Imperial College London

De novo synthesis of highly substituted pyridines

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Abstract

This thesis is divided into three chapters.

Chapter 1 provides a brief survey of the methodologies currently available for the *de novo* synthesis of cyclopentadienes. Particular relevance is given to the more general methods and to the preparation of structurally interesting compounds. Mechanistic details will also be given for interesting or unusual reaction pathways.

Chapter 2 presents research findings in the field of the application of the decarboxylative Claisen rearrangement (dCr) reaction to the synthesis of aromatics. The development of a novel methodology for the preparation of substituted pyridines will be described. Firstly, the feasibility of the method will be shown by detailing the preparation of simple pyridines, carrying alkyl and aryl substituents. Subsequently, efforts to expand the scope of the methodology will be discussed and attempts to prepare diversely substituted, chiral and cyclofused compounds detailed. Finally, some preliminary results concerning the use of the dCr reaction for the synthesis of cyclopentadienes and cyclopentadienyl anions will be presented.

Chapter 3 provides the experimental details and the characterisation data for all the compounds synthesised.

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Declaration

I certify that all work in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of the thesis has been submitted previously for a degree at this, or any other, university.

Acknowledgements

First and foremost I would like to thank Professor Donald Craig for having given me the opportunity to work on such an interesting project and for having been supportive and encouraging throughout all these months. His invaluable advices and his enthusiasm for chemistry have been of great help in going through the difficulties of research. Sincere thanks are also due to Dr. Steve Smith for his helpful and interesting suggestions, his professionalism and his support.

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Finally, a particular mention must go to all the great people who make my life outside the lab so wonderful, to the fantastic friends I have made in London and above all to Damien and to my family.

It is to Damien that I dedicate this thesis, because of his fundamental support and unconditional love. Thank you.

List of Abbreviations

AcOH	acetic acid
aq	aqueous
Ar	aryl
bs	broad signal
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
c	concentration
CAN	ceric(IV)ammonium nitrate
cat	catalytic
CI	chemical ionisation
CM	cross metathesis
COD	cycloocta-1,5-diene
cosy	correlation spectroscopy
Cp	cyclopentadienyl
[Cp_2Zr]	low valent zyrconocene complex
d	doublet, days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dCr	decarboxylative Claisen rearrangement
dd	doublet of doublets
ddd	doublet of doublet of doublets
de	diastereoisomeric excess
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)-pyridine
DMF	dimethylformamide
DMSO	dimethylsulphoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dt	doublet of triplets
dq	doublet of quartets
ed.	edition
ee	enantiomeric excess

EMS	enhanced microwave synthesis
equiv	equivalents
ES+	positive mode electrospray
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FT	Fourier transform
Grubbs II	Grubbs second-generation catalyst
h	hours
[H]	reducing agent
HPLC	high performance liquid chromatography
IPA	*iso*-propanol
i-Pr	*iso*-propyl
IR	infrared
KOAc	potassium acetate
L.A.	Lewis acid
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
L.G.	leaving group
LHMDS	lithium hexamethyldisilazane
m	multiplet
M	molar (mol/L), metal
Me	methyl
min	minutes
mp	melting point
m/w	microwave
n-BuLi	*normal*-butyllithium
n.d.	not determined
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
nOesy	nuclear Overhauser effect spectroscopy
[O]	oxidising agent

o-DCB	*ortho*-dichlorobenzene
o/n	overnight
p	page
PDC	pyridinium dichromate
Ph	phenyl
PINDY	pinene-derived bipyridine
PKR	Pauson–Khand reaction
PMB	*para*-methoxybenzyl
PNP	*para*-nitrophenyl
ppm	parts per million
PTFE	polytetrafluoroethylene
p-TsOH	*para*-toluenesulfonic acid
Py	pyridine
RCM	ring closing olefin metathesis
q	quartet
qq	quartet of quartets
rt	room temperature
s	singlet
sept	septuplet
SMEAH	sodium bis(2-methoxyethoxy)aluminium hydride
t	triplet
T	temperature
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDMSOTf	*tert*-butyldimethylsilyl triflate
t-BuOK	potassium *tert*-butoxide
Tf	tetrafluoromethansulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSOAc	trimethylsilylacetate
Tol	tolyl
Tp	tris(1-pyrazolyl)borate

tq	triplet of quartets
Ts	*para*-toluenesulfonyl, tosyl
tt	triplet of triplets
UV	ultraviolet
Vol.	volume

Stereochemical Notation

Throughout this thesis the Maehr convention[1] has been adopted in order to aid rapid visual identification of relative and absolute stereochemistry.

Solid and broken lines represent racemates, while solid and broken wedges denote absolute configurations. For the latter, narrowing of both solid and broken wedges denotes increasing distance from the viewer (**Figure 0.1**).

Racemate
Relative Stereochemistry

Single enantiomer
Absolute Stereochemistry

Figure 0.1 The stereochemical notation according to Maehr.

1. Maehr, H. *J. Chem. Ed.* **1985**, *62*, 114.

CHAPTER 1

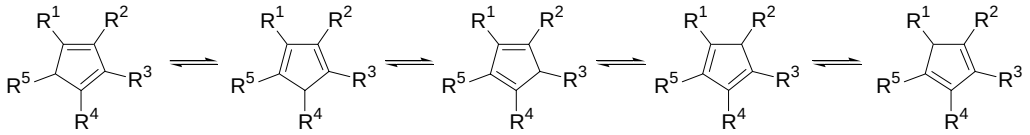
Review: *de novo* synthesis of cyclopentadienes

1.1 Introduction and scope

Cyclopentadienes are compounds of paramount importance both in organic and organometallic chemistry as they are most often used either as dienes in Diels–Alder cycloadditions[1,2] or, in their anionic form, as ligands for sandwich[3,4] and half-sandwich[5,6] compounds. The chemistry of metallocenes in particular, has been largely developed since the discovery of ferrocene in 1951.[7,8] Sandwich complexes have been thoroughly studied and have found important applications,[4] especially as catalysts in polymerisation processes.[9,10] The properties and activities of these complexes are directly related to the functionalisation and substitution pattern of the cyclopentadienyl ligands.[11] Most of the methods for the synthesis of these ligands are based on the alkylation or functionalisation of cyclopentadiene itself, either free or complexed.[12-15] Fewer methods are available for the *de novo* synthesis of the ring.

This review documents the various methodologies available for the synthesis of cyclopentadienes from organic fragments. The synthesis of fulvenes and indenes will be mentioned only when built *via* methodologies also used for the synthesis of cyclopentadienes.

It needs to be noted that cyclopentadienes most often undergo facile migration of the endocyclic double bonds by [1,5]-sigmatropic shift of hydrogen, giving rise to a mixture of isomeric products (**Scheme 1.1**).[16]

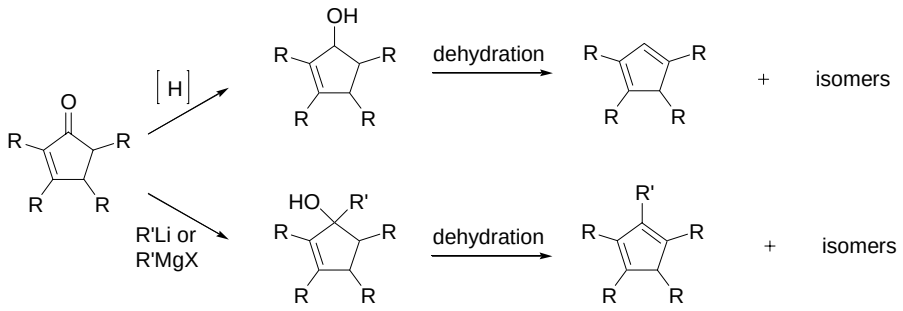


Scheme 1.1 Cyclopentadienes undergo [1,5]-sigmatropic hydrogen shift giving rise to a mixture of isomeric products.

Herein, when cyclopentadienes were isolated as an isomeric mixture, indication will be given. However, this feature of the chemistry will not be discussed.

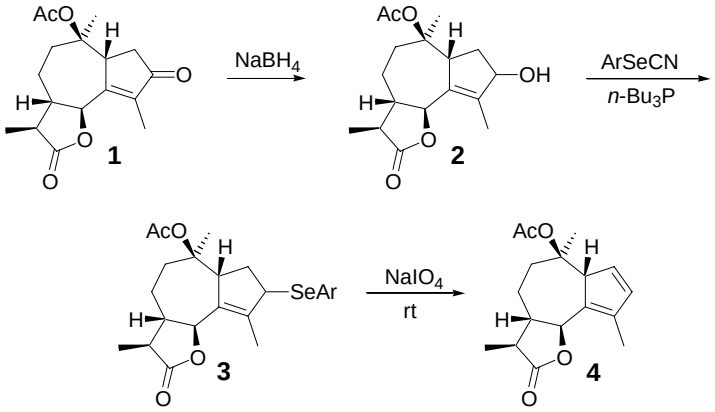
1.2 Synthesis of cyclopentadienes *via* cyclopentenones

One of the most widely used methods of synthesising cyclopentadienes is by modification of the corresponding cyclopentenones. Most commonly the first step is the conversion of the carbonyl group into a hydroxyi, either by reduction or by nucleophilic attack of an alkyllithium or of a Grignard reagent. Subsequent dehydration, triggered by acid catalysis or by the presence of a dehydrating agent, provides the desired cyclopentadienes (**Scheme 1.2**).



Scheme 1.2 Synthesis of cyclopentadienes from cyclopentenones via reduction–dehydration or alkylation–dehydration.

Other methodologies, such as the Shapiro reaction[17] and conversion of the alcohol into the corresponding sulfonate[18] or bromide[19] followed by base-promoted elimination, can be used to carry out this transformation. Indeed, depending on the substrate characteristics, dehydration may fail to provide the desired cyclopentadiene and less common techniques may be required. An example has recently been reported in the context of the total synthesis of Absinthin.[20] The key cyclopentadiene-containing intermediate **4** was obtained by manipulation of the corresponding cyclopentenone **1**. Reduction of **1** followed by Mitsunobu arylselenation gave selenide **3**, which was then oxidised and underwent selenoxide β-elimination (**Scheme 1.3**).

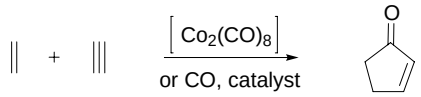


Scheme 1.3 Cyclopentadiene formation in the pathway leading to the total synthesis of Absinthin.

The synthetic challenge transfers therefore to the construction of the cyclopentenones themselves. Numerous methods have been used and a few of these can be considered of general applicability. The most common methods for the synthesis of cyclopentenones as cyclopentadienes precursors will be described and examples of interesting target molecules achieved by these methodologies given.

1.2.1 Synthesis of cyclopentadienes *via* Pauson–Khand reaction

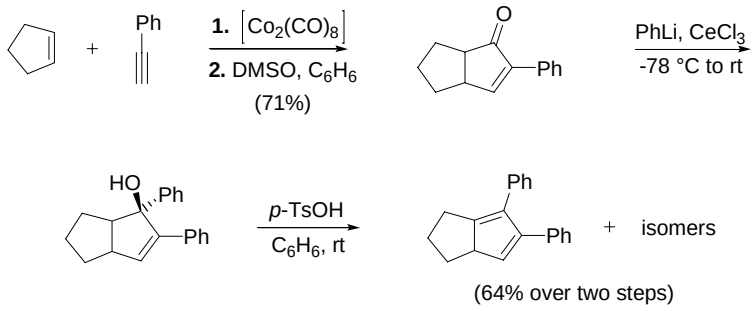
The Pauson–Khand reaction (PKR) is a formal [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide in presence of dicobalt octacarbonyl.[21] A catalytic version of this reaction has been developed in the past decade and has rendered this chemistry particularly attractive (**Scheme 1.4**).[22]



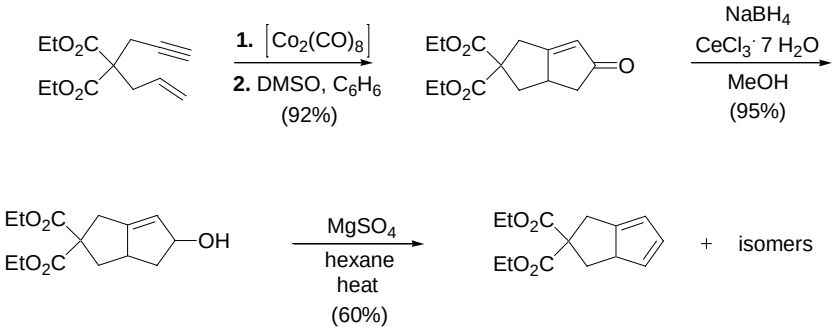
Scheme 1.4 The Pauson–Khand reaction.

This high yielding and robust transformation has been utilised for the synthesis of various cyclopentadienes.[17,21,23-25]

As demonstrated by Chung and co-workers,[26] cyclofused compounds can also be achieved *via* PKR, either by reacting a cyclic alkene (**Scheme 1.5**) or by intramolecular reaction of an α,ω-enyne (**Scheme 1.6**).

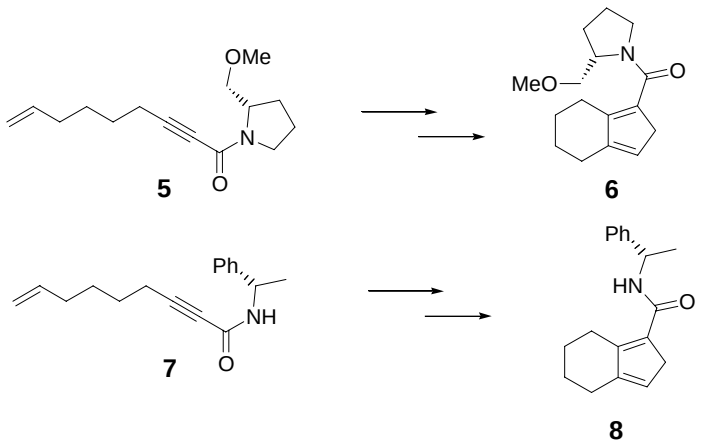


Scheme 1.5 Synthesis of a bicyclic cyclopentadiene *via* PKR of cyclopentene and ethynylbenzene.



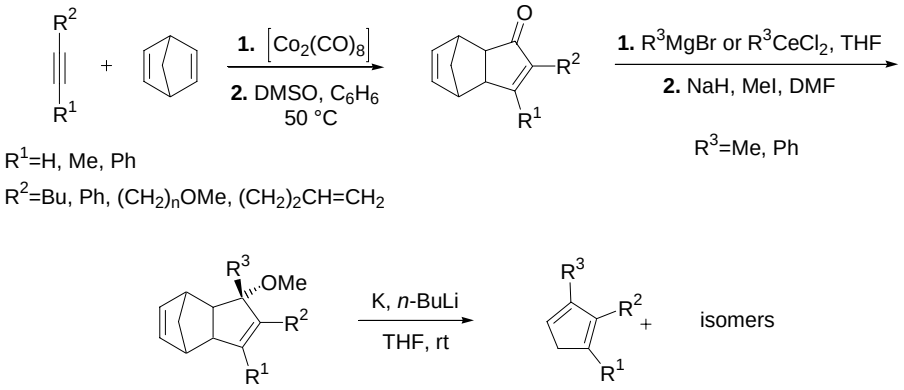
Scheme 1.6 Synthesis of a bicyclic cyclopentadiene *via* intramolecular PKR of an α,ω-enyne.

The Pauson–Khand reaction can also be carried out on electron-deficient enynes.[27,28] For instance, an intramolecular cyclisation allowed the synthesis of cyclopentadienes **6** and **8**, bearing enantiopure amide groups (**Scheme 1.7**).[29]



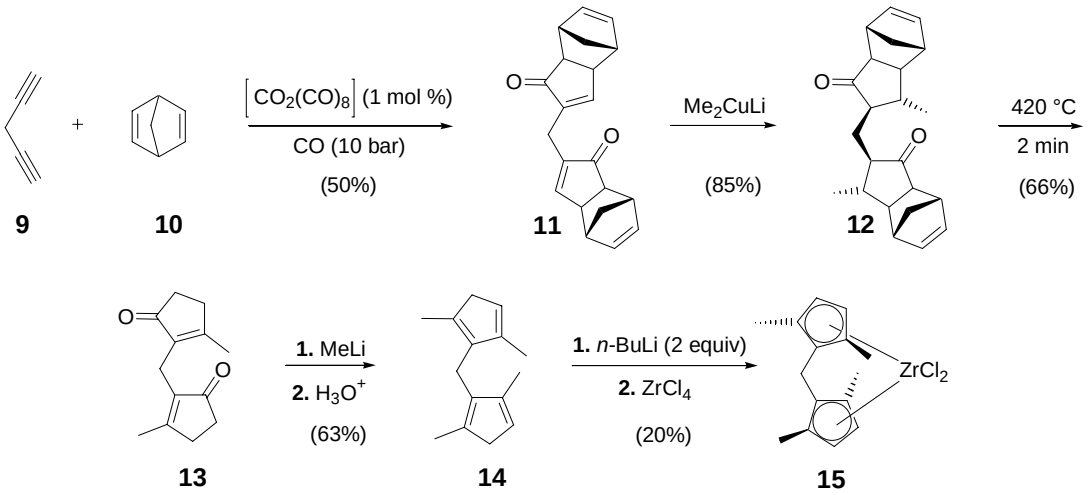
Scheme 1.7 Synthesis of (*S*)-2-(methoxymethyl)pyrrolidine and (*S*)-2-phenylethylamine containing cyclopentadienes **6** and **8** *via* PKR.

The PKR chemistry has in some instances been combined with the retro-Diels–Alder reaction for the preparation of 1,2- and 1,2,3-trisubstituted cyclopentadienes (**Scheme 1.8**).[30-32]



Scheme 1.8 Synthesis of cyclopentadienes *via* Pauson–Khand and retro-Diels–Alder reactions.

An interesting application for this reaction sequence has been recently highlighted by Lee and co-workers for the synthesis of ansa-zirconocene **15** which performs ethylene–norbornene co-polymerisation.[31] The required bis(cyclopentadienide) ligand was synthesised starting from 1,4-pentadiyne **9** and norbornadiene **10**. Catalytic intermolecular PKR provided bis(cyclopentenone) **11**, which underwent 1,4-addition followed by retro-Diels–Alder. Subsequently, double bond isomerisation, 1,2-addition of MeLi and acid-catalysed dehydration afforded the desired bis(cyclopentadiene). (**Scheme 1.9**).

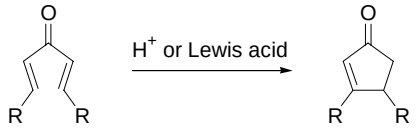


Scheme 1.9 Synthesis of ansa-zirconocene **15** by catalytic PKR and retro-Diels–Alder reactions.

Other linked cyclopentadienes have been synthesised using a double Pauson–Khand cyclisation approach, such as the ones reported by Halterman[17] and Grossman[33] in the mid- and late-nineties.

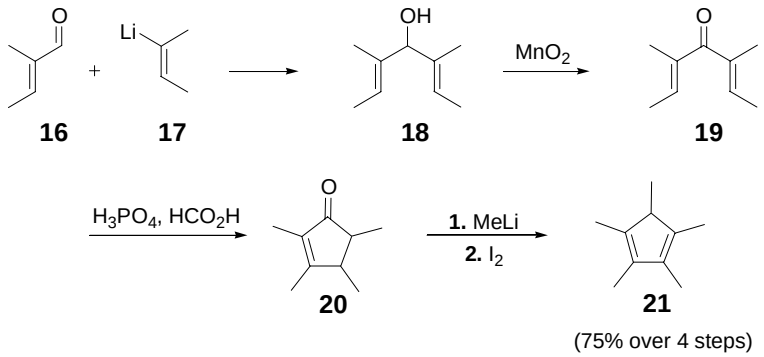
1.2.2 Cyclopentadienes *via* Nazarov cyclisation

The Nazarov cyclisation is an electrocyclic, acid-catalysed, conrotatory cyclisation of a divinylketone into a cyclopentenone (**Scheme 1.10**).[34]



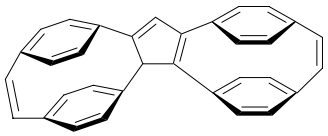
Scheme 1.10 The Nazarov cyclisation.

A historically important example[35] of the application of this reaction for the synthesis of cyclopentadienes was given by the first preparation of the 1,2,3,4,5-pentamethylated product **21**.[36] This procedure, reported by de Vries, started by the alkylation of (*E*)-2-methyl-2-butenal to give alcohol **18**. This secondary alcohol was then oxidised to divinylketone **19** and subsequently underwent Nazarov cyclisation in presence of a combination of formic and phosphoric acid. Treatment with methyl lithium and dehydration then gave the desired compound **21** in 75% overall yield (**Scheme 1.11**).



Scheme 1.11 De Vries synthesis of 1,2,3,4,5-pentamethylcyclopentadiene **21**.

The Nazarov cyclisation can been applied to the synthesis of complex cyclopentadienes, such as the bis(paracyclophane)-anellated compound **22** (**Figure 1**).[37,38]



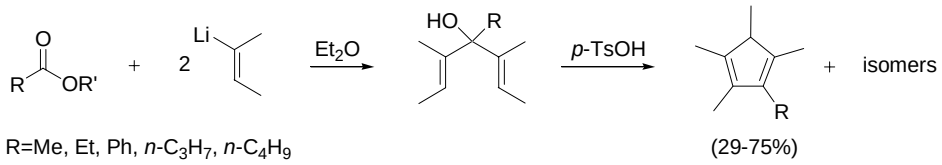
22

Figure 1 Bis([2.2]paracyclophane)-anellated cyclopentadiene **22**.

Mechanistically analogous to the Nazarov cyclisation is the acid-catalysed electrocyclic ring closure of 2,5-dien-4-ols. Although this method doesn't involve the formation of a cyclopentenone, it will be discussed in this section because of its mechanistic similarity to the reaction just illustrated.

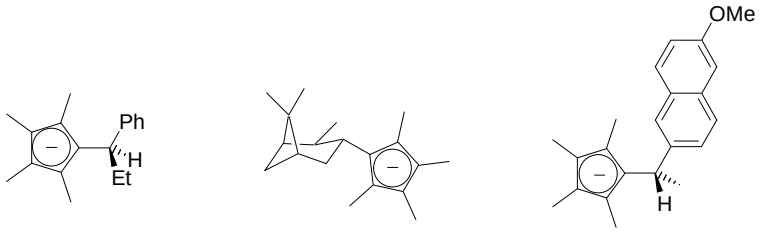
1.2.2.1 Bercaw's method for cyclopentadiene synthesis

In 1977 Bercaw used the pentadienyl-cyclopentenyl cation rearrangement[39,40] for the synthesis of phenyltetramethylcyclopentadiene and alkyltetramethylcyclopentadienes (**Scheme 1.12**).[41]



Scheme 1.12 Bercaw's synthesis of phenyltetramethylcyclopentadiene and alkyltetramethylcyclopentadienes.

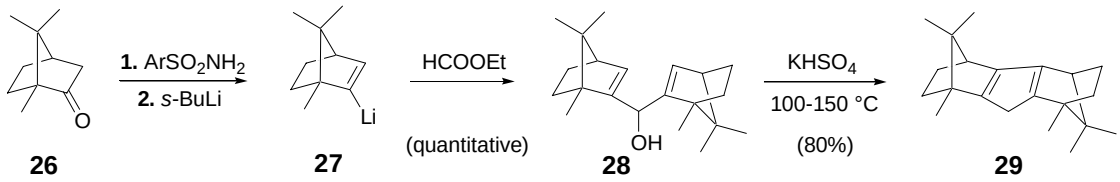
This method was initially developed with the aim of finding a more straightforward approach to the pentamethylated compound **21**. In addition, by using the appropriate ester, various R groups can be introduced on the cyclopentadiene skeleton. Indeed, this sequence has been utilised for the synthesis of 1,2,3,4-tetramethyl-5-trifluoromethylcyclopentadiene[42] and of cyclopentadienides bearing chiral groups such as **23**–**25** (**Scheme 1.13**).[43-45]



23 **24** **25**

Scheme 1.13 Synthesis of chiral cyclopentadienides **23-25** *via* Bercaw's method.

Moreover, the use of the appropriate lithium-alkene can allow the synthesis of interesting polycyclic structures, such as dibornacyclopentadiene **29**, whose anion's complex with zirconium was used to perform asymmetric naphthol hydroxyalkylation. 2-Bornen-2-yllithium **27** was obtained using a modified Shapiro reaction[46] and then reacted with ethyl formate to generate the substrate for the electrocyclisation (**Scheme 1.14**).[47-50]

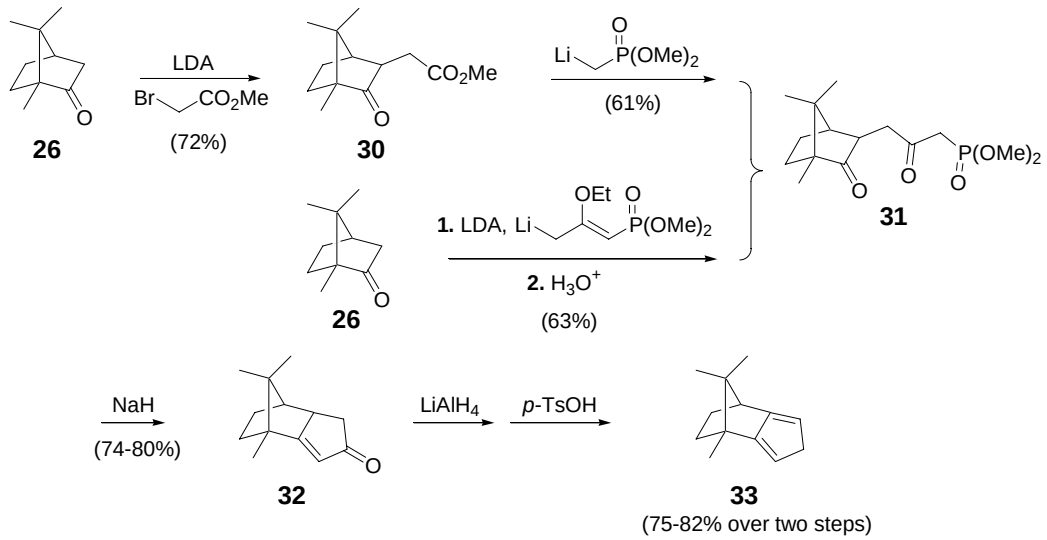


26 **27** **28** **29**

Scheme 1.14 Synthesis of dibornacyclopentadiene **29** *via* Bercaw's method.

1.2.3 Cyclopentadienes *via* Horner–Emmons reaction

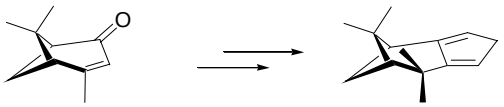
Intramolecular Horner–Emmons reactions have been used most remarkably for the synthesis of chiral annulated cyclopentadienes such as **33** and **35**. For the synthesis of bornacyclopentadiene **33**, the required phosphonate **31** was initially synthesised by alkylation of (+)-camphor with methyl bromoacetate, followed by reaction of ketoester **30** with the lithium-anion of dimethyl methylphosphonate.[51] A one-step procedure involving the use of a 3-carbon phosphonate was later developed.[52,53] Exposure of **31** to NaH afforded the ring closure to cyclopentenone **32**, which then underwent reduction and acid-catalysed dehydration (**Scheme 1.15**).



26 **30** **31** **26** **32** **33**

Scheme 1.15 Synthesis of tricyclic cyclopentadiene **33**.

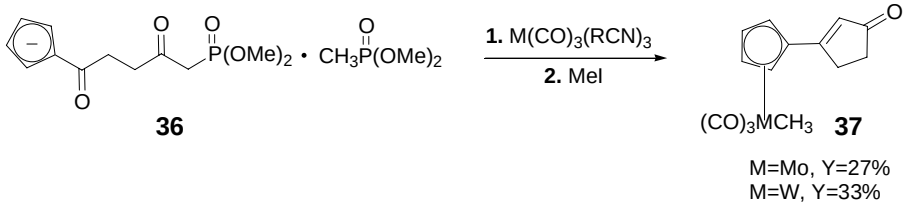
The same strategy has also been used for the synthesis of annulated cyclopentadiene **35**, starting from verbenone **34** (**Scheme 1.16**).[54]



34 **35**

Scheme 1.16 Annulated cyclopentadiene **35** can be synthesised starting from verbenone **34**.

Construction of a cyclopentadiene *via* this method has even been carried out onto substituted cyclopentadienide **36** and occurred with concomitant metalation of the free ligand (**Scheme 1.17**).[55]



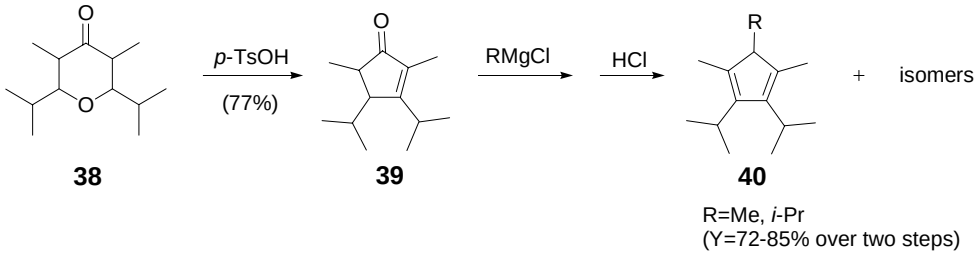
36 **37**

M=Mo, Y=27%
M=W, Y=33%

Scheme 1.17 Cyclopentenone synthesis *via* Horner–Emmons with concomitant complexation of the adjacent cyclopentadienide.

1.2.4 Other methods for the synthesis of cyclopentenones

Other methods for the synthesis of cyclopentenones as cyclopentadienes precursors have been used occasionally. Among these, the procedure developed by Jutzi for the synthesis of 1,2,3,4,5-pentamethylcyclopentadiene **21**[56] has been applied for the synthesis of peralkylated cyclopentadienes.[57] It allowed the synthesis of penta-substituted compounds such as **40** *via* dehydration of tetrahydro-γ-pyrone **38** followed by Grignard addition and subsequent loss of water (**Scheme 1.18**).

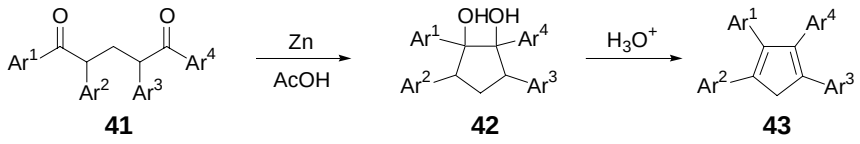


Scheme 1.18 Application of Jutzi's procedure for the synthesis of penta-alkylated cyclopentadienes **40**.

Other approaches include the intramolecular base-catalysed cyclisation of a 1,4-dicarbonyl compound,[58,59] the use of 3,3-dialkylglutarates for the synthesis of geminal-substituted cyclopentadienes[19] and the rearrangement of spirolactones into bicyclic enones.[60]

1.3 Synthesis of cyclopentadienes by reductive cyclisation

Dihydroxycyclopentanes such as **42** can be obtained by reductive cyclisation of 1,5-diketones and then undergo double dehydration to give cyclopentadienes. This approach was first reported by Wislicenus in 1898.[61] Pauson subsequently used this method for the synthesis of 1,2,3-triphenylcyclopentadiene[62] and Becker elaborated it for the synthesis of tetra-arylcyclopentadienes **43** (**Scheme 1.19**).[63]



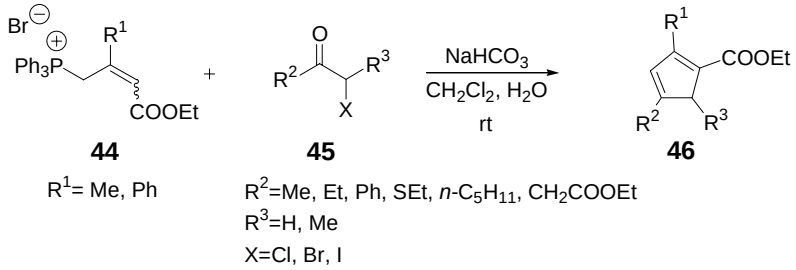
Scheme 1.19 Synthesis of tetra-arylcyclopentadienes **43** by dual dehydration of dihydroxycyclopentanes.

Symmetrical diketones **41** (Ar^1=Ar^2 and Ar^3=Ar^4) were synthesised by coupling of two molecules of a substituted α-phenylacetophenone with formaldehyde, while unsymmetrical substrates were obtained by Michael addition of substituted α-phenylacetophenones to α-arylacrylophenones. Substituents on the aryl groups included methyl, methoxy, chlorine and dimethylamino and the cyclopentadienes were obtained in poor to good yields.

This same methodology has been more recently used for the synthesis of di-*tert*-butylcyclopentadienes;[64] however it cannot be considered of wide applicability.

1.4 Synthesis of cyclopentadienes *via* [3+2] annulation of allylidene triphenylphosphoranes.

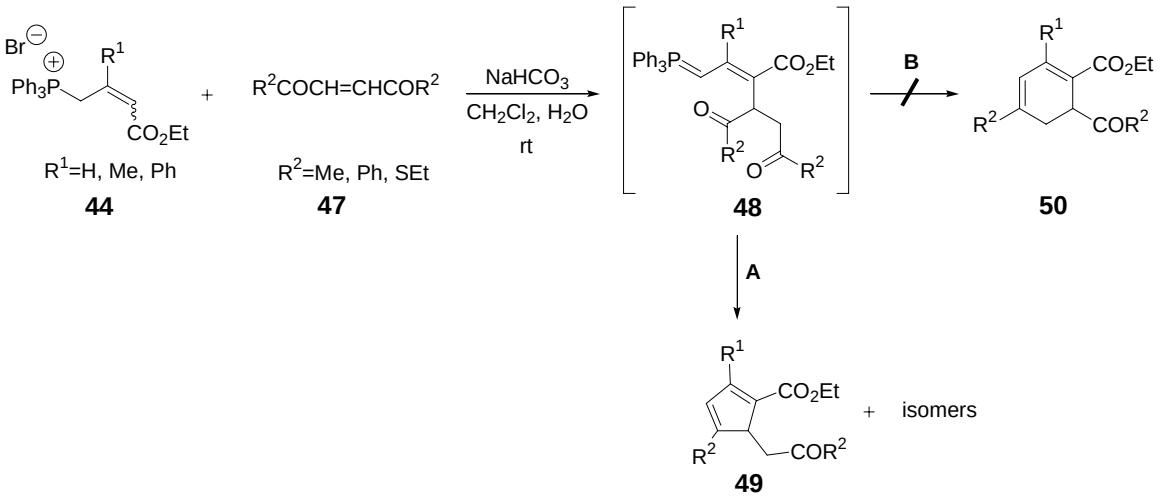
In 1990 Hatanaka reported that the reaction of stabilised allylidene phosphoranes with α-haloketones allows regioselective formation of substituted cyclopentadienes **46** *via* a [3+2] annulation (**Scheme 1.20**).[65]



Scheme 1.20 Synthesis of cyclopentadienes **46** by [3+2] annulation of allylidene triphenylphosphoranes with α-haloketones.

This approach takes advantage of the bifunctional nature of the phosphoranes and most likely involves nucleophilic substitution of the halide followed by intramolecular Wittig reaction. It allowed the synthesis of variously substituted cyclopentadienes in good to excellent yields, under mild reaction conditions, from readily available starting materials and in a one-pot fashion. Furthermore, when carried out under anhydrous conditions and starting from phosphonium salts **44** bearing an ethoxy substituent at the 2-position, this reaction also allowed the synthesis of ethoxycyclopentadienes (R^1=OEt).[66]

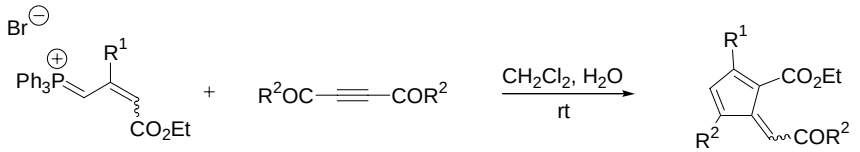
It was later discovered by the same authors that allylphosphonium bromides **44** also react with 1,2-diacylethylenes to give cyclopentadienes **49**, containing two ester functionalities (**Scheme 1.21**).[67,68]



Scheme 1.21 Synthesis of cyclopentadienes **49** by [3+2] annulation of allylidene triphenylphosphoranes with diacylethylenes.

Intermediates **48**, arising from Michael addition of the allylidenephosphorane with **47**, undergo intramolecular Wittig reaction exclusively *via* path **A** to provide isomeric mixtures of cyclopentadienes **49** in good to excellent yields. Remarkably, cyclohexadienes **50**, which could be formed by intramolecular reaction of the phosphorane group with the other carbonyl of intermediates **48**, were never detected. Once again the above annulation was found to provide the desired products **49** also when phosphonium salts **44** carried an ethoxy group in the 2-position.[69]

Finally, it needs to be mentioned that this procedure can also be used for the synthesis of fulvenes **52**, by reacting allylidene phosphoranes **44** with 1,2-diacylacetylenes **51** (**Scheme 1.22**).[68]

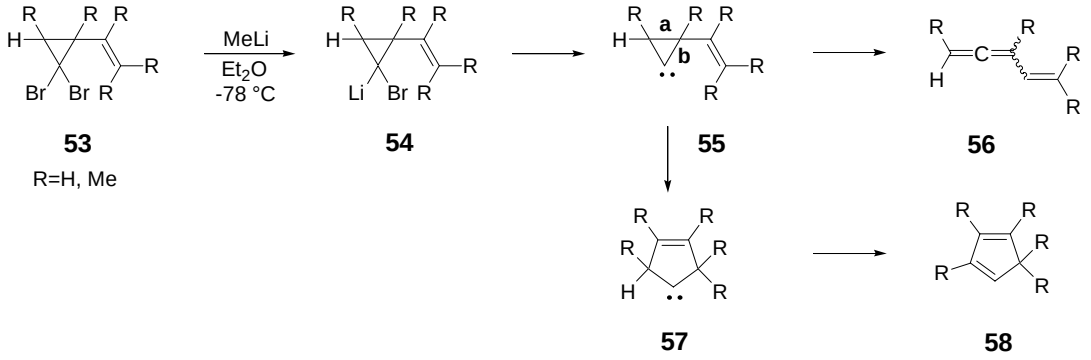


44 **51** **52**

Scheme 1.22 Synthesis of fulvenes by [3+2] annulation of allylidene triphenylphosphoranes with diacylacetylenes.

1.5 Synthesis of cyclopentadienes *via* Skatteboel rearrangement

In the early sixties Skatteboel published a novel application of the chemistry of *gem*-dihalocyclopropanes **53**.[70,71] It was found that when these three-membered carbocycles carry a vinyl group, they rearrange into cyclopentadienes upon treatment with methyl lithium at low temperature. Small amounts of allenes **56** were often formed as by-products (**Scheme 1.23**).

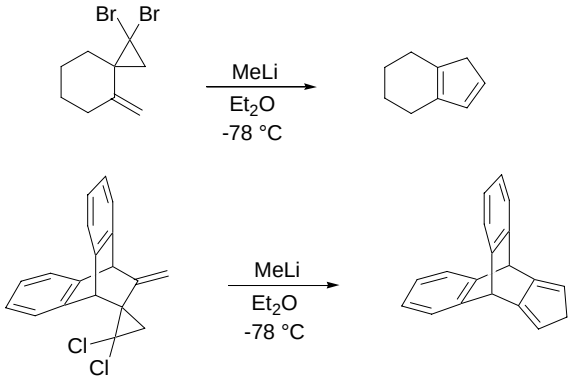


53 R=H, Me **54** **55** **56** **57** **58**

Scheme 1.23 The Skatteboel rearrangement.

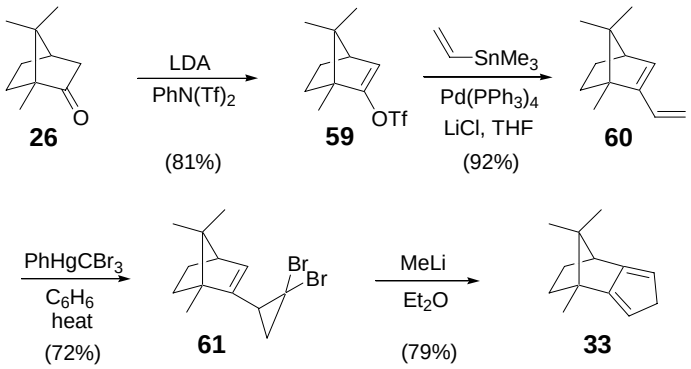
The mechanism of this reaction was interpreted on the basis of the formation of a carbene (cyclopropylidene) intermediate **55**, generated by elimination of LiBr from the lithium-bromo cyclopropane **54**. According to the mechanism proposed, cyclopropylidene **55** undergoes skeletal rearrangement to carbene **57**. A rapid [1,2]-hydrogen shift then allows the formation of cyclopentadiene **58**. Competitive vinylallene formation can be explained by cleavage of bond **a** rather than **b** in **55**.
Labelling studies[72,73] and calculations[74] on the transformation of **55** into **57** have been reported and confirm the validity of the proposed mechanism.[72]

In terms of synthetic applicability, the Skatteboel rearrangement was initially used for the preparation of various methylcyclopentadienes (see **Scheme 1.23**, R=Me)[71] and later found application in the synthesis of cyclofused compounds (**Scheme 1.24**).[75-78]



Scheme 1.24 Synthesis of cyclofused cyclopentadienes *via* Skatteboel rearrangement.

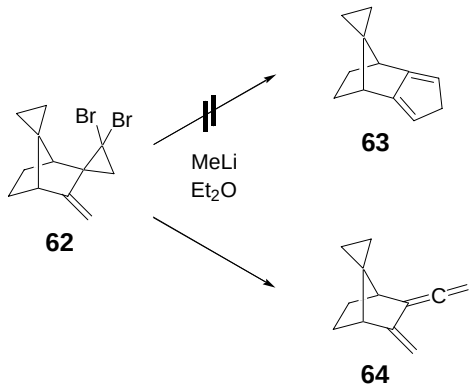
Notably, this reaction has been used for the synthesis of bornacyclopentadiene **33** (**Scheme 1.25**),[77,79,80] which, as shown previously (see section **1.2.3**, **Scheme 1.15**), can also be obtained by intramolecular Horner–Emmons reaction.



Scheme 1.25 Synthesis of bornacyclopentadiene **33** *via* Skatteboel rearrangement.

In this case, the enol triflate of (+)-camphor (**59**) was coupled with vinyltrimethylstannane to give diene **60**. Subsequently, dibromocyclopropene **61** was prepared by regiospecific addition of dibromocarbene, obtained upon decomposition of phenyl(tribromomethyl)mercury, to **60**. Crucial to the success of this strategy is the positioning of the dihalocyclopropane external to the norbornene ring. In fact this pathway was proposed after discovering that a high level of strain in the cyclopropane causes the cyclopropylidene intermediate to rearrange into the vinylallene only. For

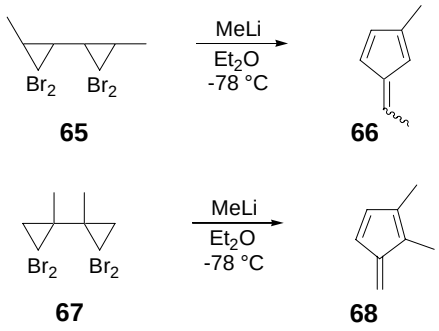
instance, treatment of **62** with ethereal methyl lithium yielded compound **64** and none of the desired cyclopentadiene **63** (**Scheme 1.26**).[81]



Scheme 1.26 Formation of vinylallene **63** from dibromocyclopropane **62**.

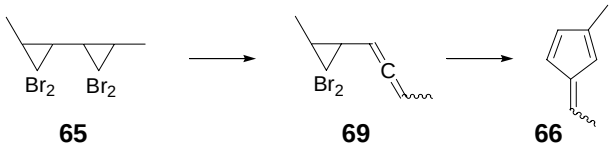
As suggested by molecular models,[79] the conversion of **62** into **64** appears to reflect the inability of the carbene empty p-orbital to interact with the neighbouring double bond.

Finally, it needs to be noted that Skatteboel himself also reported the synthesis of fulvenes by treatment of tetrabromobicyclopropanes **65** and **67** with ethereal methyl lithium (**Scheme 1.27**).[71]



Scheme 1.27 Synthesis of fulvenes by Skatteboel rearrangement of tetrabromocyclopropanes.

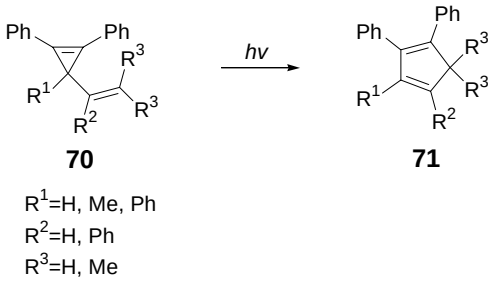
The mechanism depicted in **Scheme 1.23** can be utilised to explain the fulvene synthesis under the assumption that cyclopropylallene **69** is formed first. Subsequently, a second cyclopropylidene rearranges into the end product (**Scheme 1.28**).



Scheme 1.28 Mechanism of fulvene formation *via* Skatteboel rearrangement.

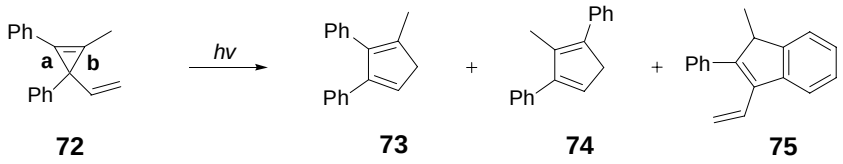
1.6 Synthesis of cyclopentadienes by rearrangement of 3-vinylcyclopropenes

In 1977 Padwa[82] and Zimmerman[83] reported in parallel the photochemical rearrangement of 3-vinylcyclopropenes into cyclopentadienes. 3-Vinyl substituted diphenylcyclopropenes **70**, prepared by treating the corresponding cyclopropenyl cations with Grignard reagents, were irradiated and resulted in the formation of cyclopentadienes **71** (**Scheme 1.29**).



Scheme 1.29 Synthesis of cyclopentadienes by rearrangement of vinylcyclopropenes.

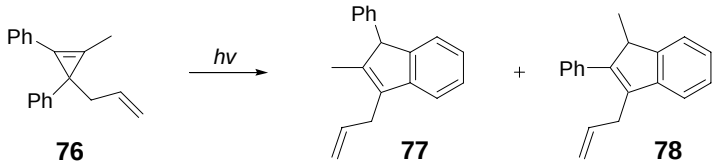
For certain substrates however, clean formation of one cyclopentadiene was not possible. For instance, photolysis of **72** produced a mixture of three compounds (**Scheme 1.30**).



Scheme 1.30 Irradiation of 1,3-diphenyl-2-methyl-3-vinylcyclopropene **72**.

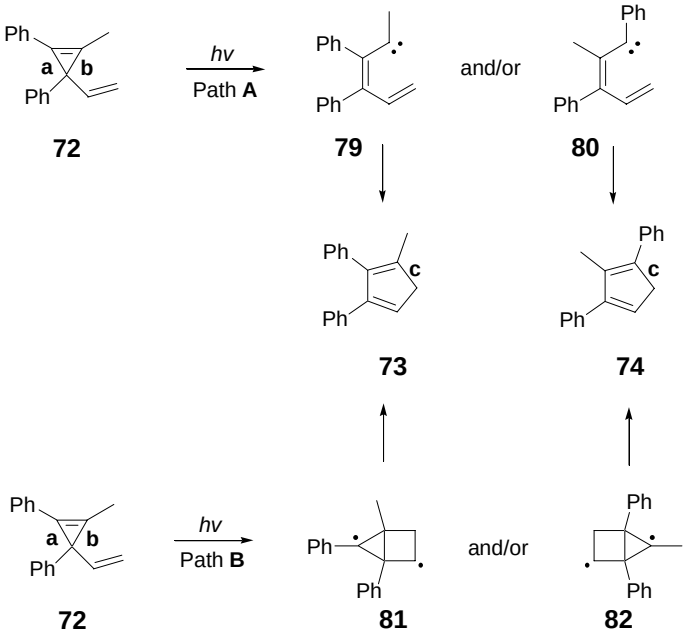
Cyclopentadienes **73** and **74** derive from cleavage of bonds **b** and **a** respectively, the major product being **73** and corresponding to the preferential cleavage of bond **b**.

Formation of indene **75** was rationalised on the basis of a previously reported reaction, as in absence of a vinyl substituent diarylcyclopropenes such as **76** were known to undergo rearrangement to indenes (**Scheme 1.31**).[84]



Scheme 1.31 Photolysis of 3-phenylcyclopropene **76**.

On the basis of these observations, two different mechanisms were proposed for the rearrangement of vinylcyclopropenes, as depicted in **Scheme 1.32** for **72**.



Scheme 1.32 The two plausible mechanisms for the synthesis of cyclopentadienes **73** and **74** by irradiation of cyclopropane **72**.

Path **A** involves the formation of two butadienyl carbenes, obtained *via* cleavage of bonds **a** and **b**. These carbenes were proposed to undergo ring closure to yield cyclopentadienes isomers **73** and **74**. The alternate mechanism **B**, begins with π-π bridging of the excited vinylcyclopropene **72** to give two possible housane biradicals, whose subsequent cleavage was suggested to yield the two isomeric products **73** and **74**.

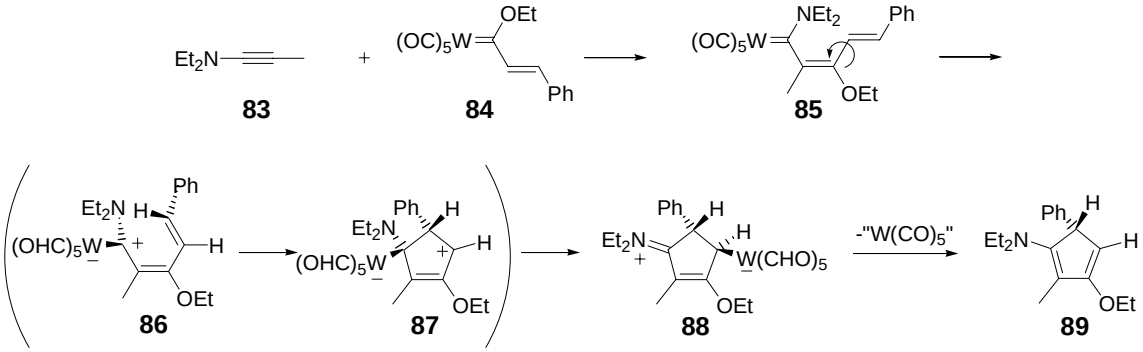
The discussion on which of the two plausible mechanisms was the correct one continued for some time[82,83,85-87] but no definite conclusion was ever reached. Indeed, in the latest paper published on the subject,[88] Zimmerman concludes by noting that the two proposed pathways differ mainly in the chronology of cleavage of bonds **a** and **b** and formation of bond **c**. Therefore, paths **A** and **B** can be considered two extremes and their overlapping is conceptually possible.

It needs to be noted that from a synthetic point of view, this mechanistically interesting transformation has not found significant application.

1.7 Metal-mediated synthesis of cyclopentadienes

1.7.1 Synthesis of cyclopentadienes *via* metallahexatrienes

In 1991 Aumann and co-workers described the formation of cyclopentadienes by π-cyclisation of amino-substituted pentacarbonyl-1-tungsta-1,3,5-hexatrienes.[89,90] Compound **85** was synthesised by chain extension of Fischer carbene **84**, *via* insertion of 1-diethylaminoprop-1-yne **83** between the W=C and C=C bonds. The newly formed metallahexatriene **85** then underwent ring closure at room temperature to give an unusually coordinated $W(CO)_5$ complex **88**. Subsequent extrusion of the metal unit allowed the synthesis of cyclopentadiene **89** (**Scheme 1.33**).[91]

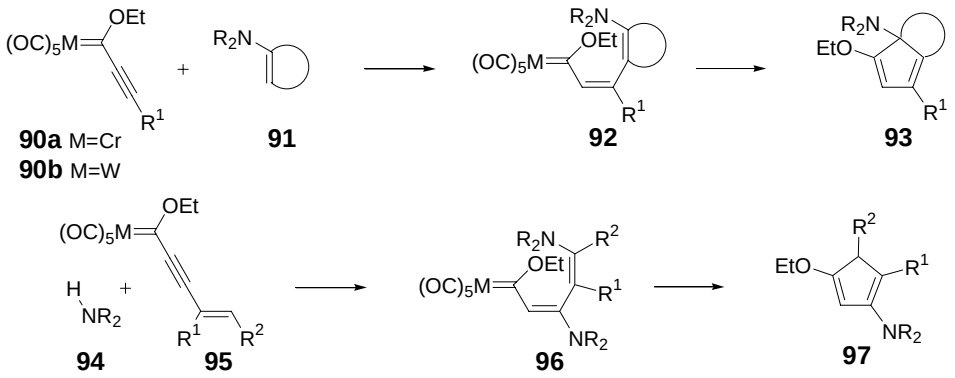


Scheme 1.33 Synthesis of aminocyclopentadiene **89** by cyclisation of 2-amino-1,3,5-metallahexatriene **85**.

Complex **88** was thought to derive from a conrotatory ring closure of zwitterionic intermediate **86**. This interesting mechanism was proposed through X-ray crystallography; the structure of **88** showed an unusual η^1-coordination mode of the

cyclopentadiene to the $W(CO)_5$ unit and allowed establishing the complex's dipolar nature by measurement of the C=N and W–C bond lengths.

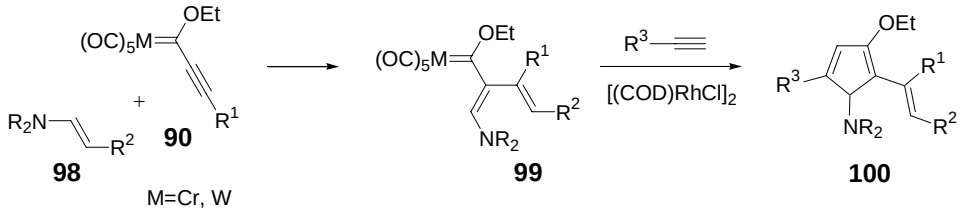
The same group also developed two other approaches for the synthesis of amino-1-metalla-1,3,5-hexatrienes, bearing the amino substituent in the 4- and 6-position respectively. Insertion of a cyclic enamine to (1-alkynyl)carbene complexes **90** of chromium and tungsten, allowed the synthesis of 6-aminometallahexatrienes **92**,[92-94] while reaction of secondary amines with metallaenynes **95** yielded 4-aminometallahexatrienes **96** (**Scheme 1.34**).[95]



Scheme 1.34 Approaches to aminocyclopentadienes **93** and **97** *via* amino-1-metalla-1,3,5-hexatrienes.

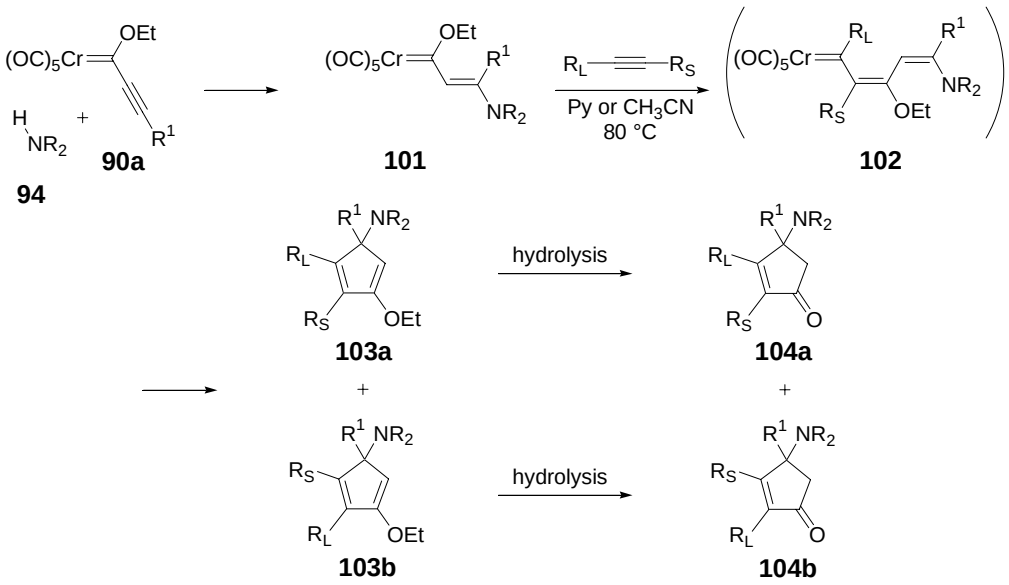
Carbenes **92** and **96** could then be smoothly transformed into the corresponding ethoxyaminocyclopentadienes **93** and **97** in good yields.

Amino metallahexatrienes were also shown to allow the synthesis of highly sensitive vinylcyclopentadienes. In this case the required precursors were cross-conjugated carbenes **99**, generated in excellent yields by addition of open-chain enamines of type **98** to **90**. In presence of catalytic $[(COD)RhCl]_2$ these metallahexatrienes reacted with terminal alkynes under mild conditions to give cyclopentadienes **100** in good yields (**Scheme 1.35**).[96]



Scheme 1.35 Synthesis of vinylcyclopentadienes **100** *via* cross-conjugated metallahexatrienes.

The use of Fischer carbenes for the synthesis of aminoethoxycyclopentadienes was also described in independent studies by de Meijere and co-workers (**Scheme 1.36**).[97-99]



Scheme 1.36 Synthesis of cyclopentadienes **103a** and **103b** from Fischer carbenes and amines.

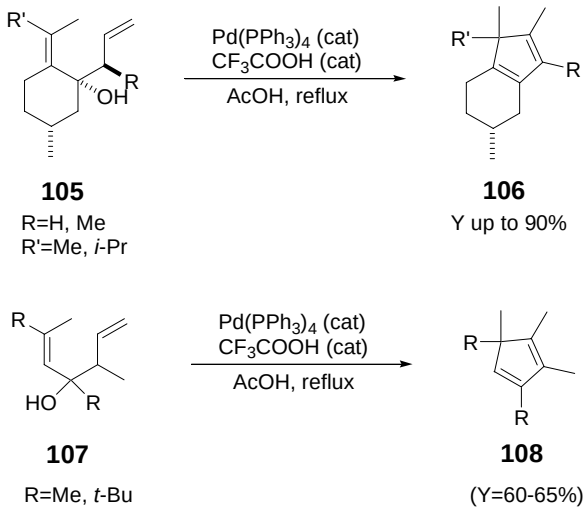
Chromium was used as the only metal and the formation of 6-amino-1,3,5-hexatrienes of type **101** as key intermediates was hypothesised, even though they were never isolated. Nevertheless, more than 80 examples of this reaction were reported and the products used as cyclopentenones precursors.[99] The regioselectivity of this transformation was found to depend on the steric bulk of the substituents on both alkyne and carbene (R^1, R_L, R_S). The group on the metalated species was found to have a particularly large effect.[99]

1.7.2 Synthesis of cyclopentadienes *via* Pd-mediated cyclisation

Two non general methods for the synthesis of cyclopentadienes by Pd-mediated cyclisation of unsaturated acyclic precursor have been reported. The first afforded highly substituted compounds bearing alkyl chains, whilst the other gave products carrying ester functionalities.

1.7.2.1 Pd-mediated cyclisation of 1,5-hexadien-3-ols

The study of the cyclisation of 1,5-hexadien-3-ols, readily synthesised by reaction of unsaturated ketones with allyl Grignard, was undertaken in the early nineties by Santelli and co-workers.[100,101] It was found that refluxing a solution of alcohols **105** and **107** in acetic acid in presence of Pd(0) and trifluoroacetic acid afforded penta-substituted cyclopentadienes in good yield (**Scheme 1.37**).

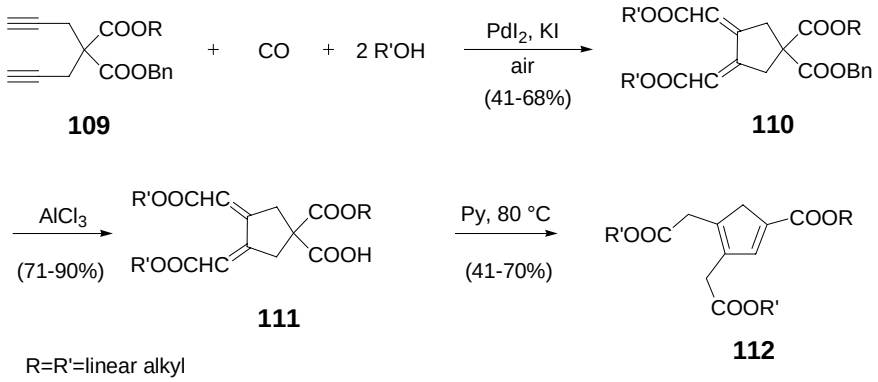


Scheme 1.37 Palladium-mediated synthesis of cyclopentadienes **106** and **108** from alcohols **105** and **107** respectively.

However, the authors reported only few examples of this reaction and proposed a mechanism that needed to be ascertained by further study.

1.7.2.2 Pd-catalysed oxidative carbonylation of diynes

A series of tri-substituted cyclopentadienes bearing ester groups was obtained by the Costa group *via* the three-steps procedure depicted in **Scheme 1.38**.[102,103]

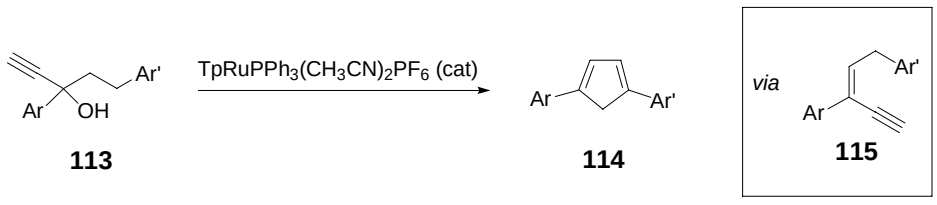


Scheme 1.38 Synthesis of tri-substituted cyclopentadienes **112** from diynes **109**.

Dipropynylmalonates **109** underwent oxidative carbonylation with concomitant cyclisation to give carbocycles **110** in moderate to good yields. Subsequent deprotection of the benzyl ester by aluminium trichloride was followed by pyridine-mediated decarboxylation and isomerisation of the double bonds to afford cyclopentadienes **112**. The anions of **112** were employed as ligands and coordinated to various metals. Among the products, half sandwich rhodium complexes have found application as catalysts for the cyclotrimerisation of alkynes and nitriles to pyridines and for the hydroformylation of styrene.[103]

1.7.3 Ru-catalysed synthesis of cyclopentadienes from 1-ethynyl-3-ols

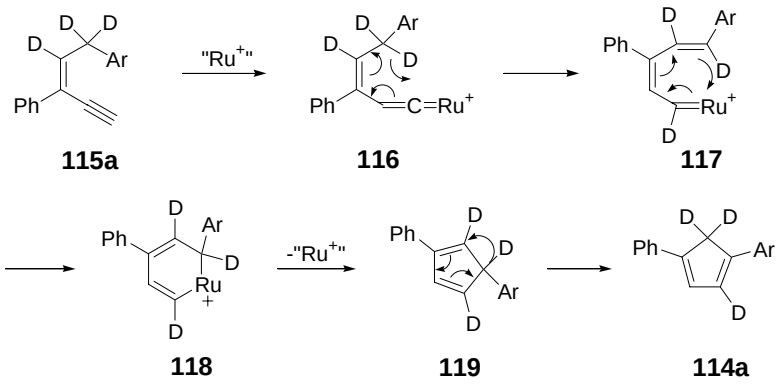
1,4-Diarylcyclopentadienes **114** can be obtained in high yields by cyclisation of propargylic alcohols **113** in presence of the ruthenium catalyst $TpRuPPh_3(CH_3CN)_2PF_6$ (**Scheme 1.39**).[104]



Scheme 1.39 Ruthenium-catalysed cyclisation of propargylic alcohols **113**.

This transformation was shown to proceed *via* formation of *cis*-3-en-1,5-ynes **115**. Indeed, these compounds, obtained upon dehydration of **113**, were also transformed into **114** by using the ruthenium-based catalytic system employed for the one-pot synthesis of **114**.

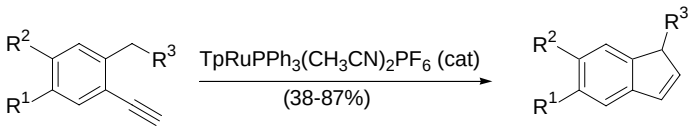
On the basis of deuterium-labelling experiments performed on **115a**, a reaction mechanism based on the [1,5]-sigmatropic shift of hydrogen on a ruthenium–vinylidene intermediate was proposed (**Scheme 1.40**).



Scheme 1.40 Proposed mechanism for the synthesis of cyclopentadienes **114** by [1,5]-sigmatropic hydrogen shift of ruthenium–vinylidene intermediates **116**.

According to the suggested mechanism, the ruthenium–vinylidene intermediate **116** is formed first. This subsequently undergoes [1,5]-sigmatropic hydrogen shift to give intermediate **117** which, upon electrocyclisation, provides ruthenacycle **118**. Reductive elimination of the metal gives cyclopentadiene **119**, which is then transformed into its most stable isomer **114a** by [1,5]-sigmatropic shift of hydrogen.

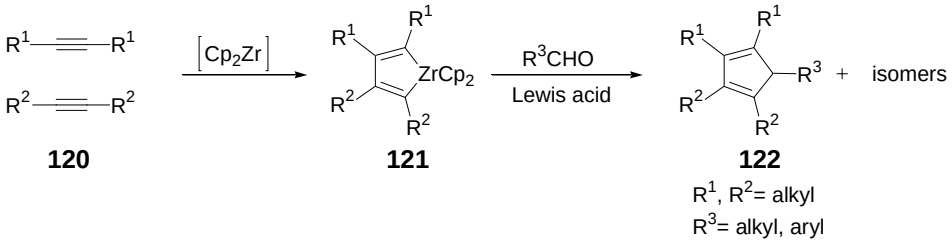
Unfortunately the scope of this reaction is restricted to substrates bearing no functionality on the aryl substituents. However, this transformation has been very recently applied to the synthesis of indenes (**Scheme 1.41**).[105]



Scheme 1.41 Ruthenium-catalysed synthesis of indenes.

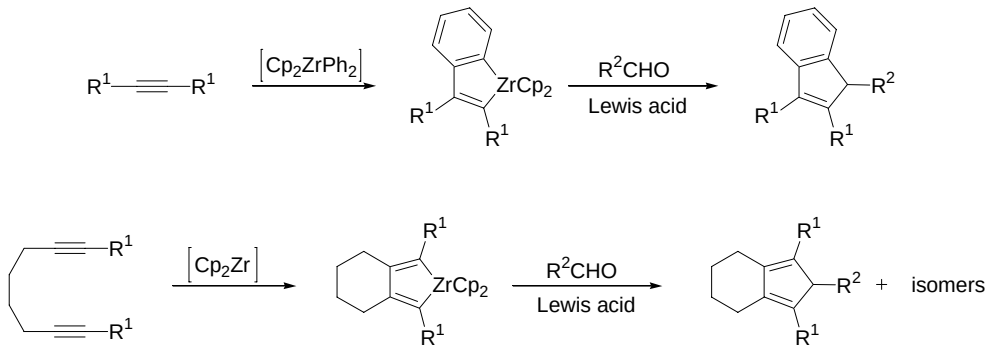
1.7.4 Synthesis of cyclopentadienes *via* zirconacycles

In 2000 Xi[106,107] published the first zirconocene-mediated cyclisation of two alkyne molecules with an aldehyde to give substituted cyclopentadienes by deoxygenation of the C=O bond. Zirconacyclopentadienes **121**, obtained by reductive coupling of a low-valent zirconocene complex with two molecules of the same or different alkynes, readily reacted with two equivalents of aldehyde in presence of Lewis acids ($AlCl_3$ and BF_3 were shown to work particularly well)[108] to give carbocycles **122** (**Scheme 1.42**).



Scheme 1.42 Formation of multiply-substituted cyclopentadienes **122** *via* Lewis-acid mediated reaction of zirconacyclopentadienes **121** with aldehydes.

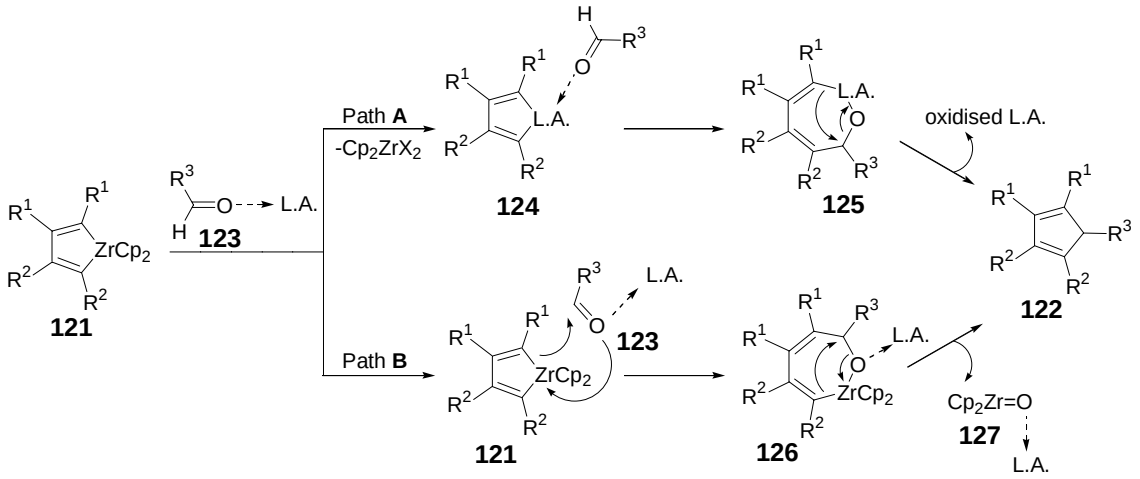
This transformation is associated with several attractive features: it can be carried out in one-pot, gives multiply substituted cyclopentadienes in good yields by reaction of aliphatic, aromatic and heteroaromatic aldehydes and can be used to obtain indenes and tetrahydroindene derivatives (**Scheme 1.43**).[108]



Scheme 1.43 Synthesis of indenes and tetrahydroindenes *via* zirconocenes.

Indenes were formed by participation of a benzyne provided by $[Cp_2ZrPh_2]$ whist reaction of diynes allowed the synthesis of tetrahydroindenes.

Mechanistically, two possible pathways were proposed, as depicted in **Scheme 1.44** for **121**.[108,109]

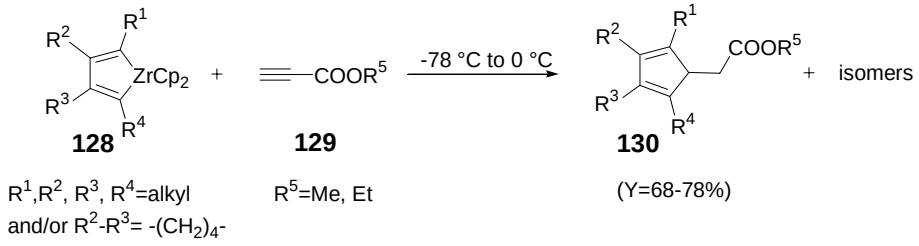


Scheme 1.44 Proposed reaction mechanisms for the Lewis acid-mediated transformation of zirconacyclopentadienes into cyclopentadienes.

Path **A** involves transmetalation of the zirconacyclopentadiene followed by insertion of the aldehyde into the carbon-metal bond of the newly formed metallacycle **124**. Alternatively (path **B**) the aldehyde, activated by the Lewis acid, was proposed to react with **121** directly, affording oxazirconacycle **126**. Both **125** and **126** can then rearrange to give compound **122**. As the synthesis of cyclopentadienes from **121** was initially discovered to take place in presence of $AlCl_3$, the formation of aluminacyclopentadienes **124** (L.A.=AlCl) as key intermediates was originally proposed.[106,110] Indeed, in absence of the Lewis acid the reaction did not take place. Subsequently, the observation that other Lewis acids that cannot undergo transmetalation also promote the reaction, led to the elaboration of the alternate mechanisms (Path **B**).[108,109] However, formation of an aluminacyclopentadiene was considered likely in the case of $AlCl_3$.

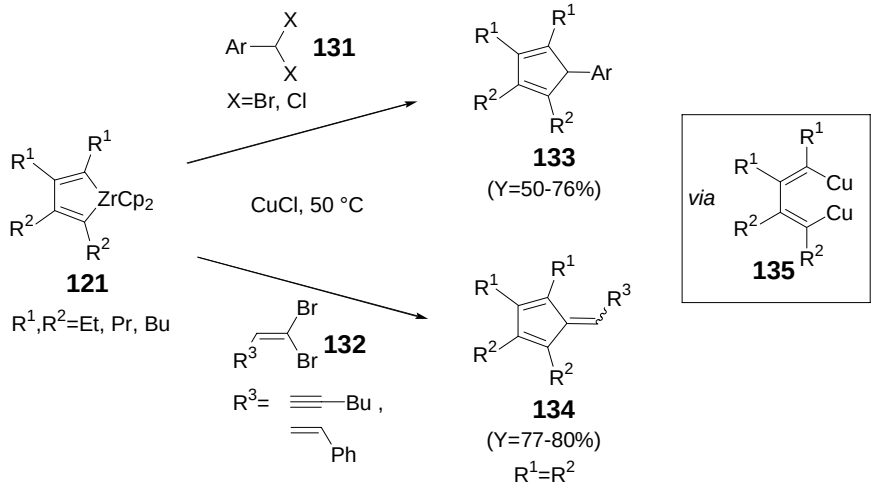
Other reactions of five-membered zirconacyclic compounds with a one-carbon unit building block are known to afford cyclopentadienes.

Takahashi's group reported the 1,1-cycloaddition of alkyl-substituted zirconacyclopentadienes **128** to propynoates to afford ester-containing cyclopentadienes **130** (**Scheme 1.45**) and tetrahydroindenes.[111]



Scheme 1.45 Reaction of zirconacyclopentadienes **128** with propynoates to form cyclopentadienes **130**.

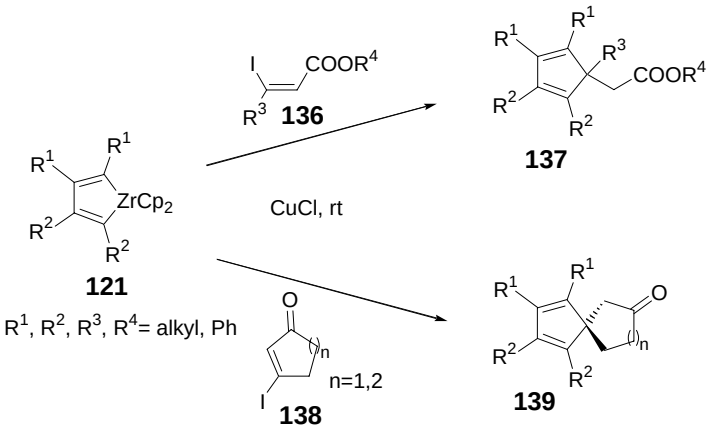
Cyclopentadienes **133** and fulvenes **134** can be obtained by reaction of **121** with 1,1-dihalocompounds in presence of stoichiometric copper(I)chloride, *via* a mechanism believed to involve transmetalation of the zirconacyclopentadiene to form bis(cuprate) **135** (**Scheme 1.46**).[112]



Scheme 1.46 Reaction of zirconacyclopentadienes **121** with 1,1-dihalo compounds.

Unfortunately this reaction works only for aromatic dihalides **131** and conjugated dihaloalkenes such as **132**, thus limiting the scope of the transformation.

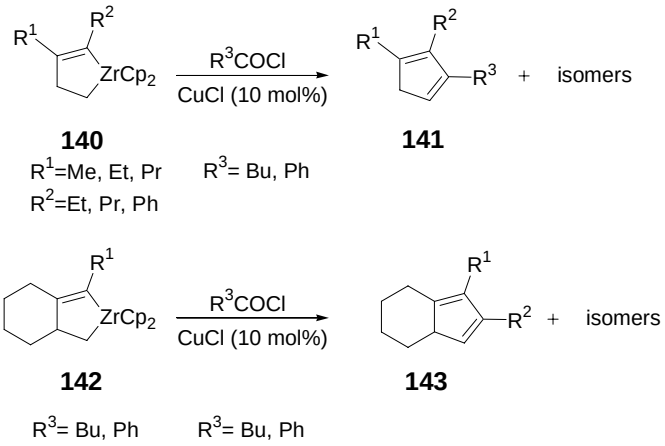
Formation of intermediate **135** has also been hypothesised by the same leading author for the reaction of zirconacycles **121** with 3-iodopropenoates[113] and 3-iodocycloenones[114] (**Scheme 1.47**).



Scheme 1.47 Synthesis of spirocyclic and penta-substituted cyclopentadienes from zirconacycles.

Penta-substituted and spirocyclic cyclopentadienes were obtained in good to excellent yields, by a combination of Michael addition and cross coupling reaction to achieve the formation of two new C-C bonds.

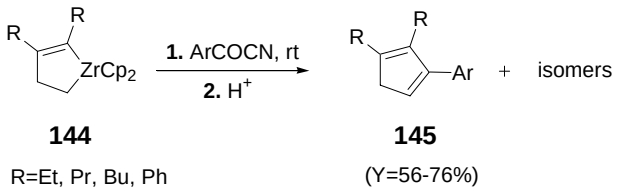
Finally, cyclopentadiene derivatives can be obtained by reaction of zirconacyclopentenes with acid chlorides[115] and aroyl cyanides.[116] In 1996 Takahashi reported the copper-catalysed preparation of 1,2,3-trisubstituted cyclopentadienes and tetrahydroindenes from zirconacycles **140** and **142** in good yields.[115]



Scheme 1.48 Synthesis of cyclopentadienes and tetrahydroindenes from zirconacyclopentenes **140** and **142**.

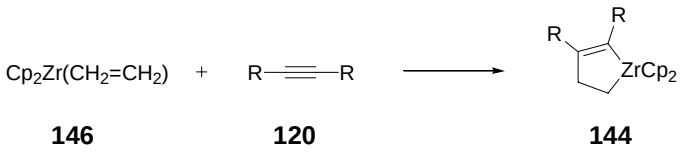
Nearly ten years later, the high yielding formation of 1,2,3-trisubstituted cyclopentadienes by reaction of zirconacycles **144** and aroyl cyanides was disclosed. No copper catalyst was in this case required, probably because acyl cyanides are more

powerful acylating agents than acid chlorides, since the cyano group enhances the reactivity of the adjacent carbonyl (**Scheme 1.49**).



Scheme 1.49 Reaction of zirconacyclopentenes with acid cyanides to form cyclopentadienes.

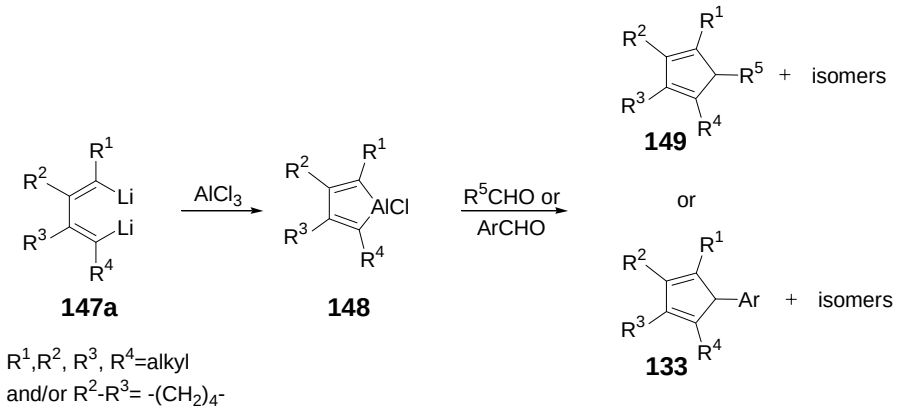
Since zirconacyclopentenes are easily obtained by reaction of a C-C triple bond with a low-valent zirconocene complex (**Scheme 1.50**), this procedure represents a preparative route to cyclopentadienes from unactivated alkynes.



Scheme 1.50 Synthesis of zirconacyclopentenes.

1.7.5 Synthesis of cyclopentadienes *via* aluminacyclopentadienes

When Xi first encountered the formation of cyclopentadienes from zirconacyclopentadienes in presence of $AlCl_3$ (see section **1.7.1**), the formation of aluminacyclopentadienes was hypothesised (Path **A**, **Scheme 1.44**).[106,110] Therefore the reaction of aluminacyclopentadienes **148**, obtained by treatment of 1,4-dilithio-1,3-dienes with $AlCl_3$, with aldehydes was investigated (**Scheme 1.51**).[117]

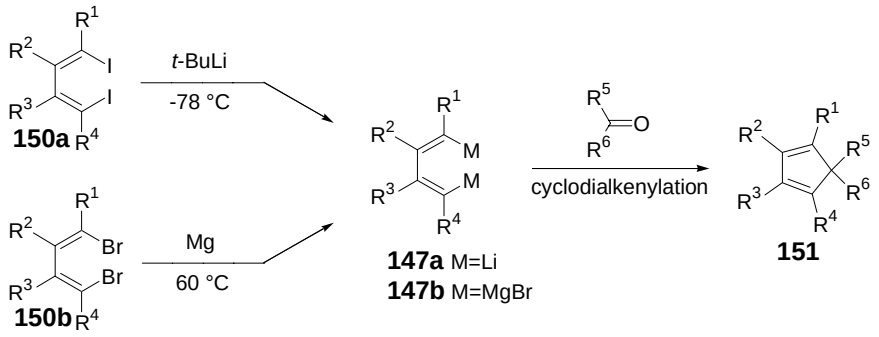


Scheme 1.51 Synthesis of cyclopentadienes *via* aluminacyclopentadienes.

Indeed, both aliphatic and aromatic aldehydes react with metallacycles **148** to provide penta-substituted cyclopentadienes in modest to very good isolated yields; however limited substituent variety could be achieved (most often $R^1=R^2=R^3=R^4$). Tetrahydroindenes can also be synthesised *via* this method, by reaction of a cyclic aluminacyclopentadiene.

1.7.6 Synthesis of cyclopentadienes from 1,4-dilithio- and 1,4-bis (magnesiobromo)-1,3-dienes

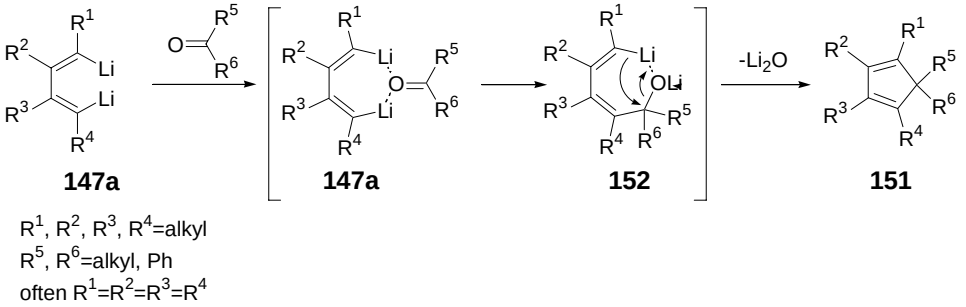
Following his interest in the metal-mediated synthesis of cyclopentadienes, Xi has recently disclosed a new reaction of carbonyl compounds with organolithium and Grignard reagents. Normally the combination of aldehydes and ketones with these reagents results in the formation of alcohols. Deoxygenation of the C=O moiety was instead achieved in presence of 1,4-dilithio- and 1,4-bis(magnesiobromo)-1,3-dienes **147a** and **147b**.[110,118-120] Both butadienes **147a** and **147b** were generated *in situ* from the corresponding diiodo- and dibromo-compounds and then reacted with aldehydes and ketones (**Scheme 1.52**).



Scheme 1.52 Formation of cyclopentadienes by reaction of 1,4-dilithiobutadienes and 1,4-bis(bromomagnesio)butadienes with ketones and aldehydes.

