Transannular cascade approaches to diterpene analogues

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of the

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Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2013 and November 2017. 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.

Antti Lahdenperä
Acknowledgements:

To science. You have been a worthy opponent. I may have lost this battle but one day you will kneel before me.

I guess this is the most important part of the thesis or at least the most read part. It took longer than planned and it took blood, toil, tears and sweat. First, I want to thank my supervisor Professor Martin Smith. He is a well respected supervisor and he has earned it. Thank you, Martin.

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<td>distortionless enhancement by polarization transfer</td>
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<td>longitudinal relaxation time</td>
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<td>&lt;i&gt;tert&lt;/i&gt;-Butyldiphenylsilyl</td>
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<td>TBME</td>
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<td>&lt;i&gt;p&lt;/i&gt;-toluenesulfonyl</td>
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<tr>
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Abstract

The aim of this project is to apply the chemistry developed in our group and to extend it to asymmetric transannular methodology for the generation of different fused, diterpene-like, polycyclic ring systems. Construction of these ring systems is predicated on an intramolecular Michael reaction cascade or an ionic Diels-Alder reaction catalysed by chiral quaternary ammonium salts under basic phase transfer conditions. We demonstrate a rapid synthesis of the transannular cascade precursor that undergoes cyclisation producing three new stereocenters in high enantioselectivity (Scheme I & II).

Furthermore we demonstrate an isomerisation of the precursor under UV-irradiation obtaining all the enone-Z,E-isomers of the cascade precursor scaffold. We were able to obtain either a single Michael-addition or a cyclisation, via transannular Diels-Alder or Michael-Michael cascade reaction depending on the configuration of the enones. These cascades undergo cyclisation in moderate to high enantioselectivity (Scheme II).
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1. Introduction

1.1 Phase-transfer catalysis

Phase-transfer catalysis is where reactants are transferred between phases in biphasic system by a catalyst; the reactivity of reactants that are not soluble in reaction media, may be increased under these conditions. For example; Ionic, water soluble reactants are often insoluble in organic phases for reactivity, yet in the presence of a phase-transfer catalyst can be transferred to the organic phase. Biphasic systems include for example heterogenous liquid-liquid, solid-liquid or liquid-gas. Most commonly quaternary ammonium or phosphonium salts are used as a catalyst but cryptanes,\textsuperscript{1} crown ethers\textsuperscript{2} and polyethers\textsuperscript{3} have also been used.

The first example of phase-transfer catalysis was published in 1946 by Rueggeberg \textit{et al.}\textsuperscript{4} where benzylethylammonium chloride was made \textit{in situ} and used in a reaction to form benzyl benzoate from sodium benzoate and benzyl chloride. The term phase-transfer catalysis comes from Charles Stark more than 20 years later than the first example.\textsuperscript{5} Stark provided an explanation for the mechanism of phase-transfer catalysis in which the catalyst is described as an agent that transfers reactants across the interface enabling the reactivity. This explanation came to be known as the Stark extraction mechanism. Another mechanism was postulated by Makosza which is known as an interfacial mechanism. In this mechanism base deprotonates the reactive species at the phase interface, where it is then transferred to the other phase by a phase-transfer catalyst (\textbf{Scheme 1}).\textsuperscript{6}
Because the complex biphasic systems are difficult to examine the absolute mechanism of the phase-transfer catalysis remains unclear. Despite this, phase-transfer catalysis is a versatile and valuable method for many organic transformations and is widely used in many industrial processes.
1.2 Asymmetric phase-transfer catalysed Michael additions of 1,3-dicarboxyls

Cram and Sogah\(^9\) reported a phase-transfer catalysed method for the enantioselective Michael-addition of aromatic \(\beta\)-ketoester to methyl vinyl ketone (Scheme 2). A chiral crown complex, as catalyst 4 was used in the asymmetric reaction that provided the products up to 99% ee optical purity in moderate yields. In the reaction the crown ether complexes with the potassium cation of the deprotonated malonate. The chiral crown ether causes a steric hindrance on the other side of the nucleophile that causes the enantioinduction.

\[
\text{Scheme 2: Enantioselective Michael-addition of } \beta\text{-ketoesters catalysed by chiral crown complexes.}^9
\]

A similar phase-transfer catalysed Michael-addition was published by Najera \textit{et al.} where high enantioselectivity was obtained by using dimeric catalyst 7 and isopropylethyl amine as a base (Scheme 3).\(^10\)

\[
\text{Scheme 3: Enantioselective Michael-addition of } \beta\text{-ketoesters catalysed by dimeric catalyst 7.}^10
\]

Perrard \textit{et al.}\(^11\) used an asymmetric phase-transfer catalysed reaction in the synthesis of both enantiomers of methyl dihydrojasmonate 12 and 13 (Scheme 2). In the enantioselective addition of dimethylmalonate to a \(\alpha\)-substituted cyclopentenone 8, pseudoenantiomers of chiral \textit{cinchona} derivatives catalyst 14 and catalyst 15 were used as the phase-transfer catalyst which provided both enantiomers of the Michael-addition. Catalyst 15 gave a lower yield of 60% and 80% ee compared to the catalyst 14 (yield 91%, 90%). The author didn’t provide an explanation
for the different results of the catalyst pseudoenantiomers. The Michael-addition was followed by a Krapcho reaction\textsuperscript{12} that provided unracemised methyl dihydrojasmonates 12 and 13.

\begin{center}
\textbf{Scheme 4: Synthesis of methyl dihydrojasmonates via asymmetric phase-transfer catalysed Michael-reaction.}\textsuperscript{11}
\end{center}

A Cinchona derived phase-transfer catalyst has also been used alongside with dimethylmalonates in the asymmetric Michael-addition by Dere et al.\textsuperscript{13} (\textbf{Scheme 5}) The group used ionic liquids as a reaction media for the asymmetric reaction. Interestingly, reversed enantiocontrol was observed compared to common organic solvents.

\begin{center}
\textbf{Scheme 5: Phase-transfer catalysed asymmetric Michael-addition in ionic liquids.}\textsuperscript{14}
\end{center}

Kim \textit{et al.}\textsuperscript{14} reported a similar asymmetric Michael-addition to chalcones. Dibenzylmalonates were used, to give products in modest yields and enantioselectivities using allylated cinchonidine derived quaternary ammonium salts, such as a catalyst 18 (\textbf{Scheme 6}). Crown ethers have also been used as catalysts in highly enantioselective fashion in similar reactions to chalcones with ethylmalonates by Bako \textit{et al.}\textsuperscript{15}
Scheme 6: Phase-transfer catalysed Michael-addition of dibenzylmalonates.\textsuperscript{15}

Additionally, Maruoka’s group has published highly enantioselective Michael-addition
malonate/chalcone system (Scheme 7).\textsuperscript{16} \textit{N}-spiro \textit{C}_2-symmetric chiral quaternary ammonium bromide 25 was used as a catalyst with variety of chalcone derivatives in reaction with
diethylmalonate 23.

Scheme 7: Phase-transfer catalysed diethylmalonate addition to chalcones.\textsuperscript{16}

Another example of the work of the Maruoka’s group is a phase-transfer catalysed addition of
5-membered \(\beta\)-keto esters 26\textit{a} and 26\textit{b} to acrolein 27 and methyl vinyl ketone 2 in high yields
and enantioselectivities (Scheme 8).\textsuperscript{17}
The same group has also been able to use the same 5-membered β-keto esters in enantioselective, high yielding Michael-addition to acetylenic ketones 32. The reaction gives a 1.2:1 mixture of E/Z-enone isomers as the product with slightly different enantiomeric excess (E: 90% ee, Z: 85% ee) (Scheme 9).  

**Scheme 9**: Asymmetric phase-transfer catalysed addition β-keto ester addition to acetylenic ketone.
1.3 Transannular Michael-Michael cascades

Evans group have used in the total synthesis of Salvinorin A, a transannular base mediated cyclisation of β,β-disubstituted bisenone 35 to obtain a single diastereomer of tricycle 36 (Scheme 10).\textsuperscript{20} TBAF was used as a base that afford the fused ring-system in impressive 99% yield. The authors presumed that the mechanism proceeds via stepwise mechanism however a concerted mechanism via an exo-selective Diels-Alder could not be excluded.

### Scheme 10: Transannular cyclisation in the total synthesis of Salvinorin A.\textsuperscript{20}

Models studies were carried out to observe the effect of the stereocenters on the diastereoselectivity of the cyclisation (Scheme 11). The first model 37 evaluated the effect of the furyl-group at C1 on the diastereoselectivity of the reaction and the second, the combination of the acetal- and furyl-group on the selectivity. It was observed that the both reactions resulted in complete diastereoocontrol and furthermore the dimethyl acetal seemed to reinforce the diastereoselection.
A recent study published in 2017 by Sherwood et al. examined a small range of Salvinorin A type κ-opioid ligands (Scheme 12). The group synthesised a E,E-bis-enone 39 in 11 steps, very similar to the precursor for the cascade used by Evans group. This cascade product was further modified to give different κ-opioid ligands. In contrast to Evans system the bis-enone 39 substrate did not have any substituents on the enone olefin. Under TBAF cyclisation the transannular reaction produced 80% yield of 40. The diastereoselectivity is similar than in the synthesis of Salvinorin A although in this study 2:1 mixture of diastereomers were formed. The other diastereomer wasn’t characterised. Also in this case the diastereoselectivity is controlled by the substituents at C1, C6 and C8 that force the cascade transition state to an all-chair conformation in bis-Michael mechanism. As in the total synthesis of Salvinorin A the diastereoselectivity could be explained also by exo-Diels-Alder transition state (Scheme 10).

Xue et al. used a similar kind of cyclisation system in the synthesis towards natural product Norzoanthamine. The synthesis relies on a base promoted cyclisation of β,β-disubstituted E,E-bis-enone 41 (Scheme 13). This transannular process is highly stereoselective and only the product 42 was isolated in the reaction. The product obtained in the reaction is consistent with the all-chair-like transition state of a Michael-reaction cascade; the authors noted that the Diels-Alder pathway cannot be excluded due to the formation of the enolate-form of the product.
and the resulting loss of stereochemical information of the 1,3-dicarbonyl addition to the enone. Without enolisation of the 1,3-dicarbonyl there could be a possibility to exclude the Diels-Alder mechanism if the methyl-group at C13 and proton at C16 ended on the same or opposite sides of the formed fused-ringsystem.

**Scheme 13:** Cyclisation of bis-enone 41 used in the synthesis towards Norzoanthamine.\(^{22}\)

The same group continued with a stereochemical study of their transannular Michael reaction cascade. All bis-enone E,Z-isomers of the corresponding cascade precursors were synthesised with slight modifications.\(^{23}\) In addition to the previous cascade in **Scheme 13**, Xue et al. synthesised in a 12-step route E,Z-1,7-bis-enone 43 that cyclised under basic conditions to afford single diastereomer of a fused-ring-system 44 in 88% yield (**Scheme 14**). In the cyclisation all the substituents on newly formed stereocenters ended on the same side of the fused ring-system. The stereoselectivity could be explained by either Michael-reaction pathway or Diels-Alder pathway. The authors stated that the diastereoselectivity could be rationalised either by a Michael-reaction or Diels-Alder pathway proceeding through transition states in **Scheme 10**.
Similarly a \(E,E\)-1,7-bis-enone 32 formed a cyclised fused ring-system 33 as a single diastereomer in 93% yield under basic condition (Scheme 15). In contrast to the cyclisation of \(Z,E\)-bis-enone 30, in the \(E,E\)-1,7-bis-enone cyclisation the \(\beta\)-methyl substituents on the enones ended on the same side of the formed fused ring-system, while the \(\alpha\)-proton ends on the opposite side of the ring. The stereochemical outcome of both of the cyclisations can be explained via a transition state where all incipient six-membered rings are in chairlike conformation. Equally, the reaction outcomes can be explained by chair-chair-boat-chair transition states in transannular Diels-Alder reaction.
Whilst the E,Z- and E,E-bis-enones undergo the cyclisation, no reactivity was observed with Z,E-bis-enones 47 and 48 or Z,Z-bis-enones 50 (Scheme 16). The macrocycles 47, 48 and 50 were recoverable after treatment with TBAF at ambient temperature. At elevated temperatures decomposition of the starting materials were observed without cyclisation.
The reactivity of the bis-enones by Xue et al. were examined using quantum chemical calculations by using density functional theory by Nguyen et al. Conclusions of this research stated that a stepwise mechanism was the predominant pathway in the formation of the fused ring-systems (Scheme 14, Scheme 15, Scheme 16). Overall cycloaddition barriers of 18 and 22 kcal/mol were casculated for E,Z-1,7-bis-enone 40 and E,E-1,7-bis-enone 38 – the substrate that cyclised under the reaction conditions. The barriers of 28-29 kcal/mol for the Z,E- and Z,Z-bis-enones 47 and 50 which did not produce cycloaddition products due to hindering steric and strain effects.

In addition to the previous examples, Yang and co-workers have also synthesised all-carbon core Z,E-1,7-bis-enone 56 by using an elegant isoxazole-stategy to be used in a synthetic study towards natural product Celastrol (Scheme 17). The core was built by using 1,3-dipolar cycloaddition to form isoxazole 54 that acts as a masked dicarbonyl that is eventually cleaved by Mo(CO)₆. The cascade precursor 56 is obtained following treatment with acid. Along with
the previous attempts with Z,E-bis-enones the all-carbon macrocycle did not provide any cyclised product 57 when treated with TBAF or NaOMe at various temperatures.

Scheme 17: Synthesis of 1,3-diketone containing Z,E-bisenone 44.25
1.4 Project background

To date there are few stereoselective transannular processes that rely on a chiral catalyst rather than a premade chiral ring system.\textsuperscript{27-29} As far as we know there are only four methods using a substoichiometric amount of the catalyst in transannular asymmetric transformations.\textsuperscript{30-32} The only catalytic enantioselective transannular reaction producing more than two new stereocentres is Jacobsen’s developed method for the transannular Diels-Alder reaction (Scheme 18).\textsuperscript{33}

\textbf{Scheme 18:} Enantioselective catalytic transannular Diels-Alder reaction.\textsuperscript{33}

Previously Smith group has studied an intramolecular Michael-Michael cascade followed by cyclopropanation that produced tricyclic fused cyclopropanes \textbf{50} with five new stereocentres in high diastereoselectivity under phase-transfer conditions.\textsuperscript{34} The computational studies suggest the cyclisation proceeds though a Michael-Michael cascade rather than through Diels-Alder mechanism (Scheme 19).

\textbf{Scheme 19:} Phase-transfer catalysed Michael-Michael-cyclopropanation.\textsuperscript{34}
Furthermore, Smith group has worked on a 5-endo-trig cyclisation forming indenes. This quaternary chiral ammonium salt catalysed cyclisation forms three new stereocenters in excellent diastereoselectivity and enantioselectivity under basic conditions (Scheme 20).

**Scheme 20:** Phase-transfer catalysed 4-endo-trig cyclisation.

We postulated that the phase-transfer catalysed cyclisations could be extended to transannular scaffolds in building fused polycyclic ring-systems. Scaffold was chosen to be the target of the investigation because of similarity to macrocyclic bis-enone-system that has been used in the total synthesis of Salvinorin \( ^2 \) (Scheme 10). We already had the information that the scaffold is able to cyclise in high yield and enantioselectivity. We also though that the synthesis of the macrolactone core would be easier than the corresponding all-carbon scaffold.

**Scheme 21:** Transannular cyclisation of 67.
The ability to introduce several stereocentres in an asymmetric cascade fashion is particularly attractive as an efficient means to prepare complex natural product-like scaffolds (Scheme 22). In addition to Salvorin A, we postulated that the methodology would be valuable in building steroid structures like Androstenedione and Estrone. Furthermore, Betulinic acid core is another example of natural products where transannular cyclisation could be used.

Scheme 22: Examples of naturally occuring significant diterpenes.
2. Synthesis of the macrolactone core

We chose model substrate 67 on which to base our investigations, which we envisaged could be prepared via two key disconnections: ring closing metathesis\(^\text{36}\) and a Horner-Wadsworth-Emmons (HWE) reaction (Scheme 23).\(^\text{37}\)

**Scheme 23: Retrosynthesis plan for the macrolactone 67.**

2.1 Synthesis of the aldehyde 71

Synthesis of the macrolactone 67 began with a protective ozonolysis\(^\text{38}\) of cyclopentene 72 which gave monoacetylated aldehyde 78 in 37% yield. In the literature common yield for the ozonolysis reaction is 42-48%.\(^\text{39,40,41,42}\) One of the reasons for a low yield is probably a cyclic acetal 81 sideproduct formed in the reaction.\(^\text{43}\) This was followed by a Grignard reaction to form acetylated allylic alcohol 79 in 43% yield.\(^\text{44}\) Attempts to deprotect the acetal 79 in acidic conditions gave only cyclic hemiacetal 82. We tried to protect the allylic alcohol immediately after formation using the crude mixture of the acid deprotection to give 80 but also in that case the reaction preferred the protected cyclic hemiacetal 84. To circumvent this problem a one-pot protection-deprotection using triethyloxysilyl trifluoromethanesulfonate and 2,6-lutidine was used to produce the aldehyde 80 in good 74% yield (Scheme 24).\(^\text{45}\)
The synthesis of protected allylic alcohol aldehyde 80.

The yields of the ozonolysis of cyclopentadiene and subsequent Grignard reaction were too low to produce sufficient amounts of the protected aldehyde 80 for HWE-reaction. Therefore, we chose to investigate a second approach for the synthesis (Scheme 25). This route relied on the synthesis of the ethyl 5-hydroxyhept-6-enoate 86, previously synthesised by Fischer et al., the protection of the allylic alcohol 87, and finally reduction of the ester to give aldehyde 80.

The synthesis starts with a Negish-type coupling reaction between acrylic acid and commercially available ethyl 4-bromobutanoate. First, bromobutanoate was converted to a corresponding iodide by a Finkelstein reaction in dry acetone, before formation of the organo-zinc reagent by using zinc-copper couple. Negishi-type reaction gave the enone 86 in 56% yield. This route proved much easier than the previous approach to scale up. Enone 87 was reduced to the allylic alcohol using sodium borohydride with cerium (III) chloride at –78 °C. These Luche-reaction conditions operate by generating “harder” mono-, di- and trisubstituted alcoxyborohydrides that prefer the 1,2-reduction of enones. Allylic alcohol 87 was silyl-protected with triethylsilyl trifluoromethanesulfonate and 2,6-lutidine in good yield. Finally, The silyl-protected ester was reduced to the HWE-aldehyde 80 in excellent yield by using diisopropylaluminium hydride.
All the reactions in the second-generation synthesis of the aldehyde 80 could be done on multigram scale with a 34% overall yield (Scheme 24). This was a vast improvement on the 11% yielded by the ozonolysis route. The synthesis still requires 4 steps. We felt this was too many for the synthesis of the precursor that still needs to be used for the optimisation of the main cascade methodology.

A Grignard reaction between commercially available 4-chloro-1,1-dimethoxybutane 89 and acrolein 27 has been demonstrated by Felkin et al.\textsuperscript{51}. Using this chemistry would reduce the steps required to synthesise the aldehyde 80 to two. The Grignard reaction proved to be very challenging, especially because the formation of the Grignard reagent from the acetal 89 was tricky. To form the Grignard reagent it was essential to use 1,2-dibromoethane to activate the magnesium metal. Despite these conditions we still had difficulties in the reproducibility of the Grignard reaction (Scheme 26). Issue with the reproducibility was also noted by Felkin et al. Eventually, we managed to obtain a yield of 85% by using 2 equivalents of the Grignard reagent.

Scheme 26: Synthesis of acetal 79 via Grignard addition to acrolein
We now had a two-step route for the synthesis of the aldehyde 80 on our hand. This was a major improvement to the two previous 4-step routes. Also, the overall yield of 63% is superior to the other routes (Scheme 27).

2.2 Synthesis of the phosphonate 74

The synthesis of the required Horner-Wadsworth-Emmons (HWE) reagent 74 began with a thermally promoted transesterification of commercially available reagents 75 and 76 to give a 45% yield of the product 90 (Scheme 28). Unlike similar transesterifications that use a catalytic amount of DMAP we discovered a catalyst was unnecessary for the transformation. When 2,6-Lutidine catalysed transesterification was attempted, no improvement in yield was observed. A cleaner conversion was observed when molecular sieves were used in the reaction, although, the yields were reduced.
Phosphonate 74 was made by using a Michaelis-Becker reaction, starting from diethyl phosphite and the α-chloro compound 90 (Scheme 28). First attempts of the reaction were made by using a equimolar sodium hydride (NaH) to deprotonate 90 following by addition of a slight excess (1.1 eq) of deprotonated diethyl phosphite 77. Initially, we only isolated low yields from this reaction. After optimisation, the best conditions for this transformation proved to be the initial deprotonation of the most acidic proton of the ketoester 90, followed by addition of an excess (2.3 eq) of deprotonated diethyl phosphite 77. At least two equivalents of the phosphite anion was needed since the product of the Michaelis-Becker reaction is more acidic than the diethyl phosphite. The reaction gave us 88% yield of the phosphonate 74 required in the HWE-reaction (Scheme 28).

The trans-selective HWE reaction through an double anionic phosphonate between compounds 74 and 80 gave no product when sodium hydride was used as the base at 0 °C. Pleasingly, using 2.8 equivalents of KHMDS as the base afforded the desired unsaturated enone ester 91 in excellent yield and as a single E-isomer (Scheme 29). When the reaction warmed to ambient temperature after reacting at −78 °C for half an hour, we isolated 70% yield from the reaction. We realised that −78 °C was a sufficient temperature for reactivity and after 3 hours we could isolate 91% of the unsaturated ketoester 91.
2.3 Synthesis of the macrolactone via ring closing metathesis

The initial plan to synthesise protected macrolactone 92 was to use a ring closing metathesis (RCM)\(^{57,58,59}\) (Table 1). We started the investigation by using Grubbs 1\(^{\text{st}}\) generation catalyst,\(^{24}\) in CH\(_2\)Cl\(_2\), at reflux but the reaction gave no product (Table 1, entry 1). Similar results were obtained when we increased the temperature by using toluene as a solvent (Table 1, entry 2). Use of Grubbs 2\(^{\text{nd}}\) generation catalyst\(^{60}\) also yielded no product (Table 1, entry 3). To avoid possible isomerisation we changed the solvent to 1,2-dichloro ethane (DCE) and added 2,6-dichloro-1,4-benzoquinone as an additive.\(^{61}\) When neither Grubbs 1\(^{\text{st}}\) or Grubbs 2\(^{\text{nd}}\) generation catalyst gave the desired macrocycle 92 Hoveyda-Grubbs 2\(^{\text{nd}}\) generation catalyst\(^{62}\) was tested. This catalyst gave us a very complex crude mixture without desired product. However, when the concentration was lowered, and the reaction time reduced, we were able to isolate the desired product form a complex mixture in 14\% yield. To avoid plausible coordination of the ruthenium-catalyst to the 1,3-dicarbonyl of the starting material or product we used titanium(IV)isopropoxide as a competing cordinator,\(^{63}\) but we observed a lower yield (7\%) than without the Lewis-acid (Table 1, entry 8).
<table>
<thead>
<tr>
<th>Ent.</th>
<th>Catalyst</th>
<th>Conc. (M)</th>
<th>Time (h)</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Additive</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs 1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>0.005</td>
<td>24</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Reflux</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs 1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>0.005</td>
<td>1</td>
<td>Toluene</td>
<td>Reflux</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>0.005</td>
<td>24</td>
<td>Toluene</td>
<td>Reflux</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>0.005</td>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Reflux</td>
<td>2,6-dichloro-1,4-benzoquinone</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>HG 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>0.005</td>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Reflux</td>
<td>2,6-dichloro-1,4-benzoquinone</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
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<td>1</td>
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<td>Reflux</td>
<td>Triphenylphosphine oxide</td>
<td>-</td>
</tr>
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<td>0.25</td>
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<tr>
<td>8</td>
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<td>0.25</td>
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<td>Reflux</td>
<td>Ti(OiPr)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Table 1: Optimisation of RCM reaction of compound 91*

We hypothesised that the product is not stable under these RCM conditions and that the catalyst could re-enter the catalytic cycle reacting with either the formed type I olefin or with the undesired type IV enone olefin. The bulkiness of the formed type I olefin with the nearby TES-group, also present in the starting material, makes it likely that the catalyst prefers to react with the enone. Interestingly, we could only observe the formation of the E,E-isomer of the product.

Since the Ring-closing metathesis of 91 did not produce sufficient yields the next plan was to deprotect the allylic alcohol before the RCM, to decrease the bulkiness of the olefin and to direct the first addition of a catalyst to this allylic alcohol olefin. Deprotection of the alcohol with tetrabutylammonium fluoride (TBAF) gave us the free alcohol 93 in 61% yield. The
deprotected alcohol 93 appeared to be unstable after purification undergoing quantitative oxy-Michael addition, even when stored at –20 °C (Scheme 30).

Scheme 30: RCM and deprotection of compounds 93.

We decided to swap the order of the steps of the synthesis by first oxidising the allylic alcohol to enone 96 and closing the macrocycle afterwards avoiding the oxy-Michael reaction. Attempts at a Dess-Martin periodinate oxidation and a MnO₂ oxidation resulted in favoured formation of the oxy-Michael product 95. In addition, enone 96 proved to be highly unstable. The RCM reaction was also attempted immediately following purification of 93 but no desired free alcohol product 94 was observed, and instead only the tetrahydropyranyl-marcolactone 95 was isolated (Scheme 31).

Scheme 31: Oxidations of the allylic alcohol 93.
In contrast to TES-protected 91, RCM of 95 smoothly produced the Z-olefin of macrolactone 97 in 75% yield (Scheme 32).

![Scheme 32: RCM of the compound 85.](image)

Exploiting natural reactivity of free alcohol 93 to form oxy-Michael product 95 we postulated that as the oxy-Michael reaction is generally reversible, we may be able to utilise the oxy-Michael adduct and reveal the allylic alcohol 94 after RCM via a retro-oxy-Michael reaction. Furthermore, we postulated that the free macrolactone alcohol 94 could be the thermodynamic product which would not recyclise because of the possible change in ring conformation (Scheme 33).

![Scheme 33: Plans for the retro-Oxy-Michael reaction and the oxidation of the formed alcohol 94.](image)

Kanematsu et al. has used a transannular Oxy-Michael-reaction in the synthesis of the natural product Aspergillide A (Scheme 34). The system closely resembles of our macrocycle scaffold. Since Kanematsu et al. could isolate the free alcohol 98 we postulated that in our system, which has the same disconnection between an enone and an allylic alcohol, the free macrocyclic alcohol 94 could be isolable. Kanematsu et al. was showed that the syn-macrolactone 99 could be converted to the corresponding thermodynamic anti-macrocycle 100 under strong basic conditions. Furthermore, Aspergillide A could be converted to
Aspergillide B via an retro-oxy-Michael reaction similar to what is needed for the synthesis of our cascade precursor 67.

Scheme 34: Transannular Oxy-Michael reaction used in the totalsynthesis of Aspergillide A. 67

In our system, under basic TBAF deprotection conditions of the TES-protected alcohol 91 we could not observe any oxy-Michael product 95 (Scheme 30). Basic conditions could prevent the possible oxy-Michael reaction by enolization of the RCM product 97 that could be more acidic than the freed allylic alcohol. Therefore, we wanted to know if the oxy-Michael could be acid catalysed and then we could be able to combine the acidic deprotection of the alcohol and the oxy-Michael. At the early stage of the investigation of the oxy-Michael reaction we found that acidified chloroform was indeed able to combine these two steps together giving combined 93% yield of 95 in 1:14 E:Z tetrahydropyran-ring isomers (Scheme 35). When acetic acid/water mixture in THF was used the reaction preferred surprisingly the free alcohol 93 rather than the oxy-Michael product.

Scheme 35: oxy-Michael reaction of the compound 91.
2.4 Optimisation of the RCM of the oxy-Michael product 95

We wanted to optimise the Ring-closing metathesis result we had previously obtained (Table 2, entry 1). When we increased the scale of the reaction from 20 mg to 66 mg we observed a decrease in the yield of the reaction to 59% (Table 2, entry 2). One of the aims of the optimisation was to reduce the amount of the relatively expensive catalyst required, so we performed a catalyst screen using 5 mol% of the catalyst in CH₂Cl₂ (Table 2, entries 3-6). Grubbs 2̊ generation catalyst (70% yield) and the Hoveyda-Grubbs 2̊ generation catalyst (69% yield) gave the best results from the screen. Surprisingly, when the amount of catalyst was lowered from 20 mol% to 5 mol% the yield was increased (Table 2, entry 4). Also when using 10 mol% of the catalyst lower yield was isolated (56%) (Table 2, entry 7). The reason for this could be a complexation of the transition metal to the product or starting material. We can’t, however, fully explain the observation but this could also be due to an experimental error.

![Chemical structure](image)

**Table 2**: Optimisation of the RCM reaction of the oxy-Michael product 95.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Cat. loading</th>
<th>Conc.</th>
<th>mass</th>
<th>Temp.</th>
<th>Yield</th>
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<td>20 mg</td>
<td>RT</td>
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<td>Grubbs 2̊</td>
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<td>0.005 M</td>
<td>66 mg</td>
<td>RT</td>
<td>59%</td>
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<tr>
<td>3</td>
<td>Hoveyda-Grubbs 2̊</td>
<td>5 mol%</td>
<td>0.003 M</td>
<td>0.1 g</td>
<td>RT</td>
<td>69%</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs 2̊</td>
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<td>0.003 M</td>
<td>0.1 g</td>
<td>RT</td>
<td>70%</td>
</tr>
<tr>
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<td>RT</td>
<td>56%</td>
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With an optimal catalyst in hand, we proceeded to investigate the influence of temperature, solvents and metathesis additives on the yields of the reaction (Table 3). Slight increase in yield (72%) was observed when the reaction was done in refluxing CH₂Cl₂ for 2 hours (Table 3, entry 1). An increase in yield was also observed when benzoquinone was added to the reaction mixture to prevent the formation of isomerisation side products. In all of the RCM reactions the product was always reddish coloured after column chromatography purification. This indicates a presence of ruthenium in the product. To eliminate the ruthenium, we quenched the reaction by adding activated carbon to the mixture and stirred it overnight prior to purification. We were able to remove parts of the red colour from the product but this extra purification also caused a decrease in yield (66%) (Table 3, entry 3).

The quality of the solvent had a major effect on the yield of the reaction. When bottled CH₂Cl₂ purchased from Sigma-Aldrich was used, the yield of the reaction dropped to 47% and when the CH₂Cl₂ was from a solvent stills the isolated yield was 71% (Table 3). This result could be due to insufficient degassing of the bottled solvent, whereas solvent from the stills has already been degassed. Other reasons could be different levels of amylene (2-methyl-2-butene) used as a stabiliser in commercial CH₂Cl₂. As when the concentrations of RCM have to be low to prevent homodimerization, even low amounts amylene could have an effect on the yields. Amylene bearing a double bond could participate in the metathesis reaction by inserting more hindered olefin to the substrate. We tried the RCM reaction in two different solvent, but both toluene (59% yield) and chloroform (46%) gave lower yields than CH₂Cl₂ (Table 3, entries 6 & 7). These solvents again were straight from the bottle and it is possible that degassing was insufficient.
We also tried to increase the yield by adding the catalyst loading in two different batches. This reaction was done in larger scale (0.3 g) and we noticed that the second addition of the catalyst wasn’t necessary. Even though the reaction looked pure by TLC we could only isolate 27% yield. Unfortunately we don’t know what was driving the lower yield in this reaction.

It is known that metathesis reaction can be performed under acidic conditions. So we thought it could be possible to combine the deprotection, oxy-Michael reaction and the ring-closing metathesis in a one pot procedure. The three-reaction sequence gave the desired product 97 in 55% yield (1:8 E:Z tetrahydropyran-ring isomers) and no E-olefin was observed (Scheme 36). In the combined reaction we also isolated 10% of the oxy-Michael product 95 that did not undergo the RCM reaction. The combined yield of the acidified RCM reaction based on the recovered oxy-Michael intermediate 95 was 65%.

Table 3: Optimisation of the RCM reaction of the oxy-Michael product 95 with Grubbs 2nd generation catalyst.
**Scheme 36**: One-pot reaction combining the deprotection, Oxy-Michael reaction and the RCM reaction.

When the one-pot reaction was done in CH$_2$Cl$_2$ we were able to increase the yield of the product 97 to 65% (**Scheme 36**). We also could reduce the amount of used Grubbs 2$^{\text{nd}}$ edition RCM catalyst from 20 mol% to 10 mol%. We were pleased to be able to confirm the structure of 97 by single crystal X-ray diffraction (**Figure 1**).

**Figure 1**: X-ray structure of the RCM product 97.
2.5 Retro-Oxy-Michael Reaction

We postulated that the free alcohol 94 formed in the retro-oxy-Michael reaction could be the thermodynamic product and that we could obtain the alcohol with relatively weak bases. The reaction requires the deprotonation of the α-proton rather than the more acidic protons between the carbonyls. On the other hand, the reaction could proceed via a double anionic ketoester intermediate giving a product that is in the enolate form. This could provide us with an irreversible retro-oxy-Michael reaction.

![Diagram of the Retro-Oxy-Michael Reaction]

Table 4: Retro-oxy-Michael reaction attempts. a 5 equivalents of base unless otherwise stated

<table>
<thead>
<tr>
<th>Entry</th>
<th>Basea</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs$_2$CO$_3$</td>
<td>PhMe</td>
<td>RT to Reflux</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>TBAF (4 eq.)</td>
<td>THF</td>
<td>RT</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>THF</td>
<td>RT</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOK</td>
<td>THF</td>
<td>0 °C</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>LDA (2.2 eq.)</td>
<td>THF</td>
<td>-78 °C</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78 to RT</td>
<td>20%</td>
</tr>
</tbody>
</table>

With weak bases no reactivity was observed (Table 4, entries 1-3). Furthermore, no reactivity was observed when potassium tert-butoxide at 0 °C or lithium diisopropyl amide were employed at −78 °C (Table 4, entries 4-5). However when 5 equivalents of potassium bis(trimethylsilyl)amide was used we obtained the anticipated retro-oxy-Michael product in 20% yield (Table 4, entry 6).
When the reaction temperature was gradually increased we observed the formation of the product at -10 – 0 °C.

When the retro-oxy-Michael reaction was carried out at 0 °C using KHMDS as the base, we obtained the desired product 94 in 26% yield (23% b.r.s.m.) after 3 hours. This result demonstrates that the retro-oxy-Michael requires a strong base to work, indicating that it may proceed via double deprotonation 93 of the starting material (Scheme 37).

Scheme 37: Retro-oxy-Michael reaction via double deprotonation mechanism.

To increase the yield by reducing the temperature to -20 °C resulted in a reaction rate that was too slow to be synthetically useful. We monitored the reaction by using an internal standard (2,2'-dimethoxy-1,1'-binaphtalene) in the reaction mixture. Part of the mixture was quenched after specific time intervals and 1H-NMR was measured of the crude mixture. We discovered that the reaction has the highest ratio of the starting material and the product already after 20 minutes (1H-NMR-yield 39%, 43% starting material remaining) (Table 5). Increasing the reaction time to 1 hour only results in a slightly increased formation of 94 and led to a significant decrease in the recovered starting material 97. After 5 hours the yield of the retro-oxy-Michael product has decreased to 27% and only 13% of the starting material remaining. This might be because the product is not stable under the reaction conditions.
Table 5: Retro-Oxy-Michael reaction, $^1$H-NMR-yield of the starting material and the product

When the reaction was repeated and quenched after 20 minutes, the product was isolated in 36% yield (42% based on recovered starting material (b.r.s.m.)). We also tried other solvents for the reaction and under the same conditions, using Et$_2$O as a solvent (Table 6, entry 2) gave us 30% yield of 94. In toluene we obtained 26% yield with 42% of starting material and in DMF 11% yield with 67% of the recovered starting material 97 (Table 6, entries 3 & 4). When LiHMDS was used the yield dropped to 3% after 20 minutes and longer reaction time did not increase the yield.

![Chemical structure](image)

Table 6: Retro-oxy-Michael reaction with different solvents and bases.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>SM ($^1$H-NMR yield %)</th>
<th>Yield ($^1$H-NMR yield (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS</td>
<td>THF</td>
<td>20</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS</td>
<td>Et$_2$O</td>
<td>20</td>
<td>-</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS</td>
<td>DMF</td>
<td>20</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>KHMDS</td>
<td>Toluene</td>
<td>20</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS</td>
<td>THF</td>
<td>40</td>
<td>93</td>
<td>3</td>
</tr>
</tbody>
</table>
We postulated that the reaction could be reversible under basic conditions and might produce only small amount of the free alcohol product. We thought it could be possible to oxidise the free alcohol 94 in situ to the cascade precursor 67, which could form the cascade product 56 under the same conditions. We tried three different bases: Potassium carbonate, DBU and TBAF for the retro-oxy-Michael part of the reaction. We choose to use tetropropylammonium perruthenate (TPAP) as a quaternary ammonium salt oxidant with a co-oxidant N-methylmorpholine N-oxide (NMO). The use of quaternary ammonium salt as the oxidant could have provided the opportunity to replace the tetrabutyl ammonium cation with a chiral counter cation to obtain enantioselectivity in the reaction (Scheme 38). Unfortunately, no product was formed under the reaction conditions.

\[ \text{Scheme 38: Combined Retro-Oxy-Michael, Oxidation and the transannular cascade.} \]

The first attempt at the oxidation of the alcohol 94 was performed with Dess-Martin periodinane at 0 °C which gave the target cascade cyclisation substrate 67 in 57% yield. 67 exists entirely as the keto-tautomer and no isomerisation of alkene geometry was observed during the oxidation (Scheme 39).
We were uncertain if the retro-oxy-Michael product is stable under the purification conditions so we decided to carry out the oxidation with the crude reaction mixture. This resulted in an isolated yield of 36% over 2 steps (74% b.r.s.m.) (Scheme 40).

We also tried a one-pot procedure where the retro-oxy-Michael was quenched with monopotassium phosphate before the addition of Dess-Martin periodinate but the reaction gave only 5% yield of 67 and 30% of recovered starting material 97. We also tried to trap the formed free allylic alcohol by quenching the reaction with triethylsilyl triflate but the reaction gave no product.
2.6 Conclusions of the synthesis of the cascade precursor

We had now developed a six linear steps route for the cascade precursor, that is using Horner-Wadsworth-Emmons reaction and RCM reaction of the oxy-Michael product as the major disconnections. The total combined yield for the cascade precursor over the 6 steps is 8.4%. Despite the relatively good overall yield the Grignard addition to acrolein, RCM reaction and the retro-oxy-Michael reaction can be difficult to reproduce (Scheme 41).

Scheme 41: Summary of the synthetic route for the cascade precursor 67.
3. The transannular cascade

With the key substrate 67 in hand we now commenced investigations on the transannular cascade process. Aware of the risk of substrate decomposition and polymerisation we first examined the cascade reaction at low temperature, high dilution and weak base. With Cs₂CO₃ no reaction or substrate decomposition was observed even at ambient temperature. This indicates relatively high stability of the double enone macrolactone even to geometric isomerisation. As was observed by Evans group in the total synthesis of salvinorin A ²⁰, the use of TBAF as base was effective for the transannular cascade of our precursor 67. Upon closer examination of the reaction temperature the reaction did not proceed below –20 °C, and was even slow at 0 °C: after 12 h, reaction gave 29% of the cascade product 101 as a single diastereomer, alongside 20% recovery of the macrolactone starting material 67. The product was determined to exist entirely as its enol-tautomer by ¹H-NMR in a variety of NMR-solvents. The stereochemistry of the tricyclic product was determined by coupling constant and NOESY analyses (Scheme 42). We were also able to confirm the cascade product 101 by single crystal X-ray diffraction.

