Synthesis of the Taxol Core Using Asymmetric 1,4-Additions



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Abbreviations

Δ	heat
°C	Degree/s Celsius
ACA	asymmetric conjugate addition
APCI	Atmospheric-pressure chemical ionization
aq.	aqueous
Bn	benzyl
br	broad
brsm	based on recovered starting material
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
cm^{-1}	wave number
COSY	correlated spectroscopy
δ	chemical shift
d	doublet(s) or day(s)
dba	dibenzylideneacetone
DME	dimethoxyethane
DMF	dimethylformamide
DMAP	4-dimethylaminopyridine
DIBAL	diisobutylaluminium hydride
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)-ferrocene
EI	electron impact
equiv.	(molar) equivalent(s)
ESI	electrospray ionisation
Et	ethyl
eV	electron Volts
hr(s)	hour(s)
HMBC	heteronuclear multiple bond correlation

HMDS	hexamethyldisilane	Ph	phenyl
HMPA	hexamethylphosphoramide	pin	pinacol
HRMS	high resolution mass spectrometry	ppm	parts per million
		Pr	propyl
HSQC	heteronuclear single quantum coherence	pyr	pyridine
		q	quartet
HPLC	high pressure liquid chromatagraphy	RCM	ring-closing metathesis
		rt	room temperature
Hz	Hertz	s	singlet or seconds
J	coupling constant	SFC	supercritical fluid chromatography
M	molar ($mol.L^{-1}$)		
M+	molecular ion	TBS	*tert*-butyldimethylsilyl
Me	methyl	TES	triethylsilyl
min	minute	Tf	trifluoromethanesulfonyl
MHz	megahertz	THF	tetrahydrofuran
m/z	mass to charge ratio	TLC	thin layer chromatography
nOe	nuclear Overhauser effect	TMS	trimethylsilyl
NOESY	nuclear Overhauser effect and exchange spectroscopy	TMSCl	chlorotrimethylsilane
		Ts	*para*-toluenesulfonyl
NMR	nuclear magnetic resonance spectroscopy	*p*-TsOH	*para*-toluenesulfonic acid

Abstract

The topic of this thesis is the synthesis of Taxane derivatives using the asymmetric conjugate addition of alkenes. Taxol is an important anti-cancer drug and owing to its complex structure, remains a subject of fascination by chemists. The asymmetric conjugate addition of alkenes is a power transformation and holds promise in synthesising complex molecules such as Taxol. In Chapter 1, we prove that this is a feasible undertaking by synthesising the C-ring of the Taxol core containing the C8 stereocenter. A complex nucleophile containing a bromide and substituted alkene was successfully synthesised on decagram scale and underwent asymmetric conjugate addition to give this intermediate in 95% yield and 88% *ee*.

In Chapter 2, the trapping of zirconium enolates generated from asymmetric conjugate additions was investigated. Several electrophiles were screened and it was found that only formaldehyde or the Vilsmeier-Haack reagent would give rise to any trapped products. The Vilsmeier-Haack reagent, gave β-chloroaldehydes in modest yields (between 41-60%) and high enantioselectivities (up to 98% *ee*) for adducts containing quaternary stereocenters. The synthetic utility of these compounds was also demonstrated by synthesising derivatives (Grignard addition and Suzuki-Miyaura couplings).

In Chapter 3, we envisged using an unprecedented transannular electrocyclic reaction as a key step to simultaneously form the A and B rings. The precursor 10-membered ring was synthesised by cross metathesis of an intermediate prepared in chapter 2, with a geminal diboron butadiene followed by ring closing Suzuki coupling. Ultimately, we were unsuccessful in carrying out the desired electrocyclic reaction. We discuss possible reasons as to why this was the case.

In Chapter 4, the type-II intramolecular Diels–Alder reaction is reviewed in the context of Taxane syntheses and then applied to our model substrate. Using this reaction, we were able to achieve our original objective by synthesising the Taxol core in five steps from simple starting materials in 11% yield, 92% *ee* and 1:1 *d.r.* at C1.

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Chapter 1

Studies towards the synthesis of the taxol core

1.1 Introduction and structure of the thesis

The layout of this thesis will be as follows. In the first part of this chapter, a brief history of Taxol is given and all syntheses to date are discussed. In the second part of this chapter, asymmetric conjugate additions ACAs using alkene pronucleophiles is discussed with a particular emphasis on quaternary-center-forming reactions. The purpose of these two sections is to provide the context for our approach, which is to use the asymmetric conjugate addition ACA to assemble the Taxol core; specifically, to set the stereochemistry at C8 (see Scheme 1.1 for compound numbering). The third part of chapter 1 shows early results which confirmed that our approach towards the Taxol core would be feasible.

In the second chapter, the focus is on functionalising zirconium enolates gen-

erated through asymmetric conjugate additions. The prior art is reviewed and examples containing zirconium enolates are shown to be far fewer in number compared to enolates involving lithium, aluminium and magnesium. The motivation behind chapter 2 is to address a shortcoming identified in chapter 1, namely the difficulty of α-functionalisation of ACA electrophiles. A procedure is presented that obtains β-chloroaldehydes from zirconium enolates. This constitutes a formal trapping reaction of the zirconium enolates derived from asymmetric conjugate additions of alkenes and is a partial solution to the problem we initially set out to solve.

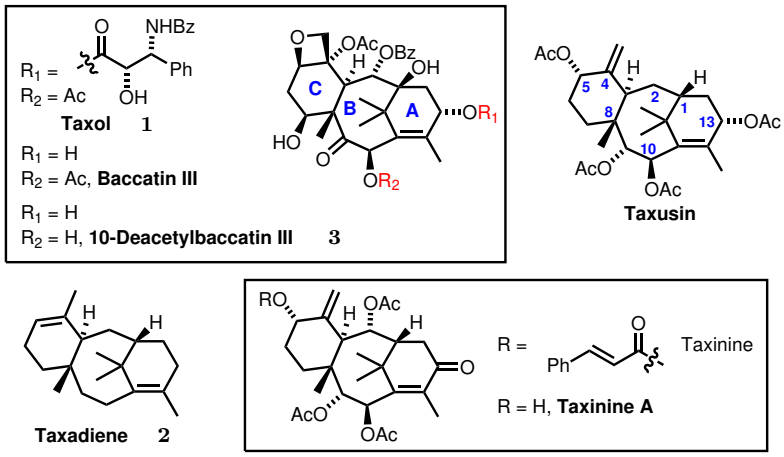
Finally, chapter 3 and 4 chronicle our approaches towards synthesising the Taxol core. Chapter 3 describes our attempts to prepare a 10-membered ring. The ambitious but ultimately unsuccessful idea behind this chapter, is the simultaneous formation of both A/B rings (see Scheme 1.1 for ring labelling) using a transannular electrocyclic reaction. In the fourth and final chapter, we complete the synthesis of the Taxol core using a strategy previously reported in the literature: the type II intramolecular Diels–Alder reaction. Future work is also discussed in this section.

1.2 Background and project aims

1.2.1 Taxol: history, biosynthesis and a review of synthetic efforts

Taxol (**1** in Scheme 1.1) is a multibillion dollar anticancer drug and one of the most widely studied natural metabolites. Its successful use in treating various

types of cancer has led to numerous studies on its mechanism of action. Taxol's cellular target is the β unit of tubulin heterodimers.[1] It binds to microtubules and by promoting their polymerisation, cellular proliferation is inhibited even in the absence of GTP.[2]



Scheme 1.1: Some key taxanes including Taxol **1**. Ring labels and skeleton numbering are shown on Baccatin III and Taxusin, respectively.

Structurally, Taxol is a tetracyclic diterpene and was first isolated from the Western Yew tree *Taxus brevifolia* in 1970 by Wani and co-workers[3] (although several species of the genus *Taxus* are known to produce Taxanes).[4] The main source of Taxol **1** is in the bark of the yew and exists in concentrations between 0.01 – 0.05%wt. The scarcity of Taxol in nature has led to great efforts in developing synthetic sources. Additionally, the process is entirely unsustainable: one kilogram of the compound can treat five hundred patients but requires ten tons of bark (three hundred Yew trees) whereupon the harvesting process kills the sixty year old trees.[5d]

Chemical synthesis was once hailed as the 'golden goose' for solving this supply problem. Due to the difficulty of assembling Taxol from scratch, semi-syntheses were exclusively used in early commercial routes. Two examples are the Potier route and the collaboration between Holton's group and Bristol-Myers-Squibb. Both entailed the transformation of 10-decacetylbaccatin III **3**, isolated from the English Yew, into Taxol **1**. The advantage of this route was the shrub from which **3** was obtained, could be grown in a farm style layout. The harvesting process involved trimming the leaves of the shrub which would regrow in three to four years after each harvest. Since this did not kill the plant, it was a much more sustainable source of a Taxol precursor compared to using the bark of the Yew tree.[5b]

More recently, Taxol and related intermediates used in its semi synthesis have been grown from cell cultures, obviating the need for labour-intensive harvesting of plants. These biochemical methods include the use of plant tissue cultures, microbial fermentation and fungi that produce Taxol.[5]

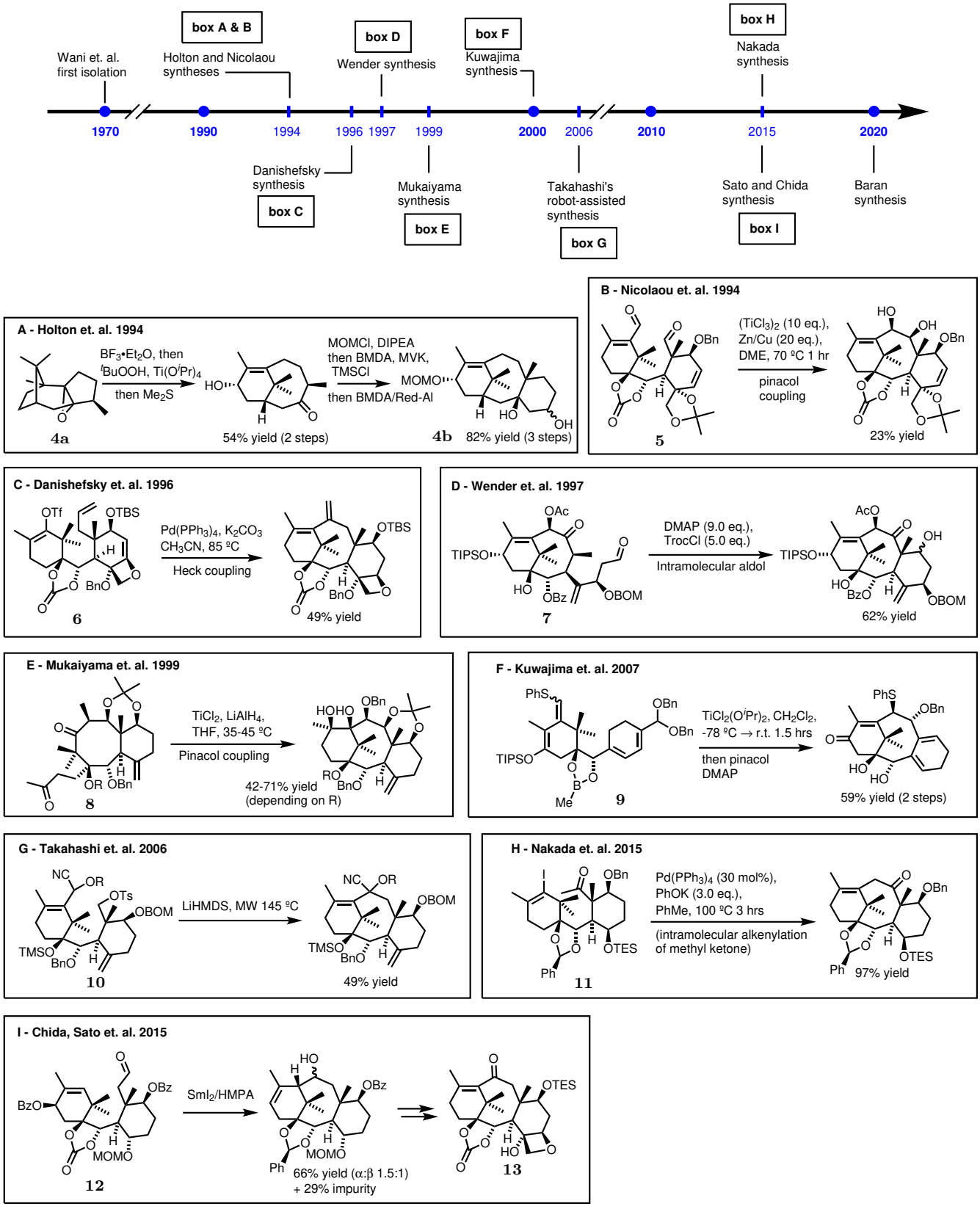
Although the total synthesis of Taxol **1** was originally undertaken to solve a supply problem, it was never an adequate solution to preparing useful quantities of the compound.[6] Rather, it was used to synthesise taxane analogues for studying structure-activity relationships. Perhaps more relevant to a synthetic chemist and for the purpose of this thesis, the synthesis of Taxol serves two major aims: 1) generate new chemical understanding by identifying unusual disconnections of the Taxol framework and then developing the corresponding forward synthetic transformation 2) testing cutting edge synthetic methods to see if they hold up in the

demanding environment of a complex molecule and 3) meeting the challenge of synthesising the target itself.

To date, there have been ten syntheses of Taxol and seven of these were published in the year 2006 or before. The general format for work published after 2006 tended to showcase a new methodology which then intercepted an earlier route towards **1**. Nakada and co-workers demonstrate the utility of a palladium-catalysed alkenylation of a methyl ketone as their key step while Chida, Sato and co-workers employ a SmI_2-mediated ring closing reaction to prepare a key intermediate towards **1**. Given the structural complexity of Taxol, a general feature for all the syntheses described are long step counts (more than 30 individual synthetic transformations), extensive use of protecting groups and collaboration between multiple researchers in order to achieve the final target. Additionally, the existing syntheses have low material throughput: as of late-2020, only 65 mg of Taxol **1** has been prepared using total syntheses. Scheme 1.2 summarises the major events of Taxol isolation and synthesis, focusing on the key ring forming steps of each synthesis.

The Holton and Nicolaou research groups were the first to publish completed syntheses of Taxol in 1994, in what was termed a "photo" finish. Holton's approach towards Taxol[7a,7b] (see Scheme 1.2 – Box A) was similar to an earlier synthesis of taxadiene.[7c,7d] For clarity the key step of the taxadiene synthesis is shown instead.* The synthesis began with β-patchouline-oxide **4a** , which was converted in two-steps to ketone-MOM-protected alcohol to simultaneously form the AB rings. The C-ring was installed using a Michael reaction with methylvinyl ketone followed

*In the synthesis of Taxol, Holton uses an intermediate from his Taxusin synthesis[7d] instead.



Scheme 1.2: Timeline of major syntheses of Taxol as well as the key, carbon-skeleton-forming steps of each synthesis. Abbreviations: *MOMCl* = CH_3OCH_2Cl, *DIPEA* = $EtN(iPr)_2$, *DMAP* = 4-dimethylaminopyridine, *BMDA* = bromomagnesium diisopropylamide, *Red-Al* = sodium bis(2-methoxyethoxy)aluminium hydride, *DME* = dimethoxyethane, *TrocCl* = trichloroethyl chloroformate, *HMPA* = Hexamethylphosphoramide.

by base-mediated intramolecular aldol reaction giving diol **4b** . Holton's synthesis used a linear sequence which was able to access **1** in 4.3% overall yield in 55 steps.

Nicolaou's synthesis of Taxol[8] was published in the same year as Holton's synthesis. In contrast to Holton's route, it used a convergent strategy to access **1** in 0.0078% yield over 39 steps. The A and C rings were both synthesised using Diels–Alder reactions before being combined using a Shapiro reaction. The key step of the synthesis is shown in (Scheme 1.2 – Box B). In this step, the eight-membered B-ring is formed using a McMurry coupling **5** ($(TiCl_3)_2-(DME)_3$ (10 eq.), Zn/Cu couple (20 eq.)).

Danishefsky's synthesis (1996) could be designated as the first to have used a catalytic asymmetric approach. The synthesis started from trimethylcyclohexane-1,3-dione which was used as the building block for the C-ring while an *L*-proline-catalysed enantioselective synthesis of a Wieland Miescher ketone furnished the A-ring fragment. The route was also convergent and delivered **1** in 0.63% yield over 49 steps.[9] Scheme 1.2 – Box C shows the key strategy employed in the syntheses to assemble Taxol's B-ring; a Pd-catalysed Heck reaction on triflate precursor **6**.

Wender's synthesis,[10] completed in 1997, was the second example of a catalytic asymmetric synthesis of **1**. It differs however, from Danishefsky's synthesis in the choice of starting material and in this case, (1*R*)-(+)-verbenone was used. The key step used to prepare the Taxane skeleton, bears similarity to Holton's strategy. The C-ring was formed when **7** underwent an intramolecular aldol reaction in the presence of either DMAP or 4-pyrrolidinopyridine (Scheme 1.2 – Box D). Wender's

synthesis was relatively short compared to other syntheses at the time. Despite using a linear sequence towards **1**, the final product was obtained in 0.63% yield in 37 steps.

Mukaiyama's catalytic asymmetric synthesis of **1** (1999) employed a different disconnection of the Taxane ring compared to the approaches completed up until that point (Scheme 1.2 – Box E). The convergent strategy entailed the construction of the B-ring, followed by the C-ring and finally the A-ring. The key step used to form the A-ring involved an intramolecular pinacol coupling of **8**, mediated by $TiCl_2/LiAlH_4$). The route delivered the target molecule in 60 steps in 0.17% overall yield.

Kuwajima's synthesis of Taxol was completed in 2000. This synthesis employed a linear strategy to access **1** in 60 steps and 0.014% yield. The C8 methyl group was introduced via a Simmons-Smith cycloproponation followed by reductive ring cleavage using SmI_2. Their key step featured a $TiCl_2(O^iPr)_2$-mediated vinylogous aldol cyclisation to form the eight-membered B-ring, see Scheme 1.2 – Box F.

In 2006, Takahashi's group synthesised **1** (racemic) starting from geraniol.[11] Due to the large number of steps typically associated with Taxol syntheses, the preparation of late-stage synthetic intermediates on scale is an ardous process. In an effort to circumvent this issue, Takahashi and co-workers devised a convergent route and performed the synthesis of protected cyanohydrin **10** in a ChemKonzert automated synthesiser. Thus **10** could be accessed on scales between 100 mg up to 300 g. The key step used to form the B-ring was a microwave-mediated in-

tramolecular alkylation of **10** in the presence of LiHMDS (Scheme 1.2 – Box G). Taxol **1** was obtained in 48 steps in 0.0070% overall yield.

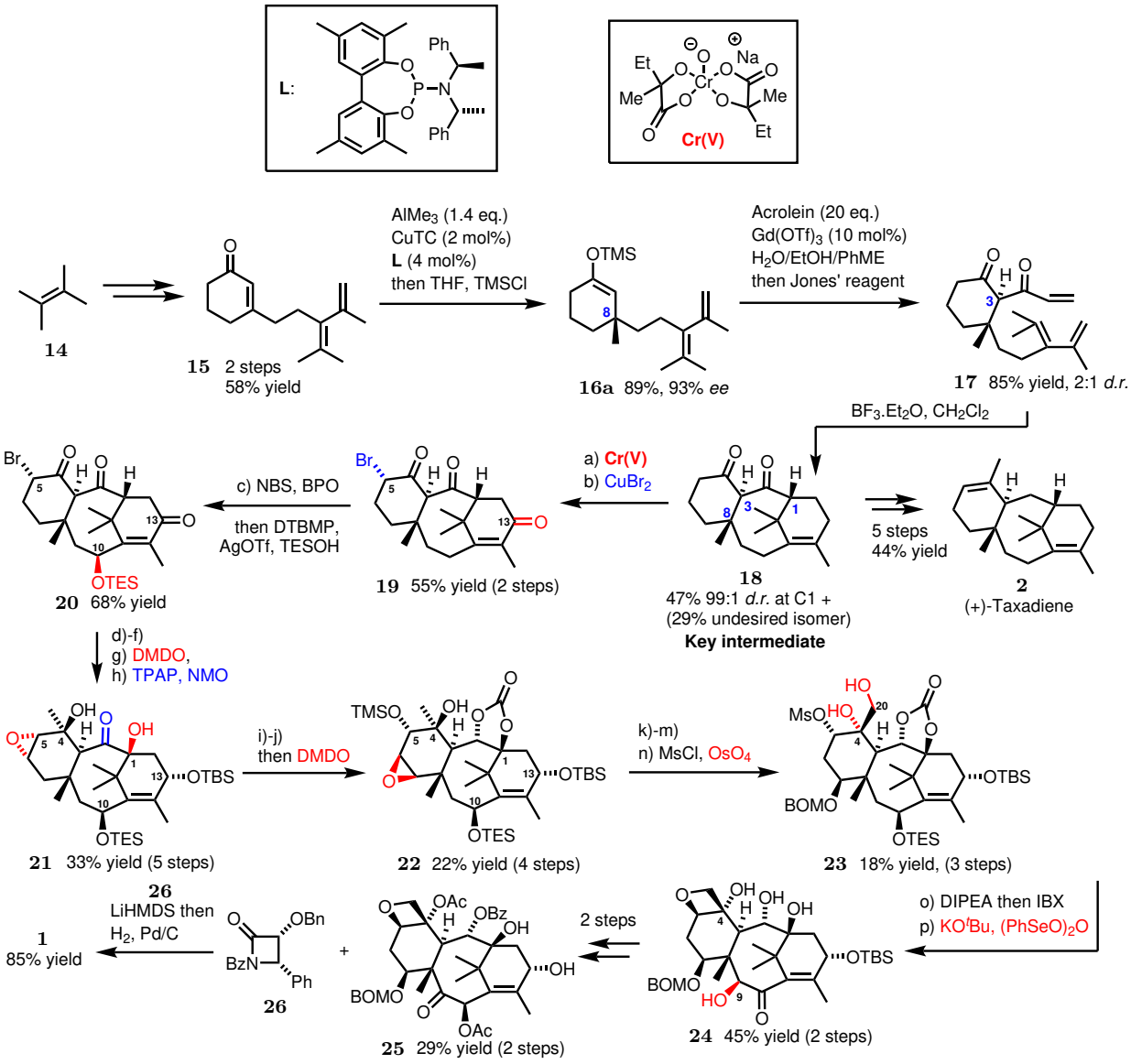
Between the years 2006-2015, there were relatively few syntheses of Taxol. In 2015, Nakada and co-workers described a formal synthesis of **1** by intercepting an intermediate from Nicolaou's synthesis.[12] Their key step is shown in Scheme 1.2 – Box H, where a Pd-catalysed intramolecular alkenylation of a methyl ketone was used to form the B-ring. Sato, Chida and co-workers also reported a methodology-based formal synthesis of Taxol (Scheme 1.2 – Box I).[13] Using a SmI_2 mediated cyclisation of **12** to prepare the Taxol B-ring, the authors were able to intercept Takahashi's oxetane intermediate of taxadiene. The reaction is sensitive to the stereochemistry at the C13 (benzoyl group). As drawn, the desired transformation would occur and in the absence of HMPA, only reduction of the aldehyde would be observed. The impurity arises from a direct coupling of the aldehyde to C13. According to the authors, the use of 13-*epi*-**12** instead of **12** would lead to a complex reaction mixture.

Kanda and co-workers from the Baran group, are the latest team to have undertaken the synthesis of Taxol (Scheme 1.3).[14a] Their approach is known as the two-phase synthesis and represents a paradigm shift compared to traditional approaches depicted in Scheme 1.2. The two-phase synthesis of terpenoids entails two distinct steps: the preparation of the carbocyclic core (termed the cyclase phase) followed by late stage installation of the required oxygenation pattern (termed the oxidase phase).[14b] It attempts to emulate the process by which complex terpenoids are prepared in nature through biosynthesis. This approach has been successfully

used to prepare a variety of terpenoids including ingenol,[15a] phorbol,[15b] majucin and jiadifenoxolane A,[15c] thapsigargin,[15d] and phomactin terpenoids.[15e]

This synthesis towards Taxol began by converting 2,3-dimethyl-2-butene **14** into enone **15**. A tandem asymmetric conjugate addition (ACA) followed by trapping with chlorotrimethylsilane gave TMS enol ether **16a** in 89% yield and 93% *ee*. A cross-aldol reaction followed by Jones oxidation gave ketone **17** which underwent Diels-Alder reaction to give Taxol core **18**; a key intermediate from which futher Taxane derivatives could be prepared including the least oxidised member of the family (+)-taxadiene **2**.[14b] Biosynthetically, this series of transformations is accomplished in two steps. Farnesyl diphosphate and isopentyl diphosphate combine in the presence of a synthase to give geranylgeranyl diphosphate which is then cyclised by taxadiene synthase to give **2**.

Transformations onwards from **18** constitute the oxidase phase of the Taxol synthesis. Oxidations at C13, C5 and C10 were performed using a chromium(V) complex, copper(II) bromide and silver(I) respectively (to give **20**). The preparation of **21** from **20** was a highly challenging transformation which used deuterium (incorporated using $LiAlD_4$) to function as a protecting group. If the order of addition of MeMgBr, DIBAL-H and $LiAlD_4$ was changed, no hydroxylation at C1 would be observed. C7 oxidation was accomplished by a redox relay. Thus the C5/C6 epoxide was converted to the C6 iodide, the $\Delta^{6,7}$ olefin, the C6/C7 epoxide **22** and finally to the C7 alcohol after Ti-mediated reductive epoxide opening (step k - Scheme 1.3). Concurrently, OsO_4-mediated dihydroxylation installed the hydroxyl group at C20 to form **23**. The remaining oxygen at C9 was installed



Scheme 1.3: Synthesis of Taxol using the two-phase approach. (a) Cr(V), HFIP, TMSOH, t-BuOH, 80 °C. (b) $CuBr_2$, THF, rt, 55%, over two steps. (c) NBS, BPO, CCl_4, then DTBMP, AgOTf, TESOH, 4 Å MS, PhMe, rt, 68%. (d) LiBr, Li_2CO_3, DMF, 100 °C, 88%. (e) MeMgBr, CH_2Cl_2, 0 °C to rt, then DIBAL, -78 °C, CH_2Cl_2, then $LiAlD_4$, THF, 60 °C, 74%. (f) NaHMDS, TBSCl, THF, 0 °C to rt, 94%. (g) DMDO, 0 °C, 49%. (h) TPAP, NMO, CH_2Cl_2, rt, 81%. (i) Na, i-PrOH, Et_2O, rt, then triphosgene, pyr, DMAP, CH_2Cl_2, -78 to 0 °C. (j) TBAI, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C, then 2-Fpyr, -78 °C, then TMSIm, rt, then DMDO, -78 °C to rt, 43%. (k) Cp_2TiCl, Et_3SiH, THF, -78 °C to rt, 67%. (l) BOMCl, TBAI, DIPEA, DCE, 45 °C, 84%. (m) Burgess reagent, PhMe, dioxane, then HF, H_2O, pyr, MeCN, rt, 32%. (n) MsCl, pyr, 0 °C to rt, then OsO_4, THF, pyr, 0 °C to rt, 68%. (o) DIPEA, PhMe, then IBX, DMSO, H_2O, 80 °C, 62%. (p) KO^{t}Bu, $(PhSeO)_2O$, THF, H_2O, -78 to 0 °C, 73%. Abbreviations: *CuTC* = copper(I) thiophene-2-carboxylate, *NBS* = *N*-bromosuccinimide, *BPO* = benzoyl peroxide, *DTBMP* = 2,6-di-*tert*-butyl-4-methylpyridine, *TESOH* = triethylsilanol, *DMDO* = dimethyldioxirane, *TPAP* = tetrapropylammonium perruthenate, *NMO* = *N*-methylmorpholine *N*-oxide, *MsCl* = methanesulfonyl chloride ,*TMSIm* = 1-(Trimethylsilyl)imidazole, *TBAI* = tetrabutylammonium iodide, *2-Fpyr* = 2-fluoropyridine, *DCE* = 1,2-dichloroethane, *DIPEA* = *N*,*N*-Diisopropylethylamine, *IBX* = 2-Iodoxybenzoic acid

using benzeneseleninic anhydride upon which global deprotection furnished Baccatin III **24**. Finally, the side chain was appended to give Taxol **1** using Ojima's procedure.[16]

Biosynthetically, the oxidase phase is typically effected by Cytochrome P450 oxidases which are aptly named after the position which the enzyme oxidises. Several of these biosynthetic steps have been studied in detail, even though the exact ordering of these steps is not well understood.[5a, 17] The first oxidation of taxadiene **2** is performed by T5αH (taxadiene-5α-hydroxylase) forming taxa-4(20),11(12)-dien-5-α-ol which constituted a formal hydroxylation at C5 followed by double bond transposition. C10 hydroxylation is mediated by T10αH (Taxoid Cytochrome P450 10β-hydroxylase). From this point, the exact order of biosynthetic steps are not precisely known and there are various branch points that can lead to other related taxoids. Formation of the oxetane is generally accepted to proceed via epoxidation of the 4(20) double bond followed by α-acetoxy migration from C5 to C4 along with expansion of the epoxide to the oxetane.[5e] The enzymes responsible for intermediates up to 10-deacetylbaccatin III have not been characterised, however it is known that 10-deacetyl baccatin III-10-*O*-acetyltransferase is involved in its transformation to Baccatin III **24**. Finally the side chain, present as β-phenylalanineCoA, is appended to Baccatin III using the enzyme 13-*O*-phenylpropanoyltransferase, a cytochrome P450 hydroxylase, and *N*-benzoyltransferase.[5e]

1.2.2 Asymmetric conjugate additions of alkylzirconium reagents to form quaternary centers

The conjugate addition (1,4-addition) is a powerful C-C bond forming (Figure 1.1). So-called "hard" nucleophiles, are transmetallated to copper and the resulting decrease in metal-carbon bond polarisation results in greater selectivity for 1,4-addition over 1,2-addition.[18] When the reaction uses a prochiral electrophile and is conducted in the presence of a suitable chiral catalyst/ligand, the resulting addition product may be enantioenriched and the asymmetric conjugate reaction is the new name given to the transformation. These systems have been studied extensively[19] and applied to the syntheses of natural products.[20]

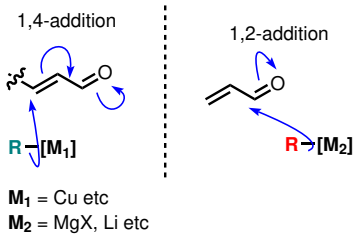
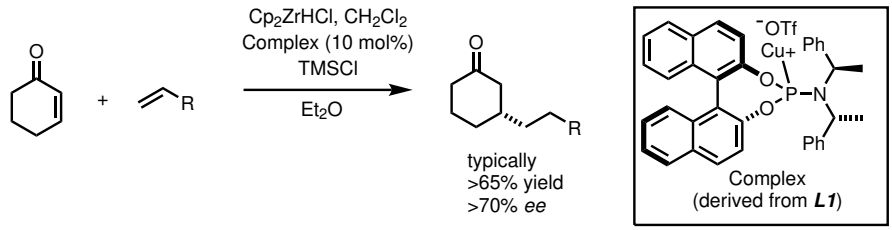


Figure 1.1: Comparison of conjugate addition with direct addition

In 2012, the Fletcher group reported an asymmetric conjugate addition (ACA) reaction using alkenes as pronucleophiles.[21] The reaction proceeds via reductive hydrometallation of the alkene using the Schwartz reagent to generate an alkylzirconium species. This organometallic reagent adds, in the presence of a chiral phosphoramidite ligand and copper salt, to cyclic α,β-unsaturated ketones to give saturated ketones in high yields (up to 93%) and enantioselectivity (up to 96%) (Scheme 1.4). The reaction tolerates a variety of functional groups including

alkyl and aromatic halides, protected (TBS, benzyl) alcohols and disubstituted acetylenes. Compared to ACAs using traditional nucleophiles, the ACA using alkenes has a number of advantages. These include complete and efficient transfer of the alkyl substituents (relevant for trialkyl aluminium and dialkyl zinc reagents), safety (organozirconium reagents are not pyrophoric) as well as a greater variety of nucleophiles.[†]



Scheme 1.4: Asymmetric Conjugate Addition of alkenes by Schwartz-reagent-mediated hydrometallation

This procedure was extended to include the use of different Michael acceptors including six-membered cyclic lactones[22] (see Scheme 1.5 – Box A) and cyclopent-4-ene-1,3-dione monoacetals[23] (Scheme 1.5 – Box B). The reaction using acyclic α,β-unsaturated ketones[24] (Scheme 1.5 – Box C) was especially challenging to realise. Due to *s-cis*/*s-trans* interconversion, the catalyst needs to be able to differentiate between these conformers or produce the same enantiomer from both isomers. Identifying the nontrivial dependence of reaction yield/*ee* on experimental conditions[25] was in part solved using a quantitative-structure-selectivity-relationship (QSSR) approach[26] and employing an aminoindane phosphoramidite.[27] The same phosphoramidite ligand allowed the preparation of qua-

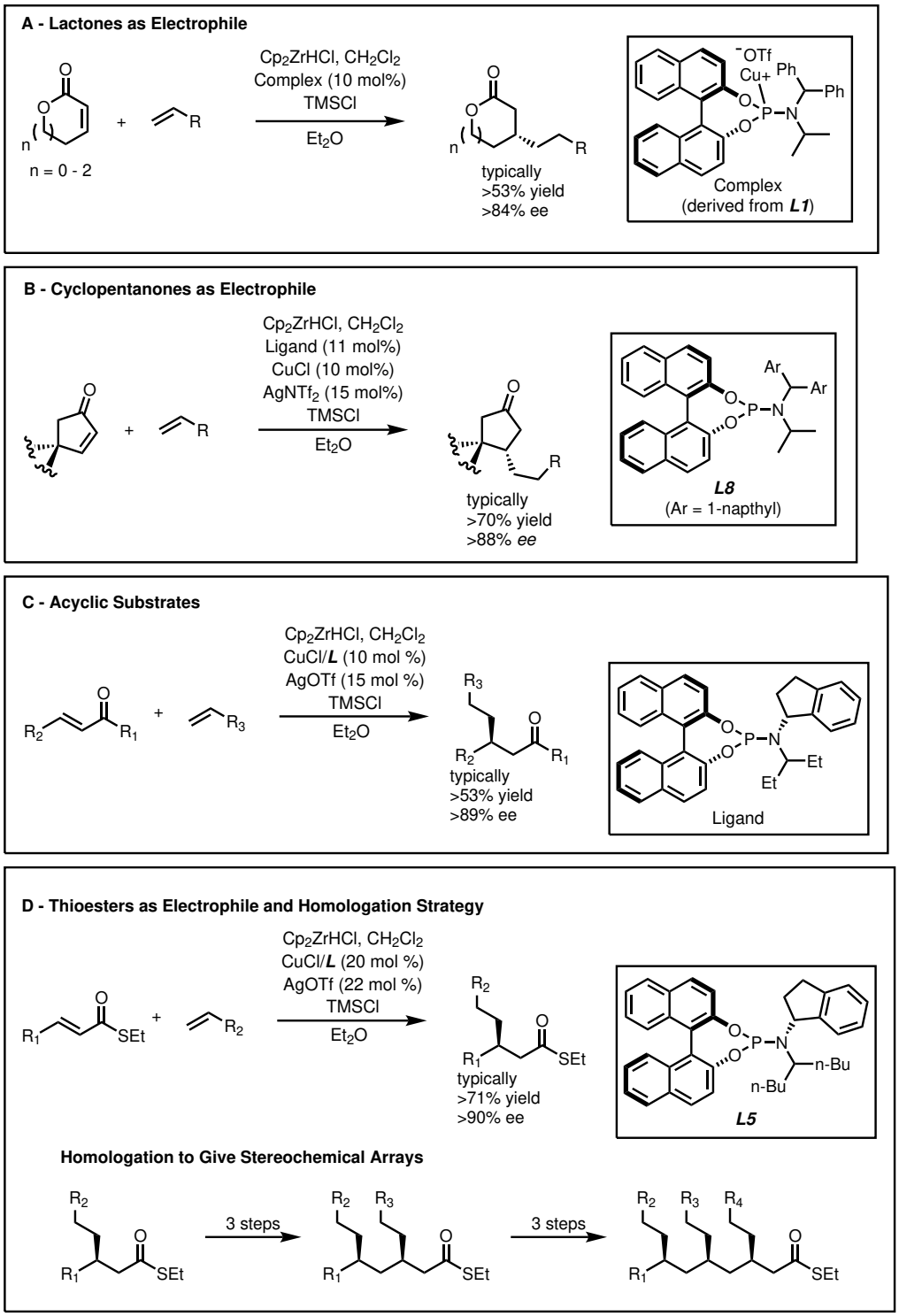
[†]the diversity of terminal alkenes is much greater than commercially available pre-made organometallic reagents.

ternary stereocenters[28] (Scheme 1.6 – Box B) and faciliated additions to α,β-unsaturated linear thioesters.[29] In the latter case, the resulting product may be reduced using DIBAL and the α,β-unsaturated thioester regenerated using a Horner-Wadsworth-Emmons reaction to produce stereochemical arrays (Scheme 1.5 – Box D).

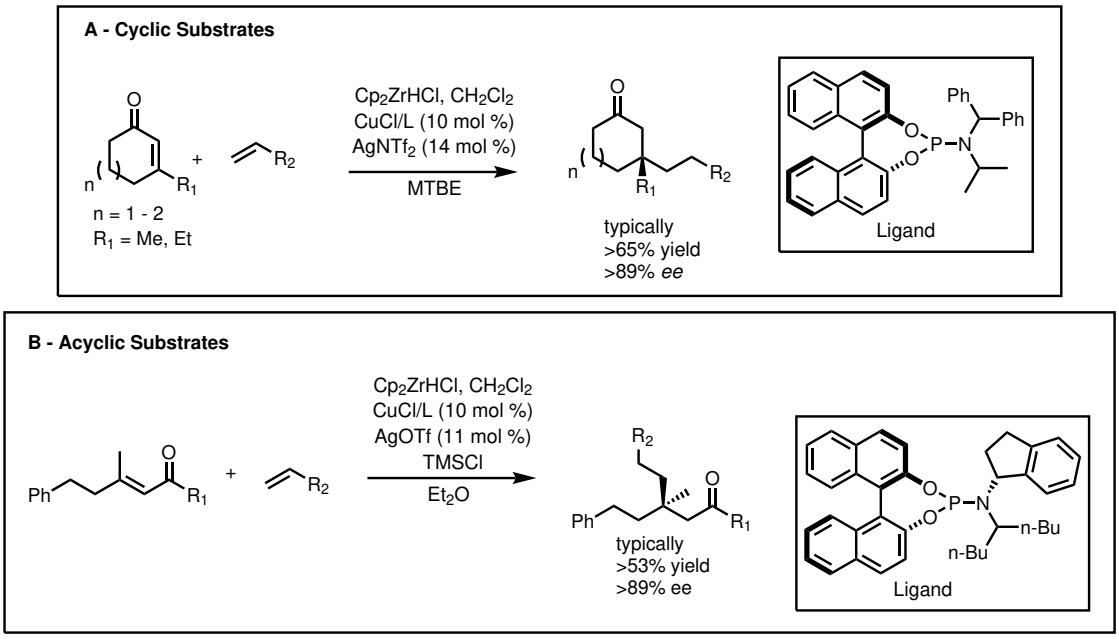
Quaternary stereocenters are ubiquitous in natural products and their synthesis is known to be a challenging problem.[30] In addition to the preparation of quaternary stereocenters for linear substrates, the ACA using alkenes has also been used to synthesise cyclic quaternary stereocenters (Scheme 1.6 – Box A).[31] Sidera and co-workers used similar reaction conditions as Maksymowicz and co-workers to enable the addition of alkenes to 3-subsituted cyclic enones. As with the transformation in Scheme 1.4, the reaction tolerated a variety of functional groups on the alkene and gave enantioenriched ketones in good yields and *ee*'s. For the case of substituted cyclopentenones, Ardkhean and co-workers employed QSSR to identify the best ligand for the transformation giving yields up to 87% and *ee*'s up to 92%.[32]

In the context of complex molecular synthesis, the ACA of alkenes has been used as the keys step for a number of targets.[‡] For example, in 2015 Diego and Fletcher used the addition of 9-bromonon-1-ene to steroid **27a** as the key step towards the synthesis of the breast cancer drug Fulvestrant (Faslodex) **27c** (Scheme 1.7 – Box A).[33] In the presence of standard reaction conditions, the diastereoselective 1,6-addition reaction gave intermediate **27b** in 60% yield (in 4.6:1

[‡]For a review of recent work employing other organometallic reagents, of which there are many more examples, see the review by Vargova and co-workers.[20]



Scheme 1.5: Extension of ACA to different Michael acceptors



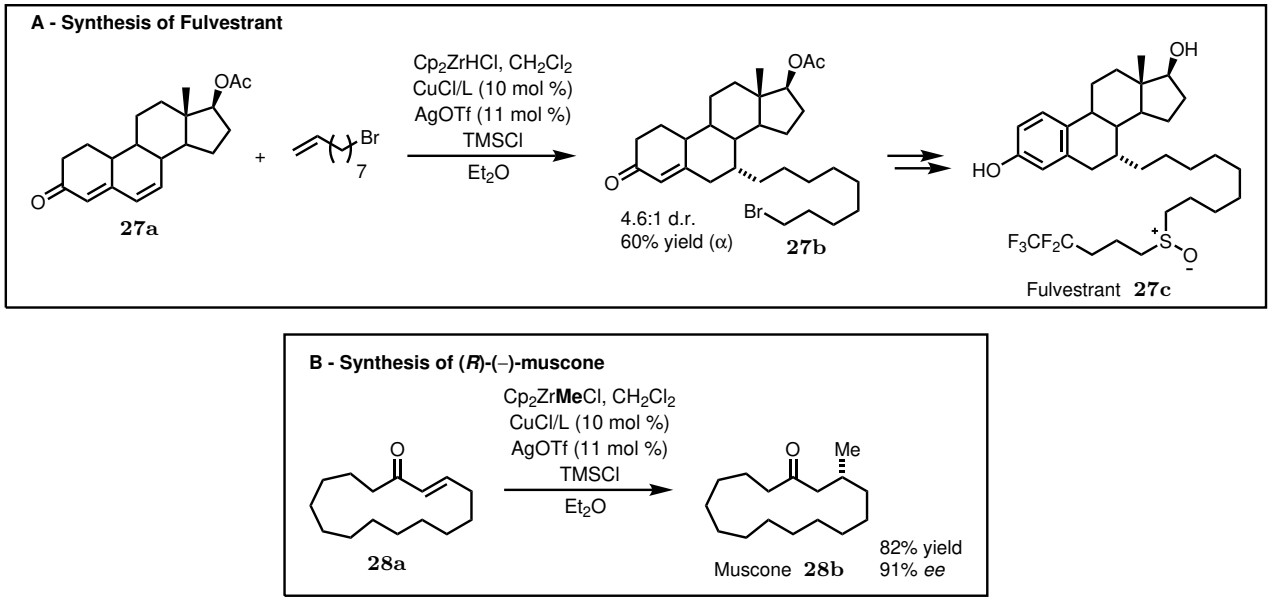
Scheme 1.6: Synthesis of quarternary-center-containing substrates

d.r.). Selectivity of 1,6-addition over 1,4-addition arises from the steric hindrance at the β position of the dienone system.

In 2016, Garec and Fletcher disclosed that $Cp_2ZrMeCl$ enabled asymmetric additions of methyl groups to various electrophiles.[34] As an application of the methodology, the reagent was added to *E*-cyclopentadecenone **28a** to obtain Muscone **28b** .

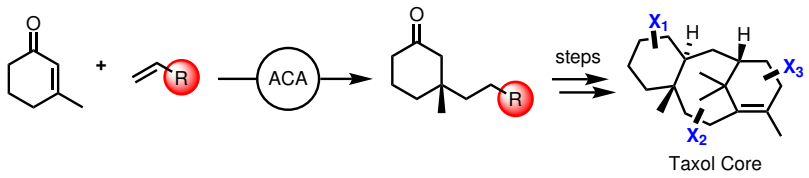
1.2.3 Project aims and thesis structure

Inspired by Baran's concise synthesis of taxadiene **2** and the use of Alexakis's 1,4-addition as a key step, we wondered if the ACA employing an alkene could lead to alternative and more efficient disconnections of the Taxol skeleton. The



Scheme 1.7: Syntheses using ACA reaction

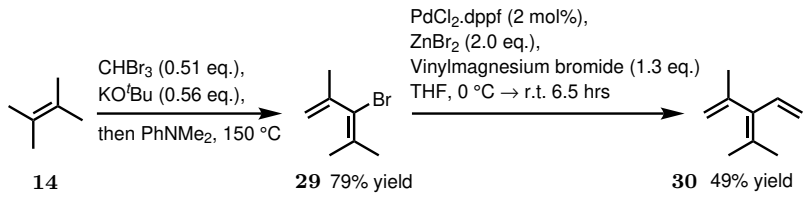
structure of this thesis is as follows. The remainder of Chapter one will discuss our initial proof-of-concept studies which established the feasibility of using the ACA of alkenes for the synthesis of Taxol core intemediates. Chapter two describes a novel trapping procedure for zirconium enolates generated in our ACA reactions. Chapter three discloses our various disconnections and attempts towards the Taxol core while Chapter four describes a successful synthesis using the combination of the ACA and type II intramolecular Diels-Alder reaction. Future work and perspectives on the project are also discussed in this chapter.



Scheme 1.8: Project aims: Can we perform ACAs with more elaborate nucleophiles?

1.3 Feasibility studies towards the Taxol core - ACA reaction

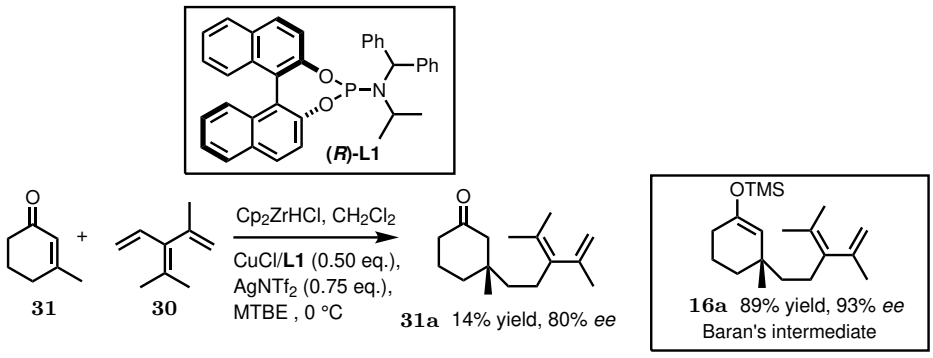
In order to probe whether this approach would be feasible for the synthesis of the Taxol core, we investigated the addition of poylene **30** to 3-methyl-2-cyclohexenone **31**. The product of this reaction, **31a** is the hydrolysed version of **16a** : a late stage intermediate encountered in Baran's synthesis of (+)-taxadiene **2**. Scheme 1.9 shows the preparation of branched, cross-conjugated polyene **30**. It is a reactive hydrocarbon reported by Bradford and co-workers.[35] Compound **30** was obtained in 49% yield from Negishi cross-coupling of bromide precursor[14b] **29** and in situ generated vinylzinc bromide; the latter being derived from the vinyl Grignard reagent.



Scheme 1.9: Preparation of cross conjugated polyene **30**

A variety of different conditions – including ligand, copper source, silver addi-

tives, temperature and solvent mixtures – were screened in order to improve the reaction. After exhaustive searching, our best result for this ACA reaction to form **31a** (14% yield, 80% *ee*) was observed using 3.0 equivalents alkene, 0.50 equivalents of copper/ligand, MTBE as solvent and silver trifluoromethanesulfonimide $AgNTf_2$ as an additive. The reaction showed some promising enantioselectivity however the yield could not be improved, even with a high catalyst loading. Side product formation was not the issue; only low conversion. Despite the presence of multiple olefins on **30**, side products corresponding to hydrozirconation at positions other than the terminal olefin were not observed. We attribute the reaction's low yield to the combined steric effect of the substituted alkene and double coordinated η_5 cyclopentadienyl zirconocene complex. For these reasons, we sought an alkene with a smaller steric profile.



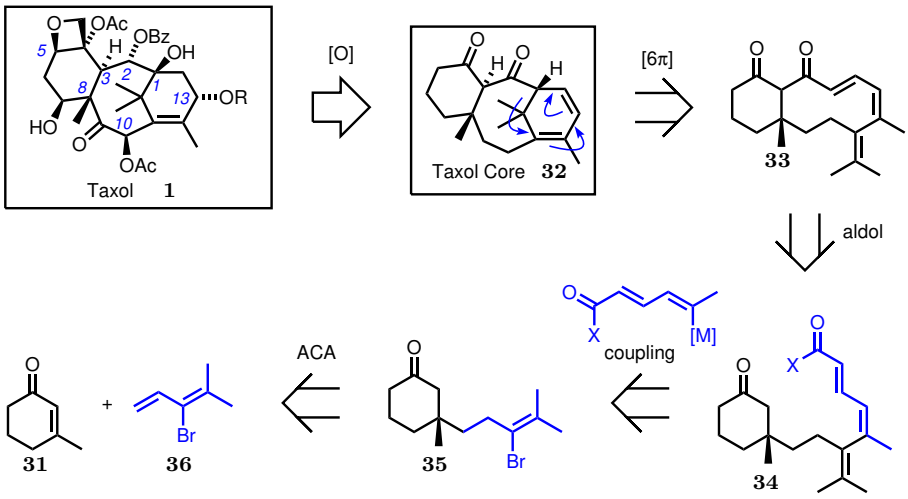
Scheme 1.10: ACA of **30** to **31** to prepare intermediate **31a**

1.3.1 Retrosynthetic analysis - initial approach

The previous section showed that it might be possible to use an ACA reaction for the synthesis of the Taxol core, although a lot more work needed to be done to make this a viable approach. We thus sought an alternative disconnection to the target molecule – one that employed a coupling fragment with a smaller steric profile. Scheme 1.11 shows our first generation retrosynthetic analysis of target **32**. Rather than use the well-studied, type-II intramolecular Diels-Alder reaction to form the A/B rings in **32**, we investigated an alternative disconnection using a transannular 6π electrocyclic reaction. There are two main challenges associated with the transformation from **33** to **32**. Invariably, ring strain will increase along the reaction pathway towards the transition state as the exocyclic alkene approaches the diene. More concerning however, is that the same exocyclic double bond is fully substituted, which would result in steric clash as the alkene approaches the diene. This factor strongly disfavours 6π processes and is probably one of the reasons why no such intramolecular transanular electrocyclisation has been reported in the literature. Nevertheless, we regard this as an excellent opportunity for developing a new method and that the problems could potentially be alleviated using a stepwise rather than concerted process.

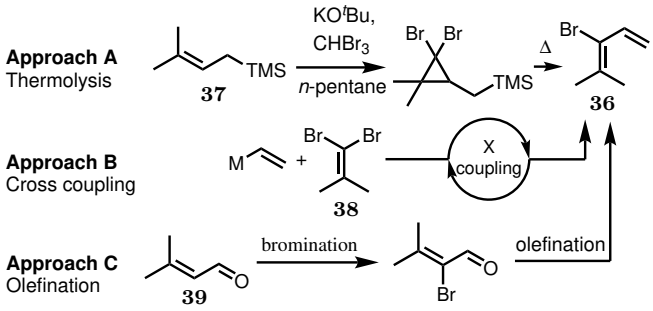
The precursor of **32** is ten-membered ring **33**. This ten-membered ring would be prepared by an intramolecular aldol/acylation reaction from **34** with the idea that stereochemical control at C3 could be dictated by the configuration at C8. Intermediate **34** could be prepared using a cross coupling reaction of bromoketone **35** which in turn would be prepared via our proposed ACA of bromodiene **36** with

commercially available 3-methyl-2-cyclohexenone **31**.



Scheme 1.11: Preparation of Taxol core: retrosynthetic analysis

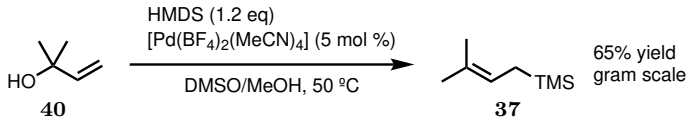
1.3.2 Synthesis of an alkene with a smaller steric profile



Scheme 1.12: Overview of approaches towards **36**

Bromodiene **36** seemed a promising replacement to triene **30** and to synthesise it, we considered a number of approaches (summarised in Scheme 1.12). The first approach considered, was the dibromocyclopropanation of prenyl trimethylsilane **37** followed by thermolysis (Scheme 1.12 – Approach A).[36] This procedure had

been previously reported in the literature by Ogasawara and co-workers. A useful method to access **37** on scale is via the addition of TMS−Li to prenyl bromide.[37] The reaction however, required HMPA as an additive and so we continued searching for procedures in the interest of using safer reagents. Another approach that we came across was Selander's allylic C-OH substitution,[38a] later improved by Shenje and co-workers,[38b] which was able to deliver required silane **37** from branched alcohol **40** (Scheme 1.13).



Scheme 1.13: Palladium catalysed C-OH functionalisation for the synthesis of allylsilanes[38]

Although the reaction in Scheme 1.13 is catalytic in palladium, the high molecular weight of the catalyst meant that the preparation was limited to gram-scale syntheses. Another major drawback to the dibromocyclopropanation approach was that an unknown side product was obtained after the thermolysis step. Despite our best attempts to purify the bromodiene, we could not remove this impurity nor could we characterise it. Figure 1.2 shows an NMR spectrum of the bromodiene and its side product prepared via Approach A. The presence of the impurity did not affect the outcome of the ACA experiment, provided that the amount of the bromodiene to be used was determined by NMR concentration standardisation.

The second approach that was considered in the preparation of bromodiene **36** was the mono cross coupling reaction between dibromide **38** and an appropriate

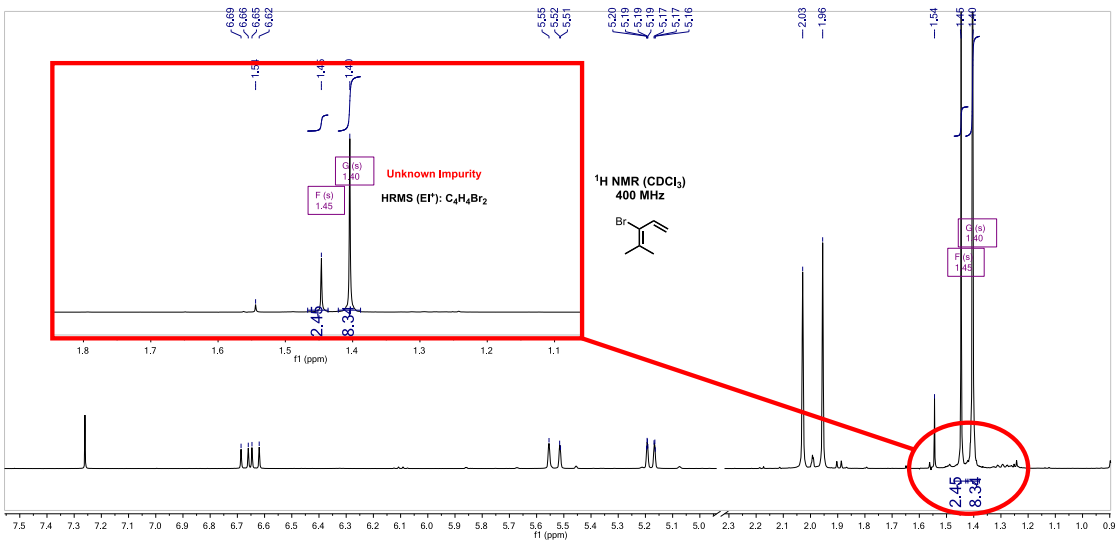
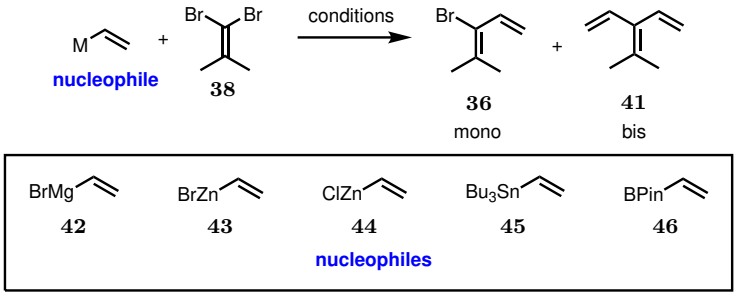


Figure 1.2: 1 H NMR spectrum of **36** Prepared According to Approach A (Scheme 1.12).

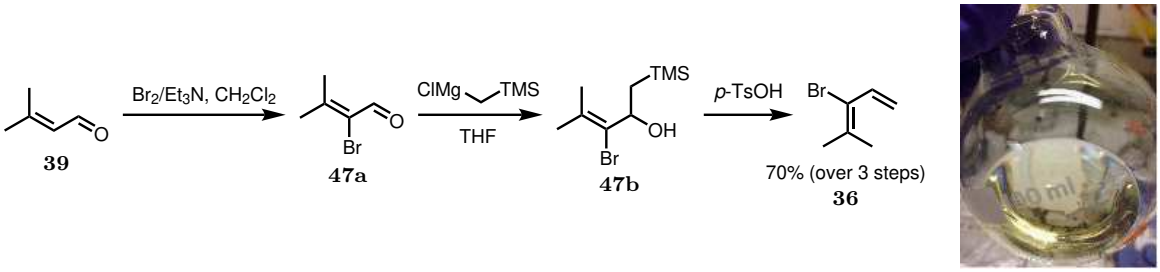
vinyl organometallic reagent. Table 1.1 summarises the most important findings for this approach (detailed optimisation tables can be found in the experimental section – 5.2.1). Many different conditions for the mono cross coupling reaction have been reported in the literature,[39] including procedures for Suzuki-Miyaura,[40] Negishi,[41] Kumada[42] and Stille[43] type couplings. The two best results obtained after extensive screening were using Negishi conditions (entry 4: 5 mol % $PdCl_2$dppf, 1.1 equiv *in situ* generated vinyl zinc bromide in tetrahydrofuran at room temperature overnight, 44% conversion 3:1 mono:bis selectivity) and Stille conditions (entry 8: 6 mol % Pd_2dba_3, 20 mol % $AsPh_3$, 1.1 equiv vinyltributystannane in tetrahydrofuran at 50 °C overnight, 48% conversion 1.7:1 mono:bis selectivity). A common drawback to these reactions was low conversion and poor mono/double cross coupled product selectivity. Even in reaction mixtures enriched with **36**, it was not possible to remove double cross coupled product **41**.



entry	nucleophile	catalyst	temp. (°C)	conversion (%)	**36**:**41**
1	**42**	$PdCl_2 \cdot$dppf (2 mol %)	25	10	1:1
2	**42**	$NiCl_2 \cdot$dppb (5 mol %)	25	10	0:1
3	**43**	$Pd(PPh_3)_4$ (2 mol %)	25	0	-
4	**43**	$PdCl_2 \cdot$dppf (5 mol %)	25	44	1:0.3
5	**44**	$NiCl_2 \cdot$dppb (5 mol %)	25	10	0:1
6	**44**	$Pd(PPh_3)_4$ (2 mol %)	50	9	2:1
7	**45**	Pd_2dba_3/TFP (3 mol %)	50	39	1.3:1
8	**45**	Pd_2dba_3/$AsPh_3$ (6 mol %)	50	48	1.7:1
9[a]	**46**	$Pd(PPh_3)_4$ (25 mol %)	25	0	-
10[b]	**46**	$Pd(OAc)_2$/XPhos (10 mol %)	25	13	10:3
11[b]	**46**	$Pd(OAc)_2$/SPhos (10 mol %)	25	11	1.2:1

Table 1.1: Preparation of **36** using mono cross coupling approach – a summary. Unless otherwise specified, all reactions were conducted in anhydrous THF using 1.1 eq. nucleophile. a) solvent: $THF/MeOH_{(aq)}$ b) solvent: PhMe and 3.0 eq. K_3PO_4. Abbreviations: *dppf* = 1,1'-bis(diphenylphosphino)ferrocene, *dppb* = 1,4-bis(diphenylphosphino)butane, *dba* = dibenzylideneacetone.

Due to the limitations of the reactions in Table 1.1 we were motivated to devise an alternative route and the culmination of this effort is shown in Scheme 1.14. Bromination followed by elimination of 3-methylcrotonaldehyde **39** gave 2-bromo-3-methylcrotonaldehyde **47a** . Subjecting this compound to Peterson conditions followed by an acid mediated elimination, gave desired bromodiene **36** after distillation. This route was found to be scalable and the desired starting bromodiene could be obtained on a 20 gram scale in 70% overall yield.

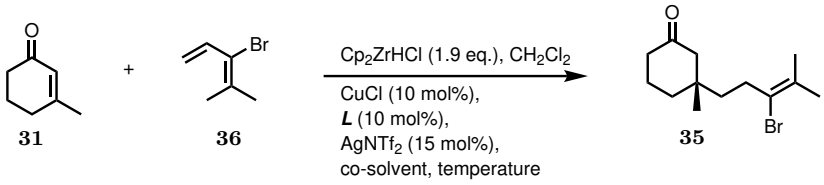


Scheme 1.14: Preparation of **36** (Approach C) on decagram scale

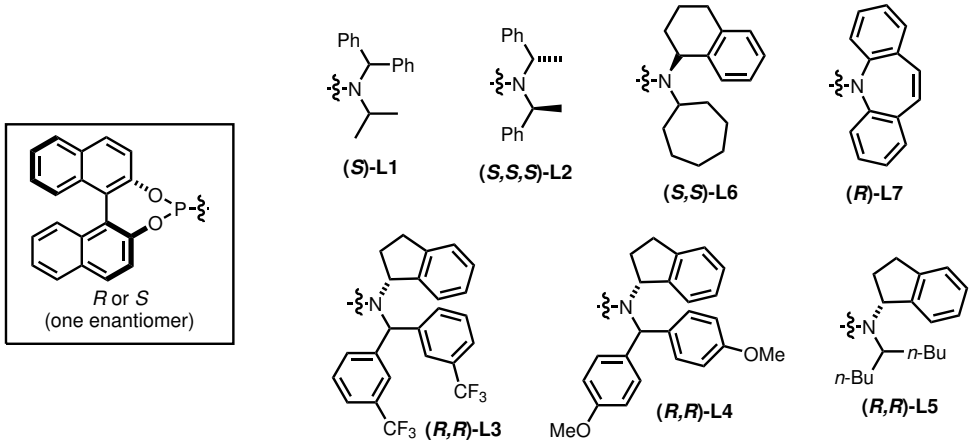
1.3.3 ACA of bromodiene 36 to 3-methyl-2-cyclohexenone 31

With bromodiene **36** in hand, we investigated its addition to 3-methyl-2-cyclohexenone **31**. Scheme 1.15 shows representative experiments during optimisation. Additional screening experiments and tables can be found in the experimental section – 5.2.2.

The greatest effect on the reaction yield and ligand was the phosphoramidite ligand. The Feringa ligand (**L1**) gave good yields but poor enantioselectivity (entry 1). **L2** previously used in the preparation of cyclic quarternary stereocenters also did not give satisfactory enantioselectivity (entry 2). Further experiments were made to probe solvent and additive influences, but no improvements to results were observed. Carreira's ligand **L6** also did not give good yield/selectivity (entry 3). The use of Gao's dibutyl aminoindane ligand[27] **L5** gave a promising hit result which formed the basis for further optimisation experiments (entry 7). Ligands **L3** and **L4** were synthesised in an attempt to improve the result obtained with **L5**. **L3** ended up giving inferior enantioselectivities and while **L4** gave a slightly better enantioselectivity, it was significantly more challenging to prepare and



31 + **36** → **35**



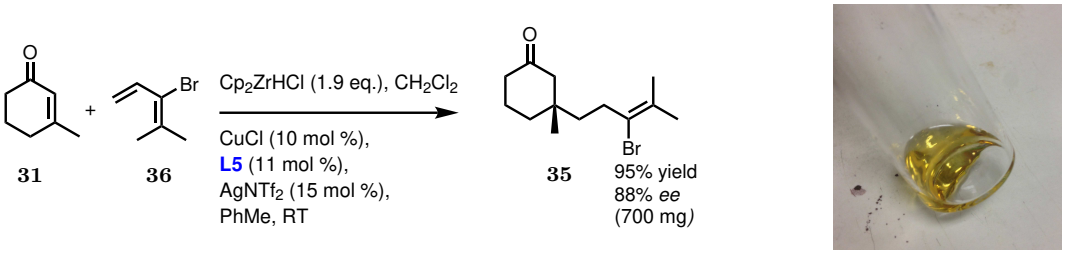
entry	ligand	solvent	temp.	yield (%)	*ee* (%)
1	**L1**	MTBE	RT	70	6
2	**L2**	MTBE	RT	63	18
3	**L6**	MTBE	RT	66	50
4	**L7**	$Cl(CH_2)_2Cl$	0 °C	55	6
5	**L3**	MTBE	RT	42	64
6	**L4**	MTBE	RT	49	86
7	**L5**	MTBE	RT	81	82
8	**L5**	$Cl(CH_2)_2Cl$	RT	45	90
9	**L5**	PhMe	RT	70	84
10	**L5**	2-Me-THF	RT	77	76
11	**L5**	Et_2O	RT	49	80
12	**L5**	$CHCl_3$	RT	54	88
13	**L5**	CH_2Cl_2	RT	37	84
14	**L5**	$Cl(CH_2)_2Cl$	0 °C	39	92
15	**L5**	PhMe	0 °C	44	14
16[a]	**L5**	PhMe	RT	48	60
17[b]	**L5**	PhMe	RT	71	88
18[a]	**L5**	$Cl(CH_2)_2Cl$	RT	28	90
19[b]	**L5**	$Cl(CH_2)_2Cl$	RT	31	86
20[b]	**L5**	PhMe	0 °C	28	28
21	**L5**	*o*−$PhCl_2$	RT	36	88
22[c]	**L5**	PhMe	RT	66	90

Scheme 1.15: Representative screening reactions of ACA between **31** and **36**. Reactions were performed on 0.5 mmol scale and isolated yields are reported. a) 12:1 Solvent:CH_2Cl_2. b) 4:1 Solvent:CH_2Cl_2. c) 2:1 Solvent:CH_2Cl_2. *MTBE* = methyl tert-butylether.

could not be synthesised on scale (entries 5 and 6). Therefore, we decided to use readily accessible **L5** in future experiments.

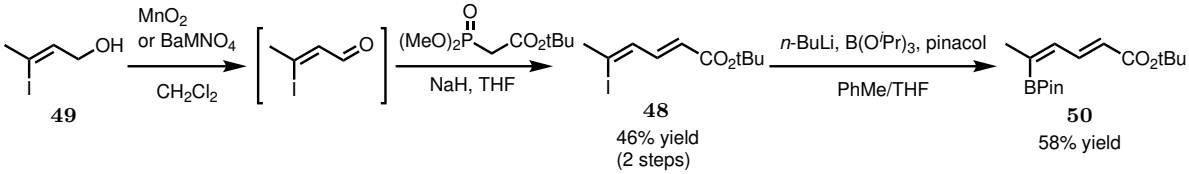
Next, we screened the silver salt (see experimental section – 5.2.2). Only the silver salt with the NTf_2 counterion gave good conversions/*ee*'s and this is consistent with observations from previous experiments. The use of chlorotrimethylsilane as an additive did not improve the reaction. A key aspect of the reaction that influenced both yield and enantioselectivity was the choice of co-solvent. Chlorinated co-solvents gave better enantioselectivies but lower yields (entries 8, 12-13) and with hydrocarbon/ethereal co-solvents, higher yields were obtained at the expense of enantioselectivity (entries 7, 9-11). By varying the ratio of the hydrocarbon co-solvent and CH_2Cl_2, a balance between these two effects could be achieved (entries 16-17, 20). When temperature is decreased to 0 °C and PhMe is used as a co-solvent (entry 20), the yield and *ee* drops substantially. Eventually, we decided that entries 17 (PhMe 71% yield/88% *ee*) and 14 ($Cl(CH_2)_2Cl$ 39% yield/92% *ee*) were a satisfactory balance between reaction yield and enantioselectivity.

Upon scale-up of entry 17 (3 mmol of **31**), the product could be obtained in 96% yield with 88% ee (Scheme 1.16). ACAs of alkylzirconium nucleophiles often work better on scale; it is easier to measure and mix the reaction components on larger scales, and larger scales minimize the impact of trace air and moisture on the organozirconium reagent.



Scheme 1.16: Scale up of optimised ACA reaction between **31** and **36**

1.3.4 Preparation of coupling fragment for first generation Taxol core synthesis



Scheme 1.17: Synthesis of **50**

Along with bromoketone **35**, we expected **50** to provide the remaining carbon atoms in our initial route towards **32**. Compound **50** had been described in the literature by Tseng and co-workers[44] however, attempts to prepare it according to the original procedure were thwarted by irreproducibility issues. It was found that the source of MnO_2 used in the oxidation of **49** to the aldehyde was critical for the success of the reaction. Alternatively, the use of $BaMnO_4$ (Barium Manganate) reliably delivered the expected aldehyde.[45]

(*Z*)-3-Iodo-2-butenol **49**, the precursor to **50**, was prepared by hydroalumination of 3-methyl-2-butynol followed by trapping with elemental iodine. On large scale, it was crucial to use finely powdered iodine and slowly warm the reaction from

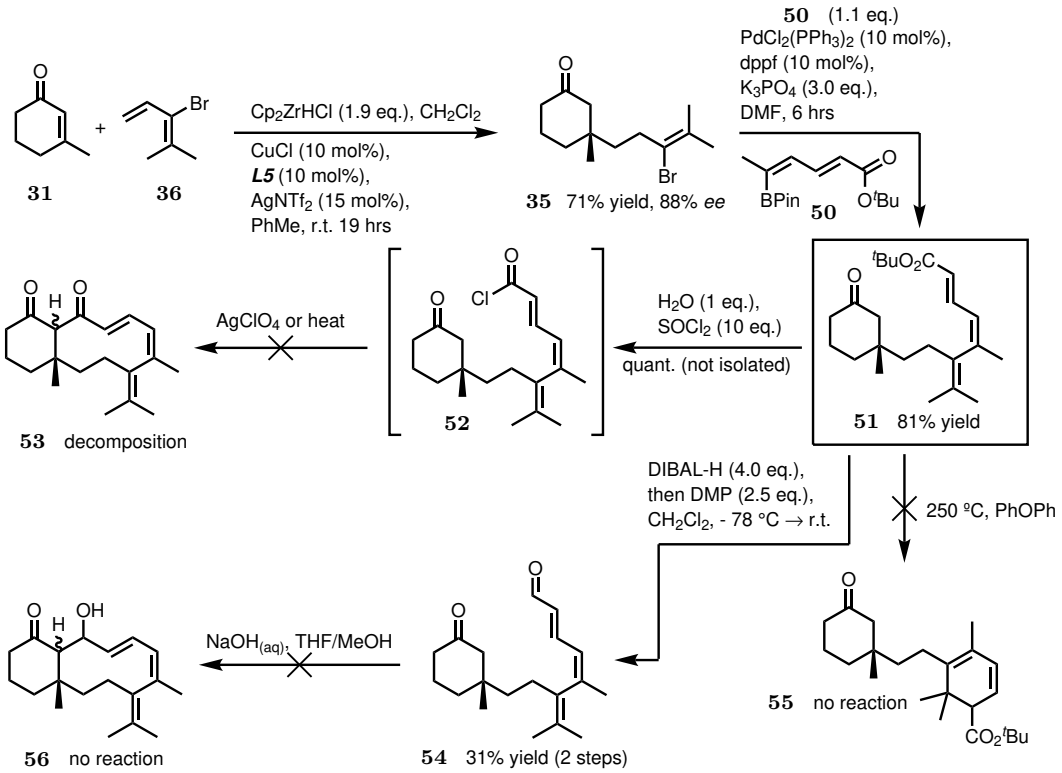
−75 °C to room temperature over 6 hours. Doing otherwise would result in thermal runaway leading to significant product loss.[§]

With a reliable means to obtain the iodoaldehyde, Horner-Wadsworth-Emmons reaction was performed according to the original procedure to give iodo-tert-butyl ester **48** in 46% yield over two steps. Finally, borylation gave the desired coupling fragment **50** in 58% yield.

1.3.5 Attempts to complete the synthesis

Having prepared the two requisite coupling fragments bromoketone **35** (1.3.3) and boronic ester **50** (1.3.4), we attempted to complete the synthesis of the Taxol core. The Suzuki-Miyaura cross coupling between **35** and **50** gave desired product **51**. The yield of the reaction however, dropped on scaling up. On closer investigation, it was found that the source of the problem came from the boronic ester fragment. In some cases, an excess of pinacol was present and this inhibited the cross coupling reaction. Upon addressing this issue, the reaction was scalable and found to give **51** in 81% yield. Next, we sought to synthesise ten-membered ring **33**, the penultimate step in our first approach towards the Taxol core. In order to do this, the *tert*-butyl ester was converted to a more reactive electrophile. Two different approaches were considered. In the first reaction,[46] the direct conversion of **51** to acid chloride **52** was achieved in a sealed tube. Due to the reactivity of the **52**, it was subject directly without further purification to cyclisation conditions. Both thermal conditions and a silver mediated process[47] were investigated but no ring closure products were observed.

[§]from author's own experiences.



Scheme 1.18: Unsuccessful attempts to complete the synthesis. Abbreviations: *dppf* = 1,1'-Bis(diphenylphosphino)ferrocene, *DIBAL-H* = diisobutylaluminium hydride, *DMP* = Dess-Martin periodinane.

The second approach involved a global reduction of both carbonyl groups in **51** using diisobutylaluminium hydride followed by Dess-Martin periodinane oxidation to give ketoaldehyde **54** in 31% yield. While the reduction step was near quantitative yielding, the oxidation step suffered from low yields. We were not able to determine the cause of this, neither were we able to improve reaction any further. The amount of **54** prepared up to this point was sufficient to probe the cyclisation step. Unfortunately, the substrate did not undergo the desired aldol reaction[48] despite investigating a variety of temperatures and concentrations. Over a long period of time (3 days), the starting material is observed to decompose into a number of unidentifiable products.

Even though more conditions for the aldol cyclisation could have been screened, we chose not to pursue this line of investigation. The cyclisation is a challenging transformation due to entropic effects. Thus we decided to relocate the aldol/acylation reaction to earlier in the sequence and use a more robust carbon-carbon bond forming reaction to close the ten-membered ring (for instance, ring closing metathesis and cross-coupling reactions). For this to be possible, an enolate trapping reaction was required. Such a reaction has the added benefit in that the synthesis could be reduced by one step. The next chapter looks at the development of this reaction with the synthesis of the Taxol core in mind.

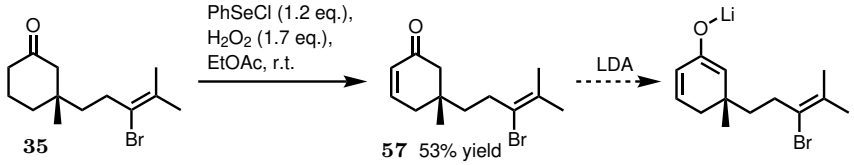
Chapter 2

Trapping of zirconium enolates generated from asymmetric 1,4-additions of alkylzirconium reagents

2.1 Background

In the previous chapter, the asymmetric conjugate reaction (ACA) was discussed. A key intermediate in these ACA reactions is the metal enolate. Reactivity profiles of these intermediates have been well studied and intercepting them allows for the design of multi-bond-forming processes. Several research groups have reported the successful trapping of metal enolates generated using ACA reactions. The metals used are derived from common organometallic reagents and include magnesium (from Grignard reagents), aluminium, zinc and lithium. Electrophiles that have

been used include allylic and benzylic halides (Cook group),[49a] α-amino ethers (Alexakis group),[49b] vinylsulfones (Alexakis group),[49c] carbenium ions (Sebesta group),[49d] nitro-olefins[49e,49c] and Mander's reagent (Herzon group).[49f] For a comprehensive summary on trappings of enantioenriched enolates up to 2019, see the review by Vargova and co-workers.[50]

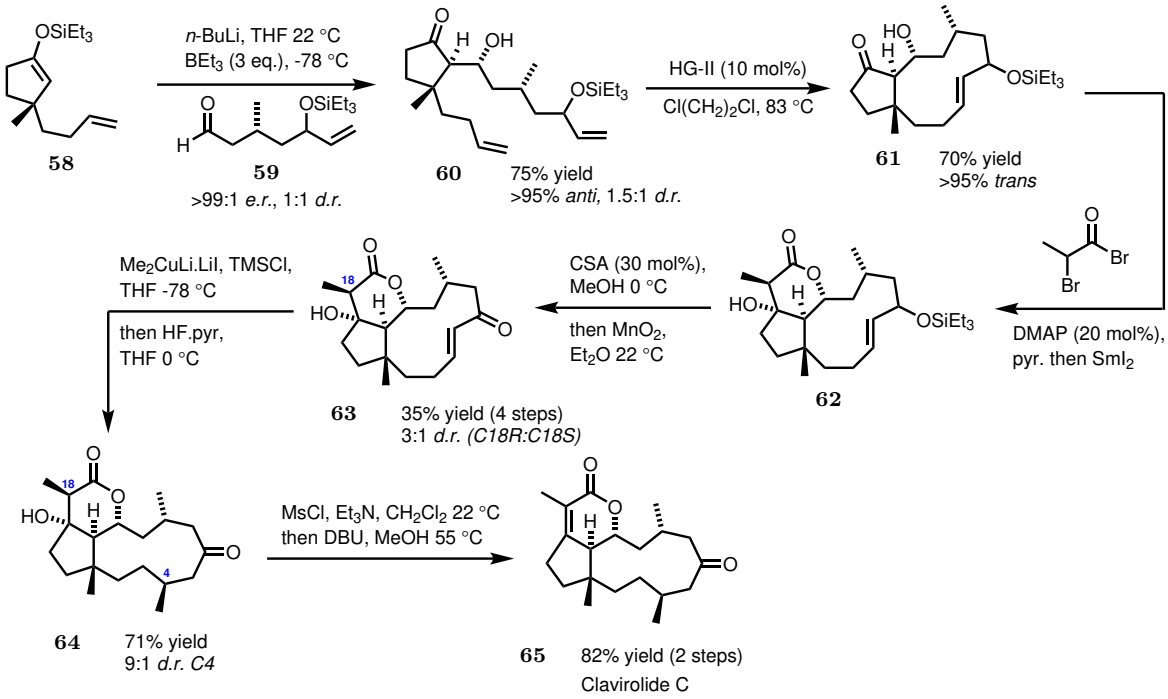


Scheme 2.1: α functionalisation of cyclic ketone **35** without a trapping reaction.

The resulting ACA/trapping sequence is an even more powerful reaction than the ACA alone and is extremely desirable for the synthesis of complex molecules.[51] In the absence of a trapping reaction, functionalisation at the α position of the ketone could be accomplished by protecting the kinetically enolisable side as a double bond as shown in Scheme 2.1. This however, is a contrived approach and its inefficiency can be seen when studying examples of syntheses that employ ACA/trapping reactions in their key steps.

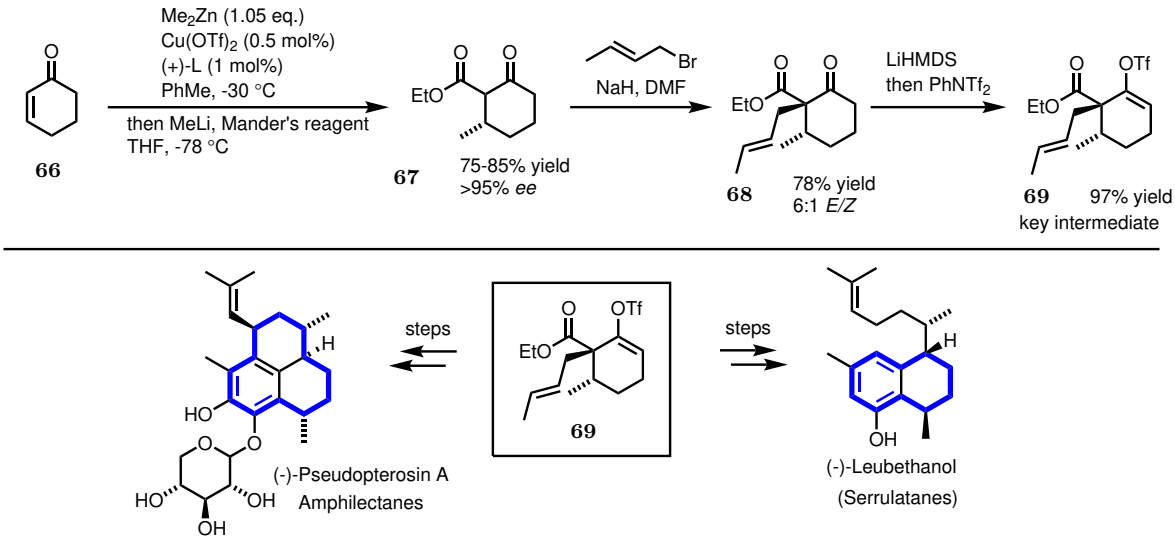
One such example has already been shown in Chapter 1 – Scheme 1.3, where acrolein was trapped with silyl enol ether **16a** eventually leading to the synthesis of (+)-taxadiene **2**. In Brown and Hoveyda's synthesis of clavirolide C,[52] silyl enol ether **58** was converted to the lithium enolate and then trapped using **59** to give aldol product **60** in 75% yield (Scheme 2.2). The use of BEt_3 was crucial for high diastereoselectivity in the reaction. Later in the synthesis, a substrate-controlled

diastereoselective conjugate addition reaction on *trans* macrocyclic enone **63** furnished macrocycle **64** which was elaborated to the desired natural product **65**.



Scheme 2.2: Synthesis of clavirolide C by Brown and Hoveyda. Abbreviations: *pyr.* = pyridine, *HG-II* = Hovedya-Grubbs catalyst second generation.

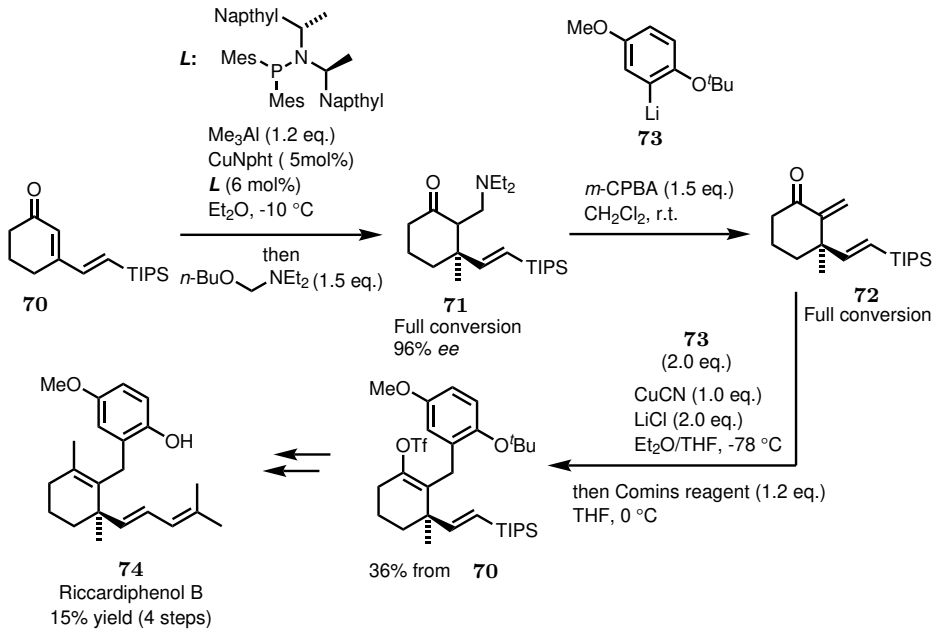
In 2016, Yu and co-workers (from the Luo laboratory) reported a general procedure for the synthesis of the amphilectane and serrulatane class of natural products.[53] The key step for the preparation of these diterpenoids, shown in Scheme 2.3, features the ACA of dimethylzinc to 2-cyclohexenone **66**, followed by trapping with ethyl cyanoformate (Mander's reagent) to give the key β-dicarbonyl intermediate **67**. Following substrate-controlled stereoselective alkylation (**68**) and triflation, intermediate **69** was elaborated to access a variety of different natural products, two of which are pseudopterosin A and leubethanol.



Scheme 2.3: Unified syntheses of amphilectanes and serrulatanes by Yu and co-workers. Abbreviations: *Mander's reagent* = ethyl cyanoformate.

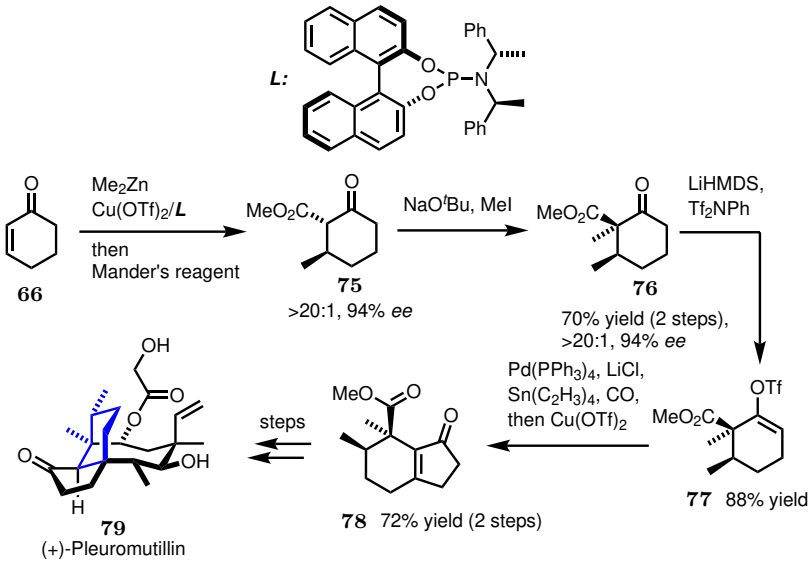
In Cottet and co-workers' (from the Alexakis laboratory) synthesis of riccardiphenol B[54] a trapping reaction of an enolate, derived from an ACA with trimethylaluminium, was performed to obtain diethylamino adduct **71** (Scheme 2.4). An interesting feature of this synthesis is that later in the sequence, a second trapping reaction was used when **73** was added to **72** followed by *O*-selective triflation with Comins' reagent. This triflate intermediate was then converted to the title natural product riccardiphenol B **74** in 4 steps.

In 2017, Zeng and co-workers (from the Herzon laboratory) reported the synthesis of (+)-pleuromutilin Scheme 2.5.[55] Early in the synthesis, a 4-component coupling reaction was used, where methyl addition to 2-cyclohexenone **66** was followed by trapping with Mander's reagent to give **75**. Base catalysed methylation



Scheme 2.4: Synthesis of riccardiphenol B using an ACA/trapping sequence. Abbreviations: *CuNpht* = copper(II) napthenate in pentane, *m-CPBA* = *meta*-chloroperbenzoic acid.

gave **76** in 70% yield with high stereochemical purity over two steps. Triflation of this intermediate followed by a carbonylative-alkenylation/Nazarov cyclisation gave hydrindanone **78** in 50% yield over three steps. This key intermediate was then elaborated in order to access pleuromutilin **79** and related structures.

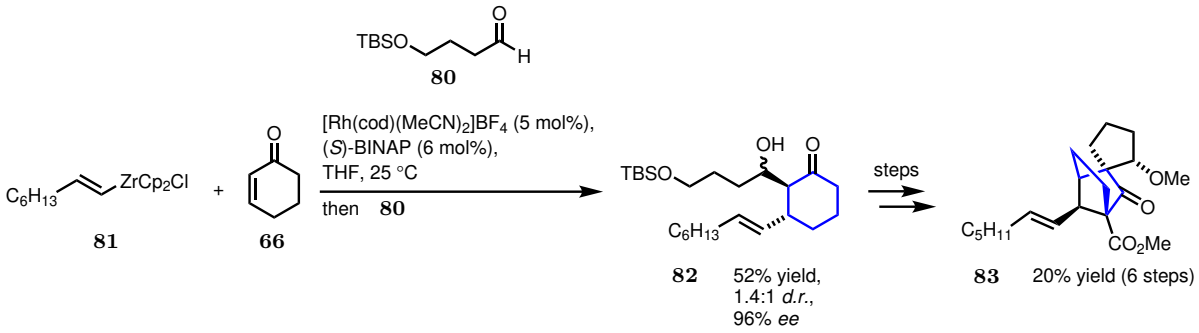


Scheme 2.5: Synthesis of (+)-pleuromutilin using an ACA/trapping sequence.

The examples shown above illustrate the power of using the tandem ACA/trapping sequence in complex molecule synthesis. It would be highly desirable to supplement zirconium enolates generated from ACA reactions, discussed in Chapter 1 of this thesis (see section 1.2.2), with a trapping component. Compared to other enolates, there are fewer examples of successful trapping of zirconium enolates, especially those generated through ACAs.

In 2005, Nicolaou and co-workers reported the synthesis of a key spirocyclic

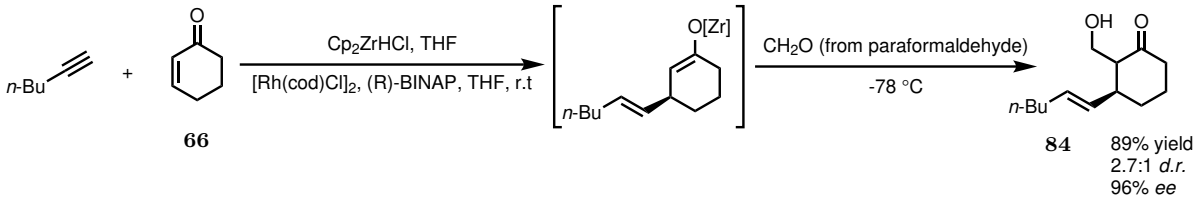
intermediate of vannusal A (Scheme 2.6).[56] The key step of the synthesis used an ACA/trapping sequence. In this step alkenylzirconium nucleophile **81**, derived from hydrozirconation of 1-octyne, was added to 2-cyclohexenone **66** and trapped with aldehyde **80** to give intermediate **82** in 52% yield and 96% *ee* as a mixture of diastereomers. The title compound **83** was then prepared from this intermediate in six steps and 20% overall yield. When **82** was subject to one-pot aldol condensation conditions, a higher yield of the elimination product was obtained (85% yield instead of 52% yield).



Scheme 2.6: Trapping of zirconium enolates: twards the synthesis of vannusal A

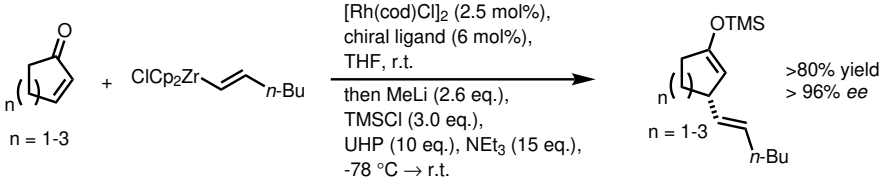
An example in 2007 reported by Vrielynck and De Clercq[57] used formaldehyde gas as the electrophile (Scheme 2.7). Zirconium enolates were generated through the rhodium catalysed ACA of alkenylzirconium reagents to 2-cyclohexenone **66**. The trapped products **84** were obtained in good yields and enantioselectivity.

Westmeier and co-workers reported the preparation of silyl enol ethers from cyclic enones in 2013 (Scheme 2.8).[58a] Following a rhodium catalysed conjugate addition of alkenylzirconium species, the intermediate enolate was activated us-



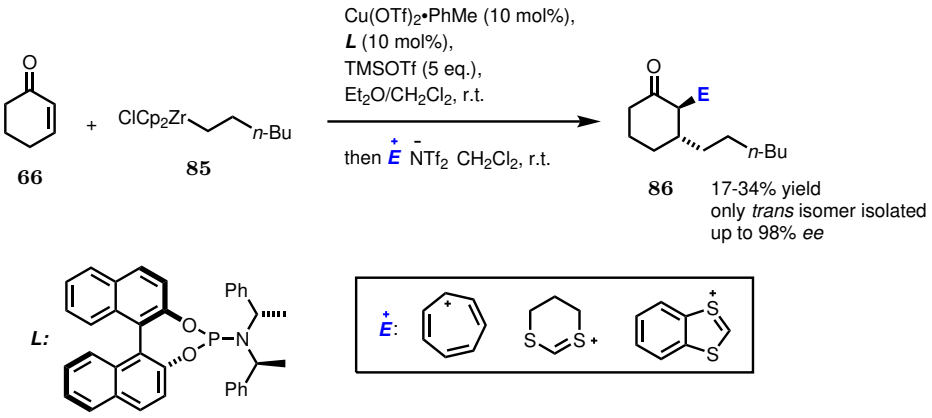
Scheme 2.7: Trapping of zirconium enolates using formaldehyde gas

ing a slight excess of methyllithium. NMR studies showed that the active species were the monomeric lithium enolate, lithium cyclopentadienide and $Li[CpZrMe_4]$. Addition of chlorotrimethylsilane gave the desired silyl enol ether. Unfortunately, under the reaction conditions, $Cp_2Zr(SiMe_3)_2$ is also formed as a side product, presumably from reaction of dimethylzirconocene with chlorotrimethylsilane. Attempts to isolate the silyl enol ether using distillation or chromatography were not successful. A purification method was devised where an oxidising agent, urea hydrogen peroxide (UHP), would be used to decompose the nonpolar $Cp_2Zr(SiMe_3)_2$ which would then be removed by filtration over activated charcoal. The presence of excess NEt_3 was required to prevent hydrolysis of the silyl enol ether. In a separate publication, the procedure was applied to the synthesis of a natural product, (R)-sarkomycin.[58b]



Scheme 2.8: Preparation of Silyl Enol Ethers from Zirconium Enolates. Abbreviations: *TMSCl* = chlorotrimethylsilane, *UHP* = urea hydrogen-peroxide adduct, *chiral ligand* = (R) or (S) SEGPHOS or BINAP.

Recently in 2017, Nemethova and co-workers reported the trapping of zirconium enolates generated using highly electrophillic carbocations (Scheme 2.9).[59] The enolates were generated by the addition of alkenes via hydrometallation, to cyclic enones using conditions discussed in section 1.2.2. Counterintuitively, the yields obtained were much lower than the examples previously reported, suggesting that more is at play than what is typically taught at the undergraduate level for enolate chemistry. DFT calculations showed that zirconium enolates were the least reactive compared to lithium, zinc and magnesium enolates. Trapping reactions of these enolates were also performed and they were consistent with the theoretical predictions.



Scheme 2.9: Preparation of Zirconium Enolates using Reactive Electrophiles. Abbreviations: *TMSOTf* = trimethylsilyl trifluoromethanesulfonate.

From the examples described above, it is clear that the trapping reaction of zirconium enolates are dependent on reaction conditions in non trivial ways. Thus, there remains to be discovered, a general procedure amenable to ACAs employing any combination of substrates.

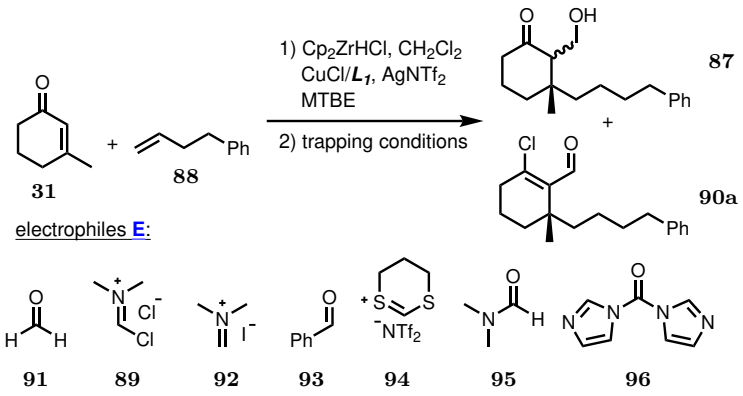
2.2 Initial experiments and exploratory studies

2.2.1 Trapping of zirconium enolates using formaldehyde

To begin our investigation, we performed the ACA between **31** and **88** and subjected the crude reaction mixture to a variety of electrophiles as shown in Scheme 2.10. The results shown in the preceeding table summarise the exploratory experiments in the project and were performed by Thomas Palacin, a former member of the Fletcher group (2015-2020). It can be seen that only two successful reactions occurred: using formaldehyde **91** to give **87** and the Vilsmeier-Haack reagent **89** to give **90a** (to be discussed in detail in section 2.3). Eschenmoser's salt **92**, carbocation **94**, amides **95** and CDI **96** all did not give any trapped product. The method used to generate the formaldehyde was critical to the success of the hydroxymethylation reaction. It was found that only freshly prepared formaldehyde solution* gave the desired product. The setup for formaldehyde depolymerisation is shown in Figure 2.1.

Inspired by these initial results, we focused on the hydroxymethylation of zirconium enolates and attempted to understand its scope. Using the same ACA system between **31** and **88**, we varied the reaction conditions namely, reaction time, equivalents of formaldehyde, solvent, concentration and reaction temperature. To our surprise, we could not find an apparent relationship between reaction variables and yield; the experiments are presented in Scheme 2.11. This made further improvements to the reaction very difficult. In general, the hydroxymethy-

*Formaldehyde gas was generated by cracking *para* formaldehyde at 150 °C and dissolved in dry solvent (Et_2O). Disposable, long needles were used for gas transfer because the solidifying formaldehyde rendered cleaning impossible.



entry	E	product	yield %	conditions
1	**91**	**87**	Up to 50	Freshly cracked, anhydrous CH_2O
2	**91**	**87**	0	35% wt. aqueous solution of CH_2O
3	**89**	**90**	41	**89** ($POCl_3$, DMF)

Scheme 2.10: Screening of electrophiles for zirconium enolate trapping

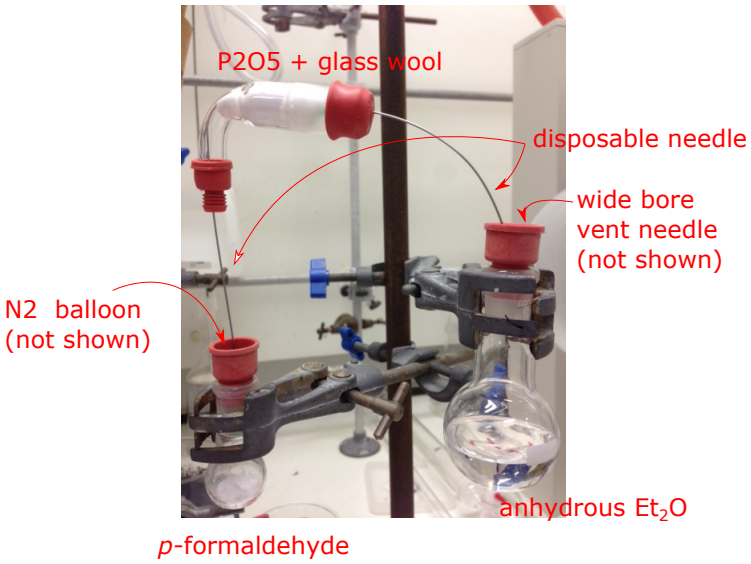
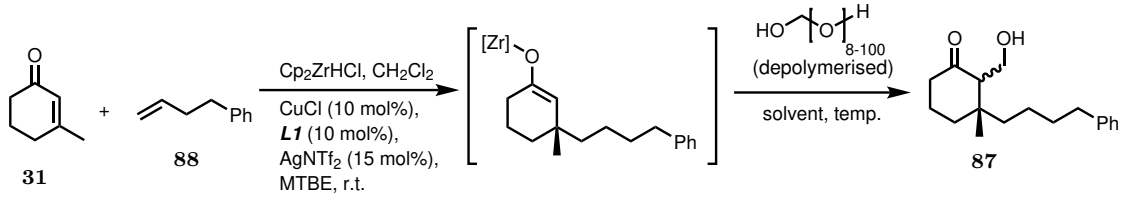


Figure 2.1: Cracking of *p*-formaldehyde: experimental setup. Nitrogen balloon and exit needle not shown in photo for clarity. In normal operation, gaseous formaldehyde from the leftmost flask would be bubbled through the anhydrous ether. The amount of solid *p*-formaldehyde used was based on 20 equivalents of monomer.

lation of zirconium enolates using formaldehyde gas did not work well for many substrates: even changing the alkene partner sometimes caused the yield to drop significantly (up to 20% decrease).

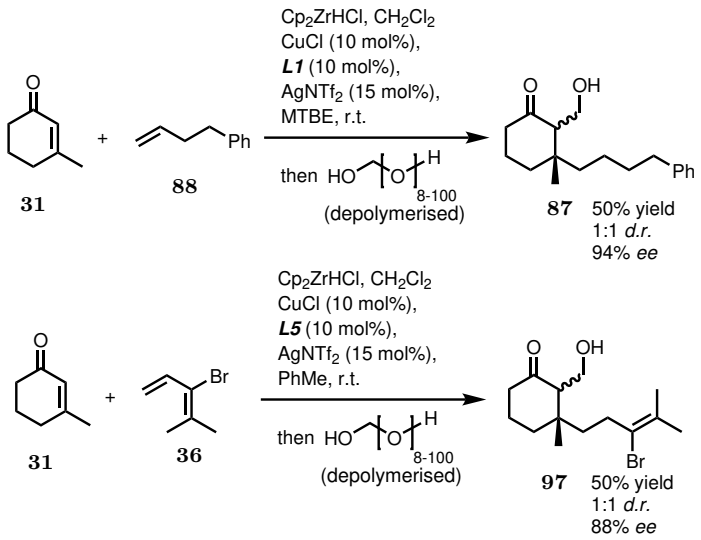


entry	trap time (min)	HCOH(g) (eq.)	solvent (M)	T (°C)	yield (%)	*d.r.*
1	5 (sec)	20	Et_2O (0.03)	RT	51	1:1
2	5	10	Et_2O (0.03)	RT	45	1.2:1
3	5	20	Et_2O (0.03)	RT	50	1:1
4	20	20	Et_2O (0.03)	RT	48	1.6:1
5[a]	20	20	Et_2O (0.03)	RT	N.R.	-
6	20	20	CH_2Cl_2 (0.03)	RT	49	1.4:1
7	20	20	THF (0.03)	RT	49	1.4:1
8	20	20	MTBE (0.03)	RT	43	1.5:1
9	20	20	$Cl(CH_2)_2Cl$ (0.03)	RT	43	1.2:1
10	20	20	THF (0.06)	RT	43	1.4:1
11	20	20	THF (0.1)	RT	38	1.4:1
12	20	20	THF (0.06)	40	28	1.2:1
13	20	20	THF (0.1)	40	42	1.5:1
14	20	20	THF (0.06)	60	11	1.5:1
15	20	20	THF (0.1)	60	27	1.4:1

Scheme 2.11: Attempted optimisation of ACA/trapping with freshly cracked formaldehyde. [a]TMSCl (5.0 eq.) was added during the ACA step. **L1** is from Scheme 1.15

One of the few substrates to work using the ACA/trapping conditions involving formaldehyde was when bromodiene **36** was employed as the alkene. When no more **31** remained by TLC, the crude reaction mixture was directly added to a solution of freshly cracked formaldehyde which delivered trapped product **97** in 50%

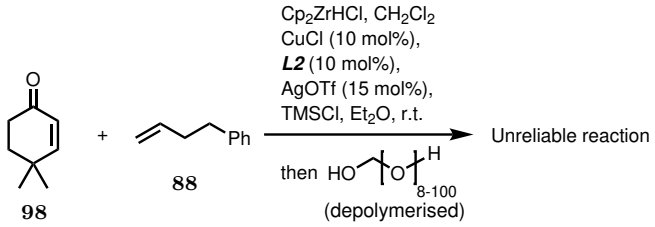
yield, as a 1:1 mixture of diastereomers. Scheme 2.12 shows the two substrates for which it was possible to isolate the α-hydroxy ketones.



Scheme 2.12: ACA/trapping with formaldehyde of cyclic, quaternary stereocenter-containing products: successful reactions

In an attempt to improve the scope of the formaldehyde hydroxymethylation reaction, different ACA conditions developed by our group were investigated Scheme 2.13. The use of the standard procedure[21] for preparing tertiary stereocenter cyclic ketones was found to be unreliable in giving the trapped products (see experimental section – Scheme 5.6 for a complete list of experiments attempted). Using additives such as 3Å and $Cu(OTf)_2$ as a Lewis acid, with the reasoning that they would remove adventitious moisture and activate the electrophile respectively, did not promote the reaction. The product was only observed when a different phosphoramidite ligand (**L1** instead of **L2**, see Scheme 1.15), silver salt ($AgNTf_2$ instead of AgOTf), solvent (MTBE instead of Et_2O) were used and TMSCl was

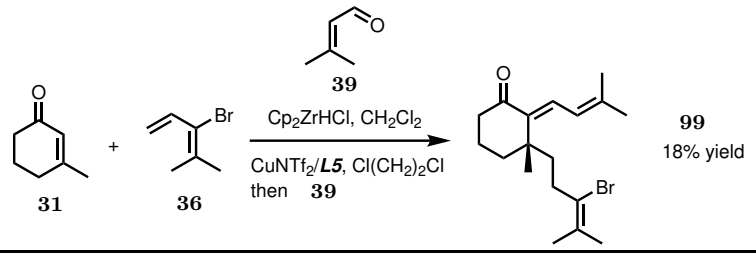
not used in the reaction. These conditions are used to prepare quaternary stereocenter cyclic ketones.[31] It is not clear how or why the ACA conditions have such an effect on the trapping step of the reaction however, the change of ACA conditions is extremely undesirable because these conditions have been previously optimised for the particular substrate at hand. Another system that was investigated was Mukaiyama and co-workers' cross-aldol system involving $TiCl_4$/1,3,5-trioxane and a silyl enol ether.[60] Several studies in the group proposed the formation of an intermediate silyl enol ether in the ACA reactions that employed TMSCl where the role of TMSCl was to improve catalyst turnover. Our idea was to instead trap this intermediate with the hope that it might be more reactive than the corresponding zirconium enolate. Unfortunately, no trapping products were observed despite extensive optimisation.



Scheme 2.13: Attempted ACA/trapping with formaldehyde of cyclic, tertiary stereocenter-containing products.

Despite the initial screening experiments (Scheme 2.10) showing that zirconium enolates could not be trapped using benzaldehyde **93**, we were unconvinced that aldehydes would behave significantly different from formaldehyde. Thus we subject the enolate generated from the ACA between 3-methyl-2-cyclohexenone **31** and bromodiene **36**, to reaction with 3-methyl-crotonaldehyde **39** (Table 2.1).

To our delight, aldol condensation product **99** was isolated in 19% yield (entry 1). Although increasing the equivalents of 3-methyl-crotonaldehyde **39** led to a greater yield (entry 2), it was more difficult to separate the product from the excess electrophile. Attempts to enhance the reactivity of the enolate using Westmeier's procedure did not improve the yield (entry 3). Increasing temperature up to 60 °C resulted in decomposition (entry 4).



entry	**39** eq.	trapping conditions	yield (%)
1	2	direct addition, 60 °C	19[a]
2	4	direct addition, 60 °C	31
3	2	MeLi (1.1 eq.), −78 °C to r.t.	21
4	2	MeLi (1.1 eq.), −78 to 60 °C	Decomp.

Table 2.1: ACA/trapping of aldehydes. Yields were determined by NMR internal standard measurements unless specified otherwise. [a]Isolated yield. **L5** is from Scheme 1.15

It is strange that the the intermediate enolate from the ACA reaction of 4-phenyl-1-butene **88** or bromodiene **36** to 3-methyl-2-cyclohexenone **31**, using an otherwise identical catalytic system, would react differently in the presence of aldehydes. Steric hindrance of the alkene partner should not be a contributing factor here because both alkenes have similar profiles. This suggests that the nature of the zirconium enolate in the ACA reaction is more complicated than is currently understood. Earlier examples of trapping with non-chiral zirconium enolates support this proposition. Evans and co-workers reported the direct re-

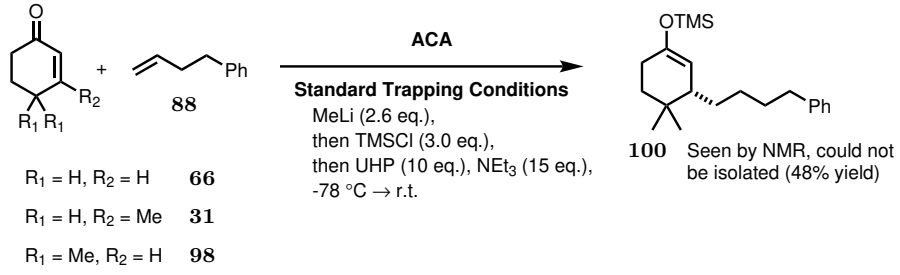
action of a zirconium enolate, prepared via transmetallation of the corresponding lithium enolate, with a variety of aldehydes.[61] When benzaldehyde was used, the trapped product was obtained in 71% yield, substantially better than what was observed in our experiments.[61a] According to Wipf and Takahashi,[62] the success of the zirconium enolate trapping reaction depends on when the aldehyde is added after the addition of the Michael acceptor. We tried their conditions on our system but did not observe the same positive effects.

2.2.2 Attempted preparation of silyl enol ethers from zirconium enolates

Although the tandem ACA / trapping to prepare **87** and **97** using formaldehyde was a success (Scheme 2.12), we foresaw that low yields and limited scope could be a limitation for its eventual use towards the synthesis of the Taxol core. Furthermore, the handling of gaseous formaldehyde is tedious and these reasons prompted us to search for more general and easier to carry out trapping reactions. Trapping with chlorotrialkylsilanes was seen as a promising goal for the following reasons: 1) the chemistry of these silyl enol ethers is well known and versatile, making the trapping reaction more useful to chemists 2) there is precedence for the trapping reaction (see the work by Westmeier and co-workers[58]) meaning that in theory, it should also work with enolates generated with our conditions.

Unfortunately, despite many attempts, the reaction shown in Scheme 2.14 was found to be irreproducible when using our ACA conditions. The source of irreproducibility could not be determined and the best explanation that can be given is

the ill-defined nature of the intermediate zirconium enolate. In similar fashion to Scheme 2.11, we considered variables such as temperature, enolate activation with methyllithium, workup procedure and ACA conditions. Complicating the matter was that work up of hydrolytically sensitive enol **100** was also unpredictable. Baran's conditions[14b] called for the use of Florisil (magnesium silicate), as a filter aid and stationary phase for subsequent chromatography. In our hands, we found that even using the same brand (Alfa Aesar 1321870 100-200 mesh) but different batch numbers resulted in one reaction working (LOT10177933) and the other not working (LOT10205673). Unfortunately, the non-working batch of Florisil was a recent addition to the lab whereas the working batch was from an old bottle that could not be replenished. While the synthesis of TMS enol ethers would have represented a great achievement, we were not able to develop a procedure that was compatible with our ACA reactions.

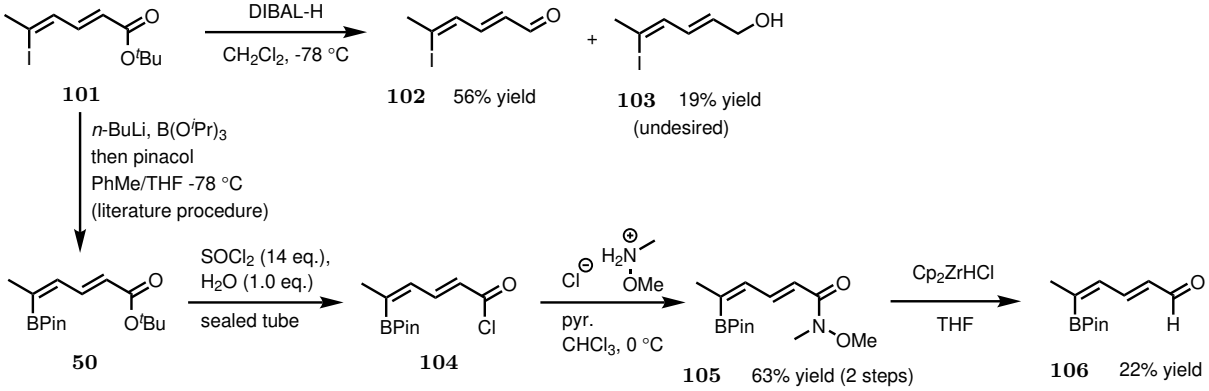


Scheme 2.14: Unsuccessful trapping of zirconium enolates using TMSCl.

2.2.3 Attempts to apply zirconium enolate trapping towards the synthesis of the Taxol core

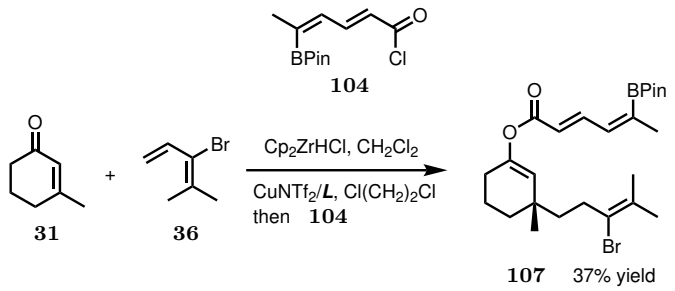
With a procedure to execute the tandem ACA / trapping reaction, we returned to the synthesis of the Taxol core. As mentioned at the end of Chapter 1, performing the trapping reaction early on in the sequence so that the more reliable cross coupling reaction could be conducted in the later stages of the synthesis would be a better strategy. The first task we set out to accomplish was to synthesise the appropriate fragments. Scheme 2.15 summarises the coupling partners prepared beginning with known[44] iodoester **101**. Direct reduction with diisobutylaluminium hydride at low temperature gave at best a mixture of alcohol and aldehydes in combined 75% yield (2.9:1 ratio). BPin *tert*-butyl ester **50** could be converted to corresponding acid chloride **104** using the procedure described by Greenberg and Sammakia.[46] From this intermediate, Weinreb amide **105** could be prepared (65% yield over 2 steps) which was then reduced using Schwartz reagent to give **106** in 22% yield. If this reaction was left for too long, only the alcohol was obtained from the reaction mixture.

Our first trapping attempt was using acid chloride **104** since it is relatively easy to prepare. Upon completion of the ACA reaction (as determined by TLC), acid chloride **104** prepared according to Scheme 2.15 and used without purification, was directly injected into the crude reaction mixture to give *O*-trapped product **107** in 37% yield (entry 1). Attempting to modify the trapping conditions including dilution/heat (entry 2; 29% yield) and acid chloride activation (entry 3; 17% yield) all led to reduced yields. Attempting to activate the enolate as an -ate com-



Scheme 2.15: Synthesis of electrophiles to be used in tandem ACA / trapping for Taxol core synthesis. Abbreviations: *DIBAL-H* = diisobutylaluminium hydride, *pyr.* = pyridine, *Pin.* = pinacol

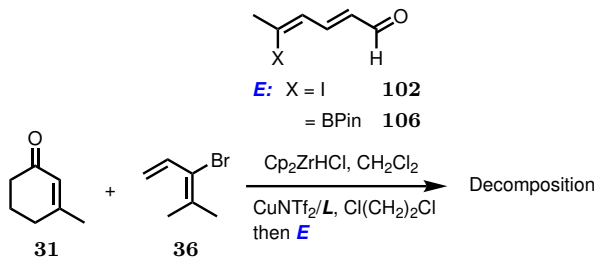
plex (entry 4) caused decomposition and no trapped product was observed. The selectivity for *O*-trapping can be explained using a hard soft acid base (HSAB) argument, where the (relatively) hard electrophilic carbonyl center would prefer to react at the hard nucleophilic oxygen.



entry	Trapping conditions	Yield (%)
1	**104** (2.0 eq.), direct addition	37
2	**104** (2.0 eq.), Et_2O 0.16M, reflux	29
3	**104** (2.0 eq.), DMAP · HCl (10 mol%)	17
4	**104** (2.0 eq.), MeLi (1.1 eq.), −78 °C	Decomp.

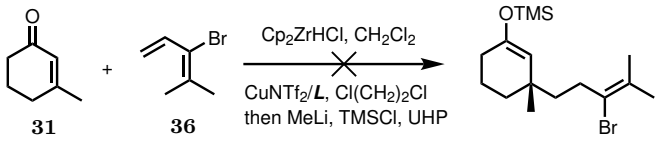
Table 2.2: Trapping of zirconium enolates using an acid chloride. ACA was carried out as for Scheme 1.16.

Results using aldehydes as trapping agents (see Table 2.1) suggest that the next logical electrophile to try would be one that is consistent with the HSAB rationalisation (Scheme 2.16). Unfortunately in both experiments using iodoaldehyde **102** or BPin aldehyde **106**, decomposition occurred and no identifiable products could be found.



Scheme 2.16: Trapping of zirconium enolates with aldehydes – attempts to synthesise a Taxol core intermediate. ACA was carried out as for Scheme 1.16.

In a final, desperate attempt to prepare a useful intermediate towards the Taxol core, we revisited the silyl trapping reaction in the hopes that it would work for the specific combination of ACA partners **31** and **36** (see Scheme 2.17). The reaction decomposed after all reagents had been added and the mixture was warmed to room temperature. No trapped products were observed.