Metallabutadienes **147a** and **147b** differ slightly in their reactivity. When the carbonyl is a ketone (both aromatic and aliphatic) compounds **147a** react smoothly, whilst dienes **147b** fail to give any reaction. Instead the Grignard reagents **147b** afford penta-substituted cyclopentadienes in high yields in presence of aldehydes. On the other hand, dilithiobutadienes **147a** react less cleanly with aldehydes, giving lower yields of the desired products. [121]

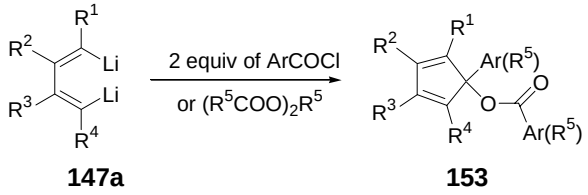
From a mechanistic point of view, it was proposed that chelation of the carbonyl oxygen with the alkenylmetal moieties occurred first, as depicted in **Scheme 1.53** for the reaction of **147a**. The first nucleophilic attack then allowed the formation of **152**, which subsequently underwent intramolecular reaction with the remaining alkenyllithium moiety to give cyclopentadienes and lithium oxide.



Scheme 1.53 Proposed mechanism for the reaction of dilithiobutadienes **147a** with aldehydes.

The initial chelation of the carbonyl was thought to be essential to the success of the reaction. Its inter/intramolecular nature, combined with the formation of stable cyclopentadienes and lithium oxide, were assumed to be the driving forces.

1,4-Dilithio-1,3-butadienyl reagents were also reported to react with CO,[122] CO_2[123] and isothiocyanates[124] to give cyclopentenones, cyclopentadienones and cyclopentadienyl imines respectively.[110,120] More recently, their reaction with aromatic acid chlorides and anhydrides was studied and was found capable of affording cyclopentadiene derivatives **153** in high isolated yields (**Scheme 1.54**).[125]

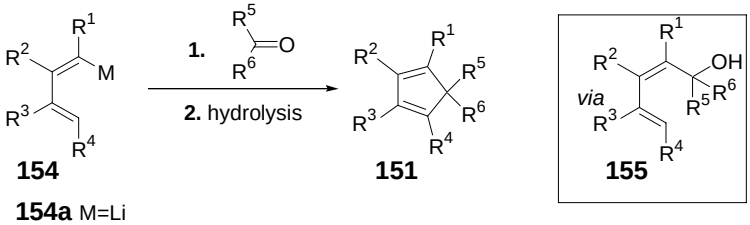


147a **153**

Scheme 1.54 Formation of cyclopentadienes **153** by reaction of dilithioalkenyl compounds **147a** with acid chlorides and anhydrides.

1.7.7 Synthesis of cyclopentadienes from 1-lithio- and 1-bromomagnesio-1,3-butadienes

Related to the transformations discussed in the above section is the reaction of lithio- and bromomagnesiobutadienes **154** with carbonyl compounds. These monometalated dienes, readily available from the corresponding halides, were found to react with aldehydes and ketones to give cyclopentadienes when a strong acidic work-up was used (**Scheme 1.55**).[126,127]



154 **151** **155**

154a M=Li
154b M=MgBr

Scheme 1.55 Reaction of 1-lithiobutadienes **154a** and 1-bromomagnesiobutadienes **154b** with aldehydes and ketones.

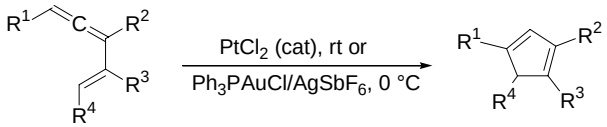
This reaction was rationalised by acid-promoted cyclisation of the intermediate dienols **155**. Indeed, allylic alcohols **155** were obtained selectively from **154** when a mild work-up procedure was used and then converted into the corresponding cyclopentadienes by treatment with strong acids.

This approach allows the synthesis of highly substituted cyclopentadienes in good yields. However, as it was in the case of the reaction of 1,4-dilithio- and 1,4-bis(bromomagnesio)-butadienes **147a** and **147b**, the 1-, 2-, 3- and 4-positions are most often occupied by the same substituents.

1.7.8 Synthesis of cyclopentadienes by cyclisation of 1,2,4-trienes

Very recently the Iwasawa's and Toste's groups reported in independent studies the transition metal-mediated cyclisation of 1,2,4-trienes **156** to give cyclopentadienes **157**.[128,129]

Iwasawa employed platinum(II)chloride as the catalyst[128] while Toste proposed the use of a phosphinegold(I) complex (**Scheme 1.56**).[129]

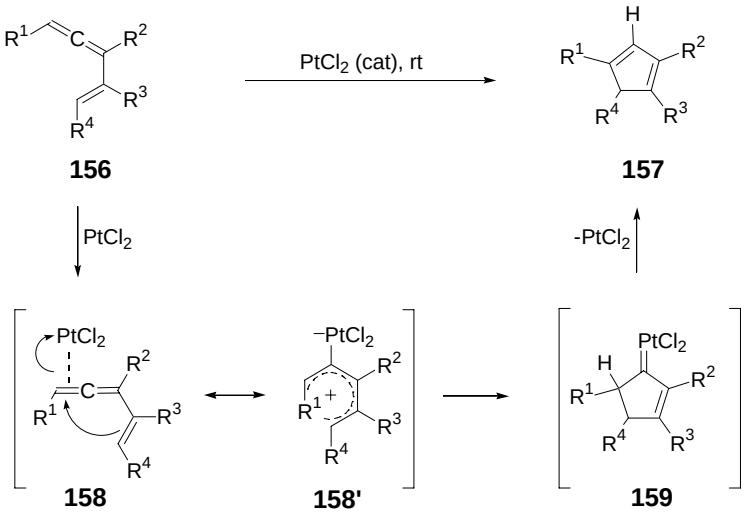


156 **157**

Scheme 1.56 Metal-mediated cyclisation of 1,2,4-trienes **156** to give cyclopentadienes **157**.

The two methods share many similarities and allow the synthesis of highly substituted cyclopentadienes in good to excellent yields. Furthermore, Toste's examples showed that many functionalities can be tolerated. These include alkyl, phenyl, protected amines and oxygenated substituents.[129]

In both cases the same reaction pathway, shown in **Scheme 1.57** for the Pt(II)-mediated cyclisation reaction, was proposed.



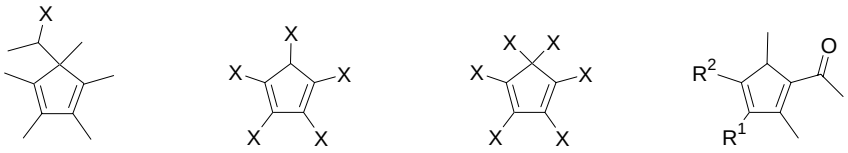
Scheme 1.57 Proposed mechanism for the Pt(II)-mediated transformation of trienes **156** into cyclopentadienes **157**.

Coordination of the allene by the metal was suggested to take place first. Carbenoid **159** would then be formed either by intramolecular nucleophilic attack of the olefinic double bond to the metal-allene π-complex in **158** or by Nazarov-type electrocyclisation (see section **1.2.2**) of tautomer **158'**. [1,2]-Sigmatropic hydrogen shift would then allow the synthesis of the cyclopentadiene products with concomitant regeneration of the catalyst.

1.8 Other methods for the synthesis of cyclopentadienes

Other non general methods for the synthesis of cyclopentadienes have been reported. This author considers them of scarce interest both from a mechanistic point of view and because of their limited applicability.

These include the reaction of Dewar benzene with inorganic acids to give penta-methylated cyclopentadienes **160**,[130] the synthesis of highly electron-deficient carbocycles **161**[131,132] and **162**[133,134] and the synthesis of highly alkylated acetylcyclopentadienes **163** by reaction of allylic chlorides with acetylacetone (**Scheme 1.58**).[135]



160 X=Cl, Br **161** X=COOMe, CN, CF_3 **162** X=Cl, CF_3 **163**

Scheme 1.58 Highly substituted cyclopentadienes **160**–**163** synthesised by substrate-specific methods.

1.9 Conclusions

A number of methodologies are currently available for the synthesis of cyclopentadienes. They generally pertain to the preparation of highly substituted products or of compounds carrying stabilizing groups such as aryl substituents. This is because the preparation of cyclopentadienes with a low degree of substitution is complicated by their tendency to undergo endocyclic double bond migration and Diels–Alder cycloadditions with themselves. Nevertheless, a high degree of substitution is often desirable as it can be associated with interesting compound properties.

It is fascinating that various metal-mediated approaches to cyclopentadienes have been developed in the past ten years. These are relevant both because they allow the synthesis of structurally interesting compounds and from a mechanistic point of view.

However, it needs to be noted that the methodologies described in the course of this review rarely represent general approaches to cyclopentadienes as they allow the synthesis of carbocycles with a given substitution pattern. The only general method seems to be the preparation and modification of cyclopentenones described in section **1.2**.

In conclusion, the development of novel and versatile methodologies for the synthesis of this class of products is still needed, especially considering the paramount importance of cyclopentadienes in both organic and inorganic synthesis.

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CHAPTER 2

Results and Discussion

2.1 Introduction

This chapter discusses the results of research carried out during the course of this PhD and is divided into two parts. Firstly, the development of methodology for the synthesis of pyridines *via* a novel variant of the Ireland–Claisen rearrangement - the decarboxylative Claisen rearrangement - is described. Secondly, the application of the decarboxylative Claisen rearrangement chemistry for the synthesis of cyclopentadienes and cyclopentadienyl anions is detailed.

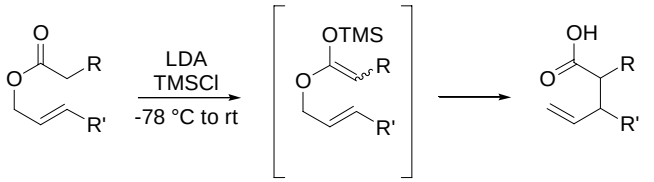
2.2 The decarboxylative Claisen rearrangement-based methodology for the de novo synthesis of pyridines

Due to their fundamental role as building blocks of biologically active compounds[1] and as ligands in coordination chemistry,[2,3] pyridines are key in both organic and inorganic synthesis.

A variety of methodologies is available for their *de novo* preparation.[1,4] Although difficult to classify, the main general methods either rely on cycloaddition reactions or on the cyclisation of a linear precursor. The methodology developed during this PhD belongs to the second category and utilises a novel variant of the Ireland–Claisen rearrangement, discovered by the Craig group in 2000,[5-10] to build the acyclic array. Cyclisation and aromatisation are then performed by use of an ozonolysis–ammonolysis sequence also introduced by the Craig group.[11]

2.2.1 The decarboxylative Claisen rearrangement reaction

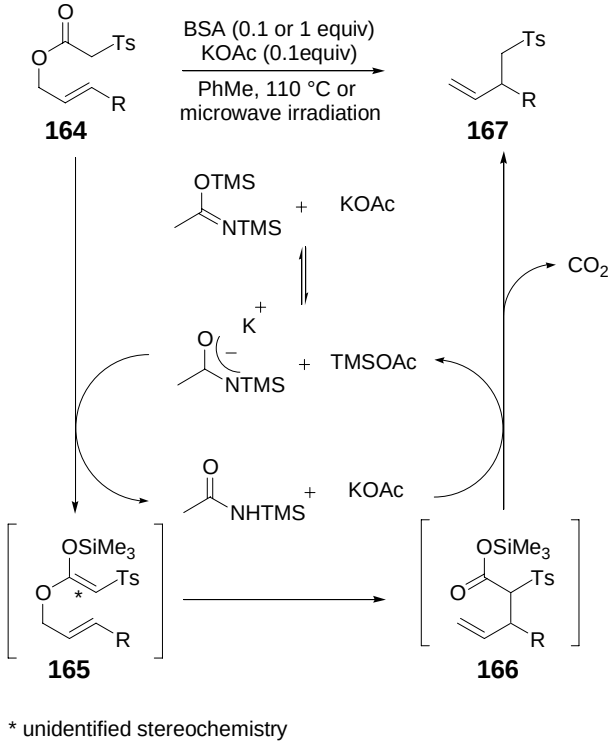
The Ireland–Claisen rearrangement,[12] a variant of the Claisen rearrangement[13] reported by Ireland in 1972, consists of the [3,3]-sigmatropic reaction of a silyl ketene acetal, typically prepared *in situ* from the corresponding allyl ester, into a γ,δ-unsaturated carboxylic acid on hydrolysis of the initial silyl ester product (**Scheme 2.1**).



Scheme 2.1 The Ireland–Claisen rearrangement.

The ready availability of the of the allylic ester substrates, the mildness of the rearrangement conditions and the high levels of stereoselectivity achievable in this transformation have resulted in the flourishing of its applications over the past three decades.[14-16]

A catalytic, decarboxylative variant of the Ireland–Claisen rearrangement was recently disclosed by the Craig group and involves the *in situ* formation of α-tosyl silyl ketene acetals **165** from allylic tosylacetates **164**, their rearrangement and a desilylation–decarboxylation sequence to give homoallylic sulfones **167** (**Scheme 2.2**).

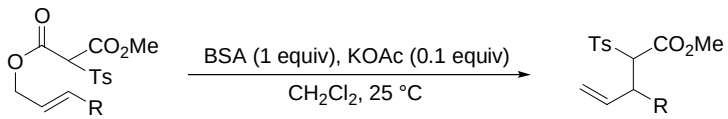


Scheme 2.2 Synthesis of homoallylic sulfones by decarboxylative Claisen rearrangement reaction.

The decarboxylative Claisen rearrangement (dCr) reaction involves the use of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the silyl source in presence of a sub-

stoichiometric amount of KOAc. In the proposed mechanism (**Scheme 2.2**),[5,8] the acetate anion functions as the silyl transfer agent. TMSOAc is formed through reversible combination of BSA with KOAc, which also provides the conjugate base of *N*-trimethylsilylacetamide. The latter deprotonates substrate **164** and the resulting enolate is silylated by TMSOAc to give the silyl ketene acetal **165** which undergoes [3,3]-sigmatropic rearrangement. The resulting silyl ester **166** then reacts with KOAc to give the carboxylate anion that evolves into the conjugate base of homoallylic sulfone **167**, with concomitant regeneration of TMSOAc. The conjugate base of product **167** can either abstract a proton directly from starting material **164** or from *N*-trimethylsilylacetamide, in both cases restarting the catalytic cycle.

Following the discovery of this transformation, various studies on its characteristics and possible applications have been carried out.[6,7,9,10,17] For instance, in order to prove that the presence of an electron-withdrawing functionality at the ester α-position would facilitate the rearrangement, the dCr reaction was performed on tosylmalonic mono(allylic) esters **168** (**Scheme 2.3**).[6]

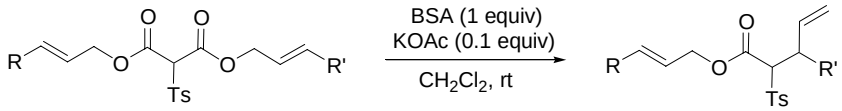


168 **169**

Scheme 2.3 Decarboxylative Claisen rearrangement of tosylmalonic mono(allylic) esters.

Indeed, the rearrangement took place at room temperature during reaction times ranging from 4 to 16 h whilst allylic acetates **164** required overnight reflux in toluene.

The behaviour of diallylic 2-tosylmalonates **170** was also studied.[10] Because of the presence of two allylic portions, these substrates can in principle undergo dCr chemistry twice. However, while the first rearrangement is facile and takes place in good yields under mild reaction conditions, the second reaction cycle is much more difficult, since sulfonylesters **171** lack the activating electron-withdrawing carboalkoxy substituent (**Scheme 2.4**).



170 **171**

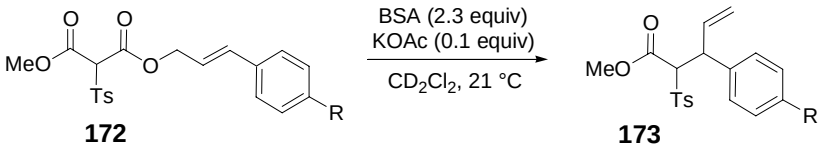
Scheme 2.4 Single decarboxylative Claisen rearrangement of diallylic tosylmalonates **170**.

The study of the mono-rearrangement of non symmetric tosylmalonic diallylic esters **170** (R≠R') also showed that rearrangement was faster with more electron-rich allylic double bonds (**Table 2.1**).[10]

Table 2.1 Reactivity of the allylic portions of tosylmalonates **170**

R (less reactive)	R' (more reactive)
H	Ph
Ph	*p*-methoxyphenyl
Ph	$CH{=}CHCH_3$
$CH{=}CHCH_3$	*p*-methoxyphenyl
Et	Ph
H	Ph

Quantitative kinetic studies of these effects have also been carried out on a series of methyl (*E*)-3-(phenyl)allyl tosylmalonates **172** (**Scheme 2.5**) and provided further support for the idea that electronic effects strongly influence the rate of the dCr reaction.[17]

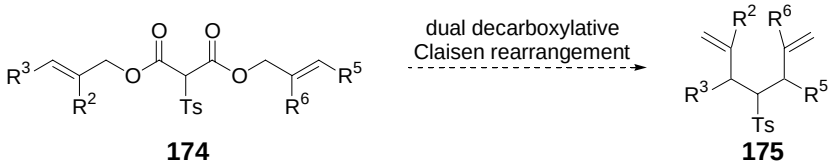


172 **173**

R=OMe, Me, H, F, Cl, Br, CN

Scheme 2.5 Single dCr of methyl (*E*)-3-(aryl)allyl tosylmalonates **172**.

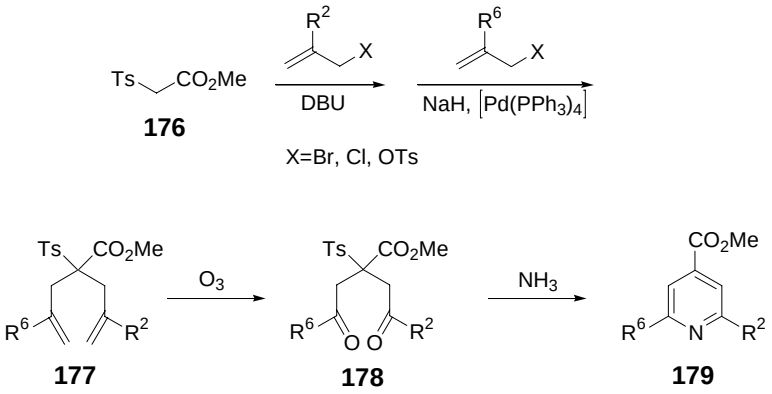
The development of reliable reaction conditions for the transformation of variously substituted diallylic tosylmalonates **174** into dienes **175** *via* a dual dCr approach is the subject of this thesis (**Scheme 2.6**).



Scheme 2.6 Proposed transformation of tosylmalonates **174** into dienes *via* dual dCr.

2.2.2 Sulfone-mediated pyridine synthesis and aim of the work

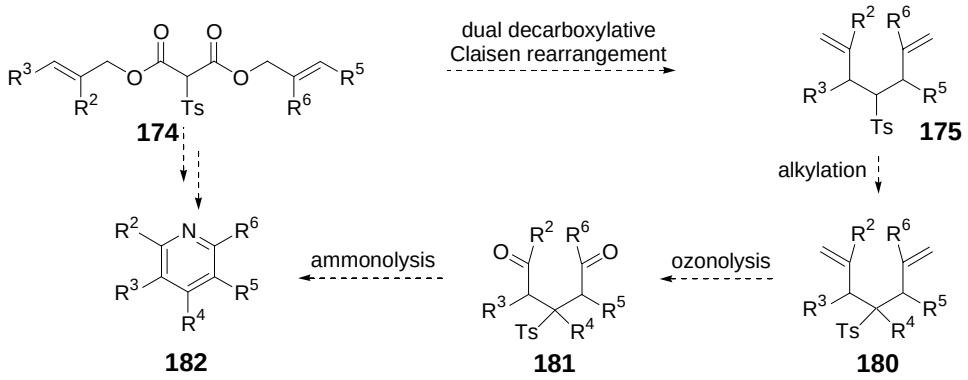
In recent years, a sulfone-mediated approach to pyridine synthesis has been developed by the Craig group.[11] Palladium-catalysed bis(allylation) of 2-tosyl methyl acetate allowed the synthesis of a series of 3-tosyl-3-carboxymethyl-1,5-dienes **177** which could be ozonolysed to the corresponding 3-tosyl-1,5-dicarbonyl compounds and then transformed into 2,4,6-trisubstituted pyridines in good to excellent yields (**Scheme 2.7**).



Scheme 2.7 Sulfone-mediated synthesis of pyridines.

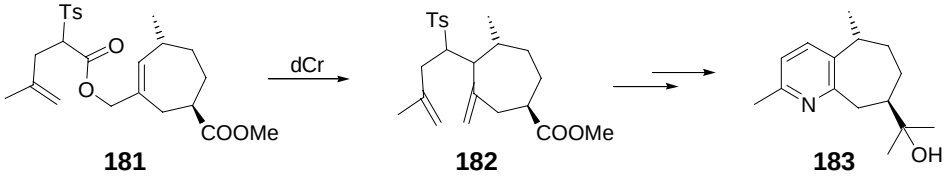
This strategy uses the same concept encountered in the Kröhnke pyridine synthesis,[18] where a pyridinium, quinolinium or picolinium salt incorporated into the key 1,5-dicarbonyl intermediate acts as a leaving group during the aromatisation process.

The use of the dual dCr on 2-tosylmalonates **174** was expected to achieve the synthesis of more substituted dienes, which would be amenable to alkylation α- to the tosyl group, thus extending this chemistry to a general synthesis of pyridines possessing almost any substitution pattern (**Scheme 2.8**).



Scheme 2.8 Synthetic pathway leading to pyridines *via* dual dCr of diallylic tosylmalonates.

The only precedent for the use of the dCr chemistry for the synthesis of a pyridine-containing compound is represented by the route to the natural product cananodine **183** (**Scheme 2.9**).[19]



Scheme 2.9 Synthesis of cananodine **183** *via* single dCr.

4-Tosyl-1,6-heptadiene **182** was obtained by single rearrangement of methallylated tosylacetate **181**. Ozonolysis–ammonolysis and manipulation of the methyl ester subsequently afforded anellated pyridine **183**.

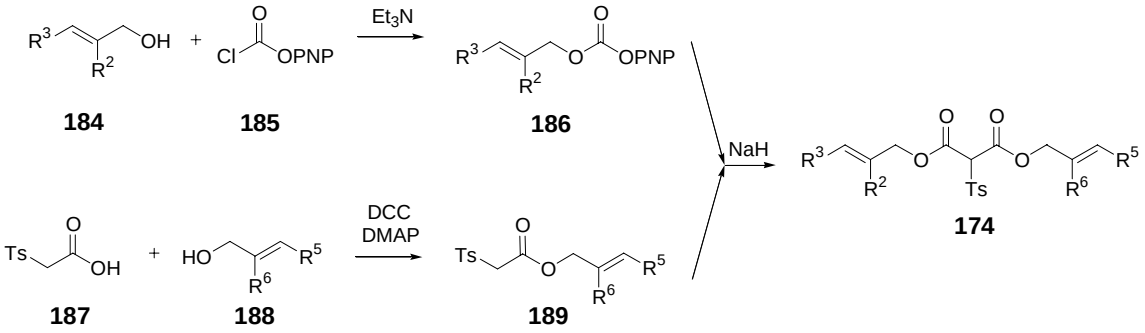
2.2.3 Development of the methodology

2.2.3.1 Synthesis of unsymmetrical diallylic 2-tosylmalonates

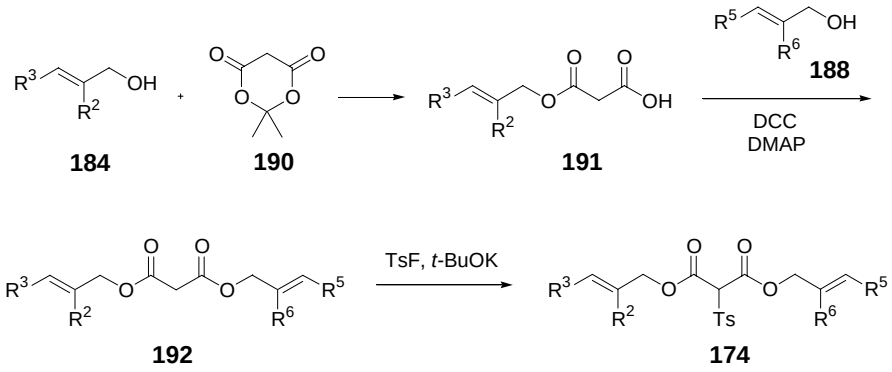
Before the dual dCr reaction and its application to pyridine synthesis could be investigated, a series of variously substituted 2-tosylmalonates was required.

Previous work had shown that two routes were available for the synthesis of compounds **174**. The first method (**Scheme 2.10**) consists of coupling a chosen tosylacetic acid allylic ester **189** with the appropriate *p*-nitrophenyl allylic carbonate[10] **186** while the second (**Scheme 2.11**) was discovered and applied for the synthesis of methyl allylic

malonates **192**[6] and involves the direct tosylation of the corresponding malonic acid diester.



Scheme 2.10 C-Carboxylation of allylic tosylacetates to give diallylic tosylmalonates.



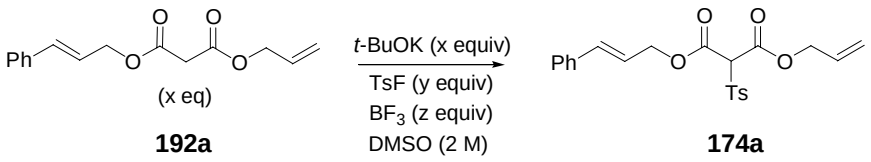
Scheme 2.11 Synthesis of tosylmalonates *via* direct tosylation of the corresponding malonate.

Although successful, both strategies were unsatisfactory. The first method presented the advantage of being convergent, however it typically generated the products in variable and moderate overall yields. In addition, difficulties in separation of the final tosylmalonate product from *p*-nitrophenol were encountered. The direct tosylation of malonate diesters, on the other hand, was high-yielding and utilised starting materials that could be synthesised in a straightforward manner, but required a large excess of malonate. Indeed, four equivalents of malonate anion in a very concentrated solution of DMSO (~ 2 M) were combined with one equivalent of tosyl fluoride. Hence, even though the unconsumed malonates were usually recoverable in high yields, optimisation of the procedure was considered necessary.

In order to perform the optimisation, the model tosylmalonate **174a** bearing R^2,R^5,R^6=H and R^3=Ph was used. **174a** was chosen because its synthesis *via* C-carboxylation of a tosylacetate-derived enolate had previously been carried out in the group and provided the desired compound in 56% yield, by far the highest ever obtained for this approach.[10] The necessary allyl malonate **191a** was prepared in quantitative yield by heating Meldrum's acid **190** under reflux with an equimolecular amount of allyl alcohol in the absence of solvent. Subsequent condensation with cinnamyl alcohol in presence of DCC and DMAP provided the substrate for tosylation in 76% yield.[20]

Tosylation of **192a** was attempted under a series of reaction conditions which varied in the equivalents of substrate, base and tosylating agent (**Table 2.2**).

Table 2.2 Optimisation of the tosylation reaction for allyl cinnamyl malonate **192a**.



Entry	x	y	z	Yield[a]	Unreacted 192a recovered	Unreacted TsF recovered
1	3.9	1	-	63%	81%	-
2	2	1	-	71%	80%	-
3	1.5	1	-	38%	67%	-
4	1	1.2	-	36%	78%	-
5	1	2.1	-	27%	46%	59%
6	1	1	1	-	73%	61%

[a] isolated yield.

The benchmark reaction using literature conditions (entry 1)[6] afforded the desired product in 63% yield and unreacted malonate in 81% yield. The diminution of the equivalents of malonate versus tosylating agent to a 2:1 ratio resulted in a slight improvement (entry 2). However, low yields were obtained when the reaction was carried out on less than two equivalents of substrate (entries 3 and 4). Increasing the amount of tosyl fluoride also brought no improvement (entry 4 and 5). On one occasion (entry 6) equimolecular amounts of malonate and tosylating agent were combined in the

presence of boron trifluoride to test the activating effect of the Lewis acid on tosyl fluoride.[21] Unfortunately, tosylation did not occur and only the starting materials could be isolated.

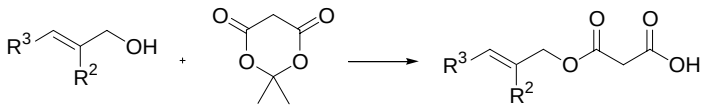
It was reasoned that the necessity of having at least a two-fold excess of malonate anion with respect to the tosylating agent might be due to the proton α- to the carbonyl groups in the product being more acidic than the ones in the 2-position of the starting material. Hence, once one equivalent of the malonate anion has been converted into the product, the second equivalent acts as a base for the tosylated species and is no longer available as a nucleophile.

Overall, optimisation of the original procedure was only possible by lowering the excess of starting material needed to obtain good conversion. Nevertheless, the tosylation was the method of choice for the synthesis of compounds **174** since purification was straightforward and yields were reliable and higher than those obtained using the *C*-carboxylation approach.[10]

A series of variously substituted tosylmalonates **174** was then synthesised in order to test the dependence of the dual dCr rearrangement on the degree of substitution of the allylic double bonds, and ultimately to obtain variously substituted pyridines.

Reaction of Meldrum's acid **190** with commercially available allyl alcohol, methallyl alcohol and (*E*)-2-methyl-3-phenyl-2-propen-1-ol gave the corresponding malonic acid monoesters in good to excellent yields (see **Table 2.3**).

Table 2.3 Synthesis of malonic acid monoesters



184 **190** **191**

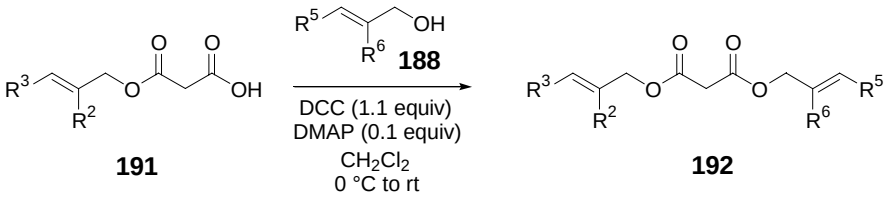
Entry	R^2	R^3	Reaction Conditions	Yield of 191[a]
1	H	H	Neat, reflux overnight	Quantitative (**191a**)
2	Me	H	Neat, reflux overnight	77% (**191b**)
3	Me	Ph	In toluene, heating at 90 °C overnight	94% (**191c**)

[a] isolated yield.

Malonic esters **192** were synthesised by refluxing the reaction mixture neat when the allylic alcohols were low boiling solvents (entries 1 and 2) and in toluene at 90 °C otherwise, and were used crude in the following step.

Standard DCC/DMAP-mediated condensation reactions[20] of **191** with the second allylic alcohols afforded the desired malonates **192** (see **Table 2.4**).

Table 2.4 Synthesis of diallylic malonates



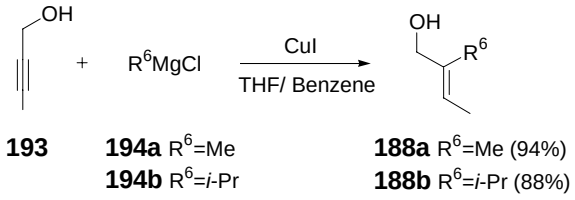
191 **192**

Entry	191	R^2	R^3	R^5	R^6	Malonate	Yield[a]
1	**191a**	H	Ph	H	H	**192a**	76%
2	**191a**	Me	Ph	H	H	**192b**	75%
3	**191a**	*i*-Pr	Me	H	H	**192c**	69%
4	**191b**	Me	H	Ph	Me	**192d**	39%
5	**191c**	Me	Ph	H	Me	**192d**	73%
6	**191c**	Me	Ph	Me	Me	**192e**	91%
7	**191c**	Me	Ph	Me	*i*-Pr	**192f**	74%

[a] isolated yield.

As exemplified by the synthesis of methallyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **192d** (entry 4 and 5) the best option is, in general, to introduce the more nucleophilic alcohol earlier in the synthetic pathway. Indeed, as testified by the reaction conditions (i.e. reflux of the mixture against stirring at room temperature), the reaction of Meldrum's acid with an alcohol is characterised by a higher activation energy compared to the DCC-mediated esterification.

In two instances the required allylic alcohols were not commercially available and were synthesised *via* Cu(I)-catalysed addition of the appropriate Grignard reagent **194** to 2-butyn-1-ol (**Scheme 2.12**).[22]



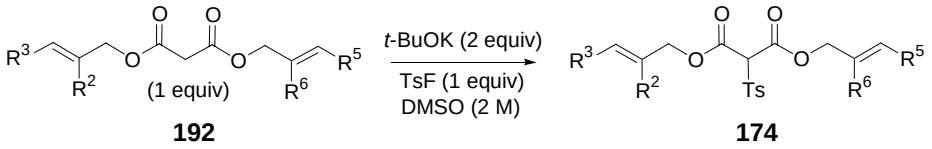
193 **194a** R^6=Me **188a** R^6=Me (94%)
194b R^6=*i*-Pr **188b** R^6=*i*-Pr (88%)

Scheme 2.12 Cu(I)-mediated synthesis of (*E*)-2,3-substituted allyl alcohols from 2-butyn-1-ol.

(*E*)-2-Methyl-2-buten-1-ol **188a** and (*E*)-2-isopropyl-2-buten-1-ol **188b** were incorporated into the malonates in the second step, regardless of their nucleophilicity compared to the other allylic portion.

Tosylation of the mixed diallylic malonates **192** (see **Scheme 2.11**) was carried out as previously described and the results obtained for multi-gram scale reactions are reported in **Table 2.5**.

Table 2.5 Synthesis of tosylmalonates **174a–f**



192 **174**

Entry	R^2	R^3	R^5	R^6	192	Yield[a]	Unreacted 192 recovered	Scale (g of 192)
1	H	Ph	H	H	**192a**	76%	83%	10.9 g
2	Me	Ph	H	H	**192b**	72%	87%	4.5 g
3	*i*-Pr	Me	H	H	**192c**	73%	82%	3.9 g
4	Me	Ph	H	Me	**192d**	71%	91%	3.6 g
5	Me	Ph	Me	Me	**192e**	71%	81%	9.3 g
6	Me	Ph	Me	*i*-Pr	**192f**	71%	87%	3.9 g

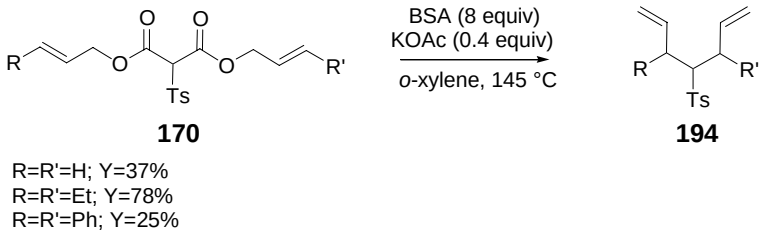
[a] isolated yield.

The yields reported in **Table 2.5** are typical for this transformation and do not depend on the scale of the reaction. However, it needs to be noted that the deprotonation of malonates **192** is an exothermic process, and therefore slow addition of the base to the solution of the starting material **192** in DMSO and careful control of the temperature so that it did not exceed 25 °C were crucial to avoid lowering of the yield. Unidentified decomposition products were observed when no precaution was taken to prevent an increase in the temperature of the reaction mixture.

2.2.3.2 Dual decarboxylative Claisen rearrangement of 2-tosylmalonates

2.2.3.2.1 Previous work and optimisation of the reaction conditions for a mono-substituted tosylmalonate

With a series of variously substituted diallylic tosylmalonates **174** in hand, the study of their transformation into 1,6-dienes **175** *via* dual dCr chemistry was undertaken. As previously mentioned (see section **2.2.1**), the first rearrangement of bis(allyl) 2-tosylmalonates **174** was found to take place at ambient temperature, while further dCr reaction of the mono-rearranged products was much less facile.[10] When this project was started no reliable method was available for the transformation of tosylmalonates into dienes. Under thermal reaction conditions tosylmalonates **170**, substituted at the outer end of the allylic double bonds only, had occasionally been converted into dienes. However, low to moderate yields were obtained for symmetric substrates only (**Scheme 2.13**).[23]



170

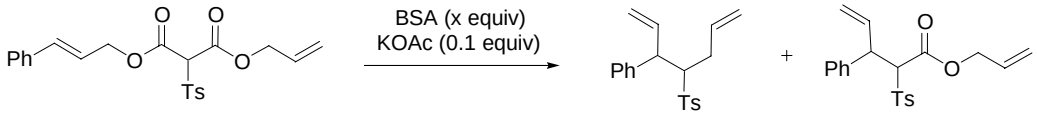
R=R'=H; Y=37%
R=R'=Et; Y=78%
R=R'=Ph; Y=25%

194

Scheme 2.13 Dual dCr of some symmetric 2-tosylmalonates.

Substrate **174a** (**Table 2.6**) was used to investigate and optimise the one-pot, dual rearrangement of unsymmetric substrates **174** since reactivity data were available for its transformation into the mono-rearranged product **195a** (see section 2.2.1, **Table 2.1**).[10] Indeed, **174a** contains two allylic portions characterised by very different reactivity towards dCr. In fact, while the cinnamyl side bears the cation-stabilising phenyl group, the absence of any substituent on the allyl arm renders the rearrangement more difficult. The most significant attempts towards the synthesis of 3-phenyl-4-tosyl-1,6-heptadiene **175a** are reported in **Table 2.6**.

Table 2.6 Dual decarboxylative Claisen rearrangement of **174a**



174a **175a** **195a**

Entry	Solvent	BSA (x equiv)	Reaction Conditions	Yield of 175a[a]	Side Products
1	PhMe	6	Reflux, 53 h	-	**195a**[b]
2	CH_2Cl_2	1	microwave, 15 min at 110 °C	-	**195a** (47%)[c]
3	*o*-DCB	1	microwave, 5 min at 180 °C	66%	-
4	$ClCH_2CH_2Cl$	1	microwave, 15 min at 170 °C	50%	-
5	-	3[d]	microwave, 4 min at 170 °C	86%	-

[a] isolated yield.
[b] **195a** and unidentified decomposition products were isolated together with un reacted starting material.
[c] 42% of unreacted starting material was also isolated.
[d] the reaction was carried out neat.

Initially a mixture of **174a**, BSA (1.0 equiv) and KOAc (0.1 equiv) was heated under reflux in toluene for several hours (entry 1). Progressive decomposition of BSA and starting material was observed, while only trace amounts of **175a** were detected, with predominant formation of the mono-rearrangement product **195a**. Addition of more BSA (5.0 equiv) and longer reaction times failed to improve the transformation. Conventional heating not being suited for this transformation, our attention turned to the use of microwave irradiation, which was known to reduce significantly the reaction time for the mono-rearrangement of allylic tosylacetates **168**.[5,8]

When the reaction mixture was subjected to microwave irradiation in dichloromethane (entry 2) only the product of mono-rearrangement (47%) and unreacted starting material **174a** (42%) could be isolated. At this point it was reasoned that one of the key parameters for the success of a microwave-assisted reaction is the choice of the solvent

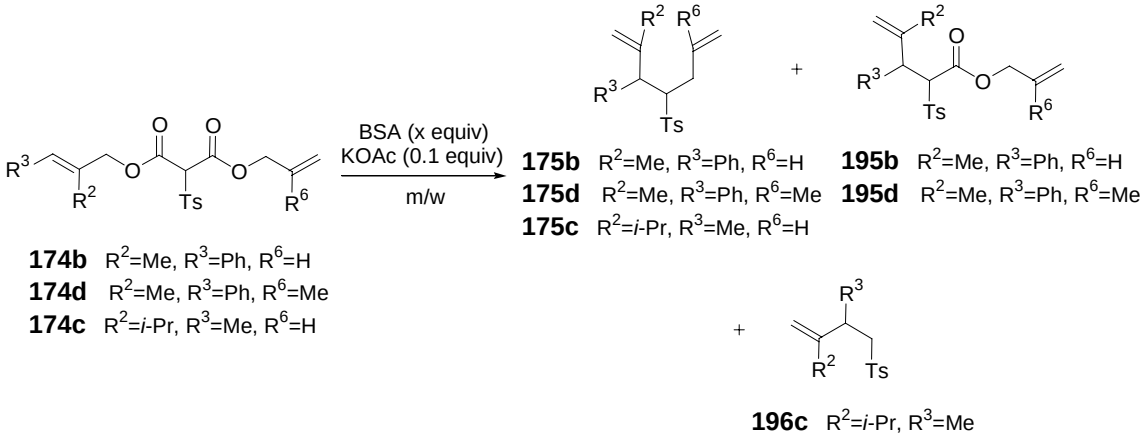
because the better its ability to absorb microwave irradiation the more efficient the heating of the reaction mixture.[24] Dichloromethane is a poor microwave absorber, hence the use of alternative solvents was considered. It was brought to our attention that Ley and co-workers performed a Claisen rearrangement under microwave irradiation in *ortho*-dichlorobenzene at 180 °C.[25] The same solvent and temperature were therefore used and finally allowed the formation of **175a** as the major product (entry 3). The yield was further improved when the reaction was carried out in the absence of solvent and the desired diene could be isolated in 86% yield as a 1:1 mixture of diastereoisomers (entry 5). Notably, this transformation could be performed on a several-gram scale without affecting the yield.

Compound **175a** was obtained as a 1:1 mixture of two diastereoisomers. The non-selectivity of the dual dCr reaction had been previously observed[6,10] and it is of a general nature. Indeed, all dienes **175** have been synthesised as a mixture of all the possible diastereoisomers, as will described in the following sections.

2.2.3.2.2 The dual dCr reaction of di- and tri-substituted tosylmalonates

Further experimentation showed the use of microwave acceleration to be essential for the realisation of efficient dual dCr reactions. In particular, when studying the effect of substituent introduction to the 2-position of the allylic double bonds of malonates **174**, microwave irradiation was necessary to achieve high conversion (**Table 2.7**).

Table 2.7 Dual decarboxylative Claisen rearrangement of **174b–d**



174b R^2=Me, R^3=Ph, R^6=H
174d R^2=Me, R^3=Ph, R^6=Me
174c R^2=*i*-Pr, R^3=Me, R^6=H

175b R^2=Me, R^3=Ph, R^6=H
175d R^2=Me, R^3=Ph, R^6=Me
175c R^2=*i*-Pr, R^3=Me, R^6=H

195b R^2=Me, R^3=Ph, R^6=H
195d R^2=Me, R^3=Ph, R^6=Me

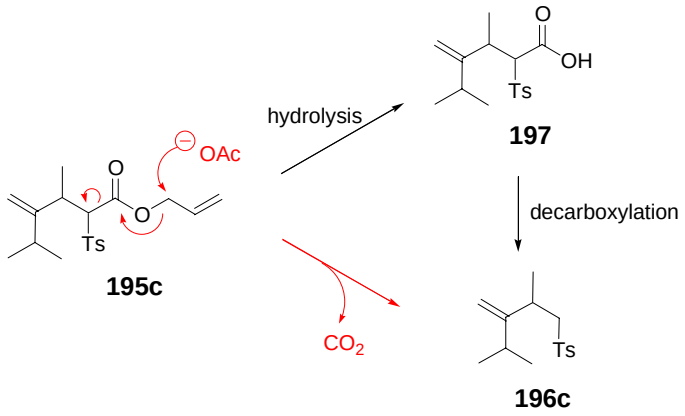
196c R^2=*i*-Pr, R^3=Me

Entry	174	Solvent	BSA (x equiv)	Reaction Conditions	Yield of 175[a]	Side Products
1	**174b**	*o*-DCB	1	30 min at 180 °C	55% (**175b**)	**195b** (10%)
2	**174b**	-	3[b]	15 min at 170 °C	55% (**175b**)	**195b** (16%)
3	**174b**	-	8[b]	4 × 3 min at 200 °C	77% (**175b**)	**195b** (7%)
4	**174d**	*o*-DCB	1	60 min at 180 °C	23% (**175d**)	**195d** (20%)
5	**174d**	-	6[b]	65 min at 170 °C	19% (**175d**)	**195d** (26%)
6	**174d**	-	8[b]	2 × 3 min at 240 °C	70% (**175d**)	-
7	**174c**	-	4[b]	30 min at 250 °C	8% (**175c**)	(n.d.) **196c**
8	**174c**	-	3[b]	4 min at 240 °C	81% (**175c**)	-

[a] isolated yield.
[b] the reaction was carried out neat.

Both tosylmalonates **174b** and **174d** could only be partially converted into the di-rearranged product both when *o*-DCB was used as the solvent and when the reaction was carried out neat while under continuous microwave heating (entries 1, 2, 4 and 5). The main by-product of the reaction for these two substrates was the monoallylic ester. This derives from the more facile rearrangement of the more electron-rich allylic portion (compounds **195b** and **195d**). Interestingly, the use of sequential cycles of microwave heating followed by cooling, allowed significant improvement in the efficiency of the reaction, and dienes **175b** and **175d** were obtained in 77% and 70% yield respectively (entries 3 and 6). The beneficial effect of carrying out irradiation in a number of short pulses rather than over longer, continuous periods has been previously reported,[25,26] although this phenomenon is poorly understood.

In order to test the behaviour of a substrate bearing a bulky group (*i*-Pr) in the inner position of the double bond, the dual dCr of tosylmalonate **174c** was undertaken. Forcing conditions (250 °C, 30 min) were at first employed (entry 7) as the bulk of the *i*-Pr substituent was expected to disfavour the rearrangement. Diene **175c** was isolated in very modest yield together with traces of sulfone **196c**. This unexpected by-product is thought to arise through decomposition of the intermediate mono-rearranged ester **195c** by a process that involves either hydrolysis of the ester functionality and decarboxylation of the resulting carboxylic acid **197**, or a direct KOAc-promoted Krapcho-type reaction[27] (**Scheme 2.14**).



Scheme 2.14 Proposed decomposition pathways for the formation of sulfone **196c**.

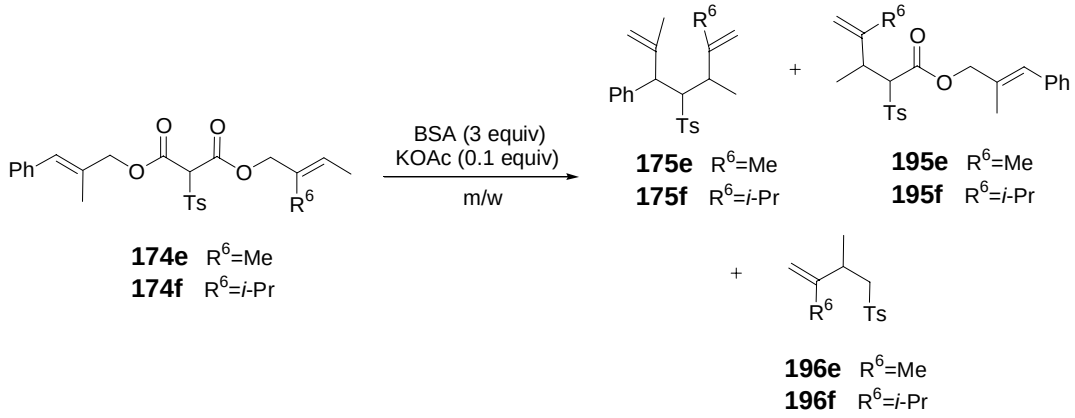
A high level of conversion of **174c** into diene **175c** was achieved when the reaction time was shortened (8 min) and the reaction temperature lowered by 10 °C (entry 8). Product

175c was isolated in 81% yield as a 1:1 mixture of diastereoisomers and no by-product was observed, thus indicating that no significant deactivation of the substrate is caused by the presence of a bulky group in the R^2 position.

2.2.3.2.3 The dual dCr reaction of fully substituted tosylmalonates

The synthesis of 2,3,5,6-tetrasubstituted heptadienes was studied. These compounds were of particular interest in order to access tetra- and penta-substituted pyridines. The best results obtained for the preparation of **175e** and **175f** are collected in **Table 2.8**.

Table 2.8 Double decarboxylative Claisen rearrangement of **174e** and **174f**



174e R^6=Me
174f R^6=*i*-Pr

175e R^6=Me
175f R^6=*i*-Pr

195e R^6=Me
195f R^6=*i*-Pr

196e R^6=Me
196f R^6=*i*-Pr

Entry	174	Reaction Conditions	Yield of 175[a]	Side Products
1	**174e**	6 × 1 min at 180 °C	56% (**175e**)	**195e** (23%)
2	**174f**	7 × 1 min at 230 °C	7% (**175f**)[b]	**196f** (47%)[b]

[a] isolated yield.
[b] The yields reported are approximate values due to the impossibility of recovering the products in a pure form.

Substrates **174e** and **174f** were resistant to the dual dCr reaction under a variety of conditions. In all cases the reactions were carried out neat, and three equivalents of BSA were used in order to reach the minimum volume required for microwave reactions. This is because microwave reactions need to be carried out within a volumetric range, dependant on the size of the vial used. Three equivalents were chosen arbitrarily and always employed to ensure reproducibility.

Upon extensive screening, six cycles of microwave irradiation of one minute each at 180 °C were identified as the optimal reaction conditions for the synthesis of diene **175e** (entry 1). In this case, the best result was obtained by preventing the complete transformation of the mono-rearranged product into **175e**, to minimise contamination of the diene with **196e** and other decomposition products.

The last dual dCr reaction studied on simple substrates was attempted on tosylmalonate **174f**. In this case neither the use of high reaction temperatures nor pulsed heating as described above, allowed efficient conversion into **175f** (entry 3, **Table 2.8**). Numerous by-products including sulfone **196f** were detected, and this again made diene purification problematic.

Synthesis of diene **175f** was also attempted step-wise with the aim of testing each of the two rearrangements singularly. Tosylmalonate **174f** underwent mono-rearrangement to give tosyl ester **195f** upon treatment with TBDMSOTf–DBU at rt.[a] Microwave irradiation of **195f** (7 × 1 min at 230 °C) was used to perform the second, less facile rearrangement. The first step gave monoester **195f** in only 29% yield while the following microwave reaction gave the dual rearrangement product in 17% yield (overall yield: 5%). Once again purification of the complex product mixtures was problematic. Neither of the rearrangements seemed to be an efficient process and compound **174f** was not studied further.

2.2.3.2.4 The use of enhanced microwave synthesis (EMS)

The efficiency of microwave-assisted synthesis is believed by most scientists to be based on the ability of the materials (mainly the reaction solvents) to absorb microwave energy and to convert it into heat. Indeed, microwave irradiation raises the temperature of the whole volume simultaneously providing a very efficient heating system, whereas in classical oil-bath heating the reaction mixture in contact with the vessel wall is heated first (**Figure 2.1**).

[a] The use of silyl triflate (TBDMSOTf) and DBU was proved to perform the mono-rearrangement of tosylmalonic mono(allylic) esters **168**. This set of conditions gave comparable yields to the ones obtained using the BSA–KOAc combination of reagents for all the substrates studied, but yielded the products much more rapidly.[6]

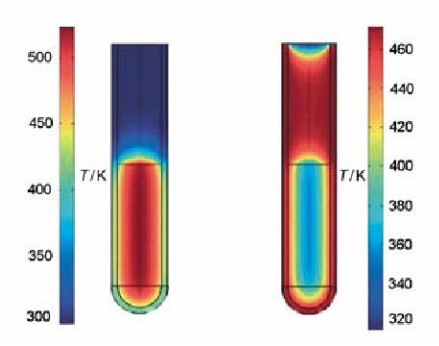


Figure 2.1 Inverted temperature gradients in microwave versus oil-bath heating: difference in the temperature profiles (finite element modelling) after one minute of microwave irradiation (left) and treatment in an oil-bath (right).[24,b]

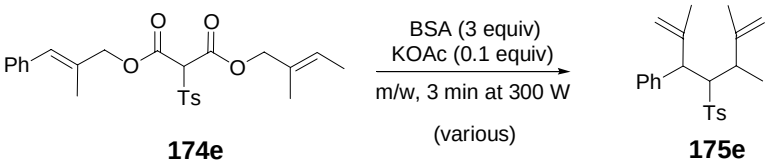
On the basis of this consideration, conventionally the microwave reactors are programmed so as to modulate the microwave energy furnished to the reaction mixture in order to attain a set temperature as quickly as possible and then maintain it. This means that the microwave energy provided to the reaction vial is very high at the beginning of heating, and decreases significantly afterwards.

Recently, an alternative method of performing microwave-assisted reactions, termed "enhanced microwave synthesis" (EMS) has been studied.[28] EMS refers to the application of microwave irradiation to the reaction vessel whilst simultaneously cooling it externally with compressed air. This method allows the reaction mixture to be irradiated with more energy. Operationally, the controlled parameter is the microwave power rather than the target temperature, such that this stays constant during the whole reaction while the flow of cooling air keeps the temperature low.

With the dual dCr reaction, it was previously observed that providing the microwave heating in intermittent cycles rather than continuously has a very beneficial effect on the yields (see section **2.2.3.2.2**, **Table 2.7**). It was considered that in this way the reaction mixture is irradiated with more microwave energy since the target temperature needs to be reached repeatedly. Therefore, since EMS ensures that a high, constant level of microwave energy is applied, it was wondered if it might be used to improve the dual dCr chemistry further.

[b] **Figure 2.1** was taken without the author's permission.

To explore this idea, the conversion of **174e** into **175e** by EMS was investigated. Various reaction times were screened, and the best reaction conditions were found to be irradiation at a power of 300 W for three minutes. However, although in the first instance diene **175e** was isolated in 46% yield, this result could never be reproduced and yields varying between 10% and 25% were subsequently obtained (**Scheme 2.15**).



174e **175e**

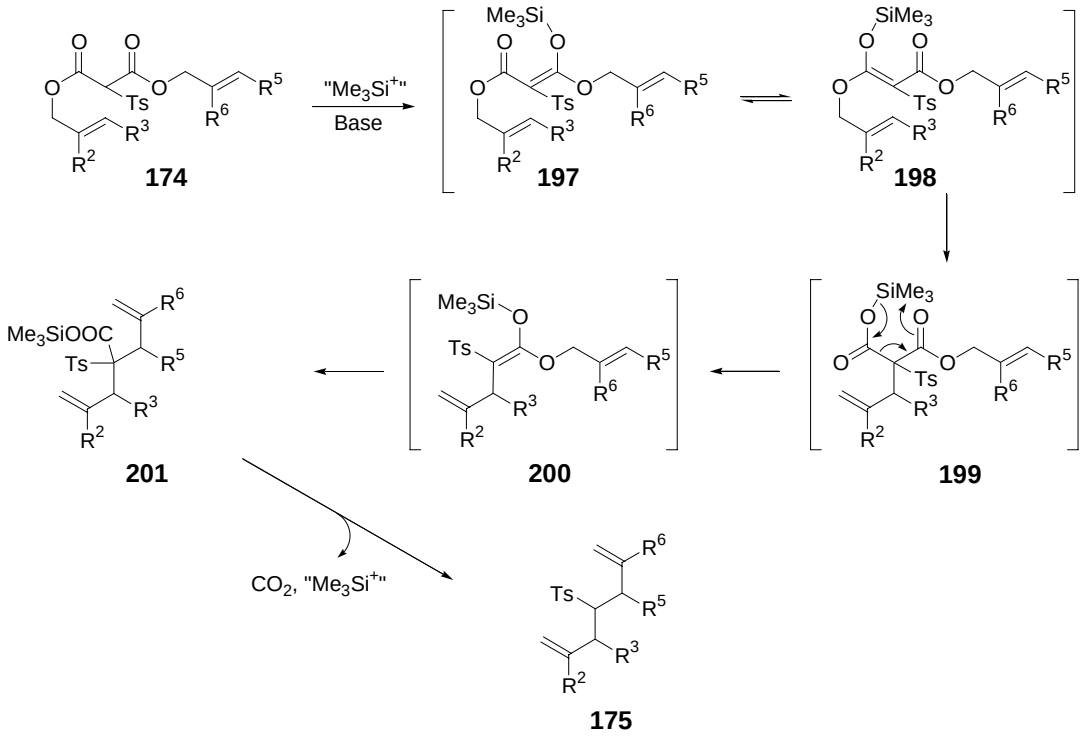
Scheme 2.15 Synthesis of diene **175e** by enhanced microwave synthesis.

Although recently published research supports the use of the EMS technique and claims that it helps in achieving greater yields,[28-30] in our hands reproducible results were not obtained. This might be a consequence of our use of the Biotage Initiator for microwave-assisted reactions. In this instrument, the temperature measurement takes place outside the vial by an IR-pyrometric sensor. The presence of the cooling gas is likely to interfere with the temperature reading, so that the value given by the instrument does not represent the true temperature inside the reaction vial but an estimation of the one outside the vessel. Because temperature is a key parameter in any chemical reaction, the practical impossibility of controlling it with accuracy might pose serious reproducibility problems.

2.2.3.2.5 Mechanistic observation

The mechanism of decarboxylative Claisen rearrangement for tosylmalonates **174** is proposed to differ slightly from the one previously described for the reaction of tosylacetates **164** (see section **2.2.1**, **Scheme 2.2**).[6] Indeed, silyl ester **199**, formed upon mono-rearrangement of **174**,[31] can be thought to undergo silatropic rearrangement to give a new silyl ketene acetal, which is then transformed into diene **175** (**Scheme 2.16**).[c]

[c] The occurrence of a silatropic rearrangement was for the first time hypothesised during the investigation of the mono-rearrangement of methyl allylic tosylmalonates **168**. [6]



Scheme 2.16 Proposed mechanism for the dCr of tosylmalonate esters.

The dual dCr reaction may be in principle sub-stoichiometric in silylating agent. Nevertheless, it was in all cases carried out in the presence of at least one equivalent of BSA. The reason for this seems to be related to the forcing reaction conditions needed for the dual rearrangement to take place, which might cause decomposition of BSA.

2.2.3.2.6 Conclusions

In conclusion, dual dCr reaction of tosylmalonates **174** with varying degrees of substitution can be achieved in one-pot in moderate to good yields by using microwave irradiation. As a general trend, it appears that as the degree of substitution of the allylic double bonds increases, the substrate becomes more and more reluctant to undergo dCr chemistry. The reaction conditions for each rearrangement need to be studied separately as the optimal ones vary significantly with the nature and position of the substituents. Nevertheless, the examples reported so far define a trend of reactivity and provide a useful starting point for the identification of the best reaction conditions for the synthesis of dienes from the corresponding diallylic 2-tosylmalonates.

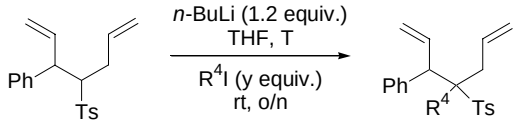
2.2.3.3 Synthesis of pyridines substituted at the 4-position

2.2.3.3.1 Alkylation of 4-tosyl-1,6-heptadienes at the 4-position

Double dCr of tosylmalonates **174** allows the synthesis of 4-tosyl dienes carrying a maximum of four substituents. It occurred to us that incorporation of a fifth substituent might be possible by alkylation α- to the tosyl group.[11,32-34] This would allow the synthesis of pyridines substituted additionally at the 4-position (see section **2.2.2**, **Scheme 2.8**).

In order to study the alkylation chemistry, the behaviour of the least substituted substrate so far synthesised was investigated (**Table 2.9**).

Table 2.9 Alkylation of 3-phenyl-4-tosyl-1,6-heptadiene **175a**



175a **180a**,**b**

Entry	Temperature (T)	R^4I (y)	Product	Yield
1	–78 °C	CH_3I (1.5 equiv)	**180a**	32%[a]
2	0 °C	*n*-$C_9H_{19}I$ (1.2 equiv)	**180b**	86%[b]

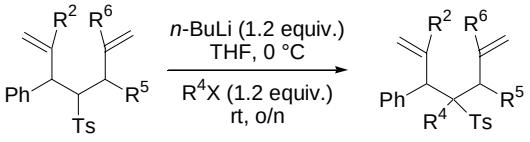
[a] yield determined by ^1H NMR analysis; 42% of unreacted **175a** was also detected.
[b] isolated yield.

Following the reaction conditions previously reported within the group,[11] the anion of diene **175a** was formed by addition of *n*-BuLi to a THF solution of the substrate at –78 °C (entry 1). The solution turned from colourless to bright yellow and addition of a slight excess of iodomethane resulted in the formation of the desired product **180a** in 32% yield, while 42% of **175a** was still present in the reaction mixture. Effective separation of the product from the starting material by column chromatography was not possible because of their similar R_f values. Therefore, in order to both overcome this and explore the scope of the reaction, substrate **175a** was reacted with 1-iodononane (entry 2). In an attempt to improve the reaction conditions, the synthesis of **180a** was re-examined and the anion of the starting material was formed at 0 °C. Pleasingly, addition

of the electrophile resulted in the formation of the desired alkylated diene **180b** in 86% yield; no purification issues were encountered.

Unfortunately however, when the study of the alkylation of more substituted dienes was undertaken, significantly lower yields or no reaction were obtained (**Table 2.10**).

Table 2.10 Alkylation of heptadienes **175b**,**c**,**e**



175b,**c**,**e** **180c**,**d**

Entry	175	R^2	R^5	R^6	R^4X	Yield of 180[a]
1	**175b**	Me	H	H	*n*-$C_9H_{19}I$	40% (**180c**)[b]
2	**175b**	Me	H	H	$PhCH_2Br$	56% (**180d**)[c]
3	**175c**	Me	H	Me	*n*-$C_9H_{19}I$	-
4	**175c**	Me	H	Me	$PhCH_2Br$	-
5	**175e**	Me	Me	Me	*n*-$C_9H_{19}I$	-
6	**175e**	Me	Me	Me	$PhCH_2Br$	-
7	**175e**	Me	Me	Me	CH_2=$CHCH_2Br$	-

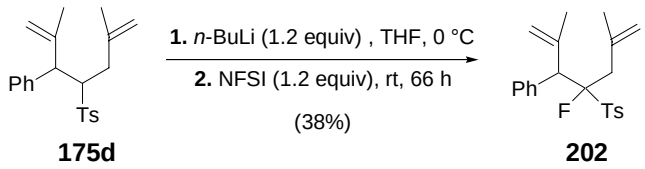
[a] isolated yield.
[b] 34% of unreacted starting material was also recovered.
[c] 4% of unreacted starting material was also recovered.

Under the same reaction conditions used to obtain **180b**, di-substituted heptadiene **175b** gave the tri-substituted analogue **180c** in 40% yield only (entry 1). The use of a better electrophile such as benzyl bromide resulted only in a slight improvement in the yield of **180d** (entry 2). When further substitution was introduced (entries 3 and 4) no alkylation was observed. Even when more powerful electrophiles such as benzyl and allyl bromide were used, the reactions failed to provide the desired products. Similarly, when the reactions were carried out at high concentration (~1.6 M), in presence of an excess of electrophile and using THF:DMPU–1:1 as the solvent mixture, no alkylated product could be isolated.

Particular attention was devoted to the study of the behaviour of diene **175e**, since its 4-alkylated product would be the direct precursor of a penta-substituted pyridine. In order to assess that the substrate was successfully deprotonated, a THF solution of **175e** at 0 °C was treated with *n*-BuLi as previously described, and then exposed to $^{2}H_2O$. ^{1}H-^{2}H exchange at the 4-position was observed *via* ^{1}H NMR analysis, therefore it was hypothesised that steric hindrance was responsible for the observed low anion reactivity.

Having demonstrated the anion formation, it was considered that an electrophilic fluorine source might provide an electrophile small enough to be incorporated into the diene. The interest in electrophilic fluorine is motivated not only by its significance in terms of defining the scope and limitation of the methodology, but also by the attention that fluorinated compounds continue to attract in the field of medicinal chemistry.[35]

Hence, the anion of 2,5,6-trimethyl-3-phenyl-4-tosyl-1,6-heptadiene **175e** was treated with a solution of *N*-fluorobenzenesulfonimide (NFSI) in THF. Unfortunately, again no product formation was observed, the reaction mixture being composed mainly of starting material. In contrast, when NFSI-mediated fluorination was attempted on the tri-substituted diene **175d**, the desired 4-fluoro compound **202** was isolated in 38% yield, together with 20% of unreacted starting material (**Scheme 2.17**).



175d **202**

Scheme 2.17 Fluorination of 2,6-dimethyl-3-phenyl-4-tosyl-1,6-heptadiene **175d**.

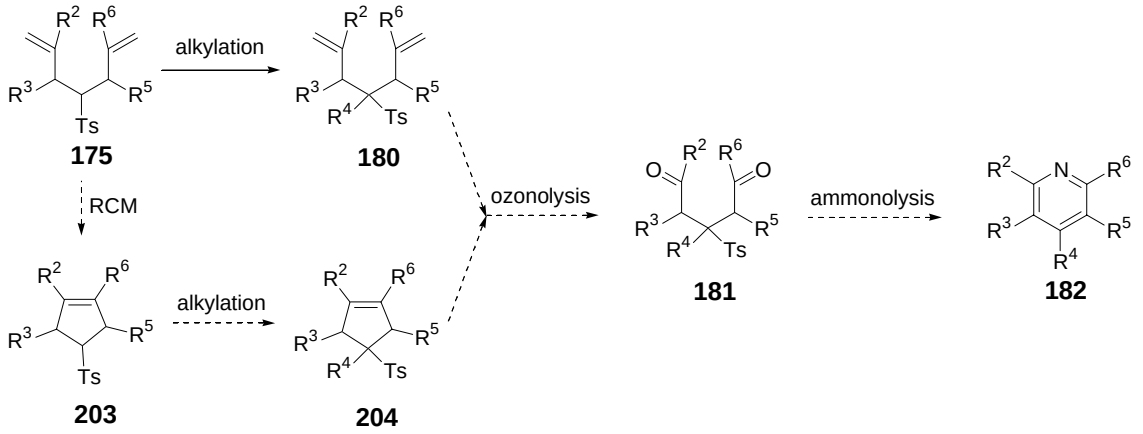
To the best of our knowledge NFSI is the only reagent reported to be effective for the fluorination of the α-position of a sulfone.[36] However, in an attempt to optimise the reaction, other fluorinating agents (Selectfluor®, *N*-fluoropyridinium triflate, 2-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzoisothiazole-1,1-dioxide and *N*-fluoro-*N*-methyl *p*-toluenesulfonamide)[37,38] were used. Amongst all the reagents tested, only 2-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzoisothiazole-1,1-dioxide gave any product, fluorodiene **202** being obtained in 16% yield.

These results suggest that synthesis of 4-substituted pyridines with a maximum of two other substituents in the 2- and 3-position *via* the methodology discussed herein is possible. In addition, the introduction of a fluoro group on diene **175d** could open the way to the synthesis of highly substituted 4-fluoropyridines. The transformation of **202** into the nitrogen heterocycle will be discussed later (see section **2.2.3.4**)

With the aim of countering the problems caused by the low nucleophilicity of highly substituted dienes **175** a different approach involving the use of ring-closing olefin metathesis[39,40] (RCM) was considered and is now discussed.

2.2.3.3.2 Alkylation of 4-tosylcyclopentenes at the 4-position

The rationale behind the use of RCM to access 4-tosylcyclopentenes **203** from dienes **175**, was that ozonolysis of the cyclopentenes was expected to produce the same 1,5-dicarbonyl compounds that can be obtained from the corresponding dienes. Moreover, compared to dienes **175**, cyclopentenes **203** should have the advantage of giving sterically less constrained and therefore more nucleophilic anions on base treatment. Thus they should undergo alkylation more readily than their acyclic counterparts (**Scheme 2.18**).[41]

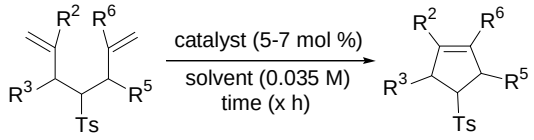


Scheme 2.18 Proposed pathways for the synthesis of 4-substituted pyridines.

Ring closing metathesis of dienes **175b**,**d**,**e** bearing at least two substituents other than the tosyl in the 2- and 3-positions, was studied (**Table 2.11**). Synthesis of 3-phenyl-4-

tosylcyclopentene from **175a** was not considered necessary as alkylation of the diene itself was high-yielding (see section **2.2.3.3.1**).

Table 2.11 Ring closing metathesis of dienes **175b**,**d**,**e**



175b,**d**,**e** **203**

Entry	175	R^2	R^3	R^5	R^6	Catalyst	Solvent (T)	Time (x h)	Yield of 203[a]
1	**175b**	Me	Ph	H	H	Grubbs II	CH_2Cl_2 (40 °C)	0.5 h	81% (**203b**)
2	**175b**	Me	Ph	H	H	Hoveyda	CH_2Cl_2 (40 °C)	18 h	94% (**203b**)
3	**175d**	Me	Ph	H	Me	Grubbs II	CH_2Cl_2 (40 °C)	66 h	-
4	**175e**	Me	Ph	Me	Me	various[b]	various[c]	various[d]	-

[a] isolated yield
[b] Hoveyda's and Grubbs' 2nd generation catalysts were employed
[c] reflux in CH_2Cl_2 and toluene were attempted; microwave acceleration was also tried
[d] times of reaction ranging between 2 hours and 1 day were monitored

Synthesis of cyclopentenes from 1,6-heptadienes bearing no substituents in the 2- and 6-position had been previously reported[23] and was achieved using both Grubbs' 1st- and 2nd-generation catalysts[42,43].

In the case of compound **175b** (entries 1 and 2) both 2nd-generation Grubbs's catalyst and Hoveyda's catalyst[44] allowed the synthesis of the desired cyclopentene in excellent yield.[d] However, metathesis of compounds **175d** and **175e** was never observed, even when high temperatures (reflux in toluene), high catalyst loadings and microwave acceleration were employed (entries 3 and 4). The reluctance of these substrates to undergo RCM was attributed to the difficulty of forming tetra-substituted double bonds in highly-functionalised ring systems. Even when the attempted metathesis of diene

[d] Cyclopentene **203b** was obtained as a 1:1 mixture of diastereoisomers as the reaction was carried out on an equimolar diastereoisomeric mixture of **175b**.

175d was carried out at high concentration of starting material (~0.3 M) neither cross metathesis nor ring closing metathesis products were observed, indicating the poor reactivity of the double bonds.

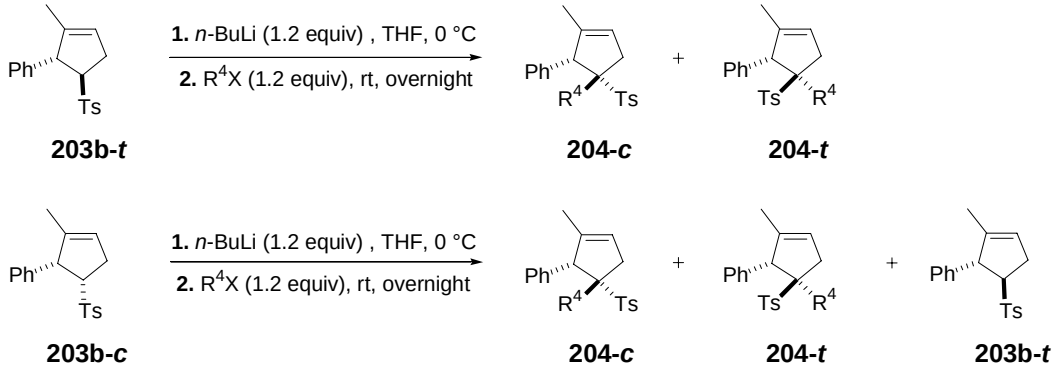
The synthesis of ring structures containing tetra-substituted olefins using ruthenium (Grubbs' type) catalysts is known to be a difficult process.[45-47] However, the study of novel olefin metathesis catalysts is ongoing and recently highly efficient ruthenium complexes have been proposed for the synthesis of rings which, although less substituted than **175d**,**e**, possess a tetra-substituted double bond.[48-50] Future developments in the field might open the way to the synthesis of highly substituted tosylcylopentenes from the corresponding dienes.

Schrock's alkylidene catalyst[51] is reported to be more active for the formation of tetra-substituted cycloalkene products.[52] However, its use has not been tested because it would require the use of glove-box techniques, hence limiting the applicability of the methodology in terms of ease of operation.

Having synthesised **203b** in high yield, its behaviour towards alkylation was studied. As the two diastereoisomers of **203b** could be separated by chromatography,[e] their individual reactivity towards alkylation could be assessed (**Table 2.12**).

[e] X-ray crystallography of the *trans*-diastereoisomer allowed unequivocal identification of the stereochemistry of the two isomers.

Table 2.12 Alkylation of 1-methyl-5-phenyl-4-tosylcyclopentene **203b**



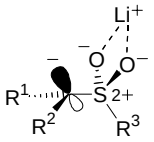
Entry	203	R^4X	Yield of 204-*c*[a]	Yield of 204-*t*[a]	Yield of 203b-*t*[a]
1	**203b-*t***	*n*-$C_9H_{19}I$	60% (**204a-*c***)	12% (**204a-*t***)	-
2	**203b-*t***	$PhCH_2Br$	64% (**204b-*c***)	14% (**204b-*t***)	-
3	**203b-*c***	*n*-$C_9H_{19}I$	10% (**204a-*c***)	1% (**204a-*t***)	72%
4	**203b-*c***	$PhCH_2Br$	25% (**204b-*c***)	9% (**204b-*t***)	36%

[a] isolated yield.

Unexpectedly, it was found that the two diastereoisomers differed significantly in their reactivity towards alkylation. The *trans*-diastereoisomer **203b-*t*** was found to be much more reactive than its *cis*- counterpart **203b-*c***, and could be converted into the alkylated products in overall yields above 70% (entries 1 and 2). On the other hand, the *cis*-diastereoisomer **203b-*c*** could be transformed into the desired products **204** in much lower yields (entries 3 and 4) and the anion of starting material **203b-*c*** was in both cases partially re-protonated to form diastereoisomer **203b-*t***, believed to be thermodynamically more stable. In all cases the major alkylation product was the one resulting from electrophilic attack *anti* to the phenyl ring, as confirmed by X-ray crystallography of **204b-*c*** (see **Appendix**). The diastereoisomeric ratio is also similar in all cases (~ 8:2).

The different reactivity of the sulfonyl anions of **203b-*c*** and **203b-*t*** suggests that they are non-planar. Lithiosulfones, both linear[53-55] and bi-cyclic,[56] have been reported to have pyramidal geometry. The most favourable conformation seems to be the one in

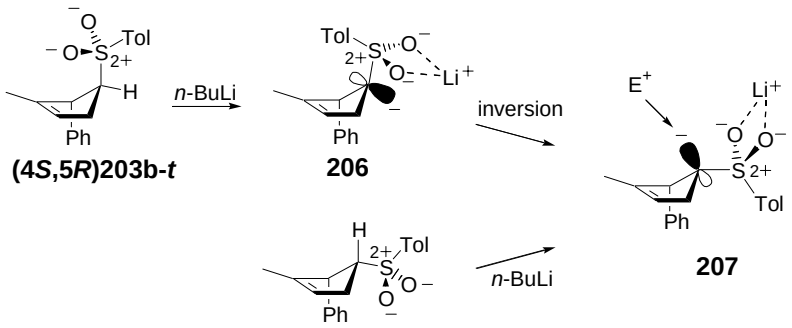
which the two sulfonyl oxygens, which are likely to be lithium-coordinated, are arranged *gauche* with respect to the lone pair of the anion (**Figure 2.2**).



205

Figure 2.2 *Gauche* conformation of lithiosulfone **205**.

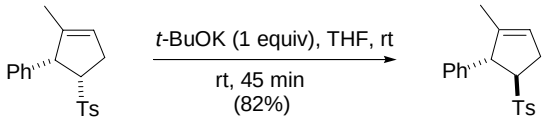
In addition, α-sulfonyl carbanions are reported to react with electrophiles preferentially from the side *syn* to the sulfonyl oxygens. Therefore, it can be hypothesised that the anions of tosylcyclopentenes **203b** were approached by electrophiles when they were in a similar conformation, as depicted in **Scheme 2.19** for **(4*S*,5*R*)203b-*t*** and **(4*R*,5*R*)203b-*c***.



Scheme 2.19 Formation of the hypothetically most reactive conformation of the anion of **(4*S*,5*R*)203b-*t*** and **(4*R*,5*R*)203b-*c***.

This way the electrophile attacked the anion from the less hindered side whilst pushing the tosyl group into the sterically more crowded position. It is interesting that the *trans*-compound, whose anion needs to undergo inversion of configuration to give **207**, was a better alkylation substrate than **203b-*c***. To determine the reason for this as well as to give a detailed description of the reaction stereochemistry, further studies are required.

Additionally, it was found that the *cis*-cyclopentene could be converted into the *trans*-isomer in good yield upon exposure to potassium *tert*-butoxide in THF (**Scheme 2.20**).



203b-*c* **203b-*t***

Scheme 2.20 Conversion of *cis*-cyclopentene **203b-*c*** in its *trans*- counterpart.

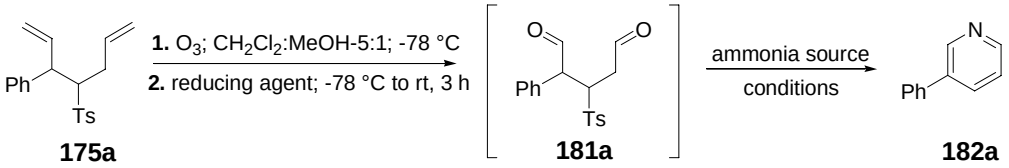
This result confirms the greater thermodynamic stability of **203b-*t*** compared to **203b-*c*** and is significant from a synthetic point of view, since the *trans*-cyclopentene is a better alkylation substrate than the *cis*-.

In conclusion, cyclopentenes **34** were shown to undergo more efficient alkylation than dienes **14**. However, this chemistry is currently limited by the difficulty of accessing substrates **34** themselves by ring closing olefin metathesis.

2.2.3.4 Pyridine synthesis

The conversion of dienes **175a**–**e**, **180a**–**d** and cyclopentenes **204a**,**b** into pyridines remained to be explored. The synthesis of commercially available 3-phenylpyridine **182a** from 3-phenyl-4-tosyl-1,6-heptadiene **175a** was firstly undertaken and then used to optimise the reaction conditions for pyridine synthesis (**Table 2.13**).

Table 2.13 Synthesis of 3-phenylpyridine



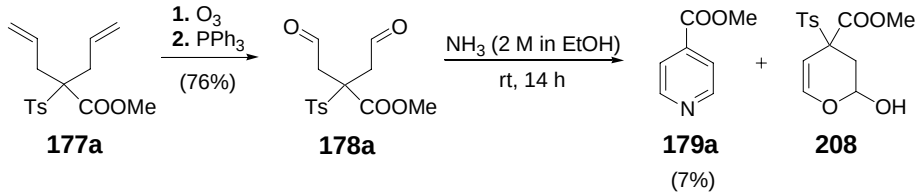
175a **181a** **182a**

Entry	Reducing agent[a]	NH_3 source[b]	Ammonolysis conditions	Yield of 182a[c]
1	solid supported PPh_3	2.0 M solution in MeOH	stirring o/n at rt	13%
2	solid supported PPh_3	NH_4HCO_3	m/w, 10 min at 100 °C	53%
3	Me_2S	NH_4HCO_3	m/w, 10 min at 100 °C	48%

[a] 3 equivalents of reducing agent were normally used; 100 equivalents were employed in the case of Me_2S.
[b] excess ammonia was always used: ~ 20 equivalents of the methanolic solution and ~ 8 equivalents of NH_4HCO_3.
[c] isolated yield.

Previous work carried out in the group had shown that 3-tosyl-1,5-dicarbonyl compounds are unstable over several hours at room temperature and that better results can be obtained when the ozonolysis–ammonolysis sequence resulting in the pyridine formation is performed in a one-pot fashion.[11] Therefore, dialdehyde **181a** was in all cases formed *in situ* by ozonolytic cleavage of diene **175a**, and then treated with an excess of an ammonia source. As a first attempt (entry 1) solid supported-triphenylphosphine was used as the reducing agent in the ozonolysis step and a methanolic solution of ammonia provided the nitrogen for the cyclocondensation.[11] Unfortunately the yield was low (13%) and the use of different reducing agents in the ozonolysis step (such as thiourea and ammonia itself) did not result in any significant

improvement. It was considered that 1,5-dialdehydes are very reactive and unstable compounds and difficulties associated with their manipulation had already been observed within the group.[57] Indeed, in the attempt of synthesising 4-carboxymethyl pyridine **179a** starting from diene **177a** (**Scheme 2.21**), only yields as high as 7% could be obtained. This was thought to be associated with the formation of the stable cyclic intermediate **208**, which was isolated from the reaction mixture.[11]



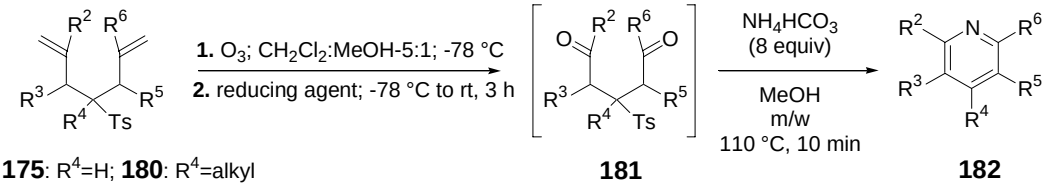
Scheme 2.21 Synthesis of 4-carbomethoxypyridine **179a**.

A similar transformation of dialdehyde **181a** into its unreactive, masked form was hypothesised also in the case of the synthesis of 3-phenyl pyridine **182a**.

At this point our attention turned towards the use of microwave acceleration (entry 2, **Table 2.13**), which was expected to significantly shorten the reaction time and therefore help minimise the decomposition of the dicarbonyl intermediate. Ammonium hydrogencarbonate, which decomposes into ammonia, water and CO_2 at *ca.* 60 °C, provided the ammonia source.[58] The reaction was carried out in methanol and solid-supported PPh_3 was used as the reducing agent, resulting in a considerable improvement of the yield (53%). Subsequently, while seeking for a cheap and easy to remove reductant for the ozonolysis step, the employment of an excess of dimethylsulfide was found to provide pyridine **182a** in 48% yield (entry 3, **Table 2.13**).

This optimal set of reaction conditions was then used to convert dienes **175** and **180** into pyridines (**Table 2.14**).

Table 2.14 Pyridine synthesis



175: R^4=H; **180**: R^4=alkyl **181** **182**

Entry	Diene	Reducing agent[a]	R^2	R^3	R^4	R^5	R^6	Yield of 182[b]
1	**175b**	PPh_3[c]	Me	Ph	H	H	H	86% (**182b**)[d]
2	**175c**	PPh_3	*i*-Pr	Me	H	H	H	-
3	**175d**	PPh_3	Me	Ph	H	H	Me	73% (**182d**)
4	**175e**	Me_2S	Me	Ph	H	Me	Me	81% (**182e**)
5	**180b**	Me_2S	H	Ph	*n*-C_9H_{19}	H	H	98% (**182f**)[d]
6	**180c**	Me_2S	Me	Ph	*n*-C_9H_{19}	H	H	99% (**182g**)[d]
7	**180d**	Me_2S	Me	Ph	$PhCH_2$	H	H	75% (**182h**)

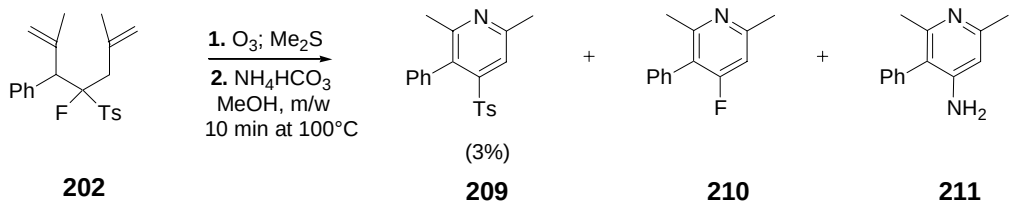
[a] 3 equivalents of PPh_3 were used; 100 equivalents were employed in the case of Me_2S.
[b] isolated yield.
[c] solid-supported.
[d] yield of crude material.

In all but one case the desired products were obtained in good to excellent yield. The exception was the synthesis of 2-(*iso*-propyl)-3-methylpyridine starting from **175c**. TLC analysis and ^{1}H NMR data of the crude showed the formation of the expected heterocycle **182c** as the major product, but no material could be recovered after work-up and purification. Because of this, and having considered the singularity of the result, it was speculated that the reason might be associated with the volatility of the product pyridine. However, the occurrence of decomposition reactions cannot be excluded.
In the case of compounds **182b**, **182f** and **182g** (entries 1, 5 and 6) a very pure crude product was synthesised (see ^{1}H NMR spectra, **Appendix**). Nevertheless, purification by chromatography was carried out for analysis purposes.