We managed to increase the yield of the cascade to 54% under phase-transfer conditions using tetrabutylammonium bisulfate (TBABs) as a phase-transfer catalyst and saturated aqueous
potassium hydroxide as a base at 0 °C (Scheme 43). The bisulfate counter anion is considered a weakly coordinating anion. That means it has weaker interaction in phase-transfer catalysis with an organic cation. Furthermore, the interaction with base-generated anions or other Lewis acids should be stronger when the competition between the catalyst’s own anion is smaller.

Scheme 43: Transannular cascade using TBABs as a phase-transfer catalyst.

3.1 1st optimisation of the base and the catalyst

3.1.1 Aqueous and solid potassium hydroxide

We decided to start the optimisation of the asymmetric cascade by choosing to use saturated aqueous potassium hydroxide as a base. We first screened seven different phase transfer catalysts including quinidinium (Table 7, entry 1), cinchoninium (Table 7, entries 2,5), cinchonidinium (Table 7, Entries 3-4, 6) and Maruoka-type (Table 7, entries 7-8) catalysts 69. In almost all of the cases the reaction gave only racemic mixture of the product 101. Only O-allyl-N-benzylcinchonidinium bromide 106 provided very low enantioselectivity in the cascade (Table 7, entry 4). The yields of the reactions varied from traces to 70% in the best result obtained using Maruoka-type catalyst 108 (Table 7, entry 8). With caesium hydroxide all material was lost and no product was observed. We also tried to reduce the temperature to -20 °C but no reaction was observed under these conditions. When the reaction done at -20 °C was brought to 0 °C all starting material disappeared without giving any product.
When almost all the reactions using aqueous KOH proved to be racemic we decided to change the base to solid potassium hydroxide. The asymmetric reactions were done by using six different catalysts (Table 8). We choose the 6-allyl-N-benzylechinonidinium bromide 105 which gave the only reaction with slight enantiomeric excess (Table 7, entry 4), the Maruoka-type catalyst 101 which gave the best yield (Table 7, entry 8) in the last screen and the (8S, 9R)-(-)-N-Benzylechinonidinium chloride 104 for the reactions. In addition to these we chose three other catalysts that we previously haven’t used in the cascade. Due to the lack

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (isolated)(^A)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH (aq)</td>
<td>102</td>
<td>1.5</td>
<td>26%</td>
<td>Racemic</td>
</tr>
<tr>
<td>2</td>
<td>KOH (aq)</td>
<td>103</td>
<td>2</td>
<td>36%</td>
<td>Racemic</td>
</tr>
<tr>
<td>3</td>
<td>KOH (aq)</td>
<td>104</td>
<td>2.5</td>
<td>49%</td>
<td>Racemic</td>
</tr>
<tr>
<td>4</td>
<td>KOH (aq)</td>
<td>105</td>
<td>1.5</td>
<td>58%</td>
<td>52:48</td>
</tr>
<tr>
<td>5</td>
<td>KOH (aq)</td>
<td>106</td>
<td>2</td>
<td>26%</td>
<td>Racemic</td>
</tr>
<tr>
<td>6</td>
<td>CsOH (aq)</td>
<td>104</td>
<td>1</td>
<td>&lt;20%</td>
<td>Racemic</td>
</tr>
<tr>
<td>7</td>
<td>KOH (aq)</td>
<td>107</td>
<td>1.5</td>
<td>30%</td>
<td>Racemic</td>
</tr>
<tr>
<td>8</td>
<td>KOH (aq)</td>
<td>108</td>
<td>1.5</td>
<td>70%</td>
<td>Racemic</td>
</tr>
</tbody>
</table>

*Table 7: Asymmetric transannular phase-transfer catalysed cascades using KOH (aq) as a base.\(^A\) The reactions were completed on a 5 mg scale. When ‘<20%’ is stated, the yield of the product is less than 1 mg.*
of available starting material we performed the reactions in analytical scale (Table 8, entries 1,3-6).

![Chemical structure](image1)

![Chemical structure](image2)

**Table 8**: Asymmetric phase transfer catalysed transannular cascade using KOH (s) as a base.\(^A\)

The reactions were completed on a 5 mg scale. When <20% is stated, the yield of the product is less than 1 mg.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Cat.</th>
<th>Time (h)</th>
<th>Yield (isolated)(^A)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH (s) 105</td>
<td>1</td>
<td>&lt;20%</td>
<td>57:43</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>KOH (s) 104</td>
<td>1</td>
<td>30%</td>
<td>63:37</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>KOH (s) 108</td>
<td>1</td>
<td>&lt;20%</td>
<td>53:47</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>KOH (s) 106</td>
<td>1</td>
<td>&lt;20%</td>
<td>51:49</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KOH (s) 109</td>
<td>2</td>
<td>&lt;20%</td>
<td>Racemic</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>KOH (s) 110</td>
<td>2.5</td>
<td>&lt;20%</td>
<td>52:48</td>
<td></td>
</tr>
</tbody>
</table>

Reactions done using solid potassium hydroxide as the base gave higher enantioselectivity than the corresponding reaction done with the aqueous base (Table 8, entries 1-3). The highest enantioselectivity so far was obtained when (8S,9R)-(−)-N-Benzylcinchonidinium chloride 104 was used as the phase transfer catalyst (Table 8, entry 2). The yield for this reaction was 30% which was lower than with aqueous base (49%). The new catalysts tried produced none or very low enantioselectivity (Table 8, entries 4-6).

In theory, the cascade reaction could be reversible and this could cause the low enantiocontrol in the reactions. Therefore we resubjected the enantioenriched material obtained from the reaction done with solid potassium hydroxide as the base and (8S,
9R)-(−)-N-Benzylcinchonidinium chloride 104 as the phase-transfer catalyst (Table 8, entry 2) to aqueous potassium hydroxide. We did not observe any loss in the enantioenrichment of the material or formation of the cascade precursor. This implies that the transannular cascade is not reversible.

We have been using 5 equivalents of base in the reactions and wanted to see if the amount of base has an effect on the enantioselectivity. Therefore, we reduced the amount of base to 0.5 equivalents. When the reaction (Table 8, entry 2) was done with reduced amount of base we observed the same enantioselectivity (e.r.: 63:37) but interestingly we also observed a new diastereomer 111 that exists as a 66:44 equilibrium mixture ratio of keto 111k and enol 111e tautomers (Scheme 44). Purification of the other diastereomer proved to be extremely difficult and even after purification we could still see the main diastereomer by NMR. The 2D-TLC proved that the new diastereomer is unstable on silica gel and transforms into the main product 101. This observation also may imply that the diastereomer is an intermediate in the reaction. This could explain why it’s formation is not observed when 5 equivalents of base. When more base is used all the compound 111 could be transformed to the diastereomer 101. Unfortunately, we could not measure the enantiomeric ratio of the other diastereomer. Chiral HPLC gave us a very broad single peak of the diastereomer, possibly because of the keto-enol tautomerism of the compound that must be a result of different configuration of the cyclised product that allows both forms to be present.
**Scheme 44**: The Asymmetric transannular cascade with catalytic amount of KOH (s).

Configuration of the newly found diastereomer **111** of the reaction was characterised using NOESY and J-couplings from the total correlation spectroscopy (TOCSY) of the keto-enol tautomers (**Figure 2**). TOCSY spectrum shows correlation between all protons in the same spin-spin system. TOCSY is not limited to correlations to only geminal or vicinal protons whereas COSY is.

**Figure 2**: NOESY and J-coupling analysis of the cascade diastereomer **111**.
In addition, we observed formation of acyclic unsaturated enone 112 in the reaction. This is a product from a decarboxylation reaction caused by a deprotonation of the γ-proton of the enone and the formation of the extended enolate 113. This is also one of the side reactions that reduces the yield of the cascade (Scheme 45).

![Scheme 45: Plausible mechanism for decarboxylation of cascade precursor 111.](image)

3.1.2 Use of NMR-standard

Because of the lack of cascade precursor, we were forced to use NMR-standard in the optimisations of the cascade due to the small scale of reactions. This made optimisation of the cascade much faster and allowed us to observe the yields of the products and side products of the reaction more accurately. This is especially important for observation of the elimination product 112 and the diastereomer 111 which could both be unstable under silica gel purification conditions. The use of small reaction scale unfortunately increases the uncertainty in the reaction preparation. While using stock solutions is an accurate way of measuring the cascade precursor, the problem arises when insoluble solid reagents have to be used. Controlling the amount of aqueous base was easy but the measurement of solid bases has an unwanted variability. Controlling the amount of phase-transfer catalyst in the reactions proved to be tricky as well because it’s insolubility in various solvents restricted the use of stock solutions. We were able to use stock solutions of the catalyst dissolved in CH₂Cl₂ but results from these reactions proved to be unreproducible even when the CH₂Cl₂ was evaporated before adding other reagents and solvents. Despite the disadvantages of the small-scale reaction optimisation we decided to carry on using 1 milligram of the starting material per reaction.
3.1.3 Optimisation of other bases

As we were able to improve the enantioselectivity of the asymmetric cascade by changing from aqueous to solid base we decided to continue the optimisation of the cascade by doing a base screening. We selected aqueous and solid forms of 5 different bases. The use of aqueous NaOH as the base surprisingly gave us also the other diastereomer 111 even when 5 equivalents was used (Table 9, entries 1-2), unlike with aqueous KOH only one diastereomer (Table 7). With either with aqueous or solid NaOH the enantioselectivity was racemic or poor and therefore we chose to use mainly potassium bases in this optimisation. No elimination product was observed either with potassium or sodium hydroxide. This does not necessarily mean that the elimination product does not form it could also be unstable under these conditions. (Table 9, Entries 1-2). In contrast, the largest amount of elimination product (24%) was observed when solid potassium phosphate (K$_3$PO$_4$) was used (Table 9, entry 5).
With aqueous K\textsubscript{2}CO\textsubscript{3} the yield was 18\% with 65:35 e.r whereas the reaction with solid K\textsubscript{2}CO\textsubscript{3} gave 11\% yield with enantiomeric ratio of 70:30 (Table 9, entries 4-5). Compared to potassium carbonate, solid caesium carbonate gave similar 12\% yield but with lower 61:39 e.r (Table 9, entry 9). Slightly better yields were obtained with potassium phosphate (K\textsubscript{3}PO\textsubscript{4}) bases. Solid K\textsubscript{3}PO\textsubscript{4} gave 37\% yield (68:32 e.r) which was the second best observed in the base screen (Table 9, entry 5). The best base in terms of yield was KF (aq) with 43\% yield and 65:35 e.r.. Potassium

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time</th>
<th>Elimination</th>
<th>Yield</th>
<th>d.r.</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH (s)</td>
<td>1.5</td>
<td>-</td>
<td>24%</td>
<td>1:1</td>
<td>52:48</td>
</tr>
<tr>
<td>2</td>
<td>NaOH (aq)</td>
<td>1.5</td>
<td>-</td>
<td>26%</td>
<td>1.6:1</td>
<td>Racemic</td>
</tr>
<tr>
<td>3</td>
<td>K\textsubscript{2}CO\textsubscript{3} (s)</td>
<td>24</td>
<td>11%</td>
<td>11%</td>
<td>1.75:1</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>K\textsubscript{2}CO\textsubscript{3} (aq)</td>
<td>23</td>
<td>6%</td>
<td>18%</td>
<td>2.2:1</td>
<td>65:35</td>
</tr>
<tr>
<td>5</td>
<td>K\textsubscript{3}PO\textsubscript{4} (s)</td>
<td>25</td>
<td>24%</td>
<td>37%</td>
<td>2.7:1</td>
<td>68:32</td>
</tr>
<tr>
<td>6</td>
<td>K\textsubscript{3}PO\textsubscript{4} (aq)</td>
<td>20</td>
<td>1%</td>
<td>12%</td>
<td>&gt;20:1</td>
<td>53:47</td>
</tr>
<tr>
<td>7</td>
<td>KF (aq)</td>
<td>20</td>
<td>8%</td>
<td>43%</td>
<td>4:1</td>
<td>65:35</td>
</tr>
<tr>
<td>8</td>
<td>KF (s)</td>
<td>24</td>
<td>-</td>
<td>32%</td>
<td>1:1</td>
<td>73:27</td>
</tr>
<tr>
<td>9</td>
<td>Cs\textsubscript{2}CO\textsubscript{3} (s)</td>
<td>24</td>
<td>4%</td>
<td>12%</td>
<td>2:1</td>
<td>61:39</td>
</tr>
</tbody>
</table>

*Table 9: Optimisation of the bases used in asymmetric transannular cascade*
fluoride also effected the highest enantioselectivity as the solid base gave 73:27 e.r. and yield of 32% (Table 9, entries 7-8).

Some general trends were observed in the base screen. We noticed that aqueous bases gave higher yields and diastereomeric ratios compared to the corresponding solid bases. At the same time, the aqueous bases gave lower enantioselectivities than the solid bases. When aqueous potassium phosphate was used only the diastereomer 101 was obtained (Table 9, entry 6). Aqueous potassium fluoride also gave relatively high ratio of diastereomer 101 compared to the minor isomer 111 (4:1) (Table 9, entry 7). Surprisingly when solid KF was used the ratio of diastereomers was 1:1 (Table 9, entry 8). In addition to these inorganic bases we tried a few different organic bases and also chiral phosphoric acid 114 \(^{70}\) and Schreiner’s thiourea catalyst 116 \(^{38}\). The phosphoric acid catalyst along with quinine and the thiourea catalyst did not show any reactivity (Table 10, entries 4-6). With potassium tert-butoxide 23% yield was obtained without any enantiomeric excess (Table 10, entry 1) and with potassium acetate no reactivity was observed (Table 10, entry 2). With strong phosphazene base 115 \(^{71}\) reaction gave 22% yield of racemic mixture of only the major diastereomer (Table 10, entry 3).
When we observed that with stronger bases the enantioselectivities were lower than with weaker bases we decided to make different potassium phenoxides with known basicity.\textsuperscript{72} We found that $p$-nitro phenoxide that has $pK_a$ of 14.5 in DMSO produced 10\% of the product. With more basic phenoxides; potassium 3-fluoro phenoxide ($pK_a$ 15.8 in DMSO)\textsuperscript{73} gave yield of 68\% and potassium phenoxide ($pK_a$ 18 in DMSO, $pK_a$ 10 in water)\textsuperscript{73} gave 41\% yield. Unfortunately, all phenoxide bases gave racemic mixtures of the product. The reactions indicate that the cascade requires at least a base that has $pK_a$ of 14.5 in DMSO. These $pK_a$ values are measured in DMSO which does not give the absolute $pK_a$ that the reaction requires in toluene.

\textit{Table 10: Optimisation of the cascade with organic bases and and a chiral phosphoric acid}

\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Base & Time & Cat. & Yield & d.r. & e.r. \\
& & (h) & & & (101):(11) & (101) \\
\hline
1 & KOrBu & 24 & 97 & 23\% & 1:1 & racemic \\
& (s) & & & & & \\
2 & KOAc & 97 & N.R. & - & - & \\
& (s) & & & & & \\
3 & 112 & 0.25 & 97 & 22\% & >20:1 & 52:48 \\
& & & & & & \\
4 & - & 111 & N.R. & - & - & \\
& & & & & & \\
5 & - & quinine & N.R. & - & - & \\
& & & & & & \\
6 & - & 113 & N.R. & - & - & \\
\hline
\end{tabular}
Table 11: The cascade with potassium phenoxides as bases.

The difference in yields and enantioselectivities between solid and aqueous potassium hydroxide could be explained with amphiphilic nature of the product and different basicity of KOH in aqueous and in organic solution. Deprotonation of the macrocycle can occur on the interface of the organic and aqueous phase as well in aqueous phase. It is possible that the low enantiocontrol is due to a background reaction occurring without the chiral phase-transfer catalyst. Because the pKₐ of acetoacetates are usually lower in the aqueous environment the deprotonation is much faster in aqueous phase where the phase-transfer catalyst operates less efficiently because of the competing electrostatic and hydrogen bonding interactions. One of the reasons why potassium fluoride proved to be the optimal base could be that it’s conjugate acid has very low pKₐ (3.15) in aqueous media minimising the reaction to operate in aqueous phase. The reaction occurs preferentially in the organic phase where the interaction between
catalyst and the cascade precursor could be better and fluoride anion has higher basicity (pK\textsubscript{a} of 15 in DMSO).

We tested if the reaction happens without the phase-transfer catalyst by using aqueous potassium hydroxide solution. When the reaction was done in toluene at 0 °C we could observe 95% yield of the diastereomer 101 (Scheme 46). The high yield of the reaction with just aqueous potassium hydroxide as a base shows that the background reaction is fast without the catalyst. This is very likely a reason for the mostly racemic results when aqueous potassium hydroxide was used together with chiral phase-transfer catalysts (Table 7). Furthermore, the reaction without catalysts produces higher yield compared to the catalysed reactions. Catalyst hydroxy-group promoted hydrolysis of the ester in the starting material or in the product could be an explanation for the lowered yields. This could also explain why two of the best yields in table 7 have been obtained when the catalyst doesn’t have a free alcohol.

![Scheme 46: The cascade without phase-transfer catalyst with KOH (aq) as a base.](image)

3.2 Second-generation catalyst screen

As the base screen did not provide satisfactory results we performed a new catalyst screen using aqueous potassium fluoride as the base (Table 12). Potassium fluoride was chosen because it has given the best result so far (Table 9, entry 8). Further, with potassium fluoride we didn’t observe any background reaction. Since we had not observed high enantioselectivity with the catalysts previously used we decided to attempt the reaction with new catalysts but some of the previously used catalyst were also chosen.
Table 12: Secondary catalyst screen.
In the secondary catalyst screen we observed that quinidinium (Table 12, entries 8-10) and quininum (Table 12, entries 11-12) catalysts provided poor yields and poor enantioinduction in the reaction. In general, better, albeit still poor, yields and enantioselectivities were observed with cinchonidinium (Table 12, entries 1-4) and cinchoninium (Table 12, entries 5-7) catalysts. It was observed that the catalyst requires a free alcohol (Table 12, entry 1-2) rather than allylated (Table 12, entry 2) or benzylated (Table 12, entry 12) catalysts that both gave only trace amounts of product. Electron rich or poor benzyl groups on the catalyst did not have a large effect on the yields or selectivities of the reaction, with electron rich arenes giving slightly higher yields and enantioinduction. We were delighted to observe that 119 (Table 12, entry 3) and it’s pseudoenantiomer 123 (Table 12, entry 7) provided us high levels of enantioselectivity and a pleasing increase in the yields of the transannular cascade. The reaction with 119 as the catalyst provided us with yield of 61% yield with enantiomeric ratio of 89:11 with 123 as catalyst gave a 56% yield, and a 11:89 enantiomeric ratio. These anthracenyl catalysts also gave the best diastereomeric ratios which were 4:1 with 119 and 6:1 with 123. This suggests that the bulkiness of the quaternising substituent has a major effect on the outcome of the reaction. We also tried the corresponding quinidinium 131 and quininum catalyst 132 but no reactivity was observed (Scheme 47).
Scheme 47: Transannular cascade with N-(9-anthracenylmethyl)quinindinium 131 and N-(9-anthracenylmethyl) quininium catalysts 132.

We decided to confirm the results of the catalyst screen, using catalyst 119 (Table 12, entry 3), by increasing the amount of the starting material from 1 to 5 mg. On the larger scale the enantiomeric ratio was improved to 94:6 and also the isolated yield of the thermodynamic diastereomer (40%) of the 5 mg scale reaction was higher than the $^1$H-NMR yield of the reaction done on a 1 mg scale (49%).

Scheme 48: The asymmetric transannular cascade with N-(9-anthracenylmethyl)cinchonidinium chloride 119.
3.2.1 Second generation base screen

With the optimal catalyst in hand we continued with a second optimisation of the base. When potassium hydroxide was used we also received an increase in yield (58%) and enantioselectivity (e.r. 80:20) (Figure 3). This result shows that even with strong base, high enantioselectivity can be obtained with the catalyst 119. Due to the high enantioselectivity the background reaction must be slower than the catalysed one. The reaction also afforded us a high dr (8.3:1) as seen with many strong bases. A general trend was observed that strong, aqueous bases gave a higher ratio of the thermodynamic diastereomer 101. The highest diastereoselectivity (22:1) was observed in aqueous potassium carbonate (K$_2$CO$_3$ (aq)). The yield with K$_2$CO$_3$ (aq) was 48% and the enantiomeric ration 84:16. Slightly lower enantioselectivity of 82:18, yield 46% and diastereoselectivity (d.r. 6.6:1) was obtained when solid potassium carbonate was used. Aqueous potassium phosphate (K$_3$PO$_4$ (aq)) gave an enantiomeric ratio of 87:13, yield of 46% and 6.6:1 dr. Similar enantioselectivity (81:19) and yield (52%) was obtained when solid potassium phosphate (K$_3$PO$_4$ (s)) was used, though with a higher diastereoselectivity of (9.2:1). As previously observed, the weaker fluoride bases gave the best results. Cesium fluoride (CsF) gave enantiomeric ratio of 89:11 with lower diastereoselectivity (3.1:1) in 65% yield. The best result with the new catalyst was using solid potassium fluoride (KF (s)) as a base, giving an enantiomeric ratio of 94:6 with a 78% yield and diastereoselectivity of 1.2:1. Surprisingly when sodium fluoride was used no reactivity was observed with both solid and aqueous base (Figure 3).
Figure 3: Secondary base screen.

The best bases for the asymmetric cascade proved to be solid and aqueous potassium fluoride, although the diastereoselectivities were lowest. In general, it appeared that strong bases gave good diastereoselectivity but poor enantioselectivity, while weak bases, such as KF, gave the opposite result.

3.2.2 Optimisation of the solvent and concentration

After the second base screen, we continued with optimisation, by investigating the solvent (Figure 4). We found that in cyclohexane and acetonitrile no reaction occurred. We attribute lack of reactivity with cyclohexane to the insolubility of the starting material. With chlorinated aprotic solvents lower enantioselectivity was observed. With CH$_2$Cl$_2$ as a solvent the reaction gave yield of 28% with enantiomeric ratio of 67:33, with the reaction favouring the kinetic diastereomer 111 in 1:5.7 ratio. Chloroform as a solvent also favours formulation of the kinetic diastereomer 111 in 1:4.6, with a yield of 66% and 74:26 enantiomeric ratio. Methyl tert-butyl ether gave a yield of 33% and enantioselectivity of 92:8 dr. Better results were obtained with aromatic solvents. Chlorobenzene gave a yield of 47% and enantiomeric ratio of 87:13. Similar results to toluene were obtained with benzene as a solvent: the cascade giving a yield of 66% and high enantioselectivity (94:6) though preferring the kinetic product 111 in a 1:1.4 ratio. With benzene as a solvent the reaction still had 20% starting material left after 24 hours of reaction time (Figure 4).
After the solvent screen we decided to see how the concentration of the reaction affects the yield and selectivity. We increased the concentration of substrate in toluene to 0.2 M and we observed lowering of the enantioselectivity to 91:1. The yield of the reaction decreased to 48% with diastereoselectivity of 1.25:1. When the concentration was decreased to 0.025 M, the enantioselectivity slightly increased to 95:5 with the major product being the kinetic diastereomer in 1:1.35 dr. After 24 hours of reaction we still could see 30% of the starting material remaining unreacted. Surprisingly, we also observed starting material in the 0.2 M reaction while in the 0.05 M reaction no starting material was seen. Neither of the reactions produced as good yield of the product as the 0.05 M concentration (Figure 5).

**Figure 4:** Secondary solvent screen.

**Figure 5:** Screen of concentration of the cascade.
3.2.3 Solid and aqueous potassium fluoride

After investigating the effect of concentration, we wanted to see the effect of base loading on the reaction. We performed this screen using aqueous potassium fluoride in toluene. We observed a clear trend that when the amount of base was increased the enantioselectivity of the reaction decreased, though, the diastereoselectivity increased in favour of the thermodynamic product 101. When 2 equivalents of aqueous base were used the reaction gave a 74% yield of a 1:1.3 mixture of the diastereomers favouring the kinetic product 111. The thermodynamic diastereomer 101 was still highly enantioenriched (93:7) in contrast when 50 equivalents was used, the reaction give only the thermodynamic diastereomer 101 in 88:12 enantiomeric ratio (Figure 6).

![Figure 6: Optimisation of the amount of potassium fluoride (KF (aq))](image)

When increasing the amount of aqueous base lowered the enantioselectivity, we decided to see if solid base showed the same effect. We performed the reaction in toluene with 1 and 5 equivalents of the solid potassium fluoride as a base. Both reactions gave high enantioselectivity and we did not observe any decrease when the amount of base was increased. With 5 equivalents of base we obtained 91% yield with 1:2.3 diastereoselectivity in favour of the kinetic product 111. The enantioenrichment of the thermodynamic diastereomer 101 remained at 94:6 (Figure 7).
While we saw high enantioselectivity in toluene we also wanted to see if we would be able to improve the reaction in benzene. We performed the reaction with 1 and 2 equivalents of both aqueous and solid potassium fluoride in benzene. We did see an improvement in the yield when using solid base (Figure 8). 1 equivalent of solid KF gave us 95% yield and 2 equivalents gave 93% yield and the enantioselectivity in the reactions stayed at 95:5. With aqueous base we saw a decrease in enantioselectivity when the amount of base was increased, as previously observed in the reactions done in toluene (Figure 8). With 1 equivalent of the aqueous base, 20% of the starting material was still present after 24 hours reaction.

**Figure 7**: Amount of the solid potassium fluoride in toluene.

**Figure 8**: The effect of the amount of potassium fluoride in benzene.
We increased the reaction time and the amount of base so we could increase the yield of the thermodynamic diastereomer 101. The 2 day reaction with 5 equivalents of base increased the diastereoselectivity to 1.3:1 while still maintaining the enantiomeric ratio of 95:5. When the amount of solid base was increased to 20 equivalents we saw lower yield but increased diastereoselection to 2:1 and only a slight decrease in enantioselectivity to 94:6 (Figure 9).

**Figure 9:** Increased reaction time in the reaction with solid potassium fluoride (KF) in benzene.

When the reaction time was increased, we were able to increase the yield and also diastereoselectivity of the reaction with 1 equivalent of aqueous potassium fluoride to 3.4:1. Enantioselectivity decreased when the reaction time was 48 hours (Figure 10).

**Figure 10:** Increase in reaction time from 24 hours to 48 hours with 1 equivalents of aqueous potassium fluoride (KF (aq)).
We also briefly screened the catalyst loading used in the reaction. The yield of the reaction was greatest when 20 mol% catalyst was used, though diastereoselectivity was poorest (1:1.6). The enantioselectivity of the reaction did not seem to be affected by the amount of catalyst. Thus, we decided to continue with 10 mol% of the catalyst because the yield of the thermodynamic diastereomer highest under these conditions (Figure 11).

![Figure 11: The effect of the catalyst loading on the reaction.](image)

Our optimised conditions were to use 5 equivalents of solid potassium fluoride as a base in benzene with catalyst 119 giving 85% yield of 1.3:1 ratio of the diastereomers with 95:5 enantiomeric ratio of the thermodynamic product 101 (Scheme 49).

![Scheme 49: Optimised conditions with N-(9-anthracenylmethyl)cinchonindinium 119.](image)

With optimised conditions in hand for the asymmetric transannular cascade we wanted to see if the optimised conditions are applicable when the pseudo enantiomer of the catalyst 123 is used. This is done to see if we could also control the formation of the other enantiomer of the
cascade product. When the N-(9-anthracenylmethyl)cinchonium bromide 123 was used, we pleasingly observed similar results those with the optimised catalyst. The reaction gave a 1H NMR-yield of 85% with diastereomeric ratio of 1.7:1 favouring the thermodynamic product 101 with an enantiomeric ratio of 5:95. We isolated the thermodynamic product 101 in 60% yield and while this is bit higher than the 1H-NMR-yield, it could be explained by conversion of the kinetic product 111 to the thermodynamic product 101 during silica gel purification (Scheme 50). The kinetic product was not isolated.

![Scheme 50: Asymmetric cascade with catalyst pseudoisomer 123.](image)

### 3.3 Possible kinetic resolution

Because we saw a correlation between yield, diastereoselectivity and the enantioenrichment of the thermodynamic product. We suspected a kinetic resolution could be taking place.

When the reaction was monitored by TLC analysis we first saw formation of the kinetic diastereomer 111 and then formation of the thermodynamic product 101. We believe this observation is evidence that 111 is an intermediate in the formation of 101 from the cascade precursor. In previous examples we have observed a correlation between diastereoselectivity and enantioselectivity. In the reactions where the thermodynamic product 101 was the major diastereomer we have observed lower enantioselectivity than in the reactions where the kinetic product 111 was the major isomer. We postulated it could partly be due to a kinetic resolution of the kinetic diastereomer (Scheme 51). When the reaction time is increased more of the
kinetic diastereomer with lower enantioselectivity is converted to the thermodynamic product \textbf{101} causing lower enantioenrichment of \textbf{101}.

\textbf{Scheme 51: Kinetic resolution of the cyclisation product 111.}

To investigate this, we first wanted to verify that the decline of the enantioselectivity through the reaction, is not due to erosion of the enantioenriched product under basic conditions. We exposed purified enantioenriched (e.r. 94:6) \textbf{101} to aqueous potassium hydroxide for 30 minutes in toluene (\textbf{Scheme 52}). After a normal workup and purification we did not observe any decline in the enantioenrichment. This indicates that erosion of enantioselectivity in the reaction is not because the product is decomposed/racemised under basic conditions. We did not obtain any other products from this reaction, which confirms that the reaction is irreversible when using aqueous potassium hydroxide as the base.

\textbf{Scheme 52: Enantioselectivity of the product with aqueous potassium hydroxide.}
Because we could not measure the enantioenrichment of the kinetic diastereomer, we wanted to confirm that the kinetic diastereomer 111 converts to the thermodynamic product 101 under basic conditions. We also wanted to see the effect that the conversion has on the enantioselectivity. We performed the transannular cascade using solid potassium fluoride as a base and N-(9-anthracenylmethyl)cinchonidinium chloride 119 as a phase-transfer catalyst. From the 24 hour reaction we obtained a yield of 81% (1H-NMR yield) of a 1:2.1 mixture favouring the kinetic diastereomer 111 (62% yield), with the desired diastereomer 101 (29% yield) having a 95:5 enantiomeric ratio. The crude mixture was filtered through silica gel to remove the catalyst and was then subjected to an aqueous potassium hydroxide solution for 30 minutes. After workup this reaction afforded a 40% (1H-NMR) yield of only the desired thermodynamic diastereomer 101 with a corresponding decrease in enantioenrichment (87:13) (Scheme 53).

**Scheme 53:** Treatment of the enantioenriched material with aqueous potassium hydroxide.

Even though the experiment results in lower overall yield, it confirms that the kinetic product 111 is converted to the thermodynamic product 101. The yield of 101 is increased from 26% to 40%. We could calculate the enantiomeric excess for the additional thermodynamic product 101 obtained from the treatment of the enantioenriched material with base. If we don’t take into account any possible erosion of the already obtained thermodynamic product, we get 11% yield for the extra material. When the e.r. of the product from the phase-transfer reaction is 95:5 we
can calculate that the rest of the material is converted to the thermodynamic product 101 at 76:36. Hence this is the lowest e.r. that the kinetic product 111 can have because if there is any loss of the enantioenriched thermodynamic product obtained in the first step that would mean the converted product has to have higher e.r. to obtain the final 87:13 enantiomeric ratio.

We also treated the enantioenriched crude mixture of diastereomers (95:5 e.r.) with aqueous potassium fluoride under phase transfer conditions. This was done to see the effect that the aqueous potassium fluoride base has on the kinetic resolution. The treatment of the catalyst free crude material lowered the combined from 93% to 77%. From 1:1.3 d.r. the ratio changed during the aqueous base treatment to 6.7:1 d.r. favouring the thermodynamic product 101. The enantioselectivity also reduced from 95:5 to 92:8 (Scheme 54).

![Scheme 54: Enantioenriched material under phase-transfer conditions with aqueous potassium fluoride as the base.](image-url)
When we used the same calculation that we did for the previous reaction (Scheme 53), we could calculate the enantiomeric ratio of 88:12 for the additional product from the conversion of the kinetic product to the thermodynamic product. In this case we can’t say what the e.r. of the kinetic product was because there still was kinetic product remaining after the reaction. If a kinetic resolution was in operation the material still left after the reaction would have lower enantioenrichment than the material converted.

We also decided to use TBAF for the racemic cascade and then treat the crude mixture of products with a chiral phase-transfer catalyst to see if we can observe a kinetic resolution. Unfortunately, the first time we used TBAF, we only observed the formation of the thermodynamic product. We attribute this to any kinetic product being converted to thermodynamic product by the strongly basic TBAF. We decided to lower the temperature to 0 °C and lower the amount of TBAF to 1 equivalent. With these milder conditions we received a mixture of both diastereomers that we quenched and filtered through silica gel and then divided into two. One portion was treated with \(N\)-(9-anthracenylmethyl)cinchonidinium chloride \(119\) and the second with the \(N\)-(9-anthracenylmethyl)cinchoninium bromide \(123\) under phase-transfer conditions using solid potassium fluoride as a base (Scheme 55).
Scheme 55: Kinetic resolution of the racemic mixture of the cascade diastereomers.

This time we did not use a $^1$H-NMR standard in the reactions so we only have the relative ratios of the diastereomers. Even with the use of a NMR standard it would be a challenge to calculate the absolute enantioselectivity of 111 because, as we often seen, part of the product is lost as byproducts during the resolution (Scheme 53). We can however see a change in the diastereomeric ratio favouring the thermodynamic product. This change is small because the
TBAF reaction favours the thermodynamic product. We could observe slight enantioselectivity in the resolution with both catalysts (Scheme 55).

After this investigation, we conclude that the reaction proceeds though the kinetic product that is converted to the thermodynamic product. With a strong base the kinetic product can be entirely converted to the thermodynamic product, but with weaker bases, like potassium fluoride, the conversion of the kinetic product does not go to completion. The results also indicate the presence of a kinetic resolution and a lower enantioselectivity of the initial cascade to form the kinetic product during the kinetic resolution. Some of the kinetic product is converted to the thermodynamic product in good enantioenrichment, while some of the kinetic diastereomer is lost to decomposition as the overall yield decreases.
4. Synthesis of the substrates for the cascade.

4.1 Synthesis of the methylated 1,3-dicarbonyl

Having established a successful synthetic route to the model substrate we began investigation of related substrates to broaden the reaction scope. We envisaged that the most facile route to synthesise related substrates was by modifying the core of the precursor by functionalising the acidic methylene position between the ketoester carbonyls. We postulated that this would provide a simple means to form a range of substrates for examination as cascade precursors.

We decided to start the modification from a methylation of the dicarbonyl 95. The methyl group was introduced at the stage before the ring-closing metathesis. With iodomethane in refluxing acetone we were successfully able to synthesise the methylated open-chain diene 134 in 70% yield as an inseparable 50:50 mixture of the methyl diastereomers (Scheme 56).

We also tried to methylate the RCM-product 97 with the same conditions using potassium carbonate in refluxing acetone but in this reaction only 15% yield was isolated after 18 hours reaction. This is likely to be attributed to the steric crowding of the ring system, reducing the rate of the mono-cyclic system (Scheme 56).

Scheme 56: Methylation of the RCM-product 97 and RCM-precursor 95.
With the ring-closing metathesis of the methylated product 134 using Grubbs 2\textsuperscript{nd} edition catalyst under refluxing CH\textsubscript{2}Cl\textsubscript{2} gave us the closed methyl containing RCM-product 135 as a single geometrical isomer in 56\% yield, therefore affording the methylated substrate in 39\% from the unfunctionalised precursor 95. In an attempt to improve the alkylation rate, the methylation of the RCM-product was also attempted by using a strong potassium base. Using 1.05 equivalent of the KHMD\textsubscript{S} in THF gave the methylated product 135 in 64\% and overalkylation product 136 in 10\% yield after 44 hour of reaction time at ambient temperature. (Scheme 56).

We were pleased to find that the methylated macrolactone 135 underwent retro-oxy-Michael reaction followed by Dess-Martin oxidation to give the cascade precursor in 35\% yield over two steps (Scheme 57).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme57.png}
\end{center}

\textit{Scheme 57: Retro-oxy Michael reaction of the methylated cascade precursor.}

As a side-product from the reaction, we observed a decarboxylation process occurring of the starting material. This was not observed when the non-methylated starting material was used. The obtained side-product 138 implies a competing kinetic deprotonation of the allylic proton (Scheme 58). This is probably due to the slower deprotonation of the $\alpha$-proton and possibly too fast a rate of addition of the KHMD\textsubscript{S}. When deprotonated, the enolate should suppress this decarboxylation pathway.
With our methylated cascade substrate in hand, we set about investigating the cascade process. Unfortunately, when we attempted the optimised asymmetric cascade for the methylated precursor 137 using KF (s) as base we could not observe any formation of the cascade product. Similarly, no reaction was observed with aqueous potassium fluoride, aqueous potassium hydroxide or solid potassium phosphate.

Instead of affording the cascade product, the product observed was a decarboxylation of the ester via formation of the extended enolate 141 (Scheme 59) that we also observed when the non-methylated precursor was used (Scheme 44).

Scheme 58: Plausible mechanism of the decarboxylation side reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Catalyst</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KF (aq)</td>
<td>119</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>KF (s)</td>
<td>119</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>KF (s)</td>
<td>123</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>K3PO4 (s)</td>
<td>119</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td>KOH (aq)</td>
<td>Decomp.</td>
<td></td>
</tr>
</tbody>
</table>

Table 13: Transannular cascade of the methylated cascade precursor 137.
Scheme 59: Plausible mechanism of the decarboxylation of the methylated cascade precursor 137.

The result implies that, unlike in the non-methylated cascade, the competing decarboxylation is predominant reaction when a methyl group is present on the precursor. We were surprised and disappointed that so small change in the molecule prevented the cascade reaction. This also prevented us of using the most obvious access to different substrates. The first plausible explanation for the failure of the cascade is the different pK_a of the methylated substrate, although the difference is small. A second explanation is that the methyl-group provide sufficient steric hindrance to block the enolate addition to the enone (Figure 12). We have observed previously that the catalyst has the largest effect on the yield and selectivity of the cascade. It could be that the methyl group prevents the docking of the catalyst to the enolate or if the deprotonation is catalyst-induced, the methyl-group prevents the deprotonation.

Figure 12: Structure of the deprotonated methylated precursor.
4.2 Synthesis of the substrates via 1,3-dioxin-4-ones

To synthesise different substrates we needed a different approach for the synthesis. We realised that using 1,3-dioxin-4-one 145 could provide us relatively easy access to substrates with different length carbon chains via the thermolysis reaction developed by Jäger and Wenzelburger\(^7\) and Sato \textit{et al.}\(^{77,78,80,81,82,83}\). This strategy does not alter the synthetic route excessively and enables us to use the same aldehyde 67 in the HWE-reaction as before (Scheme 60).

\begin{align*}
\text{OTES} & \quad \text{OTES} \\
\text{H} & \quad \text{OTES} \\
80 & \quad 144 \\
\end{align*}

\textit{Scheme 60: Retro-synthetic analysis for access to different substrates.}

In the thermolysis, an acylketene 145 is formed which can be trapped with different nucleophiles\(^8\). The method could be used with different unsaturated alcohols, to replace the ester with an amide or thioester linkage, and also enable the synthesis of substrates with aromatic groups on the nucleophile’s core (Figure 13).

\begin{align*}
\text{OTES} & \quad \text{OTES} \\
\text{OTES} & \quad \text{OTES} \\
145 & \quad 147 \\
\end{align*}

\textit{Scheme 61: Thermolysis of the 1,3-dioxin-4-one intermediate.}
In the synthesis of the HWE-reagent 150 we used the method published by R. K. Boeckman with small modifications. The chlorination of commercial 2,2,6-trimethyl-1,3-dioxen-4-one 148 using LDA as a base and hexachloroethane as a chlorinating agent provided us the 6-chloromethyl-2,2-dimethyl-1,3-dioxen-4-one 149 in 57% yield. In the phosphonate formation instead of using the potassium tert-butoxide as a base (as in the published) work we used sodium hydride as the base. The yield of the reaction gave the same yield of 54% as previously reported (Scheme 62).

