Rhodium-Catalysed C–H and C–C Bond Activation towards the Formation of Medium-Sized Rings

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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October 2011

UNIVERSITY OF LIVERPOOL

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Abstract

Rhodium-catalysed hydroacylation is an elegant methodology which affords ketones in an atom-economical fashion. In this manuscript, the rhodium-catalysed intramolecular hydroacylation of aldehyde-tethered alkylidenecyclopropanes, alkylidenecyclobutanes or alkylideneazetidines is described. This rearrangement which includes a first step of carbon–hydrogen bond activation, a hydrometallation step followed by a ring enlargement and a final reductive elimination of the metal catalyst, leads to the formation of cycloheptenones and cyclooctenones in good to excellent yield.

In chapter 1, an overview of the literature on rhodium-catalysed hydroacylation is described. In chapter 2, our efforts to optimise the catalytic conditions and build the scope of 7-membered rings are reported while chapter 3 outlines the results of the mechanistic investigations carried out with aldehyde-tethered alkylidenecyclopropanes. The formation of 8-membered rings is described in chapter 4 and chapter 5 is devoted to the study on the regioselectivity of the ring opening of cyclobutane moieties.

Acknowledgements

I would like to begin by thanking my advisor Doctor Christophe Aïssa who gives me the opportunity to carry out my thesis in his group. Christophe's help, guidance and enthusiasm for chemistry contribute to a great part of my scientific development.

I would like to thank Professor Joe Harrity and Doctor Andrew Carnell who accepted to judge my thesis.

I am also thankful to the analytical services and particularly Doctor John Bacsa for the X-ray analysis.

I am grateful to all the members of the Aïssa's group, both past and present, especially to James Davick, Coralie Tugny and James Murray who have been directly involved in the work presented in this thesis. I am also thankful to the Evan's group members. Special thanks go to Ryan, Sam and Sergio with whom I spent these 4 years in and outside the lab.

I would like to thank Kate, Rachel and Sean. I had a really good time with all of you outside the lab and I have been very lucky to meet you. I am also thankful to my friends stayed in France, especially to David, Amandine, Anne-Catherine, Vanessa and Rémi.

Finally, I am very grateful to my parents, sister and brother who have provided constant support during these 4 years. I could not have completed my PhD without

them. *Je suis également extrêmement reconnaissant envers mes parents, ma sœur et mon frère qui m'ont continuellement apporté leur soutien pendant ces 4 années et sans qui je n'aurais pu finir ma thèse.*

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List of Abbreviations

$\tilde{\nu}$	Wavenumber
δ	Chemical shift
°C	Degree Celsius
1,2-DCE	1,2-dichloroethane
2D	2-dimensional
4Å MS	4 Angstrom molecular sieves
acac	Acetylacetonate
Ar	Aryl
Binap	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	Benzyl
br	Broad
calcd	Calculated
Chiraphos	2,3-bis(diphenylphosphino)butane
CI	Chemical ionisation
cod	Cyclooctadiene
coe	Cyclooctene
COSY	Correlation spectroscopy
d	Doublet
dba	Dibenzylidene
DEAD	Diethyl azodicarboxylate
DiBAl-H	Diisobutylaluminum hydride
Diop	[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis(diphenylphosphine)
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMBinap	2,2′-Bis[di(3,5-xylyl)phoshino]-1,1′-binaphthyl
DMF	*N*,*N*-dimethylformamide
DMS	Dimethyl sulfide
DMSegphos	[(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-dimethylphenyl)phosphine]
DMSO	Dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
d.r.	Diastereomeric ratio
DTBMSegphos	[(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine]
E	Entgegen
ee	Enantiomeric excess
eq	Equivalent
ES	Electrospray
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
GC	Gas chromatography

h	Hour
H_8Binap	[5,5′,6,6′,7,7′,8,8′-octahydro-(1,1′-binaphthalene)-2,2′-diyl]bis(diphenylphosphine)
HMBC	Heteronuclear multiple bond coherence
HRMS	High resolution mass spectroscopy
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
iPrDuphos	2,2′,5,5′-tetraisopropyl-1,1′-(o-phenylene)diphospholane
IR	Infrared
J	Coupling constant
JonhPhos	(2-Biphenylyl)di-*tert*-butylphosphine
LDA	Lithium diisopropylamide
m	Multiplet
M	Molar
m.p.	Melting point
*m*CPBA	3-chloroperbenzoic acid
MeDuphos	2,2′,5,5′-tetramethyl-1,1′-(o-phenylene)diphospholane
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mmol	Millimole
mol	Mole
MS	Mass spectroscopy
NaHMDS	Sodium bis(trimethylsilyl)amide
nbd	Norbornadiene
NMO	4-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
PDC	Pyridinium dichromate
PE	Petroleum ether (40:60)
Ph	Phenyl
Piv	Pivaloyl
ppm	Part per million
PT	1-phenyl-1*H*-tetrazole
q	Quadruplet
QuinoxP*	2,3-bis(*tert*-butylmethylphosphino)quinoxaline
quint	Quintuplet
r.t.	Room temperature
rac	Racemic
rel.	Relative
s	Singlet
Segphos	[(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis(diphenylphosphine)
T	Temperature
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBinap	2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TBS	*Tert*-butyldimethylsilyl
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TPAP	Tetrapropylammonium perruthenate
Ts	Tosylate
Tunephos	(6,6`-O-(1,3-propylene)-oxylbiphenyl-2,2`-diyl)bis(diphenyl)phosphine
Z	Zusammen

Chapter 1

Rhodium-Catalysed Hydroacylation

Atom-economical methods to form carbon–carbon (C–C) bonds are currently the subject of intense investigations. Among them, transition-metal catalysed carbon–hydrogen (C–H) and C–C bond activation have become a powerful approach used for the formation of elaborated molecules.[1] Hydroacylation belongs to this group of reactions. This reaction involves the activation of the C–H bond of an aldehyde by a transition metal followed by the insertion of an alkene or an alkyne into the newly formed metal–hydrogen (M–H) bond, affording ketones after reductive elimination of the metal (Figure 1.1). Both intermolecular and intramolecular hydroacylation have been reported and recently reviewed by Willis;[2] most examples being catalysed by rhodium complexes. However, examples of ruthenium,[3] nickel,[4] iridium[5] and cobalt-catalysed[6] hydroacylation have also been described.

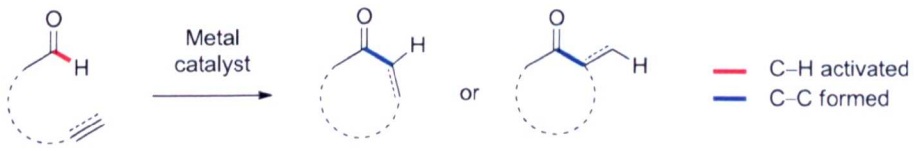


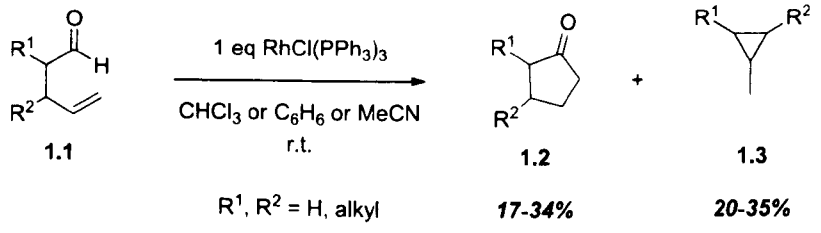
Figure 1.1: Rhodium-catalysed intramolecular or intermolecular hydroacylation

1 – Rhodium-catalysed hydroacylation of alkenes

1 – 1 – Intramolecular hydroacylation

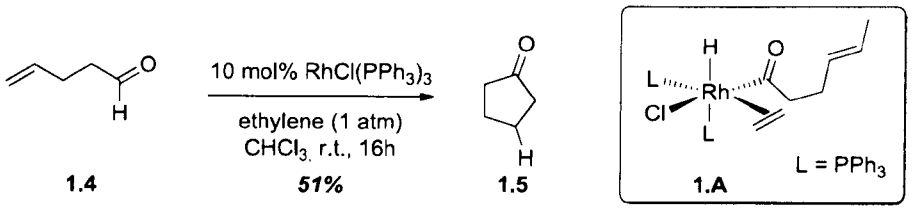
1 – 1 – a – First developments in rhodium-catalysed intramolecular hydroacylation

Early reports on rhodium-catalysed decarbonylation of cinnamaldehyde described by Tsuji[7] prompted Sakai to treat 4-pentenals **1.1** with stoichiometric amounts of Wilkinson's catalyst (Scheme 1.1).[8] Under these conditions, cyclopentanones **1.2** were obtained in 17-34% yield, hence constituting the first examples of intramolecular hydroacylation. Besides obtaining cyclopentanones **1.2**, cyclopropanes **1.3**, resulting from a decarbonylation processus, were also obtained in similar yields.



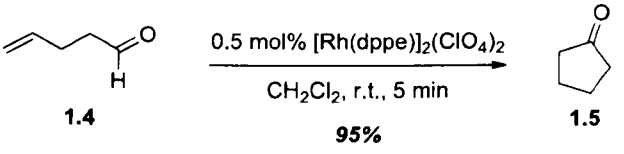
Scheme 1.1: First example of hydroacylation mediated by stoichiometric amount of Wilkinson catalyst

Miller reported the first catalytic version of rhodium-catalysed intramolecular hydroacylation of 4-pentenal (Scheme 1.2).[9] Exposure of 4-pentenal **1.4** to 10 mol% of $RhCl(PPh_3)_3$ in benzene saturated with ethylene afforded cyclopentanone **1.5** in 51% yield. Importantly, while building the scope of the reaction, Larock also found that the use of ethylene increases the rate and yield of the reaction.[10] The authors put forward the hypothesis that ethylene would coordinate to the metal centre. Hence, the formation of saturated rhodium complex **1.A** would prevent the decarbonylation.



Scheme 1.2: First example of rhodium-catalysed intramolecular hydroacylation

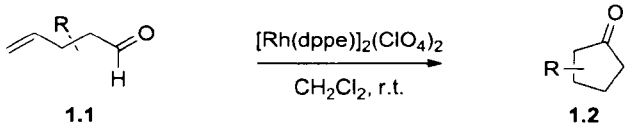
A major breakthrough in rhodium-catalysed intramolecular hydroacylation of 4-pentenals was achieved by Bosnich.[11,12] Increase of the rate of the reaction and yield of cyclopentanone **1.5** were obtained when cationic complex $[Rh(dppe)]_2(ClO_4)_2$ was used as catalyst (Scheme 1.3). Using only 1 mol% of rhodium catalyst, full conversion of 4-pentenal **1.4** was obtained within 5 minutes at room temperature. Under these conditions cyclopentanone **1.5** was obtained in 95% yield. Two side products, 3-pentenal and butene, were also obtained in 4% and 0.7% yield, respectively.



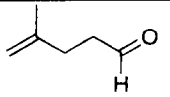
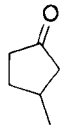
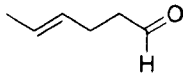
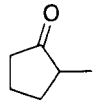
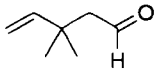
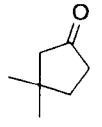
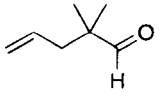
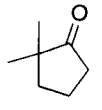
Scheme 1.3: First example of cationic rhodium complex catalysed intramolecular hydroacylation

In weakly coordinating dichloromethane, the cyclisation proceeded smoothly (Table 1.1). 4- and 5-monosubstituted 4-pentenals (entries 1 and 2) afforded the corresponding cyclopentanones in excellent yield. Interestingly, 3,3-dimethyl-4-pentenal (entry 3) was quantitatively rearranged into 3,3-dimethylcyclopentanone whereas 2,2-dimethyl-4-pentenal (entry 4) gave 2,2-dimethylcyclopentanone in poor yield. Instead, isomerisation of the C–C double bond was observed and 2,2-dimethyl-3-pentenal was obtained in 66% yield.

Table 1.1: Selected examples of 4-pentenals rearranged into their corresponding cyclopentanones by cationic rhodium catalyst



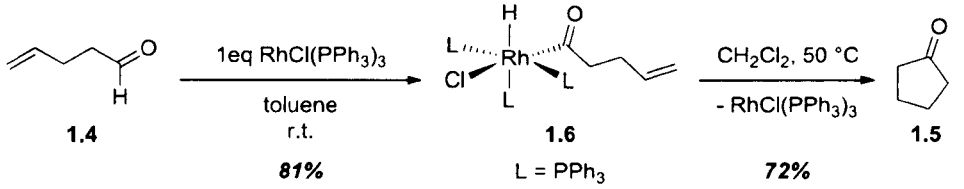
1.1 1.2

Entry	Aldehyde	Cyclopentanone	Loading (mol%)	GC Yield
1			0.5	98%
2			2	79%
3			0.5	100%
4			3.5	23%[a]

[a]: 17% of starting material and 66% of 3-pentenals were recovered

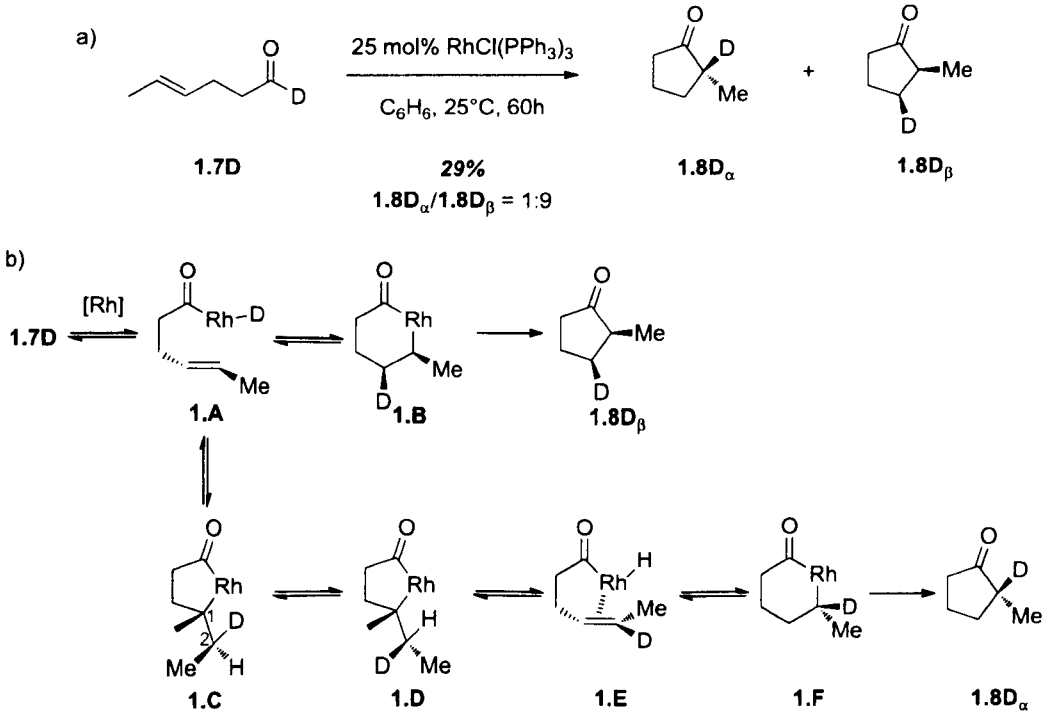
1 – 1 – b – Mechanistic considerations

The first mechanistic study of intramolecular hydroacylation was reported by Milstein (Scheme 1.4).[13] Treating 4-pentenal **1.4** with one equivalent of Wilkinson's catalyst in toluene at room temperature resulted in the isolation of stable complex **1.6** in 81% yield. Moreover, heating **1.6** in dichloromethane led to cyclopentanone **1.5** in 72% yield. This result confirmed that the rhodium catalyst oxidatively inserts into the C–H bond of the aldehyde moiety and that hydrido acylrhodium species such as **1.6** are intermediates in intramolecular hydroacylation.



Scheme 1.4: Isolation of acyl rhodium hydride 1.6 and its rearrangement into cyclopentanone **1.5**

Miller investigated the mechanism by using deuterium-labelled *trans*-4-hexenal (Scheme 1.5a).[9b] Scrambling of the deuterium atom was observed when 4-hexenal **1.7D** was exposed to 25 mol% of Wilkinson's catalyst. After 60 hours at room temperature cyclopentanones **1.8D$_\alpha$** and **1.8D$_\beta$** were obtained in 29% yield in a 1:9 ratio and 48% of starting material was also recovered. Moreover a complex mixture of decarbonylation products was also obtained in 18% yield.

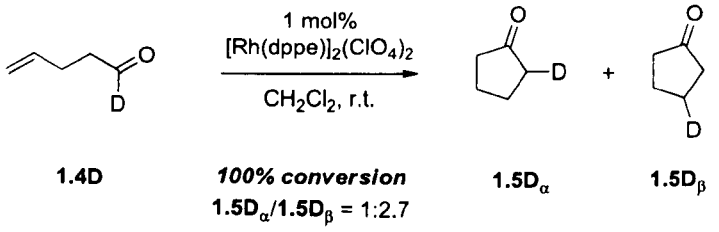


Scheme 1.5: a) Scrambling of the deuterium atom; b) Proposed mechanism accounting for the formation of **1.8Dα** and **1.8Dβ**

In scheme 1.5b, the proposed pathways accounting for the formation of **1.8D$_\alpha$** and **1.8D$_\beta$** are described. Oxidative insertion of the rhodium into the C–D bond of the aldehyde group would afford **1.A**. Then both hexarhodacycle **1.B** and

pentarhodacycle **1.C** would be formed via *syn*-hydrometallation of the C–C double bond. **1.B** would undergo reductive elimination towards **1.8D$_\beta$**, whereas conformational rearrangement of **1.C** (*i.e.* rotation around the C_1–C_2 bond) would give **1.D**. *Syn*-β-hydride elimination would afford **1.E** which would be prone to undergo *syn*-hydrometallation and give **1.F**. Reductive elimination of the metal would give **1.8D$_\alpha$**.

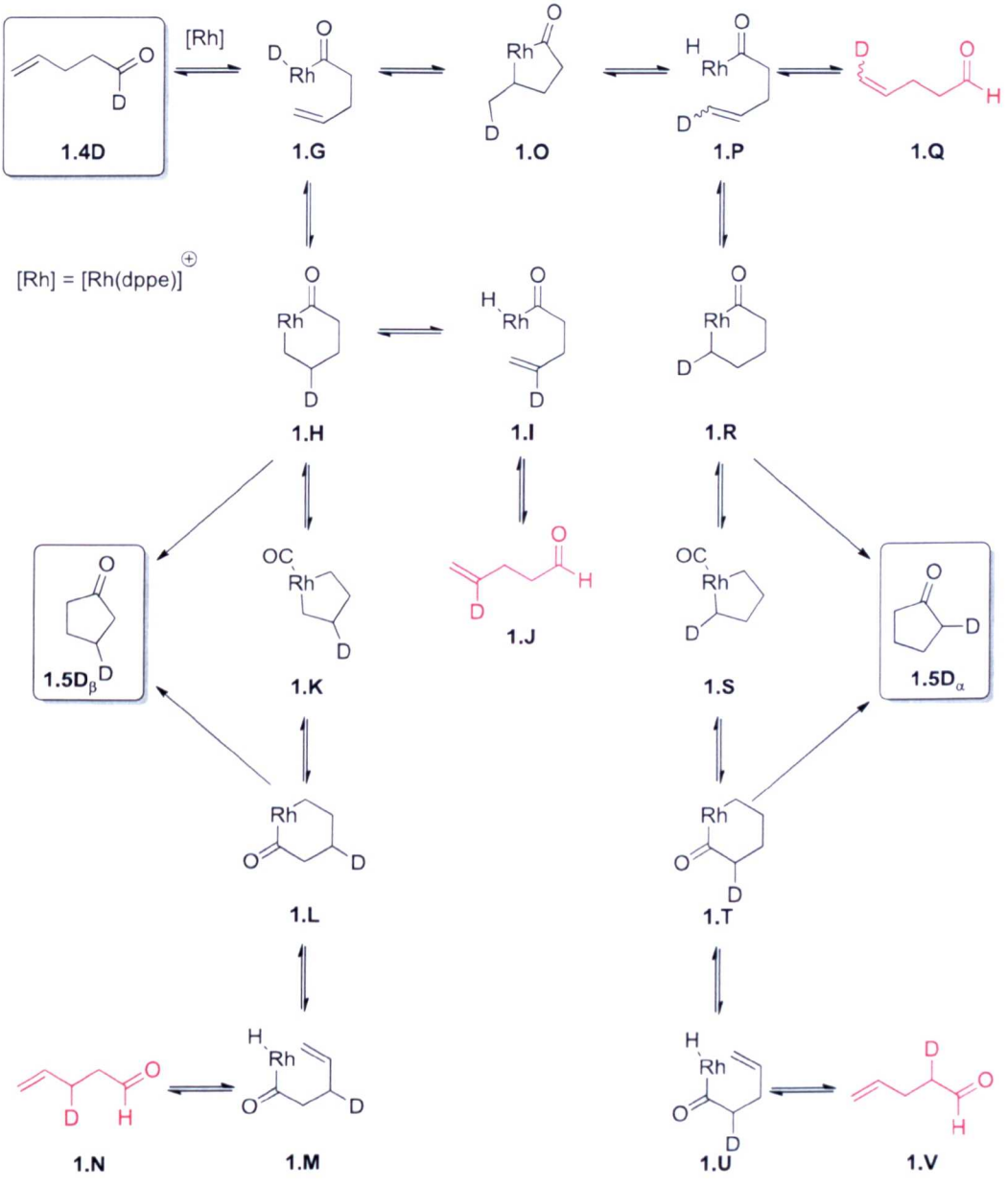
Bosnich also investigated the reaction mechanism by exposing deuterium-labelled 4-pentenal **1.4D** to cationic rhodium complex $[Rh(dppe)]_2(ClO_4)_2$ (Scheme 1.6).[11,12] Scrambling of the deuterium atom was also observed and cyclopentanones **1.5D$_\alpha$** and **1.5D$_\beta$** were isolated. Moreover, monitoring the conversion of **1.4D** by ^1H NMR also revealed a complete scrambling of the deuterium atom on all carbon atoms of 4-pentenal during the course of the reaction. Hence, intermediates **1.J**, **1.N**, **1.Q**, **1.V** were identified before the reaction reached completion (Scheme 1.7).



Scheme 1.6: Scrambling of the deuterium atom observed during cationic rhodium-catalysed intramolecular hydroacylation of **1.4D**

Taking into account of these observations, Bosnich proposed the mechanism depicted in scheme 1.7. Aldehyde **1.4D** would undergo oxidative addition, leading to **1.G**. Hydrometallation of the alkene would afford both rhodacycles **1.H** and **1.O**. Hexarhodacycle **1.H** would either undergo reductive elimination towards **1.5D$_\beta$**, β-hydride elimination towards **1.I**, or carbon monoxide extrusion towards **1.K**. While reductive elimination from **1.I** would explain the transient formation of **1.J**, **1.K** would afford hexarhodacycle **1.L**. Reductive elimination from **1.L** would also give

1.5D$_\beta$. Aldehyde **1.N** would also be formed from **1.L** via intermediate **1.M**, formed by β-hydride elimination.



Scheme 1.7: Proposed mechanism for the cationic rhodium-catalysed intramolecular hydroacylation of 4-pentenal **1.4D**

Pentarhodacycle **1.O** would undergo β-hydride elimination, leading to **1.P**. Reductive elimination would afford **1.Q** but **1.P** would also be prone to undergo hydrometallation towards **1.R**. Then, reductive elimination affording **1.5D$_\alpha$** would compete with carbon monoxide extrusion leading to **1.S**. Reinsertion of carbon

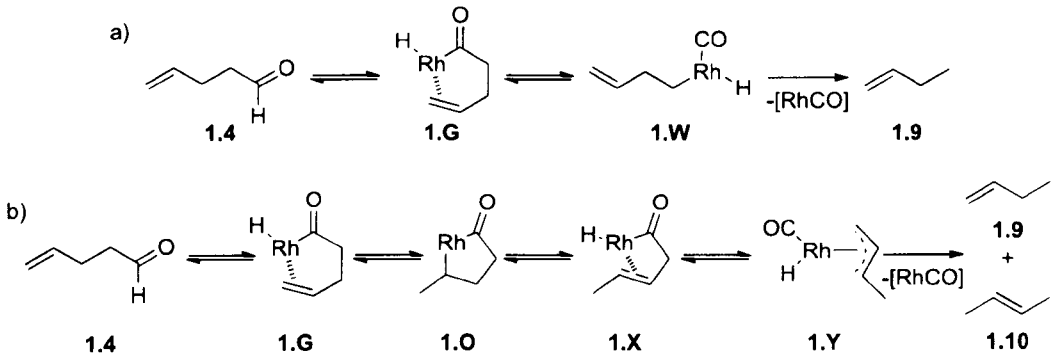
monoxide would afford **1.T**. The latter would undergo reductive elimination, giving **1.5D$_\alpha$**. 4-Pentenal **1.V** would also be formed from **1.T** via the formation of acyl rhodahydride **1.U**. This complex mechanism was described as a 'black box' by the authors who also suggested that there is not a rate determining step. Once the starting material enters the catalytic cycle, none of the intermediates have a concentration sufficiently high enough to be detected at any time. Hence, none of the intermediates could be isolated.

Importantly, the ratio between both cyclopentanones **1.5D$_\beta$** and **1.5D$_\alpha$** varied from 20:1 to 2.7:1 during the reaction which seems to indicate that hexarhodacycle **1.H** would be formed faster pentarhodacycle **1.O**. However, at low conversion, the sum of products **1.5Dα**, **1.Q** and **1.V** is slighty higher as compared to the sum of products **1.5Dβ**, **1.J** and **1.N** indicating that pentarhodacycle **1.O** is actually formed faster than hexarhodacycle **1.H**.

Recent theoretical studies on intramolecular hydroacylation of 4-pentenal catalysed by $[Rh(dppe)]^+$ were published by Sargent.[14] The calculations revealed that two different hydrido acylrhodium species **1.G** gives hexarhodacycle **1.H** and pentarhodacycle **1.O**, respectively. In acetone, the energy barrier associated with the oxidative addition step is almost the same in both cases ($\Delta\Delta G^{\neq}$ = 0.2 kcal.mol^{-1}). However, the resulting hydrido acylrhodium intermediate which leads to hexarhodacycle **1.H** is stabilised by 2.3 kcal.mol^{-1} as compared to the one which leads to pentarhodacycle **1.O**. The energy barrier associated to the alkene insertion step is also similar ($\Delta\Delta G^{\neq}$ = 0.1 kcal.mol^{-1}) and both hexarhodacycle **1.H** and pentarhodacycle **1.O** have similar energy levels (–0.8 and –0.6 kcal.mol^{-1},

respectively). Hence, these calculations indicate that the formations of hexarhodacycle **1.H** and pentarhodacycle **1.O** are reversible processes.

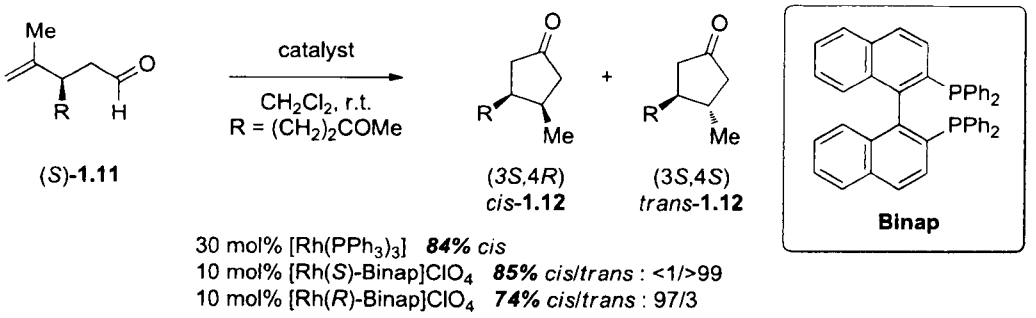
Importantly, while Bosnich suggested that **1.W** is a key intermediate in the decarbonylation pathway (Scheme 1.8a),[12] the calculations indicated that the energy barrier between **1.G** and **1.W** is too high (+40.7 kcal.mol^{-1}). Instead the decarbonylation pathway would involve the formation of pentarhodacycle **1.O** (Scheme 1.8b). β-hydride elimination giving **1.X** followed by carbon monoxide extrusion would afford **1.Y**, leading to the formation of butenes **1.9** and **1.10**.



Scheme 1.8: Mechanism of decarbonylation proposed by a) Bosnich; b) Sargent

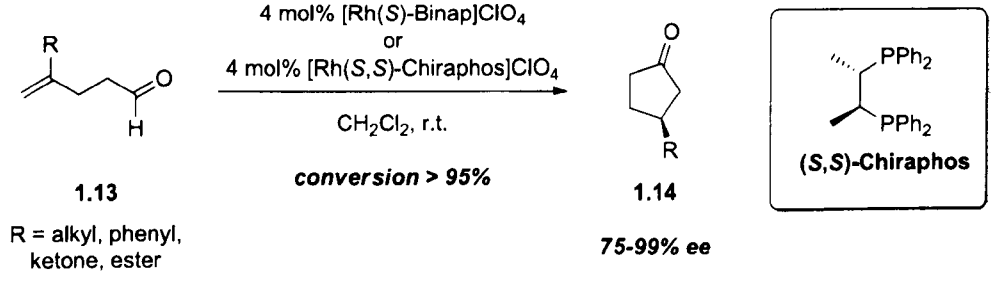
1 – 1 – c – Stereoselective intramolecular hydroacylation

The first example of diastereoselective rhodium-catalysed intramolecular hydroacylation was reported by Sakai.[15] Exposing aldehyde **1.11** to 30 mol% of Wilkinson's catalyst, the authors reported the exclusive formation of racemic cyclopentanone *cis*-**1.12** (Scheme 1.9). Later the same group found that starting from chiral aldehyde (*S*)-**1.11** and chiral cationic rhodium complex allowed for the selective formation of *cis*-**1.12** or *trans*-**1.12**.[16] Starting from (*R*)-**1.11** gave the two other diastereoisomers.



Scheme 1.9: Diastereoselective formation of cyclopentanone obtained from (S)-**1.11**

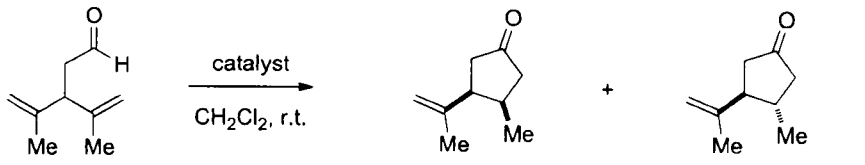
Using chiral rhodium complex, James and Young reported the kinetic resolution of 2-methyl-2-phenyl-4-pentenal.[17] Despite the low yield of cyclopentanone (17%), the enantiomeric excess reached 69%. Sakai[16b] and later Bosnich [18] described the enantioselective rearrangement of 4-substituted 4-pentenals **1.13** (Scheme 1.10). Using [Rh(*S*)-Binap]ClO_4 or [Rh(*S,S*)-Chiraphos]ClO_4, cyclopentanones **1.14** were obtained with high enantiomeric excess.



Scheme 1.10: Enantioselective intramolecular hydroacylation

More recently, Morehead also described the formation of chiral 3-substituted indanones via intramolecular hydroacylation of 2-formyl styrenes.[19]

The enantioselective desymmetrisation of prochiral aldehyde **1.15** was reported by Sakai, Suemune and Tanaka (Scheme 1.11).[20] Treating **1.15** with cationic rhodium complex led to the formation of the *trans*-cyclopentanone **1.16** with excellent enantioselectivity.

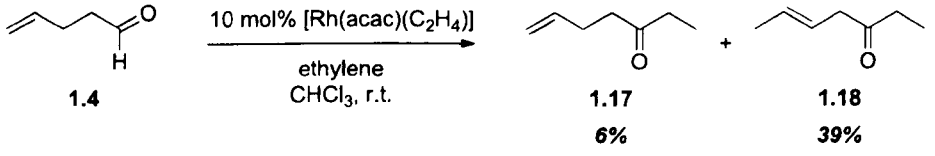


5 mol% [Rh(*S*)-Binap]ClO_4, ***84%***, *cis*/*trans* : 4/96, ***>95% ee*** (3*R*, 4*R*)
5 mol% [Rh(*R*)-Binap]ClO_4, ***81%***, *cis*/*trans* : 3/97, ***>95% ee*** (3*S*, 4*S*)

Scheme 1.11: Enantioselective desymmetrisation of prochiral aldehyde **1.15**

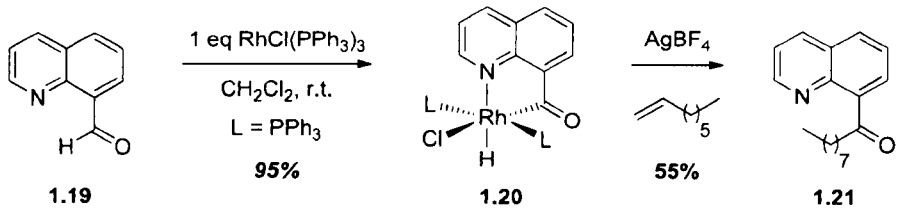
1 – 2 – Intermolecular hydroacylation

Rhodium-catalysed intermolecular hydroacylation is a challenging reaction, suffering from decarbonylation process. However, decarbonylation can be circumvented if a saturated rhodium complex is used. This can be achieved by addition of ethylene or by coordination of the lone pair of an heteroatom to the metal centre. Hence, Miller reported the first example of intermolecular hydroacylation.[21] While studying the intramolecular hydroacylation of 4-pentenal **1.4** with [Rh(acac)$(C_2H_4)_2$] in ethylene-saturated chloroform, Miller obtained aliphatic ketones **1.17** and **1.18** in 6% and 39% yield respectively (Scheme 1.12).



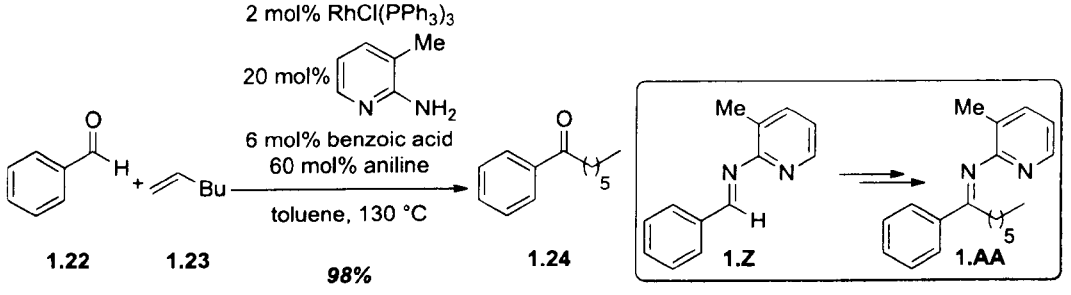
Scheme 1.12: First example of rhodium-catalysed intermolecular hydroacylation

Prior to this result, Suggs first isolated acyl rhodahydride complex **1.20** when 8-quinolinecarboxaldehyde **1.19** was treated with one equivalent of Wilkinson's catalyst (Scheme 1.13).[22] The author later reported that exposure of **1.20** to silver salt and 1-octene gave ketone **1.21**.[23]



Scheme 1.13: Isolation of acyl rhodahydride complex **1.21** and its rearrangement into ketone **1.21**

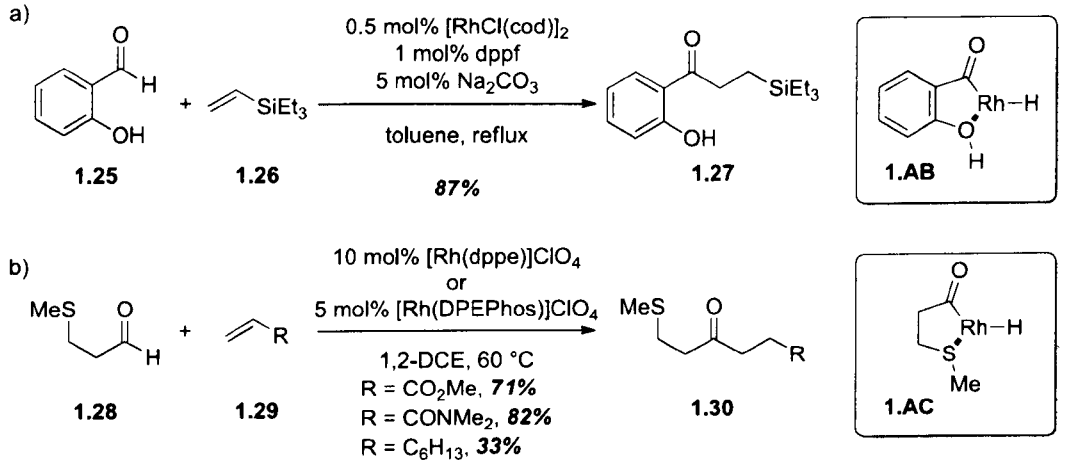
Jun took advantage of this chelation-strategy by generating in situ picolyl imime intermediate **1.Z** from benzaldehyde **1.22** and 2-amino-β-picoline (Scheme 1.14).[24] Benzoic acid would catalyse the formation of imine **1.Z**, whereas aniline would promote the hydrolysis of **1.AA** into **1.24**.



Scheme 1.14: Rhodium-catalysed intermolecular hydroacylation of aldimine **1.Z**

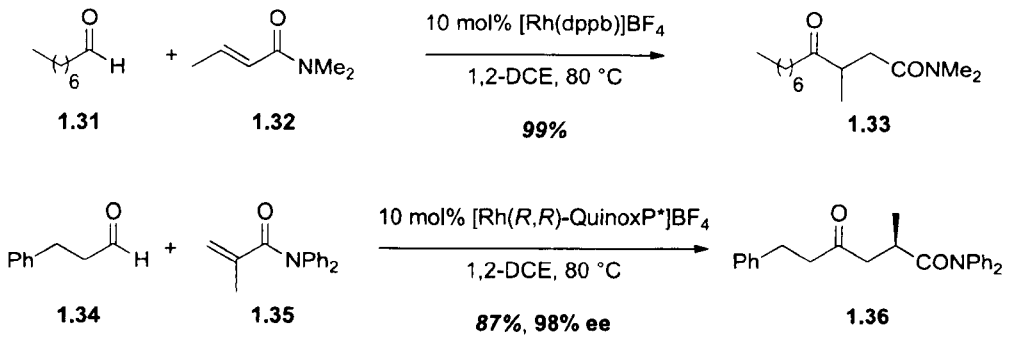
Miura reported the synthesis of linear ketone **1.27** via intermolecular hydroacylation of salicylaldehyde **1.25** (Scheme 1.15a).[25] The authors found that this methodology was limited to the use of vinylsilane **1.26**, other alkenes affording poor yield of ketone. Later Suemune and Tanaka developed the intermolecular hydroacylation between salicylaldehyde **1.25** and 1,4- or 1,5-dienes using Wilkinson's catalyst.[26] Dong and co-workers also reported the intermolecular hydroacylation of salicaldehyde **1.25**. The authors demonstrated that homoallylic sulfides [27] or cyclopropene[28] can both be used as olefin. The authors proposed the formation of complex **1.AB** in which the oxygen coordinates the metal centre. This coordination is believed to prevent decarbonylation, by generating a saturated rhodium complex.

The Willis group reported the rhodium-catalysed intermolecular hydroacylation of sulfur derivative **1.28** and electron-poor alkenes **1.29** (Scheme 1.15b).[29] In the case of a simple alkene (R = C_6H_{13}), the yield of ketone **1.30** was considerably decreased. Using aldehyde **1.28**, the same group also described the rhodium-catalysed intermolecular hydroacylation of allenes.[30] Willis also suggested that complex **1.AC** would be formed and would prevent side reactions.



Scheme 1.15: Rhodium-catalysed intermolecular hydroacylation of a) Salicylaldehyde **1.25**; b) β-S-substituted aldehyde **1.28**

Similarly, Tanaka and co-workers reported the intermolecular hydroacylation between acrylamides and simple aromatic or aliphatic aldehydes.[31] Chelation between the oxygen of the amide and the rhodium would be involved in this rearrangement. For instance, octanal **1.31** and N,N-dimethyl acrylamide **1.32** afforded **1.33** in excellent yield (Scheme 1.16). Tanaka also reported an enantioselective variant using [Rh(*R*,*R*)-QuinoxP*]BF_4. Hence, **1.36** was obtained in excellent yield and enantiomeric excess after reaction of aldehyde **1.34** and amide **1.35**.



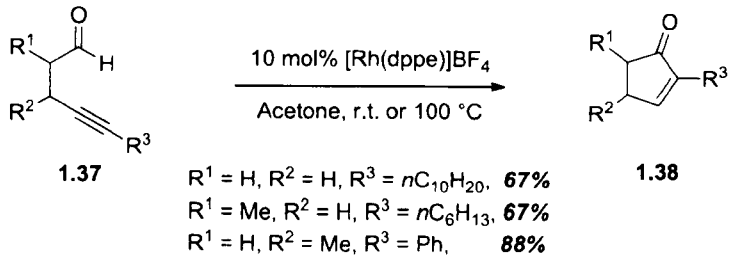
Scheme 1.16: Selected examples of rhodium-catalysed intermolecular hydroacylation of acrylamides

2 – Rhodium-catalysed hydroacylation of alkynes

Rhodium-catalysed hydroacylation of alkynes is a far less studied reaction compared to the hydroacylation of alkenes. However, in the last decade, Fu and Tanaka have made considerable progress in intramolecular hydroacylation of alkynes.

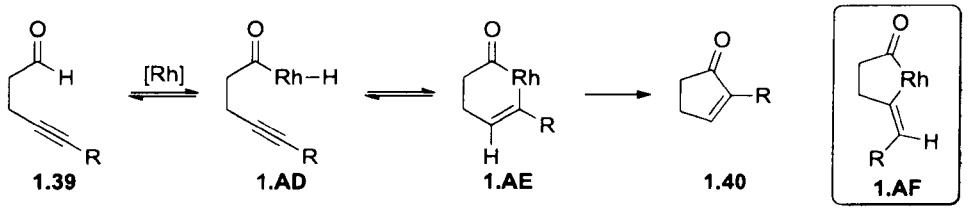
2 – 1 – Intramolecular hydroacylation

Fu and Tanaka developed the intramolecular variant of rhodium-catalysed hydroacylation of alkynes. Exposing alkynes **1.37** to 5 mol% of $[Rh(dppe)]BF_4$ resulted in the formation of cyclopentenone **1.38** in good to excellent yield (Scheme 1.17).[32] Interestingly, a divergence of reactivity was observed when $[Rh(Binap)]BF_4$ was used instead of $[Rh(dppe)]BF_4$, leading to 2-formyl-1,3-diene derivatives.[33]



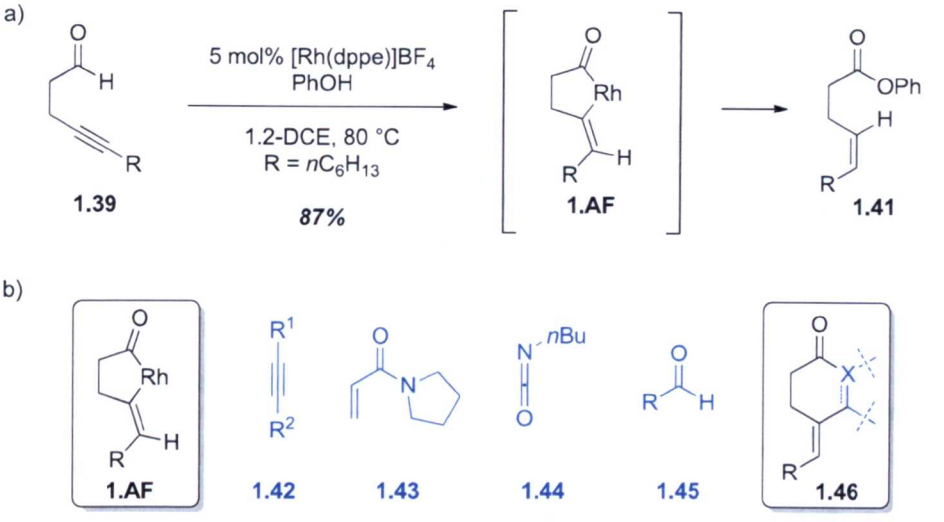
Scheme 1.17: First example of intramolecular hydroacylation of alkynes

The authors proposed the mechanism depicted in scheme 1.18. Oxidative addition of the rhodium would give acyl rhodahydride **1.AD**. *Trans*-addition of the alkyne into the Rh–H bond would then afford hexarhodacycle **1.AE** which would undergo reductive elimination towards cyclopentenone **1.40**.



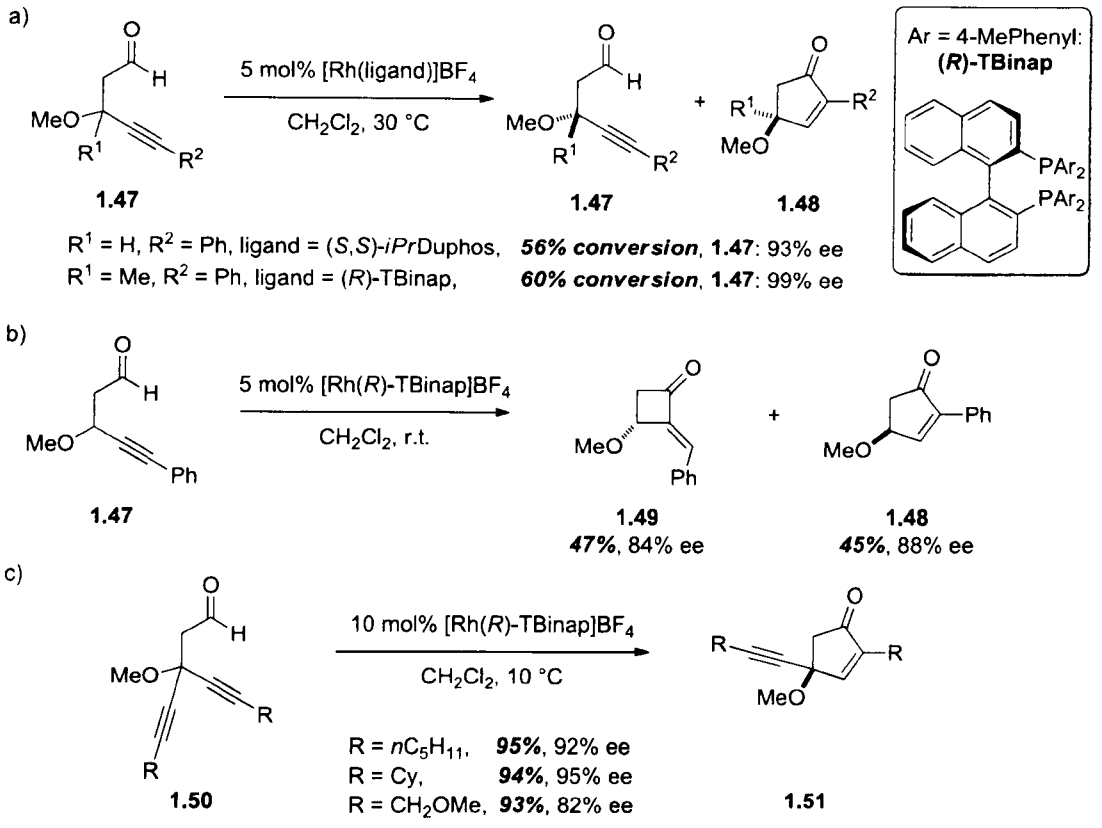
Scheme 1.18: Proposed mechanism for the rearrangement of 4-alkynal **1.47**

The formation of pentarhodacycle **1.AF** from **1.AD** via *cis*-addition of the alkyne into the Rh–H bond was also envisioned. Computational calculations of the reaction later suggested that the formation of pentarhodacycle **1.AF** is kinetically favoured over the formation of hexarhodacycle **1.AE**.[34] The formation of **1.AF** was indirectly demonstrated via its trapping with phenol (Scheme 1.19a).[35] Pentarhodacyle **1.AF** was also used as a four-carbon transient unit in the intermolecular [4+2] cycloaddition with external alkynes **1.42**,[36] acrylamide **1.43**,[37] isocyanate **1.44**[38] and aldehyde **1.45**[39] towards the formation of **1.46** (Scheme 1.19b). Moreover, Tanaka also developed the rhodium-catalysed intramolecular hydroacylation of 6-alkynals enabling the synthesis of cyclohexanones.[40]



Scheme 1.19: a) Trapping of pentarhodacyle **1.AF** with phenol;
b) Intermolecular [4+2] cycloaddition examples

Fu and Tanaka investigated the enantioselective formation of cyclopentenones via kinetic resolution or desymmetrisation of 4-alkynals. In scheme 1.20a, the kinetic resolution of racemic **1.47** is described.[41] For approximately 60% conversion, excellent enantiomeric excesses were obtained for **1.47**. In Scheme 1.20b, the parallel kinetic resolution of racemic **1.47** is depicted.[42] Using [Rh(*R*)-TBinap]BF_4, the two enantiomers of **1.47** gave selectively cyclobutanone **1.49** and cyclopentenone **1.48**, respectively. Finally, Fu and Tanaka reported the desymmetrisation of prochiral bisalkynal **1.50**. Using [Rh(*R*)-TBinap]BF_4, cyclopentenones **1.51** were obtained in excellent yield and selectivity, (Scheme 1.20c).[42]

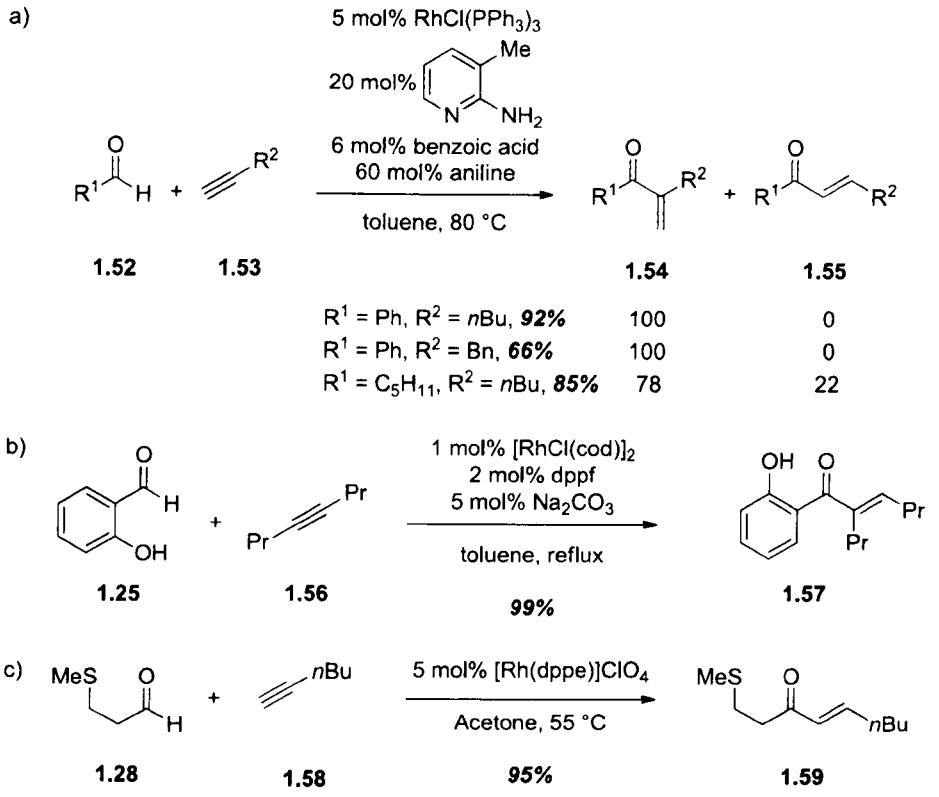


Scheme 1.20: Rhodium-catalysed a) Kinetic resolution of 5-alkynal **1.47**; b) Parallel kinetic resolution of 5-alkynal **1.47**; c) Desymmetrisation of 5-alkynal **1.50**

2 – 2 – Intermolecular hydroacylation

The chelation-assisted methodologies previously described for the hydroacylation of alkenes have also been applied to alkynes. Hence, Jun reported the hydroacylation of picolyl imine (generated in situ by reaction of aldehydes **1.52** and 2-amino-β-picoline) and alkynes **1.53** (Scheme 1.21a).[43] Using Wilkinson's catalyst, branched α,β-insaturated ketones **1.54** were obtained as unique or main isomer over linear ketone **1.55**. Miura obtained aromatic ketone **1.57** in excellent yield when treating salicaldehyde **1.25** and symmetrical alkyne **1.56** with $[RhCl(cod)]_2$ (Scheme 1.21b).[25] While the use of terminal alkynes resulted in a mixture of branched and linear ketones under Miura's conditions, Willis and co-workers found that aldehyde **1.28**

underwent selective intermolecular hydroacylation with alkyne **1.58**, affording linear α,β-insaturated ketone **1.59** in 95% yield (Scheme 1.17c).[29c,44]

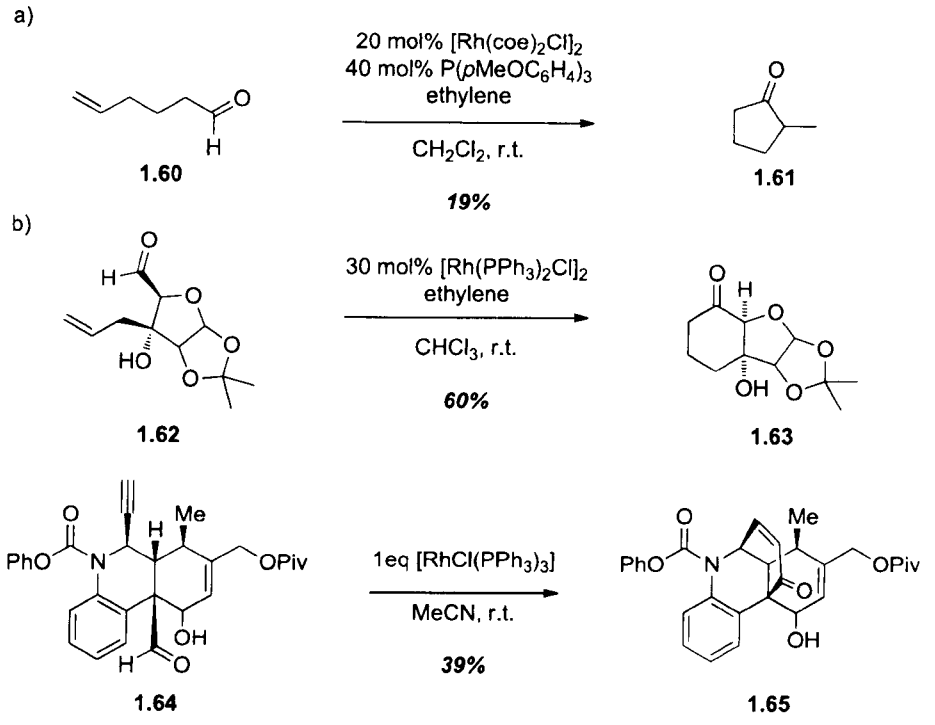


Scheme 1.21: Selected examples of rhodium-catalysed intermolecular hydroacylation of alkynes; a) Jun's methodology; b) Miura's methodology; c) Willis' methodology

3 – Recent developments in rhodium-catalysed intramolecular hydroacylation towards the formation of larger-sized rings

Rhodium-catalysed intramolecular hydroacylation towards the formation of cyclopentanones and cyclopentenones has been intensively investigated. On the other hand, the synthesis of larger-sized rings remains challenging despite the [4+2] strategy developed by Fu and Tanaka which affords cyclohexanones and cyclohexenones.[36,37,38,39] Indeed, Larock reported the low yielding formation of 2-

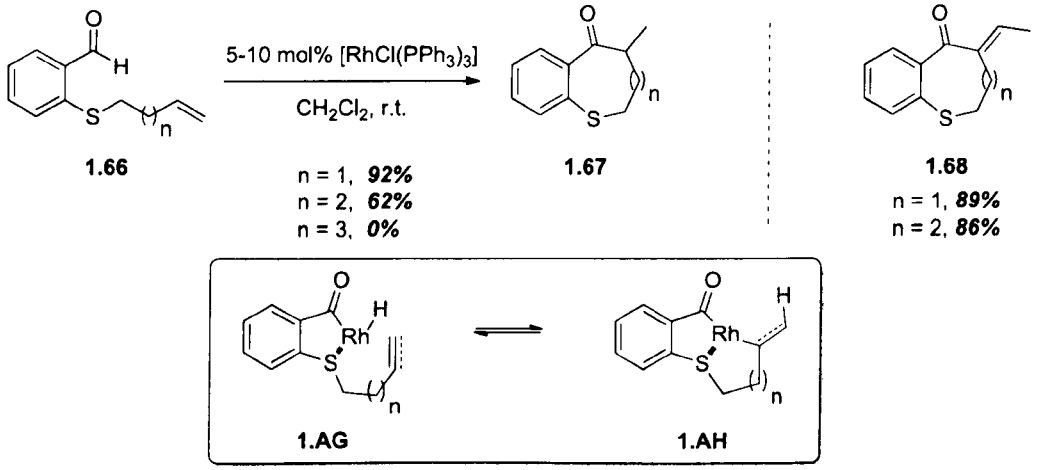
methylcyclopentanone **1.61** when 5-hexenal **1.60** was treated with neutral rhodium complex (Scheme 1.22a).[10]



Scheme 1.22: a) Rearrangement of 5-hexenal **1.60** towards cyclopentanone **1.61**; b) Formation of 6-membered rings from 5-hexenal **1.62** and 5-hexynal **1.64**

Moreover, only two examples of 6-membered rings obtained via hydroacylation of 5-alkenal and 5-alkynal are known (Scheme 1.22b). Gable [45] reported the rearrangement of 5-hexenal **1.62** into cyclohexanone **1.63** while Nicolaou[46] reported the unexpected formation of cyclohexenone **1.65** in an attempt to decarbonylate **1.64** with stoichiometric amount of Wilkinson's catalyst. Nevertheless, during the last decade, several strategies have been developed and successively applied for the synthesis of 7- and 8-membered rings.

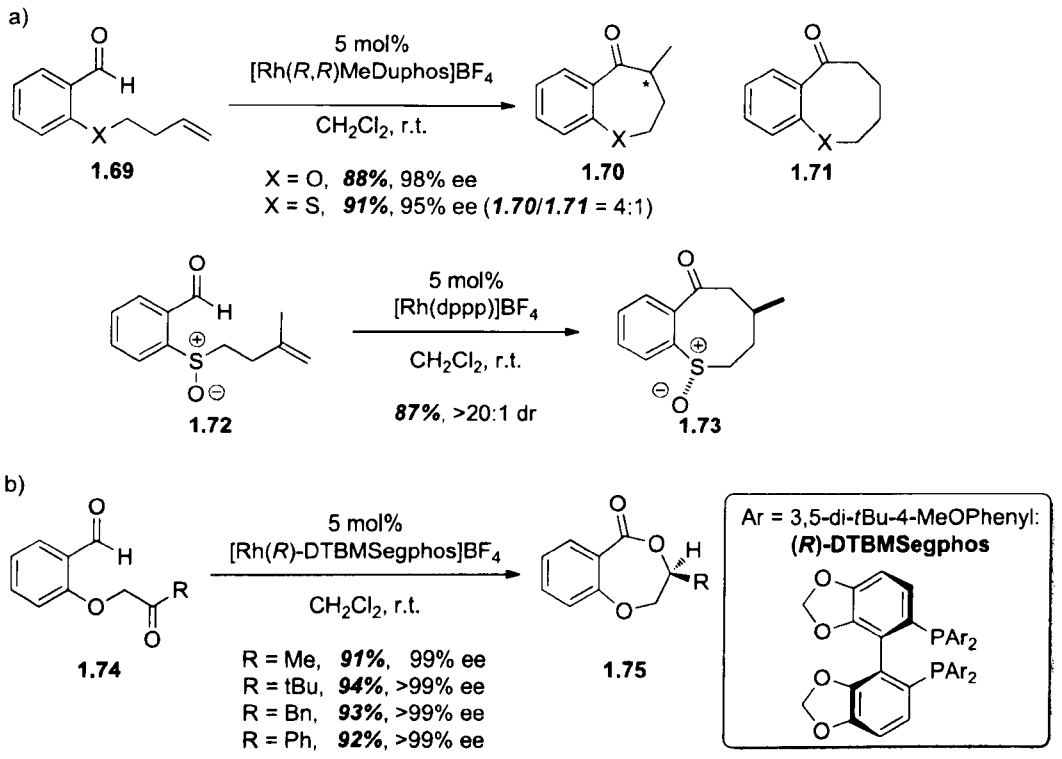
Bendorf reported the formation of 7- and 8-membered rings **1.67** by treating aldehydes **1.66** with Wilkinson's catalyst (Scheme 1.23).[47] The alkene moiety was also replaced with an alkyne, hence affording 7- and 8-membered heterocycles **1.68** in excellent yields. The mechanism proposed by the authors first involves C–H bond activation towards **1.AG**. Chelation of lone pair of the sulfur atom to the rhodium would favour the hydrometallation of the insaturation over decarbonylation. Intermediate **1.AH** would be formed and stabilised by transannular sulfur coordination. Finally, reductive elimination would afford ketones **1.67** or **1.68**. It is noteworthy that substrates in which the sulfur atom was replaced by an oxygen atom or a methylene failed to undergo rearrangement.



Scheme 1.23: Transannular sulfur chelation-assisted intramolecular hydroacylation

Recently, the Dong group was also interested in the chelation-assisted intramolecular hydroacylation and developed an enantioselective and diastereoselective variant (Scheme 1.24).[48] Using a sulfur or oxygen tether and chiral cationic rhodium-complex, 7-membered rings **1.70** were obtained with excellent enantiomeric excesses. Importantly, for X=S, a mixture of 7- and 8-membered rings was obtained in a 4:1

1.70/1.71 ratio. The authors also reported that sulfoxide group can be used as chelating group. Hence, starting form racemic benzaldehyde **1.72**, *trans*-**1.73** was obtained in a 20:1 diastereoisomeric ratio. Finally, Dong and co-workers developed the intramolecular hydroacylation of ketone which gave cyclic lactones **1.75**.[49] For instance, treating aldehydes **1.74** with [Rh(R)-DTBMSegphos]BF_4 led to 7-membered rings **1.75** in excellent yield and enantiomeric excess.

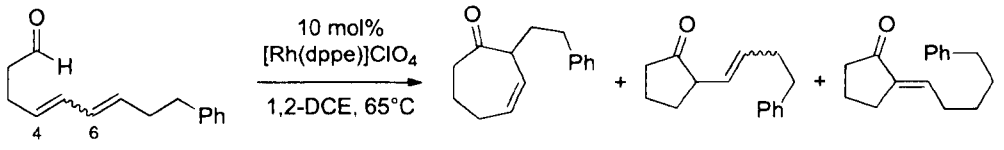


Scheme 1.24: a) Enantioselective and distereoselective variants of the chelation-assisted methodology developped by Dong; b) Intramolecular hydroacylation of ketones.

3 – 2 – Intramolecular hydroacylation of dienals

Mori and co-workers investigated the rhodium-catalysed intramolecular hydroacylation of dienals.[50] Treating aldehyde **1.76** with [Rh(dppe)]ClO_4 resulted in the formation of 7-membered ring **1.77** (Scheme 1.25). Cyclopentanones **1.78** and **1.79** were also obtained. Moreover, the authors found that the geometry of the C–C

double bond at the C_6 position has a great influence on the outcome of the cyclisation. While an *E*-alkene at the C_6 position mainly gave 7-membered ring **1.77**, its *Z*-isomer led to cyclopentanone **1.78** in 49%, starting material (4*E*,6*Z*)-**1.76** being recovered in 38% yield.

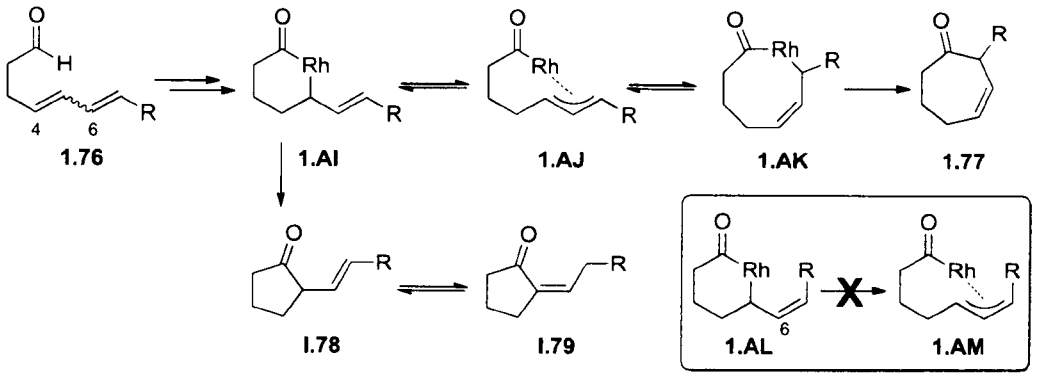


1.76	**1.77**	**1.78**	**1.79**
(4*E*,6*E*)-**1.76**	***62%***	***13%*** (*E*)	***6%***
(4*Z*,6*E*)-**1.76**	***65%***	***11%*** (*E*)	***5%***
(4*E*,6*Z*)-**1.76**	***traces***	***49%*** (*Z*)	***traces***

Scheme 1.25: Rhodium-catalysed intramolecular hydroacylation of dienals

These results were rationalised with the mechanism depicted in scheme 1.26. C–H activation and hydrometallation of the C_4–C_5 double bond would give hexarhodacycle **1.AI** which would be rearranged into octarhodacycle **1.AK** via π-allylrhodium intermediate **1.AJ**. Reductive elimination of the metal would afford cycloheptenone **1.77**. Cyclopentanone **1.78** would result from the reductive elimination of the rhodium from hexarhodacycle **1.AI** and **1.79** would be formed upon double bond migration of **1.78**. Moreover, 1,3-allylic strain[51] generated in *Z* hexarhodacycle **1.AL** would prevent the formation of π-allylrhodium complex **1.AM**, hence explaining the rearrangement **1.AL** in cyclopentanone (*Z*)-**1.78**.

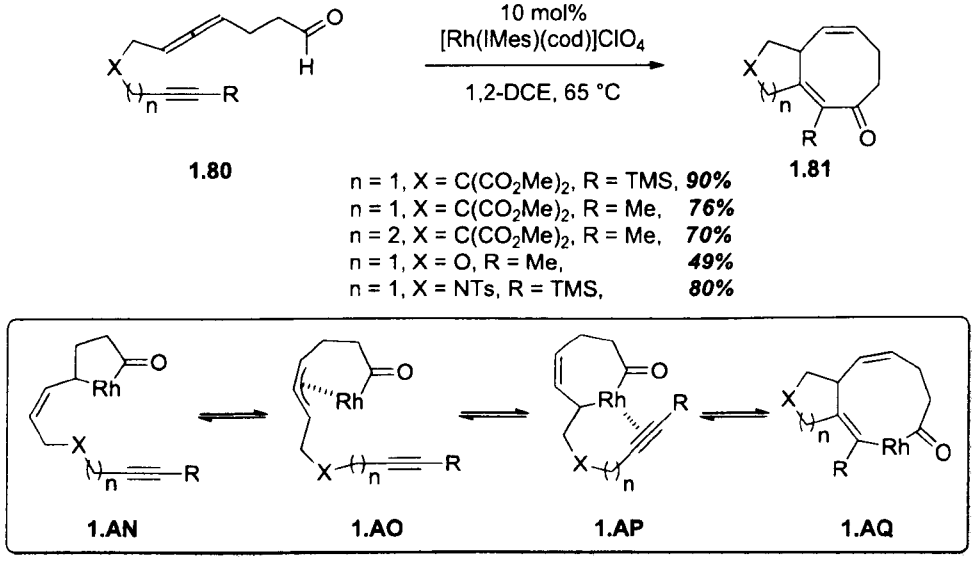
The authors later reported the rhodium-catalysed hydroacylation of 1,3-dienal/cycloisomerisation cascade reaction towards the formation of tricyclic structures.[52]



Scheme 1.26: Proposed mechanism for the rhodium-catalysed hydroacylation of dienals

3 – 3 – Intramolecular hydroacylation of allenes

Recently, Sato reported the first example of rhodium-catalysed intramolecular hydroacylation of allenes within a more complex cycloisomerisation process (Scheme 1.27).[53]



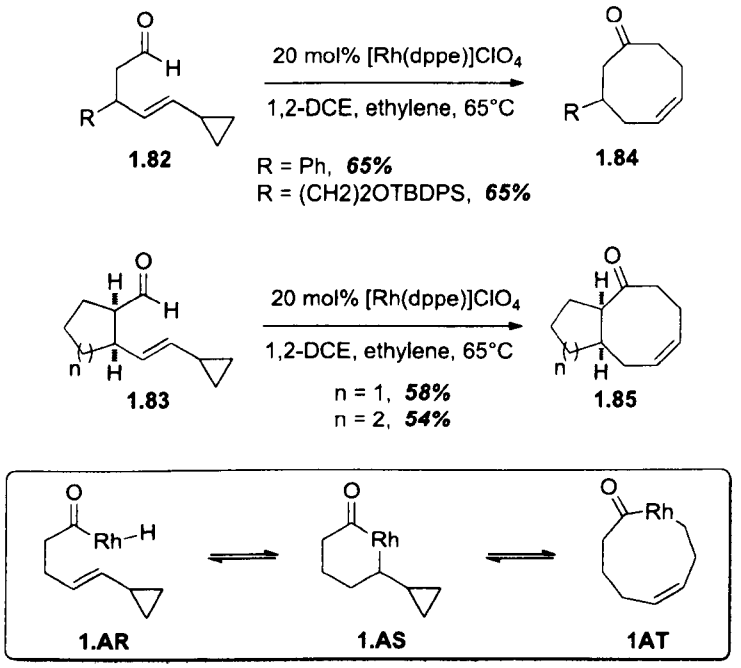
Scheme 1.27: Rhodium-catalysed intramoilecular hydroacylation of allenes

Treating **1.80** with 10 mol% of $[Rh(IMes)(cod)]ClO_4$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene) in 1,2-DCE led to the formation of [5,8]- and [6,8]-fused bicyclic structures **1.81**. Initial oxidative addition of the rhodium catalyst

into the C–H bond of the aldehyde moiety followed by hydrometallation of the allene would afford pentarhodacycle **1.AN**. Heptarhodacycle **1.AP** would be formed via π-allylrhodium complex **1.AO**. Insertion of the alkyne into the Rh–C bond would then afford **1.AQ** and reductive elimination of the metal would lead to **1.81**.

3 – 4 – Intramolecular hydroacylation of vinylcyclopropane

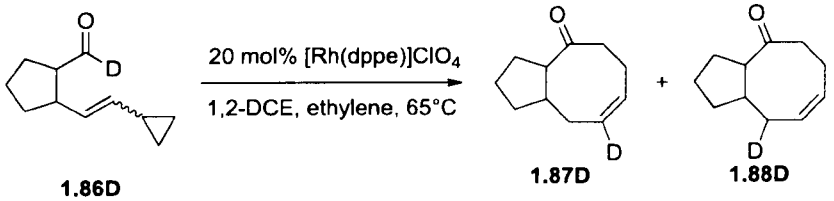
In 2000, Shair described the rhodium-catalysed intramolecular hydroacylation of vinylcyclopropanes.[54] Upon exposure of aldehydes **1.82** and **1.83** to 20 mol% $[Rh(dppe)]ClO_4$ in ethylene-saturated 1,2-DCE, 8-membered rings **1.84** and **1.85** were obtained in good yields (Scheme 1.28).



Scheme 1.28: Rhodium-catalysed intramolecular hydroacylation of vinylcyclopropane

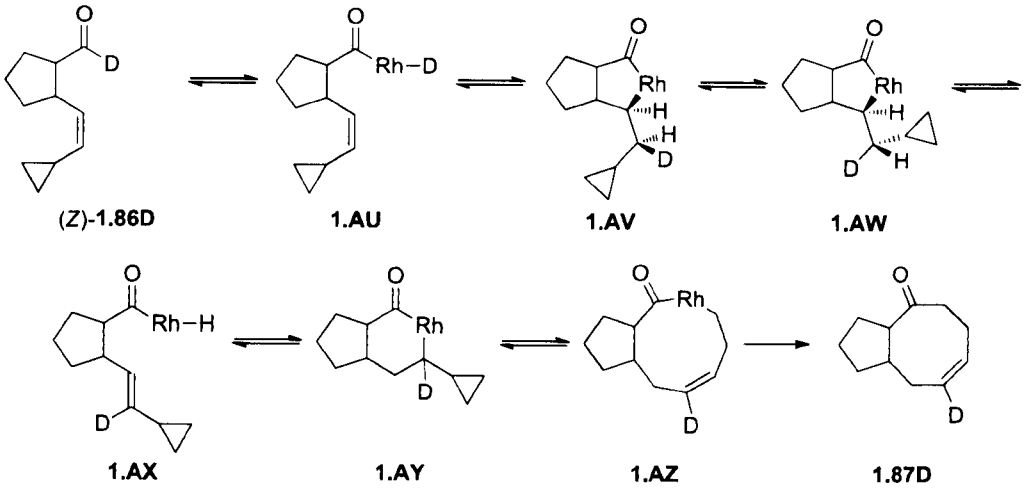
The mechanism would first involve the oxidative addition of the metal; leading to intermediate **1.AR**. Hydrometallation of the C–C double bond would afford

hexarhodacycle **1.AS**. The release of the strain energy of the cyclopropane moiety would be the driving force of the ring enlargement which would afford nonarhodacycle **1.AT**. Finally, reductive elimination of the metal centre would afford cyclooctenones **1.84** and **1.85**. In order to get more insight into the mechanism, Shair also prepared deuterium-labelled aldehyde **1.86D** as mixtures of *E* and *Z* isomers (Scheme 1.29). Interestingly, a scrambling of the deuterium atom onto two positions was observed. Moreover, starting with a given *E*/*Z* ratio of **1.86D** led to the same ratio **1.87D**/**1.88D**. This result indicates that both isomers are rearranged into the 8-membered ring following a different mechanism.



Scheme 1.29: Rearrangement of **1.86D**

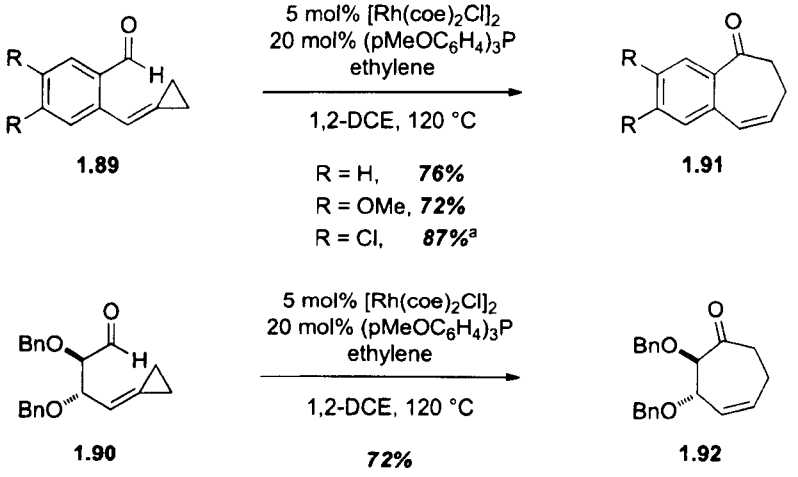
While the *E* isomer would be rearranged according to the mechanism described in scheme 1.28 (*i.e.* via the direct formation of hexarhodacycle **1.AS**), the mechanism depicted in scheme 1.30 would account for the rearrangement of the *Z* isomer. After activation of C–D bond, hydrometallation would afford pentarhodacycle **1.AV**. Rotation around the C_1–C_2 bond would place the C_1–Rh bond and the C_2–H bond *syn*-coplanar (**1.AW**). β-hydride elimination would give acyl rhodahydride intermediate **1.AX** and hydrometallation of the C–C double bond would give hexarhodacycle **1.AY**. β-carbon elimination would then afford **1.AZ** which would undergo reductive elimination of the metal towards **1.87D**.



Scheme 1.30: Proposed mechanism for the rearrangement of (*Z*)-**1.86D**

3 – 5 – Intramolecular hydroacylation of alkylidenecyclopropane

Aïssa and Fürstner investigated the rhodium-catalysed intramolecular hydroacylation of aldehydes embedding a methylenecyclopropane (Scheme 1.31).[55]

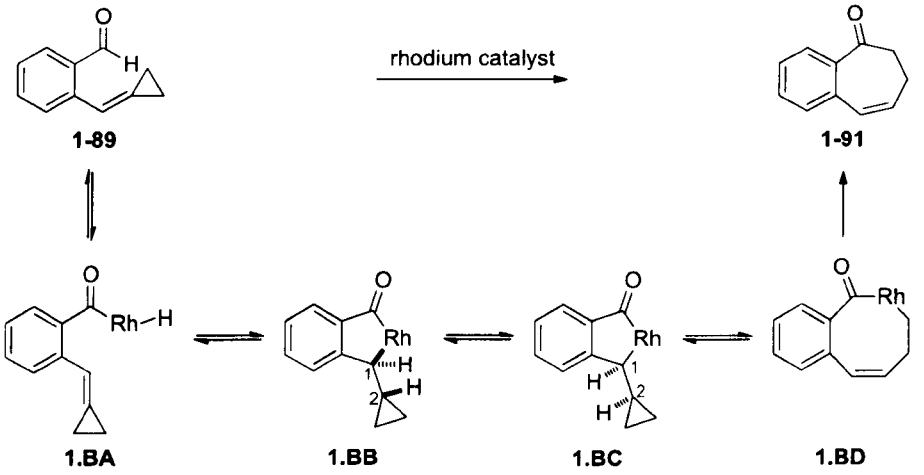


a: 2.5 mol% $[Rh(coe)_2]Cl_2$, 10 mol% ($pMeOC_6H_4)_3P$, ethylene, 1,2-DCE, 80 °C

Scheme 1.31: Rhodium-catalysed intramolecular hydroacylation of alkylidenecyclopropane

Exposure of aromatic aldehydes **1.89** and aliphatic compound **1.90** to 5 mol% of $[Rh(coe)_2Cl]_2$ and 20 mol% of P(*p*-$MeOC_6H_4)_3$ in 1,2-DCE saturated by ethylene at

120°C, led to the formation of cycloheptanones **1.91** and **1.92**, respectively. The catalyst loading could be reduced to 2.5 mol% in the case of the 4,5-bis-chloro derivative **1.89** and the reaction was carried out at 80°C. Under these conditions, the corresponding cycloheptenone **1.91** was isolated in 87% yield. The mechanism of this rearrangement is described in scheme 1.32. Oxidative addition of the rhodium catalyst into the C–H bond of the aldehyde would afford acyl rhodahydride intermediate **1.BA**. Hydrometallation of the C–C double bond would give pentarhodacycle **1.BB**. The *cis*-configuration of the alkene in **1.91**, implies a rotation around the C_1–C_2 bond in **1.BB**. Hence, **1.BC** in which the C_1–H and C_2–H bonds are *syn*-coplanar would be formed and would undergo ring enlargement towards **1.BD**. Reductive elimination of the metal centre would afford **1.91**.



Scheme 1.32: Proposed mechanism accounting for the formation of cycloheptenone **1.89**

4 - Conclusion

Rhodium-catalysed intramolecular hydroacylation of 4-pentenal is a well-established method, allowing for the formation of cyclopentanone. Several groups have investigated the mechanism as well as the scope of this reaction. However, the

formation of larger rings via intramolecular hydroacylation remains challenging. Different strategies have been developed in order to obtain 7- and 8-membered rings. Our group has developed the rhodium-catalysed intramolecular hydroacylation of alkylidenecyclopropanes. The success of this approach relies on the release of the strain energy occurring during the ring opening of the cyclopropane moiety. Hence, this driving force prevents side-reactions from taking place. Shair also employed cyclopropane moieties and obtained 8-membered rings. However, Shair and our proposed mechanism differ in respect to the key intermediate involved in the ring opening of the cyclopropane moiety.

In this context, the aim of this work presented herein was to:

- Expand the scope of the reaction.
- Investigate the mechanism of the reaction and confirm the formation of pentarhodacycles. This study led us to investigate the chemoselectivity between alkylidenecyclopropane and alkene or alkyne.
- Extend the methodology to the formation of 8-membered rings by replacing the alkylidenecyclopropane moiety by an alkylidenecyclobutane moiety.
- Study the regioselectivity of the ring opening of substituted alkylidenecyclobutanes.

5 – References

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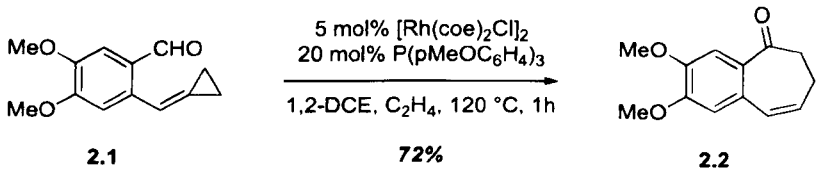
Chapter 2

Rhodium-Catalysed Intramolecular Hydroacylation of Alkylidenecyclopropanes: Optimisation and Scope of 7-Membered Rings

1 – Optimisation of the catalytic conditions

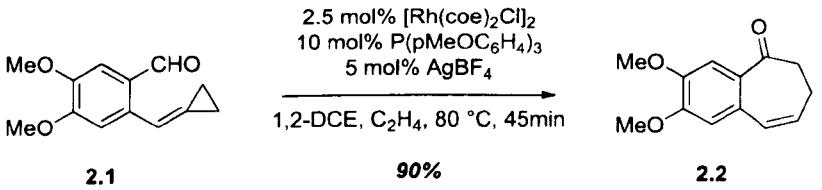
As previously described, our group has reported that a neutral rhodium complex catalyses the intramolecular hydroacylation of alkylidenecyclopropanes (Scheme 2.1).[1] Although 7-membered ring **2.2** was obtained in good yield under these initial conditions, our first objective was the improvement of the catalytic system. Indeed, we wanted to avoid the use of ethylene as well as reduce the catalyst loading.



2.1 **72%** **2.2**

Scheme 2.1: Neutral rhodium complex catalysed intramolecular hydroacylation of alkylidenecyclopropane

Aldehyde **2.1** was used as model substrate for the improvement of the conditions because of its ease of preparation, in a two-step procedure, from commercially available 6-bromoveratraldehyde. Bosnich reported that cationic rhodium complexes are very efficient for the cyclisation of 4-pentenals into cyclopentanones.[2,3] Therefore, we decided to explore the reactivity of **2.1** with cationic rhodium complexes. The cationic rhodium complex was generated in situ, by adding $AgBF_4$ to the initial conditions (Scheme 2.2). Under these new conditions, ethylene was no longer required and both reactivity and yield of the reaction were improved. The catalyst loading was reduced to 2.5 mol% of $[Rh(coe)_2Cl]_2$ and the temperature of reaction decreased to 80 °C. Furthermore, the yield of isolated cycloheptenone **2.2** was increased to 90%.



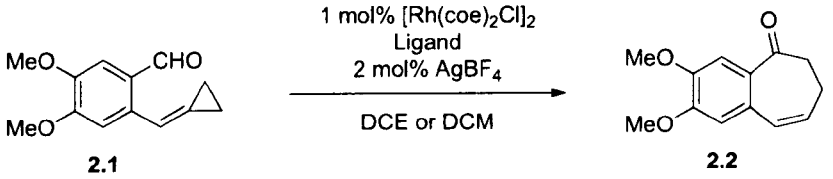
2.1 **90%** **2.2**

Scheme 2.2: Cationic rhodium complex catalysed intramolecular hydroacylation of **2.1**

With these new conditions in hand, we decided to examine the ligand effect in order to find a new catalytic system which would further enable reducing the catalyst loading (Table 2.1). Using electron-rich monophosphines $P(pMeOC_6H_4)_3$ and PPh_3 (entries 1 and 2) seemed to be beneficial for the conversion of **2.1** into **2.2**, although the rate of the reaction was considerably reduced when 1 mol% of $[Rh(coe)_2Cl]_2$ was utilised (respectively 50% and 20% conversion after 21 hours at 80 °C). When monophosphite $P(OPh)_3$ was used, complete decomposition was observed (entry 3), whereas the bulky monophosphine JohnPhos-based catalyst gave poor reactivity (entry 4). Interestingly, a diverse reactivity was observed when bisphosphine ligands were employed. The dppe-based catalyst led to complete decomposition of the

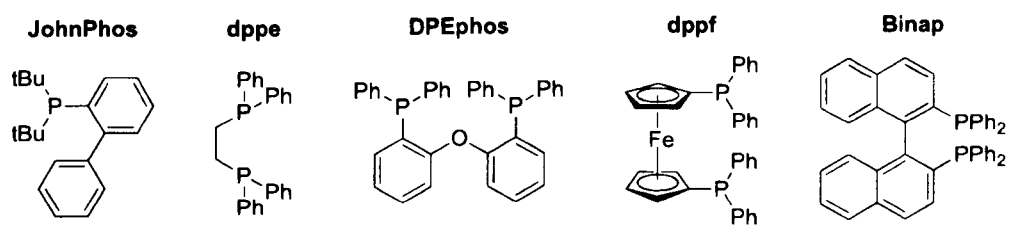
aldehyde (entry 5). On the other hand, DPEphos- and dppf-based catalysts (entries 6 and 7) showed poor reactivity. Conversely, when Binap was utilised, excellent reactivity was obtained (entry 8). Indeed, complete conversion was observed after 1 hour at 40 °C when aldehyde **2.1** was treated with 1 mol% of $[Rh(coe)_2Cl]_2$, 2 mol% of Binap and 2 mol% of $AgBF_4$ in dichloromethane, giving **2.2** in excellent 86% yield.