For one substrate the efficiency of the pyridine formation step in isolation was tested. Ammonolysis of 3-phenyl-4-tosylheptane-2,6-dione **181d**, obtained in 72% isolated yield by ozonolysis of **175d** was carried out. Diketone **181d** was converted into **182d** in 98% yield, both by using ammonia in methanol (overnight, rt) and ammonium

hydrogencarbonate (microwave) as the nitrogen source. This result suggests that, when the dicarbonyl intermediate does not contain an aldehyde functionality, the nature of the ammonia source, as well as the length of time needed to perform the reaction, does not affect its outcome.

The ozonolysis–ammonolysis sequence carried out on fluorinated diene **202** was of particular interest because of its potential of representing a novel way of introducing fluorine into a pyridine.[59-62] Although the substrate bears two potential leaving groups at the 4-position, it was reasoned that the weaker C-sulfonyl bond should be selectively cleaved in the aromatisation step, giving access to a fluorinated pyridine. Unfortunately, a range of products was obtained instead, 4-tosylpyridine **209** being the major one. Traces of the desired 2,6-dimethyl-3-phenyl-4-fluoropyridine **210** and of 2,6-dimethyl-3-phenyl-4-aminopyridine **211** were also detected by LC-MS analysis. However, their isolation was not possible due to the small scale at which the reaction was performed (**Scheme 2.22**).



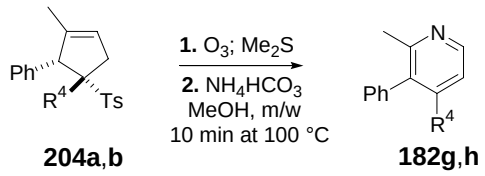
202 **209** **210** **211**

Scheme 2.22 Synthesis of 4-tosylpyridine **209**.

In addition, pyridine **209** was obtained in an unsatisfactory 3% yield, thus showing the inadequacy of the methodology for the synthesis of both 4-tosyl- and 4-fluoropyridines.

Regarding the transformation of alkylated cyclopentenes **204** into pyridines, we were surprised to discover that the reaction gave the desired products in a low yield and an impure form (**Table 2.15**).

Table 2.15 Synthesis of pyridines **182g**,**h** starting from cyclopentenes **204a**,**b**



204a,**b** **182g**,**h**

Entry	R^4	Yield of 182[a]
1	*n*-C_9H_{19}	15% (**182g**)
2	$PhCH_2$	21% (**182h**)

[a] isolated yield.

The reaction conditions previously optimised for the synthesis of pyridines from the corresponding dienes were employed. However, products **182g**,**h** were obtained in yields no higher than 21%. Moreover, unidentified impurities, which could not be completely removed by chromatography, were observed in the crude reaction mixtures. The reasons for this behaviour are currently unclear.

In conclusion, the ring-closing metathesis approach is unsuitable for the efficient synthesis of variously substituted pyridines *via* the methodology developed in the course of this PhD. Nevertheless, it allows access to substrates that can be employed for the synthesis of cyclopentadienes and cyclopentadienyl anions *via* elimination of *p*-toluenesulfinate. The discovery and development of this strategy will be discussed later, in section **2.3**.

2.2.3.5 Conclusions

A novel research programme aimed at the synthesis of poly-substituted pyridines using a dual dCr reaction as a key step has been developed for simple substrates.

The scope and limitations of the approach have been highlighted and show that pyridines bearing a maximum of four substituents in various positions can be synthesised in good yields. The main limitation is the difficulty of accessing 4-substituted heterocycles in the presence of more than two other substituents.

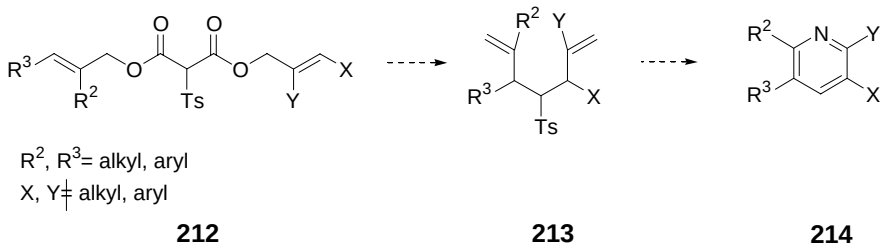
Only pyridines bearing alkyl and phenyl groups have been described so far, in order to prove the feasibility of the methodology. Attempts of expanding its scope by

introducing other substituents onto the ring and by targeting more complex heterocycles such as anellated and chiral pyridines will be described in the following sections.

2.2.4 Expanding the scope of the methodology for pyridine synthesis

2.2.4.1 Studies towards the synthesis of pyridines carrying substituents other than aryl and alkyl groups

With the aim of expanding the scope of the methodology discussed here, the introduction of substituents other than alkyl and aryl onto the pyridine ring *via* dCr chemistry was evaluated. To achieve this goal the allylic double bonds of tosylmalonates **212** need to carry the functional groups of choice (**Scheme 2.23**). Upon dual rearrangement they would lead to functionalised dienes that could in principle be transformed into the corresponding pyridines.



Scheme 2.23 Proposed pathway for the synthesis of pyridines bearing different functionalities.

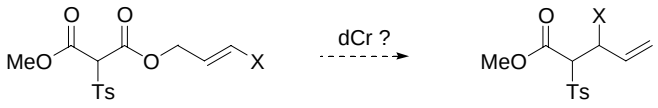
The choice of functional groups was influenced by various factors. Firstly, the introduction of a carbomethoxy group was investigated (X=COOMe), in order to obtain a pyridine bearing a carboxylic group in the 3-position. This would complement the results previously obtained by our group, when the acyclic array for the sulfone-mediated pyridine synthesis was constructed using palladium chemistry and the carbomethoxy group could ultimately be incorporated into the 4-position of the ring (see section **2.2.2**, **Scheme 2.7**).[11]

Secondly, direct introduction of a chlorine was studied because this would represent an alternative to its incorporation *via* electrophilic aromatic substitution of the pyridine ring.[63,64] In addition, substitution reactions of halogenated pyridines are widely used for the synthesis of synthetically or industrially important compounds.[65]

Finally, the incorporation of a trimethylsilyl group was undertaken in order to provide an alternative to the insertion of such groups by metalation of the pyridine ring followed by quenching with chlorosilanes.[66]

Moreover, to our knowledge dCr reactions of compounds containing -COOMe, -Cl and -TMS substituents have never been attempted. The investigation into the behaviour of a chlorine-containing tosylmalonate was considered of particular interest as chlorine is an electron-rich as well as inductively electron-withdrawing group. Therefore, its effect on the reactivity of the tosylmalonate towards dCr chemistry might be significant (see section **2.2.1**, **Scheme 2.4** and **Scheme 2.5**).[10]

To test the viability of the dCr chemistry alone, the behaviour of methyl allylic tosyl malonates **215** was investigated first, as only one rearrangement is possible (**Scheme 2.24**).



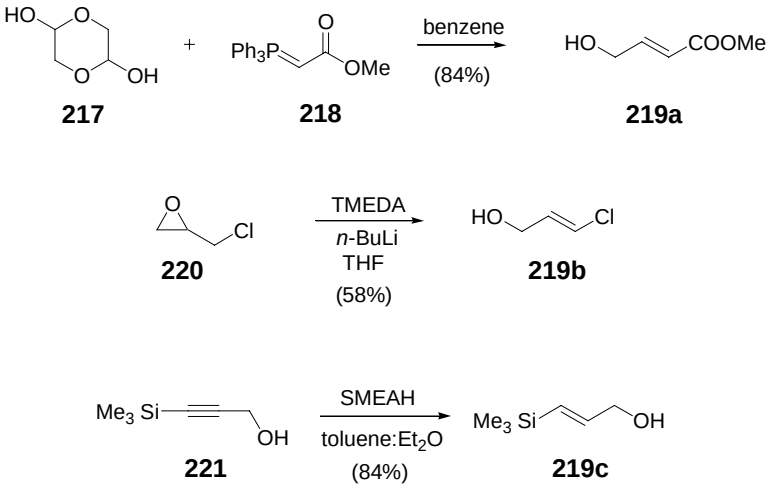
215 **216**

X=COOMe, Cl, $SiMe_3$

Scheme 2.24 Proposed dCr of methyl allylic tosylmalonates **215**.

Synthesis of substrates **215** using the methodology previously described for the diallylic tosylmalonate analogues was undertaken (see section **2.2.3.1**, **Scheme 2.11**).

(*E*)-3-Carbomethoxy-2-propen-1-ol **219a**, (*E*)-3-chloro-2-propen-1-ol **219b**, and (*E*)-3-trimethylsilyl-2-propen-1-ol **219c** were synthesised according to procedures reported in the literature (**Scheme 2.25**).



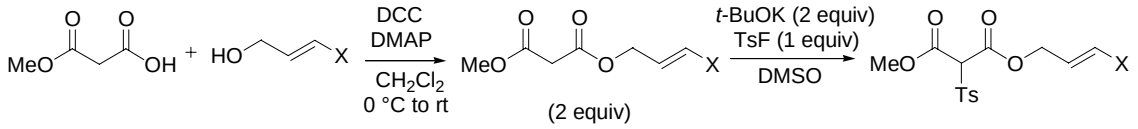
Scheme 2.25 Synthesis of allylic alcohols **219a**–**c**.

(*E*)-3-Carbomethoxy-2-propen-1-ol **219a** was obtained in 84% yield by reaction of the dimer of glycol aldehyde with phosphorane **218**;[67] *n*-BuLi-mediated ring opening of *epi*-chlorohydrin afforded **219b** in 58% yield,[68,69] and **219c** was isolated in 84% yield as a single stereoisomer *via* SMEAH-mediated reduction of 3-trimethylsilylpropargyl alcohol.[70,71]

Coupling of alcohols **219a**–**c** with methyl malonate **222**[6, f] afforded the desired diesters in yields varying between 67% and 80%, whilst tosylation of **223** gave the desired product only in the case of compounds **215b** and **215c** (**Table 2.16**).

[f] Compound **222** was obtained in 94% yield by treatment of Meldrum's acid with methanol.

Table 2.16 Synthesis of tosylmalonates **215a–c**

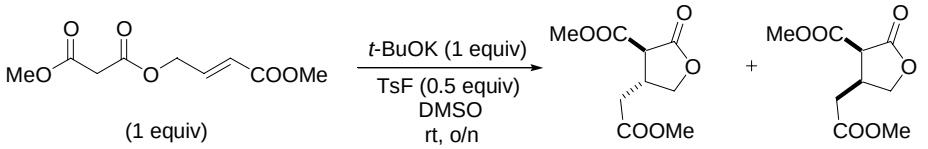


222 **219** **223** **215**

Entry	X	Yield of 223[a]	Yield of 215[a]
1	COOMe	67% (**223a**)	-
2	Cl	80% (**223b**)	64% (**215b**)[b]
3	$SiMe_3$	70% (**223c**)	41% (**215c**)[c]

[a] isolated yield.
[b] 66% of unreacted starting material was also recovered.
[c] 58% of unreacted starting material was also recovered.

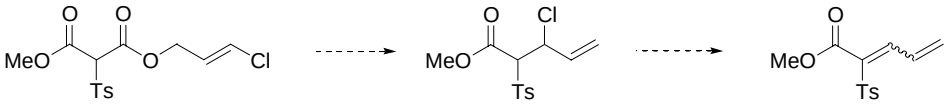
When compound **223a** was subjected to standard tosylation reaction conditions, intramolecular Michael addition[17,23] occurred instead, and no tosylation product could be isolated (**Scheme 2.26**).



223a **224-*t*** **224-*c***

Scheme 2.26 Intramolecular Michael cyclisation of malonate **223a** under basic conditions.

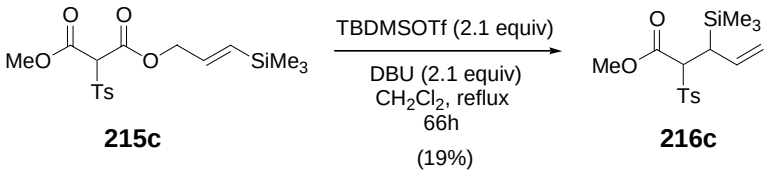
Mono-rearrangement of chlorinated substrate **215b** was first attempted using BSA–KOAc in dichloromethane at room temperature (see section **2.2.1**, **Scheme 2.4**). Even after prolonged stirring, these conditions failed to provide the desired product and only unreacted starting material was recovered from the reaction mixture. The use of more forcing conditions (TBDMSOTf–DBU; see section **2.2.3.2**, footnote a) allowed the formation of a new product, as observed by TLC analysis. However, its identification proved to be challenging. Mass spectrometry seemed to indicate degradation of the rearranged ester **216b** into **225** but NMR analysis could not confirm the result (**Scheme 2.27**).



Scheme 2.27 Proposed dCr of **215b** followed by decomposition of the rearranged product.

It seems plausible that in compound **216b** the chloride might act as a leaving group. In addition, the newly formed ester **225** would have the characteristics of a Michael acceptor, and hence it might undergo a series of conjugated addition processes leading to polymeric materials, which would likely be difficult to analyse and characterise. In other words, it is reasonable to believe that if **216b** is formed, it would be inherently unstable. Therefore its synthesis *via* dCr of the corresponding tosylmalonate was not pursued further.

Like the chlorine-containing analogue **215b**, the silyl-bearing tosylmalonate **215c** proved to be reluctant to undergo dCr. However, upon prolonged reflux of the reaction mixture in the presence of TBDMSOTf–DBU in dichloromethane, its partial transformation into ester **216c** was observed (**Scheme 2.28**).



Scheme 2.28 Synthesis of ester **216c** *via* dCr of tosylmalonate **215c**.

Unfortunately, the yield of the reaction was low. Therefore, the incorporation of the -TMS onto a diallylic tosylmalonate with a view to transformation into a pyridine was not attempted.

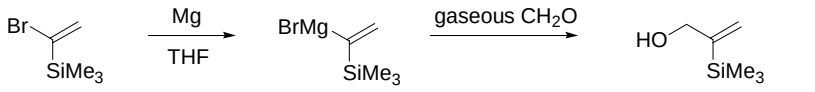
The last attempt to access functionalised pyridines was carried out by exploring the behaviour of a tosylmalonate carrying a -TMS group in the 2-position of the allylic double bond. It was thought that the ability of silicon to stabilise an adjacent negative charge[72] might have a beneficial effect on the rearrangement. To the best of our

knowledge, although substituent effects on the Claisen rearrangement have been studied,[16] the influence of a silyl group has never been investigated.[g]

However, previous work had shown that the presence of electron-rich substituents on the terminal sp^2 carbon atom of the allylic moiety in tosylmalonates **170** causes rate enhancement in the dCr chemistry.[10] It was therefore speculated that a small build up of negative charge at the inner position of the allylic double bond might take place. Hence, substitution at this carbon with an anion-stabilising group could have a positive effect on the overall reaction.

Synthesis of the required tosylmalonate **229** was carried out using the methodology previously described and an overall 30% yield was obtained starting from methyl malonate **222**.

In this case the required allylic alcohol **228** was obtained through a one-pot, two-step procedure starting from (1-bromovinyl)trimethylsilane **226**.[75] Reaction of the bromoalkene with magnesium gave the corresponding Grignard reagent, which was quenched with gaseous formaldehyde to give the desired alcohol **228** (**Scheme 2.29**)[h].



226 **227** **228**

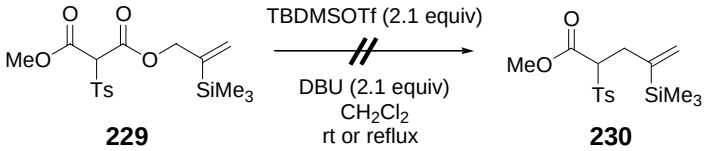
(7% over two steps)

Scheme 2.29 Synthesis of allylic alcohol **228**.

Decarboxylative Claisen rearrangement of **229** was attempted using TBDMSOTf–DBU, both at room temperature and under reflux, but no reaction was observed (**Scheme 2.30**).

[g] The effect of silicon has been studied for other sigmatropic rearrangements, such as the aza-[2,3]-Wittig.[73,74]

[h] Gaseous formaldehyde was generated by cracking paraformaldehyde[75] and then introducing it into the flask containing the Grignard solution through Teflon (PTFE) tubing. The poor overall yield of alcohol **226** (7%) was due to the continuous blockage of the connections between the two flasks, due to prompt re-polymerisation of the formaldehyde.

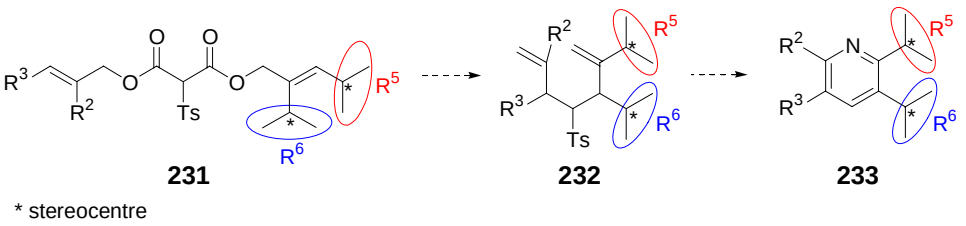


Scheme 2.30 Attempted dCr reaction of 1-methyl 3-[2-(trimethylsilyl)allyl] 2-tosylmalonate **229**.

On the basis of these results, clear limitations of the use of the dCr methodology for the synthesis of diversely substituted pyridines were identified and the direct introduction of substituents other than alkyl and aryl onto the pyridine ring was not pursued further.

2.2.4.2 The synthesis of chiral pyridines

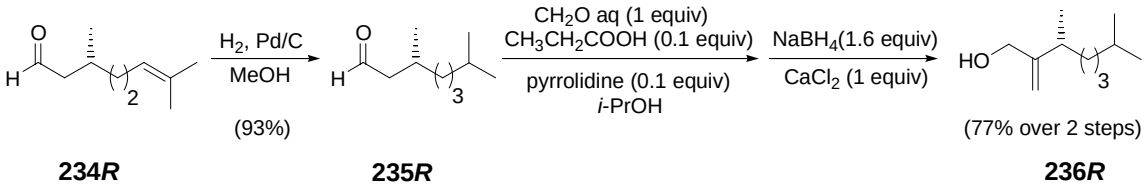
The methodology discussed has the potential to allow access to chiral heterocycles when a chiral allylic alcohol is incorporated into the tosylmalonate that undergoes dual dCr reaction (**Scheme 2.31**).



Scheme 2.31 Synthesis of chiral pyridines *via* dCr-based methodology.

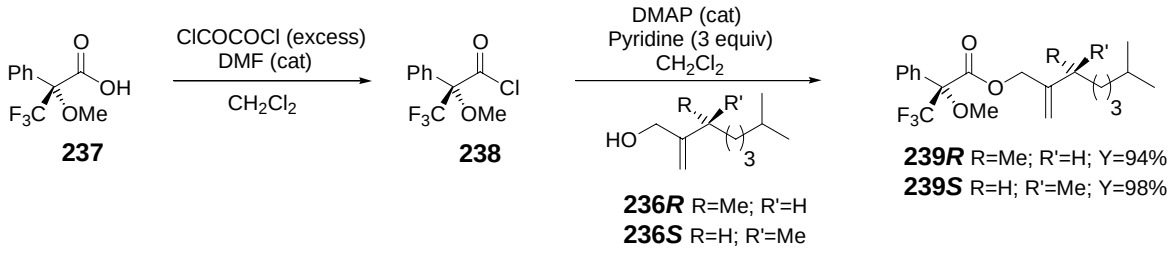
The synthesis of pyridines where R^6 possesses a stereocentre was targeted. In this case, the dicarbonyl intermediate bears the stereocentre at an enolisable position. Although this might cause a decrease in the enantiopurity of the final product, it was considered that this case was worthy of study, as success would add value to the methodology.

The chiral allylic alcohol of choice was synthesised starting from enantiopure (*R*)-citronellal **234*R***. Hydrogenation of the double bond yielded the corresponding saturated aldehyde **235*R*** and Mannich reaction[76] gave the α,β-unsaturated aldehyde, whose *in situ* reduction allowed the synthesis of **236*R*** in 72 % overall yield (**Scheme 2.32**).



Scheme 2.32 Synthesis of (*R*)-3,7-dimethyl-2-methyleneoctan-1-ol **236*R***.

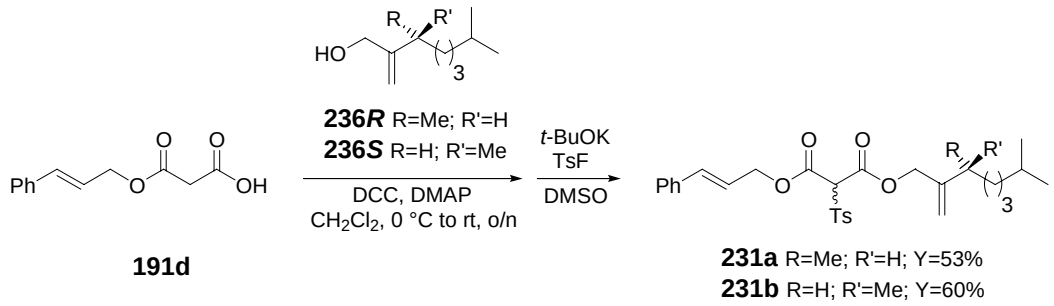
In order to evaluate the enantiomeric excess *en route* to pyridine synthesis, the same sequence was repeated on (*S*)-citronellal and (*S*)-3,7-dimethyl-2-methyleneoctan-1-ol **236*S*** was obtained in 47% overall yield. In order to determine the ee of **236*R*** and **236*S*** the corresponding Mosher's esters were synthesised and their NMR spectra evaluated (**Scheme 2.33**).[77]



Scheme 2.33 Synthesis of Mosher's esters **239*R*** and **239*S***.

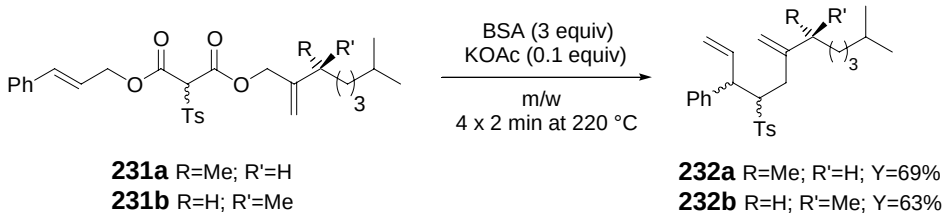
Because the spectra of **239*R*** and **239*S*** overlapped, HPLC analysis of the esters was carried out. This showed that **239*R*** and **239*S*** had been formed in 93% and 97% de respectively, indicating minimum ee values of 93% and 97% respectively for the precursor chiral alcohols **236*R*** and **236*S***. The difference in the ee values was attributed to the different degree of enantiopurity of the commercially available (*R*)- and (*S*)-citronellal starting materials **234**.

Enantiomerically enriched alcohols **236*R*** and **236*S*** were subsequently converted into tosylmalonates following the strategy previously described (see section **2.2.3.1**, **Scheme 2.11**) and compounds **231a** and **231b** were obtained in 41% and 55% yield respectively starting from cinnamyl malonate **191d** (**Scheme 2.34**).



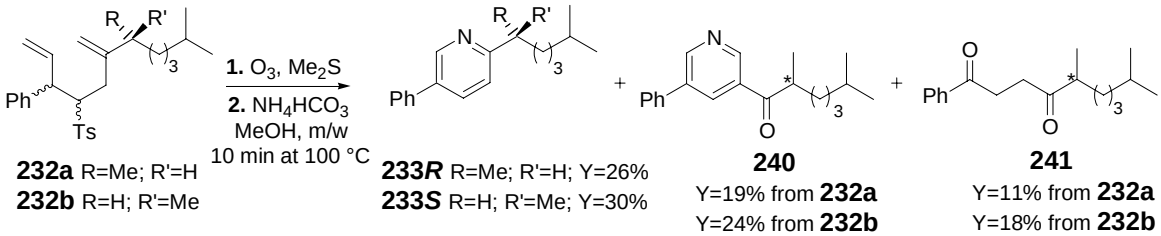
Scheme 2.34 Synthesis of tosylmalonates **231a** and **231b**; each compound was obtained in a 1:1 diastereoisomeric mixture.

Optimisation of the reaction conditions for the dual dCr of **231a** and **231b** allowed the synthesis of the corresponding dienes in 69% and 63% isolated yields respectively (**Scheme 2.35**).



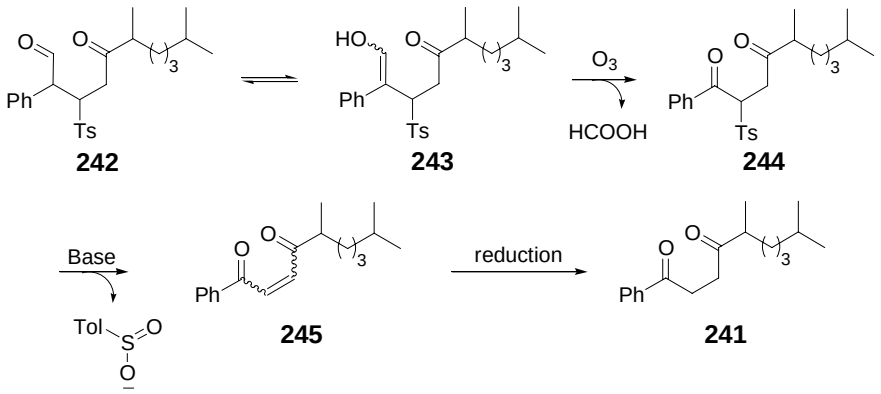
Scheme 2.35 Dual dCr of tosylmalonates **231a** and **231b**.

Transformation of dienes **232a** and **232b** into pyridines was carried out following the procedure previously established (see section **2.2.3.4**). Unexpectedly, for both **232a** and **232b** the desired product **233** could be obtained only in modest yields, varying between 26% and 30%, and by-products **240** and **241** were also isolated (**Scheme 2.36**).



Scheme 2.36 Synthesis of chiral pyridines **233*R*** and **233*S***.

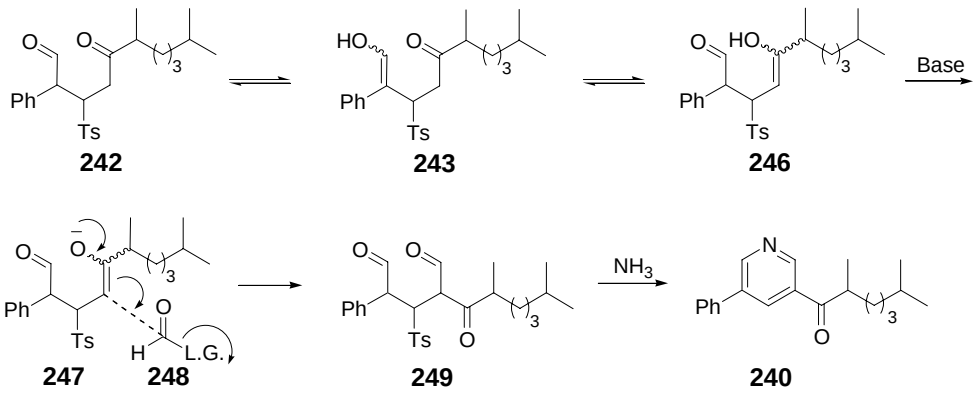
By-product formation was also observed when ammonia in methanol was used[i] as the nitrogen source in the ammonolysis step (see section **2.2.3.4**, **Scheme 2.21**) for the reaction of **232a**. It is conceivable that diketone **241** originates from the fragmentation of the 1,5-dicarbonyl intermediate **242**, the enol of which undergoes ozonolysis to give compound **244** and formic acid.[78,79] Subsequently, base-promoted elimination of *p*-toluenesulfinate affords dione **245**, which is then reduced to product **241**.



Scheme 2.37 Proposed mechanistic pathway for the formation of diketone **241**.

Para-toluenesulfinic acid can be hypothesised to perform the reduction of **245**, as the oxidation state of the sulfur allows it to act as a reducing agent.[80]

A possible mechanism for the formation of **240** is depicted in **Scheme 2.38**



Scheme 2.38 Proposed mechanistic pathway for the formation of pyridine **240**.

[i] Reaction conditions: stirring at rt for 72 h. **233*R*** was formed in 22%, **240** in 15% and **241** in 6% isolated yield respectively.

It is proposed that enol **246**, obtained upon ozonolysis of diene **232**, reacts under basic conditions with a formyl donor to give compound **249**, which in turn undergoes ammonolysis to afford pyridine **240**. The formyl donor might be formic acid, formed as a by-product during the ozonolysis of **243** to give **241**.

Determination of the enantiomeric excess was carried out solely for pyridine **233**. This is because identification of **240** and **241** was possible only at a late stage and no precaution had previously been taken to avoid exposure of the by-products to acid (such as silica gel for chromatography and non-base-washed $CDCl_3$ for NMR analysis). Indeed, this might have caused some degree of racemisation of the stereocentres in **240** and **241**, both of which are α- to a carbonyl group.
Determination of the enantiopurity of pyridines **233** was carried out by HPLC analysis, and revealed a high degree of conservation of the stereocentre throughout the pathway. Product **233*R*** was isolated in 74% ee when both ammonia and ammonium hydrogencarbonate were used as the nitrogen source and **233*S*** in 91% ee. The different level of enantiopurity observed for the two pyridine enantiomers is likely to be associated to the lower ee of **236*R*** compared to that of **236*S***. Amplification effects taking place during tosylation and/or dual dCr reaction can also be postulated. However, as intermediates **231** and **232** were obtained as an inseparable mixture of diastereoisomers, no investigation of these effects could be carried out.

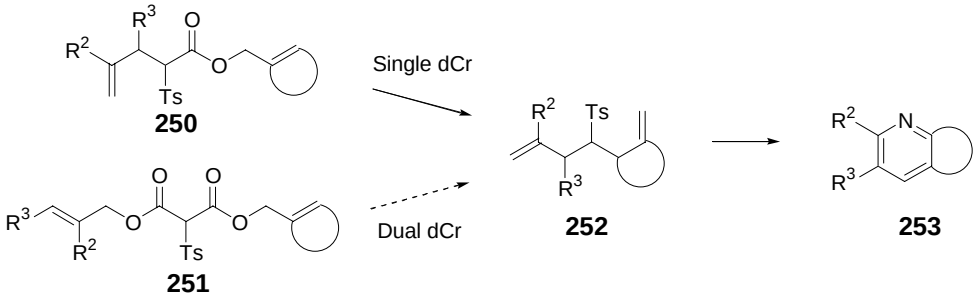
Overall, the methodology developed during this PhD has been shown to allow access to chiral pyridines, albeit in modest yields. Furthermore, the formation of unusual by-products has been observed, and mechanisms for their formation have been proposed.

2.2.4.3 The synthesis of anellated pyridines

It was envisaged that the dCr-based methodology for pyridine synthesis described here could be applied to the synthesis of anellated pyridines. 2,3-Anellated heterocycles can be obtained by incorporation of a cyclic allylic alcohol onto the tosylmalonate, while 3,4-anellated compounds can be accessed by *exo-trig* cyclisation of a modified 1,6-heptadiene.

2.2.4.3.1 2,3-Anellated pyridines

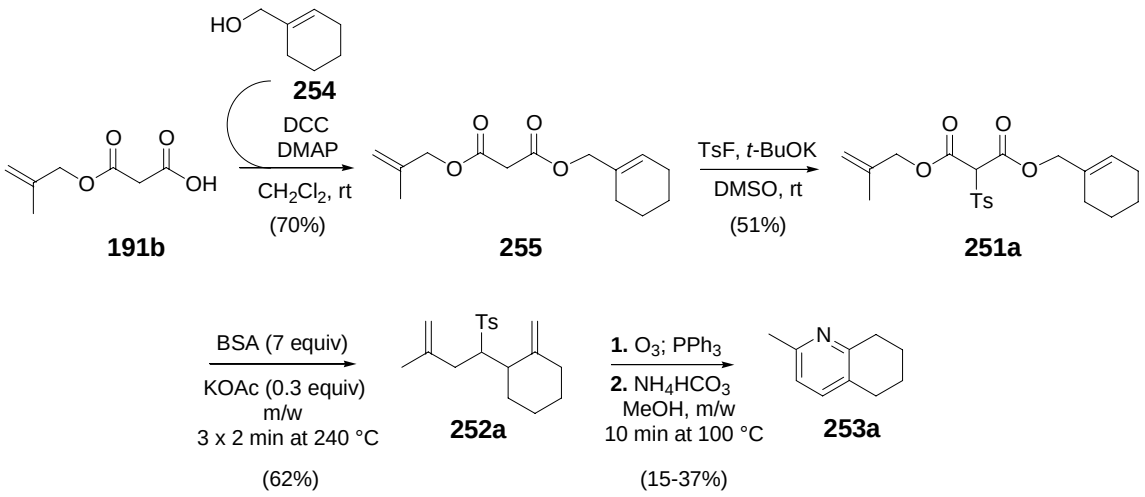
An example of the synthesis of a 2,3-anellated pyridine starting from a 4-tosyl-1,6-heptadiene had already been reported within our group (see section **2.2.2**, **Scheme 2.9**) for the preparation of the natural product cananodine.[19] However, in that case the required cyclic diene was obtained *via* single decarboxylative Claisen rearrangement of a pre-allylated tosylacetate of type **250**. We wanted to demonstrate that 2,3-anellated heterocycles can also be obtained using a dual dCr approach (**Scheme 2.39**).



Scheme 2.39 Synthesis of anellated pyridines *via* dCr chemistry.

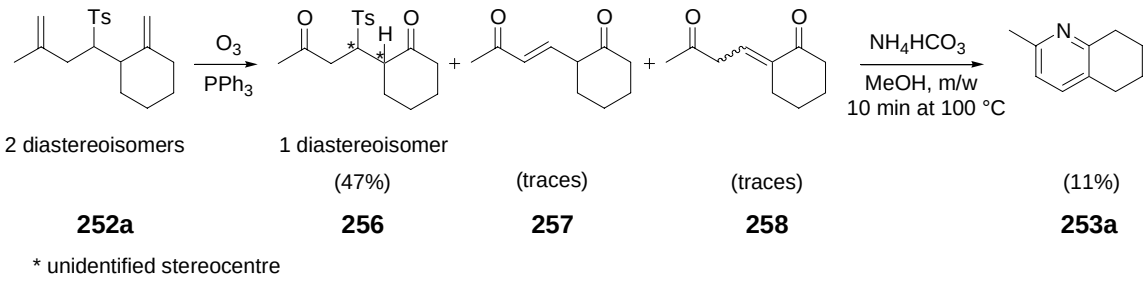
The synthesis of 2-methyl-5,6,7,8-tetrahydroquinoline **253a** was therefore targeted. The previously established synthetic pathway was followed and DCC-mediated condensation of methallyl malonate **191b** with 1-hydroxymethylcyclohexene **254** (obtained in 74% yield from the corresponding acid by $LiAlH_4$-mediated reduction)[81] gave diester **255** in 70% yield. Tosylation of **255** and carefully optimised dCr reaction conditions allowed the synthesis of diene **252a** as a 1:1 diastereoisomeric mixture. Transformation of **252a** into the desired pyridine was straightforward, however the yield was lower than expected and reproducibility problems were encountered. The best

result was obtained when triphenylphosphine was used as the reducing agent in the ozonolysis step (**Scheme 2.40**).



Scheme 2.40 Synthesis of 2-methyl-5,6,7,8-tetrahydroquinoline **253a**.

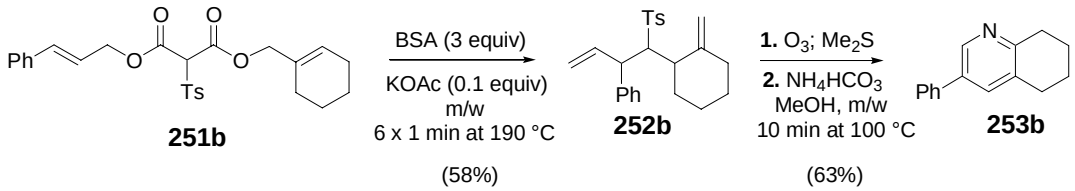
In order to have some insight into the reaction process the formation of the intermediate, diketone **256** and its subsequent transformation into compound **253a** were studied separately (**Scheme 2.41**).



Scheme 2.41 Two-step synthesis of 2-methyl-5,6,7,8-tetrahydroquinoline **253a** starting from diene **252a**.

Interestingly, upon ozonolysis, only one of the two possible diastereoisomers of compound **256** was isolated by column chromatography. In addition, traces of elimination products **257** and **258** could be detected by ^{1}H NMR analysis of the tosyl diketone-containing sample.[j] Compound **256** (contaminated with products **257** and **258**) was then subjected to pyridine-forming reaction conditions. However the desired heterocycle could only be isolated in 11% yield. Bearing in mind that pyridine **253a** has been obtained in variable yields and considering these last results, it is suggested that the reason for the inefficiency of the pyridine-formation reaction is two-fold. Firstly, ozonolysis of diene **252a** seems to be ineffective, as only one of the two possible diastereoisomeric tosyldiones **256** was isolated and the products of sulfinate elimination were observed. Secondly, the boiling point of tetrahydroquinoline **253a** is reported to be 63–65 °C at 0.2 torr.[82] Pyridine-forming reactions are typically carried out on a 100-200 mg scale of starting material, and therefore in this case some product might have been lost while removing the solvent by using a high vacuum pump.

To support the latter hypothesis, the synthesis of 3-phenyl-5,6,7,8-tetrahydroquinoline **253b**, which has a higher boiling point, was undertaken (**Scheme 2.42**).



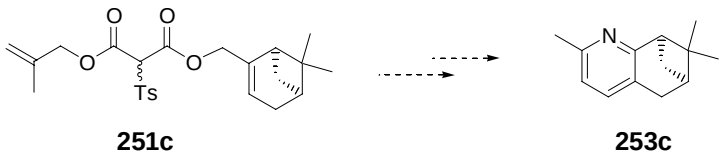
Scheme 2.42 Synthesis of 3-phenyl-5,6,7,8-tetrahydroquinoline **253b**.

Tosylmalonate **251b** (obtained in 69% overall yield starting from cinnamyl malonate) was converted into a mixture of all the possible diastereoisomers of diene **252b** by use

[j] Characteristic ^{1}H NMR signals for enone **257** are: δ_H ($CDCl_3$, 400 MHz) 7.49 (1H, dd, *J* 16.5, 7.0 Hz, C*H*=CHCO), 6.01 (1H, dq, *J* 16.5, 1.0 Hz, CH=C*H*CO). Characteristic ^{1}H NMR signal for the *trans*-stereoisomer of enone **258** is: δ_H ($CDCl_3$, 400 MHz) 6.73 (1H, tt, *J* 7.5, 2.5 Hz, =C*H*CH_2). Characteristic ^{1}H NMR signal for the *cis*-stereoisomer of enone **258** is: δ_H ($CDCl_3$, 400 MHz) 5.89 (1H, tt, *J* 7.0, 2.0 Hz, =C*H*CH_2).

of a sequence of microwave pulses at 190 °C and, as expected, synthesis of compound **253b** was achieved in 63% yield.

Having established the applicability of the methodology for the synthesis of anellated pyridines, our attention then turned towards obtaining more interesting tricyclic structures such as the pinene-derived pyridine **253c**.

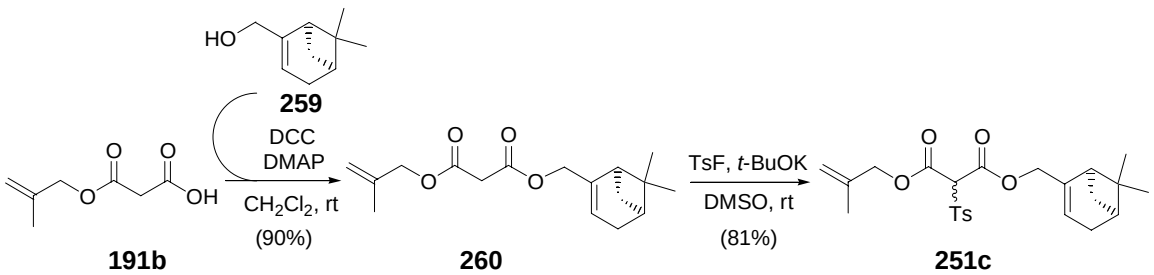


251c **253c**

Scheme 2.43 Proposed synthesis of tricyclic pinene-derived pyridine **253c**.

The interest in compound **253c** resides in its structural similarity with a novel bipyridine ligand (PINDY), recently developed by by Kočovský and co-workers, whose copper complex exhibits attractive properties in asymmetric allylic oxidation.[83-85]

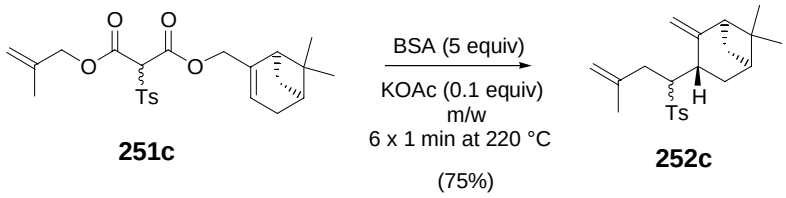
The synthesis of **253c** had already been attempted within our group using a mono-dCr approach without any success.[86] Having in hand an improved methodology which had so far been successful in the synthesis of variously substituted pyridines, the synthetic challenge of accessing pyridine **253c** was once more addressed. The required tosylmalonate **251c** was synthesised as a 1:1 mixture of diastereoisomers in 73% overall yield starting from methallyl malonate **191b** (**Scheme 2.44**).



191b **260** **251c**

Scheme 2.44 Synthesis of tosylmalonate **251c**.

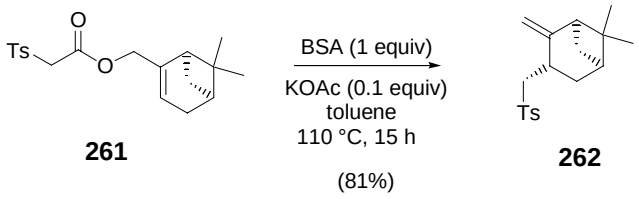
After optimisation, the double rearrangement of **251c** was achieved in 75% yield by six one-minute cycles of microwave irradiation at 220 °C (**Scheme 2.45**).



251c **252c**

Scheme 2.45 Dual dCr of myrtenyl tosylmalonate **251c**.

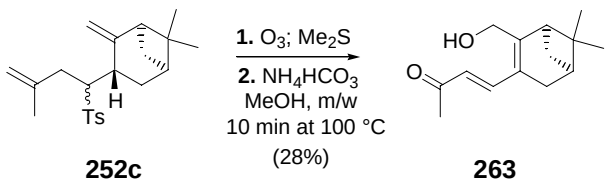
This is the only case encountered in the course of this thesis where only two of the four possible diastereoisomers are formed upon dual dCr of a tosylmalonate. Complete stereocontrol was observed with regard to C-3 of the bicycle, with the sulfonyl moiety being delivered *anti* with respect to the more hindered face of the allylic double bond. Assignment of the stereochemistry at C-3 was possible by comparison of this result with a previously obtained one, where mono-rearrangement of tosylacetate **261** gave a single diastereoisomer of sulfone **262** (**Scheme 2.46**). In that case, X-ray crystallography of **262** allowed establishing unambiguously the stereochemistry of the product.[5]



261 **262**

Scheme 2.46 Single dCr of (-)-myrtenyl tosylacetate **261**.

Transformation of diene **262c** into the pyridine was then attempted but failed to yield the desired heterocyclic product. Instead, enone **263** was isolated in 28% yield (**Scheme 2.47**).

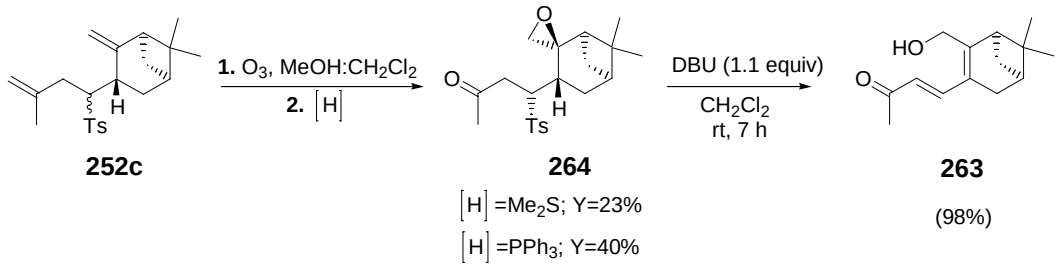


252c **263**

Scheme 2.47 One-pot synthesis of bicyclic enone **263**.

This surprising result could be explained when the ozonolysis and the ammonolysis steps were carried out separately. Indeed, upon treatment of **252c** with ozone, only the

double bond on the tosylbutenyl chain was cleaved, while the exocyclic alkene underwent epoxidation (**Scheme 2.48**).



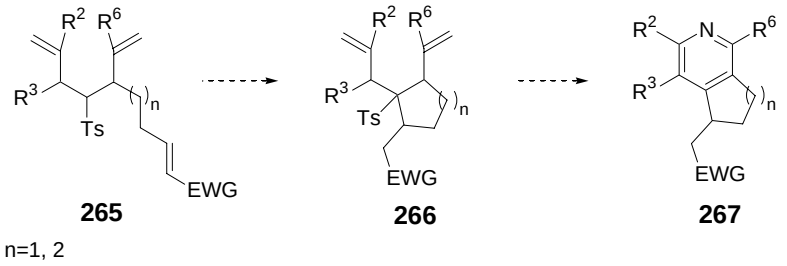
Scheme 2.48 Two steps synthesis of bicyclic enone **263**.

Ketoepoxide **264** was formed in 23% yield when dimethylsulfide was used as the reducing agent in the ozonolysis step and in 40% yield when PPh_3 was employed. X-Ray crystallographic analysis allowed unequivocal assignment of the stereochemistry of **264**, thus indicating that only one of the two diastereosiomeric starting materials underwent selective epoxidation–ozonolysis. No product of transformation of the other diastereoisomer was isolated, the rest of the reaction mixture being composed of unidentifiable decomposition products. Exposure of **264** to one equivalent of DBU effected its complete conversion into compound **263**, thus explaining the impossibility of forming the desired tricyclic pyridine **253c**.

Steric hindrance might be responsible of the unexpected outcome of the ozonolysis reaction for the exocyclic double bond of **252c**. Indeed, epoxidation of hindered olefins upon treatment with ozone is a precedented process.[87-90]

2.2.4.3.2 3,4-Anellated pyridines

It was envisaged that the synthesis of 3,4-anellated pyridines could be achieved by cyclisation of a substituted 1,6-heptadiene carrying a Michael acceptor in a suitable position within one of its substituents (**Scheme 2.49**).

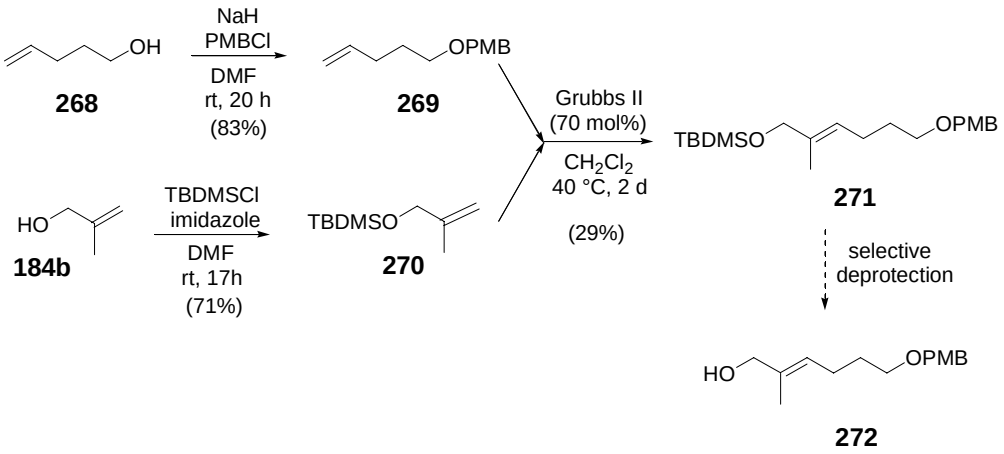


Scheme 2.49 Proposed synthesis of 3,4-anellated pyridines.

According to Baldwin's rules,[91] both 5- and 6-*exo-trig* cyclisations are favoured processes. Because base-catalysed 5-*exo-trig* cyclisation of a sulfone, albeit α- to a ketone, onto an acrylate ester is precedented,[92] the synthesis of cyclopentane-fused pyridine **267a** (where n=1, R^2=H, R^3=Ph, EWG=COOMe and R^6=Me) was targeted to establish the feasibility of the reaction sequence.

Cyclisation precursor **265a** was accessed by modification of a diene obtained upon dual dCr of the appropriate tosylmalonate. Firstly, the synthesis of a modified allylic alcohol to be incorporated into the tosylmalonic diester was necessary.

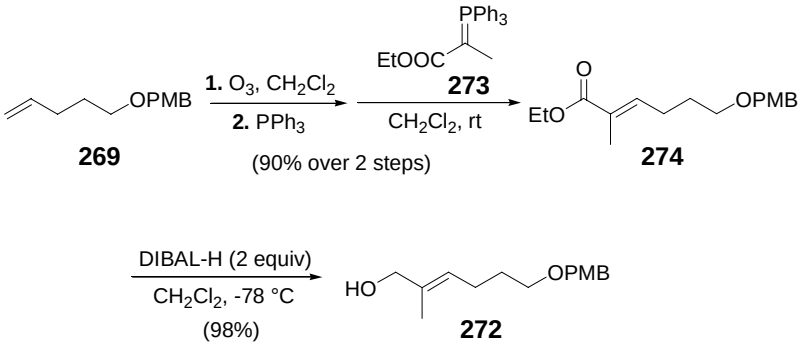
The successful synthetic strategy for the synthesis of the required allylic alcohol **272** was developed after obtaining unsatisfactory results from a more convergent approach involving the use of olefin cross metathesis (CM)[39,93] for the formation of the tri-substituted double bond (**Scheme 2.50**).



Scheme 2.50 Initial synthetic pathway for the synthesis of (*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-en-1-ol **272**.

The cross metathesis partners **269** and **270** were synthesised in good yield by protection of the corresponding alcohols.[94-98] Their cross metathesis reaction was expected to be straightforward, as Grubbs had reported diastereoselective and high-yielding reactions of analogous substrates.[99] However, in our hands combination of **269** and **270** mediated by the Grubbs II catalyst was found to be problematic. Even when high catalyst loading and long reaction times were employed, the desired fully protected diol **271** could be isolated only in 29% yield, and in an impure form.

A second route to **272** was therefore studied. This allowed the synthesis of the desired monoprotected diol in 88% overall yield starting from 1-(4-methoxybenzyloxy)pent-4-ene **269** (**Scheme 2.51**).

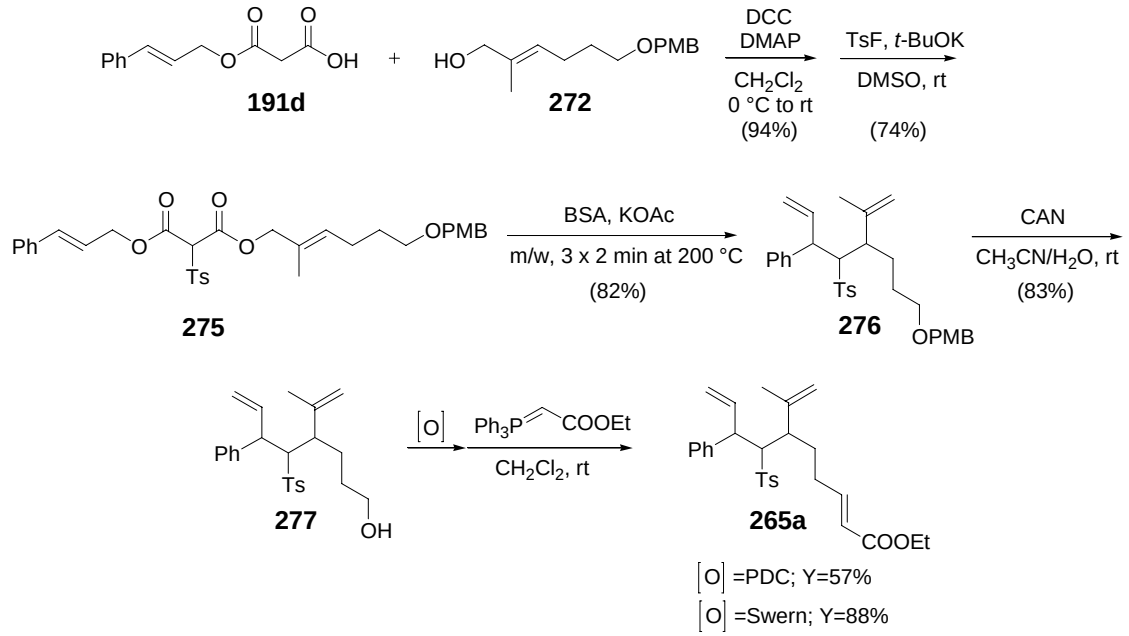


Scheme 2.51 Synthesis of (*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-en-1-ol **272**.

Ozonolysis of PMB-protected pentenol **269** followed by *in situ* Wittig reaction of the newly formed aldehyde, gave α,β-unsaturated ester **274**, which was reduced to the corresponding allylic alcohol **272** in 98% yield.

Since the PMB protecting group is in some instances reported to be labile under ozonolytic cleavage conditions,[100,101] ozonolysis of **269** was carried out carefully, by ensuring that the temperature did not exceed –78 °C and by avoiding exposure of the reaction mixture to an excess of ozone. In addition, freshly prepared rather than commercial phosphorane **273** was employed, as it resulted in an improved overall yield of **274**.

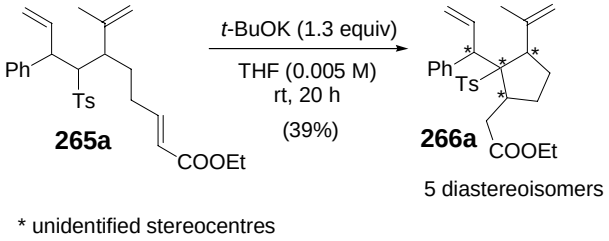
Allylic alcohol **272** was then coupled with cinnamyl malonate **191d**, and the resulting diester was tosylated to give the rearrangement substrate **275** (**Scheme 2.52**).



Scheme 2.52 Synthesis of cyclisation precursor **265a**.

Tosylmalonate **275** was subjected to three cycles of microwave irradiation of two minutes each to obtain 1,6-heptadiene **276** in 82% yield, as a chromatographically inseparable mixture of four diastereoisomers. Deprotection of the *para*-methoxybenzyl group gave alcohol **277** in 83% yield, and an optimised one-pot Swern–Wittig procedure allowed the synthesis of target compound **265a** in high yield.

Having obtained **265a** in a satisfactory yield, its cyclisation was investigated. Numerous reaction conditions were attempted, by varying the temperature and time of reaction as well as the base and solvent used. The best yield of **266a** was obtained by room temperature treatment of a very dilute THF solution of the diastereoisomeric mixture of **265a** with a slight excess of potassium *tert*-butoxide. The desired cyclopentane **266a** was isolated as a mixture of five of the eight possible diastereoisomers in 39% yield (**Scheme 2.53**).

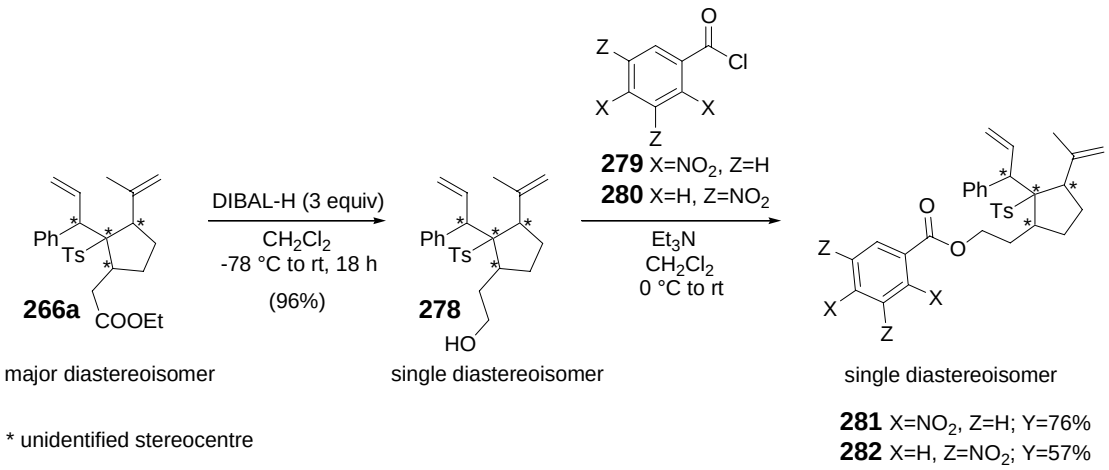


Scheme 2.53 Synthesis of cyclopentane **266a**.

The key features of this reaction are the nature and amount of base used and the concentration. Potassium *tert*-butoxide was the only base found to effect cyclisation amongst the ones screened (which include NaH,[92] LHMDS and LDA). Furthermore, although in principle the reaction could be catalytic in base, the use of a stoichiometric amount was necessary as virtually no reaction was observed otherwise. High dilution was also found to be of paramount importance as much lower yields of **266a** (5-10%) were isolated when the transformation was carried out at higher concentrations (0.1-0.2 M).

Only five diastereoisomers of **266a** were isolated one of which predominated. Chromatographic separation was found to be very challenging, and only the major diastereoisomer could be partially separated from the others. Careful ^{1}H NMR analysis showed that 64% of **266a** was composed of one diastereoisomer while the diastereoisomeric ratio of the others could not be identified due to overlapping signals.

The identification of the relative configuration of the adjacent stereocentres in the major diastereoisomer of **266a** was attempted. A sample of the major diastereoisomer of **266a**[k] was subjected to reduction and esterification with dinitrobenzoyl chlorides **279** and **280**. The aim was to obtain crystalline products, suitable for X-ray analysis (**Scheme 2.54**).

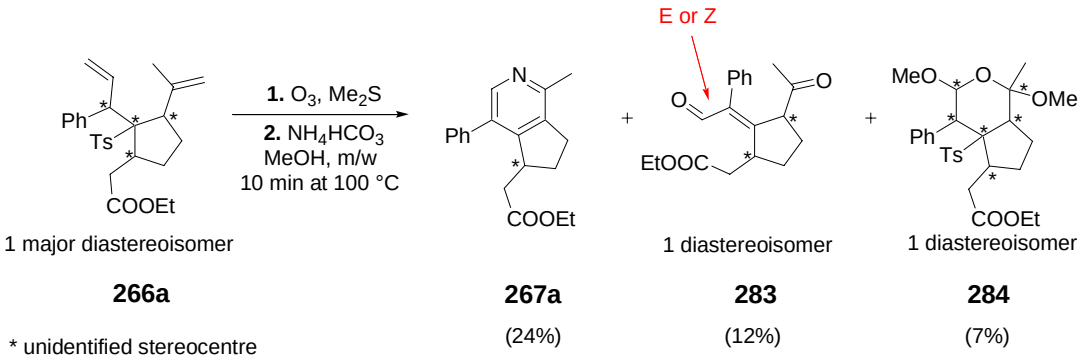


Scheme 2.54 Synthesis of dinitrobenzoyl esters **281** and **282**.

Unfortunately both **281** and **282** were obtained as white foams. Attempts to grow X-ray quality crystals were unsuccessful, and therefore determination of the stereochemistry of the major isomer of **266a** was not possible.

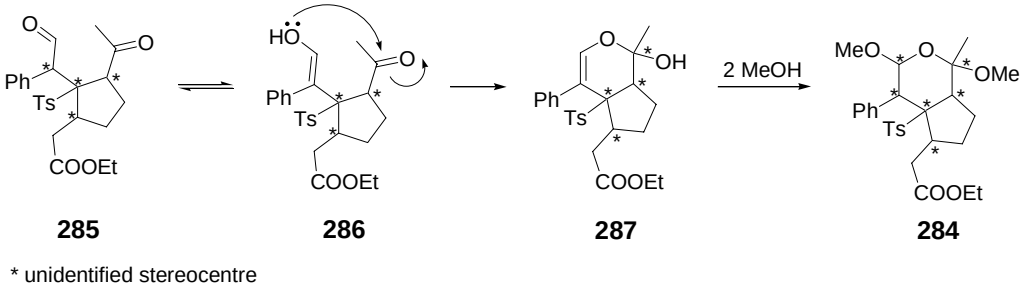
Formation of pyridine **267a** remained to be studied. A diastereoisomeric mixture of **266a**, composed mainly of its major diastereoisomer, was subjected to the general pyridine-forming procedure described above. The desired heterocycle **267a** was formed in 24% yield (**Scheme 2.55**).

[k] Isolation of the major cyclised diene **266a** as a single isomer was very difficult to achieve. Therefore the reduction–esterification sequence described here was carried out on samples having a diastereoisomeric purity greater than or equal to 72%.



Scheme 2.55 Synthesis of 2,3-anellated pyridine **267a**.

Additionally, ketoaldehyde **283** and a tetrahydropyrane **284** were formed alongside the desired pyridine in 12% and 7% yield respectively. Compound **283** is likely to be derived from the elimination of *p*-toluenesulfinate from one of the intermediate ketoaldehydes formed in the ozonolysis step. NOe analysis of **283** was attempted in order to determine the stereochemistry of the carbon-carbon double bond, but it was not conclusive. Tetrahydropyran **284** is believed also to arise from one of the ketoaldehydes obtained upon ozonolysis. In this case cyclisation, followed by incorporation of two molecules of methanol is proposed as a mechanistic rationale (**Scheme 2.56**). Stable cyclic intermediates such as **287** has been previously observed within the group (see section **2.2.3.4**, **Scheme 2.21**).[11]



Scheme 2.56 Proposed mechanism of formation for tetrahydropyrane **284**.

Remarkably, both compounds **283** and **284** were isolated as a single diastereoisomer, suggesting that only some configurations of compound **266a** can undergo the ozonolysis–ammonolysis sequence to give pyridines, while others follow different pathways after ozonolytic cleavage.

2.2.4.4 Conclusions

With the aim of expanding the scope of the methodology for pyridine synthesis developed in the course of this PhD, the synthesis of chlorine-, carbomethoxy-, trimethylsilyl-substituted, chiral and anellated heterocycles was undertaken.

While the synthesis of pyridines carrying substituents other than alkyl and aryl directly attached to the ring failed at an early stage, the synthesis of chiral and anellated compounds was achieved. In almost all cases however, the target molecules were obtained in modest yields due to the formation of unexpected side-products. Nevertheless, interesting decomposition pathways were disclosed and the versatility of the methodology demonstrated.

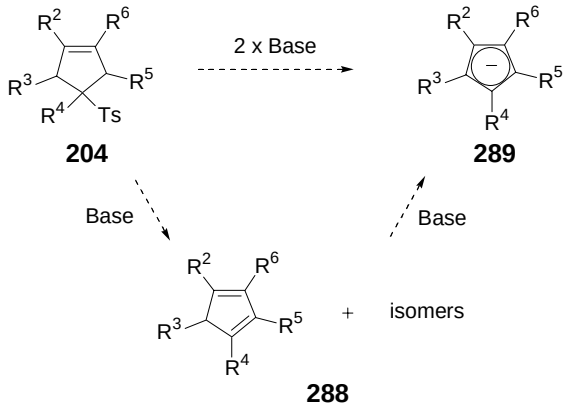
2.3 The dCr based methodology for the *de novo* synthesis of cyclopentadienes and cyclopentadienyl anions

2.3.1 Introduction

Cyclopentadienes are useful building blocks in organic and inorganic synthesis, which are most widely used either as 4π-systems in Diels–Alder cycloadditions[102,103] or in their anionic form, as aromatic ligands for transition metals.[104-106]

Since few general methodologies are available for the *de novo* synthesis of these 5-membered carbocyclic rings (see chapter **1**), we wanted to develop a novel approach to their synthesis based on the decarboxylative Claisen rearrangement chemistry.

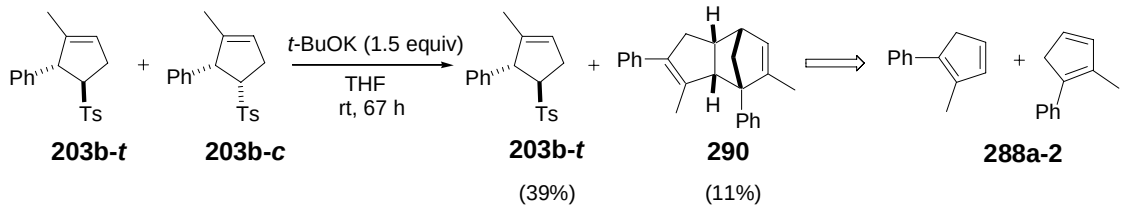
During the course of the development of the dCr-mediated pyridine synthesis methodology, some 4-tosylcyclopentenes **204** were synthesised (see section **2.2.3.3.2**). If the elimination of sulfinate from such compounds could be triggered, the decarboxylative Claisen rearrangement reaction could also be employed for the synthesis of cyclopentadienes **288** and cyclopentadienyl anions **289** (**Scheme 2.57**).



Scheme 2.57 Proposed synthesis of cyclopentadienes and cyclopentadienyl anions starting from 4-tosylcyclopentenes **204**.

2.3.2 An encouraging preliminary result

During the study of the alkylation of cyclopentenes **203b** (see section **2.2.3.3.2**), a serendipitous discovery was made. Multi-gram quantities of 1-methyl-4-tosyl-5-phenylcyclopent-1-ene **203b-*t*** were required, and therefore ring closing metathesis of the corresponding diene was performed on a large scale. This reaction gives rise to an equimolecular mixture of diastereoisomers **203b-*c*** and **203b-*t***, but it was found that the *cis*-compound can be transformed into the thermodynamically more stable *trans*-product by exposure to potassium *tert*-butoxide (see **Scheme 2.20**). Hence, a mixture of **203b-*c*** and **203b-*t*** was subjected to the reaction conditions that previously had allowed quantitative conversion of a pure sample of **203b-*c*** into **203b-*t***. In this instance however, the experimental procedure was slightly modified, in that a moderate excess of base was used and the reaction was run at room temperature for 67 h rather than for 45 minutes. Nevertheless a high yield of the *trans*-cyclopentene **203b-*t*** was expected. Instead of the expected efficient epimerisation, *trans*-cyclopentene **203b-*t*** was obtained in only 39% yield alongside cyclopentadiene dimer **290**, which was isolated in 11% yield (**Scheme 2.58**).



Scheme 2.58 Unexpected synthesis of cyclopentadienes dimer **290**.

The identity of tricycle **290** was established by detailed NMR analysis, supported by mass spectrometric and infrared spectroscopic evidences. Initial examination of the ^{1}H and ^{13}C NMR spectra revealed the absence of the tosyl group. Moreover, the molecular peak for **290** was observed in the CI mass spectrum, suggesting the formation of a cyclopentadiene dimer. The detection of a single olefinic proton in the ^{1}H NMR spectrum clearly indicated the existence of one tetra-substituted and one tri-substituted double bond. However, determination of the stereochemistry and regiochemistry of **290** required more careful analysis. In particular, the formation of the expected *endo*-diastereoisomer[107-109] was confirmed by the presence of a nOe interaction between CH-2 and one of the C-10 methylene protons. In addition, the construction of a ball-and-stick model suggested that a coupling constant between CH-6 and CH-7 would only be observed if **290** were an *endo*-cycloadduct, as otherwise a dihedral angle of 90° would exist between the two C-H bonds. Significant in determining the regiochemistry of **290** were the nOe interactions observed for the *ortho*-protons of the two phenyl rings. The *ortho*-protons of the C-1 phenyl group were found to interact with both CH_3-3 and CH_3-9, while correlation with CH_3-3 and CH_2-5 was observed for phenyl-4 (see **Figure 2.3**).

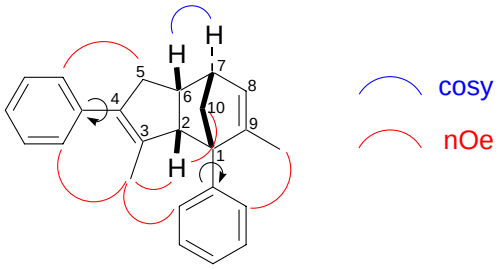
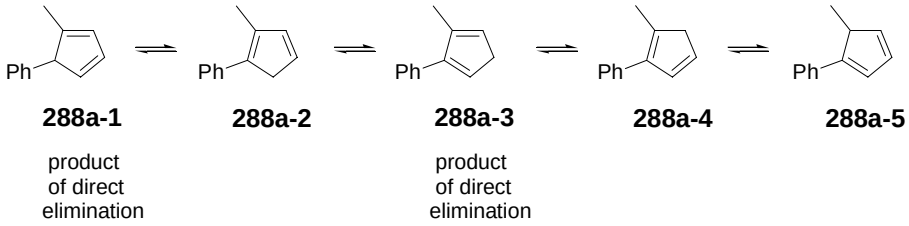


Figure 2.3 The interactions observed on the cosy and nOesy spectra allowed the determination of the stereochemistry and regiochemistry of cyclopentadiene dimer **290**.

It is remarkable that only one of the numerous possible Diels-Alder adducts was isolated. The sole product is that derived from the reaction of cyclopentadiene **288a-2**

with itself. Cyclopentadiene **288a-2** is not derived from direct elimination of sulfinate from the cyclopentene starting material. Instead it is formed *via* [1,5]-sigmatropic hydrogen shifts taking place on **288a-1** and/or on **288a-3** (**Scheme 2.59**).



Scheme 2.59 The five possible isomers of cyclopentadiene **288a**.

Isomers **288a-2** and **288a-4** are the only two bearing a tetra-substituted double bond and because of their greater thermodynamic stability they can be plausibly hypothesised to be the major species present that at the equilibrium. It can be speculated that preferential reaction of **288a-2** over **288a-4** with maleic anhydride is associated with a significant difference in the free energy of the transition state for the two cycloadditions.[110] However, further synthetic data and computational studies would be needed in order to propose a plausible theory on the observed selectivity of the reaction.

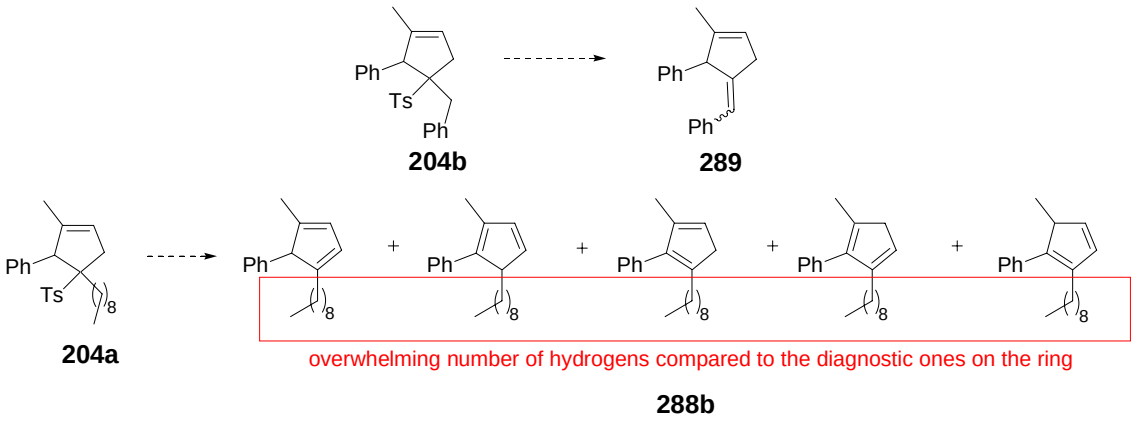
This encouraging preliminary result suggested that the *de novo* synthesis of cyclopentadienes *via* a dCr based methodology might be feasible. A systematic study of this subject was commenced and will be discussed in the following section.

2.3.3 The synthesis of cyclopentadienes and cyclopentadienyl anions starting from alkylated 4-tosylcyclopentenes

In order to investigate the formation of cyclopentadienes from the corresponding tosylcyclopentenes, the synthesis of an appropriate starting material was necessary. It was decided to initially study the behaviour of substrates substituted α- to the sulfone, as they bear the most acidic carbon β- to the leaving group.

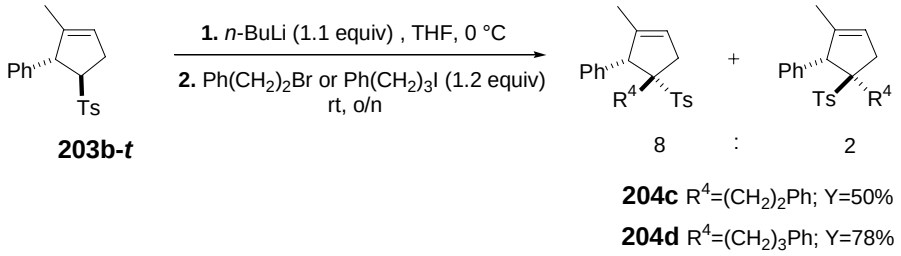
4-Substituted cyclopentenes **204a** and **204b**, previously synthesised to study their transformation into pyridines (see section **2.2.3.3.2**), were not considered suitable. Indeed, whilst **204b** could undergo β-elimination of *p*-toluenesulfinate by deprotonation at the acyclic benzyl position, the long aliphatic side-chain of **204a** might complicate

NMR analysis of the elimination product, as five cyclopentadiene isomers are viable (**Scheme 2.60**).



Scheme 2.60 Potential problems associated with the transformation of **204a** and **204b** into cyclopentadienes.

Synthesis of phenylethyl-substituted cylopentene **204c** was therefore undertaken but was found to be low-yielding, as under basic conditions β-elimination of HBr from 2-phenylbromoethane might occur. In addition, chromatographic separation of the two diastereoisomeric products was difficult. Therefore, compound **204d**, carrying an extra carbon on the 4-substituent, was targeted and its synthesis achieved in 78% overall yield (**Scheme 2.61**).



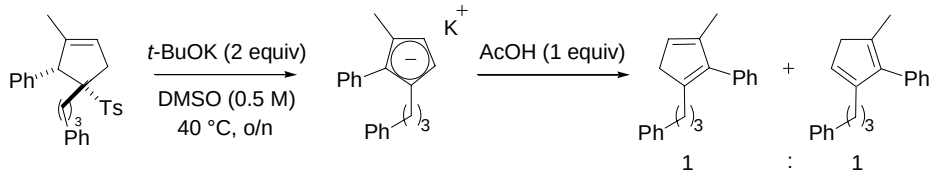
Scheme 2.61 Synthesis of alkylated cyclopentenes **204c** and **204d**.

Chromatographic separation of the *cis*- and *trans*-diastereoisomers of **204d** was feasible, and therefore their individual behaviour towards elimination could be tested.

Elimination of tolylsulfinate to form acyclic C=C bonds is a known process and has been applied to the synthesis of various alkenes,[111-114] amongst which are vitamin A[115] and building blocks for carotenoids.[116] A number of bases, including sodium amide,[115]

potassium *tert*-butoxide,[113,114] potassium trimethylsilanoate[113] and sodium ethoxide[116] have been used to achieve olefin formation. Herein, the study of the transformation of cyclopentenes into cyclopentadienes started with the examination of the reaction of **204d-*c*** (major diastereoisomer) with one equivalent of potassium *tert*-butoxide in THF at room temperature, since under these conditions formation of cyclopentadiene dimer **290** had been observed previously. However, no reaction was detected. Higher temperatures and the use of DMSO as the solvent[114] did not result in any improvement.

A breakthrough was achieved when the starting material was treated with two equivalents of base, allowing direct formation of the aromatic anion. *In situ* acidic quench of the cyclopentadienide provided the desired cyclopentadiene products in good yield (**Scheme 2.62**).



204d-*c* **289a** **288c**; Y=70%, SM=21%

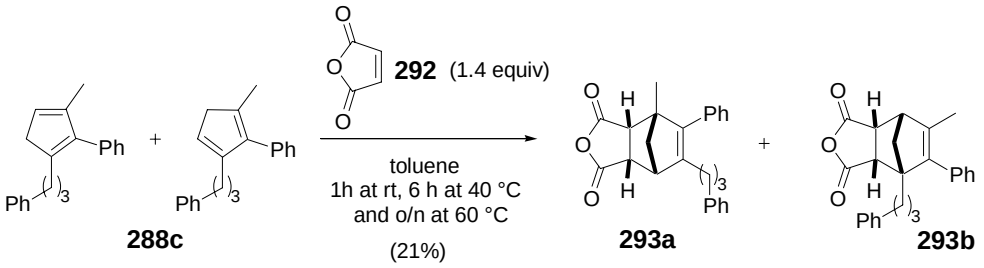
Scheme 2.62 Thermal synthesis of cyclopentadienes **288c**.

Two of the five possible cyclopentadiene isomers were isolated as a 1:1 mixture. As before (see section **2.3.2**, **Scheme 2.58**), the isomers formed were those having the double bonds with the highest degree of substitution possible. Moreover, no dimerisation of the products was observed.

Unfortunately, when cyclopentadiene formation was attempted starting from **204d-*t***, the desired products **288c** were isolated in an impure form. The same was observed for the reaction of a diastereoisomeric mixture of **204d**. Nevertheless, the transformation worked well when carried out on the major diastereoisomer of starting material.

Finally, optimisation of the successful reaction conditions allowed quantitative synthesis of **288c** starting from **204d-*c*** when microwave irradiation was used instead of conventional heating.

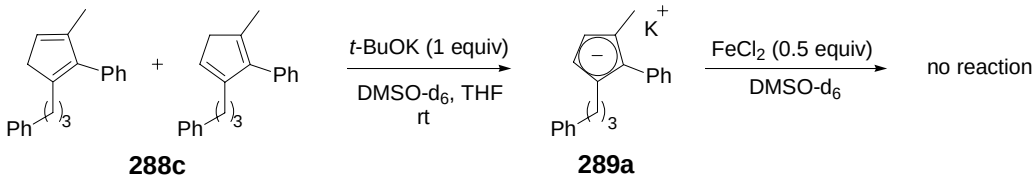
Subsequently, a mixture of cyclopentadienes **288c** was reacted with maleic anhydride (**Scheme 2.63**).



Scheme 2.63 Synthesis of Diels–Alder adducts **293a** and **293b**.

Diels–Alder adducts **293a** and **293b** were formed as expected, although they could be isolated in only 21% yield. Considering that the ^{1}H NMR spectrum of the crude reaction mixture had shown **293a** and **293b** to be the only species present, product decomposition during purification was hypothesised; hydrolysis of the anhydride groups on silica gel would give rise to bicyclic diacids, which likely would be retained by the stationary phase.

Furthermore, an attempt to complex the anion of **288c** with iron(II) was carried out on an NMR scale. Firstly, a solution of dienes **288c** in DMSO-d_6 was treated with one equivalent of potassium *tert*-butoxide in THF (**Scheme 2.64**).



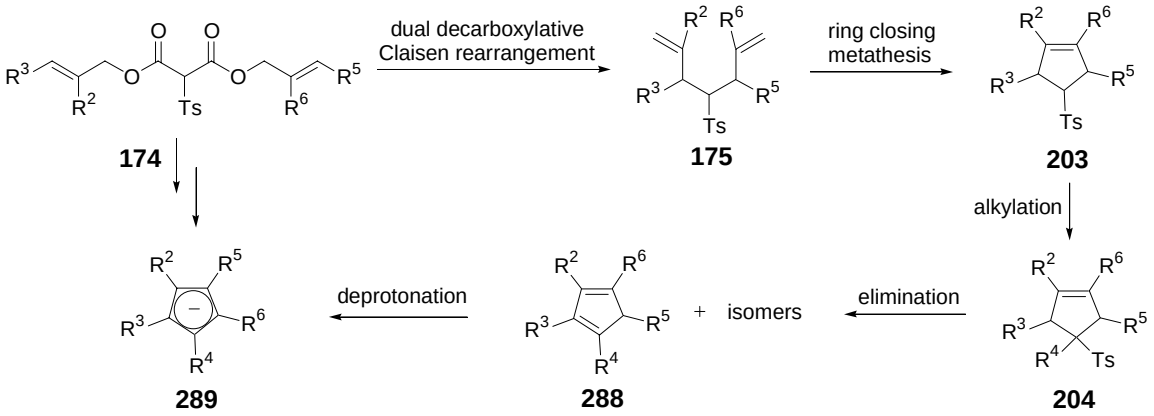
Scheme 2.64 Attempted complexation of **289a** with $FeCl_2$.

Immediate change of colour signalled deprotonation, whose occurrence was confirmed by ^{1}H NMR analysis of the reaction mixture (see **Appendix**). Although full assignment of the peaks was hampered by the presence of the THF and *tert*-butyl signals, formation of a single aromatic compound was observed. Particularly indicative was the presence of two doublets, coupled to each other, at *ca.* 5.2 ppm, which replaced the quartet and triplet of the starting materials at *ca.* 6 ppm.

Ferrocene synthesis was attempted by addition of a solution of iron dichloride in DMSO-d_6 to the previously formed anion, but no product formation was observed.
Nevertheless, it is the opinion of this author that further experimentation will succeed in achieving the synthesis of metallocenes from cyclopentadienes obtained by the presently described methodology.

2.3.4 Conclusions and future perspectives

Further research efforts have succeeded in proving that a methodology based on a tandem decarboxylative Claisen rearrangement–ring closing metathesis approach can be used for the *de novo* synthesis of cyclopentadienes and cyclopentadienyl anions (**Scheme 2.65**).



Scheme 2.65 General scheme for the synthesis of cyclopentadienyl anions *via* a tandem dCr–RCM approach.

This discovery will be the subject of further study in the Craig group, as numerous aspects of this chemistry remain to be investigated. For instance, the studies of the possible substitution patterns and of functional group tolerance will be addressed. Applications of this chemistry will also be sought, in particular concerning the synthesis of metallocenes with interesting properties and applications.[106]

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CHAPTER 3

Experimental

3.2 General Experimental

Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 5000 FTIR spectrometer and on a Perkin-Elmer Spectrum RX FT-IR System. Proton magnetic resonance (^{1}H NMR), carbon magnetic resonance (^{13}C NMR) and fluorine magnetic resonance (^{19}F NMR) spectra were recorded in $CDCl_3$ unless otherwise stated on a Jeol GSX-270, a Brüker DRX-300, a Brüker AV-400, a Brüker AV-500, an Inova 400 Varian or an Inova AS 400 spectrometer. Chemical shifts are in part per million (ppm) and are referenced relative to the residual proton-containing solvent (^{1}H NMR: 7.26 ppm for $CDCl_3$; ^{13}C NMR: 77.0 ppm for $CDCl_3$). Where proton magnetic resonance (^{1}H NMR) was used to determine yields, peak integrals gave molar ratios from which yields could be estimated when the molecular weights were known. Mass spectra (CI, ESI) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Elemental analyses were performed at the microanalytical laboratory of the London Metropolitan University. Optical rotations were measured on an Optical Activity Ltd instrument. Chiral HPLC was performed on an Agilent/HP 1100 Series HPLC system. Analytical thin layer chromatography (TLC) was performed on precoated aluminium-backed Merck Kiesegel 60 F_{254} plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as appropriate. Flash chromatography was performed using BDH (40-63 μm) silica gel unless otherwise stated. Fraction Lynx purification refers to purification by mass directed preparative HPLC using a mixed trigger of UV with ES+ on a Waters Fraction Lynx system. Standard solvents were distilled under nitrogen prior to use; Et_2O, THF and toluene from sodium-benzophenone ketyl, DMSO and CH_2Cl_2 from CaH_2. Benzene was supplied by Fluka, >99.5% pure, over molecular sieves (<0.005% H_2O). All other solvents were reagent-grade. Petrol refers to the fraction with bp_{760} 40–60 °C. All liquid reagents except HCl and Me_2S were distilled prior to use. KOAc was oven-dried at 120 °C for several days prior to use. Grignard reagents[1] and *n*-BuLi[2] were titrated before use. All other reagents were purchased from Aldrich, Fluka, Acros, Alfa Aesar Lancaster and used as such unless otherwise stated. Microwave reactions were performed in a Biotage Initiator. Ozonolyses were performed with an Ozonia Triogen LAB2B.

