Transannular cascade approaches to diterpene analogues

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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

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

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Abbreviations

Å	Ångströms
Ac	acetyl
ADP	anisotropic displacement parameters
AH/HA	*denotes a generic Brønsted acid*
aq	aqueous
Ar	*denotes a generic aromatic system*
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
^{i}Bu	*iso*-butyl
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
°C	degrees Celsius
cat	catalytic/catalyst
CCD	charge-coupled device
CCDC	Cambridge Crystallographic Data Centre
CI	Chemical Ionization
cm	centimetre
COSY	^{1}H-^{1}H correlation spectroscopy
CRL	Chemistry Research Laboratory
cryo	cryogenic
CSA	camphorsulfonic acid
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
dec.	decomposed
DEPT	distortionless enhancement by polarization transfer

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethylpyridin-4-amine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
E	*denotes a generic electrophile*
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
eq	equivalents
ESI	electrospray ionization
ESPT	excited state proton transfer
Et	Ethyl
FI	field ionization
FTIR	Fourier-transform infra-red spectroscopy
h	hours
HA/AH	*denotes a generic Brønsted acid*
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSAB	hard and soft acids and bases
HSQC	heteronuclear single-quantum correlation spectroscopy
hν	*denotes irradiation with either visible light or UV photons*
i	*iso*
IPA	*iso*-propanol
ISC	intersystem crossing
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
K	Kelvin
kcal	kilocalorie

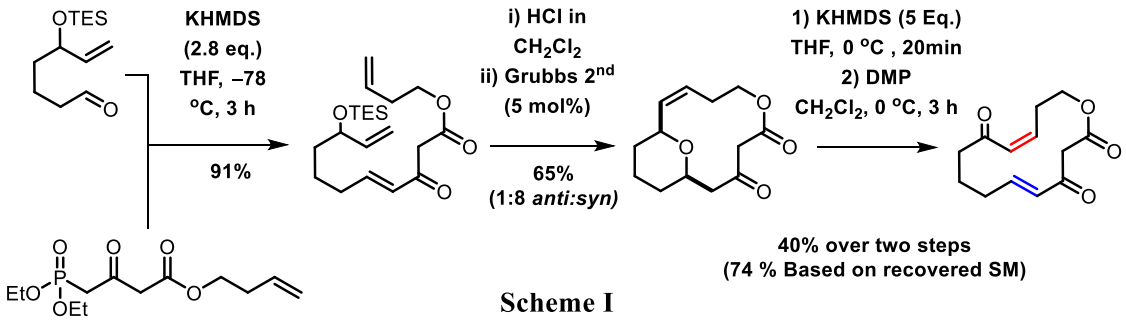
λ	wavelength
LA	*denotes a generic Lewis acid*
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	low-resolution mass spectrometry
M	moles per litre
m	*meta*-
maj	major enantiomer
mAU	milli-absorbance unit
mbar	millibar
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
Me	Methyl
MeCN	acetonitrile
MHz	megahertz
min	minutes/minor enantiomer
mL	millilitres
mm	millimetres
mol	moles
MS	molecular sieves/mass spectrometry
Ms	mesyl
µL	microlitres
NBP	*N*-bromophthalimide
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
nm	nanometres
NMR	nuclear magnetic resonance
o	*ortho*-
^{i}Pr	isopropyl
petrol 40-60	petroleum ether, boiling point range 40-60 °C
Ph	phenyl

PhEt	ethyl benzene
PhH	benzene
PhMe	toluene
PhSH	benzene thiol
PhEt	ethyl benzene
PMB	4-methoxybenzyl ether
PPA	polyphosphoric acid
ppm	parts per million
PTC	phase-transfer catalysis
***p*-TSA**	p-toluenesulfonic acid
quant.	quantitative
Quat	quaternary
R	*denotes a generic substituent*
r.t.	room temperature
rac	racemization/racemic
S	Selectivity factor
s	seconds
semi-prep	semi-preparative
SENS	*denotes a generic sensitizer*
t	tertiary
T1	longitudinal relaxation time
TBAB	tetra-*n*-butylammonium bromide
TBDPS	*tert*-Butyldiphenylsilyl
TBME	methyl tert-butyl ether
TET	triplet energy transfer
Tf	triflyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

UV	ultraviolet
vs.	versus
w/w	ratio of weights
wt	weight

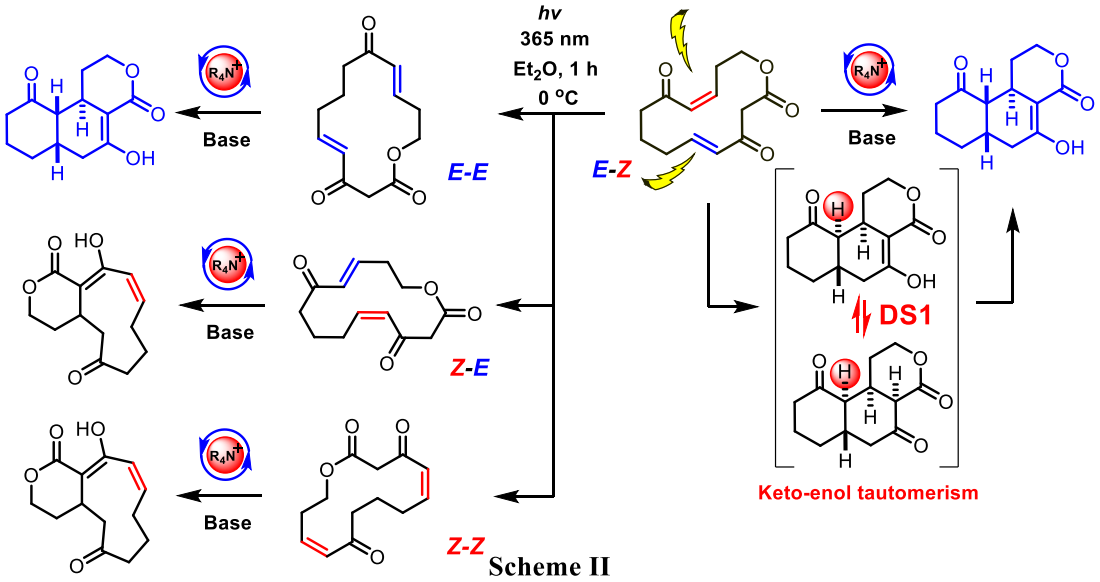
Abstract

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**).



Scheme I

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**).



Scheme II

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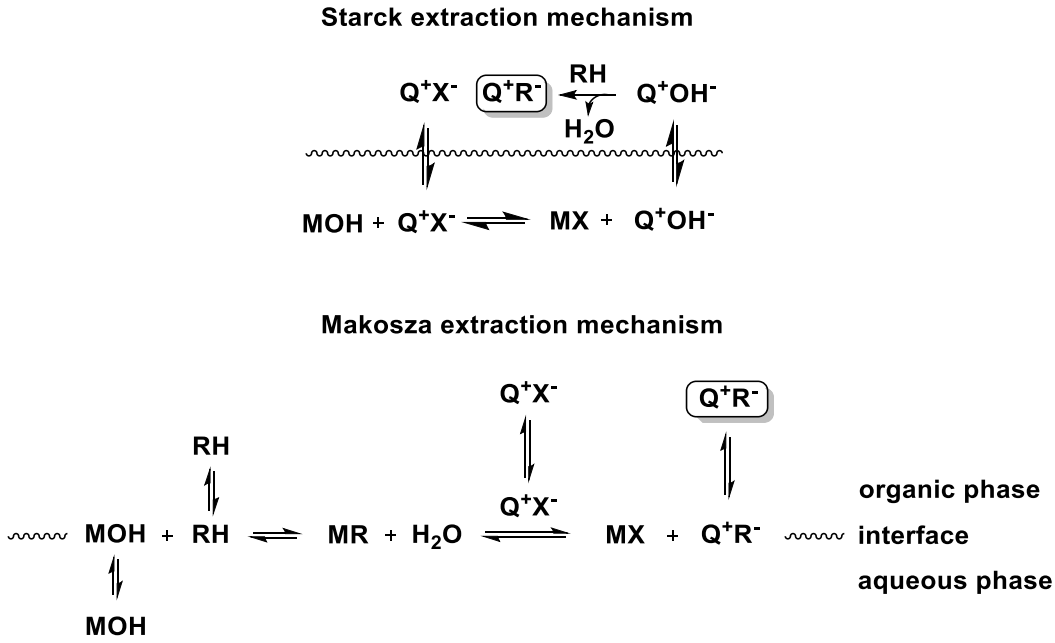
1. Introduction

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,[1] crown ethers[2] and polyethers[3] have also been used.

The first example of phase-transfer catalysis was published in 1946 by Rueggeberg *et al.*[4] where benzylethylammonium chloride was made *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.[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 (**Scheme 1**).[6]

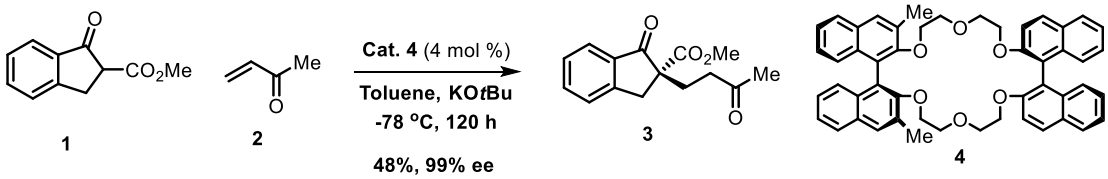


Scheme 1*:Stark extraction mechanism and Makosza extraction mechanism.*

Because the complex biphasic systems are difficult to examine the absolute mechanism of the phase-transfer catalysis remains unclear[7]. Despite this, phase-transfer catalysis is a versatile and valuable method for many organic transformations and is widely used in many industrial processes.[8]

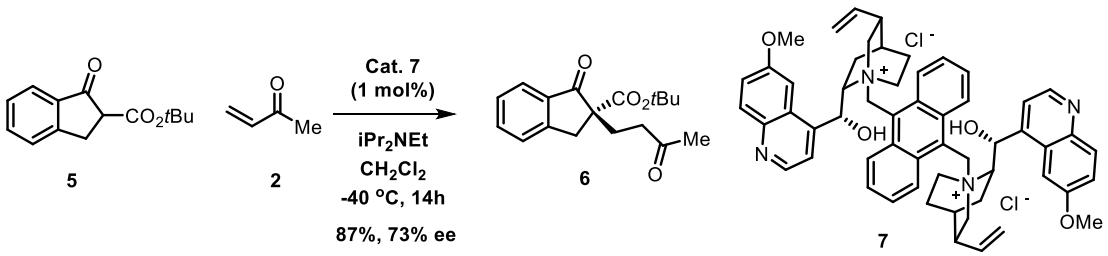
1.2 Asymmetric phase-transfer catalysed Michael additions of 1,3-dicarbonyls

Cram and Sogah[9] reported a phase-transfer catalysed method for the enantioselective Michael-addition of aromatic β-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.



***Scheme 2**: Enantioselective Michael-addition of β-ketoesters catalysed by chiral crown complexes.*[9]

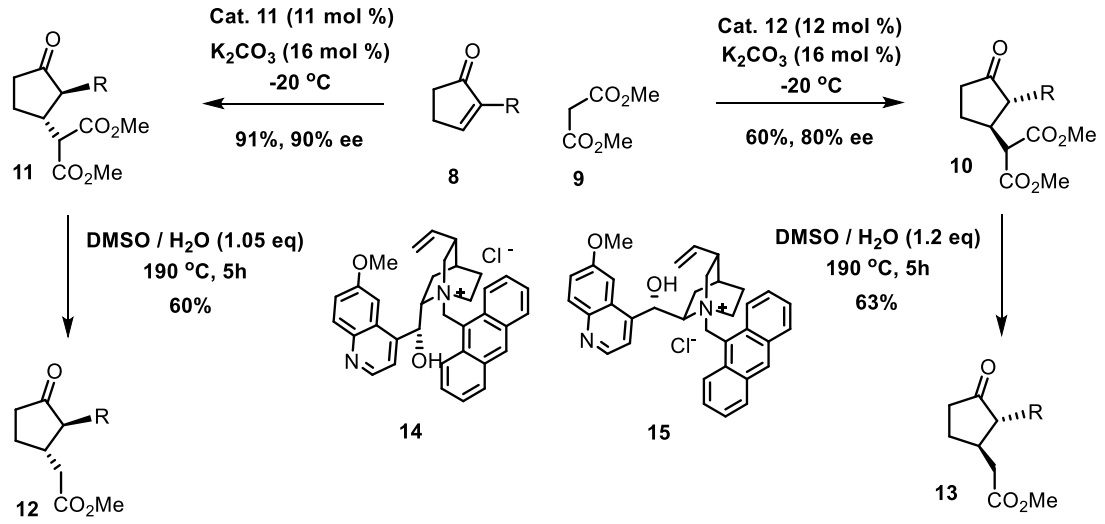
A similar phase-transfer catalysed Michael-addition was published by Najera *at al.* where high enantioselectivity was obtained by using dimeric catalyst **7** and isopropylethyl amine as a base **(Scheme 3).**[10]



***Scheme 3**: Enantioselective Michael-addition of β-ketoesters catalysed by dimeric catalyst **7**.* [10]

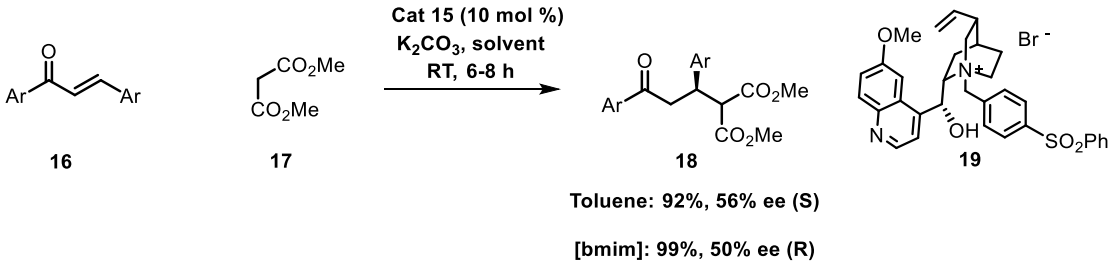
Perrard *et al.*[11] used an asymmetric phase-transfer catalysed reaction in the synthesis of both enantiomers of methyl dihydrojasmonate **12** and **13 (Scheme 2)**. In the enantioselective addition of dimethylmalonate to a α-substituted cyclopentenone **8**, pseudoenantiomers of chiral *cinchona* 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[12] that provided unracemised methyl dihydrojasmonates **12** and **13**.



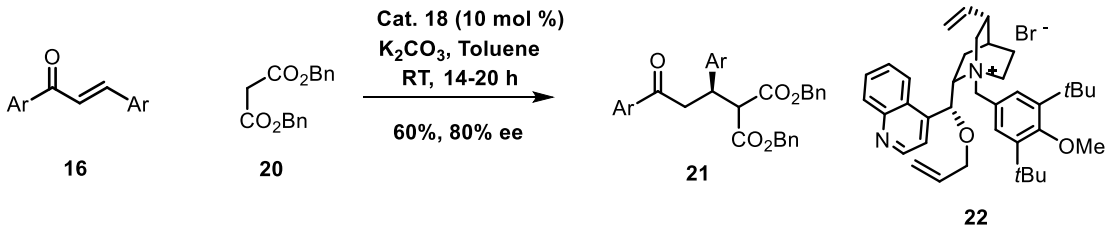
***Scheme 4**: Synthesis of methyl dihydrojasmonates via asymmetric phase-transfer catalysed Michael-reaction.[11]*

A Cinchona derived phase-transfer catalyst has also been used alongside with dimethylmalonates in the asymmetric Michael-addition by Dere *et al.*[13] (**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.



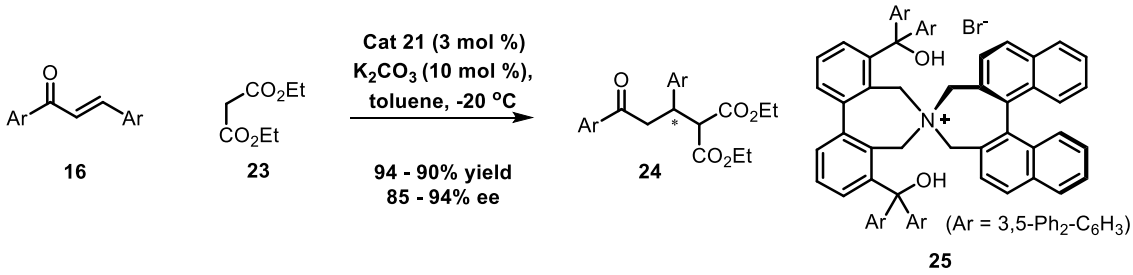
***Scheme 5**: Phase-transfer catalysed asymmetric Michael-addition in ionic liquids.[13]*

Kim *et al.*[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** (**Scheme 6**). Crown ethers have also been used as catalysts in highly enantioselective fashion in similar reactions to chalcones with ethylmalonates by Bako *et al.*[15]



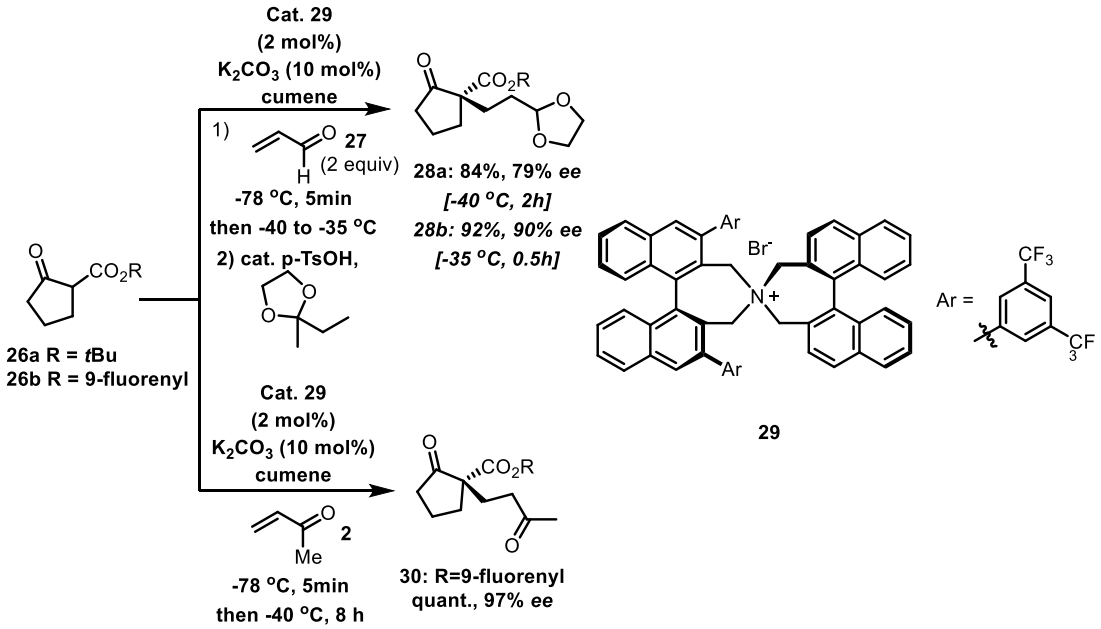
***Scheme 6**: Phase-transfer catalysed Michael-addition of dibenzylmalonates.*[15]

Additionally, Maruoka's group has published highly enantioselective Michael-addition malonate/chalcone system (**Scheme 7**).[16] *N*-spiro C_2-symmetric chiral quaternary ammonium bromide **25** was used as a catalyst with variety of chalcone derivatives in reaction with diethylmalonate **23**.



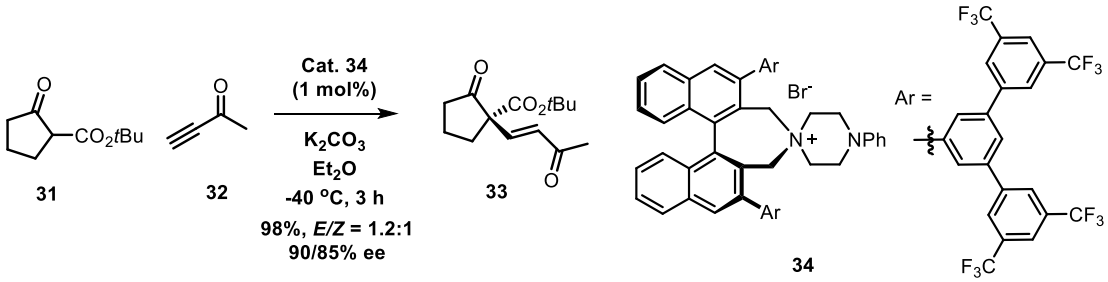
***Scheme 7**: Phase-transfer catalysed diethylmalonate addition to chalcones.*[16]

Another example of the work of the Maruoka's group is a phase-transfer catalysed addition of 5-membered β-keto esters **26a** and **26b** to acrolein **27** and methyl vinyl ketone **2** in high yields and enantioselectivities (**Scheme 8**).[17]



***Scheme 8**: Asymmetric phase-transfer catalysed addition β-keto ester addition to acrolein and methyl vinyl ketone.*[17]

The same group has also been able to use the same 5-membered β-keto esters in enenatioselective, 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***).*[18]

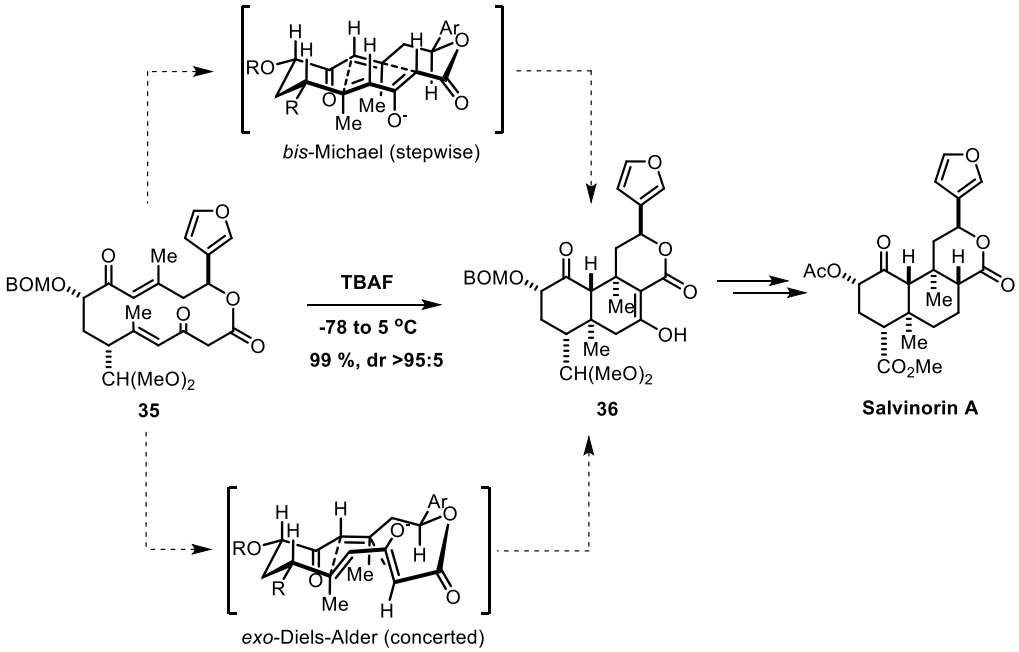


***Scheme 9**: Asymmetric phase-transfer catalysed addition β-keto ester addition to acetylenic ketone.*[18]

Maruoka's research group has been heavily involved in the modern asymmetric phase-transfer catalysis research. The group is also behind the catalysts used in the two previous examples (**Scheme 7**, **Scheme 8**).[19] This type of *N*-spiro C_2-symmetric chiral quaternary ammonium catalyst is widly used in phase-transfer catalysis research.

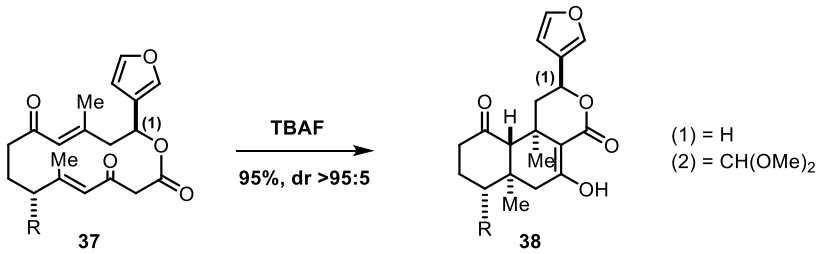
1.3 Transannular Michael-Michael cascades

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**).[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.



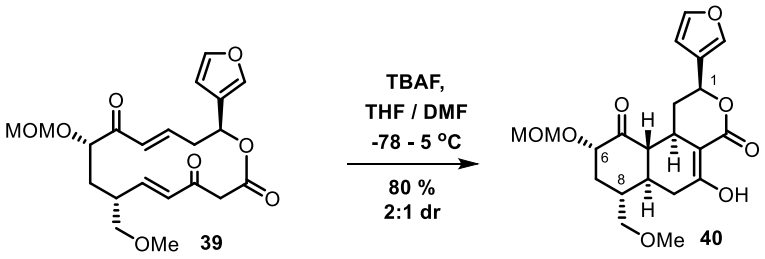
***Scheme 10**: Transannular cyclisation in the total synthesis of Salvinorin A.*[20]

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 diastereocontrol and furthermore the dimethyl acetal seemed to reinforce the diastereoselection.



***Scheme 11**: Cyclisation of the model systems.*[20]

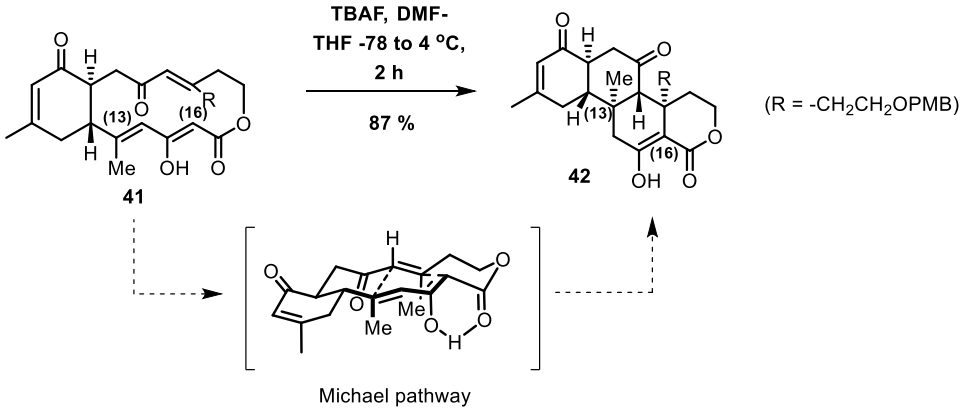
A recent study published in 2017 by Sherwood *et al.*[21] examined a small range of Salvinorin A type κ-opioid ligands (**Scheme 12**). The group synthesised a *E,E*-bis-enone **39** in 11 steps, very similar to the precursor for the cascade used by Evans group. This cascade product was further modified 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 transitionstate (**Scheme 10**).



***Scheme 12**: Transannular cascade by Sherwood* et al.[21]

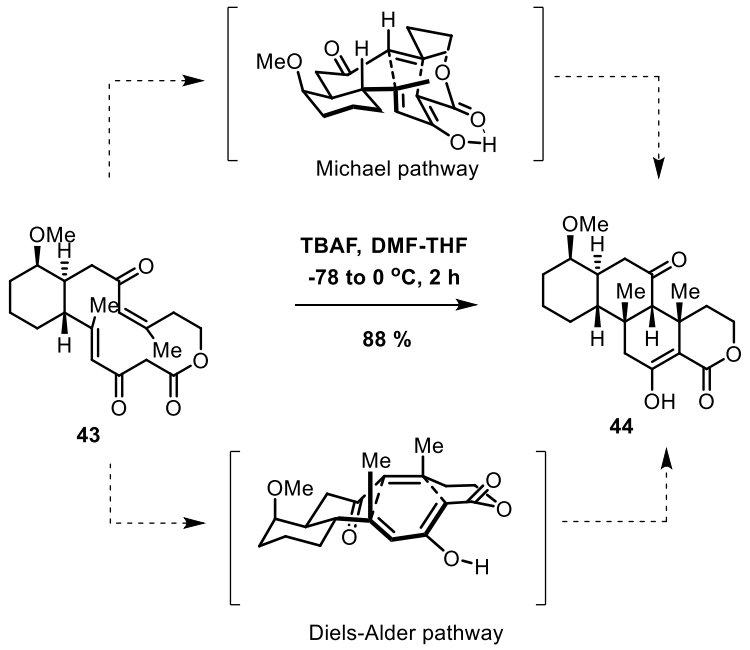
Xue *et al*.[22] used a similar kind of cyclisation system in the synthesis towards natural product Norzoanthamine. The synthesis relies on a base promoted cyclisation of *β,β*-disubstituted *E,E*-bis-enone **41** (**Scheme 13**). This transannular process is highly stereoselective and only the product **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.



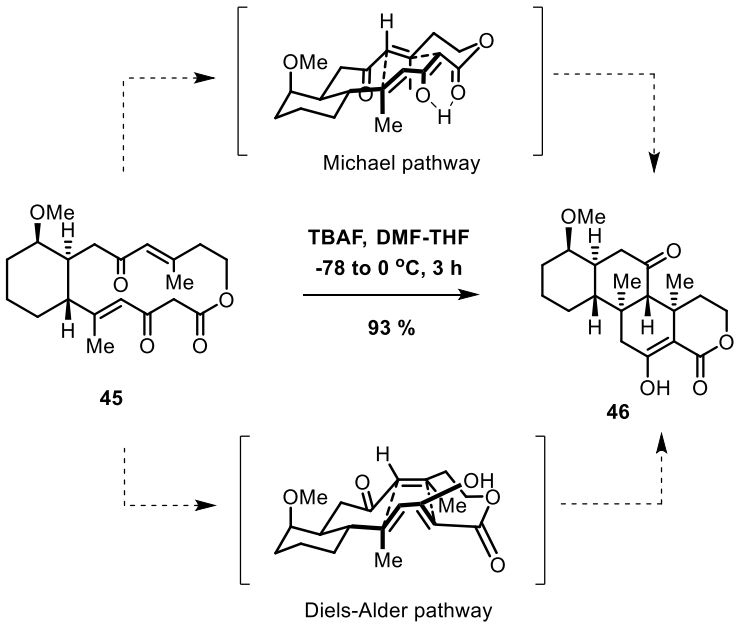
***Scheme 13**: Cyclisation of bis-enone **41** used in the synthesis towards Norzoanthamine.*[22]

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**.



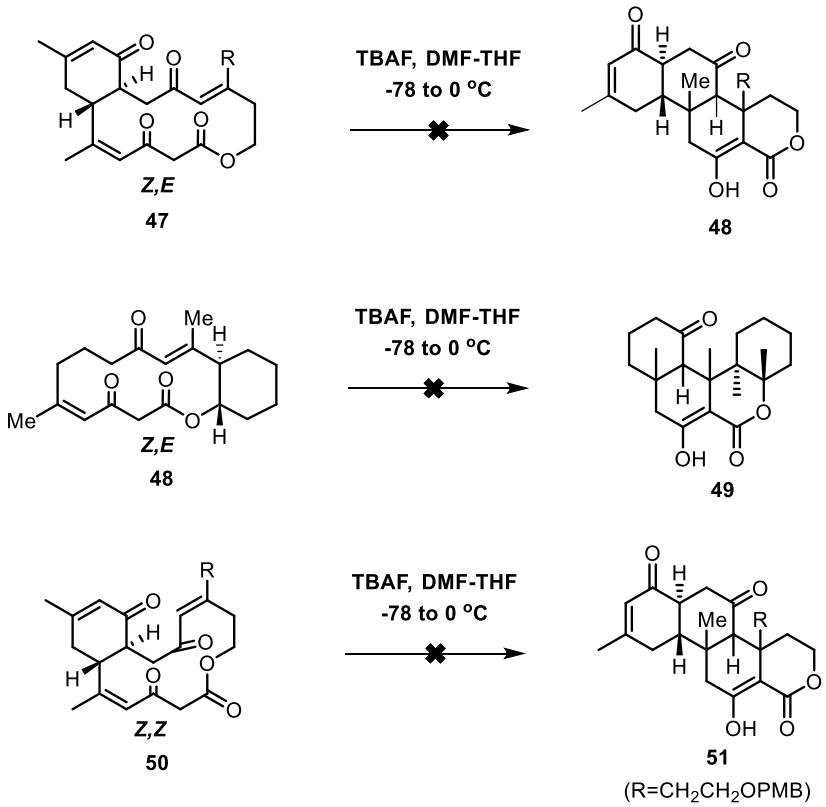
***Scheme 14**: Base promoted cyclisation of the E,Z-1,7-bis-enone **43**.*[23]

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 β-methyl substituents on the enones ended on the same side of the formed fused ring-system, while the α-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.



*Scheme 15: Cylisation of E,E-bis-enone **32** under basic conditions.*[23]

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.

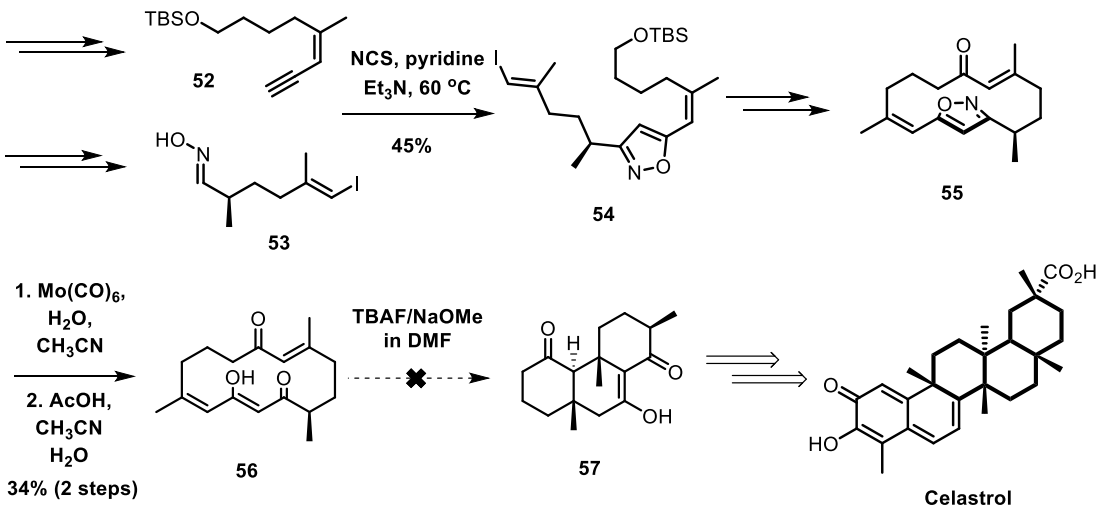


***Scheme 16**: Cyclisation attempts of* Z,E-*bis-enones **47** and **48** and* Z,Z-*bis-enone **50**.*[23]

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*.[24] 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**).[25] The core was built by using 1,3-dipolar cycloaddition[26] 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

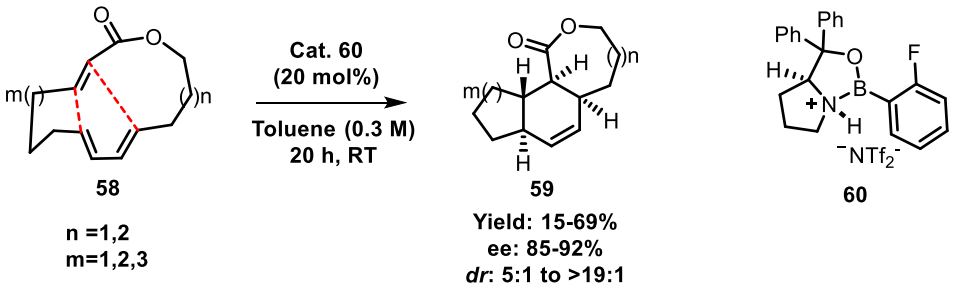
the previous attempts with *Z,E*-bis-enones the all-carbon macrocycle did not provide any cyclised product **57** when treated with TBAF or NaOMe at various temperatures.



***Scheme 17**: Synthesis of 1,3-diketone containing* Z,E*-bisenone **44**.*[25]

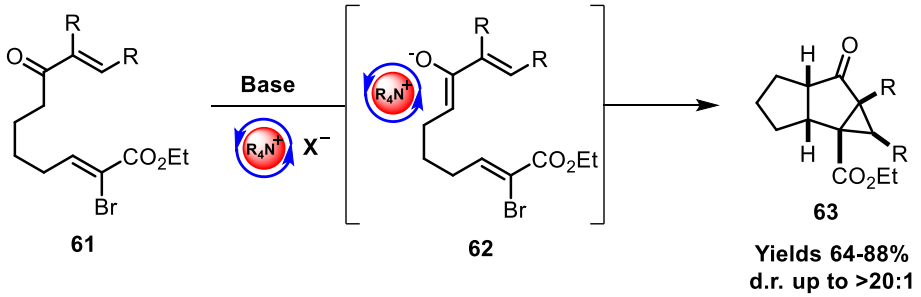
1.4 Project background

To date there are few stereoselective transannular processes that rely on a chiral catalyst rather than a premade chiral ring system.[27-29] As far as we know there are only four methods using a substoichiometric amount of the catalyst in transannular asymmetric transformations.[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**).[33]



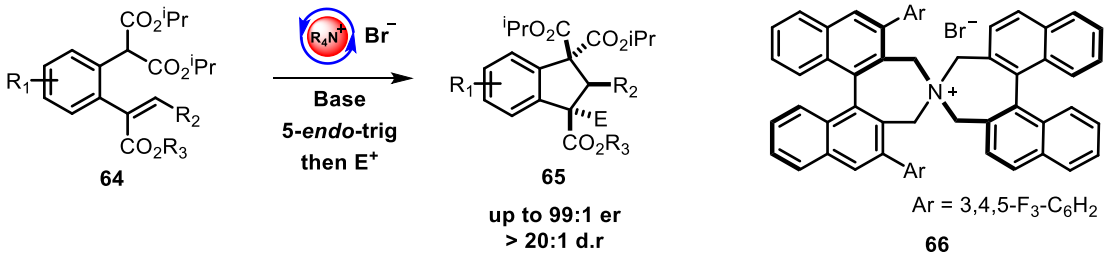
***Scheme 18**: Enantioselective catalytic transannular Diels-Alder reaction.*[33]

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



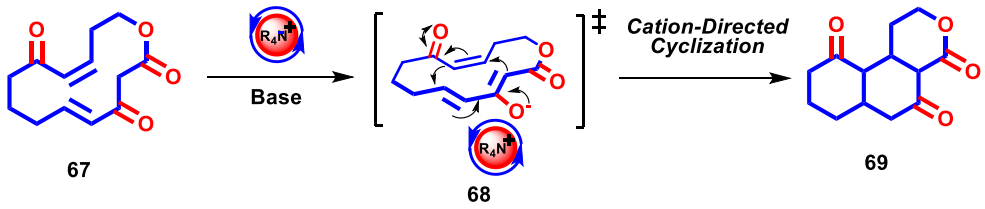
***Scheme 19**:Phase-transfer catalysed Michael-Michael-cyclopropanation.*[34]

Furthermore, Smith group has worked on a 5-*endo-trig* cyclisation forming indenes.[35] This quaternary chiral ammonium salt **64** catalysed cyclisation forms three new stereocenters in excellent diastereoselectivity and enantioselectivity under basic conditions (**Scheme 20**).



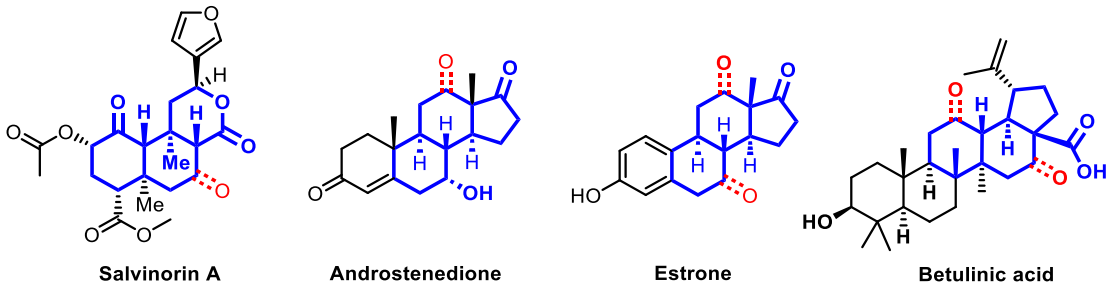
***Scheme 20**: Phase-transfer catalysed 4-endo-trig cyclisation.*[35]

We postulated that the phase-transfer catalysed cyclisations could be extended to transannular scaffolds in building fused polycyclic ring-systems. Scaffold **67** was chosen to be the target of the investigation because of similarity to macrocyclic bis-enone-system **35** that has been used in the total synthesis of Salvinorin A[20] (**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**.*

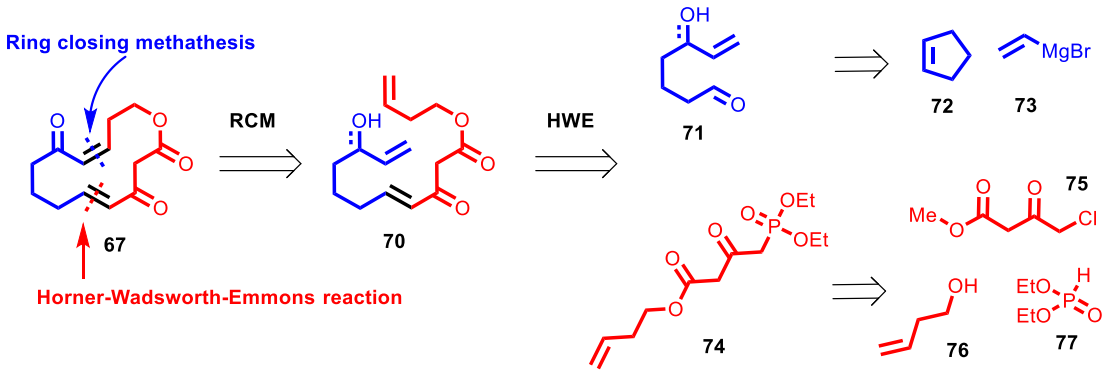
The ability to introduce several stereocentres in an asymmetric cascade fashion is particularly attractive as an efficient means to prepare complex natural product-like scaffolds (**Scheme 22**). In addition to Salvinorin A, we postulated that the methodology would be valuable in building steroid structures 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 signifigcant diterpenes.*

2. Synthesis of the macrolactone core

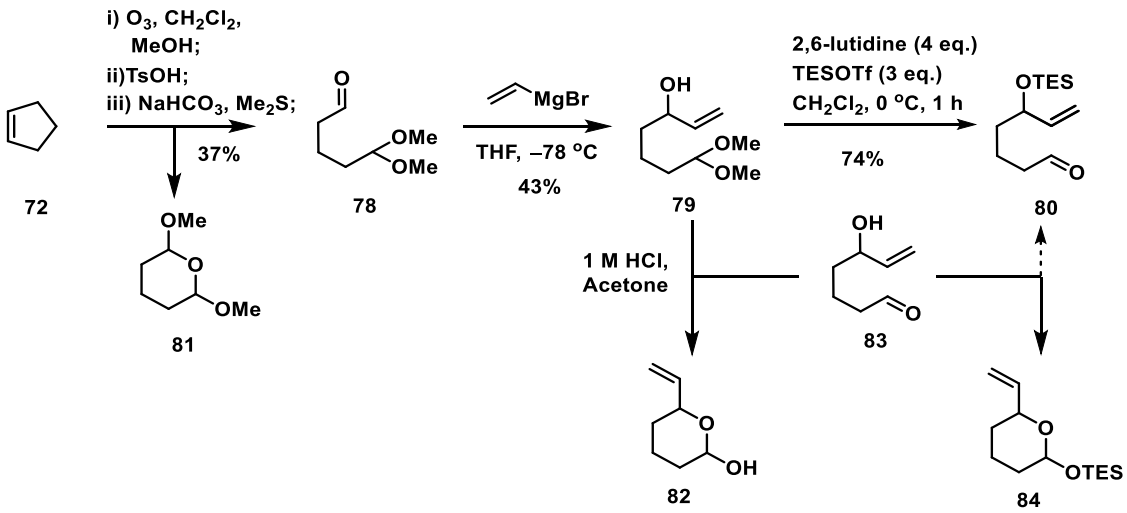
We chose model substrate **67** on which to base our investigations, which we envisaged could be prepared *via* two key disconnections: ring closing metathesis[36] and a Horner-Wadsworth-Emmons (HWE) reaction (**Scheme 23**).[37]



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

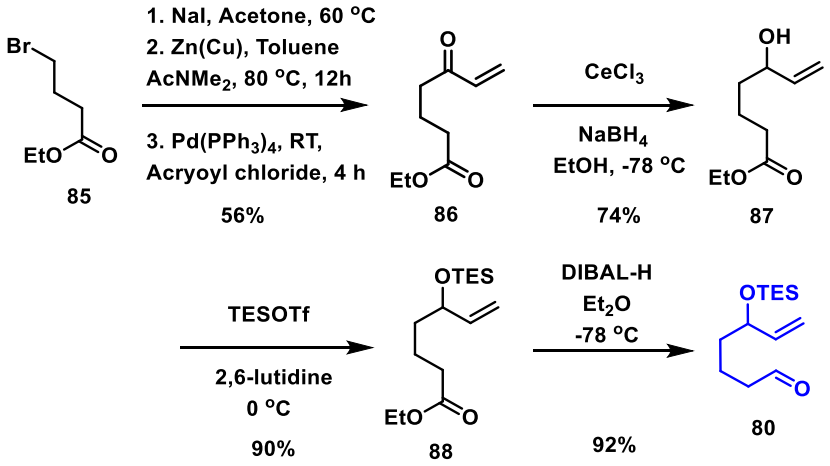
2.1 Synthesis of the aldehyde 71

Synthesis of the macrolactone **67** began with a protective ozonolysis[38] of cyclopentene **72** which gave monoacetylated aldehyde **78** in 37% yield. In the literature common yield for the ozonolysis reaction is 42-48%.[39,40,41,42] One of the reasons for a low yield is probably a cyclic acetal **81** sideproduct formed in the reaction.[43] This was followed by a Grignard reaction to form acetylated allylic alcohol **79** in 43% yield.[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 triethylsilyl trifluoromethanesulfonate and 2,6-lutidine was used to produce the aldehyde **80** in good 74% yield (**Scheme 24**).[45]



***Scheme 24**: Synthesis of protected allylic alcohol aldehyde **80**.*

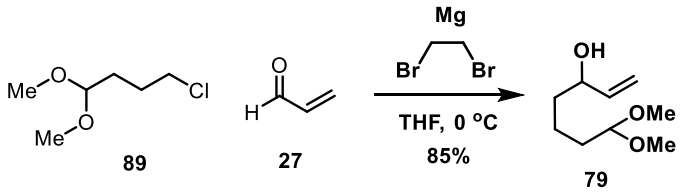
The yields of the ozonolysis of cyclopentadiene[46] and subsequent Grignard reaction[47] were too low to produce sufficient amounts of the protected aldehyde **80** for HWE-reaction. Therefore, we chose to investigate a second approach for the synthesis (**Scheme 25**). This route relied on the synthesis of the ethyl 5-hydroxyhept-6-enoate **86**, previously synthesised by Fischer *et al.*[48] the protection of the allylic alcohol **87**, and finally reduction of the ester to give aldehyde **80**. The synthesis starts with a Negishi-type coupling reaction between acrylic acid and commercially available ethyl 4-bromobutanoate.[49] 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.[48] 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.[50]



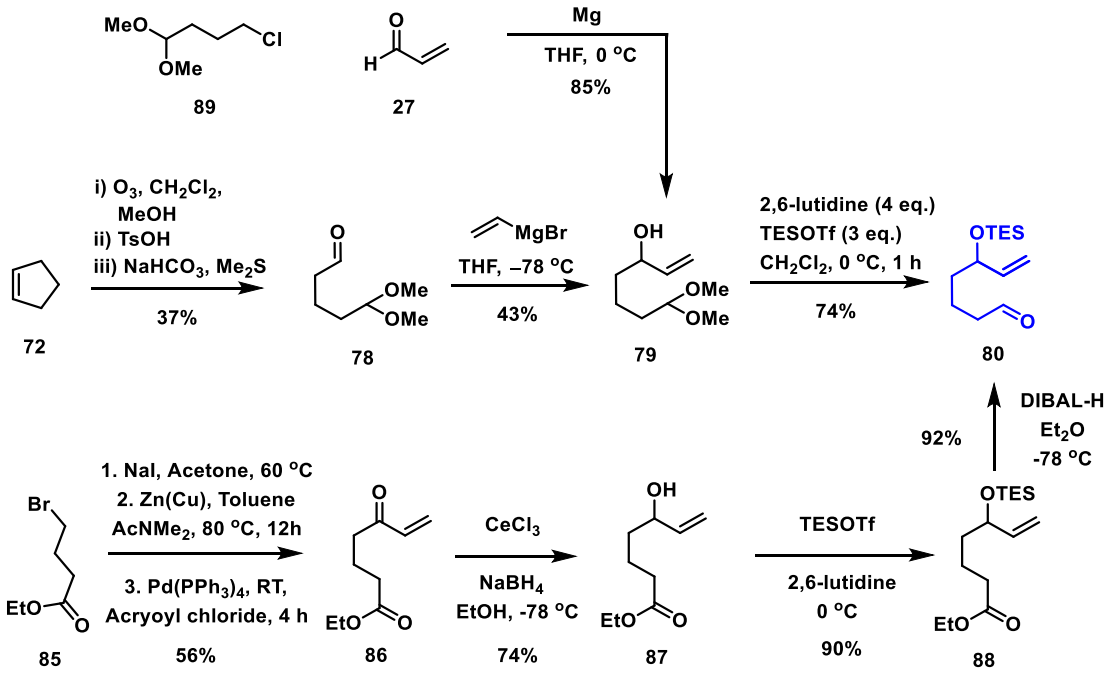
***Scheme 25**: Second generation synthesis of the aldehyde **80**.*

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.*[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*

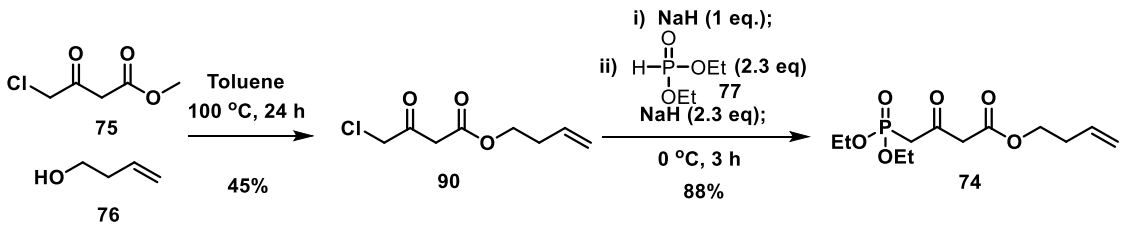


***Scheme 27**: Synthesis of the aldehyde **67**.*

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**).