**Scheme 62: Synthesis of the 1,3-dioxin-4-one HWE-reagent 150.**
In the HWE-reaction we decided to use the same conditions that we had used before with the HWE-reagent 80 (Scheme 63). To our delight, the first attempt gave us an excellent 91% yield of the unsaturated 1,3-dioxin-4-one 145 as a single (E)-isomer. (Scheme 63). The 1,3-dioxin-4-one HWE-reagent 149 could also be converted to the ketoester phosphonate 80 by using the thermolysis conditions, affording a 61% yield.

**Scheme 63: Synthesis of the HWE-products.**

Thermolysis of the 1,3-dioxinone product 145 in the presence of but-3-en-1-ol gave the unsaturated 1,3-dicarbonyl compound 91 used for the synthesis of the cascade precursor in high 89% yield (Scheme 63).
4.3 Synthesis of the 5,6,6-substrate

Using the route through 1,3-dioxin-4-one substrate 145, we decided to synthesis the cascade precursor 153 that would give us the 5,6,6 fused ring system 154 (Scheme 64). This substrate could be synthesised by using the same chemistry as for the synthesis of the 6,6,6-precursor.

**Scheme 64**: Synthesis plan of the 5,6,6-cascade precursor 153.

The synthesis began with a thermolysis of the 1,3-dioxin-4-one 145 with allyl alcohol at 110 °C in toluene giving the unsaturated ketoester 151 in 84% yield, which was then treated with acidified chloroform at 0 °C. The deprotective oxy-Michael reaction gave excellent 97% yield of the tetrahydropyran product 155 favouring the syn-product over anti-product in 13.7:1 dr. (Scheme 65).

**Scheme 65**: Thermolysis of the 1,3-dioxin-4-one compound 145 and the deprotective oxy-Michael reaction of the compound 151.
Figure 14: NOESY-analysis of the minor diastereomer 156 of the oxy-Michael reaction.

In the ring-closing metathesis with Grubbs 2nd generation catalyst in refluxing CH₂Cl₂ we obtained 43% yield of both Z- and E-macrocycles 157 and 158 in 2.6:1 ratio (Scheme 66). It is surprising that in the ring-closing metathesis forming an 11-membered system, we can also obtain the E-isomer 156, but when with the one carbon longer chain in the 12-membered ring formation we only observe the formation of Z-isomer (Scheme 32).

Scheme 66: RCM reaction of the 5,6,6-system.

One could assume that when the ring size increases reduced ring strain enable increased formation of the E-product 157. This could be due to a chelation of the formed metalallocarbene ruthenium intermediate 157 to the carbonyl-oxygen. In the RCM reaction of the 5,6,6-system, the possible carbonyl-chelation forms a 6-membered ring whereas in the 6,6,6-system the ring size for the chelate would be 7-membered 158. In the 6,6,6-system the chelation could even be to the ester oxygen rather than to the carbonyl. In this chelation 5-membered chelation 159 could be formed. This type of chelation would not be easily formed in the 5,6,6-system as it would require the formation of strained 4-membered ring (Scheme 67).
Scheme 67: Postulated chelation of the metallocarbene with the ester moiety.

The retro-oxy-Michael reaction proved to be very challenging with the 5,6,6-ring system. The conditions that had been optimised for the 6,6,6-system did not give any product, even after the reaction was attempted several times. We figured out that with the 5,6,6 system the reaction is much faster and also the decomposition of the product seemed to be rapid.

Scheme 68: Retro-oxy-Michael reaction of E-isomer.

With the E-macrolactone 157 we unfortunately observed only trace amount of a product we assume is the $E,E$-cascade precursor 161 (Scheme 68). By inspection of the crude $^1$H-NMR small peaks of two sets of possible enone-protons having $J$-coupling of 16.0 Hz and 16.5 Hz. The amount of the material was too low for the full characterisation of the product.
With the Z-isomer 152 we were eventually able to obtain 12% yield of the 5,6,6 E,Z-cascade precursor 153 when KHMDS was used at 0 °C after 10 minutes of the reaction. To our surprise, we also observed the formation of the Z,Z-product 162 in the reaction (Scheme 69).

Scheme 69: Retro-oxy-Michael reaction of the Z-isomer 152 of the 5,6,6-system

The formation of the Z,Z-product 162 can be rationalised to arise from a base induced isomerisation of the E-enone. With the 6,6,6-system, we did not observe the isomerisation of the cascade precursor in the retro-oxy-Michael reaction.

4.4 5,6,6 Transannular cascades

Although we had only a very small quantity of the Z,Z-cascade precursor 162, we wished to examine the suitability of the substrate to the cascade process before committing further resources. We used the same conditions as described with 6,6,6-system using solid potassium fluoride as the base, benzene as a solvent and N-(9-anthracenylmethyl)cinchonium bromide 123 as the chiral phase transfer catalyst. We used NMR-standards in the reactions to perform quantitative 1H-NMR analysis monitoring of the effectiveness of the cascade under different conditions. Quantitative 1H-NMR was measured of both the starting material and standard mixture and after the reaction of the crude mixture (filtered through small pad of silica to remove the catalyst). When subjected to optimal conditions we obtained 58% NMR-yield of a cyclisation product 162 which appears to be a result from a single transannular Michael-addition (Scheme 70).
**Scheme 70: Transannular Michael-reaction of the Z,Z-cascade precursor 162.**

Unfortunately, due to the low quantity of material full characterisation for the product could not be carried out. During the purification, low recovery of the product was obtained as indicated by comparison of the product integration to the integration of the satellites peaks of the NMR-solvent. This resulted in not having sufficient material either for $^{13}\text{C}$ or for $^1\text{H}$-$^{13}\text{C}$ HSQC NMR analysis.

Our belief is that only a single transannular Michael-addition had occurred. In addition to correct mass on low-resolution mass spectrum the result can be rationalised by the following:

In the proton NMR spectrum we can clearly see one set of enone-type signals ($H$-9, $H$-8) (Scheme 38) that are connected to one another having $J$-coupling of 10.0 Hz, characteristic for Z-enone. These enones are furthermore by COSY connected to the aliphatic region of the $^1\text{H}$-NMR. In this 5,10-fused ring-system we could not observe the enol-signal in the spectrum.

The reason for this could be that the signal in above 17 ppm. We still believe that the product is in the enol form because the proton corresponding to $H$-2 has no observable coupling to anything else that 1-H and $H$-3. Also, $H$-9 signal is further downfield on the NMR-spectrum compared to $H$-8 which is characteristic for unsaturated enols. This is usually inversed in the corresponding keto-form. Furthermore, in the purified spectrum we could not find plausible 11-H signal of the methylene position. We cannot see a doublet that would be the proton $H$-11 between the carbonyls in the keto-form of the compound. Also, the $H$-1 diastereotopic protons show splitting characteristic for a 5-membered ring-system.86
**Figure 15:** 1H-1H COSY-spectra of the crude cyclisation mixture.

**Figure 16:** Michael-addition product of the 5,6,6-system.

With the $E,Z$-precursor 153 the cascade produced surprisingly a dimer, where the cascade product had reacted with another equivalent of the starting material. The phase-transfer catalysed reaction gave 42% isolated yield of the dimer (Scheme 71). The reaction is highly diastereoselective and the dimer is the only product isolated from the reaction. The recovery of product with low enantioselectivity indicates that the initial cascade process is not particularly enantiodiscriminatory.
Scheme 71: The transannular asymmetric cascade of the E,Z-isomer 153.

Figure 17: NOESY and COSY analyses of the cascade dimer 164.

4.5 Cascade precursor via enyne methathesis

Our attempts at making methylated cascade precursor 137 from 135 using a retro-oxy-Michael reaction followed by DMP oxidation were successful, albeit in a low yield 35%. We believe this to be due to side reactions in both the product and the starting material resulting from elimination to the open chain, followed by decarboxylation (Scheme 72). We believed that with a removal of the γ-protons we could reduce the amount of the side reaction observed and increase the yields of the cascade and the yields of the last retro-oxy-Michael reaction.
Scheme 72: Decarboxylation of the cascade precursor 137 and the RCM-product 135.

We realised an opportunity to use a ring closing enyne-metathesis in the synthesis of the cascade precursors. This could lead to two different cyclic products 167 (endo) and 169 (exo) both lacking the γ-hydrogens causing the undesirable side reactions. In addition, Ring-closing enyne metathesis (RCEYM) could produce two interesting intermediates 166 and 168 that could be used in the synthesis of different cascade starting materials (Scheme 73).

Scheme 73: endo- and exo-products of the enyne-metathesis.

The RCEYM product bearing a terminal alkene could also for the rapid diversification of the cascade precursor via Pd-catalysed Heck-coupling reactions to form the corresponding secondary alkene.
Scheme 74: synthesis of the precursor for the enyne-metathesis.

Thermolysis of 1,3-dioxin-4-one 145 with propargyl alcohol gave the protected open-chain enone 170 in 99% yield. The deprotective oxy-Michael reaction in acidified chloroform (conc. HCl extracted with chloroform) gave a 86% yield, as a 21:1 mixture of syn-anti diastereomers of tetrahydropyran 165.

The first attempt at the Ring-closing enyne metathesis under an ethylene/argon atmosphere produced a mixture of both exo-168 and endo-form 166 in 11% and 13% yields, respectively. However, the major product, in 18% yield proved to be open-chain diene 171 formed from the reaction between the starting material enyne 165 and ethylene (Scheme 75). Ethylene atmosphere is known to improve the yields of enyne-metathesis by improving catalyst regeneration and also by preventing alkyne polymerisation.92

Scheme 75: Enyne-metathesis.
Even though we obtained the desired products the enyne metathesis attempts at optimising the reaction proved difficult. The reproducibility of the reaction proved to be an issue. With some attempts failing to give either recovered starting material or products. This was especially noticeable when we moved from a small test scale to a larger scale. Usually the lack of any separable products was accompanied by the mixture gaining a deep blue colour.

Although ethylene is generally considered to improve the yields of RCEYM reactions \(^{93}\), we thought in our case it could have a negative effect on the yield of the reaction. When the ethylene was removed after 2.5 hours of reaction by purging nitrogen through the reaction mixture we could increase the amount of the open-chain diene 171 (27% yield). This resulted in higher overall 44% yield (exo-168 (11%) and endo-166 (6%)), but unfortunately it also biased the products distribution towards the undesirable open chain diene. When the reaction was refluxed in CH\(_2\)Cl\(_2\) the reaction gave 54% yield for the diene 171 and the lowest yields for the endo (4%) and exo (4%) products (Scheme 76).

**Scheme 76: Enyne-metathesis with in ethylene atmosphere removed during the reaction.**

We tried to improve the yield by using Hoveyda-Grubbs 2\(^{nd}\) edition catalyst but no improved reactivity was observed. Also adding Ti(OiPr)\(_4\) to the reaction mixture to prevent chelation to the 1,3-dicarbonyl did not improve the yields. We also tried to improve the yields with benzoquinone to prevent the possible isomerisation but no improvement to the yields were observed.

After many attempts of the enyne-metathesis we had plenty of the uncylised diene in our hands. We wanted to see if we still could close the diene using ring-closing metathesis. When we tried
to close the macrocycle using the isolated intermediate diene 171 we observed low reactivity (Scheme 77). Only 5% yield of the exo-product 168 was isolated from the reaction. The reaction also produced a complex mixture side products that contained aromatic proton signals in the $^1$H NMR spectrum. These could be the products from the first metathesis between the catalyst styrene and the starting material. This could indicate that the product formed from the first cross-metathesis between the catalyst forms a too stable compound that cannot re-enter the catalytic cycle. It could also be that even the diene requires ethylene to improve the yields. With ethylene atmosphere the catalyst can start the catalytic cycle by reacting first with the ethylene and later with the diene. In that case the reaction could form reduced amounts of the possible styrenyl intermediates.

![Scheme 77: Ring-closing metathesis with the enyne-metathesis intermediate.](image)

While optimisation of the Ring-closing enyne metathesis was ongoing we still had enough material to test the next retro-oxy-Michael and subsequent DMP oxidation. Disappointingly both endo-166 and exo-168-enzyme-metathesis products failed to give any significant yields of the desired products 169 and 167. The exo-starting material gave two inseparable products with almost identical $^1$H-NMR spectra. Unfortunately, we could not obtain enough material for the full characterisation of the products.
Figure 18: Retro-oxy-Michael reaction of the enyne metathesis products 168 and 166.

At this stage we realised that to obtain sufficient amounts of the diene-cascade precursors we would need to heavily reoptimise both the Ring-closing-eneyn metathesis and the retro-oxy-Michael, oxidation sequence. While we believe this is possible but unfortunately, we did not have the time required on our hands.

4.6 Unsaturated 1,3-diketone precursor

To the best of our knowledge carbon nucleophiles that have been used with 1,3-dioxin-4-ones are silylenolethers by Wang and List\textsuperscript{94} (Scheme 78). This Mukayama-Claisen type reaction proceeds likely through a thermally promoted acetoketene 179 formation.
We postulated that, mechanistically, a Grignard addition to form 1,3 diketones should be also possible as in Figure 13. The addition of the Grignard reagent to the 1,3-dioxin-4-one 145 should result in a formation of the anionic unsaturated 1,3-diketone 178 that should be unable to react further under the reaction conditions. To avoid the undesired side reactions caused by the loss of acetone we decided to use 2 equivalents of the Grignard reagent so that the acetone will be trapped as well (Scheme 79).

When the reaction was done for the first time at ambient temperature, we obtained the product 180 in 16% yield and a side product that we believe is a mixture of two diastereoisomers of 1,6-addition product 181 that still has the 1,3-dioxinone core intact. The next step was to reduce the temperature to increase the ratio of 1,2-addition. We attempted the reaction at −78 °C, but only starting material was observed. When the reaction was done at 0 °C we observed the formation of the product 181 in 9 % yield and the 1,6-addition product in 58 % yield. When we could not change the ratios of the products to favour 1,2-addition by changing the temperature
we postulated that using CeCl₃ could provide us with a better nucleophile for direct 1,2 addition. Indeed, this provided us the necessary change in the reactivity giving us 58% yield (72% b.r.s.m.) of the 1,2-addition product 180. In the cerium (III) chloride reaction also 19% of the 1,6-products 181 were observed (Scheme 80).

![Scheme 80: Grignard addition to 1,3-dioxin-4-one 145.](image)

On a larger scale, we obtained a much better yield of 93% for the 1,2-addition product 180, potentially making the reaction very useful for the general formation of unsaturated 1,3-diketones and saturated ones from 1,3-dioxin-4-ones. The Grignard reaction was followed by the deprotective oxy-Michael reaction with acidified chloroform that gave a excellent yield of 93% of tetrahydropyran 185 in a 5:1 syn:anti ratio (Scheme 81).

![Scheme 81: Gignard reaction and the deprotective oxy-Michael reaction of the 1,3-diketone substrates 145 and 180.](image)
Figure 19: NOESY analysis of the minor product of the oxy-Michael reaction.

The Ring-closing metathesis of the all-carbon chain 184 gave us the desired product 186 in 43% yield and in 1.14:1 E:Z ratio (Scheme 82).

Scheme 82: RCM-reaction of the 1,3-diketone 184.

Perhaps unsurprisingly with the diketone substrate we observe the formation of both double bond geometries whereas with the corresponding ester analogue we only observe the formation of the Z-olefin. This can be explained by esters preference to Z-conformation due the hyperconjugation and dipole minimisation. Since the ketone substrate 184 does not have α-heteroatom that could donate lone pair electron density into the empty orbital of the carbonyl it causes a higher flexibility of the diketone substrate. Furthermore, with the diketone substrate there is no possibility for an easy chelation of the possible metallocarbene intermediate to the ester oxygen which we believe increases the amount of the Z-product. Also, the formation of the chelate with the ketone would result in non-favourable 7-membered system (Scheme 83).
Scheme 83: Chelation of the ester-and diketone starting materials in the RCM to the metallocarbene.

Again, the retro-oxy-Michael reaction proved to be a challenge. After many attempts, we finally managed to obtain the cascade precursor 191 in 15% yield (Scheme 84). Unfortunately, after all the data for the characterisation of the product was obtained we observed some decomposition products in the re-run NMR-spectrum and decided to re-purify the compound. During this purification large amount of the material was lost and we could not recover sufficient amount of the cascade precursor for the transannular cascade reaction.

Scheme 84: retro-oxy-Michael reaction of the Z-isomer 186.
When the trans-macrocycle was subjected to the retro-oxy-Michael reaction no product was observed. This could be caused by the different conformation compared to the ester-macrolactone that slows down the initial deprotonation of the 1,3-dicarbonyl 186. With the 1,3-diketone substrate the second deprotonation could take place on either of two α-carbons.

Scheme 85: Retro-oxy-Michael reaction of the E-isomer 193.

4.7 Synthesis of other ester substrates

Because all substrates synthesised are aliphatic we decided to synthesise ester substrates to form phenolic esters so that we could investigate how the cascade behaves with aromatic substrates. When working, aromatic core can provide rapid access to substrate diversification. More interestingly if the aromatic core is large enough, this could provide us with helically chiral molecule 195 (Scheme 86).

Scheme 86: Plan for the synthesis of the aromatic cascade precursors.

The synthesis of the aromatic cascade precursor started form the synthesis of the 2-vinylphenol via Wittig-reaction of salicylic aldehyde and methyltriphenylphosphonium bromide. The Wittig reaction using KOtBu as a base gave 66% yield of the 2-vinylphenol 199 (Scheme 87).
Next step was a thermolysis of the 1,3-dioxin-4-one compound 145 with 2-vinylphenol 197. The reaction produced after purification, a complex mixture of compounds that we believe were caused by the keto-enol tautomers, giving products that can have either E- or Z-enol configurations. Despite the 1H-NMR-signal complexity of the purified phenolic ester 198 we decided to continue with the deprotective oxy-Michael reaction. Treatment of our product with acidified chloroform gave us tetrahydropyran 199 in 20% yield over two steps (Scheme 87).

**Scheme 87: Synthesis of the aromatic oxy-Michel product 199.**

Even after the purification of the oxy-Michael product we could still see the 2-vinylphenol 197 by TLC analysis. This made us doubt the stability of the phenolic ester, which could also explain the complexity of the purified thermolysis product 198. In the next RCM reaction no product was observed either with Grubbs 2nd generation catalyst or with the Hoveyda-Grubbs catalyst. Also increase in the temperature did not provide us any product 200. This could be caused by the instability of the phenolic ester.

**Scheme 88: RCM reaction of the phenolic ester 200.**
4.8 Synthesis of the Methylated Olefin substrate

Next we wanted to focus on the influence that β-substituents on the enone would have on the first Michael-addition in the cascade. We postulate it could be possible to introduce a substituent on the olefin of the macrocycle 97 by using Pd-catalysed oxidative Heck-type coupling. Under the reaction conditions using phenylboronic acid 201 as the coupling partner we did not observe any oxidative addition to the double-bond and when the temperature was increased we only observed a decarboxylation of the starting material forming the alcohol 203 (Scheme 89).

![Scheme 89: Pd-coupling for the modification of the macrolactone olefin 97.](image)

After the failed Pd-coupling the substrate we wanted to synthesise was the one with a β-methylated enone 206. This substrate would provide us a precursor for a cascade that cyclises to form in addition to the tertiary carbons also one quaternary carbon (Scheme 90). In the synthesis we decided to continue with the route using thermolysis of the substrate 145 with 3-methylbut-3-en-1-ol.
**Scheme 90:** Synthesis plan for the β-methyl-enone 208.

The product of thermolysis with 3-methylbut-3-en-1-ol was used without a purification in the next deprotective oxy-Michael reaction which gave 79% yield of the syn-product 208 (Scheme 91).

**Scheme 91:** Thermolysis and oxy-Michael reaction of 208.

The ring-closing metathesis of the methylated olefin 208 gave after 2 hours of reaction 45% yield of the macrocycle 205 without any formation of the E-isomer (Scheme 92).

**Scheme 92:** RCM of 208.

The retro-oxy-Michel reaction and the subsequent oxidation gave the cascade precursor 206 in low 13% yield over two steps (Scheme 93).
4.9 Transannular cascade with the methylated enone substrate

The cascade precursor 206 was treated under the optimised phase-transfer conditions but unfortunately, we observed no reactivity or product and only starting material was recovered. It is surprising that so small changes in the core of the cascade precursor can prevent the cascade from cyclising. On the other hand the substituent is at the site of first Michael-addition. (Scheme 94).
4.10 Bromination of macrocycle 97

We also tried to modify the α-carbon of the oxy-Michael macrolactone by using elemental bromine in the reaction. With acetoacetates bromine interestingly forms α-brominated product rather than reacting with the carbon between the carbonyls.\textsuperscript{97} This α-brominated compound \textbf{208} could be reacted further with different nucleophiles to obtain α-substituted enones. We decided to use bromide even though we had olefin in the same molecule that may prefer to react. Even though the bromide reacted with the olefin we believed that the formed dibromide \textbf{210} could be modified via elimination to a useful compound in the synthesis of the cascade precursors (Scheme 95).

\textit{Scheme 95: Planned bromination of the macrocycle 97.}
In the bromide reaction we indeed observed the reaction with the olefin rather than with the α-carbon. We isolated from the reaction a dibromide compound 211 in 29% yield (Scheme 96).

Scheme 96: Bromination of the macrolactone 97.

Interesting reactivity must be due a participation of the ester in the reaction. We postulated that ester carbonyl reaction with the bromonium ion 212 to form the oxonium ion 213. This intermediate reacts with the bromide formed in the reaction to release the ester 211 (Scheme 97).

Scheme 97: Plausible mechanism of the bromination.

We tried to double-eliminate the dibromine 211 to form a diene 215 that could be used in a phase-transfer catalysed intramolecular 1,6-Michael addition to form bridged ring-system 216. No reactivity was observed in the elimination reaction when tetrabutylammonium iodide and pyridine as a base was used or when silver acetate was used (Scheme 98).
We also attempted the methylation of the α-carbon by formation of the double anion. Unfortunately, the methylation requires similar temperatures than the retro-oxy-Michael reaction which start to dominate when the temperature is raised (Scheme 99).

5. Isomerisation of the cascade precursor:

Isomerisation of medium and large ring-systems under photochemical conditions is well known. The first isomerisation of the macrocyclic Z-2-cyclooctenone to E-2-cyclooctenone was achieved by Eaton and Lin$^{98}$ and a year later the isomerisation of Z-2-cycloheptenone to E-2-cycloheptenone was observed by Cory et al.$^{99}$ and Eaton and Lin$^{100}$. While smaller cyclohexenones and cyclopentenones readily react in many photochemical reactions, the larger rings undergo isomerisation preferentially over other photoreactions.$^{101}$

We predicated that it could be possible to isomerise cascade precursor 67 under UV-light and thus obtain all the different olefin isomers of the macrocyclic dienone. Ideally, we should be able to find a temperature where the UV-irradiation could effect the isomerisation without significant amounts of possible side products. The isomerised product would allow us to
research the behaviour and origin of the cascade selectivity under both racemic and asymmetric conditions to be investigated (Figure 20).

Figure 20: UV-isomerisation of the cascade precursor.

By irradiating the macrocycle in a custom made irradiation vessel (Scheme 101) with 365 nm UV-light at 0 °C we were able to obtain all the 4 possible cascade isomers. Photon energy for 356 nm photon is 87 kcal/mol \((E = \frac{hc}{\lambda})\) whereas the energy of olefins is usually around 146 kcal/mol. The conjugated enone system lowers the energy needed for electron excitation and offers in addition to \(\pi - \pi^*\) transition an \(n - \pi^*\) transition. In this transition a non-bonding electron on carbonyl is exited to a \(\pi^*\) antibonding molecular orbital.

The purification of the isomerised mixture of macrocycles proved to be very difficult. To obtain each isomer in pure form the mixture required two purifications by preparative thin layer chromatography with different solvent systems. Such extensive purification unfortunately reduced the isolated yield of the products. Furthermore the \(Z,E\)-cascade precursor 221 proved to be slightly unstable on silica and possibly also the \(Z,Z\)-macrocycle 220. In the crude NMR after 45 minutes reaction time the ratios of the isomerised macrocycles were roughly 1 : 0.84 : 0.54 : 0.82 (67 : 222 : 221 : 220) when the ratios of the isolated material were 1 : 0.37 : 0.14 :
0.65 respectively (Scheme 100). The reaction also gave 8% yield of a 5-6-7-fused ring-systems 223 and 224.

Scheme 100: Isomerisation of the cascade precursor.


We tried to increase the amount of the Z,E-cascade precursor 221 by increasing the time of the reaction from 1 hour to 2 hours. Disappointingly we could only slightly increase the isolated yield of Z,E-precursor 221, under these conditions at the cost of reducing the overall yield of the isomerisation from 76% to 49% (Scheme 102).
Scheme 102: Isomerisation of the cascade precursor (reaction time: 2 hours reaction).

As a side product in the reaction we isolated a 5-6-7-fused ring system 223 and 224 likely formed from an extended enol via a Norrish type II reaction followed by γ-hydrogen abstraction and a subsequent thermal Diels-Alder reaction (Scheme 103). The regioselectivity of the Diels-Alder reaction is reversed compared that one would anticipate. This may be due to the conformational constraints of the macrocycle disfavouring the predicted selectivity.

Scheme 103: potential mechanism of formation of side products 223 and 224.
Future attempts at increasing the yield of product 223 and 224 by varying the temperature or reaction time were unsuccessful.

5.1 Transannular cascade reactions of the isomerised precursors.

5.2 Racemic transannular cascades

Under basic conditions we noticed that only the $E,Z$- and $E,E$-unsaturated ketoesters (67, 222) seemed to produce the cascade product 101. In contrast the $Z,Z$- and $Z,E$-unsaturated ketoesters (220, 221) gave Michael-addition product 225 forming a 6,10-fused ring system. This may be caused by the strained Z-olefin containing ring 228, preventing the enolate orbital overlapping with the enone electrophile. The $Z,Z$-starting material 220 is likely already too strained for the first addition to occur. Interestingly the $E,E$-precursor 222 gives the same cascade product 101 as the $E,Z$-precursor 67. Although we observed that the $E,Z$-cascade proceeds via a different diastereomer 111. In the $E,E$-cascade no formation of the kinetic diastereomer 111 was observed. Additionally, $Z,Z$- and $Z,E$-precursors 220 and 221 produce the same product 225 under basic conditions (Scheme 104).
Scheme 104: Transannular cascades of the isomerised precursor under basic conditions.

An alternative explanation is that the enolate 226 formed after the first Michael-addition reacts instantly when $E,Z$- or $E,E$-precursors are used whilst when $Z,E$- or $Z,Z$-starting materials are used the enolate 228 is quenched by the more acidic proton between the 1,3-dicarbonyl and cannot be formed again (Scheme 105).

Scheme 105: Transannular cascade via enolate intermediate
These findings in reactivity are in accordance with the results of Xue et al.\textsuperscript{22,23} where $E,Z$-bis-enone 43 and $E,E$-bis-enone 41 were shown to cyclise under basic conditions to form a fused tricycle whereas when $Z,E$-bis-enone 47 or $Z,Z$-bis-enone 50 were used no cyclisation products were observed (Scheme 106).

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{Scheme106.png}
\caption{Scheme 106: Cyclisation of enone isomers by Xue et al.\textsuperscript{22,23}}
\end{figure}
\end{center}

Although, the reactivity is very dependent on the conformation of the enones, it seems substrates on a macrolactone core determine exo/endo stereoselectivity of the cyclisation. In all published transannular cyclisations of $E,E$-bis-enones the starting materials have substituents at C1, C6, or C8 positions and the cyclisations gives a product where $\beta$-enone substituents (C3, C9) end up on the same face of the formed tricycle 230 whereas the $\alpha$-hydrogen (C4) ends up on the opposing face (anti-anti diastereomers) (Scheme 107). Similar stereoselectivity was observed by Scheerer et al.\textsuperscript{20}, in a system where 14-membered $E,E$-bis-enone macrolactone has a substituent at the C1-position. In this cyclisation the substituent at C1 ends on the same face as the $\alpha$-proton (C4) and opposite face compared to the $\beta$-methyl-enone. Enhancement of this selectivity was observed when a C8-substituent anti to the C1 substituent was added.\textsuperscript{20} a further increase in selectivity was observed when an anti C6 substituent was added. It can be concluded that anti-C1, syn-C6 and syn-C8 substituents
enhance the stereoselectivity of 230 formation. Xue et al.\textsuperscript{22,23} has showed that the stereoselectivity remains the same when C1-substituent is removed and C7-substituent is added on anti-side to C8-substituent 41. Furthermore, Sherwood et al.\textsuperscript{21} has showed that when both \(\beta\)-methyl-enone substituents are replaced with protons in a system used in the total synthesis of Salvinorin A, the diastereoselectivity decreases and another uncharacterised diastereomer is obtained. This suggests that \(\beta\)-methyl substituted enones enhance the diastereoselectivity of the transannular cyclisation reaction.

![Scheme 107: Stereoselectivity of the substituted E,E-bis-enone macrolactone.\textsuperscript{20}](image)

We have observed with our unsubstituted \(E,E\)-bis-enone macrolactone 222 that the natural diastereoselectivity is significantly different compared to what has previously been seen with substituted macrolactones. In our cyclisation with 222, the protons on C4 and C9 end up on the same face and the proton at C3 on the opposing face (\textit{syn-anti} diastereomer) (\textbf{Scheme 108}). Prior to our work, only one \(E,Z\)-bis-enone cyclisation 43 has been reported by Xue et al.\textsuperscript{23} and because of the different stereochemical outcome compared to ours (67) it seems that also with \(E,Z\)-systems substitution has a large effect on the stereochemistry of the cyclised product (\textbf{Scheme 108}).
Scheme 108: Stereoselectivity of substituted and unsubstituted cascades.

The observation of single transannular Michael-additions with Z,E-bis-enone 221 and Z,Z-bis-enone 220 suggest that the reaction’s mechanism is stepwise rather than a concerted Diels-Alder like [4+2] cycloaddition. However, this does not exclude the possibility of a Diels-Alder-type cyclisation with E,Z or E,E-isomers.

In the cyclisation of E,Z-precursor 67 the cascade can proceed through either E,Z,Z-enolate 231 or E,Z,E-enolate 232 forming either 233 or 105 (Scheme 109). In crude $^1$H-NMR we could only observe keto-form 105 and enol-form 106 but we cannot rule out formation of 233 followed by epimerisation. Eventually, the kinetic product is epimerised to the corresponding thermodynamic product 101. Likewise, cyclisation of E,E-bis-enone 222 proceeds through either unobserved keto-forms 234 or 235 which enolise to form the thermodynamic product 101.

The stereochemistry of product 106 from E,Z-bis-enone cyclisation can be explained by an exo-Diels-Alder transition state with either E,Z,Z-enolate 231 or E,Z,E-enolate 232 (Scheme 109). In contrast, the stereochemistry of 101, formed by cyclisation of E,E-bis-enone 222 can only be explained via endo-Diels-Alder transition states. However, in our cases, we cannot rule out a Michael-Michael mechanism.
5.3 Asymmetric transannular cascade

5.3.1 \(E,E\)-macrocycle

With the \(E,E\)-precursor 222, we began our investigations using the optimised conditions obtained in the asymmetric cascade of the \(E,Z\)-macrocycle 67. Under the same conditions using potassium fluoride as a base and \(N\)-(9-anthracenylmethyl)cinchoninium bromide 123 as a phase-transfer catalyst we obtained the product in only 15% yield as a 76:24 mixture of enantiomers (Scheme 110).

\[ \text{Scheme 110: Asymmetric cascade of the } E,E\text{-macrocycle 222.} \]

Because of the disappointing yield and enantioselectivity we decided to perform optimisation of the cascade for the \(E,E\)-precursor 222. Previously we had seen that the catalyst selection had the largest effect on the outcome of the reaction, so we decided to screen different catalysts for the \(E,E\)-cascade (Scheme 111).
Scheme 111: Catalyst screen for the E,E-asymmetric cascade.

For the optimisation we investigated 10 different catalyst. As previously the best yields and enantioselectivities were obtained with anthracenyl cinchonidinium and anthracenyl cinchonium catalysts. Unfortunately, 119 and 123 respectively no other catalyst used gave any improvement in the enantioselectivity. The highest yields were obtained when bulky catalyst,
237 (26% yield) and 239 (34% yield) were used. Of these catalyst, the more electron rich 237 gave a better enantiomeric ratio of 74:26 than the corresponding trifluoromethyl containing catalyst 240, which gave an enantiomeric ratio of 41:59. Surprisingly 237 gave the opposite enantioselectivity to the corresponding anthracenyl catalyst 123, as did N-(phenyl)cinchoninium chloride 106 gave the enantiomeric ratio of 61:39.

The change in selectivity in the E,E-cascade is strongly influenced by the aryl-group more so than we anticipated after the optimisation for the E,Z-cascade precursor 67.

5.3.2 Z,Z-macrocycle

With the Z,Z-macrocycle 220 we observed no reactivity under the optimised conditions. (Scheme 112).

Scheme 112: Z,Z-precursor 220 under the optimised cascade conditions.
We postulated that the different conformation could change the acidity of the macrolactone, and thus the reaction may need a stronger base. Indeed when other bases were used we started to see reactivity with the Z,Z-precursor. With cesium fluoride (CsF) or potassium carbonate (K₂CO₃) we observed the single transannular Michael-addition on an analytical scale. CsF gave us the product in a pleasing e.r. of 89:11, and with K₂CO₃ we obtained an e.r. of 20:80 (Scheme 113).

Scheme 113: Base screen for Z,Z-precursor 220 cyclisation.

The best results albeit still with poor yields were obtained when potassium phosphate was used as a base. After 48 hours we isolated product 225 in 11% yield for both of the reactions using anthracenyl catalyst 123 and 119 as the phase-transfer catalysts. In spite of the poor yield, the enantioselectivities were high, with catalyst 119 giving an enantiomeric ratio of 96:4 and catalyst 123 a 7:93 enantiomeric ratio (Scheme 114).
Scheme 114: Z,Z-precursor 220 cyclisation under asymmetric phase-transfer conditions.

5.3.3 Z,E-macrocycle

With the Z,E-macrocycle 221, we had only a small amount of material available for a cascade optimisation due to the instability of the precursor. We choose 5 different catalysts for the short optimisation of the cascade. Catalyst 119 and 123 again proved to be the best catalyst for the transannular reaction (Scheme 115). Only moderate enantioselectivity was observed in the Michael-addition, with catalyst 119 giving a 85:15 enantiomeric ratio with 87% NMR-yield, catalyst 123 giving a 20:80 enantiomeric ratio with 87% NMR-yield. Pleasingly, the single transannular Michael-reaction proved to be the highest yielding of all the transannular reactions we attempted. With bulky electron poor triphenyl containing catalyst 239 we obtained an impressive 99% yield from the reaction.
Scheme 115: Catalyst screen for the Z,E-precursor 221.

5.4 Transannular cascades – Results and conclusion

With all four isomers of the macrolactone we observed reactivity in the transannular reactions. With E,Z-67 and E,E-macrocycle 222 we observed the cascade product while with Z,Z-220 and Z,E-precursor 221 we observed only 225, arising from single Michael-addition. Under asymmetric phase transfer conditions good to excellent enantioselectivity was observed with all isomers of the cascade precursors (Scheme 116).
**Scheme 116**: Asymmetric phase-transfer catalysed transannular cyclisation of E,Z- and E,E-bis-enones 67 and 222.

The E,Z-precursor 67 provided us with 101 in a high enantiomeric ratio of 95:5. Using pseudoenantiomeric catalyst 123, the opposite enantiomer could also be obtained in 95:5 e.r.

In these the reaction proceed through a diastereomer 111 without going to completion. Part of the high enantioselectivity is caused by kinetic resolution of the kinetic diastereomer. Unfortunately, we could not measure the enantioenrichment of the minor diastereomer 111 due to the keto-enol tautomerisism (one broad peak on chiral HPLC) and instability of the compound. Yet it must be lower than the isolated thermodynamic product. Combined yields of the diastereomers proved to be good (85% for both phase-transfer catalysed reactions) (**Scheme 116**).
The $E,E$-precursor 222 gave 22% and 19% yields of the cascade product under asymmetric conditions. The enantioselectivities also remained low in $E,E$-cascade (Scheme 116). In comparison, using aqueous potassium hydroxide without phase-transfer catalyst the yield of the cascade was 71%.

With the $Z,Z$-precursor 220, the reaction gave excellent enantioselectivities with both catalysts and slightly higher yield of 11% compared to the racemic conditions. The $Z,Z$-cascade required stronger base to achieve conversion to 225 (Scheme 117).

Scheme 117: Asymmetric phase-transfer catalysed transannular Michael-addition of $E,Z$- and $E,E$-bis-enones 220 and 221

With the $Z,E$-precursor 221 we observed high reactivity under asymmetric phase-transfer conditions. When catalyst 239 was used we obtained an impressive 99% NMR-yield with low enantiocontrol (41:59 e.r.). Using the optimised conditions for the $E,Z$-precursor 67 the reaction with 87% yield with a good enantioselectivity (20:80 e.r.) and with 119 74% yield with 85:15 enantiomeric ratio (Scheme 117).
The results for the asymmetric cascades with different precursors showed that it is necessary to have either E,Z- or E,E-enone configuration to obtain the Michael-Michael cascade. With Z,Z-220 and Z,E-precursor 221 the reaction favours single Michael-addition and gives a fused 6,10-ring system 225. With all four precursors we observed enantioselectivity but unfortunately it seems that each precursor requires further optimisation to obtain better yields and enantioselectivities. With anthracenyl-catalysts 119 and 123 it seems we have high enantiocontrol in the first transannular addition to Z-enones, but for addition to E-enones the enantioselectivities are lower.

With the 5,6,6-system 153 we observed an interesting dimer 164 formation after the cascade in 42% yield (Scheme 118). This is likely explained by the conformation of the tricycle enolates. When in 5,6,6-system syn-protons on C2 and C3 provides easier Michael-addition than in 6,6,6-system where C3 and C4 protons are opposing sides making neither side available for the addition (Figure 22).

**Figure 22**: Conformations of 5,6,6- and 6,6,6-tricycle enolates.

The Z,Z-precursor of the 5,6,6-system 162 gave us product 163, resulting from a single Michael-addition in 58% NMR-yield rather than the cascade product. This result is similar to that obtained in the 6,6,6-system with Z,Z-precursor 220.
Scheme 118: Transannular reaction of the 5,6,6-system.\textsuperscript{a} This reaction was carried out on a small scale and the product 162 was quantitatively characterised by $^1$H-NMR, COSY and MS.

With the methylated ketoester 138 the reaction started to prefer the elimination-decarboxylation of the precursor. With methylated Z-enone 208 no reactivity was observed.

Scheme 119: Other cascade precursors.
5 Synthesis of aromatic scaffold for transannular Michael-reaction

J. S. Yadav et al.\textsuperscript{102} have described a relatively short total synthesis of Sporostatin which relies on a intramolecular Friedel-Crafts acylation\textsuperscript{103,104} as the macrocycle-closing step (Scheme 120). The natural product contains a macrocyclic enone that has an 1,6-connection to a benzylic ester. We postulated that the scaffold could be used in the phase-transfer catalysed transannular Michael-addition to form a fused tricyclic ring-system.

\textbf{Scheme 120:} Total synthesis of Sporostatin by J. S. Yadav et al.\textsuperscript{102}

Because of the short 4-step access to the macrocyclic core we decided to follow the synthesis with minor modifications. The esterification of aromatic acid 244 gave 248 quantitative yield. In the cross-methathesis we relied on Grubbs 2\textsuperscript{nd} generation catalyst rather than the Hoveyda-Grubbs 2\textsuperscript{nd} generation the authors used. The methathesis gave 45\% yield of the \textit{E}-enonic acid 249 (Scheme 121).
Unlike in the total synthesis of the Sporostatin by J. S. Yadav et al. in our synthesis the intramolecular Friedel-Crafts reaction gave a low 4.5% yield of only the Z-conformer 250 of the macrocycle whereas in the total synthesis the authors reported E-isomer 247 for the product. Authors used refluxing conditions for the cyclisation but in our hands under reflux only starting material decomposition was observed. The authors did not include any data at this stage of the synthesis. We believe that the reason for the E-configuration lies in the demethylation step of the total synthesis where AlI₃ could also isomerise the enone 247.

