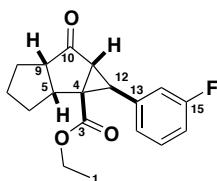


Following **General Procedure 5**, using cyclisation precursor **158b** (*E* isomer) (50 mg, 0.13 mmol), THF (3 mL), NaH (10 mg, 0.26 mmol) afforded compound **161b** (29 mg, 75%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.32-7.27 (m, 3 H, Ar*H*), 7.26-7.22 (m, 2 H, Ar*H*), 3.93-3.82 (m, 2 H, *H*2), 3.23 (q, *J* = 8.0 Hz, 1 H, *H*5), 2.97 (d, *J* = 4.5 Hz, 1 H, *H*11), 2.87 (d, *J* = 4.5 Hz, 1 H, *H*12), 2.77-2.72 (m, 1 H, *H*9), 2.14-2.08 (m, 1 H, *H*6), 1.95-1.89 (m, 2 H, *H*8), 1.70-1.53 (m, 2 H, *H*7), 1.41-1.30 (m, 1 H, *H*6'), 0.89 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 213.7 (C10), 168.6 (C3), 134.1 (C13), 128.5 (C14/C15), 128.3 (C14/C15), 127.4 (C16), 60.7 (C2), 49.9 (C9), 45.2 (C5), 44.8 (C4), 38.4 (C11), 37.4 (C12), 31.5 (C6), 28.2 (C8), 26.5 (C7), 13.8 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₈H₂₀NaO₃ 307.1310, found 307.1302; **IR** ν_{max} /cm⁻¹ (thin film) 2980, 2875, 1723 (C=O), 1484, 1376, 1248, 1128.

N.B. Key nOe interactions are highlighted. Bold dark blue indicate a strong correlation and light blue indicate a weak correlation

Preparation of (1a*R,1b*R**,4a*S**,5a*R**)-ethyl 1-(3-fluorophenyl)-5-oxooctahydro-1*H*-cyclopropa[*a*]pentalene-1a-carboxylate **160c****



Following **General Procedure 4**, using cyclisation precursor **158c** (*E* isomer) (50 mg, 0.13 mmol), toluene (4 mL), KOH (29 mg, 0.52 mmol), tetrabutylammonium bisulfate (4 mg, 0.01 mmol) at RT afforded compound **160c** (25 mg, 64%) as a colourless oil.

Following **General Procedure 4**, using cyclisation precursor **159c** (*Z* isomer) (50 mg, 0.13 mmol), toluene (4 mL), KOH (29 mg, 0.52 mmol), tetrabutylammonium bisulfate (4 mg, 0.01 mmol) at RT afforded compound **160c** (22 mg, 56%) as a colourless oil.

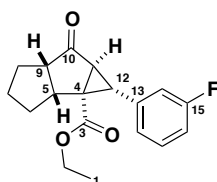
Following **General Procedure 5**, using cyclisation precursor **159c** (*Z* isomer) (50 mg, 0.13 mmol), THF (4 mL), NaH (6 mg, 0.26 mmol) afforded compound **160c** (26 mg, 66%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.19-7.15 (m, 1 H, Ar*H*), 6.93 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 6.88-6.85 (m, 2 H, Ar*H*), 3.79 (q, *J* = 7.0 Hz, 2 H, *H*₂), 3.44-3.39 (m, 1 H, *H*₅), 2.94 (dd, *J* = 5.0, 1.0 Hz, 1 H, *H*₁₁), 2.87 (q, *J* = 10.5 Hz, 1 H, *H*₉), 2.82 (d, *J* = 5.0 Hz, 1 H, *H*₁₂), 2.25-2.19 (m, 1 H, *H*₆), 1.92-1.85 (m, 1 H, *H*₈), 1.85-1.78 (m, 2 H, *H*_{6'}, *H*₇), 1.68-1.60 (m, 1 H, *H*_{7'}), 1.54-1.45 (m, 1 H, *H*_{8'}) 0.81 (t, *J* = 7.0 Hz, 3 H, *H*₁); **¹³C NMR (126 MHz, CDCl₃)** δ_C 212.0 (C₁₀), 169.1 (C₃), 162.6 (d, *J* = 246.0 Hz, C₁₅), 136.6 (d, *J* = 7.5 Hz, C₁₃), 129.8 (d, *J* = 8.5 Hz, CAr), 124.5 (d, *J* = 2.5 Hz, CAr), 115.9 (d, *J* = 22.0 Hz, CAr), 114.3 (d,

$J = 21.0$ Hz, CAr), 60.8 (C2), 54.4 (C9), 44.5 (C4), 42.8 (C5), 42.2 (C11), 33.7 (C12), 31.7 (C6), 30.4 (C8), 29.7 (C7), 13.7 (C1); ^{19}F NMR (377 MHz, CDCl_3) δ_{F} -113.2; HRMS (ESI $^{+}$) m/z calculated for $[\text{M}+\text{Na}]^{+}$ $\text{C}_{18}\text{H}_{19}\text{NaFO}_3$ 325.1210, found 325.1207; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2959, 1722 (C=O), 1613 (C=O), 1587, 1446, 1373, 1211, 1149.

N.B. Stereochemistry assigned by nOe analysis similar to compound **160b**

Preparation of (1*S,1*aS**,1*bR**,4*aS**,5*aS**)-ethyl 1-(3-fluorophenyl)-5-oxooctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **161c****

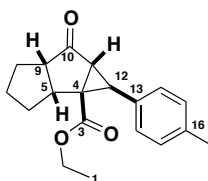


Following **General Procedure 5**, using cyclisation precursor **158c** (*E* isomer) (50 mg, 0.13 mmol), THF (4 mL), NaH (6 mg, 0.26 mmol) afforded compound **161c** (35 mg, 88%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.19-7.14 (m, 1 H, Ar*H*), 6.94 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 6.88-6.84 (m, 2 H, Ar*H*), 3.84 (qd, *J* = 7.0, 2.0 Hz, 2 H, *H*2), 3.12 (q, *J* = 8.0 Hz, 1 H, *H*5), 2.84 (d, *J* = 4.5 Hz, 1 H, *H*11), 2.74 (d, *J* = 4.5 Hz, 1 H, *H*12), 2.65 (q, *J* = 7.5 Hz, 1 H, *H*9), 2.05-1.99 (m, 1 H, *H*6), 1.83 (q, *J* = 6.5 Hz, 2 H, *H*8), 1.61-1.45 (m, 2 H, *H*7), 1.30-1.25 (m, 1 H, *H*6'), 0.86 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 213.3 (C10), 168.3 (C3), 162.6 (d, *J* = 246.0 Hz, C15), 136.6 (d, *J* = 7.5 Hz, C13), 129.9 (d, *J* = 8.5 Hz, CAr), 124.2 (CAr), 115.5 (d, *J* = 22.0 Hz, CAr), 114.4 (d, *J* = 21.0 Hz, CAr), 60.9 (C2), 49.8 (C9), 45.2 (C5), 44.8 (C4), 38.4 (C11), 36.9 (C12), 31.5 (C6), 28.2 (C8), 26.5 (C7), 14.1 (C1); **¹⁹F NMR (377 MHz, CDCl₃)** δ_{F} -113.2; **HRMS (ESI⁺)** *m/z* calculated for [M+H]⁺ C₁₈H₂₀FO₃ 303.1397, found 303.1390; **IR** ν_{max} /cm⁻¹ (**thin film**) 2980, 2890, 1745 (C=O), 1625 (C=O), 1595, 1452, 1238, 1166.

N.B. Stereochemistry assigned by nOe analysis similar to compound **161b**

Preparation of (1*R1*aR**,1*bR**4*aS**,5*aR**)-ethyl 5-oxo-1-(*p*-tolyl)octahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **160d****



Following **General Procedure 4**, using cyclisation precursor **158d** (*E* isomer) (50 mg, 0.13 mmol), toluene (3 mL), KOH (30 mg, 0.53 mmol), tetrabutylammonium bisulfate (4 mg, 0.01 mmol) at RT afforded compound **160d** (34 mg, 88%) as a colourless oil.

Following **General Procedure 4**, using cyclisation precursor **159d** (*Z* isomer) (50 mg, 0.13 mmol), toluene (3 mL), KOH (30 mg, 0.53 mmol), tetrabutylammonium bisulfate (4 mg, 0.01 mmol) at RT afforded compound **160d** (23 mg, 59%) as a colourless oil.

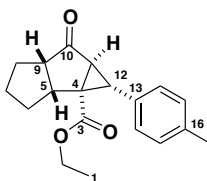
Following **General Procedure 5**, using cyclisation precursor **159d** (*Z* isomer) (50 mg, 0.13 mmol), THF (3 mL), NaH (10 mg, 0.26 mmol) afforded compound **160d** (26 mg, 74%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.12-7.08 (m, 4 H, ArH), 3.86 (qd, *J* = 7.0, 1.0 Hz, 2 H, H2), 3.50-3.45 (m, 1 H, H5), 3.03 (dd, *J* = 5.0, 1.5 Hz, 1 H, H11), 2.98-2.93 (m, 1 H, H9), 2.91 (d, *J* = 5.0 Hz, 1 H, H12), 2.33 (s, 3 H, H17), 2.31-2.25 (m, 1 H, H6), 1.98-1.89 (m, 3 H, H8, H7, H6'), 1.76-1.68 (m, 1 H, H7'), 1.60-1.55 (m, 1 H, H8'), 0.88 (t, *J* = 7.0 Hz, 3 H, H1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 213.1 (C10), 170.2 (C3), 136.9 (C16), 130.8 (C13), 128.9 (CAr), 128.6 (CAr), 60.7 (C2), 54.4 (C9), 44.5 (C4), 42.8 (C5), 42.3 (C11), 34.1 (C12), 31.7 (C6), 30.4 (C8), 29.7 (C7), 21.1 (C17), 13.7 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺

$\text{C}_{19}\text{H}_{22}\text{NaO}_3$ 321.1467, found 321.1458; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2983, 1742 (C=O), 1371, 1248, 1180.

N.B. Stereochemistry assigned by nOe analysis similar to compound **160b**

Preparation of (1*R,1*aS**,1*bR**,4*aS**,5*aS**)-ethyl 5-oxo-1-(*p*-tolyl)octahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **161d****

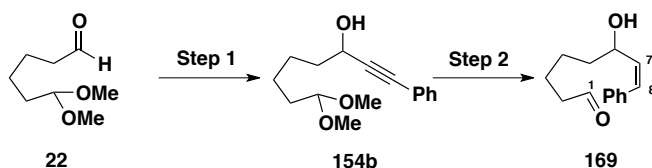


Following **General Procedure 5**, using cyclisation precursor **158d** (*E* isomer) (50 mg, 0.13 mmol), THF (3 mL), NaH (10 mg, 0.26 mmol) afforded compound **161d** (29 mg, 75%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.03-6.99 (m, 4 H, ArH), 3.81 (qd, *J* = 7.0, 2.0 Hz, 2 H, H2), 3.12 (q, 1 H, *J* = 8.0 Hz, H5), 2.84 (d, *J* = 4.5 Hz, 1 H, H11), 2.74 (d, 1 H, *J* = 4.0 Hz, H12), 2.65 (dt, *J* = 8.0, 4.5 Hz, 1 H, H9), 2.23 (s, 3 H, H17), 2.64-1.98 (m, 1 H, H6), 1.85-1.80 (m, 2 H, H8) 1.60-1.44 (m, 2 H, H7), 1.31-1.24 (m, 1 H, H6'), 0.85 (t, *J* = 7.0 Hz, 3 H, H1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 213.1 (C10), 168.7 (C3), 137.0 (C16), 131.0 (C13), 129.0 (CAr), 128.3 (CAr), 60.7 (C2), 49.9 (C9), 45.2 (C5), 44.9 (C4), 38.5 (C11), 37.3 (C12), 31.6 (C6), 28.2 (C8), 26.5 (C7), 21.1 (C17), 13.9 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+H]⁺ C₁₉H₂₃O₃ 299.1642, found 299.1637; **IR ν_{max} /cm⁻¹ (thin film)** 2956, 2945, 1742 (C=O), 1520, 1320, 1240, 1160.

N.B. Stereochemistry assigned by nOe analysis similar to compound **161d**

Preparation of (Z)-6-hydroxy-8-phenyloct-7-enal **168**



Step 1:

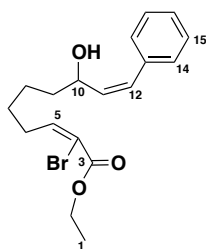
Phenyl acetylene (1.5 mL, 13.75 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to -78 °C. *n*BuLi (1.6 M, 9 mL, 14.4 mmol) was added dropwise and the resulting solution stirred for 30 min. Aldehyde **22** (2.0 g, 12.5 mmol) was dissolved in THF (20 mL) and was added dropwise to the cooled solution. The reaction mixture was then let warm to RT, and then stirred for 1 hr at this temperature. The reaction mixture was quenched with H₂O and then the aqueous layer extracted with Et₂O (x 3). The layers were separated and the organic layer was dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford alkyne **154b** (3.3 g, quant.).

Step 2:

Alkyne **154b** (500 mg, 1.9 mmol) was dissolved in EtOH (6 mL) and Lindlar's catalyst (50 mg, 10 wt%) and quinoline (10 µL, 0.1 mmol) were added to the flask under an H₂ atmosphere. The resulting suspension was stirred at RT for 3 hr and then the reaction mixture was diluted with EtOAc and filtered through Celite, eluting with EtOAc. The resulting residue was dissolved in acetone (10 mL), and HCl (1.0 M aq., 5 mL) and H₂O (5 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **169** (415 mg, quant.).

¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_{H} 9.67 (t, $J = 1.5$ Hz, 1 H, *H*1), 6.49 (d, $J = 11.5$ Hz, 1 H, *H*8), 5.59 (dd, $J = 11.5, 9.5$ Hz, 1 H, *H*7), 4.51 (q, $J = 7.5$ Hz, 1 H, *H*6).

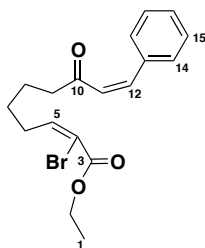
Preparation of (2Z,9Z)-ethyl 2-bromo-8-hydroxy-10-phenyldeca-2,9-dienoate **170**



Following **General Procedure 2**, using HWE reagent **25** (514 mg, 2.29 mmol), NaH (183 mg, 4.58 mmol), NBS (408 mg, 2.29 mmol) and aldehyde **169** (500 mg, 2.29 mmol) afforded the title compound **170** (350 mg, 42%).