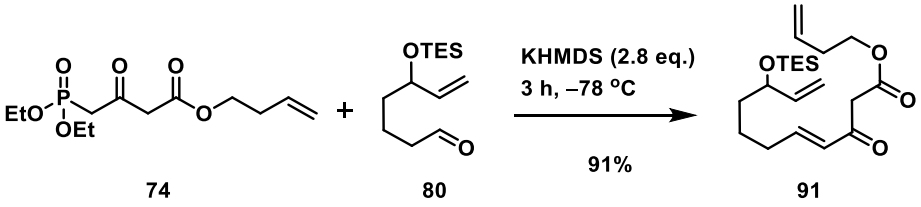
2.2 Synthesis of the phosphonate 74

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[52] 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.



***Scheme 28**: Synthesis of the phoshonate **80**.*

Phosphonate **74** was made by using a Michaelis-Becker reaction,[53] starting from diethyl phosphite and the α-chloro compound **90** (**Scheme 28**).[54] First attempts of the reaction was 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**).

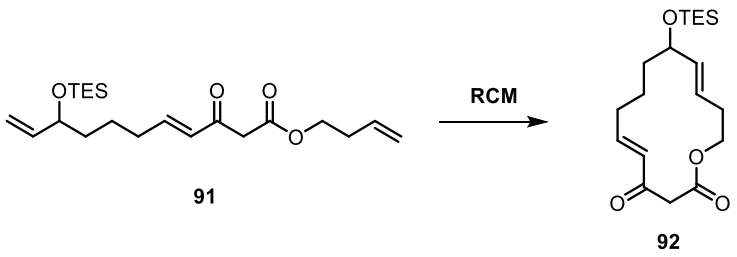


***Scheme 29**: HWE reaction to form the E-enone structure **91**.*

The *trans*-selective HWE reaction through an double anionic phosphonate[54,55,56] 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 1st generation catalyst,[24] in CH_2Cl_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 2nd 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 1st or Grubbs 2nd generation catalyst gave the desired macrocycle **92** Hoveyda-Grubbs 2nd 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).



91 92

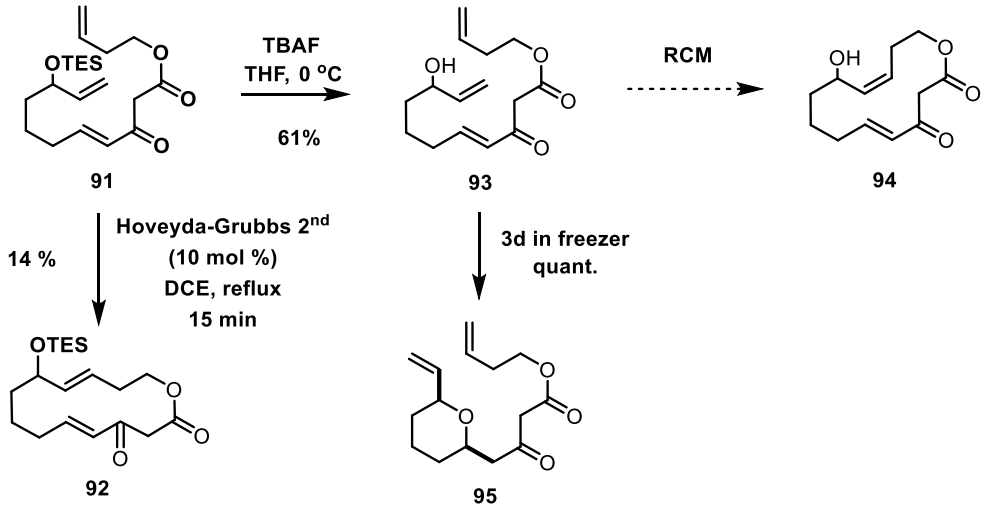
Ent.	Catalyst	Conc. (M)	Time (h)	Solvent	Temp.	Additive	Yield
1	Grubbs 1st	0.005	24	CH_2Cl_2	Reflux	-	-
2	Grubbs 1st	0.005	1	Toluene	Reflux	-	-
3	Grubbs 2nd	0.005	24	Toluene	Reflux	-	-
4	Grubbs 2nd	0.005	1	CH_2Cl_2	Reflux	2,6-dichloro-1,4-benzoquinone	-
5	HG 2nd	0.005	1	CH_2Cl_2	Reflux	2,6-dichloro-1,4-benzoquinone	-
6	HG 2nd	0.005	1	CH_2Cl_2	Reflux	Triphenylphosphine oxide	-
7	HG 2nd	0.003	0.25	CH_2Cl_2	Reflux	-	14%
8	HG 2nd	0.003	0.25	CH_2Cl_2	Reflux	$Ti(OiPr)_4$	7%

*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.[64] The bulkiness of the formed type I olefin with the nearby TES-group, also present in the starting material, makes in 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.

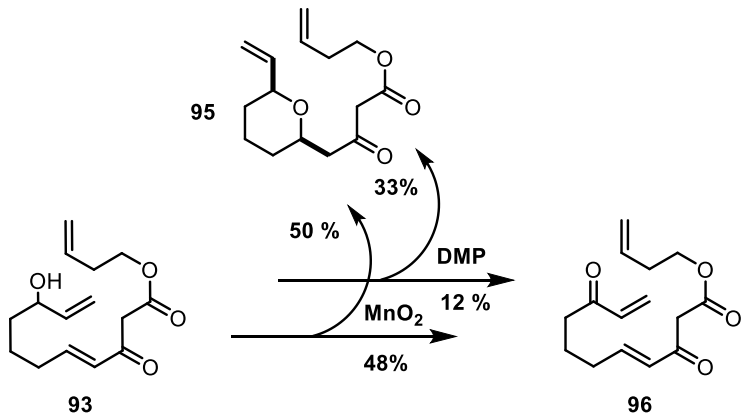
Since the Ring-closing metathesis of **91** did not produce sufficient yields the next plan was to deprotect the allylic alcohol before the RCM, to decrease the bulkiness of the olefin and to direct the first addition of a catalyst to this allylic alcohol olefin. Deprotection of the alcohol with tetrabutylammonium 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 ºC (**Scheme 30**).



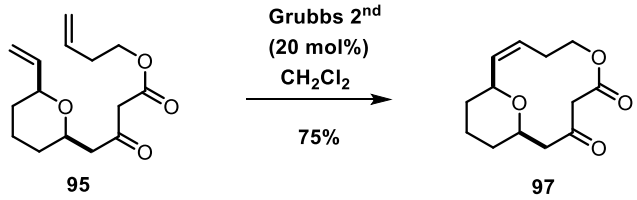
***Scheme 30**: RCM and deprotection of compounds **93**.*

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[65] and a MnO_2 oxidation[66] 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**).



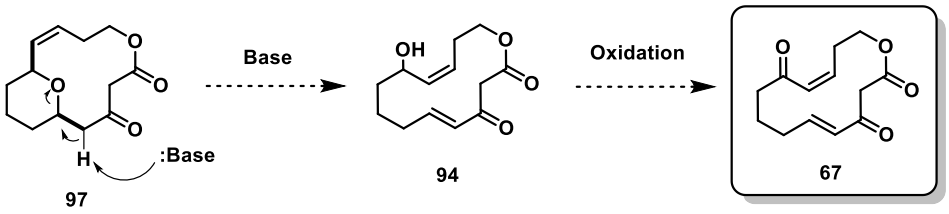
***Scheme 31**: Oxidations of the allylic alcohol **93**.*

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**.*

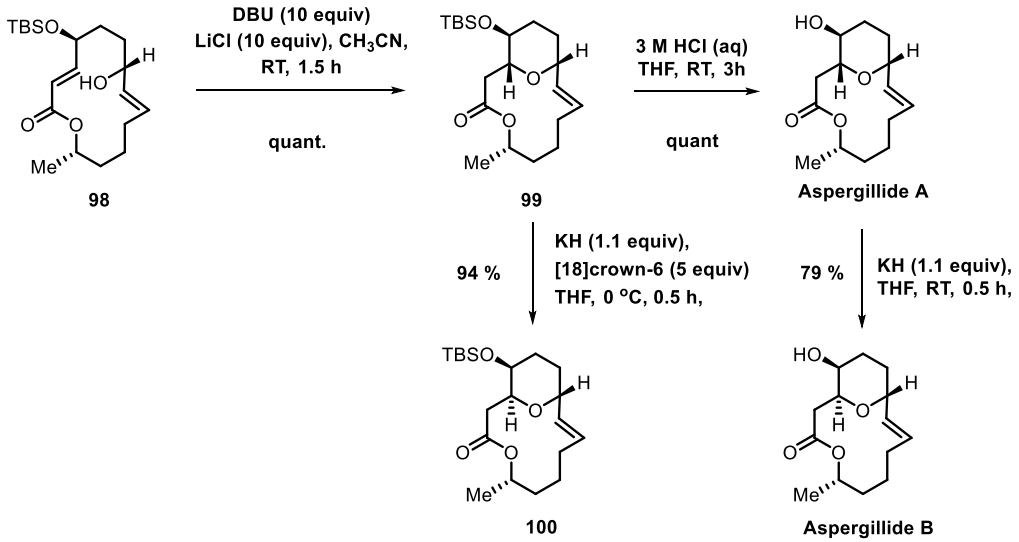
Exploiting natural reactivity of free alcohol **93** to form oxy-Michael product **95** we postulated that as the oxy-Michael reaction is generally reversible, we may be able to utilise the oxy-Michael adduct and reveal the allylic alcohol **94** after RCM via a retro-oxy-Michael reaction. Furthermore, 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**.*

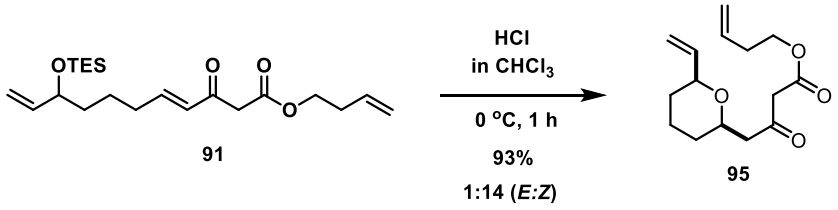
Kanematsu *et al*. has used a transannular Oxy-Michael-reaction in the synthesis of the natural product Aspergillide A (**Scheme 34**).[67] The system closely resembles of our macrocycle scaffold. Since Kanematsu *et al.* could isolate the free alcohol **98** we postulated that in our system, which has 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]

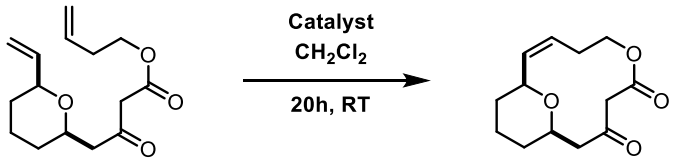
In our system, under basic TBAF deprotection conditions of the TES-protected alcohol **91** we could not observe any oxy-Michael product **95** (**Scheme 30**). Basic conditions could prevent the possible oxy-Michael reaction by enolization of the RCM product **97** that could be more acidic than the 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 CH_2Cl_2 (**table 2**, entries 3-6). Grubbs 2nd generation catalyst (70% yield) and the Hoveyda-Grubbs 2nd 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.



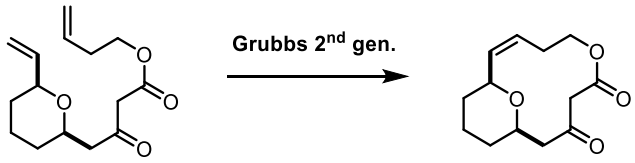
95 97

Entry	Catalyst	Cat. loading	Conc.	mass	Temp.	Yield
1	Grubbs 2nd	20 mol%	0.005 M	20 mg	RT	75%
2	Grubbs 2nd	20 mol%	0.005 M	66 mg	RT	59%
3	Hoveyda-Grubbs 2nd	5 mol%	0.003 M	0.1 g	RT	69%
4	Grubbs 2nd	5 mol%	0.003 M	0.1 g	RT	70%
5	Grubbs 1st	5 mol%	0.003 M	0.1 g	RT	29%
6	Grubbs 3rd	5 mol%	0.003 M	0.1 g	RT	9%
7	Grubbs 2nd	10 mol%	0.003 M	0.1 g	RT	56%

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

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 CH_2Cl_2 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[68]. 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 CH_2Cl_2 purchased from Sigma-Aldrich was used, the yield of the reaction dropped to 47% and when the CH_2Cl_2 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 comercial CH_2Cl_2. 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 CH_2Cl_2 (**Table 3**, entries 6 & 7). These solvents again were straight from the bottle and it is possible that degassing was insufficient.



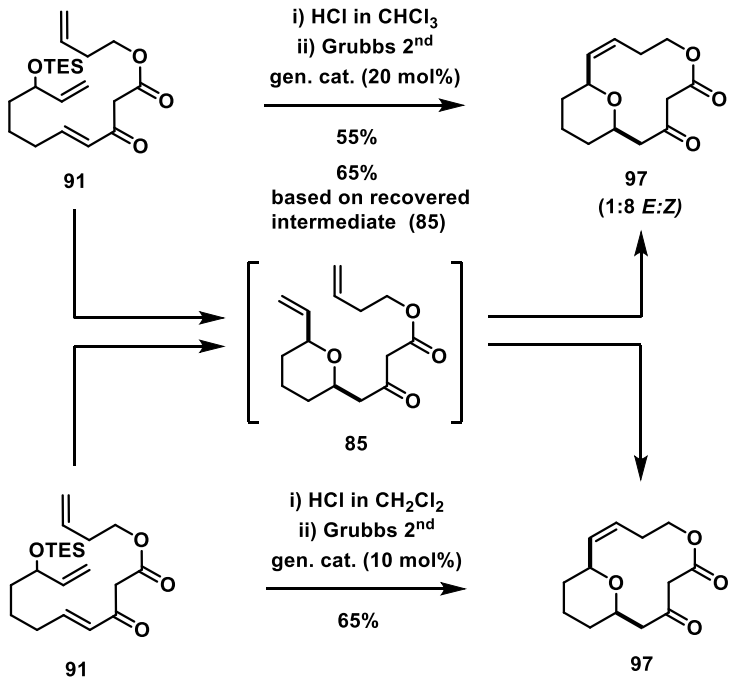
95 97

Entry	Catalyst (5 mol%)	Conc.	mass	Temp.	Additives / notes	Yield
1	Grubbs 2nd	0.003 M	0.1 g	Reflux		72%
2	Grubbs 2nd	0.003 M	0.1 g	RT	Benzoquinone	71%
3	Grubbs 2nd	0.003 M	0.1 g	RT	Purification by activated carbon	66%
4	Grubbs 2nd	0.003 M	0.1 g	RT	Stills	71%
5	Grubbs 2nd	0.003 M	0.1 g	RT	Solvent from a bottle	47%
6	Grubbs 2nd	0.003 M	0.1 g	RT	In toluene	59%
7	Grubbs 2nd	0.003 M	0.1 g	RT	In chloroform	46%

***Table 3**: Optimisation of the RCM reaction of the oxy-Michael product **95** with Grubbs 2nd generation catalyst.*

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%.



***Scheme 36**: One-pot reaction combining the deprotection, Oxy-Michael reaction and the RCM reaction.*

When the one-pot reaction was done in CH_2Cl_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 2nd 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**)

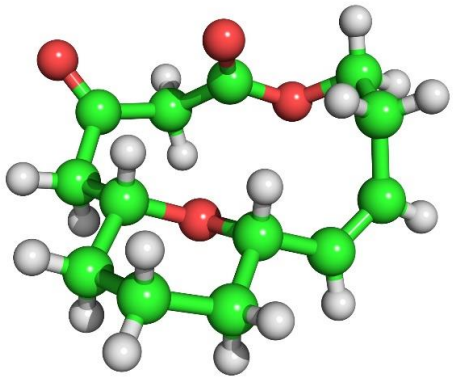
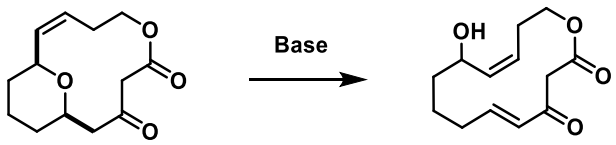


***Figure 1**: X-ray structure of the RCM product **97**.*

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.



97 **94**

Entry	Base[a]	Solvent	Temp (°C)	Yield
1	Cs_2CO_3	PhMe	RT to Reflux	N.R.
2	TBAF (4 eq.)	THF	RT	N.R.
3	DBU	THF	RT	N.R.
4	*t*-BuOK	THF	0 °C	N.R.
5	LDA (2.2 eq.)	THF	–78 °C	N.R.
6	KHMDS	THF	-78 to RT	20%

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

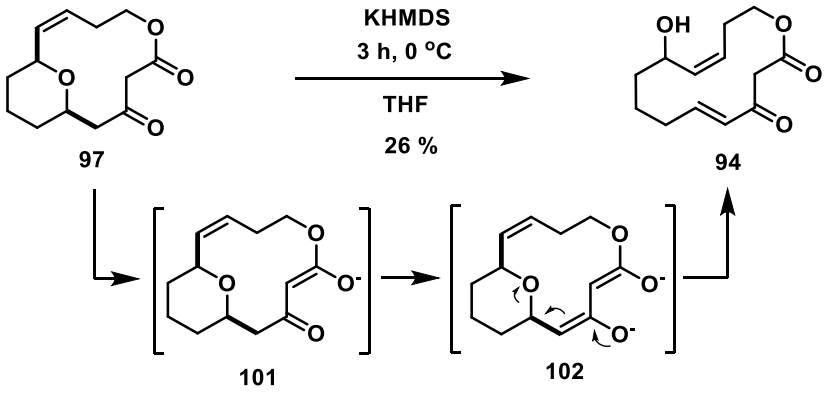
With weak bases no reactivity was observed (

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 ^{1}H-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 (^{1}H-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.

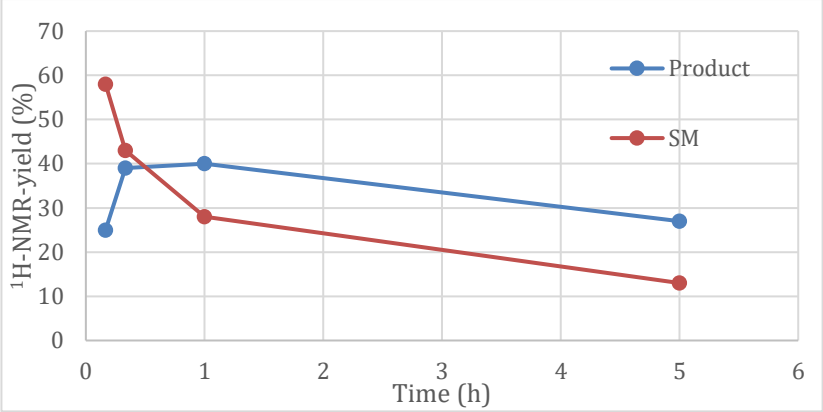
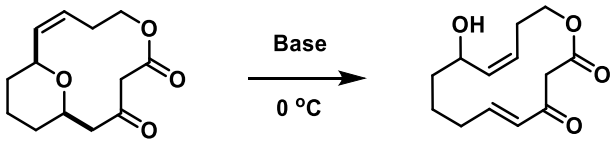


***Table 5**: Retro-Oxy-Michael reaction, ^{1}H-NMR-yield of the starting material and the product*

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_2O 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.

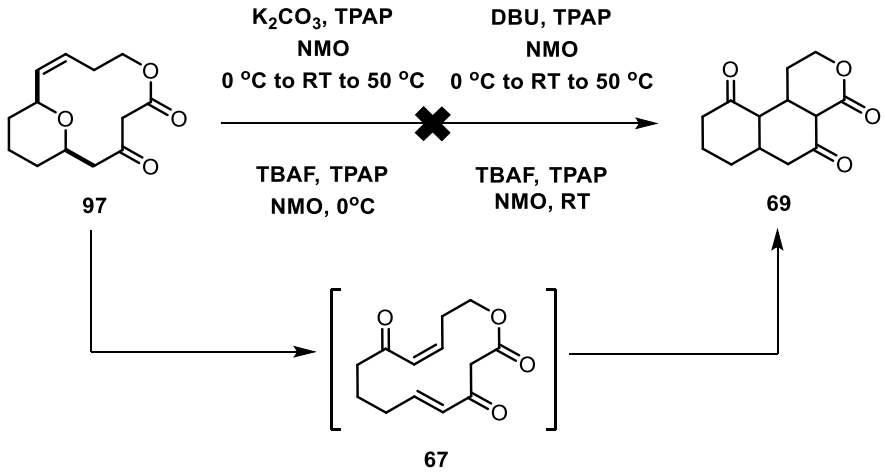


97 **94**

Entry	Base	Solvent	Time (min)	SM (^{1}H-NMR yield %)	Yield (^{1}H-NMR yield (%))
1	KHMDS	THF	20	43	39
2	KHMDS	Et_2O	20	-	N.R.
3	KHMDS	DMF	20	53	12
4	KHMDS	Toluene	20	21	36
5	LiHMDS	THF	40	93	3

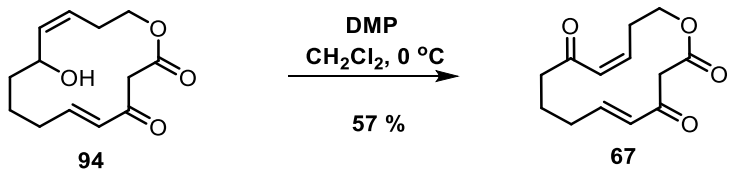
***Table 6**: Retro-oxy-Michael reaction with different solvents and bases.*

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.



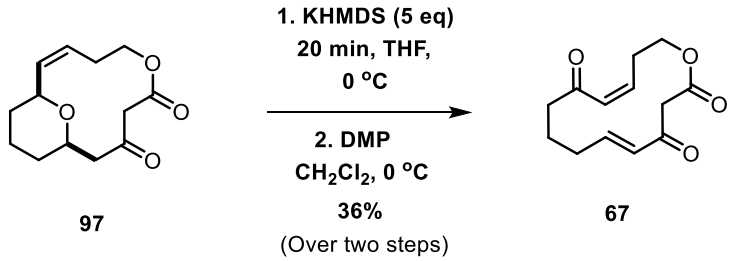
***Scheme 38**: Combined Retro-Oxy-Michael, Oxidation and the transannular cascade.*

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**).



***Scheme 39**: Oxidation of the allylic alcohol of the macrocycle X*

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**).

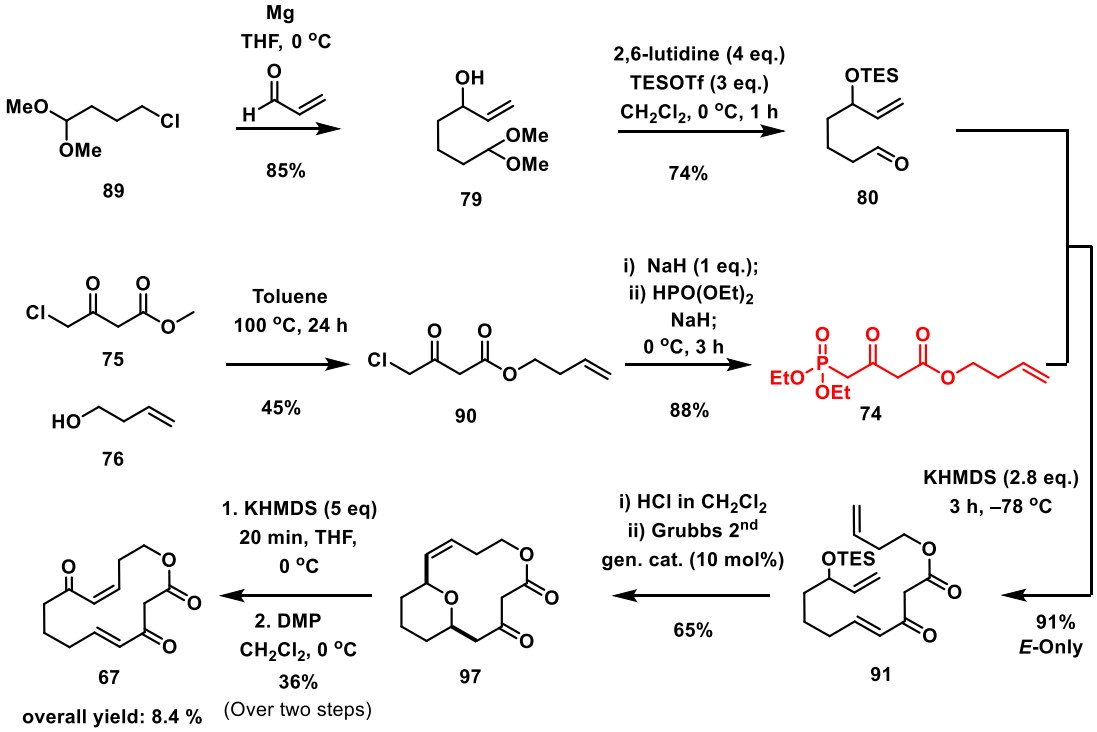


***Scheme 40**: Combined retro-oxy-Michael and oxidation to obtain the cascade precursor **67**.*

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

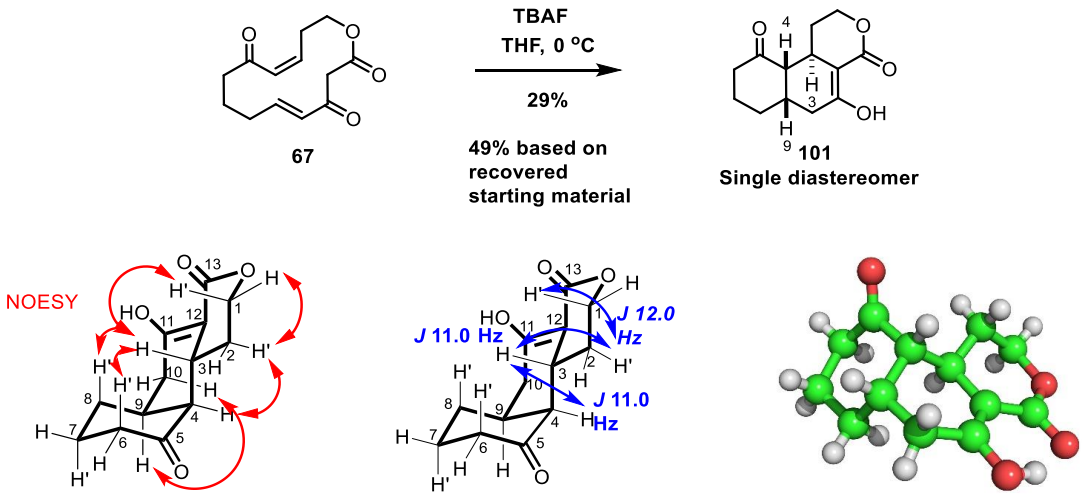
We had now developed a six linear steps route for the cascade precursor, that is using Horner-Wadsworth-Emmons reaction and RCM reaction of the oxy-Michael product as the major disconnections. The total combined yield for the cascade precursor over the 6 steps is 8.4%. Despite the relatively good overall 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

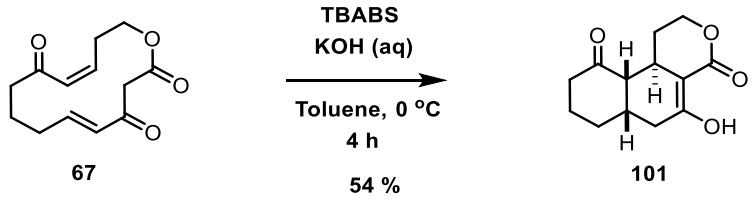
With the key substrate **67** in hand we now commenced investigations on the transannular cascade process. Aware of the risk of substrate decomposition and polymerisation we first examined the cascade reaction at low temperature, high dilution and weak base. With Cs_2CO_3 no reaction or substrate decomposition 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 ^{1}H-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.



***Scheme 42**: Transannular Michael reaction cascade and NOESY and coupling constant analyses and crystal structure of the product **101**.*

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.

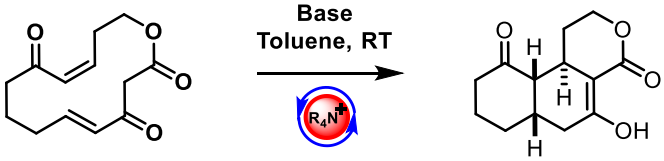


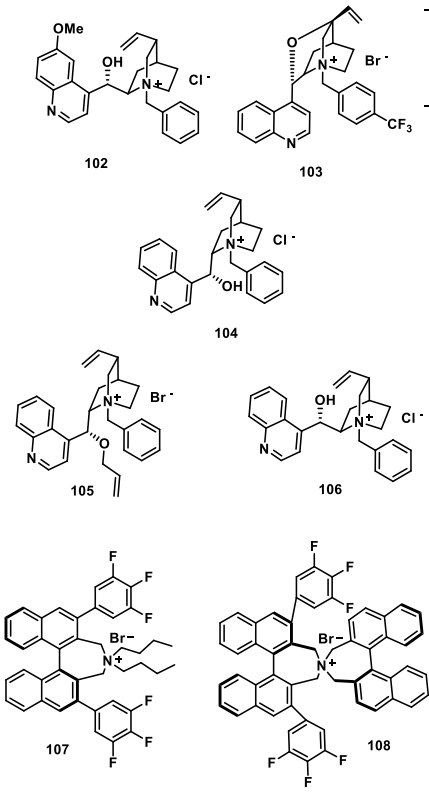
***Scheme 43**: Transannular cascade using TBABs as a phase-transfer catalyst.*

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.



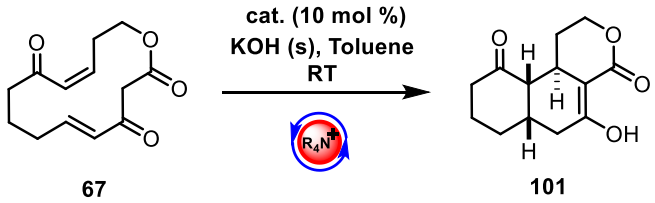


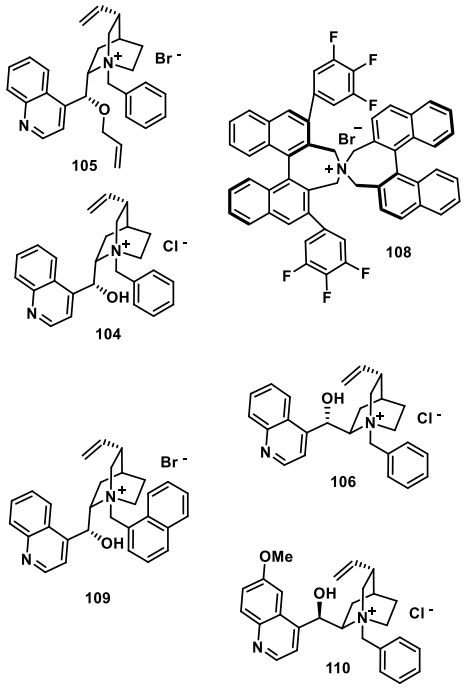
Entry	Base	Catalyst	Time (h)	Yield (isolated)[A]	e.r.
1	KOH (aq)	**102**	1.5	26%	Racemic
2	KOH (aq)	**103**	2	36%	Racemic
3	KOH (aq)	**104**	2.5	49%	Racemic
4	KOH (aq)	**105**	1.5	58%	52:48
5	KOH (aq)	**106**	2	26%	Racemic
6	CsOH (aq)	**104**	1	<20%	Racemic
7	KOH (aq)	**107**	1.5	30%	Racemic
8	KOH (aq)	**108**	1.5	70%	Racemic

***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.*

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 catalyst (**Table 8**). We choose the *O*-allyl-*N*-benzylcinchonidinium 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*-Benzylcinchonidinium 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

of available starting material we performed the reactions in analytical scale (**Table 8**, entries 1,3-6).





Entry	Base	Cat.	Time (h)	Yield (isolated)[A]	e.r.
1	KOH (s)	**105**	1	<20%	57:43
2	KOH (s)	**104**	1	30%	63:37
3	KOH (s)	**108**	1	<20%	53:47
4	KOH (s)	**106**	1	<20%	51:49
5	KOH (s)	**109**	2	<20%	Racemic
6	KOH (s)	**110**	2.5	<20%	52:48

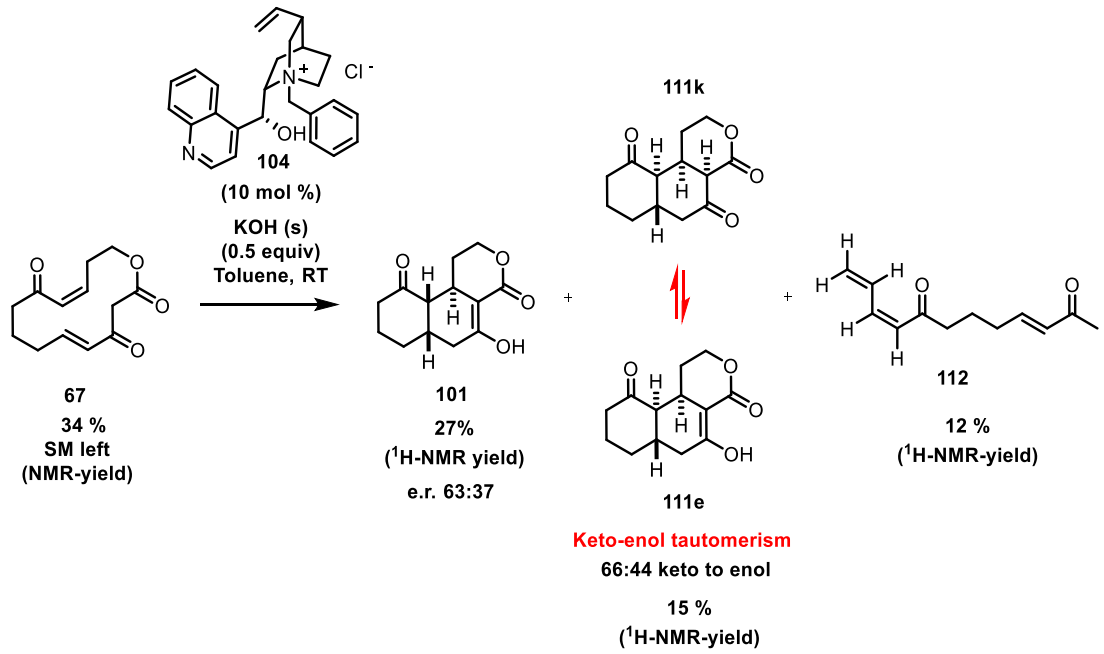
***Table 8**: Asymmetric phase transfer catalysed transannular cascade using KOH (s) as a base.[A] The reactions were completed on a 5 mg scale. When <20% is stated, the yield of the product is less than 1 mg.*

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.

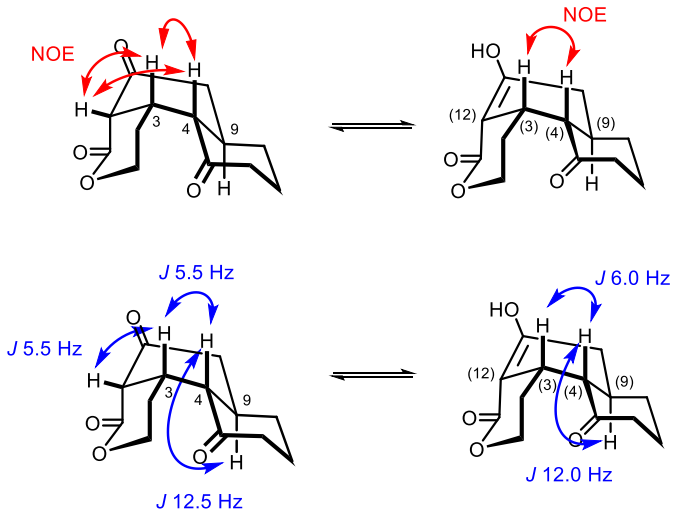
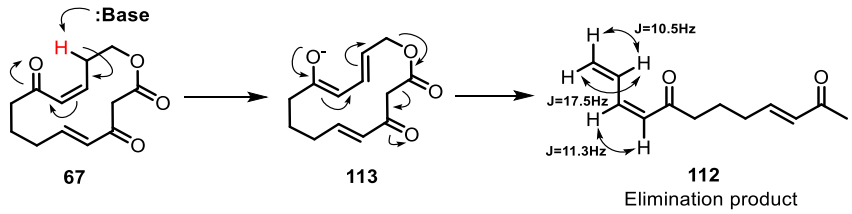


***Figure 2**: NOESY and* J*-coupling analysis of the cascade diastereomer **111**.*

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**).



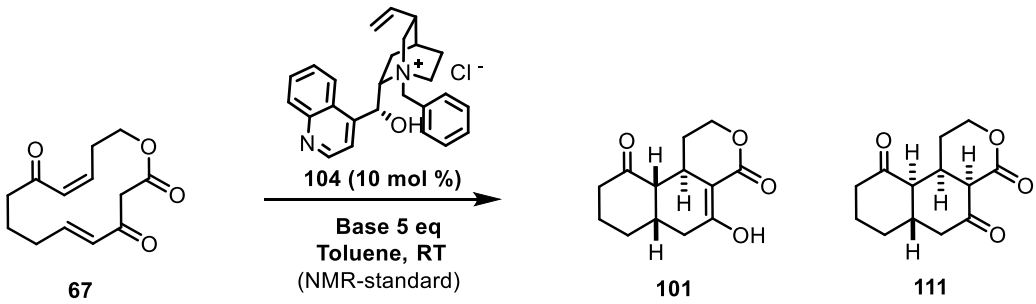
Scheme 45*: Plausible mechanism for decarboxylation of cascade precursor* ***111****.*

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 CH_2Cl_2 but results from these reactions proved to be unreproducible even when the CH_2Cl_2 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_3PO_4) was used (**Table 9**, entry 5).



Entry	Base	Time (h)	Elimination (**112**)	Yield **(101) + (111)**	d.r. **(101) : (111)**	e.r. **(101)**
1	NaOH (s)	1.5	-	24%	1 : 1	52:48
2	NaOH (aq)	1.5	-	26%	1.6 : 1	Racemic
3	K_2CO_3 (s)	24	11%	11%	1.75 : 1	70:30
4	K_2CO_3 (aq)	23	6%	18%	2.2 : 1	65:35
5	K_3PO_4 (s)	25	24%	37%	2.7 : 1	68:32
6	K_3PO_4 (aq)	20	1%	12%	> 20 :1	53:47
7	KF (aq)	20	8%	43%	4 : 1	65:35
8	KF (s)	24	-	32%	1 : 1	73:27
9	Cs_2CO_3 (s)	24	4%	12%	2 : 1	61:39

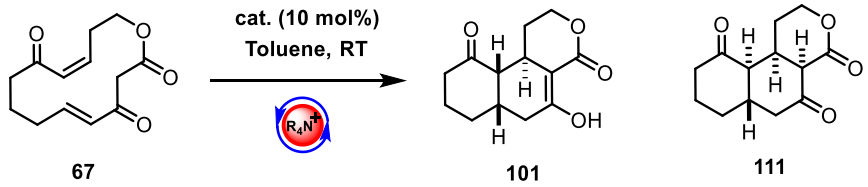
***Table 9**: Optimisation of the bases used in asymmetric transannular cascade*

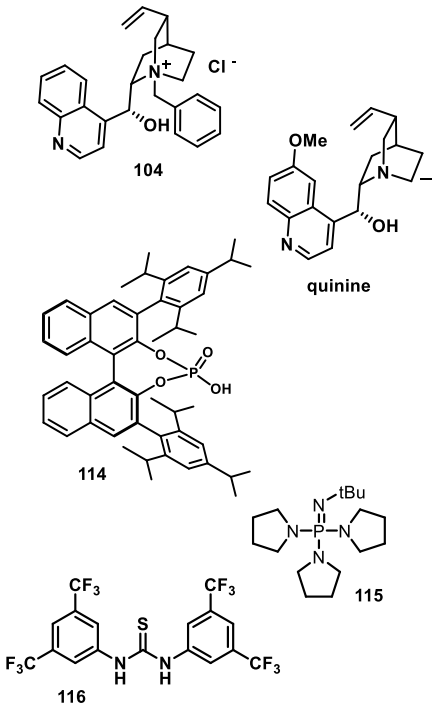
With aqueous K_2CO_3 the yield was 18% with 65:35 e.r whereas the reaction with solid K_2CO_3 gave 11% yield with enantiomeric ratio of 70:30 (**Table 9**, entries 4-5). Compared to potassium carbonate, solid caesium carbonate gave similar 12% yield but with lower 61:39 e.r (**Table 9**, entry 9). Slightly better yields were obtained with potassium phosphate (K_3PO_4) bases. Solid K_3PO_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

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).