Table 2.1: Screening of ligands



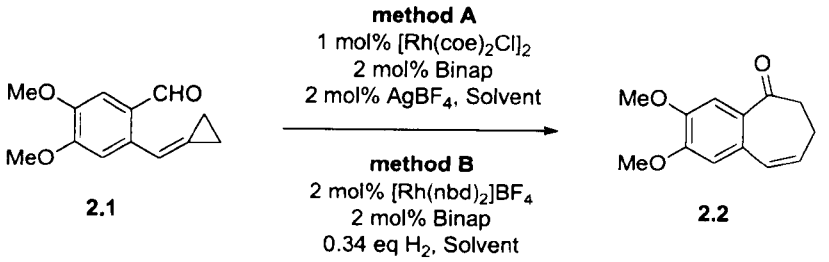
Entry	Ligand (mol%)	T (°C)	Time	NMR yield
1	P(*p*MeOC$_6$H$_4$)$_3$ (4)	80	21 h	50%
2	PPh$_3$ (4)	80	21 h	20%
3	P(OPh)$_3$ (4)	40	21 h	Degradation
4	JohnPhos (4)	40	3 h	8%
5	dppe (2)	40	21 h	Degradation
6	DPEphos (2)	40	3 h	20%
7	dppf (2)	40	1 h	10%
8	Binap (2)	40	1 h	86%[a]

[a]: isolated yield.



Next, we decided to investigate the effect of the solvent on the reaction (Table 2.2). Preparing the cationic rhodium catalyst in situ (method A), we found that using acetonitrile left the starting material nearly untouched. However, both dichloromethane and acetone were effective solvents for the reaction (entries 1 and 2), enabling full conversion toward cycloheptenone **2.2** at comparable rate; a higher yield being obtained in acetone. Surprisingly, a strong difference of reactivity between 1,2-DCE and acetone was observed when cationic pre-catalyst $[Rh(nbd)_2]BF_4$ was used (method B). In 1,2-DCE (entry 3), full conversion of aldehyde **2.1** required 10 mol% of $[Rh(nbd)_2]BF_4$, whereas only 2 mol% were needed in acetone (entry 4). Furthermore, in acetone, the reaction occurred at room temperature and was complete after 30 minutes, whereas 80 °C and 3 hours reaction time were required in 1,2-DCE. The active catalyst was prepared by bubbling an excess of H_2 to an equimolar solution of $[Rh(nbd)_2]BF_4$ and Binap in acetone. The ^1H NMR shows characteristic signals of norbornane and the ^{31}P NMR is consistent with a monomeric structure. Indeed, the ^{31}P NMR shows only a doublet at 51.9 ppm ($J_{P\text{-}Rh}$ = 201 Hz) indicating that the two phosphorus atoms are in identical environment. Therefore, they are not involved in bridging (see Appendix 2, p 298).[2] Presumably, the same cationic catalyst is generated with the two methods (preparation in situ by addition of $AgBF_4$ or use of cationic pre-catalyst $[Rh(nbd)_2]BF_4$). These results could suggest that the formation of AgCl salts have a deleterious effect on the reaction rate when the reaction is carried out in acetone (entry 2 vs 4).

Table 2.2: Comparison between Acetone and Dichloromethane



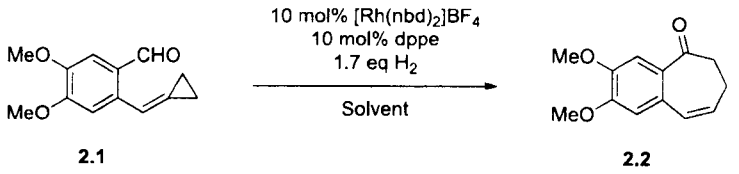
2.1 **2.2**

Entry	Method	Solvent	T (°C)	Time	Isolated yield
1	A	CH_2Cl_2	40	1 h	86%
2	A	Acetone	60	1 h 15	97%
3	B	1,2-DCE	80	3 h	99%[a,b]
4	B	Acetone	r.t.	30 min	95%

[a]: 10 mol% of $[Rh(nbd)_2]BF_4$ and 10 mol% of Binap were required.
[b]: yield determined by ^1H NMR.

As mentioned previously, when the cationic complex was prepared in situ by addition of $AgBF_4$ to $[Rh(coe)_2Cl]_2$ and dppe, the starting material decomposed (Table 2.1, entry 5). Surprisingly, under the silver-free conditions, dppe proved to be an effective ligand in acetone, delivering cyloheptenone **2.2** in 93% yield (Table 2.3, entry 1). A rapid screening of the solvent showed that the active catalyst $[Rh(dppe)]BF_4$ mainly gave products of decomposition in 1,2-DCE or acetonitrile (entries 2 and 3).

Table 2.3: Reactivity of the dppe-based catalyst prepared from $[Rh(nbd)]_2BF_4$

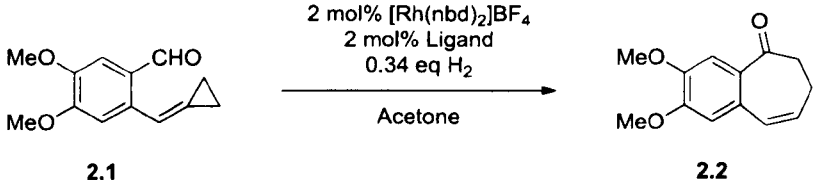


2.1 2.2

Entry	Solvent	T (°C)	Time	Isolated yield
1	Acetone	r.t.	15 min	93%
2	1,2-DCE	120	2 h	36%
3	Acetonitrile	80	13 h	22%

Therefore, it was necessary to re-evaluate the use of dppe as ligand (Table 2.4). Using the same catalyst loading, in acetone, the Binap-based catalyst clearly showed higher reactivity than the dppe-based catalyst (entry 1 vs 2). Two hypotheses can be postulated to explain this difference of rate. Either the rearrangement is slower with the dppe-based catalyst than it is with the Binap-based catalyst, or the initial exchange between the bisphosphine and acetone may be slower with dppe than with Binap.

Table 2.4: Re-evaluation of the dppe-based catalyst



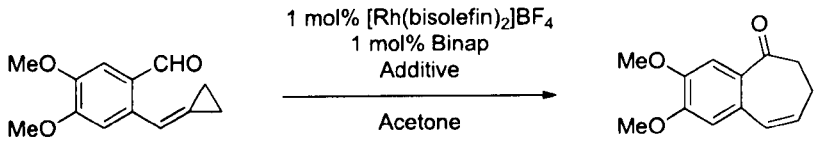
2.1 2.2

Entry	Ligand	T (°C)	Time	Yield
1	dppe	60	60 h	90%[a]
2	Binap	r.t.	30 min	95%[b]

[a]: yield determined by ^1H NMR.
[b]: isolated yield.

Next, the influence of the hydrogenation of the norbornadiene ligand on the reaction was investigated (Table 2.5). Comparing entries 1 and 2 clearly shows that the hydrogenation of the diene allows for much quicker conversions. Indeed, only 29% conversion is obtained after treatment of aldehyde **2.1** for 16 hours under reflux when the norbornadiene was not hydrogenated (entry 2). If a facile exchange between the diene and Binap occurs when the diene is not hydrogenated, this difference of reactivity could be explained by a slow rate of exchange between starting material **2.1** and the remaining diene. Hence, the exchange between cyclooctadiene and **2.1** would be easier than the exchange between norbornadiene and **2.1** (entry 2 vs 3). Therefore, using 1 mol% of $[Rh(cod)]_2BF_4$ and 1 mol% of Binap in acetone aldehyde **2.1** underwent the rearrangement at 60 °C and 7-membered ring **2.2** was isolated in 90% yield (entry 3).

Table 2.5: Importance of H_2 and use of $[Rh(cod)_2]BF_4$ as source of rhodium



2.1 **2.2**

Entry	bisolefin	Additive	T (°C)	Time	Isolated yield
1	nbd	H_2	r.t.	30 min	95%[a]
2	nbd	none	60	16 h	29%[b]
3	cod	none	60	20 min	90%

[a]: 2 mol% of $[Rh(nbd)_2]BF_4$ and 2 mol% of Binap were utilised.
[b]: yield determined by ^1H NMR.

The previous results point out two general trends. The reactivity and the selectivity towards the formation of 7-membered ring **2.2** are better in acetone than in acetonitrile or chlorinated solvent (dichloromethane or 1,2-DCE). Moreover, after a rapid screening of the ligand, Binap appears to be the best ligand for the transformation.

We found that five conditions cleanly afford 7-membered ring **2.2** in good to excellent yields. Upon exposure of aldehyde **2.1** to:

- 5 mol% of $[Rh(coe)_2Cl]_2$, 20 mol% of $P(p MeOC_6H_4)_3$ in 1,2-DCE saturated with ethylene at 120°C during 2.5 hours, **2.2** is obtained in 72% yield.
- 2.5 mol% of $[Rh(coe)_2Cl]_2$, 10 mol% $P(p MeOC_6H_4)_3$, 5 mol% of $AgBF_4$ in 1,2-DCE at 80°C during 45 minutes, **2.2** is obtained in 90% yield.
- 1 mol% of $[Rh(coe)_2Cl]_2$, 2 mol% of Binap, 2 mol% of $AgBF_4$ in dichloromethane or 1,2-DCE at 40°C during 1 hour, **2.2** is obtained in 86% yield.
- 2 mol% of $[Rh(nbd)_2]BF_4$, 2 mol% of Binap, 34 mol% of H_2 in acetone at room temperature during 30 minutes, **2.2** is obtained in 95% yield.
- 1 mol% $[Rh(cod)_2]BF_4$, 1 mol% of Binap in refluxed acetone during 20 minutes, **2.2** is obtained in 90% yield.

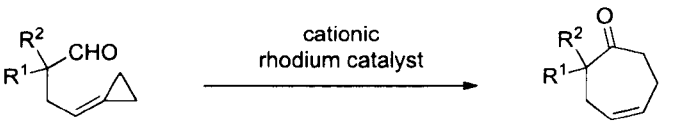
We decided to keep this set of five conditions to investigate the scope of the reaction. Indeed among these conditions, both cationic and neutral rhodium catalysts can be used. Moreover, phosphines ligands possessing different properties (steric and electronic) are used. This diversity could turn out to be important in our next studies.

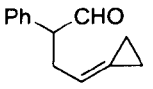
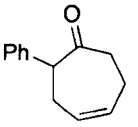
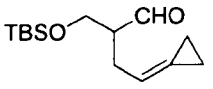
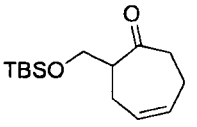
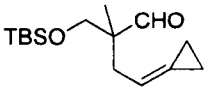
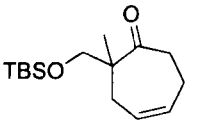
2 – Scope of the reaction: synthesis of aliphatic 7-membered rings

2 – 1 – Cyclisation of aliphatic aldehydes

After improving the initial conditions of cyclisation, we decided to focus on the scope of the reaction. The optimisation was carried out using aromatic aldehyde **2.1**. Therefore, we wondered if substrates having an aliphatic tether between the aldehyde moiety and the alkylidenecyclopropane would undergo the cyclisation under the new catalytic conditions. Aldehydes **2.3 – 2.5** were prepared and treated with cationic rhodium catalyst (Table 2.6).

Table 2.6: Cyclisation of aliphatic aldehydes



Starting material	Product	Conditions	Isolated yield
 **2.3**	 **2.6**	2.5 mol% $[Rh(coe)_2Cl]_2$ 10 mol% $P(pMeOC_6H_4)_3$ 5 mol% $AgBF_4$ 1,2-DCE, 80 °C, 40 min	77%
 **2.4**	 **2.7**	2 mol% $[Rh(nbd)_2]BF_4$ 2 mol% Binap 0.34 eq H_2 Acetone, r.t., 1 h	93%
 **2.5**	 **2.8**	10 mol% $[Rh(nbd)_2]BF_4$ 10 mol% Binap 1.7 eq H_2 Acetone, 60 °C, 2 h	87%

The three cyclisations worked well. When the cationic rhodium complex is prepared in situ with $AgBF_4$ salts, 7-membered ring **2.6** was isolated in 77% yield. Aldehyde **2.4** underwent smooth rearrangement at room temperature, upon exposure to only 2 mol% of $[Rh(nbd)_2]BF_4$ and 2 mol% of Binap, yielding **2.7** in 93%. Finally, when aldehyde **2.5** was treated with 10 mol% $[Rh(nbd)_2]BF_4$ and 10 mol% of Binap, α,α-disubstituted 7-membered ring **2.8** was isolated in excellent yield. This result is in sharp contrast with previous reports which showed that α,α-disubstituted pentenals are reluctant to undergo rearrangement into the corresponding α,α-disubstituted cyclopentanone.[2,4]

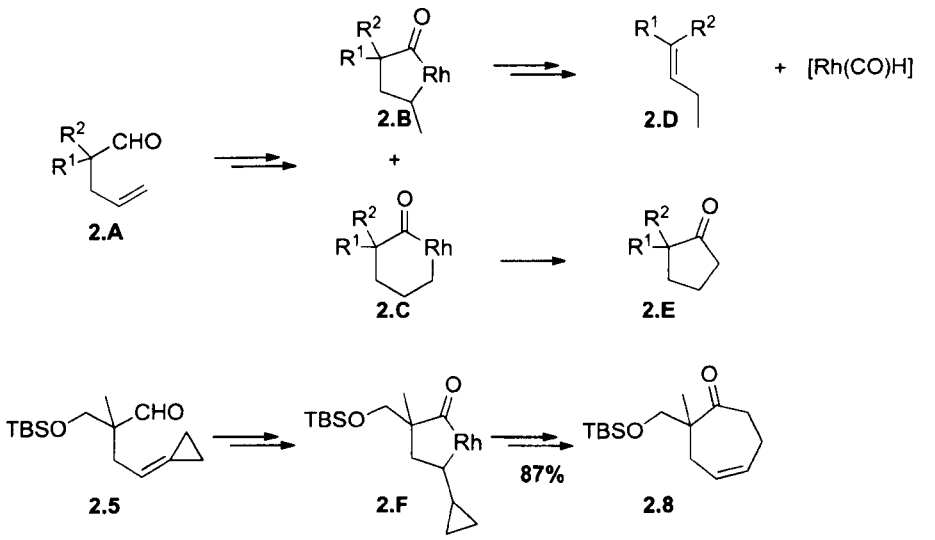
2 – 2 – Cyclisation of α,α-disubstituted 4-alkylidenecyclopropanals

As previously mentioned, α,α-disubstituted 7-membered ring **2.8** was obtained in excellent yield, contrasting with previous reports. When α,α-disubstituted 4-pentenals were treated with rhodium catalyst either drastic conditions are required or side products such as decarbonylation and isomerisation products were obtained.[2,4] Therefore, we wondered if the cyclisation of α,α-disubstituted 4-alkylidenecyclopropanals would be a general process.

2 – 2 – a – Scope of α,α-disubstituted cycloheptenones

Experimental studies[2,3] as well as theoretical calculations [5] suggest that both pentarhodacycle **2.B** and hexarhodacycle **2.C** are generated from **2.A** (Scheme 2.3).

While **2.B** leads to the decarbonylation product **2.D**, **2.C** gives cyclopentanone **2.E** after reductive elimination. Hence, the difficult cyclisation of α,α-disubstituted-4-pentenals could be explained by the gem-disubstituent effect of R^1 and R^2 which would favour the formation of pentarhodacycle **2.B** over hexarhodacycle **2.C**.[6,7] Conversely, our mechanistic proposal which relies on the formation of pentarhodacycle **2.F** and on its diversion into **2.8** from the decarbonylative pathway would explain the facile cyclisation of **2.5**.

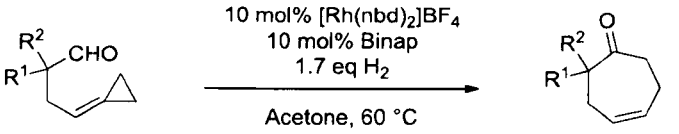


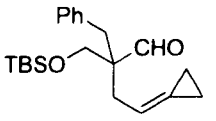
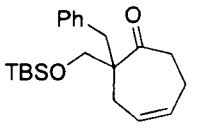
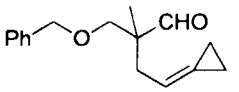
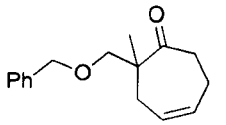
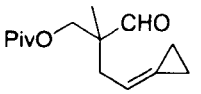
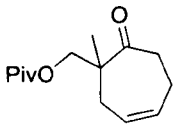
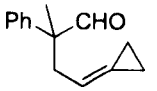
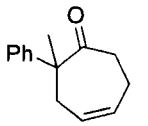
Scheme 2.3: Proposed mechanisms for the cyclisation of 4-alkylidenecyclopropanals and 4-pentenals

Therefore, aldehydes **2.9** – **2.12** were prepared and treated with 10 mol% of [Rh(Binap)]BF_4 (Table 2.7). Gratifyingly, the corresponding 7-membered rings were isolated in good to excellent yields, indicating the systematic diversion of the pentarhodacycle from the decarbonylative pathway. Alkyl, phenyl as well as protected alcohols were tolerated under these conditions (entries 1 and 2). The lower yield obtained for cycloheptenone **2.15** can be explained by the instability of starting material **2.11** which decomposes at room temperature even in the absence of active catalyst (entry 3). Finally, aldehyde **2.12** underwent smooth rearrangement into **2.16** at room temperature (entry 4). We also found that the catalyst loading can be reduced

to 3 mol% (entry 5). Under those conditions, full conversion was obtained after 14 hours at 60 °C.

Table 2.7: Scope of α,α-disubstituted cycloheptenones

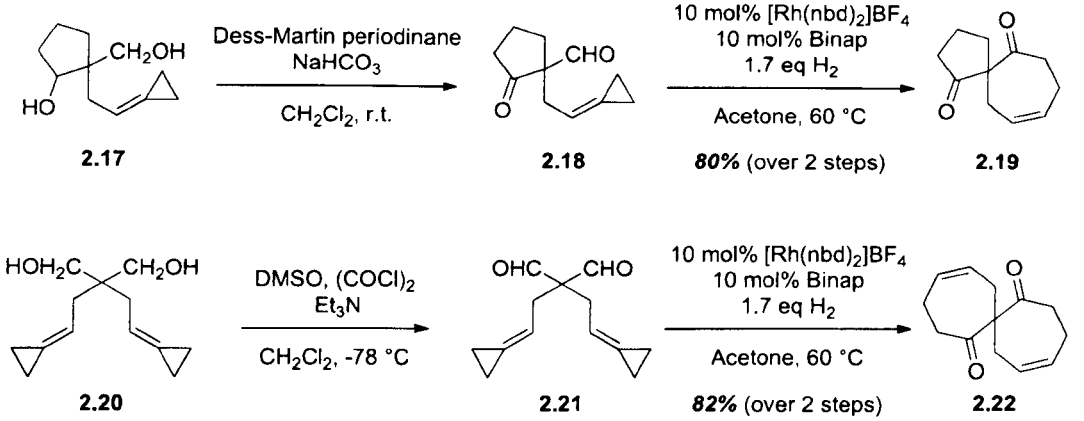


Entry	Starting material	Product	Time	Isolated yield
1	 **2.9**	 **2.13**	3 h	93%
2	 **2.10**	 **2.14**	4 h	77%
3	 **2.11**	 **2.15**	8 h	54%[a]
4	 **2.12**	 **2.16**	2 h	85%[b]
5			14 h	86%[c]

[a]: 15 mol% of rhodium catalyst were used.
[b]: reaction performed at r.t..
[c]: 3 mol% of rhodium catalyst were used.

The cyclisation of **2.18** and **2.21** was also investigated (Scheme 2.4). Diol **2.17** was oxidised using Dess-Martin periodinane while Swern's conditions were used for the oxidation of **2.20** into **2.21**. Given the instability of aldehydes **2.18** and **2.21**, simple filtration or aqueous wash of the crude material using a saturated solution of copper

sulphate were performed, respectively, before treatment under our optimised conditions which led to the isolation of spiro-1,3-bisketones **2.19** and **2.22** in 80% and 82% yield over the two steps, respectively.

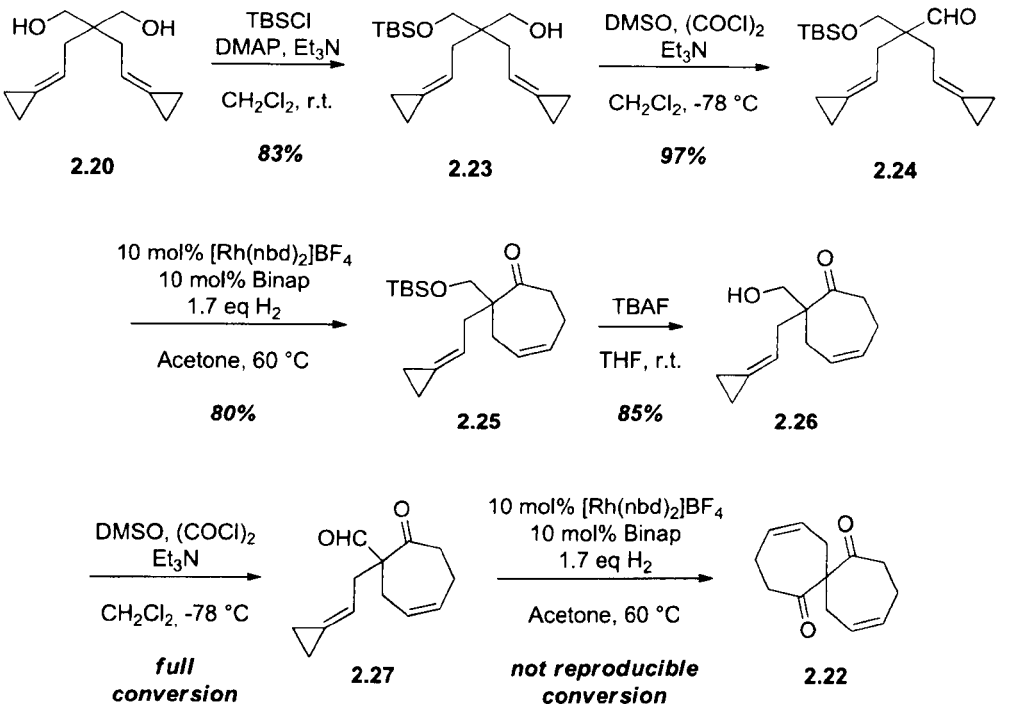


2.17 **2.18** ***80%*** (over 2 steps) **2.19**

2.20 **2.21** ***82%*** (over 2 steps) **2.22**

Scheme 2.4: Synthesis of spiro-1,3-bisketones

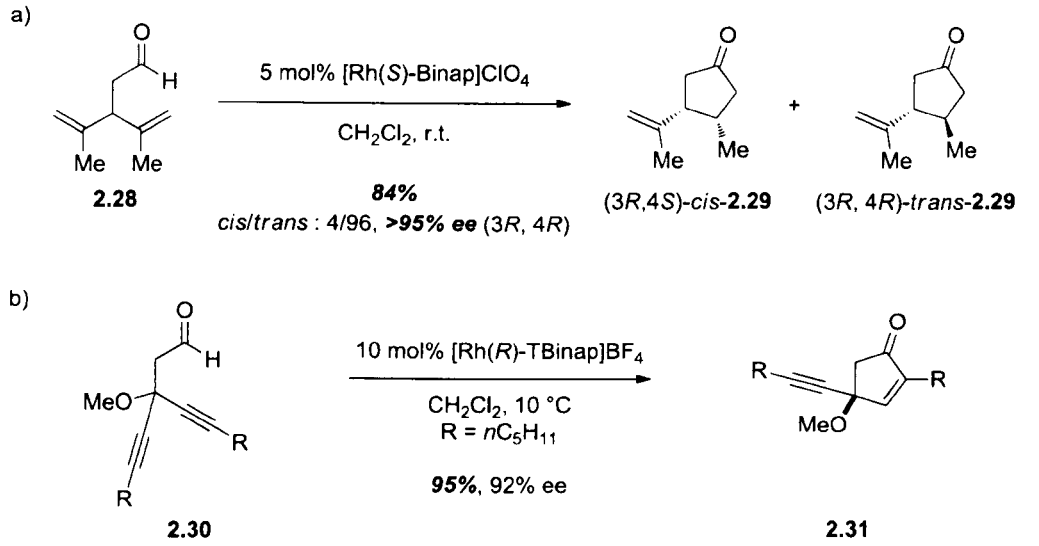
The bidirectional intramolecular hydroacylation of **2.21** into **2.22** is an efficient alternative to the sequential synthesis depicted in scheme 2.5, which involved the manipulation of functional groups. Monoprotection of bisalcohol **2.20** was achieved using TBSCl, affording alcohol **2.23**. Treatment of **2.23** under Swern's conditions gave aldehyde **2.24**. The latter was treated with rhodium catalyst giving 7-membered ring **2.25** in 80% yield. The TBS group was then cleaved using TBAF, yielding alcohol **2.26**. Oxidation under Swern's conditions gave crude aldehyde **2.27** which was treated under our optimised conditions giving spiro-1,3-bisketone **2.22**. This cyclisation step was particularly difficult. Indeed, incomplete conversion of aldehyde **2.27** was observed and the isolated yield of **2.22** was not reproducible. This can likely be imputed to the lability of ketoaldehyde **2.27**.



Scheme 2.5: Sequential synthesis of spiro-1,3-bisketone **2.22**

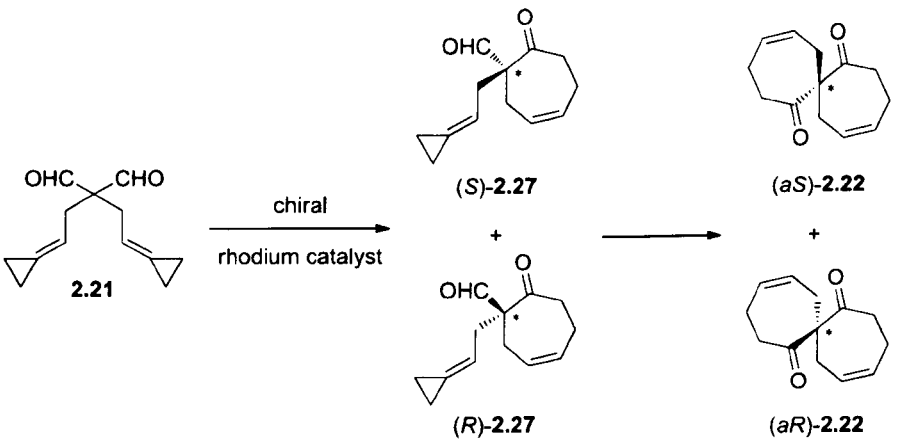
2 – 2 – b – Attempts of desymmetrisation of prochiral bisaldehyde

As discussed in chapter 1 the desymmetrisation of prochiral aldehydes in intramolecular hydroacylation has previously been described.[8] For instance, Tanaka and Suemune reported the diastereoselective desymmetrisation of prochiral aldehyde **2.28** (Scheme 2.6a).[8b,c,d] Using cationic rhodium catalyst, the *trans*-cyclopentanone **2.29** was obtained as main isomer in excellent selectivity. The enantioselective desymmetrisation of alkynes was studied by Fu and Tanaka (Scheme 2.6b).[9] Treating aldehyde **2.30** with 10 mol% of [Rh(*R*)-TBinap]BF_4 led to the formation of cyclopentenone **2.31** in excellent yield and enantiomeric excess.



Scheme 2.6: a) Diastereoselective desymmetrisation of bis-alkene **2.28**; b) Enantioselective desymmetrisation of bis-alkyne **2.30**

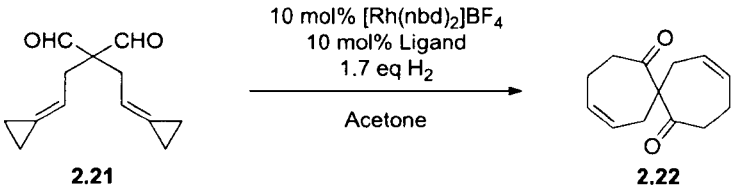
In this context, we decided to investigate the enantioselective desymmetrisation of prochiral bisaldehyde **2.21** (Scheme 2.7). The desymmetrisation would occur during the first cyclisation step. Therefore, a chiral system which would favour the formation of one of the two enantiomers **2.27**, would finally lead to an enantioenriched mixture of spiro-1,3-bisketone **2.22**.



Scheme 2.7: Catalytic asymmetric desymmetrisation of prochiral 1,3-bisaldehyde **2.21**

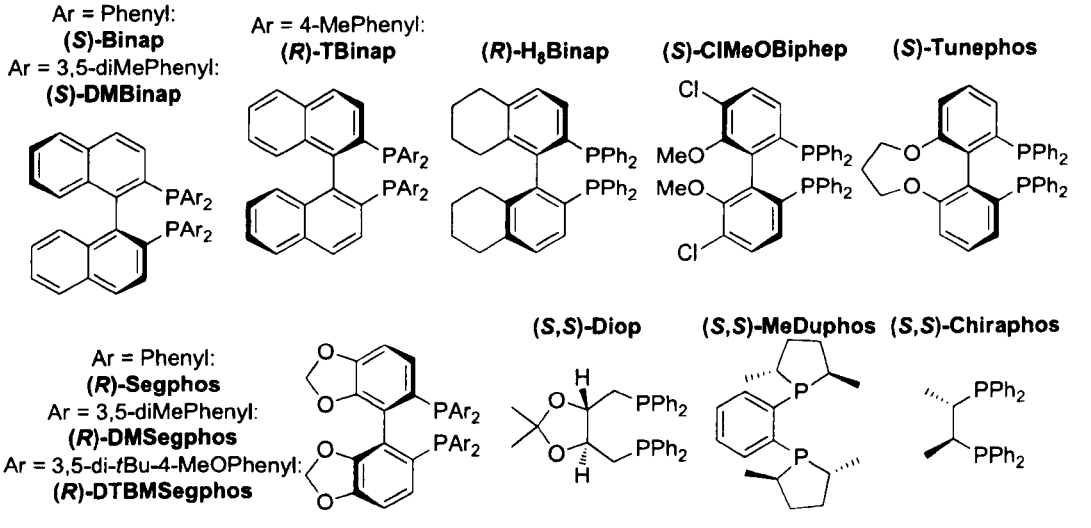
We first investigated the effect of different chiral bisphosphines ligands on the selectivity of the reaction (Table 2.8).

Table 2.8: Screening of chiral ligands



2.21 **2.22**

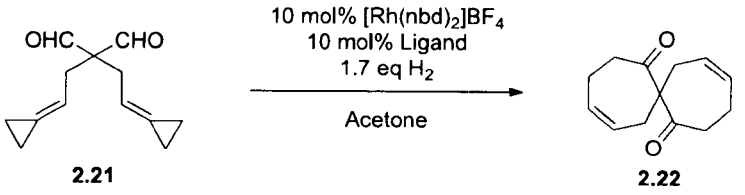
Entry	Ligand	T (°C)	Time	NMR yield	ee
1	(*S*)-Binap	r.t.	2 h	100%	29%
2	(*S*)-DMBinap	r.t.	2 h 30	100%	42%
3	(*R*)-TBinap	r.t.	2 h	100%	41%
4	(*R*)-H_8Binap	r.t.	2 h	100%	22%
5	(*S*)-ClMeOBiphep	r.t.	14 h	100%	0%
6	(*S*)Tunephos	r.t.	2 h	100%	21%
7	(*R*)-Segphos	r.t.	2 h	100%	42%
8	(*R*)-DMSegphos	r.t.	2 h	100%	41%
9	(*R*)-DTBMSegphos	60	60 h	Degradation	n.d.
10	(*S*,*S*)-Diop	r.t.	36 h	20%	0%
11	(*S*,*S*)-MeDuphos	60	36 h	20%	0%
12	(*S*,*S*)-Chiraphos	60	36 h	Degradation	n.d.



Using 10 mol% of $[Rh(nbd)_2]BF_4$, racemic Binap was first replaced by (*S*)-Binap (entry 1). Full conversion was observed in 2 hours at room temperature and **2.22** was obtained with an enantiomeric excess (ee) of 29% in favour of the (*S*) isomer. Changing (*S*)-Binap for (*S*)-DMBinap (entry 2) or (*R*)-TBinap (entry 3) for which the phenyl groups are replaced with the bulkier 3,5-xylyl groups and *p*-tolyl groups respectively, led to an increase of the ee to 41% and 42%, respectively. On the other hand, the modified (*R*)-H_8Binap-based catalyst gave **2.22** with an ee of 22% only (entry 4). The selectivity was completely lost (entry 5) or poor (entry 6) when changing the bisnaphthyl backbone of the ligand for a biphenyl backbone. Interestingly, when (*R*)-Segphos and (*R*)-DMSegphos (entries 7 and 8), similar levels of selectivity (42% and 41%) were obtained as with (*S*)-DMBinap. However, the bulkier (*R*)-DTBMSegphos-based catalyst was unreactive at room temperature, leading to decomposed products at 60 °C (entry 9). Finally, when (*S*,*S*)-Diop, (*S*,*S*)-MeDuphos and (*S*,*S*)-Chiraphos were used, poor reactivity and poor selectivity were obtained (entries 10, 11 and 12).

From this screening, (*S*)-DMBinap, (*R*)-TBinap and (*R*)-Segphos gave the best selectivity and were selected before examining the effect of the temperature on the reactivity and selectivity of the reaction (Table 2.9). Although decreasing the temperature from room temperature to 0 °C improved the ee, the rate of the reaction was considerably diminished (entry 1 vs 2, 3 vs 4 and 5 vs 6). Increasing the catalyst loading to 20 mol% in order to get full conversion resulted in the loss of selectivity (entry 7).

Table 2.9: Effect of the temperature



2.21 2.22

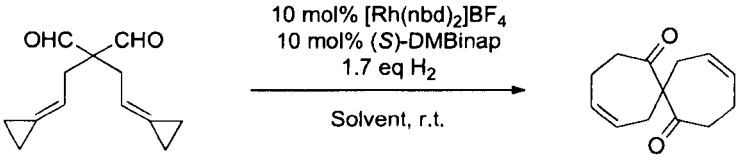
Entry	Ligand	T (°C)	Time	NMR yield	ee
1	(*S*)-DMBinap	r.t.	2 h 30	100%	42%
2	(*R*)-DMBinap	0	60 h	54%	61%
3	(*R*)-TBinap	r.t.	2 h	100%	41%
4	(*R*)-TBinap	0	36 h	traces	n.d.
5	(*R*)-Segphos	r.t.	2 h	100%	42%
6	(*R*)-Segphos	0	24 h	35%	70%
7	(*R*)-Segphos	0	24 h	100%	43%[a]

[a]: 20 mol% of catalyst were utilised.

We then looked at the solvent effect (Table 2.10). This study was carried out with 10 mol% of [Rh(*S*)-DMBinap] complex. When carrying out the reaction in dichloromethane, the reaction rate was considerably slower than in acetone (entry 1 vs 2); however, a better selectivity was observed. Using a mixture acetone/dichloromethane (1:1) resulted in full conversion but only a slight increase of the selectivity was observed as compared to acetone (entry 1 vs 3). In tetrahydrofuran, an ee of 72% was obtained for 46% conversion (entry 4). Although this result seemed encouraging, we found that the rate of the reaction was considerably reduced for higher conversion indicating that the catalyst is no longer active (entry 5). Moreover, a loss of the selectivity was observed (from 72% to 63%). While studying the rhodium-catalysed intramolecular hydroacylation of 4-pentynals,

Fu and Tanka obtained better results when acetonitrile was added to the mixture.[10] In our case, the addition of 0.1 equivalent of acetonitrile did not seem to increase the selectivity of the reaction (entry 6) while the addition of 0.2 equivalent of acetonitrile considerably slowed the reaction (entry 7). Presumably, acetonitrile strongly coordinates the catalyst, preventing the reaction from taking place. Finally, degradation was observed when weakly coordinating nitromethane was utilised (entry 8) whereas in diethyl ether, dimethoxyethane or methyl *t*-butyl ether, **2.21** was unreactive.

Table 2.10: Effect of the solvent

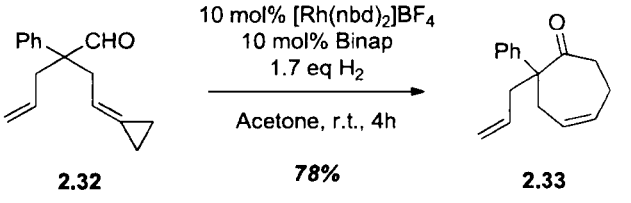


2.21 **2.22**

Entry	Solvent	Time	NMR yield	ee
1	Acetone	2 h	100%	42%
2	CH_2Cl_2	16 h	17%	59%
3	CH_2Cl_2/Acetone = 1 : 1	96 h	100%	47%
4	THF	6 h	46%	72%
5	THF	96 h	74%	63%
6	Acetone + 0.1 eq MeCN	30 min	64%	53%
7	Acetone + 0.2 eq MeCN	15 h	17%	56%
8	CH_3NO_2	120 h	Degradation	n.d.

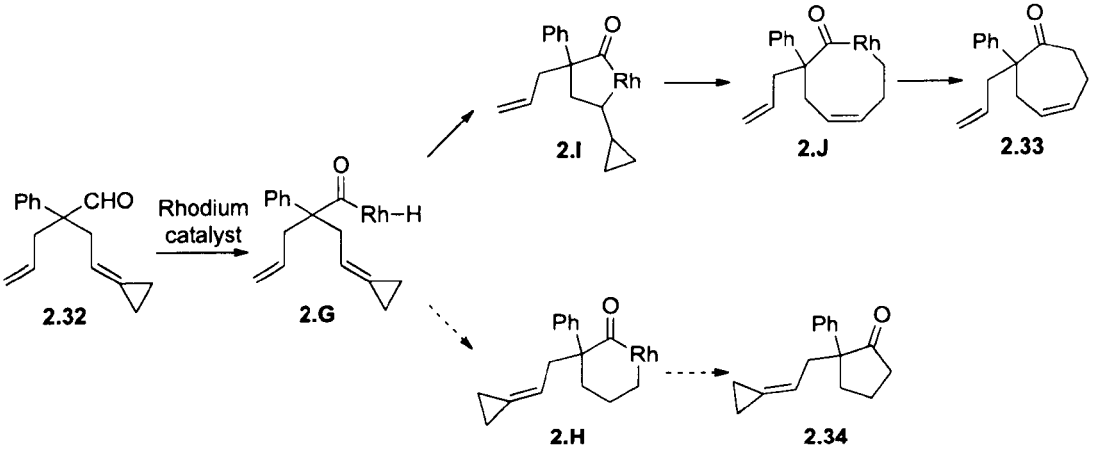
2 – 2 – c – Competition between alkylidenecyclopropane and alkenes

While investigating the cyclisation of α,α-disubstituted 4-alkylidenecyclopropanals, we found that aldehyde **2.32**, embedding a second unsaturation, selectively afforded 7-membered ring **2.33** in 78% yield (Scheme 2.8).



Scheme 2.8: Chemoselective synthesis of 7-membered ring **2.33**

This result is particularly interesting because it can easily be envisioned that the terminal alkene would react to give cyclopentanone **2.34** after reductive elimination from **2.H** (Scheme 2.9). Instead pentarhodacycle **2.I** appears to be formed exclusively over hexarhodacycle **2.H**. Intermediate **2.I** would undergo β–carbon elimination towards **2.J** and reductive elimination would afford **2.33**.

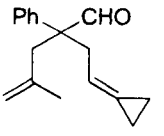
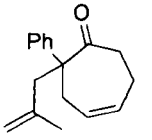
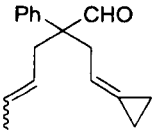
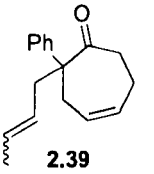
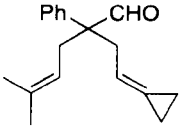
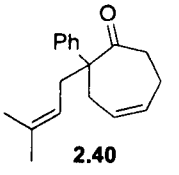


Scheme 2.9: Mechanistic proposal for the formation of 7-membered ring **2.33**

This chemoselectivity proved to be general. Aldehydes **2.35** – **2.37** were prepared by undergraduate student Coralie Tugny and were treated with 10 mol% of [Rh(Binap)]BF_4 in acetone (Table 2.11). Independently of the substitution on the

alkene, only 7-membered rings **2.38** – **2.40** were obtained in good yields; cyclopentanone derivatives were not observed.

Table 2.11: Chemoselective formation of 7-membered rings – Generality of the reaction[a]

Entry	Starting material	Product	Isolated yield
1	 **2.35**	 **2.38**	89%
2	 **2.36** *E/Z* : 5/1	 **2.39** *E/Z* : 4/1	70%
3	 **2.37**	 **2.40**	75%

[a]: Conditions used: 10 mol% of $[Rh(nbd_2)]BF_4$, 10 mol% of Binap, 1.7 eq H_2, acetone, r.t., 12h.

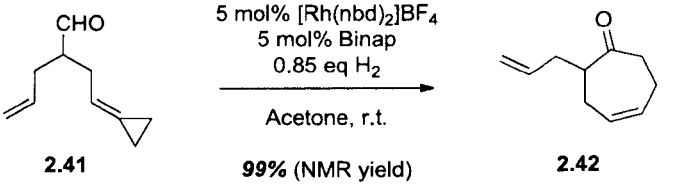
Aldehyde **2.41** was also synthesised and treated with 5 mol% $[Rh(Binap)]BF_4$ in acetone (Scheme 2.10). The complete chemoselective rearrangement of **2.41** into 7-membered ring **2.42** was observed by ^1H NMR. This result also showed that substitution in position α to the formyl group is not necessary for a chemoselective rearrangement. Attempts to isolate ketone **2.42** by flash chromatography gave variable yields (45 - 65%) due to the volatility of the compound.

Interestingly, in rhodium-catalysed intramolecular hydroacylation of 4-pentenals, Bosnich obtained the fastest turnovers for 4-pentenals having an unsubstituted alkene moiety.[2,3] Hence, the exclusive formation of cycloheptenones **2.33** and **2.42** from

aldehydes **2.32** and **2.41**, respectively, shows the complete chemoselectivity in favour of the alkylidenecyclopropane moiety.

Given that alkylidenecyclopropane is a more electron-rich olefin, we could envision that its coordination to the cationic rhodium complex would stabilised the metal complex and would explain the preferred formation of pentarhodacycle **2.I** over hexarhodacycle **2.H** (Scheme 2.9). Although alkyl substituents on the alkene moiety increase the electron density, these alkenes are also more sterically hindered. Hence, aldehydes **2.35** – **2.37** gave only 7-membered rings **2.38** – **2.40**, respectively.

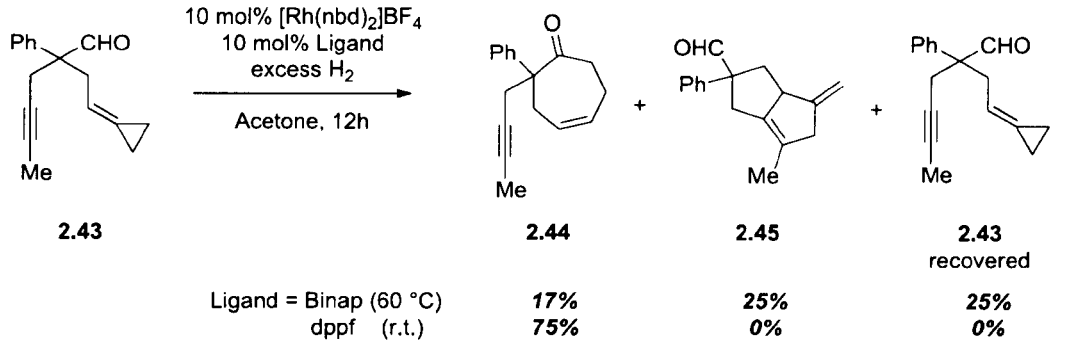
Finally, the release of strain energy during the coordination of the alkylidenecyclopropane to the catalyst, the hydrometallation step and the ring opening of the cyclopropane moiety is likely kinetically favourable and would contribute to the complete chemoselectivity in favour of the alkylidenecyclopropanes.



2.41 **99%** (NMR yield) **2.42**

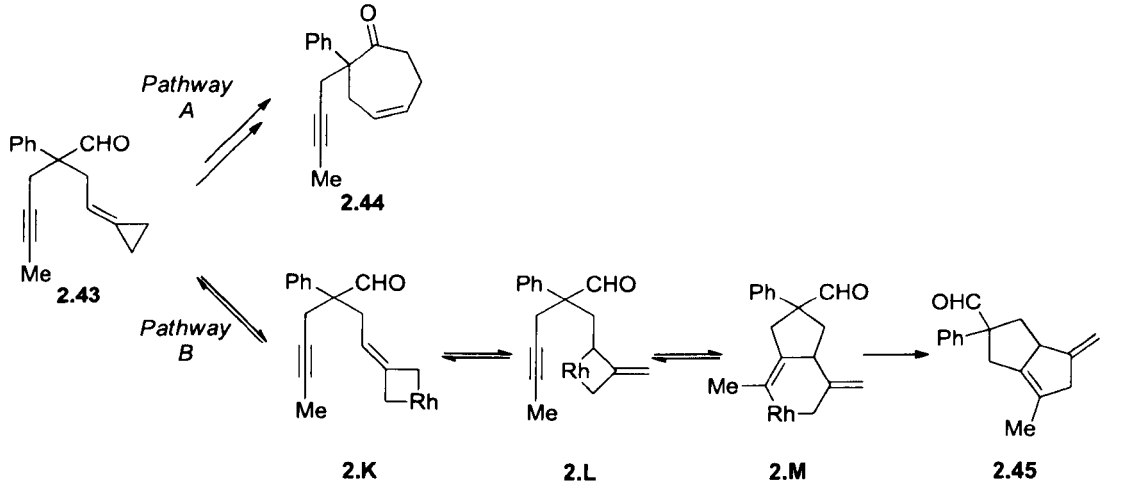
Scheme 2.10: Chemoselective formation of cycloheptenone **2.42**

Replacing the additional alkene by an alkyne gave a different result depending on the phosphine ligand used (Scheme 2.11). Exposure of **2.43** to the optimised conditions gave a mixture of 25% of 7-membered ring **2.44**, 25% of fused bicyclic structure **2.45** and 17% of starting material **2.43** was also recovered. Interestingly, undergraduate student James Murray found that changing Binap for dppf led to the full conversion of **2.43** into 7-membered ring **2.44** in 75% yield.



Scheme 2.11: Intramolecular hydroacylation vs [3+2] cycloaddititon

Cycloadduct **2.45** results from the intramolecular [3+2] cycloaddition between the alkyne and the alkylidenecyclopropane moieties, therefore, constituting the first example of [3+2] cycloaddition catalysed by a rhodium catalyst.[11] The proposed mechanism of this [3+2] cycloaddition is depicted in scheme 2.12.



Scheme 2.12: Proposed mechanism for the formation of **2.45**

Pathway A which leads to 7-membered ring **2.44** would be in competition with pathway B. The distal insertion of the rhodium catalyst into the cyclopropane moiety would give intermediate **2.K** which would rearrange into intermediate **2.L**. Intramolecular carbometallation of the alkyne would then afford **2.M** which would undergo reductive elimination towards **2.45**.

3 – Conclusion

The optimisation of the initial conditions allowed for the reduction of the catalyst loading. Moreover, smooth rearrangement of aldehyde-tethered alkylidenecyclopropanes was observed, allowing for the reaction to be carried out at room temperature for the best cases. While broadening the scope of the reaction, we found that α,α-bissubstituted aldehydes underwent the rearrangement. This result is in sharp contrast with the cyclisation of α,α-bissubstituted-4-pentenals which is known to be a difficult process, affording isomerised aldehydes and decarbonylation products. The two substituents in α position to the aldehyde moiety would favour the formation of pentarhodacycles which are known to be key intermediates for the decarbonylation products. Since pentarhodacycles appeared to be systematically diverted from the decarbonylative pathway by the ring expansion of a judiciously positioned cyclopropane, good to excellent yields of α,α-bissusbstituted cycloheptenones were obtained.

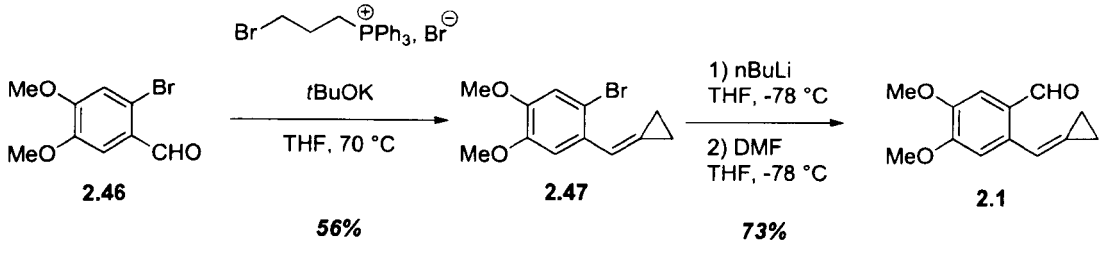
Finally, the system is completely chemoselective towards the alkylidenecyclopropane moiety. Indeed, an additional alkene or alkyne which could undergo intramolecular hydroacylation and give a cyclopentanone or a cyclopentenone, respectively, did not react; instead, cycloheptenones were the only products obtained.

4 – Synthesis of Precursors

The key step for the preparation of the aldehydes was the formation of the alkylidenecyclopropane. This was achieved by a Wittig reaction, using commercially available 3-(bromopropyl)triphenylphosphonium for the synthesis of **2.1**. Alternatively, the alkylidenecyclopropane moiety was synthesised via Tsuji-Trost allylation of enolates and malonates, using 1-vinylcyclopropyl 4-methylbenzenesulfonate.[12]

4 – 1 – Synthesis of the precursor of optimisation **2.1**

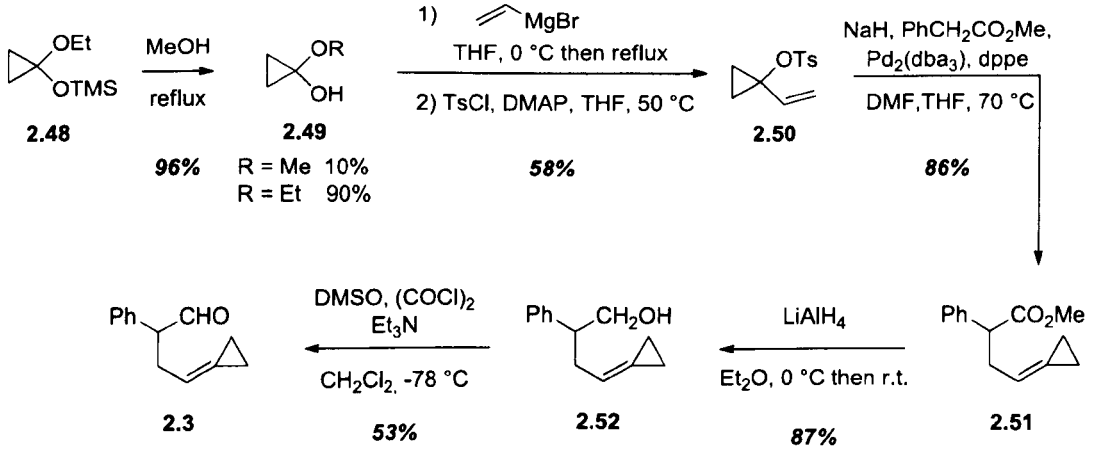
Substrate **2.1** was easily synthesised in a two-step procedure from 6-bromoveratraldehyde **2.46** (Scheme 2.13).



Scheme 2.13: Synthesis of the precursor of optimisation **2.1**

Compound **2.47** was obtained by preparing the ylide in situ, by reaction of 3-(bromopropyl)triphenylphosphonium bromide with two equivalents of potassium *t*-butoxide in THF, followed by the addition of 6-bromoveratraldehyde **2.46**. Then bromine-lithium exchange followed by addition of DMF afforded **2.1** in 73% yield.[1]

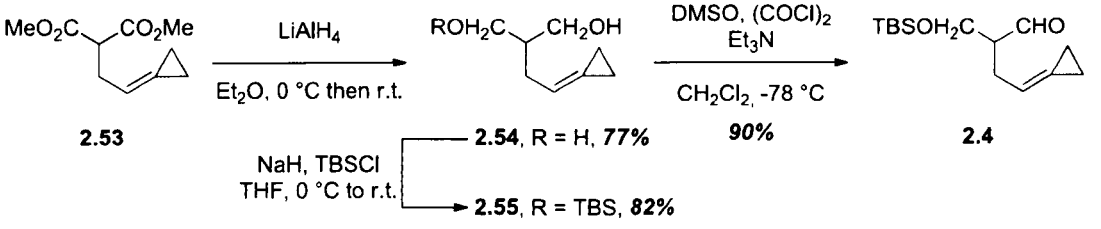
The synthesis of aldehyde **2.3** began with the solvolysis of commercially available acetal **2.48** in methanol, affording **2.49** as a mixture of methyl and ethyl hemiacetals (Scheme 2.14). This mixture was used as crude material in the next step. Exposure of **2.49** to vinylmagnesium bromide followed by tosylation of the alcohol group gave **2.50** in 58% yield. Alkylidenecyclopropane **2.51** was then obtained by Tsuji-Trost's allylation, as developed by de Meijere.[12] Exposure of **2.50** to a mixture of $Pd_2(dba)_3$ and dppe, followed by addition of the anion of methylphenyl acetate afforded **2.51** in 86% yield. Interestingly, either one or two equivalents of dppe compared to $Pd_2(dba)_3$ can be used without lowering the yield of the reaction; only the rate of the reaction was slower, presumably due to the lower concentration of active catalyst. Having ester **2.51** in hands, reduction using $LiAlH_4$ gave alcohol **2.52** which was oxidised into **2.3** using Swern's conditions.[13]



Scheme 2.14: Synthesis of 2-phenyl-4-alkylidenecyclopropanals **2.3**

The synthesis of aldehyde **2.4** started from bisester **2.53** which was prepared by Tsuji-Trost's allylation of **2.50** following the procedure described by de Meijere (Scheme 2.15).[12] ^1H NMR, ^{13}C NMR, IR and mass analyses were in good accordance

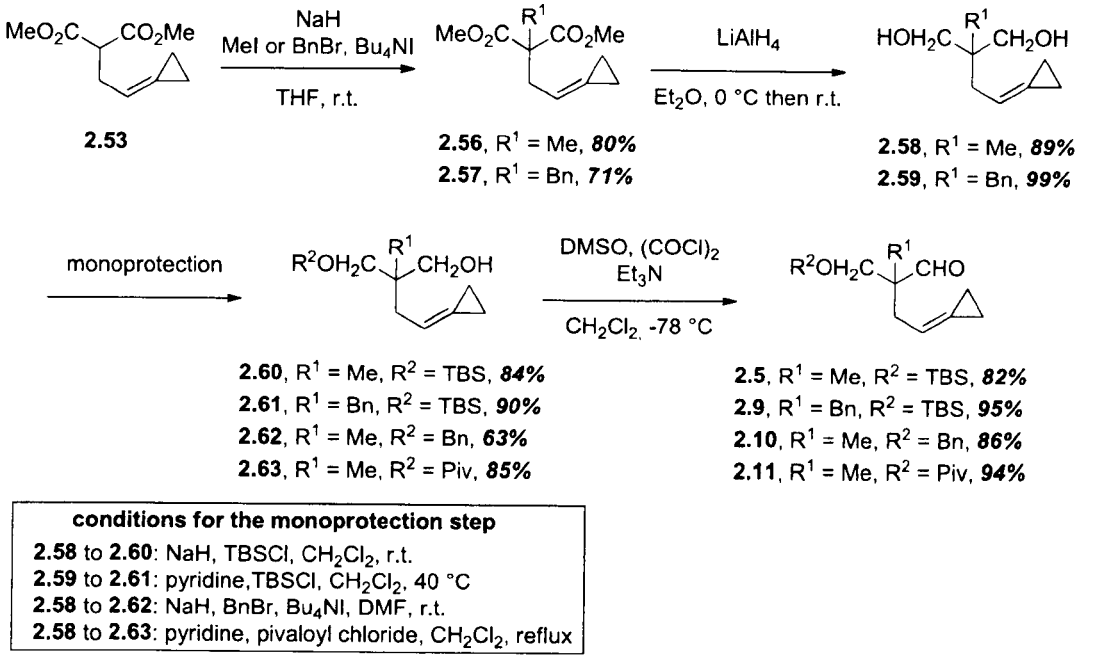
with the literature.[12] Reduction of the ester moiety using 3 equivalents of $LiAlH_4$ gave diol **2.54** which was monoprotected with a *t*-butyldimethylsilyl group. Finally, under Swern's conditions,[13] monoalcohol **2.55** was oxidised into aldehyde **2.4**.



Scheme 2.15: Synthesis of precursor **2.4**

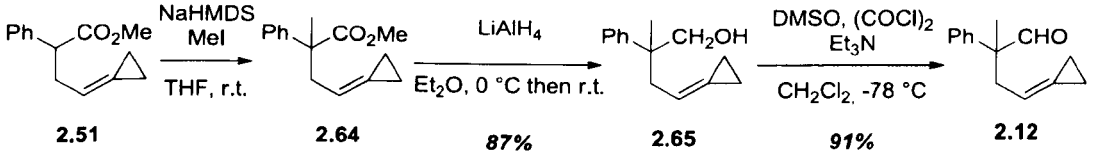
*4 – 3 – Synthesis of α,α-disubstituted 4-alkylidenecyclopropanals **2.5**, **2.9** - **2.12**, **2.18** and **2.21***

The preparation of **2.5**, **2.9**, **2.10** and **2.11** began with the alkylation of **2.53**, using either iodomethane or benzylbromide as electrophile (Scheme 2.16). Resulting bisesters **2.56** and **2.57** were reduced using $LiAlH_4$, giving bisalcohols **2.58** and **2.59**, respectively. Then TBSCl, benzylbromide or pivaloyl chloride were used, giving monoprotected alcohols **2.60** – **2.63** in 63% to 90% yield. Finally the oxidation of these alcohols was accomplished by using Swern's conditions,[13] affording aldehydes **2.5**, **2.9**, **2.10** and **2.11** in good yield (82% to 95%). Aldehydes **2.9** and **2.11** were particularly sensitive and were used the same day in the cyclisation step.



Scheme 2.16: Synthesis of α,α-disubstituted 4-alkylidenecyclopropanals **2.5**, **2.9**, **2.10** and **2.11**

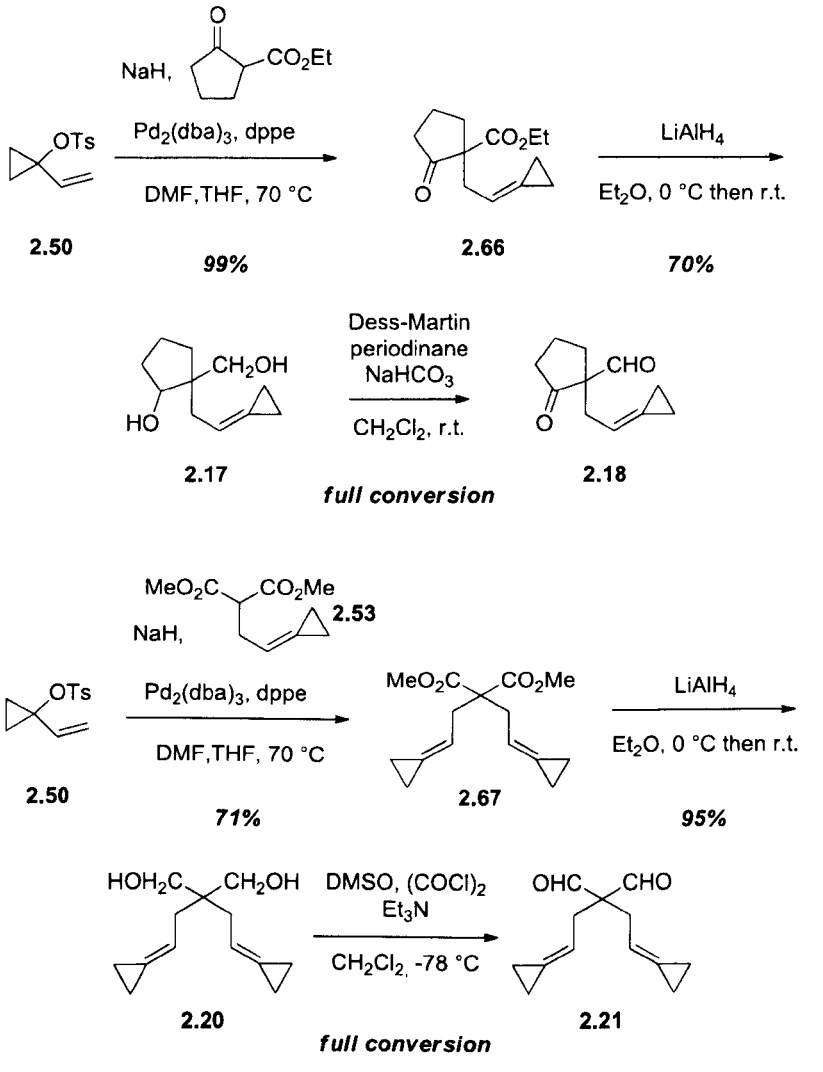
The same strategy was used for the synthesis of **2.12** (Scheme 2.17). Ester **2.51** was first alkylated using NaHMDS as base. Reduction of the ester moiety using $LiAlH_4$ gave alcohol **2.65** and aldehyde **2.12** was obtained by Swern's oxidation.[13]



Scheme 2.17: Synthesis of α,α-disubstituted 4-alkylidenecyclopropanals **2.12**

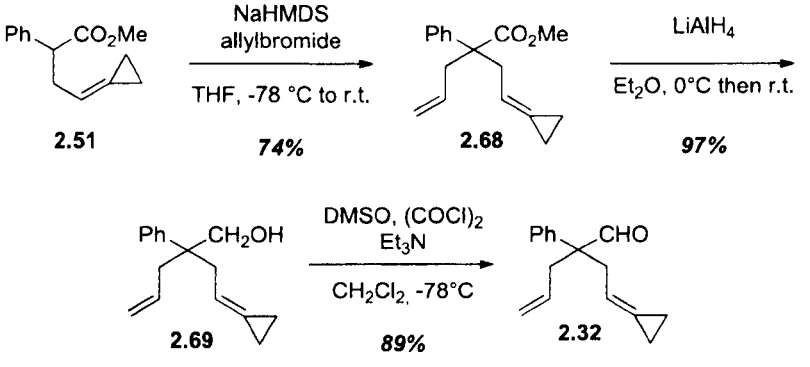
The synthesis of spiro-1,3-bisaldehydes **2.18** and **2.21** is described in scheme 2.18. Tsuji-Trost's alkylation between tosylate **2.50** and ethyl 2-oxocyclopentanecarboxylate or bisester **2.53** gave **2.66** and **2.67** in 99% and 71% yield, respectively.[12] Reduction of ketoester **2.66** and bisester **2.67** gave diols **2.17** and **2.20**, respectively. As previously mentioned, the aldehydes were obtained using the Dess-Martin [14] and Swern procedures.[13] These aldehydes were particularly sensitive and were used as crude in the cyclisation step. Attempts of purification on

silica promoted the decarbonylation of the compounds. However, aldehyde **2.18** could be filtered through a pad of celite in order to remove all insoluble periodinane residues and sodium bicarbonate. Aldehyde **2.21** was simply washed with a saturated solution of copper sulfate then was washed two times with water in order to remove the ammonium salts and the dimethyl sulfide.[15]



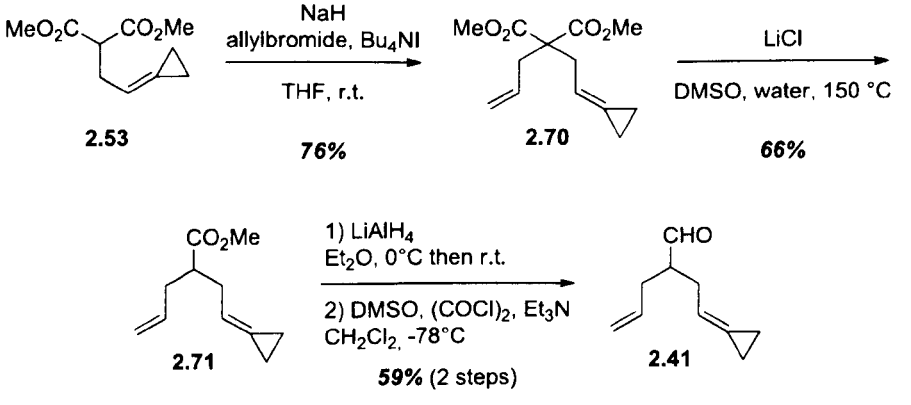
Scheme 2.18: Synthesis of aldehydes **2.18** and **2.21**

Aldehyde **2.32** was prepared from ester **2.51** (Scheme 2.19). Substitution using allylbromide gave compound **2.68**. Reduction of the ester moiety afforded alcohol **2.69** and was followed by oxidation using Swern's conditions.[13]



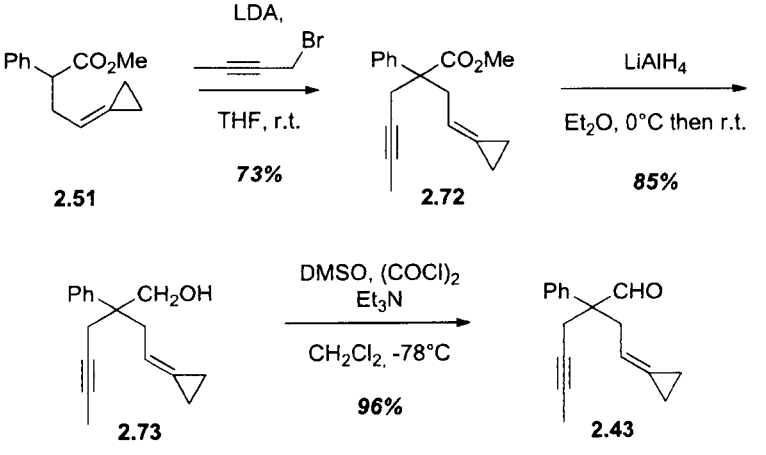
Scheme 2.19: Synthesis of **2.32**

The synthesis of aldehyde **2.41** is described in scheme 2.20. Allylation of bisester **2.53** gave **2.70** in 76% yield. Then, Krapcho decarboxylation using lithium chloride afforded monoester **2.71**.[16] This ester was reduced and the crude alcohol was oxidised under Swern's conditions,[13] affording aldehyde **2.41** in 59% yield over the two steps.



Scheme 2.20: Synthesis of aldehyde **2.41**

The synthesis of **2.43** began with the propargylation of **2.51** which gave **2.72** in 73% yield (Scheme 2.21). Reduction of the ester moiety afforded alcohol **2.73** which was oxidised into aldehyde **2.43** using Swern's conditions.[13]



Scheme 2.21: Synthesis of aldehydes **2.43**

5 – References

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893.

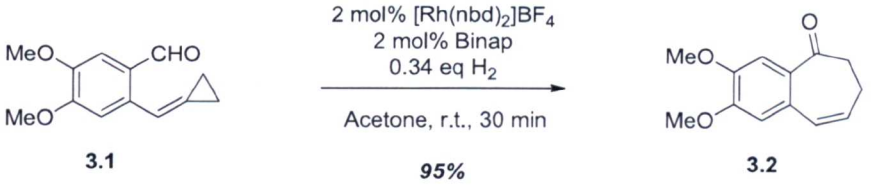
Chapter 3

Mechanistic Investigations

In this chapter, our efforts towards the understanding of the mechanism of the rearrangement are described. We first undertook kinetics studies and deuterium-labelled experiments in order to verify our mechanistic proposal. Intrigued by the chemoselective formation of cycloheptenone in the presence of another alkene, further investigations have also been carried out and our progress towards the understanding of this chemoselectivity is reported. In a final part, our efforts to explain the moderate enantiomeric excess obtained during the desymmetrisation of the prochiral bisaldehdyde **2.21** (numbered **3.13** in this chapter) are described.

1 – Kinetics studies

We decided to use aldehyde **3.1** to carry out kinetic studies because it can easily be prepared in two steps (Scheme 3.1). As previously reported, cycloheptenone **3.2** was isolated in 95% yield when aldehyde **3.1** was treated with 2 mol% of $[Rh(Binap)]BF_4$ in acetone.



Scheme 3.1: Cyclisation of aldehyde **3.1**

The kinetic studies were carried out with the same active catalyst, prepared in a Schlenk flask by mixing $[Rh(nbd)_2]BF_4$ and Binap in deuterated acetone and adding hydrogen. After 1 hour stirring at room temperature, the Schlenk flask containing active catalyst $[Rh(Binap)]BF_4$ was placed in the glove box. The desired amount of active catalyst was then added to substrate **3.1**. The resulting mixture was transferred in a sealed NMR tube and the conversion of **3.1** into 7-membered ring **3.2** was monitored by ^1H NMR. In figure 3.1, the concentration of starting material **3.1** ([**3.1**]) is plotted vs the time. Using the same concentration of rhodium catalyst of 0.001 mM, we varied the initial concentration of aldehyde **3.1** ($[\mathbf{3.1}]_0$) from 0.1 mM to 0.03 mM.

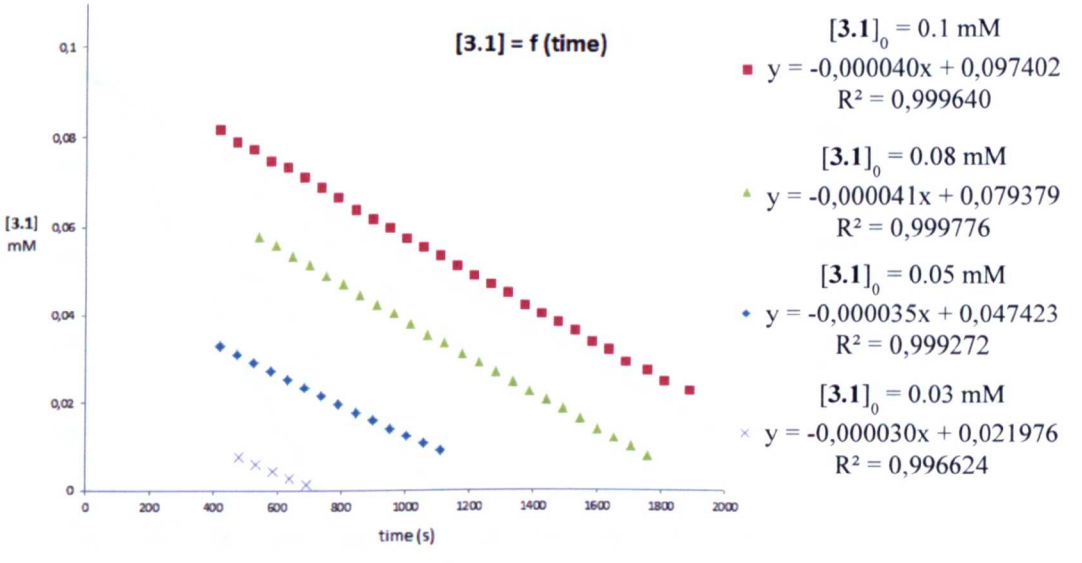


Figure 3.1: Evolution of the concentration of aldehyde **3.1** vs the time for different initial concentrations of **3.1**

The linear correlation obtained in each case, indicates a zero order dependence on substrate **3.1**. Moreover, the reaction occurs without induction period. Indeed, although the first measure is taken at 7 minutes, the initial concentration of **3.1** (x = 0) calculated from the trend line equations, match the experimental values, within experimental errors (0.097, 0.079 and 0.047 mM for 0.100, 0.080 and 0.050 mM, respectively). Given this zero order dependence on **3.1**, the rate law can be formulated by the following equation:

$$\text{rate} = k_{obs}\,[Rh]^n$$

with kobs = k $[\mathbf{3.1}]^0$ = k.

The order dependence on rhodium catalyst (n) was then calculated. In figure 3.2, the concentration of **3.1** ([**3.1**]) vs time is plotted for different concentrations of catalyst ([Rh] = 0.001, 0.002, 0.003 and 0.004 mM). For each experiment, the initial concentration of **3.1** was equal to 0.1 mM.

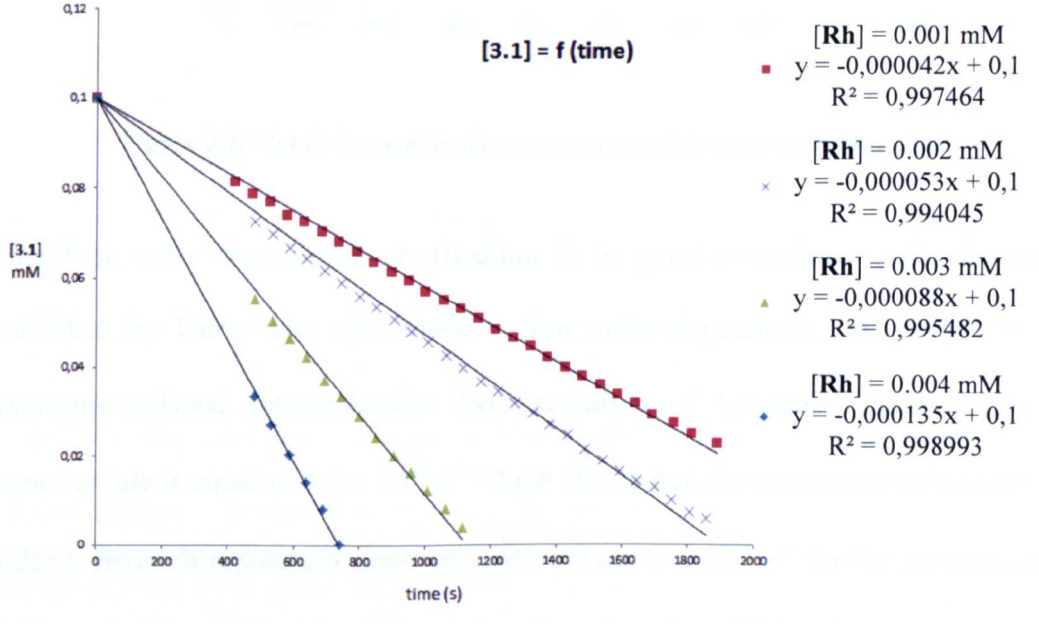


Figure 3.2: Evolution of the concentration of **3.1** vs time for different concentrations of catalyst

Not surprisingly, linear correlations were found, indicating a zero order dependence on substrate **3.1**. The slope of each trend line corresponds to the rate of the reaction for the given concentration of rhodium catalyst. Consequently, given the rate law established in equation 1, a first order dependence on rhodium (n = 1) was found. Indeed, in figure 3.3, the plot of these rates vs the concentration of rhodium to the power one gave the best linear correlation; this correlation obviously includes the coordinate (0,0).

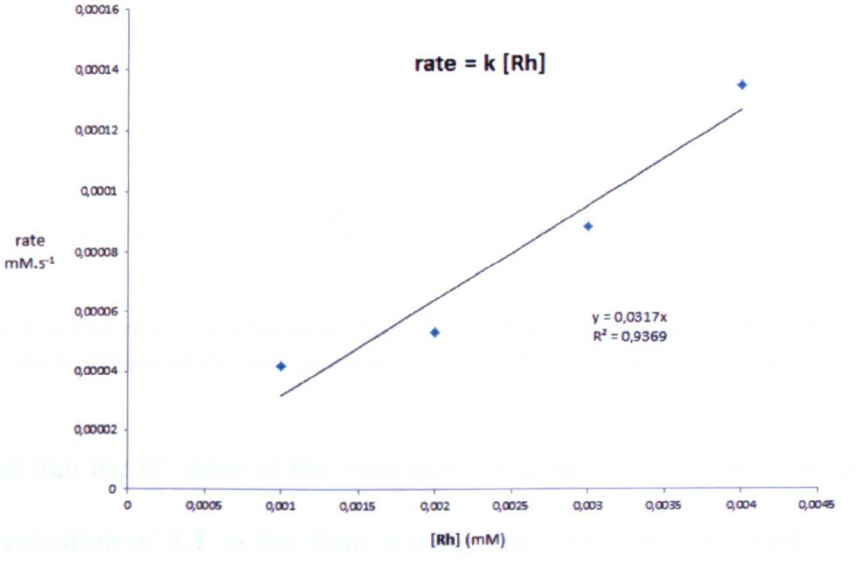


Figure 3.3: Plot of the rates vs the concentration of rhodium to the power one

This first order dependence on rhodium is in good accordance with the results published by Dong who also found a first order dependence on catalyst for the rhodium-catalysed intramolecular hydroacylation of ketones. [1] Interestingly, the turnover rate is equal to 3.2×10^{-2} s^{-1} which shows that the rearrangement is very fast. Indeed, Bosnich reported a turnover rate of about 3×10^{-1} s^{-1} for the intramolecular hydroacylation of 4-pentenal,[2] meaning that that the additional ring-opening step slows the reaction rate only by one order magnitude.

Interestingly, for higher conversion, the plot of the concentration of **3.1** vs time is not linear anymore. For instance, for the initial concentration $[\mathbf{3.10}]_0$ = 0.05 mM, a change of the rate law was observed when [**3.1**] = 0.009 mM, which corresponded to 82% conversion (Figure 3.4a). In figure 3.4b, the plot of the concentration of **3.1** ([**3.1**]) vs time and the plot of the logarithm of the concentration of **3.1** (ln ([**3.1**])) vs time are presented for conversion higher than 82%.

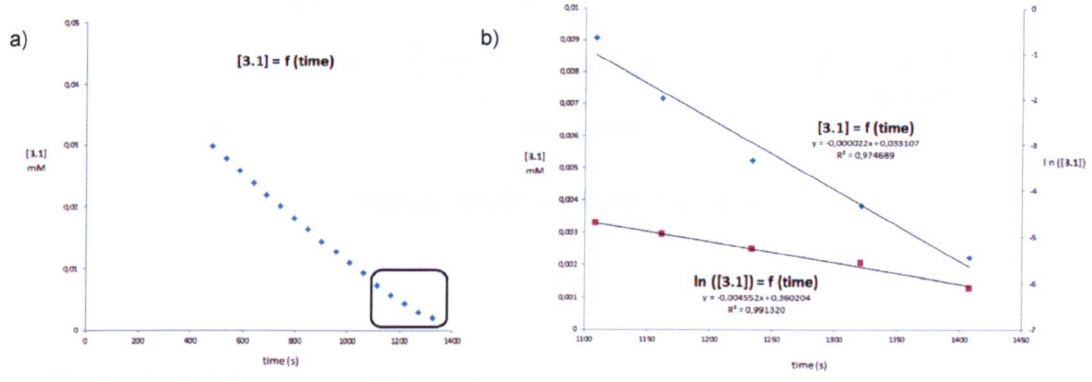
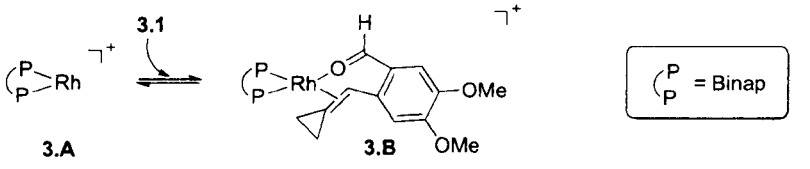


Figure 3.4: a) Plot of the concentration of **3.1** vs time b) Plot of the concentration of **3.1** ([**3.1**]) and the logarithm of the concentration of **3.1** (ln ([**3.1**])) vs time for high conversion

We found that the R^2 value of the trend line associated to the plot of the logarithm of the concentration of **3.1** vs the time is better than the value obtained for the plot of the concentration of **3.1** vs the time, indicating that for high conversion, the reaction rate exhibits a first order dependence in substrate concentration.

These kinetic studies gave us interesting insights into the mechanism of the reaction. In acetone, the commonly accepted form of active catalyst is a monomeric rhodium catalyst of type **3.A** where the two phosphorus atoms of the bisphosphine ligand and two molecules of acetone (not represented) coordinate the metal centre (Scheme 3.2).[2,3] We found that, as the reaction proceeds, the order dependence on substrate **3.1** varies from zero to one. For conversion inferior than 80%, **3.B** corresponds to the resting state.[4] For conversion higher than 80% (in the case where $[\mathbf{3.1}]_0$ = 0.05 mM

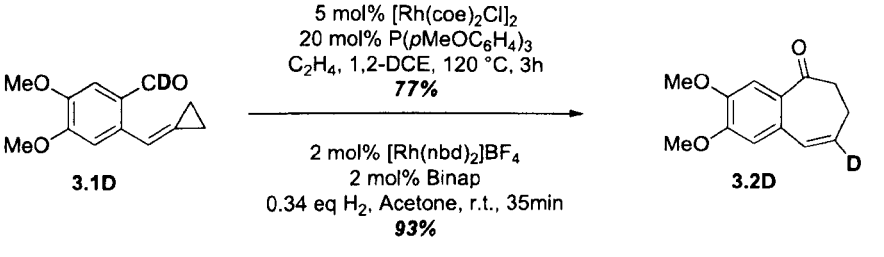
and [Rh] = 0.001mM), this change in the rate law could be imputed to a change of the equilibrium between **3.A** and **3.B**. Therefore, for low concentrations of **3.1** the equilibrium would be in favour of complex **3.A**. Hence, at high conversions, the complexation of **3.1** with **3.A** to form **3.B** would become the rate-limiting step, explaining the first order dependence on the concentration of **3.1**.



Scheme 3.2: Plausible intermediates

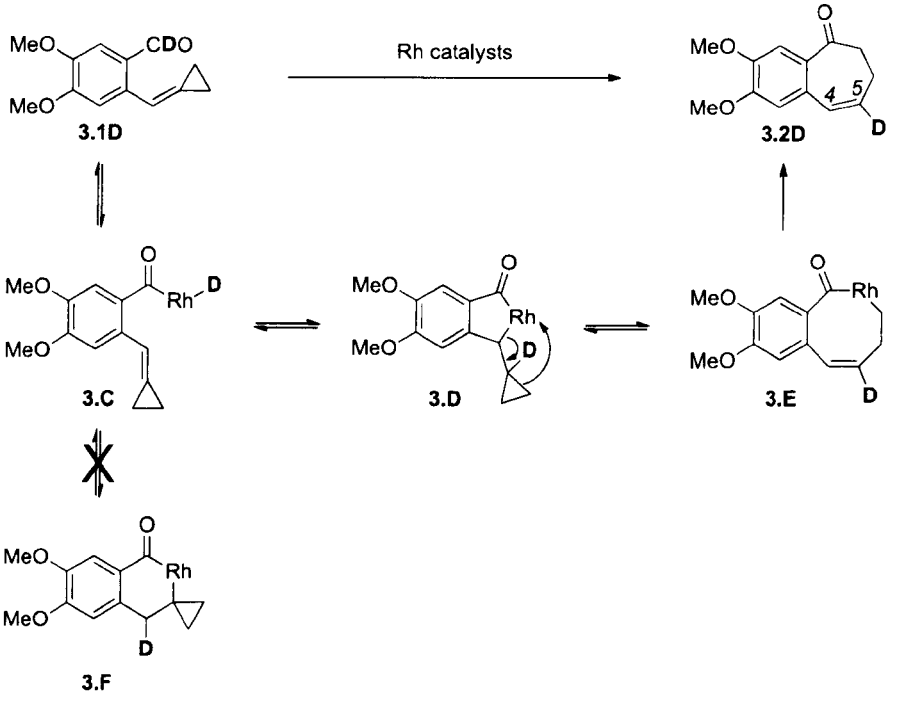
2 – Deuterium-labelling experiment

In order to verify our mechanistic hypothesis formulated in chapter 1, deuterium-labelled aldehyde **3.1D** was synthesised. Exposure of **3.1D** to both neutral and cationic rhodium catalyst, affords 7-membered ring **3.2D** in 77% and 93% yield, respectively, with complete transfer of the deuterium label at the indicated position (Scheme 3.3).



Scheme 3.3: Complete transfer of the deuterium atom

This result supports the proposed mechanism depicted in scheme 3.4. Initially, a Rh(I) species would oxidatively insert into the C–D bond, giving Rh(III)-hydride complex **3.C**. Hydrometallation of the C–C double bond would then afford pentarhodacycle **3.D**. Driven by the release of the strain energy of the cyclopropane moiety, **3.D** would be prone to undergo ring enlargement towards octarhodacycle **3.E**. Final reductive elimination would afford 7-membered ring **3.2D**. The complete transfer of the deuterium atom on position 5 suggests an exclusive formation of pentarhodacycle **3.D**. If hexarhodacycle **3.F** was a transient intermediate, a scrambling of the deuterium atom on both carbon atoms 4 and 5 would have been observed. Presumably, the steric hindrance between the cyclopropyl moiety and the ligand sphere on the rhodium catalyst in **3.F** prevents its formation.

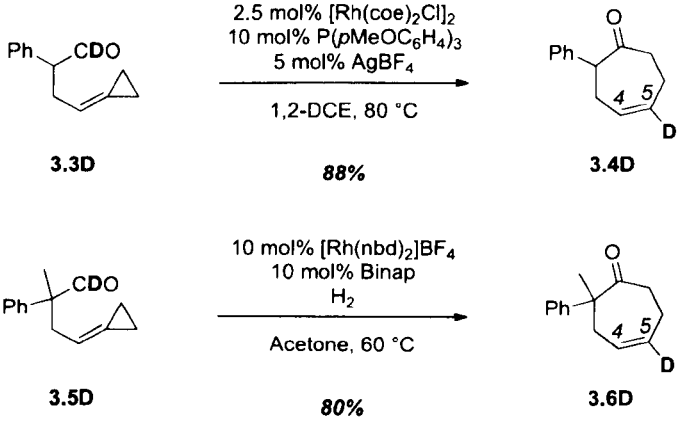


Scheme 3.4: Proposed mechanism accounting for the conversion of **3.1D** into **3.2D**

The conversion of an equimolar mixture of **3.1** and **3.1D** was also monitored by ^{1}H NMR and a kinetic isotope effect of 1.3-1.4 was found during the course of the

reaction. This value is in good accordance with the value found by Miller who obtained a kinetic isotope effect of 1.3-1.6 for the neutral rhodium-catalysed intramolecular hydroacylation of 4-pentenal.[5]

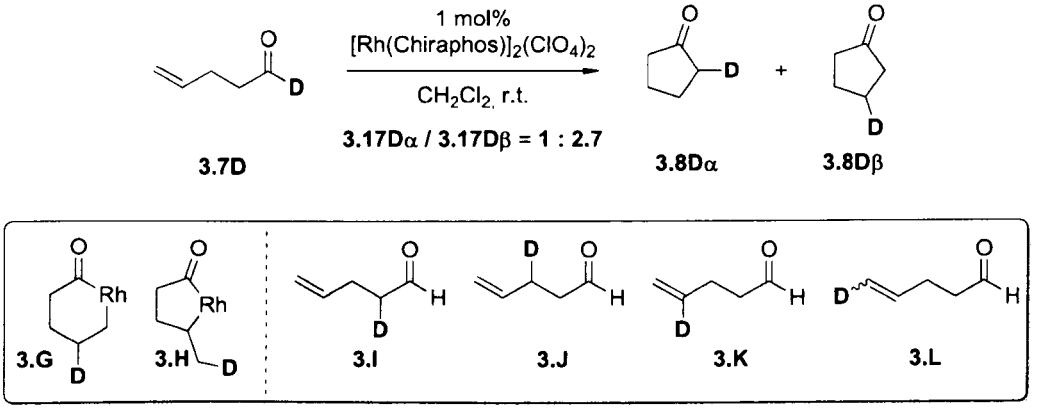
The complete transfer of the deuterium atom on carbon 5 was also observed with aliphatic aldehyde **3.3D** (Scheme 3.5). The cationic rhodium complex was generated in situ by adding $AgBF_4$ to $[Rh(coe)_2Cl]_2$ and $P(pMeOC_6H_4)_3$. Under these conditions, **3.4D** was isolated in 88% yield. Finally, exposure of α,α-disubstituted aldehyde **3.5D** to 10 mol% of $[Rh(Binap)]BF_4$ also resulted in the complete transfer of the deuterium atom on position 5 in **3.6D**.