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.28 (t, J = 7.5 Hz, 1 H, H_5), 7.22-7.18 (m, 5 H, ArH), 6.50 (d, J = 12.0 Hz, 1 H, H_{12}), 5.62-5.57 (m, 1 H, H_{11}), 4.50 (br. s, 1 H, H_{10}), 4.20 (q, J = 7.0 Hz, 2 H, H_2), 2.27 (q, J = 7.0 Hz, 2 H, H_6), 1.66-1.55 (m, 1 H, H_9), 1.55-1.30 (m, 6 H, H_7 , H_8 , $H_{9'}$, OH), 1.26 (t, J = 7.0 Hz, 3 H H_1); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 162.5 (C3), 145.9 (C5), 136.6 (C13), 134.4 (C11), 131.3 (C12), 128.7 (CAr), 128.4 (CAr), 127.3 (CAr), 116.6 (C4), 67.7 (C10), 62.4 (C2), 37.3 (C9), 32.1 (C6), 27.5 (C8), 25.1 (C7), 14.2 (C1); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₃BrNaO₃ 389.0723, found 389.0725; **IR ν_{max} /cm⁻¹ (thin film)** 3396 (OH), 2986 (C-H), 1760 (C=O), 1714, 1256, 914.

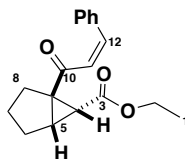
Preparation of (2Z,9Z)-ethyl 2-bromo-8-oxo-10-phenyldeca-2,9-dienoate **171**



Following **General Procedure 3**, using DMP (521 mg, 1.23 mmol) and alcohol **170** (300 mg, 0.82 mmol) afforded the title compound **171** (200 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.55-7.53 (m, 3 H, ArH), 7.37 (dd, $J = 5.5, 1.5$ Hz, 2 H, ArH), 7.37 (t, $J = 7.0$ Hz, 1 H, H₅), 6.88 (d, $J = 12.5$ Hz, 1 H, H₁₂), 6.21 (d, $J = 12.5$ Hz, 1 H, H₁₁), 4.29 (q, $J = 7.0$ Hz, 2 H, H₂), 2.50 (t, $J = 7.5$ Hz, 2 H, H₉), 2.33 (q, $J = 7.5$ Hz, 2 H, H₆), 1.70-1.63 (m, 2 H, H₈), 1.53-1.44 (m, 2 H, H₇), 1.35 (t, $J = 7.0$ Hz, 3 H, H₁); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 202.7 (C₁₀), 162.4 (C₃), 148.0 (C₁₃), 145.5 (C₅), 140.1 (C₁₂), 129.7 (CAr), 129.2 (C₁₁), 128.5 (CAr), 128.3 (CAr), 116.7 (C₄), 62.4 (C₂), 43.1 (C₉), 31.9 (C₆), 28.2 (C₇), 23.7 (C₈), 14.2 (C₁); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₁NaO₃Br 387.0566, found 387.0565; **IR** ν_{max} /cm⁻¹ (**thin film**) 2986, 2936, 1722 (C=O), 1691 (C=O), 1256, 1096, 981, 863.

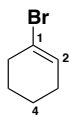
Preparation of (1*R,5*S**,6*R**)-ethyl 1-((*Z*)-3-phenylacryloyl)bicyclo[3.1.0]-hexane-6-carboxylate **172****



Following **General Procedure 4**, using cyclisation precursor **171** (*Z* isomer) (50 mg, 0.13 mmol), toluene (3 mL), KOH (31 mg, 0.55 mmol), tetrabutylammonium bisulfate (5 mg, 0.01 mmol) at RT afforded compound **172** (13 mg, 14%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.60 (dd, $J = 7.5, 2.0$ Hz, 2 H, ArH), 7.36-7.34 (m, 3 H, ArH), 6.80 (d, $J = 12.5$ Hz, 1 H, H₁₂), 6.28 (d, $J = 12.5$ Hz, 1 H, H₁₁), 4.15-4.07 (m, 2 H, H₂), 2.41 (t, $J = 4.5$ Hz, 1 H, H₅), 2.13-2.00 (m, 2 H, H₈), 1.94 (d, $J = 4.5$ Hz, 1 H, H₄), 1.84 (dd, $J = 12.0, 8.0$ Hz, 1 H, H₆), 1.72-1.64 (m, 2 H, H_{6'}, H₇), 1.28-1.20 (m, 1 H, H_{7'}), 1.23 (t, $J = 7.0$ Hz, 3 H, H₁); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 199.6 (C₁₀), 170.8 (C₃), 139.8 (C₁₂), 135.4 (CAr), 129.8 (CAr), 129.7 (CAr), 128.2 (CAr), 127.2 (C₁₁), 60.9 (C₂), 48.2 (C₉), 33.9 (C₅), 30.7 (C₈), 29.7 (C₄), 27.2 (C₆), 20.6 (C₇), 14.2 (C₁); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₈H₂₀NaO₃ 307.1305, found 307.1303; **IR ν_{max} /cm⁻¹ (thin film)** 2959, 2866, 1722 (C=O), 1662, 1494, 1204, 1095, 1068.

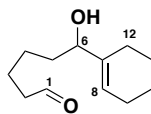
Preparation of 1-bromocyclohex-1-ene **174**



Triphenylphosphite (2.9 mL, 11.2 mmol) was dissolved in CH₂Cl₂ (35 mL) and the resulting solution cooled to -60 °C. Br₂ (0.62 mL, 12.2 mmol), Et₃N (1.8 mL, 13.3 mmol) and cyclohexanone (1 mL, 10.2 mmol) were added sequentially and the reaction mixture let warm slowly to RT overnight. The reaction mixture was then refluxed for 2 hr and then let cool to RT. The reaction mixture was quenched by addition of Na₂S₂O₃ (sat. aq.) and NH₄Cl (sat. aq.), and the layers separated. The aqueous layers were extracted with CH₂Cl₂ (x 3) and the combined extracts were dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product (N.B. product is very volatile, care must be taken when removing solvent under reduced pressure). This crude product was purified by flash column chromatography (SiO₂, pet 30-40) to afford compound **174** (1.3 g, 82%) as a volatile colourless oil with identical spectra to those reported in the literature.³⁰

¹H NMR (400 MHz, CDCl₃) δ_H 6.06 (dd, *J* = 4.0, 1.5 Hz, 1 H, *H*₂) 2.46-2.41 (m, 2 H, *H*₆), 2.13-2.06 (m, 2 H, *H*₃), 1.79-1.72 (m, 2 H, *H*_{4/5}), 1.66-1.59 (m, 2 H, *H*_{4/5}); **¹³C NMR (101 MHz, CDCl₃)** δ_C 128.9 (C₂), 122.3 (C₁), 35.2 (C₆), 27.4 (C₃), 25.0 (C_{4/5}), 21.1 (C_{4/5}); **LRMS** not obtained due to high volatility.

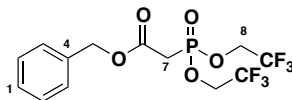
Preparation of 6-(cyclohex-1-en-1-yl)-6-hydroxyhexanal **175**



Following **General Procedure 1**, using 1 bromo cyclohex-1-ene (1 g, 6.25 mmol) and aldehyde **22** (1 g, 6.25 mmol) in THF (12.5 mL) afforded compound **175** (600 mg, 49%) as a yellow oil, which was unstable to any purification.

^1H NMR (200 MHz, CDCl_3) showed characteristic peaks at δ_{H} 9.91 (s, 1 H, *H*1), 6.10 (t, $J = 7.5$ Hz, 1 H, *H*8), 4.33 (t, $J = 7.5$ Hz, 1 H, *H*6).

Preparation of benzyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetate **184**



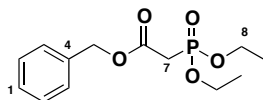
According to a modified literature procedure,⁵ *n*BuLi (10 mL, 1.6 M in hexanes, 16 mmol) was cooled to -20 °C. HMDS (3.7 mL, 18 mmol) was dissolved in THF (14 mL) and added dropwise to the cooled *n*BuLi solution. The resulting solution was cooled to -78 °C, and a solution of bis(2,2,2-trifluoroethyl) methylphosphonate (2 g, 7.7 mmol) and benzyl chloroformate (1.1 mL, 8.1 mmol) in THF (34 mL) was added dropwise. The resulting solution was kept in the -78 °C bath overnight, allowing to gradually warm, and was then treated with HCl (1.0 M) until acidic. The layers were separated, the aqueous layer extracted with Et₂O (x 2), and the combined organic extracts were washed with brine. The organic layer was then dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. The crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (1:1)) to afford compound **184** (1.6 g, 53%) as a colourless oil.

N.B. yields of this reaction vary. Leaving the reaction mixture below -20 °C overnight generally affords the best yields.

¹H NMR (400 MHz, CDCl₃) δ_H 7.25-7.14 (m, 5 H, ArH), 5.02 (s, 2 H, H₅), 4.30-4.11 (m, 4 H, H₈), 3.00 (d, *J* = 21.0 Hz, 2 H, H₇); **¹³C NMR (101 MHz, CDCl₃)** δ_C 164.4 (C₆), 134.6 (C₄), 128.8 (CAr), 128.7 (CAr), 128.6 (CAr), 123.0 (q, *J* = 280.0 Hz, C₉), 68.0 (C₅), 62.8 (qd, *J* = 38.0, 5.5 Hz, C₈), 34.0 (d, *J* = 144.0 Hz, C₇); **LRMS *m/z* (ESI⁺)** 417.0 ([M+Na]⁺ 100%).

¹⁹F NMR (377 MHz, CDCl₃) δ_F -75.4

Preparation of benzyl 2-(diethoxyphosphoryl)acetate **182**

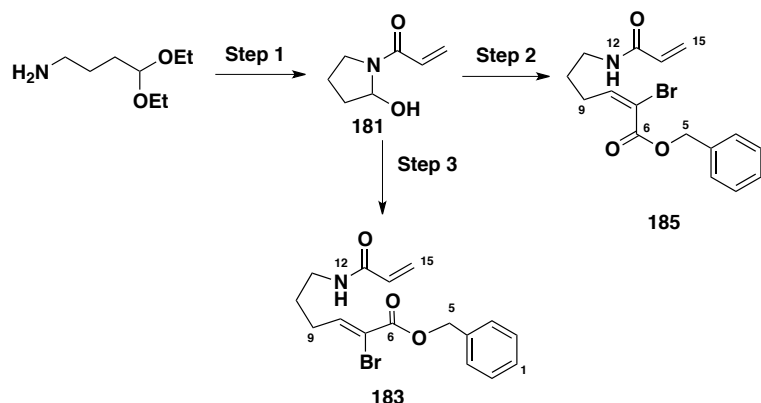


According to a modified literature procedure,⁵ *n*BuLi (27.6 mL, 2.5 M in hexanes, 69 mmol) was cooled to -20 °C. HMDS (17 mL, 76 mmol) was dissolved in THF (25 mL) and added dropwise to the cooled *n*BuLi solution. The resulting solution was cooled to -78 °C, and a solution of diethyl methylphosphonate (4.8 g, 33 mmol) and benzyl chloroformate (4.9 mL, 34.5 mmol) in THF (55 mL) was added dropwise. The resulting solution was kept in the -78 °C bath overnight, allowing to gradually warm, and was then treated with HCl (1.0 M) until acidic. The layers were separated, the aqueous layer extracted with Et₂O (x 2), and the combined organic extracts were washed with brine. The organic layer was then dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. The crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (1:1)) to afford compound **182** (7.0 g, 75%) as a colourless oil.

N.B. yields of this reaction vary. Leaving the reaction mixture below -20 °C overnight generally affords the best yields.

¹H NMR (400 MHz, CDCl₃) δ_H 7.41-7.32 (m, 5 H, ArH), 5.18 (s, 2 H, H₅), 4.16-4.09 (m, 4 H, H₈), 3.01 (d, *J* = 22.0 Hz, 2 H, H₇), 1.30 (t, *J* = 7.0 Hz, 6 H, H₉); **¹³C NMR (101 MHz, CDCl₃)** δ_C 165.7 (C₆), 135.3 (C₄), 128.5 (CAr), 128.4 (CAr), 128.3 (CAr), 67.3 (C₅), 62.7 (C₈), 34.4 (d, *J* = 134.5 Hz, C₇), 16.3 (C₉); **LRMS m/z (ESI⁺)** 287.1 ([M+H]⁺ 100%).

Preparation of (*E* and *Z*)-benzyl 6-acrylamido-2-bromohex-2-enoate **183** and **185**



Step 1:

According to a modified literature procedure,³¹ 4,4-diethoxybutan-1-amine (1.0g, 6.2 mmol) was dissolved in CH_2Cl_2 (10 mL) and NaHCO_3 (sat. aq., 10 mL) was added. The resulting biphasic mixture was cooled to 0 °C and acrolyl chloride (0.89 mL, 11 mmol) was added dropwise. The resulting reaction mixture was allowed to warm to RT, and stirred at this temperature for 1 hr. The layers were separated, the organic layer dried over K_2CO_3 , filtered, and the filtrate concentrated under reduced pressure to afford the crude acetal-amide. This was dissolved in acetone (20 mL) and HCl (3% aq., 10 mL), and the resulting solution stirred at RT for 3 hr. The reaction mixture was neutralised with NaHCO_3 (sat. aq., ~10 mL), and concentrated under reduced pressure. The resulting residue was dissolved in CHCl_3 , the layers separated and aqueous layer extracted with CHCl_3 (x 2). The combined extracts were washed with brine, dried over K_2CO_3 , filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. This crude product was purified by filtering through a pad of silica, eluting with EtOAc. The solvent was removed under reduced pressure to afford the amide **181** which was used immediately in the next step.

Step 2:

According to a modified literature procedure, Still-Gennari reagent **184** (276 mg, 0.70 mmol) was dissolved in THF (6 mL). NaH (60% in mineral oil, 56 mg, 1.4 mmol) and NBS (125 mg, 0.7 mmol) were added and the resulting suspension stirred for 1 hr. Amide **181** (100 mg, 0.70 mmol) was dissolved in THF (2 mL), and added to the reaction mixture and the resulting suspension stirred overnight. The reaction mixture was quenched with NH₄Cl (sat. aq.), the layers separated and the aqueous layer extracted with EtOAc (x 2). The combined extracts were washed with brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (6:4)) to afford compound **185** (110 mg, 45%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.50-7.35 (m, 6 H, ArH, H12), 6.69 (t, J = 8.0 Hz, 1 H, H8), 6.29 (dd, J = 17.5, 1.5 Hz, 1 H, H15), 6.10 (dd, J = 17.0, 10.0 Hz, 1 H, H14), 5.95 (dd, J = 10.0, 1.5 Hz, 1 H, H15'), 5.27 (s, 2 H, H5), 3.33 (q, J = 6.5 Hz, 2 H, H11), 2.54 (q, J = 8.0 Hz, 2 H, H9), 1.81-1.69 (m, 2 H, H10); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 165.6 (C13), 163.0 (C6), 147.8 (C8), 135.0 (C4), 131.0 (C14), 128.7 (CAr), 128.6 (CAr), 128.5 (CAr), 128.0 (C15), 111.4 (C7), 68.0 (C5), 39.0 (C11), 28.5 (C9), 28.0 (C10); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₈BrNNaO₃ 374.0362, found 364.0370; **IR ν_{max} /cm⁻¹ (thin film)** 3300 (NH), 1715 (C=O), 1656 (C=O), 1545, 1377, 1215.