Entry	Base	Time (h)	Cat.	Yield	d.r. **(101):(111)**	e.r. **(101)**
1	KO*t*Bu (s)	24	**97**	23%	1:1	racemic
2	KOAc (s)		**97**	N.R.	-	-
3	**112**	0.25	**97**	22%	>20:1	52:48
4	-		**111**	N.R.	-	-
5	-		**quinine**	N.R.	-	-
6	-		**113**	N.R.	-	-

***Table 10**: Optimisation of the cascade with organic bases and and a chiral phosphoric acid*

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.[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)[73] gave yield of 68% and potassium phenoxide (pK_a 18 in DMSO, pK_a 10 in water)[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.

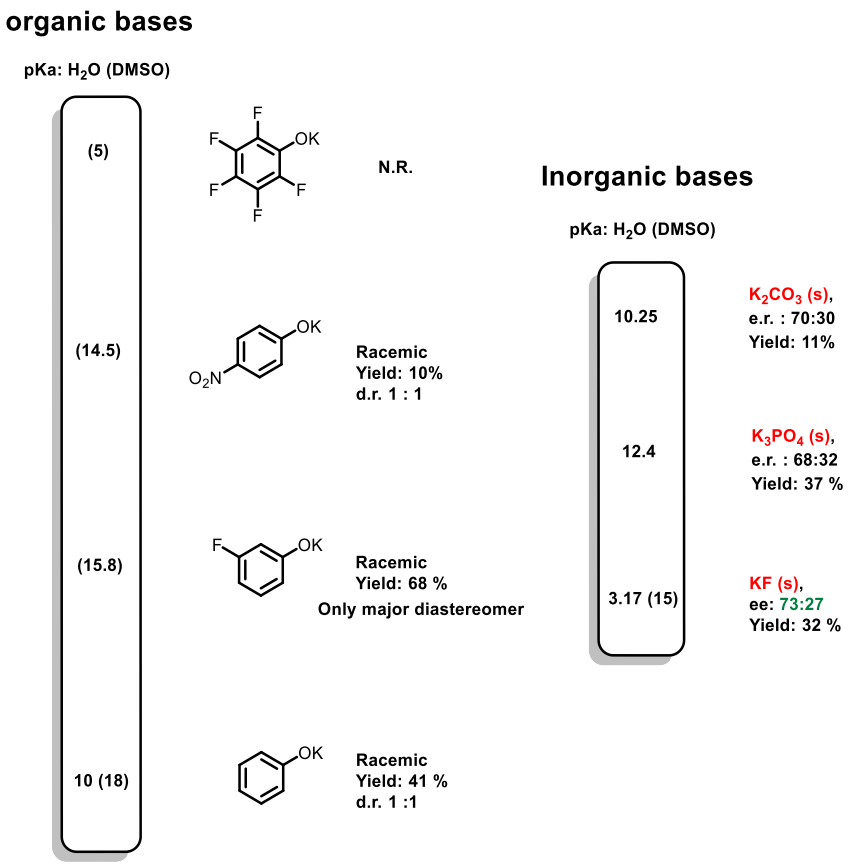
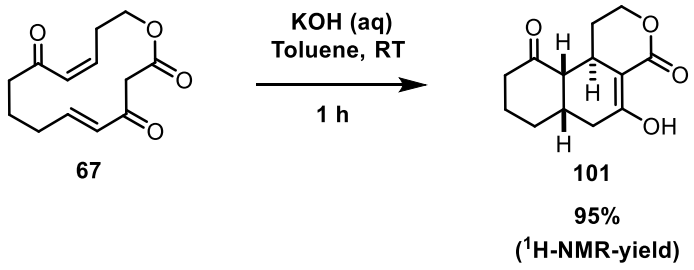


Table 11: The cascade with potassium phenoxides as bases.

The difference the 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 pK_a of acetoacetates are usually lower in the aqueous environment [74] 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 pK_a (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_a of 15 in DMSO).

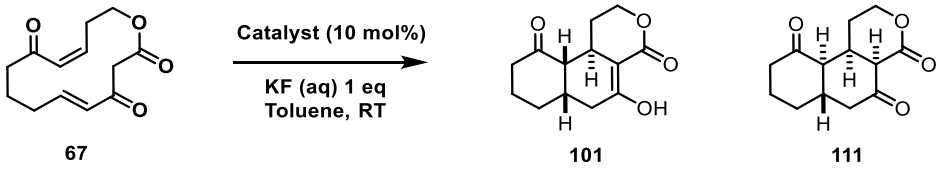
We tested if the reaction happens without the phase-transfer catalyst by using aqueous potassium hydroxide solution. When the reaction was done in toluene at 0 °C we could observe 95% yield of the diastereomer **101** (**Scheme 46**). The high yield of the reaction with just aqueous potassium hydroxide 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.



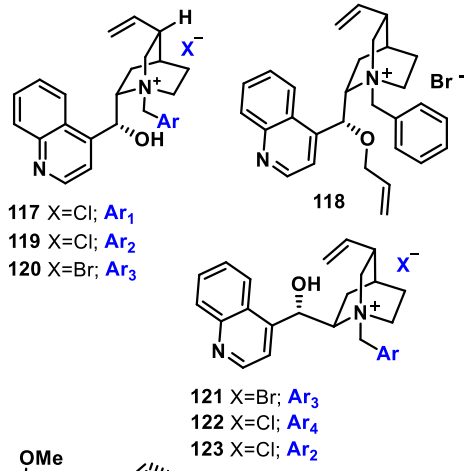
***Scheme 46**: The cascade without phase-transfer catalyst with KOH (aq) as a base.*

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.



67 101 111



Entry	Cat.	Elimination	Yield (101 + 111)	d.r. (101:111)	e.r.
1	117	6%	9%	81 : 2	67:33
2	118	-	N.R.	-	-
3	**119**	**3%**	**61%**	**4 : 1**	**89:11**
4	120	6%	9%	1 : 2	46:54
5	121	-	11%	1 : 3.5	44:56
6	122	5%	14%	1 : 1	27:73
7	**123**	**1%**	**56%**	**6 : 1**	**11:89**
8	124	13%	7%	1 : 2	52:48
9	125	-	4%	1 : 2	Racemic
10	126	11%	17%	2.4 : 1	Racemic
11	127	5%	5%	1	48:52
12	128	6%	traces	-	-
13	129	5%	14%	1 : 1	57:43
14	130	-	27%	1 : 2.5	66:34

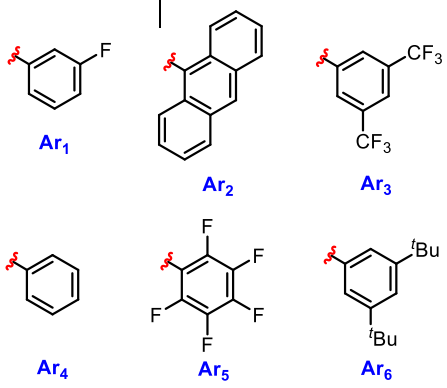
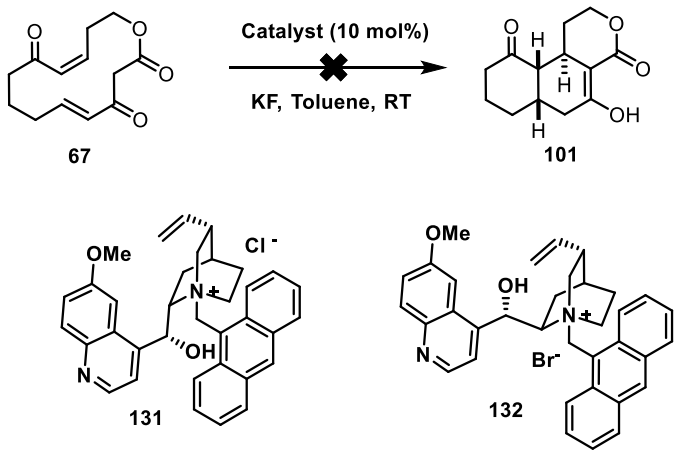


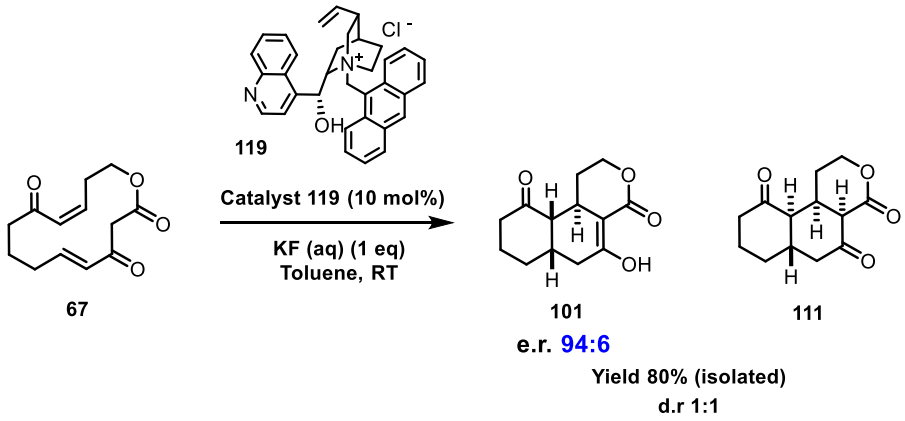
***Table 12**: Secondary catalyst screen.*

In the secondary catalyst screen we observed that quinidinium (**Table 12**, entries 8-10) and quininium (**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 *N*-(9-anthracenylmethyl)cinchonidinium chloride[75] **119** (**Table 12**, entry 3) and it's pseudoenantiomer *N*-(9-anthracenylmethyl)cinchoninium chloride (**Table 12**, entry 7) provided us high levels of enantioselectivity and a pleasing increase in the yields of the transannular cascade. The reaction with *N*-(9-anthracenylmethyl)cinchonidinium chloride as the catalyst provided us with yield of 61% yield with enantiomeric ratio of 89:11 with *N*-(9-anthracenylmethyl)cinchoninium bromide **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 quininium 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_2CO_3 (aq)). The yield with K_2CO_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_3PO_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_3PO_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**).

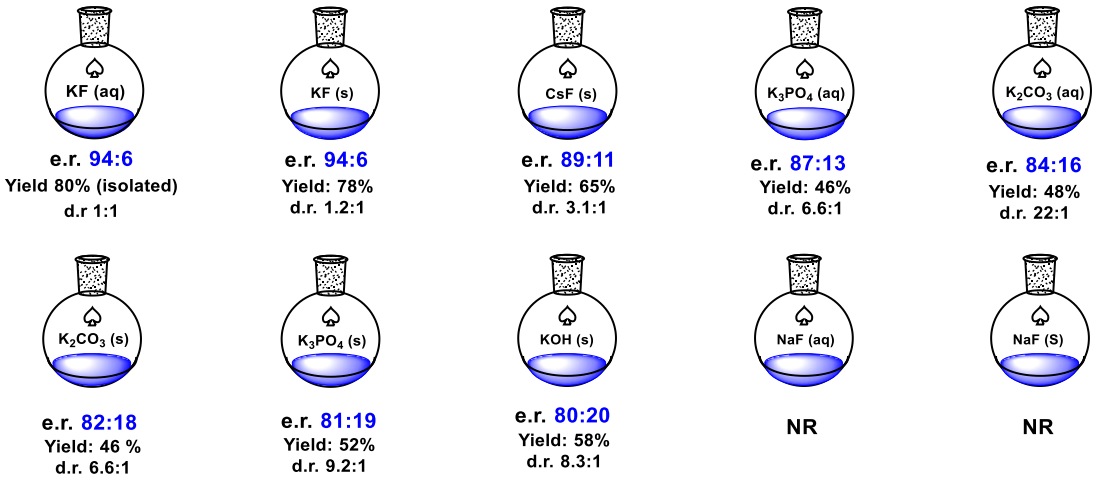


***Figure 3**: Secondary base screen.*

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_2Cl_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 enantomeric 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**).

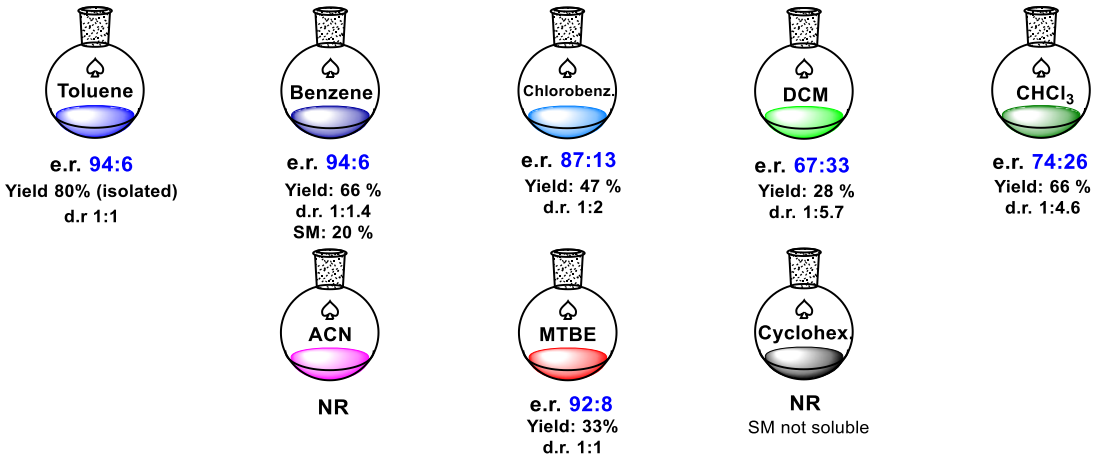


***Figure 4**: Secondary solvent screen.*

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**).

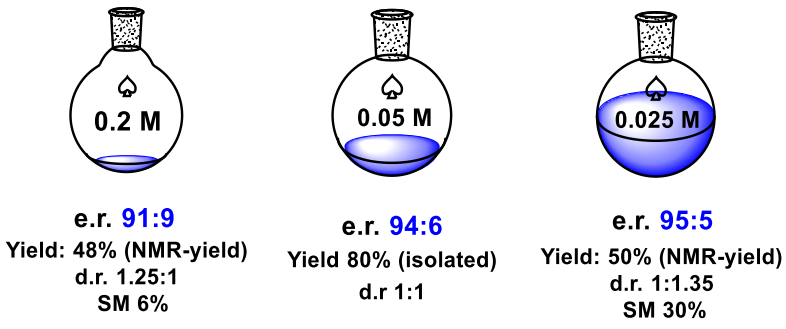


***Figure 5**: Screen of concentration of the cascade.*

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**).

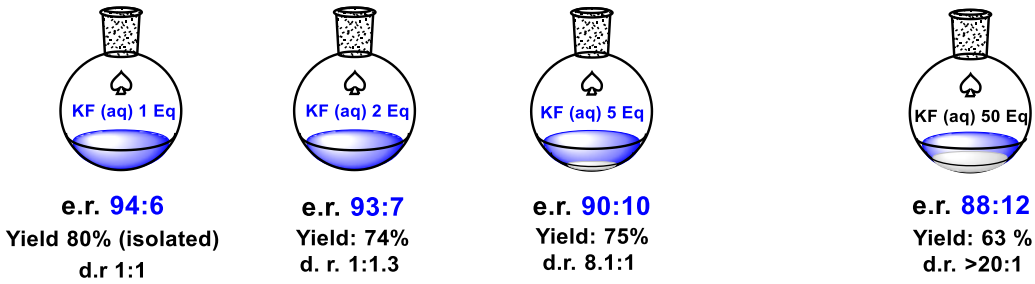


***Figure 6**: Optimisation of the amount of potassium fluoride (KF (aq))*

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**).

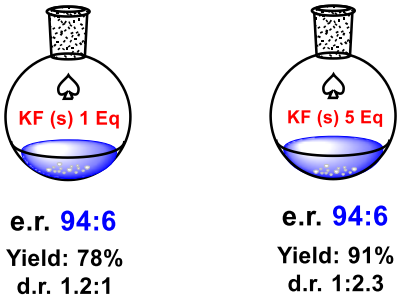


***Figure 7**: Amount of the solid potassium fluoride in toluene.*

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.

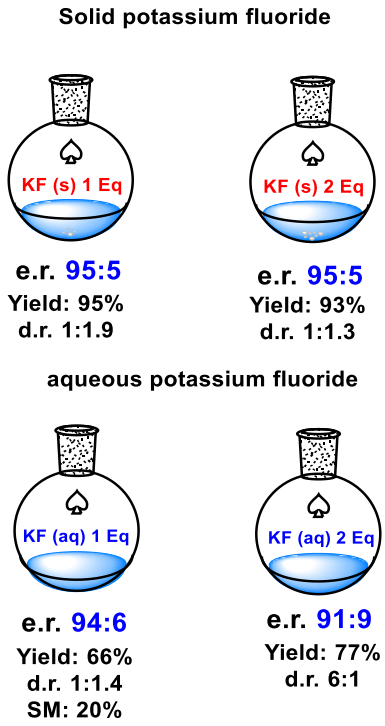


***Figure 8**: The effect of the amount of potassium fluoride in benzene.*

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**).

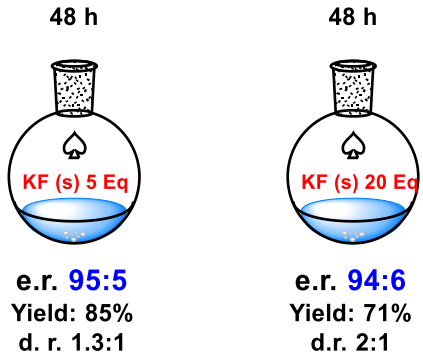


***Figure 9**: Increased reaction time in the reaction with solid potassium fluoride (KF) in benzene.*

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**).

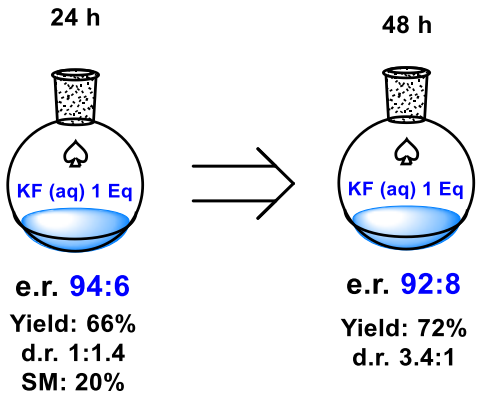


***Figure 10**:Increase in reaction time from 24 hours to 48 hours with 1 equivalents of aqueous potassium fluoride (KF (aq)).*

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**).

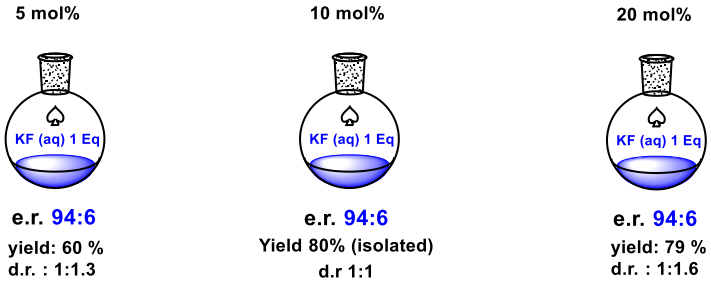
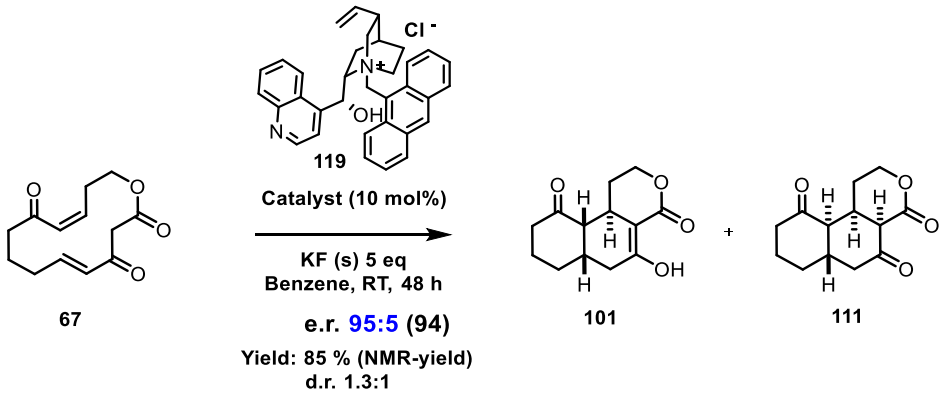


Figure 11*: The effect of the catalyst loading on the reaction.*

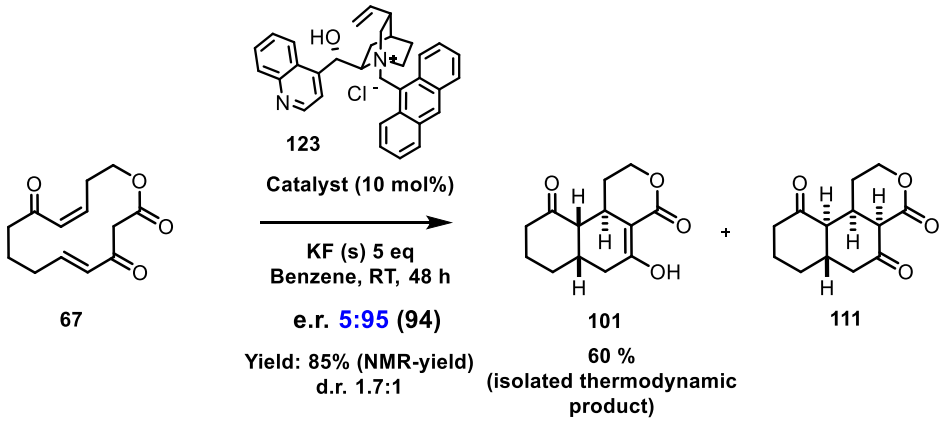
Our optimised conditions were to use 5 equivalents of solid potassium fluoride as a base in benzene with catalyst **119** giving 85% yield of 1.3: 1 ratio of the diastereomers with 95:5 enantiomeric ratio of the thermodynamic product **101** (**Scheme 49**).



Scheme 49*: Optimised conditions with* N-*(9-anthracenylmethyl)cinchonindinium **119**.*

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 ^{1}H-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.



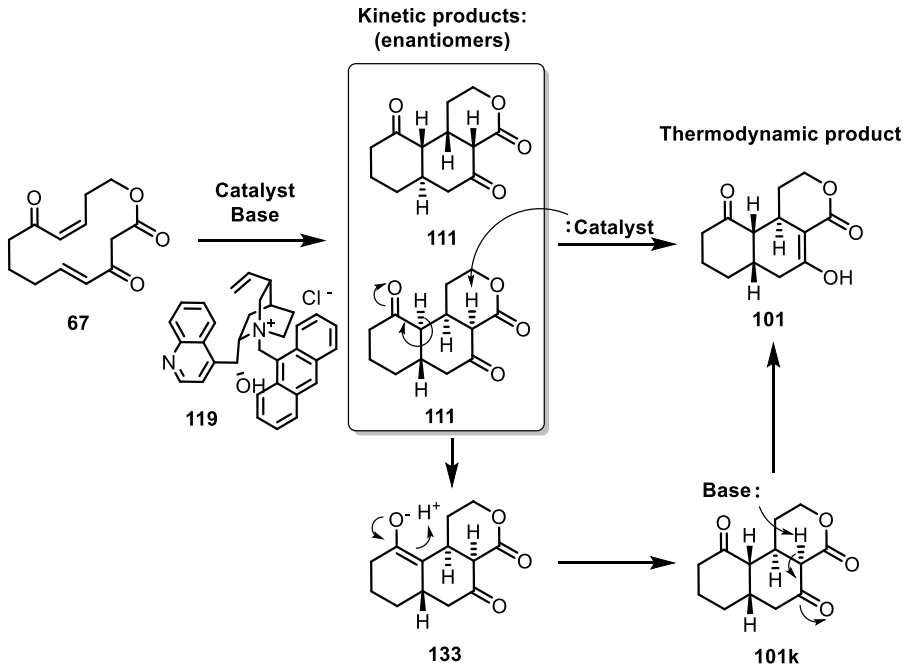
***Scheme 50**: Asymmetric cascade with catalyst pseudoisomer **123**.*

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.

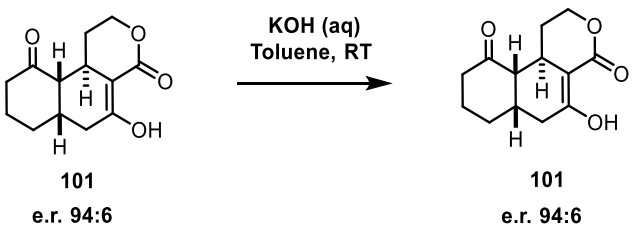
When the reaction was monitored by TLC analysis we first saw formation of the kinetic diastereomer **111** and then formation of the thermodynamic product **101**. We believe this observation is evidence that **111** is an intermediate in the formation of **101** from the cascade precursor. In previous 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 **101** causing lower enantioenrichment of **101**.



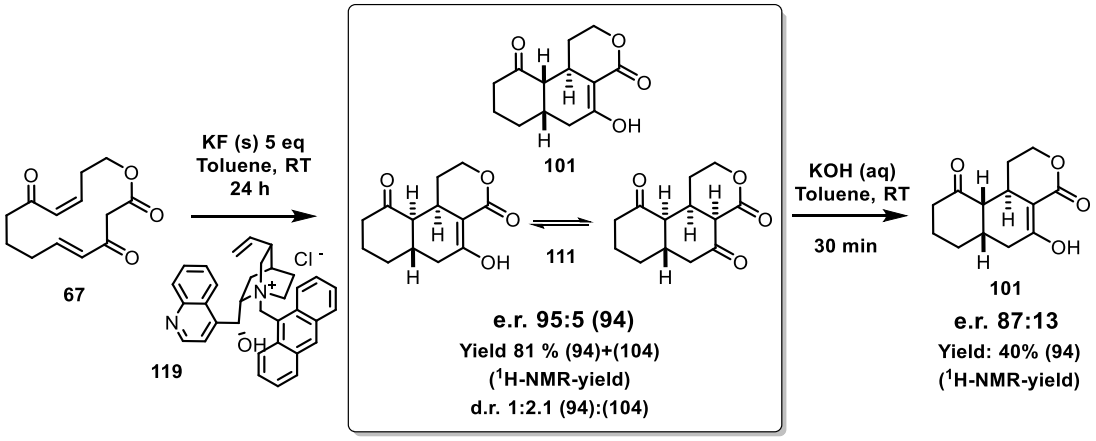
***Scheme 51**: Kinetic resolution of the cyclisation product **111**.*

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) **101** to aqueous potassium hydroxide for 30 minutes in toluene (**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.



***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% (^{1}H-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% (^{1}H-NMR) yield of only the desired thermodynamic diastereomer **101** with a corresponding decrease in enantioenrichment (87:13) (**Scheme 53**).

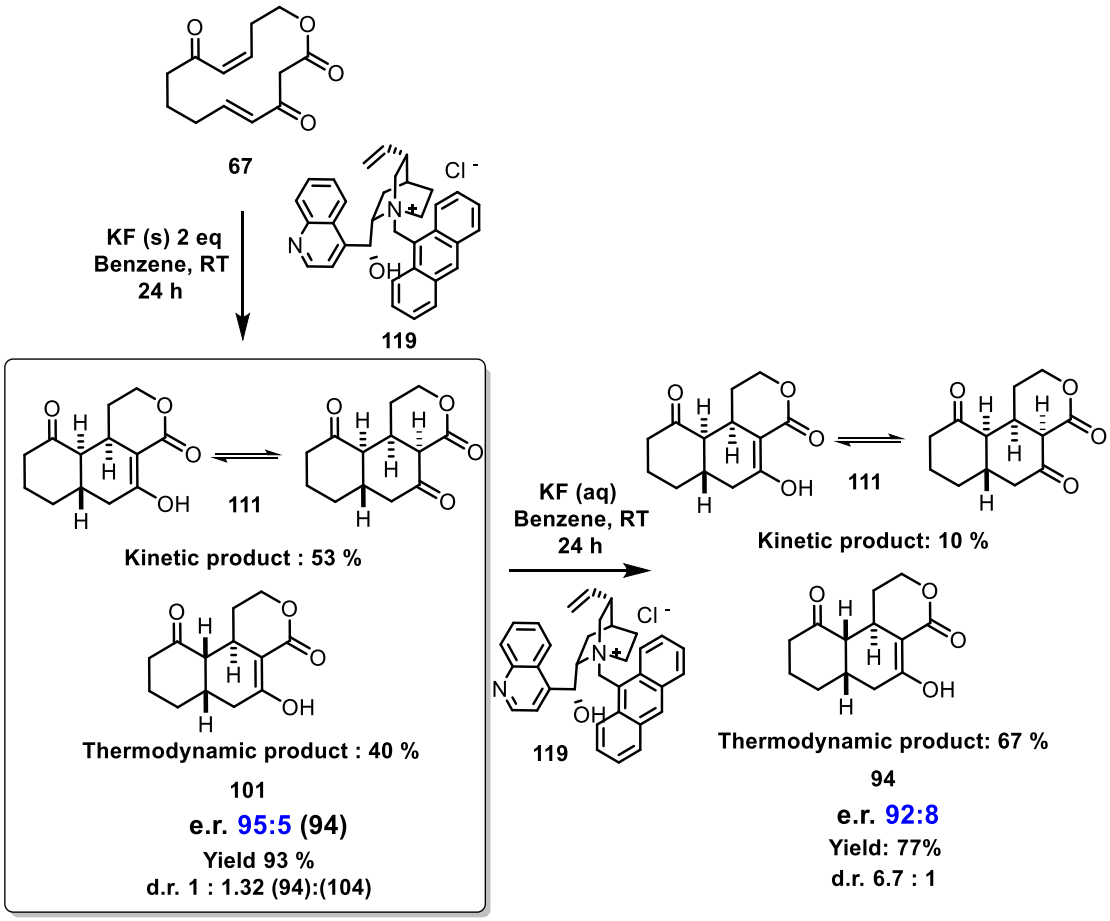


***Scheme 53**: Treatment of the enantioenriched material with aqueous potassium hydroxide.*

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.

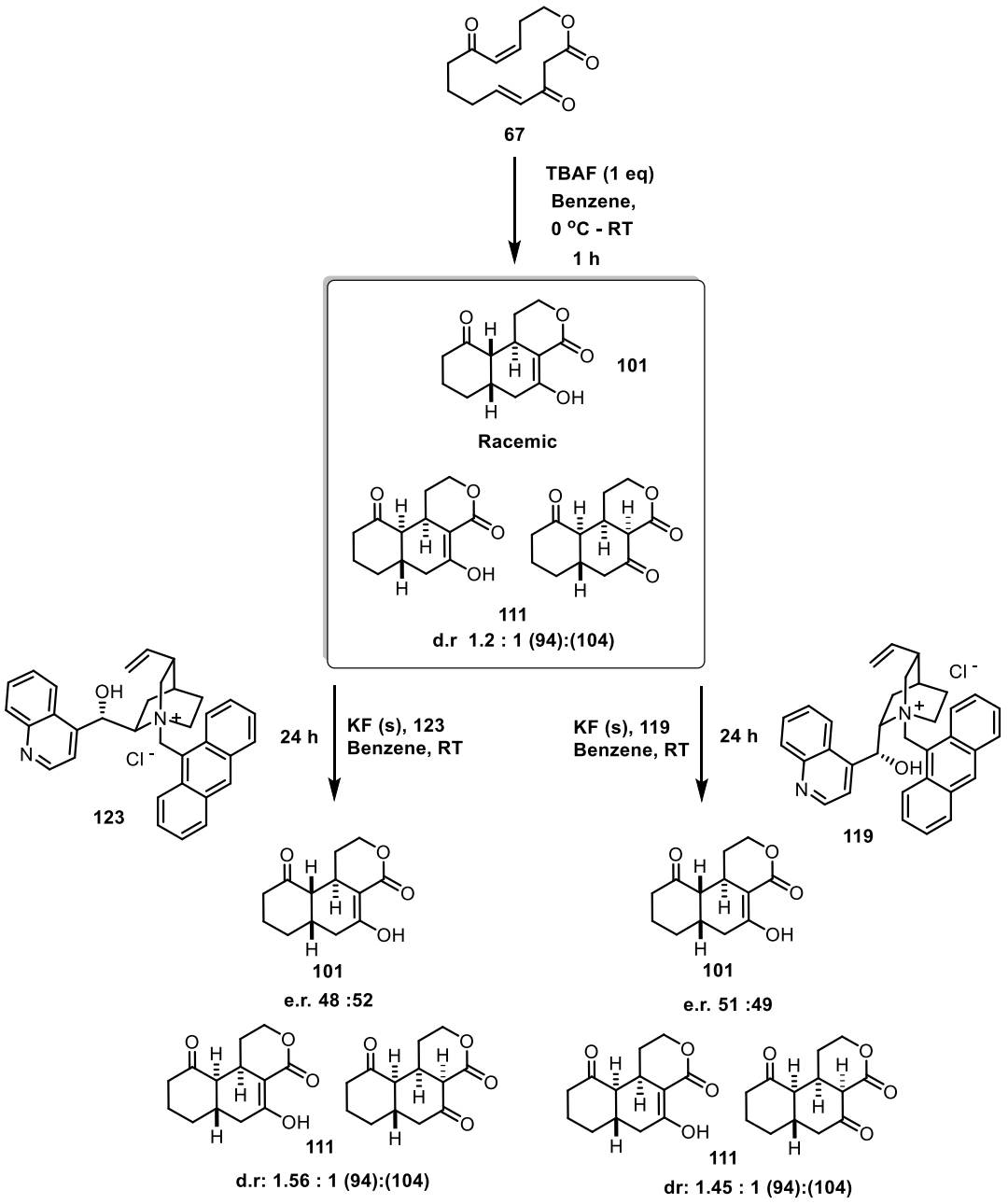
We also treated the enantioenriched crude mixture of diastereomers (95:5 e.r.) with aqueous potassium fluoride under phase transfer conditions. This was done to see the effect that the aqueous potassium fluoride base has on the kinetic resolution. The treatment of the catalyst free crude material lowered 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.*

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 ^{o}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.

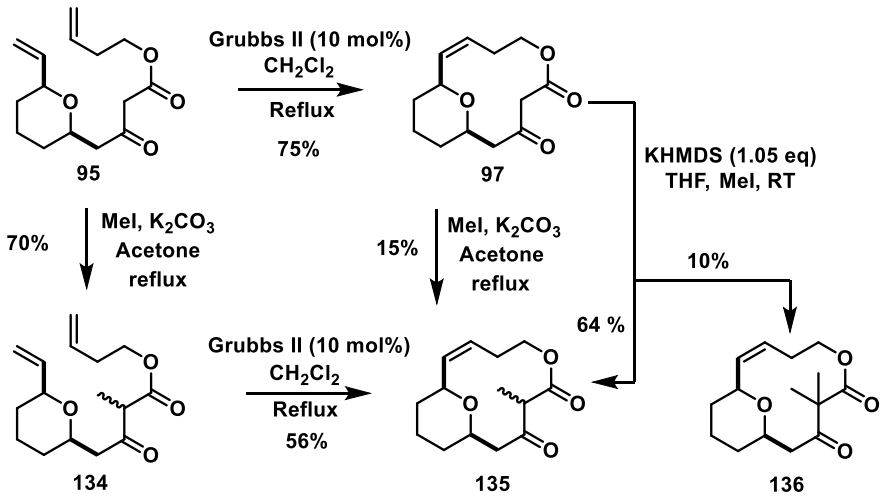
4. Synthesis of the substrates for the cascade.

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 [76] 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**).

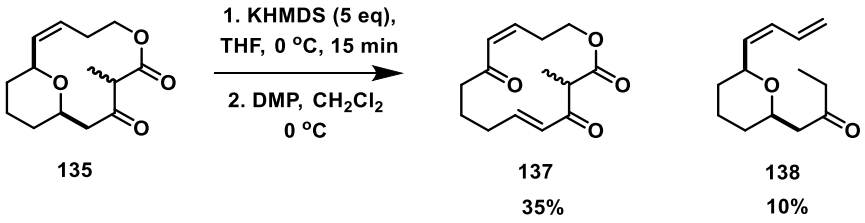
We also tried to methylate the RCM-product **97** with the same conditions using potassium carbonate in refluxing acetone but in this reaction only 15% yield was isolated after 18 hours reaction. This is likely to be attributed to the steric crowding of the ring system, reducing the rate of the mono-cyclic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



***Scheme 56**: Methylation of the RCM-product **97** and RCM-precursor **95**.*

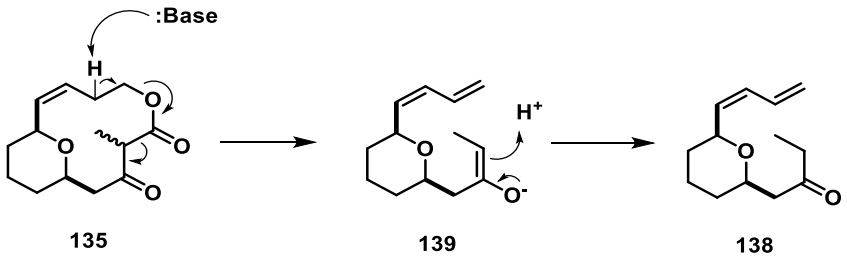
With the ring-closing metathesis of the methylated product **134** using Grubbs 2nd edition catalyst under refluxing CH_2Cl_2 gave us the closed methyl containing RCM-product **135** as a single geometrical isomer in 56% yield, therefore affording the methylated substrate in 39% from the unfunctionalised 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 KHMDS 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**).



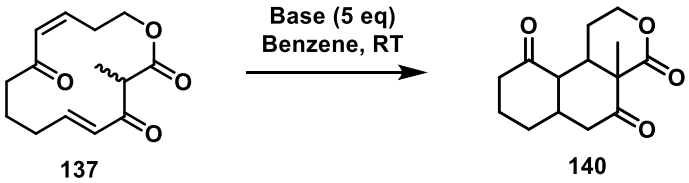
***Scheme 57**: Retro-oxy Michael reaction of the methylated cascade precursor.*

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 α-proton and possibly too fast a rate of addition of the KHMDS. When deprotonated, the enolate should suppress this decarboxylation pathway.



***Scheme 58**: Plausible mechanism of the decarboxylation side reaction.*

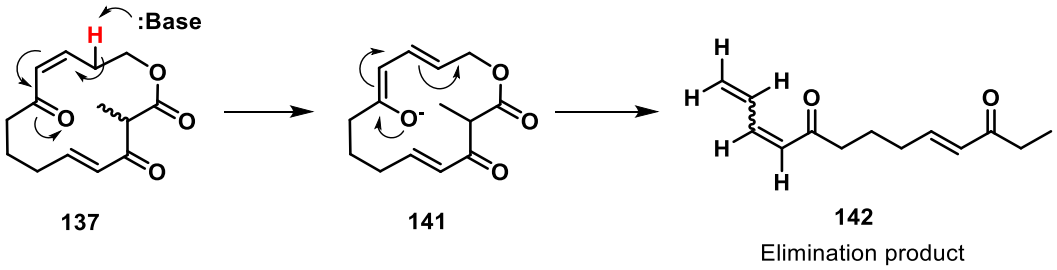
With our methylated cascade substrate in hand, we set about investigating the cascade process. Unfortunately, when we attempted the optimised asymmetric cascade for the methylated precursor **137** using KF (s) as base we could not observe any formation of the cascade product. Similarly, no reaction was observed with aqueous potassium fluoride, aqueous potassium hydroxide or solid potassium phosphate.



Entry	Base	Catalyst	Yield
1	KF (aq)	**119**	N.R.
2	KF (s)	**119**	N.R.
3	KF (s)	**123**	N.R.
4	K_3PO_4 (s)	**119**	Decomp.
5	KOH (aq)		Decomp.

*Table 13: Transannular cascade of the methylated cascade precursor **137**.*

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 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.

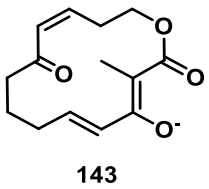
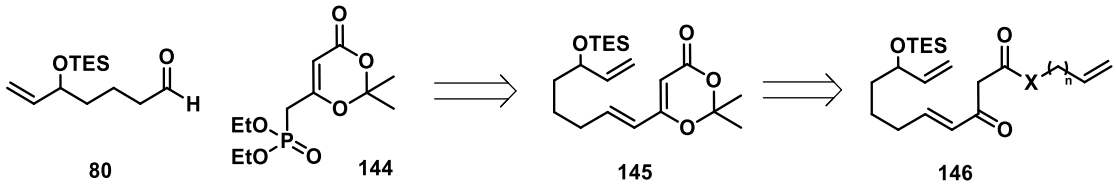


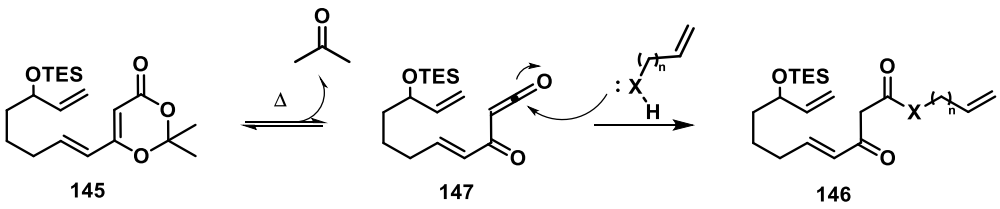
***Figure 12**: Structure of the deprotonated methylated precursor.*

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[77] and Sato *et al.*[78,79,80,81,82,83]. 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**).



***Scheme 60**: Retro-synthetic analysis for access to different substrates.*



***Scheme 61**: Thermolysis of the 1,3-dioxin-4-one intermediate.*

In the thermolysis, an acylketene **145** is formed which can be trapped with different nucleophiles[84].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**).

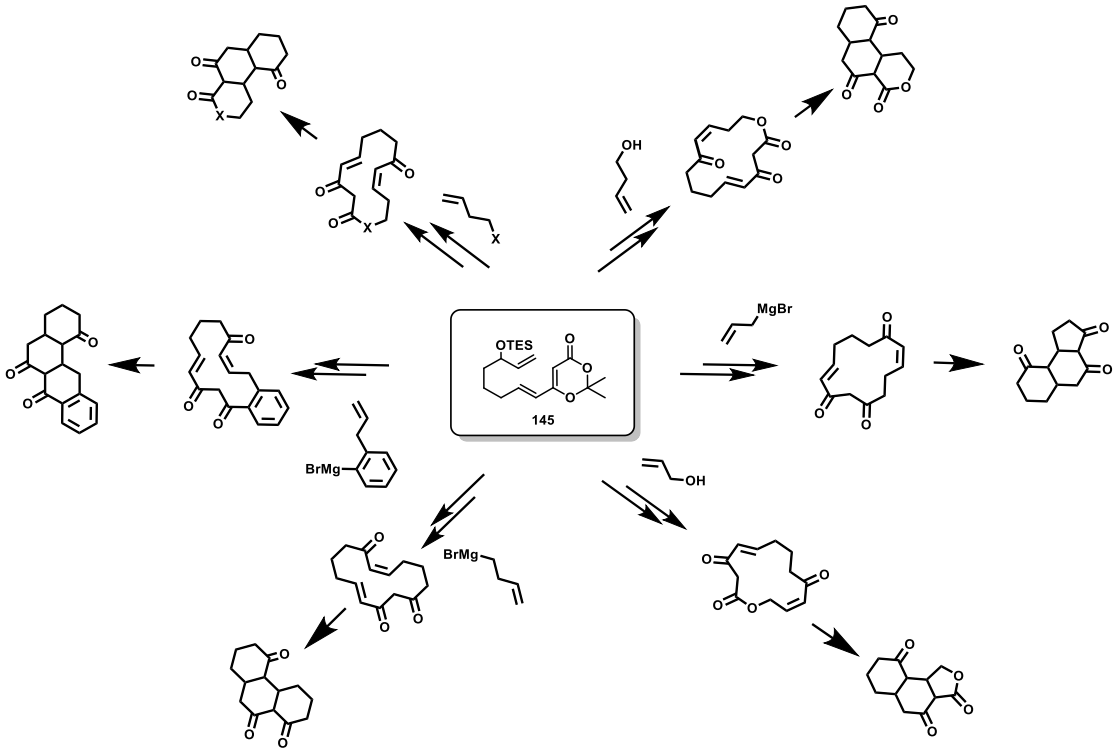
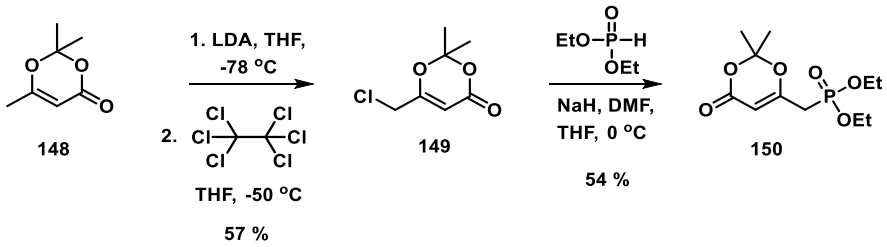


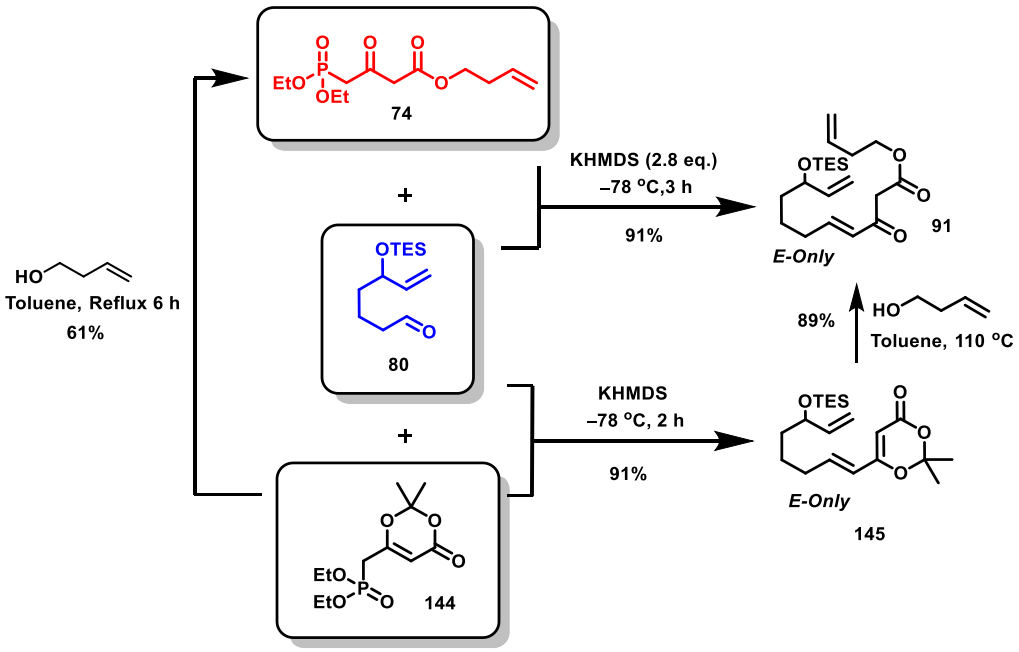
***Figure 13**: Possible substrates via 1,3-dioxin-4-one **145** intermediate.*

In the synthesis of the HWE-reagent **150** we used the method published by R. K. Boeckman [85] 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**)[85].