Scheme 3.5: Complete transfer of the deuterium atom for aliphatic aldehyde

These results strongly support the exclusive formation of pentarhodacycle over hexarhodacycle. Our proposed mechanism is clearly different from the mechanistic conclusions drawn by Bosnich[2,3] and Miller[5] on intramolecular hydroacylation of 4-pentenals. Indeed, as previously discussed in chapter 1 (see page 8), treating deuterium-labelled 4-pentenal **3.7D** with cationic rhodium catalyst resulted in the scrambling of the deuterium atom, furnishing **3.8Dα** and **3.8Dβ** (Scheme 3.6). Moreover, monitoring the reaction by ^1H NMR, Bosnich identified products **3.I** –

3.L as transient intermediates, a phenomenon we did not observe with **3.3D** and **3.5D**. After C–D activation of **3.7D** by the rhodium catalyst, hydrometallation of the C–C double bond affords hexarhodacycle **3.G** and pentarhodacycle **3.H**. While **3.8Dβ**, **3.J** and **3.K** come from hexarhodacycle **3.G**, **3.8Dα**, **3.I** and **3.L** arise from pentarhodacycle **3.H**. For complete conversion, **3.8Dα/3.8Dβ** were obtained in 1:2.7 ratio. However, at the early stage of the reaction, the sum of products **3.8Dα**, **3.I** and **3.L** is slightly higher than the sum of products **3.8Dβ**, **3.J** and **3.K**. Hence, this result indicates that pentarhodacycle is formed faster than hexarhodacycle. Conversely, our mechanism relies on the unique formation of pentarhodacycle intermediates.



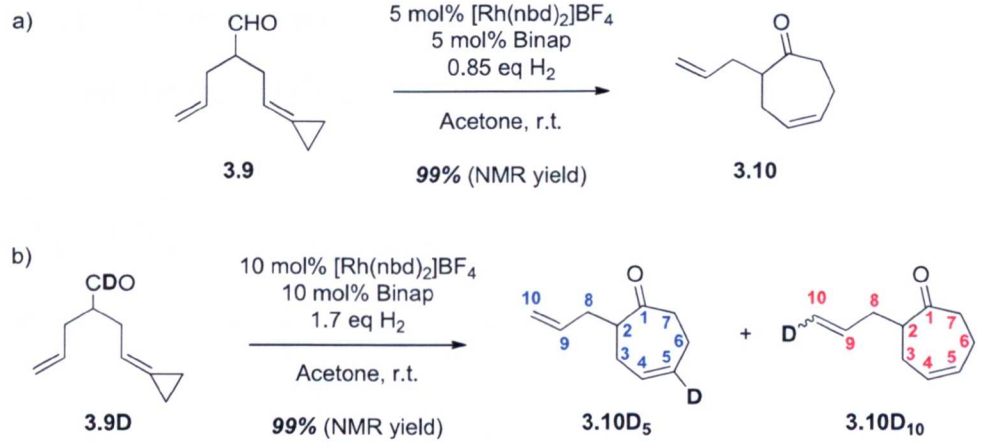
Scheme 3.6: Rhodium-catalysed intramolecular hydroacyclation of 4-pentenal **3.7D**

3 – Competition between terminal alkene and alkylidenecyclopropane

3 – 1 – Mechanistic investigation

As previously mentioned in chapter 2, **3.9** is chemoselectivity rearranged into 7-membered ring **3.10** (Scheme 3.7a). In order to gain more insight on the role of the terminal alkene, deuterium-labelled aldehyde **3.9D** was prepared and exposed to 10 mol% of $[Rh(Binap)]BF_4$ in acetone at room temperature (Scheme 3.7b).

Interestingly, scrambling of the deuterium atom onto positions 5 and 10 was observed.



Scheme 3.7: Scrambling of the deuterium atom

The two structures **3.10D$_5$** and **3.10D$_{10}$**, obtained in 55:45 ratio, were identified by ^{13}C NMR by comparison with the non-deuterated 7-membered ring **3.10** (Figure 3.5).

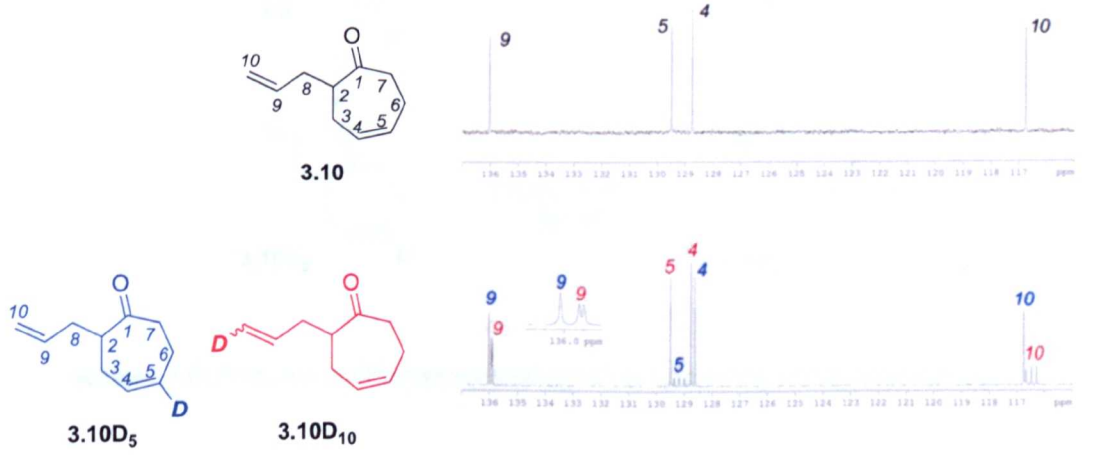
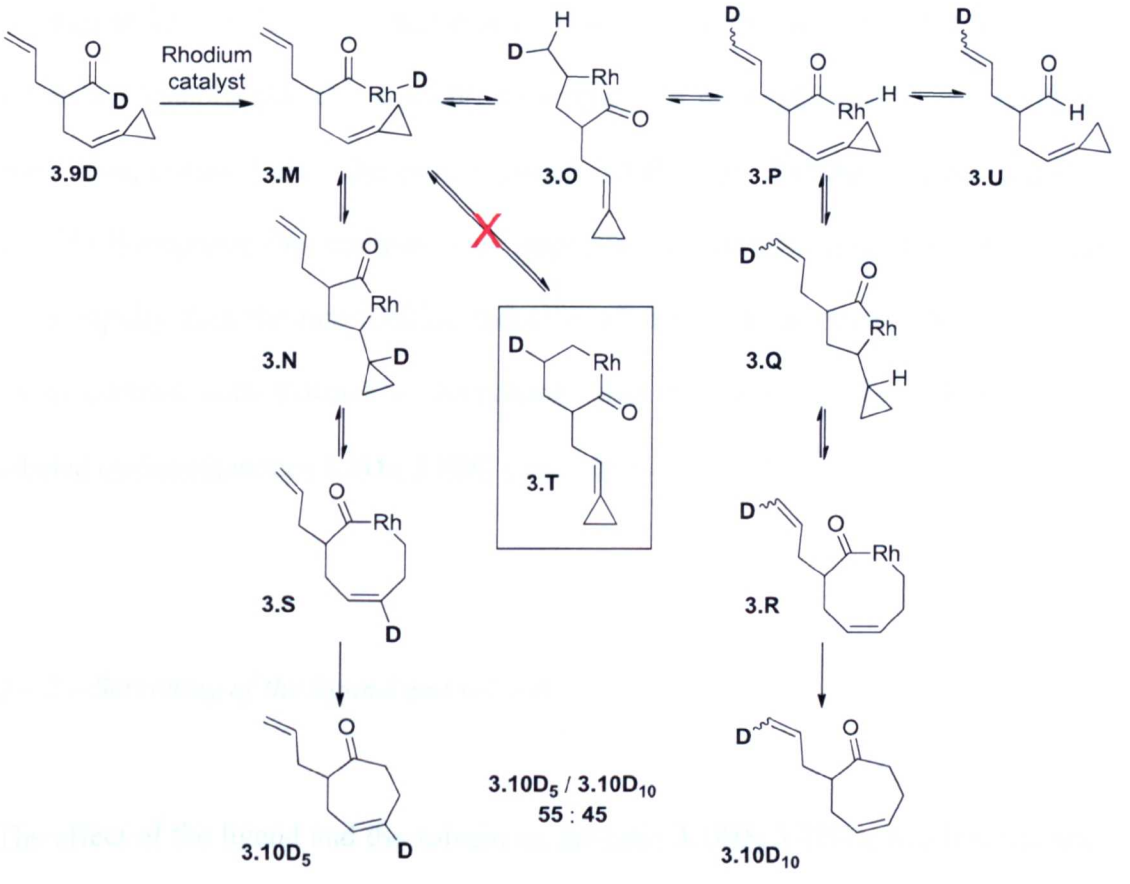


Figure 3.5: Identification of **3.10D$_5$** and **3.10D$_{10}$** by comparison of their ^{13}C NMR with **3.10**

The scrambling of the deuterium atom indicates that the terminal alkene is involved in the rearrangement. Therefore, the following mechanism is proposed (Scheme 3.8). Oxidative addition of the rhodium catalyst into the formyl C–D bond would afford **3.M**. Then, both pentarhodacycles **3.N** and **3.O** would be formed. **3.N** would successively undergo β–carbon elimination giving octarhodacycle **3.S** and reductive elimination of the rhodium would afford **3.10D$_5$**. On the other hand, **3.O** would give

acyl-hydride-rhodium **3.P** via β–hydride elimination. Then, the C–C double bond of the alkylidenecyclopropane would undergo hydrometallation toward **3.Q**. β–carbon elimination followed by reductive elimination would successively give **3.R** and the other 7-membered ring **3.10D$_{10}$**.



Scheme 3.8: Proposed mechanism accounting for the scrambling of the deuterium atom

Importantly, hexarhodacycle **3.T** is not a transient intermediate since deuterium atom was not found on position 9. This result is in sharp contrast with the theoretical studies reported by Sargent and co-workers on rhodium-catalysed intramolecular hydroacylation of 4-pentenals. [6] Hence, their DFT calculations suggest that hexarhodacycles are formed as fast as pentarhodacycles in acetone.

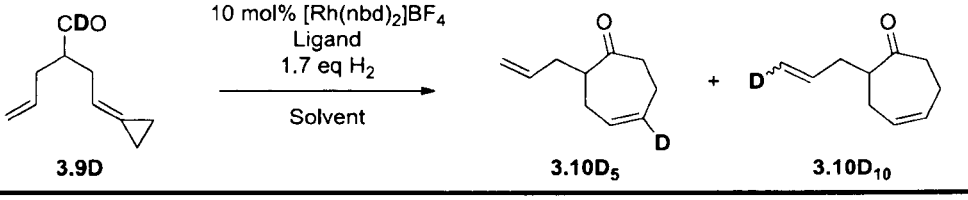
Interestingly, exposing **3.9D** under the same reaction conditions (10 mol% of [Rh(Binap)]BF_4 in acetone) but at -20 °C resulted in a scrambling of the deuterium label after 2.5 hours of reaction. Indeed, a peak at 9.64 ppm corresponding to the aldehyde shift appeared in ^1H NMR. A mixture of aldehydes **3.9D** and **3.U** was isolated in 1:0.4 ratio. This result implies that the equilibrium between **3.N** and **3.Q** is quickly established. The equilibrium is likely to be established more rapidly at room temperature hence the ratio between **3.10D$_5$** and **3.10D$_{10}$** remains constant (55:45) throughout the reaction. This suggests that the equilibrium is established more rapidly than the rate-limiting reductive elimination can occur. This is also in sharp contrast with Bosnich's observations that the ratio of α- and β-deuterium-labeled cyclopentanones **3.8Dα/3.8Dβ** varied from 1:20 to 1:2.7.[2,3]

3 – 2 – Screening of the ligand and solvent

The effect of the ligand and the solvent on the ratio **3.10D$_5$/3.10D$_{10}$** was investigated (Table 3.1). Interestingly, among the phosphines tested, [Rh(Binap)]BF_4 was the only catalyst which gave a scrambling of the deuterium atom (entry 1). Dppe, dppb, dppf, Xantphos and DPEPhos-based catalysts (entries 2 – 6) only gave 7-membered ring **3.10D$_5$**. Switching for P(*p*MeOC_6H_4)$_3$ also afforded **3.10D$_5$** as single isomer alongside 7-membered ring **3.11D** in approximately 25% yield. **3.11D** likely results from the migration of the C–C double bond from compound **3.11D**.[7] Changing acetone for nitromethane or dichloromethane lead to the same conclusion; Binap-based catalyst promotes the scrambling of the deuterium atom while dppe-based

catalyst does not. Interestingly, in dichloromethane, small amounts of cyclopentanones **3.12D** were identified.

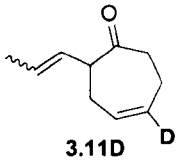
Table 3.1: Screening of the ligand and solvent: effect on the ratio **3.10D$_5$/3.10D$_{10}$**



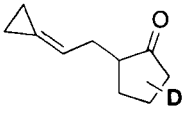
3.9D **3.10D$_5$** **3.10D$_{10}$**

Entry	Ligand (mol%)	Solvent	T (°C)	Time	Isolated Yield	Ratio **3.10D$_5$ /3.10D$_{10}$**
1	Binap (10)	Acetone	r.t.	20 min	61%	55:45
2	dppe (10)	Acetone	r.t.	20 min	65%	100:0
3	dppb (10)	Acetone	r.t.	40 min	78%	100:0
4	dppf (10)	Acetone	60	20 h	42%[a]	100:0
5	Xantphos (10)	Acetone	60	20 h	41%[b]	100:0
6	DPEPhos (10)	Acetone	60	20 h	66%	100:0
7	P(*p*MeOC$_6$H$_4$)$_3$ (20)	Acetone	60	18 h	37%[c]	100:0
8	P(*p*MeOC$_6$H$_4$)$_3$ (10)	Acetone	60	2 h	32%[c]	100:0
9	Binap (10)	CH_3NO_2	r.t.	20 min	57%	55:45
10	Binap (10)	CH_2Cl_2	40	2 h 30	47%[d]	55:45
11	dppe (10)	CH_3NO_2	r.t.	18 h	71%	100:0
12	dppe (10)	CH_2Cl_2	40	12 h	48%[d]	100:0

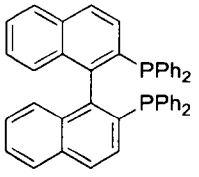
[a]: 26% of **3.9D** was recovered.
[b]: 16% of **3.9D** was recovered.
[c]: approximately 25% of compound **3.11D** was identified.
[d]: approximately 5 to 10% of cyclopentanones **3.12D** were identified.



3.11D

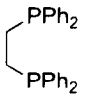


3.12D



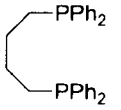
Binap

bite angle 93°



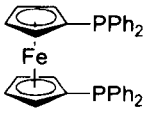
dppe

86°



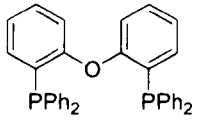
dppb

94°



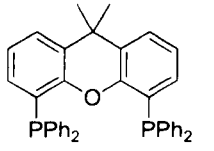
dppf

99°



DPEphos

104°



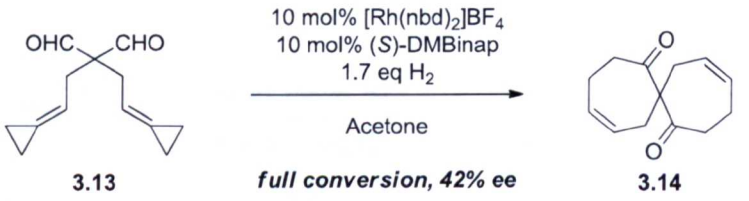
Xantphos

108°

Several conclusions can be drawn from this screening. Firstly, the bite angle[8] of the bisphosphine ligand does not have any effect on the chemoselectivity. Indeed, Binap and dppb have a similar bite angle (93° and 94°, respectively) but complete chemoselectivity towards **3.10D$_5$** was observed when [Rh(dppb)]BF_4 was used (entry 1 vs 3). The bidentate vs monodentate character of the phosphine ligand does not seem to control the chemoselectivity outcome (entry 1 vs 7). We also hypothesized that Binap would act as a monodentate phosphine ligand which would explain is unique behaviour. However, using only 1 equivalent of P(pMeOC_6H_4)$_3$ as compared to [Rh(nbd)$_2$]BF_4 only seems to accelerate the rate of the reaction without changing the result of the chemoselectivity (entry 7 vs 8). Hence, this study showed again that our system favours the formation of pentarhodacycle over hexarhodacycle even in the presence of a simple alkene. The screening of the ligand and solvent on the chemoselectivity of the reaction showed the unique behaviour of Binap.

4 – Desymmetrisation of prochiral bisaldehyde: attempts to explain the low enantioselectivity

As described in chapter 2, the ee obtained during the desymmetrisation of prochiral bishaldehyde **3.13** remained moderate (Scheme 3.9).



Scheme 3.9: Desymmetrisation of aldehyde 3.13 using chiral phosphine ligand

Intriguingly, a decrease of the selectivity with the conversion was observed in several occasions. We therefore, carefully monitored the reaction and observed an apparent erosion of the ee with the conversion (Figure 3.6). When **3.13** was exposed to 10 mol% of [Rh(*S*)-DMBinap]BF_4 in acetone at room temperature, a linear erosion of the ee was found and the trend line equation gave a theoretical ee of 44% for full conversion, in very good accordance with the experimental value of 42% found in previous attempts (Chapter 2, Table 2.8, entry 2).

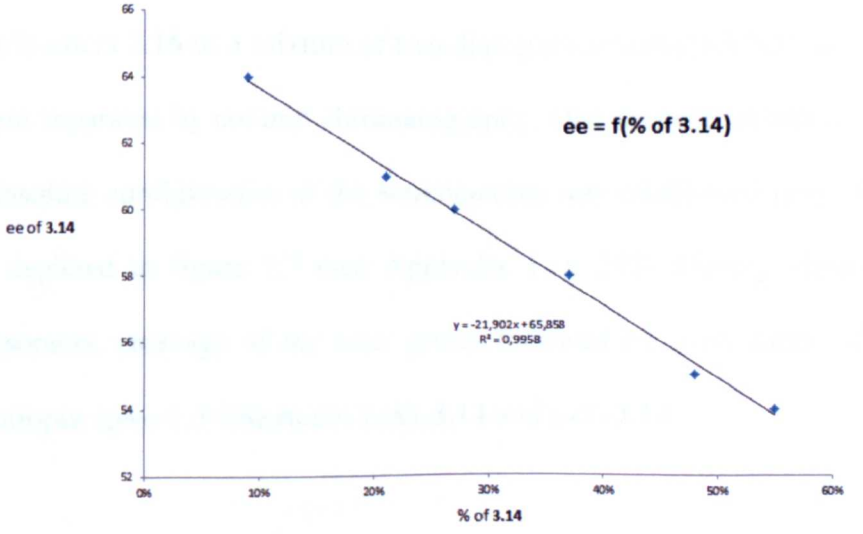
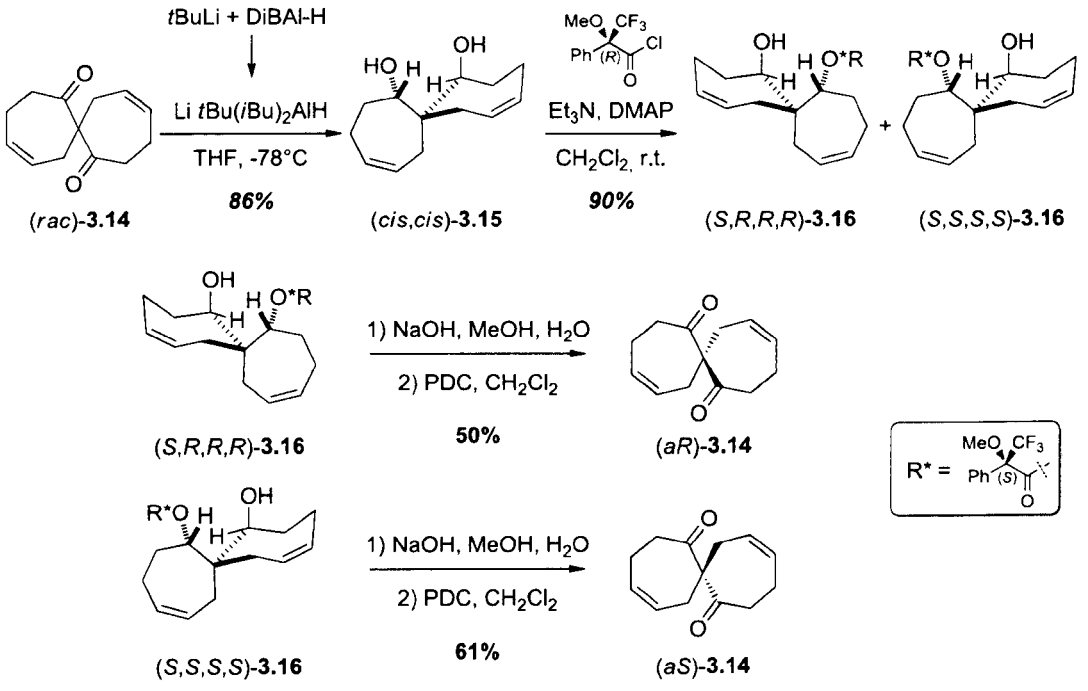


Figure 3.6: Erosion of the ee vs the conversion

In order to study this erosion of ee both enantiomers of spiro-1,3-bisketone **3.14** were synthesised separately allowing for their identification, using GC (Scheme 3.10).



Scheme 3.10: Synthesis of enantiopure (*aR*)- and (*aS*)-**3.14**

Racemic spiro-1,3-bisketone **3.14** was selectively reduced into the racemic mixture of *cis,cis*-bisalcohols **3.15** (*S,aS,S* and *R,aR,R*) with only traces of the other diastereoisomers detected. This was achieved by preparing in situ, the bulky reducing agent Li*t*Bu(iBu)$_2$Al.[9] Mono-esterification of **3.15**, using (*R*)-Mosher's acid chloride afforded (*S*)-esters **3.16** as a mixture of two diastereoisomers ((*S,S,S,S*) and (*S,R,R,R*)) which were separated by column chromatography. One diastereoisomer crystallised, and the absolute configuration of the stereocentres was established from the X-Ray structure depicted in figure 3.7 (see Appendix 1, p 287). Having identified both diastereoisomers, cleavage of the ester group followed by re-oxidation of the diol gave enantiopur spiro-1,3-bisketones (*aR*)-**3.14** and (*aS*)-**3.14**.

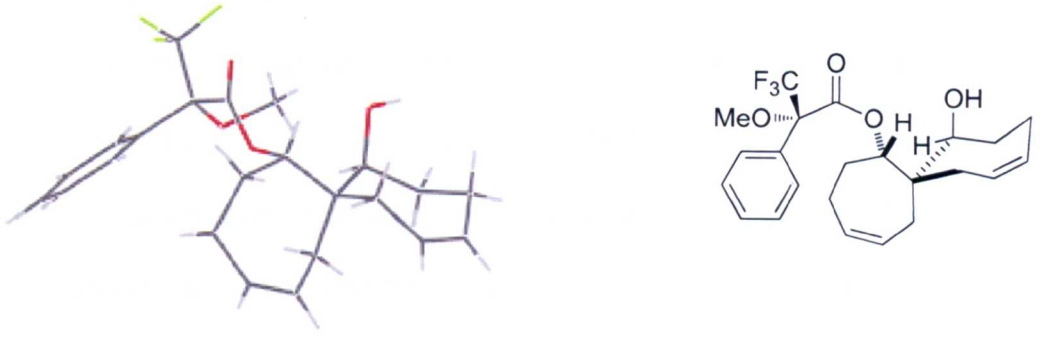
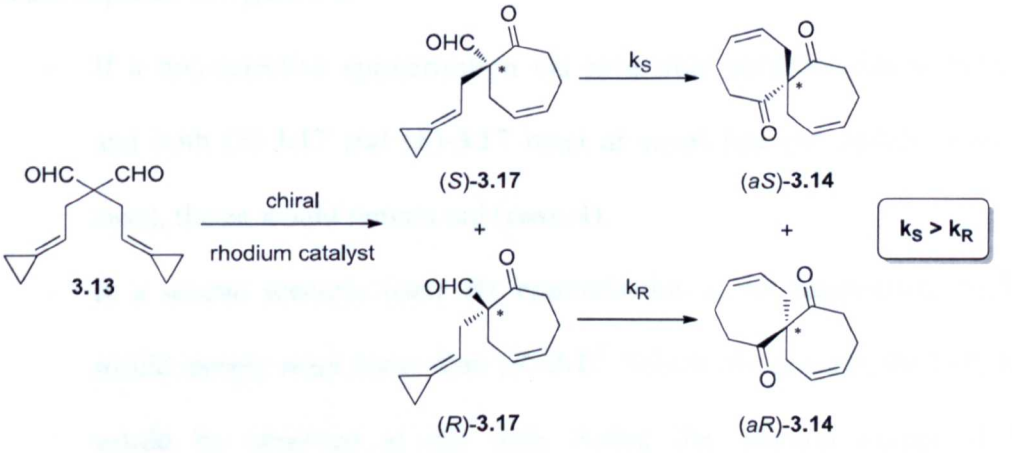


Figure 3.7: X-Ray structure of (*S*,*S*,*S*,*S*)-**3.16**

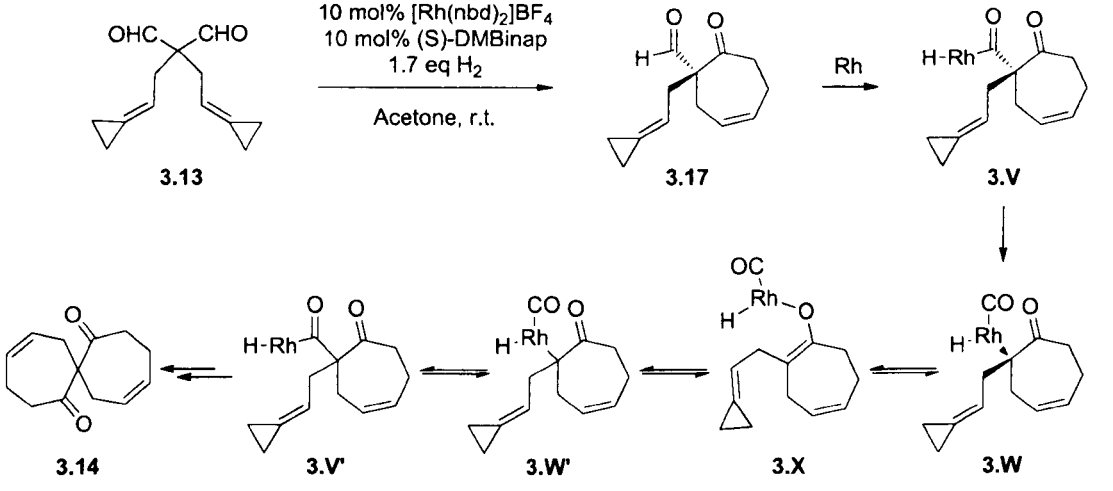
Several hypotheses could be postulated to explain this apparent erosion. First, we verified that spiro-1,3-bisketone **3.14** did not undergo racemisation under the reaction conditions. An enantioenriched sample of **3.14** (ee = 42%) was treated with 10 mol% [Rh(*S*)-DMBinap]BF_4 in acetone. After 48 hours at room temperature **3.14** was recovered with the same ee, ruling out this hypothesis.

Second, the erosion could be explained by a match/mismatch case. Treating 1,3-bisaldehyde **3.13** with 10 mol% [Rh(*S*)-DMBinap]BF_4 would afford intermediate (*S*)-**3.17** with an ee of 42% (Scheme 3.11). Then, (*S*)-**3.17** would be transformed in (*aS*)-**3.14** faster than (*R*)-**3.17** is transformed in (*aR*)-**3.14**; resulting in the apparent erosion of the ee of (*aS*)-**3.14** with the conversion.



Scheme 3.11: Match/mismatch case

A third explanation would rely on the racemisation of intermediate **3.17** (Scheme 3.12). After the C–H activation of the formyl bond of **3.17** giving **3.V**, extrusion of carbon monoxide[10] would give intermediate **3.W**. Then, **3.W** would give racemic **3.W'** via the formation of rhodium enolate complex **3.X**.[11,12] Hence, this would result in the loss of the stereochemistry of the quaternary carbon and affect the final ee of **3.14**. Finally, **3W'** would undergo carbon monoxide insertion,[13,14,15] giving **3.V'** which would then undergo the second cyclisation towards racemic **3.14**.



Scheme 3.12: Proposed mechanism accounting for the racemisation of intermediate **3.17**

It is also possible that several reactions are at play simultaneously. The different cases are depicted in figure 3.8:

- If a non-selective epimerisation via reversible decarbonylation happens and both (*S*)-**3.17** and (*R*)-**3.17** react at equal rate (no match/mismatch case), the ee would remain nul (***case A***).
- In a second scenario (***case B***), epimerisation is not happening, (*S*)-**3.17** would simply react faster than (*R*)-**3.17**. Selectivity towards the (*aS*)-**3.14** would be observed at any time during the reaction except at full conversion when a racemic mixture of **3.14** would finally be obtained.

- If (*S*)-**3.17** is selectively epimerised into (*R*)-**3.17** at a rate competitive to the hydroacylation and both (*S*)-**3.17** and (*R*)-**3.17** undergo hydroacylation at equal rate, (*aR*)-**3.14** would be the major enantiomer at any time and the ee would evolve linearly (***case C***).
- If (*S*)-**3.17** is selectively epimerised into (*R*)-**3.17** at a rate competitive to the hydroacylation and (*S*)-**3.17** undergoes hydroacylation faster than (*R*)-**3.17**, a selectivity towards (*aS*)-**3.14** would first be observed but (*aR*)-**3.14** would finally be obtained as the main enantiomer (***case D***).
- If (*S*)-**3.17** is selectively epimerised into (*R*)-**3.17** at a rate competitive to the hydroacylation and (*R*)-**3.17** undergoes hydroacylation faster than (*S*)-**3.17**, (*aR*)-**3.14** would be obtained as main enantiomer; in this case the ee of (*aR*)-**3.14** would first strongly increase before reaching a plateau when (S)-**3.17** finally reacts (***case E***).

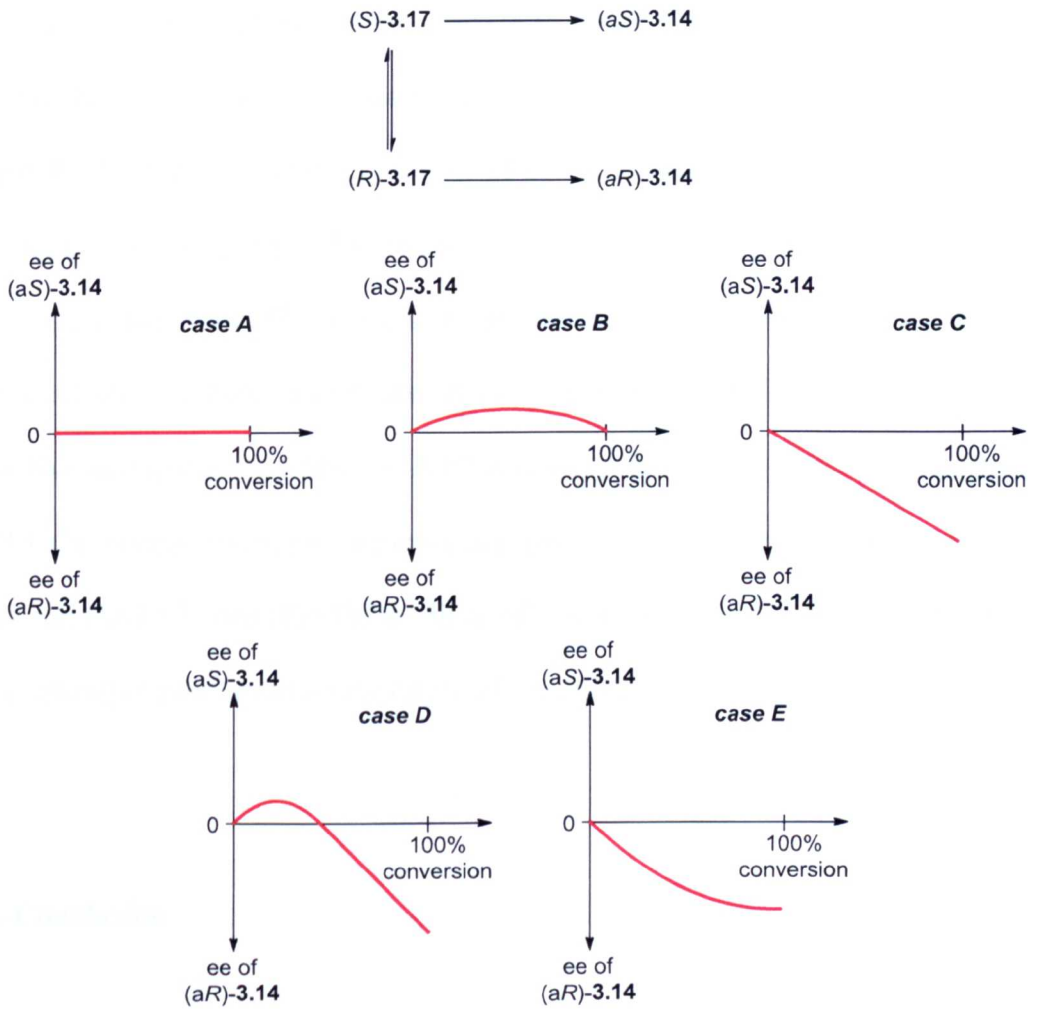


Figure 3.8: Qualitative evolution of the ee of **3.14** vs the conversion; different possible cases when a racemic mixture of **3.17** is exposed to 10 mol% of [Rh(*S*)-DMBinap]BF_4 in acetone

Given that the treatment of prochiral 1,3-bisaldehyde **3.13** with 10 mol% of [Rh(*S*)-DMBinap]BF_4 gave (*aS*)-**3.14**, these hypotheses were verified by exposing a racemic mixture of (*S*)-**3.17** to 10 mol% of [Rh(*S*)-DMBinap]BF_4 in acetone at room temperature. Under these conditions, (*aS*)-**3.14** was obtained as major enantiomer at 60% conversion. The ee of (*aS*)-**3.14** was equal to 13% while the remaining starting material **3.17** was enantioenriched in (*R*) isomer. An enantiomeric excess of 11% was found for (*R*)-**3.17**, closely matching the absolute value of the enantiomeric excees of (*aS*)-**3.14**. Therefore, these results indicate that the erosion is not due to the situations described in ***cases A***, ***C***, ***E***. Unfortunately, **3.17** proved to be particularly

difficult to handle and we did not manage to obtain full conversion. However, it is reasonable to assume that this apparent erosion is due to a match/mismatch case (***case B***). Indeed, a significant erosion of the ee is observed when we started from prochiral 1,3-bisaldehyde **3.13** (from 65% to 42%). Therefore an ee of 13% in favour of the (*aS*) isomer for 60% conversion, does not seem compatible with ***case D***.

It should also be noticed that ***case B*** could also correspond to the case of a non-selective epimerisation where (*S*)-**3.17** is reacting faster than (*R*)-**3.17**. Therefore, it will be important to prepare enantiopure aldehyde **3.17**. Hence, treating separately (*R*)- and (*S*)-**3.17** with [Rh(*S*)-DMBinap]BF_4 and observing the final ee should give us a definitive conclusion on the origin of the erosion.

5 – Conclusion

The kinetic studies revealed a first order dependence on the concentration of rhodium catalyst. The order of dependence on aldehyde concentration varied with the conversion. Until 80% conversion a zero order dependence on the concentration of aldehyde was found while for higher conversion a first order dependence on the concentration of aldehyde was obtained.

The rearrangement of deuterium-labelled aldehydes corroborated our mechanistic proposal which relies on the formation of pentarhodacycles. Importantly, the complete transfer of deuterium label into a single position indicates that hexarhodacycles are not formed as transient intermediates.

The chemoselectivity towards alkylidenecyclopropane was further investigated using deuterium-labelled aldehyde. This study revealed that [Rh(Binap)]BF_4 was the only

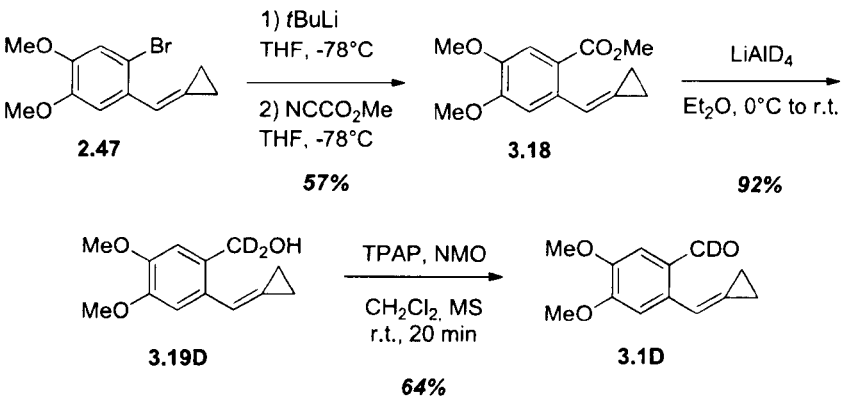
catalyst promoting the scrambling of the deuterium atom, hence, indicating that the terminal alkene is involved in the rearrangement under our optimised conditions. Further investigations will consist on the screening of ligands having different backbones.

The attempts of desymmetrisation of the prochiral bisaldehyde **3.13** were problematic due to its low stability. The apparent erosion of enantioselectivity observed during the course of the reaction likely results from the fact that one of the two enantiomers undergoes the second cyclisation faster than the other. It will be necessary to prepare the enantiopure 1,3-ketoaldehyde in order to validate this hypothesis. Moreover, further screening of the chiral ligands could be envisioned.

6 – Synthesis of Precursors

*6 – 1 – Synthesis of aldehyde **3.1D***

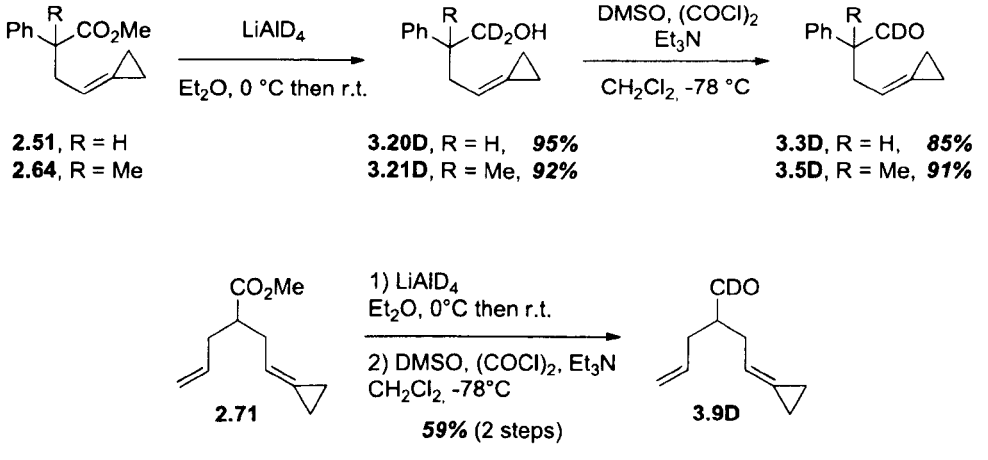
Deuterium-labelled aldehyde **3.1D** was synthesised from compound **2.47** (Scheme 3.13). Bromine-lithium exchange using *t*-butyllitium, followed by the addition of methyl cyanoformate gave ester **3.18** in 57% yield. Subsequent reduction of the ester moiety using lithium aluminium deuteride afforded benzylic alcohol **3.19D** in 92% yield and oxidation using Ley's conditions led to aldehyde **3.1D** in 64% yield.[16]



Scheme 3.13: Synthesis of the precursor of optimisation **3.1D**

*6 – 2 – Synthesis of aldehydes **3.3D**, **3.5D** and **3.9D***

Alcohols **3.20D** and **3.21D** were obtained by reduction of esters **2.51** and **2.64**, respectively, using lithium aluminium deuteride (Scheme 3.14). Both aldehydes were obtained via Swern's oxidation.[17] Aldehyde **3.9D** was obtained from ester **2.71** following the same sequence. The intermediate alcohol was not isolated.



Scheme 3.14: Synthesis of **3.3D**, **3.5D** and **3.9D**

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Chapter 4

Formation of 8-Membered Rings via Rhodium-catalysed Intramolecular Hydroacylation of Alkylidenecyclobutanes

As described in chapter 2, 7-membered rings have been obtained via rhodium-catalysed intramolecular hydroacylation of aldehyde-tethered alkylidenecyclopropanes. We envisioned replacing the cyclopropane moiety by a cyclobutane moiety given the similar strain energy associated to these small rings (strain energy of cyclopropane = 27.5 kcal.mol^{-1}, strain energy of cyclobutane = 26.3 kcal.mol^{-1}).[1] This would afford 8-membered rings.

Several reviews focussing on the ring opening of cyclobutane derivatives have appeared.[2] The different possibilities of ring opening of cyclobutane are summarised in figure 4.1. Hence, two mains pathways of ring opening have been described, the 1,2-carbon shift which can be promoted by Lewis acid (case a) or by transition-metal catalyst (case b), and the transition-metal catalysed C–C bond activation (cases c and

d). Direct C–C bond activation of cyclobutanone by rhodium catalysts was reported (case c) as well as the β-carbon elimination involving a carbon–metal, an oxygen–metal or a nitrogen–metal bond (case d).

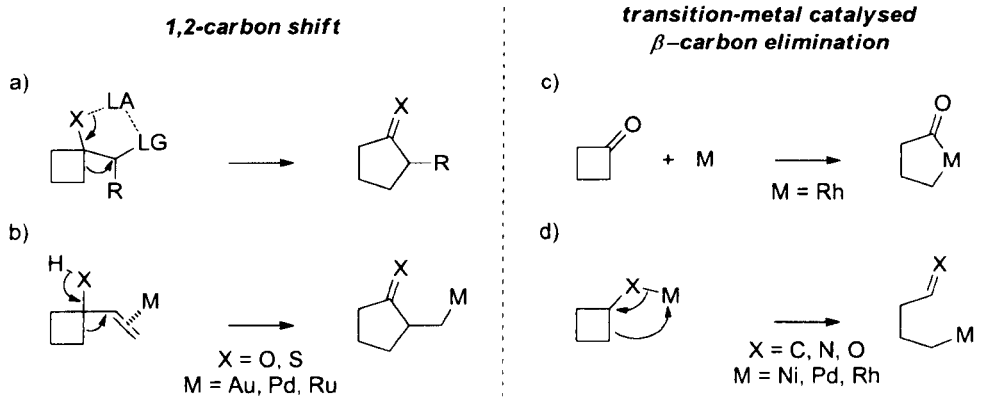
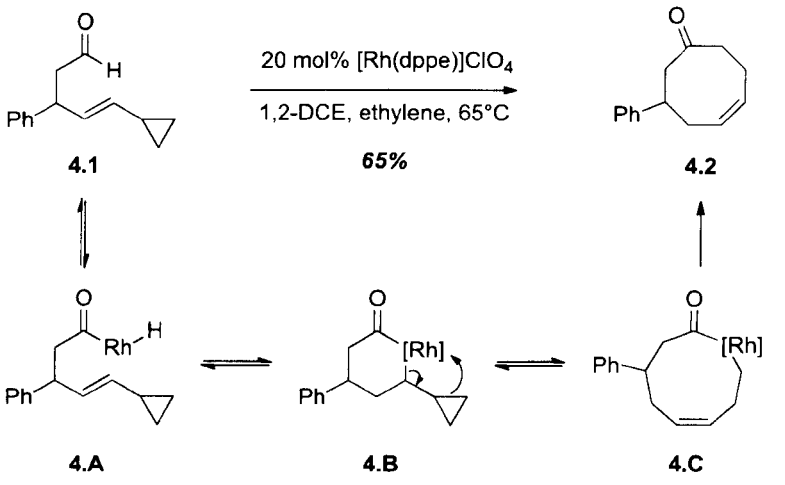


Figure 4.1: Different pathways of ring opening of cyclobutane derivatives: a) Lewis acid promoted 1,2-carbon shift; b) Transition-metalcatalysed 1,2-carbon shift; c) Transition-metal catalysed direct C–C activation of cyclobutanone; d) Transition-metal catalysed β-carbon elimination

1 – Formation of 8-membered rings via transition-metal catalysed ring-opening of cyclopropane and cyclobutane derivatives.

1 – 1 – Intramolecular hydroacylation of aldehyde-tethered vinylcyclopropane

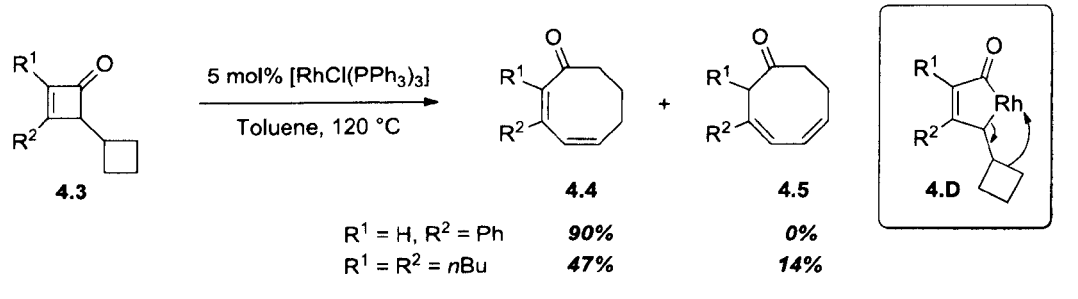
As described in chapter 1, Shair reported that treatment of aldehydes embedding a vinylcyclopropane moiety with rhodium catalyst afforded cyclooctenones (Scheme 4.1).[3] The rearrangement likely proceeds via oxidative addition of the rhodium into the formyl bond of aldehyde **4.1**, giving intermediate **4.A**, followed by hydrometallation of the C–C double bond which would give hexarhodacycle **4.B**. The strained-driven ring expansion would then afford intermediate **4.C** and final reductive elimination would lead to cyclooctenone **4.2** in 65% yield.



Scheme 4.1: Selected example of intramolecular hydroacylation of aldehyde-tethered vinylcyclopropane

1 – 2 – Ring enlargement of cyclobutenone-tethered cyclobutane

In 1993, Liebeskind reported the rhodium-catalysed ring enlargement of strained cyclobutenone **4.3** into cyclooctenone **4.4** (Scheme 4.2).[4] For $R^1 = R^2 = n$-Butyl, cyclooctenone **4.5** which resulted from a thermal 1,5–hydrogen shift in **4.4**, was also obtained. This rearrangement likely involves the formation of pentarhodacycle **4.D** which would be prone to undergo ring expansion via β–carbon elimination before a final reductive elimination step.

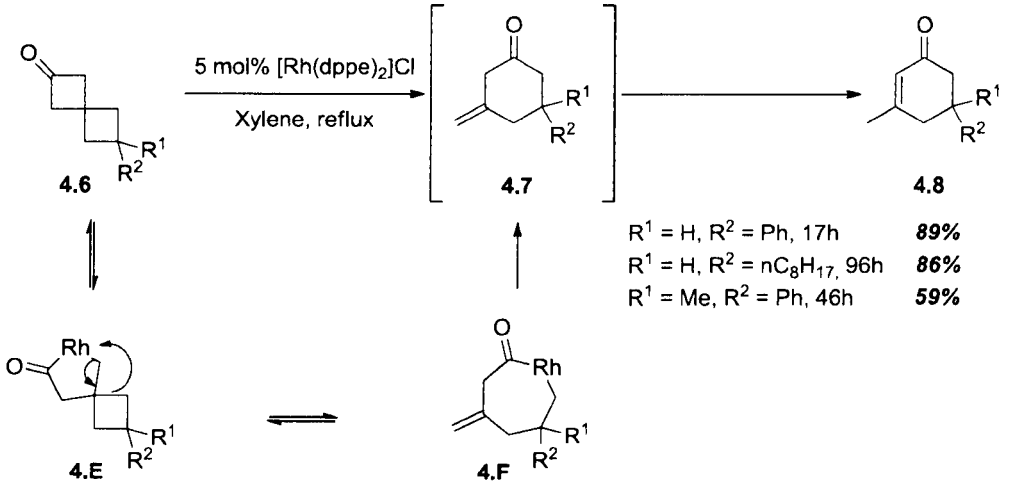


Scheme 4.2: Ring expansion of cyclobutenones-tethered cyclobutane

1 – 3 – Murakami's approaches towards 8-membered rings

1 – 3 – a – Use of strained spirocyclobutanone

Liebeskind rearrangement inspired Murakami's ring expansion of spirocyclobutanone depicted in scheme 4.3.[5]

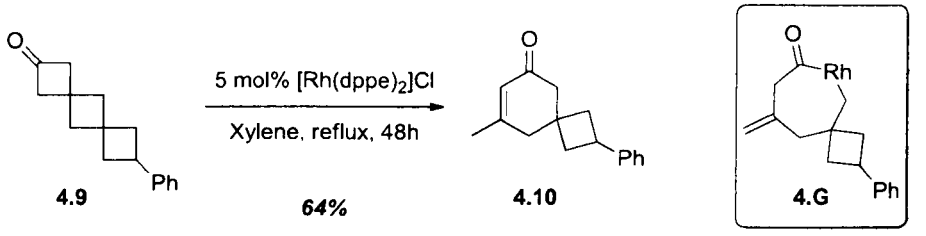


Scheme 4.3: Selected examples of rearrangement of spirocyclobutanone

Exposure of strained spirocyclobutanone **4.6** to 5 mol% of $[Rh(dppe)_2]Cl$ in xylene gave cyclohexanone **4.7** which isomerised into more stabilised cyclohexenone **4.8**. Oxidative addition of the metal centre into C–C bond adjacent to the carbonyl would give **4.E** which would be followed by a ring enlargement towards **4.F**. Final reductive elimination would afford **4.7** which would isomerise under the reaction conditions.

An attempt to apply this strategy to the formation of 8-membered ring resulted in the formation of compound **4.10** (Scheme 4.4). Presumably, the treatment of compound **4.9** with 5 mol% of $[Rh(dppe)_2]Cl$ led to heptarhodacycle **4.G**. This latter would

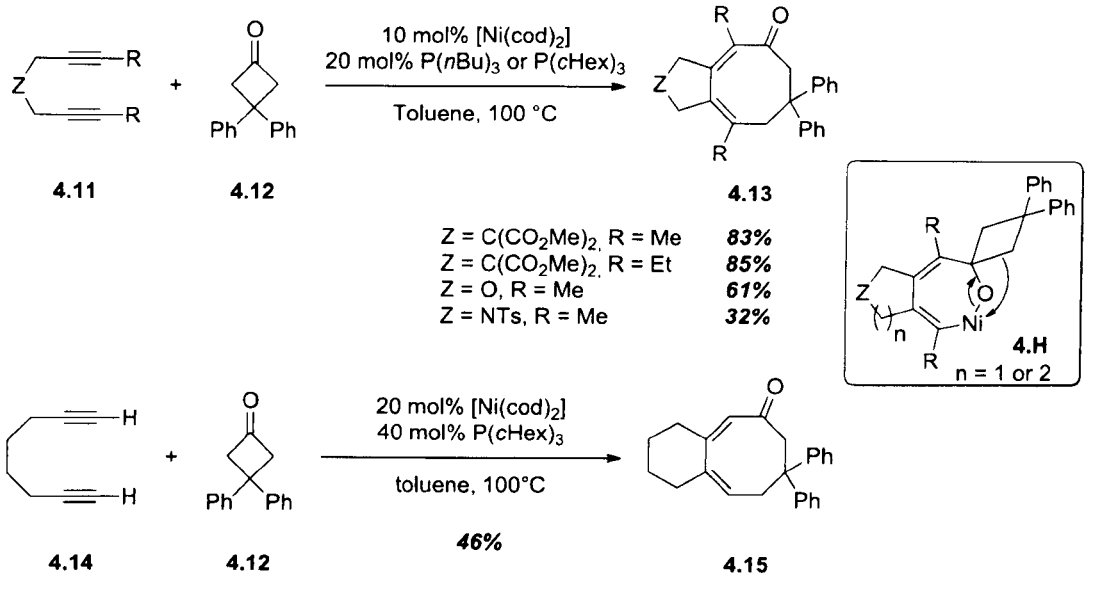
undergo reductive elimination rather than ring expansion towards a hypothetical nonarhodacycle.



Scheme 4.4: Attempt to obtain 8-membered ring from **4.9**

1 – 3 – b – Intermolecular [4+(2+2)] cycloaddition

Although the previous approach did not afford cyclooctenones, Murakami successfully demonstrated that nickel-catalysed intermolecular [4+(2+2)] cycloaddition between cyclobutanone **4.12** and diynes **4.11** or **4.14** gave [5,8]- and [6,8]-fused bicyclic structures **4.13** and **4.15** (Scheme 4.5). [6] The proposed mechanism involves the formation of an intermediate of type **4.H** which would undergo ring enlargement, delivering the 8-membered ring after reductive elimination.

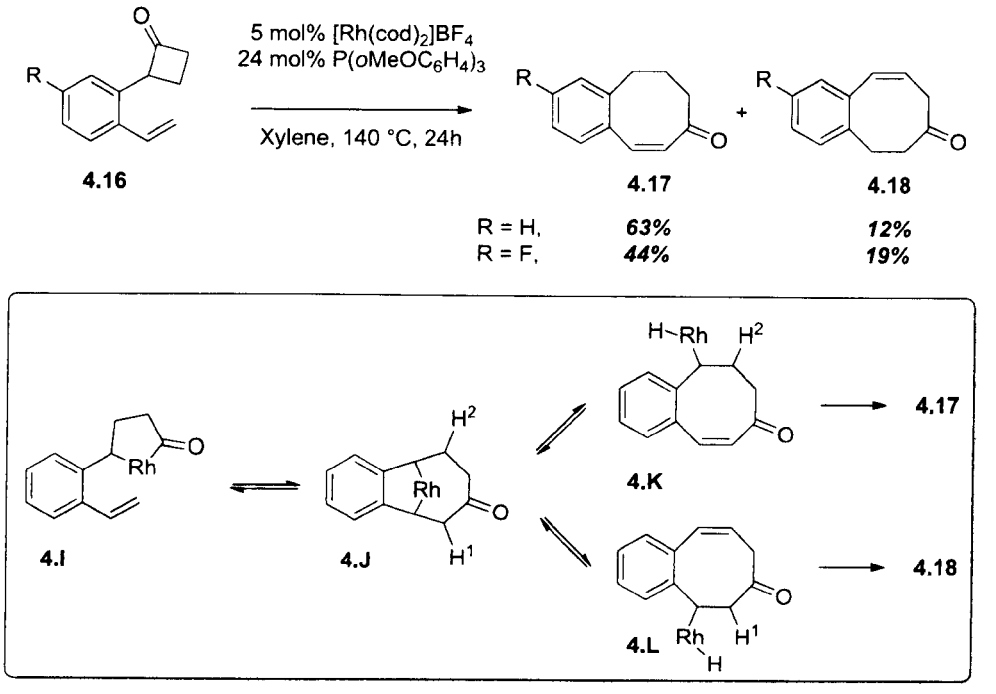


Scheme 4.5: Selected examples of [4+(2+2)] cycloadducts

1 – 4 – Synthesis of 8-membered rings via intramolecular cycloaddition

1 – 4 – a – Rhodium-catalysed rearrangement of 2-(*o*-styryl)cyclobutanone

Murakami reported the formation of 8-membered rings from 2-(o-styryl)cyclobutanones **4.16** (Scheme 4.6).[7] A mixture of two 8-membered rings **4.17** and **4.18** were obtained in good overall yield. The authors also mentioned the formation of decarbonylation products. The mechanism of this rearrangement would involve the oxidative addition of the rhodium catalyst towards pentarhodacycle **4.I**. Insertion of the alkene would afford **4.J** which would undergo β-hydride elimination with H^1 and H^2, leading to **4.K** and **4.L**, respectively. Reductive elimination of the metal would give **4.17** and **4.18**, respectively.



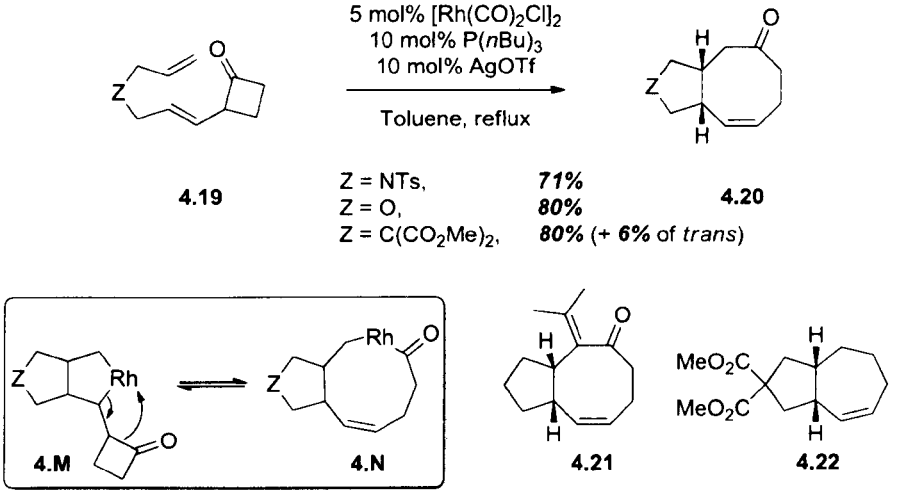
Scheme 4.6: Rhodium-catalysed rearrangement of 2-(o-styryl)cyclobutanone **4.16**

1 – 4 – b – Rhodium-catalysed [6+2] cycloaddition between vinylcyclobutanone and alkene

Following their discovery on rhodium-catalysed [5+2] cycloaddition between vinylcyclopropane and π-systems,[8] Wender and co-workers reported examples of rhodium-catalysed intramolecular [6+2] cycloaddition between vinylcyclobutanones and alkenes (Scheme 4.7).[9] Importantly, the use of vinylcyclobutanone moiety was essential for a smooth transformation. The equivalent vinylcyclobutane precursors were unreactive or led to degradation products.

Precursors **4.19** embedding sulphonamides, ether or diester tethers (Z = NTs, O or $C(CO_2Me)$) afforded the 8-membered rings **4.20** in good yield. When the terminal alkene was replaced by an allene moiety, 8-membered ring **4.21** was also obtained in excellent yield. The authors postulated that this rearrangement involves the formation

of pentarhodacycle **4.M** which would undergo ring expansion towards nonarhodacycle **4.N**. This mechanism was further supported by the theoretical study on rhodium-catalysed intramolecular [6+2] cycloaddition between vinylcyclobutanones and alkenes.[10] Interestingly, for Z = $C(CO_2Me)_2$, compound **4.22** was isolated in 8% yield. This compound likely results from decarbonylation of **4.N** followed by reductive elimination of the metal centre.

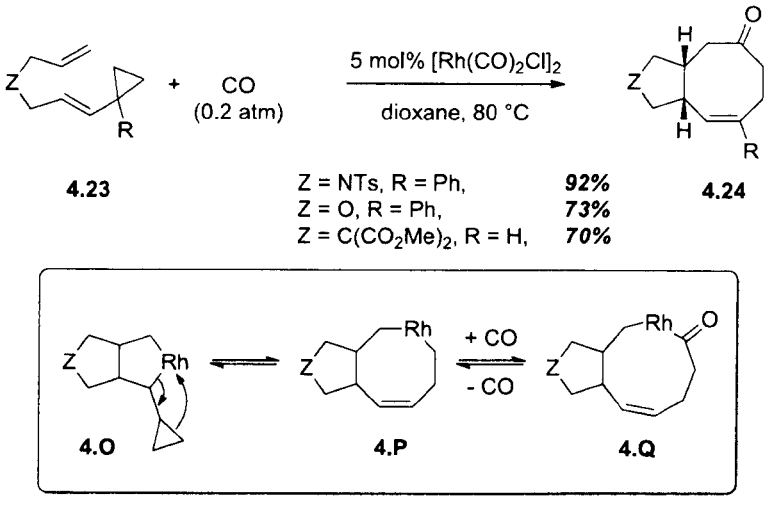


Scheme 4.7: Selected examples of [6+2] cycloadducts

1 – 4 – c – Rhodium-catalysed [5+2+1] cycloaddition

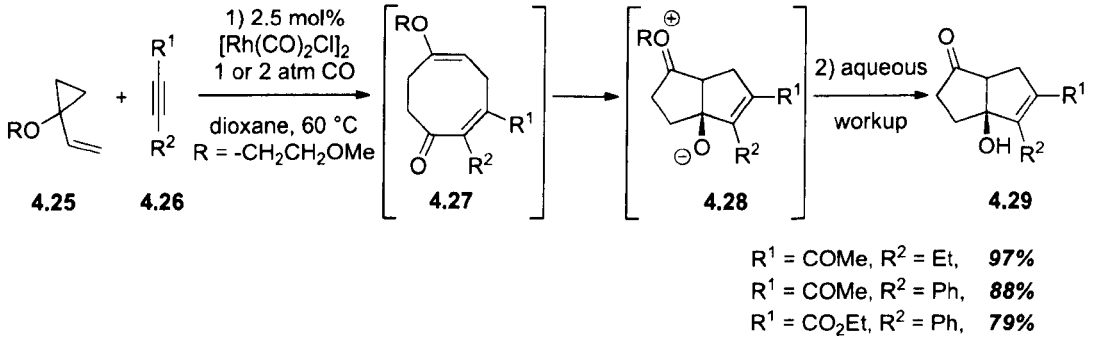
Based on the observation that 7-membered ring **4.22** resulted from the decarbonylation of nonarhodacycle **4.N**, Wender anticipated that under an atmosphere of carbon monoxide, alkenes-tethered vinylcyclopropane **4.23** could undergo a [5+2+1] cycloaddition affording 8-membered rings **4.24** (Scheme 4.8).[11] The mechanism relies on the formation of pentarhodacycle **4.O** which would give octarhodacycle **4.P**. Carbon monoxide insertion would afford nonarhodacycle **4.Q**, which would lead to **4.24** after reductive elimination of the rhodium. This pathway would be favoured over an early reductive elimination from intermediate **4.P**. Indeed,

a reductive elimination generating a $C(sp^2)$–$C(sp^3)$ bond is easier than a reductive elimination which leads to the formation of a $C(sp^3)$–$C(sp^3)$ bond.[12]



Scheme 4.8: Rhodium-catalysed intramolecular [5+2+1] cycloaddition

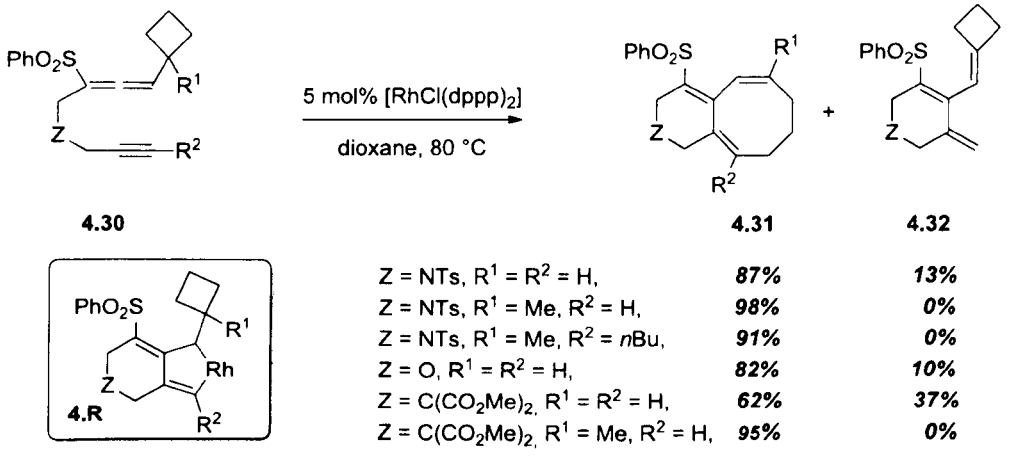
Wender and co-workers also investigated the rhodium-catalysed intermolecular [5+2+1] cycloadditition between vinylcyclopropane **4.25** and alkynes **4.26** under an atmosphere of carbon monoxide (Scheme 4.9).[13] Bicyclo[3,3,0]octenone **4.29** was obtained in excellent yields. **4.29** results from the transannular cyclisation of cyclooctenone **4.27** into **4.28**, aqueous workup affording bicyclo[3,3,0]octenone **4.29**.



Scheme 4.9: Rhodium-catalysed intramolecular [5+2+1] cycloaddition

1 – 4 – d – Rhodium-catalysed [6+2] cycloaddition between allenylcyclobutane and alkyne

Mukai has recently reported the rhodium-catalysed [6+2] cycloaddition between allenylcyclobutane and alkyne (Scheme 4.10).[14] Exposure of **4.30** to 5 mol% of $[RhCl(dppp)_2]$ resulted in the formation of [6,8]-fused bicyclic compounds **4.31**. The authors postulated that the rearrangement involves the formation of pentarhodacycle **4.R**, corroborating the fact that **4.32** is also obtained when R^1 = H. This can easily be understood if β–hydrogen elimination from intermediate **4.R** is in competition with the ring enlargement pathway.



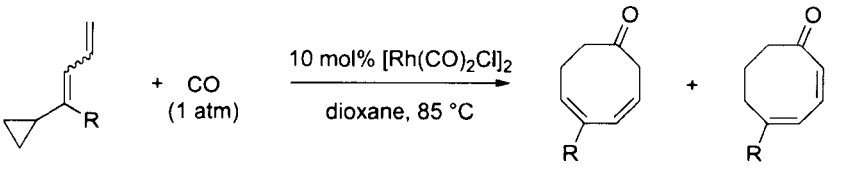
Z = NTs, R^1 = R^2 = H,	***87%***	***13%***
Z = NTs, R^1 = Me, R^2 = H,	***98%***	***0%***
Z = NTs, R^1 = Me, R^2 = *n*Bu,	***91%***	***0%***
Z = O, R^1 = R^2 = H,	***82%***	***10%***
Z = $C(CO_2Me)_2$, R^1 = R^2 = H,	***62%***	***37%***
Z = $C(CO_2Me)_2$, R^1 = Me, R^2 = H,	***95%***	***0%***

Scheme 4.10: Selected examples of [6+2] cycloadducts obtained from Mukai methodology

1 – 4 – e – Rhodium-catalysed [7+1] cycloaddition between buta-1,3-dienylcyclopropanes and carbon monoxide

Recently, Yu reported the rhodium-catalysed [7+1] cycloaddition between buta-1,3-dienylcyclopropanes **4.33** and carbon monoxide (Scheme 4.11).[15] Exposure to 10

mol% of $[Rh(CO)_2Cl]_2$ and one atmosphere of carbon monoxide gave cyclooctenone **4.34** which partially isomerised into conjugated cyclooctenone **4.35**.



4.33

R =Ph, (*Z*/*E* = 2.9)
R = Bn, (*Z*/*E* = 0.8)

4.34 **4.35**

R =Ph, ***77%*** (1:6)
R = Bn, ***85%*** (1:15)

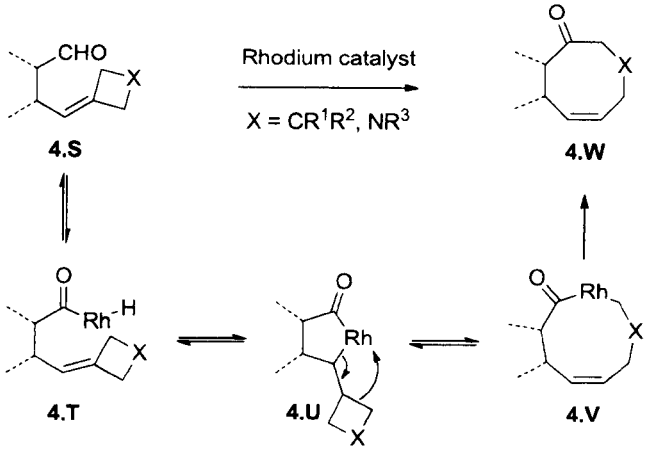
Scheme 4.11: Selected examples of [7+1] cycloadducts

2 – Formation of 8-membered rings via rhodium-catalysed intramolecular hydroacylation of alkylidenecyclobutane.

2 – 1 – Hypothesis and first example of 8-membered ring formation

Our efforts to understand the rhodium-catalysed intramolecular hydroacylation of alkylidenecyclopropane led us to the conclusion that pentarhodacycles, in which a carbonyl group is bound to rhodium, are fundamental intermediates for the formation of 7-membered rings. Inspired by Liebeskind[3] and Murakami[4] reports which demonstrated that such pentarhodacycles, attached to a cyclobutane moiety, were prone to undergo ring enlargement towards larger-sized rings, we envisioned that aldehyde-tethered alkylidenecyclobutanes would afford 8-membered rings (Scheme 4.12). We hypothesised that the oxidative addition of rhodium into the formyl bond of aldehyde **4.S** would give **4.T**. The hydrometallation of the C–C bond would afford pentarhodacycle **4.U** which would undergo β–carbon elimination, giving nonarhodacycle **4.V**. Reductive elimination would then furnish **4.W**. We also anticipated that the cyclobutane ring (X = CR^1R^2) could also be replaced by an

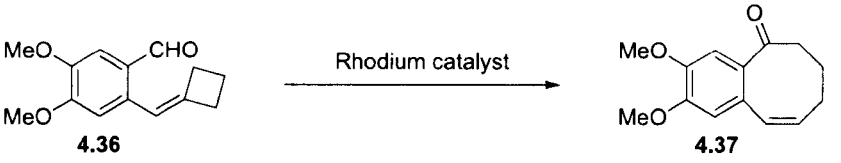
azetidine ring (X = NR^3) given their similar strain energy (strain energy of cyclobutane = 26.3 $kcal.mol^{-1}$, strain energy of azetidine is estimated at 26.2 $kcal.mol^{-1}$).[16]



Scheme 4.12: Proposed mechanistic hypothesis

Our hypothesis was tested with aldehyde **4.36** (Table 4.1). Aldehyde **4.36** was synthesised by undergraduate student James Dawick and was first treated with neutral rhodium catalyst (entry 1). Under these conditions, 8-membered ring **4.37** was obtained in 94% yield. With cationic rhodium catalyst prepared in situ by adding 5 mol% $AgBF_4$ to 2.5 mol% $[Rh(coe)_2Cl]_2$ and 10 mol% $P(pMeOC_6H_4)_3$ in 1,2-DCE, the reaction was much faster and full conversion was obtained only after 30 minutes at 80°C (entry 2). The use of commercially available cationic rhodium catalyst (entry 3) was also suitable although 3.5 hours were necessary to obtain full conversion. In both cases the isolated yields of **4.37** remained good (89% and 85%, respectively).

Table 4.1: First example of 8-membered ring obtained by rhodium-catalysed intramolecular hydroacylation of alkylidenecyclobutane



4.36 **4.37**

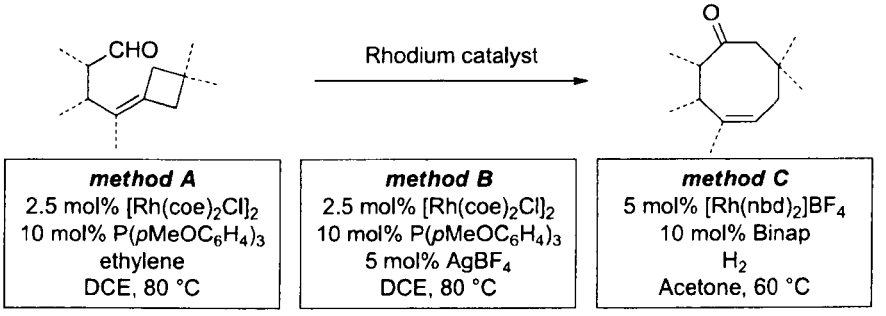
Entry	Method	T (°C)	Time	Isolated yield
1	2.5 mol% $Rh(coe)_2Cl]_2$ 10 mol% $P(pMeOC_6H_4)_3$ Ethylene 1,2-DCE	80	17 h	94%
2	2.5 mol% $[Rh(coe)_2Cl]_2$ 10 mol% $P(pMeOC_6H_4)_3$ 5 mol% $AgBF_4$ 1,2-DCE	80	30 min	89%
3	5 mol% $[Rh(nbd)_2]BF_4$ BINAP (5 mol%) excess H_2 Acetone	60	3 h 30	85%

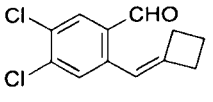
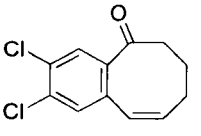
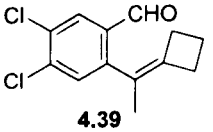
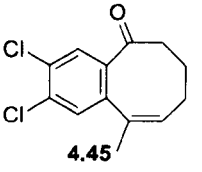
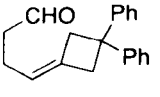
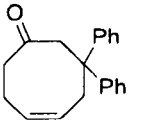
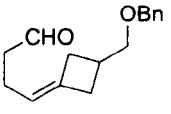
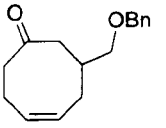
2 – 2 – Scope of 8-membered rings

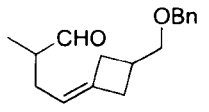
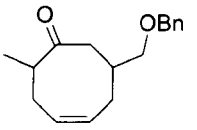
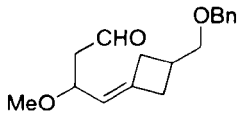
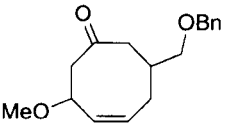
Encouraged by this first example, the scope of the reaction was investigated (Table 4.2). Aldehydes **4.38** – **4.43** were prepared (Aldehydes **4.38** and **4.39** were prepared by James Dawick) and treated with rhodium catalyst following methods A, B or C. As compared to the 7-membered rings precursors, a general trend was that the precursors of 8-membered rings were found to be more reluctant to undergo the cyclisation, requiring higher catalyst loading, temperature and time of reaction as compared to the 7-membered rings precursors. Moreover, cationic rhodium catalysts (methods B or C) were much more effective than the neutral catalyst (method A). While aromatic aldehyde **4.38** afforded **4.44** in excellent yield, an additional substitution on the alkene moiety (aldehyde **4.39**) prevented the cyclisation from occurring. Instead, most of starting material **4.39** was recovered. Substitution in

position 3 of the alkylidenecyclobutane moiety was tolerated. Aldehydes **4.40** and **4.41** gave 8-membered rings **4.46** and **4.47** in 79% and 69% yield, respectively. Precursors **4.42** and **4.43** which have a substituent in position α and β to the formyl group, respectively, were prepared as a mixture of diastereoisomers. Treatment of these aldehydes with rhodium catalysts gave 8-membered carbocycles **4.48** and **4.49** in good yields with the same diastereoisomeric ratio.

Table 4.2: Scope of 8-membered rings

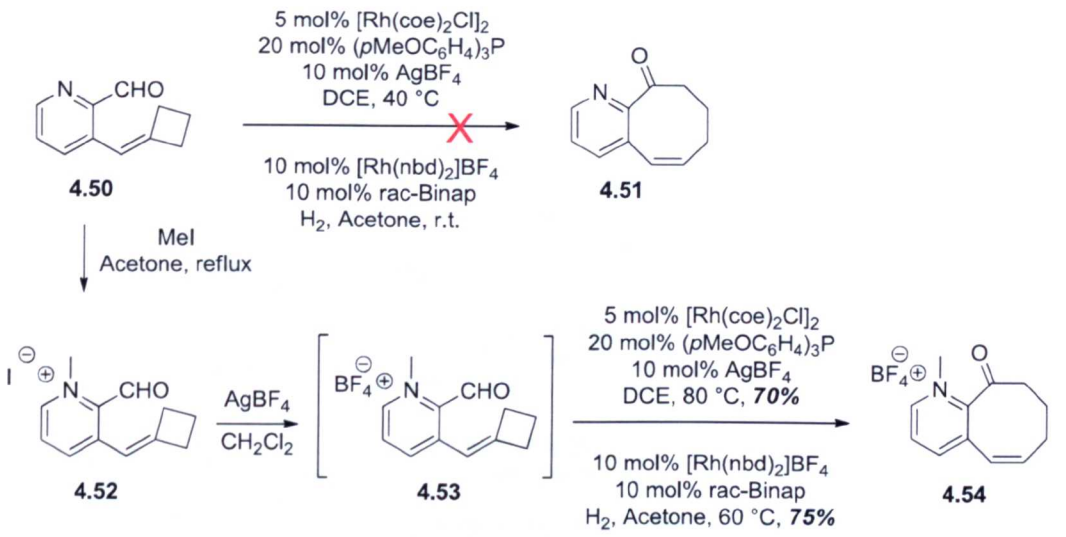


Starting material	Product	Conditions	Time	Isolated yield
 **4.38**	 **4.44**	A	17 h	92%
		B	30 min	89%
 **4.39**	 **4.45**	A, B or C[a]	24 h	n.r.[b]
 **4.40**	 **4.46**	B[c]	22 h	79%
 **4.41**	 **4.47**	B[d]	16 h	69%[e]

 **4.42** d.r. = 50/50	 **4.48** d.r. = 50/50	A[f]	86 h	75%
		C[d]	25 h	71%[g]
 **4.43** d.r. = 50:50	 **4.49** d.r. = 50:50	C[d]	24 h	75%

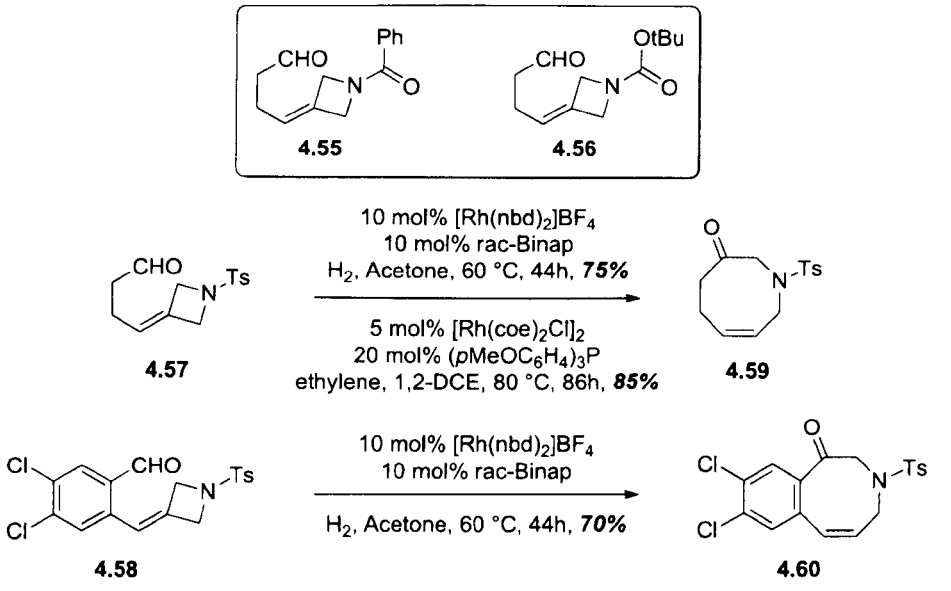
[a]: 10 mol% in rhodium was used.
[b]: **4.39** recovered in 87-95% yield.
[c]: 10 mol% of catalyst was used.
[d]: 5 mol% of catalyst was used.
[e]: **4.41** was recovered in 16% yield.
[f]: 15 mol% of catalyst was used.
[g]: **4.42** was recovered in 16 % yield.

We then turned our attention to the rearrangement of picolinaldehyde derivative **4.50** (Scheme 4.13). Treatment with cationic rhodium catalysts did not give 8-membered ring **4.51** and aldehyde **4.50** was recovered. The coordination of the lone pair of nitrogen to the active catalyst likely prevents the rearrangement of **4.50**.[17] Pyridinium salt **4.52** was then prepared by reacting iodomethane and **4.50** in acetone. After counteranion exchange using one equivalent of $AgBF_4$, crude **4.53** was treated with cationic rhodium catalysts, delivering the corresponding 8-membered ring **4.54** in 70% and 75% yield, as a tetrafluoroborate salt.



Scheme 4.13: Cyclisation of pyridinium salt **4.53**

As previously described, cyclobutane and azetidine moieties have similar strain energy. We therefore investigated the rearrangement of aldehyde-tethered alkylideneazetidines which could afford 8-membered heterocycles (Scheme 4.14).[18,19] Blocking the lone pair of the nitrogen was essential for the rearrangement of the picolinaldehyde **4.50**. Therefore, we looked at the rearrangement of azetidine derivatives which were protected by electron-withdrawing groups. The delocalisation of the nitrogen lone pair would prevent unproductive coordination to the catalyst. Aldehydes **4.55**, **4.56** and **4.57** were prepared by Dr. Christophe Aïssa. Interestingly, while amide **4.55** and carbamate **4.56** were reluctant to undergo the cyclisation, azetidines protected with a tosyl group were suitable for the reaction. Indeed, both aliphatic and aromatic aldehydes **4.57** and **4.58** afforded 8-membered heterocycles **4.59** and **4.60**. Aliphatic heterocycle **4.59** was obtained in 75% and 15% of starting material was recovered when cationic rhodium complex was used. Using neutral rhodium complex, Dr. Christophe Aïssa isolated **4.59** in 85%. The rhodium-catalysed rearrangement of aldehyde **4.58** was also investigated by Dr. Christophe Aïssa. Using cationic rhodium catalyst, **4.60** was isolated in 70% yield.



Scheme 4.14: Formation of 8-membered heterocycles via the rearrangement of azetidine derivatives

Interestingly, reported examples of ring expansion towards pyrrolidines and azepanes or ring opening of an azetidine, azetidinium salt or azetidinium ylide moiety, involve the cleavage of a carbon–nitrogen bond.[18a,19] Similarly, the silver-[18b] and cobalt-catalysed [20] ring opening of azetidine derivatives also involved a β-nitrogen elimination. Conversely, the rearrangements of **4.57** and **4.58** into **4.59** and **4.60**, respectively, constitute the first examples of ring opening of azetine via β-carbon elimination.

3 – Conclusion

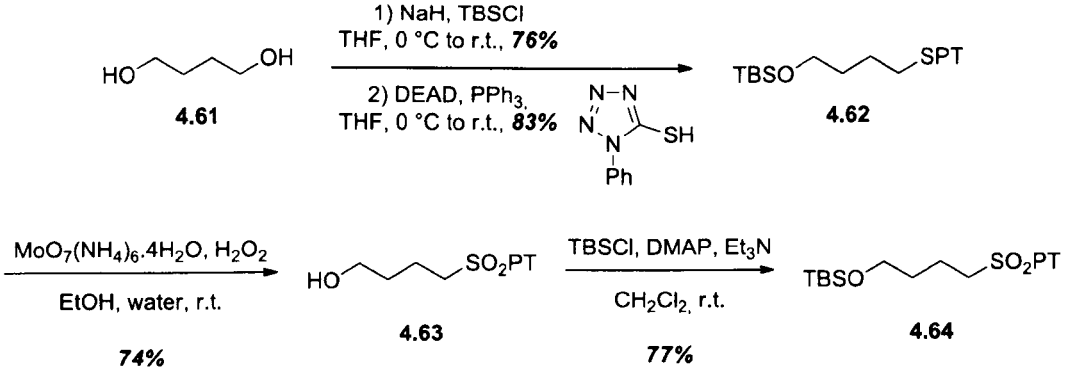
The initial methodology of rhodium-catalysed intramolecular hydroacylation of aldehyde-tethered alkylidenecyclopropanes which gives 7-membered rings was successively used for the formation of 8-membered rings by replacing the cyclopropane moiety with a cyclobutane or azetidine moiety. Interestingly, the first

example of ring opening of azetidine via β-carbon elimination was observed, suggesting the possibility of new reactions.