In our hands after several attempts, the intramolecular Friedel-Crafts acylation did not give any improved yields. The acylation probably gives low yield because of dimerisation of the acid starting material and also possibly because of acid catalysed hydrolysis of the lactone ring.

### 7.1 Transannular Michael-addition

Despite the low yield, we still had enough material to test the intramolecular Michael-reaction. Unfortunately, the reaction did not produce any Michael-addition product 251 under phase-transfer conditions using potassium hydroxide as the base (Scheme 122). After 2 hours only 24% of the starting material 250 could be seen crude ¹H-NMR. Under these conditions,
the starting material is probably hydrolysed to the corresponding acid. We also attempted strong base KHMDS in the reaction but no product could be observed.

\[
\text{Scheme 122: Attempted transannular Michael-reaction of 250 under phase-transfer conditions.}
\]

As the reaction did not produce any Michael-addition product we postulated that the reason for this is either the low acidity of the α-proton or the conformation of the macrolactone that prevents the nucleophile from reacting with the enone. As we had previously carried out enone-macrocyle isomerisations, we decided to isomerise the Z-macrolactone 250 to E-macrolactone 252 under UV-light to obtain a conformation where the α-proton and the Michael-acceptor are closer to each other.

The isomerisation gave 25% yield of the E-enone 252 which could be fully separated from unreacted Z-enone 250 by column chromatography. The yield could probably be improved by using a longer reaction time (Scheme 123).

\[
\text{Scheme 123: Isomerisation of the macrocyclic enone 250.}
\]

When the cascade was attempted the E-macrocyle 252 did not give any expected desired transannular Michael-addition product under phase-transfer conditions (Scheme 124).
Scheme 124: Transannular Michael-reaction of the Z-macroyclic enone 252.

To increase the acidity of the α-proton, we synthesised the corresponding ketone macrocycle using a similar route that used for the synthesis of 250. The synthesis of the ketone macrocycle started with formation of a Weinreb amide\(^{105}\) 253\(^{106}\), in 98% yield. After addition of pent-4-en-1-ylmagnesium bromide 256 we obtained a yield of 61%. In a reliable cross-methathesis reaction with acrylic acid the ketone gave good yield of 73% of the corresponding E-acid 255 (Scheme 125).

Scheme 125: Synthesis of a ketone starting material for the transannular Michael-addition.

The intramolecular Friedel-Crafts reaction of acid 255 proved to be problematic as with the corresponding ester analogue. We only obtained traces of the macrocycle from the reaction and were unable to improve the yield by using other conditions (Scheme 126).
Scheme 126: Intramolecular Friedel-Crafts reaction to form macrocycle 256.

When the reaction was done in neat polyphosphoric acid the reaction gave surprisingly 257, containing a natural product like phenanthrene core\textsuperscript{107,108}. We postulated that the reaction could proceed either via Friedel-Crafts acylation (Scheme 127 (1.)) forming macrocyclic enone 268 or via enolate acylation (Scheme 127 (2.)) forming 6-membered ring 273 followed by Pechmann-type condensation\textsuperscript{109} (Scheme 127).

Scheme 127: Friedel-Crafts reaction of 255 in PPA and postulated mechanisms.

As the Friedel-Crafts acylation produces only the Z-isomer 256 of the macrocycle, the olefin must isomerise during the reaction. It could be that only the Z-isomer 265 of the open-chain acid can cyclise and therefore the yields are low when E-enonic acid 264 is used (Scheme 128).
We decided to examine the effect the configuration of the enonic acid has on the reaction by isomerising the olefin with UV-light and using the isolated Z-enonic acid 249 in the Friedel-Crafts acylation reaction. Under irradiation with 365 nm wavelength UV-light no isomerisation was observed but when lower 265 nm wavelength UV-light was used the Z-isomer 268 was isolated in 16% yield (Scheme 129).

**Scheme 128: Isomerisation of the open-chain enonic acic 264.**

We also isomerised the ketone containing enonic acid 255 under the same conditions. By crude NMR the ratio of Z and E-products were almost 1:1 but after column chromatography, Z-enone 269 was isolated in only 16% yield. This could imply that the product isomerise back to the thermodynamic E-product 255 on silica gel (Scheme 130).

**Scheme 129: Isomerisation of the enonic acic 249.**
The Friedel-Crafts acylation with the Z-enonic acid did not give major improvements to the yield of the reaction. Only 6% yield of the closed macrocyclic ring was isolated (Scheme 131). With the ketone starting material no product was obtained.

After observing low reactivity with 250, we decided to modify the macrolactone core. By changing the ester to a malonate the pKₐ of the α-proton should be reduced and we hoped that it could react better with the Michel-acceptor.

We decided to add a tert-butyl ester in the early stage of the synthesis. The acylation¹⁰ of the ester 248 gave us the product 270 as an inseparable mixture with the starting material. We carried out cross-metathesis with the mixture and the reaction gave us a mixture of the acids 270 and 257. After difficult purification we obtained the product in 13% yield over two steps (Scheme 132).
In the Friedel-Crafts acylation of 270 we did not observe any product. This could be because tert-butyl esters are readily decarboxylated under acidic conditions.

To avoid the possible decarboxylation we synthesised the corresponding isopropyl ester. In the acylation we isolated 27% yield of double addition product 273 and also obtained an inseparable mixture of the starting material and the acylated product 272. We carried out the cross metathesis with the most pure fractions of 272, but could not isolate any pure product from this reaction. With the isopropyl ester the crude reaction mixture after cross metathesis was less soluble than with the tert-butyl ester. We tried to recrystallise the product but without success (Scheme 134).
We used the impure material for the intramolecular acetylation but the reaction did not produce any desired macrolactone 274 (Scheme 135).

Scheme 134: Synthesis of the enoic acid 272.

Because of the difficulties in the synthesis and in the cascade, we decided to refocus our efforts on synthesis of other cascade precursors.

7.3 Synthesis of transannular Michael-addition precursor 287

We realised that the protected allylic alcohol-containing aldehyde 67 we had used in the synthesis of the cascade precursor 67 could also be used in the synthesis of a simpler transannular scaffold (Scheme 136). By relying again on the ring-closing metathesis and Grignard addition to the aldehyde we postulated that we could form a reactive precursor 287 for the transannular Michael-addition.
Our synthesis began with a reported Stille coupling\(^{111}\) that gave the unsaturated benzylic alcohol 279 in 97\% yield\(^{112}\). This was followed by an Appel reaction\(^{113}\) that converted the alcohol to a benzylic bromide 280\(^{114}\) (Scheme 137).

When the unsaturated protected diene 281 was used in the RCM-reaction the metathesis product 284 was not observed. Therefore, we deprotected the alcohol to enable the catalyst to react better with the allylic alcohol 285. Despite the deprotection the RCM reaction of the deprotected diene did not produce any macrocyclic product. In the crude NMR of the reaction we observed the protons of the styrenyl olefin but could not see the protons from the other allylic olefin. We tried both Grubbs 2\(^{\text{nd}}\) generation catalyst and Hoveyda-Grubbs 2\(^{\text{nd}}\) generation catalyst for the metathesis reaction (Scheme 138).
7.4 Cascade precursor via allylic olefin oxidation

Posner et al.\textsuperscript{115} have reported a one-pot, four component, Michael-Michael-Michael-ring closure annulation followed by oxidative cleavage to form 9-, 10- and 11-membered macrolactones. This efficient methodology uses simple commercially available compounds to form macrocycles that we believed could be modified to produce starting materials for transannular Michael-reaction. We postulated that allylic oxidation of olefin 286 could provide either or both macrocyclic enones 287 and 289. These precursors could be used to form 7,5- or 6,6-membered fused ring systems under basic phase-transfer catalysed conditions (Scheme 139).

Scheme 138: RCM-reaction of the diene 281 and deprotected diene 282.

Scheme 139: Plan for the synthesis of cascade precursors 287 and 289.
Under published conditions the one-pot, Michael-Michael-Michael-ring closure annulation followed by oxidative cleavage by lead tetraacetate gave us 20% of the syn-macrocycle \(291\) and 10% of the anti-product \(292\). In addition we also isolated 22% of a mixture of the both compounds which we did not further purify (Scheme 140).

**Scheme 140: Synthesis of macrolactones 291 and 292.**

Unfortunately, attempts to oxidise olefin \(291\) to corresponding enones \(293\) and \(294\) did not produce any desired products. A number of oxidation conditions were attempted; chromium(VI)oxide in acetic acid, chromium(VI)oxide in pyridine and selenium dioxide in water-dioxane (Scheme 141). These, however, failed to produce compounds with observable signals on \(^1\)H-NMR.

**Scheme 141: Allylic oxidation of the macrolactone 291.**
6 Experimental

6.2 General Information

8.1.1 Naming and Numbering

Compounds were named according to IUPAC nomenclature recommendations or according to known trivial names where appropriate.

IUPAC recommendations were not adhered to when numbering compounds, but a uniform numbering system was employed to allow the consistent assignment of spectra.

8.1.2 Reaction Conditions

Reactions were carried out in flame-dried glassware under an atmosphere of argon unless stated otherwise. Ambient temperature refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of −78 °C were obtained using a dry ice/acetone bath. Reflux conditions were obtained using an oil bath or a Drysyn® heating block equipped with a contact thermometer. Temperatures of 0 °C or below which had to be maintained for extended periods of time were obtained using a Julabo FT902 immersion cooler.

8.1.3 Solvents

Acetonitrile, CH₂Cl₂, diethyl ether, methanol and tetrahydrofuran were purified by filtration through activated alumina columns employing the method of Grubbs et al.¹¹⁶ Dimethylsulfoxide was purchased as an anhydrous solvent in a Sure/Seal™ bottle from Sigma-Aldrich. All other solvents were used as supplied without prior purification.
Solvents for phase-transfer catalyzed reactions were degassed by freeze-pump-thawing as described by Perrin and Armarego.\textsuperscript{117}

8.1.4 Reagents

Anhydrous cerium(III) chloride was obtained by vigorously stirring cerium(III) chloride heptahydrate (purchased from Acros Organics) at 150 °C for 6 hours under vacuum (\textit{c.a.} 0.1 mbar). K\textsubscript{3}PO\textsubscript{4} was ground with a pestle and mortar prior to use in phase-transfer catalyzed reactions. All other reagents were used directly as supplied by major chemical suppliers, or following purification procedures described by Perrin and Armarego.\textsuperscript{117}

8.1.5 Chromatography

Thin layer chromatography was performed on Merck Merck Kieselgel 60 F\textsubscript{254} 0.25 mm precoated aluminium plates. Product spots were visualized under UV light (\(\lambda = 254\) nm) and/or by staining with potassium permanganate solution or vanillin solution. Flash chromatography was performed using VWR silica gel 60 (40-63 \(\mu\)m particle size) using head pressure by means of a nitrogen line.

8.1.6 Nuclear Magnetic Resonance Spectrometry

NMR spectroscopy was carried out using Bruker Avance spectrometers in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sex), septet (sept), octet (oct), nonet (non) and multiplet (m). The abbreviation br. is to denote broad and app. to denote apparent. Coupling constants, \(J\), are measured to the nearest 0.5 Hz and are presented as observed. Assignment of spectra was assisted by the results of DEPT, COSY, HSQC and HMBC experiments.
8.1.7 Infrared Spectroscopy

Infrared spectra were recorded neat on a Bruker Tensor 27 FTIR spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima ($\lambda_{\text{max}}$) are quoted in wavenumbers (cm$^{-1}$).

8.1.8 Mass Spectrometry

Low resolution mass spectra were recorded on a Micromass LCT Premier spectrometer under conditions of electrospray ionization (ESI). High resolution mass spectra were carried out using Bruker MicroTOF and Micromass GCT spectrometers under conditions of electrospray ionization (ESI), field ionization (FI) and chemical ionization (CI).

8.1.9 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

8.1.10 Melting Points

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

8.1.11 HPLC

Chiral HPLC was performed on a Dionex UltiMate 3000 system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode-array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø x 25 cm) and corresponding guard column (0.4 cm ø x 1 cm).
Wavelengths (\(\lambda\)) are reported in nm, retention times (\(t_R\)) are reported in minutes and solvent flow rates are reported in mL min\(^{-1}\).

8.1.12 X-ray Crystallography

Single crystal X-ray diffraction experiments were carried out by myself under the supervision of Dr Amber Thompson and Dr Russel Driver on Oxford Diffraction Supernova and Nonius KappaCCD diffractometers in the Oxford Chemical Crystallography suite.
(5E,11Z)-Oxacyclotetradeca-5,11-diene-2,4,10-trione (67)

Dess-Martin periodinate (53 mg, 0.12 mmol) was added to a stirred solution of 94 (25 mg, 0.104 mmol) in CH$_2$Cl$_2$ (1mL) at 0 °C. After 1 hour, further DMP (53 mg, 0.125 mmol) was added to the solution. The reaction was quenched after 3 hours by addition of a saturated solution of Na$_2$S$_2$O$_3$ and water. The mixture was stirred until a clear solution was obtained. The mixture was extracted with CH$_2$Cl$_2$, combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The product was purified by column chromatography (20% EtOAc in petroleum ether) which gave the product 67 in 57% yield as a colourless viscous oil (14.1 mg, 0.062 mmol) that exists entirely in the keto form.

IR (neat) $\nu_{\text{max}}$ 3621, 2935, 2360, 1736, 1691, 1668, 1624, 1434, 1417, 1313, 1257, 1112, 1031, 1006

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.68 (1H, td, $J = 15.5, 7.5$ Hz, $H$-9), 6.17 (1H, td, $J = 11.5, 1.0$ Hz, $H$-4), 6.03 (1H, td, $J = 15.5, 1.0$ Hz, $H$-10), 6.00 (1H, td, $J = 11.5, 8.5$ Hz, $H$-3), 4.26 (1H, t, $J = 5.5$ Hz, $H$-1), 3.10 (1H, dtd, $J = 8.5, 5.5, 1.0$ Hz, $H$-2), 2.48–2.41 (1H, m, $H$-6), 2.34 (1H, dddd, $J = 7.5, 6.5, 6.0, 1.0$ Hz, $H$-8), 2.04–1.96 (1H, m, C-7).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 203.0 (C-5), 192.2 (C-11), 166.9 (C-13), 150.1 (C-9), 155.1 (C-3), 131.8 (C-10), 129.3 (C-4), 63.9 (C-1), 46.2 (C-12), 43.2 (C-6), 33.6 (C-8), 28.6 (C-2), 21.1 (C-7).

$m/z$ LRMS (ESI $^+$) 259.1 [M+Na]$^+$; HRMS (ESI$^+$) 259.0936 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 259.0941).
**But-3-en-1-yl 4-(diethoxyphosphoryl)-3-oxobutanoate (74)**

To the solution of NaH (60% in mineral oil, 356 mg, 8.9 mmol) in THF (9 mL) was added compound 77 (1.7 g, 8.9 mmol) at 0 °C. The solution was stirred for 30 min. To a separate solution of NaH (60% in mineral oil, 820 mg, 20.5 mmol) in THF (20 mL) was added diethyl phosphite (2.6 mL, 20.5 mmol) at 0 °C and the reaction mixture was stirred for 30 min. The deprotonated diethyl phosphite was cannulated to the solution of compound 90. The reaction mixture was stirred for 1.5 h at 0 °C and quenched by pouring onto saturated aqueous NH₄Cl solution. The organic layer was separated and the remaining aqueous layer with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (70% EtOAc in petroleum ether) gave the product 74 as a pale yellow liquid in 88% yield (2.3 g, 7.87 mmol) that exist at equilibrium as an 88:12 ratio of keto to enol tautomers.

**IR (neat)** $v_{\text{max}}$ 3468, 3080, 2983, 2932, 2911, 2361, 1744, 1717, 1642, 1394, 1324, 1249, 1018, 968, 797.

$^1$H NMR (400 MHz, CDCl₃) $\delta$ 12.09 (<1H, s, H-(11)), 5.77 – 5.61 (1H, m, H-2,(2)), 5.03 (2H,dd, $J = 13.5, 12.5$ Hz, H-1,(1)), 4.18 – 4.01 (6H,m, H-9,4,(9),(4),(8)), 3.61 (<2H, s, H-6), 3.19 (2H, d, $J = 22.5$ Hz, H-8), 2.72 (<1H, d, $J = 22.5$ Hz, H-(8)), 2.39 (2H, q, $J = 6.7$ Hz, H-3,(3)), 1.29 (2H, dt, $J = 9.8, 7.1$ Hz, H-10).

$^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 194.9, 167.9, 133.9, 117.9, 64.8, 63.1 (d, $J = 6.5$ Hz), 49.9, 42.9 (d, $J = 126.5$ Hz), 33.2, 16.6 (d, $J = 6.1$ Hz).
\[ m/z \] LRMS (ESI\(^+\)) 315.0 [M+Na]\(^+\); HRMS (ESI\(^+\)) 315.0957 ([M+Na]\(^+\).\(C_{12}H_{21}O_{6}PNa\) requires 315.0968).

NB: Assignments in parentheses indicate the minor enol tautomer

Alternative synthesis for compound 74:

diethyl ((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)phosphonate (4.58 g, 16.46 mmol) and 3-buten-1-ol (4.75 g, 65.8 mmol) was refluxed in toluene (8 mL) for 6h. The reaction mixture was concentrated in vacuo and the concentrate was purified by flash chromatography (70% EtOAc in petroleum ether) that gave the product 74 in 61% yield (3.1 g, 10.61 mmol).

Alternative synthesis for compound 74:

but-3-en-1-yl 3-oxobutanoate (0.9 g, 5.8 mmol) was slowly added to a suspension of NaH 60% in mineral oil (254 mg, 6.38 mmol) in THF (50 mL) at 0 \(^\circ\)C. The mixture was stirred for 0.5 h, n-butyllithium 2.5 M (2.5 mL, 6.38 mmol) was added dropwise the solution was stirred for further 0.5 h. Diethyl chlorophosphate (0.420 mL, 2.9 mmol) in THF (20 mL) was added slowly to the reaction mixture. The mixture was stirred for 2 hours and was quenched by saturated aqueous NH\(_4\)Cl. The solution was acidified by adding 1 M HCl, extracted with Et\(_2\)O and the combined organic layers were washed with brine, dried (\(Na_2SO_4\)), filtered and concentrated in vacuo. Purification by flash chromatography (70% EtOAc in petroleum ether) gave the title compound 74 as a pale yellow liquid in 14% yield (0.121 g, 0.414 mmol).
5,5-Dimethoxypentanal (78)

\[
\begin{array}{c}
\text{O} \\
\text{OMe} \\
\text{OMe} \\
\text{78}
\end{array}
\]

To a two necked flask was added the cyclopentene (10.2 g, 150 mmol), CH\textsubscript{2}Cl\textsubscript{2} (500 mL), methanol (100 mL) and the mixture was cooled to –78 °C. Ozone was purged through the mixture until a blue colour formed. Cooling bath was removed and p-toluenesulfonic acid monohydrate (2.20 g, 11.6 mmol) was added. After warming to ambient temperature the mixture was stirred for further 40 min. NaHCO\textsubscript{3} (4.00 g, 47.6 mmol) was added and the solution was stirred for 15 minutes after which, dimethyl sulfide (24 mL, 8.1 g, 116 mmol) was added. After 1 hour the mixture was concentrated \textit{in vacuo} and CH\textsubscript{2}Cl\textsubscript{2} (300 mL) was added to the concentrate. The mixture was washed two times with water, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The crude product was purified by column chromatography (10% EtOAc in petroleum ether) to afford the title compound as a colourless viscous liquid (8.30 g, yield 37%).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 9.75 (1H, t, \(J = 1.5\) Hz, \(H\text{-}5\)), 4.35 (1H, t, \(J = 5.5\) Hz, \(H\text{-}1\)), 3.30 (6H, br. s, \(H\text{-}6\)) 2.46 (2H, dt, \(J = 7.0, 1.5\) Hz, \(H\text{-}4\)), 1.73–1.56 (4H, m, \(H\text{-}2,3\)).

\(^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 202.6, 104.5, 104.4, 53.1, 53.1, 43.8, 33.8, 32.1, 32.0, 20.2, 17.5.

\(m/z\) LRMS (ESI \(^{+}\)) 169.1 [M+Na]\(^{+}\).

Data in accordance with the literature.\(^{38}\)
7,7-Dimethoxyhept-1-en-3-ol (79)

To a stirred solution of aldehyde 78 (2.00 g, 12.7 mmol) in THF (27 mL) was added dropwise a 1 M solution of vinylmagnesium bromide (1.98 g, 15.1 mL, 15 mL) in THF at −78 °C. The mixture was stirred for 1 hour and quenched with addition of saturated aqueous NH₄Cl. The mixture was extracted three times with diethyl ether, the combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (50% Et₂O in petroleum ether) gave the title compound 79 as a colourless viscous liquid in 43 % yield. (yield 0.34 g, 1.95 mmol).

^1H NMR (400 MHz, CDCl₃) δ 5.84 (1H, ddd, J = 17.0, 10.5, 6.5 Hz, H-6), 5.21 (1H, dt, J = 17.0, 1.5 Hz, H-7), 5.21 (1H, dt, J = 10.5, 1.5 Hz, H-7’), 4.35 (1H, t, J = 5.5 Hz, H-1), 4.08 (1H, q, J = 6.0 Hz, H-5), 3.29 (6H, d, J = 1.5 Hz, H-9), 1.81 (1H, br. s, H-8), 1.61–1.57 (2H, m, H-2), 1.56–1.49 (2H, m, H-4), 1.49–1.32 (2H, m, H-3).

^13C NMR (101 MHz, CDCl₃) δ 141.1, 114.7, 104.4, 73.0, 52.7, 36.79, 32.3, 20.5.

m/z LRMS (ESI +) 197.1 [M+Na]⁺.

Data in accordance with the literature. 44
5-((Triethylsilyl)oxy)hept-6-enal (80)

2,6-Lutidine (300 mg, 2.8 mmol, 0.32 mL) and triethylsilyl trifluoromethanesulfonate (555 mg, 2.1 mmol, 0.47 mL) was added to a solution of acetal 79 in CH₂Cl₂ (0.1 M) at 0 °C under nitrogen gas. The mixture was stirred for 1 hour and quenched by adding water to the solution. The mixture was extracted with CH₂Cl₂, combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (2.5% EtOAc in petroleum ether) gave aldehyde 80 in 76% yield (0.443 g, 1.54 mmol), as a colourless liquid.

IR (neat) νmax 3078, 2954, 2912, 2876, 2715, 2360, 2341, 1727, 1644, 1458, 1414, 1238, 1213, 1089, 921, 822, 741.

¹H NMR (400 MHz, CDCl₃) δ 9.69 (1H, t, J = 1.5 Hz, H-1), 5.72 (1H, ddd, J = 17.0, 10.5, 6.5 Hz, H-7), 5.09 (1H, dt, J = 17.0, 1.5 Hz, H-6), 5.00 – 4.95 (1H, dt, J = 10.5, 1.5 Hz H-6), 4.08 – 4.00 (1H, m, H-5), 2.37 (2H, m, J = 7.5, 1.5 Hz, H-2), 1.68 – 1.51 (2H, m, H-3), 1.51 – 1.38 (2H, m, H-4), 0.88 (9H, t, J = 8.0 Hz, H-9), 0.52 (6H, q, J = 8.0 Hz, H-8).

¹³C NMR (101 MHz, CDCl₃) δ 202.6 (C-1), 141.3 (C-7), 114.2 (C-6), 73.5 (C-5), 43.8 (C-2), 37.4 (C-4), 17.8 (C-3), 6.8 (C-8), 4.9 (C-8).


Data in accordance with the literature.⁴⁵
Synthesis via DIBAL-H reduction:

To a solution of ethyl 5-((triethylsilyl)oxy)hept-6-enoate 74 (200 mg, 0.698 mmol) in Et₂O (1.5 mL) at −78 °C was added dropwise a 1 M hexane solution of DIBAL (0.768 mmol, 0.767 mL). The reaction mixture was stirred for 2 hours, the temperature was raised to −40 °C and EtOAc (5 mL) was added to the solution. The temperature was raised to ambient and 30 mL of water was added. The mixture was stirred for further 1 hour. The reaction mixture was extracted with Et₂O, dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (eluent: Et₂O 0% to 10% in petroleum ether) gave the aldehyde 67 in 92% yield (156 mg, 0.54 mmol).

Ethyl 5-oxohept-6-enoate (86)

Ethyl 4-bromobutanoate 71 (20g, 102 mmol, 14.7 mL) was added to a suspension of NaI (46.1g, 308mmol) in acetone (140 mL) and the mixture was stirred overnight at 60 °C. The reaction was cooled to ambient temperature and diluted with Et₂O, washed with saturated aqueous solution of sodium thiosulfate Na₂S₂O₃, dried over MgSO₄, filtered and concentrated in vacuo. The concentrate was dissolved in 140 mL of toluene and 70 mL of DMA. The solution was slowly added to a suspension of Zn(Cu) (19.8 g, 154 mmol) in 30 mL of toluene and the mixture was stirred for 1 hour at ambient temperature and then at 80 °C for overnight. The heating was removed and Pd(PPh₃)₄ (0.710g, 0.615 mmol) in toluene (30 mL) was added. The reaction was stirred for 5 minutes and acryloyl chloride (10.2 g, 113 mmol, 8.95 mL) in toluene (30 mL) was cannulated slowly from a flame dried round bottom flask. The mixture was stirred for 4h and
filtered through a pad of celite. The celite was washed with additional 50mL of EtOAc. The combined organics were washed with saturated aqueous NH₄Cl, saturated aqueous Na₂CO₃, Brine, dried over MgSO₄, filtered and concentrated in vacuo. Product was purified by vacuum distillation that gave the title compound 86 as a colourless liquid in 64% yield (11.22 g).

1H NMR (400 MHz, CDCl₃) δ 6.33 (1H, dd, J = 17.5, 10.5 Hz, H-2), 6.21 (1H, dd, 17.5, 1.5 Hz, H-1), 5.82 (1H, dd, J = 10.5, 1.5 Hz, H-1’), 4.11 (2H, q, J = 7.0 Hz, H-9), 2.65 (2H, t, J = 7.5 Hz, H-4), 2.34 (2H, t, J = 7.5 Hz, H-6), 1.93 (2H, qn, J = 7.5 Hz, H-5), 1.24 (3H, t, J = 7.0 Hz, H-9).

13C NMR (101 MHz, CDCl₃) δ 200.2 (C-3), 173.5 (C-7), 136.7 (C-2), 128.5 (C-1), 60.6 (C-8), 38.6 (C-4), 33.5 (C-6), 19.3 (C-5), 14.5 (C-9).

m/z LRMS (ESI +) 193.1 [M+Na]+;

Data in accordance with the literature¹¹⁹.

**Ethyl 5-hydroxyhept-6-enoate (87)**

Flame-dried CeCl₃ (8.69 g, 35.2 mmol) was dissolved in ethanol (73 mL) stirred for 30 min. Ethyl 5-oxohept-6-enoate 86 (5 g, 29.4 mmol) in EtOH (35 mL) was added to the cerium-solution. The reaction mixture was stirred for 30 minutes and cooled to −78 °C. Sodium borohydride (1.22 g, 32.3 mmol) was added in the solution in three portions. The reaction was stirred at −78°C for 3h and quenched with saturated aqueous NH₄Cl solution. The mixture was extracted with CH₂Cl₂, combined organic layers were dried over MgSO₄, filtered and
concentrated in vacuo. Purification by flash chromatography (eluent: 30% EtOAc in petroleum ether) gave the title compound 87 as a colourless liquid in 77% yield (3.91 g).

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.86 (1H, ddd, $J = 17.0, 10.5, 6.0$ Hz, $H$-2), 5.56 (1H, ddd, $J = 17.0, 1.5, 1.5$ Hz, $H$-1), 5.11 (1H, ddd, $J = 10.5, 1.5, 1.5$ Hz, $H$-1’), 4.13 (2H, q, $J = 7.0$ Hz, $H$-8), 4.16-4.07 (1H, m, $H$-3), 2.33 (2H, t, $J = 7.0$ Hz, $H$-6), 1.81-1.60 (2H, m, $H$-5), 1.56 (2H, dt, $J = 8.5, 7.0$ Hz, $H$-4), 1.51 (3H, t, $J = 7.0$ Hz, $H$-9).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.0 (C-7), 141.2 (C-2), 115.3 (C-1), 73.1 (C-3), 60.7 (C-8), 36.6 (C-4), 34.4 (C-6), 21.1 (C-5), 14.6 (C-9).

$m/z$ LRMS (ESI $^+$) 195.1

Data in accordance with the literature.\textsuperscript{119}

**Ethyl 5-((triethylsilyl)oxy)hept-6-enoate (88)**

![Chemical Structure](image)

2,6-Lutidine (7.28 g, 68 mmol, 7.9 mL) was added to a solution of ethyl 5-hydroxyhept-6-enoate 73 (2.34 g, 13.6 mmol) in CH$_2$Cl$_2$ (200 mL) at 0 °C. TESOTf (3.77g, 14.7 mmol, 3.24 mL) was added dropwise to the solution. The reaction mixture was stirred for 1h and quenched with water. Organic layer was separated and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by flash chromatography (Eluent: 20% Et$_2$O in petroleum ether) gave the title compound 88 in 99% yield (3.85 g) as a colourless liquid.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.79 (1H, ddd, \(J = 17.0, 10.5, 6.5\) Hz, \(H-2\)), 5.16 (1H, dt, \(J = 17.0, 1.5\) Hz, \(H-1\)), 5.03 (1H, dt, \(J = 10.5, 1.5\) Hz, \(H-1'\)), 4.11 (2H, q, \(J = 7.0\) Hz, \(H-8\)), 4.12-4.06 (1H, m, \(H-3\)), 2.30 (2H, t, \(J = 7.0\) Hz, \(H-6\)), 1.76-1.58 (2H, m, \(H-5\)), 1.58-1.42 (2H, m, \(H-4\)), 1.25 (3H, t, \(J = 7.0\) Hz, \(H-9\)), 0.94 (9H, t, \(J = 8.0\) Hz, \(H-11\)), 0.59 (6H, q, \(J = 8.0\) Hz, \(H-10\)).

\(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 174.0 (C-7), 141.7 (C-2), 114.4 (C-1), 73.8 (C-3), 60.5 (C-8), 37.7 (C-4), 34.6 (C-6), 21.1 (C-5), 14.6 (C-9), 7.18 (C-11), 5.22 (C-10).

\(m/z\) LRMS (ESI \(^+\)) 309.2 [M+Na]\(^+\); HRMS (ESI \(^+\)) 309.18556 ([M+Na]\(^+\), \(C_{13}H_{16}O_4\)Na requires 309.18564).

**But-3-en-1-yl 4-chloro-3-oxobutanoate (90)**

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To a solution of methyl 4-chloro-3-oxobutanoate 75 (1.45 g, 9.63 mmol) in toluene (10 mL) was added but-3-en-1-ol 7 (2.08 g, 28.3 mmol). Using a Dean-Stark apparatus the mixture was heated at reflux for 24h. The reaction mixture was cooled down to ambient temperature and concentrated in vacuo. Purification by flash chromatography (EtOAc 10% in petroleum ether) gave the title compound 90 as a colourless liquid in 45% yield (0.828g, 4.34 mmol) that exists at equilibrium as a 91:9 ratio of keto to enol tautomers.

IR (neat) \(\nu_{max}\) 2962, 1725, 1642, 1401,1324, 1194, 990, 921, 810, 622.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.92 (<1H, s, \(H-(9)\)), 5.77 – 5.64 (1H, m, \(H-I\)), 5.27 (<1H, s, \(H-(6)\)), 5.11 – 4.99 (2H, m, \(H-I\)), 4.19 – 4.12 (4H, m, \(H-4,(4),8\)), 3.95 (<1H, s, \(H-(8)\)), 3.59 (2H, s, \(H-6\)), 2.38 – 2.31 (2H, m, \(H-3,(3)\)).

\(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 195.4 (C-7), 172.1 (C-5), 170.8 (C-7), 166.4 (C-5), 133.7 (C-1), 133.5 (C-1), 117.7 (C-2), 117.5 (C-2), 91.3 (C-6), 64.7 (C-4), 63.7 (C-4), 48.1 (C-8), 46.1 (C-6), 42.4 (C-8), 33.0 (C-3), 32.9 (C-3).
\[ m/z \] LRMS (ESI⁻) 213.0 [M−H]; HRMS (ESI⁻) 189.0326 ([M−H].C₈H₁₀O₃Cl requires 189.0324).

NB: Assignments in parentheses indicate the minor enol tautomer.

But-3-en-1-yl (E)-3-oxo-9-((triethylsilyl)oxy)undeca-4,10-dienoate (91)

![Chemical Structure](image)

To a stirred solution of but-3-en-1-yl 4-(diethoxyphosphoryl)-3-oxobutanoate 74 (675 mg, 2.31 mmol) in THF (23 mL) at −78 °C was added dropwise KHMD (0.5 M in toluene) (4.62 mmol, 9.24 mL). The solution was stirred for further 15 minutes before solution of aldehyde 80 (400 mg, 1.65 mmol) in THF (8.25 mL) was added. The reaction mixture was stirred for 3 hours at −78 °C. The reaction was quenched by pouring onto saturated aqueous NH₄Cl solution. The organic layer was separated and the remaining aqueous solution was extracted three times with EtOAc. The combined organic layers were washed with water, brine and dried (Na₂SO₄), filtered and evaporated in vacuo. Purification by flash chromatography (10% EtOAc in petroleum ether) gave the title compound 91 in 91% yield (399 mg, 1.05 mmol) that exists at equilibrium as a 65:35 ratio of keto to enol tautomers.

IR (neat) \( \nu_{\text{max}} \) 3079, 2954, 2911, 2876, 2360, 2341, 1746, 1665, 1642, 1598, 1419, 1234, 1148, 1075, 1005, 727.

\(^1\)H NMR (400 MHz, CDCl₃) δ 11.77 (<1H, s, H-18), 6.79 (<1H, dt, \( J = 16.0, 7.0 \) Hz, H-9), 6.57 (<1H, dt, \( J = 15.5, 7.0 \) Hz, H-9), 6.08 (<1H, dt, \( J = 16.0, 1.5 \) Hz, H-8), 5.79–5.63 (<3H, m, H-2,(2),14,(14),(8)), 5.11–4.93 (4H, m, H-15,(15),1,(1)), 4.91 (<1H, s, H-(6)), 4.16–4.08 (2H, m, H-4,(4)), 4.06–3.97 (1H, m, H-13,(13)), 3.51 (<2H, s, H-6), 2.40–2.27 (2H, m, H-3,(3)), 2.10–1.80 (2H, m, H-3,14).
2.22–2.07 (2H, m, H-10,(10)), 1.52–1.33 (4H, m, H-11,(11),12,(12)), 0.88 (9H, t, J = 7.8 Hz, H-17, (17)), 0.52 (6H, q, J = 7.8 Hz, H-16,(16)).

$^1$C NMR (101 MHz, CDCl$_3$) δ 192.0 (C-7), 172.9 (C-(7)), 169.7 (C-(5)), 167.4 (C-5), 149.8 (C-9), 141.6 (C-(14)), 141.4 (C-14), 141.0 (C-(9)), 133.9 (C-2), 133.7 (C-(2)), 129.7 (C-8), 124.5 (C-(8)), 117.4 (C-15), 117.3 (C-(15)), 114.1 (C-1), 113.9 (C-(1)), 89.9 (C-(6)), 73.6 (C-(13)), 73.5 (C-13), 64.4 (C-4), 63.2 (C-(4)), 46.9 (C-6), 37.6 (C-(12)), 37.5 (C-12), 33.1 (C-(3)), 32.9 (C-3), 32.6 (C-10,(10)), 24.1 (C-(11)), 23.6 (C-11), 6.9 (C-17, (17)), 4.9 (C-16, (16)).

$m/z$ LRMS (ESI $^+$) 403.1 [M+Na]$^+$; HRMS (ESI$^+$) 403.2264 ([M+Na]$^+$,C$_{21}$H$_{36}$O$_4$SiNa requires 403.2275).

NB: Assignments in parentheses indicate the minor enol tautomer

(5$^E$,11$^E$)-10-((Triethylsilyl)oxy)oxacyclotetradeca-5,11-diene-2,4-dione (92)

To a stirred refluxing solution of 91 (30.0 mg, 0.075 mmol) in degassed 1,2-dichloroethane (27 mL) under nitrogenatmosphere was added Hoveyda-Grubbs 2$^\text{nd}$ generation catalyst (5.0 mg, 0.080 mmol). Reaction mixture was stirred at reflux (84 °C) for 10 min. Activated carbon (0.7 g) was added to the refluxing mixture and the reaction was cooled down in a water bath. The mixture was concentrated in vacuo and the crude product was purified by flash chromatography
(5% to 10% EtOAc in petroleum ether) which gave the title compound 92 in 24% yield as a viscous colourless liquid (6.8 mg, 0.019 mmol).

IR (neat) \( \nu_{\text{max}} \) 2953, 2876, 1738, 1672, 1625, 1458, 1418, 1237, 1149, 1084, 1006, 972, 812, 743.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.88 (1H, dt, \( J = 16.0, 6.5 \) Hz, \( H-9 \)), 6.21 (1H, d, \( J = 16.0 \) Hz, \( H-10 \)), 5.58 (1H, dd, \( J = 16.0, 6.0 \) Hz, \( H-4 \)), 5.51 (1H, dt, \( J = 16.0, 5.5 \) Hz, \( H-3 \)), 4.26 (2H, t, \( J = 5.0 \) Hz, \( H-1 \)), 4.09 (1H, br. t, \( J = 6.61 \) Hz, \( H-5 \)), 3.58 (1H, d, \( J = 14.0 \) Hz, \( H-12 \)), 3.49 (1H, d, \( J = 14.0 \) Hz, \( H-12' \)), 2.42 (2H, dt, \( J = 5.5, 5.0 \) Hz, \( H-2 \)), 2.29 – 2.16 (2H, m, \( H-8 \)), 1.70 – 1.43 (4H, m, \( H-7,6 \)), 0.94 (9H, t, \( J = 7.9 \) Hz, \( H-15 \)), 0.57 (6H, q, \( J = 7.9 \) Hz, \( H-14 \)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 191.8 (\( C-11 \)), 167.5 (\( C-13 \)), 150.5 (\( C-9 \)), 136.0 (\( C-4 \)), 129.7 (\( C-10 \)), 125.9 (\( C-3 \)), 72.3 (\( C-5 \)), 64.5 (\( C-1 \)), 48.3 (\( C-12 \)), 36.3 (\( C-6 \)), 32.3 (\( C-2 \)), 31.4 (\( C-8 \)), 20.8 (\( C-7 \)), 7.2 (\( C-15 \)), 5.3 (\( C-14 \)).

\( m/z \) LRMS (ESI \( ^+ \)) 375.1 [M+Na]\(^+\); HRMS (ESI\(^+\)) 375.1958 ([M+Na]\(^+\); \( C_{19}H_{32}O_4SiNa \) requires 375.1962).

**But-3-en-1-yl (E)-9-hydroxy-3-oxoundeca-4,10-dienoate (93)**

To a stirred solution of 91 (100 mg, 0.262 mmol) in THF (9 mL) at 0 \( ^\circ \)C was added a solution of TBAF (1 M in THF, 1.58 mL, 1.58 mmol) and the mixture was stirred for 30 minutes. The reaction was quenched by pouring the solution into 7 \( \text{pH} \) phosphate buffer solution. The solution was extracted with EtOAc and the combined organic layers were washed with water, brine, dried (Na\(_2\)SO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography
(30% EtOAc in petroleum ether) gave the title compound 93 in 61% yield as a colourless viscous oil (43 mg, 0.161 mmol) that exist at equilibrium as a 64:36 ratio of keto to enol tautomers.