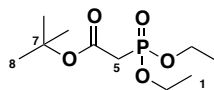
Step 3:

According to a modified literature procedure, Horner-Wadsworth-Emmons reagent **182** (1.2 g, 4.2 mmol) was dissolved in THF (15 mL). NaH (60% in mineral oil, 340 mg, 8.4 mmol) and NBS (750 mg, 4.2 mmol) were added and the resulting suspension

stirred for 1 hr. Amide **181** (600 mg, 4.2 mmol) was dissolved in THF (10 mL), and added to the reaction mixture and the resulting suspension stirred overnight. The reaction mixture was quenched with NH₄Cl (sat. aq.), the layers separated and the aqueous layer extracted with EtOAc (x 2). The combined extracts were washed with brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (6:4)) to afford compound **183** (110 mg, 45%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.28-7.12 (m, 6 H, ArH, H8), 6.11 (dd, J = 17.0, 1.5 Hz, 1 H, H15), 5.92 (dd, J = 17.0, 10.5 Hz, 1 H, H14), 5.77 (br. s, 1 H, H12), 5.47 (dd, J = 10.5, 1.5 Hz, 1 H, H15'), 5.08 (s, 2 H, H5), 3.20 (q, J = 7.0 Hz, 2 H, H11), 2.24 (q, J = 7.0 Hz, 2 H, H9), 1.59 (quin., J = 7.0 Hz, 2 H, H10); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 165.7 (C13), 162.1 (C6), 147.8 (C8), 135.3 (C4), 130.7 (C14), 128.7 (CAr), 128.6 (CAr), 128.5 (CAr), 128.4 (C15), 116.9 (C7), 68.0 (C5), 39.0 (C11), 28.6 (C9), 28.0 (C10); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₆H₁₈BrNNaO₃ 374.0362, found 364.0361; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 3279 (NH), 1714 (C=O), 1657 (C=O), 1546, 1454, 1407.

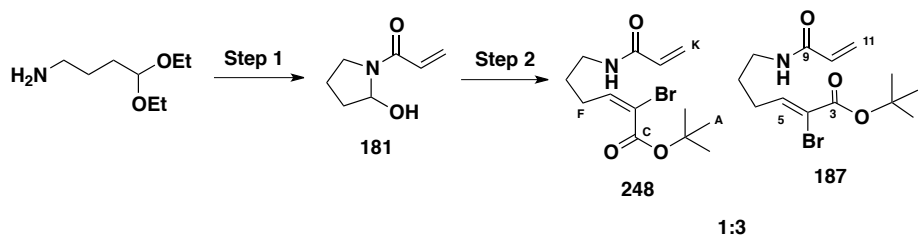
Preparation of *tert*-butyl 2-(diethoxyphosphoryl)acetate **186**



According to a literature procedure,³² *tert*-butyl bromoacetate (1.5 mL, 10.3 mmol) was dissolved in triethylphosphite (1.8 mL, 10.3 mmol) and the resulting solution stirred at 50 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to afford the crude product **186** (2.6 g, quant.) as a colourless oil which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_H 4.17 (quin., *J* = 7.0 Hz, 2 H, *H*₂) 3.68 (quin., *J* = 7.0 Hz, 2 H, *H*₂'), 2.89 (d, *J* = 21.0 Hz, 2 H, *H*₅), 1.48, (d, *J* = 3.0 Hz, 9 H, *H*₈), 1.35 (t, *J* = 7.0 Hz, 3 H, *H*₁), 1.27 (t, *J* = 7.0 Hz, 3 H, *H*₁'); ¹³C NMR (101 MHz, CDCl₃) δ_C 165.0 (*C*₆), 82.0 (*C*₇), 62.5 (*C*₂), 58.0 (*C*₂'), 35.0 (d, *J* = 133.0 Hz, *C*₅), 27.8 (*C*₈), 16.9 (*C*₁'), 16.4 (*C*₁); LRMS *m/z* (ESI⁺) 527.2 ([2M+Na]⁺ 100%).

Preparation of (*E* and *Z*)-*tert*-butyl 6-acrylamido-2-bromohex-2-enoate **187** and **248**



Step 1:

According to a modified literature procedure,³³ 4,4-diethoxybutan-1-amine (1.0g, 6.2 mmol) was dissolved in CH₂Cl₂ (10 mL) and NaHCO₃ (sat. aq., 10 mL) was added. The resulting biphasic mixture was cooled to 0 °C and acryloyl chloride (0.89 mL, 11 mmol) was added dropwise. The resulting reaction mixture was allowed to warm to RT, and stirred at this temperature for 1 hr. The layers were separated, the organic layer dried over K₂CO₃, filtered, and the filtrate concentrated under reduced pressure to afford the crude acetal-amide. This was dissolved in acetone (20 mL) and HCl (3% aq., 10 mL), and the resulting solution stirred at RT for 3 hr. The reaction mixture was neutralised with NaHCO₃ (sat. aq., ~10 mL), and concentrated under reduced pressure. The resulting residue was dissolved in CHCl₃, the layers separated and aqueous layer extracted with CHCl₃ (x 2). The combined extracts were washed with brine, dried over K₂CO₃, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. This crude product was purified by filtering through a pad of silica, eluting with EtOAc. The solvent was removed under reduced pressure to afford the amide **181** which was used immediately in the next step.

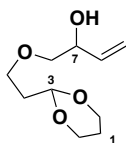
Step 2:

According to a modified literature procedure, Horner-Wadsworth-Emmons reagent **186** (882 mg, 3.5 mmol) was dissolved in THF (10 mL). NaH (60% dispersion in mineral

oil, 280 mg, 7.0 mmol) and NBS (623 mg, 3.5 mmol) were added and the resulting suspension stirred for 1 hr. Amide **181** (500 mg, 3.5 mmol) was dissolved in THF (10 mL), and added to the reaction mixture and the resulting suspension stirred overnight. The reaction mixture was quenched with NH₄Cl (sat. aq.), the layers separated and the aqueous layer extracted with EtOAc (x 2). The combined extracts were washed with brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (7:3)) to afford compounds **248** and **187** (500 mg, 45%) as a inseparable 1:3 mixture of isomers.

¹H NMR (400 MHz, CDCl₃) δ_H 7.10 (t, *J* = 7.5 Hz, 3 H, *H*5), 6.45 (t, *J* = 8.0 Hz, 1 H, *H*E), 4.46 (br. s, 1 H, *NH*), 6.25-6.22 (m, 1 H, *H*K), 6.20-6.18 (m, 3 H, *H*11), 6.0-5.99 (m, 4 H, *H*J, *H*10), 5.89 (br. s, 3 H, *NH*), 5.60-5.80 (m, 3 H, *H*11'), 5.70-5.45 (m, 1 H, *H*K'), 3.34-3.25 (m, 8 H, *H*8, *H*H), 2.41 (q, *J* = 7.5 Hz, 2 H, *H*F), 2.31 (q, *J* = 7.5 Hz, 6 H, *H*6), 1.75-1.60 (m, 8 H, *H*7, *H*G), 1.46 (s, 9 H, *H*A), 1.44 (s, 27 H, *H*1); **¹³C NMR (101 MHz, CDCl₃)** δ_C 165.7 (C9, CI), 161.2 (C3, CC), 144.7 (CE), 143.5 (C5), 131.1 (CJ), 130.8 (C10), 126.5 (C11), 126.1 (CK), 119.1 (C4), 113.4 (CD), 83.6 (CB), 82.9 (C2), 39.1 (C8), 38.1 (CH), 29.6 (C6), 28.3 (CF), 27.9 (C1), 27.8 (CA), 27.7 (CG), 27.4 (C7); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₃H₂₀BrNNaO₃ 340.0519, found 340.0506; **IR** ν_{max}/cm⁻¹ (**thin film**) 3289 (NH), 1711 (C=O), 1658 (C=O), 1625, 1545, 1368.

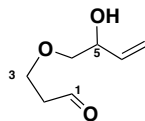
Preparation of 1-(2-(1,3-dioxan-2-yl)ethoxy)but-3-en-2-ol **192**



3,4-Dihydroxy-1-butene (0.95 mL, 11.4 mmol) was dissolved in DMF (30 mL) and the resulting solution was cooled to 0 °C. NaI (164 mg, 1.10 mmol) and NaH (60% suspension in mineral oil, 455 mg, 11.4 mmol) were added and the reaction mixture was stirred for 1 hr. 2-(2-Bromoethyl)-1,3-dioxane (1.56 mL, 11.4 mmol) was added and the resulting solution was let warm to RT, and stirred at RT overnight. The reaction mixture was quenched by the addition of water, the layers separated and the aqueous layer extracted with EtOAc (x 3). The combined extracts were dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product. The crude product was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (6:4)) to afford compound **192** (450 mg, 20%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 5.61 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1 H, *H*₈), 5.23 (dt, *J* = 17.5, 1.5 Hz, 1 H, *H*₉), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1 H, *H*_{9'}), 4.64 (t, *J* = 5.0 Hz, 1 H, *H*₃), 4.10-4.00 (m, 2 H, *H*₂), 3.81-3.65 (m, 3 H, *H*_{2'}, *H*₇), 3.54-3.35 (m, 4 H, *H*₅, *H*₆), 2.10-1.95 (m, 2 H, *H*₁), 1.82 (dd, *J* = 11.0, 6.0 Hz, 2 H, *H*₄); ¹³C NMR (126 MHz, CDCl₃) δ_C 136.6 (*C*₈), 118.4 (*C*₉), 100.4 (*C*₃), 81.8 (*C*₇), 67.0 (*C*₂), 66.9 (*C*_{5/6}), 64.4 (*C*_{5/6}), 35.3 (*C*₄), 25.7 (*C*₁); HRMS (FI⁺) *m/z* calculated for [M+Na]⁺ C₁₀H₁₈NaO₄ 225.1097, found 225.1101; IR ν_{max}/cm⁻¹ (thin film) 3451 (OH), 2857 (C-H), 1379, 1242, 1139, 1091, 996.

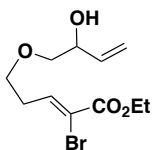
Preparation of 3-((2-hydroxybut-3-en-1-yl)oxy)propanal **193**



Acetal **192** (300 mg, 1.49 mmol) was dissolved in acetone (10 mL) and H₂O (5 mL) and HCl (1.0 M aq., 5 mL) were added, and the resulting solution stirred at RT for 12 hr. NaHCO₃ (sat. aq.) was added, and the aqueous layer extracted with EtOAc (x 3). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the title compound **193** that was unstable to further purification.

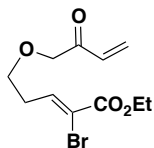
¹H NMR (200 MHz, CDCl₃) showed characteristic peaks at δ_H 9.76 (s, 1 H, *H*1), 5.78 (ddd, *J* = 17.5, 10.5, 5.5 Hz, 1 H, *H*6), 5.31 (dd, *J* = 17.5, 1.5 Hz, 1 H, *H*7), 5.16 (dd, *J* = 10.5, 1.5 Hz, 1 H, *H*7'), 4.66 (ddd, *J* = 7.5, 5.5, 2.5 Hz, 1 H, *H*5), 2.85 (br. s, OH).

Preparation of (Z)-ethyl 2-bromo-5-((2-hydroxybut-3-en-1-yl)oxy)pent-2-enoate **194**



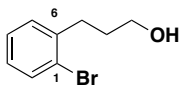
Following **General Procedure 2**, using HWE reagent **25** (664 mg, 2.1 mmol), NaH (160 mg, 4.2 mmol), NBS (370 mg, 0.21 mmol) and aldehyde **193** (300 mg, 2.1 mmol) afforded the title compound **194** (200 mg, 35%), which was contaminated with ~10% of an unknown impurity, so was taken on crude to the next step.

Preparation of (Z)-ethyl 2-bromo-5-((2-oxobut-3-en-1-yl)oxy)pent-2-enoate **195**



Following **General Procedure 3**, using DMP (145 mg, 0.34 mmol) and alcohol **194** (50 mg, 0.17 mmol) afforded the title compound **195** (32 mg, 65%), which was contaminated with ~20% of an unknown impurity which increased in concentration upon standing in solution.

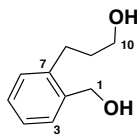
Preparation of 3-(2-bromophenyl)propan-1-ol **250**



3-(2-Bromophenyl)propionic acid (2.0 g, 8.7 mmol) was dissolved in Et₂O (10 mL) and the resulting solution was cooled to 0 °C. LiAlH₄ (1.0 M in Et₂O, 17.5 mL, 17.5 mmol) was added dropwise and the resulting solution was let warm to RT, and stirred at RT for 4 hr. The reaction mixture was cooled to 0 °C and H₂O (9 mL) was added cautiously over 30 min. The layers were separated and the aqueous layer extracted with EtOAc (x 2). The combined extracts were washed with brine, dried over MgSO₄, filtered, and the filtrate concentrated under reduced pressure to afford the crude product as a colourless oil. The residue was passed through a short pad of silica gel, and eluted with Et₂O, to afford compound **250** (1.5 g, 83%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 7.54 (d, *J* = 7.5 Hz, 1 H, *H*₂), 7.31-7.23 (m, 2 H, *H*₄, *H*₅), 7.09-7.04 (m, 1 H, *H*₃), 3.71 (t, *J* = 6.5 Hz, 2 H, *H*₉), 2.84 (t, *J* = 8.0 Hz, 2 H, *H*₇), 1.94-1.86 (m, 2 H, *H*₈), 1.65 (br. s, 1 H, OH); **¹³C NMR (126 MHz, CDCl₃)** δ_C 141.0 (*C*₆), 132.8 (*C*₂), 130.4 (*C*₅), 127.6 (*C*₃), 127.5 (*C*₄), 124.4 (*C*₁), 62.1 (*C*₉), 32.7 (*C*₈), 32.4 (*C*₇); **HRMS (EI⁺)** *m/z* calculated for [M+H]⁺ C₉H₁₁BrO 213.9993, found 213.9995; **IR** ν_{max}/cm⁻¹ (**thin film**) 2927 (C-H), 1669 (C=O), 1618 (C=O), 1578, 1447, 1342.