4 – Synthesis of precursors

4 – 1 – Synthesis of aldehyde ***4.40***

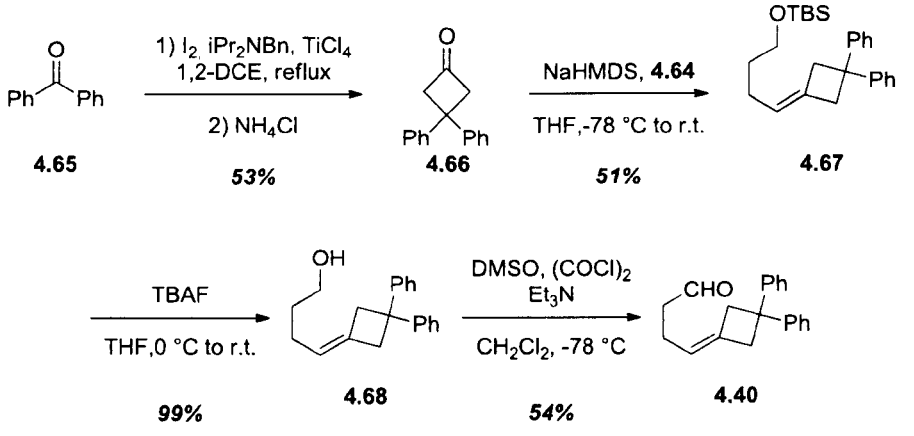
The C–C double bond of compound **4.40** was installed by a Julia-Kocienski olefination between sulfone **4.64** and ketone **4.66**.[21] The synthesis of sulfone **4.64** started with the monoprotection of 1,4-butanediol **4.61** (Scheme 4.15). Mitsonobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol gave sulfide **4.62**.[22] Molybdenum-catalyzed oxidation of **4.62** using a 35% solution of H_2O_2 in water gave sulfone **4.63**.[23] Under these conditions the TBS group was also cleaved. Using *m*CPBA buffered with $NaHCO_3$, in dichloromethane at 0 °C did not prevent the desylilation. The desired sulfone **4.64** was therefore obtained by reprotecting the primary alcohol.



Scheme 4.15: Synthesis of sulfone **4.64**

Cyclobutanone **4.66** was obtained following the one-step procedure developed by Periasamy (Scheme 4.16).[24] Exposure of benzophenone **4.65** to iodine, N,N-

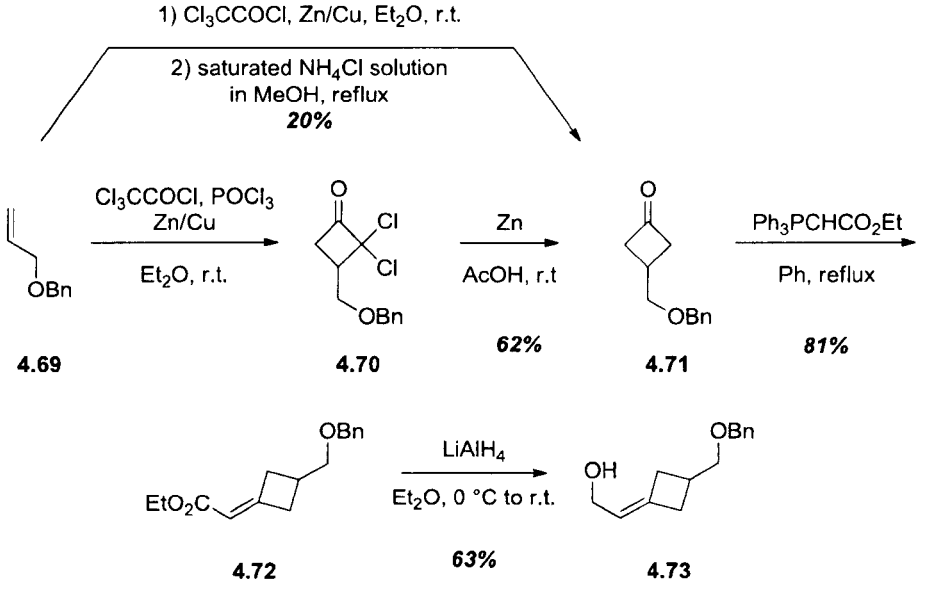
diisopropylbenzylamine and titanium chloride followed by hydrolysis of the intermediate imminium gave cyclobutanone **4.66** in 53% yield. Julia-Kocienski olefination between sulfone **4.64** and cyclobutanone **4.66** gave alkylidenecyclobutane **4.67** in 51% yield.[23] Deprotection of the primary alcohol followed by Swern oxidation afforded aldehyde **4.40**.[25]



Scheme 4.16: Synthesis of aldehyde **4.40**

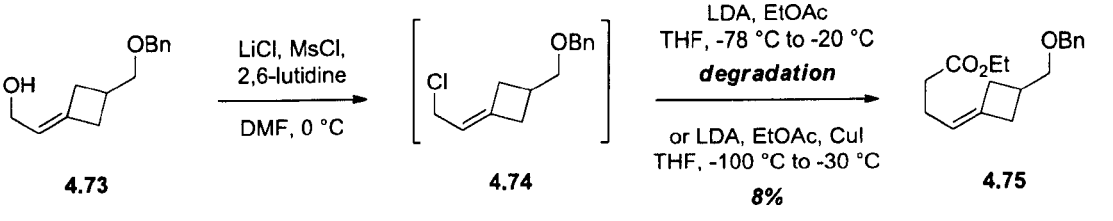
*4 – 2 – Synthesis of aldehyde **4.41**, **4.42** and **4.43***

Aldehydes **4.41**, **4.42** and **4.43** were prepared from allylic alcohol **4.73** (Scheme 4.17). [2+2] cycloaddition between allylic ether **4.69** and bischloroketene afforded α,α-bischlorocyclobutanone **4.70** and was used as crude material in the next step.[26] Zinc-promoted dechlorination gave ketone **4.71** in 62% yield over the two steps. Our attempt to prepare cyclobutanone **4.71** in a one-pot procedure from **4.69** failed to give reasonable yields.[27] Having cyclobutanone **4.71** in hand, Wittig reaction using ethyl(triphenylphosphoranyliden)acetate gave cyclobutylidene acetate **4.72**. [28] Reduction of the ester moiety into the corresponding allylic alcohol **4.73** was achieved using lithium aluminium hydride.



Scheme 4.17: Synthesis of intermediate alcohol **4.73**

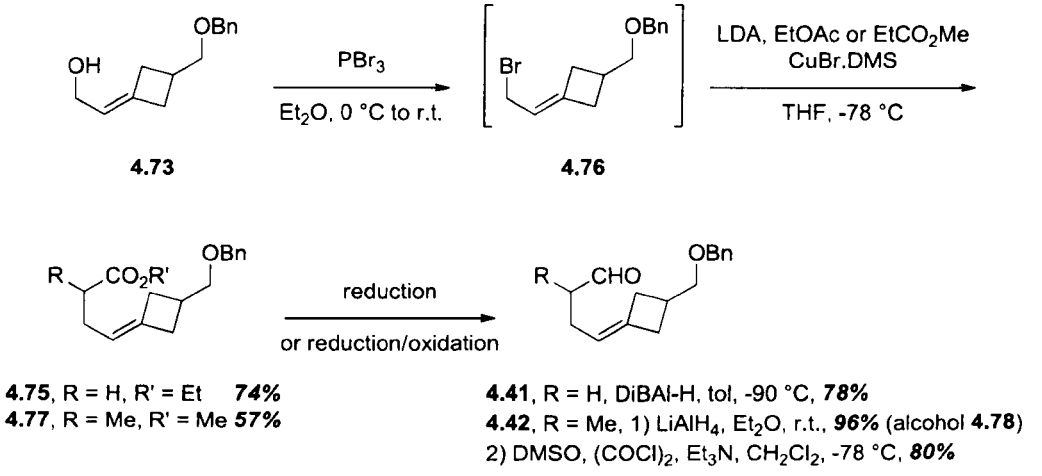
The homologation of the chain was first attempted by transforming the allylic alcohol into choride **4.74** followed by substitution using ethylacetate enolate (Scheme 4.18). Chlorination was performed using lithium chloride, methanesulfonyl chloride and 2,6-lutidine.[29] Under these conditions, **4.74** was obtained in 72% yield and was immediately utilised in the next step, as crude material. Two attempts of substitution were carried out. Using LDA and ethylacetate, degradation was observed and 45% of starting material was recovered while an attempt using Kuwajima's conditions gave **4.75** in 8% yield only.[30]



Scheme 4.18: First attempts to synthesise ester **4.75**

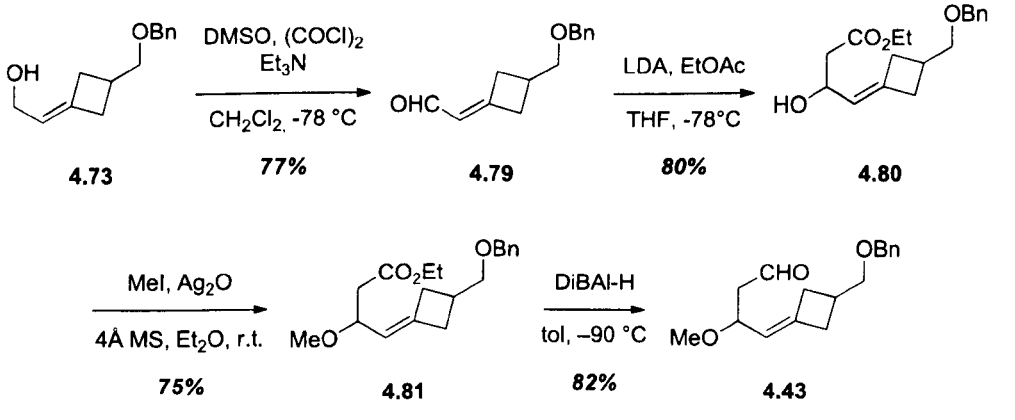
Bromination was achieved by treatment with phosphorus tribromide (Scheme 4.19).[31] Substitution of crude allylic bromide **4.76** was achieved by using the copper enolate of ethyl acetate (R = H) or methyl propionate (R = Me). Under these

conditions, esters **4.75** and **4.77** were isolated in 74% and 57% yield over the two steps, respectively. Reduction of the ester moiety using DiBAl-H at -90 °C[32] afforded precursor **4.41** in 78% yield whereas aldehyde **4.42** was obtained via reduction of the ester into alcohol **4.78** followed by reoxidation.



Scheme 4.19 Synthesis of aldehydes **4.41** and **4.42**

The synthesis of aldehyde **4.43** started with the oxidation of allylic alcohol **4.73** (Scheme 4.20). Aldol reaction between the lithium enolate of ethyl acetate and aldehyde **4.79** gave allylic alcohol **4.80** in 80% yield.[33] The silver oxide-mediated methylation[34] of the alcohol moiety was achieved using iodomethane and afforded **4.81** which was reduced into aldehyde **4.43** by treatment with DiBAl-H at -90 °C.

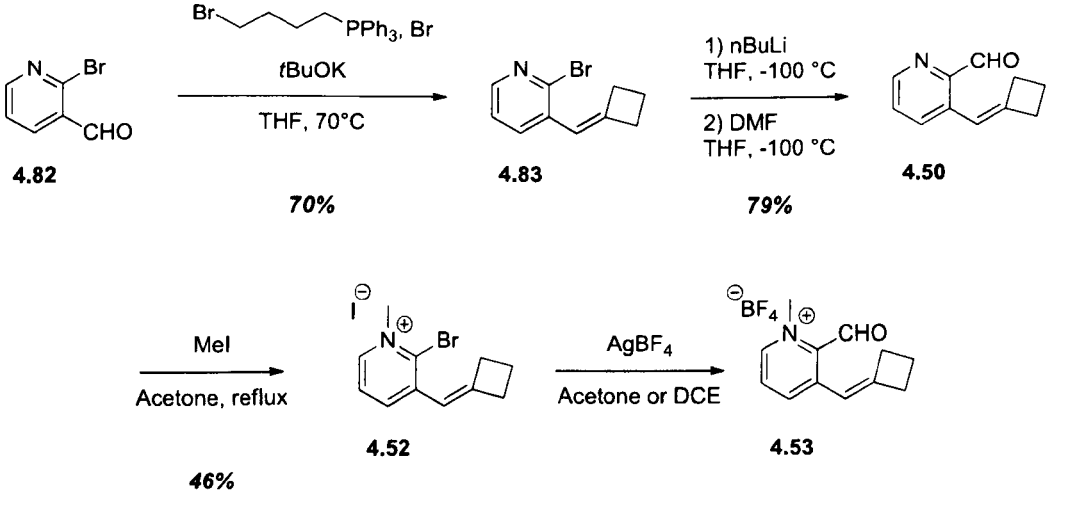


Scheme 4.20: Synthesis of aldehyde **4.43**

4 – 4 – Synthesis of aldehydes ***4.50*** *and* ***4.53***

The synthesis of **4.50** and **4.53** began with a Wittig reaction between the ylide derived from 4-(bromobutyl)triphenylphosphonium and commercially available 6-bromo-3-pyridinecarboxaldehyde **4.82** (Scheme 4.21).[30, 35] Alkylidenecyclobutane **4.83** was isolated in 70% yield. Exchange between bromine and lithium using *n*-butyllithium was carried out at -100 °C followed by addition of DMF to give aldehyde **4.50**. Importantly attempts at -78 °C gave the debrominated product in 70% isolated yield.

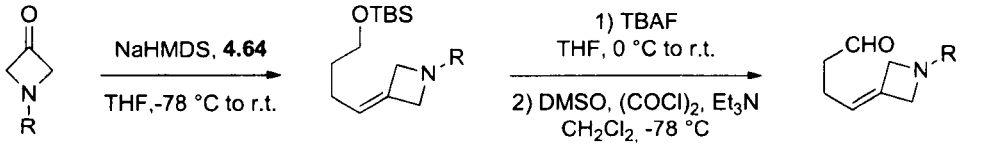
The methylation was achieved by treating pyridine **4.50** with iodomethane in acetone.[36] Complete conversion was observed after three days under reflux. Finally, treating **4.52** with one equivalent of $AgBF_4$ in acetone or 1,2-DCE gave **4.53**. Silver iodide precipitated and the supernatant was utilised in the rhodium-catalysed rearrangement without further purification.



Scheme 4.21: Synthesis of precursor **4.50** and **4.53**

4 – 4 – Synthesis of aldehydes ***4.55*** *to* ***4.58***

Aldehydes **4.55**, **4.56** and **4.57** were prepared by Dr. Christophe Aïssa (Scheme 4.22). Spectral characteristics are described in the supporting information.



4.84, R = COPh
4.85, R = CO_2tBu
4.86, R = Ts

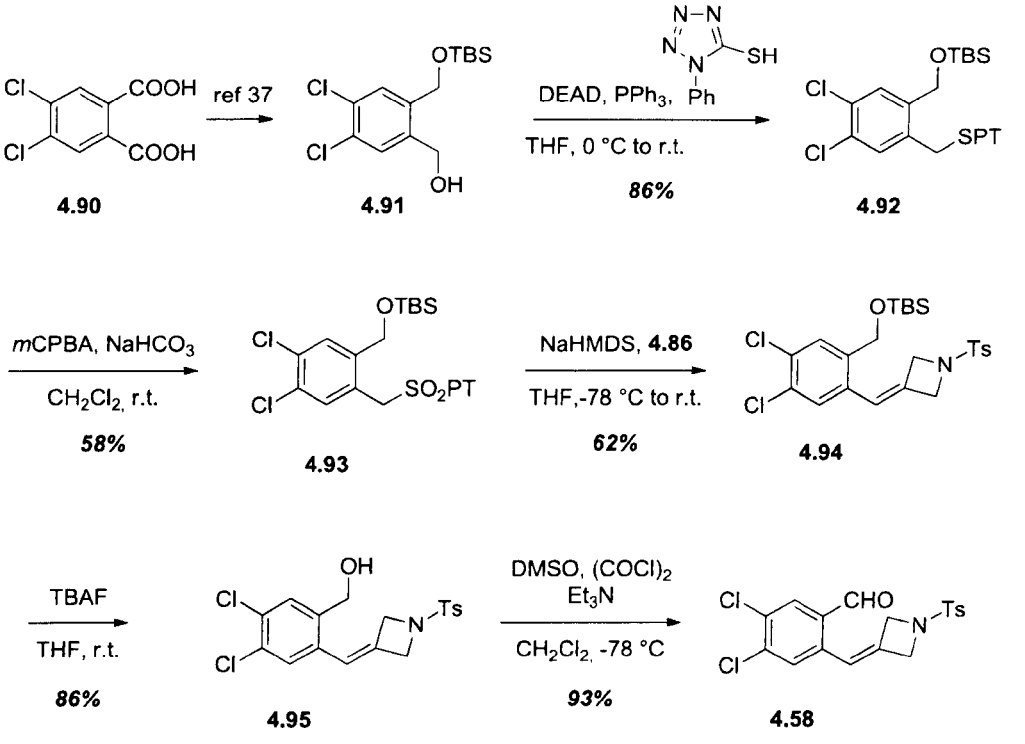
4.87, R = COPh, ***45%***
4.88, R = CO_2tBu, ***74%***
4.89, R = Ts, ***68%***

4.55, R = COPh, ***68%***
4.56, R = CO_2tBu, ***85%***
4.57, R = Ts, ***69%***

Scheme 4.22: Preparation of alkylideneazetidine derivatives **4.55**, **4.56** and **4.57**

Azetidinone **4.84** was prepared from commercially available 1-(diphenylmethyl)-3-hydroxyazetidine hydrochloride.[37] Azetidinone **4.85** was commercially available while azetidinone **4.86** was prepared from 1,4-butanediol and propylamine.[38] The unsaturation was installed via a Julia-Kocienski reaction,[23] using sulfone **4.64**. Cleavage of the TBS group followed by oxidation under Swern's conditions[27] gave aldehydes **4.55, 4.56** and **4.57**.

The synthesis of aldehyde **4.58** began with the preparation of monoprotected alcohol **4.91** obtained from 4,5-dichlorophthalic acid **4.90** (Scheme 4.23).[37] Sulfide **4.92** was obtained via a Mitsonobu reaction[24] between **4.91** and 1-phenyl-1*H*-tetrazole-5-thiol and was oxidised into sulfone **4.93** using *m*CPBA buffered with $NaHCO_3$. Julia-Kocienski reaction[23] between **4.93** and azetidinone **4.86** gave alkylideneazetidine **4.94** in 62% yield. Deprotection of the alcohol using TBAF followed by Swern's oxidation[27] afforded aldehyde **4.58**.



Scheme 4.23: Synthesis of aldehyde **4.58**

5 - References

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Chapter 5

Investigation of the Regioselectivity of the Ring Opening of Alkylidenecyclobutane

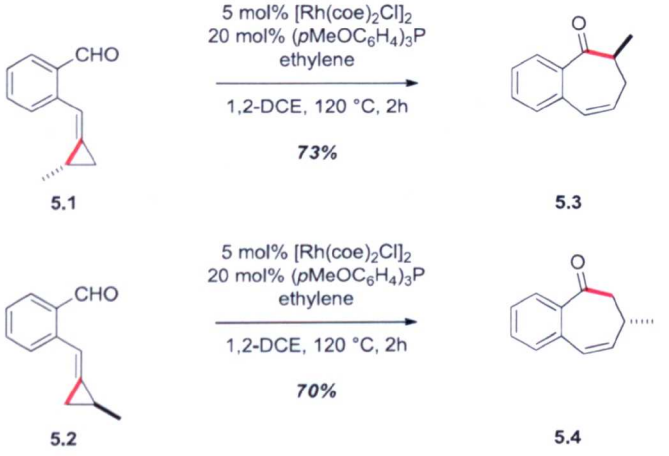
In chapter 4, the formation of 8-membered rings via rhodium-catalysed intramolecular hydroacylation of alkylidenecyclobutanes has been successfully achieved. We then turned our attention on the mechanism of this rearrangement, investigating more specifically the regioselectivity of the ring opening of α-substituted cyclobutane derivatives.

1 – Introduction

1 – 1 – Regioselectivity studies of the ring opening of cyclopropane moieties

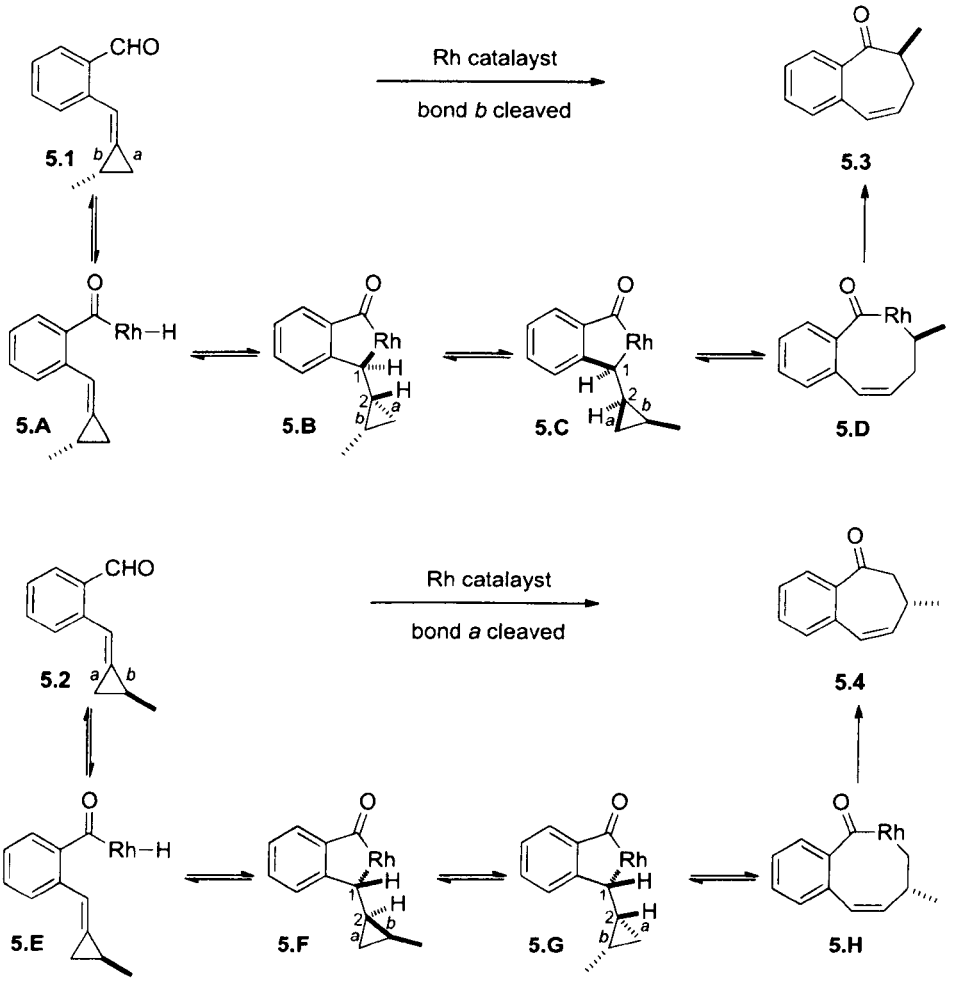
The regioselectivity of the ring opening of α-substituted cyclopropane during the rhodium-catalysed intramolecular hydroacylation of alkylidenecyclopropane has previously been studied within the group.[1] Treating enantiopure aldehydes **5.1** and **5.2** with rhodium catalyst resulted in the formation of 7-membered rings **5.3** and **5.4**,

respectively, indicating that the C–C bond of the cyclopropane which is *cis* to the aromatic unit (colour-coded in red) is broken in both cases, independently of the substitution of the cyclopropane ring (Scheme 5.1).



Scheme 5.1: Rhodium-catalysed intramolecular hydroacylation of alkylidenecyclopropane **5.1** and **5.2**

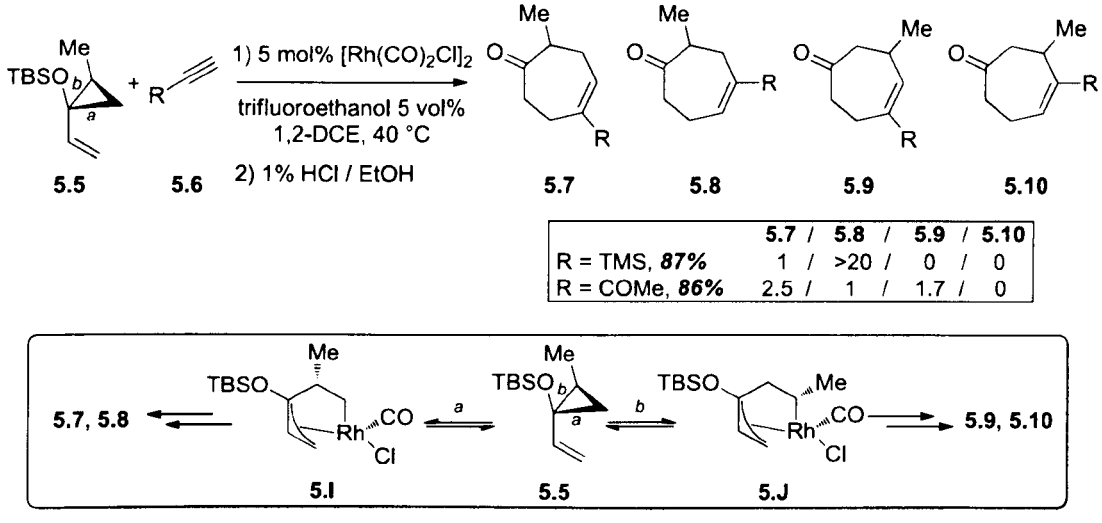
The regiospecificity of the ring opening can be explained with the mechanisms depicted in scheme 5.2.



Scheme 5.2: Proposed mechanism for the rearrangement of alkylidenecyclopropane derivatives

(*Z*) aldehyde **5.1** and (*E*) aldehyde **5.2** would first undergo C–H activation resulting in the formation of **5.A** and **5.E**, respectively. *Syn*-hydrometallation of the C–C double bond would give pentarhodacycles **5.B** and **5.F**. The (*Z*)-configuration of the C–C double bond in 7-membered rings **5.3** and **5.4** implies that the C_1–H and C_2–H bonds must be *syn*-coplanar during the ring enlargement. Hence, rotation around the C_1–C_2 bound would give intermediates **5.C** and **5.G**. This rotation also places the C_1–Rh bond and bond *b* *syn*-coplanar in **5.C** whereas in **5.G** the C_1–Rh bond is *syn*-coplanar with bond *a*. Therefore, *syn*-β-carbon elimination would lead to octarhodacycles **5.D** and **5.H**, respectively. Reductive elimination would furnish cycloheptenones **5.3** and **5.4**, respectively.

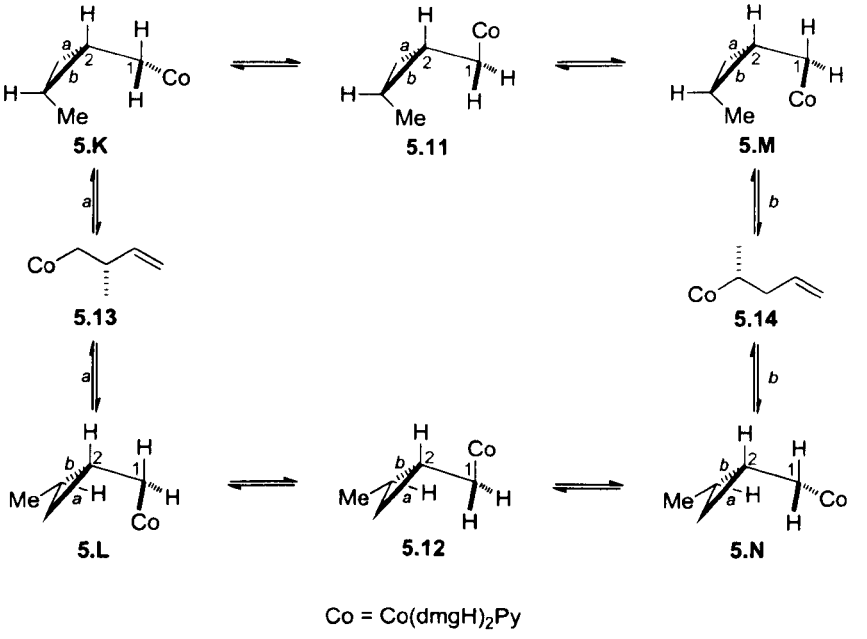
The observed regiospecificity of the ring opening of alkylidenecyclopropane **5.1** and **5.2** is in very good accordance with previous studies. Indeed, the moderate steric hindrance of a methyl group on the cyclopropane moiety allows for the cleavage of both bonds *a* and *b*. For instance, DFT calculations reported by Wender and Houk showed that the cleavage of bonds *a* and *b* is a facile process in the rhodium-catalysed intermolecular [5+2] cycloaddition between vinylcyclopropane **5.5** and alkynes **5.6** (Scheme 5.3).[2] The equilibrium between intermediates **5.I** and **5.J** is rapidly established. The distribution of cycloheptenones **5.7** – **5.10** only reflects the activation barriers of the insertion of alkynes **5.6** in each case.



Scheme 5.3: Rhodium-catalysed intermolecular [5+2] cycloaddition between vinylcyclpropane and alkyne

Our mechanistic proposal also relies on the *syn*-coplanar character of the β–carbon elimination. This is in good agreement with previous observations. Indeed, unexpected outcomes in palladium-catalysed Heck reactions[3] and in nickel-catalysed cascade reactions[4] can be explained by a mechanism which involves a *syn*-coplanar relationship between the two bonds cleaved during β–carbon elimination. The *syn*-coplanar characteristic of β–carbon elimination was also demonstrated by Golding and Johnson who reported the cobalt-catalysed rearrangement of cyclopropanes **5.11**

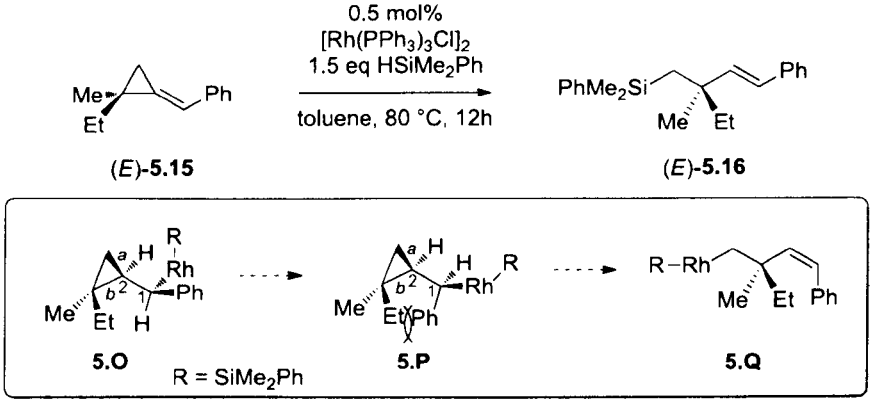
and **5.12** into 3-butenyl derivatives **5.13** and **5.14** by treating an equimolar mixture of racemic **5.11** and **5.12** in chloroform at room temperature (Scheme 5.4).[5] 3-butenylcobalt derivatives **5.13** and **5.14** were obtained in a 9:1 ratio which corresponds to the relative stability of both 3-butenylcobalt compounds. Moreover, when separately treated with trifluoroacetic acid, (*R*)-**5.14** and (*S*)-**5.14** equilibrates in a stereospecific fashion with (*S*)-**5.13** and (*R*)-**5.13**, respectively. These results are in good accordance with a mechanism involving a *syn*-coplanar β-carbon elimination. Indeed, rotation around the C_1–C_2 bond in **5.11** and **5.12** would place bond *a* *syn*-coplanar with the C_1–Co bond affording **5.K** and **5.L**, respectively, which would be prone to undergo *syn*-coplanar β–carbon elimination towards **5.13**. Rotation around the C_1–C_2 bond would also give **5.M** and **5.N** in which the C_1–Co bond is *syn*-coplanar with bond *b*. *Syn*-coplanar β-carbon elimination would finally afford **5.14**.



Scheme 5.4: Cobalt-catalysed *syn*-coplanar β–carbon elimination

Conversely, a *syn*-coplanar β–carbon elimination cannot explain the outcome obtained by Marek during the rhodium-catalysed hydrosilylation of alkylidenecyclopropanes (Scheme 5.5).[6] Treating (*E*)-**5.15** with 0.5 mol% of

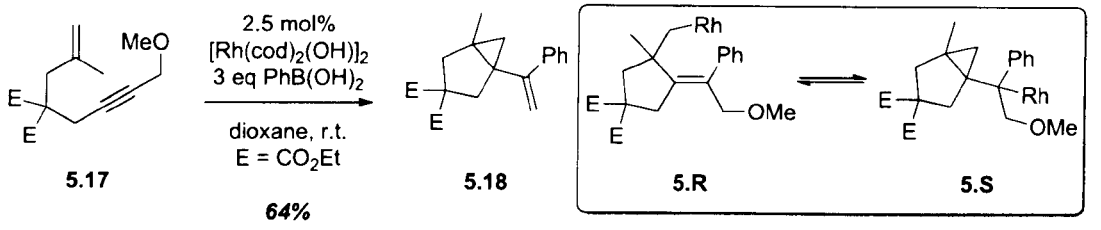
$[Rh(PPh_3)_3Cl]_2$ and 1.5 equivalent of $HSiMe_2Ph$ in toluene gave (*E*)-**5.16**. This result implies the cleavage of less substituted bond *a*. Hydrometallation of the C–C double bond could give intermediate **5.O**. Rotation around the C_1–C_2 bond would place the C_1–Rh bond and bond *a* *syn*-coplanar. *Syn*-coplanar β–carbon elimination in **5.P** would afford **5.Q** in which the alkene is in a (*Z*)-configuration. One could argue that rotation between conformers **5.O** and **5.P** would be disfavoured by steric interactions between the phenyl group and the substituents on the cyclopropane. Hence, another mechanism must be involved for this rearrangement.



Scheme 5.5: Rhodium-catalysed hydrosilylation of alkylidenecyclopropane (*E*)-**5.15**

Finally, although the release of the strain energy during the ring opening of a cyclopropane moiety is a favourable driving force, one must take into account that this step is reversible when studying the regioselectivity of the ring opening of the substituted cyclopropanes. Hence, the reversibility of β–carbon elimination (*i.e.* cyclopropanation step) was observed in palladium-catalysed intramolecular Heck reaction with the formation of cyclopropane derivatives via a 3-*exo-trig* cyclisation.[7] Rhodium-catalysed 3-*exo-trig* cyclisation was also described by Murakami (Scheme 5.6).[8] Indeed, the exposure of alkenyl **5.17** to $[Rh(cod)_2(OH)]_2$ resulted in the formation of 3,5-fused bicyclic structure **5.18**. This rearrangement likely involves the

formation of intermediate **5.R** which would be prone to undergo 3-*exo-trig* cyclisation towards **5.S**.



Scheme 5.6: Formation of cyclopropane via rhodium-catalysed 3-*exo-trig* cyclisation

1 – 2 – General trends

Generally, the ring opening of cyclopropane moiety via β–carbon elimination is controlled by steric factors (Figure 5.1); less sterically hindered bond *a* being mainly or exclusively cleaved (R = alkyl, protected alcohols, phenyl).[5,9,10,11] However, if the substituent R is an electron-withdrawing group both bonds can be cleaved. Detailed studies reported by Wender[12] and Trost[13] on rhodium- and ruthenium-catalysed intramolecular [5+2] cycloadditions of vinylcyclopropanes showed that the regioselectivity of the ring opening of the cyclopropane moiety not only depends on the relative stereochemistry between the cyclopropane substituents and the vinyl moiety (*i.e. cis*- vs *trans*- 2-substituted-1-vinylcyclopropane) but also on the nature of the catalyst (*i.e.* possible coordination to a vacant site on the metal). Similarly, coordination of a phenyl substituent to a vacant site on the catalyst would favour the cleavage of more sterically hindered bond *b*.[14]

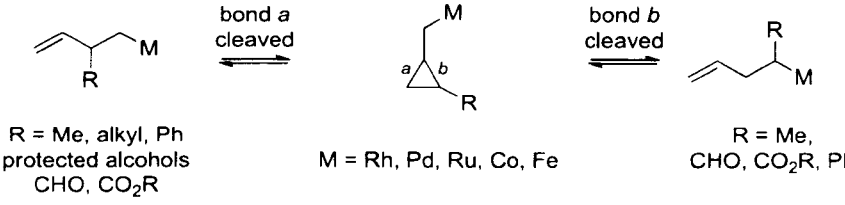
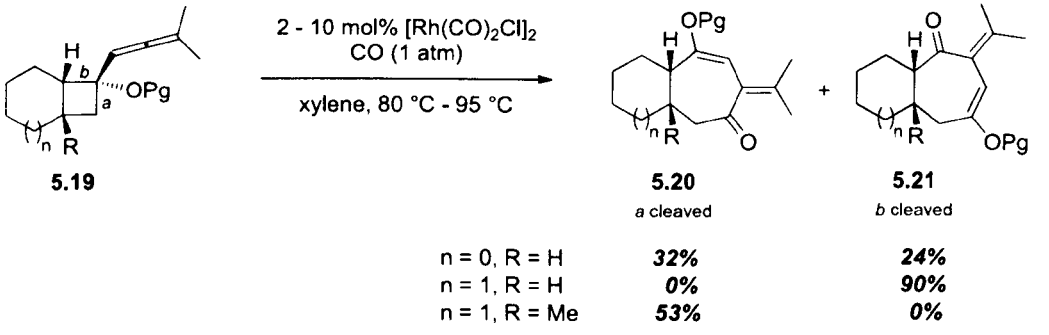


Figure 5.1: General trends observed for the regioselective ring opening of cyclopropane moiety

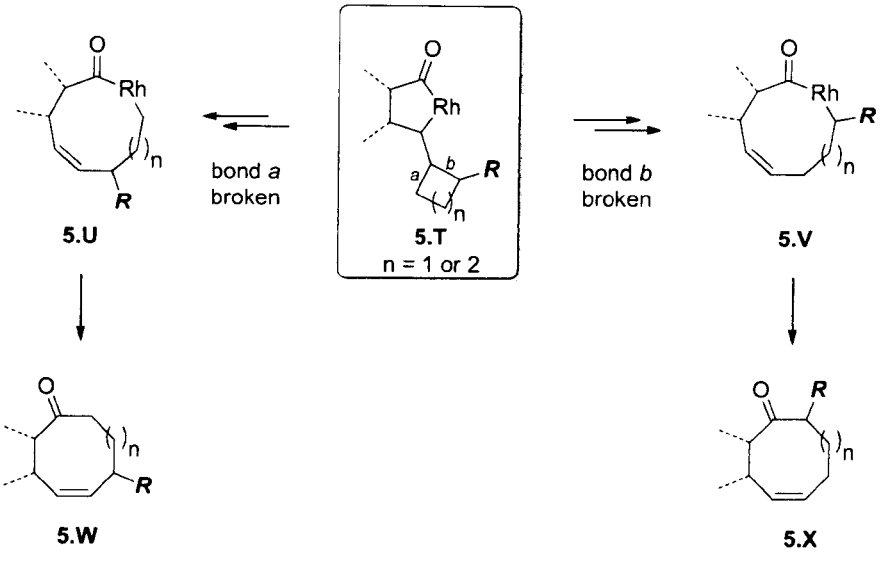
On the other hand, reports on the regioselective ring opening of α–substituted cyclobutanes are scarce and general trends cannot easily be drawn.[15] For instance, Wender reported that small changes of substituent have a strong impact on the regioselectivity of the ring opening during the rhodium-catalysed ring expansion of allenylcyclobutane **5.19** (Scheme 5.7).[16] Bicyclo[5.2.0]decane derivative (n = 0, R = H) was obtained as a mixture of regioisomers **5.20** and **5.21**. Interestingly, **5.21** which results from the cleavage of more hindered bond *b* was selectively obtained when the size of the cycloalkane was increased (n = 1, R = H). Surprisingly, an additional methyl group (n = 1, R = Me) selectively gave the opposite regioisomer **5.20**.



Scheme 5.7: Rhodium-catalysed ring opening of allenylcyclobutane

In this context, our efforts towards the understanding of the ring opening of α–substituted alkylidenecyclobutane derivatives are described in this chapter. The ring enlargement of pentarhodacycle **5.T** can occur following two pathways (Scheme 5.8). β–carbon elimination involving the cleavage of less substituted C–C bond *a* would

give nonarhodacycle **5.U** whereas cleavage of the more substituted C–C bond *b* would afford **5.V**. Reductive elimination of the metal centre would afford two regioisomers **5.W** and **5.X** from **5.U** and **5.V**, respectively.

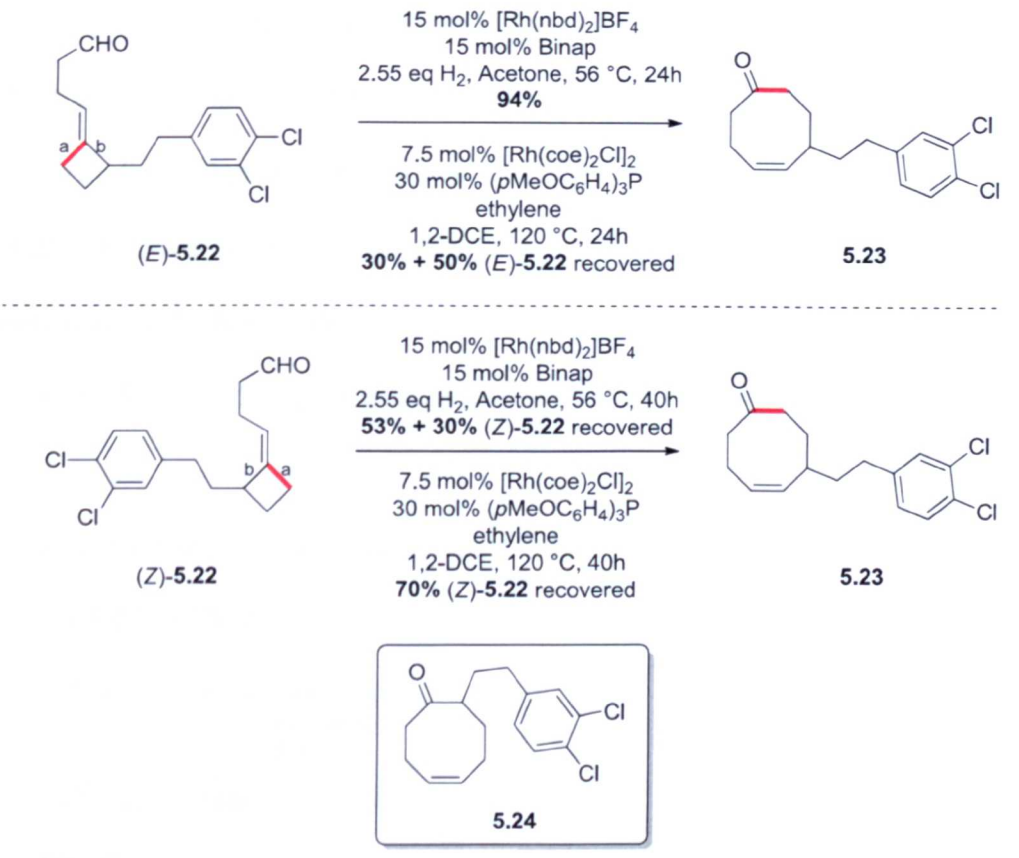


Scheme 5.8: Possible regioisomers for the ring opening of intermediate **5.T**

2 – Study of the regioselectivity in the rhodium-catalysed intramolecular hydroacylation of α–substituted alkylidenecyclobutane

2 – 1 – Regioconvergent ring-opening of α-substituted cyclobutane

Aldehydes (*E*)-**5.22** and (*Z*)-**5.22** were synthesised from commercially available 3-(3,4-dichlorophenyl)propanoic acid and treated with cationic or neutral rhodium catalysts (Scheme 5.9).

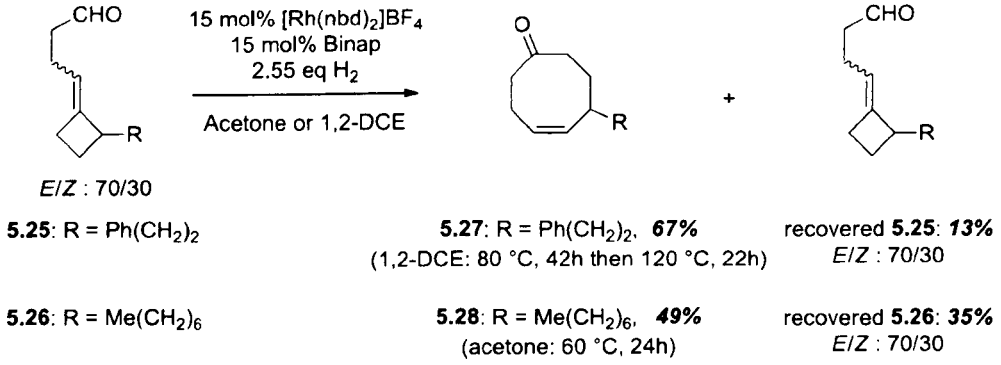


Scheme 5.9: Rhodium-catalysed regioconvergent cyclisation of (*E*)-**5.22** and (*Z*)-**5.22**

Surprisingly, both aldehydes gave the same regioisomer **5.23**. This result is in sharp contrast with the regiospecific ring opening of similar alkylidenecyclopropane derivatives.[1] Cationic rhodium catalyst [Rh(Binap)]BF_4 was much more efficient to promote the rearrangement. Indeed, **5.23** was isolated in 94% yield from (*E*)-**5.22** within 24 hours at 60 °C. On the other hand, treating (*E*)-**5.22** with neutral rhodium complex for 24 hours at 120 °C gave **5.23** in only 30% yield and (*E*)-**5.22** was recovered in 50% yield. Although longer reaction times were required for the rearrangement of (*Z*)-**5.22** into **5.23**, a similar trend was observed. Cationic rhodium complex gave cyclooctenone **5.23** in 53% yield within 40 hours whereas neutral rhodium catalyst was inefficient to promote the cyclisation. The rhodium-catalysed isomerisation of the C–C double bond of (*Z*)-**5.22** into (*E*)-**5.22** prior to the cyclisation could explain the regioconvergence of the ring opening.[17] However, in

both cases, the geometry of the alkene of the recovered aldehyde remains the same; (*Z*)-**5.22** was re-isolated in 30% and 70% yield. Treating (*Z*)-**5.22** under the same reaction conditions but stopping the reaction after 4 hours did not show any traces of (*E*)-**5.22**. Moreover, exposure of (*Z*)-**5.22** to the cationic rhodium catalyst at room temperature for 18 hours left (*Z*)-**5.22** unchanged. These observations indicate that the isomerisation of (*Z*)-**5.22** into (*E*)-**5.22** prior to the cyclisation is unlikely.

The regioconvergent ring opening of alkylidenecyclobutane was also observed with aldehydes **5.25** and **5.26** (Scheme 5.10).

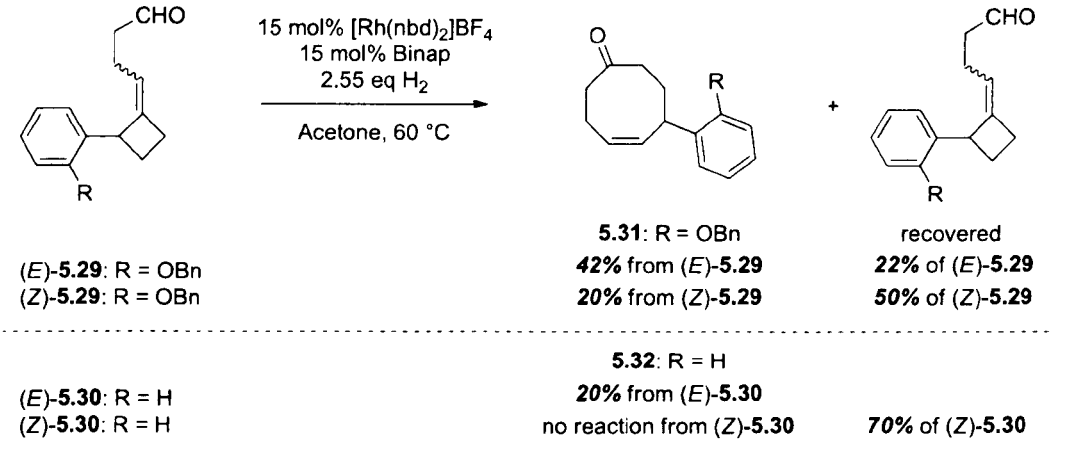


Scheme 5.10: Regioconvergent ring opening of **5.25** and **5.26**

Both aldehydes were prepared by Dr. Christophe Aïssa as a 70:30 *E/Z* mixture and treated with cationic rhodium catalysts. Under these conditions, only one regioisomer was obtained in each case. Interestingly, aldehyde **5.25** which has a similar steric congestion as compared to **5.22** was more reluctant to undergo the cyclisation. We also found that using 1,2-DCE gave cleaner conversion. Cyclooctenone **5.27** was isolated in 67% yield and starting material **5.25** was recovered in 13% yield with the same *E/Z* ratio. An apolar fraction which is presumably a mixture of products of decarbonylation, was also collected. Aldehyde **5.26** in which the homobenzylic chain

is replaced with a simple alkyl chain, gave 8-membered ring **5.28** in 49% yield. Moreover, starting material **5.26** with the same *E*/*Z* ratio was recovered in 35% yield.

We then turned our attention to the rearrangement of alkylidenecyclobutanes substituted with an aromatic group (Scheme 5.11).



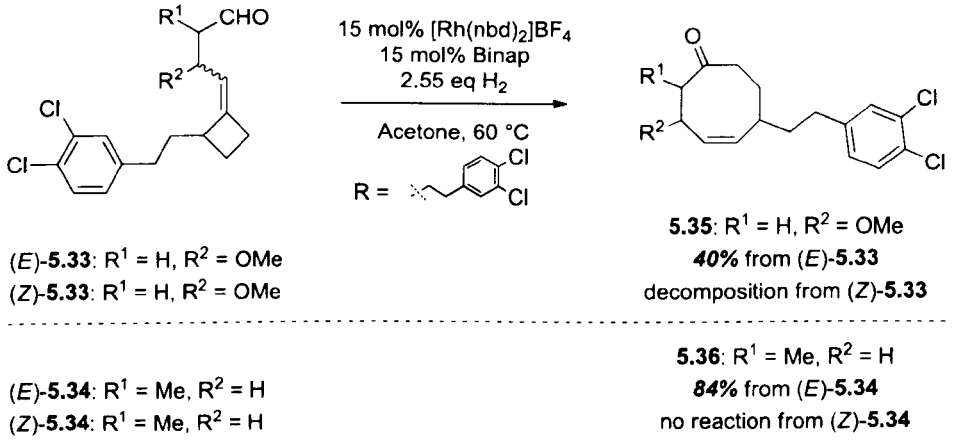
Scheme 5.11: Regioselective ring opening of substrates substituted with aromatics

(*E*)-**5.29** was prepared and treated with 15 mol% of [Rh(Binap)]BF_4 in acetone at 60 °C for 36 hours. Under these conditions, 42% of 8-membered ring **5.31** was isolated and starting material (*E*)-**5.29** was also recovered in 22% yield. When (*Z*)-**5.29** was treated under the same conditions, 8-membered ring **5.31** was isolated in 20% yield. Starting material (*Z*)-**5.29** contaminated with other aldehydes was also recovered in 50% yield. Although the starting material partially decomposed under these conditions, the result showed the regioconvergence of the ring opening. Indeed in both cases, the less substituted bond of the cyclobutane ring is cleaved.

Aldehydes (*E*)-**5.30** and (*Z*)-**5.30** having a simple phenyl group as substitutent were also prepared and treated with 15 mol% of [Rh(Binap)]BF_4 in acetone. Unfortunately, their rearrangement turned out to be difficult. After 96 hours of reaction (*E*)-**5.30**

gave only 20% of 8-membered ring **5.32**. On the other hand, (*Z*)-**5.30** was completely unreactive under these conditions and 70% of (*Z*)-**5.30** was recovered.

Finally we investigated the effect of a substituent in α or β position to the aldehyde moiety (Scheme 5.12). Aldehydes (*E*)- and (*Z*)-**5.33** were synthesised, both as a mixture of two diastereoisomers, and treated with 15 mol% of cationic rhodium catalyst (Scheme 5.12). Unfortunately, the cyclisations did not proceed well. (*E*)-**5.33** gave 8-membered ring **5.35** in 40% yield after 2 days of reaction while (*Z*)-**5.33** led to the decomposition of the starting material. In both cases, starting material **5.33** was not stable; products resulting from the elimination of the methoxy substituent were also identified by ^{1}H NMR. Aldehydes (*E*)- and (*Z*)-**5.34** were also synthesised and treated under the optimised conditions. While (*E*)-**5.34** gave the expected 8-membered ring **5.36** in excellent 84% yield, (*Z*)-**5.34** was found to be unreactive under these conditions. After 4 days at 60 °C, (*Z*)-**5.34** was recovered in 64% yield.



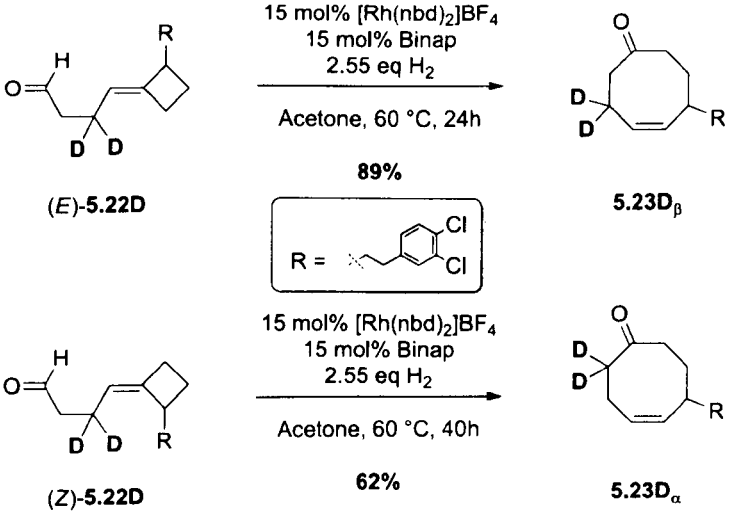
Scheme 5.12: Regioconvergent ring opening of substrates embedding substituent on carbon α or β to the aldehyde group

2 – 2 – Origins of the observed regioconvergence

The isomerisation of the C–C double bond of the (*Z*)-isomers into the *E* configuration prior to the cyclisation is unlikely. As previously mentioned, in all attempts where the (Z)-isomer partially underwent intramolecular cyclisation, the configuration of the alkene of the recovered starting material remained the same (*ie.* (*Z*)-configuration). Hence, we envisioned that the (*E*)-**5.22** and (*Z*)-**5.22** would be rearranged into **5.23** following two distinct mechanisms.

2 – 2 – a – Deuterium-labelling experiment

In order to gain more insights about the mechanism, deuterium-labelled precursors (*E*)-**5.22D** and (*Z*)-**5.22D** were prepared and treated with 15 mol% of [Rh(Binap)]BF_4 in acetone at 60 °C (Scheme 5.13).

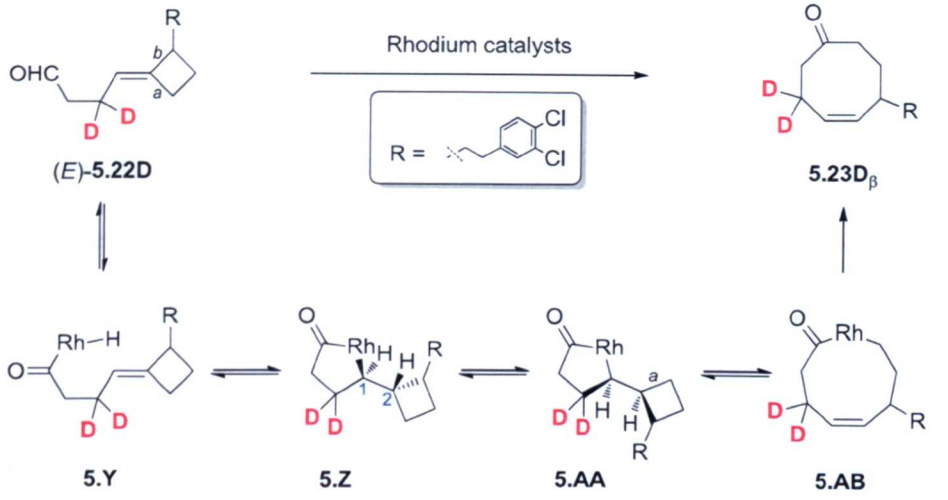


Scheme 5.13: Rearrangement of (*E*)-**5.22D** and (*Z*)-**5.22D**

Cyclooctenones **5.23D$_\alpha$** and **5.23D$_\beta$** were obtained in yield comparable to those obtained from the non-labelled substrates. More importantly, while (*E*)-**5.22D** gave **5.23D$_\beta$**, (*Z*)-**5.22D** afforded **5.23D$_\alpha$** in which the carbon labelled with the two deuterium atoms is α to the carbonyle (see Appendix 4, p 302). 2D NMR analysis allowed for the assignment of each carbon of **5.23**. Hence, the position of the deuterium atoms in **5.23D$_\alpha$** and **5.23D$_\beta$** was easily identified by comparing their ^{13}C NMR spectra with **5.23**. This outcome clearly suggests that two different mechanisms are involved for the rearrangement of (*E*)-**5.22** and (*Z*)-**5.22** into **5.23**.

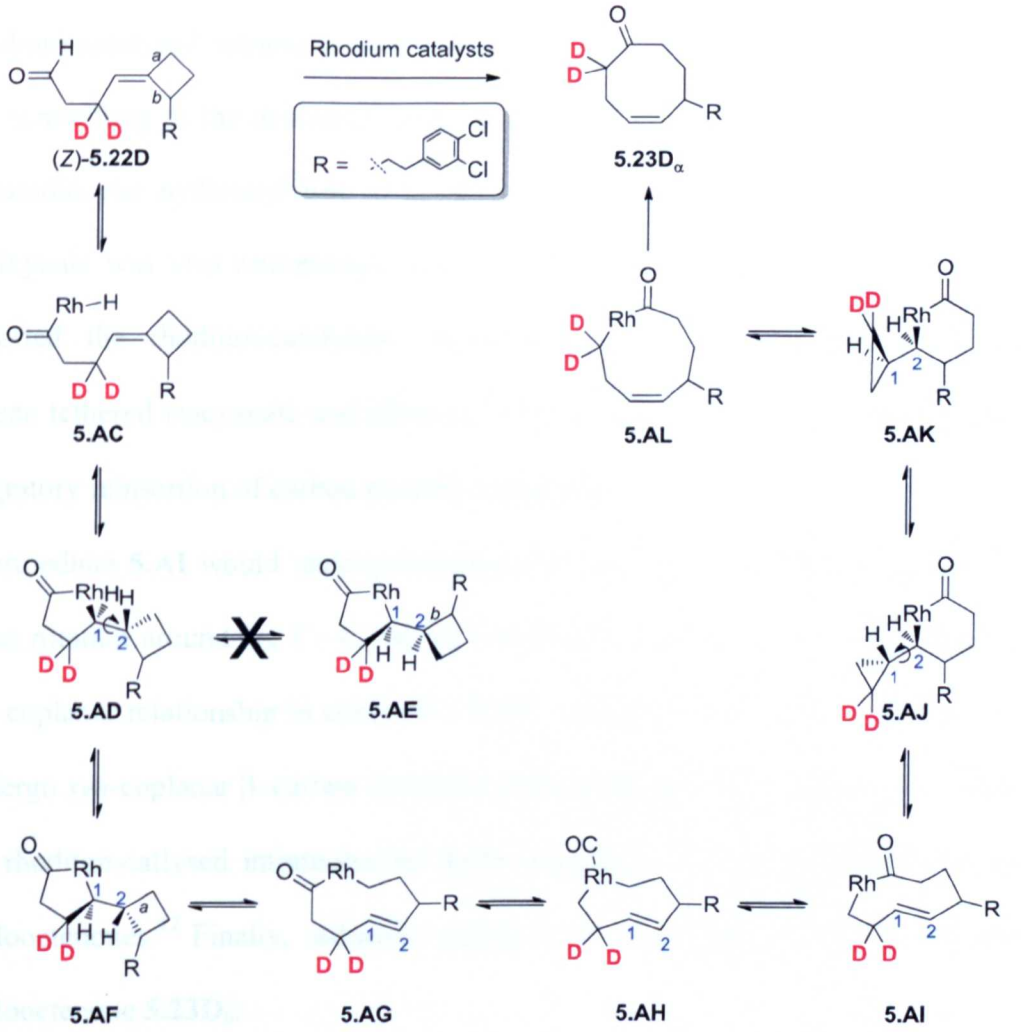
2 – 2 – b – Proposed mechanism for the cyclisation of (*E*)-**5.22D** and (*Z*)-**5.22D**

The mechanism of cyclisation of (*E*)-**5.22D** is described in scheme 5.14. Oxidative addition of the rhodium into the formyl bond would give **5.Y** and would be followed by *syn*-hydrometallation of the C–C double bond affording pentarhodacycle **5.Z**. Rotation around the C_1–C_2 bond, placing the C_1–H and C_2–H bonds in a *syn*-coplanar relationship, would also place C_1–Rh and less substituted bond *a* in a *syn*-coplanar relationship. Hence, **5.AA** would be prone to undergo β–carbon elimination towards **5.AB** and reductive elimination of the metal would afford **5.23D$_\beta$**. (*E*)-**5.22** would therefore undergo intramolecular hydroacylation according to a mechanism identical to the rationale proposed for the alkylidenecyclopropane derivatives.



Scheme 5.14: Proposed mechanism for the rearrangement of (*E*)-**5.22D**

The mechanism depicted in scheme 5.15 would explain the formation of **5.23D$_\alpha$**.



Scheme 5.15: Proposed mechanism for the rearrangement of (*Z*)-**5.22D**

C–H activation would give intermediate **5.AC** and would be followed by *syn*-hydrometallation of the C–C double bond, giving intermediate **5.AD**. Conformer **5.AE** reached by rotation around the C_1–C_2 bond would be disfavoured due to the steric clash between the ligand sphere of the catalyst and the substituent R. Instead, **5.AF** would be preferred. In this intermediate, less substituted bond *a* and the C_1–Rh bond are also *syn*-coplanar but the C_1–H and C_2–H bonds are not. Hence, β–carbon elimination would lead to **5.AG** embedding a *E* double bond. Carbon monoxide deinsertion would give **5.AH** and α–migratory reinsertion of carbon monoxide would afford **5.AI**. Mechanisms involving deinsertion and α-migratory reinsertion of carbon monoxide were proposed to account for the formation of 4-phenyl-4-pentenal in rhodium-catalysed intramolecular hydroacylation of 3-phenyl-4-pentenal[18] and for the scrambling of the deuterium label in all positions during the rhodium-catalysed intramolecular hydroacylation of 4-pentenal.[19] Rhodium-catalysed isomerisation of 4-alkynals was also rationalised with a mechanism involving these steps.[20] Rovis reported the rhodium-catalysed intermolecular [2+2+2] cycloaddition between alkene tethered isocyanate and alkynes,[21] which would also involve a deinsertion/α-migratory reinsertion of carbon monoxide sequence.

Intermediate **5.AI** would undergo transannular 3-*exo-trig* cyclisation towards **5.AJ**. Then rotation around the C_1–C_2 bound would place the C_1–H and C_2–H bonds in a *syn*-coplanar relationship in conformer **5.AK**. The latter would therefore be prone to undergo *syn*-coplanar β–carbon elimination towards *cis*-**5.AL** as reported by Shair in the rhodium-catlysed intramolecular hydroacylation of vinylcyclopropanal towards cyclooctenones.[22] Finally, reductive elimination of the metal centre would afford cyclooctenone **5.23D**$_a$.

In line with the results obtained with the labelled-precursors, this mechanism nicely explain the formation of **5.23D$_\alpha$** in which the carbon atom labelled with the two deuterium atoms is α to the ketone. This mechanism is characterised by multiple C–H/C–C bonds cleavages and formations. Overall, one C–H bond and three C–C bonds are cleaved and the same number of bonds is formed, respectively.

The formation of *trans*-**5.AG** is not thermodynamically favoured as compared to the *cis* conformer.[23] Hence, this would explain the fact that (*Z*)-isomers are generally more reluctant to undergo the cyclisation as compared to (*E*)-isomers.

The formation of hexarhodacycle **5.AJ** from nonarhodacycle **5.AI** represents the first example of rhodium-catalysed transannular 3-*exo-trig* cyclisation. Transition-metal catalysed 3-*exo-trig* cyclisations are well-known, especially in palladium-catalysed Heck reactions,[7] in nickel-catalysed cascade reactions[4] or in rhodium-catalysed carbocyclisation.[8,24] However, none of them have been reported in a transannular fashion.

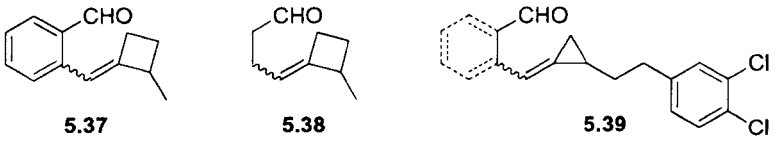
Finally, as previously reported, the *Z* isomer of precursors substituted in position α (methyl substituent) or β (methoxy substitutent) was unreactive or decomposed, respectively, under our optimised conditions. This could be explained by disfavoured steric hindrance between the substituents and the sphere of ligands in intermediates **5.AJ** and **5.AI**.

3 – Conclusion and outlook

Unlike the regiospecific ring opening of alkylidenecyclopropanes which involves the cleavage of the C–C bond of the cyclopropane *cis* to the aromatic unit, the ring

opening of alkylidenecyclobutane appears to be regioconvergent. Indeed, the cleavage of the less sterically hindered bond was systematically observed. Despite the difficulties encountered to build the scope of the reaction, the deuterium-labelled experiments displayed interesting features. While the mechanism of rearrangement of (*E*)-**5.22** seems to follow the classic steps (Scheme 5.14), (*Z*)-**5.22** is rearranged into **5.23** via a much more intricated mechanism (Scheme 5.15) featuring a unique transannular 3-*exo-trig* cyclisation of an organorhodium species.

The future work will consist in the preparation of precursors **5.37** and **5.38** and study their cyclisation in order to gain more insight about the regioselectivity of the ring opening of cyclobutane moiety (Figure 5.2). Aldehydes **5.37** will allow the direct comparison with alkylidenecyclopropane derivatives **5.1** and **5.2**. Importantly, the *Z* isomer cannot be rearranged following the mechanism depicted in scheme 5.15 which involves a transannular 3-*exo-trig* cyclisation, hence, the regioconvergence of the ring opening of the cyclobutane moiety cannot be observed. Conversely, the rearrangement of precursor (*Z*)-**5.38** (which also embeds a methyl group, the smallest sterically hindered substituent) can follow the same mechanistic pathway depicted in scheme 5.15. Therefore, the rearrangement of this precursor would enable us to conclude on the influence of the steric hindrance generated by a substituent on the regioselectivity of the ring opening of the cyclobutane moiety. Finally, we intend to prepare aldehydes **5.39** in order to see if the ring opening of the cyclopropane is regiospecific with the same homobenzylic substituent.



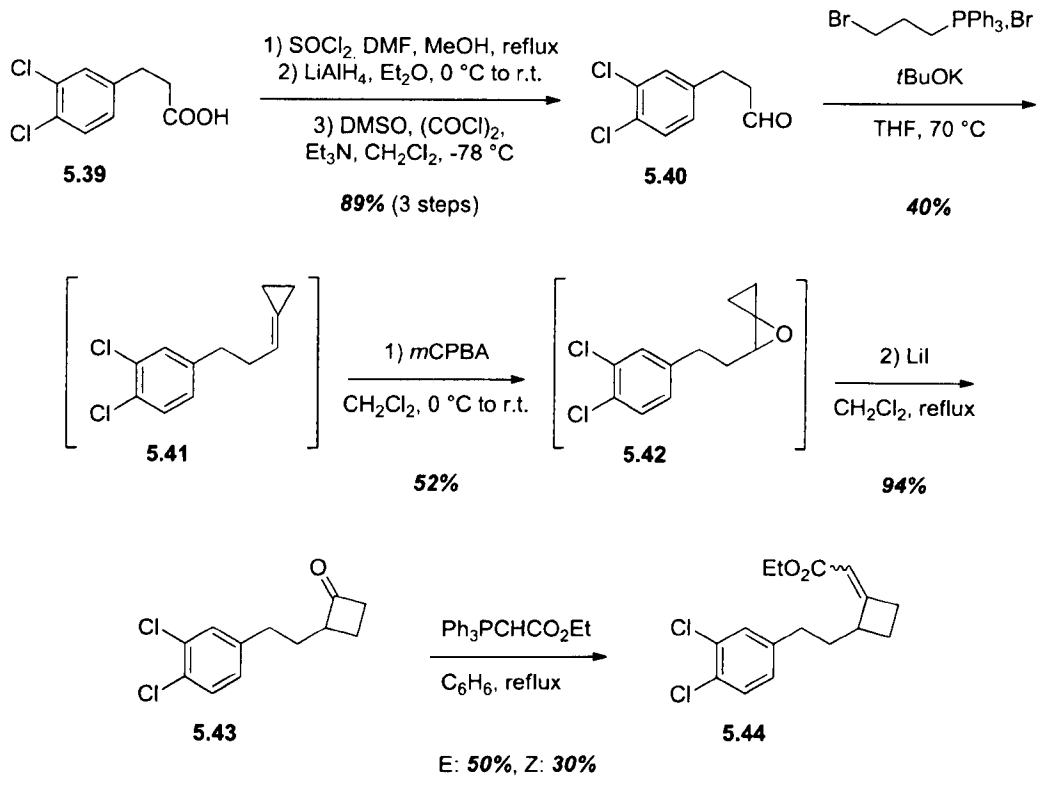
5.37 5.38 5.39

Figure 5.2: Envisioned precursors in order to complete the study on the regioselectivity of the ring opening of alkylidenecyclopropane and alkylidenecyclobutanes

4 – Synthesis of precursors

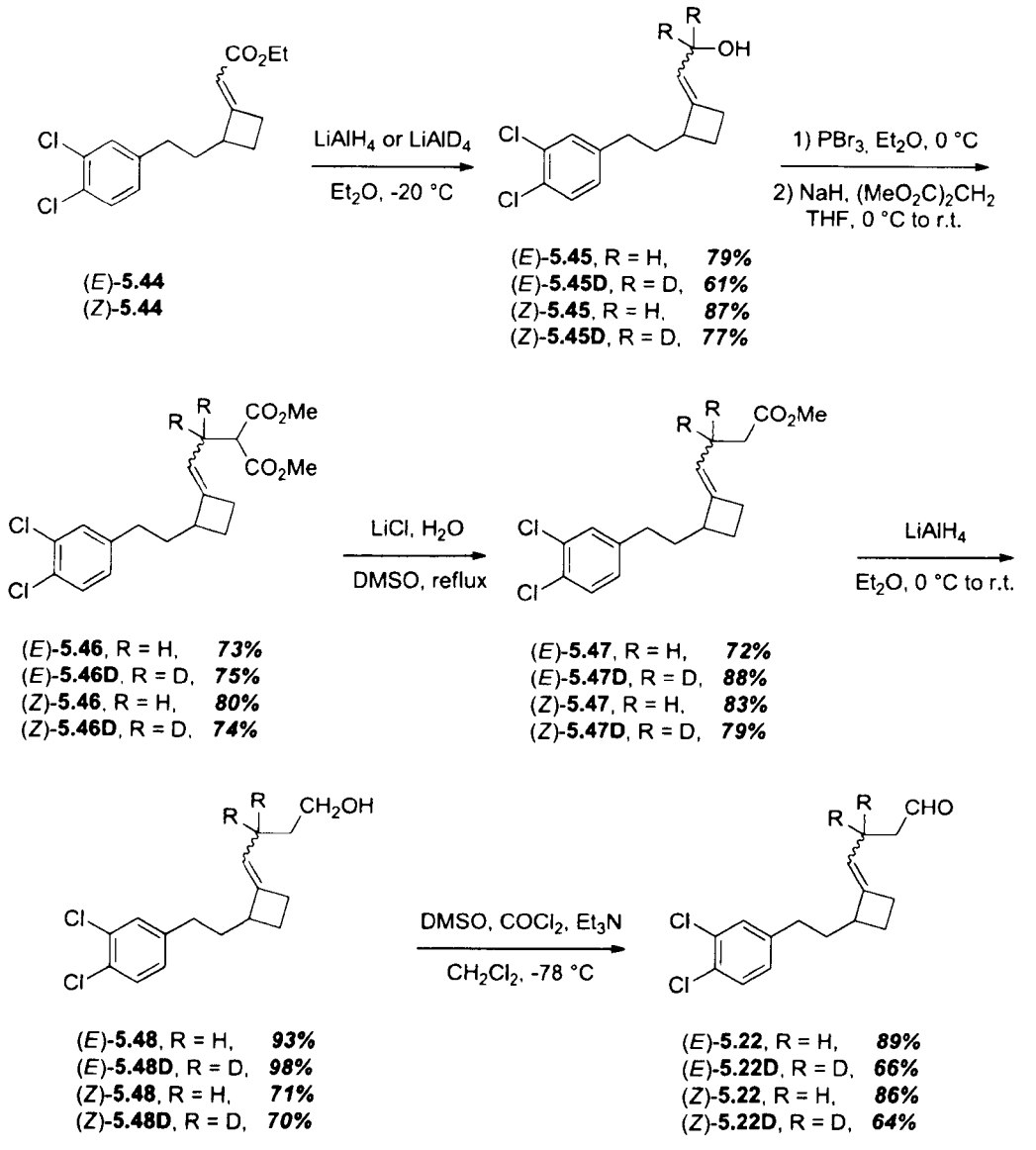
*4 – 1 – Synthesis of (E)- and (Z)- isomers of **5.22** and **5.22D***

Aldehydes **5.22**, and **5.22D** were synthesised from commercially available 3-(3,4-dichlorophenyl)propanoic acid **5.39** (Scheme 5.16). Esterification of **5.39** followed by reduction to the alcohol and reoxidation gave aldehyde **5.40**. Alkylidenecyclopropane derivative **5.41** was obtained via a Wittig reaction with (3-bromopropyl)triphenylphosphonium bromide. Despite full conversion observed by TLC, **5.41** was obtained in moderate yield. Epoxidation using *m*CPBA gave spiro epoxide **5.42**. The latter was rearranged into cyclobutanone **5.43** by treatement with lithium iodide. Finally, α,β-insaturated ester **5.44** was obtained by Wittig reaction between cyclobutanone **5.43** and (ethoxycarbonylmethylene) triphenylphosphorane. Fortunately, *E* and *Z* isomers were separable by performing several column chromatographies.



Scheme 5.16: Preparation of α,β-insaturated ester **5.44**

Having separated (*E*)- and (*Z*)-**5.44**, both esters were reduced using lithium aluminium hydride (R = H) or lithium aluminium deuteride (R = D) at -20 °C (Scheme 4.27). The full assignment of the ^{1}H NMR and ^{13}C NMR spectra was achieved with 2D NMR while nOe experiment allowed for the identification of both isomers (see Appendix 3, p 299). The four alcohols **5.45** were treated with phosphorus tribromide and the crude allylic bromides were treated with the dimethylmalonate anion, resulting in the formation of bisesters **5.46**. Krapcho decarboxylation using lithium chloride in refluxed DMSO gave monoesters **5.47**.[25] Under these conditions, the (*Z*) isomers partially isomerised into the (*E*) isomers in a 9:1 E/Z ratio. Fortunately, both isomers were separable by doing several column chromatographies at the next stage. Hence, alcohols **5.48** were reoxidised using Swern's conditions,[26] giving (*E*)- and (*Z*)- isomers of **5.22** and **5.22D**.



(*E*)-**5.44**
(*Z*)-**5.44**

(*E*)-**5.45**, R = H, ***79%***
(*E*)-**5.45D**, R = D, ***61%***
(*Z*)-**5.45**, R = H, ***87%***
(*Z*)-**5.45D**, R = D, ***77%***

(*E*)-**5.46**, R = H, ***73%***
(*E*)-**5.46D**, R = D, ***75%***
(*Z*)-**5.46**, R = H, ***80%***
(*Z*)-**5.46D**, R = D, ***74%***

(*E*)-**5.47**, R = H, ***72%***
(*E*)-**5.47D**, R = D, ***88%***
(*Z*)-**5.47**, R = H, ***83%***
(*Z*)-**5.47D**, R = D, ***79%***

(*E*)-**5.48**, R = H, ***93%***
(*E*)-**5.48D**, R = D, ***98%***
(*Z*)-**5.48**, R = H, ***71%***
(*Z*)-**5.48D**, R = D, ***70%***

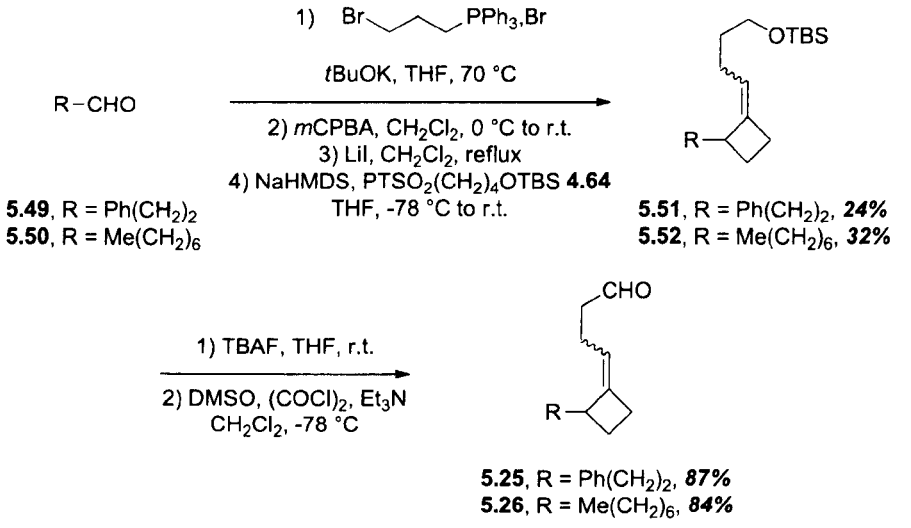
(*E*)-**5.22**, R = H, ***89%***
(*E*)-**5.22D**, R = D, ***66%***
(*Z*)-**5.22**, R = H, ***86%***
(*Z*)-**5.22D**, R = D, ***64%***

Scheme 5.17: Synthesis of (*E*)-**5.22**, (*E*)-**5.22D**, (*Z*)-**5.22** and (*Z*)-**5.22D**

*4 – 2 – Synthesis of **5.25** and **5.26***

Aldehydes **5.25** and **5.26** were prepared by Dr. Christophe Aïssa. The synthetic approach utilised is described in scheme 5.18. Starting with commercially available 3-phenylpropionaldehyde **5.49** and octanal **5.50**, a four-steps sequence, including Wittig reaction, epoxidation, rearrangement into the cyclobutanone and Julia-Kocienski reaction,[27] afforded alkylidenecyclobutane derivatives **5.51** and **5.52** in

24% and 32% yield, respectively. The Julia-Kocienski reaction gave a mixture of (*E*) and (*Z*) isomers in 70:30 *E*/*Z* ratio in both cases. Cleavage of the TBS group liberated the primary alcohols which were oxidised following Swern's conditions.[25] The spectral data of aldehydes **5.25** and **5.26** are reported in the supporting information section.

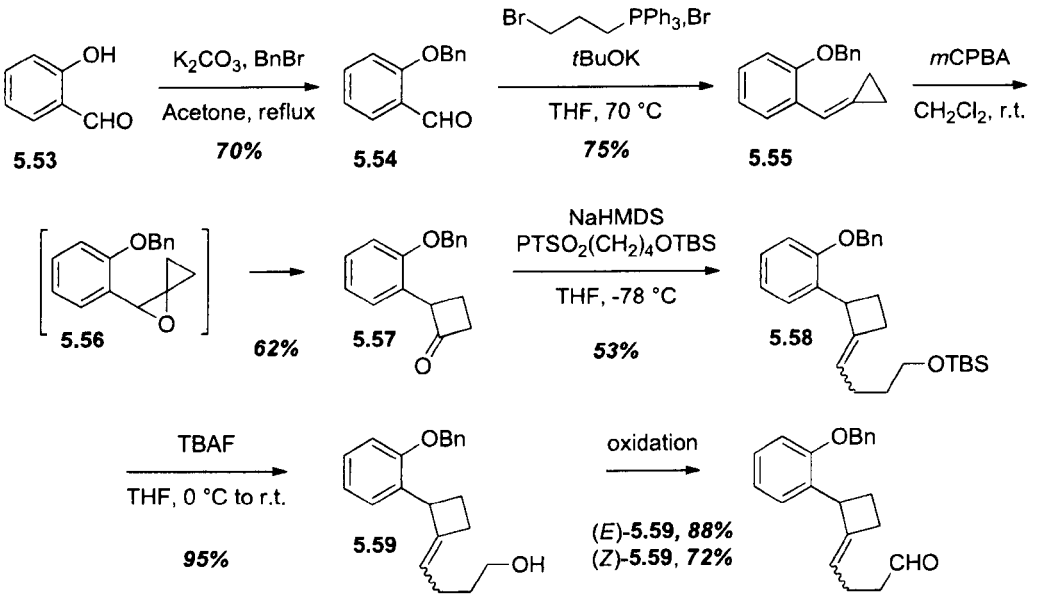


Scheme 5.18: Preparation of aldehydes **5.25** and **5.26**

*4 – 3 – Synthesis of **5.29** and **5.30***

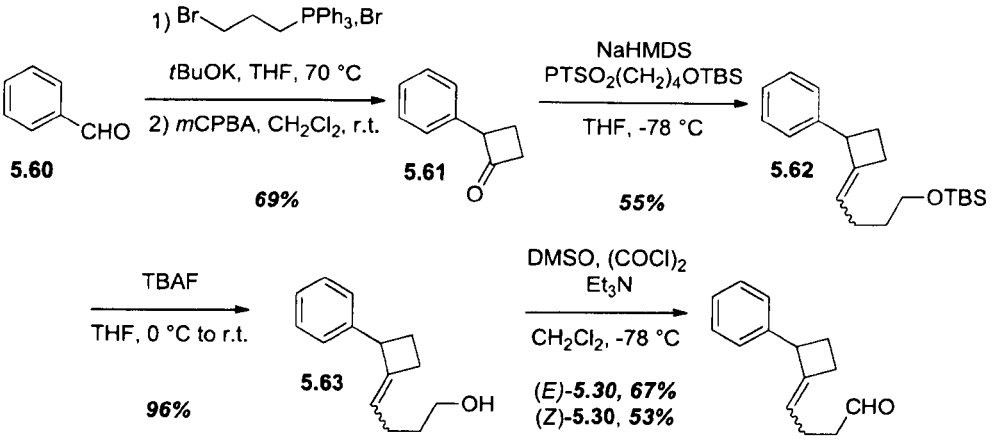
Salicylaldehyde **5.53** was first protected into benzylether **5.54** and Wittig reaction with (3-bromopropyl)triphenylphosphonium bromide gave alkylidenecyclopropane derivative **5.55** (Scheme 5.19). Epoxidation of the C–C double using *m*CPBA intermediately afforded epoxide **5.56** as crude material but was later rearranged into cyclobutanone **5.57** when the crude material was purified by column chromatography indicating that silica is acidic enough to promote this rearrangement. Julia-Kocienski reaction[26] gave **5.58** as a mixture of *E* and *Z* isomers in a 70:30 *E*/*Z* ratio. Deprotection liberated primary alcohol **5.59** and both isomers were separated at this

stage by doing several column chromatographies. Swern's conditions[25] were utilised for the oxidation of (*E*)-**5.59** into (*E*)-**5.29** while (*Z*)-**5.29** was obtained using Dess-Martin periodinane.[28]



Scheme 5.19: Synthesis of (*E*)-**5.29** and (*Z*)-**5.29**

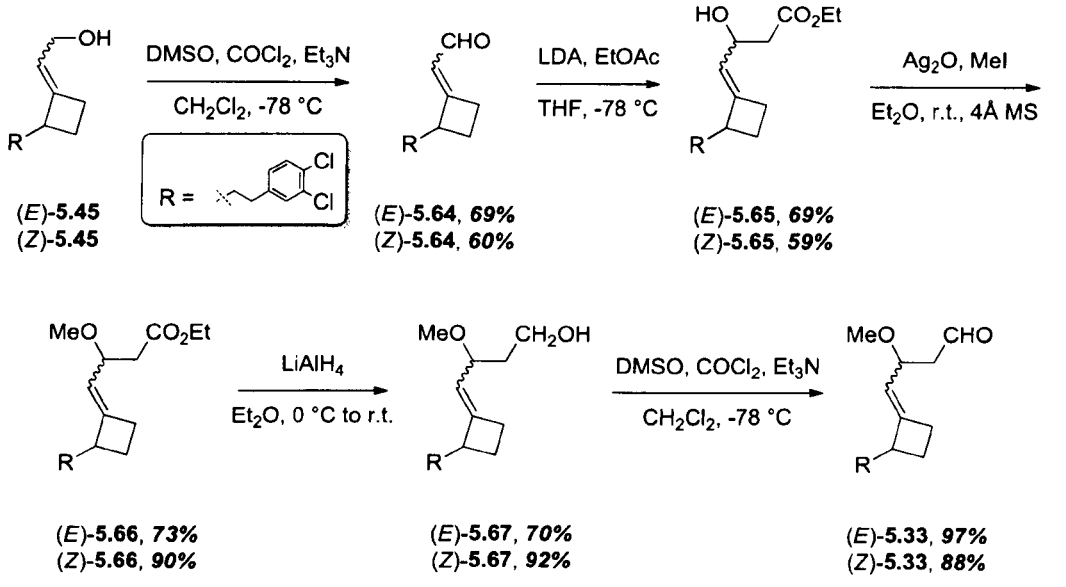
Aldehyde **5.30** was obtained following a similar route as compared to **5.29** (Scheme 5.20). Wittig reaction between benzaldehyde **5.60** and the same phosphonium salt followed by epoxidation of the C–C double and subsequent rearrangement into cyclobutanone **5.61** was achieved in 69% yield over the two steps. Julia-Kocienski reaction[26] afforded compound **5.62**. Cleavage of the TBS ether using TBAF followed by Swern oxidation[25] gave aldehyde **5.30**.



Scheme 5.20: Synthesis of (*E*)-**5.30** and (*Z*)-**5.30**

4 – 4 – Synthesis of ***5.33*** *and* ***5.34***

The synthesis of **5.33** began with the oxidation of **5.45** into allylic aldehyde **5.64** (Scheme 5.21).