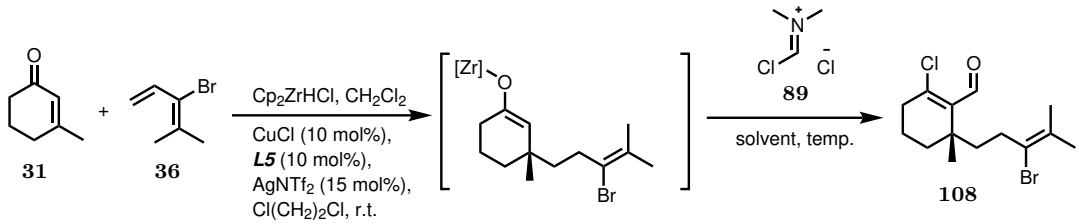


Scheme 2.17: Trapping of zirconium enolates with chlorotrimethylsilane – attempt to synthesise a Taxol core intermediate. ACA was carried out as for Scheme 1.16. Abbreviations: *UHP* = urea hydrogen peroxide complex.

2.3 Trapping of zirconium enolates using the Vilsmeier-Haack reagent

2.3.1 Reaction development

With other electrophile options exhausted, we revisited the trapping reaction using the Vilsmeier-Haack reagent **89** (for the initial screening hit, see Scheme 2.10 – entry 3). When the ACA between 3-methyl-2-cyclohexenone **31** and bromodiene **36** was used, the reaction displayed much better characteristics compared to the formaldehyde trapping and representative optimisation examples are summarised in Scheme 2.18. The most important variable for the success for the trapping was the reaction temperature. Only at elevated temperatures would product **108** be formed however, quenching needed to be performed at 0 °C to prevent decomposition (entry 13). Solvents were screened and it was found that chlorinated solvents gave better yields (entry 11) compared to hydrocarbon solvents (entries 8-10). Reactions typically required efficient stirring while trapping time did not have a substantial effect on the yield. Another important factor for the reaction was the use of 20 equivalents of **89**. At least 10 equivalents was required but 20 gives the product more reliably. On a large scale, 10 equivalents could be used in conjunction with a longer reaction time with no adverse effect on the yield (see Chapter 3 – Scheme 3.2, where this was done to prepare a key intermediate on scale).



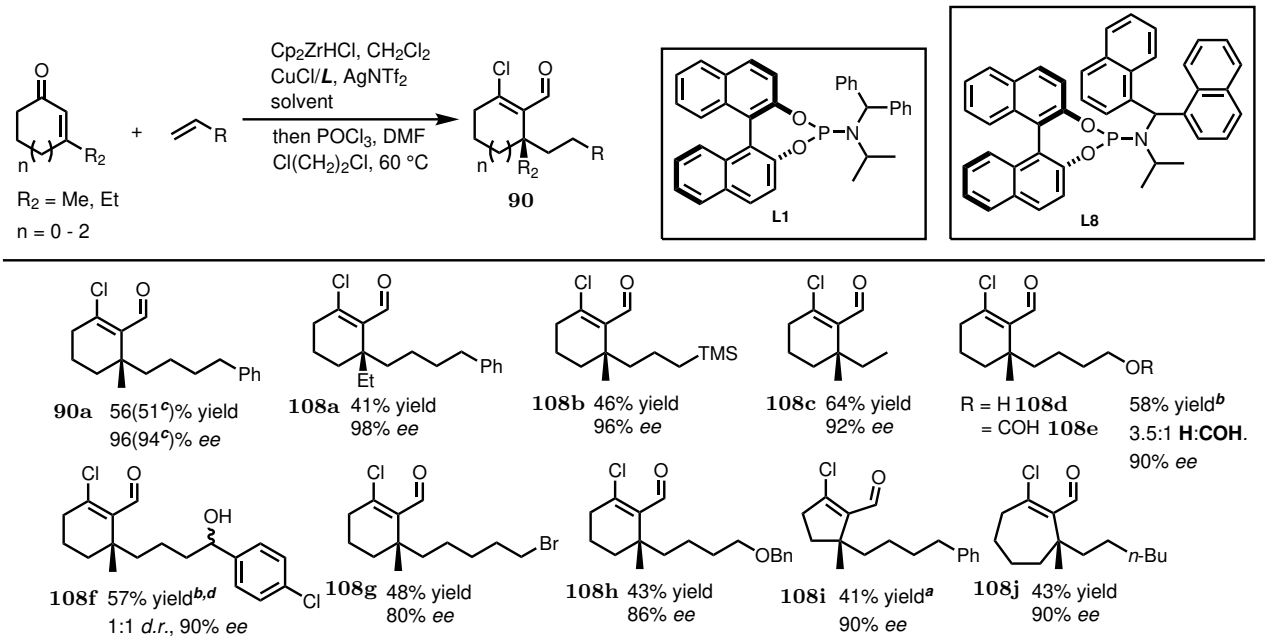
entry	trap time (min)	**89** (eq)	solvent (M)	T (°C)	yield (%)
1	20	10	CH_2Cl_2 (0.03)	RT	12
2	20	5	CH_2Cl_2 (0.03)	RT	5
3	60	5	CH_2Cl_2 (0.03)	RT	1
4	20	10	CH_2Cl_2 (0.06)	RT	24
5	20	20	CH_2Cl_2 (0.03)	RT	31
6	20	20	CH_2Cl_2 (0.1)	RT	17
7	20	20	CH_2Cl_2 (0.06)	40	40
8	20	20	THF (0.06)	RT	21
9	20	20	DMF (0.06)	RT	19
10	20	20	TBME (0.06)	RT	0
11	20	20	$CHCl_3$ (0.06)	RT	25
12[a]	20	20	CH_2Cl_2 (0.06)	60	54
13[a]	20	20	$Cl(CH_2)_2Cl$ (0.06)	60	61
14[a]	20	20	$CHCl_3$ (0.06)	60	44
15	20	10	$Cl(CH_2)_2Cl$ (0.06)	60	44
16	150	5	$Cl(CH_2)_2Cl$ (0.06)	60	41
17	150	2	$Cl(CH_2)_2Cl$ (0.06)	60	21
18	150	2	$Cl(CH_2)_2Cl$ (0.06)	105	21

Scheme 2.18: Optimisation of ACA/trapping with Vilsmeier-Haack reagent **89**. [a]Reaction quenched at 0 °C. **L5** is from Scheme 1.15

2.3.2 Scope of Vilsmeier-Haack trapping reaction – preparation of β-chloroaldehydes containing quaternary centers

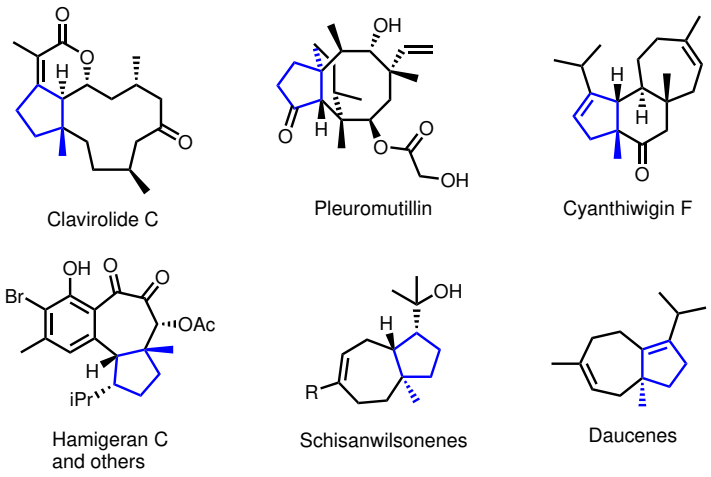
Having identified the key variables responsible for a successful reaction, we began to study the reaction's scope.[21a,31a] For the ACA step, standard conditions for the preparation of quaternary centers were used. Using these conditions, a range of different β-chloroaldehydes **90** could be formed. The chloroformylation reaction was found to be compatible with a range of cyclic ketones and alkenes. Enantioselectivities were unaffected as the stereo-determining step occured in the ACA. In regards to ketones, substitution at the 3 position did not significantly affect the reaction yield. The reaction however, was limited to the compatibility of substrates in the parent ACA reaction. This meant, that various alkenes containing alkyl chains (**108c** and **108j**), aromatic rings (**90a** and **108a**), halides (both aromatic **108f** and alphatic **108g**), silanes **108b** and benzyl protected alcohols **108h** were tolerated. Interestingly, when a TBS protected alcohol was used, the corresponding free alcohol was obtained (**108d** and **108f**). In the latter case, formate **108e** was also obtained under the reaction conditions. This species is formed when the acid-labile TBS group falls off under the reaction conditions and excess **89** reacts with the free alcohol.

The preparation of five-membered ring products is especially significant for two reasons. Several natural products contain a 1,2,3-substituted cyclopentane motif and the chloroformylation procedure discussed here could be used to access these compounds in the future (see Scheme 2.20). Two of these natural products, pleu-



Scheme 2.19: Scope of tandem ACA/trapping to prepare β-chloroaldehydes. All yields are quoted as isolated. Unless specified otherwise, ACA reactions were conducted using **L1** with MTBE as solvent. *ee*'s were determined by HPC or SFC. [a]ACA reaction was conducted using ***L8***, Et_2O as solvent, and TMSCl (5.0 equiv). [b]Asymmetric addition using TBS protected alcohols. [c]5 mmol scale to give 0.79 g of **90a** . [d]The alkene elimination product was also observed in trace amounts.

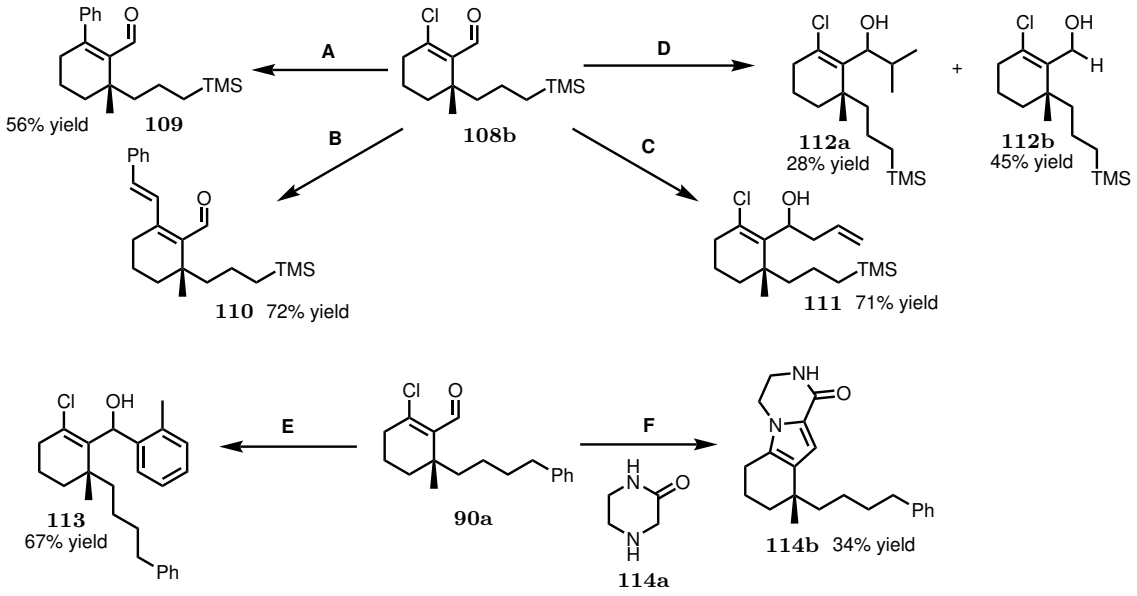
romutilin and clavirolide, have already been discussed earlier in the chapter. The second reason is that this experiment adds further confirmation of the complex nature of the intermediate zirconium enolate. In earlier trapping experiments involving formaldehyde, it was reasoned that the unsuccessful reactions could have been due to an unreactive TMS enol ether intermediate being formed. The successful preparation of cyclopentene containing β-chloroaldehyde **108i** refutes this hypothesis. Five equivalents of chlorotrimethylsilane is used in the reaction and yet the product is still formed. It is clear that our understanding of the reaction and its substrate dependence is still incomplete.



Scheme 2.20: Examples of Natural Products Containing 1,2,3-substituted Cyclopentanes.

To illustrate the versatility of β-chloroaldehyde products obtained from the tandem ACA/trapping sequence, a number of products shown in Scheme 2.21 were subject to a number of transformations. β-chloroaldehydes underwent Suzuki-Miyaura couplings with aryl and alkenyl boronic acids to give the expected coupling

product (**109** and **110**) with yields of 56% and 72% respectively. Addition of Grignard reagents gave diastereomeric alcohols with yields between 67-71% (**111** and **113**). When isopropylmagnesium chloride was used, addition product **112a** was only isolated in 28% yield. Reduction product **112b** was obtained in 45% yield and this type of behaviour has been observed for certain alkyl Grignards possessing β hydrogens.[63] Finally, β-chloroaldehyde **90a** also underwent condensation with 2-piperazinone **114a** in the presence of *N*-methylmorpholine to give dihydropyrrolopyrazinone **114b** in 34% yield using conditions described by Sandoval and coworkers.[64]



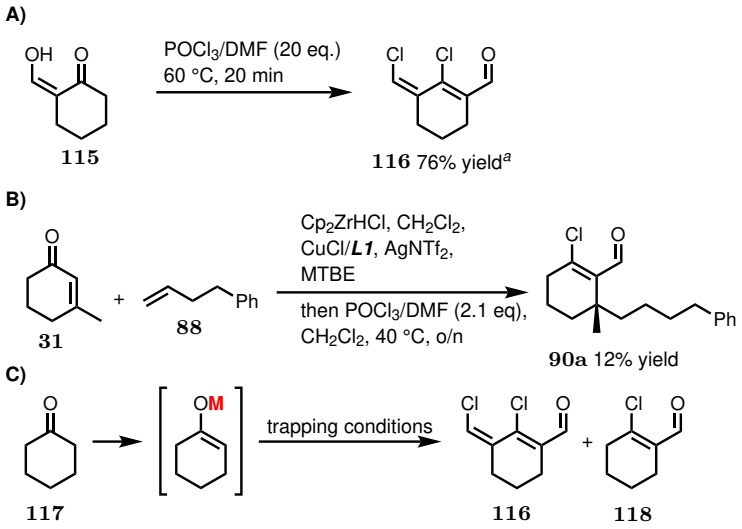
Scheme 2.21: Derivatisation of β-chloroaldehydes **90** obtained from Tandem ACA/Trapping. Conditions: *A)* phenylboronic acid (1.1 eq.), $Pd(OAc)_2$ (0.050 eq.), XPhos (0.050 eq.), K_3PO_4 (3.0 eq.), $MeCN/H_2O$, 40 °C 4.5 hrs. ; *B)* styrenylboronic acid (1.1 eq.), $Pd(OAc)_2$ (0.050 eq.), XPhos (0.050 eq.), K_3PO_4 (3.0 eq.), $MeCN/H_2O$, 30 °C 6 hrs. ; *C)* Allylmagnesium bromide (1.2 eq.), Et_2O −40 °C to r.t. 5.5 hrs. ; *D)* isopropylmagnesium chloride (1.2 eq.), Et_2O −40 °C to r.t. 5.5 hrs. ; *E)* *o*-Tolylmagnesium bromide (1.2 eq.), Et_2O 0 °C to r.t. 6 hrs. ; *F)* 2-oxopiperazine **114a** (0.67 eq.), NMO (1.0 eq.), DMF 115 °C 5 hrs.

2.3.3 Mechanism of chloroformylation reaction

In order to gain further insight into the ACA/trapping reaction using the Vilsmeier-Haack reagent **89**, we performed experiments to probe the transformation's mechanism. Scheme 2.22 summarises the experiments conducted.

Initially, hydroxymethylene cyclohexanone,[65] a simple model of a 1,3-dicarbonyl compound which might be formed through formylation, was treated with **89** which gave doubly chlorinated unsaturated aldehyde **116** in 76% yield. This species was not observed in our reactions which suggests against dicarbonyl or related (tautomeric) intermediates (Scheme 2.22 – A). Unfortunately, the use of other simple model systems also gave rise to **116** as shown below.

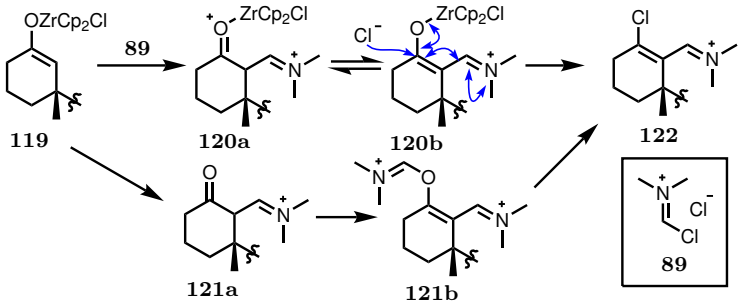
Conditions reported by Sandoval and co-workers for the chlorination of cyclohexanone[64] gave decreased yield of trapped product (12%, Scheme 2.22 – B). The identity of the metal enolate played a significant role in product formation (Scheme 2.22 – C). The use of lithium enolate[61a] gave 10% yield of dichloride **116** with mostly starting material being recovered and no monochlorinated product **118**. The zirconium enolate,[61a] formed from the transmetallation of the lithium enolate with Cp_2ZrHCl, gave 48% yield of dichloride **116** exclusively. Interestingly, treating cyclohexanone using our optimised trapping conditions, gave dichloride **116** in 4% yield whereas using Sandoval's conditions gave exclusively the monochloride **118** in 71% yield.



entry	M	trapping conditions	yield % (**116**:**118**)
1	Li	$POCl_3$/DMF (20 eq.) 60 °C, 1 hr	10 (1:0)
2	Cp_2ZrCl[c]	$POCl_3$/DMF (20 eq.) 60 °C, 1 hr	48 (1:0)
3	H[e]	$POCl_3$/DMF (20 eq.) 60 °C, 1 hr	4 (1:0)
4[ab]	H[e]	$POCl_3$/DMF (2.1 eq.) 40 °C, 27 h	71 (0:1)

Scheme 2.22: Selected experiments for mechanistic studies. Unless specified otherwise, yields were determined by NMR internal standard measurements. [a]Isolated yield. [b]Data consistent with literature.[66,64] [c] Lithiation and transmetallation procedures were carried out according to the procedure of Evans and co-workers.[61] [d]Cyclohexanone was used. [e]Yield was based on average over two experiments.

From these experiments, a plausible mechanism was proposed (Scheme 2.23). Zirconium enolate **119** initially reacts with one equivalent of **89** to form **120a** . This intermediate then loses a proton to form **120b** . The last step is the addition of chloride followed by elimination of an O-Zr species, giving iminium **122** which would furnish the β-chloroaldehyde upon hydrolysis. Alternatively, species **121a** could also be formed when another equivalent of **89** reacts at oxygen, resulting in species **121b** . This compound could then undergo substitution with chloride as above to provide **122**.

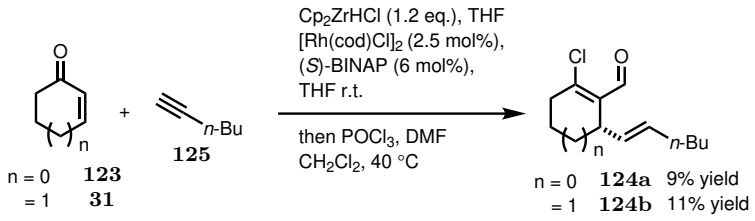


Scheme 2.23: Possible mechanisms for trapping reaction using **89**.

2.3.4 Scope of chloroformylation reaction – other classes of ACA reactions

We began our investigation by consider the rhodium catalysed ACA of alkenylzirconium reagents, initially disclosed by the research groups of Inoue[67] and Hanzawa[68] and later used by Westmeier and co-workers in their trapping procedure[58a] (Scheme 2.24). The alkenylzirconium reagent was prepared via hydrometallation of 1-hexyne using Schwartz reagent. After the ACA was deemed complete (followed by TLC), the reaction was treated with a mixture of $POCl_3$ and DMF in dichloromethane at 40 °C overnight. Note that this differs from the procedure used for the synthesis of quaternary center-containing cyclic ketones described in the previous section. It was found that these milder trapping conditions originally described by Sandoval and co-workers[64] gave low yields of the product (approximately 10%) whereas the use of using 20 equivalents of the Vilsmeier-Haack reagent at 60 °C as was done for Scheme 2.19 gave no product.

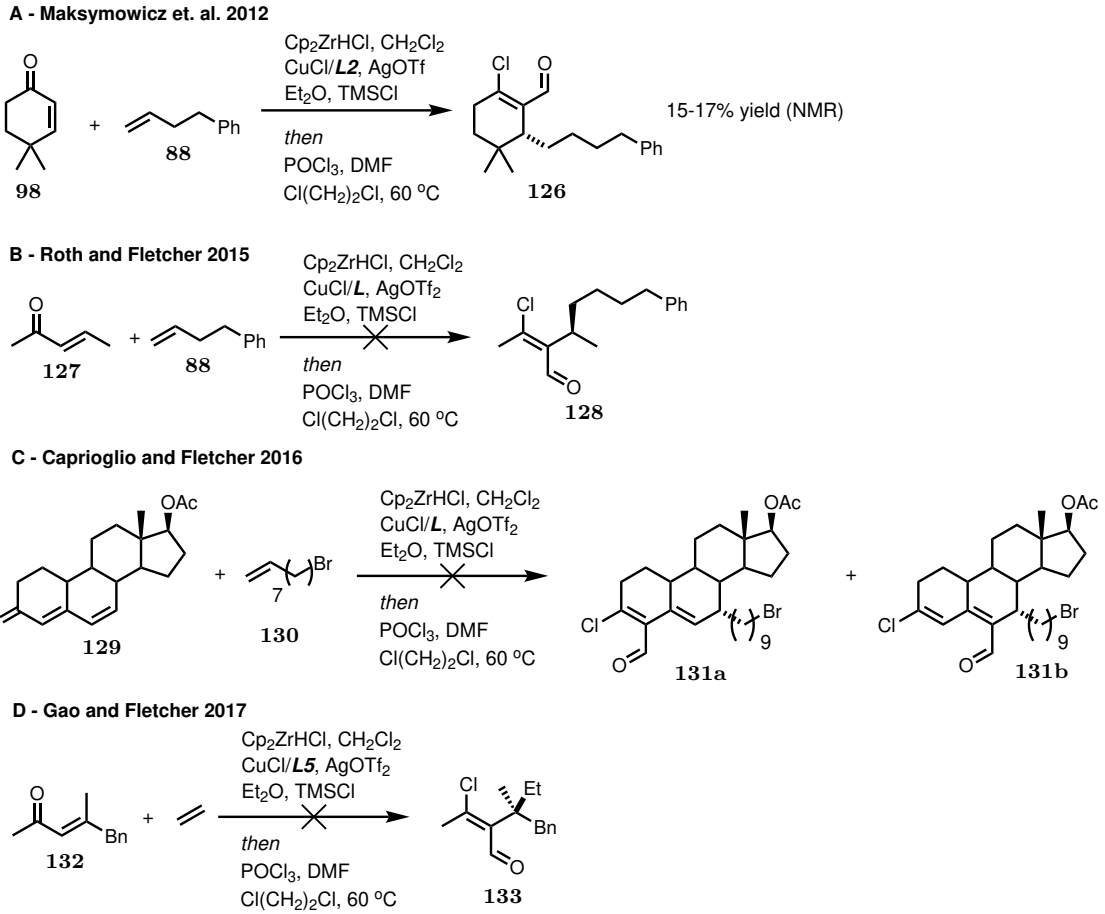
Next, we revisited the ACA reactions developed in the group (Scheme 2.25). For all the processes in Scheme 2.25 and Scheme 2.26, the reaction was performed



Scheme 2.24: Tandem rhodium-catalysed ACA of alkenylzirconium reagents and chloroformylation to prepare β-chloroaldehydes.

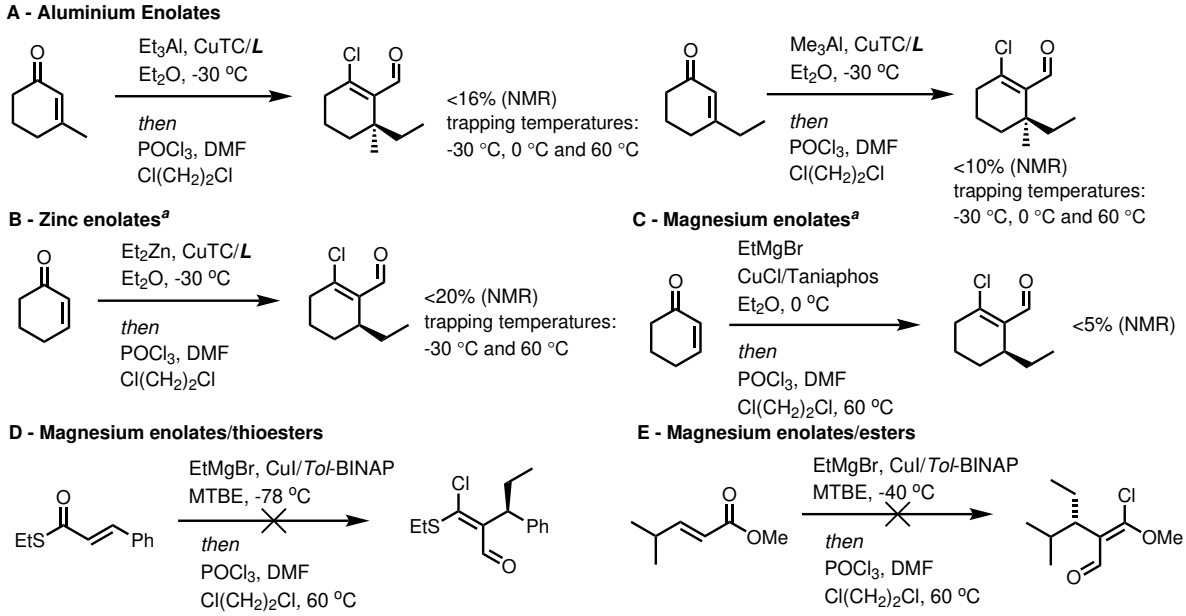
initially without the Vilsmeier-Haack reagent to confirm reproducibility. The use of 4,4-dimethyl-2-cyclohexenone **98** which employed standard conditions to prepare tertiary center-containing cyclic ketones (Scheme 2.25 – A) gave the product in only 15% yield. The product could only be observed by NMR spectroscopy and not isolated. When 6-dehydronandrolone acetate **129**, previously used in the synthesis of Fulvestrant,[33] regioisomeric products **131a** and **131b** were not seen in the reaction mixture. No trapped products were observed when the acyclic enones were used (Scheme 2.25 – B and D).

To complete the scope study of the trapping reaction, ACA reactions that generated different enolates were considered (Scheme 2.26). Using Augustin and co-workers' procedure[69a] to prepare aluminium enolates (Scheme 2.26 – A) gave trace amounts of the expected trapped product (<16% yield) that was only visible by NMR (could not be isolated). The same group[69b] also managed to successfully add organozinc reagents to cyclohexenone (Scheme 2.26 – B). Attempted trapping with **89** gave low yields of the desired product (<20% yield) which once again, could not be isolated. In the two examples, various trapping temperatures were investigated but no improvements to yield could be made. Finally, we investi-



Scheme 2.25: Unsuccessful attempts to extend the reaction of the Vilsmeier-Haack reagent **89** with other enolates formed from ACAs developed in the group.

gated magnesium enolates generated using the procedures of Feringa,[69c] Ruiz[69d] and Wang.[69e] When cyclohexenone was employed as the Michael acceptor, trace amounts of the product were observed in the reaction mixture (Scheme 2.26 – C). When thioesters (Scheme 2.26 – D) and esters (Scheme 2.26 – E) were used, no β-chloroaldehyde products were formed.



Scheme 2.26: Unsuccessful attempts to extend trapping with **89** to other enolates and electrophiles. [a]Also attempted trapping with the corresponding zirconium enolate, obtained by transmetallation with Cp_2ZrCl_2 (1.2 eq.).

This chapter discussed the tandem ACA/trapping reaction and our efforts to extend ACA reactions using alkylzirconium nucleophiles. Despite the simplicity of the transformation when drawn on paper, the experiments that were performed suggest that our understanding of enolate trapping reactions is still incomplete. Traditional electrophiles used in enolate trapping reactions were studied includ-

ing aldehydes, acid chlorides and chlorosilanes but were shown to be unreactive. While we originally set out to design a reaction with the most generality as possible, the chloroformylation that we eventually optimised was suitable only for preparing quaternary center-containing products. With this procedure studied and optimised, the subject of the following chapter is the application of this transformation towards the synthesis of the Taxol core.

Chapter 3

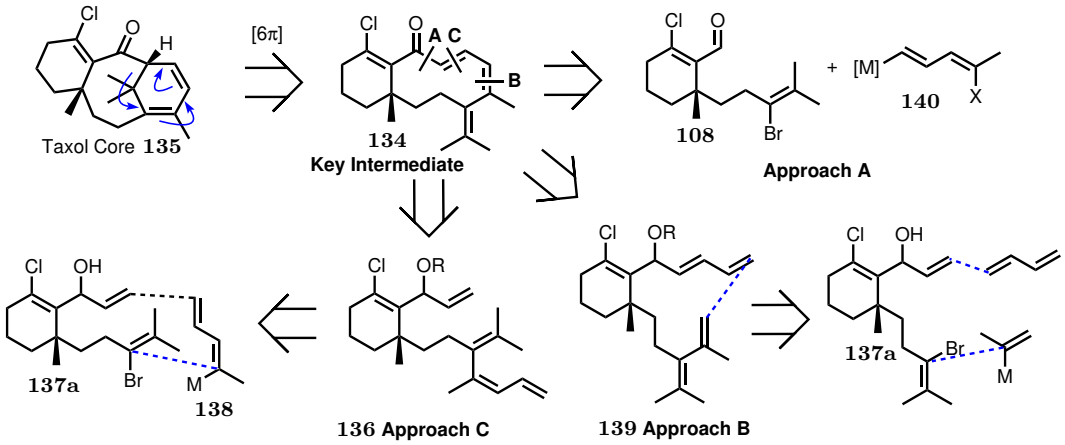
Attempts to prepare the Taxol core via transannular electrocyclisation

3.1 Overview and retrosynthetic analysis

In these next two chapter, we describe our efforts towards synthesising the Taxol core using asymmetric conjugate additions (ACAs) of alkenes. This work is built upon the foundation of Chapter 1 where the ACA of a bromodiene was used to prepare an enantioenriched bromoketone intermediate and Chapter 2, where the procedure was extended with a trapping component. The focus of this chapter is the disconnection of Taxol core **135** to ten-membered ring **134** using a 6π electrocyclisation, in an analogous fashion to the unsuccessful first generation synthesis reported in Chapter 1. In Chapter 4, an entirely different initial disconnection using an intramolecular Diels–Alder reaction will be discussed.

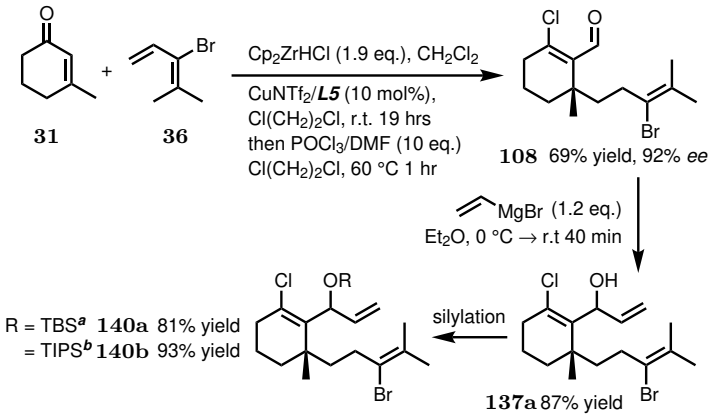
Scheme 3.1 summarises the approaches that were used to prepare "key interme-

diate" **134**. Common to all the approaches is the use of a cross coupling reaction to prepare the tetrasubstituted olefin. These approaches will be discussed separately, beginning with the preparation of the relevant building blocks.



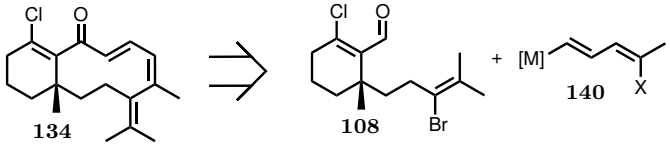
Scheme 3.1: Summary of synthetic approaches towards Taxol core **135**.

We first set out to prepare the intermediate containing the C-ring of the Taxol core (Scheme 3.2), derived from **108**. Dichloroethane was used in the ACA step because it gave the best *ee*'s (see Scheme 1.15) and the yields were improved compared to the original screening experiment due to the increase in reaction scale (16 mmol of **31**). Addition of vinyl Grignard furnished a mixture of diastereomeric alcohols **137a** in 87% yield which were then protected using *tert*-butyldimethylsilyl trifluoromethanesulfonate or tri*iso*propylsilyl trifluoromethanesulfonate to give **140a** or **140b** respectively.



Scheme 3.2: Preparation of Taxol core C-ring. All yields are quoted as isolated. Chloroformylation was conducted according to conditions developed in Chapter 2 Scheme 2.18. *ee*'s were determined by HPC or SFC. [a]*tert*-butyldimethylsilyl trifluoromethanesulfonate (1.1 eq.), 2,6-lutidine (1.1 eq.), Et_2O, 0 °C to r.t. 3.5 hrs ; [b]tri*iso*propylsilyl trifluoromethanesulfonate (1.5 eq.), 2,6-lutidine (1.5 eq.), Et_2O, 0 °C to r.t. 3.5 hrs

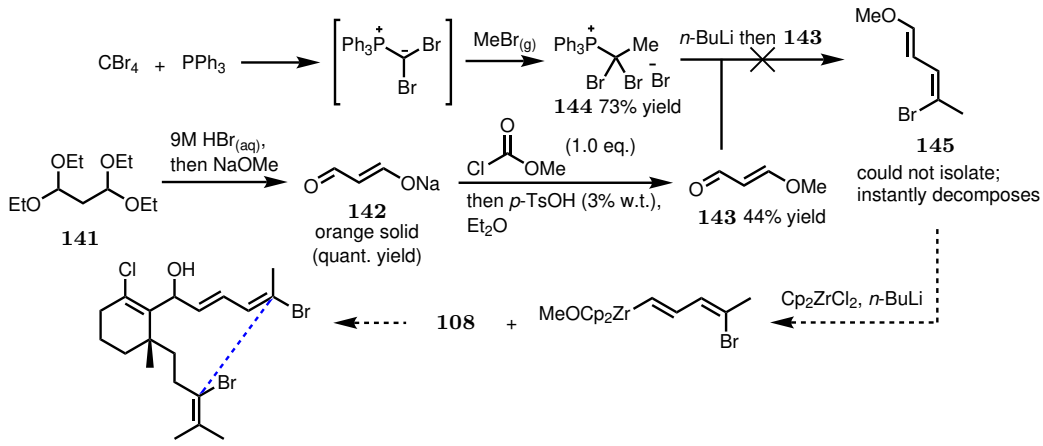
3.2 Disconnection A – Attempts to prepare key intermediate 134



Scheme 3.3: Overview of Disconnection A

Scheme 3.3 shows an overview of Disconnection A. In order to carry out disconnection A in the forward direction, a synthetic equivalent of **140** would be required. A search through the literature revealed a preparation of **145** as reported by Smithers (Scheme 3.4).[70] It was the only fragment possessing the correct chain lenth and double bond geometry. Furthermore, it could be converted to an organozirconium reagent using Negishi's reagent[71] which would allow it to

undergo 1,2-addition to **108**. Initially, malondialdehyde was liberated from 1,1,3,3-tetraethoxypropane **141** and deprotonated with sodium methoxide to give **142** as an orange solid. This compound was reacted with methyl chloroformate followed by acid-mediated decomposition to give 3-methoxypropenal **143** as a pale yellow oil. **143** was extraordinarily difficult to handle; much more so that reported in the original preparation. It fumed and decomposed rapidly and had to be handled at 0 °C (pre-cooling syringes), in the dark.



Scheme 3.4: Preparation of coupling fragment for disconnection A (Smithers).

Concurrently, carbon tetrabromide and triphenylphosphine were reacted to give a phosphonium ylid which was trapped with methyl bromide to give phosphonium salt **144**. Unfortunately, the geographical location of our laboratory made it difficult and expensive to procure methyl bromide and we resorted to making it ourselves.[72] Attempts to replace methyl bromide with the more easily handled methyl iodide led to decomposition as did any other variation on the original procedure. Next, we attempted to perform the Wittig reaction using **144** and 3-methoxypropenal **143**. Despite several attempts, we were not successful in prepar-

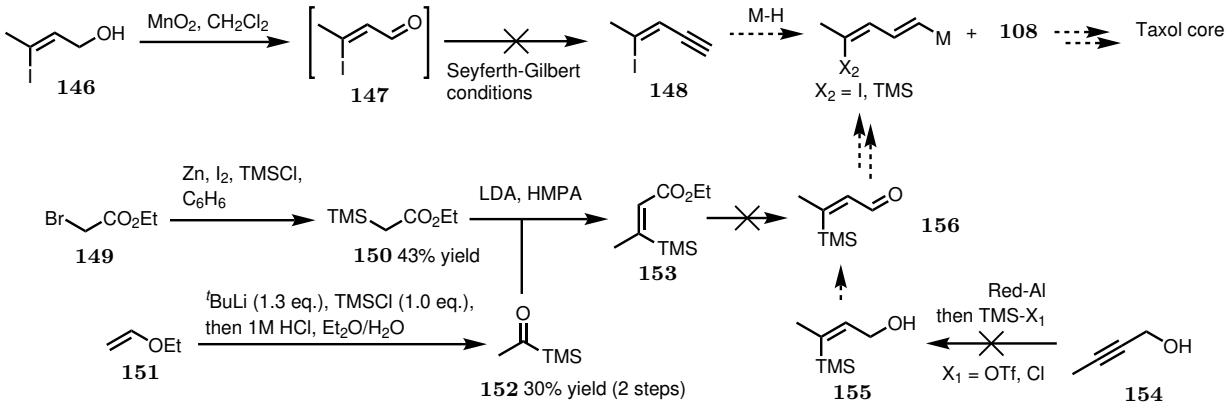
ing the diene **145**. The crude product was obtained with properties consistent with the original report only to instantaneously decompose before it could be properly purified. The reaction could not be scaled up beyond a gram due to the limited amount of methyl bromide we could prepare and therefore we couldn't purify the compound by distillation (original procedure). Attempts to purify the compound using chromatography led to decomposition and no product recovered.

Having exhausted the only literature lead available to use, we set out to synthesise two alkynes: **148** and the one derived from homologation of aldehyde **156**. It was reasoned was that the correct double bond geometry of the coupling fragment could be obtained by hydrometallation (using Cp_2ZrHCl or DIBAL-H) of the alkyne to prepare a synthetic equivalent of **140** (Scheme 3.1). This organometallic reagent could then undergo 1,2-addition to **108**. It was expected that the TMS group on **156** could be converted to the halide readily[73] while being less reactive than the corresponding iodide.

Initially, we attempted to synthesise **156** by direct trapping of the organometallic intermediate derived from hydroalumination of **154**. This was unsuccessful presumably due to the poor nucleophillicity of the organoaluminium reagent. We therefore decided on an alternative route using Peterson conditions between **150** and **152**. Both of these building blocks were prepared according to literature procedures. **152** was prepared by lithiation of ethylvinyl ether **151** followed by trapping with chlorotrimethylsilane and hydrolysis.[74] **150** was prepared by Reformatsky reaction of **149**. α,β-unsaturated ester **153**[75] was prepared by reaction of **150** and **152** in the presence of LDA and HMPA. It was found to be a volatile oil.

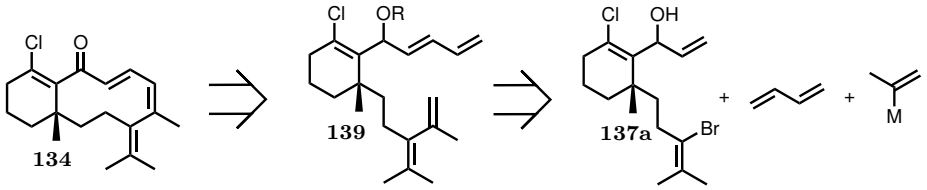
Attempted reduction to the aldehyde using diisobutylaluminium hydride caused only decomposition.

Our final attempt at synthesising fragments relevant for disconnection A was to target **148** using Seyferth-Gilbert conditions.[76] This approach had the advantage in that the precursor aldehyde **147** had already been used in one of our earlier approaches to the Taxol core. Several procedures were tried for the homologation but ultimately, none gave promising leads. The collection of results above show that this endeavour was more challenging than expected and we therefore, decided to move on and consider another disconnection approach.



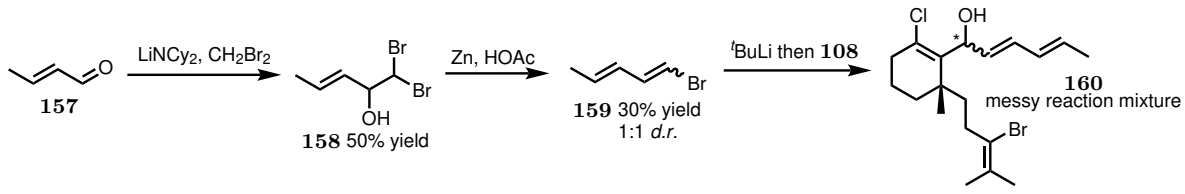
Scheme 3.5: Unsuccessful preparation of other coupling fragments for disconnection A. Abbreviations: *LDA* = lithium diisopropylamide, *HMPA* = hexamethylphosphoramide, *Red-Al* = sodium bis(2-methoxyethoxy)aluminium hydride

3.3 Disconnection B – Attempts to prepare key intermediate 134



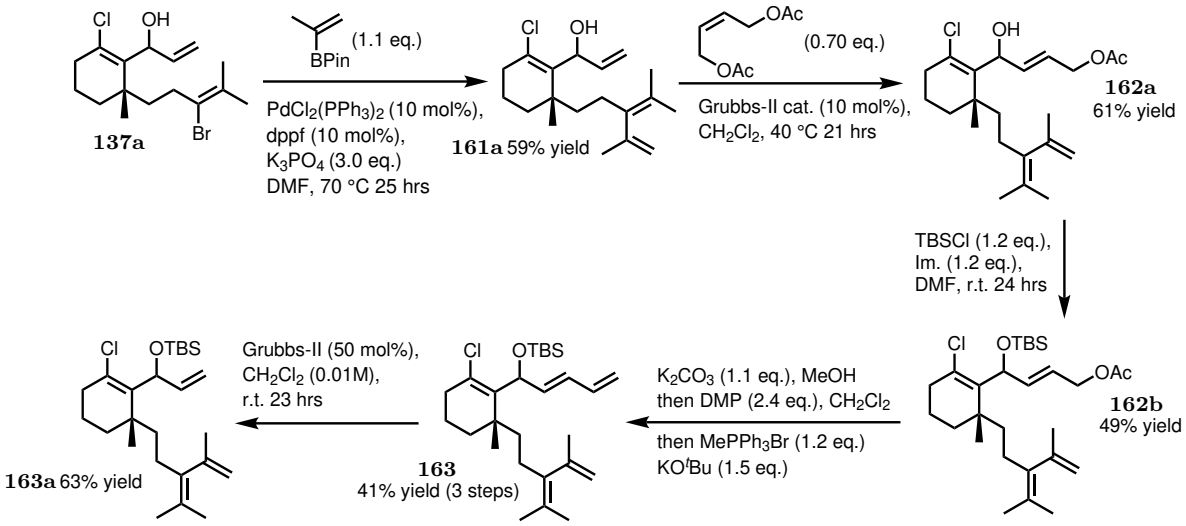
Scheme 3.6: Overview of Disconnection B

While appearing promising on paper, disconnection A was unsuccessful because it was difficult to obtain the required coupling partner. Disconnections B and C were devised in order to alleviate this problem by sourcing more easily accessible building blocks for the coupling fragment. Scheme 3.6 shows an overview of Disconnection B. In this approach, ten-membered ring **134** could be prepared by ring closing metathesis of **139**. This intermediate would in turn, be synthesised from **137a** (see Scheme 3.1). After searching the literature, we found a relevant substrate[77] which could be lithiated and undergo 1,2-addition to aldehyde **108**. Although the preparation was successful to give **159** in 30% yield, subsequent lithiation and addition to **137a** gave a mixture of diastereomers that was difficult to characterise. The inability to prepare stereochemically pure **159** was the main reason why we discontinued this approach in pursuit of others.



Scheme 3.7: Addition approach for disconnection B

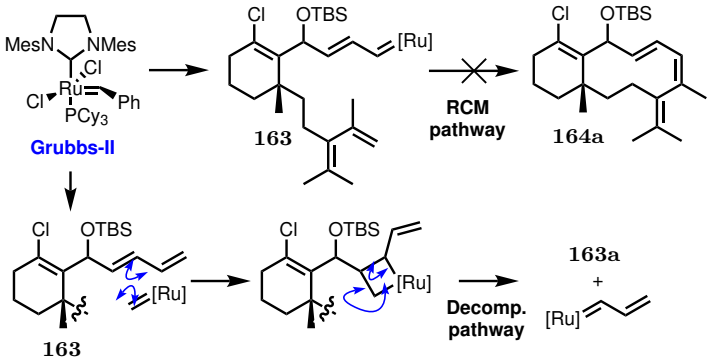
In order to test out the key step of disconnection B, we sacrificed the possibility for a convergent synthesis and attempted to directly functionalise alcohol **137a** . Cross coupling with isopropenylboronic acid pinacol ester gave triene **161a** . Cross metathesis with 1,4-diacetoxybutene using Grubbs second generation catalyst gave acetate **162a** which was subsequently protected as the silyl ether. Protected alcohol **162b** was then subject to a three step procedure to convert the acetate into a terminal olefin to give **163** in 41% yield. Finally, we attempted our key step: the ring closing metathesis reaction to form the ten-membered ring. Unfortunately, only uncyclised product **163a** was recovered.



Scheme 3.8: Metathesis approach for disconnection B. Abbreviations: *dppf* = 1,1'-Bis(diphenylphosphino)ferrocene, *DMP* = Dess-Martin periodinane, *TBSCl* = chloro-*tert*-butyldimethylsilane, *Im.* = imidazole.

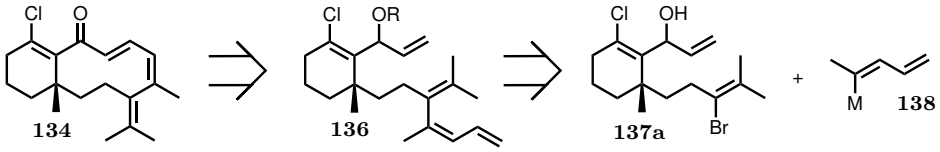
The observation for the transformation **163** to **163a** is rationalised in Scheme 3.9. In a productive pathway towards ten-membered ring product **164a** , the catalyst initiates either at the gem disubstituted olefin or on the terminus of the diene followed by metathesis at the other terminal olein. This is not observed due to

the challenge of achieving conformational control. Instead, a methylidene complex reacts at the internal olefin on the diene which leads to the formation of **163a** . The unfavourable conditions for the ring closing metathesis observed in this section prompted us to devise a third disconnection approach which is discussed in the following section.



Scheme 3.9: Origins of regioselectivity in RCM

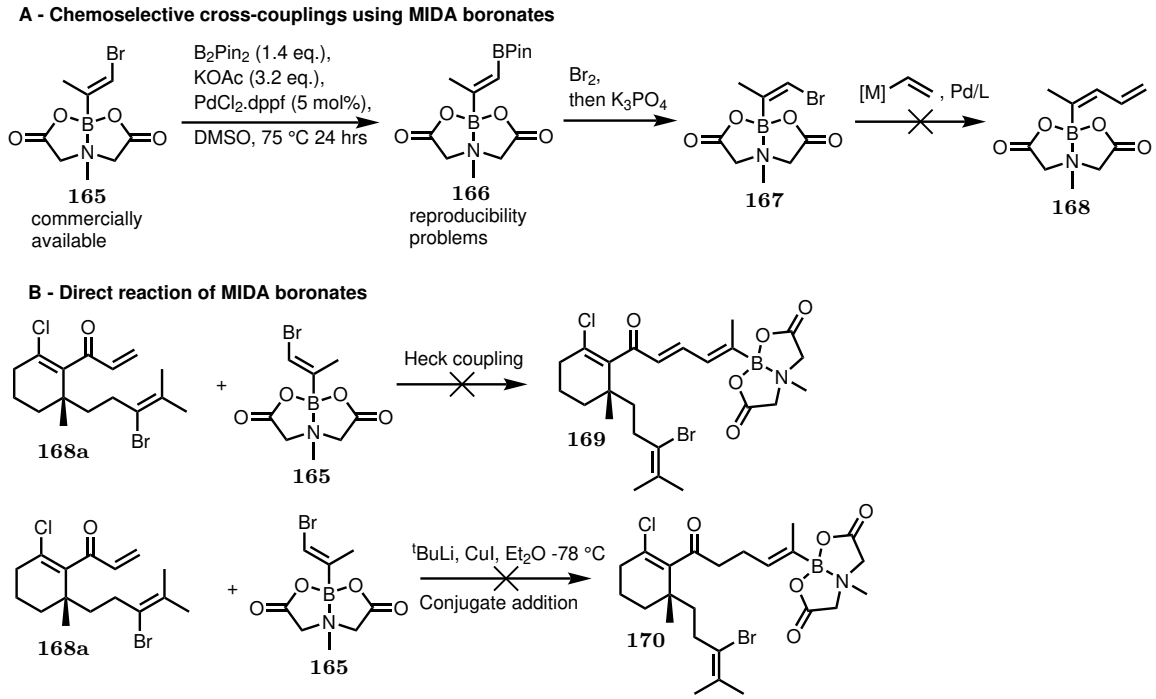
3.4 Disconnection C – Attempts to prepare key intermediate 134



Scheme 3.10: Overview of Disconnection C

Scheme 3.10 shows an overview of Disconnection C. Initially, MIDA boronates[73] developed in the Bourke group were investigated as a synthon for **138** (Scheme 3.11 – A). The property allowing MIDA boronates to function as transient protecting groups made them promising substrates since at least two orthogonal cross coupling reactions were required in our synthesis to prepare **134**. The use of these

reagents unfortunately, did not bear any fruit. Although **165** is commercially available in small quantities, the opposite alkene geometry was required. Thus we carried out the steps shown in Scheme 3.11 (A) in order to obtain the correct geometry. Irreproducibility issues were encountered which were eventually traced to the source of B_2Pin_2; even from a new unopen bottle, the reagent needed to be recrystallised for the reaction to give any product at all. Attempting to perform the cross coupling reaction from **169** to **170** (Negishi and Stille conditions) did not give the desired product.

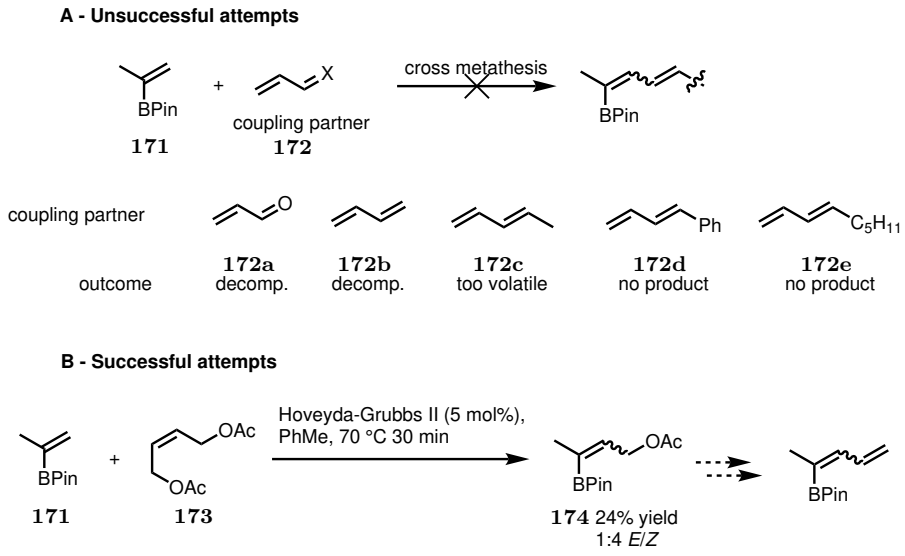


Scheme 3.11: Unsuccessful approaches using MIDA boronates

Undeterred, we next attempted to perform the direct reaction between C-ring fragment **168a** and MIDA boronate **165** (Scheme 3.11 – B). Heck conditions[78] (using Hermann's palladacycle and palladium(II) acetate) gave only recovered starting

material whereas attempted lithiation followed by transmetallation and conjugate addition decomposed both starting materials.

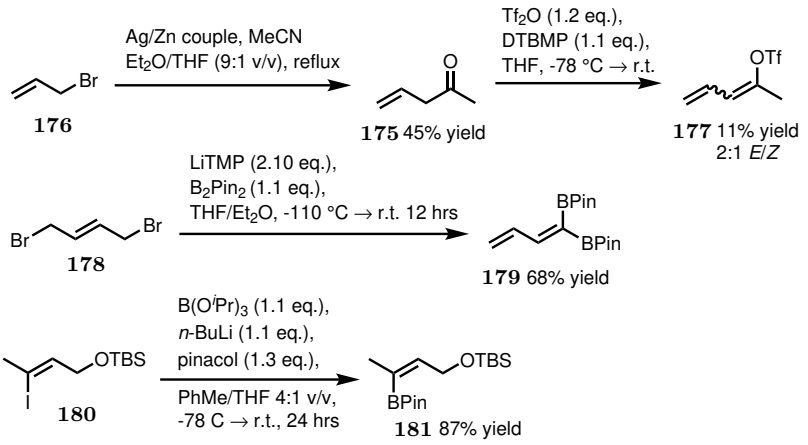
Our next approach towards the coupling fragment was to use an ene-diene cross methathesis (CM) with isopropenylboronic acid pinacol ester (Scheme 3.12).* Acrolein **172a** had been used as a CM coupling partner in the synthesis of the C1-C14 fragment of amphidinol 3[80] but did not give the desired product in our reaction. The use of butadiene **172b** gave the same result. In an attempt to vary the steric and electronic parameters of the CM coupling partner, a variety of dienes were prepared from aldehydes using Wittig reactions.[81] Piperylene **172c** was found to be volatile and despite sealing the reaction vessel, cross metathesis products were not observed. Dienes **172d** and **172e** did not give any of the desired cross metathesis products but dimerisation was observed in certain experiments.

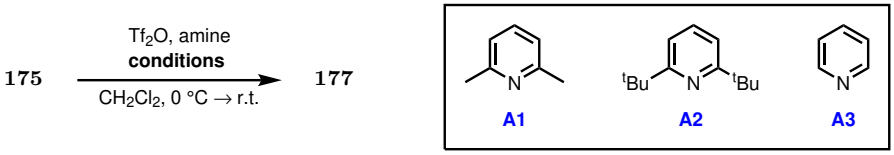


*for precedence of this transformation, see the following references.[79]

Scheme 3.12: Attempted preparation of coupling fragment by cross metathesis with isopropenyl boronic acid pinacol ester.

The only reaction to give any CM product was when electron deficient alkene **173** was used to give **174** in 24% yield. The use of Grubbs second generation catalyst also gave the desired product in comparable yield (23%). Hoveyda-Grubbs second generation catalyst using dichloroethane as solvent gave similar levels of selectivity (1:2.8 *E*/*Z*) but substantially lower yield (15%). There are several reasons why we decided to discontinue this approach. **174** could only be obtained in low yield and with poor diastereoselectivity. Preliminary experiments to remove the acetate and liberate the free alcohol gave at best 10% yield which made this approach unviable as a route for preparing a starting fragment.





entry	amine	time	temperature	yield[a] (%)	*d.r.*
1	A1	5.5 hrs	0 °C, then immediately r.t.	12	1:1.8
2	A2	5.5 hrs	0 °C, then immediately r.t.	18	1.6:1
3	A3	5.5 hrs	0 °C, then immediately r.t.	5	0:1
4	A2	o/n	0 °C, then immediately r.t.	24	1:0.6
5	A2	o/n	0 °C, slowly warm to r.t.	25	1:0.8
6[b]	A2	o/n	0 °C, slowly warm to r.t.	18	1:2.2

Scheme 3.13: Preparation of coupling fragments for approach C and representative optimisation experiments for **177**. Unless specified otherwise, Tf_2O (2.1 eq.) and amine (2.0 eq.) were used. [a] Yields were determined by NMR internal standard measurements. [b]Using Tf_2O (2.1 eq.) and amine (2.0 eq.) were used. Abbreviations: *DTBMP* = 2,6-di-tert-butyl-4-methylpyridine, *LiTMP* = lithium 2,2,6,6-tetramethylpiperidide.

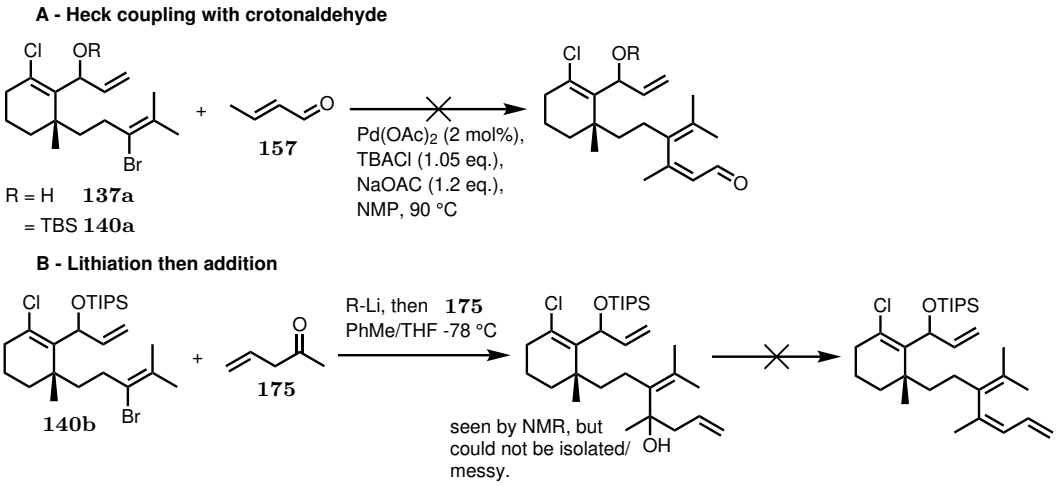
Scheme 3.13 summarises the other approaches that were used towards a relevant coupling fragment. 4-penten-2-one **175** was prepared using a Barbier-type addition of allyl bromide **176** to acetonitrile using conditions by Rousseau and Conia.[82] Triflation was attempted using a variety of conditions and it was surprisingly difficult to obtain good yields and *E/Z* selectivity. The best results were obtained when using triflic anhydride and hindered pyridine A2 base as shown in the table beneath Scheme 3.13. Attempts to use a stronger base along with phenyl bis(trifluoromethanesulfonamide) or Comins' reagent gave only decomposition products.

Preparation of butadiene geminal diboronic ester **179** was conducted according to Hata's procedure starting from dibromide **178**.[83] The original procedure called for the reaction to be performed at −90 °C but when this was repeated in our laboratory, only 15% yield of the desired product was obtained. Eventually, it was determined that conducting the reaction at the lower temperature of −110 °C improved the reaction yield.

Fragment **181** was prepared using previously known *Z*-iodo-3-but-2-enol **146** (Scheme 3.5) by protection with *tert*-butyldimethylsilyl trifluoromethanesulfonate followed by borylation.

Initially, we attempted the direct (Heck) coupling of crotonaldehyde **157** with **137a** and its silyl protected form **140a** but this did not give any of the desired product when various conditions were tried (see experimental section – Scheme 5.7 for optimisation table).[78]

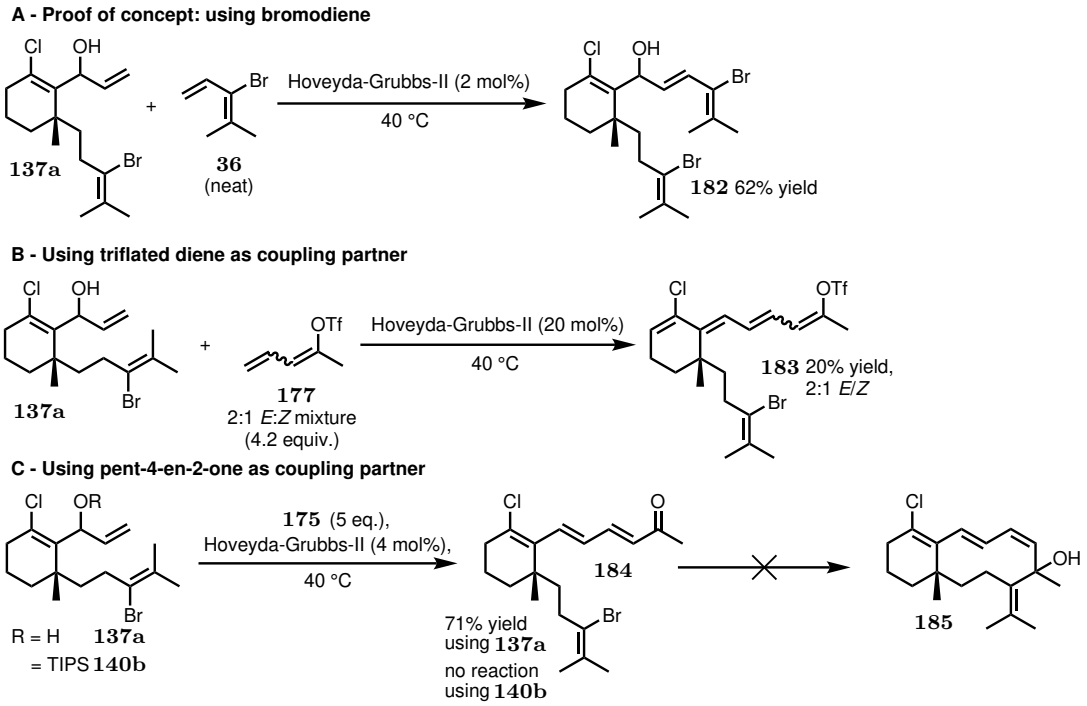
Direct metallation of TIPS protected C-ring fragment **140a** followed by trapping with pent-4-en-2-one **175** was attempted next. At first, *n*-BuLi was used for the lithium halogen exchange but when only starting material was recovered, *tert*-BuLi was used instead (see experimental section – Scheme 5.8). Promising signals in the NMR spectrum corresponding to the tertiary alcohol product were observed, but our attempts to purify and isolate this compound were unsuccessful.



Scheme 3.14: Early attempts to directly prepare carbocyclic skeleton of the Taxol core. Abbreviations: *NMP* = N-Methyl-2-pyrrolidone, *TBACl* = tetra-*N*-butylammonium chloride.

Next, we attempted to build the carbocyclic skeleton of the Taxol core using a cross metathesis of C-ring fragment **137a** and a relevant couping partner. A proof-of-concept experiment was conducted where **137a** was subject to Hoveyda-Grubbs second generation catalyst in neat bromodiene **36** (Scheme 3.15 – A). The cross metathesis product **182** was isolated from this reaction in 62% yield and only the *E* product was observed. Indeed, it was later found that metathesis reactions involving **137a** generally showed complete *E* selectivity. The use of triflated diene **177** as a cross metathesis partner (4.2 equivalents added as a 2:1 *E*:*Z* mixture) was desirable because the product might be able to undergo an Ulmann-type cross coupling reaction to close the ring. When the reaction was performed dimerisation of the triflated diene was observed and conjugated polyene was formed **183** (20% yield, in approximately 1:1 *E*:*Z* mixture of diastereomers) (Scheme 3.15 – B). Due to the relatively low yield of this approach, the limited scale for preparing triflated diene and lack of stereochemical purity of the product, we continued investigating alternative cross metathesis reactions. Cross metathesis of the C-ring fragment was also performed with pent-4-en-2-one **175**, the precursor of **177**, as shown in Scheme 3.15 – C. Interestingly, the use of unprotected alcohol **137a** was crucial for the success of the reaction, giving 71% yield of **184** whereas using TIPS protected alcohol **140b** gave no product even after extended reaction times. This is likely due to steric bulk of the TIPS group which blocks the metathesis catalyst from approaching the terminal alkene. The cross metathesis product obtained in this reaction spontaneously eliminates water to give **184**. Despite investigating a

variety of metal-mediated coupling reactions,[†] no cyclised products such as **185** were observed.



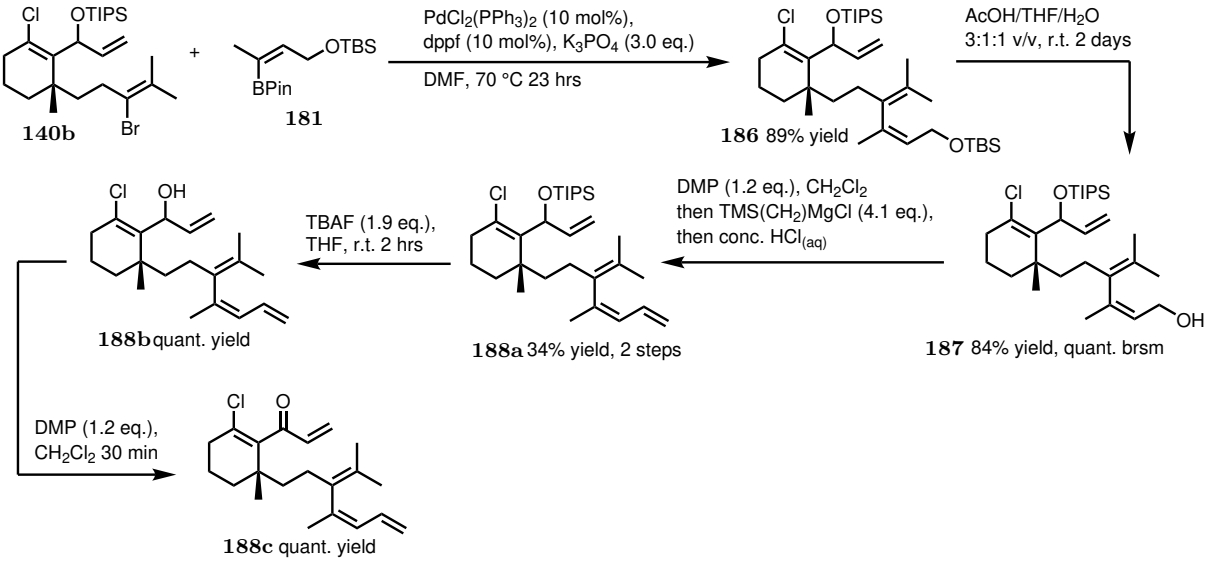
Scheme 3.15: Cross metathesis approach to prepare carbocyclic skeleton of the Taxol core.

Scheme 3.16 summarises our efforts towards using a RCM reaction to prepare key intermediate **134**. TIPS protected C-ring intermediate **140b** and fragment **181** underwent Suzuki-Miyaura coupling to give protected diol **186** in 89% yield. Selective TBS deprotection in the presence of TIPS[86] was accomplished using a mixture of acetic acid, tetrahydrofuran and water to give free alcohol **187** in near quantitative yield. At this point, a range of procedures were investigated to transform the primary alcohol into an alkene. The allylic oxidation was initially carried

[†]for example: Nozaki-Hiyama-Kishi type couplings or Barbier-type couplings using magnesium and Ag/Zn (see experimental section – Scheme 5.9).[43b, 84] In future, n–$Bu_2CuCN \cdot LiCN$ mediated Barbier coupling developed by Rizzo and Trauner could be attempted.[85]

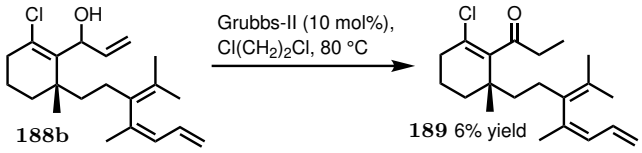
out using manganese(IV) dioxide and although the product was observed by TLC, conversion and isolated yield was poor. Attempts to increase the reaction rate and prevent the product from decomposing by using a large excess of oxidant (60 eq.) and conducting reaction at low temperature did not improve the outcome. The use of Dess-Martin periodinane gave the desired product but it was always contaminated with an unknown byproduct that could not be removed by purification. It was later discovered that the presence of this impurity did not affect the subsequent methylenation step and that yields could be improved if the crude oxidation mixture was carried directly into the next step.

A series of methylenation conditions were investigated. The Wittig reaction gave trace amounts of product whilst the Petasis[87] (dimethyltitanocene) reagent caused decomposition. The Tebbe reagent[88] furnished **188a** in low yields (10%). Eventually, Peterson conditions were used because they gave the best yields (34%) and had the added advantage that the reagent was easier to prepare than the Tebbe reagent. With **188a** in hand, we now had the first of our series of ten-membered ring precursors. Deprotection of the TIPS group using tetrabutylammonium fluoride gave free alcohol **188b** , the second ten-membered ring precursor, and oxidation using Dess-Martin periodinane gave α, β-unsaturated ketone **188c** .



Scheme 3.16: Preparation of ring closing metathesis substrates **188a** , **188b** and **188c** . Abbreviations: *dppf* = 1,1'-Bis(diphenylphosphino)ferrocene, *DMP* = Dess-Martin periodinane, *TBAF* = tetrabutylammonium fluoride.

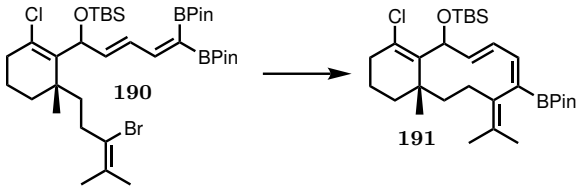
We investigated various metathesis conditions using different catalysts (Grubbs first generation, Grubbs second generation and Hovedya-Grubbs second generation), solvents, temperatures and additives. Unfortunately, no ring closing metathesis products were observed. Using protected alcohol **188a** gave only recovered starting materials[‡] Ketone **188c** gave no ring-closure products while the reaction using free alcohol **188b** gave the intramolecular transfer hydrogenation product in low yield (6%) when forcing conditions were used (Scheme 3.17).[89]



Scheme 3.17: Transfer hydrogenation as an unproductive pathway during attempted RCM.

[‡]the steric clash between the bulky TIPS group and the metathesis catalyst is likely the reason for the disfavoured reaction; see Scheme 3.14.

The final strategy we investigated began with the cross metathesis of geminal diboron species **179** and C-ring fragment **137a** where **179** was specifically chosen in order to avoid mixtures of diastereomers. The reaction proceeded to give alcohol **192** in 58% yield which was subsequently protected with a TBS group **190**. After screening several palladium cross coupling conditions, it was found that cyclised product **191** could be formed in 18% using bistriphenylphosphine palladium(II) chloride (one equivalent), dppf ligand (one equivalent) and tripotassium phosphate base (Table 3.2). The identity of **191** was confirmed by full characterisation. Attempts to perform the coupling reaction on the unprotected alcohol **192** caused decomposition of the starting material. This was undoubtedly an exciting moment, as it was the first instance that the ten-membered ring **191** had been observed. We were not able to improve the yield beyond 18%. Scheme 3.18 is an overview of the successful approach used to prepare ten-membered ring **191**.



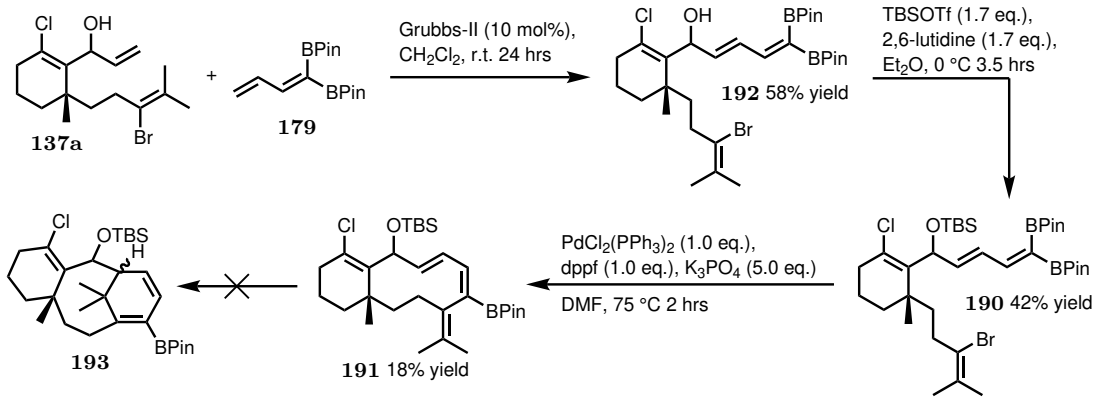
entry	conditions	outcome
1	(R1=H), $PdCl_2(PPh_3)_2$/dppf (1 eq), K_3PO_4 (5 eq), DMF (0.01M), 75 °C. 0.068 mmol scale	Decomposition
2	(R1=TBS), $PdCl_2(PPh_3)_2$/dppf (1 eq), K_3PO_4 (5 eq), DMF (0.01M), 75 °C. 0.068 mmol scale.	18% isolated
3	(R1=TBS), $Pd(PPh_3)_4$ (1 eq), 3M KOH (5 eq), THF (0.01M), RT	Decomposition
4	(R1=TBS), $PdCl_2$dppf (1 eq), 3M KOH (5 eq), THF (0.01M), 40 °C	7% (NMR)
5	(R1=TBS), $Pd_2dba_3/P(^tBu)_3$ (1 eq), 3M KOH (5 eq), THF (0.01M), 60 °C	Decomposition.

entry	conditions	outcome
6	(R1=TBS), $Pd(OAc)_2$ (1 eq), K_2CO_3 (5 eq), MeOH (0.01M), RT	Decomposition
7	(R1=TBS), $Pd(PPh_3)_4$ (0.5 eq), 3M KOH (5 eq), THF (0.005M), RT	No product. 22% recovered s/m.
8	(R1=TBS), $PdCl_2$ppf (0.5 eq), 3M KOH (5 eq), THF (0.01M), 40 °C	5% (NMR)
9	(R1=TBS), $PdCl_2$dppf (0.5 eq), 3M KOH (5 eq), THF (0.005M), 40 °C	7% (NMR)
10	(R1=TBS), $PdCl_2$dppf (0.5 eq), 3M KOH (1.5 eq), THF (0.005M), 40 °C	9% (NMR)
11	(R1=TBS), $PdCl_2$dppf (1 eq), K_3PO_4 (5 eq), DMF (0.01M), 75 °C	<5% (NMR)
12	(R1=TBS), $PdCl_2$dppf (0.5 eq), K_3PO_4 (1.5 eq), DMF (0.005M), 40 °C	Decomposition.
13	(R1=TBS), XPhos Pd G3 (0.1 eq), 0.5M K_3PO_4 (5 eq), THF (0.01M), RT	<5% (NMR)
14	(R1=TBS), SPhos Pd G3 (0.1 eq), 0.5M K_3PO_4 (5 eq), THF (0.01M), RT	<5% (NMR)
15	(R1=TBS), DavePhos Pd G3 (0.1 eq), 0.5M K_3PO_4 (5 eq), THF (0.01M), RT	<5% (NMR)

Table 3.2: Screening of Suzuki-Miyaura cross coupling conditions for the synthesis of ten-membered ring **191**.

Unfortunately, despite several attempts to perform the electrocyclisation on this substrate, only starting material was recovered. In future, structural modifications could be made to vary the steric and electronic properties of **191** to facilitate a transannular electrocyclisation. Possible modifications include: 1) changing the boronic ester into a methyl group via cross coupling 2) deprotecting the alcohol and 3) oxidising the alcohol to the corresponding ketone. Electrocyclisations are powerful transformations and their use in synthesis are testament to this.[90] Realising the transannular electrocyclisation could one day lead to new methods to form complex polycyclic systems. As it stands currently however, the use of

this route is not more than an academic exercise because of the low yields of the Suzuki-Miyaura cyclisation step **190** to **191**. The next chapter will describe an alternative and more practical approach towards the Taxol core using an intramolecular Diels–Alder reaction.



Scheme 3.18: Preparation of key intermediate **191** and unsuccessful electrocyclisation to prepare **193**. Abbreviations: *dppf* = 1,1'-Bis(diphenylphosphino)ferrocene, *TBSOTf* = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Chapter 4

Synthesis of the Taxol core using an intramolecular Diels–Alder reaction and future work

4.1 Background

In Chapter 1, various disconnections of the Taxol skeleton were reviewed and it was shown that an ACA reaction could be used as a key step for the synthesis of the Taxol core. Chapter 2 extended the ACA reaction disclosed in Chapter 1 with a trapping component. With this minor modification, the transformation became more powerful and it was possible to access a range of synthetically useful β-chloroaldehydes. Chapter 3 summarised our second generation approach towards the Taxol core with the key, final step employing a transannular electrocyclic reaction. While several disconnections of the precursor ten-membered ring were considered, only one was successful in the forward direction. Ultimately, this

ten-membered ring did not undergo the desired electrocyclic reaction to give the Taxol core. In this final chapter we present our route towards the Taxol core using an intramolecular Diels–Alder (IMDA) reaction. The first report of a Diels–Alder reaction being used in the context of Taxane synthesis was by Sakan and Craven (Scheme 4.1 – A).[91] Their approach was used to simultaneously form the B/C rings to prepare **206**. The bridged cyclohexane **205** was used as an A-ring source to limit conformational flexibility and improve stereoselectivity.

In 1986, Brown and Jenkins reported the preparation of Taxol core **195** using the IMDA of **194** R = H (Scheme 4.1 – B).[92a] The use of diethylaluminium chloride gave the product **195a** in 72% yield as a single diastereomer. This approach differs from the one reported by Sakan and Craven in that the C-ring is supplied and the A/B rings are formed instead. Later, it was shown that the gem-dimethyl substrate **194** R = Me could undergo the same transformation using $BF_3 \cdot Et_2O$ to give cyclised product **195b** in 56% yield.[92b]

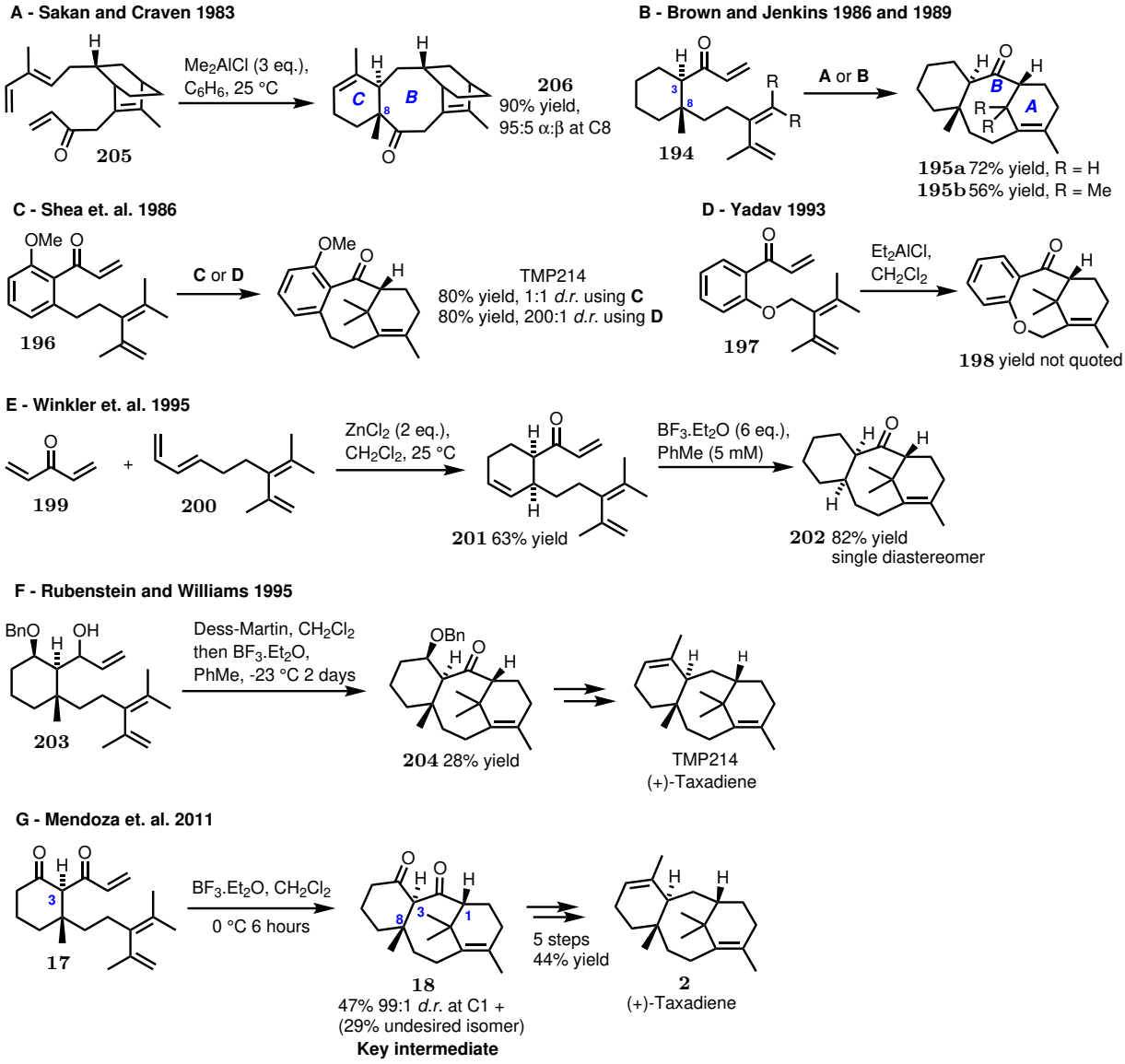
In the same year, Shea[93a] showed that Taxane **2** could be prepared from aromatic substrate **196** using both thermal and catalysed conditions (Scheme 4.1 – C). Both conditions gave equivalent yields however the use of zinc(II) chloride gave a 200:1 *endo* to *exo* ratio while thermal conditions gave a 1:1 mixture of diastereomers. Interestingly, it was found that the *endo* and *exo* forms of **2** are diastereomeric atropisomers. Under thermal conditions, these diastereomers are equilibrated which requires the torsion about five carbon-carbon single bonds. The Lewis acid catalysed approach was eventually used to prepare more oxidised derivatives of the Taxol core including a C1 *epi* taxinine intermediate[93b] and an

advanced taxusin intermediate.[93c]

In 1993, Yadav reported the synthesis of aromatic ether **198** using Lewis acid catalysed conditions.[94] During their investigation, it was found that the reaction was strongly substrate dependent, with variations in ring structure or substitution leading to an unproductive ene pathway. The reaction giving only the IMDA product used precursor **197** is shown in Scheme 4.1 – D.

In 1995, Winkler and co-workers disclosed a concise route towards the synthesis of the Taxol core featuring a double Diels–Alder reaction (Scheme 4.1 – E).[95a] Polyene **200** was reacted with ketodiene **199** in the presence of zinc(II) chloride to give cyclohexene **201** which underwent a type II intramolecular Diels–Alder reaction using boron trifluoride etherate to give **202** in 52% over two steps. It is interesting to note that neither of these Lewis acids was able to catalyse both Diels–Alder reactions alone.

The previous approach had the disadvantage of giving C8 epimers due to the selectivity of the first Diels–Alder reaction. Refluxing in concentrated basic solutions caused epimerisation of the C3 center. In order to prepare taxadiene with the required relative stereochemistry, Rubenstein and Williams prepared **203** in 15 steps from a readily available Robinson annulation product. The allylic alcohol was oxidised using Dess-Martin periodinane followed by Diels–Alder reaction to give **204** in 28% yield. After deoxygenation (reduction followed by Barton-McCombie reaction), deprotection (Birch conditions) and methylation/dehydration (Burgess reagent) taxadiene **2** was prepared.



Scheme 4.1: Use of intramolecular Diels–Alder reactions in the preparation of Taxanes. *A)* R = H, Et_2AlCl (1.0 eq.), CH_2Cl_2, r.t., 15 hrs. ; *B)* R = Me, $BF_3 \cdot Et_2O$ (1.0 eq.), PhMe, −40 °C, 24 hrs. ; *C)* xylene, 150 °C, 70 hrs. ; *D)* $ZnCl_2$ (6-10 eq.), $CHCl_3$, 25 °C, 2 hrs.

More recently, Baran's synthesis of Taxol (Scheme 4.1 – G, see also Chapter 1) uses the type II intramolecular Diels–Alder reaction in a similar fashion to

Rubenstein and William's synthesis. With substantial precedence of the type-II IMDA being used in the synthesis of Taxanes, we were confident that this transformation could be employed as a key step to our synthesis.

4.2 Synthesis of the Taxol core using type-II intramolecular Diels–Alder reaction

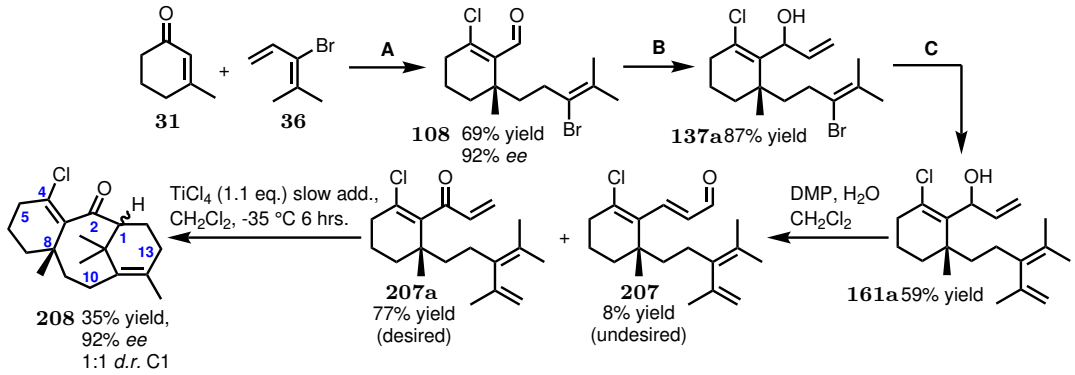
Initially, we set out to prepare a relevant Diels–Alder precursor **207a** . In Chapter 3, the C-ring fragment **137a** of the Taxol core was prepared by vinyl Grignard addition to β-chloroaldehyde ACA/products **108** developed in Chapter 2. This intermediate then underwent cross coupling with isopropenyl boronic acid pinacol ester using Suzuki-Miyaura conditions to give trienol **161a** .

A range of different oxidants* were then screened to promote the allylic oxidation of **161a** to **207a** . Jones' reagent, used by Baran and co-workers on a similar substrate[14b] gave quantitative yields† as did the the use of Dess-Martin periodinane. Dess-Martin periodinane was chosen for the scale up reaction because it was safer to handle and less toxic than the chromium(VI) based Jones' reagent. Initially, when we performed the oxidation on 0.071 mmol scale, a low yield of the desired ketone **207a** was observed (55%). A byproduct was observed in the reaction mixture and its identity was determined to be α,β-unsaturated aldehyde **207** arising from an oxidative allylic transposition. This was an unexpected result because although the allylic transposition is observed when tertiary alcohols are oxidised with a Cr(VI) reagent, it is rarely seen when using hypervalent iodine

*references using Dess-Martin periodinane,[96] Ley conditions,[97] Parikh-Doering conditions,,[98] MnO_2,,[99] nickel peroxide,,[100] Swern, CrO_3/pyr. and PCC oxidations.[101]

†when determined by NMR

reagents.[102] We rationalised that speeding up the oxidation step before rearrangement could take place, would prevent the formation of the undesired aldehyde. The rate of the Dess-Martin oxidation is known to be accelerated by the addition of water[103] and to our delight, the addition of 0.5 equivalents of water gave quantitative yield with a selectivity of greater than 10:1 of the desired ketone to the aldehyde. The reaction could be scaled up and the desired product isolated in 77% yield with a ratio >10:1 ketone:aldehyde. For a summary of screening experiments conducted, please see the experimental section: Scheme 5.10 and Scheme 5.11).



Scheme 4.2: Synthesis of the Taxol core using a type-II intramolecular Diels–Alder reactions. *A)* Cp_2ZrHCl (1.9 eq.), CuCl/L5 (8 mol%), $AgNTf_2$ (14 mol%), $Cl(CH_2)_2Cl/CH_2Cl_2$, rt 17 hrs; then $POCl_3$/DMF (10 eq.), $Cl(CH_2)_2Cl$ 60 °C 1 hr ; *B)* vinylmagnesium bromide (1.2 eq.), Et_2O, 0 °C 1 hr ; *C)* isopropenylboronic acid pinacol ester (1.1 eq.), $PdCl_2(PPh_3)_2$/dppf (0.10 eq), K_3PO_4 (3.0 eq.), DMF 65 °C 17 hrs. Abbreviations: *NTf_2* = bis(trifluoromethanesulfonyl)amide, *dppf* = 1,1'-bis(diphenylphosphino)ferrocene, *DMP* = Dess-Martin periodinane, *DMF* = dimethylformamide.

Next, we screened conditions to promote the key Diels–Alder reaction of **207a** . Our initial round of screening results indicated that Lewis acid catalysed conditions were the most promising (thermal conditions caused decomposition of the substrate) (see experimental section – Scheme 5.12). The use of boron trifluoride etherate gave only 10% **208** with incomplete conversion despite having been used

in similar transformations. Nevertheless, it was a promising result and the first time we had seen the Taxol core being formed and so we refined our screening conditions for various Lewis acids and temperatures (Table 4.1). Although the use of iron(III) chloride gave similar levels of yield initially to titanium tetrachloride, the difficulty of purifying the product led us choosing another Lewis acid. Dimethylaluminium chloride, used in early examples of the IMDA for Taxane synthesis gave very low yields, as did tin tetrachloride. Eventually, the use of titanium tetrachoride and optimising the balance between temperature and addition time gave Taxol core **208** in 35% yield, 92% *ee* (entry 7).

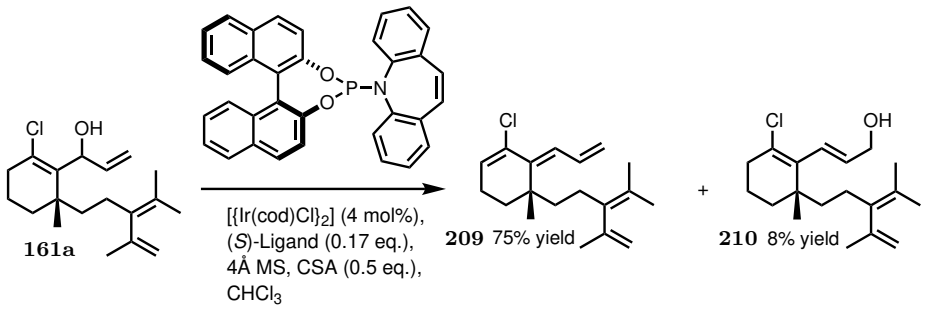
Interestingly, the reaction gave a mixture of diastereomers (1:1 *d.r.* at C1). While intuitively, the origin of diastereoselectivity in the Diels–Alder reaction would be influenced by the configuration at C8, experimentally this is not the case. Experimental and computational studies by Winkler and co-workers[95b] concluded that it was in fact, the configuation at C3 that is responsible for stereoinduction at C1. The absence of this stereocenter in Taxol core **208** means that the diastereomeric ratio at C1 is expected to be 1:1, which is observed experimentally.

entry	Lewis Acid	conditions	yield	comments
1	$FeCl_3$	−10 °C, added over 7 min	6%	Difficult to purify
2	Me_2AlCl	−20 °C, added over 7 min	3%	
3	$TiCl_4$	−20 °C, added over 7 min	6%	Cleanest reaction.
4	$SnCl_4$	−20 °C, added over 7 min	3%	
5	$TiCl_4$	−20 °C, added over 60 min	26%	
6	$TiCl_4$	−78 °C, added over 60 min	-	Decomposition
7	$TiCl_4$	−40 °C, added over 60 min	35%	
8a	$TiCl_4$	−40 °C, added over 60 min	n.d	Incomplete
9b	$TiCl_4$	−40 °C, added over 60 min	9%	Messy

Table 4.1: Screening of Lewis acids for Diels–Alder reaction of **208**. Unless specified otherwise, reactions were conducted using CH_2Cl_2 as solvent and 1.1 eq. Lewis Acid was used. Reactions were monitored by TLC and stopped when no more starting material remained. All yields are quoted as isolated. [a]0.75 equiv LA. [b]2.4 equiv LA.

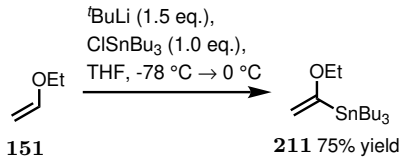
The Diels–Alder reaction of **207a** gave substantially lower yields compared to previous procedures.[‡] This is likely due to our substrate containing the chloroalkene and therefore being more reactive. In an attempt to improve yields in the last step of the synthetic sequence shown in Scheme 4.2 specifically, from **161a** to **208**, an iridium catalysed allyl-alkene coupling reaction was attempted.[104] Had this approach been successful, it would have had the benefit of not requiring an extra oxidation step to prepare the Taxol core. Unfortunately, no cyclised product was observed and it was clear that substrate **161a** , being acid sensitive, decomposed to give **209** and **210** in 75% and 8% yield respectively.

[‡]see for instance Scheme 4.1 and Chapter 1 – Scheme 1.3



Scheme 4.3: Attempted intramolecular allyl-alkene coupling of **161a**

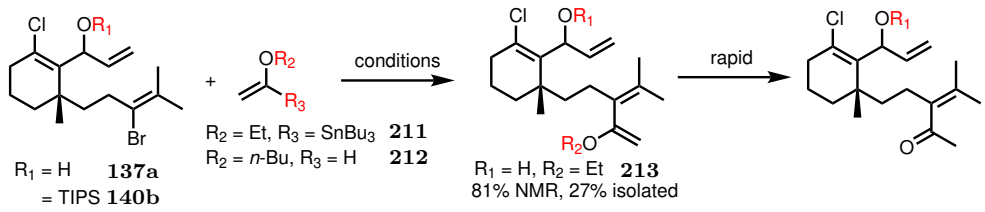
Finally, we sought to increase the reactivity of Diels–Alder substrate **161a** by increasing the electron density of the diene. This structural modification was expected to come about through a cross coupling of a relevant fragment. Thus, tributyl(1-ethoxyvinyl)tin **211**[105] was prepared according by lithiation of ethylvinyl ether **151** using *tert*-butyllithium, followed by trapping with chlorotributylstannane (see Scheme 4.4).



Scheme 4.4: Preparation of organostannane **211**

Next, we began to investigate cross coupling conditions of alcohol **137a** (and its TIPS protected version **137**c) with **211**. Various Stille conditions from previously described syntheses[106] were attempted and the best result was observed using palladium(II) dichloride dppf complex with lithium(I) iodide and copper(I) iodide as additives (Scheme 4.5 – entry 8). These conditions gave the desired product in 81% yield when determined by NMR internal standard measurements however, attempts to isolate it gave only 27% yield. Attempts to vary our purification

methods did not result in substantial yields improvements (see Scheme 4.5), underscoring the acid lability of **213**. We also investigated a report by Gao and co-workers using Heck conditions[107] to couple butyl vinyl ether **212** with alcohol **137**a (or its TIPS protected derivative **137**c) but no reaction occurred.

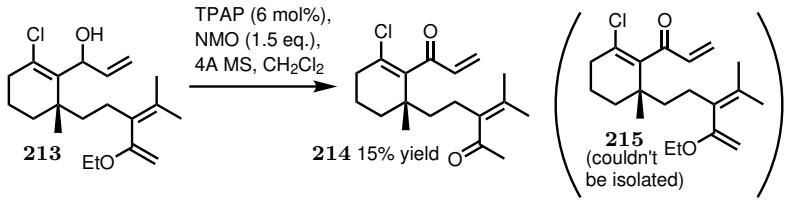


entry	conditions	outcome
1	(R_1=H, R_2=Et, R_3=SnBu3), $PdCl_2(PPh_3)_2$ (0.1 eq), PhMe, 100 °C	decomp.
2	(R_1=H, R_2=Et, R_3=SnBu3), $PdCl_2(PPh_3)_2$ (0.1 eq), PhMe, 80 °C	incomplete conv.
3	(R_1=H, R_2=Et, R_3=SnBu3), $Pd(PPh_3)_4$ (0.01 eq), DMF, 80 °C	5% isolated
4	(R_1=TIPS, R_2=Et, R_3=SnBu3), $PdCl_2(PPh_3)_2$ (0.1 eq), PhMe, 80 °C	N.R. (44% recovered s/m)
5	Entry 3, strictly no air/moisture + fresh solvent	14% (NMR)
6	Entry 3, same as entry 5. Injected 0.5 mL air	8% (NMR)
7	(R_1=TIPS, R_2=Et, R_3=SnBu3), $Pd(PPh_3)_4$ (0.05 eq), DMF, 80 °C	decomp.
8	(R_1=H, R_2=Et, R_3=SnBu3), Pd(dppf)Cl_2 (0.1 eq), CuI (0.1 eq), LiCl (5.3 eq), DMF 40 °C (3 hrs) then 70 °C (2 days)	81% (NMR), 27% isolated
9	(R_1=H, R_2=Et, R_3=SnBu3), Pd_2dba_3/TFP (0.08 eq), LiCl (5 eq), THF reflux	decomp.
10	(R_1=H, R_2=Et, R_3=SnBu3), $Pd(PPh_3)_4$ (0.15 eq), LiCl (3 eq), THF reflux	N.R.
11	Scale up of entry 8. 70 °C (3 days) in sand bath	incomplete conv. 36% (NMR)
12	(R_1=TIPS, R_2=Et, R_3=SnBu3), Pd(dppf)Cl_2 (0.1 eq), CuI (0.1 eq), LiCl (5.3 eq), DMF 70 °C (3 days)	93% recov. s/m
13	Repeat entry 11 (scaled up entry 8). 75 °C oil bath. Purified by 10%wt K2CO3/silica	39% isolated

entry	conditions	outcome
14	Repeat entry 11 (scaled up entry 8). 105 °C oil bath	15% (NMR)
15	Scale up entry 13 (1 mmol). Purified by 10%wt K_2CO_3/silica	39% isolated
16	Repeat entry 15. Purified by neutral Al_2O_3 Brockmann I	decomp.
17	Repeat entry 15. Purified by Florisil 100-200 mesh	19% isolated
18	(R_1=H, R_2=n-Bu, R_3=H), $Pd(OAc)_2/PPh_3$ (0.05 eq)„ NEt3 (10 eq), 75 °C	N.R. 58% recov. s/m
19	(R_1=TIPS, R_2=n-Bu, R_3= H), $Pd(OAc)_2/PPh_3$ (0.05 eq), NEt_3 (10 eq), 75 °C	N.R. 88% recov. s/m
20	(R_1=H, R_2=n-Bu, R_3= H), TBABr (0.2 eq), NaOAc (1.1 eq), Hermann's palladacycle (0.01 eq), 75 °C	decomp.
21	(R_1=TIPS, R_2=n-Bu, R_3= H), TBABr (0.2 eq), NaOAc (1.1 eq), Hermann's palladacycle (0.01 eq), 75 °C	N.R. 52% recov. s/m

Scheme 4.5: Optimisation of cross coupling (Stille/Heck) between **137a** or **140b** and **211**.

Despite the instability of **213**, we still harboured hope that an oxidation of the alcohol would give a suitable Diels–Alder precursor **215** shown in Scheme 4.6. We investigated several oxidation conditions but all resulted in hydrolysis to diketone **214**; Scheme 4.6 shows the reaction conducted under Ley conditions.



Scheme 4.6: Oxidation of **213** leads to hydrolysis instead. Abbreviations: *TPAP* = tetrapropylammonium perruthenate, *NMO* = N-methylmorpholine N-oxide.

4.3 Conclusion and future directions

In summary, this thesis disclosed a synthesis of the Taxol core using asymmetric conjugate additions. The procedure for ACAs of alkenes developed in our group, was a suitable reaction for the synthesis of Taxanes, in particular for assembling the C-ring and setting the stereochemistry at C8. In Chapter 1, we proved that this was a feasible approach by synthesising a C-ring intermediate in 95% yield and 88% *ee*. Our first generation synthesis employed a ring closing aldol cyclisation followed by transannular electrocyclisation as the key steps. Ultimately, the aldol step was unsuccessful and we were not able to test the transannular electrocyclic reaction.

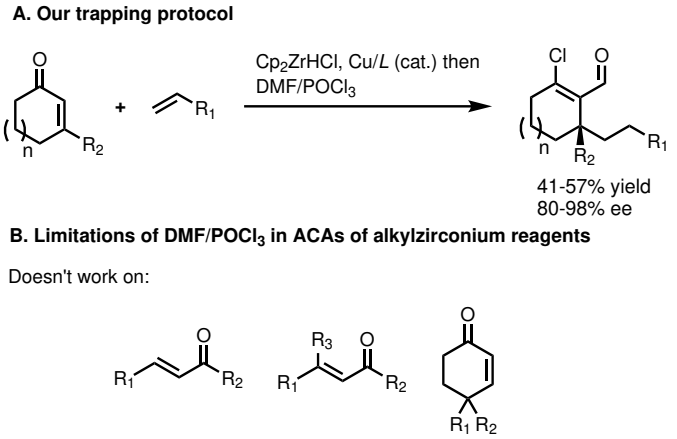
In Chapter 2, we visited the long standing challenge of trapping zirconium enolates generated from ACAs. After considering several electrophiles, formaldehyde was found to give the hydroxymethylated product as a diastereomeric mixture at the alkylated carbon. The limited scope and tedious procedure encouraged us to continue our search for a different electrophile. Eventually, it was found that treating the intermediate enolates with a mixture of $POCl_3$ and DMF would convert them into β-chloroaldehydes. Their synthetic utility was demonstrated by derivatising the products (Grignard addition and Suzuki Miyaura couplings). Despite attempts to generalise the procedure to other ACAs, we found that it was only suitable for preparing quaternary center containing cyclic ketones. Nevertheless, the ACA/trapping sequence gave β-chloroaldehydes in modest yields (between 41-60%) and high enantioselectivities (up to 98% *ee*).

In Chapter 3, our focus returned to the synthesis of the Taxol core, particularly with using an unprecedented transannular electrocyclic reaction in the final key step. Starting from a β-chloroaldehyde synthesised using the ACA/trapping procedure, a variety of C-ring intermediates were prepared. After several failed attempts, the ten-membered ring was eventually synthesised and shown to not undergo the desired electrocyclic reaction.

In this chapter, a type-II Diels–Alder reaction was investigated as the key step for preparing the A/B rings of the Taxol core. The relevant substrate underwent the desired Diels–Alder reaction to give a Taxane bearing the β-chloroketone functionality in 35% yield, 92% *ee* and 1:1 *d.r.* at C1.

4.3.1 Future work for trapping of zirconium enolates

Although the trapping procedure, developed in Chapter 2 – 2.3, generates synthetically useful β-chloroaldehydes, the method has its drawbacks. In particular, the procedure is highly substrate dependent and works only for ACAs to prepare quaternary stereocenters of cyclic ketones Scheme 4.7.



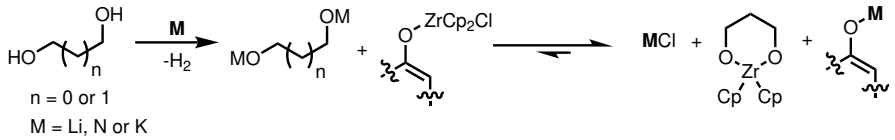
Scheme 4.7: a) ACA / trapping procedure developed in 2.3 and b) current limitations of the procedure.

The most likely cause for limited substrate scope is the undefined nature and low reactivity of the zirconium enolate encountered in these reactions. One approach that could improve the trapping reaction would be to activate the zirconium enolate.[§] Unfortunately, as described in Chapter 2 – 2.2.2, this approach did not work with our ACA reactions. As mentioned in that section, the high substrate dependence of our trapping protocol, led us to believe that the nature of the zirconium enolates were somehow different in each reaction and were forming aggregates. Thus to improve the trapping reaction, we would have to find alternative conditions to activate the zirconium enolate. It should be mentioned at this point that the use of any strong activating reagents could negate the benefits associated with using alkylzirconium reagents in ACAs, especially in regards to functional group compatibility.

Our idea for future work would be the use of bidentate group I alkoxides[108] in activating the zirconium enolate. This could be extended to other metals by first

[§]as discusssed by Westmeier and co-workers[58a]

preparing the Rieke metal in question. The reasoning behind this approach is using a linear diol with suitable chain length, a 5- or 6-membered metallocycle would be formed (Scheme 4.8). Along with the chelate effect, this would preferentially displace the alkoxide corresponding to the enolate and generate monomeric dialkoxyzirconocene. We began our initial studies by attempting to prepare suitable alkoxides derived from ethylene glycol.



Scheme 4.8: Use of bidentate alkoxides to improve zirconium enolate trapping reactions.

Our initial attempts to prepare and use these bidentate alkoxides was fraught with problems. In the case where a solid alkali metal was used, passivation of the metal surface prevented complete reaction of the diol. A possible solution to this problem, would be to heat the metal to its melting point in a high boiling point solvent (such as xylene) and use a Hershberg wire stirrer.[109]¶ When *n*-BuLi was used, the heterogeneous nature of the alkoxide solutions made the addition of the solution to the ACA reactions very difficult. Furthermore, the untrapped product was also observed in appreciable quantities suggesting that the diol had not completely reacted with the alkali metal.

Going forward, the first problem to solve in continuing with this approach would be to find a way to make the bidentate alkoxides reliably and without contamination

¶his approach has been used to prepare 'sodium sand' which in turn was used to synthesise sodium cyclopentadienide.

by free alcohol. This would be closely tied to developing a simple procedure for adding these heterogeneous solutions to the crude ACA mixture: the solid forms of the alkoxide could also be used. Once these issues are addressed, further considerations would include preventing the formation of long chain zirconocene oligomers and studying alkoxide-substitution kinetics. Oligomerisation can be controlled by adjusting the stoichiometry of the reaction components. Improvements to the kinetics of the reaction could be accomplished by performing a mechanistic study on substitution at the zirconium center.

4.3.2 Future work for the synthesis of Taxol core

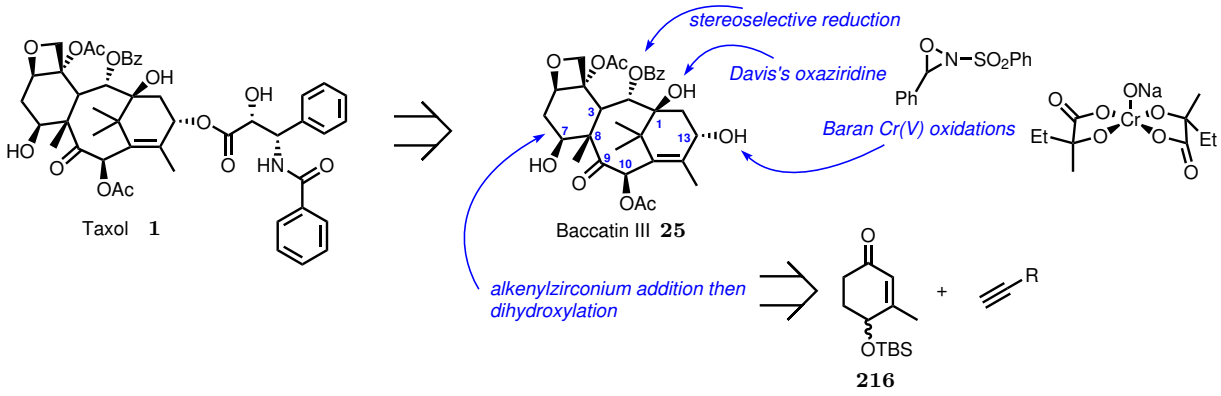
Our synthesis of the Taxol core demonstrated the advantages of using alkylzirconium reagents in forming key carbon-carbon bonds. Despite extensive optimisation of the Diels–Alder step, yields and diastereoselectivity remained poor (35% yield and 1:1 *d.r.*). Diastereoselectivity could be addressed by setting the stereochemistry at C3 as discussed in the previous section.[‖] Alternatively, base-mediated epimerisation could be used to adjust C1 in **208** however, model studies need to be conducted to understand the relative stability of epimers and hence the expected product distribution.

The organocatalytic Diels–Alder reaction first disclosed by Ahrendt and co-workers could be used instead of Lewis acid conditions.[110] Using an organocatalyst would decrease the cationic side reactions involving olefins and promoted by Lewis acids whilst still activating the LUMO of substrate **161a** towards the Diels–Alder reac-

[‖] recall that stereochemistry at C3 directly influences the stereochemistry of C1 when using type-II intramolecular Diels–Alder reactions.

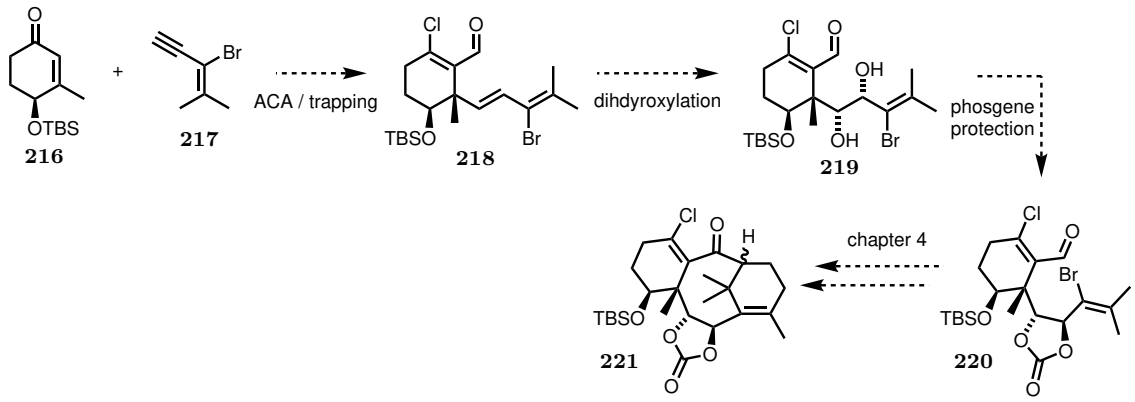
tion. Since there are enantioselective variants of the organocatalytic Diels–Alder reaction, this could be another way to adjust the diastereoselectivity at C1 via catalyst control.

In the final section of this chapter, we describe an extension of the Taxol synthesis by presenting disconnections towards Baccatin III **25** – a known precursor to Taxol **1** itself.



Scheme 4.9: Synthetic plan for a future synthesis of Taxol.

Scheme 4.9 is an overview of the transformations that could be used to oxidise the Taxol core. Oxidations at C7, C9 and C10 are by far the most challenging; for this reason, it would be more practical to install them early on through an ACA/trapping sequence. Conversion of the chloroalkene moiety to the oxetane is also non-trivial. While Baran and co-workers have recently reported the oxidations at C7, C9 and C10,[14a] we propose an alternative approach to installing these oxygens, depicted in Scheme 4.10.



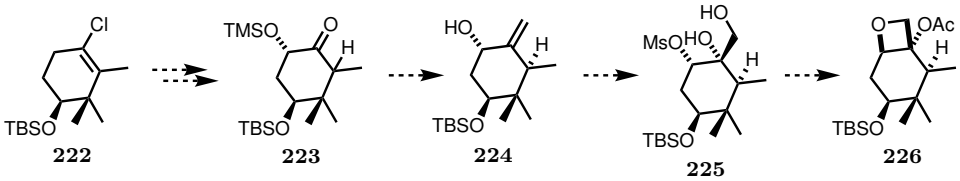
Scheme 4.10: Synthesis of oxidised Taxanes, installation of C7, C9 and C10 oxygens.

Scheme 4.10 shows an ACA / trapping reaction in the first step. A major limitation of the current ACA of alkenes employed by our group is that alkenylzirconium reagents have not been used as fragments and both of the coupling partner's shown in Scheme 4.10 have far greater complexity than anything that has been added before. Therefore, this would be an excellent opportunity to expand the scope of ACAs to use alkynes. Additionally, ACA of alkynes / trapping sequence, when developed, would be able furnish structurally complex intermediate **218** in only few steps, greatly increasing the viability of using ACA / trapping sequences in future syntheses of complex molecules. Hydrometallation of **217** using Schwartz reagent will mean that the alkene in **218** will have *E*-configuration and thus dihydroxylation will give the correct stereochemistry in **219**. While in principle, using ACA / trapping with highly functionalised substrates to access oxidised Taxanes will be more efficient, it sacrifices the diversity-orientated characteristic that the two-phase approach allows for.

Oxidations at C1 and C13 as performed by Kanda and co-workers, have already

been discussed in the Chapter 1 literature review (see Chapter 1 – Scheme 1.3). C13 oxidation can be performed using a chromium(V) based oxidant to give a ketone at position C5. Oxidation at C1 is more involved. Enolisation at this position is difficult because of the anti-Bredt character of the formed enolate. Thus the approach described by Kanda called for selective double-reduction using DIBAL-H and $LiAlD_4$, upon which the substrate was then ideally suited, for a DMDO-mediated oxidation at C1.[14a] It should be noted that the authors' discuss the DMDO oxidation's strict dependence on the taxane's substitution. Therefore, given our substrate's significant structural difference to that reported in the manuscript, experimentation will be needed to determine optimal conditions for the C1 oxidation to occur.

The most substantial challenge in preparing **1** from Taxol core **221** is the conversion of the chloroalkene **222**, to the oxetane **226**. One way this could be accomplished is shown in Scheme 4.11. Conversion of **222** to ketone **223** could be achieved by radical dehalogenation followed by oxymercuration / oxidation. The ketone can then be transformed via the sequence **224** to **226** using the known procedure described Holton and co-workers in their synthesis of Taxol.[7a,7b]



Scheme 4.11: Proposed oxetane synthesis.

Chapter 5

Experimental section

5.1 General experimental details

All reactions involving air/moisture sensitive reagents were performed under a positive pressure of N_2 or Ar in dried glassware (flame dried once and allowed to cool under high vacuum using standard Schlenk technique). Cooling to −78 °C was achieved using dry ice and acetone, cooling to 0 °C was achieved using ice and all other temperatures were attained using a Julabo FT902 immersion cooler. Heating was achieved using a hotplate coupled to Drysyn® heating blocks or sand baths.

Analytical thin-layer chromatography was performed on aluminium backed plates, pre-coated with silica gel (Silica Gel 60, F_{254}; Merck) unless otherwise specified. Visualisation was aided using UV light (λ = 254 nm) and then stained using aqueous $KMnO_4$, acidic *p*-anisaldehyde in ethanol or vanillin where specified. Column chromatography was conducted either via 'flash', wherein N_2 pressure was applied above a pre-packed column of silica with solvent or via the 'dry column

method' in which case a vacuum source was used to collect individual fractions of known volume and solvent composition.[1] Merck 60 Å silica gel was used unless otherwise stated.

5.1.1 Instrumentation

NMR spectra were acquired on Bruker DPX200 (200 MHz), DPX300 (300 MHz) or AVIIIHD 400 nanobays (400 MHz) instruments in deuterated solvents. Chemical shifts (δ) were referenced according to the residual solvent peak.[2] Coupling constants (J) were quoted to the nearest 0.1 Hz. Peaks were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), broad (br) and multiplet. Assignments of peaks were performed with the assistance of other NMR experiments including COSY, HSQC and HMBC.

Low resolution mass spectra were recorded on a Waters LCT with a time-of-flight detector for electrospray (ESI+) ionisation mode. High resolution mass spectra were recorded on a Bruker μTOF with a time-of-flight detector for electrospray (ESI+) ionization mode or Waters GCT classic GC-MS with a time-of-flight detector for electron impact (EI+) ionization mode at 70 eV.

Infrared spectroscopy measurements were carried out using a Bruker Tensor 27 FTIR with internal calibration over the range of 4000 – 600 cm^{-1}. Optical rotation were recorded using a Schmidt Haensh Unipol L2000 Polarimeter.

Analytical gas chromatography was performed on an Agilent 7820A system equipped with an autosampler and flame ionisation detector for quantitation. The column employed was an Agilent 1909, J-413 HP-5 (30 m length, 0.320 mm diam-

eter and 0.25 μm film).

Analytical and semi-preparatory HPLC were carried out using an Aglilent 1260 Infinity series normal phase unit equipped with an autosampler. Columns were protected by column guards and all solvents used were of HPLC quality.

5.1.2 Reagents

Dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), toluene (PhMe), diethyl ether (Et_2O), pentane, tetrahydrofuran (THF), dimethylformamide (DMF) and benzene (PhH) were obtained from a Braun solvent purifier system (SP-800) having been passed through a column of activated Al_2O_3. Methyl *tert*-butyl ether (MTBE), 1,2-dichloroethane ($ClCH_2CH_2Cl$), 1,2-dichlorobenzene (*o*-$PhCl_2$) and 2-methyl tetrahydrofuran were obtained commercially in an anhydrous state and stored over activated 3 Å molecular sieves. Other solvents were dried according to standard procedure.[3] Solvents were degassed either by bubbling a stream of Ar through the solvent for 10 minutes or using the freeze-pump-thaw method. Petrol refers to $40-60$ °C b.p. petroleum spirits.