Preparation of 3-(2-(hydroxymethyl)phenyl)propan-1-ol **197**

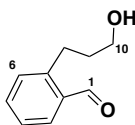


According to a literature procedure,³⁴ MeOH (40 mL) was added to a -78 °C solution of 1,2-dihydronaphthalene (2 mL, 15.4 mmol) in CH₂Cl₂ (40 mL). Ozone was bubbled through the solution until the solution turned blue, after which ozone addition was stopped and oxygen was passed through the solution until the blue colour was discharged. The cold bath was removed and sodium borohydride (1.16 g, 30.8 mmol) was added cautiously. The solution was allowed to warm to RT and was stirred for 1 hr. NH₄Cl (sat. aq.) was added slowly, the layers separated and the aqueous layer extracted with CH₂Cl₂ (x 2). The combined extracts were washed with H₂O and dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford compound **197** (2.6 g, quant.) as a colourless oil, which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ_H 7.22-7.15 (m, 2 H, ArH), 7.13-7.07 (m, 2 H, ArH), 4.72 (br. s, 1 H, OH), 4.56 (s, 2 H, H₁), 3.44 (t, *J* = 6.0 Hz, 2 H, H₁₀), 3.09 (v. br. s, 1 H, OH), 2.71 (t, *J* = 7.0 Hz, 2 H, H₈), 1.79 (quin., *J* = 6.0 Hz, 2 H, H₉); **¹³C NMR (101 MHz, CDCl₃)** δ_C 140.3 (CAr), 138.3 (CAr), 130.2 (CAr), 129.4 (CAr), 128.5 (CAr), 126.2 (CAr), 63.3 (C₁), 60.9 (C₁₀), 34.2 (C₉), 27.8 (C₈); **LRMS (ESI⁺)** 189 ([M+Na]⁺ 70%), 335 ([2M+Na]⁺ 100%).

Spectroscopic properties of this compound were consistent with the data reported in the literature.³⁵

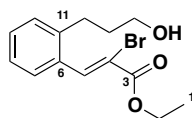
Preparation of 2-(3-hydroxypropyl)benzaldehyde **198**



According to a literature procedure,³⁴ diol **197** (500 mg, 3.0 mmol) was dissolved in PhMe (20 mL) and MnO₂ (1.3 g, 15.0 mmol) was added. The resulting suspension was stirred for 1 hr, and MnO₂ (1.30 g, 15.0 mmol) was added. The reaction mixture was stirred for a further hr and MnO₂ (1.30 g, 15.0 mmol) was added and stirred for a further hr. The reaction mixture was then filtered through Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure to afford compound **198** (440 mg, 90%) as a yellow oil, which was used crude in the next reaction.

¹H NMR (400 MHz, CDCl₃) δ_{H} 10.25 (s, 1 H, *H*₁), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H, *ArH*), 7.54 (td, *J* = 7.5, 1.5 Hz, 1 H, *ArH*), 7.41 (td, *J* = 7.5, 1.0 Hz, 1 H, *ArH*), 7.33 (d, *J* = 7.5 Hz, 1 H, *ArH*), 3.70 (t, *J* = 6.0 Hz, 2 H, *H*₁₀), 3.17 (t, *J* = 7.5 Hz, 2 H, *H*₈), 2.68 (br. s, 1 H, OH), 1.90 (quin., *J* = 6.0 Hz, 2 H, *H*₉); **¹³C NMR (101 MHz, CDCl₃)** δ_{C} 192.6 (C₁), 144.7 (C₂/7), 133.1 (C_{Ar}), 132.4 (C_{Ar}) 132.1 (C_{Ar}), 129.4 (C₂/7), 128.2 (C_{Ar}), 67.1 (C₁₀), 34.7 (C₈), 29.4 (C₉); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₀H₁₂NaO₂ 187.0730, found 187.0729; **IR ν_{max} /cm⁻¹ (thin film)** 3251 (OH), 2939 (C-H), 1723 (C=O), 1598, 1487, 1209, 1192, 1056.

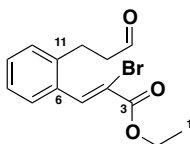
Preparation of (Z)-ethyl 2-bromo-3-(2-(3-hydroxypropyl)phenyl)acrylate **200**



Aldehyde **198** (400 mg, 2.4 mmol) was dissolved in CH₂Cl₂ (20 mL) and Wittig reagent **199** (2.0 g, 4.9 mmol) was added. The resulting solution was heated to reflux and stirred at the temperature overnight. The reaction mixture was let to cool to RT and was concentrated under reduced pressure. The resulting residue was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet ether:Et₂O (7:3)) to afford compound **200** (600 mg, 80 %) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 8.36 (s, 1 H, H₅), 7.63 (d, *J* = 7.5 Hz, 1H, H₇), 7.34 (td, *J* = 7.5, 1.0 Hz, 1 H, H₉), 7.30-7.26 (m, 2 H, H₈, H₁₀), 4.37 (q, *J* = 7.0 Hz, 2 H, H₂), 3.66 (t, *J* = 6.5 Hz, 2 H, H₁₄), 2.73 (t, *J* = 8.0 Hz, 2 H, H₁₂), 1.86-1.80 (m, 2 H, H₁₃), 1.59 (s, 1 H, OH), 1.40 (t, *J* = 7.0 Hz, 3 H, H₁); ¹³C NMR (126 MHz, CDCl₃) δ_C 163.1 (C₃), 140.8 (C₁₁), 140.7 (C₅), 133.5 (C₆), 129.5 (C₉), 129.3 (C₁₀), 129.0 (C₇), 125.9 (C₈), 116.1 (C₄), 62.8 (C₂), 62.0 (C₁₄), 33.6 (C₁₃), 29.8 (C₁₂), 14.2 (C₁); HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₁₄H₁₇BrNaO₃ 335.0253, found 335.0241; IR ν_{max}/cm⁻¹ (thin film) 3389 (OH), 2939 (C-H), 1713 (C=O), 1613, 1480, 1367, 1257.

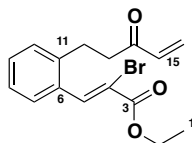
Preparation of (Z)-ethyl 2-bromo-3-(2-(3-oxopropyl)phenyl)acrylate **201**



According to a modified literature procedure,¹³ DMP (544 mg, 1.28 mmol) was added to a solution of alcohol **200** (200 mg, 0.64 mmol) in CH₂Cl₂ (15 mL), and the resulting suspension was stirred at RT for 3 hr. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a white solid. This crude product was adsorbed onto silica and purified quickly by flash column chromatography (SiO₂, pet 40-60:Et₂O (8.5:1.5)) to afford compound **201** (180 mg, 91%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 9.82 (s, 1 H, *H*14), 8.34 (s, 1 H, *H*5), 7.59 (d, *J* = 7.5 Hz, 1H, *H*7), 7.40-7.26 (m, 3 H, *H*8, *H*9, *H*10), 4.39 (q, *J* = 7.0 Hz, 2 H, *H*2), 2.97 (t, *J* = 8.0 Hz, 2 H, *H*12), 2.75 (t, *J* = 8.0 Hz, 2 H, *H*13), 1.42 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 200.9 (*C*14), 162.9 (*C*3), 140.4 (*C*11), 139.1 (*C*5), 133.7 (*C*6), 129.6 (*C*8/9/10), 129.2 (*C*8/9/10), 129.2 (*C*7), 129.1 (*C*8/9/10), 117.0 (*C*4), 62.9 (*C*2), 44.6 (*C*13), 25.8 (*C*12), 14.2 (*C*1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₄H₁₅BrNaO₃ 333.0097, found 333.0089; **IR** ν_{max} /cm⁻¹ (thin film) 2366 (C-H), 1720 (C=O), 1257, 1038, 763.

Preparation of (Z)-ethyl 2-bromo-3-(2-(3-oxopent-4-en-1-yl)phenyl)acrylate **202**

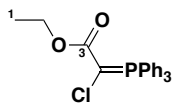


Aldehyde **201** (100 mg, 0.30 mmol) was dissolved in THF (5 mL), and the reaction mixture cooled to -78 °C. Vinyl magnesium bromide (1.0 M in THF, 0.4 mL, 0.4 mmol) was added, the reaction mixture stirred at this temp for 30 min and then the reaction mixture was let warm to RT. The solution was diluted with EtOAc, washed with NH₄Cl, the layers separated and the aqueous layer extracted with EtOAc (x 2). The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. The crude product (100 mg, 0.30 mmol) was dissolved in CH₂Cl₂ (10 mL), DMP (251 mg, 0.6 mmol) was added and the resulting suspension was stirred at RT for 3 hr. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a white solid. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **202** (90 mg, 89%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_H 8.34 (s, 1 H, H₅), 7.59 (d, J = 7.5 Hz, 1H, H₇), 7.33 (t, J = 7.5 Hz, 1 H, H₉), 7.30-7.24 (m, 2 H, H₈, H₁₀), 6.34 (dd, J = 18.0, 10.5 Hz, 1 H, H₁₅), 6.20 (d, J = 18.0 Hz, 1 H, H₁₆), 5.84 (d, J = 10.5 Hz, 2 H, H_{16'}), 4.37 (q, J = 7.0 Hz, 2 H, H₂), 2.94 (t, J = 7.0 Hz, 2 H, H₁₂), 2.84 (t, J = 7.5 Hz, 2 H, H₁₃), 1.40 (t, J = 7.0 Hz, 3 H, H₁); ¹³C NMR (126 MHz, CDCl₃) δ_C 199.3 (C₁₄), 162.9 (C₃), 140.6 (C₅), 139.8 (C₁₁),

136.3 (C15), 133.6 (C6), 129.5 (C9), 129.0 (C7) 129.2 (C10), 128.6 (C16), 126.2 (C8), 116.8 (C4), 62.9 (C2), 40.3 (C13), 27.6 (C12), 14.2 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₆H₁₇BrNaO₃ 359.0253, found 359.0246; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2366 (C-C), 2357 (C=C), 1725 (C=O), 1412, 1376, 1217.

Preparation of ethyl 2-chloro-2-(triphenylphosphoranylidene)acetate **203**

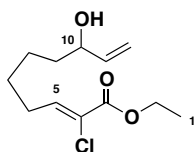


According to a literature procedure,³⁶ a solution of diacetoxyiodobenzene (3.60 g, 11.0 mmol) and fluoroboric acid (1.49 mL, 11.4 mmol) in MeOH (10 mL) was added dropwise to a 0 °C solution of ethyl 2-(triphenylphosphoranylidene)acetate (4.00 g, 11.4 mmol) in MeOH (10 mL) over 20 min. The resulting solution was stirred at this temperature for 90 min, and then filtered under reduced pressure, washing the precipitate with Et₂O (x 3). The crude precipitate was dissolved in CH₂Cl₂ (60 mL), tetramethylammonium chloride (1.40 g, 12.5 mmol) was added and the resulting solution stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the residue dissolved in acetone (50 mL). This was filtered and the filtrate concentrated under reduced pressure to afford the crude product. This crude product was recrystallised from acetone-hexane to afford compound **203** (3.4 g, 78%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ_H 7.90-7.25 (m, 15 H, ArH), 4.04 (q, *J* = 7.0 Hz, 2 H, H₂), 1.05 (t, *J* = 7.0 Hz, 3 H, H₁); **¹³C NMR (101 MHz, CDCl₃)** δ_C 163.4 (C3), 132.2 (CAr), 132.0 (CAr), 130.5 (CAr), 129.7 (CAr), 118.0 (C4), 63.2 (C2), 13.7 (C1); **Mpt** 145-147 °C (lit: 151-152 °C).

Spectroscopic properties of this compound were consistent with the data reported in the literature.³⁰

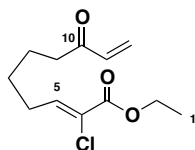
Preparation of (Z)-ethyl 2-chloro-8-hydroxydeca-2,9-dienoate **204**



Wittig reagent **203** (323 mg, 0.850 mmol) was added to a solution of aldehyde **23** (100 mg, 0.70 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture brought to reflux for 24 hr. The reaction mixture was then allowed to cool to RT and concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO_2 , pet 40-60:Et₂O (8:2)) to afford compound **204** (110 mg, 65%) as a colourless oil.

¹H NMR (400 MHz, CDCl_3) δ_{H} 7.07 (t, $J = 7.0$ Hz, 1 H, H_5), 5.87 (ddd, $J = 17.5, 10.5, 6.5$ Hz, 1 H, H_{11}), 5.23 (dd, $J = 17.5, 1.0$ Hz, 1 H, H_{12}), 5.12 (dd, $J = 10.5, 1.0$ Hz, 1 H, H_{12}'), 4.28 (q, $J = 7.0$ Hz, 2 H, H_2), 4.05 (dd, $J = 6.5, 6.0$ Hz, 1 H, H_{10}), 2.38 (q, $J = 7.0$ Hz, 2 H, H_6), 1.65-1.40 (m, 7 H, H_7, H_8, H_9, OH), 1.34 (t, $J = 7.0$ Hz, 3 H, H_1); **¹³C NMR (101 MHz, CDCl_3)** δ_{C} 162.5 (C_3), 143.9 (C_5), 141.9 (C_{11}), 141.1 (C_4), 115.5 (C_{12}), 73.5 (C_{10}), 62.6 (C_2), 36.8 (C_9), 29.5 (C_6), 27.7 (C_7), 25.2 (C_8), 14.2 (C_1); **HRMS (ESI⁺)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{19}^{35}\text{ClNaO}_3$ 269.0915, found 269.0925; **IR ν_{max} /cm⁻¹ (thin film)** 3400 (br., OH), 2932 (C-H), 1718 (C=O), 1630 (C=C), 1265, 1096, 1045.

Preparation of (Z)-ethyl 2-chloro-8-oxodeca-2,9-dienoate **205**



According to a modified literature procedure,¹³ DMP (150 mg, 0.350 mmol) was added to a solution of alcohol **204** (50 mg, 0.200 mmol) in CH₂Cl₂ (5 mL), and the resulting solution was stirred at RT for 1 hr. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a white solid. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **205** (47 mg, quant.) as a colourless oil.

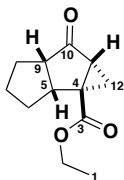
¹H NMR (400 MHz, CDCl₃) δ_{H} 7.06 (t, J = 7.0 Hz, 1 H, H_5), 6.35 (dd, J = 17.5, 10.5 Hz, 1 H, H_{11}), 6.20 (dd, J = 17.5, 1.0 Hz, 1 H, H_{12}), 5.83 (dd, J = 10.5, 1.0 Hz, 1 H, $H_{12'}$), 4.28 (q, J = 7.0 Hz, 2 H, H_2), 2.62 (t, J = 7.0 Hz, 2 H, H_9), 2.38 (q, J = 7.0 Hz, 2 H, H_6), 1.69 (quin., J = 7.0 Hz, 2 H, H_8), 1.53 (quin., J = 7.0 Hz, 2 H, H_7), 1.33 (t, J = 7.0 Hz, 3 H, H_1);

¹³C NMR (101 MHz, CDCl₃) δ_{C} 201.6 (C10), 163.4 (C3), 145.2 (C4), 142.5 (C5), 137.3 (C11), 128.9 (C12), 62.5 (C2), 39.3 (C9), 29.3 (C6), 27.4 (C8), 23.6 (C7), 14.2 (C1);

(ESI⁺) m/z calculated for [M+Na]⁺ C₁₂H₁₇³⁵ClNaO₃ 267.0758, found 267.0769;

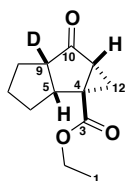
IR ν_{max} /cm⁻¹ (thin film) 2938 (C-H), 1725 (C=O), 1681 (C=O), 1630 (C=C), 1401, 1262, 1044.