3.2 General Procedures

3.2.1 General procedure for the preparation of malonic acid monoesters 191 and 222[3]

A mixture of Meldrum's acid (1 equiv) and alcohols (1 equiv) neat or in toluene (c ~ 2 M) was heated at the boiling point of the alcohol or at 90 °C under nitrogen overnight. The solution was then cooled to rt and the residual acetone was evaporated under reduced pressure to give malonic acid monoester **191a**–**d** and **222**.

3.2.2 General procedure for the preparation of allylic alcohols 188[4]

To a stirred mixture of 2-butyn-1-ol (1 equiv) and CuI (0.1 equiv) in benzene at rt and under nitrogen was added over 30 min a commercial solution of the appropriate Grignard reagent (~ 2.5-3.0 equiv) in THF. The reaction mixture was heated at 50 °C overnight and then cooled to 0 °C and carefully quenched with aqueous NH_4Cl (saturated solution). The mixture was acidified to pH 3 by addition of concentrated HCl to dissolve the black magnesium salts and then extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated to give alcohols **188a**,**b**.

3.2.3 General procedure for the preparation of malonates 192, 223, 255, 260 and 295–299

To a solution of malonic acid monoesters **191a**–**d** and **222** (1 equiv) and allylic alcohols (1 equiv) in CH_2Cl_2 (c ~ 0.1–0.2 M) at 0 °C and under nitrogen, were added DMAP (0.1 equiv) and DCC (1.1 equiv). The reaction was allowed to warm to rt overnight and the precipitate was filtered through celite. The filtrate was washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography gave malonates **192a**–**f**, **223a**–**c**, **255**, **260** and **295**–**299**.

3.2.4 General procedure for the preparation of 2-tosylmalonates 174, 215, 229, 231, 251 and 275

To a solution of malonates **192a**–**f**, **223b**,**c**, **255**, **260** and **295**–**299** (2 equiv) in DMSO (c ~ 2 M) at rt and under nitrogen was added very slowly solid *t*-BuOK (2 equiv). The reaction was then stirred for 30 min before the addition of TsF (1 equiv). After stirring overnight at rt, the mixture was poured into aqueous HCl (10%) and extracted twice with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated under

reduced pressure. Chromatography gave tosylmalonates **174a**–**f**, **215b**,**c**, **229**, **231a**,**b**, **251 a**–**c** and **275** and the excess starting malonates. Yields cited for tosylmalonates are based on TsF; yields cited for recovered starting material are calculated from the total recoverable amount based on the yield of tosylmalonate and the amount of malonate used (2 equiv). For example, a 70% yield of **174a** means the total recoverable amount of malonate is (2 - 0.7) = 1.3 equiv; 74% recovery means that (0.74 × 1.3) = 0.962 equiv of starting material was recovered.

3.2.5 General procedure for the addition of electrophile to heptadienes 175 and cyclopentene 203b

To a solution of heptadienes **175a**,**b**,**d**,**e** or cyclopentenes **203b** (1 equiv) in THF (c ~ 0.2 M) at 0 °C and under nitrogen was added dropwise a commercial solution of *n*-BuLi in hexanes (1.2 equiv). The electrophiles (1.2 equiv) were immediately added. The reaction was allowed to warm to rt and after stirring overnight the excess *n*-BuLi was quenched with MeOH. Concentration under reduced pressure and chromatography gave dienes **180a**–**d**, **202**, **294** and cyclopentenes **204a**–**d**.

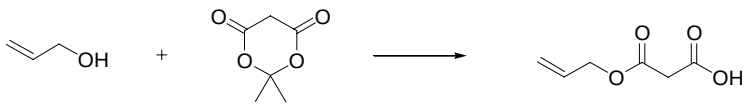
3.2.6 General procedure for the preparation of pyridines 182, 209, 233, 253 and 267a

Ozone was bubbled through a solution of a diastereoisomeric mixture of dienes **175a**,**b**,**d**,**e**, **180b**–**d**, **202**, **232a**,**b**, **252a**,**b**, **266a** and cyclopentenes **204a**,**b** (1 equiv) in MeOH:CH_2Cl_2 (1:5, c ~ 0.1 M) at –78 °C, until a blue colour persisted. After bubbling O_2 through the reaction mixture until it returned colourless, the reducing agent was added. After stirring for 3 h at –78 °C the mixture was concentrated under reduced pressure, previous filtering of the resin when solid supported PPh_3 was used as the reducing agent. To a solution of the crude dicarbonyls in MeOH (c ~ 0.1-0.4 M) was added NH_4HCO_3 (~ 8 equiv) and the mixture was exposed to microwave irradiation for 10 min at 100 °C. The solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and then washed twice with H_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give pyridines **182b**,**f**,**g** in a pure form. Further purification was always carried out; chromatography gave pyridines **182a**,**b**,**d**–**h**, **233*R***,***S***, **253a**,**b** and **267a**; HPLC gave **209**.

3.3 Individual Procedures

3.3.1 Compounds relevant to the development of the methodology for pyridine synthesis

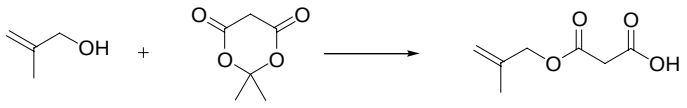
Allyl malonate (191a)



190 **191a**

According to general procedure **3.2.1**, Meldrum's acid **190** (3.862 g, 26.79 mmol, 1 equiv) was reacted with allyl alcohol (1.82 mL, 26.8 mmol, 1 equiv) at 97 °C to give *allyl malonate* **191a** (3.84 g, 99%) as a yellow liquid; ν_{max} (film) 3580, 3090, 2952, 1736, 1413, 1324, 1278, 1198, 1157, 993, 934 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 9.57 (1H, bs, OH), 5.98-5.83 (1H, m, CH), 5.38-5.25 (2H, m, $=CH_2$), 4.66 (2H, d, *J* 6.0 Hz, CH_2O), 3.46 (2H, s, CH_2COOH); δ_C (67.5 MHz) 171.9 (COOH), 166.4 ($COOCH_2$), 131.2 (CH), 119.2 ($=CH_2$), 66.5 (CH_2O), 40.9 (CH_2COOH); *m/z* (CI) 162 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 162.0769. $C_6H_8O_4$ requires $[M+NH_4]^+$, 162.0767).

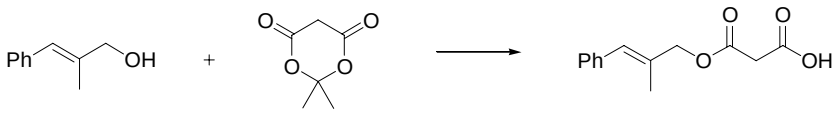
Methallyl malonate (191b)



190 **191b**

According to general procedure **3.2.1**, Meldrum's acid **190** (1.36 g, 9.46 mmol, 1 equiv) was reacted with methallyl alcohol (796 μL, 9.46 mmol, 1 equiv) at 115 °C to give *methallyl malonate* **191b** (1.25 g, 77%) as a yellow liquid; ν_{max} (film) 3584, 3087, 2947, 1735, 1411, 1278, 1201, 1154, 1004, 907 cm^{-1}; δ_H (270 MHz) 5.01-4.95 (2H, m, $=CH_2$), 4.59 (2H, s, CH_2O), 3.47 (2H, s, CH_2COOH), 1.75 (3H, s, CH_3); δ_C (67.5 MHz) 171.6 (COOH), 166.4 ($COOCH_2$), 139.1 ($=CCH_3$), 113.8 ($=CH_2$), 69.1 (CH_2O), 41.0 (CH_2COOH), 19.4 (CH_3); *m/z* (CI) 176 $[M+NH_4]^+$, 230 (Found: $[M+NH_4]^+$, 176.0922. $C_7H_{10}O_4$ requires $[M+NH_4]^+$, 176.0923).

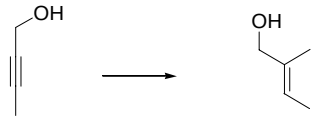
[(*E*)-2-Methyl-3-phenyl-2-propen]yl malonate (191c)



190 **191c**

According to general procedure **3.2.1**, Meldrum's acid **190** (15.64 g, 108.5 mmol, 1 equiv) was reacted with (*E*)-2-methyl-3-phenyl-2-propen-1-ol (15.62 mL, 108.5 mmol, 1 equiv) in toluene (100 mL) at 90 °C to give *[(*E*)-2-methyl-3-phenyl-2-propen]yl malonate* **191c** (23.86 g, 94%) as a colourless liquid; ν_{max} (film) 3335, 1735, 1275, 1154, 749 cm^{-1}; δ_H (270 MHz) 7.34-7.25 (5H, m, Ph), 6.55 (1H, s, =CHPh), 4.74 (2H, s, CH_2O), 3.50 (2H, s, C*H*$_2$COOH), 1.90 (3H, d, *J* 1.5 Hz, CH_3); δ_C (67.5 MHz) 171.8 (COOH), 166.6 (*C*OOCH_2), [136.9 and 132.0 (*ipso* Ph and =*C*CH_3)], [129.4 and 127.0 (*para* Ph and =CHPh)], [129.0 and 128.2 (*ortho* Ph and *meta* Ph)], 71.7 (CH_2O), 40.6 (*C*H_2COOH), 15.5 (CH_3); *m/z* (CI) 252 $[M+NH_4]^+$, 148, 131 (Found: $[M+NH_4]^+$, 252.1235. $C_{13}H_{14}O_4$ requires $[M+NH_4]^+$, 252.1236).

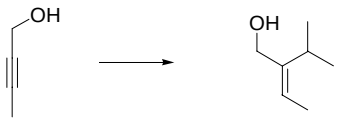
(*E*)-2-Methyl-2-buten-1-ol (188a)[5]



188a

According to general procedure **3.2.2**, MeMgCl in THF (1.79 M, 34 mL, 61 mmol, 2.9 equiv) was reacted with 2-butyn-1-ol (1.5 g, 21 mmol, 1 equiv) and CuI (402 mg, 2.11 mmol, 0.1 equiv) in benzene (40 mL) to give (*E*)-2-methyl-2-buten-1-ol **188a** (1.7 g, 94%) as a yellow liquid; R_f 0.11 (10% AcOEt–petrol); ν_{max} (film) 3267, 2958, 2924, 2856, 1462, 1444, 1379, 1005 cm^{-1}; δ_H (500 MHz) 5.49 (1H, qq, *J* 6.5, 1.0 Hz, CH), 3.99 (2H, s, CH_2), 1.66 (3H, s, CH_3-2), 1.62 (3H, dd, *J* 6.5, 1.0 Hz, CH_3-3), 1.46 (1H, bs, OH); δ_C (100 MHz) 135.5 (C-2), 120.6 (CH), 69.0 (CH_2), [13.3 and 13.0 (2 × CH_3)]. Data in agreement with those previously reported.

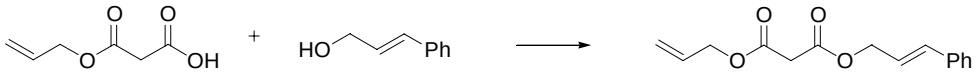
(*E*)-2-Isopropyl-2-buten-1-ol (188b)[6]



188b

According to general procedure **3.2.2**, *i*-PrMgCl in THF (1.95 M, 43 mL, 84 mmol, 2.6 equiv) was reacted with 2-butyn-1-ol (2.4 mL, 32 mmol, 1 equiv) and CuI (612 mg, 3.21 mmol, 0.1 equiv) in benzene (60 mL) to give (*E*)-2-isopropyl-2-buten-1-ol **188b** (3.2 g, 88%) as a yellow liquid; R_f 0.23 (CH_2Cl_2); δ_H (270 MHz) 5.46 (1H, q, *J* 6.5 Hz, =CH), 4.07 (2H, s, CH_2), 2.83 (1H, sept, *J* 7.0 Hz, CH *i*-Pr), 1.63 (3H, d, *J* 6.5 Hz, =CHC*H*$_3$), 1.04 (6H, d, *J* 7.0 Hz, 2 × CH_3 *i*-Pr). Data in agreement with those previously reported.

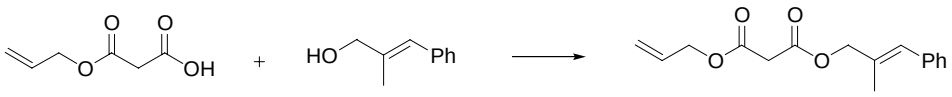
Allyl cinnamyl malonate (192a)[7]



191a **192a**

According to general procedure **3.2.3**, allyl malonate **191a** (1.615 g, 11.20 mmol, 1 equiv) was reacted with cinnamyl alcohol (1.505 g, 11.22 mmol, 1 equiv), DMAP (138 mg, 1.13 mmol, 0.1 equiv) and DCC (2.576 g, 12.25 mmol, 1.1 equiv) in CH_2Cl_2 (55 mL). Chromatography (10% AcOEt–petrol) gave allyl cinnamyl malonate **192a** (2.223 g, 76%) as a colourless oil; R_f 0.21 (20% AcOEt–petrol); ν_{max} (film) 3082, 2947, 2885, 1740, 1728, 1495, 1446, 1410, 1379, 1325, 1263, 1144, 987, 966, 746, 692 cm^{-1}; δ_H (270 MHz) 7.39-7.28 (5H, m, Ph), 6.66 (1H, d, *J* 16 Hz, =CHPh), 6.32-6.21 (1H, m, C*H*=CHPh), 5.95-5.85 (1H, m, C*H*=CH_2), 5.36-5.20 (2H, m, =CH_2), 4.80 (2H, dd, *J* 6.5, 1.0 Hz, C*H*$_2$CH=CHPh), 4.66-4.63 (2H, m, C*H*$_2$CH=CH_2), 3.44 (2H, s, $OOCCH_2COO$); δ_C (67.5 MHz) [166.3 and 166.2 (2 × C=O)], 136.1 (*ipso* Ph), [134.8, 131.6, 128.3 and 122.5 (*C*H=CH_2, *C*H=CHPh, =CHPh and *para* Ph)], [128.7 and 126.8 (*ortho* Ph and *meta* Ph)], 118.8 (=CH_2), 66.1 (2 × CH_2O), 41.6 ($OOCCH_2COO$); *m/z* (CI) 278 $[M+NH_4]^+$, 134, 117. Data in agreement with those previously reported.

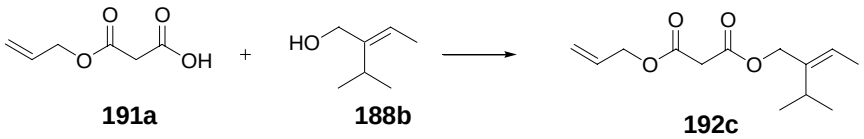
Allyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate (192b)



191a **192b**

According to general procedure **3.2.3**, allyl malonate **191a** (1.815 g, 12.60 mmol, 1 equiv) was reacted with (*E*)-2-methyl-3-phenyl-2-propen-1-ol (1.80 mL, 12.5 mmol, 1 equiv), DMAP (157 mg, 1.28 mmol, 0.1 equiv) and DCC (2.881 g, 13.96 mmol, 1.1 equiv) in CH_2Cl_2 (60 mL). Chromatography (5% AcOEt–petrol) gave *allyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate* **192b** (2.60 g, 75%) as a colourless oil; R_f 0.33 (10% AcOEt–petrol); ν_{max} (film) 2946, 1752, 1735, 1366, 1328, 1273, 1181, 994, 748, 670 cm^{-1}; δ_H (300 MHz) 7.39-7.24 (5H, m, Ph), 6.57 (1H, s, =CHPh), 6.00-5.87 (1H, m, C*H*=CH_2), 5.40-5.25 (2H, m, =CH_2), 4.74 (2H, s, C*H*$_2$CCH_3=), 4.69-4.67 (2H, m, C*H*$_2$CH=CH_2), 3.51 (2H, s, OOCCH_2COO), 1.97 (3H, s, CH_3); δ_C (67.5 MHz) [166.3 and 166.2 (2 × C=O)], [136.9 and 132.2 (*ipso* Ph and =*C*CH_3)], [131.6, 128.9, and 127.0 (*para* Ph, =CHPh and *C*H=CH_2)], [129.0 and 128.3 (*ortho* Ph and *meta* Ph)], 118.8 (=CH_2), [71.2 and 66.1 (2 × CH_2O)], 41.6 (OOC*C*H_2COO), 15.6 (CH_3); *m/z* (CI) 292 $[M+NH_4]^+$, 202, 148, 131 (Found: $[M+NH_4]^+$, 292.1559. $C_{16}H_{18}O_4$ requires $[M+NH_4]^+$, 292.1549) (Found: C, 70.16; H, 6.71. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.61%).

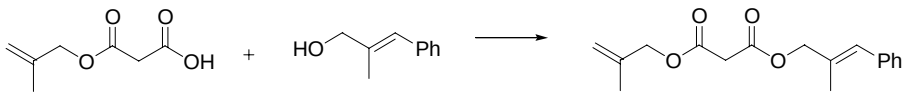
Allyl [(*E*)-2-isopropyl-2-buten]yl malonate (192c)



191a **188b** **192c**

According to general procedure **3.2.3**, allyl malonate **191a** (1.489 g, 10.33 mmol, 1.3 equiv) was reacted with (*E*)-2-isopropyl-2-buten-1-ol **188b** (895 mg, 7.84 mmol, 1 equiv), DMAP (128 mg, 1.05 mmol, 0.1 equiv) and DCC (2.454 g, 11.89 mmol, 1.5 equiv) in CH_2Cl_2 (50 mL). Chromatography (5% AcOEt–petrol) gave *allyl [(*E*)-2-isopropyl-2-buten]yl malonate* **192c** (1.30 g, 69%) as a colourless oil; R_f 0.30 (5% AcOEt–petrol); ν_{max} (film) 2963, 1752, 1649, 1454, 1413, 1365, 1328, 1270, 1148, 1037, 1008, 934, 822 cm^{-1}; δ_H (270 MHz) 5.95-5.82 (1H, m, C*H*=CH_2), 5.53 (1H, q, *J* 7.0 Hz, =C*H*CH_3), 5.36-5.22 (2H, m, =CH_2), 4.62 (2H, dt, *J* 4.5, 1.5 Hz, =CHC*H*$_2$), 4.58 (2H, s, =C*i*-PrCH_2), 3.40 (2H, s, $OOCCH_2COO$), 2.84 (1H, sept, *J* 7.0 Hz, CH *i*-Pr), 1.64 (3H, d, *J* 7.0 Hz, =CHC*H*$_3$), 1.01 (6H, d, *J* 7.0 Hz, 2 × CH_3 *i*-Pr); δ_C (67.5 MHz) [166.3 and 166.2 (2 × C=O)], 139.0 (=C*i*-Pr), [131.6 and 125.6 (*C*H=CH_2 and =*C*HCH_3)], 118.8 (=CH_2), [67.8 and 66.1 (2 × CH_2O)], 41.8 ($OOCCH_2COO$), [27.5 and 13.0 (CH *i*-Pr and =C*C*H$_3$)], 21.0 (2 × CH_3 *i*-Pr); *m/z* (CI) 258 $[M+NH_4]^+$, 162, 114, 97 (Found: $[M+NH_4]^+$, 258.1715. $C_{13}H_{20}O_4$ requires $[M+NH_4]^+$, 258.1705) (Found: C, 65.09; H, 8.30. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%).

Methallyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate (192d)

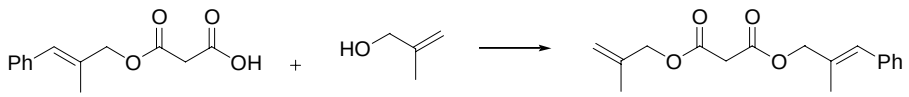


191b **192d**

Procedure A

According to general procedure **3.2.3**, methallyl malonate **191b** (909 mg, 5.75 mmol, 1 equiv) was reacted with (*E*)-2-methyl-3-phenyl-2-propen-1-ol (828 μL, 5.75 mmol, 1 equiv), DMAP (74 mg, 0.61 mmol, 0.1 equiv) and DCC (1.286 g, 6.234 mmol, 1.1

equiv) in CH_2Cl_2 (60 mL). Chromatography (5% AcOEt–petrol) gave *methallyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate* **192d** (693 mg, 39%) as a colourless oil.



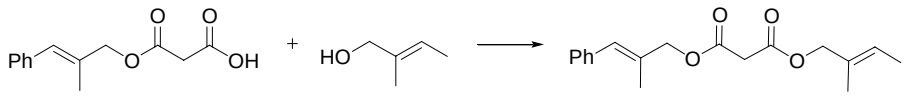
191c **192d**

Procedure B

According to general procedure **3.2.3**, [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **191c** (1.109 g, 4.733 mmol, 1 equiv) was reacted with methallyl alcohol (400 μL, 4.75 mmol, 1 equiv), DMAP (60 mg, 0.491 mmol, 0.1 equiv) and DCC (1.177 g, 5.705 mmol, 1.2 equiv) in CH_2Cl_2 (40 mL). Chromatography (5% AcOEt–petrol) gave methallyl [(E)-2-methyl-3-phenyl-2-propen]yl malonate **192d** (1.7 g, 73%) as a colourless oil.

192d; R_f 0.30 (5% AcOEt–petrol); ν_{max} (film) 1734, 1697, 1447, 1329, 1267, 1148, 1037, 1003 cm^{-1}; δ_H (270 MHz) 7.33-7.24 (5H, m, Ph), 6.54 (1H, s, =CHPh), [5.00-4.99 (1H, m) and 4.93-4.92 (1H, m), $=CH_2$)], [4.71 (2H, s) and 4.57 (2H, s), 2 × CH_2O], 3.48 (2H, s, $OOCCH_2COO$), [1.89 (3H, s) and 1.73 (3H, s), 2 × CH_3)]; δ_C (67.5 MHz) [166.4 and 166.2 (2 × C=O)], [139.4, 136.9 and 132.2 (*ipso* Ph and 2 × $=\!\!C\!CH_3$)], [129.0, 128.3 and 127.0 (*ortho* Ph, *meta* Ph, *para* Ph and $CCH_3\!=\!\!C\!HPh$)], 113.7 ($=CH_2$), [71.3 and 68.8 (2 × CH_2O)], 41.6 ($OOC\!\!C\!H_2COO$), [19.5 and 15.6 (2 × CH_3)]; *m/z* (CI) 306 $[M+NH_4]^+$, 176, 148, 131 (Found: $[M+NH_4]^+$, 306.1707. $C_{17}H_{20}O_4$ requires $[M+NH_4]^+$, 306.1705) (Found: C, 70.76; H, 6.87. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%).

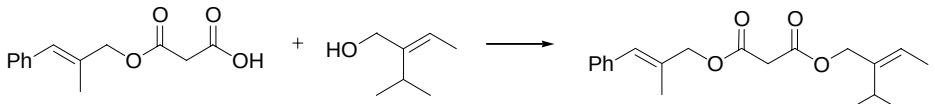
[(*E*)-2-Methyl-2-buten]yl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate (192e)



191c **188a** **192e**

According to general procedure **3.2.3**, [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **191c** (8.0 g, 34 mmol, 1 equiv) was reacted with (*E*)-2-methyl-2-buten-1-ol **188a** (3.1 g, 36 mmol, 1.1 equiv), DMAP (453 mg, 3.71 mmol, 0.1 equiv) and DCC (10.5 g, 50.8 mmol, 1.5 equiv) in CH_2Cl_2 (240 mL). Chromatography (3%→5% AcOEt–petrol) gave *[(*E*)-2-methyl-2-buten]yl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate* **192e** (9.40 g, 91%) as a colourless oil; R_f 0.33 (5% AcOEt–petrol); ν_{max} (film) 2985, 2939, 2922, 1734, 1645, 1446, 1373, 1327, 1275, 1147, 993, 748, 700 cm^{-1}; δ_H (270 MHz) 7.36-7.22 (5H, m, Ph), 6.53 (1H, s, =CHPh), 5.59-5.52 (1H, m, =C*H*CH_3), [4.70 (2H, s) and 4.53 (2H, s), 2 × CH_2O], 3.46 (2H, s, OOCCH_2COO), [1.88 (3H, d, *J* 1.5 Hz) and 1.63 (3H, d, *J* 1.0 Hz), 2 × =CCH_3], 1.62-1.59 (6H, m, =CHC*H*$_3$); δ_C (100 MHz) [166.4 and 166.4 (2 × C=O)], [136.9, 132.1 and 130.2 (*ipso* Ph and 2 × =*C*CH_3)], [128.9, 128.2, 126.8 and 124.9 (*ortho* Ph, *meta* Ph, *para* Ph, =CHPh and =*C*HCH_3)], [71.4 and 71.1 (2 × CH_2O)], 41.7 (OOC*C*H_2COO), [15.4, 13.6 and 13.2 (3 × CH_3)]; *m/z* (CI) 320 $[M+NH_4]^+$, 199, 148, 131 (Found: $[M+NH_4]^+$, 320.1859. $C_{18}H_{22}O_4$ requires $[M+NH_4]^+$, 320.1862) (Found: C, 71.46; H, 7.25. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%).

[(*E*)-2-Isopropyl-2-buten]yl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate (192f)

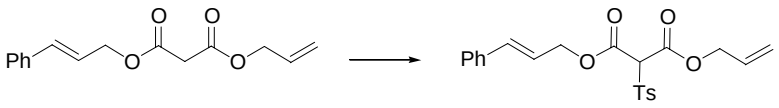


191c **188b** **192f**

According to general procedure **3.2.3**, [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **191c** (4.081 g, 17.42 mmol, 1 equiv) was reacted with (*E*)-2-isopropyl-2-buten-1-ol **188b** (2.112 g, 18.50 mmol, 1.1 equiv), DMAP (280 mg, 2.29 mmol, 0.1 equiv) and DCC (4.579 g, 22.19 mmol, 1.3 equiv) in CH_2Cl_2 (180 mL). Chromatography (5% AcOEt–petrol) gave *[(*E*)-2-isopropyl-2-buten]yl [(*E*)-2-methyl-3-phenyl-2-propen]yl*

malonate **192f** (4.26 g, 74%) as a colourless oil; R_f 0.39 (10% AcOEt–petrol); ν_{max} (film) 2965, 1732, 1643, 1264, 1147, 990, 749, 701 cm^{-1}; δ_H (300 MHz) 7.36-7.20 (5H, m, Ph), 6.53 (1H, s, =CHPh), 5.53 (1H, q, *J* 7.0 Hz, =C*H*CH_3), [4.70 (2H, s) and 4.59 (2H, s), 2 × CH_2O], 3.44 (2H, s, $OOCCH_2COO$), 2.83 (1H, sept, *J* 7.0 Hz, CH *i*-Pr), 1.88 (3H, s, =CC*H*$_3$), 1.63 (3H, d, *J* 7.0 Hz, =CHC*H*$_3$), 1.01 (6H, d, *J* 7.0 Hz, 2 × CH_3 *i*-Pr); δ_C (100 MHz) [166.3 and 166.3 (2 × C=O)], [139.0, 136.9 and 132.2 (*ipso* Ph, =*C*CH_3 and =C*i*-Pr)], [128.9, 128.2, 126.9 and 125.5 (*ortho* Ph, *meta* Ph, *para* Ph, =CHPh and =*C*HCH_3)], [71.2 and 67.7 (2 × CH_2O)], 41.9 ($OOCCH_2COO$), [27.5, 15.5 and 12.9 (=CH*C*H_3, CH *i*-Pr and =C*C*H_3)], 21.0 (2 × CH_3 *i*-Pr); *m/z* (CI) 348 $[M+NH_4]^+$, 331 $[M+H]^+$, 148, 131 (Found: $[M+H]^+$, 331.1908. $C_{20}H_{26}O_4$ requires $[M+H]^+$, 331.1909) (Found: C, 72.66; H, 7.84. $C_{20}H_{26}O_4$ requires C, 72.70; H, 7.93%).

(±)-1-Allyl 3-cinnamyl 2-(*p*-toluenesulfonyl)malonate (174a)

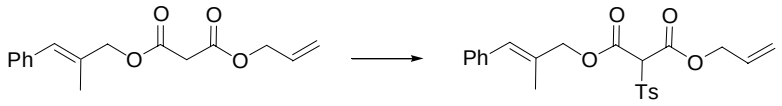


192a **174a**

According to general procedure **3.2.4**, allyl cinnamyl malonate **192a** (10.89 g, 41.82 mmol, 2 equiv) was reacted with *t*-BuOK (4.707 g, 41.94 mmol, 2 equiv) and TsF (3.670 g, 21.07 mmol, 1 equiv) in DMSO (20 mL). Chromatography (10% AcOEt–petrol) gave (±)-1-allyl 3-cinnamyl 2-(p-toluenesulfonyl)malonate **174a** (6.585 g, 76%) as a colourless gum and the excess starting malonate **192a** (5.627 g, 83% unreacted); R_f 0.21 (10% AcOEt–petrol); ν_{max} (film) 3058, 3027, 2946, 1743, 1667, 1596, 1494, 1449, 1336, 1305, 1292, 1276, 1193, 1180, 1151, 1084, 988, 970, 939, 846, 815, 747, 705, 694, 673 cm^{-1}; δ_H (270 MHz) 7.84 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.35-7.25 (7H, m, Ph, CH-3 Ts and CH-5 Ts), 6.63 (1H, d, *J* 16.0 Hz, =CHPh), 6.21-6.10 (1H, m, C*H*=CHPh), 5.89-5.76 (1H, m, C*H*=CH_2), 5.35-5.21 (2H, m, =CH_2), 5.02 (1H, s, CHTs), [4.80 (2H, d, *J* 6.5 Hz) and 4.66 (2H, d, *J* 6.5 Hz), 2 × CH_2O], 2.37 (3H, s, CH_3); δ_C (100 MHz) [160.6 and 160.6 (2 × C=O)], 145.9 (C-1 Ts), [135.7 and 134.0 (*ipso* Ph and C-4 Ts)], 135.6 (*C*H=CH_2), [130.4, 128.3 and 121.2 (*para* Ph, =CHPh and *C*H=CHPh)], [130.1, 129.4, 128.6 and 126.6 (*ortho* Ph, *meta* Ph and 4 × CH Ts)] 119.5 (=CH_2), 74.4 (CHTs), [67.3 and 67.3 (2 × CH_2O)], 21.6 (CH_3 Ts); *m/z* (CI) 432

$[M+NH_4]^+$, 388, 356 $[M+NH_4\text{-}CH_3Ph]^+$, 272, 202, 188, 174 $[M+NH_4\text{-Ts-CH=CHPh}]^+$, 134, 117 (Found: $[M+NH_4]^+$, 432.1481. $C_{22}H_{22}O_6S$ requires $[M+NH_4]^+$, 432.1481) (Found: C, 63.78; H, 5.40. $C_{22}H_{22}O_6S$ requires C, 63.75; H, 5.35%). Data in agreement with those previously reported.

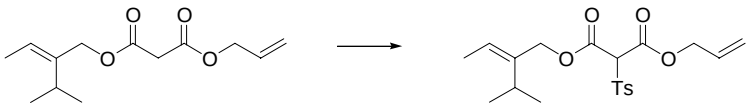
(±)-1-Allyl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate (174b)



192b **174b**

According to general procedure **3.2.4**, allyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **192b** (4.491 g, 16.37 mmol, 2 equiv) was reacted with *t*-BuOK (1.849 g, 16.47 mmol, 2 equiv) and TsF (1.433 g, 8.226 mmol, 1 equiv) in DMSO (8.2 mL). Chromatography (10% AcOEt–hexane) gave *(±)-1-allyl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate* **174b** (2.517 g, 72%) as a colourless gum and the excess starting malonate **192b** (2.495 g, 87% unreacted); R_f 0.15 (10% AcOEt–petrol); ν_{max} (film) 2937, 1743, 1596, 1446, 1335, 1292, 1276, 1150, 1082, 1019, 992, 937, 815, 749 cm^{-1}; δ_H (270 MHz) 7.85 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.31-7.25 (7H, m, Ph, CH-3 Ts and CH-5 Ts), 6.49 (1H, s, =CHPh), 5.88-5.76 (1H, m, C*H*=CH_2), 5.35-5.21 (2H, m, =CH_2), 5.03 (1H, s, CHTs), 4.72 (2H, s, C*H*$_2$CCH_3=), 4.67-4.64 (2H, m, C*H*$_2$CH=CH_2), 2.40 (3H, s, CH_3 Ts), 1.83 (3H, d, *J* 1.5 Hz, =CCH_3); δ_C (67.5 MHz) [160.9 and 160.8 (2 × C=O)], 146.2 (C-1 Ts), [136.3, 133.9 and 131.3 (*ipso* Ph, C-4 Ts and =*C*CH_3)], [130.6, 129.8 and 127.1 (*para* Ph, =CHPh and *C*H=CH_2)], [130.2, 129.7, 129.0 and 128.3 (*ortho* Ph, *meta* Ph, and 4 × CH Ts)] 119.7 (=CH_2), 74.6 (CHTs), [72.7 and 67.5 (2 × CH_2O)], 21.8 (CH_3 Ts), 15.5 (=C*C*H_3); *m/z* (CI) 446 $[M+NH_4]^+$, 362, 356, 344, 292, 272, 208, 202, 188, 174, 165, 148, 131 (Found: $[M+NH_4]^+$, 446.1625. $C_{23}H_{24}O_6S$ requires $[M+NH_4]^+$, 446.1638) (Found: C, 64.45; H, 5.54. $C_{23}H_{24}O_6S$ requires C, 64.47; H, 5.65%).

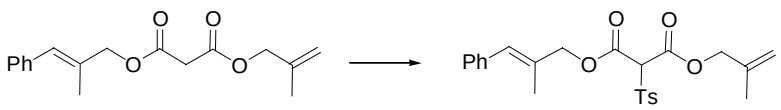
(±)-1-Allyl 3-[(*E*)-2-isopropyl-2-buten]yl ester 2-(*p*-toluenesulfonyl)malonate (174c)



192c **174c**

According to general procedure **3.2.4**, allyl [(*E*)-2-isopropyl-2-buten]yl malonate **192c** (3.887 g, 16.17 mmol, 2 equiv) was reacted with *t*-BuOK (1.847 g, 16.46 mmol, 2 equiv) and TsF (1.422 g, 8.163 mmol, 1 equiv) in DMSO (8 mL). Chromatography (5%→10% AcOEt–petrol) gave *(±)-1-allyl 3-[(*E*)-2-isopropyl-2-buten]yl ester 2-(p-toluenesulfonyl)malonate* **174c** (2.315 g, 73%) as a yellow gum and the excess starting malonate **192c** (2.030 g, 82% unreacted); R_f 0.26 (10% AcOEt–petrol); ν_{max} (film) 2963, 1741, 1647, 1599, 1336, 1290, 1152, 1083 cm^{-1}; δ_H (270 MHz) 7.85 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.33 (2H, d, *J* 8.5 Hz, CH-3 Ts and CH-5 Ts), 5.90-5.76 (1H, m, C*H*=CH_2), 5.50 (1H, q, *J* 7.0 Hz, =C*H*CH_3), 5.35-5.23 (2H, m, =CH_2), 4.96 (1H, s, CHTs), 4.65-4.62 (2H, m, CHCH_2O), 4.57 (2H, s, C*i*-PrCH_2O), 2.78 (1H, sept, *J* 7.0 Hz, CH *i*-Pr), 2.44 (3H, s, CH_3 Ts), 1.63 (3H, d, *J* 7.0 Hz, =CHCH_3), 0.94 (6H, dd, *J* 7.0, 2.5 Hz, 2 × CH_3 *i*-Pr); δ_C (67.5 MHz) [160.6, 145.8, 138.1, 134.1, and 99.8 (2 × C=O, 2 × C Ts and =C*i*-Pr)], [130.4 and 126.5 (2 × =CH)], [130.1 and 129.3 (4 × CH Ts)], 119.5 (=CH_2), 74.5 (CHTs), [69.0 and 67.2 (2 × CH_2O)], [27.2, 21.6, 20.7 and 12.8 (CH *i*-Pr and 4 × CH_3)]; *m/z* (CI) 412 $[M+NH_4]^+$, 328, 316, 258, 174, 162, 114, 97 (Found: $[M+NH_4]^+$, 412.1793. $C_{20}H_{26}O_6S$ requires $[M+NH_4]^+$, 412.1794) (Found: C, 61.00; H, 6.61. $C_{20}H_{26}O_6S$ requires C, 60.89; H, 6.64%).

(±)-1-Methallyl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate (174d)

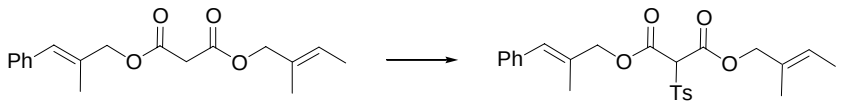


192d **174d**

According to general procedure 3.2.4, methallyl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **192d** (3.586 g, 12.44 mmol, 2 equiv) was reacted with *t*-BuOK (1.405 g,

12.52 mmol, 2 equiv) and TsF (1.087 g, 6.240 mmol, 1 equiv) in DMSO (6.2 mL). Chromatography (10% AcOEt–petrol) gave *(±)-1-methallyl 3-[(E)-2-methyl-3-phenyl-2-propen]yl 2-(p-toluenesulfonyl)malonate* **174d** (1.958 g, 71%) as a yellow gum and the excess starting malonate **192d** (2.111 g, 91% unreacted); R_f 0.14 (10% AcOEt–petrol); ν_{max} (film) 2928, 1742, 1653, 1596, 1447, 1335, 1292, 1150, 1083, 1027, 916, 814 cm^{-1}; δ_H (270 MHz) 7.85 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.37-7.22 (7H, m, Ph, CH-3 Ts and CH-5 Ts), 6.49 (1H, s, =CHPh), 5.04 (1H, s, CHTs), [4.98 (1H, bs) and 4.93 (1H, bs), $=CH_2$], [4.71 (2H, s) and 4.58 (2H, s), 2 × CH_2O], 2.39 (3H, s, CH_3 Ts), [1.83-1.82 (3H, m) and 1.70 (3H, s), 2 × $=CCH_3$]; δ_C (67.5 MHz) [160.9 and 160.8 (2 × C=O)], [146.1, 138.5, 136.7, 134.3 and 131.3 (*ipso* Ph, 2 × C Ts and 2 × $=\mathit{C}CH_3$)], [130.2, 129.6, 129.0 and 128.3 (*ortho* Ph, *meta* Ph, 4 × CH Ts)], [129.9 and 127.1 (*para* Ph and =CHPh)], 114.7 ($=CH_2$), 74.7 (CHTs), [72.8 and 70.2 (2 × CH_2O)], 21.8 (CH_3 Ts), [19.4 and 15.5 (2 × $=C\mathit{C}H_3$)]; *m/z* (CI) 460 $[M+NH_4]^+$, 286, 188, 174, 148, 131 (Found: $[M+NH_4]^+$, 460.1802. $C_{24}H_{26}O_6S$ requires $[M+NH_4]^+$, 460.1794) (Found: C, 65.07; H, 5.97. $C_{24}H_{26}O_6S$ requires C, 65.14; H, 5.92%).

(±)-1-[(*E*)-2-Methyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate (174e)

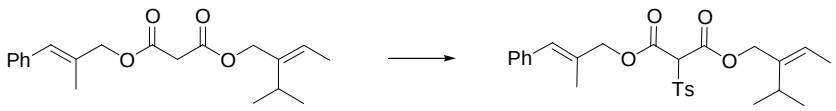


192e **174e**

According to general procedure **3.2.4**, [(*E*)-2-methyl-2-buten]yl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **192e** (9.284 g, 30.71 mmol, 2 equiv) was reacted with *t*-BuOK (3.466 g, 30.89 mmol, 2 equiv) and TsF (2.705 g, 15.53 mmol, 1 equiv) in DMSO (15 mL). Chromatography (5%→10% AcOEt–petrol) gave *(±)-1-[(*E*)-2-methyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate* **174e** (4.946 g, 71%) as a colourless gum and the excess starting malonate **192e** (4.862 g, 81% unreacted); R_f 0.17 (10% AcOEt–petrol); ν_{max} (film) 2924, 1741, 1645, 1598, 1446, 1335, 1290, 1180, 1151, 1082, 814, 702, 665 cm^{-1}; δ_H (270 MHz) 7.85 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), 7.37-7.22 (7H, m, Ph, CH-3 Ts and CH-5 Ts), 6.49 (1H, s,

=CHPh), 5.56-5.50 (1H, m, =C*H*CH_3), 5.02 (1H, s, CHTs), [4.71 (2H, s) and 4.54 (2H, s), 2 × CH_2O], 2.39 (3H, s, CH_3 Ts), 1.82 (3H, d, *J* 1.0 Hz, CC*H*$_3$=CHPh), 1.60-1.57 (3H, m, =CHC*H*$_3$), 1.57 (3H, s, CC*H*$_3$=CHCH_3); δ_C (100 MHz) 160.9 (2 × C=O), [145.9, 136.6, 134.3, 131.3 and 129.6 (*ipso* Ph, 2 × C Ts and 2 × =*C*CH_3)], [130.2, 129.5, 128.9 and 128.2 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], [129.8, 127.0 and 125.9 (*para* Ph, =CHPh and =*C*HCH_3)], 74.7 (CHTs), [72.9 and 72.6 (2 × CH_2O)], [21.7, 15.4, 13.5 and 13.3 (4 × CH_3)]; *m/z* (CI) 474 $[M+NH_4]^+$, 362, 323, 300, 174, 148, 131 (Found: $[M+NH_4]^+$, 474.1947. $C_{25}H_{28}O_6S$ requires $[M+NH_4]^+$, 474.1950) (Found: C, 65.79; H, 6.12. $C_{25}H_{28}O_6S$ requires C, 65.77; H, 6.18%).

(±)-1-[(*E*)-2-Isopropyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate (174f)

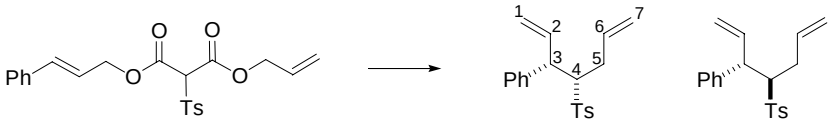


192f **174f**

According to general procedure **3.2.4**, [(*E*)-2-isopropyl-2-buten]yl [(*E*)-2-methyl-3-phenyl-2-propen]yl malonate **192f** (3.895 g, 11.79 mmol, 2 equiv) was reacted with *t*-BuOK (1.330 g, 11.85 mmol, 2 equiv) and TsF (1.033 g, 5.930 mmol, 1 equiv) in DMSO (6 mL). Chromatography (5%→10% AcOEt–petrol) gave *(±)-1-[(*E*)-2-isopropyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-(p-toluenesulfonyl)malonate* **174f** (2.034 g, 71%) as a colourless gum and the excess starting malonate **192f** (2.190 g, 87% unreacted); R_f 0.32 (10% AcOEt–petrol); ν_{max} (film) 2962, 1742, 1597, 1448, 1336, 1291, 1181, 1083, 815, 703, 672 cm^{-1}; δ_H (270 MHz) 7.86 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.30-7.24 (7H, m, Ph, CH-3 Ts and CH-5 Ts), 6.49 (1H, s, =CHPh), 5.50 (1H, q, *J* 7.0 Hz, =C*H*CH_3), 5.00 (1H, s, CHTs), [4.70 (2H, s) and 4.58 (2H, s), 2 × CH_2O], 2.78 (1H, sept, *J* 7.0 Hz, CH *i*-Pr), 2.39 (3H, s, CH_3 Ts), 1.83 (3H, d, *J* 1.0 Hz, =CCH_3), 1.61 (3H, d, *J* 7.0 Hz, =CHC*H*$_3$), 0.94 (6H, dd, *J* 7.0, 2.0 Hz, 2 × CH_3 *i*-Pr); δ_C (67.5 MHz) [160.8 and 160.8 (2 × C=O)], [145.8, 138.2, 136.6, 134.3 and 131.2 (*ipso* Ph, 2 × C Ts, =*C*CH_3 and =C*i*-Pr)], [130.2, 129.4, 128.9 and 128.2 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], [129.8, 127.0 and 126.5 (*para* Ph, =CHPh and =*C*HCH_3)], 74.7 (CHTs), [72.7 and 69.2 (2 × CH_2O)], [27.4, 21.7, 20.8,

15.5 and 13.0 (5 × CH_3)]; *m/z* (CI) 502 $[M+NH_4]^+$, 362, 328, 165, 148, 131, 114 (Found: $[M+NH_4]^+$, 502.2260. $C_{27}H_{32}O_6S$ requires $[M+NH_4]^+$, 502.2263) (Found: C, 67.01; H, 6.60. $C_{27}H_{32}O_6S$ requires C, 66.92; H, 6.66%).

(3*S,4*S**)-3-Phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (175a)**

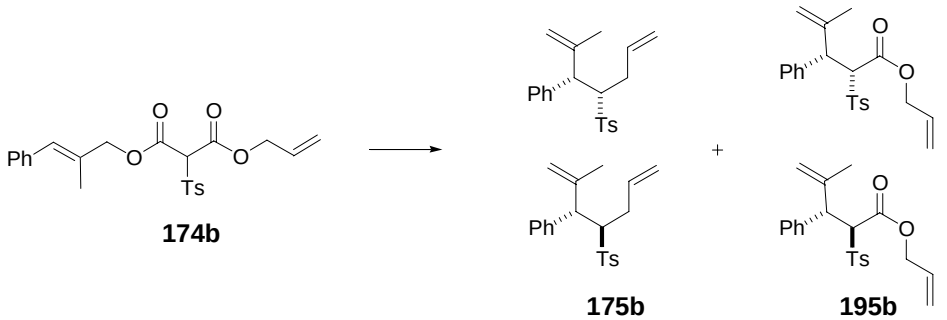


174a **175a**

To a mixture of acid (±)-1-allyl 3-cinnamyl 2-tosylmalonate **174a** (3.96 g, 9.64 mmol, 1 equiv) and KOAc (101 mg, 1.03 mmol, 0.1 equiv) under nitrogen was added BSA (7.0 mL, 27 mmol, 2.9 equiv). The mixture was exposed to microwave irradiation for 4 min at 170 °C. Chromatography (5%→10% AcOEt–petrol) gave *3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene* **175a** in a 1:1 mixture of diastereoisomers (2.7 g, 86%) as a colourless gum; R_f 0.34 (10% AcOEt–petrol); ν_{max} (film) 3028, 2980, 2921, 1638, 1597, 1493, 1452, 1300, 1289, 1143, 1085, 992, 919, 815 cm^{-1}; δ_H (270 MHz) [7.69 (2H, d, *J* 8.5 Hz) and 7.58 (2H, d, *J* 8.5 Hz), CH-2 Ts and CH-6 Ts of both diastereoisomers], 7.29-7.08 (14H, m, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), [6.20-6.01 (2H, m) and 5.67-5.54 (2H, m), CH-2 and CH-6 of both diastereoisomers], 5.22-4.72 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), [4.09 (1H, dd, *J* 8.5, 5.0 Hz) and 4.00-3.94 (1H, m), CHPh of both diastereoisomers], 3.55-3.44 (2H, m, CHTs of both diastereoisomers), 2.74-2.67 (2H, m, CH_2-5 of one diastereoisomer), [2.41 (3H, s), 2.39 (3H, s) and 2.41-2.33 (2H, m), CH_3 of both diastereoisomers and CH_2-5 of one diastereoisomer]; δ_C (67.5 MHz) [144.5, 144.3, 141.1, 140.4, 136.7 and 136.4 (*ipso* Ph and 2 × C Ts of both diastereoisomers)], [138.1, 135.8, 134.6, 133.6, 127.1 and 126.9 (*para* Ph, CH-2 and CH-6 of both diastereoisomers)], [129.7, 129.6, 128.9, 128.7, 128.6, 128.6, 128.4 and 128.2 (*ortho* Ph, *meta* Ph and 4 × CH Ts of both diastereoisomers)], [118.7, 118.2, 117.7 and 117.0 (CH_2-1 and CH_2-7 of both diastereoisomers)], [68.9 and 68.5 (CHTs of both diastereoisomers)], [49.4 and 48.3 (CHPh of both diastereoisomers)], [31.9 and 30.1

(CH_2-5 of both diastereoisomers)], 21.7 (CH_3 of both diastereoisomers); *m/z* (CI) 344 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 344.1676. $C_{20}H_{22}O_2S$ requires $[M+NH_4]^+$, 344.1684).

(3*S,4*S**)-2-Methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene, (3*S**,4*R**)-2-methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (175b), (2*R**,3*S**)-4-methyl-3-phenyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid allyl ester and (2*S**,3*S**)-4-methyl-3-phenyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid allyl ester (195b)**



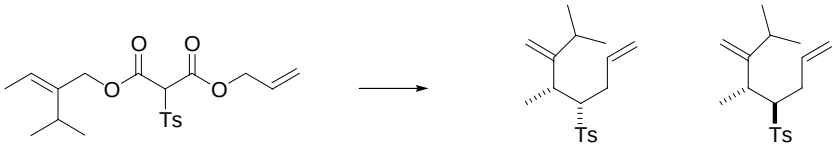
To a mixture of (±)-1-allyl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-tosylmalonate **174b** (1.032 g, 2.407 mmol, 1 equiv) and KOAc (56 mg, 0.57 mmol, 0.2 equiv) under nitrogen was added BSA (1.9 mL, 7.5 mmol, 3.1 equiv). The mixture was exposed to 4 cycles of microwave irradiation of 3 min each at 200 °C. Chromatography (6%→10% AcOEt–petrol) gave *2-methyl-3-phenyl-4-(*p-*toluenesulfonyl)-1,6-heptadiene* **175b** in a 1:1 mixture of diastereoisomers (630 mg, 77%) as a white solid and *4-methyl-3-phenyl-2-(p-toluenesulfonyl)-4-pentenoic acid allyl ester* **195b** in a 1:1 mixture of diastereoisomers (68 mg, 7%) as a white solid.

175b; R_f 0.31 (10% AcOEt–petrol); ν_{max} (film) 3077, 3028, 2978, 2923, 1640, 1597, 1493, 1452, 1300, 1290, 1142, 1085, 913, 815, 756, 731, 702 cm^{-1}; δ_H (270 MHz) 7.74 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of both diastereoisomers), [7.31-7.17 (8H, m) and 7.00-6.94 (6H, m), Ph, CH-3 Ts and CH-5 Ts of both diastereoisomers], 6.09-5.97 (1H, m, CH-6 of one diastereoisomer), 5.62-5.50 (1H, m, CH-6 of one diastereoisomer), 5.13-4.59 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), 4.04-3.75 (4H, m, CH-3 and CH-4 of both diastereoisomers), 2.83-2.33 (4H, m, CH_2-5 of both diastereoisomers), 2.42 (3H, s, CH_3 Ts of one diastereoisomer), 2.31 (3H, s, CH_3 Ts of

one diastereoisomer), 1.59 (3H, s, CH_3-2 of one diastereoisomer), 1.51 (3H, s, CH_3-2 of one diastereoisomer); δ_C (67.5 MHz) [145.1, 144.9, 144.5, 143.3, 138.9, 138.8, 137.8 and 136.9 (*ipso* Ph, 2 × C Ts and C-2 of both diastereoisomers)], [134.8, 133.9, 127.2 and 126.6 (*para* Ph, and CH-6 of both diastereoisomers)], [129.6, 129.2, 129.1, 128.9, 128.4, 127.9, 127.9 (*ortho* Ph, *meta* Ph, 4 × CH Ts of both diastereoisomers)], [118.0, 117.7, 113.7 and 113.5 (CH_2-1 and CH_2-7 of both diastereoisomers)], [66.2 and 65.7 (CHTs of both diastereoisomers)], [53.3 and 52.2 (CHPh of both diastereoisomers)], [31.9 and 31.8 (CH_2-5 of both diastereoisomers)], [21.7, 21.5, 21.1 and 20.6 (2 × CH_3 of both diastereoisomers)]; *m/z* (CI) 358 $[M+NH_4]^+$, 341 $[M+H]^+$, 268 (Found: $[M+H]^+$, 341.1580. $C_{21}H_{24}O_2S$ requires $[M+H]^+$, 341.1575).

195b; R_f 0.22 (10% AcOEt–petrol); ν_{max} (film) 3070, 1741, 1647, 1597, 1493, 1452, 1323, 1293, 1145, 1083, 900 cm^{-1}; δ_H (270 MHz) 7.81 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.31-7.05 (16H, m, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), 5.90-5.76 (2H, m, =CH of both diastereoisomers), 5.38-4.50 (12H, m, 3 × CH_2 of both diastereoisomers), 4.12-4.06 (4H, m, CH-2 and CH-3 of both diastereoisomers), [2.44 (3H, s) and 2.32 (3H, s) CH_3 Ts of both diastereoisomers], 1.61 (6H, bs, CH_3-4 of both diastereoisomers); δ_C (100 MHz) [165.1 and 164.9 (C=O of both diastereoisomers)], [145.6, 145.3, 144.4, 142.5, 138.8, 136.9, 136.1 and 135,2 (*ipso* Ph, 2 × C Ts and C-4 of both diastereoisomers)], [131.1, 130.7, 129.9, 129.7, 129.2, 129.0, 128.9, 128.6, 128.4, 128.2, 128.0 and 127.3 (*ortho* Ph, *meta* Ph, *para* Ph, 4 × CH Ts and =CH of both diastereoisomers)], [119.2, 118.9, 114.7 and 111.5 (2 × =CH_2 of both diastereoisomers)], [74.5 and 72.8 (CHTs of both diastereoisomers)], [66.8 and 66.4 (CH_2O of both diastereoisomers)], [52.2 and 51.5 (CHPh of both diastereoisomers)], [21.9, 21.8, 21.7 and 21.5 (2 × CH_3 of both diastereoisomers)]; *m/z* (CI) 402 $[M+NH_4]^+$, 318 (Found: $[M+NH_4]^+$, 402.1752. $C_{22}H_{24}O_4S$ requires $[M+NH_4]^+$, 402.1739).

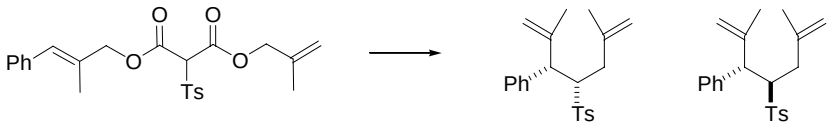
(3*S,4*S**)-2-Isopropyl-3-methyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-2-isopropyl-3-methyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (175c)**



174c **175c**

To a mixture of (±)-1-allyl 3-[(*E*)-2-isopropyl-2-buten]yl 2-tosylmalonate **174c** (1.059 g, 2.68 mmol, 1 equiv) and KOAc (30 mg, 0.31 mmol, 0.1 equiv) under nitrogen was added BSA (2.0 mL, 7.9 mmol, 3 equiv). The mixture was exposed to microwave irradiation for 4 min at 230 °C. Chromatography (2% AcOEt–petrol) gave *2-isopropyl-3-methyl-4-(*p-*toluenesulfonyl)-1,6-heptadiene* **175c** in a 1:1 mixture of diastereoisomers (669 mg, 81%) as a colourless gum; R_f 0.38 (5% AcOEt–petrol); ν_{max} (film) 2962, 2927, 1644, 1597, 1457, 1313, 1301, 1219, 1145, 1086, 900, 769 cm^{-1}; δ_H (270 MHz) 7.75-7.72 (4H, m, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.32-7.30 (4H, m, CH-3 Ts and CH-5 Ts of both diastereoisomers), 5.60-5.45 (2H, m, CH-6 of both diastereoisomers), 4.93-4.81 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), [3.19-3.12 (1H, m), 3.08-3.03 (1H, m), 3.00-2.93 (1H, m) and 2.85-2.74 (1H, m), CH-3 and CH-4 of both diastereoisomers], 2.67-1.90 (6H, m, CH_2-5 and CH *i*-Pr of both diastereoisomers), 2.43 (6H, s, CH_3 Ts of both diastereoisomers), [1.32 (3H, d, *J* 7.0 Hz), 1.16 (3H, d, *J* 7.0 Hz), 1.03-0.96 (9H, m) and 0.88 (3H, d, *J* 7.0 Hz), CH_3-3 and 2 × CH_3 *i*-Pr of both diastereoisomers]; δ_C (67.5 MHz) [157.5, 157.0, 144.6, 144.4, 137.1 and 136.2 (2 × C Ts and C-2 of both diastereoisomers)], [135.8 and 134.4 (CH-6 of both diastereoisomers)], [129.8, 129.7, 128.8 and 128.7 (4 × CH Ts of both diastereoisomers)], [117.4, 116.7, 108.9 and 108.8 (CH_2-1 and CH_2-7 of both diastereoisomers)], [64.3 and 66.6 (CHTs of both diastereoisomers)], [38.5, 35.9, 33.2, 32.7, 23.2, 22.9, 22.1, 21.8, 21.7 and 19.9 (CH *i*-Pr, CH-3 and 4 × CH_3 of both diastereoisomers)], [32.4 and 27.9 (CH_2-5 of both diastereoisomers)]; *m/z* (CI) 324 $[M+NH_4]^+$, 307 $[M+H]^+$ (Found: $[M+H]^+$, 307.1725, $[M+NH_4]^+$, 324.1986. $C_{18}H_{26}O_2S$ requires $[M+H]^+$, 307.1732, $[M+NH_4]^+$, 324.1997).

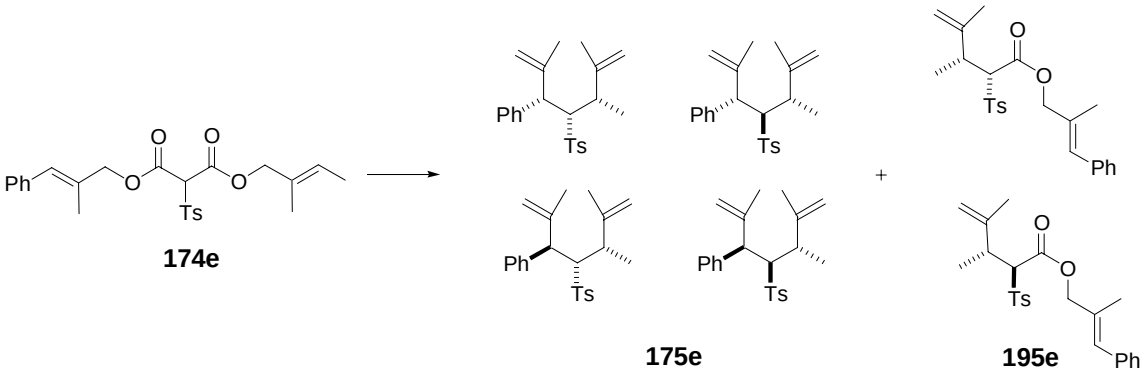
(3*S,4*S**)-2,6-Dimethyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-2,6-dimethyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (175d)**



174d **175d**

To a mixture of (±)-1-methallyl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-tosylmalonate **174d** (743 mg, 1.69 mmol, 1 equiv) and KOAc (22 mg, 0.22 mmol, 0.1 equiv) under nitrogen was added BSA (2.0 mL, 7.9 mmol, 4.7 equiv). The mixture was exposed to 2 cycles of microwave irradiation of 3 min each at 240 °C. Chromatography (2%→10% AcOEt–petrol) gave *2,6-dimethyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene* **175d** in a 1:1 mixture of diastereoisomers (419 mg, 70%) as a colourless gum; R_f 0.35 (10% AcOEt–petrol); ν_{max} (film) 3070, 3027, 2970, 2920, 1649, 1597, 1493, 1451, 1301, 1290, 1143, 1085, 895, 753, 701, 667 cm^{-1}; δ_H (270 MHz) 7.71 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.34-7.02 (16H, m, CH-2 Ts and CH-6 Ts of one diastereoisomer, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), 4.99-3.81 (12H, m, CH_2-1, CH-3, CH-4 and CH_2-7 of both diastereoisomers), 2.88-2.13 (4H, m, CH_2-5 of both diastereoisomers), [2.42 (3H, s) and 2.33 (2H, s), CH_3 Ts of both diastereoisomers], [1.70 (3H, s), 1.60 (3H, s), 1.57 (3H, s) and 1.37 (3H, s), CH_3-2 and CH_3-6 of both diastereoisomers]; δ_C (67.5 MHz) [145.7, 144.9, 144.4, 143.6, 142.5, 141.2, 139.2, 138.6, 137.3 and 136.8 (*ipso* Ph, 2 × C Ts, C-2 and C-6 of both diastereoisomers)], [129.7, 129.4, 129.3, 128.9, 128.3 and 128.0 (*ortho* Ph, *meta* Ph, 4 × CH Ts of both diastereoisomers)], [127.2 and 126.7 (*para* Ph of both diastereoisomers)], [114.2, 112.6, 112.6 and 112.1 (CH_2-1 and CH_2-7 of both diastereoisomers)], [64.8 and 64.1 (CHTs of both diastereoisomers)], [54.3 and 52.0 (CHPh of both diastereoisomers)], [35.4 and 34.8 (CH_2-5 of both diastereoisomers)], [22.8, 22.2, 22.0, 21.7, 21.6 and 21.3 (3 × CH_3 of both diastereoisomers)]; *m/z* (CI) 372 $[M+NH_4]^+$, 219, 182 (Found: $[M+H]^+$, 355.1736. $C_{22}H_{26}O_2S$ requires $[M+H]^+$, 355.1732).

(3*S,4*S**,5*S**)-3-Phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene, (3*S**,4*R**,5*S**)-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene, (3*R**,4*S**,5*S**)-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene, (3*R**,4*R**,5*S**)-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene (175e), (2*R**,3*S**)-3,4-dimethyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid [(*E*)-2-methyl-3-phenyl-2-propen]yl ester and (2*R**,3*R**)-3,4-dimethyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid [(*E*)-2-methyl-3-phenyl-2-propen]yl ester (195e)**



To a mixture of (±)-1-[(*E*)-2-methyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-tosylmalonate **174e** (2.817 g, 6.170 mmol, 1 equiv) and KOAc (76 mg, 0.77 mmol, 0.1 equiv) under nitrogen was added BSA (5.0 mL, 20 mmol, 3 equiv). The mixture was exposed to 6 cycles of microwave irradiation of 1 min each at 180 °C. Chromatography (1%→5% AcOEt–petrol) gave *3-phenyl-4-(*p-*toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene* **175e** in a mixture of diastereoisomers (1.3 g, 56%) as a white solid and *3,4-dimethyl-2-(*p-*toluenesulfonyl)-4-pentenoic acid [(E)-2-methyl-3-phenyl-2-propen]yl ester* **195e** in a 3:2 mixture of diastereoisomers (576 mg, 23%) as a white solid.

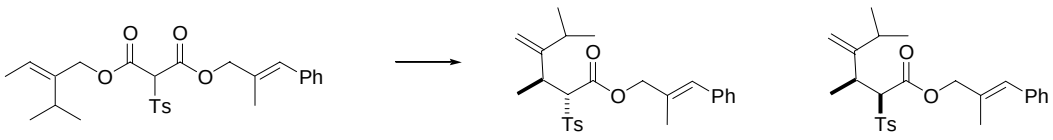
175e; R_f 0.35 (10% AcOEt–petrol); ν_{max} (film) 3061, 3028, 2970, 2924, 1643, 1597, 1493, 1452, 1379, 1300, 1144, 1086, 893, 814, 760, 702, 665 cm^{-1}; δ_H (400 MHz) [7.78 (2H, d, *J* 8.5 Hz) and 7.73 (2H, d, *J* 8.5 Hz), CH-2 Ts and CH-6 Ts of 2 diastereoisomers], 7.33-6.87 (32H, m, CH-2 Ts and CH-6 Ts of 2 diastereoisomers and CH-3 Ts, CH-5 Ts and Ph of all diastereoisomers), 5.09-4.01 (24H, m, 2 × CH_2, CH-3 and CH-4 of all diastereoisomers), [3.43-3.38 (1H, m), 2.96-2.91 (1H, m), 2.84-2.78 (1H, m), CH-5 of 3 diastereoisomers], [2.45 (3H, s), 2.43 (3H, s), 2.38-2.36 (1H, m), 2.33 (3H, s) and 2.30 (3H, s), CH-5 of one diastereoisomer and CH_3 Ts of all

diastereoisomers], [2.05 (3H, s), 1.90 (3H, s), 1.80 (3H, s), 1.62 (3H, s) and 1.56-1.14 (24H, m), CH_3-2, CH_3-5 and CH_3-6 of all diastereoisomers]; δ_C (125 MHz) [146.8, 146.2, 145.1, 144.8, 144.8, 144.6, 144.5, 144.2, 143.9, 142.8, 142.6, 140.2, 140.1, 139.7, 139.5, 139.2, 139.1, 138.4 and 138.0 (*ipso* Ph, 2 × C Ts, C-2 and C-6 of all diastereoisomers)], [129.5, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 127.8, 127.7, 127.6, 127.2, 127.0, 126.9 and 126.4 (*ortho* Ph, *meta* Ph, *para* Ph and 4 × CH Ts of all diastereoisomers)], [114.5, 114.4, 114.1, 113.8, 111.9, 111.4 and 111.2 (2 × CH_2 of all diastereoisomers)], [67.5, 67.3, 67.1 and 67.0 (CHTs of all diastereoisomers)], [54.1, 53.3, 52.5 and 51.9 (CHPh of all diastereoisomers)], [39.7, 39.3, 38.5 and 38.4 (*C*HCH_3 of all diastereoisomers)], [22.7, 22.7, 22.3, 21.8, 21.7, 21.5, 21.4, 20.9, 20.8, 20.5, 20.1 and 19.3 (3 × CH_3-2, CH_3 of all diastereoisomers)], [14.6, 13.8, 12.7 and 12.6 (CH_3- 5 of all diastereoisomers)]; *m/z* (CI) 386 $[M+NH_4]^+$, 369 $[M+H]^+$, 198 (Found: $[M+H]^+$, 369.1880; $[M+NH_4]^+$, 386.2152. $C_{23}H_{28}O_2S$ requires $[M+H]^+$, 369.1888; $[M+NH_4]^+$, 386.2154).

195e; R_f 0.31 (10% AcOEt–petrol); ν_{max} (film) 2972, 2938, 2924, 1739, 1596, 1493, 1451, 1322, 1290, 1209, 1143, 1083, 902, 815, 751 cm^{-1}; δ_H (270 MHz) 7.79 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of the major diastereoisomer), 7.77 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of the minor diastereoisomer), 7.37-7.20 (14 H, m, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), 6.47 (1H, s, CHPh of the minor diastereoisomer), 6.35 (1H, s, CHPh of the major diastereoisomer), 4.86-4.02 (10H, m, CHTs, CH_2-5 and CH_2O of both diastereoisomers), 3.12-3.02 (2H, m, CH-3 of both diastereoisomers), 2.36 (3H, s, CH_3 Ts of the minor diastereoisomer), 2.35 (3H, s, CH_3 Ts of the major diastereoisomer), 1.80 (3H, d, *J* 1.0 Hz, CCH_3=CHPh of the minor diastereoisomer), 1.72 (3H, d, *J* 1.0 Hz, CCH_3=CHPh of the major diastereoisomer), 1.68 (3H, s, CH_3-3 of the major diastereoisomer), 1.67 (3H, s, CH_3-3 of the minor diastereoisomer), 1.41 (3H, d, *J* 7.0 Hz, CH_3-4 of the major diastereoisomer), 1.12 (3H, d, *J* 7.0 Hz, CH_3-4 of the minor diastereoisomer); δ_C (100 MHz) [165.7 and 165.6 (C=O of both diastereoisomers)], [145.7, 145.2, 145.1, 144.5, 136.7, 135.3, 135.1, 131.5 and 131.5 (*ipso* Ph, 2 × C Ts, C-4 and *C*CH_3=CHPh of both diastereoisomers)], [129.6, 129.6, 129.5, 129.4, 129.4, 129.2, 129.0, 128.8, 128.1 and 126.9 (*ortho* Ph, *meta* Ph, *para* Ph, 4 × CH Ts and =CHPh of both diastereoisomers)], [114.0 and 113.2 (CH_2-5 of both

diastereoisomers)], [75.5 and 73.4 (CHTs of both diastereoisomers)], [71.8 and 71.6 (CH_2O of both diastereoisomers)], [40.8 and 40.3 (CH-3 of both diastereoisomers)], [21.5, 19.2, 18.3, 18.2, 17.7, 15.5 and 15.5 (4 × CH_3 of both diastereoisomers)]; *m/z* (CI) 430 $[M+NH_4]^+$, 318 (Found: $[M+NH_4]^+$, 430.2047. $C_{24}H_{28}O_4S$ requires $[M+NH_4]^+$, 430.2052).

(2*R,3*R**)-4-Isopropyl-3-methyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid [(*E*)-2-methyl-3-phenyl-2-propen]yl ester and (2*R**,3*S**)-4-isopropyl-3-methyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid [(*E*)-2-methyl-3-phenyl-2-propen]yl ester (195f)**

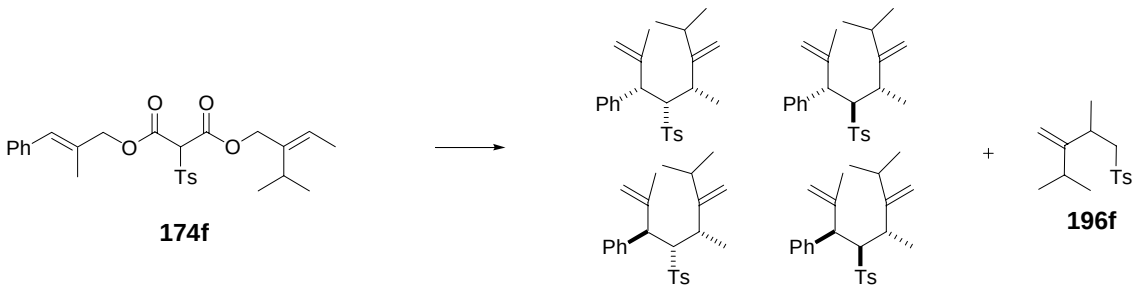


175f **195f**

To a solution of (±)-1-[(*E*)-2-isopropyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen]yl 2-tosylmalonate **175f** (1.126 g, 2.324 mmol, 1 equiv) in CH_2Cl_2 (12 mL) at rt and under nitrogen, were added simultaneously TBDMSOTf (1.125 mL, 4.899 mmol, 2.1 equiv) and DBU (730 μL, 4.88 mmol, 2.1 equiv). After 1h 30 min of stirring, the reaction mixture was concentrated under reduced pressure. Chromatography (0%→5% AcOEt–petrol) gave *4-isopropyl-3-methyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid [(*E*)-2-methyl-3-phenyl-2-propen]yl ester* **195f** in a 1:1 mixture of diastereoisomers (293 mg, 29%) as a colourless oil; R_f 0.37 (10% AcOEt–petrol); ν_{max} (film) 2966, 2341, 1740, 1597, 1495, 1452, 1323, 1288, 1142, 1084, 814 cm^{-1}; δ_H (400 MHz) 7.83-7.77 (4H, m, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.37-7.16 (14H, m, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), [6.43 (1H, s) and 6.34 (1H, s), CHPh of both diastereoisomers], [4.91 (1H, d, *J* 0.5 Hz), 4.87 (1H, s), 4.82 (1H, s) and 4.80 (1H, s) CH_2-5 of both diastereoisomers], 4.58-4.09 (6H, m, CHTs and CH_2O of both diastereoisomers), 3.20-3.01 (2H, m, CH-3 of both diastereoisomers), [2.40-2.19 (2H, m) and 2.37 (6H, s) CH *i*-Pr and CH_3 Ts of both diastereoisomers], [1.77 (3H, d, *J* 1.0 Hz) and 1.73 (3H, d, *J* 0.5 Hz), $=CCH_3$ of both diastereoisomers], [1.44 (3H, d, *J* 7.0 Hz) and 1.28 (3H, d, *J* 7.0 Hz), CH_3-3 of both diastereoisomers], [1.07-1.03 (6H, m), 1.01 (3H, d, *J* 7.0 Hz) and 0.97 (3H, d, *J* 7.0 Hz), 2 × CH_3 *i*-Pr of both

diastereoisomers]; δ_C (125 MHz) [166.0 and 165.3 (C=O of both diastereoisomers)], [158.2, 156.5, 145.3, 145.2, 136.8, 135.8, 135.3, 131.6 and 131.5 (*ipso* Ph, 2 × C Ts, C-4 and =*C*$CH_3$of both diastereoisomers)], [129.7, 129.6, 129.6, 129.3, 129.1, 128.9, 128.2 and 127.0 (*ortho* Ph, *meta* Ph, *para* Ph, 4 × CH Ts and =CHPh of both diastereoisomers)], [109.2 and 108.4 (CH_2-5 of both diastereoisomers)], [76.5 and 74.1 (CHTs of both diastereoisomers)], [71.7 and 71.6 (CH_2O of both diastereoisomers)], [38.4, 37.1, 33.9, 33.4, 22.6, 22.2, 22.1, 22.0, 21.6, 20.8, 17.9 and 15.6 (CH *i*-Pr, CH-3 and 5 × CH_3 of both diastereoisomers)]; *m/z* (CI) 458 $[M+NH_4]^+$, 304, 284, 148 (Found: $[M+NH_4]^+$, 458.2363. $C_{26}H_{32}O_4S$ requires $[M+NH_4]^+$, 458.2365).

(3*S,4*S**,5*S**)-2,5-Dimethyl-6-isopropyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene, (3*S**,4*R**,5*S**)-2,5-dimethyl-6-isopropyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene, (3*R**,4*S**,5*S**)-2,5-dimethyl-6-isopropyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*R**,4*R**,5*S**)-2,5-dimethyl-6-isopropyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (175f) and 2-isopropyl-3-methyl-4-(*p*-toluenesulfonyl)-1-butene (196f)**

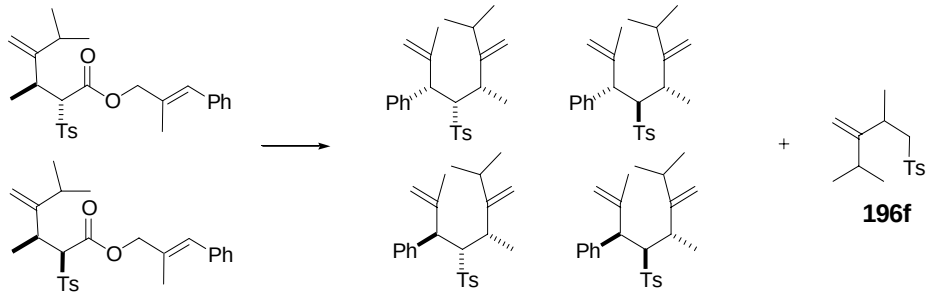


174f **175f** **196f**

Procedure A

To a mixture of (±)-1-[(*E*)-2-isopropyl-2-buten]yl 3-[(*E*)-2-methyl-3-phenyl-2-propen])yl 2-tosylmalonate **174f** (141 mg, 0.290 mmol, 1 equiv) and KOAc (10 mg, 0.10 mmol, 0.4 equiv) under nitrogen was added BSA (250 μL, 0.991 mmol, 3.4 equiv). The mixture was exposed to 7 cycles of microwave irradiation of 1 min each at 230 °C. Chromatography (1%→2% AcOEt–petrol) gave *2,5-dimethyl-6-isopropyl-3-phenyl-4-(*p-*toluenesulfonyl)-1,6-heptadiene* **175f** in a mixture of diastereoisomers (8 mg, 7%) as

a yellow gum and *2-isopropyl-3-methyl-4-(*p-*toluenesulfonyl)-1-butene* **196f** (36 mg, 47%) as a yellow gum.



195f **175f** **196f**

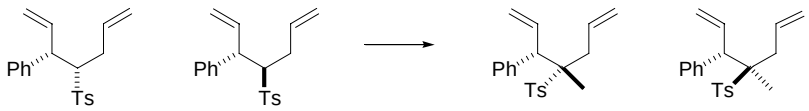
Procedure B

To a diastereoisomeric mixture of 4-isopropyl-3-methyl-2-(*p*-toluenesulfonyl)-4-pentenoic acid [(E)-2-methyl-3-phenyl-2-propen]yl ester **195f** (225 mg, 0.511 mmol, 1 equiv) and KOAc (9 mg, 0.09 mmol, 0.2 equiv) under nitrogen was added BSA (2.0 mL, 7.9 mmol, 15 equiv). The mixture was exposed to 7 cycles of microwave irradiation of 1 min each at 230 °C. Chromatography (3 times, 1%→3% AcOEt–petrol) gave 2,5-dimethyl-6-isopropyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene **175f** in a mixture of diastereoisomers as a yellow gum (34 mg, 17%) and 2-isopropyl-3-methyl-4-(*p*-toluenesulfonyl)-1-butene **196f** as a yellow gum.

175f; R_f 0.42 (10% AcOEt–petrol); ν_{max} (film) 2963, 2873, 1640, 1598, 1493, 1453, 1311, 1143, 1085, 895, 813 cm^{-1}; δ_H (270 MHz) [7.78 (2H, d, *J* 8.5 Hz) and 7.68 (2H, d, *J* 8.5 Hz), CH-2 Ts and CH-6 Ts of 2 diastereoisomers], 7.29-6.85 (32H, m, CH-2 Ts and CH-6 Ts of 2 diastereoisomers and CH-3 Ts, CH-5 Ts and Ph of all diastereoisomers)], 5.18-3.84 (24H, m, 2 × $=CH_2$, CH-3 and CH-4 of all diastereoisomers), [3.58-3.50 (1H, m), 3.39-3.34 (1H, m), 3.10-3.00 (1H, m) and 2.91-2.83 (1H, m), CH-5 of all diastereoisomers], [2.50-1.97 (4H, m), 2.42 (3H, s), 2.40 (3H, s), 2.32 (3H, s) and 2.27 (3H, s), CH *i*-Pr and CH_3 Ts of all diastereoisomers], 1.66-0.62 (32H, m, CH_3-2, CH_3-5 and 2 × CH_3 *i*-Pr of all diastereoisomers); *m/z* (CI) 414 $[M+NH_4]^+$, 397 $[M+H]^+$ (Found: $[M+H]^+$, 397.2200. $C_{25}H_{32}O_2S$ requires $[M+H]^+$, 397.2201).

196f; R_f 0.34 (10% AcOEt–petrol); ν_{max} (film) 2962, 2926, 2872, 1644, 1597, 1494, 1454, 1313, 1144, 1086, 896, 835, 815 cm^{-1}; δ_H (270 MHz) 7.77 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.33 (2H, d, *J* 8.5 Hz, CH-3 Ts and CH-5 Ts), [4.79 (1H, s) and 4.67 (1H, s), CH_2-1], 3.20-2.99 (2H, m, CH_2-4), 2.75-2.63 (1H, m, CH-2), 2.43 (3H, s, CH_3 Ts), 2.12 (1H, sept, *J* 7.0 Hz, CH *i*-Pr), 1.26 (3H, d, *J* 7.0 Hz, CH_3-2), 0.94 (6H, dd, *J* 7.0, 1.5 Hz, 2 × CH_3 *i*-Pr); *m/z* (CI) 284 $[M+NH_4]^+$, 267 $[M+H]^+$, 110 (Found: $[M+H]^+$, 267.1423; $[M+NH_4]^+$, 284.1693. $C_{15}H_{22}O_2S$ requires $[M+H]^+$, 267.1419; $[M+NH_4]^+$, 284.1684).

(3*S,4*S**)-4-Methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-4-methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (180a)**

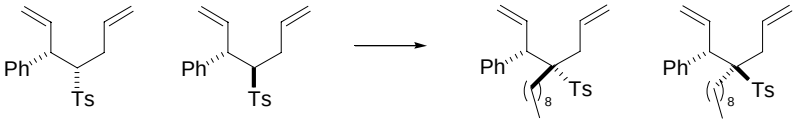


175a **180a**

To a solution of a 1:1 diastereoisomeric mixture of 3-phenyl-4-tosyl-1,6-heptadiene **175a** (238 mg, 0.729 mmol, 1 equiv) in THF (4 mL) at -78 °C and under nitrogen was added dropwise a commercial solution of *n*-BuLi in hexane (2.5 M, 330 μL, 0.825 mmol, 1.1 equiv). The solution turned bright yellow and MeI (66μL, 1.1 mmol, 1.5 equiv) was immediately added. The reaction was allowed to warm to rt and after 21 h of stirring the excess *n*-BuLi was quenched with MeOH (300 μL). Concentration under reduced pressure and chromatography (5% AcOEt–petrol) gave *4-methyl-3-phenyl-4-(*p-*toluenesulfonyl)-1,6-heptadiene* **180a** in a mixture of diastereoisomers (80 mg, 32%) as a colourless gum and starting diene **175a** (99 mg, 42%) as calculated by ^1H NMR analysis; R_f 0.36 (10% AcOEt–petrol); ν_{max} (film) 2980, 2922, 1637, 1598, 1454, 1297, 1140, 917, 751 cm^{-1}; δ_H (270 MHz) 7.71 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of the minor diastereoisomer), 7.63 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of the major diastereoisomer), 7.28-7.20 (14H, m, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), [6.56-6.38 (2H, m), 6.11-5.95 (1H, m) and 5.78-5.63 (1H, m), CH-2 and CH-6 of both diastereoisomers], 5.20-4.86 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), 4.01 (1H, d, *J* 9.0 Hz, CHPh of the minor diastereoisomer), 3.94 (1H,

d, *J* 9.0 Hz, CHPh of the major diastereoisomer), 2.79-2.17 (4H, m, CH_2-5 of both diastereoisomers), 2.42 (3H, s, CH_3 Ts of the minor diastereoisomer), 2.41 (3H, s, CH_3 Ts of the major diastereoisomer), 1.41 (3H, s, CH_3-4 of the minor diastereoisomer), 1.19 (3H, s, CH_3-4 of the major diastereoisomer); δ_C (100 MHz) [144.5, 144.4, 140.0, 140.0, 134.3 and 134.3 (*ipso* Ph and 2 × C Ts of both diastereoisomers)], [137.3 and 132.4 (CH-2 and CH-6 of the minor diastereoisomer)], [136.7 and 132.9 (CH-2 and CH-6 of the major diastereoisomers)], [130.7, 130.5, 130.2, 130.1, 129.3, 129.2, 128.2, 128.2, 127.1 and 127.1 (*ortho* Ph, *meta* Ph, *para* Ph and 4 × CH Ts of both diastereoisomers)], [119.1, 118.3 and 117.8 (CH_2-1 and CH_2-7 of both diastereoisomers)], 69.1 (C-4 of the minor diastereoisomer), 68.9 (C-4 of the major diastereoisomer), 53.5 (CHPh of the minor diastereosiomer), 53.2 (CHPh of the major diastereoisomer), 39.2 (CH_2-5 of the minor diastereoisomer), 37.7 (CH_2-5 of the major diastereoisomer), [21.6, 20.9 and 18.5 (2 × CH_3 of both diastereoisomers)]; *m/z* (CI) 358 $[M+NH_4]^+$, 185, 174 (Found: $[M+NH_4]^+$, 358.1845. $C_{21}H_{24}O_2S$ requires $[M+NH_4]^+$, 358.1841).