Commercially available chemicals were purchased at the highest commercial quality and used directly without intermediate purification. Molecular sieves were activated by heating with a flame under high vacuum, allowed to cool and then backfilled with N2. The procedure was repeated three times. Organometallic reagents were titrated using salicylaldehyde phenylhydrazone before use.[4] MnO_2 was activated prior to use in a glassware drying oven overnight. Powdered molecular sieve powder was obtained through grinding whole molecular sieves in a mortar and pestle before fame drying under high vacuum three times (or until no more

water vapour was evolved). The following chemicals were synthesised according to standard literature procedures: Bis(cyclopentadienyl)zirconium(IV) chloride hydride Cp_2ZrHCl (Schwartz reagent),[111] Silver bis(trifluoromethanesulfonyl)imide $AgNTf_2$,[112] 3-ethyl-2-cyclohexen-1-one,[113] (but-3-en-1-yloxy)(tert-butyl)dimethylsilane,[114] tert-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane III,[31a] ((but-3-en-1-yloxy)methyl)benzene,[114] and 3-methyl-2-cyclohepten-1-one.[113]

5.2 Representative screening reactions

5.2.1 Mono cross coupling reactions to prepare bromodiene 36

Cross coupling reactions were monitored using gas chromatography coupled to a flame ionisation detector or with NMR. Pure dibromo olefin **38** and bromodiene **36** were available from separate sources and were used as standards to obtain retention times. The double cross coupled product's **41** identity was inferred using gas chromatography (equipped with an identical column) connected to a high resolution mass spectrometer. (Figure 5.2 shows a sample chromatogram with peaks assigned). Aliquots were taken and the relative proportions of products were taken at specified intervals (Figure 5.2 shows a typical conversion vs time graph).

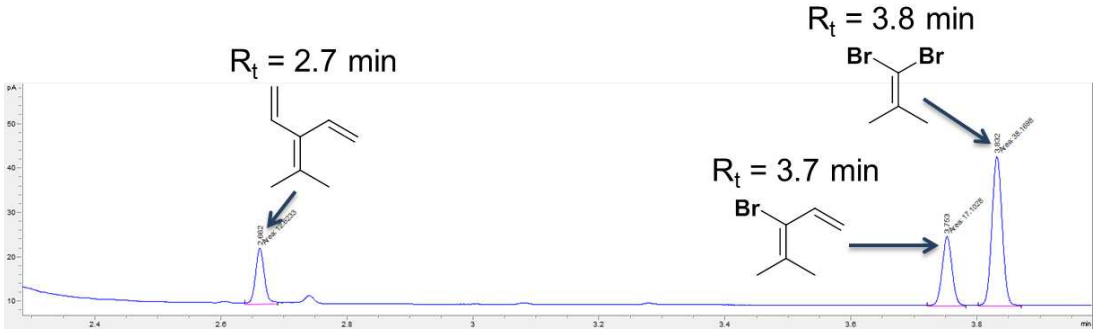


Figure 5.1: Typical GC-FID trace showing dibromo olefin **38**, the desired mono cross coupled product **36** and undesired double cross coupled product **41**.

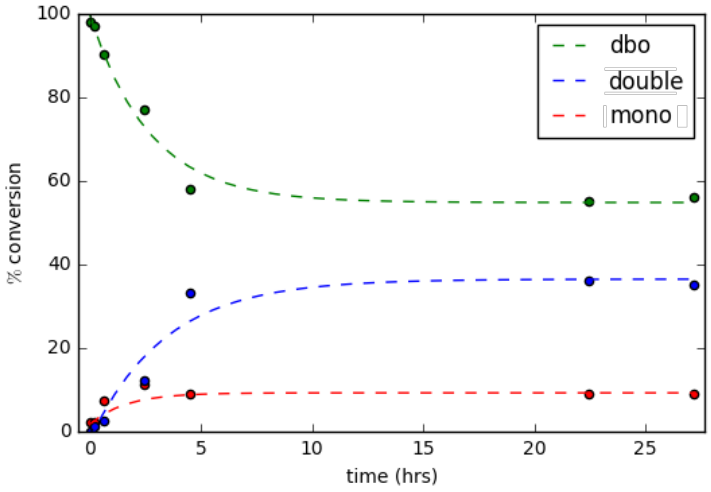
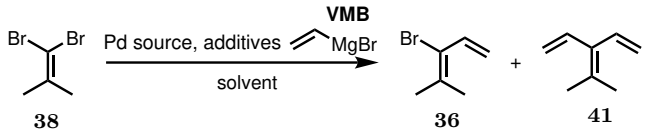


Figure 5.2: Typical conversion/consumption graph of dbo **38**, mono cross coupled product **36** and double cross coupled product plotted over time. Beyond 10 hours, the reaction stalls.

5.2.1.1 General procedure for Negishi/Kumada type coupling reactions

1,1-dibromo-2-methylprop-1-ene **38** (1.0 mol equiv) was dissolved in the desired solvent in a flame dried 5 mL round bottom + stirrer bar. Catalyst was added along with any solid additives and the flask was purged with Argon. For Negishi type couplings, anhydrous zinc(II) halide in THF was added at this point followed

by vinylmagnesium bromide (VMB) and for Kumada type couplings, only vinylmagnesium bromide was added. The reaction was stirred under an Argon balloon at the specified temperature for the allotted time.



38 **36** **41**

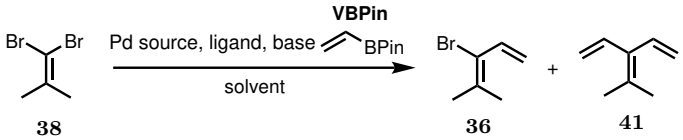
entry	conditions	conversion	mono:bis
1	2 mol % $PdCl_2 \cdot dppf$, 1.1 eq. VMB, THF RT, 4 hrs	10%	1:1
2	5 mol % $NiCl_2 \cdot dppb$, 1.1 eq. VMB, THF RT, overnight	10%	0:1
3	2 mol % $PdCl_2 \cdot dppf$, 1.2 eq. $ZnBr_2$, 1.1 eq. VMB, 4 hrs	10%	1.7:1
4	2 mol % $Pd(PPh_3)_4$, 1.2 eq. $ZnBr_2$, 1.1 eq. VMB, THF RT, 4 hrs	0%	-
5	2 mol % $PdCl_2 \cdot dppf$, 2.0 eq. $ZnBr_2$, 1.1 eq. VMB, THF RT, 4 hrs	15%	1:1
6	2 mol % $PdCl_2 \cdot dppf$, 1.5 eq. $ZnBr_2$, 1.5 eq. VMB, THF RT, 4 hrs	4%	3:1
7	2 mol % $PdCl_2 \cdot dppf$, 1.2 eq. $ZnBr_2$, 1.1 eq. VMB, 1.0 eq. MgBr2, THF RT, 4 hrs	0%	-
8	2 mol % $PdCl_2 \cdot dppf$, 1.2 eq. $ZnBr_2$, 1.1 eq. VMB, 1.0 eq. Mg(OH)2, THF RT, 4 hrs	4%	2:1
9	2 mol % $PdCl_2 \cdot dppb$, 1.2 eq. $ZnBr_2$, 1.1 eq. VMB, THF RT, 2 hrs	7%	2:1
10	2 mol % $PdCl_2 \cdot dppf$, 1.2 eq. $ZnBr_2$, 1.1 eq. VMB, 0.5 eq. MgBr2, THF RT, 4.5 hrs	13%	2:1
11	5 mol % $PdCl_2 \cdot dppf$, 1.1 eq. $ZnBr_2$, 1.1 eq. VMB, THF RT, overnight	44%	1:0.3
12	5 mol % $NiCl_2 \cdot dppb$, 1.1 eq. $ZnCl_2$, 1.1 eq. VMB, THF RT, overnight	10%	0:1
13	2 mol % $Pd(PPh_3)_4$, 1.2 eq. $ZnCl_2$, 1.1 eq. VMB, THF RT, overnight	0%	-

entry	conditions	conversion	mono:bis
14	2 mol % $Pd(PPh_3)_4$, 1.2 eq. $ZnCl_2$, 1.1 eq. VMB, THF 50 °C, overnight	9%	2:1
15	5 mol % $PdCl_2 \cdot$ dppf, 1.1 eq. $ZnBr_2$, 1.1 eq. VMB, THF 50 °C, overnight	49%	0.4:1
16	5 mol % $PdCl_2 \cdot$ dpephos, 1.2 eq. $ZnCl_2$, 1.1 eq. VMB, THF 50 °C, 5 hrs	27%	2.4:1

Scheme 5.1: Optimisation of Negishi/Kumada type couplings.

5.2.1.2 General procedure for Suzuki type coupling reactions

Palladium salt and ligand were added to a 5 mL round bottom flask + stirrer bar. The desired solvent was added followed by 1,1-dibromo-2-methylprop-1-ene **38** (1.0 mol equiv). Vinylboronic acid pinacol ester was added immediately followed by 1M aqueous potassium phosphate tribasic. The reaction was stirred under an Argon balloon at the specified temperature for the allotted time.



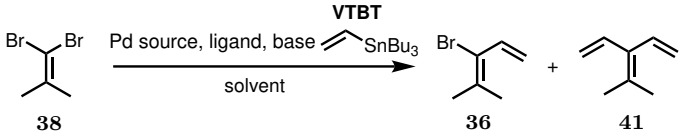
38 **36** **41**

entry	conditions	conversion	mono:bis
1	25 mol % $Pd(PPh_3)_4$, 3.0 eq. $Ba(OH)_2 \cdot 8\,H_2O$, 1.1 VBPin, THF/MeOH/H_2O RT, overnight	0%	-
2	10 mol % $Pd(OAc)_2$, 20 mol % XPhos, 1.1 eq. VBPin, 3.0 eq. K_3PO_4, MeCN RT, overnight	67%	0:1
3	10 mol % $Pd(OAc)_2$, 20 mol % XPhos, 1.1 eq. VBPin, 3.0 eq. K_3PO_4, toluene RT, overnight	13%	10:3
4	10 mol % $Pd(OAc)_2$, 20 mol % SPhos, 1.1 eq. VBPin, 3.0 eq. K_3PO_4, MeCN RT, overnight	20%	1:0.7
5	10 mol % $Pd(OAc)_2$, 20 mol % SPhos, 1.1 eq. VBPin, 3.0 eq. K_3PO_4, toluene RT, overnight	11%	1.2:1

Scheme 5.2: Optimisation of Suzuki type couplings. Conversions were determined using gas chromatography equipped with a flame ionisation detector.

5.2.1.3 General procedure for Stille type coupling reactions

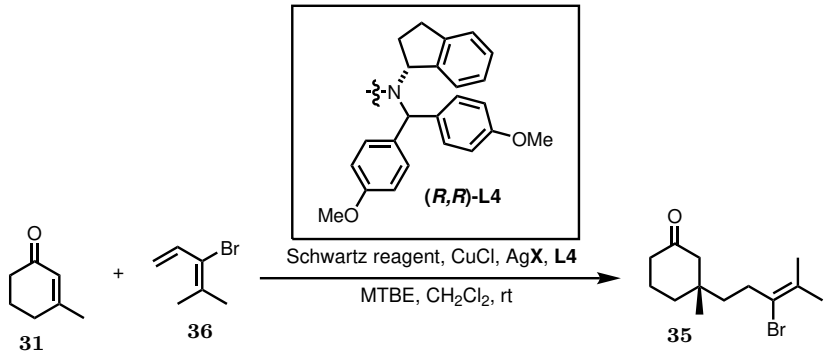
1,1-dibromo-2-methylprop-1-ene **38** (1.0 mol equiv) was dissolved in the desired solvent in a flame dried 5 mL round bottom flask + stirrer bar. Vinyltributylstannane VTBT was added followed by palladium source and ligand before the flask was purged with Argon. The reaction was stirred under an Argon balloon at the specified temperature for the allotted time.



entry	conditions	conversion	mono:bis
1	3 mol % Pd_2dba_3, 15 mol % TFP, 1.1 eq. VTBT, toluene 100 °C, overnight	65%	1.3:1
2	3 mol % Pd_2dba_3, 15 mol % TFP, 1.1 eq. VTBT, THF RT, overnight	42%	01:00.3
3	6 mol % Pd_2dba_3, 20 mol % $AsPh_3$, 1.1 eq. VTBT, THF 50 °C, overnight	48%	1.7:1
4	3 mol % Pd_2dba_3, 15 mol % TFP, 1.1 eq. VTBT, THF 50 °C, overnight	39%	1.3:1

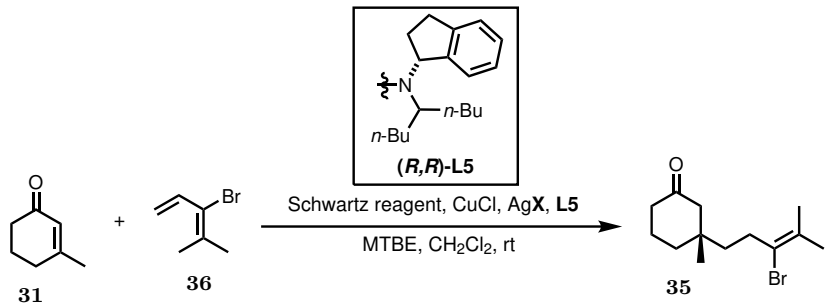
Scheme 5.3: Optimisation of Stille type couplings. Abbreviations: *TFP* = tri(2-furyl)phosphine.

5.2.2 1.3.3 – Asymmetric Conjugate Addition of 36 to 3-methyl-2-cyclohexenone



entry	Ag**X**	yield (%)	*ee* (%)
1	$AgBF_4$	68	4
2	$AgPF_6$	70	0
3	$AgSbF_6$	67	6
4	$AgClO_4$	52	10
5	AgOTf	42	4

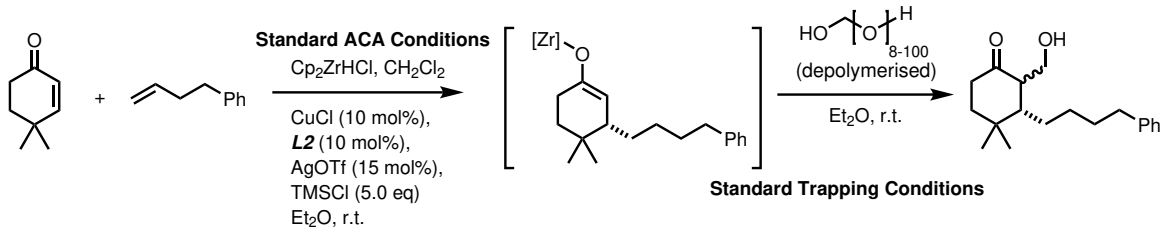
Scheme 5.4: Silver salt screening using L4.



entry	Ag**X**	yield (%)	*ee* (%)
1	AgBF4	53	6
2	AgPF6	36	4
3	AgSbF6	33	24
4	AgClO4	58	12

Scheme 5.5: Silver salt screening using L5.

5.2.3 Attempted trapping of zirconium enolates generated from the ACA of 88 to 98 using formaldehyde

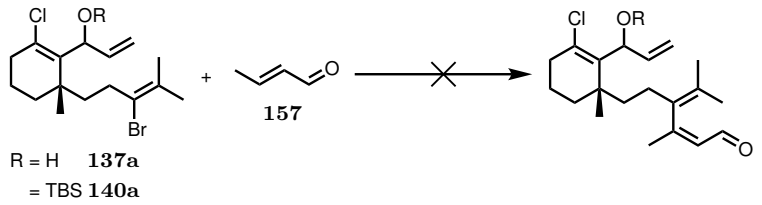


entry	deviation from standard ACA	deviation from standard trapping	outcome
1	none	none	decomp.
2	none	PhMe r.t. to 100 °C	decomp.
3	no TMSCl	PhMe r.t. to 100 °C	decomp.
4	$AgNTf_2$ instead of AgOTf	none	N.R.
5	$AgNTf_2$ instead of AgOTf, no TMSCl	none	N.R.
6	none	$+Cu(OTf)_2$ (20 mol%)	N.R.
7	no TMSCl	$+Cu(OTf)_2$ (20 mol%)	N.R.
8	L1 (10 mol%), $AgNTf_2$ (15 mol%), MTBE, no TMSCl	none	40% trapped product
9	L2 (10 mol%), $AgNTf_2$ (15 mol%), MTBE, no TMSCl	none	Trapped product formed (TLC; yield n.d.)
10	L5 (10 mol%), $AgNTf_2$ (15 mol%), MTBE, no TMSCl	none	Trapped product formed (TLC; yield n.d.)
11	no TMSCl	none	N.R.
12	none	1,3,5-trioxane (4 eq.), $TiCl_4$ (2.0 eq.)	decomp.
13	none	$+TiCl_4$ (2 eq.), 20 min	N.R.
14	none	$+TiCl_4$ (2 eq.), 1 hr	N.R.
15	none	$+TiCl_4$ (2 eq.), 2 hrs	N.R.
16	none	$+TiCl_4$ (2 eq.) & 3A MS (100wt%), 20 min	N.R.

entry	deviation from standard ACA	deviation from standard trapping	outcome
17	none	+$TiCl_4$ (2 eq.) & 3A MS (100wt%), 1 hr	N.R.
18	none	+$TiCl_4$ (2 eq.) & 3A MS (100wt%), 2 hrs	N.R.
19	none	1,3,5-trioxane (4 eq.), $TiCl_4$ (2.0 eq.), 3A MS (100wt%)	N.R.
20	ACA reaction time 2.5 hrs (monitor TLC)	none	N.R.
21	ACA reaction time 2.5 hrs (monitor TLC), no TMSCl	none	N.R.

Scheme 5.6: Attempted formaldehyde trapping of tetiary stereocenter-containing ketones. All ACA reactions were run for 17 hours. Irreproducible outcomes were a frequently encountered problem using this procedure.

5.2.4 Representative screening/optimisation reactions from Chapter 3

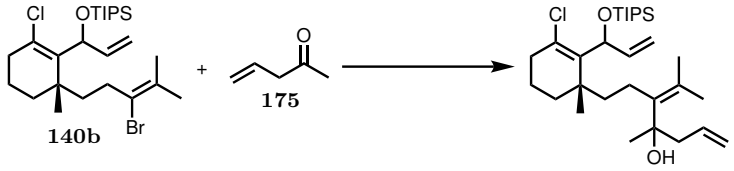


R = H **137a**
= TBS **140a**

entry	conditions	outcome
1	$Pd(OAc)_2$ (2 mol%), crotonaldehyde (2.0 eq.), NaOAc (1.2 eq.), TBACl.xH2O (1.05 eq.), NMP, 90 °C	N.R.
2	$Pd(OAc)_2$ (2 mol%), crotonaldehyde (2.0 eq.), NaOAc (1.2 eq.), TBACl(anhydr.) (1.05 eq.), NMP, 90 °C	N.R.
3	$Pd(OAc)_2$ (4 mol%), crotonaldehyde (2.0 eq.), NaOAc (1.2 eq.), TBACl(anhydr.) (1.05 eq.), NMP, 90 °C	N.R.
4	$Pd(OAc)_2$ (50 mol%), crotonaldehyde (2.0 eq.), NaOAc (1.2 eq.), TBACl(anhydr.) (1.05 eq.), NMP, 90 °C	N.R.

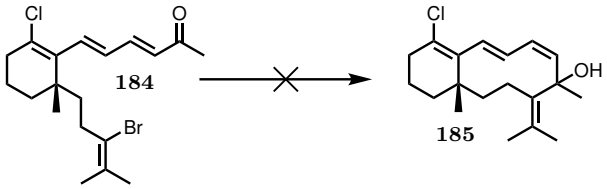
entry	conditions	outcome
5	$Pd(OAc)_2$ (4 mol%), PPh_3 (8 mol%), crotonaldehyde (2.0 eq.), NaOAc (1.2 eq.), TBACl(anhydr.) (1.05 eq.), NMP, 90 °C	N.R.
6	Herman-Beller catalyst (1 mol%), crotonaldehyde (1.4 eq.), NaOAc (1.1 eq.), TBABr (anhydr.) (0.2 eq.), DMAc, 100 °C	N.R.
7	Herman-Beller catalyst (1 mol%), crotonaldehyde (1.4 eq.), NaOAc (1.1 eq.), TBABr (anhydr.) (0.2 eq.), DMAc, 140 °C	N.R.

Scheme 5.7: Heck couplings with crotonaldehyde **157**. Abbreviations: *NMP* = N-methyl-2-pyrrolidone, *DMAc* = dimethylacetamide.



entry	R-Li	equiv (R-Li, E)	lithiation time	yield
1	*n*-BuLi	1.1:1.3	30 min	recovered s/m
2	*t*-BuLi	2:1.3	45 min	>33 %
3	*t*-BuLi	2:2.1	2 min	>26 %
4	*t*-BuLi	2:2.1	15 min	>29 %
5	*t*-BuLi	2:2.1	30 min	>18 %

Scheme 5.8: Attempted direct lithiation of **140b** . All reactions conducted at −78 °C.

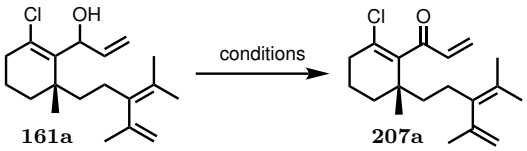


entry	conditions	outcome
1	$CrCl_2$ (4 eq), $NiCl_2$ (cat.), DMF (0.05M)	Low mass recovery. Complex mixture
2	Repeat above	Low mass recovery. Complex mixture
3	*tert*-BuLi (2.05 eq), THF (0.05M)	Decomposition
4	Mg(0) turnings (4.1 eq), THF (0.05M)	63% recovered s/m
5	Ag/Zn couple (1.4 eq), THF (0.05M)	Decomposition
6	$CrCl_2$ (4 eq), $NiCl_2$ (cat.), DMF (0.10M)	Low mass recovery. Complex mixture

entry	conditions	outcome
7	$CrCl_2$ (10 eq), $NiCl_2$ (cat.), 1% v/v Me_2S/ DMSO (0.01M)	Decomposition
8	$CrCl_2$ (10 eq), $NiCl_2$ (cat.), 1% v/v DMSO/Me_2S (0.01M)	No reaction

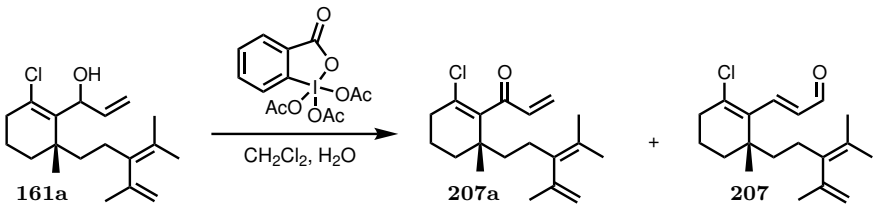
Scheme 5.9: Attempted reductive cyclisation of **184**. All reactions conducted at r.t.

5.2.5 Representative screening/optimisation reactions from Chapter 4



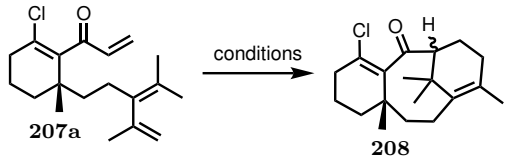
entry	oxidant	TLC outcome	yield(b.r.s.m.) %
1	NiO_2	Incomplete	2(14)
2	TPAP, NMO	Incomplete	38(45)
3	CrO_3, H_2SO_4	Complete	quant.
4	MnO_2	Incomplete	24(35)
5	$(COCl)_2$, DMSO, NEt_3	Decomposition	-
6	CrO_3, pyr.	Complete	31
7	DMP	Complete	quant.

Scheme 5.10: Coarse screening for oxidation of allylic alcohol **161a** to ketone **207a** . All reactions performed on 0.071 mmol scale. Yields were determined by NMR internal standard measurements. The use of DMP as oxidant was preferred given the known hazards of hexavalent chromium compounds in Jones' reagent.



entry	equiv H_2O	yield	**207a** :**207**
1	0	91% (isolated)	1.5:1
2	0.5	quant. (NMR)	>10:1
3	1	80% (isolated)	>10:1
4	0.5	85% (isolated)	>10:1

Scheme 5.11: Oxidation of allylic alcohol **161**a to ketone **161**c using Dess-Martin periodinane. All reactions performed on 0.071 mmol scale except entry 4 (0.66 mmol scale).



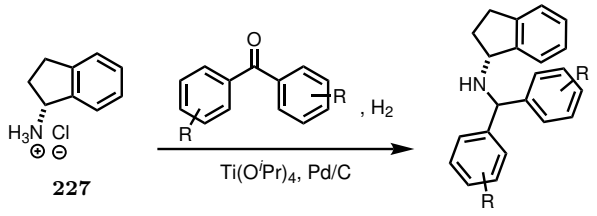
207a **208**

entry	Lewis Acid	conditions	TLC outcome	yield %
1	Me_2AlCl	1.5 h	Product only	6
2	$BF_3 \cdot Et_2O$	17 h, slowly warmed to 0 °C	Incomplete	10
3	$TiCl_4$	1.5 h	Product only	8
4	$ZnCl_2$	5 h, gradually increased temperature to 65 °C	Decomposition	0
5	$ZnCl_2 \cdot pyr$	5 h, gradually increased temperature to 100 °C (sealed tube)	No reaction	0
6	$FeCl_3$	1.5 h	Product only	19
7	$SnCl_4$	1.5 h	Product only	9
8	-	230 °C sealed tube, PhOPh	Decomposition	0

Scheme 5.12: Coarse screening for Diels–Alder reaction of **208**. Unless specified otherwise, reactions were conducted at −10 °C using 1.1 eq. Lewis acid on 0.03 mmol scale. Yields were determined by NMR internal standard measurements. Reactions were monitored by TLC and stopped when no more starting material remained.

5.3 Experimental procedures and characterisation data

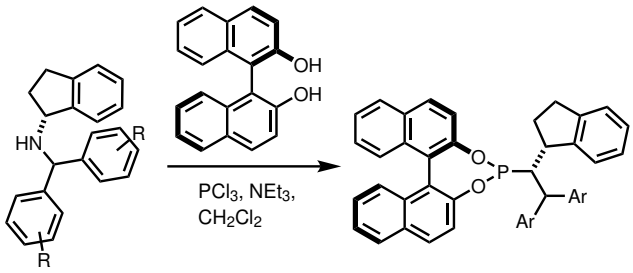
5.3.0.1 General procedure A – synthesis of chiral amines



(*R*)-2,3-dihydro-1H-inden-1-amine.HCl salt **227** (850 mg, 5.00 mmol, 1.00 mol equiv) was dissolved in 50 mL 1M NaOH and this solution was extracted (3xCH_2Cl_2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. This crude oil was added to a flame dried 50 mL round bottom flask with stirrer bar, followed by titanium(IV) isopropoxide (7.6 mL, 25 mmol, 5.0 mol equiv) and benzophenone (5.00 mmol, 1.00 mol equiv). This mixture was allowed to stir, protected from the atmosphere, for one hour. 10% palladium on carbon (530 mg, 0.50 mmol, 0.10 mol equiv) was added and the reaction mixture was saturated with hydrogen gas (1 atmosphere, purged three times with a balloon). The reaction was stirred under these conditions for the allotted time and monitored in the following manner: an aliquot of the reaction mixture was taken, diluted with Et_2O and 3M NaOH was added (equal volume to Et_2O). After shaking vigorously, the organic (top) phase was carefully decanted off, dried over $MgSO_4$ and the volatile constituents removed. The residual oil was then subject to ^{1}H MR spectroscopy which gave the corresponding product and starting material ratios.

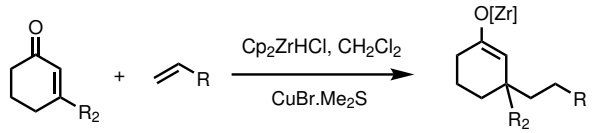
The reaction was quenched by adding 15 mL EtOAc followed by 7.5 mL 3M NaOH (caution: exothermic). After stirring for one hour, $MgSO_4$ was added as a flocculent before the solid particles were removed by filtration. The filter cake was washed with copious amounts of Et_2O. After removal of solvent under vacuum, the crude product was purified by flash chromatography to give the desired product as an oil.

5.3.0.2 General procedure B – synthesis of phosphoramidites



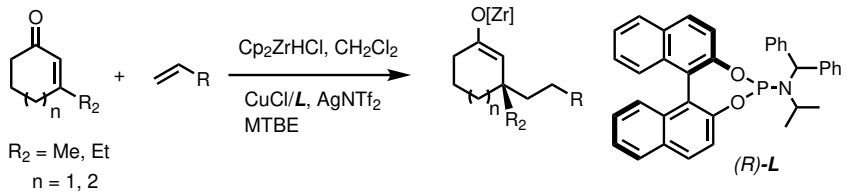
PCl_3 (1.0 mol equiv) was added to dry CH_2Cl_2 (7.4 mL per mmol of amine) under Ar and then cooled to 0 °C. Dry triethylamine (5.0 mol equiv) was then added dropwise resulting in vigorous fuming. After addition, the reaction was allowed to stir for 10 minutes, upon which the chiral amine (1.0 mol equiv) was added dropwise (slightly less vigorous fuming). This mixture was stirred for 5 hours before (*R*)-1,2-binapthol (1.0 mol equiv) was added in one portion. The cooling bath was immediately removed and the reaction was stirred overnight. After TLC (the product fluoresces under a UV lamp) showed complete consumption of starting amine, the reaction was filtered to remove solid particles and then loaded directly onto neutral alumina Al_2O_3 (although celite can also be used). The crude product was then purified by flash chromatography.

5.3.0.3 General procedure C – synthesis of racemic 1,4-addition products



Racemic samples for ee determination were prepared according to a literature procedure.[31a] Cp_2ZrHCl (113 mg, 0.438 mmol, 1.8 mol equiv) was added to a 7 mL vial equipped with a stirrer bar before a rubber septum and inert gas balloon were fitted. Dry CH_2Cl_2 (1.2 mL) and then alkene (0.50 mmol, 2.0 mol equiv) were added and the reaction stirred for 40 min (a clear yellow solution was obtained). $CuBr \cdot Me_2S$ (52 mg, 0.25 mmol, 1.0 mol equiv) was then added, minimising exposure of the reaction to atmosphere and the black slurry stirred for 10 additional minutes. The enone (0.25 mmol) was added via syringe and stirring was allowed to continue overnight. At this point, TLC (30% Et_2O/n-pentane) showed complete consumption of the enone. The zirconium enolates were trapped at this point (using general procedures F-H) or subject to work up conditions.

5.3.0.4 General procedure D – copper catalysed 1,4-addition reactions to 3-substituted cyclohexenones



1,4-addition reactions were performed according to a literature procedure.[31a]

CuCl (5.2 mg, 0.053 mmol, 0.10 mol equiv) and then ligand **L1** (29 mg, 0.054 mmol, 0.10 mol equiv) were added to a 7 mL vial equipped with a rubber septum and stirrer bar (flask A). Three cycles of vacuum and back filling with N_2 were then performed, after which methyl-tert-butylether (2.5 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment.

Concurrently, Cp_2ZrHCl (232 mg, 0.899 mmol, 1.70 mol equiv) was added to a separate 7 mL vial equipped with a stirrer bar and rubber septum (flask B). Three cycles of vacuum and back filling with N_2 were then performed, after which dry CH_2Cl_2 (0.4 mL) and then alkene (1.1 mmol, 2.1 mol equiv) were added. After stirring for one hour, a clear orange solution was obtained. In some instances (dependent on the quality of alkene and Schwartz reagent used) hydrozirconation was not complete within the allotted time. In these situations, it was helpful to apply heat to the flask which usually resulted in the formation of a clear orange solution.

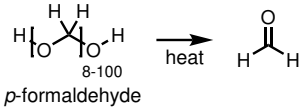
After stirring for the allotted time, Silver bis(trifluoromethanesulfonyl)imide (31 mg, 0.080 mmol, 0.15 mol equiv) was tipped into flask A in one portion (minimising exposure to the atmosphere). After stirring for 10 minutes, the solution from flask A was then filtered (using a syringe filter) into flask B over a period of one minute. The resulting solution became dark within 10 seconds. After stirring for 5 minutes, 3-methyl-2-cyclohexenone was added at a rate of 1 drop every 2 seconds (60 μL, $\rho = 0.97$ g.mL^{-1}, 0.53 mmol, 1.0 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. The zirconium enolates were trapped at this

point (using general procedures F-H) or subject to work up conditions.

For the purpose of ee determination, an aliquot of the reaction mixture was loaded directly onto a small silica column (using a pipette) and eluted with 10% Et_2O/n-pentane.

Absolute stereochemical assignments were made based on analogy of existing compounds.[31a]

5.3.0.5 General procedure E – cracking of p-formaldehyde to prepare monomeric formaldehyde solution

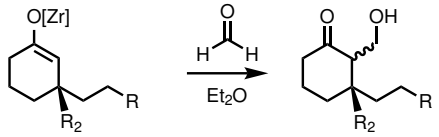


The formaldehyde solution used in trapping procedure D should be prepared immediately before use and have low water content for optimal yields. This procedure for cracking the polymer is for a 0.53 mmol scale 1,4-addition reaction.

To a round bottom flask equipped with a stirrer bar was added p-formaldehyde (318 mg, monomer molecular weight 30, 10.6 mmol monomer equivalent, 20 mol equiv). A Suba–Seal® and canula were then fitted and the canula was directed into another flask containing dry Et_2O (15 mL). A nitrogen balloon was then fitted to the *p*-formaldehyde containing flask and a vent needle was inserted into the ether-containing flask. Care must be taken throughout these steps to prevent suck back of the solvent into the p-formaldehyde flask. Three cycles of vacuum and back filling with N_2 were then performed, after which the p-formaldehyde-containing

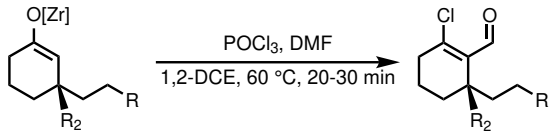
flask was heated gently with a heat gun under a nitrogen stream (from the balloon) and the magnetic stirrer bar was occasionally agitated using a magnetic rod. When the white solid in the *p*-formaldehyde flask had vanished, the system was allowed to cool for 5 minutes and the formaldehyde/Et_2O solution used immediately in the subsequent trapping reaction.

5.3.0.6 General procedure F – trapping with formaldehyde



Upon completion of the 1,4-addition reaction as judged by TLC, the contents of the asymmetric reaction were transferred via syringe into freshly prepared formaldehyde/Et_2O solution. After stirring for 5 minutes TLC showed the formation of two new spots corresponding to the diastereomers of the hydroxymethylated product and untrapped 1,4-addition product. The reaction was quenched with 4 mL 1M $NH_4Cl^{(aq)}$ to form an emulsion after approximately 3 minutes which was diluted with H_2O until two phases formed. The phases were partitioned and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude products were dry loaded onto celite and purified by flash chromatography.

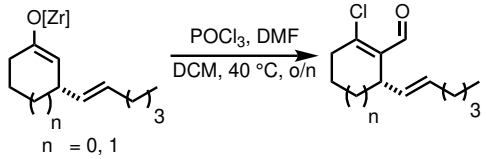
5.3.0.7 General procedure G – trapping with Vilsmeier-Haack reagent



The following procedure is based on a 0.53 mmol scale 1,4-addition reaction.

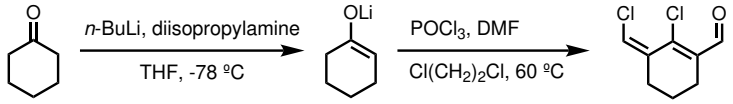
$POCl_3$ (1.1 mL, $\rho = 1.64$ g.mL^{-1}, 12 mmol, 22 mol equiv) was added in one portion to a stirred, room temperature solution of *N,N*-dimethylformamide (0.82 mL, $\rho = 0.944$ g.mL^{-1}, 11 mmol, 20 mol equiv) in 1,2-dichloroethane (7 mL) in a sealed round bottom flask under a N_2 atmosphere. On large scale, the addition should be performed at 0 °C and stirring continued for 5 minutes before warming to room temperature (to prevent thermal runaway). After stirring for 15 minutes, the flask was heated at 60 °C for a further 5 minutes before the contents of the 1,4-addition reaction (judged complete by TLC) were added by syringe. After 20 minutes stirring at 60 °C (TLC control) the reaction flask was cooled to 0 °C and the reaction mixture diluted with one-third volume CH_2Cl_2. Saturated $NaHCO_{3(aq)}$ (7 mL) was then added dropwise via syringe (on large scale use a dropping funnel) and the mixture was stirred vigorously for 15 minutes. An orange sludge is obtained, which was transferred to a separatory funnel. Upon standing, two phases are formed and the upper, solid-containing, aqueous phase is extracted (3x) with CH_2Cl_2. The combined organic extracts were washed with water twice, dried over Na_2SO_4, and concentrated *in vacuo*. The orange residue was purified by flash chromatography to furnish the desired products.

5.3.0.8 General procedure H – mild conditions trapping with Vilsmeier-Haack reagent



The following reaction was performed according to a literature procedure.[64] To a 7 mL vial equipped with stirrer bar was added N,N-dimethylformamide (97 μL, 1.25 mmol, 2.5 mol equiv) and CH_2Cl_2 (1 mL). $POCl_3$ (98 μL, 1.05 mmol, 2.1 mol equiv) was added at room temperature and the solution was allowed to stir for 20 minutes. After this time, 1,4-addition reaction (0.50 mmol scale with respect to the enone) was added resulting in slight warming of the solution. After 5 minutes, the vial was sealed with a cap and heated at 40 °C overnight. Quenching and work up procedure is identical to general procedure G.

5.3.0.9 Procedures for mechanistic studies – Preparation of cyclohexanone lithium enolate and usage in trapping reaction



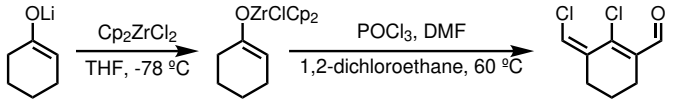
117 **116**

Cyclohexanone lithium enolate was prepared as follows. *n*-Butyllithium (0.45 mL of a 2.5 M solution in hexanes, 1.1 mmol, 1.1 mol equiv) was added to diisopropylamine (0.17 mL, ρ = 0.717 g.mL^{-1}, 1.2 mmol, 1.2 mol equiv) in dry THF (3 mL) at −78 °C and then immediately warmed to room temperature. After stirring at room temperature for 10 minutes, the solution was cooled to −78 °C again, and cyclohexanone (0.10 mL, ρ = 0.948 g.mL^{-1}, 1.0 mmol, 1.0 mol equiv) in dry THF (2 mL) was added by syringe. After stirring for 30 min, the enolate was subject to transmetallation with Cp_2ZrCl_2 or trapping procedure (general procedure G).

In the case where the trapping procedure was used, ^{1}H NMR analysis (1,2-dichloroethane internal standard) showed that the doubly chlorinated product was obtained (10%

yield, 0.10 mmol).

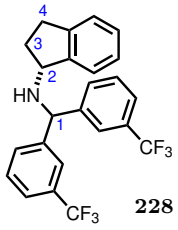
5.3.0.10 Procedures for mechanistic studies – Preparation of cyclohexanone zirconium enolate and usage in trapping reaction



116

Cp_2ZrCl_2 (321 mg, 1.1 mmol, 1.1 mol equiv) was dissolved in dry THF (6.8 mL). This solution was added to the cyclohexanone lithium enolate at −78 °C (as prepared above) and then immediately warmed to room temperature. After stirring for 30 min, the enolate was subject to trapping procedure (general procedure G). ^{1}H NMR analysis (1,2-dichloroethane internal standard) showed that the doubly chlorinated product was obtained (48% yield, 0.48 mmol).

5.3.0.11 (*R*)-N-(bis(3-(trifluoromethyl)phenyl)methyl)-2,3-dihydro-1H-inden-1-amine 228



228

Prepared according to the general procedure A. This compound was synthesised using bis(3-(trifluoromethyl)phenyl)methanone (1.59 g, 5.00 mmol, 1.00 mol equiv). Flash chromatography (30% EtOAc/petrol) gave the product as a colourless oil 1.21 g (56% yield).

R_f = 0.50 (30% EtOAc/petrol, stains pink with vanillin);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, overlapped Ar-H), 7.65 (2H, overlapped Ar-H), 7.56 (d, J = 7.7 Hz, 1H, Ar-H), 7.47 – 7.34 (m, 4H, Ar-H), 7.16 (d, J = 6.7 Hz, 4H, Ar-H), 5.15 (s, 1H, 1), 4.11 – 3.92 (m, 1H, 2), 2.91 (m, 1H, 3), 2.69 (dt, J = 15.9, 8.0 Hz, 1H, 4), 2.39 (dddd, J = 12.2, 8.0, 7.1, 4.1 Hz, 1H, 3'), 1.75 (dq, J = 12.2, 8.0 Hz, 1H, 4') ppm;

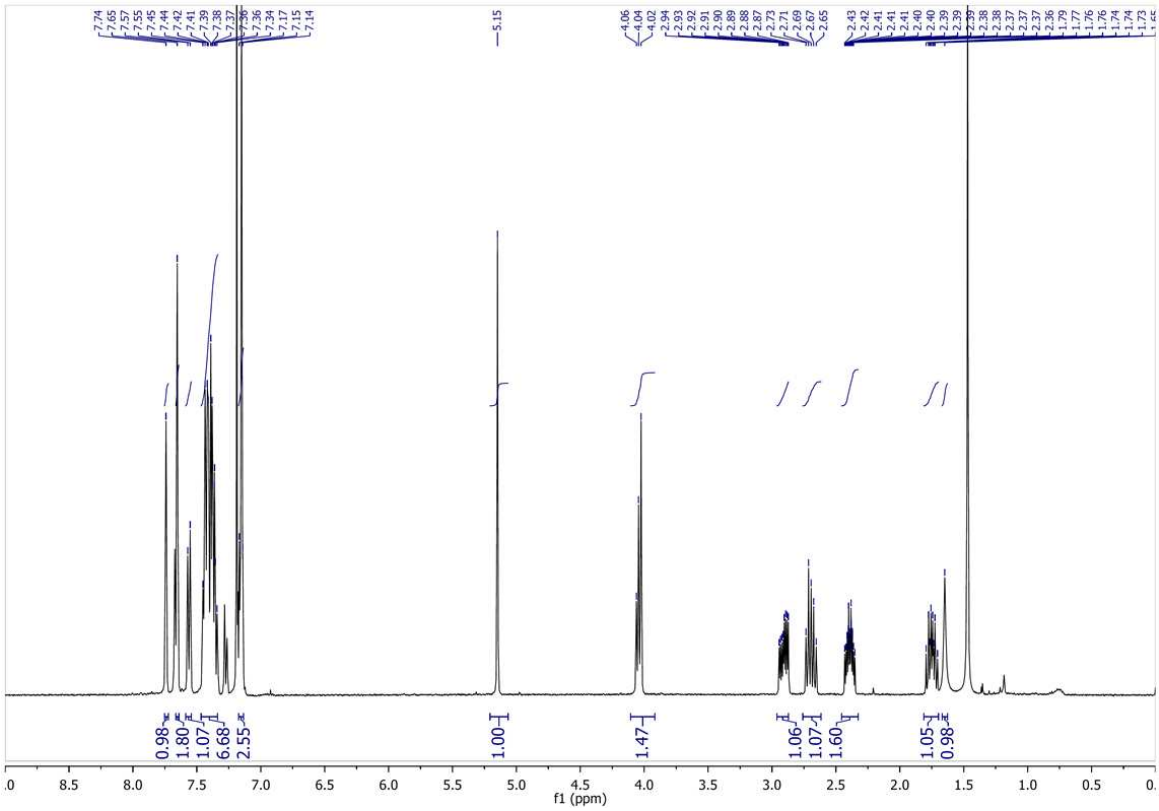
^{13}C NMR (101 MHz, $CDCl_3$): δ 145.3 144.3, 143.4, 130.9, 130.8, 129.4, 127.8, 126.6, 124.9, 124.6, 124.5, 124.50 124.3, 64.7, 61.1, 34.5, 30.3 ppm;

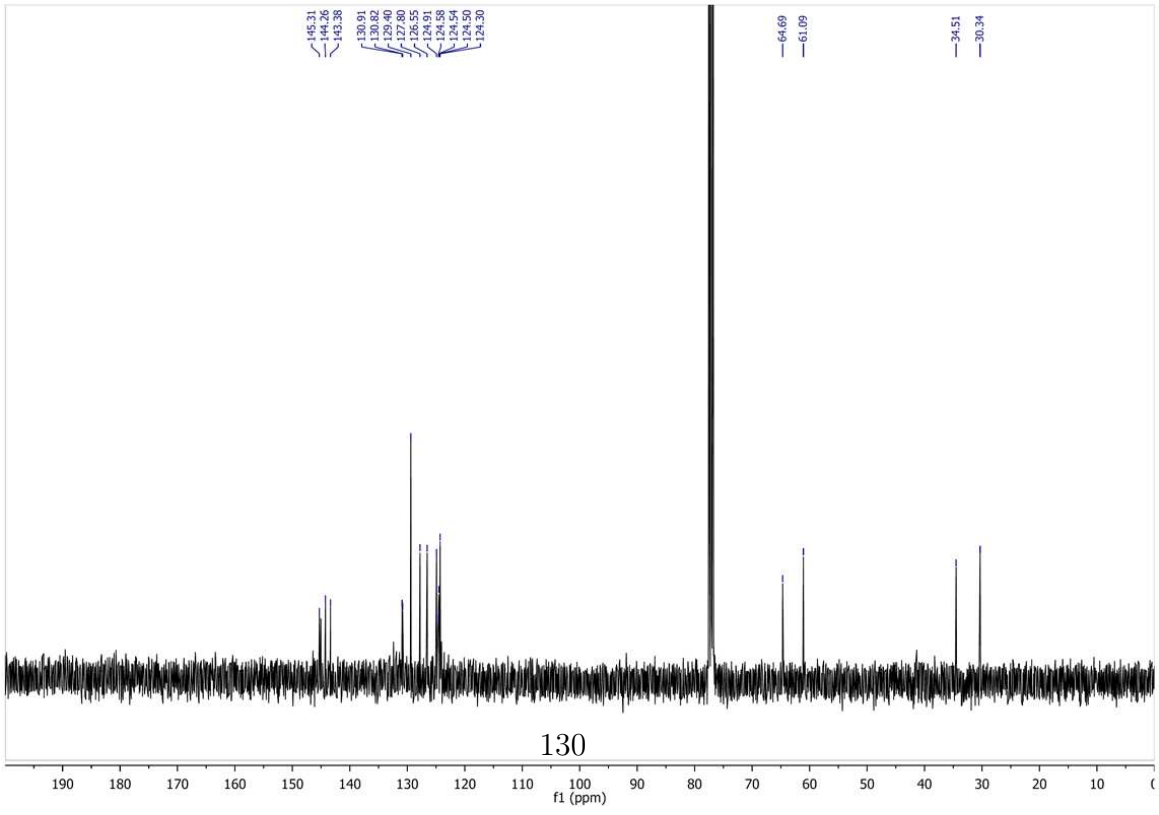
FT-IR thin film, neat (ATR): 3070, 3025, 2936, 2854, 2361, 2343, 1491, 1300, 1123, 1073 cm^{-1};

HRMS (EI^+): calculated for $C_{24}H_{19}F_6NO$, $[M+H]^{+\bullet}$: 435.1422 found 435.1382 (Δ = 7.9 ppm);

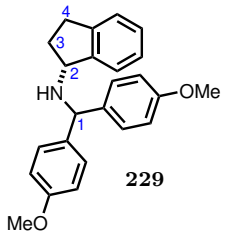
$[\alpha]_D^{25}$ = + 14° (c = 0.4, CH_2Cl_2);

$^{1}H/^{13}C$ NMR


7.74
7.65
7.57
7.55
7.45
7.44
7.42
7.41
7.39
7.38
7.36
7.34
7.17
7.15
7.14
5.15
4.06
4.04
4.02
2.94
2.93
2.92
2.91
2.90
2.89
2.88
2.87
2.73
2.71
2.69
2.67
2.65
2.43
2.42
2.41
2.41
2.41
2.40
2.40
2.39
2.39
2.38
2.38
2.37
2.37
2.36
1.79
1.77
1.76
1.76
1.74
1.74
1.73
0.98
1.80
1.07
6.68
2.55
1.00
1.47
1.06
1.07
1.60
1.05
0.98
f1 (ppm)


145.31
144.26
143.38
130.91
130.82
129.40
127.80
126.55
124.91
124.58
124.54
124.50
124.30
64.69
61.09
34.51
30.34
f1 (ppm)

5.3.0.12 (*R*)-N-(bis(4-methoxyphenyl)methyl)-2,3-dihydro-1H-inden-1-amine 229



229

Prepared according to general procedure A. This compound was synthesised using bis(4-methoxyphenyl)methanone (1.21 g, 5.00 mmol, 1.0 mol equiv). Starting material remained even after 4 days stirring under the reaction conditions. Flash chromatography (25% EtOAc/petrol) gave the product as a colourless oil 822 mg (46% yield).

R_f = 0.36 (30% EtOAc/petrol, stains pink with vanillin);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.47 (m, 1H, Ar-H), 7.43 (d, J = 8.7 Hz, 2H, Ar-H), 7.36 (d, J = 8.6 Hz, 2H, Ar-H), 7.24 – 7.17 (m, 3H, Ar-H), 6.85 (dd, J = 11.2, 8.7 Hz, 4H, Ar-H), 5.04 (s, 1H, 1), 4.46 (s, 1H, N-H), 4.14 (t, J = 6.9 Hz, 1H, 2), 3.80 – 3.74 (m, 6H, O-Me), 2.95 (ddd, J = 15.9, 8.5, 4.0 Hz, 1H, 4), 2.73 (dt, J = 15.9, 8.0 Hz, 1H, 4), 2.45 (dddd, J = 12.4, 8.0, 6.9, 4.0 Hz, 1H, 3), 1.80 (dtd, J = 12.4, 8.2, 6.9 Hz, 1H, 3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 146.2, 143.4, 128.5, 128.4, 127.4, 126.3, 124.7, 124.3, 113.9, 63.9, 61.0, 55.4, 34.7, 30.4 ppm;

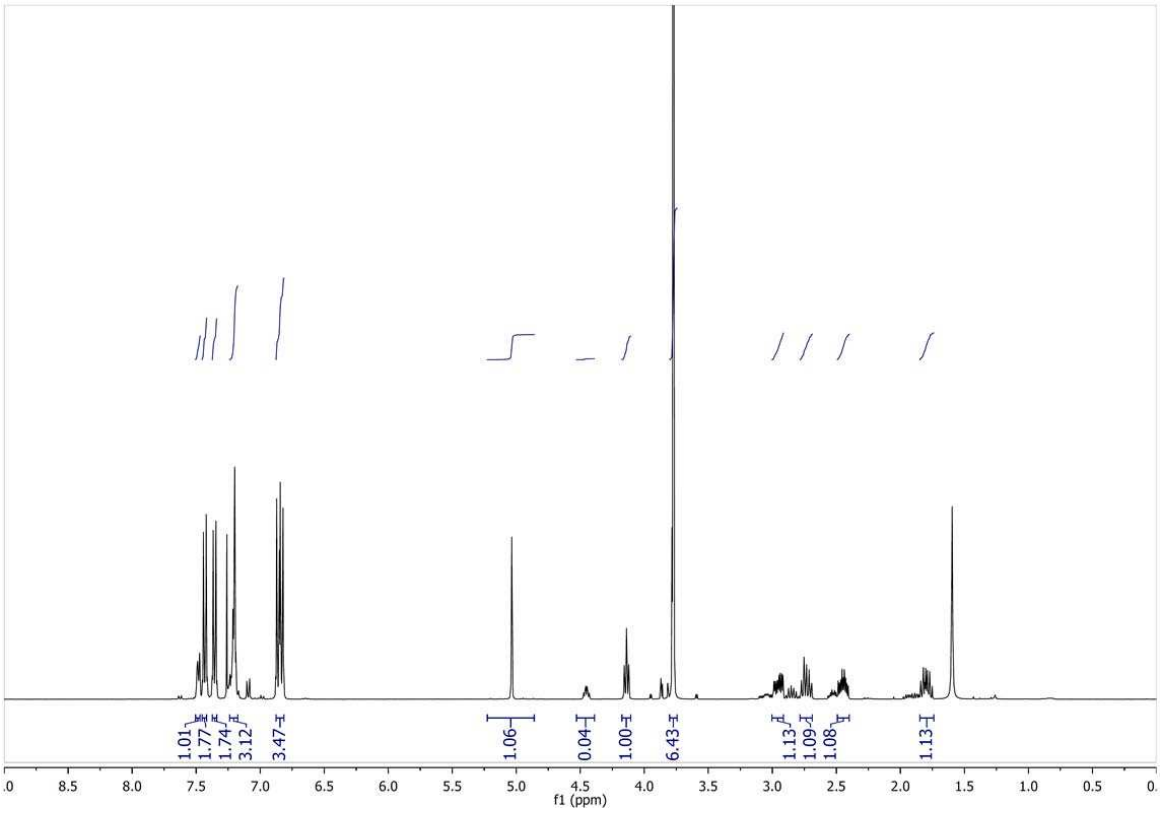
FT-IR thin film, neat (ATR): 2951, 2933, 2835, 2360, 2341, 1609, 1508, 1459, 1245, 1172, 1035 cm^{-1};

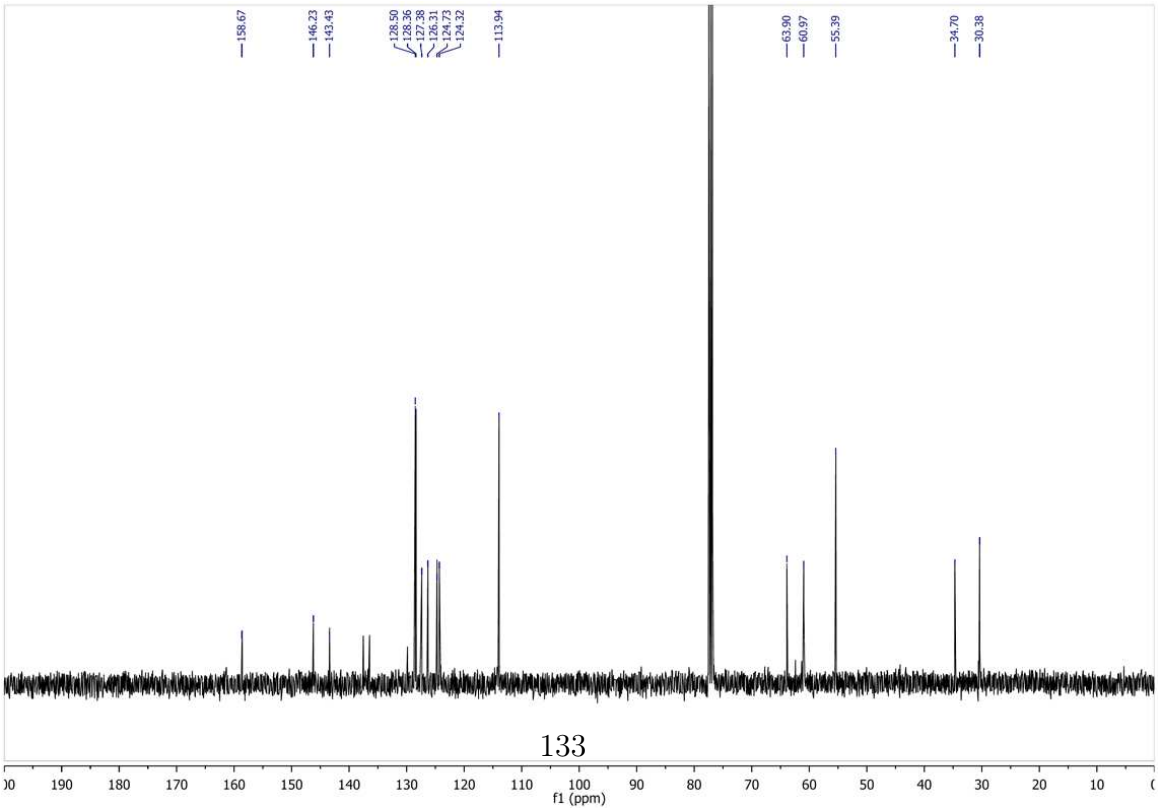
HRMS (ESI^+): calculated for $C_{24}H_{24}NO_2$, $[M+H]^{+\bullet}$: 358.1807 found 358.1809

($\Delta = 0.6$ ppm);

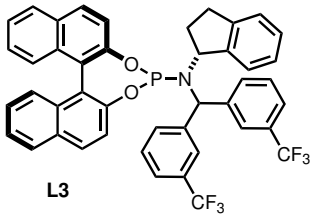
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +\ 6.6°$ ($c = 0.9$, CH_2Cl_2);

$^{1}H/^{13}C$ NMR


1.01
1.77
1.74
3.12
3.47
1.06
0.04
1.00
6.43
1.13
1.09
1.08
1.13
f1 (ppm)


158.67
146.23
143.43
128.50
128.36
127.38
126.31
124.73
124.32
113.94
63.90
60.97
55.39
34.70
30.38
f1 (ppm)

5.3.0.13 *N*-(bis(3-(trifluoromethyl)phenyl)methyl)-*N*-((*R*)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (R,R) L3



L3

Prepared according to general procedure B. This compound was synthesised using amine **228** (1.6 mmol). Flash chromatography (20% CH_2Cl_2/petrol) gave the product as a fluffy white powder 810 mg (68% yield).

R_f = 0.66 (70% CH_2Cl_2/petrol stains pink with vanillin);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.8 Hz, 1H, Ar-H), 7.93 (d, J = 8.2 Hz, 2H, Ar-H), 7.85 – 7.74 (m, 5H, Ar-H), 7.65 – 7.60 (m, 2H, Ar-H), 7.56 – 7.50 (m, 3H, Ar-H), 7.50 – 7.40 (m, 5H, Ar-H), 7.38 (d, J = 6.2 Hz, 3H, Ar-H), 7.33 (d, J = 7.2 Hz, 1H, Ar-H), 7.21 (d, J = 7.1 Hz, 1H, Ar-H), 7.15 (d, J = 8.2 Hz, 1H, Ar-H), 5.62 (d, J = 12.4 Hz, 1H, N-CH(benzylic side)), 4.20 – 4.11 (m, 1H, N-CH(indane side)), 3.00 (ddd, J = 15.9, 8.6, 4.1 Hz, 1H, alkyl-H), 2.79 (dt, J = 16.0, 8.0 Hz, 1H, Ar-H), 2.57 – 2.44 (m, 1H, Ar-H), 1.84 (dt, J = 12.5, 7.6 Hz, 1H, Ar-H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5, 145.3, 145.1, 144.3, 144.0, 143.4, 132.9, 132.7, 131.6, 130.9, 130.7, 130.6, 129.6, 129.4, 129.0, 129.0, 128.5, 128.4, 128.2, 127.8, 127.2, 126.6, 126.6, 126.3, 126.2, 125.9, 125.3, 125.1, 124.9, 124.7, 124.5, 124.3, 124.1, 124.1, 122.9, 122.1, 121.9, 64.7, 62.8, 62.7, 61.1, 34.5, 30.3, 30.3 ppm;

^{31}P NMR (162 MHz, $CDCl_3$): δ 145.14 ppm;

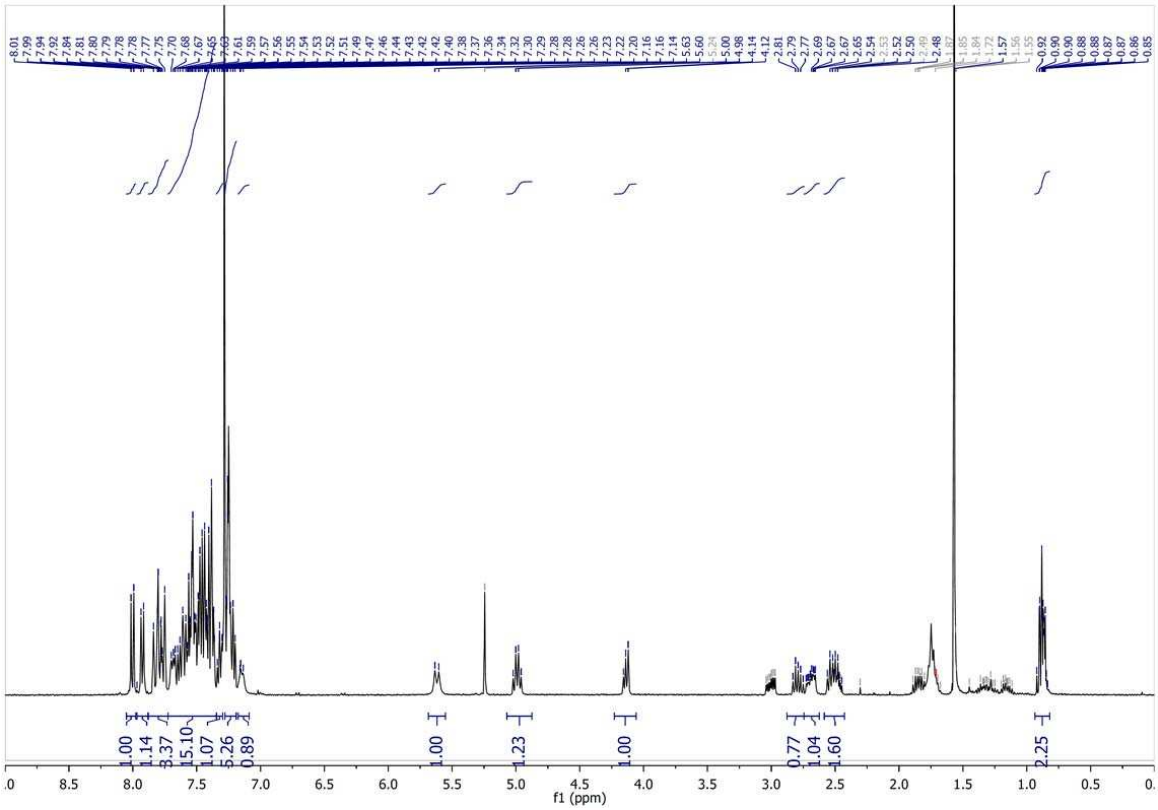
^{19}F NMR (377 MHz, $CDCl_3$): δ -62.49 ppm;

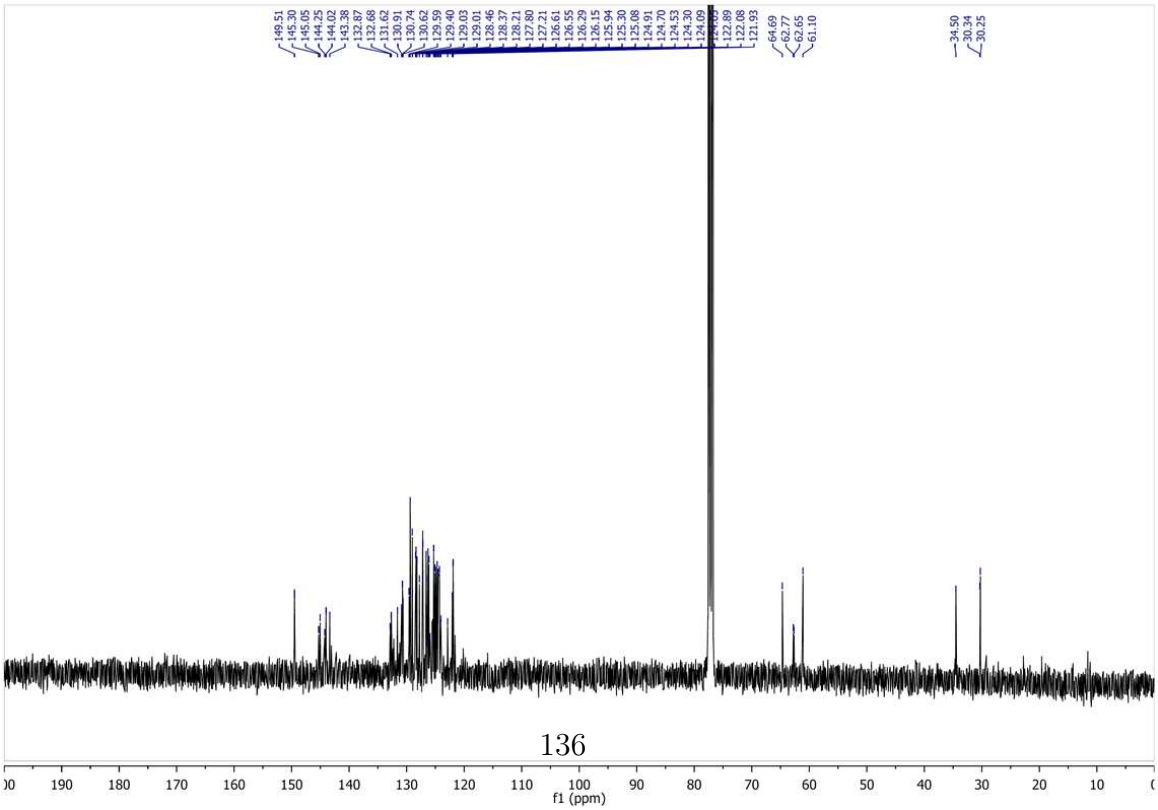
FT-IR thin film, neat (ATR): 3068, 2930, 2853, 2361, 2341, 1618, 1462, 1449, 1329, 1166, 1125, 1074 cm^{-1};

HRMS (ESI^+): calculated for $C_{44}H_{31}NO_2F_6P$, $[M+H]^{+\bullet}$: 750.1991 found 750.1993 (Δ = 0.2 ppm);

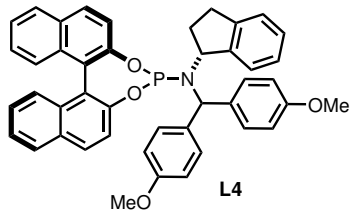
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 2.6° (c = 0.4, CH_2Cl_2);

$^{1}H/^{13}C$ NMR





5.3.0.14 *N*-(bis(4-methoxyphenyl)methyl)-*N*-((*R*)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (*R*,*R*) L4



L4

Prepared according to general procedure B. This compound was synthesised using amine **229** (1.75 mmol). Flash chromatography (70% CH_2Cl_2/petrol) gave the product as a fluffy white powder 462 mg (39% yield).

R_f = 0.27 (70% CH_2Cl_2/petrol stains pink with vanillin);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.8 Hz, 1H, Ar-H), 7.88 (d, J = 8.5 Hz, 1H, Ar-H), 7.77 (t, J = 8.4 Hz, 2H, Ar-H), 7.58 (d, J = 8.8 Hz, 1H, Ar-H), 7.54 (dd, J = 8.7, 3.1 Hz, 1H, Ar-H), 7.43 – 7.28 (m, 5H, Ar-H), 7.25 – 7.19 (m, 6H, Ar-H), 7.18 – 7.13 (m, 3H, Ar-H), 6.89 – 6.80 (m, 4H, Ar-H), 5.43 (d, J = 11.8 Hz, 1H, N-CH(benzylic side)), 4.95 (q, J = 8.2 Hz, 1H, N-CH(indane side)), 3.82 (d, J = 5.7 Hz, 6H, O-Me), 2.66 – 2.38 (m, 2H, alkyl-H), 1.73 (q, J = 7.6 Hz, 2H, alkyl-H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 158.7, 158.6, 150.3, 150.2, 150.1, 149.9, 144.2, 143.0, 135.9, 132.9, 132.7, 131.5, 130.5, 130.4, 130.1, 129.9, 129.5, 128.4, 128.3, 128.3, 127.7, 127.2, 126.4, 126.1, 125.9, 125.6, 125.1, 124.9, 124.4, 122.5, 122.5, 121.5, 121.5, 114.0, 113.9, 113.6, 113.5, 113.4, 62.6, 62.5, 55.4, 55.4, 30.3 ppm;

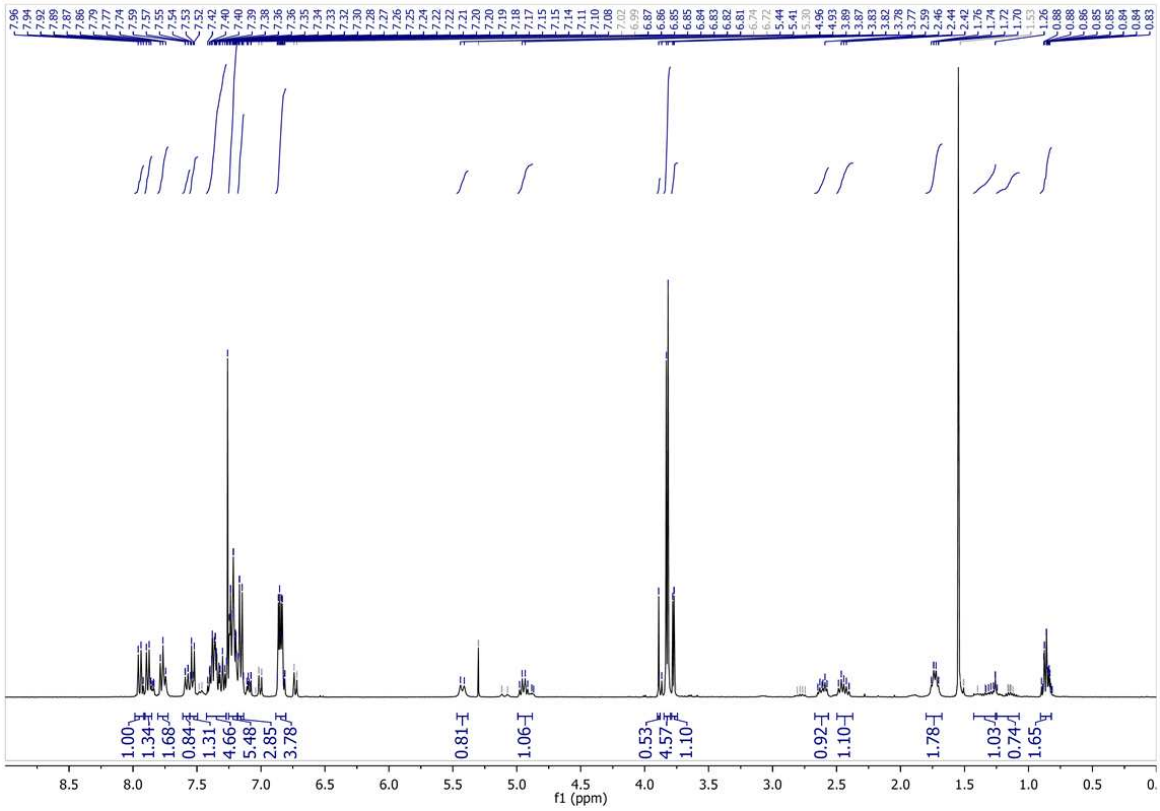
^{31}P NMR (162 MHz, $CDCl_3$): δ 147.08 ppm;

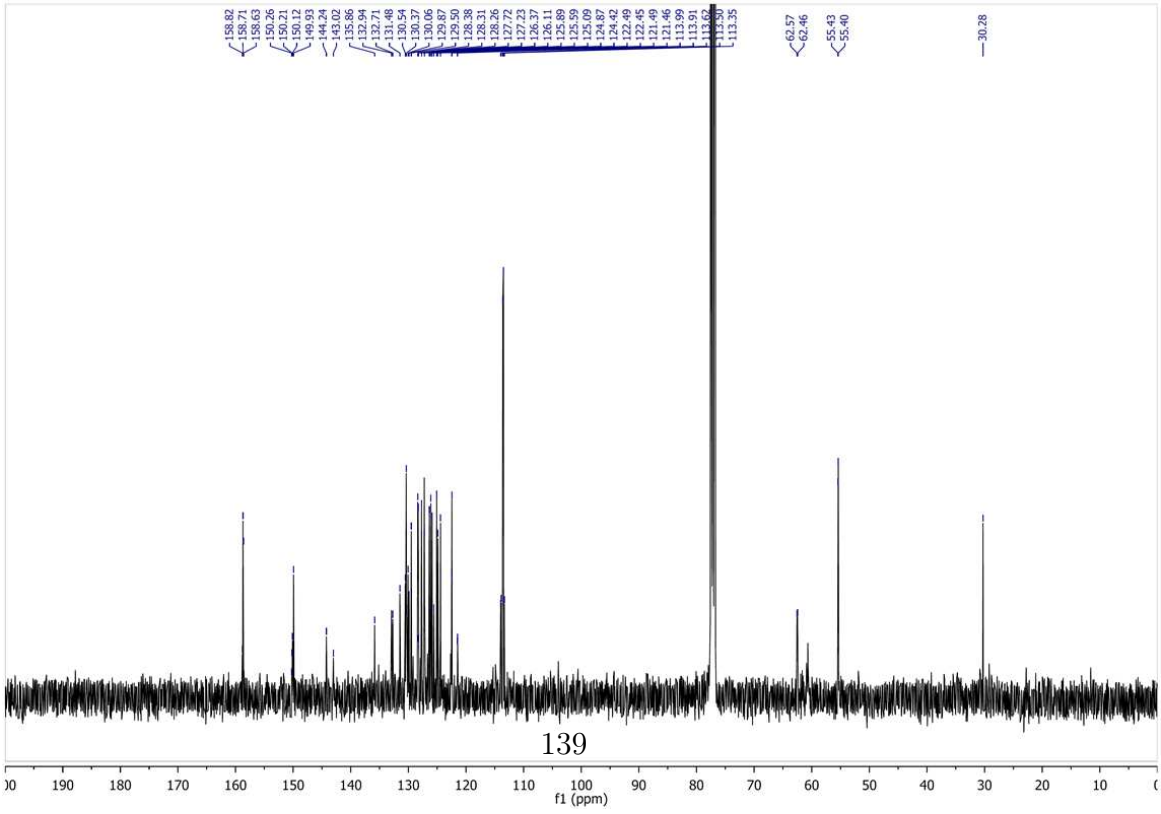
FT-IR thin film, neat (ATR): 3064, 2951, 2835, 2360, 2341, 1609, 1588, 1509, 1462, 1248, 1155, 1034 cm^{-1};

HRMS (ESI^+): calculated for $C_{44}H_{37}NO_4P$, $[M+H]^{+\bullet}$: 674.2455 found 674.2449 (Δ = 0.9 ppm);

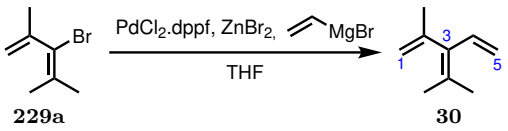
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -0.20°$ (c = 0.3, CH_2Cl_2);

$^{1}H/^{13}C$ NMR


1.00
1.34
1.68
0.84
1.31
4.66
5.48
2.85
3.78
0.81
1.06
0.53
4.57
1.10
0.92
1.10
1.78
1.03
0.74
1.65
f1 (ppm)


f1 (ppm)

5.3.0.15 2,4-dimethyl-3-vinylpenta-1,3-diene 30



229a **30**

To a flame-dried round bottom flask, 3-bromo-2,4-dimethylpenta-1,3-diene[14b] (2.28 g, 13.0 mmol, 1.0 equiv) was dissolved in 1.0 mL THF. $PdCl_2$.dppf (191 mg, 0.261 mmol, 0.020 equiv) was added in one portion and the reaction mixture was cooled to 0 °C. Anhydrous $ZnBr_2$ solution (27 mL of a 0.97 M solution in THF, 26.1 mmol, 2.0 equiv) as prepared below was added via syringe dropwise, upon which the reaction became a clear dark brown colour. Vinylmagnesium bromide (21 mL of a 0.82 M solution in THF, 16.9 mmol, 1.3 equiv) was added dropwise with vigorous stirring. After the addition, the cooling bath was removed and the beige coloured mixture was allowed to stir at room temperature for 6.5 hours or until NMR indicated the complete disappearance of starting material. After dilution with CH_2Cl_2, the reaction was carefully quenched with saturated aqueous NH_4Cl. The mixture was partitioned in a separatory funnel and the aqueous phase was extracted (3 x 50 mL CH_2Cl_2). The combined organic extracts were washed (brine), dried ($MgSO_4$) and carefully concentrated *in vacuo* (caution: product is volatile). The product was purified by flash chromatography (100% pentane on silica, R_f = 0.50) to give 770 mg (49% yield) of a volatile, vile smelling and colourless oil. The neat compound was stored in the freezer under an atmosphere of Ar and in the dark.

^{1}H NMR (400 MHz, CD_2Cl_2): δ 6.71 (dd, J = 17.2, 10.7 Hz, 1H, 4), 5.13 (dq, J = 3.1, 1.5 Hz, 1H, 1-trans), 5.05 (dd, J = 17.2, 2.2 Hz, 1H, 5-trans), 4.97

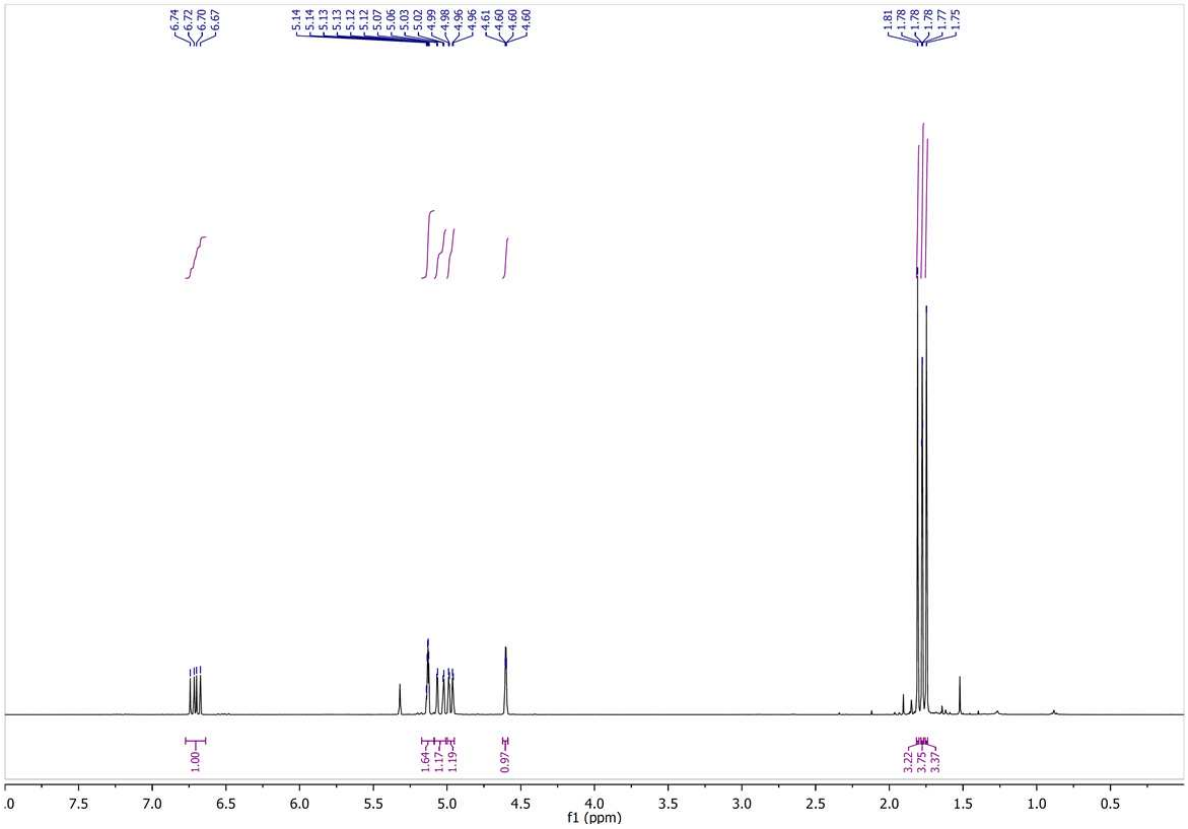
(dd, J = 10.7, 2.2 Hz, 1H, 5-cis), 4.60 (dd, J = 2.6, 1.0 Hz, 1H, 1-cis), 1.81 (s, 3H, CH_3), 1.78 (dd, J = 1.1, 1.0 Hz, 3H, CH_3),), 1.75 (s, 3H, CH_3) ppm;

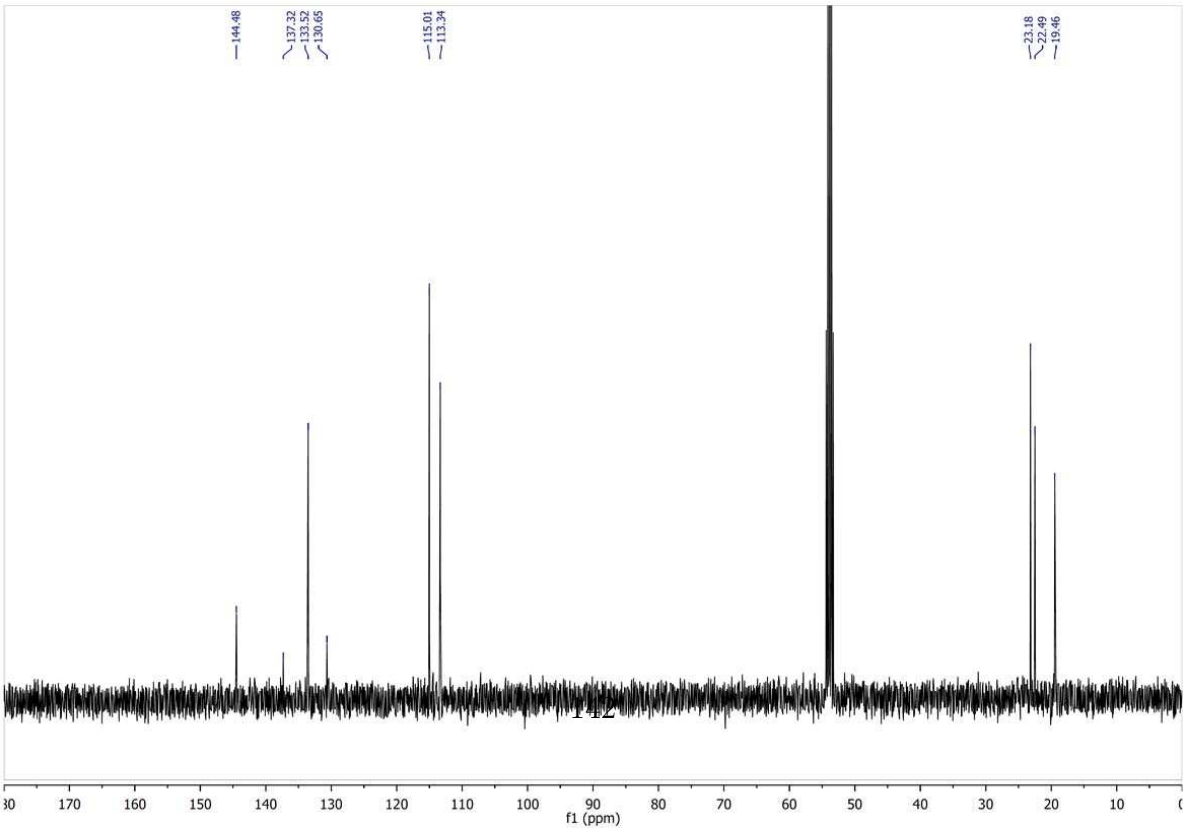
^{13}C NMR (101 MHz, CD_2Cl_2) δ 144.5, 137.3, 133.5, 130.7, 115.0, 113.3, 23.2, 22.5, 19.5 ppm;

FT-IR thin film, neat (ATR): 3080, 2982, 2927, 2361, 2341, 1457, 1376 cm^{-1};

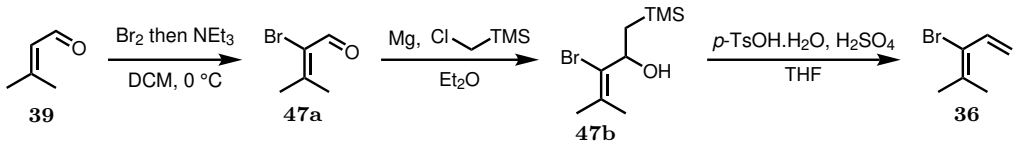
HRMS (EI$^+$) m/z: $[M]^{+\bullet}$ Calcd for C_9H_{14}; 122.1096 found 122.1094 (Δ = 2.9 ppm);

$^{1}H/^{13}C$ NMR


6.74
6.72
6.70
6.67
5.14
5.14
5.13
5.13
5.12
5.12
5.07
5.06
5.03
5.02
4.99
4.98
4.96
4.61
4.60
4.60
4.60
1.81
1.78
1.78
1.78
1.77
1.75
1.00
1.64
1.17
1.19
0.97
3.22
3.25
3.37
f1 (ppm)


144.48
137.32
133.52
130.65
115.01
113.34
23.18
22.49
19.46
f1 (ppm)

5.3.0.16 Revised procedure for the preparation of bromodiene 36



39 **47a** **47b** **36**

Bromine (9.4 mL, ρ = 3.12 g.mL^{-1}, 183 mmol, 1.1 equiv) was added drop wise to a solution of 3-methyl-2-butenal **39** (16 mL, ρ = 0.878 g.mL^{-1}, 165 mmol, 1.0 equiv) in dichloromethane (400 mL) at 0 °C. Next, triethylamine (28 mL, ρ = 0.726 g.mL^{-1}, 198 mmol, 1.2 equiv) was added drop wise using a dropping funnel and the cold bath was removed immediately after addition. The reaction was quenched with saturated $Na_2S_2O_{3(aq)}$ until the cloudy mixture became clear. The aqueous layer was extracted (3 x 400 mL CH_2Cl_2). The combined organic extracts were washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was filtered through a silica plug, eluting with 30% EtOAc/*n*-hexane. 2-bromo-3-methylbut-2-enal (26.2 g, 161 mmol, >95% yield if assumed to be pure) was obtained as a yellow/orange oil which was used in subsequent steps without modification.

Magnesium turnings (4.05 g, 169 mmol, 1.05 equiv) were flame-dried in a 2-neck 500 mL round bottom flask equipped with a stirrer bar and reflux condenser. A crystal of iodine was added, followed by dry ether (2 mL) and the magnesium turnings were stirred until the brown color dissipated. (Chloromethyl)trimethylsilane (18.8 mL, ρ = 0.879 g.mL^{-1}, 174 mmol, 1.08 equiv) in dry ether (70 mL) was added carefully until the Grignard reaction initiated, upon which it was added at a rate that maintained a gentle reflux. After the chloride had been added, the entire reaction was heated at 55 °C until complete consumption of the mag-

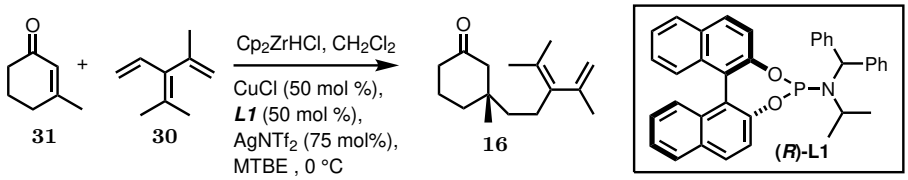
nesium was observed (about 30 min). The reaction was then cooled to −78 °C and crude 2-bromo-3-methylbut-2-enal **47a** (26.2 g, 161 mmol, 1.0 equiv) from the previous step was added drop wise. After stirring for 20 minutes, TLC (30% EtOAc/*n*-hexane) showed that no starting aldehyde remained. The reaction was quenched by pouring it onto a vigorously stirred slurry of NH_4Cl and ice. After partitioning the layers in a separatory funnel, the aqueous layer was extracted (3 x 200 mL Et_2O), the combined organic extracts were washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. 3-bromo-4-methyl-1-(trimethylsilyl)pent-3-en-2-ol **47b** was obtained as a yellow oil which was used in the next step without further purification.

p-toluenesulfonic acid monohydrate (91.8 g, 483 mmol, 3.0 equiv) was dissolved in 400 mL ether followed by the dropwise addition of concentrated sulfuric acid (8.6 mL, $\rho = 0.879\ \mathrm{g.mL^{-1}}$, 161 mmol, 1.0 equiv). 3-bromo-4-methyl-1-(trimethylsilyl)pent-3-en-2-ol **47b** from the previous step was added dropwise to the vigorously stirred solution. After addition of the alcohol, the mixture was allowed to stir for an additional 10 minutes before pouring the reaction onto a vigorously stirred slurry of ice and $NaHCO_{3(aq)}$. The aqueous phase was extracted (3 x 200 mL Et_2O), the combined organic extracts were dried ($MgSO_4$) before being concentrated *in vacuo* (630 mbar@40 °C). The crude product was carefully transferred to a 100 mL round bottom flask equipped with a stirrer bar and a short path distillation apparatus was fitted (air cooled condenser). The collection flask was cooled to −78 °C. Residual solvents were initially removed under high vacuum (oil pump) until no more colourless distillate appeared in the collection flask. The temperature of the distillation was then increased to 30 °C and this temperature was held for 20

minutes. At this point, a heat gun was used to distill over the desired product, discarding approximately 1 mL of forerun and collecting a single fraction (a pale yellow oil) until approximately 5 mL of material remained in the distilling flask. The title compound was obtained as a pale yellow oil with a pungent odor (18.7 g, 116 mmol, 70% yield over three steps). The diene was stored in an amber glass bottle under N_2 in the freezer when not in use. Spectroscopic data matched those as reported by the literature.[36]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (dd, J = 16.1, 10.6 Hz, 1H), 5.54 (d, J = 16.1 Hz, 1H), 5.18 (d, J = 10.6 Hz, 1H), 2.03 (s, 3H), 1.96 (s, 3H) ppm;
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 131.8, 119.9, 117.9, 26.6, 21.3 ppm;

5.3.0.17 (+)-Taxadiene intermediate 16: 1,4-addition of triene 30 to 3-methyl-2-cyclohexenone



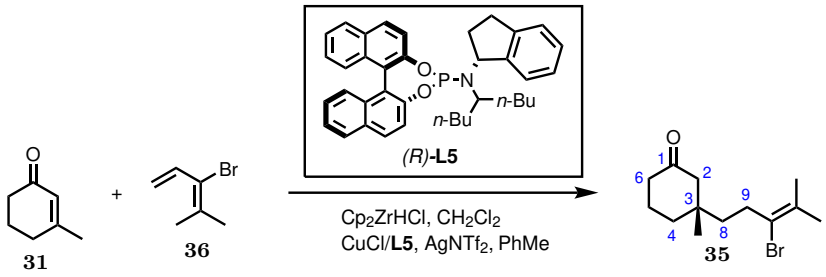
To a flame-dried 10 mL round bottom flask equipped with a stirrer bar (flask A), was added copper(I) chloride (15 mg, 0.15 mmol, 0.50 equiv) and phosphoramidite (*R*)-**L** (82 mg, 0.15 mmol, 0.50 equiv). After purging the flask with Argon, dry MTBE (4 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment. Concurrently, Schwartz reagent (203 mg, 0.79 mmol, 2.6 equiv) was added to a separate flame-dried 10 mL round bottom flask equipped with a stirrer bar (flask B). After purging the flask with Argon and fitting the reaction vessel with a balloon of inert gas, dry dichloromethane (0.4 mL) was added followed by triene **30** (0.26 mL of a 3.5M solution in n-pentane, 0.91 mmol, 3.0 equiv). After stirring for 2 hours, this reaction became clear orange signifying the completion of hydrozirconation. After stirring for the allotted time, silver(I) triflimide (88 mg, 0.23 mmol, 0.75 equiv) was added in one portion to flask A, minimising exposure to the atmosphere where possible. After stirring for 10 minutes, the solution from flask A was then filtered (using a syringe filter) into flask B (pre-cooled to 0 °C). The resulting solution became black within 10 seconds. After stirring for 5 minutes, 3-methyl-2-cyclohexenone was added dropwise (34 μL, ρ = 0.97 g.mL-1, 0.30 mmol, 1.0 equiv). The reaction flask was then wrapped in foil and stirred at 0 °C for three and a half hours and then for an additional 12 hours at room temperature until the reaction was completed, as monitored by TLC (30%

Et_2O/n-hexane).

To quench the reaction, the mixture was first diluted with Et_2O (equal to the volume of the reaction mixture), then 1M $NH_4Cl_{(aq)}$ was added (1 mL). After stirring for 15 minutes, the solids were filtered off using cotton wool. The mixture was partitioned and the aqueous layer was extracted (3 x 50 mL Et_2O). The combined organic extracts were washed (saturated $NaHCO_{3(aq)}$), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (10% Et_2O/*n*-hexane, silica) gives the desired product as colourless residue (9.4 mg, 0.040 mmol, 14% yield). Spectroscopic data matched those as reported by the literature.[14b] Chiral HPLC (Chiralpak AY-H column 250 × 4.6 mm, 1% iPrOH/n-hexane, 0.8 $mL.min^{-1}$): ee = 80% (major enantiomer tR = 6.5 min, minor enantiomer tR = 7.0 min).

R_f = 0.32 (30% Et_2O/*n*-hexane, stains blue with p-anisaldehyde);
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 (dq, J = 2.9, 1.5 Hz, 1H), 4.53 (dq, J = 2.8, 1.0 Hz, 1H), 2.31 – 2.24 (m, 2H), 2.23 – 2.09 (m, 2H), 2.09 – 1.94 (m, 2H), 1.91 – 1.82 (m, 2H), 1.74 (dd, J = 1.5, 0.9 Hz, 3H), 1.64 (d, J = 1.9 Hz, 6H), 1.59 – 1.50 (m, 2H), 1.29 – 1.23 (m, 2H), 0.93 (s, 3H) ppm;
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4, 146.5, 136.3, 125.2, 113.3, 53.9, 41.2, 40.2, 38.7, 35.9, 25.1, 24.9, 22.9, 22.3, 21.9, 19.6 ppm;

5.3.0.18 (−)-3-(3-bromo-4-methylpent-3-en-1-yl)-3-methylcyclohexan-1-one 35

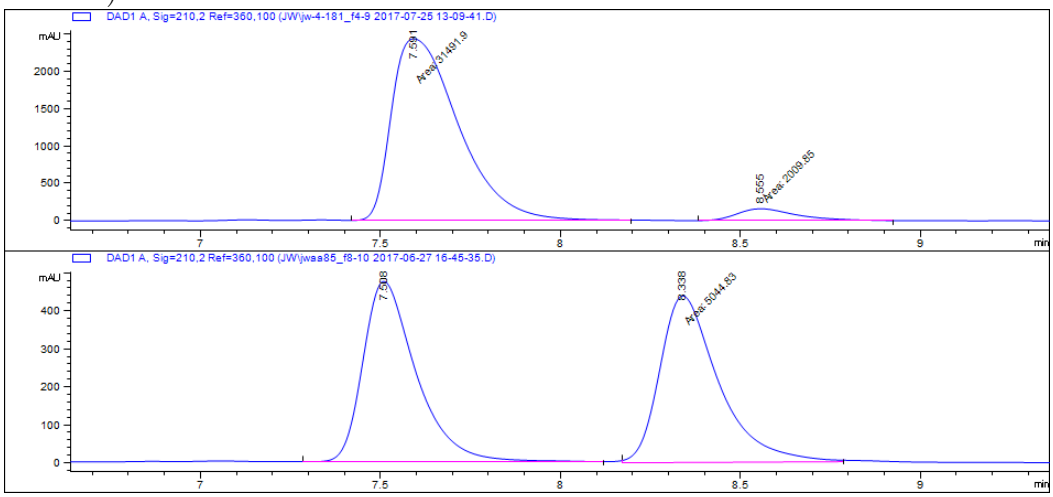


Optimised procedure

To a flame dried 5 mL round bottom flask equipped with a stirrer bar (flask **A**), was added copper(I) chloride (4.5 mg, 0.045 mmol, 0.085 mol equiv) and phosphoramidite **L5** (29 mg, 0.051 mmol, 0.096 mol equiv). After purging the flask with Argon, dry toluene (2mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment. Concurrently, Schwartz reagent (256 mg, 0.991 mmol, 1.87 mol equiv) was added to a separate flame dried 5 mL round bottom flask equipped with a stirrer bar (flask **B**). After purging the flask with Argon and fitting the reaction vessel with a balloon of inert gas, dry dichloromethane (0.5 mL) was added followed by bromodiene **4** (160 μL, $\rho = 1.3$ g.mL^{-1}, 1.29 mmol, 2.43 mol equiv). After stirring for one hour, this reaction became clear orange signifying the completion of hydrozirconation. In some instances dependent on the quality of the bromodiene as well as the Schwartz reagent used, hydrozirconation was not complete within the allotted time. In these situations, it was found that the use of a heat source applied briefly to the flask pushed the hydrozirconation towards completion. After stirring for the allotted time, silver(I) trifliimide (29 mg, 0.074 mmol, 0.14 mol equiv) was added in one portion to flask **A**, minimising exposure to the atmosphere where possible. After stirring for 10 minutes, the solution from

flask **A** was then filtered (using a syringe filter) into flask **B** over a period of one minute. The resulting solution became dark green/black within 10 seconds. After stirring for 5 minutes, 3-methyl-2-cyclohexenone **1** was added at a rate of 1 drop every 2 seconds (60 μL, $\rho = 0.97$ g.mL^{-1}, 0.53 mmol, 1.00 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC (30% EtOAc/petrol).

To quench the reaction, the mixture was first diluted with Et_2O (equal to the volume of the reaction mixture), then 1M $NH_4Cl_{(aq)}$ was added (1 mL). After stirring for 3 minutes, the solids were filtered off using cotton wool. The mixture was partitioned and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ and then dried over $MgSO_4$. Purification by flash chromatography (10% Et_2O/*n*-hexane or 10% EtOAc/petrol, silica) gave the desired product as 103 mg pale yellow oil (71% yield). Chiral HPLC (Chiralpak IB column 250 × 4.6 mm, 1% ^{i}PrOH/*n*-hexane, 1 mL.min^{-1}): ee = 88% (major enantiomer t_R = 7.5 min, minor enantiomer t_R = 8.4 min).



Scale up

On scale up (to 3mmol of 3-methyl-2-cyclohexenone **1**) it was the found that the procedure gave a higher yield: 784 mg yellow oil (corresponding to 96% yield) with the same enantioselectivity as the small scale reaction (88% ee).

$\mathbf{R_f}$ = 0.43 (30% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 – 2.34 (m, 2H, 9), 2.29 (t, J = 6.8 Hz, 2H, 6), 2.18 (q, J = 13.5 Hz, 2H, 2), 1.97 – 1.86 (m, 2H, 5), 1.84 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.64 (m, 2H, 4), 1.56 – 1.40 (m, 2H, 8), 0.95 (s, 3H, 7) ppm;

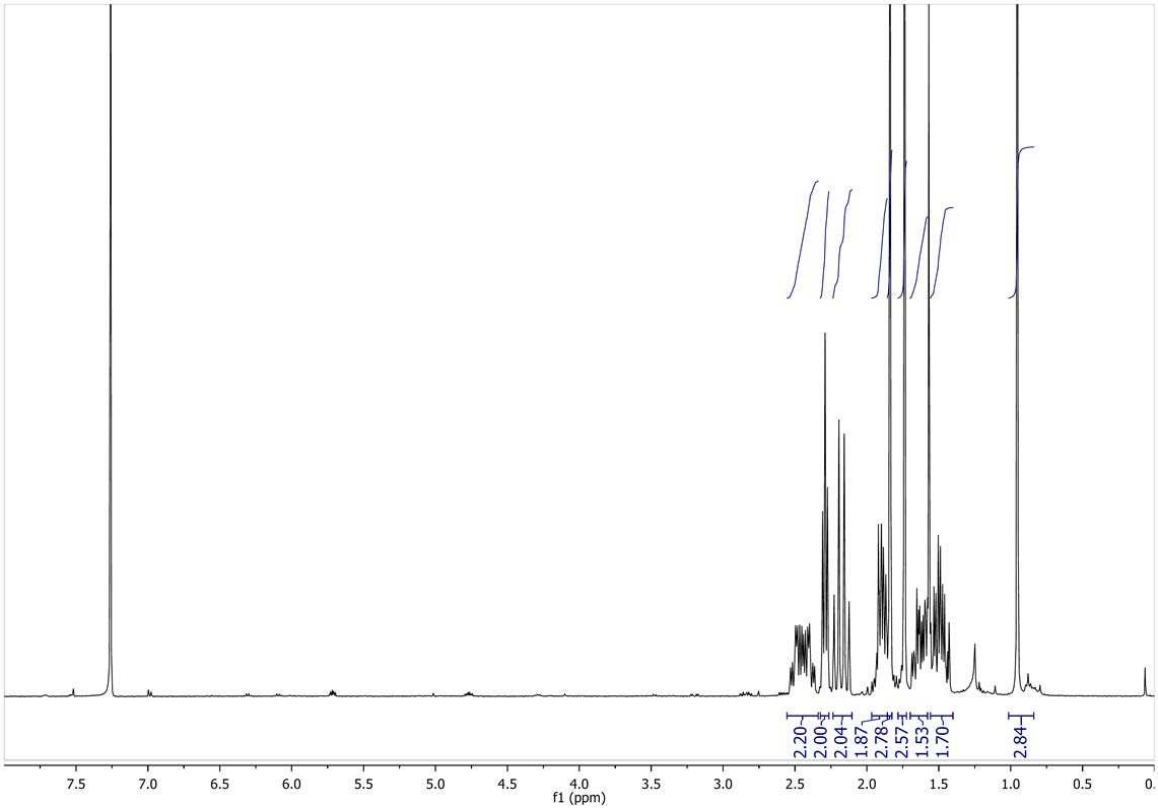
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.0 1, 130.2, 121.3, 53.7 2, 41.1 6, 39.9 8, 38.5 3, 35.9 4, 32.4 9, 25.5 CH_3, 24.9 7, 22.2 5, 20.2 CH_3 ppm;

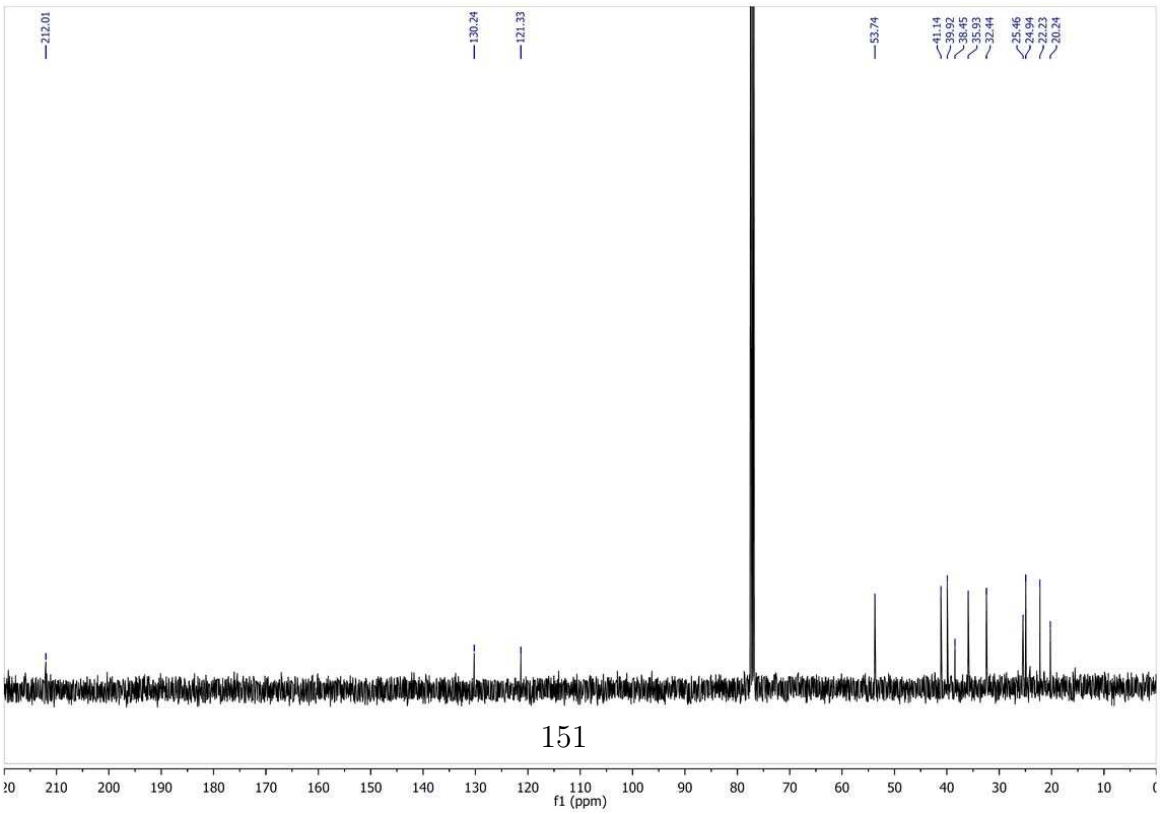
FT-IR thin film, neat (ATR): 2981, 2360, 2341, 1713 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{13}H_{22}O^{79}Br^{35}$, $[M+H]^{+\bullet}$: 273.08485 found 273.08481 (Δ = -0.17 ppm);

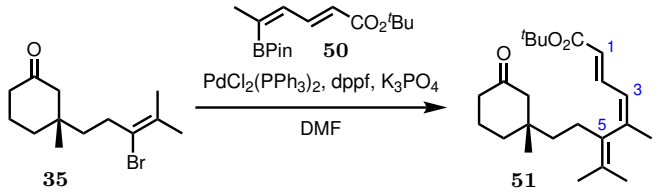
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -2.6°$ (c = 0.47, CH_2Cl_2), based on a sample of 88% *ee*;

$^{1}H/^{13}C$ NMR


2.20
2.00
2.04
1.87
2.78
2.57
1.53
1.70
2.84
f1 (ppm)


212.01
130.24
121.33
53.74
41.14
39.92
38.45
35.93
32.44
25.46
24.94
22.23
20.24
f1 (ppm)

5.3.0.19 tert-butyl (2E,4Z)-5,7-dimethyl-6-(2-((*S*)-1-methyl-3-oxocyclohexyl)ethyl)oct 2,4,6-trienoate 51



$PdCl_2(PPh_3)_2$ (126 mg, 0.179 mmol, 0.10 mol equiv), dppf ligand (100 mg, 0.179 mmol, 0.10 mol equiv) and K_3PO_4 (1.151 g, 5.37 mmol, 3.0 mol equiv) were added to a flame dried 22 mL vial equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were then performed, after which a solution of bromoketone **35** (490 mg, 1.79 mmol, 1.0 mol equiv) and boronic ester **50** (590 mg, 1.97 mmol, 1.1 mol equiv) in dry/degassed DMF (3.6 mL). After 6 hours or when the reaction was deemed complete by TLC, the reaction was quenched with water (equal to volume of the reaction mixture). The aqueos phase was extracted with benzene. The combined organic extracts were washed (water then brine), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (30 – 40% Et_2O/*n*-pentane, silica column) to give the title compound as an orange oil (523 mg, 1.45 mmol, 81% yield).

R_f = 0.29 (30% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (dd, J = 15.4, 11.4 Hz, 1H, 2), 6.01 (d, J = 11.4 Hz, 1H, 3), 5.70 (d, J = 15.4 Hz, 1H, 1), 2.27 (t, J = 5.5 Hz, 2H, alkyl-H), 2.19 – 2.09 (m, 2H, alkyl-H), 1.89 – 1.82 (m, 2H, alkyl-H), 1.86 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.47 (s, 9H, O^{t}Bu-CH_3), 1.30 – 1.20 (m, 6H, alkyl-H), 0.92 (s, 3H, CH3) ppm;

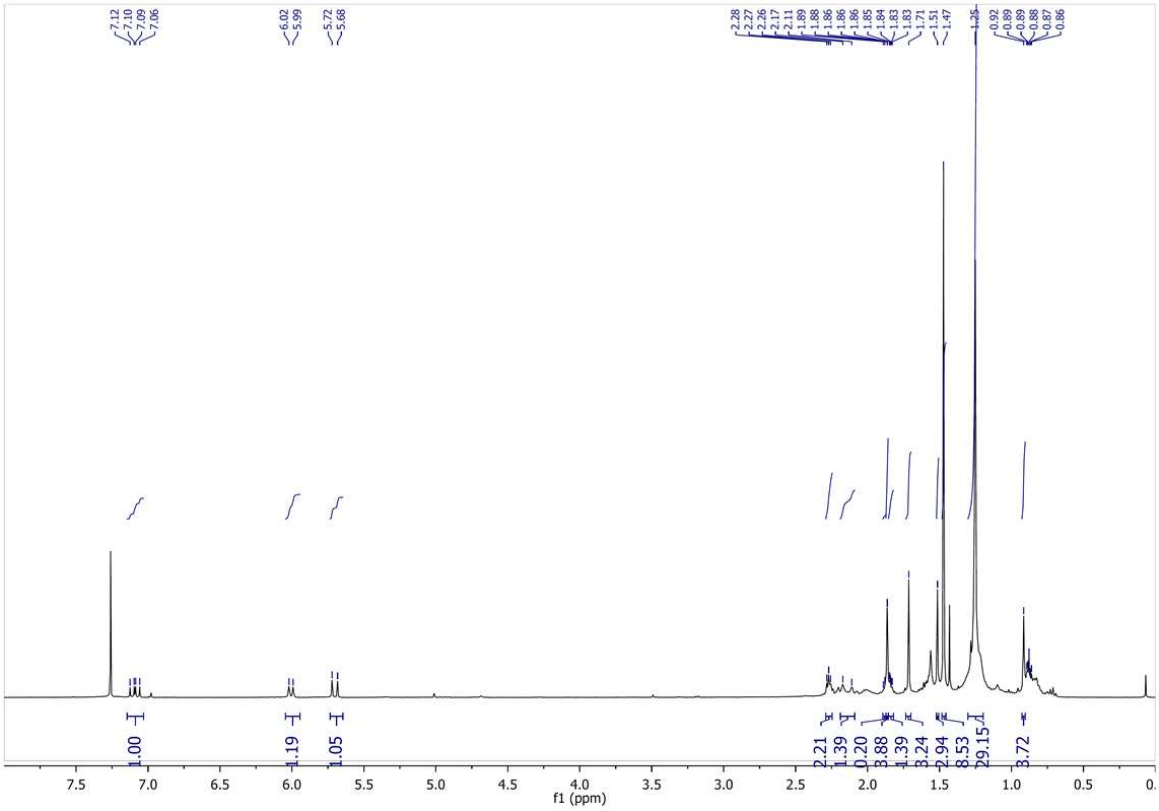
^{13}C NMR (101 MHz, $CDCl_3$): δ 212.2, 167.2, 150.4, 142.1, 132.5, 125.3, 120.9, 79.9, 41.2, 40.3, 38.7, 28.4, 25.5, 24.0, 22.3, 22.0, 19.6 ppm;

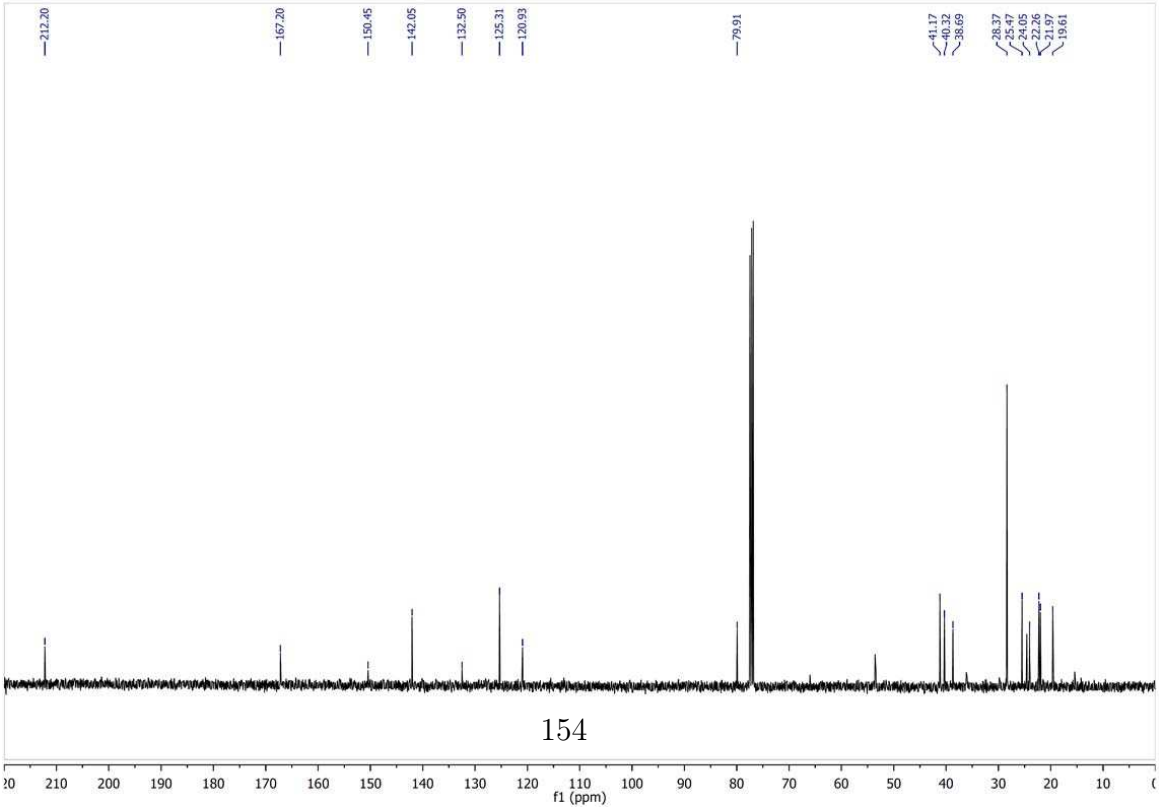
FT-IR thin film, neat (ATR): 2957, 2921, 2851, 2361, 2341, 1710, 1628, 1458, 1366, 1138 cm^{-1};

HRMS (ESI^+): calculated for $C_{23}H_{37}O_3$, $[M+H]^{+\bullet}$: 361.27372 found 361.27356 (Δ = 0.4 ppm);

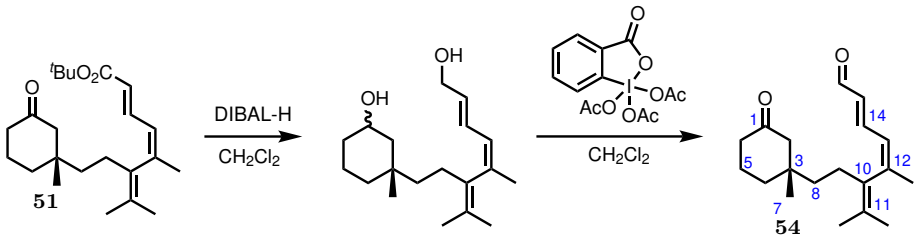
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -3.6°$ (c = 0.76, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


7.12
7.10
7.09
7.06
6.02
5.99
5.72
5.68
2.28
2.27
2.26
2.17
2.11
1.89
1.88
1.86
1.86
1.86
1.85
1.84
1.83
1.83
1.71
1.51
1.47
1.25
0.92
0.89
0.89
0.88
0.87
0.86
1.00
1.19
1.05
2.21
1.39
0.20
3.88
1.39
3.24
2.94
8.53
29.15
3.72
f1 (ppm)


212.20
167.20
150.45
142.05
132.50
125.31
120.93
79.91
41.17
40.32
38.69
28.37
25.47
24.05
22.26
21.97
19.61
f1 (ppm)

5.3.0.20 Ketoaldehyde 54



tert-Butyl ester **51** (45.3 mg, 0.13 mmol, 1.0 eq.) and dry CH_2Cl_2 (2.1 mL) were added to a flame dried 22 mL vial equipped with a stirrer bar and rubber septum. The solution was cooled to −78 °C and diisobutylaluminium hydride (0.50 mL of a 1M solution in CH_2Cl_2, 0.50 mmol, 4.0 eq.) was added dropwise (down the side of the vial) over 4 minutes. After stirring for 1 hour and 20 minutes, the cooling bath was removed and after an additional 45 minutes, a saturated solution of Rochelle's salt was added (2 mL). When a biphasic mixture had formed, the reaction contents were diluted (H_2O) and extracted ($3xCH_2Cl_2$). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through a plug of silica (eluting with 10% MeOH/CH_2Cl_2) to give 35.5 mg yellow oil ($\mathbf{R_f}$ = 0.31 10% MeOH/CH_2Cl_2, stains dark blue/purple with *p*-anisaldehyde) which was immediately carried forward to the next step.

To a flame dried 3 mL vial equipped with a stirrer bar was added the yellow oil from the previous step and dry dichloromethane (0.43 mL). Dess-Martin periodinane (70 mg, 0.17 mmol, 1.3 eq) was added and the reaction mixture stirred for 15 minutes before another portion of Dess-Martin periodinane (66 mg, 0.16 mmol, 1.2 eq) was added. After 25 minutes, TLC showed complete consumption of the starting material and the reaction was quenched by the addition of an

equal volume of saturated $NaHCO_{3(aq)}$ and $Na_2S_2O_{3(aq)}$ (1 mL combined volumne). The biphasic mixture was stirred for 15 minutes and the lower CH_2Cl_2 layer was collected. The aqueous layer was extracted (3xEt_2O) and the combined organic extracts were washed ($NaHCO_{3(aq)}$, water then brine) dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (20 – 40% Et_2O/pentane, silica column) to furnish the title compound as a cloudy white oil (5.1 mg, 15% yield over two steps).

The chromatography purification step should be done as fast as possible since it was found that the title compound is unstable on silica.