***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.

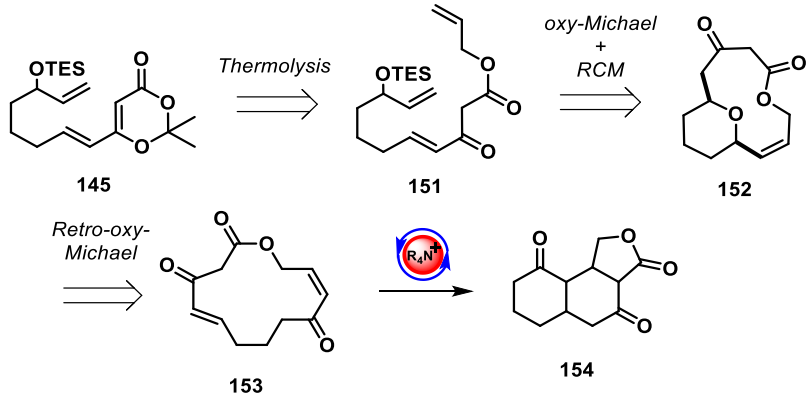


Scheme 63*: Synthesis of the HWE-products.*

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**).

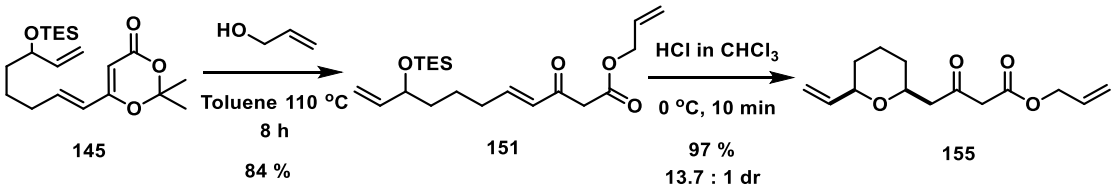
4.3 Synthesis of the 5,6,6-substrate

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 ^{o}C in toluene giving the unsaturated ketoester **151** in 84% yield, which was then treated with acidified chloroform at 0 ^{o}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**.*

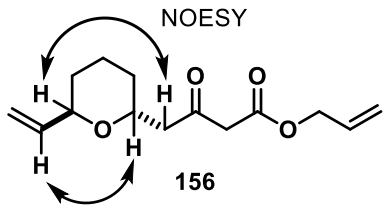
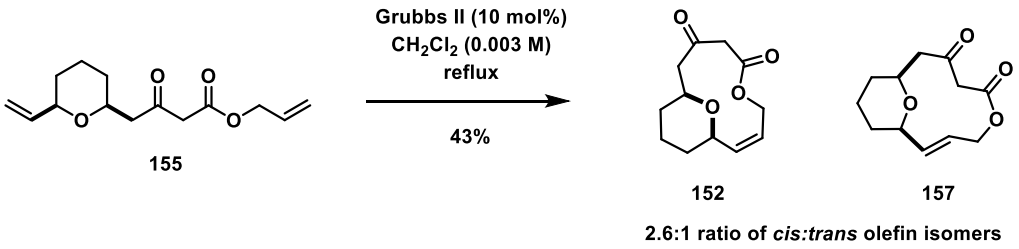


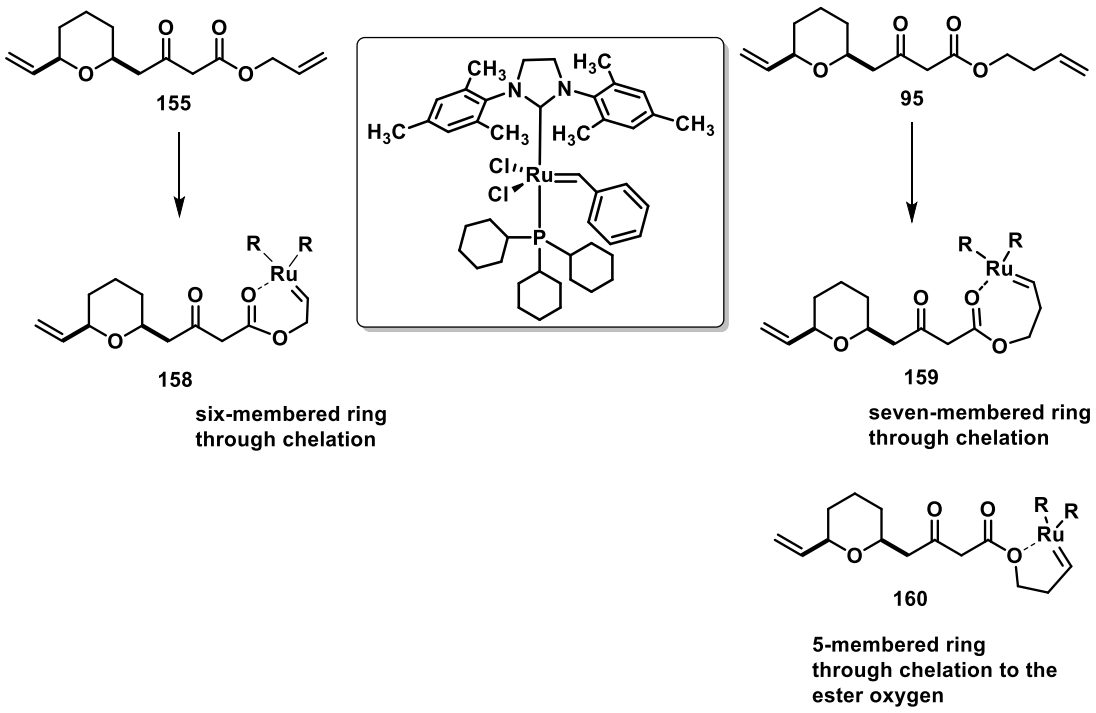
***Figure 14**: NOESY-analysis of the minor diastereomer **156** of the oxy-Michael reaction.*

In the ring-closing metathesis with Grubbs 2nd generation catalyst in refluxing CH_2Cl_2 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**).



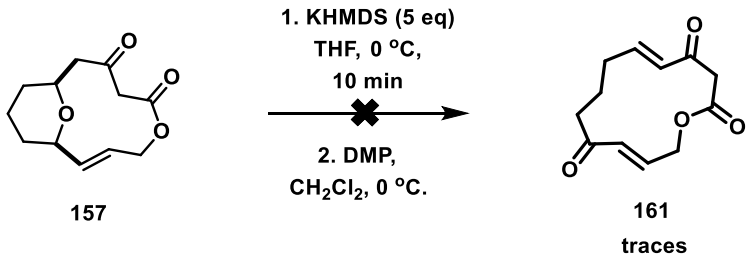
***Scheme 66**: RCM reaction of the 5,6,6-system.*

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 metallocarbene 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[63] 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.[63] 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.*

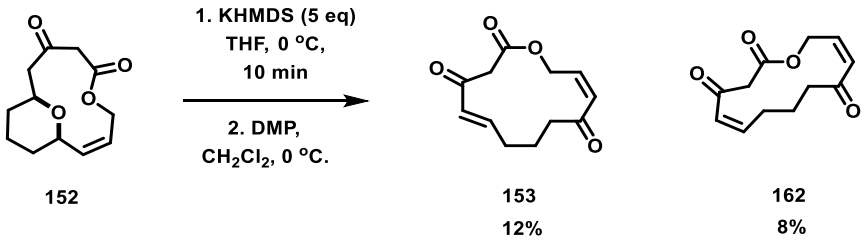
The retro-oxy-Michael reaction proved to be very challenging with the 5,6,6-ring system. The conditions that had been optimised for the 6,6,6-system did not give any product, even after the reaction was attempted several times. We figured out that with the 5,6,6 system the reaction is much faster and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

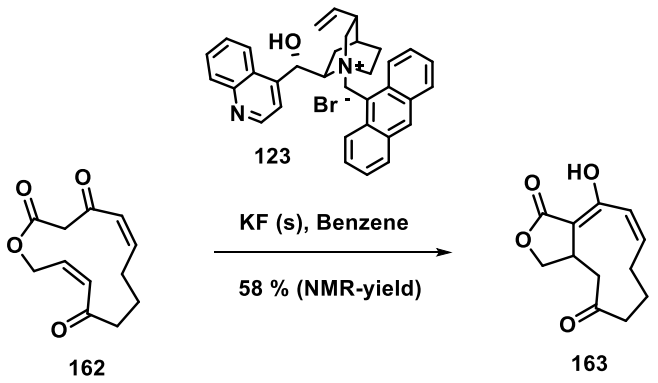


***Scheme 69**: Retro-oxy-Michael reaction of the Z-isomer **152** of the 5,6,6-system*

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 ^{1}H-NMR analysis monitoring of the effectiveness of the cascade under different conditions. Quantitative ^{1}H-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}C or for ^{1}H-^{13}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}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]

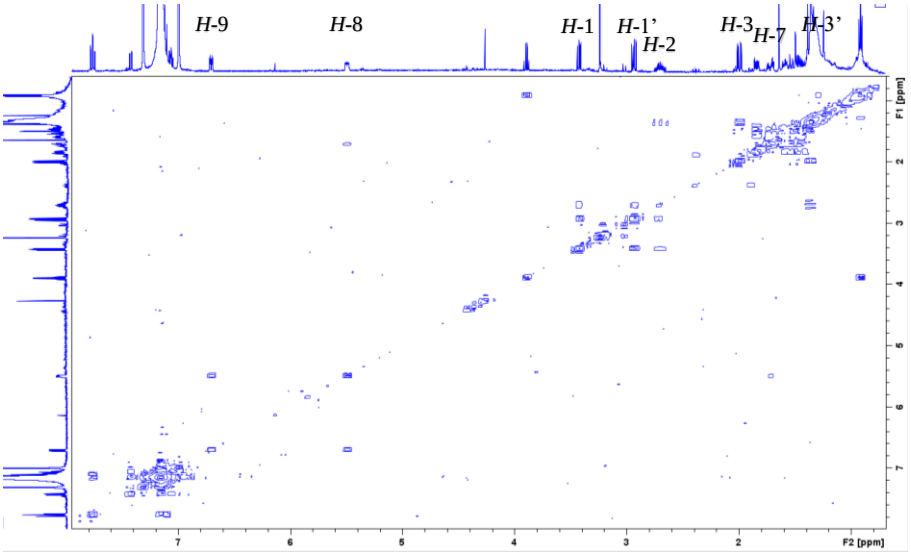
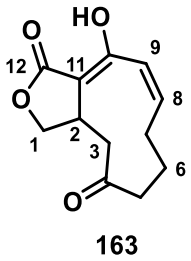


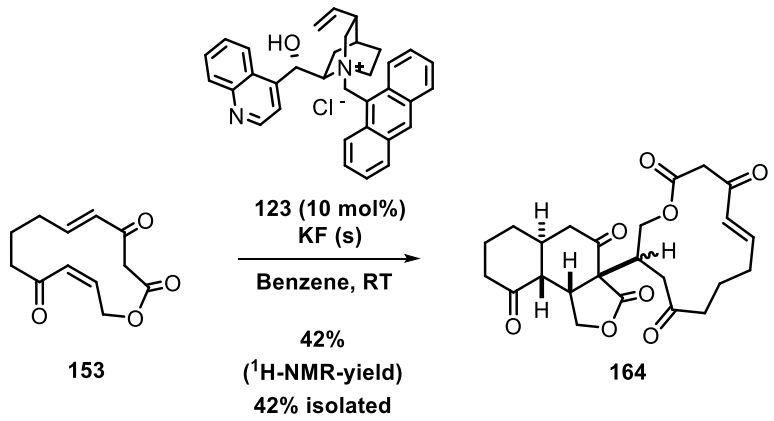
***Figure 15**: 1H-1H COSY-spectra of the crude cyclisation mixture.*



163

***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 in not particularly enantiodiscriminatory.



***Scheme 71**: The transannular asymmetric cascade of the E,Z-isomer **153**.*

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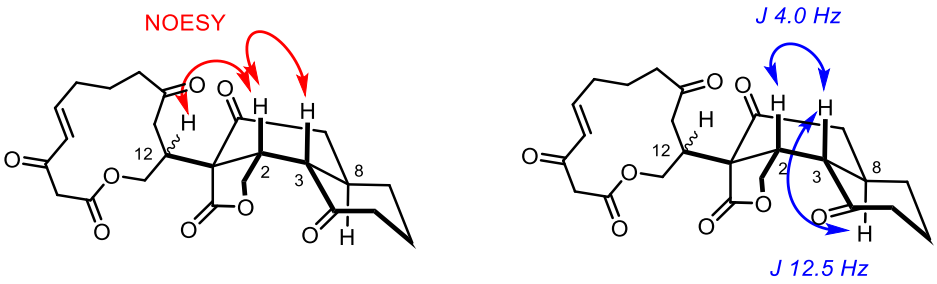
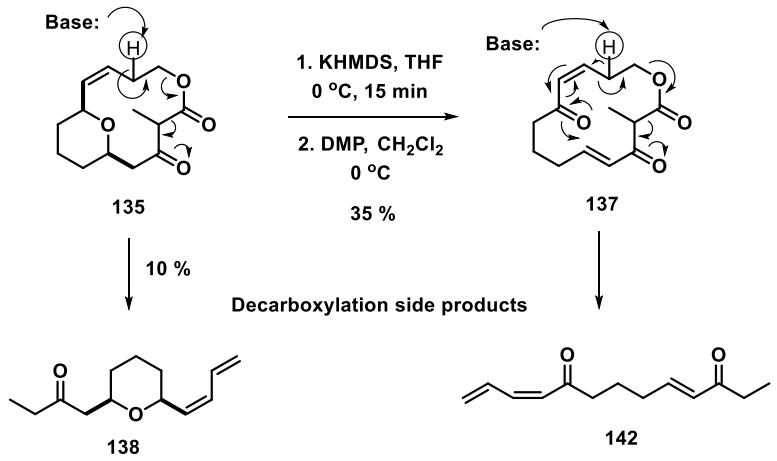


***Figure 17**: NOESY and COSY analyses of the cascade dimer **164**.*

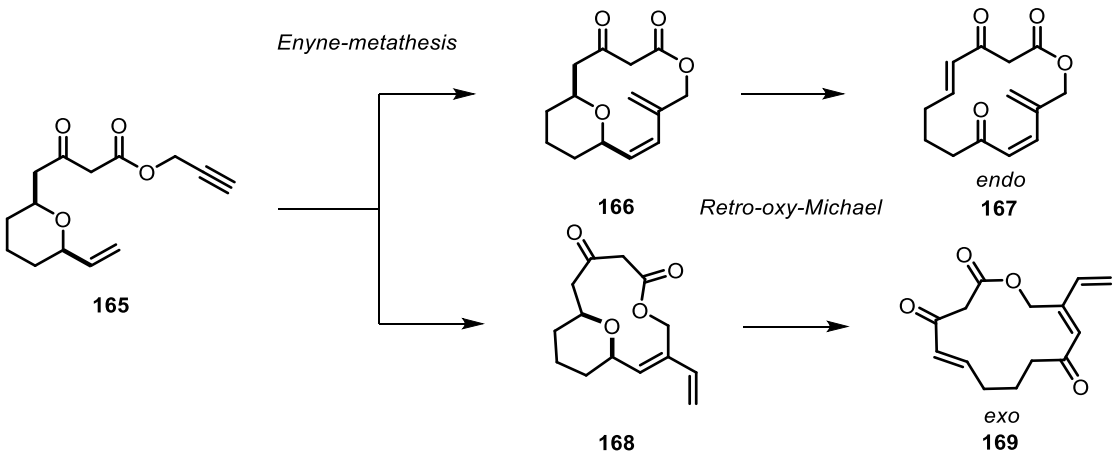
4.5 Cascade precursor via enyne methathesis

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.



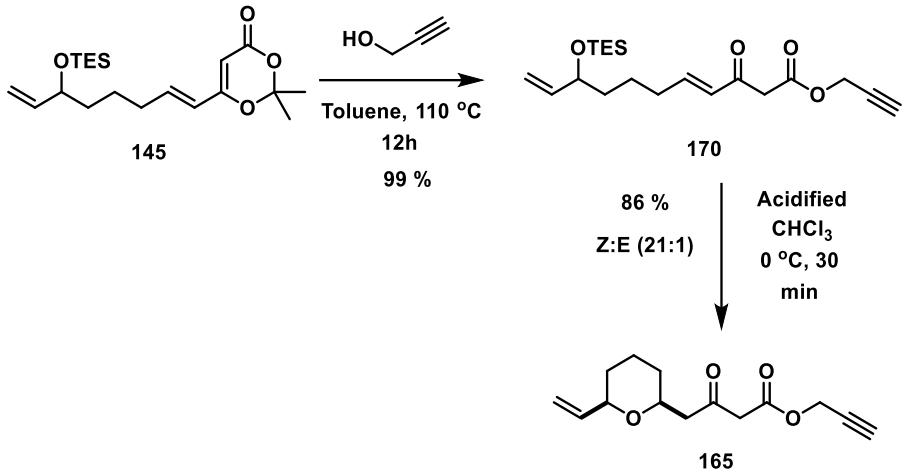
***Scheme 72**: Decarboxylation of the cascade precursor **137** and the RCM-product **135**.*

We realised an opportunity to use a ring closing enyne-metathesis[87,88,89] 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.*

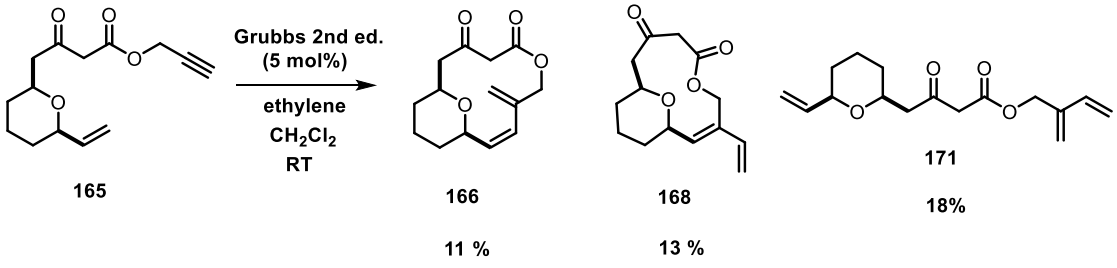
The RCEYM product bearing a terminal alkene could also for the rapid diversification of the cascade precursor *via* Pd-catalysed Heck-coupling[90,91] reactions to form the corresponding secondary alkene.



***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**.

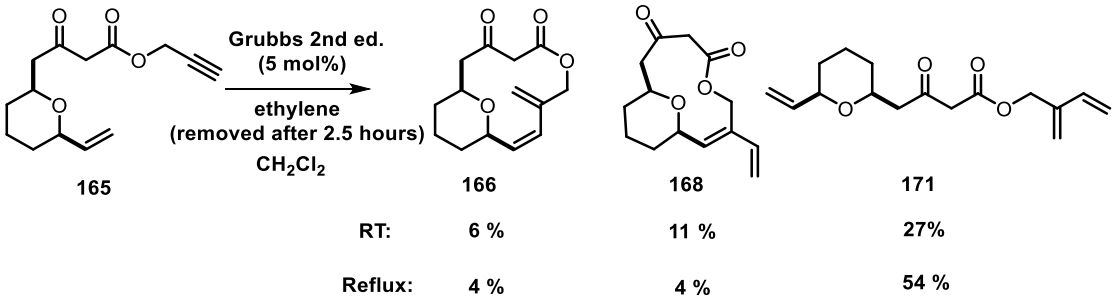
The first attempt at the Ring-closing enyne metathesis under an ethylene/argon atmosphere produced a mixture of both *exo*-**168** and *endo*-form **166** in 11% and 13% yield, respectively. However, the major product, in 18 % yield proved to be open-chain diene **171** formed from the reaction between the starting material enyne **165** and ethylene (**Scheme 75**). Ethylene atmosphere is known to improve the yields of enyne-metathesis by improving catalyst regenareation 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_2Cl_2 the reaction gave 54% yield for the diene **171** and the lowest yields for the *endo* (4%) and *exo* (4%) products (**Scheme 76**).

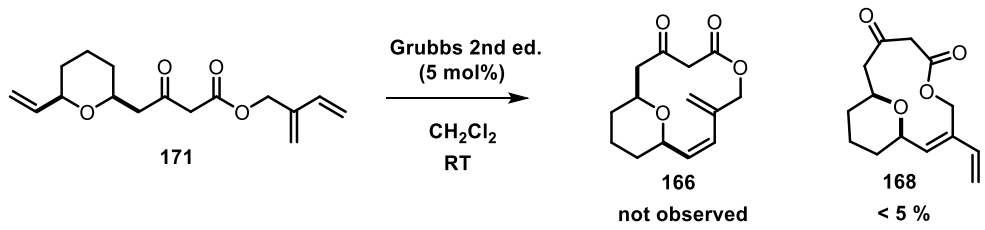


***Scheme 76**: Enyne-metathesis with in ethylene atmosphere removed during the reaction.*

We tried to improve the yield by using Hoveyda-Grubbs 2nd 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.*

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**-enyne-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.

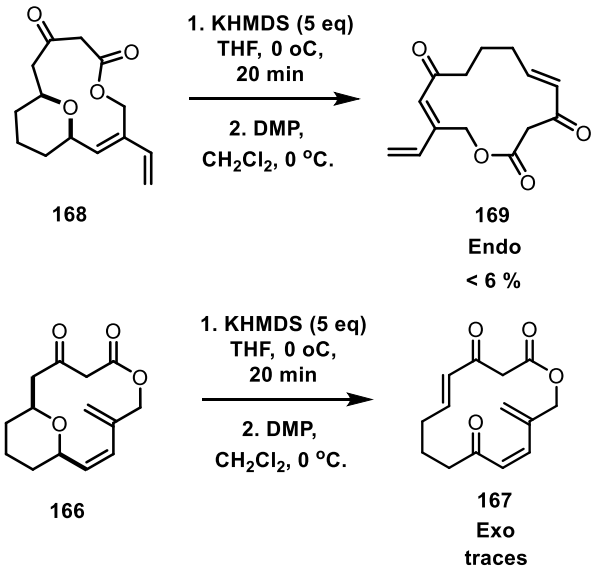
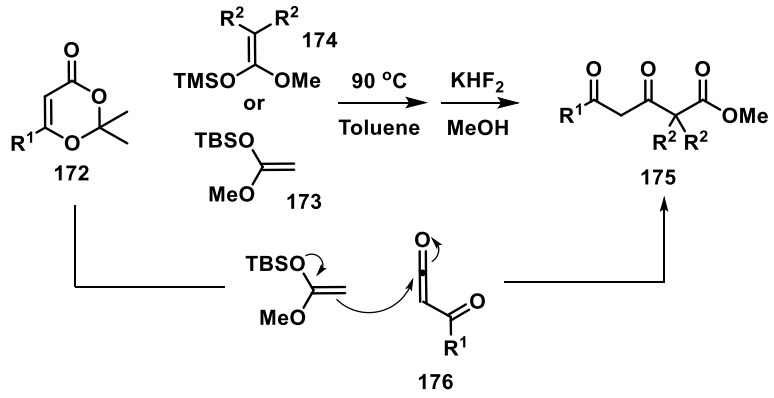


*Figure 18: Retro-oxy-Michael reaction of the enyne metathesis products **168** and **166**.*

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-enyne 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.

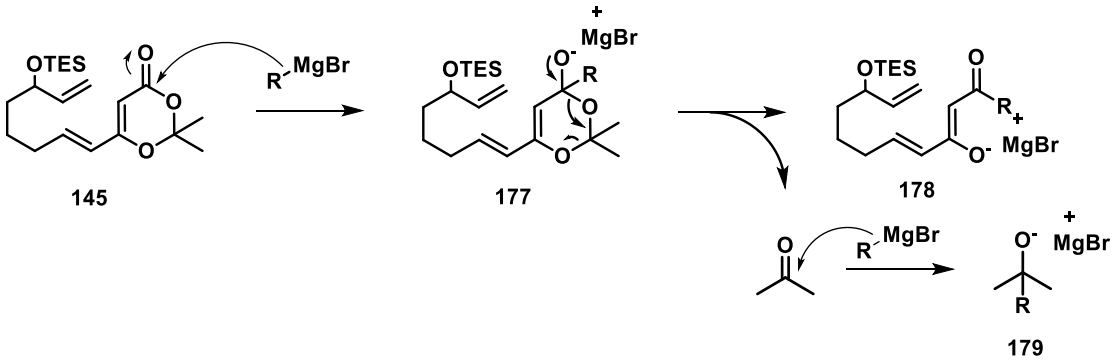
4.6 Unsaturated 1,3-diketone precursor

To the best of our knowledge carbon nucleophiles that have been used with 1,3-dioxin-4-ones are silylenolethers by Wang and List[94] (**Scheme 78**). This Mukayama-Claisen type reaction proceeds likely through a thermally promoted acetoketene **179** formation.



***Scheme 78**: Mukayama-claisen reaction of 1,3-dioxin-4-ones*[94].

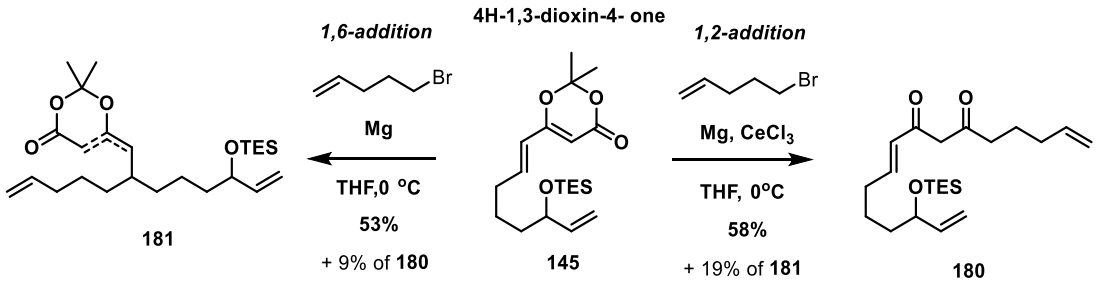
We postulated that, mechanistically, a Grignard addition to form 1,3 diketones should be also possible as in **Figure 13**. The addition of the Grignard reagent to the 1,3-dioxin-4-one **145** should result in a formation of the anionic unsaturated 1,3-diketone **178** that should be unable to react 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**).



***Scheme 79**: Mechanism of the Grignard addition to the 1,3-dioxin-4-one compound **145**.*

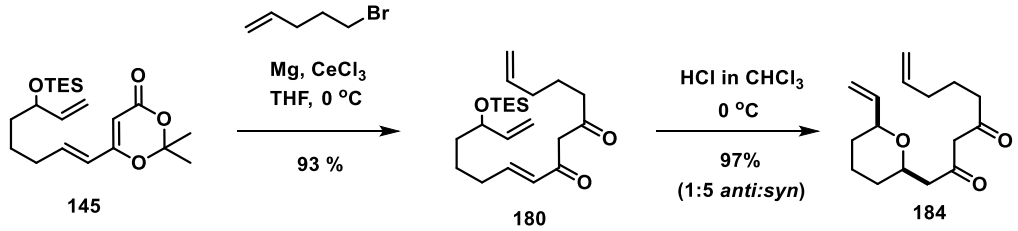
When the reaction was done for the first time at ambient temperature, we obtained the product **180** in 16% yield and a side product that we believe is a mixture of two diastereoisomers of 1,6-addition product **181** that still has the 1,3-dioxinone core intact. The next step was to reduce the temperature 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 $CeCl_3$ 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**.*

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-Michel reaction of the 1,3-diketone substrates **145** and **180**.*

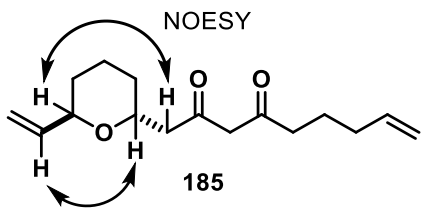
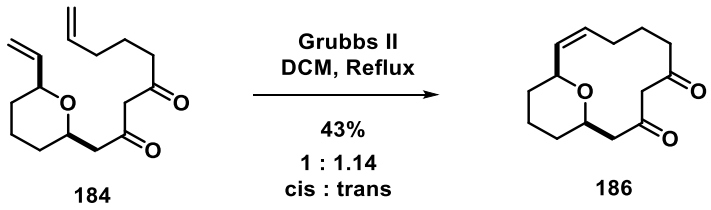


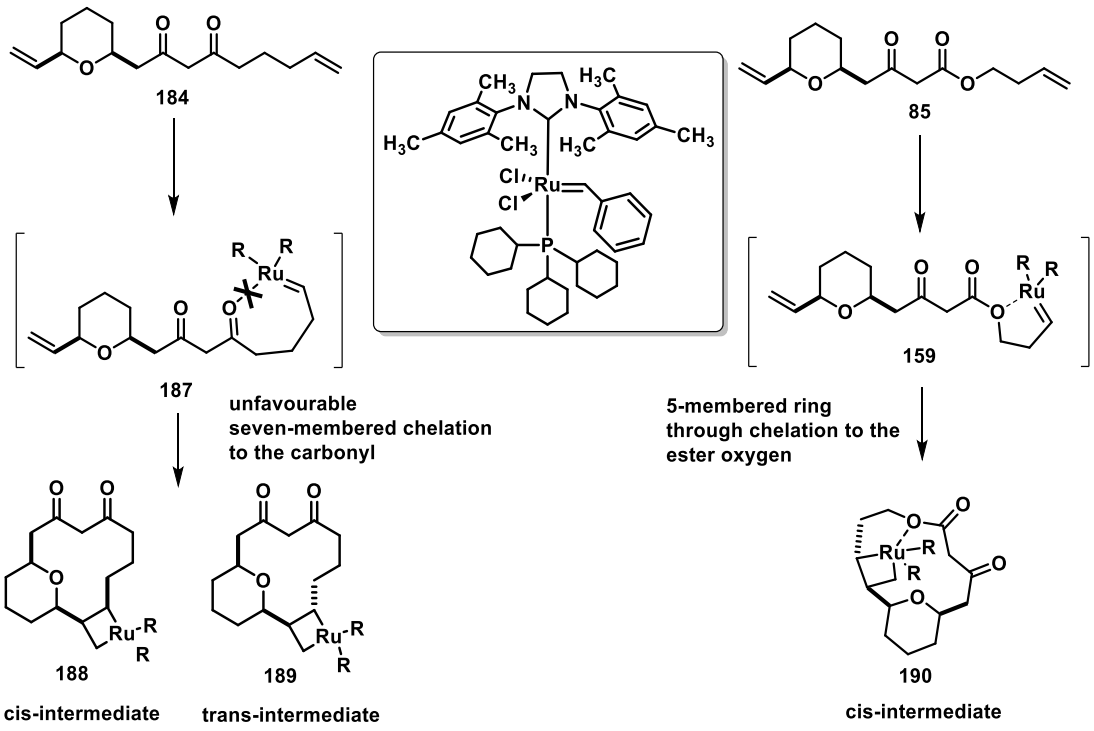
***Figure 19**: NOESY analysis of the minor product of the oxy-Michael reaction.*

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**).



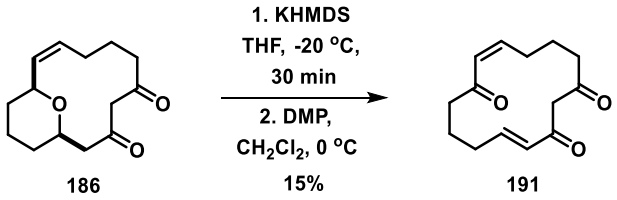
***Scheme 82**: RCM-reaction of the 1,3-diketone **184**.*

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.[95] 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**).



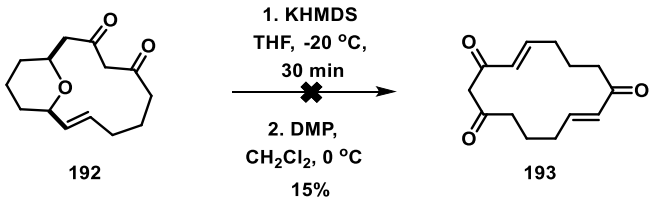
***Scheme 83**: Chelation of the ester-and diketone starting materials in the RCM to the metallocarbene.*

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**.*

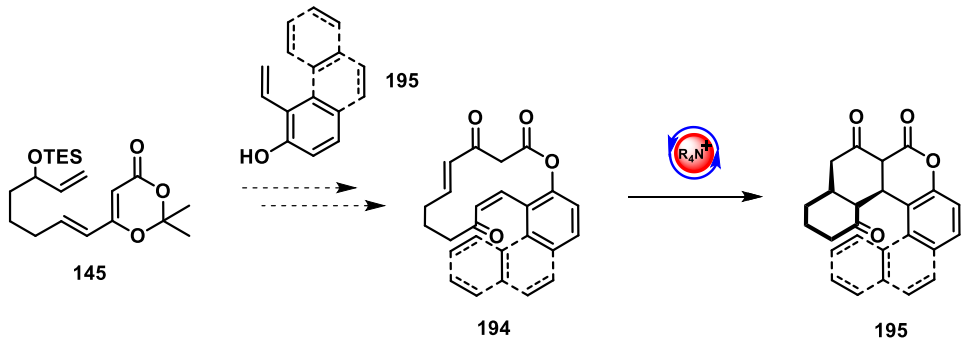
When the trans-macrocycle was subjected to the retro-oxy-Michael reaction no product was observed. This could be caused by the different conformation compared to the ester-macrolactone that slows down the initial deprotonation of the 1,3-dicarbonyl **186**. With the 1,3-diketone substrate the second 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

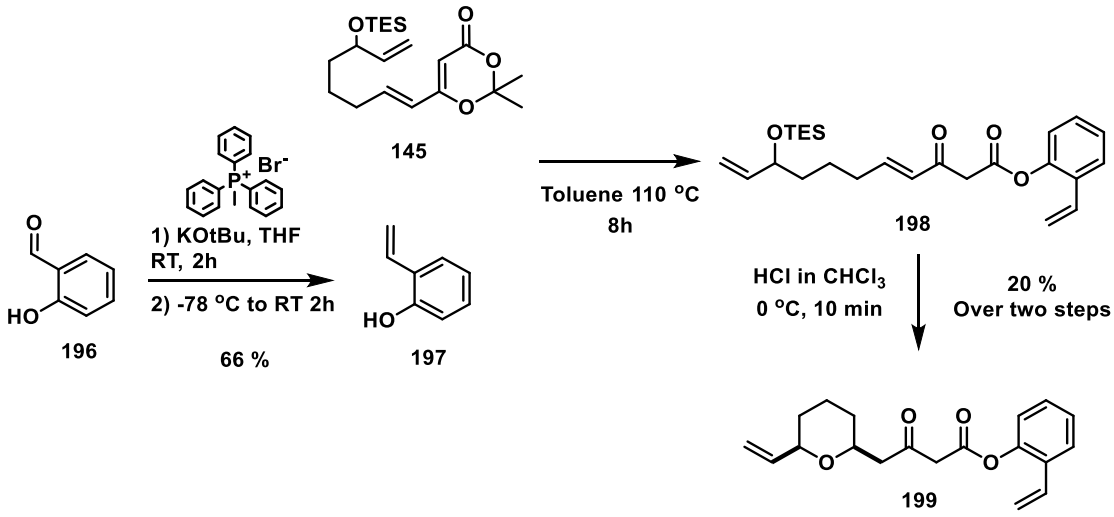
Because all substrates synthesised are aliphatic we decided to synthesise ester substrates to form phenolic esters so that we could investigate how the cascade behaves with aromatic substrates. When working, aromatic core can provide rapid access to substrate diversification. More interestingly if the 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.*

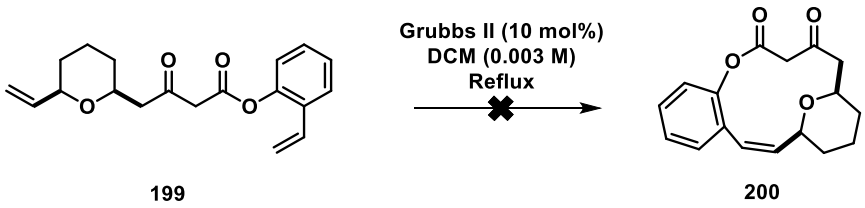
The synthesis of the aromatic cascade precursor started form the synthesis of the 2-vinylphenol via Wittig-reaction of salicylic aldehyde and methyltriphenylphosphonium bromide.[96] The Wittig reaction using KOtBu as a base gave 66% yield of the 2-vinylphenol **199** (**Scheme 87**).

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**.*

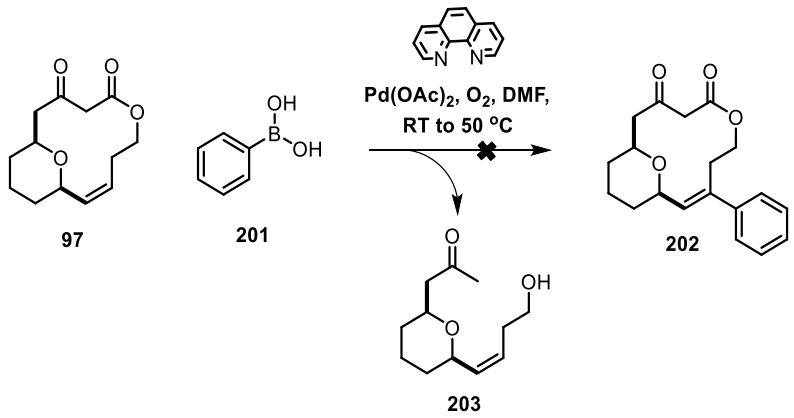
Even after the purification of the oxy-Michael product we could still see the 2-vinylphenol **197** by TLC analysis. This made us doubt the stability of the phenolic ester, which could also explain the complexity of the purified thermolysis product **198**. In the next RCM reaction no product was observed 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**.*

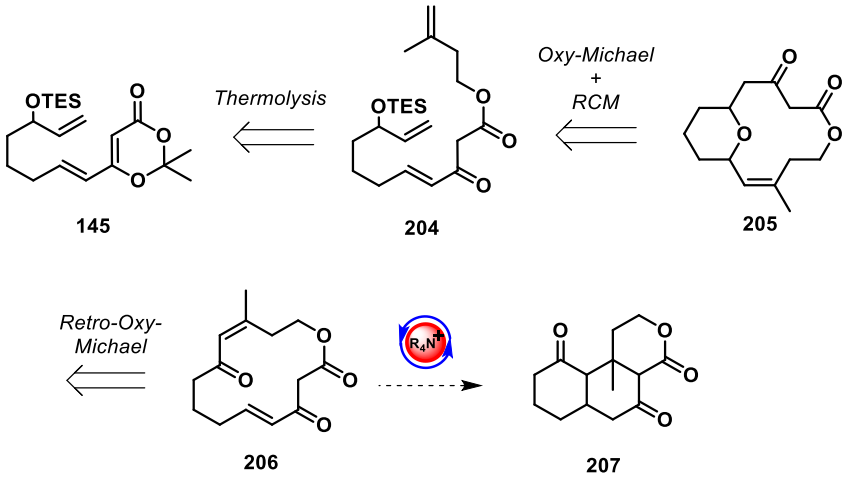
4.8 Synthesis of the Methylated Olefin substrate

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**).



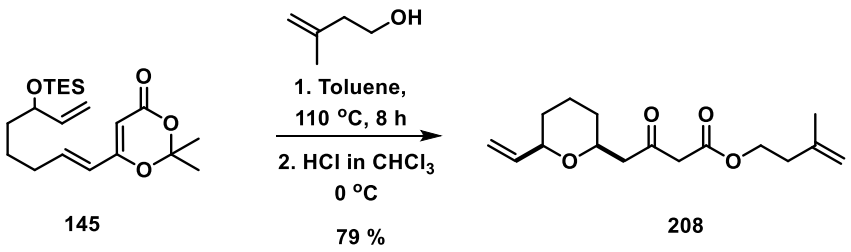
Scheme 89*:Pd-coupling for the modification of the macrolactone olefin **97**.*

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.



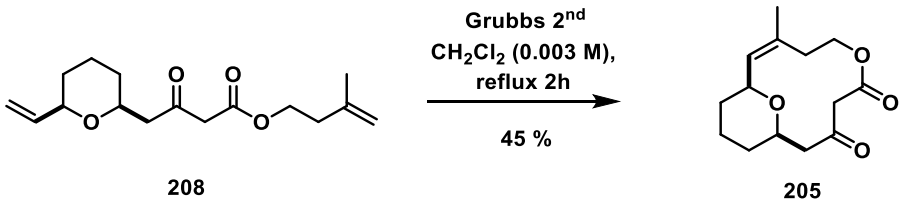
***Scheme 90**: Synthesis plan for the β-methyl-enone **208**.*

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**).



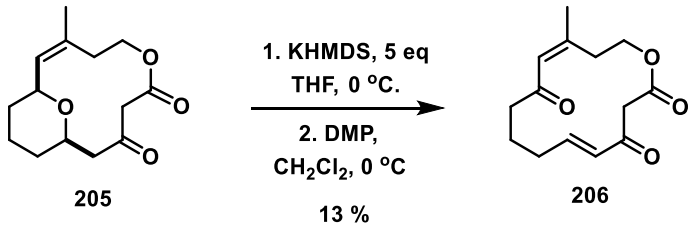
***Scheme 91**: Thermolysis and oxy-Michael reaction of **208**.*

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**.*

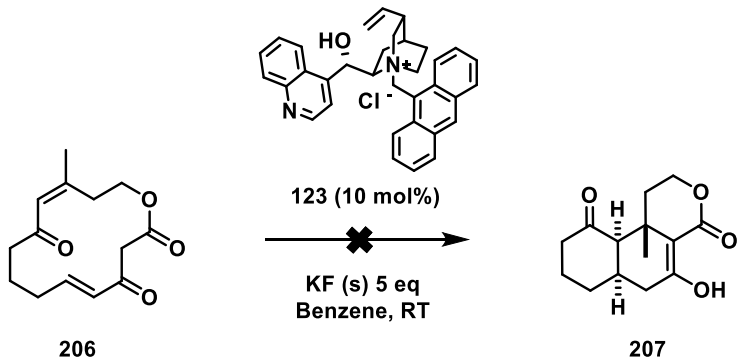
The retro-oxy-Michel reaction and the subsequent oxidation gave the cascade precursor **206** in low 13% yield over two steps (**Scheme 93**).



Scheme 93*:Retro-oxy-Michael of the methylated macrolactone* ***205****.*

4.9 Transannular cascade with the methylated enone substrate

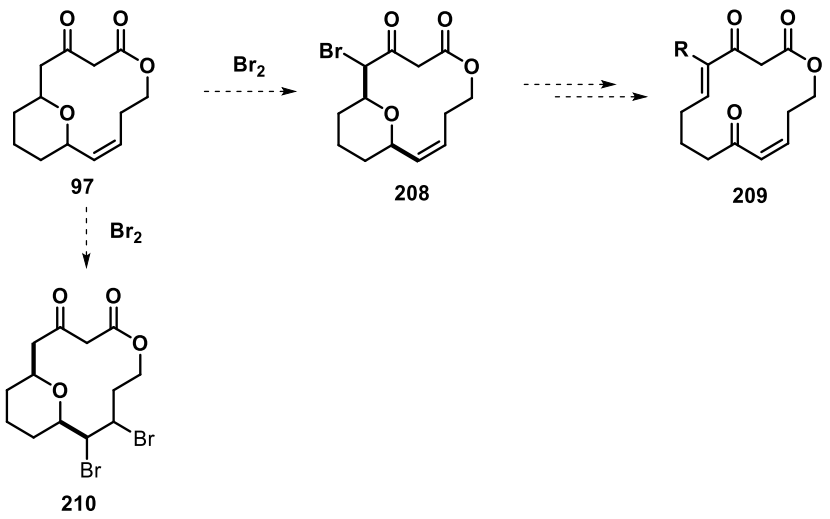
The cascade precursor **206** was treated under the optimised phase-transfer conditions but unfortunately, we observed no reactivity or product and only starting material was recovered. It is surprising that so small changes in the core of the cascade precursor can prevent the cascade from cyclising.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



Scheme 94*: Transannular cascade of the methylated enone precursor* ***206****.*

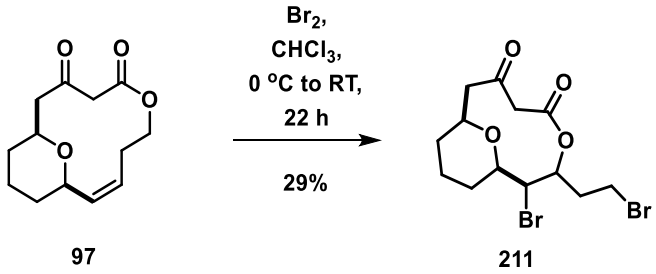
4.10 Bromination of macrocycle 97

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.[97] This α-brominated compound **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 **210** could be modified via elimination to a useful compound in the synthesis of the cascade precursors (**Scheme 95**).