IR (neat) \( \nu_{\text{max}} \) 3424, 2918, 2360, 1733, 1666, 1640, 1598, 1420, 1240, 1149, 989, 920, 988, 729, 668.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 11.82 (<1H, s, \( H-16 \)), 6.87 (<1H, dt, \( J = 16.0, 7.0 \) Hz, \( H-9 \)), 6.64 (<1H, dt, \( J = 15.5, 7.0 \) Hz, \( H-(9) \)), 6.16 (<1H, dt, \( J = 16.0, 1.5 \) Hz, \( H-8 \)), 5.79 (<1H, d, \( J = 15.5 \) Hz, \( H-(8) \)), 5.85 – 5.70 (2H, m, \( H-2,(2),14,(14) \)), 5.26 – 5.04 (4H, m, \( H-15,(15),1,(1) \)), 4.98 (<1H, s, \( H-(6) \)), 4.18 (2H, sep. \( J = 3.4 \) Hz, \( H-4,(4) \)), 3.57 (<1H, s, \( H-6 \)), 2.39 (2H, dt, \( J = 7.0, 6.5 \) Hz, \( H-3,(3) \)), 2.27 (<2H, q, \( J = 6.5 \) Hz, \( H-10 \)), 2.22 (<1H, q, \( J = 6.5 \) Hz, \( H-(10) \)) 1.72 (1H, br. s, \( H-17,(17) \)), 1.66 – 1.48 (4H, m, \( H-11,(11),12,(12) \)).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 192.3 (C-7), 149.5 (C-9), 140.9 (C-14), 140.6 (C-9)), 133.7 (C-2), 129.8 (C-8), 124.7 (C-8), 117.4 (C-15), 117.3 (C-15)), 115.0 (C-1), 114.9 (C-1)), 90.1 (C-6)), 74.1 (C-13)), 73.0 (C-13), 64.4 (C-4), 63.2 (C-4)), 49.9 (C-6), 36.4 (C-12)), 36.3 (C-12), 33.09 (C-3)), 32.9 (C-3), 32.4 (C-10)), 32.4 (C-10), 24.3 (C-11)), 23.7 (C-11),

\( m/z \) LRMS (ESI +) 289.0 [M+Na]+; HRMS (ESI+) 261.14213 ([M+Na]+, \( C_{15}H_{22}O_4Na \) requires 289.14216)

NB: Carbonyl carbons C-5,(5),(7) not observed in 13C NMR spectrum.

NB: Assignments in parentheses indicate the minor enol tautomer.
(5E,11Z)-10-Hydroxyoxacyclotetradeca-5,11-diene-2,4-dione (94)

KHMDS (0.5 M in toluene, 1.35 mL, 1.35 mmol) was added dropwise to a solution of 97 (62.5 mg, 0.262 mmol) in THF (1.35 mL) at 0 °C. The mixture was stirred for 3 h. The reaction was quenched by pouring the mixture into a pH 7 phosphate buffer solution. The solution was extracted with EtOAc and the combined organic phases were washed with brine, dried (Na₂SO₄) and filtered. The crude product was concentrated in vacuo and purified by flash chromatography (50% EtOAc in petroleum ether) to give the product 94 in 36% yield (22.7 mg, 0.095 mmol).

IR (neat) ν max 3408, 2947, 1731, 1667, 1624, 1435, 1251, 1129, 981, 743.

1H NMR (400 MHz, CDCl₃) δ 6.81 (1H, ddd, J = 16.0, 9.0, 5.5 Hz, C-9), 6.19 (1H, td, J = 16.0, 1.0 Hz, C-10), 5.61 (1H, ddd, J = 10.5, 7.5, 1.0 Hz, C-4), 5.43 (1H, ddt, J = 10.5, 3.5, 1.0 Hz, C-3), 4.52–4.46 (1H, m), 4.38 (1H, ddd, J = 11.0, 4.5, 3.5 Hz, C-1), 4.14 (1H, dt, J = 11.0, 2.2 Hz, C-1'), 3.66 (1H, d, J = 14.4 Hz, C-12), 3.44 (1H, d, J = 14.4 Hz, C-12'), 2.61 (1H, m, C-2), 2.47–2.38 (1H, m, H-8), 2.34–2.20 (2H, m, H-2',8'), 1.87–1.74 (1H, m, H-7), 1.70–1.57 (3H, m, H-6, 6',7'), 1.52 (1H, br. s, H-14).

13C NMR (101 MHz, CDCl₃) δ 192.0 (C-13), 167.5 (C-11), 150.6 (C-9), 135.7 (C-4), 131.1 (C-10), 128.8 (C-3), 67.1 (C-5), 65.2 (C-1), 47.5 (C-12), 35.8 (C-6), 31.5 (C-8), 28.4 (C-2), 21.5 (C-7).

But-3-en-1-yl 3-oxo-4-(6-vinyltetrahydro-2H-pyran-2-yl)butanoate (95)

To an acidified solution of chloroform (54 mL, washed with conc. HCl (10 ml)) in ice water bath was added the compound 91 (101 mg, 0.265 mmol). The reaction mixture was stirred in an ice bath for 2 hours. The reaction was quenched by adding saturated NaHCO₃. The organic layers were separated and the water phase was extracted with chloroform. The combined organic layers were washed with water, dried (Na₂SO₄), filtered, and evaporated in vacuo. Purification by flash chromatography (5% to 10% EtOAc in petroleum ether) gave the title compound 95 in 91% yield (66 mg, 0.248 mmol) that exists at equilibrium as a 78:22 ratio of keto to enol tautomers.

IR (neat) vₓₐₓ 2935, 2855, 2358, 1747, 1644, 1411, 1312, 1253, 1151, 1049, 989, 919.

¹H NMR (400 MHz, CDCl₃) δ 12.03 (<1H, s, H-16), 5.88–5.70 (2H, m, H-14,(14),2,(2)), 5.25–5.03 (4H, m, H-15,(15),I,(I),(6)), 4.17 (2H, t, J = 6.7 Hz, H-4,(4)), 3.87–3.78 (<2H, m, H-9,13,(13)), 3.71 (<1H, dddd, J = 11.1, 6.5, 6.5, 2.0 Hz, H-(9)), 3.45 (<2H, s, H-6), 2.79 (<1H, dd, J = 15.5, 7.5 Hz, H-8), 2.52 (<1H, dd, J = 15.5, 5.0 Hz, H-8), 2.51 (<1H, dd, J = 14.0, 6.5 Hz, H-(8’)), 2.43–2.32 (2H, m, H-3,(3)), 2.27 (<1H, dd, J = 14.0, 6.5 Hz, H-(8)), 1.90–1.81 (1H, m, H-11,(11)), 1.67–1.49 (3H, m, H-12,11,(11)), 1.29–1.09 (2H, m, H-10,(10)).

¹³C NMR (101 MHz, CDCl₃) δ 201.9 (C-7), 175.8 (C-(7)), 172.9 (C-(5)), 167.5 (C-5), 139.5 (C-(14)), 139.4 (C-14), 134.2 (C-(2)), 134.0 (C-2), 117.7 (C-15), 117.6 (C-(15)), 114.8 (C-(1)), 114.7 (C-1), 91.0 (C-(6)), 78.5 (C-(13)), 78.5 (C-13), 74.9 (C-(9)), 74.4 (C-9), 64.6 (C-4), 63.4 (C-(4)), 50.5 (C-6), 49.9 (C-8), 42.6 (C-(8)), 33.4 (C-(3)), 33.2 (C-3), 31.4 (C-10,(12), 31.3 (C-12,(10)), 23.6 (C-(11)), 23.5 (C-11).

NB: Assignments in parentheses indicate the minor enol tautomer

The minor product was also isolated and characterized:

**But-3-en-1-yl 3-oxo-4-((2S,6S)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate ((E)-95)**

![Chemical structure](image)

Z,E-product exist at equilibrium as a 77:23 ratio of keto to enol tautomers.

IR (neat) νmax 2935, 2855, 2360, 1744, 1715, 1643, 1458, 1409, 1316, 1260, 1148, 1035, 991, 919.

¹H NMR (500 MHz, CDCl₃) δ 5.83 (1H, ddd, J = 17.0, 11.5, 5.0 Hz, H-14, (14)), 5.71 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz, H-2,(2)), 5.17 (2H, ddd, J = 7.5, 1.5, 1.5 Hz, H-15,(15)), 5.07-4.99 (2H, m, H-1,(1)), 4.98 (<1H, s, H-(6)), 4.31–4.26 (1H, br. s, H-13,(13)), 4.16–4.09 (3H, m, H-9,4,(9),(4)), 3.44 (<2H, s, H-(6)), 2.74 (<1H, dd, J = 15.5, 8.5 Hz, H-(8)), 2.50 (<1H, dd, J = 15.5, 5.0 Hz, H-8'), 2.39 (<1H, dd, 14.5, 8.0 Hz, H-(8)), 2.36–2.30 (2H, m ,H-3,3), 2.24 (<1H, dd, 14.5, 6 Hz, H-(8')) 1.72–1.49 (5H, m, H-10,11,12,(11),(12), 1.32 – 1.15 (1H, m, H-10'), (10'))

¹³C NMR (126 MHz, CDCl₃) δ 201.7 (C-7), 176.1 (C-(7)),172.9 (C-(5)), 167.5(C-5),138.6 (C-(14)) 138.3 (C-(14)),134.2 (C-(2)), 134.0 (C-(2)), 117.7 (C-I), 117.6 (C-(1)), 116.8 (C-15), 116.5 (C-(15)), 91.0 (C-(6)), 73.0 (C-13), 67.8 (C-9), 64.6 (C-4), 50.3 (C-6), 48.7 (C-8), 41.1 (C-(8)), 33.4 (C-(3)), 33.2 (C-3), 31.1 (C-10), 30.9 (C-(10)), 28.9 (C-(12)), 28.71 (C-12), 18.9 (C-(11)), 18.9 (C-11).

161
m/z LRMS (ESI⁺) 289.1 [M+Na]⁺; HRMS (ESI⁺) 289.1404 ([M+Na]⁺, C₁₅H₂₂O₄Na requires 289.1410)

((Z)-6,15-Dioxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (97)

To a stirred solution of 95 (20.0 mg, 0.075 mmol) in degassed CH₂Cl₂ (15 mL) under an argon atmosphere was added Grubbs 2nd generation catalyst (12.7 mg, 0.015 mmol). The reaction mixture was stirred at ambient temperature for 20 hours. The reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography (5% to 10% EtOAc in petroleum ether) to give the title compound 97 as a liquid viscous in 75% yield (13.5 mg, 0.057 mmol).

IR (neat) νmax 3012, 2933, 2858, 2358, 1735, 1707, 1490, 1320, 1190, 1142, 1046.

1H NMR (500 MHz, CD₆D₆) δ 5.45 (1H, tdd, J = 11.0, 8.5, 1.0 Hz, H-4), 5.27 (1H, ddt, J = 11.0, 6.2, 0.5 Hz, H-3), 4.08 (1H, ddd, J = 11.0, 4.0, 3.0 Hz, H-1), 3.67 (1H, ddd, J = 10.0, 8.5, 2.0 Hz, H-5), 3.49–3.42 (2H, m, H-1',9), 3.42 (1H, d, J = 14.5 Hz, H-12), 3.01 (1H, dd, J = 14.5, 1.0 Hz, H-12'), 2.85 (1H, J = 13.5, 11.5, 4.0 Hz, H-2), 2.32 (1H, dd, J = 13.0, 11.0 Hz, H-10), 2.15 (1H, dddd, J = 13.0, 1.7, 1.1 Hz, H-10'), 1.65 (1H, dddd, J = 6.0, 3.0, 1.0, H-2'),
1.41–1.34 (1H, m, H-7), 1.26–1.20 (1H, m, H-6), 1.17–1.07 (1H, m, H-6’), 1.05 (1H, qt, J = 12.5, 4.0 Hz, H-7’), 0.95–0.87 (2H, m, H-8).

$^{13}$C NMR (126 MHz, C$_6$D$_6$) δ 201.2 (C-11), 168.1 (C-13), 134.6 (C-4), 130.9 (C-3), 75.5 (C-9), 73.1 (C-5), 64.0 (C-I), 51.6 (C-10), 32.3 (C-8), 32.0 (C-6), 28.2 (C-2), 24.0 (C-7).

$m/z$ LRMS (ESI *) 261.0 [M+Na]$^+$; HRMS (ESI*) 261.1095 ([M+Na]$^+$, C$_{13}$H$_{18}$O$_4$Na requires 261.1097).

IR (neat) $v_{max}$ 2934, 2858, 2360, 2341, 1739, 1712, 1646, 1438, 1378, 1313, 1249, 1148, 1081.

$^1$H NMR (400 MHz, C$_6$D$_6$) δ 5.55 (1H, dd, J = 11.0, 8.0 Hz, H-4), 5.31 (1H, tdd, J = 11.0, 5.5, 1.0, H-3), 4.31 (1H, dt, J = 8.0, 4.0, H-5), 4.08 (1H, dt, J = 11.0, 3.35 Hz, H-1), 3.78 (1H, dddd, J = 11.0, 8.0, 2.5, 2.0, H-9), 3.55 (1H, dddd, J = 12.5, 11.0, 2.0, H-1’), 3.22 (1H, d, J = 14.5 Hz, H-12) 3.16 (1H, d J 14.5 Hz, H-12’), 2.80–2.67 (1H, m, H-2), 2.68 (1H, dd, J = 13.0, 11.0 Hz, H-10), 1.80 (1H, dd, J = 13.0, 2.0 Hz, H-10’), 1.45–1.34 (2H, m, H-2’,6), 1.34–1.24 (1H, m, H-7), 1.22 – 1.04 (3H, m, H-6’,7’,8), 0.95–0.87 (1H, m, H-8’).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 201.6 (C-11), 167.3 (C-13), 132.5 (C-4), 131.7 (C-3), 69.2 (C-9), 66.8 (C-5), 63.9 (C-I), 50.1 (C-10), 50.0 (C-12), 32.2 (C-8), 30.0 (C-6), 28.5 (C-2), 19.1 (C-7)

$m/z$ LRMS (ESI *) 261.0 [M+Na]$^+$; HRMS (ESI*) 261.1095 ([M+Na]$^+$, C$_{13}$H$_{18}$O$_4$Na requires 261.1097).
(6aR,10aR,10bS)-5-Hydroxy-1,2,6a,7,8,9,10a,10b-octahydro-4H-benzo[f]isochromene-4,10(6H)-dione (101)

A stock solution of the NMR-standard 2,2’-dimethoxy-1,1’-binaphthalene (0.1 equiv, 0.67 mg, 0.0021 mmol) in D6-benzene (0.529 mL) was mixed with the starting material (5E,11Z)-oxacyclotetradeca-5,11-diene-2,4,10-trione 67 (5.0 mg, 0.021 mmol). A quantitative 1H-NMR spectrum of the mixture was obtained and the solution was transferred to an oven-dry vial and the deuterated solvents were removed in vacuo. Dry benzene (0.423 mL) and N-(9-anthracenylmethyl)cinchonium bromide (1.2 mg, 0.0021 mmol) were added and the mixture was stirred for 10 minutes prior to the addition of vacuum oven dried potassium fluoride (12 mg, 0.21 mmol). The reaction mixture was flushed with nitrogen, stirred for 48 hours and quenched with saturated aqueous ammonium chloride. The mixture was extracted with EtOAc and the combined organic phases were filtered through a small pad of silica to remove the phase-transfer catalyst. The solvents were removed in vacuo to afford the product 101 (54% yield based on 1H-NMR) and diastereomer 111 (31% yield based on 1H-NMR). The NMR solvent was removed and the crude product was purified by preparatory TLC (EtOAc 50% in petroleum ether) to afford tricycle 101 in 60% yield as a colourless oil (3.0 mg, 0.012 mmol). The product was found to exist entirely in its enol form.

IR (neat) ν\text{max} 2919, 2951, 2361, 1706, 1647, 1476, 1418, 1292, 1208, 877.

1H NMR (500 MHz, CDCl3) δ 13.25 (1H, s, H-14), 4.50–4.45 (1H, ddd, J = 11.5, 4.5, 2.0 Hz, H-1), 4.31–4.24 (1H, ddd, J = 12.0, 11.5, 3.0 Hz, H-1’), 2.94 (1H, br. t, J = 11.0 Hz, H-6), 2.68–2.60 (1H, ddd, J = 19.5, 7.0, 2.0 Hz, H-10), 2.48–2.39 (1H, app. m, H-6), 2.28 (1H, d, J
= 11.0 Hz, \( H-4 \) 2.38–2.22 (3H, m, \( H-6',10',9 \)), 2.15–2.07 (1H, app. m, \( H-7 \)), 1.87–1.76 (1H, app. m, \( H-8 \)), 1.76–1.70 (3H, m, \( H-2,8',7' \)), 1.64 (1H, ddd, \( J = 13.0, 12.0, 4.5, H-2' \))

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 212.1 (C-5), 173.6 (C-11), 171.1 (C-13), 94.7 (C-12), 69.3 (C-J), 55.3 (C-4), 38.1 (C-6), 35.4 (C-9), 34.1 (C-10), 31.1 (C-3), 27.9 (C-2), 27.8 (C-8), 25.6 (C-7).

\( m/z \) LRMS (ESI \(^+\)) 259.1 [M+Na]+; HRMS (ESI\(^+\)) 259.0939 ([M+Na]+, C\(_{13}\)H\(_{16}\)O\(_4\)Na requires 259.0940).

\([\alpha]\)\(_{D}^{25} = +25 \) (c = 0.001, CHCl\(_3\)).

\((4aR,6aS,10aR,10bR)\)-octahydro-4H-benzo[f]isochromene-4,5,10(4aH,6H)-trione (111)

(4aR,6aS,10aR,10bR)-octahydro-4H-benzo[f]isochromene-4,5,10(4aH,6H)-trione (111)

IR (neat) \( \nu_{\text{max}} \) 2932, 2868, 1748, 1702, 1649, 1613, 1476, 1290, 1220, 1075, 1064.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 12.07 (<1H, s, H-(14)), 4.49 (<1H, ddd, \( J = 11.5, 5.5, 1.0 \) Hz, H-(1)), 4.43 (<1H, ddd, \( J = 13.0, 11.5, 4.0 \) Hz, H-(1’)), 4.40 (<1H, ddd, \( J = 11.5, 5.5, 3.5 \) Hz, H-1), 4.32 (<1H, ddd, \( J = 11.5, 11.0, 4.0 \) Hz, H-1’), 3.59 (<1H, ddd, \( J = 5.5, 2.0, 0.5 \) Hz, H-12), 3.10 (<1H, ddd, \( J = 12.0, 5.5, 3.5, 3.5 \) Hz, H-3), 2.94 (<1H, ddd, \( J = 12.0, 6.0, 2.0, 2.0 \) Hz, H-3')
Hz, H-(3)), 2.65 (<1H, dd, J = 13.5, 4.0 Hz, H-10), 2.59 (<1H, dd, J = 12.5, 3.5 Hz, H-4), 2.54-2.47 (<3H, m, H-6,(6),2), 2.44 (<1H, dd, J = 17.5, 4.0 Hz, H-(10)), 2.42-2.30 (<3H, m, H-(6',10',6')), 2.31 (<1H, dd, J = 12.0, 6.0 Hz, H-(4)), 2.27-2.21 (<1H, ddd, J = 17.5, 11.5, 2.0 Hz, H-(10')), 2.24 (<1H, dtt, J = 12.5, 12.0, 4.0 Hz, H-9), 2.21-2.11 (<2H, m, H-(2),7), 2.11-2.02 (<2H, app. m, H-(8),(7)), 2.01-1.95 (<1H, m, H-8), 1.87 (<1H, app. tdt, J = 12.0, 11.5, 4.0 Hz, H-(9)), 1.75-1.65 (<2H, m, H-7',(7')), 1.70-1.59 (<1H, app. m, H-8'), 1.56-1.47 (<2H, m, H-2',(2')), 1.45-1.39 (<1H, m, H-(8)).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 209.1 (C-(5)), 207.8 (C-5), 202.8 (C-11), 171.4 (C-(13)), 169.5 (C-(11)), 166.8 (C-13), 99.1 (C-(12)), 70.5 (C-(1)), 69.1 (C-12), 58.7 (C-12), 54.8 (C-4), 52.2 (C-(4)), 48.2 (C-10), 41.7 (C-6), 41.7 (C-(6)), 38.9 (C-9), 37.8 (C-(10)), 35.3 (C-3), 33.6 (C-(9)), 32.8 (C-8), 31.8 (C-(3)), 31.2 (C-(8)), 26.2 (C-2)), 25.1 (C-7), 23.6 (C-(7)), 22.1 (C-2).

m/z LRMS (ESI $^+$) 259.0 [M+Na]$^+$; HRMS (ESI$^+$) 259.09408 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 259.09408).
(1S,11R,Z)-4-methyl-6,15-dioxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (135)

KHMDMS solution in 0.5 M toluene (1.42 mL, 0.709 mmol) was added dropwise to a solution of 87 (161 mg, 0.675 mmol) in THF (6 mL) at 0 °C. After 30 minutes iodomethane (126 µL, 2.03 mmol) was added and the mixture was warmed to ambient temperature and stirred for a further 44 hours. The reaction was diluted with water and extracted with CH$_2$Cl$_2$ and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and the solvent was removed in vacuo. The crude mixture was purified by column chromatography (5 to 10% EtOAc in petroleum ether) which gave an inseparable mixture of the diastereomers in 64% yield (109 mg, 0.432 mmol). The absolute configuration of the diastereomers wasn’t obtained. As an impurity the reaction gave 10% (18 mg, 0.067 mmol) of double methylated product 136.

IR (neat) $\nu_{\text{max}}$ 2936, 2858, 1729, 1708, 1455, 1370, 1276, 1223, 1180, 1125, 1087, 1002, 884.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.69-5.57 (>1H, m, $\text{H-1}$), 5.57-5.51 (<1H, m, $\text{H-1'}$), 4.48 (<1H, ddd, $J = 11.0, 4.0, 3.0$ Hz, $\text{H-1}$), 4.39 (<1H, ddd, 11.0, 8.0, 3.0 Hz, $\text{H-(1)}$), 3.98 (<1H, ddd, 11.0, 6.0, 3.0 Hz, $\text{H-1'}$), 3.95-3.84 (>1H, m, $\text{H-5},(5)$), 3.86 (<1H, ddd, $J = 12.0, 11.0, 2.5$ Hz, $\text{H-1}'$), 3.81-3.75 (<1H, m, $\text{H-9}$), 3.76 (<1H, q, $J = 7.5$ Hz, $\text{H-12}$), 3.71-3.62 (<1H, m, $\text{H-9}$), 3.53 (<1H, q, $J = 7.0$ Hz, $\text{H-12}$), 3.00 (<1H, ddd, $J = 14.0, 11.5, 10.5, 4.0$ Hz, $\text{H-2}$), 2.87 (<1H, dd, $J = 12.50, 11.50$ Hz, $\text{H-10}$), 2.66 (<1H, ddd, $J = 13.0, 11.0$ Hz, $\text{H-10}$), 2.58-2.46 (<2H, m, $\text{H-2},(2')$), 2.38 (<1H, dd, $J = 13.0, 1.5$ Hz, $\text{H-10}'$), 2.37 (<1H, dd, $J = 14.0, 3.5$ Hz, $\text{H-10}'$), 2.10 (<1H, dddd, 14.0, 5.0, 2.5, 2.5 Hz, $\text{H-2}'$), 1.90-1.80 (1H, m, $\text{H-7},(7)$), 1.64-1.57 (1H, m,
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.59-5.54 (2H, m, $H$-4,5), 4.35 (1H, ddd, $J = 10.5, 8.5, 2.0$ Hz, $H$-1), 4.03 (1H, ddd, 10.5, 7.5, 3.0 Hz, $H$-1’), 3.81 (1H, ddd, $J = 11.0, 6.5, 2.0$ Hz, $H$-5), 3.70 (1H, dddd, $J = 10.5, 11.0, 2.0, 2.0$ Hz, $H$-9), 3.03 (1H, dd, $J = 13.0, 10.5$ Hz, $H$-10), 2.61 (1H, dddd, $J = 14.5, 7.5, 7.5, 2.0$ Hz $H$-2), 2.49 (1H, dddd, 14.5, 8.5, 8.5, 2.5 Hz, $H$-2’), 2.28 (1H, dd, $J = 13.0, 2.5$ Hz, $H$-10’), 1.88-1.79 (1H, m, $H$-7), 1.64-1.46 (2H, m, $H$-6,7’), 1.40 (3H, s, $H$-15) 1.36-1.24 (3H, m, $H$-6,8,8’), 1.32 (3H, s, $H$-14).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 207.9 (C-11), 173.6 (C-13), 132.8 (C-4), 129.8 (C-3), 76.4 (C-9), 74.2 (C-5), 64.3 (C-1), 56.5 (C-12), 45.0 (C-10), 42.5 (C-2), 31.3 (C-8), 31.2 (C-6), 28.4 (C-2), 23.6 (C-7), 22.6 (C-15), 22.2 (C-14)

**but-3-en-1-yl 2-methyl-3-oxo-4-(6-vinyltetrahydro-2H-pyran-2-yl)butanoate (134)**

Compound 95 (50 mg, 0.187 mmol) and K₂CO₃ (26 mg, 0.187 mmol) were stirred for 5 minutes in acetone (0.4 mL) in oven dried vial. MeI (14 µL, 0.225 mmol) was added, and the mixture heated at 50 °C for 9 hours. The reaction was quenched by adding saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The combined organic phases where dried over Na₂SO₄, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (5% EtOAc in petroleum ether) which gave the title compound 134 as a colourless oil in 70% yield (37 mg, 0.133 mmol).

IR (neat) v_max 3080, 2983, 2937, 2860, 1743, 1715, 1643, 1455, 1336, 1196, 1072, 1047, 919.

¹H NMR (500 MHz, CDCl₃) δ 5.81-5.69 (2H, m, H-15, 15', 2, 2'), 5.25-5.00 (4H, m, H-1, 1', 16, 16'), 4.22-4.11 (2H, m, H-4, 4'), 3.90-3.77 (2H, m, H-10, 10', 14, 14'), 3.66-3.55 (1H, m, H-6, 6'), 2.89-2.77 (1H, m, H-9, 9'), 2.64-2.52 (1H, m, H-9, 9'), 2.43-2.33 (2H, m, H-3, 3'), 1.89-1.79 (1H, m, H-12, 12'), 1.69-1.51 (4H, m, H-12, 12', 11, 11', 13, 13'), 1.36-1.26 (3H, m, H-7, 7'), 1.26-1.14 (1H, m, H-13, 13')

¹³C NMR (126 MHz, CDCl₃) δ 204.8 (C-8), 204.6 (C-8'), 170.8 (C-5), 170.7 (C-5'), 139.5 (C-15), 139.5 (C-15'), 134.1 (C-2), 134.0 (C-2'), 117.8 (C-1), 117.8 (C-1'), 114.6 (C-16, 16'), 78.5 (C-14), 78.5 (C-14'), 74.7 (C-10), 74.2 (C-10'), 64.5 (C-4, 4'), 53.9 (C-6), 53.5 (C-6'), 48.9 (C-9), 48.4 (C-9'), 33.3 (C-3, 3'), 31.5 (C-11), 31.4 (C-11', 13, 13'), 23.6 (C-12, 12'), 12.9 (C-7), 12.7 (C-7').

(5E,11Z)-3-methylxacyclotetradeca-5,11-diene-2,4,10-trione (137)

KHMDS (0.5 M, in toluene, 0.218 mmol, 0.435 mL) was added dropwise in a solution of 133 (11 mg, 0.043 mmol) in THF (0.217 mL) at 0 °C. The mixture was stirred for 15 min. The reaction was quenched by adding saturated aqueous NH₄Cl solution. The mixture was extracted with EtOAc and combined organic phases was washed with brine, dried (Na₂SO₄) and filtered. The solvents were removed in vacuo. The crude was dissolved to a 0.220 mL of CH₂Cl₂ and the solution was cooled down to 0 °C. Dess-Martin periodinate (28 mg, 0.65 mmol) was added and the mixture was stirred for 1 hour and quenched by addition of saturated solution of Na₂S₂O₃ and water. The mixture was stirred until a clear solution was obtained. The mixture was extracted with CH₂Cl₂, combined organic layers were washed with brine, dried (Na₂SO₄), filtered and the crude was concentrated in vacuo. The product was purified by column chromatography (20% EtOAc in petroleum ether) which gave the product 137 as a colourless viscous oil (3.8 mg, 35%) that exist entirely in the keto form. The reaction gave also 10% yield of a decarboxylation side product 138 (1 mg, 0.004 mmol).

IR (neat) νmax 2918, 2849, 2363, 1738, 1693, 1628, 1454, 1337, 1218, 1115, 1072.

¹H NMR (500 MHz, CDCl₃) δ 6.76 (1H, ddd, J = 15.60, 8.60, 6.94 Hz, H-9), 6.17 (1H, ddd, J = 11.43, 1.42 Hz, H-4), 6.09 (1H, ddd, J = 15.61, 1.82, 1.82 Hz, H-10), 5.97 (1H, ddd, J = 11.50, 9.15, 7.16 Hz, H-3), 4.29–4.21 (2H, m, H-1), 3.76 (1H, q, J = 6.99 Hz, H-12), 3.54–
3.44 (1H, m, H-2), 2.68–2.60 (1H, m, H-2’), 2.48–2.40 (3H, m, H-6,8), 2.31–2.22 (1H, m, H-8’), 2.17–2.07 (1H, m, H-7), 1.91–1.82 (1H, m, H-7’), 1.30 (3H, d, J = 7.09 Hz, H-13)

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 220.7 (C-5), 194.7 (C-11), 170.2 (C-13), 148.4 (C-9), 143.4 (C-3), 130.5 (C-10), 129.3 (C-4), 63.7 (C-1), 49.0 (C-12), 42.5 (C-13), 32.7 (C-8), 30.0 (C-13), 28.7 (C-2), 21.2 (C-7)

m/z LRMS (ESI+) 273.0 [M+Na]$^+$; HRMS (ESI+) 273.1097 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 273.1097).

1-((2S,6R)-6-((Z)-buta-1,3-dien-1-yl)tetrahydro-2H-pyran-2-yl)butan-2-one (138)

IR (neat) $\nu_{max}$ 2933, 2850, 1715, 1653, 1558, 1375, 1073, 1057, 915.

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.59 (1H, dddd, J = 17.0, 11.0, 10.0, 1.0 Hz, H-2), 6.01 (1H, dd, J = 11.0, 11.0 Hz, H-3), 5.39 (1H, dd, J = 11.0, 7.5 Hz, H-4), 5.22 (1H, d, J = 17.0 Hz, H-1) 5.15 (1H, dd, J = 10.0 Hz, H-1’), 4.30 (1H, m, H-5), 3.90-3.82 (1H, m, H-9), 2.71 (1H, dd, J = 15.5, 7.0 Hz, H-9), 2.47 (2H, q, J = 7.5 Hz, H-12) 2.42 (1H, dd, J = 15.5, 5.5 Hz, H-9’), 1.90-1.81 (1H, m, H-7), 1.66-1.54 (3H, m, H-6,7’,8), 1.39-1.29 (1H, m, H-6’), 1.29-1.19 (1H, m, H-8’), 1.03 (3H, t, J = 7.5 Hz, H-13).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 210.4 (C-11), 132.7 (C-4), 132.6 (C-2), 130.8 (C-3), 119.2 (C-1), 74.8 (C-5), 74.6 (C-9), 49.4 (C-10), 37.6 (C-12), 31.9 (C-6), 31.4 (C-8), 23.6 (C-7), 7.9 (C-13).

m/z LRMS (ESI+) 231.2 [M+Na]$^+$; HRMS (ESI+) 231.13555 ([M+Na]$^+$, C$_{13}$H$_{20}$O$_2$Na requires 231.13575).

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(E)-2,2-dimethyl-6-(6-((triethylsilyl)oxy)octa-1,7-dien-1-yl)-4H-1,3-dioxin-4-one (145)

KHMDS 0.5 M in toluene was added to a solution of diethyl ((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)phosphonate 144 (161 mg, 0.577 mmol) in THF (6 mL) at −78 °C. The solution was stirred for 30 minutes and 5-((triethylsilyl)oxy)hept-6-enal (100 mg, 0.412 mmol) in THF (2 mL) was added dropwise to the deprotonated solution. The reaction mixture was stirred for 4 h and quenched by adding saturated aqueous NH₄Cl. The mixture was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The title compound 145 was purified by column chromatography (eluent: 10 to 20% Et₂O in petroleum ether). Yield 91% (99.5 mg, 0.271 mmol).

IR (neat) v max 3000, 2954, 2936, 2875, 1729, 1654, 1593, 1390, 1373, 1273, 1205, 1018, 725.

¹H NMR (400 MHz, CDCl₃) δ 6.54 (1H, dt, J = 15.5, 7.0 Hz, H-7), 5.89 (1H, dt, J = 15.5, 1.5 Hz, H-8), 5.79 (1H, ddd, J = 17.0, 10.5, 6.5 Hz, H-2), 5.23 (1H, s, H-10), 5.15 (1H, ddd, J = 17.0, 1.5, 1.5 Hz, H-1), 5.04 (1H, ddd, J = 10.5, 1.5, 1.0 Hz, H-1'), 4.14-4.06 (1H, m, H-3), 2.26-2.16 (2H, m, H-6), 1.70 (6H, s, H-13), 1.57-1.42 (4H, m, H-4,5), 0.95 (9H, t, J = 7.95 Hz, H-15), 0.59 (6H, q, J = 7.5 Hz, H-14).

¹³C NMR (101 MHz, CDCl₃) δ 163.7 (C-9), 162.4 (C-11), 142.6 (C-7), 141.7 (C-2), 122.9 (C-8), 114.4 (C-1), 106.6 (C-12), 93.7 (C-10), 73.8 (C-3), 37.8 (C-4), 33.0 (C-6), 25.4 (C-13), 24.2 (C-5), 7.2 (C-15), 5.2 (C-14).

Freshly distilled diisopropylamine (31.9 g, 315 mmol, 44.2 mL) in THF (200 mL) was deprotonated by adding dropwise 2.5 M n-butyllithium (31.9 g, 303 mmol, 121 mL) at 0 °C in a 500 mL flame-dried two-necked round bottomed flask. The mixture was stirred for 30 minutes and cooled to −78 °C. 2,2,6-trimethyl-4H-1,3-dioxin-4-one 148 (32 g, 225 mmol, 29.9 mL) in THF (20 mL) was added dropwise over 20 minutes and stirred for further 15 min. The mixture was cannulated in a flame-dried 1 L flask containing hexachloroethane (79.9 g, 338 mmol) in THF (150 mL) at -50 °C over 30 min. The temperature was allowed slowly rise to -25 °C over 30 min. The reaction was quenched by pouring the mixture to ice-cold 10% HCl (200 mL) and was shaken so the red colour of the reaction mixture disappeared. The aqueous layer was extracted with Et<sub>2</sub>O (2 x 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (100 mL), saturated aqueous brine (100 mL), Dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Purification by column chromatography (eluent: 20% Ethyl acetate in hexane) gave the title compound 149 as a yellow liquid in 57% yield (22.5 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.53 (1H, s, H-2), 4.02 (2H, s, H-4), 1.74 (6H, s, H-6)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 164.5 (C-3), 160.5 (C-1), 107.7 (C-5), 95.7 (C-2), 41.1 (C-4), 24.9 (C-6).

Data in accordance with the literature.<sup>118</sup>
diethyl ((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)phosphonate (150)

Freshly distilled diethyl phosphite was added dropwise to a mixture of NaH (3.79 g, 158 mmol) in THF (200 mL) and DMF (20 mL) at RT. The reaction mixture is stirred for 30 minutes and cooled to 0 °C. 6-(chloromethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (149) in THF (50 mL) was added dropwise to the deprotonated diethyl phosphite solution. The mixture was slowly allowed to warm to ambient and stirred for a further 30 min. The mixture was cooled to 0 °C and 3M HCl (40 mL) was added to the solution. The suspension was filtered through a pad of celite. The celite layer was washed with 50 mL EtOAc. The mixture was concentrated in vacuo and DMF was removed under high vacuum. The title compound was purified by column chromatography (eluent: EtOAc). Yield 54% (11.3 g)

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.39 (1H, d, $J = 4.0$ Hz, H-2), 4.19-4.11 (4H, m, H-8), 2.82 (1H, s, H-4), 2.77 (1H, s, H-4'), 1.70 (6H, s, H-6), 1.34 (6H, app. t, $J = 7.0$ Hz, H-8).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.3 (d, C-3), 160.9 (d, C-1), 107.5 (C-5), 96.5 (d, C-2), 63.0 (d, C-4), 33.4 (C-7), 32.2 (C-7'), 25.3 (C-6), 16.7 (C-8).

Data in accordance with the literature.
Allyl (E)-3-oxo-9-((triethylsilyl)oxy)undeca-4,10-dienoate (151)

![Chemical Structure of 151]

A solution of the compound 145 (800 mg, 2.18 mmol) and allylic alcohol (0.600 ml, 8.73 mmol) in dry toluene (2 ml) was heated at 110 °C in a closed vial for 8 hours. The reaction mixture was concentrated in vacuo and purified by flash chromatography (2% Et₂O in petroleum ether) which gave the product 151 as a colourless oil (84%, 675 mg, 1.83 mmol).

IR (neat) νmax 3080, 2953, 2913, 2876, 1744, 1667, 1597, 1412, 1228, 1148, 1005, 742, 724.

1H NMR (500 MHz, CDCl₃) δ 6.87 (<1H, dt, J = 16.0, 6.5 Hz, H-8), 6.65 (<1H, dt, J = 15.0, 7.0 Hz, H-8)), 6.15 (<1H, dt, J = 16.0, 1.5, 1.5 Hz, H-7), 5.98–5.85 (<2H, m, H-2, (2), (7)), 5.83–5.73 (1H, m, H-13,(13)), 5.33 (1H, br. d, J = 17.0 Hz, H-1, (1)), 5.24 (1H, br. d, J = 10.5 Hz, H-1’,(1’)), 5.14 (1H, br. d, J = 17.0 Hz, H-14,(14)), 5.06–5.00 (1H, m, H-14’,(14’)), 5.01 (<1H, s, H-(5)), 4.65 (<1H, ddd, J = 5.5, 1.5, 1.5 Hz, H-(12)), 4.63 (<1H, ddd, J = 5.5, 1.5, 1.5 Hz, H-12), 4.12–4.04 (1H, m, H-12,(12)), 3.60 (<2H, s, H-5), 2.24 (<2H, tdd, J = 7.5, 6.5, 1.5 Hz, H-9), 2.19 (<1H, tdd, J = 7.0, 7.0, 1.5 Hz, H-(9)), 1.59–1.41 (4H, m, H-10,(10), 11, (11)), 0.94 (9H, t, J = 8.0 Hz, H-15, (15)), 0.58 (6H, q, J = 8.0 Hz).

13C NMR (126 MHz, CDCl₃) δ 192.3 (C-6), 172.9 (C-(4)), 170.1 (C-(6)), 167.4 (C-4), 150.2 (C-8), 141.9 (C-(13)), 141.7 (C-13), 141.5 (C-(8)), 132.4 (C-(2)), 132.0 (C-2), 130.0 (C-7), 124.8 (C-(7)), 119.9 (C-1),118.5 (C-(1)), 114.4 (C-14), 114.2 (C-(14)), 90.1 (C-(5)), 73.9 (C-(12)), 73.8 (C-12), 66.2 (C-3), 65.0 (C-(3)), 47.1 (C-5), 37.9 (C-(11)), 37.8 (C-11), 32.9 (C-9,(9)), 24.4 (C-(10)), 23.9 (C-10), 7.2 (C-15,(15)), 5.3 (C-16,16)).
**m/z** LRMS (ESI⁺) 389.2 [M+Na]⁺; HRMS (ESI⁺) 389.21195 ([M+Na]⁺, C₂₀H₃₄O₄SiNa requires 389.21186).