(3*S,4*S**)-4-Nonyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-4-Nonyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (180b)**

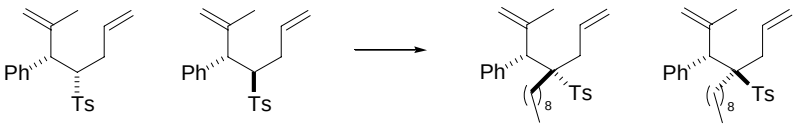


175a **180b**

According to general procedure **3.2.5**, a 1:1 diastereoisomeric mixture of 3-phenyl-4-tosyl-1,6-heptadiene **175a** (630 mg, 1.93 mmol, 1 equiv) in THF (10 mL) was treated with *n*-BuLi in hexane (2.16 M, 1.1 mL, 2.4 mmol, 1.2 equiv) and then reacted with 1-iodononane (460 μL, 2.33 mmol, 1.2 equiv). Chromatography (3%→5% AcOEt–petrol) gave *3-phenyl-4-nonyl-4-(*p*-toluenesulfony)l-1,6-heptadiene* **180b** in a 4:6 mixture of diastereoisomers (754 mg, 86%) as a colourless gum; R_f 0.69 (10% AcOEt–petrol); ν_{max} (film) 2924, 2853, 1635, 1598, 1454, 1286, 1129, 1079, 917, 815 cm^{-1}; δ_H (270 MHz) 7.47-7.43 (4H, m, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.27-7.13 (14H, m, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), [6.42-6.27 (2H, m), 6.20-6.07 (1H, m) and 5.82-5.70 (1H, m), CH-2 and CH-6 of both diastereoisomers], 5.19-4.97 (8H, m,

CH_2-1 and CH_2-7 of both diastereoisomers), 4.19-4.12 (2H, m, CHPh of both diastereoisomers), 2.78-2.43 (4H, m, CH_2-5 of both diastereoisomers), 2.37 (6H, s, CH_3 Ts of both diastereoisomers), 1.97-1.55 (4H, m, $CH_2(CH_2)_7$ of both diastereoisomers), 1.26 (28H, bs, $CH_2(CH_2)_7$ of both diastereoisomers), 0.90-0.85 (6H, m, CH_2CH_3 of both diastereoisomers); δ_C (100 MHz) [144.0, 140.0, 135.6 and 135.4 (*ipso* Ph and 2 × C Ts of both diastereoisomers)], [137.6 and 132.8 (CH-2 and CH-6 of the major diastereoisomer)], [137.5 and 133.2 (CH-2 and CH-6 of the minor diastereoisomers)], [130.6, 130.5, 130.3, 130.2, 129.0, 129.0, 128.2, and 127.1 (*ortho* Ph, *meta* Ph, *para* Ph and 4 × CH Ts of both diastereoisomers)], [118.9 and 118.1 (CH_2-1 and CH_2-7 of the minor diastereoisomer)], [118.9 and 117.8 (CH_2-1 and CH_2-7 of the major diastereoisomer)], 73.4 (C-4 of the minor diastereoisomer), 73.2 (C-4 of the major diastereoisomer), 53.3 (CHPh of the minor diastereosiomer), 52.7 (CHPh of the major diastereoisomer), [37.7, 36.4, 33.2, 32.6, 31.9, 31.9, 30.4, 30.3, 29.6, 29.5, 29.4, 29.3, 29.3, 29.3, 23.8, 23.6 and 22.7 (CH_2-5 and $C(CH_2)_8$ of both diastereoisomers)], [21.5 and 14.1 (2 × CH_3 of both diastereoisomers)]; *m/z* (CI) 470 $[M+NH_4]^+$, 297, 174 (Found: $[M+NH_4]^+$, 470.3094. $C_{29}H_{40}O_2S$ requires $[M+NH_4]^+$, 470.3093).

(3S*,4*S)-2,6-Dimethyl-4-nonyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4R*)-2,6-dimethyl-4-nonyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (180c)**

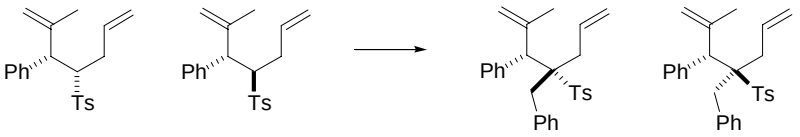


175b **180c**

According to general procedure **3.2.5**, a solution of a 1:1 diastereoisomeric mixture of 2-methyl-3-phenyl-4-tosyl-1,6-heptadiene **175b** (245 mg, 0.720 mmol, 1 equiv) in THF (3.6 mL) was treated with *n*-BuLi in hexane (2.42 M, 300 μL, 0.708 mmol, 1.2 equiv) and then reacted with1-iodononane (140 μL, 0.799 mmol, 1.1 equiv). Chromatography (2%→10% AcOEt–petrol) gave *2,6-dimethyl-3-phenyl-4-nonyl-4-(*p-*toluenesulfonyl)-1,6-heptadiene* **180c** in a 4:6 mixture of diastereoisomers (136 mg, 40%) as a pale yellow oil and the starting diene **175b** (83 mg, 34%) as a colourless oil; R_f 0.34 (10%

AcOEt–hexane); ν_{max} (film) 2955, 2925, 2854, 1455, 1276, 1261, 1130, 1077, 1041, 763 cm^{-1}; δ_H (400 MHz) 7.47-7.10 (18H, m, Ph and Ts of both diastereoisomers), 6.23-6.13 (1H, m, CH-6 of the major diastereoisomer), 5.86-5.76 (1H, m, CH-6 of the minor diastereoisomer), 5.19-4.93 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), 4.34 (1H, s, CH-3 of the minor diastereoisomer), 4.24 (1H, s, CH-3 of the major diastereoisomer), 3.00-2.71 (4H, m, CH_2-5 of both diastereoisomers), 2.37 (6H, s, CH_3 Ts of both diastereoisomers), [2.27-1.84 (4H, m) and 1.40-1.20 (28H, m), $C(CH_2)_8$ of both diastereoisomers], 1.74 (3H, s, CH_3-2 of the minor diastereoisomer), 1.69 (3H, s, CH_3-2 of the major diastereoisomer), 0.97-0.87 (6H, m, $CH_2C\mathit{H_3}$ of both diastereoisomers); δ_C (100 MHz) [145.1, 144.8, 143.9, 143.8, 139.0, 138.7, 136.0 and 135.9 (*ipso* Ph, 2 × C Ts and C-2 of both diastereoisomers)], [133.4, 133.1, 127.1 and 127.0 (*para* Ph, and CH-6 of both diastereoisomers)], [131.3, 131.2, 130.1, 129.9, 128.8, 127.9 and 127.8 (*ortho* Ph, *meta* Ph and 4 × CH Ts of both diastereoisomers)], [118.9, 118.9, 113.9 and 113.7 (CH_2-1 and CH_2-7 of both diastereoisomers)], [75.4 and 74.8 (C-4 of both diastereoisomers)], [54.1 and 53.4 (CHPh of both diastereoisomers)], [37.6, 36.8, 33.4, 32.8, 31.9, 31.8, 30.3, 30.2, 29.5, 29.4, 29.3, 29.3, 29.2, 23.9 and 22.7 (CH_2-5 and $C(\mathit{C}H_2)_{\mathit{8}}$ of both diastereoisomers)], [25.4, 25.1 and 21.5 (CH_3-2 and CH_3 Ts of both diastereoisomers)], 14.1 ($CH_2\mathit{C}H_3$ of both diastereoisomers); *m/z* (CI) 484 $[M+NH_4]^+$, 358, 301, 264, 218, 200, 188, 148 (Found: $[M+NH_4]^+$, 484.3258. $C_{30}H_{42}O_2S$ requires $[M+H]^+$, 484.3249).

(3*S,4*S**)-4-Benzyl-2-methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-4-benzyl-2-methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (180d)**

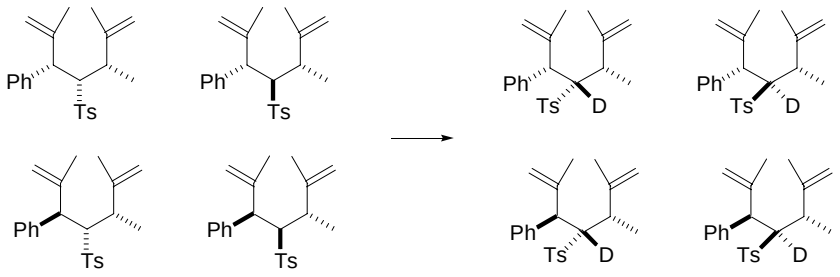


175b **180d**

According to general procedure **3.2.5**, a solution of a 1:1 diastereoisomeric mixture of 2-methyl-3-phenyl-4-tosyl-1,6-heptadiene **175b** (732 mg, 2.15 mmol, 1 equiv) in THF (10 mL) was treated with *n*-BuLi in hexane (1.50 M, 1.750 mL, 2.625 mmol, 1.2 equiv) and then reacted with BnBr (310 μL, 2.61 mmol, 1.2 equiv). Chromatography

(3%→4% AcOEt–petrol) gave *4-benzyl-2-methyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene* **180d** in a 4:6 mixture of diastereoisomers (523 mg, 56%) as a colourless gum and the diene starting material **175b** (28 mg, 4%) as a white solid; R_f 0.59 (10% AcOEt–petrol); ν_{max} (film) 3062, 3030, 2925, 2853, 1670, 1638, 1597, 1494, 1453, 1374, 1286, 1185, 1134, 1076, 918, 815, 758, 738, 703, 650 cm^{-1}; δ_H (400 MHz) 7.61-7.59 (4H, m, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.41-6.99 (24H, m, 2 × Ph, CH-3 Ts and CH-5 Ts of both diastereoisomers), 6.26-6.13 (2H, m, CH-6 of both diastereoisomers), 5.30-4.98 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), 4.45 (1H, s, CH-3 of the major diastereoisomer), 4.05 (1H, s, CH-3 of the minor diastereoisomer), [3.69 (2H, s), 3.65 (1H, d, *J* 15.5 Hz) and 3.45 (1H, d, *J* 15.5 Hz), $PhCH_2$ of both diastereoisomers], [3.07 (1H, dd, *J* 16.5, 8.0 Hz) and 2.65-2.59 (1H, m), CH_2-5 of the major diastereoisomer], [2.91 (1H, dd, *J* 16.5, 7.5 Hz) and 2.52-2.46 (1H, m), CH_2-5 of the minor diastereoisomer], 2.32 (3H, s, CH_3 Ts of the minor diastereoisomer), 2.31 (3H, s, CH_3 Ts of the major diastereoisomer), 1.67 (3H, s, CH_3-2 of the major diastereoisomer), 1.55 (3H, s, CH_3-2 of the minor diastereoisomer); δ_C (100 MHz) [145.2, 144.9, 143.5, 143.4, 138.5, 138.0, 136.1, 135.9 and 135.6 (2 × *ipso* Ph, 2 × C Ts and C-2 of both diastereoisomers)], [132.8 and 132.5 (CH-6 of both diastereoisomers)], [131.8, 131.8, 131.5, 131.4, 130.0, 130.0, 128.5, 128.5, 127.9, 127.9, 127.7 and 127.6 (2 × *ortho* Ph, 2 × *meta* Ph and 4 × CH Ts of both diastereoisomers)], [127.1, 127.1, 126.8 and 126.6 (2 × *para* Ph of both diastereoisomers)], [119.3, 119.1, 114.1 and 113.1 (CH_2-1 and CH_2-7 of both diastereoisomers)], [76.4 and 76.0 (C-4 of both diastereoisomers)], [54.1 and 53.1 (CHPh of both diastereoisomers)], [38.6, 38.4 and 38.1 (CH_2-5 and CH_2Ph of both diastereoisomers)], [26.0, 25.7 and 21.3 (2 × CH_3 of both diastereoisomers)]; *m/z* (CI) 448 $[M+NH_4]^+$, 431 $[M+H]^+$, 299, 275, 174, 52 (Found: $[M+H]^+$, 431.2044. $C_{28}H_{30}O_2S$ requires $[M+H]^+$, 431.2045).

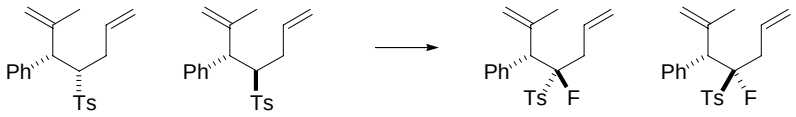
(3*S,4*S**,5*S**)-4-Deuterium-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene, (3*S**,4*R**,5*S**)-4-deuterium-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene, (3*R**,4*S**,5*S**)-4-deuterium-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene and (3*R**,4*R**,5*S**)-4-deuterium-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene (294)**



175e **294**

According to general procedure **3.2.5**, a solution of a diastereoisomeric mixture of 3-phenyl-4-tosyl-2,5,6-trimethyl-1,6-heptadiene **175e** (43 mg, 0.12 mmol, 1 equiv) in THF (0.6 mL) was treated with *n*-BuLi in cyclohexane (1.6 M, 80 μL, 0.13 mmol, 1.1 equiv) and then reacted with D_2O (10 μL, 0.55 mmol, 4.8 equiv). Chromatography (5%→15% AcOEt–hexane) gave *4-deuterium-3-phenyl-4-(*p*-toluenesulfonyl)-2,5,6-trimethyl-1,6-heptadiene* **294** in a mixture of diastereoisomers (31 mg, 72%) as a colourless gum; δ_H (400 MHz) [7.79 (2H, d, *J* 8.5 Hz) and 7.73 (2H, d, *J* 8.5 Hz), CH-2 Ts and CH-6 Ts of 2 diastereoisomers], 7.32-6.87 (32H, m, CH-2 Ts and CH-6 Ts of 2 diastereoisomers and CH-3 Ts, CH-5 Ts and Ph of all diastereoisomers), 5.02-4.00 (20H, m, 2 × CH_2 and CH-4 of all diastereoisomers), [3.40 (1H, q, *J* 7.0 Hz), 2.92 (1H, q, *J* 7.0 Hz), 2.80 (1H, q, *J* 7.0 Hz), CH-5 of 3 diastereoisomers], 2.45 (3H, s, CH_3 Ts of one diastereoisomer), 2.43 (3H, s, CH_3 Ts of one diastereoisomer), 2.43-2.37 (1H, m, CH-5 of one diastereoisomer), 2.32 (3H, s, CH_3 Ts of one diastereoisomer), and 2.29 (3H, s, CH_3 Ts of one diastereoisomer), [2.05 (3H, s), 1.89 (3H, s), 1.80 (3H, s), 1.63 (3H, s), 1.56 (3H, s), 1.53 (3H, s), 1.51 (3H, s), and 1.35 (3H, s), CH_3-2 and CH_3-6 of all diastereoisomers], [1.56 (3H, d, *J* 7.0 Hz), 1.49 (3H, d, *J* 7.0 Hz), 1.24 (3H, d, *J* 7.0 Hz) and 1.16 (3H, d, *J* 7.0 Hz), CH_3-5 of all diastereoisomers].

(3*S,4*S**)-2,6-Dimethyl-4-fluoro-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene and (3*S**,4*R**)-2,6-dimethyl-4-fluoro-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene (202)**

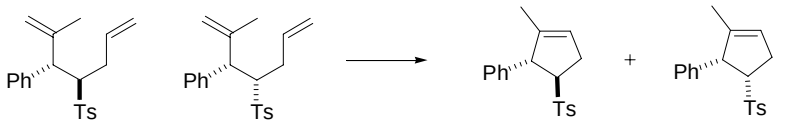


175d **202**

According to general procedure **3.2.5**, a solution of a diastereoisomeric mixture of 2,6-dimethyl-3-phenyl-4-tosyl-1,6-heptadiene **175d** (129 mg, 0.364 mmol, 1 equiv) in THF (1 mL) was treated with *n*-BuLi in cyclohexane (1.6 M, 270 μL, 0.432 mmol, 1.2 equiv). and then reacted with a solution of NFSI (141 mg, 0.447 mmol, 1.2 equiv) in THF (1.5 mL). Chromatography (5%→15% AcOEt–hexane) gave *2,6-dimethyl-4-fluoro-3-phenyl-4-(*p-*toluenesulfonyl)-1,6-heptadiene* **202** in a 4:6 mixture of diastereoisomers (51 mg, 38%) as a pale yellow oil and the starting diene **175d** (26 mg, 20%) as a white solid; R_f 0.33 (10% AcOEt–hexane); δ_H (400 MHz) 7.80 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.36-6.97 (16H, m, CH-2 Ts and CH-6 Ts of one diastereoisomer, CH-3 Ts, CH-5 Ts and Ph of both diastereoisomers), 5.23-4.46 (8H, m, CH_2-1 and CH_2-7 of both diastereoisomers), 4.25 (1H, d, *J* 34.0 Hz, CH-3 of the major diastereoisomer), 4.03 (1H, d, *J* 34.0 Hz, CH-3 of the minor diastereoisomer), [3.30-3.14 (2H, m) and 2.90-2.78 (2H, m), CH_2-5 of both diastereoisomers], 2.45 (3H, s, CH_3 Ts of the major diastereoisomer), 2.34 (3H, s, CH_3 Ts of the minor diastereoisomer), [1.81 (3H, s), 1.70 (3H, s), 1.55 (3H, s) and 1.53 (3H, s), CH_3-2 and CH_3-6 of both diastereoisomers]; δ_F (376.5 MHz) –148.4-–148.6 (1F, m, CF-4 of the minor diastereoisomer), –149.6-–149.8 (1F, m, CF-4 of the major diastereoisomer); δ_C (100 MHz) [144.9, 143.8, 143.5, 142.7, 138.4 (d, *J* 8.0 Hz), 137.8, 137.7 (d, *J* 8.0 Hz), 136.6 and 134.1 (*ipso* Ph, 2 × C Ts, C-2 and C-6 of both diastereoisomers)], [131.0, 130.6 (d, *J* 2.5 Hz), 129.9 (d, *J* 2.5 Hz), 129.7, 128.9, 128.8, 128.3 and 127.8 (*ortho* Ph, *meta* Ph and 4 × CH Ts of both diastereoisomers)], [127.3 and 127.1 (*para* Ph of both diastereoisomers)], [117.8, 117.6, 117.4 and 115.4 (d, *J* 3.0 Hz), (CH_2-1 and CH_2-7 of both diastereoisomers)], [115.1 (d, *J* 6.0 Hz) and 112.8 (d, *J* 5.0 Hz), (CF of both diastereoisomers)], 56.5 (d, *J* 17.5 Hz, CH-3 of the major

diastereoisomer), 56.1 (d, *J* 17.5 Hz, CH-3 of the minor diastereoisomer), 41.0 (d, *J* 21.0 Hz, CH_2-5 of the major diastereoisomer), 40.1 (d, *J* 21.0 Hz, CH_2-5 of the minor diastereoisomer), [24.0 (d, *J* 2.0 Hz), 23.8 (d, *J* 2.5 Hz), 23.0, 21.7, 21.5 and 21.5 (3 × CH_3 of both diastereoisomers)].

(4*S,5*S**)-1-Methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (203b-*c*) and (4*R**,5*S**)-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (203b-*t*)**



175b **203b-*t*** **203b-*c***

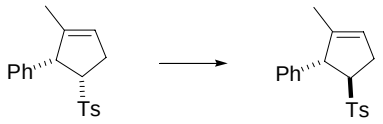
Procedure A

To a solution of a 1:1 diastereoisomeric mixture of 2-methyl-3-phenyl-4-tosyl-1,6-heptadiene **175b** (274 mg, 0.805 mmol, 1 equiv) in refluxing CH_2Cl_2 (22 mL) under nitrogen, was added (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (35 mg, 5 mol%) in CH_2Cl_2 (1.0 mL). The mixture was heated under reflux for 30 min and then concentrated under reduced pressure. Chromatography (5%→20% AcOEt–hexane) gave *(4*R**,5*S**)-1-methyl-5-phenyl-4-(*p-*toluenesulfonyl)cyclopent-1-ene* **203b-*t*** (102 mg, 41%) as a white solid and *(4*S**,5*S**)-1-methyl-5-phenyl-4-(*p-*toluenesulfonyl)cyclopent-1-ene* **203b-*c*** (101 mg, 40%) as a white solid.

Procedure B

To a solution of a 1:1 diastereoisomeric mixture of 2-methyl-3-phenyl-4-tosyl-1,6-heptadiene **175b** (40 mg, 0.12 mmol, 1 equiv) in refluxing CH_2Cl_2 (3.5 mL) under nitrogen, was added (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (4 mg, 5 mol%) in CH_2Cl_2 (500 μL). The mixture was heated under reflux for 18 h and then concentrated under reduced pressure. Chromatography (5%→20% AcOEt–hexane) gave (4*R**,5*S**)-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **203b-*t*** (18 mg, 48%) as a white solid and (4*S**,5*S**)-1-

methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **203b-*c*** (17 mg, 46%) as a white solid.



203b-*c* **203b-*t***

Procedure C

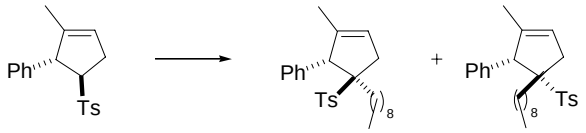
To a solution of (4*S**,5*S**)-1-methyl-4-tosyl-5-phenylcyclopent-1-ene **203b-*c*** (22 mg, 0.070 mmol, 1 equiv) in THF (500 μL) was added *t*-BuOK (8 mg, 0.07 mmol, 1 equiv). The mixture was left stirring at rt for 45 min and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), washed with H_2O (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give (4*R**,5*S**)-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **203b-*t*** (18 mg, 82%) as a yellow solid.

203b-*t*; mp 78-80 °C (50% CH_2Cl_2–petrol); R_f 0.21 (10% AcOEt–hexane); ν_{max} (film) 3069, 2959, 2846, 1455, 1313, 1299, 1277, 1144, 1086, 1041, 1026, 811 cm^{-1}; δ_H (400 MHz) 7.80 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), [7.37-7.24 (5H, m) and 6.98 (2H, dd, *J* 8.0, 1.5 Hz), Ph, CH-3 Ts and CH-5 Ts)], 5.55 (1H, m, CH-2), 4.17 (1H, m, CH-5), 3.83-3.79 (1H, m, CH-4), [3.05-2.99 (1H, m) and 2.87-2.79 (1H, m), CH_2], 2.51 (3H, s, CH_3 Ts), 1.56 (3H, m, CH_3-1); δ_C (100 MHz) [144.5, 141.7, 141.0 and 135.3 (*ipso* Ph, 2 × C Ts and C-1)], [129.7, 128.6 and 127.4 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], [126.9 and 123.6 (*para* Ph and CH-2)], 70.9 (CH-4), 55.9 (CH-5), 32.8 (CH_2), [21.6 and 14.9 (2 × CH_3)]; *m/z* (CI) 330 $[M+NH_4]^+$, 157 (Found: $[M+NH_4]^+$, 330.1528. $C_{19}H_{20}O_2S$ requires $[M+NH_4]^+$, 330.1528) (Found: C, 73.04; H, 6.46. $C_{19}H_{20}O_2S$ requires C, 73.04; H, 6.45%).

203b-*c*; mp 92-94 °C (20% AcOEt–petrol); R_f 0.16 (10% AcOEt–hexane); ν_{max} (film) 2924, 2857, 1596, 1492, 1453, 1316, 1299, 1145, 1087, 1029, 815 cm^{-1}; δ_H (400 MHz) 7.37 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), [7.26-7.23 (3H, m), 7.11-7.09 (2H, m) and 7.16 (2H, d, *J* 8.0 Hz), CH-3 Ts, CH-5 Ts and Ph], 5.58 (1H, m, CH-2), 4.18-4.12 (1H, m, CH-4), 4.93-4.91 (1H, m, CH-5), [3.00-2.92 (1H, m) and 2.56-2.49 (1H, m),

CH_2], 2.39 (3H, s, CH_3 Ts), 1.51 (3H, bs, CH_3-1); δ_C (100 MHz) [143.8, 142.7, 136.6 and 135.7 (*ipso* Ph, 2 × C Ts and C-1)], [129.3, 128.3 and 127.9 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], [127.5 and 123.1 (*para* Ph and CH-2)], 67.7 (CH-4), 55.6 (CH-5), 33.2 (CH_2-3), [21.5 and 15.0 (2 × CH_3)]; *m/z* (CI) 330 $[M+NH_4]^+$, 198, 157, 72, 58 (Found: $[M+NH_4]^+$, 330.1529. $C_{19}H_{20}O_2S$ requires $[M+NH_4]^+$, 330.1528) (Found: C, 73.11; H, 6.36. $C_{19}H_{20}O_2S$ requires C, 73.04; H, 6.45%).

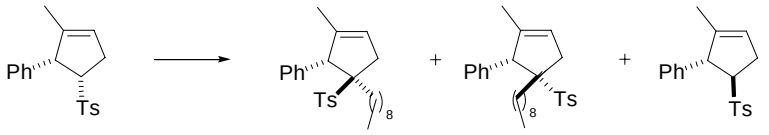
(4*R,5*S**)-1-Methyl-4-nonyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (204a-*t*) and (4*S**,5*S**)-1-methyl-4-nonyl--5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (204a-*c*)**



203b-*t* **204a-*t*** **204a-*c***

Procedure A

According to general procedure **3.2.5**, a solution of (4*R**,5*S**)-1-methyl-4-tosyl-5-phenylcyclopent-1-ene **203b-*t*** (117 mg, 0.374 mmol, 1 equiv) in THF (2 mL) was treated with *n*-BuLi in hexanes (2.42 M, 170 μL, 0.411 mmol, 1.1 equiv) and then reacted with 1-iodononane (90 μL, 0.46 mmol, 1.2 equiv). Chromatography (2%→4% AcOEt–petrol) gave *(4*R*,*5*S*)-1-methyl-4-nonyl-5-phenyl-4-(*p-*toluenesulfonyl)cyclopent-1-ene* **204a-*t*** (15 mg, 12%) as a colourless oil and *(4*S*,*5*S*)-1-methyl-4-nonyl-5-phenyl-4-(*p-*toluenesulfonyl)cyclopent-1-ene* **204a-*c*** (77 mg, 60%) as a colourless oil.



203b-*c* **204a-*t*** **204a-*c*** **203a-*t***

Procedure B

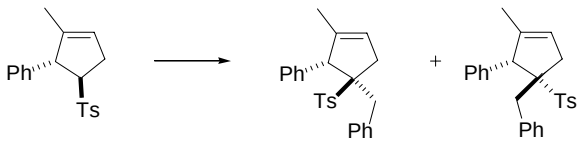
According to general procedure **3.2.5**, a solution of (4*S**,5*S**)-1-methyl-4-tosyl-5-phenylcyclopent-1-ene **203b-*c*** (101 mg, 0.322 mmol, 1 equiv) in THF (1.8 mL) was treated with *n*-BuLi in hexanes (2.42 M, 150 μL, 0.363 mmol, 1.1 equiv) and reacted with 1-iodononane (80 μL, 0.41 mmol, 1.3 equiv). Chromatography (2%→10% AcOEt–petrol) gave (4*R**,5*S**)-1-methyl-4-nonyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **204a-*t*** (2 mg, 1%) as a colourless oil, (4*S**,5*S**)-1-methyl-4-nonyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **204a-*c*** (14 mg, 10%) as a colourless oil and (4*R**,5*S**)-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **203b-*t*** (72 mg, 72%) as a white solid.

204a-*t*; R_f 0.45 (5% AcOEt–petrol); ν_{max} (film) 2925, 2853, 1598, 1492, 1455, 1314, 1299, 1289, 1143, 1085, 815 cm^{-1}; δ_H (400 MHz) 7.40 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), [2.26 (5H, bs) and 7.16 (2H, d, *J* 8.0 Hz), Ph, CH-3 Ts and CH-5 Ts], 5.53 (1H, bs, CH-2), 3.71 (1H, bs, CH-5), [3.48-3.44 (1H, m) and 2.13-2.09 (1H, m), CH_2-3], 2.38 (3H, s, CH_3 Ts), [1.96-1.88 (1H, m) and 1.75-1.64 (1H, m), $CH_2(CH_2)_7$], 1.51 (3H, bs, CH_3-1), [1.44-1.38 (1H, m) and 1.32-1.26 (13H, m), $CH_2(CH_2)_7$], 0.89 (3H, t, *J* 7.0 Hz, CH_2CH_3); δ_C (100 MHz) [143.6, 141.2, 136.4 and 135.9 (*ipso* Ph, 2 × C Ts and C-1)], [129.5, 129.0 and 127.5 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], [127.2 and 123.0 (*para* Ph and CH-2)], 75.3 (C-4), 62.0 (CH-5), [39.6, 39.0, 31.8, 30.3, 29.5, 29.4, 29.2, 24.7 and 22.6 ($C(CH_2)_8$ and CH_2-3)], [21.4, 14.8 and 14.1 (3 × CH_3)]; *m/z* (CI) 456 $[M+NH_4]^+$, 283 (Found: $[M+NH_4]^+$, 456.2943. $C_{28}H_{38}O_2S$ requires $[M+NH_4]^+$, 456.2936) (Found: C, 76.77; H, 8.62. $C_{28}H_{38}O_2S$ requires C, 76.66; H, 8.73%).

204a-*c*; R_f 0.29 (5% AcOEt–petrol); ν_{max} (film) 2955, 2921, 2851, 1681, 1660, 1652, 1633, 1469, 1457, 1276, 1263, 763, 750 cm^{-1}; δ_H (400 MHz) 7.79 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), [7.30-7.21 (5H, m) and 7.02 (2H, m), Ph, CH-3 Ts and CH-5 Ts], 5.18 (1H, bs, CH-2), 4.15 (1H, m, CH-5), [3.11 (1H, dt, *J* 18.5, 2.0 Hz) and 2.54 (1H,

dq, *J* 18.5, 2.0 Hz), CH_2-3], 2.43 (3H, s, CH_3 Ts), [1.65-1.57 (1H, m) and 1.47-1.41 (1H, m), $CH_2(CH_2)_7$], 1.28-0.98 (17H, m, $CH_2(CH_2)_7$ and CH_3-1), 0.85 (3H, t, *J* 7.0 Hz, CH_2CH_3); δ_C (100 MHz) [144.1, 141.6, 137.5 and 134.9 (*ipso* Ph, 2 × C Ts and C-1)], [130.1, 129.1 and 128.3 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], [127.2 and 124.4 (*para* Ph and CH-2)], 77.6 (C-4), 60.0 (CH-5), 39.4 (CH_2-3), [33.6, 31.8, 30.4, 29.4, 29.2, 29.1, 25.2 and 22.6 ($C(CH_2)_8$)], [21.6, 15.1 and 14.1 (3 × CH_3)]; *m/z* (CI) 456 $[M+NH_4]^+$, 231, 121 (Found: $[M+NH_4]^+$, 456.2946. $C_{28}H_{38}O_2S$ requires $[M+NH_4]^+$, 456.2936) (Found: C, 76.54; H, 8.66. $C_{28}H_{38}O_2S$ requires C, 76.66; H, 8.73%).

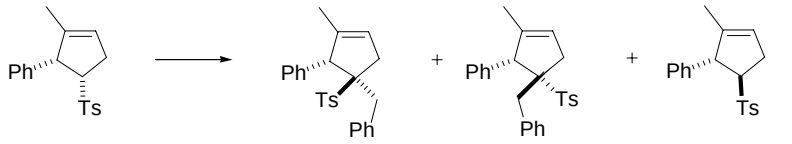
(4*S,5*S**)-4-Benzyl-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (204b-*t*) and (4*R**,5*S**)-4-benzyl-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (204b-*c*)**



203b-*t* **204b-*t*** **204b-*c***

Procedure A

According to general procedure **3.2.5**, a solution of (4*R**,5*S**)-1-methyl-5-phenyl-4-tosylcyclopent-1-ene **203b-*t*** (211 mg, 0.674 mmol, 1 equiv) in THF (5 mL) was treated with *n*-BuLi in hexanes (1.50 M, 540 μL, 0.810 mmol, 1.2 equiv) and then reacted with BnBr (100 μL, 0.841 mmol, 1.2 equiv). Chromatography (10%→50% AcOEt–petrol) gave *(4*S*,*5*S**)-4-benzyl-1-methyl-5-phenyl-4-(*p-*toluenesulfonyl)cyclopent-1-ene* **204b-*t*** (38 mg, 14%) as a white solid and *(4*R*,*5*S**)-4-benzyl-1-methyl-5-phenyl-4-(*p-*toluenesulfonyl)cyclopent-1-ene* **204b-*c*** (175 mg, 64%) as a white solid.



203b-*c* **204b-*t*** **204b-*c*** **203b-*t***

Procedure B

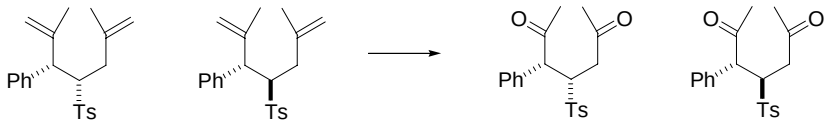
According to general procedure 3.2.5, a solution of (4*S**,5*S**)-1-methyl-5-phenyl-4-tosylcyclopent-1-ene **203b-*c*** (118 mg, 0.568 mmol, 1 equiv) in THF (3 mL) was treated with *n*-BuLi in hexanes (1.50 M, 540 μL, 0. 810 mmol, 1.4 equiv) and then reacted with BnBr (80 μL, 0.67 mmol, 1.2 equiv). Chromatography (10%→50% AcOEt–petrol) gave (4*S**,5*S**)-4-benzyl-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **204b-*t*** (21 mg, 9%) as a white solid, (4*R**,5*S**)-4-benzyl-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **204b-*c*** (57 mg, 25%) as a white solid and (4*R**,5*S**)-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene **203b-*t*** (64 mg, 36%) as a white solid.

204b-*t*; mp 124-126 °C (20% Et_2O–hexane); R_f 0.33 (10% AcOEt–petrol); ν_{max} (film) 3028, 2919, 1595, 1448, 1312, 1300, 1285, 1138, 1084, 817, 746, 692, 659, 594, 572, 512 cm^{-1}; δ_H (400 MHz) 7.75 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.35-6.95 (12H, m, 2 × Ph, CH-3 Ts and CH-5 Ts), 5.13 (1H, bs, CH-2), 4.13 (1H, bs, CH-5), 3.36 (1H, d, *J* 15.0 Hz, PhC*H*H), [2.93 (1H, dt, *J* 18.5, 2.0 Hz) and 2.75 (1H, dq, *J* 18.5, 2.0 Hz), CH_2-3], 2.41 (1H, d, *J* 15.0 Hz, PhCH*H*), 2.43 (3H, s, CH_3 Ts),1,10 (3H, s, CH_3-1); δ_C (100 MHz) [144.1, 141.2, 137.4, 137.1 and 135.1 (2 × *ipso* Ph, 2 × C Ts and C-1)], [130.8, 130.1, 129.8, 129.1, 128.8, 127.7, 127.6, 126.4 and 125.0 (2 × *ortho* Ph, 2 × *meta* Ph, 2 × *para* Ph, 4 × CH Ts and CH-2)], 78.6 (C-4), 61.1 (CH-5), [38.3 and 37.2 (CH_2-3 and CH_2Ph)], [21.6 and 14.9 (CH_3-1 and CH_3 Ts)]; *m/z* (CI) 420 $[M+NH_4]^+$, 344, 330, 247, 174 (Found: $[M+NH_4]^+$, 420.2008. $C_{26}H_{26}O_2S$ requires $[M+NH_4]^+$, 420.1997).

204b-*c*; mp 160-164 °C with decomposition (10% AcOEt–petrol); R_f 0.24 (10% AcOEt–petrol); ν_{max} (film) 3028, 2919, 1491, 1456, 1312, 1300, 1285, 1142, 1084, 1092, 817, 752, 700, 668, 594, 572, 518, 468 cm^{-1}; δ_H (400 MHz) 7.44 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.26-7.18 (12H, m, 2 × Ph, CH-3 Ts and CH-5 Ts), 5.11 (1H,

bs, CH-2), 3.86 (1H, bs, CH-5), 3.52-3.48 (1H, m, C*H*H-3), [3.47 (1H, d, *J* 13.0 Hz) and 2.97 (1H, d, *J* 13.0 Hz), $PhCH_2$], 2.43-2.41 (1H, m, CH*H*-3), 2.41 (3H, s, CH_3 Ts), 1.08 (3H, s, CH_3-1) ; δ_C (100 MHz) [143.8, 141.5, 136.2 and 135.6 (2 × *ipso* Ph, 2 × C Ts and C-1)], [131.3, 129.9, 129.8, 129.2, 127.9, 127.6, 127.4, 126.9 and 122.9 (2 × *ortho* Ph, 2 × *meta* Ph, 2 × *para* Ph, 4 × CH Ts and CH-2)], 75.9 (C-4), 61.5 (CH-5), [44.0 and 39.1 (CH_2-3 and CH_2Ph)], [21.5 and 14.3 (2 × CH_3)]; *m/z* (CI) 420 $[M+NH_4]^+$, 344, 330, 247, 174, 52 (Found: $[M+NH_4]^+$, 420.1994. $C_{26}H_{26}O_2S$ requires $[M+NH_4]^+$, 420.1997) (Found: C, 77.49; H, 6.51. $C_{26}H_{26}O_2S$ requires C, 77.58; H, 6.51%).

(3*R,4*S**)-3-Phenyl-4-(*p*-toluenesulfonyl)heptane-2,6-dione and (3*R**,4*S**)-3-phenyl-4-(*p*-toluenesulfonyl)heptane-2,6-dione (181d)**



175d **181d**

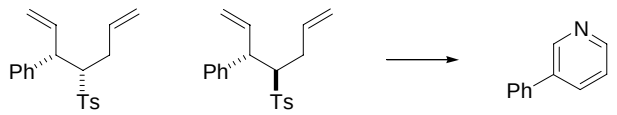
Ozone was bubbled through a solution of a 1:1 diastereoisomeric mixture of 2,6-dimethyl-3-phenyl-4-tosyl-1,6-heptadiene **175d** (179 mg, 0.504 mmol, 1 equiv) in MeOH:CH_2Cl_2 (1:5, 6 mL) at -78 °C for 10 min, until a blue colour persisted. After 5 min of bubbling O_2 through the reaction mixture, PPh_3 (414 mg, 1,58 mmol, 3.1 equiv) was added. After stirring for 3 h at -78 °C the mixture was concentrated under reduced pressure and chromatography (20% AcOEt–petrol) gave *3-phenyl-4-(*p-*toluenesulfonyl)heptane-2,6-dione* **181d** in a 1:1 mixture of diastereoisomers (130 mg, 72%), the less polar as a white solid, the more polar as a colourless gum.

*Less polar diastereoisomer of 3-phenyl-4-(*p-*toluenesulfonyl)heptane-2,6-dione* **181d**; mp 144-146 °C with decomposition (20% AcOEt–petrol); R_f 0.23 (20% AcOEt–petrol); ν_{max} (film) 1718, 1644, 1419, 1358, 1276, 1210, 1085 cm^{-1}; δ_H (270 MHz) 7.73 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.36-7.11 (7H, m, CH-3 Ts, CH-5 Ts and Ph), 5.08-4.99 (1H, m, CHTs), 4.36 (1H, d, *J* 11.0 Hz, CHPh), [2.82 (1H, dd, *J* 18.0, 7.0 Hz), 2.25 (1H, dd, *J* 18.0, 4.5 Hz), CH_2-5], 2.44 (3H, s, CH_3 Ts), [2.18 (3H, s) and 1.73 (3H, s), CH_3-1 and CH_3-7]; δ_C (67.5 MHz) [204.4 and 203.9 (2 × C=O)], [144.9, 136.5 and 133.9 (*ipso*

Ph and 2 × C Ts)], [129.8, 129.7, 129.4 and 128.5 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], 128.6 (*para* Ph), 61.6 (CHTs), 57.1 (CHPh), 40.8 (CH_2-5), [29.9, 29.5 and 21.8 (3 × CH_3)]; *m/z* (CI) 376 $[M+NH_4]^+$, 220, 203, 174 (Found: $[M+NH_4]^+$, 376.1571. $C_{20}H_{22}O_4S$ requires $[M+NH_4]^+$, 376.1583).

*More polar diastereoisomer of 3-phenyl-4-(*p-*toluenesulfonyl)heptane-2,6-dione* **181d**; R_f 0.12 (20% AcOEt–petrol); ν_{max} (film) 1717, 1644, 1419, 1358, 1276, 1210, 1085 cm^{-1}; δ_H (270 MHz) 7.33-7.05 (9H, m, Ts and Ph), 4.65-4.58 (1H, m, CHTs), 4.37 (1H, d, *J* 9.0 Hz, CHPh), [3.36 (1H, dd, *J* 18.0, 8.5 Hz), 2.71 (1H, dd, *J* 18.0, 2.5 Hz), CH_2-5], 2.34 (3H, s, CH_3 Ts), [2.18 (3H, s) and 2.08 (3H, s), CH_3-1 and CH_3-7]; δ_C (100 MHz) [205.3 and 203.9 (2 × C=O)], [143.9, 136.7 and 133.7 (*ipso* Ph and 2 × C Ts)], [129.4, 128.9, 128.1 and 127.9 (*ortho* Ph, *meta* Ph, *para* Ph and 4 × CH Ts)], 63.1 (CHTs), 57.3 (CHPh), 39.8 (CH_2-5), [30.1, 30.0 and 21.6 (3 × CH_3)]; *m/z* (CI) 376 $[M+NH_4]^+$, 220 $[M+NH_4\text{-Ts}]^+$, 203, 174 (Found: $[M+NH_4]^+$, 376.1578. $C_{20}H_{22}O_4S$ requires $[M+NH_4]^+$, 376.1583).

3-Phenylpyridine (182a)[8]

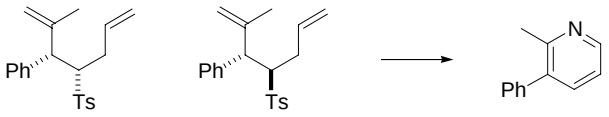


175a **182a**

According to general procedure **3.2.6**, a 1:1 diastereoisomeric mixture of 3-phenyl-4-tosyl-1,6-heptadiene **175a** (344 mg, 1.05 mmol, 1 equiv) in MeOH:CH_2Cl_2 (7.5 mL) was ozonolised and reduced with polymer bound PPh_3 (3 mmol/g resin, 1.1 g, 3.3 mmol, 3.1 equiv). The crude dialdehydes in MeOH (4 mL) were then reacted with NH_4HCO_3 (655 mg, 8.29 mmol, 7.9 equiv). Chromatography on basic alumina (BDH, 63-200 μm, 3%→5% AcOEt–petrol) gave 3-phenylpyridine **182a** (86 mg, 53%) as a colourless oil; R_f 0.25 (20% AcOEt–petrol); ν_{max} (film) 3058, 3031, 2923, 1652, 1582, 1473, 1451, 1408, 1276, 1025, 1006, 814, 755, 711, 698 cm^{-1}; δ_H (270 MHz) 8.84 (1H, d, *J* 2.0 Hz, CH-2), 8.58 (1H, dd, *J* 5.0, 2.0 Hz, CH-6), 7.86 (1H, dt, *J* 8.0, 2.0 Hz, CH-4), 7.59-7.25 (6H, m, CH-5 and Ph); δ_C (100 MHz) [148.2 and 148.1 (CH-2 and CH-6)], [137.7 and 136.8 (*ipso* Ph and C-3)], 134.6 (CH-4), [129.1 and 127.1 (*ortho* Ph and

meta Ph)], 128.2 (*para* Ph), 123.6 (CH-5); *m/z* (CI) 156 $[M+H]^+$ (Found: $[M+H]^+$, 156.0815. $C_{11}H_9N$ requires $[M+H]^+$, 156.0813) (Found: C, 84.99; H, 5.90; N, 8.97. $C_{11}H_9N$ requires C, 85.13; H, 5.85, N, 9.03). Data in agreement with those previously reported.

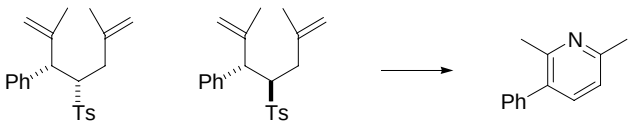
2-Methyl-3-phenylpyridine (182b)[9]



175b **182b**

According to general procedure **3.2.6**, a 1:1 diastereoisomeric mixture of 2-methyl-3-phenyl-4-tosyl-1,6-heptadiene **175b** (520 mg, 1.59 mmol, 1 equiv) in MeOH:CH_2Cl_2 (10.5 mL) was ozonolised and reduced with polymer bound PPh_3 (3 mmol/g resin, 1.6 g, 4.7 mmol, 3 equiv). The crude ketoaldehydes in MeOH (4 mL) were then reacted with NH_4HCO_3 (964 mg, 12.2 mmol, 7.7 equiv). Work-up gave a red oil (230 mg, 86%). Chromatography (10% AcOEt–petrol) gave 2-methyl-3-phenylpyridine **182b** (180 mg, 67%) as a colourless oil; R_f 0.23 (20% AcOEt–petrol); ν_{max} (film) 3083, 2925, 1657, 1428, 1377, 763, 737, 703 cm^{-1}; δ_H (270 MHz) 8.49 (1H, dd, *J* 5.0, 1.5 Hz, CH-6), 7.49-7.15 (7H, m, CH-4, CH-5 and Ph), 2.50 (3H, s, CH_3) ; δ_C (67.5 MHz) 155.9 (C-2), 148.0 (CH-6), [140.0 and 137.0 (C-3 and *ipso* Ph)], 137.2 (CH-4), [129.1 and 128.5 (*ortho* Ph and *meta* Ph)], 127.5 (*para* Ph), 121.1 (CH-5), 23.5 (CH_3); *m/z* (CI) 170 $[M+H]^+$ (Found: $[M+H]^+$, 170.0965. $C_{12}H_{11}N$ requires $[M+H]^+$, 170.0970) (Found: C, 85.08; H, 6.49; N, 8.14. $C_{12}H_{11}N$ requires C, 85.17; H, 6.55; N, 8.28). Data in agreement with those previously reported.

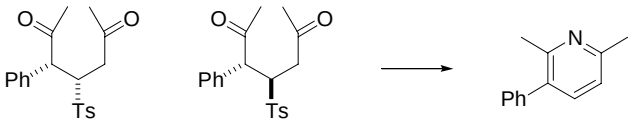
2,6-Dimethyl-3-phenylpyridine (182d)[10]



175d **182d**

Procedure A

According to general procedure **3.2.6**, a 1:1 diastereoisomeric mixture of 2,6-dimethyl-3-phenyl-4-tosyl-1,6-heptadiene **175d** (220 mg, 0.619 mmol, 1 equiv) in MeOH:CH_2Cl_2 (6 mL) was ozonolised and reduced with PPh_3 (528 mg, 2.01 mmol, 3.3 equiv). The crude diketones in MeOH (2 mL) were then reacted with NH_4HCO_3 (399 mg, 5.05 mmol, 8.2 equiv). Chromatography (5%→10% AcOEt–petrol) gave 2,6-dimethyl-3-phenylpyridine **182d** (83 mg, 73%) as a yellow oil.



181d **182d**

Procedure B

To a solution of a 1:1 diastereoisomeric mixture of 3-phenyl-4-tosylheptane-2,6-dione **181d** (71 mg, 0.198 mmol, 1 equiv) in CH_2Cl_2:MeOH (1:2; 4.5 mL) at rt was added NH_4HCO_3 (153 mg, 1.94 mmol, 9.8 equiv) and the mixture was exposed to microwave irradiation for 10 min at 100 °C. The yellow solution was concentrated under reduced pressure. The red residue was dissolved in CH_2Cl_2 (30 mL) and then washed with H_2O (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 2,6-dimethyl-3-phenylpyridine **182d** (36 mg, 98%) as a yellow oil.

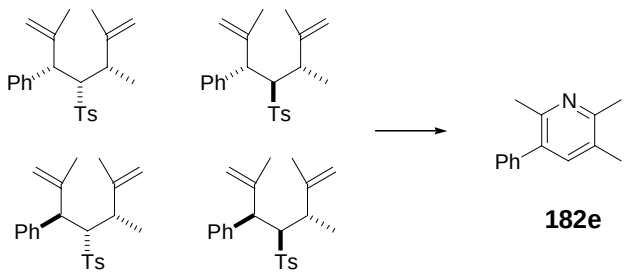
Procedure C

A solution of a 1:1 diastereoisomeric mixture of 3-phenyl-4-tosyl-heptane-2,6-dione **181d** (67 mg, 0.187 mmol, 1 equiv) in CH_2Cl_2:MeOH (5:1; 3 mL) at rt and under nitrogen was treated with a methanolic solution of NH_3 (2 M, 1 mL) for 15 h. The

orange solution was concentrated under reduced pressure. The orange residue was dissolved in CH_2Cl_2 (25 mL), washed with H_2O (2 × 25 mL), dried ($MsSO_4$) and concentrated under reduced pressure to give 2,6-dimethyl-3-pheny pyridine **182d** (34 mg, 98%) as a yellow oil.

182d, R_f 0.26 (10% AcOEt–petrol); ν_{max} (film) 2923, 1644, 1461, 1434, 1388, 1262, 1010, 766, 701 cm^{-1}; δ_H (270 MHz) 7.41-7.26 (6H, m, CH-4 and Ph), 7.00 (1H, d, *J* 7.5 Hz, CH-5), [2.55 (3H, s) and 2.46 (3H, s), 2 × CH_3]; δ_C (67.5 MHz) [156.5 and 155.0 (C-2 and C-6)], [140.2 and 134.0 (C-3 and *ipso* Ph)], 137.6 (CH-4), [129.2 and 128.4 (*ortho* Ph and *meta* Ph)], 127.3 (*para* Ph), 120.6 (CH-5), [24.3 and 23.4 (2 × CH_3)]; *m/z* (CI) 184 $[M+H]^+$ (Found: $[M+H]^+$, 184.1118. $C_{13}H_{13}N$ requires $[M+H]^+$, 184.1126) (Found: C, 85.11; H, 7.03; N, 7.54. $C_{13}H_{13}N$ requires C, 85.21; H, 7.15; N, 7.64). Data in agreement with those previously reported.

3-Phenyl-2,5,6-trimethylpyridine (182e)

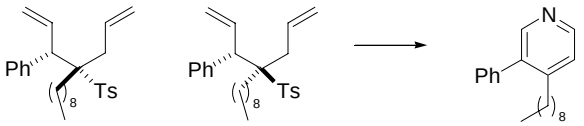


175e **182e**

According to general procedure 3.2.6, a diastereoisomeric mixture of 3-phenyl-4-tosyl-2,5,6-trimethyl-1,6-heptadiene **175e** (78 mg, 0.211 mmol, 1 equiv) in MeOH:CH_2Cl_2 (2 mL) was ozonolised and reduced with Me_2S (0.9 mL, 21 mmol, 99 equiv). The crude diketones in MeOH (1 mL) were then reacted with NH_4HCO_3 (133 mg, 1.68 mmol, 8 equiv). Chromatography (10% AcOEt–petrol) gave *3-phenyl-2,5,6-trimethylpyridine* **182e** (21 mg, 81%) as a pale yellow oil; R_f 0.17 (10% AcOEt–petrol); ν_{max} (film) 2922, 2856, 1605, 1554, 1460, 1429, 1367, 1203, 1142, 1074, 1018, 1001, 958, 906, 762, 702 cm^{-1}; δ_H (270 MHz) 7.44-7.25 (6H, m, CH-4 and Ph), [2.52 (3H, s) and 2.45 (3H,s), CH_3-2 and CH_3-6], 2.27 (3H, s, CH_3-5); δ_C (67.5 MHz) [155.1 and 151.9 (C-2 and C-

6)], [140.0, 134.6 and 128.7 (C-3, C-5 and *ipso* Ph)], 139.0 (CH-4), [129.2 and 128.4 (*ortho* Ph and *meta* Ph)], 127.3 (*para* Ph), [22.6, 22.1 and 18.7 (3 × CH_3)]; *m/z* (CI) 198 $[M+H]^+$, (Found: $[M+H]^+$, 198.1282. $C_{14}H_{15}N$ requires $[M+H]^+$, 198.1283) (Found: C, 85.33; H, 7.59; N, 6.99. $C_{13}H_{13}N$ requires C, 85.24; H, 7.66; N, 7.10).

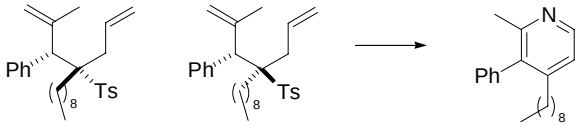
4-Nonyl-3-phenylpyridine (182f)



180b **182f**

According to general procedure **3.2.6**, a 3:7 diastereoisomeric mixture of *3-phenyl-4-nonyl-4-tosyl-1,6-heptadiene* **180b** (320 mg, 0.706 mmol, 1 equiv) in MeOH:CH_2Cl_2 (8.2 mL) was ozonolised and reduced with Me_2S (3.1 mL, 71 mmol, 101 equiv). The crude dialdehydes in MeOH (3.5 mL) were then reacted with NH_4HCO_3 (443 mg, 5.60 mmol, 7.9 equiv). Work-up gave a red oil (196 mg, 98%). Chromatography on basic alumina (BDH, 63-200 μm, 4% AcOEt–petrol) gave *4-nonyl-3-phenylpyridine* **182f** (147 mg, 74%) as a red oil; R_f 0.19 (10% AcOEt–petrol); ν_{max} (film) 2954, 2854, 1638, 1465, 1377, 1007, 830, 763, 702 cm^{-1}; δ_H (270 MHz) 8.47 (1H, d, *J* 5.0 Hz, CH-6), 8.40 (1H, s, CH-2), 7.48-7.20 (6H, m, CH-5 and Ph), 2.60-2.54 (2H, m, $CH_2(CH_2)_7$), [1.46-1.40 (2H, m) and 1.23-1.16 (12H, m), $CH_2(CH_2)_7$], 0.85 (3H, t, *J* 6.5 Hz, CH_3); δ_C (100 MHz) 150.0 (C-4), [149.5 and 147.7 (CH-2 and CH-6)], 137.7 (C-3 and *ipso* Ph), [129.3 and 128.4 (*ortho* Ph and *meta* Ph)], [127.7 and 124.1 (*para* Ph and CH-5)], [32.4, 31.8, 30.2, 29.3, 29.2, 29.2 and 29.2 ($(CH_2)_7CH_2$)], 22.6 ($(CH_2)_7CH_2$), 14.1 (CH_3); *m/z* (CI) 563 $[2M+H]^+$, 282 $[M+H]^+$, 156 (Found: $[M+H]^+$, 282.2214. $C_{20}H_{27}N$ requires $[M+H]^+$, 282.2222) (Found: C, 85.28; H, 9.57; N, 4.89. $C_{20}H_{27}N$ requires C, 85.35; H, 9.67; N, 4.98%).

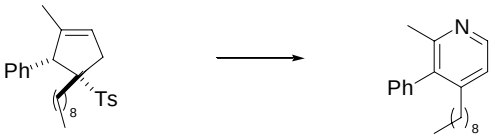
2-Methyl-4-nonyl-3-phenylpyridine (182g)



180c **182g**

Procedure A

According to general procedure **3.2.6**, a 4:6 diastereoisomeric mixture of 2,6-dimethyl-4-nonyl-3-phenyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene **180c** (89 mg, 0.19 mmol, 1 equiv) in MeOH:CH_2Cl_2 (2 mL) was ozonolised and reduced with Me_2S (830 μL, 19.2 mmol, 100 equiv). The crude ketoaldehydes in MeOH (1.5 mL) were then reacted with NH_4HCO_3 (120 mg, 4.87 mmol, 7.9 equiv). Work-up gave an orange oil (56 mg, 99%). Chromatography (10% AcOEt–petrol) gave *2-methyl-4-nonyl-3-phenylpyridine* **182g** (41 mg, 73%) as a pale yellow oil.



204a-*c* **182g**

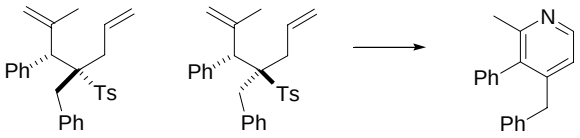
Procedure B

According to general procedure **3.2.6**, (4*S**-5*S**)-2-methyl-4-nonyl-3-phenyl-4-tosylcyclopent-1-ene **204-*c*** (127 mg, 0.290 mmol, 1 equiv) in MeOH:CH_2Cl_2 (3 mL) was ozonolised and reduced with Me_2S (1.30 mL, 30.0 mmol, 104 equiv). The crude ketoaldehydes in MeOH (2 mL) were then reacted with NH_4HCO_3 (191 mg, 2.42 mmol, 8.3 equiv). Chromatography (10% AcOEt–petrol) gave 2-methyl-4-nonyl-3-phenylpyridine **182g** (13 mg, 15%) as a pale yellow oil and in an impure form.

182g; R_f 0.27 (10% AcOEt–petrol); ν_{max} (film) 2954, 2923, 2855, 1683, 1660, 1649, 1633, 1465, 1409, 1151, 1091, 1068, 1061, 761 cm^{-1}; δ_H (400 MHz) 8.37 (1H, d, *J* 5.0 Hz, CH-6), [7.46-7.38 (3H, m) and 7.15-7.14 (2H, m), Ph], 7.06 (1H, d, *J* 5.0 Hz, CH-5), 2.33-2.29 (2H, m, $CH_2(CH_2)_7$), 2.26 (3H, s, CH_3-2), [1.42-1.39 (2H, m) and 1.25-

1.13 (12H, m), $CH_2(CH_2)_7$], 0.87 (3H, t, *J* 7.0 Hz, CH_2CH_3); δ_C (100 MHz) 156.2 (C-2), 149.9 (C-4), 147.4 (CH-6), [138.5 and 136.6 (C-3 and *ipso* Ph)], [129.1 and 128.5 (*ortho* Ph and *meta* Ph)], [127.2 and 121.5 (*para* Ph and CH-5)], [32.9, 31.8, 30.1, 29.3, 29.2, 29.2 and 29.1 ($(CH_2)_7CH_2$)], 23.7 (CH_3-2), 22.6 ($(CH_2)_7CH_2$), 14.1 (CH_2CH_3); *m/z* (CI) 591 $[2M+H]^+$, 296 $[M+H]^+$, 282 (Found: $[M+H]^+$, 296.2369. $C_{21}H_{29}N$ requires $[M+H]^+$, 296.2378) (Found: C, 85.28; H, 9.87; N, 4.89. $C_{20}H_{27}N$ requires C, 85.37; H, 9.89; N, 4.74%).

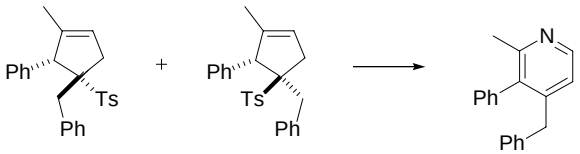
4-Benzyl-2-methyl-3-phenylpyridine (182h)



180d **182h**

Procedure A

According to general procedure **3.2.6**, a 4:6 diastereoisomeric mixture of 2-methyl-3-phenyl-4-benzyl-4-(*p*-toluenesulfonyl)-1,6-heptadiene **180d** (92 mg, 0.21 mmol, 1 equiv) in MeOH:CH_2Cl_2 (2.5 mL) was ozonolised and reduced with Me_2S (950 μL, 21.9 mmol, 103 equiv). The crude ketoaldehydes in MeOH (2 mL) were then reacted with NH_4HCO_3 (139 mg, 1.76 mmol, 8.3 equiv). Chromatography (20% AcOEt–petrol) gave *4-benzyl-2-methyl-3-phenylpyridine* **182h** (42 mg, 75%) as a pale yellow oil.



204b-*c* **204b-*t*** **182h**

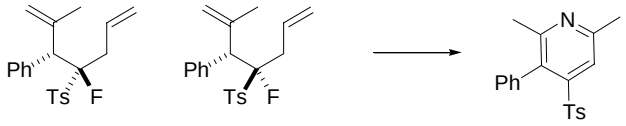
Procedure B

According to general procedure **3.2.6**, a 7:3 diastereosiomeric mixture of (4*R**,5*S**)-4-benzyl-1-methyl-5-phenyl-4-tosylcyclopent-1-ene **204b-*c*** and (4*S**,5*S**)-4-benzyl-1-methyl-5-phenyl-4-tosylcyclopent-1-ene **204b-*t*** (106 mg, 0.262 mmol, 1 equiv) in MeOH–CH_2Cl_2 (3 mL) was ozonolised and reduced with Me_2S (1.2 mL, 27 mmol, 106

equiv). The crude ketoaldehydes in MeOH (2 mL) were then reacted with NH_4HCO_3 (174 mg, 2.20 mmol, 8.4 equiv). Chromatography (20% AcOEt–petrol) gave *4-benzyl-2-methyl-3-phenylpyridine* **182h** (14 mg, 21%) as a pale yellow oil and in an impure form.

182h; R_f 0.31 (20% AcOEt–petrol); ν_{max} (film) 3028, 2923, 2851, 1602, 1579, 1561, 1495, 1453, 1444, 1407, 1243, 1156, 1074, 1030, 1009, 915, 848, 812, 763, 701, 633 cm^{-1}; δ_H (400 MHz) 8.39 (1H, d, *J* 5.0 Hz, CH-6), [7.43-7.34 (3H, m), 7.22-7.14 (3H, m), 7.10-7.09 (2H, m) and 6.92-6.90 (2H, m), 2 × Ph], 6.96 (1H, d, *J* 5.0 Hz, CH-5), 3.69 (2H, s, CH_2), 2.28 (3H, s, CH_3); δ_C (100 MHz) 156.6 (C-2), 148.0 (C-4), 147.8 (CH-6), [139.4, 138.3 and 136.8 (C-3 and 2 × *ipso* Ph)], [129.2, 129.0, 128.7 and 128.4 (2 × *ortho* Ph and 2 × *meta* Ph)], [127.4 and 126.3 (2 × *para* Ph)], 122.3 (CH-5), 39.1 (CH_2), 23.8 (CH_3); *m/z* (CI) 260 $[M+H]^+$ (Found: $[M+H]^+$, 260.1445. $C_{19}H_{17}N$ requires $[M+H]^+$, 260.1439) (Found: C, 88.12; H, 6.70; N, 5.33. $C_{19}H_{17}N$ requires C, 87.99; H, 6.61; N, 5.40%).

2,6-Dimethyl-3-phenyl-4-(*p*-toluenesulfonyl)pyridine (209)



202 **209**

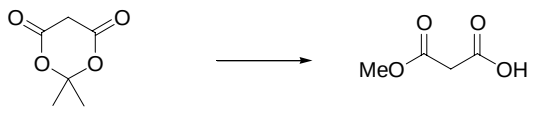
According to general procedure **3.2.6**, a 4:6 diastereoisomeric mixture of 2,6-dimethyl-3-phenyl-4-fluoro-4-(*p*-toluenesulfonyl)-1,6-heptadiene **202** (93 mg, 0.25 mmol, 1 equiv) in MeOH:CH_2Cl_2 (3 mL) was ozonolised and reduced with Me_2S (1.8 mL, 25 mmol, 100 equiv). The crude diketones in MeOH (1.5 mL) were then reacted with NH_4HCO_3 (163 mg, 2.06 mmol, 8 equiv). Fractionlynx purification gave *2,6-dimethyl-3-phenyl-4-(*p*-toluenesulfonyl)pyridine* **209** (3 mg, 3%) as a colourless oil; R_f 0.55 (50% AcOEt–hexane); δ_H (400 MHz) 8.01 (1H, s, CH-5), [7.34-7.31 (1H, m), 7.23-7.21 (2H, m), 7.09-7.02 (4H, m) and 6.78 (2H, d, *J* 5.0 Hz), Ph and Ts], [2.73 (3H, s), 2.37 (3H, s) and 2.19 (3H, s), 3 × CH_3]; δ_C (100 MHz) [159.1 and 157.8 (C-2 and C-6)], [148.9 and 144.3 (C-4 and C-4 Ts)], [136.7, 134.1 and 131.6 (C-3, *ipso* Ph and C-1 Ts)], [130.1,

129.3, 128.0, 128.0 and 127.9 (*ortho* Ph, *meta* Ph, *para* Ph and 4 × CH Ts)], 118.6 (CH-5), [24.0, 23.0 and 21.6 (CH_3-2, CH_3-6 and CH_3 Ts)]; *m/z* (CI) 338 $[M+H]^+$, 201 (Found: $[M+H]^+$, 338.1209. $C_{20}H_{19}NO_2S$ requires $[M+H]^+$, 338.1215).

3.3.2 Compounds relevant to the attempts towards expanding the scope of the methodology for pyridine synthesis

3.3.2.1 Towards the introduction of chlorine-, carboxymethyl- and TMS- groups onto the pyridine

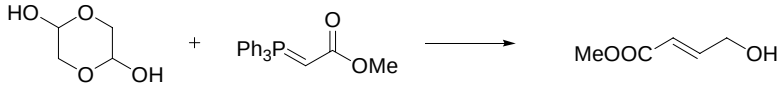
Methyl malonate (222)[3,11]



190 **222**

According to general procedure **3.2.1**, Meldrum's acid **190** (1.523 g, 10.56 mmol, 1 equiv) was reacted with methanol (500 μL, 12.3 mmol, 1.2 equiv) at 90 °C to give methyl malonate **222** (1.24 g, 94%) as a colourless liquid; δ_H (300 MHz) 3.82 (3H, s, CH_3), 3.48 (2H, s, CH_2); δ_C (125 MHz) 170.4 (COOH), 167.6 (*C*$OOCH_3$), 52.9 (CH_3), 40.3 (CH_2); *m/z* (CI) 136 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 136.0610. $C_4H_6O_4$ requires $[M+NH_4]^+$, 136.0610). Data in agreement with those previously reported.

(*E*)-3-Carbomethoxy-2-propen-1-ol (219a)[12]

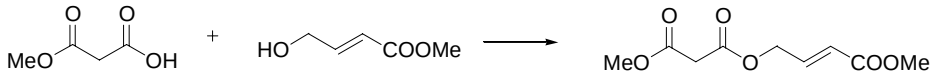


217 **218** **219a**

To a solution/suspension of glycol aldehyde dimer **217** (499 mg, 4.16 mmol, 1 equiv) in refluxing benzene (50 mL) under nitrogen was added, via dropping funnel, a solution of methoxycarbonylmethylenetriphenylphosphorane **218** (2.809 g, 8.340 mmol, 2 equiv) in benzene (60 mL). As the product formed, the undissolved glycol aldehyde dimer was taken into solution. The mixture was refluxed for 4 h and then concentrated under reduced pressure. Chromatography (30% Et_2O–petrol) gave (*E*)-3-carbomethoxy-2-

propen-1-ol **219a** (818 mg, 84%) as a colourless liquid; R_f 0.38 (50% Et_2O–petrol); ν_{max} (film) 3421, 2954, 2360, 1722, 1707, 1662, 1438, 1309, 1290, 1197, 1173, 1099, 1014, 959, 929, 834, 749 cm^{-1}; δ_H (270 MHz) 7.02 (1H, dt, *J* 16.0, 4.0 Hz, CH-2), 6.09 (1H, dt, *J* 16.0, 2.0 Hz, CH-3), 4.33 (2H, dd, *J* 4.0, 2.0 Hz, CH_2), 3.72 (3H, s, CH_3); δ_C (67.5 MHz) 167.0 (C=O), 147.3 (CH-2), 119.7 (CH-3), 61.9 (CH_2), 51.8 (CH_3). Data in agreement with those previously reported.

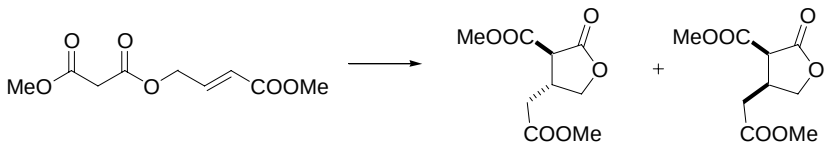
(*E*)-3-Carbomethoxy-2-propenyl methyl malonate (223a)



222 **219a** **223a**

According to general procedure **3.2.3**, methyl malonate **222** (965 mg, 8.17 mmol, 1.3 equiv) was reacted with (*E*)-3-carbomethoxy-2-propen-1-ol **219a** (747 mg, 6.43 mmol, 1 equiv), DMAP (115 mg, 0.941 mmol, 0.1 equiv) and DCC (2.062 g, 9.99 mmol, 1.6 equiv) in CH_2Cl_2 (50 mL). Chromatography (30% Et_2O–petrol) gave *(*E*)-3-carbomethoxy-2-propenyl methyl malonate* **223a** (925 mg, 67%) as a colourless liquid; R_f 0.25 (30% Et_2O–petrol); ν_{max} (film) 2954, 1731, 1725, 1455, 1440, 1339, 1316, 1197, 1176, 1151, 1072, 1019, 967, 763, 751 cm^{-1}; δ_H (270 MHz) 6.92 (1H, dt, *J* 16.0, 4.5 Hz, C*H*CH_2O), 6.05 (1H, dt, *J* 16.0, 2.0 Hz, =C*H*$COOCH_3$), 4.86 (2H, dd, *J* 4.5, 2.0 Hz, CH_2O), [3.76 (3H, s) and 3.74 (3H, s), 2 × CH_3], 3.44 (2H, s, $OOCCH_2COO$); δ_C (67.5 MHz) [166.6, 166.1 and 165.8 (3 × C=O)], 140.7 (*C*HCH_2O), 122.1 (=*C*$HCOOCH_3$), 63.4 (CH_2O), [52.7 and 51.8 (2 × CH_3)], 41.1 ($OOCCH_2COO$); *m/z* (CI) 234 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 234.0969. $C_9H_{12}O_6$ requires $[M+NH_4]^+$, 234.0978) (Found: C, 50.02; H, 5.56. $C_9H_{12}O_6$ requires C, 50.00; H, 5.59%).

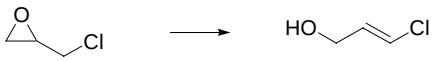
(3*S,4*R**)-Methyl-4-(2-methoxy-2-oxoethyl)-2-oxotetrahydrofuran-3-carboxylate (224-*t*) and (3*S**,4*S**)-methyl-4-(2-methoxy-2-oxoethyl)-2-oxotetrahydrofuran-3-carboxylate (224-*c*)**



223a **224-*t*** **224-*c***

According to general procedure **3.2.4**, (*E*)-3-carbomethoxy-2-propenyl methyl malonate **223a** (843 mg, 3.90 mmol, 2 equiv) was reacted with *t*-BuOK (438 mg, 3.91 mmol, 2 equiv) and TsF (358 mg, 2.05 mmol, 1 equiv) in DMSO (2 mL). Chromatography (30% petrol–Et_2O) gave *(3*S**,4*R**)-methyl-4-(2-methoxy-2-oxoethyl)-2-oxotetrahydrofuran-3-carboxylate* **224-*t*** and *(3*S**,4*S**)-methyl-4-(2-methoxy-2-oxoethyl)-2-oxotetrahydrofuran-3-carboxylate* **224-*c*** in a 9:1 mixture (329 mg, 39%) as a yellow gum; R_f 0.26 (30% petrol–Et_2O); ν_{max} (film) 2957, 1780, 1737, 1438, 1358, 1264, 1207, 1153, 1021 cm^{-1}; δ_H (500 MHz) [4.67-4.63 (1H, m) and 4.02-4.00 (1H, m), CH_2-5 of **224-*t***], [4.57-4.54 (1H, m) and 4.19-4.16 (1H, m), CH_2-5 of **224-*c***], [3.83 (3H, s) and 3.70 (3H, s), 2 × CH_3 of **224-*t***], [3.78 (3H, s) and 3.71 (3H, s), 2 × CH_3 of **224-*c***], 3.41-3.31 (3H, m, CH-3 of **224-*t***, CH-3 of **224-*c*** and CH-4 of **224-*t***), 3.30-3.20 (1H, m, CH-4 of **224-*c***), 3.69-2.45 (2H, m, C*H*$_2$COOCH$_3$ of **224-*c***), [2.63 (1H, dd, *J* 16.5, 6.0 Hz) and 2.55 (1H, dd, *J* 16.5, 7.5 Hz), C*H*$_2$COOCH$_3$ of **224-*t***]; δ_C (100 MHz) [171.6, 171.1, 170.8, 167.4 and 166.9 (3 × C=O of **224-*t*** and **224-*c***)], 71.8 (CH_2-5 of **224-*c***), 71.2 (CH_2-5 of **224-*t***), [53.1, 52.8, 52.0, 51.3, 49.4, 36.0 and 35.3 (CH-3, CH-4 and 2 × CH_3 of **224-*t*** and **224-*c***)], 35.7 (*C*H_2COOCH$_3$ of **224-*t***), 32.5 (*C*H_2COOCH$_3$ of **224-*c***); *m/z* (CI) 234 $[M+NH_4]^+$, 217 $[M+H]^+$ (Found: $[M+H]^+$, 217.0707. $C_9H_{12}O_6$ requires $[M+H]^+$, 217.0712).

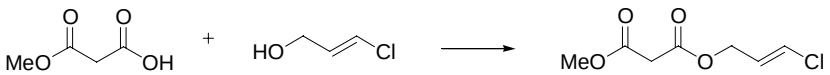
(*E*)-3-Chloro-2-propen-1-ol (219b)[13,14]



220 **219b**

To a solution of *epi*-chlorhydrin **220** (4.0 mL, 51 mmol, 1 equiv) and TMEDA (7.8 mL, 52 mmol, 1 equiv) in THF (200 mL) at –78 °C and under nitrogen was added dropwise a solution of *n*-BuLi in hexanes (2.36 M, 26 mL, 61 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min at –78 °C and for 2h at 0 °C, then quenched with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (9 × 250 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (10% AcOEt–petrol) gave (*E*)-3-chloro-2-propen-1-ol **219b** (2.8 g, 58%) as a pale yellow liquid; R_f 0.26 (20% AcOEt–petrol); ν_{max} (film) 3301, 2925, 2873, 1636, 1263, 1088, 1016, 962, 929, 806, 759 cm^{-1}; δ_H (270 MHz) 6.20 (1H, dd, *J* 13.5, 1.5 Hz, CH-3), 6.06-5.94 (1H, m, CH-2), 4.06 (2H, dd, *J* 6.0, 1.5 Hz, CH_2), 3.88 (1H, bs, OH); δ_C (67.5 MHz) 132.2 (CH-2), 120.5 (CH-3), 61.1 (CH_2). Data in agreement with those previously reported.

(*E*)-3-Chloroallyl methyl malonate (223b)

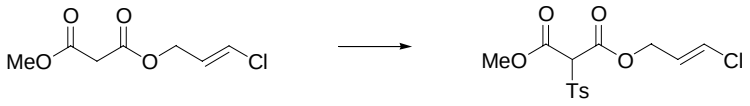


222 **219b** **223b**

According to general procedure **3.2.3**, methyl malonate **222** (528 mg, 4.47 mmol, 1 equiv) was reacted with (*E*)-3-chloro-2-propen-1-ol **219b** (550 mg, 5.95 mmol, 1.3 equiv), DMAP (56 mg, 0.46 mmol, 0.1 equiv) and DCC (1.13 g, 5.48 mmol, 1.2 equiv) in CH_2Cl_2 (40 mL). Chromatography (10% AcOEt–petrol) gave *(*E*)-3-chloroallyl methyl malonate* **223b** (691 mg, 80%) as a colourless oil; R_f 0.26 (10% AcOEt–petrol); ν_{max} (film) 2956, 1754, 1737, 1438, 1341, 1276, 1205, 1150, 1020, 937, 763, 750 cm^{-1}; δ_H (270 MHz) 6.37-6.32 (1H, m, CHCl), 6.07-5.97 (1H, m, C*H*=CHCl), 4.61 (2H, dd, *J* 6.5, 1.0 Hz, CH_2O), 3.74 (3H, s, CH_3), 3.39 (2H, s, $OOCCH_2COO$); δ_C (100 MHz) [166.7 and 166.0 (2 × C=O)], [126.8 and 124.1 (*C*H=CHCl and CH=*C*HCl)], 63.2

(CH_2O), 52.6 (CH_3), 41.1 ($OOCCH_2COO$); *m/z* (CI) 210 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 210.0527. $C_7H_9ClO_4$ requires $[M+NH_4]^+$, 210.0533) (Found: C, 43.72; H, 4.80. $C_7H_9ClO_4$ requires C, 43.65; H, 4.71%).

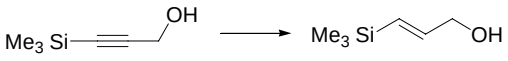
(±)-(*E*)-1-(3-Chloroallyl) 3-methyl 2-(*p*-toluenesulfonyl)malonate (215b)



223b **215b**

According to general procedure **3.2.4**, (*E*)-3-chloroallyl methyl malonate **223b** (549 mg, 2.85 mmol, 2 equiv) was reacted with *t*-BuOK (324 mg, 2.89 mmol, 2 equiv) and TsF (259 mg, 1.49 mmol, 1 equiv) in DMSO (1.5 mL). Chromatography (10%→20% AcOEt–petrol) gave *(±)-(*E*)-1-(3-chloroallyl) 3-methyl 2-(*p*-toluenesulfonyl)malonate* **215b** (315 mg, 64%) as a colourless gum and the excess starting malonate **223b** (245 g, 66% unreacted); R_f 0.16 (20% AcOEt–petrol); ν_{max} (film) 2955, 1743, 1713, 1595, 1437, 1334, 1275, 1253, 1147, 1081, 763, 750 cm^{-1}; δ_H (270 MHz) 7.83 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.36 (2H, d, *J* 8.5 Hz, CH-3 Ts and CH-5 Ts), 6.34-6.29 (1H, m, CHCl), 5.98-5.89 (1H, m, C*H*=CHCl), 4.69 (1H, s, CHTs), 4.64-4.61 (2H, m, CH_2O), 3.78 (3H, s, CH_3O), 2.46 (3H, s, CH_3 Ts); δ_C (100 MHz) [161.2 and 160.6 (2 × C=O)], [146.3 and 140.0 (2 × C Ts)], [130.1 and 129.6 (4 × CH Ts)], [125.8 and 125.1 (CHCl and *C*H=CHCl)], 74.3 (CHTs), 64.4 (CH_2O), 53.8 (CH_3O), 21.8 (CH_3 Ts); *m/z* (CI) 364 $[M+NH_4]^+$, 210, 174 (Found: $[M+NH_4]^+$, 364.0625. $C_{14}H_{15}ClO_6S$ requires $[M+NH_4]^+$, 364.0622) (Found: C, 48.51; H, 4.25. $C_{14}H_{15}ClO_6S$ requires C, 48.49; H, 4.36%).

(*E*)-3-Trimethylsilyl-2-propen-1-ol (219c)[15,16]

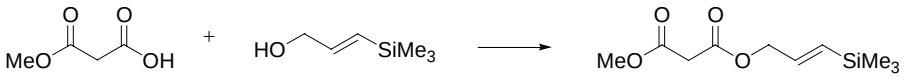


221 **219c**

To a commercial solution of SMEAH in toluene (3.5 M, 7.2 mL, 25 mmol, 1.6 equiv) and Et_2O (10 mL) at 0 °C and under nitrogen, was added over 30 min a solution of 3-

trimethylsilyl propargyl alcohol **221** (2.007 g, 15.65 mmol, 1 equiv) in Et_2O (10 mL). After complete addition the cooling bath was removed and the solution was left stirring at rt for 1 h. The mixture was then cooled to 0 °C, quenched with aqueous HCl (2N, 100 mL) and then extracted with Et_2O (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give (*E*)-3-trimethylsilyl-2-propen-1-ol **219c** (1.7 g, 84%) as a colourless liquid; R_f 0.24 (10%, AcOEt–petrol); δ_H (400 MHz) 6.19 (1H, dt, *J* 19.0, 4.5 Hz, CH-2), 5.93 (1H, dt, *J* 19.0, 1.5 Hz, CH-3), 4.19 (2H, dd, *J* 4.5, 1.5 Hz, CH_2), 0.08 (9H, s, 3 × CH_3); δ_C (100 MHz) 144.8 (CH-2), 129.6 (CH-3), 65.6 (CH_2), -1.36 (3 × CH_3). Data in agreement with those previously reported.

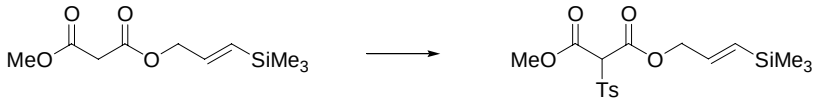
(*E*)-Methyl 3-(trimethylsilyl)allyl malonate (223c)



222 **219c** **223c**

According to general procedure **3.2.3**, methyl malonate **222** (1.388 g, 11.76 mmol, 1 equiv) was reacted with (*E*)-3-trimethylsilyl-2-propen-1-ol **219c** (1.599 g, 12.27 mmol, 1 equiv), DMAP (148 mg, 1.21 mmol, 0.1 equiv) and DCC (2.993 g, 14.51 mmol, 1.2 equiv) in CH_2Cl_2 (60 mL). Chromatography (4%→8% AcOEt–hexane) gave *(*E*)-methyl 3-(trimethylsilyl)allyl malonate* **223c** (1.90 g, 70%) as a colourless oil; R_f 0.43 (10% AcOEt–petrol); ν_{max} (film) 2956, 1756, 1741, 1438, 1334, 1249, 1208, 1150, 1021, 991, 863, 840, 692 cm^{-1}; δ_H (400 MHz) 6.06 (1H, dt, *J* 18.5, 5.0 Hz, C*H*=CHTMS), 5.98-5.93 (1H, m, CH=C*H*TMS), 4.67 (2H, dd, *J* 4.5, 1.0 Hz, CH_2O), 3.76 (3H, s, CH_3O), 3.43 (2H, s, $OOCCH_2COO$), 0.08 (9H, s, 3 × CH_3 TMS); δ_C (100 MHz) [166.9 and 166.1 (2 × C=O)], [138.4 and 134.1 (*C*H=CHTMS and CH=*C*HTMS)], 67.8 (CH_2O), 52.5 (CH_3O), 41.3 ($OOCCH_2COO$), -1.5 (3 × CH_3 TMS); *m/z* (CI) 248 $[M+NH_4]^+$, 175, 90 (Found: $[M+NH_4]^+$, 248.1317. $C_{10}H_{18}O_4Si$ requires $[M+NH_4]^+$, 248.1318) (Found: C, 52.26; H, 7.79. $C_{10}H_{18}O_4Si$ requires C, 52.14; H, 7.88%).

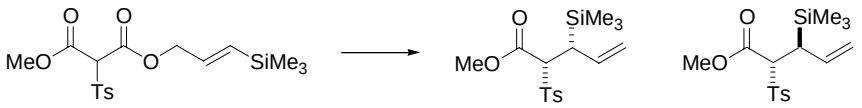
(±)-(*E*)-1-Methyl 3-[3-(trimethylsilyl)allyl] 2-(*p*-toluenesulfonyl)malonate (215c)



223c **215c**

According to general procedure **3.2.4**, (*E*)-methyl 3-(trimethylsilyl)allyl malonate **223c** (1.901 g, 8.253 mmol, 2 equiv) was reacted with *t*-BuOK (935 mg, 8.33 mmol, 2 equiv) and TsF (724 mg, 4.16 mmol, 1 equiv) in DMSO (4.1 mL). Chromatography (2%→10% AcOEt–hexane) gave *(±)-(*E*)-1-methyl 3-[3-(trimethylsilyl)allyl] 2-(*p*-toluenesulfonyl)malonate* **215c** (651 mg, 41%) as a colourless gum and the excess starting malonate **223c** (880 mg, 58% unreacted); R_f 0.07 (10% AcOEt–hexane); ν_{max} (film) 2955, 1746, 1436, 1338, 1305, 1290, 1275, 1249, 1212, 1194, 1181, 1151, 1082, 863, 840, 817 cm^{-1}; δ_H (400 MHz) 7.86 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), 7.35 (2H, d, *J* 8.0 Hz, CH-3 Ts and CH-5 Ts), 5.98-5.96 (2H, m, 2 × =CH), 5.01 (1H, s, CHTs), 4.67-4.66 (2H, m, CH_2), 3.79 (3H, s, CH_3O), 2.45 (3H, s, CH_3 Ts), 0.07 (9H, s, 3 × CH_3 TMS); δ_C (100 MHz) [161.4 and 160.6 (2 × C=O)], 146.1 (C-4 Ts), [137.3 and 135.3 (2 × =CH)], 134.1 (C-1 Ts), [130.2 and 129.5 (4 × CH Ts)], 74.4 (CHTs), 69.1 (CH_2), 53.7 (CH_3O), 21.8 (CH_3 Ts), -1.6 (3 × CH_3 TMS); *m/z* (CI) 402 $[M+NH_4]^+$, 344, 304, 248, 194, 174, 90 (Found: $[M+NH_4]^+$, 402.1396. $C_{17}H_{24}O_6SSi$ requires $[M+NH_4]^+$, 402.1407) (Found: C, 53.16; H, 6.35. $C_{17}H_{24}O_6SSi$ requires C, 53.10; H, 6.29%).