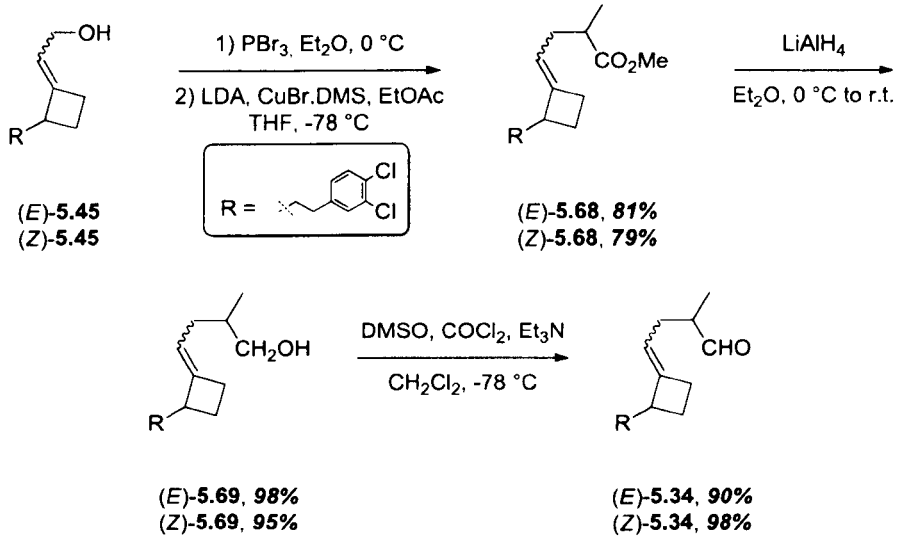


Scheme 5.21: Synthesis of (*E*)-**5.33** and (*Z*)-**5.33**

Both aldehydes were utilised in an aldol reaction, delivering (*E*)- and (*Z*)-**5.65** in moderate yield. Methyl ethers **5.66** were obtained by treating these alcohols with iodomethane in the presence of silver oxide for four days at room temperature.

Reduction of the ester moiety followed by reoxidation under Swen's conditions[25] gave aldehydes (*E*)- and (*Z*)-**5.33**.

The preparation of aldehyde **5.34** also started from alcohols (*E*)- and (*Z*)-**5.45** (Scheme 5.22). Treatment of (*E*)- and (*Z*)-**5.45** with phosphorus tribromide followed by substitution of the crude bromide with methyl propionate anion gave (*E*)- and (*Z*)-**5.68**. Reduction of the ester moiety using lithium aluminium hydride followed by Swern's oxidation[25] afforded aldehydes (*E*)- and (*Z*)-**5.34**.



(*E*)-**5.45**
(*Z*)-**5.45**

(*E*)-**5.68**, ***81%***
(*Z*)-**5.68**, ***79%***

(*E*)-**5.69**, ***98%***
(*Z*)-**5.69**, ***95%***

(*E*)-**5.34**, ***90%***
(*Z*)-**5.34**, ***98%***

Scheme 5.22: Synthesis of (*E*)-**5.34** and (*Z*)-**5.34**

5 – References

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Chapter 6

Experimental Part

1 – General

Otherwise noted, all reactions were carried out in flame-dried glassware under an inert atmosphere of dry N_2.

The solvents were purified either with the solvent purification system Pure Solv MD-6 (THF, Et_2O, CH_2Cl_2, benzene, toluene, hexane) or by distillation over the drying agents indicated and were transferred under N_2. 1,2-DCE was distilled from CaH_2, acetone was distilled from anhydrous Ca_2SO_4 and stored over 4Å MS.

Diisopropylamine was distilled from sodium hydroxide and ethyl acetate (used as reagent) was distilled from potassium carbonate and stored over 4Å MS.

TLC were carried out on aluminium-backed plates pre-coated with silica (0.2 mm, 60F 254 nm, Merck) and were visualised using ultraviolet light (λmax = 254 nm) before being developed in a potassium permanganate solution, *p*-anisaldehyde solution or phosphomolybdic acid solution.

Column chromatography were performed on Merck silica gel 60 (230-400 mesh).

NMR spectra were recorded on a Bruker DRX 500 or a Bruker DPX 400 spectrometer in $CDCl_3$, C_6D_6 or C_3D_6O; chemical shifts (δ) are given in ppm relative

to TMS and coupling constants (J) are given in Hertz (Hz). The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.24 ppm; C_6D_6: δ_C = 128.3 ppm; residual C_6H_6 in C_6D_6: δ_H = 7.35 ppm; C_3D_6O: δ_C = 30.9 ppm; residual C_3H_6O in C_3D_6O: δ_H = 2.16 ppm). Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m).

IR spectra of neat products were recorded with a PerkinElmer Spectrum 100 FT-IR spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}.

HRMS were obtained at the University of Liverpool: VG7070E (CI), micromass LCT mass spectrometer (ES+), or were obtained from the EPSRC National Mass Spectrometry Service Centre at Swansea.

GC analyses were performed on a Agilent 7890A instrument, using a cyclodex-B column (30 m × 0.252 mm × 0.25 μm). n-pentadecane was used as internal standard (*130 °C to 140 °C (ramp: 2 °C per minute) then 55 minutes at 140 °C* / t_R = *3. 65 min*). Melting points were obtained from a Griffin melting point apparatus (not corrected).

Elemental analyses: University of Liverpool.

The optical rotation data were recorded on Perkin Elmer polarimeter 343 Plus.

All commercially available compounds were used as received.

2 – Representative procedures for the rhodium-catalysed intramolecular hydroacylation

$[Rh(coe)_2Cl]_2$[1] and $[Rh(cod)_2]BF_4$[2] were synthesized from $RhCl_3.3H_2O$, following the procedures reported in the literature. Commercially available $[Rh(nbd)_2]BF_4$ was used as received.

Representative procedures are described for the formation of 7-membered ring **2.2**

Method I. Under a flow of N_2, a Teflon-screw Schlenk flask equipped which with a small stir bar (which was previously evacuated, dried and refilled with Argon) was charged with compound **2.1** (32 mg, 0.147 mmol), $[Rh(coe)_2Cl]_2$ (5.3 mg, 0.00734 mmol), $P(p\text{MeOC}_6H_4)_3$ (10.3 mg, 0.0293 mmol) and 1,2-DCE (2.7 mL). Ethylene was bubbled through the solution via a needle for 60 sec before the flask was sealed and immersed into a pre-heated oil bath (120 °C bath temperature). After stirring for 2.5 hours at that temperature, the mixture was allowed to cool before evaporation. Purification by flash chromatography (PE/EtOAc, 10:1) gave ketone **2.2** (23 mg, 72%).

Method II. Under a flow of N_2, a Teflon-screw Schlenk flask equipped which with a small stir bar (which was previously evacuated, dried and refilled with Argon) was charged with compound **2.1** (50 mg, 0.229 mmol), $[Rh(coe)_2Cl]_2$ (4.1 mg, 0.00573 mmol), $P(p\text{MeOC}_6H_4)_3$ (8.1 mg, 0.0229 mmol), $AgBF_4$ (2.2 mg, 0.0115 mmol) and 1,2-DCE (4.6 mL) under N_2. The Schlenk flask was sealed and immersed into a pre-heated oil bath (80 °C bath temperature). After stirring for 45 minutes at that

temperature, the mixture was allowed to cool before evaporation. Purification by flash chromatography (PE/EtOAc, 10:1) gave ketone **2.2** (45 mg, 90%).

Method III. Under a flow of N_2, a Teflon-screw Schlenk flask equipped which with a small stir bar (which was previously evacuated, dried and refilled with Argon) was charged with compound **2.1** (55 mg, 0.252 mmol), $[Rh(coe)_2Cl]_2$ (1.8 mg, 0.00252 mmol), Binap (3.1 mg, 0.00504 mmol), $AgBF_4$ (1.0 mg, 0.00504 mmol) and 1,2-DCE (5.0 mL) under N_2. The Schlenk flask was sealed and immersed into a pre-heated oil bath (40 °C bath temperature). After stirring for 1 hour at that temperature, the mixture was allowed to cool before evaporation. Purification by flash chromatography (PE/EtOAc, 10:1) gave ketone **2.2** (47 mg, 86%).

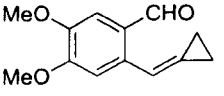
Method IV. Under N_2, a Teflon-screw Schlenk flask equipped with a small stir bar (which was previously evacuated, dried and refilled with Argon) was charged with $[Rh(nbd)_2]BF_4$ (3.0 mg, 0.00802 mmol), Binap (5.0 mg, 0.00802 mmol), and acetone (2 mL) before bubbling H_2 (3.3 mL, 0.136 mmol) via syringe over a period of 5.5 minutes (flow = 0.6 $mL.min^{-1}$) and sealing the flask. After stirring for 1 hour at room temperature, 0.46 mL of this solution was added to a solution aldehyde **2.1** (20 mg, 0.0916 mmol) in acetone (1.37 mL). The Schlenk flask was sealed and the mixture was stirred at room temperature for 30 minutes. The mixture was evaporated. Purification by flash chromatography (PE/EtOAc, 10:1) gave ketone **2.2** (19 mg, 95%).

Method V. Under a flow of N_2, a Teflon-screw Schlenk flask equipped which with a small stir bar (which was previously evacuated, dried and refilled with Argon) was

charged with compound **2.1** (55 mg, 0.252 mmol), $[Rh(cod)_2]BF_4$ (1.0 mg, 0.00252 mmol), Binap (1.6 mg, 0.00252 mmol) and acetone (5.0 mL) under N_2. The Schlenk flask was sealed and immersed into a pre-heated oil bath (60 °C bath temperature). After stirring for 20 minutes at that temperature, the mixture was allowed to cool before evaporation. Purification by flash chromatography (PE/EtOAc, 10:1) gave ketone **2.2** (49 mg, 90%).

3 – Compound data and reaction procedures

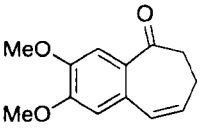
Compound 2.1



Under N_2, a solution of *n*-butyllithium in hexanes (0.9 mL, 2.24 mmol) was added to a cooled solution (–78 °C) of bromide **2.47** (500 mg, 1.87 mmol) in THF (18 mL). The mixture was stirred at –78 °C during 3 hours then DMF (0.29 mL, 3.73 mmol) was added and the stirring at –78 °C was continued during 2 hours. The mixture was quenched with few drops of methanol and allowed to warm at room temperature, diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 7:1) gave compound **2.1** as a yellow solid (337 mg, 83%). m.p.: 91–93 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 10.31 (s, 1H), 7.55–7.50 (m, 1H), 7.33 (s, 1H), 7.26 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 1.42–1.36 (m, 2H), 1.29–1.23 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 190.0, 153.7, 148.3, 136.1, 129.2, 125.7, 113.1, 110.1, 108.9, 56.0, 55.9, 4.2, 1.7; **IR (neat):** $\tilde{\nu}$ = 2967, 2934,

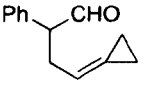
2854, 1666, 1590, 1504, 1463, 1419,1366, 1324, 1271, 1260, 1212, 1182, 1104, 1000, 929, 870, 854, 783, 744,715 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 222 (18), 221 (31), 220 (22), 219 (100), 205 (21), 203 (21); HRMS (CI) calcd for ($C_{13}H_{14}O_3$ + H): 219.10212; found: 219.10218; **elemental analysis** (%) calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found: C 71.43, H 6.54.

Compound 2.2[3]



Yellow solid. m.p.: 78–80 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.52 (s, 1H), 6.63 (s, 1H), 6.37 (d, *J* = 11.9 Hz, 1H), 6.18–6.11 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.90–2.85 (m, 2H), 2.44–2.37 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 200.2, 152.2, 147.6, 132.4, 131.3, 131.1, 129.0, 113.6, 112.1, 56.0, 55.9, 42.2, 23.1; **IR (neat):** $\tilde{\nu}$ = 2997, 2958, 2922, 2849, 1652, 1593, 1564, 1514, 1461, 1439, 1377, 1364, 1318, 1257, 1214, 1192, 1128, 1073, 1034, 1012, 965, 906, 875, 850, 803, 786, 747, 732 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 221 (12), 220 (15), 219 (100); HRMS (CI) calcd for ($C_{13}H_{14}O_3$ + H): 219.1016; found: 219.1019; **elemental analysis** (%) calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found: C 71.50, H 6.49.

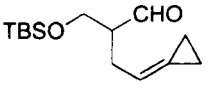
Compound 2.3



Under N_2, DMSO (0.186 mL, 2.62 mmol) in CH_2Cl_2 (0.3 mL) was added to a solution of oxalyl chloride (0.113 mL, 1.31 mmol) in CH_2Cl_2 (3.3 mL) at –78 °C. After 10 minutes stirring at –78 °C, a solution of alcohol **2.52** (190 mg, 1.01 mmol)

in CH_2Cl_2 (1 mL) was added. After 20 minutes stirring at –78 °C, triethylamine (0.70 mL, 5.05 mmol) was added rapidly and the mixture was stirred at room temperature during 20 minutes. A saturated solution of NH_4Cl (5 mL) was added to the reaction mixture which was then extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 80:1) gave compound **2.3** as colourless oil (100 mg, 53%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.74 (s, 1H), 7.42–7.36 (m, 2H), 7.34–7.30 (m, 1H), 7.27–7.22 (m, 2H), 5.79–5.71 (m, 1H), 3.73 (t, J = 6.8 Hz, 1H), 3.05–2.96 (m, 1H), 2.72–2.63 (m, 1H), 1.07–0.87 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 200.5, 136.1, 128.9 (2C), 128.8 (2C), 127.4, 124.2, 114.2, 58.8, 32.1, 2.4, 1.8; **IR (neat):** $\tilde{\nu}$ = 3058, 3003, 2922, 1720, 1685, 1598, 1494, 1450, 1362, 1267, 1205, 1179, 1026, 828, 757, 699 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 204 (38); HRMS (CI) calcd for ($C_{13}H_{14}O$ + NH_4): 204.13884; found: 204.13905; **elemental analysis** (%) calcd for $C_{13}H_{14}O$: C 83.83, H 7.58; found: C 81.34, H 7.86.

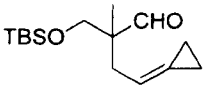
Compound 2.4



This compound was prepared from **2.55** (298 mg, 1.16 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (266 mg, 90%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.75 (s, 1H), 5.79–5.73 (m, 1H), 3.91–3.84 (m, 2H), 2.66–2.53 (m, 2H), 2.46–2.38 (m, 1H), 1.10–0.99 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 204.6, 123.9, 114.4, 61.6, 53.9, 27.8, 25.7 (3C), 18.2, 2.4, 2.0, –5.6 (2C); **IR (neat):** $\tilde{\nu}$ = 2954, 2929, 2891, 2857, 1727, 1472, 1389, 1361, 1252, 1096, 1006, 976, 937, 835, 776 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 255

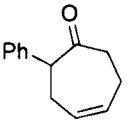
(19); HRMS (CI) calcd for ($C_{14}H_{26}O_2Si$ + H): 255.17803; found: 255.17844; **elemental analysis** (%) calcd for $C_{14}H_{26}O_2Si$: C 66.09, H 10.30; found: C 66.11, H 10.32.

Compound 2.5



This compound was prepared from **2.60** (210 mg, 0.78 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (181 mg, 82%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.57 (s, 1H), 5.68–5.62 (m, 1H), 3.66 (d, J = 9.7 Hz, 1H), 3.56 (d, J = 9.7 Hz, 1H), 2.44–2.39 (m, 1H), 2.35–2.30 (m, 1H), 1.07–1.02 (m, 2H), 0.99 (s, 3H), 0.97–0.93 (m, 2H), 0.84 (s, 9H), 0.00 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 206.3, 125.5, 112.4, 66.6, 51.9, 34.6, 25.7 (3C), 18.1, 16.0, 2.8, 1.8, –5.7 (2C); **IR (neat):** $\tilde{\nu}$ = 2952, 2930, 2886, 2857, 1730, 1472, 1464, 1391, 1363, 1252, 1102, 1004, 969, 936, 835, 777, 670 cm^{-1}; **MS (CI):** m/z (rel. intensity): 286 (14), 271 (32), 269 (100), 268 (18), 251 (18), 136 (33), 132 (35), 119 (28); HRMS (CI) calcd for ($C_{15}H_{28}O_2Si$ + H): 269.19368; found: 269.19364; **elemental analysis** (%) calcd for $C_{15}H_{28}O_2Si$: C 67.11, H 10.51; found: C 67.00, H 10.54.

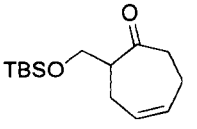
Compound 2.6



Starting from aldehyde **2.3** (36 mg, 0.193 mmol). **2.6** (30 mg, 82%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.17 (m, 5H), 5.88–5.76 (m, 2H), 4.04 (dd, J = 11.4 Hz, J = 3.8 Hz, 1H), 3.03–2.93 (m, 1H), 2.85–2.79 (m, 1H),

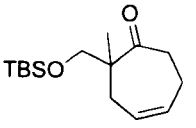
2.54–2.47 (m, 3H), 2.41–2.31 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 211.8, 139.6, 129.6, 128.5 (2C), 128.3, 128.0 (2C), 127.0, 57.7, 41.3, 31.2, 25.2; **IR (neat):** $\tilde{\nu}$ = 3061, 3024, 2902, 1706, 1602, 1496, 1450, 1348, 1309, 1222, 1193, 1138, 1080, 1033, 898, 840, 146, 697 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 204 (47); HRMS (CI) calcd for ($C_{13}H_{14}O$ + NH_4): 204.13884; found: 204.13944; **elemental analysis** (%) calcd for $C_{13}H_{14}O$: C 83.83, H 7.58; found: C 83.08, H 7.77.

Compound 2.7



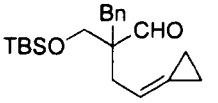
Starting from aldehyde **2.4** (40 mg, 0.158 mmol). **2.7** (38.8 mg, 97%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.78–5.68 (m, 2H), 3.82 (dd, *J* = 10.1 Hz, *J* = 4.5 Hz, 1H), 3.63 (dd, *J* = 10.1 Hz, *J* = 6.8 Hz, 1H), 2.95–2.88 (m, 1H), 2.76 (ddd, , *J* = 14.4 Hz, *J* = 11.7 Hz, *J* = 3.7 Hz, 1H), 2.52–2.37 (m, 3H), 2.31–2.18 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 213.9, 129.2, 128.5, 63.5, 53.8, 42.3, 27.2, 25.8 (3C), 24.5, 18.2, –5.48, –5.53; **IR (neat):** $\tilde{\nu}$ = 2953, 2929, 2881, 2857, 1704, 1463, 1389, 1361, 1252, 1193, 1098, 1059, 1006, 939, 833, 775, 664 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 255 (100), 140 (61); HRMS (CI) calcd for ($C_{14}H_{26}O_2Si$ + H): 255.17803; found: 255.17819; **elemental analysis** (%) calcd for $C_{14}H_{26}O_2Si$: C 66.09, H 10.30; found: C 66.13, H 10.32.

Compound 2.8



Starting from aldehyde **2.5** (40 mg, 0.149 mmol). **2.8** (34.8 mg, 87%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.73–5.65 (m, 1H), 5.59–5.53 (m, 1H), 3.65 (d, *J* = 9.3 Hz, 1H), 3.37 (d, *J* = 9.3 Hz, 1H), 3.03 (td, *J* = 11.2 Hz, *J* = 5.3 Hz, 1H), 3.00–2.93 (m, 1H), 2.56–2.49 (m, 1H), 2.44–2.21 (m, 2H), 1.91 (dd, *J* = 15.9 Hz, *J* = 7.7 Hz, 1H), 1.00 (s, 3H), 0.84 (s, 9H), –0.01 (s, 3H), –0.03 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 217.4, 129.0, 126.7, 70.1, 56.0, 39.9, 31.5, 27.6, 25.8 (3C), 19.9, 18.2, –5.86 (2C); **IR (neat):** $\tilde{\nu}$ = 2954, 2929, 2896, 2857, 1706, 1464, 1383, 1362, 1311, 1251, 1203, 1089, 1006, 939, 907, 834, 774, 734, 657 cm^{-1}; **MS (CI):** m/z (rel. intensity): 271 (12), 269 (100); HRMS (CI) calcd for ($C_{15}H_{28}O_2Si$ + H): 269.19368; found: 255.19440; **elemental analysis** (%) calcd for $C_{15}H_{28}O_2Si$: C 67.11, H 10.51; found: C 68.00, H 10.70.

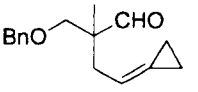
Compound 2.9



This compound was prepared from **2.61** (166 mg, 0.48 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (157 mg, 95%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.64 (s, 1H), 7.26–7.22 (m, 2H), 7.21–7.18 (m, 1H), 7.15–7.12 (m, 2H), 5.76–5.71 (m, 1H), 3.62 (d, *J* = 10.1 Hz, 1H), 3.55 (d, *J* = 10.1 Hz, 1H), 2.98 (d, *J* = 13.9 Hz, 1H), 2.87 (d, *J* = 13.9 Hz, 1H), 2.37 (d, *J* = 7.1 Hz, 2H), 1.10–1.05 (m, 2H), 1.00–0.95 (m, 2H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 206.0, 136.7, 130.3 (2C), 128.1 (2C), 126.4,

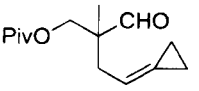
125.8, 112.3, 62.8, 56.0, 35.8, 32.7, 25.8 (3C), 18.1, 2.9, 2.1, –5.6 (2C); **IR (neat):** $\tilde{\nu}$ = 3053, 3028, 2954, 2929, 2857, 2714, 1726, 1603, 1496, 1471, 1390, 1360, 1252, 1095, 1031, 1006, 968, 937, 835, 775, 723, 700, 669 cm^{-1}; **MS (ES+):** m/z (rel.intensity): 367 (100); HRMS (ES+) calcd for $(C_{21}H_{32}O_2Si + Na)^+$: 367.2069; found: 367.2075; **elemental analysis** (%) calcd for $C_{21}H_{32}O_2Si$: C 73.20, H 9.36; found: C 72.12, H 9.42.

Compound 2.10



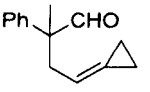
This compound was prepared from **2.62** (166 mg, 0.68 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (141 mg, 86%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.58 (s, 1H), 7.35–7.31 (m, 2H), 7.29–7.25 (m, 3H), 5.67–5.61 (m, 1H), 4.48 (s, 2H), 3.53 (d, *J* = 9.3 Hz, 1H), 3.43 (d, *J* = 9.3 Hz, 1H), 2.44 (dd, *J* = 13.8 Hz, *J* = 7.6 Hz, 1H), 2.38 (dd, *J* = 13.8 Hz, *J* = 7.6 Hz, 1H), 1.06 (s, 3H), 1.07–1.02 (m, 2H), 0.98–0.93 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 205.6, 138.0, 128.3 (2C), 127.6, 127.4 (2C), 125.9, 112.1, 73.4 (2C), 51.0, 35.0, 16.5, 2.9, 1.8; **IR (neat):** $\tilde{\nu}$ = 3027, 2979, 2857, 2704, 1726, 1492, 1454, 1406, 1361, 1305, 1257, 1205, 1093, 1028, 967, 934, 900, 798, 735, 697 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 267 (100); HRMS (ES+) calcd for $(C_{16}H_{20}O_2 + Na)^+$: 267.1361; found: 267.1359.

Compound 2.11



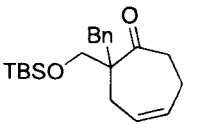
This compound was prepared from **2.63** (207 mg, 0.86 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (194 mg, 94%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.54 (s, 1H), 5.68–5.61 (m, 1H), 4.14 (d, J = 11.2 Hz, 1H), 4.05 (d, J = 11.2 Hz, 1H), 2.39 (d, J = 7.7 Hz, 2H), 1.14 (s, 9H), 1.07 (s, 3H), 1.08–1.03 (m, 2H), 0.98–0.93 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 203.6, 178.0, 126.7, 111.3, 66.2, 50.3, 38.8, 34.9, 27.0 (3C), 16.3, 2.9, 1.8; **IR (neat):** $\tilde{\nu}$ = 2978, 2937, 2906, 2871, 2709, 1728, 1481, 1461, 1398, 1366, 1282, 1144, 1036, 993, 936, 872, 787, 769, 718 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 261 (100); HRMS (ES+) calcd for $(C_{14}H_{22}O_3 + Na)^+$: 261.1467; found: 261.1468.

Compound 2.12



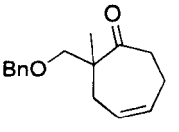
This compound was prepared from **2.65** (50 mg, 0.25 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (45 mg, 91%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.56 (s, 1H), 7.39–7.36 (m, 2H), 7.31–7.25 (m, 3H), 5.61–5.55 (m, 1H), 2.80 (d, J = 7.2 Hz, 2H), 1.44 (s, 3H), 1.08–0.98 (m, 2H), 0.96–0.83 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.4, 139.8, 128.7 (2C), 127.2 (3C), 125.9, 112.6, 54.4, 38.4, 19.0, 2.9, 1.7; **IR (neat):** $\tilde{\nu}$ = 3056, 2979, 2934, 2806, 2707, 1722, 1600, 1495, 1446, 1389, 1372, 1267, 1075, 1029, 967, 935, 837, 760, 733, 698 cm^{-1}; **MS (CI):** m/z (rel. intensity): 219 (12), 218 (100), 201 (3), 200 (1); HRMS (CI) calcd for $(C_{14}H_{16}O + NH_4)$: 218.1539; found: 218.1539.

Compound 2.13



Starting from aldehyde **2.9** (25 mg, 0.0726 mmol). **2.13** (23.4 mg, 93%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.24–7.16 (m, 3H), 7.06 (d, *J* = 7.2 Hz, 2H), 5.70–5.61 (m, 1H), 5.53 (dt, *J* = 11.4 Hz, *J* = 3.8 Hz, 1H), 3.65 (d, *J* = 9.2 Hz, 1H), 3.46 (d, *J* = 9.2 Hz, 1H), 2.87 (s, 2H), 2.69 (ddd, *J* = 11.3 Hz, *J* = 7.9 Hz, *J* = 6.0 Hz, 1H), 2.62 (dd, *J* = 15.6 Hz, *J* = 6.5 Hz, 1H), 2.55 (ddd, *J* = 11.3 Hz, *J* = 7.7 Hz, *J* = 6.0 Hz, 1H), 2.36–2.23 (m, 2H), 2.16 (dd, *J* = 15.6 Hz, *J* = 6.3 Hz, 1H), 0.87 (s, 9H), 0.00 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 216.6, 137.5, 130.2 (2C), 129.2, 128.0 (2C), 126.3 (2C), 66.5, 60.4, 40.0, 39.9, 27.7, 27.4, 25.8 (3C), 18.2, –5.6, –5.7; **IR (neat):** $\tilde{\nu}$ = 3026, 2952, 2928, 2856, 1702, 1603, 1495, 1471, 1441, 1388, 1361, 1311, 1251, 1195, 1095, 1031, 1022, 1004, 939, 900, 834, 775, 733, 701, 667 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 367 (100); HRMS (ES+) calcd for $(C_{21}H_{32}O_2Si + Na)^+$: 367.2069; found: 367.2066; **elemental analysis** (%) calcd for $C_{21}H_{32}O_2Si$: C 73.20, H 9.36; found: C 72.98, H 9.30.

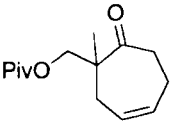
Compound 2.14



Starting from aldehyde **2.10** (20 mg, 0.0819 mmol). **2.14** (15.3 mg, 77%) was isolated as colourless oil. **^{1}H NMR (500 MHz, C_6D_6):** δ = 7.22–7.17 (m, 4H), 7.10–7.08 (m, 1H), 5.58–5.49 (m, 1H), 5.38–5.30 (m, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.52 (d, *J* = 8.6 Hz, 1H), 3.17 (d, *J* = 8.6 Hz, 1H), 2.97–2.91 (m, 1H), 2.88 (dt, *J* = 11.6 Hz, *J* = 8.2 Hz, 1H), 2.42 (dt, *J* = 11.5 Hz, *J* = 5.7 Hz, 1H),

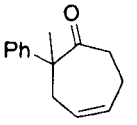
2.04–1.96 (m, 2H), 1.75 (dd, J = 15.7 Hz, J = 7.8 Hz, 1H), 1.09 (s, 3H); **^{13}C NMR (125 MHz, C_6D_6):** δ = 214.4, 138.9, 129.6, 128.6 (2C), 127.73, 127.66 (2C), 126.7, 77.6, 73.4, 54.9, 39.7, 32.2, 27.7, 20.6; **IR (neat):** $\tilde{\nu}$ = 3064, 3023, 2967, 2928, 2901, 2855, 1704, 1494, 1454, 1371, 1312, 1252, 1205, 1100, 1029, 907, 776, 737, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 267 (100); HRMS (ES+) calcd for ($C_{16}H_{20}O_2$ + Na)$^+$: 267.1361; found: 267.1356; **elemental analysis** (%) calcd for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 77.99, H 8.41.

Compound 2.15



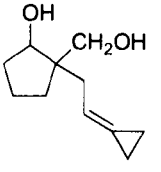
Starting from aldehyde **2.11** (10 mg, 0.0420 mmol). **2.15** (5.4 mg, 54%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.74–5.60 (m, 2H), 4.06 (d, J = 10.7 Hz, 1H), 4.03 (d, J = 10.7 Hz, 1H), 2.91 (ddd, J = 15.2 Hz, J = 10.0 Hz, J = 5.2 Hz, 1H), 2.69–2.62 (m, 2H), 2.45–2.363 (m, 1H), 2.356–2.58 (m, 1H), 2.11 (dd, J = 15.6 Hz, J = 6.5 Hz, 1H), 1.16 (s, 9H), 1.12 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.6, 178.1, 129.8, 125.9, 69.8, 53.7, 39.0, 32.0, 29.7, 27.3, 27.1 (3C), 20.5; **IR (neat):** $\tilde{\nu}$ = 3023, 2967, 2929, 2871, 2856, 1732, 1708, 1479, 1463, 1396, 1365, 1283, 1152, 1080, 1035, 989, 905, 769 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 261 (100); HRMS (ES+) calcd for ($C_{14}H_{22}O_3$ + Na)$^+$: 261.1467; found: 261.1455.

Compound 2.16



Starting from aldehyde **2.12** (29.7 mg, 0.144 mmol). **2.16** (25.2 mg, 85%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.33–7.28 (m, 2H), 7.24–7.20 (m, 3H), 5.85–5.77 (m, 1H), 5.68–5.61 (m, 1H), 3.09 (dd, J = 15.4 Hz, J = 5.9 Hz, 1H), 2.98 (ddd, J = 12.2 Hz, J = 9.5 Hz, J = 6.9 Hz, 1H), 2.47–2.38 (m, 2H), 2.32–2.24 (m, 2H), 1.39 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 213.6, 143.5, 130.3, 128.6 (2C), 127.0, 126.7, 126.1 (2C), 58.6, 38.7, 34.7, 26.7, 26.4; **IR (neat):** $\tilde{\nu}$ = 3053, 3022, 2969, 2928, 2851, 1706, 1600, 1580, 1495, 1445, 1371, 1309, 1194, 1153, 1075, 1031, 894, 766, 699, 678, 656 cm^{-1}; **MS (CI):** m/z (rel. intensity) 219 (13), 218 (100), 201 (9), 200 (3); HRMS (CI) calcd for ($C_{14}H_{16}O$ + NH_4): 218.1539; found: 218.1542; **elemental analysis** (%) calcd for $C_{14}H_{16}O$: C 83.96 H 8.05; found: C 83.17, H 8.17.

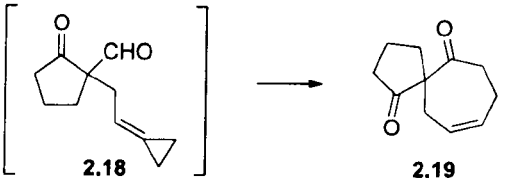
Compound 2.17



Under N_2, ester **2.66** (64 mg, 0.29 mmol) in Et_2O (0.5 mL) was added to a suspension of lithium aluminium hydride (11 mg, 0.29 mmol) in Et_2O (4 mL) at 0 °C. After stirring for 20 minutes at room temperature, lithium aluminium hydride (11 mg, 0.29 mmol) was added at 0 °C. After stirring for another 30 minutes at room temperature, a saturated aqueous solution of Na_2SO_4 was added dropwise, first at 0 °C then at room temperature, until a white precipitate appeared. The mixture was

filtered through a pad of celite and concentrated. Purification by flash chromatography (PE/Et_2O, 1:1 to 1:2) afforded compound **2.17** as a white solid (37 mg, 70%). m.p.: 53–55 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.90–5.80 (m, 1H), 4.05 (m, 1H), 3.61 (d, J = 10.3 Hz, 1H), 3.34 (d, J = 10.9 Hz, 1H), 2.51 (dd, J = 14.2 Hz, J = 7.8 Hz, 1H), 2.29–2.24 (s, 1H), 2.20 (dd, J = 14.2 Hz, J = 7.1 Hz, 1H), 2.06–1.94 (m, 2H), 1.79–1.68 (m, 1H), 1.66–1.584 (m, 1H), 1.582–1.47 (m, 2H), 1.27–1.17 (m, 1H), 1.11–1.05 (m, 2H), 1.04–0.97 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 124.2, 114.9, 79.4, 68.9, 49.4, 32.3, 31.1, 30.4, 19.6, 2.9, 1.8; **IR (neat):** $\tilde{\nu}$ = 3320, 3038, 2962, 2922, 2901, 2871, 2860, 1467, 1440, 1356, 1319, 1254, 1202, 1136, 1090, 1048, 1036, 1017, 962, 948, 929, 905, 878, 850, 792, 766, 719 cm^{-1}; **MS (CI):** m/z (rel. intensity): 201 (11), 200 (100), 183 (31), 165 (31), 158 (12), 147 (38), 141 (22); HRMS (CI) calcd for ($C_{11}H_{18}O_2$ + NH_4): 200.1645; found: 200.1643; **elemental analysis** (%) calcd for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 71.99, H 9.90.

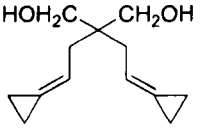
Compound 2.18 - Compound 2.19



Under N_2, diol **2.17** (14 mg, 0.0768 mmol) was added to a suspension of Dess Martin periodinane (137 mg, 0.323 mmol) and $NaHCO_3$ (84 mg, 0.999 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. The mixture was filtered through deactivated neutral alumina and rinsed with a mixture PE/Et_2O (2:1). The filtrate was evaporated and the filtration was repeated. Crude ketoaldehyde **2.18** was obtained as colourless oil. [**^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.43 (s, 1H), 5.58–5.50 (m, 1H), 2.76 (dd, J = 14.0 Hz, J = 7.6 Hz, 1H), 2.55 (dd, J = 14.1 Hz, J =

7.1 Hz, 1H), 2.48 (dd, J = 11.7 Hz, J = 5.9 Hz, 1H), 2.53–2.17 (m, 2H), 1.98–1.76 (m, 3H), 1.09–1.03 (m, 2H), 1.02–0.94 (m, 2H)]. This crude material was not further purified due to its inherent instability. Instead, a solution of [Rh(Binap)]BF_4 (0.00768 mmol) in 1.5 mL acetone prepared according to the general procedure was added under N_2 to crude ketoaldehyde **2.18**. Spirobisketone **2.19** (10.8 mg, 80%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.72–5.64 (m, 1H), 5.63–5.56 (m, 1H), 3.28 (dt, J = 11.7 Hz, J = 5.6 Hz, 1H), 3.03–2.95 (m, 1H), 2.65–2.57 (m, 1H), 2.56–2.49 (m, 1H), 2.46 (dt, J = 11.6 Hz, J = 4.9 Hz, 1H), 2.42–2.35 (m, 2H), 2.33–2.23 (m, 1H), 2.08–2.04 (m, 1H), 2.03 (dd, J = 15.6 Hz, J = 8.0 Hz, 1H), 1.89–1.75 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 215.6, 210.0, 130.2, 125.5, 69.5, 39.1, 38.2, 33.2, 30.7, 27.3, 19.3; **IR (neat):** $\tilde{\nu}$ = 3018, 2961, 2854, 1736, 1699, 1626, 1608, 1442, 1405, 1349, 1312, 1274, 1199, 1147, 1089, 1044, 1011, 951, 916, 860, 824, 774, 693, 662 cm^{-1}; **MS (CI):** m/z (rel. intensity): 196 (100), 179 (12), 151 (10); HRMS (CI) calcd for ($C_{11}H_{14}O_2$ + H): 179.1067; found: 179.1069.

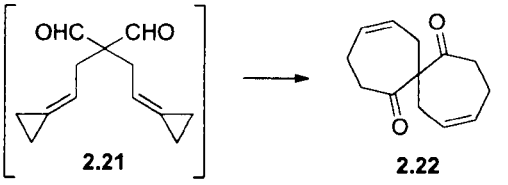
Compound 2.20



This compound was prepared from **2.67** (286 mg, 1.08 mmol) according to the procedure described for the preparation of **2.17**. White solid (214 mg, 95%). m.p.: 39–41 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.86–5.78 (m, 2H), 3.59 (s, 4H), 2.20 (d, J = 7.9 Hz, 4H), 2.11–1.96 (m, 2H), 1.11–1.06 (m, 4H), 1.03–0.97 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 124.7 (2C), 113.5 (2C), 68.6 (2C), 43.4, 33.9 (2C), 2.9 (2C), 1.8 (2C); **IR (neat):** $\tilde{\nu}$ = 3346 (br), 3051, 2978, 2923 1464, 1438, 1408,

1312, 1211, 1091, 1025, 965, 933, 871, 785, 748, 717 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 231 (100); HRMS (ES+) calcd for $(C_{13}H_{20}O_2 + Na)^+$: 231.1361; found: 231.1364; **elemental analysis** (%) calcd for: C 74.96, H 9.68; found: C 75.09, H 9.82.

Compound 2.21 - Compound 2.22

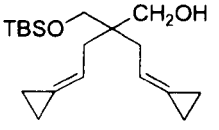


2.21 **2.22**

Under N_2, DMSO (30 µL, 0.425 mmol) was added to a solution of oxalyl chloride (18 µL, 0.210 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C. After 10 minutes stirring at –78 °C, a solution of alcohol **2.20** (21 mg, 0.103 mmol) in CH_2Cl_2 (0.6 mL) was added. After 20 minutes stirring at –78 °C, triethylamine (0.12 mL, 0.83 mmol) was added rapidly and the mixture was stirred at room temperature during 30 minutes. The mixture was quenched with a saturated aqueous solution of $CuSO_4$ (4 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were concentrated before being dissolved in CH_2Cl_2 (5 mL) and washed with water (2 × 3 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated, affording compound **2.21** as colourless oil. This aqueous work up was repeated until the complete removal of Me_2S. [**^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.71 (s, 2H), 5.73–5.62 (m, 2H), 2.70 (d, *J* = 7.2 Hz, 4H), 1.10–1.03 (m, 4H), 1.01–0.93 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 201.5 (2C), 127.2 (2C), 110.9 (2C), 65.5, 33.2 (2C), 3.0 (2C), 2.1 (2C)]. This crude material was not further purified due to its inherent instability. Instead, a solution of [Rh(Binap)]BF_4 (0.01 mmol) in 2 mL acetone prepared according to the general procedure was added under N_2 to crude bisaldehyde **2.21**. Spirobisketone **2.22** (16.7 mg, 82%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ

= 5.73–5.59 (m, 4H), 3.23 (dt, J = 11.4 Hz, J = 5.5 Hz, 2H), 3.20–3.14 (m, 2H), 2.48–2.40 (m, 2H), 2.35 (dt, J = 11.4 Hz, J = 5.1 Hz, 2H), 2.33–2.23 (m, 2H), 2.18 (dd, J = 15.7 Hz, J = 7.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 209.6 (2C), 130.2 (2C), 126.1 (2C), 75.6, 38.5 (2C), 28.5 (2C), 27.4 (2C); **IR (neat):** $\tilde{\nu}$ = 3023, 2973, 2896, 2856, 1709, 1691, 1469, 1440, 1382, 1349, 1311, 1195, 1140, 1112, 1076, 1043, 980, 934, 902, 836, 794, 746, 669 cm^{-1}; **MS (CI):** m/z (rel. intensity): 222 (100), 205 (32); HRMS (CI) calcd for ($C_{13}H_{16}O_2$ + H): 205.1223; found: 205.1221; **elemental analysis** (%) calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 75.49, H 7.81; **GC:** *cyclodex-B / 130 °C to 140 °C (ramp: 2 °C per minute) then 55 minutes at 140 °C / = 13.60 min / = 50.26 min / = 52.35 min.*

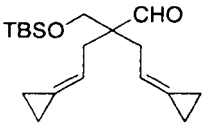
Compound 2.23



DMAP (6 mg, 0.049 mmol) followed by triethylamine (70 μL, 0.504 mmol) and *t*-butyldimethylsilyl chloride (72 mg, 0.480 mmol) were added to a solution of **2.20** (100 mg, 0.480 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The resulting mixture was stirred at room temperature for 16 hours. The mixture was quenched with a saturated solution of NH_4Cl (4 mL) then extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 10:1 to 5:1) afforded **2.23** as a colourless oil (129 mg, 83%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.81–5.75 (m, 2H), 3.55 (s, 2H), 3.53 (d, J = 6.3 Hz, 2H), 2.72 (t, J = 5.9 Hz, 1H), 2.23–2.13 (m, 4H), 1.09–1.03 (m, 4H), 1.01–0.94 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 124.2 (2C), 113.8 (2C), 69.2, 68.9, 43.2, 34.0 (2C), 25.8 (3C), 18.1, 2.8 (2C), 1.8 (2C), –5.7 (2C); **IR (neat):**

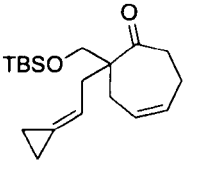
$\tilde{\nu}$ = 3463 (br), 3052, 2980, 2954, 2929, 2896, 2857, 1472, 1462, 1438, 1411, 1389, 1361, 1255, 1083, 1039, 1005, 966, 937, 834, 774, 668 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 345 (100); HRMS (ES+) calcd for $(C_{19}H_{34}O_2Si + Na)^+$: 345.2226; found: 345.2223; **elemental analysis** (%) calcd for $C_{19}H_{34}O_2Si$: C 70.75, H 10.62; found: C 70.45, H 10.60.

Compound 2.24



This compound was prepared from **2.23** (30 mg, 0.093 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (29 mg, 97%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.57 (s, 1H), 5.71–5.65 (m, 2H), 3.67 (s, 2H), 2.49–2.37 (m, 4H), 1.08–1.01 (m, 4H), 0.99–0.92 (m, 4H), 0.85 (s, 9H), 0.00 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 206.3, 125.3 (2C), 112.5 (2C), 64.0, 55.5, 32.3 (2C), 25.7 (3C), 18.1, 2.8 (2C), 1.9 (2C), –5.7 (2C); **IR (neat):** $\tilde{\nu}$ = 3054, 2981, 2954, 2929, 2896, 2857, 2704, 1725, 1472, 1438, 1410, 1386, 1362, 1252, 1100, 1006, 967, 934, 836, 815, 776, 670 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 343 (100); HRMS (ES+) calcd for $(C_{19}H_{32}O_2Si + Na)^+$: 343.2069; found: 343.2073.

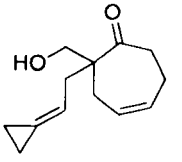
Compound 2.25



Starting from aldehyde **2.24** (28.8 mg, 0.0897 mmol). **2.25** (23.1 mg, 80%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.69–5.61 (m, 2H),

5.59–5.52 (m, 1H), 3.64 (d, J = 9.6 Hz, 1H), 3.55 (d, J = 9.6 Hz, 1H), 2.82–2.75 (m, 1H), 2.74–2.64 (m, 2H), 2.45–2.37 (m, 2H), 2.35–2.28 (m, 2H), 2.21 (dd, J = 15.7 Hz, J = 6.7 Hz, 1H), 1.06–1.01 (m, 2H), 0.99–0.90 (m, 2H), 0.85 (s, 9H), –0.01 (s, 3H), –0.02 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 216.6, 129.2, 126.7, 124.9, 113.4, 66.9, 59.8, 39.9, 36.1, 28.4, 27.5, 25.8 (3C), 18.1, 2.8, 1.8, –5.65, –5.69; **IR (neat):** $\tilde{\nu}$ = 3018, 2953, 2929, 2856, 1703, 1464, 1440, 1408, 1386, 1361, 1312, 1251, 1197, 1095, 1005, 960, 938, 902, 834, 775, 667 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 343 (100); HRMS (ES+) calcd for $(C_{19}H_{32}O_2Si + Na)^+$: 343.2069; found: 343.2067; **elemental analysis** (%) calcd for $C_{19}H_{32}O_2Si$: C 71.19, H 10.06; found: C 71.30, H 10.30.

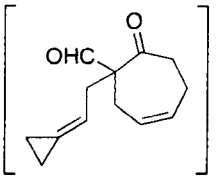
Compound 2.26



A 1M solution of TBAF in THF (0.106 mL, 0.106 mmol) was added to a solution of **2.25** (34 mg, 0.106 mmol) in THF (0.50 mL) at 0 °C. The mixture was stirred at 0 °C during 2 hours before being quenched with a saturated solution of NH_4Cl (4 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 10:1 to 7:1 to 4:1) afforded compound **2.26** as a colourless oil (19 mg, 87%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.76–5.58 (m, 3H), 3.68 (dd, J = 11.3 Hz, J = 4.3 Hz, 1H), 3.57 (dd, J = 11.3 Hz, J = 8.2 Hz, 1H), 2.92 (ddd, J = 11.5 Hz, J = 10.6 Hz, J = 5.0 Hz, 1H), 2.60–2.36 (m, 6H), 2.34–2.24 (m, 1H), 2.17 (dd, J = 15.7 Hz, J = 6.4 Hz, 1H), 1.11–1.04 (m, 2H), 1.02–0.95 (m, 2H); **^{13}C NMR (100 MHz,**

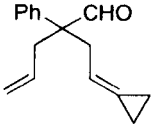
$CDCl_3$): δ = 218.4, 129.6, 126.6, 126.1, 112.4, 66.9, 58.7, 39.4, 36.2, 29.7, 26.9, 3.0, 2.0; **IR (neat):** $\tilde{\nu}$ = 3437, 3048, 3020, 2978, 2907, 2841, 1691, 1459, 1439, 1411, 1353, 1312, 1194, 1143, 1046, 1028, 994, 968, 936, 901, 870, 837, 778, 748, 715, 659 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 224 (62), 207 (58), 194 (47), 178 (12), 177 (100); **elemental analysis** (%) calcd for $C_{13}H_{18}O_2$: C 75.69, H 8.80; found: C 74.58, H 9.02.

Compound 2.27



This compound was prepared from **2.26** according to the procedure described for the preparation of **2.21**. This crude material was not further purified due to its inherent instability and was used in the cyclisation step. **GC:** *cyclodex-B / 130 °C to 140 °C (ramp: 2 °C per minute) then 55 minutes at 140 °C / = 37.82 min / = 39.61 min.*

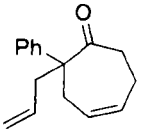
Compound 2.32



This compound was prepared from **2.69** (36 mg, 0.158 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (32 mg, 89%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.53 (s, 1H), 7.39–7.32 (m, 2H), 7.30–7.25 (m, 1H), 7.24–7.19 (m, 2H), 5.61–5.50 (m, 2H), 5.02 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 12.9 Hz, 1H), 2.85 (dd, *J* = 14.2 Hz, *J* = 7.7 Hz, 1H), 2.79 (dd, *J* = 14.2 Hz, *J* = 7.0 Hz, 1H), 2.69 (d, *J* = 7.5 Hz, 2H), 1.07–0.96 (m, 2H), 0.93–0.81 (m, 2H); **^{13}C NMR (125**

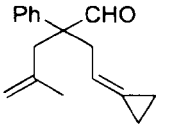
MHz, $CDCl_3$): δ = 202.3, 138.3, 133.1, 128.7 (2C), 127.7 (2C), 127.3, 126.1, 118.6, 112.2, 57.7, 37.1, 34.8, 2.9, 2.0; **IR (neat):** $\tilde{\nu}$ = 3057, 2980, 2921, 2804, 2709, 1722, 1640, 1599, 1580, 1496, 1446, 997, 967, 918, 875, 842, 759, 738, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 249 (100); HRMS (ES+) calcd for $(C_{16}H_{18}O + Na)^+$: 249.1255; found: 249.1258.

Compound 2.33



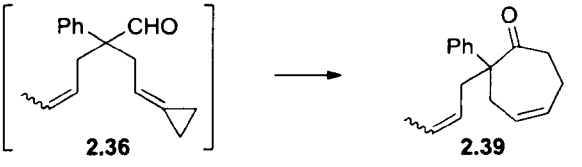
Starting from aldehyde **2.32** (20.8 mg, 0.0919 mmol). **2.33** (15.6 mg, 75%) was isolated as colourless oil. **^{1}H NMR (500 MHz, CDCl3):** δ = 7.34–7.28 (m, 2H), 7.23–7.18 (m, 3H), 5.81–5.73 (m, 1H), 5.66–5.59 (m, 1H), 5.39–5.28 (m, 1H), 4.94 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 9.0 Hz, 1H), 3.07 (dd, *J* = 15.4 Hz, *J* = 5.5 Hz, 1H), 2.98–2.91 (m, 1H), 2.78 (dd, *J* = 14.2 Hz, *J* = 5.9 Hz, 1H), 2.54 (dd, *J* = 14.5 Hz, *J* = 12.2 Hz, 1H), 2.53 (t, *J* = 14.3 Hz, 1H), 2.35–2.25 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 212.4, 140.3, 134.7, 130.4, 128.5 (2C), 126.9 (3C), 126.8, 117.8, 61.8, 42.2, 38.3, 29.8, 26.7; **IR (neat):** $\tilde{\nu}$ = 3063, 3022, 2972, 2927, 2856, 1705, 1638, 1598, 1578, 1495, 1472, 1445, 1345, 1308, 1196, 1134, 1090, 1075, 1035, 998, 948, 913, 840, 785, 761, 727, 698, 673 cm^{-1}; **MS (CI):** m/z (rel. intensity): 245 (16), 244 (100), 228 (10), 227 (70); HRMS (CI) calcd for $(C_{16}H_{18}O + H)$: 227.1430; found: 227.1433; **elemental analysis** (%) calcd for $C_{16}H_{18}O$: C 84.91, H 8.02; found: C 84.96, H 8.18.

Compound 2.35



2.35 was prepared by undergraduate student Coralie Tugny from the corresponding alcohol by Swern oxidation. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.54 (s, 1H), 7.37–7.32 (m, 2H), 7.29–7.21 (m, 3H), 5.65–5.59 (m, 1H), 4.81–4.78 (m, 1H), 4.62–4.58 (m, 1H), 2.89 (d, *J* = 7.2 Hz, 2H), 2.74 (d, *J* = 14.2 Hz, 1H), 2.67 (d, *J* = 14.4 Hz, 1H), 1.37 (s, 3H), 1.04–0.94 (m, 2H), 0.92–0.81 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.3, 141.3, 138.6, 128.6 (2C), 127.9 (2C), 127.3, 126.0, 115.3, 112.5, 57.6, 41.0, 34.8, 24.3, 2.8, 2.0; **IR (neat):** $\tilde{\nu}$ = 3057, 2979, 2709, 1721, 1643, 1544, 1495, 1446, 1377, 1091, 1030, 1002, 967, 930, 894, 759, 697 cm^{-1}; **MS (CI)**: m/z (rel. intensity): 259 (17), 258 (100), 242 (12), 241 (69), 173 (14); **elemental analysis** (%) calcd for $C_{17}H_{20}O$: C 84.16, H 8.83; found: C 83.20, H 8.44.

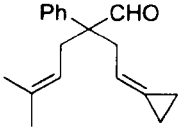
Compound 2.36 - Compound 2.39



2.36 was prepared by undergraduate student Coralie Tugny from the corresponding alcohol by Swern oxidation. [**^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.52 (s, 1H), 7.40–7.32 (m, 2H), 7.31–7.17 (m, 3H), 5.62–5.39 (m, 2H), 5.26–5.14 (m, 1H), 2.90–2.56 (m, 4H), 1.58 (d, *J* = 6.5 Hz, 3H), [*1.48 (d, J = 6.5 Hz, 3H)*], 1.05–0.94 (m, 2H), 0.92–0.78 (m, 2H).[4] This crude material was not further purified due to its inherent instability. Instead, a solution of $[Rh(Binap)]BF_4$ (0.0093 mmol) in 1.9 mL acetone prepared according to the general procedure was added under N_2 to the crude

aldehyde. 7-membered ring **2.39** (16.3 mg, 70%) (E/Z 4:1, ratio determined by ^{1}H NMR) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.33–7.27 (m, 2H), 7.24–7.16 (m, 3H), 5.81–5.71 (m, 1H), 5.66–5.57 (m, 1H), [*5.49 (dqt, J = 11.0 Hz, J = 6.8 Hz, J = 1.5 Hz, 1H)*], 5.39 (dq, *J* = 15.1 Hz, *J* = 6.5 Hz, 1H), 5.03–4.92 (m, 1H), 3.05–2.92 (m, 1H), 2.92 (dt, *J* = 11.9 Hz, *J* = 8.2 Hz, 1H), 2.67–2.58 (m, 1H), 2.49 (dd, *J* = 15.3 Hz, *J* = 7.0 Hz, 1H), 2.43 (dd, *J* = 14.1 Hz, *J* = 8.6 Hz, 1H), 2.37–2.301 (m, 1H), 2.297–2.22 (m, 2H), 1.54 (d, *J* = 6.3 Hz, 3H), [*1.46 (d, J = 6.8 Hz, 3H)*];[4] **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 212.8, 140.7, [*140.5*], [*130.5*], 130.2, 128.4 (2C), 128.3, [*127.04*], 126.96, 126.92 (2C), 126.9, [*126.8*], 126.7, [*125.9*], 62.1, 41.2, 38.6, [*38.4*], [*34.7*], [*30.05*], 30.04, 26.7, [*26.8*], [*17.97*], 17.96;[4] **IR (neat):** $\tilde{\nu}$ = 3058, 3022, 2916, 2854, 1706, 1598, 1578, 1495, 1467, 1445, 1377, 1345, 1308, 1196, 1142, 1074, 1036,1002, 970, 912, 770, 753, 728, 698, 665 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 263 (100); HRMS (ES+) calcd for $(C_{17}H_{20}O + Na)^+$: 263.1412; found: 263.1410.

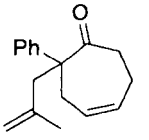
Compound 2.37



2.37 was prepared by undergraduate student Coralie Tugny from the corresponding alcohol by Swern oxidation. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.53 (s, 1H), 7.38–7.32 (m, 2H), 7.29–7.19 (m, 3H), 5.56–5.50 (m, 1H), 4.99–4.92 (m, 1H), 2.83 (dd, *J* = 14.1 Hz, *J* = 7.6 Hz, 1H), 2.76 (*J* = 14.1 Hz, *J* = 6.9 Hz, 1H), 2.67 (dd, *J* = 15.0 Hz, *J* = 7.5 Hz, 1H), 2.58 (dd, *J* = 15.0 Hz, *J* = 6.9 Hz, 1H), 1.62 (s, 3H), 1.49 (s, 3H), 1.04–0.93 (m, 2H), 0.89–0.76 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.8, 138.8, 134.7, 128.6 (2C), 127.8 (2C), 127.2, 125.7, 118.3, 112.6, 58.2, 35.2, 31.1,

26.1, 18.0, 3.0, 1.9; **IR (neat):** $\tilde{\nu}$ = 3055, 2980, 2916, 2707, 1722, 1599, 1496, 1446, 1377, 1088, 1030, 1002, 967, 932, 880, 858, 759, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 277 (100); HRMS (ES+) calcd for $(C_{18}H_{22}O + Na)^+$: 277.1568; found: 277.1566.

Compound 2.38

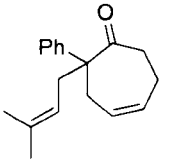


Starting from aldehyde **2.35** (28 mg, 0.117 mmol). **2.38** (25 mg, 89%) was isolated as white solid. m.p.: 41–43 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32–7.16 (m, 5H), 5.83–5.73 (m, 1H), 5.64–5.56 (m, 1H), 4.76–4.71 (m, 1H), 4.54–4.49 (m, 1H), 3.15–3.06 (m, 1H), 3.00–2.91 (m, 1H), 2.70 (d, *J* = 13.6 Hz, 1H), 2.59 (dd, *J* = 15.0 Hz, *J* = 7.5 Hz, 1H), 2.53 (d, *J* = 13.6 Hz, 1H), 2.36–2.21 (m, 3H), 1.06 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 212.2, 143.2, 140.6, 130.3, 128.4 (2C), 127.2 (2C), 127.0, 126.9, 115.0, 61.8, 44.9, 37.9, 29.1, 27.1, 23.9; **IR (neat):** $\tilde{\nu}$ = 3069, 3022, 2947, 2918, 2851, 1702, 1641, 1597, 1580, 1497, 1472, 1445, 1375, 1343, 1308, 1267, 1196, 1139, 1032, 963, 893, 793, 770, 728, 698, 680, 661 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 263 (100); HRMS (ES+) calcd for $(C_{17}H_{20}O + Na)^+$: 263.1412; found: 263.1408.

Compound 2.39

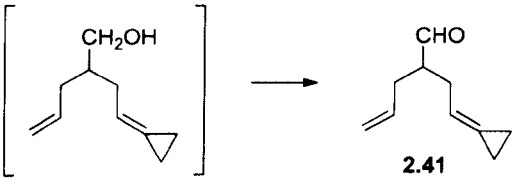
See compound **2.36**

Compound 2.40



Starting from aldehyde **2.37** (23 mg, 0.0904 mmol). **2.40** (17.2 mg, 75%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31–7.27 (m, 2H), 7.23–7.16 (m, 3H), 5.81–5.71 (m, 1H), 5.66–5.57 (m, 1H), 4.76–4.67 (m, 1H), 2.98 (dd, *J* = 15.3 Hz, *J* = 5.8 Hz, 1H), 2.91 (dt, *J* = 16.4 Hz, *J* = 8.1 Hz, 1H), 2.58 (dd, *J* = 14.8 Hz, *J* = 6.6 Hz, 1H), 2.52 (dd, *J* = 15.0 Hz, *J* = 8.7 Hz, 1H), 2.49 (dd, *J* = 15.3 Hz, *J* = 6.9 Hz, 1H), 2.39–2.34 (m, 1H), 2.31–2.22 (m, 2H), 1.58 (s, 3H), 1.44 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 213.0, 140.8, 134.3, 130.3, 128.3 (2C), 127.09, 127.05 (2C), 126.7, 119.8, 62.3, 38.6, 36.1, 30.1, 26.7, 25.9, 17.8; **IR (neat):** $\tilde{\nu}$ = 3084, 3053, 3022, 2967, 2914, 2851, 1706, 1599, 1580, 1496, 1445, 1376, 1345, 1308, 1195, 1140, 1110, 1031, 1002, 981, 948, 899, 844, 774, 751, 724, 698, 681, 667 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 277 (100); HRMS (ES+) calcd for $(C_{18}H_{22}O + Na)^+$: 277.1568; found: 277.1568; **elemental analysis** (%) calcd for $C_{18}H_{22}O_2$: C 84.99, H 8.72; found: C 84.94, H 8.71.

Compound 2.41

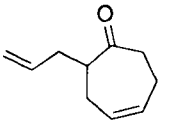


2.41

This compound was prepared from **2.71** (160 mg, 0.89 mmol) according to the procedure described for the preparation of **2.17**, using only one equivalent of lithium aluminium hydride. The crude alcohol was then oxidised according to the procedure

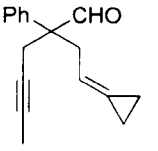
described for the preparation of **2.3**. Colourless oil (79 mg, 59% over two steps). **^{1}H NMR (500 MHz, C_3D_6O):** δ = 9.64 (s, 1H), 5.79 (ddt, *J* = 17.3 Hz, *J* = 10.4 Hz, *J* = 6.9 Hz, 1H), 5.78–5.70 (m, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 2.63–2.55 (m, 1H), 2.54–2.48 (m, 1H), 2.46–2.36 (m, 2H), 2.30–2.22 (m, 1H), 1.07–0.98 (m, 4H); **^{13}C NMR (125 MHz, C_3D_6O):** δ = 204.5, 136.5, 124.6, 117.1, 115.4, 51.7, 32.2, 31.2, 2.7, 2.3; **IR (neat):** $\tilde{\nu}$ = 3078, 3048, 2981, 2922, 2849, 2718, 1725, 1641, 1440, 1413, 1393, 1070, 994, 966, 915, 835, 776, 749, 719 cm^{-1}; **MS (CI):** m/z (rel. intensity): 168 (100), 152 (21), 150 (22), 135 (17), 133 (14); HRMS (CI) calcd for ($C_{10}H_{14}O$ + NH_4): 168.13884; found: 168.13860.

Compound 2.42



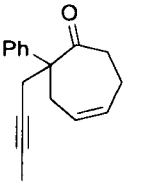
Starting from aldehyde **2.41** (10 mg, 0.0666 mmol). **2.42** (full conversion observed by ^{1}H NMR). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.80–5.65 (m, 3H), 5.018 (dq, *J* = 17.1 Hz, *J* = 1.6 Hz, 1H), 5.017–4.98 (m, 1H), 2.91–2.83 (m, 1H), 2.68 (ddd, *J* = 15.1 Hz, *J* = 11.3 Hz, *J* = 3.9 Hz, 1H), 2.53 (dd, *J* = 6.5 Hz, *J* = 3.7 Hz, 1H), 2.52–2.43 (m, 2H), 2.37–2.29 (m, 1H), 2.23–2.15 (m, 1H), 2.12–2.00 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.0, 136.0, 129.5, 128.8, 116.8, 50.3, 42.2, 35.1, 30.1, 24.1; **IR (neat):** $\tilde{\nu}$ = 3073, 3018, 2916, 2851, 1706, 1641, 1436, 1373, 1259, 1219, 1194, 991, 913 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 150 (6), 96 (48), 95 (27), 81 (24), 79 (53), 67 (44), 65 (18), 53 (44), 51 (21), 41 (59), 39 (100); HRMS (CI) calcd for $(C_{10}H_{14}O)^+$: 150.1030; found: 150.1037.

Compound 2.43



This compound was prepared from **2.73** (32 mg, 0.133 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (29 mg, 91%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 9.57 (s, 1H), 7.39–7.32 (m, 2H), 7.30–7.26 (m, 1H), 7.24–7.21 (m, 2H), 5.57–5.49 (m, 1H), 2.99–2.88 (m, 2H), 2.79 (dq, J = 16.8 Hz, J = 2.6 Hz, 1H), 2.67 (dq, J = 16.8 Hz, J = 2.6 Hz, 1H), 1.70 (t, J = 2.6 Hz, 3H), 1.06–0.82 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 201.4, 137.8, 128.7 (2C), 127.5 (2C), 127.4, 126.5, 112.0, 79.0, 74.4, 57.4, 35.3, 23.2, 3.5, 2.9, 1.9; **IR (neat):** $\tilde{\nu}$ = 3055, 2980, 2919, 2854, 2800, 2712, 1723, 1599, 1580, 1496, 1446, 1384, 1317, 1257, 1231, 1090, 1070, 1002, 967, 933, 910, 874, 837, 759, 733, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 261 (100); HRMS (ES+) calcd for $(C_{17}H_{18}O + Na)^+$: 261.1255; found: 261.1257.

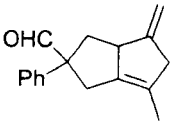
Compound 2.44



Starting from aldehyde **2.43** (10 mg, 0.042 mmol). **2.44** (7.5 mg, 75%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.33–7.28 (m, 2H), 7.26–7.20 (m, 3H), 5.87–5.79 (m, 1H), 5.64 (dt, J = 11.4 Hz, J = 4.3 Hz, 1H), 3.13–3.06 (m, 1H), 2.92 (dt, J = 12.5 Hz, J = 8.0 Hz, 1H), 2.81 (dd, J = 15.5 Hz, J = 6.8 Hz, 1H), 2.75–2.69 (m, 1H), 2.60 (dq, J = 16.9 Hz, J = 2.6 Hz, 1H), 2.40 (dt, J = 12.5 Hz, J = 5.8 Hz, 1H), 2.28–2.21 (m, 2H), 1.66 (t, J = 2.6 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):**

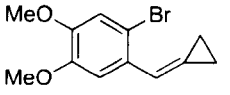
δ = 211.9, 140.1, 130.6, 128.3 (2C), 127.1, 126.9 (2C), 126.8, 78.4, 75.7, 61.3, 38.9, 30.5, 28.7, 26.5, 3.5; **IR (neat):** $\tilde{\nu}$ = 3053, 3023, 2920, 2853, 1702, 1598, 1578, 1497, 1446, 1308, 1196, 1142, 1037, 758, 698, 670 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 261 (100); HRMS (ES+) calcd for $(C_{17}H_{18}O + Na)^+$: 261.1255; found: 261.1264.

Compound 2.45



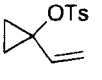
Starting from aldehyde **2.43** (30 mg, 0.126 mmol). **2.45** (7.5 mg, 25%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.41 (s, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.28–7.24 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 4.84 (s br, 2H), 3.39 (d br, *J* = 20.2 Hz, 1H), 3.36–3.30 (m, 1H), 3.22 (d br, *J* = 16.9 Hz, 1H), 2.90 (d br, *J* = 20.2 Hz, 1H, 2.76 (dd, *J* = 11.9 Hz, *J* = 6.8 Hz, 1H), 2.44 (d br, *J* = 16.9 Hz, 1H), 1.71 (t, *J* = 11.9 Hz, 1H), 1.61 (s br, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 199.6, 152.8, 140.6, 140.1, 128.9 (2C), 127.43, 127.36, 127.3 (2C), 106.0, 66.8, 53.5, 47.9, 36.1, 30.5, 14.3; **IR (neat):** $\tilde{\nu}$ = 3068, 3023, 2925, 2853, 2818, 2706, 1724, 1657, 1599, 1578, 1494, 1447, 1379, 1325, 1301, 1261, 1196, 1097, 1072, 1026, 963, 913, 882, 834, 798, 759, 699 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 257 (19), 256 (100), 240 (12), 239 (69), 238 (62), 237 (19), 223 (17), 209 (16), 195 (13), 131 (22).

Compound 2.47



Under N_2, potassium *t*-butoxide (2.3 g, 20.4 mmol) was added to a suspension of 3-bromopropyltriphenylphosphonium bromide (4.8 g, 10.2 mmol) in THF (93 mL) at room temperature. The mixture was refluxed during 2 hours and a solution of 6-bromoveratraldehyde **2.46** (2.3 g, 9.3 mmol) in THF (19 mL) was added to the refluxing suspension. The mixture was stirred during 13 hours before being allowed to cool at room temperature. The mixture was quenched with water (30 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 25:1) afforded compound **2.47** as white solid (1.48 g, 56%). m.p.: 100–102 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.34 (s, 1H), 7.04–7.01 (m, 1H), 6.99 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 1.42–1.36 (m, 2H), 1.22–1.17 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 148.5, 148.3, 129.8, 124.9, 116.7, 115.1, 113.6, 109.4, 56.1, 55.8, 3.7, 0.7; **IR (neat):** $\tilde{\nu}$ = 2960, 2935, 2833, 1596, 1501, 1462, 1383, 1306, 1255, 1208, 1161, 1026, 956, 941, 856, 829, 809, 730 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 271 (96), 268 (100), 191 (36); HRMS (CI) calcd for ($C_{12}H_{13}BrO_2$ + H): 269.01772; found: 269.01687; **elemental analysis** (%) calcd for $C_{12}H_{13}BrO_2$: C 53.55, H 4.87; found: C 53.15, H 4.82.

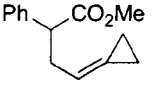
Compound 2.50[5]



Compound **2.50** was obtained according to the procedure described by De Meijere. m.p.: 32–34 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d,

J = 8.3 Hz, 2H), 5.86 (dd, J = 17.5 Hz, J = 11.1 Hz, 1H), 5.08 (d, J = 17.5 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 2.42 (s, 3H), 1.37–1.31 (m, 2H), 0.94–0.86 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.8, 136.5, 135.0, 129.7 (2C), 127.9 (2C), 113.5, 65.4, 27.7, 14.0 (2C); **IR (neat):** $\tilde{\nu}$ = 3089, 3002, 2926, 1644, 1597, 1421, 1349, 1164, 1090, 950, 906, 820, 704 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 256 (100); HRMS (CI) calcd for ($C_{12}H_{14}O_3S + NH_4$): 256.10074; found: 256.10128; **elemental analysis** (%) calcd for $C_{12}H_{14}O_3S$: C 60.48, H 5.92; found: C 60.27, H 5.95.

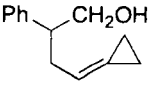
Compound 2.51



Under N_2, methyl phenylacetate (1.27 mL, 8.82 mmol) was added at 0 °C to a suspension of sodium hydride (336 mg, 8.40 mmol) in DMF (16 mL) and the mixture was stirred at room temperature for 40 minutes. In another flask, tosylate **2.50** (1 g, 4.20 mmol) was added to a suspension of tris(dibenzylideneacetone)dipalladium (115 mg, 0.126 mmol) and dppe (100 mg, 0.252 mmol) in THF (24 mL) and the mixture was stirred at room temperature for 30 minutes. The palladium complex was cannulated to the enolate and the resulting mixture was stirred at 60 °C for 3 hours. The mixture was quenched with water (25 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/Et_2O, 50:1) gave compound **2.51** as a pale yellow oil (778 mg, 86%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.40–7.25 (m, 5H), 5.80–5.71 (m, 1H), 3.77 (t, J = 7.7 Hz, 1H), 3.68 (s, 3H), 3.09–2.93 (m, 1H), 2.76–2.63 (m, 1H), 1.14–0.98 (m, 3H), 0.97–0.88 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 174.1, 138.9, 128.5 (2C), 128.0 (2C), 127.2,

124.0, 114.8, 51.9, 51.4, 35.8, 2.3, 1.9; **IR (neat):** $\tilde{\nu}$ = 3030, 2980, 2951, 2845, 1734, 1602, 1495, 1435, 1266, 1223, 1157, 836, 729, 697 cm^{-1}; **MS (CI):** m/z (rel. intensity): 234 (100), 217 (17); HRMS (CI) calcd for ($C_{14}H_{16}O_2$ + NH_4): 234.14940; found: 234.14907; **elemental analysis** (%) calcd for $C_{14}H_{16}O_2$: C 77.75, H 7.46; found: C 77.86, H 7.48.

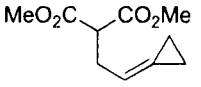
Compound 2.52



Under N_2, ester **2.51** (260 mg, 1.20 mmol) in Et_2O (1.5 mL) was added to a suspension of lithium aluminium hydride (23 mg, 0.60 mmol) in Et_2O (5 mL) at 0 °C. After stirring for 20 minutes at room temperature, lithium aluminium hydride (23 mg, 0.60 mmol) was added at 0 °C. After stirring for another 30 minutes at room temperature, a saturated aqueous solution of Na_2SO_4 was added dropwise, first at 0 °C then at room temperature, until a white precipitate appeared. The mixture was filtered through a pad of celite and concentrated. Purification by flash chromatography (PE/EtOAc, 20:1 to 10:1) afforded **2.52** as colourless oil (205 mg, 91%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.37–7.33 (m, 2H), 7.28–7.23 (m, 3H), 5.76–5.69 (m, 1H), 3.84 (dd, *J* = 11.0 Hz, *J* = 5.8 Hz, 1H), 3.77 (dd, *J* = 11.0 Hz, *J* = 7.9 Hz, 1H), 3.02–2.94 (m, 1H), 2.67–2.59 (m, 1H), 2.57–2.48 (m, 1H), 1.50 (s, 1H), 1.09–0.87 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 142.3, 128.5 (2C), 128.1 (2C), 126.6, 123.3, 115.6, 67.0, 48.4, 34.6, 2.5, 1.7; **IR (neat):** $\tilde{\nu}$ = 3351, 3052, 3028, 2978, 2923, 1602, 1493, 1452, 1062, 1027, 963, 931, 758, 699 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 208 (41), 206 (100); HRMS (CI) calcd for ($C_{13}H_{16}O$ + NH_4):

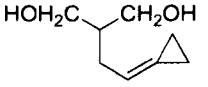
206.15449; found: 206.15465; **elemental analysis** (%) calcd for $C_{13}H_{16}O$: C 82.94, H 8.57; found: C 82.85, H 8.62.

Compound 2.53[5]



Compound **2.53** was obtained according to the procedure described by De Meijere. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.70–5.64 (m, 1H), 3.66 (s, 6H), 3.50 (t, *J* = 7.7 Hz, 1H), 2.72–2.69 (m, 2H), 0.99–0.95 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 169.4 (2C), 124.5, 113.4, 52.3 (2C), 51.3, 31.0, 2.2, 1.8; **IR (neat):** $\tilde{\nu}$ = 2983, 2955, 1733, 1436, 1339, 1268, 1232, 1152, 1045, 1020, 959, 933, 848, 778, 750 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 216 (100), 199 (33); HRMS (CI) calcd for ($C_{10}H_{14}O_4$ + H): 199.09703; found: 199.09627; **elemental analysis** (%) calcd for $C_{10}H_{14}O_4$: C 60.59, H 7.12; found: C 57.69, H 6.88.

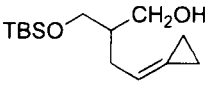
Compound 2.54



This compound was prepared from **2.53** (115 mg, 0.58 mmol) according to the procedure described for the preparation of **2.17**. Colourless oil (63mg, 77%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.76–5.69 (m, 1H), 3.74 (dd, *J* = 10.9 Hz, *J* = 4.2 Hz, 2H), 3.61 (dd, *J* = 10.9 Hz, *J* = 7.7 Hz, 2H), 3.33 (s, 2H), 2.13–2.10 (m, 2H), 1.95–1.86 (m, 1H), 1.07–0.94 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 123.2, 115.4, 65.3 (2C), 42.2, 30.3, 2.5, 1.7; **IR (neat):** $\tilde{\nu}$ = 3319, 2978, 2923, 2881, 1467, 1439, 1411, 1072,1026, 963, 934, 773, 719 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 160 (100);

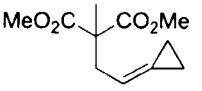
HRMS (CI) calcd for ($C_8H_{14}O_2$ + H): 143.10720; found: 143.10750; **elemental analysis** (%) calcd for $C_8H_{14}O_2$: C 67.57, H 9.92; found: C 65.78, H 10.15.

Compound 2.55



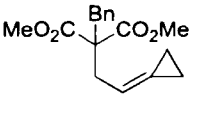
Under N_2, a solution of **2.54** (240 mg, 1.690 mmol) in THF (6 mL) was added to a suspension of sodium hydride (40 mg, 1.690 mmol) in THF (10 mL) cooled at 0 °C. The mixture was stirred at room temperature for 18 hours then *t*-butyldimethylsilyl chloride (254 mg, 1.690 mmol) was added. The mixture was stirred at room temperature for another hour then quenched with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/Et_2O, 25:1) afforded compound **2.55** as a colourless oil (354 mg, 82%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.74–5.68 (m, 1H), 3.76 (dd, *J* = 9.7 Hz, *J* = 4.1 Hz, 1H), 3.69 (dd, *J* = 10.4 Hz, *J* = 3.7 Hz, 1H), 3.62–3.57 (m, 2H), 2.75 (s, 1H), 2.11–2.08 (m, 2H), 1.93–1.85 (m, 1H), 1.05–0.94 (m, 4H), 0.86 (s, 9H), 0.03 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 123.0, 115.7, 67.0, 66.4, 42.3, 30.3, 25.8 (3C), 18.1, 2.5, 1.8, –5.59, –5.65; **IR (neat):** $\tilde{\nu}$ = 3338, 2952, 2928, 2886, 2856, 1471, 1439, 1408, 1386,1360, 1252, 1082, 1031, 965, 935, 835, 776 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 259 (31), 257 (100); HRMS (CI) calcd for ($C_{14}H_{28}O_2Si$ + H): 257.19368; found: 257.19304; **elemental analysis** (%) calcd for $C_{14}H_{28}O_2Si$: C 65.57, H 11.00; found: C 65.43, H 11.03.

Compound 2.56



Under N_2, **2.53** (300 mg, 1.51 mmol) in THF (4 mL) was added to a suspension of sodium hydride (44 mg, 1.82 mmol) in THF (12 mL) cooled at 0 °C. The mixture was stirred at room temperature for 1 hour, then iodomethane (141 μL, 2.27 mmol) was added and the mixture was stirred for another 40 minutes at room temperature. The mixture was quenched with brine (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/Et_2O, 40:1 to 30:1) afforded compound **2.56** as a colourless oil (257 mg, 80%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.63–5.57 (m, 1H), 3.67 (s, 6H), 2.70 (d, J = 7.6 Hz, 2H), 1.35 (s, 3H), 1.06–1.01 (m, 2H), 0.98–0.92 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 172.5 (2C), 126.5, 112.0, 53.9, 52.4 (2C), 38.2, 19.8, 2.9, 1.7; **IR (neat):** $\tilde{\nu}$ = 2985, 2954, 1731, 1454, 1434, 1377, 1287, 1242, 1202, 1159, 1110, 982, 936, 874, 755 cm^{-1}; **MS (CI):** m/z (rel. intensity): 232 (42), 230 (95), 215 (82), 213 (100), 164 (93), 147 (10); HRMS (CI) calcd for ($C_{11}H_{16}O_4$ + H): 213.11268; found: 213.11277; **elemental analysis** (%) calcd for $C_{11}H_{16}O_4$: C 62.25, H 7.60; found: C 62.32, H 7.63.

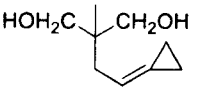
Compound 2.57



Under N_2, a solution of ester **2.53** (200 mg, 1.01 mmol) in THF (3 mL) was added to a suspension of sodium hydride (29 mg, 1.21 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred at room temperature during 2 hours then benzyl

bromide (145 μL, 1.21 mmol) followed by tetrabutylammonium iodide (149 mg, 0.40 mmol) were added. The resulting mixture was stirred at room temperature during 14 hours. The mixture was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 60:1 to 40:1) gave compound **2.57** as a colourless oil (445 mg, 71%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.29–7.18 (m, 3H), 7.09–7.04 (m, 2H), 5.74–5.68 (m, 1H), 3.67 (s, 6H), 3.23 (s, 2H), 2.68 (d, J = 7.5 Hz, 2H), 1.11–1.06 (m, 2H), 1.02–0.96 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 171.4 (2C), 136.0, 129.8 (2C), 128.2 (2C), 126.9, 126.4, 112.0, 59.1, 52.3 (2C), 38.1, 34.5, 2.9, 2.0; **IR (neat):** $\tilde{\nu}$ = 3031, 2977, 2952, 1732, 1497, 1434, 1328, 1278, 1242, 1201, 1175, 1084, 1044, 1003, 953, 899, 862, 821, 780, 743, 700 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 311 (100); HRMS (ES+) calcd for $(C_{17}H_{20}O_4 + Na)^+$: 311.1259; found: 311.1260; **elemental analysis** (%) calcd for $C_{17}H_{20}O_4$: C 70.81, H 6.99; found: C 70.25, H 6.97.

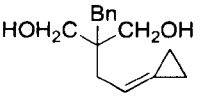
Compound 2.58



Under N_2, a solution of **2.56** (250 mg, 1.18 mmol) in Et_2O (6 mL) was added to a suspension of lithium aluminum hydride (67 mg, 1.77 mmol) in Et_2O (12 mL) at 0 °C. The mixture was stirred during 20 minutes at room temperature then lithium aluminum hydride (67 mg, 1.77 mmol) was added at 0 °C. After 30 minutes of stirring at room temperature, few drops of a saturated solution of Na_2SO_4 was added until a white precipitate appeared. The mixture was filtered through a pad of celite and evaporated. Colourless oil (164 mg, 89%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ =

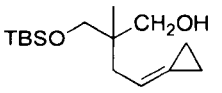
5.82–5.72 (m, 1H), 3.53 (d, J = 10.6 Hz, 2H), 3.47 (d, J = 10.6 Hz, 2H), 2.90 (s, 2H), 2.16 (d, J = 7.7 Hz, 2H), 1.09–0.94 (m, 4H), 0.81 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 124.6, 113.5, 70.0 (2C), 40.0, 36.4, 18.5, 2.8, 1.7; **IR (neat):** $\tilde{\nu}$ = 3246 (br), 2962, 2936, 2877, 1470, 1429, 1387, 1367, 1295, 1251, 1223, 1156, 1096, 1044, 1018, 988, 964, 941, 887, 871, 807, 755, 715 cm^{-1}; **MS (CI):** m/z (rel. intensity): 176 (24), 174 (100), 159 (16), 157 (43), 139 (14), 132 (13), 128 (16), 126 (23), 115 (17), 109 (16); HRMS (CI) calcd for ($C_9H_{16}O_2$ + H): 157.12285; found: 157.12310; **elemental analysis** (%) calcd for $C_9H_{16}O_2$: C 69.19, H 10.32; found: C 69.32, H 10.37.

Compound 2.59



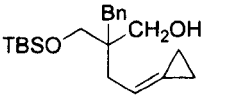
This compound was prepared from **2.57** (197 mg, 0.68 mmol) according to the procedure described for the preparation of **2.59**. Colourless oil (157 mg, 99%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30–7.25 (m, 3H), 7.23–7.19 (m, 2H), 5.91–5.85 (m, 1H), 3.60 (d, J = 10.7 Hz, 2H), 3.54 (d, J = 10.7 Hz, 2H), 2.98 (s, 2H), 2.71 (s, 2H), 2.11 (d, J = 7.5 Hz, 2H), 1.14–1.08 (m, 2H), 1.04–0.98 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 137.6, 130.4 (2C), 128.0 (2C), 126.1, 124.9, 113.4, 67.8 (2C), 43.3, 37.4, 34.0, 2.9, 2.0; **IR (neat):** $\tilde{\nu}$ = 3349, 3058, 3028, 2978, 2923, 2876, 1603, 1496, 1453, 1333, 1211, 1089, 1064, 1027, 967, 933, 870, 797, 722, 701 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 255 (100); HRMS (ES+) calcd for $(C_{15}H_{20}O_2 + Na)^+$: 255.1361; found: 255.1366.

Compound 2.60



This compound was prepared from **2.58** (170 mg, 1.088 mmol) according to the procedure described for the preparation of **2.55**. Colourless oil (247 mg, 84%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.79–5.70 (m, 1H), 3.51 (d, *J* = 9.7 Hz, 2 H), 3.49–3.42 (m, 2H), 3.02–2.56 (m, 1H), 2.19 (dd, *J* = 13.6 Hz, *J* = 7.5 Hz, 1H), 2.13 (dd, *J* = 13.7 Hz, *J* =7.6 Hz, 1H), 1.08–1.00 (m, 2H), 0.99–0.93 (m, 2H), 0.86 (s, 9H), 0.78 (s, 3H), –0.03 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 124.3, 113.7, 71.2, 70.6, 39.9, 36.4, 25.8 (3C), 18.6, 18.1, 2.8, 1.8, –5.7 (2C); **IR (neat):** $\tilde{\nu}$ = 3436, 2955, 2929, 2857, 1472, 1389, 1362, 1252, 1088, 1039, 1006, 968, 937, 834, 774, 667 cm^{-1}; **MS (CI):** m/z (rel. intensity): 273 (61), 271 (100), 132 (20), 109 (13); HRMS (CI) calcd for ($C_{15}H_{30}O_2Si$ + H): 271.20933; found: 271.20890; **elemental analysis** (%) calcd for $C_{15}H_{30}O_2Si$: C 66.61, H 11.18; found: C 67.06, H 11.26.

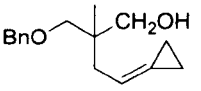
Compound 2.61



Under N_2, pyridine (51 μL, 0.698 mmol) was added to a solution of **2.59** (135 mg, 0.582 mmol) in CH_2Cl_2 (4 mL) at room temperature. The mixture was stirred at room temperature during 2 hours before adding *t*-butyldimethylsilyl chloride (85 mg, 0.564 mmol). The resulting mixture was stirred at 40 °C during 14 hours. The mixture was quenched with a saturated solution of NH_4Cl (4 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 70:1 to 50:1) afforded compound

2.61 as a colourless oil (181 mg, 90%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31–7.19 (m, 5H), 5.90–5.83 (m, 1H), 3.63–3.54 (m, 2H), 3.52–3.44 (m, 2H), 2.81 (d, J = 12.7 Hz, 1H), 2.78–2.73 (m, 1H), 2.67 (d, J = 12.9 Hz, 1H), 2.15–2.03 (m, 2H), 1.14–1.08 (m, 2H), 1.04–0.98 (m, 2H), 0.94 (s, 9H), –0.09 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 137.9, 130.6 (2C), 127.9 (2C), 126.0, 124.6, 113.6, 68.7, 68.1, 43.4, 37.3, 34.0, 25.8 (3C), 18.1, 2.8, 2.0, –5.6, –5.7; **IR (neat):** $\tilde{\nu}$ = 3454 (br), 3028, 2953, 2928, 2857, 1603, 1492, 1471, 1391, 1360, 1252, 1070, 1034, 1006, 967, 938, 834, 774, 723, 701, 669 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 369 (100); HRMS (ES+) calcd for $(C_{21}H_{34}O_2Si + Na)^+$: 369.2226; found: 369.2236.