R_f = 0.67 (50% EtOAc/pentane, stains green with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (d, J = 8.1 Hz, 1H, 16), 6.97 (dd, J = 15.3, 11.3 Hz, 1H, 14), 6.23 – 6.17 (m, 1H, 13), 6.07 (dd, J = 15.3, 8.1 Hz, 1H, 15), 2.27 – 1.98 (m, 6H, alkyl-H), 1.94 (d, J = 1.3 Hz, 3H, CH_3), 1.86 (p, J = 6.6 Hz, 2H, alkyl-H), 1.76 (s, 3H, CH_3), 1.65 – 1.55 (m, 2H, alkyl-H), 1.53 (s, 3H, CH_3), 1.31 – 1.19 (m, 2H, alkyl-H), 0.94 (s, 3H, 7) ppm;

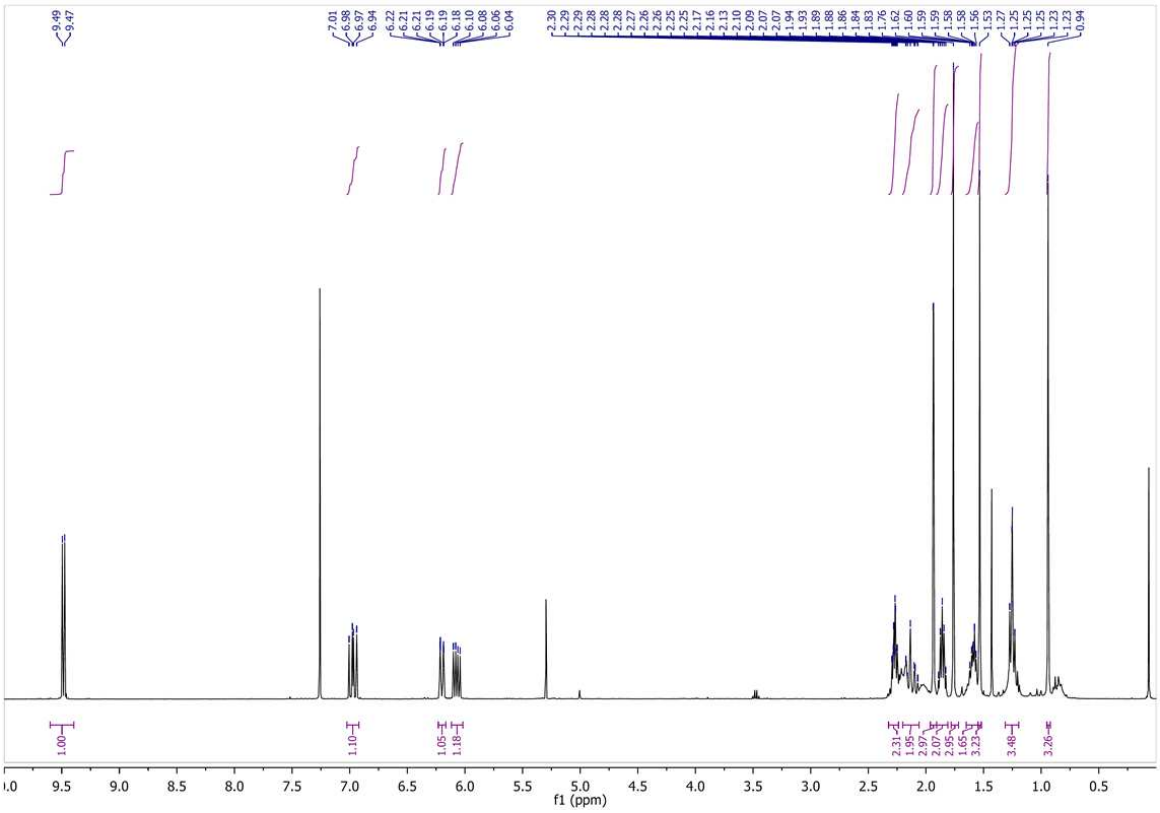
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9 1, 194.4 16, 154.1, 150.5 14, 132.4, 130.3 15, 128.7, 125.8 13, 53.4 (CH_2), 41.1 (CH_2), 40.0 (CH_2), 38.7 3, 36.2 (CH_2), 25.4 (CH_2), 24.9 7, 24.3 CH_3, 22.3 (CH_2), 22.0 CH_3, 19.7 CH_3 ppm;

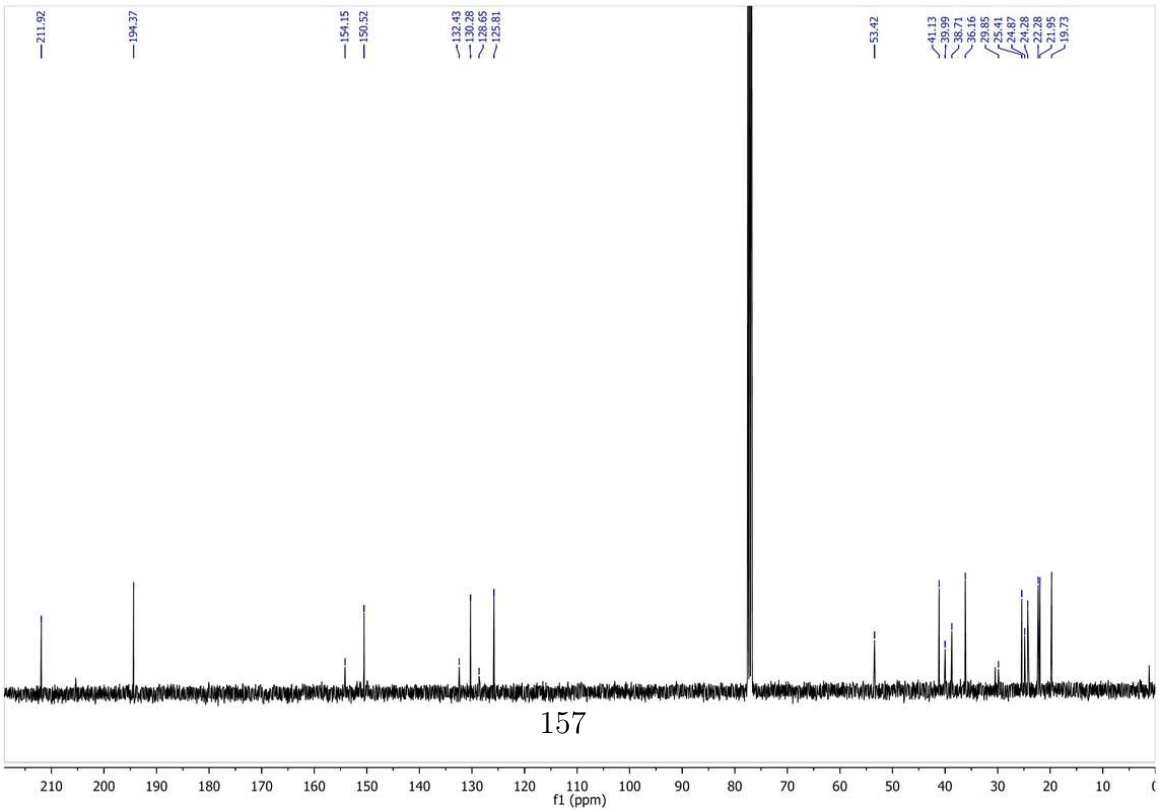
FT-IR thin film, neat (ATR): 2922, 2361, 1712, 1680, 1620 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{19}H_{28}O_2$, $[M+H]^{+\bullet}$: 289.21621 found 289.21594 (Δ = −0.91 ppm);

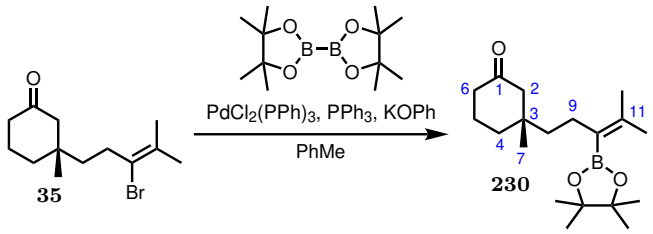
$[\alpha]_D^{25}$ = −4.9° (c = 0.46, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


9.49
9.47
7.01
6.98
6.97
6.94
6.22
6.21
6.21
6.19
6.19
6.18
6.10
6.08
6.06
6.04
2.30
2.29
2.29
2.28
2.28
2.28
2.27
2.26
2.26
2.25
2.25
2.17
2.16
2.13
2.10
2.09
2.07
2.07
1.94
1.93
1.89
1.88
1.86
1.84
1.83
1.76
1.62
1.60
1.59
1.59
1.58
1.58
1.56
1.53
1.27
1.25
1.25
1.25
1.23
1.23
0.94
1.00
1.10
1.05
1.18
2.31
1.95
2.97
2.07
2.95
1.65
3.23
3.48
3.26
f1 (ppm)


211.92
194.37
154.15
150.52
132.43
130.28
128.65
125.81
53.42
41.13
39.99
38.71
36.16
29.85
25.41
24.87
24.28
22.28
21.95
19.73
f1 (ppm)

5.3.0.21 BPin ketone 230



$PdCl_2(PPh_3)_2$ (67 mg, 0.095 mol, 0.055 mol equiv), PPh_3 (49 mg, 0.19 mmol, 0.11 mol equiv), bispinacoldiboron (443 mg, 1.74 mmol, 1.03 mol equiv) and potassium phenoxide (315 mg, 2.39 mmol, 1.4 mol equiv) were added to a flame dried round bottom flask equipped with a stirrer bar and rubber septum. Three cycles of vacuum and back filling with N_2 were then performed, after which bromoketone **35** (471 mg, 1.72 mmol, 1.0 mol equiv) was added as a solution in dry/degassed PhMe (9.2 mL). The reaction was heated to 70 °C and stirred for 2 days. Both TLC and ^{1}H NMR spectroscopy did not conclusively yield insight to reaction progress. Water was added and the biphasic mixture was extracted (3x) with benzene. The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) followed by semi-preparative HPLC (ZORBAX CN, 2 mL/min 97:3 hexane:IPA) to furnish trace quantities of the title compound (2.5 mg) sufficient for characterisation.

R_f = 0.36 (30% Et_2O/*n*-pentane, UV active);

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.27 (t, J = 6.8 Hz, 2H, alkyl-H), 2.24 – 2.01 (m, 4H, alkyl-H), 1.94 (s, 3H, CH_3), 1.92 – 1.79 (m, 2H, alkyl-H), 1.70 (s, 3H, CH_3), 1.70 – 1.48 (m, 2H, alkyl-H), 1.25 (s, 12H, BPin-Me), 1.24 – 1.13 (m, 2H,

alkyl-H), 0.95 (s, 3H, 7) ppm;

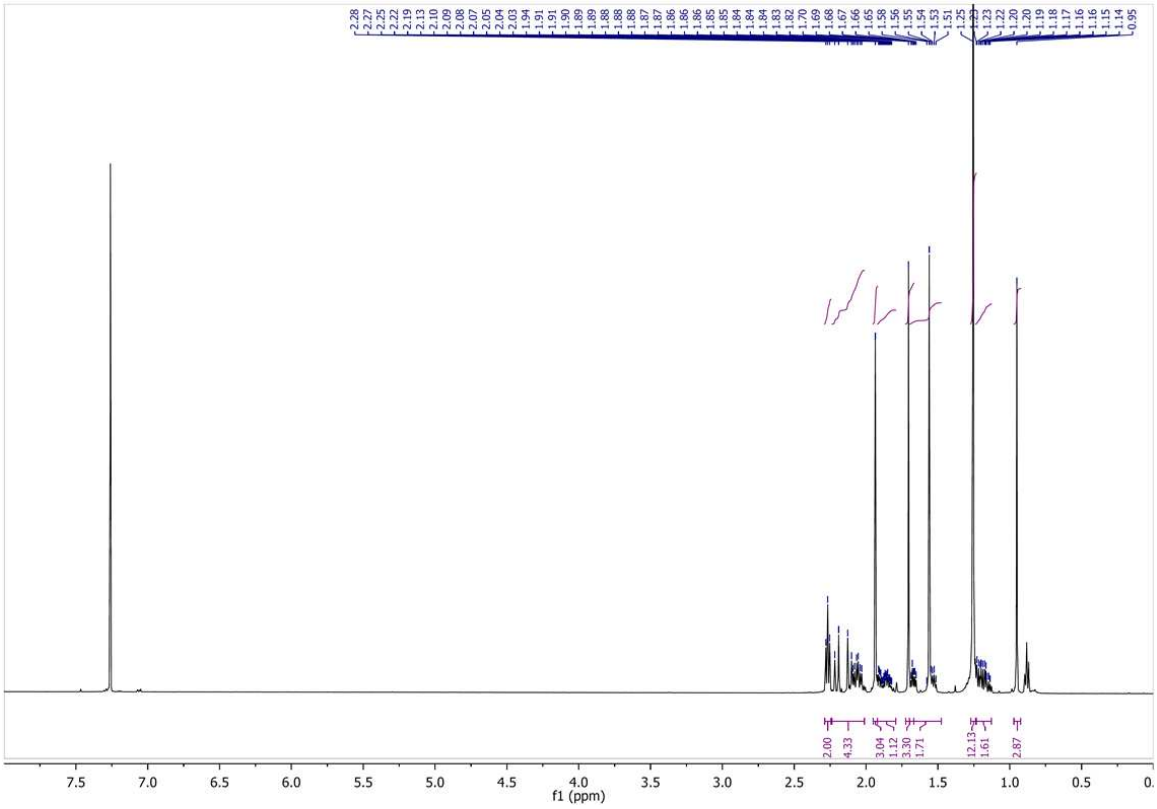
^{13}C NMR (126 MHz, $CDCl_3$): δ 212.6 1, 147.2 11, 82.9 BPin-C, 54.0 (CH_2), 41.7 (CH_2), 41.2 (CH_2), 38.8 3, 35.6 (CH_2), 25.2 (CH_2), 25.1 7, 25.0 BPin-Me, 24.8 CH_3, 22.2 (CH_2), 20.7 CH_3 ppm;

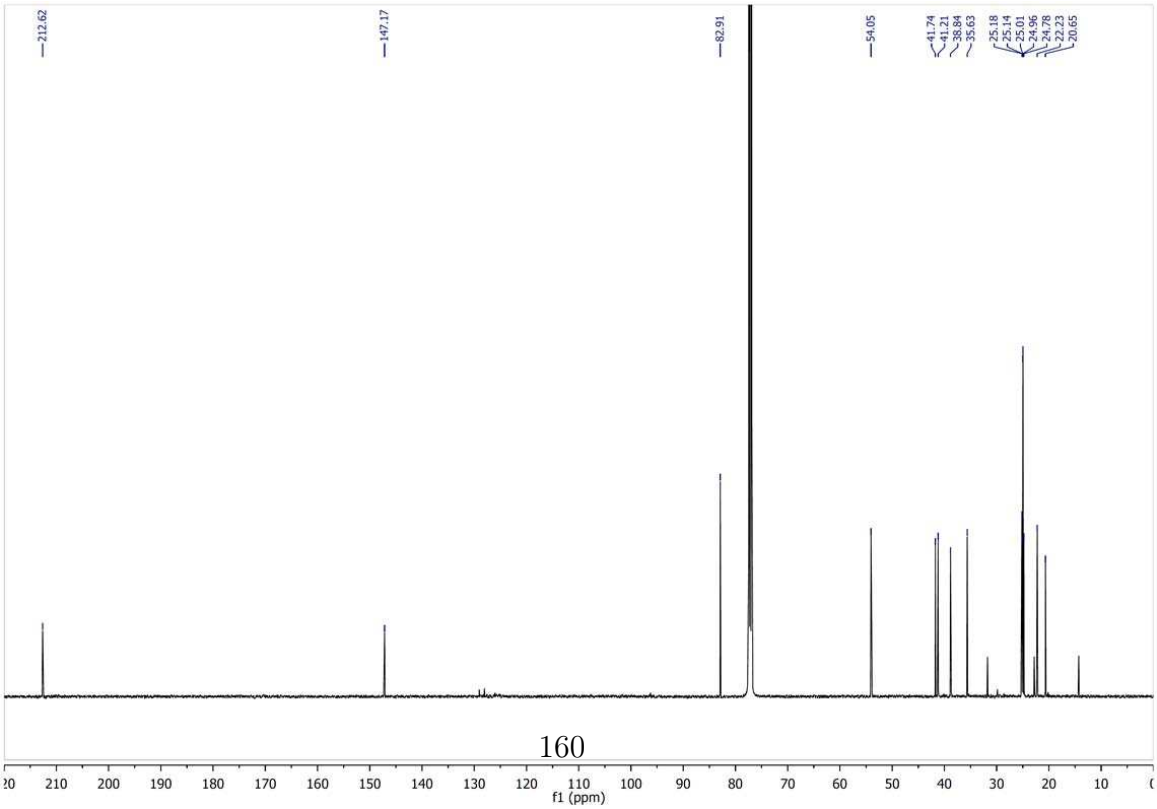
FT-IR thin film, neat (ATR): 2975, 2363, 1713, 1373, 1352, 1294 cm^{-1};

HRMS ($APCI^+$): calculated for $C_{19}H_{34}O_3{}^{10}B$, $[M+H]^{+\bullet}$: 320.26318 found 320.26328 (Δ = 0.29 ppm);

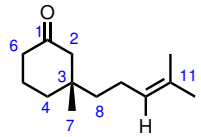
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 5.4° (c = 0.25, CH_2Cl_2), based on a sample of 62% *ee*;

$^{1}H/^{13}C$ NMR


2.28 2.27 2.25 2.22 2.19 2.13 2.10 2.09 2.08 2.07 2.05 2.04 2.03 1.94 1.91 1.90 1.89 1.88 1.88 1.88 1.87 1.87 1.86 1.86 1.86 1.85 1.85 1.84 1.84 1.84 1.83 1.82 1.70 1.69 1.68 1.67 1.66 1.65 1.58 1.56 1.55 1.54 1.53 1.51 1.25 1.23 1.22 1.20 1.20 1.19 1.18 1.17 1.16 1.15 1.14 0.95
2.00 4.33 3.04 1.12 3.30 1.71 12.13 1.61 2.87
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
f1 (ppm)


212.62
147.17
82.91
54.05
41.74
41.21
38.84
35.63
25.18
25.14
25.01
24.96
24.78
22.23
20.65
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

(*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)cyclohexan-1-one 231



231

This product was isolated from the reaction mixture when impure **50** contamined with pinacol was used.

R_f = 0.38 (30% Et_2O/*n*-pentane, stains pale blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (ddq, J = 8.5, 5.7, 1.4 Hz, 1H, 10), 2.31 – 2.24 (m, 2H, 6), 2.23 – 2.09 (m, 2H, 5), 1.97 – 1.82 (m, 4H, 8/9), 1.67 (d, J = 1.4 Hz, 3H, 12), 1.65 – 1.51 (m, 2H, 2), 1.59 (d, J = 1.3 Hz, 3H, 13), 1.33 – 1.24 (m, 2H, 4), 0.93 (s, 3H, 7) ppm;

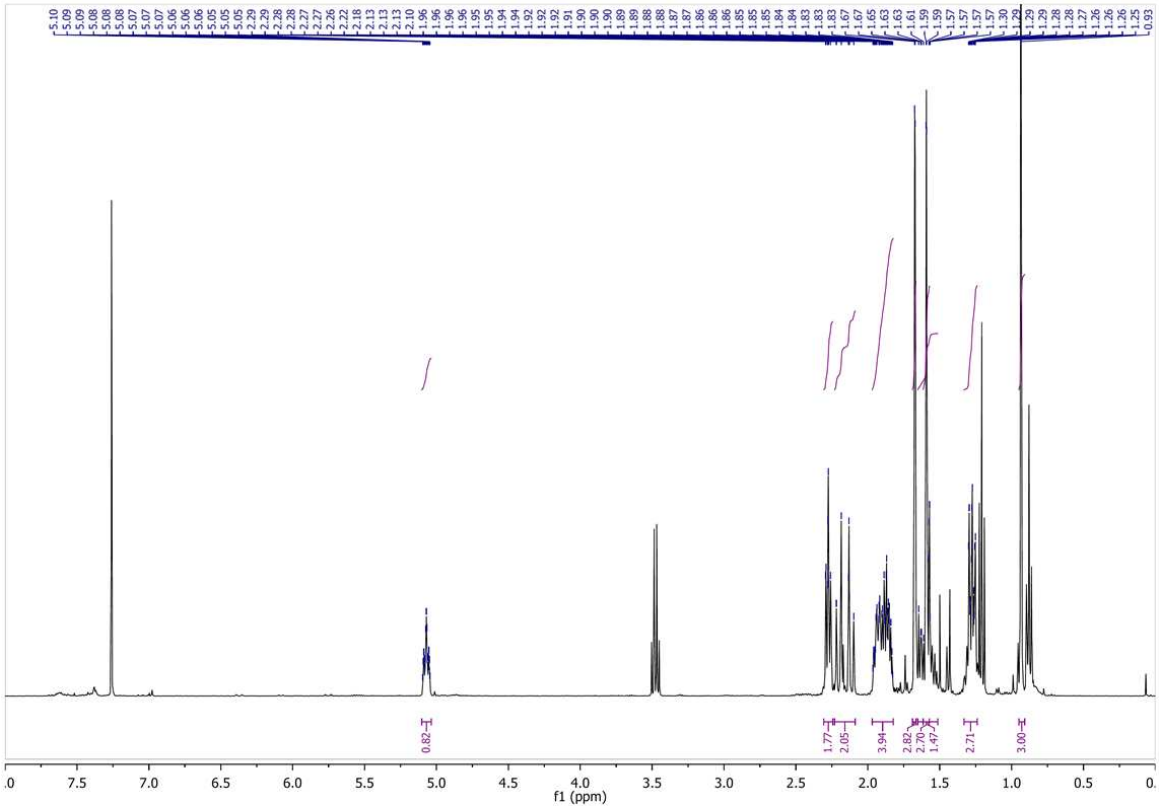
^{13}C NMR (101 MHz, $CDCl_3$): δ 212.5 1, 131.7 11, 124.4 10, 53.9 (CH_2), 41.8 (CH_2), 41.2 (CH_2), 38.8 3, 36.0 (CH_2), 25.8 CH_3, 25.1 7, 22.3 (CH_2), 22.2 (CH_2), 17.7 CH_3 ppm;

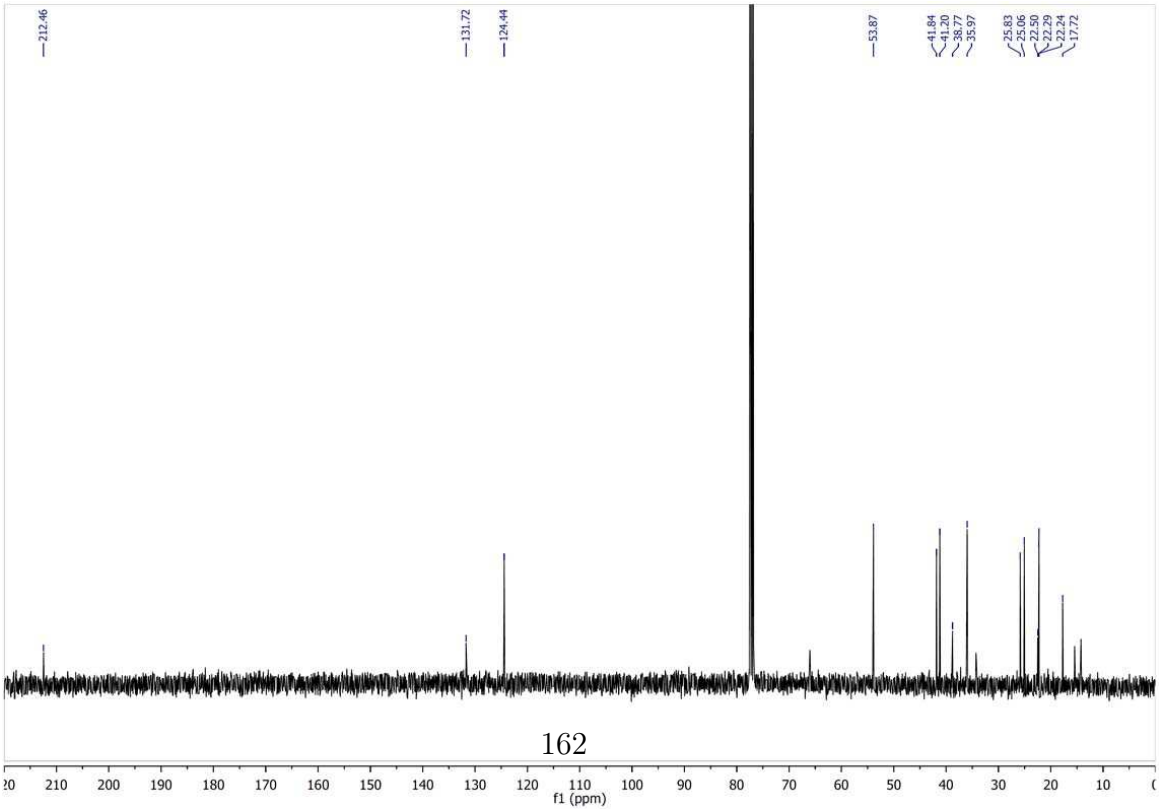
FT-IR thin film, neat (ATR): 2930, 1713, 1454 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{13}H_{23}O$, $[M+H]^{+\bullet}$: 195.17434 found 195.17459 (Δ = 1.28 ppm);

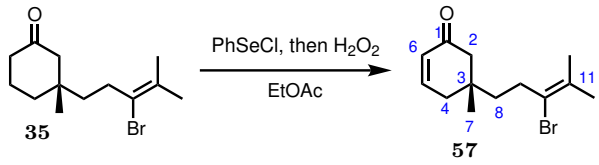
$[\alpha]_D^{25} = -1.8°$ (c = 0.46, CH_2Cl_2), based on a sample of 88% *ee*;

$^{1}H/^{13}C$ NMR


f1 (ppm)


212.46
131.72
124.44
53.87
41.84
41.20
38.77
35.97
25.83
25.06
22.50
22.29
22.24
17.72
f1 (ppm)

5.3.0.22 (*R*)-5-(3-bromo-4-methylpent-3-en-1-yl)-5-methylcyclohex-2-en-1-one 57



Phenyl selenium chloride (781 mg, 4.07 mmol, 1.2 mol equiv) was added to a flame dried vial equipped with a stirrer bar and rubber septum. Three cycles of vacuum and back filling with N_2 were then performed, after which bromoketone **35** (925 mg, 3.39 mmol, 1.0 mol equiv) was added as a solution in ethyl acetate (27 mL). After stirring for 1 hour TLC indicated complete consumption of starting material. The reaction mixture was washed with water, $Na_2CO_{3(aq)}$, dried over $MgSO_4$ then diluted in 200 mL EtOAc. Hydrogen peroxide (1.0 mL of a 30% solution in water, 5.9 mmol, 1.7 mol equiv) was added dropwise over 10 minutes, ensuring the temperature did not exceed 40 °C. The cloudy solution was stirred for 4 hours before being washed (H_2O then $Na_2CO_{3(aq)}$). The aqueous phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a yellow oil (491 mg, 1.81 mmol, 53% yield).

R_f = 0.22 (30% Et_2O/*n*-pentane, stains grey/purple with *p*-anisaldehyde);
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (dtd, J = 9.8, 4.3, 3.7, 1.2 Hz, 1H, 6), 6.04 (dd, J = 10.1, 2.1 Hz, 1H, 5), 2.56 – 2.37 (m, 2H, 9), 2.37 – 2.30 (m, 2H, 2), 2.30 – 2.15 (m, 2H, 4), 1.83 (d, J = 1.5 Hz, 3H, CH_3), 1.73 (d, J = 1.5 Hz, 3H, CH_3), 1.62 – 1.53 (m, 2H, 8), 1.04 (d, J = 1.6 Hz, 3H, 7) ppm;

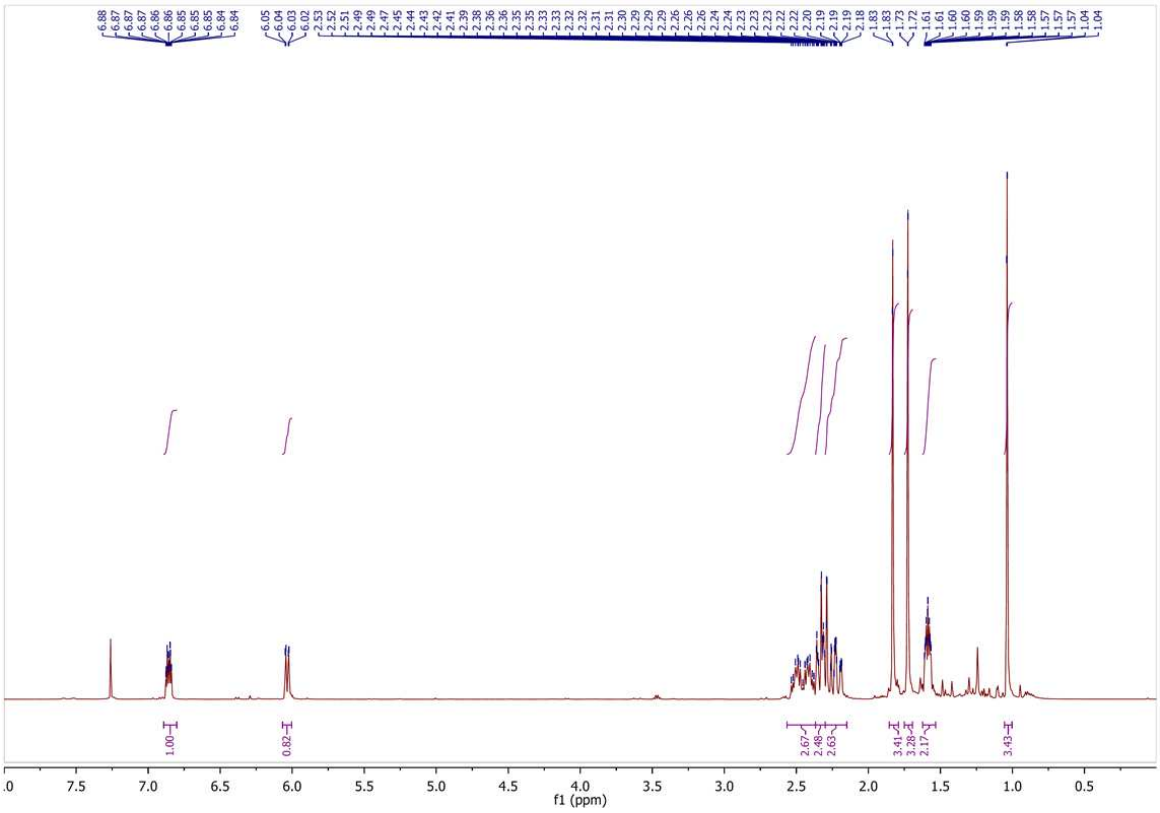
^{13}C NMR (101 MHz, $CDCl_3$): δ 199.6 1, 148.1 6, 130.4 11, 129.3 5, 121.1 10, 50.2 2, 39.9 8, 38.3 4, 36.4 3, 32.6 9, 25.4 CH_3, 24.7 7, 20.2 CH_3 ppm;

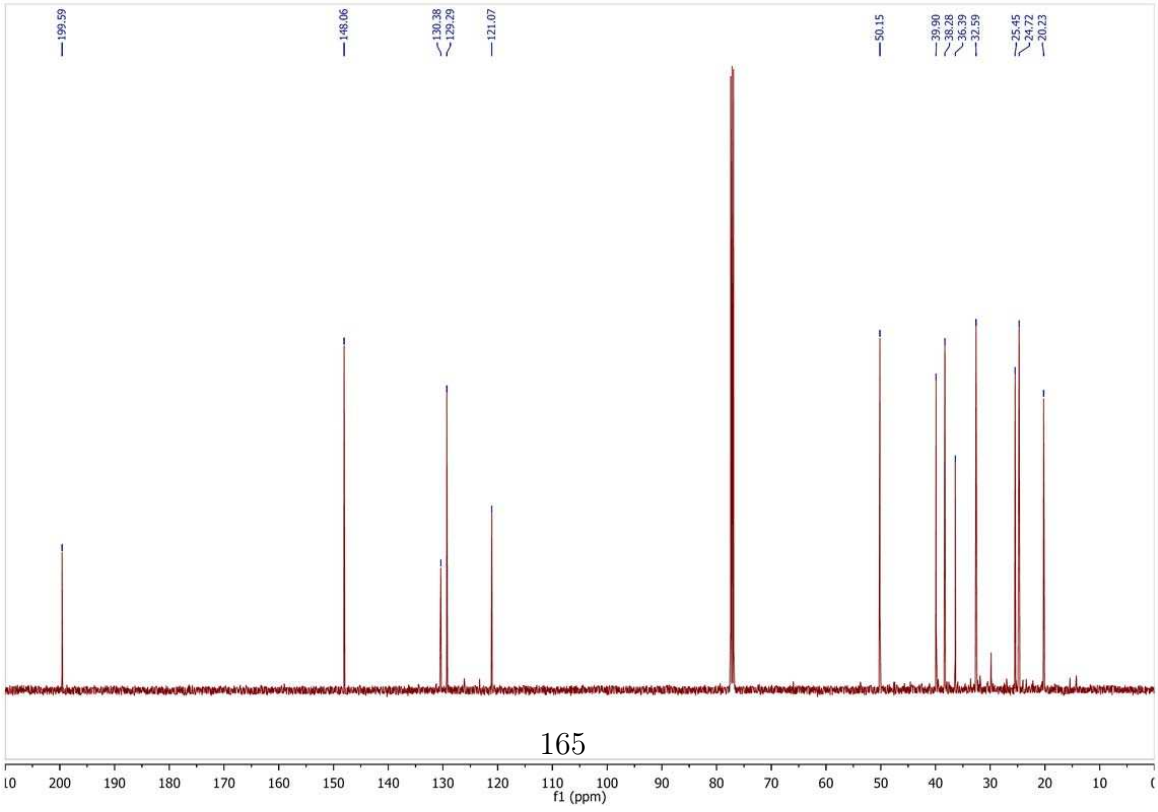
FT-IR thin film, neat (ATR): 2918, 2360, 1678 cm^{-1};

HRMS ($APCI^+$): calculated for $C_{13}H_{20}O^{79}Br$, $[M+H]^{+\bullet}$: 271.06920 found 271.06955 (Δ = 1.27 ppm);

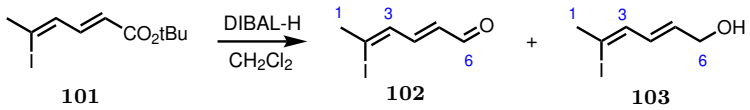
$[\alpha]_D^{25} = -7.5°$ (c = 1.0, CH_2Cl_2), based on a sample of 41% *ee*;

$^{1}H/^{13}C$ NMR


f1 (ppm)


199.59
148.06
130.38
129.29
121.07
50.15
39.90
38.28
36.39
32.59
25.45
24.72
20.23
f1 (ppm)

5.3.0.23 Iodoaldehyde 102 and iodoalcohol 103



101 **102** **103**

tert-Butyl ester **101** (0.91 mL, 4.0 mmol, 1.0 mol equiv) and dry CH_2Cl_2 (64 mL) was added to a flame dried round bottom flask equipped with a rubber septum and stirrer bar. After cooling −78 °C, diisobutylaluminium hydride (4.4 mL of a 1M solution in CH_2Cl_2, 4.4 mol equiv, 1.1 mol equiv) was added over 30 min via syringe pump. After 1 hour, TLC indicated the formation of the desired product as well as the alcohol. Saturated Rochelle's salt solution was added and the reaction warmed to room temperature. After stirring for 1 hour, the emulsion was observed to disappear. The biphasic mixture was extracted (3xCH_2Cl_2), the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (10–20% then flushed with 50% Et_2O/*n*-pentane, silica column) to give the aldehyde as an orange oil (500 mg, 2.25 mmol, 56% yield) and alcohol as a yellow oil (168 mg, 0.75 mmol, 19% yield) (3:1 aldehyde:alcohol ratio).

Aldehyde 102

$\mathbf{R_f}$ = 0.43 (30% Et_2O/*n*-pentane, stains with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (d, J = 7.9 Hz, 1H, 6), 7.14 (dd, J = 15.3, 10.2 Hz, 1H, 4), 6.44 – 6.34 (m, 1H, 3), 6.31 – 6.18 (m, 1H, 5), 2.73 (d, J = 1.4 Hz, 3H, 1) ppm;

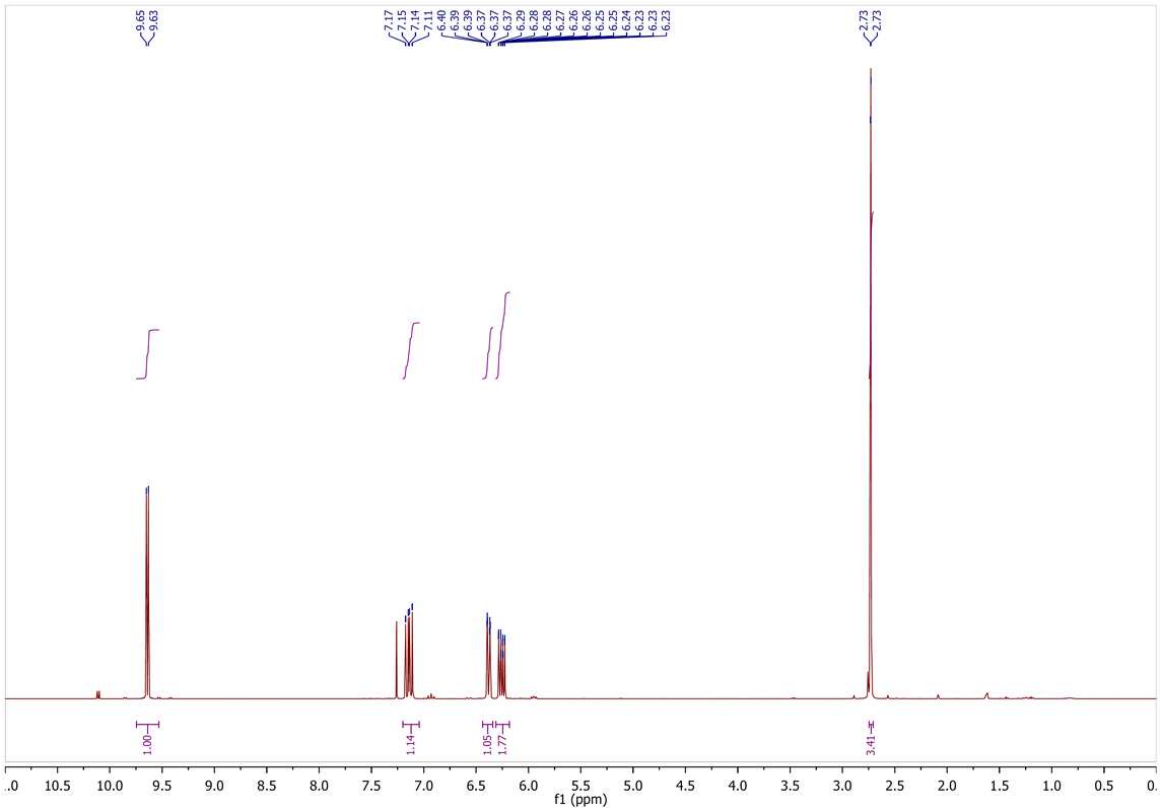
^{13}C NMR (101 MHz, $CDCl_3$): δ 193.8 6, 153.3 4, 133.2 3, 133.0 5, 115.4 2,

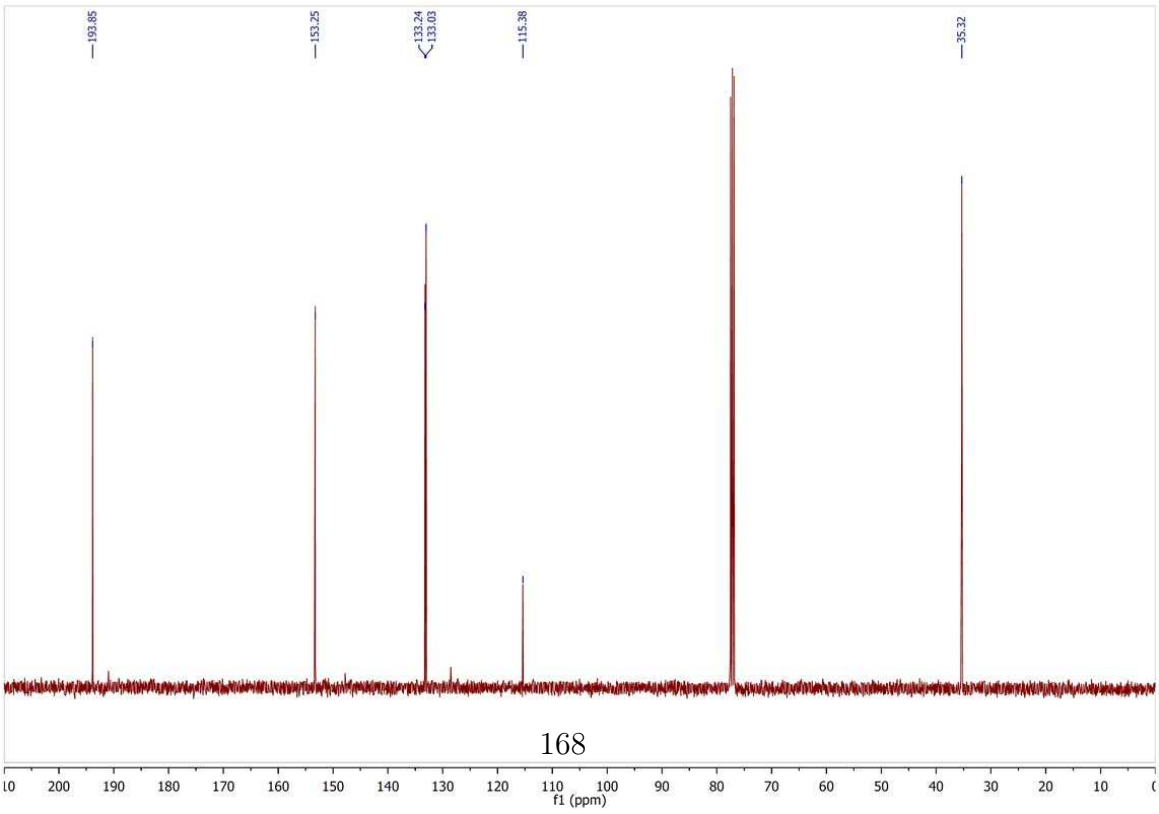
35.3 1 ppm;

FT-IR thin film, neat (ATR): 2814, 1680, 1622, 1119 cm^{-1};

HRMS ($APCI^+$): calculated for $C_6H_8O^{127}I$, $[M+H]^{+\bullet}$: 222.96143 found 222.96169 (Δ = 1.12 ppm);

$^{1}H/^{13}C$ NMR


9.65
9.63
7.17
7.15
7.14
7.11
6.40
6.39
6.39
6.37
6.37
6.37
6.29
6.28
6.28
6.27
6.26
6.26
6.25
6.25
6.24
6.23
6.23
6.23
2.73
2.73
1.00
1.14
1.05
1.77
3.41
f1 (ppm)


193.85
153.25
133.24
133.03
115.38
35.32
f1 (ppm)

Alcohol 103

R_f = 0.11 (30% Et_2O/*n*-pentane, stains with $KMnO_4$);

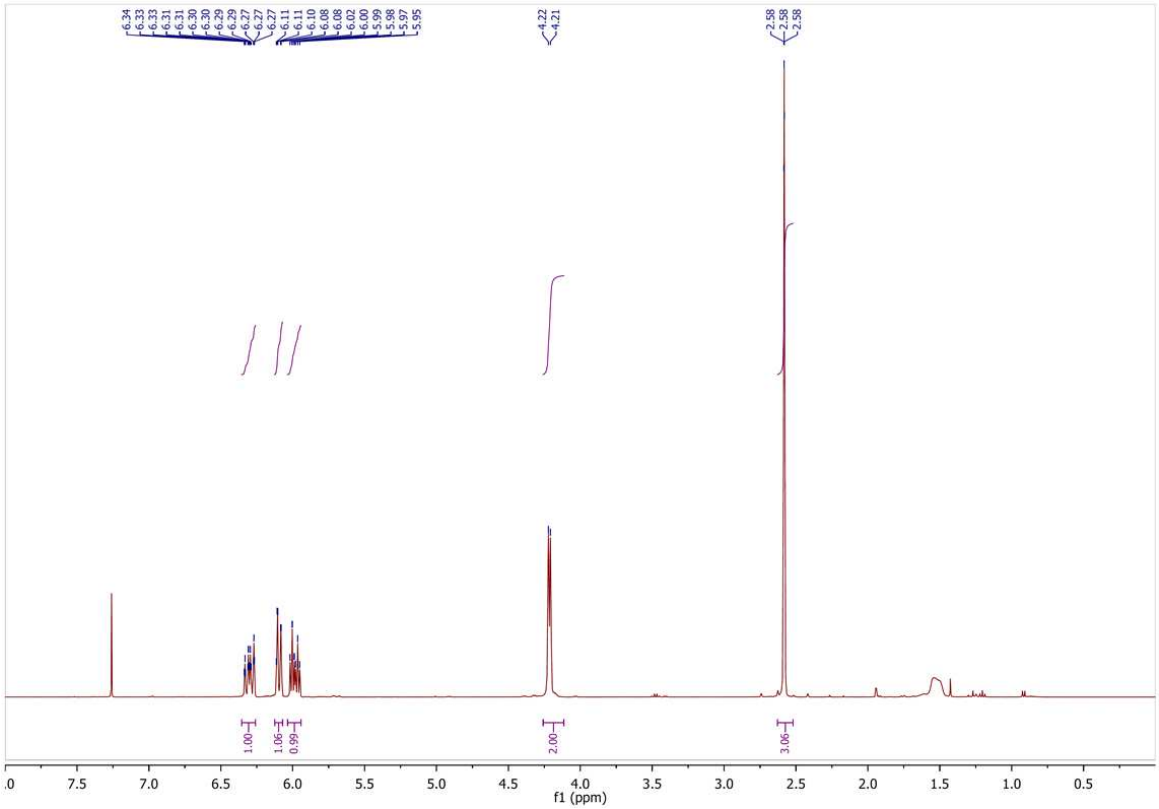
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (ddt, J = 15.3, 9.6, 1.6 Hz, 1H, 4), 6.09 (dd, J = 9.6, 1.6 Hz, 1H, 3), 5.98 (dt, J = 15.3, 5.8 Hz, 1H, 5), 4.21 (d, J = 5.8 Hz, 2H, 6), 2.58 (d, J = 1.6 Hz, 3H, 1) ppm;

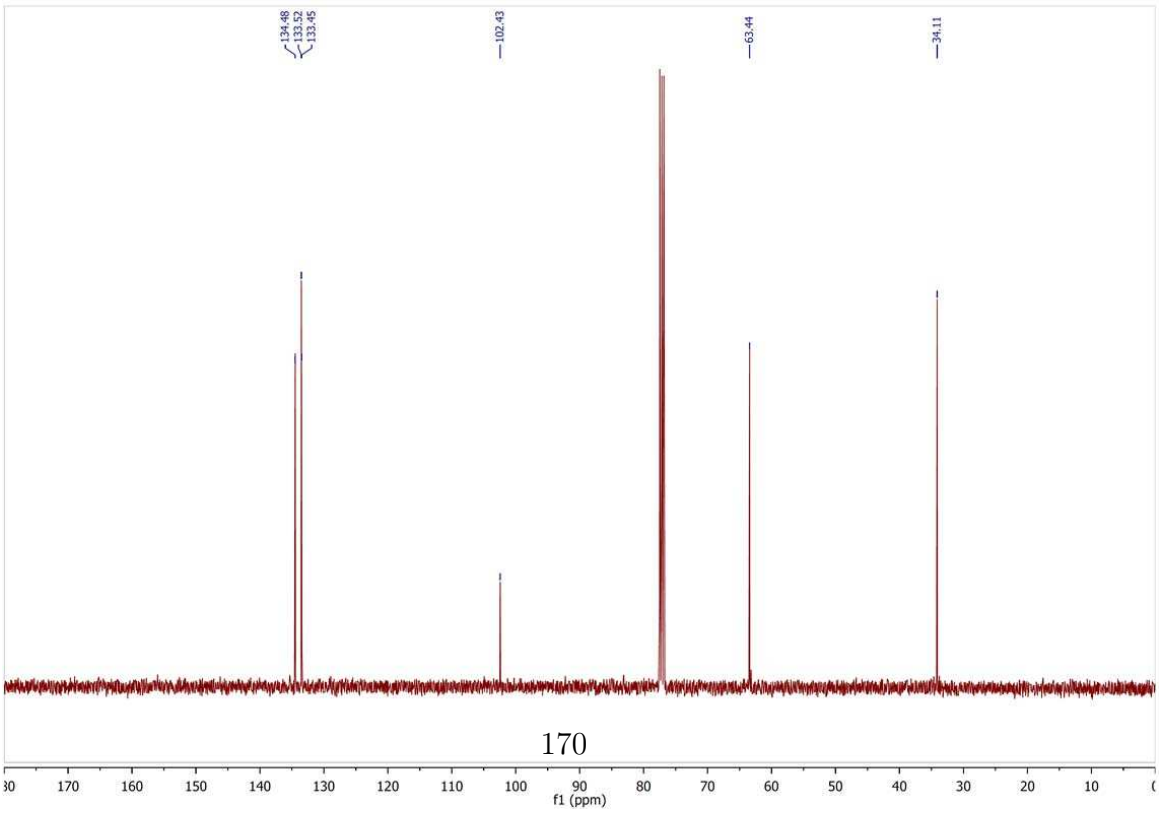
^{13}C NMR (101 MHz, $CDCl_3$): δ 134.5 5, 133.5 3, 133.5 4, 102.4 2, 63.4 6, 34.1 1 ppm;

FT-IR thin film, neat (ATR): 3317, 2860, 1424, 1097, 1061, 966 cm^{-1};

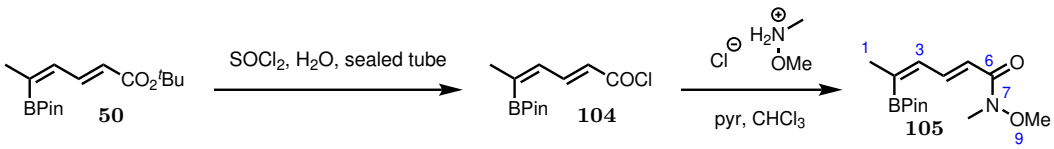
HRMS (EI^+): spectrum was collected with an ionisation energy of 20eV. Calculated for C_6H_9IO, $[M]^{+\bullet}$: 223.9693 found 223.9692 (Δ = 0.26 ppm);

$^{1}H/^{13}C$ NMR


6.34
6.33
6.33
6.31
6.31
6.30
6.30
6.29
6.29
6.27
6.27
6.27
6.11
6.11
6.10
6.08
6.08
6.02
6.00
5.99
5.98
5.97
5.95
4.22
4.21
2.58
2.58
2.58
1.00
1.06
0.99
2.00
3.06
f1 (ppm)


134.48
133.52
133.45
102.43
63.44
34.11
f1 (ppm)

5.3.0.24 (2E,4E)-N-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,4-dienamide 105



The process for converting *tert*-butyl ester to acid chloride is based on a literature procedure.[46] To a 7 mL vial, was added *tert*-butyl ester **50** (294 mg, 1.00 mmol, 1.00 mol equiv) and thionyl chloride (1 mL, 13.8 mmol, 13.8 mol equiv). Water (18μL, 1.0 mmol, 1.00 mol equiv) was then added and the vial was immediately capped. The sealed tube was allowed to stir overnight behind a blast shield. After 24 hours had elapsed, the vial was opened (caution: contents under pressure!) and dry toluene (1 mL) added. The solvents were removed *in vacuo* and this process repeated twice to azeotropically remove any residual thionyl chloride. The resulting black oil was used in the next step immediately.

To a round bottom flask containing the crude acid chloride, was added *N,O*-dimethylhydroxylamine hydrochloride (100 mg, 1.64 mmol, 1.64 mol equiv) followed by dry chloroform (10 mL). The reaction was cooled to 0 °C and pyridine (0.17 mL, 2.0 mmol, 2.0 mol equiv) added drop wise. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and allowed to stir for an additional 1 hour. The solvents were removed *in vacuo* and the residue was dissolved in 10 mL 1:1 CH_2Cl_2:Et_2O and washed with brine (lower phase). The product was purified by flash chromatography (30% EtOAc/*n*-hexane, load with *n*-hexane) to give (176 mg, 0.63 mmol, 63% yield) yellow oil.

R_f = 0.31 (50% EtOAc/petrol, stains green with *p*-anisaldehyde);

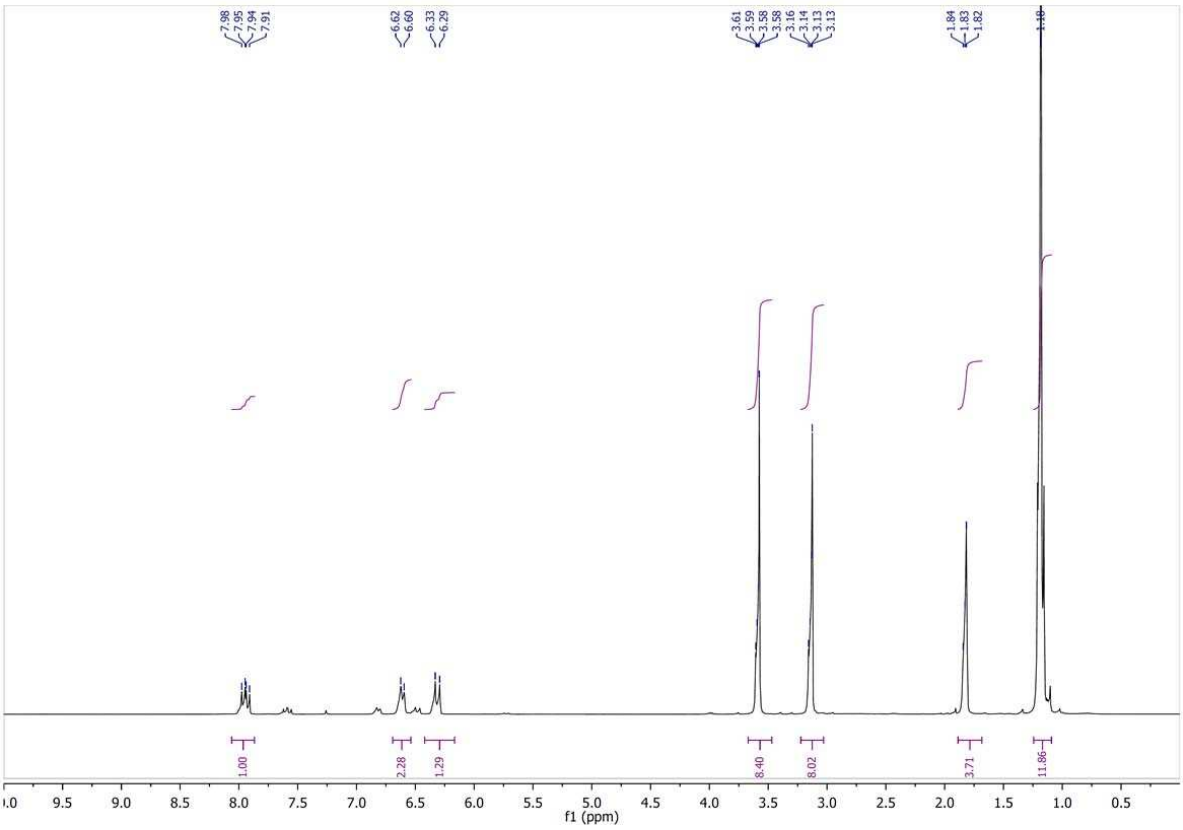
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J = 15.1, 11.6 Hz, 1H, 4), 6.61 (d, J = 11.6 Hz, 1H, 3), 6.31 (d, J = 15.1 Hz, 1H, 5), 3.67 – 3.47 (m, 3H, O-Me), 3.22 – 3.03 (m, 3H, N-Me), 1.82 (s, 3H, 1), 1.18 (s, 12H, BPin-Me) ppm;

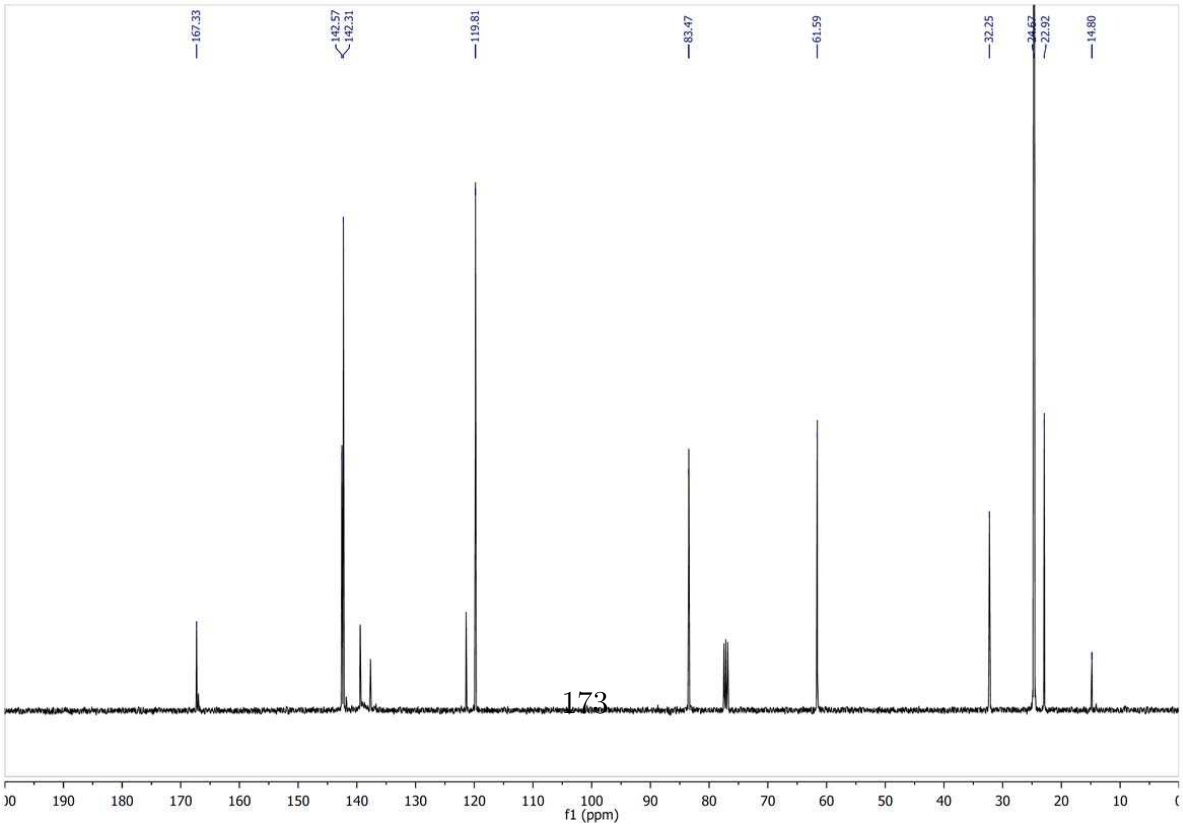
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 6, 142.6 4, 142.3 3, 119.8 5, 83.5 BPin-C, 61.6 O-Me, 32.3 N-Me, 24.7 BPin-Me, 22.9 1, 14.8 ppm;

FT-IR thin film, neat (ATR): 2978, 1653, 1614, 1591, 1369, 11143 cm^{-1};

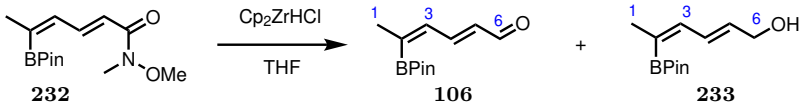
HRMS (APCI$^+$): calculated for $C_{14}H_{25}O_4NB$, $[M+1]^{+\bullet}$: 281.19075 found 281.19089 (Δ = 0.5 ppm);

$^{1}H/^{13}C$ NMR


7.98
7.95
7.94
7.91
6.62
6.60
6.33
6.29
3.61
3.59
3.58
3.58
3.16
3.14
3.13
3.13
1.84
1.83
1.82
1.18
1.00
2.28
1.29
8.40
8.02
3.71
11.86
f1 (ppm)


167.33
142.57
142.31
119.81
83.47
61.59
32.25
24.67
22.92
14.80
f1 (ppm)

5.3.0.25 2E,4E)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,4-dienal 106



To a 7 mL vial containing Schwartz reagent Cp_2ZrHCl (86 mg, 0.33 mmol, 1.2 mol equiv) in tetrahydrofuran (3 mL), was added Weinreb amide **105** (77 mg, 0.27 mmol, 1.0 mol equiv) in tetrahydrofuran (2 mL). After 5 minutes the solution became clear yellow and TLC showed the complete disappearance of the starting amide. The reaction was quenched by the addition of silica gel and the solvent was removed *in vacuo*. The aldehyde product **106** was obtained by directly loading the silica gel onto a silica plug and eluting with 20% EtOAc/*n*-hexane (13 mg, 0.059 mmol, 22% yield). If the reaction is left on too long, the alcohol **233** is obtained instead (11 mg, 0.048 mmol, 18% yield). No double bond isomerisation was observed under the reaction conditions.

α,β-unsaturated aldehyde 106

R_f = 0.58 (30% EtOAc/petrol, stains green with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (d, J = 8.1 Hz, 1H, 6), 7.93 (dd, J = 15.3, 11.4 Hz, 1H, 4), 6.97 – 6.66 (m, 1H, 3), 6.09 (ddt, J = 15.2, 8.1, 0.7 Hz, 1H, 5), 1.98 (d, J = 1.7 Hz, 3H, 1), 1.32 (s, 12H, BPin-Me) ppm;

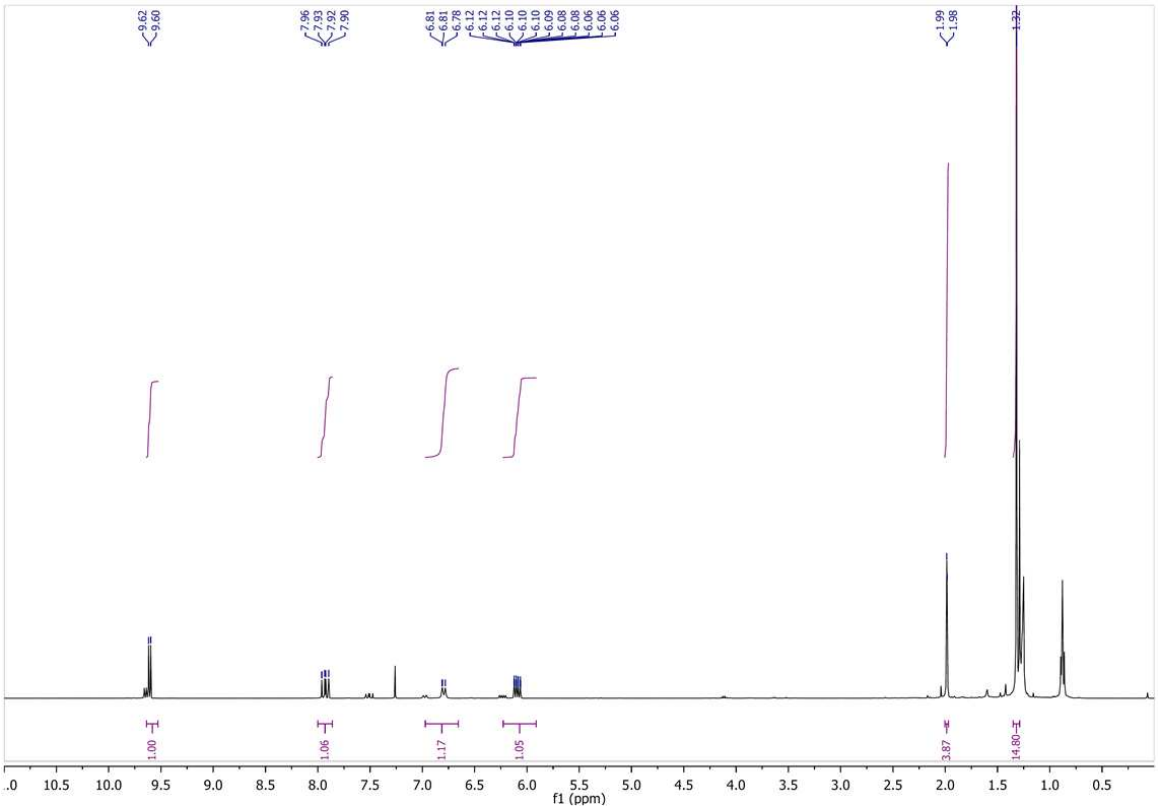
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7 6, 151.5 4, 142.1 3, 132.5 5, 84.0 BPin-C, 25.0 BPin-Me, 23.6 1 ppm;

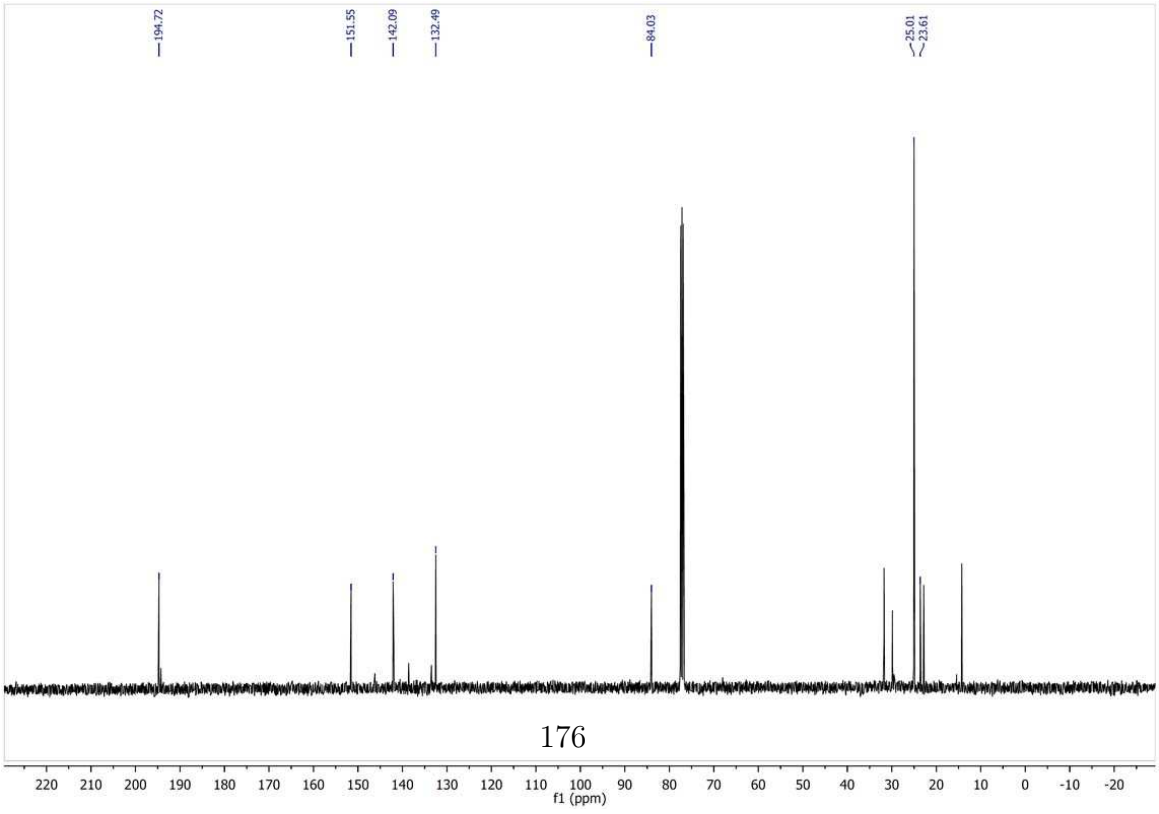
FT-IR thin film, neat (ATR): 2979, 1678, 1269, 1143 cm^{-1};

HRMS ($APCI^+$): calculated for $C_{12}H_{20}O_3B$, $[M+H]^{+\bullet}$: 222.15363 found 222.15396

(Δ = 1.48 ppm);

$^{1}H/^{13}C$ NMR


9.62
9.60
7.96
7.93
7.92
7.90
6.81
6.81
6.78
6.12
6.12
6.12
6.10
6.10
6.10
6.09
6.08
6.08
6.06
6.06
6.06
1.99
1.98
1.32
1.00
1.06
1.17
1.05
3.87
14.80
f1 (ppm)


194.72
151.55
142.09
132.49
84.03
25.01
23.61
f1 (ppm)

Allylic alcohol 233

The product was co-isolated with compound **106**.

R_f = 0.36 (30% EtOAc/petrol, stains blue with *p*-anisaldehyde);

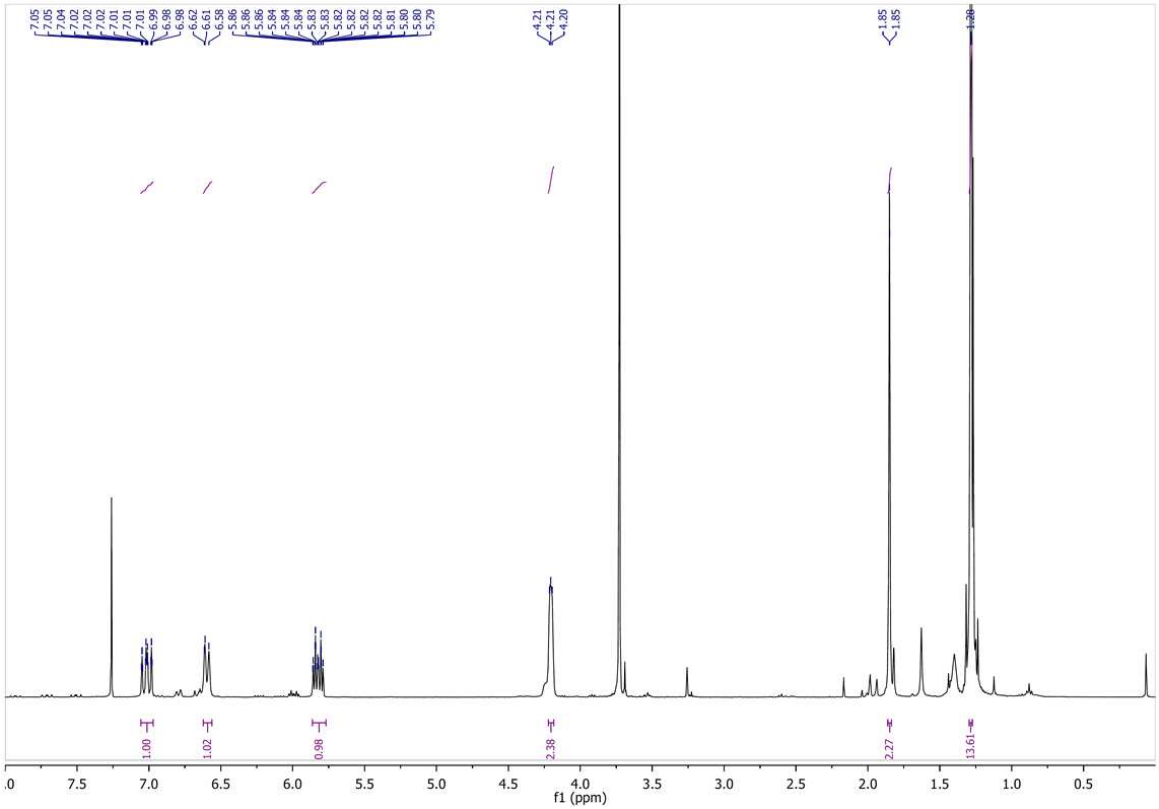
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (ddt, J = 15.2, 11.0, 1.5 Hz, 1H, 4), 6.62 – 6.56 (m, 1H, 3), 5.86 – 5.77 (m, 1H, 5), 4.22 – 4.18 (m, 2H, 6), 1.86 – 1.84 (m, 3H, 1), 1.28 (s, 12H, BPin-Me) ppm;

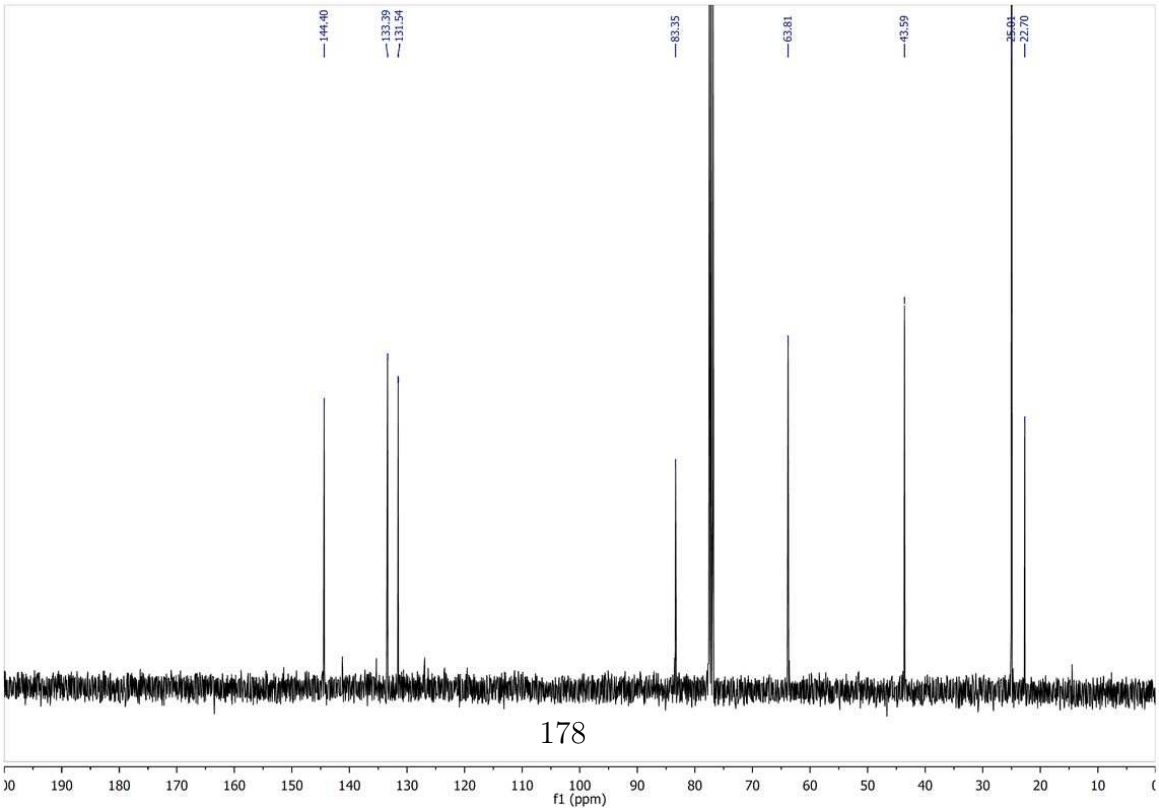
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 3, 133.4 5, 131.5 4, 83.4 BPin-C, 63.8 6, 25.0 BPin-Me ppm;

FT-IR thin film, neat (ATR): 3386, 2979, 2360, 1372, 1144, 965 cm^{-1};

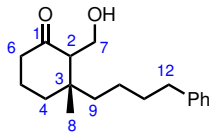
HRMS (APCI$^-$): calculated for $C_{12}H_{20}O_3B$, $[M-H]^{-\bullet}$: 222.15473 found 222.15498 (Δ = 1.14 ppm);

$^{1}H/^{13}C$ NMR


7.05
7.05
7.04
7.02
7.02
7.02
7.01
7.01
7.01
6.99
6.98
6.98
6.62
6.61
6.58
5.86
5.86
5.86
5.84
5.84
5.83
5.83
5.82
5.82
5.82
5.81
5.80
5.80
5.79
4.21
4.21
4.20
1.85
1.85
1.20
1.00
1.02
0.98
2.38
2.27
13.61
f1 (ppm)


144.40
133.39
131.54
83.35
63.81
43.59
25.01
22.70
f1 (ppm)

5.3.0.26 (2S,3R)-2-(hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one (*trans* 87)



Trans diastereomer. 1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using 4-phenyl-1-butene as the alkene. Trapping was conducted according to general procedure F. Flash chromatography (30% EtOAc/petrol) gave the product as a 1:1 separable mixture of diastereomers (colourless oil) with a combined mass of 68 mg (0.25 mmol, 50% total yield). Relative stereochemistry was assigned on the basis of NOE experiments. Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[31a] *ee* = 94%.

R_f = 0.15 (50% EtOAc/petrol, stains orange with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 3H, Ar-H), 7.23 – 7.14 (m, 2H, Ar-H), 4.03 (ddd, J = 11.4, 9.4, 4.1 Hz, 1H, 7), 3.63 (td, J = 11.4, 9.8, 3.3 Hz, 1H, 7), 2.69 – 2.55 (m, 2H, alkyl-H), 2.49 – 2.28 (m, 2H, alkyl-H), 2.46 – 2.39 (m, 1H, 2), 1.96 – 1.64 (m, 2H, Ar-H), 1.83 – 1.52 (m, 2H, alkyl-H), 1.62 – 1.55 (m, 2H, alkyl-H), 1.21 (td, J = 8.4, 8.0, 5.0 Hz, 4H, alkyl-H), 1.09 (s, 3H, 8) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0 C=O, 142.5 Ar-C, 128.5 (2C) Ar-C, 128.4 (2C) Ar-C, 125.8 Ar-C, 63.9 2, 58.4 7, 41.7 (CH_2), 41.0 3, 35.9 (CH_2), 35.7 (CH_2), 33.6 (CH_2), 32.1 (CH_2), 26.1 8, 22.8 (CH_2), 22.0 (CH_2) ppm;

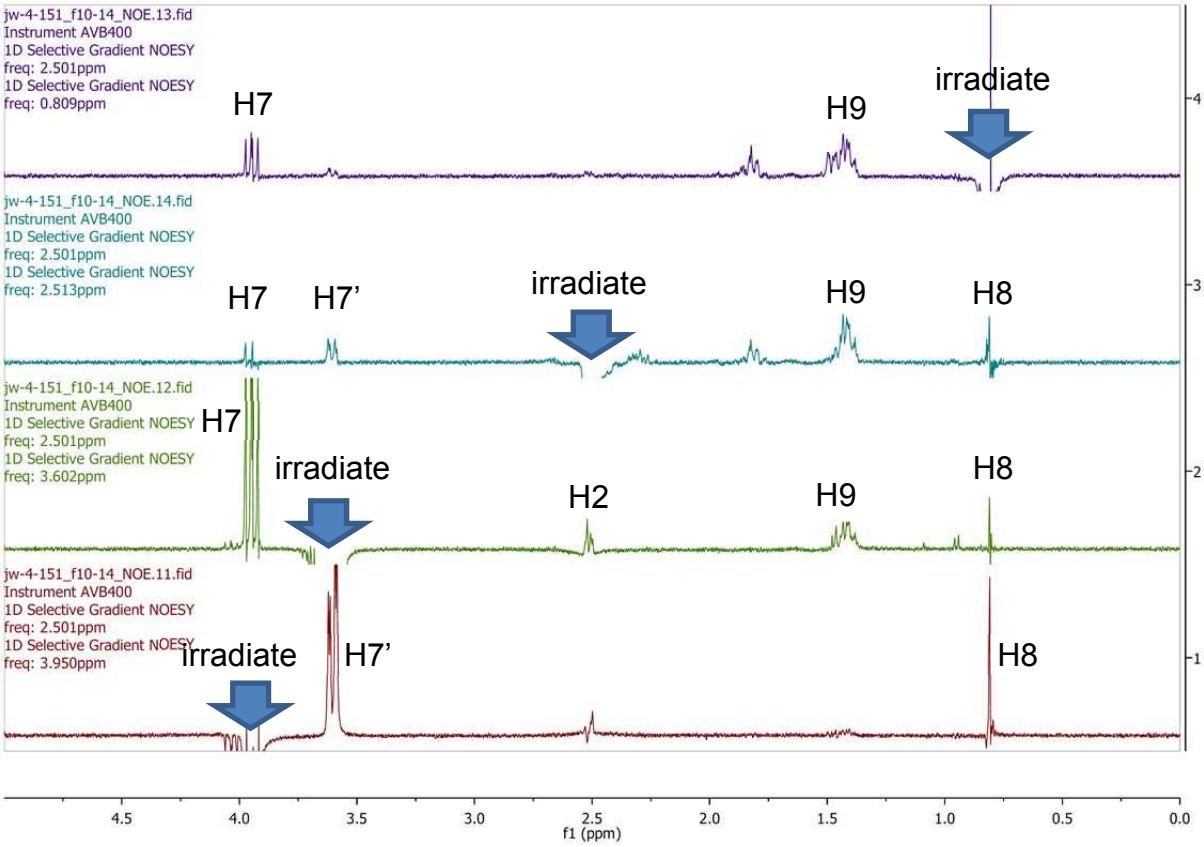
FT-IR thin film, neat (ATR): 3427, 3026, 2934, 2858, 2361, 1703, 1496, 1454,

1034 cm^{-1};

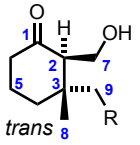
HRMS (ESI$^+$): calculated for $C_{18}H_{26}O_2{}^{23}Na$, $[M+Na]^{+\bullet}$: 297.18250 found 297.18262 (Δ = 0.39 ppm);

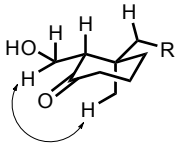
$[\alpha]_D^{25} = -3.6°$ (c = 0.40, CH_2Cl_2), based on a sample of 94% *ee*;

^{1}H/^{1}H NOE interactions:

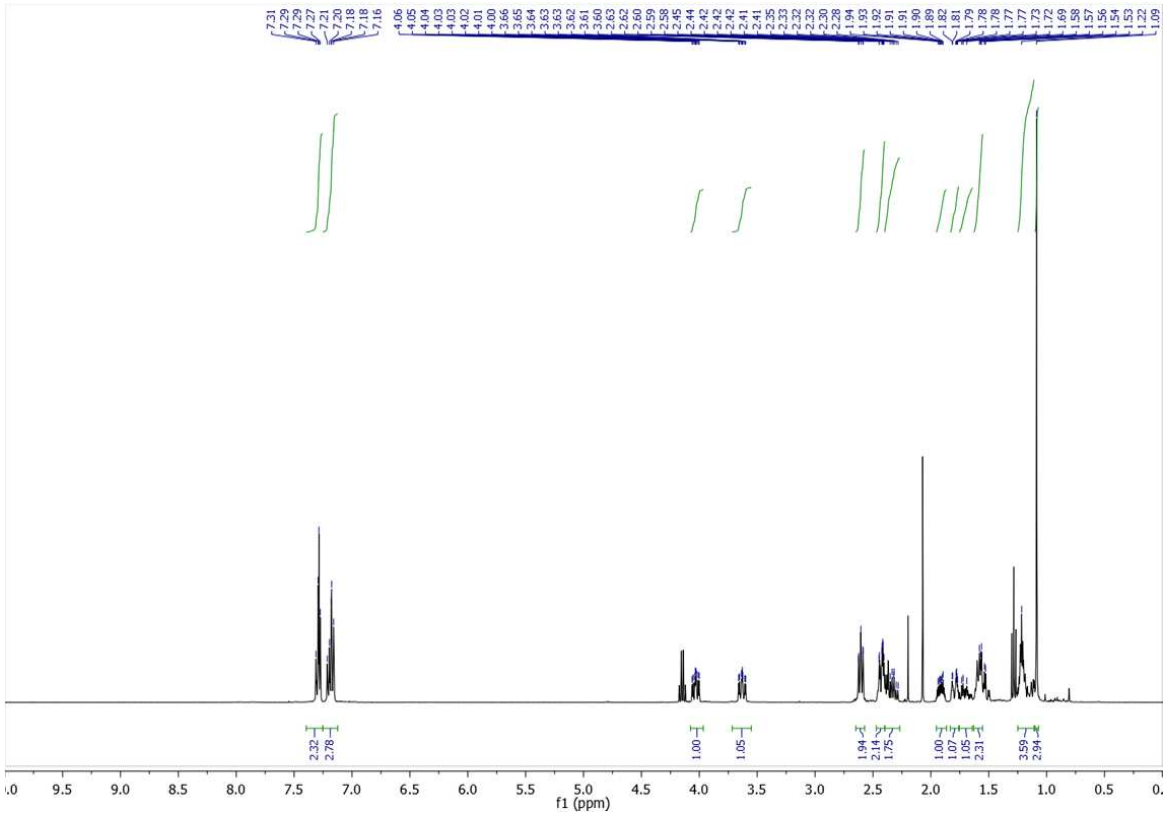


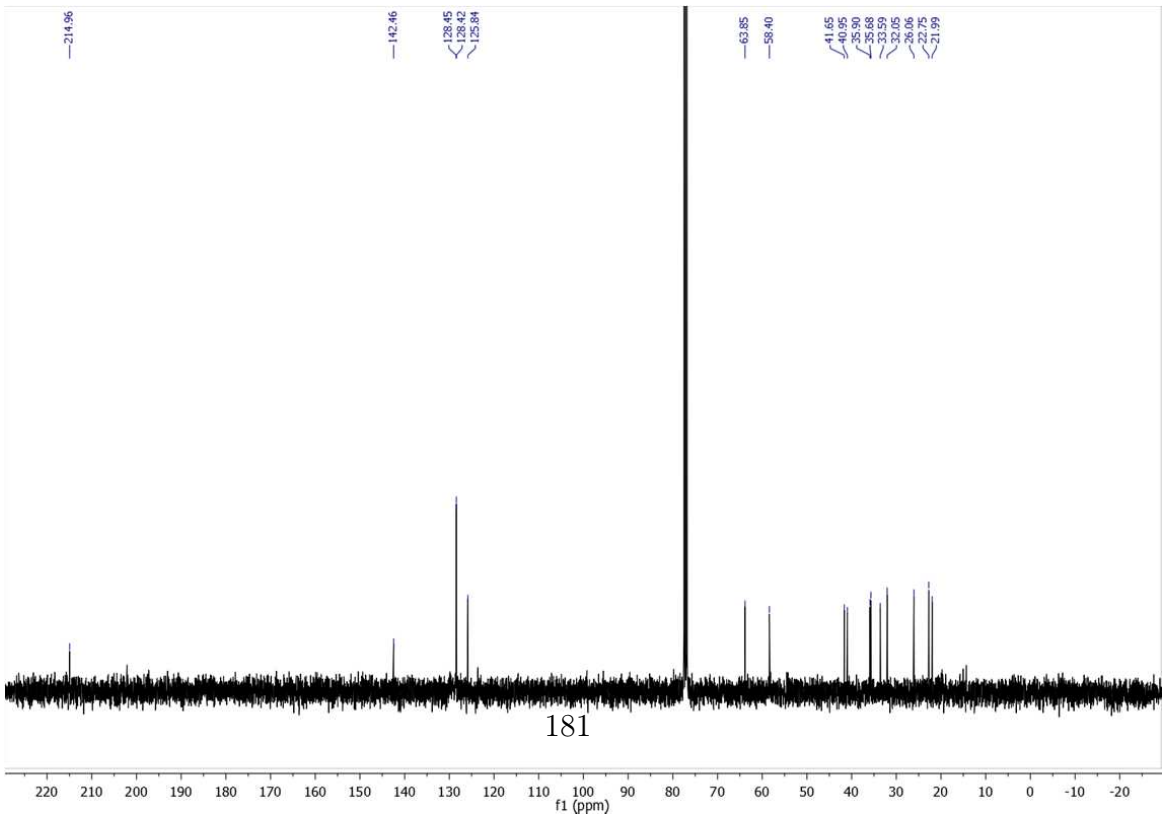
Irradiated ^{1}H	**Response (strong, medium weak)**
3.95 ppm H7	H7' strong, H8 strong
3.60 ppm H7'	H7 strong, H2 medium, H9 medium, H8 weak
2.51 ppm H2	H7 medium, H7' medium, H9 medium, H8 weak
0.81 ppm H8	H7 strong, H9 strong





$^{1}H/^{13}C$ NMR





5.3.0.27 (2R,3R)-2-(hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one (*cis* 87)

Cis diastereomer. The product was co-isolated with *trans* **87**. Relative stereochemistry was assigned on the basis of NOE experiments.

R_f = 0.25 (50% EtOAc/petrol, stains orange with *p*-anisaldehyde);

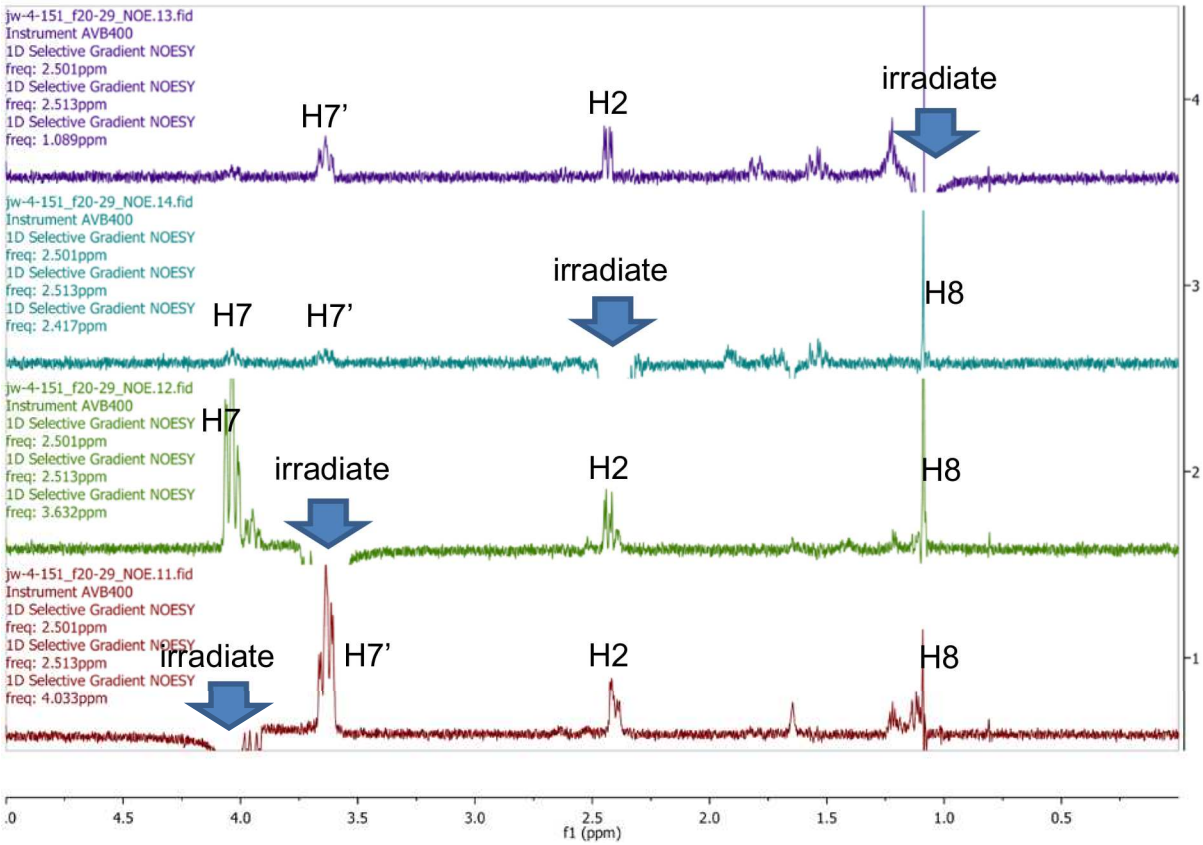
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H, Ar-H), 7.21 – 7.16 (m, 3H, Ar-H), 3.92 (ddd, J = 11.5, 9.3, 4.1 Hz, 1H, 7), 3.57 (ddd, J = 11.5, 10.0, 3.3 Hz, 1H, 7), 2.63 (td, J = 7.5, 2.7 Hz, 2H, alkyl-H), 2.49 (dd, J = 10.0, 4.1 Hz, 1H, 2), 2.45 – 2.24 (m, 2H, alkyl-H), 2.33 – 2.23 (m, 2H, alkyl-H), 2.00 – 1.73 (m, 3H, alkyl-H), 1.67 – 1.56 (m, 2H, alkyl-H), 1.50 – 1.33 (m, 4H, alkyl-H), 0.78 (s, 3H, 8) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8 C=O, 142.6 Ar-C, 128.5 (2C) Ar-C, 128.5 (2C Ar-C), 125.9 Ar-C, 59.7 2, 58.5 7, 41.7 (CH_2), 41.4 (CH_2), 41.1 3, 36.5 (CH_2), 36.0 (CH_2), 32.2 (CH_2), 23.2 (CH_2), 22.3 (CH_2), 21.6 8 ppm;

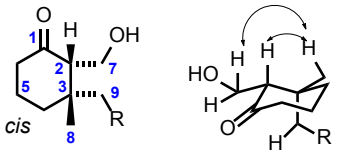
FT-IR thin film, neat (ATR): 3430, 3026, 2934, 2857, 1702, 1496, 1454, 1351, 1228, 1179, 1037 cm^{-1};

$[\alpha]_D^{25} = -5.3°$ (c = 1.1, CH_2Cl_2), based on a sample of 94% *ee*;

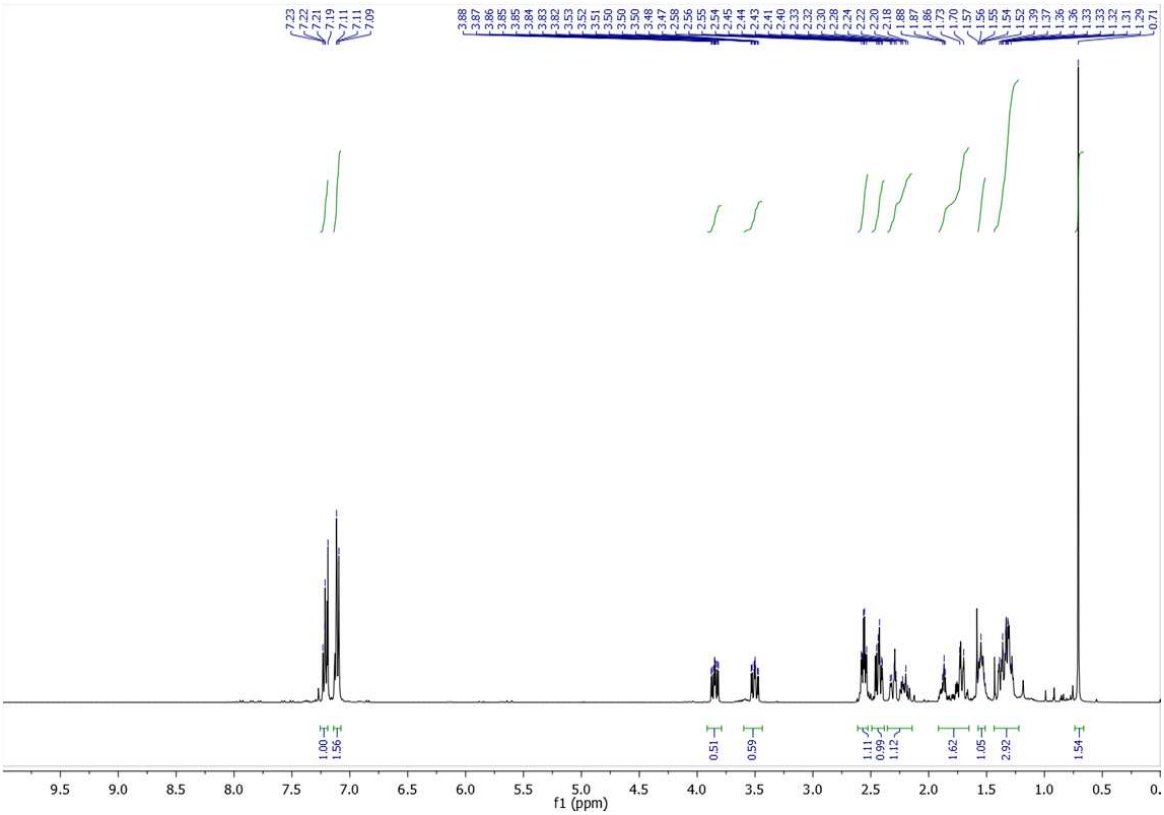
^{1}H/^{1}H NOE interactions:

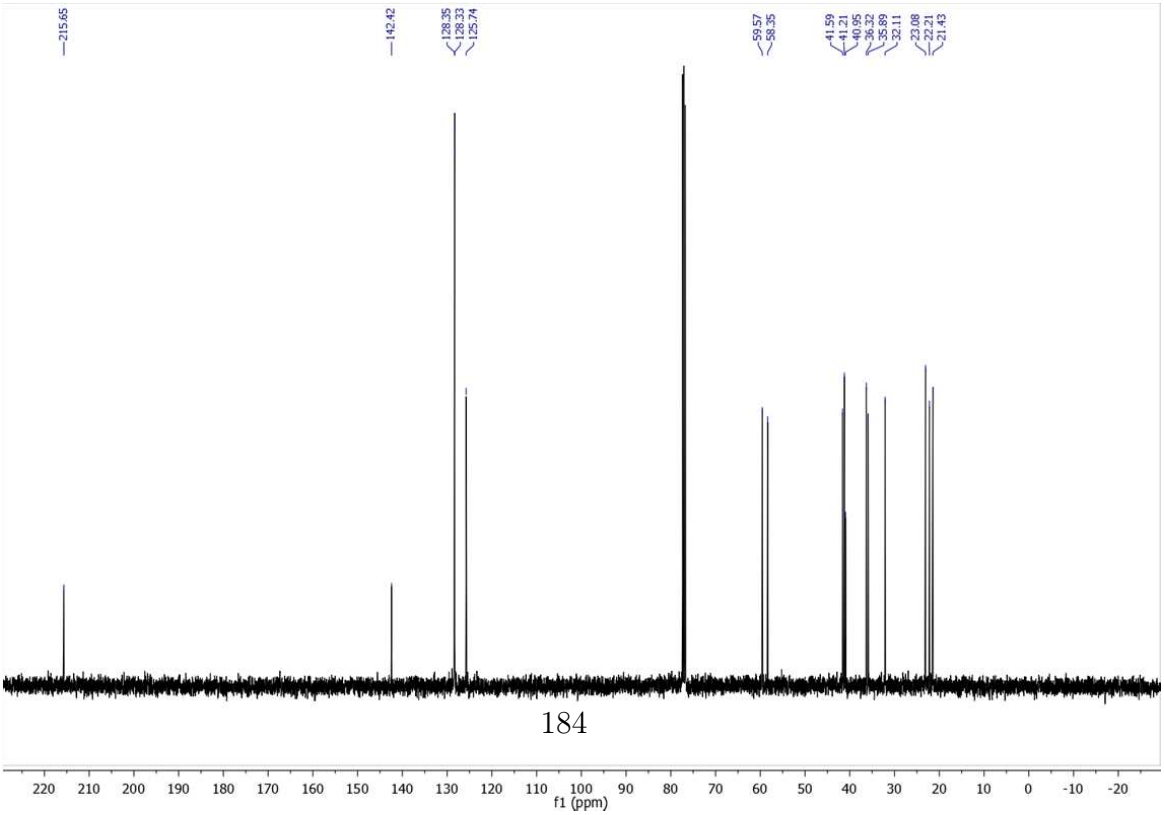


Irradiated ^{1}H	**Response (strong, medium weak)**
4.03 ppm H7	H7' strong, H2 medium, H8 weak
3.63 ppm H7'	H7 strong, H2 medium, H8 strong
2.42 ppm H2	H7 weak, H7' weak, H8 strong
1.09 ppm H8	H7' strong, H2 strong

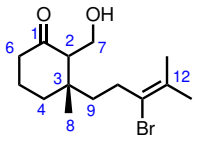


$^{1}H/^{13}C$ NMR


7.23
7.22
7.21
7.19
7.11
7.11
7.09
3.88
3.87
3.86
3.85
3.85
3.84
3.83
3.82
3.53
3.52
3.51
3.50
3.50
3.50
3.48
3.47
2.58
2.56
2.55
2.54
2.45
2.44
2.43
2.41
2.40
2.33
2.32
2.30
2.28
2.24
2.22
2.20
2.18
1.88
1.87
1.86
1.73
1.70
1.57
1.56
1.55
1.54
1.52
1.39
1.37
1.36
1.36
1.33
1.33
1.32
1.31
1.29
0.71
1.00
1.56
0.51
0.59
1.11
0.99
1.12
1.62
1.05
2.92
1.54
9.5 9.0 8.5 8.0 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 0.
f1 (ppm)


215.65
142.42
128.35
128.33
125.74
59.57
58.35
41.59
41.21
40.95
36.32
35.89
32.11
23.08
22.21
21.43
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

5.3.0.28 (2S,3S)-3-(3-bromo-4-methylpent-3-en-1-yl)-2-(hydroxymethyl)-3-methylcyclohexan-1-one (*trans* **97**)



Trans diastereomer. 1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using bromodiene **36** as the alkene. Trapping was conducted according to general procedure F. Flash chromatography (30% EtOAc/petrol) gave the product as a 1:1 separable mixture of diastereomers (colourless oil) with a combined mass of 56 mg (0.25 mmol, 50% total yield). Relative stereochemistry was assigned on the basis of NOE experiments. Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis.

R_f = 0.23 (50% EtOAc/petrol, stains red with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (ddd, J = 11.5, 9.5, 3.0 Hz, 1H, 7), 3.64 (ddd, J = 11.5, 9.5, 3.0 Hz, 1H, 7), 2.5 (m, 4H, alkyl-H/2), 1.99 – 1.85 (m, 1H, alkyl-H), 1.82 (s, 3H, CH_3), 1.81 – 1.74 (m, 1H, alkyl-H), 1.71 (s, 3H, CH_3), 1.63 – 1.47 (m, 2H, alkyl-H), 1.45 – 1.17 (m, 3H, alkyl-H), 1.12 (s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.4 C=O, 130.3, 121.0, 63.7 2, 58.3 7, 41.6 (CH_2), 40.6 3, 35.6 (CH_2), 32.2 (CH_2), 32.6 (CH_2), 25.9 (CH_2), 25.4 CH_3, 21.9 CH_3, 20.3 CH_3 ppm;

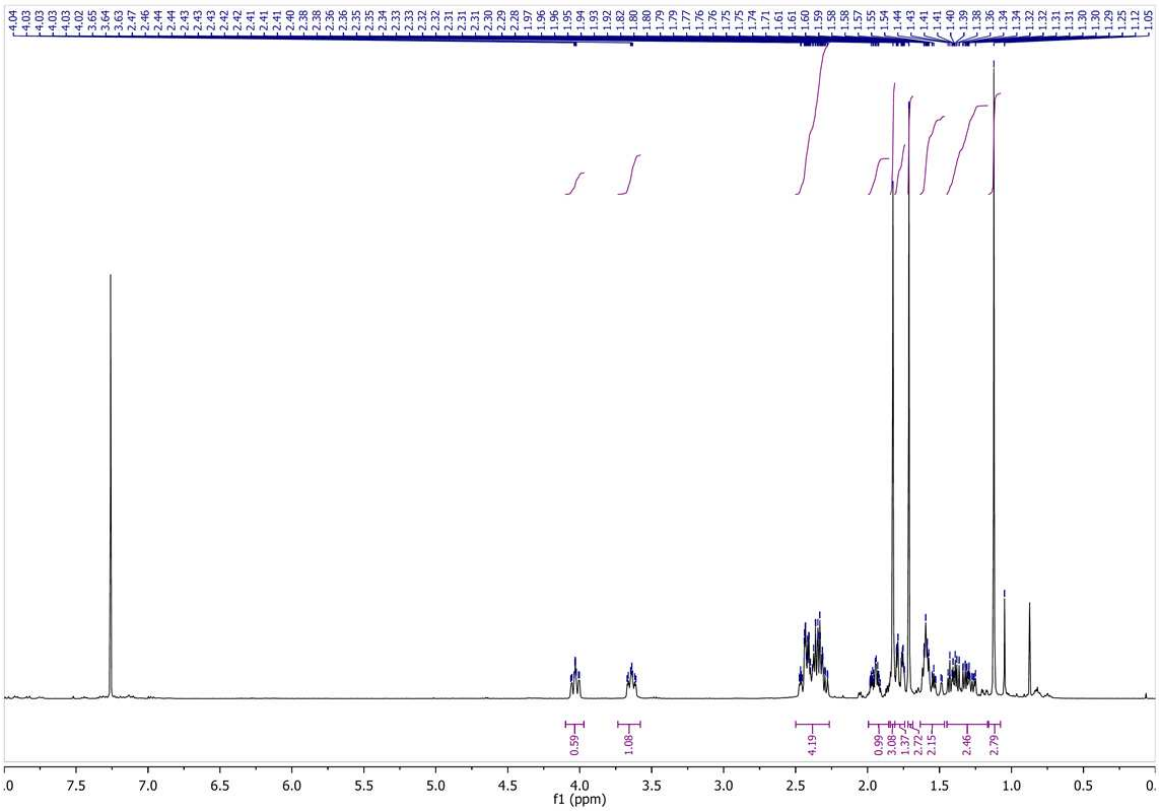
FT-IR thin film, neat (ATR): 3413, 2934, 2871, 2360, 1704, 1457, 1309, 1222, 1034 cm^{-1};

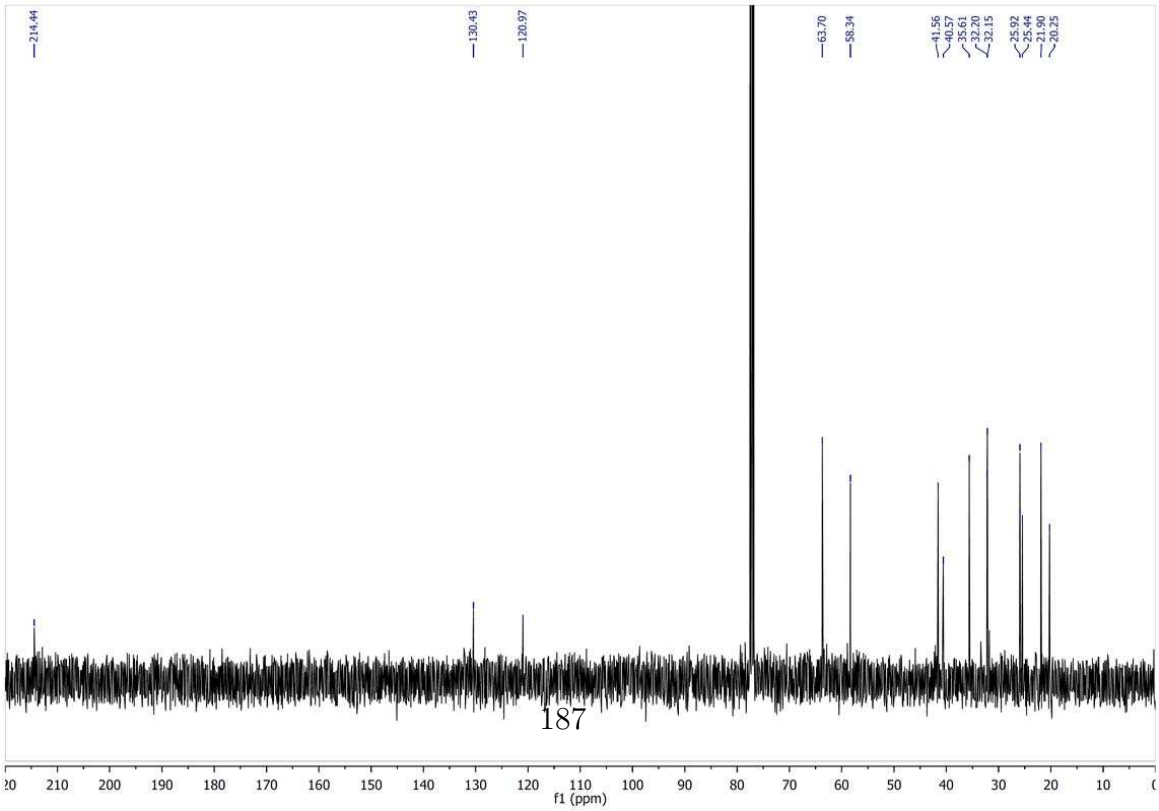
HRMS (ESI^+): calculated for $C_{14}H_{23}O_2{}^{79}Br^{23}Na$, $[M+Na]^{+\bullet}$: 325.07736 found

325.07745 (Δ = 0.28 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 8.8° (c = 0.40, CH_2Cl_2), based on a sample of 88% *ee*;

$^{1}H/^{13}C$ NMR


0.59
1.08
4.19
0.99
3.08
1.37
2.72
2.15
2.46
2.79
f1 (ppm)


214.44
130.43
120.97
63.70
58.34
41.56
40.57
35.61
32.20
32.15
25.92
25.44
21.90
20.25
f1 (ppm)

5.3.0.29 (2R,3S)-3-(3-bromo-4-methylpent-3-en-1-yl)-2-(hydroxymethyl)-3-methylcyclohexan-1-one (*cis* 97)

Cis diastereomer. The product was co-isolated with trans **97**. Relative stereochemistry was assigned on the basis of NOE experiments.

$\mathbf{R_f}$ = 0.29 (50% EtOAc/petrol, stains orange with *p*-anisaldehyde);

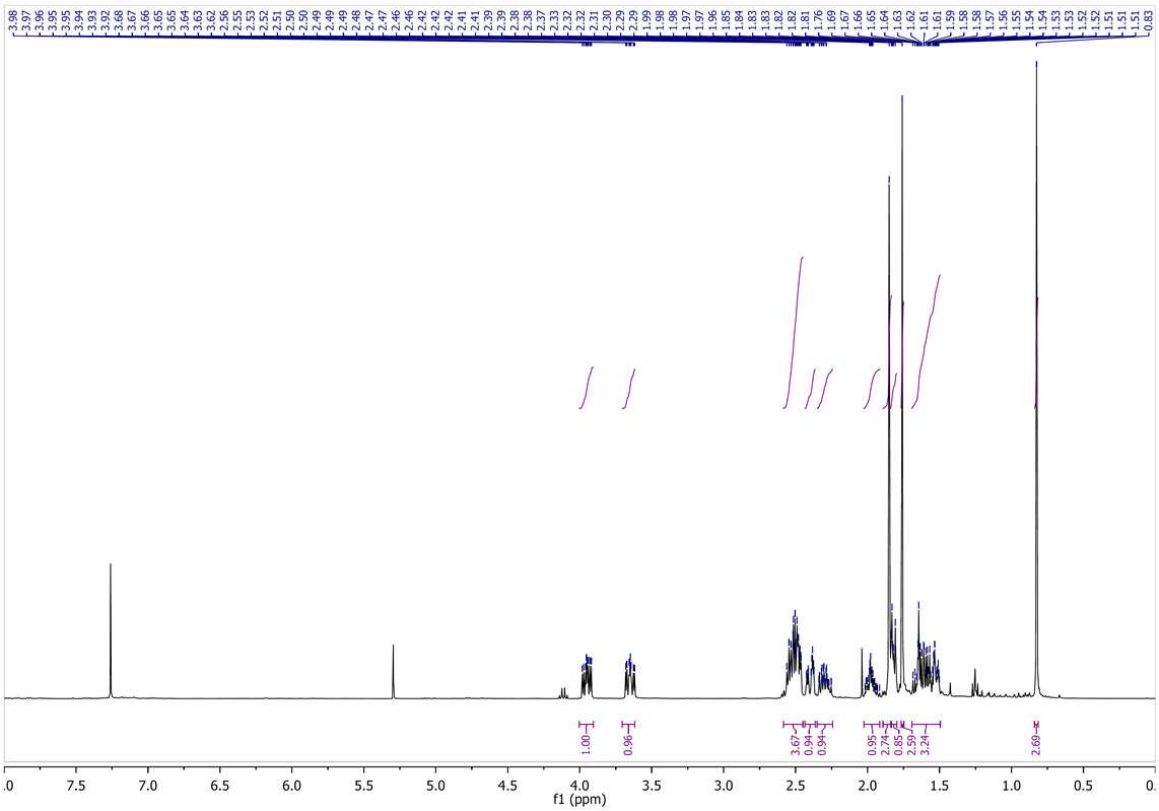
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (ddd, J = 11.5, 9.2, 4.2 Hz, 1H, 7), 3.65 (ddd, J = 11.5, 9.7, 3.3 Hz, 1H, 7), 2.58 – 2.45 (m, 4H, alkyl-H/2), 2.44 – 2.36 (m, 1H, alkyl-H), 2.35 – 2.24 (m, 1H, alkyl-H), 2.02 – 1.92 (m, 1H, alkyl-H), 1.85 (s, 3H, CH_3), 1.84 – 1.80 (m, 1H, alkyl-H), 1.76 (s, 3H, CH_3), 1.69 – 1.49 (m, 3H, alkyl-H), 0.83 (s, 3H, 8) ppm;

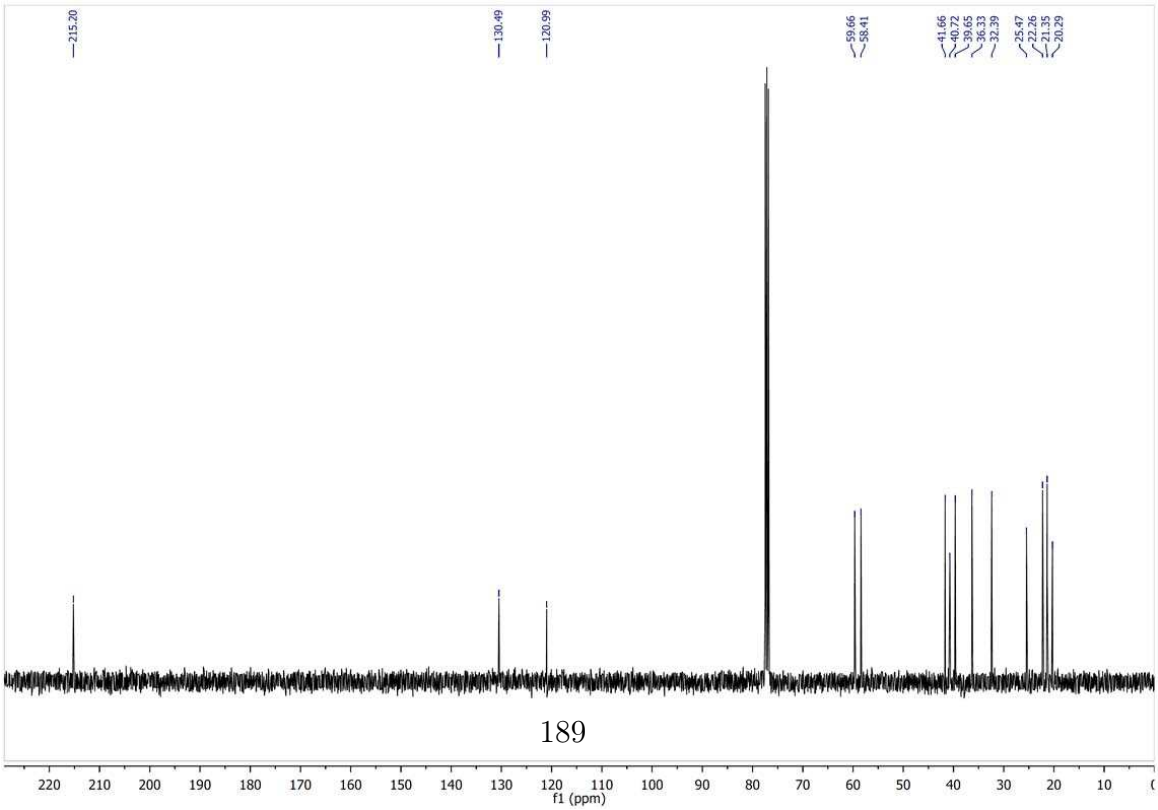
^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 C=O, 130.5, 121.0, 59.7 2, 58.4 7, 41.7 3, 40.7 (CH_2), 39.7 (CH_2), 36.3 (CH_2), 32.4 (CH_2), 25.5 CH_3, 22.3 (CH_2), 21.4 CH_3, 20.3 CH_3 ppm;

FT-IR thin film, neat (ATR): 3445, 2936, 2858, 2363, 1704, 1454, 1312, 1223, 1020 cm^{-1};

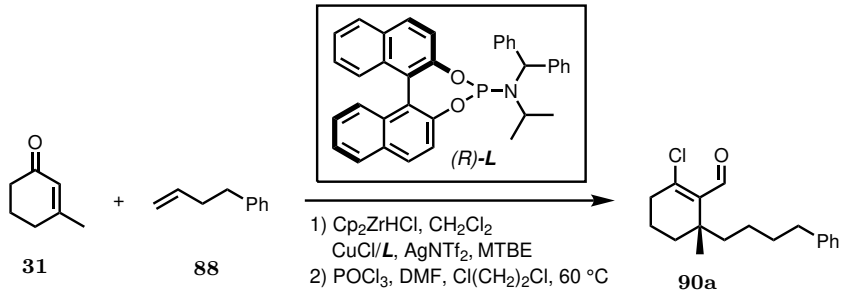
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 3.3° (c = 0.27, CH_2Cl_2), based on a sample of 88% *ee*;

$^{1}H/^{13}C$ NMR


1.00
0.96
3.67
0.94
0.94
0.95
2.74
0.85
2.59
3.24
2.69
f1 (ppm)


215.20
130.49
120.99
59.66
58.41
41.66
40.72
39.65
36.33
32.39
25.47
22.26
21.35
20.29
f1 (ppm)

5.3.1 Representative procedure: preparation of 90a (5 mmol scale)



CuCl (52 mg, 0.53 mmol, 0.10 mol equiv) and then ligand **L1** (290 mg, 0.054 mmol, 0.10 mol equiv) were added to a 50 mL flask equipped with a rubber septum and stirrer bar (flask **A**). Three cycles of vacuum and back filling with N_2 were then performed, after which methyl-*tert*-butylether (25 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment.