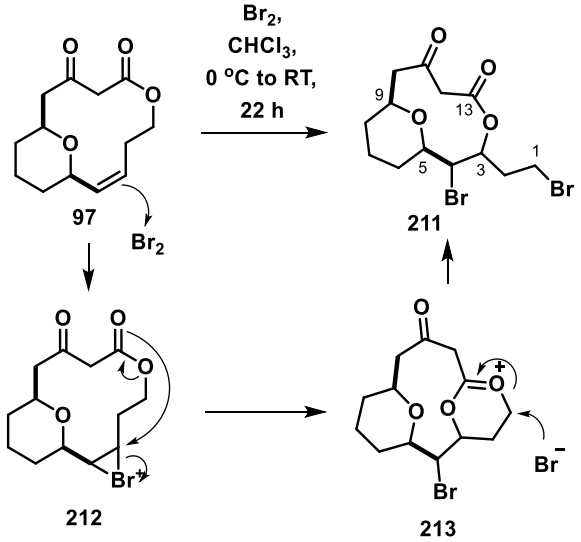
***Scheme 95**: Planned bromination of the macrocycle **97**.*

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**).



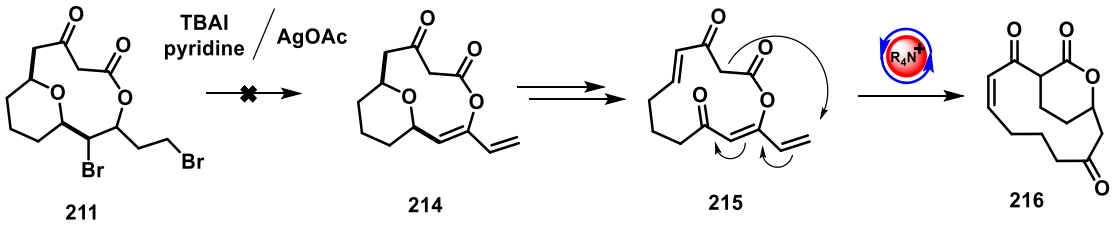
Scheme 96*: Bromination of the macrolactone **97**.*

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**).



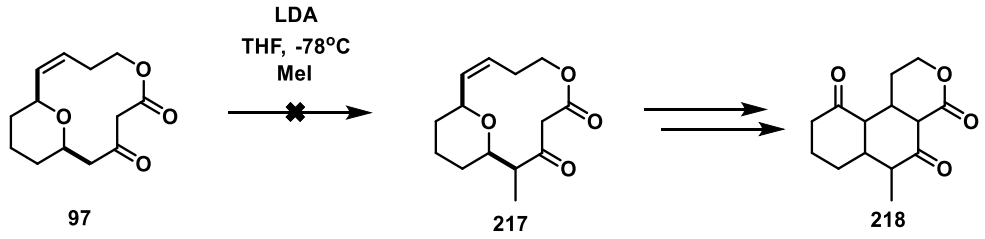
Scheme 97*: Plausible mechanism of the bromination.*

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**).



***Scheme 98**: Elimination of the dibromide **211**.*

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**).



***Scheme 99**: Methylation of the α-proton via double anion.*

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**).

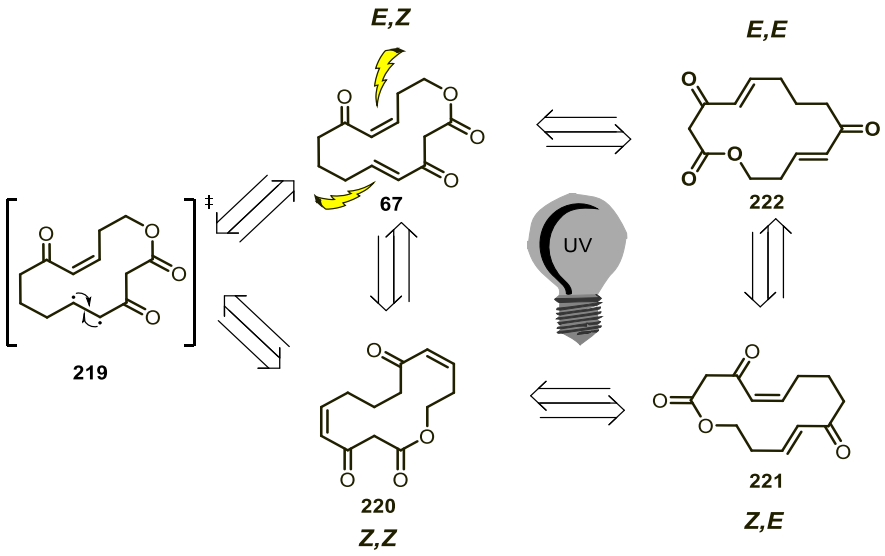
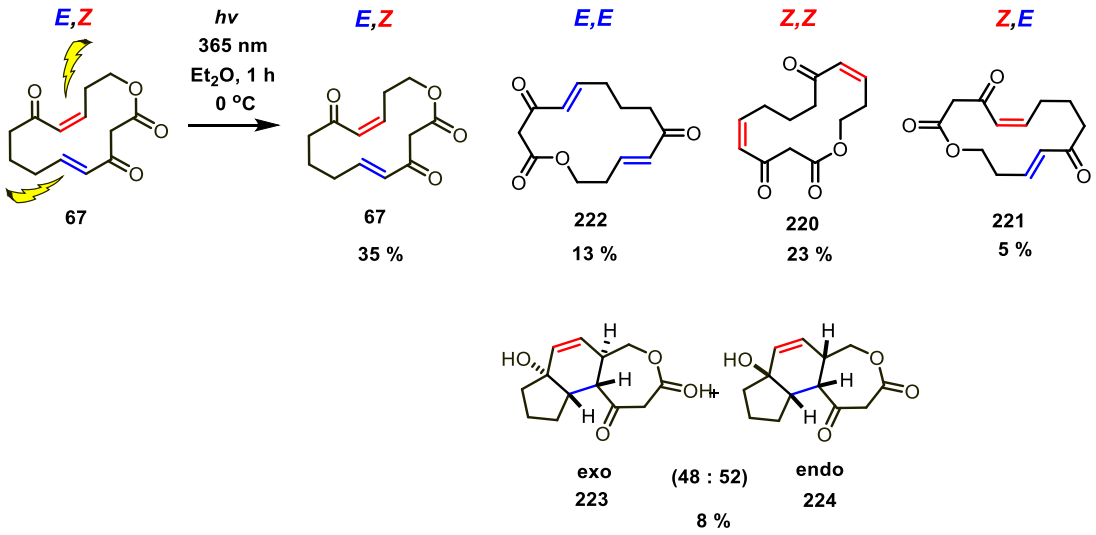


***Figure 20**: UV-isomerisation of the cascade precursor.*

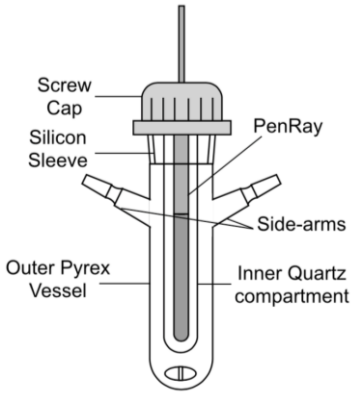
By irradiating the macrocycle in a custom made irradiation vessel (**Scheme 101**) with 365 nm UV-light at 0 °C we were able to obtain all the 4 possible cascade isomers. Photon energy for 356 nm photon is 87 kcal/mol ($E = hc / \lambda$) whereas the energy of olefins is usually around 146 kcal/mol.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

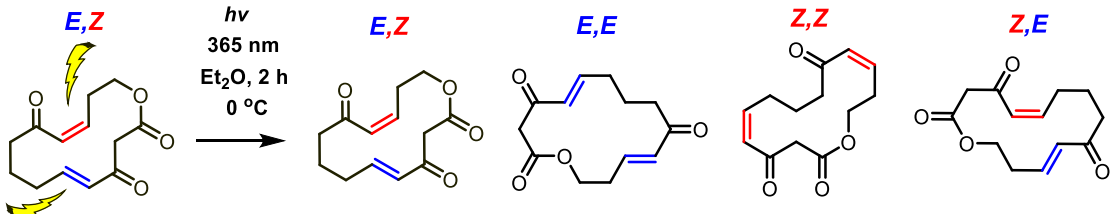


***Scheme 100**: Isomerisation of the cascade precursor.*



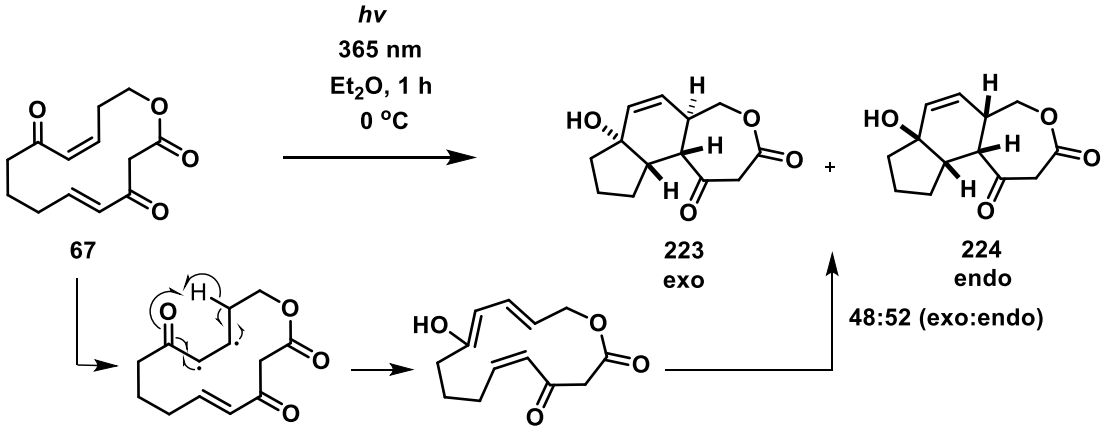
***Scheme 101**:Used irradiation vessel custom-made by Terri Adams (University of Oxford). Image courtesy of Jack Hoffman.*

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**.*

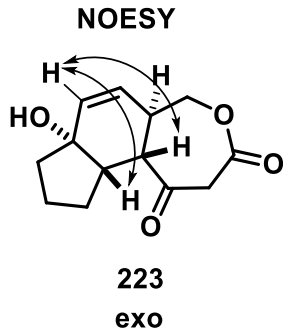


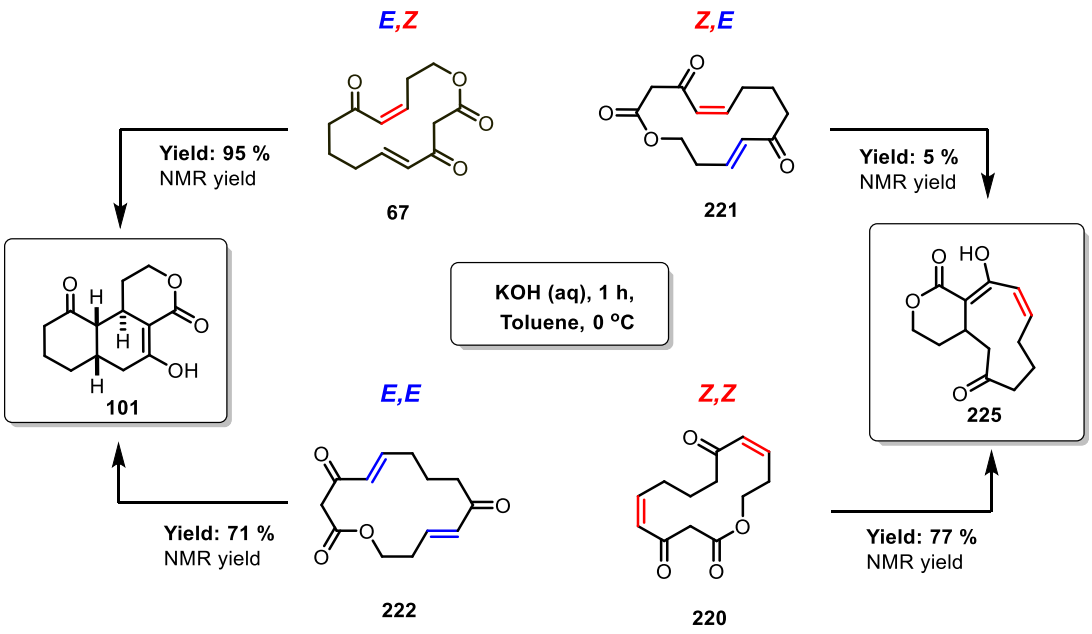
Figure 21*: NOESY analysis of the exo-**223**.*

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.

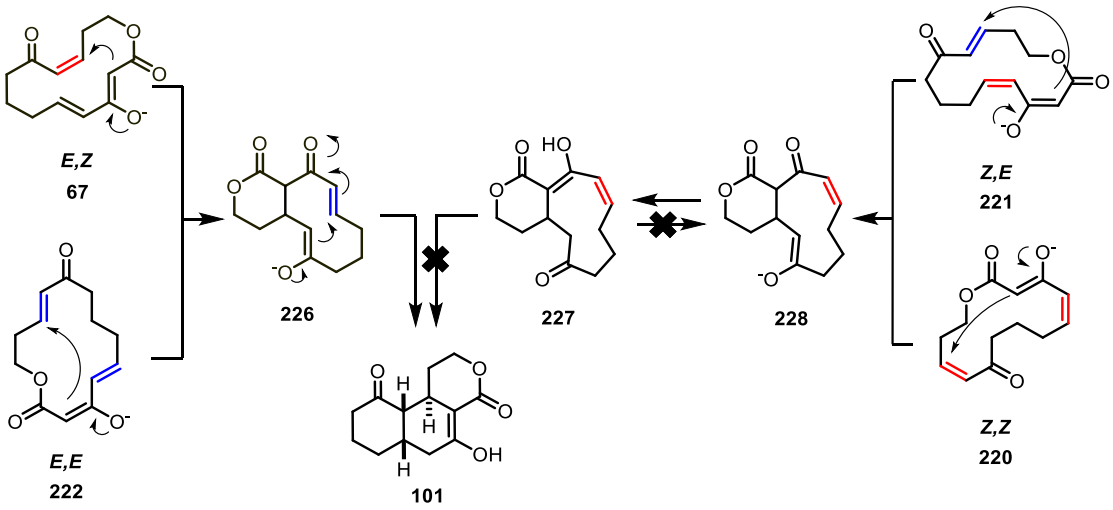
5.2 Racemic transannular cascades

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**).



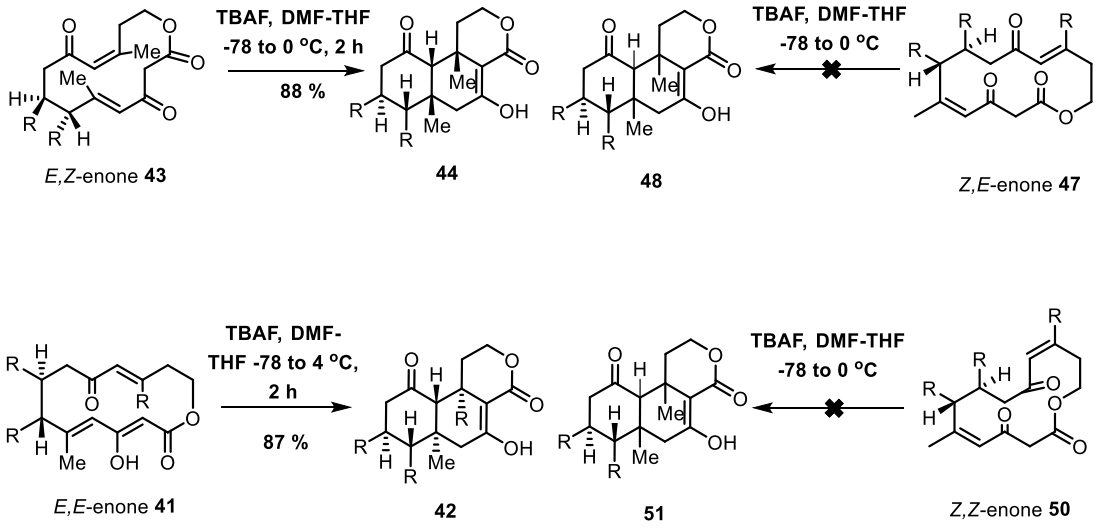
***Scheme 104**: Transannular cascades of the isomerised precursor under basic conditions.*

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*

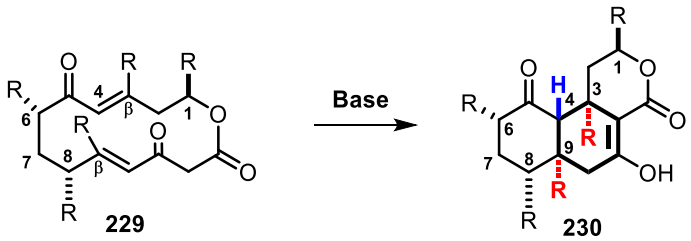
These findings in reactivity are in accordance with the results of Xue *et al.*[22,23] where *E,Z*-bis-enone **43** and *E,E*-bis-enone **41** were shown to cyclise under basic conditions to form a fused tricycle whereas when *Z,E*-bis-enone **47** or *Z,Z*-bis-enone **50** were used no cyclisation products were observed (**Scheme 106**).



***Scheme 106**: Cyclisation of enone isomers by Xue* et al.[22,23]

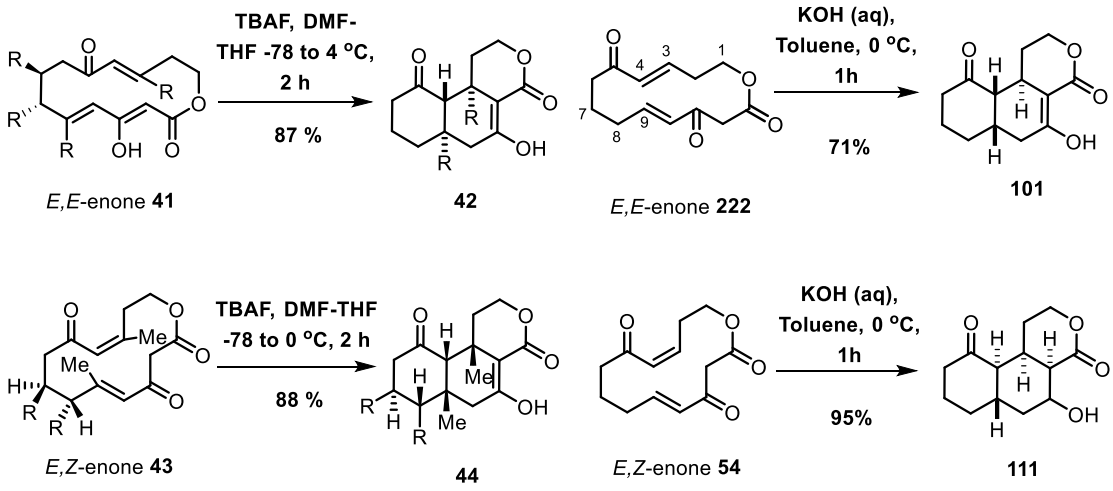
Although, the reactivity is very dependent on the conformation of the enones, it seems substrates on a macrolactone core determine exo/endo stereoselectivity of the cyclisation. In all published transannular cyclisations of *E,E*-bis-enones the starting materials have substituents at C1, C6, or C8 positions and the cyclisations gives a product where *β*-enone substituents (C3, C9) end up on the same face of the formed tricycle **230** whereas the α-hydrogen (C4) ends up on the opposing face (**anti-anti** diastereomers) (**Scheme 107**). Similar stereoselectivity was observed by Scheerer *et al.*[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 α-proton (C4) and opposite face compared to the β-methyl-enone. Enhancement of this selectivity was observed when a C8-substituent anti to the C1 substituent was added.[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.*[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.*[21] has showed that when both β-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 β-methyl substituted enones enhance the diastereoselectivity of the transannular cyclisation reaction.



***Scheme 107**: Stereoselectivity of the substituted E,E-bis-enone macrolactone.*[20]

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 (*syn-anti* diastereomer) (**Scheme 108**). Prior to our work, only one *E,Z*-bis-enone cyclisation **43** has been reported by Xue *et al.*[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 (**Scheme 108**).

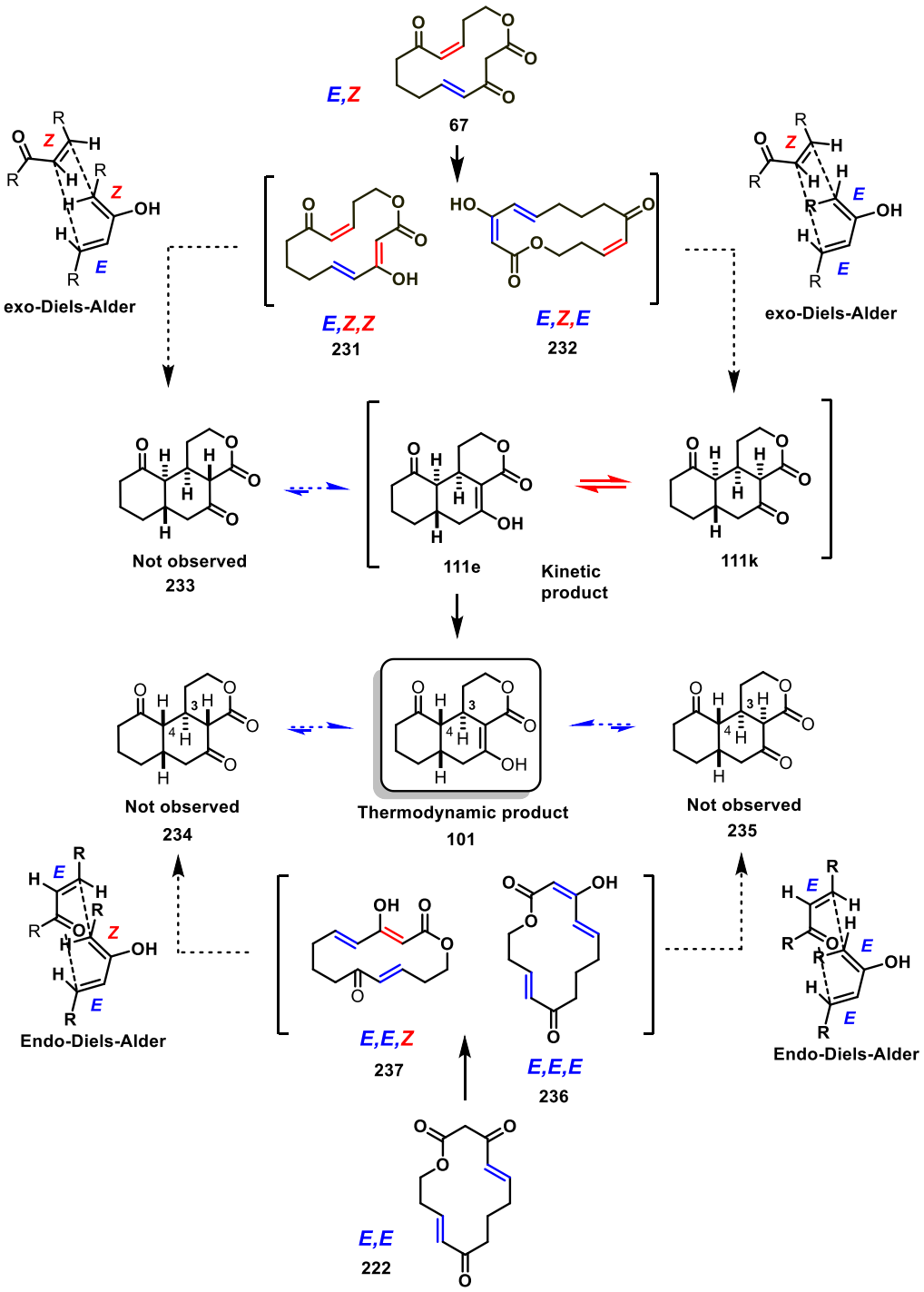


***Scheme 108**: Stereoselectivity of substituted and unsubstituted cascades.*

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.

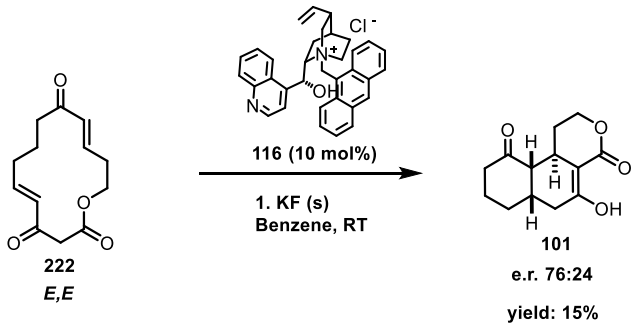


Scheme 109**: Stereoselectivity of* E,E-*bis-enone* ***222 *and* E,Z-*bis-enone* ***67***.

5.3 Asymmetric transannular cascade

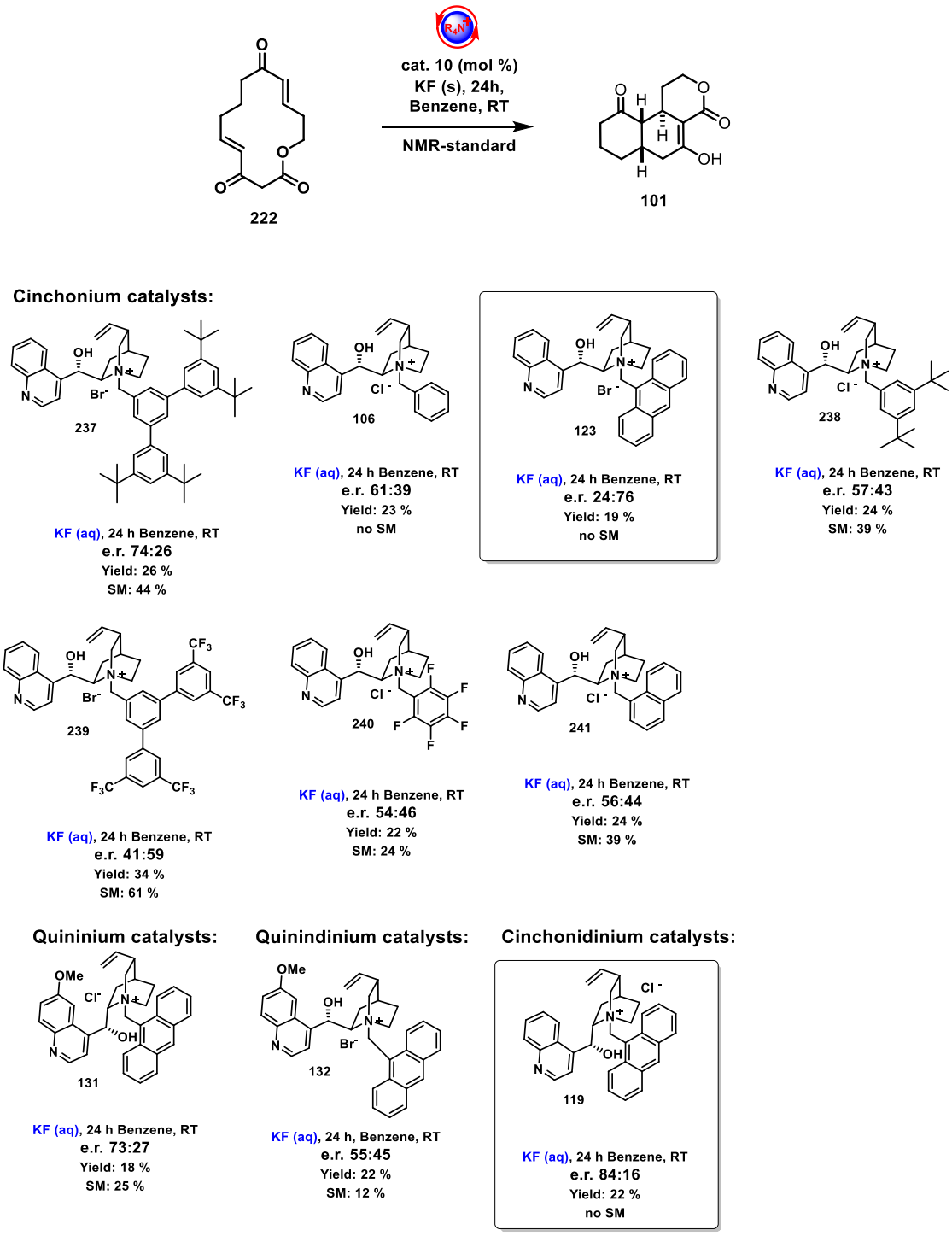
5.3.1 E,E-macrocycle

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**).



***Scheme 110**: Asymmetric cascade of the* E,E-*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*-asymetric cascade.*

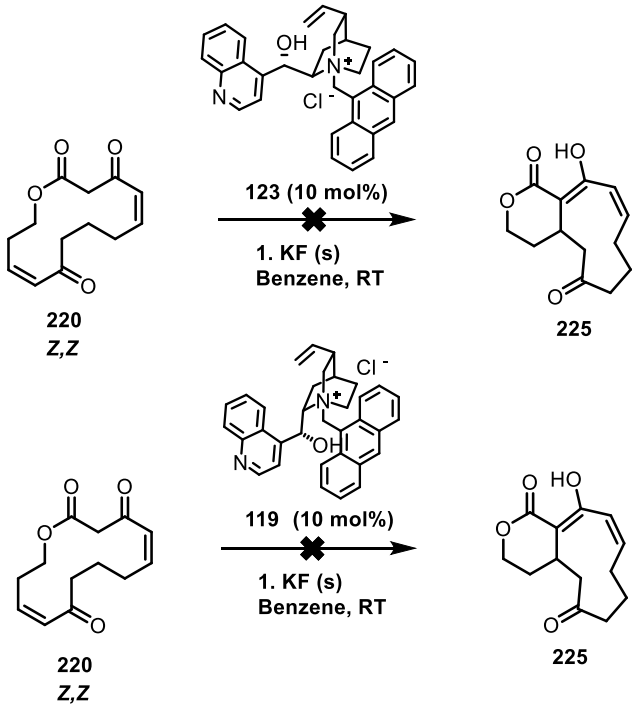
For the optimisation we investigated 10 different catalyst. As previously the best yields and enantioselectivities were obtained with anthracenyl cinchonidinium and anthracenyl cinchonium catalysts. Unfortunately, **119** and **123** respectively no other catalyst used gave any improvement in the enantioselectivity. 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**.

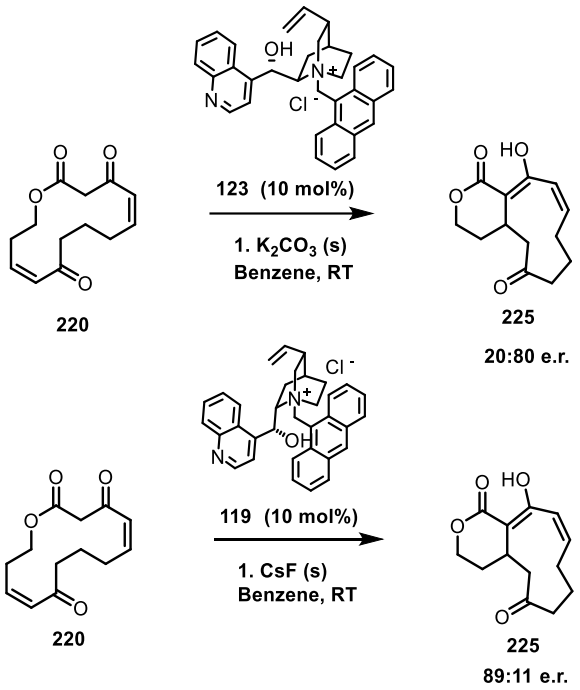
5.3.2 Z,Z-macrocycle

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



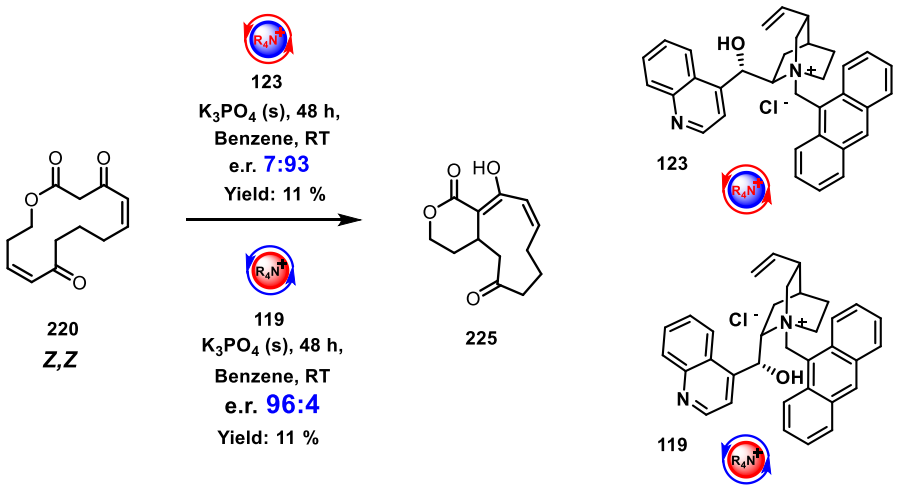
***Scheme 112**: Z,Z-precursor **220** under the optimised cascade conditions.*

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 (K_2CO_3) 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 K_2CO_3 we obtained an e.r. of 20:80 (**Scheme 113**).



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

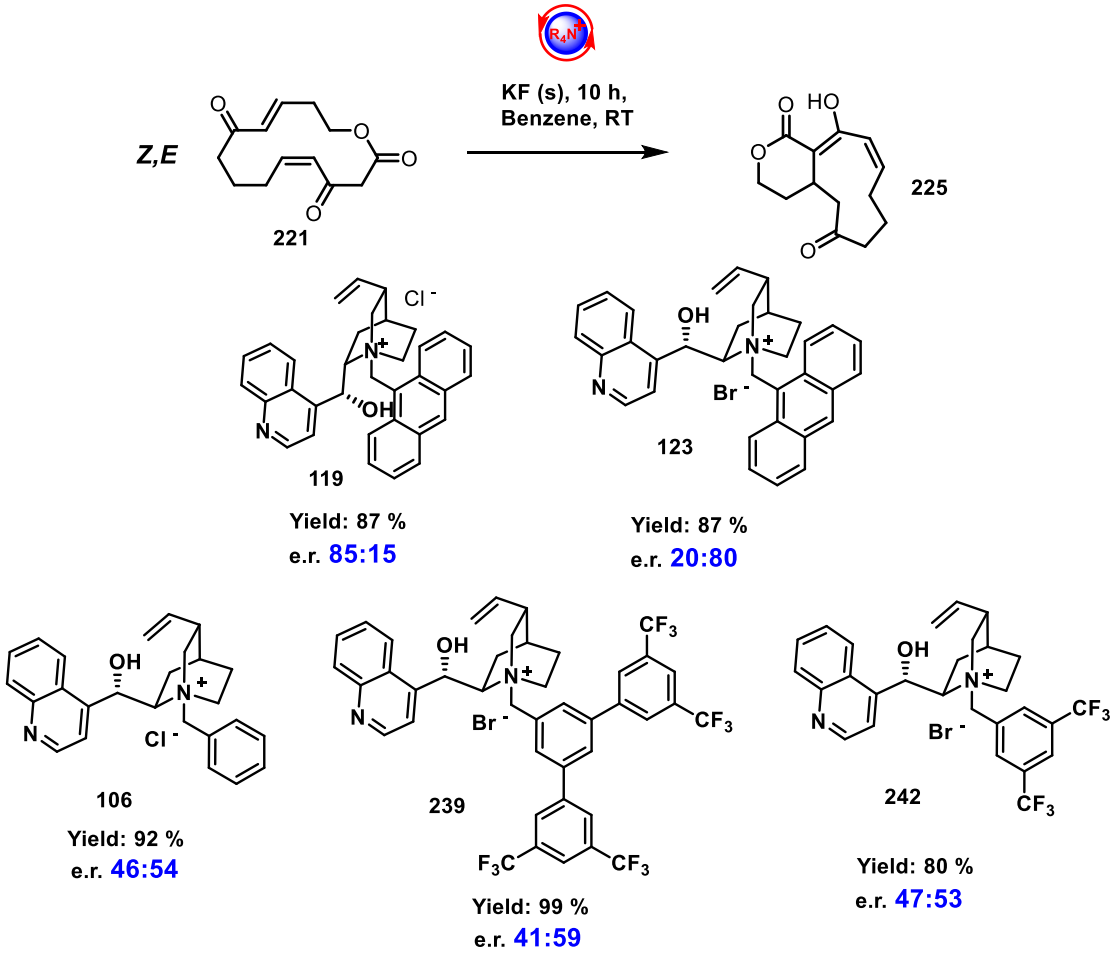
The best results albeit still with poor yields were obtained when potassium phosphate was used as a base. After 48 hours we isolated product **225** in 11% yield for both of the reactions using anthracenyl catalyst **123** and **119** as the phase-transfer catalysts. In spite of the poor yield, the enantioselectivities 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

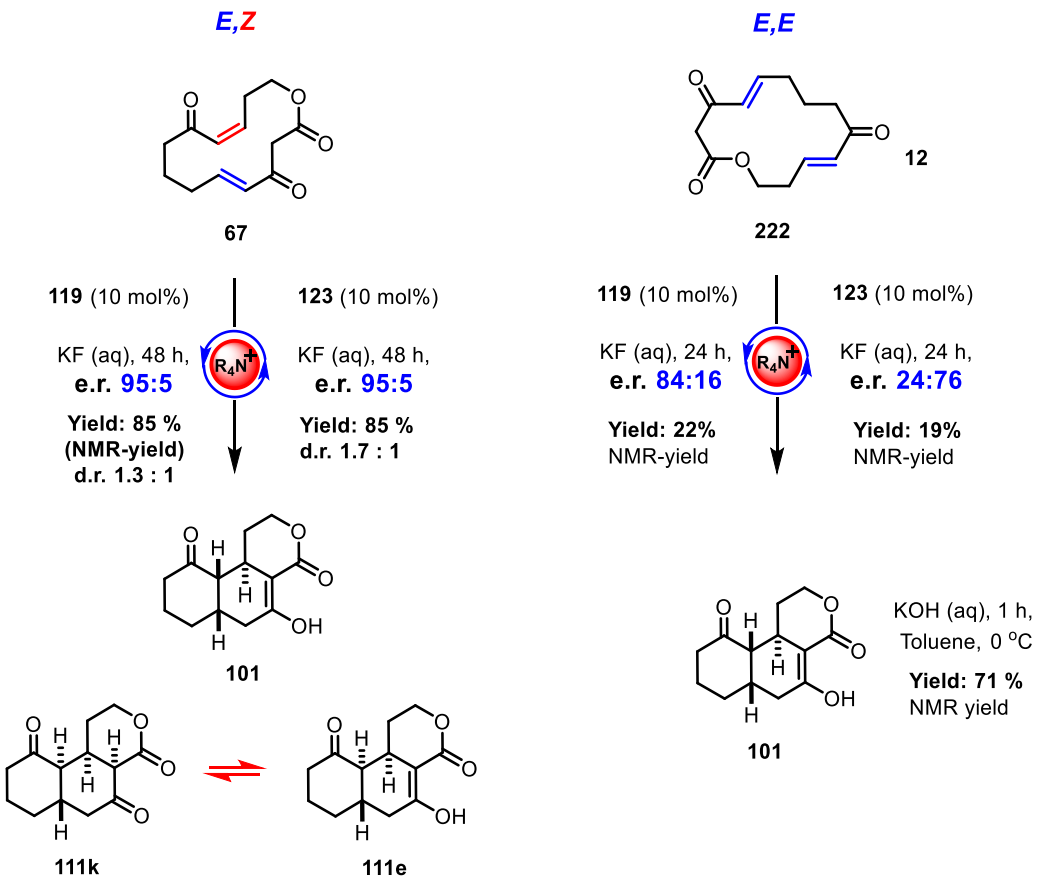
With the *Z,E*-macrocycle **221**, we had only a small amount of material available for a cascade optimisation due to the instability of the precursor. We choose 5 different catalysts for the short optimisation of the cascade. Catalyst **119** and **123** again proved to be the best catalyst for the 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 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**).

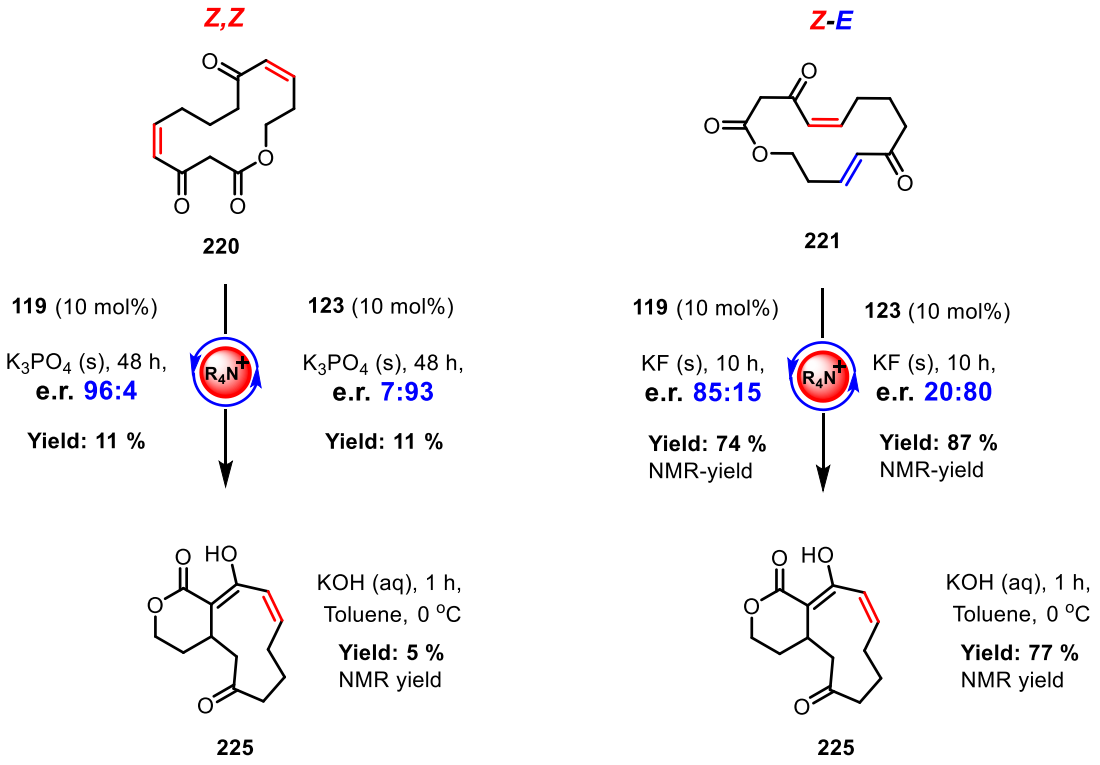


***Scheme 116**: Asymmetric phase-transfer catalysed transannular cyclisation of E,Z- and E,E-bis-enones **67** and **222**.*

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**).