Alternative preparation of (1a*S**, 1b*R**, 4a*S**, 5a*R**)-ethyl 5-oxooctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate **21**



Following **General Procedure 4**, using cyclisation precursor **205** (47 mg, 0.19 mmol), toluene (5 mL), KOH (45 mg, 0.80 mmol), tetrabutylammonium bisulfate (9 mg, 0.02 mmol) at RT afforded compound **77** (27 mg, 65%) as a colourless oil with identical spectroscopic properties to those given previously.

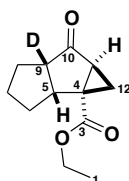
Preparation of (1aS*, 1bR*, 4aS*, 5aR*)-ethyl 5-oxooctahydro-1H-cyclopropa[a]pentalene-1a-carboxylate-4a-d **84**



Sodium (6 mg, 0.25 mmol) was dissolved in ethanol-OD (3 mL) and the reaction mixture stirred until the sodium was fully dissolved. Ketone **77** (50 mg, 0.25 mmol) was dissolved in ethanol-OD (2 mL) and added dropwise into the solution of sodium ethoxide in ethanol. The resulting solution was stirred for 24 hr, quenched with D₂O and extracted with Et₂O (x 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **84** (48 mg, 92%).

¹H NMR (500 MHz, CDCl₃) δ_{H} 4.09 (q, $J = 7.0$ Hz, 2 H, *H*₂), 3.51-3.46 (m, 1 H, *H*₅), 2.36 (dd, $J = 10.0, 4.5$ Hz, 1 H, *H*₁₁), 2.02-1.94 (m, 1 H, *H*₆), 1.83-1.67 (m, 3 H, *H*₇, *H*₈, *H*₁₂), 1.59-1.51 (m, 2 H, *H*_{6'}, *H*_{7'}), 1.43-1.37 (m, 1 H, *H*_{8'}), 1.32 (t, $J = 5.0$ Hz, 1 H, *H*_{12'}), 1.19 (t, $J = 7.0$ Hz, 3 H, *H*₁); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 213.2 (*C*₁₀), 172.1 (*C*₃), 61.1 (*C*₂), {53.8, 53.6, 53.4, 1:1:1 t, $J_{\text{C-D}} = 20.5$ Hz, (*C*₉)}, 40.2 (*C*_{5/11}), 40.1 (*C*_{5/11}), 37.7 (*C*₄), 30.9 (*C*₆), 30.1 (*C*₈), 29.5 (*C*₇), 22.7 (*C*₁₂), 14.2 (*C*₁); **HRMS (ESI⁺)** m/z calculated for [*M*+*H*]⁺ C₁₂H₁₆²HO₃ 210.1235, found 210.1236; **IR ν_{max} /cm⁻¹ (thin film)** 2957 (C-C), 1720 (C=O), 1451, 1380, 1247, 1202, 1132.

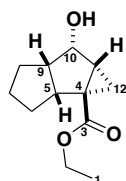
Preparation of (1aR*, 1bR*, 4aS*, 5aS*)-ethyl 5-oxooctahydro-1H-cyclopropa[a]pentalene-1a-carboxylate-4a-d 251



Sodium (6 mg, 0.25 mmol) was dissolved in ethanol-OD (3 mL) and the reaction mixture stirred until the sodium was fully dissolved. Ketone **21** (50 mg, 0.25 mmol) was dissolved in ethanol-OD (2 mL) and added dropwise into the solution of sodium ethoxide in ethanol. The resulting solution was stirred for 24 hr, quenched with D₂O and extracted with Et₂O (x 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **251** (50 mg, 96%).

¹H NMR (500 MHz, CDCl₃) δ_H 4.17-4.02 (m, 2 H, H₂), 2.83 (t, *J* = 8.5 Hz, 1 H, H₅), 2.36 (dd, *J* = 9.5, 4.0 Hz, 1 H, H₁₁), 2.18 (dtd, *J* = 13.0, 8.0, 4.0 Hz, 1 H, H₆), 1.75 (dd, *J* = 8.5, 6.0 Hz, 2 H, H₈), 1.69 (dd, *J* = 9.5, 4.5 Hz, 1 H, H₁₂), 1.65-1.56 (m, 1 H, H₇), 1.48-1.40 (m, 1 H, H_{7'}), 1.31 (t, *J* = 4.5 Hz, 1 H, H_{12'}), 1.20-1.16 (m, 1 H, H_{6'}), 1.19 (t, *J* = 7.0 Hz, 3 H, H₁); ¹³C NMR (126 MHz, CDCl₃) δ_C 213.7 (C₁₀), 171.4 (C₃), 60.9 (C₂), {48.8, 48.6, 48.4, 1:1:1 t, *J*_{C-D} = 20.5 Hz (C₉)}, 43.5 (C₅), 36.7 (C₄), 34.8 (C₁₁), 31.9 (C₆), 26.7 (C_{7/8}), 26.6 (C_{7/8}), 22.7 (C₁₂), 14.2 (C₁); HRMS (ESI⁺) *m/z* calculated for [M+H]⁺ C₁₂H₁₆²HO₃ 210.1235, found 210.1236; IR ν_{max}/cm⁻¹ (thin film) 2958 (C-C), 1721 (C=O), 1449, 1375, 1234, 1147, 1017.

Preparation of (1a*S,1b*R**,4a*S**,5*S**,5a*R**)-ethyl 5-hydroxyoctahydro-1*H*-cyclopropa[*a*]pentalene-1a-carboxylate **207****

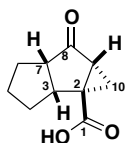


Ketone **77** (50 mg, 0.25 mmol) was dissolved in THF (5 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. L-Selectride (1.0 M in THF, 0.25 mL) was added, the reaction stirred for 5 min at $-78\text{ }^{\circ}\text{C}$ and then quenched with H_2O . The reaction mixture was allowed to warm to RT and then extracted with Et_2O ($\times 3$). The combined organics were dried over MgSO_4 , filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO_2 , pet 40-60: Et_2O (6:4)) to afford compound **207** (50 mg, 95%) as a single diastereomer.

^1H NMR (500 MHz, CDCl_3) δ_{H} 4.65 (dd, $J = 9.5, 5.5\text{ Hz}$, 1 H, H_{10}), 4.03 (q, $J = 7.0\text{ Hz}$, 2 H, H_2), 3.24-3.17 (m, 1 H, H_5), 2.69-2.62 (m, 1 H, H_9), 2.21 (dt, $J = 9.0, 5.5\text{ Hz}$, 1 H, H_{11}), 1.98-1.93 (m, 1 H, H_6), 1.83-1.78 (m, 1 H, H_8), 1.50-1.35 (m, 5 H, $H_{6'}$, $H_{8'}$, H_7 , OH), 1.25-1.22 (m, 1 H, H_{12}), 1.16 (t, $J = 7.0\text{ Hz}$, 3 H, H_1), 1.12 (t, $J = 5.5\text{ Hz}$, 1 H, $H_{12'}$); **^{13}C NMR (126 MHz, CDCl_3)** δ_{C} 174.9 (C3), 72.5 (C10), 60.5 (C2), 48.8 (C9), 44.1 (C5), 38.8 (C11), 36.5 (C4), 30.8 (C6), 28.9 (C8), 27.7 (C7), 16.8 (C12), 14.3 (C1); **HRMS (ESI $^+$)** m/z calculated for $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{18}\text{NaO}_3$ 233.1148, found 233.1155; **IR ν_{max} /cm $^{-1}$ (thin film)** 3434 (OH), 2955 (C-H), 1718 (C=O), 1449, 1382, 1286.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (1a*S,1b*R**,4a*S**,5a*R**)-5-oxooctahydro-1*H*-cyclopropa[*a*]pentalene-1a-carboxylic acid **208****



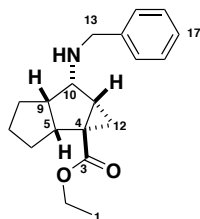
Ketone **77** (50 mg, 0.25 mmol) was dissolved in 3:1 THF:H₂O (6 mL:2 mL) and LiOH (5 mg, 0.25 mmol) was added. The reaction was stirred for 4 hr, quenched with NH₄Cl (sat. aq.) and extracted with EtOAc (× 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (7:3)) to afford compound **208** (41 mg, 91%) as a single diastereomer.

¹H NMR (500 MHz, CDCl₃) δ_H 3.50-3.45 (m, 1 H, *H*3), 2.82 (q, *J* = 10.0 Hz, 1 H, *H*7), 2.45 (ddd, *J* = 10.5, 5.0, 1.5 Hz, 1 H, *H*9), 2.04-1.96 (m, 1 H, *H*4), 1.85-1.77 (m, 2 H, *H*10, *H*6), 1.73-1.67 (m, 1 H, *H*5), 1.60-1.50 (m, 2 H, *H*4', *H*5'), 1.45-1.42 (m, 1 H, *H*6'), 1.40 (t, *J* = 5.0 Hz, 1 H, *H*10);^j ¹³C NMR (126 MHz, CDCl₃) δ_C 212.6 (C8), 179.0 (C1), 54.1 (C7), 40.8 (C9), 39.9 (C3), 37.2 (C2), 30.9 (C4), 30.2 (C6), 29.7 (C5), 19.1 (C10); HRMS (ESI⁺) *m/z* calculated for [M+Na]⁺ C₁₀H₁₂NaO₃ 203.0679, found 203.0682; IR ν_{max}/cm⁻¹ (thin film) 3232 (OH), 2958 (C-H), 1728 (C=O), 1448, 1228, 1156.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

^j COOH was not observed in the ¹H NMR spectrum

Preparation of (1a*S,1b*R**,4a*S**,5*S**,5a*R**)-ethyl 5-(benzylamino)octahydro-1*H*-cyclopropa[*a*]pentalene-1a-carboxylate **209****



Ketone **77** (130 mg, 0.63 mmol) was dissolved in THF (10 mL) and benzylamine (60 μ L, 0.50 mmol) and AcOH (26 μ L, 0.50 mmol) were added. The reaction mixture was stirred overnight, then NaBH₄ (10 mg, 0.25 mmol) was added. The reaction was quenched with NH₄Cl (sat. aq.) and extracted with EtOAc (x 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **209** (54 mg, 75% based on BnNH₂) as a single diastereomer.

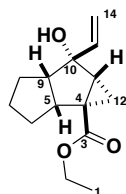
¹H NMR (500 MHz, CDCl₃) δ_{H} 7.40-7.33 (m, 3 H, Ar*H*), 7.30-7.26 (m, 2 H, Ar*H*), 4.12 (q, *J* = 7.0 Hz, 2 H, *H*₂), 3.85 (q, *J* = 12.5 Hz, 2 H, *H*₁₃), 3.71 (dd, *J* = 9.0, 5.5 Hz, 1 H, *H*₁₀), 3.33-3.25 (m, 1 H, *H*₅), 2.77-2.66 (m, 1 H, *H*₉), 2.21 (dt, *J* = 9.0, 5.0 Hz, 1 H, *H*₁₁), 2.10-2.03 (m, 1 H, *H*₆), 1.67-1.60 (m, 1 H, *H*₇), 1.56-1.45 (m, 1 H, *H*₈), 1.46-1.31 (m, 3 H, *H*_{6'}, *H*_{7'}, *H*_{8'}), 1.31-1.28 (m, 1 H, *H*₁₂), 1.25 (t, *J* = 7.0 Hz, 1 H, *H*₁), 1.07 (t, *J* = 5.0 Hz, 1 H, *H*_{12'});^k **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 154.4 (C₃), 140.4 (CAr), 128.5 (CAr), 128.2 (CAr), 127.0 (CAr), 60.4 (C₂), 58.8 (C₁₀), 53.0 (C₁₃), 47.5 (C₉), 44.0 (C₅), 37.6 (C₁₁), 36.6 (C₄), 30.6 (C₆), 28.6 (C₇), 28.2 (C₈), 17.2 (C₁), 14.3 (C₁₂); **HRMS (ESI⁺)** *m/z* calculated for

^k NH not observed in ¹H NMR

[M+H]⁺ C₁₉H₂₆NO₂ 300.1958, found 30.1963; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2951, 2316, 2314, 1703 (C=O), 1496, 1454, 1380, 1288, 1233, 1167, 1038.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (1aS*,1bR*,4aS*,5S*,5aR*)-ethyl 5-hydroxy-5-vinyloctahydro-1H-cyclopropa[a]pentalene-1a-carboxylate **210**

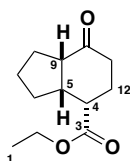


Ketone **77** (50 mg, 0.25 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Vinylmagnesium bromide (1.0 M in THF, 0.25 mL) was added, the reaction stirred for 1 hr and then quenched with NH₄Cl (sat. aq.). The reaction mixture was allowed to warm to RT and then extracted with EtOAc (× 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40:60:EtO (8:2)) to afford compound **210** (46 mg, 78%) as a single diastereomer.

¹H NMR (500 MHz, CDCl₃) δ_H 6.07 (dd, *J* = 17.5, 10.5 Hz, 1 H, *H*13), 5.16 (dd, *J* = 17.5, 1.0 Hz, 1 H, *H*14), 4.96 (dd, *J* = 10.5, 1.0 Hz, 1 H, *H*14'), 4.04 (q, *J* = 7.0 Hz, 2 H, *H*2), 3.24-3.19 (m, 1 H, *H*5), 2.41 (q, *J* = 9.0 Hz, 1 H, *H*9), 2.05 (dd, *J* = 9.0, 5.0 Hz, 1 H, *H*11), 2.00-1.95 (m, 1 H, *H*6), 1.85-1.80 (m, 1 H, *H*7), 1.62 (br. s, 1 H, OH), 1.53-1.46 (m, 2 H, *H*6', *H*8), 1.45-1.39 (m, 2 H, *H*8', *H*7') 1.26 (ddd, *J* = 9.0, 5.0, 1.5 Hz, 1 H, *H*12), 1.21 (t, *J* = 5.0 Hz, 1 H, *H*12'), 1.16 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_C 173.7 (C3), 145.9 (C13), 109.8 (C14), 80.0 (C10), 60.5 (C2), 54.7 (C9), 43.7 (C5), 42.0 (C11), 37.0 (C4), 30.9 (C6), 28.7 (C8, C7), 17.4 (C12), 14.2 (C1); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₄H₂₀NaO₃ 259.1305, found 259.1312; **IR** ν_{max}/cm⁻¹ (thin film) 3483 (OH), 2957 (C-H), 1719 (C=O), 1449, 1382, 1285.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (3aR*,4R*,7aS*)-ethyl 7-oxooctahydro-1H-indene-4-carboxylate **211**



N.B. Magnetic stirring bars were not used in this reaction, due to their ability to quench the reagent.