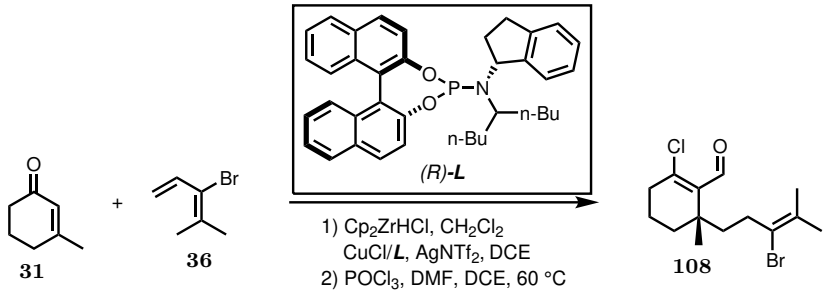
Concurrently, Cp_2ZrHCl (2.32 g, 8.99 mmol, 1.70 mol equiv) was added to a separate 100 mL flask equipped with a stirrer bar and rubber septum (flask **B**). Three cycles of vacuum and back filling with N_2 were then performed, after which dry CH_2Cl_2 (4.0 mL) and then 4-phenyl-1-butene **88** (1.6 mL, ρ = 0.88 g.mL^{-1}, 11 mmol, 2.0 mol equiv) was added. After stirring for one hour, a clear orange solution was obtained.

After stirring for the allotted time, silver bis(trifluoromethanesulfonyl)imide (310 mg, 0.80 mmol, 0.15 mol equiv) was tipped into flask **A** in one portion (minimising exposure to the atmosphere). After stirring for 10 minutes, the solution from flask **A** was then filtered (using a syringe filter) into flask **B** over a period of one minute.

The resulting solution became dark within 10 seconds. After stirring for 5 minutes, 3-methyl-2-cyclohexenone **31** was added dropwise at a rate of 1 drop every 2 seconds (0.60 mL, ρ = 0.97 g.mL^{-1}, 5.3 mmol, 1.0 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. An aliquot of the reaction mixture was loaded directly onto a small silica column (eluted with 10% Et_2O/*n*-pentane) in order to furnish a sample suitable for HPLC analysis (*ee* determination).

$POCl_3$ (5.5 mL, ρ = 1.64 g.mL^{-1}, 59 mmol, 11 mol equiv) was added in one portion to a stirred solution of *N*,*N*-dimethylformamide (4.1 mL, ρ = 0.944 g.mL^{-1}, 53 mmol, 10 mol equiv) in 1,2-dichloroethane (20 mL) at 0 °C under a N_2 atmosphere. After stirring for 5 minutes, the flask was warmed to room temperature, stirred for 15 minutes and then stirred at 60 °C for a further 5 minutes. The asymmetric conjugate addition reaction was then added by syringe and the dark brown solution was stirred for 2 hours at this temperature. The mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ (100 mL) was added drop wise using a separatory funnel under vigorous stirring. When the addition was complete, the slurry was stirred for an additional 15 minutes before the upper, solid-containing, aqueous phase is extracted (5x) with CH_2Cl_2. The combined organic extracts were washed with water (2x), dried over Na_2SO_4, and concentrated *in vacuo*. The orange residue was purified by flash chromatography (5–10% Et_2O/pentane) to furnish the desired product as a yellow oil (789 mg, 2.71 mmol, 51% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[31a] *ee* = 94%.

5.3.1.1 (*S*)-6-(3-bromo-4-methylpent-3-en-1-yl)-2-chloro-6-methylcyclohex-1-ene-1-carbaldehyde 108



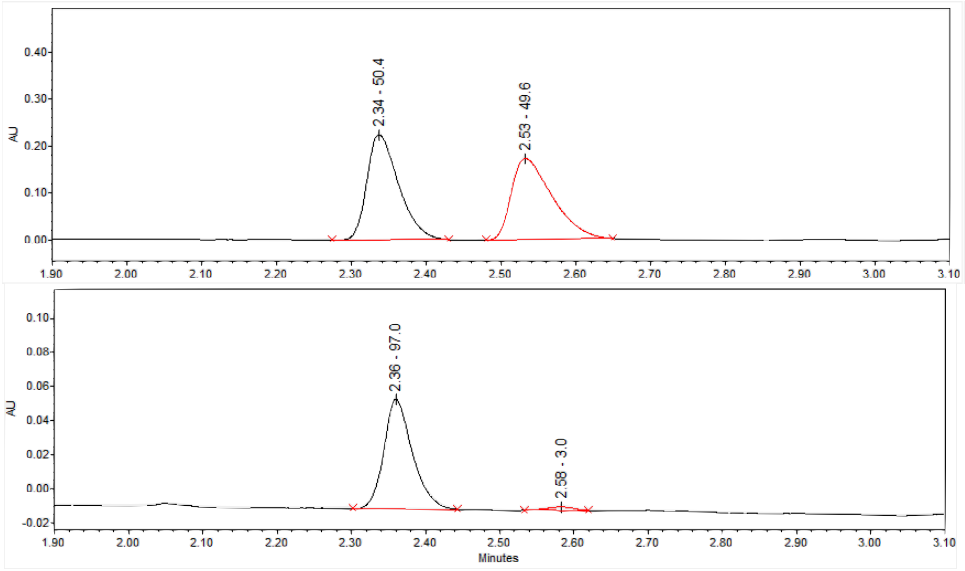
CuCl (136 mg, 1.37 mmol, 0.083 equiv) and then ligand (*R*)-**L** (929 mg, 1.62 mmol, 0.098 equiv) were added to a 100 mL flask equipped with a rubber septum and stirrer bar (flask **A**). Three cycles of vacuum and back filling with N_2 were then performed, after which 1,2-dichloroethane (61 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment.

Concurrently, Cp_2ZrHCl (7.93 g, 30.7 mmol, 1.86 equiv) was added to a separate 250 mL flask equipped with a stirrer bar and rubber septum (flask **B**). Three cycles of vacuum and back filling with N_2 were then performed, after which CH_2Cl_2 (15.5 mL) and then bromodiene **36** (5.0 mL, ρ = 1.22 g.mL^{-1}, 37.9 mmol, 2.3 equiv) were added. After stirring for one hour, a clear orange solution was obtained.

After stirring for the allotted time, silver bis(trifluoromethanesulfonyl)imide (929 mg, 2.39 mmol, 0.14 equiv) was tipped into flask **A** in one portion (minimising exposure to the atmosphere). After stirring for 10 minutes, the solution from flask **A** was then filtered (using a syringe filter) into flask **B** over a period of 10 minutes. After stirring for 5 minutes, 3-methyl-2-cyclohexenone **31** was added dropwise at

a rate of 1 drop every 2 seconds (1.87 mL, ρ = 0.97 g.mL^{-1}, 16.5 mmol, 1.0 equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. An aliquot of the reaction mixture was loaded directly onto a small silica column (eluted with 10% Et_2O/*n*-pentane) in order to furnish a sample suitable for HPLC analysis (*ee* determination).

$POCl_3$ (17.1 mL, ρ = 1.64 g.mL^{-1}, 183 mmol, 11 equiv) was added in one portion to a stirred solution of *N*,*N*-dimethylformamide (12.9 mL, ρ = 0.94 g.mL^{-1}, 167 mmol, 10 equiv) in 1,2-dichloroethane (63 mL) at 0 °C under a N_2 atmosphere. After stirring for 5 minutes, the flask was warmed to room temperature, stirred for 15 minutes and then stirred at 60 °C for a further 5 minutes. The asymmetric conjugate addition reaction was then added by syringe and the dark brown solution was stirred for 1 hour at this temperature. The mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ (120 mL) was added drop wise using a separatory funnel under vigorous stirring. When the addition was complete, the slurry was filtered through a sintered funnel. The remaining solids were washed (3 x 400 mL CH_2Cl_2) and the filtrate was transferred to a separatory funnel. The upper, aqueous phase is extracted (5 x 200 mL CH_2Cl_2). The combined organic extracts were washed (2 x 200 mL H_2O), dried ($MgSO_4$) and concentrated *in vacuo*. The orange residue was loaded onto celite and purified by dry column vacuum chromatography (0–11% Et_2O/hexane) to furnish the desired product as a yellow oil (3.62 g, 11.3 mmol, 69% yield). SFC (Chiralpak IA column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 92% (minor enantiomer t_R = 2.58 min, major enantiomer t_R = 2.36 min).



R_f = 0.58 (30% Et_2O/*n*-pentane, stains with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 2.52 – 2.44 (m, 2H), 2.44 – 2.20 (m, 4H), 1.85 (s, 3H), 1.75 (s, 3H), 1.57 – 1.49 (m, 2H), 1.51 – 1.44 (m, 2H), 0.97 (s, 3H) ppm;

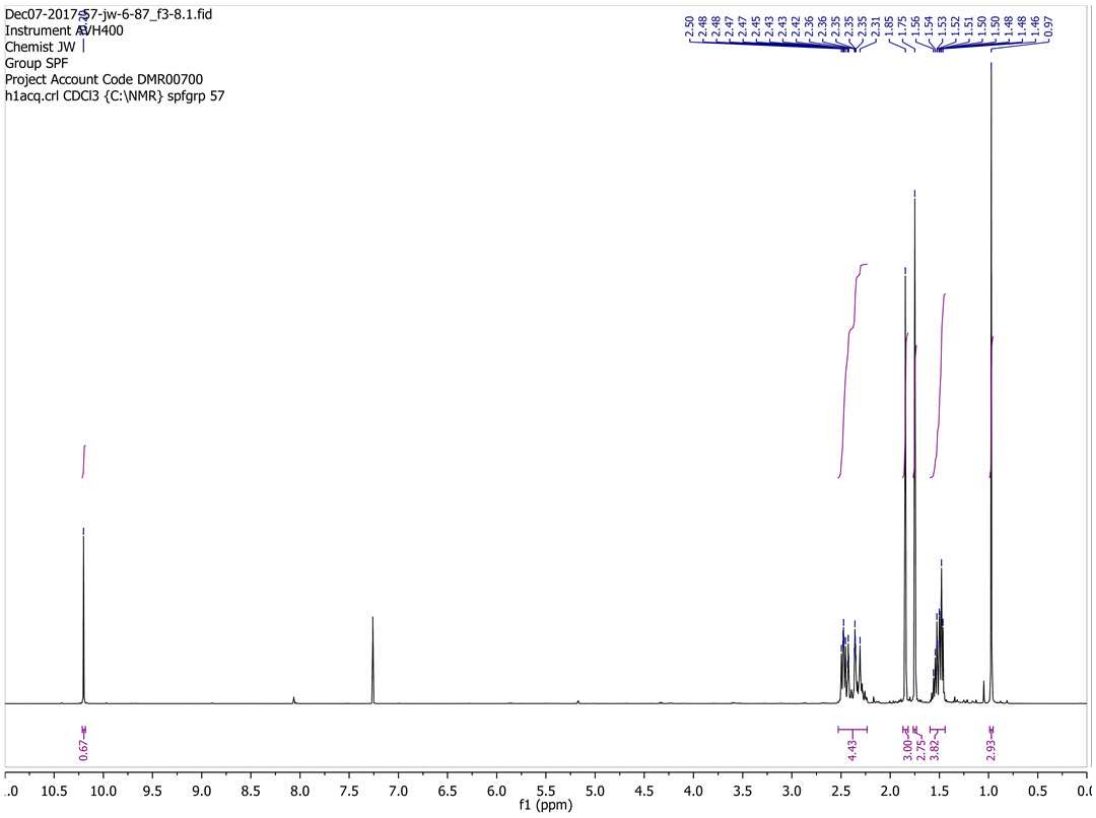
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 150.1, 132.4, 130.3, 121.3, 48.4, 39.3, 33.7, 32.4, 31.8, 25.5, 24.3, 21.2, 20.3 ppm;

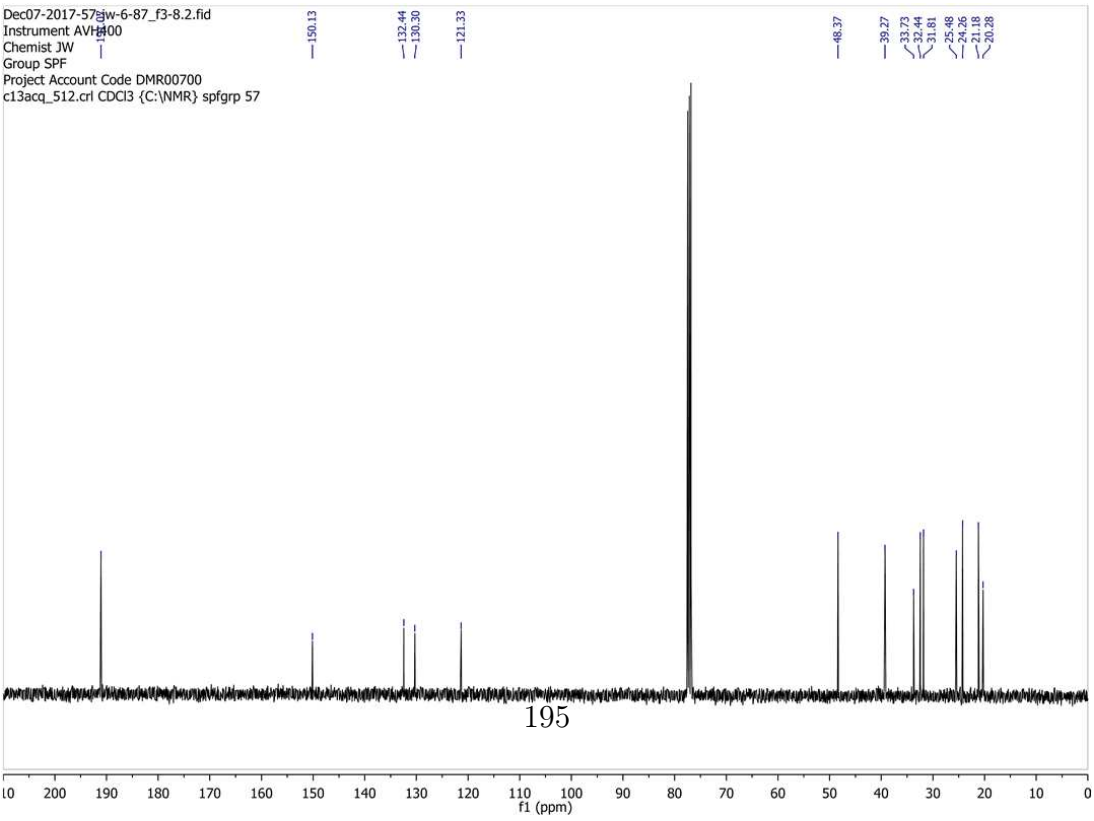
FT-IR thin film, neat (ATR): 2957, 2924, 2857, 1679, 1624, 1226 cm^{-1};

HRMS (APCI$^+$) m/z: [M+H]+ Calcd for $C_{14}H_{21}O^{79}Br^{35}Cl$; 319.0459 found 319.0461 (Δ = 0.72 ppm);

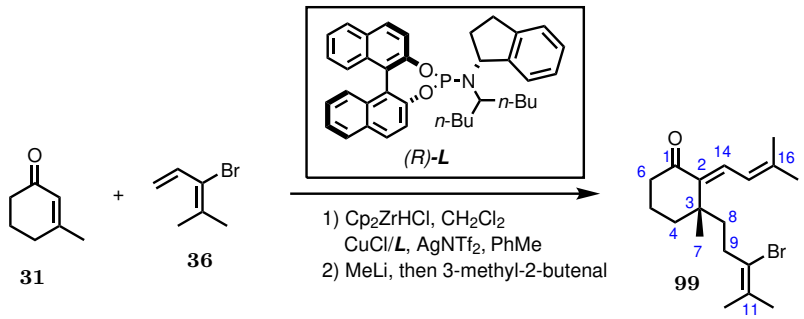
$[\alpha]_D^{25}$ = + 35° (*c* = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


Dec07-2017-57-jw-6-87_f3-8.1.fid
Instrument AVH400
Chemist JW
Group SPF
Project Account Code DMR00700
h1acq.crl CDCl3 {C:\NMR} spfgrp 57
f1 (ppm)


Dec07-2017-57-jw-6-87_f3-8.2.fid
Instrument AVH400
Chemist JW
Group SPF
Project Account Code DMR00700
c13acq_512.crl CDCl3 {C:\NMR} spfgrp 57
150.13
132.44
130.30
121.33
48.37
39.27
33.73
32.44
31.81
25.48
24.26
21.18
20.28
f1 (ppm)

5.3.1.2 (S,E)-3-(3-bromo-4-methylpent-3-en-1-yl)-3-methyl-2-(3-methylbut-2-en-1-ylidene)cyclohexan-1-one 99



The asymmetric conjugate addition was performed according to the procedure for compound **35** (0.265 mmol of 3-methyl-2-cyclohexenone). When the reaction was deemed complete, the flask was cooled to −78 °C and methyl lithium (0.18 mL of a 1.6M solution in Et_2O, 0.29 mmol, 1.1 mol equiv) was added dropwise. The cooling bath was removed immediately and after stirring at room temperature for 1 hour, 3-methyl-butenal (51 μL, 0.53 mmol, 2.0 mol equiv) was added. After stirring for 1.5 hours, the reaction was diluted with Et_2O and quenched with $NH_4Cl_{(aq)}$. The biphasic mixture was passed through a phase separator and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a yellow oil (16 mg, 0.047 mmol, 18% yield).

R_f = 0.43 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dt, J = 12.1, 2.3 Hz, 1H, 14), 6.07 (dt, J = 12.1, 1.4 Hz, 1H, 15), 2.65 – 2.61 (m, 2H, 4), 2.56 – 2.36 (m, 2H, 8), 2.29 – 2.24 (m, 2H, 6), 1.92 (d, J = 1.3 Hz, 6H, 17/18), 1.83 (s, 3H, 12/13), 1.74 (s, 3H, 12/13), 1.70 – 1.59 (m, 2H, 5), 1.56 – 1.45 (m, 2H, 9), 0.98 (s, 3H, 7) ppm;

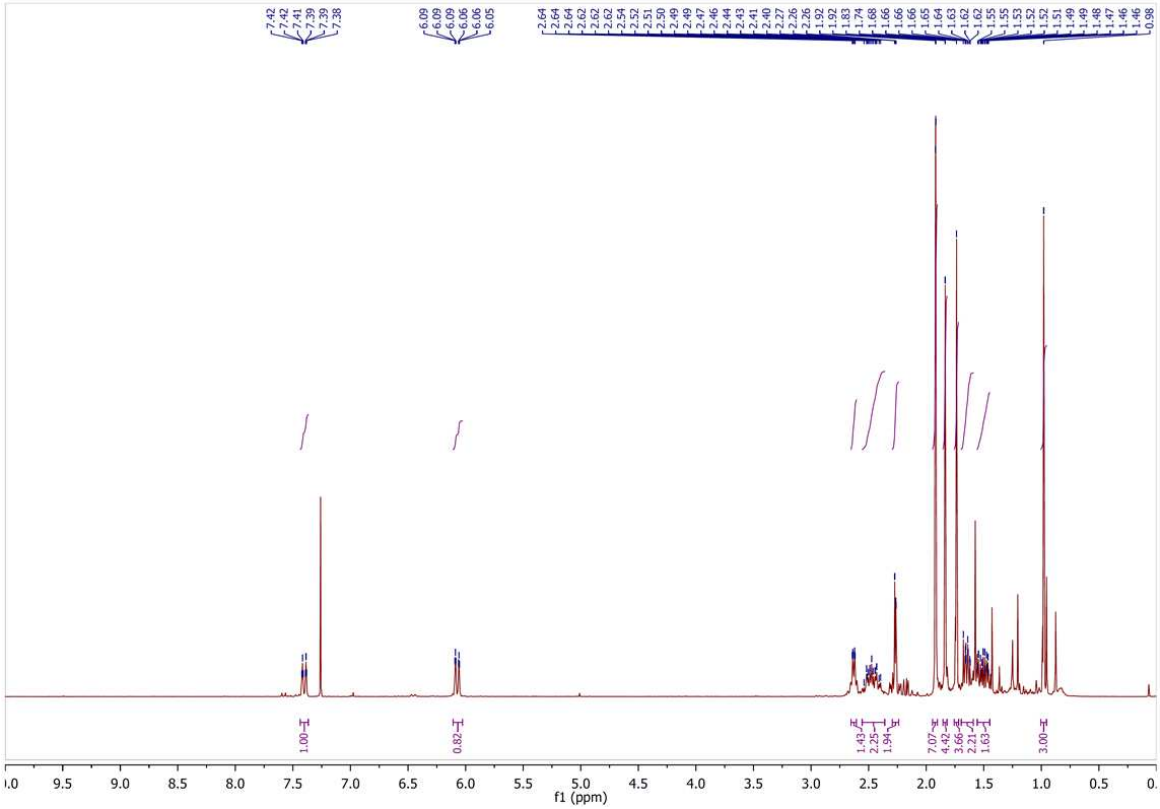
^{13}C NMR (101 MHz, $CDCl_3$): δ 200.8 1, 147.8 2, 132.0 14, 130.5 10, 130.1 11, 121.5 16, 120.8 15, 52.3 6, 39.7 9, 34.0 3, 33.9 5, 32.6 8, 27.4 CH_3, 25.5 7, 24.9 CH_3, 22.6 4, 20.3 CH_3, 19.2 CH_3 ppm;

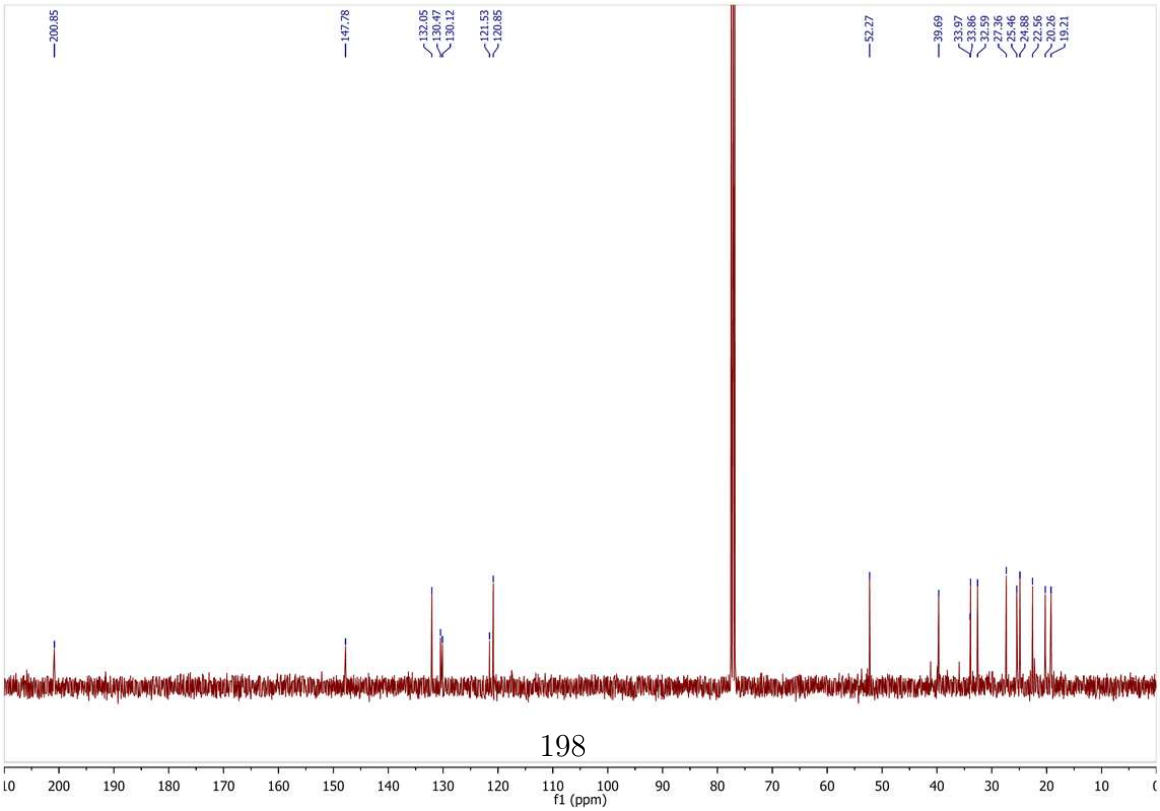
FT-IR thin film, neat (ATR): 2922, 2854, 2360, 1706, 1447, 1022 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{18}H_{28}O^{79}Br$, $[M+H]^{+\bullet}$: 339.13180 found 339.13211 (Δ = 0.9 ppm);

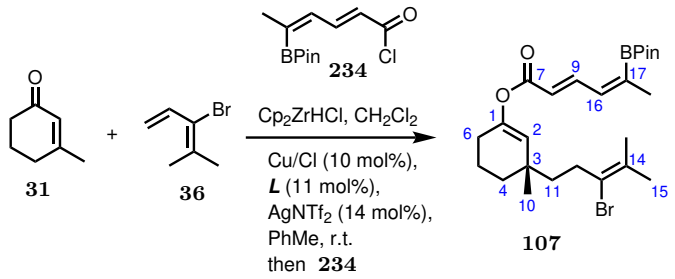
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -2.9°$ (c = 0.57, CH_2Cl_2), based on a sample of 88% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.3 Acyl trapped product 107



Conjugate addition was performed as for compound **35** using 0.51 mmol 3-methyl-2-cyclohexen-1-one. When the enone was deemed to have been completely consumed by TLC, acid chloride **234** (256 mg, 1.0 mmol, 2.0 mol equiv), prepared according to the procedure by Greenberg,[46] was injected into the reaction mixture. The reaction mixture was stirred for 6 hours, diluted with Et_2O and then quenched with 1M $NH_4Cl_{(aq)}$ (0.5 mL). The aqueous phase was extracted (3 x 0.5 mL) with Et_2O and the combined organic extracts were washed ($NaHCO_{3(aq)}$), dried (Na_2SO4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–7% Et_2O/*n*-pentane, silica column) to give the title compound as an orange oil (48 mg, 0.19 mmol, 37% yield).

R_f = 0.57 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, J = 15.1, 11.8 Hz, 1H, 9), 6.67 (d, J = 11.4 Hz, 1H, 16), 5.86 (d, J = 15.2 Hz, 1H, 8), 5.16 (s, 1H, 2), 2.51 – 2.42 (m, 2H, alkyl-H), 2.14 (q, J = 6.7, 5.9 Hz, 2H, alkyl-H), 1.94 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.77 (m, 2H, alkyl-H), 1.74 (s, 3H, CH_3), 1.62 – 1.36 (m, 4H, alkyl-H), 1.30 (s, 12H, BPin-CH_3), 1.04 (s, 3H, CH_3) ppm;

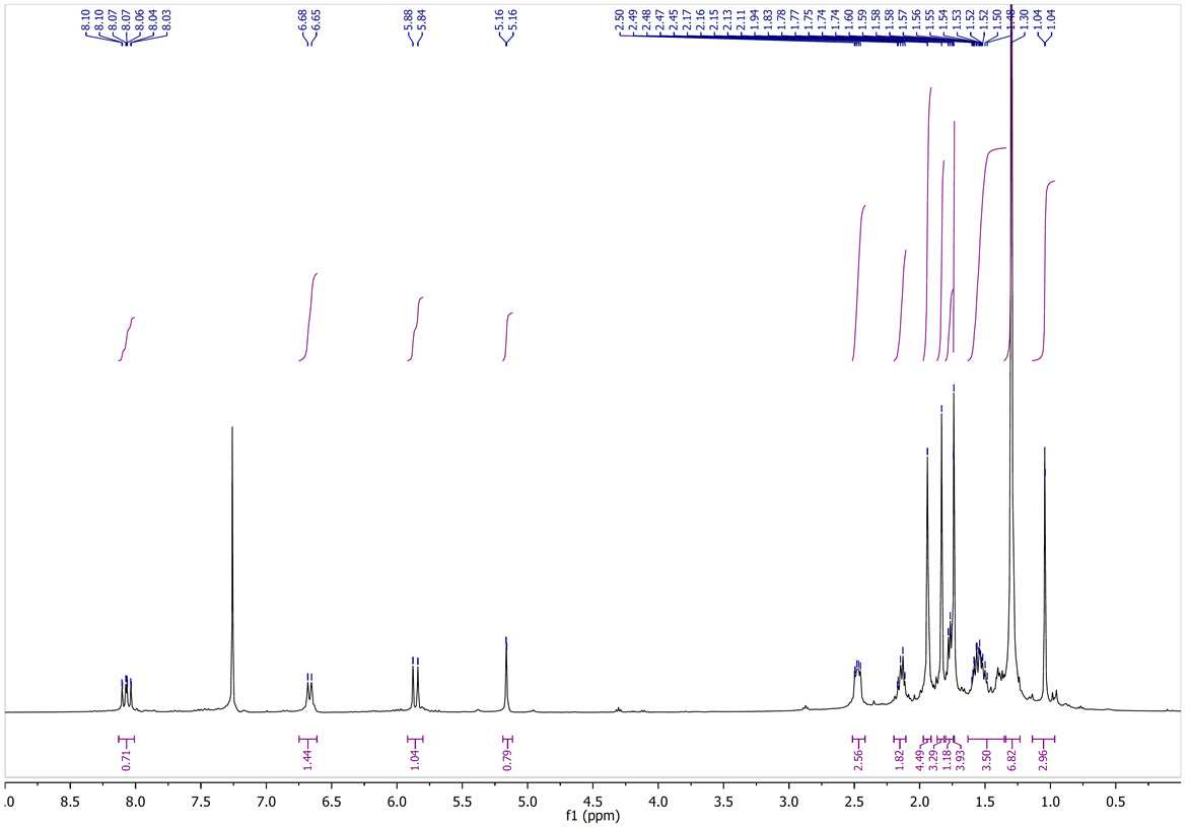
^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6 7, 147.8 1, 144.9 9, 141.6 16, 129.6 14, 122.2 13, 122.0 2, 121.5 8, 83.7 C-O-B, 41.0 (CH_2), 34.6 3, 33.8 (CH_2), 33.0 (CH_2),

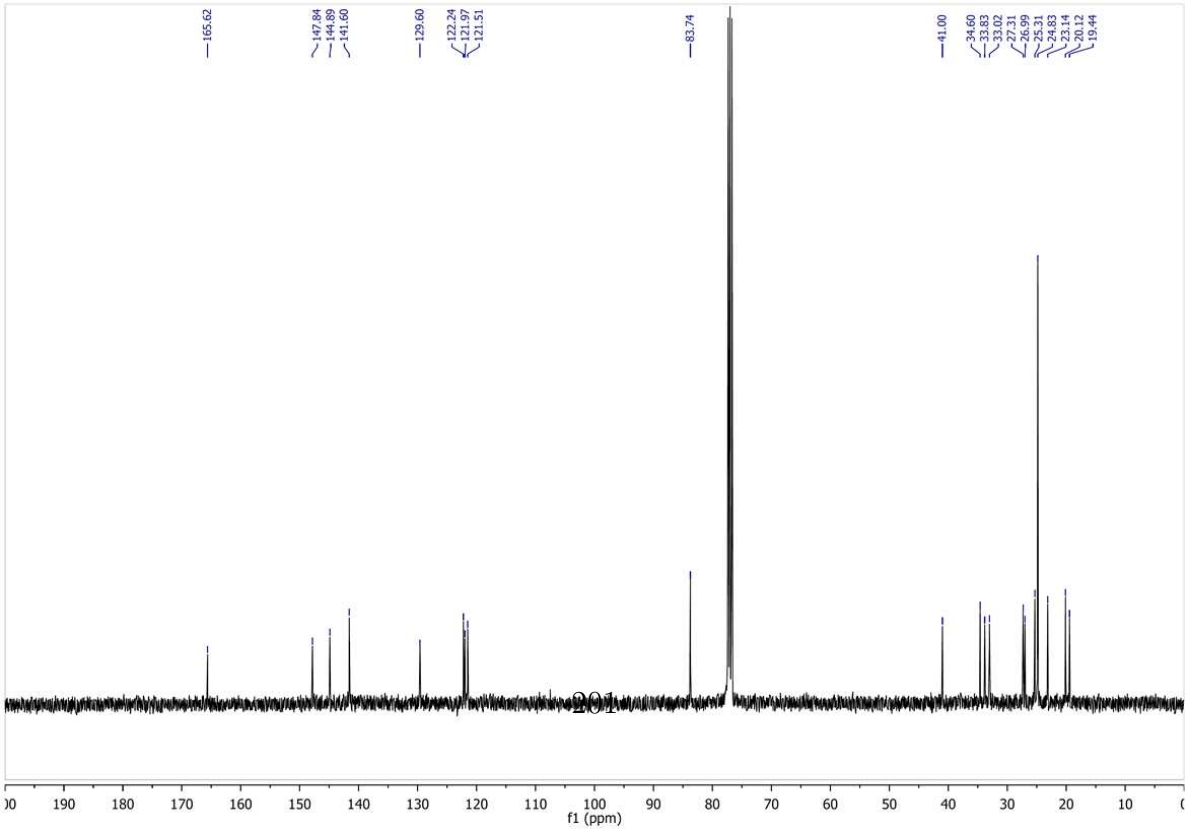
27.3 CH_3, 27.0 (CH_2), 25.3 CH_3, 24.8 BPin-CH_3, 23.1 CH_3, 20.1 CH_3, 19.4 (CH_2) ppm;

HRMS (APCI$^+$): calculated for $C_{25}H_{39}O_4{}^{10}B^{79}Br$, $[M+H]^{+\bullet}$: 492.21555 found 492.21556 (Δ = -0.03 ppm);

Due to the coronavirus 2019 situation and corresponding laboratory shutdown, it was not possible to obtain reliable α_D and IR measurements.

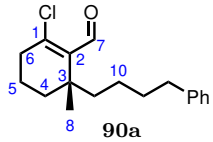
$^{1}H/^{13}C$ NMR


8.10
8.10
8.07
8.07
8.06
8.04
8.03
6.68
6.65
5.88
5.84
5.16
5.16
2.50
2.49
2.48
2.47
2.45
2.17
2.16
2.15
2.13
2.11
1.94
1.83
1.78
1.77
1.75
1.74
1.74
1.60
1.59
1.58
1.58
1.57
1.56
1.55
1.54
1.53
1.52
1.52
1.50
1.48
1.30
1.04
1.04
0.71
1.44
1.04
0.79
2.56
1.82
4.49
3.29
1.18
3.93
3.50
6.82
2.96
f1 (ppm)


165.62
147.84
144.89
141.60
129.60
122.24
121.97
121.51
83.74
41.00
34.60
33.83
33.02
27.31
26.99
25.31
24.83
23.14
20.12
19.44
f1 (ppm)

5.3.1.4 (*R*)-2-chloro-6-methyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehydecarbald

90a



90a

1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using 4-phenyl-1-butene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane) gave the title product as a yellow oil (87 mg, 0.30 mmol, 56% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[31a] *ee* = 96%.

R_f = 0.54 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

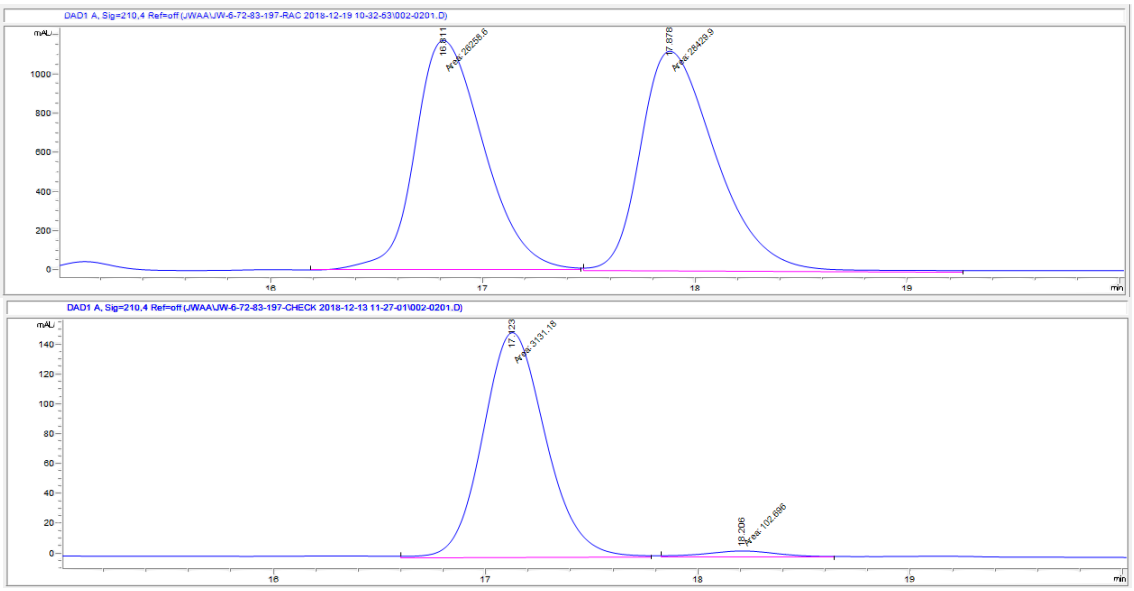
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.23 (s, 1H, 7), 7.34 – 7.27 (m, 2H, Ar-H), 7.23 – 7.17 (m, 3H, Ar-H), 2.69 – 2.60 (m, 2H, 12), 2.49 – 2.25 (m, 4H, 1/2), 1.68 – 1.57 (m, 2H, 11), 1.46 (t, J = 6.5 Hz, 2H, 4), 1.39 – 1.28 (m, 4H, 9/10), 0.94 (s, 3H, 8) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2 8, 150.6 1, 142.6, 132.5 2, 128.5 (2C), 128.4 (2C), 125.8, 48.5 6, 41.1 9, 36.0 12, 34.0 3, 32.3 11, 32.0 4, 24.4 8, 23.2 10, 21.3 5 ppm;

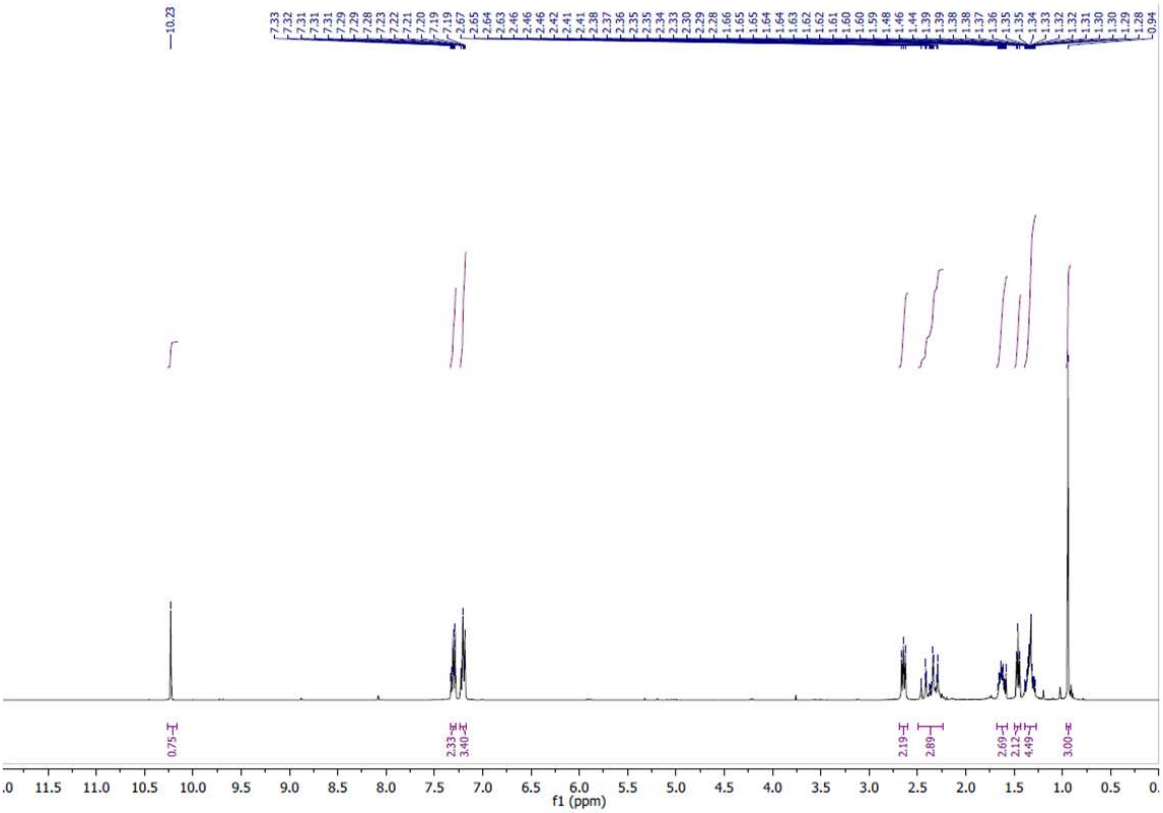
FT-IR thin film, neat (ATR): 2932, 2857, 1678, 1624 cm^{-1};

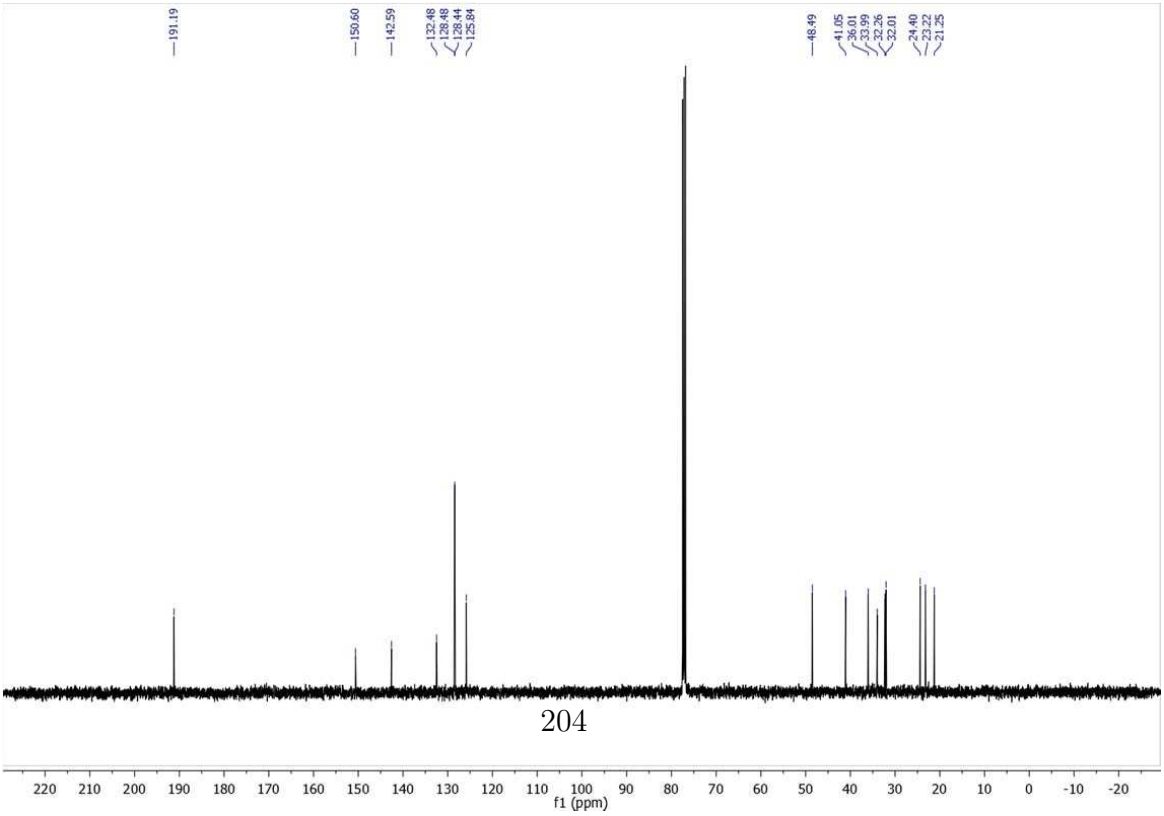
HRMS (ESI^+): calculated for $C_{18}H_{24}O^{35}Cl$, $[M+H]^{+\bullet}$: 291.15102 found 291.15112 (Δ = 0.36 ppm);

$[\alpha]_D^{25}$ = + 18° (*c* = 1.0, CH_2Cl_2), based on a sample of 96% *ee*;

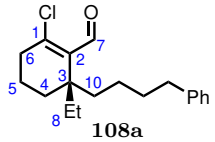

DAD1 A, Sig=210,4 Ref=off (JWAA\JW-6-72-83-197-RAC 2018-12-19 10-32-53\002-0201.D)
mAU
16.911
Area: 26258.6
17.678
Area: 26429.9
min
DAD1 A, Sig=210,4 Ref=off (JWAA\JW-6-72-83-197-CHECK 2018-12-13 11-27-01\002-0201.D)
mAU
17.123
Area: 31311.18
18.206
Area: 102.686
min

$^{1}H/^{13}C$ NMR


10.23
7.33
7.32
7.31
7.31
7.29
7.29
7.28
7.23
7.22
7.21
7.20
7.19
7.19
7.67
2.65
2.64
2.63
2.46
2.46
2.46
2.42
2.41
2.41
2.38
2.37
2.36
2.35
2.35
2.34
2.33
2.30
2.29
2.28
1.66
1.65
1.65
1.64
1.63
1.62
1.62
1.61
1.60
1.60
1.59
1.48
1.46
1.44
1.39
1.39
1.38
1.38
1.37
1.36
1.35
1.35
1.34
1.33
1.32
1.32
1.31
1.30
1.30
1.29
1.28
0.94
0.75
2.33
3.40
2.19
2.89
2.69
2.12
4.49
3.00
f1 (ppm)


191.19
150.60
142.59
132.48
128.48
128.44
125.84
48.49
41.05
36.01
33.99
32.26
32.01
24.40
23.22
21.25
f1 (ppm)

5.3.1.5 (*R*)-2-chloro-6-ethyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehyde 108a



108a

1,4-addition reaction was conducted according to general procedure D using 3-ethyl-2-cyclohexenone[113] (0.53 mmol) as the enone and 4-phenyl-1-butene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane) gave the title product as a yellow oil (66 mg, 0.22 mmol, 41% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak ID column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 98% (minor enantiomer t_R = 2.92 min, major enantiomer t_R = 3.14 min).

R_f = 0.59 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H, 7), 7.23 – 7.17 (m, 2H, ArH), 7.10 (m, 3H, ArH), 2.54 (dd, J = 8.7, 6.8 Hz, 2H, 13), 2.28 (t, J = 2.3 Hz, 2H, 6), 2.18 (m, 2H, 5), 1.58 – 1.47 (m, 2H, 12), 1.37 (t, J = 6.4 Hz, 2H, 4), 1.30 – 1.13 (m, 6H, 8/10/11), 0.73 (t, J = 7.5 Hz, 3H, 9(Me)) ppm;

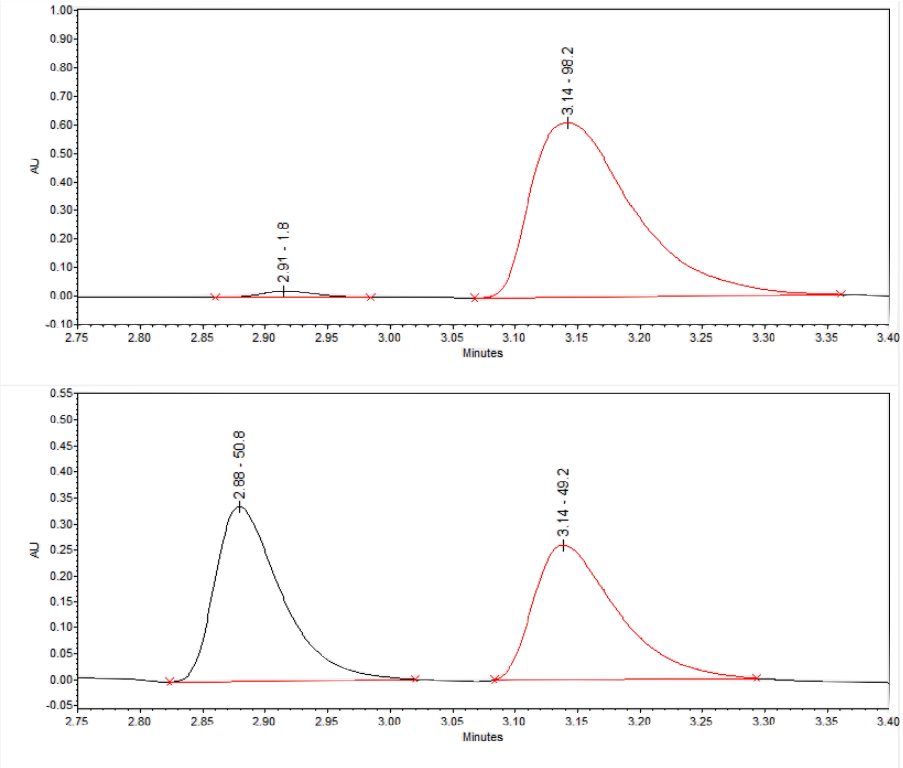
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0 7, 150.7 1, 142.4, 132.5 2, 128.3 (2C), 128.3 (2C), 125.7, 46.9 6, 36.3 3, 35.9 13, 35.8 (CH_2), 32.1 12, 29.5 4, 28.8 (CH_2), 22.6 (CH_2), 20.8 5, 7.5 9(Me) ppm;

FT-IR thin film, neat (ATR): 2963, 2933, 2858, 1678, 1624 cm^{-1};

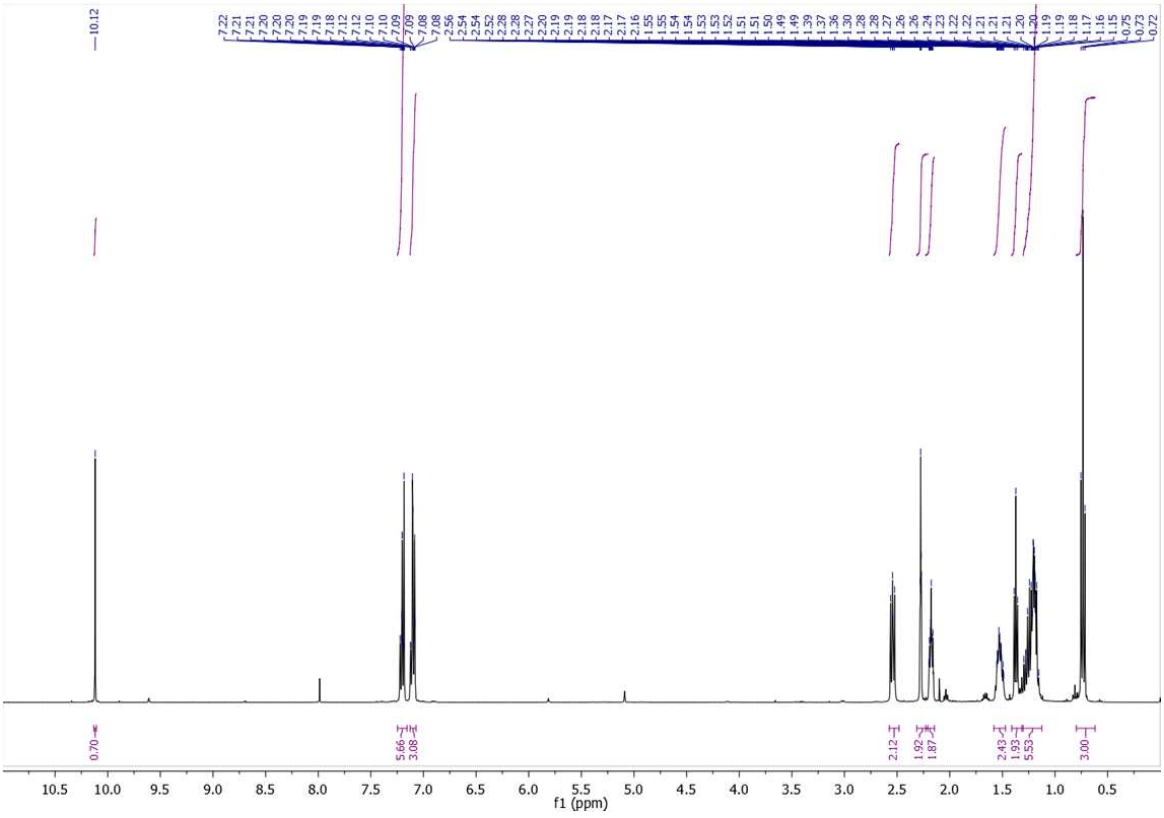
HRMS (APCI$^+$): calculated for $C_{19}H_{24}O^{35}Cl$, $[M+H]^{+\bullet}$: 303.15212 found 303.15173

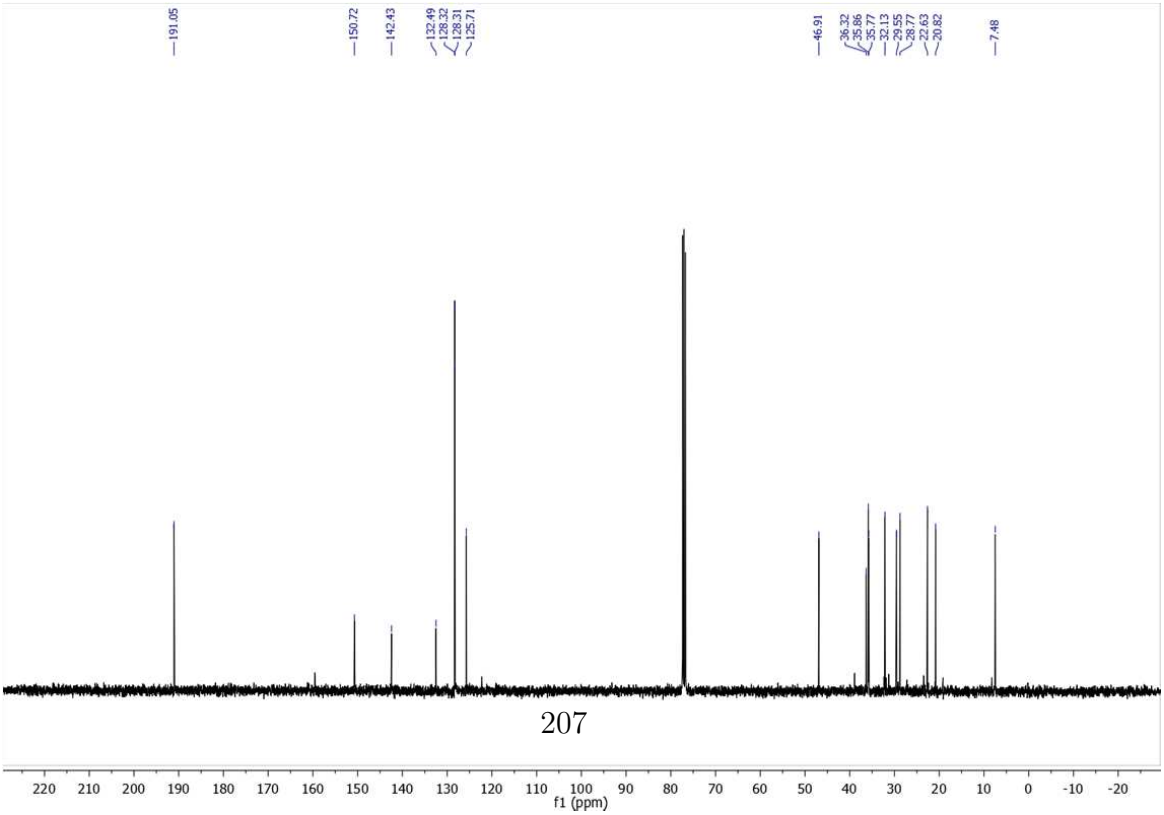
(Δ = -1.26 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 13° (c = 1.0, CH_2Cl_2), based on a sample of 98% *ee*;

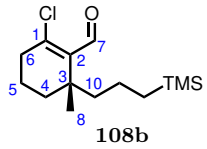


$^{1}H/^{13}C$ NMR


10.12
7.22 7.21 7.21 7.20 7.20 7.20 7.19 7.19 7.18 7.12 7.10 7.10 7.09 7.09 7.08 7.08 2.56 2.54 2.54 2.52 2.28 2.28 2.27 2.20 2.19 2.19 2.18 2.18 2.17 2.17 2.16 1.55 1.55 1.54 1.54 1.53 1.53 1.52 1.51 1.51 1.50 1.49 1.49 1.39 1.37 1.36 1.30 1.28 1.27 1.26 1.26 1.24 1.23 1.22 1.22 1.21 1.21 1.21 1.20 1.20 1.19 1.19 1.18 1.17 1.17 1.16 1.15 0.75 0.73 0.72
0.70
5.66
3.08
2.12
1.92
1.87
2.43
1.93
5.53
3.00
f1 (ppm)


191.05
150.72
142.43
132.49
128.32
128.31
125.71
46.91
36.32
35.86
35.77
32.13
29.55
28.77
22.63
20.82
7.48
f1 (ppm)

5.3.1.6 (*S*)-2-chloro-6-methyl-6-(3-(trimethylsilyl)propyl)cyclohex-1-ene-1-carbaldehyde 108b



108b

1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using allyl trimethylsilane as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane) gave the product as a yellow oil (66 mg, 0.24 mmol, 46% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IF column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 96% (minor enantiomer t_R = 1.54 min, major enantiomer t_R = 1.60 min).

R_f = 0.91 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

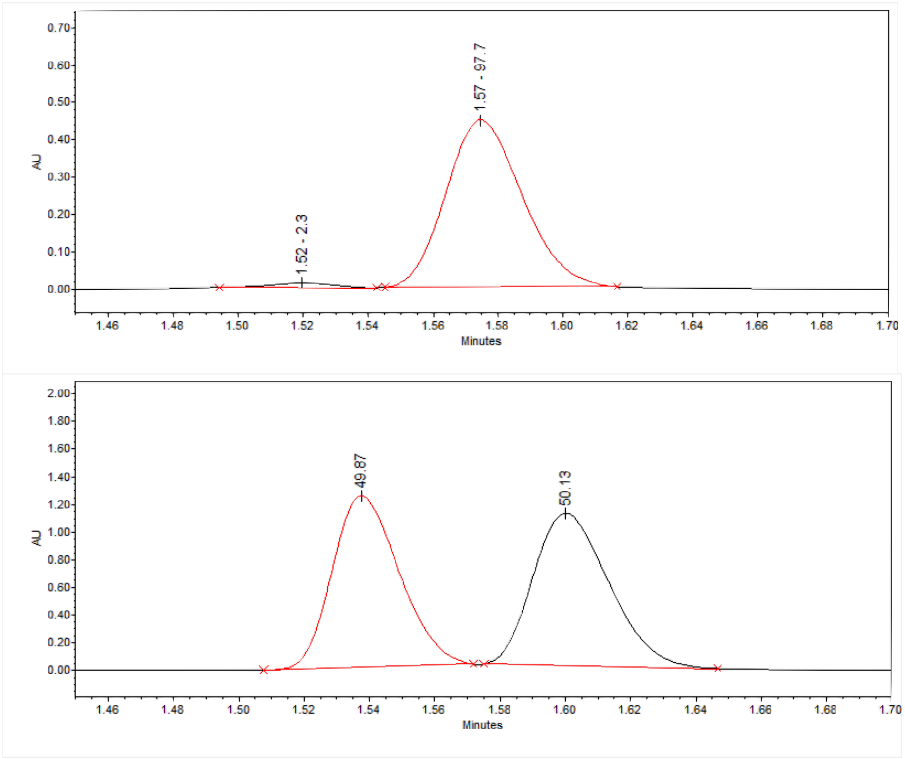
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H, 7), 2.46 – 2.22 (m, 4H, 6/5), 1.44 (dd, *J* = 7.3, 5.8 Hz, 2H, 4), 1.28 (ddd, J = 6.5, 4.5, 1.6 Hz, 4H, 10/11), 0.92 (s, 3H, 8), 0.49 – 0.41 (m, 2H, 12), −0.02 (s, 9H, TMS) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2 7, 150.7 1, 132.5 2, 48.5 5, 45.6 10, 34.2 3, 32.0 6, 24.4 8, 21.3 4, 17.9 11, 17.6 12, −1.4 (3C) TMS ppm;

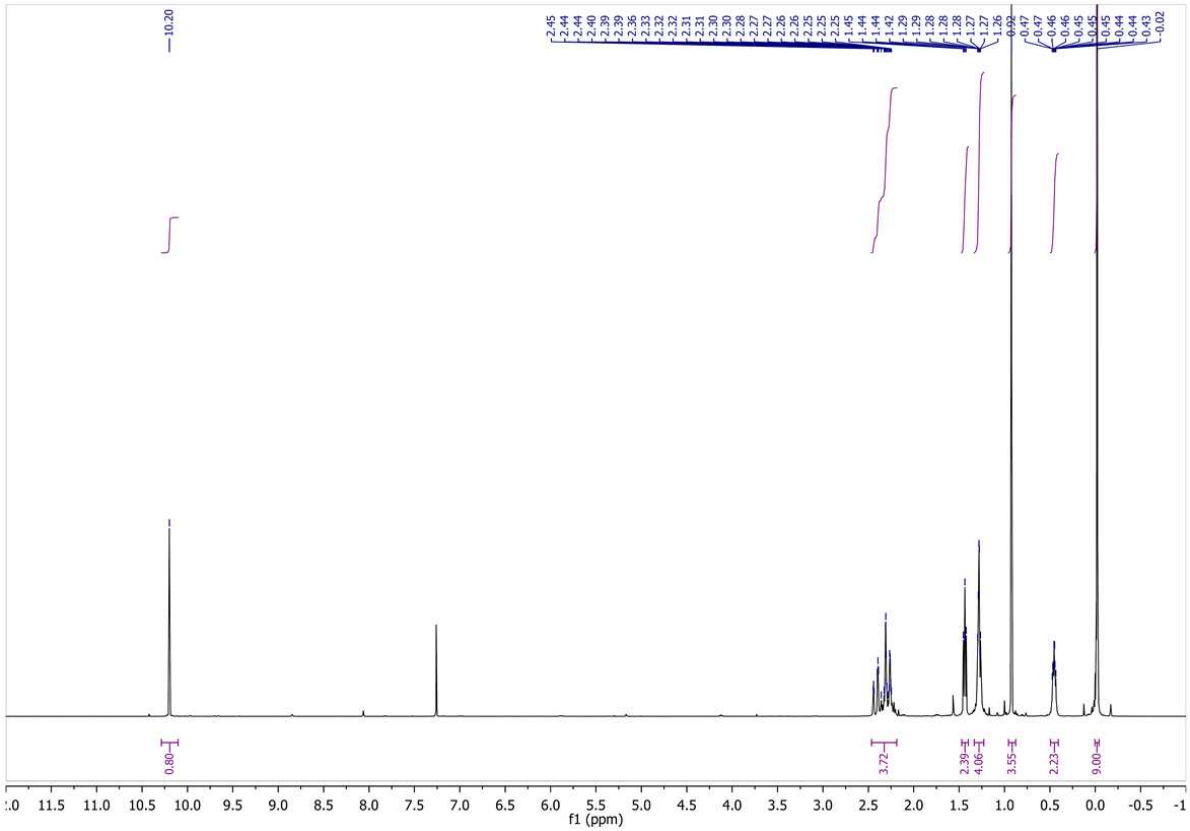
FT-IR thin film, neat (ATR): 2932, 2861, 1681, 1625 cm^{-1};

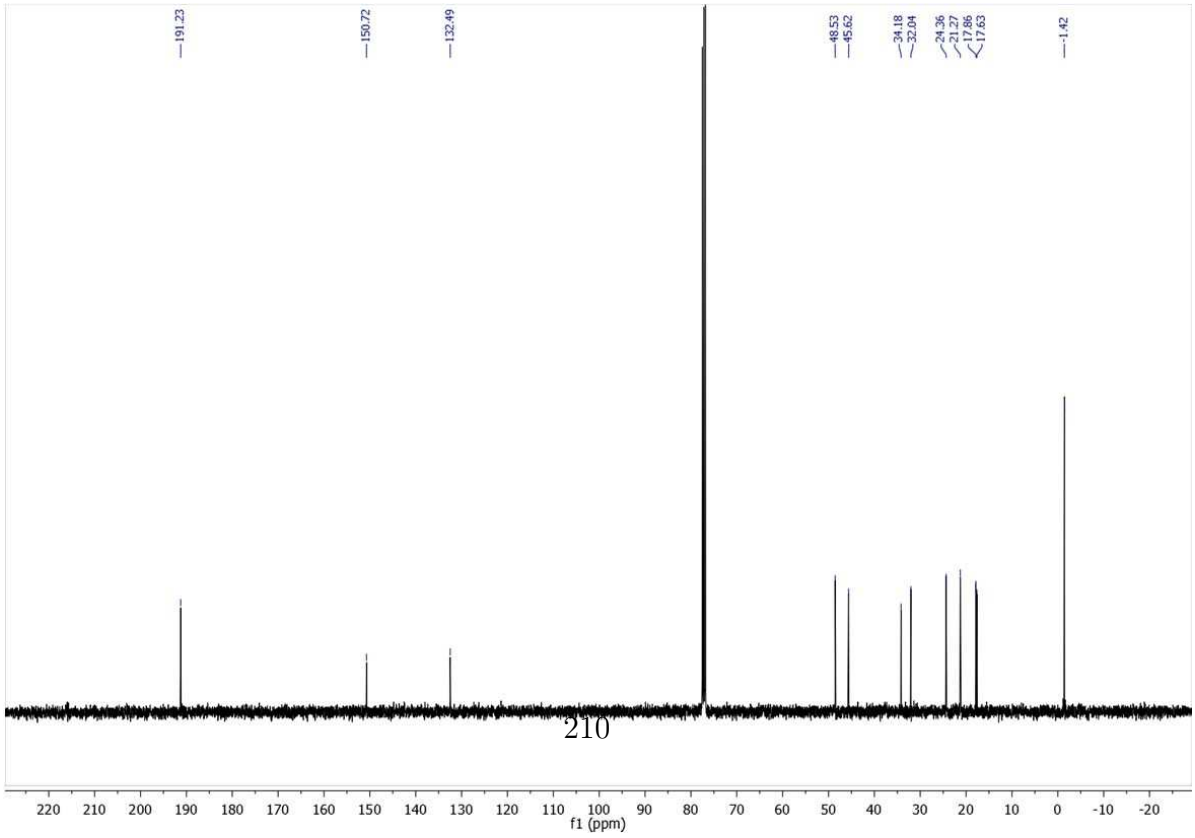
HRMS (APCI$^-$): calculated for $C_{14}H_{24}O^{35}Cl^{28}Si$, $[M\text{-}H]^{+\bullet}$: 271.12795 found 271.12872 (Δ = 2.87 ppm);

$[\alpha]_D^{25}$ = + 20° (*c* = 1.0, CH_2Cl_2), based on a sample of 96% *ee*;

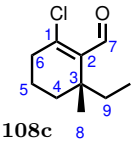

1.52 - 2.3
1.57 - 57.7
AU
Minutes
49.87
50.13
AU
Minutes

$^{1}H/^{13}C$ NMR


10.20
2.45
2.44
2.44
2.40
2.39
2.39
2.36
2.33
2.32
2.32
2.31
2.31
2.30
2.30
2.28
2.27
2.27
2.26
2.26
2.25
2.25
2.25
1.45
1.44
1.44
1.42
1.29
1.29
1.28
1.28
1.28
1.27
1.27
1.26
0.02
0.47
0.47
0.46
0.46
0.46
0.45
0.45
0.45
0.44
0.44
0.43
-0.02
0.80
3.72
2.39
4.06
3.55
2.23
9.00
f1 (ppm)


191.23
150.72
132.49
48.53
45.62
34.18
32.04
24.36
21.27
17.86
17.63
1.42
f1 (ppm)

5.3.1.7 (*R*)-2-chloro-6-ethyl-6-methylcyclohex-1-ene-1-carbaldehyde 108c



108c

1,4-addition reaction was conducted according to general procedure D on 0.5 mmol scale. An ethylene-filled balloon was attached directly to the Cp_2ZrHCl/CH_2Cl_2 mixture for the hydrozirconation step. All other procedures remain unchanged. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane) gave the title product as a yellow oil (61 mg, 0.31 mmol, 62% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IF column 250 × 4.6 mm, 1-30% $MeOH/CO_2$ gradient over 5 min, 1.5 $mL.min^{-1}$): *ee* = 98% (major enantiomer t_R = 2.00 min, minor enantiomer t_R = 1.91 min).

R_f = 0.60 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

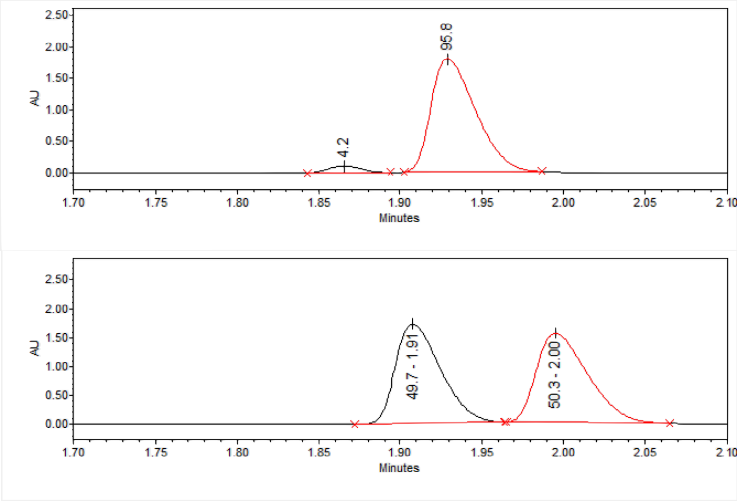
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H, 7), 2.44 – 2.20 (m, 4H, 6/5), 1.43 (dd, J = 7.3, 5.8 Hz, 2H, 4), 1.32 (qd, J = 7.5, 3.8 Hz, 2H, 9), 0.91 (s, 3H, 8), 0.87 (t, J = 7.5 Hz, 3H, 10) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2 7, 150.7 1, 132.5 2, 48.1 65, 34.0 3, 33.5 9, 31.6 4, 23.8 8, 21.3 5, 7.9 10 ppm;

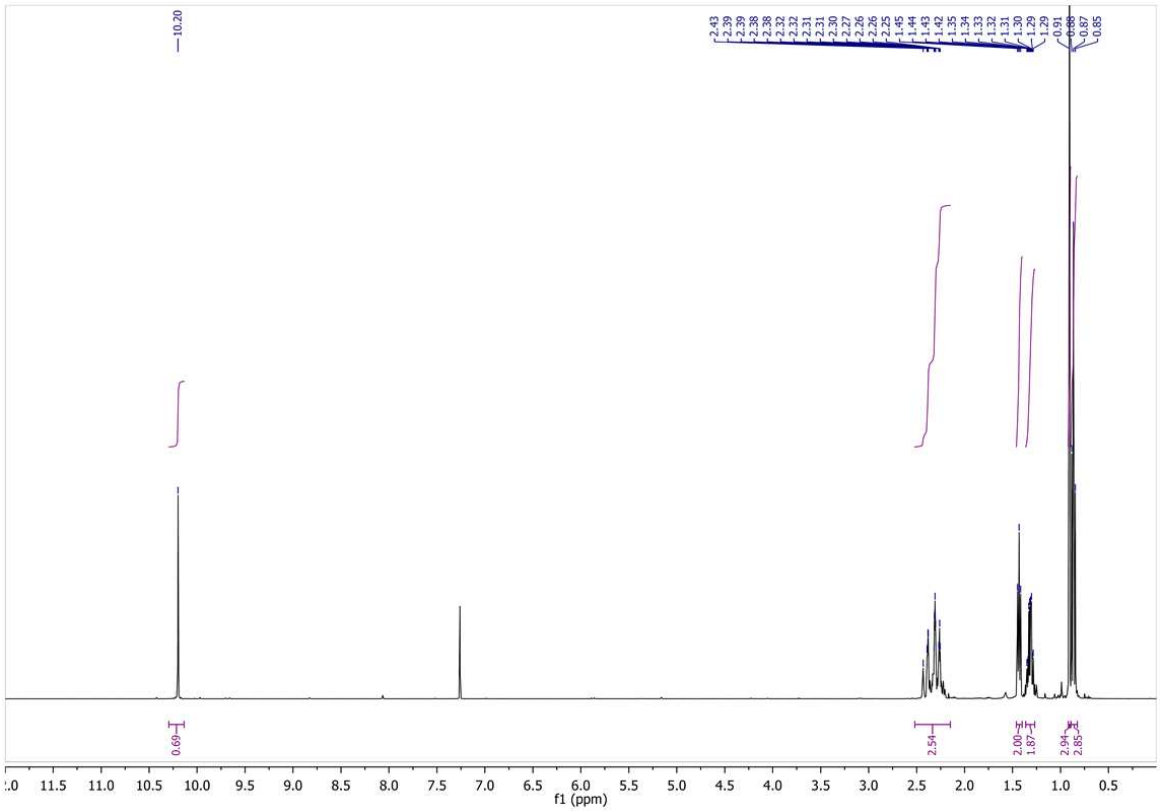
FT-IR thin film, neat (ATR): 2964, 2926, 2879, 1678, 1623 cm^{-1};

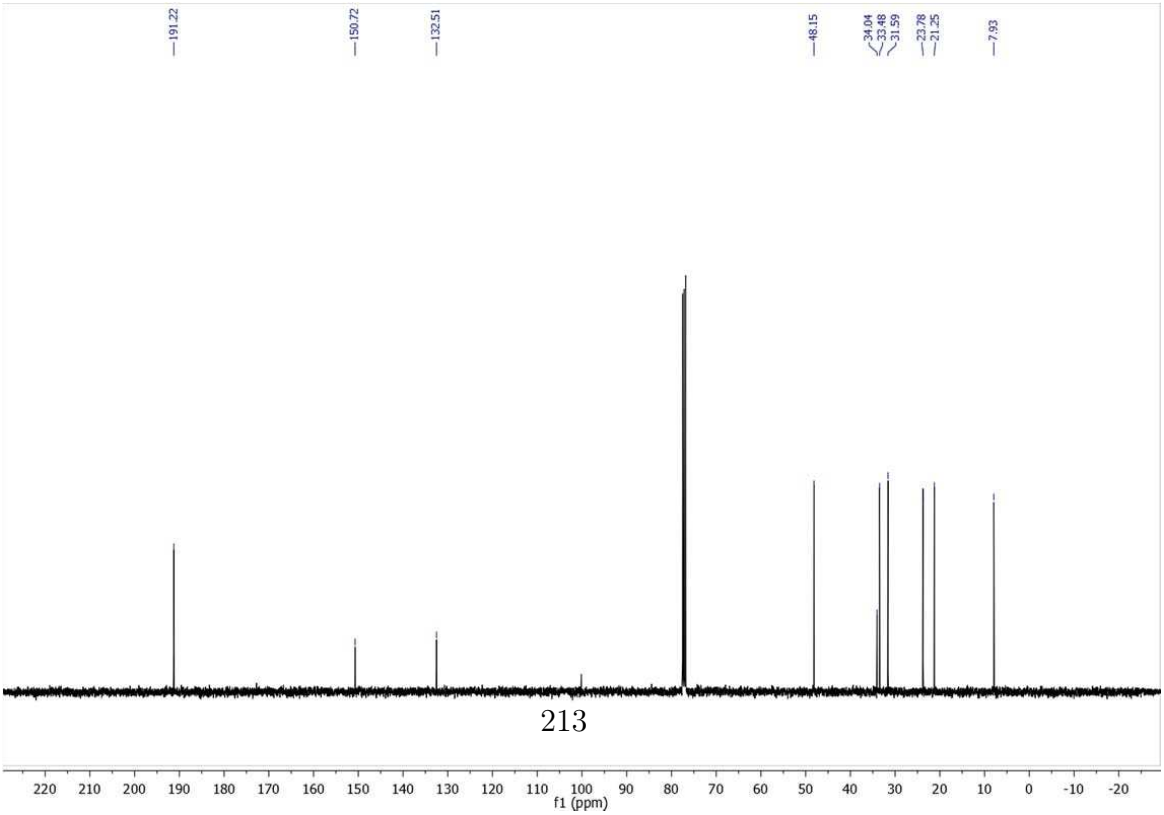
HRMS ($APCI^+$): calculated for $C_{10}H_{16}O^{35}Cl$, $[M+H]^{+\bullet}$: 187.08842 found 187.08850 (Δ = 0.44 ppm);

$[\alpha]_D^{25}$ = + 14° (*c* = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

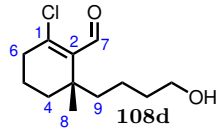

AU
2.50
2.00
1.50
1.00
0.50
0.00
4.2
95.8
1.70
1.75
1.80
1.85
1.90
1.95
2.00
2.05
2.10
Minutes
AU
49.7 - 1.91
50.3 - 2.00
Minutes

$^{1}H/^{13}C$ NMR


10.20
2.43
2.39
2.39
2.38
2.38
2.32
2.32
2.31
2.31
2.30
2.27
2.26
2.26
2.25
1.45
1.44
1.43
1.42
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.29
0.91
0.88
0.87
0.85
0.69
2.54
2.00
1.87
2.94
2.85
f1 (ppm)


191.22
150.72
132.51
48.15
34.04
33.48
31.59
23.78
21.25
7.93
f1 (ppm)

5.3.1.8 (*R*)-2-chloro-6-(4-hydroxybutyl)-6-methylcyclohex-1-ene-1-carbaldehyde 108d



108d

1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using (but-3-en-1-yloxy)(tert-butyl)dimethylsilane[114] as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5-20% Et_2O/*n*-pentane gradient, silica column) gave the title product as a colourless oil (16 mg, 0.069 mmol) as well as the formate ester **108e** (colourless oil 46 mg, 0.17 mmol). The total yield of the reaction was thus 45%. Enantiomeric excess was determined by comparison with an authentic racemic sample. HPLC (Chiralpak IB column 250 × 4.6 mm, 1% ^{i}PrOH/*n*-hexane, 1.0 mL.min^{-1}): *ee* = 94% (major enantiomer t_R = 13.19 min, minor enantiomer t_R = 12.59 min).

R_f = 0.54 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.29 (s, 1H, 7), 3.64 (t, J = 6.5 Hz, 2H, 12), 2.58 – 2.34 (m, 4H, 6/5), 1.91 – 1.79 (m, 2H, 11), 1.60 – 1.51 (m, 4H, 9/10), 1.41 – 1.30 (m, 2H, 4), 1.03 (s, 3H, 8) ppm;

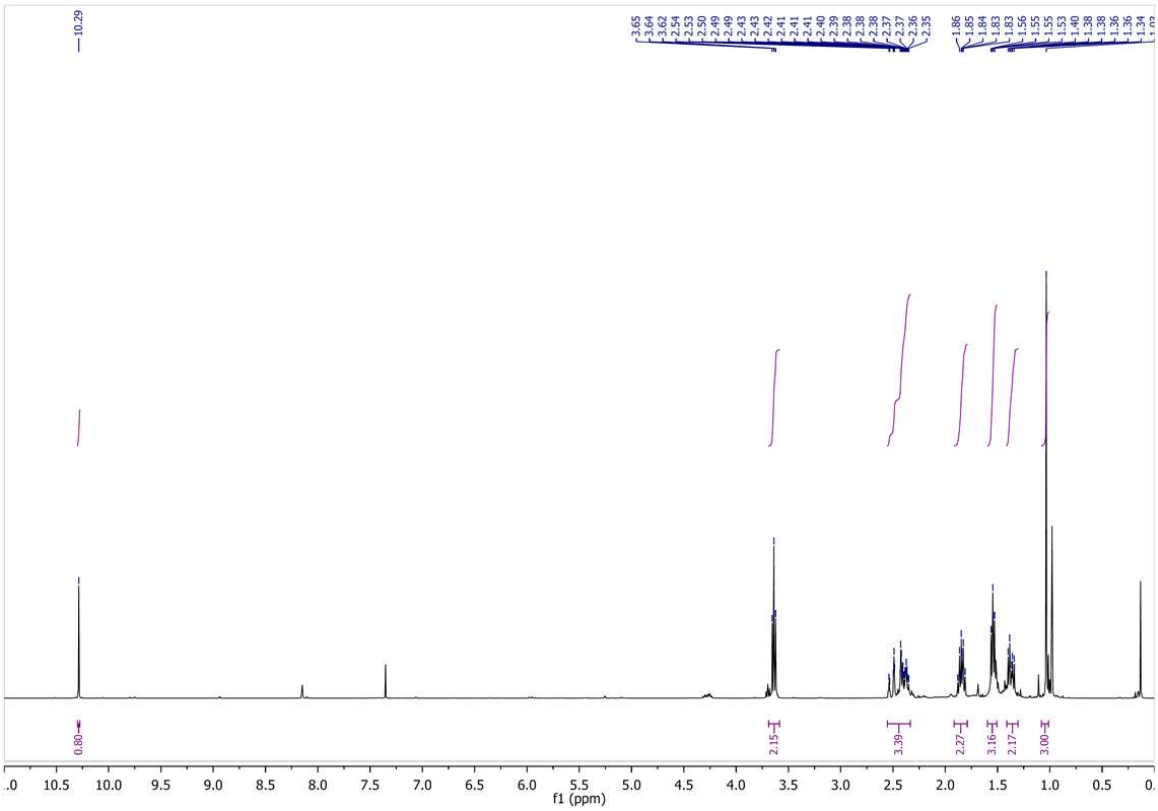
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1 7, 150.3 1, 132.4 2, 48.4 6, 45.0 12, 40.4 4, 34.0 3, 33.2 11, 31.9 9, 24.3 8, 21.2 5, 20.9 10 ppm;

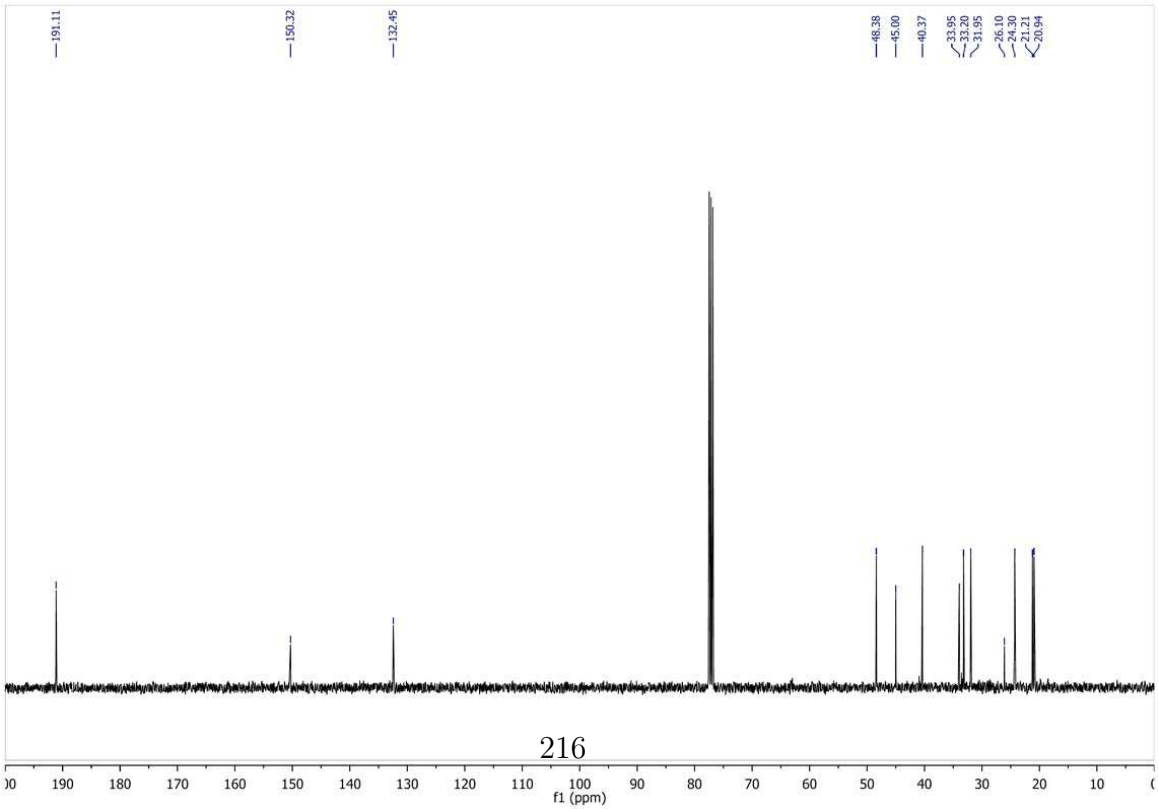
FT-IR thin film, neat (ATR): 2931, 2858, 1678, 1624, 1229 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{13}H_{24}O_3{}^{35}Cl$, $[M+CH_3OH+H]^{+\bullet}$: 263.14085 found 263.14064 (Δ = 0.78 ppm);

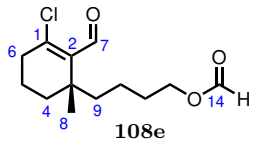
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +18^{\circ}$ ($c = 1.0$, CH_2Cl_2), based on a sample of 94% *ee*;

$^{1}H/^{13}C$ NMR


10.29
0.80
2.15
3.39
2.27
3.16
2.17
3.00
f1 (ppm)


191.11
150.32
132.45
48.38
45.00
40.37
33.95
33.20
31.95
26.10
24.30
21.21
20.94
f1 (ppm)

5.3.1.9 (*R*)-4-(3-chloro-2-formyl-1-methylcyclohex-2-en-1-yl)butyl formate 108e



108e

The product was co-isolated with compound **108d** .

R_f = 0.32 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H, 7), 8.06 (d, J = 0.8 Hz, 1H, 14), 4.17 (td, J = 6.6, 0.8 Hz, 2H, 12), 2.46 – 2.25 (m, 4H, 5/6), 1.65 (dq, J = 7.8, 6.6 Hz, 2H, 11), 1.45 (dd, J = 7.2, 5.9 Hz, 2H, 4), 1.40 – 1.24 (m, 4H, 9/10), 0.93 (s, 3H, 8) ppm;

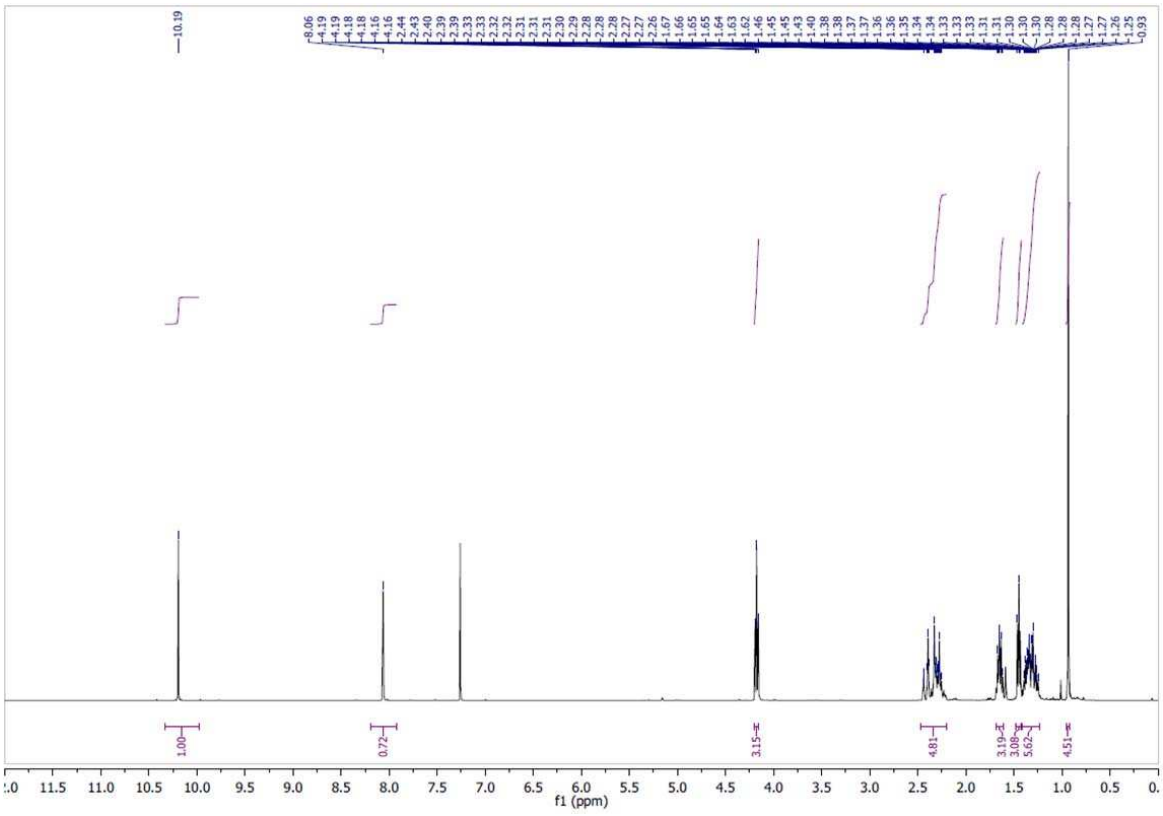
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1 7, 161.2 14, 150.3 1, 132.4 2, 63.9 12, 48.4 6, 40.8 9, 33.9 3, 31.9 4, 29.3 11, 24.3 8, 21.2 5, 20.0 10 ppm;

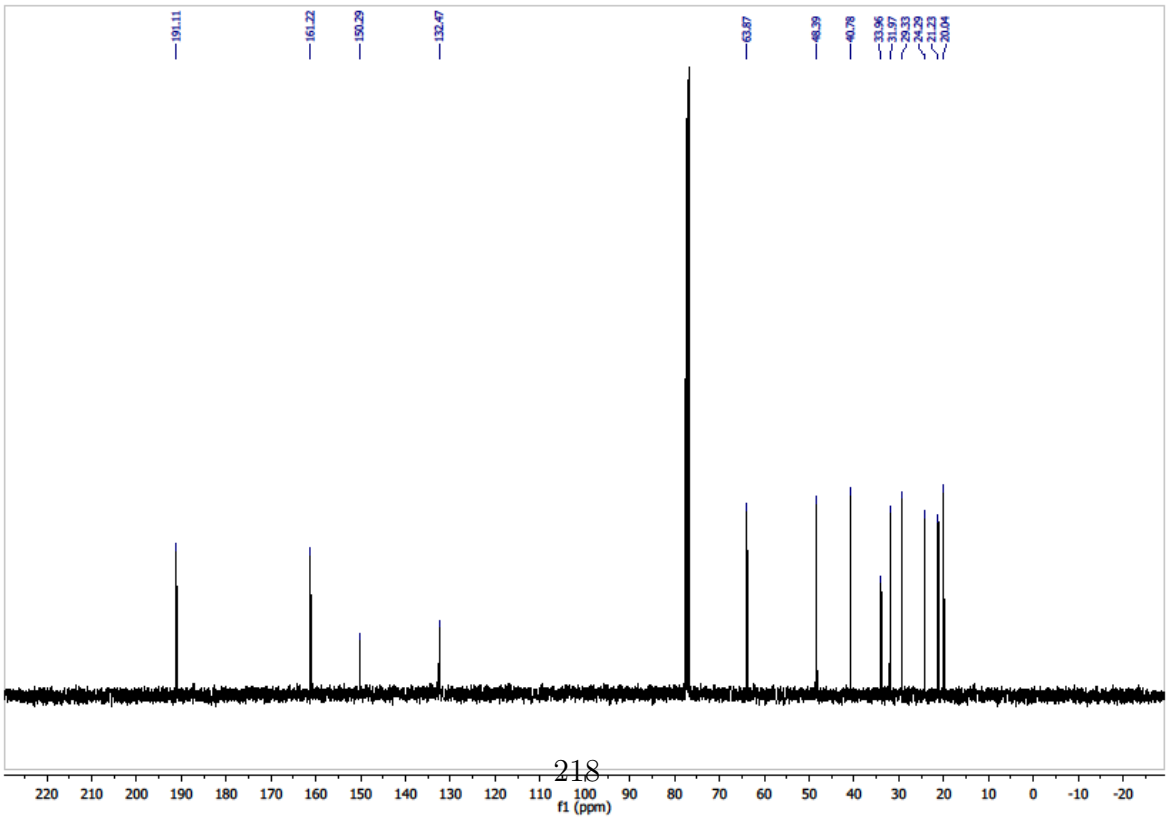
FT-IR thin film, neat (ATR): 2933, 2870, 1724, 1677, 1624, 1170 cm^{-1};

HRMS (ESI^+): calculated for $C_{13}H_{19}O_3{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 281.09149 found 281.09143 (Δ = -0.22 ppm);

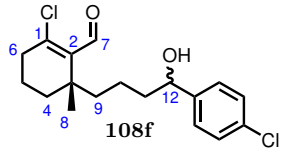
$[\alpha]_D^{25}$ = + 22° (c = 0.78, CH_2Cl_2), based on a sample of 94% *ee*;

$^{1}H/^{13}C$ NMR


10.19
1.00
0.72
3.15
4.81
3.19
3.08
5.62
4.51
f1 (ppm)


191.11
161.22
150.29
132.47
63.87
48.39
40.78
33.96
31.97
29.33
24.29
21.23
20.04
f1 (ppm)

5.3.1.10 (6R)-2-chloro-6-(4-(4-chlorophenyl)-4-hydroxybutyl)-6-methylcyclohex-1-ene-1-carbaldehyde 108f



108f

1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using *tert*-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane[31a] as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane gradient, silica column) gave the title product as a mixture of diastereomers (103 mg yellow oil, 0.30 mmol, 57% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step, hydrolyzing the *tert*-butyldimethylsilyl group using TBAF and submitting it to HPLC analysis according to the conditions reported by Sidera et. al.[31a] *ee* = 90%.

R_f = 0.52 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.22 (s, 1H, 7), 4.84 (t, J = 7.4 Hz, 1H, 12), 2.45 – 2.19 (m, 4H, alkyl-H), 2.17 – 1.91 (m, 2H, alkyl-H), 1.57 – 1.20 (m, 6H, alkyl-H), 0.94 (s, 3H, 8) ppm;

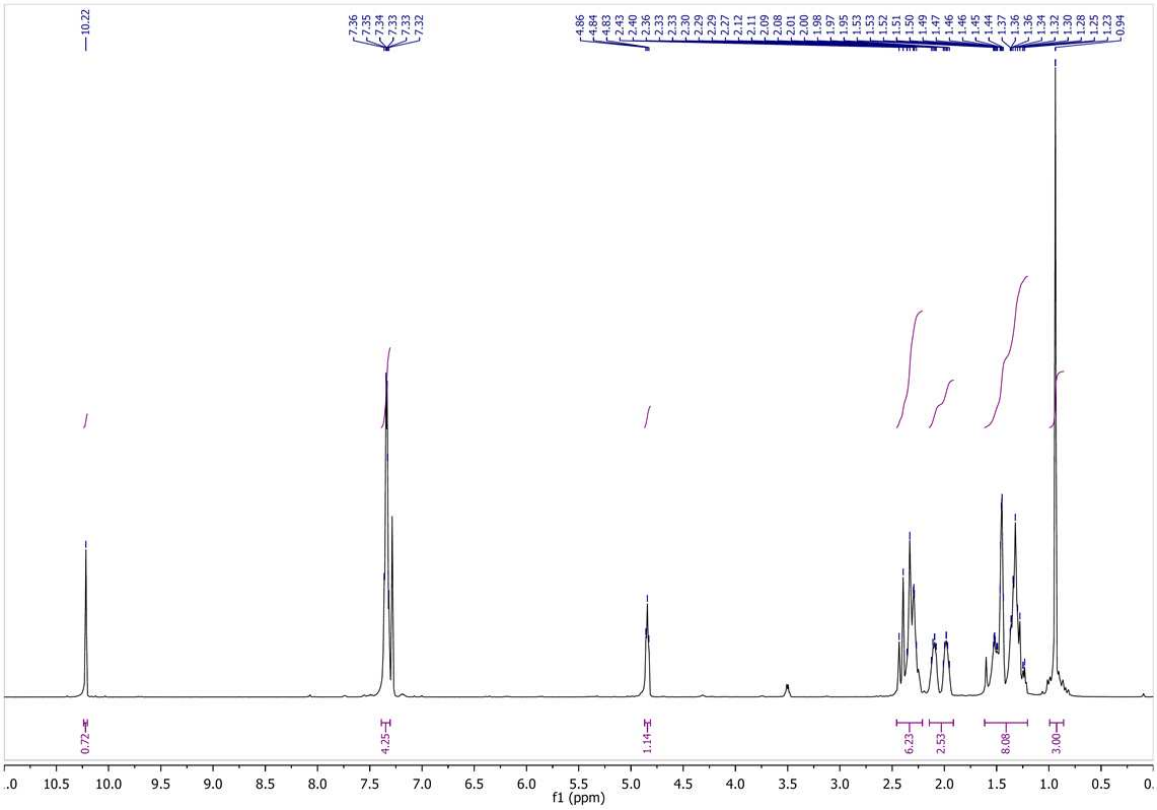
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1 7, 150.2 1, 140.4 Ar-C, 134.2 Ar-C, 132.4 2, 129.0 (2C) Ar-C, 128.4 (2C) Ar-C, 62.7 12, 48.3 (CH_2), 40.6 (CH_2), 40.4(40.3) (CH_2), 33.9 3, 31.9 (CH_2), 24.3 8, 21.2 (2C) (CH_2) ppm;

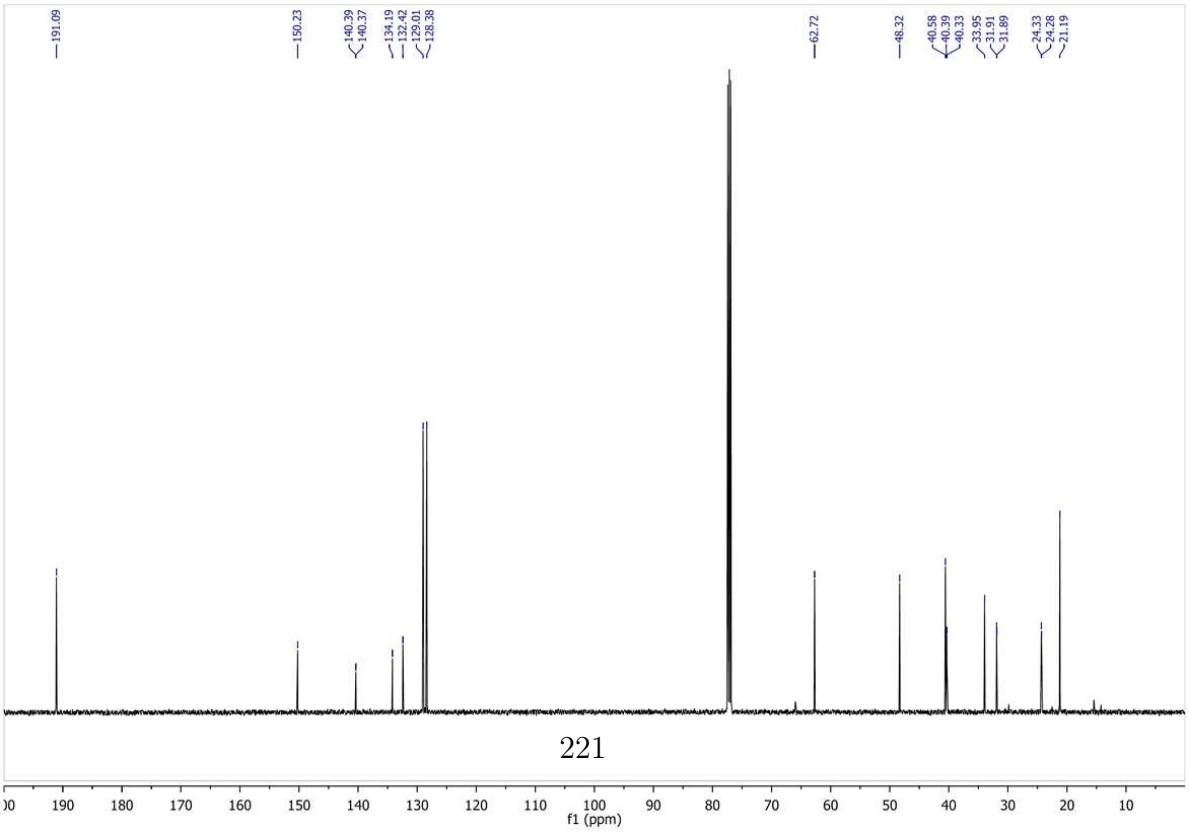
FT-IR thin film, neat (ATR): 2930, 2869, 1677, 1624, 1493, 1230, 1092, 1015, 821 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{18}H_{21}O^{35}Cl_2$, [M-OH]$^{+\bullet}$: 323.09640 found 323.09638 (Δ = 0.05 ppm);

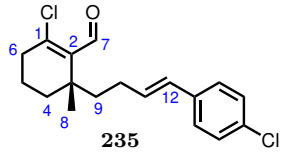
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 13° (c = 1.0, CH_2Cl_2), based on a sample of 90% *ee*;

$^{1}H/^{13}C$ NMR


10.22
7.36
7.35
7.34
7.33
7.33
7.32
4.86
4.84
4.83
2.43
2.40
2.36
2.33
2.30
2.29
2.27
2.12
2.11
2.09
2.08
2.01
2.00
1.98
1.97
1.95
1.53
1.53
1.52
1.51
1.50
1.49
1.47
1.46
1.46
1.45
1.44
1.37
1.36
1.36
1.34
1.32
1.30
1.28
1.25
1.23
0.94
0.72
4.25
1.14
6.23
2.53
8.08
3.00
f1 (ppm)


191.09
150.23
140.39
140.37
134.19
132.42
129.01
128.38
62.72
48.32
40.58
40.39
40.33
33.95
31.91
31.89
24.33
24.28
21.19
f1 (ppm)

5.3.1.11 (S,E)-2-chloro-6-(4-(4-chlorophenyl)but-3-en-1-yl)-6-methylcyclohex-1-ene-1-carbaldehyde 235



235

The product was co-isolated with compound **108f** .

$\mathbf{R_f}$ = 0.52 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.22 (s, 1H, 7), 7.36 – 7.23 (m, 4H, Ar-H), 6.36 (dt, J = 15.8, 1.7 Hz, 1H, 11), 6.18 (dt, J = 15.8, 6.8 Hz, 1H, 12), 2.52 – 2.31 (m, 4H, 5/6), 2.21 (dtt, J = 10.3, 6.8, 1.7 Hz, 2H, 10), 1.51 (t, J = 6.4 Hz, 2H, 4), 1.49 – 1.43 (m, 2H, 9), 1.00 (s, 3H, 8) ppm;

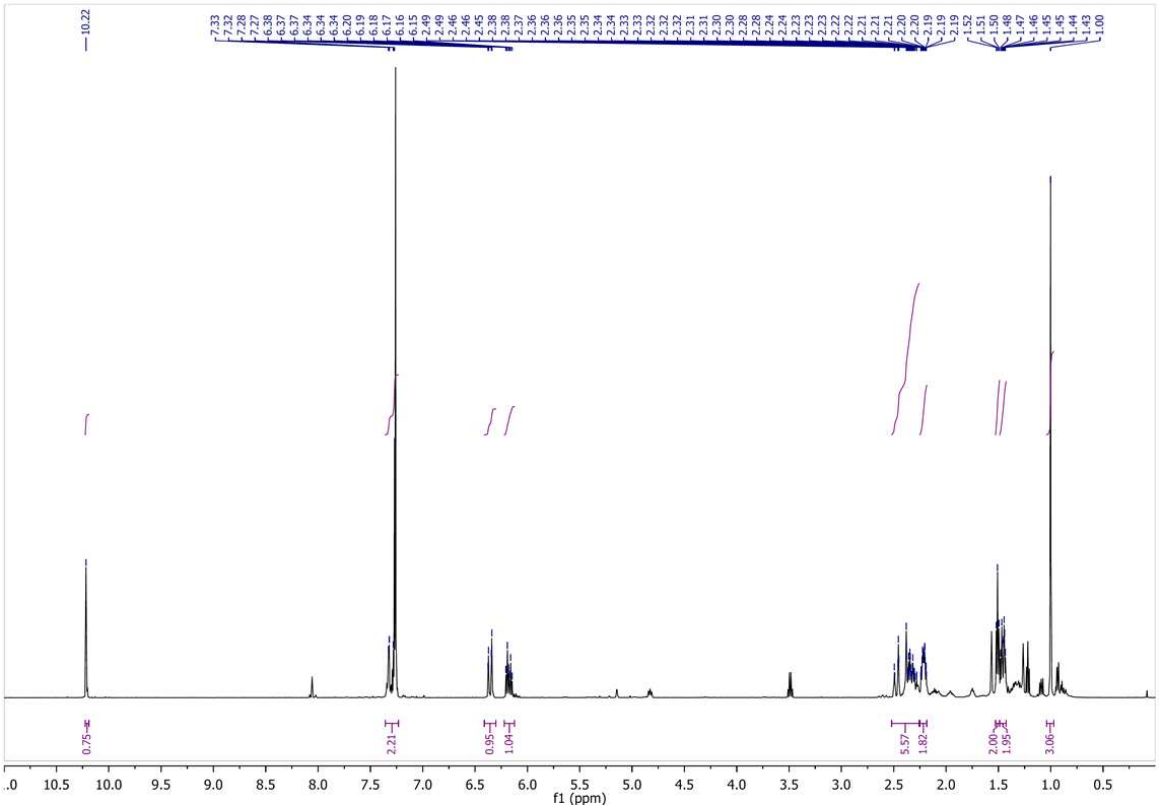
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1 7, 150.2 1, 136.2 Ar-H, 132.7 2, 132.5 Ar-H, 131.3 14, 129.0 13, 128.8 (2C) Ar-H, 127.2 (2C) Ar-H, 48.4 6, 40.5 9, 34.0 3, 32.0 4, 27.3 10, 24.4 8, 21.2 5 ppm;

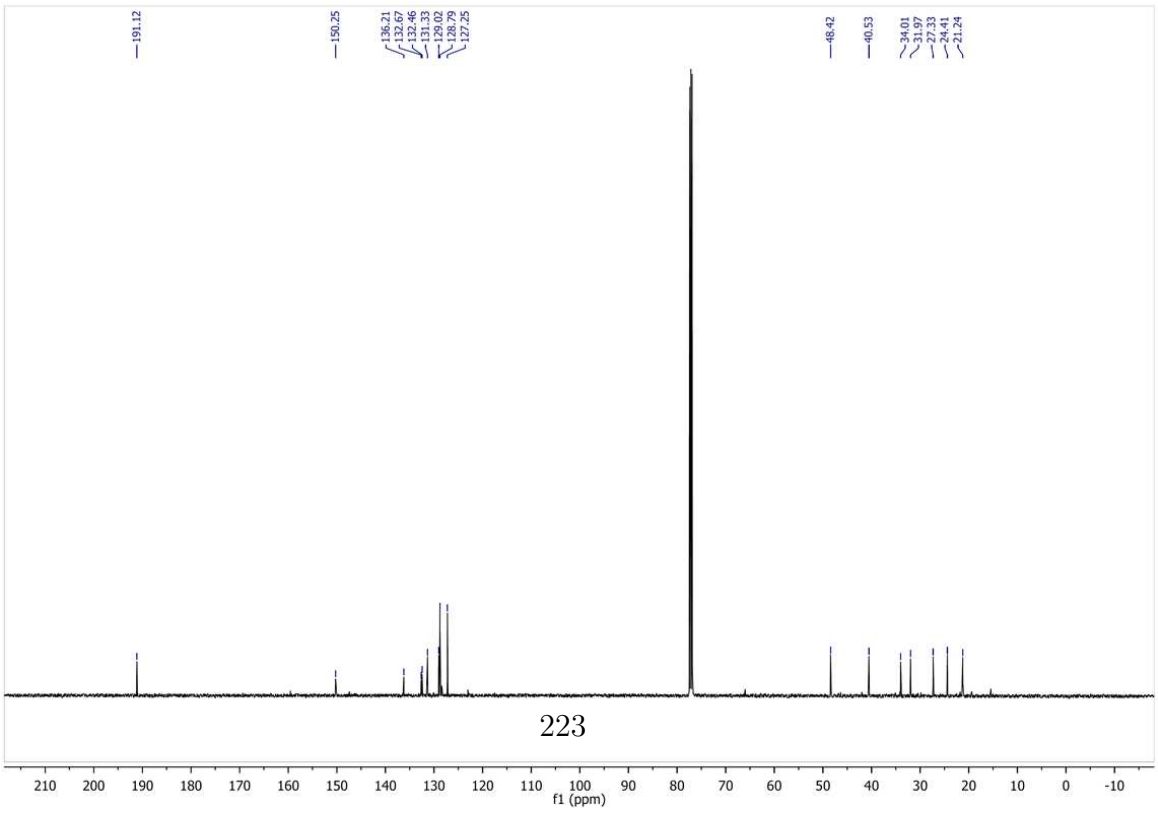
FT-IR thin film, neat (ATR): 2927, 2851, 1678, 1624, 1491, 1229, 1092 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{18}H_{21}O^{31}Cl_2$, $[M+H]^{+\bullet}$: 323.09640 found 323.09641 (Δ = 0.02 ppm);

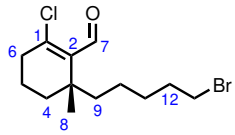
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 25° (c = 0.71, CH_2Cl_2), based on a sample of 90% *ee*;

$^{1}H/^{13}C$ NMR


10.22
7.33 7.32 7.28 7.27 6.38 6.37 6.37 6.34 6.34 6.34 6.20 6.19 6.18 6.17 6.16 6.15 6.14 2.49 2.46 2.46 2.45 2.38 2.38 2.37 2.36 2.36 2.35 2.35 2.34 2.34 2.33 2.33 2.32 2.32 2.31 2.31 2.30 2.30 2.28 2.28 2.24 2.24 2.23 2.23 2.23 2.22 2.22 2.21 2.21 2.20 2.20 2.19 2.19 1.52 1.51 1.50 1.48 1.47 1.46 1.45 1.45 1.44 1.43 1.00
0.75
2.21
0.95
1.04
5.57
1.82
2.00
1.95
3.06
f1 (ppm)


191.12
150.25
136.21
132.67
132.46
131.33
129.02
128.79
127.25
48.42
40.53
34.01
31.97
27.33
24.41
21.24
f1 (ppm)

5.3.1.12 (*R*)-6-(5-bromopentyl)-2-chloro-6-methylcyclohex-1-ene-1-carbaldehyde 108g



108g

1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using 5-bromo-1-pentene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (0–5% Et_2O/*n*-pentane) gave the title product as a yellow oil (78 mg, 0.25 mmol, 48% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IA column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 80% (major enantiomer t_R = 2.91 min, minor enantiomer t_R = 2.49 min).

R_f = 0.64 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

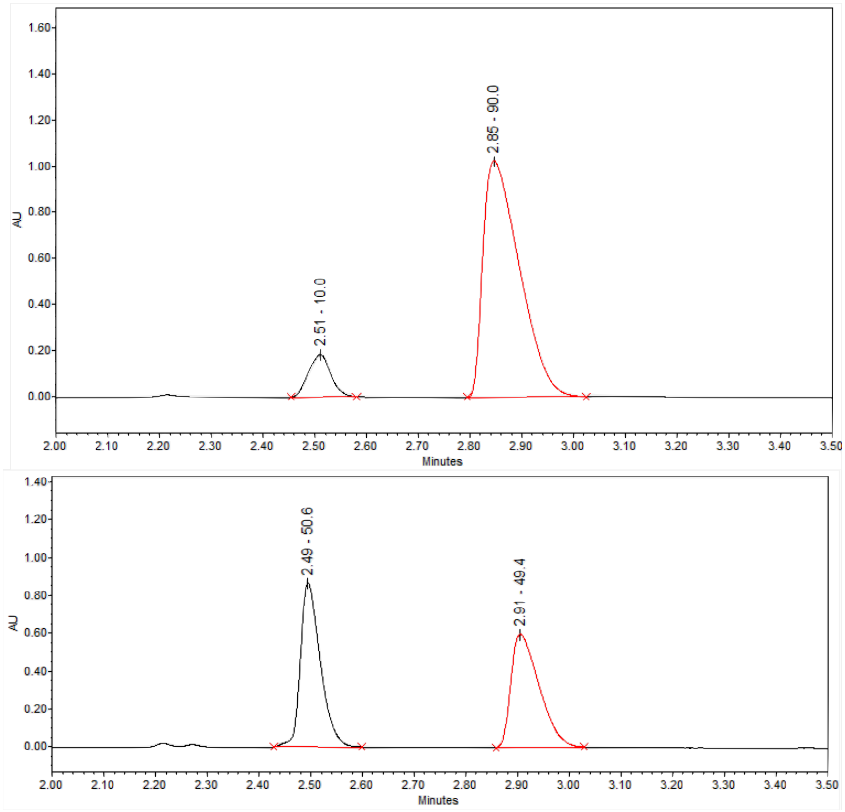
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.20 (s, 1H, 7), 3.40 (t, J = 6.8 Hz, 2H, 13), 2.45 – 2.21 (m, 4H, alkyl-H), 1.91 – 1.82 (m, 2H, alkyl-H), 1.48 – 1.37 (m, 4H, alkyl-H), 1.35 – 1.24 (m, 4H, alkyl-H), 0.93 (s, 3H, 8) ppm;

^{3}C NMR (126 MHz, $CDCl_3$) δ 191.2 7, 150.5 1, 132.4 2, 48.5 (CH_2), 41.0 (CH_2), 34.0 3, 33.9 13, 32.85 (CH_2), 32.0 (CH_2), 29.0 (CH_2), 24.4 8, 22.8 (CH_2), 21.2 (CH_2) ppm;

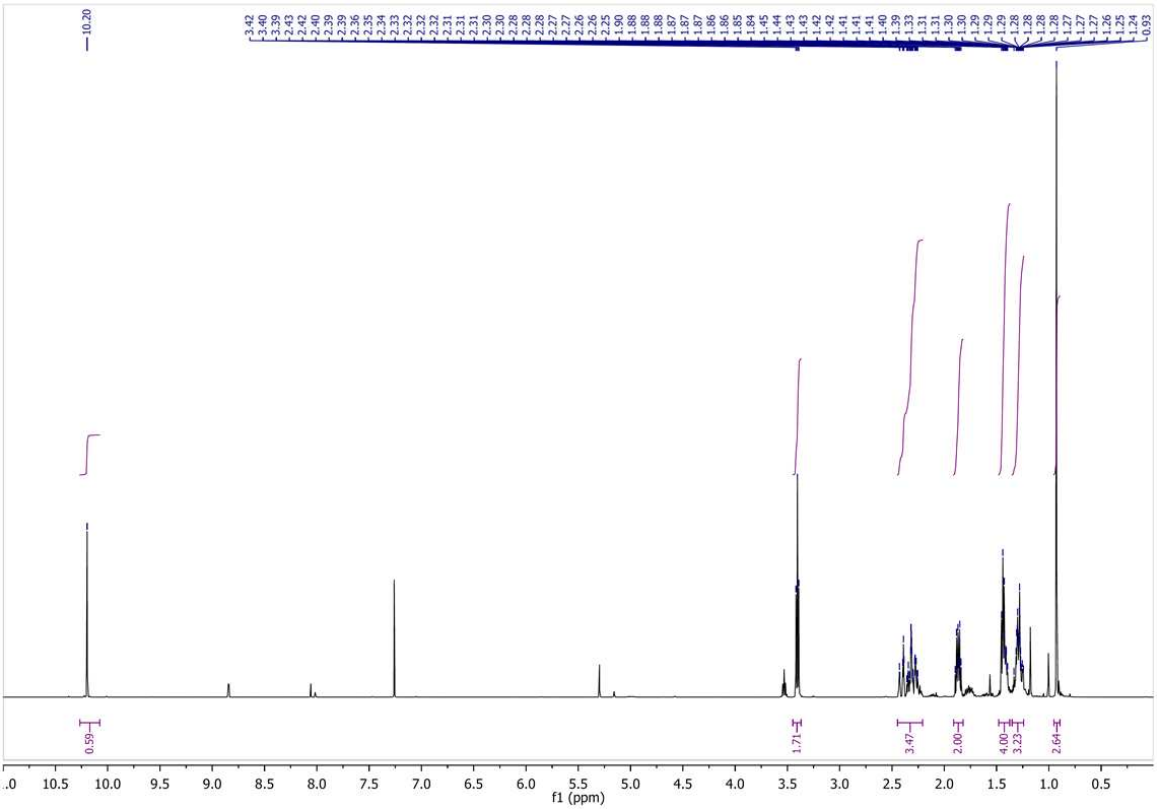
FT-IR thin film, neat (ATR): 2933, 2858, 1678, 1624, 1228 cm^{-1};

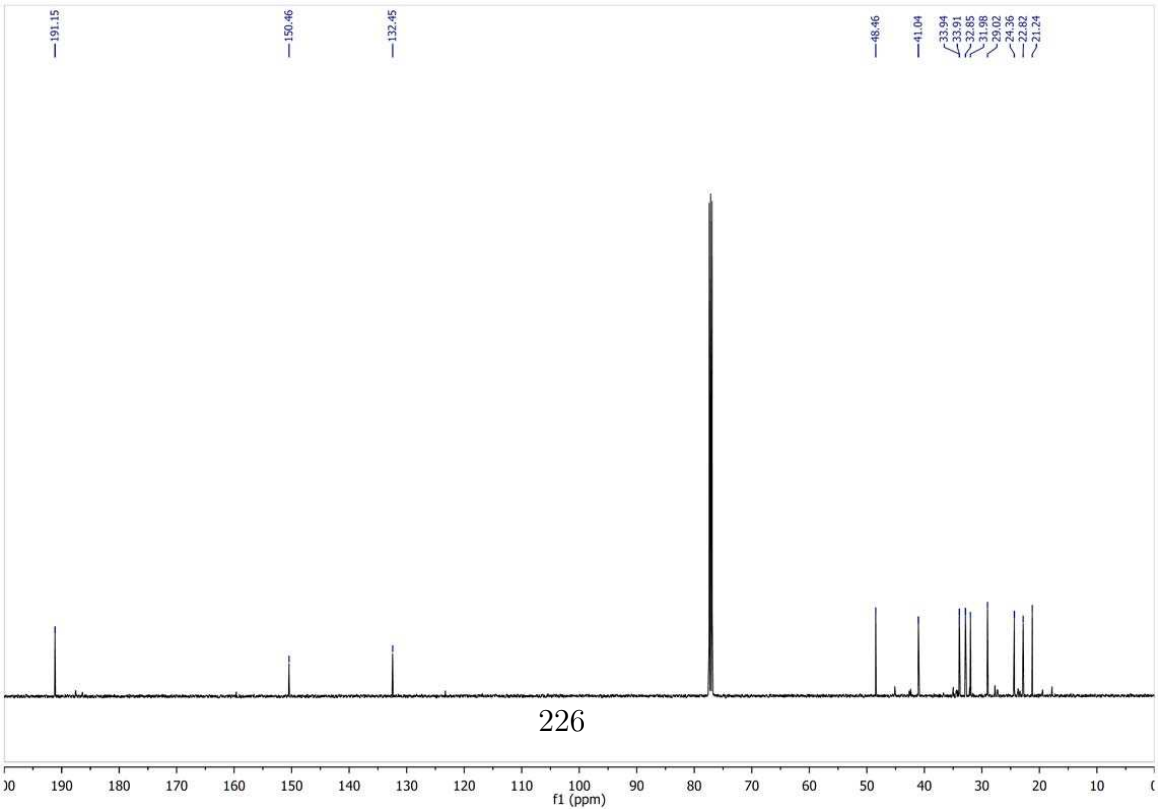
HRMS (ESI$^+$): calculated for $C_{13}H_{21}O^{79}Br^{35}Cl$, $[M+H]^{+\bullet}$: 307.04588 found 307.04605 (Δ = 0.55 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +17^{\circ}$ ($c = 1.0$, CH_2Cl_2), based on a sample of 80% *ee*;

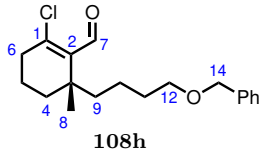


$^{1}H/^{13}C$ NMR


10.20
0.59
1.71
3.47
2.00
4.00
3.23
2.64
f1 (ppm)


191.15
150.46
132.45
48.46
41.04
33.94
33.91
32.85
31.98
29.02
24.36
22.82
21.24
f1 (ppm)

5.3.1.13 (*R*)-6-(4-(benzyloxy)butyl)-2-chloro-6-methylcyclohex-1-ene-1-carbaldehyde 108h



108h

1,4-addition reaction was conducted according to general procedure D on 0.53 mmol scale and using ((but-3-en-1-yloxy)methyl)benzene[114] as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane) gave the title product as a yellow oil (77 mg, 0.23 mmol, 43% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[31a] *ee* = 86%.