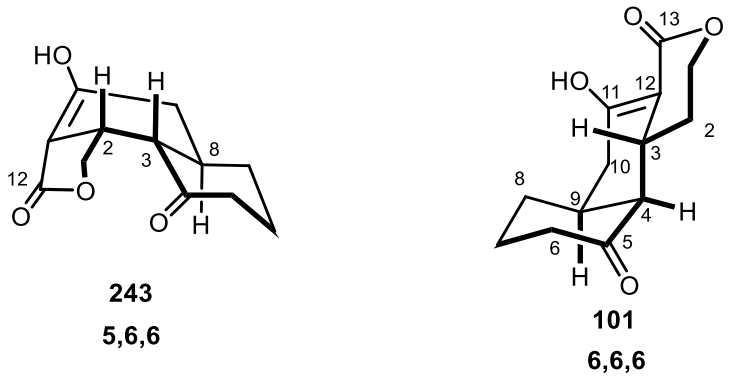
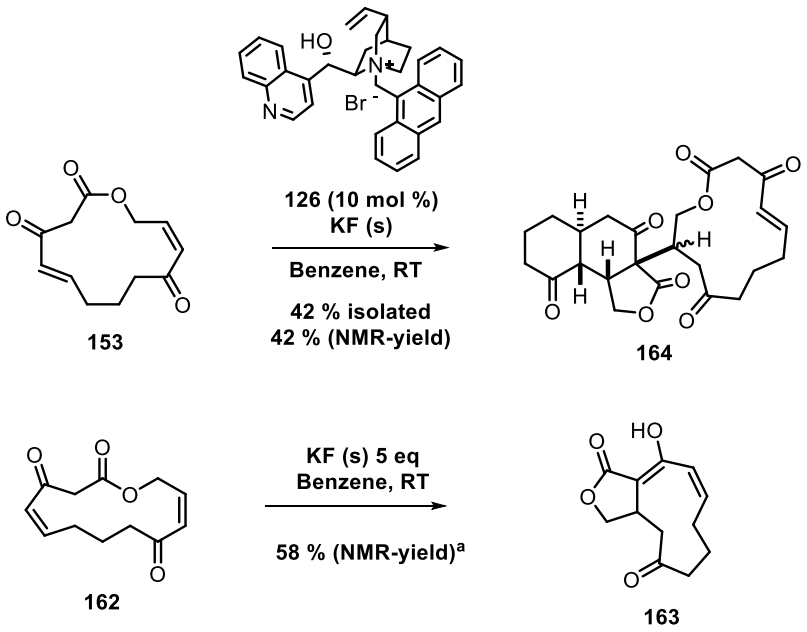


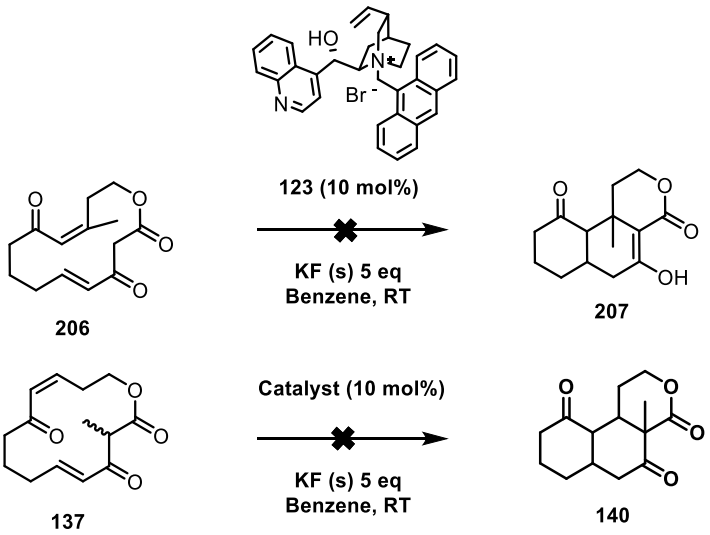
Figure 22*:Conformations of 5,6,6- and 6,6,6-tricycle enolates.*

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.[a] This reaction was carried out on a small scale and the product **162** was quantitatively characterised by ^{1}H-NMR, COSY and MS.*

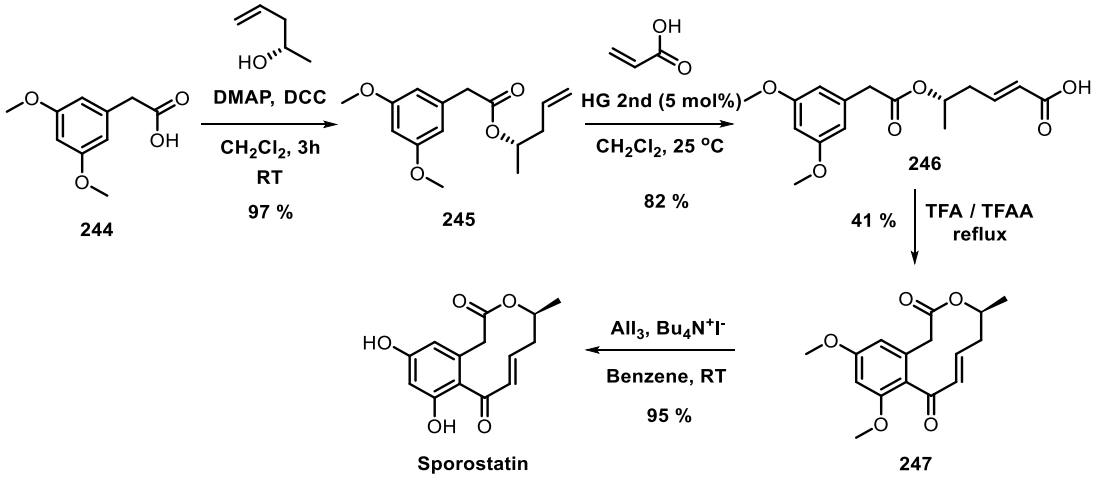
With the methylated ketoester **138** the reaction started to prefer the elimination-decarboxylation of the precursor. With methylated *Z*-enone **208** no reactivity was observed.



***Scheme 119**: Other cascade precursors.*

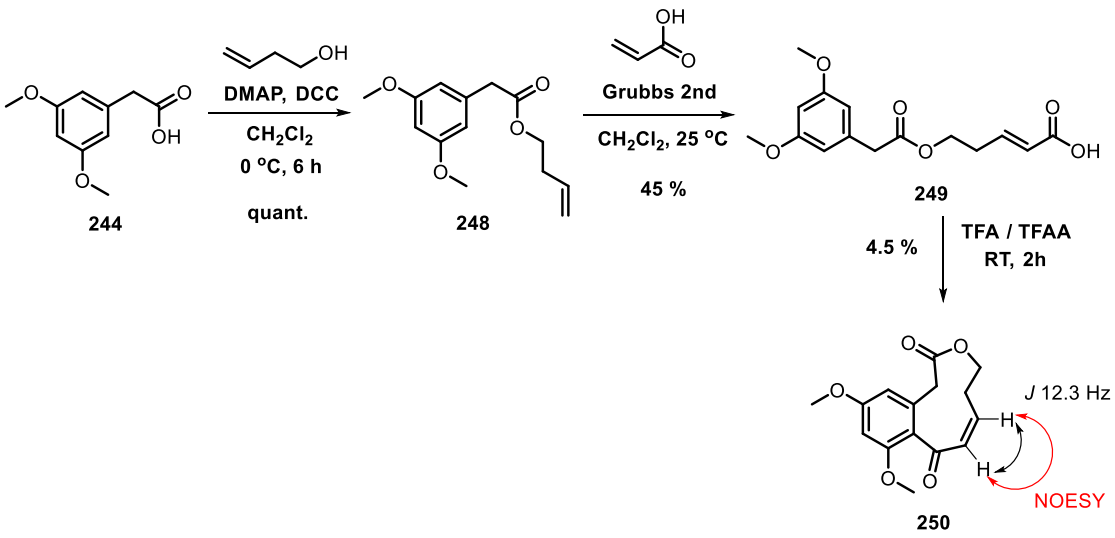
5 Synthesis of aromatic scaffold for transannular Michael-reaction

J. S. Yadav *et al.*[102] have described a relatively short total synthesis of Sporostatin which relies on a intramolecular Friedel-Crafts acylation[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.



***Scheme 120**: Total synthesis of **Sporostatin** by J. S. Yadav et al.*[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 2nd generation catalyst rather than the Hoveyda-Grubbs 2nd generation the authors used. The methathesis gave 45% yield of the *E*-enonic acid **249** (**Scheme 121**).



***Scheme 121**: Synthesis of the unsaturated macrocycle **250**.*

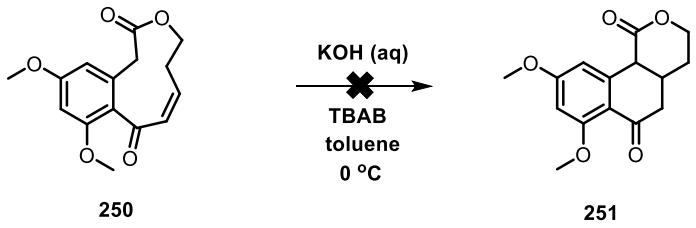
Unlike in the total synthesis of the Sporostatin by J. S. Yadav *et al.* in our synthesis the intramolecular Friedel-Crafts reaction gave a low 4.5% yield of only the *Z*-conformer **250** of the macrocycle whereas in the total synthesis the authors reported *E*-isomer **247** for the product. Authors 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 AlI_3 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 ^{1}H-NMR. Under these conditions,

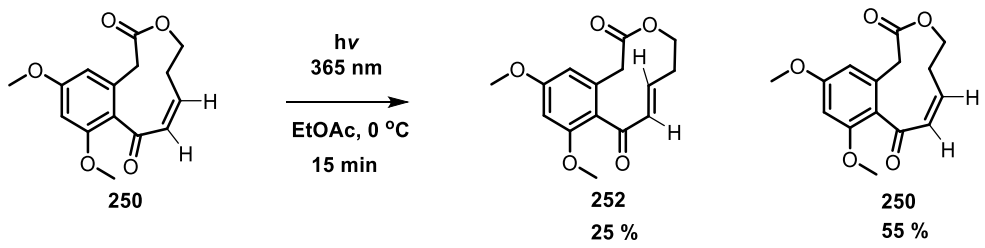
the starting material is probably hydrolysed to the corresponding acid. We also attempted strong base KHMDS in the reaction but no product could be observed.



***Scheme 122**: Attempted transannular Michael-reaction of **250** under phase-transfer conditions.*

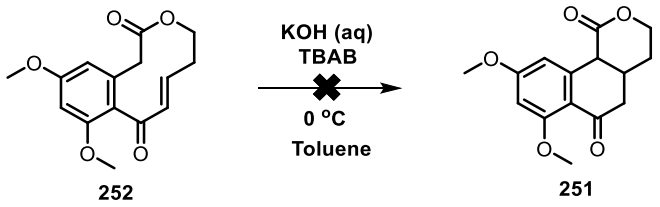
As the reaction did not produce any Michael-addition product we postulated that the reason for this is either the low acidity of the α-proton or the conformation of the macrolactone that prevents the nucleophile from reacting with the enone. As we had previously carried out enone-macrocycle isomerisations, 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**).



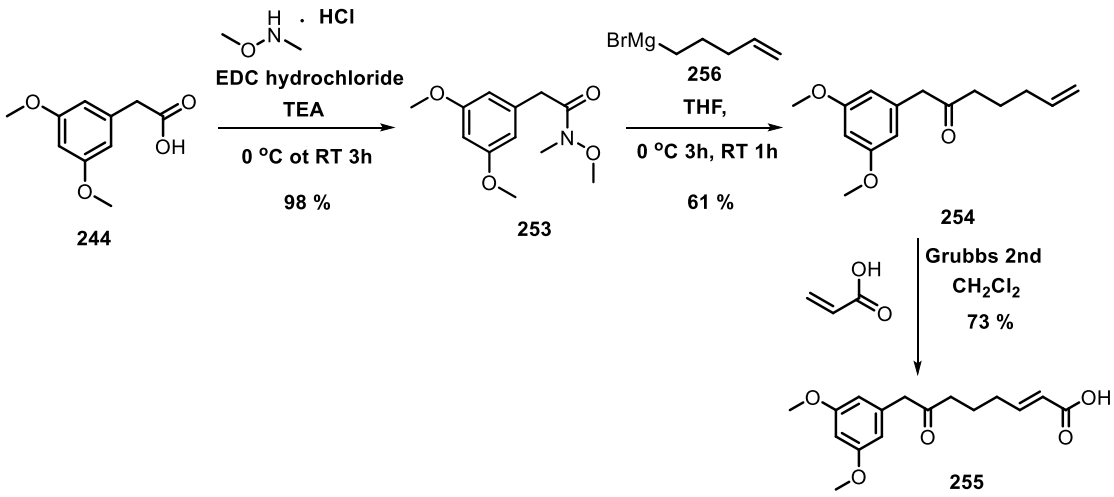
***Scheme 123**: Isomerisation of the macrocyclic enone **250**.*

When the cascade was attempted the *E*-macrocycle **252** did not give any expected desired transannular Michael-addition product under phase-transfer conditions (**Scheme 124**).



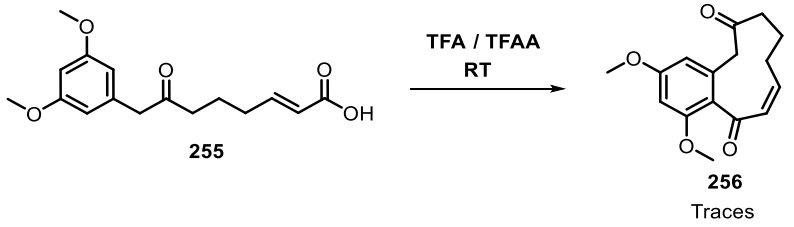
***Scheme 124**: Transannular Michael-reaction of the Z-macrocyclic enone **252**.*

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 arcylic acid the ketone gave good yield of 73% of the corresponding *E*-acid **255** (**Scheme 125**).



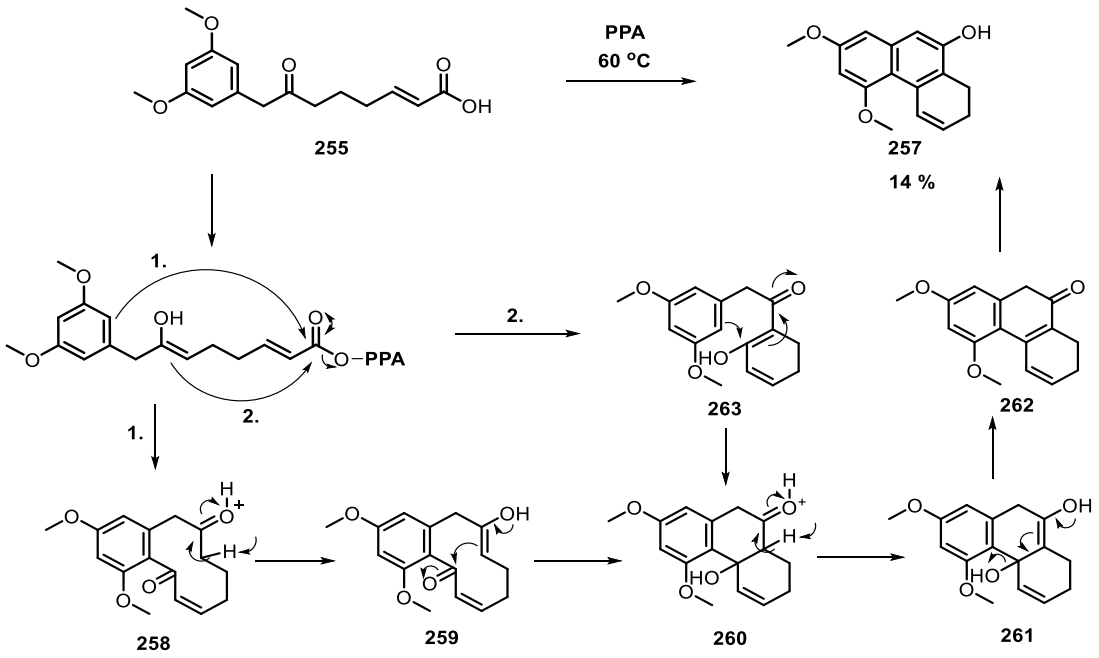
***Scheme 125**: Synthesis of a ketone starting material for the transannular Michael-addition.*

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**).



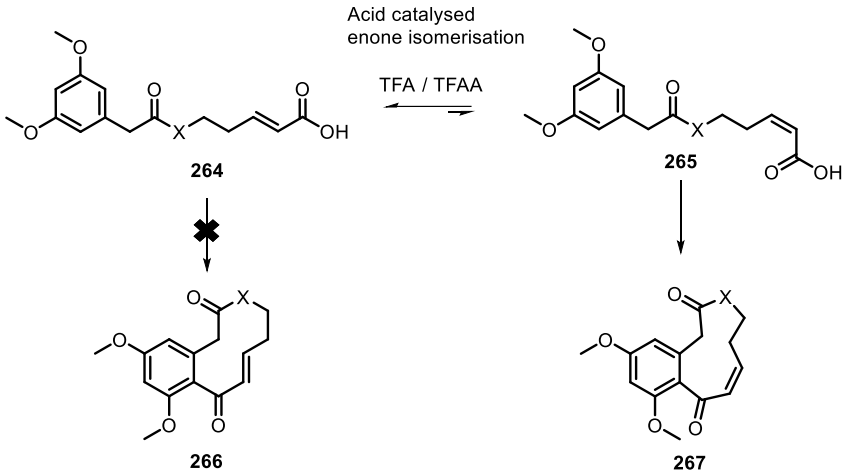
***Scheme 126**: Intramolecular Friedel-Crafts reaction to form macrocycle **256**.*

When the reaction was done in neat polyphosphoric acid the reaction gave surprisingly **257**, containing a natural product like phenanthrene core[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[109] (**Scheme 127**).



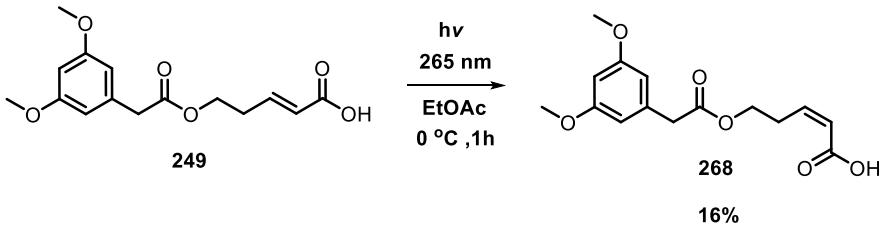
***Scheme 127**: Friedel-Crafts reaction of **255** in PPA and postulated mechanisms.*

As the Friedel-Crafts acylation produces only the *Z*-isomer **256** of the marcrocycle, 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**).



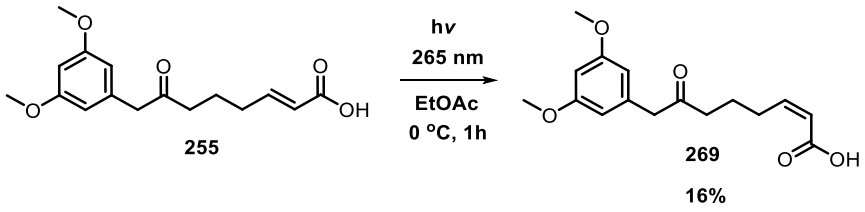
***Scheme 128**: Isomerisation of the open-chain enoic acic **264**.*

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**).



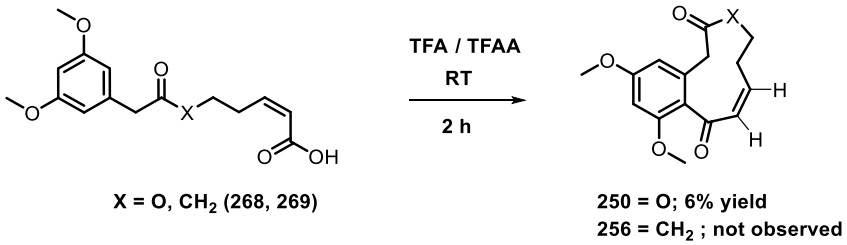
***Scheme 129**: Isomerisation of the enonic acic **249**.*

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 130**: Isomerisation of the acic **255**.*

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.

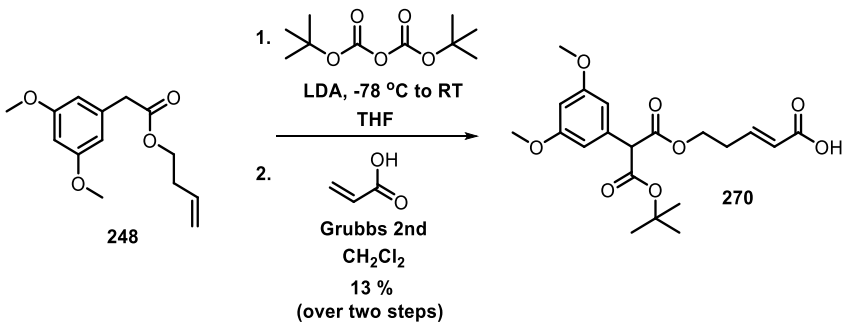


***Scheme 131**: Friedel-Crafts acylation of the Z-enonic acid.*

7.2 Synthesis of more acidic scaffold for the transannular Michael-addition

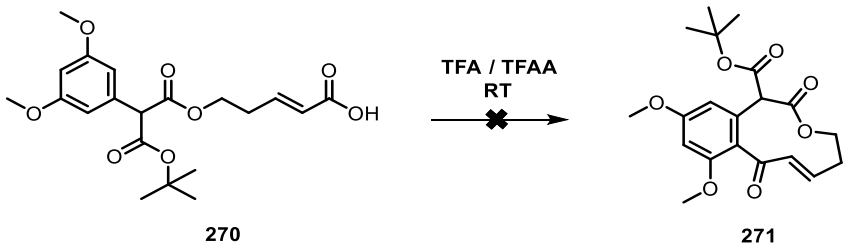
After observing low reactivity with **250**, we decided to modify the macrolactone core. By changing the ester to a malonate the pK_a of the α-proton should be reduced and we hoped that it could react better with the Michel-acceptor.

We decided to add a *tert*-butyl ester in the early stage of the synthesis. The acylation[110] 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**).



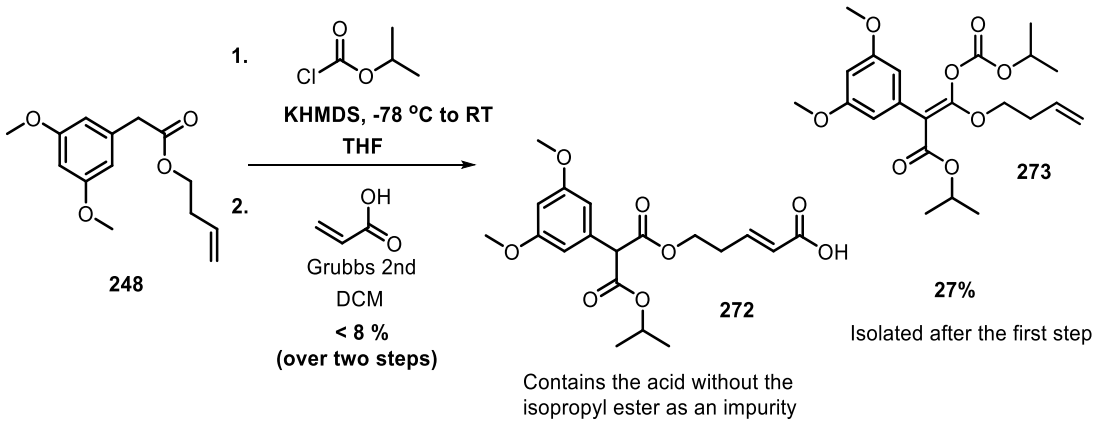
***Scheme 132**: Synthesis of the enoic acid **270**.*

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.



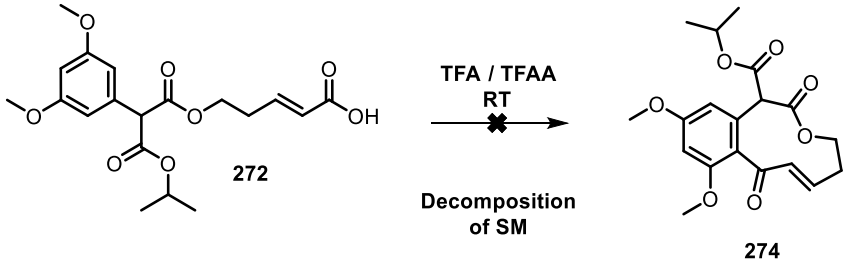
***Scheme 133**:Intramolecular Friedel-Crafts reaction of **270**.*

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**).



***Scheme 134**: Synthesis of the enoic acid **272**.*

We used the impure material for the intramolecular acetylation but the reaction did not produce any desired macrolactone **274** (**Scheme 135**).

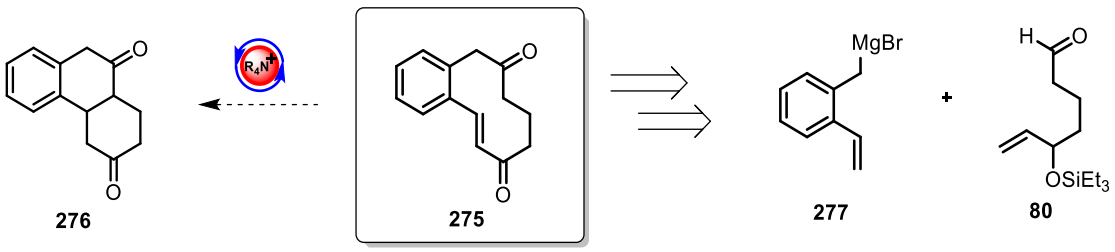


***Scheme 135**: Intramolecular Friedel-Crafts acylation with the enoic acid **272**.*

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

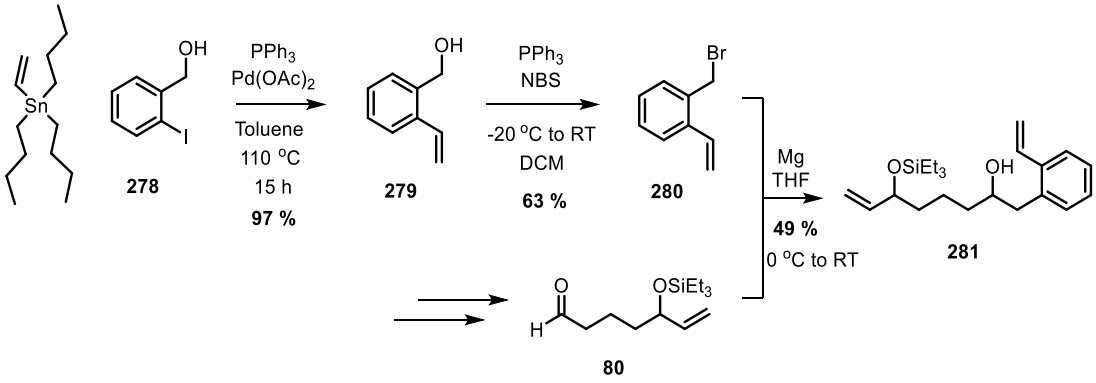
7.3 Synthesis of transannular Michael-addition precursor 287

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.



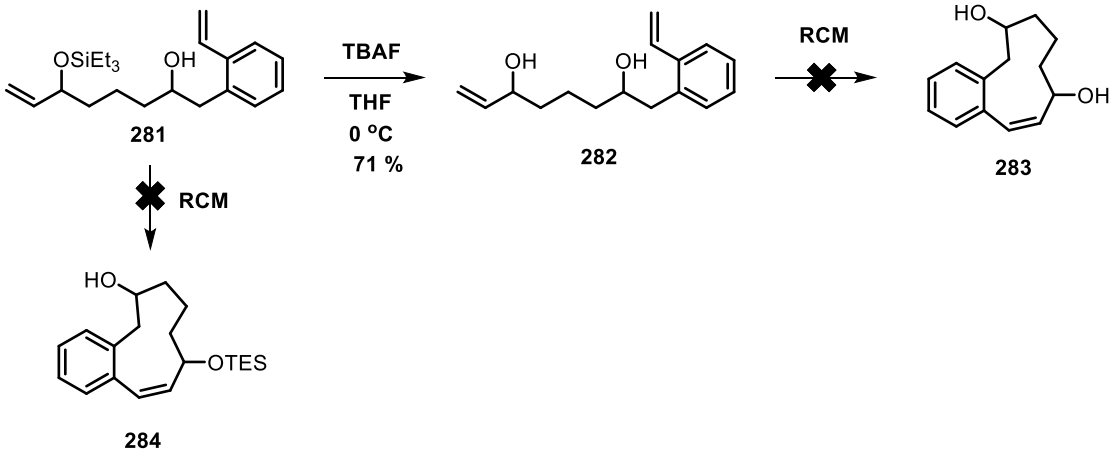
***Scheme 136**: Plan for the synthesis of transannular Michael-addition precursor **275**.*

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**).



***Scheme 137**: Synthesis of diene **281**.*

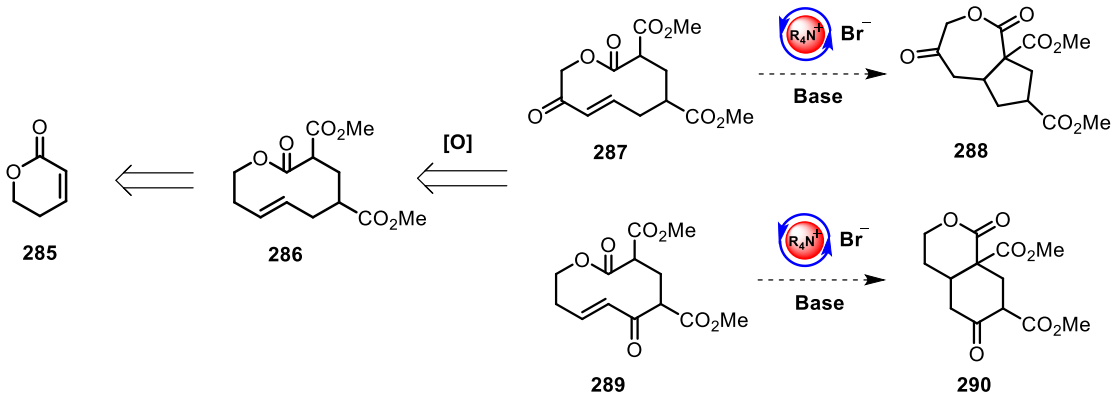
When the unsaturated protected diene **281** was used in the RCM-reaction the metathesis product **284** was not observed. Therefore, we deprotected the alcohol to enable the catalyst to react better with the allylic alcohol **285**. Despite the deprotection the RCM reaction of the deprotected diene 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 2nd generation catalyst and Hoveyda-Grubbs 2nd generation catalyst for the metathesis reaction (**Scheme 138**).



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

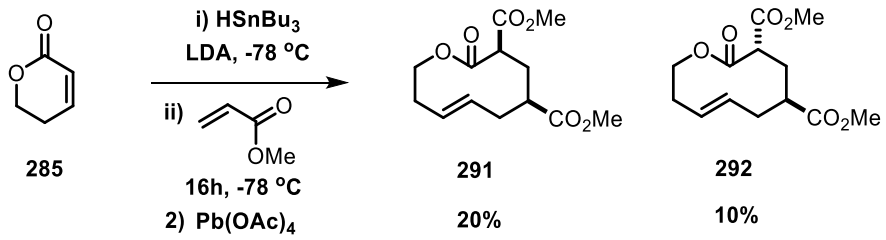
7.4 Cascade precursor via allylic olefin oxidation

Posner *et al.*[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**).



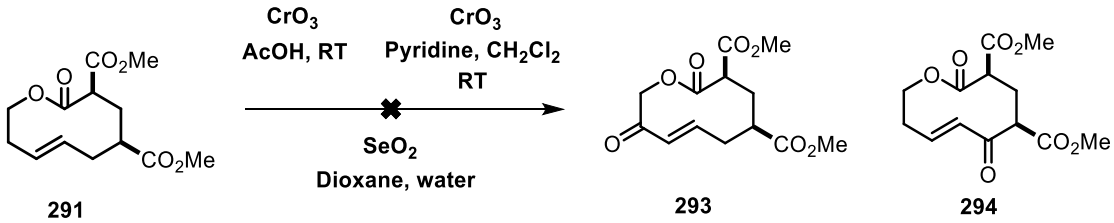
***Scheme 139**: Plan for the synthesis of cascade precursors **287** and **289**.*

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 macrolacotones **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, CH_2Cl_2, 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^{TM} 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.[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 (*c.a.* 0.1 mbar). K_3PO_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. [117]

8.1.5 Chromatography

Thin layer chromatography was performed on Merck Merck Kieselgel 60 F_{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 μm 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 residiual 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 (λ_{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

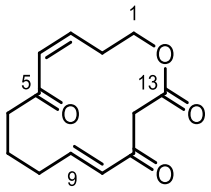
Chiral HPLC was performed on a Dionex UltiMate 3000 system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode-array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø x 25 cm) and corresponding guard column (0.4 cm ø x 1 cm).

Wavelengths (λ) 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.

(5*E*,11*Z*)-Oxacyclotetradeca-5,11-diene-2,4,10-trione (67)



67

Dess-Martin periodinate (53 mg, 0.12 mmol) was added to a stirred solution of **94** (25 mg, 0.104 mmol) in CH_2Cl_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 $Na_2S_2O_3$ and water. The mixture was stirred until a clear solution was obtained. The mixture was extracted with CH_2Cl_2, combined organic layers were washed with brine, dried (Na_2SO_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.

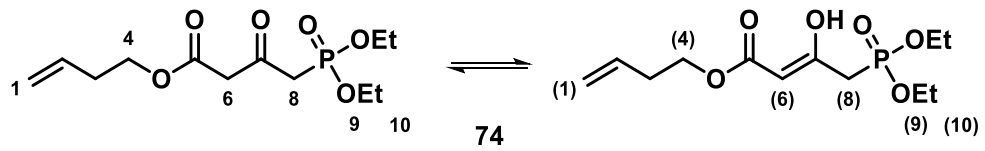
IR (neat) ν_{max} 3621, 2935, 2360, 1736, 1691, 1668, 1624, 1434, 1417, 1313, 1257, 1112, 1031, 1006

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 259.0941).

But-3-en-1-yl 4-(diethoxyphosphoryl)-3-oxobutanoate (74)



74

To the solution of NaH (60% in mineral oil, 356 mg, 8.9 mmol) in THF (9 mL) was added compound **77** (1.7g, 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 NH_4Cl solution. The organic layer was separated and the remaining aqueous layer with EtOAc. 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 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) ν_{max} 3468, 3080, 2983, 2932, 2911, 2361, 1744, 1717, 1642, 1394, 1324, 1249, 1018, 968, 797.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^{+}$,$C_{12}H_{21}O_6PNa$ requires 315.0968).

NB: Assignments in parentheses indicate the minor enol tautomer

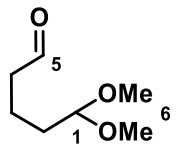
Alternative synthesis for compound **74:**

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 ^{o}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_4Cl. The solution was acidified by adding 1 M HCl, extracted with Et_2O 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, 0.414mmol).

5,5-Dimethoxypentanal (78)



78

To a two necked flask was added the cyclopentene (10.2 g, 150 mmol), CH_2Cl_2 (500 mL), methanol (100 mL) and the mixture was cooled to – 78 ºC. 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. $NaHCO_3$ (4.00g, 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 *in vacuo* and CH_2Cl_2 (300 mL) was added to the concentrate. The mixture was washed two times with water, dried (Na_2SO_4), filtered and concentrated *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%).

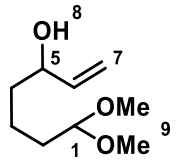
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, t, *J* = 1.5 Hz, *H*-5), 4.35 (1H, t, *J* = 5.5 Hz, *H-1*), 3.30 (6H, br. s, *H*-6) 2.46 (2H, dt, *J* = 7.0, 1.5 Hz, *H*-4), 1.73–1.56 (4H, m, *H*-2,*3*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 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)



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 NH_4Cl. The mixture was extracted three times with diethyl ether, the the combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (50% Et_2O in petroleum ether) gave the title compound **79** as a colourless viscous liquid in 43 % yield. (yield 0.34 g, 1.95 mmol).

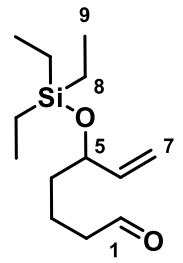
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz, *H*-6), 5.21 (1H, dt, *J* = 17.0, 1.5 Hz, *H*-7), 5.21 (1H, dt, *J* = 10.5, 1.5 Hz, *H*-7´), 4.35 (1H, t, *J* = 5.5 Hz, *H-1*), 4.08 (1H, q, *J* = 6.0 Hz, *H*-5), 3.29 (6H, d, *J* = 1.5 Hz, *H*-9), 1.81 (1H, br. s, *H*-8), 1.61–1.57 (2H, m, *H*-2), 1.56–1.49 (2H, m, *H*-4), 1.49–1.32 (2H, m, *H*-3).

^{13}C NMR (101 MHz, $CDCl_3$) 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)



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 CH_2Cl_2 (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 CH_2Cl_2, combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (2.5% EtOAc in petroleum ether) gave aldehyde **80** in 76% yield (0.443g, 1.54 mmol), as a colourless liquid.

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

^{1}H NMR (400 MHz, $CDCl_3$) 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, td, *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).

^{13}C NMR (101 MHz, $CDCl_3$) 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).

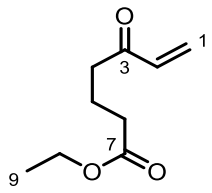
m/z LRMS (ESI $^+$) 265.1 $[M+Na]^+$; HRMS (ESI$^-$) 241.1633 ($[M–H]^–$,$C_{13}H_{25}O_2Si$ requires 241.1629).

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 Et_2O (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 Et_2O, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (eluent: Et_2O 0% to 10% in petroleum ether) gave the aldehyde **67** in 92% yield (156 mg, 0.54 mmol).

Ethyl 5-oxohept-6-enoate (86)



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 Et_2O, washed with saturated aqueous solution of sodium thiosulfate $Na_2S_2O_3$, dried over $MgSO_4$, 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 $Pd(PPh_3)_4$ (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 NH_4Cl, saturated aqueous Na_2CO_3, Brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Product was purified by vacuum distillation that gave the title coumpound **86** as a coulourles liquid in 64% yield (11.22 g).

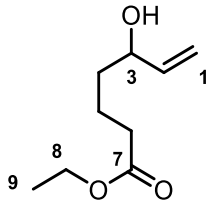
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (1H, dd, *J* = 17.5, 10.5 Hz, *H*-2), 6.21 (1H, dd, 17.5, 1.5 Hz, *H*-1), 5.82 (1H, dd, *J* = 10.5, 1.5 Hz, *H*-1'), 4.11 (2H, q, *J* = 7.0 Hz, *H*-9), 2.65 (2H, t, *J* = 7.5 Hz, *H*-4), 2.34 (2H, t, *J* = 7.5 Hz, *H*-6), 1.93 (2H, qn, *J* = 7.5 Hz, *H*-5), 1.24 (3H, t, *J* = 7.0 Hz, *H*-9).

^{13}C NMR (101 MHz, $CDCl_3$) 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 literature[119].

Ethyl 5-hydroxyhept-6-enoate (87)



87

Flame-dried $CeCl_3$ (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^{o}C for 3h and quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2, combined organic layers were dried over $MgSO_4$, 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).

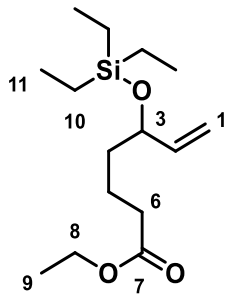
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, ddd, *J* = 17.0, 10.5, 6.0 Hz, *H*-2), 5.56 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz, *H*-1), 5.11 (1H, ddd, *J* = 10.5, 1.5, 1.5 Hz, *H*-1'), 4.13 (2H, q, *J* = 7.0 Hz, *H*-8), 4.16-4.07 (1H, m, *H*-3), 2.33 (2H, t, *J* = 7.0 Hz, *H*-6), 1.81-1.60 (2H, m, *H*-5), 1.56 (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[119].

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



88

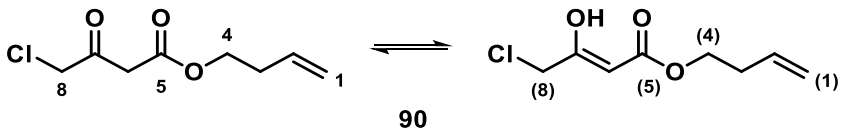
2,6-Lutidine (7.28 g, 68 mmol, 7.9 mL) was added to a solution of ethyl 5-hydroxyhept-6-enoate **73** (2.34 g, 13.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C. TESOTf (3.77g, 14.7 mmol, 3.24 mL) was added dropwise to the solution. The reaction mixture was stirred for 1h and quenched with water. Organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*, Purification by flash chromatography (Eluent: 20% Et_2O in petroleum ether) gave the title compound **88** in 99% yield (3.85 g) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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).

^{13}C NMR (101 MHz, $CDCl_3$) δ 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 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 309.18564).

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



90

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) ν_{max} 2962, 1725, 1642, 1401,1324, 1194, 990, 921, 810, 622.

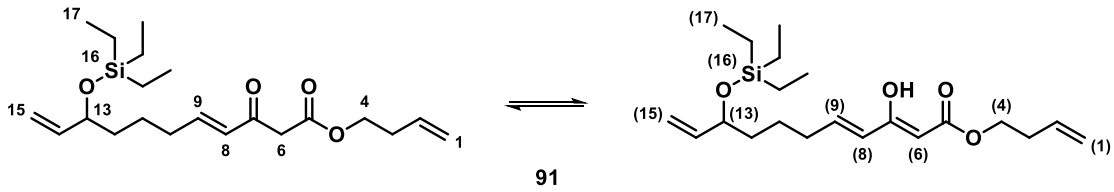
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (<1H, s, *H*-(9)), 5.77 – 5.64 (1H, m, *H-1*), 5.27 (<1H, s, *H*-(6)), 5.11 – 4.99 (2H ,m, *H-1*), 4.19 – 4.12 (4H, m, *H*-4,*(4),8*), 3.95 (<1H, s, *H*-(8)), 3.59 (2H, s, *H*-6), 2.38 – 2.31 (2H, m, *H*-3,*(3)*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 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 ($[M–H]^–$,$C_8H_{10}O_3Cl$ 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)



91

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 KHMDS (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 NH_4Cl 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 (Na_2SO_4), 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) ν_{max} 3079, 2954, 2911, 2876, 2360, 2341, 1746, 1665, 1642, 1598, 1419, 1234, 1148, 1075, 1005, 727.

^{1}H NMR (400 MHz, $CDCl_3$) 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)),

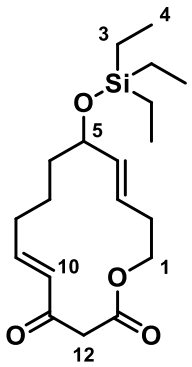
2.22–2.07 (2H, m, *H*-10,(10)), 1.52–1.33 (4H, m, *H*-11,(11),12,(12)), 0.88 (9H, t, *J* = 7.8 Hz, *H*-17, (17)), 0.52 (6H, q, *J* = 7.8 Hz, *H*-16,(16)).

^{13}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 ($[M+Na]^+$,$C_{21}H_{36}O_4SiNa$ 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)



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 2nd generation catalyst (5.0 mg, 0.080 mmol). Reaction mixture was stirred at reflux (84 ^{o}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).

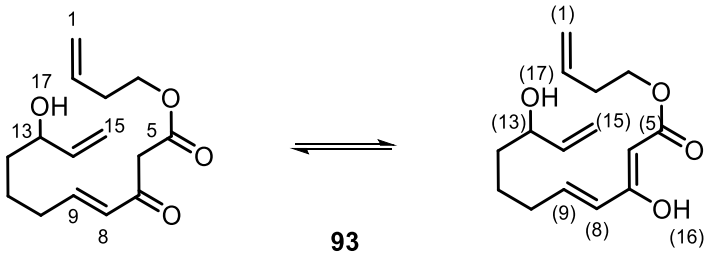
IR (neat) ν_{max} 2953, 2876, 2369, 1738, 1672, 1625, 1458, 1418, 1237, 1149, 1084, 1006, 972, 812, 743.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



93

To a stirred solution of **91** (100 mg, 0.262 mmol) in THF (9 mL) at 0 ^{o}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 pH phosphate buffer solution. The solution was extracted with EtOAc and the combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and concentrated *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) ν_{max} 3424, 2918, 2360, 1733, 1666, 1640, 1598, 1420, 1240, 1149, 989, 920, 988, 729, 668.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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)).

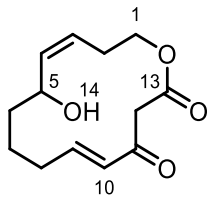
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3 (*C*-7), 149.5 (*C*-9), 140.9 (*C*-14), 140.6 (*C*-(9)), 133.7 (*C*-2), 129.8 (*C*-8), 124.7 (*C*-(8)), 117.4 (*C*-15), 117.3 (*C*-(15)), 115.0 (C-1), 114.9 (C-(1)), 90.1 (C-(6)), 74.1 (*C*-(13)), 73.0 (*C*-13), 64.4 (C-4), 63.2 (C-(4)), 49.9 (*C*-6), 36.4 (*C*-(12)), 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)



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 ºC. 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 (Na_2SO_4) 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 (22.7mg, 0.095 mmol).

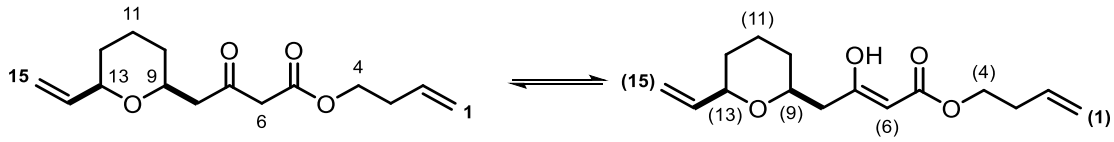
IR (neat) ν_{max} 3408, 2947, 1731, 1667, 1624, 1435, 1251, 1129, 981, 743.

^{1}H NMR (400 MHz, $CDCl_3$) 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, *C*-5), 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).

^{13}C NMR (101 MHz, $CDCl_3$) 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).

m/z LRMS (ESI $^+$) 261.1 $[M+Na]^+$; HRMS (ESI^+) 261.1094 ($[M+Na]^+$, $C_{13}H_{18}O_4Na$ requires 261.1097).

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



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 $NaHCO_3$. The organic layers was separated and the water phase was extracted with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4), 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) ν_{max} 2935, 2855, 2358, 1747, 1644, 1411, 1312, 1253, 1151, 1049, 989, 919.

^{1}H NMR (400 MHz, $CDCl_3$) 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)*,1,*(1)*,*(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)*).

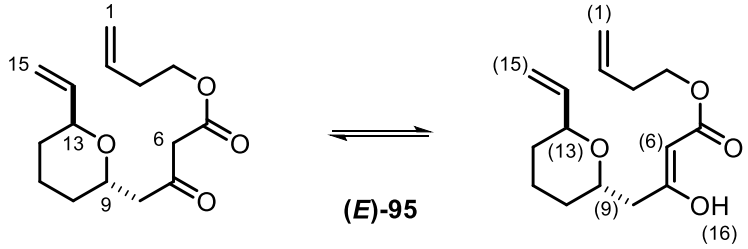
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9 (*C*-7), 175.8 (*C*-(7)), 172.9 (*C*-(5)), 167.5 (*C*-5), 139.5 (*C*-(14)), 139.4 (*C*-14), 134.2 (*C*-(2)), 134.0 (*C-2*), 117.7 (*C*-15), 117.6 (*C*-(15)), 114.8 (*C*-(1)), 114.7 (*C-1*), 91.0 (*C*-(6)), 78.5 (*C*-(13)), 78.5 (*C*-13), 74.9 (*C*-(9)), 74.4 (*C*-9), 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).

m/z LRMS (ESI $^{+}$) 289.1 $[M+Na]^{+}$; HRMS (ESI^{+}) 289.1470 ($[M+Na]^{+}$, $C_{15}H_{22}O_4Na$ requires 289.1410).