(2*R,3*R**)-2-(*p*-Toluenesulfonyl)-3-trimethylsilyl-4-pentenoic acid methyl ester and (2*R**,3*S**)-2-(*p*-toluenesulfonyl)-3-trimethylsilyl-4-pentenoic acid methyl ester (216c)**

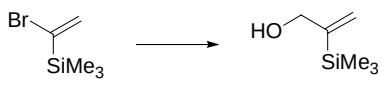


215c **216c**

To a solution of (±)-1-methyl 3-[(*E*)-3-trimethylsilyl-2-propen]yl 2-(*p*-toluenesulfonyl)malonate **215c** (127 mg, 0.330 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at rt and under nitrogen, were added simultaneously TBDMSOTf (160 μL, 0.700 mmol, 2.1

equiv) and DBU (105 μL, 0.693 mmol, 2.1 equiv). The reaction mixture was heated under reflux for 66 h and then concentrated under reduced pressure. Chromatography (10% AcOEt–hexane) gave *2-(*p-*toluenesulfonyl)-3-trimethylsilyl-4-pentenoic acid methyl ester* **216c** in a 1:1 mixture of diastereoisomers (21 mg, 19%) as a yellow oil and the malonate starting material (18 mg, 14%); R_f 0.16 (10% AcOEt–hexane); ν_{max} (film) 2954, 2923, 1743, 1331, 1305, 1274, 1259, 1249, 1145, 1083, 843, 750 cm^{-1}; δ_H (400 MHz) 7.75 (4H, d, *J* 8.5 Hz, Ch-2 Ts and CH-6 Ts of both diastereoisomers), 7.33-7.30 (4H, m, CH-3 Ts and CH-5 Ts of both diastereoisomers), 6.00-5.91 (1H, m, =CH of one diastereoisomer) 5.78-5.68 (1H, m, =CH of one diastereoisomer), 5.10-4.85 (4H, m, $=CH_2$ of both diastereoisomers), 4.13 (1H, d, *J* 12.5 Hz, CHTs of one diastereoisomer), 4.02 (1H, d, *J* 3.0 Hz, CHTs of one diastereoisomer), 3.67 (3H, s, CH_3O of one diastereoisomer), 3.62 (3H, s, CH_3O of one diastereoisomer), 2.50 (1H, dd, *J* 10.5, 3.0 Hz, CHTMS of one diastereoisomer), 2.45 (6H, s, CH_3 Ts of both diastereoisomers), 2.31 (1H, dd, *J* 12.5, 10.5 Hz, CHTMS of one diastereoisomer), 0.02 (9H, s, 3 × CH_3 TMS of one diastereoisomer), -0.03 (9H, s, 3 × CH_3 TMS of one diastereoisomer); δ_C (100 MHz) [166.9 and 166.2 (C=O of both diastereoisomers)], [145.1 and 135.2 (2 × C Ts of both diastereoisomers)], [134.3 and 133.2 (=CH of both diastereoisomers)], [130.0, 129.6, 129.5 and 129.2 (4 × CH Ts of both diastereoisomers)], [115.3 and 115.3 ($=CH_2$ of both diastereoisomers)], [72.6 and 72.6 (CHTs of both diastereoisomers)], [52.7 and 52.6 (CH_3O of both diastereoisomers)], [34.3 and 33.3 (CHTMS of both diastereoisomers)], 21.7 (CH_3 Ts of both diastereoisomers), [-2.7 and -2.9 (3 × CH_3 TMS of both diastereosiomers)]; *m/z* (CI) 358 $[M+NH_4]^+$, 341, 306, 246, 229, 90 (Found: $[M+NH_4]^+$, 358.1502. $C_{16}H_{24}O_4SSi$ requires $[M+NH_4]^+$, 358.1508).

Trimethylsilyl-2-propen-1-ol (228)[17]

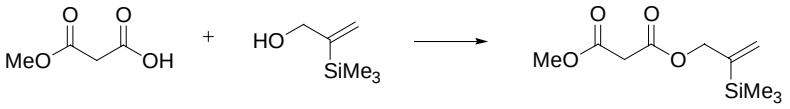


226 **228**

To a suspension of magnesium (785 mg, 32.3 mmol, 1 equiv) in THF (23 mL) at rt and under nitrogen was added a solution of (1-bromovinyl)trimethylsilane **226** (4.96 mL, 32.2 mmol, 1 equiv) in THF (7 mL). The reaction mixture was heated under reflux for 1

h 30 min and then cooled to 0 °C. Gaseous formaldehyde, generated by heating *para*-formaldehyde at 160 °C, was passed through the reaction flask under a slow nitrogen flow. The reaction mixture was stirred at rt for 2 d and then quenched with H_2O (30 mL). The THF was removed by distillation under reduced pressure. The residue was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (5%→20% AcOEt–hexane) gave trimethylsilyl-2-propen-1-ol **228** (300 mg, 7%) as a colourless liquid; R_f 0.19 (10% AcOEt–hexane); δ_H (400 MHz) 5.80-5.78 (1H, m, *cis* CH-3), 5.42-5.40 (1H, m, *trans* CH-3), 4.27 (2H, bs, CH_2-1), 2.04 (1H, bs, OH), 0.12 (9H, s, 3 × CH_3); δ_C (100 MHz) 151.7 (C-2), 122.7 (CH_2-3), 66.5 (CH_2-1), -1.6 (3 × CH_3). Data in agreement with those previously reported.

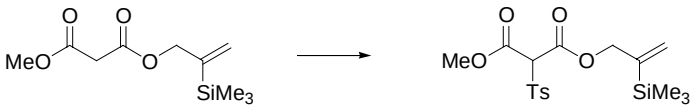
Methyl 2-(trimethylsilyl)allyl malonate (295)



222 **228** **295**

According to general procedure **3.2.3**, methyl malonate **222** (307 mg, 2.60 mmol, 1 equiv) was reacted with trimethylsilyl-2propen-1-ol **228** (284 mg, 2.18 mmol, 1 equiv), DMAP (36 mg, 0.29 mmol, 0.1 equiv) and DCC (619 mg, 3.00 mmol, 1.2 equiv) in CH_2Cl_2 (22 mL). Chromatography (5%→15% AcOEt–hexane) gave *methyl 2-(trimethylsilyl)allyl malonate* **295** (351 mg, 70%) as a colourless liquid; R_f 0.24 (10% AcOEt–hexane); ν_{max} (film) 2971, 1756, 1740, 1438, 1413, 1360, 1332, 1254, 1149, 1023, 841, 759, 692 cm^{-1}; δ_H (400 MHz) 5.80-5.78 (1H, m, *cis* CH-3), 5.48-5.47 (1H, m, *trans* CH-3), 4.77-4.76 (2H, m, CH_2O), 3.75 (3H, s, CH_3O), 3.42 (2H, s, $OOCCH_2COO$), 0.13 (9H, s, 3 × CH_3 TMS); δ_C (100 MHz) [166.9 and 166.1 (2 × C=O)], 145.7 (=C), 126.0 (=CH_2), 69.0 (CH_2O), 52.5 (CH_3O), 41.4 ($OOCCH_2COO$), -1.7 (3 × CH_3 TMS); *m/z* (CI) 248 $[M+NH_4]^+$, 215, 207, 175, 90 (Found: $[M+NH_4]^+$, 248.1307. $C_{10}H_{18}O_4Si$ requires $[M+NH_4]^+$, 248.1318) (Found: C, 52.06; H, 7.87. $C_{10}H_{18}O_4Si$ requires C, 52.14; H, 7.88%).

(±)-1-Methyl 3-[2-(trimethylsilyl)allyl] 2-(*p*-toluenesulfonyl)malonate (229)

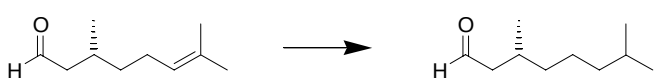


295 **229**

According to general procedure 3.2.4, methyl 2-(trimethylsilyl)allyl malonate **295** (340 mg, 1.48 mmol, 2 equiv) was reacted with *t*-BuOK (170 mg, 1.51 mmol, 2 equiv) and TsF (136 mg, 0.778 mmol, 1 equiv) in DMSO (0.7 mL). Chromatography (10%→20% AcOEt–hexane) gave *(±)-1-methyl 3-[2-(trimethylsilyl)allyl] 2-(*p*-toluenesulfonyl)malonate* **229** (122 mg, 43%) as a colourless gum and the excess starting malonate **295** (193 mg, 72% unreacted); R_f 0.10 (10% AcOEt–hexane); ν_{max} (film) 2956, 1745, 1439, 1338, 1290, 1275, 1252, 1193, 1180, 1151, 1087, 842, 817, 759 cm^{-1}; δ_H (400 MHz) 7.86 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), 7.35 (2H, d, *J* 8.0 Hz, CH-3 Ts and CH-5 Ts), 5.77-5.75 (1H, m, *cis* CH-3), 5.47-5.45 (1H, m, *trans* CH-3), 5.00 (1H, s, CHTs), 4.77-4.76 (2H, m, CH_2O), 3.78 (3H, s, OCH_3), 2.46 (3H, s, CH_3 Ts), 0.10 (9H, s, 3 × CH_3 TMS); δ_C (100 MHz) [161.4 and 160.7 (2 × C=O)], [146.1 and 144.7 (C-4 Ts and =C)], 134.1 (C-1 Ts), [130.2 and 129.5 (4 × CH Ts)], 126.4 (=CH_2), 74.4 (CHTs), 70.2 (CH_2O), 53.6 (CH_3O), 21.8 (CH_3 Ts), -1.8 (3 × CH_3 TMS); *m/z* (CI) 402 $[M+NH_4]^+$, 336, 330, 319, 248, 90, 52 (Found: $[M+NH_4]^+$, 402.1425. $C_{17}H_{24}O_6SSi$ requires $[M+NH_4]^+$, 402.1407) (Found: C, 53.19; H, 6.22. $C_{17}H_{24}O_6SSi$ requires C, 53.10; H, 6.29%).

3.3.2.2 The synthesis of chiral pyridines

(*R*)-3,7-Dimethyloctanal (235*R*)[18,19]

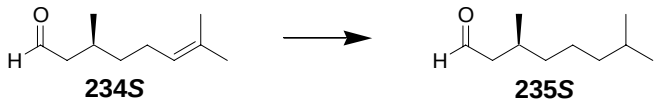


234*R* **235*R***

To a solution of (*R*)-citronellal **234*R*** (580 μL, 3.20 mmol, 1 equiv) in MeOH (6.5 mL) at rt and under nitrogen was added palladium on carbon (10% w/w, 69 mg, 0.065 mmol, 2 mol %). The mixture was cooled to –10 °C, evacuated and then purged with H_2. The

catalyst was filtered through celite and the filtrate was concentrated under reduced pressure to give (*R*)-3,7-dimethyloctanal **235*R*** (464 mg, 93%) as a colourless liquid; $[\alpha]_D^{24}$ +8.3 (*c* 9.68, $CHCl_3$); ν_{max} (film) 2956, 2928, 2871, 1728, 1464, 1384, 1148, 992 cm^{-1}; δ_H (400 MHz) 9.76 (1H, t, *J* 2.5 Hz, CHO), [2.40 (1H, ddd, *J* 16.0, 5.5, 2.0 Hz) and 2.22 (1H, ddd, *J* 16.0, 8.0, 2.5 Hz), CH_2-2], 2.09-2.00 (1H, m, CH-3), 1.52 (1H, nonet, *J* 6.5 Hz, CH-7), 1.32-1.12 (6H, m, CH_2-4, CH_2-5 and CH_2-6), 0.96 (3H, d, *J* 6.5 Hz, CH_3-3), 0.86 (6H, d, *J* 6.5 Hz, CH_3-7 and CH_3-8); δ_C (100 MHz) 203.2 (CHO), 51.1 (CH_2-2), [40.0 and 37.1 (CH_2-4 and CH_2-6)], [28.2 and 27.9 (CH-3 and CH-7)], 24.7 (CH_2-5), [22.6 and 22.6 (CH_3-7 and CH_3-8)], 20.0 (CH_3-3). Data in agreement with those previously reported.

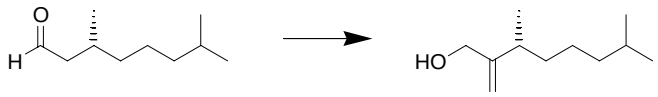
(*S*)-3,7-Dimethyloctanal (235*S*)[20]



234*S* **235*S***

To a solution of (*S*)-citronellal **234*S*** (1.045 g, 6.775 mmol, 1 equiv) in MeOH (15 mL) at rt and under nitrogen was added palladium on carbon (10% w/w, 154 mg, 0.146 mmol, 2 mol %). The mixture was cooled to –10 °C, evacuated and then purged with H_2. The catalyst was filtered through celite and the filtrate was concentrated under reduced pressure to give *(*S*)-3,7-dimethyloctanal* **235*S*** (892 mg, 84%) as a colourless liquid; $[\alpha]_D^{19}$ –6.1 (*c* 6.02, $CHCl_3$); ν_{max} (film) 2956, 2926, 2864, 1710, 1464, 1411, 1384, 1366, 1294, 1220, 938 cm^{-1}; δ_H (400 MHz) 9.76 (1H, t, *J* 2.5 Hz, CHO), [2.39 (1H, ddd, *J* 16.0, 5.5, 2.0 Hz) and 2.22 (1H, ddd, *J* 16.0, 8.0, 2.5 Hz), CH_2-2], 2.09-2.01 (1H, m, CH-3), 1.52 (1H, nonet, *J* 6.5 Hz, CH-7), 1.32-1.12 (6H, m, CH_2-4, CH_2-5 and CH_2-6), 0.96 (3H, d, *J* 6.5 Hz, CH_3-3), 0.87 (6H, d, *J* 6.5 Hz, CH_3-7 and CH_3-8); δ_C (100 MHz) 203.2 (CHO), 51.1 (CH_2-2), [39.0 and 37.1 (CH_2-4 and CH_2-6)], [28.2 and 27.9 (CH-3 and CH-7)], 24.7 (CH_2-5), [22.6 and 22.6 (CH_3-7 and CH_3-8)], 20.0 (CH_3-3). Data in agreement with those previously reported.

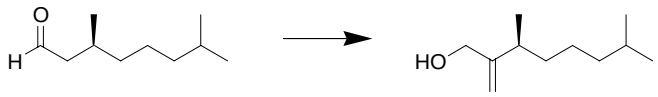
(*R*)-3,7-Dimethyl-2-methyleneoctan-1-ol (236*R*)



235*R* **236*R***

To a stirred solution of (*R*)-3,7-dimethyloctanal **235*R*** (3.580 g, 22.91 mmol, 1 equiv) in *i*-PrOH (1.75 mL) at rt were added aqueous formaldehyde (37% w/w, 1.75 mL, 23.4 mmol, 1 equiv), propionic acid (180 μL, 2.41 mmol, 0.1 equiv) and pyrrolidine (200 μL, 2.40 mmol, 0.1 equiv). The resulting mixture was heated at 45 °C for 20 h. The crude enal-containing solution was diluted with MeOH (46 mL) and pre-dried $CaCl_2$ (2.595 g, 23.38 mmol, 1 equiv) was added. The mixture was then cooled to –10 °C and $NaBH_4$ (1.341 g, 35.45 mmol, 1.6 equiv) was added portion-wise. The effervescing suspension was stirred at –10 °C for 1 h and then at rt for 1 h, after which a mixture of CH_2Cl_2 (100 mL) and aqueous HCl (2M, 100 mL) was added. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (5%→10% Et_2O–petrol) gave *(R)-3,7-dimethyl-2-methyleneoctan-1-ol* **236*R*** (2.98 g, 77%) as a colorless liquid; $[\alpha]_D^{20}$ –9.8 (*c* 16.3, $CHCl_3$); R_f 0.54 (10% AcOEt–petrol); ν_{max} (film) 3341, 2956, 2928, 2864, 1460, 1381, 1361, 1026, 898 cm^{-1}; δ_H (400 MHz) [5.03 (1H, q, *J* 1.5 Hz) and 4.88 (1H, bs), $=CH_2$], 4.10 (2H, bs, CH_2-1), 2.20-2.12 (1H, m, CH-3), 1.53 (1H, nonet, *J* 6.5 Hz, CH-7), 1.48-1.11 (6H, m, CH_2-4, CH_2-5 and CH_2-6), 1.05 (3H, d, *J* 7.0 Hz, CH_3-3), 0.86 (6H, d, *J* 6.5 Hz, CH_3-7 and CH_3-8); δ_C (100 MHz) 154.2 (C-2), 107.7 ($=CH_2$), 64.8 (CH_2-1), [39.1 and 36.0 (CH_2-4 and CH_2-6)], 37.0 (CH-3), 27.9 (CH-7), 25.1 (CH_2-5), 22.6 (CH_3-7 and CH_3-8)], 20.1 (CH_3-3); (Found: C, 77.46; H, 12.97. $C_{11}H_{22}O$ requires C, 77.58; H, 13.02%).

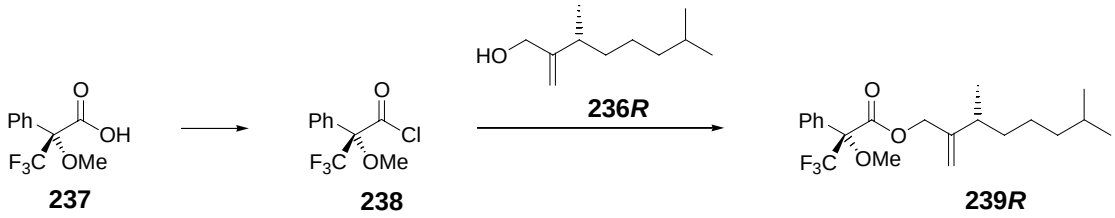
(*S*)-3,7-Dimethyl-2-methyleneoctan-1-ol (236*S*)



235*S* **236*S***

To a stirred solution of (*S*)-3,7-dimethyloctanal **235*S*** (648 mg, 4.15 mmol, 1 equiv) in *i*-PrOH (400 μL) at rt were added aqueous formaldehyde (37% w/w, 350 μL, 4.17 mmol, 1 equiv), propionic acid (31 μL, 0.42 mmol, 0.1 equiv) and pyrrolidine (35 μL, 0.42 mmol, 0.1 equiv). The resulting mixture was heated at 45 °C for 15 h. The crude enal-containing solution was diluted with MeOH (8 mL) and pre-dried $CaCl_2$ (486 mg, 4.37 mmol, 1.1 equiv) was added. The mixture was then cooled to –10 °C and $NaBH_4$ (248 mg, 6.57 mmol, 1.6 equiv) was added portion-wise. The effervescing suspension was stirred at –10 °C for 1 h and then at rt for 1 h, after which a mixture of CH_2Cl_2 (20 mL) and aqueous HCl (2M, 20 mL) was added. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (5%→10% Et_2O–petrol) gave *(*S*)-3,7-dimethyl-2-methyleneoctan-1-ol* **236*S*** (394 mg, 56%) as a colorless liquid; $[\alpha]_D^{23}$ +5.0 (*c* 0.79, $CHCl_3$); R_f 0.54 (10% AcOEt–petrol); ν_{max} (film) 3354, 2955, 2927, 2864, 1653, 1464, 1423, 1366, 1025, 898 cm^{-1}; δ_H (400 MHz) [5.03 (1H, q, *J* 1.5 Hz) and 4.88 (1H, bs), $=CH_2$], 4.10 (2H, bs, CH_2-1), 2.20-2.12 (1H, m, CH-3), 1.53 (1H, nonet, *J* 6.5 Hz, CH-7), 1.47-1.11 (6H, m, CH_2-4, CH_2-5 and CH_2-6), 1.05 (3H, d, *J* 7.0 Hz, CH_3-3), 0.86 (6H, d, *J* 6.5 Hz, CH_3-7 and CH_3-8); δ_C (100 MHz) 154.2 (C-2), 107.7 ($=CH_2$), 64.8 (CH_2-1), [39.1 and 36.0 (CH_2-4 and CH_2-6)], 37.0 (CH-3), 27.9 (CH-7), 25.1 (CH_2-5), 22.6 (CH_3-7 and CH_3-8)], 20.1 (CH_3-3); (Found: C, 77.61; H, 12.86. $C_{11}H_{22}O$ requires C, 77.58; H, 13.02%).

(*R*)-[(*R*)-3,7-Dimethyl-2-methyleneoctyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (239*R*)

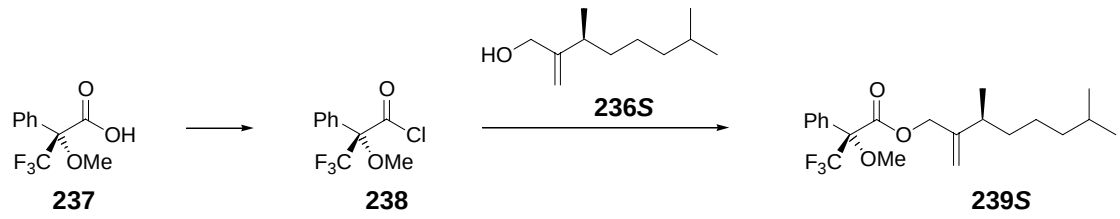


To a solution of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid **237** (141 mg, 0.601 mmol, 1.4 equiv) and oxalyl chloride (105 μL, 1.20 mmol, 2.8 equiv) in CH_2Cl_2 (6 mL) at rt and under nitrogen, was added DMF (3 drops). The mixture was left stirring at rt for 2 h until effervescence stopped. Concentration under reduced pressure gave (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride **238** as a yellow oil.

To a stirred solution of (*R*)-3,7-dimethyl-2-methyleneoctan-1-ol **236*R*** (74 mg, 0.43 mmol, 1 equiv), DMAP (3 mg, 0.03 mmol, 0.1 equiv) and pyridine (98 μL, 1.2 mmol, 2.8 equiv) in CH_2Cl_2 (1 mL) at rt and under nitrogen, was added the crude acid chloride **238** in CH_2Cl_2 (3 mL). After stirring at rt for 21 h, the mixture was diluted with CH_2Cl_2 (10 mL), washed with aqueous $CuSO_4$ (5%, 2 × 10 mL), aqueous $NaHCO_3$ (saturated solution, 10 mL) and H_2O (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave *(*R*)-[(*R*)-3,7-dimethyl-2-methyleneoctyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* **239*R*** (155 mg, 94%) as a green oil; $[\alpha]_D^{23}$ +45.7 (*c* 0.59, $CHCl_3$); R_f 0.84 (5% Et_2O–petrol); ν_{max} (film) 2931, 2854, 2119, 1750, 1451, 1271, 1239, 1187, 1170, 1123, 1026, 995, 912, 720 cm^{-1}; δ_H (400 MHz) [7.54-7.52 (2H, m) and 7.41-7.39 (3H, m), Ph], [5.04 (1H, s) and 4.96 (1H, s), $=CH_2$], [4.81 (1H, d, *J* 13.0 Hz) and 4.73 (1H, d, *J* 13.0 Hz), CH_2O], 3.56 (3H, q, *J* 1.0 Hz, CH_3O), 2.13 (1H, sestet, *J* 6.5 Hz, =CCH), 1.49 (1H, nonet, *J* 6.5 Hz, C*H*$(CH_3)_2$), [1.42-1.35 (1H, m) and 1.26-1.10 (5H, m), CH(CH_2)$_3$], 1.01 (3H, d, *J* 6.5 Hz, =CCHCH_3), 0.85 (6H, d, *J* 6.5 Hz, CH(CH_3)$_2$); δ_C (100 MHz) 166.4 (C=O), 147.6 (=C), 132.2 (*ipso* Ph), [129.6, 128.4 and 127.4 (*ortho* Ph, *meta* Ph and *para* Ph)], 120.5 (q, *J* 288.5 Hz, CF_3), 112.5 ($=CH_2$), 84.6 (q, *J* 27.5 Hz, *C*C=O), 67.6 (CH_2O), 55.5 (CH_3O), [39.0 and 35.6 (CH*C*$H_2$$(CH_2)_2$ and $CH(CH_2)_2$*C*H_2)], 37.1 (=C*C*H), 27.9 (*C*H$(CH_3)_2$), 25.0 (=CCHCH$_2$*C*H_2), [22.6 and 22.6 (CH(*C*H_3)$_2$)], 19.5 (=CCH*C*H_3); *m/z* (CI) 404 $[M+NH_4]^+$, 52 (Found: $[M+NH_4]^+$,

404.2420. $C_{21}H_{29}F_3O_3$ requires $[M+NH_4]^+$, 404.2413). HPLC analysis (Daicel Chiralpak® AS-H, hexane, flow rate 0.5 mL/min, λ = 254 nm) t_R = 5.55 (major), 6.30 (minor) reveals this material to be 93% ee.

(*R*)-[(*S*)-3,7-Dimethyl-2-methyleneoctyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (239*S*)

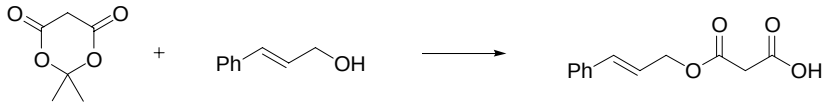


To a solution of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid **237** (142 mg, 0.606 mmol, 1.4 equiv) and oxalyl chloride (110 μL, 1.26 mmol, 2.9 equiv) in CH_2Cl_2 (6 mL) at rt and under nitrogen, was added DMF (3 drops). The mixture was left stirring at rt for 2 h until effervescence stopped. Concentration under reduced pressure gave (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride **238** as a yellow oil.

To a stirred solution of (*S*)-3,7-dimethyl-2-methyleneoctan-1-ol **236*S*** (73 mg, 0.43 mmol, 1 equiv), DMAP (2 mg, 0.02 mmol, 0.1 equiv) and pyridine (100 μL, 1.3 mmol, 2.9 equiv) in CH_2Cl_2 (1 mL) at rt and under nitrogen, was added the crude acid chloride **238** in CH_2Cl_2 (3 mL). After stirring at rt for 23 h, the mixture was diluted with CH_2Cl_2 (10 mL), washed with aqueous $CuSO_4$ (5%, 2 × 10 mL), aqueous $NaHCO_3$ (saturated solution, 10 mL) and H_2O (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave *(*R*)-[(*S*)-3,7-dimethyl-2-methyleneoctyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* **239*S*** (163 mg, 98%) as a green oil; $[\alpha]_D^{23}$ +48.7 (*c* 0.36, $CHCl_3$); R_f 0.84 (5% Et_2O–petrol); ν_{max} (film) 2956, 2870, 1752, 1453, 1272, 1170, 1124, 1026, 1000, 915, 721, 697 cm^{-1}; δ_H (400 MHz) [7.54-7.53 (2H, m) and 7.42-7.40 (3H, m), Ph], [5.04 (1H, s) and 4.96 (1H, s), $=CH_2$], [4.81 (1H, d, *J* 13.0 Hz) and 4.73 (1H, d, *J* 13.0 Hz), CH_2O], 3.56 (3H, q, *J* 1.0 Hz, CH_3O), 2.13 (1H, sestet, *J* 6.5 Hz, =CCH), 1.49 (1H, nonet, *J* 6.5 Hz, C*H*$(CH_3)_2$), [1.42-1.36 (1H, m) and 1.29-1.08 (5H, m), CH(C*H*$_2)_3$], 1.01 (3H, d, *J* 6.5 Hz, =CCHC*H*$_3$), 0.84 (6H, d, *J* 6.5 Hz, CH(C*H*$_3)_2$); δ_C (100 MHz) 166.4 (C=O), 147.6 (=C), 132.2 (*ipso* Ph), [129.6, 128.4 and 127.4 (*ortho* Ph, *meta* Ph

and *para* Ph)], 123.0 (q, *J* 288.5 Hz, CF_3), 112.5 (=CH_2), 84.6 (q, *J* 27.5 Hz, *C*C=O), 67.6 (CH_2O), 55.5 (CH_3O), [39.0 and 35.6 (CH*C*$H_2(CH_2)_2$ and $CH(CH_2)_2$*C*H_2)], 37.1 (=C*C*H), 27.9 (*C*H(CH_3)$_2$), 25.0 (=CCHCH$_2$*C*H$_2$), [22.6 and 22.6 (CH(*C*H_3)$_2$)], 19.5 (=CCH*C*H_3); *m/z* (CI) 404 $[M+NH_4]^+$, 189 (Found: $[M+NH_4]^+$, 404.2427. $C_{21}H_{29}F_3O_3$ requires $[M+NH_4]^+$, 404.2413). HPLC analysis (Daicel Chiralpak® AS-H, hexane, flow rate 0.5 mL/min, λ = 254 nm) t_R = 6.24 (minor), 7.82 (major) reveals this material to be 97% ee.

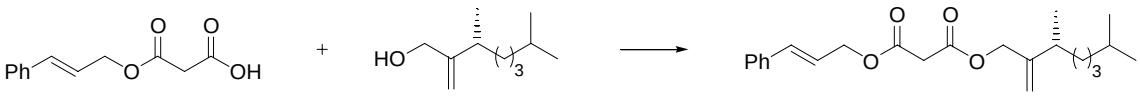
Cinnamyl malonate (191d)[21]



190 **191d**

According to general procedure **3.2.1**, Meldrum's acid **190** (27.3 g, 189 mmol, 1 equiv) and cinnamyl alcohol (25.4 g, 189 mmol, 1 equiv) were reacted in toluene (150 mL) at 90 °C. The crude malonic acid was dissolved in CH_2Cl_2 (150 mL) and extracted with aqueous $NaHCO_3$ (saturated solution, 3 × 200 mL). The aqueous phase was acidified to pH 1 and then extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give cinnamyl malonate **191d** (29.6 g, 71%) as a pale yellow solid; mp 62-64 °C (30% CH_2Cl_2–petrol); ν_{max} (film) 3026, 2945, 1742, 1495, 1449, 1411, 1384, 1322, 1191, 1155, 971, 911, 750, 692 cm^{-1}; δ_H (400 MHz) 10.68 (1H, bs, COOH), 7.41-7.26 (5H, m, Ph), 6.69 (1H, d, *J* 16.0 Hz, =CHPh), 6.28 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), 4.84 (2H, dd, *J* 6.5, 1.0 Hz, CH_2O), 3.49 (2H, s, CH_2COOH); δ_C (100 MHz) 171.5 (COOH), 166.4 (HOOCCH$_2$*C*O), 136.8 (*ipso* Ph), [135.0, 128.1 and 121.9 (*para* Ph, =CHPh and *C*H=CHPh)], [128.5 and 126.6 (*ortho* Ph and *meta* Ph)], 66.3 (CH_2O), 40.7 (*C*H_2COOH); *m/z* (CI) 238 $[M+NH_4]^+$, 151, 134, 117 (Found: $[M+NH_4]^+$, 238.1082. $C_{12}H_{12}O_4$ requires $[M+NH_4]^+$, 238.1079). Data in agreement with those previously reported.

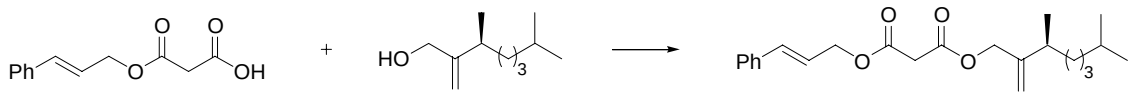
(*R*)-Cinnamyl 3,7-dimethyl-2-methyleneoctyl malonate (296)



191d **236*R*** **296**

According to general procedure **3.2.3**, cinnamyl malonate **191d** (3.228 g, 14.66 mmol, 1 equiv) was reacted with (*R*)-3,7-dimethyl-2-methyleneoctan-1-ol **236*R*** (2.492 g, 14.64 mmol, 1 equiv), DMAP (188 mg, 1.67 mmol, 0.1 equiv) and DCC (3.138 g, 15.21 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL). Chromatography (5%→10% Et_2O–petrol) gave *(*R*)-cinnamyl 3,7-dimethyl-2-methyleneoctyl malonate* **296** (4.250 g, 78%) as a colourless oil; $[\alpha]_D^{24}$ –6.6 (*c* 1.68, $CHCl_3$); R_f 0.06 (5% Et_2O–petrol); ν_{max} (film) 3030, 2955, 2926, 2864, 1752, 1734, 1653, 1495, 1450, 1383, 1327, 1265, 1145, 966, 908, 745, 692 cm^{-1}; δ_H (400 MHz) 7.40-7.25 (5H, m, Ph), 6.67 (1H, d, *J* 16.0 Hz, =CHPh), 6.27 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), [5.05 (1H, m) and 4.94 (1H, bs), $=CH_2$], 4.81 (2H, dd, *J* 6.5, 1.0 Hz, CH_2CH=), 4.62 (2H, s, CH_2C=), 3.46 (2H, s, $OOCCH_2COO$), 2.21-2.13 (1H, m, =CCH), 1.50 (1H, nonet, *J* 6.5 Hz, C$H(CH_3)_2$), 1.44-1.10 (6H, m, $CH(CH_2)_3$), 1.04 (3H, d, *J* 7.0 Hz, =CCHCH_3), 0.85 (6H, d, *J* 6.5 Hz, $CH(CH_3)_2$); δ_C (100 MHz) [166.2 and 166.2 (2 × C=O)], 148.0 (=C), 136.0 (*ipso* Ph), [134.8, 128.2 and 122.4 (*para* Ph and 2 × =CH)], [128.6, and 126.7 (*ortho* Ph and *meta* Ph)], 111.5 ($=CH_2$), [66.7 and 66.1 (2 × CH_2O)], 41.6 ($OOCCH_2COO$), [39.0 and 35.7 (=CCHCH_2 and $=CCH(CH_2)_2CH_2$)], 37.3 (=C*C*H), 27.9 (*C*H$(CH_3)_2$), 25.0 ($=CCHCH_2CH_2$), 22.6 ($CH(CH_3)_2$), 20.0 (=CCH*C*H_3); *m/z* (CI) 390 $[M+NH_4]^+$, 376, 134 (Found: $[M+NH_4]^+$, 390.2660. $C_{23}H_{32}O_4$ requires $[M+NH_4]^+$, 390.2644) (Found: C, 74.17; H, 8.58. $C_{23}H_{32}O_4$ requires C, 74.16; H, 8.66%).

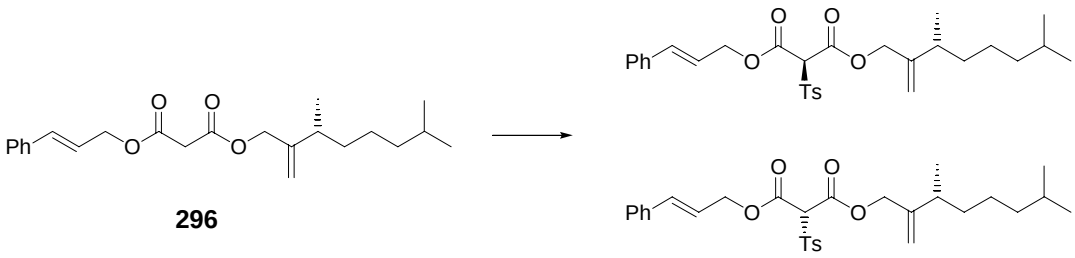
(*S*)-Cinnamyl 3,7-dimethyl-2-methyleneoctyl malonate (297)



191d **236*S*** **297**

According to general procedure **3.2.3**, cinnamyl malonate **191d** (668 mg, 3.03 mmol, 1.3 equiv) was reacted with (*S*)-3,7-dimethyl-2-methyleneoctan-1-ol **236*S*** (390 mg, 2.29 mmol, 1 equiv), DMAP (36 mg, 0.29 mmol, 0.1 equiv) and DCC (620 mg, 3.00 mmol, 1.3 equiv) in CH_2Cl_2 (23 mL). Chromatography (5%→10% Et_2O–petrol) gave *(*S*)-cinnamyl 3,7-dimethyl-2-methyleneoctyl malonate* **297** (784 mg, 92%) as a colourless oil; $[\alpha]_D^{24}$ +4.7 (*c* 0.38, $CHCl_3$); R_f 0.06 (5% Et_2O–petrol); ν_{max} (film) 2956, 2930, 2869, 1750, 1737, 1453, 1383, 1366, 1330, 1269, 1149, 968, 910, 746, 694 cm^{-1}; δ_H (400 MHz) 7.40-7.25 (5H, m, Ph), 6.67 (1H, d, *J* 16.0 Hz, =CHPh), 6.28 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), [5.05 (1H, m) and 4.94 (1H, bs), $=CH_2$], 4.81 (2H, dd, *J* 6.5, 1.0 Hz, CH_2CH=), 4.62 (2H, s, CH_2C=), 3.46 (2H, s, $OOCCH_2COO$), 2.21-2.13 (1H, m, =CCH), 1.50 (1H, nonet, *J* 6.5 Hz, C*H*$(CH_3)_2$), 1.44-1.10 (6H, m, CH(CH_2)$_3$), 1.04 (3H, d, *J* 7.0 Hz, =CCHCH_3), 0.85 (6H, d, *J* 6.5 Hz, CH(CH_3)$_2$); δ_C (100 MHz) [166.2 and 166.2 (2 × C=O)], 148.0 (=C), 136.0 (*ipso* Ph), [134.8, 128.2 and 122.4 (*para* Ph and 2 × =CH)], [128.6, and 126.7 (*ortho* Ph and *meta* Ph)], 111.5 ($=CH_2$), [66.7 and 66.1 (2 × CH_2O)], 41.6 ($OOCCH_2COO$), [39.0 and 35.7 (=CCHCH_2 and =CCH$(CH_2)_2CH_2$)], 37.3 (=C*C*H), 27.9 (*C*H$(CH_3)_2$), 25.0 (=CCHCH_2CH_2), 22.6 (CH(*C*H_3)$_2$), 19.8 (=CCH*C*H_3); *m/z* (CI) 390 $[M+NH_4]^+$, 373 $[M+H]^+$, 269, 134, 117 (Found: $[M+H]^+$, 373.2384. $C_{23}H_{32}O_4$ requires $[M+H]^+$, 373.2379) (Found: C, 74.17; H, 8.62. $C_{23}H_{32}O_4$ requires C, 74.16; H, 8.66%).

(*S*)-1-Cinnamyl 3-(*R*)-3,7-dimethyl-2-methyleneoctyl 2-(*p*-toluenesulfonyl)malonate and (*R*)-1-cinnamyl 3-(*R*)-3,7-dimethyl-2-methyleneoctyl 2-(*p*-toluenesulfonyl)malonate (231a)

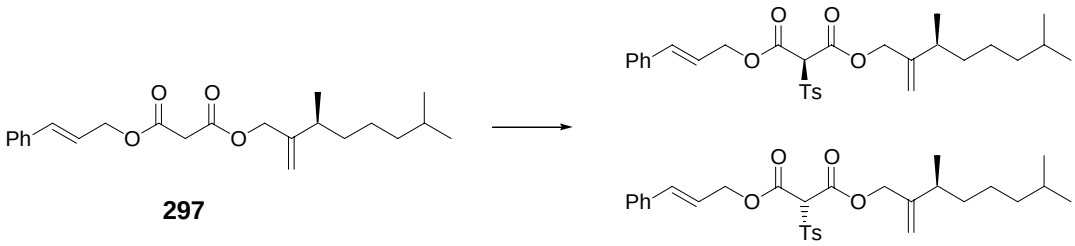


296 **231a**

According to general procedure **3.2.4**, (*R*)-cinnamyl 3,7-dimethyl-2-methyleneoctyl malonate **296** (3.939 g, 10.66 mmol, 2 equiv) was reacted with *t*-BuOK (1.208 g, 10.76 mmol, 2 equiv) and TsF (929 mg, 5.331 mmol, 1 equiv) in DMSO (5 mL). Chromatography (5%→20% Et_2O–petrol) gave *1-cinnamyl 3-(*R*)-3,7-dimethyl-2-methyleneoctyl 2-(*p*-toluenesulfonyl)malonate* **231a** in a 1:1 mixture of diastereoisomers (1.50 g, 53%) as a colourless gum and the excess starting malonate **296** (2.34 g, 80% unreacted); R_f 0.23 (10% AcOEt–petrol); ν_{max} (film) 2955, 2926, 2864, 1744, 1597, 1449, 1337, 1291, 1151, 1083, 968, 907, 814, 746, 704, 694 cm^{-1}; δ_H (400 MHz) 7.88 (4H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.40-7.28 (14H, m, Ph, CH-3 Ts and CH-5 Ts of both diastereoisomers), 6.66 (2H, d, *J* 16.0 Hz, =CHPh of both diastereoisomers), 6.19 (2H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh of both diastereoisomers), 5.05 (2H, s, CHTs of both diastereoisomers), [5.05-5.04 (2H, m) and 4.94 (2H, bs), $=CH_2$ of both diastereoisomers], 4.84 (4H, d, *J* 6.5 Hz, CH_2CH= of both diastereoisomers), 4.65 (4H, s, CH_2C= of both diastereoisomers), 2.41 (6H, s, CH_3 Ts of both diastereoisomers), 2.18-2.10 (2H, m, =CCH of both diastereoisomers), 1.52 (2H, nonet, *J* 6.5 Hz, C*H*$(CH_3)_2$ of both diastereoisomers), 1.42-1.12 (12H, m, CH$(CH_2)_3$ of both diastereoisomers), [1.02 (3H, d, *J* 7.0 Hz) and 1.02 (3H, d, *J* 7.0 Hz), =CCHCH_3 of both diastereoisomers], 0.87 (12H, d, *J* 6.5 Hz, CH$(CH_3)_2$ of both diastereoisomers); δ_C (100 MHz) [160.8 and 160.7 (2 × C=O of both diastereoisomers)], [147.1 and 146.0 (=C and C-4 Ts of both diastereoisomers)], [135.7 and 134.1 (*ipso* Ph and C-1 Ts of both diastereoisomers)], [135.7, 128.4 and 121.2 (*para* Ph and 2 × =CH of both diastereoisomers)], [130.2, 129.5, 128.6, and 126.7 (*ortho* Ph, *meta* Ph and 4 × CH Ts

of both diastereoisomers)], 112.2 (=CH_2 of both diastereoisomers), 74.6 (CHTs of both diastereoisomers), [68.1 and 67.4 (2 × CH_2O of both diastereoisomers)], [39.0 and 35.6 (=CCH*C*H_2 and =CCH$(CH_2)_2$*C*H_2 of both diastereoisomers)], 37.1 (=*C*CH of both diastereoisomers), 27.9 (*C*H$(CH_3)_2$ of both diastereoisomers), 24.9 (=CCHCH$_2$*C*H_2 of both diastereoisomers), 22.6 (CH(*C*H_3)$_2$ of both diastereoisomers), [21.7 and 19.6 (CH_3 Ts and =CCH*C*H_3 of both diastereoisomers)]; *m/z* (CI) 544 $[M+NH_4]^+$, 427, 384, 348, 231, 174, 134, 117 (Found: $[M+NH_4]^+$, 544.2740. $C_{30}H_{38}O_6S$ requires $[M+NH_4]^+$, 544.2733).

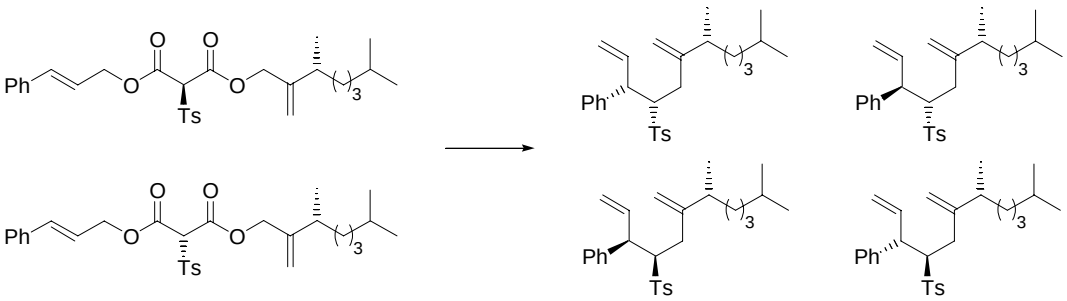
(*S*)-1-Cinnamyl 3-(*S*)-3,7-dimethyl-2-methyleneoctyl 2-(*p*-toluenesulfonyl)malonate and (*R*)-1-cinnamyl 3-(*S*)-3,7-dimethyl-2-methyleneoctyl 2-(*p*-toluenesulfonyl)malonate (231b)



According to general procedure **3.2.4**, (*S*)-cinnamyl 3,7-dimethyl-2-methyleneoctyl malonate **297** (784 mg, 2.10 mmol, 2 equiv) was reacted with *t*-BuOK (235 mg, 2.10 mmol, 2 equiv) and TsF (194 mg, 1.11 mmol, 1 equiv) in DMSO (1 mL). Chromatography (5%→20% Et_2O–petrol) gave *1-cinnamyl 3-(*S*)-3,7-dimethyl-2-methyleneoctyl 2-(*p*-toluenesulfonyl)malonate* **231b** in a 1:1 mixture of diastereoisomers (333 mg, 60%) as a colourless gum and the excess starting malonate **297** (484 mg, 88% unreacted); R_f 0.23 (10% AcOEt–petrol); ν_{max} (film) 2923, 2850, 1744, 1468, 1338, 1293, 1152, 1083, 910, 809, 703, cm^{-1}; δ_H (400 MHz) 7.88 (4H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of both diastereoisomers), 7.40-7.29 (14H, m, Ph, CH-3 Ts and CH-5 Ts of both diastereoisomers), 6.66 (2H, d, *J* 16.0 Hz, =CHPh of both diastereoisomers), 6.19 (2H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh of both diastereoisomers), 5.05 (2H, s, CHTs of both diastereoisomers), [5.05-5.04 (2H, m) and 4.94 (2H, bs), =CH_2 of both diastereoisomers], 4.84 (4H, d, *J* 6.5 Hz, C*H*$_2$CH= of both diastereoisomers), 4.65 (4H,

s, CH_2C= of both diastereoisomers), 2.41 (6H, s, CH_3 Ts of both diastereoisomers), 2.19-2.10 (2H, m, =CCH of both diastereoisomers), 1.53 (2H, nonet, *J* 6.5 Hz, C*H*$(CH_3)_2$ of both diastereoisomers), 1.46-1.14 (12H, m, CH(C*H*$_2$)$_3$ of both diastereoisomers), [1.03 (3H, d, *J* 7.0 Hz) and 1.03 (3H, d, *J* 7.0 Hz), =CCHC*H*$_3$ of both diastereoisomers], 0.88 (12H, d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$ of both diastereoisomers); δ_C (100 MHz) [160.8 and 160.7 (2 × C=O of both diastereoisomers)], [147.1 and 145.9 (=C and C-4 Ts of both diastereoisomers)], [135.8 and 134.1 (*ipso* Ph and C-1 Ts of both diastereoisomers)], [135.7, 128.4 and 121.2 (*para* Ph and 2 × =CH of both diastereoisomers)], [130.2, 129.5, 128.6, and 126.7 (*ortho* Ph, *meta* Ph and 4 × CH Ts of both diastereoisomers)], 112.2 (=CH_2 of both diastereoisomers), 74.6 (CHTs of both diastereoisomers), [68.1 and 67.4 (2 × CH_2O of both diastereoisomers)], [39.0 and 35.6 (=CCH*C*H$_2$ and =CCH(CH$_2$)$_2$*C*H$_2$ of both diastereoisomers)], 37.1 (=C*C*H of both diastereoisomers), 27.9 (*C*H$(CH_3)_2$ of both diastereoisomers), 24.9 (=CCHCH$_2$*C*H$_2$ of both diastereoisomers), 22.6 (CH(*C*H$_3$)$_2$ of both diastereoisomers), [21.7 and 19.6 (CH_3 Ts and =CCH*C*H$_3$ of both diastereoisomers)]; *m/z* (CI) 544 $[M+NH_4]^+$, 384, 348, 174, 134, 117 (Found: $[M+NH_4]^+$, 544.2740. $C_{30}H_{38}O_6S$ requires $[M+NH_4]^+$, 544.2733).

(3*S*,4*S*,7*R*)-7,11-Dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene, (3*R*,4*S*,7*R*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene, (3*R*,4*R*,7*R*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene and (3*S*,4*R*,7*R*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene (232a)

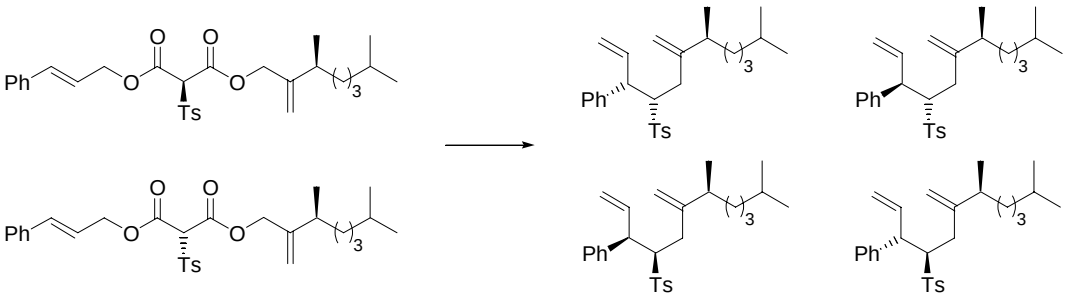


231a **232a**

To a 1:1 diastereoisomeric mixture of 1-cinnamyl 3-[(*R*)-3,7-dimethyl-2-methyleneoctyl]-2-tosylmalonate **231a** (667 mg, 1.27 mmol, 1 equiv) and KOAc (25

mg, 0.26 mmol, 0.2 equiv) under nitrogen was added BSA (1.00 mL, 3.96 mmol, 3 equiv). The mixture was exposed to 4 cycles of microwave irradiation of 2 min each at 220 °C. Chromatography (2%→3% AcOEt–petrol) gave *(*7R*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p-*toluenesufonyl)dodec-1-ene* **232a** in a mixture of diastereoisomers (382 mg, 69%) as a colourless gum; R_f 0.28 (5% AcOEt–petrol); ν_{max} (film) 2956, 2929, 2868, 1641, 1597, 1495, 1453, 1315, 1302, 1146, 1086, 922, 900, 815, 745, 701, 665, 577 cm^{-1}; δ_H (400 MHz) [7.71 (2H, d, *J* 8.5 Hz), 7.70 (2H, d, *J* 8.5 Hz), 7.68 (2H, d, *J* 8.5 Hz) and 7.67 (2H, d, *J* 8.5 Hz) CH-2 Ts and CH-6 Ts of all diastereoisomers], 7.29-7.17 (28H, m, Ph, CH-3 Ts and CH-5 Ts of all diastereoisomers), [6.51-6.37 (2H, m) and 6.33-6.19 (2H, m), =CH of all diastereosiomers], 5.28-4.65 (16H, m, 2 × $=CH_2$ of all diastereoisomers), [4.27-4.24 (2H, m), 4.08-4.03 (2H, m), 3.77-3.69 (2H, m) and 3.68-3.62 (2H, m), CHTs and CHPh of all diastereoisomers], [2.79 (1H, dd, *J* 16.5, 6.5 Hz), 2.71 (1H, dd, *J* 16.5, 5.5 Hz) and 2.62-2.31 (18H, m), CH_2-5 and CH_3 Ts of all diastereoisomers], 1.80-1.45 (8H, m, CH-7 and CH-11 of all diastereoisomers), 1.08-0.97 (24 H, m, CH_2-8, CH_2-9 and CH_2-10 of all diastereoisomers), 0.87-0.84 (24 H, m, CH_3-11 and CH_3-12 of all diastereoisomers), 0.77-0.72 (12 H, m, CH_3-7 of all diastereoisomers); δ_C (100 MHz) [150.0, 150.0, 149.9 and 149.8 (C-6 of all diastereoisomers)], [144.2, 141.4, 141.3, 140.9, 140.7, 136.4 and 136.2 (2 × C Ts and *ipso* Ph of all diastereoisomers)], [136.9, 136.6, 135.6 and 135.4 (=CH of all diastereoisomers)], [129.5, 129.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 126.8, 126.7 and 126.7 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph of all diastereoisomers)], [118.8, 118.7, 118.1, 118.0, 110.8 and 110.3 (2 × $=CH_2$ of all diastereoisomers)], [67.1, 67.0, 66.9 and 66.8 (CHTs of all diastereoisomers)], [49.3, 49.1, 48.3 and 48.1 (CHPh of all diastereoisomers)], 39.0 (CH_2-10 of all diastereoisomers), [38.8, 38.2, 38.1 and 38.0 (CH-7 of all diastereoisomers)], [35.6, 35.4, 35.3, 35.3, 32.7, 32.3, 30.8, 30.6, 25.0, 24.8, 24.6 and 24.6 (CH_2-5, CH_2-8 and CH_2-9 of all diastereoisomers)], 27.8 (CH-11 of all diastereoisomers), [22.6, 22.6, and 21.5 (CH_3 Ts, CH_3-11 and CH_3-12 of all diastereoisomers)], [19.6, 19.0 and 18.9 (CH_3-7 of all diastereoisomers)]; *m/z* (CI) 456 $[M+NH_4]^+$, 439 $[M+H]^+$, 365, 340, 174, 52 (Found: $[M+NH_4]^+$, 456.2947. $C_{28}H_{38}O_2S$ requires $[M+NH_4]^+$, 456.2936).

(3*S*,4*S*,7*S*)-7,11-Dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene, (3*R*,4*S*,7*S*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene, (3*R*,4*R*,7*S*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene and (3*S*,4*R*,7*S*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p*-toluenesufonyl)dodec-1-ene (232b)

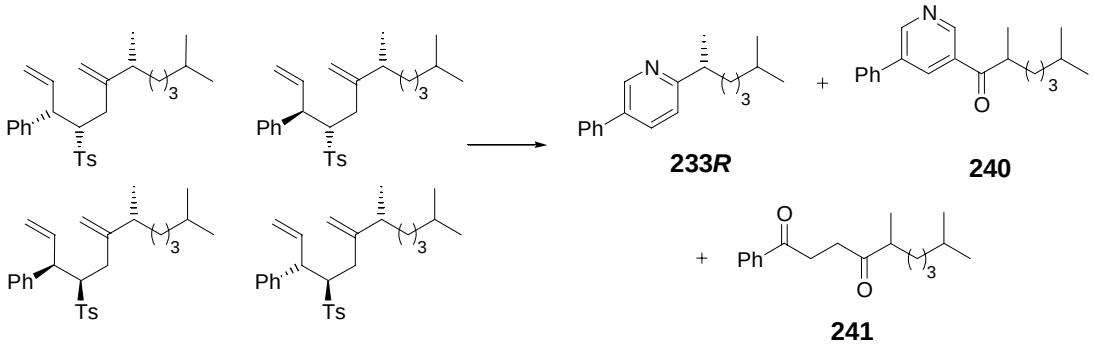


231b **232b**

To a 1:1 diastereoisomeric mixture of 1-cinnamyl 3-[(*S*)-3,7-dimethyl-2-methyleneoctyl]-2-tosylmalonate **231b** (314 mg, 0.596 mmol, 1 equiv) and KOAc (12 mg, 0.12 mmol, 0.2 equiv) under nitrogen was added BSA (500 μL, 1.98 mmol, 3 equiv). The mixture was exposed to 4 cycles of microwave irradiation of 2 min each at 220 °C. Chromatography (2%→3% AcOEt–petrol) gave *(7*S*)-7,11-dimethyl-6-methylene-3-phenyl-4-(*p-*toluenesufonyl)dodec-1-ene* **232b** in a mixture of diastereoisomers (164 mg, 63%) as a colourless gum; R_f 0.28 (5% AcOEt–petrol); ν_{max} (film) 3083, 3029, 2956, 2928, 2868, 1641, 1598, 1495, 1454, 1315, 1302, 1146, 1087, 920, 901, 815, 746, 701, 665, 577 cm^{-1}; δ_H (400 MHz) [7.68 (2H, d, *J* 8.5 Hz), 7.67 (2H, d, *J* 8.5 Hz), 7.65 (2H, d, *J* 8.5 Hz) and 7.64 (2H, d, *J* 8.5 Hz) CH-2 Ts and CH-6 Ts of all diastereoisomers], 7.27-7.04 (28H, m, Ph, CH-3 Ts and CH-5 Ts of all diastereoisomers), [6.48-6.35 (2H, m) and 6.30-6.16 (2H, m), =CH of all diastereosiomers], 5.26-4.62 (16H, m, 2 × $=CH_2$ of all diastereoisomers), [4.23-4.21 (2H, m), 4.05-4.00 (2H, m), 3.74-3.66 (2H, m) and 3.65-3.59 (2H, m), CHTs and CHPh of all diastereoisomers], [2.77 (1H, dd, *J* 16.5, 6.5 Hz), 2.68 (1H, dd, *J* 16.5, 5.5 Hz) and 2.59-2.30 (18H, m), CH_2-5 and CH_3 Ts of all diastereoisomers], 1.79-1.41 (8H, m, CH-7 and CH-11 of all diastereoisomers), 1.08-0.93 (24 H, m, CH_2-8, CH_2-9 and CH_2-10 of all diastereoisomers), 0.85-0.82 (24 H, m, CH_3-11 and CH_3-12 of all diastereoisomers), 0.74-0.70 (12 H, m, CH_3-7 of all diastereoisomers); δ_C (100 MHz) [150.0, 149.9 and

149.8 (C-6 of all diastereoisomers)], [144.3, 141.4, 141.4, 140.9, 140.8, 136.4 and 136.2 (2 × C Ts and *ipso* Ph of all diastereoisomers)], [136.9, 136.6, 135.7 and 135.4 (=CH of all diastereoisomers)], [129.5, 129.5, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 126.8 and 126.7 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph of all diastereoisomers)], [118.9, 118.8, 118.2, 118.0, 110.9 and 110.3 (2 × $=CH_2$ of all diastereoisomers)], [67.1, 67.0, 66.9 and 66.8 (CHTs of all diastereoisomers)], [49.3, 49.1, 48.3 and 48.1 (CHPh of all diastereoisomers)], 39.1 (CH_2-10 of all diastereoisomers), [38.8, 38.2, 38.1 and 38.1 (CH-7 of all diastereoisomers)], [35.6, 35.4, 35.3, 32.8, 32.4, 30.8, 30.6, 25.1, 24.8, 24.7 and 24.6 (CH_2-5, CH_2-8 and CH_2-9 of all diastereoisomers)], 27.9 (CH-11 of all diastereoisomers), [22.7, 22.6, and 21.6 (CH_3 Ts, CH_3-11 and CH_3-12 of all diastereoisomers)], [19.5, 19.1 and 19.0 (CH_3-7 of all diastereoisomers)]; *m/z* (CI) 456 $[M+NH_4]^+$, 439 $[M+H]^+$, 283, 174, 52 (Found: $[M+H]^+$, 439.2670. $C_{28}H_{38}O_2S$ requires $[M+H]^+$, 439.2671).

(*R*)-2-(6-Methylheptan-2-yl)-5-phenylpyridine (233*R*), 3-(1-oxo-2,6-dimethylheptyl)-5-phenylpyridine (240) and 5,9-dimethyl-1-phenyldecane-1,4-dione (241)



232a

Procedure A

According to general procedure **3.2.6**, a diastereoisomeric mixture of (7*R*)-7,11-dimethyl-6-methylene-3-phenyl-4-tosyl dodec-1-ene **232a** (90 mg, 0.21 mmol, 1 equiv) in MeOH:CH_2Cl_2 (2.5 mL) was ozonolised and reduced with Me_2S (1.1 mL, 25 mmol, 124 equiv). The crude ketoaldehydes in MeOH (1.5 mL) were then reacted with NH_4HCO_3 (172 mg, 2.17 mmol, 11 equiv). Chromatography (3% Et_2O–petrol) gave

*(*R*)-2-(6-methylheptan-2-yl)-5-phenylpyridine* **233*R*** (14 mg, 26%) as a colourless oil, *3-(1-oxo-2,6-dimethylheptyl)-5-phenylpyridine* **240** (12 mg, 19%) as a yellow oil and *5,9-dimethyl-1-phenyldecane-1,4-dione* **241** (6 mg, 11%) as a colourless oil.

Procedure B

According to general procedure **3.2.6**, a diastereoisomeric mixture of (7*S*)-7,11-dimethyl-6-methylene-3-phenyl-4-tosyl dodec-1-ene **232a** (272 mg, 0.620 mmol, 1 equiv) in MeOH:CH_2Cl_2 (6 mL) was ozonolised and reduced with Me_2S (2.7 mL, 63 mmol, 101 equiv). After stirring for 3 h at –78 °C, the solution of the crude ketoaldehydes were treated with a methanolic solution of NH_3 (2 M, 19 mL) for 72 h. The red solution was concentrated under reduced pressure. The red residue was dissolved in CH_2Cl_2 (30 mL) and then washed with H_2O (2 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (3% Et_2O–petrol) gave (*R*)-2-(6-methylheptan-2-yl)-5-phenylpyridine **233*R*** (37 mg, 22%) as a colourless oil, 3-(1-oxo-2,6-dimethylheptyl)-5-phenylpyridine **240** (28 mg, 15%) as a yellow oil and 5,9-dimethyl-1-phenyldecane-1,4-dione **241** (10 mg, 6%) as a colourless oil.

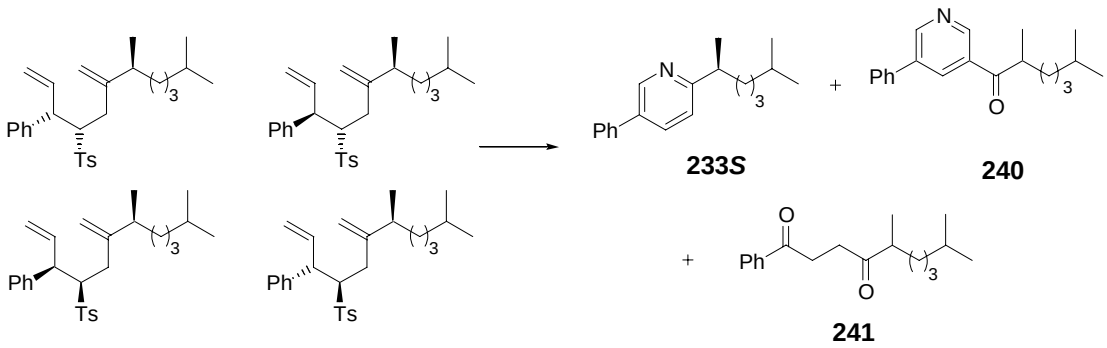
233*R*; $[\alpha]_D^{20}$ –24.2 (*c* 0.70, $CHCl_3$); R_f 0.43 (5% Et_2O–petrol); ν_{max} (film) 2955, 2932, 2864, 1595, 1476, 1379, 1374, 1277, 1135, 1071, 1003, 838, 782, 745, 696, 519 cm^{-1}; δ_H (400 MHz) 8.78 (1H, d, *J* 2.5 Hz, CH-6), 7.80 (1H, dd, *J* 8.0, 2.5 Hz, CH-4), 7.59-2.57 (2H, m, *ortho* Ph), 7.48-7.45 (2H, m, *meta* Ph), 7.40-7.36 (1H, m, *para* Ph), 7.20 (1H, d, *J* 8.0 Hz, CH-3), 2.93 (1H, sestet, *J* 7.0 Hz, CH-2 heptyl), [1.80-1.71 (2H, m), 1.63-1.57 (1H, m) and 1.37-1.14 (3H, m), 3 × CH_2 heptyl], 1.50 (1H, nonet, *J* 6.5 Hz, CH-6 heptyl), 1.32 (3H, d, *J* 7.0 Hz, CH_3-1 heptyl), [0.84 (3H, d, *J* 6.5 Hz) and 0.83 (3H, d, *J* 6.5 Hz), CH_3-6 and CH_3-7 heptyl]; δ_C (100 MHz) 165.6 (C-2), 147.5 (CH-6), [138.0 and 133.9 (C-5 and *ipso* Ph)], 134.7 (CH-4), [129.0 and 127.0 (*ortho* Ph and *meta* Ph)], 127.7 (*para* Ph), 121.3 (CH-3), 41.7 (CH-2 heptyl), [39.0 and 37.4 (CH_2-3 and CH_2-5 heptyl)], 27.8 (CH-6 heptyl), 25.4 (CH_2-4 heptyl), [22.6 and 22.6 (CH_3-6 and CH_3-7 heptyl)], 20.8 (CH_3-1 heptyl); *m/z* (CI) 268 $[M+H]^+$, 183, 52 (Found: $[M+H]^+$, 268.2075. $C_{19}H_{25}N$ requires $[M+H]^+$, 268.2065) (Found: C, 85.41; H, 9.38; N, 5.09. $C_{19}H_{25}N$ requires C, 85.34; H, 9.42; N, 5.24%). HPLC analysis (Daicel Chiralpak® AD-

H, 5% IPA:hexane, flow rate 0.5 mL/min, λ = 254 nm) t_R = 26.0 (major), 35.7 (minor) reveals this material to be 74% ee.

240; R_f 0.10 (5% Et_2O–petrol); ν_{max} (film) 2954, 2868, 1725, 1687, 1588, 1462, 1432, 1366, 1302, 1217, 1146, 1031, 984, 902, 765, 750, 698 cm^{-1}; δ_H (400 MHz) [9.12 (1H, d, *J* 1.5 Hz) and 9.00 (1H, d, *J* 2.0 Hz), CH-2 and CH-6)], 8.41-8.40 (1H, m, CH-4), 7.64-7.62 (2H, m, *ortho* Ph), 7.53-7.49 (2H, m, *meta* Ph), 7.45-7.43 (1H, m, *para* Ph), 2.49 (1H, sestet, *J* 7.0 Hz, CH-2 heptyl), [1.87-1.78 (1H, m) and 1.51-1.42 (1H, m), CH_2-3 heptyl], 1.52 (1H, nonet, *J* 6.5 Hz, CH-6 heptyl), 1.38-1.30 (2H, m, CH_2-4 heptyl), 1.25 (3H, d, *J* 7.0 Hz, CH_3-2 heptyl), 1.22-1.15 (2H, m, CH_2-5 heptyl), 0.85 (6H, d, *J* 6.5 Hz, CH_3-6 and CH_3-7 heptyl); δ_C (100 MHz) 203.3 (C=O), 151.7 (CH-6), 148.1 (CH-2), [136.9, 136.8 and 131.8 (C-3, C-5 and *ipso* Ph)], 133.9 (CH-4), 129.2 (*meta* Ph), 128.6 (*para* Ph), 127.2 (*ortho* Ph), 41.4 (CH-2 heptyl), 38.9 (CH_2-5 heptyl), 33.7 (CH_2-3 heptyl), 27.8 (CH-6 heptyl), 25.1 (CH_2-4 heptyl), [22.6 and 22.5 (CH_3-6 and CH_3-7 heptyl)], 17.0 (CH_3-2 heptyl); *m/z* (CI) 296 $[M+H]^+$ (Found: $[M+H]^+$, 296.2014. $C_{20}H_{26}NO$ requires $[M+H]^+$, 296.2014) (Found: C, 81.38; H, 8.47; N, 4.60. $C_{20}H_{25}NO$ requires C, 81.31; H, 8.53; N, 4.74%).

241; R_f 0.38 (5% Et_2O–petrol); ν_{max} (film) 2925, 2869, 1709, 1686, 1458, 1364, 1241, 1207, 1179, 1079, 1018, 744, 689 cm^{-1}; δ_H (400 MHz) 8.00-7.98 (2H, m, *ortho* Ph), 7.58-7.54 (1H, m, *para* Ph), 7.48-7.44 (2H, m, *meta* Ph), 3.27 (2H, td, *J* 6.5, 2.0 Hz, CH_2-2), 2.98-2.84 (2H, m, CH_2-3), 2.64 (1H, sestet, *J* 7.0 Hz, CH-5), 1.74-1.65 (1H, m, C*H*H-6), 1.53 (1H, nonet, *J* 6.5 Hz, CH-9), 1.40-1.20 (3H, m, CH*H*-6 and CH_2-7), 1.16-18 (2H, m, CH_2-8), 1.13 (3H, d, *J* 7.0 Hz, CH_3-5), 0.87 (6H, d, *J* 6.5 Hz, CH_3-9 and CH_3-10); δ_C (100 MHz) 213.4 (C-4), 198.7 (C-1), 136.8 (*ipso* Ph), 133.1 (*para* Ph), [128.5 and 128.0 (*meta* Ph and *para* Ph)], 46.5 (CH-5), [39.0, 34.8, 33.3 and 32.3 (CH_2-2, CH_2-3, CH_2-6 and CH_2-8)], 27.8 (CH-9), 25.0 (CH_2-7), 22.6 (CH_3-9 and CH_3-10), 16.4 (CH_3-5); *m/z* (CI) 292 $[M+NH_4]^+$, 275 $[M+H]^+$, 268 (Found: $[M+NH_4]^+$, 292.2282; $[M+H]^+$, 275.2019. $C_{18}H_{26}O_2$ requires $[M+NH_4]^+$, 292.2277; $[M+H]^+$, 275.2011).

(*S*)-2-(6-Methylheptan-2-yl)-5-phenylpyridine (233*S*), 3-(1-oxo-2,6-dimethylheptyl)-5-phenylpyridine (240) and 5,9-dimethyl-1-phenyldecane-1,4-dione (241)



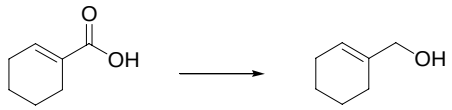
According to general procedure **3.2.6**, a diastereoisomeric mixture of (7*S*)-7,11-dimethyl-6-methylene-3-phenyl-4-tosyl dodec-1-ene **232b** (128 mg, 0.292 mmol, 1 equiv) in MeOH:CH_2Cl_2 (3 mL) was ozonolised and reduced with Me_2S (1.3 mL, 30 mmol, 103 equiv). The crude ketoaldehydes in MeOH (3 mL) were then reacted with NH_4HCO_3 (193 mg, 2.44 mmol, 8 equiv). Chromatography (3% Et_2O–petrol) gave *(S)-2-(6-methylheptan-2-yl)-5-phenylpyridine* **233*S*** (24 mg, 30%) as a colourless oil, 3-(1-oxo-2,6-dimethylheptyl)-5-phenylpyridine **240** (21 mg, 24%) as a yellow oil and 5,9-dimethyl-1-phenyldecane-1,4-dione **241** (14 mg, 18%) as a colourless oil.

233*S*; $[\alpha]_D^{20}$ +42.1 (*c* 0.19, $CHCl_3$); R_f 0.43 (5% Et_2O–petrol); ν_{max} (film) 2955, 2932, 2864, 1595, 1476, 1379, 1368, 1277, 1135, 1071, 839, 753, 696, 520 cm^{-1}; δ_H (400 MHz) 8.77 (1H, d, *J* 2.5 Hz, CH-6), 7.80 (1H, dd, *J* 8.0, 2.5 Hz, CH-4), 7.59-7.57 (2H, m, *ortho* Ph), 7.49-7.45 (2H, m, *meta* Ph), 7.40-7.36 (1H, m, *para* Ph), 7.20 (1H, d, *J* 8.0 Hz, CH-3), 2.93 (1H, sestet, *J* 7.0 Hz, CH-2 heptyl), [1.80-1.71 (2H, m), 1.63-1.54 (1H, m) and 1.35-1.14 (3H, m), 3 × CH_2 heptyl], 1.50 (1H, nonet, *J* 6.5 Hz, CH-6 heptyl), 1.32 (3H, d, *J* 7.0 Hz, CH_3-1 heptyl), [0.84 (3H, d, *J* 6.5 Hz) and 0.83 (3H, d, *J* 6.5 Hz), CH_3-6 and CH_3-7 heptyl]; δ_C (100 MHz) 165.6 (C-2), 147.5 (CH-6), [138.0 and 133.9 (C-5 and *ipso* Ph)], 134.7 (CH-4), [129.0 and 127.0 (*ortho* Ph and *meta* Ph)], 127.7 (*para* Ph), 121.3 (CH-3), 41.7 (CH-2 heptyl), [39.0 and 37.4 (CH_2-3 and CH_2-5 heptyl)], 27.8 (CH-6 heptyl), 25.4 (CH_2-4 heptyl), [22.6 and 22.6 (CH_3-6 and CH_3-7

heptyl)], 20.8 (CH_3-1 heptyl); *m/z* (CI) 268 $[M+H]^+$, 100 (Found: $[M+H]^+$, 268.2066. $C_{19}H_{25}N$ requires $[M+H]^+$, 268.2065) (Found: C, 85.22; H, 9.36; N, 5.34. $C_{19}H_{25}N$ requires C, 85.34; H, 9.42; N, 5.24%). HPLC analysis (Daicel Chiralpak® AD-H, 5% IPA:hexane, flow rate 0.5 mL/min, λ = 254 nm) t_R = 25.1 (minor), 33.7 (major) reveals this material to be 91% ee.

3.3.2.3 The synthesis of 2,3-cyclofused pyridines

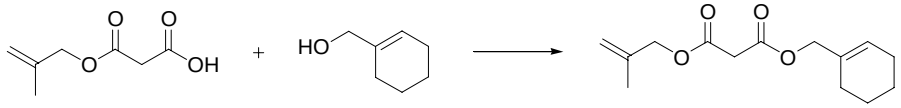
1-Hydroxymethylcyclohexene (254)[22]



254

To a stirred solution of $LiAlH_4$ in THF (1.0 M, 13.4 mL, 13.4 mmol, 0.75 equiv) in THF (6.6 mL) at 0 °C and under nitrogen was added dropwise methyl 1-cyclohexene-1-carboxylate (2.43 mL, 17.9 mmol, 1 equiv). After 2 h of stirring at 0 °C excess Na_2SO_4 decahydrate was added and the solids were separated by filtration through a short pad of silica gel and washed with AcOEt (3 × 10 mL). The combined filtrates were concentrated under reduced pressure to give 1-hydroxymethylcyclohexene **254** (1.49 g, 74%) as a colourless oil; R_f 0.14 (10% AcOEt–hexane); ν_{max} (film) 3394, 2864, 2856, 2833, 1650, 1448, 1425, 1050, 1035, 1009 cm^{-1}; δ_H (400 MHz) 5.68 (1H, m, CH-2), 3.98 (2H, s, C*H*$_2$OH), 2.03-2.01 (4H, m, CH_2-3 and CH_2-6), 1.67-1.55 (4H, m, CH_2-4 and CH_2-5); δ_C (100 MHz) 137.5 (C-1), 123.0 (CH-2); 67.7 (CH_2OH), [25.6, 24.9, 22.5 and 22.4 (CH_2-3, CH_2-4, CH_2-5 and CH_2-6)]; *m/z* (CI) 130 $[M+NH_4]^+$, 112, 95 (Found: $[M+NH_4]^+$, 130.1233. $C_7H_{12}O$ requires $[M+NH_4]^+$, 130.1232). Data in agreement with those previously reported.

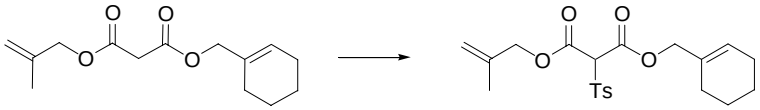
Cyclohex-1-enylmethyl methallyl malonate (255)



191b **254** **255**

According to general procedure **3.2.3**, methallyl malonate **191b** (1.805 g, 11.41 mmol, 1 equiv) was reacted with 1-hydroxymethylcyclohexene **254** (1.297 g, 11.56 mmol, 1 equiv), DMAP (159 mg, 1.30 mmol, 0.1 equiv) and DCC (2.557 g, 12.39 mmol, 1.1 equiv) in CH_2Cl_2 (100 mL). Chromatography (2%→10% AcOEt–hexane) gave *cyclohex-1-enylmethyl methallyl malonate* **255** (2.03 g, 70%) as a colourless liquid; R_f 0.37 (10% AcOEt–hexane); ν_{max} (film) 2933, 1737, 1451, 1411, 1376, 1328, 1270, 1149, 1036 1006, 906 cm^{-1}; δ_H (400 MHz) 5.75 (1H, bs, CH-2 cyclohexenyl), [5.00 (1H, bs) and 4.95-4.94 (1H, m), CH_2], [4.57 (2H, bs) and 4.51 (2H, bs) 2 × CH_2O], 3.44 (2H, s, $OOCCH_2COO$), 2.05-1.96 (4H, m, CH_2-3 and CH_2-6 cyclohexenyl), 1.76 (3H, s, CH_3), 1.67-1.54 (4H, m, CH_2-4 and CH_2-5 cyclohexenyl); δ_C (100 MHz) [166.4 and 166.2 (2 × C=O)], [139.3 and 132.3 (2 × =C)], 127.1 (=CH), 113.5 (=CH_2), [70.0 and 68.7 (2 × CH_2O)], 41.6 ($OOCCH_2COO$), [25.7, 25.0, 22.3 and 22.0 (4 × CH_2 cyclohexenyl)], 19.4 (CH_3); *m/z* (CI) 270 $[M+NH_4]^+$, 230, 176, 112, 95 (Found: $[M+NH_4]^+$, 270.1711. $C_{14}H_{20}O_4$ requires $[M+NH_4]^+$, 270.1705) .

(±)-1-Cyclohex-1-enylmethyl 3- methallyl 2-(*p*-toluenesulfonyl)malonate (251a)

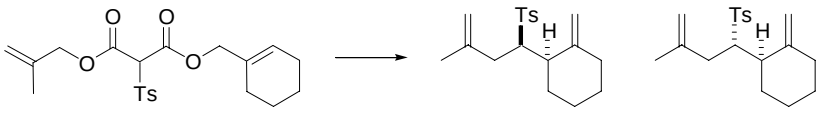


255 **251a**

According to general procedure **3.2.4**, cyclohex-1-enylmethyl methallyl malonate **255** (1.619 g, 6.418 mmol, 2 equiv) was reacted with *t*-BuOK (740 mg, 6.59 mmol, 2 equiv) and TsF (561 mg, 3.22 mmol, 1 equiv) in DMSO (3.2 mL). Chromatography (2%→20% AcOEt–hexane) gave *(±)-1-cyclohex-1-enylmethyl 3- methallyl 2-(*p*-toluenesulfonyl)malonate* **251a** (663 mg, 51%) as a colourless gum and the excess starting malonate **255** (828 mg, 69 % unreacted); R_f 0.10 (10% AcOEt–hexane); ν_{max}

(film) 2931, 1743, 1455, 1336, 1277, 1193, 1180, 1151, 1082, 763, 750, 705 cm^{-1}; δ_H (400 MHz) 7.86 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), 7.34 (2H, d, *J* 8.0 Hz, CH-3 Ts and CH-5 Ts), 5.74 (1H, bs, =CH), 5.01 (1H, s, CHTs), [4.99 (1H, bs) and 4.95 (1H, bs), $=CH_2$], [4.58 (2H, bs) and 4.52 (2H, bs), 2 × CH_2O], 2.45 (3H, s, CH_3 Ts), [2.03-2.02 (2H, m) and 1.90 (2H, m), CH_2-3 and CH_2-6 cyclohexenyl], 1.71 (3H, s, $=CCH_3$), 1.64-1.54 (4H, m, CH_2-4 and CH_2-5 cyclohexenyl); δ_C (100 MHz) [160.8 and 160.7 (2 × C=O)], [145.8, 138.3, 134.2 and 131.5 (2 × C Ts, =*C*Me and C-1 cyclohexenyl)], [130.1 and 129.4 (4 × CH Ts)], 128.0 (=CH), 114.4 ($=CH_2$), 74.5 (CHTs), [71.4 and 69.9 (2 × CH_2O)], [25.5, 24.9, 22.1 and 21.8 (4 × CH_2 cyclohexenyl)], [21.6 and 19.2 (2 × CH_3)]; *m/z* (CI) 424 $[M+NH_4]^+$, 336, 330, 270, 189, 172, 112, 95 (Found: $[M+NH_4]^+$, 424.1808. $C_{21}H_{26}O_6S$ requires $[M+NH_4]^+$, 424.1794) (Found: C, 61.95; H, 6.45. $C_{21}H_{26}O_6S$ requires C, 62.05; H, 6.45%).

1-Methyl-4-{(*R)-3-methyl-1-[(*S**)-2-methylenecyclohexyl]but-3-enylsulfonyl}benzene and 1-methyl-4-{(*S**)-3-methyl-1-[(*S**)-2-methylenecyclohexyl]but-3-enylsulfonyl}benzene (252a)**

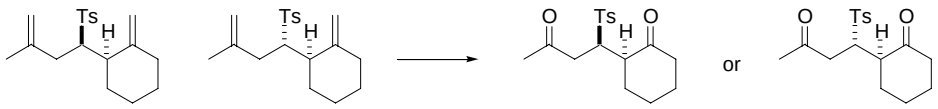


251a **252a**

To a mixture of 2-tosyl malonic acid methallyl ester cyclohex-1-enymethyl ester **251a** (65 mg, 0.16 mmol, 1 equiv) and KOAc (5 mg, 0.05 mmol, 0.3 equiv) under nitrogen was added BSA (300 μL, 1.19 mmol, 7 equiv). The mixture was exposed to 6 cycles of microwave irradiation of 1 min each at 220 °C followed by 3 cycles of microwave irradiation of 2 min each at 240 °C. Chromatography (0%→10% AcOEt–hexane) gave *1-methyl-4-[3-methyl-1-(2-methylenecyclohexyl)but-3-enylsulfonyl]benzene* **252a** in a 1:1 mixture of diastereoisomers (32 mg, 62%) as a colourless gum; R_f 0.22 (10% AcOEt–hexane); ν_{max} (film) 2931, 2859, 1668, 1596, 1448, 1311, 1301, 1293, 1145, 1085, 892, 815 cm^{-1}; δ_H (400 MHz) 7.77 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.73 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.33 (2H, d, *J* 8.0 Hz, CH-3 Ts and CH-5 Ts of one diastereoisomer), 7.29 (2H, d, *J* 8.0

Hz, CH-3 Ts and CH-5 Ts of one diastereoisomer), 4.83-4.46 (8H, m, 2 × =CH_2 of both diastereoisomers), [3.70 (1H, dt, *J* 9.5, 2.5 Hz) and 3.60-3.56 (1H, m), CHTs of both diastereoisomers], [2.97-2.94 (1H, m), 2.76-2.65 (2H, m), 2.50-2.00 (8H, m) and (11H, m), CH-1 and 5 × CH_2 cyclohexyl of both diastereoisomers], [2.44 (3H, s) and 2.43 (3H, s), CH_3 Ts of both diastereoisomers], [1.56 (3H, s) and 1.46 (3H, s), =CCH_3 of both diastereoisomers]; δ_C (100 MHz) [149.6, 148.7, 144.3, 144.2, 141.4, 141.0, 137.1 and 136.7 (2 × C Ts and 2 × =C of both diastereoisomers)], [129.5, 129.4 and 128.8 (4 × CH Ts of both diastereoisomers)], [112.7, 112.5, 110.1 and 105.5 (2 × =CH_2 of both diastereoisomers)], [62.8 and 61.9 (CHTs of both diastereoisomers)], [44.3 and 41.7 (CH-1 cyclohexyl of both diastereoisomers)], [37.1, 36.3, 34.5, 33.2, 30.4, 28.6, 28.0, 28.0, 25.8 and 23.3 (5 × CH_2 cyclohexenyl of both diastereoisomers)], [22.2, 21.9 and 21.6 (2 × CH_3 Ts of both diastereoisomers)]; *m/z* (CI) 336 $[M+NH_4]^+$, 319 $[M+H]^+$, 296, 174, 163, 52 (Found: $[M+NH_4]^+$, 336.1993; $[M+H]^+$, 319.1731. $C_{19}H_{26}O_2S$ requires $[M+NH_4]^+$, 336.1997; $[M+H]^+$, 319.1732).

(*S)-2-[(*R**)-3-Oxo-1-(*p*-toluenesulfonyl)butyl]cyclohexanone or (*S**)-2-[(*S**)-3-oxo-1-(*p*-toluenesulfonyl)butyl]cyclohexanone (256)**

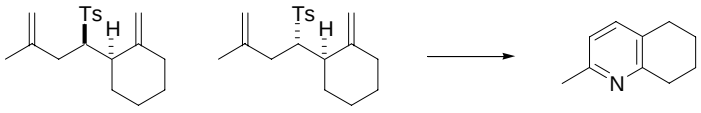


252a **256**

Ozone was bubbled through a solution of a 1:1 diastereoisomeric mixture of 1-methyl-4-[(*R*)-3-methyl-1-(2-methylenecyclohexyl)but-3-enylsulfonyl]benzene **252a** (87 mg, 0.27 mmol, 1 equiv) in MeOH:CH_2Cl_2 (1:5, 3 mL) at -78 °C for 5 min, until a blue color persisted. After 3 min of bubbling O_2 through the reaction mixture, PPh_3 (217 mg, 0.829 mmol, 3 equiv) was added. After stirring for 3 h at -78 °C the mixture was concentrated under reduced pressure and chromatography (10%→30% AcOEt–petrol) gave one diastereoisomer of *2-[3-oxo-1-(*p-*toluenesulfonyl)butyl]cyclohexanone* **256** (41 mg, 47%) as a colourless gum; R_f 0.34 (30% AcOEt–petrol); δ_H (400 MHz) 7.71 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), 7.32 (2H, d, *J* 8.0 Hz, CH-3 Ts and CH-5 Ts), 4.51-4.47 (1H, m, CHTs), [3.22 (1H, d, *J* 7.5 Hz) and 2.99 (1H, dd, *J* 17.5, 7.5 Hz),

CH_3COCH_2], 3.20-3.15 (1H, m, CH-2 cyclohexanone), 2.42 (3H, s, CH_3 Ts), 2.31-2.25 (2H, m, CH_2-6 cyclohexanone), 2.06 (3H, s, CH_3CO), 1.77-1.44 (6H, m, CH_2-3, CH_2-4 and CH_2-5 cyclohexanone); δ_C (100 MHz) [208.5 and 203.0 (2 × C=O)], 145.0 (C-4 Ts), 135.2 (C-1 Ts), [129.8 and 128.5 (4 × CH Ts)], 57.5 (CHTs), 48.4 (CH-2 cyclohexanone), [42.0 and 39.1 (CH_3COCH_2 and CH_2-6 cyclohexanone)], [29.5, 29.1, 27.1, 24.8 and 21.6 (CH_3CO, CH_3 Ts and CH_2-3, CH_2-4, CH_2-5 cyclohexanone)]; *m/z* (CI) 340 $[M+NH_4]^+$, 200, 186, 184, 167, 148 (Found: $[M+NH_4]^+$, 340.1582. $C_{17}H_{22}O_4S$ requires $[M+NH_4]^+$, 340.1583).