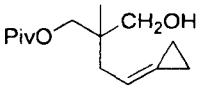
Compound 2.62



Under N_2, a solution of **2.58** (153 mg, 0.979 mmol) in DMF (0.4 mL) was added to a suspension of sodium hydride (24 mg, 0.979 mmol) in DMF (1 mL). The resulting mixture was stirred at room temperature during 2 hours. Then, benzyl bromide (117 μL, 0.979 mmol) followed by tetrabutylammonium iodide (217 mg, 0.588 mmol) were added. The mixture was stirred at room temperature during 16 hours. The mixture was quenched with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 40:1 to 10:1) afforded compound **2.62** as a colourless oil (152 mg, 63%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.37– 7.26 (m, 5H), 5.78–5.71 (m, 1H), 4.49 (s, 2H), 3.50 (s, 2H), 3.39 (d, J = 9.1 Hz, 1H), 3.33 (d, J = 8.8 Hz, 1H), 2.73–2.50 (m, 1H), 2.29–2.17 (m, 2H), 1.10–1.03 (m, 2H), 1.00–0.93 (m, 2H), 0.85 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 138.0, 128.4 (2C), 127.7, 127.4 (2C),

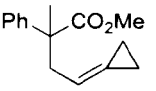
124.6, 113.6, 78.1, 73.5, 70.5, 39.8, 36.8, 19.0, 2.8, 1.8; **IR (neat):** $\tilde{\nu}$ = 3434 (br), 3031, 2977, 2916, 2856, 1497, 1454, 1406, 1362, 1307, 1292, 1249, 1206, 1095, 1075, 1028, 967, 936, 902, 801, 734, 696 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 269 (100); HRMS (ES+) calcd for $(C_{16}H_{22}O_2 + Na)^+$: 269.1517; found: 269.1508; **elemental analysis** (%) calcd for $C_{16}H_{22}O_2$: C 78.01, H 9.00; found: C 77.17, H 9.40.

Compound 2.63



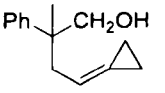
Under N_2, pyridine (42 µL, 0.518 mmol) was added to a solution of **2.58** (140 mg, 0.896 mmol) in CH_2Cl_2 (14 mL). The resulting mixture was stirred at room temperature during 2 hours. Then, pivaloyl chloride (111 µL, 0.905 mmol) was added and the mixture was stirred under reflux for 14 hours. The mixture was quenched with brine (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 50:1 to 25:1 to 10:1) afforded compound **2.63** as a colourless oil (183 mg, 85%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.80–5.70 (m, 1H), 3.95 (d, *J* = 11.2 Hz, 1H), 3.90 (d, *J* = 11.2 Hz, 1H), 3.30 (d, *J* = 11.5 Hz, 1H), 3.26 (d, *J* = 11.6 Hz, 1H), 2.65–2.35 (m, 1H), 2.16 (dd, *J* = 13.6 Hz, *J* = 7.9 Hz, 1H), 2.10 (dd, *J* = 13.5 Hz, *J* = 7.6 Hz, 1H), 1.19 (s, 9H), 1.09–1.02 (m, 2H), 1.00–0.93 (m, 2H), 0.86 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 179.4, 125.2, 112.9, 67.5, 66.9, 40.2, 39.0, 36.5, 27.2 (3C), 18.6, 2.8, 1.7; **IR (neat):** $\tilde{\nu}$ = 3452 (br), 2976, 2937, 2876, 1728, 1710, 1481, 1462, 1398, 1366, 1284, 1155, 1096, 1034, 986, 968, 937, 890, 793, 771, 750, 714 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 263 (100); HRMS (ES+) calcd for $(C_{14}H_{24}O_3 + Na)^+$: 263.1623; found: 263.1617.

Compound 2.64



Under N_2, NaHMDS (407 mg, 2.22 mmol) was added as solid in one portion to a solution of **2.51** (320 mg, 1.48 mmol) in THF (15 mL) at 0 °C. The mixture was stirred at room temperature during 1 hour. Then iodomethane (0.55 mL, 8.88 mmol) was added via syringe and the mixture was stirred for another 4 hours at room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 60:1) gave compound **2.64** as a colourless oil (270 mg, 79%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32–7.31 (m, 4H), 7.24–7.20 (m, 1H), 5.62–5.56 (m, 1H), 3.64 (s, 3H), 2.94 (dd, J = 13.2 Hz, J = 7.2 Hz, 1H), 2.77 (dd, J = 13.2 Hz, J = 7.6 Hz, 1H), 1.52 (s, 3H), 1.06–0.98 (m, 2H), 0.95–0.84 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 176.5, 143.5, 128.3 (2C), 126.7, 126.0 (2C), 125.6, 113.4, 52.1, 50.5, 41.6, 22.7, 2.8, 1.7; **IR (neat):** $\tilde{\nu}$ = 3053, 3023, 2980, 2950, 1729, 1601, 1497, 1446, 1434, 1377, 1268, 1227, 1203, 1147, 1120, 1074, 1031, 986, 968, 935, 857, 810, 764, 732, 697 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 253 (100); HRMS (ES+) calcd for $(C_{15}H_{18}O_2 + Na)^+$: 253.1204; found: 253.1194; **elemental analysis** (%) calcd for $C_{15}H_{18}O_2$: C 78.23, H 7.88; found: C 77.32, H 7.74.

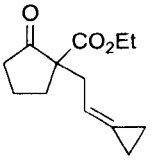
Compound 2.65



This compound was prepared from **2.64** (117 mg, 0.508 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (81 mg, 79%). **^{1}H**

NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.1 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.20 (t, *J* = 7.1 Hz, 1H), 5.61–5.53 (m, 1H), 3.76 (d, *J* = 10.8 Hz, 1H), 3.60 (dd, *J* = 10.8 Hz, *J* = 4.7 Hz, 1H), 2.63 (dd, *J* = 13.9 Hz, *J* = 6.5 Hz, 1H), 2.47 (dd, *J* = 13.9 Hz, *J* = 7.9 Hz, 1H), 1.33 (s, 3H), 1.30–1.22 (s, 1H), 1.04–0.82 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.8, 128.4 (2C), 126.7 (2C), 126.2, 124.5, 113.9, 71.8, 43.9, 40.9, 21.9, 2.8, 1.7; **IR (neat):** $\tilde{\nu}$ = 3367 (br), 3053, 2977, 2926, 2871, 1601, 1497, 1445, 1373, 1296, 1156 1024, 966, 935, 894, 830, 760, 697 cm^{-1}; **MS (CI):** m/z (rel. intensity): 221 (15), 220 (100), 185 (5); HRMS (CI) calcd for ($C_{14}H_{18}O$ + NH_4): 220.1696; found: 220.1692.

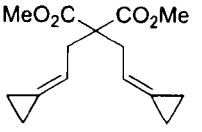
Compound 2.66



This compound was prepared from **2.50** (200 mg, 0.84 mmol) and commercially available 2-ethoxycarbonylcyclopentanone according to the procedure described for the preparation of **2.51**. Colourless oil (184 mg, 99%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.68–5.61 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.76 (dd, *J* = 13.7 Hz, *J* = 7.0 Hz, 1H), 2.49 (dd, *J* = 13.7 Hz, *J* = 7.5 Hz, 1H), 2.46–2.34 (m, 2H), 2.29–2.17 (m, 1H), 2.04–1.82 (m, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.09–1.03 (m, 2H), 1.01–0.95 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.8, 171.0, 126.1, 112.5, 61.2, 60.3, 38.0, 35.7, 32.0, 19.4, 13.9, 2.8, 1.8; **IR (neat):** $\tilde{\nu}$ = 2980, 2906, 1749, 1718, 1448, 1406, 1366, 1278, 1223, 1146, 1117, 1094, 1028, 965, 934, 921, 861, 788, 761, 722 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 245 (100); HRMS (ES+) calcd for ($C_{13}H_{18}O_3$ + Na)$^+$:

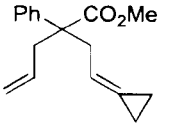
245.1154; found: 245.1157; **elemental analysis** (%) calcd for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.33, H 8.29.

Compound 2.67[5]



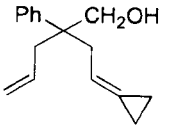
Under N_2, at room temperature, a solution of **2.53** (470 mg, 2.37 mmol) was added to a suspension of sodium hydride (56 mg, 2.37 mmol) in DMF (8 mL). The mixture was stirred at room temperature during 1 hour. In another flask, under N_2, **2.50** (564 mg, 2.37 mmol) was added to a solution of tris(dibenzylideneacetone)dipalladium (66 mg, 0.071 mmol) and dppe (28 mg, 0.071 mmol) in THF (15 mL) at room temperature. The resulting mixture was stirred at room temperature during 30 minutes before being canulated to the enolate. The resulting mixture was stirred during 48 hours at room temperature. The mixture was quenched with water (15 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/Et_2O, 50:1 to 20:1) gave compound **2.67** as a colourless oil (445 mg, 71%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.65–5.57 (m, 2H), 3.65 (s, 6H), 2.75 (d, J = 7.8 Hz, 4H), 1.07–1.00 (m, 4H), 0.96–0.90 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 171.6 (2C), 126.2 (2C), 111.9 (2C), 58.0, 52.3 (2C), 35.0 (2C), 2.9 (2C), 1.7 (2C); **IR (neat):** $\tilde{\nu}$ = 3053, 2982, 2953, 2841, 1732, 1436, 1411, 1307, 1281, 1245, 1198, 1180, 1109, 1071, 1000, 969, 947, 931, 861, 826, 794, 756 733 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 287 (100); HRMS (ES+) calcd for $(C_{15}H_{20}O_4 + Na)^+$: 287.1259; found: 287.1266; **elemental analysis** (%) calcd for: C 68.16, H 7.63; found: C 68.15, H 7.69.

Compound 2.68



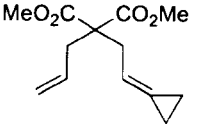
Under N_2, NaHMDS (188 mg, 1.023 mmol) was added as solid in one portion to a solution of **2.51** (170 mg, 0.787 mmol) in THF (5 ml) at –78 °C. The mixture was stirred for 1.5 hours at –78 °C then allyl bromide (89 μL, 1.023 mmol) and tetrabutylammonium iodide (116 mg, 0.315 mmol) were added. The mixture was slowly warmed at room temperature overnight. The mixture was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 30:1) gave compound **2.68** as a colourless oil (150 mg, 74%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.33–7.27 (m, 2H), 7.26–7.20 (m, 3H), 5.57 (ddt, *J* = 17.2 Hz, *J* = 10.5 Hz, *J* = 7.1 Hz, 1H), 5.51–5.47 (m, 1H), 5.04–5.01 (m, 1H), 5.01–4.97 (m, 1H), 3.62 (s, 3H), 2.93 (dd, *J* = 13.7 Hz, *J* = 7.7 Hz, 1H), 2.85 (dd, *J* = 13.7 Hz, *J* = 7.0 Hz, 1H), 2.79 (dd, *J* = 13.9 Hz, *J* = 7.9 Hz, 1H), 2.75 (dd, *J* = 13.9 Hz, *J* = 7.0 Hz, 1H), 1.05–0.94 (m, 2H), 0.92–0.85 (m, 1H), 0.85–0.77 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 175.7, 142.0, 133.6, 128.2 (2C), 126.7, 126.5 (2C), 125.6, 118.3, 112.8, 54.2, 51.9, 39.1, 37.2, 2.8, 1.9; **IR (neat):** $\tilde{\nu}$ = 2980, 2950, 1729, 1640, 1600, 1581, 1498, 1445, 1320, 1301, 1268, 1206, 1138, 1108, 1088, 1035, 996, 916, 889, 847, 811, 763, 729, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 295 (16), 280 (19), 279 (100); HRMS (ES+) calcd for $(C_{17}H_{20}O_2 + Na)^+$: 279.1361; found: 279.1362; **elemental analysis** calcd (%) for $C_{17}H_{20}O_2$: C 79.65, H 7.86; found: C 79.59, H 7.87.

Compound 2.69



This compound was prepared from **2.68** (251 mg, 0.98 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (217 mg, 97%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.41–7.29 (m, 3H), 7.23–7.18 (m, 2H), 5.74–5.57 (m, 2H), 5.07 (d, J = 16.9 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 3.78 (s, 2H), 2.64 (dd, J = 13.8 Hz, J = 7.4 Hz, 1H), 2.59–2.53 (m, 2H), 2.48 (dd, J = 13.3 Hz, J = 7.3 Hz, 1H), 1.48–1.30 (s, 1H), 1.06–0.98 (m, 2H), 0.97–0.87 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 143.6, 134.6, 128.3 (2C), 126.9 (2C), 126.2, 124.7, 117.6, 113.7, 68.1, 46.5, 39.7, 37.7, 2.8, 1.9; **IR (neat):** $\tilde{\nu}$ = 3403 (br), 3057, 2977, 2925, 1638, 1498, 1446, 1413, 1043, 997, 963, 697 cm^{-1}; **MS (CI):** m/z (rel. intensity): 246 (100); HRMS (CI) calcd for ($C_{16}H_{20}O$ + NH_4): 246.1852; found: 246.1855.

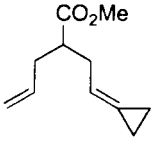
Compound 2.70[5]



Under N_2, a solution of **2.53** (500 mg, 2.52 mmol) in THF (7 mL) was added to a suspension of sodium hydride (61 mg, 2.55 mmol) in THF (7 mL) at 0 °C. The resulting mixture was stirred at room temperature during 40 minutes then cooled down at 0 °C. Allyl bromide (0.22 mL, 2.55 mmol) followed by tetrabutylammonium iodide (186 mg, 0.50 mmol) were added and the mixture was stirred at room temperature for 1 hour. The mixture was quenched with brine (10 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were dried over Na_2SO_4, filtered and

evaporated. Purification by flash chromatography (PE/EtOAc, 40:1) gave compound **2.70** as colourless oil (396 mg, 66%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.71–5.61 (m, 1H), 5.60–5.54 (m, 1H), 5.07–5.04 (m, 2H), 3.68 (s, 6H), 2.75 (d, *J* = 7.4 Hz, 2H), 2.60 (d, *J* = 7.4 Hz, 2H), 1.07–1.02 (m, 2H), 0.98–0.93 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 171.4 (2C), 132.5, 126.5, 118.9, 111.7, 57.9, 52.3 (2C), 36.9, 34.9, 2.9, 1.8; **IR (neat):** $\tilde{\nu}$ = 3078, 3048, 2983, 2954, 2841, 1731, 1642, 1436, 1284, 1249, 1198, 1142, 1082, 1043, 996, 968, 921, 859, 823, 756, 721 cm^{-1}; **MS (CI):** m/z (rel. intensity): 257 (10), 256 (84), 240 (12), 239 (100); HRMS (CI) calcd for $(C_{13}H_{18}O_4 + H)^+$: 239.1278; found: 239.1275; **elemental analysis** (%) calcd for $C_{13}H_{18}O_4$: C 65.53, H 7.61; found: C 65.52, H 7.62.

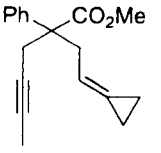
Compound 2.71



Lithium chloride (149 mg, 3.51mmol) was added to a solution of **2.70** (380 mg, 1.60 mmol) in DMSO (11 mL). Water (100 μL) was added then the mixture was stirred at 150 °C (oil bath temperature) during 6 hours. At room temperature, the mixture was partitioned between brine (10 mL) and Et_2O and extracted with Et_2O (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (pentane/Et_2O, 50:1) gave compound **2.71** as a colourless oil (188 mg, 66%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.77–5.64 (m, 2H), 5.02 (dd, *J* = 17.2 Hz, *J* = 1.8 Hz, 1H), 4.99 (d, *J* = 11.0 Hz, 1H), 3.62 (s, 3H), 2.62–2.54 (m, 1H), 2.51–2.42 (m, 1H), 2.39–2.29 (m, 2H), 2.27–2.20 (m, 1H), 1.05–0.94 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 175.6, 135.4, 123.9, 116.7, 114.7, 51.4, 45.2, 35.8,

33.8, 2.5 1.9; **IR (neat):** $\tilde{\nu}$ = 3078, 3053, 2982, 2951, 2911, 2846, 1736, 1642, 1436, 1370, 1340, 1262, 1232, 1164, 1120, 1067, 1046, 995, 964, 916, 857, 834, 754, 718 cm^{-1}; **MS (CI):** m/z (rel. intensity): 198 (100), 181 (73), 121 (26); HRMS (CI) calcd for ($C_{11}H_{16}O_2$ + H): 181.12285; found: 181.12233; **elemental analysis** (%) calcd for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.25, H 8.99.

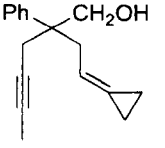
Compound 2.72



Under N_2, a solution of LDA (1.80 mmol), prepared from 0.72 mL of a solution of *n*BuLi (2.5 M in hexane) and 0.25 mL of diisopropylamine in THF (3.60 mL) at 0 °C, was added to a solution of **2.51** (150 mg, 0.694 mmol) in THF (3.30 mL) at –78 °C. The resulting solution was stirred at –78 °C for 1.5 hours then 4-bromo-2-butyne (0.16 mL, 1.80 mmol) was slowly added. The mixture was stirred at –78 °C for another 30 minutes before being quenched with few drops of methanol and allowed to warm at room temperature. The mixture was diluted with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 200:1 to 175:1 to 150:1) afforded compound **2.72** as a colourless oil (136 mg, 73%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.33–7.28 (m, 2H), 7.26–7.21 (m, 3H), 5.53–5.46 (m, 1H), 3.64 (s, 3H), 3.10–3.01 (m, 2H), 2.88 (dq, *J* = 16.3 Hz, *J* = 2.5 Hz, 1H), 2.75 (dq, *J* = 16.3 Hz, *J* = 2.5 Hz, 1H), 1.71 (t, *J* = 2.5 Hz, 3H), 1.05–0.91 (m, 3H), 0.91–0.84 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 175.1, 141.3, 128.2 (2C), 126.9, 126.34 (2C), 126.31, 112.7, 78.1, 75.1, 54.0, 52.2, 37.4, 25.6, 3.5,

2.9, 1.8; **IR (neat):** $\tilde{\nu}$ = 3053, 3023, 2981, 2951, 2921, 2851, 1731, 1601, 1580, 1498, 1436, 1322, 1302, 1270, 1207, 1070, 1002, 964, 910, 849, 764, 731, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 291 (100); HRMS (ES+) calcd for $(C_{18}H_{20}O_2 + Na)^+$: 291.1361; found: 291.1357; **elemental analysis** (%) calcd for $C_{18}H_{20}O_2$: C 80.56, H 7.51; found: C 80.85, H 7.59.

Compound 2.73

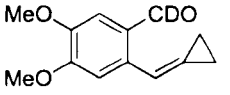


This compound was prepared from **2.72** (83 mg, 0.31 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (63 mg, 84%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.43–7.28 (m, 4H), 7.23–7.15 (m, 1H), 5.55–5.45 (m, 1H), 3.87 (d, *J* = 5.8 Hz, 2H), 2.75–2.65 (m, 2H), 2.63–2.57 (m, 1H), 2.56 (dq, *J* = 16.4 Hz, *J* = 2.6 Hz, 1H), 1.75 (t, *J* = 2.6 Hz, 3H), 1.60–1.56 (m, 1H), 1.03–0.90 (m, 3H), 0.89–0.82 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 143.0, 128.3 (2C), 126.9 (2C), 126.3, 125.0, 113.3, 78.2, 76.1, 68.9, 46.7, 38.4, 24.9, 3.5, 2.8, 1.8; **IR (neat):** $\tilde{\nu}$ = 3412, 3084, 3048, 2978, 2918, 1602, 1580, 1498, 1445, 1378, 1075, 1028, 966, 937, 860, 846, 761, 698 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 263 (100); HRMS (ES+) calcd for $(C_{17}H_{20}O + Na)^+$: 263.1412; found: 263.1410.

Compound 3.1

See compound **2.1**

Compuond 3.1D

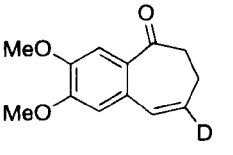


Tetrapropylammonium perruthenate (9.5 mg, 0.027 mmol) was added at room temperature, in portions, to a mixture of alcohol **3.19D** (120 mg, 0.54 mmol), 4-methylmorpholine *N*-oxide (292 mmol, 2.16 mmol) and 260 mg of 4Å MS in CH_2Cl_2 (6 mL). The mixture was stirred at room temperature during 20 minutes. The mixture was concentrated. Purification by flash chromatography (PE/EtOAc, 14:1 to 12:1) afforded compound **3.1D** as a yellow solid (76 mg, 64%). m.p. = 83–84 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.53 (s, 1H), 7.34 (s, 1H), 7.28 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 1.44–1.37 (m, 2H), 1.32–1.25 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 189.6 (t, J = 26.5 Hz), 153.5, 148.2, 135.9, 128.9, 125.5, 112.9, 110.0, 108 .8, 55.9, 55.8, 4.2, 1.6; **IR (neat):** $\tilde{\nu}$ = 3084, 3034, 2972, 2939, 2851, 2825, 2114, 1651, 1590, 1505, 1463, 1429, 1405, 1380, 1323, 1269, 1219, 1198, 1181, 1137, 1030, 994, 973, 928, 888, 857, 843, 785, 762, 742, 705 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 222 (83), 220 (100); HRMS (CI) calcd for ($C_{13}H_{13}DO_3$ + H): 220.10840; found: 220.10886.

Compound 3.2

See compound **2.2**

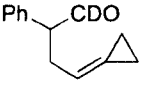
Compound 3.2D



Starting from aldehyde **3.1D** (20 mg, 0.0912 mmol). **3.2D** (18.6 mg, 93%) was isolated as yellow solid. m.p.: 85–87 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.54 (s,

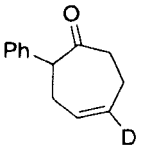
1H), 6.64 (s, 1H), 6.37 (s, 1H), 3.919 (s, 3H), 3.915 (s, 3H), 2.91–2.86 (m, 2H), 2.44–2.38 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 200.2, 152.2, 147.6, 132.0 (t, *J* = 23.7 Hz), 131.4, 131.0, 129.0, 113.6, 112.1, 55.99, 55.98, 42.3, 23.1; **IR (neat):** $\tilde{\nu}$ = 2952, 2916, 2846, 1650, 1592, 1512, 1563, 1512, 1467, 1439, 1399, 1356, 1332, 1259, 1222, 1188, 1164, 1136, 1067, 1030, 1009, 915, 879, 845, 798, 772 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 220 (100), 204 (5); HRMS (CI) calcd for ($C_{13}H_{13}DO_3$ + H): 220.10840; found: 220.10894.

Compound 3.3D



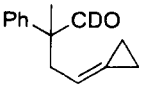
This compound was prepared from **3.20D** (85 mg, 0.45 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (72 mg, 85%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.26 (m, 3H), 7.21–7.18 (m, 2H), 5.72–5.66 (m, 1H), 3.68 (t, *J* = 7.4 Hz, 1H), 2.99–2.91 (m, 1H), 2.66–2.58 (m, 1H), 1.03–0.82 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 200.3 (t, *J* = 26.6 Hz), 136.1, 128.9 (2C), 128.8 (2C), 127.5, 124.2, 114.3, 58.6 (t, *J* = 3.7 Hz), 32.1, 2.4, 1.9; **IR (neat):** $\tilde{\nu}$ = 3053, 3030, 2980, 2918, 2850, 2071, 1708, 1601, 1590, 1493, 1453, 1408, 1308, 1184, 1089, 1001, 964, 929, 841, 754, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 205 (100); HRMS (CI) calcd for ($C_{13}H_{13}DO$ + NH_4): 205.14512; found: 205.14578.

Compound 3.4D



Starting from aldehyde **3.3D** (17.8 mg, 0.0951 mmol). **3.4D** (15.6 mg, 88%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.37–7.30 (m, 2H), 7.29–7.25 (m, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 5.88–5.82 (m, 1H), 4.05 (dd, *J* = 11.2 Hz, *J* = 3.7 Hz, 1H), 3.05–2.95 (m, 1H), 2.90–2.80 (m, 1H), 2.66–2.48 (m, 3H), 2.42–2.32 (m, 1H); **^{13}C NMR (500 MHz, $CDCl_3$):** δ = 211.9, 139.6, 129.3 (t, *J* = 23.5 Hz), 128.5 (2C), 128.2, 128.0 (2C), 127.0, 57.7, 41.4, 31.2, 25.1; **IR (neat):** $\tilde{\nu}$ = 3058, 3030, 2937, 2901, 2846, 1709, 1603, 1497, 1451, 1328, 1193, 1135, 880, 769, 717, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 206 (14), 205 (100), 188 (3); HRMS (CI) calcd for ($C_{13}H_{13}DO + NH_4$): 205.1446; found: 205.1447.

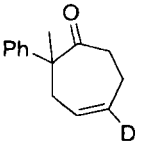
Compound 3.5D



This compound was prepared from **3.21D** (80 mg, 0.39 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (77 mg, 98%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.38–7.33 (m, 2H), 7.28–7.23 (m, 3H), 5.59–5.53 (m, 1H), 2.78 (d, *J* = 7.4 Hz, 2H), 1.42 (s, 3H), 1.06–0.95 (m, 2H), 0.94–0.81 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.1 (t, *J* = 26.7 Hz), 39.9, 128.7 (2C), 127.2 (3C), 125.8, 112.6, 54.2 (t, *J* = 2.9 Hz), 38.5, 19.1, 2.9, 1.7; **IR (neat):** $\tilde{\nu}$ = 3056, 3023, 2979, 2934, 2106, 2051, 1713, 1600, 1580, 1495, 1446, 1375, 1265, 1159, 1078, 1048, 1029, 1002, 968, 938, 852, 809, 755, 722, 697 cm^{-1}; **MS (ES+):** m/z (rel.

intensity): 224 (100); HRMS (ES+) calcd for $(C_{14}H_{15}DO + Na)^+$: 224.1162; found: 224.1158.

Compound 3.6D

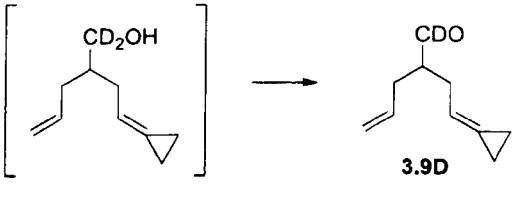


Starting from aldehyde **3.14D** (26.5 mg, 0.132 mmol). **3.15D** (23.3 mg, 88%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.37–7.30 (m, 2H), 7.28–7.21 (m, 3H), 5.87–5.80 (m, 1H), 3.11 (dd, *J* = 15.4 Hz, *J* = 5.8 Hz, 1H), 3.09–2.96 (m, 1H), 2.49–2.40 (m, 2H), 2.34–2.25 (m, 2H), 1.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCL_3$):** δ = 213.7, 143.6, 130.1 (t, *J* = 23.8 Hz), 128.6 (2C), 126.9, 126.8, 126.1 (2C), 58.7, 38.7, 34.7, 26.6, 26.4; **IR (neat):** $\tilde{\nu}$ = 3053, 3031, 2967, 2928, 2233, 1701, 1600, 1494, 1445, 1371, 1328, 1308, 1196, 1150, 1074, 1030, 999, 919, 883, 802, 763, 698 cm^{-1}; **MS (CI):** m/z (rel. intensity): 220 (15), 219 (100); HRMS (CI) calcd for $(C_{14}H_{15}DO + NH_4)$: 219.1602; found: 219.1600.

Compound 3.9

See compound **2.37**

Compound 3.9D



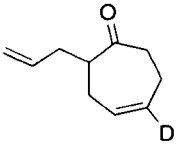
This compound was prepared from **2.71** (175 mg, 0.971 mmol) according to the procedure described for the preparation of **2.52**, using lithium aluminium deuteride.

Colourless oil (92 mg, 63%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.77–5.64 (m, 2H), 5.01 (d, *J* = 16.9 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 2.54–2.42 (m, 2H), 2.31–2.24 (m, 2H), 2.24–2.16 (m, 1H), 1.05–0.91 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 204.2 (t, *J* = 25.6 Hz), 135.0, 124.3, 117.1, 114.2, 50.8 (t, *J* = 3.8 Hz), 32.6, 30.6, 2.5, 2.0; **IR (neat):** $\tilde{\nu}$ = 3073, 3048, 2981, 2918, 2846, 2062, 1712, 1641, 1440, 1413, 1093, 1070, 997, 964, 916, 867, 749, 717 cm^{-1}.

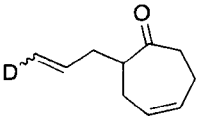
Compound 3.10

See compound **2.42**

Compound $3.10D_5$ - Compound $3.10D_{10}$



$3.10D_5$



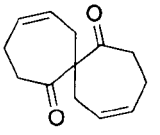
$3.10D_{10}$

Starting from aldehyde **3.9D**. Full conversion was observed by ^{1}H NMR. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.80–5.66 (m, 5H), 5.07–4.96 (m, 3H), 2.91–2.82 (m, 2H), 2.68 (ddd, *J* = 15.1 Hz, *J* = 11.3 Hz, *J* = 3.9 Hz, 2H), 2.55–2.43 (m, 6H), 2.37–2.29 (m, 2H), 2.24–2.15 (m, 2H), 2.12–2.01 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.1, 136.01, 135.91, 135.88, 129.5, 129.2 (t, *J* = 23.6 Hz), 128.8, 128.6, 116.8, 116.5 (t, *J* = 23.6 Hz), 50.2, 42.2, 35.07, 35.02, 30.07, 30.04, 24.01, 23.90; **IR (neat):** $\tilde{\nu}$ = 3073, 3023, 2925, 2846, 1704, 1638, 1438, 1376, 1195, 1140, 983, 915, 805, 756, 663 cm^{-1}.

Compound 3.13

See compound **2.21**

Compound 3.14

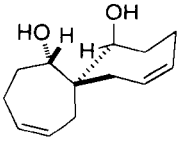


a) See compound **2.22** for characterisation

b) Preparation enantiopure bisketone **3.14** from enantiopure Mosher ester **3.16**

A solution of sodium hydroxide (95 mg, 2.38 mmol) in water (0.6 mL) was added to a solution of enantiopure alcohol (*S*,*R*,*R*,*R*)-**3.16** (101 mg, 0.238 mmol) in methanol (6 mL). The mixture was stirred at room temperature for 14 hours. The mixture was acidified with a 2M solution of HCl before being extracted with EtOAc (3 × 6 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. The enantiopure bisalcohol (*R*,*aR*,*R*)-**3.15** was used in the oxidation step without further purification. Pyridinium dichromate (537 mg, 1.428) was added to a solution of crude (*R*,*aR*,*R*)-**3.15** in CH_2Cl_2 (6 mL). The resulting mixture was stirred at room temperature for 14 hours. The mixture was concentrated, dissolved with a mixture PE/Et_2O (25:1) and filtrated through celite. The filtrate was concentrated affording spirobisketone (*aR*)-**3.14** (24 mg, 50% over two steps). (*aS*)-**3.14** was obtained according to the same procedure starting from (*S*,*S*,*S*,*S*)-**3.16**. (*aR*)-**3.14**: = +82° (*c* 0.100, $CHCl_3$); (*aS*)-**3.14**: = –80° (*c* 0.103, $CHCl_3$).

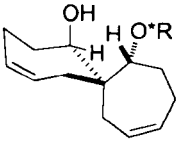
Compound 3.15



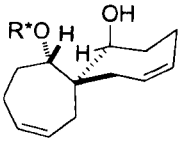
Under N_2, *t*-butyllithium (1.6 M in hexane, 0.46 mL, 0.734 mmol), was added to a solution of DiBAl-H (1M solution in hexane, 0.73 mL, 0.734 mmol) in THF (1 mL) at –78 °C. The mixture was allowed to warm at 0 °C over 40 minutes and stirred at 0 °C for another 25 minutes. Once the initially yellow solution became nearly colourless, the mixture was cooled at –78 °C. A solution of racemic spirobisketone **3.14** (50 mg, 0. 245mmol) in THF (0.5 mL) was slowly added at –78 °C. The resulting mixture was stirred at –78 °C for another 50 minutes until full reduction. At –78 °C, a solution of potassium bisulfate (230 mg) in water (4 mL) and CH_2Cl_2 (1 mL) was added. At room temperature, the mixture was extracted with CH_2Cl_2 (2 × 5 mL) and EtOAc (1 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 20:1 to 10:1 to 8:1 to 6:1) afforded compound **3.15** (racemic mixture of *cis*,*cis*-bisalcohol) as a colourless oil (44 mg, 86%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 5.92–5.82 (m, 2H), 5.63–5.55 (m, 2H), 3.97–3.90 (m, 2H), 2.94 (d, *J* = 4.3 Hz, 2H), 2.85 (dd, *J* = 15.0 Hz, *J* = 6.4 Hz, 2H), 2.44–2.34 (m, 2H), 2.00–1.91 (m, 2H), 1.75–1.61 (m, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 132.7 (2C), 128.7 (2C), 79.2 (2C), 42.9, 31.7 (2C), 30.1 (2C), 22.4 (2C); **IR (neat):** $\tilde{\nu}$ = 3292 (br), 3030, 2929, 2847, 1654, 1440, 1343, 1285, 1249, 1191, 1134, 1098, 1079, 1059, 1012, 951, 910, 896, 875, 832, 769, 727, 679 cm^{-1}; **MS (CI):** m/z (rel. intensity): 226 (26), 209 (25), 208 (20), 207 (15), 193 (11), 192 (16), 191 (100), 173 (50); HRMS (CI) calcd for ($C_{13}H_{20}O_2$ + NH_4):

226.1802; found: 226.1803; **elemental analysis** (%) calcd for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 73.18, H 9.54.

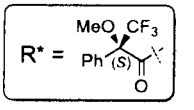
Compound 3.16



(*S,R,R,R*)-**3.16**



(*S,S,S,S*)-**3.16**



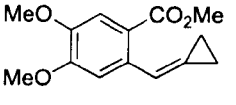
Under N_2, triethylamine (0.39 mL, 2.784 mmol) followed by DMAP (34 mg, 0.278 mmol) were added to a solution of *cis,cis*-**3.15** (116 mg, 0.557 mmol) in CH_2Cl_2 (3.4 mL). Then a solution of (*R*) Mosher's acid chloride (155 mg, 0.613 mmol) in CH_2Cl_2 (3.4 mL) was added. The resulting mixture was stirred for 7 hours at room temperature. The mixture was quenched with water (6 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. Several flash chromatographies (PE/EtOAc, 10:1 to 6:1) allowed for the separation of (*S,R,R,R*)-**3.16** and (*S,S,S,S*)-**3.16**. Overall, 212 mg of **3.16** were isolated (90% yield). <u>(*S,R,R,R*)-**3.16**:</u> **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.59–7.53 (m, 2H), 7.43–7.35 (m, 3H), 5.93–5.81 (m, 2H), 5.62–5.54 (m, 1H), 5.52–5.44 (m, 1H), 5.39–5.31 (m, 1H), 3.57 (s, 4H), 2.51–2.28 (m, 4H), 2.02–1.76 (m, 6H), 1.70 (dd, *J* = 14.1 Hz, *J* = 8.5 Hz, 1H), 1.65–1.57 (m, 1H), 1.50–1.42 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 165.8, 133.7, 132.5, 132.2, 129.7, 128.44 (2C), 128.3, 127.5, 127.1 (2C), 123.3 (q, 287.1 Hz), 84.2 (q, 27.5 Hz), 82.6, 73.4, 55.6, 42.5, 29.1, 29.0, 28.3, 26.6, 21.7, 21.0; **IR (neat):** $\tilde{\nu}$ = 3570 (br), 3026, 2935, 2854, 1743, 1654, 1497, 1451, 1398, 1363, 1328, 1268, 1166, 1121, 1081, 1065, 1008, 991, 964, 910, 876, 766, 726, 718, 697, 662 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 447 (100); HRMS (ES+) calcd for $(C_{23}H_{27}F_3O_4 + Na)^+$: 447.1759; found: 447.1767; (*S,R,R,R*)-**3.16**:

= –86° (*c* 0.200, $CHCl_3$); (*S,S,S,S*)-**3.16**: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.61–7.49 (m, 2H), 7.44–7.35 (m, 3H), 5.95–5.80 (m, 2H), 5.61–5.47 (m, 2H), 5.35 (d, *J* = 5.7 Hz, 1H), 3.67 (t, *J* = 5.4 Hz, 1H), 3.50 (s, 3H), 2.53 (dd, *J* = 14.5 Hz, *J* = 5.7 Hz, 1H), 2.48 (dd, *J* = 14.8 Hz, *J* = 5.9 Hz, 1H), 2.45–2.38 (m, 1H), 2.23–2.13 (m, 1H), 2.12 (d, *J* = 5.4 Hz, 1H), 1.93–1.80 (m, 4H), 1.78–1.65 (m, 3H), 1.58–1.49 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 165.8, 133.7, 132.7, 131.7, 129.7, 128.5 (2C), 128.3, 127.54, 127.46 (2C), 123.4 (q, 287.1 Hz), 83.1 (q, 27.1 Hz), 82.8, 74.3, 55.4, 42.5, 29.4, 29.2, 28.8, 26.2, 21.5, 21.3; **IR (neat):** $\tilde{\nu}$ = 3590, 3027, 2957, 2928, 2853, 1732, 1651, 1489, 1451, 1381, 1361, 1324, 1273, 1238, 1216, 1200,1166, 1121, 1096, 1079, 1057, 1040, 1018, 1008, 995, 937, 916, 879, 861, 816, 776, 765, 730, 717, 697, 663 cm^{-1}; **MS (ES+):** m/z (rel. intensity): 447 (100); HRMS (ES+) calcd for $(C_{23}H_{27}F_3O_4 + Na)^+$: 447.1759; found: 447.1756; (*S,S,S,S*)-**3.16**: = +36° (*c* 0.215, $CHCl_3$).

Compound 3.17

See compound **2.27**

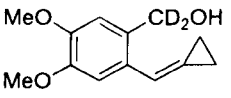
Compound 3.18



Under N_2, a solution of *t*-butyllithium in hexanes (2.5mL, 3.69 mmol) was added to a cooled solution (–78 °C) of bromide **2.47** (900 mg, 3.36 mmol) in THF (36 mL). The mixture was stirred at –78 °C during 3.5 hours then methyl cyanoformate (0.7 mL, 8.40 mmol) was added and the stirring at –78 °C was continued during 2.5 hours. The mixture was quenched with few drops of methanol and allowed to warm at room

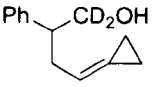
temperature before being diluted with water (30 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 9:1) afforded compound **3.18** as a yellow solid (475 mg, 57%). m.p.: 55–57 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.26–7.23 (m, 1H), 7.41 (s, 1H), 7.40 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 1.42–1.36 (m, 2H), 1.24–1.19 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 167.8, 151.7, 147.2, 134.2, 125.4, 120.0, 116.3, 112.7, 109.4, 55.9, 55.7, 51.9, 4.0, 1.1; **IR (neat):** $\tilde{\nu}$ = 2953, 2848, 1706, 1600, 1566, 1511, 1436, 1238, 1199, 1148, 999, 869, 776 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 249 (58); HRMS (CI) calcd for ($C_{14}H_{16}O_4$ + H): 249.11268; found: 249.11329; **elemental analysis** (%) calcd for $C_{14}H_{16}O_4$: C 67.73, H 6.50; found: C 67.70, H 6.52.

Compound 3.19D



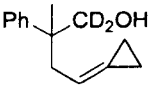
This compound was prepared from **3.18** (465 mg, 1.873 mmol) according to the procedure described for the preparation of **2.52**, using lithium aluminium deuteride. White solid (383 mg, 92%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36 (s, 1H), 7.01–6.98 (m, 1H), 6.86 (s, 1H), 3.88 (s, 6H), 1.55 (s, 1H), 1.43–1.37 (m, 2H), 1.21–1.16 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 148.5, 147.9, 129.7, 129.1, 124.0, 114.2, 111.7, 109.0, 55.8, 55.7, 4.0, 0.8, (CD_2 not visible); **IR (neat):** $\tilde{\nu}$ = 3429, 3002, 2932, 2832, 1603, 1513, 1454, 1367, 1318, 1264, 1204, 1124, 1090, 1032, 960, 862, 746 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 207 (65), 205 (100); HRMS (CI) calcd for ($C_{13}H_{14}D_2O_3$ + H): 223.13032; found: 223.13042.

Compound 3.20D



This compound was prepared from **2.51** (97 mg, 0.448 mmol) according to the procedure described for the preparation of **2.52**, using lithium aluminium deuteride. Colourless oil (81 mg, 95%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.33–7.28 (m, 2H), 7.23–7.19 (m, 3H), 5.72–5.65 (m, 1H), 2.92 (d, *J* = 7.3 Hz, 1H), 2.62–2.54 (m, 1H), 2.52–2.44 (m, 1H), 1.43 (s, 1H), 1.04–0.83 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 142.2, 128.4 (2C), 128.0 (2C), 126.5, 123.2, 115.6, 66.1 (quint, *J* = 21.7 Hz), 48.2, 34.5, 2.4, 1.7; **IR (neat):** $\tilde{\nu}$ = 3345 (br), 3051, 3029, 2979, 2918, 2847, 2200, 2087, 1602, 1494, 1452, 1410, 1305, 1247, 1125, 1100, 966, 929, 757, 699 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 210 (22), 208 (100); HRMS (CI) calcd for ($C_{13}H_{14}D_2O$ + NH_4): 208.16704; found: 208.16771.

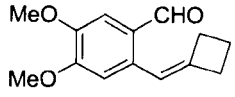
Compound 3.21D



This compound was prepared from **2.64** (166 mg, 0.72 mmol) according to the procedure described for the preparation of **2.52**, using lithium aluminium deuteride. Colourless oil (135 mg, 92%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.38 (d, *J* = 7.7 Hz, 2H), 7.33 (m, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.63–5.56 (m, 1H), 2.64 (dd, *J* = 13.8 Hz, *J* = 6.8 Hz, 1H), 2.49 (dd, *J* = 13.8 Hz, *J* = 7.8 Hz, 1H), 1.73–1.53 (s, 1H), 1.34 (s, 3H), 1.06–0.99 (m, 2H), 0.98–0.87 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 145.0, 128.4 (2C), 126.8 (2C), 126.2, 124.5, 114.0, 71.0 (quint, *J* = 21.3 Hz), 44.0, 40.9, 21.9, 2.9, 1.8; **IR (neat):** $\tilde{\nu}$ = 3372 (br), 3088, 3054, 2978, 2927, 2201, 2083, 2601, 2497, 1445, 1410, 1375, 1282, 1153, 1108, 1060, 1031, 974, 939, 757, 697 cm^{-}

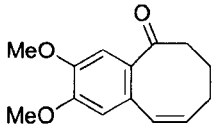
[1]; **MS (ES+):** m/z (rel. intensity): 227 (100); HRMS (ES+) calcd for ($C_{14}H_{16}D_2O$ + Na)$^+$: 227.1381; found: 227.1373.

Compound 4.36



4.36 was prepared by undergraduate student James Dawick. m.p.: 98–101 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 10.14 (s, 1H), 7.30 (s, 1H), 6.71 (s, 1H), 6.70–6.68 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.89–2.81 (m, 4H), 2.10–2.00 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 190.2, 153.4, 148.3, 147.6, 135.8, 125.8, 115.6, 110.1, 109.7, 55.9 (2C), 32.6, 32.4, 17.9; **IR (neat):** $\tilde{\nu}$ = 3013, 2978, 2938, 2907, 2827, 2609, 2027, 1738, 1667, 1654, 1592, 1509, 1462, 1445, 1365, 1336, 1258, 1212, 1186, 1101, 1032, 1001, 921, 897, 868, 837, 736, 704 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 233 (100), 219 (12), 217 (8); HRMS (CI) calcd for ($C_{14}H_{16}O_3$ + H): 233.11777; found: 233.11817; **elemental analysis** (%) calcd for $C_{14}H_{16}O_3$: C 72.39, H 6.94; found: C 72.27, H 6.98.

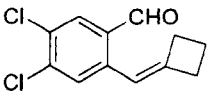
Compound 4.37



Starting from aldehyde **4.36** (30 mg, 0.129 mmol). **4.37** (25.5 mg, 85%) was isolated as white solid. m.p.: 68–70 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.55 (s, 1H), 6.77 (d, *J* = 11.6 Hz, 1H), 6.64 (s, 1H), 6.04 (dt, *J* = 11.6 Hz, *J* = 8.2 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.91–2.77 (m, 2H), 2.15–2.00 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 204.6, 152.0, 148.0, 132.2, 131.7, 131.2, 129.7, 113.0, 111.2, 55.9 (2C), 37.6,

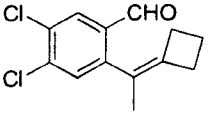
31.7, 25.5; **IR (neat):** $\tilde{\nu}$ = 3080, 2921, 2852, 2624, 1723, 1651, 1591, 1561, 1512, 1443, 1362, 1332, 1303, 1258, 1215, 1156, 1115, 1062, 1046, 999, 971, 918, 890, 862, 852, 827, 797, 771, 758, 728, 697, 665 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 233 (100), 217 (17); HRMS (CI) calcd for ($C_{14}H_{16}O_3$ + H): 233.11777; found: 233.11795; **elemental analysis** (%) calcd for $C_{14}H_{16}O_3$: C 72.39, H 6.94; found: C 72.44, H 6.96.

Compound 4.38



4.38 was prepared by undergraduate student James Dawick. m.p.: 81–83 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 10.14 (d, *J* = 1.8 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.38 (s, 1H), 6.73–6.70 (m, 1H), 2.92–2.84 (m, 4H), 2.13–2.05 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 190.0, 152.1, 139.3 (2C), 138.0, 131.7, 130.6, 130.2, 114.4, 33.0, 32.5, 17.9; **IR (neat):** $\tilde{\nu}$ = 3059, 2987, 2954, 2921, 2897, 2801, 1837, 1679, 1650, 1572, 1537, 1485, 1459, 1417, 1370, 1276, 1243, 1192, 1155, 1135, 1083, 1037, 991, 970, 942, 922, 871, 839, 738, 686, 670 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 245 (12), 244 (16), 243 (65), 242 (27), 241 (100); HRMS (CI) calcd for ($C_{12}H_{10}Cl_2O$ + H): 241.01870; found: 241.01896; **elemental analysis** (%) calcd for $C_{12}H_{10}Cl_2O$: C 59.78, H 4.18; found: C 59.84, H 4.24.

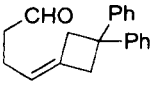
Compound 4.39



4.39 was prepared by undergraduate student James Dawick. m.p.: 43–45 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.94 (s, 1H), 7.90 (s, 1H), 7.34 (s, 1H), 2.81–2.74 (m,

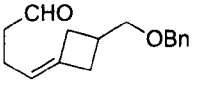
2H), 2.36–2.29 (m, 2H), 1.97–1.85 (m, 2H), 1.88 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 190.4, 145.3, 143.2, 138.1, 132.6, 131.6, 130.9, 128.9, 121.3, 30.4, 30.1, 19.1, 16.0; **IR (neat):** $\tilde{\nu}$ = 2981, 2957, 2911, 2851, 2737, 1684, 1571, 1462, 1436, 1359, 1283, 1265, 1234, 1177, 1045, 948, 928, 893, 880 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 274 (23), 272 (35), 257 (64), 255 (100), 228 (11), 226 (16); HRMS (CI) calcd for ($C_{13}H_{12}Cl_2O$ + H): 255.03435; found: 255.03476.

Compound 4.40



This compound was prepared from **4.73** (220 mg, 0.79 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (118 mg, 54%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.79 (s, 1H), 7.36–7.29 (m, 8H), 7.24–7.18 (m, 2H), 5.30–5.23 (m, 1H), 3.45 (s, 4H), 2.52–2.49 (m, 2H), 2.35–2.31 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.2, 149.1, 135.2 (2C), 128.2 (4C), 126.4 (4C), 125.7 (2C), 119.5, 46.9, 45.2, 43.59, 43.56, 21.1; **IR (neat):** $\tilde{\nu}$ = 3057, 3024, 2953, 2914, 2821, 2721, 1722, 1598, 1493, 1446, 754, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 294 (100), 277 (3), 276 (6); HRMS (CI) calcd for ($C_{20}H_{20}O$ + NH_4): 294.18579; found: 294.18639; **elemental analysis** (%) calcd for $C_{20}H_{20}O$: C 86.92, H 7.29; found: C 86.11, H 7.35.

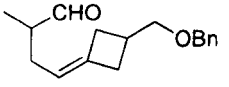
Compound 4.41



Under N_2, DiBAl-H (1M in hexane, 0.27 mL, 0.27 mmol) was added under N_2 to a solution of **4.80** (60 mg, 0.21 mmol) in toluene (0.5 mL) at –90 °C. The mixture was

stirred at –90 °C during 50 minutes then was quenched with EtOAc (0.3 mL). The mixture was allowed to warm at room temperature and a 1M solution of citric acid (0.75 mL) was added. The resulting mixture was extracted with EtOAc (3 × 3 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 30:1) afforded aldehyde compound **4.41** as a colourless oil (40 mg, 78%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.72 (s, 1H), 7.35–7.24 (m, 5H), 5.11–5.04 (m, 1H), 4.51 (s, 2H), 3.26 (d, *J* = 7.2 Hz, 2H), 2.78–2.67 (m, 2H), 2.62–2.52 (m, 1H), 2.44–2.40 (m, 2H), 2.38–2.30 (m, 2H), 2.21–2.19 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.5, 138.5, 138.3, 128.3 (2C), 127.6, 127.5 (2C), 119.3, 74.3, 73.0, 43.6, 33.7, 32.1, 29.9, 20.9; **IR (neat):** $\tilde{\nu}$ = 3031, 2913, 2851, 2719, 1723, 1496, 1454, 1411, 1464, 1322, 1256, 1204, 1092, 1028, 963, 936, 908, 847, 736, 697 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 262 (100), 245 (26), 227 (12); HRMS (CI) calcd for ($C_{16}H_{20}O_2$ + H): 245.15415; found: 245.15338; **elemental analysis** (%) calcd for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 78.57, H 8.28.

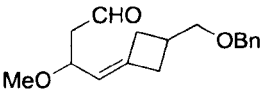
Compound 4.42



This compound was prepared from **4.83** (150 mg, 0.58 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (120 mg, 80%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.60 (s, 1H), 7.37–7.24 (m, 5H), 5.09–5.05 (m, 1H), 4.51 (s, 2H), 3.46 (d, *J* = 6.9 Hz, 2H), 2.77–2.68 (m, 2H), 2.62–2.53 (m, 1H), 2.39–2.29 (m, 3H), 2.26–2.18 (m, 1H), 2.03–1.95 (m, 1H), 1.053 (d, *J* = 7.1 Hz, 3H), [*1.047 (d, J = 7.0 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 205.0, 139.2, 138.4, 128.3 (2C), 127.6, 127.5 (2C), 117.6, 74.25,

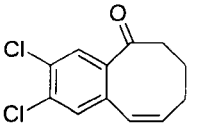
[*74.24*], 72.93, [*72.92*], 46.4, 33.7, 32.2, 29.82, [*29.80*], 29.0, 12.91, [*12.89*]; **IR (neat):** $\tilde{\nu}$ = 3058, 3028, 2947, 2931, 2912, 2851, 2712, 1726, 1496, 1454, 1413, 1393, 1364, 1320, 1305, 1254, 1205, 1098, 1029, 926, 911, 737, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 276 (100), 259 (24), 258 (4), 241 (9), 223 (6); HRMS (CI) calcd for ($C_{17}H_{22}O_2$ + H): 259.16980; found: 259.16891; **elemental analysis** (%) calcd for $C_{17}H_{22}O_2$: C 79.03, H 8.58; found: C 78.89, H 8.64.

Compound 4.43



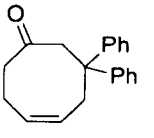
This compound was prepared from **4.86** (39 mg, 0.123 mmol) according to the procedure described for the preparation of **4.41**. Colourless oil (28 mg, 82%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.73 (s, 1H), 7.36–7.25 (m, 5H), 5.07–5.00 (m, 1H), 4.51–4.46 (m, 2H), 4.13–4.04 (m, 1H), 3.53–3.43 (m, 2H), 3.23 (s, 3H), [*3.18 (s, 3H)*], 2.88–2.73 (m, 2H), 2.67–2.57 (m, 2H), 2.50–2.38 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 201.2, 143.5, [*143.2*], 138.4, 128.4 (2C), 127.7 (2C), 127.6, 120.4, [*120.2*], 74.0, [*73.8*], 73.05, [*73.02*], 72.98, [*72.95*], 55.80, [*55.77*], 49.2, 33.9, [*33.8*], 32.8, [*32.6*], 30.4, [*30.1*]; **IR (neat):** $\tilde{\nu}$ = 3058, 3028, 2918, 2850, 2724, 1724, 1649, 1494, 1454, 1408, 1363, 1257, 1204, 1181, 1091, 1028, 936, 908, 883, 860, 737, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 292 (10), 260 (41), 243 (100); HRMS (CI) calcd for ($C_{17}H_{22}O_3$ + NH_4): 292.19127; found: 292.19117; **elemental analysis** (%) calcd for $C_{17}H_{22}O_3$: C 74.42, H 8.08; found: C 73.93, H 8.35.

Compound 4.44



Starting from aldehyde **4.38** (251 mg, 1.04 mmol). **4.44** (231 mg, 92%) was isolated as white solid. m.p.: 74–75 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.03 (s, 1H), 7.30 (s, 1H), 6.70 (d, *J* = 11.6 Hz, 1H), 6.12 (dt, *J* = 11.6 Hz, *J* = 8.1 Hz, 1H), 2.85–2.78 (m, 2H), 2.13–2.03 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 203.7, 136.5, 135.8, 135.4, 134.1, 133.1, 131.9, 131.3, 130.4, 37.2, 30.9, 25.4; **IR (neat):** $\tilde{\nu}$ = 3084, 3062, 3013, 2933, 2866, 1820, 1713, 1663, 1575, 1530, 1465, 1448, 1347, 1303, 1245, 1213, 1181, 1163, 1145, 1130, 1060, 1040, 990, 977, 953, 917, 889, 861, 807, 791, 756, 718, 679, 652 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 262 (15), 260 (70), 259 (11), 258 (100), 245 (11), 244 (13), 243 (60), 242 (25), 241 (91), 226 (17), 224 (37), 214 (34), 212 (49); HRMS (CI) calcd for ($C_{12}H_{10}Cl_2O$ + H): 241.01870; found: 241.01809; **elemental analysis** (%) calcd for $C_{12}H_{10}Cl_2O$: C 59.78, H 4.18; found: C 59.43, H 4.14.

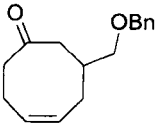
Compound 4.46



Starting from aldehyde **4.40** (30 mg, 0.109 mmol). **4.46** (24 mg, 79%) was isolated as white solid. m.p.: 104–106 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.35–7.28 (m, 4H), 7.26–7.19 (m, 6H), 6.01–5.97 (m, 1H), 5.50–5.45 (m, 1H), 3.35 (s, 2H), 3.00 (d, *J* = 9.1 Hz, 2H), 2.56–2.51 (m, 2H), 2.51–2.44 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 211.5, 147.1 (2C), 130.4, 129.1, 128.1 (4C), 127.3 (4C), 126.0 (2C),

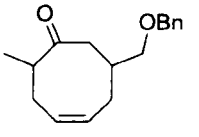
119.5, 49.4, 47.2, 36.5, 23.4; **IR (neat):** $\tilde{\nu}$ = 3084, 3048, 3023, 2987, 2943, 2922, 2881, 2851, 1704, 1646, 1597, 1495, 1470, 1444, 1340, 1327, 1299, 1229, 1201, 1190, 1151, 1112, 1080, 1057, 1025, 999, 925, 905, 824, 804, 774, 756, 740, 716, 694 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 294 (100), 277 (28), 259 (16); HRMS (CI) calcd for ($C_{20}H_{20}O$ + H): 277.15924; found: 277.15988; **elemental analysis** (%) calcd for $C_{20}H_{20}O$: C 86.92, H 7.29; found: C 86.10, H 7.69.

Compound 4.47



Starting from aldehyde **4.41** (20 mg, 0.0819 mmol). **4.47** (14 mg, 69%) was isolated as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.25 (m, 5H), 5.79–5.71 (m, 1H), 5.70–5.61 (m, 1H), 4.50 (s, 2H), 3.33 (dd, *J* = 6.4 Hz, *J* = 2.8 Hz, 2H), 2.75–2.62 (m, 1H), 2.61–2.51 (m, 2H), 2.44–2.24 (m, 2H), 2.27–2.13 (m, 3H), 2.04–1.92 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 213.5, 138.3, 130.9, 129.4, 128.4 (2C), 127.6 (3C), 74.1, 72.9, 47.1, 43.3, 36.0, 29.4, 21.9; **IR (neat):** $\tilde{\nu}$ = 3020, 2924, 2855, 1702, 1610, 1496, 1454, 1364, 1257, 1213, 1099, 1028, 735, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 262 (49), 245 (100); HRMS (CI) calcd for ($C_{16}H_{20}O$ + H): 245.15415; found: 245.15381.

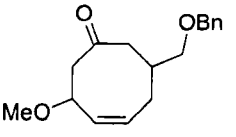
Compound 4.48



Starting from aldehyde **4.42** (24 mg, 0.0929 mmol). **4.48** (18 mg, 75%) was isolated as colourless oil, equimolar mixture of diastereomers. Diastereomer a: **^{1}H NMR (500**

MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5H), 5.82–5.732 (m, 1H), 5.727–5.61 (m, 1H), 4.49 (s, 2H), 3.33 (d, *J* = 6.3 Hz, 2H), 2.82–2.73 (m, 2H), 2.63–2.51 (m, 1H), 2.27 (dd, *J* = 12.0 Hz, *J* = 3.2 Hz, 1H), 2.24–2.09 (m, 3H), 2.09–2.01 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.4, 138.3, 129.8, 129.5, 128.3 (2C), 127.6, 127.5 (2C), 74.2, 72.8, 50.3, 40.4, 36.2, 29.4, 29.2, 14.3; Diastereomer b: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.35–7.25 (m, 5H), 5.727–5.61 (m, 2H), 4.50 (s, 2H), 3.42–3.35 (m, 2H), 2.63–2.51 (m, 2H), 2.47–2.38 (m, 1H), 2.31 (dd, *J* = 11.8 Hz, *J* = 3.0 Hz, 1H), 2.24–2.09 (m, 3H), 1.99–1.91 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 215.8, 138.3, 130.1, 129.7, 128.3 (2C), 127.6, 127.5 (2C), 74.4, 72.9, 51.5, 43.3, 36.9, 30.3, 29.7, 16.3; **IR (neat):** $\tilde{\nu}$ = 3021, 2960, 2930, 2857, 1703, 1455, 1364, 1258, 1206, 1103, 1073, 1028, 740, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 276 (26), 259 (100), 151 (6); HRMS (CI) calcd for ($C_{17}H_{22}O_2$ + H): 259.16980; found: 259.16989; **elemental analysis** (%) calcd for $C_{17}H_{22}O_2$: C 79.03, H 8.58; found: C 78.89, H 8.63.

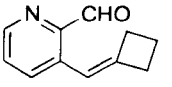
Compound 4.49



Starting from aldehyde **4.43** (12 mg, 0.0437 mmol). **4.49** (9 mg, 75%) was isolated as colourless oil, equimolar mixture of diastereomers. Diastereomer a: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.25 (m, 5H), 5.79–5.72 (m, 1H), 5.66–5.58 (m, 1H), 4.26–4.19 (m, 1H), 4.54–4.44 (m, 2H), 3.41–3.27 (m, 2H), 3.33 (s, 3H), 3.03 (dd, *J* = 12.3 Hz, *J* = 5.1 Hz, 1H), 2.57 (t, *J* = 10.9 Hz, 1H), 2.53–2.45 (m, 1H), 2.44–2.39 (m, 1H), 2.35–2.25 (m, 1H), 2.18–2.16 (m, 1H), 2.01–1.91 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 210.1, 138.3, 135.3, 129.9, 128.4 (2C), 127.7, 127.62 (2C), 74.6, 74.1,

73.0, 56.7, 53.6, 44.8, 38.0, 31.0; Diastereomer b: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.25 (m, 5H), 5.79–5.72 (m, 1H), 5.66–5.58 (m, 1H), 4.68–4.61 (m, 1H), 4.54–4.44 (m, 2H), 3.41–3.27 (m, 2H), 3.32 (s, 3H), 2.83 (dd, *J* = 11.0 Hz, *J* = 4.1 Hz, 1H), 2.67 (t, *J* = 11.0 Hz, 1H), 2.53–2.45 (m, 1H), 2.44–2.39 (m, 1H), 2.35–2.25 (m, 1H), 2.24–2.20 (m, 1H), 2.16–2.08 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 209.5, 138.2, 135.0, 128.4 (2C), 127.61 (2C), 127.57, 127.4, 73.0, 72.8, 72.1, 56.6, 53.6, 42.9, 36.0, 28.1; **IR (neat):** $\tilde{\nu}$ = 3027, 2925, 2853, 1703, 1454 1365, 1271, 1205, 1094, 739, 699 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 297 (100); HRMS (ES+) calcd for $(C_{17}H_{22}O_3 + Na)^+$: 297.1467; found: 297.1468.

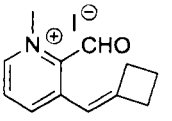
Compound 4.50



Under N_2, a solution of *n*-butyllithium in hexanes (214 μL, 0.534 mmol) was added to a solution of **4.88** (114 mg, 0.509 mmol) in THF (32 mL) at –100 °C. The mixture was stirred at –100 °C during 2 hours then DMF (197 μL, 2.544 mmol) was added and the stirring was continued for 1 hour at –100 °C. The mixture was quenched with few drops of methanol at –100 °C and allowed to warm at room temperature. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/Et_2O, 10:1 to 8:1) afforded compound **4.50** as a colourless oil (70 mg, 79%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 10.12 (s, 1H), 8.53 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 8.1 Hz, *J* = 4.5 Hz, 1H), 7.13–7.09 (m, 1H), 3.01–2.86 (m, 4H), 2.07 (quint, *J* = 7.9 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 195.0, 151.8, 147.4, 147.0, 135.7, 134.7, 126.3,

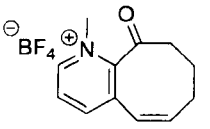
115.3, 33.1, 32.9, 18.1; **IR (neat):** $\tilde{\nu}$ = 3058, 3033, 2955, 2918, 2813, 2714, 1708, 1660, 1557, 1455, 1420, 1371, 1212, 1169, 1120, 1060, 884, 810, 788, 749, 665 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 176 (20), 175 (21), 174 (100), 173 (12), 162 (54), 160 (81), 148 (32), 146 (44).

Compound 4.52



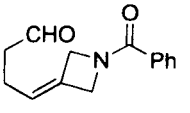
Under N_2, in a Teflon-screw Schlenk flask, methyl iodide (70 µL, 1.127 mmol) was added to a solution of **4.50** (65 mg, 0.376 mmol) in acetone (0.3 mL). The Schlenk flask was sealed and the mixture stirred under reflux during 60 hours. At room temperature, the mixture was filtered and the solid rinsed with pentane to afford compound **4.52** as a yellow solid (55 mg, 46%). m.p.: 110–112 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 10.50 (s, 1H), 9.11 (d, *J* = 6.0 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.09 (dd, *J* = 7.9 Hz, *J* = 6.0 Hz, 1H), 6.54–6.49 (m, 1H), 4.58 (s, 3H), 2.98–2.91 (m, 2H), 2.89–2.82 (m, 2H), 2.15 (quint, *J* = 7.9 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 182.6, 159.4, 145.53, 145.48, 142.6, 139.8, 129.0, 111.6, 49.0, 33.5, 32.6, 17.6; **IR (neat):** $\tilde{\nu}$ = 3013, 2989, 2911, 2901, 1706, 1654, 1598, 1585, 1466, 1444, 1394, 1284, 1246, 1201, 1165, 1130, 1092, 926, 867, 819, 751, 693 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 220 (100); HRMS (ES+) calcd for ($C_{12}H_{14}NO$ + CH_3OH): 220.1338; found: 220.1329.

Compound 4.54



Under N_2, $AgBF_4$ (10 mg, 0.051 mmol) was added to a solution of **4.52** (16 mg, 0.051 mmol) in acetone (0.5 mL). The resulting suspension was stirred during 50 minutes at room temperature. The supernatant was directly submitted to rhodium-catalysis without further purification. The same procedure for counteranion exchange was used with 1,2-DCE as solvent. In both cases, clean compound **4.54** was obtained by triturating the crude material in pentane at 0 °C. **4.54** (10 mg, 75%) was isolated as a white solid. m.p.: 83–86 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.77 (d, J = 6.1 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H) 7.99 (dd, J = 8.0 Hz, J = 6.2 Hz, 1H), 6.44 (d, J = 11.7 Hz, 1H), 6.11 (dt, J = 11.6 Hz, J = 7.9 Hz, 1H), 4.26 (s, 3H), 3.04 (t, J = 6.8 Hz, 2H), 2.41–2.34 (m, 2H), 2.00–1.92 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.3, 149.8, 146.3, 145.9, 138.2, 133.9, 127.6, 122.3, 46.3, 41.8, 27.3, 23.2; **IR (neat):** $\tilde{\nu}$ = 3124, 2923, 2861, 1710, 1611, 1487, 1454, 1438, 1318, 1290, 1274, 1228, 1174, 1036, 956, 913, 878, 785, 750, 722, 702 cm^{-1}; **elemental analysis** (%) calcd for $C_{12}H_{14}BF_4NO$: C 52.40, H 5.13, N 5.09; found: C 52.34, H 5.09, N 5.05.

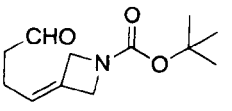
Compound 4.55



4.55 was prepared by Dr. Christophe Aïssa. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.72 (m, 1H), [*9.71 (m, 1H)*], 7.64–7.56 (m, 2H), 7.45–7.33 (m, 3H), 5.36–5.24 (m, 1H), 4.77 (br s, 1H), 4.73–4.66 (m, 2H), 4.63 (br s, 1H), 2.54–2.45 (m, 2H), 2.27–2.19 (m, 1H), 2.18–2.11 (m, 1H);[7] **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 201.1, [*201.0*], 170.4,

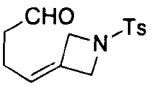
133.1, 131.0 (2C), 128.8, [*128.7*], 128.3 (2C), 127.7, 120.8, 61.1, [*60.3*], 57.1, [*56.2*], 42.8, 21.1 (2C);[7] **IR (neat):** $\tilde{\nu}$ = 2925, 2859, 2726, 1720, 1627, 1574, 1448, 1400, 1353, 795, 708 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 252 (100); HRMS (ES+) calcd for $(C_{20}H_{31}NO_2Si + Na)^+$: 252.1000; found: 252.1010.

Compound 4.56



4.56 was prepared by Dr. Christophe Aïssa. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.76–9.75 (m, 1H), 5.29–5.22 (m, 1H), 4.48–4.44 (m, 2H), 4.42–4.37 (m, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 2.24–2.17 (m, 2H), 1.42 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 201.2, 156.2, 129.3, 120.1, 79.4, 61.0, 42.9, 28.2 (3C), 21.1 (2C); **IR (neat):** $\tilde{\nu}$ = 2977, 2932, 2866, 2723, 1724, 1694, 1479, 1452, 1388, 1365, 1278, 1253, 1181, 1152, 1117, 940, 860, 772 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 226 (8), 187 (11), 126 (100); HRMS (CI) calcd for $(C_{12}H_{19}NO_3 + H)$: 226.1438; found: 226.1436.

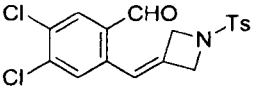
Compound 4.57



4.57 was prepared by Dr. Christophe Aïssa. m.p.: 52–56 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.69 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.21–5.15 (m, 1H), 4.38–4.35 (m, 2H), 4.32–4.29 (m, 2H), 2.48–2.41 (m, 2H), 2.44 (s, 3H), 2.10 (q, *J* = 7.2 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 200.9, 144.1, 131.6, 129.8 (2C), 128.3 (2C), 126.5, 121.4, 58.9, 58.1, 42.7, 21.5, 20.8; **IR (neat):** $\tilde{\nu}$ = 2901, 2845, 2739, 1709, 1595, 1450, 1434, 1403, 1387, 1331, 1303, 1271, 1159,

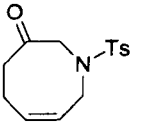
1148, 1099, 1067, 1033, 1023, 940, 816, 668 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 334 (100); HRMS (ES+) calcd for $(C_{14}H_{17}NO_3 + Na)^+$: 302.0827; found: 302.0826; **elemental analysis** (%) calcd for $C_{14}H_{17}NO_3$: C 60.19, H 6.13, N 5.01; found: C 59.78, H 6.09, N 4.97.

Compound 4.58



This compound was prepared from **4.99** (125 mg, 0.314 mmol) according to the procedure described for the preparation of **2.3**. White solid (96 mg, 77%). m.p.: 140–143 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.99 (s, 1H), 7.83 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 7.05–7.01 (m, 1H), 4.62–4.58 (m, 2H), 4.57–4.54 (m, 2H), 2.44 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 189.8, 144.6, 138.5, 136.0, 134.2, 134.0, 132.3, 131.9, 131.7, 130.0 (2C), 129.7, 129.5, 128.4 (2C), 60.0, 59.4, 21.6; **IR (neat):** $\tilde{\nu}$ = 1694, 1596, 1537, 1469, 1451, 1433, 1341, 1209, 1155, 1088, 1074, 1018, 958, 935, 916, 875, 819 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 418 (100); HRMS (ES+) calcd for $(C_{18}H_{15}Cl_2NO_3S + Na)^+$: 418.0047; found: 418.0035.

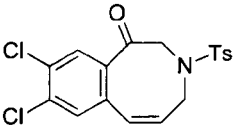
Compound 4.59



Starting from aldehyde **4.57** (20 mg, 0.0716 mmol). **4.59** (17 mg, 85%) was isolated as white solid. m.p.: 102–105 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.63 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.95–5.84 (m, 1H), 5.36 (dt, *J* = 11.0, 4.3 Hz, 1H),

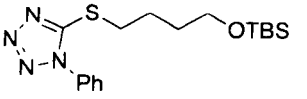
3.85–3.81 (m, 2H), 3.68 (s, 2H), 2.88–2.79 (m, 4H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 209.7, 144.0, 134.6, 132.9, 130.0 (2C), 127.1 (2C), 123.6, 58.4, 48.9, 41.8, 22.1, 21.6; **IR (neat):** $\tilde{\nu}$ = 3026, 2955, 2918, 1702, 1599, 1452, 1331, 1254, 1241, 1150, 1096, 922, 825, 812 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 302 (100); HRMS (ES+) calcd for $(C_{14}H_{17}NO_3S + Na)^+$: 302.0827; found: 302.0818; **elemental analysis** (%) calcd for $C_{14}H_{17}NO_3S$: C 60.19, H 6.13, N 5.01; found: C 60.25, H 6.17, N 4.97.

Compound 4.60



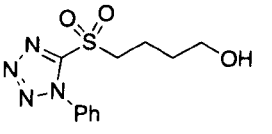
Starting from aldehyde **4.58** (20 mg, 0.0505 mmol). **4.60** (14 mg, 70%) was isolated as white solid. m.p.: 106–110 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.54 (d, *J* = 8.5 Hz, 2H), 7.49 (s, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.18 (s, 1H), 6.59 (d, *J* = 12.0 Hz, 1H), 5.83 (dt, *J* = 11.9 Hz, 5.9 Hz, 1H), 4.11 (s, 2H), 3.96 (dd, *J* = 5.7 Hz, 1.4 Hz, 2H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 199.4, 144.1, 136.2, 135.8, 135.1, 133.9, 132.4, 131.4, 130.8, 130.5, 129.8 (2C), 127.3 (2C), 126.6, 55.2, 47.3, 21.6; **IR (neat):** $\tilde{\nu}$ = 3087, 3062, 3026, 2920, 2853, 1718, 1598, 1578, 1471, 1432, 1326, 1254, 1239, 1228, 1154, 1094, 899, 870 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 418 (100); HRMS (ES+) calcd for $(C_{18}H_{15}Cl_2NO_3S + Na)^+$: 418.0047; found: 418.0031.

Compound 4.62



Diethyl azodicarboxylate (5.1 mL, 32.3 mmol) was added under N_2 to a solution of triphenylphosphine (8.46 g, 32.3 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (5.75 g, 32.3 mmol) in THF (240 mL) at room temperature. The mixture was cooled at 0 °C and a solution of TBS-monoprotected 1,4-butanediol **4.61** (6.00 g, 29.35 mmol) in THF (5 mL) was added via a syringe. After stirring at room temperature for 2 hours, the mixture was concentrated. Purification by flash chromatography (PE/EtOAc, 30:1 to 20:1 to 15:1) afforded compound **4.62** as a colourless oil (8.89 g, 83%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.57–7.47 (m, 5H), 3.61 (t, *J* = 8.8 Hz, 2H), 3.40 (t, *J* = 7.8 Hz, 2H), 1.91–1.83 (m, 2H), 1.67–1.60 (m, 2H), 0.84 (s, 9H), 0.02 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 154.4, 133.7, 130.0, 129.7 (2C), 123.8 (2C), 62.3, 33.2, 31.5, 25.9 (3C), 25.6, 18.2, –5.4 (2C); **IR (neat):** $\tilde{\nu}$ = 2951, 2928, 2856, 1597, 1499, 1471, 1463, 1387, 1248, 1099, 1014, 834, 760, 694 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 365 (100); HRMS (CI) calcd for ($C_{17}H_{28}N_4OSSi$ + H): 365.18314; found: 365.18243; **elemental analysis** (%) calcd for $C_{17}H_{28}N_4OSSi$: C 56.00, H 7.74, N 15.37; found: C 55.83, H 7.79, N 15.29.

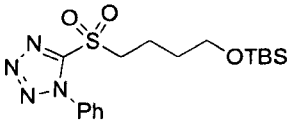
Compound 4.63



Ammonium molybdate tetrahydrate (2.55 g, 2.06 mmol) was dissolved in a 20% aqueous solution of hydrogen peroxide (25 mL, 293 mmol) and added to a solution of **4.62** (8.89 g, 24.38 mmol) in EtOH (125 mL) at 0 °C. After stirring for 15 hours at

room temperature, the mixture was quenched with a saturated solution of $NaHCO_3$ then diluted with water and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 3:1 to 1:2) gave compound **4.63** as a colourless oil (5.05 g, 74%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.66 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, 2H), 7.63–7.56 (m, 3H), 3.81–3.77 (m, 2H), 3.70 (t, *J* = 5.8 Hz, 2H), 2.11–2.03 (m, 2H), 1.78–1.71 (m, 2H), 1.68 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 153.4, 133.0, 131.5, 129.7 (2C), 125.1 (2C), 61.7, 55.7, 30.5, 19.1; **IR (neat):** $\tilde{\nu}$ = 3403, 2927, 1595, 1497, 1460, 1338, 1151, 1055, 763, 735, 689 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 300 (100), 283 (19); HRMS (CI) calcd for ($C_{11}H_{14}N_4O_3S$ + H): 283.08649; found: 283.08574.

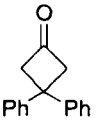
Compound 4.64



DMAP (214 mg, 1.76 mmol), Et_3N (2.6 mL, 18.43 mmol), and TBSCl (2.65 g, 17.55 mmol) were added in this order to a solution of **4.63** (4.95 g, 17.55 mmol) in CH_2Cl_2 (70 mL) at 0 °C under N_2. After stirring for 2 hours at room temperature, the mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 10:1 to 5:1) gave compound **4.64** as a colourless solid (5.40 g, 77%). m.p.: 28–31 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.69–7.64 (m, 2H), 7.62–7.54 (m, 3H), 3.81–3.75 (m, 2H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.07–1.99 (m, 2H), 1.73–1.65 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 153.4, 133.0, 131.4, 129.7 (2C), 125.0 (2C), 62.0,

55.8, 30.8, 25.9 (3C), 19.1, 18.2, –5.4 (2C); **IR (neat):** $\tilde{\nu}$ = 2953, 2929, 2884, 2857, 1596, 1498, 1463, 1340, 1254, 1148, 1099, 834, 761, 687 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 419 (100); HRMS (ES+) calcd for $(C_{17}H_{28}N_4O_3SSi + Na)^+$: 419.1549; found: 419.1536; **elemental analysis** (%) calcd for $C_{17}H_{28}N_4O_3SSi$: C 51.49, H 7.12, N 14.13; found: C 51.47, H 7.13, N 14.17.

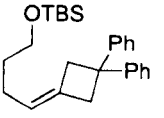
Compound 4.66



Diisopropylbenzylamine (960 mg, 5 mmol) was added to a solution of iodine (630 mg, 2.5 mmol) in 1,2-DCE (40 mL) under N_2. After heating at reflux for 2 hours, a solution of benzophenone **4.65** (460 mg, 2.5 mmol) in 1,2-DCE (5 mL) was added and the mixture was cooled to 0 °C before adding a molar solution of titanium chloride in dichloromethane (7.5 mL, 7.5 mmol) and diisopropylbenzylamine (1.43 g, 7.5 mmol). After stirring at 0 °C for another 10 minutes, the mixture was heated at reflux for 6 hours until completion. A saturated solution of NH_4Cl in methanol (20 mL) was added at room temperature and the resulting mixture was stirred for further 30 minutes. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with a solution of HCl (5M, 10 mL), water (15 mL), and brine (15 mL), and then dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 100:1 to 80:1 to 70:1) gave compound **4.66** as a yellow solid (292 mg, 53%). m.p.: 76–78 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.41–7.35 (m, 8H), 7.20–7.15 (m, 2H), 3.86 (s, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 205.6, 147.6 (2C), 128.7 (4C), 126.7 (4C), 126.4 (2C), 60.5, 41.0 (2C); **IR (neat):** $\tilde{\nu}$ = 3026, 2924, 2854, 1784, 1595, 1492,

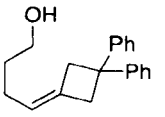
1448, 1372, 1128, 1084, 774, 747, 708 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 223 (100); HRMS (CI) calcd for ($C_{16}H_{14}O$ + H): 223.11229; found: 223.11283; **elemental analysis** (%) calcd for $C_{16}H_{14}O_4$: C 86.45, H 6.35; found: C 86.54, H 6.38.

Compound 4.67



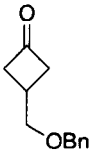
NaHMDS (99 mg, 0.540 mmol) was added under N_2 to a solution of cyclobutanone **4.66** (171 mg, 0.432 mmol) and sulfone **4.64** (80 mg, 0.360 mmol) in THF (4 mL) at –78 °C. The mixture was slowly allowed to warm to room temperature overnight by maintaining the flask dipped in the dry ice bath. The mixture was quenched with a saturated solution of NH_4Cl (3 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 130:1) gave compound **4.67** as a colourless oil (73 mg, 51%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.32 (m, 8H), 7.25–7.19 (m, 2H), 5.34–5.27 (m, 1H), 3.66 (t, *J* = 7.5 Hz, 2H), 3.49 (s, 4H), 2.11–2.03 (m, 2H), 1.67–1.59 (m, 2H), 0.96 (s, 9H), 0.11 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 149.5, 133.4 (2C), 128.3 (4C), 126.5 (4C), 125.6 (2C), 121.5, 62.6, 47.0, 45.4, 43.8, 32.8, 26.0 (3C), 24.6, 18.8, –5.0 (2C); **IR (neat):** $\tilde{\nu}$ = 3058, 3018, 2951, 2928, 2857, 1598, 1493, 1443, 1255, 1100, 836, 775, 700 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 415 (100); HRMS (ES+) calcd for $(C_{26}H_{36}OSi + Na)^+$: 415.2433; found: 415.2414; **elemental analysis** (%) calcd for $C_{26}H_{36}OSi$: C 79.53, H 9.24; found: C 79.43, H 9.26.

Compound 4.68



A molar solution of TBAF in THF (1.6 mL, 1.63 mmol) was added to a solution of **4.67** (320 mg, 0.815 mmol) in THF (3.2 mL) at 0 °C. After stirring at room temperature for 1.5 hours, the mixture was partitioned between a saturated solution of NH_4Cl (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 9:1 to 5:1) gave compound **4.68** as a colourless oil (927 mg, 99%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31–7.27 (m, 8H), 7.20–7.14 (m, 2H), 5.29–5.22 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.41 (s, 4H), 2.07–2.02 (m, 2H), 1.65–1.59 (m, 2H), 1.49 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 149.2, 133.9 (2C), 128.2 (4C), 126.4 (4C), 125.7 (2C), 121.1, 62.4, 46.9, 45.2, 43,6, 32.4, 24.5; **IR (neat):** $\tilde{\nu}$ = 3322, 3057, 3024, 2915, 1599, 1493, 1446, 1052, 1022, 754 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 296 (100), 279 (58), 278 (6); HRMS (CI) calcd for ($C_{20}H_{22}O$ + H): 279.17489; found: 279.17560.

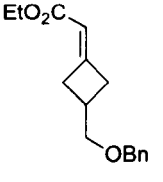
Compound 4.71



Under N_2, activated Zn/Cu couple[8] (178 mg, 2.7 mmol) was added to a solution of allyl benzyl ether (0.23 mL, 1.5 mmol) in Et_2O (2 mL). Trichloroacetyl chloride (0.27 mL, 2.4 mmol) followed by a solution of phosphorus oxychloride (0.22 mL,

2.4 mmol) in THF (2 mL) were added. The mixture was stirred at room temperature during 15 hours. The mixture was filtrated through celite, rinsed with Et_2O (20 mL) and the filtrate was carefully washed with a saturated solution of $NaHCO_3$ (50 mL) then with brine (15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue of evaporation was dissolved in AcOH (3 mL) and was added to a suspension of zinc (789 mg, 12 mmol) in AcOH (3 mL). The mixture was stirred 3 hours at room temperature then filtered through celite and rinsed with Et_2O (10 mL). The filtrate was washed with water (10 mL) followed by a saturated solution of $NaHCO_3$ (15 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 25:1) afforded compound **4.71** as colourless oil (178 mg, 62%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.41–7.25 (m, 5H), 4.54 (s, 2H), 3.57 (d, J = 5.9 Hz, 2H), 3.15–3.06 (m, 2H), 2.91–2.82 (m, 2H), 2.72–2.63 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 207.5, 138.0, 128.4 (2C), 127.7, 127.6 (2C), 73.1, 72.8, 49.9 (2 C), 23.5; **IR (neat):** $\tilde{\nu}$ = 3068, 3037, 2920, 1772, 1715, 1602, 1584, 1451, 1272, 1173, 1111, 1024, 712 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 224 (100); HRMS (CI) calcd for ($C_{12}H_{14}O_2$ + NH_4): 208.13375; found: 208.13435.

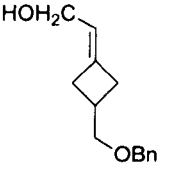
Compound 4.72



Commercially available (Ethoxycarbonylmethylene)triphenylphosphorane (85 mg, 0.243 mmol) was added under N_2 to a solution of **4.71** (42 mg, 0.221) in benzene (0.5 mL) at room temperature. After 15 hours heating at reflux, the mixture was

concentrated. Purification by flash chromatography (PE/EtOAc, 40:1) gave compound **4.72** as a colourless oil (42 mg, 73%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.42–7.29 (m, 5H), 5.68–5.63 (m, 1H), 4.56 (s, 2H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.58–3.50 (m, 2H), 3.31–3.22 (m, 1H), 3.00–2.84 (m, 2H), 2.80–2.70 (m, 1H), 2.69–2.60 (m, 1H), 1.29 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 166.5, 164.0, 138.4, 128.3 (2C), 127.58, 127.56 (2C), 113.5, 73.7, 73.1, 59.6, 36.5, 35.2, 30.8, 14.3; **IR (neat):** $\tilde{\nu}$ = 3031, 2925, 2852, 1709, 1675, 1496, 1453, 1366, 1335, 1265, 1216, 1187, 1093, 1039, 857, 736, 797 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 278 (100), 261 (38); HRMS (CI) calcd for ($C_{16}H_{20}O_3$ + H): 261.14907; found: 261.14870; **elemental analysis** (%) calcd for $C_{16}H_{20}O_3$: C 73.82, H 7.74; found: C 72.51, H 8.02.

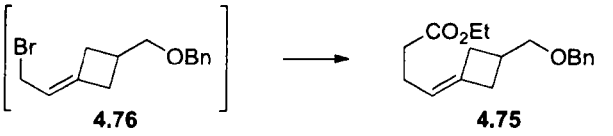
Compound 4.73



Under N_2, ester **4.72** (450 mg, 1.730 mmol) in Et_2O (1.8 mL) was added to a suspension of $LiAlH_4$ (33 mg, 0.865 mmol) in Et_2O (6.3 mL) at –20 °C (bath temperature). After stirring for 20 minutes at –20 °C, $LiAlH_4$ (33 mg, 0.865 mmol) was added as solid. After stirring for 35 minutes at –20 °C, few drops of a saturated solution of Na_2SO_4 were added until a white precipitate appeared. The mixture was then allowed to stir at room temperature before being filtered through a pad of celite and concentrated. Purification by flash chromatography (PE/EtOAc, 5:1 to 5:2) afforded compound **4.73** as a colourless oil (255 mg, 68%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.41–7.28 (m, 5H), 5.43–5.37 (m, 1H), 4.55 (s, 2H), 4.02 (d, *J* = 7.4 Hz, 2H), 3.51 (d, *J* = 7.4 Hz, 2H), 2.89–2.77 (m, 2H), 2.70–2.60 (m, 1H), 2.47–2.44 (m,

2H), 1.80 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 141.4, 138.3, 128.3 (2C), 127.6, 127.5 (2C), 120.5, 74.1, 72.9, 59.3, 33.8, 32.1, 30.0; **IR (neat):** $\tilde{\nu}$ = 3359, 3030, 2946, 2912, 2854, 1496, 1453, 1412, 1363, 1206, 1070, 1028, 990, 736, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 236 (100), 219 (19), 218 (96), 201 (70); HRMS (CI) calcd for ($C_{14}H_{18}O_2$ + NH_4): 236.16505; found: 236.16535; **elemental analysis** (%) calcd for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found: C 76.80, H 8.41.