**Allyl 3-oxo-4-((2S,6R)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate (155)**

The compound 150 (606 mg, 1.65 mmol) was dissolved in chloroform (30 ml) and the solution was added dropwise to an acidified chloroform (300 mL, washed with 20 ml of conc. HCl) at 0 °C. Reaction mixture was stirred for 1 hour at ambient temperature. The reaction was quenched by adding saturated aqueous NaHCO₃ (xx ml). Layers were separated and the combined organic phases were washed with brine (xx ml), dried over Na₂SO₄ filtered, and evaporated *in vacuo*. Purification by flash chromatography (10% to 25% Et₂O in petroleum ether) gave the title compound 153 as a major isomer (342 mg, 1.36 mmol, 82%) that exists at equilibrium as a 20:3 ratio of keto to enol tautomers. The reaction gave compound 154 (23 mg, 0.092 mmol, 6%) as a minor diastereomer. Combined yield of 97%.

**IR (neat)** ν<sub>max</sub> 3085, 2936, 2859, 1744, 1716, 1647, 1411, 1312, 1225, 1151, 989, 924.

**¹H NMR** (500 MHz, CDCl₃) δ 11.99 (<1H, s, H-(15)), 5.97–5.85 (<1H, m, H-(13)), 5.90 (<1H, ddt, J = 17.0, 11.0, 6.0 Hz, H-13), 5.85–5.76 (<1H, m, H-(2)), 5.80 (<1H, ddd, J = 17.5, 10.5, 5.0 Hz, H-2), 5.35–5.29 (<1H, m, H-(14)), 5.32 (<1H, ddt, J = 17.0, 1.5, 1.5 Hz, H-14), 5.26–5.22 (<1H, m, H-(14’)), 5.24 (<1H, ddt, J = 10.5, 1.5, 1.5 Hz, H-14’), 5.21–5.15 (<1H, m, H-(1)), 5.18 (<1H, ddd, J = 17.5, 1.5, 1.5 Hz, H-1), 5.09 (<1H, s, H-(10)), 5.08–5.05 (<1H, m, H-(1’)), 5.05 (<1H, ddd, J = 10.5, 1.5, 1.5 Hz, H-1’), 4.64–4.60 (<1H, m, H-(12)), 4.62 (<1H, ddd, J = 5.5, 1.5, 1.5 Hz, H-12), 3.87–3.78 (<2H, m, H-3,7,(3)), 3.71 (<1H, dddd, J = 11.0, 6.5, 6.5, 2.0 Hz, H-(7)), 3.55 (<2H, s, H-10), 2.79 (<1H, dd, J = 15.5, 7.5 Hz, H-8), 2.58 (<1H, dd, J = 15.5, 5.0 Hz, H-8’), 2.51 (<1H, dd, J = 14.0, 7.0 Hz, H-8), 2.27 (<1H, dd, J = 14.0, 6.0 Hz, H-8’).
Hz, \( H-(8') \)), 1.90–1.81 (1H, m, \( H-5,(5) \)), 1.69–1.60 (2H, m, \( H-4,(4),6,(6) \)), 1.61–1.50 (1H, m, \( H-5',(5') \)), 1.32–1.18 (1H, m, \( H-6',4',(6'),(4') \)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 201.9 (C-9), 176.1 (C-(9)), 172.6 (C-(11)), 167.2 (C-11), 139.5 (C-(2)), 139.4 (C-2), 132.5 (C-(13)), 132.0 (C-13), 119.1 (C-14), 118.6 (C-(14)), 114.8 (C-(1)), 114.8 (C-1), 90.9 (C-(10)), 78.5 (C-3,(3)), 74.9 (C-(7)), 74.4 (C-7), 74.4 (C-7), 66.2 (C-12), 64.9 (C-(12)), 50.4 (C-10), 49.9 (C-8), 42.6 (C-(8)), 31.4 (C-6,(4)), 31.3 (C-4,(6)), 23.6 (C-5), 23.5 (C-5).

\( m/z \) LRMS (ESI\(^{+}\)) 275.1 [M+Na]\(^{+}\); HRMS (ESI\(^{+}\)) 275.12536 ([M+Na]\(^{+}\), \( C_{14}H_{20}O_{4}Na \) requires 275.12536).

**allyl 3-oxo-4-((2R,6R)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate (156)**

![Chemical Structure](image)

IR (neat) \( \nu_{\max } \) 2926, 2851, 1746, 1717, 1647, 1410, 1362, 1227, 1149, 1087, 1087, 926.

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 12.02 (<1H, s, \( H-15 \)), 5.96–5.85 (2H, m, \( H-2,(2),13,(13) \)), 5.34 (1H, br. d, \( J = 17.0 \text{ Hz}, \ H-14,(14) \)), 5.27–5.19 (3H, m, \( H-1,1',1,(1'),14',(14') \)), 5.09 (<1H, s, \( H-(10) \)), 4.63 (2H, br. d, \( J = 5.67 \text{ Hz}, \ H-12,(12) \)), 4.40–4.33 (1H, m, \( H-3,(3) \)), 4.24–4.17 (<1H, m, \( H-7 \)), 4.14–4.07 (<1H, m, \( H-(7) \)), 3.54 (<2H, s, \( H-10 \)), 2.81 (<1H, dd, \( J = 15.5, 8.0 \text{ Hz}, \ H-8 \)), 2.57 (<1H, dd, \( J = 15.5, 4.5 \text{ Hz}, \ H-8' \)), 2.46 (<1H, dd, \( J = 14.0, 8.0 \text{ Hz}, \ H-(8) \)), 2.32 (<1H, dd, \( J = 14.0, 5.5 \text{ Hz}, \ H-(8') \)), 1.80–1.70 (1H, m, \( H-4,(4) \)), 1.69–1.55 (3H, m, \( H-4',(4'),5,(5),5',(5') \)), 6, (6)), 1.39–1.29 (1H, m, \( H-4',(4') \)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 201.7 (C-9), 176.3 (C-(9)), 172.6 (C-(11)), 167.2 (C-11), 138.6 (C-(2)), 138.3 (C-2), 132.5 (C-(13)), 132.0 (C-13), 119.1 (C-14), 118.6 (C-(14)), 116.8 (C-1), 116.6 (C-(1)), 90.9 (C-(10)), 73.1 (C-3), 73.0 (C-(3)), 68.6 (C-(7)), 67.9 (C-7), 66.2 (C-12),
65.0 (C-(12)), 50.2 (C-10), 48.8 (C-8), 41.2 (C-(8)), 31.1 (C-6), 30.9 (C-(6)), 28.9 (C-(4)), 28.7 (C-4), 18.9 (C-(5)), 18.9 (C-5).

\textit{m/z} LRMS (ESI\textsuperscript{+}) 275.1 [M+Na]\textsuperscript{+}; HRMS (ESI\textsuperscript{+}) 275.12542 ([M+Na]\textsuperscript{+}, C\textsubscript{14}H\textsubscript{20}O\textsubscript{4}Na requires 275.12538).

![NOESY diagram](image)

(\textit{1R,10S,Z})-5,14-Dioxabicyclo[8.3.1]tetradec-2-ene-6,8-dione (151)

To a stirred solution of 154 (227 mg, 0.899 mmol) in degassed CH\textsubscript{2}Cl\textsubscript{2} (300 mL) under argon atmosphere was added Grubbs 2\textsuperscript{nd} generation catalyst (38 mg, 0.045 mmol). Reaction mixture was refluxed for 1 h. The reaction mixture was filtered through a small pad silica eluting with 70% Et\textsubscript{2}O in petroleum ether and concentrated in vacuo. The crude product was purified by flash chromatography (50% Et\textsubscript{2}O in petroleum ether). Purification gave the tittle Z-isomer 151 as a white solid in (16%, 32 mg, 0.143 mmol) and the \textit{E}-isomer 156 as a white solid (19%, 38 mg, 0.170 mmol). Combined yield 35%.

IR (neat) \(\nu_{\text{max}}\) 2931, 2852, 1745, 1708, 1435, 1299, 1236, 1131, 1084, 1031, 943.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.81 (1H, dddd, \(J = 11.5, 5.5, 4.0, 1.5\) Hz, \(H\)-2), 5.53 (1H, ddd, \(J = 11.5, 7.0, 2.5\) Hz, \(H\)-3), 4.78 (1H, dd, \(J = 14.5, 5.5\) Hz, \(H\)-1), 4.71 (1H, ddd, \(J = 14.5, 4.0, 1.5\) Hz, \(H\)-1), 4.71 (1H, ddd, \(J = 14.5, 4.0, 1.5\) Hz, \(H\)-1).
2.5 Hz, $H-1'$), 4.11 (1H, dddd, $J = 11.0, 7.0, 2.5, 1.5$ Hz, $H-4$), 3.90 (1H, dddd, $J = 11.0, 11.0, 3.5, 2.0$ Hz, $H-8$), 3.70 (1H, d, $J = 12.0$ Hz, $H-11$), 3.26 (1H, d, $J = 12.0$ Hz, $H-11'$), 2.64 (1H, dd, $J = 16.0, 11.0$ Hz, $H-9$), 2.49 (1H, dd, $J = 16.0, 3.5$ Hz, $H-9'$), 1.93–1.85 (1H, m, $H-6$), 1.72–1.65 (1H, m, $H-5$), 1.65–1.55 (2H, m, $H-6,8$), 1.51–1.41 (1H, m, $H-5$), 1.35–1.26 (1H, m, $H-8$).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.0 (C-10), 165.9 (C-12), 133.9 (C-3), 130.2 (C-2), 75.4 (C-8), 74.5 (C-4), 61.5 (C-1), 50.6 (C-9), 48.3 (C-11), 31.3 (C-5), 30.7 (C-8), 23.4 (C-6).

$m/z$ LRMS (ESI$^+$) 247.0 [M+Na]$^+$; HRMS (ESI$^+$) 247.09408 ([M+Na]$^+$, C$_{12}$H$_{16}$O$_4$Na requires 247.09413).

MP: 105–110 °C

(1R,10S,E)-5,14-Dioxabicyclo[8.3.1]tetradec-2-ene-6,8-dione (156)

IR (neat) $\nu_{\max}$ 2935, 2850, 1744, 1715, 1652, 1315, 1261, 1200, 1148, 1082, 974.

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.78 (1H, dddd, $J = 15.5, 5.0, 5.0$ Hz, $H-2$), 5.73 (1H, dd, $J = 15.5, 3.0$ Hz, $H-3$), 4.60 (2H, d, $J = 5.0$ Hz, $H-1$), 3.86 (1H, br. d, $J = 11.5$ Hz, $H-4$), 3.80 (1H, br. t, $J = 11.0$ Hz, $H-8$), 3.70 (1H, d, $J = 16.5$ Hz, $H-11$), 3.60 (1H, d, $J = 16.5$ Hz, $H-11'$), 2.71 (1H, dd, $J = 14.0, 10.0$ Hz, $H-9$), 2.47 (1H, dd, $J = 14.0, 3.0$ Hz, $H-9'$), 1.93–1.82 (1H, m, $H-6$), 1.72–1.48 (3H, m, $H-6',5,7$), 1.37–1.15 (2H, m, $H-5',7'$).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.9 (C-10), 167.6 (C-12), 135.8 (C-3), 123.4 (C-2), 75.4 (C-4), 65.7 (C-8), 51.1 (C-1), 51.1 (C-11), 49.7 (C-9), 31.4 (C-7), 31.3 (C-5), 23.6 (C-6).

$m/z$ LRMS (ESI$^+$) 259.2 [M+Na]$^+$; HRMS (ESI$^+$) 259.13043 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 259.13047).

MP: 105–110 °C.

(5E,11Z)-Oxacyclotrideca-5,11-diene-2,4,10-trione (153)

KHMDS solution in toluene (0.5 M, 0.71 ml, 0.35 mmol) was added dropwise to the compound 151 (16 mg, 0.071 mmol) in THF (0.4 ml) at 0 °C. The reaction mixture was quenched after 10 minutes by pouring it to a saturated aqueous NH$_4$Cl solution (xx ml). The mixture was extracted with CH$_2$Cl$_2$ (40 ml) the combined organic layers were washed with brine (5 ml), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude mixture was dissolved in 2 ml of CH$_2$Cl$_2$ and cooled to 0 °C. DMP (45 mg, 0.11 mmol) was added to the solution and the reaction was stirred for further 1 hour. The mixture was quenched by adding aqueous saturated sodium thiosulphate solution (5 ml). The mixture was stirred until it was clear. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 10 ml) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (2 ml) and brine (6 ml). The organic layers were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude mixture was purified by using preparative TLC (50% EtOAc in petroleum ether) which gave the compound 153 in 12% yield (1.8 mg, 0.008 mmol) and compound 161 in 8% yield (1.3 mg, 0.006 mmol).

IR (neat) $\nu_{\text{max}}$ 2926, 2851, 1735, 1696, 1668, 1630, 1300, 1258, 1223, 1200, 1008, 978.
\( ^1 \text{H NMR} \ (500 \text{ MHz}, \ C_6D_6) \ \delta \ 6.15 \ (1\text{H}, \ dt, \ J = 16.0, \ 7.5 \text{ Hz}, \ H-8), \ 5.76 \ (1\text{H}, \ br. \ d, \ J = 16.0 \text{ Hz}, \ H-9), \ 5.45 \ (1\text{H}, \ br. \ d, \ J = 11.5 \text{ Hz}, \ H-3), \ 5.41 \ (1\text{H}, \ dt, \ J = 11.5, \ 5.5 \text{ Hz}, \ H-2), \ 4.53 \ (2\text{H}, \ d, \ J = 5.5 \text{ Hz}, \ H-1), \ 3.30 \ (2\text{H}, \ s, \ H-11), \ 1.72–1.68 \ (2\text{H}, \ m, \ H-5), \ 1.65–1.59 \ (2\text{H}, \ m, \ H-7), \ 1.49–1.44 \ (2\text{H}, \ m, \ H-6). \)

\( ^{13} \text{C NMR} \ (126 \text{ MHz}, \ C_6D_6) \ \delta \ 199.9 \ (C-4), \ 192.0 \ (C-10), \ 166.5 \ (C-12), \ 148.9 \ (C-8), \ 135.9 \ (C-2), \ 132.9 \ (C-9), \ 131.9 \ (C-3), \ 59.7 \ (C-1), \ 45.6 \ (C-11), \ 42.9 \ (C-5), \ 34.5 \ (C-7), \ 20.3 \ (C-6). \)

\( m/\ell \ \text{LRMS (ESI')} \ 245.0 \ [M+Na]^+; \ \text{HRMS (ESI')} \ 245.07843 \ ((M+Na)^+, \ C_{12}H_{14}O_4Na \ \text{requires} \ 245.07854). \)

(5Z,11Z)-Oxacyclotrideca-5,11-diene-2,4,10-trione (162)

\( ^1 \text{H NMR} \ (500 \text{ MHz}, \ C_6D_6) \ \delta \ 5.72 \ (1\text{H}, \ dt, \ J = 11.5, \ 1.5 \text{ Hz}, \ H-9), \ 5.58 \ (1\text{H}, \ dt, \ J = 11.5, \ 8.0 \text{ Hz}, \ H-8), \ 5.52 \ (1\text{H}, \ br. \ d, \ J = 11.5 \text{ Hz}, \ H-3), \ 5.47 \ (1\text{H}, \ dt, \ J = 11.5, \ 6.0 \text{ Hz}, \ H-2), \ 4.42 \ (2\text{H}, \ d, \ J = 6.0 \text{ Hz}, \ H-1), \ 2.96 \ (2\text{H}, \ s, \ H-11), \ 2.57–2.51 \ (2\text{H}, \ m, \ H-7), \ 1.90–1.86 \ (2\text{H}, \ m, \ H-5), \ 1.43–1.36 \ (2\text{H}, \ m, \ H-6) \)

\( ^{13} \text{C NMR} \ (126 \text{ MHz}, \ C_6D_6) \ \delta \ 200.6 \ (C-4), \ 192.7 \ (C-10), \ 166.5 \ (C-12), \ 147.9 \ (C-8), \ 134.5 \ (C-3), \ 132.6 \ (C-2), \ 128.1 \ (C-9), \ 59.6 \ (C-1), \ 50.8 \ (C-11), \ 41.6 \ (C-5), \ 28.4 \ (C-7), \ 21.6 \ (C-6). \)

\( m/\ell \ \text{LRMS (ESI')} \ 245.0 \ [M+Na]^+; \ \text{HRMS (ESI')} \ 245.07843 \ ((M+Na)^+, \ C_{12}H_{14}O_4Na \ \text{requires} \ 245.07855). \)
A stock solution of the NMR-standard 2,2'-dimethoxy-1,1'-binaphthalene (0.1 equiv, 0.67 mg, 0.0021 mmol) in D6-benzene (0.529 mL) was mixed with the starting material (5E,11Z)-oxacyclotrideca-5,11-diene-2,4,10-trione 153 (5.0 mg, 0.023 mmol). A quantitative 1H-NMR spectrum of the mixture was obtained, the solution was transferred to an oven-dry vial and the deuterated solvents were removed in vacuo. Dry benzene (0.449 mL) and N-(9-anthracenylmethyl)cinchonium bromide (1.3 mg, 0.0023 mmol) were added and the mixture was stirred for 10 minutes prior to the addition of vacuum oven dried potassium fluoride (12.3 mg, 0.21 mmol). The reaction mixture was flushed with nitrogen, stirred for 12 hours and quenched with saturated aqueous ammonium chloride. The mixture was extracted with EtOAc and the combined organic phases were filtered through a small pad of silica to remove the phase-transfer catalyst. The solvents were removed in vacuo to obtain product 163 (42% yield based on 1H-NMR). The NMR solvent was removed and the crude product was purified by preparatory TLC (EtOAc 50% in petroleum ether) to afford tricycle 163 in 42% yield (2.1 mg, 0.012 mmol).

IR (neat) $\nu_{\text{max}}$ 2921, 2851, 1777, 1740, 1706, 1671, 1247, 1205, 978, 733.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.78 (1H, ddd, $J = 15.5, 10.0, 5.5$ Hz, H-19), 6.08 (1H, d, $J = 15.5$ Hz, H-20), 4.78 (1H, dd, $J = 10.0, 8.0$ Hz, H-1), 4.56 (1H, dd, $J = 10.5, 3.5$ Hz, H-24), 3.78 (1H, dd, $J = 11.0, 10.0$ Hz, H-1’), 3.70 (1H, dd, $J = 11.0, 10.5$ Hz, H-24’), 3.66 (1H, d, $J$
= 15.0 Hz, H-22), 3.41 (1H, d, J = 15.0 Hz, H-22’), 3.39 (1H, ddd, J = 11.0, 8.0, 4.0 Hz, H-2), 3.35-3.28 (1H, m, H-13), 3.10 (1H, dd, J = 12.5, 4.0 Hz, H-3), 2.90 (1H, dd, J = 20.5, 4.0 Hz, H-14), 2.81 (1H, dd, J = 20.5, 5.0 Hz, H-14’), 2.73 (1H, dd, J = 14.0, 12.5 Hz, H-9), 2.57-2.46 (3H, m, H-18, H-5, H-5’), 2.42 (1H, dd, J = 14.0, 4.0 Hz, H-9’), 2.39-2.34 (2H, m, H-16,16’), 2.26-2.14 (3H, m, H-7,8,17), 2.14-2.05 (1H, m, H-18’), 1.97-1.90 (1H, m, H-6’), 1.82-1.62 (3H, m, H-6’,7’,17’).

^1^C NMR (126 MHz, CDCl$_3$) δ 208.3 (C-15), 208.0 (C-4), 204.8 (C-10), 191.2 (C-21), 172.0 (C-12), 166.5 (C-23), 149.3 (C-19), 131.2 (C-20), 131.2 (C-24), 131.2 (C-24), 65.1 (C-11), 50.6 (C-3), 46.3 (C-22), 44.9 (C-9), 42.2 (C-14), 41.6 (C-5), 41.3 (C-16), 40.7 (C-2), 40.1 (C-8), 33.6 (C-18), 32.4 (C-6), 30.2 (C-13), 25.6 (C-8), 20.4 (C-7), 20.4 (C-17).

m/z LRMS (ESI^+^) 467.2 [M+Na]^+^; HRMS (ESI^+^) 467.16764 ([M+Na]^+^, C$_{24}$H$_{28}$O$_{8}$Na requires 467.16776).

![NOESY](image1.png)

![J 4.0 Hz](image2.png)
The compound 170 (689 mg, 1.89 mmol) was dissolved in 10 mL chloroform and the solution was added dropwise to acidified chloroform (150 mL, washed with 5-10 mL of conc. HCl) at 0 °C. The reaction mixture was stirred for 1 hour and quenched by adding saturated NaHCO₃ (10 mL). The layers were separated and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash chromatography (10% to 25% Et₂O in petroleum ether) gave the title compound 171 as a major isomer in 82% yield (387 mg, 1.55 mmol), which was found to exist as a 88:12 ratio of keto to enol tautomers (at equilibrium). The reaction gave compound 175 in 4% yield (17 mg, 0.068 mmol) as a minor diastereomer, which was found to exist as a 86:14 ratio of keto to enol tautomers (at equilibrium). Combined yield of 86%.

IR (neat) \( \nu_{ \text{max}} \) 3282, 2936, 2849, 1749, 1717, 1652, 1625, 1438, 1370, 1312, 1266, 1150, 1072, 924.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \( \delta \) 11.79 (<1H, s, H-(15)), 5.88-5.78 (<1H, app. m, H-(2)), 5.80 (<1H, ddd, \( J = 17.5, 10.5, 5.0 \text{ Hz} \), H-2), 5.21 (<1H, ddd, 17.0, 1.5, 1.5 Hz, H-(1)), 5.18 (<1H, ddd, \( J = 17.5, 1.5, 1.5 \text{ Hz} \), H-1), 5.18 (<1H, s, H-(10)), 5.07 (<1H, app. br. d, \( J = 10.5 \), H-(1’)), 5.06 (<1H, ddd, \( J = 10.5, 1.5, 1.5 \text{ Hz} \), H-1’), 4.73-4.71 (<2H, app. m, H-12), 4.72 (<1H, d, \( J = 2.5 \text{ Hz} \), H-12), 3.89-3.77 (<2H, m, H-3,7,(7)), 3.75-3.66 (<1H, app. m, H-(3)), 3.57 (<2H, s, H-10), 2.78 (<1H, dd, \( J = 15.0, 8.0 \text{ Hz} \), H-8), 2.58 (<1H, dd, \( J = 15.0, 5.0 \text{ Hz} \), H-8’), 2.51 (<1H, dd, \( J = 14.0, 7.0 \text{ Hz} \), H-(8)), 2.49-2.47 (<1H, app. m, H-(12’)), 2.49 (<2H, t, \( J = 2.5 \text{ Hz} \), H-14, (14)), 2.29 (<1H, dd, \( J = 14.0, 6.0 \text{ Hz} \), H-(8’)), 1.91-1.80 (1H, m, H-5,(5)), 1.69-1.58 (2H, m, H-6,(6),4,(4)), 1.59-1.49 (1H, m, H-5’,(5’)), 1.34-1.16 (2H, m, H-6’,(6’), 4’,(4’)).
13C NMR (126 MHz, CDCl3) δ 201.4 (C-9), 176.9 (C-(9)), 171.9 (C-(11)), 166.7 (C-11), 139.5 (C-(2)), 139.3 (C-2), 114.8 (C-1,(1)), 90.4 (C-(10)), 78.5 (C-3), 77.6 (C-(3)), 77.4 (C-13,(13)), 75.6 (C-14), 75.2 (C-(14)), 74.9 (C-(7)), 74.5 (C-7), 52.9 (C-12), 51.8 (C-(12)), 50.1 (C-10), 49.9 (C-8), 42.6 (C-(8)), 31.4 (C-6,(6)), 31.3 (C-(4)), 31.3 (C-4), 23.6 (C-(5)), 23.5 (C-5).

m/z LRMS (ESI⁺) 273.1 [M+Na]⁺; HRMS (ESI⁺) 273.10965 ([M+Na]⁺, C_{14}H_{18}O_{4}Na requires 273.10973).

Prop-2-yn-1-yl 3-oxo-4-((2R,6R)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate ((E)-165)

IR (neat) νmax 3280, 2937, 2852, 1749, 1717, 1653, 1440, 1411, 1365, 1312, 1266, 1145, 1072, 1039, 923, 668.

1H NMR (500 MHz, CDCl3) δ 11.82 (<1H, s, H-15), 5.93 (<1H, m, H-(2)), 5.89 (<1H, ddd, J = 18.0, 10.5, 4.5 Hz, H-2), 5.25-5.19 (2H, m, H-1,1′,(1),(1′)), 5.10 (<1H, s, H-(10)), 4.73 (2H, d, J = 2.5 Hz, H-12, (12)), 4.39-4.32 (1H, m, H-3, (3)), 4.23-4.16 (<1H, app. m, H-7), 4.13-4.07 (<1H, m, app. H-(7)), 4.73 (<2H, s, H-10), 2.81 (<1H, dd, J = 15.5, 8.0 Hz, H-8), (<1H, dd, J = 15.5, 4.5 Hz, H-8′), 2.49 (1H, t, J = 2.5 Hz, H-14, (14)), 2.47 (<1H, dd, J = 14.0 Hz, H-(8)), 2.33 (<1H, dd, J = 14.0, 5.5 Hz, H-8′), 1.80-1.70 (1H, m, H-4,(4)), 1.70-1.57 (4H, m, H-5,(5),5′,(5′),4′,(4′),6,(6)), 1.40-1.29 (1H, m, H-6′,(6′)).

13C NMR (126 MHz, CDCl3) δ 201.2 (C-9), 177.1 (C-(9)), 171.9 (C-(11)), 166.7 (C-11), 138.5 (C-(2)), 138.3 (C-2), 116.9 (C-1), 116.6 (C-(1)), 90.5 (C-(10)), 77.6 (C-13), 77.4 (C-(13)), 75.6 (C-14), 75.2 (C-(14)), 73.0 (C-3), 73.0 (C-(3)), 68.6 (C-(7)), 67.9 (C-7), 53.0 (C-12), 51.8 (C-
(12)), 49.9 (C-10), 48.8 (C-8), 41.2 (C-8)), 31.1 (C-6), 30.9 (C-6)), 28.9 (C-4), 28.7 (C-4), 18.9 (C-5), 18.9 (C-5).


(Z)-3-Vinyl-5,14-dioxabicyclo[8.3.1]tetradec-2-ene-6,8-dione (168)

To a stirred solution of 165 (15 mg, 0.90 mmol) in degassed CH₂Cl₂ (19 mL) under an argon atmosphere was added Grubbs 2nd generation catalyst (5 mg, 0.006 mmol) and a balloon of ethylene was inserted on top of the closed round bottom flask. Reaction mixture was stirred at ambient temperature for 15 h. The reaction mixture was filtered through a small pad of silica and concentrated *in vacuo*. The crude product was purified by flash chromatography (10 to 20% EtOAc in petroleum ether). Purification gave the title *exo*-isomer 168 as in 13% yield (2 mg, 0.008 mmol) and the *endo*-isomer 166 in 11% yield (1.7 mg, 0.007 mmol) and the open-chain diene 171 in 18% yield (3.0 mg, 0.011 mmol).

IR (neat) *ν*max 2930, 2851, 2360, 2341, 1748, 1711, 1438, 1311, 1206, 1083, 991, 873.

1H NMR (500 MHz, CDCl₃) δ 6.32 (1H, dd, *J* = 17.5, 11.0 Hz, H-3), 5.57 (1H, br. d, *J* = 7.0 Hz, H-5), 5.31 (1H, d, *J* = 7.5 Hz, H-4), 5.16 (1H, d, *J* = 11.0 Hz, H-4’), 5.07 (1H, dd, *J* = 13.5, 1.5 Hz, H-1), 4.86 (1H, d, *J* = 13.5 Hz, H-1’), 4.17-4.11 (1H, m, H-6), 3.89-3.80 (1H, m, H-10) 3.60 (1H, d, *J* = 12.5 Hz, H-13), 3.34 (1H, d, *J* = 12.5 Hz, H-13’), 2.63 (1H, dd, *J* = 181.9 (C-5), 18.9 (C-5).
15.5, 11.5 Hz, H-11), 2.48 (1H, dd, $J = 15.5, 2.5$ Hz, H-11'), 1.94-1.81 (1H, app. m, H-8), 1.76-1.68 (1H, app. m, H-7), 1.67-1.42 (3H, m, H-8',7',9), 1.36-1.20 (1H, m, H-9').

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 200.7 (C-12), 166.4 (C-14), 140.0 (C-2), 138.2 (C-3), 134.4 (C-5), 114.8 (C-4), 75.3 (C-6), 74.1 (C-10), 59.9 (C-1), 51.2 (C-11), 48.9 (C-13), 31.5 (C-7), 31.0 (C-9), 23.4 (C-8).

$m/z$ LRMS (ESI $^+$) 273.1 [M+Na]$^+$; HRMS (ESI$^+$) 273.10979 ([M+Na]$^+$, C$_{14}$H$_{18}$O$_4$Na requires 273.10973).

MP: 95-98 °C

(Z)-8-Methylene-6,15-dioxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (166)

IR (neat) $\nu_{\max}$ 2927, 2851, 2360, 2341, 1742, 1709, 1316, 1195, 1130, 1052, 842.

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.09 (1H, br. d, $J = 11.5$ Hz, H-4), 5.60 (1H, dd, 11.5, 9.0 Hz, H-5), 5.35 (1H, app. s, H-3), 5.05 (1H, app. s, H-3'), 4.97 (1H, d, $J = 12.0$ Hz, H-1) 4.39 (1H, d, $J = 12.0$ Hz, H-1'), 4.08 (1H, br. ddd, $J = 11.0, 9.0, 1.5$ Hz, H-6), 3.69 (1H, d, $J = 14.0$ Hz, H-13), 3.66 (1H, dddd, $J = 11.0, 11.0, 2.0, 2.0$ Hz, H-10), 3.26 (1H, dd, $J = 14.5, 1.0$ Hz, H-13'), 2.59 (1H, dd, $J = 13.5, 11.0$ Hz, H-11), 2.39 (1H, ddd, $J = 13.5, 2.0, 1.0$ Hz H-11'), 1.89-1.79 (1H, app. m, H-8), 1.67-1.58 (1H, app. m, H-7), 1.58-1.46 (2H, m, H-7',9), 1.46-1.36 (1H, app. m, H-8'), 1.33-1.17 (1H, app. m, H-9')
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.1 (C-12), 167.5 (C-14), 140.9 (C-2), 134.9 (C-5), 132.7 (C-4), 119.6 (C-3), 75.0 (C-10), 72.3 (C-6), 68.2 (C-1), 52.3 (C-13), 49.2 (C-9), 31.2 (C-7), 23.4 (C-8).

*m/z* LRMS (ESI $^+$) 273.1 [M+Na]$^+$; HRMS (ESI $^+$) 273.10976 ([M+Na]$^+$, C$_{14}$H$_{18}$O$_4$N$^+$ requires 273.10973).

2-Methylenebut-3-en-1-yl 3-oxo-4-(6-vinyltetrahydro-2H-pyran-2-yl)butanoate (171)

IR (neat) $\nu_{\text{max}}$ 3091, 3012, 2935, 2849, 2360, 2341, 1747, 1717, 1647, 1311, 1152, 914.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.98 ($<1$H, s, OH-), 6.43-6.35 ($<1$H, app. m, H-(15)), 6.37 ($<1$H, dd, $J$ = 18.0, 11.0 Hz, H-15), 5.89-5.80 ($<1$H, app. m, H-(2)), 5.81 ($<1$H, ddd, 17.0, 10.5, 5.5 Hz, H-2), 5.31-5.04 ($<1$H, m, H-(14),(14'),(16), (16'), (1),(1'), 5.32-5.22 ($<3$H, m, H-14,14', 16), 5.19 ($<1$H, dd, $J$ = 17.5, 1.5, 1.5 Hz, H-1), 5.14 ($<1$H, br. d, $J$ = 11.0 Hz, H-16'), 5.12 ($<1$H, s, H-(10)), 5.06 ($<1$H, ddd, 10.5, 1.5, 1.5 Hz, H-1'), 4.82 (2H, br. s, H-12,(12)), 3.87-3.79 (2H, m, H-3,(3), 7, (7)), 3.58 ($<2$H, s, H-10), 2.79 ($<1$H, dd, $J$ = 15.5, 7.5 Hz, H-8), 2.59 ($<1$H, dd, $J$ = 15.5, 5.0 Hz, H-8'), 2.53 ($<1$H, dd, 14.0, 7.0 (H-(8))), 2.29 ($<1$H, dd, $J$ = 13.5, 7.0 Hz, H-(8')), 1.91-1.81 (1H, m, H-5,(5)), 1.70-1.50 (3H, m, H-5',(5'),4,(4), 6, (6)), 1.36-1.17 (2H, m, H-4',(4'), 6', (6')).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.8 (C-9), 176.3 (C-(9)), 172.2 (C-(11)), 167.3 (C-11), 140.8 (C-(13)), 140.3 (C-13), 139.5 (C-(2)), 139.4 (C-2), 136.3 (C-(15)), 136.2 (C-15), 118.9 (C-14), 118.4 (C-(14)), 115.2 (C-16), 115.1 (C-(16)), 114.9 (C-(1)), 114.8 (C-1), 90.94 (C-(10)), 78.6
(C-3, (3)), 74.9 (C-(7)), 74.5 (C-7), 64.7 (C-12), 63.3 (C-(12)), 50.5 (C-10), 50.0 (C-8), 42.7 (C-8)), 32.3 (C-4) 31.4 (C-4), 31.3 (C-6), 30.0 (C-(6)), 23.6 (C-(5)), 23.5 (C-5),

$\text{m/z}$ LRMS (ESI $^+$) 301.1 [M+Na]$^+$; HRMS (ESI$^+$) 301.14108 ([M+Na]$^+$, C$_{16}$H$_{20}$O$_4$Na requires 301.14103).

**Prop-2-yn-1-yl (E)-3-oxo-9-((triethylsilyl)oxy)undeca-4,10-dienoate (170)**

A mixture of compound 145 (723 mg, 1.96 mmol) and propargyl alcohol (0.457 mL, 7.86 mmol) in dry toluene (2 mL) was heated at 110 °C in a closed vial for 12 hours. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (2% Et2O in petroleum ether) to give the product 170 as a colourless oil in 99% yield (708 mg, 1.94 mmol).

IR (neat) $\nu_{\text{max}}$ 3308, 2952, 2912, 2876, 1750, 1697, 1666, 1642, 1596, 1415, 1220, 1147, 1005, 726.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.60 (<1H, d, $J = 1.5$ Hz, H-(17)), 6.87 (<1H, dt, $J = 15.5$, 7.0 Hz, H-(7)), 6.68 (<1H, dt, $J = 16.0$, 7.0 Hz, H-7)), 6.15 (<1H, dt, $J = 15.5$, 1.5 Hz, H-(8)), 5.85-5.72 (<2H, m, H-2,8,(2)), 5.14 (1H, br. d, $J = 17.0$ Hz H-1,(1)), 5.07-4.70 (1H, m, H-1',(1')), 4.75 (1H, d, J = 2.5 Hz, H-(12)), 4.74 (1H, d, J = 2.5 Hz, H-12), 4.13-4.02 (1H, m, H-3,(3)), 3.64 (<2H, s, H-10), 2.49 (1H, br. t, $J = 2.5$ Hz, H-14,(14)), 2.30-2.15 (2H, m, H-6,(6)), 1.60-1.40 (4H, m, H-4,5,(4),(5)), 0.94 (9H, t, $J = 7.5$ Hz H-16,(16)), 0.59 (6H, q, $J = 7.5$ Hz, H-15,(15)).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 191.8 (C-9), 172.3 (C-(9)), 170.2 (C-(11)), 167.0 (C-11), 150.5 (C-(7)),142.2 (C-7),141.8 (C-(2)), 141.7 (C-2), 129.9 (C-(8)), 124.6 (C-8), 114.4 (C-1), 114.3
(C-1), 89.5 (C-(10)), 75.6 (C-13), 75.3 (C-(13)), 73.9 (C-(3)), 73.8 (C-3), 53.0 (C-12), 51.9 (C-(12)), 46.8 (C-10), 37.9 (C-(4)), 37.8 (C-4), 32.9 (C-6,(6)), 24.4 (C-(5)), 23.9 (C-5), 7.2 (C-16, (16)), 5.2 (C-15, (15)).

\[ m/z \text{ LRMS (ESI}^+\text{)} 387.2 \, [M+Na]^+; \text{ HRMS (ESI}^+\text{)} 387.19621 \, ([M+Na]^+, \text{ C}_{20}\text{H}_{32}\text{O}_4\text{SiNa requires 387.19615}). \]

(E)-14-((triethylsilyl)oxy)hexadeca-1,9,15-triene-6,8-dione (180)

The compound 145 (700 mg, 1.91 mmol) in THF (3.5 mL) was added to a dry CeCl₃ (564.7 mg, 2.29 mmol) and stirred for 1.5 hours at ambient temperature. Preparation of the Grignard reagent: Dry magnesium turnings (244 mg, 10.0 mmol) in dry THF (21.8 mL) were activated by adding few drops of dibromoethane. 5-bromopent-1-ene (1.62 g, 1.29 mL, 10.9 mmol) was added dropwise to the solution and the mixture was stirred for further 1h at ambient temperature . 9.55 mL of the stock solution of the Grignard reagent (2.5 e.q) was added to the mixture of compound 145 and CeCl₃ in THF at 0°C and stirred for 30 minutes. The mixture was quenched pouring into ice cold saturated aqueous NH₄Cl. The mixture was extracted with CH₂Cl₂ and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography (2% Et₂O in petroleum ether) which gave the title compound 180 as a colourless oil in 93% yield (670 mg, 1.77 mmol).

IR (neat) νₘₚₓ 3078, 2954, 2935, 2875, 1655, 1583, 1458, 1239, 1093, 1016, 990, 744.

¹H NMR (400 MHz, CDCl₃) δ 6.83 (1H, dt, J = 15.5, 7.0 Hz, H-7), 5.83 (1H, dt, J = 15.5, 1.0 Hz, H-8), 5.84-5.72 (2H, m, H-2,15), 5.47 (1H, s, H-10), 5.14 (1H, ddd, J = 17.0, 1.5, 1.5 Hz,
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.47 ($<1$H, s, $H$-(17)), 5.88-5.71 (2H, m, $H$-15,(15),16,(16)), 5.55 ($<1$H, s, $H$-10), 5.21 ($<1$H, ddd, $J = 17.5, 1.5, 1.5$ Hz, $H$-1), 5.18 ($<1$H, ddd, $J = 17.5, 1.5,$ $1.5$ Hz, $H$-1), 5.07-4.95 (3H, m, $H$-1’,16,16’), 4.12-4.04 (1H, m, $H$-3), 2.35 (2H, t, $J = 7.5$ Hz, $H$-12), 2.26-2.18 (2H, m, $H$-6), 2.14-2.05 (2H, m, $H$-14), 1.72 (2H, qn, $J = 7.5$ Hz, $H$-14), 1.60-1.41 (4H, m, $H$-4,5), 0.95 (9H, t, $J = 8.0$ Hz, $H$-18), 0.59 (6H, q, $J = 8.0$ Hz, $H$-17)

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 200.2 (C-9), 178.5 (C-11), 144.7 (C-7), 141.8 (C-15), 138.2 (C-2), 126.3 (C-8), 115.6 (C-16), 114.3 (C-1), 99.6 (C-10), 73.9 (C-3), 39.6 (C-12), 37.9 (C-4), 33.5 (C-14), 33.0 (C-6), 24.9 (C-13), 24.3 (C-5), 7.2 (C-18), 5.2 (C-17).