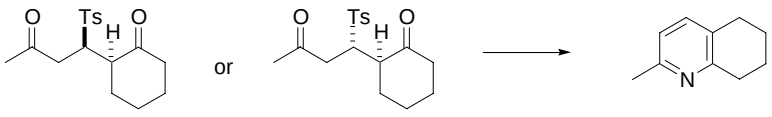
2-Methyl-5,6,7,8-tetrahydroquinoline (253a)[23]



252a **253a**

Procedure B

According to general procedure **3.2.6**, a 1:1 diastereoisomeric mixture of 1-methyl-4-[(*R**)-3-methyl-1-(2-methylenecyclohexyl)but-3-enylsulfonyl]benzene **252a** (187 mg, 0.587 mmol, 1 equiv) in MeOH:CH_2Cl_2 (6 mL) was ozonolised and reduced with PPh_3 (478 mg, 1.82 mmol, 3 equiv). The crude diketones in MeOH (3 mL) were then reacted with NH_4HCO_3 (385 mg, 4.87 mmol, 8.3 equiv). Chromatography (40%→60% AcOEt–hexane) gave 2-methyl-5,6,7,8-tetrahydroquinoline **253a** (32 mg, 37%) as a colourless oil.



256 **253a**

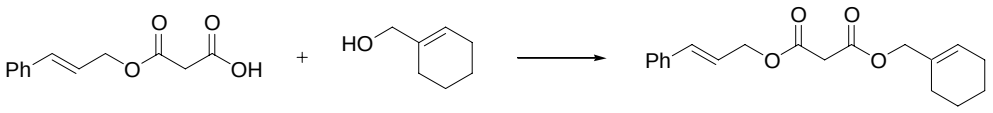
Procedure B

To a solution of one diastereoisomer of 2-[3-oxo-1-(*p*-toluenesulfonyl)butyl]cyclohexanone **256** (41 mg, 0.126 mmol, 1 equiv) in MeOH (1.5 mL) was added NH_4HCO_3 (82 mg, 1.037 mmol, 8.2 equiv) and the mixture was

exposed to microwave irradiation for 10 min at 100 °C. The red solution was concentrated under reduced pressure. The red residue was dissolved in CH_2Cl_2 (10 mL) and then washed with H_2O (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 2-methyl-5,6,7,8-tetrahydroquinoline **253a** (2 mg, 11%) as an orange oil.

253a; R_f 0.30 (50% AcOEt–hexane); ν_{max} (film) 2931, 2859, 1597, 1573, 1470, 1454, 1261, 1092, 1021, 805 cm^{-1}; δ_H (400 MHz) 7.23 (1H, d, *J* 7.5 Hz, CH-4), 6.88 (1H, d, *J* 7.5 Hz, CH-3), 2.89-2.85 (2H, m, CH_2-8), 2.73-2.70 (2H, m, CH_2-5), 2.48 (3H, s, CH_3), 1.91-1.76 (4H, m, CH_2-6 and CH_2-7); δ_C (100 MHz) [156.4 and 155.0 (C-2 and C-8a)], 137.1 (CH-4), 128.9 (C-4a), 120.4 (CH-3), [32.5, 28.4, 23.2 and 22.8 (CH_2-5, CH_2-6, CH_2-7 and CH_2-8)], 24.1 (CH_3); *m/z* (CI) 148 $[M+H]^+$, (Found: $[M+H]^+$, 148.1127. $C_{10}H_{13}N$ requires $[M+H]^+$, 148.1126). Data in agreement with those previously reported.

Cinnamyl cyclohex-1-enylmethyl malonate (298)

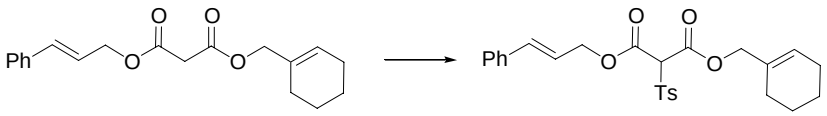


191d **254** **298**

According to general procedure **3.2.3**, cinnamyl malonate **191d** (1.807 g, 8.205 mmol, 1.2 equiv) was reacted with 1-hydroxymethylcyclohexene **254** (781 mg, 6.96 mmol, 1 equiv), DMAP (109 mg, 0.888 mmol, 0.1 equiv) and DCC (1.982 g, 9.604 mmol, 1.2 equiv) in CH_2Cl_2 (80 mL). Chromatography (3%→5% AcOEt–petrol) gave *cinnamyl cyclohex-1-enylmethyl malonate* **298** (2.03 g, 93%) as a colourless liquid; R_f 0.65 (10% AcOEt–petrol); ν_{max} (film) 3058, 3027, 3003, 2932, 2837, 1747, 1732, 1495, 1449, 1411, 1379, 1327, 1270, 1149, 969, 922, 831, 801, 747, 694 cm^{-1}; δ_H (400 MHz) 7.34-7.25 (5H, m, Ph), 6.67 (1H, d, *J* 16.0 Hz, =CHPh), 6.28 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), 5.75 (1H, bs, CH-2 cyclohexenyl), 4.81 (2H, dd, *J* 6.5, 1.5 Hz, =CHC*H*$_2$O), 4.52 (2H, s, OCH_2cyclohexenyl), 3.44 (2H, s, $OOCCH_2COO$), 2.01-1.97 (4H, m, CH_2-3 and $=CCH_2O$), 1.63-1.53 (4H, m, CH_2-4 and CH_2-5 cyclohexenyl); δ_C (100 MHz) [166.4 and 166.4 (2 × C=O)], [136.0 and 132.3 (*ipso* Ph and C-1

cyclohexenyl)], [134.8, 128.2, 127.1 and 122.4 (*para* Ph, =CHPh, *C*H=CHPh and CH-2 cyclohexenyl)], [128.6 and 126.7 (*ortho* Ph and *para* Ph)], [70.0 and 66.1 (2 × CH_2O)], 41.6 (OOC*C*H_2COO), [25.8, 25.0, 22.3 and 22.0 (4 × CH_2 cyclohexenyl)]; *m/z* (CI) 332 $[M+NH_4]^+$, 315 $[M+H]^+$, 211, 151, 134, 117, 52 (Found: $[M+NH_4]^+$, 322.1860. $C_{19}H_{22}O_4$ requires $[M+NH_4]^+$, 322.1862) (Found: C, 72.52; H, 7.12. $C_{19}H_{22}O_4$ requires C, 72.59; H, 7.05%).

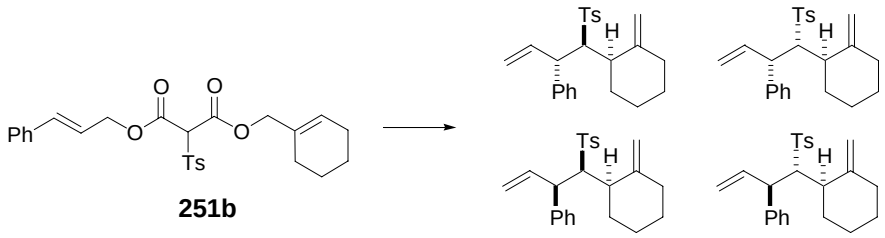
(±)-1-Cinnamyl 3-cyclohex-1-enylmethyl 2-(*p*-toluenesulfonyl)malonate (251b)



298 **251b**

According to general procedure **3.2.4**, cinnamyl cyclohex-1-enylmethyl malonate **298** (1.958 g, 6.229 mmol, 2 equiv) was reacted with *t*-BuOK (699 mg, 6.23 mmol, 2 equiv) and TsF (572 mg, 3.28 mmol, 1 equiv) in DMSO (3 mL). Chromatography (10%→20% AcOEt–petrol) gave *(±)-1-cinnamyl 3-cyclohex-1-enylmethyl 2-(*p*-toluenesulfonyl)malonate* **251b** (1.08 g, 74%) as a colourless gum and the excess starting malonate **298** (1.08 g, 88% unreacted); R_f 0.13 (10% AcOEt–petrol); ν_{max} (film) 3059, 3028, 2928, 2857, 1743, 1656, 1597, 1494, 1449, 1376, 1336, 1272, 1151, 1083, 1018, 969, 921, 815, 746, 706, 695, 673, 569, 515 cm^{-1}; δ_H (400 MHz) 7.85 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.37-7.26 (7H, m, CH-3 Ts, CH-5 Ts and Ph), 6.64 (1H, d, *J* 16.0 Hz, =CHPh), 6.17 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), 5.73 (1H, bs, CH-2 cyclohexenyl), 5.01 (1H, s, CHTs), 4.81 (2H, d, *J* 6.5 Hz, =CHC*H*$_2$O), 4.53 (2H, s, =CCH_2O), 2.39 (3H, s, CH_3 Ts), [1.99 (2H, bs) and 1.90 (2H, bs), CH_2-3 and CH_2-6 cyclohexenyl], 1.59-1.53 (4H, m, CH_2-4 and CH_2-5 cyclohexenyl); δ_C (100 MHz) 160.9 (2 × C=O), 145.9 (C-4 Ts), [135.8, 134.2 and 131.6 (*ipso* Ph, C-1 Ts and C-1 cyclohexenyl)], [135.7, 128.4, 128.1 and 121.3 (*para* Ph, =CHPh, *C*H=CHPh and CH-2 cyclohexenyl)], [130.2, 129.5, 128.6 and 126.7 (*ortho* Ph, *meta* Ph and 4 × CH Ts)], 74.6 (CHTs), [71.5 and 67.4 (2 × CH_2O)], [25.6, 25.0, 22.2 and 21.9 (4 × CH_2 cyclohexenyl)], 21.7 (CH_3 Ts); *m/z* (CI) 486 $[M+NH_4]^+$, 348, 326, 174, 134, 117 (Found: $[M+NH_4]^+$, 486.1962. $C_{26}H_{28}O_6S$ requires $[M+NH_4]^+$, 486.1950) (Found: C, 66.72; H, 5.93. $C_{26}H_{28}O_6S$ requires C, 66.65; H, 6.02%).

1-Methyl-4-{(1*S,2*R**)-1-[(*S**)-2-methylenecyclohexyl]-2-phenylbut-3-enylsulfonyl}benzene, 1-methyl-4-{(1*R**,2*R**)-1-[(*S**)-2-methylenecyclohexyl]-2-phenylbut-3-enylsulfonyl}benzene, 1-methyl-4-{(1*S**,2*S**)-1-[(*S**)-2-methylenecyclohexyl]-2-phenylbut-3-enylsulfonyl}benzene and 1-methyl-4-{(1*R**,2*S**)-1-[(*S**)-2-methylenecyclohexyl]-2-phenylbut-3-enylsulfonyl}benzene (252b)**

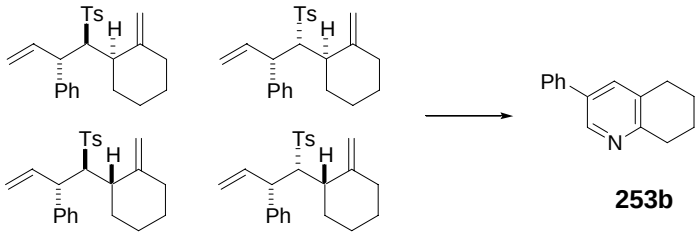


251b **252b**

To a mixture of (±)-1-cinnamyl 3-cyclohex-1-enylmethyl 2-(*p*-toluenesulfonyl)malonate **251b** (543 mg, 1.16 mmol, 1 equiv) and KOAc (14 mg, 0.15 mmol, 0.1 equiv) under nitrogen was added BSA (900 μL, 3.57 mmol, 3 equiv). The mixture was exposed to 6 cycles of microwave irradiation of 1 min each at 190 °C. Chromatography (1%→2% AcOEt–petrol) gave *1-methyl-4-[1-(2-methylenecyclohexyl)-2-phenylbut-3-enylsulfonyl]benzene* **252b** in a mixture of diastereoisomers (257 mg, 58%) as a colourless gum; R_f 0.33 (5% AcOEt–petrol); ν_{max} (film) 3064, 2932, 2857, 1598, 1494, 1451, 1314, 1301, 1143, 1085, 906, 815, 740, 700, 662 cm^{-1}; δ_H (400 MHz) 7.70 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.56-6.97 (26H, m, Ph, CH-3 Ts and CH-5 of all diastereoisomers and CH-2 Ts and CH-6 Ts of three diastereoisomers), [6.71-6.62 (1H, m), 6.35 (1H, dt, *J* 17.0, 10.0 Hz) and 6.25-6.15 (2H, m), =CH of all diastereosiomers], 5.33-4.86 (16H, m, 2 × $=CH_2$ of all diastereoisomers), [4.64 (1H, s), 4.44 (1H, s), 4.36-4.32 (1H, m), 4.23 (1H, dd, *J* 9.0, 3.0 Hz) and 4.16-4.02 (4H, m), CHTs and CHPh of all diastereoisomers], [3.30-3.25 (1H, m), 3.01-2.93 (2H, m) and 2.68-2.65 (1H, m), CH-1 cyclohexyl of all diastereoisomers], [2.42 (3H, s), 2.40 (3H, s), 2.39 (3H, s) and 2.36 (3H, s), CH_3 Ts of all diastereoisomers)], 2.33-1.28 (32H, m, 4 × CH_2 cyclohexyl of all diastereoisomers); δ_C (100 MHz) [149.7, 148.9, 148.5 and 148.3 (C-2 cyclohexyl of all diastereoisomers)], [144.0, 143.7, 143.5, 143.1, 142.9, 142.3, 141.4, 140.8, 139.4, 138.6, 138.4 and 137.7 (2 × C Ts and *ipso* Ph of all

diastereoisomers)], [137.9, 137.5, 136.9 and 134.6 (=CH of all diastereoisomers)], [129.4, 129.4, 129.3, 129.0, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.4, 126.5, 126.4 and 125.9 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph of all diastereoisomers)], [120.0, 117.9, 117.7, 117.5, 110.8, 109.1, 108.6 and 108.0 (2 × $=CH_2$ of all diastereoisomers)], [69.6, 69.5, 68.5 and 68.2 (CHTs of all diastereoisomers)], [49.3, 48.5, 48.3 and 48.2 (CHPh of all diastereoisomers)], [44.2, 43.7, 43.2 and 42.0 (CH-1 cyclohexyl of all diastereoisomers)], [35.7, 35.6, 35.1, 33.4, 30.2, 29.6, 29.4, 28.3, 27.9, 27.8, 27.3, 25.2, 25.0, 24.3 and 22.1 (4 × CH_2 cyclohexyl of all diastereoisomers)], [21.5, 21.5 and 21.4 (CH_3 of all diastereoisomers)]; *m/z* (CI) 398 $[M+NH_4]^+$, 381 $[M+H]^+$, 52 (Found: $[M+H]^+$, 381.1888. $C_{24}H_{28}O_2S$ requires $[M+H]^+$, 381.1888).

3-Phenyl-5,6,7,8-tetrahydroquinoline (253b)[24]

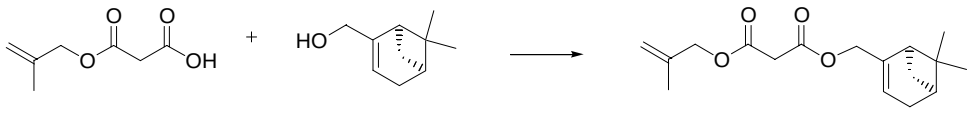


252b **253b**

According to general procedure **3.2.6**, a diastereoisomeric mixture of 1-methyl-4-[1-(2-methylenecyclohexyl)-2-phenylbut-3-enylsulfonyl]benzene **252b** (205 mg, 0.539 mmol, 1 equiv) in MeOH:CH_2Cl_2 (5.5 mL) was ozonolised and reduced with Me_2S (2.4 mL, 55 mmol, 103 equiv). The crude ketoaldehydes in MeOH (3 mL) were then reacted with NH_4HCO_3 (401 mg, 5.07 mmol, 9.4 equiv). Chromatography (20% AcOEt–petrol) gave 3-phenyl-5,6,7,8-tetrahydroquinoline **253b** (72 mg, 63%) as a pale yellow oil; R_f 0.30 (20% AcOEt–hexane); ν_{max} (film) 3060, 3030, 2934, 2860, 1604, 1582, 1558, 1460, 1427, 1394, 1352, 1249, 1150, 1076, 1028, 989, 928, 911, 823, 763, 698 cm^{-1}; δ_H (400 MHz) 8.58 (1H, d, *J* 1.5 Hz, CH-2), [7.57-7.55 (3H, m) and 7.47 (2H, m), CH-4, *ortho* Ph and *meta* Ph], 7.37 (1H, tt, *J* 7.0, 2.0 Hz, *para* Ph), 2.97 (2H, t, *J* 6.5 Hz, CH_2-8), 2.84 (2H, t, *J* 6.5 Hz, CH_2-5), [1.97-1.91 (2H, m) and 1.88-1.82 (2H, m), CH_2-6 and CH_2-7); δ_C (100 MHz) 156.3 (C-8a), 145.2 (CH-2), [138.1, 133.9 and 132.1 (C-3, C-4a

and *ipso* Ph)], 135.1 (CH-4), [128.9 and 127.0 (*ortho* Ph and *meta* Ph)], 127.6 (*para* Ph), [32.2, 28.9, 23.1 and 22.7 (4 × CH_2)]; *m/z* (CI) 210 $[M+H]^+$, 52 (Found: $[M+H]^+$, 210.1287. $C_{15}H_{15}N$ requires $[M+H]^+$, 210.1283) (Found: C, 85.97; H, 7.19; N, 6.67. $C_{13}H_{13}N$ requires C, 86.08; H, 7.22; N, 6.69). Data in agreement with those previously reported.

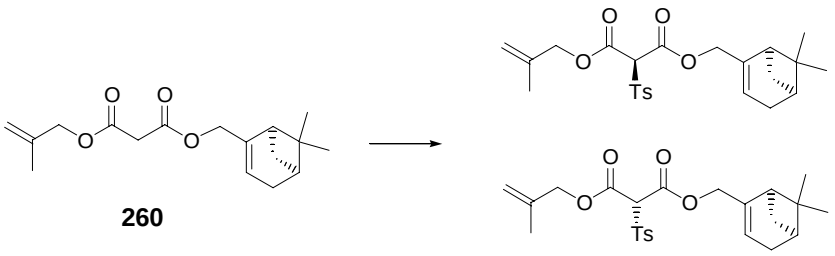
{(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl methallyl malonate (260)



191b **259** **260**

According to general procedure **3.2.3**, methallyl malonate **191b** (5.9 g, 37 mmol, 1 equiv) was reacted with (-)-myrtenol **259** (6.6 mL, 41 mmol, 1.1 equiv), DMAP (462 mg, 3.78 mmol, 0.1 equiv) and DCC (9.278 g, 44.97 mmol, 1.2 equiv) in CH_2Cl_2 (180 mL). Chromatography (1%→2% AcOEt–petrol) gave *{(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl methallyl malonate* **260** (9.79 g, 90%) as a colourless oil; $[\alpha]_D^{26}$ -41.0 (*c* 0.059, $CHCl_3$); R_f 0.39 (30% AcOEt–petrol); ν_{max} (film) 2984, 2936, 2927, 1753, 1737, 1450, 1367, 1328, 1274, 1264, 1204, 1147, 1003, 981, 763, 750 cm^{-1}; δ_H (500 MHz) 5.59-5.56 (1H, m, CH-3 bicycle), [5.00 (1H, s) and 4.94 (1H, s), $=CH_2$], 4.56 (2H, s, $=CCH_3C\mathit{H}_2O$), 4.52 (2H, dd, *J* 8.0, 1.5 Hz, bicycleCH_2O), 3.42 (2H, s, $OOCCH_2COO$), 2.41-3.37 (1H, m, CH-7 equatorial bicycle), 2.33-2.22 (2H, m, CH_2-4 bicycle), 2.13-2.09 (2H, m, CH-1 and CH-5 bicycle), [1.76 (3H, s) and 0.81 (3H, s), 2 × CH_3-6 bicycle], 1.28 (3H, s, $=CCH_3$), 1.17 (1H, d, *J* 8.5 Hz, CH-7 axial bicycle); δ_C (125 MHz) [166.4 and 166.2 (2 × C=O)], [142.4 and 139.3 (C-2 bicycle and $=\mathit{C}CH_3$)], 122.2 (CH-3 bicycle), 113.5 ($=CH_2$), [68.7 and 68.1 (2 × CH_2O)], [43.5 and 40.6 (CH-1 and CH-5 bicycle)], 41.6 ($OOC\mathit{C}H_2COO$), 38.1 (C-6 bicycle), [31.5 and 31.3 (CH_2-4 and CH_2-7 bicycle)], [26.1 and 21.0 (2 × CH_3-6 bicycle)], 19.5 ($=C\mathit{C}H_3$); *m/z* (CI) 310 $[M+NH_4]^+$, 176, 135 (Found: $[M+NH_4]^+$, 310.2022. $C_{17}H_{24}O_4$ requires $[M+NH_4]^+$, 310.2018) (Found: C, 69.86; H, 8.17. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27%).

(*R*)-1-{(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl 3-methallyl 2-(*p*-toluenesulfonyl)malonate and (*S*)-1-{(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl 3-methallyl 2-(*p*-toluenesulfonyl)malonate (251c)

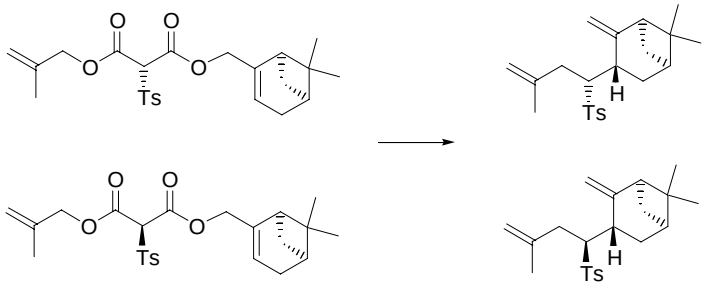


260 **251c**

According to general procedure **3.2.4**, {(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl methallyl malonate **260** (8.507 g, 29.10 mmol, 2 equiv) was reacted with *t*-BuOK (3.275 g, 29.19 mmol, 2 equiv) and TsF (2.581 g, 14.81 mmol, 1 equiv) in DMSO (14 mL). Chromatography (2%→12% AcOEt–petrol) gave *1-{(1*R,*5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl 3-methallyl-2 (*p-*toluenesulfonyl)malonate* **251c** (5.277 g, 81%) in a 1:1 mixture of diastereoisomers as a pale yellow gum and the excess starting malonate **260** (4.274 g, 85% unreacted); R_f 0.40 (10% AcOEt–petrol); ν_{max} (film) 2973, 2934, 2921, 1743, 1596, 1450, 1367, 1337, 1290, 1274, 1180, 1083, 908, 813, 722, 706 cm^{-1}; δ_H (500 MHz) 7.86 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.85 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.34 (4H, d, *J* 8.0 Hz, CH-3 Ts and CH-5 Ts of both diastereoisomers), 5.56-5.55 (2H, m, CH-3 bicycle of both diastereoisomers), [4.99 (4H, s) and 4.95 (2H, s), CHTs and $=CH_2$ of both diastereoisomers], 4.58-4.51 (8H, m, 2 × CH_2O of both diastereoisomers), 2.45 (6H, s, CH_3 Ts of both diastereoisomers), 2.39-2.35 (2H, m, CH-7 equatorial bicycle of both diastereoisomers), 2.31-2.19 (4H, m, CH_2-4 bicycle of both diastereoisomers), 2.08-2.02 (4H, m, CH-1 and CH-5 bicycle of both diastereoisomers), [1.72 (6H, s), 0.77 (3H, s) and 0.76 (3H, s), 2 × CH_3-6 bicycle of both diastereoisomers], 1.26 (6H, s, $=CCH_3$ of both diastereoisomers), [1.13 (1H, d, *J* 8.5 Hz) and 1.12 (1H, d, *J* 8.5 Hz), CH-7 axial bicycle of both diastereoisomers]; δ_C (125 MHz) [160.9 and 160.8 (2 × C=O of both diastereoisomers)], [145.9, 141.5, 138.4, 134.3 and 134.2 (2 × C Ts, C-2 bicycle and $=CCH_3$ of both diastereoisomers)], [130.2

and 129.5 (4 × CH Ts of both diastereoisomers)], 123.2 (CH-3 bicycle of both diastereoisomers), 114.5 (=CH_2 of both diastereoisomers), 74.6 (CHTs of both diastereoisomers), [70.1 and 69.5 (2 × CH_2O of both diastereoisomers)], [43.4, 43.4 and 40.5 (CH-1 and CH-5 bicycle of both diastereoisomers)], 38.0 (C-6 bicycle of both diastereoisomers), [31.4 and 31.3 (CH_2-4 and CH_2-7 bicycle of both diastereoisomers)], [26.0 and 21.8 (2 × CH_3-6 bicycle of both diastereoisomers)], 21.0 (=C*C*H_3 of both diastereoisomers), 19.4 (CH_3 Ts of both diastereoisomers); *m/z* (CI) 464 $[M+NH_4]^+$, 366, 286, 152, 135 (Found: $[M+NH_4]^+$, 464.2097. $C_{24}H_{30}O_6S$ requires $[M+NH_4]^+$, 464.2107).

(1*R*,3*S*,5*R*)-6,6-Dimethyl-3-[(*R*)-3-methyl-1-(*p*-toluenesulfonyl)but-3-enyl]-2-methylenebicyclo[3.1.1]heptane and (1*R*,3*S*,5*R*)-6,6-dimethyl-3-[(*S*)-3-methyl-1-(*p*-toluenesulfonyl)but-3-enyl]-2-methylenebicyclo[3.1.1]heptane (252c)

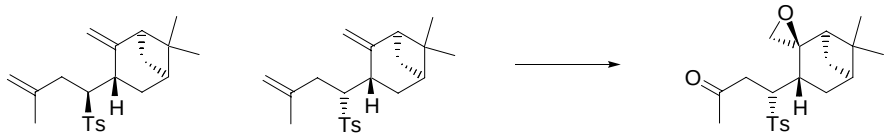


251c **252c**

To a 1:1 diastereoisomeric mixture of 1-{(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}methyl 3-methallyl-2 (*p*-toluenesulfonyl)malonate **251c** (3.489 g, 7.813 mmol, 1 equiv) and KOAc (84 mg, 0.86 mmol, 0.1 equiv) under nitrogen was added BSA (10 mL, 40 mmol, 5 equiv). The mixture was exposed to 6 cycles of microwave irradiation of 1 min each at 220 °C. Chromatography (2% AcOEt–petrol) gave *(1*R*,3*S*,5*R*)-6,6-dimethyl-3-[3-methyl-1-(*p-*toluenesulfonyl)but-3-enyl]-2-methylenebicyclo[3.1.1]heptane* **252c** in a 1:1 mixture of diastereoisomers (2.1 g, 75%) as a pale yellow gum; R_f 0.33 (5% AcOEt–petrol); ν_{max} (film) 2977, 2970, 2921, 2866, 1637, 1597, 1455, 1310, 1143, 1085, 890, 815 cm^{-1}; δ_H (400 MHz) 7.78 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.77 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of one diastereoisomer), 7.33 (2H, d, *J* 8.5 Hz, CH-3 Ts and CH-5 Ts of one

diastereoisomer), 7.31 (2H, d, *J* 8.5 Hz, CH-3 Ts and CH-5 Ts of one diastereoisomer), 4.86-4.62 (8H, m, 2 × =CH_2 of both diastereoisomers), [3.75-3.71 (1H, m), 3.64-3.52 (2H, m), 3.22-3.19 (1H, m), 2.80-2.74 (1H, m) and 2.60-1.97 (13H, m), CHTs, =CCH_3CH_2, CH-1, CH-3, CH_2-4, CH-5 and CH-7 equatorial of both diastereoisomers], [2.45 (3H, s) and 2.44 (3H, s), CH_3 Ts of both diastereoisomers], [1.64 (1H, d, *J* 10.0 Hz) and 1.10 (1H, d, *J* 10.0 Hz), CH-7 axial of both diastereoisomers], [1.47 (3H, s), 1.42 (3H, s), 0.82 (3H, s) and 0.76 (3H, s), 2 × CH_3-6 of both diastereoisomers], [1.26 (3H, s) and 1.25 (3H, s), =CCH_3 of both diastereoisomers)]; δ_C (100 MHz) [152.4, 151.4, 144.3, 141.0, 140.8, 137.2 and 136.8 (2 × C Ts and 2 × =C of both diastereoisomers)], [129.6, 129.4, 128.8 and 128.6 (4 × CH Ts of both diastereoisomers)], [114.3, 114.0, 109.2 and 108.0 (2 × =CH_2 of both diastereoisomers)], [67.7 and 66.0 (CHTs of both diastereoisomers)], 52.8 (CH-1 of both diastereoisomers), [40.8, 40.6, 33.5, 33.3, 26.3, 26.2, 21.9, 21.8, 21.6 and 21.4 (CH-3, CH-5 and 4 × CH_3 of both diastereoisomers)], 40.1 (C-6 of both diastereoisomers), [35.9, 33.6, 29.6, 29.6, 28.5 and 26.9 (3 × CH_2 of both diastereoisomers)]; *m/z* (CI) 376 $[M+NH_4]^+$, 359 $[M+H]^+$ (Found: $[M+H]^+$, 359.2034. $C_{22}H_{30}O_2S$ requires $[M+H]^+$, 359.2045).

(*R*)-4-{(1*R*,2*S*,3*S*,5*R*)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-2,2'-oxirane]-3-yl}-4-(*p*-toluenesulfonyl)butan-2-one (264)

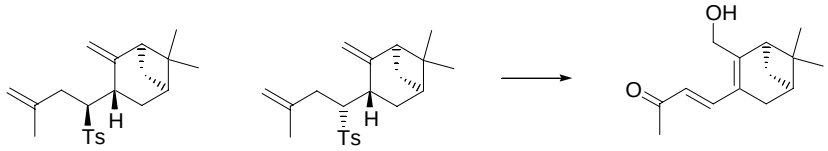


252c **264**

Ozone was bubbled through a solution of a 1:1 diastereoisomeric mixture of (1*R*,3*S*,5*R*)-6,6-dimethyl-3-[3-methyl-1-(*p*-toluenesulfonyl)but-3-enyl]-2-methylenebicyclo[3.1.1]heptane **252c** (202 mg, 0.563 mmol, 1 equiv) in MeOH:CH_2Cl_2 (1:5, 6 mL) at -78 °C for 15 min, until a blue color persisted. After 5 min of bubbling O_2 through the reaction mixture, PPh_3 (456 mg, 1.74 mmol, 3 equiv) was added. After stirring for 1 h at -78 °C the mixture was concentrated under reduced pressure and chromatography (15%→30% AcOEt–hexane) gave *(*R*)-4-{(1*R*,2*S*,3*S*,5*R*)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2,2'-oxirane]-3-yl}-4-(*p*-toluenesulfonyl)butan-2-*

one **264** (85 mg, 40%) as a white solid; $[\alpha]_D^{30}$ +29 (*c* 0.55, $CHCl_3$); mp 134-136 °C (15% CH_2Cl_2–petrol); R_f 0.37 (30% AcOEt–petrol); ν_{max} (film) 2986, 2925, 2878, 1718, 1596, 1455, 1415, 1370, 1363, 1309, 1301, 1280, 1269, 1145, 1086, 817, 763, 748, 722 cm^{-1}; δ_H (400 MHz) 7.72 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.34 (2H, d, *J* 8.5 Hz, CH-3 Ts and CH-5 Ts), 3.66-3.64 (1H, m, CHTs), 3.44 (1H, dd, *J* 18.0, 9.5 Hz, C*H*HCOCH$_3$), 3.07-3.02 (1H, m, CH-3), 2.83 (1H, d, *J* 3.5 Hz, C*H*HO), 2.47-2.42 (3H, m, CH*H*COCH$_3$, C*H*H-4 and C*H*H-7), 2.44 (3H, s, CH_3 Ts), 2.21 (1H, d, *J* 3.5 Hz, CH*H*O), 2.20 (3H, s, CH_3CO), 2.09-2.06 (1H, m, CH-5), 1.78 (1H, ddd, *J* 10.0, 7.5, 2.5 Hz, CH*H*-7), 1.48 (1H, m, CH-1), [1.23 (3H, s) and 1.04 (3H, s), 2 × CH_3-6], 0.92 (1H, d, *J* 10.5 Hz, CH*H*-4); δ_C (100 MHz) 203.9 (C=O), 145.1 (C-4 Ts), 134.9 (C-1 Ts), 130.0 (CH-3 Ts and CH-5 Ts), 128.4 (CH-2 Ts and CH-6 Ts), 62.8 (C-2), 59.8 (CHTs), 50.7 (CH-1), 50.2 (CH_2O), 40.6 (CH-5), 38.6 (C-6), 38.1 (*C*H$_2$COCH$_3$), 32.8 (CH-3), 30.5 (CO*C*H$_3$), 29.9 (CH_2-7), 27.9 (CH_2-4), [26.8 and 21.7 (2 × CH_3-6 and CH_3 Ts)]; *m/z* (CI) 394 $[M+NH_4]^+$, 377 $[M+H]^+$, 359, 355, 337, 238, 221, 203 (Found: $[M+H]^+$, 377.1790. $C_{21}H_{28}O_4S$ requires $[M+H]^+$, 377.1787) (Found: C, 67.07; H, 7.57. $C_{21}H_{28}O_4S$ requires C, 66.99; H, 7.50%).

(*E*)-4-{(1*R*,5*R*)-2-Hydroxymethyl-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl}-3-buten-2-one (263)

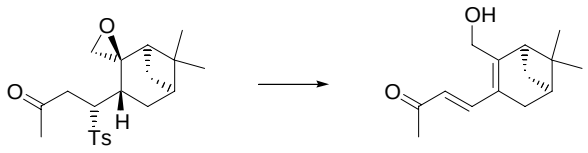


252c **263**

Procedure A

According to general procedure **3.2.6**, a 1:1 diastereoisomeric mixture of (1*R*,3*S*,5*R*)-6,6-dimethyl-3-[3-methyl-1-(*p*-toluenesulfonyl)but-3-enyl]-2-methylenebicyclo[3.1.1]heptane **2528c** (264 mg, 0.735 mmol, 1 equiv) in MeOH:CH_2Cl_2 (1:5, 7.2 mL) was ozonolysed and reduced with Me_2S (3.0 mL, 69 mmol, 94 equiv). The crude ozonolysis product in MeOH:CH_2Cl_2 (4 mL) was then reacted with NH_4HCO_3 (475 mg, 6.01 mmol, 8.2 equiv). Chromatography (20%

AcOEt–petrol) gave *(*E*)-4-[(1*R,5R*)-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]-3-buten-2-one* **263** (45 mg, 28%) as a yellow oil.



264 **263**

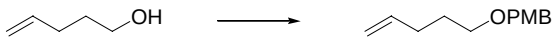
Procedure B

To a solution of (*R*)-4-[(1*R*,2*S*,3*S*,5*R*)-6,6-dimethylspiro(bicyclo[3.1.1]heptane-2,2'-oxirane)-3-yl]-4-(*p*-toluenesulfonyl)butan-2-one **264** (30 mg, 0.079 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) at rt was added DBU (13 μL, 0.086 mmol, 1.1 eq). After 7 h of stirring, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (2 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give *(*E*)-4-[(1*R,5R*)-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl]-3-buten-2-one* **263** (17 mg, 98%) as a yellow gum.

263; R_f 0.13 (20% AcOEt–petrol); ν_{max} (film) 3414, 2973, 2920, 1664, 1637, 1610, 1467, 1430, 1363, 1265, 1222, 1206, 1181, 1083, 1020, 990, 972 cm^{-1}; δ_H (400 MHz) 7.71 (1H, d, *J* 15.5 Hz, =CHCO), 6.13 (1H, d, *J* 15.5 Hz, C*H*=CHCO), [4.37 (1H, d, *J* 13.0 Hz) and 4.33 (1H, d, *J* 13.0 Hz), CH_2O], [2.55-2.53 (1H, m), 2.49-2.37 (3H, m) and 1.19-1.14 (2H, m), CH-1, CH_2-4, CH-5 and CH_2-7], 2.28 (3H, s, CH_3CO), [1.32 (3H, s) and 0.76 (3H, s), 2 × CH_3-6]; δ_C (100 MHz) 199.1 (C=O), [156.1 and 126.9 (C-2 and C-3)], 138.6 (*C*H=CHCO), 124.7 (*C*HCO), 61.0 (CH_2O), [45.7, 39.8, 27.6, 25.8 and 21.2 (CH-1, CH-5, 3 × CH_3)], 39.4 (C-6), [31.6 and 31.4 (CH_2-4 and CH_2-7)]; *m/z* (CI) 458 $[2M+NH_4]^+$, 441 $[2M+H]^+$, 238 $[M+NH_4]^+$, 221 $[M+H]^+$, 203, 189 (Found: $[M+H]^+$, 221.1542. $C_{14}H_{20}O_2$ requires $[M+H]^+$, 221.1542).

3.3.2.4 The Synthesis of 3,4-cyclofused pyridines

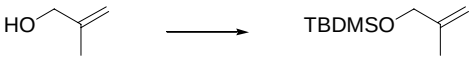
p-Methoxybenzyl-4-pentenyl ether (269)[25-27]



268 **269**

To a suspension of NaH (60% w/w dispersion in mineral oil, 4.209 g, 105.2 mmol, 1.1 equiv) in DMF (150 mL) at rt and under nitrogen was added 4-penten-1-ol **268** (10.0 mL, 96.8 mmol, 1 equiv). After 2 h of stirring *p*-methoxybenzylchloride (15.8 mL, 117 mmol, 1.2 equiv) was added and the mixture left stirring at rt for 20 h. The reaction was quenched with aqueous K_2CO_3 (10%, 100 mL). The resulting solution was poured into H_2O (500 mL) and extracted with Et_2O (3 × 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (1%→4% AcOEt–petrol) gave *p*-methoxybenzyl-4-pentenyl ether **269** (16.6 g, 83%) as a colourless liquid; R_f 0.68 (5% AcOEt–petrol); ν_{max} (film) 2933, 2853, 1612, 1513, 1463, 1362, 1302, 1247, 1173, 1098, 1035, 911, 820, 668 cm^{-1}; δ_H (400 MHz) 7.27 (2H, d, *J* 8.5 Hz, *ortho* PMB), 6.88 (2H, d, *J* 8.5 Hz, *meta* PMB), 5.87-5.76 (1H, m, =CH), 5.05-4.94 (2H, m, $=CH_2$), 4.43 (2H, s, CH_2 PMB), 3.81 (3H, s, CH_3), 3.46 (2H, t, *J* 6.5 Hz, CH_2CH_2O), 2.16-2.11 (2H, m, $=CHCH_2$), 1.74-1.67 (2H, m, CH_2CH_2O); δ_C (100 MHz) 159.1 (*para* PMB), 138.3 (=CH), 130.7 (*ipso* PMB), 129.2 (*ortho* PMB), 114.7 ($=CH_2$), 113.7 (*meta* PMB), 72.5 (CH_2 PMB), 69.4 (CH_2CH_2O), 55.3 (CH_3), [30.4 and 28.9, $=CHCH_2$ and CH_2CH_2O]; *m/z* (CI) 224 $[M+NH_4]^+$, 138, 121 (Found: $[M+NH_4]^+$, 224.1657. $C_{13}H_{18}O_2$ requires $[M+NH_4]^+$, 224.1651).

3-(*Tert*-butyldimethylsilyloxy)-2-methylprop-1-ene (270)[28,29]

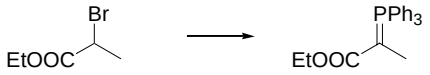


270

To a solution of methallyl alcohol (16.0 mL, 190 mmol, 1 equiv) and imidazole (20.8 g, 306 mmol, 1.6 equiv) in DMF (40 mL) at rt and under nitrogen was added dropwise a solution of *tert*-butylchlorodimethylsilane (40.6 g, 269 mmol, 1.4 equiv) in DMF. After

17 h of stirring at rt, the reaction was quenched with aqueous K_2CO_3 (10%, 60 mL). The resulting solution was poured into H_2O (400 mL) and extracted with Et_2O (3 × 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol) gave 3-(*tert*-butyldimethylsilyloxy)-2-methylprop-1-ene **270** (25.1 g, 71%) as a colourless liquid; R_f 0.19 (10% AcOEt–petrol); δ_H (400 MHz) [4.98 (1H, bs) and 4.81-4.80 (1H, m), CH_2-1], 4.03 (2H, s, CH_2O), 1.70 (3H, s, CH_3-2), 0.92 (9H, s, 3 × CH_3 *tert*-butyl TBDMS), 0.07 (6H, s, 2 × CH_3 TBDMS); δ_C (100 MHz) 144.6 (C-2), 109.1 (CH_2-1), 66.8 (CH_2O), 25.9 (3 × CH_3 *tert*-butyl TBDMS), 18.9 (CH_3-2), 18.4 (C *tert*-butyl TBDMS), -5.40 (2 × CH_3 TBDMS); *m/z* (CI) 204 $[M+NH_4]^+$, 187 $[M+H]^+$, 132. Data in agreement with those previously reported.

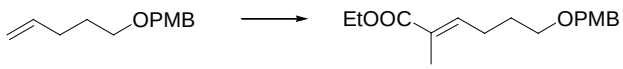
Methylcarboethoxyethylene triphenylphosphorane (273)[30]



273

To a solution of PPh_3 (98.5 g, 376 mmol, 1 equiv) in toluene (100 mL) at rt was added ethyl-2-bromopropionate (68.0 mL, 524 mmol, 1.4 equiv) and tetrabutylammonium iodide (6.89 g, 18.7 mmol, 5 mol%). The mixture was left stirring at rt for 15 h and heated at 40 °C for 24 h. The dense white precipitate formed was collected by filtration, washed with petrol and dried under vacuum to give ethyl-2-(triphenylphosphonium bromide)propionate (153 g, 67%) as a white solid. The phosphonium salt was then dissolved in water (1.6 L) with heating and any excess PPh_3 filtered off. Aqueous NaOH (1 M) was added dropwise with stirring until pH 10. The yellow precipitate was collected by filtration, dissolved in CH_2Cl_2 (500 mL), washed with H_2O (500 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization (20% AcOEt–petrol) gave methylcarboethoxyethylene triphenylphosphorane **273** (74.5 g, 60%) as pale yellow crystals; mp 156-158 °C (20% AcOEt–petrol). Data in agreement with those previously reported.

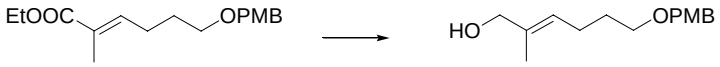
(*E*)-Ethyl 6-(4-methoxybenzyloxy)-2-methylhex-2-enoate (274)



269 **274**

Ozone was bubbled through a solution of a *p*-methoxybenzyl-4-pentenyl Et_2O **269** (14.7 g, 71.3 mmol, 1 equiv) in CH_2Cl_2 (230 mL) at -78 °C for 1 h 15 min, until disappearance of the starting material. After 5 min of bubbling O_2 through the reaction mixture, PPh_3 (23.3 g, 88.8 mmol, 1.3 equiv) was added. After stirring for 3 h at -78 °C and for 1 h at rt the mixture was concentrated under reduced pressure to half of its volume. The solution of the crude aldehyde was added dropwise and under nitrogen to a solution of methylcarboethoxyethylene triphenylphosphorane **273** (50.2 g, 139 mmol, 1.9 equiv) in CH_2Cl_2 (140 mL) at rt. After 18 h of stirring the solution was concentrated under reduced pressure to a tenth of its volume and Et_2O (300 mL) was added. Triphenylphosphine oxide was filtered off and the filtrate concentrated under reduced pressure. Column chromatography (5%→8% Et_2O–petrol) gave *(*E*)-ethyl 6-(4-methoxybenzyloxy)-2-methylhex-2-enoate* **274** (18.7 g, 90%) as a colourless liquid; R_f 0.49 (10% AcOEt–petrol); ν_{max} (film) 2922, 2852, 1708, 1612, 1513, 1462, 1366, 1248, 1093, 1035, 820, 744 cm^{-1}; δ_H (400 MHz) 7.26 (2H, d, *J* 8.5 Hz, *ortho* PMB), 6.88 (2H, d, *J* 8.5 Hz, *meta* PMB), 6.75 (1H, tq, *J* 7.5, 1.5 Hz, CH-3), 4.43 (2H, s, CH_2 PMB), 4.18 (2H, q, *J* 7.0 Hz, CH_3CH_2O), 3.80 (3H, s, OCH_3), 3.46 (2H, t, *J* 6.5 Hz, CH_2-6), 2.27 (2H, q, *J* 7.5 Hz, CH_2-4), 1.83 (3H, s, CH_3-2), 1.78-1.71 (2H, m, CH_2-5), 1.29 (3H, t, *J* 7.0 Hz, CH_3CH_2O); δ_C (100 MHz) 168.2 (C=O), 159.2 (*para* PMB), 141.5 (CH-3), [130.5 and 128.3 (C-2 and *ipso* PMB)], 129.2 (*ortho* PMB), 113.8 (*meta* PMB), 72.6 (CH_2 PMB), 69.2 (CH_2-6), 60.4 (CH_3CH_2O), 55.3 (OCH_3), [28.7 and 25.4 (CH_2-4 and CH_2-5)], [14.3 and 12.3 (CH_3-2 and CH_3CH_2O)]; *m/z* (CI) 310 $[M+NH_4]^+$, 190, 138, 121, 52 (Found: $[M+NH_4]^+$, 310.2024. $C_{17}H_{24}O_4$ requires $[M+NH_4]^+$, 310.2018) (Found: C, 69.89; H, 8.31. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27%).

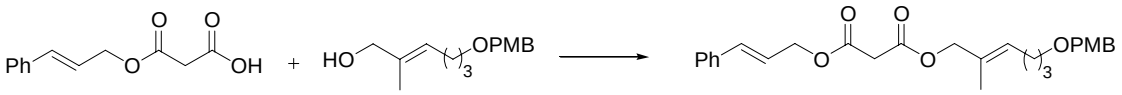
(*E*)-6-(4-Methoxybenzyloxy)-2-methylhex-2-en-1-ol (272)



274 **272**

To a solution of (*E*)-ethyl 6-(4-methoxybenzyloxy)-2-methylhex-2-enoate **274** (18.70 g, 63.96 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at –78 °C and under nitrogen was added dropwise DIBAL-H (1.0 M solution in toluene, 190 mL, 190 mmol, 3 equiv). The mixture was allowed to warm to rt over 20 h, then cooled to –78 °C and quenched with aqueous La Rochelle salt (10%, 40 mL). The mixture was left warming to rt over 3 h and then partitioned between CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and then purified by column chromatography (20%→30% AcOEt–petrol) to give *(*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-en-1-ol* **272** (15.7 g, 98%) as a colourless liquid; R_f 0.45 (30% AcOEt–petrol); ν_{max} (film) 3393, 2937, 2864, 1612, 1509, 1462, 1358, 1301, 1244, 1171, 1097, 1031, 813, 751 cm^{-1}; δ_H (400 MHz) 7.26 (2H, d, *J* 8.5 Hz, *ortho* PMB), 6.88 (2H, d, *J* 8.5 Hz, *meta* PMB), 5.40 (1H, tq, *J* 7.5, 1.5 Hz, CH-3), 4.43 (2H, s, CH_2 PMB), 3.99 (2H, s, CH_2-1), 3.81 (3H, s, OCH_3), 3.44 (2H, t, *J* 6.5 Hz, CH_2-6), 2.12 (2H, q, *J* 7.5 Hz, CH_2-4), 1.66 (3H, s, CH_3-2), 1.70-1.63 (2H, m, CH_2-5); δ_C (100 MHz) 159.0 (*para* PMB), 135.2 (C-2), 130.6 (*ipso* PMB), 129.2 (*ortho* PMB), 125.4 (CH-3), 113.7 (*meta* PMB), [72.5, 69.4 and 68.8 (CH_2 PMB, CH_2-6 and CH_2-1)], 55.2 (OCH_3), [29.4 and 24.2 (CH_2-5 and CH_2-4)], 13.6 (CH_3-2); *m/z* (CI) 268 $[M+NH_4]^+$, 233, 138, 121 (Found: $[M+NH_4]^+$, 268.1918. $C_{15}H_{22}O_3$ requires $[M+NH_4]^+$, 268.1913) (Found: C, 71.75; H, 8.86. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

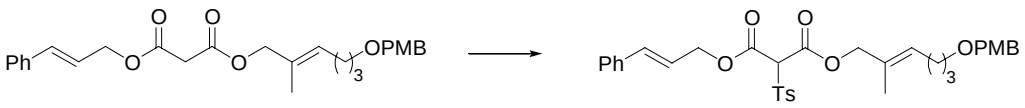
Cinnamyl (*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-enyl malonate (299)



191d **272** **299**

According to general procedure **3.2.3**, cinnamyl malonate **191d** (11.7 g, 53.1 mmol, 1 equiv) was reacted with (*E*)-6-(4-methoxybenzyloxy)-2-methyl-2-en-1-ol **272** (13.3 g, 53.1 mmol, 1 equiv), DMAP (653 mg, 5.34 mmol, 0.1 equiv) and DCC (12.4 g, 60.1 mmol, 1.1 equiv) in CH_2Cl_2 (270 mL). Chromatography (10%→20% AcOEt–petrol) gave *cinnamyl (E)-6-(4-methoxybenzyloxy)-2-methylhex-2-enyl malonate* **299** (22.5 g, 94%) as a colourless oil; R_f 0.22 (10% AcOEt–petrol); ν_{max} (film) 2938, 2859, 1749, 1732, 1613, 1514, 1450, 1410, 1373, 1328, 1303, 1249, 1173, 1149, 1099, 1033, 970, 822, 748, 694 cm^{-1}; δ_H (400 MHz) 7.39-7.24 (7H, m, Ph and *ortho* PMB), 6.89-6.87 (2H, m, *meta* PMB), 6.67 (1H, d, *J* 16.0 Hz, =CHPh), 6.27 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), 5.47 (1H, tq, *J* 7.0, 1.0 Hz, CH_3C=C*H*), 4.80 (2H, dd, *J* 6.5, 1.0 Hz, =CHCH_2O), 4.56 (2H, s, =CCH_3CH_2O), 4.42 (2H, s, CH_2 PMB), 3.80 (3H, s, OCH_3), 3.44 (2H, s, OOCCH_2COO), 3.42 (2H, t, *J* 6.5 Hz, CH_2OPMB), 2.11 (2H, q, *J* 7.0 Hz, CH_3C=CHCH_2), 1.64 (3H, s, =CCH_3), 1.69-1.62 (2H, m, CH_2CH_2OPMB); δ_C (100 MHz) 166.3 (2 × C=O), 159.1 (*para* PMB), [136.0, 130.6 and 130.0 (=*C*CH_3, *ipso* Ph and *ipso* PMB)], [134.8, 129.9, 128.2 and 122.4 (*para* Ph and 3 × =CH)], [129.2, 128.6 and 126.6 (*ortho* Ph, *meta* Ph and *ortho* PMB)], 113.7 (*meta* PMB), [72.5, 71.3, 69.3 and 66.0 (4 × CH_2O)], 55.3 (OCH_3), 41.6 (OOC*C*H_2COO), [29.2 and 24.3 (CH_3C=CH*C*H_2, *C*H_2CH_2OPMB)], 13.8 (=C*C*H_3); *m/z* (CI) 470 $[M+NH_4]^+$, 355, 300, 138, 121, 52 (Found: $[M+NH_4]^+$, 470.2547. $C_{27}H_{32}O_6$ requires $[M+NH_4]^+$, 470.2543) (Found: C, 71.72; H, 7.17. $C_{27}H_{32}O_6$ requires C, 71.66; H, 7.13%).

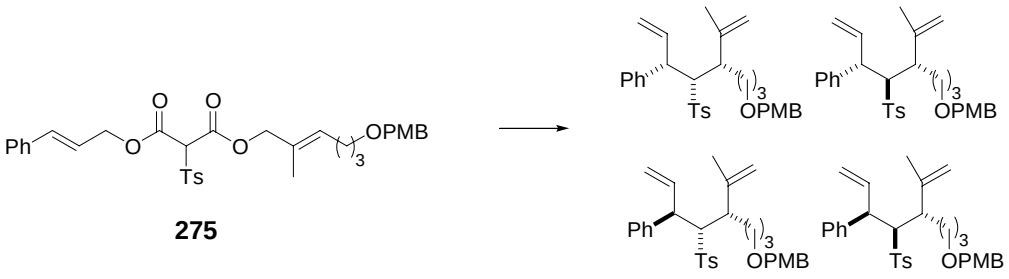
(±)-1-Cinnamyl 3-(*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-enyl 2-(*p*-toluenesulfonyl)malonate (275)



299 **275**

According to general procedure **3.2.4**, cinnamyl (*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-enyl malonate **299** (21.83 g, 48.24 mmol, 2 equiv) was reacted with *t*-BuOK (5.447 g, 48.54 mmol, 2 equiv) and TsF (4.227 g, 24.27 mmol, 1 equiv) in DMSO (24 mL). Chromatography (10%→30% AcOEt–petrol) gave *(±)-1-cinnamyl 3-(*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-enyl 2-(*p*-toluenesulfonyl)malonate* **275** (10.88 g, 74%) as a colourless gum and the excess starting malonate **299** (12.93 g, 94% unreacted); R_f 0.22 (20% AcOEt–petrol); ν_{max} (film) 3029, 2937, 2860, 1743, 1613, 1538, 1514, 1494, 1450, 1368, 1336, 1248, 1180, 1151, 1083, 1033, 969, 923, 817, 737, 706, 694, 673, 640 cm^{-1}; δ_H (400 MHz) 7.87 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.40-7.26 (9H, m, Ph, CH-3 Ts, CH-5 Ts and *ortho* PMB), 6.91-6.89 (2H, m, *meta* PMB), 6.65 (1H, d, *J* 16.0 Hz, =CHPh), 6.18 (1H, dt, *J* 16.0, 6.5 Hz, C*H*=CHPh), 5.50-5.47 (1H, m, C*H*=CCH_3), 5.04 (1H, s, CHTs), 4.83 (2H, dt, *J* 6.5, 1.0 Hz, =CHCH_2O), 4.58 (2H, s, =CCH_3CH_2O), 4.44 (2H, s, CH_2 PMB), 3.82 (3H, s, OCH_3), 3.44 (2H, t, *J* 6.5 Hz, CH_2OPMB), 2.40 (3H, s, CH_3 Ts), 2.12 (2H, q, *J* 7.0 Hz, CH_3C=CHCH_2), 1.66 (2H, m, C$H_2$$CH_2$OPMB), 1.61 (3H, s, =$CCH_3$); δ_C (100 MHz) [160.8 and 159.1 (2 × C=O and *para* PMB)], 145.9 (C-4 Ts), [135.8, 134.2, 130.6 and 129.3 (=*C*CH_3, *ipso* Ph, C-1 Ts and *ipso* PMB)], [135.7, 130.9, 128.4 and 121.3 (*para* Ph, 3 × =CH)], [130.6, 129.5, 129.2, 128.7 and 126.7 (*ortho* Ph, *meta* Ph, 4 × CH Ts and *ortho* PMB)], 113.7 (*meta* PMB), 74.6 (CHTs), [72.8, 72.6, 69.2 and 67.4 (4 × CH_2O)], 55.3 (OCH_3), [29.2 and 24.4 (CH_3C=C*H*CH_2, *C*$H_2$$CH_2$OPMB)], 21.7 ($CH_3$ Ts), 13.8 (=*C*CH_3); *m/z* (ESI) 629 $[M+Na]^+$, 624, 338 (Found: $[M+Na]^+$, 629.2173. $C_{34}H_{38}O_8S$ requires $[M+Na]^+$, 629.2185) (Found: C, 67.41; H, 6.27. $C_{34}H_{38}O_8S$ requires C, 67.31; H, 6.31%.

1-Methoxy-4-{[(4*S,5*S**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-enyloxy]methyl}benzene, 1-methoxy-4-{[(4*S**,5*R**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-enyloxy]methyl}benzene, 1-methoxy-4-{[(4*R**,5*S**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-enyloxy]methyl}benzene and 1-methoxy-4-{[(4*R**,5*R**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-enyloxy]methyl}benzene (276)**

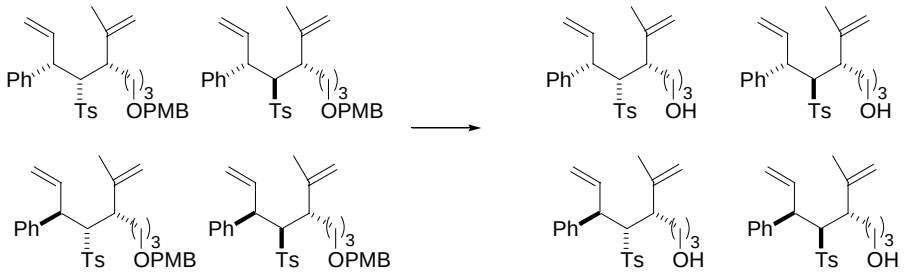


275 **276**

To a mixture of (±)-1-cinnamyl 3-(*E*)-6-(4-methoxybenzyloxy)-2-methylhex-2-enyl 2-(*p*-toluenesulfonyl)malonate **275** (8.881 g, 14.64 mmol, 1 equiv) and KOAc (158 mg, 1.61 mmol, 0.1 equiv) under nitrogen was added BSA (11.0 mL, 43.6 mmol, 3 equiv). The mixture was exposed to 3 cycles of microwave irradiation of 2 min each at 200 °C. Chromatography (10%→15% AcOEt–petrol) gave *1-methoxy-4-{[6-phenyl-4-(prop-1-en-2-yl)-5-(*p-*toluenesulfonyl)oct-7-enyloxy]methyl}benzene* **276** in a mixture of 4 diastereoisomers (6.24 g, 82%) as a colourless gum; R_f 0.46 (20% AcOEt–petrol); ν_{max} (film) 3062, 3028, 2935, 2858, 1639, 1613, 1598, 1513, 1495, 1453, 1315, 1302, 1248, 1180, 1144, 1086, 1035, 904, 817, 738, 702, 664 cm^{-1}; δ_H (400 MHz) [7.61 (2H, d, *J* 8.5 Hz), 7.51 (2H, d, *J* 8.0 Hz), 7.47 (2H, d, *J* 8.0 Hz) and 7.39 (2H, d, *J* 8.5 Hz), CH-2 Ts and CH-6 Ts of all diastereoisomers], 7.30-6.87 (44H, m, Ph, CH-3 Ts, CH-5 Ts, *ortho* PMB and *meta* PMB of all diastereoisomers), [6.62 (1H, dt, *J* 17.0, 9.5 Hz), 6.31-6.17 (2H, m) and 6.04 (1H, dt, *J* 17.0, 10.0 Hz), =CH of all diastereosiomers], 5.23-4.67 (16H, m, 2 × $=CH_2$ of all diastereoisomers), [4.44 (2H, s), 4.43 (2H, s), 4.42 (2H, s) and 4.40 (2H, s), CH_2 PMB of all diastereoisomers], [4.21 (1H, dd, *J* 9.0, 7.5 Hz), 4.04-3.81 (5H, m), 4.62 (1H, dd, *J* 5.0, 3.5 Hz) and 3.60-3.58 (1H, m), CHTs and CHPh of all diastereoisomers], 3.81 (12H, s, OCH_3 of all diastereoisomers), 3.48-3.34 (8H, m, CH_2OPMB of all diastereoisomers), [3.06-3.03 (1H, m), 2.82 (1H, dt, *J* 12.0, 3.0 Hz),

2.72-2.66 (1H, m) and 2.56-2.53 (1H, m), C*H*$(CH_2)_3$ of all diastereoisomers], [2.40 (6H, s), 2.39 (3H, s) and 2.36 (3H, s), CH_3 Ts of all diastereoisomers)], 2.20-1.34 (16H, m, C*H*$_2$$CH_2$OPMB and CH_2C*H*$_2$OPMB of all diastereoisomers), [1.71 (3H, s), 1.65 (3H, s), 1.52 (3H, s) and 1.37 (3H, s), =CCH_3 of all diastereoisomers]; δ_C (100 MHz) 158.8 (*para* PMB of all diastereoisomers), [143.9, 143.8, 143.5, 143.4, 143.2, 143.1, 142.4, 142.1, 142.0, 141.9, 141.5, 141.0, 139.1, 138.2, 138.1, 137.5 and 137.1 (2 × C Ts, *ipso* Ph, *ipso* PMB and =*C*CH_3 of all diastereoisomers)], [137.5, 135.9 and 135.1 (=CH of all diastereoisomers)], [130.5, 130.4, 129.3, 129.2, 129.0, 128.9, 128.9, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.2, 126.4, 126.1, 126.1 and 125.9 (4 × CH Ts, *ortho* PMB, *ortho* Ph, *meta* Ph and *para* Ph of all diastereoisomers)], [119.2, 118.1, 117.4, 117.2, 115.7, 115.7, 114.4 and 113.5 (2 × =CH_2 of all diastereoisomers)], 113.5 (*meta* PMB of all diastereoisomers), [72.3 and 72.2 (CH_2 PMB of all diastereoisomers)], [72.0, 71.7, 70.7 and 69.9 (CHTs of all diastereoisomers)], [69.7, 69.7 and 69.5 (CH_2OPMB of all diastereoisomers)], 54.9 (OCH_3 of all diastereoisomers), [49.3, 48.8, 48.5, 47.1, 46.8, 45.4, 44.8 and 44.6 (CHPh and *C*H$(CH_2)_3$ of all diastereoisomers)], [28.2, 28.1, 27.7 and 27.7 (*C*$H_2$$CH_2$OPMB of all diastereoisomers)], [25.6, 25.2, 24.5 and 23.5 (*C*$H_2$$(CH_2)_2$OPMB of all diastereoisomers)], [21.6, 21.2, 20.9, 20.2 and 19.3 (CH_3 Ts and =C*C*H_3 of all diastereoisomers)]; *m/z* (CI) 536 $[M+NH_4]^+$, 519 $[M+H]^+$, 121 (Found: $[M+H]^+$, 519.2570. $C_{32}H_{38}O_4S$ requires $[M+H]^+$, 519.2569).

(4*S,5*S**,6*S**)-6-Phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-en-1-ol, (4*S**,5*R**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-en-1-ol, (4*R**,5*S**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-en-1-ol and (4*R**,5*R**,6*S**)-6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-en-1-ol (277)**

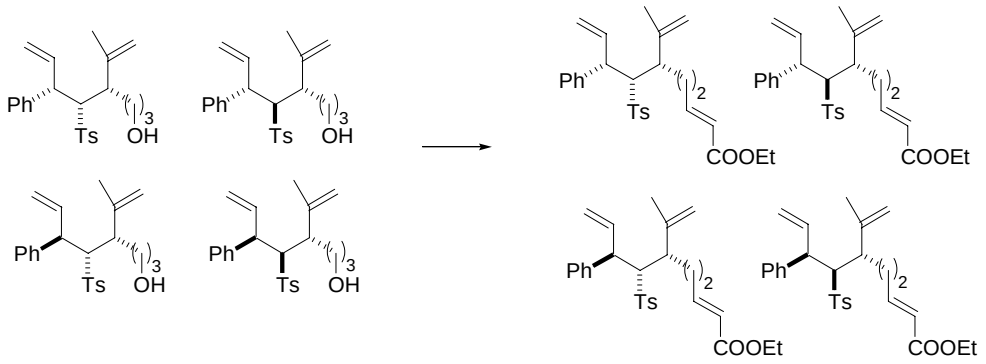


276 **277**

To a solution of a diastereoisomeric mixture of 1-methoxy-4-{[6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-enyloxy]methyl}benzene **276** (4.958 g, 9.559 mmol, 1 equiv) in CH_3CN:H_2O (10:1, 90 mL) at rt and under nitrogen was added ceric(IV)ammonium nitrate (10.53 g, 19.20 mmol, 2 equiv). After 2 h 30 min of stirring at rt, the mixture was partitioned between Et_2O and H_2O and the organic layer washed with H_2O (2 × 100 mL) and aqueous $NaHCO_3$ (saturated solution, 2 × 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (20%→30% AcOEt–petrol) gave *6-phenyl-4-(prop-1-en-2-yl)-5-(*p-*toluenesulfonyl)oct-7-en-1-ol* **277** in a mixture of 4 diastereoisomers (3.166 g, 83%) as a colourless gum; R_f 0.13 (20% AcOEt–petrol); ν_{max} (film) 3512, 3063, 3028, 2931, 1598, 1494, 1452, 1314, 1301, 1288, 1142, 1084, 903, 815, 738, 701, 663 cm^{-1}; δ_H (400 MHz) [7.61 (2H, d, *J* 8.0 Hz), 7.50 (2H, d, *J* 8.5 Hz), 7.46 (2H, d, *J* 8.5 Hz) and 7.33 (2H, d, *J* 8.0 Hz), CH-2 Ts and CH-6 Ts of all diastereoisomers], 7.26-6.93 (28H, m, Ph, CH-3 Ts and CH-5 Ts of all diastereoisomers), [6.63 (1H, dt, *J* 17.0, 10.0 Hz), 6.29-6.16 (2H, m) and 6.01 (1H, dt, *J* 17.0, 9.5 Hz), =CH of all diastereosiomers], 5.28-4.70 (16H, m, 2 × $=CH_2$ of all diastereoisomers), [4.21-4.17 (1H, m) and 4.04-3.55 (15H, m), CHTs, CHPh and CH_2O of all diastereoisomers], [3.14-3.11 (1H, m), 2.84 (1H, dt, *J* 11.5, 3.0 Hz), 2.75-2.70 (1H, m) and 2.61-2.58 (1H, m), C*H*$(CH_2)_3O$ of all diastereoisomers], [2.40 (3H, s), 2.38 (3H, s), 2.35 (3H, s) and 2.34 (3H, s), CH_3 Ts of all diastereoisomers)], 2.20-1.26 (16H, m, C*H*$_2CH_2O$ and CH_2CH_2O of all diastereoisomers), 1.92 (OH of all diastereoisomers),

[1.76 (3H, s), 1.73 (3H, s), 1.55 (3H, s) and 1.39 (3H, s), $=CCH_3$ of all diastereoisomers]; δ_C (100 MHz) [144.2, 143.9, 143.8, 143.7, 143.4, 143.3, 142.4, 142.2, 142.0, 141.9, 141.5, 141.1, 139.1, 138.2, 138.1 and 137.2 (2 × C Ts, *ipso* Ph and $=\mathit{C}CH_3$ of all diastereoisomers)], [138.0, 137.5, 136.0 and 134.9 (=CH of all diastereoisomers)], [129.5, 129.4, 129.2, 128.3, 128.2, 128.2, 128.0, 127.9, 127.9, 127.8, 127.6, 127.3, 126.6, 126.4, 126.3 and 126.1 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph of all diastereoisomers)], [119.7, 118.4, 117.9, 117.0, 116.1, 115.6, 114.7 and 113.5 (2 × $=CH_2$ of all diastereoisomers)], [72.1, 71.8, 70.9 and 69.8 (CHTs of all diastereoisomers)], [62.5, 62.2 and 62.1 (CH_2O of all diastereoisomers)], [49.5, 49.1, 48.8, 47.3, 46.6, 45.1, 44.9 and 43.9 (CHPh and $\mathit{C}H(CH_2)_3O$ of all diastereoisomers)], [31.4, 30.9, 30.5 and 30.4 ($\mathit{C}H_2CH_2O$ of all diastereoisomers)], [25.1, 24.2, 24.1 and 22.8 ($\mathit{C}H_2(CH_2)_2OH$ of all diastereoisomers)], [21.9, 21.6, 21.5, 21.5, 21.4, 20.4 and 19.4 (2 × CH_3 of all diastereoisomers)]; *m/z* (CI) 416 $[M+NH_4]^+$, 399 $[M+H]^+$, 174 (Found: $[M+H]^+$, 399.1996. $C_{24}H_{30}O_3S$ requires $[M+H]^+$, 399.1994).

(6*S,7*S**,8*S**,*E*)-Ethyl 8-phenyl-6-(prop-1-en-2-yl)-7-(*p*-toluenesulfonyl)deca-2,9-dienoate, (6*S**,7*R**,8*S**,*E*)-ethyl 8-phenyl-6-(prop-1-en-2-yl)-7-(*p*-toluenesulfonyl)deca-2,9-dienoate, (6*S**,7*S**,8*R**,*E*)-ethyl 8-phenyl-6-(prop-1-en-2-yl)-7-(*p*-toluenesulfonyl)deca-2,9-dienoate and (6*S**,7*R**,8*R**,*E*)-Ethyl 8-phenyl-6-(prop-1-en-2-yl)-7-(*p*-toluenesulfonyl)deca-2,9-dienoate (265a)**



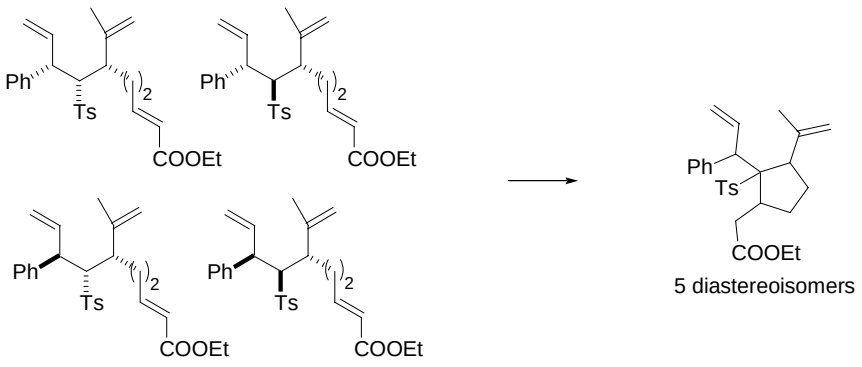
277 **265a**

To a solution of oxalyl chloride (160 μL, 1.83 mmol, 1.2 equiv) in CH_2Cl_2 (3 mL) at -78 °C and under nitrogen was added dropwise DMSO (270 μL, 3.81 mmol, 2.5 equiv) and

the mixture was left stirring at -78 °C for 20 min. To this was added dropwise a solution of a disastereoisomeric mixture of 6-phenyl-4-(prop-1-en-2-yl)-5-(*p*-toluenesulfonyl)oct-7-en-1-ol **277** (603 mg, 1.51 mmol, 1 equiv) in CH_2Cl_2 (4.2 mL) at -78 °C and the mixture was left stirring at -78 °C for 2.5 h. Et_3N (1.1 mL) was then added and the mixture was allowed to reach rt over 16 h before dilution with CH_2Cl_2 and washing with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and used without further purification. To a solution of a distereoisomeric mixture of the crude aldehyde in CH_2Cl_2 (9 mL) was added a solution of carboethoxyethylene triphenylphosphorane (796 mg, 2.29 mmol, 1.5 equiv) in CH_2Cl_2 (6 mL) at rt and under nitrogen. The resulting solution was left stirring at rt for 24 h and then concentrated under reduced pressure. Chromatography (10% AcOEt–petrol) gave *(*E*)-ethyl 8-phenyl-6-(prop-1-en-2-yl)-7-(p-toluenesulfonyl)deca-2,9-dienoate* **265a** in a mixture of 4 diastereoisomers (621 mg, 88%) as a colourless gum; R_f 0.68 (20% AcOEt–petrol); ν_{max} (film) 2925, 2854, 1718, 1654, 1598, 1494, 1452, 1368, 1316, 1302, 1286, 1144, 1085, 1042, 904, 816, 702 cm^{-1}; δ_H (400 MHz) [7.64 (2H, d, *J* 7.5 Hz), 7.51 (2H, d, *J* 7.5 Hz), 7.50 (2H, d, *J* 7.5 Hz) and 7.40 (2H, d, *J* 7.5 Hz), CH-2 Ts and CH-6 Ts of all diastereoisomers], 7.28-6.85 (32H, m, Ph, CH-3 Ts, CH-5 Ts and CH-3 of all diastereoisomers), [6.69 (1H, dt, *J* 17.0, 9.5 Hz), 6.23 (1H, dt, *J* 17.0, 10.0 Hz), 6.17 (1H, dt, *J* 17.0, 10.0 Hz), and 6.05 (1H, dt, *J* 17.0, 9.5 Hz), C*H*=CH_2 of all diastereosiomers], 5.84-5.71 (4H, m, CH-2 of all diastereoisomers), 5.30-4.68 (16H, m, 2 × =CH_2 of all diastereoisomers), 4.27-4.17 (8H, m, OCH_2 of all diastereoisomers), 4.04-3.94 (4H, m, CHTs of all diastereoisomers), [3.88 (1H, dd, *J* 7.0, 4.5 Hz), 3.83 (1H, dd, *J* 7.0, 4.0 Hz), 3.65 (1H, dd, *J* 5.5, 3.5 Hz) and 3.58-3.56 (1H, m), CHPh of all diastereoisomers], [3.06-3.03 (1H, m), 2.85-2.81 (1H, m), 2.72-2.67 (1H, m) and 2.53-2.50 (1H, bd, *J* 12.0 Hz), CH-6 of all diastereoisomers], [2.41 (3H, s), 2.40 (3H, s), 2.39 (3H, s) and 2.37 (3H, s), CH_3 Ts of all diastereoisomers)], 2.33-1.88 (16H, m, CH_2-4 and CH_2-5 of all diastereoisomers), [1.73 (3H, s), 1.67 (3H, s), 1.57 (3H, s) and 1.37 (3H, s), =CCH_3 of all diastereoisomers], 1.35-1.29 (12H, m, OCH_2CH_3); δ_C (100 MHz) [166.5 and 166.4, C=O of all diastereoisomers], [148.5, 148.4 and 148. 3 (CH-3 of all diastereoisomers)], [144.3, 143.9, 143.7, 143.5, 143.4, 142.1, 141.9, 141.8, 141.6, 141.4, 140.9, 139.0, 138.2 and 136.9 (2 × C Ts, *ipso* Ph and =C of all diastereoisomers)], [137.9, 137.4, 135.9 and 135.2 (*C*H=CH_2 of all

diastereoisomers)], [129.5, 129.4, 129.3, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 127.8, 127.4, 126.6, 126.5, 126.4 and 126.2 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph of all diastereoisomers)], [121.9, 121.8, 121.6 and 121.5 (CH-2 of all diastereoisomers)], [119.5, 118.5, 117.9, 117.2, 116.2, 115.8, 115.0 and 113.5 (2 × $=CH_2$ of all diastereoisomers)], [71.7, 71.5, 70.6 and 69.7 (CHTs of all diastereoisomers)], [60.1 and 60.0 (OCH_2 of all diastereoisomers)], [49.6, 49.0, 48.9, 47.3, 46.5, 44.9, 44.5 and 44.3 (CHPh and CH-6 of all diastereoisomers)], [30.6, 30.5, 30.3 and 30.0 (CH_2-4 of all diastereoisomers)], [27.1, 26.7, 26.1 and 25.1 (CH_2-5 of all diastereoisomers)], [21.8, 21.5, 21.5, 21.4, 20.4 and 19.5 (CH_3 Ts and $=CCH_3$ of all diastereoisomers)], 14.2 (OCH_2CH_3 of all diastereoisomers); *m/z* (CI) 484 $[M+NH_4]^+$, 467 $[M+H]^+$, 330, 313, 174 (Found: $[M+H]^+$, 467.2259. $C_{28}H_{34}O_4S$ requires $[M+H]^+$, 467.2256).

Mixture of 5 diastereoisomers of ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p*-toluenesulfonyl)cyclopentyl] acetate (266a)



265a **266a**

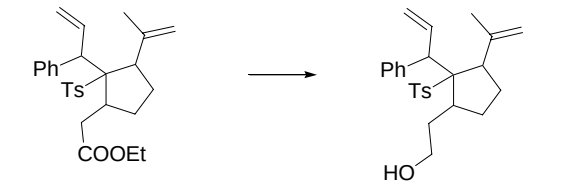
To a colourless solution of a diastereoisomeric mixture of (*E*)-ethyl 8-phenyl-6-(prop-1-en-2-yl)-7-(*p*-toluenesulfonyl)deca-2,9-dienoate **265a** (169 mg, 0.363 mmol, 1 equiv) in THF (73 mL) at rt and under nitrogen was added *t*-BuOK (53 mg, 0.474 mmol, 1.3 equiv). The orange mixture was left stirring at rt for 20 h. Concentration under reduced pressure and chromatography (2%→10% AcOEt–petrol) gave *ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p*-toluenesulfonyl)cyclopentyl] acetate* **266a** in a mixture of 5 diastereoisomers (one major, 42 mg, 25%; 4 minor, 24 mg, 14%) as a colourless gum and the unreacted starting ester **265a** (27 mg, 16%).

*Major diastereoisomer of ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p-*toluenesulfonyl)cyclopentyl] acetate* **266a**; R_f 0.35 (10% AcOEt–petrol); δ_H (400 MHz) 7.74 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.58 (2H, d, *J* 8.0, CH-3 Ts and CH-5 Ts), 7.28-7.25 (5H, m, Ph), 6.21-6.12 (1H, m, =CH), 5.01-4.71 (4H, m, 2 × $=CH_2$), 4.02-3.97 (2H, m, OCH_2), 3.94 (1H, d, *J* 6.5 Hz, CHPh), 3.49 (1H, dd, *J* 8.5, 3.5 Hz, $=CCH_3CH$), 3.17-3.03 (1H, m, $CHCH_2CO$), 2.68 (1H, dd, *J* 17.0, 11.0 Hz, $CHHCO$), 2.45 (3H, s, CH_3 Ts), 2.29 (1H, dd, *J* 17.0, 1.5 Hz, $CHHCO$), [2.24-2.16 (1H, m), 1.77-1.67 (2H, m) and 1.34-1.25 (1H, m), 2 × CH_2 cyclopentyl], 1.84 (3H, s, $=CCH_3$), 1. 18 (3H, t, *J* 7.0 Hz, OCH_2CH_3); δ_C (100 MHz) 172.9 (C=O), [145.3, 144.3, 138.4 and 137.6 (2 × C Ts, *ipso* Ph and =C)], 138.0 (=CH), [131.9, 130.8, 129.0 and 127.9 (4 × CH Ts, *ortho* Ph and *meta* Ph)], 127.1 (*para* Ph), [117.2 and 116.9 (2 × $=CH_2$)], 84.8 (CTs), 60.0 (OCH_2), [55.0 and 53.7 (CHPh and $=CCH_3CH$)], 45.4 ($CHCH_2CO$), [35.7, 31.6 and 30.4 (CH_2CO and 2 × CH_2 cyclopentyl)], [22.0 and 21.5 (CH_3 Ts and $=CCH_3$)], 14.1 (OCH_2CH_3).

*Mixture of 5 diastereoisomers of ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p-*toluenesulfonyl)cyclopentyl] acetate* **266a**; R_f 0.35-0.45 (10% AcOEt–petrol); ν_{max} (film) 2925, 1732, 1595, 1454, 1288, 1185, 1135, 1077, 1032, 917, 817 cm^{-1}; δ_H (400 MHz) [7.96 (2 H, d, *J* 8.5 Hz), 7.91 (2H, d, *J* 8.5 Hz), 7.88 (2H, d, *J* 8.5 Hz), 7.79 (2H, d, *J* 8.5 Hz) and 7.74 (2H, d, *J* 8.5 Hz), CH-2 Ts and CH-6 Ts of all diastereoisomers], 7.71-7.08 (35H, m, CH-3 Ts, CH-5 Ts and Ph of all diastereoisomers), [7.04-6.95 (1H, m), 6.87-6.78 (1H, m), 6.60-6.44 (2H, m) and 6.21-6.13 (1H, m), =CH of all diastereoisomers], 5.32-4.45 (20H, m, 2 × $=CH_2$ of all diastereoisomers), 4.25-3.93 (15H, m, OCH_2 and CHPh of all diastereoisomers), 3.71-2.95 (10H, m, $=CCH_3CH$ and $CHCH_2CO$ of all diastereoisomers), 2.86-1.17 (75H, m, CH_2CO, 2 × CH_2 cyclopentyl and 3 × CH_3 Ts of all diastereoisomers); δ_C (100 MHz) [173.0, 172.9, 172.8, 172.7 and 172.2 (C=O of all diastereoisomers)], [145.2, 144.6, 144.3, 144.2, 144.1, 144.1, 143.7, 143.5, 142.7, 140.8, 140.7, 140.6, 140.3, 138.3, 137.6, 136.8, 136.4, 136.3 and 133.8 (2 × C Ts, *ipso* Ph and =C of all diastereoisomers)], [139.8, 138.9, 138.8, 138.4 and 138.0 (=CH of all diastereoisomers)], [132.0, 131.9, 131.6, 131.6, 131.1, 130.9, 130.9, 130.8, 130.7, 130.6, 130.5, 130.4, 129.3, 129.0, 128.4, 128.3, 128.1, 127.8, 127.7, 127.4, 127.3, 127.1 and 127.0 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph of all

diastereoisomers)], [119.0, 118.2, 118.1, 117.8, 117.6, 117.3, 117.2, 117.0, 116.9, 116.7, 116.6 and 116.5 (2 × =CH_2 of all diastereoisomers)], [85.3, 84.8, 83.2, 81.5 and 80.2 (CTs of all diastereoisomers)], [60.5, 60.4, 60.3, 60.3 and 59.9 (OCH_2 of all diastereoisomers)], [54.9, 53.8, 53.7, 53.5, 52.9, 52.6, 51.9, 51.5, 51.0 and 48.9 (CHPh and =CCH_3*C*H)], [45.3, 43.9, 43.6, 43.6 and 43.0 (*C*HCH_2CO)], [37.9, 37.2, 36.6, 36.3, 35.7, 35.6, 31.6, 31.5, 30.5, 30.5, 30.4, 30.2, 27.3 and 26.9 (*C*H_2CO and 2 × CH_2 cyclopentyl of all diastereoisomers)], [25.8, 25.7, 23.9, 23.5, 22.7, 22.0, 21.5 and 21.5 (CH_3 Ts and =C*C*H_3 of all diastereoisomers)], [14.3, 14.2 and 14.1 (OCH_2*C*H_3 of all diastereoisomers)]; *m/z* (CI) 484 $[M+NH_4]^+$, 467 $[M+H]^+$, 355, 328, 311, 174, 139, 52 (Found: $[M+H]^+$, 467.2261. $C_{28}H_{34}O_4S$ requires $[M+H]^+$, 467.2256).