Compound 4.75 - Compound 4.76



4.76 **4.75**

Under N_2, phosphorus tribromide (0.06 mL, 0.688 mmol) was added to a solution of alcohol **4.73** (300 mg, 1.376 mmol) in Et_2O (8 mL) at 0 °C. The mixture was stirred at room temperature for 45 minutes then quenched with brine (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Crude bromide **4.76** was used without further purification.

Under N_2, *n*-butyllithium (1.08 mL, 2.711 mmol) was added to a solution of diisopropylamine (0.38 mL, 2.711 mmol) in THF (10 mL) at 0 °C and the mixture was stirred for 20 minutes at the same temperature before being added by canula to a suspension of CuBr·Me_2S (1.11 g, 5.41 mmol) and EtOAc (0.26 mL, 2.68 mmol) in THF (12.5 mL) at –78 °C over a period of 2 minutes. After 30 minutes stirring at –78 °C, a solution of crude bromide **4.76** (387 mg, 1.376 mmol) in THF (3 mL) was canulated under N_2 to the mixture over a period of 5 minutes (Note: it was important for reproducible results to cool the solution of **4.76** at –78 °C prior to the addition). After stirring for 45 minutes at –78 °C, the mixture was quenched with few drops of

methanol, allowed to warm at room temperature, and partitioned between EtOAc and saturated solution of NH_4Cl (15 mL). The aqueous layer was reextracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 40:1 to 30:1) afforded compound **4.75** as colourless oil (293 mg, 74%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.41–7.28 (m, 5H), 5.16–5.09 (m, 1H), 4.55 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.50 (d, *J* = 7.3 Hz, 2H), 2.83–2.71 (m, 2H), 2.67–2.56 (m, 1H), 2.42–2.35 (m, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.26–2.19 (m, 2H), 1.28 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 173.2, 138.4, 138.0, 128.3 (2C), 127.5, 127.4 (2C), 119.6, 74.4, 72.9, 60.1, 34.3, 33.7, 32.0, 29.8, 23.6, 14.2; **IR (neat):** $\tilde{\nu}$ = 3029, 2956, 2910, 2852, 1733, 1495, 1453, 1416, 1367, 1252, 1167, 1096, 1029, 855, 736, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 306 (100), 289 (89); HRMS (CI) calcd for ($C_{18}H_{24}O_3$ + H): 289.18037; found: 289.18070; **elemental analysis** (%) calcd for $C_{18}H_{24}O_3$: C 74.97, H 8.39; found: C 74.66, H 8.45.

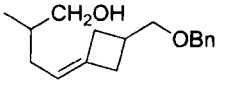
Compound 4.77

4.76 **4.77**

This compound was prepared from **4.76** (120 mg, 0.43 mmol) and methyl propionate (80 μL, 0.83 mmol) according to the procedure described for the preparation of **4.75**. Colourless oil (70 mg, 57%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.37–7.25 (m, 5H), 5.09–5.01 (m, 1H), 4.50 (s, 2H), 3.64 (s, 3H), [*3.63 (s, 3H)*], 3.46 (d, *J* = 7.2 Hz, 2H), [*3.45 (d, J = 7.0 Hz, 2H)*], 2.78–2.67 (m, 2H), 2.62–2.51 (m, 1H), 2.46–2.39 (m, 1H), 2.38–2.27 (m, 2H), 2.24–2.15 (m, 1H), 2.05–1.96 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), [*1.10 (d, J = 7.0 Hz, 3H)*]; **^{13}C NMR (125**

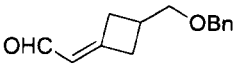
MHz, $CDCl_3$): δ = 176.8, 138.9, 138.5, 128.3 (2C), 127.6, 127.5 (2C), 118.28, [*118.26*], 74.4, 72.96, [*72.95*], 51.4, 39.6, 33.7, 32.2, [*32.16*], 32.1, 29.9, 16.41, [*16.40*]; **IR (neat):** $\tilde{\nu}$ = 3063, 3028, 2949, 2916, 2849, 1735, 1496, 1454, 1435, 1362, 1325, 1275, 1251, 1194, 1171, 1140, 1095, 1028, 985, 905, 859, 832, 736, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 306 (100), 289 (58); HRMS (CI) calcd for ($C_{18}H_{24}O_3$ + H): 289.18037; found: 289.17936; **elemental analysis** (%) calcd for $C_{18}H_{24}O_3$: C 74.97, H 8.39; found: C 75.13, H 8.41.

Compound 4.78



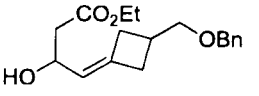
This compound was prepared from **4.77** (238 mg, 0.825 mmol) according to the procedure described for the preparation of **2.51**. Colourless oil (205 mg, 96%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.26–7.24 (m, 5H), 5.14–5.11 (m, 1H), 4.51 (s, 2H), 3.47 (d, *J* = 7.7 Hz, 2H), 3.49–3.44 (m, 1H), 3.41–3.36 (m, 1H), 2.79–2.67 (m, 2H), 2.62–2.52 (m, 1H), 2.38–2.27 (m, 2H), 1.97–1.89 (m, 1H), 1.79–1.71 (m, 1H), 1.70 (s, 1H), 1.68–1.60 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), [*0.88 (d, J = 6.7 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 138.4, 137.73, [*137.69*], 128.3 (2C), 127.6 (2C), 127.5, 119.66, [*119.65*], 74.4, 72.9, 68.01, [*67.99*], 36.2, 33.7, 32.3, 31.82, [*31.78*], 29.8, 16.4; **IR (neat):** $\tilde{\nu}$ = 3384, 3063, 3031, 2950, 2910, 2853, 1496, 1454, 1413, 1364, 1205, 1095, 1029, 985, 936, 905, 867, 736, 697 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 278 (42), 261 (100); HRMS (CI) calcd for ($C_{17}H_{24}O_2$ + H): 261.18545; found: 261.18523; **elemental analysis** (%) calcd for $C_{17}H_{24}O_2$: C 78.42, H 9.29; found: C 78.28, H 9.34.

Compound 4.79



This compound was prepared from **4.73** (200 mg, 0.92 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (177 mg, 77%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.61 (d, J = 8.2 Hz, 1H), 7.37–7.24 (m, 5H), 5.87–5.83 (m, 1H), 4.53 (s, 2H), 3.52 (d, J = 6.1 Hz, 2H), 3.29–3.20 (m, 1H), 2.89–2.83 (m, 2H), 2.83–2.72 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 190.3, 170.3, 138.1, 128.4 (2C), 127.7, 127.6 (2C), 124.3, 73.1, 72.9, 36.0, 33.9, 30.9; **IR (neat):** $\tilde{\nu}$ = 3058, 3031, 2952, 2911, 2854, 2738, 1676, 1633, 1496, 1454, 1396, 1365, 1325, 1205, 1149, 1092, 1028, 908, 861, 738, 699 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 234 (100), 217 (61); HRMS (CI) calcd for ($C_{14}H_{16}O_2$ + H): 217.12285; found: 217.12290.

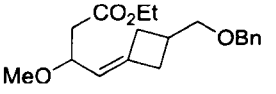
Compound 4.80



Under N_2, *n*-butyllithium (0.39 mL, 0.98 mmol) was added to a solution of diisopropylamine (0.14 mL, 0.84 mmol) in THF (3.5 mL) at 0 °C. After 20 minutes stirring at 0 °C, the solution of LDA was cooled at –78 °C and EtOAc (95 µL, 0.98 mL) was added. The resulting mixture was stirred at that temperature for 1 hour. Then, a solution of **4.79** (211 mg, 0.98 mmol) in THF (2.3 mL) cooled at –78 °C was added via canula. After 45 minutes at –78 °C, the mixture was quenched with few drops of acetic acid and allowed to warm at room temperature. The mixture was partitioned between a saturated solution of $NaHCO_3$ and EtOAc and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (PE/EtOAc, 10:1 to 7:1)

afforded compound **4.80** as pale yellow oil (238 mg, 80%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.35–7.25 (m, 5H), 5.21–5.17 (m, 1H), 4.49 (m, 3H), 4.140 (q, *J* = 7.0 Hz, 2H), [*4.135 (q, J = 7.0 Hz, 2H)*], 3.47 (d, *J* = 7.1 Hz, 2H), [*3.45 (d, J = 6.9 Hz, 2H)*], 2.96–2.70 (m, 3H), 2.66–2.54 (m, 1H), 2.54–2.33 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H), [*1.24 (t, J = 7.0 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 172.34, [*172.31*], 141.4, [*141.3*], 138.4, [*138.3*], 128.3 (2C), 127.60, [*127.57*], 127.5 (2C), 122.5, [*122.3*], 74.1, [*74.0*], 73.0, [*72.9*], 65.63, [*65.60*], 60.6, 41.5, 33.9, [*33.8*], 32.5, [*32.4*], 30.2, [*30.0*], 14.1; **IR (neat):** $\tilde{\nu}$ = 3441, 3062, 3029, 2951, 2912, 2853, 1733, 1492, 1452, 1410, 1369, 1268, 1176, 1096, 1027, 937, 857, 739, 699, 603 cm^{-1}; **elemental analysis** (%) calcd for $C_{18}H_{24}O_4$: C 71.03, H 7.95; found: C 71.16, H 7.97.

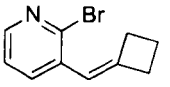
Compound 4.81



Ag_2O (457 mg, 1.971 mmol) and iodomethane (0.37 mL, 5.914 mmol) were added in this order at room temperature to a suspension of alcohol **4.80** (150 mg, 0.493 mmol) and 4Å MS (1 g) in Et_2O (6 mL) under N_2. After 3 days stirring at room temperature, the mixture was filtered through a pad of celite and the filtrate was concentrated. Purification by flash chromatography (PE/EtOAc, 15:1) afforded compound **4.81** as colourless oil (118 mg, 75%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.35–7.24 (m, 5H), 5.04–4.97 (m, 1H), 4.54–4.46 (m, 2H), 4.10 (q, *J* = 6.9 Hz, 2H), 4.02 (m, 1H), 3.47 (d, *J* = 7.1 Hz, 2H), [*3.44 (d, J = 6.9 Hz, 2H)*], 3.22 (s, 3H), [*3.17 (s, 3H)*], 2.88–2.72 (m, 2H), 2.67–2.59 (m, 1H), 2.562 (dd, *J* = 14.9 Hz, *J* = 8.3 Hz, 1H), [*2.558 (dd, J = 14.7 Hz, J = 8.1 Hz, 1H)*], 2.49–2.40 (m,

2H), 2.36 (dd, J = 14.9 Hz, J = 9.5 Hz, 1H), [*2.35 (dd, J = 14.7 Hz, J = 9.1 Hz, 1H)*], 1.23 (t, J = 7 Hz, 3H), [*1.22 (t, J = 7.2 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 170.9, 143.2, [*142.9*], 138.30, [*138.28*], 128.2 (2C), 127.52 (2C), 127.46, 120.4, [*120.3*], 74.21, [*74.17*], 74.0, [*73.8*], 72.9, 60.3, 55.80, [*55.77*], 40.9, 33.8, [*33.7*], 32.7, [*32.6*], 30.2, [*30.0*], 14.1; **IR (neat):** $\tilde{\nu}$ = 2976, 2918, 2853, 2820, 1734, 1698, 1496, 1454, 1414, 1367, 1304, 1271, 1247, 1196, 1167, 1089, 1029, 998, 967, 936, 860, 736, 698, 606 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 336 (10), 319 (1), 304 (100), 289 (16), 287 (70); HRMS (CI) calcd for ($C_{19}H_{26}O_4$ + NH_4): 336.21748; found: 336.21694; **elemental analysis** (%) calcd for $C_{19}H_{26}O_4$: C 71.67, H 8.23; found: C 71.66, H 7.27.

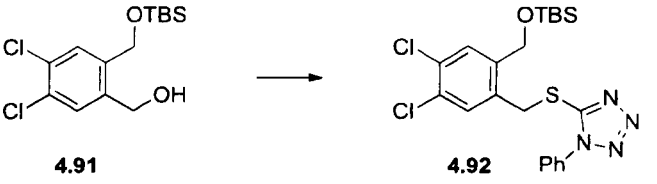
Compound 4.83



This compound was prepared from commercially available 2-bromo-3-formylpyridine **4.82** (375 mg, 2.02 mmol) and 4-bromobutyltriphenylphosphonium bromide (1.06 g, 2.22 mmol) according to the procedure described for the preparation of **2.45**. The mixture was heated 3 hours after the addition of the **4.82**. Colourless oil (319 mg, 70%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.07 (dd, J = 4.6 Hz, J = 2.0 Hz, 1H), 7.46 (dd, J = 7.5 Hz, J = 2.0 Hz, 1H), 7.12 (dd, J = 7.5 Hz, J = 4.6 Hz, 1H), 6.30–6.24 (m, 1H), 2.94–2.82 (m, 4H), 2.06 (quint, J = 7.9 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 149.9, 146.7, 142.6, 135.4, 134.3, 122.4, 117.9, 32.9, 32.2, 18.0; **IR (neat):** $\tilde{\nu}$ = 3040, 2977, 2953, 2910, 1667, 1570, 1550, 1445, 1388, 1330, 1239, 1184, 1121, 1083, 1046, 854, 798, 742, 723, 683 cm^{-1}; **MS (CI):** *m/z* (rel. intensity):

226 (73), 224 (70), 148 (7), 146 (100); HRMS (CI) calcd for ($C_{10}H_{10}BrN$ + H): 224.0069; found: 224.0072.

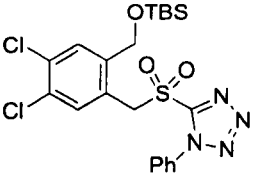
Compound 4.92



4.91 **4.92**

This compound was prepared from known compound **4.91**[3] (1.5 g, 4.67 mmol) according to the procedure described for the preparation of **4.62**. White solid (1.99 g, 86%). m.p.: 62–64 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.55 (s, 1H), 7.54–7.48 (m, 5H), 7.46 (s, 1H), 4.75 (s, 2H), 4.59 (s, 2H), 0.89 (s, 9H), –0.07 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 153.5, 139.7, 133.4, 132.7, 132.4, 132.0, 131.3, 130.2, 129.8 (2C), 129.5, 123.7 (2C), 62.2, 33.3, 25.8 (3C), 18.3, –5.3 (2C); **IR (neat):** $\tilde{\nu}$ = 2959, 2929, 2856, 1596, 1499, 1471, 1425, 1389, 1359, 1278, 1250, 1226, 1175, 1140, 1118, 1090, 1062, 1015, 975, 946, 903, 887, 836, 815, 778, 761, 747, 694, 686 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 503 (100); HRMS (ES+) calcd for $(C_{21}H_{26}Cl_2N_4OSSi + Na)^+$: 503.0871; found: 503.0881; **elemental analysis** (%) calcd for $C_{21}H_{26}Cl_2N_4OSSi$: C 52.38, H 5.44, N 11.64; found: C 52.29, H 5.44, N 11.58.

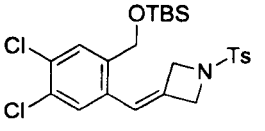
Compound 4.93



Sodium hydrogen carbonate (1.05 g, 12.47 mmol) and *m*CPBA (1.08 g, 6.23 mmol) were added consecutively to a solution of **4.92** (1.2 g, 2.49 mmol) in CH_2Cl_2 (12 mL)

at 0 °C. The mixture was stirred at room temperature during 3 hours. The mixture was cooled at 0 °C and sodium hydrogen carbonate (418 mg, 4.98 mmol) followed by *m*CPBA (430 mg, 2.49 mmol) were added. The mixture was stirred during 1 hour at room temperature. The mixture was quenched with water (10 mL) then extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (CH_2Cl_2) afforded compound **4.93** as a white solid (737 mg, 58%). m.p.: 116–118 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.66–7.51 (m, 5H), 7.50 (s, 1H), 7.46 (s, 1H), 5.14 (s, 2H), 4.74 (s, 2H), 0.89 (s, 9H), –0.07 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 153.2, 142.0, 134.4, 134.2, 132.7, 131.6, 131.5, 130.3, 129.6 (2C), 125.0 (2C), 122.2, 62.7, 57.6, 25.7 (3C), 18.2, –5.4 (2C); **IR (neat):** $\tilde{\nu}$ = 3001, 2955, 2930, 2881, 2857, 1773, 1594, 1496, 1472, 1427, 1390, 1359, 1349, 1251, 1225, 1159, 1103, 1063, 1017, 948, 905, 881, 837, 766, 725 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 535 (100); HRMS (ES+) calcd for $(C_{21}H_{26}Cl_2N_4O_3SSi + Na)^+$: 535.0770; found: 535.0767; **elemental analysis** (%) calcd for $C_{21}H_{26}Cl_2N_4O_3SSi$: C 49.12, H 5.10, N 10.91; found: C 48.74, H 4.83, N 9.33.

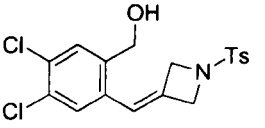
Compound 4.94



This compound was prepared from **4.93** (513 mg, 1.00 mmol) and azetidinone **4.86** (225 mg, 1.00 mmol) according to the procedure described for the preparation of **4.67**. Yellow oil (320 mg, 62%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.76 (d, *J* = 8.2 Hz, 2H), 7.46 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.88 (s, 1H), 6.24–6.19 (m, 1H), 4.61–4.57 (m, 2H), 4.55 (s, 2H), 4.54–4.49 (m, 2H), 2.43 (s, 3H), 0.87 (s, 9H), –0.04

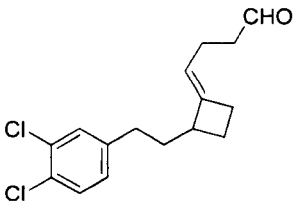
(s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.4, 138.5, 132.3, 131.6, 131.2, 130.8, 130.4, 129.9 (2C), 129.0, 128.4 (2C), 127.7, 118.1, 62.0, 59.8, 59.5, 25.7 (3C), 21.6, 18.2, –5.4 (2C); **IR (neat):** $\tilde{\nu}$ = 2953, 2929, 2886, 2856, 1598, 1469, 1454, 1385, 1348, 1253, 1226, 1159, 1091, 1007, 915, 890, 836, 815, 778, 709, 672 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 534 (100); HRMS (ES+) calcd for $(C_{24}H_{31}Cl_2NO_3SSi + Na)^+$: 534.1069; found: 534.1063.

Compound 4.95



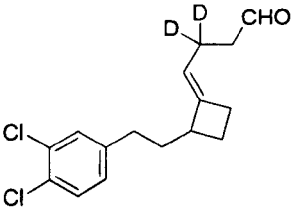
This compound was prepared from **4.94** (190 mg, 0.37 mmol) according to the procedure described for the preparation of **4.68**. White solid (127 mg, 86%). m.p.: 163–165 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.76 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.93 (s, 1H), 6.37–6.33 (m, 1H), 4.62–4.59 (m, 2H), 4.57 (s, 2H), 4.54–4.51 (m, 2H), 2.44 (s, 3H), 1.78–1.70 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.5, 137.7, 133.2, 131.8, 131.7, 131.4, 131.1, 130.1, 130.0 (2C), 128.4, 128.1 (2C), 118.1, 62.1, 59.9, 59.5, 21.6; **IR (neat):** $\tilde{\nu}$ = 3522, 3084, 3013, 2947, 2899, 2851, 1708, 1596, 1547, 1471, 1436, 1393, 1340, 1309, 1272, 1228, 1149, 1111, 1089, 1072, 1022, 971, 935, 917, 882, 820, 804, 728, 684, 675 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 420 (100); HRMS (ES+) calcd for $(C_{18}H_{17}Cl_2NO_3S + Na)^+$: 420.0204; found: 420.0197.

Compound (*E*)-5.22



This compound was prepared from (*E*)-**5.48** (90 mg, 0.30 mmol) according to the procedure described for the preparation of **2.3**. Colorless oil (80 mg, 89%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.72 (t, *J* = 1.6 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 1H), 6.97 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 1H), 5.11–4.99 (m, 1H), 2.89–2.77 (m, 1H), 2.61–2.47 (m, 4H), 2.43 (dt, *J* = 7.2 Hz, *J* = 1.6 Hz, 2H), 2.23–2.16 (m, 2H), 2.10–2.01 (m, 1H), 1.87–1.78 (m, 1H), 1.67–1.58 (m, 1H), 1.57–1.50 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.4, 145.7, 142.7, 132.0, 130.2, 130.1, 129.5, 127.9, 117.0, 43.7, 42.7, 35.8, 32.4, 26.4, 23.5, 20.7; **IR (neat):** $\tilde{\nu}$ = 2917, 2854, 2720, 1723, 1593, 1562, 1472, 1395, 1353, 1260, 1207, 1131, 1030, 870, 816, 707, 684 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 319 (100); HRMS (ES+) calcd for $(C_{16}H_{18}Cl_2O + Na)^+$: 319.0632; found: 319.0647; **elemental analysis** (%) calcd for $C_{16}H_{18}C_{l2}O$: C 64.66, H 6.10; found: C 65.83, H 6.30.

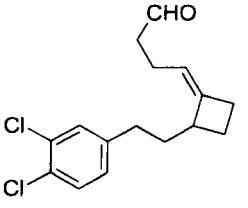
Compound (*E*)-5.22D



This compound was prepared from (*E*)-**5.48D** (100 mg, 0.332 mmol) according to the procedure described for the preparation of **2.3**.Colourless oil (65 mg, 66%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.73 (t, *J* = 1.6 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H),

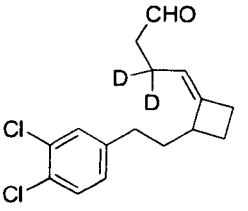
7.22 (d, J = 1.8 Hz, 1H), 6.97 (dd, J = 8.2 Hz, J = 1.8 Hz, 1H), 5.08–5.03 (m, 1H), 2.89–2.77 (m, 1H), 2.62–2.44 (m, 4H), 2.41 (s, 2H), 2.13–2.00 (m, 1H), 1.87–1.78 (m, 1H), 1.70–1.48 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.4, 145.8, 142.7, 132.0, 130.3, 130.1, 129.5, 127.9, 116.9, 43.6, 42.7, 35.8, 32.5, 26.4, 23.5, 20.1 (quint, J = 20 Hz); **IR (neat):** $\tilde{\nu}$ = 3027, 2918, 2856, 2820, 2720, 2197, 2111, 1722, 1593, 1561, 1472, 1395, 1350, 1327, 1257, 1208, 1131, 1071, 1030, 872, 817, 705, 684, 660 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 320 (13), 319 (11), 318 (65), 317 (16), 316 (100), 139 (16); **MS (ES+):** *m/z* (rel. intensity): 299 (100); HRMS (CI) calcd for ($C_{16}H_{16}D_2Cl_2O$ + H): 299.0933; found: 299.0937.

Compound (*Z*)-5.22



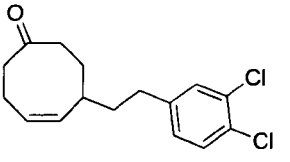
This compound was prepared from (*Z*)-**5.48** (47 mg, 0.16 mmol) according to the procedure described for the preparation of **2.3**. Colorless oil (40 mg, 86%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.73 (t, J = 1.5 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 5.03–4.97 (m, 1H), 3.00–2.89 (m, 1H), 2.66–2.54 (m, 2H), 2.52–2.46 (m, 2H), 2.43 (dt, J = 7.2 Hz, J = 1.5 Hz, 2H), 2.27–2.18 (m, 2H), 2.13–2.04 (m, 1H), 1.98–1.89 (m, 1H), 1.79–1.69 (m, 1H), 1.62–1.53 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.3, 144.2, 142.5, 132.1, 130.3, 130.2, 129.6, 127.8, 119.1, 44.1, 42.1, 35.6, 32.5, 28.0, 22.6, 21.0; **IR (neat):** $\tilde{\nu}$ = 2923, 2854, 2718, 1725, 1591, 1559, 1473, 1396, 1346, 1258, 1204, 1131, 1030, 871, 818, 705, 686, 659, 589 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 351 (100); HRMS (ES+) calcd for ($C_{16}H_{18}Cl_2O$ + MeOH + Na): 351.0895; found: 351.0880.

Compound (*Z*)-5.22D



This compound was prepared from (*Z*)-**5.48D** (54 mg, 0.179 mmol) according to the procedure described for the preparation of **2.3**. Colorless oil (35 mg, 64%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.74 (t, *J* = 1.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H), 5.02–4.97 (m, 1H), 3.00–2.90 (m, 1H), 2.65–2.59 (m, 2H), 2.53–2.43 (m, 2H), 2.42 (s, 2H), 2.14–2.04 (m, 1H), 1.99–1.89 (m, 1H), 1.80–1.69 (m, 1H), 1.63–1.53 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.3, 144.3, 142.6, 132.2, 130.31, 130.26, 129.7, 127.9, 119.1, 44.0, 42.2, 35.7, 32.6, 28.1, 22.7, 20.4 (quint, *J* = 19.7 Hz); **IR (neat):** $\tilde{\nu}$ = 2936, 2856, 2820, 2719, 2208, 2106, 1724, 1593, 1560, 1473, 1396, 1322, 1257, 1204, 1131, 1077, 1030, 956, 872, 819, 685, 658 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 353 (100); HRMS (ES+) calcd for ($C_{16}H_{16}D_2Cl_2O$ + MeOH + Na): 353.1020; found: 353.1022.

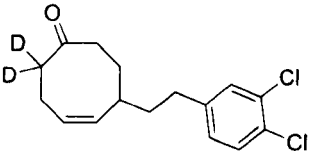
Compound 5.23 (see Appendix 4, p 302)



Starting from aldehyde (*E*)-**5.22** (18.0 mg, 0.0606 mmol) or (*Z*)-**5.22** (19.0 mg, 0.0639 mmol). **5.23** (17.1 mg, 94% from (*E*)-**5.22;** 10.0 mg, 53% from (*Z*)-**5.22**) was isolated as white solid. m.p.: 40–42 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 1.9 Hz, 1H), 6.94 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 1H), 5.85–5.77 (m, 1H), 5.35 (dd, *J* = 9.5 Hz, *J* = 9.5 Hz, 1H), 2.62–2.35 (m, 7H), 2.28–2.13 (m,

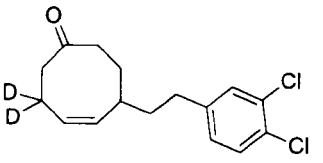
2H), 1.71–1.53 (m, 3H), 1.30–1.19 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.6, 142.3, 135.8, 132.1, 130.3, 130.2, 129.7, 129.6, 127.8, 47.4, 39.8, 37.8, 36.5, 32.9, 30.1, 22.8; **IR (neat):** $\tilde{\nu}$ = 3010, 2926, 2853, 1703, 1590, 1562, 1471, 1456, 1397, 1345, 1333, 1257, 1201, 1132, 1076, 1030, 965, 875, 820, 740, 688, 666 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 319 (100); HRMS (ES+) calcd for $(C_{16}H_{18}Cl_2O + Na)^+$: 319.0632; found: 319.0643; **elemental analysis** (%) calcd for $C_{16}H_{18}Cl_2O$: C 64.66, H 6.10; found: C 64.56, H 6.12.

Compound 5.23Dα (see Appendix 4, p 302)



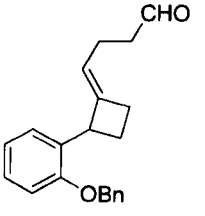
Starting from aldehyde (*Z*)-**5.22D** (22.5 mg, 0.0752 mmol). **5.23Dβ** (14.0 mg, 62%) was isolated as white solid. m.p.: 41–43 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 1.9 Hz, 1H), 6.94 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 1H), 5.86–5.78 (m, 1H), 5.35 (t, *J* = 9.2 Hz, 1H), 2.58 (ddd, *J* = 5.5 Hz, *J* = 8.7 Hz, *J* = 14.0 Hz, 1H), 2.52–2.36 (m, 4H), 2.29–2.20 (m, 1H), 2.17 (dd, *J* = 13.7 Hz, *J* = 7.1 Hz, 1H), 1.73–1.50 (m, 3H), 1.30–1.24 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.6, 142.3, 135.8, 132.1, 130.3, 130.2, 129.7, 129.7, 127.8, 46.8 (quint, *J* = 20 Hz), 39.8, 37.8, 36.5, 32.9, 30.1, 22.7; **IR (neat):** $\tilde{\nu}$ = 3053, 3010, 2926, 2854, 2218, 1703, 1593, 1561, 1472, 1456, 1397, 1346, 1317, 1261, 1198, 1132, 1097, 1030, 893, 874, 820, 726, 688, 664 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 321 (100); HRMS (ES+) calcd for $(C_{16}H_{16}D_2Cl_2O + Na)^+$: 321.0758; found: 321.0772.

Compound 5.23Dβ (see Appendix 4, p 302)



Starting from aldehyde (*E*)-**5.22D** (16.4 mg, 0.0548 mmol). **5.23Dα** (15.5 mg, 95%) was isolated as white solid. m.p.: 42–44 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 6.94 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H), 5.81 (d, *J* = 10.6 Hz, 1H), 5.34 (dd, *J* = 10.6 Hz, *J* = 8.8 Hz, 1H), 2.64–2.35 (m, 6H), 2.30–2.17 (m, 1H), 1.73–1.52 (m, 3H), 1.32–1.19 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 214.5, 142.3, 135.7, 132.1, 130.3, 130.2, 129.63, 129.59, 127.8, 47.3, 39.8, 37.8, 36.5, 32.8, 30.1, 22.1 (quint, *J* = 20 Hz); **IR (neat):** $\tilde{\nu}$ = 3053, 3011, 2932, 2910, 2861, 2850, 2216, 2106, 1692, 1593, 1560, 1470, 1456, 1439, 1417, 1399, 1350, 1291, 1259, 1193, 1142, 1129, 1098, 1079, 1027, 1001, 966, 952, 916, 902, 879, 854, 815, 805, 761, 728, 688, 664 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 321 (100); HRMS (ES+) calcd for $(C_{16}H_{16}D_2Cl_2O + Na)^+$: 321.0758; found: 321.0753.

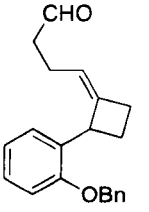
Compound (*E*)-5.29



This compound was prepared from (*E*)-**5.59** (190 mg, 0.617 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (166 mg, 88%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.75 (s, 1H), 7.43 (d, *J* = 8 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.38–7.31 (m, 2H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 5.14–5.09 (m, 1H), 5.07 (s, 2H), 4.57–4.49 (m, 1H), 2.68 (t, *J* = 7.9

Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.44–2.37 (m, 1H), 2.33–2.26 (m, 2H), 2.10–2.01 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.4, 156.2, 144.3, 137.3, 131.9, 128.4 (2C), 127.6, 127.4, 127.1, 127.0 (2C), 120.6, 118.8, 111.5, 69.8, 43.6, 42.6, 26.6, 25.3, 20.8; **IR (neat):** $\tilde{\nu}$ = 3063, 3033, 2941, 2917, 2856, 2825, 2721, 1721, 1598, 1585, 1489, 1450, 1382, 1330, 1289, 1237, 1161, 1110, 1050, 1024, 912, 852, 750, 696 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 329 (100); HRMS (ES+) calcd for $(C_{21}H_{22}O_2 + Na)^+$: 329.1517; found: 329.1501; **elemental analysis** (%) calcd for $C_{21}H_{22}O_2$: C 82.32, H 7.24; found: C 81.69, H 7.17.

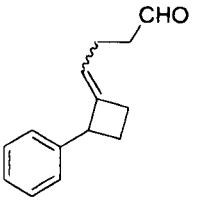
Compound (*Z*)-5.29



This compound was prepared from (*Z*)-**5.59** (41 mg, 0.134 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (31 mg, 75%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.53 (t, J = 1.8 Hz, 1H), 7.44 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.35–7.29 (m, 2H), 7.17 (dt, J = 7.8 Hz, J = 1.6 Hz, 1H), 6.97–6.89 (m, 2H), 5.27–5.18 (m, 1H), 5.07 (s, 2H), 4.58–4.46 (m, 1H), 2.77–2.672 (m, 1H), 2.667–2.57 (m, 1H), 2.51–2.40 (m, 1H), 2.35–2.18 (m, 2H), 2.09–2.01 (m, 2H), 1.96–1.87 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.5, 155.8, 143.5, 137.3, 132.9, 128.5 (2C), 127.8, 127.6, 127.21, 127.15 (2C), 120.8, 120.1, 111.7, 69.9, 43.5, 41.5, 28.1, 25.9, 20.8; **IR (neat):** $\tilde{\nu}$ = 3064, 3032, 2942, 2918, 2856, 2721, 1722, 1598, 1585, 1489, 1450, 1407, 1381, 1319, 1288, 1236, 1178, 1161, 1108, 1050, 1024, 935, 915, 853, 751, 696 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 361 (100), 329 (33); HRMS (ES+) calcd for $(C_{21}H_{22}O_2 + Na)^+$: 329.1517; found:

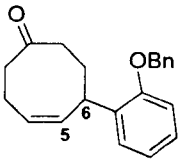
329.1531; HRMS (ES+) calcd for $(C_{21}H_{22}O_2 + MeOH + Na)^+$: 361.1780; found: 361.1778.

Compound (*E*)-5.30 - Compound (*Z*)-5.30



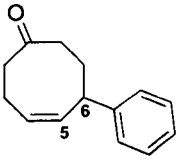
This compound was prepared from a mixture of (*E*)-**5.63** and (*Z*)-**5.63** (*E*/*Z*, 76:24) (35 mg, 0.173 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (30 mg, 87%).[9] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = [*9.74 (t, J = 1.7 Hz, 1H)*], 9.49 (t, *J* = 1.9 Hz, 1H), 7.31–7.21 (m, 4H), 7.20–7.15 (m, 1H), 5.22–5.14 (m, 1H), [*5.05–4.98 (m, 1H)*], 4.17–4.03 (m, 1H), 2.79–2.61 (m, 2H), 2.49–2.31 (m, 1H), 2.31–2.12 (m, 2H), 2.11–1.90 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 202.4, [*202.3*], [*145.2*], 144.1, 143.9, [*143.3*], 128.5 (2C), [*128.3*], [*127.3*], 127.2 (2C), 126.18, [*126.16*], 120.3, [*118.6*], [*48.6*], 47.8, [*43.7*], 43.4, 28.3, 26.9, [*26.8*], [*26.1*], [*20.7*], 20.6; **IR (neat):** $\tilde{\nu}$ = 3058, 3026, 2947, 2916, 2851, 2825, 2719, 1724, 1601, 1493, 1454, 1408, 1389, 1257, 1195, 1077, 1030, 838, 747, 700 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 255 (100); HRMS (ES+) calcd for $(C_{14}H_{16}O_2 + MeOH + Na)^+$: 255.1361; found: 255.1357.

Compound 5.31



Starting from aldehyde (*E*)-**5.30** (26.0 mg, 0.0849 mmol). **5.31** (10.9 mg, 42%) was isolated as colorless oil. Starting from aldehyde (*Z*)-**5.30** (21.6 mg, 0.0706 mmol). **5.31** (5.0 mg, 22%) was isolated as colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.45–7.345 (m, 4H), 7.341–7.28 (m, 1H), 7.25–7.20 (m, 1H), 7.19–7.12 (m, 1H), 7.00–6.86 (m, 2H), 5.81–5.62 (m, 2H), 5.05 (s, 2H), 4.23–4.06 (m, 1H), 2.90–2.74 (m, 1H), 2.72–2.58 (m, 2H), 2.54–2.40 (m, 2H), 2.24–2.11 (m, 1H), 1.96–1.79 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.3, 155.8, 137.3, 135.5, 133.9, 128.47 (2C), 128.45, 127.7, 127.3, 127.14, 127.06 (2C), 121.2, 112.2, 70.2, 47.7, 40.3, 37.0, 30.3, 22.3; **IR (neat):** $\tilde{\nu}$ = 3062, 3031, 2923, 1702, 1599, 1583, 1490, 1450, 1380, 1343, 1291, 1239, 1163, 1105, 1047, 1024, 972, 875, 849, 800, 751, 735, 697 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 329 (100); HRMS (ES+) calcd for $(C_{21}H_{22}O_2 + Na)^+$: 329.1517; found: 329.1509; note: The COSY experiment gave a correlation between H_5 and H_6.

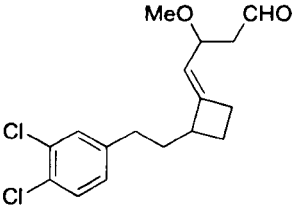
Compound 5.32



Starting from aldehyde (*E*)-**5.30** (30.0 mg, 0.150 mmol). **5.32** (5.9 mg, 20%) was isolated as colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31–7.27 (m, 2H), 7.22–7.17 (m, 3H), 5.81–5.73 (m, 1H), 5.72–5.64 (m, 1H), 3.63–3.54 (m, 1H), 2.84–2.73 (m, 1H), 2.69–2.60 (m, 2H), 2.55–2.45 (m, 2H), 2.31–2.21 (m, 1H), 2.00–1.89 (m,

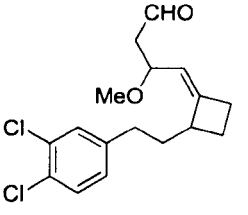
1H), 1.82–1.72 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 214.3, 145.2, 135.7, 128.6 (2C), 128.4, 127.0 (2C), 126.4, 47.6, 43.7, 40.0, 31.4, 22.5; **IR (neat):** $\tilde{\nu}$ = 3063, 3026, 2924, 2854, 1703, 1602, 1492, 1454, 1342, 1292, 1233, 1190, 1164, 1105, 1062, 1027, 969, 885, 874, 840, 827, 760, 737, 701 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 329 (100); HRMS (ES+) calcd for $(C_{14}H_{16}O + Na)^+$: 329.1517; found: 329.1509; note: The COSY experiment gave a correlation between H_5 and H_6.

Compound (*E*)-5.33



This compound was prepared from (*E*)-**5.67** (17 mg, 0.0508 mmol) according to the procedure described for the preparation of **2.3**. colourless oil (16mg, 96%). ^{1}H NMR of the crude showed the presence of the aldehyde contaminated with others unidentified products. This compound was directly used in the cyclisation, due to instability.

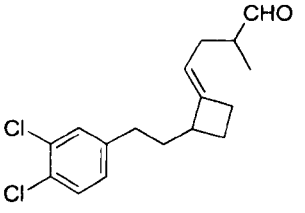
Compound (*Z*)-5.33



This compound was prepared from (*Z*)-**5.67** (35 mg, 0.106 mmol) according to the procedure described for the preparation of **2.3**. colourless oil (31mg, 88%). ^{1}H NMR of the crude showed the presence of the aldehyde contaminated with others

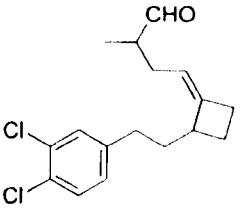
unidentified products. This compound was directly used in the cyclisation, due to instability.

Compound (*E*)-5.34



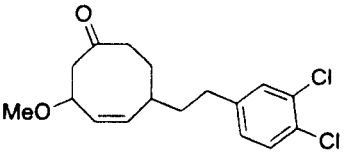
This compound was prepared from (*E*)-**5.69** (45 mg, 0.144 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (40 mg, 90%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.607 (s, 1H), [*9.605 (s, 1H)*], 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 5.09–5.02 (m, 1H), 2.89–2.79 (m, 1H), 2.60–2.43 (m, 4H), 2.40–2.31 (m, 1H), 2.28–2.18 (m, 1H), 2.11–1.95 (m, 2H), 1.89–1.78 (m, 1H), 1.69–1.59 (m, 1H), 1.58–1.48 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), [*1.05 (d, J = 7.0 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 204.9 146.75, [*146.73*], 142.7, 132.1, 130.3, 130.1, 129.5, 127.9, 115.4, 46.6, 42.8, [*35.9*], 35.8, 32.47, [*32.45*], 28.9, [*28.8*], 26.5, 23.5, 13.0, [*12.9*]; **IR (neat):** $\tilde{\nu}$ = 2967, 2929, 2851, 2711, 1726, 1593, 1561, 1473, 1454, 1395, 1259, 1208, 1131, 870, 816, 707, 684 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 332 (12), 331 (13), 330 (67), 329 (19), 328 (100).

Compound (*Z*)-5.34



This compound was prepared from (*Z*)-**5.69** (39 mg, 0.125 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (37 mg, 98%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.62 (d, *J* = 1.4Hz, 1H), [*9.61 (d, J = 1.7 Hz, 1H)*], 7.31 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 5.03–4.97 (m, 1H), 2.97–2.88 (m, 1H), 2.67–2.55 (m, 2H), 2.54–2.43 (m, 2H), 2.38–2.23 (m, 2H), 2.14–2.043 (m, 1H), 2.041–1.98 (m, 1H), 1.97–1.88 (m, 1H), 1.79–1.69 (m, 1H), 1.58 (septet, *J* = 5.3 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = [*204.9*], 204.8, 145.04, [*144.99*], 142.5, 132.1, 130.25, 130.21, 129.61, 127.8, [*117.6*], 117.5, 46.7, [*46.6*], 42.16, [*42.14*], [*35.6*], 35.5, 32.5, [*29.2*], 29.0, 28.1, 22.6, [*13.3*], 12.9; **IR (neat):** $\tilde{\nu}$ = 2965, 2932, 2853, 2712, 1725, 1589, 1561, 1473, 1395, 1346, 1258, 1208, 1131, 1030, 908, 871, 817, 686, 659, 589 cm^{-1}.

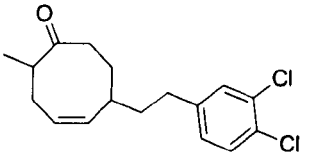
Compound 5.35



Starting from aldehyde (*E*)-**5.33** (16.1 mg, 0.0492 mmol). **5.36** (6.4 mg, 40%) was isolated as colourless oil, equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.308 (d, *J* = 8.2 Hz, 1H), [*7.305 (d, J = 8.2 Hz, 1H)*], 7.23 (d, *J* = 2.0 Hz, 1H), [*7.19 (d, J = 2.0 Hz, 1H)*], 7.00–6.93 (m, 1H), 5.76 (ddd, *J* = 11.4 Hz, *J* =

6.1 Hz, J = 0.8 Hz, 1H), [*5.72 (ddd, J = 11.0 Hz, J = 7.3 Hz, J = 1.1 Hz, 1H)*], 5.51 (dd, J = 11.4 Hz, J = 9.2 Hz, 1H), [*5.40 (ddd, J = 11.0 Hz, J = 9.2 Hz, J = 1.6 Hz, 1H)*], [*4.30–4.19 (m, 1H)*], 4.12–4.05 (m, 1H), [*3.34 (s, 3H)*], 3.24 (s, 3H), [*2.91 (dd, J = 11.4 Hz, J = 4.6 Hz, 1H)*], 2.88–2.81 (m, 1H), 2.77 (dd, J = 12.4 Hz, J = 4.0 Hz, 1H), 2.67–2.36 (m, 5H), 2.18–2.07 (m, 1H), 1.88–1.78 (m, 1H), [*1.77–1.69 (m, 1H)*], 1.67–1.58 (m, 2H), [*1.57–1.46 (m, 2H)*], [*1.40–1.30 (m, 1H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = [*212.2*], 210.9, 142.6, [*141.9*], 137.8, [*134.9*], 134.4, 132.2, [*132.1*], 130.4, [*130.32*], [*130.26*], 130.22, 129.9, [*129.7*], [*128.9*], 127.9, [*127.8*], 75.3, [*74.1*], [*56.8*], 56.4, [*54.0*], 52.6, [*40.5*], 40.1, 38.2, [*37.6*], [*37.2*], 36.7, 33.3, [*32.8*], 31.7, [*29.6*]; **IR (neat):** $\tilde{\nu}$ = 2925, 2854, 1706, 1593, 1560, 1473, 1397, 1351, 1273, 1203, 1123, 1102, 1187, 1030, 984, 895, 877, 820, 748, 706, 688 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 349 (100); HRMS (ES+) calcd for $(C_{17}H_{20}Cl_2O_2 + Na)^+$: 349.0738; found: 349.0749.

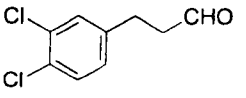
Compound 5.36



Starting from aldehyde (*E*)-**5.34** (13.4 mg, 0.0431 mmol). **5.36** (11.3 mg, 84%) was isolated as colourless oil, equimolar mixture of diastereomers.[6] **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.30 (d, J = 8.2 Hz, 1H), [*7.29 (d, J = 8.2 Hz, 1H)*], 7.20 (d, J = 2.0 Hz, 1H), [*7.19 (d, J = 2.1 Hz, 1H)*], 6.94 (dd, J = 8.2 Hz, J = 2.0 Hz, 1H), [*6.93 (dd, J = 8.2 Hz, J = 2.1 Hz, 1H)*], 5.87–5.73 (m, 1H), 5.37 (ddd, J = 10.7 Hz, J = 7.9 Hz, J = 0.9 Hz, 1H), 2.95–2.87 (m, 1H), [*2.85–2.78 (m, 1H)*], 2.65–2.62 (m, 2H), 2.49–2.26 (m, 3H), 2.23–2.11 (m, 1H), 2.07–1.98 (m, 1H), [*1.76–1.68 (m, 1H)*], 1.66–1.52 (m,

2H), 1.46–1.36 (m, 1H), 1.27–1.17 (m, 1H), 1.064 (d, J = 6.8 Hz, 3H), [*1.059 (d, J = 6.7 Hz, 3H)*]; **^{13}C NMR (100 MHz, $CDCl_3$):** δ = [*216.7*], 215.1, [*142.4*], 142.3, 137.1, [*135.6*], 132.1, 130.34, [*130.31*], 130.2, 129.7, [*129.1*], 128.3, 127.9, [*127.8*], [*51.5*], 50.8, 39.5, [*38.1*], 38.0, [*37.7*], 37.3, [*36.4*], [*32.9*], 32.8, [*31.9*], 31.7, [*30.0*], 29.1, [*16.4*], 13.4; **IR (neat):** $\tilde{\nu}$ = 3012, 2926, 2853, 1705, 1593, 1561, 1472, 1459, 1397, 1377, 1354, 1259, 1194, 1132, 1082, 1030, 939, 873, 819, 765, 740, 684, 665 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 333 (100); HRMS (ES+) calcd for $(C_{17}H_{20}Cl_2O + Na)^+$: 333.0789; found: 333.0793.

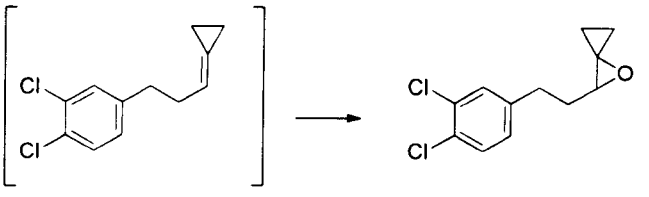
Compound 5.40



$SOCl_2$ (5.3 ml, 73 mmol) was slowly added via a dropping funnel to a solution of commercially available 3-(3,4-dichlorophenyl)propanal **5.39** (2 g, 9.1 mmol) in anhydrous methanol (43 ml) over 30 minutes. 3 drops of DMF were added and the mixture was stirred under reflux during 3 hours. The mixture was concentrated the residue was dissolved in EtOAc (20 mL) before being quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 30 ml). The combined organic layers were then washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude ester (2.07 g, 8.9 mmol) was diluted in Et_2O (10 ml), and added to a suspension of $LiAlH_4$ (169 mg, 4.45 mmol) in Et_2O (50 ml) at 0 °C. The resulting mixture stirred at room temperature during 20 minutes before being cooled at 0 °C. $LiAlH_4$ (169 mg, 4.45 mmol) was added and the reaction stirred for another 20 minutes at room temperature. The reaction was quenched with a saturated solution of Na_2SO_4 allowing for the precipitation of the aluminium salts. The mixture

was filtered through a short pad of silica and rinsed with Et_2O. The filtrate was evaporated giving the corresponding alcohol as colourless oil (1.88 g). The crude alcohol was engaged in a Swern oxidation. Oxalyl chloride (1 mL, 11.5 mmol) in CH_2Cl_2 (37 mL) was cooled at –78 °C, then a solution of DMSO (1.64 mL, 23.1 mmol) in CH_2Cl_2 (4 mL) was added. The resulting mixture was stirred at –78 °C during 10 minutes, then a solution of crude alcohol (1.88 g, 8.9 mmol) was added to the mixture at –78 °C. The resulting mixture was stirred for 15 minutes, then triethylamine (6.2 mL, 44.4 mmol) was added. The mixture stirred at room temperature during 20 minutes. The mixture was quenched with a saturated solution of NH_4Cl (30 mL) before being extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 30:1 to 20:1) afforded compound **5.40** as colourless oil (1.63 g, 89% over three steps). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.78 (s, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 8.2 Hz, J = 2.1 Hz, 1H), 2.88 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 200.5, 140.6, 132.3, 130.4, 130.25, 130.21, 127.8, 44.7, 27.0; **IR (neat):** $\tilde{\nu}$ = 2932, 2891, 2826, 2726, 1721, 1594, 1561, 1473, 1390, 1357, 1260, 1208, 1131, 1056, 1030, 883, 848, 815, 737, 679 cm^{-1}.

Compound 5.41 - Compound 5.42

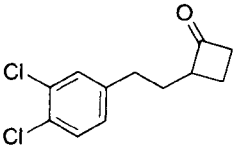


5.41 **5.42**

Under N_2, potassium *t*-butoxide (2.2 g, 19.5 mmol) was added to a suspension of 3-bromopropyltriphenylphosphonium bromide (4.5 g, 9.8 mmol) in THF (60 mL), at room temperature. The mixture was refluxed during 2 hours and a solution of **5.40** (1.6 g, 7.9 mmol) in THF (5 mL) was added to the refluxing suspension. After stirring for 13 hours, the mixture was quenched with water (30 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue of evaporation was filtered through a pad of silica and rinsed with petroleum ether. The filtrate was evaporated, affording crude **5.41** as colourless oil. This material was diluted in CH_2Cl_2 (10 mL) and *m*CPBA (305 mg, 1.77 mmol) was added at 0 °C. After stirring for 24 hours at room temperature, the mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 20:1 to 10:1) afforded compound **5.42** as colourless oil (223 mg, 52% over two steps). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.1 Hz, *J* = 2.1 Hz, 1H), 3.44 (t, *J* = 5.7 Hz, 1H), 2.79 (ddd, *J* = 14.0 Hz, *J* = 8.5 Hz, *J* = 5.7 Hz, 1H), 2.72–2.66 (m, 1H), 2.04–1.89 (m, 2H), 1.05 (dt, *J* = 10.6 Hz, *J* = 6.2 Hz, 1H), 0.98–0.93 (m, 1H), 0.88 (dt, *J* = 10.2 Hz, *J* = 6.2 Hz, 1H), 0.63 (dt, *J* = 10.2 Hz, *J* = 6.4 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 141.4, 132.2, 130.3, 130.2, 129.9, 127.8, 58.8, 58.6, 33.0, 31.1, 3.1, 1.6; **IR (neat):**

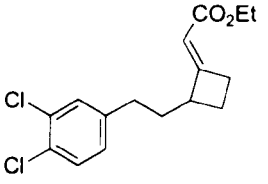
$\tilde{\nu}$ = 3078, 2945, 2861, 1580, 1563, 1473, 1397, 1328, 1259, 1206, 1148, 1131, 1089, 1031, 1004, 948, 892, 842, 820, 749, 684 cm^{-1}.

Compound 5.43

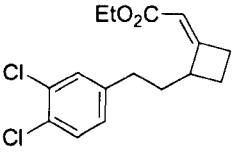


Under N_2, lithium iodide (12 mg, 0.091 mmol) was added to a solution of **5.42** (220 mg, 0.91 mmol) in CH_2Cl_2 (2 mL) at room temperature. After stirring at reflux for 14 hours, the mixture was washed with brine (2 × 2 mL) and the organic layer was dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 1:0 to 10:1) afforded **5.43** as colourless oil (208 mg, 94%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 3.29–3.19 (m, 1H), 3.03 (dddd, *J* = 17.7 Hz, *J* = 10.2 Hz, *J* = 7.7 Hz, *J* = 2.7 Hz, 1H), 2.92 (dddd, *J* = 17.7 Hz, *J* = 9.7 Hz, *J* = 5.2 Hz, *J* = 2.7 Hz, 1H), 2.71–2.59 (m, 2H), 2.16 (ddd, *J* = 21.3 Hz, *J* = 10.3 Hz, *J* = 5.1 Hz, 1H), 2.01–1.94 (m, 1H), 1.81–1.73 (m, 1H), 1.67–1.60 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 211.4, 141.7, 132.2, 130.4, 130.3, 129.9, 128.0, 59.3, 44.6, 32.3, 31.0, 16.9; **IR (neat):** $\tilde{\nu}$ = 2992, 2926, 2860, 1773, 1593, 1561, 1473, 1395, 1351, 1258, 1206, 1131, 1079, 1030, 948, 871, 818, 704, 683, 657 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 265 (100); HRMS (ES+) calcd for $(C_{12}H_{12}Cl_2O + Na)^+$: 265.0163; found: 265.0151.

Compound 5.44



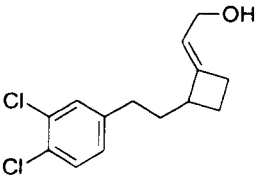
(*E*)-**5.44**



(*Z*)-**5.44**

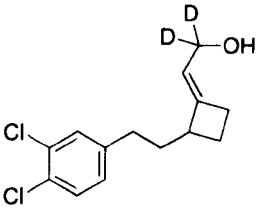
This compound was prepared from **5.43** (205 mg, 0.847 mmol) according to the procedure described for the preparation of **4.72**. Purification by flash chromatography (PE/EtOAc, 50:1 to 40:1) enabled the partial separation of both isomers, (*E*)-**5.44** (115 mg, 50%) and (*Z*)-**5.44** (70 mg, 30%) as colourless oils. (*E*)-**5.44**: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.29 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 1.9 Hz, 1H), 6.96 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H), 5.60–5.57 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.12–3.031 (m, 1H), 3.028–2.90 (m, 2H), 2.62–2.47 (m, 2H), 2.24–2.13 (m, 1H), 1.94–1.84 (m, 1H), 1.76–1.64 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 170.4, 166.4, 141.9, 132.1, 130.2 (2C), 129.7, 127.7, 111.3, 59.6, 44.0, 34.7, 32.1, 30.8, 23.9, 14.3; (*Z*)-**5.44**: **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.01 (dd, J = 8.2 Hz, J = 2.0 Hz, 1H), 5.59–5.54 (m, 1H), 4.10 (dq, J = 7.1 Hz, J = 1.5 Hz, 2H), 3.40–3.30 (m, 1H), 2.93–2.80 (m, 1H), 2.73–2.57 (m, 2H), 2.56–2.46 (m, 1H), 2.33–2.15 (m, 2H), 1.82–1.69 (m, 2H), 1.21 (t, J = 7.3 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 169.2, 165.8, 142.4, 132.0, 130.3, 130.1, 129.6, 127.9, 113.2, 59.6, 45.2, 34.0, 32.4, 29.8, 22.9, 14.3; **IR (neat):** $\tilde{\nu}$ = 2977, 2940, 2861, 1712, 1673, 1474, 1393, 1368, 1337, 1266, 1241, 1191, 1131, 1087, 1031, 858, 817 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 335 (100); HRMS (ES+) calcd for $(C_{16}H_{18}Cl_2O_2 + Na)^+$: 335.0582; found: 335.0571; **elemental analysis** (%) calcd for $C_{16}H_{18}Cl_2O_2$: C 61.35, H 5.79; found: C 62.37, H 6.05; (IR, mass and elemental analysis were performed on a mixture of *E* and *Z* isomers).

Compound (*E*)-5.45 (see Appendix 3, p 299)



This compound was prepared from (*E*)-**5.44** (125 mg, 0.4 mmol) according to the procedure described for the preparation of **4.73**. Colourless oil (86 mg, 79%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32 (d, J = 8.2 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 6.99 (dd, J = 8.2 Hz, J = 2.0 Hz, 1H), 5.41–5.34 (m, 1H), 4.03 (d, J = 7.2 Hz, 2H), 2.94–2.85 (m, 1H), 2.70–2.48 (m, 4H), 2.16–2.06 (m, 1H), 1.94–1.84 (m, 1H), 1.74–1.641 (m, 1H), 1.636–1.55 (m, 1H), 1.54–1.45 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 148.8, 142.5, 132.0, 130.2, 130.1, 129.5, 127.8, 118.2, 59.3, 42.9, 35.4, 32.4, 26.5, 23.7; **IR (neat):** $\tilde{\nu}$ = 3324, 2925, 2858, 1696, 1593, 1562, 1473, 1396, 1206, 1131, 1067, 1030, 992, 871, 817, 686 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 293 (100); HRMS (ES+) calcd for $(C_{14}H_{16}Cl_2O + Na)^+$: 293.0476; found: 293.0475; (IR and mass were performed on a mixture of *E* and *Z* isomers).

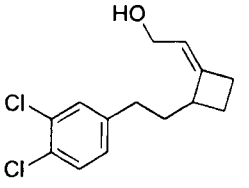
Compound (*E*)-5.45D



This compound was prepared from (*E*)-**5.44** (634 mg, 2.02 mmol) according to the procedure described for the preparation of **4.73**, using lithium aluminium deuteride. Colourless oil (333 mg, 61%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 5.40–5.31 (m, 1H), 2.93–2.84 (m, 1H), 2.68–2.45 (m, 4H), 2.13–2.06 (m, 1H), 1.92–1.85 (m, 1H),

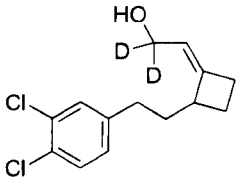
1.73–1.63 (m, 1H), 1.62–1.53 (m, 1H), 1.15–1.05 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 148.8, 142.5, 132.0, 130.2, 130.0, 129.5, 127.8, 118.1, 58.6 (quint, *J* = 21 Hz), 42.9, 35.4, 32.4, 26.5, 23.6; **IR (neat):** $\tilde{\nu}$ = 3312, 2926, 2857, 2187, 2083, 1693, 1593, 1561, 1472, 1396, 1353, 1312, 1257, 1207, 1131, 1094, 1071, 1030, 953, 905, 870, 816, 704, 684, 661 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 295 (100); HRMS (ES+) calcd for $(C_{14}H_{14}D_2Cl_2O + Na)^+$: 295.0601; found: 295.0594.

Compound (*Z*)-5.45 (see Appendix 3, p 299)



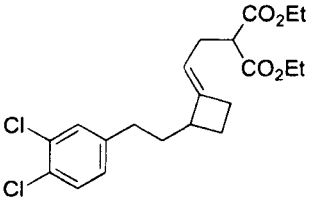
This compound was prepared from (*Z*)-**5.44** (70 mg, 0.224 mmol) according to the procedure described for the preparation of **4.73**. Colourless oil (53 mg, 87%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 5.38–5.31 (m, 1H), 4.02 (d, *J* = 7.5 Hz, 2H), 3.06–2.96 (m, 1H), 2.74–2.64 (m, 1H), 2.64–2.53 (m, 2H), 2.52–2.44 (m, 1H), 2.19–2.09 (m, 1H), 1.98–1.88 (m, 1H), 1.85–1.75 (m, 1H), 1.67–1.58 (m, 1H), 1.49–1.33 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 147.9, 142.4, 132.1, 130.24, 130.18, 129.6, 127.8, 120.3, 59.3, 42.2, 36.1, 32.4, 28.2, 22.7; (IR, mass: see Compound (*E*)-**5.45**).

Compound (*Z*)-5.45D



This compound was prepared from (*Z*)-**5.44** (324 mg, 1.034 mmol) according to the procedure described for the preparation of **4.73**, using lithium aluminium deuteride. Colourless oil (217 mg, 77%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.29 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.8 Hz, 1H), 6.97 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H), 5.32–5.27 (m, 1H), 3.02–2.93 (m, 1H), 2.70–2.61 (m, 1H), 2.60–2.49 (m, 2H), 2.45 (ddd, *J* = 13.8 Hz, *J* = 10.3 Hz, *J* = 6.8 Hz, 1H), 2.14–2.06 (m, 1H), 1.94–1.85 (m, 1H), 1.81–1.71 (m, 1H), 1.69–1.63 (s, 1H), 1.62–1.56 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 147.9, 142.5, 132.1, 130.24, 130.2, 129.7, 127.9, 120.3, 58.6 (quint, *J* = 21.9 Hz), 42.3, 36.2, 32.5, 28.3, 22.8; **IR (neat):** $\tilde{\nu}$ = 3321, 2937, 2857, 2187, 2096, 1694, 1593, 1562, 1473, 1396, 1348, 1208, 1131, 1070, 1030, 969, 951, 872, 817, 703, 686, 659 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 295 (100); HRMS (ES+) calcd for $(C_{14}H_{14}D_2Cl_2O + Na)^+$: 295.0601; found: 295.0601.

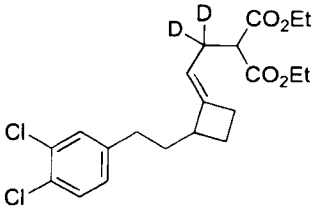
Compound (*E*)-5.46



Intermediate allylic bromide was prepared from (*E*)-**5.45** (29 mg, 0.107 mmol) according to the procedure described for the preparation of **4.76**, except that the reaction was carried out at 0 °C.

Diethyl malonate (175 μL, 1.153 mmol) was added to a suspension of sodium hydride (2 mg, 0.917 mmol) in THF (5 mL) at 0 °C. The resulting homogeneous mixture was stirred at room temperature during 30 minutes before being cooled down at 0 °C. Then, 0.7 mL of this enolate solution was added to a solution of crude bromide in THF (0.6 mL) at 0 °C via syringe. After stirring at room temperature for 2 hours, the mixture was quenched at 0 °C with a saturated solution of NH_4Cl (2 mL) and was then extracted with Et_2O (3 × 4 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 50:1 to 40:1) gave compound (*E*)-**5.46** as colourless oil (32 mg, 73% over two steps). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 1H), 6.96 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 1H), 5.10–5.01 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 4H), 3.30 (t, *J* = 7.6 Hz, 1H), 2.87–2.77 (m, 1H), 2.64–2.41 (m, 6H), 2.10–1.99 (m, 1H), 1.87–1.76 (m, 1H), 1.67–1.57 (m, 1H), 1.56–1.47 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 169.1 (2C), 147.5, 142.7, 132.1, 130.3, 130.1, 129.5, 127.9, 114.7, 61.28, 61.27, 52.1, 42.7, 35.8, 32.4, 27.3, 26.4, 23.4, 14.1 (2C); **IR (neat):** $\tilde{\nu}$ = 2976, 2931, 2853, 1731, 1591, 1562, 1473, 1394, 1369, 1331, 1264, 1227, 1175, 1151, 1097, 1031, 861, 818, 685, 642, 587, 555, 525 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 435 (100); HRMS (ES+) calcd for $(C_{21}H_{26}Cl_2O_4 + Na)^+$: 435.1106; found: 435.1095.

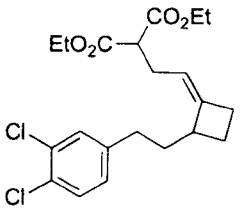
Compound (*E*)-5.46D



Intermediate allylic bromide was prepared from (*E*)-**5.45D** (330 mg, 1.21 mmol) according to the procedure described for the preparation of **4.76**, except that the reaction was carried out at 0 °C.

This compound was prepared from the intermediate allylic bromide (1.21 mmol) according to the procedure described for the preparation of (*E*)-**5.46**. Colourless oil (375 mg, 75% over two steps). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 5.08–5.01 (m, 1H), 4.21–4.11 (m, 4H), 3.29 (s, 1H), 2.86–2.76 (m, 1H), 2.63–2.43 (m, 4H), 2.10–2.00 (m, 1H), 1.86–1.77 (m, 1H), 1.66–1.56 (m, 1H), 1.55–1.47 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 169.1 (2C), 147.5, 142.6, 132.0, 130.2, 130.1, 129.5, 127.8, 114.6, 61.2 (2C), 51.9, 42.7, 35.7, 32.3, 26.4, 23.4, 14.1 (2C) (Note: CD_2 at 26.6 is hidden by CH_2 at 26.4); **IR (neat):** $\tilde{\nu}$ = 2980, 2937, 2861, 1730, 1590, 1560, 1473, 1394, 1368, 1318, 1210, 1175, 1150, 1131, 1096, 1030, 952, 868, 818, 684, 658 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 437 (100); HRMS (ES+) calcd for $(C_{21}H_{24}D_2Cl_2O_4 + Na)^+$: 437.1231; found: 437.1215.

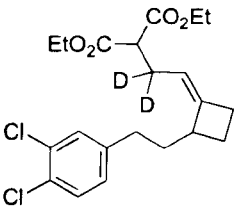
Compound (*Z*)-5.46



Intermediate allylic bromide was prepared from (*Z*)-**5.45** (95 mg, 0.350 mmol) according to the procedure described for the preparation of **4.76**, except that the reaction was carried out at 0 °C.

This compound was prepared from the intermediate allylic bromide (0.350 mmol) according to the procedure described for the preparation of (*E*)-**5.46**. Colourless oil (116 mg, 80% over two steps). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.2 Hz, *J* = 2.1 Hz, 1H), 5.03–4.96 (m, 1H), 4.19–4.12 (m, 4H), 3.27 (dd, *J* = 8.3 Hz, *J* = 6.5 Hz, 1H), 3.00–2.91 (m, 1H), 2.65–2.547 (m, 2H), 2.540–2.41 (m, 4H), 2.11–2.02 (m, 1H), 2.01–1.92 (m, 1H), 1.77–1.68 (m, 1H), 1.61–1.52 (m, 1H), 1.25–1.20 (m, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 169.09, 169.07, 145.9, 142.6, 132.1, 130.3, 130.2, 129.5, 127.8, 116.7, 61.35, 61.28, 52.3, 42.1, 35.5, 32.5, 28.1, 27.5, 22.6, 14.05, 14.03; **MS (ES+):** *m/z* (rel. intensity): 435 (100); HRMS (ES+) calcd for ($C_{21}H_{26}Cl_2O_4$ + Na): 435.1106; found: 435.1104; **elemental analysis** (%) calcd for $C_{21}H_{26}Cl_2O_4$: C 61.02, H 6.34; found: C 61.21, H 6.37.

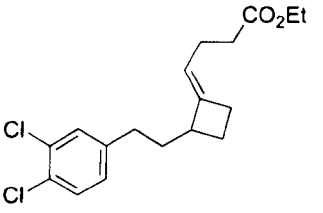
Compound (*Z*)-5.46D



Intermediate allylic bromide was prepared from (*Z*)-**5.45D** (315 mg, 1.15 mmol) according to the procedure described for the preparation of **4.76**, except that the reaction was carried out at 0 °C.

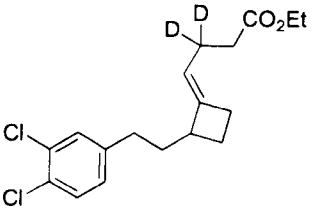
This compound was prepared from the intermediate allylic bromide (1.15 mmol) according to the procedure described for the preparation of (*E*)-**5.46**. Colourless oil (353 mg, 74% over two steps). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 5.01–4.96 (m, 1H), 4.20–4.12 (m, 4H), 3.26 (s, 1H), 3.01–2.91 (m, 1H), 2.66–2.54 (m, 2H), 2.52–2.42 (m, 2H), 2.12–2.02 (m, 1H), 2.01–1.92 (m, 1H), 1.78–1.68 (m, 1H), 1.61–1.53 (m, 1H), 1.27–1.19 (m, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 169.0 (2C), 145.8, 142.5, 131.9, 130.2, 130.1, 129.4, 127.8, 116.6, 61.22, 61.16, 52.1, 42.0, 35.4, 32.4, 28.0, 26.9 (quint, *J* = 19.4 Hz), 22.5, 14.0 (2C); **IR (neat):** $\tilde{\nu}$ = 2979, 2938, 2856, 1730, 1590, 1562, 1473, 1393, 1368, 1319, 1209, 1175, 1151, 1131, 1096, 1030, 942, 868, 818, 686, 659 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 437 (100); HRMS (ES+) calcd for $(C_{21}H_{24}D_2Cl_2O_4 + Na)^+$: 437.1231; found: 437.1215.

Compound (*E*)-5.47



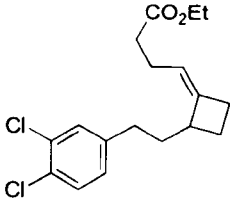
Lithium chloride (7 mg, 0.170 mmol) was added to a solution of (*E*)-**5.46** (32 mg, 0.078 mmol) in DMSO (1.7 mL). Water (50 μL) were added then the mixture was stirred at 155°C (oil bath temperature) during 16 hours. At room temperature, the mixture was partitioned between brine (2 mL) and EtOAc (3 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 90:1) gave (*E*)-**5.47** as colourless oil (19 mg, 72%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 6.97 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H), 5.10–5.04 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.88–2.78 (m, 1H), 2.61–2.46 (m, 4H), 2.32–2.26 (m, 2H), 2.22–2.15 (m, 2H), 2.10–2.01 (m, 1H), 1.88–1.79 (m, 1H), 1.68–1.59 (m, 1H), 1.57–1.49 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 173.3, 145.5, 142.8, 132.1, 130.3, 130.1, 129.5, 127.9, 117.4, 60.2, 42.8, 35.9, 34.5, 32.5, 26.4, 23.52, 23.45, 14.3; **IR (neat):** $\tilde{\nu}$ = 2971, 2927, 2853, 1734, 1591, 1559, 1473, 1394, 1372, 1255, 1166, 1132, 1092, 1031, 873, 817, 683, 570 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 363 (100); HRMS (ES+) calcd for $(C_{18}H_{22}Cl_2O_2 + Na)^+$: 363.0895; found: 363.0881; **elemental analysis** (%) calcd for $C_{18}H_{22}Cl_2O_2$: C 63.35, H 6.50; found: C 63.45, H 6.60.

Compound (*E*)-5.47D



This compound was prepared from (*E*)-**5.46D** (48 mg, 0.116 mmol) according to the procedure described for the preparation of (*E*)-**5.47**. Colourless oil (35 mg, 88%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 5.09–5.04 (m, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.87–2.78 (m, 1H), 2.61–2.46 (m, 4H), 2.28 (s, 2H), 2.09–2.01 (m, 1H), 1.87–1.79 (m, 1H), 1.68–1.58 (m, 1H), 1.57–1.49 (m, 1H), 1.23 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 173.2, 145.5, 142.7, 132.0, 130.2, 130.1, 129.4, 127.8, 117.2, 60.2, 42.7, 35.8, 34.2, 32.4, 26.3, 23.5, 22.8 (quint, *J* = 19 Hz), 14.2; **IR (neat):** $\tilde{\nu}$ = 2972, 2931, 2851, 2203, 2106, 1732, 1593, 1562, 1473, 1395, 1369, 1339, 1263, 1182, 1131, 1031, 871, 817, 684, 658 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 365 (100); HRMS (ES+) calcd for $(C_{18}H_{20}D_2Cl_2O_2 + Na)^+$: 365.1020; found: 365.1012.

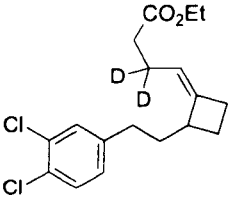
Compound (*Z*)-5.47



This compound was prepared from (*Z*)-**5.46** (110 mg, 0.266 mmol) according to the procedure described for the preparation of (*E*)-**5.47**. Colourless oil (75 mg, 83%). Under these conditions, partial isomerisation of the C–C double bond was observed

(*E*/*Z*, 10:90). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31(d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 5.05–4.98 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.01–2.89 (m, 1H), 2.66–2.54 (m, 2H), 2.53–2.43 (m, 2H), 2.31–2.255 (m, 2H), 2.245–2.16 (m, 2H), 2.12–2.03 (m, 1H), 1.99–1.90 (m, 1H), 1.79–1.69 (m, 1H), 1.61–1.53 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 173.3, 144.0, 142.7, 132.1, 130.3, 130.2, 129.6, 127.9, 119.5, 60.3, 42.1, 35.7, 34.8, 32.6, 28.1, 23.8, 22.7, 14.3; **MS (ES+):** *m/z* (rel. intensity): 363 (100); HRMS (ES+) calcd for $(C_{18}H_{22}Cl_2O_2 + Na)^+$: 363.0895; found: 363.0879.

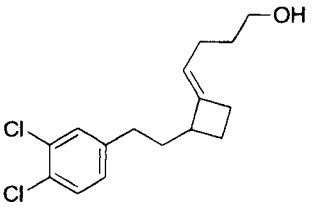
Compound (*Z*)-5.47D



This compound was prepared from (*Z*)-**5.46D** (353 mg, 0.85 mmol) according to the procedure described for the preparation of (*E*)-**5.47**. Colourless oil (242 mg, 71%). Under these conditions, partial isomerisation of the C–C double bond was observed (*E*/*Z*, 4:96). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 5.03–4.98 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.01–2.90 (m, 1H), 2.66–2.54 (m, 4H), 2.27 (s, 2H), 2.12–2.03 (m, 1H), 1.99–1.90 (m, 1H), 1.78–1.68 (m, 1H), 1.61–1.52 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 173.2, 143.9, 142.6, 132.0, 130.2, 130.0, 129.5, 127.8, 119.3, 60.2, 42.0, 35.6, 34.5, 32.5, 28.0, 22.6, 14.2 (Note: CD_2 not visible); **IR (neat):** $\tilde{\nu}$ = 2967, 2937, 2856, 2203, 2106, 1732, 1593, 1563, 1473, 1395, 1369, 1339, 1263, 1182, 1130, 1030, 949, 871, 817, 706, 686, 659 cm^{-1}; **MS (ES+):** *m/z*

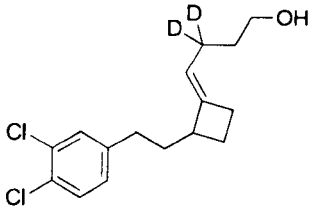
(rel. intensity): 365 (100); HRMS (ES+) calcd for $(C_{18}H_{20}D_2Cl_2O_2 + Na)^+$: 365.1020; found: 365.1019.

Compound (*E*)-5.48



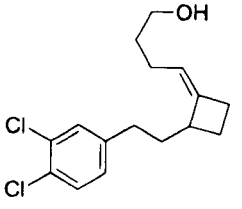
This compound was prepared from (*E*)-**5.47** (110 mg, 0.32 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (90 mg, 93%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 1.8 Hz, 1H), 6.97 (dd, J = 8.2 Hz, J = 1.8 Hz, 1H), 5.15–5.05 (m, 1H), 3.62 (t, J = 6.3 Hz, 2H), 2.89–2.78 (m, 1H), 2.61–2.46 (m, 4H), 2.11–2.02 (m, 1H), 1.97–1.93 (m, 2H), 1.90–1.80 (m, 1H), 1.69–1.49 (m, 4H), 1.33–1.26 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.7, 142.8, 132.1, 130.3, 130.1, 129.5, 127.9, 118.7, 62.7, 42.8, 36.0, 32.6, 32.5, 26.4, 24.2, 23.6; **IR (neat):** $\tilde{\nu}$ = 3338, 2932, 2856, 1593, 1560, 1473, 1454, 1396, 1348, 1257, 1206, 1131, 1049, 1031, 871, 817, 685 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 321 (100); HRMS (ES+) calcd for $(C_{16}H_{20}Cl_2O + Na)^+$: 321.0789; found: 321.0778; (IR and mass were performed on a mixture of *E* and *Z* isomers).

Compound (*E*)-5.48D



This compound was prepared from (*E*)-**5.47D** (250 mg, 0.728 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (215 mg, 98%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.28 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 1H), 5.11–5.05 (m, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.87–2.77 (m, 1H), 2.60–2.44 (m, 4H), 2.10–2.00 (m, 1H), 1.89–1.79 (m, 1H), 1.78–1.67 (s, 1H), 1.66–1.58 (m, 1H), 1.57–1.48 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.6, 142.7, 132.0, 130.2, 130.1, 129.4, 127.8, 118.6, 62.5, 42.7, 35.9, 32.5, 32.3, 26.4, 23.5, 23.4 (quint, *J* = 18.8 Hz); **IR (neat):** $\tilde{\nu}$ = 3323, 2929, 2859, 2187, 2100, 1593, 1561, 1472, 1396, 1350, 1258, 1207, 1131, 1052, 1030, 906, 870, 816, 684, 658 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 323 (100); HRMS (ES+) calcd for $(C_{16}H_{18}D_2Cl_2O + Na)^+$: 323.0914; found: 323.0902.

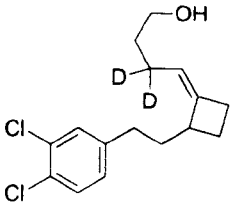
Compound (*Z*)-5.48



This compound was prepared from (*Z*)-**5.47** (75 mg, 0.22 mmol) (contaminated with some (*E*)-**5.47**) according to the procedure described for the preparation of **2.52**. Colourless oil (47 mg, 71%). The *E* and *Z* isomers were separable at this stage. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 1.9 Hz, 1H),

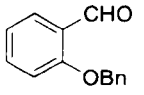
6.99 (dd, J = 8.3 Hz, J = 1.9 Hz, 1H), 5.08–5.02 (m, 1H), 3.61 (t, J = 6.4 Hz, 2H), 2.99–2.89 (m, 1H), 2.66–2.54 (m, 2H), 2.53–2.42 (m, 2H), 2.13–2.04 (m, 1H), 2.01–1.90 (m, 3H), 1.79–1.68 (m, 1H), 1.62–1.53 (m, 3H), 1.48–1.39 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 143.0, 142.7, 132.0, 130.2, 130.1, 129.5, 127.8, 120.9, 62.6, 42.1, 35.7, 32.9, 32.5, 28.0, 24.5, 22.7; (IR, mass: see Compound (*E*)-**5.48**).

Compound (*Z*)-5.48D



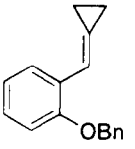
This compound was prepared from (*Z*)-**5.47D** (240 mg, 0.699 mmol) (contaminated with some (*E*)-**5.47D**) according to the procedure described for the preparation of **2.52**. Colourless oil (128 mg, 61%). The *E* and *Z* isomers were separable at this stage. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.31 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 5.07–5.02 (m, 1H), 3.62 (t, J = 6.4 Hz, 2H), 3.01–2.89 (m, 1H), 2.67–2.55 (m, 2H), 2.54–2.42 (m, 2H), 2.14–2.02 (m, 1H), 2.01–1.90 (m, 1H), 1.81–1.68 (m, 1H), 1.63–1.51 (m, 3H), 1.28–1.17 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 143.0, 142.7, 132.0, 130.2, 130.1, 129.5, 127.8, 120.6, 62.5, 42.1, 35.6, 32.7, 32.5, 28.0, 23.8 (quint, J = 19 Hz), 22.7; **IR (neat):** $\tilde{\nu}$ = 3320, 2933, 2861, 2187, 2106, 1593, 1562, 1473, 1396, 1347, 1259, 1208, 1131, 1051, 1030, 949, 907, 871, 816, 732, 686, 659 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 323 (100); HRMS (ES+) calcd for $(C_{16}H_{18}D_2Cl_2O + Na)^+$: 323.0914; found: 323.0916.

Compound 5.54



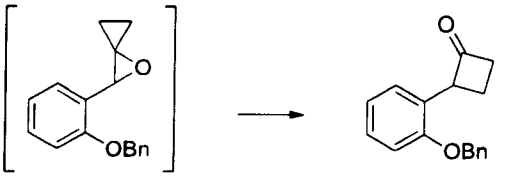
Under N_2, potassium carbonate (5.9 mg, 43 mmol) followed by benzyl bromide (3.9 mL, 33 mmol) were added to a solution of salicylaldehyde (3 mL, 28.7 mmol) in acetone (60 mL) at room temperature. The mixture was stirred under reflux during 4 hours before being cooled at room temperature and filtered through celite. The filtrate was concentrated. The residue of evaporation was dissolved in EtOAc (50 mL) and washed with water (50 mL) then with brine (50 mL). The organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 99:1) afforded compound **5.54** as a white solid (4.22g, 70%). m.p.: 42–44 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 10.56 (s, 1H), 7.85 (dd, J = 7.5 Hz, J = 1.9 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.46–7.403 (m, 2H), 7.401–7.37 (m, 2H), 7.36–7.32 (m, 1H), 7.06–7.01 (m, 2H), 5.18 (s, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 189.7, 161.0, 136.0, 135.9, 128.7 (2C), 128.4, 128.2, 127.2 (2C), 125.1, 121.0, 113.0, 70.4; **IR (neat):** $\tilde{\nu}$ = 3063, 3035, 2863, 2759, 1684, 1597, 1498, 1481, 1453, 1397, 1378, 1303, 1285, 1236, 1188, 1160, 1102, 1043, 1002, 915, 852, 833, 800, 755, 734, 657 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 230 (68), 213 (100); HRMS (CI) calcd for ($C_{14}H_{12}O_2$ + H): 213.0910; found: 213.0906; **elemental analysis** (%) calcd for $C_{14}H_{12}O_2$: C 79.22, H 5.70; found: C 79.27, H 5.68.

Compound 5.55



This compound was prepared from **5.54** (1.01 g, 4.78 mmol) according to the procedure described for the preparation of **2.47**. White solid (844 g, 75%). m.p.: 50–53 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.79 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.35–7.29 (m, 1H), 7.23–7.21 (m, 1H), 7.18–7.15 (m, 1H), 7.00–6.91 (m, 2H), 5.10 (s, 2H), 1.42–1.36 (m, 2H), 1.18–1.12 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 155.2, 137.2, 128.5 (2C), 127.8, 127.6, 127.4, 127.3 (2C), 126.6, 124.2, 120.9, 112.4, 112.1, 70.3, 3.9, 0.6; **IR (neat):** $\tilde{\nu}$ = 3063, 3035, 2971, 2876, 1593, 1488, 1451, 1434, 1422, 1404, 1384, 1348, 1287, 1241, 1155, 1111, 1069, 1048, 1026, 1011, 975, 946, 927, 914, 860, 806, 741, 694 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 263 (15), 254 (12), 237 (100); HRMS (CI) calcd for ($C_{17}H_{16}O$ + H): 237.1274; found: 237.1274.

Compound 5.56 - Compound 5.57

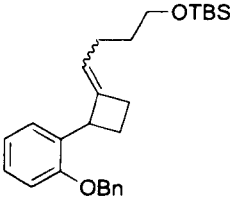


5.56 **5.57**

This compound was prepared from **5.55** (700 mg, 2.97 mmol) according to the procedure described for the preparation of **5.41**. Crude epoxide **5.56** was purified by flash chromatography (PE/EtOAc, 30:1 to 15:1 to 10:1), promoting the rearrangement of **5.56** into cyclobutanone **5.57.** White solid (480 mg, 64%). m.p.: 59–61 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.44–7.355 (m, 4H), 7.347–7.30 (m,

1H), 7.21 (t, J = 7.9 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 6.95–6.85 (m, 2H), 5.02 (s, 2H), 4.51–4.42 (m, 1H), 3.07–2.96 (m, 1H), 2.85–2.75 (m, 1H), 2.34 (ddd, J = 21.0 Hz, J = 10.4 Hz, J = 4.8 Hz, 1H), 2.26–2.16 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 209.3, 156.5, 136.5, 129.5, 128.6, 128.5 (2C), 128.1, 127.8 (2C), 126.1, 120.8, 111.7, 70.3, 62.0, 44.9, 18.1; **IR (neat):** $\tilde{\nu}$ = 3058, 3028, 2997, 2952, 2920, 2886, 1779, 1597, 1583, 1491, 1467, 1454, 1381, 1336, 1295, 1264, 1233, 1211, 1180, 1158, 1117, 1078, 1034, 1009, 960, 918, 882, 854, 811, 765, 747, 730, 695, 674 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 270 (100), 253 (9); HRMS (CI) calcd for ($C_{17}H_{16}O_2$ + NH_4): 270.1489; found: 270.1488; **elemental analysis** (%) calcd for $C_{17}H_{16}O_2$: C 80.93, H 6.39; found: C 80.73, H 6.41.

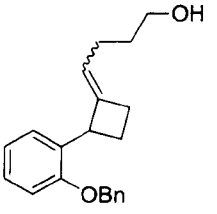
Compound 5.58



This compound was prepared from **5.57** (530 mg, 2.10 mmol) and **4.67** (1.0 g, 2.52 mmol) according to the procedure described for the preparation of **4.67**. Colourless oil (468 g, 53%). *E/Z* mixture (70:30).[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.47–7.28 (m, 6H), 7.19–7.13 (m, 1H), 7.96–7.89 (m, 2H), [*5.31–5.24 (m, 1H)*], 5.16–5.09 (m, 1H), 5.07 (s, 2H), 4.59–4.45 (m, 1H), 3.62 (d, J = 6.0 Hz, 1H), 3.61 (d, J = 7.2 Hz, 1H), [*3.50–3.42 (m, 2H)*], 2.77–2.57 (m, 2H), 2.45–2.35 (m, 1H), 2.06–1.94 (m, 2H), [*1.90–1.82 (m, 1H)*], 1.81–1.70 (m, 1H), 1.57 (quint, J = 7.0 Hz, 2H), [*1.46 (quint, J = 7.0 Hz, 2H)*], 0.90 (s, 9H), [*0.84 (s, 9H)*], 0.052 (s, 3H), 0.051 (s, 3H), [*–0.02 (s, 3H)*], [*–0.03 (s, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 156.3, [*155.9*], 142.5, [*141.1*], 137.5, [*132.7*], 132.6, 128.5 (2C), 127.7, [*127.6*], 127.4, 127.1 (2C), [*127.0*],

[*122.5*], 121.1, 120.7, 111.6, [*111.5*], 69.9, [*69.8*], [*62.9*], 62.8, 42.5, [*41.7*], 32.9, [*32.7*], 28.1, 26.6, [*26.2*], 26.0 (3C), [*25.9 (3C)*], 25.7, [*24.3*], 24.1, [*18.4*], 18.3, –5.25, –5.31; **IR (neat):** $\tilde{\nu}$ = 3064, 3028, 2942, 2929, 2857, 1599, 1583, 1490, 1469, 1451, 1382, 1360, 1285, 1241, 1100, 1052, 1026, 963, 835, 812, 775, 750, 696 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 445 (100); HRMS (ES+) calcd for $(C_{27}H_{38}O_2Si + Na)^+$: 445.2539; found: 445.2522; **elemental analysis** (%) calcd for $C_{27}H_{38}O_2Si$: C 76.72, H 9.06; found: C 76.51, H 9.11.