To an acidified chloroform (250 mL, washed with 50 mL of conc. HCl) at 0 °C was added dropwise the compound 184 (642 mg, 1.70 mmol) in 5 mL of chloroform. Reaction mixture was stirred in ice bath for 30 minutes. The reaction was washed with saturated aqueous NaHCO$_3$ solution, brine, dried over Na$_2$SO$_4$ and filtered. The solvent was and evaporated in vacuo and the crude mixture was purified by flash chromatography (5% Et$_2$O in petroleum ether) that gave the title compound 185 in 86% yield (385 mg, 1.46 mmol) as a major diastereomer that exist at equilibrium as a 18:82 ratio of keto to enol tautomers. Compound 185 was separated as a minor diastereomer in 12% yield (54 mg, 0.203 mmol) that exist at equilibrium as a 17:83 ratio of keto to enol tautomers. Combined yield 98%.

IR (neat) $v_{max}$ 3078, 2935, 2859, 1704, 1607, 1413, 1310, 1199, 1070, 1052, 990, 916.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.47 ($<1$H, s, $H$-(17)), 5.88-5.71 (2H, m, $H$-15,(15),16,(16)), 5.55 ($<1$H, s, $H$-10), 5.21 ($<1$H, ddd, $J = 17.5, 1.5, 1.5$ Hz, $H$-1), 5.18 ($<1$H, ddd, $J = 17.5, 1.5,$ $1.5$ Hz, $H$-1), 5.07-4.95 (3H, m, $H$-1’,16,16’), 4.12-4.04 (1H, m, $H$-3), 2.35 (2H, t, $J = 7.5$ Hz, $H$-12), 2.26-2.18 (2H, m, $H$-6), 2.14-2.05 (2H, m, $H$-14), 1.72 (2H, qn, $J = 7.5$ Hz, $H$-14), 1.60-1.41 (4H, m, $H$-4,5), 0.95 (9H, t, $J = 8.0$ Hz, $H$-18), 0.59 (6H, q, $J = 8.0$ Hz, $H$-17)
1.5 Hz, H-(1)), 5.07 (1H, d, J = 10.5, 1.5 Hz, H-1), 5.07-4.95 (3H, m, H-(1')), 16, 16', (16), (16')), 3.88-3.81 (1H, m, H-3(3)), 3.81-3.74 (1H, m, H-7(7)), 3.62 (1H, s, H-(10)), 2.74 (1H, d, J = 16.0, 8.5 Hz, H-(8)), 2.58 (1H, d, J = 14.5, 7.0 Hz, H-8), 2.53 (1H, d, J = 16.0, 5.5 Hz, H-(8')), 2.49 (1H, t, J = 7.5 Hz, H-(12)), 2.36 (1H, dd, J = 15.0, 5.0 Hz, H-8'), 2.29 (1H, t, J = 8.0 Hz, H-12), 2.08 (2H, br. dt, J = 7.5, 7.5 Hz, H-14), 2.04 (1H, br. dt, J = 7.0, 7.0 Hz, H-(14)), 1.90-1.82 (1H, m, H-5(5)), 1.7 (2H, qn, J = 7.5 Hz, H-13), 1.67-1.52 (4H, m, H-4(4),5'(5'),6(6),13), 1.34-1.18 (3H, m, H-6'(6'),4'(4')).

13C NMR (126 MHz, CDCl3) δ 204.6 (C-(11)), 203.7 (C-(9)), 194.7 (C-(11)), 191.7 (C-9), 139.5 (C-2), 139.4 (C-(2)), 138.2 (C-(15)), 138.1 (C-15), 115.6 (C-16(16)), 114.8 (C-1(1)), 100.9 (C-10), 78.6 (C-(3)), 78.5 (C-3), 75.0 (C-7), 74.5 (C-(7)), 58.4 (C-(10)), 50.6 (C-(8)), 45.8 (C-8), 43.1 (C-(12)), 37.9 (C-12), 33.4 (C-14), 33.2 (C-(14)), 31.5 (C-6), 31.4 (C-(6)), 31.4 (C-4), 31.3 (C-(4)), 25.1 (C-13), 23.7 (C-5), 23.5 (C-(5)), 22.7 (C-13).


1-(2S,6S)-6-vinyltetrahydro-2H-pyran-2-yl)non-8-ene-2,4-dione (185)

IR (neat) νmax 3078, 2933, 2859, 1715, 1608, 1457, 1441, 1200, 1038, 916.

1H NMR (500 MHz, CDCl3) δ 5.93-5.84 (1H, m, H-15, (15)), 5.84-5.71 (1H, m, H-2, (2)), 5.54 (1H, s, H-7), 5.25-5.18 (2H, m, H-16, (16)), 5.05-4.95 (2H, m, H-1(1)), 4.40-4.35 (1H, m, H-14), 4.35-4.30 (1H, m, H-(14)), 4.19-4.13 (1H, m, H-10, (10)), 3.61 (1H, s, H-(7)), 2.78 (1H, dd J 15.5, 8.5 Hz, H-(9)), 2.58 (1H, dd, J = 14.0, 7.0 Hz, H-(9')) 2.53 (1H, dd, J = 14.0, 8.0 Hz, H-9), 2.44 (1H, t, J = 7.5 Hz, H-(5)), 2.37 (1H, dd, J = 14.5, 5.5 Hz, H-9'),
2.28 (<2H, t, J = 7.5 Hz, H-5), 2.11-2.06 (<2H, m, H-3), 2.05-2.00 (<1H, m, H-(3)), 1.82-1.53 (<7H, m, H-13,(13), 13',(13’), 4, (4), (12), 11, (11)), 1.41-1.29 (<1H, m, H-(11), (11’)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 194.8 (C-8), 191.6 (C-6), 138.5 (C-15), 138.1 (C-2), 116.6 (C-16), 115.6 (C-1), 73.0 (C-10), 68.6 (C-10), 44.6 (C-9), 38.0 (C-5), 33.4 (C-3), 31.1 (C-11), 28.9 (C-13), 25.0 (C-4), 19.0 (C-12).

\(m/z\) LRMS (ESI \(+\)) 287.2 [M+Na]\(^+\); HRMS (ESI\(^+\)) 287.16177 ([M+Na]\(^+\), C\(_{16}\)H\(_{24}\)O\(_3\)Na requires 287.16179).

NOESY does not give correlation between H-10 and H-14.

\((1S,11R,Z)-15\)-oxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (186)

Grubbs 2\(^{nd}\) generation catalyst (5.6 mg, 0.0066 mmol) was added to a stirred solution of 184 (35.0 mg, 0.132 mmol) in degassed CH\(_2\)Cl\(_2\) (15 mL) under argon atmosphere. Reaction mixture was heated at reflux for 1 h. The reaction mixture was filtered through a small pad silica and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography (10% to 20% EtOAc in petroleum ether). Purification gave the title compound 186 as a white solid in 27% yield (8.4 mg, 0.035 mmol).
IR (neat) $v_{\text{max}}$ 3007, 2931, 2860, 1728, 1696, 1368, 1300, 1074, 1037, 938, 881.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.52 (1H, dd, $J = 11.0, 8.0$ Hz, H-5), 5.46 (1H, ddd, $J = 11.0, 11.0, 5.0$ Hz, H-4), 4.84 (1H, ddd, $J = 10.5, 8.0, 2.0$ Hz, H-6), 3.73 (1H, d, $J = 13.0$ Hz, H-12), 3.71 (1H, ddd, $J = 11.0, 11.0, 2.5, 2.0$ Hz, H-10), 3.36 (1H, d, $J = 13.0$ Hz, H-12'), 2.77 (1H, ddd, $J = 19.5, 12.0, 2.5$ Hz, H-1), 2.67-2.58 (1H, m, H-3), 2.58 (1H, dd, $J = 13.0, 11.0$ Hz, H-11), 2.42 (1H, ddd, $J = 13.0, 2.5, 1.0$ Hz, H-11'), 2.37 (1H, ddd, $J = 19.5, 5.0, 2.0$ Hz, H-1'), 2.05-1.99 (1H, m, H-3'), 1.99-1.90 (1H, m, H-2), 1.87-1.79 (1H, m, H-8), 1.60-1.48 (3H, m, H-7,8',9), 1.41-1.29 (2H, m, H-2,7), 1.29-1.20 (1H, m, H-9).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 203.3 (C-12), 202.7 (C-14), 134.4 (C-4), 132.5 (C-5), 74.7 (C-10), 72.5 (C-6), 58.7 (C-12), 52.6 (C-11), 38.6 (C-1), 32.0 (C-9), 31.4 (C-7), 25.6 (C-3), 23.5 (C-8), 21.0 (C-2).

$m/z$ LRMS (ESI $^+$) 259.2 [M+Na]$^+$; HRMS (ESI$^+$) 259.13040 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 259.13047).

MP: 48-52 °C

(4E,10Z)-cyclotetradeca-4,10-diene-1,3,9-trione (191)

KHMDS solution in toluene (0.5 M, 0.296 mL, 0.148 mmol) was added dropwise to 186 (7 mg, 0.030 mmol) in dry THF (0.1 mL) at -15-20 °C. The reaction mixture was quenched after 30 minutes pouring into a saturated aqueous NH$_4$Cl solution. The mixture was extracted by CH$_2$Cl$_2$, the combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated using stream of nitrogen. The crude mixture was dissolved in CH$_2$Cl$_2$ (0.5 mL)
and DMP (19 mg, 0.044 mmol) was added to the solution at 0 °C and the reaction was stirred for 1 hour. The mixture was quenched by adding saturated aqueous sodium thiosulphate solution and the mixture was stirred until a clear solution was obtained. The reaction mixture was extracted with CH$_2$Cl$_2$ and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated using stream of nitrogen. The crude mixture was purified by using preparative TLC (50% EtOAc in petroleum ether) which gave the compound 191 in 15% yield (1 mg, 0.004 mmol) that exist at equilibrium as a 81:19 ratio of keto to enol tautomers.

IR (neat) $\nu_{\text{max}}$ 2919, 2850, 1715, 1660, 1618, 1447, 1416, 1295, 1118.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 14.15 (<1H, s, H-(15)), 6.69 (1H, dt, $J = 15.0, 8.0$ Hz, H-10), 6.10 (1H, d, $J = 11.0$ Hz, H-5), 5.99 (1H, d, 15.0 Hz, H-11), 5.96 (1H, dt, $J = 11.0, 9.0$ Hz, H-4), 3.60 (2H, s, H-13), 2.85-2.78 (2H, br. dt, $J = 9.0, 6.0$ Hz, H-3), 2.47-2.42 (2H, m, H-7), 2.42-2.37 (2H, m, H-1), 2.36-2.30 (2H, m, H-9), 2.04-1.95 (2H, m, H-8), 1.79-1.71 (2H, m, H-2).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.5 (C-13), 201.1 (C-6), 151.6 (C-11), 148.9 (C-3), 132.2 (C-10), 128.0 (C-4), 55.5 (C-13), 43.4 (C-7), 39.5 (C-1), 34.4 (C-9), 27.5 (C-3), 20.9 (C-2,8).

$m/z$ LRMS (ESI $^+$) 257.1 [M+Na]$^+$; HRMS (ESI$^+$) 257.11490 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 257.11482).

Only the keto tautomer reported.
2-vinylphenol\textsuperscript{120} (197)

![Structure of 2-vinylphenol](image)

To a stirred solution of methyltriphenylphosphonium bromide (13.46 g, 37.67 mmol) in dry
THF (37 ml) was added dropwise a solution of \(t\)-BuOK (4.23 g, 37.67 mmol) in dry THF (37
ml). The mixture was stirred for 2 hours at ambient temperature and the mixture was cooled to
\(-78\,^\circ\text{C}\). Salicylaldehyde \textsuperscript{196} (1.74 ml, 2.00 g, 16.38 mmol) was added dropwise to the mixture
and the reaction was allowed to slowly warm to ambient temperature and stirring was continued
for 20 hours. The reaction was quenched by pouring the mixture to ice cold aqueous 1 M HCl
solution (30 ml). EtOAc (120 ml) was added and the mixture was washed with brine (30 ml).
The organic layer was separated, solvents were removed \textit{in vacuo} and the crude mixture was
purified by flash chromatography (5 to 10% EtOAc in petroleum ether) which gave the title
compound \textsuperscript{197} as a colourless oil in 95% yield (1.87 g, 15.56 mmol).

\(\textsuperscript{1}H\) NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.39\) (1H, dd, \(J = 7.5, 1.5\,\text{Hz, H-7}\)), 7.15 (1H, ddd, \(J = 7.5, 7.5, 1.5\,\text{Hz, H-5}\)), 7.00–6.90 (2H, m, H-2,6), 6.80 (1H, dd, \(J = 8.0, 1.5\,\text{Hz, H-4}\)), 5.75 (1H, dd, \(J = 17.5, 1.5\,\text{Hz, H-1}\)), 5.37 (1H, dd, \(J = 11.5, 1.5\,\text{Hz, H-1'}\)).

\(\textsuperscript{13}C\) NMR (101 MHz, CDCl\textsubscript{3}) \(\delta 153.1\) (C-8), 131.8 (C-6), 129.2 (C-5), 127.7 (C-7), 125.1 (C-3),
121.3 (C-2), 116.2 (C-4), 116.2 (C-1).

\textit{m/z} LRMS (ESI\textsuperscript{-}) 119.1 [M-H]\textsuperscript{-}

Data in accordance with the literature\textsuperscript{120}. 
2-vinylphenyl 3-oxo-4-((2R,6S)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate (199)

(E)-2,2-dimethyl-6-((triethylsilyl)oxy)octa-1,7-dien-1-yl)-4H-1,3-dioxin-4-one 145 (1.00 g, 2.73 mmol) was dissolved in toluene (3 ml) with 2-vinylphenol (1.31 g, 1.56 mmol) and the mixture was heated in a closed vial at 110 °C for 8 hours. The crude mixture was purified by flash chromatography (5% Et₂O in petroleum ether). The purified mixture (443 mg, 1.03 mmol) was dissolved in chloroform (10 ml) and the solution was added dropwise to an acidified chloroform (150 mL, washed with 5–10 ml of conc. HCl) at 0 °C. Reaction mixture was stirred for 1 hour at ambient temperature and quenched by adding saturated aqueous NaHCO₃ (10 ml). Layers were separated and the organic phases were washed with brine (20 ml), dried over Na₂SO₄, filtered, and evaporated in vacuo. Purification by flash chromatography (10% to 20% Et₂O in petroleum ether) gave the title compound 199 (52%, 172 mg, 0.547 mmol) that exist at equilibrium as a 82:18 mixture of keto to enol tautomers.

IR (neat) ʋ max. br. 3420, 3084, 2935, 2858, 1764, 1716, 1647, 1485, 1454, 1249, 1212, 1136, 1095, 1048, 991, 764.

1H NMR (400 MHz, CDCl₃) δ 11.83 (<1H, s, H-20), 7.38 (1H, dd, J = 7.5, 2.0 Hz, H-16, 16'), 7.32–7.20 (2H, m, H-14,14',15,15'), 7.10 (1H, dd, J = 7.5, 1.0 Hz, H-13,13'), 6.87 (<1H, dd, J = 17.5, 11.0 Hz, H-18), 6.74 (<1H, dd, J = 17.5, 11.0 Hz, H-(18)) 5.92-5.78 (1H, m, H-2,2'), 5.75 (<1H, dd, J = 17.5, 1.0 Hz, H-19), 5.74 (<1H, dd, J = 17.5, 1.0 Hz, H-(19)), 5.36 (<1H, s, H-(10)) 5.35 (<1H, dd, J = 11.0, 1.0 Hz, H-19'), 5.32 (<1H, dd, J = 11.0, 1.0 Hz, H-(19')) 5.26 (<1H, dd, J = 17.0, 1.5 Hz, H-(1)), (<1H, dd, J = 17.5, 1.5 Hz, H-1), 5.11 (<1H, ddd, J = 12.0, 1.5, 1.5 Hz, H-(1')) 5.08 (<1H, ddd, J = 10.5, 1.5, 1.5 Hz, H-1'), 3.94–3.72 (2H, m,
H-3,7,(3),(7), 3.82 (<2H, s, H-10), 2.87 (<1H, dd, J = 15.0, 7.5 Hz, H-8), 2.67 (<1H, dd, J = 15.0, 5.0 Hz, H-8'), 2.59 (<1H, dd, J = 14.5, 7.0 Hz, H-(8)), 2.38 (<1H, dd, J = 14.5, 6.0 Hz, H-(8')), 1.95–2.38 (1H, m, H-5,(5)), 1.73–1.63 (2H, m, H-4.6, (4),(6)), 1.65–1.52 (1H, m, H-5',(5')), 1.38–1.19 (2H, m, H-4',6',(4'),(6')).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 201.6 (C-9), 178.2 (C-12), 166.0 (C-11), 148.0 (C-2), 139.3 (C-18), 130.5 (C-14), 129.0 (C-16), 126.8 (C-15), 126.7 (C-13), 122.8 (C-17), 116.8 (C-1), 114.9 (C-19), 78.6 (C-3), 74.5 (C-7), 50.4 (C-10), 50.1 (C-8), 31.4 (C-4), 31.3 (C-6), 23.5 (C-5).

$m/z$ LRMS (ESI$^+$) 353.0 [M+K]$^+$ HRMS (ESI$^+$) 337.14101 ([M+Na]$^+$, C$_{19}$H$_{22}$O$_4$Na requires 337.14102).

1-((2S,6R)-6-((Z)-4-Hydroxybut-1-en-1-yl)tetrahydro-2H-pyran-2-yl)propan-2-one (203)

![Chemical Structure](image)

A solution of compound 97 (10 mg, 0.042 mmol), iodo benzene (8.5 mg, 0.042 mmol) and tetrabutylammonium acetate (25 mg, 0.083 mmol) in dry DMF (0.5 – 1 mL) was bubbled with argon for 30 minutes. Palladium (II) acetate (1 mg, 0.004 mmol) was added to the mixture and the degassing was continued for 10 minutes. The reaction was stirred at 90 °C for 2 hours and diluted with Et$_2$O. The mixture was washed with water, brine, dried over Na$_2$SO$_4$ and filtered. The solvents were evaporated in vacuo and the crude product was purified by column chromatography (70% EtOAc in petroleum ether) to give the title compound 203 in 41% yield (3.6 mg, 0.017 mmol).

IR (neat) $\nu_{\text{max}}$ br. 3339, 3930, 2840, 1715, 1566, 1415, 1072, 1058, 915
\[ \text{H NMR (500 MHz, C}_6\text{D}_6 \delta 5.74 (1H, dd, } J = 11.0, 7.0 \text{ Hz, H-4), 5.56 (1H, dtd, } J = 11.0, 8.0, 
1.0 \text{ Hz, H-3), 4.19-4.13 (1H, app. m, H-5), 4.03-3.96 (1H, app. m, H-9), 3.74-3.66 (1H, app. m, H-1), 3.63-3.55 (1H, app. m, H-1'), 2.64 (1H, dd, } J = 16.5, 7.5 \text{ Hz, H-10), 2.55-2.46 (1H, app. m, H-2), 2.27-2.19 (1H, app. m, H-2'), 2.13 (1H, dd, } J = 16.5, 5.5 \text{ Hz, H-10'), 1.93 (3H, s, H-12), 1.72-1.67 (1H, app. m, H-7), 1.60-1.35 (4H, m, H-6,6',7',8), 1.21-1.10 (1H, app. m, H-8').} \]

\[ \text{C NMR (126 MHz, C}_6\text{D}_6 \delta 205.5 (C-11), 134.1 (C-4), 130.3 (C-3), 74.2 (C-5), 74.1 (C-9), 61.7 (C-1), 50.0 (C-10), 32.4 (C-2), 32.0 (C-6), 31.3 (C-8), 30.8 (C-12), 23.9 (C-7).} \]

\[ \text{m/z LRMS (ESI}^+ \text{) 235.2 [M+Na]}^+; \text{ HRMS (ESI}^+ \text{) 235.13049 ([M+Na]}^+, \text{ C}_{13}\text{H}_{16}\text{O}_4\text{Na requires 235.13047).} \]

(1S,11R,Z)-9-Methyl-6,15-dioxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (205)

Compound 208 (22 mg, 0.078 mmol) in CH\(_2\)Cl\(_2\) (30 mL) was degassed by bubbling nitrogen though the solution for 30 min. Grubbs 2\(^{nd}\) generation catalyst (3 mg, 0.004 mmol) was added to the solution and the bubbling of nitrogen was continued for 5 minutes. The reaction mixture was stirred under reflux for 2 hours, allowed to cool to ambient temperature and the solvents were removed in vacuo. The crude mixture was purified by column chromatography (30% Et\(_2\)O in petroleum ether) to give the title compound 205 as a white solid in 45% yield (8.9 mg, 0.035 mmol).

IR (neat) \( \nu_{\text{max}} \) 2980, 2931, 2859, 1736, 1708, 1672, 1446, 1320, 1270, 1187, 1025, 951.
1H NMR (500 MHz, CDCl₃) δ 5.37 (1H, d, J = 8.5 Hz, H-5), 4.48 (1H, ddd, J = 11.0, 4.5, 2.5 Hz, H-1), 4.03 (1H, ddd, J = 12.5, 11.0, 2.5 Hz, H-1’), 3.83 (1H, ddd, J = 11.0, 9.0, 2.0 Hz, H-6), 3.70 (1H, br. d, J = 11.0 Hz, H-10), 3.68 (1H, d, J = 14.0 Hz, H-13), 3.21 (1H, ddd, J = 13.5, 13.0, 5.0 Hz, H-2), 3.20 (1H, dd, J = 14.0, 1.5 Hz, H-13’), 2.64 (1H, dd, J = 13.0, 11.0 Hz, H-11), 2.38 (1H, ddd, J = 13.0, 1.5, 1.5 Hz, H-11’), 1.89-1.81 (2H, m, H-2’,8), 1.80 (3H, d, J = 1.0 Hz, H-4), 1.63-1.48 (3H, m, H-7,8’,9), 1.46-1.35 (1H, m, H-7’), 1.33-1.22 (1H, m, H-9’).

13C NMR (126 MHz, CDCl₃) δ 202.9 (C-12), 161.6 (C-14), 138.3 (C-3), 129.7 (C-5), 75.2 (C-10), 73.5 (C-6), 62.5 (C-1), 52.3 (C-11), 49.3 (C-13), 32.1 (C-9), 32.1 (C-2), 31.7 (C-7), 23.6 (C-8), 22.9 (C-4).


MP: 78-82 ºC white solid

(5E,11Z)-12-Methyloxacyclotetradeca-5,11-diene-2,4,10-trione (206)

![Chemical Structure](image)

KHMDS (0.5 M, in toluene, 0.178 mmol, 0.356 mL) was added dropwise in a solution of 207 (9.0 mg, 0.036 mmol) in THF (0.1 mL) at 0 ºC. The mixture was stirred for 15 minutes and quenched by pouring onto an ice-cold saturated aqueous NH₄Cl solution. The solution was extracted with CH₂Cl₂ and the combined organic phases were washed with brine, dried (Na₂SO₄) and filtered. The crude product was concentrated in vacuo, dissolved in CH₂Cl₂ and cooled to 0 ºC. Dess-Martin periodinate (23 mg, 0.054 mmol) was added to the solution and
the reaction was stirred for 1 hour. The reaction was quenched by adding saturated aqueous sodium thiosulphate (2 mL) to the solution. The mixture was stirred for 20 minutes and extracted with CH$_2$Cl$_2$. The combined organic layers where washed with saturated aqueous sodium bicarbonate, then with brine, dried over Na$_2$SO$_4$ and filtered. The solvents were removed *in vacuo* and the crude product was purified by preparatory thin layer chromatography (50% EtOAc in petroleum ether) to give the title compound **206** in 12% yield (1 mg, 0.004 mmol).

IR (neat) $\nu_{\max}$ 2918, 2850, 1739, 1690, 1669, 1623, 1440, 1260, 1218, 1116, 1027.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.69 (1H, dt, $J = 15.5$, 8.0 Hz, H-10), 6.69 (1H, s, H-5), 5.99 (1H, d, $J = 15.5$ Hz, H-11), 4.32 (2H, t, $J = 5.5$ Hz, H-1), 4.32 (2H, s, H-13), 3.18 (2H, t, $J = 5.5$ Hz, H-2), 2.43-2.38 (2H, app. m, H-7), 2.36-2.30 (2H, app. m, H-9), 2.03-1.98 (2H, app. m, H-8), 1.88 (3H, s, H-4).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.8 (C-6), 192.7 (C-12), 166.9 (C-14), 154.8 (C-10), 151.1 (C-3), 132.1 (C-11), 126.7 (C-5), 62.6 (C-1), 45.2 (C-13), 43.8 (C-7), 34.4 (C-9), 31.9 (C-2), 30.1 (C-4), 24.7 (C-8).

$m/z$ LRMS (ESI $^+$) 273.1 [M+Na]$^+$; HRMS (ESI$^+$) 273.10976 ([M+Na]$^+$, C$_{14}$H$_{18}$O$_4$Na requires 273.10973).
A mixture of compound 145 (500 mg, 1.36 mmol) and 3-methyl-3-buten-1-ol (0.567 mL, 5.46 mmol, 97 w/w%) in dry toluene (2 mL) was heated at 110 °C in a closed vial for 12 hours. The reaction mixture was filtered through a small pad of silica and the filtrate was thoroughly concentrated in vacuo. The crude mixture was dissolved in 10 mL chloroform and the solution was added dropwise to acidified chloroform (150 mL, washed with 10 mL of conc. HCl) at 0 °C. The reaction mixture was stirred for 1 hour. The reaction was quenched by adding saturated NaHCO₃. The layers were separated and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash chromatography (10% to 25% Et₂O in petroleum ether) gave the title compound 210 as a major isomer in 79% yield (302 mg, 1.08 mmol) which was found to exist as a 94:6 ratio of keto to enol tautomers (at equilibrium).

IR (neat) \( \nu_{\text{max}} \) 3078, 2935, 2857, 1743, 1715, 1649, 1311, 1224, 1152, 1073, 1041, 918, 892.

\(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 12.03 (<1H, s, H-(17)), 5.18 (<1H, app. br. d, \( J = 17.5 \), H-1,(1)), 5.06 (<1H, s, H-(10)), 5.05 (<1H, app. br. d, \( J = 10.5 \) Hz, H-1',(1')), 4.79 (1H, br. s, H-16,(16)), 4.72 (1H, br. s, H-16',(16')), 4.23 (2H, t, \( J = 6.90 \) Hz, H-2,(2)), 3.88-3.76 (<2H, m, H-3,7,(3),(7)), 3.50 (<2H, s, H-10), 2.78 (<1H, dd, \( J = 15.5, 7.5 \) Hz, H-8), 2.72 (<1H, dd, \( J = 16.0, 8.0 \) Hz, H-(8)), 2.57 (<1H, dd, \( J = 15.5, 5.0 \) Hz, H-8'), 2.44 (<1H, dd, \( J = 15.5, 5.5 \) Hz, H-(8')), 2.34 (2H, t, \( J = 7.0 \) Hz, H-12,(12)), 1.91-1.80 (1H, m, H-5,(5)), 1.73 (3H, br. s, H-15,(15)), 1.71-1.50 (3H, m, H-5',(5'), 4, (4), 6, (6)), 1.35-1.14 (2H, m, H-4',(4'), 6', (6')).
\[^{13}\text{C}\] NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.9 (C-9), 175.8 (C-(9)), 172.9 (C-(11)), 167.5 (C-11), 141.9 (C-(14)), 141.7 (C-14), 139.5 (C-16), 139.4 (C-16), 114.8 (C-(1)), 114.7 (C-1), 112.7 (C-2), 112.6 (C-(2)), 91.1 (C-(10)), 78.5 (C-3), 77.6 (C-(3)), 74.5 (C-(7)), 74.4 (C-7), 63.7 (C-12), 62.6 (C-(12)), 50.6 (C-8), 50.5 (C-10), 49.9 (C-8), 40.0 (C-(13)), 36.8 (C-13), 31.5 (C-(4)), 31.4 (C-6), 31.4 (C-(6)), 31.3 (C-4), 23.6 (C-(5)), 23.5 (C-5), 22.9 (C-(15)), 22.7 (C-15).

\(m/z\) LRMS (ESI \(^+\)) 303.2 [M+Na\(^+\)]; HRMS (ESI\(^+\)) 303.15653 ([M+Na\(^+\)], \(\text{C}_{16}\text{H}_{24}\text{O}_{4}\text{Na}\) requires 303.15668).

2-Bromo-3-(2-bromoethyl)-4,13-dioxabicyclo[7.3.1]tridecane-5,7-dione (211)

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\begin{array}{c}
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\text{Br} \\
\text{O} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{Br} \\
\text{Br}
\end{array}
\]

211

A stock solution of bromine (6.7 mg, 0.042 mmol) in CH\(_2\)Cl\(_2\) (0.3 mL) was added to a solution of macrocycle 87 (10 mg, 0.042 mmol) in CHCl\(_3\) (2 mL) at 0 \(^\circ\)C. The solution was allowed to warm to ambient temperature and the reaction was stirred for 12 hours. The solvents were removed by bubbling nitrogen through the mixture. The crude material was purified by column chromatography (10% EtOAc in CHCl\(_3\)) to give the product 211 as white solid in 29% yield (4.8 mg, 0.012 mmol).

IR (neat) \(\nu_{\text{max}}\) 2956, 2940, 2917, 2850, 1739, 1701, 1300, 1196, 989, 949, 892, 646.
\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.38 (1H, ddd, \(J = 9.0, 3.5, 1.5\) Hz, H-3), 3.46 (1H, ddd, \(J = 12.0, 2.5, 2.5\) Hz, H-5), 3.32 (1H, dd, \(J = 2.0, 2.0\) Hz, H-4), 3.30 (1H, d, \(J = 11.5\) Hz, H-12) 3.12-3.05 (1H, app. m, H-9), 2.95-2.88 (2H, app. m, H-1), 2.91 (1H, d, \(J = 11.5\) Hz, H-12'), 2.38 (1H, dd, \(J = 12.0, 5.5\) Hz, H-10), 2.21 (1H, dddd, \(J = 15.0, 9.0, 6.0, 5.5\) Hz, H-2), 2.07 (1H, ddd, \(J = 12.0, 4.0, 1.0\) Hz, H-10'), 1.62 (1H, dddd, \(J = 15.0, 8.0, 6.5, 3.5\) Hz, H-2'), 1.41-1.20 (3H, m, H-6,7,8), 0.91-0.83 (1H, app. m, H-8'), 0.83-0.71 (2H, m, H-7',6').

\(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 199.1 (C-11), 168.7 (C-13), 82.0 (C-5), 75.1 (C-9), 69.7 (C-1), 57.7 (C-4), 51.5 (C-12), 50.6 (C-10), 38.1 (C-2), 28.9 (C-3), 28.4 (C-6), 27.8 (C-8), 22.8 (C-7).

\(\text{m/z LRMS (ESI} ^+\)) 418.9 [M+Na]; \(\text{HRMS (ESI} ^+\)) 418.94635 ([M+Na]\(^+\), \(\text{C}_{13}\)H\(_{18}\)Br\(_2\)O\(_4\)Na requires 418.94641).

\((\text{5E,11E)}-\text{Oxacyclotetradeca-5,11-diene-2,4,10-trione (222)}\)

\[
\begin{array}{c}
O \\
\includegraphics[width=0.2\textwidth]{222.png}
\end{array}
\]

A solution of enone 67 (20 mg, 0.085 mmol) in diethyl ether was added to the irradiation vessel. The insert was added, screw cap fitted and the vessel was degassed by bubbling nitrogen through the mixture for 30 min at 0 °C. The vessel was kept under a gentle flow of nitrogen, a 365 nm UVP pen-Ray was placed in the insert and switched on, and the reaction was stirred at 0 °C (ice bath) for 1 hour. After switching off the light source, the solvents were removed \(\text{in vacuo}\) and the crude product was purified twice by thin layer chromatography. First purification (Et\(_2\)O as eluent) afforded \((\text{5Z,11Z)}-\text{oxacyclotetradeca-5,11-diene-2,4,10-trione 220}\) in 23% yield (4.5
mg, 0.019 mmol) and (5E,11E)-oxacyclotetradeca-5,11-diene-2,4,10-trione 222 in 13% yield (2.5 mg, 0.011 mmol) and the Diels-Alder products 223 and 224 in 8% yield (1.6 mg, 0.007). The second purification (Et₂O in CH₂Cl₂) afforded the recovered starting material 67 in 35% yield (7 mg, 0.030 mmol) and (5Z,11E)-oxacyclotetradeca-5,11-diene-2,4,10-trione 221 in 5% yield (1 mg, 0.004 mmol).

IR (neat) ν max 2917, 2849, 2360, 2342, 1737, 1629, 1667, 1624, 1341, 1257, 978.

¹H NMR (500 MHz, CDCl₃) δ 6.83 (1H, dt, J = 15.5, 8.0 Hz, H-9), 6.69 (1H, dt, J = 16.0, 7.0 Hz, H-3), 6.18 (1H, dt, J = 15.5, 1.5 Hz, H-10), 6.10 (1H, dt, J = 16.0, 1.5 Hz, H-4), 4.37 (2H, t, J = 5.5 Hz, H-1), 3.45 (2H, s, H-12), 2.61 (2H, dtd, J = 7.0, 5.5, 1.5 Hz, H-2), 2.49 (2H, t, J = 6.5 Hz, H-6), 2.25 (2H, dtd, J = 8.0, 6.0, 1.5 Hz, H-8), 2.00–1.95 (2H, app. m, H-7),

¹³C NMR (126 MHz, CDCl₃) δ 201.1 (C-5), 190.3 (C-11), 167.1 (C-13), 148.7 (C-9), 143.4 (C-3), 134.7 (C-4), 130.2 (C-10), 63.3 (C-1), 49.9 (C-12), 36.1 (C-6), 31.9 (C-2), 31.3 (C-8), 23.4 (C-7).

m/z LRMS (ESI⁺) 259.0 [M+Na]⁺; HRMS (ESI⁺) 259.09407 ([M+Na]⁺, C₁₃H₁₆O₄Na requires 259.09408).
(5Z,11Z)-Oxacyclotetradeca-5,11-diene-2,4,10-trione (220)

IR (neat) $\nu_{\text{max}}$ 2918, 2850, 1739, 1693, 1628, 1414, 1375, 1253, 1112.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.20 (1H, br. d, $J = 11.5$ Hz, $H$-4), 6.18 (1H, d, $J = 11.5$ Hz, $H$-10), 6.18 (1H, dt, $J = 11.5$, 9.5 Hz, $H$-9), 5.88 (1H, dt, $J = 11.5$, 8.0 Hz, $H$-3), 4.26 (2H, t, $J = 5.5$ Hz, $H$-1), 3.39 (2H, s, $H$-12), 2.95-2.89 (2H, m, $H$-2), 2.76-2.70 (2H, m, $H$-8), 2.55-2.50 (2H, m, $H$-6), 1.94-1.88 (2H, m, $H$-7).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.4 (C-5), 193.1 (C-11), 167.1 (C-13), 151.0 (C-9), 141.4 (C-3), 130.9 (C-4), 126.8 (C-10), 63.9 (C-1), 51.1 (C-12), 43.0 (C-6), 29.2 (C-8), 28.6 (C-2), 22.0 (C-7).

$\text{m/z}$ LRMS (ESI$^+$) 259.0 [M+Na]$^+$; HRMS (ESI$^+$) 259.09408 ([M+Na]$^+$; C$_{13}$H$_{16}$O$_3$Na requires 259.09408).

MP: 78-84 °C
7a-Hydroxy-5,5a,7a,8,9,10,10a,10b-octahydro-1H-indeno[5,4-c]oxepine-1,3(2H)-dione

(223 and 224)

IR (neat) ν\text{max} \text{ br.} 3432, 2925, 2851, 1743, 1449, 1364, 1257, 1225, 1184, 1119, 999, 916, 730.

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.18 (1H, ddd, J = 10.5, 7.5, 3.0 Hz, H-4), 6.17-6.12 (1H, app. m, H-4), 6.00 (1H, dddd, J = 10.5, 6.0, 4.0, 1.5 Hz, H-3), 5.64 (1H, br. d, J = 11.5 Hz, H-(3)), 4.97 (1H, dd, J = 13.0, 6.0 Hz, H-1), 4.89 (1H, dd, J = 15.5, 4.5 Hz, H-(1)), 4.72 (1H, br. d, J = 15.5 Hz, H-(1’), 4.33 (1H, dd, J = 13.0, 4.0, 3.0 Hz, H-1’), 3.79 (1H, d, J = 9.5 Hz, H-12), 3.55 (1H, d, J = 16.5 Hz, H-(12)), 3.36 (1H, d, J = 16.5 Hz, H-(12’)), 3.31 (1H, br. d, 8.0 Hz, H-12), 3.27-3.18 (4H, m, H-2, 10, (10)), 2.29 (1H, br. t, J = 6.5 Hz, H-9), 2.64 (1H, br. t, J = 8.0 Hz, H-(9)), 2.18-2.05 (1H, app. m, H-(7)), 2.00-1.85 (6H, m, H-7, 7’, (7), (6), (8)), 1.82-1.67 (4H, m, H-8’, (7’), (6’), 6’), 1.62-1.48 (2H, m, H-(8’), 6’).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.9 (C-13), 197.2 (C-(13)), 166.2 (C-11), 164.5 (C-(11), 130.5 (C-4), 128.8 (C-3), 128.0 (C-4), 125.0 (C-3), 82.2 (C-5), 81.3 (C-5), 63.4 (C-1), 62.7 (C-(1)), 55.6 (C-12), 53.7 (C-2), 51.0 (C-(12)), 48.2 (C-2), 47.8 (C-10), 47.1 (C-9), 46.0 (C-9), 45.7 (C-10), 41.7 (C-6), 41.2 (C-6), 31.0 (C-8), 27.3 (C-7), 26.0 (C-8), 25.9 (C-7).

$\text{m/z}$ LRMS (ESI $^+$) 259.0 [M+Na]$^+$; HRMS (ESI $^+$) 259.09408 ([M+Na]$^+$, C$_{13}$H$_{16}$O$_4$Na requires 259.09423).
(10Z,12Z)-12-Hydroxy-3,4,4a,7,8,9-hexahydro-1H-cyclodeca[c]pyran-1,6(5H)-dione

(225)

A solution of (5Z,11Z)-oxacyclotetradeca-5,11-diene-2,4,10-trione 220 (5.5 mg, 0.023 mmol) and N-(9-anthracenylmethyl)cinchonium bromide (1.3 mg, 0.0023 mmol) in dry benzene (0.423 mL) was stirred for 10 minutes prior to the addition of vacuum oven dried potassium fluoride (12.3 mg, 0.21 mmol). The reaction mixture was flushed with nitrogen, stirred for 48 hours and quenched by adding saturated aqueous ammonium chloride. The combined organic layers were dried over Na$_2$SO$_4$, filtered and the solvents were removed \textit{in vacuo}. The crude product was purified by preparatory TLC (EtOAc 50% in petroleum ether) to afford the title compound 225 in 11% yield as a colourless oil (1.1 mg, 0.0025 mmol). The product was found to exist entirely in its enol form.
IR (neat) $\nu_{\text{max}}$ br. 3413, 2917, 2849, 1706, 1633, 1587, 1418, 1259, 1259, 1225, 1196, 1022, 798.

$^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 14.39 (1H, s, H-$O$), 5.63 (1H, d, $J = 11.62$ Hz, H-10), 5.46 (1H, ddd, $J = 11.5, 11.5, 5.5$ Hz, H-9), 3.61-3.56 (2H, app. m, H-1), 2.59-2.50 (1H, app. m, H-3), 2.23-2.14 (1H, m, H-8), 1.96 (1H, dd, $J = 12.0, 10.5$ Hz, H-4), 1.87-1.66 (4H, m, H-7,8’,6,6’), 1.57 (1H, dd, $J = 10.0, 3.0$ Hz, H-4’), 1.27-1.16 (2H, m, H-7’,2), 0.67 (1H, ddd, $J = 14.0, 4.5, 2.5$ Hz, H-2’).