Preparation of sodium naphthalenide:

Naphthalene (256 mg, 2.0 mmol) was dissolved in THF (10 mL) and freshly cut Na (92 mg, 4.0 mmol) was added. The colourless solution was sonicated under Ar for 30 min, with intermittent swirling, after which time the solution had turned deep green and the Na was consumed. This was used immediately, and assumed to be a 0.2 M solution of sodium naphthalenide.

*Preparation of **211**:*

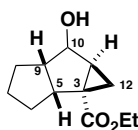
Ketone **77** (50 mg, 0.2 mmol) was dissolved in THF (6 mL) and cooled to -78°C . Sodium naphthalenide (~ 4 eq.) was added dropwise, with intermittent swirling, until the green colour persisted in the reaction mixture. After this time, MeOH (1 drop) was added and the reaction mixture was slowly warmed to RT. H_2O was added and extracted with Et_2O ($\times 3$). The combined organics were dried over MgSO_4 , filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO_2 , pet 40-60: Et_2O (8:2)) to afford compound **211** (32 mg, 75%) as an inseparable 4:1 mixture of isomers. The relative stereochemistry of the minor isomer could not be ascertained.

For clarity, the minor isomer was omitted from the NMR data assignments:

¹H NMR (500 MHz, CDCl₃) δ_{H} 4.23-4.15 (m, 2 H, *H*2), 3.13 (dt, *J* = 12.5, 4.5 Hz, 1 H, *H*4), 2.86-2.79 (m, 1 H, *H*5), 2.76-2.69 (m, 1 H, *H*9), 2.49 (ddd, *J* = 14.5, 4.0, 3.0 Hz, 1 H, *H*11), 2.41-2.32 (m, 2 H, *H*11', *H*8), 2.18-2.12 (m, 1 H, *H*12), 2.11-2.01 (m, 1 H, *H*12'), 1.71-1.65 (m, 1 H, *H*7), 1.58-1.52 (m, 3 H, *H*8', *H*7', *H*6), 1.32-1.26 (m, 1 H, *H*6'), 1.29 (t, *J* = 7.0 Hz, 3 H, *H*1); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 211.1 (*C*10), 174.7 (*C*3), 60.6 (*C*2), 52.4 (*C*9), 44.5 (*C*5), 42.4 (*C*4), 40.1 (*C*11), 26.9 (*C*6), 26.6 (*C*8), 24.9 (*C*12), 23.5 (*C*7), 15.3 (*C*1); **HRMS (ESI⁺)** *m/z* calculated for [*M*+Na]⁺ C₁₂H₁₈NaO₃ 233.1148, found 233.1145; **IR** ν_{max} /cm⁻¹ (**thin film**) 2953 (C-H), 1712 (C=O), 1710 (C=O), 1595, 1434, 1375, 1314, 1269, 1194.

N.B. Stereochemistry assigned by nOe analysis similar to compound **77**

Preparation of (1aR*,1bR*,4aS*,5aS*)-ethyl 5-hydroxyoctahydro-1H-cyclopropa-[a]pentalene-1a-carboxylate **212**



Ketone **21** (50 mg, 0.25 mmol) was dissolved in THF (5 mL) and cooled to -78 °C. L-Selectride (1.0 M in THF, 0.25 mL) was added, the reaction stirred for 5 min at -78 °C and then quenched with H₂O. The reaction mixture was allowed to warm to RT and then extracted with Et₂O (× 3). The combined organics were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product. This was purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (6:4)) to afford compound **212** (50 mg, 95%) as a 1:1 mixture of diastereomers.

¹H NMR (400 MHz, CDCl₃) δ_H 4.45 (d, *J* = 6.0 Hz, 1 H, *H*₁₀), 4.34-4.30 (m, 1 H, *H*_{10'}), 4.12-3.93 (m, 4 H, *H*₂), 2.47-2.39 (m, 2 H, *H*₅), 2.18-2.05 (m, 4 H, *H*₉, *H*₈), 2.02-1.90 (m, 2 H, *H*₁₁), 1.79-1.72 (m, 2 H, *H*_{7/6}), 1.63-1.30 (m, 8 H, *H*_{6/7}, *H*_{8'}), 1.15-1.18 (m, 2 H, *H*₁₂), 1.18 (t, *J* = 7.0 Hz, 3 H, *H*₁), 1.86 (t, *J* = 7.0 Hz, 3 H, *H*_{1'}); 0.75-0.70 (m, 2 H, *H*_{12'}), **¹³C NMR (101 MHz, CDCl₃)** δ_C 173.9 (C3), 73.4 (C10), 60.3 (C2), 48.0 (C5), 46.1 (C9), 35.1 (C11), 32.2 (C8), 27.7 (C6/7), 22.4 (C6/7), 19.4 (C12), 13.9 (C1);¹ **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₂H₁₈NaO₃ 233.1148, found 233.1158; **IR** ν_{max}/cm⁻¹ (thin film) 3705 (OH), 2976, 1715 (C=O), 1549, 1478, 1257, 1184.

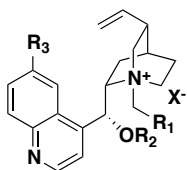
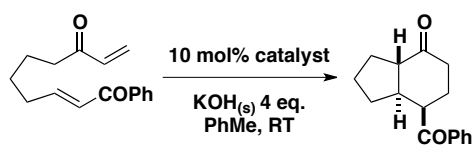
N.B. When NaBH₄ was used as the reducing agent, 1:1 d.r. was also obtained

¹ C4 was not observed in the ¹³C spectrum

Asymmetric preparation of 7-benzoylhexahydro-1*H*-inden-4(2*H*)-one 130

Initial Catalyst Screen: using 10 mol% catalyst, 4 eq. KOH_(s) and PhMe (0.5 mL/10 mg).

All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC. Enantiomers were separated by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm x 250 mm, 5:95 2-propanol:hexane, 1.0 mL/min, retention times of enantiomers: 10.59 min, 12.15 min.}



2 R₁ = Ph, R₂ = H, R₃ = H, X = Cl

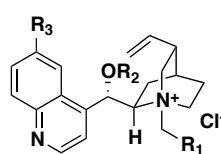
214 R₁ = 9-anthracenyl, R₂ = H, R₃ = H, X = Cl

215 R₁ = (4-CF₃)C₆H₄, R₂ = H, R₃ = H, X = Br

216 R₁ = 9-anthracenyl, R₂ = allyl, R₃ = H, X = Br

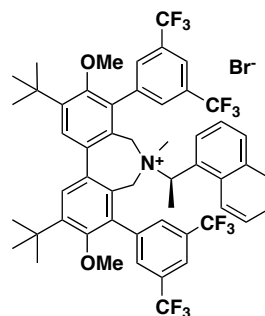
217 R₁ = Ph, R₂ = allyl, R₃ = H, X = Br

218 R₁ = Ph, R₂ = H, R₃ = OMe, X = Cl



219 R₁ = Ph, R₂ = H, R₃ = H

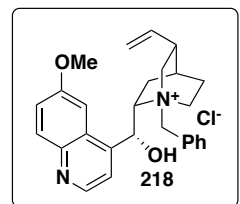
220 R₁ = (4-CF₃)C₆H₄, R₂ = H, R₃ = H



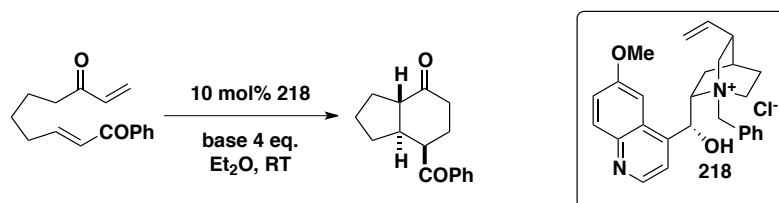
221

Entry	Catalyst	ee (%)
1	2	(+) 10
2	214	(+) 20
3	215	(+) 5
4	219	(-) 10
5	220	(-) 17
6	216	(+) 5
7	217	(+) 10
8	218	(+) 37
9	221	(-) 30

Reaction scheme showing the intramolecular aldol condensation of 2-(2-oxocyclohexyl)acrylaldehyde catalyzed by 218 to form 2-(2-oxocyclohexyl)acrylaldehyde. The reaction conditions are 10 mol% 218, KOH(s) 4 eq., solvent, RT. The structure of 218 is shown as a complex organic molecule with a quaternary ammonium cation and a chloride counterion.

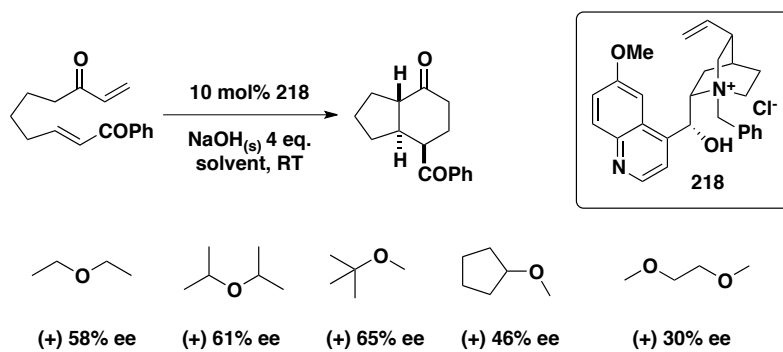


Initial Base Screen: using 10 mol% *N*-benzyl quininium chloride, 4 eq. base and Et₂O (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.

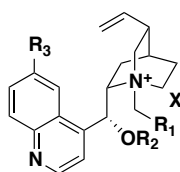
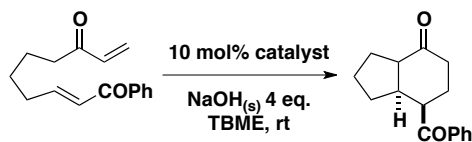


Entry	Base	ee (%)	Reaction time
1	KOH _(s)	(+) 45	2 hr
2	KOH _(aq)	(+) 18	4 hr
3	NaOH _(s)	(+) 58	2 hr
4	CsOH.H ₂ O _(s)	(+) 41	2 hr
5	K ₂ CO _{3(s)}	(+) 45	Overnight
6	Cs ₂ CO _{3(s)}	(+) 48	Overnight
7	KH ₂ PO _{4(s)}	No product	96 hr
8	NaOMe _(s)	(+) 51	2 hr

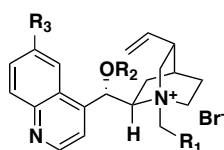
Second Solvent Screen: using 10 mol% *N*-benzyl quininium chloride, 4 eq. KOH_(s) and solvent (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



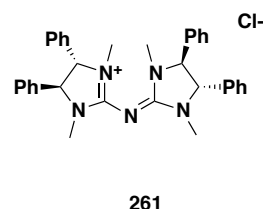
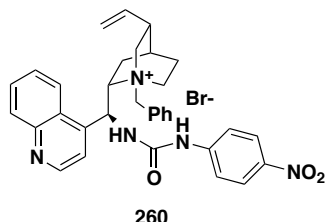
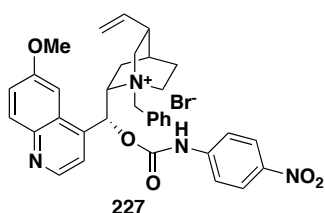
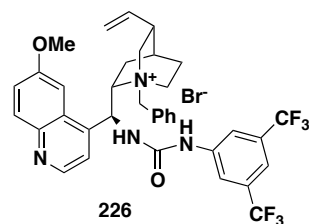
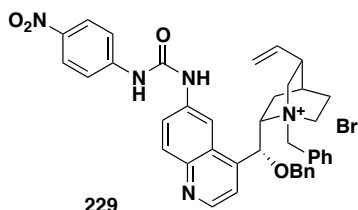
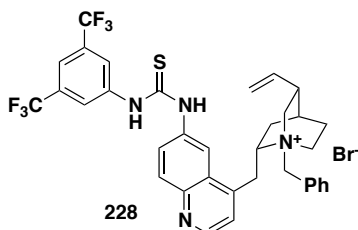
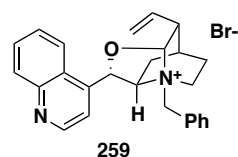
Second Catalyst Screen: using 10 mol% catalyst, 4 eq. KOH_(s) and PhMe (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



- 218 R₁ = Ph, R₂ = H, R₃ = OMe, X = Cl
 223 R₁ = Ph, R₂ = H, R₃ = OⁱPr, X = Br
 224 R₁ = Ph, R₂ = Bn, R₃ = OH, X = Br
 225 R₁ = Ph, R₂ = allyl, R₃ = OMe, X = Br
 252 R₁ = 9-anthracenyl, R₂ = Me, R₃ = H, X = Br
 253 R₁ = 4-NO₂Ph, R₂ = H, R₃ = H, X = Br
 254 R₁ = 3-FPh, R₂ = H, R₃ = H, X = Br

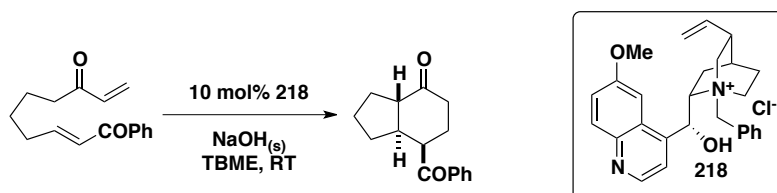


- 255 R₁ = C₆F₅, R₂ = H, R₃ = H
 239 R₁ = 3,5-CF₃Ph, R₂ = H, R₃ = H
 256 R₁ = 4-CF₃Ph, R₂ = Me, R₃ = H
 257 R₁ = 4-FPh, R₂ = H, R₃ = H
 258 R₁ = 4-NO₂Ph, R₂ = H, R₃ = H
 236 R₁ = 2,3,4-FPh, R₂ = H, R₃ = H



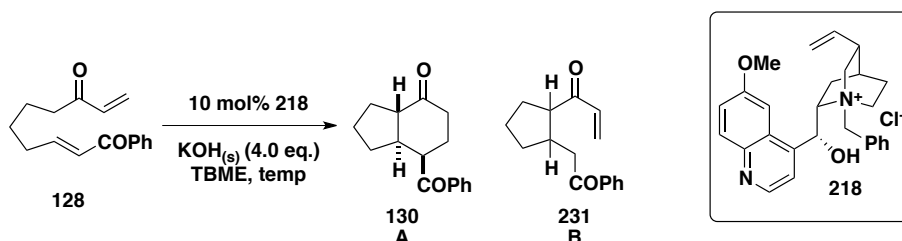
Catalyst	ee (%)	Catalyst	ee (%)
218	(+) 65	257	(-) 10
223	(+) 62	258	(-) 6
224	0	236	(-) 5
225	0	259	(-) 1
252	(+) 10	226	(-) 7
253	(+) 5	228	0
254	(+) 10	229	(+) 10
255	No reaction	227	(+) 10
239	(-) 15	260	(-) 5
256	(-) 10	261	No reaction

Base Equivalents Screen: using 10 mol% *N*-benzyl quininium chloride, {see table for} eq. NaOH_(s) and TBME (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



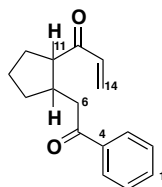
Entry	Equivalents NaOH _(s)	ee (%)
1	0.1	53
2	1	56
3	4	65
4	10	64

Reaction Temperature Screen: using 10 mol% *N*-benzyl quininium chloride, 4 eq. NaOH_(s) and TBME (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



Entry	Temperature (°C)	Product	ee (%)
1	-30	n.r. after 3 days	-
2	-15	B	-
3	0	A	(+) 60
4	RT	A	(+) 65

The reaction at -15 °C was performed on a 50 mg scale to allow isolation of intermediate B **231**.