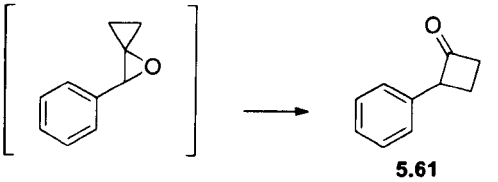
Compound 5.59



This compound was prepared from **5.58** (460 mg, 1.09 mmol) according to the procedure described for the preparation of **4.68**. Colourless oil (320 mg, 95%). Purification by flash chromatography allowed for the partial separation of both isomers (87 mg of *E* isomer (26%), 190 mg of *Z* isomer (57%)). <u>(*E*)-**5.59:**</u> **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.44 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.36–7.29 (m, 2H), 7.18 (dt, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.28–5.21 (m, 1H), 5.08 (s, 2H), 4.56–4.48 (m, 1H), 3.44 (dt, *J* = 6.4 Hz, *J* = 2.4 Hz, 2H), 2.77–2.674 (m, 1H), 2.667–2.59 (m, 1H), 2.51–2.41 (m, 1H), 1.97–1.87 (m, 1H), 1.85–1.74 (m, 2H), 1.55–1.39 (m, 2H), 1.37–1.26 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 155.8, 142.1, 137.3, 132.6, 128.5 (2C), 127.73, 127.66, 127.13 (2C), 127.10, 122.0, 120.8, 111.6, 69.9, 62.5, 41.5, 32.4, 28.1, 25.9, 24.1; <u>(*Z*)-**5.59:**</u> **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.46 (d, *J* = 7.5 Hz, 2H), 7.43–7.364 (m, 3H), 7.359–7.30 (m, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J*

= 8.1 Hz, 1H), 5.18–5.11 (m, 1H), 5.08 (s, 2H), 4.59–4.48 (m, 1H), 3.64 (t, J = 6.3 Hz, 2H), 2.73–2.62 (m, 2H), 2.47–2.37 (m, 1H), 2.11–2.00 (m, 3H), 1.62 (quint, J = 6.9 Hz, 2H), 1.59–1.51 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 156.2, 143.1, 137.3, 132.3, 128.4 (2C), 127.6, 127.4, 127.04 (2C), 127.01, 120.7, 120.6, 111.5, 69.8, 62.6, 42.6, 32.5, 26.6, 25.4, 24.2; **IR (neat):** $\tilde{\nu}$ = 3334, 3063, 3033, 2934, 2866, 1598, 1585, 1489, 1449, 1380, 1330, 1288, 1237, 1161, 1110, 1049, 1024, 914, 848, 813, 749, 695 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 331 (100); HRMS (ES+) calcd for $(C_{21}H_{24}O_2 + Na)^+$: 331.1674; found: 331.1679; **elemental analysis** (%) calcd for $C_{21}H_{24}O_2$: C 81.78, H 7.84; found: C 81.49, H 7.86; (IR and mass were performed on a mixture of *E* and *Z* isomers).

Compound 5.61[10]

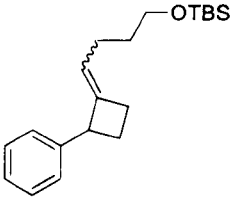


5.61

Under N_2, potassium *t*-butoxide (8.2 g, 75 mmol) was added to a suspension of 3-bromopropyltriphenylphosphonium bromide (17.4 g, 37.5 mmol) in THF (200 mL), at room temperature. The mixture was refluxed during 2 hours and neat benzaldehyde (2.5 mL, 25 mmol) was carefully added to the refluxing suspension. After stirring for 35 minutes, the mixture was cooled at room temperature then quenched with water (30 mL) and extracted with PE (3 × 60 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude alkylidenecyclopropane was diluted in CH_2Cl_2 (125 mL) and *m*CPBA (4.3 g, 25 mmol) was added at 0 °C. After stirring for 24 hours at room temperature, the mixture was quenched at 0 °C with a saturated solution of $NaHCO_3$ (50 mL) and

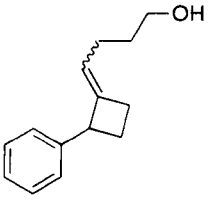
extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (PE/EtOAc, 1:0 to 100:1) afforded compound **5.61** as white solid (2.51 g, 69% over two steps). m.p.: 29–30 °C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.36–7.29 (m, 2H), 7.24–7.20 (m, 3H), 4.58–4.49 (m, 1H), 3.26–3.17 (m, 1H), 3.02 (dddd, *J* = 14.8 Hz, *J* = 9.8 Hz, *J* = 5.0 Hz, *J* = 2.7 Hz, 1H), 2.53 (dq, *J* = 10.7 Hz, *J* = 5.0 Hz, 1H), 2.28–7.19 (m, 1H).

Compound 5.62



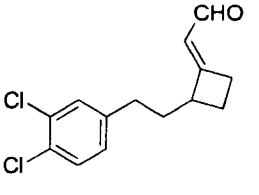
This compound was prepared from **5.61** (300 mg, 2.05 mmol) according to the procedure described for the preparation of **4.67**. Colourless oil (487 mg, 75%), equimolar mixture of *E* and *Z* isomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.35 (m, 4H), 7.22–7.15 (m, 1H), 5.28–5.19 (m, 1H), [*5.10–5.02 (m, 1H)*], 4.17–4.06 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 1H), 3.49–3.35 (m, 1H), 2.81–2.62 (m, 2H), 2.51–2.35 (m, 1H), 2.12–1.90 (m, 2H), 1.80–1.62 (m, 1H), 1.60–1.51 (m, 1H), 1.46–1.35 (m, 1H), 0.91 (s, 9H), [*0.86 (s, 9H)*], 0.06 (s, 6H), [*–0.01 (s, 3H)*], [*–0.02 (s, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.5, [*143.8*], [*143.4*], 141.7, 128.32 (2C), [*128.25 (2C)*], [*127.4 (2C)*], 127.2 (2C), 126.0, [*125.9*], 122.5, [*120.7*], 62.8, [*62.7*], 48.6, [*47.8*], [*32.8*], 32.6, 28.4, [*27.1*], 26.8, [*26.3*], [*26.0 (3C)*], 25.9 (3C), 24.1, [*24.0*], [*18.33*], 18.29, –5.27 (2C), [*–5.32 (2C)*]; **IR (neat):** $\tilde{\nu}$ = 3062, 3027, 2950, 2929, 2856, 1603, 1494, 1472, 1463, 1388, 1361, 1254, 1097, 1031, 1006, 963, 939, 833, 773, 697, 661, 597, 542, 531, 522 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 339 (100); HRMS (ES+) calcd for $(C_{20}H_{32}OSi + Na)^+$: 339.2120; found: 339.2117.

Compound 5.63



This compound was prepared from **5.62** (65 mg, 0.205 mmol) according to the procedure described for the preparation of **4.68**. Colourless oil (40 mg, 96%), (*E*/*Z*, 56:44).[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.34–7.25 (m, 4H), 7.21–7.15 (m, 1H), 5.24–5.16 (m, 1H), [*5.09–5.01 (m, 1H)*], 4.16–4.04 (m, 1H), [*3.63 (t, J = 6.5 Hz, 2H)*], 3.38 (t, *J* = 6.5 Hz, 2H), 2.81–2.63 (m, 2H), 2.50–2.33 (m, 1H), 2.12–1.92 (m, 2H), 1.77–1.69 (m, 1H), 1.60 (quint, *J* = 6.9 Hz, 1H), 1.45 (setuplet, *J* = 6.8 Hz, 1H), [*1.35 (setuplet, J = 6.8 Hz, 1H)*], 1.30–1.07 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 144.5, [*144.0*], [*143.6*], 142.7, 128.4 (2C), [*128.3*], [*127.34*], 127.28 (2C), 126.1, 122.1, [*120.3*], [*62.6*], 62.4, [*48.6*], 47.8, [*32.5*], 32.3, 28.4, 26.9, [*26.8*], [*26.2*], [*24.1*], 23.9; **IR (neat):** $\tilde{\nu}$ = 3343, 3061, 3026, 2938, 2876, 1699, 1602, 1492, 1452, 1272, 1178, 1110, 1047, 1031, 917, 868, 837, 758, 744, 698 cm^{-1}; **MS (CI):** *m/z* (rel. intensity): 221 (14), 220 (100), 203 (15).

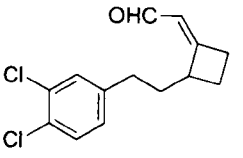
Compound (*E*)-5.64



This compound was prepared from (*E*)-**5.44** (60 mg, 0.221 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (41 mg, 69%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.65 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 5.85 (dq, *J* = 8.0 Hz, *J*

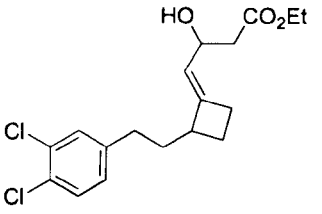
= 2.2 Hz, 1H), 3.21–3.08 (m, 2H), 3.07–2.97 (m, 1H), 2.64–2.52 (m, 1H), 2.34–2.23 (m, 1H), 2.01–1.91 (m, 2H), 1.85–1.71 (m, 2H).

Compound (*Z*)-5.64



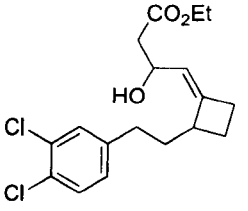
This compound was prepared from (*Z*)-**5.44** (200 mg, 0.738 mmol) according to the procedure described for the preparation of **2.3**. Colourless oil (120 mg, 60%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 9.66 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 5.84 (dq, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 3.46–3.32 (m, 1H), 3.01–2.91 (m, 1H), 2.87–2.78 (m, 1H), 2.67 (ddd, *J* = 14.1 Hz, *J* = 9.4 Hz, *J* = 4.9 Hz, 1H), 2.55 (ddd, *J* = 14.0 Hz, *J* = 9.5 Hz, *J* = 7.0 Hz, 1H), 2.32 (ddd, *J* = 11.4 Hz, *J* = 9.1 Hz, *J* = 6.7 Hz, 1H), 2.12–2.04 (m, 1H), 2.03–1.94 (m, 1H), 1.84 (septet, *J* = 5.4 Hz ,1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 189.8, 175.6, 141.4, 132.3, 130.4, 130.2, 130.0, 127.7, 124.6, 43.8, 36.7, 32.2, 30.4, 22.8; **IR (neat):** $\tilde{\nu}$ = 2944, 2858, 2741, 1672, 1593, 1562, 1472, 1394, 1347, 1260, 1208, 1145, 1059, 1030, 856, 819, 686, 659 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 291 (100); HRMS (ES+) calcd for $(C_{14}H_{14}Cl_2O + Na)^+$: 291.0319; found: 291.0318.

Compound (*E*)-5.65



This compound was prepared from (*E*)-**5.64** (40 mg, 0.149 mmol) according to the procedure described for the preparation of **4.80**. Colourless oil (37 mg, 69%), equimolar mixture of diastereomers. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.29 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 1.7 Hz, 1H), 6.96 (dd, *J* = 8.1 Hz, *J* = 1.7 Hz, 1H), 5.23–5.14 (m, 1H), 4.57–4.47 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.96–2.75 (m, 2H), 2.72–2.38 (m, 6H), 2.01–1.92 (m, 1H), 1.92–1.77 (m, 1H), 1.72–1.48 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).[11]

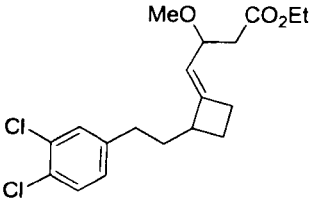
Compound (*Z*)-5.65



This compound was prepared from (*Z*)-**5.64** (120 mg, 0.446 mmol) according to the procedure described for the preparation of **4.80**. Colourless oil (94 mg, 59%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.29 (d, *J* = 8.0 Hz, 1H), [*7.28 (d, J = 8.0 Hz, 1H)*], 7.24 (d, *J* = 2.0 Hz, 1H), [*7.22 (d, J = 2.0 Hz, 1H)*], 6.99 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), [*6.97 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H)*], 5.18–5.09 (m, 1H), 4.57–4.46 (m, 1H), 4.119 (q, *J* = 7.2 Hz, 2H), [*4.116 (q, J = 7.2 Hz, 2H)*], 3.12–3.006 (m, 1H), [*2.998–2.93 (m, 1H)*], 2.92–2.79 (s, 1H), 2.69–2.38 (m, 6H), 2.17–1.67 (m, 3H), 1.65–1.54 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), [*1.22 (t, J =*

7.2 Hz, 3H)]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 172.30, [*172.28*], 147.8, [*147.3*], 142.4, [*142.2*], 132.1, [*132.0*], 130.24, [*130.19*], 130.15, [*130.11*], 129.6, [*129.5*], 127.83, [*127.76*], 122.2, [*122.0*], 65.23, [*65.22*], 60.7, [*60.6*], 42.4, [*42.2*], 41.9, [*41.7*], 36.1, [*35.6*], 32.4, [*32.2*], 28.1, [*28.0*], 22.6, 14.07, [*14.06*]; **IR (neat):** $\tilde{\nu}$ = 3455, 2977, 2937, 2856, 1726, 1593, 1562, 1473, 1396, 1371, 1265, 1175, 1131, 1029, 948, 909, 872, 853, 817, 734, 705, 686, 660 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 379 (100) ; HRMS (ES+) calcd for $(C_{18}H_{22}Cl_2O_3 + Na)^+$: 379.0844; found: 379.0831.

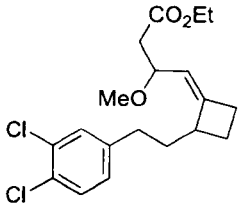
Compound (*E*)-5.66



This compound was prepared from (*E*)-**5.65** (37 mg, 0.104 mmol) according to the procedure described for the preparation of **4.81**. Colourless oil (28 mg, 73%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 6.98 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 1H), 5.04–4.95 (m, 1H), 4.17–4.079 (m, 2H), 4.075–4.00 (m, 1H), [*3.23 (s, 3H)*], 3.21 (s, 3H), 2.98–2.83 (m, 1H), 2.74–2.45 (m, 5H), 2.40–2.33 (m, 1H), 2.16–2.04 (m, 1H), 1.95–1.79 (m, 1H), 1.73–1.51 (m, 2H), 1.228 (t, *J* = 7.2 Hz, 3H), [*1.225 (t, J = 7.2 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 171.01, [*170.98*], 150.4, [*150.3*], 142.5, 132.1, 130.3, 130.2, 129.6, 127.8, 118.3, [*118.1*], 74.2, [*74.0*], 60.4, 55.9, [*55.8*], [*43.0*], 42.8, 41.1, [*41.0*], 35.63, [*35.58*], [*32.4*], 32.3, [*27.1*], 27.0, [*23.8*], 23.5, 14.21, [*14.20*]; **IR (neat):** $\tilde{\nu}$ = 2972, 2926, 2815, 1735, 1697, 1590, 1560, 1473, 1394, 1371, 1348, 1271, 1247, 1196, 1165, 1095, 1031, 969, 933, 817, 680 cm^{-1}; **MS**

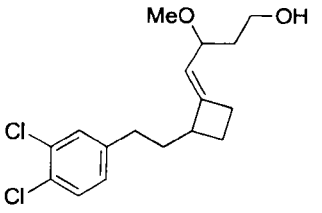
(ES+): *m/z* (rel. intensity): 393 (100) ; HRMS (ES+) calcd for $(C_{19}H_{24}Cl_2O_3 + Na)^+$: 393.1000; found: 393.1000.

Compound (*Z*)-5.66



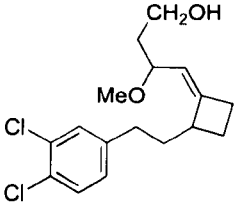
This compound was prepared from (*Z*)-**5.65** (90 mg, 0.252 mmol) according to the procedure described for the preparation of **4.81**. Colourless oil (84 mg, 90%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), [*7.25 (d, J = 2.0 Hz, 1H)*], 7.015 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), [*7.011 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H)*], 5.02–4.95 (m, 1H), 4.17–4.04 (m, 3H), [*3.23 (s, 3H)*], 3.21 (s, 3H), 3.07–2.93 (m, 1H), 2.74–2.45 (m, 5H), 2.39–2.31 (m, 1H), 2.20–1.90 (m, 2H), 1.84–1.71 (m, 1H), 1.68–1.59 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), [*1.21 (t, J = 7.0 Hz, 3H)*]; **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 171.0, [*170.9*], 148.9, [*148.3*], [*142.32*], 142.25, [*132.13*], 132.12, 130.3, [*130.22*], 130.20, 129.6, 127.80, [*127.77*], [*120.9*], 120.6, [*74.2*], 74.0, 60.41, [*60.39*], 56.1, [*55.9*], 42.7, [*42.2*], 41.5, [*41.2*], 36.1, [*35.2*], 32.4, [*32.3*], 28.20, [*28.15*], 22.7, [*22.6*], [*14.15*], 14.14; **IR (neat):** $\tilde{\nu}$ = 2978, 2934, 2820, 1734, 1697, 1593, 1562, 1473, 1395, 1372, 1349, 1297, 1270, 1249, 1235, 1196, 1164, 1131, 1093, 1030, 998, 968, 853, 818, 687, 659 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 393 (100); HRMS (ES+) calcd for $(C_{19}H_{24}Cl_2O_3 + Na)^+$: 393.1000; found: 393.1014.

Compound (*E*)-5.67



This compound was prepared from (*E*)-**5.66** (27 mg, 0.0728 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (17 mg, 70%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 6.98 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 1H), 5.09–4.98 (m, 1H), 3.88–3.79 (m, 1H), 3.78–3.67 (m, 2H), [*3.24 (s, 3H)*], 3.22 (s, 3H), 2.98–2.85 (m, 1H), 2.71–2.44 (m, 5H), 2.17–2.06 (m, 1H), 1.96–1.75 (m, 2H), 1.73–1.62 (m, 3H), [*1.61–1.49 (m, 1H)*].

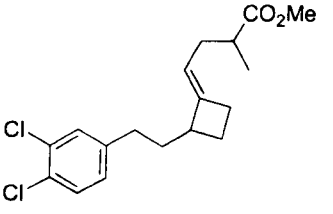
Compound (*Z*)-5.67



This compound was prepared from (*Z*)-**5.66** (80 mg, 0.216 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (65 mg, 92%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), [*6.98 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H)*], 5.05–4.98 (m, 1H), 3.92 (dt, *J* = 8.5 Hz, *J* = 4.7 Hz, 1H), [*3.92 (ddd, J = 9.5 Hz, J = 8.5 Hz, J = 4.0 Hz, 1H)*], [*3.24 (s, 3H)*], 3.22 (s, 3H), 3.05–2.97 (m, 1H), [*2.96–2.89 (m, 1H)*], 2.76–2.42 (m, 5H), 2.20–2.01 (m, 2H), 2.15 (s, 1H), 1.92–1.59 (m, 5H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 148.2, 147.2, 132.1,

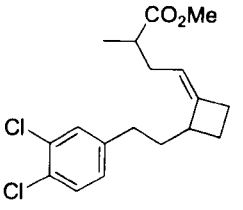
130.2, 129.7, 127.7, 121.8, 121.5, [*77.5*], 77.3, 60.85, [*60.80*], [*55.9*], 55.6, 42.6, [*42.1*], 38.01, [*37.97*], 36.3, [*35.1*], 32.4, [*32.3*], [*28.2*], 28.1, 22.7, [*22.6*]; **IR (neat):** $\tilde{\nu}$ = 3419, 2937, 2821, 1694, 1593, 1562, 1473, 1424, 1397, 1353, 1257, 1209, 1181, 1131, 1082, 1051, 1031, 915, 871, 854, 817, 687, 660 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 351 (100); HRMS (ES+) calcd for $(C_{17}H_{22}Cl_2O_2 + Na)^+$: 351.0895; found: 351.0896; **elemental analysis** (%) calcd for $C_{17}H_{22}Cl_2O_2$: C 62.01, H 6.73; found: C 61.89, H 6.77.

Compound (*E*)-5.68



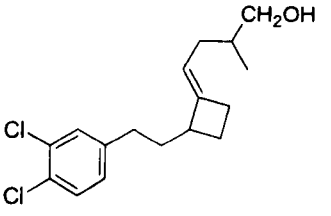
This compound was prepared from (*E*)-**5.45** (50 mg, 0.184 mmol) according to the procedure described for the preparation of **4.77**. Colourless oil (51 mg, 81%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.30 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 5.08–5.00 (m, 1H), [*3.65 (s, 3H)*], 3.64 (s, 3H), 2.89–2.79 (m, 1H), 2.59–2.470 (m, 4H), 2.467–2.39 (m, 1H), 2.24–2.15 (m, 1H), 2.10–1.97 (m, 2H), 1.88–1.79 (m, 1H), 1.68–1.58 (m, 1H), 1.57–1.48 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H).

Compound (*Z*)-5.68



This compound was prepared from (*Z*)-**5.45** (50mg, 0.184 mmol) according to the procedure described for the preparation of **4.77**. Colourless oil (51 mg, 81%), equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), [*7.25 (d, J = 2.0 Hz, 1H)*], 7.03–6.96 (m, 1H), 5.04–4.94 (m, 1H), 3.6 (s, 3H), 2.98–2.87 (m, 1H), 2.67–2.54 (m, 2H), 2.53–2.45 (m, 2H), 2.44–2.36 (m, 1H), 2.29–2.19 (m, 1H), 2.12–1.99 (m, 2H), 1.98–1.89 (m, 1H), 1.79–1.67 (m, 1H), 1.64–1.52 (m, 1H), [*1.11 (d, J = 7.0 Hz, 3H)*], 1.10 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 176.7, 144.7, [*144.6*], 142.7, 132.1, 130.3, [*130.18*], 130.16, [*129.55*], 129.53, 127.84, [*127.82*], 118.2, [*118.1*], 51.51, [*51.49*], 42.2, [*42.1*], [*39.9*], 39.8, [*35.59*], 35.55, [*32.51*], 32.47, 32.1, 28.1, 22.6, [*16.8*], 16.3; **IR (neat):** $\tilde{\nu}$ = 2967, 2937, 2856, 1736, 1593, 1560, 1473, 1436, 1393, 1360, 1252, 1194, 1171, 1133, 1031, 885, 821, 683 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 363 (100); HRMS (ES+) calcd for $(C_{18}H_{22}Cl_2O_2 + Na)^+$: 363.0895; found: 363.0882.

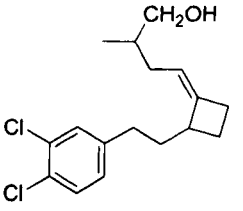
Compound (*E*)-5.69



This compound was prepared from (*E*)-**5.68** (51 mg, 0.149 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (46 mg, 98%),

equimolar mixture of diastereomers.[6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 6.98 (dd, *J* = 8.2 Hz, *J* = 1.5 Hz, 1H), 5.18–5.06 (m, 1H), 3.50 (dd, *J* = 6.1 Hz, *J* = 3.3 Hz, 1H), 3.41 (dd, *J* = 10.5 Hz, *J* = 6.2 Hz, 1H), 2.92–2.78 (m, 1H), 2.65–2.45 (m, 4H), 2.13–2.05 (m, 1H), 2.00–1.91 (m, 1H), 1.90–1.82 (m, 1H), 1.81–1.73 (m, 1H), 1.71–1.60 (m, 2H), 1.59–1.50 (m, 1H), 1.49–1.36 (s, 1H), 0.89 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 145.4, [*145.3*], 142.79, [*142.77*], 132.1, 130.3, 130.1, 129.5, 117.4, 117.3, 68.15, [*68.11*], 42.9, [*42.8*], 36.2, 36.0, 32.5, [*31.57*], 31.55, 26.5, 23.6, [*16.5*], 16.4; **IR (neat):** $\tilde{\nu}$ = 3332 (br), 2917, 2871, 1593, 1561, 1473, 1396, 1351, 1258, 1207, 1131, 1029, 983, 939, 868, 816, 707, 684 cm^{-1}; **MS (ES+):** *m/z* (rel. intensity): 335 (100); HRMS (ES+) calcd for $(C_{17}H_{22}Cl_2O + Na)^+$: 335.0945; found: 335.0953.

Compound (*Z*)-5.69



This compound was prepared from (*Z*)-**5.68** (43 mg, 0.126 mmol) according to the procedure described for the preparation of **2.52**. Colourless oil (39 mg, 99%), equimolar mixture of diastereoisomers.[6] The crude material was used in the following step. **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 7.32 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 1.7 Hz, 1H), 7.00 (dd, *J* = 8.2 Hz, *J* = 1.7 Hz, 1H), 5.11–5.03 (m, 1H), 3.54–3.38 (m, 2H), 2.98–2.88 (m, 1H), 2.68–2.55 (m, 2H), 2.54–2.42 (m, 2H), 2.13–2.04 (m, 1H), 2.03–1.92 (m, 2H), 1.85–1.70 (m, 2H), 1.69–1.615 (m, 1H), 1.604–1.54 (m, 1H), 1.28 (t, J = 6.3 Hz, 1H), [*0.90 (d, J = 6.8 Hz, 3H)*], 0.87 (d, *J* = 6.7 Hz, 3H).

4 – References

[1] A. V. D. Ent, L. A. Onderdelinden, *Inorg. Synth.*, **1973**, *14*, 93.

[2] G. Schenck, J. M. Downes, C. R. C. Milne, P. B. Mackenzie, H. Boucher, J. Whelan, B. Bosnich, *Inorg. Chem.*, **1985**, *24*, 2334.

[3] C. Aïssa, A. Fürstner, *J. Am. Chem. Soc.*, **2007**, *129*, 14836.

[4] Additional signals for the minor isomer are included into brackets.

[5] A. Stolle, J. Ollivier, P. P. Piras, J. Salaün, A. de Meijere, *J. Am. Chem. Soc.*, **1992**, *114*, 4051.

[6] Both diastereoisomers have similar chemical shifts and additional signals are included into brackets.

[7] Extra peaks due to the tautomer form of the amide group are visible in ^{1}H and ^{13}C NMR and are given in brackets.

[8] T. Lectka, in Active metals (Ed.: A. Fürstner), VCH Publishers, New York, **1996**, chap. 3, 91.

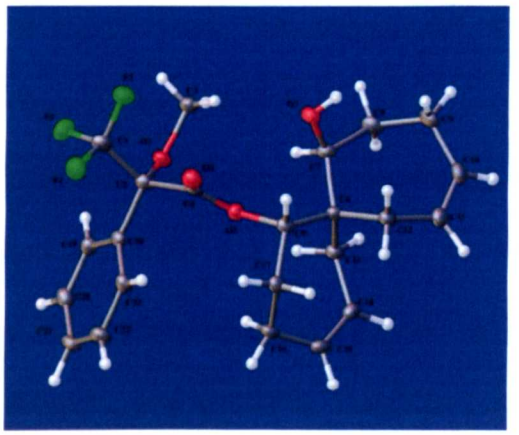
[9] Additional shifts for the minor isomer are given in brackets.

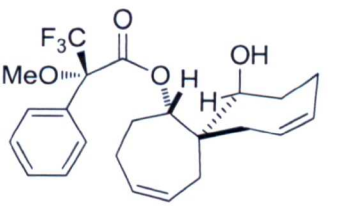
[10] a) C. Beard, A. Burger, J. Org. Chem., 1961, 26, 2335; b) T. Matsuda, M. Makino, M. Murakami, *Bull. Chem. Soc. Jpn.*, **2005**, *78*, 1528.

[11] Both diastereoisomers have the same chemical shifts.

Appendices

1 – X-ray data for compound (*S*,*S*,*S*,*S*)-3.16





(*S*,*S*,*S*,*S*)-**3.16**

$C_{23}H_{27}F_3O_4$
$M = 424.45$
colourless needle,
0.2 ´ 0.03 ´ 0.02 mm^3
Orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$
$a = 9.483(4)$,
$b = 9.942(4)$,
$c = 21.233(10)$ Å
$V = 2001.8(15)$ $Å^3$
$Z = 4$
$D_c = 1.408$ g/cm^3
MoKa radiation, l = 0.71073 Å
$T = 110(2)K$
$2q_{max} = 50.7°$
19389 reflections collected,
3664 unique
Multi-scan absorption correction
$R_{int} = 0.1332$
Final *GooF* = 1.062
R1 = 0.0557
wR2 = 0.1328
355 parameters, 46 restraints
$m = 0.113$ mm^{-1}

Data collection, structure solution and refinement

The crystals were supplied by Damien Crepin from the research group of Dr. Christophe Aissa. The crystals grew as very thin, long needles. A crystal was

mounted onto a nylon fibre with paratone oil and placed under a cold stream at 110K. Single crystal X-ray data were collected on a Bruker APEX diffractometer with 1.5 kW graphite monochromated Mo radiation. The data were from a merohedrally twinned crystal. Two components were indexed with cell_now and the second domain was rotated from first domain by 125.5 degrees about the *a*-axis. The data collection nominally covered a full sphere of reciprocal space by a combination of 3 sets of ω scans each set at different φ angles and each scan (60 s exposure) covering -0.30° degrees in ω yielding data in the θ range 1.92 to 25.35° with an average completeness of 99.8%. The crystal to detector distance was 5.985 cm. The frames were integrated with the SAINT v7.68a (Bruker, 2009).[1]

Two twin components were present. The data from both components were scaled and treated for absorption by the program TWINABS V2008-1 (Bruker, 2008)[2].

The structure was solved and refined with Olex2[3] and X-SEED[4], graphical interfaces to SHELX (Sheldrick, 2008).[5] The hydrogen atoms were located from difference electron density maps but were refined with constraints. In the final cycles of refinement all non-hydrogen atoms were refined anisotropically.

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1 Bruker (2009). SAINT V7.68a, BRUKER AXS Inc., Madison, WI, USA.

2 Bruker (2008), TWINABS V2008-1, BRUKER AXS Inc., Madison, WI, USA.

3 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann(2009). OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. 42, 339-341.
Supramol. Chem. **2001**, *1*, 189-191.

4 Barbour, L. J. "X-Seed – A software tool for supramolecular crystallography" *J. Supramol. Chem.* **2001**, *1*, 189-191.

5 Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal data and structure refinement for twin4_FIN.

Identification code	DFC0812302	
Empirical formula	C23 H27 F3 O4	
Formula weight	424.45	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.483(4) Å	α= 90°.
	b = 9.942(4) Å	β= 90°.
	c = 21.233(10) Å	γ = 90°.
Volume	2001.8(15) $Å^3$	
Z	4	
Density (calculated)	1.408 Mg/m^3	
Absorption coefficient	0.113 mm^{-1}	
F(000)	896	
Crystal size	0.2 x 0.03 x 0.02 mm^3	
Theta range for data collection	1.92 to 25.35°.	
Index ranges	-11<=h<=11, -11<=k<=11, -25<=l<=25	
Reflections collected	3664	
Independent reflections	3664 [R(int) = 0.0000]	
Completeness to theta = 25.35°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9977 and 0.9777	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3664 / 46 / 355	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0557, wR2 = 0.1328	
R indices (all data)	R1 = 0.0655, wR2 = 0.1384	
Absolute structure parameter	-0.4(9)	
Largest diff. peak and hole	0.296 and -0.277 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for twin4_FIN. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	3659(2)	1436(2)	2086(1)	29(1)
F(2)	3665(2)	3554(2)	2289(1)	30(1)
F(3)	5243(2)	2265(2)	2694(1)	31(1)
O(2)	669(2)	2446(2)	3487(1)	20(1)
O(1)	3451(2)	2846(2)	3634(1)	21(1)
O(4)	959(2)	2497(2)	2438(1)	25(1)
O(3)	-124(2)	5300(2)	3346(1)	26(1)
C(4)	1404(3)	2387(3)	2965(1)	20(1)
C(3)	3403(4)	4287(3)	3558(2)	25(1)
C(19)	4215(3)	211(3)	3694(2)	22(1)
C(20)	4353(3)	-1129(3)	3868(2)	26(1)
C(6)	-1275(3)	3562(3)	3998(1)	19(1)
C(13)	-1042(3)	2849(3)	4630(1)	22(1)
C(15)	-2181(3)	616(3)	4469(2)	28(1)
C(18)	3102(3)	603(3)	3317(1)	21(1)
C(5)	-871(3)	2666(3)	3435(1)	20(1)
C(14)	-2080(3)	1764(3)	4791(2)	25(1)
C(10)	-3158(3)	5864(3)	4663(2)	29(1)
C(7)	-274(3)	4809(3)	3975(2)	22(1)
C(2)	2963(3)	2072(3)	3123(1)	21(1)
C(12)	-2822(3)	3980(3)	3901(2)	23(1)
C(8)	-546(3)	5961(3)	4436(2)	26(1)
C(23)	2120(3)	-356(3)	3118(2)	24(1)
C(11)	-3514(3)	4664(3)	4450(2)	28(1)
C(17)	-1537(3)	1280(3)	3358(2)	24(1)
C(1)	3881(3)	2338(3)	2542(1)	24(1)
C(16)	-1339(4)	293(3)	3903(2)	27(1)
C(22)	2252(4)	-1688(3)	3306(2)	28(1)
C(9)	-1963(4)	6685(3)	4399(2)	30(1)
C(21)	3364(4)	-2074(3)	3688(2)	29(1)

Bond lengths [Å] and angles [°] for twin4_FIN.

F(1)-C(1)	1.337(3)
F(2)-C(1)	1.339(4)
F(3)-C(1)	1.334(4)
O(2)-C(4)	1.311(4)
O(2)-C(5)	1.481(3)
O(1)-C(3)	1.442(4)
O(1)-C(2)	1.408(4)
O(4)-C(4)	1.200(4)
O(3)-C(7)	1.430(4)
O(3)-H(3)	0.79(4)
C(4)-C(2)	1.548(4)
C(3)-H(3A)	0.89(4)
C(3)-H(3B)	0.99(3)
C(3)-H(3C)	0.95(4)
C(19)-C(20)	1.389(5)
C(19)-C(18)	1.381(5)
C(19)-H(19)	0.93(3)
C(20)-C(21)	1.381(5)
C(20)-H(20)	1.01(3)
C(6)-C(13)	1.533(4)
C(6)-C(5)	1.540(4)
C(6)-C(7)	1.563(4)
C(6)-C(12)	1.539(4)
C(13)-C(14)	1.500(4)
C(13)-H(13A)	0.987(11)
C(13)-H(13B)	0.986(11)
C(15)-C(14)	1.334(5)
C(15)-C(16)	1.478(5)
C(15)-H(15)	0.95(4)
C(18)-C(2)	1.524(4)
C(18)-C(23)	1.398(4)
C(5)-C(17)	1.525(4)
C(5)-H(5)	0.97(2)
C(14)-H(14)	1.04(3)
C(10)-C(11)	1.320(5)
C(10)-C(9)	1.506(5)
C(10)-H(10)	0.96(4)
C(7)-C(8)	1.528(4)
C(7)-H(7)	0.97(2)
C(2)-C(1)	1.533(4)
C(12)-C(11)	1.501(5)
C(12)-H(12A)	0.986(11)
C(12)-H(12B)	0.986(11)
C(8)-C(9)	1.526(5)
C(8)-H(8A)	0.986(11)
C(8)-H(8B)	0.987(11)
C(23)-C(22)	1.389(5)
C(23)-H(23)	0.92(3)
C(11)-H(11)	0.99(4)
C(17)-C(16)	1.530(4)
C(17)-H(17A)	0.986(11)
C(17)-H(17B)	0.987(11)
C(16)-H(16A)	0.89(4)
C(16)-H(16B)	0.98(3)
C(22)-C(21)	1.384(5)
C(22)-H(22)	0.92(3)
C(9)-H(9A)	0.986(11)

C(9)-H(9B)	0.987(11)
C(21)-H(21)	0.99(3)

C(4)-O(2)-C(5)	117.9(2)
C(2)-O(1)-C(3)	116.5(2)
C(7)-O(3)-H(3)	109(3)
O(2)-C(4)-C(2)	109.4(2)
O(4)-C(4)-O(2)	126.7(3)
O(4)-C(4)-C(2)	123.8(3)
O(1)-C(3)-H(3A)	107(2)
O(1)-C(3)-H(3B)	113.2(19)
O(1)-C(3)-H(3C)	103(2)
H(3A)-C(3)-H(3B)	110(3)
H(3A)-C(3)-H(3C)	111(3)
H(3B)-C(3)-H(3C)	113(3)
C(20)-C(19)-H(19)	118(2)
C(18)-C(19)-C(20)	119.7(3)
C(18)-C(19)-H(19)	122(2)
C(19)-C(20)-H(20)	121.3(19)
C(21)-C(20)-C(19)	121.0(3)
C(21)-C(20)-H(20)	117.6(19)
C(13)-C(6)-C(5)	112.1(2)
C(13)-C(6)-C(7)	107.9(2)
C(13)-C(6)-C(12)	112.3(2)
C(5)-C(6)-C(7)	106.5(2)
C(12)-C(6)-C(5)	106.8(2)
C(12)-C(6)-C(7)	111.2(2)
C(6)-C(13)-H(13A)	106.8(18)
C(6)-C(13)-H(13B)	113.9(19)
C(14)-C(13)-C(6)	116.0(2)
C(14)-C(13)-H(13A)	110.3(19)
C(14)-C(13)-H(13B)	105.3(19)
H(13A)-C(13)-H(13B)	104(3)
C(14)-C(15)-C(16)	124.3(3)
C(14)-C(15)-H(15)	121(2)
C(16)-C(15)-H(15)	114(2)
C(19)-C(18)-C(2)	119.5(3)
C(19)-C(18)-C(23)	119.5(3)
C(23)-C(18)-C(2)	120.9(3)
O(2)-C(5)-C(6)	105.9(2)
O(2)-C(5)-C(17)	106.4(2)
O(2)-C(5)-H(5)	105.7(19)
C(6)-C(5)-H(5)	110(2)
C(17)-C(5)-C(6)	120.2(2)
C(17)-C(5)-H(5)	107(2)
C(13)-C(14)-H(14)	115.9(19)
C(15)-C(14)-C(13)	123.1(3)
C(15)-C(14)-H(14)	121(2)
C(11)-C(10)-C(9)	123.7(3)
C(11)-C(10)-H(10)	115(2)
C(9)-C(10)-H(10)	121(2)
O(3)-C(7)-C(6)	111.1(2)
O(3)-C(7)-C(8)	111.1(3)
O(3)-C(7)-H(7)	106.5(19)
C(6)-C(7)-H(7)	106(2)
C(8)-C(7)-C(6)	118.2(3)
C(8)-C(7)-H(7)	102.5(19)
O(1)-C(2)-C(4)	111.8(2)
O(1)-C(2)-C(18)	106.7(2)

O(1)-C(2)-C(1)	109.8(2)
C(18)-C(2)-C(4)	109.6(3)
C(18)-C(2)-C(1)	109.4(2)
C(1)-C(2)-C(4)	109.4(2)
C(6)-C(12)-H(12A)	106.8(19)
C(6)-C(12)-H(12B)	110.7(19)
C(11)-C(12)-C(6)	115.7(3)
C(11)-C(12)-H(12A)	108.8(19)
C(11)-C(12)-H(12B)	111.7(19)
H(12A)-C(12)-H(12B)	102(3)
C(7)-C(8)-H(8A)	109.0(19)
C(7)-C(8)-H(8B)	106.8(19)
C(9)-C(8)-C(7)	117.9(3)
C(9)-C(8)-H(8A)	110.7(19)
C(9)-C(8)-H(8B)	107.4(19)
H(8A)-C(8)-H(8B)	104(3)
C(18)-C(23)-H(23)	123(2)
C(22)-C(23)-C(18)	120.2(3)
C(22)-C(23)-H(23)	117(2)
C(10)-C(11)-C(12)	124.4(3)
C(10)-C(11)-H(11)	119(2)
C(12)-C(11)-H(11)	117(2)
C(5)-C(17)-C(16)	116.6(3)
C(5)-C(17)-H(17A)	107(2)
C(5)-C(17)-H(17B)	103.8(19)
C(16)-C(17)-H(17A)	107.1(19)
C(16)-C(17)-H(17B)	110.8(19)
H(17A)-C(17)-H(17B)	112(3)
F(1)-C(1)-F(2)	106.8(2)
F(1)-C(1)-C(2)	112.3(2)
F(2)-C(1)-C(2)	113.1(2)
F(3)-C(1)-F(1)	107.0(2)
F(3)-C(1)-F(2)	107.1(2)
F(3)-C(1)-C(2)	110.2(2)
C(15)-C(16)-C(17)	114.2(3)
C(15)-C(16)-H(16A)	106(2)
C(15)-C(16)-H(16B)	112.8(19)
C(17)-C(16)-H(16A)	111(2)
C(17)-C(16)-H(16B)	109.3(18)
H(16A)-C(16)-H(16B)	103(3)
C(23)-C(22)-H(22)	117(2)
C(21)-C(22)-C(23)	120.1(3)
C(21)-C(22)-H(22)	123(2)
C(10)-C(9)-C(8)	112.8(3)
C(10)-C(9)-H(9A)	109.1(18)
C(10)-C(9)-H(9B)	110(2)
C(8)-C(9)-H(9A)	107.2(18)
C(8)-C(9)-H(9B)	109.3(19)
H(9A)-C(9)-H(9B)	108(3)
C(20)-C(21)-C(22)	119.4(3)
C(20)-C(21)-H(21)	123.3(19)
C(22)-C(21)-H(21)	117.3(19)

Symmetry transformations used to generate equivalent atoms

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for twin4_FIN. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2\, a^{*2} U^{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	32(1)	28(1)	28(1)	-7(1)	4(1)	-2(1)
F(2)	33(1)	21(1)	34(1)	4(1)	3(1)	-1(1)
F(3)	21(1)	36(1)	36(1)	1(1)	3(1)	-3(1)
O(2)	16(1)	17(1)	28(1)	0(1)	0(1)	1(1)
O(1)	22(1)	11(1)	29(1)	-1(1)	-2(1)	-2(1)
O(4)	25(1)	22(1)	28(1)	-2(1)	-3(1)	-1(1)
O(3)	32(1)	15(1)	31(1)	2(1)	4(1)	1(1)
C(4)	22(1)	8(2)	30(2)	0(1)	-3(1)	-2(1)
C(3)	24(2)	17(2)	33(2)	-1(1)	2(2)	-2(1)
C(19)	21(2)	19(2)	27(2)	-3(1)	2(1)	-2(1)
C(20)	29(2)	23(2)	28(2)	-2(1)	3(2)	5(1)
C(6)	18(1)	13(2)	27(2)	2(1)	0(1)	-2(1)
C(13)	23(2)	15(2)	28(2)	2(1)	-1(1)	0(1)
C(15)	22(2)	18(2)	45(2)	10(2)	-1(2)	-2(1)
C(18)	25(2)	16(2)	22(2)	-2(1)	5(1)	1(1)
C(5)	18(1)	17(2)	26(2)	1(1)	-5(1)	0(1)
C(14)	19(2)	25(2)	30(2)	9(1)	3(1)	1(1)
C(10)	29(2)	23(2)	36(2)	1(1)	5(2)	11(1)
C(7)	23(2)	17(2)	24(2)	2(1)	-2(1)	-4(1)
C(2)	22(2)	17(2)	24(2)	-1(1)	-4(1)	-2(1)
C(12)	20(2)	16(2)	32(2)	2(1)	-1(1)	1(1)
C(8)	30(2)	17(2)	31(2)	-2(1)	-6(2)	-4(1)
C(23)	21(2)	19(2)	31(2)	-5(1)	-1(1)	1(1)
C(11)	23(2)	24(2)	37(2)	4(1)	3(2)	5(1)
C(17)	19(2)	19(2)	35(2)	1(1)	-2(1)	0(1)
C(1)	24(2)	20(2)	30(2)	-2(1)	-6(1)	-3(1)
C(16)	26(2)	12(2)	45(2)	5(1)	-1(2)	0(1)
C(22)	33(2)	16(2)	37(2)	-2(1)	1(2)	-4(1)
C(9)	39(2)	16(2)	35(2)	-4(1)	3(2)	2(1)
C(21)	38(2)	13(2)	36(2)	4(1)	6(2)	3(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for twin4_FIN.

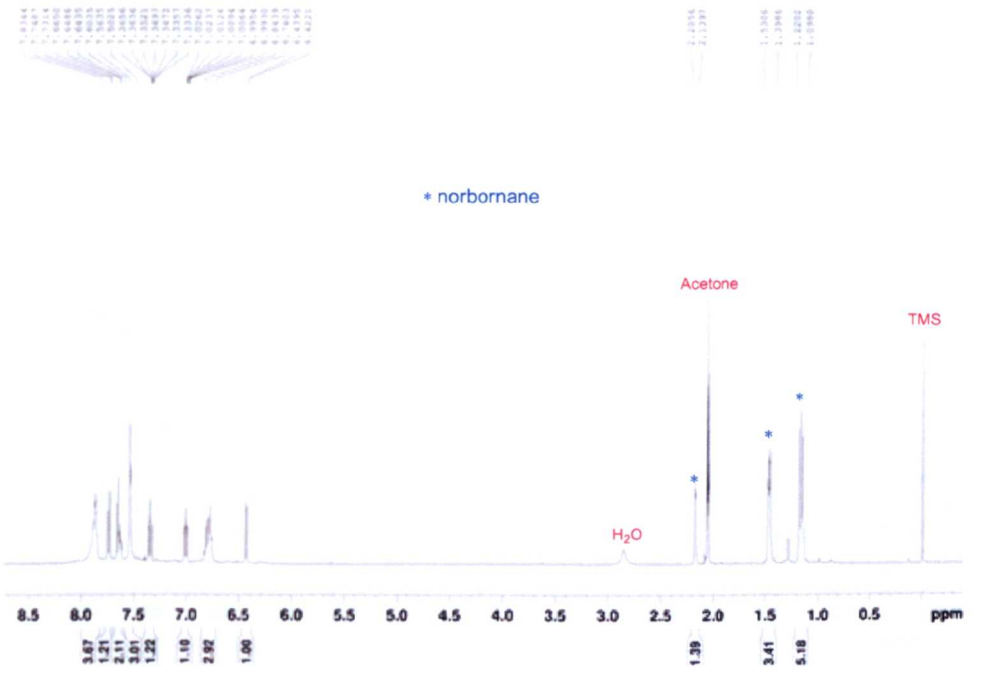
	x	y	z	U(eq)
H(3A)	4160(40)	4520(30)	3330(16)	23(2)
H(21)	3420(30)	-3040(40)	3806(15)	23(4)
H(14)	-2710(40)	1940(40)	5181(16)	29(5)
H(22)	1580(40)	-2280(30)	3170(15)	23(4)
H(7)	650(30)	4490(30)	4104(14)	23(2)
H(3B)	2530(40)	4610(30)	3345(15)	23(2)
H(20)	5180(40)	-1450(30)	4128(15)	23(4)
H(10)	-3660(40)	6160(40)	5033(16)	29(5)
H(17A)	-2560(13)	1420(30)	3306(15)	23(2)
H(9A)	-1870(30)	7524(19)	4643(13)	23(2)
H(9B)	-2160(30)	6920(30)	3956(7)	23(2)
H(19)	4890(40)	820(30)	3842(16)	23(4)
H(3C)	3490(30)	4600(30)	3980(17)	23(2)
H(23)	1390(40)	-150(30)	2850(15)	23(4)
H(5)	-1010(30)	3150(30)	3041(13)	23(2)
H(8A)	-370(30)	5640(30)	4869(7)	23(2)
H(11)	-4360(40)	4220(40)	4631(16)	29(5)
H(16A)	-440(40)	280(30)	4028(15)	23(2)
H(15)	-2850(40)	-60(40)	4583(15)	29(5)
H(8B)	200(30)	6640(30)	4363(15)	23(2)
H(17B)	-1100(30)	930(30)	2969(9)	23(2)
H(16B)	-1500(30)	-620(40)	3752(14)	23(2)
H(3)	-590(40)	5950(40)	3305(16)	23(2)
H(13A)	-76(17)	2480(30)	4622(14)	23(2)
H(13B)	-1040(30)	3460(30)	4996(10)	23(2)
H(12A)	-3350(30)	3150(20)	3801(15)	23(2)
H(12B)	-2930(30)	4500(30)	3509(9)	23(2)

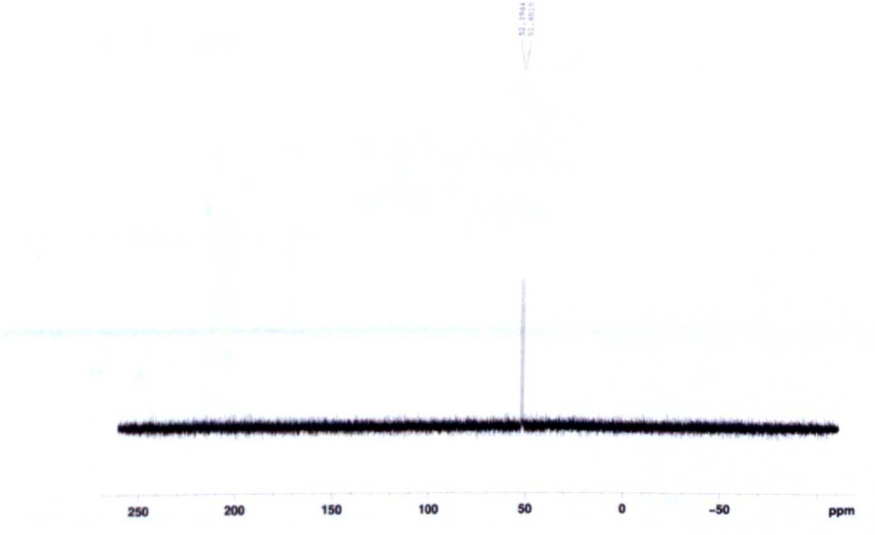
Torsion angles [°] for twin4_FIN.

O(2)-C(4)-C(2)-O(1)	-44.5(3)
O(2)-C(4)-C(2)-C(18)	73.6(3)
O(2)-C(4)-C(2)-C(1)	-166.4(2)
O(2)-C(5)-C(17)-C(16)	62.3(3)
O(1)-C(2)-C(1)-F(1)	167.0(2)
O(1)-C(2)-C(1)-F(2)	-72.1(3)
O(1)-C(2)-C(1)-F(3)	47.8(3)
O(4)-C(4)-C(2)-O(1)	138.4(3)
O(4)-C(4)-C(2)-C(18)	-103.5(3)
O(4)-C(4)-C(2)-C(1)	16.5(4)
O(3)-C(7)-C(8)-C(9)	69.3(4)
C(4)-O(2)-C(5)-C(6)	-144.0(2)
C(4)-O(2)-C(5)-C(17)	87.0(3)
C(4)-C(2)-C(1)-F(1)	-70.0(3)
C(4)-C(2)-C(1)-F(2)	51.0(3)
C(4)-C(2)-C(1)-F(3)	170.8(2)
C(3)-O(1)-C(2)-C(4)	-59.5(3)
C(3)-O(1)-C(2)-C(18)	-179.3(2)
C(3)-O(1)-C(2)-C(1)	62.1(3)
C(19)-C(20)-C(21)-C(22)	2.9(5)
C(19)-C(18)-C(2)-O(1)	-34.5(4)
C(19)-C(18)-C(2)-C(4)	-155.8(3)
C(19)-C(18)-C(2)-C(1)	84.3(3)
C(19)-C(18)-C(23)-C(22)	0.8(5)
C(20)-C(19)-C(18)-C(2)	-179.5(3)
C(20)-C(19)-C(18)-C(23)	0.6(4)
C(6)-C(13)-C(14)-C(15)	66.3(4)
C(6)-C(5)-C(17)-C(16)	-57.8(4)
C(6)-C(7)-C(8)-C(9)	-60.8(4)
C(6)-C(12)-C(11)-C(10)	66.9(4)
C(13)-C(6)-C(5)-O(2)	-64.9(3)
C(13)-C(6)-C(5)-C(17)	55.5(3)
C(13)-C(6)-C(7)-O(3)	163.4(2)
C(13)-C(6)-C(7)-C(8)	-66.5(3)
C(13)-C(6)-C(12)-C(11)	46.6(4)
C(18)-C(19)-C(20)-C(21)	-2.4(5)
C(18)-C(2)-C(1)-F(1)	50.1(3)
C(18)-C(2)-C(1)-F(2)	171.1(2)
C(18)-C(2)-C(1)-F(3)	-69.1(3)
C(18)-C(23)-C(22)-C(21)	-0.4(5)
C(5)-O(2)-C(4)-O(4)	0.2(4)
C(5)-O(2)-C(4)-C(2)	-176.8(2)
C(5)-C(6)-C(13)-C(14)	-73.2(3)
C(5)-C(6)-C(7)-O(3)	42.9(3)
C(5)-C(6)-C(7)-C(8)	173.0(3)
C(5)-C(6)-C(12)-C(11)	169.9(3)
C(5)-C(17)-C(16)-C(15)	72.6(4)
C(14)-C(15)-C(16)-C(17)	-59.5(4)
C(7)-C(6)-C(13)-C(14)	169.9(3)
C(7)-C(6)-C(5)-O(2)	52.8(3)
C(7)-C(6)-C(5)-C(17)	173.2(3)
C(7)-C(6)-C(12)-C(11)	-74.3(3)
C(7)-C(8)-C(9)-C(10)	74.2(4)
C(2)-C(18)-C(23)-C(22)	-179.1(3)
C(12)-C(6)-C(13)-C(14)	47.1(4)
C(12)-C(6)-C(5)-O(2)	171.7(2)
C(12)-C(6)-C(5)-C(17)	-67.9(3)

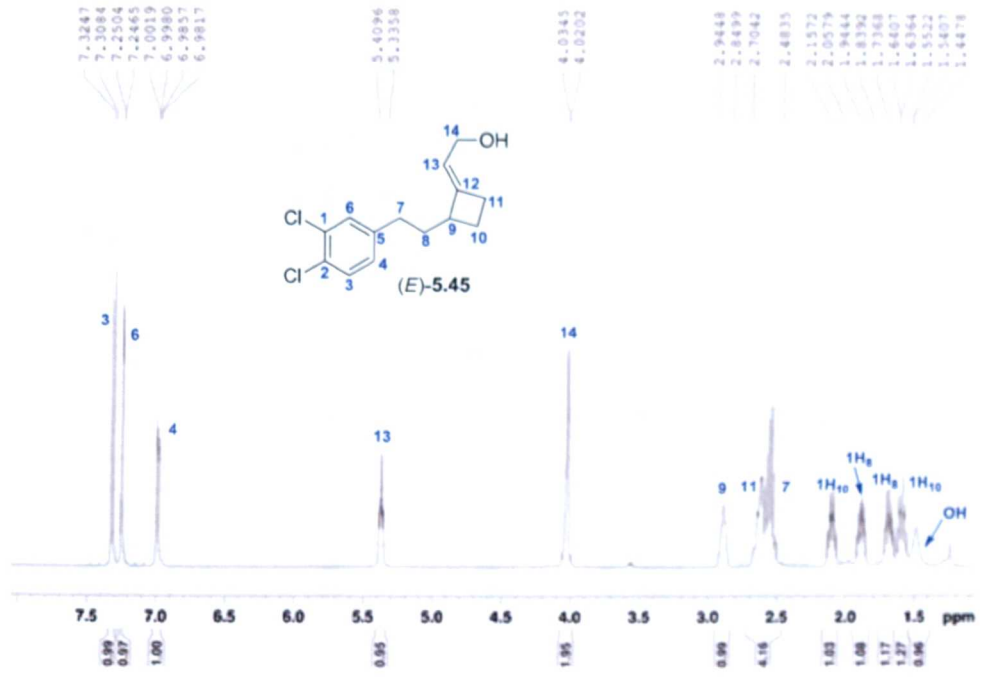
C(12)-C(6)-C(7)-O(3)	-73.1(3)
C(12)-C(6)-C(7)-C(8)	57.1(4)
C(23)-C(18)-C(2)-O(1)	145.4(3)
C(23)-C(18)-C(2)-C(4)	24.2(4)
C(23)-C(18)-C(2)-C(1)	-95.8(3)
C(23)-C(22)-C(21)-C(20)	-1.4(5)
C(11)-C(10)-C(9)-C(8)	-58.7(4)
C(16)-C(15)-C(14)-C(13)	-2.7(5)
C(9)-C(10)-C(11)-C(12)	-2.7(5)

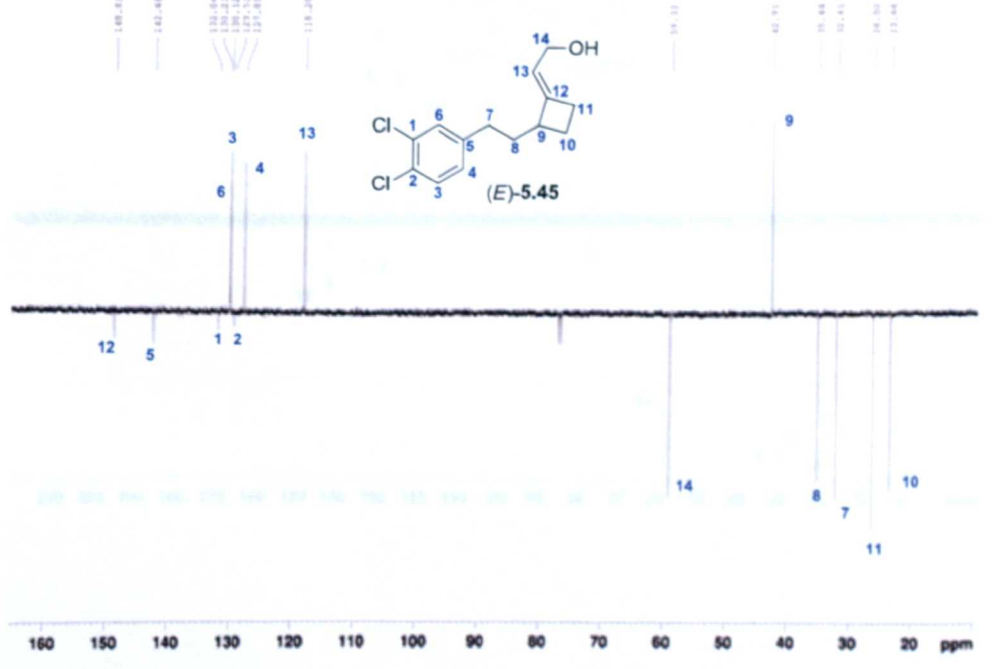
2 – ^{1}H and ^{31}P NMR of $[Rh(Binap)]BF_4$ in C_3D_6O

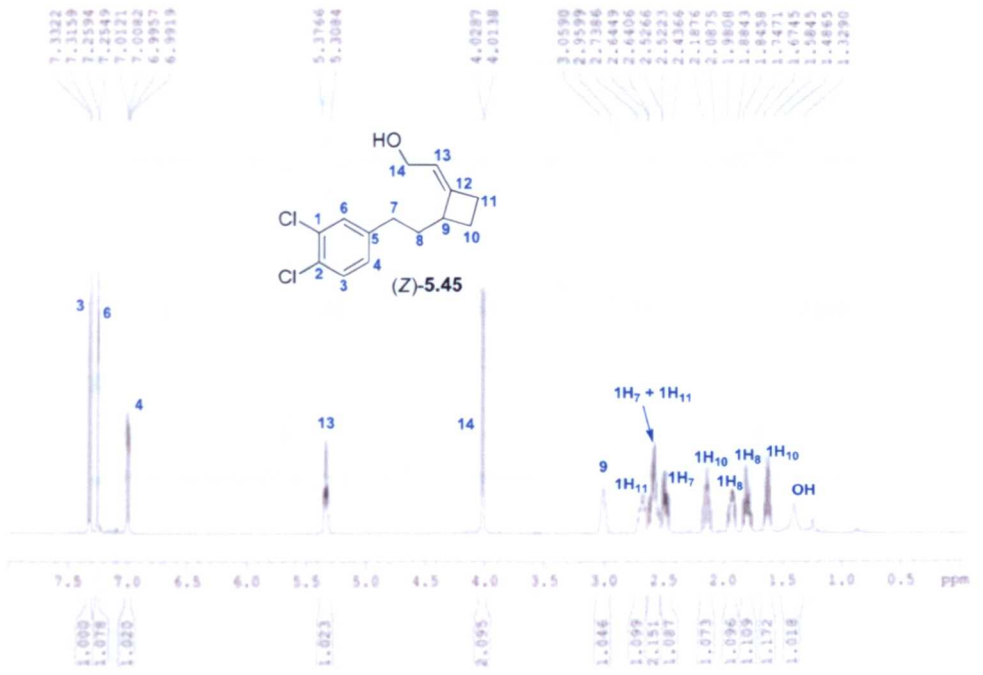


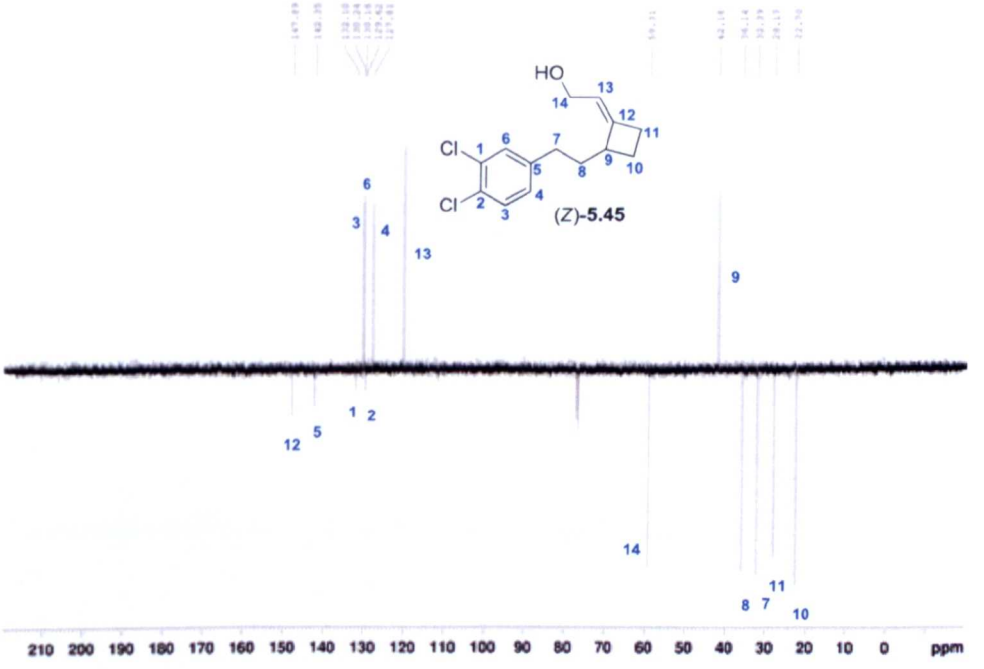


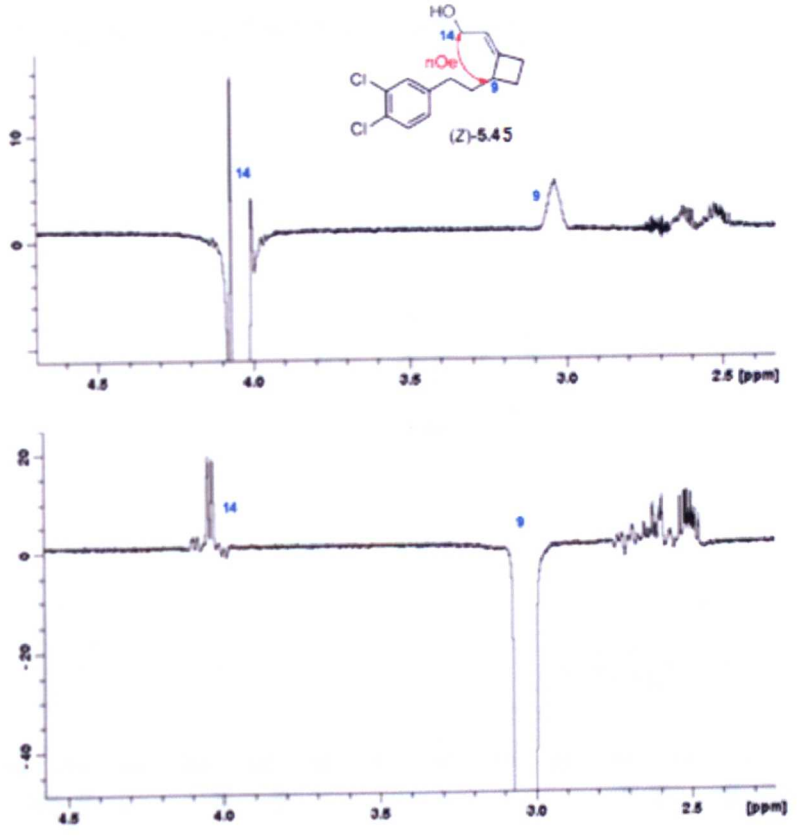
3 – NMR of compounds (*E*)-5.46 and (*Z*)-5.46



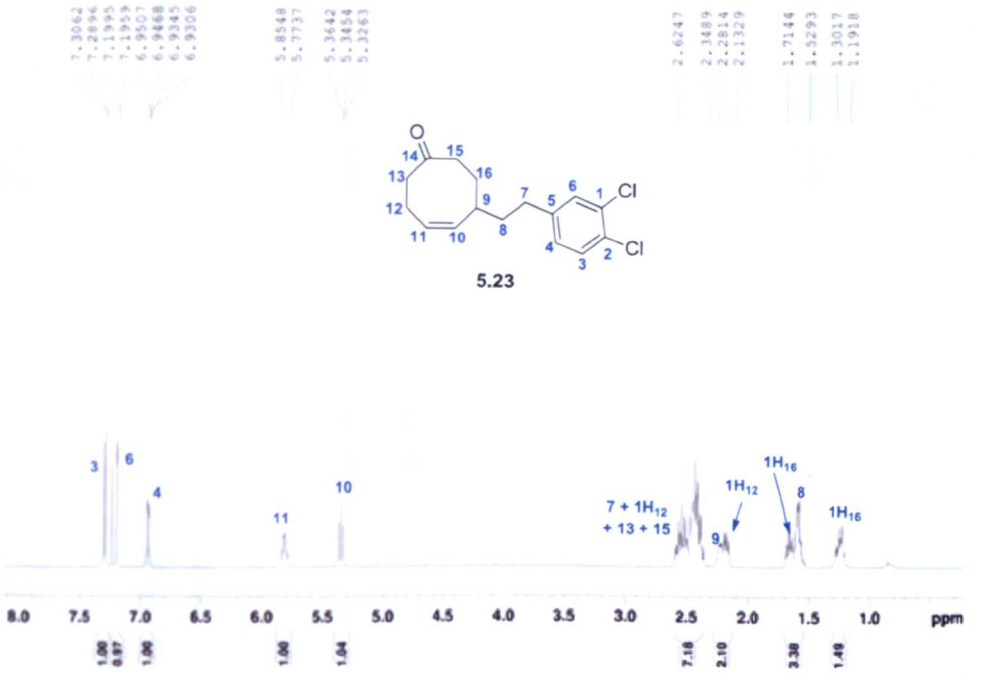


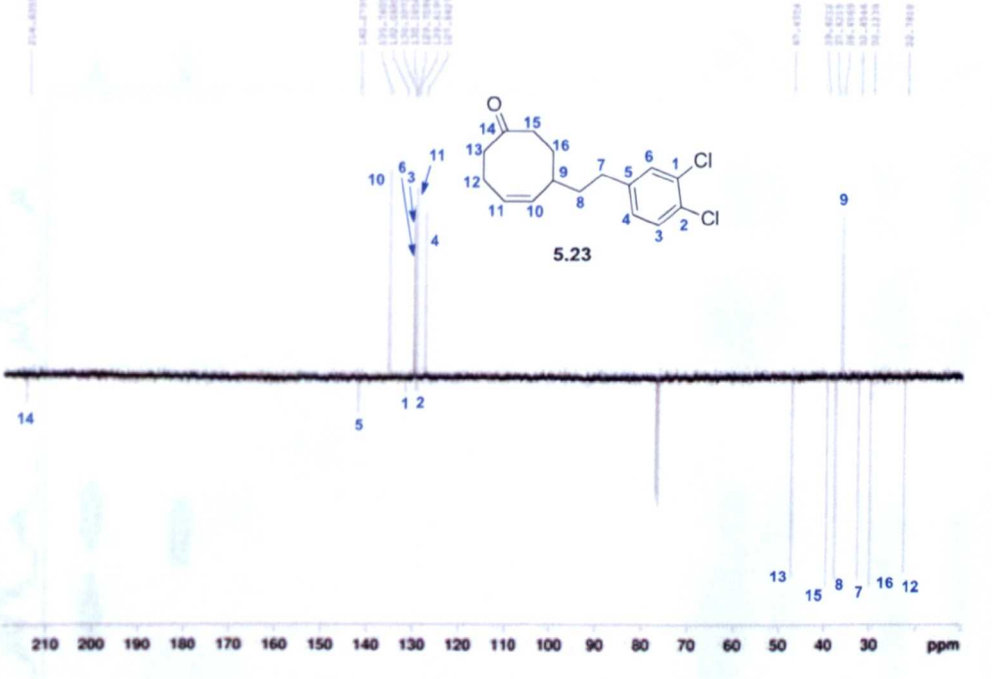

HO
13
14
12
11
Cl
1
6
7
5
8
9
10
Cl
2
4
3
(Z)-5.45
3
6
4
13
14
9
1H11
1H7 + 1H11
1H7
1H10
1H8
1H8
1H10
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


HO
13
14
12
11
Cl
1
6
7
5
8
9
10
Cl
2
4
3
(Z)-5.45
6
3
4
13
9
12
5
1
2
14
8
7
11
10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

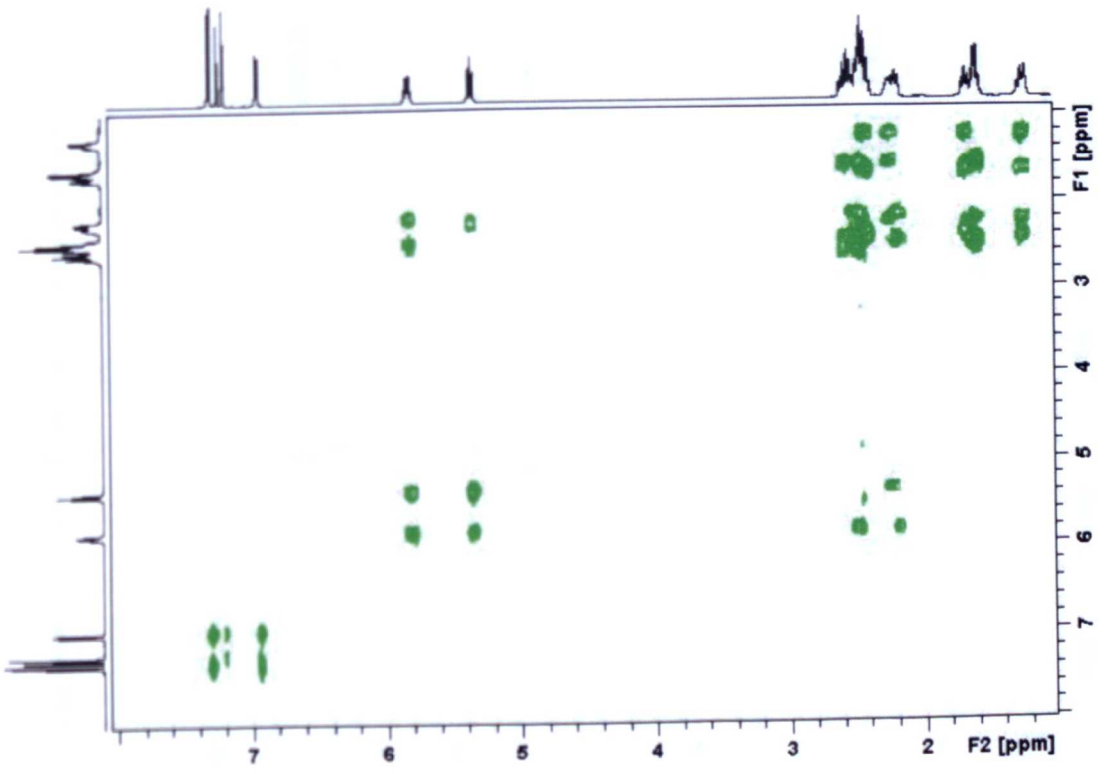

HO
14
nOe
9
Cl
Cl
(Z)-5.45
14
9
4.5
4.0
3.5
3.0
2.5 [ppm]
14
9
4.5
4.0
3.5
3.0
2.5
[ppm]

4 – NMR of compounds 5.23, 5.23Dα and 5.23Dβ

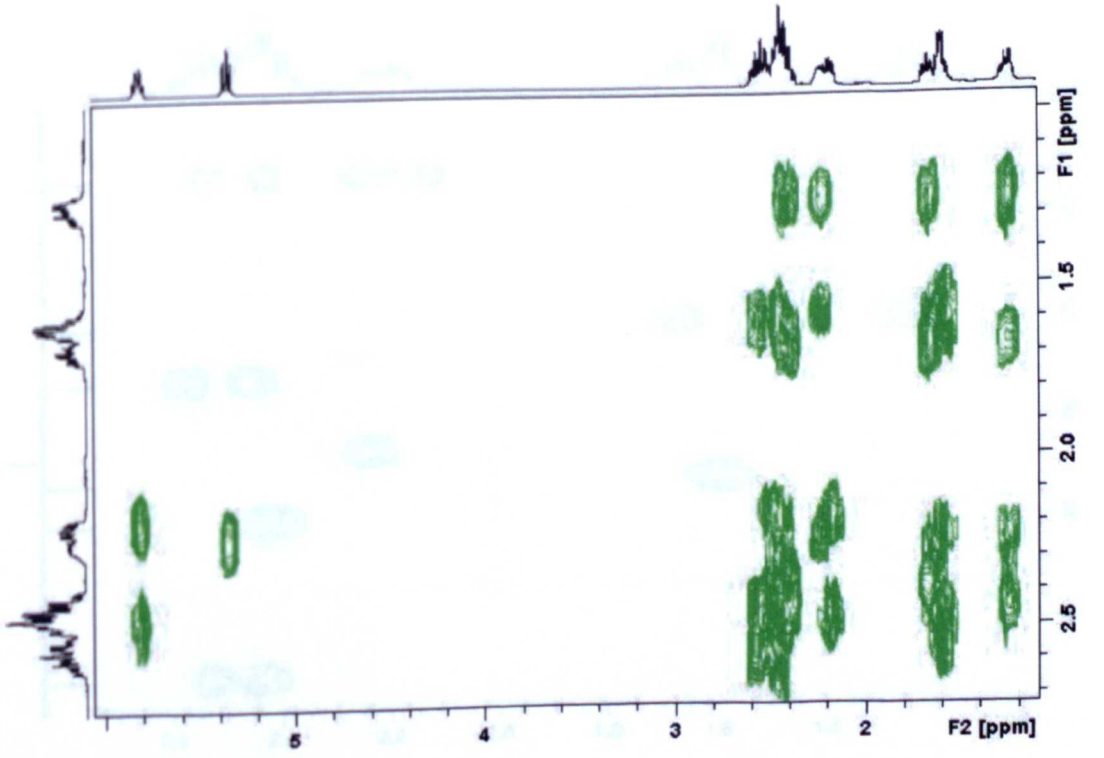




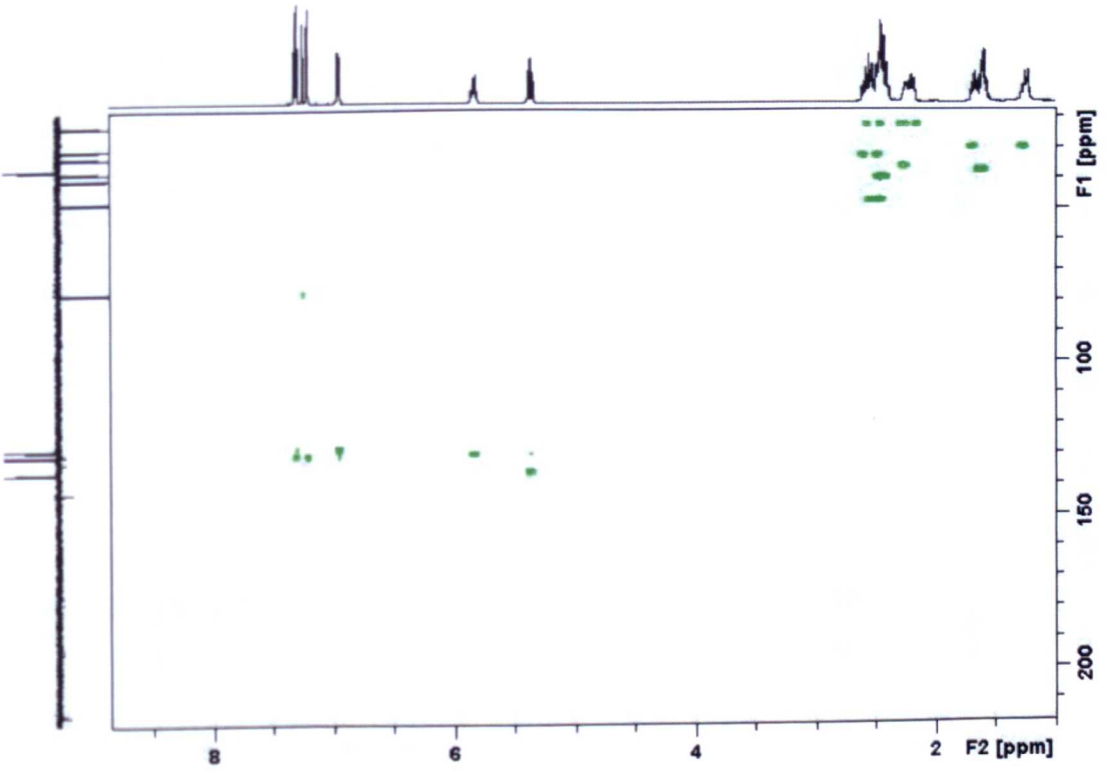
Compound **5.23** – COSY 1



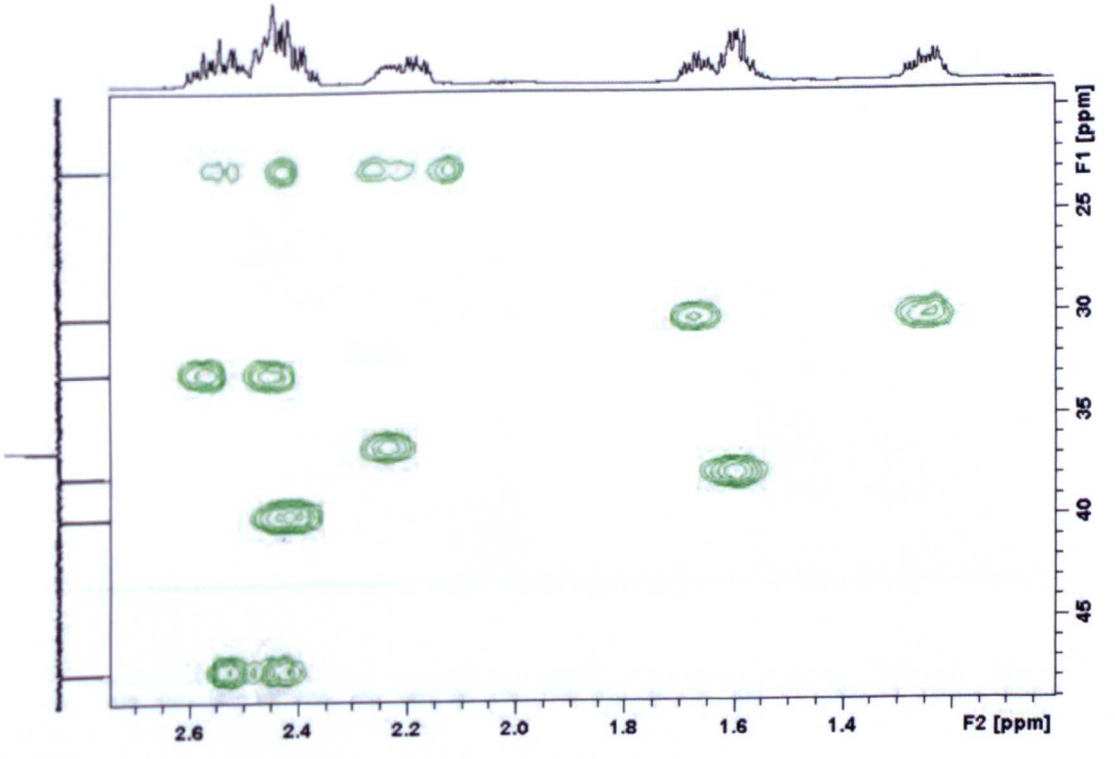
Compound **5.23** – COSY 2



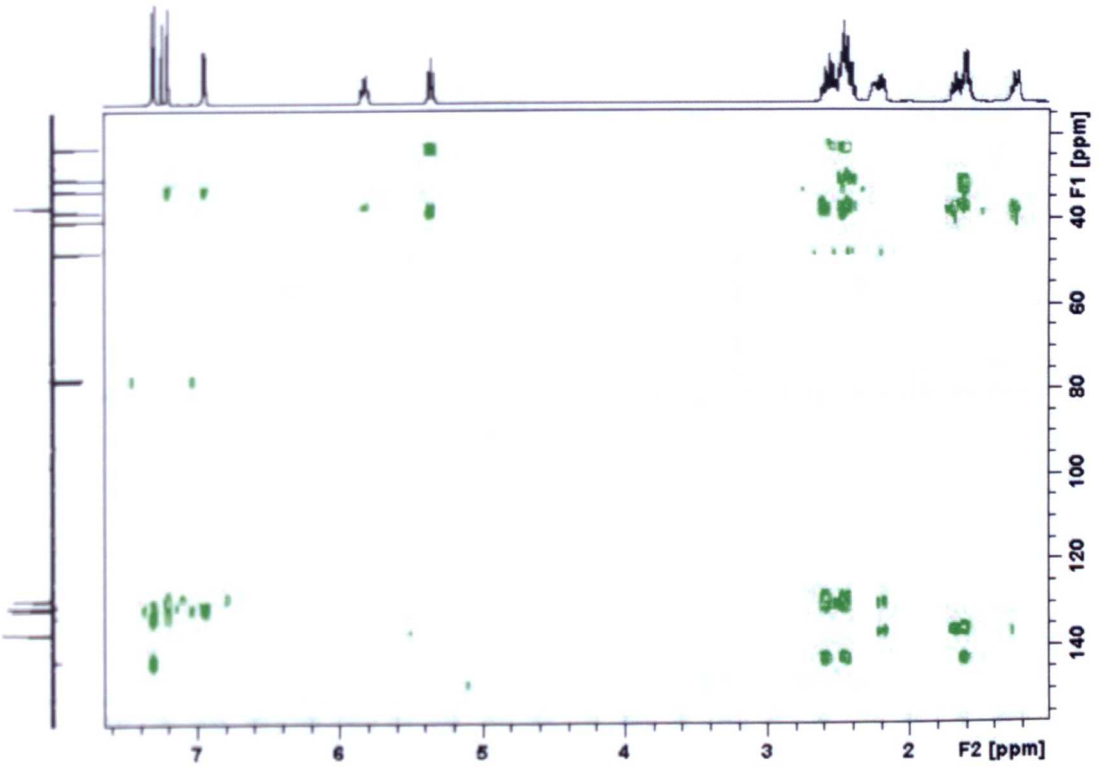
Compound **5.23** – HSQC 1



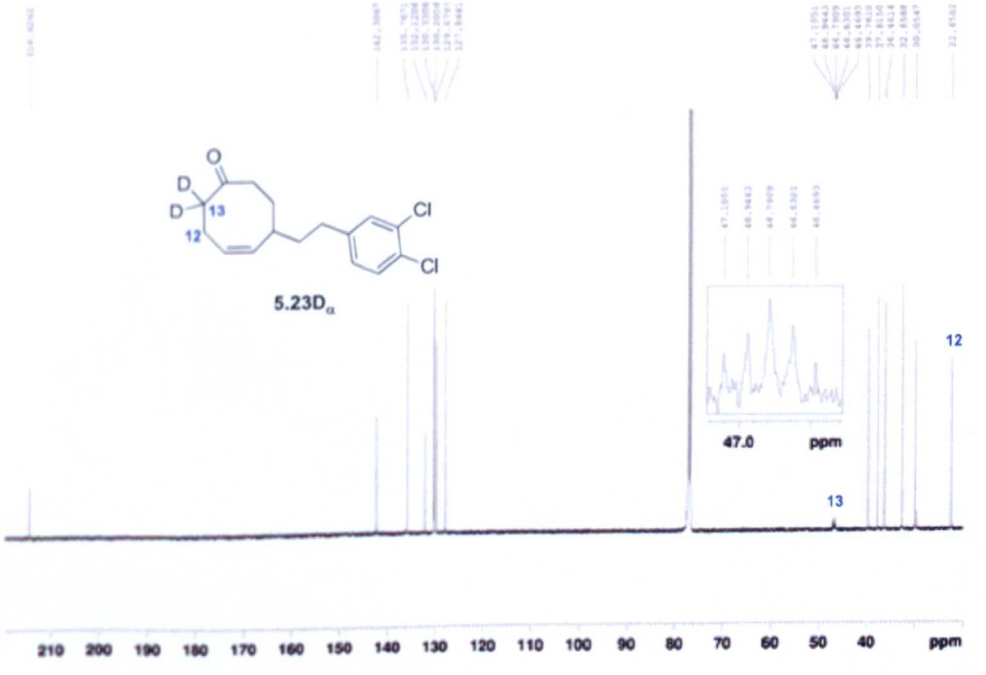
Compound **5.23** – HSQC 2



Compound **5.23** – HMBC



Compound **5.23Dα**



Compound **5.23Dβ**