R_f = 0.55 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

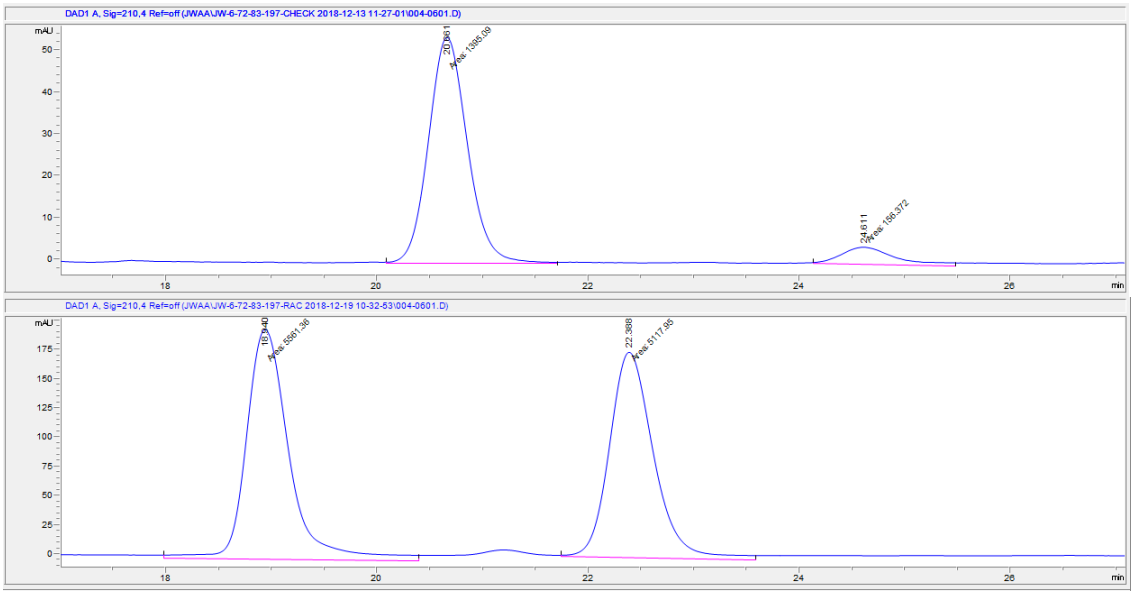
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H, 7), 7.31 – 7.26 (m, 3H, ArH), 7.23 – 7.17 (m, 2H, ArH), 4.43 (s, 2H, 14), 3.40 (dd, J = 6.8, 5.8 Hz, 2H, 12), 2.39 – 2.11 (m, 4H, alkyl-H), 1.57 – 1.46 (m, 2H, 11), 1.36 (dd, J = 7.1, 5.9 Hz, 2H, 4), 1.32 – 1.24 (m, 2H, 10), 1.23 – 1.17 (m, 2H, 9), 0.85 (s, 3H, 8) ppm;

^{3}C NMR (101 MHz, $CDCl_3$) δ 191.2 7, 150.6 1, 138.7 Ar-C, 132.5 2, 128.5 (2C) Ar-C, 127.8 (2C) Ar-C, 127.7 Ar-C, 73.1 14, 70.3 12, 48.5 6, 41.1 9, 34.0 3, 32.0 4, 30.6 10, 24.3 8, 21.2 5, 20.3 10 ppm;

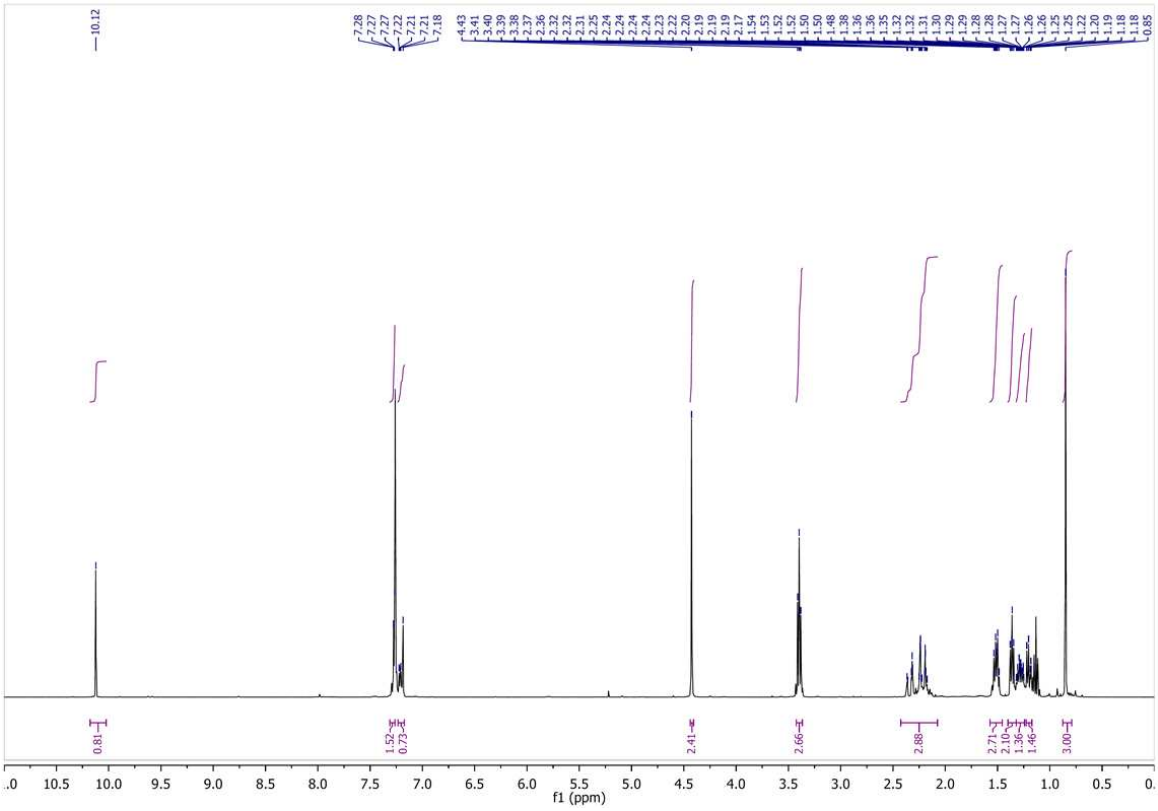
FT-IR thin film, neat (ATR): 2934, 2857, 1678, 1624, 1103 cm^{-1};

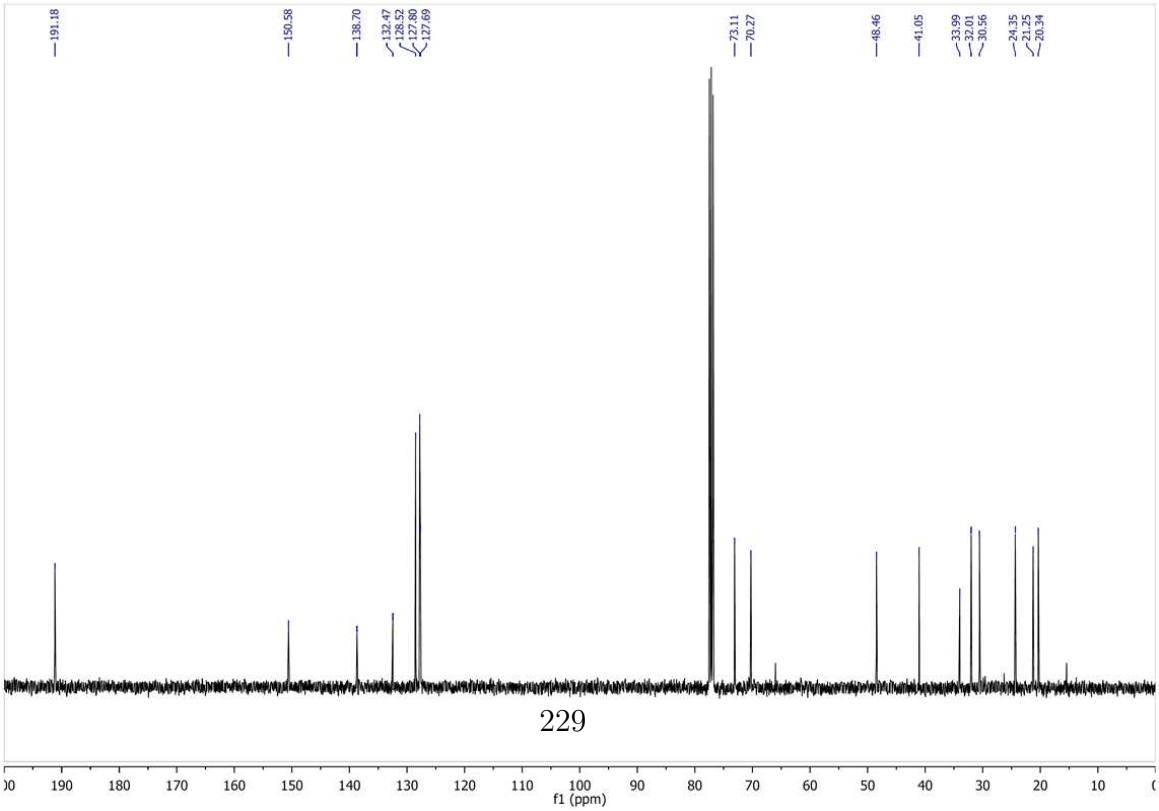
HRMS (ESI^+): calculated for $C_{19}H_{25}O_2{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 343.14353 found 343.14355 (Δ = 0.08 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +12^{\circ}$ ($c = 1.0$, CH_2Cl_2), based on a sample of 86% *ee*;

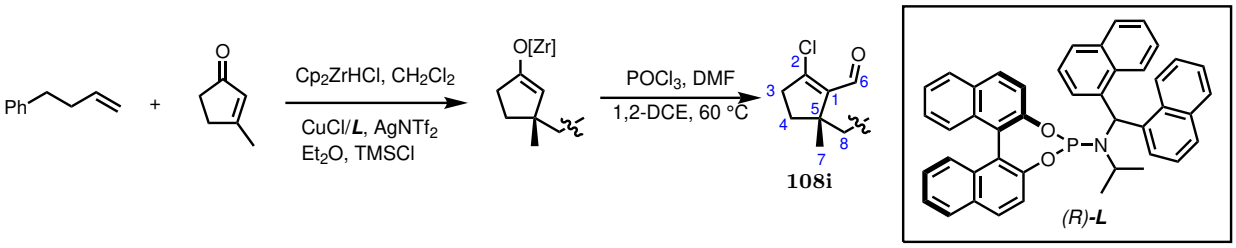


$^{1}H/^{13}C$ NMR


10.12
7.28
7.27
7.27
7.22
7.21
7.21
7.18
4.43
3.41
3.40
3.39
3.38
2.37
2.36
2.32
2.31
2.25
2.24
2.24
2.24
2.23
2.22
2.20
2.19
2.19
2.17
1.54
1.53
1.52
1.50
1.50
1.48
1.38
1.36
1.36
1.35
1.32
1.31
1.30
1.29
1.29
1.28
1.28
1.27
1.27
1.26
1.26
1.25
1.22
1.20
1.19
1.18
1.18
0.85
0.81
1.52
0.73
2.41
2.66
2.88
2.71
2.10
1.36
1.46
3.00
f1 (ppm)


191.18
150.58
138.70
132.47
128.52
127.80
127.69
73.11
70.27
48.46
41.05
33.99
32.01
30.56
24.35
21.25
20.34
f1 (ppm)

5.3.1.14 (*R*)-2-chloro-5-methyl-5-(4-phenylbutyl)cyclopent-1-ene-1-carbaldehyde 108i



The 1,4-addition reaction was performed according to a literature procedure.[32] CuCl (4.0 mg, 0.040 mmol, 0.10 mol equiv) and then the phosphoramidite ligand shown (28 mg, 0.044 mmol, 0.11 mol equiv) were added to a 5 mL round bottom flask equipped with a rubber septum and stirrer bar (flask **A**). Three cycles of vacuum and back filling with N_2 were then performed after which Et_2O (2.0 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment. Concurrently, Cp_2ZrHCl (206 mg, 0.798 mmol, 2.0 mol equiv) was added to a separate 5 mL round bottom flask equipped with a rubber septum and stirrer bar (flask **B**). Three cycles of vacuum and back filling with N_2 were then performed, after which dry CH_2Cl_2 (0.4 mL) and then alkene (0.15 mL, 1.0 mmol, 2.5 mol equiv) were added. After stirring for one hour, a clear orange solution was obtained.

Silver bis(trifluoromethanesulfonyl)imide (22 mg, 0.057 mmol, 0.14 mol equiv) was tipped into flask **A** in one portion (minimizing exposure to the atmosphere). After stirring for 10 minutes, the solution from flask **A** was then filtered (using a syringe filter) into flask **B** over a period of one minute. The resulting solution became

dark within 10 seconds. After stirring for 20 minutes, chlorotrimethylsilane (0.25 mL, ρ = 0.86 g.mL^{-1}, 2.0 mmol, 4.9 mol equiv) was added in one portion then 3-methyl-2-cyclopentenone was added at a rate of 1 drop every 2 seconds (40 μL, ρ = 0.97 g.mL^{-1}, 0.40 mmol, 1.0 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. At this point, the reaction contents were subjected to trapping procedure G with quantities scaled appropriately (0.40 mmol scale). Flash chromatography (5% Et_2O/*n*-pentane) gave the title product as a colourless oil (45 mg, 0.16 mmol, 41% yield). Enantiomeric excess determined by taking an aliquot of the reaction mixture prior to trapping and submitting it to HPLC analysis.[32] *ee* = 90%.

R_f = 0.64 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H, 6), 7.24 – 7.18 (m, 2H, ArH), 7.13 – 7.07 (m, 3H, ArH), 2.70 – 2.17 (m, 6H, alkyl-H), 1.59 – 1.48 (m, 2H, 10), 1.40 – 1.33 (m, 2H, 8), 1.28 – 1.16 (m, 2H, 9), 1.01 (s, 3H, 7) ppm;

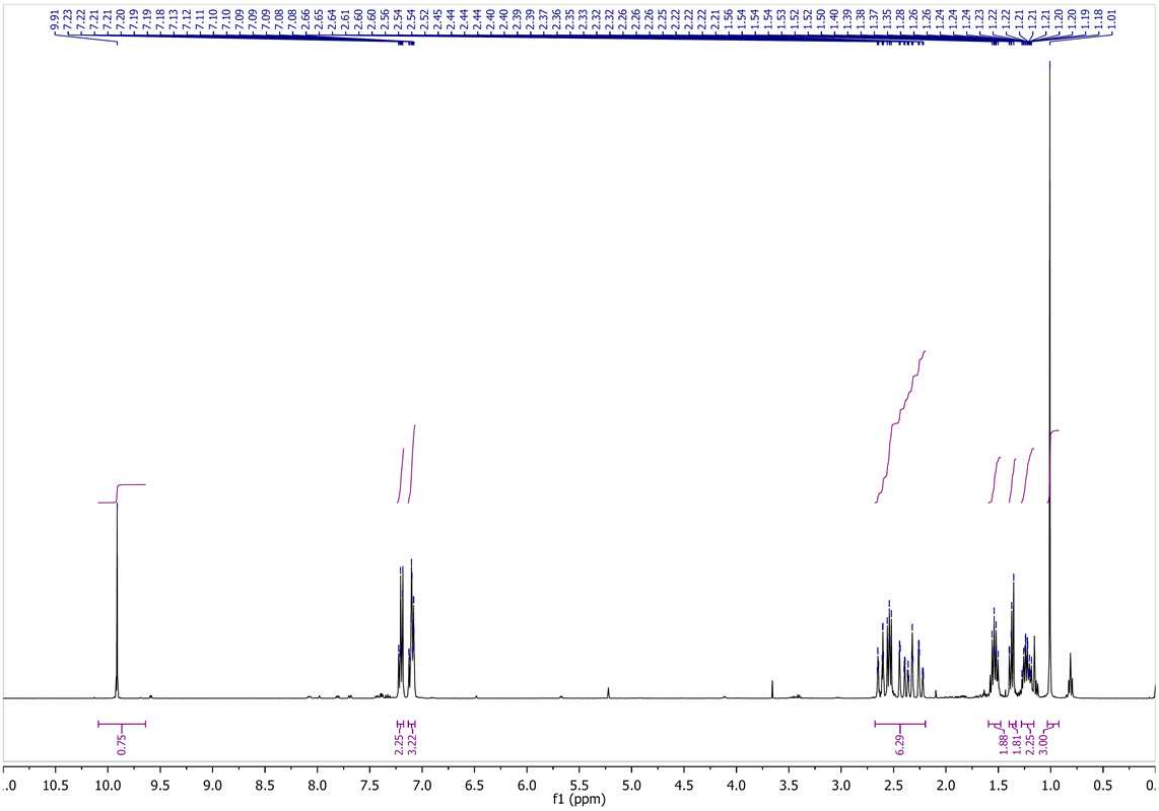
^{13}C NMR (101 MHz, $CDCl_3$) δ 187.9 6, 149.3 2, 142.4 Ar-C, 136.2 1, 128.3 (2C) Ar-C, 128.3 (2C) Ar-C, 125.7 Ar-C, 53.3 3, 42.1 4, 41.8 8, 39.7 5, 35.9 11, 32.0 10, 27.3 7, 24.6 9 ppm;

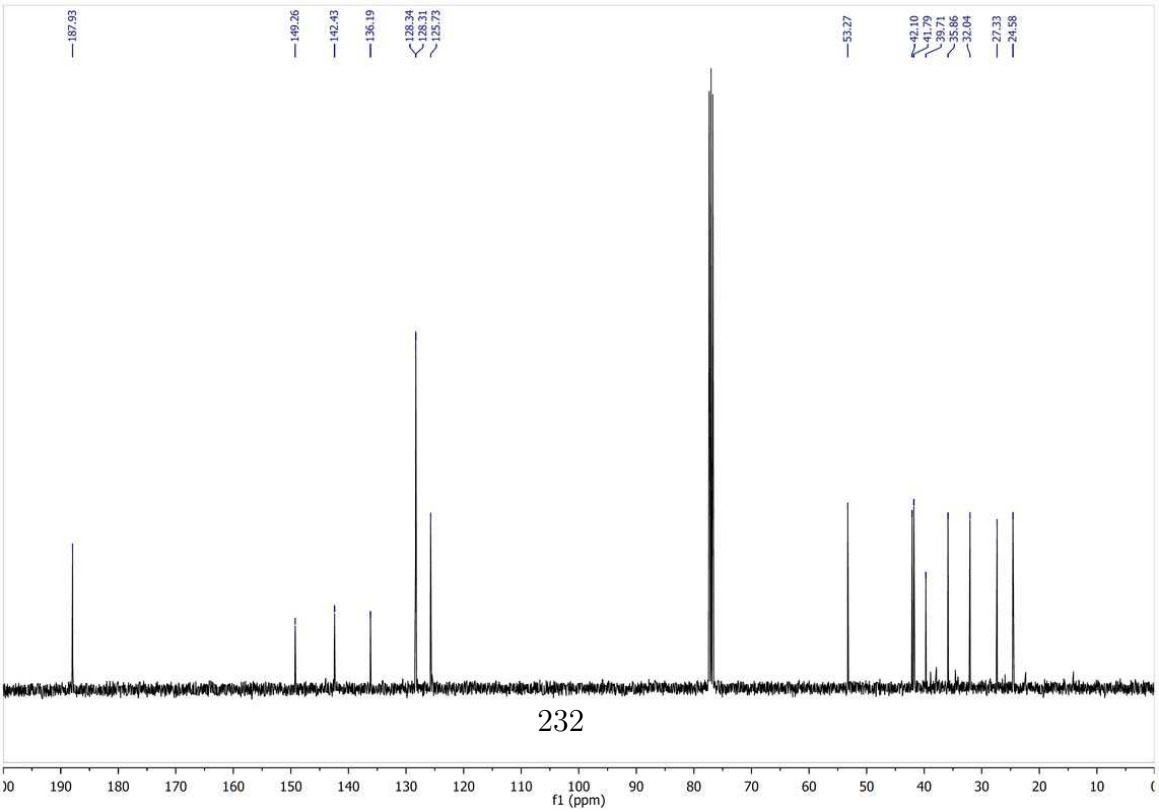
FT-IR thin film, neat (ATR): 2930, 2856, 1726, 1672, 1614 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{17}H_{22}O^{35}Cl$, $[M+H]^{+\bullet}$: 277.13537 found 277.13541 (Δ = 0.13 ppm);

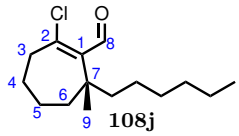
$[\alpha]_D^{25}$ = + 13° (*c* = 1.0, CH_2Cl_2), based on a sample of 90% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.15 (*R*)-2-chloro-7-hexyl-7-methylcyclohept-1-ene-1-carbaldehyde 108j



108j

1,4-addition reaction was conducted according to general procedure D using 3-ethyl-2-cycloheptenone[113] (0.53 mmol) as the enone and 1-hexene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G. Flash chromatography (5% Et_2O/*n*-pentane) gave the title product as a yellow oil (59 mg, 0.23 mmol, 43% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IF column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 96% (major enantiomer t_R = 3.51 min, minor enantiomer t_R = 2.47 min).

R_f = 0.67 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);

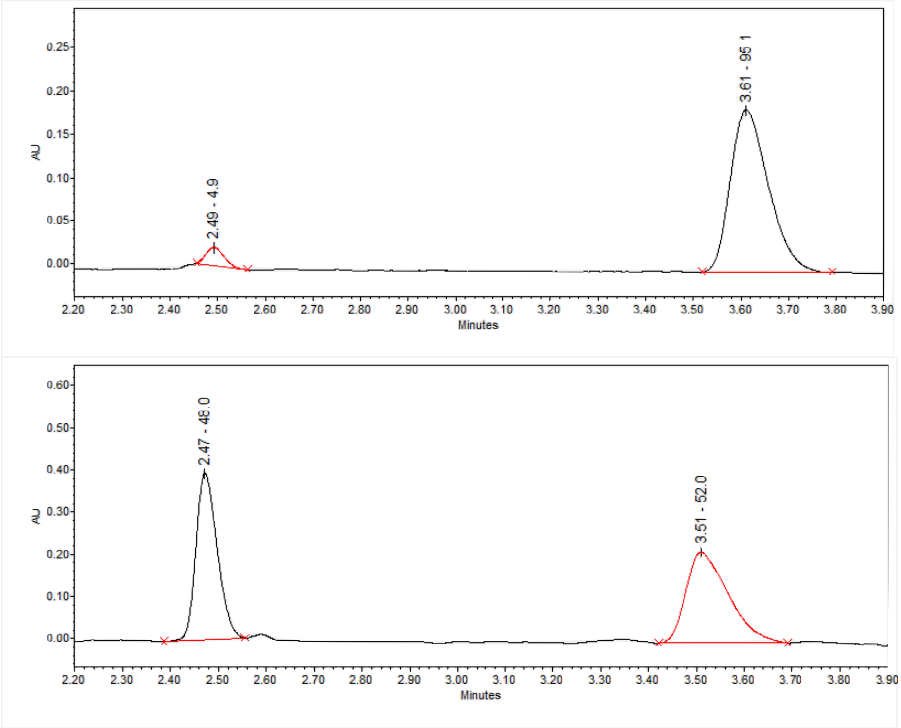
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H, 8), 2.79 – 2.63 (m, 2H, 6), 2.44 (m, 2H, 3), 1.69 – 1.50 (m, 2H, 5), 1.49 – 1.41 (m, 2H, 4), 1.33 – 1.23 (m, 10H, 10-14), 0.95 (s, 3H, 9), 0.92 – 0.85 (m, 3H, 15) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6 8, 153.6 2, 138.3 1, 52.4 6, 43.4 (CH_2), 41.3 10, 34.2 7, 32.0 13, 30.2 12, 25.3 9, 24.8 (CH_2), 22.8 (CH_2), 21.3 (CH_2), 14.2 1 ppm;

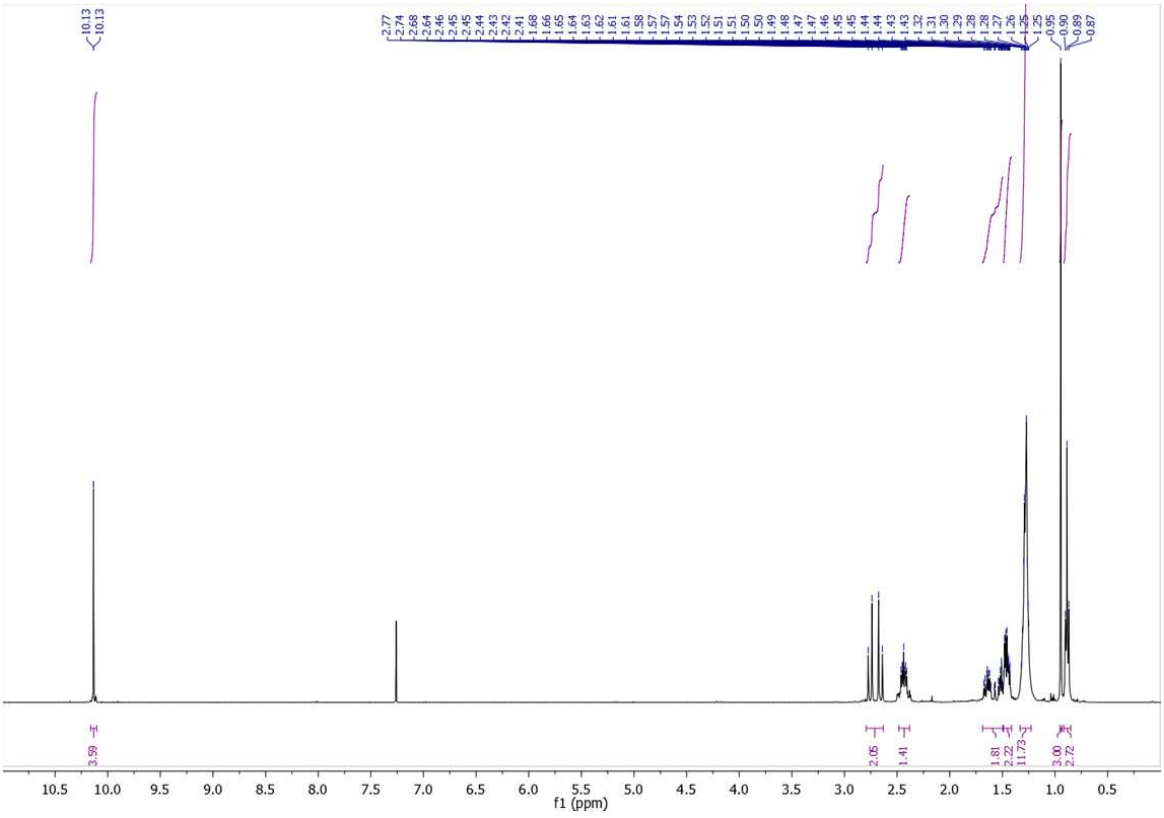
FT-IR thin film, neat (ATR): 2955, 2928, 2858, 1723, 1676, 1612 cm^{-1};

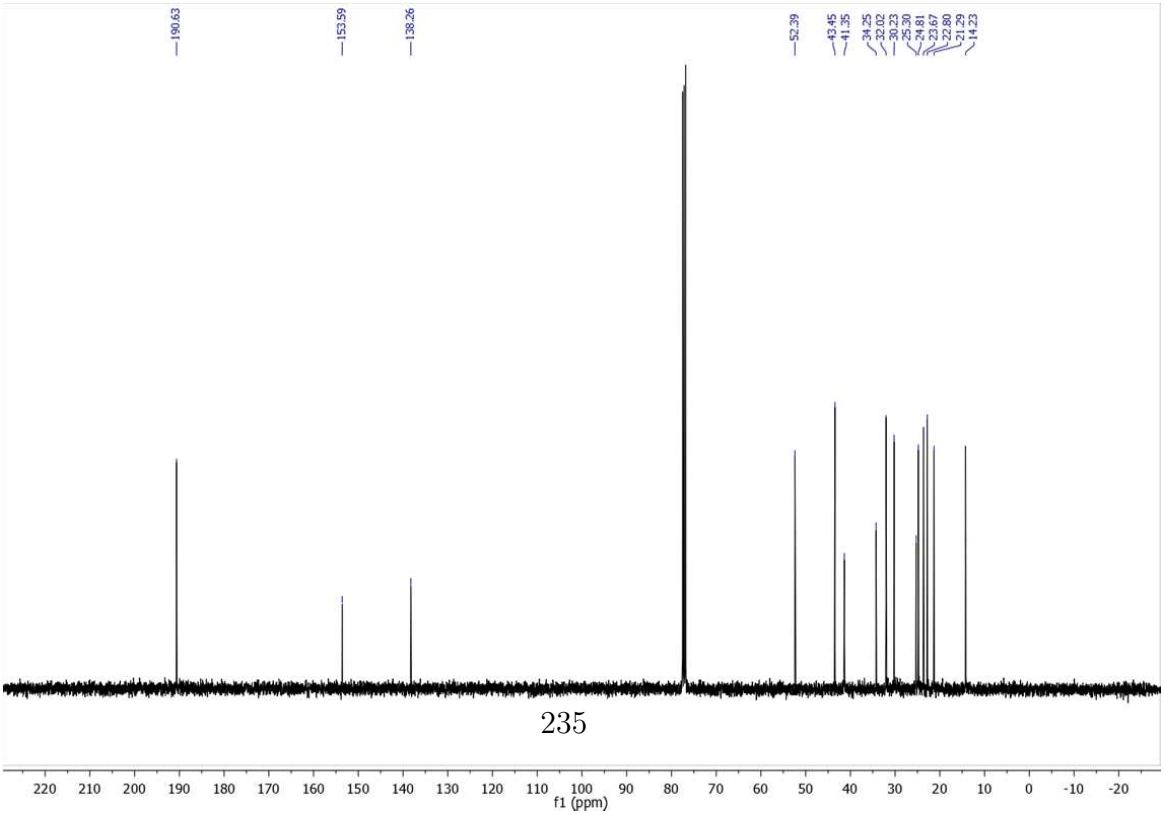
HRMS (ESI$^+$): calculated for $C_{15}H_{26}O^{35}Cl$, $[M+H]^{+\bullet}$: 257.16667 found 257.16681 (Δ = 0.54 ppm);

$[\alpha]_D^{25}$ = + 7.1° (*c* = 1.0, CH_2Cl_2), based on a sample of 90% *ee*;

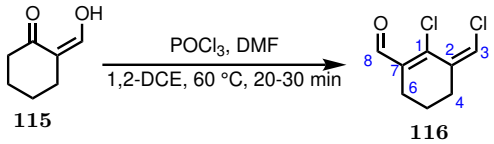

AU
0.25
0.20
0.15
0.10
0.05
0.00
2.49 - 4.9
3.61 - 95.1
2.20 2.30 2.40 2.50 2.60 2.70 2.80 2.90 3.00 3.10 3.20 3.30 3.40 3.50 3.60 3.70 3.80 3.90
Minutes
AU
0.60
0.50
0.40
0.30
0.20
0.10
0.00
2.47 - 46.0
3.51 - 52.0
2.20 2.30 2.40 2.50 2.60 2.70 2.80 2.90 3.00 3.10 3.20 3.30 3.40 3.50 3.60 3.70 3.80 3.90
Minutes

$^{1}H/^{13}C$ NMR


10.13
10.13
2.77
2.74
2.68
2.64
2.46
2.45
2.45
2.44
2.43
2.42
2.41
1.68
1.66
1.65
1.64
1.63
1.62
1.61
1.61
1.58
1.57
1.57
1.54
1.53
1.52
1.51
1.50
1.50
1.49
1.48
1.47
1.47
1.46
1.45
1.45
1.44
1.44
1.43
1.43
1.32
1.31
1.30
1.29
1.28
1.28
1.27
1.26
1.25
1.25
0.95
0.90
0.89
0.87
3.59
2.05
1.41
1.81
2.22
11.73
3.00
2.22
10.5 10.0 9.5 9.0 8.5 8.0 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
f1 (ppm)


190.63
153.59
138.26
52.39
43.45
41.35
34.25
32.02
30.23
25.30
24.81
23.67
22.80
21.29
14.23
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

5.3.1.16 (*Z*)-2-chloro-3-(chloromethylene)cyclohex-1-ene-1-carbaldehyde 115



115 **116**

Keto enol **115** was prepared according to a literature procedure.[65]

$POCl_3$ (0.90 mL, 9.6 mmol, 19.2 mol equiv) was added in one portion to a stirred solution of DMF (0.75 mL, 9.7 mmol, 19.4 mol equiv) in 1,2-dichloroethane (7 mL) in a round bottom flask at room temperature. After 15 minutes, the flask was heated at 60 °C for a further 5 minutes before **115** (58μL, ρ = 1.08 g.mL^{-1}, 0.50 mmol, 1.0 mol equiv) was added by syringe. After stirring for 20 minutes (TLC control) at 60 °C, the reaction was quenched at 0 °C by careful addition of saturated $NaHCO_{3(aq)}$ solution. After transferring to a separating funnel, the aqueous phase was extracted (3x) with CH_2Cl_2. The combine organic extracts were washed with water (2x), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% Et_2O/*n*-pentane, silica column) to give the title compound as yellow crystals (73 mg, 0.38 mmol, 76% yield).

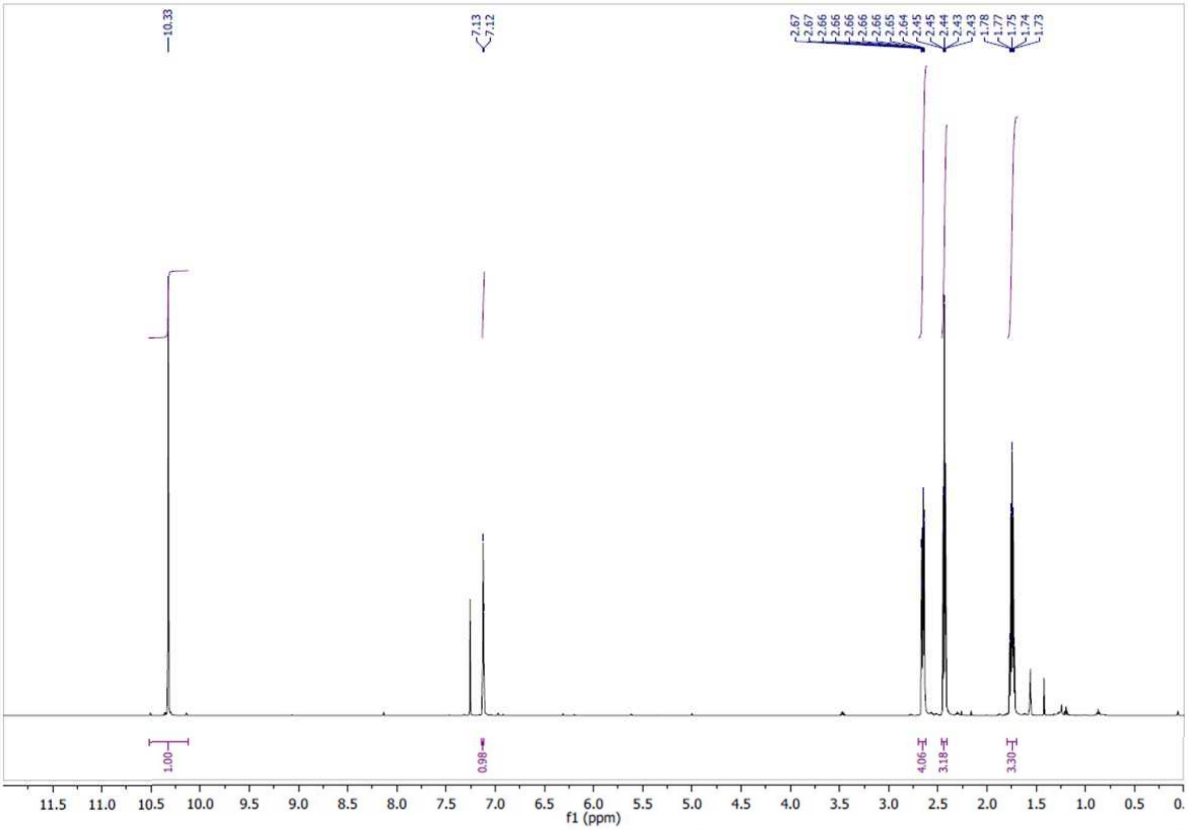
R_f = 0.55 (30% Et_2O/*n*-pentane, stains yellow with $KMnO_4$);
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.33 (s, 1H, 8), 7.12 (d, J = 2.0 Hz, 1H, 3), 2.70 – 2.62 (m, 2H, 4), 2.47 – 2.41 (m, 2H, 6), 1.75 (p, J = 6.2 Hz, 2H, 5) ppm;
^{3}C NMR (126 MHz, $CDCl_3$) δ 191.1 8, 142.9 2, 135.8 1, 134.2 7, 124.9 3, 27.6 4, 24.7 6, 20.4 5 ppm;

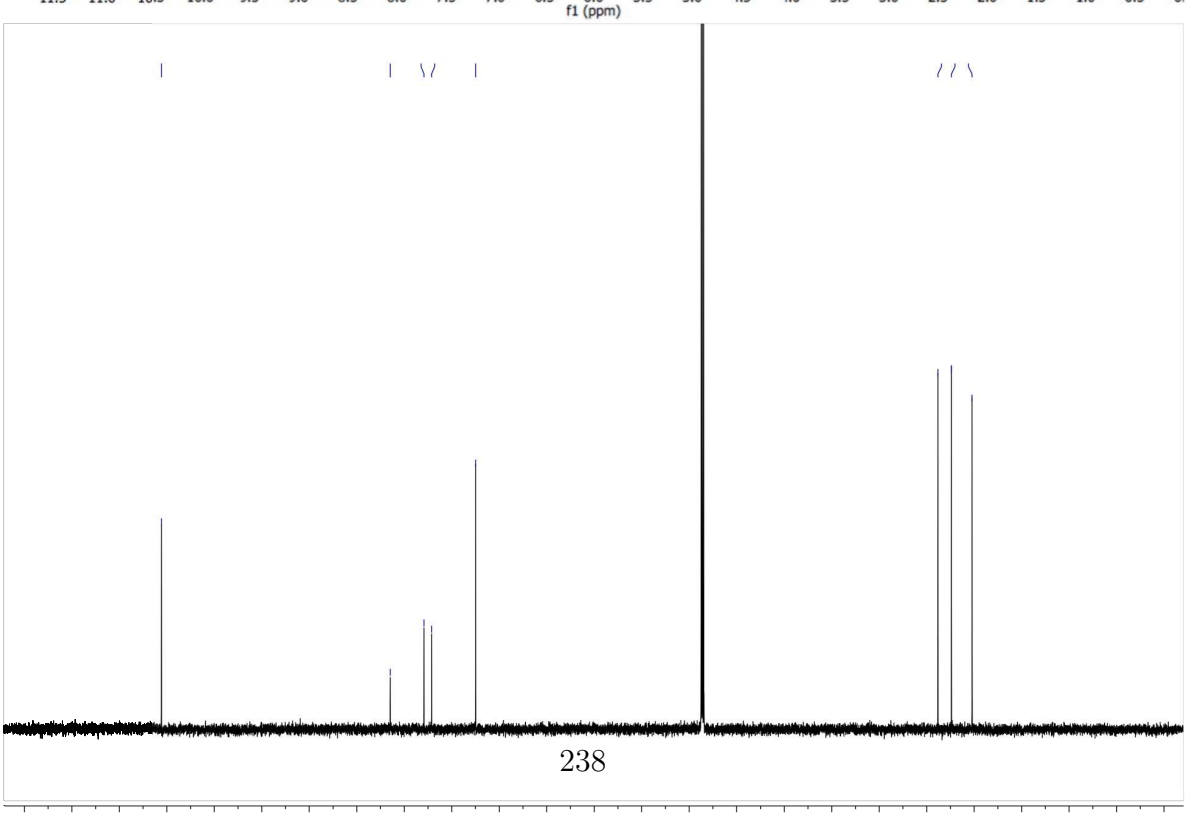
FT-IR thin film, neat (ATR): 3074, 2950, 1667, 1569, 1345, 1312, 1245 cm^{-1};

HRMS (EI^+): calculated for $C_8H_8OCl_2$, $[M+]^{+\bullet}$: 189.9947 found 189.9949 (Δ = -1.2 ppm);

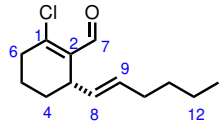
Melting Point: 38 – 42 °C

$^{1}H/^{13}C$ NMR


10.33
7.13
7.12
2.67
2.67
2.66
2.66
2.66
2.66
2.65
2.64
2.45
2.45
2.44
2.43
2.43
1.78
1.77
1.75
1.74
1.73
1.00
0.98
4.06
3.18
3.30
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 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
f1 (ppm)



5.3.1.17 (S,E)-2-chloro-6-(hex-1-en-1-yl)cyclohex-1-ene-1-carbaldehyde 124b



124b

1,4-addition reaction was conducted according to the procedure described by Westmeier and co-workers[58a] using 0.50 mmol 2-cyclohexenone as the enone. The *S* enantiomer of the chiral ligand was used. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure H. Flash chromatography (2-4% Et_2O/*n*-pentane gradient, silica) gave the title product as a colourless oil (12 mg, 0.053 mmol, 11% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IA column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 80% (major enantiomer t_R = 1.53 min, minor enantiomer t_R = 1.66 min).

R_f = 0.55 (30% Et_2O/*n*-pentane, stains blue with CAM);

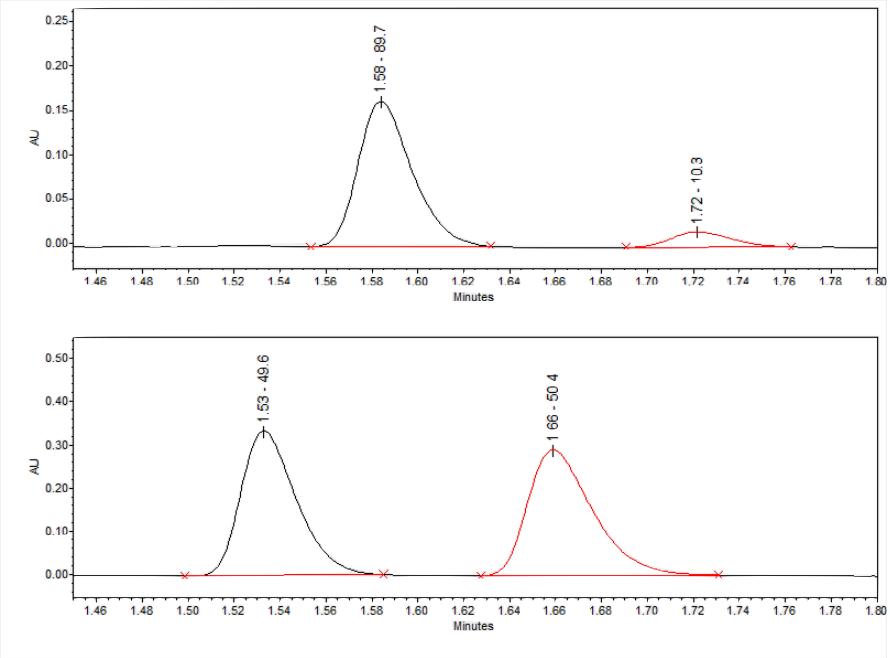
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.17 (s, 1H, 7), 5.39 – 5.32 (m, 1H, 8), 5.29 – 5.23 (m, 1H, 9), 3.43 (t, J = 5.9 Hz, 1H, 3), 2.61 – 2.53 (m, 2H, 6), 1.97 (q, J = 6.9 Hz, 2H, 10), 1.87 – 1.71 (m, 2H, 5), 1.71 – 1.52 (m, 2H, 4), 1.35 – 1.19 (m, 4H, 11/12), 0.86 (t, J = 7.0 Hz, 3H, 13) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7 7, 152.4 1, 135.4 2, 132.4 9, 130.4 8, 36.0 6, 35.7 3, 32.3 10, 31.7 11, 27.1 4, 22.3 12, 18.7 5, 14.1 13 ppm;

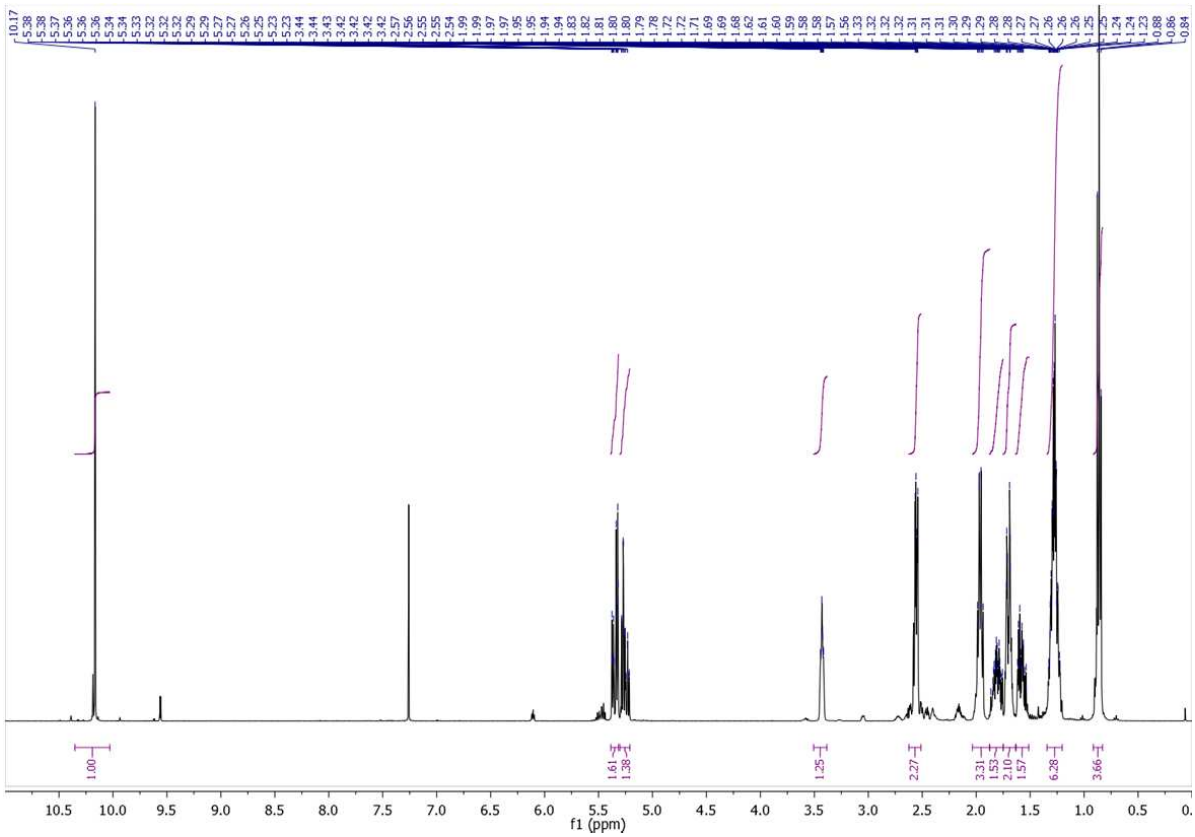
FT-IR thin film, neat (ATR): 2928, 2857, 1683, 1618, 1211 cm^{-1};

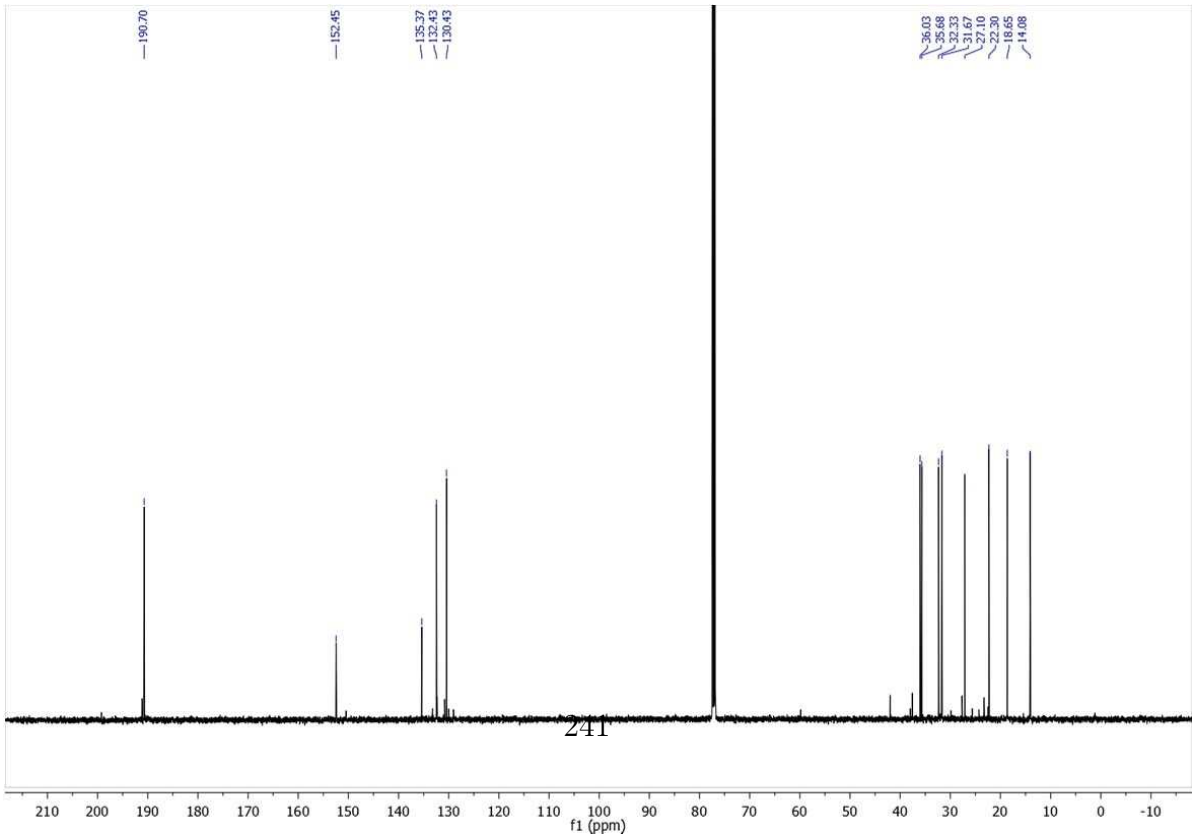
HRMS (ESI$^+$): calculated for $C_{13}H_{20}O^{35}Cl$, $[M+H]^{+\bullet}$: 227.11972 found 227.11986 (Δ = 0.63 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -99°$ ($c = 1.0$, CH_2Cl_2), based on a sample of 80% *ee*;

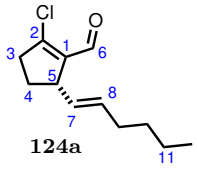


$^{1}H/^{13}C$ NMR


10.17
5.38
5.38
5.37
5.36
5.36
5.36
5.34
5.34
5.33
5.32
5.32
5.32
5.29
5.29
5.27
5.27
5.27
5.26
5.25
5.23
5.23
3.44
3.44
3.43
3.42
3.42
3.42
3.42
3.42
2.57
2.56
2.55
2.55
2.54
1.99
1.99
1.97
1.97
1.95
1.95
1.94
1.94
1.83
1.82
1.81
1.80
1.80
1.79
1.78
1.72
1.72
1.71
1.69
1.69
1.68
1.62
1.61
1.60
1.59
1.58
1.58
1.57
1.56
1.33
1.32
1.32
1.32
1.31
1.31
1.31
1.30
1.29
1.29
1.28
1.28
1.27
1.27
1.26
1.26
1.26
1.25
1.25
1.24
1.24
1.23
0.88
0.86
0.84
1.00
1.61
1.38
1.25
2.27
3.31
1.53
2.10
1.57
6.28
3.66
f1 (ppm)


190.70
152.45
135.37
132.43
130.43
36.03
35.68
32.33
31.67
27.10
22.30
18.65
14.08
f1 (ppm)

5.3.1.18 (S,E)-2-chloro-5-(hex-1-en-1-yl)cyclopent-1-ene-1-carbaldehyde 124a



124a

1,4-addition reaction was conducted according to the procedure described by Westmeier and co-workers[58a] using 0.50 mmol 2-cyclopentenone as the enone. The *R* enantiomer of the chiral ligand was used. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure H. Flash chromatography (2-4% Et_2O/*n*-pentane gradient, silica) gave the title product as a colourless oil (10 mg, 0.049 mmol, 9% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IA column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 96% (major enantiomer t_R = 1.50 min, minor enantiomer t_R = 1.64 min).

R_f = 0.64 (30% Et_2O/*n*-pentane, stains blue with CAM);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H, 6), 5.52 – 5.43 (m, 1H, 7), 5.37 (ddt, J = 15.3, 7.2, 1.2 Hz, 1H, 8), 3.59 (td, J = 6.8, 3.4 Hz, 1H, 5), 2.94 – 2.62 (m, 2H, 3), 2.28 – 1.74 (m, 2H, 4), 1.97 (q, J = 6.8 Hz, 2H, 9), 1.37 – 1.20 (m, 4H, 10/11), 0.87 (t, J = 7.1 Hz, 3H, 12) ppm;

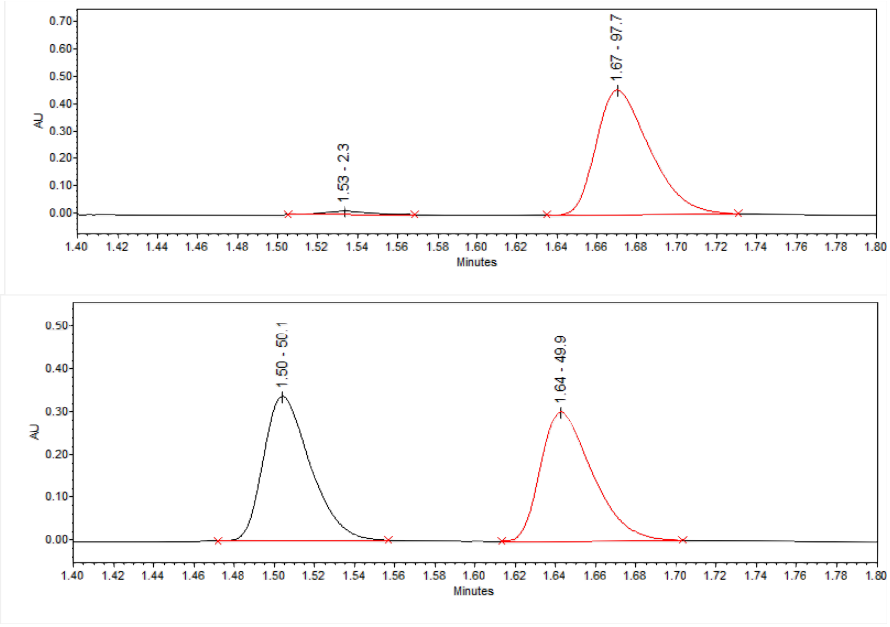
^{13}C NMR (101 MHz, $CDCl_3$) δ 187.5 6, 152.1 2, 139.2 1, 131.2 7, 129.8 8, 44.7 5, 38.9 3, 32.2 9, 31.6 10, 28.8 4, 22.3 11, 14.1 12 ppm;

FT-IR thin film, neat (ATR): 2957, 2927 1678, 1609, 1098, 965 cm^{-1};

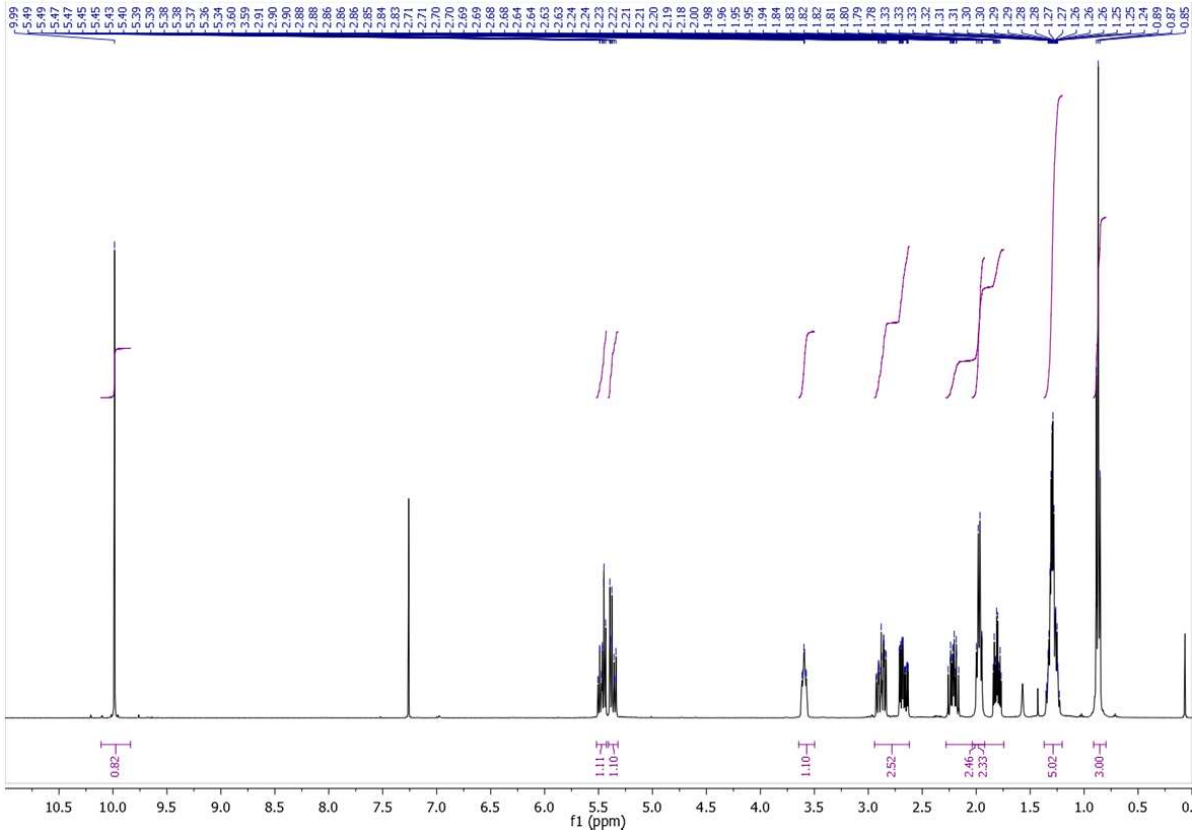
HRMS (APCI$^+$): calculated for $C_{12}H_{18}O^{35}Cl$, $[M+H]^{+\bullet}$: 213.10407 found 213.10421

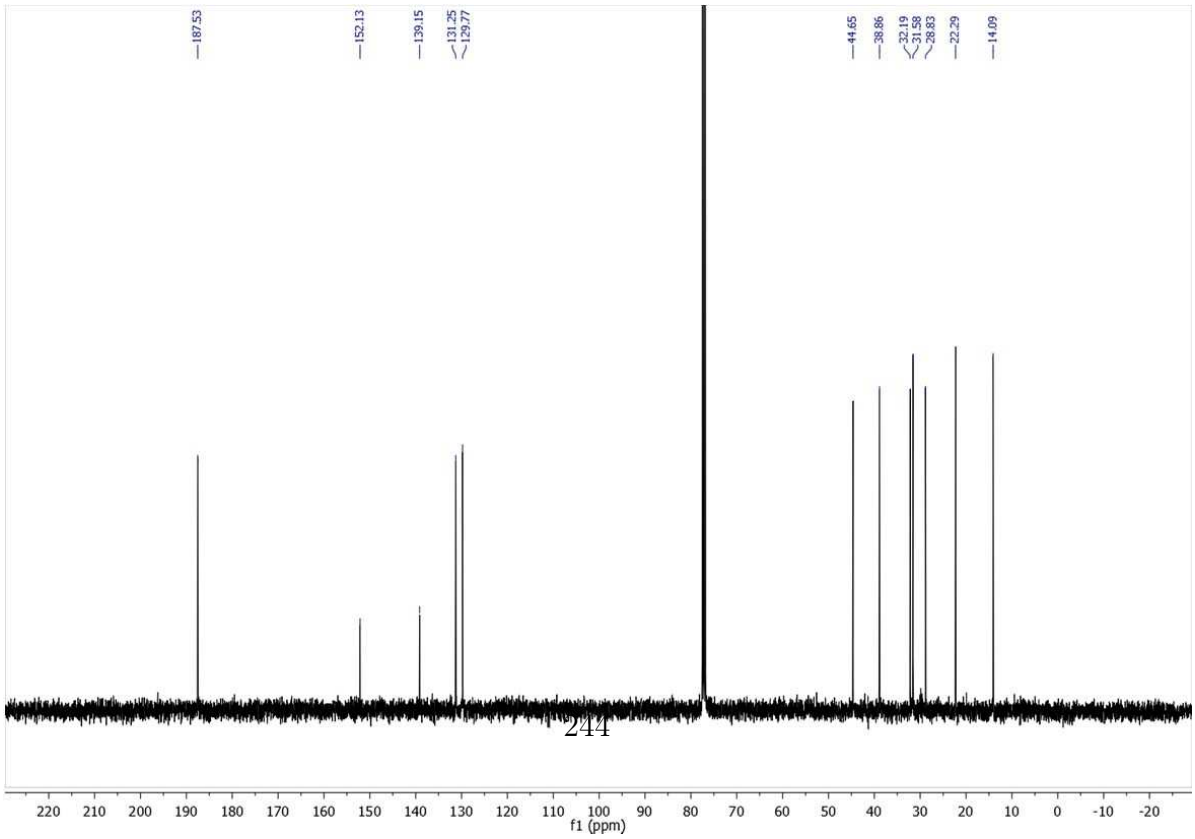
(Δ = 0.67 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 20° (c = 1.0, CH_2Cl_2), based on a sample of 96% *ee*;

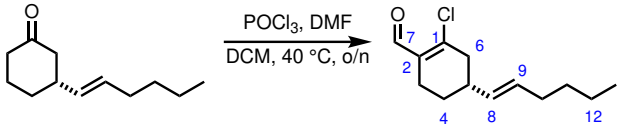


$^{1}H/^{13}C$ NMR


0.82
1.11
1.10
1.10
2.52
2.46
2.33
5.02
3.00
f1 (ppm)


187.53
152.13
139.15
131.25
129.77
44.65
38.86
32.19
31.58
28.83
22.29
14.09
f1 (ppm)

5.3.1.19 (R,E)-2-chloro-4-(hex-1-en-1-yl)cyclohex-1-ene-1-carbaldehyde



Ketone was prepared according to the procedure by Westmeier and co-workers.[58a] The *S* enantiomer of the chiral ligand was used. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure G on 0.23 mmol scale. Flash chromatography (2-4% Et_2O/*n*-pentane gradient, silica) gave the title product as a colourless oil (16 mg, 0.070 mmol, 30% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IA column 250 × 4.6 mm, 1-30% MeOH/CO_2 gradient over 5 min, 1.5 mL.min^{-1}): *ee* = 92% (major enantiomer t_R = 1.87 min, minor enantiomer t_R = 1.71 min).

R_f = 0.64 (30% Et_2O/*n*-pentane, stains blue with CAM);

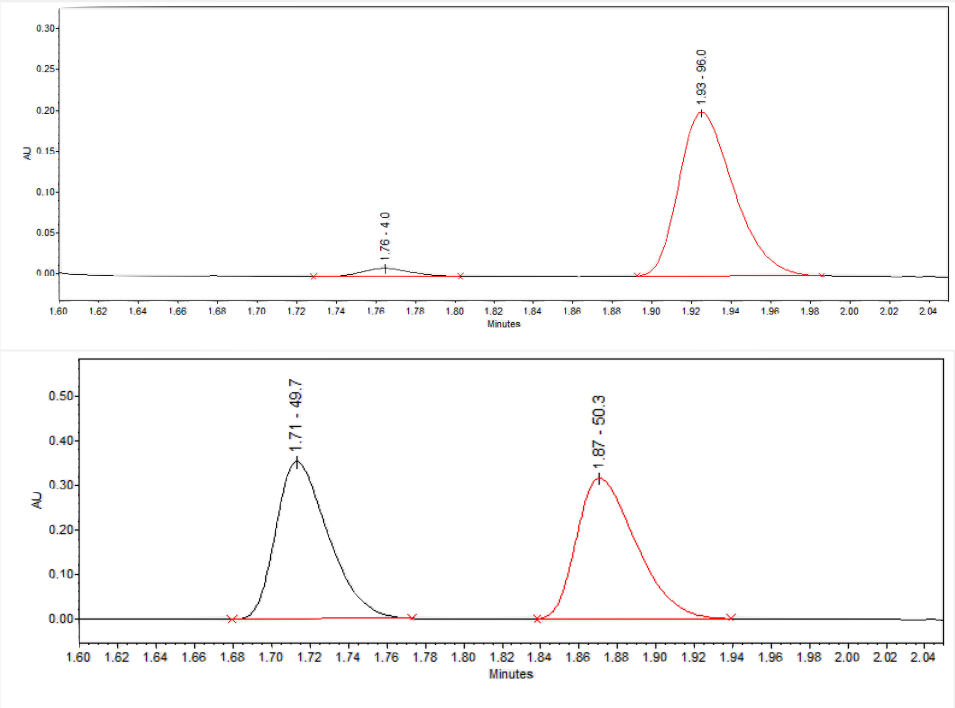
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H, 7), 5.48 (dtd, J = 15.5, 6.6, 0.9 Hz, 1H, 8), 5.40 – 5.31 (m, 1H, 9), 2.68 – 2.34 (m, 3H, 5/6), 2.52 – 2.08 (m, 2H, 3), 2.05 – 1.93 (m, 2H, 10), 1.88 – 1.35 (m, 2H, 4), 1.37 – 1.25 (m, 4H, 11/12), 0.96 – 0.87 (m, 3H, 13) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1 7, 150.4 1, 133.2 2, 132.3 9, 130.8 8, 42.0 6, 37.6 5, 32.3 10, 31.7 11, 27.7 4, 23.2 3, 22.3 12, 14.1 13 ppm;

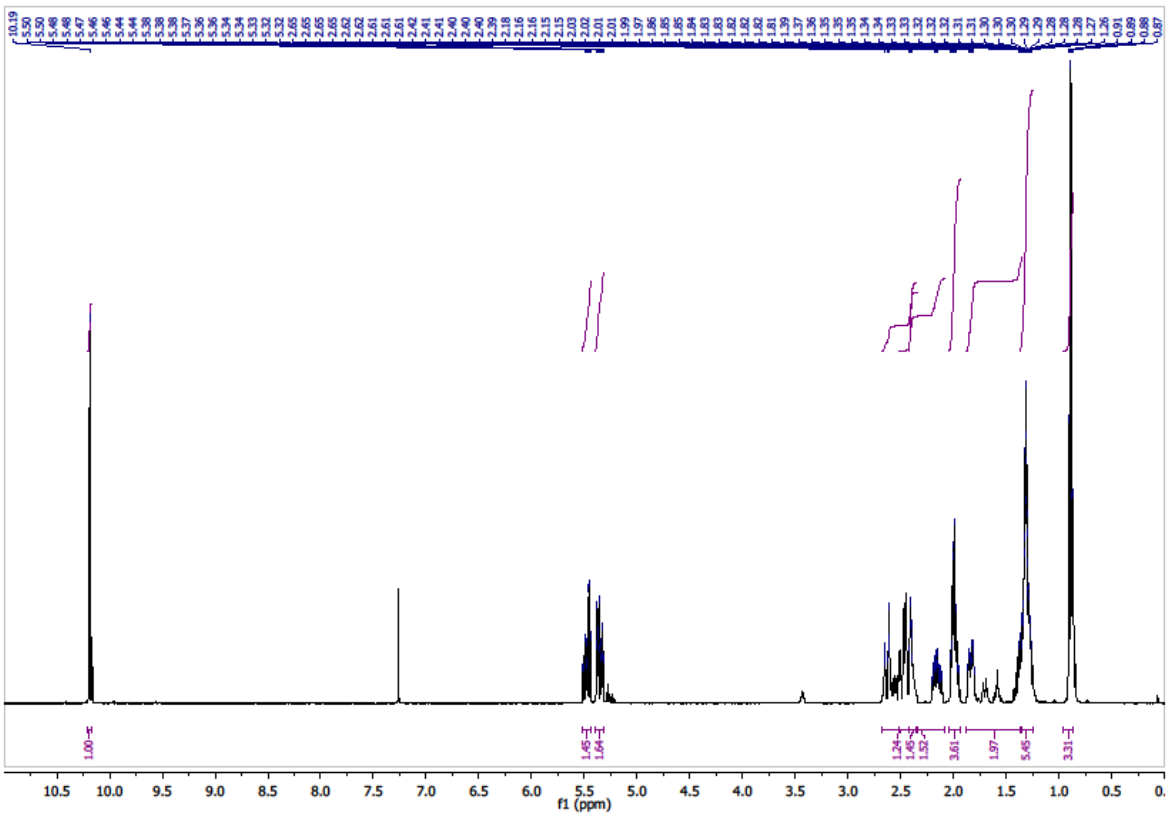
FT-IR thin film, neat (ATR): 2955, 2857, 1680, 1624, 1224, 968 cm^{-1};

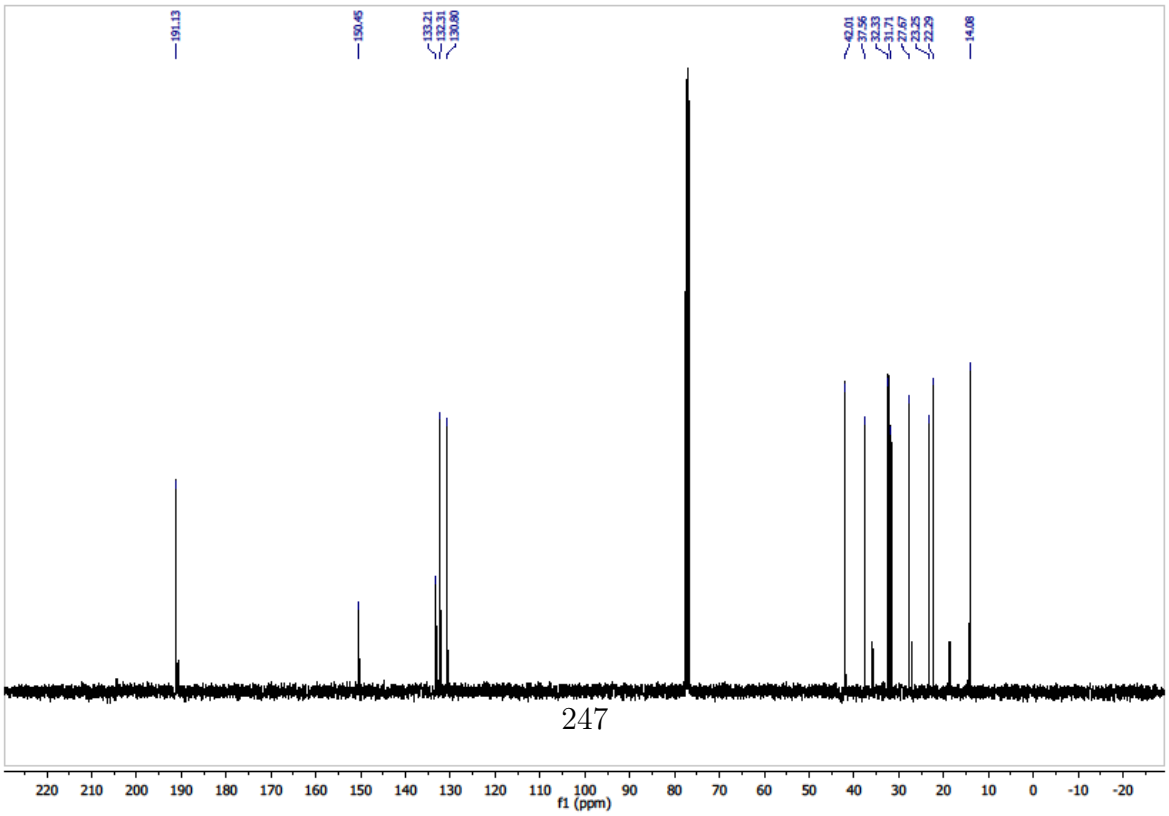
HRMS (APCI$^+$): calculated for $C_{13}H_{20}O^{35}Cl$, $[M+H]^{+\bullet}$: 227.11972 found 227.11975 (Δ = 0.14 ppm);

$[\alpha]_D^{25} = -117°$ (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

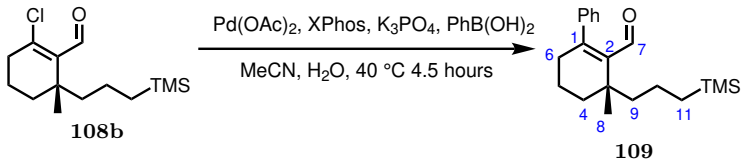

1.76 - 4.0
1.93 - 96.0
AU
Minutes
1.71 - 49.7
1.87 - 50.3
AU
Minutes

$^{1}H/^{13}C$ NMR


f1 (ppm)


191.13
150.45
133.21
132.31
130.80
62.01
37.56
32.33
31.71
27.67
23.25
22.29
14.08
f1 (ppm)

5.3.1.20 (*S*)-3-methyl-3-(3-(trimethylsilyl)propyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde 109



108b **109**

Phenylboronic acid (27 mg, 0.22 mmol, 1.1 mol equiv), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.050 mol equiv) and XPhos (5.0 mg, 0.010 mmol, 0.050 mol equiv) were added to a 7 mL vial equipped with a stir bar and a rubber septum. Three cycles of vacuum and back filling with N_2 were then performed before chloroaldehydes **108b** (55 mg, 0.20 mmol, 1.0 mol equiv) and degassed acetonitrile (0.5 mL) were added. A solution of degassed K_3PO_4 was added (0.30 mL of a 2M solution in H_2O, 0.60 mmol, 3.0 mol equiv) and the reaction stirred for 4.5 hours at 40 °C, or until the reaction was complete, as monitored by TLC. After cooling to room temperature, the reaction mixture was diluted with Et_2O and saturated $NH_4Cl_{(aq)}$ added. The contents were transferred to a separating funnel and the aqueous phase was extracted (3x) with Et_2O. The combined organic extracts were dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash chromatography (2-4% Et_2O/*n*-pentane gradient, silica column) to give the title compound as a yellow oil (31.9 mg, 0.10 mmol, 56% yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

R_f = 0.65 (30% Et_2O/*n*-pentane, stains blue with CAM);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H, 7), 7.40 – 7.34 (m, 3H, Ar-H), 7.22 – 7.18 (m, 2H, Ar-H), 2.47 – 2.20 (m, 4H, 5/6), 1.51 (td, J = 6.8, 6.4, 1.6 Hz,

2H, 4), 1.37 – 1.26 (m, 4H, 9/10), 0.96 (s, 3H, 8), 0.47 (tdd, J = 7.0, 3.5, 1.8 Hz, 2H, 11), −0.02 (s, 9H, TMS) ppm;

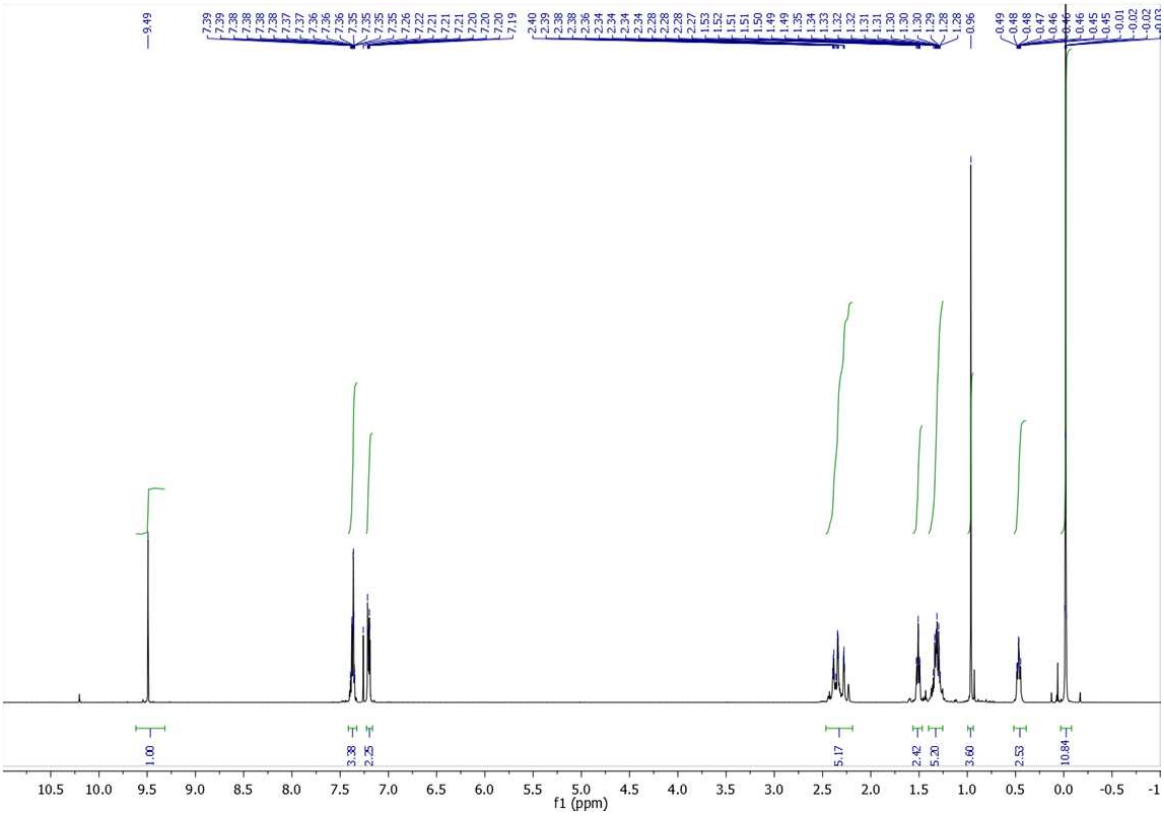
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7 7, 158.7 1, 139.8 Ar-C, 134.8 2, 128.7 (2C) Ar-C, 128.3 (2C) Ar-C, 128.3 Ar-C, 47.1 6, 45.8 9, 32.4 4, 32.2 3, 24.6 8, 20.0 5, 17.9 10, 17.8 11, −1.4 (3C) TMS ppm;

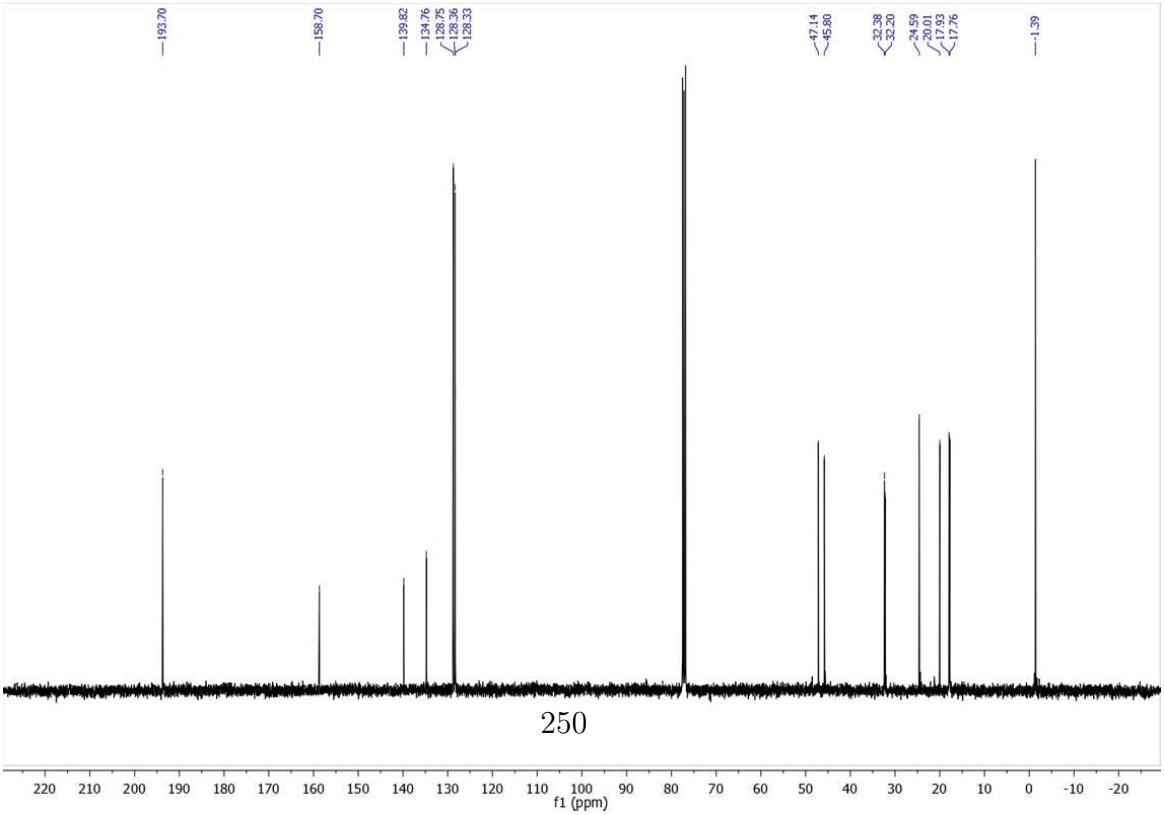
FT-IR thin film, neat (ATR): 2952, 2923, 2859, 1671, 1247 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{20}H_{31}O^{28}Si$, $[M+H]^{+\bullet}$: 315.21387 found 315.21396 (Δ = 0.29 ppm);

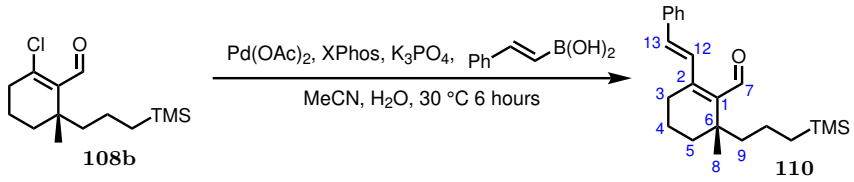
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 16° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.21 (S,E)-6-methyl-2-styryl-6-(3-(trimethylsilyl)propyl)cyclohex-1-ene-1-carbaldehyde 110



trans-2-phenylvinylboronic acid (65 mg, 0.44 mmol, 1.1 mol equiv), $Pd(OAc)_2$ (4.4 mg, 0.020 mmol, 0.050 mol equiv) and XPhos (9.5 mg, 0.020 mmol, 0.050 mol equiv) were added to a 7 mL vial equipped with a stir bar and a rubber septum. Three cycles of vacuum and back filling with N_2 were then performed before chloroaldehydes **108b** (109 mg, 0.40 mmol, 1.0 mol equiv) and degassed acetonitrile (1.0 mL) were added. A solution of degassed K_3PO_4 was added (0.60 mL of a 2M solution in H_2O, 1.2 mmol, 3.0 mol equiv) and the reaction stirred for 6 hours at room temperature and then an additional 4 hours at 30 °C. After cooling to room temperature, the reaction mixture was diluted with Et_2O and saturated $NH_4Cl_{(aq)}$ added. The contents were transferred to a separating funnel and the aqueous phase was extracted (3x) with Et_2O. The combined organic extracts were dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash chromatography (20-50% CH_2Cl_2/*n*-pentane gradient, silica column) to give the title compound as a yellow oil (99 mg, 0.29 mmol, 72% yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

R_f = 0.58 (30% Et_2O/*n*-pentane, stains blue with CAM);

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (s, 1H, 7), 7.76 (d, J = 15.9 Hz, 1H, 12), 7.53 – 7.45 (m, 2H, ArH), 7.40 – 7.35 (m, 2H, ArH), 7.34 – 7.29 (m, 1H, ArH),

6.87 (d, J = 15.9 Hz, 1H, 13), 2.47 – 2.24 (m, 4H, 3/4), 1.47 (ddd, J = 7.8, 6.2, 1.5 Hz, 2H, 5), 1.39 – 1.28 (m, 4H, 9/10), 0.95 (s, 3H, 8), 0.54 – 0.38 (m, 2H, 11), 0.00 (s, 9H, TMS-H) ppm;

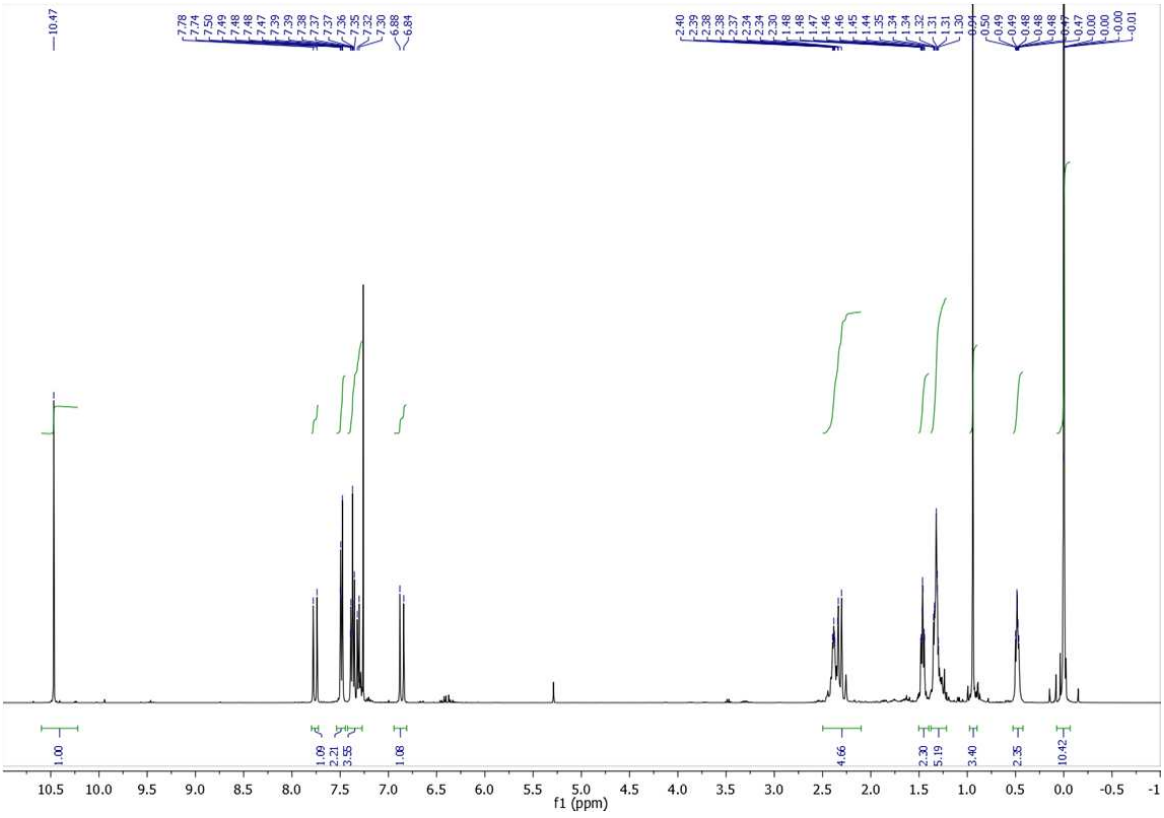
^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5 7, 150.9 2, 136.7 1, 134.8 13, 133.6 Ar-C, 129.0 (2C) Ar-C, 128.8 Ar-C, 127.1 (2C) Ar-C, 123.7 12, 45.7 9, 40.5 (CH_2), 32.1 5, 31.7 6, 24.9 8, 20.9 (CH_2), 17.9 10, 17.7 11, −1.4 (3C) TMS ppm;

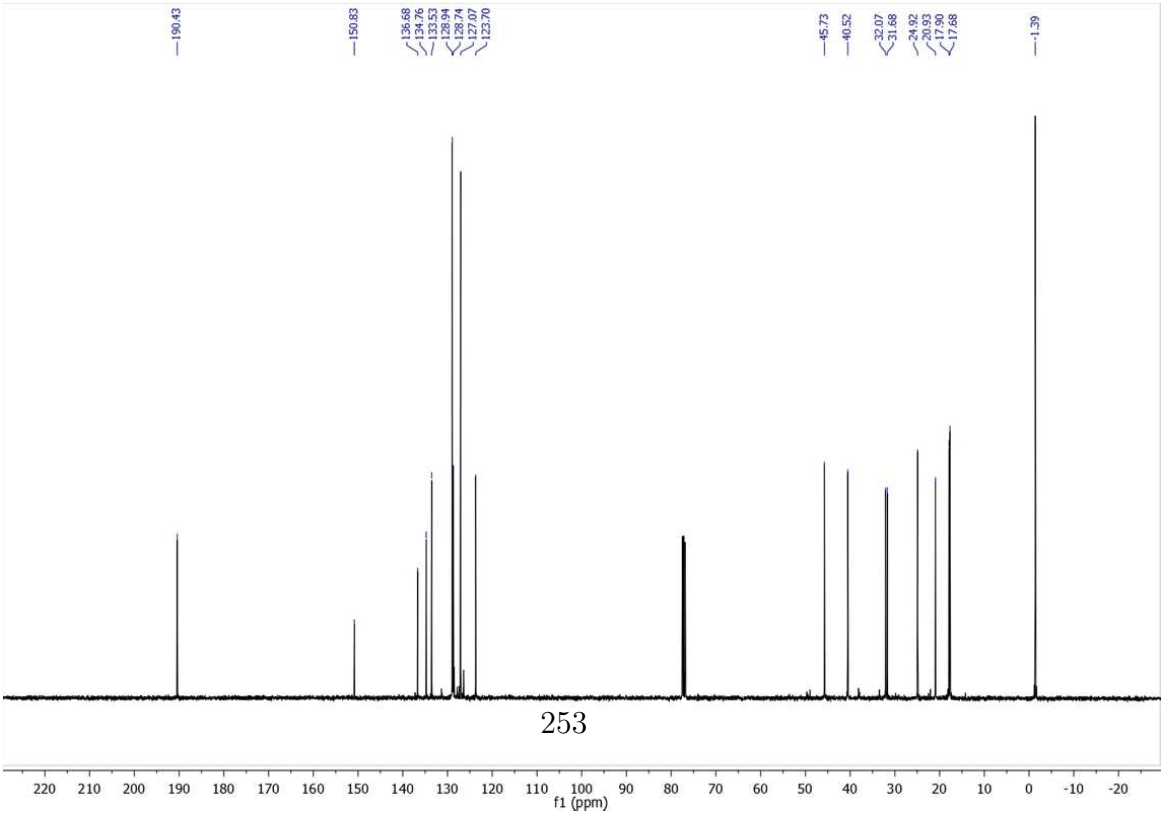
FT-IR thin film, neat (ATR): 3058, 2952, 1659, 1247 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{22}H_{33}O^{28}Si$, $[M+H]^{+\bullet}$: 341.22952 found 341.22955 (Δ = 0.1 ppm);

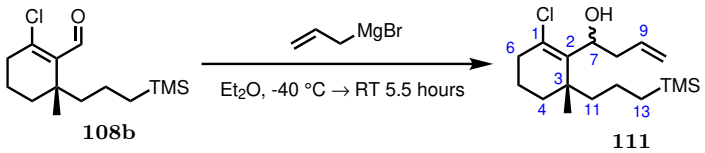
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 3.0° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


10.47
7.78
7.74
7.50
7.49
7.48
7.48
7.47
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.32
7.30
6.88
6.84
2.40
2.39
2.38
2.38
2.37
2.34
2.34
2.30
1.48
1.48
1.47
1.46
1.46
1.45
1.44
1.35
1.34
1.34
1.32
1.31
1.31
1.30
0.99
0.50
0.49
0.49
0.48
0.48
0.48
0.47
0.47
0.00
0.00
0.00
0.01
1.00
1.09
2.21
3.55
1.08
4.66
2.30
5.19
3.40
2.35
10.42
f1 (ppm)


190.43
150.83
136.68
134.76
133.53
128.94
128.74
127.07
123.70
45.73
40.52
32.07
31.68
24.92
20.93
17.90
17.68
-1.39
f1 (ppm)

5.3.1.22 1-((*S*)-2-chloro-6-methyl-6-(3-(trimethylsilyl)propyl)cyclohex-1-en-1-yl)but-3-en-1-ol 111



108b **111**

Chloroaldehyde **108b** (51 mg, 0.19 mmol, 1.0 mol equiv) and Et_2O (0.23 mL) were added to a 7 mL vial equipped with a stir bar and a rubber septum. Allylmagnesium bromide (0.23 mL of a 1M solution in Et_2O, 0.23 mmol, 1.2 mol equiv) was added dropwise at −40 °C. The cooling bath was removed immediately after the addition and stirring was continued at room temperature for 5.5 hours. The reaction was quenched with wet Et_2O and then concentrated *in vacuo*. The residue was purified by flash chromatography (10-15% Et_2O/*n*-pentane gradient, silica column) to give the product as a 1:1 separable mixture of diastereomers (colourless oil) with a combined mass of 42 mg (0.13 mmol, 71% total yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

HRMS (APCI$^+$): calculated for $C_{17}H_{31}OSi$, $[M\text{-}Cl]^{+\bullet}$: 279.21387 found 279.21386 (Δ = 0.03 ppm);

First diastereomer

R_f = 0.46 (30% Et_2O/*n*-pentane, stains blue with CAM);

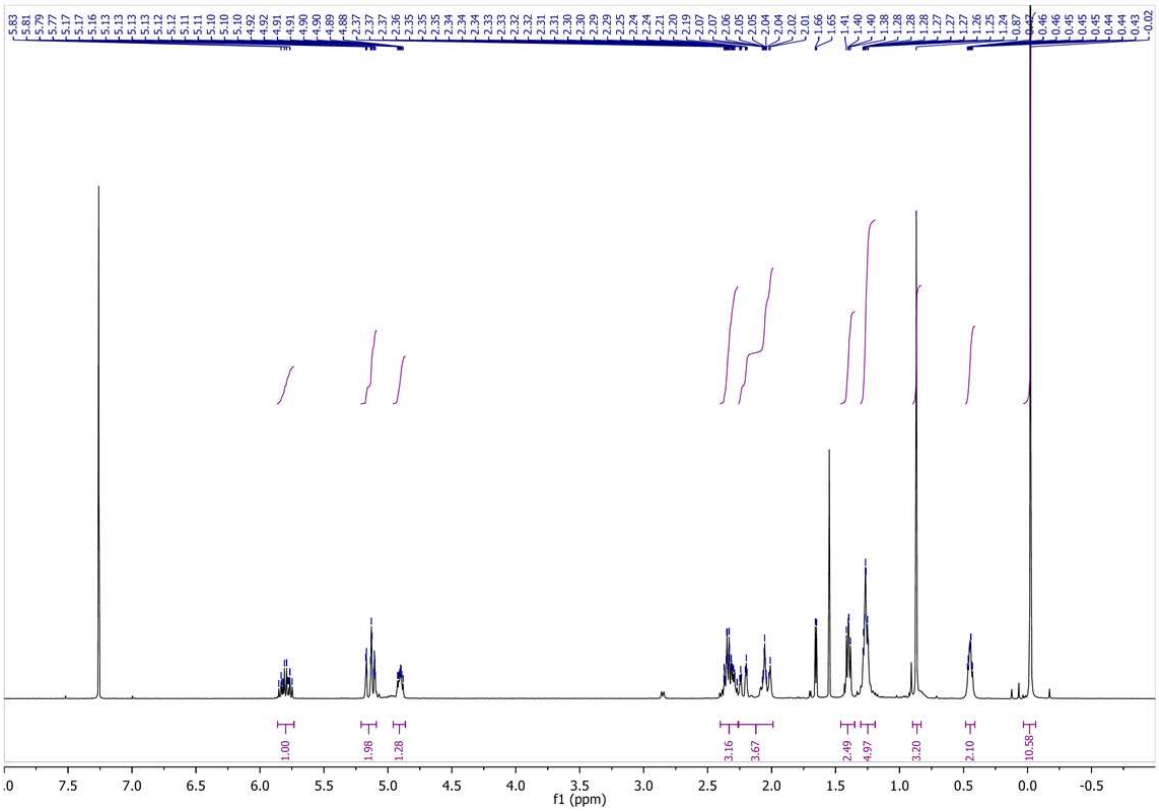
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H, 9), 5.19 – 5.07 (m, 2H, 10), 4.90 (ddd, J = 7.8, 6.0, 3.4 Hz, 1H, 7), 2.40 – 2.28 (m, 2H, 8), 2.26 – 1.99 (m, 4H, 5/6), 1.43 – 1.37 (m, 2H, 4), 1.31 – 1.24 (m, 4H, 11/12), 0.87 (s, 3H, Me), 0.45 (tdd, J = 5.3, 4.2, 1.6 Hz, 2H, 13),−0.02 (s, 9H, TMS) ppm;

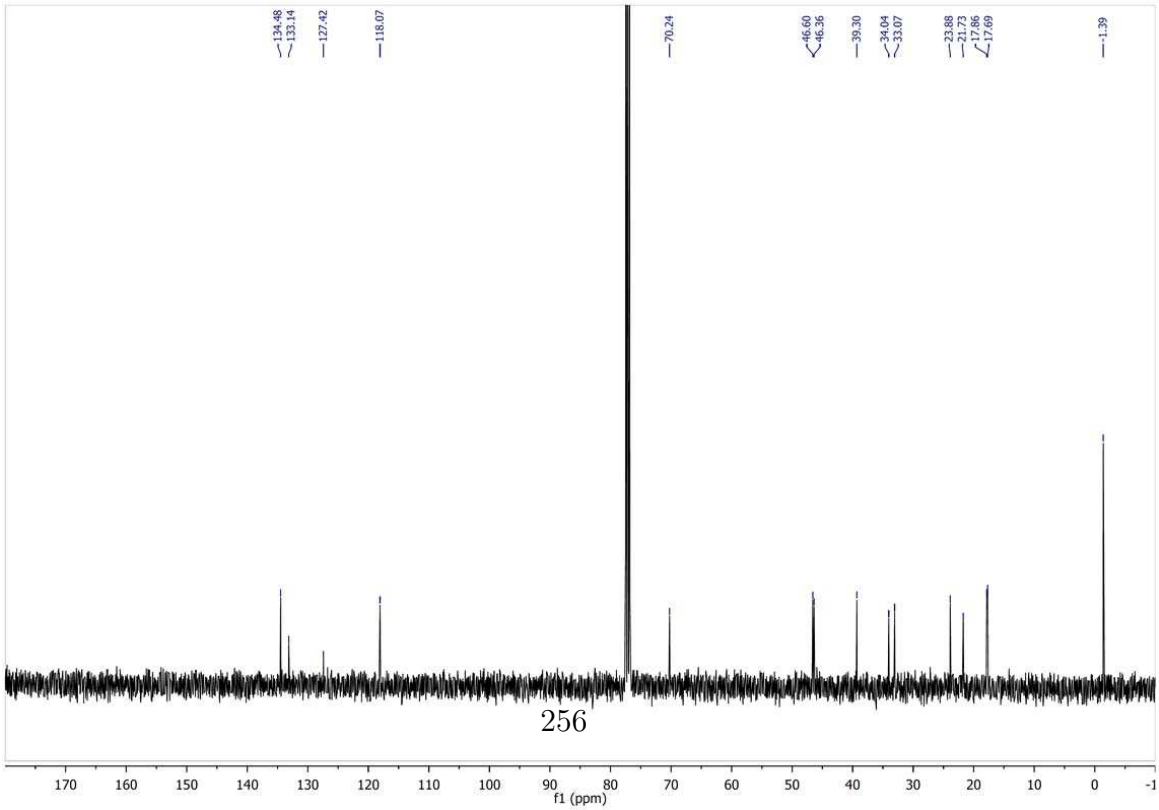
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5 9, 133.1 1, 127.4 2, 118.1 10, 70.2 12, 46.6 5, 46.4 11, 39.3 8, 34.0 3, 33.1 4, 23.9 Me, 21.7 6, 17.8 12, 17.7 13, -1.4 (3C) TMS ppm;

FT-IR thin film, neat (ATR): 3354, 2924, 1248 cm^{-1};

$[\alpha]_D^{25}$ = + 3.7° (c = 0.54, CH_2Cl_2), based on a sample of 92% *ee*;

^{1}H/^{13}C NMR (First diastereomer):





Second diastereomer

NOE studies did not afford conclusive insight into relative configuration.

$\mathbf{R_f}$ = 0.37 (30% Et_2O/*n*-pentane, stains blue with CAM);

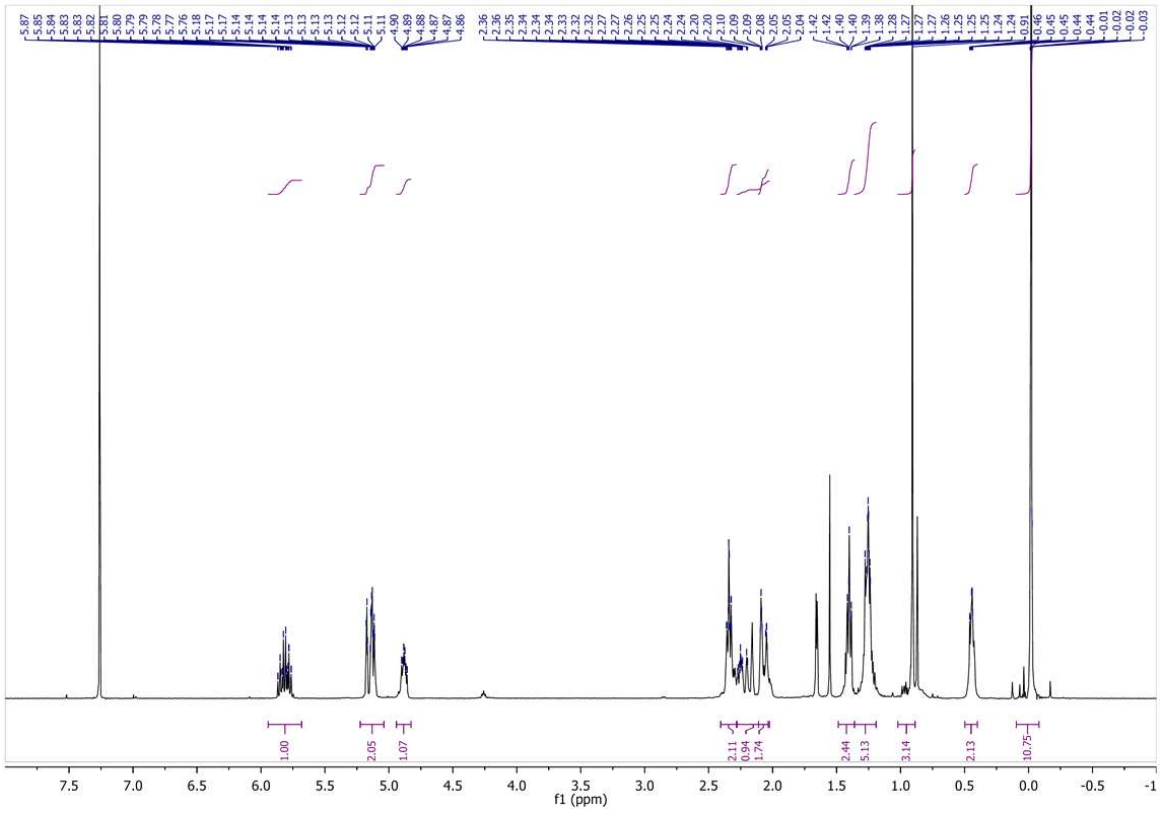
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, J = 17.3, 10.1, 7.1 Hz, 1H, 9), 5.20 – 5.10 (m, 2H, 10), 4.88 (td, J = 7.0, 3.5 Hz, 1H, 7), 2.39 – 2.31 (m, 2H, 8), 2.26 – 2.00 (m, 4H, 5/6), 1.47 – 1.34 (m, 2H, 4), 1.32 – 1.23 (m, 4H, 11/12), 0.91 (s, 3H, Me), 0.44 (ddd, J = 7.6, 5.7, 2.5 Hz, 2H, 13), −0.02 (d, J = 1.0 Hz, 9H, TMS) ppm;

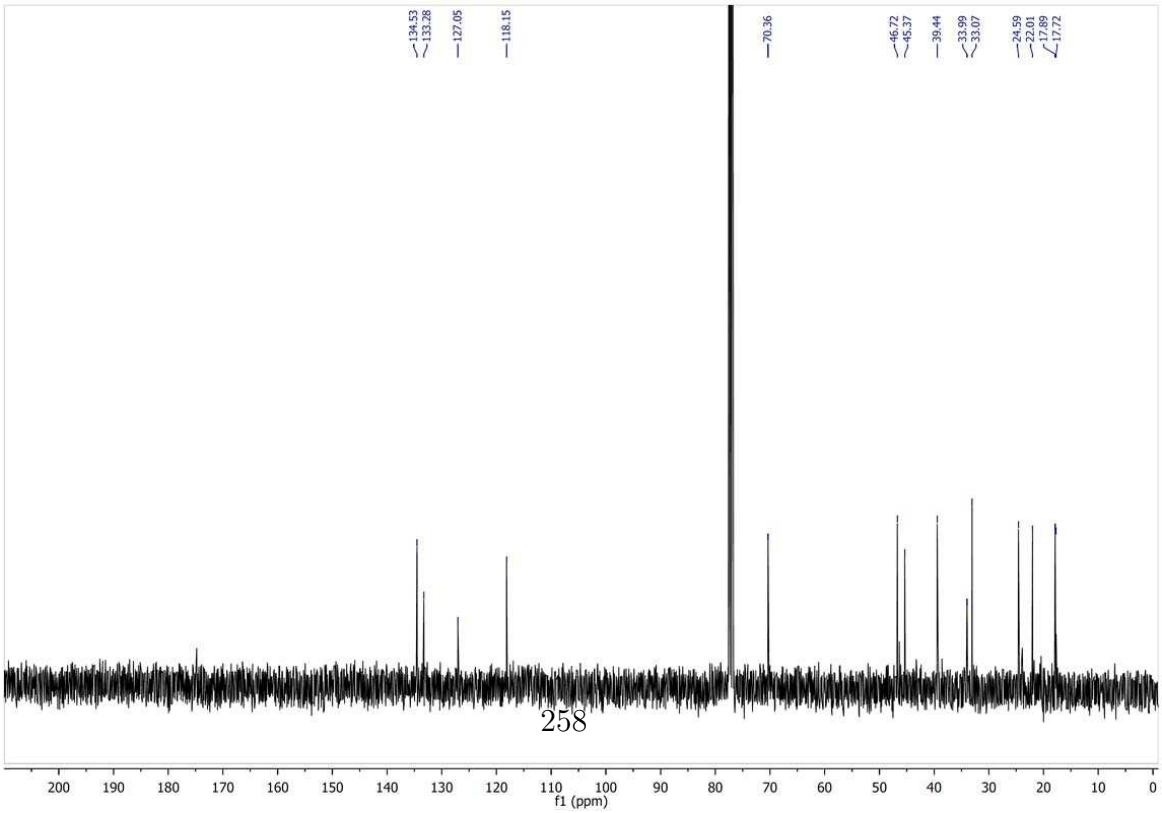
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5 9, 133.3 1, 127.0 2, 118.2 10, 70.3 7, 46.7 6, 45.4 11, 39.4 8, 34.0 3, 33.1 4, 24.6 Me, 22.0 5, 17.9 12, 17.7 13, -1.4 (3C) TMS ppm;

FT-IR thin film, neat (ATR): 3348, 29234, 1274, 860, 837 cm^{-1};

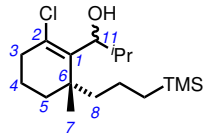
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 9.0° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.23 1-((*S*)-2-chloro-6-methyl-6-(3-(trimethylsilyl)propyl)cyclohex-1-en-1-yl)-2-methylpropan-1-ol



112a

Prepared in an analogous fashion to **111** using chloroaldehyde (109 mg, 0.40 mmol, 1.0 mol equiv) and isopropylmagnesium chloride (0.50 mL of a 1M solution in THF, 0.50 mmol, 1.2 mol equiv). The crude product was purified by flash chromatography (10-15% Et_2O/*n*-pentane gradient, silica column) to give the title compound as a 1:1 mixture of diastereomers (colourless oil) with a combined mass of (35 mg, 0.11 mmol, 28% yield) along with reduced product **112b** (46 mg, 0.18 mmol, 45% yield) (total yield = 73%). Enantiomeric excess is based off that of the starting material (92% *ee*).