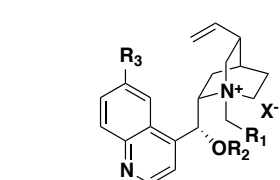
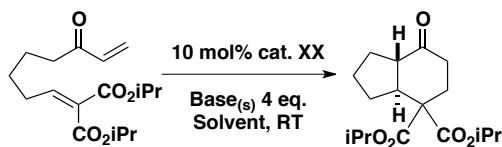


¹H NMR (400 MHz, CDCl₃) δ_H 7.91 (d, *J* = 7.5 Hz, 2 H, *H*3), 7.48 (tt, *J* = 7.5, 2.0 Hz, 1 H, *H*1), 7.39 (t, *J* = 7.5 Hz, 2 H, *H*2), 6.41 (dd, *J* = 17.5, 10.5 Hz, 1 H, *H*13), 6.20 (dd, *J* = 17.5, 1.5 Hz, 1 H, *H*14), 5.73 (dd, *J* = 10.5, 1.5 Hz, 1 H, *H*14'), 3.08 (dd, *J* = 15.5, 6.0 Hz, 1 H, *H*6), 2.90-2.71 (m, 4 H, *H*6', *H*7, *H*11), 2.05-1.89 (m, 2 H, *H*8, *H*10), 1.74-1.60 (m, 3 H, *H*9 *H*10'), 1.35-1.05 (m, 1 H, *H*8'); **¹³C NMR (101 MHz, CDCl₃)** δ_C 202.3 (*C*12), 199.7 (*C*5), 136.8 (*C*4), 135.8 (*C*13), 133.1 (*C*1), 128.6 (*C*2), 128.3 (*C*3), 128.2 (*C*14), 54.8 (*C*11), 43.8

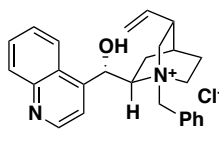
(C6), 38.4 (C7), 32.5 (C8), 30.0 (C10), 24.7 (C9); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺
C₁₆H₁₈NaO₂ 265.1199, found 265.1194; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (**thin film**) 2935 (C-H), 1716 (C=O),
1659 (C=C), 1337, 1228, 1192.

Attempted asymmetric preparation of diisopropyl 7-oxohexahydro-1*H*-indene-4,4(2*H*)-dicarboxylate 105

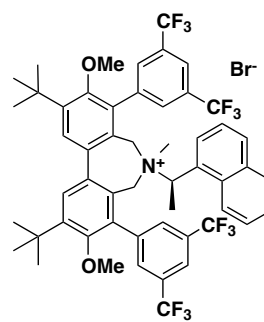
Catalyst, Base and Solvent Screen: using 10 mol% catalyst, 4 eq. base and solvent (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



- 263 R₁ = Ph, R₂ = H, R₃ = H, X = Br
 2 R₁ = Ph, R₂ = H, R₃ = H X = Cl
 264 R₁ = Ph, R₂ = Bn, R₃ = OMe, X = Br
 217 R₁ = Ph, R₂ = allyl, R₃ = H, X = Br



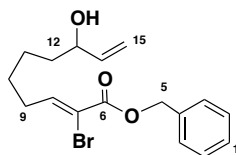
219



221

Catalyst	Solvent	Base	Product
263	PhMe	KOH	decomposed
2	PhMe	K ₂ CO ₃	SM
264	PhMe	KOH	decomposed
264	Et ₂ O	NaOH	SM
217	PhMe	KOH	decomposed
219	PhMe	KOH	decomposed
221	PhMe	K ₂ CO ₃	SM

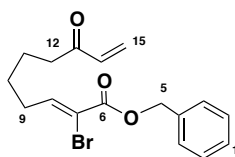
Preparation of (Z)-benzyl 2-bromo-8-hydroxydeca-2,9-dienoate **233**



NaH (60% dispersion in mineral oil, 112 mg, 2.80 mmol) was added to a solution of HWE reagent **25** (156 mg, 1.43 mmol) in THF (10 mL), and the reaction mixture stirred for 5 min. NBS (250 mg, 1.43 mmol) was added and the resulting solution stirred at RT for 1 hr. Aldehyde **23** (200 mg, 1.43 mmol) in THF (3 mL) was added dropwise to the reaction mixture, and allowed to stir at RT for 16 hr. The reaction was quenched by the addition of NH₄Cl (sat. aq.), and extracted with Et₂O (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40:60:Et₂O (8:2)) to afford compound **233** (260 mg, 53%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.45-7.32 (m, 6 H, *H*1, *H*2, *H*3, *H*8), 5.95-5.80 (m, 1 H, *H*14), 5.31 (dt, *J* = 17.0, 1.5 Hz, 1 H, *H*15), 5.28 (s, 2 H, *H*5), 5.14 (dt, *J* = 10.5, 1.5 Hz, 1 H, *H*15'), 4.13 (q, *J* = 6.5 Hz, 1 H, *H*13), 2.38 (q, *J* = 7.5 Hz, 2 H, *H*9), 1.65-1.40 (m, 7 H, *H*10, *H*11, *H*12, OH); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 162.4 (C6), 149.0 (C8), 141.1 (C14), 135.5 (C4), 128.8 (CAr), 128.2 (CAr), 126.9 (CAr), 116.2 (C7), 114.8 (C15), 73.0 (C13), 67.9 (C5) 36.6 (C10/11/12), 31.4 (C9), 28.6 (C10/11/12), 25.8 (C10/11/12); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₇H₂₁BrNaO₃ 375.0566, found 375.0573; **IR** ν_{max} /cm⁻¹ (thin film) 3400 (br. OH) 2934 (C-H), 1716 (C=O), 1622, 1498, 11455.

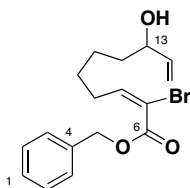
Preparation of (Z)-benzyl 2-bromo-8-oxodeca-2,9-dienoate **235**



According to a modified literature procedure,¹³ DMP (1.0 g, 2.6 mmol) was added to a solution of alcohol **233** (450 mg, 1.28 mmol) in CH₂Cl₂ (40 mL), and the resulting suspension was stirred at RT overnight. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a white solid. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **235** (400 mg, 89%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.45-7.32 (m, 6 H, ArH, H8), 6.37 (dd, J = 17.5, 10.5 Hz, 1 H, H14), 6.24 (dd, J = 17.5, 1.5 Hz, 1 H, H15), 5.85 (dd, J = 10.5, 1.5 Hz, 1 H, H15'), 5.27 (s, 2 H, H5), 2.64 (t, J = 7.5 Hz, 2 H, H12), 2.39 (q, J = 7.5 Hz, 2 H, H9), 1.71 (quin., J = 7.5 Hz, 2 H, H11), 1.55 (J = 7.5 Hz, 2 H, H10); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 200.3 (C13), 162.3 (C6), 148.7 (C8), 136.5 (C14), 135.4 (C4), 128.6 (CAr), 128.4 (CAr), 128.3 128.2 (CAr, C15), 116.5 (C7), 67.9 (C5), 39.0 (C12), 32.0 (C9), 28.2 (C10), 23.4 (C11); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₇H₁₉BrNaO₃ 373.0410, found 373.0406; **IR ν_{max} /cm⁻¹ (thin film)** 2939 (C-H), 1720 (C=O), 1680 (C=O), 1619, 1455, 1401.

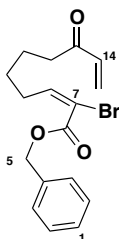
Preparation of (*E*)-benzyl 2-bromo-8-hydroxydeca-2,9-dienoate **232**



NaH (60% dispersion in mineral oil, 112 mg, 2.80 mmol) was added to a solution of Still-Gennari reagent **184** (394 mg, 1.43 mmol) in THF (10 mL), and the reaction mixture stirred for 5 min. NBS (250 mg, 1.43 mmol) was added and the resulting solution stirred at RT for 1 hr. Aldehyde **23** (200 mg, 1.43 mmol) in THF (3 mL) was added dropwise to the reaction mixture, and allowed to stir at RT for 16 hr. The reaction was quenched by the addition of NH₄Cl (sat. aq.), and extracted with Et₂O (x 3). The combined extracts were washed with H₂O, dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a yellow oil. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (8:2)) to afford compound **232** (220 mg, 45%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ_{H} 7.43-7.30 (m, 5 H, ArH), 6.70 (t, J = 8.0 Hz, 1 H, H₈), 5.85 (dd, J = 17.0, 10.5 Hz, 1 H, H₁₄), 5.25 (s, 2 H, H₅), 5.22 (dt, J = 17.0, 1.5 Hz, 1 H, H₁₅), 5.12 (dt, J = 10.5, 1.5 Hz, 1 H, H_{15'}), 4.71 (s, 1 H, OH), 4.11-4.05 (m, 1 H, H₁₃), 2.50 (q, J = 7.5 Hz, 2 H, H₉), 1.61-1.4 (m, 6 H, H₁₀, H₁₁, H₁₂); **¹³C NMR (126 MHz, CDCl₃)** δ_{C} 162.7 (C₆), 149.0 (C₈), 141.1 (C₁₄), 135.2 (C₄), 128.8 (CAr), 128.2 (CAr), 126.9 (CAr), 114.7 (C₁₅), 110.9 (C₇), 73.0 (C₁₃), 67.6 (C₅), 36.5 (C_{10/11/12}), 31.4 (C₉), 28.6 (C_{10/11/12}), 24.8 (C_{10/11/12}); **HRMS (ESI⁺)** m/z calculated for [M+Na]⁺ C₁₇H₂₁BrNaO₃ 375.0566, found 375.0559; **IR** ν_{max} /cm⁻¹ (thin film) 3400 (br. OH) 2934 (C-H), 1717 (C=O), 1455, 1378, 1344.

Preparation of (E)-benzyl 2-bromo-8-oxodeca-2,9-dienoate **234**

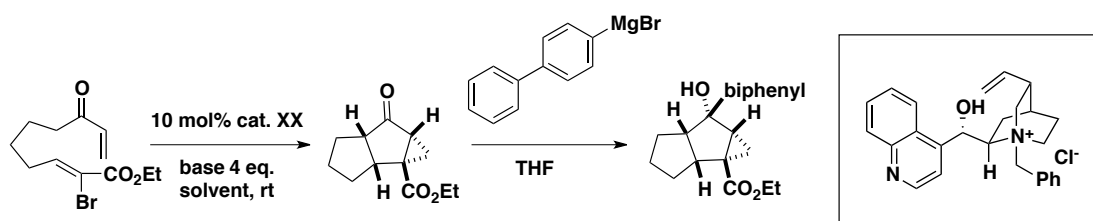


According to a modified literature procedure,¹³ DMP (241 mg, 0.57 mmol) was added to a solution of alcohol **232** (100 mg, 0.28 mmol) in CH₂Cl₂ (15 mL), and the resulting suspension was stirred at RT overnight. The solution was diluted with CH₂Cl₂, washed with Na₂S₂O₃ (sat. aq.) and NaHCO₃ (5% aq.), and the combined aqueous layers extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and the filtrate concentrated under reduced pressure to afford the crude product as a white solid. This crude product was adsorbed onto silica and purified by flash column chromatography (SiO₂, pet 40-60:Et₂O (9:1)) to afford compound **234** (90 mg, 92%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ_H 7.45-7.32 (m, 5 H, ArH), 6.71 (t, *J* = 8.0 Hz, 1 H, *H*₈), 6.35 (dd, *J* = 17.5, 10.5 Hz, 1 H, *H*₁₄), 6.23 (d, *J* = 17.5 Hz, 1 H, *H*₁₅), 5.84 (d, *J* = 10.5 Hz, 1 H, *H*_{15'}), 5.27 (s, 2 H, *H*₅), 2.61-2.49 (m, 4 H, *H*₁₂, *H*₉), 1.63 (quin., *J* = 7.5 Hz, 2 H, *H*₁₁), 1.48 (*J* = 7.5 Hz, 2 H, *H*₁₀); **¹³C NMR (126 MHz, CDCl₃)** δ_C 200.4 (C₁₃), 162.6 (C₆), 148.7 (C₈), 136.5 (C₁₄), 135.2 (C₄), 128.6 (CAr), 128.4 (CAr), 128.3 (CAr), 128.2 (C₁₅), 111.2 (C₇), 67.7 (C₅), 39.0 (C₁₂), 32.0 (C₉), 28.2 (C₁₀), 23.3 (C₁₁); **HRMS (ESI⁺)** *m/z* calculated for [M+Na]⁺ C₁₇H₁₉BrNaO₃ 373.0410, found 373.0410; **IR** ν_{max}/cm⁻¹ (thin film) 2937 (C-H), 1716 (C=O), 1680 (C=O), 1613, 1455, 1401.