$^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$ 209.8 (C-5), 173.7 (C-11), 172.0 (C-13), 140.7 (C-9), 124.1 (C-10), 99.2 (C-12), 65.2 (C-1), 48.8 (C-4), 43.8 (C-6), 31.5 (C-3), 30.2 (C-8), 29.4 (C-2), 23.2 (C-7).

$m/z$ LRMS (ESI +) 259.0 [M+Na]+; HRMS (ESI+) 259.09408 ([M+Na]+, C$_{13}$H$_{16}$O$_4$Na requires 259.09408).

$[\alpha]_D^{25} = +40$ (c = 0.001, CHCl$_3$).

**But-3-en-1-yl 2-(3,5-dimethoxyphenyl)acetate (248)**

![But-3-en-1-yl 2-(3,5-dimethoxyphenyl)acetate (248)](248)

A solution of DCC (1.26 g, 6.12 mmol) in CH$_2$Cl$_2$ (6 mL) was added to a mixture of compound 251 (1 g, 5.10 mmol), DMAP (62.0 mg, 0.510 mmol) and 3-butyl-1-ol (0.550 mL, 6.12 mmol) in CH$_2$Cl$_2$ (50 mL) at 0 °C. The reaction mixture was stirred for 6 hours at ambient temperature and water (0.2 mL) was added. The reaction was further stirred at ambient temperature for 16 hours and filtered through a small plug of silica. The crude mixture was concentrated *in vacuo*
and purified by flash chromatography (10% EtOAc in petroleum ether) to give the title compound 248 as a colourless oil in quantitative yield (1.28 g, 5.10 mmol).

IR (neat) \( \nu_{\text{max}} \): 2956, 2839, 1732, 1641, 1595, 1292, 1204, 1147, 1064, 917, 833.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 6.43 (2H, d, \( J = 2.5 \) Hz, H-8), 6.37 (1H, t, \( J = 2.5 \) Hz, H-10), 5.75 (1H, ddt, \( J = 17.0, 10.5, 7.0 \) Hz, H-2), 5.11-5.03 (2H, m, H-1,1'), 4.15 (2H, t, \( J = 6.5 \) Hz, H-4), 3.78 (6H, s, H-11), 3.55 (2H, s, H-6), 2.38 (2H, dtt, \( J = 7.0, 6.5, 1.5 \) Hz, H-3)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 171.6 (C-5), 161.1 (C-9), 136.4 (C-7), 134.2 (C-2), 117.6 (C-1), 107.7 (C-8), 99.6 (C-10), 64.2 (C-4), 55.6 (C-11), 42.0 (C-6), 33.4 (C-3).

\( m/z \) LRMS (ESI \(^+\)) 273.0 [M+Na]\(^+\); HRMS (ESI\(^+\)) 251.12773 ([M+H]\(^+\), \( C_{14}H_{19}O_4 \) requires 251.12779).

\( (E)\)-5-(2-(3,5-Dimethoxyphenyl)acetoxy)pent-2-enoic acid (249)

A mixture of compound 248 (500 mg, 2.00 mmol) and acrylic acid (0.411 mL, 5.99 mmol) in CH\(_2\)Cl\(_2\) (20 ml) was degassed by purging nitrogen trough and the amount of CH\(_2\)Cl\(_2\) was reduced to 10 mL. The Grubbs 2\(^{\text{nd}}\) generation catalyst (85 mg, 0.10 mmol) was added to the solution and the bubbling of nitrogen was continued for 10 min. The solution was then heated at reflux for 3 hours. The mixture was filtered through a small pad of silica (50% EtOAc in petroleum ether). Solvents were removed \textit{in vacuo} and the crude mixture was purified by flash
chromatography (20% to 40% EtOAc in petroleum ether) to give the title compound 249 as a white solid in 43% yield (250 mg, 0.859 mmol).

IR (neat) $v_{max}$ 3004, 2943, 2839, 1728, 1695, 1654, 1595, 1460, 1430, 1291, 1204, 1147, 1064, 979, 834, 685

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.99 (1H, dt, $J = 15.5, 7.0$ Hz, $H$-3), 6.42 (1H, d, $J = 2.0$ Hz, $H$-10), 6.37 (2H, t, $J = 2.0$ Hz, $H$-9), 5.86 (1H, dt, $J = 16.0, 1.5$ Hz, $H$-2), 4.23 (2H, t, $J = 6.5$ Hz, $H$-5), 3.77 (6H, s, $H$-12), 3.55 (2H, s, $H$-7), 2.57 (2H, dtd, $J = 7.0, 6.5, 1.5$ Hz, $H$-4).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.6 (C-1), 171.5 (C-6), 161.2 (C-10), 147.1 (C-3), 136.1 (C-8), 123.3 (C-2), 107.6 (C-9), 99.6 (C-11), 62.8 (C-5), 55.6 (C-12), 55.6 (C-12'), 41.8 (C-7), 31.8 (C-4).

$m/z$ LRMS (ESI-) 293.1 [M-H]; HRMS (ESI+) 317.09976 ([M+Na]+, C$_{15}$H$_{18}$O$_6$Na requires 317.09956).

(Z)-9,11-Dimethoxy-4,5-dihydro-2H-benzo[d]oxecine-2,8(1H)-dione (250)

TFA (4.0 mL) and TFAA (2.0 mL) was added to the compound 249 (81 mg, 0.27 mmol) at 78°C. The reaction mixture was warmed up to ambient temperature within 15 minutes and heated at gentle reflux for further 20 minutes. The reaction was quenched by adding the mixture slowly to saturated aqueous NaHCO$_3$ at 0°C. The mixture was extracted with CH$_2$Cl$_2$ and the combined organic phases were washed with water and brine and dried over Na$_2$SO$_4$. The mixture was filtered, concentrated in vacuo and purified by column chromatography (10% to 50% EtOAc...
in petroleum ether) to give the title compound 250 in 5% yield as a colourless solid (3.3 mg, 0.014 mmol).

IR (neat) $v_{\text{max}}$ 2955, 2846, 1733, 1664, 1578, 1455, 1333, 1264, 1196, 1154, 1093, 1025, 735.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.05 (1H, d, $J = 12.0$ Hz, H-4), 6.41 (1H, d, $J = 2.0$ Hz, H-8), 6.31 (1H, d, $J = 2.0$ Hz, H-10), 5.97 (1H, dt, $J = 12.0$, 8.0 Hz, H-3), 4.17 (2H, br. t, $J = 5.0$ Hz, H-1), 3.86 (2H, br. s, H-12), 3.85 (3H, s, H-15), 3.82 (3H, s, H-14), 2.63-2.55 (2H, m, H-2).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 200.3 (C-5), 170.2 (C-13), 162.2 (C-7), 159.0 (C-6), 137.2 (C-4), 135.7 (C-11), 133.1 (C-3), 122.8 (C-9), 108.8 (C-10), 97.8 (C-8), 62.6 (C-1), 56.1 (C-15), 55.8 (C-14), 41.3 (C-12), 25.2 (C-2).

$m/z$ LRMS (ESI $^+$) 299.0 [M+Na]$^+$; HRMS (ESI$^+$) 299.08893 ([M+Na]$^+$, C$_{15}$H$_{16}$O$_5$ requires 299.08899).

MP: 135-138 °C.

*(E)*-9,11-Dimethoxy-4,5-dihydro-2H-benzoxocine-2,8(1H)-dione (252)

Compound 250 (4.2 mg, 0.015 mmol) in EtOAc (8 mL) was degassed by bubbling with nitrogen for 30 min. The mixture was irradiated for 15 minutes at 0 °C with a 365 nm light source. The mixture was concentrated *in vacuo* and purified by column chromatography (10% to 50% EtOAc in petroleum ether) to give the title compound 252 in 25% yield (1.0 mg, 0.0038 mmol).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.45 (2H, s, $H$-8,10), 6.32 (1H, dd, $J = 16.0, 0.5$ Hz, $H$-4), 6.15 (1H, ddd, $J = 16.0, 12.0, 4.5$ Hz, $H$-3), 5.02-4.92 (1H, m, $H$-1), 4.27 (1H, dd, $J = 10.5, 8.5$ Hz, $H$-1$'$), 3.86 (3H, s, $H$-13), 3.78 (3H, s, $H$-14), 3.44 (2H, s, $H$-12), 2.74-2.64 (1H, m, $H$-2), 2.54-2.48 (1H, m, $H$-2$'$).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 196.5 (C-5), 174.3 (C-13), 162.0 (C-9), 159.3 (C-7), 147.1 (C-3), 138.7 (C-4), 136.4 (C-11), 122.3 (C-6), 109.6 (C-10), 98.6 (C-8), 65.5 (C-1), 59.4 (C-14), 55.8 (C-15), 42.3 (C-12), 33.6 (C-2).

$m/z$ LRMS (ESI$^+$) 299.0 [M+Na]$^+$; HRMS (ESI$^+$) 299.08899 ([M+Na]$^+$, C$_{15}$H$_{16}$O$_5$Na requires 299.08903).

1-(3,5-Dimethoxyphenyl)hept-6-en-2-one (254)

Dry magnesium turnings (406 mg, 10.0 mmol) in THF (0.5 mL) were activated by adding few drops of dibromoethane. 5-Bromopent-1-ene (95% w/w, 1.04 mL, 8.36 mmol) in THF (7 ml) was added dropwise to the solution and the mixture was stirred for further 1h at ambient temperature. The Grignard reagent 256 was added to a mixture of 2-(3,5-dimethoxyphenyl)-N-methoxy-N-methylacetamide 253 (1.00 g, 4.18 mmol) in THF (4 mL) at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C and was slowly warm to ambient temperature in 1 hour. The reaction mixture was poured to ice cold aqueous 3M HCl solution and the mixture was extracted with Et$_2$O (80 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, then brine and dried over Na$_2$SO$_4$. The mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography (10% EtOAc in petroleum ether) to give the title compound as a colourless oil 254 in 61% yield (633 mg, 2.55 mmol).
IR (neat) \( \nu_{\max} \) 3076, 2999, 2838, 1710, 1639, 1430, 1204, 1149, 1059, 912, 831, 668.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)

- 6.36 (1H, t, \( J = 2.0 \) Hz, \( H-11 \)),
- 6.35 (2H, d, \( J = 2.0 \) Hz, \( H-9 \)),
- 5.72 (1H, ddt, \( J = 17.0, 10.0, 6.5 \) Hz, \( H-2 \)),
- 4.99-4.91 (2H, m, \( H-1,1' \)),
- 3.78 (6H, s, \( H-12 \)),
- 3.59 (2H, s, \( H-7 \)),
- 2.46 (2H, t, \( J = 7.5 \) Hz, \( H-5 \)),
- 2.04-1.97 (2H, m, \( H-3 \)),
- 1.65 (2H, app. d, \( J = 7.0 \) Hz, \( H-4 \)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \)

- 208.4 (C-6),
- 161.3 (C-10),
- 138.3 (C-2),
- 136.8 (C-8),
- 115.5 (C-1),
- 101.8 (C-9),
- 99.3 (C-11),
- 55.6 (C-12),
- 50.9 (C-7),
- 41.2 (C-5),
- 33.3 (C-3),
- 23.0 (C-4).

\( m/z \) LRMS (ESI \(^+\)) 271.1 [M+Na]\(^+\); HRMS (ESI\(^+\)) 271.1316 ([M+Na]\(^+\), \( \text{C}_{15}\text{H}_{20}\text{O}_{3}\)Na requires 271.1310).

\((E)-8-(3,5\text{-Dimethoxyphenyl})-7\text{-oxooct-2-enoic acid (255)}\)

![255]

A mixture of compound 254 (300 mg, 1.21 mmol) and acrylic acid (0.248 mL, 3.62 mmol) in CH\(_2\)Cl\(_2\) (12ml) was degassed by purging with nitrogen gas until the amount of CH\(_2\)Cl\(_2\) was reduced to 6 mL. The Grubbs 2\(^{nd}\) generation catalyst (51 mg, 0.060 mmol) was added to the solution and the purging of nitrogen was continued for 10 min. The solution was heated to a gentle reflux for 3 hours. The mixture was filtered through a small pad of silica (50% EtOAc in petroleum ether). Solvents were removed \textit{in vacuo} and the crude mixture was purified by flash chromatography (20% to 50% EtOAc in petroleum ether). Solvents were removed \textit{in vacuo} and the crude mixture was purified by flash chromatography (20% to 40% EtOAc in
petroleum ether) to give the title compound 255 as a colourless solid in 82% yield (289 mg, 0.990 mmol).

IR (neat) \( \nu_{\text{max}} \) 3250, 3002, 2939, 2839, 1694, 1650, 1594, 1459, 1430, 1290, 1204, 1149, 1059, 980, 832, 811, 696.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.98 (1H, dt, \( J = 15.5, 7.0 \) Hz, \( H-3 \)), 6.37 (1H, d, \( J = 2.0 \) Hz, \( H-12 \)), 6.34 (2H, d, \( J = 2.0 \) Hz, \( H-10 \)), 5.76 (1H, dt, \( J = 15.5, 1.5 \) Hz, \( H-2 \)), 3.77 (6H, s, \( H-13 \)), 3.59 (2H, s, \( H-8 \)), 2.48 (2H, t, \( J = 7.0 \) Hz, \( H-6 \)), 2.18 (2H, dtd, \( J = 7.5, 7.0, 1.5 \) Hz, \( H-4 \)) 1.73 (2H, app. qn, \( J = 7.0 \) Hz, \( H-5 \)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 207.8 (C-7), 171.8 (C-1), 161.4 (C-12), 151.4 (C-3), 136.5 (C-9), 121.5 (C-2), 107.7 (C-10), 99.4 (C-12), 55.7 (C-13), 50.9 (C-8), 40.8 (C-6), 31.7 (C-4), 22.0 (C-5).

\( m/\zeta \) LRMS (ESI \(^+\)) 315.2 [M+Na]\(^+\); HRMS (ESI\(^+\)) 315.12027 ([M+Na]\(^+\), \( C_{16}H_{20}O_5Na \) requires 315.12029).

MP: 64-68 °C.

\((Z)-2,4\text{-Dimethoxy-9,10-dihydrobenzo[10]annulene-5,11(8H,12H)-dione (256)}\)

\[ \text{256} \]

A premixed solution of trifluoroacetic acid (12.0 mL) and trifluoroacetic anhydride (6.0 mL) was added to enonic acid 255 (50 mg, 0.171 mmol) at \(-78 \) °C. After the addition, the dry ice bath was removed and the mixture was allowed to stir at ambient temperature for 30 minutes.
The reaction mixture was poured to an ice cold solution of saturated aqueous NaHCO$_3$. The mixture was extracted with CH$_2$Cl$_2$ (150 ml), the organic layers were washed with brine and dried over Na$_2$SO$_4$. The mixture was filtered and the solvents were removed \textit{in vacuo}. The crude mixture was purified by using preparative thin layer chromatography (40% EtOAc in petroleum ether) to give the compound 256 ($<1$ mg).

IR (neat) \(\nu_{\text{max}}\) 2917, 2849, 1700, 1652, 1636, 1507, 1396, 1291, 1157.

$^1$H NMR (500 MHz, CDCl$_3$) \(\delta\) 6.46 (1H, d, \(J = 2.5\) Hz, \(H-9\)), 6.43 (1H, br. d, \(J = 12.5\) Hz, \(H-4\)), 6.41 (1H, d, \(J = 2.5\) Hz, \(H-11\)), 6.10 (1H, dt, \(J = 12.5, 9.0\) Hz, \(H-4\)), 3.84 (3H, s, \(H-16\)), 3.77 (3H, s, \(H-15\)), 3.63 (2H, s, \(H-13\)), 2.42 (2H, m, \(H-3\)), 1.97 (2H, m, \(H-1\)), 1.66 (2H, m, \(H-2\)).

No 13C-NMR of the compound due to the limited amount of material

$m/z$ LRMS (ESI $^+$) 297.1 [M+Na]$^+$; HRMS (ESI$^+$) 297.1103 ([M+Na]$^+$, C$_{16}$H$_{18}$O$_4$Na requires 315.1107).

\textbf{2,4-Dimethoxy-7,8-dihydrophenanthren-9-ol (257)}

![257]

Polyphosphoric acid (2.0 mL) was added to compound 255 (23mg, 0.078 mmol) and the mixture was mechanically stirred for 5 minutes. The reaction was heated at 70 °C for 3 hours and poured into saturated aqueous NH$_4$Cl. The solution was extracted with CH$_2$Cl$_2$ (80 mL) and the combined organic layers were washed with water and brine. The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The crude mixture was purified by
preparative thin layer chromatography (50% EtOAc in petroleum ether) to give the title compound 257 in 14% yield (2.8 mg, 0.0011 mmol).

IR (neat) \( \nu_{\text{max}} \) 3396, 2929, 2849, 1625, 1585, 1449, 1403, 1358, 1310, 1203, 1156, 1106, 1047, 859.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.28 (1H, s, -OH), 7.00 (1H, br. d, \( J = 10.0 \) Hz, \( H-2 \)), 6.92 (1H, s, \( H-8 \)), 6.62 (1H, d, \( J = 2.0 \) Hz, \( H-10 \)), 6.39 (1H, d, \( J = 2.0 \) Hz, \( H-12 \)), 6.01 (1H, dt, \( J = 10.0, 4.5 \) Hz, \( H-3 \)), 4.01 (3H, s, \( H-16 \)), 3.87 (3H, s, \( H-15 \)), 2.85 (2H, t, \( J = 8.0 \) Hz, \( H-5 \)), 2.33 (2H, tdd, \( J = 8.0, 4.5, 2.0 \) Hz, \( H-4 \)).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 157.8 (C-13), 157.7 (C-11), 149.1 (C-7), 137.6 (C-6), 136.5 (C-9), 126.4 (C-3), 122.1 (C-2), 116.4 (C-8), 115.7 (C-1), 110.1 (C-14), 99.7 (C-10), 97.4 (C-12), 56.5 (C-16), 55.7 (C-15), 28.9 (C-5), 23.5 (C-4).

\( m/z \) LRMS (ESI \(^+\)) 257.1 [M+H\(^+\)]; HRMS (ESI\(^+\)) 257.11722 ([M+Na]\(^+\), \( \text{C}_{16}\text{H}_{16}\text{O}_3\text{Na} \) requires 257.11727).

\((Z)-8-(3,5\text{-Dimethoxyphenyl})\text{-7-oxooct-2-enoic acid}\) (269)

\( \text{The enonic acid 255 (20.0 mg, 0.068 mmol) in EtOAc (10.0 mL) was degassed for 0.5 hours by purging nitrogen through the mixture. The mixture was irradiated with 265 nm light source at 0 °C for 1 hour. The solvent were removed \textit{in vacuo} and the crude mixture was purified by flash chromatography (20% to 40% EtOAc in petroleum ether) to give the title compound 269 in 15% yield (3.1 mg, 0.010 mmol).} \)
IR (neat) $v_{\text{max}}$ 2930, 1697, 1595, 1459, 1431, 1205, 1151, 1066, 830.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.36 (1H, t, $J = 2.0$ Hz, $H$-12), 6.34 (2H, d, $J = 2.0$ Hz, $H$-10), 6.27 (1H, dt, $J = 11.5$, 7.5 Hz, $H$-3), 5.79 (1H, dt, $J = 11.5$, 1.5 Hz, $H$-2), 3.77 (6H, s, $H$-13), 3.60 (2H, s, $H$-8), 2.61 (2H, tdd, $J = 7.5$, 7.5, 1.5 Hz, $H$-4), 2.50 (2H, t, $J = 7.5$ Hz, $H$-6), 7.41 (2H, app. qn, $J = 7.5$ Hz, $H$-5).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 208.1 ($C$-7), 170.4 ($C$-1), 161.3 ($C$-11), 152.2 ($C$-3), 136.7 ($C$-9), 119.8 ($C$-2), 107.8 ($C$-10), 99.4 ($C$-12), 55.7 ($C$-13), 50.9 ($C$-8), 41.3 ($C$-6), 28.7 ($C$-4), 23.0 ($C$-5).

$m/z$ LRMS (ESI $^+$) 315.1 [M+Na$^+$]; HRMS (ESI$^+$) 293.13835 ([M+H]$^+$, C$_{16}$H$_{20}$O$_3$Na requires 293.13839).

MP: 61-65 °C

(Z)-5-(2-(3,5-Dimethoxyphenyl)acetoxy)pent-2-enoic acid (279)

The enonic acid 278 (24.0 mg, 0.082 mmol) in EtOAc (10.0 mL) was degassed for 0.5 hours by purging nitrogen through the mixture. The mixture was irradiated with 265 nm light source at 0 °C for one hour. The solvent were removed in vacuo and the crude mixture was purified by flash chromatography (20% to 40% EtOAc in petroleum ether) to give the title 279 compound in 16% yield (3.9 mg, 0.013 mmol).

IR (neat) $v_{\text{max}}$ 2980, 2924, 1731, 1698, 1644, 1596, 1460, 1431, 1205, 1151, 1066, 831.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.43 (2H, d, \(J = 2.5\) Hz, \(H\)-9), 6.37 (1H, t, \(J = 2.5\) Hz, \(H\)-11), 6.31 (1H, dt, \(J = 11.5, 7.5\) Hz, \(H\)-3), 5.88 (1H, dt, \(J = 11.5, 2.0\) Hz, \(H\)-2), 4.22 (2H, t, \(J = 6.5\) Hz, \(H\)-5), 3.78 (6H, s, \(H\)-12), 3.55 (2H, s, \(H\)-7), 3.01 (2H, dtd, \(J = 7.0, 6.5, 1.5\) Hz, \(H\)-4).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 171.7 (\(C\)-6), 170.5 (\(C\)-1), 161.2 (\(C\)-10), 147.9 (\(C\)-3), 136.2 (\(C\)-8), 121.4 (\(C\)-2), 107.7 (\(C\)-9), 99.6 (\(C\)-11), 63.7 (\(C\)-5), 55.7 (\(C\)-12), 41.9 (\(C\)-7), 29.0 (\(C\)-4).

\(m/\ell\) LRMS (ESI \(+\)) 317.0. [M+Na\(^+\)]; HRMS (ESI\(^+\)) 295.11761 ([M+H\(^+\)]\(^+\), \(C_{15}H_{19}O_6\) requires 295.11774).

\((E)\)-5-((3-(tert-butoxy)-2-(3,5-dimethoxyphenyl)-3-oxopropanoyl)oxy)pent-2-enoic acid (270)

Freshly distilled diisopropylamine (0.338 mL, 2.40 mmol) in THF (1.0 mL) was deprotonated by adding dropwise a premixed solution of n-butyllithium (2.5 M in hexanes, 0.879 mL, 2.20 mmol) at 0 °C. The mixture was stirred for 30 minutes and cooled to -78°C. Aromatic ester 248 (500 mg, 2.00 mmol) in THF (3.0 mL) was added dropwise to the cooled solution and stirred for 1 hour. Boc\(_2\)O (479 mg, 2.20 mmol) was added dropwise to the reaction mixture and the reaction was slowly allowed to warm up to the ambient temperature during 3 hours. The reaction mixture was quenched by diluting with water and Et\(_2\)O (50 mL). The organic layer was separated and washed with water and brine, dried over Na\(_2\)SO\(_4\) and filtered. The solvent
was removed *in vacuo* and the crude product was purified by column chromatography (5 to 10% EtOAc in petroleum ether). The purification still gave us a mixture of starting material and the product which was used in the subsequent step. The mixture was dissolved in CH$_2$Cl$_2$ (20 mL) and before acrylic acid (0.736 mL, 11.12 mmol) was added. The volume of the mixture was reduced to 10 mL during 30 minutes of degassing the mixture by bubbling with nitrogen. Grubbs 2nd generation catalyst (86.0 mg, 0.10 mmol) was added and the solution was bubbled with nitrogen for further 5 minutes. The reaction was gently heated at reflux for further 3 hours. The solvent was removed *in vacuo* and the product was purified by column chromatography (20 to 50% EtOAc in petroleum ether) to give the product 270 in 13% yield over two steps (102 mg, 0.259 mmol).

**IR (neat)** $\nu_{\text{max}}$ 3007, 2935, 2841, 1721, 1655, 1596, 1459, 1369, 1293, 1152, 1061, 928, 844.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.98 (1H, dt, $J = 15.5$, 7.0 Hz, $H$-3), 6.51 (2H, d, $J = 2.0$ Hz, $H$-12), 6.41 (1H, t, $J = 2.0$ Hz, $H$-14), 5.85 (1H, dt, $J = 15.5$, 1.5 Hz, $H$-2), 4.46 (1H, s, $H$-7), 4.31-4.24 (2H, m, $H$-5), 3.77 (6H, s, $H$-15), 2.57 (2H, dtd, $J = 7.0$, 6.5, 2.0 Hz, $H$-4), 1.45 (9H, s, $H$-10).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.5 (C-1), 168.5 (C-6), 167.5 (C-8), 161.0 (C-13), 147.0 (C-3), 135.1 (C-11), 123.3 (C-2), 107.6 (C-12), 100.6 (C-14), 82.9 (C-9), 63.5 (C-5), 59.2 (C-7), 55.6 (C-15), 31.6 (C-4), 28.1 (C-10).

$m/z$ LRMS (ESI$^+$) 417.2. [M+Na$^+$]$^+$; HRMS (ESI$^+$) 417.1520 ([M+Na$^+$]$^+$, C$_{20}$H$_{26}$O$_8$Na requires 417.15180).
1-(But-3-en-1-yl) 3-isopropyl 2-(3,5-dimethoxyphenyl)malonate (272)

KHMDS (0.5 M, in toluene, 4.39 mL, 2.20 mmol) was added dropwise to a solution of 255 (500 mg, 2.0 mmol) in THF (4.0 mL) at −78 °C. The solution was stirred for 10 minutes and then was allowed to warm up to 0 °C. The solution was cooled to −78 °C and isopropyl chloroformate (1M in toluene, 2.20 mL, 2.20 mmol) was added dropwise. The mixture was allowed slowly warm up to 0 °C then it was stirred for further 3 hours. The reaction was quenched by pouring into saturated aqueous NH₄Cl. The mixture was extracted with CH₂Cl₂ (80 ml) and the combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The crude product was concentrated in vacuo and the product was purified by flash chromatography (5 to 20% of EtOAc in petroleum ether). Purification gave the title compound as a colourless oil in 24% yield (159 mg, 0.473 mmol) and a side product 256 as a colourless oil in 27% yield (223 mg, 0.528 mmol).

IR (neat) ν max 3080, 2982, 2938, 2939, 2839, 1730, 1596, 1460, 1291, 1204, 1102, 990, 915, 834.

¹H NMR (500 MHz, CDCl₃) δ 6.43 (2H, d, J = 2.0 Hz, H-11), 6.42 (1H, t, J = 2.0 Hz, H-13), 5.74 (1H, ddt, J = 17.5, 10.5, 7.0 Hz, H-2), 5.11-5.02 (3H, m, H-1,8), 4.50 (1H, s, H-6), 4.25-4.15 (2H, m, H-4), 3.78 (6H, s, H-14), 2.42-2.36 (2H, m, H-3), 1.28 (3H, d, J = 6.5 Hz, H-9) 1.24 (3H, d, J = 6.5 Hz, H-9’).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.3 (C-5), 167.7 (C-7), 161.0 (C-12), 135.0 (C-10), 133.9 (C-2), 117.8 (C-1), 107.7 (C-11), 100.7 (C-13), 69.8 (C-8), 65.1 (C-4), 58.5 (C-14), 55.7 (C-14), 33.2 (C-3), 21.9 (C-9), 21.9 (C-9').

$m/z$ LRMS (ESI +) 359.2 [M+Na$^+$]+; HRMS (ESI$^+$) 337.16455 ([M+H$^+$]+, C$_{18}$H$_{25}$O$_6$ requires 337.16455).

**Isopropyl(E)-3-(but-3-en-1-yloxy)-2-(3,5-dimethoxyphenyl)-3-((isopropoxycarbonyl)oxy) acrylate (273)**

IR (neat) $\nu_{\max}$ 3080, 2983, 2938, 2839, 1750, 1643, 1559, 1458, 1270, 1155, 1095, 1037, 911, 835.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.77 (2H, d, $J = 2.5$ Hz, H-16), 6.43 (1H, t, $J = 2.5$ Hz, H-14), 5.71 (1H, ddt, $J = 17.0$, 10.5, 6.5 Hz, H-2), 5.12 (1H, sept, $J = 6.5$ Hz, H-8), 5.07-4.99 (2H, m, H-1), 4.93 (1H, qn, $J = 6.5$ Hz, H-11), 4.29-4.19 (2H, m, H-4), 3.78 (6H, s, H-17), 2.40-2.34 (2H, m, H-3), 1.36 (6H, dd, $J = 6.5$, 2.0 Hz, H-12), 1.28 (3H, d, $J = 6.0$ Hz, H-9') 1.24 (3H, d, $J = 6.0$ Hz, H-9').

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 166.0 (C-5), 165.2 (C-7), 161.0 (C-15), 153.5 (C-10), 136.0 (C-13), 133.7 (C-2), 117.7 (C-1), 104.4 (C-16), 101.7 (C-14), 83.9 (C-6), 73.6 (C-11), 70.9 (C-8), 65.9 (C-4), 55.8 (C-17), 33.0 (C-3), 22.0 (C-12), 21.8 (C-9), 21.7 (C-9').
According to a modified literature procedure, triphenylphosphine (1.59 g, 6.05 mmol) and Pd(OAc)₂ (383 mg, 1.44 mmol) were added to an oven dried flask followed by 2-iodobenzyl alcohol (3.37 g, 14.4 mmol) and tributyl(vinyl)stannane (5.21 mL, 17.3 mmol). The mixture was purged with argon for 10 minutes and heated up to 110 °C. After 15 hours the mixture was filtered through celite and eluted methanol. The solvents were evaporated and the crude product was purified by flash chromatography (20% Et₂O in petroleum ether) to afford the title compound as a white solid (1.87 g, 97%).

¹H NMR (400 MHz, CDCl₃) δ 7.51 (1H, dd, J = 7.0, 2.5 Hz), 7.33 (1H, dd, J = 7.0, 2.0 Hz), 7.30-7.23 (2H, m), 7.02 (1H, dd, J = 17.5, 10.5 Hz), 5.67 (1H, dd, J = 17.5, 1.5 Hz), 5.36 (1H, dd, J = 10.5, 1.0 Hz), 4.72 (2H, s), 1.83 (1H, br. s).

¹³C NMR (101 MHz, CDCl₃) δ 137.5, 136.6, 133.7, 128.3, 128.1, 127.9, 125.9, 116.4, 63.3

Data in accordance with the literature.¹²¹
1-(Bromomethyl)-2-vinylbenzene (280)

According to a modified literature procedure, a solution of (2-vinylphenyl)methanol 279 (431 mg, 3.21 mmol) in CH₂Cl₂ (16 mL) was cooled to 0 °C. Triphenylphosphine (657 mg, 3.69 mmol) was added and the mixture was stirred for 10 minutes. NBS (657 mg, 3.69 mmol) was added portionwise over 5 minutes and the reaction was stirred for a further 20 minutes. The mixture was concentrated in vacuo and purification by flash chromatography (0 to 2.5% EtOAc in petrol) gave the title 280 compound (536 mg, 84%).

¹H NMR (400 MHz, CDCl₃) δ 7.55-7.50 (1H, app. m, H-6), 7.35-7.28 (2H, m, H-3,5), 7.27-7.22 (1H, app. m, H-4), 7.09 (1H, dd, J = 18.0, 12.0 Hz, H-8), 5.76 (1H, dd, J = 17.0, 1.0 Hz, H-9), 5.44 (1H, dd, J = 12.0, 1.0 Hz, H-9’), 4.57 (2H, s, H-1).

¹³C NMR (101 MHz, CDCl₃) δ 137.6 (C-2), 134.9 (C-7), 133.7 (C-8), 130.6 (C-3), 129.5 (C-6), 128.5 (C-4), 126.8 (C-5), 117.4 (C-9), 32.0 (C-1).

m/z LRMS (ESI⁺) 196.0 [M⁺];

Data in accordance with the literature¹¹⁴.
1-(2-Vinylphenyl)oct-7-ene-2,6-diol (282)

\[
\begin{align*}
&\text{TBAF (0.5 M in THF) (1.60 mL, 0.798 mmol) was added dropwise to a solution of compound 293 (192 mg, 0.532 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 1 hour at ambient temperature and quenched by addition of saturated aqueous NH}_4\text{Cl. The mixture was extracted by CH}_2\text{Cl}_2, the combined organic layers were washed with brine, dried over Na}_2\text{SO}_4 and filtered. The solvents were evaporated }in\text{ vacuo and the crude mixture was purified by flash chromatography (40\% EtOAc in petrol ether) to afford the title 295 compound as a yellow viscous liquid (71\%, 93 mg, 0.378 mmol).} \\
&\text{IR (neat)} \nu_{\text{max}} 3339, 3084, 2980, 2933, 1483, 1451, 1420, 1340, 1127, 1077, 989, 916, 853, 773, 700. \\
&^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.53–7.49 (1H, m, H-12), 7.25–7.21 (2H, m, H-10,13), 7.18–7.15 (1H, m, H-11), 7.00 (1H, dd, } J = 17.5, 11.0, \text{ Hz, H-15), 5.87 (1H, ddd, } J = 17.0, 10.5, 6.5 \text{ Hz, H-2), 5.65 (1H, dd, } J = 17.5, 1.0 \text{ Hz, H-16), 5.31 (1H, br. d, } J = 10.0 \text{ Hz, H-16}), 5.22 (1H, ddd, } J = 17.0, 3.0, 1.5, \text{ H-1), 5.10 (1H, ddd, } J = 10.5, 2.5, 1.5, \text{ H-1), 4.11-4.10 (1H, m, H-3), 3.81 (1H, m, H-7), 2.91 (1H, dd, } J = 14.0, 4.5, \text{ H-8), 2.74 (1H, dd, } J = 14.0, 8.5 \text{ Hz, H-8}, 1.65-1.50 (6H, m, H-4,5,6). \\
&^{13}\text{C NMR (126 MHz, CDCl}_3) \delta 141.5 (C-2), 141.5 (C-2), 137.5 (C-9), 136.3 (C-14), 135.0 (C-15), 131.1 (C-14), 128.2 (C-10), 127.3 (C-13), 126.5 (C-11), 116.3 (C-16), 115.1 (C-1), 115.0 (C-1), 73.5 (C-3), 73.4 (C-3), 41.6 (C-8), 41.6 (C-8), 37.2 (C-6/4), 37.1 (C-6/4), 37.1 (C-6/4), 37.0 (C-6/4), 21.9 (C-5), 21.8 (C-5). \\
m/z LRMS (ESI \text{ +}) 296.2 [M+Na]^+; \text{ HRMS (ESI\text{ +}) 296.15120 ([M+Na]^+).C}_{16}\text{H}_{22}\text{O}_2\text{Na requires } 269.15122).
Freshly distilled diisopropylamine (0.710 mL, 5.0 mmol) in THF (2.0 mL) was deprotonated by adding dropwise a premixed solution of n-butyllithium (2.5 M in hexanes, 2.02 mL, 5.04 mmol) at 0 °C. The mixture was stirred for 30 minutes and tributyltin hydride (1.47 g, 1.36 mmol) was added dropwise and the solution was cooled to −78 °C. After stirring for 10 minutes 5,6-Dihydro-2H-pyran-2-one (0.395 mL, 4.13 mmol, 90 w/w) in THF (3.5 mL) was added dropwise to the solution. After further 10 minutes methyl acrylate (0.990 mL, 11.0 mmol) was added and the reaction mixture was stirred for 17 hours. The reaction was quenched by adding saturated aqueous NH₄Cl. The mixture was extracted with Et₂O (100 mL) and the combined organic layers were dried over MgSO₄ and filtered and the solvents were removed in vacuo. The crude product was dissolved in benzene (8 ml) and was dropwise added into a refluxing solution of lead tetraacetate (2.03 g, 4.58 mmol) and the mixture was heated at reflux for 2 hours. The mixture was cooled to ambient temperature and water (70 ml) was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (Et₂O 20% in petroleum ether) to give the title compounds as a colourless viscous oils: 304 in 20% yield (148 mg, 0.550 mmol) and 303 in 10% yield (74 mg, 0.275 mmol) and a mixture of both compounds 304 and 303 in 22% yield (163 mg, 0.605 mmol).

¹H NMR (500 MHz, CDCl₃) δ 5.45-5.37 (1H, m, H-4), 5.36-5.28 (1H, m, H-3), 4.93-4.85 (1H, m, H-1), 4.01-3.93 (1H, m, H-1’), 3.72 (3H, s, H-11), 3.71 (3H, s, H-13), 3.55 (1H, dd, J = 9.0, 2.0 Hz, H-8), 2.97-2.90 (1H, m, H-6), 2.70-2.51 (2H, m, H-5,7), 2-38-2.18 (4H, m, H-7’,2,5’).
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.9 (C-10), 171.6 (C-9), 170.0 (C-12), 132.1 (C-4), 130.4 (C-3), 65.4 (C-1), 53.1 (C-13), 52.2 (C-11), 50.2 (C-8), 42.7 (C-6), 34.9 (C-2), 33.7 (C-5), 29.6 (C-7).

\(m/z\) LRMS (ESI \(^+\)) 293.1 [M+Na]\(^+\)

Data in accordance with the literature\(^{115}\).

dimethyl (3R,5S,E)-2-oxo-3,4,5,6,9,10-hexahydro-2H-oxecine-3,5-dicarboxylate (291)

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.36-5.27 (1H, m, H-3), 5.23-5.14 (1H, m, H-4), 4.84-4.75 (1H, m, H-1), 4.09-4.01 (1H, m, H-1’), 3.70 (3H, s, H-11), 3.67 (3H, s, H-13), 3.20 (2H, d, H-8), 2.66-2.55 (2H, m, H-5,7), 2.48-2.40 (1H, m, H-6), 2.30-2.25 (2H, m, H-2), 2.25-2.08 (2H, m, H-5’,7’).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 175.3 (C-12), 171.2 (C-9), 169.6 (C-10), 133.0 (C-4), 130.1 (C-3), 65.3 (C-1), 53.4 (C-8), 53.2 (C-11), 52.3 (C-13), 46.4 (C-6), 36.5 (C-5), 34.3 (C-2), 31.6 (C-7).

\(m/z\) LRMS (ESI \(^+\)) 293.1 [M+Na]\(^+\)

Data in accordance with the literature\(^{115}\).
References


42. Zhong, G.; Lu, M.; Zhu, D.; Chua, P. J.; Tan, B. *Processes of enantioselectively forming an aminoxo compound and an 1,2-oxazine compound* **2014**.

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7 Appendix

7.2 HPLC traces

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No.19
K₂PO₄ (s), 48 h, Benzene, RT e.r. 96:4 Yield: 11 %

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123 (10 mol%)  
KF (aq), 48 h.  
e.r. 95:5  
Yield: 85%  
d.r. 1.7:1

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119 (10 mol%)  
KF (aq), 48 h.  
e.r. 95:5  
Yield: 85%  
(NMR-yield)  
d.r. 1.3:1
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9.2 X-ray Crystallography Data

X-ray Crystallographic Data and Structure Refinement for 97, 012JDJ14

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Formula weight 238.28
Temperature 100 K
Wavelength 0.68890 Å
Crystal system Triclinic
Space group P -1
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$b = 9.1956$ Å, $\beta = 75.037^\circ$
$c = 15.8478$ Å, $\gamma = 84.235^\circ$
Volume 1229.43 Å$^3$
Z,Z’ Z: 4 Z’: 0
Density (calculated) 1.287 Mg m$^{-3}$
Absorption coefficient 0.095 mm$^{-1}$
$F(000)$ 512.0
Crystal size 0.01 x 0.04 x 0.20 mm$^3$
Theta range for data collection 2.197° to 27.623°
Reflections collected 17628
Independent reflections 5530
Absorption correction Multi-scan
Refinement method Full-matrix least squares on $F^2$
Goodness-of-fit on $F^2$ 0.990
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