HRMS (EI^+): measured using 20 eV ionisation energy. Calculated for $C_{17}H_{33}OClSi$, $[M]^{+\bullet}$: 316.1984 found 316.1994 (Δ = -3.25 pm);

First diastereomer

$\mathbf{R_f}$ = 0.51 (30% Et_2O/pentane, stains with CAM);

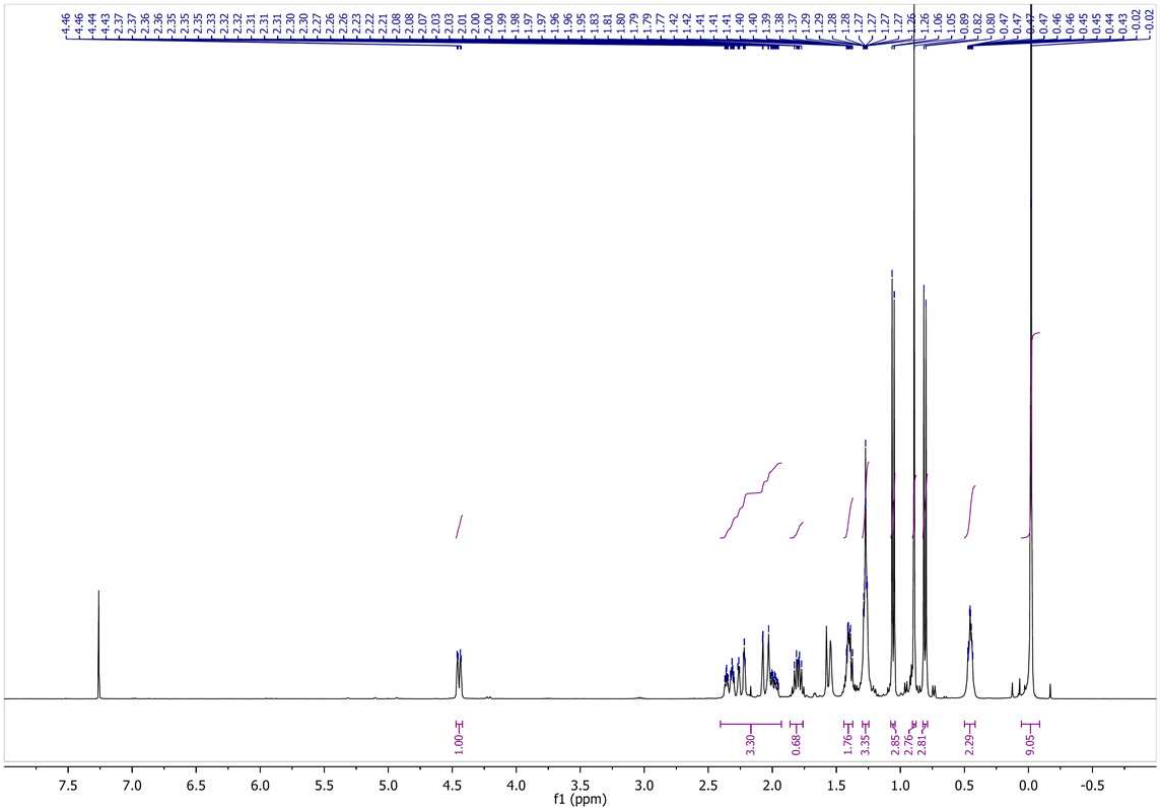
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (dd, J = 9.6, 2.2 Hz, 1H, 11), 2.38 – 1.93 (m, 4H, 3/4), 1.80 (dt, J = 9.3, 6.7 Hz, 1H, ^{i}PrH), 1.44 – 1.37 (m, 2H, 5), 1.30 – 1.25 (m, 4H, 8/9), 1.06 (d, J = 6.7 Hz, 3H, ^{i}PrMe), 0.89 (s, 3H, 7), 0.81 (d, J = 6.7 Hz, 3H, ^{i}PrMe), 0.46 (pd, J = 4.9, 3.6, 1.6 Hz, 2H, 10), −0.02 (s, 9H, TMS) ppm;

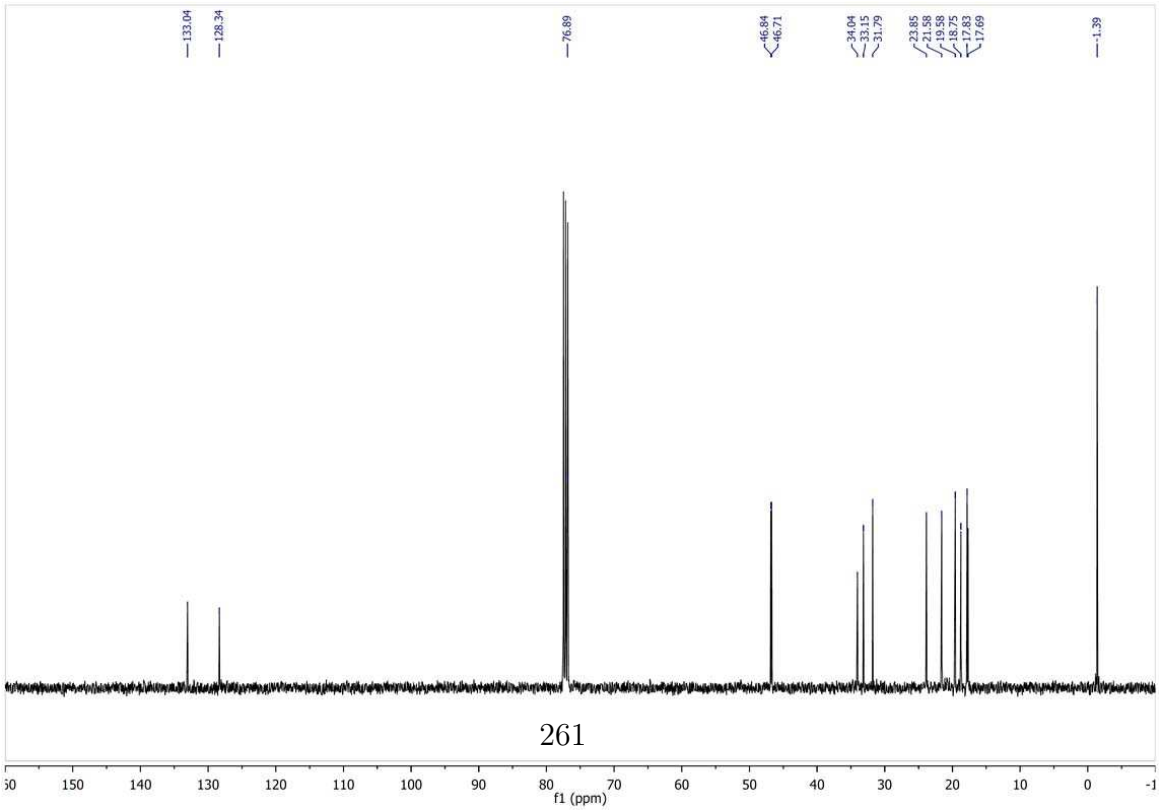
^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0 2, 128.3 1, 76.9 11, 46.8 8, 46.7 3, 34.0 6, 33.2 5, 31.8 ^{i}Pr-C, 23.9 7, 21.6 4, 19.6 ^{i}Pr-Me, 18.8 ^{i}Pr-Me, 17.8 9, 17.7 10, −1.4(3C) TMS ppm;

FT-IR thin film, neat (ATR): 3390, 2924, 2360, 1659, 1247, 1015, 837 cm^{-1};

$[\alpha]_D^{25}$ = + 25° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





Second diastereomer

R_f = 0.43 (30% Et_2O/pentane, stains with CAM);

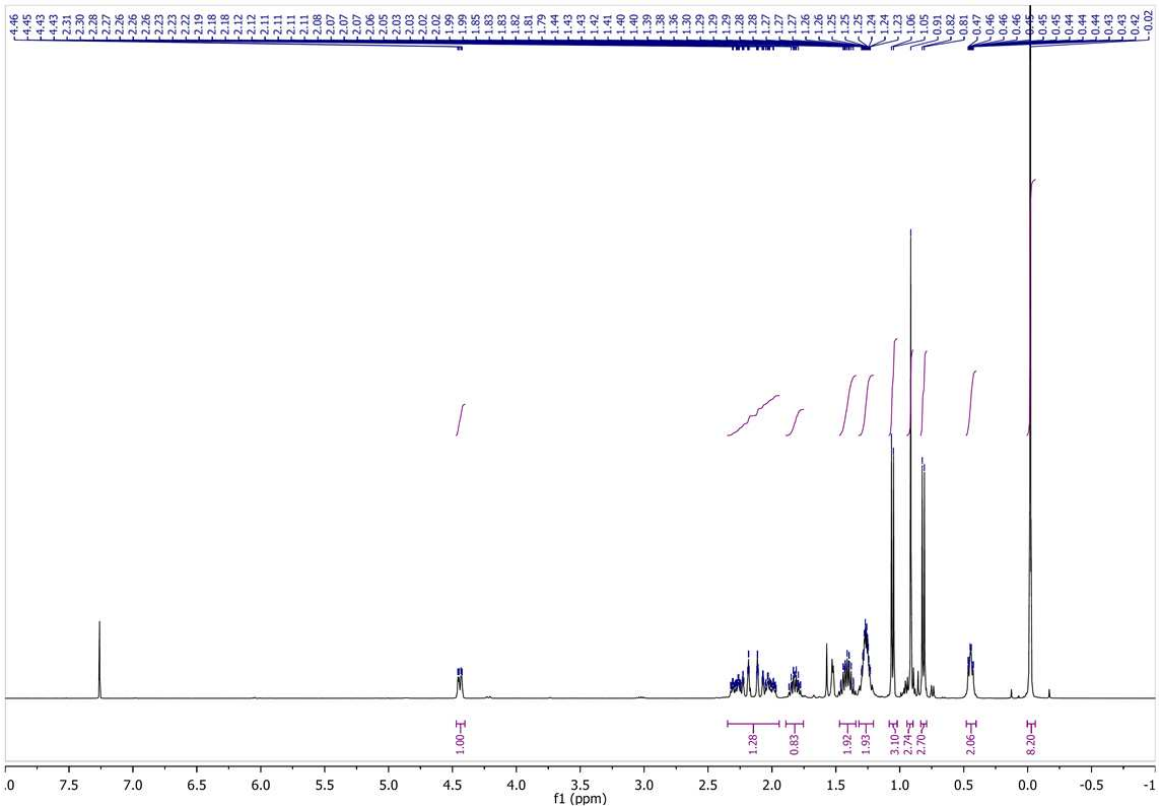
H NMR (400 MHz, $CDCl_3$): δ 4.44 (dd, J = 9.2, 3.5 Hz, 1H, 11), 2.35 – 1.94 (m, 4H, 3/4), 1.82 (dp, J = 9.2, 6.6 Hz, 1H, ^{i}PrH), 1.47 – 1.34 (m, 2H, 5), 1.32 – 1.21 (m, 4H, 8/9), 1.06 (d, J = 6.6 Hz, 3H, ^{i}PrMe), 0.91 (s, 3H, 7), 0.82 (d, J = 6.6 Hz, 3H, ^{i}PrMe), 0.48 – 0.40 (m, 2H, 10), −0.02 (s, 9H, TMS) ppm;

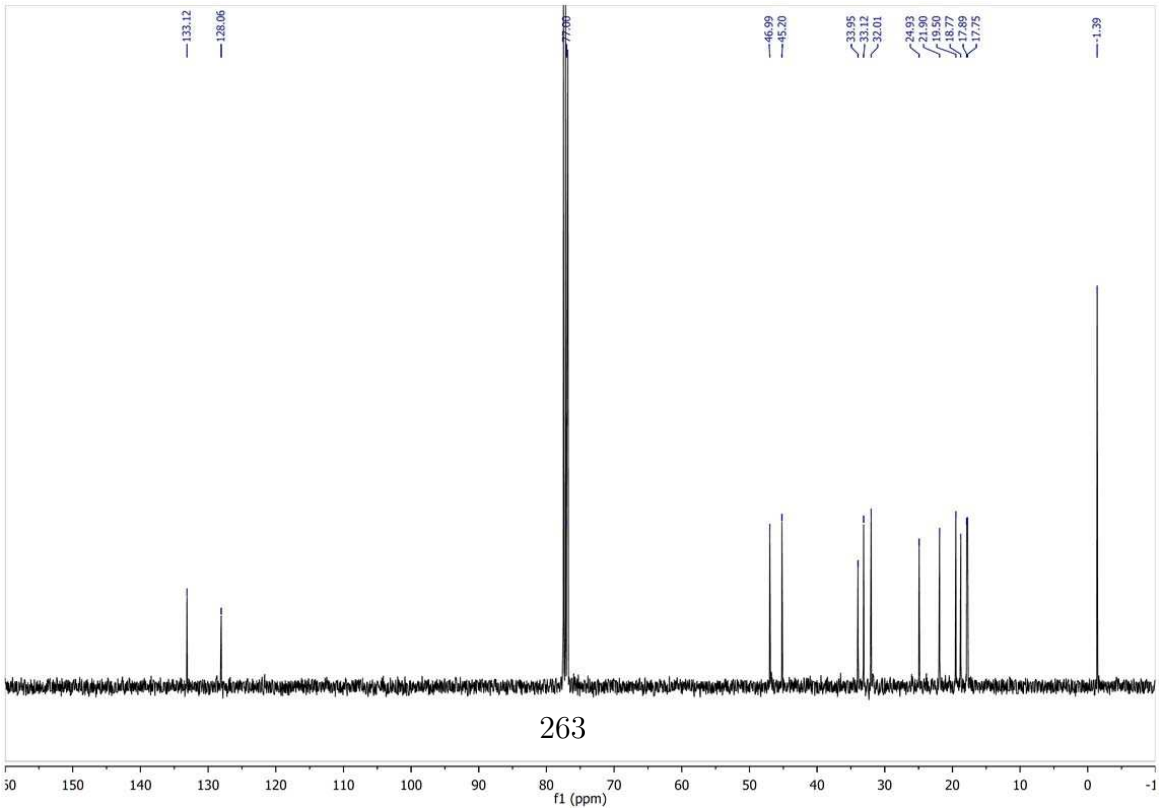
^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1 2, 128.1 1, 77.0 11, 47.0 3, 45.2 8, 34.0 6, 33.1 5, 32.0 ^{i}Pr-C, 24.9 7, 21.9 4, 19.5 ^{i}Pr-Me, 18.8 ^{i}Pr-Me, 17.9 9, 17.8 10, −1.4(3C) TMS ppm;

FT-IR thin film, neat (ATR): 3354, 2955, 2359, 1659, 1247, 1015, 836 cm^{-1};

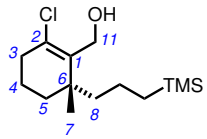
$[\alpha]_D^{25}$ = −8.1° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.24 (*S*)-(2-chloro-6-methyl-6-(3-(trimethylsilyl)propyl)cyclohex-1-en-1-yl)methanol 112b



112b

The product was co-isolated with compound **112a** .

R_f = 0.30 (30% Et_2O/pentane, stains with CAM);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 – 4.19 (m, 2H, 11), 2.26 – 1.98 (m, 4H, 3/4), 1.41 (td, J = 6.4, 2.5 Hz, 2H, 5), 1.31 – 1.23 (m, 4H, 8/9), 0.90 (s, 3H, 7), 0.49 – 0.41 (m, 2H, 10), −0.03 (s, 9H, TMS) ppm;

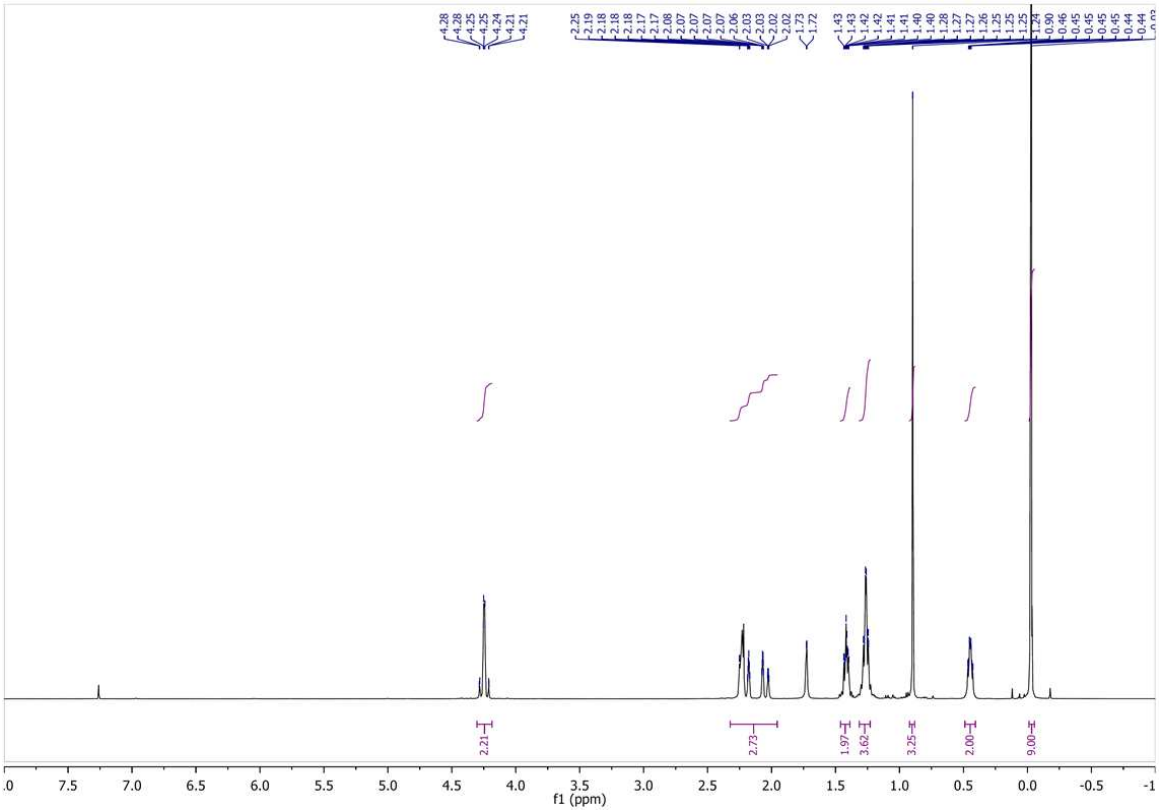
^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4 2, 128.3 1, 63.2 11, 46.3 3, 45.8 8, 34.2 6, 33.2 5, 25.7 4, 24.2 7, 17.8 9, 17.7 10, −1.4(3C) TMS ppm;

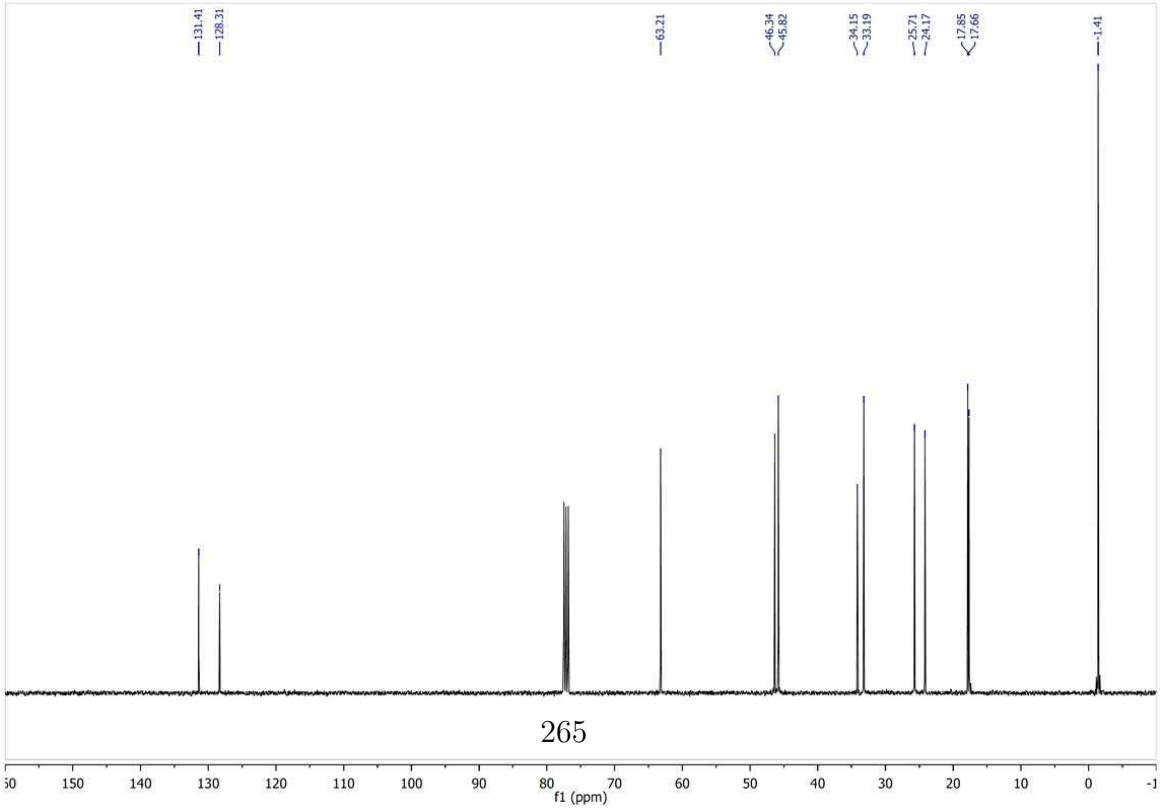
FT-IR thin film, neat (ATR): 3310, 2953, 2360, 1247, 1010, 836 cm^{-1};

HRMS (ESI^+): measured using 20 eV ionisation energy. Calculated for $C_{14}H_{27}ClOSi$, $[M]^{+\bullet}$: 274.1514 found 274.1501 (Δ = 4.82 ppm);

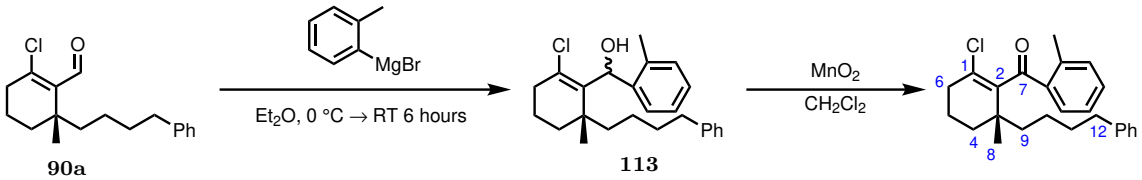
$[\alpha]_D^{25}$ = + 9.0° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.25 ((*R*)-2-chloro-6-methyl-6-(4-phenylbutyl)cyclohex-1-en-1-yl)(o-tolyl)methanol 113



90a **113**

Chloroaldehyde **90a** (58 mg, 0.20 mmol, 1.0 mol equiv) and Et_2O (0.23 mL) were added to a 7 mL vial equipped with a stir bar and a rubber septum *o*-tolylmagnesium bromide (0.24 mL of a 1M solution in tetrahydrofuran, 0.24 mmol, 1.2 mol equiv) was added dropwise at 0 °C. The cooling bath was removed after the addition and stirring was continued at room temperature for 50 minutes. The reaction was diluted with Et_2O and quenched with saturated NH_4Cl solution. After transferring the contents to a separating funnel, the aqueous phase was extracted (3x) with Et_2O. The combined organic extracts were washed (2x) with water, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-10% Et_2O/*n*-pentane gradient, silica column, R_f = 0.52 30% Et_2O/*n*-pentane, stains with $KMnO_4$) to give the title compound as a 1:1 inseparable mixture of diastereomers (colorless oil, combined mass of 51 mg, 0.13 mmol, 67% yield). Enantiomeric excess is based off that of the starting material (94% *ee*).

For characterisation purposes, the alcohol (15 mg, 0.039 mmol, 1.0 mol equiv) was treated with MnO_2 (133 mg, 1.53 mmol, 39 mol equiv) in CH_2Cl_2 (0.15 mL). After stirring for 20 hours, the mixture was filtered through celite and the filter cake

was washed (5x) with CH_2Cl_2. Concentration of the mixture *in vacuo* followed by flash chromatography(0-30% Et_2O/*n*-pentane gradient, silica column) afforded the ketone product as a colorless oil (7.9 mg, 0.021 mmol, 53% yield).

R_f = 0.60 (30% Et_2O/*n*-pentane, stains with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 7.2, 1.1 Hz, 1H, Ar-H), 7.41 – 7.36 (m, 1H, Ar-H), 7.32 – 7.24 (m, 4H, Ar-H), 7.21 – 7.16 (m, 2H, Ar-H), 2.64 (dd, J = 8.7, 6.8 Hz, 2H, 12), 2.56 (s, 3H, Ph-Me), 2.46 – 2.37 (m, 2H, alkyl-H), 2.34 – 2.11 (m, 2H, alkyl-H), 1.69 – 1.60 (m, 2H, alkyl-H), 1.54 – 1.47 (m, 2H, alkyl-H), 1.41 – 1.33 (m, 4H, alkyl-H), 1.01 (s, 3H, 8) ppm;

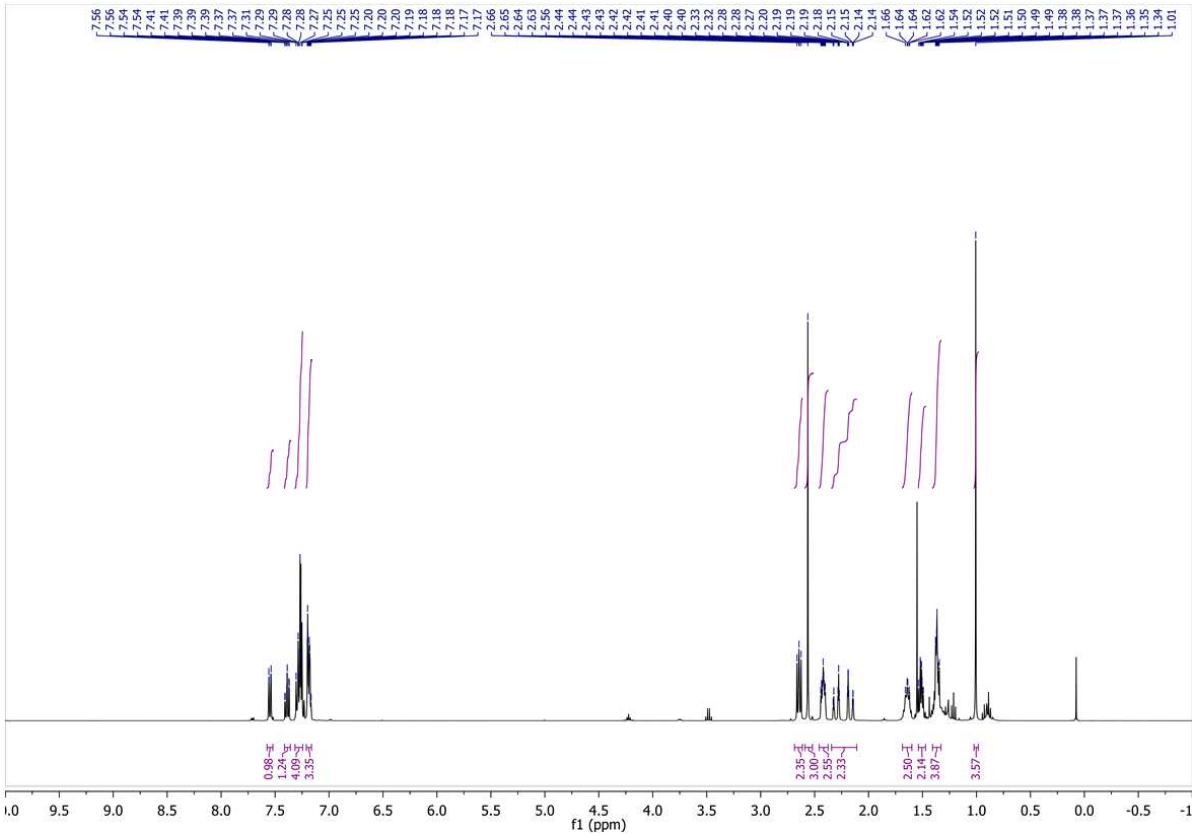
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3 7, 142.7 1, 139.5 Ar-C, 136.7 Ar-C, 134.8 2, 132.1 Ar-C, 131.9 Ar-C, 131.3 Ar-C, 130.5 Ar-C, 128.5(2C) Ar-C, 128.4(2C) Ar-C, 125.9 Ar-C, 125.8 Ar-C, 46.4 (CH_2), 41.3 (CH_2), 36.0 12, 34.1 3, 32.7 (CH_2), 32.4 (CH_2), 26.4 (CH_2), 24.5 8, 23.3 (CH_2), 21.3 Ph-Me ppm;

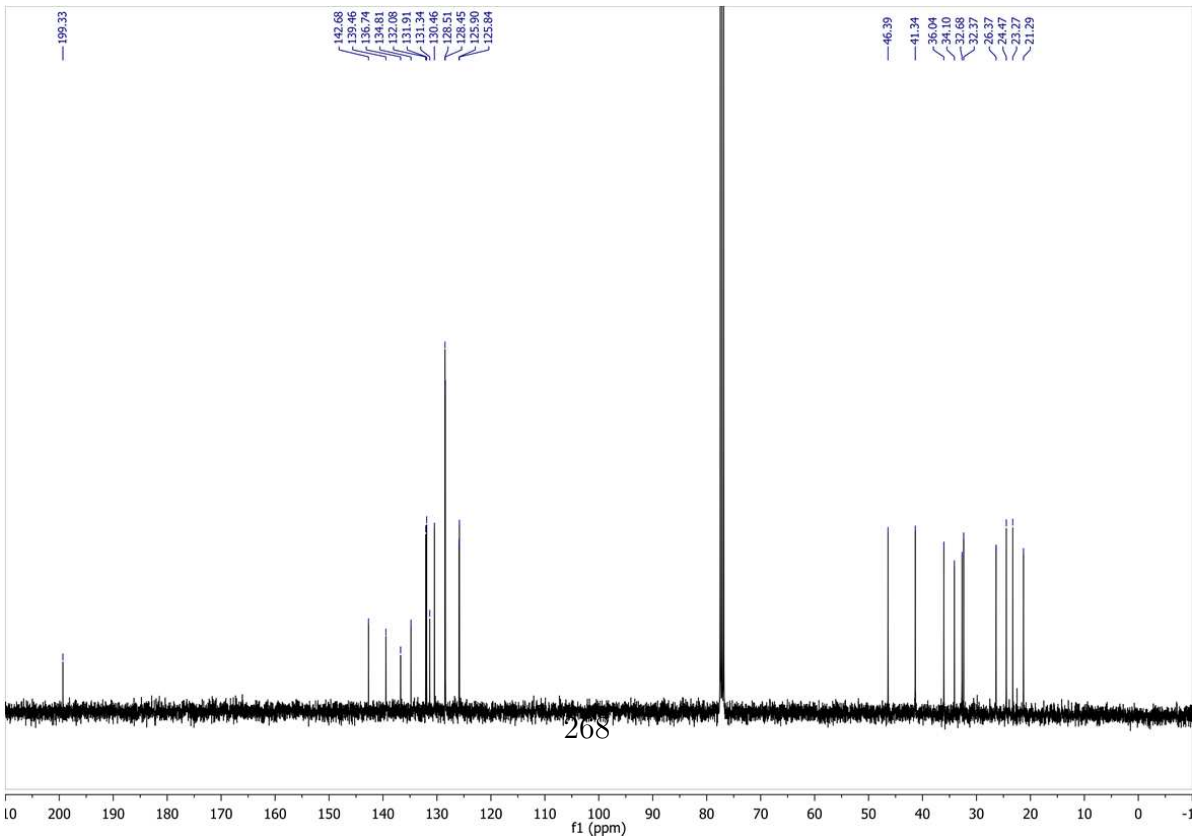
FT-IR thin film, neat (ATR): 2930, 2360, 1666, 1455, 1250 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{25}H_{30}O^{35}Cl$, $[M+1]^{+\bullet}$: 381.19797 found 381.19803 (Δ = 0.15 ppm);

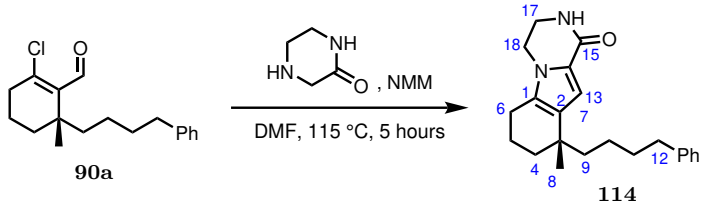
$[\alpha]_D^{25}$ = + 4.3° (c = 1.0, CH_2Cl_2), based on a sample of 94% *ee*;

^{1}H/^{13}C NMR (ketone):





5.3.1.26 (*R*)-9-methyl-9-(4-phenylbutyl)-2,3,6,7,8,9-hexahydropyrazino[1,2-a]indol-4(1H)-one 114



The condensation reaction was performed according to a literature procedure.[64] Chloroaldehyde **90a** (174 mg, 0.60 mmol, 1.5 mol equiv) and 2-oxopiperazine (40 mg, 0.50 mmol, 1.0 mol equiv) were added to a 7 mL vial equipped with a rubber septum and stirring bar. Three cycles of vacuum and back filling with N_2 were then performed, after which *N,N*-dimethylformamide (1 mL) and *N*-methylmorpholine (60 mg, 0.6 mmol, 1.5 mol equiv) were added and the reaction mixture was heated at 115 °C for 5 hours. The reaction mixture was allowed to cool, diluted with CH_2Cl_2, washed (2x) with water, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-7.5% MeOH/CH_2Cl_2 slow gradient, silica) to furnish the title compound as a white foam (56 mg, 0.17 mmol, 34% yield). Enantiomeric excess is based off that of the starting material (94% *ee*).

R_f = 0.31 (10% MeOH/CH_2Cl_2, stains yellow with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H, Ar-H), 7.20 – 7.13 (m, 3H, Ar-H), 6.73 (s, 1H, 13), 6.41 (t, J = 2.7 Hz, 1H, 16), 3.88 (2 sets of overlapping triplets J = 5.5 Hz, 2H, 18), 3.64 (m, 2H, 17), 2.62 (t, J = 7.6 Hz, 2H, 12), 2.50 (t, J = 6.3 Hz, 2H, 6), 2.37 – 2.17 (m, 2H, 5), 1.66 – 1.56 (m, 2H, 11), 1.52 (m, 2H, 4), 1.42 – 1.29 (m, 4H, 9/10), 0.96 (s, 3H, 8) ppm;

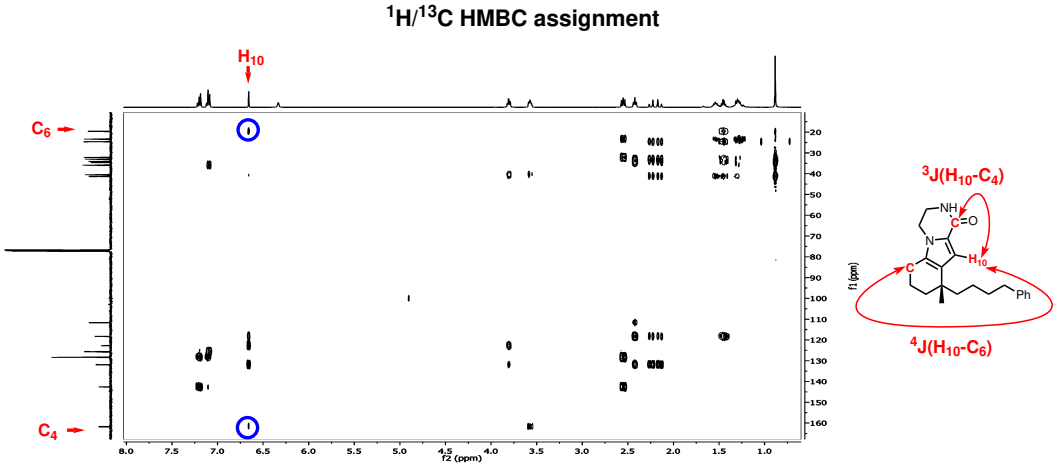
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 15, 142.8 Ar-C, 132.0, 128.5 (2C) Ar-C,

128.4 (2C) Ar-C, 125.8 Ar-H, 122.9, 118.4, 111.8 13, 41.4 9, 40.7 18, 40.6 17, 36.0 12, 34.8 4, 34.3 5, 33.1 3, 32.4 11, 24.8 8, 23.5 10, 19.8 6 ppm;

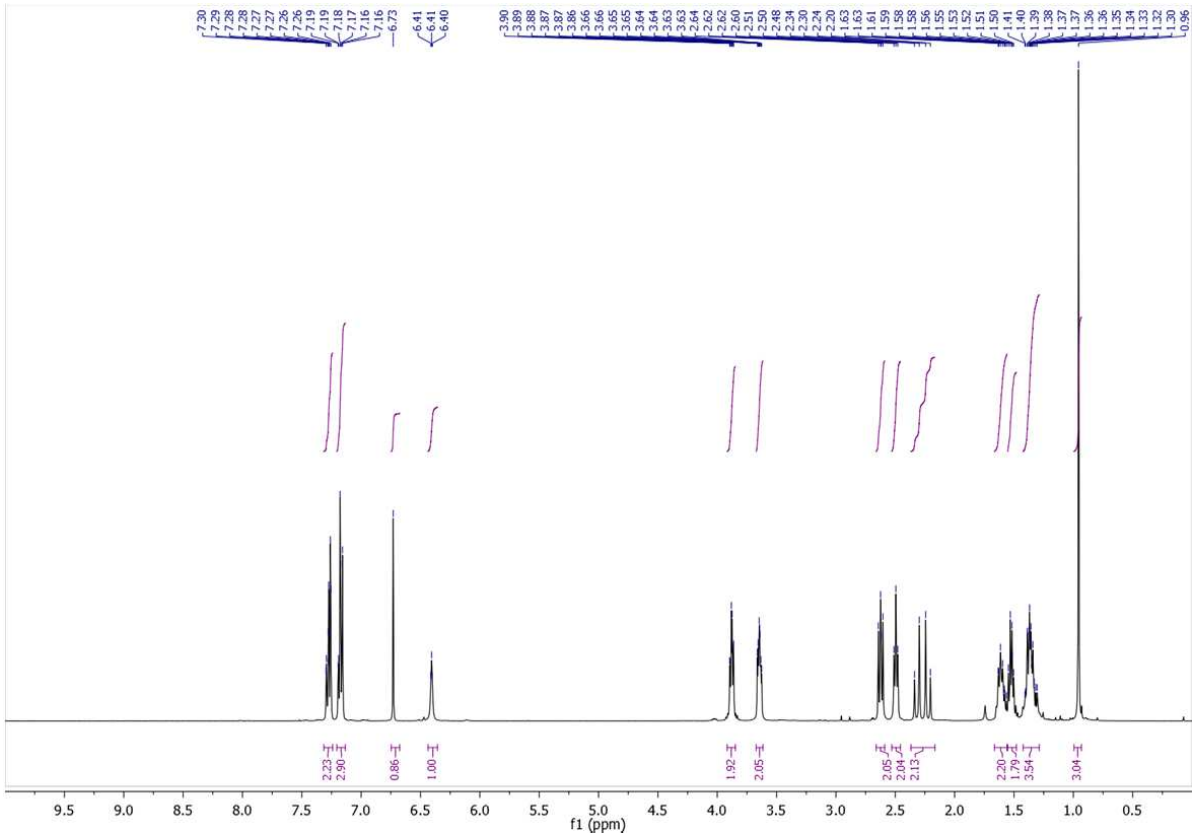
FT-IR thin film, neat (ATR): 3280, 2927, 2854, 1649, 1499, 1345 cm^{-1};

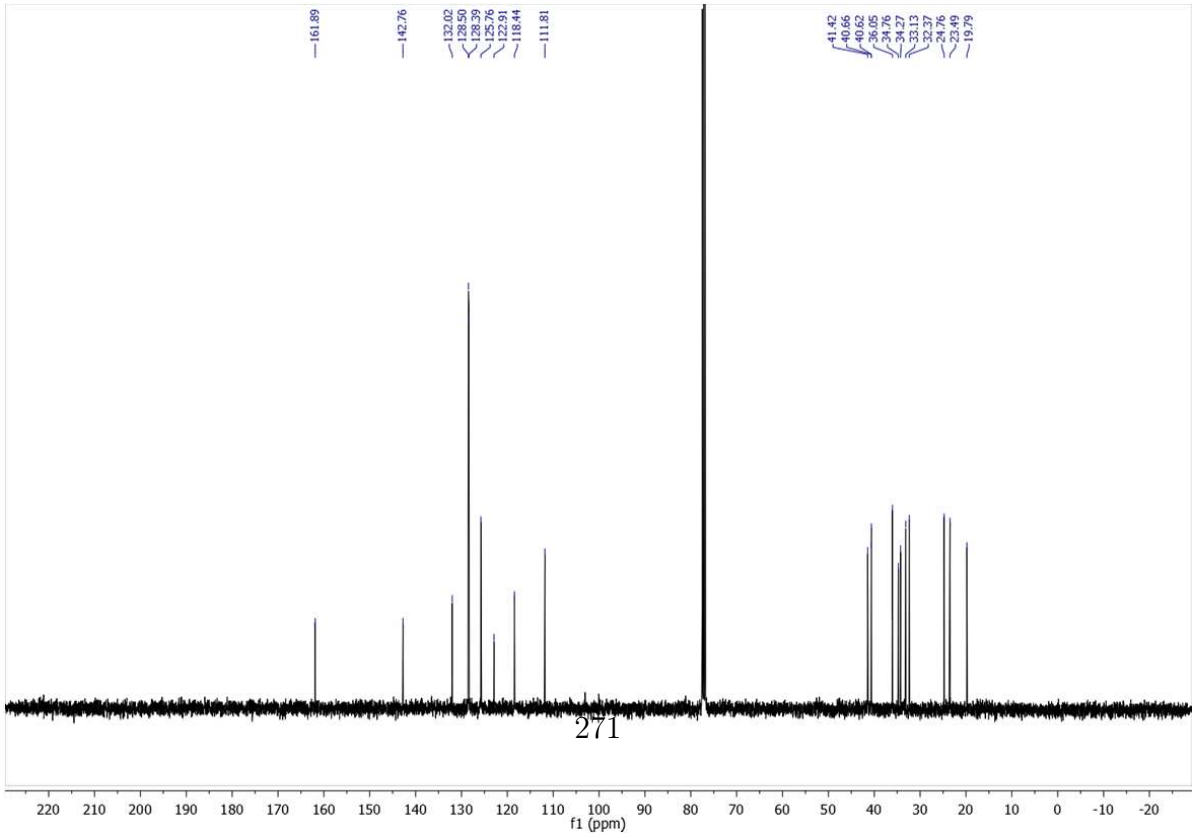
HRMS (APCI$^+$): calculated for $C_{22}H_{29}ON_2$, $[M+H]^{+\bullet}$: 337.22744 found 337.22726 (Δ = -0.52 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -18°$ (c = 1.0, CH_2Cl_2), based on a sample of 94% *ee*;

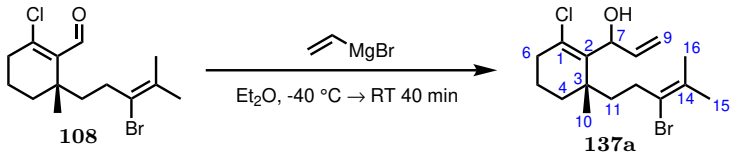


$^{1}H/^{13}C$ NMR


7.30
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.19
7.18
7.17
7.16
7.16
6.73
6.41
6.41
6.40
3.90
3.89
3.88
3.87
3.87
3.86
3.66
3.65
3.65
3.64
3.64
3.63
3.63
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2.62
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2.50
2.48
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1.61
1.59
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1.55
1.53
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1.44
1.40
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1.37
1.37
1.36
1.36
1.35
1.34
1.33
1.32
1.30
0.96
2.23
2.90
0.86
1.00
1.92
2.05
2.05
2.04
2.13
2.20
1.79
3.54
3.04
9.5
9.0
8.5
8.0
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
f1 (ppm)


161.89
142.76
132.02
128.50
128.39
128.26
122.91
118.44
111.81
41.42
40.66
40.62
36.05
34.76
34.27
33.13
32.37
24.76
23.49
19.79
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

5.3.1.27 1-((*S*)-6-(3-bromo-4-methylpent-3-en-1-yl)-2-chloro-6-methylcyclohex-1-en-1-yl)prop-2-en-1-ol 137a



Chloroaldehyde **108** (3.62 g, 11.3 mmol, 1.0 mol equiv) and Et_2O (13.5 mL) were added to a 100 mL round bottom flask equipped with a stir bar and a rubber septum. Vinylmagnesium bromide (13.6 mL of a 1M solution in tetrahydrofuran, 13.6 mmol, 1.2 mol equiv) was added dropwise at 0 °C. The cooling bath was removed immediately after the addition and stirring was continued at room temperature for 30 minutes. The reaction was quenched with Et_2O and saturated $NH_4Cl_{(aq)}$ solution. After separating the biphasic mixture, the aqueous layer was extracted (3x) with Et_2O. The combined organic extracts were dried over $MgSO_4$ and volatiles were removed *in vacuo*. The residue was purified directly using flash chromatography (0-20% Et_2O/*n*-pentane gradient, silica column) to give the product as a 1:1 separable mixture of diastereomers (colourless oil) with a combined mass of 3.427 g (9.84 mmol, 87% yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

R_f = 0.39 (30% Et_2O/*n*-pentane, stains with $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (ddd, J = 17.2, 10.5, 4.4 Hz, 1H, 8), 5.39 (t, J = 4.4 Hz, 1H, 7), 5.33 (dt, J = 17.2, 1.6 Hz, 1H, 9-*trans*), 5.17 (dt, J = 10.5, 1.6 Hz, 1H, 9-*cis*), 2.49 – 2.43 (m, 2H, alkyl-H), 2.38 – 1.97 (m, 4H, alkyl-H), 1.85 (s, 3H, 16), 1.75 (s, 3H, 15), 1.59 – 1.37 (m, 4H, alkyl-H), 0.92 (s, 3H, 10) ppm;

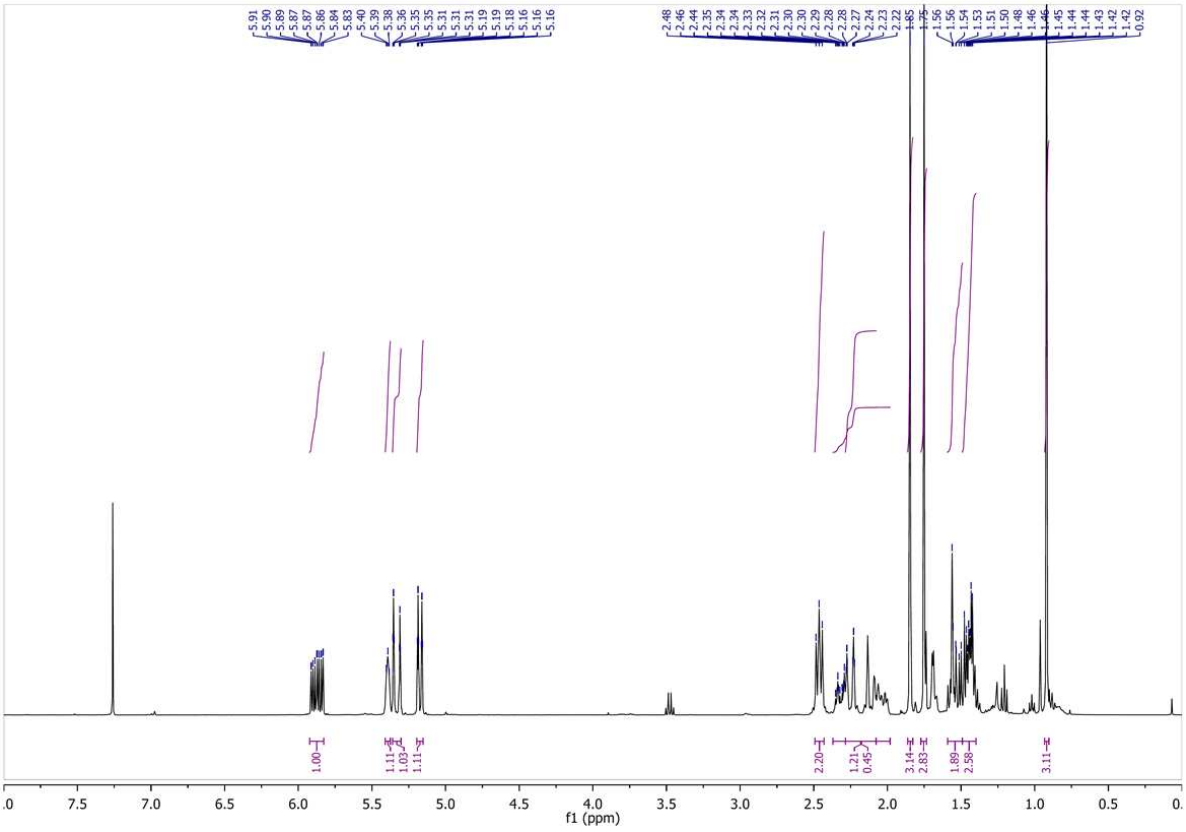
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 132.5, 130.0, 127.1, 121.8, 114.9, 71.8, 46.5, 39.4, 33.6, 32.8, 32.6, 25.5, 24.1, 21.7, 20.3 ppm;

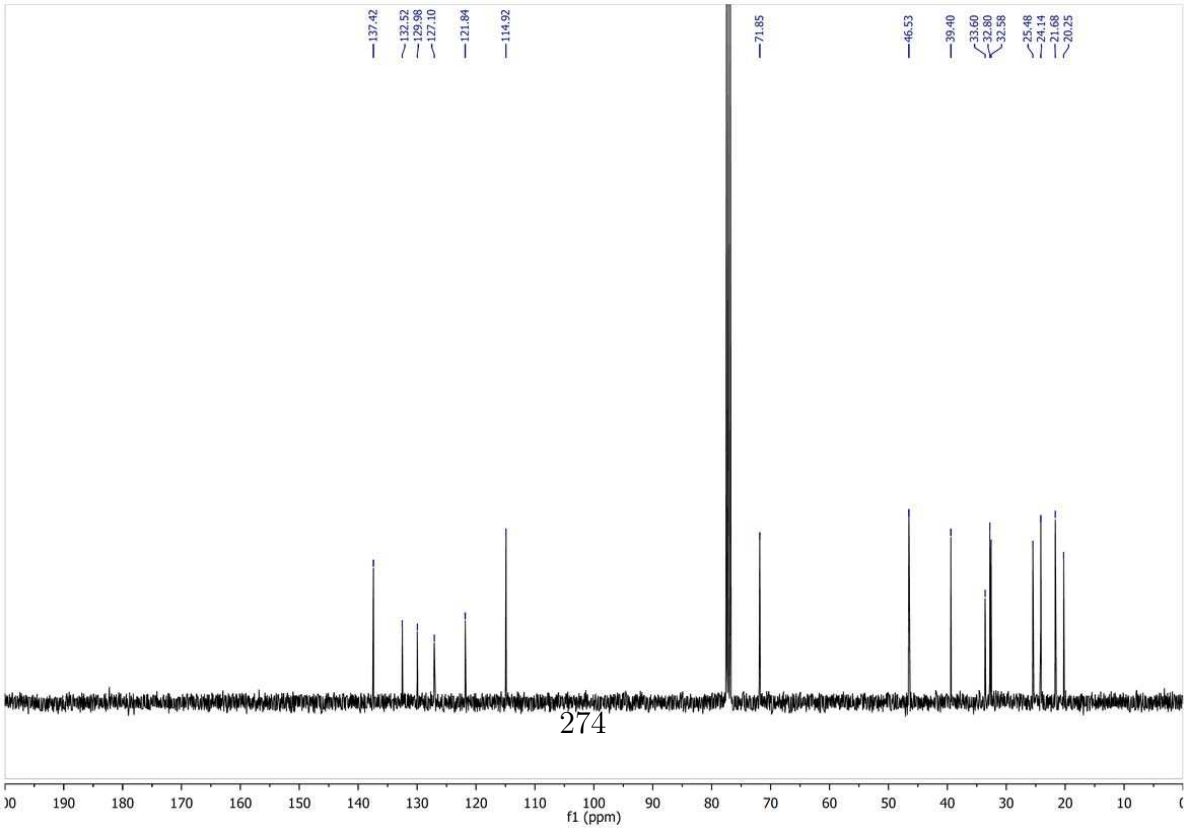
FT-IR thin film, neat (ATR): 3364, 2918, 1449, 990 cm^{-1};

HRMS (ESI^+): calculated for $C_{16}H_{24}O^{79}Br^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 369.05913 found 369.05905 (Δ = -0.2 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -28^\circ$ (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR (first diastereomer)





Second diastereomer

NOE studies did not afford conclusive insight into relative configuration.

R_f = 0.33 (30% Et_2O/*n*-pentane, stains with $KMnO_4$);

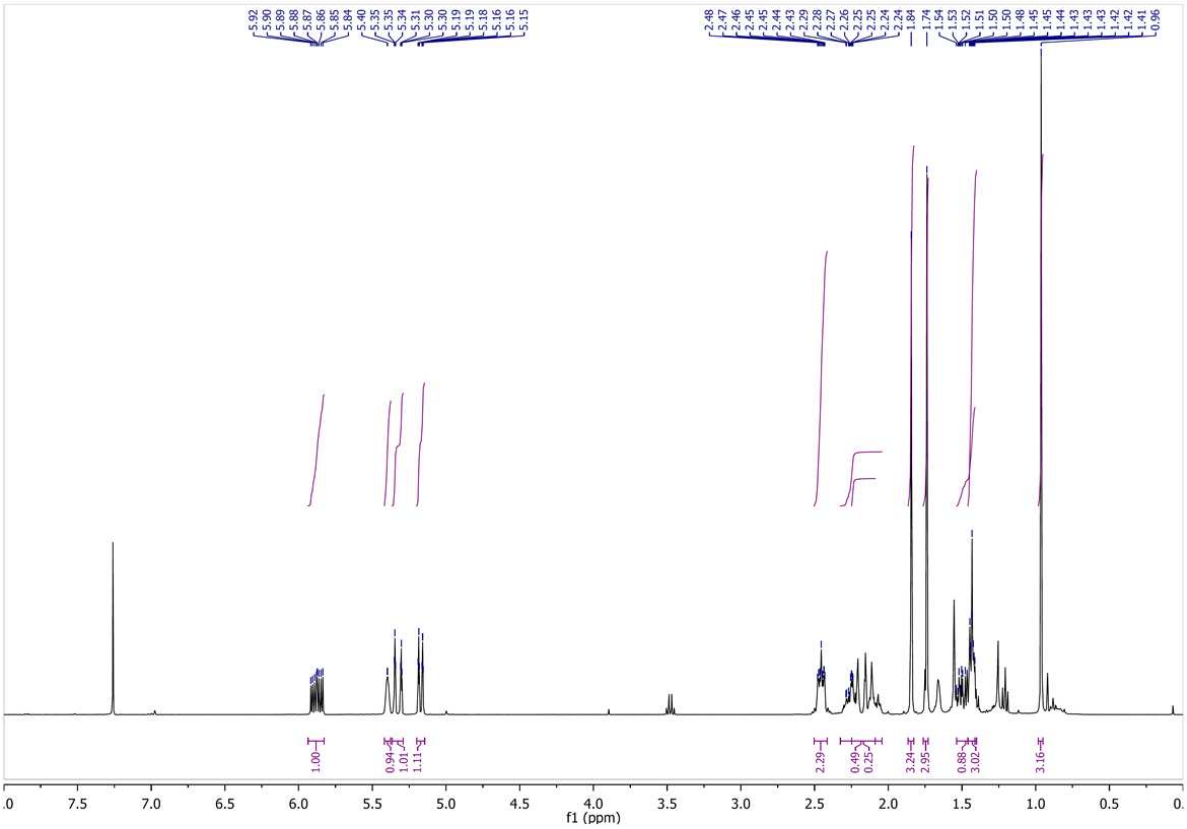
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (ddd, J = 17.3, 10.5, 4.9 Hz, 1H, 8), 5.40 (bs, 1H, 7), 5.33 (dt, J = 17.3, 1.6 Hz, 1H, 9-*trans*), 5.17 (dt, J = 10.6, 1.6 Hz, 1H, 9-*cis*), 2.45 (m, 2H, alkyl-H), 2.32 – 2.01 (m, 4H, alkyl-H), 1.84 (s, 3H, 16), 1.74 (s, 3H, 15), 1.54 – 1.38 (m, 4H, alkyl-H), 0.96 (s, 3H, 10) ppm;

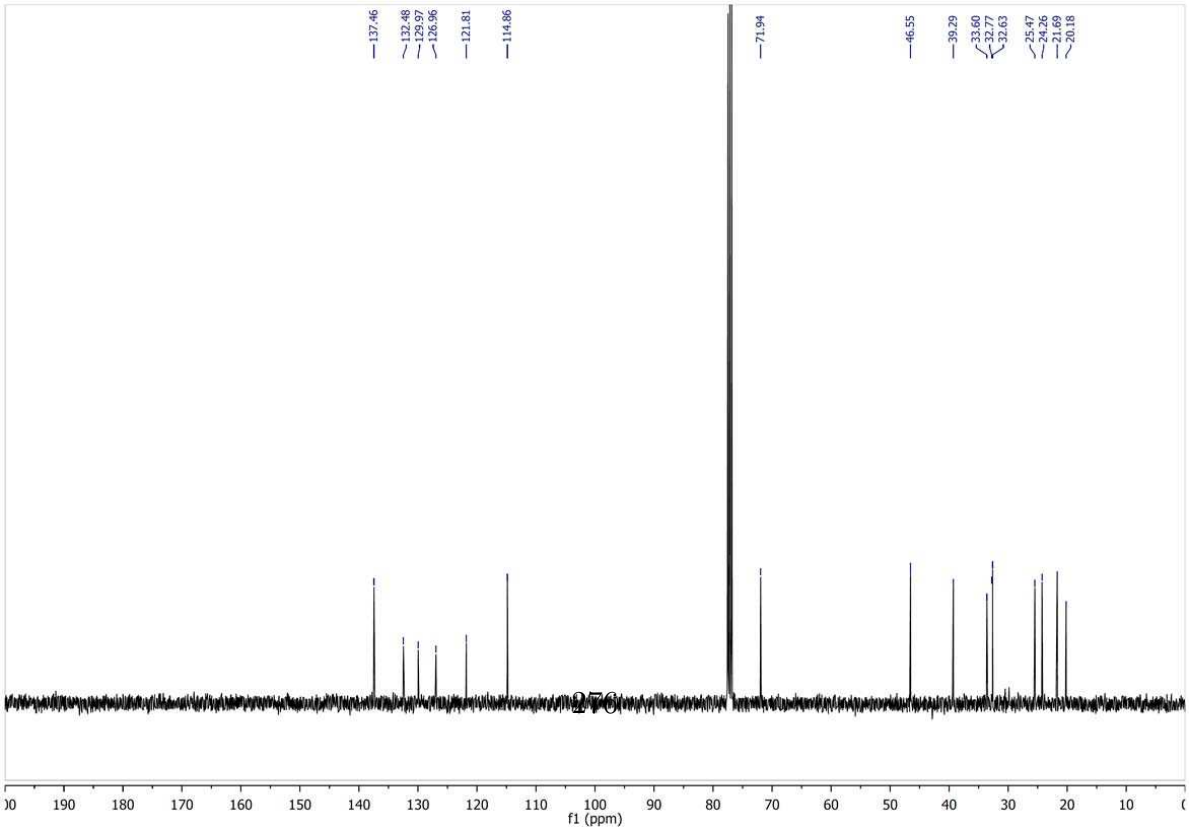
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 132.5, 130.0, 127.0, 121.8, 114.9, 71.9, 46.5, 39.3, 33.6, 32.8, 32.6, 25.5, 24.3, 21.7, 20.2 ppm;

FT-IR thin film, neat (ATR): 3365, 2919, 1458, 990 cm^{-1};

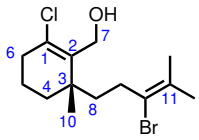
$[\alpha]_D^{25}$ = + 58° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR (second diastereomer)





5.3.1.28 (*S*)-(6-(3-bromo-4-methylpent-3-en-1-yl)-2-chloro-6-methylcyclohex-1-en-1-yl)methanol 236



236

This compound was isolated as a side product in the reaction to form **137a** .

R_f = 0.24 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (s, 2H, 7), 2.46 (dd, J = 9.9, 7.0 Hz, 2H, alkyl-H), 2.33 – 2.04 (m, 4H, alkyl-H), 1.84 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.58 – 1.38 (m, 4H, alkyl-H), 0.94 (s, 3H, CH_3) ppm;

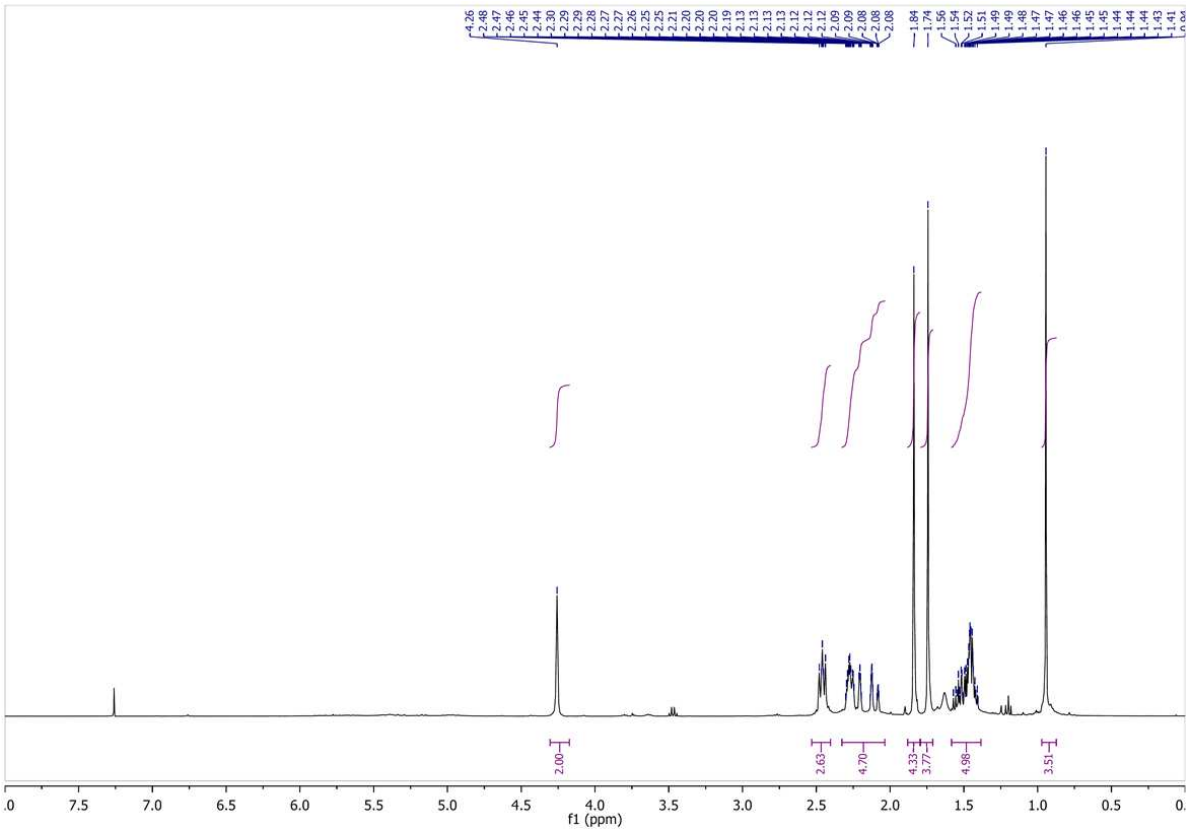
^{13}C NMR (101 MHz, $CDCl_3$): δ 131.5 1, 130.0 2, 127.8 CH_3, 121.8 CH_3, 63.1 7, 46.2 (CH_2), 39.4 (CH_2), 33.7 3, 32.9 (CH_2), 32.5 (CH_2), 25.6 (CH_2), 25.5 CH_3, 24.1 10, 20.2 CH_3 ppm;

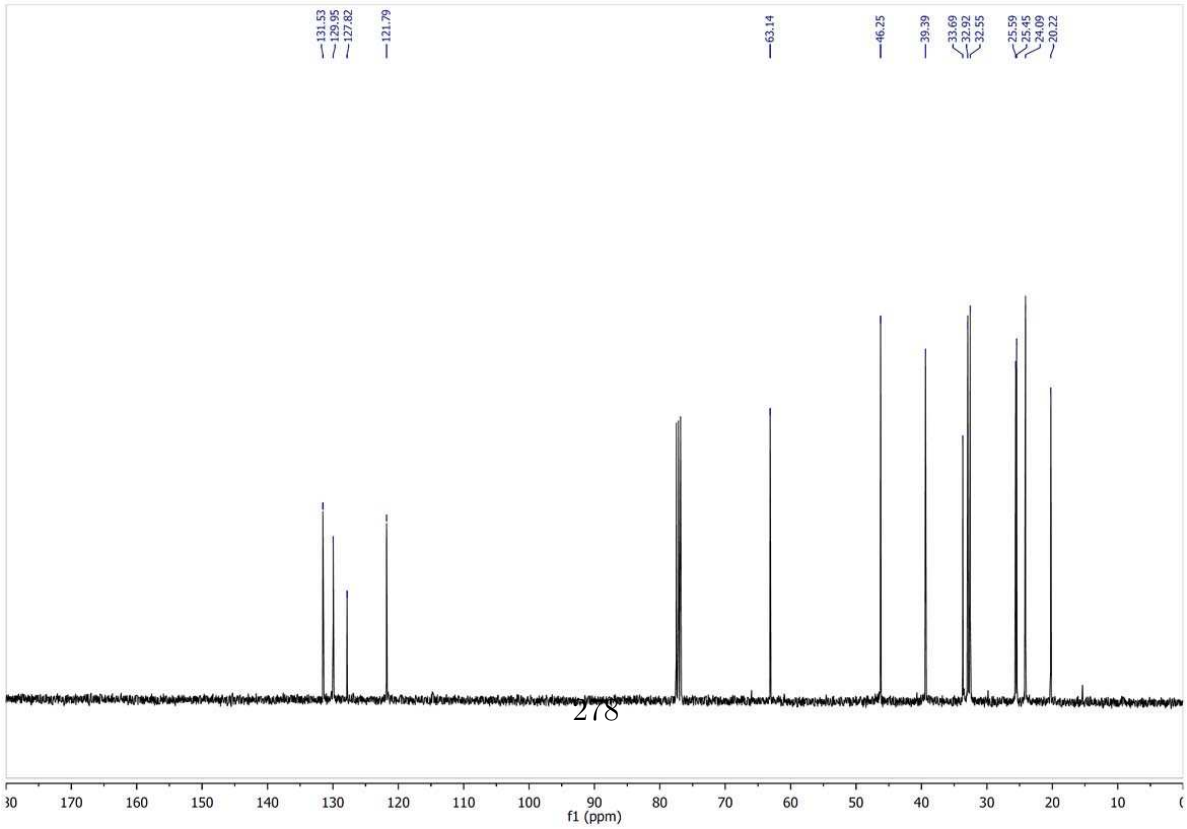
FT-IR thin film, neat (ATR): 3338, 2919, 1457, 1008 cm^{-1};

HRMS (ESI^+): calculated for $C_{14}H_{22}O^{79}Br^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 343.0435 found 343.0435 (Δ = 0.20 ppm);

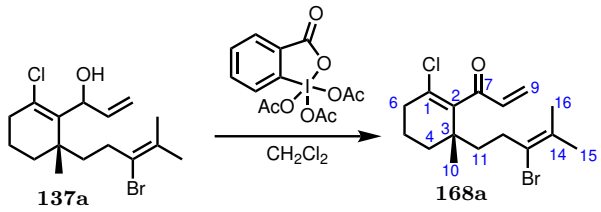
$[\alpha]_D^{25}$ = + 15° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.29 (*S*)-1-(6-(3-bromo-4-methylpent-3-en-1-yl)-2-chloro-6-methylcyclohex-1-en-1-yl)prop-2-en-1-one 168a



Allylic alcohol **137a** (196 mg, 0.612 mmol, 1.0 mol equiv) and water (6 μL, 0.31 mmol, 0.50 mol equiv) were dissolved in "wet" CH_2Cl_2 (20 mL) in a 50 mL test tube, equipped with a stirrer bar. Dess-Martin periodinane (312 mg, 0.735 mmol, 1.2 mol equiv) was added and the mixture stirred vigorously until the reaction was judged complete (TLC control, approx. 10 – 30 min). The reaction was quenched with 6 mL each of saturated $Na_2S_2O_3$ and saturated $NaHCO_{3(aq)}$. The organic layer was extracted (3x) with CH_2Cl_2, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product wass purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a pale yellow oil (22 mg, 0.065 mmol, quantitative yield).

R_f = 0.37 (10% Et_2O/*n*-pentane, $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (dd, J = 17.5, 10.4 Hz, 1H, 8), 6.24 (dd, J = 17.5, 1.2 Hz, 1H, 9-*trans*), 5.97 (dd, J = 10.4, 1.2 Hz, 1H, 9-*cis*), 2.53 – 2.44 (m, 2H, alkyl-H), 2.39 – 2.14 (m, 4H, alkyl-H), 1.85 (s, 3H, 16), 1.76 (s, 3H, 15), 1.64 – 1.46 (m, 4H, alkyl-H), 1.01 (s, 3H, 10) ppm;

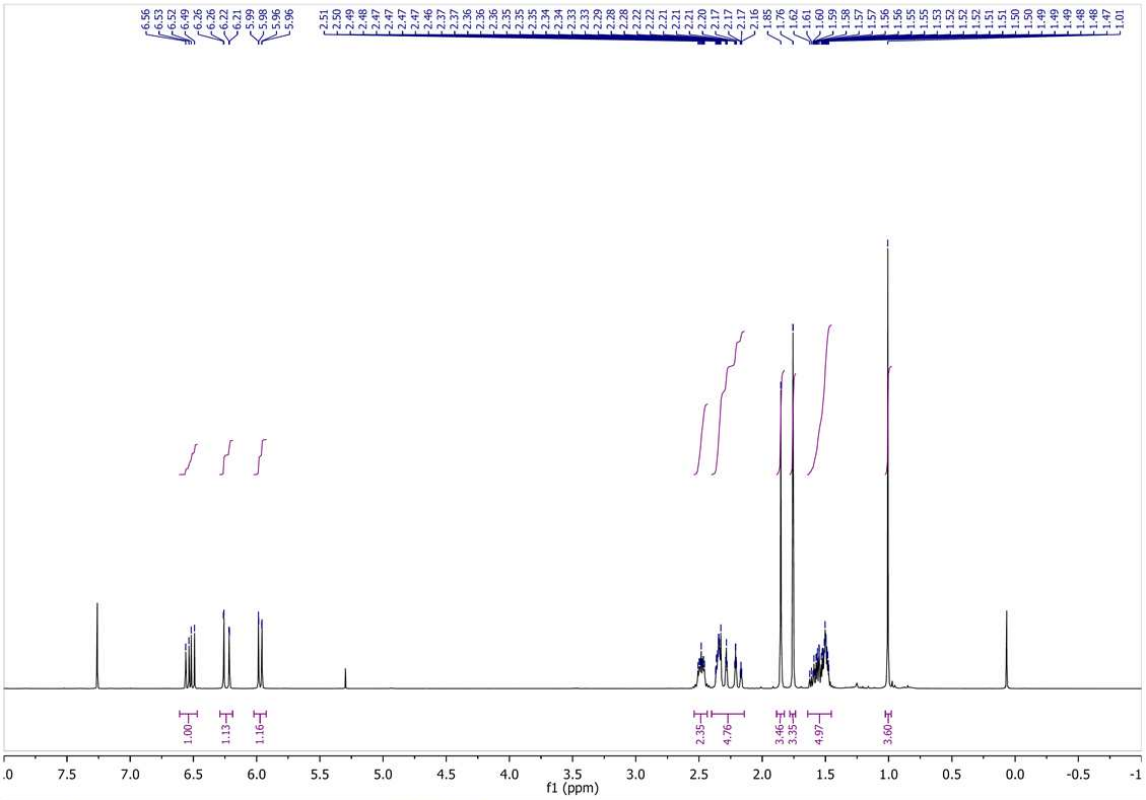
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7 7, 135.8 8, 133.44 , 130.7 9, 130.63 , 130.23 , 121.50 , 46.1 (CH_2), 39.2 (CH_2), 33.7 3, 32.5 (CH_2), 32.3 (CH_2), 25.8 (CH_2), 25.5 16, 24.3 10, 20.26 15 ppm;

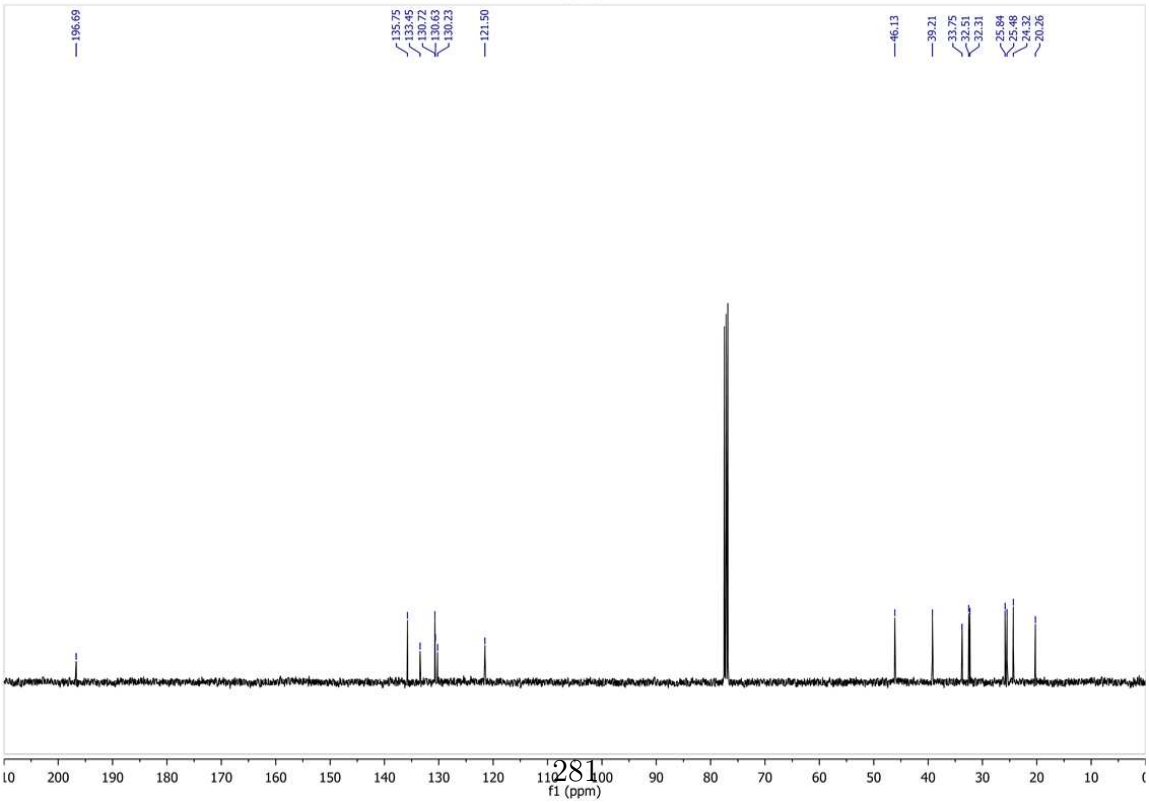
FT-IR thin film, neat (ATR): 2920, 1665, 1401, 1223, 985, 962 cm^{-1};

HRMS (ESI^+): calculated for $C_{16}H_{23}O^{79}Br^{35}Cl$, $[M+H]^{+\bullet}$: 345.06153 found 345.06152 (Δ = -0.03 ppm);

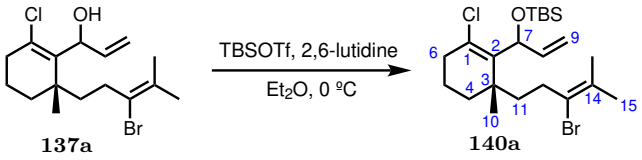
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 12° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.30 TBS protected bromide 140a



Alcohol **137a** (50 mg, 0.14 mmol, 1.0 mol equiv) and dry Et_2O (0.35 mL) were added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. 2,6-lutidine (17 μL, 0.15 mmol, 1.1 mol equiv) was added by syringe and the solution was cooled to 0 °C. *tert*-Butyldimethylsily trifluoromethanesulfonate (35 μL, 0.15 mmol, 1.1 mol equiv) was added dropwise and upon completion of addition, the cooling bath was removed. When the reaction was deemed complete by TLC (approx. 3.5 hours), the mixture was diluted with Et_2O and quenched with saturated $NaHCO_{3(aq)}$. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound (inseparable mixture of diastereomers) as a clear oil (59 mg, 0.13 mmol, 93% yield).

R_f = 0.67 (30% Et_2O/*n*-pentane, stains blue with CAM);

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (dddd, J = 17.0, 10.4, 4.0, 1.7 Hz, 1H, 8), 5.37 (dq, J = 3.9, 1.9 Hz, 1H, 7), 5.31 (dq, J = 17.0, 1.8 Hz, 1H, 9-*trans*), 5.08 (dt, J = 10.4, 1.9 Hz, 1H, 9-*cis*), 2.45 (td, J = 8.7, 8.2, 3.1 Hz, 2H, alkyl-H), 2.30 – 1.94 (m, 4H, alkyl-H), 1.84 (s, 3H, CH_3), 1.75(1.73) (s, 3H, 15/16), 1.53 – 1.32 (m, 4H, alkyl-H), 0.94(0.86) (s, 3H, 10), 0.91(0.90) (s, 9H, TBS-^{t}Bu-Me), 0.08 – 0.01 (m, 6H, TBS-Me) ppm;

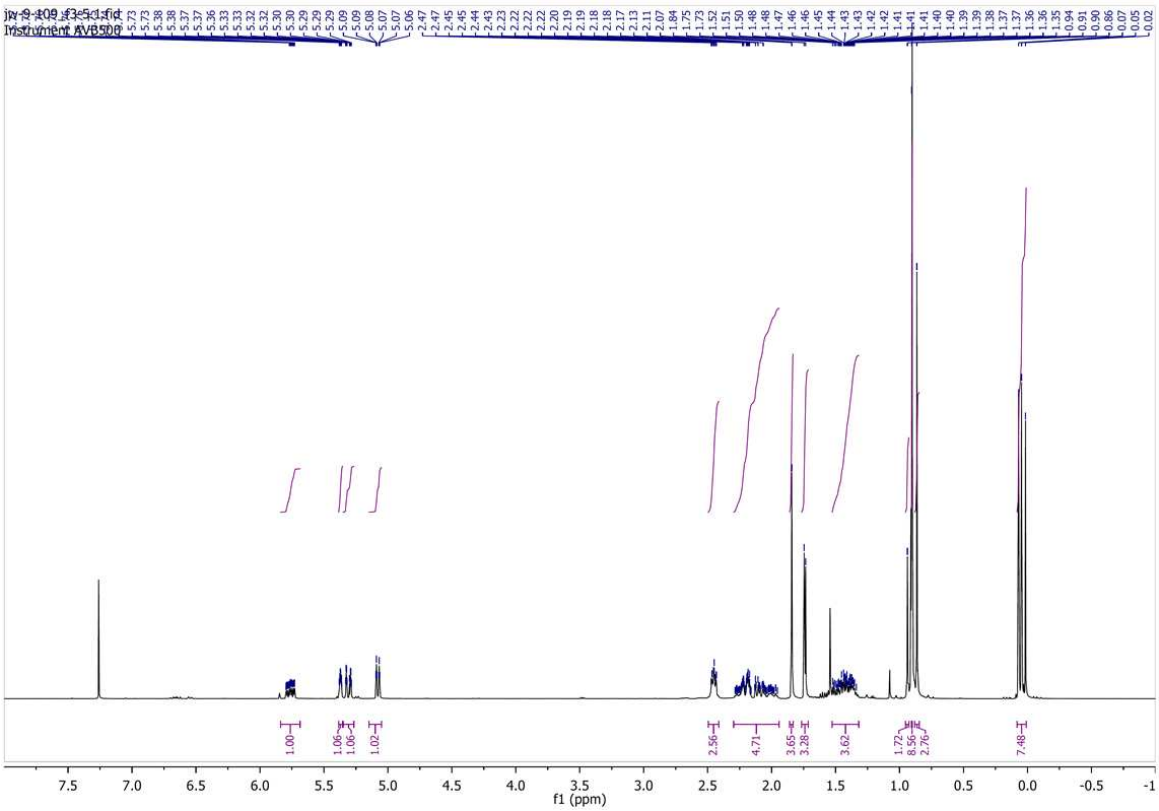
^{13}C NMR (126 MHz, $CDCl_3$): δ 138.3(138.2) 8, 133.5(133.4), 129.9(129.8), 124.9, 121.93(121.87), 113.7 9, 72.1(72.0) 7, 46.6(46.4) (CH_2), 39.8(38.8) (CH_2), 33.7 3, 32.8 (CH_2), 32.6 (CH_2), 26.02(25.97) TBS-^{t}Bu-Me, 25.5 CH_3, 23.9 10, 21.4(21.2) (CH_2), 20.3(20.2) CH_3, 18.3 TBS-^{t}Bu-C, -2.8(-4.8)(-4.88)(-4.91) TBS-Me ppm;

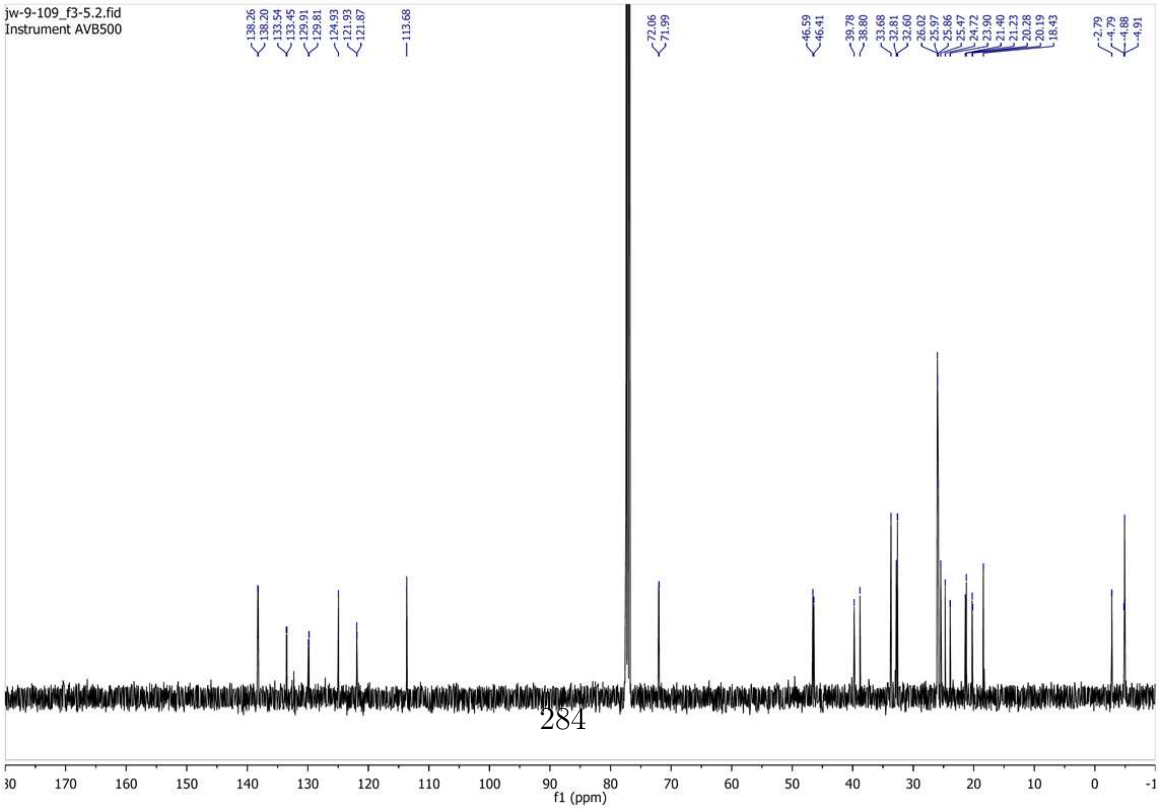
FT-IR thin film, neat (ATR): 2955, 2928, 2856, 2360, 1471, 1230, 1006, 837 cm^{-1};

HRMS: A high resolution mass spectrum could not be obtained for this compound (using EI, ESI, APCI).

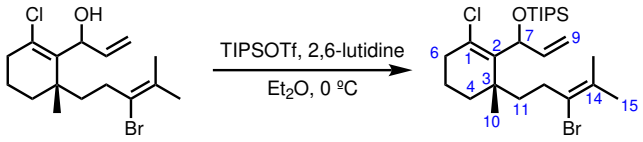
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +16^\circ$ ($c = 0.62$, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR


Instrument AVB500
1.00
1.06
1.06
1.02
2.56
4.71
3.65
3.28
3.62
1.72
8.56
2.76
7.48
f1 (ppm)


jw-9-109_f3-5.2.fid
Instrument AVB500
138.26
138.20
133.54
133.45
129.91
129.81
124.93
121.93
121.87
113.68
72.06
71.99
46.59
46.41
39.78
38.80
33.68
32.81
32.60
26.02
25.97
25.86
25.47
24.72
23.90
21.40
21.23
20.28
20.19
18.43
-2.79
-4.79
-4.88
-4.91
f1 (ppm)

5.3.1.31 TIPS protected bromide 140b



137a **140b**

Alcohol **137a** (348 mg, 1.28 mmol, 1.0 mol equiv) and dry Et_2O (6.4 mL) were added to a flame dried 21 mL vial equipped with a rubber septum and stirrer bar. 2,6-lutidine (0.22 mL, 1.92 mmol, 1.5 mol equiv) was added by syringe and the solution was cooled to 0 °C. Triisopropyl trifluoromethanesulfonate (0.52 mL, 1.92 mmol, 1.5 mol equiv) was added dropwise and upon completion of addition, the cooling bath was removed. When the reaction was deemed complete by TLC (approx. 3.5 hours), the mixture was diluted with Et_2O and quenched with saturated $NaHCO_{3(aq)}$. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound (inseparable mixture of diastereomers) as a clear oil (532 mg, 1.04 mmol, 81% yield).

R_f = 0.81 (10% Et_2O/*n*-pentane, stains blue with CAM);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddd, J = 17.1, 10.4, 4.3, 1.6 Hz, 1H, 8), 5.45 (dd, J = 4.3, 2.2 Hz, 1H, 7), 5.34 (dtd, J = 17.1, 1.9, 0.9 Hz, 1H, 9-*trans*), 5.08 (dt, J = 10.4, 1.9 Hz, 1H), 2.45 (td, J = 9.0, 8.6, 2.7 Hz, 2H, 12), 2.39 – 1.97 (m, 4H, 5–6), 1.84 (s, 3H, 15), 1.74(1.73) (s, 3H, 15'), 1.55 – 1.42 (m, 2H, 11), 1.42 – 1.32 (m, 2H, 4), 1.15 – 1.07 (m, 3H, TIPS-^{i}Pr-H), 1.05 (m, 18H, TIPS-^{i}Pr-Me), 0.94(0.90) (s, 3H, 10) ppm;

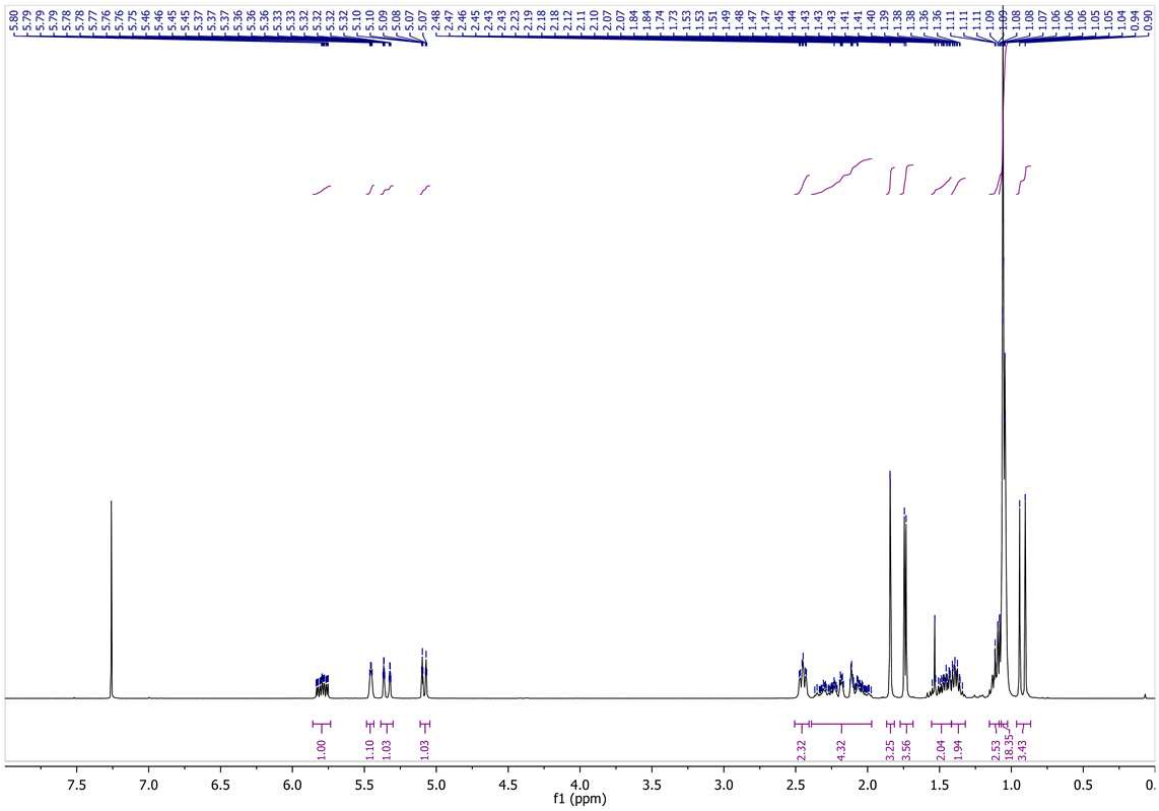
^{13}C NMR (101 MHz, $CDCl_3$): δ 138.4(138.32) 8, 133.9(133.82) 1, 129.9(1298) 2, 124.70 13, 122.0(121.9) 14, 113.6 9, 72.3(72.2) 7, 46.5(46.41) 6, 39.6(39.2) 11, 33.7 3, 32.9 4, 32.6 12, 25.5 15, 24.5(24.1) 10, 21.3(21.1) 5, 20.3(20.2) 15', 18.2(18.1) TIPS-^{i}Pr-Me, 12.4 TIPS-^{i}Pr-H ppm;

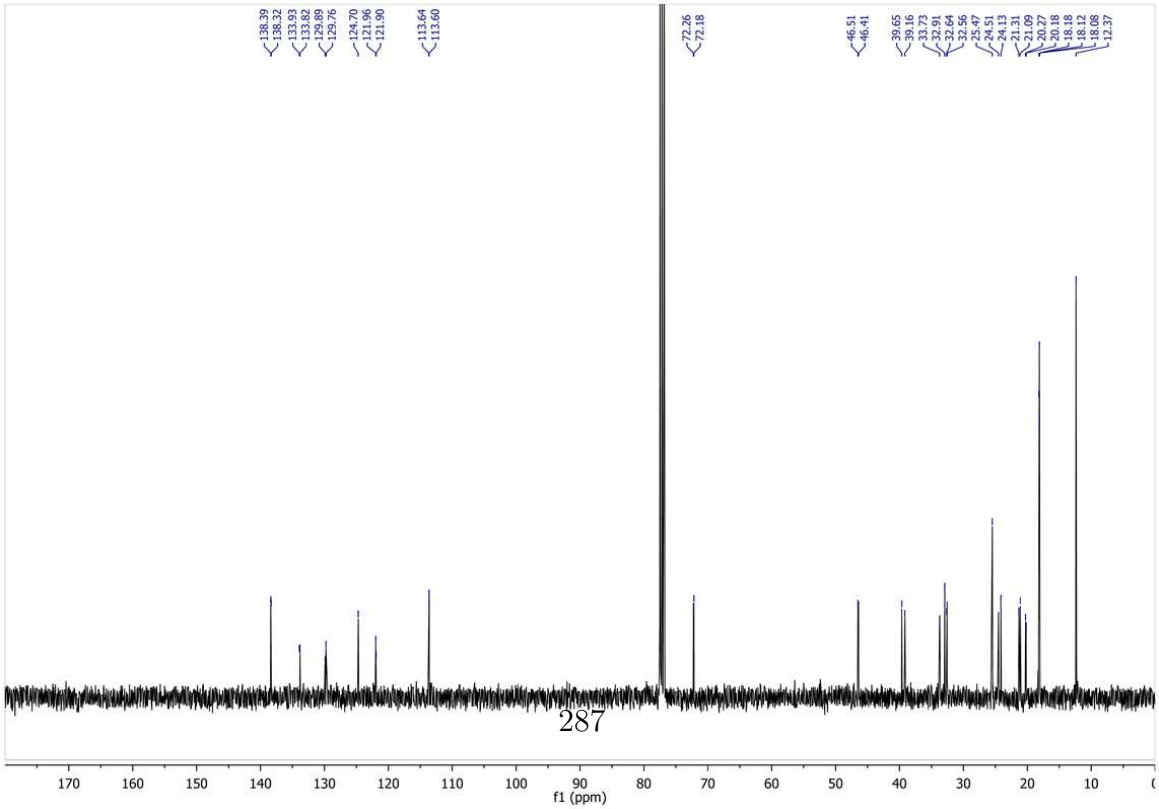
FT-IR thin film, neat (ATR): 2942, 2866, 1463, 1130, 1029 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{25}H_{44}O^{79}Br^{35}Cl^{23}Na^{28}Si$, $[M+Na]^{+\bullet}$: 525.19255 found 525.19330 (Δ = -1.4 ppm);

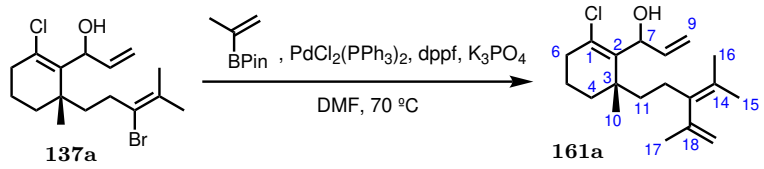
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 8.2° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.32 Trienol 161a



$PdCl_2.(PPh_3)_2$ (638 mg, 0.909 mmol, 0.10 mol equiv), dppf ligand (504 mg, 0.909 mmol, 0.10 mol equiv), and K_3PO_4 (5.781 g, 27.3 mmol, 3.0 mol equiv) were added to a flame dried 100 mL round bottom flask equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were performed and the vial was fitted with a N_2 balloon. Alcohol **137a** (3.164 g, 9.09 mmol, 1.0 mol equiv) and isopropenylboronic acid pinacol ester (1.9 mL, ρ = 0.894 g.mL^{-1}, 10.1 mmol, 1.1 mol equiv) were weighed in a separate 7 mL vial and transferred to the solid reagents using dry, degassed DMF, (rinsing once, total volume = 18 mL). The reaction was immersed in a 70 °C oil bath for 25 hours or until TLC showed complete consumption of starting material. When the reaction was deemed to be complete, the vial was cooled to room temperature, the contents were diluted with Et_2O and quenched with H_2O. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound (yellow oil) as a 1:1 mixture of diastereomers (1.638 g, 5.30 mmol, 59% yield).

R_f = 0.56 and 0.44 (mixture of diastereomers, 30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89 (dddd, J = 17.3, 10.5, 6.8, 4.9 Hz, 1H,

8), 5.41 (d, J = 4.3 Hz, 1H, 7), 5.34 (ddt, J = 17.3, 7.6, 1.6 Hz, 1H, 9-*trans*), 5.19 (ddt, J = 10.5, 5.0, 1.6 Hz, 1H, 9-*cis*), 4.95 – 4.89 (m, 1H, 19), 4.60 – 4.50 (m, 1H, 19'), 2.37 – 2.19 (m, 2H, alkyl-H), 2.18 – 1.98 (m, 4H, alkyl-H), 1.78(1.77) (s, 3H, 16), 1.68 (s, 3H, 17), 1.67(1.66) (s, 3H, 15), 1.49 – 1.40 (m, 2H, alkyl-H), 1.37 – 1.17 (m, 2H, alkyl-H), 0.97(0.92) (s, 3H, 10) ppm;

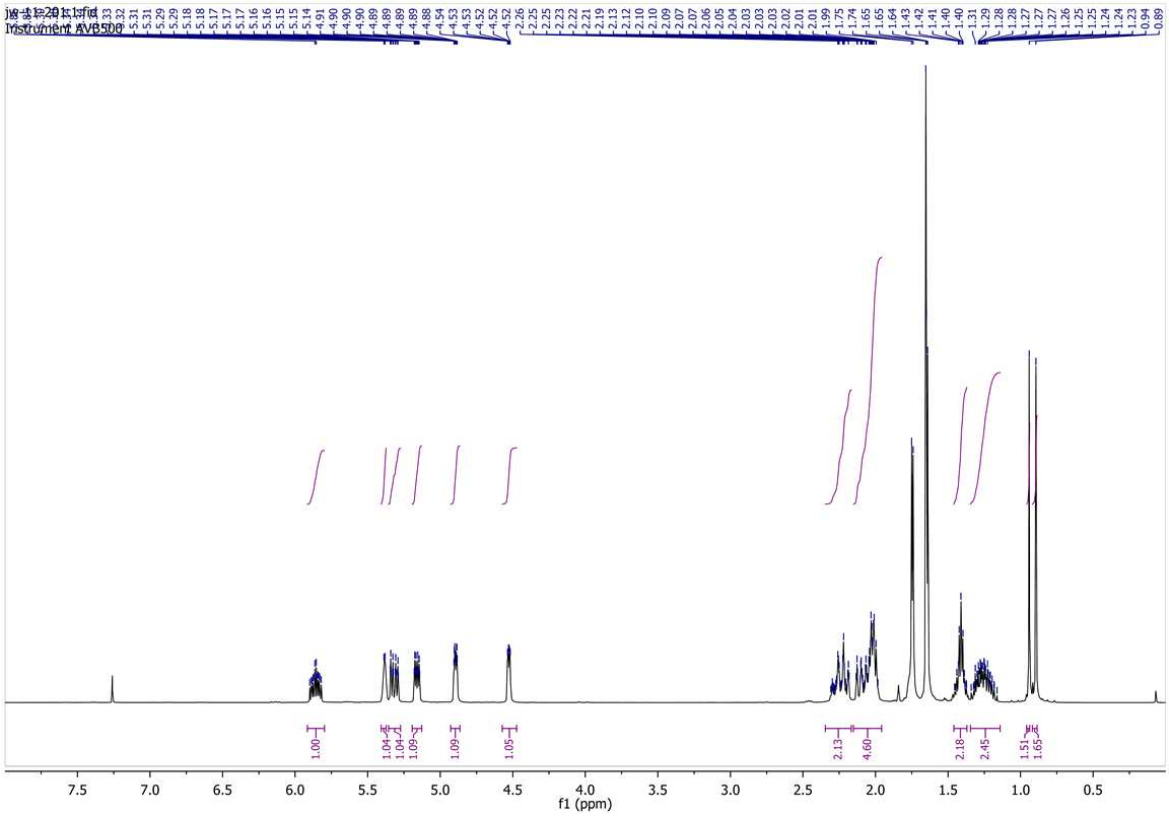
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6(146.5), 137.33(137.30) 8, 136.53(136.51) 18, 132.3(132.2), 127.3(127.1), 124.8, 114.7(114.6) 9, 113.1(113.0), 71.8(71.7) 7, 46.4(46.3) (CH_2), 39.7(39.3) (CH_2), 33.6 3, 32.7(32.6) (CH_2), 25.2(25.1) (CH_2), 24.1(23.8) 10, 22.8(22.7) 16, 21.75(21.74) 17, 21.59(21.57) (CH_2), 19.5(19.43) 15 ppm;

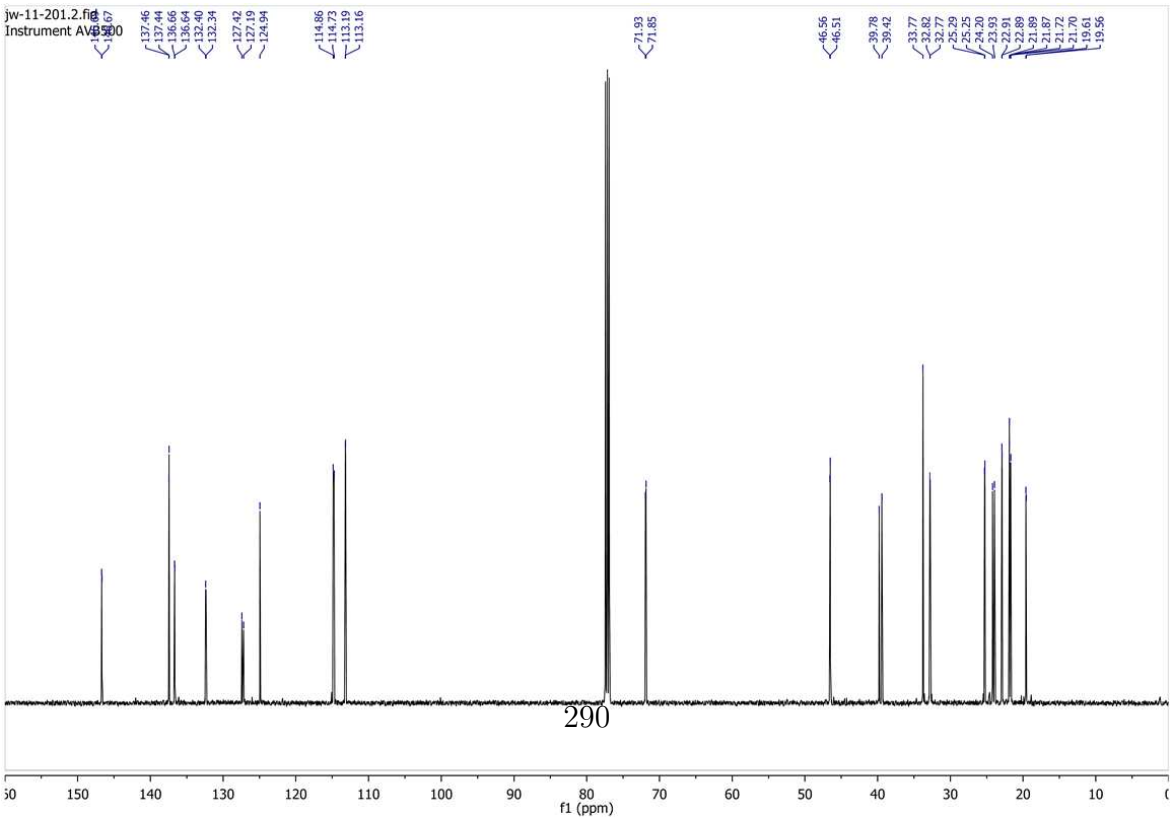
FT-IR thin film, neat (ATR): 3342, 2917, 2362, 1661, 1633, 1444, 1345, 1123, 989, 894 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{19}H_{29}O^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 331.17991 found 331.17972 (Δ = -0.59 ppm);

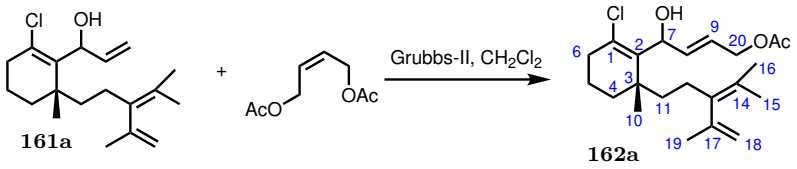
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 15° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.33 (*E*)-4-((*S*)-2-chloro-6-methyl-6-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohex-1-en-1-yl)-4-hydroxybut-2-en-1-yl acetate 162a



Alcohol **161a** (20 mg, 0.065 mmol, 1.0 mol equiv), *cis*-1,4-diacetoxy-2-butene (7.2 μL, 0.045 mmol, 0.70 mol equiv) and dry CH_2Cl_2 (0.32 mL) were added to a 7 mL vial equipped with a stirrer bar and cap. Grubbs catalysed second generation (5.5 mg, 0.0065 mmol, 0.10 mol equiv) was added in one portion and the resulting solution was stirred at 40 °C. After stirring for 21 hours, the reaction mixture was loaded onto celite and the product was purified by flash chromatography (0–10% Et_2O/*n*-pentane slow then 20–50% Et_2O/*n*-pentane fast, silica column) to give the title compound as a colorless oil (15 mg, 0.039 mmol, 61% yield). The diastereomers were separated using PTCL (37% Et_2O/*n*-pentane, silica plates) in order to furnish analytically pure material for characterisation purposes.

HRMS (ESI$^+$): calculated for $C_{22}H_{33}O_3{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 403.20104 found 403.20123 (Δ = 0.46 ppm);

First diastereomer

R_f = 0.25 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (dtd, J = 15.6, 5.8, 1.4 Hz, 1H, 9), 5.78 (ddt, J = 15.6, 4.9, 1.2 Hz, 1H, 8), 5.45 – 5.39 (m, 1H, 7), 4.90 (dd, J = 2.8, 1.4

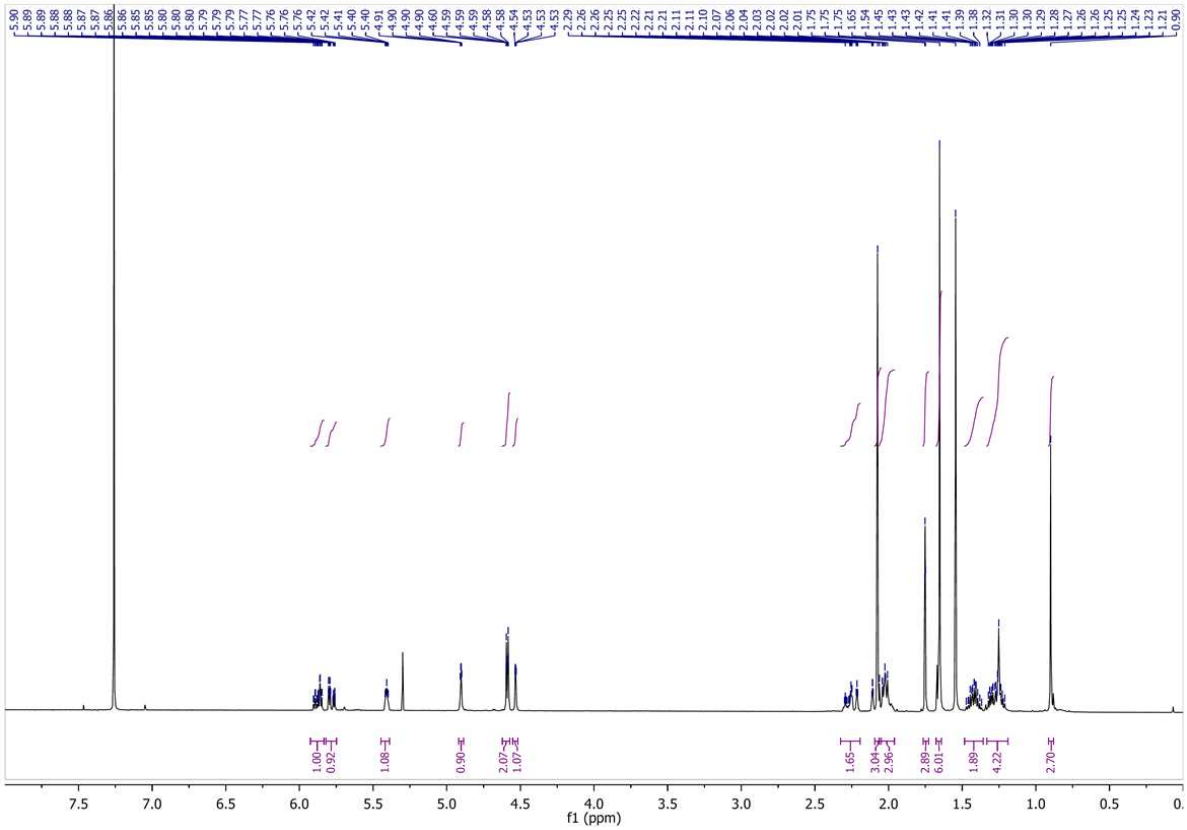
Hz, 1H, 18), 4.59 (dt, J = 5.8, 1.2 Hz, 2H, 20), 4.53 (dd, J = 2.8, 1.0 Hz, 1H, 18), 2.33 – 1.96 (m, 6H, alkyl-H), 2.07 (s, 3H, Ac-CH_3), 1.75 (t, J = 1.2 Hz, 3H, 19), 1.65 (s, 6H, 15/16), 1.48 – 1.36 (m, 2H, alkyl-H), 1.33 – 1.19 (m, 2H, alkyl-H), 0.90 (s, 3H, 10) ppm;

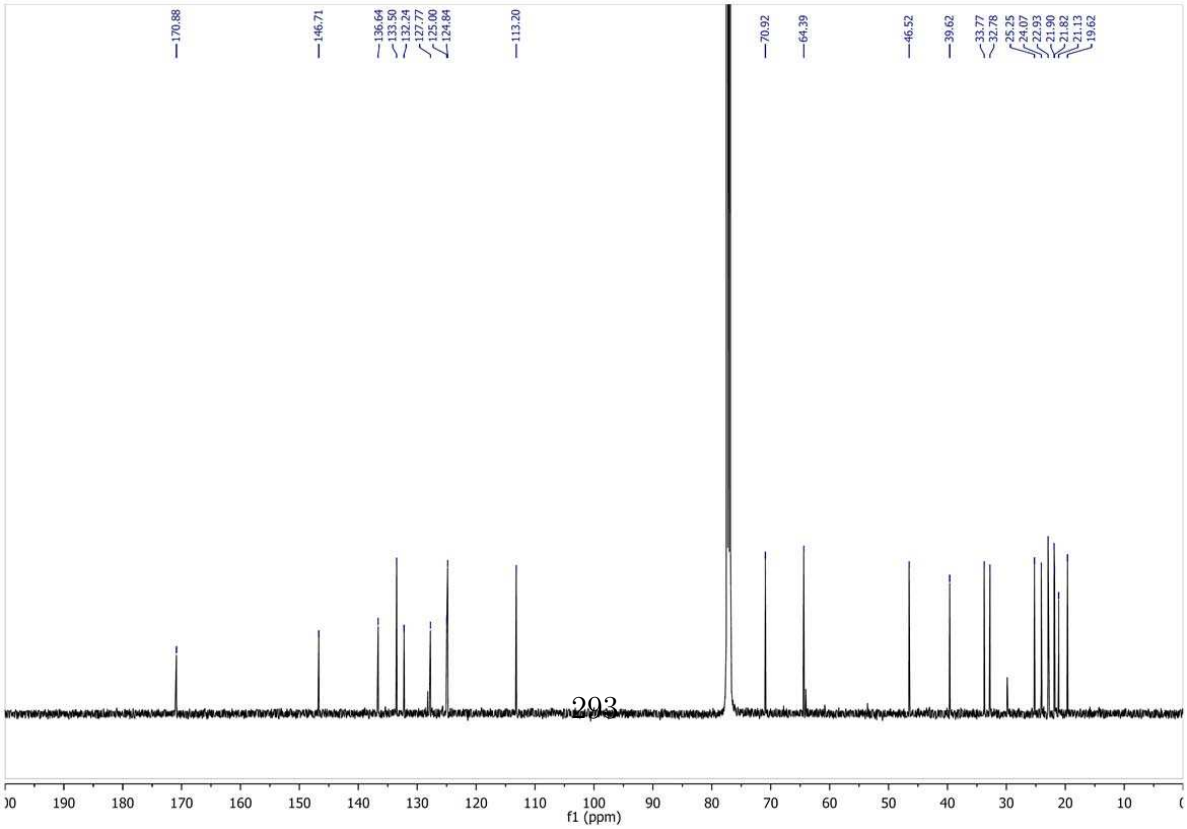
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9 C=O, 146.7 13, 136.6 17, 133.5 8, 132.2 1, 127.8 2, 125.0 14, 124.8 9, 113.2 18, 70.9 7, 64.4 20, 46.5 (CH_2), 39.6 (CH_2), 33.8 3, 32.8 (CH_2), 25.3 (CH_2), 24.1 10, 22.9 CH_3, 21.9 CH_3, 21.8 (CH_2), 21.1 CH_3, 19.6 CH_3 ppm;

FT-IR thin film, neat (ATR): 3450, 2919, 2359, 1743, 1239 cm^{-1};

$[\alpha]_D^{25} = -28°$ (c = 0.27, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR (first diastereomer)





Second diastereomer

R_f = 0.19 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

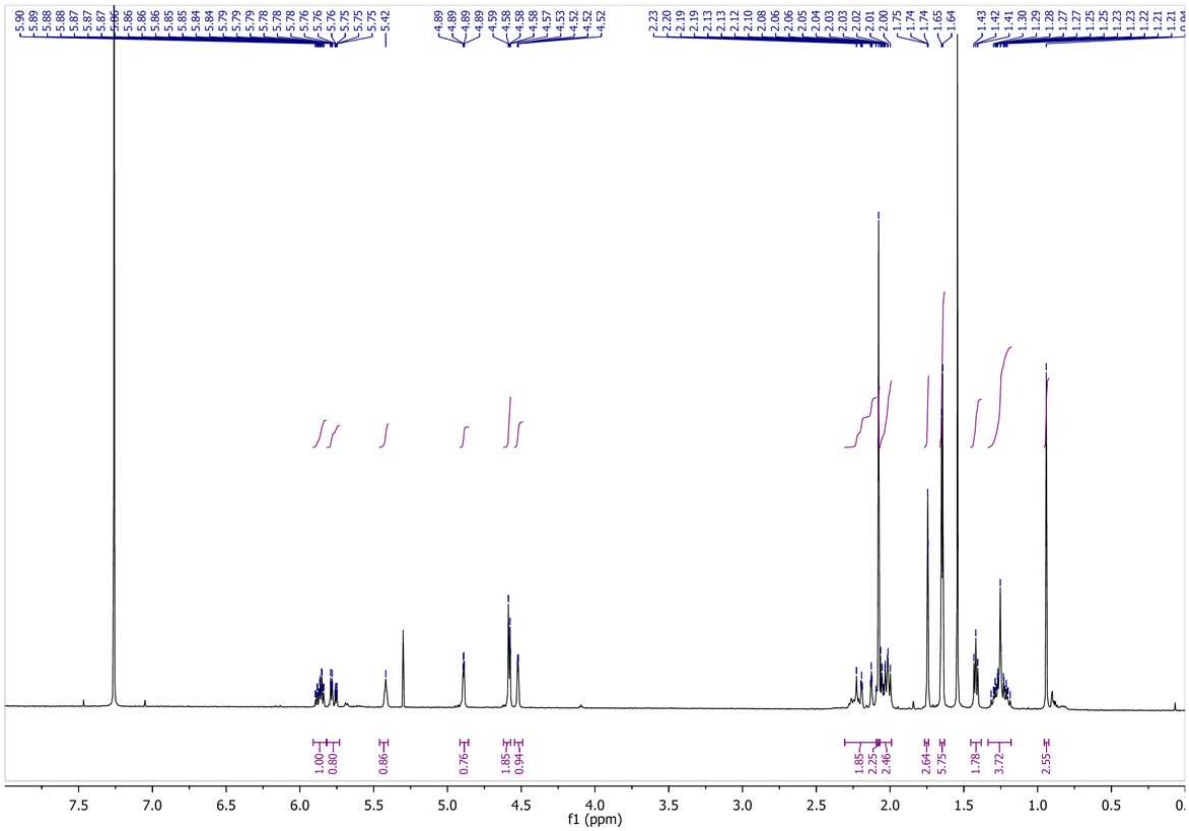
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 – 5.82 (m, 1H, 9), 5.77 (ddt, J = 15.6, 4.9, 1.2 Hz, 1H, 8), 5.42 (s, 1H, 7), 4.89 (dd, J = 2.8, 1.4 Hz, 1H, 18), 4.62 – 4.57 (m, 2H, 20), 4.52 (dd, J = 2.8, 1.0 Hz, 1H, 18), 2.31 – 1.97 (m, 6H, alkyl-H), 2.08 (s, 3H, Ac-CH_3), 1.74 (t, J = 1.2 Hz, 3H, 19), 1.65(1.64) (s, 6H, 15/16), 1.42 (t, J = 6.4 Hz, 2H, alkyl-H), 1.34 – 1.18 (m, 2H, alkyl-H), 0.94 (s, 3H, 10) ppm;

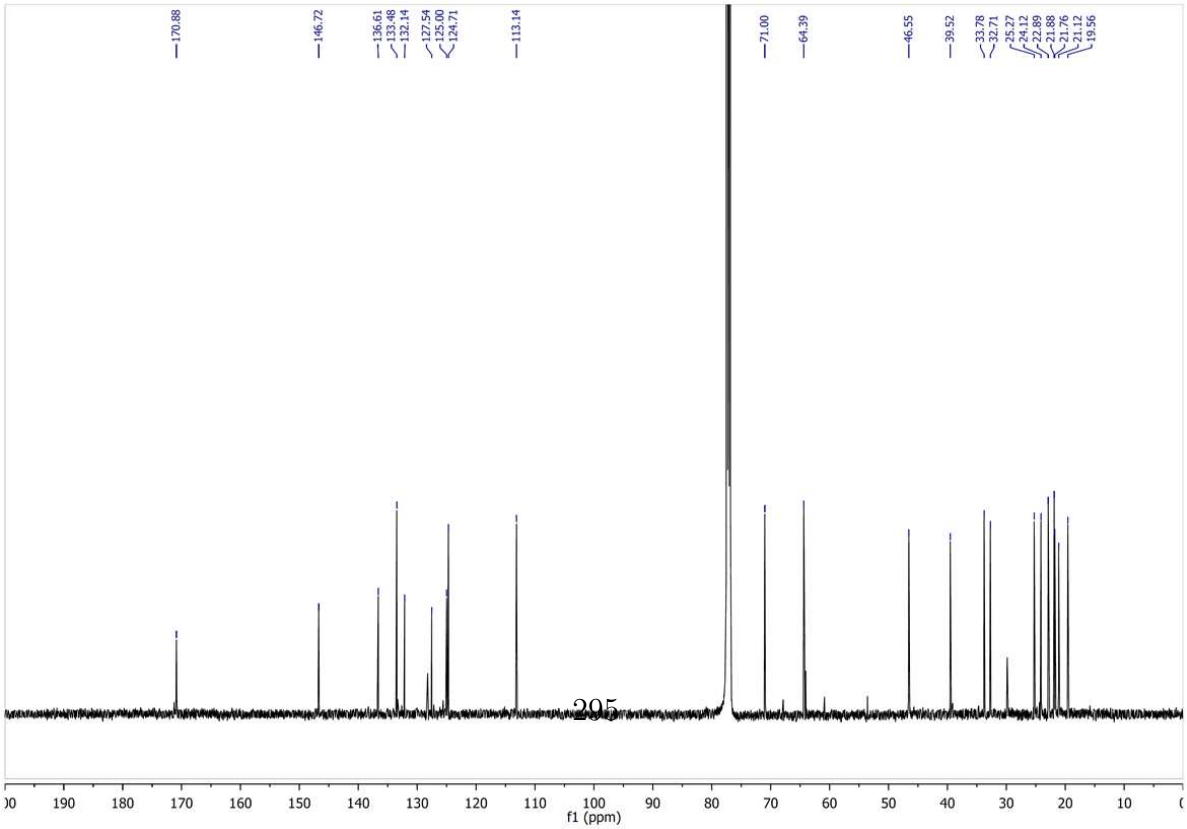
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9 C=O, 146.7 13, 136.6 17, 133.5 8, 132.1 1, 127.5 2, 125.0 14, 124.7 9, 113.1 18, 71.0 7, 64.4 20, 46.5 (CH_2), 39.5 (CH_2), 33.8 3, 32.7 (CH_2), 25.3 (CH_2), 24.1 10, 22.9 CH_3, 21.9 CH_3, 21.76 (CH_2), 21.1 CH_3, 19.6 CH_3 ppm;

FT-IR thin film, neat (ATR): 3441, 2922, 2361, 2342, 1743, 1238 cm^{-1};

$[\alpha]_D^{25}$ = + 13° (c = 0.27, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR (second diastereomer)





5.3.1.34 (*E*)-4-((tert-butyldimethylsilyl)oxy)-4-((*S*)-2-chloro-6-methyl-6-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohex-1-en-1-yl)but-2-en-1-yl acetate 162b



Alcohol **162a** (53 mg, 0.14 mmol, 1.0 mol equiv) and dry DMF (0.90 mL) were added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. Imidazole (12 mg, 0.17 mmol, 1.2 mol equiv) then *tert*-butyldimethylsilyl chloride (25 mg, 0.17 mmol, 1.2 mol equiv) were added and the reaction stirred at room temperature. When the reaction was deemed complete by TLC (approx. 24 hours), the mixture was quenched with brine (1 mL). The aqueous phase was extracted (3 x 0.5 mL) with 1:1 pentane:Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a colorless oil (58 mg, 0.14 mmol, 49% yield) (1:1 inseparable mixture of diastereomers).