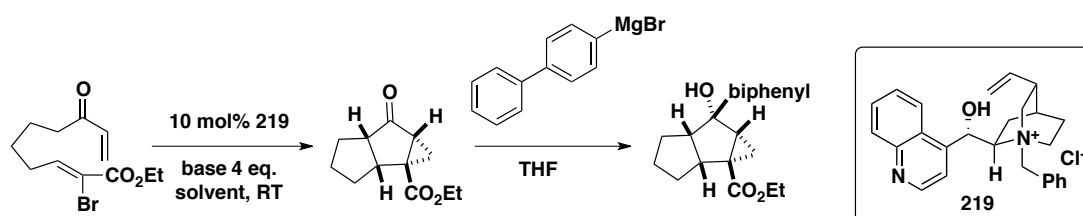
Asymmetric preparation of ethyl 5-([1,1'-biphenyl]-4-yl)-5-hydroxyoctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate

Initial Catalyst Screen: using 10 mg of starting material, 10 mol% catalyst, 4 eq. KOH_(s) and PhMe (0.5 mL). Once the reaction had gone to completion, the reaction mixture was passed through a small plug of silica, eluting with Et₂O. The solvent was removed by evaporation of the solvent under a stream of nitrogen and the residue was dissolved in THF (0.5 mL), cooled to 0 °C and biphenyl magnesium (0.5 mL in THF, 0.2 mL) was added. Once the reaction had gone to completion, the reaction mixture was directly used in a preparative TLC to obtain products for HPLC. Enantiomers were separated by chiral HPLC {Daicel CHIRALPAK AD-H, 4.6 mm x 250 mm, 10:90 2-propanol:hexane, 1.0 mL/min, retention times of enantiomers: 15.32 min, 16.71 min.}



Entry	Solvent	Base	ee (%)
1	PhMe	KOH _(s)	(-) 8
3	Ph	KOH _(s)	(-) 8
2	CH ₂ Cl ₂	KOH _(s)	(-) 6
4	MeCN	KOH _(s)	(-) 4
5	CCl ₄	KOH _(s)	0
6	Hexane	KOH _(s)	n.r.
7	MeOH	KOH _(s)	decomposed
8	Xylenes	KOH _(s)	(-) 10
9	PhMe:pet (1:1)	KOH _(s)	(-) 5
10	DMF	KOH _(s)	decomposed
11	PhMe	CsOH.H ₂ O _(s)	(-) 7
12	PhMe	Cs ₂ CO ₃	n.r.
13	PhMe	NaOH _(s)	(-) 8
14	PhMe	KOH _(aq)	decomposed

Initial Base and Solvent Screen: using 10 mol% *N*-benzyl cinchoninium chloride, 4 eq. base and solvent (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



Solvent Screen (using $\text{KOH}_{(\text{s})}$ as a base):

Entry	Solvent	ee (%)
1	PhMe	(-) 8
2	Ph	(-) 8
3	Xylenes	(-) 10
4	DMF	decomposed
5	MeOH	decomposed

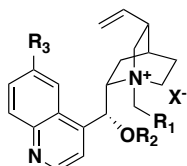
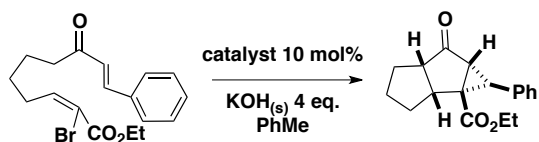
Base Screen (using PhMe as the solvent):

Entry	Base	ee (%)
1	$\text{KOH}_{(\text{aq})}$	decomposed
2	Cs_2CO_3	n.r.
3	$\text{CsOH} \cdot \text{H}_2\text{O}_{(\text{s})}$	(-) 7
4	$\text{NaOH}_{(\text{s})}$	(-) 8

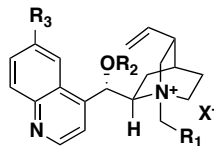
Asymmetric preparation of ethyl 5-oxo-1-phenyloctahydro-1*H*-cyclopropa[*a*]pentalene-1*a*-carboxylate 160b

Initial Catalyst Screen: using 10 mol% catalyst, 4 eq. KOH_(s) and PhMe (0.5 mL/10 mg).

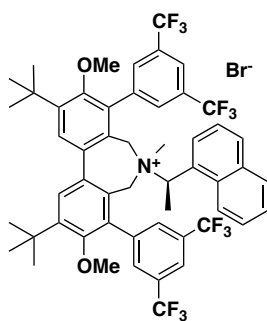
All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC. Enantiomers were separated by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm x 250 mm, 20:80 2-propanol:hexane, 1.0 mL/min, retention times of enantiomers: 6.52 min, 7.16 min.}



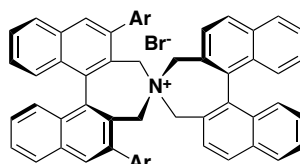
- 2 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{H}, X = \text{Cl}$
 218 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{OMe}, X = \text{Cl}$
 267 $R_1 = 2,3,4\text{-FPh}, R_2 = \text{H}, R_3 = \text{OMe}, X = \text{Br}$
 217 $R_1 = \text{Ph}, R_2 = \text{allyl}, R_3 = \text{H}, X = \text{Br}$
 268 $R_1 = 2\text{-MePh}, R_2 = \text{H}, R_3 = \text{OMe}, X = \text{Br}$



- 219 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{H}, X = \text{Cl}$
 237 $R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{OMe}, X = \text{Cl}$
 269 $R_1 = 4\text{-CF}_3\text{Ph}, R_2 = \text{H}, R_3 = \text{H}, X = \text{Br}$



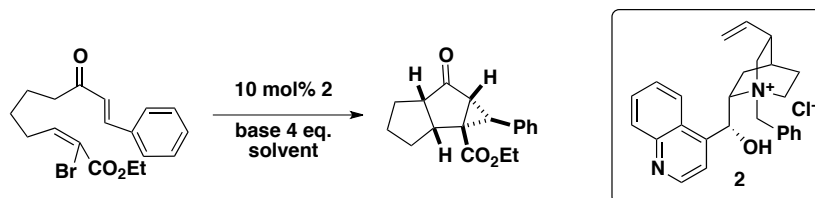
221



266

Catalyst	ee (%)
2	(+) 46
218	(+) 36
267	(+) 12
217	(+) 2
268	(+) 24
219	(-) 36
237	(-) 24
269	(-) 22
221	No reaction
266	(+) 12

Initial Base and Solvent Screen: using 10 mol% *N*-benzyl cinchoninium chloride, 4 eq. base and solvent (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for HPLC.



Solvent	Base	ee (%)
PhMe	KOH _(s)	(+) 46
CH ₂ Cl ₂	KOH _(s)	(+) 8
CCl ₄	KOH _(s)	Decomposed
Xylenes	KOH _(s)	(+) 36
Ph	KOH _(s)	(+) 40
MeCN	KOH _(s)	decomposed
TBME	KOH _(s)	(+) 10
Hexane	KOH _(s)	(+) 13
PhMe	CsOH.H ₂ O _(s)	(+) 22
PhMe	Cs ₂ CO _{3(s)}	No product
PhMe	NaOH _(s)	(+) 24
PhMe	KOH _(aq)	(+) 34
PhMe	K ₂ CO ₃	No product

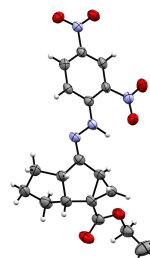
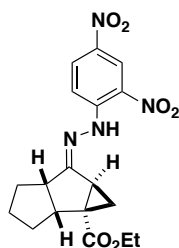
7.4 References

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8. Appendix

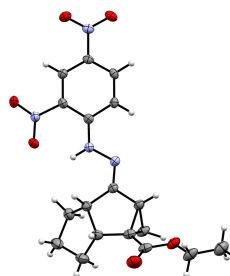
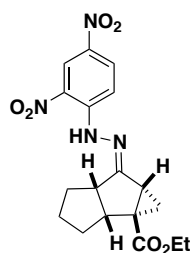
8.1 Crystal Structures

X-ray crystallographic data and structure refinement for compound 78, 097RWD13



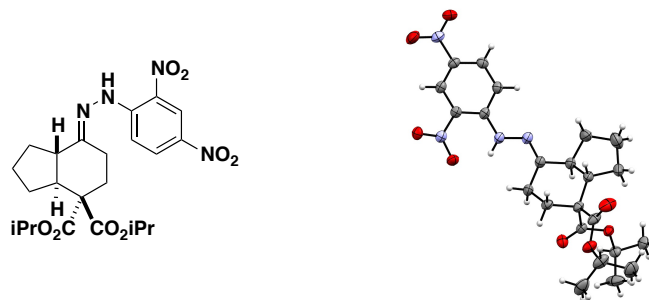
Identification code	097RWD13	
Empirical formula	C ₁₈ H ₂₀ N ₄ O ₆	
Formula weight	388.38	
Temperature	293 K	
Wavelength	0.68890 Å	
Crystal system	monoclinic	
Space group	P2 ₁ /n	
Unit cell dimensions	a = 7.289 Å	$\alpha = 90^\circ$
	b = 11.81 Å	$\beta = 98.597^\circ$
	c = 21.18 Å	$\gamma = 90^\circ$
Volume	1803 Å ³	
Z, Z'	Z: 4 Z': 0	
Density (calculated)	1.431 mg m ⁻³	
Absorption coefficient	0.101 mm ⁻¹	
F(000)	816.0	
Crystal size	0.02 x 0.02 x 0.05 mm ³	
Theta range for data collection	1.885° to 26.628°	
Reflections collected	3913	
Independent reflections	3906	
Absorption correction	none	
Refinement method	Full-matrix least squares on F ²	
Goodness-of-fit on F ²	1.227	
Final R indices [I > 2σ(I)]	R ¹ = 0.0757, wR ² = 0.2436	
R indices (all data)	R ¹ = 0.1079, wR ² = 0.2519	

X-ray crystallographic data and structure refinement for compound 79, 060RWD13



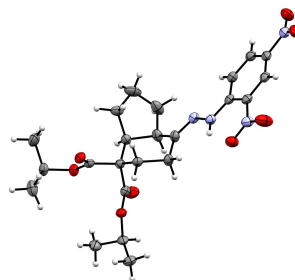
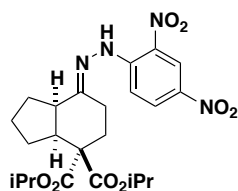
Identification code	060RWD13	
Empirical formula	C ₁₈ H ₂₀ N ₄ O ₆	
Formula weight	388.38	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	monoclinic	
Space group	P2 ₁ /c	
Unit cell dimensions	a = 19.3518 Å	α = 90°
	b = 6.3277 Å	β = 111.970°
	c = 16.0896 Å	γ = 90°
Volume	1827.13 Å ³	
Z, Z'	Z: 4 Z': 0	
Density (calculated)	1.412 mg m ⁻³	
Absorption coefficient	0.099 mm ⁻¹	
F(000)	816.0	
Crystal size	0.04 x 0.15 x 0.24 mm ³	
Theta range for data collection	5.504° to 76.704°	
Reflections collected	10836	
Independent reflections	3766	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F ²	
Goodness-of-fit on F ²	0.9689	
Final R indices [I>2σ(I)]	R ¹ = 0.0354, wR ² = 0.0904	
R indices (all data)	R ¹ = 0.0426, wR ² = 0.0972	

X-ray crystallographic data and structure refinement for compound 106, 047RWD13



Identification code	047RWD13	
Empirical formula	C ₂₃ H ₃₀ N ₄ O ₈	
Formula weight	490.51	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.6692 Å	$\alpha = 90.4796^\circ$
	b = 9.3702 Å	$\beta = 92.8552^\circ$
	c = 16.0180 Å	$\gamma = 111.2682^\circ$
Volume	1210.56 Å ³	
Z, Z'	Z: 2 Z': 0	
Density (calculated)	1.346 mg m ⁻³	
Absorption coefficient	0.103 mm ⁻¹	
F(000)	520.0	
Crystal size	0.18 x 0.56 x 0.66 mm ³	
Theta range for data collection	5.117° to 27.562°	
Reflections collected	21236	
Independent reflections	5496	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F ²	
Goodness-of-fit on F ²	0.8984	
Final R indices [I > 2σ(I)]	R ¹ = 0.0484, wR ² = 0.1168	
R indices (all data)	R ¹ = 0.0576, wR ² = 0.1244	

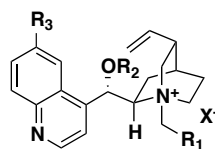
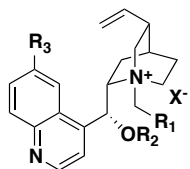
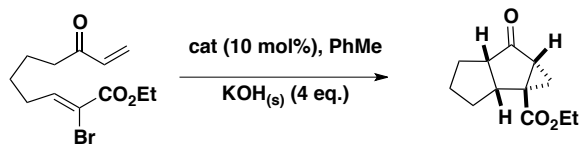
X-ray crystallographic data and structure refinement for compound 110, 015JDJ14



Identification code	015JDJ14	
Empirical formula	C ₂₃ H ₃₀ N ₄ O ₈	
Formula weight	490.51	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	monoclinic	
Space group	P2 ₁ /n	
Unit cell dimensions	a = 14.7496 Å	α = 90°
	b = 8.4562 Å	β = 99.652°
	c = 38.6953 Å	γ = 90°
Volume	4758.0 Å ³	
Z, Z'	Z: 8 Z': 0	
Density (calculated)	1.370 mg m ⁻³	
Absorption coefficient	0.096 mm ⁻¹	
F(000)	2080.0	
Crystal size	0.02 x 0.16 x 0.18 mm ³	
Theta range for data collection	2.701° to 27.575°	
Reflections collected	60485	
Independent reflections	10825	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F ²	
Goodness-of-fit on F ²	0.9917	
Final R indices [I>2σ(I)]	R ¹ = 0.0598, wR ² = 0.1336	
R indices (all data)	R ¹ = 0.0712, wR ² = 0.1396	

8.2 Chiral GC

Catalyst Screen: using 10 mol% catalyst, 4 eq. KOH_(s) and PhMe (0.5 mL/10 mg). All reactions performed on 10 mg starting material, and preparative TLC was used to obtain products for GC. Chiral GC analysis Restek Rt®-βDEXcst (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 60 cm/sec, initial temperature: 100 °C, ramp rate: 5 °C/min, t_R minor 18.7 min, t_R major 19.0 min. **Alyn Davies**, from Prof. Andy Smith's research group ran the following samples on their chiral GC:



263 R₁ = Ph, R₂ = H, R₃ = H, X = Br

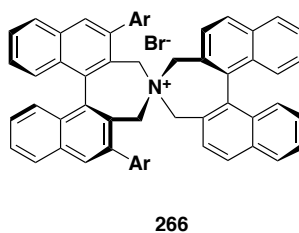
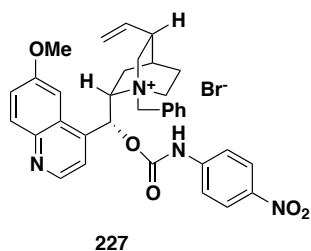
2 R₁ = Ph, R₂ = H, R₃ = OMe, X = Cl

214 R₁ = anthracenyl, R₂ = H, R₃ = H, X = Br

217 R₁ = Ph, R₂ = allyl, R₃ = H, X = Cl

219 R₁ = Ph, R₂ = H, R₃ = OMe, X = Cl

239 R₁ = 3,5-CF₃Ph, R₂ = H, R₃ = H, X = Br



Entry	Catalyst	ee (%)	Approx. d.r.
1	263	0	>20:1
2	2	(+) 5	2:1
3	219	0	2:1
4	214	0	3:1
5	239	0	>20:1
6	217	(+) 14	10:1
7	227	(+) 3	1.5:1
8	266	No reaction	-