One diastereoisomer of 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p*-toluenesulfonyl)cyclopentyl]ethanol (278)

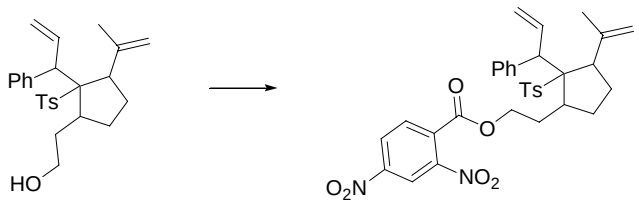


major diastereoisomer **266a** → single diastereoisomer **278**

To a solution of the major diastereoisomer of ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-tosylcyclopentyl] acetate **266a** (25 mg, 0.053 mmol, 1 equiv) in CH_2Cl_2 (300 μL) at -78 °C and under nitrogen was added dropwise DIBAL-H (20% solution in toluene, 135 μL, 0.16 mmol, 3 equiv). The mixture was allowed to warm to rt over 18 h, then cooled to -78 °C and quenched with aqueous La Rochelle salt (10%, 1.0 mL). The mixture was left warming to rt over 3 h and then partitioned between CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give one diastereoisomer of *2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p-*toluenesulfonyl)cyclopentyl]ethanol* **278** (22 mg, 96%) as a white foam; R_f 0.23 (5% AcOEt–petrol); δ_H (400 MHz) 7.71 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), [7.63-7.61 (2H, m) and 7.30-7.23 (5 H, m), CH-3 Ts, CH-5 Ts and Ph], 6.16-6.08 (1H, m, =CH), 4.97-4.70 (4H, m, 2 × =CH_2), 3.94 (1H, d, *J* 6.5 Hz, CHPh), 3.51 (1H, dd, *J* 8.5, 4.0 Hz,

=CCH$_3$C*H*), [3.44-3.38 (1H, m) and 3.23-3.16 (1H, m), CH$_2$O], [2.67 (1H, q, *J* 9.5 Hz), 2.50-2.44 (1H, m), 2.15-2.06 (1H, m), 2.02-1.93 (1H, m) and 1.81-1.52 (3H, m), 2 × CH$_2$ cyclopentyl, C*H*(CH$_2$)$_2$O and C*H*$_2$CH$_2$O], 2.44 (3H, s, CH$_3$ Ts), 1.81 (3H, s, =CCH$_3$); δ_C (100 MHz) [145.6, 144.1, 139.0 and 138.0 (2 × C Ts, *ipso* Ph and =C)], 138.4 (=CH), [132.3, 131.0, 128.9 and 127.8 (4 × CH Ts, *ortho* Ph and *meta* Ph)], 127.3 (*para* Ph), [117.2 and 116.8 (2 × =CH$_2$)], 85.5 (CTs), 62.0 (CH$_2$O), [55.2 and 54.1 (CHPh and =CCH$_3$*C*H)], 46.2 (*C*H(CH$_2$)$_2$O), [34.6, 31.2 and 30.6 (2 × CH$_2$ cyclopentyl and *C*H$_2$CH$_2$O)], [22.1 and 21.6 (2 × CH$_3$)].

One diastereoisomer of 2-[2-(1-henylallyl)-3-(prop-1-en-2-yl)-2-(*p*-toluenesulfonyl)cyclopentyl]ethyl 2,4-dinitrobenzoate (281)

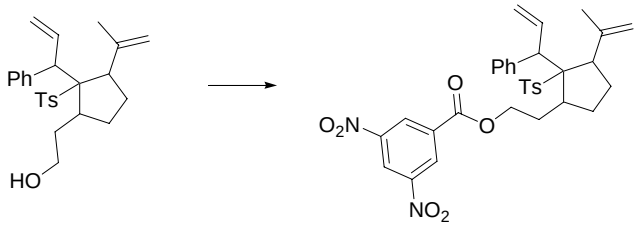


single diastereoisomer **278** single diastereoisomer **281**

To a solution of one diastereoisomer of 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-tosylcyclopentyl]ethanol **278** (41 mg, 0.097 mmol, 1 equiv), Et$_3$N (100 μL, 0.717 mmol, 7 equiv) and DMAP (2 mg, 0.02 mmol, 0.2 equiv) in CH$_2$Cl$_2$ (1.0 mL) at 0 °C and under nitrogen was added a solution of 2,4-dinitrobenzoyl chloride (58 mg, 0.25 mmol, 3 equiv) in CH$_2$Cl$_2$ (1.0 mL). The mixture was allowed to warm to rt over 20 h and then partitioned between CH$_2$Cl$_2$ and aqueous HCl (10%, 20 mL). The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography (10% AcOEt–petrol) gave one diastereoisomer of *2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p-*toluenesulfonyl)cyclopentyl]ethyl 2,4-dinitrobenzoate* **281** (46 mg, 76%) as a white foam; R_f 0.27 (10% AcOEt–petrol); ν_{max} (film) 3074, 2959, 1737, 1603, 1542, 1454, 1348, 1286, 1246, 1133, 1078, 1058, 908, 834, 817, 736, 707, 673, 586 cm^{-1}; δ_H (400 MHz) 8.83 (1H, d, *J* 2.0 Hz, CH-3 dinitrobenzoyl), 8.56 (1H, dd, *J* 8.5, 2.0 Hz, CH-5 dinitrobenzoyl), 7.90 (1H, d, *J* 8.5 Hz, CH-6 dinitrobenzoyl), 7.67 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), [7.54 (2H, d, *J* 7.0 Hz) and 7.28-7.14 (5H, m), CH-3 Ts, CH-5 Ts

and Ph], 6.14-6.05 (1H, m, =CH), 4.95-4.72 (4H, m, 2 × $=CH_2$), 4.09-3.98 (2H, m, CH_2O), 3.94 (1H, d, *J* 7.0 Hz, CHPh), 3.50 (1H, dd, *J* 8.5, 4.0 Hz, $=CCH_3CH$), [2.61-2.43 (2H, m), 2.27-2.07 (2H, m) and 1.92-1.66 (3H, m), 2 × CH_2 cyclopentyl, $CH(CH_2)_2O$ and CH_2CH_2O], 2.45 (3H, s, CH_3 Ts), 1.82 (3H, s, $=CCH_3$); δ_C (100 MHz) 163.6 (C=O), [148.9 and 148.0 (C-2 and C-4 dinitrobenzoyl)], [145.5, 144.3, 138.8, 137.7 and 133.3 (2 × C Ts, *ipso* Ph, *ipso* dinitrobenzoyl and =C)], [131.8, 130.9, 128.9 and 127.5 (4 × CH Ts, *ortho* Ph and *meta* Ph)], [131.2, 127.3, 127.2 and 119.6 (*para* Ph, =CH and CH-3, CH-5, CH-6 dinitrobenzoyl)], [117.4 and 116.8 (2 × $=CH_2$)], 86.8 (CTs), 67.2 (CH_2O), [55.2 and 53.8 (CHPh and $=CCH_3CH$)], 46.7 ($CH(CH_2)_2O$), [31.3, 30.7 and 29.9 (2 × CH_2 cyclopentyl and CH_2CH_2O)], [22.0 and 21.6 (2 × CH_3)].

One diastereoisomer of 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p*-toluenesulfonyl)cyclopentyl]ethyl 3,5-dinitrobenzoate (282)

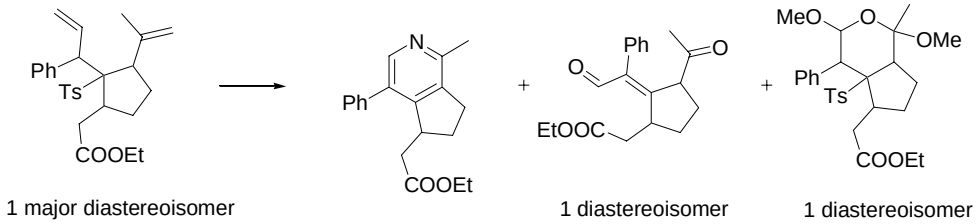


single diastereoisomer **278** → single diastereoisomer **282**

To a solution of one diastereoisomer of ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-tosylcyclopentyl]ethanol **278** (20 mg, 0.047 mmol, 1 equiv) and Et_3N (72% pure, 40 μL, 0.29 mmol, 6 equiv) in CH_2Cl_2 (500 μL) at 0 °C and under nitrogen was added a solution of 3,5-dinitrobenzoyl chloride (21 mg, 0.089 mmol, 2 equiv) in CH_2Cl_2 (500 μL). The mixture was allowed to warm to rt over 62 h and then partitioned between CH_2Cl_2 and aqueous HCl (10%, 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (10% AcOEt–petrol) gave one diastereoisomer of *2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-(*p-*toluenesulfonyl)cyclopentyl]ethyl 3,5-dinitrobenzoate* **282** (17 mg, 57%) as a white foam; R_f 0.27 (10% AcOEt–petrol); ν_{max} (film) 3103, 2955, 1731, 1601, 1539, 1345, 1282, 1242, 1129, 1078, 1054, 907, 833, 816, 730, 708, 674 cm^{-1}; δ_H (400 MHz) 9.24

(1H, t, *J* 2.0 Hz, CH-4 dinitrobenzoyl), 9.11 (2H, d, *J* 2.0 Hz, CH-2 dinitrobenzoyl and CH-6 dinitrobenzoyl), [7.61-7.57 (4H, m) and 7.23-7.21 (5H, m), Ts and Ph], 6.11-6.03 (1H, m, =CH), 5.00-4.71 (4H, m, 2 × $=CH_2$), [4.26-4.20 (1H, m) and 4.11-4.05 (1H, m), CH_2O], 3.99 (1H, d, *J* 7.0 Hz, CHPh), 3.49 (1H, dd, *J* 8.0, 3.0 Hz, $=CCH_3CH$), [2.71 (1H, q, *J* 9.5 Hz), 2.65-2.55 (1H, m), 2.38-2.29 (1H, m), 2.20-2.11 (1H, m), 2.08-2.01 (1H, m), 1.98-1.91 (1H, m) and 1.78-1.70 (1H, m) 2 × CH_2 cyclopentyl, $CH(CH_2)_2O$ and CH_2CH_2O], 2.43 (3H, s, CH_3 Ts), 1.82 (3H, s, $=CCH_3$); δ_C (100 MHz) 162.3 (C=O), 148.7 (C-3 dinitrobenzoyl and C-5 dinitrobenzoyl), [145.5, 144.3, 138.9, 137.5 and 134.1 (2 × C Ts, *ipso* Ph, C-1 dinitrobenzoyl and =C)], 138.5 (=CH), [131.8, 130.7, 129.4, 128.9 and 128.1 (4 × CH Ts, *ortho* Ph, *meta* Ph, CH-2 dinitrobenzoyl and CH-6 dinitrobenzoyl)], 127.4 (*para* Ph), 122.3 (C-4 dinitrobenzoyl), [117.6 and 116.9 (2 × $=CH_2$)], 86.0 (CTs), 66.6 (CH_2O), [55.2 and 53.8 (CHPh and $=CCH_3CH$)], 46.6 ($CH(CH_2)_2O$), [31.3, 30.6 and 30.0 (2 × CH_2 cyclopentyl and CH_2CH_2O)], [21.8 and 21.6 (2 × CH_3)].

(±)-Ethyl 2-(1-methyl-4-phenyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)acetate (267a), one diastereoisomer of ethyl 2-[3-acetyl-2-(2-oxo-1-phenylethylidene)cyclopentyl]acetate (283) and one diastereoisomer of ethyl 2-[1,3-dimethoxy-1-methyl-4-phenyl-4a-(*p*-toluenesulfonyl)octahydrocyclopenta[*c*]pyran-5-yl]acetate (284)



1 major diastereoisomer — 1 diastereoisomer — 1 diastereoisomer

266a **267a** **283** **284**

According to general procedure **3.2.6**, a solution of a diastereoisomeric mixture of ethyl 2-[2-(1-phenylallyl)-3-(prop-1-en-2-yl)-2-tosylcyclopentyl] acetate **266a** (81 mg, 0.17 mmol, 1 equiv) in MeOH:CH_2Cl_2 (2.0 mL) was ozonolysed and reduced with, Me_2S (1.0 mL, 23 mmol, 132 equiv). A solution of the resulting mixture in MeOH (1.7 mL) was reacted with NH_4HCO_3 (130 mg, 1.64 mmol, 9 equiv). Chromatography

(10%→20% AcOEt–petrol) gave *ethyl 2-(1-methyl-4-phenyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-yl)acetate* **267a** (12 mg, 24%) as a colourless oil, one diastereoisomer of *ethyl 2-[3-acetyl-2-(2-oxo-1-phenylethylidene)cyclopentyl]acetate* **283** (7 mg, 12%) as a yellow oil and one diastereoisomer of *ethyl 2-[1,3-dimethoxy-1-methyl-4-phenyl-4a-(*p*-toluenesulfonyl)octahydrocyclopenta[*c*]pyran-5-yl]acetate* **284** (6 mg, 7%) as a white solid.

267a; R_f 0.33 (20% AcOEt–petrol); ν_{max} (film) 2978, 2932, 1732, 1598, 1462, 1447, 1372, 1269, 1178, 1029, 762, 702 cm^{-1}; δ_H (400 MHz) 8.25 (1H, s, CH-3), 7.46-7.36 (5H, m, Ph), 4.03-3.97 (3H, m, OCH_2 and CH-5), 3.01-2.87 (2H, m, CH_2-7), 2.52 (CH_3-1), [2.46-2.34 (1H, m) and 1.93-1.85 (1H, m), CH_2-6], [2.20 (1H, dd, *J* 15.5, 3.5 Hz) and 2.01 (1H, dd, *J* 15.5, 10.5 Hz), CH_2CO], 1.15 (3H, t, *J* 7.0 Hz, $OCH_2C\mathit{H_3}$); δ_C (100 MHz) 172.0 (C=O), [153.2 and 151.8 (C-1 and C-4a)], 147.3 (CH-3), [137.6, 137.4 and 132.2 (C-7a, C-4 and *ipso* Ph)], [128.8 and 128.5 (*ortho* Ph and *meta* Ph)], 127.7 (*para* Ph), 60.3 (OCH_2), 40.8 (CH-5), 37.8 ($\mathit{C}H_2CO$), [30.0 and 29.1 (CH_2-6 and CH_2-7)], 21.9 (CH_3-1), 14.1 ($OCH_2\mathit{C}H_3$); *m/z* (CI) 296 $[M+H]^+$ (Found: $[M+H]^+$, 296.1653. $C_{19}H_{21}NO_2$ requires $[M+H]^+$, 296.1651) (Found: C, 77.34; H, 7.20; N, 4.67. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%).

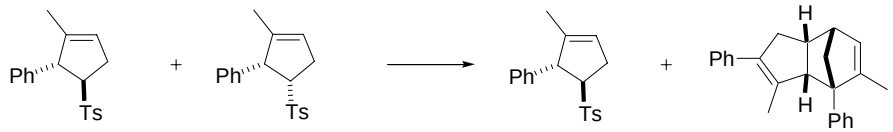
One diastereoisomer of **283**; R_f 0.37 (20% AcOEt–petrol); ν_{max} (film) 2955, 1726, 1448, 1374, 1356, 1271, 1180, 1135, 1078, 1026, 702 cm^{-1}; δ_H (400 MHz) 9.59 (CHO), 7.41-7.35 (5H, m, Ph), 4.16 (1H, q, *J* 7.0 Hz, OCH_2), 2.95 (1H, dd, *J* 9.0, 5.5 Hz, CH-1), 2.84-2.77 (CH-3), 2.37 (2H, d, *J* 7.0 Hz, CH_2CO), 2.01-1.88 (2H, m, CH_2-4), [1.78-1.71 (1H, m) and 1.31-1.22 (1H, m), CH_2-5], 1.57 (3H, s, CH_3CO), 1.28 (3H, t, *J* 7.0 Hz, $OCH_2C\mathit{H_3}$); δ_C (100 MHz) 206.4 ($CH_3\mathit{C}O$), 197.1 (HCO), 171.0 (OCO and C-2), 130.6 (*ipso* Ph and CPh), 129.1 (*para* Ph), [128.6 and 127.7 (*ortho* Ph and *meta* Ph)], 61.0 (OCH_2), 53.7 (CH-1), 40.2 (CH-3), 36.5 ($\mathit{C}H_2CO$), 30.2 (CH_2-5), 29.8 ($\mathit{C}H_3CO$), 26.9 (CH_2-4), 14.2 ($OCH_2\mathit{C}H_3$).

One diastereoisomer of **284**; ν_{max} (film) 2934, 1729, 1594, 1453, 1380, 1306, 1273, 1183, 1137, 1075, 1025, 1008, 929, 878, 816, 754, 698, 664 cm^{-1}; δ_H (400 MHz) 7.79 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), [7.56 (2H, d, *J* 6.0 Hz) and 7.35-7.28 (5H, m),

CH-3 Ts, CH-5 Ts and Ph], 5.56 (1H, d, *J* 9.5 Hz, C*H*OCH$_3$), 4.16-4.06 (2H, m, OCH$_2$), 4.03 (1H, d, *J* 9.5 Hz, CH-4), [3.34 (3H, s) and 3.26 (3H, s), 2 × OCH$_3$], 3.11 (1H, t, *J* 9.0 Hz, CH-7a), 2.86-2.79 (1H, m, CH-5), [2.72 (1H, dd, *J* 16.5, 1.5 Hz) and 2.38 (1H, dd, *J* 16.5, 12.0 Hz,), CH$_2$CO], 2.45 (3H, s, CH$_3$ Ts), [1.88-1.78 (1H, m) and 1.47-1.41 (1H, m), CH$_2$-7], [1.73-1.67 (1H, m) and 0.86-0.75 (1H, m), CH$_2$-6], 1.39 (3H, s, CH$_3$-1), 1.24 (3H, t, *J* 7.0 Hz, OCH$_2$C*H*$_3$); δ_C (125 MHz) 173.1 (C=O), [144.7, 138.1 and 136.2 (2 × C Ts and *ipso* Ph)], [130.9, 130.5, 129.6, 127.6 and 127.5 (4 × CH Ts, *ortho* Ph, *meta* Ph and *para* Ph)], 101.5 (C-1), 100.5 (CH-3), 60.3 (OCH$_2$), [55.9 and 49.2 (2 × OCH$_3$)], 53.8 (CH-4), 52.3 (CH-7a), 49.9 (CH-5), 36.2 (*C*H$_2$C=O), 31.1 (CH$_2$-6), 25.0 (CH$_2$-7), 23.6 (CH$_3$-1), 21.6 (CH$_3$ Ts), 14.2 (OCH$_2$*C*H$_3$).

3.3.3 Compounds relevant to the development of the methodology for cyclopentadiene synthesis

(1*R,2*S**,6*R**)-1,4-Diphenyl-3,9-dimethyl-tricyclo[5.2.1.0^{2,6}]-deca-3,8-diene (290)**

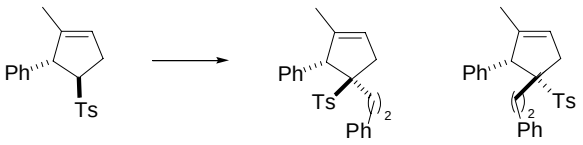


203b-*t* **203b-*c*** **203b-*t*** **290**

To a solution of a 1:1 diastereoisomeric mixture of 1-methyl-4-tosyl-5-phenylcyclopent-1-ene **203b** (6.576 g, 21.05 mmol, 1 equiv) in THF (100 mL) was added *t*-BuOK (3.639 g, 32.42 mmol, 1.5 equiv). The mixture was left stirring at rt for 67 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (2 × 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give *(4*R*,*5*S*)*-1-methyl-4-(*p-*toluenesulfonyl)-5-phenylcyclopent-1-ene* **203b-*t*** (2.593 g, 39%) as a white solid and *(1*R*,*2*S*,*6*R*)*-1,4-diphenyl-3,9-dimethyl-tricyclo[5.2.1.0^{2,6}]-deca-4,8-diene* **290** (732 mg, 11%) as a colourless oil; R_f 0.95 (5% AcOEt–petrol); ν_{max} (film) 3054, 3025, 2956, 2925, 2858, 1600, 1493, 1443, 1380, 1326, 1245, 1119, 1069, 1034, 909, 809, 757, 733, 700, 654 cm^{-1}; δ_H (500 MHz) 7.51 (2H, dd, *J* 8.5, 1.5 Hz, *ortho* Ph-1), 7.39-7.35 (2H, m, *meta* Ph-1), 7.32-7.29 (2H, m, *meta* Ph-4), 7.26-7.20 (2H, m, 2 × *para* Ph), 7.16 (2H, dd, *J* 8.5,

1.5 Hz, *ortho* Ph-4), 5.89 (1H, bs, CH-8), 4.01 (1H, d, *J* 8.5 Hz, CH-2), 3.06-2.99 (1H, m, CH-6), 2.86-2.85 (1H, m, CH-7), [2.74-2.67 (1H, m) and 2.18-2.14 (1H, m), CH_2-5], [1.77 (1H, dd, *J* 8.0, 2.0 Hz) and 1.60 (1H, d, *J* 8.0 Hz), CH_2-10], 1.74-1.73 (3H, m, CH_3-3), 1.62 (3H, d, *J* 1.5 Hz, CH_3-9); δ_C (100 MHz) [146.3, 142.5, 138.5, 138.6 and 135.1 (2 × *ipso* Ph, C-3, C-4 and C-9)], 128.6 (CH-8), [128.5, 128.0 and 127.9 (2 × *ortho* Ph and 2 × *meta* Ph)], [126.2 and 125.9 (2 × *para* Ph)], 64.8 (C-1), 60.6 (CH_2-10), 59.0 (CH-2), 44.9 (CH-7), 42.6 (CH-6), 39.0 (CH_2-5), 16.5 (CH_3-3), 15.6 (CH_3-9); *m/z* (CI) 313 $[M+H]^+$, 157 (Found: $[M+H]^+$, 313.1960. $C_{24}H_{24}$ requires $[M+H]^+$, 313.1956) (Found: C, 92.17; H, 7.85. $C_{24}H_{24}$ requires C, 92.26; H, 7.74%).

(4*R,5*S**)-1-Methyl-4-(3-phenylethyl)-4-(*p*-toluenesulfonyl)-5-phenyl cyclopent-1-ene and (4*S**,5*S**)-1-methyl-4-(3-phenylethyl)-4-(*p*-toluenesulfonyl)-5-phenyl cyclopent-1-ene (204c)**

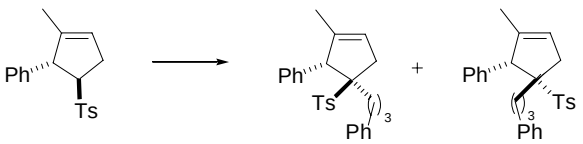


203b-*t* **204c**

According to general procedure **3.2.5**, a solution of (4*R**,5*S**)-1-methyl-4-tosyl-5-phenyl cyclopent-1-ene **203b-*t*** (894 mg, 2.86 mmol, 1 equiv) in THF (14 mL) was treated with *n*-BuLi in hexanes (8.71 M, 365 μL, 3.18 mmol, 1.1 equiv) and then reacted with (2-bromoethyl)benzene (470 μL, 3.44 mmol, 1.2 equiv). Chromatography (5% AcOEt–petrol) gave *(4*S**,5*S**)-1-methyl-4-(3-phenylethyl)-4-(*p-*toluenesulfonyl)-5-phenyl cyclopent-1-ene* and *(4*R**,5*S**)-1-methyl-4-(3-phenylethyl)-4-(*p-*toluenesulfonyl)-5-phenyl cyclopent-1-ene* **204c** in an inseparable 8:2 mixture (593 mg, 50%) as a yellow gum; R_f 0.23 (10% AcOEt–hexane); ν_{max} (film) 3057, 3023, 2932, 2864, 1595, 1493, 1453, 1288, 1135, 1083, 1032, 822, 736, 702, 577, 548, 520 cm^{-1}; δ_H (400 MHz) 7.87 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of the minor diastereoisomer), 7.43 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts of the major diastereoisomer), [7.36-7.11 (22H, m) and 6.71 (2H, d, *J* 7.0 Hz), 2 × Ph, CH-3 Ts and CH-5 Ts of both diastereoisomers], 5.57 (1H, bs, CH-2 of the major diastereoisomer), 5.16 (1H, bs, CH-2 of the minor diastereoisomer), 4.33 (1H, bs, CH-5 of the minor diastereoisomer), 3.76

(1H, bs, CH-5 of the major diastereoisomer), 3.50 (1H, dq, *J* 16.0, 2.0 Hz, C*H*H-3 of the major diastereoisomer), 3.21 (1H, dt, *J* 18.5, 2.0 Hz, C*H*H-3 of the minor diastereoisomer), 2.80-2.66 (4H, m, $PhCH_2$ of both diastereoisomers), 2.63 (1H, dq, *J* 18.5, 2.0 Hz, CH*H*-3 of the minor diastereoisomer), 2.47 (3H, s, CH_3 Ts of the minor diastereoisomer), 2. 41 (3H, s, CH_3 Ts of the major diastereoisomer), 2.18-2.14 (1H, m, CH*H*-3 of the major diastereoisomer), 2.08-2.70 (4H, m, $PhCH_2CH_2$ of both diastereoisomers), 1.55 (3H, s, CH_3-1 of the major diastereoisomer) 1.27 (3H, s, CH_3-1 of the minor diastereoisomer); δ_C (100 MHz) [144.3, 141.7, 141.4, 137.4 and 134.6 (2 × *ipso* Ph, 2 × C Ts and C-1 of the minor diastereoisomer)], [143.6, 141.2, 136.4 and 135.9 (2 × *ipso* Ph, 2 × C Ts and C-1 of the major diastereoisomer)], [131.2, 129.5, 129.0, 128.4, 128.3 and 127.3 (2 × *ortho* Ph, 2 × *meta* Ph, 4 × CH Ts of the major diastereoisomer)], [129.9, 129.7, 129.1, 128.5 and 128.1 (2 × *ortho* Ph, 2 × *meta* Ph and 4 × CH Ts of the minor diastereoisomer)], [127.5, 125.6 and 122.8 (2 × *para* Ph and CH-2 of the minor diastereoisomer)], [126.9, 126.0 and 123.0 (2 × *para* Ph and CH-2 of the major diastereoisomer)], 77.3 (C-4 of the minor diastereoisomer), 75.2 (C-4 of the major diastereoisomer), 62.0 (CH-5 of the major diastereoisomer), 59.7 (CH-5 of the minor diastereoisomer), [40.4, 35.7 and 31.7 (CH_2-3, $PhCH_2$ and $Ph(CH_2)_2$ of the minor diastereoisomer)], [39.7, 38.8 and 26.9 (CH_2-3 and $Ph(CH_2)_2$ of the major diastereoisomer)], [21.6 and 15.1 (2 × CH_3 of the minor diastereoisomer)], [21.5 and 14.9 (2 × CH_3 of the major diastereoisomer)]; *m/z* (CI) 434 $[M+NH_4]^+$, 386, 261, 174 (Found: $[M+NH_4]^+$, 434.2156. $C_{27}H_{28}O_2S$ requires $[M+NH_4]^+$, 434.2154).

(4*R,5*S**)-1-Methyl-4-(3-phenylpropyl)-4-(*p*-toluenesulfonyl)-5-phenyl cyclopent-1-ene (204d-*t*) and (4*S**,5*S**)-1-methyl-4-(3-phenylpropyl)-4-(*p*-toluenesulfonyl)-5-phenyl cyclopent-1-ene (204d-*c*)**



203b-*t* **204d-*t*** **204d-*c***

According to general procedure **3.2.5**, a solution of (4*R**,5*S**)-1-methyl-4-tosyl-5-phenyl cyclopent-1-ene **203b-*t*** (1.027 g, 3.286 mmol, 1 equiv) in THF (16 mL) was

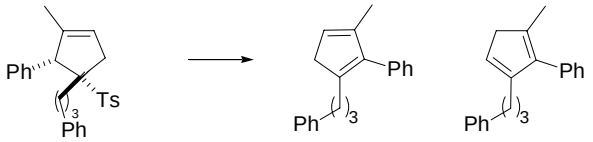
reacted with *n*-BuLi in hexane (2.40 M, 1.51 mL, 3.62 mmol, 1.1 equiv) and then reacted with (3-iodopropyl)benzene (650 μL, 4.04 mmol, 1.2 equiv). Chromatography (3% Et_2O–toluene) gave *(4*S*,*5*S*)-1-methyl-4-(3-phenylpropyl)-4-(*p*-toluenesulfonyl)-5-phenyl cyclopent-1-ene* **204d-*t*** (190 mg, 13%) as a pale yellow gum and *(4*R*,*5*S*)-1-methyl-4-(3-phenylpropyl)-4-(*p*-toluenesulfonyl)-5-phenyl cyclopent-1-ene* **204d-*c*** (924 mg, 65%) as a white solid.

204d-*t*; R_f 0.49 (5% Et_2O–toluene); ν_{max} (film) 3027, 2923, 1598, 1494, 1454, 1299, 1287, 1141, 1081, 816, 738, 699, 666 cm^{-1}; δ_H (400 MHz) 7.81 (2H, d, *J* 8.0 Hz, CH-2 Ts and CH-6 Ts), [7.32-7.27 (4H, m), 7.22-7.12 (4H, m), 7.05-7.03 (2H, m) and 6.92 (2H, d, *J* 7.0 Hz), 2 × Ph, CH-3 Ts and CH-5 Ts], 5.21 (1H, bs, CH-2), 4.22 (1H, bs, CH-5), 3.14 (1H, dt, *J* 18.5, 2.0 Hz, C*H*H-3), 2.51 (1H, dq, *J* 18.5, 2.0 Hz, CH*H*-3), 2.46 (3H, s, CH_3 Ts), 2.29-2.14 (2H, m, $PhCH_2$), 1.94-1.83 (1H, m, $PhCH_2CHH$), 1.74-1.67 (1H, m, $Ph(CH_2)_2CHH$), 1.63-1.52 (1H, m, $PhCH_2CHH$), 1.42-1.34 (1H, m, $Ph(CH_2)_2CHH$), 1.27 (3H, s, CH_3-1); δ_C (100 MHz) [144.1, 141.7, 141.4, 137.4 and 134.6 (2 × *ipso* Ph, 2 × C Ts and C-1)], [130.0, 129.6, 129.1, 128.3, 128.3 and 128.0 (2 × *ortho* Ph, 2 × *meta* Ph and 4 × CH Ts)], [127.2, 125.5 and 124.3 (2 × *para* Ph and CH-2)], 77.2 (C-4), 59.9 (CH-5), [39.3, 36.4, 33.2 and 27.1 (CH_2-3 and $Ph(CH_2)_3$)], [21.6 and 15.1 (CH_3-1 and CH_3 Ts)]; *m/z* (CI) 448 $[M+NH_4]^+$, 355, 338, 275, 174, 52 (Found: $[M+NH_4]^+$, 448.2325. $C_{28}H_{30}O_2S$ requires $[M+NH_4]^+$, 448.2310) (Found: C, 78.04; H, 6.96. $C_{28}H_{30}O_2S$ requires C, 78.10; H, 7.02%).

204d-*c*; mp 118-120 °C (5% AcOEt–petrol); R_f 0.35 (5% Et_2O–toluene); ν_{max} (film) 3027, 2925, 1598, 1494, 1454, 1287, 1140, 1080, 816, 748, 699, 666 cm^{-1}; δ_H (400 MHz) 7.44 (2H, d, *J* 8.5 Hz, CH-2 Ts and CH-6 Ts), 7.36-7.18 (12H, m, 2 × Ph, CH-3 Ts and CH-5 Ts), 5.58 (1H, bs, CH-2), 3.78 (1H, bs, CH-5), 3.53 (1H, dq, *J* 16.0, 2.0 Hz, C*H*H-3), 2.72-2.58 (2H, m, $PhCH_2$), 2.43 (3H, s, CH_3 Ts), 2.16 (1H, bd, *J* 16.0 Hz, CH*H*-3), [2.07-2.01 (1H, m) and 1.92-1.70 (3H, m), $PhCH_2(CH_2)_2$], 1.56 (3H, s, CH_3-1); δ_C (100 MHz) [143.6, 141.6, 141.3, 136.3 and 135.8 (2 × *ipso* Ph, 2 × C Ts and C-1)], [131.2, 129.5, 129.1, 128.4, 128.4 and 127.5 (2 × *ortho* Ph, 2 × *meta* Ph and 4 × CH Ts)], [127.3, 125.9 and 122.9 (2 × *para* Ph and CH-2)], 75.2 (C-4), 62.0 (CH-5), [39.7, 38.5, 36.4 and 26.6 (CH_2-3 and $Ph(CH_2)_3$)], [21.5 and 14.9 (CH_3-1 and CH_3 Ts)]; *m/z*

(CI) 448 $[M+NH_4]^+$, 294, 275 (Found: $[M+NH_4]^+$, 448.2309. $C_{28}H_{30}O_2S$ requires $[M+NH_4]^+$, 420.2310) (Found: C, 78.21; H, 7.14. $C_{28}H_{30}O_2S$ requires C, 78.10; H, 7.02%).

1-(3-Phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene (288c-1) and 1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene (288c-2)

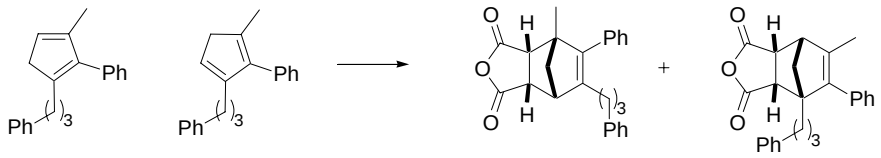


204d-*c* **288c-1** **288c-2**

A mixture of (4*S**,5*S**)-1-methyl-4-(3-phenylpropyl)-4-tosyl-5-phenyl cyclopent-1-ene **204d-*c*** (56 mg, 0.13 mmol, 1 equiv) and *t*-BuOK (32 mg, 0.29 mmol, 2.2 equiv) in DMSO (260 μL) was exposed to microwave irradiation for 20 min at 100 °C. The red-brown mixture was treated with AcOH (9.0 μL, 0.16 mmol, 1.2 equiv) and then partitioned between H_2O (10 mL) and petrol (2 × 10 mL). The aqueous layer was extracted with toluene (15 mL) and Et_2O (2 × 15 mL) and the combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give *1-(3-phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene* **288c-1** and *1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene* **288c-2** in an inseparable 1:1 mixture (34 mg, 96%) and as a yellow oil; R_f 0.86 (5% Et_2O–toluene); ν_{max} (film) 3026, 2923, 2853, 1699, 1601, 1494, 1454, 1387, 1300, 1142, 1074, 1031, 747, 700, 666 cm^{-1}; δ_H (400 MHz) 7.43-7.10 (20H, m, 2 × Ph of **288c-1** and **288c-2**), 6.02 (1H, q, *J* 1.5 Hz, CH-4 of **288c-1**), 6.00 (1H, t, *J* 1.5 Hz, CH-4 of **288c-2**), 3.03-3.01 (4H, m, CH_2-5 of **288c-1** and **288c-2**), 2.60-2.56 (4H, m, CH_2Ph of **288c-1** and **288c-2**), 2.46-2.42 (2H, m, C*H*$_2$$(CH_2)_2$Ph of **288c-1**), 2.33-2.29 (2H, m, C*H*$_2$$(CH_2)_2$Ph of **288c-2**), 2.00 (3H, s, CH_3 of **288c-2**), 1.91 (3H, q, *J* 2.0 Hz, CH_3 of **288c-1**), 1.87-1.80 (2H, m, C*H*$_2$$CH_2$Ph of **288c-1**), 1.78-1.70 (2H, m, C*H*$_2$$CH_2$Ph of **288c-2**); δ_C (100 MHz) [147.7, 144.3, 143.2, 142.6, 142.6, 142.4, 141.9, 140.0, 137.0 and 136.8 (2 × *ipso* Ph, C-1, C-2 and C-3 of **288c-1** and **288c-2**), [129.2, 129.2, 128.3, 128.2, 128.2 and 128.0 (2 × *ortho* Ph and 2 × *meta* Ph of **288c-1** and **288c-2**)], [126.4, 126.4, 125.6 and 125.5 (2 × *para* Ph of **288c-1** and **288c-2**)], 124.5 (CH-4 of **288c-1**), 123.2 (CH-4 of **288c-2**), [44.3 and 41.8 (CH_2-5

of **288c-1** and **288c-2**)], [35.7 and 35.6 (CH_2Ph of **288c-1** and **288c-2**)], 32.3 ($CH_2(CH_2)_2$Ph of **288c-1**), 30.0 ($CH_2(CH_2)_2$Ph of **288c-2**), 28.8 (CH_2CH_2Ph of **288c-2**), 28.6 (CH_2CH_2Ph of **288c-1**), 15.0 (CH_3 of **288c-1**), 14.4 (CH_3 of **288c-2**); *m/z* (CI) 275 $[M+H]^+$ (Found: $[M+H]^+$, 275.1798. $C_{21}H_{22}$ requires $[M+H]^+$, 275.1800).

(1*R,4*S**,5*S**,6*S**)-1-Methyl-2-phenyl-3-(3-phenylpropyl)-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride (293a) and (1*S**,4*R**,5*R**,6*R**)-1-(3-phenylpropyl)-2-phenyl-3-methyl-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride (293b)**



288c-1 **288c-2** **293a** **293b**

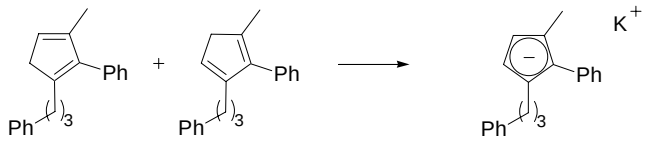
To a solution of a 1:1 mixture of 1-(3-phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene **288c-1** and 1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene **288c-2** (99 mg, 0.36 mmol, 1 equiv) in toluene (1.8 mL) at rt and under nitrogen was added maleic anhydride (51 mg, 0.52 mmol, 1.4 equiv). The mixture was stirred at rt for 1 h, at 40 °C for 6 h and at 60 °C for 15 h. The brown mixture was concentrated under reduced pressure and chromatography (5%→10% AcOEt–petrol) gave *(1R*,4S*,5S*,6S*)-1-methyl-2-phenyl-3-(3-phenylpropyl)-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride* **293a** (13 mg, 10%) as a colourless oil and *(1S*,4R*,5R*,6R*)-1-(3-phenylpropyl)-2-phenyl-3-methyl-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride* **293b** (15 mg, 11%) as a colourless oil.

293a; R_f 0.20 (10% AcOEt–petrol); ν_{max} (film) 2932, 2864, 1857, 1778, 1721, 1493, 1453, 1226, 1078, 913, 696 cm^{-1}; δ_H (400 MHz) 7.38-7.01 (10H, m, 2 × Ph), 3.84 (1H, dd, *J* 8.0, 5.0 Hz, CH-5), 3.46-3.45 (1H, m, CH-4), 3.33 (1H, d, *J* 8.0 Hz, CH-6), 2.60-2.46 (2H, m, CH_2Ph), [2.36-2.28 (1H, m) and 2.09-2.02 (1H, m), $CH_2(CH_2)_2$Ph], [1.97-1.86 (1H, m) and 1.75-1.64 (1H, m), CH_2CH_2Ph], [1.83 (1H, dd, *J* 9.0, 1.5 Hz) and 1.66 (1H, d, *J* 9.0 Hz), CH_2-7], 1.52 (3H, s, CH_3); δ_C (100 MHz) [171.2 and 171.1 (2 × C=O)], [145.2, 143.5, 141.9 and 133.6 (2 × *ipso* Ph, C-2 and C-3)], [129.1, 128.3 and 128.2 (2 × *ortho* Ph and 2 × *meta* Ph)], [127.4 and 125.8 (2 × *para* Ph)], 56.7 (CH_2-7),

59.2 (C-1), 53.1 (CH-6), 49.9 (CH-5), 47.0 (CH-4), 35.6 (CH_2Ph), 29.9 (CH_2CH_2Ph), 28.0 ($CH_2(CH_2)_2Ph$), 17.9 (CH_3); *m/z* (CI) 390 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 390.2074. $C_{25}H_{24}O_3$ requires $[M+NH_4]^+$, 390.2069) (Found: C, 80.63; H, 6.56. $C_{25}H_{24}O_3$ requires C, 80.62; H, 6.49%).

293b; R_f 0.29 (10% AcOEt–petrol); ν_{max} (film) 2932, 2853, 1852, 1776, 1726, 1453, 1282, 1226, 1078, 913, 702 cm^{-1}; δ_H (400 MHz) [7.37-7.11 (8H, m) and 7.02 (2H, d, *J* 7.0 Hz), 2 × Ph], 3.88 (1H, dd, *J* 8.5, 5.0 Hz, CH-5), 3.46 (1H, d, *J* 8.5 Hz, CH-6), 3.33 (1H, d, *J* 5.0 Hz, CH-4), 2.58-2.41 (2H, m, CH_2Ph), [2.11 (1H, ddd, *J* 16.0, 12.5, 4.0 Hz) and 1.96-1.88 (1H, m), $CH_2(CH_2)_2Ph$], [1.89 (1H, dd, *J* 8.5, 1.5 Hz) and 1.59-1.57 (1H, m), CH_2-7], 1.84 (3H, s, CH_3), [1.68-1.56 (1H, m) and 1.46-1.35 (1H, m), CH_2CH_2Ph]; δ_C (100 MHz) [172.0 and 171.0 (2 × C=O)], [143.3, 141.9, 141.4 and 134.0 (2 × *ipso* Ph, C-2 and C-3)], [129.7, 128.3, 128.3 and 128.2 (2 × *ortho* Ph and 2 × *meta* Ph)], [127.1 and 125.8 (2 × *para* Ph)], 63.8 (C-1), 56.0 (CH_2-7), 51.1 (CH-6), 49.5 (CH-5), 49.4 (CH-4), 36.2 (CH_2Ph), 30.5 ($CH_2(CH_2)_2Ph$), 27.7 (CH_2CH_2Ph), 15.0 (CH_3); *m/z* (CI) 390 $[M+NH_4]^+$ 52 (Found: $[M+NH_4]^+$, 390.2074. $C_{25}H_{24}O_3$ requires $[M+NH_4]^+$, 390.2069) (Found: C, 80.55; H, 6.48. $C_{25}H_{24}O_3$ requires C, 80.62; H, 6.49%).

Indications of the formation of potassium 1-(3-phenylpropyl)-2-phenyl-3-methylcyclopentadide (289a)



288c-1 **288c-2** **289a**

To a solution of a 1:1 mixture of 1-(3-phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene **288c-1** and 1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene **288c-2** (17 mg, 0.060 mmol, 1 equiv) in DMSO-d_6 (750 μL) was added *t*-BuOK in THF (1.0 M, 60 μL, 0.060 mmol, 1 equiv). The yellow solution immediately turns dark red-brown and ^1H NMR analysis indicates the formation of *potassium 1-(3-phenylpropyl)-2-phenyl-3-methylcyclopentadienyl* **289a**; δ_H (400 MHz) [7.24-7.03 (9H, m) and 6.67-6.63

(1H, m), 2 × Ph], [5.21 (1H, d, *J* 3.0 Hz) and 5.16 (1H, d, *J* 3.0 Hz), CH-4 and CH-5], 2.60-2.50 (6H, m, $(CH_2)_3Ph$), 2.12 (3H, s, CH_3).

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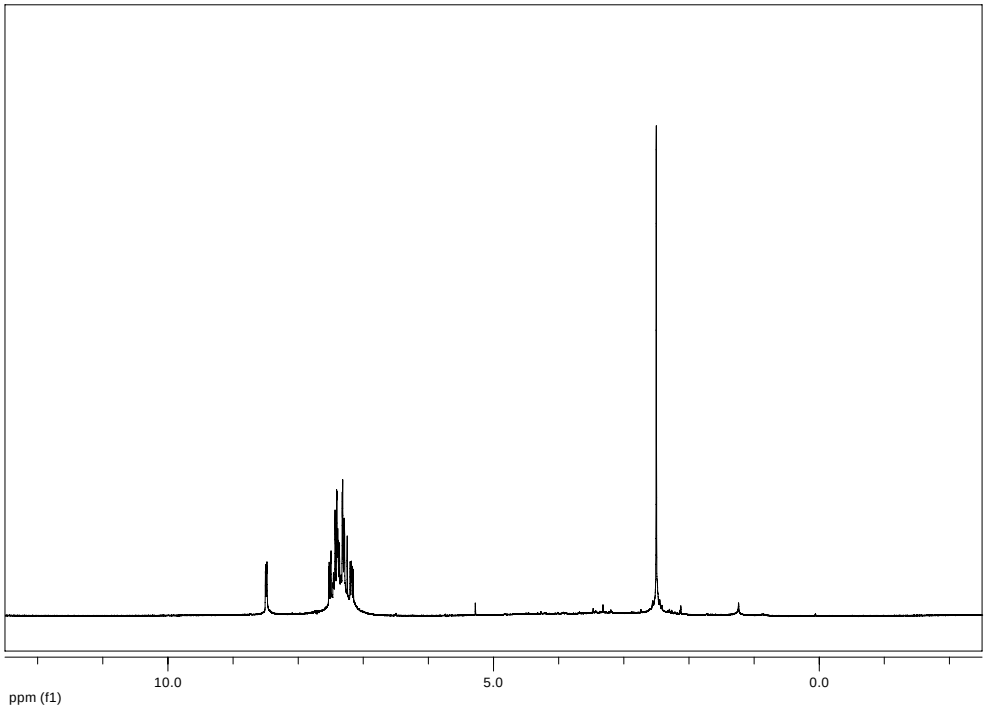
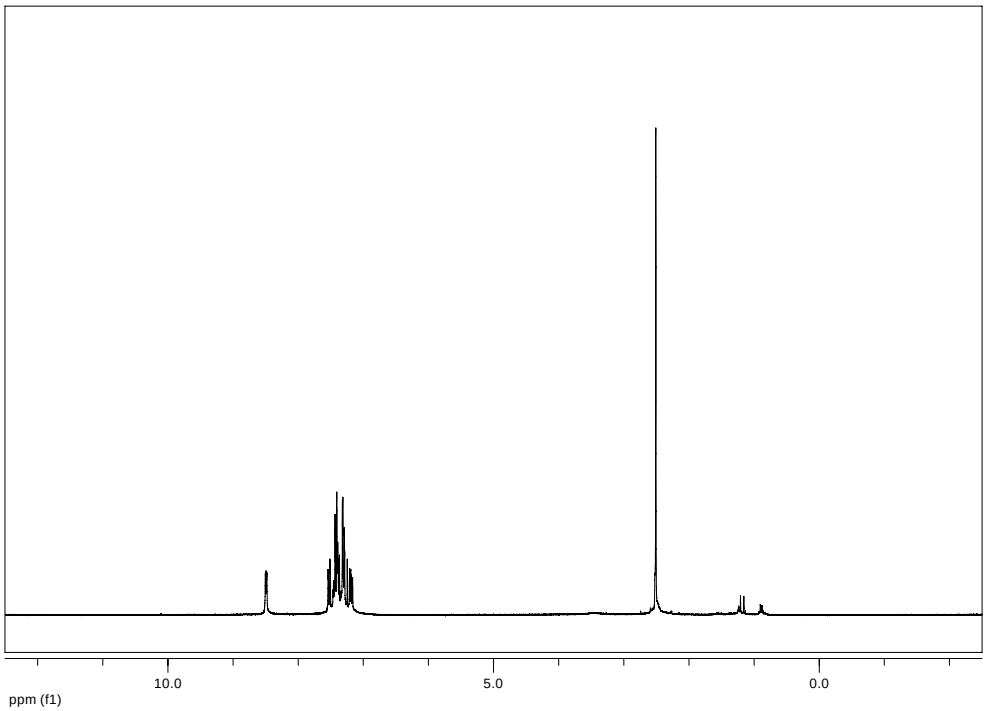
Appendix

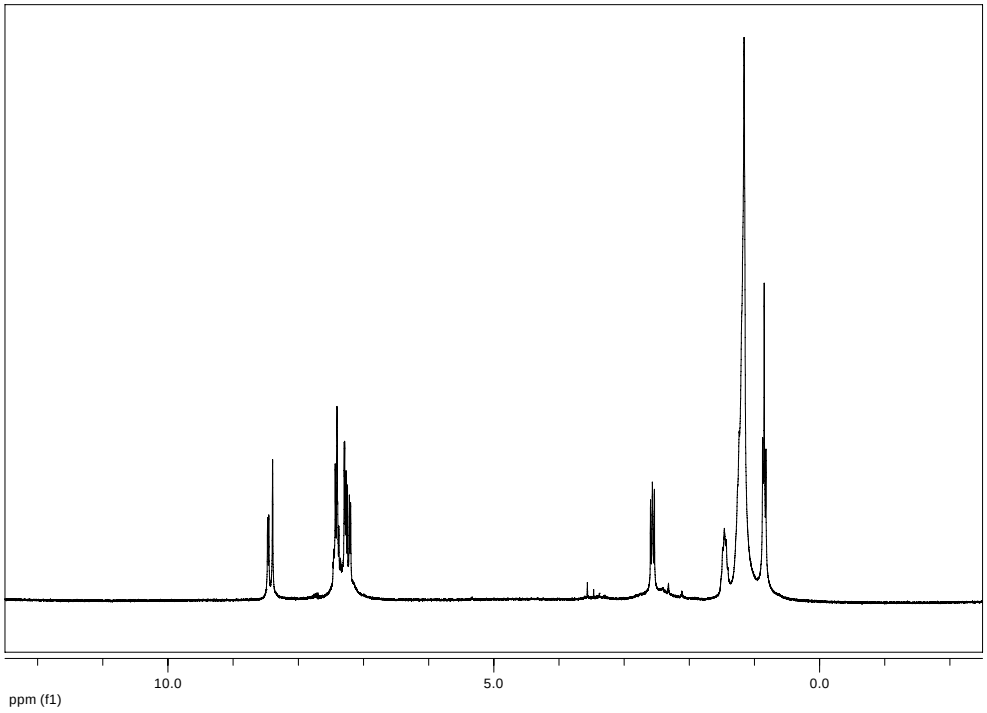
2-Methyl-3-phenylpyridine (**182b**), crude product, ^{1}H NMR spectrum in $CDCl_3$, 270 MHz



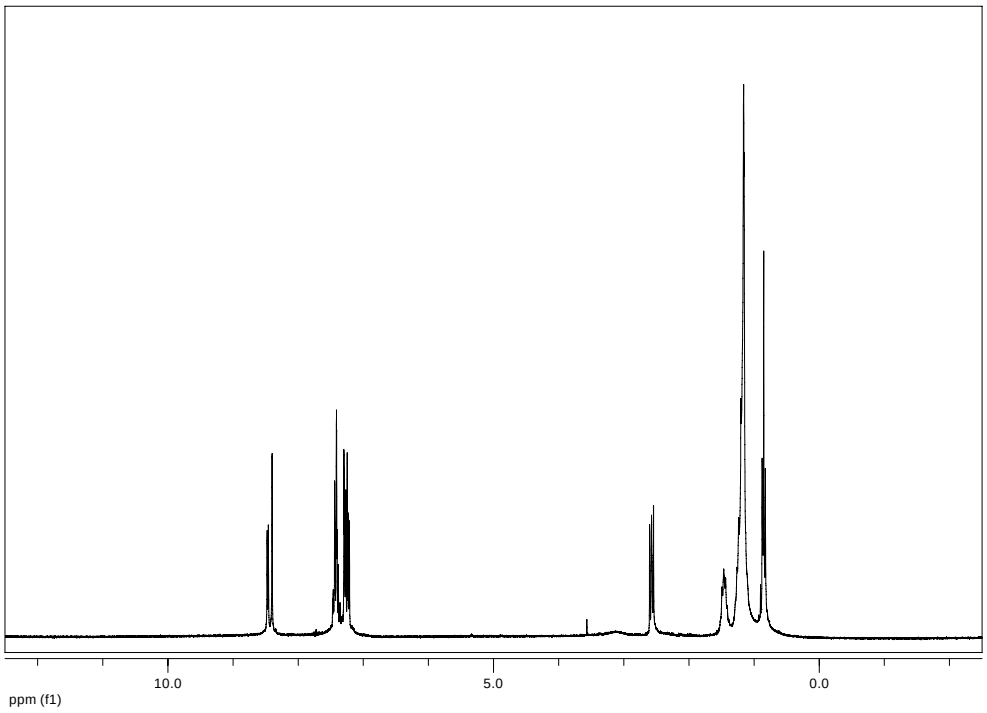
2-Methyl-3-phenylpyridine (**182b**), purified product, ^{1}H NMR spectrum in $CDCl_3$, 270 MHz



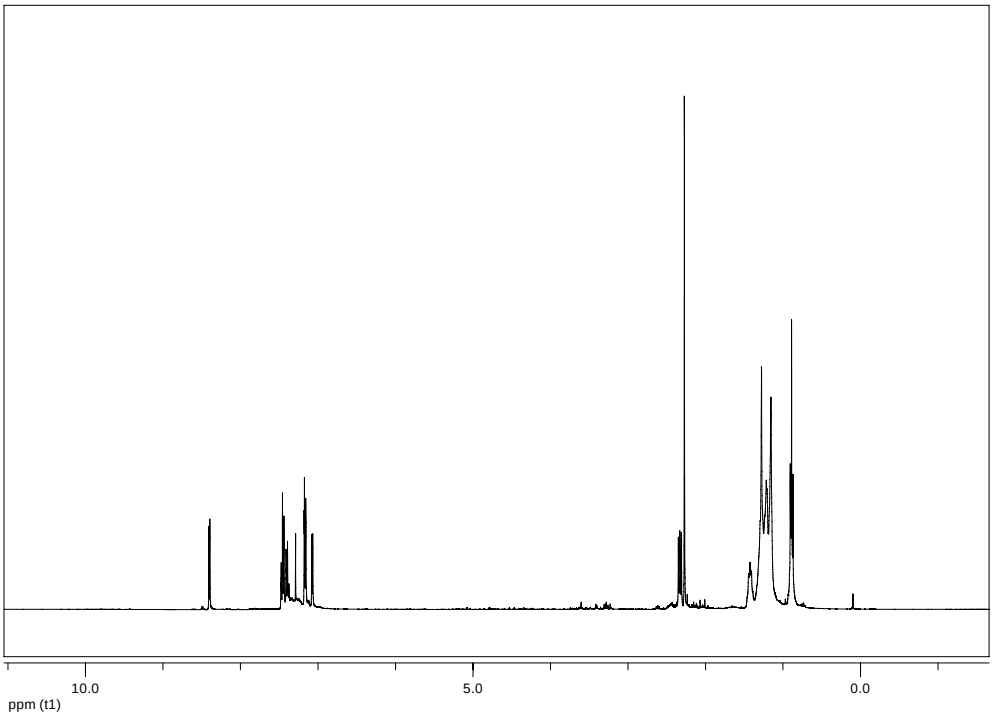
4-Nonyl-3-phenylpyridine (**182f**), crude product, ^{1}H NMR spectrum in $CDCl_3$, 270 MHz



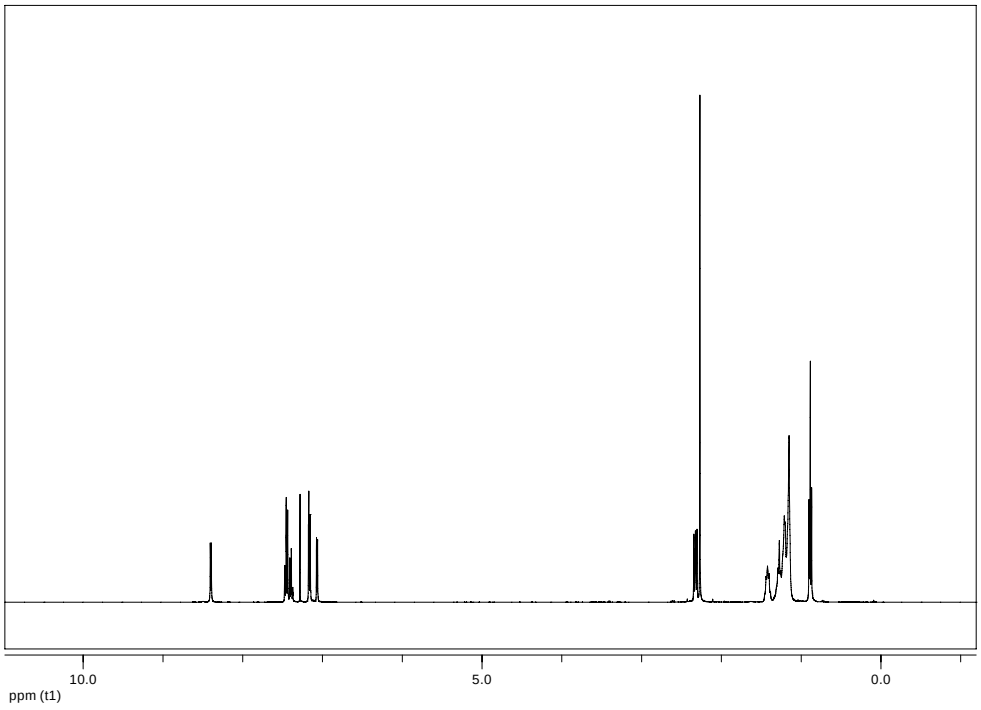
4-Nonyl-3-phenylpyridine (**182f**), purified product, ^{1}H NMR spectrum in $CDCl_3$, 270 MHz



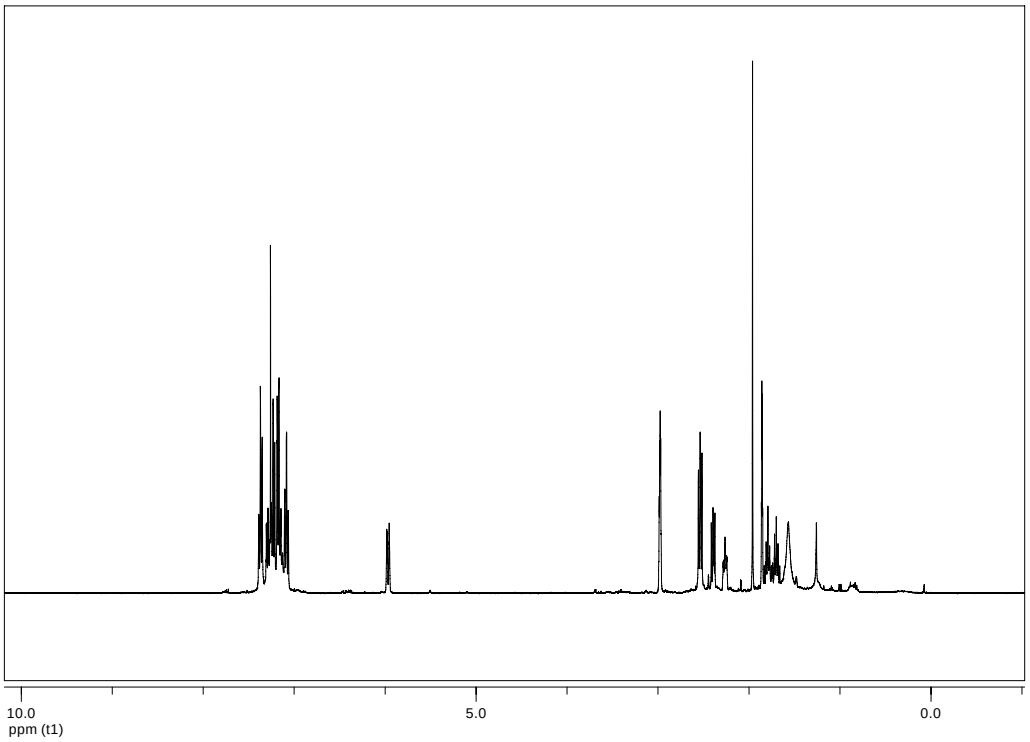
2-Methyl-4-nonyl-3-phenylpyridine (**182g**), crude product, ^{1}H NMR spectrum in $CDCl_3$, 400 MHz



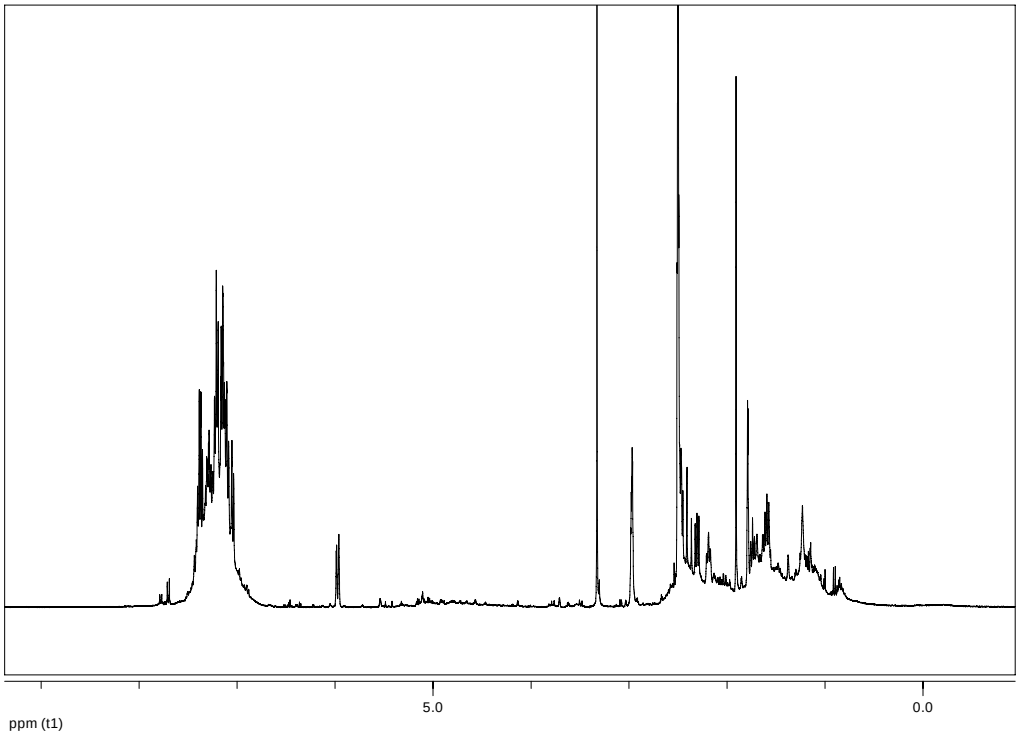
2-Methyl-4-nonyl-3-phenylpyridine (**182g**), purified product, ^{1}H NMR spectrum in $CDCl_3$, 400 MHz



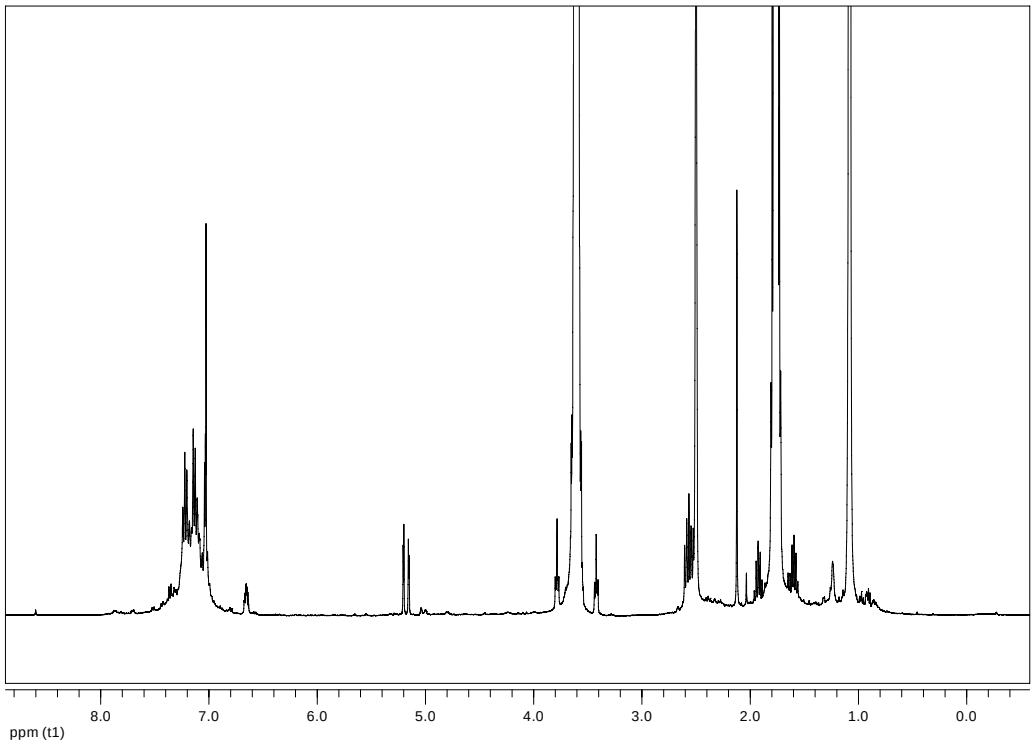
Deprotonation of 1-(3-phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene (**288c-1**) and 1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene (**288c-2**): starting materials in $CDCl_3$, 400 MHz



Deprotonation of 1-(3-phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene (**288c-1**) and 1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene (**288c-2**): starting materials in DMSO-d_6, 400 MHz



Deprotonation of 1-(3-phenylpropyl)-2-phenyl-4-methylcyclopenta-1,3-diene (**288c-1**) and 1-methyl-2-phenyl-3-(3-phenylpropyl)cyclopenta-1,3-diene (**288c-2**): potassium 1-(3-phenylpropyl)-2-phenyl-3-methylcyclopentadide (**289a**) in DMSO-d_6, 400 MHz



Crystal data of (4*R**,5*S**)-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (**203b-*t***) (DC0605)

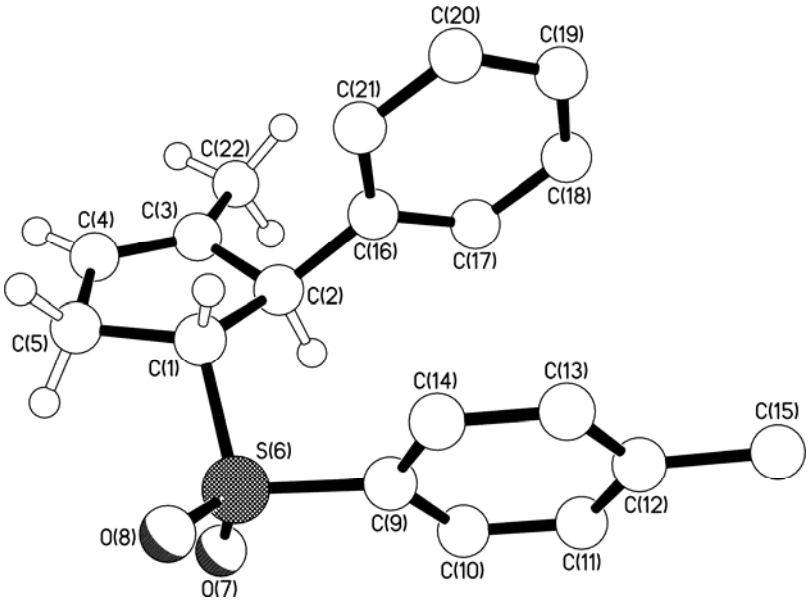


Table 1. Crystal data and structure refinement for DC0605.

Identification code	DC0605	
Empirical formula	C19 H20 O2 S	
Formula weight	312.41	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å	
Crystal system, space group	Orthorhombic, Pbca	
Unit cell dimensions	a = 17.0385(7) Å	α = 90°
	b = 9.9709(4) Å	β = 90°
	c = 19.4916(7) Å	γ = 90°
Volume, Z	3311.4(2) $Å^3$, 8	
Density (calculated)	1.253 Mg/m^3	
Absorption coefficient	0.200 mm^{-1}	
F(000)	1328	
Crystal colour / morphology	Colourless platy needles	

Crystal size	0.30 x 0.05 x 0.02 mm^3
θ range for data collection	3.93 to 25.97°
Index ranges	-17<=h<=20, -11<=k<=12, -22<=l<=23
Reflns collected / unique	12565 / 2832 [R(int) = 0.0533]
Reflns observed [F>4σ(F)]	1894
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.74209
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2832 / 0 / 201
Goodness-of-fit on F^2	1.029
Final R indices [F>4σ(F)]	R1 = 0.0420, wR2 = 0.0952
R indices (all data)	R1 = 0.0785, wR2 = 0.1103
Largest diff. peak, hole	0.345, -0.360 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for DC0605.

C(1)-C(5)	1.536(3)	C(9)-C(14)	1.376(3)
C(1)-C(2)	1.546(3)	C(9)-C(10)	1.382(3)
C(1)-S(6)	1.779(2)	C(10)-C(11)	1.370(3)
C(2)-C(16)	1.510(3)	C(11)-C(12)	1.385(3)
C(2)-C(3)	1.522(3)	C(12)-C(13)	1.392(3)
C(3)-C(4)	1.321(3)	C(12)-C(15)	1.510(4)
C(3)-C(22)	1.492(3)	C(13)-C(14)	1.382(3)
C(4)-C(5)	1.485(3)	C(16)-C(17)	1.380(3)
S(6)-O(7)	1.4366(15)	C(16)-C(21)	1.384(3)
S(6)-O(8)	1.4412(15)	C(17)-C(18)	1.383(3)
S(6)-C(9)	1.764(2)	C(18)-C(19)	1.373(4)

C(19)-C(20)	1.362(4)	C(14)-C(9)-S(6)	119.45(18)
C(20)-C(21)	1.381(3)	C(10)-C(9)-S(6)	119.71(18)
C(5)-C(1)-C(2)	107.87(18)	C(11)-C(10)-C(9)	119.4(2)
C(5)-C(1)-S(6)	111.76(16)	C(10)-C(11)-C(12)	121.4(2)
C(2)-C(1)-S(6)	112.18(15)	C(11)-C(12)-C(13)	118.1(2)
C(16)-C(2)-C(3)	115.30(18)	C(11)-C(12)-C(15)	121.4(3)
C(16)-C(2)-C(1)	114.89(18)	C(13)-C(12)-C(15)	120.5(3)
C(3)-C(2)-C(1)	102.33(18)	C(14)-C(13)-C(12)	121.1(2)
C(4)-C(3)-C(22)	127.5(2)	C(9)-C(14)-C(13)	119.2(2)
C(4)-C(3)-C(2)	111.7(2)	C(17)-C(16)-C(21)	117.7(2)
C(22)-C(3)-C(2)	120.6(2)	C(17)-C(16)-C(2)	120.7(2)
C(3)-C(4)-C(5)	114.1(2)	C(21)-C(16)-C(2)	121.5(2)
C(4)-C(5)-C(1)	102.91(19)	C(16)-C(17)-C(18)	121.4(2)
O(7)-S(6)-O(8)	117.90(9)	C(19)-C(18)-C(17)	119.9(2)
O(7)-S(6)-C(9)	108.57(10)	C(20)-C(19)-C(18)	119.4(2)
O(8)-S(6)-C(9)	109.20(10)	C(19)-C(20)-C(21)	120.9(3)
O(7)-S(6)-C(1)	109.15(10)	C(20)-C(21)-C(16)	120.6(2)
O(8)-S(6)-C(1)	108.02(10)		
C(9)-S(6)-C(1)	102.96(10)		
C(14)-C(9)-C(10)	120.8(2)		

Crystal data of (*R*)-4-{(1*R*,2*S*,3*S*,5*R*)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-2,2'-oxirane]-3-yl}-4-(*p*-toluenesulfonyl)butan-2-one (**264**) (DC0601)

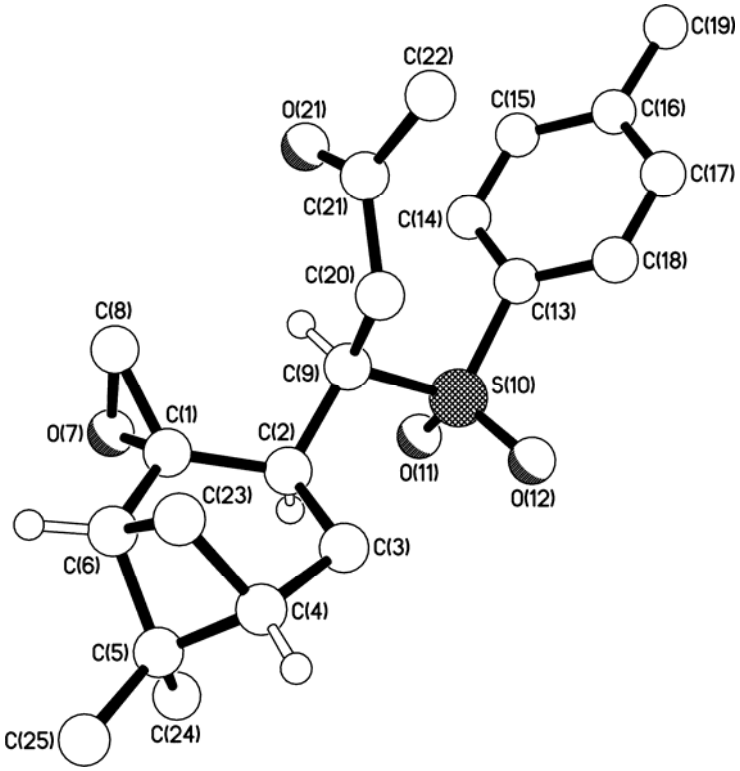


Table 1. Crystal data and structure refinement for DC0601.

Identification code	DC0601	
Empirical formula	C21 H28 O4 S	
Formula weight	376.49	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54248 Å	
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.7996(11) Å	α = 90°
	b = 11.208(2) Å	β = 90°
	c = 20.145(4) Å	γ = 90°
Volume, Z	1986.9(6) $Å^3$, 4	
Density (calculated)	1.259 Mg/m^3	

Absorption coefficient	1.629 mm^{-1}
F(000)	808
Crystal colour / morphology	Colourless tabular needles
Crystal size	0.22 x 0.21 x 0.05 mm^3
θ range for data collection	4.39 to 70.89°
Index ranges	-10<=h<=9, -13<=k<=13, -24<=l<=24
Reflns collected / unique	46494 / 3821 [R(int) = 0.0247]
Reflns observed [F>4σ(F)]	3679
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.07185 and 0.85805
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3821 / 0 / 238
Goodness-of-fit on F^2	1.078
Final R indices [F>4σ(F)]	R1 = 0.0242, wR2 = 0.0681
	R1+ = 0.0242, wR2+ = 0.0681
	R1- = 0.0423, wR2- = 0.1276
R indices (all data)	R1 = 0.0252, wR2 = 0.0686
Absolute structure parameter	x+ = 0.000(10), x- = 1.004(10)
Extinction coefficient	0.00097(15)
Largest diff. peak, hole	0.175, -0.195 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for DC0601.

C(1)-O(7)	1.4503(14)	C(4)-C(23)	1.5509(19)
C(1)-C(8)	1.4675(17)	C(4)-C(5)	1.5606(18)
C(1)-C(6)	1.5061(17)	C(5)-C(24)	1.522(2)
C(1)-C(2)	1.5488(16)	C(5)-C(25)	1.529(2)
C(2)-C(9)	1.5453(16)	C(5)-C(6)	1.5585(18)

C(2)-C(3)	1.5550(17)	C(6)-C(23)	1.5455(17)
C(3)-C(4)	1.5274(19)	O(7)-C(8)	1.4517(15)
C(9)-C(20)	1.5300(17)	C(24)-C(5)-C(25)	108.78(13)
C(9)-S(10)	1.8044(12)	C(24)-C(5)-C(6)	119.53(12)
S(10)-O(12)	1.4427(10)	C(25)-C(5)-C(6)	110.43(12)
S(10)-O(11)	1.4440(10)	C(24)-C(5)-C(4)	120.46(13)
S(10)-C(13)	1.7696(13)	C(25)-C(5)-C(4)	110.60(12)
C(13)-C(18)	1.3900(19)	C(6)-C(5)-C(4)	85.22(10)
C(13)-C(14)	1.3956(18)	C(1)-C(6)-C(23)	105.41(10)
C(14)-C(15)	1.383(2)	C(1)-C(6)-C(5)	113.63(11)
C(15)-C(16)	1.396(2)	C(23)-C(6)-C(5)	87.82(10)
C(16)-C(17)	1.388(2)	C(1)-O(7)-C(8)	60.75(8)
C(16)-C(19)	1.5053(19)	O(7)-C(8)-C(1)	59.58(7)
C(17)-C(18)	1.391(2)	C(20)-C(9)-C(2)	116.46(10)
C(20)-C(21)	1.512(2)	C(20)-C(9)-S(10)	110.38(9)
C(21)-O(21)	1.2079(19)	C(2)-C(9)-S(10)	108.20(8)
C(21)-C(22)	1.499(2)	O(12)-S(10)-O(11)	118.52(6)
O(7)-C(1)-C(8)	59.67(8)	O(12)-S(10)-C(13)	107.71(6)
O(7)-C(1)-C(6)	116.42(10)	O(11)-S(10)-C(13)	108.17(6)
C(8)-C(1)-C(6)	116.74(11)	O(12)-S(10)-C(9)	109.36(6)
O(7)-C(1)-C(2)	112.99(10)	O(11)-S(10)-C(9)	107.02(6)
C(8)-C(1)-C(2)	123.22(11)	C(13)-S(10)-C(9)	105.30(6)
C(6)-C(1)-C(2)	115.34(10)	C(18)-C(13)-C(14)	120.82(12)
C(9)-C(2)-C(1)	112.41(9)	C(18)-C(13)-S(10)	119.20(10)
C(9)-C(2)-C(3)	113.86(10)	C(14)-C(13)-S(10)	119.84(10)
C(1)-C(2)-C(3)	112.25(10)	C(15)-C(14)-C(13)	118.74(12)
C(4)-C(3)-C(2)	113.29(10)	C(14)-C(15)-C(16)	121.81(12)
C(3)-C(4)-C(23)	108.83(11)	C(17)-C(16)-C(15)	118.09(12)

C(3)-C(4)-C(5)	112.34(11)	C(17)-C(16)-C(19)	121.28(14)
C(23)-C(4)-C(5)	87.55(10)	C(15)-C(16)-C(19)	120.59(13)
C(16)-C(17)-C(18)	121.50(13)	O(21)-C(21)-C(20)	122.36(13)
C(13)-C(18)-C(17)	118.97(12)	C(22)-C(21)-C(20)	115.17(13)
C(21)-C(20)-C(9)	114.25(11)	C(6)-C(23)-C(4)	85.99(9)
O(21)-C(21)-C(22)	122.44(14)		

Symmetry transformations used to generate equivalent atoms.

Crystal data of (4*R**,5*S**)-4-benzyl-1-methyl-5-phenyl-4-(*p*-toluenesulfonyl)cyclopent-1-ene (**204b-*c***) (DC0608)

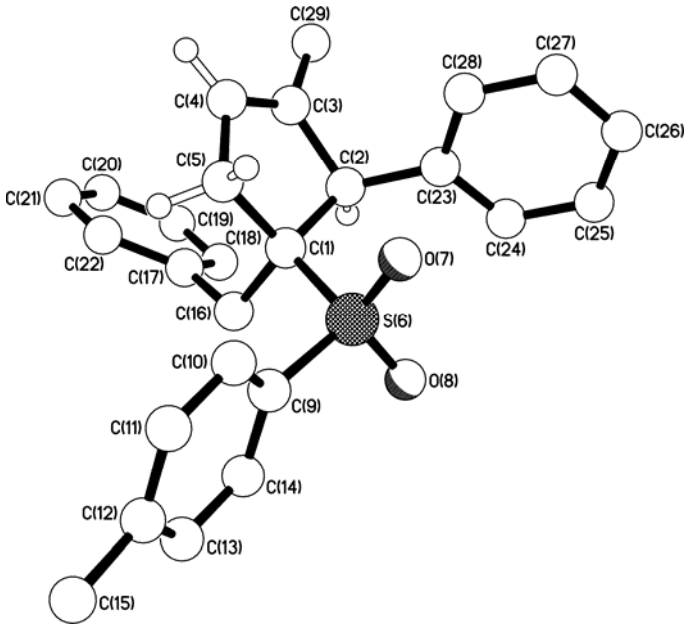


Table 1. Crystal data and structure refinement for DC0608.

Identification code	DC0608	
Empirical formula	C26 H26 O2 S	
Formula weight	402.53	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54248 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 9.653(3) Å	α = 104.40(3)°
	b = 10.727(3) Å	β = 112.96(4)°
	c = 11.580(5) Å	γ = 94.62(3)°
Volume, Z	1048.2(7) $Å^3$, 2	
Density (calculated)	1.275 Mg/m^3	
Absorption coefficient	1.514 mm^{-1}	
F(000)	428	
Crystal colour / morphology	Colourless needles	

Crystal size	0.32 x 0.04 x 0.04 mm^3
θ range for data collection	4.34 to 71.85°
Index ranges	-11<=h<=11, -13<=k<=12, -14<=l<=14
Reflns collected / unique	14432 / 3991 [R(int) = 0.0289]
Reflns observed [F>4σ(F)]	3023
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.86995
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3991 / 0 / 265
Goodness-of-fit on F^2	0.990
Final R indices [F>4σ(F)]	R1 = 0.0327, wR2 = 0.0844
R indices (all data)	R1 = 0.0457, wR2 = 0.0877
Extinction coefficient	0.0013(4)
Largest diff. peak, hole	0.273, -0.303 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for DC0608.

C(1)-C(5)	1.541(2)	C(23)-C(24)	1.387(2)
C(1)-C(16)	1.553(2)	C(23)-C(28)	1.394(2)
C(1)-C(2)	1.5741(19)	C(24)-C(25)	1.378(2)
C(1)-S(6)	1.8175(16)	C(25)-C(26)	1.376(2)
C(2)-C(3)	1.517(2)	C(26)-C(27)	1.377(3)
C(2)-C(23)	1.518(2)	C(27)-C(28)	1.385(2)
C(3)-C(4)	1.317(2)	C(5)-C(1)-C(16)	112.87(13)
C(3)-C(29)	1.496(2)	C(5)-C(1)-C(2)	105.35(12)
C(4)-C(5)	1.501(2)	C(16)-C(1)-C(2)	109.78(12)
S(6)-O(7)	1.4390(12)	C(5)-C(1)-S(6)	109.71(10)
S(6)-O(8)	1.4399(14)	C(16)-C(1)-S(6)	107.00(10)
S(6)-C(9)	1.7725(16)	C(2)-C(1)-S(6)	112.23(10)
C(9)-C(10)	1.385(2)	C(3)-C(2)-C(23)	111.80(12)
C(9)-C(14)	1.389(2)	C(3)-C(2)-C(1)	101.08(12)
C(10)-C(11)	1.385(2)	C(23)-C(2)-C(1)	119.14(12)
C(11)-C(12)	1.392(3)	C(4)-C(3)-C(29)	127.89(15)
C(12)-C(13)	1.385(3)	C(4)-C(3)-C(2)	112.32(14)
C(12)-C(15)	1.503(2)	C(29)-C(3)-C(2)	119.77(14)
C(13)-C(14)	1.378(2)	C(3)-C(4)-C(5)	112.84(14)
C(16)-C(17)	1.511(2)	C(4)-C(5)-C(1)	102.65(12)
C(17)-C(22)	1.388(2)	O(7)-S(6)-O(8)	119.24(8)
C(17)-C(18)	1.389(2)	O(7)-S(6)-C(9)	106.80(7)
C(18)-C(19)	1.406(3)	O(8)-S(6)-C(9)	107.08(8)
C(19)-C(20)	1.368(3)	O(7)-S(6)-C(1)	108.30(7)
C(20)-C(21)	1.369(3)	O(8)-S(6)-C(1)	108.73(7)
C(21)-C(22)	1.378(3)	C(9)-S(6)-C(1)	105.92(8)

C(10)-C(9)-C(14)	120.25(15)	C(17)-C(18)-C(19)	119.6(2)
C(10)-C(9)-S(6)	119.56(12)	C(20)-C(19)-C(18)	120.65(19)
C(14)-C(9)-S(6)	119.98(12)	C(19)-C(20)-C(21)	119.94(18)
C(11)-C(10)-C(9)	119.62(16)	C(20)-C(21)-C(22)	119.9(2)
C(10)-C(11)-C(12)	120.72(16)	C(21)-C(22)-C(17)	121.61(18)
C(13)-C(12)-C(11)	118.62(15)	C(24)-C(23)-C(28)	118.22(14)
C(13)-C(12)-C(15)	120.64(17)	C(24)-C(23)-C(2)	119.44(13)
C(11)-C(12)-C(15)	120.72(17)	C(28)-C(23)-C(2)	122.33(14)
C(14)-C(13)-C(12)	121.34(16)	C(25)-C(24)-C(23)	120.73(15)
C(13)-C(14)-C(9)	119.42(15)	C(26)-C(25)-C(24)	120.72(16)
C(17)-C(16)-C(1)	115.31(12)	C(25)-C(26)-C(27)	119.37(16)
C(22)-C(17)-C(18)	118.24(16)	C(26)-C(27)-C(28)	120.31(16)
C(22)-C(17)-C(16)	121.71(15)	C(27)-C(28)-C(23)	120.63(15)
C(18)-C(17)-C(16)	120.03(16)		