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)



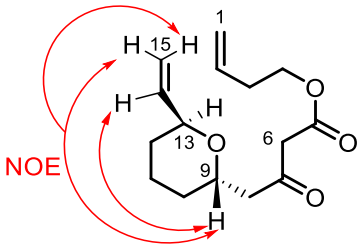
Z,E-product exist at equilibrium as a 77:23 ratio of keto to enol tautomers.

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

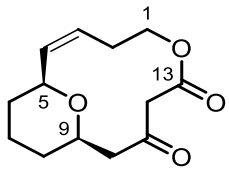
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (1H, ddd, *J* = 17.0, 11.5, 5.0 Hz, *H*-14, *(14)*), 5.71 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, *H*-2,*(2)*), 5.17 (2H, ddd, *J* = 7.5, 1.5, 1.5 Hz, *H*-15,*(15)*), 5.07-4.99 (2H, m, *H*-1,*(1)*), 4.98 (<1H, s, *H*-(6)), 4.31–4.26 (1H, br. s, *H*-13,*(13)*), 4.16–4.09 (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’))

^{13}C NMR (126 MHz, $CDCl_3$) 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-1*), 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).

m/z LRMS (ESI $^{+}$) 289.1 $[M+Na]^{+}$; HRMS (ESI^{+}) 289.1404 ($[M+Na]^{+}$, $C_{15}H_{22}O_4Na$ requires 289.1410)



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



97

To a stirred solution of **95** (20.0 mg, 0.075 mmol) in degassed CH_2Cl_2 (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).

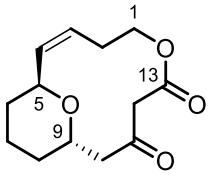
IR (neat) ν_{max} 3012, 2933, 2858, 2358, 1735, 1707, 1490, 1320, 1190, 1142, 1046.

^{1}H NMR (500 MHz, C_6D_6) 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* = dtd 13.5, 11.5, 4.0 Hz, *H-2*), 2.32 (1H, dd, *J* = 13.0, 11.0 Hz, *H*-10), 2.15 (1H, ddd, *J* = 13.0, 1.7, 1.1 Hz, *H*-10'), 1.65 (1H, ddd, *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_6D_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-1*), 51.6 (*C*-10), 49.9 (*C*-12), 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^+) 261.1096 ($[M+Na]^+$, $C_{13}H_{18}O_4Na$ requires 261.1103).



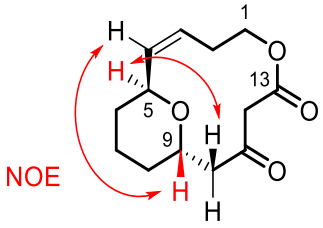
(*E*)-97

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

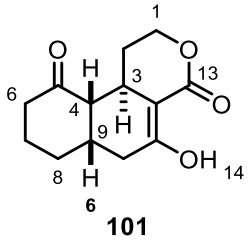
^{1}H NMR (400 MHz, C_6D_6) δ 5.55 (1H, dd, *J* = 11.0, 8.0 Hz, *H*-4), 5.31 (1H, tdd, *J* = 11.0, 5.5, 1.0, *H*-3), 4.31 (1H, dt, *J* = 8.0, 4.0, *H*-5), 4.08 (1H, dt, *J* = 11.0, 3.35 Hz, *H-1*), 3.78 (1H, dddd, *J* = 11.0, 8.0, 2.5, 2.0, *H*-9), 3.55 (1H, ddd, *J* = 12.5, 11.0, 2.0, *H-1'*), 3.22 (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-1*), 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 ($[M+Na]^+$, $C_{13}H_{18}O_4Na$ requires 261.1097).



(6aR,10aR,10bS)-5-Hydroxy-1,2,6a,7,8,9,10a,10b-octahydro-4*H*-benzo[f]isochromene-4, 10(6H)-dione (101)



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 (5*E*,11*Z*)-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_{max} 2919, 2951, 2361, 1706, 1647, 1476, 1418, 1292, 1208, 877.

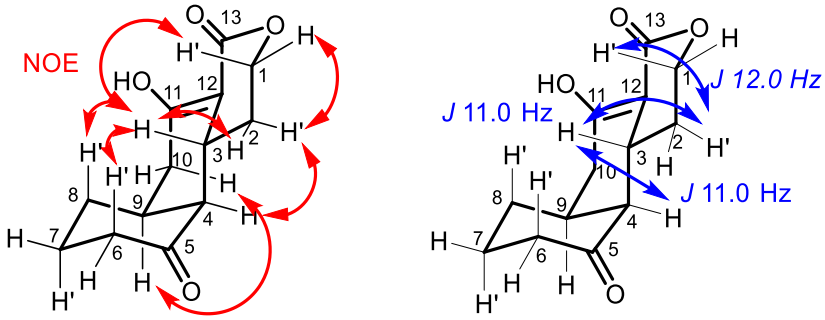
^{1}H NMR (500 MHz, $CDCl_3$) δ 13.25 (1H, s, *H*-14), 4.50–4.45 (1H, ddd, *J* = 11.5, 4.5, 2.0 Hz, *H-1*), 4.31–4.24 (1H, ddd, *J* = 12.0, 11.5, 3.0 Hz, *H-1´*), 2.94 (1H, br. t, *J* = 11.0 Hz, *H*-3), 2.68–2.60 (1H, ddd, *J* = 19.5, 7.0, 2.0 Hz, *H*-10), 2.48–2.39 (1H, app. m, *H*-6), 2.28 (1H, d, *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')

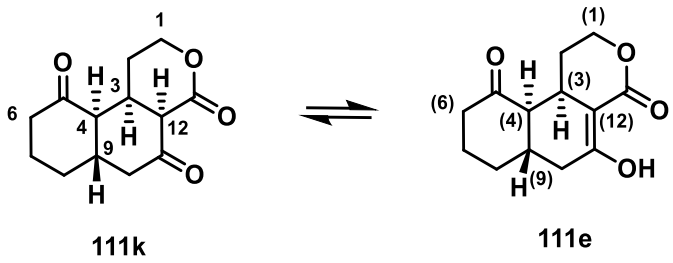
^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1 (*C*-5), 173.6 (*C*-11), 171.1 (*C*-13), 94.7 (*C*-12), 69.3 (*C*-*1*), 55.3 (*C*-4), 38.1 (*C*-6), 35.4 (*C*-9), 34.1 (*C*-10), 31.1 (*C*-3), 27.9 (*C*-2), 27.8 (*C*-8), 25.6 (*C*-7).

m/z LRMS (ESI $^+$) 259.1 $[M+Na]^+$; HRMS (ESI$^+$) 259.0939 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ 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)



111k **111e**

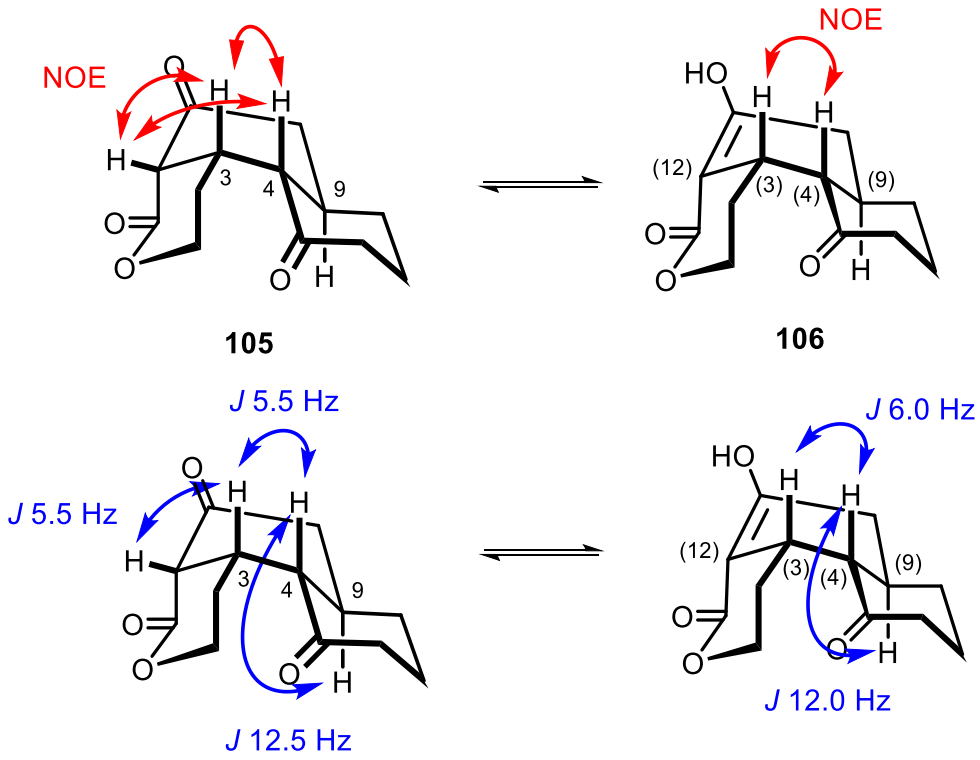
IR (neat) ν_{max} 2932, 2868, 1748, 1702, 1649, 1613, 1476, 1290, 1220, 1075, 1064.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, dddd, *J* = 12.0, 5.5, 3.5, 3.5 Hz, H-3), 2.94 (<1H, dddd, *J* = 12.0, 6.0, 2.0, 2.0

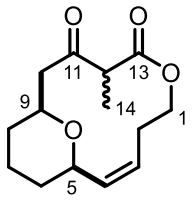
Hz, H-(3)), 2.65 (<1H, dd, *J* = 13.5, 4.0 Hz, H-10), 2.59 (<1H, dd, *J* = 12.5, 3.5 Hz, H-4), 2.54-2.47 (<3H, m, H-6,(6),2), 2.44 (<1H, dd, *J* = 17.5, 4.0 Hz, H-(10)), 2.42-2.30 (<3H, m, H-(6'),10',6'), 2.31 (<1H, dd, *J* = 12.0, 6.0 Hz, H-(4)), 2.27-2.21 (<1H, ddd, *J* = 17.5, 11.5, 2.0 Hz, H-(10')), 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*-1), 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 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 259.09408).



(1S,11R,Z)-4-methyl-6,15-dioxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (135)



135

KHMDS 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_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_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) ν_{max} 2936, 2858, 1729, 1708, 1455, 1370, 1276, 1223, 1180, 1125, 1087, 1002, 884.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69-5.57 (>1H, m, *H*-), 5.57-5.51 (<1H, m, *H*-), 4.48 (<1H, ddd, *J* = 11.0, 4.0, 3.0 Hz, *H*-1), 4.39 (<1H, ddd, 11.0, 8.0, 3.0 Hz, *H*-(1)), 3.98 (<1H, ddd, 11.0, 6.0, 3.0 Hz, *H*-(1')), 3.95-3.84 (>1H, m, *H*-5,(5)), 3.86 (<1H, ddd, *J* = 12.0, 11.0, 2.5 Hz, *H*-1'), 3.81-3.75 (<1H, m, *H*-(9)), 3.76 (<1H, q, *J* = 7.5 Hz, *H*-12), 3.71-3.62 (<1H, m, *H*-9), 3.53 (<1H, q, *J* = 7.0 Hz, *H*-(12)), 3.00 (<1H, dddd, *J* = 14.0, 11.5, 10.5, 4.0 Hz, *H*-2), 2.87 (<1H, dd, *J* = 12.50, 11.50 Hz, *H*-(10)), 2.66 (<1H, dd, *J* = 13.0, 11.0 Hz, *H*-10), 2.58-2.46 (<2H, m, *H*-(2),(2'), 2.38 (<1H, dd, *J* = 13.0, 1.5 Hz, *H*-10'), 2.37 (<1H, dd, *J* = 14.0, 3.5 Hz, *H*-(10'), 2.10 (<1H, dddd, 14.0, 5.0, 2.5, 2.5 Hz, *H*-2'), 1.90-1.80 (1H, m, *H*-7,(7)), 1.64-1.57 (1H, m,

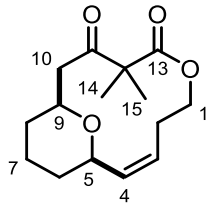
H-6,(6)), 1.57-1.48 (2H, m, *H*-7',(7'),8,(8)), 1.46-1.37 (1H, m, *H*-(6'),(6')), 1.36-1.23 (1H, m, *H*-8',(8')), 1.34 (<3H, d, *J* = 7.0 Hz, *H*-(14)), 1.28 (<3H, d, *J* = 7.0 Hz, *H*-14).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1 (*C*-(11)), 206.0(*C*-11), 171.6(*C*-13), 171.1(*C*-(13)), 134.0(*C*-3), 133.4(*C*-(3)), 131.4(*C*-4), 129.7(*C*-(4)), 76.0(*C*-(9)), 75.8(*C*-9), 74.5(*C*-(5)), 72.4(*C*-5), 64.3(*C*-(1)), 64.2(*C*-1), 53.1(*C*-(12)), 52.7(*C*-12), 51.7(*C*-10), 47.7(*C*-(10)), 32.2(*C*-8), 31.5(*C*-(8)), 31.4(*C*-6), 31.4(*C*-(6)), 28.2(*C*-(2)), 28.1(*C*-2), 23.9(*C*-(7)),23.6(*C*-7), 14.4(*C*-(14)), 14.1(*C*-14),

m/z LRMS (ESI $^+$) 275.1 $[M+Na]^+$; HRMS (ESI^+) 275.12551 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 275.12538).

MP: 91-95 ^oC

(1S,11R,Z)-4,4-dimethyl-6,15-dioxabicyclo[9.3.1]pentadec-9-ene-3,5-dione (136)



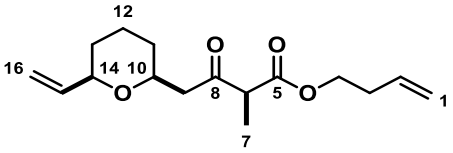
IR (neat) ν_{max} 3013, 2934, 2850, 1711, 1452, 1388, 1276, 1254, 1149, 1083, 1001.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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).

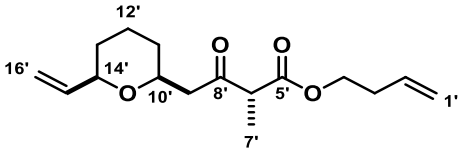
^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9 (*C*-11), 173.6 (*C*-13), 132.8 (*C*-4), 129.8 (*C*-3), 76.4 (*C*-9), 74.2 (*C*-5), 64.3 (*C*-1), 56.5 (*C*-12), 45.0 (*C*-10), 42.5 (*C*-2), 31.3 (*C*-8), 31.2 (*C*-6), 28.4 (*C*-2), 23.6 (*C*-7), 22.6 (*C*-15), 22.2 (*C*-14)

m/z LRMS (ESI $^{+}$) 289.1 $[M+Na]^{+}$; HRMS (ESI^{+}) 289.14110 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 289.14103).

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



134



134'

Compound **95** (50 mg, 0.187 mmol) and K_2CO_3 (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 ^{o}C for 9 hours. The reaction was quenched by adding *saturated aqueous* NH_4Cl and extracted with CH_2Cl_2. The combined organic phases where dried over Na_2SO_4, 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).

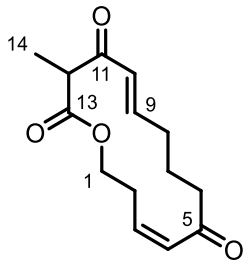
IR (neat) ν_{max} 3080, 2983, 2937, 2860, 1743, 1715, 1643, 1455, 1336, 1196, 1072, 1047, 919.

^{1}H NMR (500 MHz, $CDCl_3$) 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')

^{13}C NMR (126 MHz, $CDCl_3$) 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').

m/z LRMS (ESI $^{+}$) 303.1 $[M+Na]^{+}$; HRMS (ESI^{+}) 303.15668 ($[M+Na]^{+}$, $C_{16}H_{24}O_4Na$ requires 303.15660).

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



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 ºC. The mixture was stirred for 15 min. The reaction was quenched by adding saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc and combined organic phases was washed with brine, dried (Na_2SO_4) and filtered. The solvents were removed *in vacuo.* The crude was dissolved to a 0.220 mL of CH_2Cl_2 and the solution was cooled down to 0 ºC. 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 $Na_2S_2O_3$ and water. The mixture was stirred until a clear solution was obtained. The mixture was extracted with CH_2Cl_2, combined organic layers were washed with brine, dried (Na_2SO_4), 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) ν_{max} 2918, 2849, 2363, 1738, 1693, 1628, 1454, 1337, 1218, 1115, 1072.

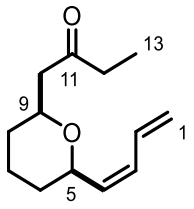
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (1H, ddd, *J* = 15.60, 8.60, 6.94 Hz, *H*-9), 6.17 (1H, ddd, *J* = 11.43, 1.42, 1.42 Hz, *H*-4), 6.09 (1H, ddd, *J* = 15.61, 1.82, 1.82 Hz, *H*-10), 5.97 (1H, ddd, *J* = 11.50, 9.15, 7.16 Hz, *H*-3), 4.29–4.21 (2H, m, *H*-1), 3.76 (1H, q, *J* = 6.99 Hz, *H*-12), 3.54–

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 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 273.1097).

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



138

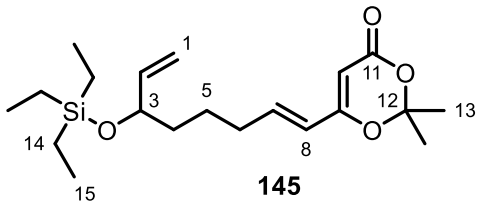
IR (neat) ν_{max} 2933, 2850, 1715, 1653, 1558, 1375, 1073, 1057, 915.

^{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, d, *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 ($[M+Na]^+$, $C_{13}H_{20}O_2Na$ requires 231.13575).

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



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 NH_4Cl. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The title compound **145** was purified by column chromatography (eluent: 10 to 20% Et_2O in petroleum ether). Yield 91% (99.5 mg, 0.271 mmol).

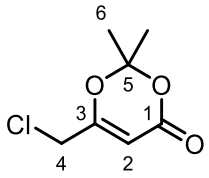
IR (neat) ν_{max} 3000, 2954, 2936, 2875, 1729, 1654, 1593, 1390, 1373, 1273, 1205, 1018, 725.

^{1}H NMR (400 MHz, $CDCl_3$) 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).

^{13}C NMR (101 MHz, $CDCl_3$) 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).

m/z LRMS (ESI $^+$) 389.2 $[M+Na]^+$; HRMS (ESI^+) 389.21173 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 289.21186).

6-(chloromethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one [85] **(149)**



149

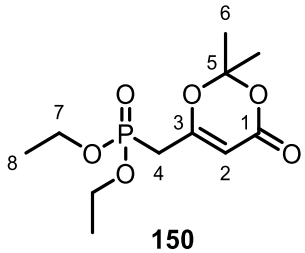
Freshly distilled diisopropylamine (31.9 g, 315 mmol, 44.2 mL) in THF (200 mL) was deprotonated by adding dropwise 2.5 M n-butyllithium (31.9 g, 303 mmol, 121 mL) at 0 ºC in a 500 mL flame-dried two-necked round bottomed flask. The mixture was stirred for 30 minutes and cooled to –78 °C. 2,2,6-trimethyl-4H-1,3-dioxin-4-one **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 (150mL) at -50 ºC over 30 min. The temperature was allowed slowly rise to -25 ºC 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_2O (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_2SO_4, 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).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (1H, s, *H*-2), 4.02 (2H, s, *H*-4), 1.74 (6H, s, *H*-6)

^{13}C NMR (101 MHz, $CDCl_3$) 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.[118]

diethyl ((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)phosphonate[85] (150)



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 **150** 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. [118]

Allyl (*E*)-3-oxo-9-((triethylsilyl)oxy)undeca-4,10-dienoate (151)

151

A solution of the compound **145** (800 mg, 2.18 mmol) and allylic alcohol (0.600ml, 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% Et_2O in petroleum ether) which gave the product **151** as a colourless oil (84%, 675 mg, 1.83 mmol).

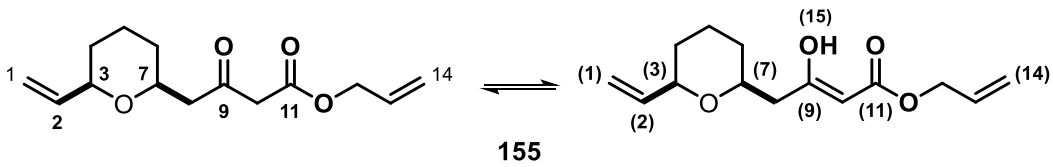
IR (neat) ν_{max} 3080, 2953, 2913, 2876, 1744, 1667, 1597, 1412, 1228, 1148, 1005, 742, 724.

^{1}H NMR (500 MHz, $CDCl_3$) 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).

^{13}C NMR (126 MHz, $CDCl_3$) 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]$^+$, $C_{20}H_{34}O_4SiNa$ requires 389.21186).

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



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 $NaHCO_3$ (xx ml). Layers were separated and the combined organic phases were washed with brine (xx ml), dried over Na_2SO_4 filtered, and evaporated *in vacuo*. Purification by flash chromatography (10% to 25% Et_2O 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_{max} 3085, 2936, 2859, 1744, 1716, 1647, 1411, 1312, 1225, 1151, 989, 924.

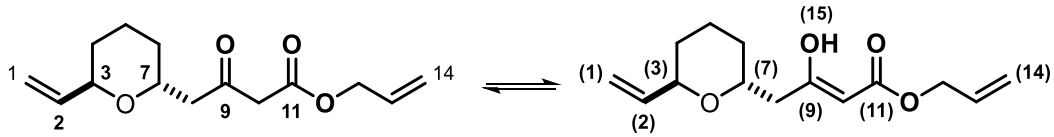
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.99 (<1H, s, *H*-(15)), 5.97–5.85 (<1H, m, *H*-(13)), 5.90 (<1H, ddt, *J* = 17.0, 11.0, 6.0 Hz, *H*-13), 5.85–5.76 (<1H, m, *H*-(2)), 5.80 (<1H, ddd, *J* = 17.5, 10.5, 5.0 Hz, *H*-2),5.35–5.29 (<1H, m, *H*-(14)), 5.32 (<1H, ddt, *J* = 17.0, 1.5, 1.5 Hz, *H*-14), 5.26–5.22 (<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')), 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, $CDCl_3$) δ 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), 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]$^+$, $C_{14}H_{20}O_4Na$ requires 275.12536).

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



156

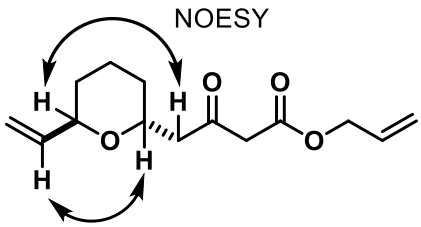
IR (neat) ν_{max} 2926, 2851, 1746, 1717, 1647, 1410, 1362, 1227, 1149, 1087, 1087, 926.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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 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 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 Hz, *H*-8), 2.57 (<1H, dd, *J* = 15.5, 4.5 Hz, *H*-8'), 2.46 (<1H, dd, *J* = 14.0, 8.0 Hz, *H*-(8)), 2.32 (<1H, dd, *J* = 14.0, 5.5 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')).

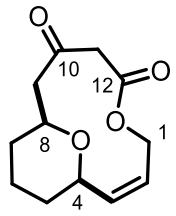
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7 (*C*-9), 176.3 (*C*-(9)), 172.6 (*C*-(11)), 167.2 (*C*-11), 138.6 (*C*-(2)), 138.3 (*C*-2), 132.5 (*C*-(13)), 132.0 (*C*-13), 119.1 (*C*-14), 118.6 (*C*-(14)), 116.8 (*C*-1), 116.6 (*C*-(1)), 90.9 (*C*-(10)), 73.1 (*C*-3), 73.0 (*C*-(3)), 68.6 (*C*-(7)), 67.9 (*C*-7), 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).

m/z LRMS (ESI^+) 275.1 $[M+Na]^+$; HRMS (ESI^+) 275.12542 ($[M+Na]^+$, $C_{14}H_{20}O_4Na$ requires 275.12538).



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



151

To a stirred solution of **154** (227 mg, 0.899 mmol) in degassed CH_2Cl_2 (300 mL) under argon atmosphere was added Grubbs 2nd 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_2O in petroleum ether and concentrated *in vacuo*. The crude product was purified by flash chromatography (50% Et_2O in petroleum ether). Purification gave the tittle *Z*-isomer **151** as a white solid in (16%, 32 mg, 0.143 mmol) and the *E*-isomer **156** as a white solid (19%, 38 mg, 0.170 mmol). Combined yield 35%.

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

^1H NMR (500 MHz, $CDCl_3$) δ 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,

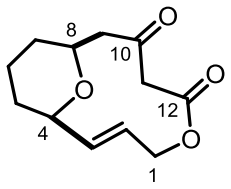
2.5 Hz, *H*-1'), 4.11 (1H, dddd, *J* = 11.0, 7.0, 2.5, 1.5 Hz, *H*-4), 3.90 (1H, dddd, *J* = 11.0, 11.0, 3.5, 2.0 Hz, *H*-8), 3.70 (1H, d, *J* = 12.0 Hz, *H*-11), 3.26 (1H, d, *J* = 12.0 Hz, *H*-11'), 2.64 (1H, dd, *J* = 16.0, 11.0 Hz, *H*-9), 2.49 (1H, dd, *J* = 16.0, 3.5 Hz, *H*-9'), 1.93–1.85 (1H, 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 ($[M+Na]^+$, $C_{12}H_{16}O_4Na$ requires 247.09413).

MP: 105–110 °C

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



156

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

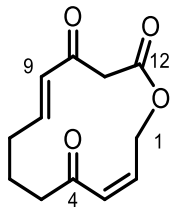
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (1H, ddd, *J* = 15.5, 5.0, 5.0 Hz, *H*-2), 5.73 (1H, dd, *J* = 15.5, 3.0 Hz, *H*-3), 4.60 (2H, d, *J* = 5.0 Hz, *H*-1), 3.86 (1H, br. d, *J* = 11.5 Hz, *H*-4), 3.80 (1H, br. t, *J* = 11.0 Hz, *H*-8), 3.70 (1H, d, *J* = 16.5 Hz, *H*-11), 3.60 (1H, d, *J* = 16.5 Hz, *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, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 259.13047).

MP: 105–110 °C.

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



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_4Cl solution (xx ml). The mixture was extracted with CH_2Cl_2 (40 ml) the combined organic layers were washed with brine (5 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in 2 ml of CH_2Cl_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_2Cl_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_2SO_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).

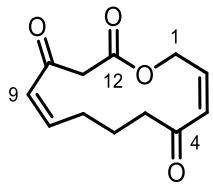
IR (neat) ν_{max} 2926, 2851, 1735, 1696, 1668, 1630, 1300, 1258, 1223, 1200, 1008, 978.

^{1}H NMR (500 MHz, C_6D_6) δ 6.15 (1H, dt, *J* = 16.0, 7.5 Hz, *H*-8), 5.76 (1H, br. d, *J* = 16.0 Hz, *H*-9), 5.45 (1H, br. d, *J* = 11.5 Hz, *H*-3), 5.41 (1H, dt, *J* = 11.5, 5.5 Hz, *H*-2), 4.53 (2H, d, *J* = 5.5 Hz, *H*-1), 3.30 (2H, s, *H*-11), 1.72–1.68 (2H, m, *H*-5), 1.65–1.59 (2H, m, *H*-7), 1.49–1.44 (2H, m, *H*-6).

^{13}C NMR (126 MHz, C_6D_6) δ 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/z LRMS (ESI$^+$) 245.0 [M+Na]$^+$; HRMS (ESI$^+$) 245.07843 ([M+Na]$^+$, $C_{12}H_{14}O_4Na$ requires 245.07854).

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



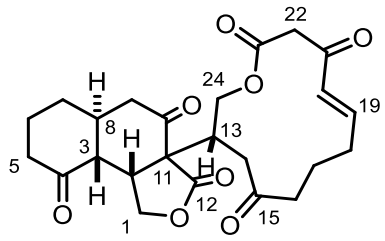
162

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

^{13}C NMR (126 MHz, C_6D_6) δ 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/z LRMS (ESI$^+$) 245.0 [M+Na]$^+$; HRMS (ESI$^+$) 245.07843 ([M+Na]$^+$, $C_{12}H_{14}O_4Na$ requires 245.07855).

(5aS,9aR,9bR)-3a-((R,E)-5,11,13-trioxooxacyclotridec-9-en-3-yl)hexahydronaphtho[1,2-c]furan-3,4,9(1H,3aH,5H)-trione (163)



163

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 (5*E*,11*Z*)-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).

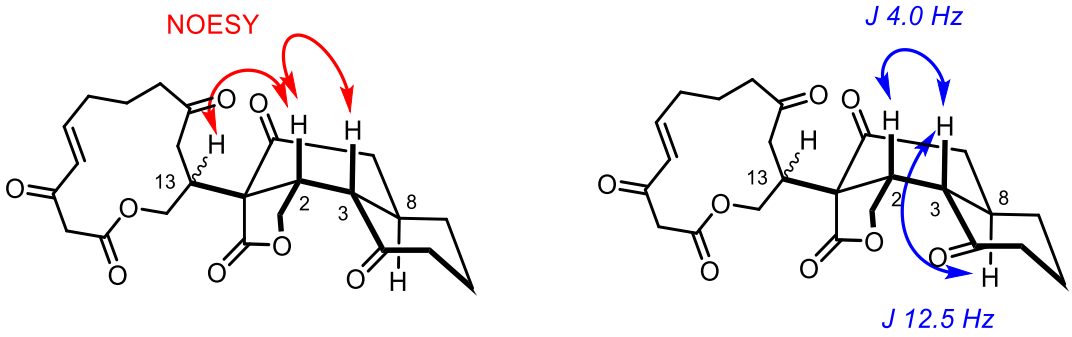
IR (neat) ν_{max} 2921, 2851, 1777, 1740, 1706, 1671, 1247, 1205, 978, 733.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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*

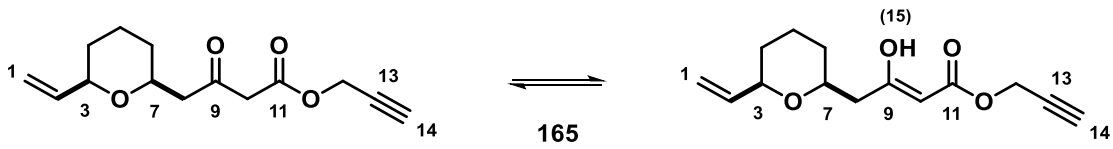
= 15.0 Hz, H-22), 3.41 (1H, d, *J* = 15.0 Hz, H-22'), 3.39 (1H, ddd, *J* = 11.0, 8.0, 4.0 Hz, H-2), 3.35-3.28 (1H, m, H-13), 3.10 (1H, dd, *J* = 12.5, 4.0 Hz, H-3), 2.90 (1H, dd, *J* = 20.5, 4.0 Hz, H-14), 2.81 (1H, dd, *J* = 20.5, 5.0 Hz, H-14'), 2.73 (1H, dd, *J* = 14.0, 12.5 Hz, H-9), 2.57-2.46 (3H, 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').

^{13}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), 66.5 (C-1), 65.1 (C-24), 62.2 (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 ($[M+Na]^+$, $C_{24}H_{28}O_8Na$ requires 467.16776).



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



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 $NaHCO_3$ (10 mL). The layers were separated and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% to 25% Et_2O 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%.

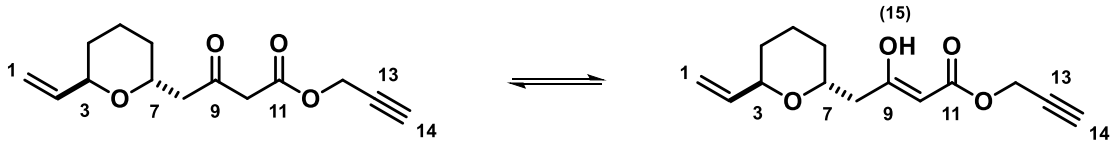
IR (neat) ν_{max} 3282, 2936, 2849, 1749, 1717, 1652, 1625, 1438, 1370, 1312, 1266, 1150, 1072, 924.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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 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 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 Hz, H-1'), 4.73-4.71 (<2H, app. m, H-12), 4.72 (<1H, d, *J* = 2.5 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 Hz, H-8), 2.58 (<1H, dd, *J* = 15.0, 5.0 Hz, H-8'), 2.51 (<1H, dd, *J* = 14.0, 7.0 Hz, H-(8)), 2.49-2.47 (<1H, app. m, H-(12')), 2.49 (<2H, t, *J* = 2.5 Hz, H-14, (14)), 2.29 (<1H, dd, *J* = 14.0, 6.0 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')).

^{13}C NMR (126 MHz, $CDCl_3$) 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 ($[M+Na]^+$, $C_{14}H_{18}O_4Na$ requires 273.10973).

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



(***E***)**-165**

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

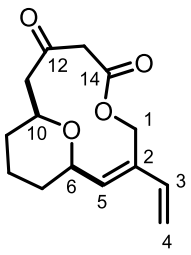
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.82 (<1H, s, H-15), 5.93 (<1H, m, H-(2)), 5.89 (<1H, ddd, *J* = 18.0, 10.5, 4.5 Hz, H-2), 5.25-5.19 (2H, m, H-1,1',(1),(1')), 5.10 (<1H, s, H-(10)), 4.73 (2H, d, *J* = 2.5 Hz, H-12, (12)), 4.39-4.32 (1H, m, H-3, (3)), 4.23-4.16 (<1H, app. m, H-7), 4.13-4.07 (<1H, m, 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')).

^{13}C NMR (126 MHz, $CDCl_3$) 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).

m/z LRMS (ESI $^{+}$) 273.1 $[M+Na]^{+}$; HRMS (ESI^{+}) 273.10962 ($[M+Na]^{+}$, $C_{14}H_{18}O_4Na$ requires 273.10973).

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



168

To a stirred solution of **165** (15 mg, 0.90 mmol) in degassed CH_2Cl_2 (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.

^{1}H NMR (500 MHz, $CDCl_3$) 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* =

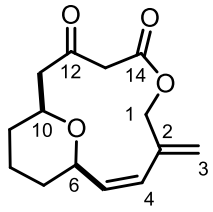
15.5, 11.5 Hz, H-11), 2.48 (1H, dd, *J* = 15.5, 2.5 Hz, H-11'), 1.94-1.81 (1H, app. m, H-8), 1.76-1.68 (1H, app. m, H-7), 1.67-1.42 (3H, m, H-8',7',9), 1.36-1.20 (1H, m, H-9').

^{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 ($[M+Na]^+$, $C_{14}H_{18}O_4Na$ requires 273.10973).

MP: 95-98 ^oC

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



166

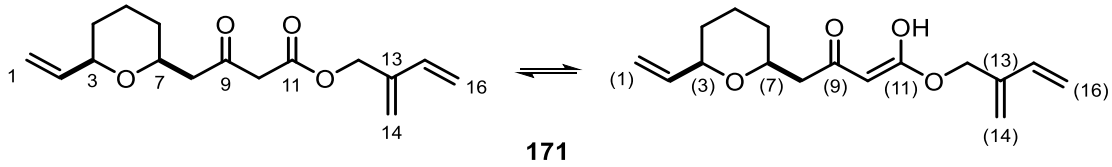
IR (neat) ν_{max} 2927, 2851, 2360, 2341, 1742, 1709, 1316, 1195, 1130, 1052, 842.

^{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, $CDCl_3$) δ 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*-11), 49.2 (*C*-13), 31.8 (*C*-9), 31.2 (*C*-7), 23.4 (*C*-8).

m/z LRMS (ESI $^+$) 273.1 $[M+Na]^+$; HRMS (ESI^+) 273.10976 ($[M+Na]^+$, $C_{14}H_{18}O_4Na$ requires 273.10973).

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



171

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

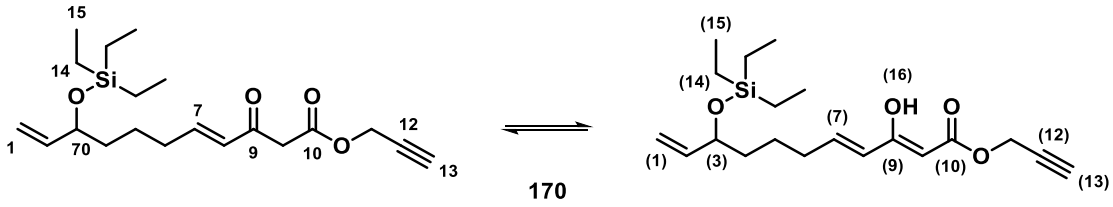
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.98 (<1H, s, OH-),6.43-6.35 (<1H, app. m, H-(15)), 6.37 (<1H, dd, *J* = 18.0, 11.0 Hz, H-15),5.89-5.80 (<1H, app. m, H-(2)), 5.81 (<1H, ddd, 17.0, 10.5, 5.5 Hz, H-2), 5.31-5.04 (<1H, m, H-(14),(14'),(16), (16'), (1),(1'), 5.32-5.22 (<3H, m, H-14,14', 16), 5.19 (<1H, dd, *J* = 17.5, 1.5, 1.5 Hz, H-1), 5.14 (<1H, br. d, *J* = 11.0 Hz, H-16'), 5.12 (<1H, s, H-(10)), 5.06 (<1H, 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 (<2H, s, H-10), 2.79 (<1H, dd, *J* = 15.5, 7.5 Hz, H-8), 2.59 (<1H, dd, *J* = 15.5, 5.0 Hz, H-8'), 2.53 (<1H, dd, 14.0, 7.0 (H-(8)), 2.29 (<1H, 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, $CDCl_3$) δ 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),

m/z LRMS (ESI $^{+}$) 301.1 $[M+Na]^{+}$; HRMS (ESI^{+}) 301.14108 ($[M+Na]^{+}$, $C_{16}H_{20}O_4Na$ 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 ^{o}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) ν_{max} 3308, 2952, 2912, 2876, 1750, 1697, 1666, 1642, 1596, 1415, 1220, 1147, 1005, 726.

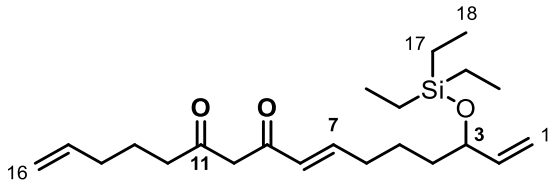
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (<1H, d, *J* = 1.5 Hz, H-(17)), 6.87 (<1H, dt, *J* = 15.5, 7.0 Hz, H-(7)), 6.68 (<1H, dt, *J* = 16.0, 7.0 Hz, H-7), 6.15 (<1H, dt, *J* = 15.5, 1.5 Hz, H-(8)), 5.85-5.72 (<2H, m, H-2,8,(2)), 5.14 (1H, br. d, *J* = 17.0 Hz H-1,(1)), 5.07-4.70 (1H, m, H-1',(1')), 4.75 (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, $CDCl_3$) δ 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 LRMS (ESI $^{+}$) 387.2 $[M+Na]^{+}$; HRMS (ESI^{+}) 387.19621 ($[M+Na]^{+}$, $C_{20}H_{32}O_4SiNa$ requires 387.19615).

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



180

The compound **145** (700 mg, 1.91 mmol) in THF (3.5 mL) was added to a dry $CeCl_3$ (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 $CeCl_3$ in THF at 0 ^{o}C and stirred for 30 minutes. The mixture was quenched pouring into ice cold saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (2% Et_2O in petroleum ether) which gave the title compound **180** as a colourless oil in 93% yield (670 mg, 1.77 mmol).

IR (neat) ν_{max} 3078, 2954, 2935, 2875, 1655, 1583, 1458, 1239, 1093, 1016, 990, 744.

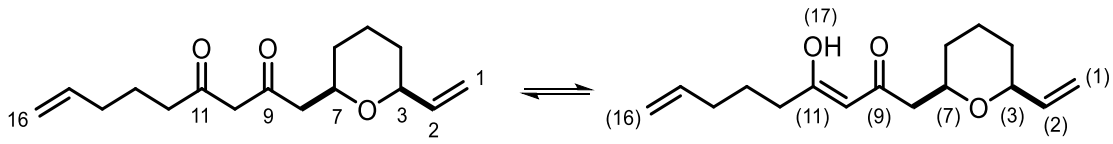
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, dt, *J* = 15.5, 7.0 Hz, *H*-7), 5.83 (1H, dt, *J* = 15.5, 1.0 Hz, *H*-8), 5.84-5.72 (2H, m, *H*-2,15), 5.47 (1H, s, *H*-10), 5.14 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz,

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, $CDCl_3$) δ 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).

m/z LRMS (ESI $^+$) 401.3 $[M+Na]^+$; HRMS (ESI^+) 401.24832 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 401.248241).

1-((2R,6S)-6-vinyltetrahydro-2H-pyran-2-yl)non-8-ene-2,4-dione (184)



184

To an acidified chloroform (250 mL, washed with 50 mL of conc. HCl) at 0 ^{o}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_2SO_4 and filtered. The solvent was and evaporated *in vacuo* and the crude mixture was purified by flash chromatography (5% Et_2O 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) ν_{max} 3078, 2935, 2859, 1704, 1607, 1413, 1310, 1199, 1070, 1052, 990, 916.

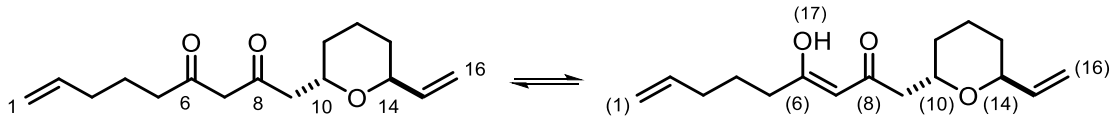
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.47 (<1H, s, *H*-(17)), 5.88-5.71 (2H, m, *H*-15,(15),16,(16)), 5.55 (<1H, s, *H*-10), 5.21 (<1H, ddd, *J* = 17.5, 1.5, 1.5 Hz, *H*-1), 5.18 (<1H, ddd, *J* = 17.5, 1.5,

1.5 Hz, *H*-(1)), 5.07 (<1H, ddd, *J* = 10.5, 1.5, 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, dd, *J* = 16.0, 8.5 Hz, *H*-(8)), 2.58 (<1H, dd, *J* = 14.5, 7.0 Hz, *H*-8), 2.53 (<1H, dd, *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')).

^{13}C NMR (126 MHz, $CDCl_3$) 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)).

m/z LRMS (ESI $^+$) 287.2 $[M+Na]^+$; HRMS (ESI^+) 287.16126 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 287.16177).

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



185

IR (neat) ν_{max} 3078, 2933, 2859, 1715, 1608, 1457, 1441, 1200, 1038, 916.

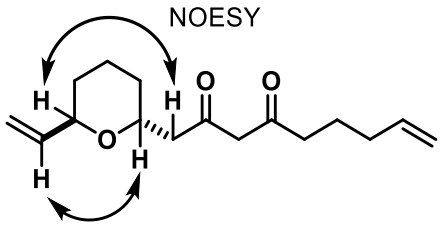
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93-5.84 (1H, m, *H*-15, (15)), 5.84-5.71 (1H, m, *H*-2, (2)), 5.54 (1H, s, *H*-7), 5.25-5.18 (2H, m, *H*-16, (16)), 5.05-4.95 (2H, m, *H*-1,(1)), 4.40-4.35 (<1H, m, *H*-14), 4.35-4.30 (<1H, m, *H*-(14)), 4.19-4.13 (1H, m, *H*-10, (10)), 3.61 (<1H, s, *H*-(7)), 2.78 (<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')).

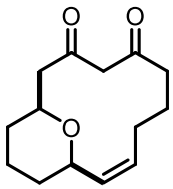
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8 (*C*-8), 191.6 (*C*-6), 138.5 (*C*-15), 138.1 (*C*-2), 116.6 (*C*-16), 115.6 (*C*-1), 100.7 (*C*-7), 73.0 (*C*-14), 68.6 (*C*-10), 44.6 (*C*-9), 38.0 (*C*-5), 33.4 (*C*-3), 31.1 (*C*-11), 28.9 (*C*-13), 25.0 (*C*-4), 19.0 (*C*-12).

m/z LRMS (ESI $^+$) 287.2 $[M+Na]^+$; HRMS (ESI^+) 287.16177 ($[M+Na]^+$, $C_{16}H_{24}O_3Na$ 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)



186

Grubbs 2nd 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_2Cl_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 *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) ν_{max} 3007, 2931, 2860, 1728, 1696, 1368, 1300, 1074, 1037, 938, 881.

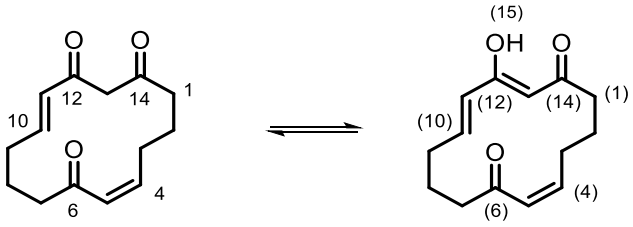
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (1H, dd, *J* = 11.0, 8.0 Hz, *H*-5), 5.46 (1H, ddd, *J* = 11.0, 11.0, 5.0 Hz, *H*-4), 4.84 (1H, ddd, *J* = 10.5, 8.0, 2.0 Hz, *H*-6), 3.73 (1H, d, *J* = 13.0 Hz, *H*-12), 3.71 (1H, dddd, *J* = 11.0, 11.0, 2.5, 2.0 Hz, *H*-10), 3.36 (1H, d, *J* = 13.0 Hz, *H*-12'), 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, $CDCl_3$) δ 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 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 259.13047).

MP: 48-52 ^{o}C

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



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 ^{o}C. The reaction mixture was quenched after 30 minutes pouring into a saturated aqueous NH_4Cl solution. The mixture was extracted by CH_2Cl_2, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated using stream of nitrogen. The crude mixture was dissolved in CH_2Cl_2 (0.5 mL)

and DMP (19 mg, 0.044 mmol) was added to the solution at 0 ºC 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_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_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) ν_{max} 2919, 2850, 1715, 1660, 1618, 1447, 1416, 1295, 1118.

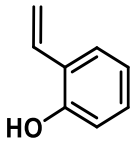
^{1}H NMR (500 MHz, $CDCl_3$) δ 14.15 (<1H, s, *H*-(15)), 6.69 (1H, dt, *J* = 15.0, 8.0 Hz, *H*-10), 6.10 (1H, d, *J* = 11.0 Hz, *H*-5), 5.99 (1H, d, 15.0 Hz, *H*-11), 5.96 (1H, dt, *J* = 11.0, 9.0 Hz, *H*-4), 3.60 (2H, s, *H*-13), 2.85-2.78 (2H, br. dt, *J* = 9.0, 6.0 Hz, *H*-3), 2.47-2.42 (2H, m, *H*-7), 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, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 257.11482).

Only the keto tautomer reported.

2-vinylphenol[120] **(197)**



197

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 °C. Salicylicaldehyde **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 separater, solvents were removed *in vacuo* and the crude mixture was purified by flash chromatography (5 to 10% EtOAc in petroleum ether) which gave the tittle compound **197** as a colourless oil in 95% yield (1.87 g, 15.56 mmol).

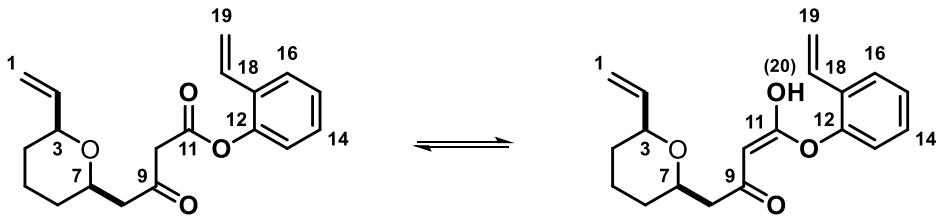
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, dd, *J* = 7.5, 1.5 Hz, *H*-7), 7.15 (1H, ddd, *J*= 7.5, 7.5, 1,5 Hz, *H*-5), 7.00–6.90 (2H, m, *H*-2,6), 6.80 (1H, dd, *J* = 8.0, 1.5 Hz, *H*-4), 5.75 (1H, dd, *J* = 17.5, 1.5 Hz, *H*-1), 5.37 (1H, dd, *J* = 11.5, 1.5 Hz, *H*-1').

^{13}C NMR (101 MHz, $CDCl_3$) δ 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).

m/z LRMS (ESI^-) 119.1 $[M-H]^-$

Data in accordance with the literature[120].

2-vinylphenyl 3-oxo-4-((2R,6S)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate (199)



199

(*E*)-2,2-dimethyl-6-(6-((triethylsilyl)oxy)octa-1,7-dien-1-yl)-4*H*-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% Et_2O 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 $NaHCO_3$ (10 ml). Layers were separated and the organic phases were washed with brine (20 ml), dried over Na_2SO_4 filtered, and evaporated *in vacuo*. Purification by flash chromatography (10% to 20% Et_2O in petroleum ether) gave the tittle compound **199** (52%, 172 mg, 0.547 mmol) that exist at equilibrium as a 82:18 mixture of keto to enol tautomers.

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

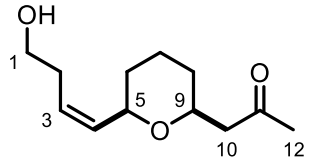
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.83 (<1H, s, *H*-20), 7.38 (1H, dd, *J* = 7.5, 2.0 Hz, *H*-16, 16'), 7.32–7.20 (2H, m, *H*-14,14',15,15'), 7.10 (1H, dd, *J* = 7.5, 1.0 Hz, *H*-13,13'), 6.87 (<1H, dd, *J* = 17.5, 11.0 Hz, *H*-18), 6.74 (<1H, dd, *J* = 17.5, 11.0 Hz, *H*-(18)) 5.92-5.78 (1H, m, *H*-2,2'), 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 ($[M+Na]^+$, $C_{19}H_{22}O_4Na$ requires 337.14102).

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



203

A solution of compound **97** (10 mg, 0.042 mmol), iodobenzene (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_2O. The mixture was washed with water, brine, dried over Na_2SO_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).

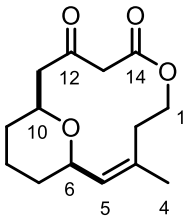
IR (neat) ν_{max} br. 3339, 3930, 2840, 1715, 1556, 1415, 1072, 1058, 915

^{1}H NMR (500 MHz, C_6D_6) δ 5.74 (1H, dd, *J* = 11.0, 7.0 Hz, H-4), 5.56 (1H, dtd, *J* = 11.0, 8.0, 1.0 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 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 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').

^{13}C NMR (126 MHz, C_6D_6) δ 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).

m/z LRMS (ESI $^{+}$) 235.2 $[M+Na]^{+}$; HRMS (ESI^{+}) 235.13049 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 235.13047).

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



205

Compound **208** (22 mg, 0.078 mmol) in CH_2Cl_2 (30 mL) was degassed by bubbling nitrogen though the solution for 30 min. Grubbs 2nd 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_2O in petroleum ether) to give the title compound **205** as a white solid in 45% yield (8.9 mg, 0.035 mmol).

IR (neat) ν_{max} 2980, 2931, 2859, 1736, 1708, 1672, 1446, 1320, 1270, 1187, 1025, 951.

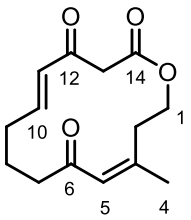
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (1H, d, *J* = 8.5 Hz, H-5), 4.48 (1H, ddd, *J* = 11.0, 4.5, 2.5 Hz, H-1), 4.03 (1H, ddd, *J* = 12.5, 11.0, 2.5 Hz, H-1'), 3.83 (1H, ddd, *J* = 11.0, 9.0, 2.0 Hz, H-6), 3.70 (1H, br. d, *J* = 11.0 Hz, H-10), 3.68 (1H, d, *J* = 14.0 Hz, H-13), 3.21 (1H, ddd, *J* = 13.5, 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').

^{13}C NMR (126 MHz, $CDCl_3$) 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).

m/z LRMS (ESI $^{+}$) 275.2 $[M+Na]^{+}$; HRMS (ESI^{+}) 275.12530 ($[M+Na]^{+}$, $C_{14}H_{20}O_4Na$ requires 275.12538).

MP: 78-82 ^{o}C white solid

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



206

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 ^{o}C. The mixture was stirred for 15 minutes and quenched by pouring onto an ice-cold saturated aqueous NH_4Cl solution. The solution was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The crude product was concentrated *in vacuo*, dissolved in CH_2Cl_2 and cooled to 0 ^{o}C. 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_2Cl_2. The combined organic layers where washed with saturated aqueous sodium bicarbonate, then with brine, dried over Na_2SO_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).

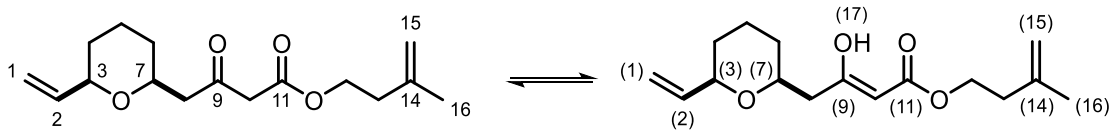
IR (neat) ν_{max} 2918, 2850, 1739, 1690, 1669, 1623, 1440, 1260, 1218, 1116, 1027.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{14}H_{18}O_4Na$ requires 273.10973).

3-Methylbut-3-en-1-yl 3-oxo-4-((2S,6R)-6-vinyltetrahydro-2H-pyran-2-yl)butanoate (208)



208

A mixture of compound **145** (500 mg, 1.36 mmol) and 3-methyl-3buten-1-ol (0.567 mL, 5.46 mmol, 97 w/w%) in dry toluene (2 mL) was heated at 110 ^{o}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 ^{o}C. The reaction mixture was stirred for 1 hour. The reaction was quenched by adding saturated $NaHCO_3$. The layers were separated and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% to 25% Et_2O 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).

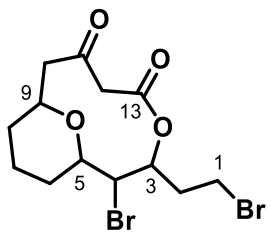
IR (neat) ν_{max} 3078, 2935, 2857, 1743, 1715, 1649, 1311, 1224, 1152, 1073, 1041, 918, 892.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (101 MHz, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{16}H_{24}O_4Na$ requires 303.15668).

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



211

A stock solution of bromine (6.7 mg, 0.042 mmol) in CH_2Cl_2 (0.3 mL) was added to a solution of macrocycle **87** (10 mg, 0.042 mmol) in $CHCl_3$ (2 mL) at 0 ºC. 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).

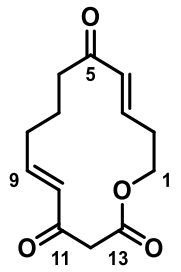
IR (neat) ν_{max} 2956, 2940, 2917, 2850, 1739, 1701, 1300,1196, 989, 949, 892, 646.

^{1}H NMR (500 MHz, C_6D_6) δ 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_6D_6) δ 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).

m/z LRMS (ESI $^{+}$) 418.9 $[M+Na]^{+}$; HRMS (ESI^{+}) 418.94635 ($[M+Na]^{+}$, $C_{13}H_{18}Br_2O_4Na$ requires 418.94641).

(5E,11E)-Oxacyclotetradeca-5,11-diene-2,4,10-trione (222)



222

A solution of enone **67** (20 mg, 0.085 mmol) in diethyl ether was added to the irradiation vessel. The insert was added, srew cap fitted and the vessel was degassed by bubbling nitrogen though 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 *in vacuo* and the crude product was purified twice by thin layer chromatography. First purification (Et_2O as eluent) afforded (5*Z*,11*Z*)-oxacyclotetradeca-5,11-diene-2,4,10-trione **220** in 23% yield (4.5

mg, 0.019 mmol) and (5*E*,11*E*)-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 (Et_2O in CH_2Cl_2) afforded the recovered starting material **67** in 35% yield (7 mg, 0.030 mmol) and (5*Z*,11*E*)-oxacyclotetradeca-5,11-diene-2,4,10-trione **221** in 5% yield (1 mg, 0.004 mmol).

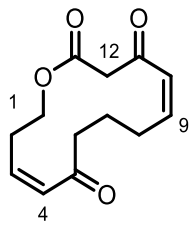
IR (neat) ν_{max} 2917, 2849, 2360, 2342, 1737, 1629, 1667, 1624, 1341, 1257, 978.

^{1}H NMR (500 MHz, $CDCl_3$) 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),

^{13}C NMR (126 MHz, $CDCl_3$) 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 ($[M+Na]^+$, $C_{13}H_{16}O_4Na$ requires 259.09408).

(5Z,11Z)-Oxacyclotetradeca-5,11-diene-2,4,10-trione (220)



220

IR (neat) ν_{max} 2918, 2850, 1739, 1693, 1628, 1414, 1375, 1253, 1112.

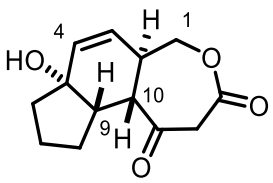
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, br. d, *J* = 11.5 Hz, *H*-4), 6.18 (1H, d, *J* = 11.5 Hz, *H*-10), 6.18 (1H, dt, *J* = 11.5, 9.5 Hz, *H*-9), 5.88 (1H, dt, *J* = 11.5, 8.0 Hz, *H*-3), 4.26 (2H, t, *J* = 5.5 Hz, *H*-1), 3.39 (2H, s, *H*-12), 2.95-2.89 (2H, m, *H*-2), 2.76-2.70 (2H, m, *H*-8), 2.55-2.50 (2H, m, *H*-6), 1.94-1.88 (2H, m, *H*-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ 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).

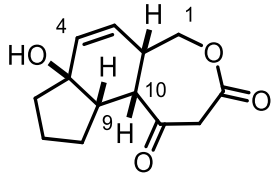
m/z LRMS (ESI $^{+}$) 259.0 $[M+Na]^{+}$; HRMS (ESI^{+}) 259.09408 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 259.09408).

MP: 78-84 ^{o}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)



223



224

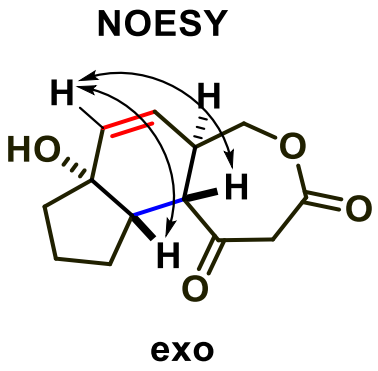
52:48 mixture of diastereomers

IR (neat) ν_{max} br. 3432, 2925, 2851, 1743, 1699, 1449, 1364, 1257, 1225, 1184, 1119, 999, 916, 730.

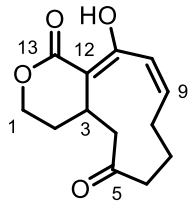
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (1H, ddd, *J* = 10.5, 7.5, 3.0 Hz, H-4), 6.17-6.12 (1H, app. m, H-(4)), 6.00 (1H, dddd, *J* = 10.5, 6.0, 4.0, 1.5 Hz, H-3), 5.64 (1H, br. d, *J* = 11.5 Hz, H-(3)), 4.97 (1H, dd, *J* = 13.0, 6.0 Hz, H-1), 4.89 (1H, dd, *J* = 15.5, 4.5 Hz, H-(1)), 4.72 (1H, br. d, *J* = 15.5 Hz, H-(1'), 4.33 (1H, ddd, *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,(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,(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).

m/z LRMS (ESI $^{+}$) 259.0 $[M+Na]^{+}$; HRMS (ESI^{+}) 259.09408 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 259.09423).



(10Z,12Z)-12-Hydroxy-3,4,4a,7,8,9-hexahydro-1H-cyclodeca[c]pyran-1,6(5H)-dione (225)



225

A solution of (5*Z*,11*Z*)-oxacyclotetradeca-5,11-diene-2,4,10-trione **220** (5.5 mg, 0.023 mmol) and 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_2SO_4, filtered and the solvents were removed *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) ν_{max} br. 3413, 2917, 2849, 1706, 1633, 1587, 1418, 1259, 1259, 1225, 1196, 1022, 798.

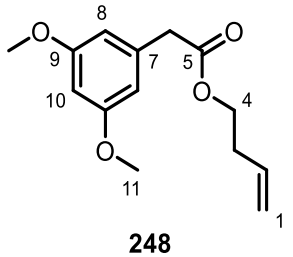
^{1}H NMR (500 MHz, C_6D_6) δ 14.39 (1H, s, H-O), 5.63 (1H, d, *J* = 11.62 Hz, H-10), 5.46 (1H, ddd, *J* = 11.5, 11.5, 5.5 Hz, H-9), 3.61-3.56 (2H, app. m, H-1), 2.59-2.50 (1H, app. m, H-3), 2.23-2.14 (1H, m, H-8), 1.96 (1H, dd, *J* = 12.0, 10.5 Hz, H-4), 1.87-1.66 (4H, m, H-7,8',6,6'), 1.57 (1H, dd, *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_6D_6) δ 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 ($[M+Na]^{+}$, $C_{13}H_{16}O_4Na$ requires 259.09408).

$[\alpha]_D^{25}$ = + 40 (c = 0.001, $CHCl_3$).

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



248

A solution of DCC (1.26 g, 6.12 mmol) in CH_2Cl_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-buten-1-ol (0.550 mL, 6.12 mmol) in CH_2Cl_2 (50 mL) at 0 ^{o}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).

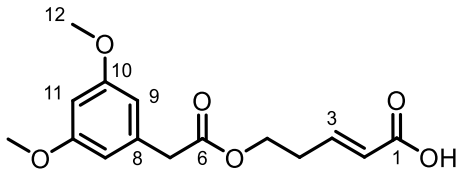
IR (neat) ν_{max} 2956, 2839, 1732, 1641, 1595, 1292, 1204, 1147, 1064, 917, 833.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



249

A mixture of compound **248** (500 mg, 2.00 mmol) and acrylic acid (0.411 mL, 5.99 mmol) in CH_2Cl_2 (20 ml) was degassed by purging nitrogen trough and the amount of CH_2Cl_2 was reduced to 10 mL. The Grubbs 2nd 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 *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).

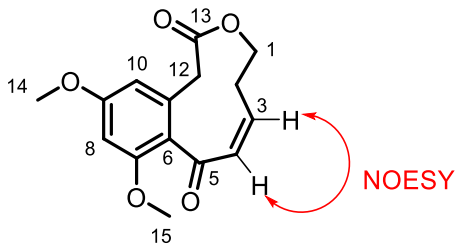
IR (neat) ν_{max} 3004, 2943, 2839, 1728, 1695, 1654, 1595, 1460, 1430, 1291, 1204, 1147, 1064, 979, 834, 685

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^{+}$, $C_{15}H_{18}O_6Na$ requires 317.09956).

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



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_2Cl_2 and the combined organic phases were washed with water and brine and dried over Na_2SO_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) ν_{max} 2955, 2846, 1733, 1664, 1600, 1578, 1455, 1333, 1264, 1196, 1154, 1093, 1025, 735.

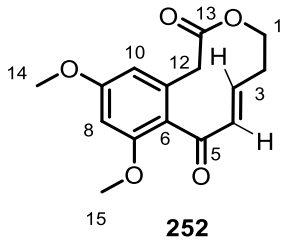
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (1H, d, *J* = 12.0 Hz, *H*-4), 6.41 (1H, d, *J* = 2.0 Hz, *H*-8), 6.31 (1H, d, *J* = 2.0 Hz, *H*-10), 5.97 (1H, dt, *J* = 12.0, 8.0 Hz, *H*-3), 4.17 (2H, br. t, *J* = 5.0 Hz, *H*-1), 3.86 (2H, br. s, *H*-12), 3.85 (3H, s, *H*-15), 3.82 (3H, s, *H*-14), 2.63-2.55 (2H, m, *H*-2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 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 ^{o}C.

(*E*)-9,11-Dimethoxy-4,5-dihydro-2H-benzo[d]oxecine-2,8(1H)-dione (252)



252

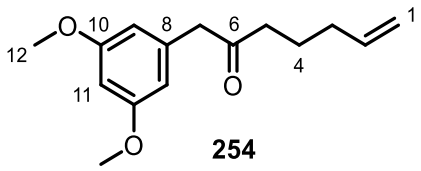
Compound **250** (4.2 mg, 0.015 mmol) in EtOAc (8 mL) was degassed by bubbling with nitrogen for 30 min. The mixture was irradiated for 15 minutes at 0 ^{o}C with a 365 nm light source. The mixture was concentrated *in vacuo* and purified by column chromatography (10% to 50% EtOAc in petroleum ether) to give the title compound **252** in 25% yield (1.0 mg, 0.0038 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^{+}$, $C_{15}H_{16}O_5Na$ requires 299.08903).

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



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_2O (80 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, then brine and dried over Na_2SO_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).

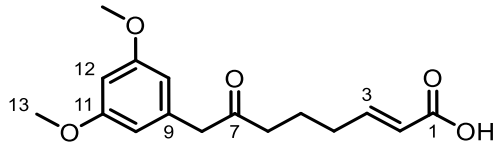
IR (neat) ν_{max} 3076, 2999, 2838, 1710, 1639, 1459, 1430, 1204, 1149, 1059, 912, 831, 668.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^{+}$, $C_{15}H_{20}O_3Na$ requires 271.1310).

(*E*)-8-(3,5-Dimethoxyphenyl)-7-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_2Cl_2 (12ml) was degassed by purging with nitrogen gas until the amount of CH_2Cl_2 was reduced to 6 mL. The Grubbs 2nd 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 *in vacuo* and the crude mixture was purified by flash chromatography (20% to 50% EtOAc in petroleum ether). Solvents were removed *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) ν_{max} 3250, 3002, 2939, 2839, 1694, 1650, 1594, 1459, 1430, 1290, 1204, 1149, 1059, 980, 832, 811, 696.

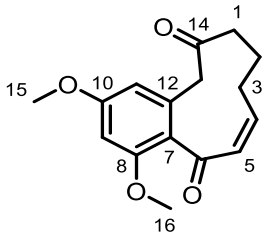
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1H, dt, *J* = 15.5, 7.0 Hz, *H*-3), 6.37 (1H, d, *J* = 2.0 Hz, *H*-12), 6.34 (2H, d, *J* = 2.0 Hz, *H*-10), 5.76 (1H, dt, *J* = 15.5, 1.5 Hz, *H*-2), 3.77 (6H, s, *H*-13), 3.59 (2H, s, *H*-8), 2.48 (2H, t, *J* = 7.0 Hz, *H*-6), 2.18 (2H, dtd, *J* = 7.5, 7.0, 1.5 Hz, *H*-4) 1.73 (2H, app. qn, *J* = 7.0 Hz, *H*-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ 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/z 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-Dimethoxy-9,10-dihydrobenzo[10]annulene-5,11(8H,12H)-dione (256)



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_2Cl_2 (150 ml), the organic layers were washed with brine and dried over Na_2SO_4. The mixture was filtered and the solvents were removed *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).

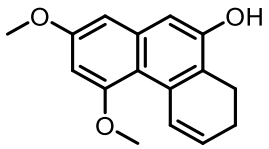
IR (neat) ν_{max} 2917, 2849, 1700, 1652, 1636, 1507, 1396, 1291, 1157.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{16}H_{18}O_4Na$ requires 315.1107).

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 ^{o}C for 3 hours and poured into saturated aqueous NH_4Cl. The solution was extracted with CH_2Cl_2 (80 mL) and the combined organic layers where washed with water and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *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).

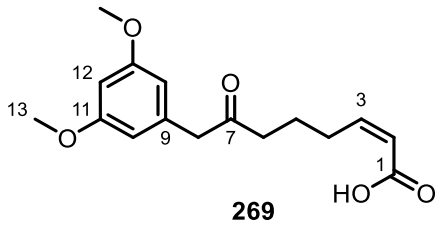
IR (neat) ν_{max} 3396, 2929, 2849, 1625, 1585, 1449, 1403, 1358, 1310, 1203, 1156, 1106, 1047, 859.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na]^+$, $C_{16}H_{16}O_3Na$ requires 257.11727).

(Z)-8-(3,5-Dimethoxyphenyl)-7-oxooct-2-enoic acid (269)



269

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 ^{o}C for 1 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 compound **269** in 15% yield (3.1 mg, 0.010 mmol).

IR (neat) ν_{max} 2930, 1697, 1595, 1459, 1431, 1205, 1151, 1066, 830.

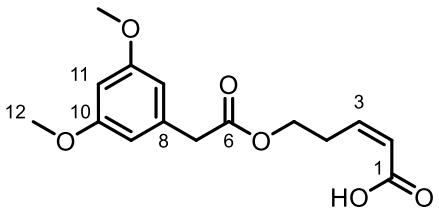
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (1H, t, *J* = 2.0 Hz, *H*-12), 6.34 (2H, d, *J* = 2.0 Hz, *H*-10), 6.27 (1H, dt, *J* = 11.5, 7.5 Hz, *H*-3), 5.79 (1H, dt, *J* = 11.5, 1.5 Hz, *H*-2), 3.77 (6H, s, *H*-13), 3.60 (2H, s, *H*-8), 2.61 (2H, tdd, *J* = 7.5, 7.5, 1.5 Hz, *H*-4), 2.50 (2H, t, *J* = 7.5 Hz, *H*-6), 7.41 (2H, app. qn, *J* = 7.5 Hz, *H*-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ 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 ($[M+H]^{+}$, $C_{16}H_{20}O_3Na$ requires 293.13839).

MP: 61-65 ^{o}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 ^{o}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).

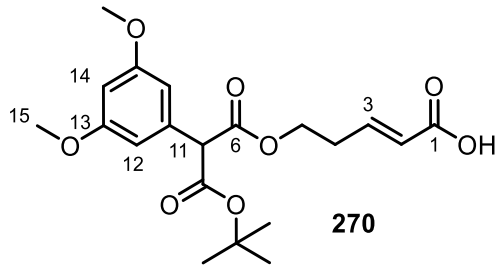
IR (neat) ν_{max} 2980, 2924, 1731, 1698, 1644, 1596, 1460, 1431, 1205, 1151, 1066, 831.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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/z 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)



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 ^{o}C. The mixture was stirred for 30 minutes and cooled to -78^{o}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_2O (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_2O (50 mL). The organic layer was separated and washed with water and brine, dried over Na_2SO_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_2Cl_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).

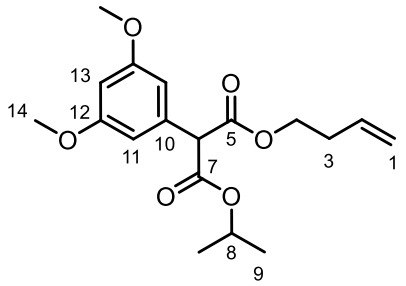
IR (neat) ν_{max} 3007, 2935, 2841, 1721, 1655, 1596, 1459, 1369, 1293, 1152, 1061, 928, 844.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($[M+Na^+]^+$, $C_{20}H_{26}O_8Na$ requires 417.15180).

1-(But-3-en-1-yl) 3-isopropyl 2-(3,5-dimethoxyphenyl)malonate (272)



256

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 NH_4Cl. The mixture was extracted with CH_2Cl_2 (80 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4 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).

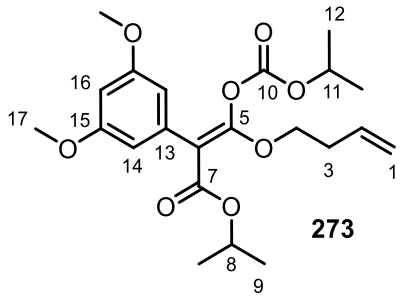
IR (neat) ν_{max} 3080, 2982, 2938, 2939, 2839, 1730, 1596, 1460, 1291, 1204, 1102, 990, 915, 834.

^{1}H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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)



273

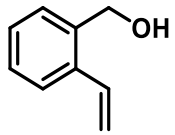
IR (neat) ν_{max} 3080, 2983, 2938, 2938, 2839, 1750, 1643, 1559, 1458, 1270, 1155, 1095, 1037, 911, 835.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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').

m/z LRMS (ESI $^{+}$) 461,2 $[M+K^{+}]^{+}$; HRMS (ESI^{+}) 423.20134 ($[M+H^{+}]^{+}$, $C_{22}H_{31}O_8$ requires 423.20136).

(2-Vinylphenyl)methanol[112] **(279)**



279

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 (3.37g, 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 ^{o}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% Et_2O in petroleum ether) to afford the title compound as a white solid (1.87 g, 97%).

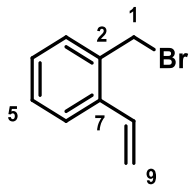
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* = 7.0, 2.5 Hz), 7.33 (1H, dd, *J* = 7.0, 2.0 Hz), 7.30-7.23 (2H, m), 7.02 (1H, dd, *J* = 17.5, 10.5 Hz), 5.67 (1H, dd, *J* = 17.5, 1.5 Hz), 5.36 (1H, dd, *J* = 10.5, 1.0 Hz), 4.72 (2H, s), 1.83 (1H, br. s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 136.6, 133.7, 128.3, 128.1, 127.9, 125.9, 116.4, 63.3

m/z LRMS (ESI $^{+}$) 135.1 $[M+H]^{+}$;

Data in accordance with the literature.[121]

1-(Bromomethyl)-2-vinylbenzene (280)



280

According to a modified literature procedure, a solution of (2-vinylphenyl)methanol **279** (431 mg, 3.21 mmol) in CH_2Cl_2 (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%).

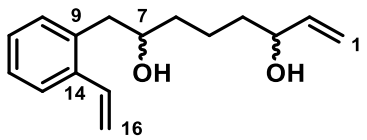
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (1H, app. m, H-6), 7.35-7.28 (2H, m, H-3,5), 7.27-7.22 (1H, app. m, H-4), 7.09 (1H, dd, *J* = 18.0, 12.0 Hz, H-8), 5.76 (1H, dd, *J* = 17.0, 1.0 Hz, H-9), 5.44 (1H, dd, *J* = 12.0, 1.0 Hz, H-9'), 4.57 (2H, s, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) 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 literature[114].

1-(2-Vinylphenyl)oct-7-ene-2,6-diol (282)



282

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_4Cl. The mixture was extracted by CH_2Cl_2, the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvents were evaporated *in 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).

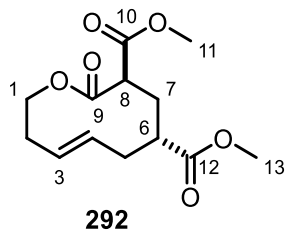
IR (neat) ν_{max} 3339, 3084, 2980, 2933, 1483, 1451, 1420, 1340, 1127, 1077, 989, 916, 853, 773, 700.

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, Hz, *H*-15), 5.87 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz, *H*-2), 5.65 (1H, dd, *J* = 17.5, 1.0 Hz, *H*-16) 5.31 (1H, br. d, *J* = 10.0 Hz, *H*-16'), 5.22 (1H, ddd, *J* = 17.0, 3.0, 1.5, *H*-1), 5.10 (1H, ddd, *J* = 10.5, 2.5, 1.5, *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, *H*-8), 2.74 (1H, dd, *J* = 14.0, 8.5 Hz, *H*-8'), 1.65-1.50 (6H, m, *H*-4,5,6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $^+$) 296.2 $[M+Na]^+$; HRMS (ESI^+) 296.15120 ($[M+Na]^+$,$C_{16}H_{22}O_2Na$ requires 269.15122).

Dimethyl (3R,5R,E)-2-oxo-3,4,5,6,9,10-hexahydro-2H-oxecine-3,5-dicarboxylate [115] **(292)**



292

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-2*H*-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 NH_4Cl. The mixture was extracted with Et_2O (100 mL) and the combined organic layers were dried over $MgSO_4$ 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 (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O 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).

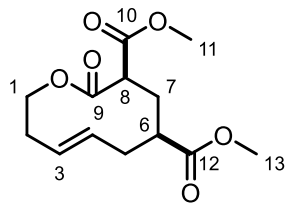
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45-5.37 (1H, m, *H*-4), 5.36-5.28 (1H, m, *H*-3), 4.93-4.85 (1H, m, *H*-1), 4.01-3.93 (1H, m, *H*-1'), 3.72 (3H, s, *H*-11), 3.71 (3H, s, *H*-13), 3.55 (1H, dd, *J* = =9.0, 2.0 Hz, *H*-8), 2.97-2.90 (1H, m, *H*-6), 2.70-2.51 (2H, m, *H*-5,7), 2-38-2.18 (4H, m, *H*-7',2,5').

^{13}C NMR (126 MHz, $CDCl_3$) δ 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)



291

^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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].

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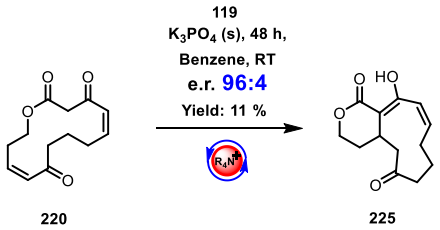
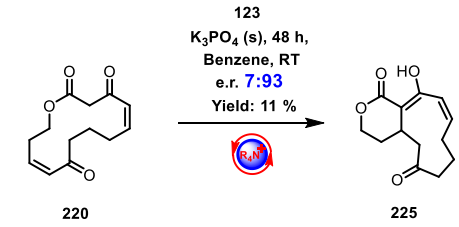
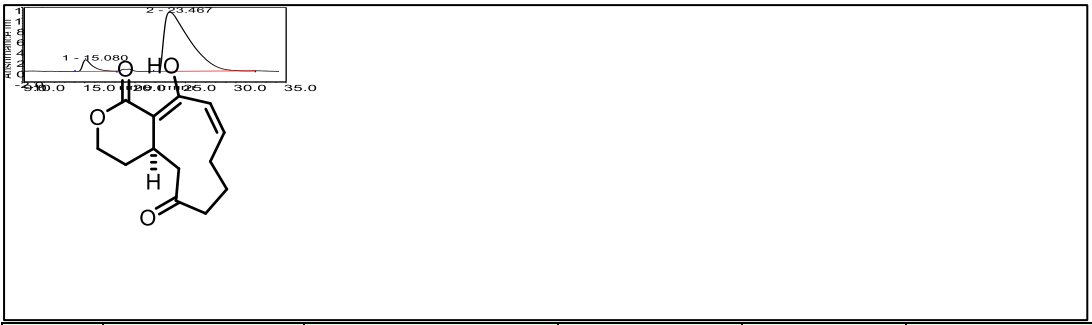
7 Appendix

7.2 HPLC traces

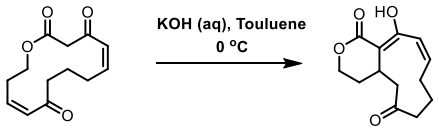


No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		13.373	42.455	25.905	95.91
2		25.453	1.809	0.849	4.09
Total:			**44.264**	**26.755**	**100.00**





No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		15.080	2.495	2.200	7.02
2		23.467	33.051	11.229	92.98
Total:			**35.546**	**13.429**	**100.00**



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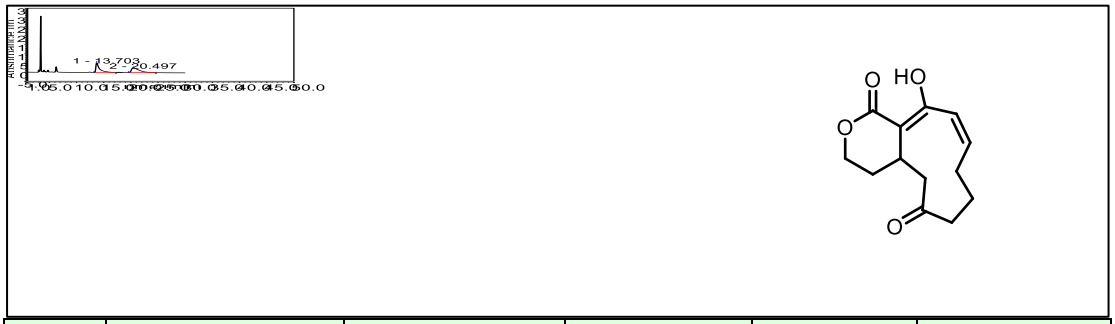
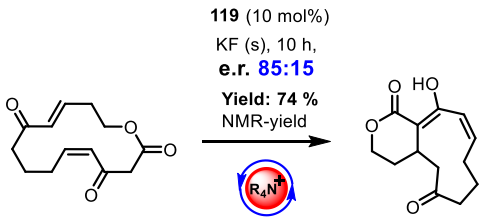
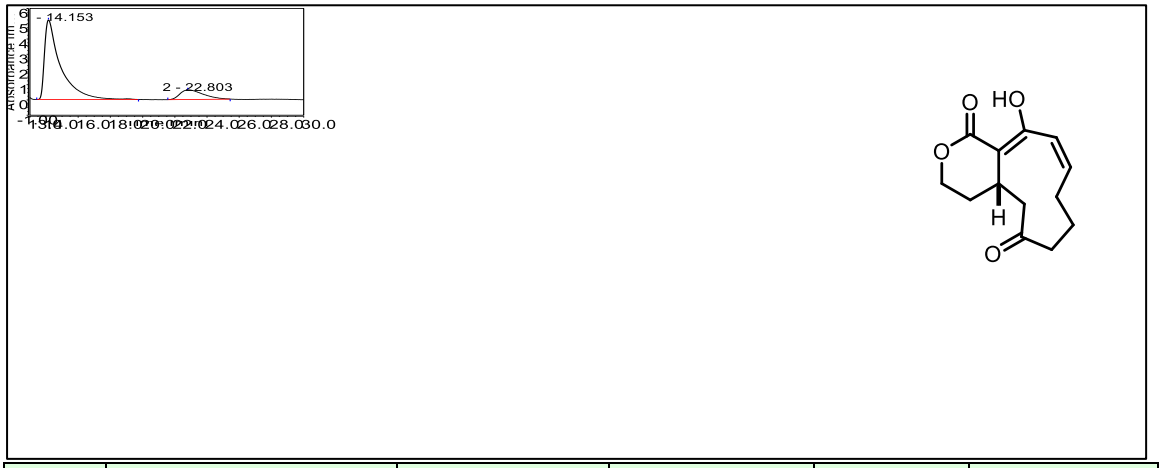
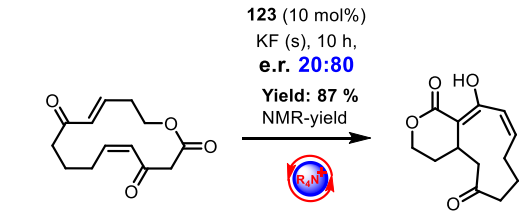


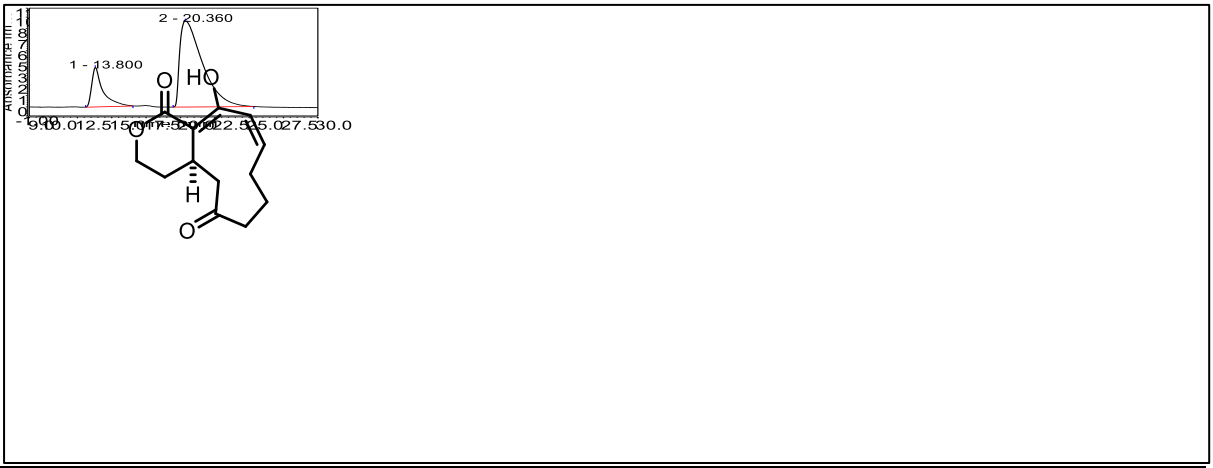
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		13.703	4.430	5.377	50.66
2		20.497	4.315	2.581	49.34
Total:			**8.745**	**7.958**	**100.00**



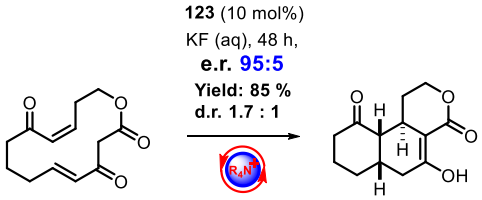


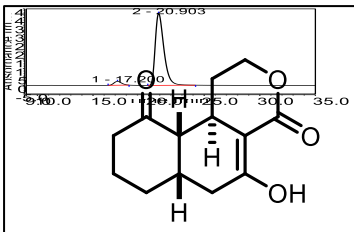
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		14.153	6.031	5.229	85.07
2		22.803	1.059	0.635	14.93
Total:			**7.090**	**5.864**	**100.00**



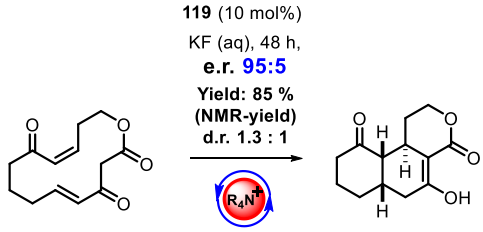


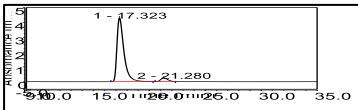
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		13.800	4.167	4.408	18.47
2		20.360	18.391	9.608	81.53
Total:			**22.558**	**14.016**	**100.00**

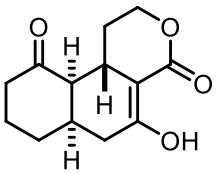




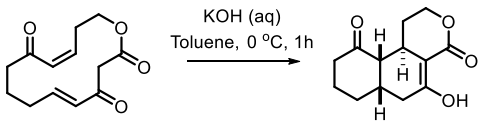
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		17.200	1.788	2.233	4.50
2		20.903	37.980	42.327	95.50
Total:			**39.768**	**44.560**	**100.00**

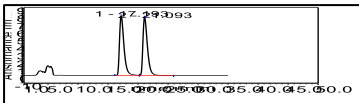


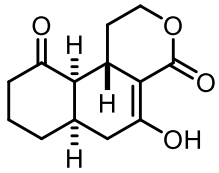




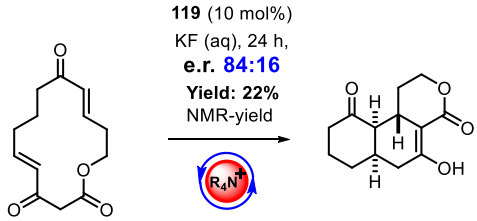
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		17.323	30.961	43.095	94.73
2		21.280	1.724	2.429	5.27
Total:			**32.685**	**45.524**	**100.00**

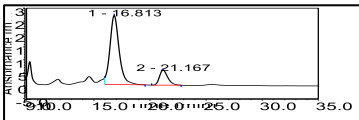


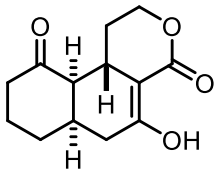




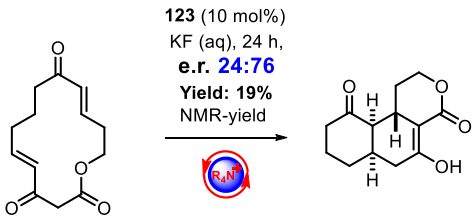
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		17.193	68.295	79.186	50.50
2		21.093	66.947	77.293	49.50
Total:			**135.242**	**156.479**	**100.00**

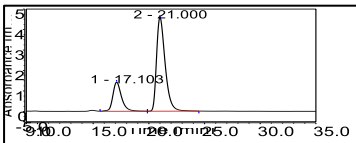


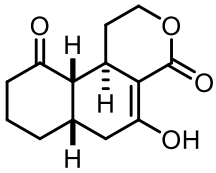




No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		16.813	25.686	26.766	83.78
2		21.167	4.973	5.832	16.22
Total:			**30.660**	**32.598**	**100.00**



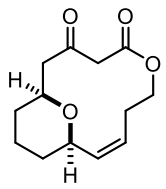




No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		17.107	3.553	4.140	22.59
2		21.003	12.176	13.608	77.41
Total:			**15.729**	**17.748**	**100.00**

9.2 X-ray Crystallography Data

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



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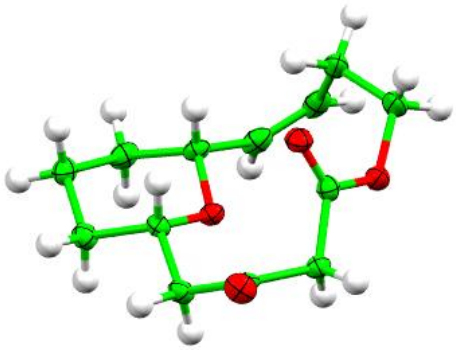
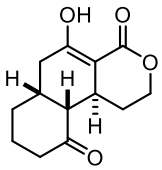
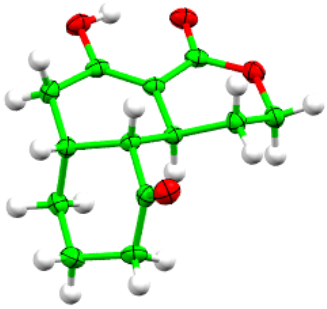


Identification code	012J	
Empirical formula	$C_{13}H_{18}O_4$	
Formula weight	238.28	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.9387 Å	α = 77.993°
	b = 9.1956 Å	β = 75.037°
	c = 15.8478 Å	γ = 84.235°
Volume	1229.43 $Å^3$	
Z,Z'	Z: 4 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	
Final R indices [I>2σ(I)]	R^1 = 0.0390, wR^2 = 0.0846	
R indices (all data)	R^1 = 0.0458, wR^2 = 0.0910	

X-ray Crystallographic Data and Structure Refinement for **101**, 022JDJ14



94



Identification code	022JDJ14	
Empirical formula	$C_{13}H_{16}O_4$	
Formula weight	236.27	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.0438 Å	α = 78.9495°
	b = 8.6673 Å	β = 84.2497°
	c = 10.0232 Å	γ = 68.9944°
Volume	560.335 $Å^3$	
Z,Z'	Z: 2 Z': 0	
Density (calculated)	1.400 Mg m^{-3}	
Absorption coefficient	0.103 mm^{-1}	
F(000)	252.0	
Crystal size	0.12 x 0.20 x 0.28 mm ^{3}	
Theta range for data collection	5.112° to 27.473°	
Reflections collected	4475	
Independent reflections	2540	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.949	
Final R indices [I>2σ(I)]	R^1 = 0.0396, wR^2 = 0.0966	
R indices (all data)	R^1 = 0.0567, wR^2 = 0.1045	