R_f = 0.67 (10% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (dtt, J = 15.2, 6.0, 1.6 Hz, 1H), 5.67 (dt, J = 15.2, 4.1 Hz, 1H), 5.39 (dt, J = 3.7, 1.6 Hz, 1H), 4.89 (tt, J = 3.0, 1.5 Hz, 1H), 4.56 (ddt, J = 6.0, 3.0, 1.6 Hz, 2H), 4.52 (dd, J = 5.0, 3.0 Hz, 1H), 2.19 (dd, J = 14.6, 4.3 Hz, 2H), 2.07(2.06) (s, 3H), 2.04 – 1.89 (m, 2H), 1.74 (s, 3H), 1.65(1.64) (s, 6H), 1.45 – 1.17 (m, 6H), 0.91 – 0.89 (m, 12H, 10 and Si-^{t}Bu-CH_3),

0.06 (d, J = 3.0 Hz, 3H, Si-CH_3), 0.03 (d, J = 7.0 Hz, 3H, Si-CH_3) ppm;

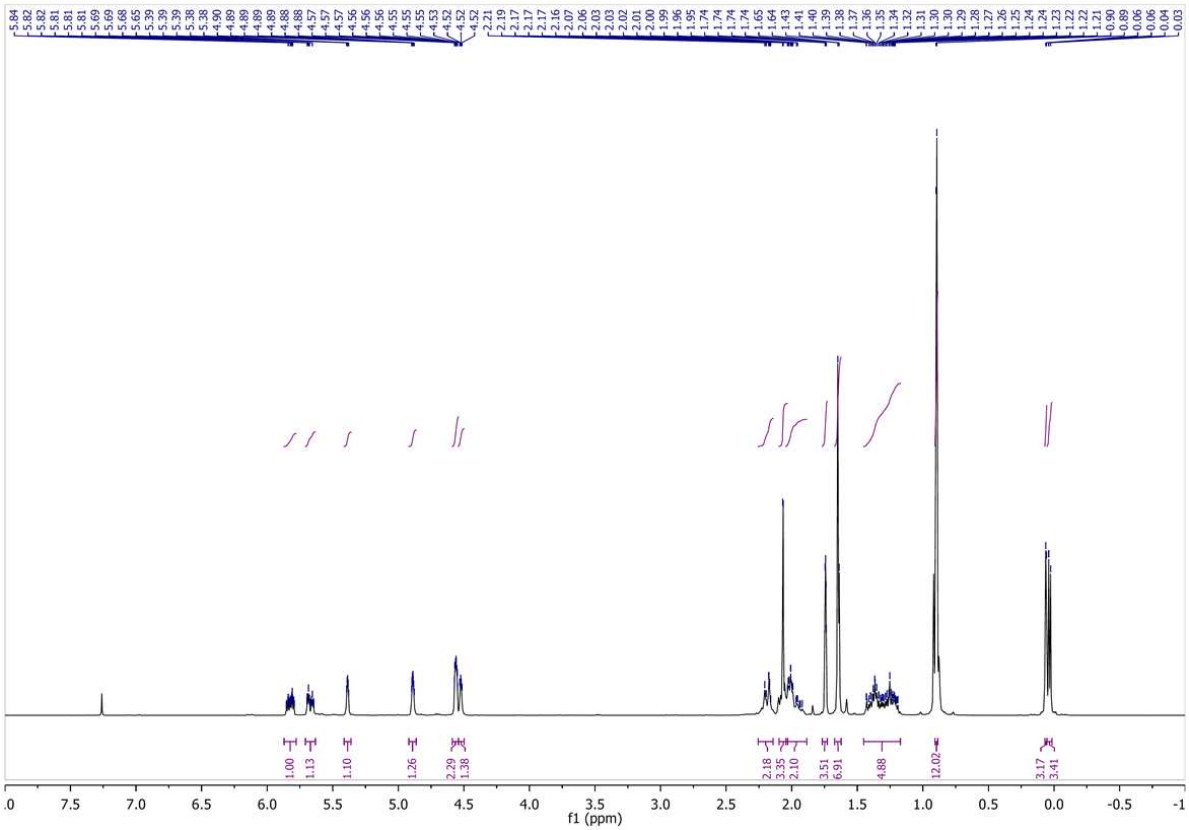
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9, 146.7(146.5), 136.8(136.7), 134.8(134.6), 133.1(133.07), 125.6(125.5), 124.9(124.8), 123.4(123.3), 113.3(113.1), 71.2(71.1), 64.6(64.5), 46.5(46.4), 39.9(39.0), 33.86, 32.9(32.7), 26.0(25.8) ^{t}Bu-CH_3, 25.3, 24.7(23.9), 22.9(22.8), 21.9(21.8), 21.5(21.3), 21.2, 19.7(19.6), 18.40(18.3), −4.82(−4.86) Si-CH_3, −4.91(−4.92) Si-CH_3 ppm;

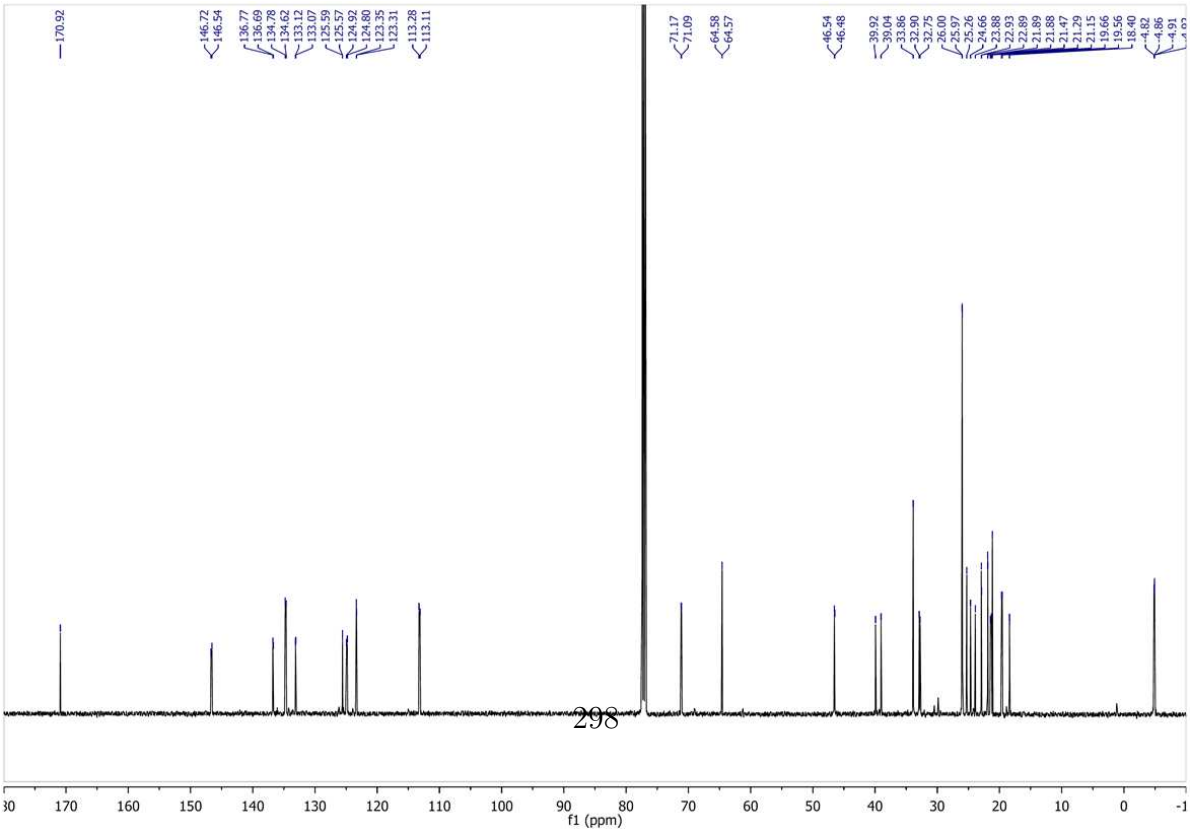
FT-IR thin film, neat (ATR): 2955, 2928, 2856, 2361, 1746, 1471, 1379, 1250, 1237, 837 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{28}H_{47}O_3{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 517.2875 found 517.2873 (Δ = -0.44 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 10° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

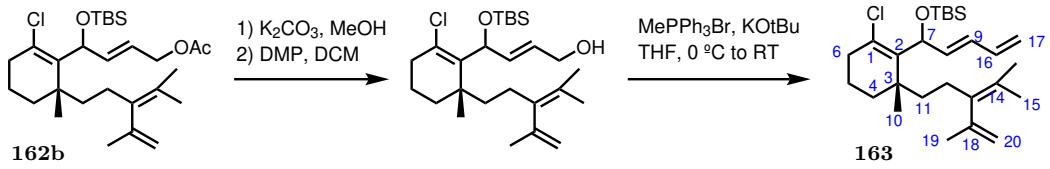
$^{1}H/^{13}C$ NMR





5.3.1.35 tert-butyl(((*E*)-1-((*S*)-2-chloro-6-methyl-6-(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)cyclohex-1-en-1-yl)penta-2,4-dien-1-yl)oxy)dimethyl

163



Acetate **162b** (33 mg, 0.067 mmol, 1.0 mol equiv) and K_2CO_3 (10 mg, 0.072 mmol, 1.08 mol equiv) were dissolved in MeOH (0.50 mL) in a 7 mL vial equipped with a Teflon lined cap. When the deprotection was deemed to be complete by TLC (approximately 1 hour), the reaction mixture was filtered through a plug of cotton wool and concentrated *in vacuo*. The crude brown oil was used the subsequent step without further purification.

The crude alcohol from the previous step was dissolved in reagent grade CH_2Cl_2 (2.2 mL) in a 7 mL vial equipped with a Teflon lined cap. Dess-Martin periodinane (68 mg, 0.16 mmol, 2.4 mol equiv) was added in two portions over 30 minutes after which TLC showed complete consumption of starting material. The reaction was subsequently quenched with 2 mL 1:1 saturated $NaHCO_{3(aq)}$:$Na_2S_2O_{3(aq)}$. The aqueous phase was extracted (3 x 1 mL) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the aldehyde as colorless oil (21 mg, 0.047 mmol, 70% yield over 2 steps) (1:1 inseparable mixture of diastereomers).

Methyltriphenylphosphonium bromide (20 mg, 0.056 mol, 1.2 mol equiv) was added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were then performed, after which dry THF (0.10 mL) was added and the suspension cooled to 0 °C. Potassium *tert*-butoxide (8.0 mg, 0.071 mmol, 1.5 mol equiv) was added in one portion, minimising exposure of the reaction contents to the atmosphere. After stirring for 10 minutes, the aldehyde from the previous step was added as a solution in THF (0.2 mL). The yellow suspension became orange at this point. The reaction was allowed to warm to room temperature and stirred for 22 hours. At this stage, TLC indicated complete consumption of starting material. The reaction mixture was loaded directly onto a prepacked silica column and eluted with 0–10% Et_2O/*n*-pentane to furnish the title compound as a pale yellow oil (31 mg, 0.027 mmol, 41% yield over 3 steps) (1:1 inseparable mixture of diastereomers).

$\mathbf{R_f}$ = 0.74 (10% Et_2O/*n*-pentane, $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 – 6.20 (m, 2H, 16/9), 5.63 (ddd, J = 14.2, 6.2, 4.4 Hz, 1H, 8), 5.42 (d, J = 4.4 Hz, 1H, 7), 5.23 – 5.15 (m, 1H, 17), 5.05 (dd, J = 9.6, 1.8 Hz, 1H, 17), 4.89 (ddd, J = 5.3, 2.7, 1.5 Hz, 1H, 20), 4.53 (ddd, J = 7.0, 2.7, 1.0 Hz, 1H, 20), 2.28 – 1.95 (m, 6H, alkyl-H), 1.79 – 1.69 (m, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.65(1.64) (s, 3H, CH_3), 1.48 – 1.16 (m, 4H, alkyl-H), 0.93 – 0.89 (m, 12H, TBS-^{t}Bu/10), 0.07(0.06) (s, 3H, TBS-Me), 0.05(0.04) (s, 3H, TBS-Me) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.7(146.6) 13, 136.8 9, 136.8(136.7) 18, 134.4(134.3) 8, 133.5(133.4) 1, 129.7(129.6) 16, 125.3(125.2) 2, 124.9(124.8) 14, 116.7(116.6) 17, 113.2(113.1) 20, 71.5(71.4) 7, 46.6(46.5) (CH_2), 39.8(39.1) (CH_2),

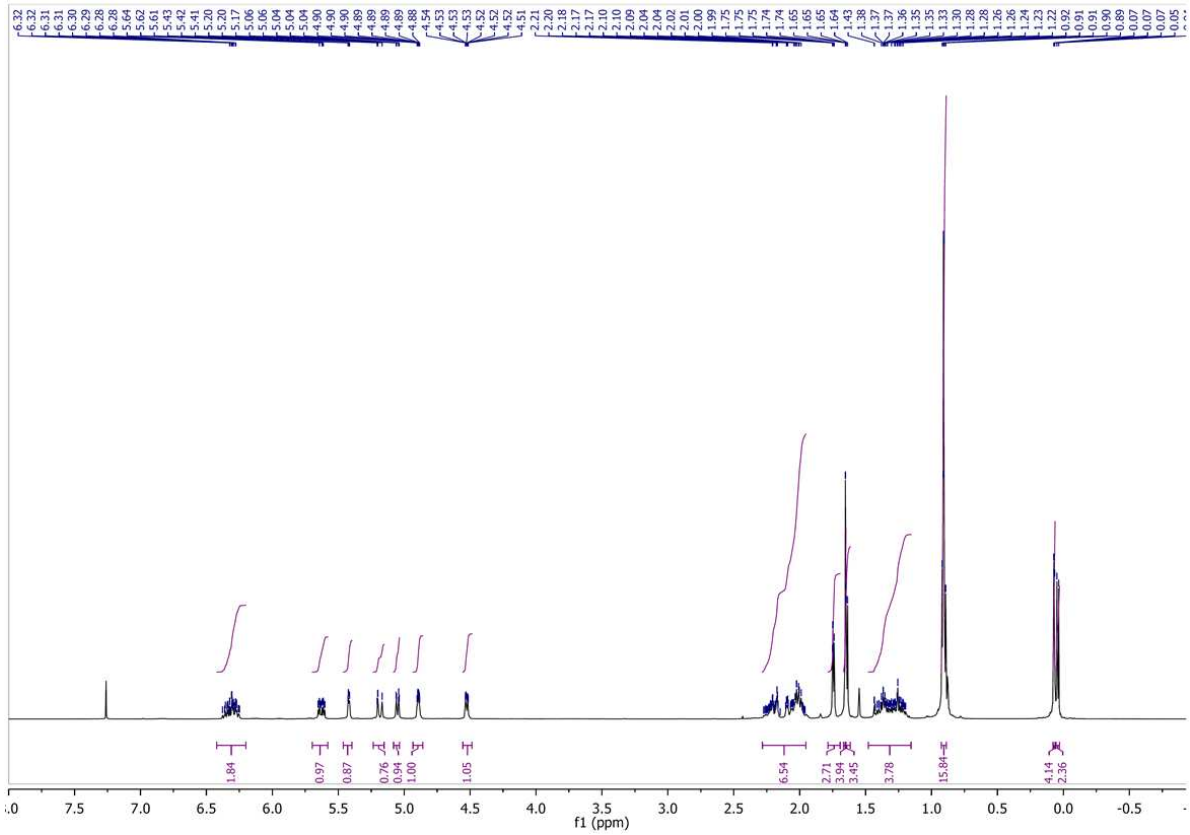
33.8 3, 33.0(32.8) (CH_2), 26.0(25.9) TBS-^{t}Bu-CH_3, 25.3 (CH_2), 24.7(24.0) 10, 23.0(22.9) CH_3, 21.9(21.8) CH_3, 21.6(21.4) (CH_2), 19.7(19.6) CH_3, 18.43(18.42) TBS-^{t}Bu-C, −4.79(−4.84) TBS-Me, −4.87 TBS-Me ppm;

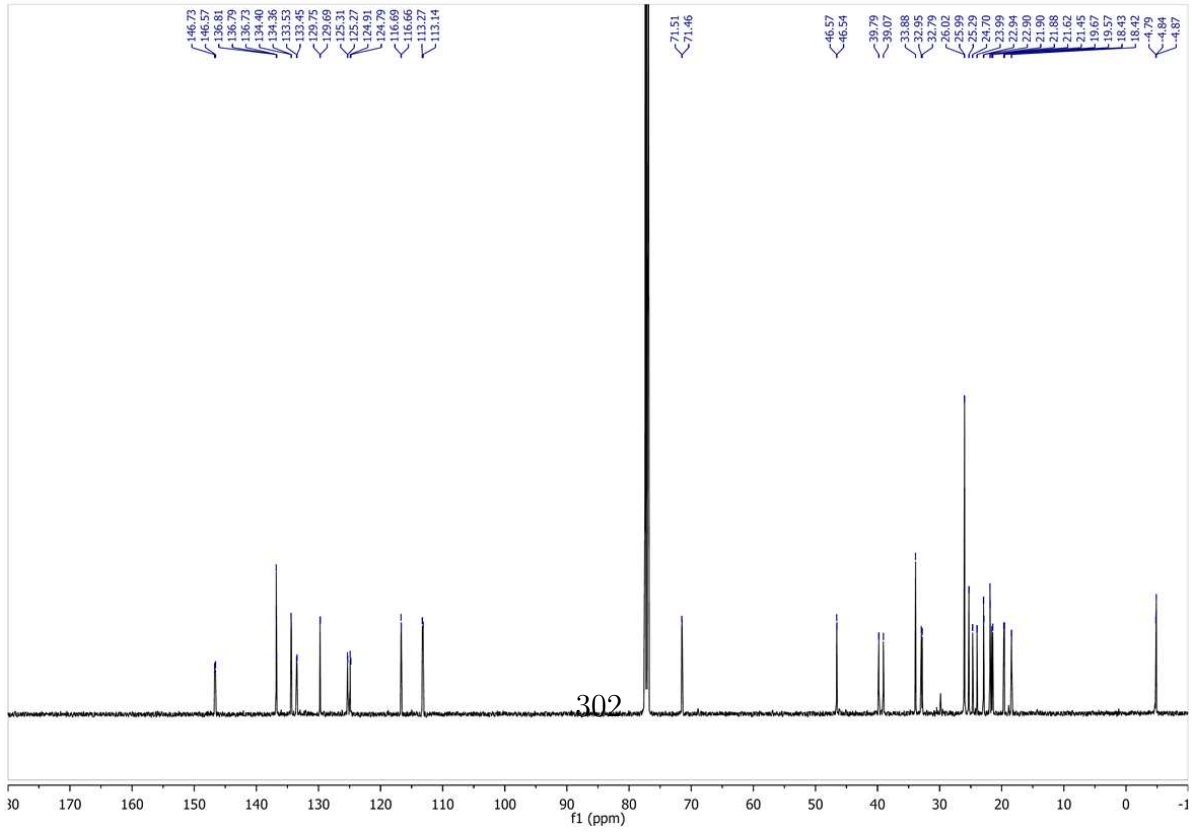
FT-IR thin film, neat (ATR): 2954, 2856, 1253, 1107, 1004, 837 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{27}H_{46}O^{35}Cl^{28}Si$, $[M+H]^{+\bullet}$: 449.3001 found 449.3001 (Δ = 0.10 ppm);

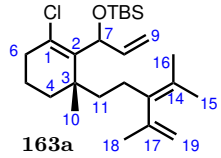
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 10° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.36 Protected trienol 161a



163a

Alcohol **161a** (50 mg, 0.16 mmol, 1.0 mol equiv) and dry DMF (1.1 mL) were added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. Imidazole (13 mg, 0.19 mmol, 1.2 mol equiv) then *tert*-butyldimethylsilyl chloride (29 mg, 0.19 mmol, 1.2 mol equiv) were added and the reaction stirred at room temperature. When the reaction was deemed complete by TLC (approx. 24 hours), the mixture was quenched with brine (equal volume to reaction solvent). The aqueous phase was extracted (3 x 0.5 mL) with 1:1 pentane:Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–5% Et_2O/*n*-pentane, silica column) to give the title compound as a colorless oil (58 mg, 0.14 mmol, 86% yield) (1:1 inseparable mixture of diastereomers).

R_f = 0.80 (30% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (ddt, J = 17.0, 10.4, 4.1 Hz, 1H, 8), 5.37 (dd, J = 4.1, 2.0 Hz, 1H, 7), 5.30 (ddt, J = 17.0, 2.8, 2.0 Hz, 1H, 9-*trans*), 5.07 (dq, J = 10.4, 2.0 Hz, 1H, 9-*cis*), 4.89 (ddd, J = 3.5, 2.8, 1.5 Hz, 1H, 19), 4.53 (ddd, J = 3.9, 2.8, 1.0 Hz, 1H, 19), 2.28 – 1.92 (m, 6H, alkyl-H), 1.78 – 1.72 (m, 3H, CH_3), 1.65(1.64) (s, 6H, 2xCH_3), 1.47 – 1.17 (m, 4H, alkyl-H), 0.95 – 0.87 (m, 12H, TBS-^{t}Bu/10), 0.07 (d, J = 1.8 Hz, 3H, TBS-Me), 0.04 (d, J = 5.0 Hz, 3H, TBS-Me) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.7(146.6) 13, 138.4(138.3) 8, 136.8(136.7)

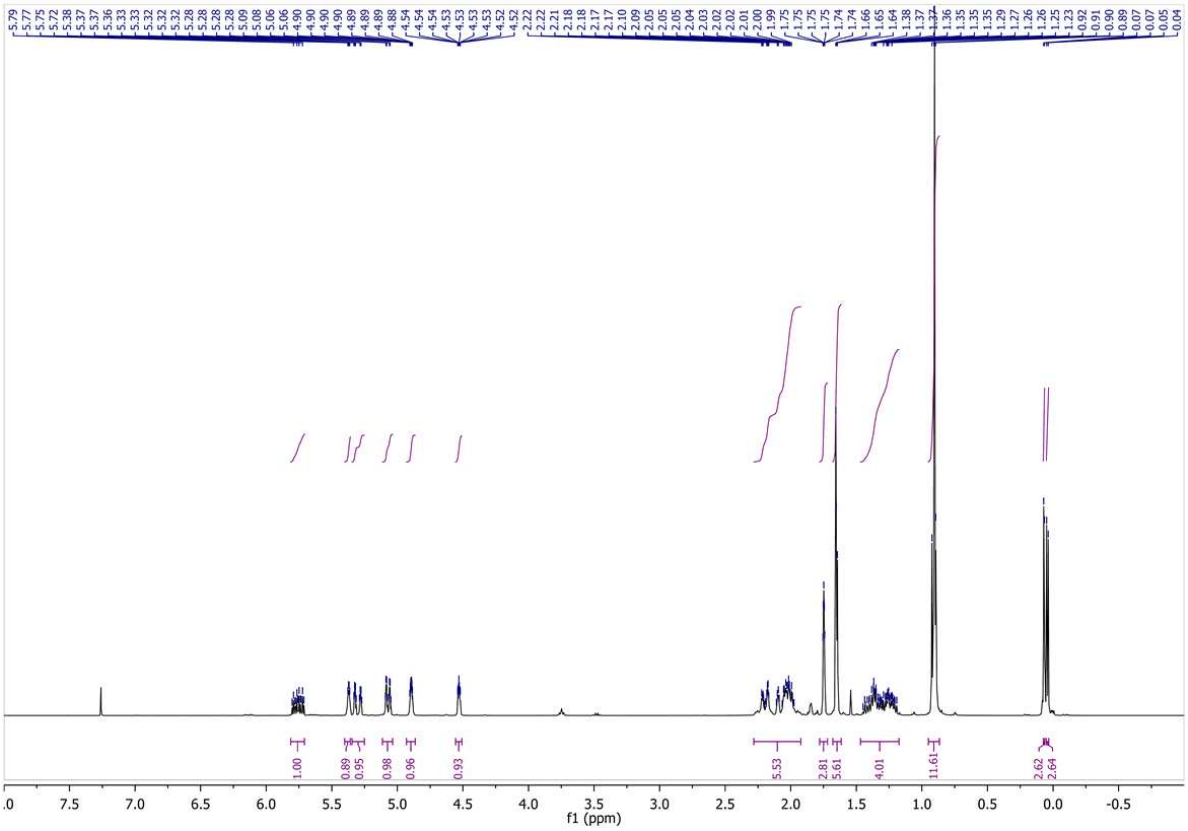
17, 133.5(133.4) 1, 125.3 2, 124.9(124.8) 14, 113.6 8, 113.3(113.1) 19, 72.1(72.0) 7, 46.6(46.5) (CH_2), 39.9(39.2) (CH_2), 33.9 3, 33.0(32.9) (CH_2), 26.0(25.9) TBS-^{t}Bu-CH_3, 25.3 (CH_2), 24.6(23.9) CH_3, 22.93(22.91) CH_3, 21.9 CH_3, 21.5(21.3) (CH_2), 19.7(19.6) CH_3, 18.4 TBS-^{t}Bu-C, −4.8(−4.9) TBS-Me, -4.91 TBS-Me ppm;

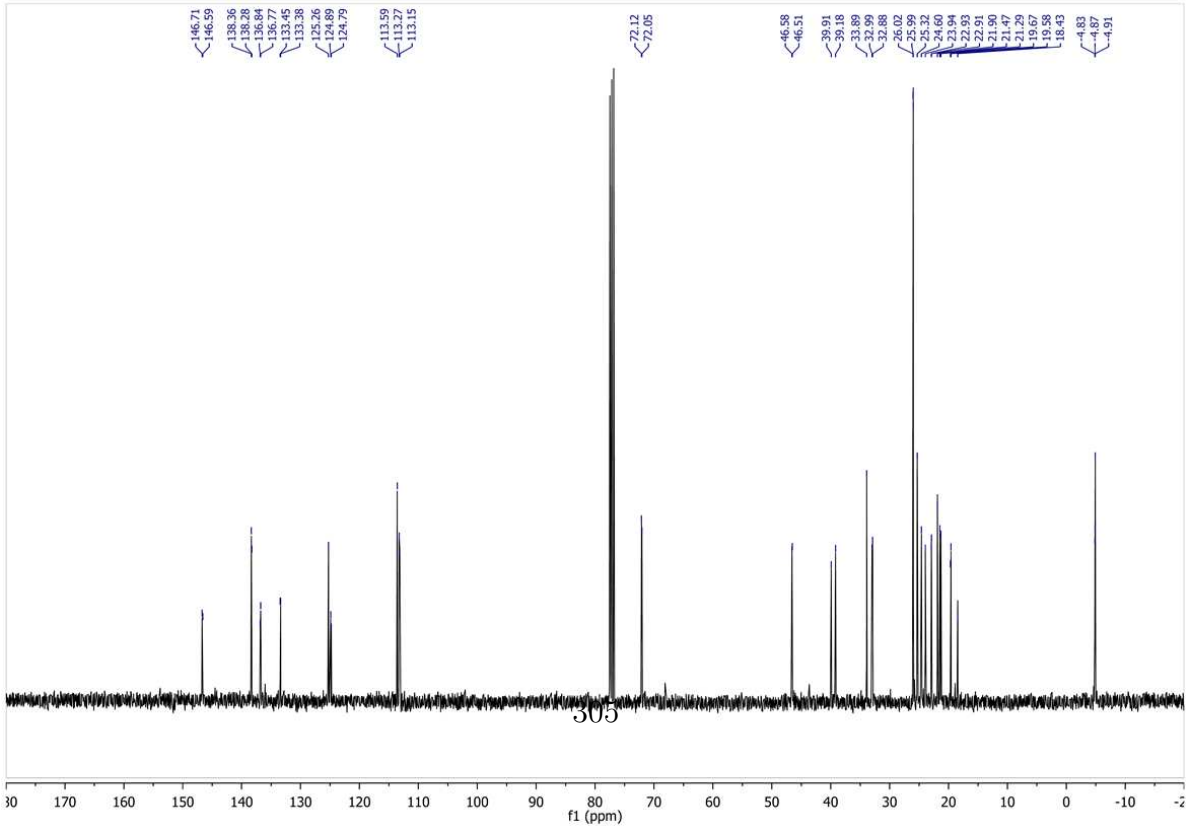
FT-IR thin film, neat (ATR): 2928, 2361, 1252, 1127, 1029, 863, 837, 777 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{25}H_{44}O^{35}Cl^{28}Si$, $[M+H]^{+\bullet}$: 423.2844 found 423.2841 (Δ = -0.92 ppm);

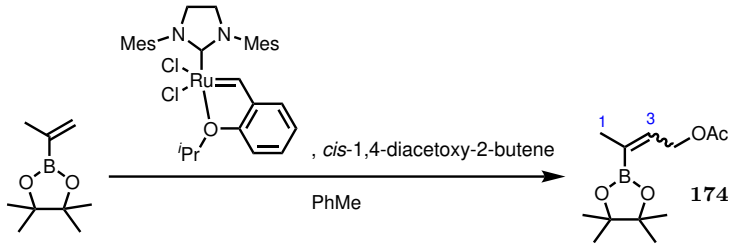
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 10° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.37 BPin acetate 174

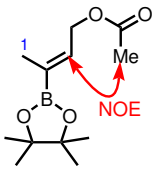


Isopropenyl boronic acid pinacol ester (30 μL, 0.16 mmol, 1.0 mol equiv), *cis*-1,4-diacetoxy-2-butene (76 μL, 0.48 mmol, 3.0 mol equiv) and dry toluene (1.5 mL) were added to a 7 mL vial equipped with a stirrer bar and cap. Hoveyda-Grubbs Second Generation Catalyst (5.0 mg, 0.0080 mmol, 0.050 mol equiv) was added in one portion and the vial was purged with a stream of nitrogen gas for 10 seconds. After sealing the vial, it was heated at 70 °C for 30 minutes. The solution was concentrated *in vacuo* then loaded onto celite. The crude product was purified by flash chromatography (0-10% Et_2O/*n*-pentane, silica column) to give the title compound (inseparable mixture of diastereomers 1:4 *E*:*Z* mixture) as an oil (9.3 mg, 0.039 mmol, 24% yield). Stereochemistry was assigned on the basis of NOE experiments.

FT-IR thin film, neat (ATR): 2979, 2360, 1742, 1374, 1311, 1230, 1136, 1027, 859 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{12}H_{21}O_4{}^{10}B^{23}Na$, $[M+Na]^{+\bullet}$: 262.14614 found 262.14633 (Δ = 0.73 ppm);

***Z* (major) diastereomer**

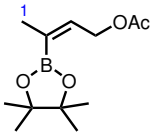


R_f = 0.46 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (ddd, J = 6.0, 5.0, 1.7 Hz, 1H, 3), 4.72 (dq, J = 6.1, 1.1 Hz, 2H, 4), 2.06 (s, 3H, OAc-Me), 1.75 – 1.71 (m, 3H, 1), 1.26 (s, 12H, BPin-Me) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1 C=O, 138.6 3, 83.7 BPin-O-C, 61.6 4, 24.9 BPin-Me, 21.1 OAc-Me, 14.4 1 ppm;

***E* (minor) diastereomer**

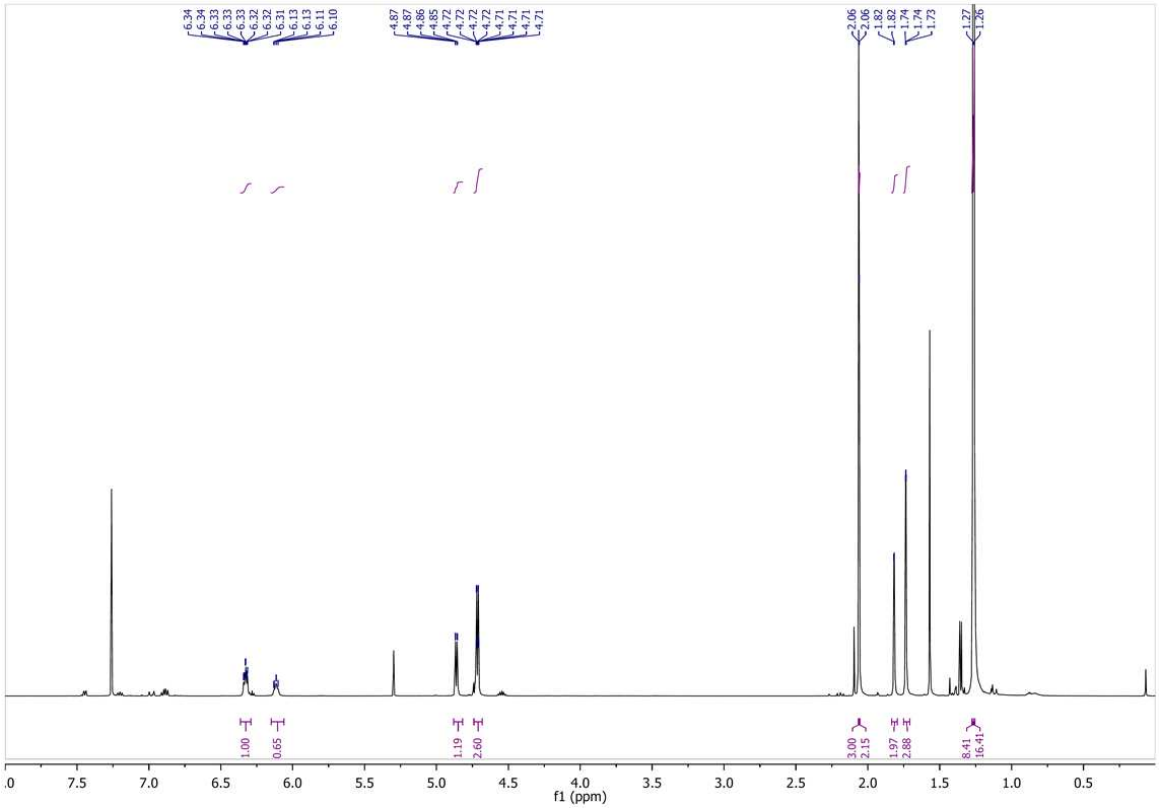


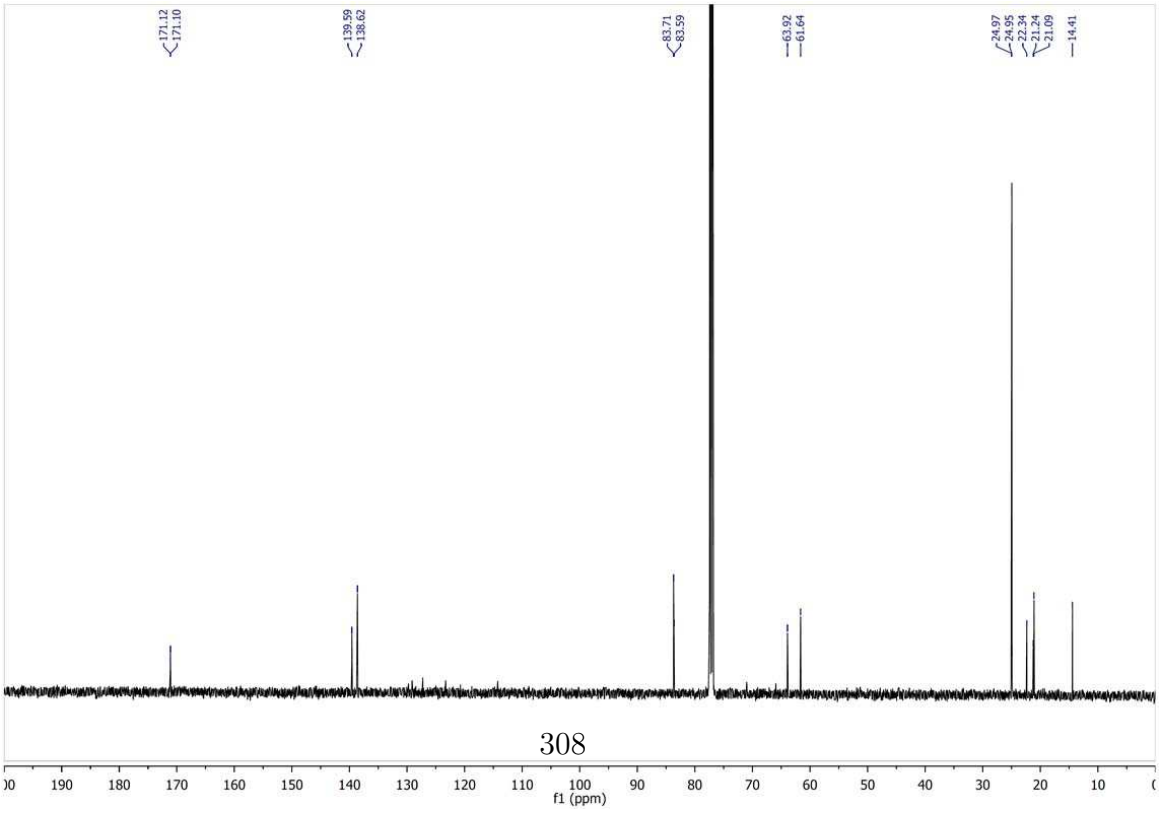
R_f = 0.49 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 – 6.06 (m, 1H, 3), 4.86 (dd, J = 6.8, 1.3 Hz, 2H, 4), 2.06 (s, 3H, OAc-Me), 1.82 (d, J = 1.5 Hz, 3H, 1), 1.27 (s, 12H, BPin-Me) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1 C=O, 139.6 3, 83.6 BPin-O-C, 63.9 4, 25.0 BPin-Me, 22.3 1, 21.2 OAc-Me ppm;

$^{1}H/^{13}C$ NMR


6.34
6.34
6.33
6.33
6.33
6.32
6.32
6.31
6.13
6.13
6.11
6.10
4.87
4.87
4.86
4.85
4.72
4.72
4.72
4.72
4.71
4.71
4.71
4.71
2.06
2.06
1.82
1.82
1.74
1.74
1.73
1.27
1.26
1.00
0.65
1.19
2.60
3.00
2.15
1.97
2.88
8.41
16.41
f1 (ppm)


171.12
171.10
139.59
138.62
83.71
83.59
63.92
61.64
24.97
24.95
22.34
21.24
21.09
14.41
f1 (ppm)

5.3.1.38 Pent-4-en-2-one 175

Ketone **175** was prepared according to literature procedure.[82]

Preparation of Ag/Zn couple

Ag/Zn couple was prepared according to literature procedure.[82] Ag_2CO_3 (83 mg, 0.30 mmol, 1.0 mol equiv) was dissolved in glacial AcOH (6 mL) and heated on a 60 °C hotplate to form a green suspension. After 15 minutes, when no more green colour was present, the solution was removed from heat and cooled to room temperature. The $Ag(OAc)_2$ was collected by vacuum filtration, washed once with AcOH and then twice with Et_2O before being dried under suction. The solid was transferred to a 250 mL round bottomed flask equipped with a stirrer bar and a reflux condenser. Glacial AcOH (100 mL) was added and the solution heated. When gentle reflux was observed, Zn dust (50.0 g, 769 mmol, 2560 mol equiv) was added in one portion, resulting in a vigorous reaction. After stirring for 30 seconds, the reaction vessel was cooled rapidly in an ice bath. The solvent was decanted off and the grey solid was washed with dry Et_2O (6x50mL) to ensure complete removal of the AcOH (test by smell). The product was dried under high vacuum and stored in a sealed round bottom flask.

Barbier coupling

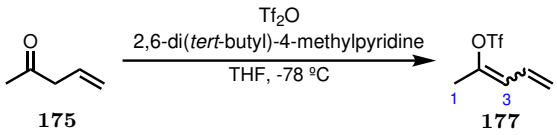
Caution! This reaction has a long latent period. Add a small amount of the allyl bromide at first, wait until the reaction initiates (visible exotherm) before adding

the remaining of the allyl bromide at a rate that maintains gentle reflux. Otherwise there is a possibility of thermal runaway occurring.

No precautions were made to exclude oxygen or moisture. To a solution of dry acetonitrile (5.2 mL, ρ = 0.786 g.mL^{-1}, 100 mmol, 1.0 mol equiv), Ag/Zn couple (8.75 g, 134 mmol, 1.34 mol equiv), in dry Et_2O/THF (25 mL, 9:1 v/v) in a 2-neck 250 mL round bottom flask equipped with a stirrer bar and condenser, was added allyl bromide (11.6 mL, ρ = 1.4 g.mL^{-1}, 134 mmol, 1.3 mol equiv) over a period of 1-3 hours. After addition, the reaction was allowed to stir overnight at 25 °C. The reaction was quenched by pouring the contents onto a mixture of ice-water (50 g), saturated $NH_4Cl_{(aq)}$ solution (100 mL) and Et_2O (50 mL). The inhomogeneous mixture was stirred vigorously for 10 min before the contents were filtered through cotton wool into a separating funnel. The aqueous phase was extracted (2x50 mL), dried (Na_2SO_4) and concentrated *in vacuo* (840 mbar@40 °C). The product was purified by distillation 108 °C (atmospheric pressure) to give the title compound as a colourless oil (3.77 g, 44.8 mmol, 45% yield).

R_f = 0.16 (30% Et_2O/*n*-pentane, $KMnO_4$);
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.19 (dq, J = 10.2, 1.4 Hz, 1H), 5.14 (dq, J = 17.1, 1.4 Hz, 1H), 3.18 (dt, J = 7.0, 1.4 Hz, 2H), 2.16 (s, 3H) ppm;
^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 130.6, 119.0, 48.7, 29.6.ppm;

5.3.1.39 Triflated diene 177



175 **177**

2,6-di(*tert*-butyl)-4-methylpyridine (3.00 g, 14.6 mmol 1.1 mol equiv), was weighed into a flame dried 100 mL flask equipped with a stirrer bar and rubber septum. Three cycles of vacuum and back filling with N_2 were then performed, after which CH_2Cl_2 (38 mL) and then pent-4-en-2-one **175** (2.46 mL, 5.4 M concentration as determined by NMR, 13.3 mmol, 1.0 mol equiv) were added. The solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (2.7 mL, 16.0 mmol, 1.2 mol equiv) was added over 4 minutes. After 3 hours, an NMR aliquot of the reaction mixture indicated 20% conversion. Thus, the reaction was allowed to stir overnight and warmed to room temperature over this time period. When complete consumption of starting material was observed (27 hours, NMR aliquot), the reaction was quenched by the addition of water. The black solution was extracted (5x) with CH_2Cl_2, dried (Mg_2SO_4) and carefully concentrated *in vacuo* (650 mbar@40 °C). The dark brown solid was titurated with pentane and the supernatant was directly loaded onto a pre-packed silica column. This tituration procedure was repeated (4x). The column was eluted with 3 volumes of pentane before switching to 2% Et_2O. All transfers of the volatile product were performed with pentane. The product was obtained as a pale yellow oil (318 mg, 1.47 mmol, 11% yield) as a chromatographically inseparable (2:1 E:Z) diastereomeric mixture (geometries were assigned with the assistance of NOESY).

Procedure to recover the amine

The black solids that could not be loaded onto the column were basified with 2M NaOH and extracted with pentane (5x). The organic phase was dried ($MgSO_4$), filtered (cotton wool) and concentrated *in vacuo* (650 mbar@40 °C). The crude product was purified by flash chromatography (pentane) and after fractions were concentrated, the pure (according to ^{1}H NMR) pyridine was obtained as a colourless oil which spontaneously crystallised into an amorphous white solid (1.40 g, 47% recovery).

R_f = 0.43 (10% Et_2O/*n*-pentane, $KMnO_4$);
FT-IR thin film, neat (ATR): 2914, 2359, 2342, 1215, 749 cm^{-1};
HRMS (ESI$^-$): calculated for $C_8H_8OCl_2$, $[M\text{-}H]^{+\bullet}$: 214.99952 found 214.99925 (Δ = -1.26 ppm);
^{19}F NMR (377 MHz, $CDCl_3$): δ −74(−75) ppm;

(*E*)-penta-2,4-dien-2-yl triflate

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (dt, J = 17.0, 10.6 Hz, 1H, 4), 5.89 (dq, J = 10.6, 1.0 Hz, 1H, 3), 5.42 – 5.24 (m, 2H, 5), 2.17 (s, 3H, 1) ppm;
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 128.1, 121.7, 120.8, 118.36 (d, $^1J_{CF}$ = 319.3 Hz), 19.8 ppm;

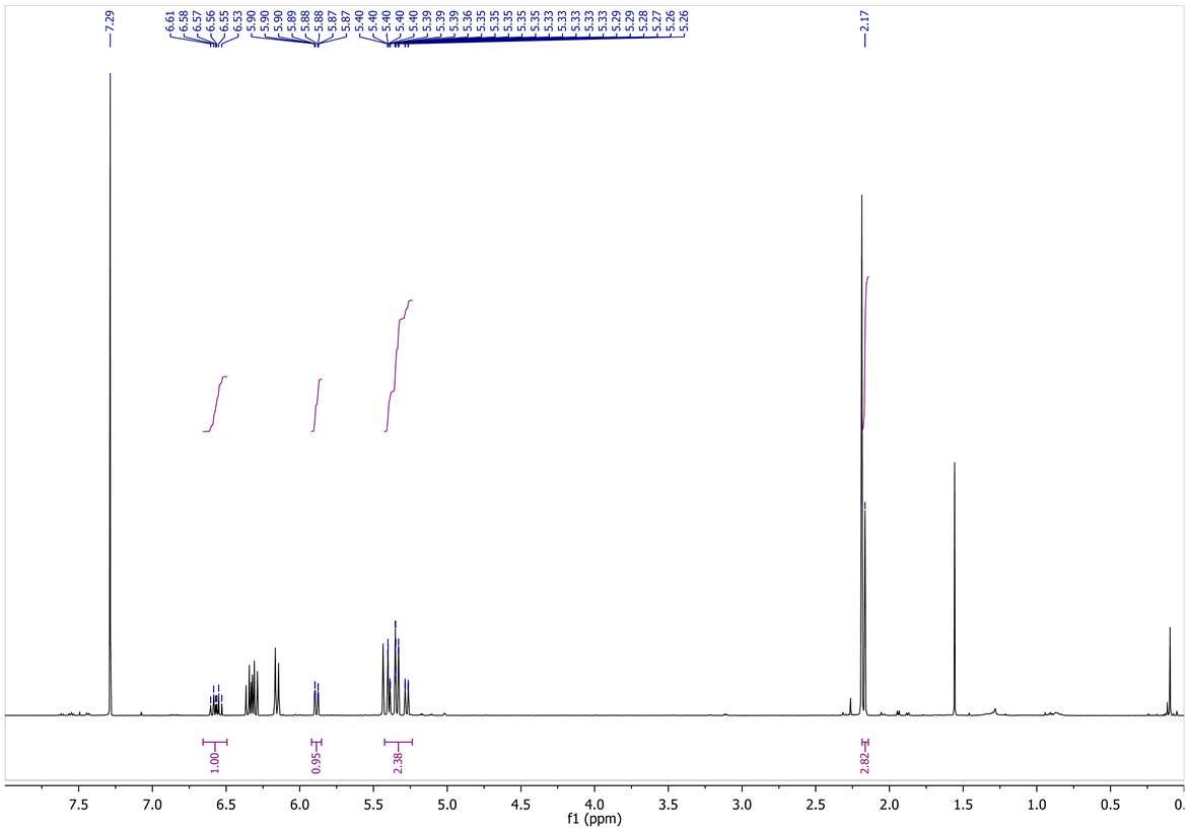
(*Z*)-penta-2,4-dien-2-yl triflate

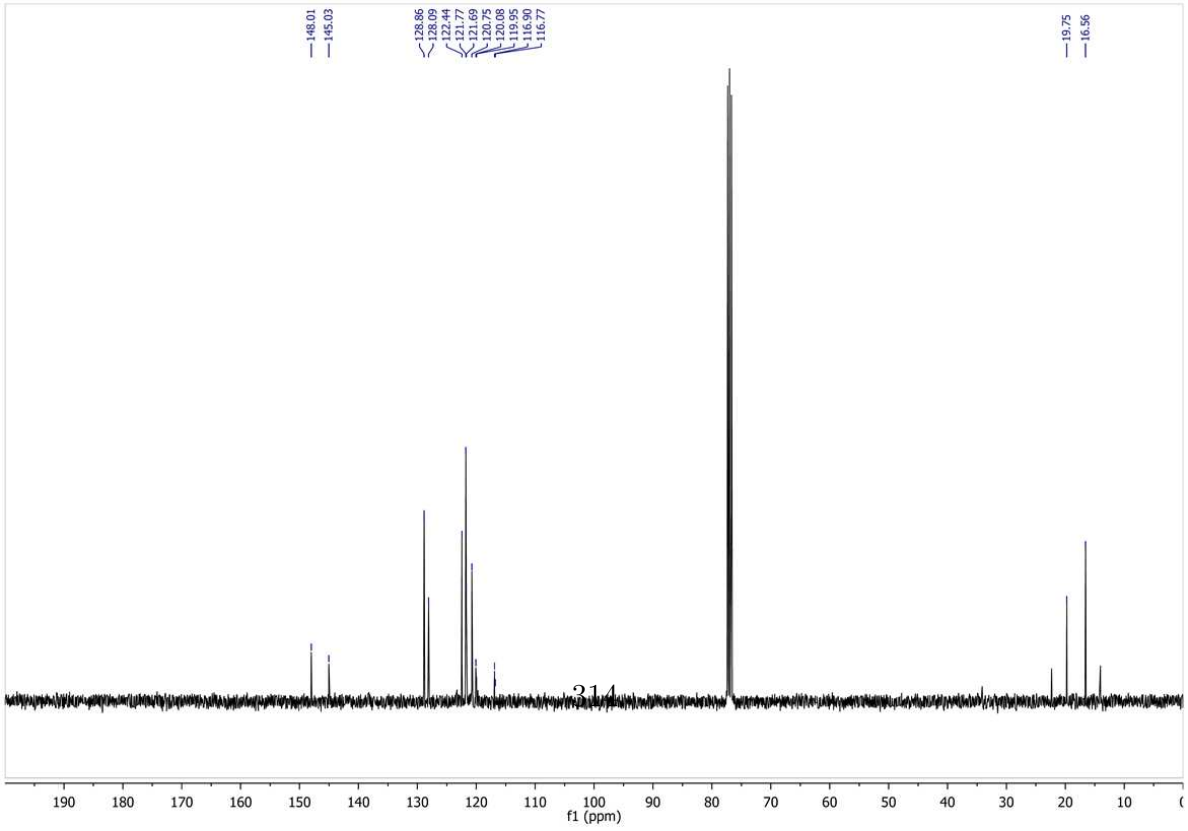
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (ddd, J = 16.8, 11.0, 10.2 Hz, 1H, 4),

6.16 (dq, J = 11.0, 0.9 Hz, 1H, 3), 5.60 – 5.26 (m, 2H, 5), 2.19 (d, J = 0.9 Hz, 3H, 1) ppm;

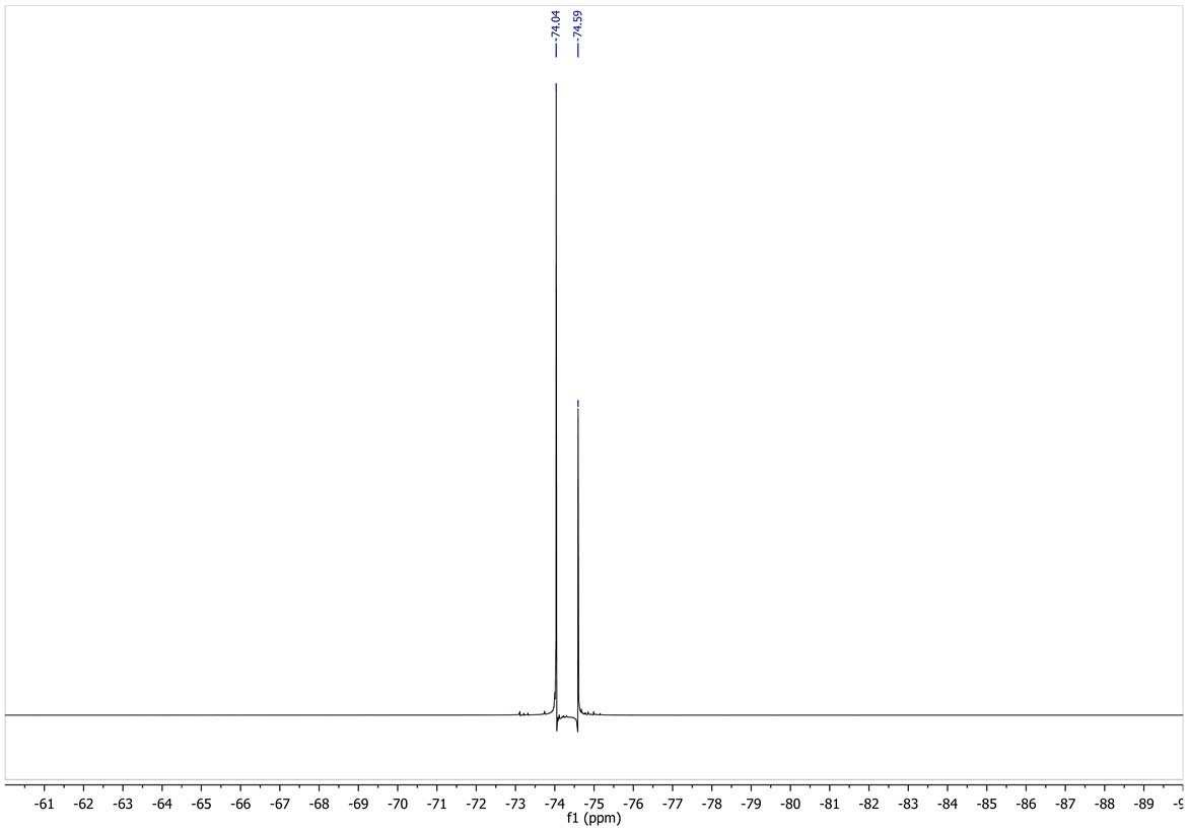
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 128.9, 122.4, 121.8, 118.49 (d, $^{1}J_{CF}$ = 320.3 Hz), 16.6 ppm;

$^{1}H/^{13}C$ NMR

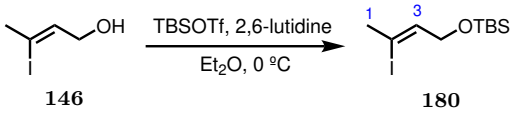

7.29
6.61
6.58
6.57
6.56
6.55
6.53
5.90
5.89
5.88
5.87
5.40
5.39
5.36
5.35
5.33
5.29
5.28
5.27
5.26
2.17
1.00
0.95
2.38
2.82
f1 (ppm)


148.01
145.03
128.86
128.09
122.44
121.77
121.69
121.35
120.08
119.95
116.90
116.77
19.75
16.56
f1 (ppm)

^{19}F NMR


-74.04
-74.59
-61 -62 -63 -64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 -84 -85 -86 -87 -88 -89
f1 (ppm)

5.3.1.40 TBS protected iodide 180



146 **180**

Allylic alcohol **146** (396 mg, 2.0 mmol, 1.0 mol equiv) and dry Et_2O (5.4 mL) were added to a flame dried round bottom flask equipped with a rubber septum and stirrer bar. 2,6-lutidine (0.26 mL, 2.2 mmol, 1.1 mol equiv) was added by syringe and the solution was cooled to 0 °C. *tert*-Butyldimethylsily trifluoromethanesulfonate (0.52 mL, 2.2 mmol, 1.1 mol equiv) was added dropwise in the dark and upon completion of addition, the cooling bath was removed. When the reaction was deemed complete by TLC (approx. 30 min), the mixture was diluted with Et_2O and quenched with saturated $NaHCO_{3(aq)}$. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (*n*-pentane, silica column) to give the title compound as a clear oil (700 mg, 0.13 mmol, 93% yield).

R_f = 0.76 (30% Et_2O/*n*-pentane, stains blue with CAM);

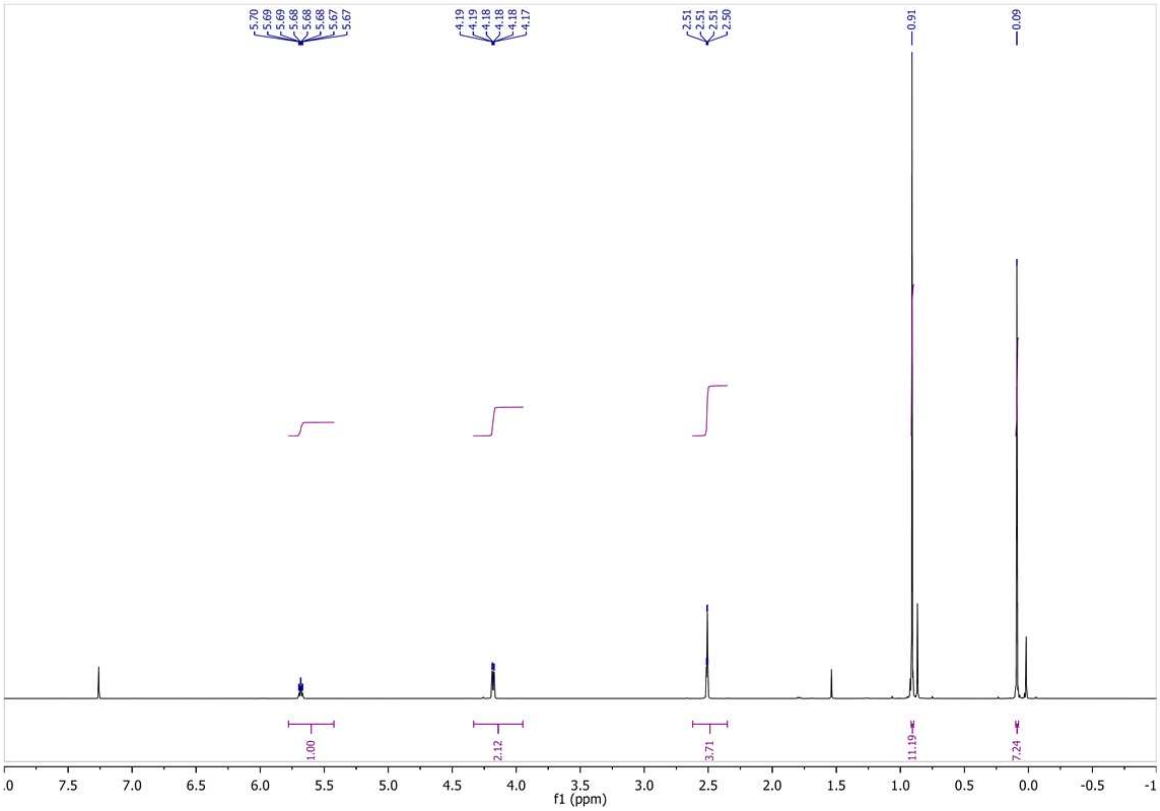
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 – 5.42 (m, 1H, 3), 4.33 – 3.95 (m, 2H, 4), 2.51 (q, J = 1.5 Hz, 3H, 1), 0.91 (s, 9H, TBS-^{t}Bu-Me), 0.09 (s, 6H, TBS-Me) ppm;

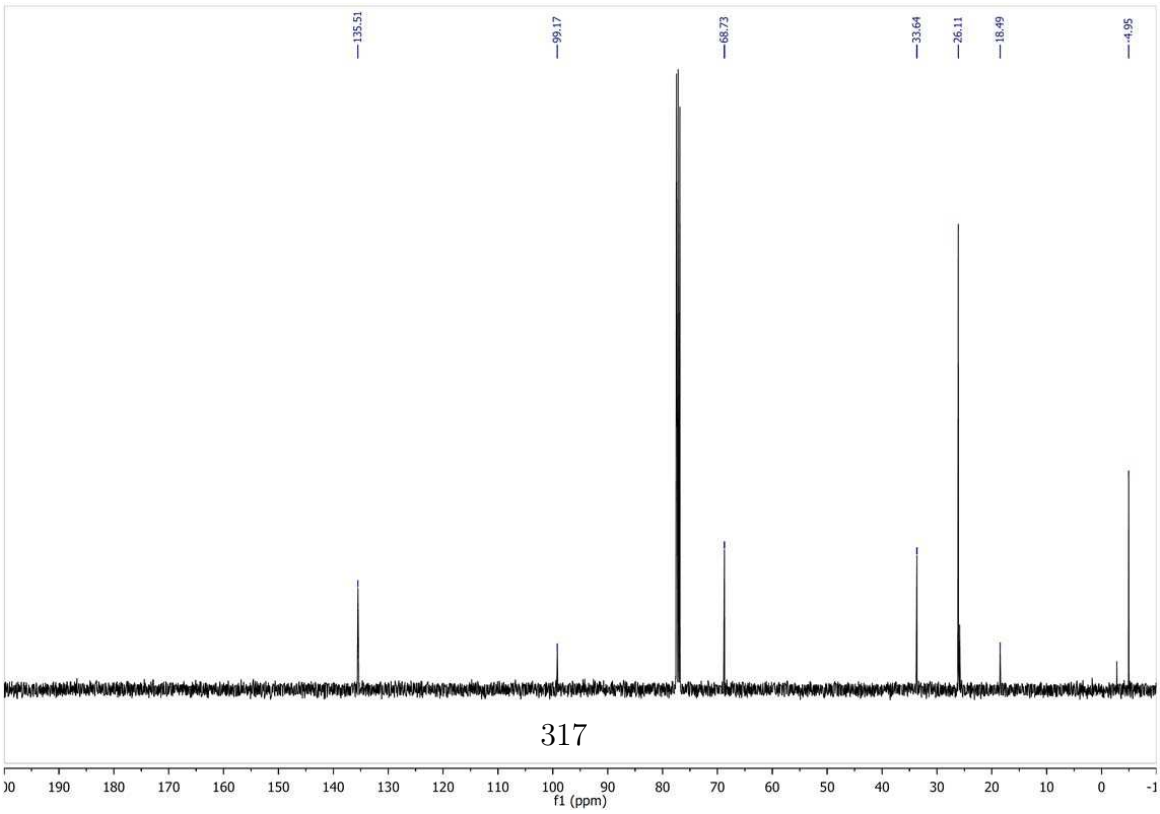
^{13}C NMR (101 MHz, $CDCl_3$): δ 135.5 3, 99.2 2, 68.7 4, 33.6 1, 26.1 TBS-^{t}Bu-Me, 18.5 TBS-^{t}Bu-C, −4.9 TBS-Me ppm;

FT-IR thin film, neat (ATR): 2954, 2929, 2857, 1255, 1097, 836 cm^{-1};

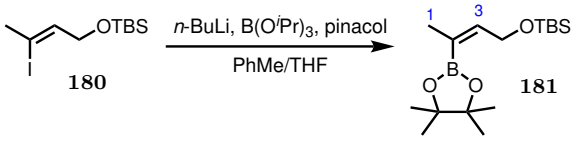
HRMS: A high resolution mass spectrum could not be obtained for this compound (using EI, ESI, APCI).

$^{1}H/^{13}C$ NMR


5.70
5.69
5.69
5.68
5.68
5.68
5.67
5.67
4.19
4.19
4.18
4.18
4.18
4.17
2.51
2.51
2.51
2.50
0.91
0.09
1.00
2.12
3.71
11.19
7.24
f1 (ppm)


135.51
99.17
68.73
33.64
26.11
18.49
-4.95
f1 (ppm)

5.3.1.41 Boronic acid pinacol ester 181



TBS-protected alcohol **180** (50 mg, 0.16 mmol, 1.0 mol equiv), triisopropylborate (42 μL, 0.18 mmol, 1.1 mol equiv), toluene (0.75 mL) and tetrahydrofuran (0.19 mL) were added to a flame dried round bottom flask equipped with a rubber septum and stirrer bar before being cooled to −78 °C. *n*-BuLi (0.13 mL of a 1.4M solution in hexane, 0.18 mmol, 1.1 mol equiv) was added dropwise and the resulting solution was stirred for 30 minutes before pinacol (25 mg, 0.21 mmol, 1.3 mol equiv) was added in one portion, minimising exposure of the reaction contents to the atmosphere. The flask was wrapped in foil, slowly warmed to room temperature and stirred at room temperature for 24 hours. The mixture was diluted with Et_2O and quenched with saturated $NH_4Cl_{(aq)}$. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-10% Et_2O/*n*-pentane, silica column) to give the title compound as a clear oil (43 mg, 0.13 mmol, 86% yield).

R_f = 0.76 (30% Et_2O/*n*-pentane, stains blue with CAM);

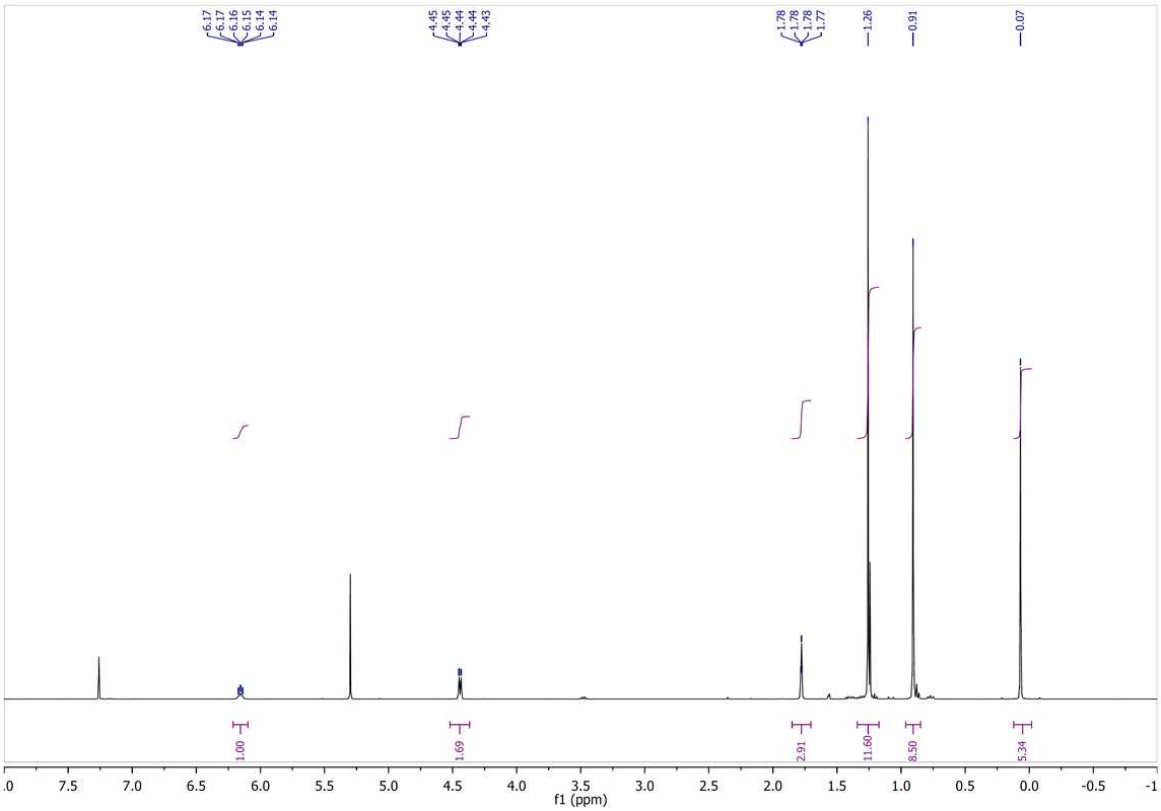
^{1}H NMR (400 MHz, $CDCl_3$): δ 56.21 – 6.10 (m, 1H, 3), 4.52 – 4.37 (m, 2H, 4), 1.78 (q, J = 1.4 Hz, 3H, 1), 1.26 (s, 12H, BPin-Me), 0.91 (s, 9H, TBS-^{t}Bu-Me), 0.07 (s, 6H, TBS-Me) ppm;

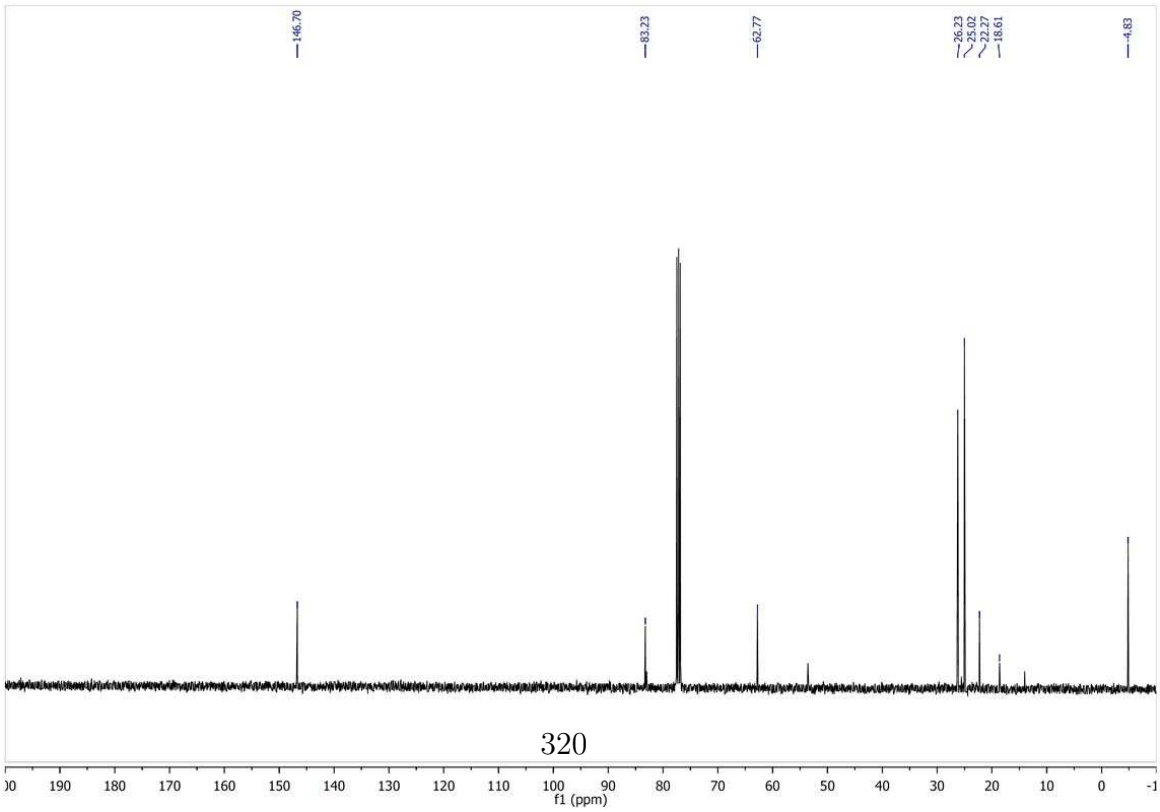
^{13}C NMR (101 MHz, $CDCl_3$): δ 146.7 3, 83.2 BPin-O-C, 62.8 4, 26.2 TBS-^{t}Bu-Me, 25.0 BPin-Me, 18.6 TBS-^{t}Bu-C, −4.8 TBS-Me ppm;

FT-IR thin film, neat (ATR): 2980, 2857, 2361, 2341, 1391, 1143, 1091, 814 cm^{-1};

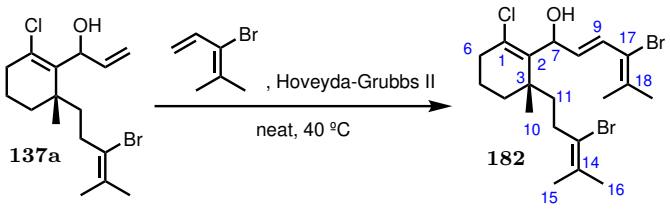
HRMS (ESI^+): calculated for $C_{16}H_{34}O_3{}^{10}B^{28}Si$, $[M+H]^{+\bullet}$: 312.24011 found 312.2402 (Δ = 0.99 ppm);

$^{1}H/^{13}C$ NMR


6.17
6.17
6.16
6.15
6.14
6.14
4.45
4.45
4.44
4.44
4.44
4.43
1.78
1.78
1.78
1.77
1.26
0.91
0.07
1.00
1.69
2.91
11.60
8.50
5.34
f1 (ppm)


146.70
83.23
62.77
26.23
25.02
22.27
18.61
4.83
f1 (ppm)

5.3.1.42 Bromo alcohol (metathesis test reaction) 182



Alcohol **137a** (39 mg, 0.11 mmol, 1.0 mol equiv) and bromodiene **36** (0.15 mL) were added to a flame dried 10 mL Schlenk tube equipped with a stirrer bar. After three cycles of freeze-pump-thaw, Hovedya-Grubbs 2nd Generation catalyst (1.4 mg, 0.0022 mmol, 0.020 mol equiv) was added to the degassed alkene mixture under a counterflow of N_2 gas. The reaction mixture went brown in colour and vigorous gas evolution was observed. After stirring at room temperature for 3 hours, the mixture was heated at 40 °C for 20 hours at which point, TLC showed complete consumption of starting material.

The reaction mixture immediately became brown in colour with vigorous gas evolution and a N_2 balloon was fitted. The reaction was heated at 40 °C and after 10 minutes (when gas evolution ceased), the balloon was removed. When the reaction was deemed to be complete as monitored by TLC (approximately 22 hours), the crude product was purified directly by flash chromatography (0–30% Et_2O/*n*-pentane, silica column) to give the title compound (inseparable mixture of diastereomers) as a yellow-orange oil (601 mg, 1.49 mmol, 62% yield).

R_f = 0.25 (30% Et_2O/*n*-pentane, stains blue with CAM);

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (dd, J = 14.7, 1.5 Hz, 1H, 9), 6.01 (dd, J = 14.7, 5.5 Hz, 1H, 8), 5.54 (s, 1H, 7), 2.52 – 2.41 (m, 2H, alkyl-H), 2.39 – 2.05

(m, 4H, alkyl-H), 2.02 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.85(1.84) (s, 3H, CH_3), 1.75(1.73) (s, 3H, CH_3), 1.59 – 1.39 (m, 4H, alkyl-H), 0.96(0.93) (s, 3H, 10) ppm;

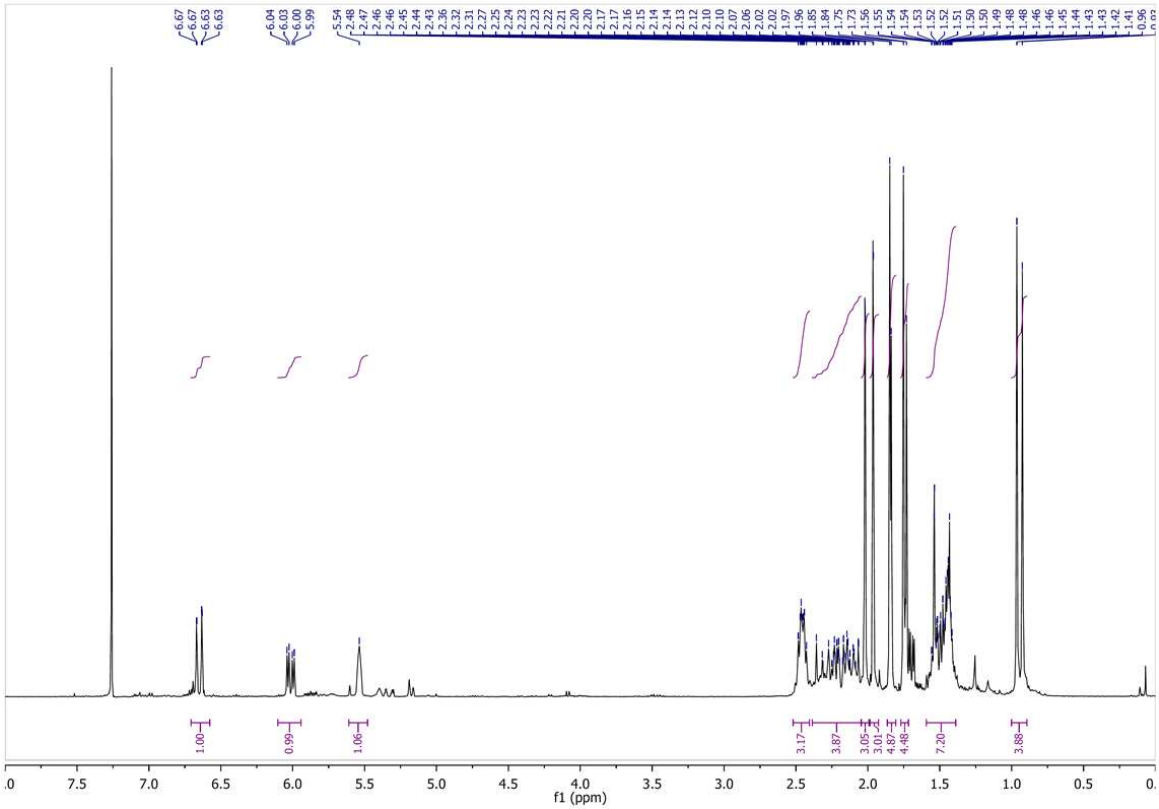
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 136.1, 133.9(132.9) 8, 132.7, 130.0(129.6), 125.8 9, 121.7, 119.4(118.4), 71.4(71.3) 7, 47.4 (CH_2), 39.5(39.1) (CH_2), 33.63(33.8) 3, 32.8 (CH_2), 32.6 (CH_2), 26.6 CH_3, 25.5 CH_3, 24.1(23.8) CH_3, 21.9 (CH_2), 21.1 CH_3, 20.3 CH_3 ppm;

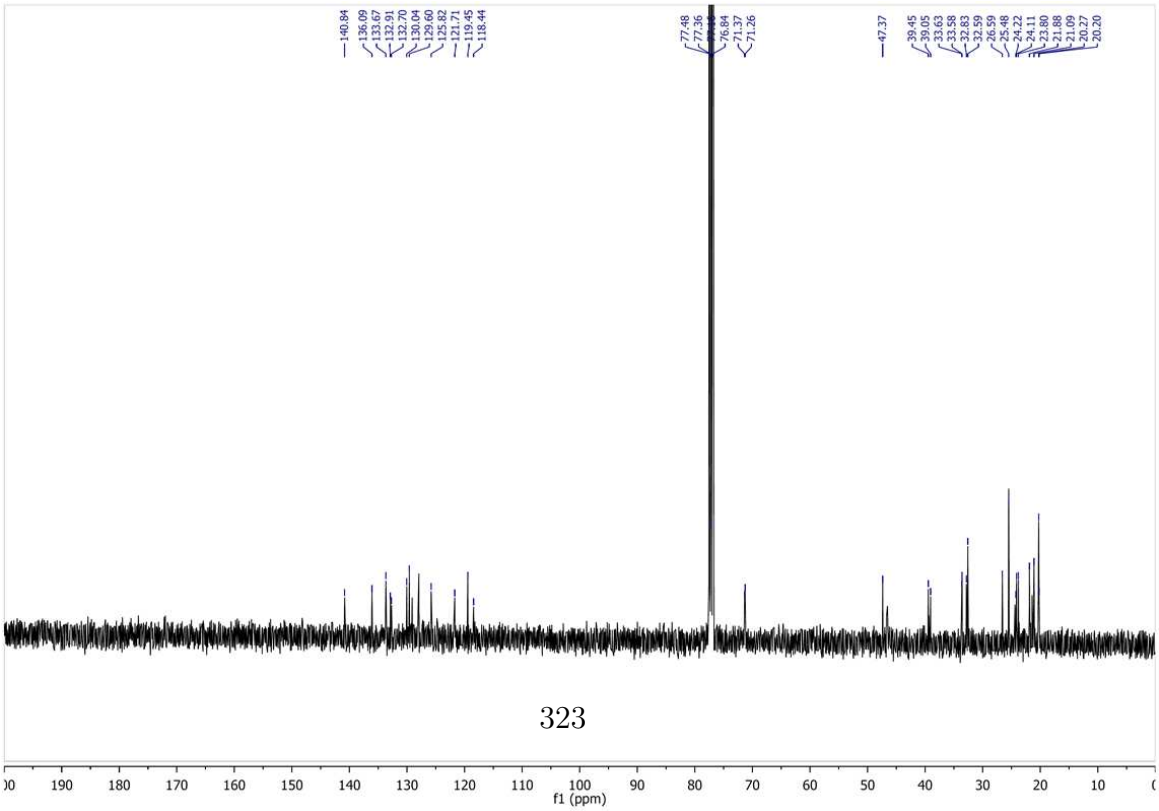
FT-IR thin film, neat (ATR): 3365, 2918, 2362, 1639, 1448, 952 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{20}H_{28}O^{79}Br_2{}^{35}Cl$, $[M\text{-}H]^{+\bullet}$: 477.01899 found 477.01883 (Δ = -0.35 ppm);

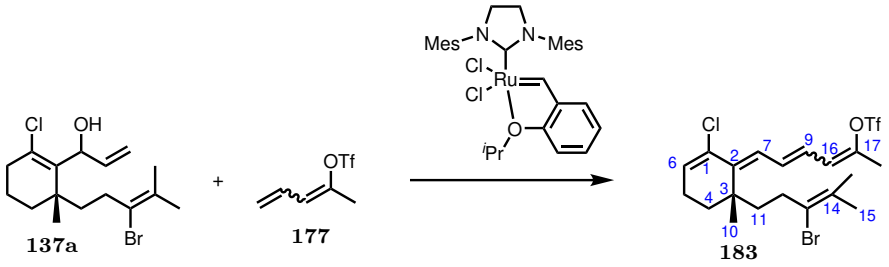
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 11° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.43 Cross metathesis product with triflated diene 183



Alcohol **137a** (10 mg, 0.031 mmol, 1.0 mol equiv) and diene **177** (0.13 mmol quantity determined by NMR, 4.2 mol equiv) were added to a 1.5 mL vial equipped with a stirrer bar. Hoveyda-Grubbs Second Generation Catalyst (3.9 mg, 0.0062 mmol, 0.20 mol equiv) was added and vigorous gas evolution was observed. The reaction was sealed with a cap when gas evolution subsided and heated to 40 °C. After stirring for 6 hours, the reaction was loaded onto celite and filtered through silica (5% Et_2O/*n*-pentane). The yellow oil thus obtained, spontaneously decomposed to give a black residue which was further purified by preparative TLC (30% Et_2O/*n*-pentane) to furnish the desired product as a mixture of diastereomers. First diastereomer (1.7 mg, 0.0033 mmol, 11% yield), second diastereomer (1.5 mg, 0.0029 mmol, 9% yield) total yield 20%.

HRMS (ESI$^+$): calculated for $C_{20}H_{26}O_3F_3S^{35}Cl^{79}Br$, $[M+H]^{+\bullet}$: 517.04212 found 517.042197 (Δ = 0.16 ppm);

First diastereomer

$\mathbf{R_f}$ = 0.70 (30% Et_2O/*n*-pentane, stains green with vanillin);

^{1}H NMR (500 MHz, C_6D_6): δ 6.87 (d, J = 11.5 Hz, 1H, 7), 6.65 (dd, J =

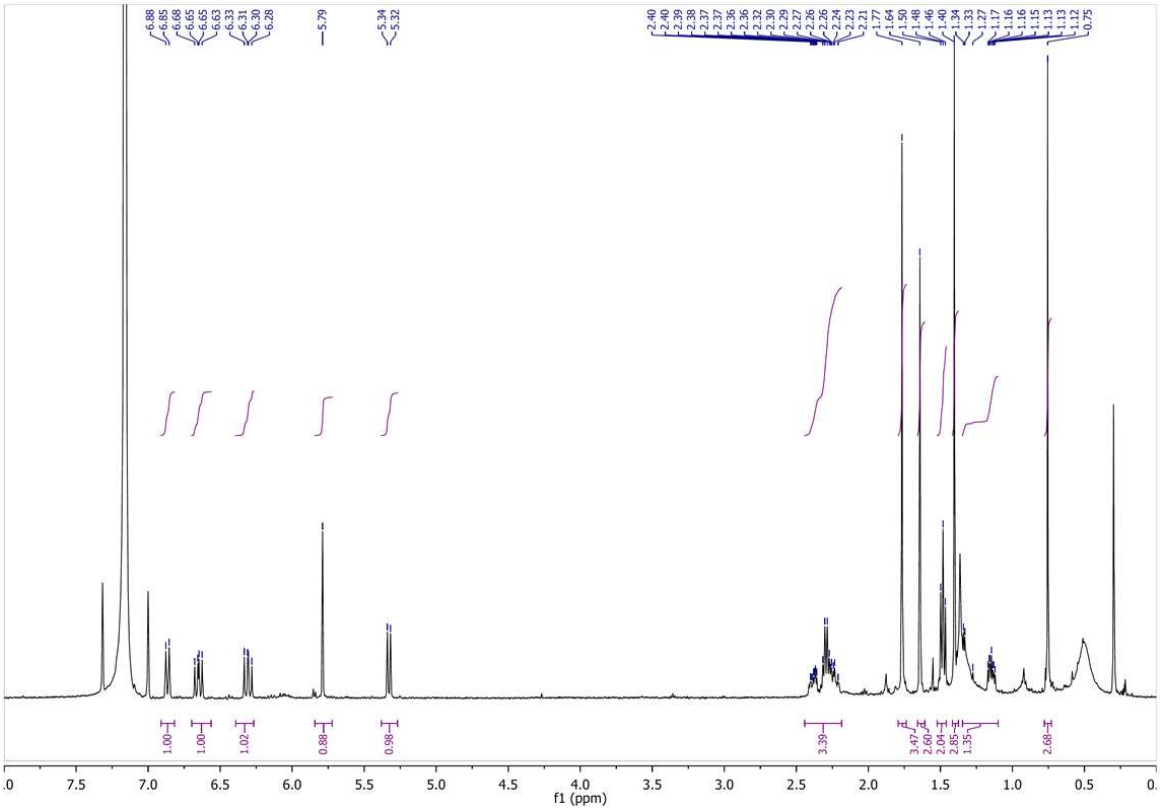
14.8, 10.9 Hz, 1H, 9), 6.31 (dd, J = 14.8, 11.5 Hz, 1H, 8), 5.79 (s, 1H, 6), 5.33 (d, J = 10.9 Hz, 1H, 16), 2.44 – 2.19 (m, 4H, alkyl-H), 1.77 (s, 3H, CH_3), 1.64 (s, 3H, 18), 1.48 (t, J = 8.3 Hz, 2H, alkyl-H), 1.40 (s, 3H, CH_3), 1.35 – 1.10 (m, 2H, alkyl-H), 0.75 (s, 3H, 10) ppm;

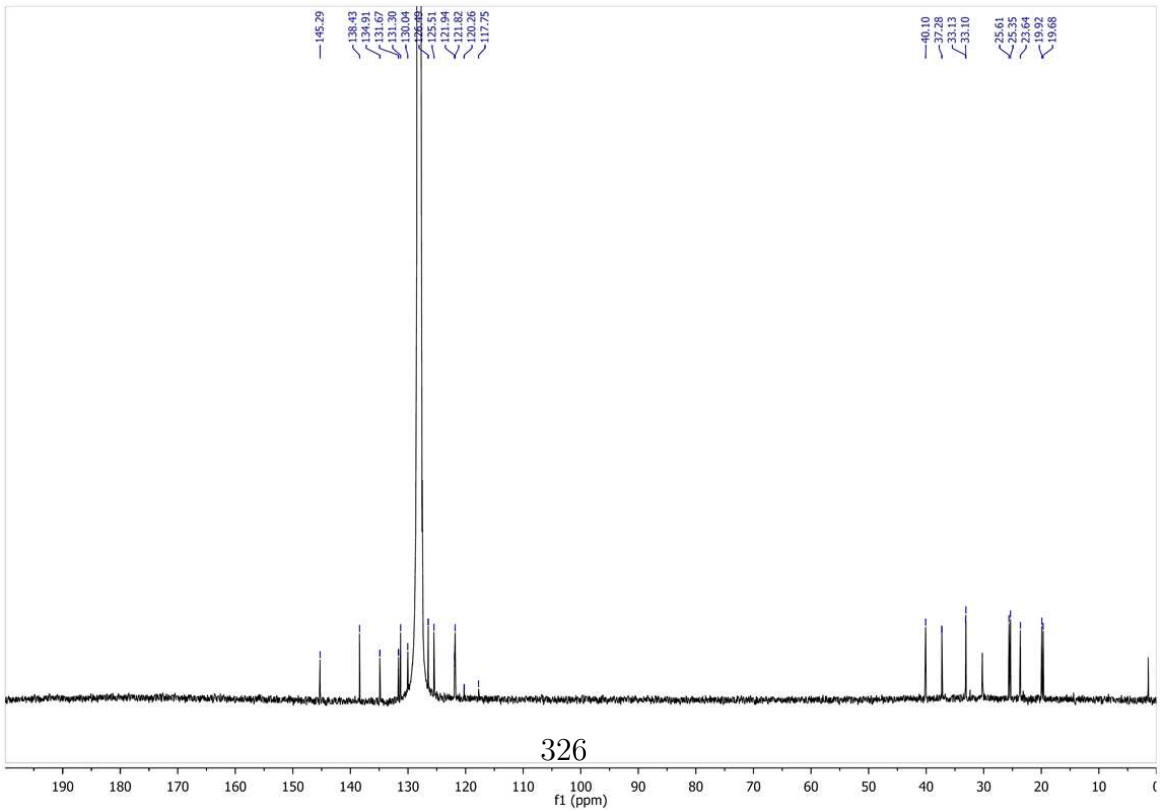
^{13}C NMR (126 MHz, C_6D_6): δ 145.3 17, 138.4 6, 134.9 1, 131.7 2, 131.3 8, 130.0 14, 126.5 7, 125.5 9, 121.9 16, 121.8 13, 119.00 (d, $^1J_{CF}$ = 316.1 Hz), 40.1 (CH_2), 37.3 3, 33.13 (CH_2), 33.10 (CH_2), 25.6 10, 25.4 CH_3, 23.6 (CH_2), 19.9 CH_3, 19.7 18 ppm;

FT-IR thin film, neat (ATR): 2920, 2361, 1418, 1211, 1142 cm^{-1};

$[\alpha]_D^{25}$ = + 43° (c = 0.17, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$


6.88
6.85
6.68
6.65
6.65
6.63
6.33
6.31
6.30
6.28
5.79
5.34
5.32
2.40
2.40
2.39
2.38
2.37
2.37
2.36
2.36
2.32
2.30
2.29
2.27
2.26
2.26
2.24
2.23
2.21
1.77
1.64
1.50
1.48
1.46
1.40
1.34
1.33
1.27
1.17
1.16
1.16
1.15
1.13
1.13
1.12
0.75
1.00
1.00
1.02
0.88
0.98
3.39
3.47
2.60
2.04
2.85
1.35
2.68
f1 (ppm)


145.29
138.43
134.91
131.67
131.30
130.04
125.51
121.94
121.82
120.26
117.75
40.10
37.28
33.13
33.10
25.61
25.35
23.64
19.92
19.68
f1 (ppm)

Second diastereomer

$\mathbf{R_f}$ = 0.45 (30% Et_2O/*n*-pentane, stains green with vanillin);

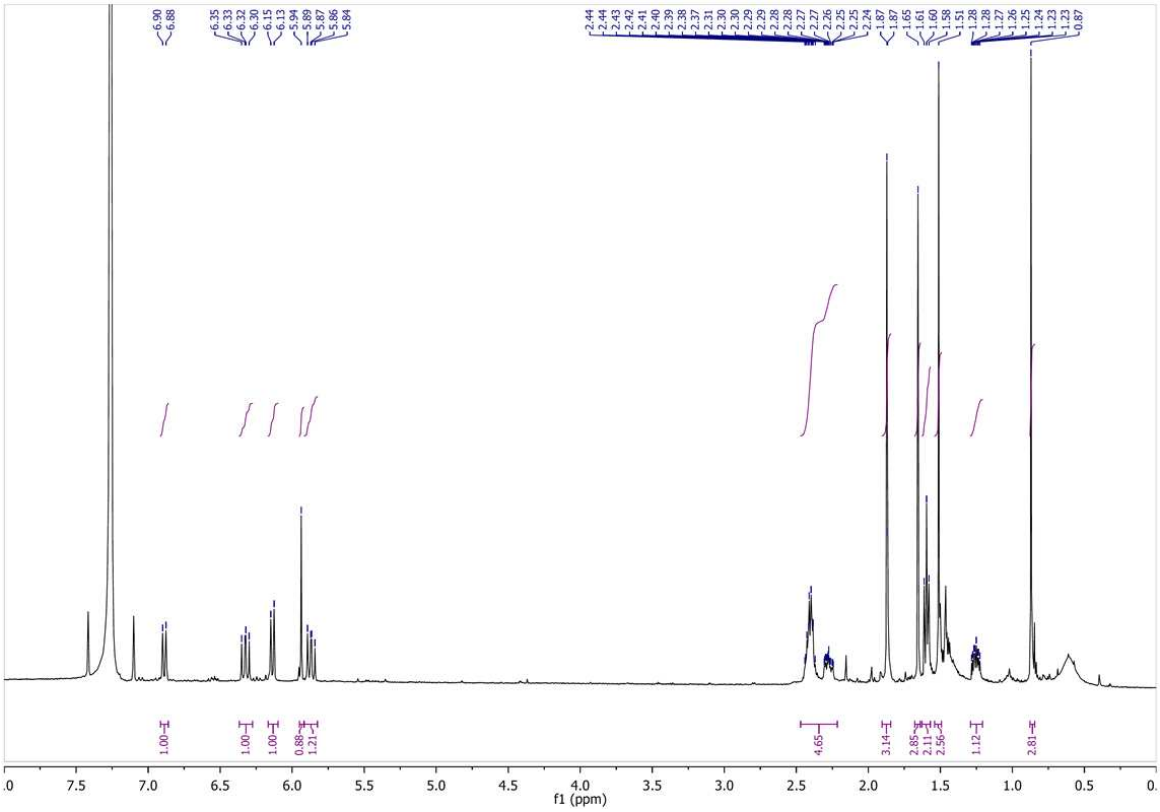
^{1}H NMR (500 MHz, C_6D_6): δ 6.89 (d, J = 11.5 Hz, 1H, 7), 6.32 (dd, J = 14.7, 11.5 Hz, 1H, 9), 6.14 (d, J = 11.5 Hz, 1H, 16), 5.94 (s, 1H, 6), 5.87 (dd, J = 14.7, 11.5 Hz, 1H, 8), 2.47 – 2.22 (m, 4H, alkyl-H), 1.87 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.60 (t, J = 8.3 Hz, 2H, alkyl-H), 1.51 (s, 3H, CH_3), 1.25 (ddt, J = 12.6, 7.6, 4.1 Hz, 2H, alkyl-H), 0.87 (s, 3H, 10) ppm;

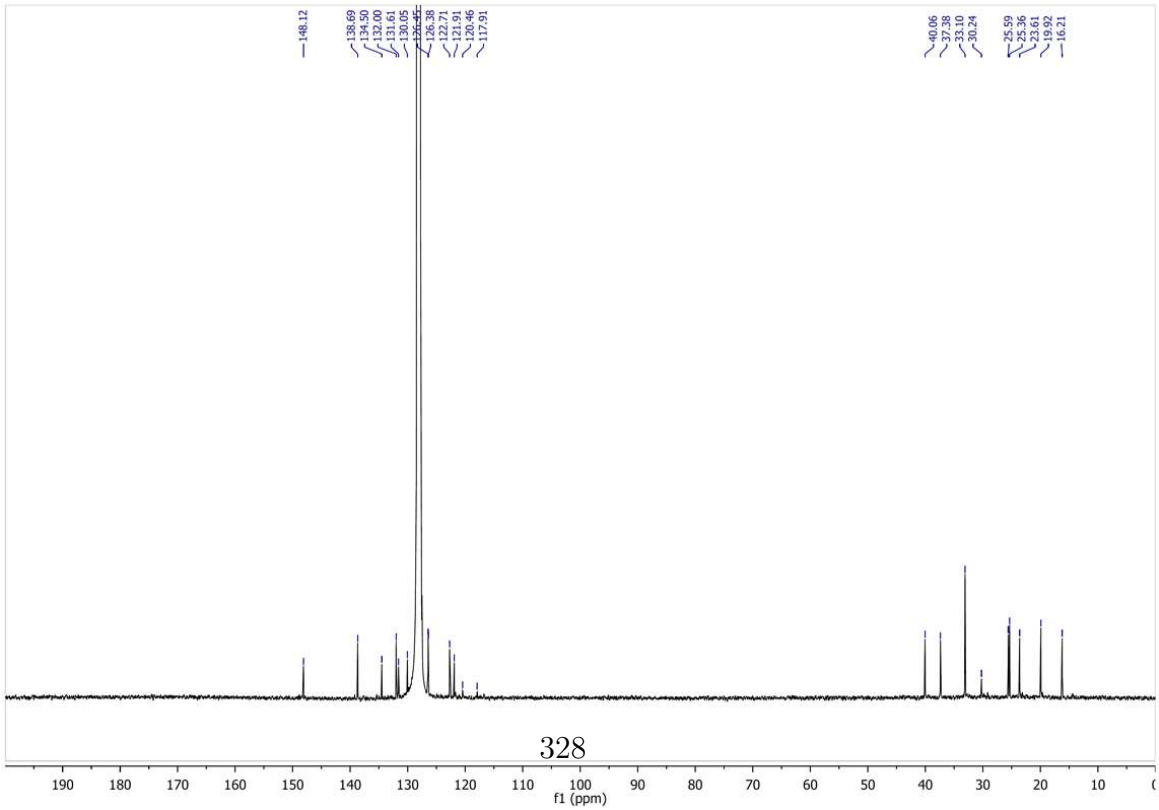
^{13}C NMR (126 MHz, C_6D_6): δ 148.1, 138.7, 134.5, 132.0, 131.6, 130.1, 126.5, 126.4, 122.7, 121.9, 119.2 (d, $^1J_{CF}$ = 320.5 Hz), 40.1, 37.4, 33.1(2C), 30.2, 25.6, 25.4, 23.6, 19.9, 16.2 ppm;

FT-IR thin film, neat (ATR): 2923, 2361, 1670, 1416, 1212, 1142, 903 cm^{-1};

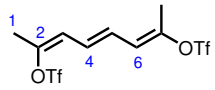
$[\alpha]_D^{25}$ = + 34° (c = 0.15, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$


6.90
6.88
6.35
6.33
6.32
6.30
6.15
6.13
5.94
5.89
5.87
5.86
5.84
2.44
2.44
2.43
2.42
2.41
2.40
2.39
2.38
2.37
2.31
2.30
2.30
2.29
2.29
2.28
2.28
2.27
2.27
2.26
2.25
2.25
2.24
1.87
1.87
1.65
1.61
1.60
1.58
1.51
1.28
1.28
1.27
1.26
1.25
1.24
1.23
1.23
0.87
1.00
1.00
1.00
0.88
1.21
4.65
3.14
2.85
2.11
2.56
1.12
2.81
f1 (ppm)


148.12
138.69
134.50
132.00
131.61
130.05
126.38
122.71
121.91
120.46
117.91
40.06
37.38
33.10
30.24
25.59
25.36
23.61
19.92
16.21
f1 (ppm)

5.3.1.44 Unsymmetrical triene 237



237

This compound was isolated as a side product in the reaction to form **183**.

R_f = 0.55 (31% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

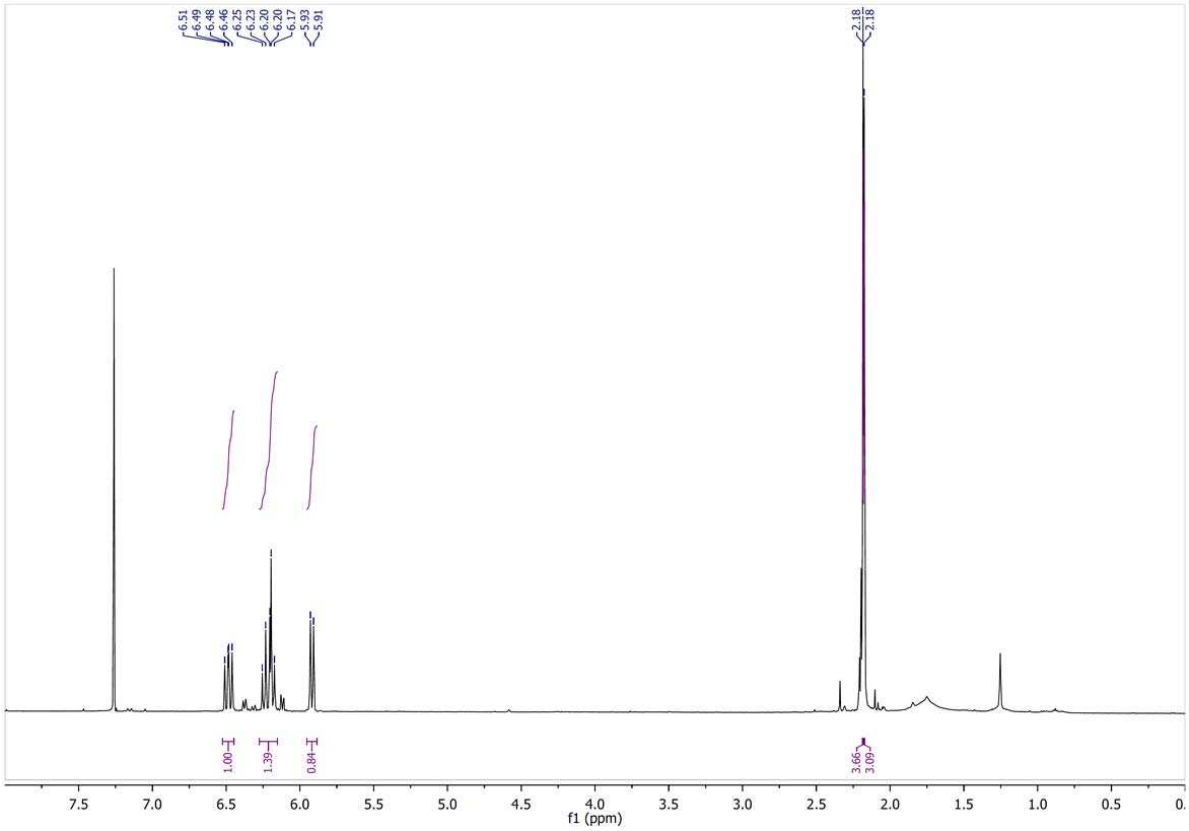
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (dd, J = 13.8, 10.8 Hz, 1H), 6.27 – 6.15 (m, 2H), 5.92 (d, J = 10.8 Hz, 1H), 2.18 (s, 3H), 2.18 (s, 3H) ppm;

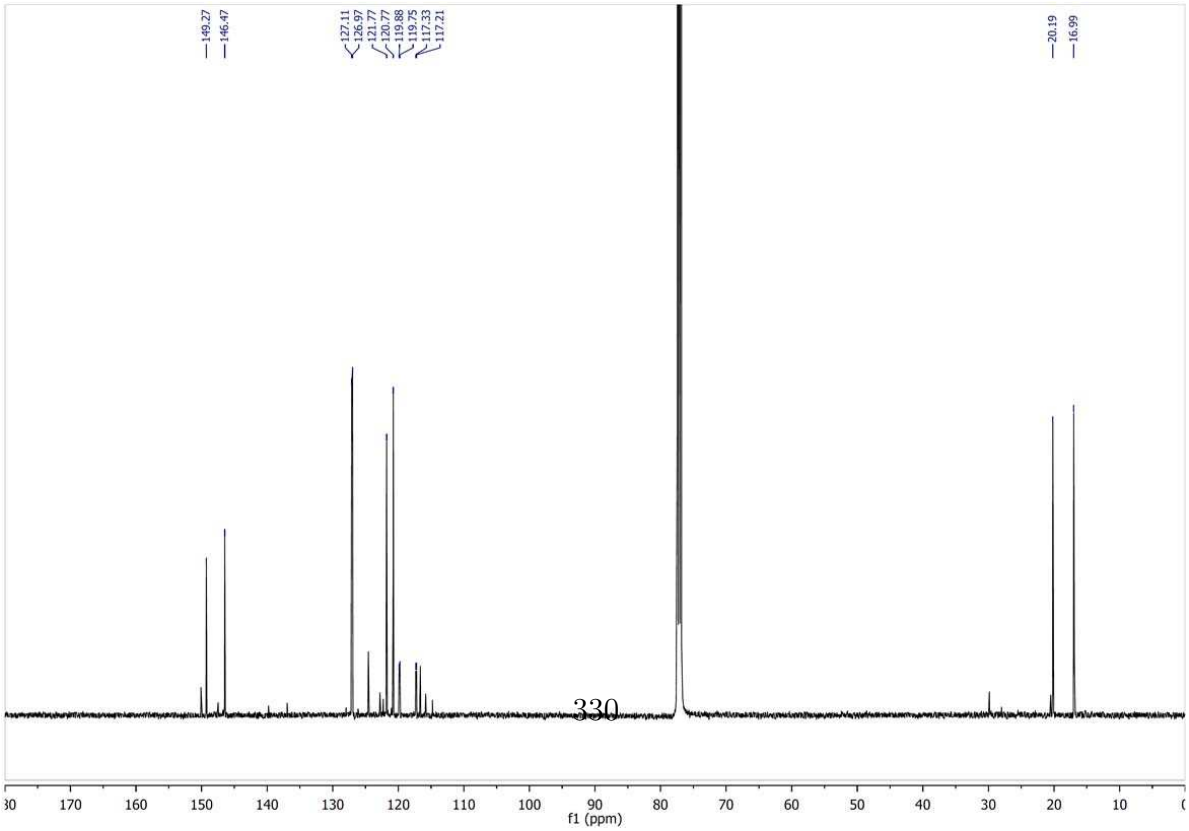
^{13}C NMR (126 MHz, $CDCl_3$): δ 149.3, 146.5, 127.1, 127.0, 121.8, 120.8, 118.6 (d, $^1J_{CF}$ = 320.4 Hz), 118.5 (d, $^1J_{CF}$ = 319.7 Hz), 20.2, 17.0 ppm;

FT-IR thin film, neat (ATR): 2359, 1418, 1210, 1140, 906, 874 cm^{-1};

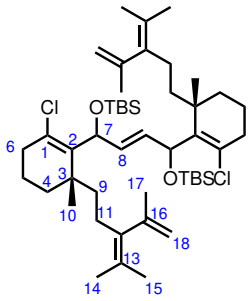
HRMS (ESI^+): calculated for $C_{10}H_{10}O_6F_6S_2{}^{23}Na$, $[M+Na]^{+\bullet}$: 426.97152 found 426.971426 (Δ = 0.23 ppm);

$^{1}H/^{13}C$ NMR


6.51
6.49
6.48
6.46
6.25
6.23
6.20
6.19
6.17
5.93
5.91
2.18
2.18
1.00
1.39
0.84
3.66
3.09
f1 (ppm)


149.27
146.47
127.11
126.97
121.77
120.77
119.88
119.75
117.33
117.21
20.19
16.99
f1 (ppm)

5.3.1.45 TBS-Dimer 238



238

This compound was isolated as a side product in the reaction to form **183**.

R_f = 0.70 (10% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 – 5.61 (m, 2H, 8), 5.43 – 5.29 (m, 2H, 7), 4.90 (dq, J = 2.8, 1.4 Hz, 2H, 18), 4.53 (d, J = 2.8 Hz, 2H, 18), 2.35 – 1.90 (m, 12H, alkyl-H), 1.75 (s, 6H, 2xCH_3), 1.65 (s, 12H, 4xCH_3), 1.41 – 1.17 (m, 8H, alkyl-H), 0.96 – 0.78 (m, 24H, 2xTBS-^{t}Bu-Me/10), 0.11 – -0.05 (m, 12H, 4xTBS-Me) ppm;

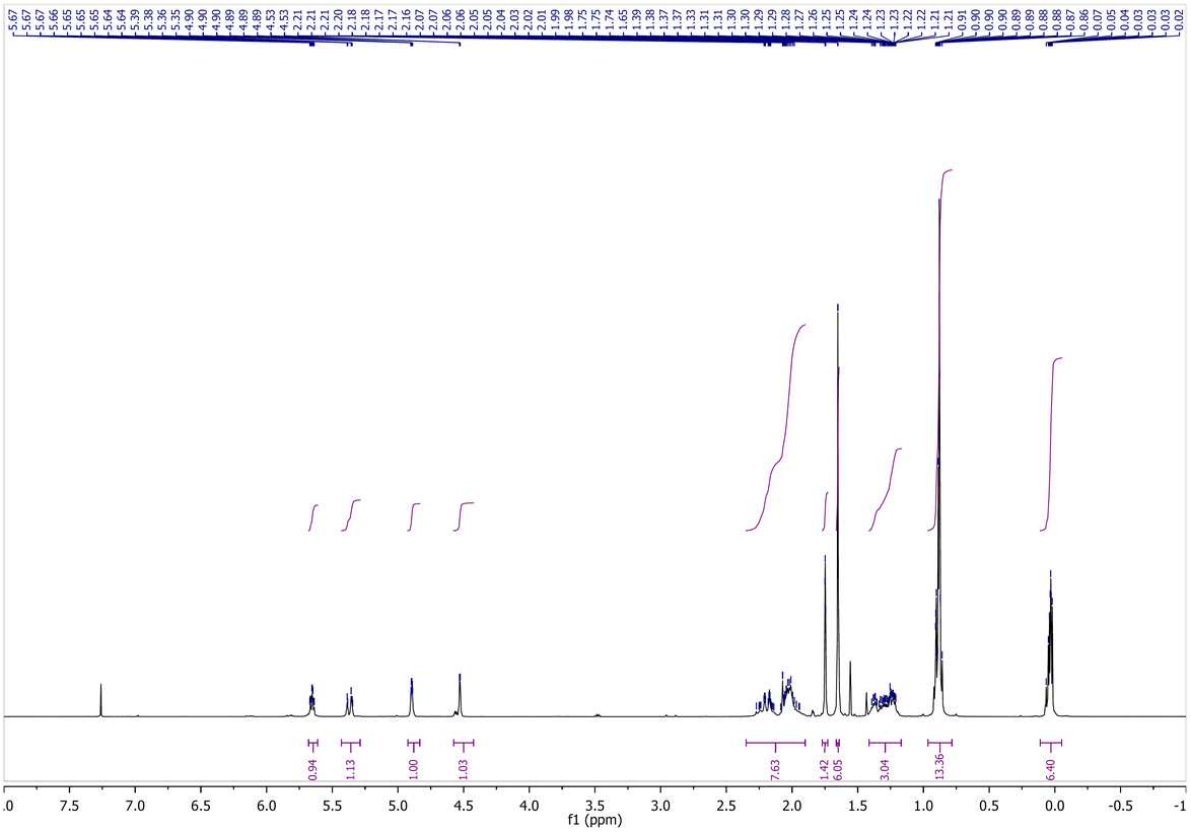
^{13}C NMR (126 MHz, $CDCl_3$): 146.7, 146.7, 146.6, 136.8, 136.8, 136.8, 133.7, 133.7, 133.6, 129.7, 129.7, 129.5, 129.3, 125.0, 124.9, 124.9, 124.8, 124.8, 124.8, 124.7, 113.2, 113.2, 113.2, 113.1, 113.1, 71.6, 71.5, 71.5, 71.3, 71.2, 46.5, 46.3, 46.0, 40.8, 40.5, 39.7, 39.4, 33.9, 33.9, 33.9, 33.4, 33.2, 32.9, 26.0, 26.0, 26.0, 25.3, 25.3, 25.2, 24.3, 24.0, 23.5, 23.2, 22.9, 22.9, 21.9, 21.9, 21.5, 21.3, 21.3, 19.7, 19.6, 19.6, 18.5, 18.4, −4.8, −4.8, −4.8, −4.9 ppm;

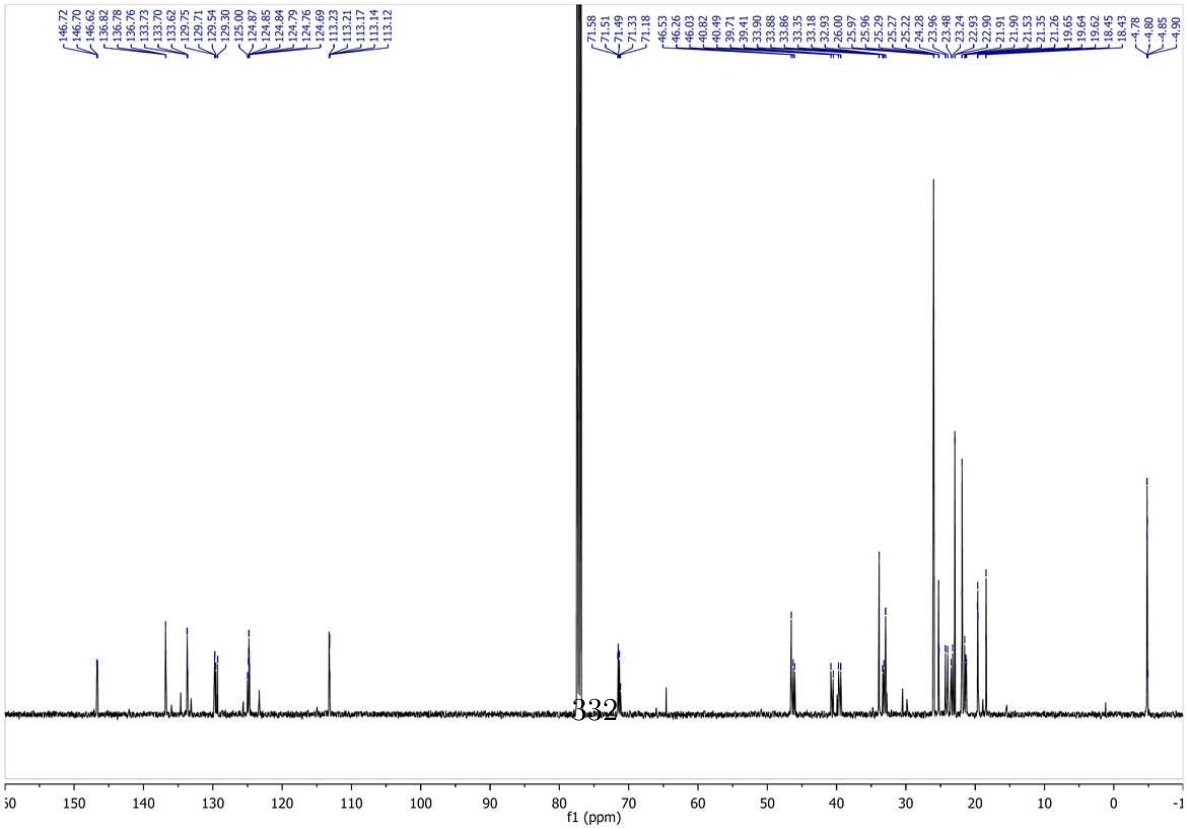
Complex mixtures of diastereomers were obtained making assignments difficult.

FT-IR thin film, neat (ATR): 2955, 2928, 2856, 2358, 1471, 1252, 1104, 837 cm^{-1};

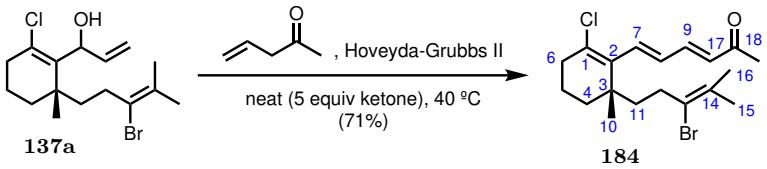
HRMS (ESI^+): calculated for $C_{48}H_{82}O_2{}^{35}Cl_2{}^{28}Si_2{}^{23}Na$, $[M+Na]^{+\bullet}$: 839.5123 found 839.5120 (Δ = -0.32 ppm);

$^{1}H/^{13}C$ NMR





5.3.1.46 Ketone 184



Alcohol **137a** (837 mg, 2.41 mmol, 1.0 mol equiv) and pent-4-en-2-one **175** (1.1 mL,ρ = 0.86 g.mL^{-1}, 11 mmol, 4.7 mol equiv) were added to a 7 mL vial equipped with a rubber septum and stirrer bar. After purging the reaction vessel with a stream of N_2, Hoveyda-Grubbs 2nd Generation catalyst (59 mg, 0.094 mmol, 0.039 mol equiv) was added in one portion, minimising the exposure of the reaction contents to the atmosphere. The reaction mixture immediately became brown in colour with vigorous gas evolution and a N_2 balloon was fitted. The reaction was heated at 40 °C and after 10 minutes (when gas evolution ceased), the balloon was removed. When the reaction was deemed to be complete as monitored by TLC (approximately 22 hours), the crude product was purified directly by flash chromatography (0–30% Et_2O/*n*-pentane, silica column) to give the title compound as a yellow-orange oil (601 mg, 1.49 mmol, 62% yield).

R_f = 0.31 (30% Et_2O/*n*-pentane, stains crimson with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 2H, 8&9), 6.37 (dd, J = 15.5, 10.9 Hz, 1H, 7), 6.18 (d, J = 15.5 Hz, 1H, 17), 2.47 (dt, J = 11.5, 5.8 Hz, 2H, alkyl-H), 2.43 – 2.32 (m, 2H, alkyl-H), 2.30 (s, 3H, 19), 2.34 – 2.24 (m, 2H, alkyl-H), 1.84 (s, 3H, 15), 1.75 (s, 3H, 16), 1.61 – 1.40 (m, 4H, alkyl-H), 0.96 (s, 3H, 10) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6 18, 144.1 8, 138.2 9, 135.3 1, 130.9 17,

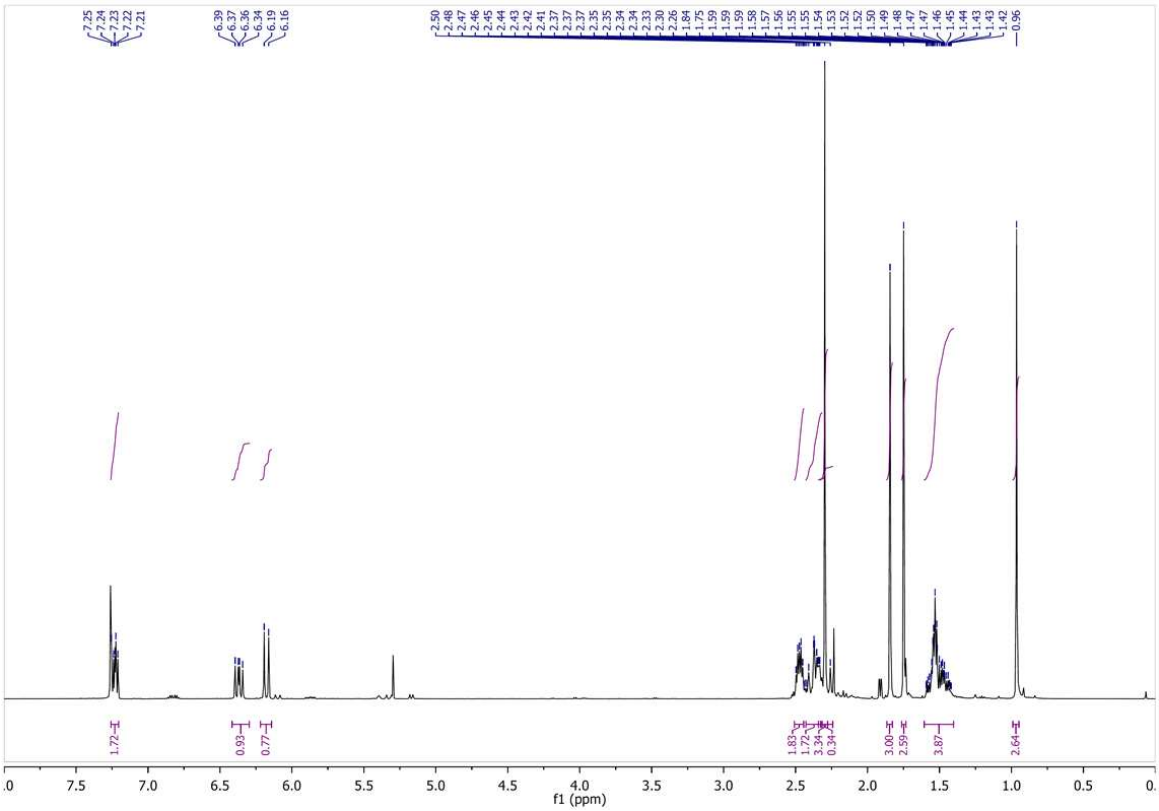
130.1 2, 128.6 13, 127.1 7, 121.6 14, 47.5 (CH_2), 39.3 (CH_2), 33.6 3, 32.6 (CH_2), 32.5 (CH_2), 27.2 19, 25.5 15, 24.1 10, 23.7 (CH_2), 20.3 16 ppm;

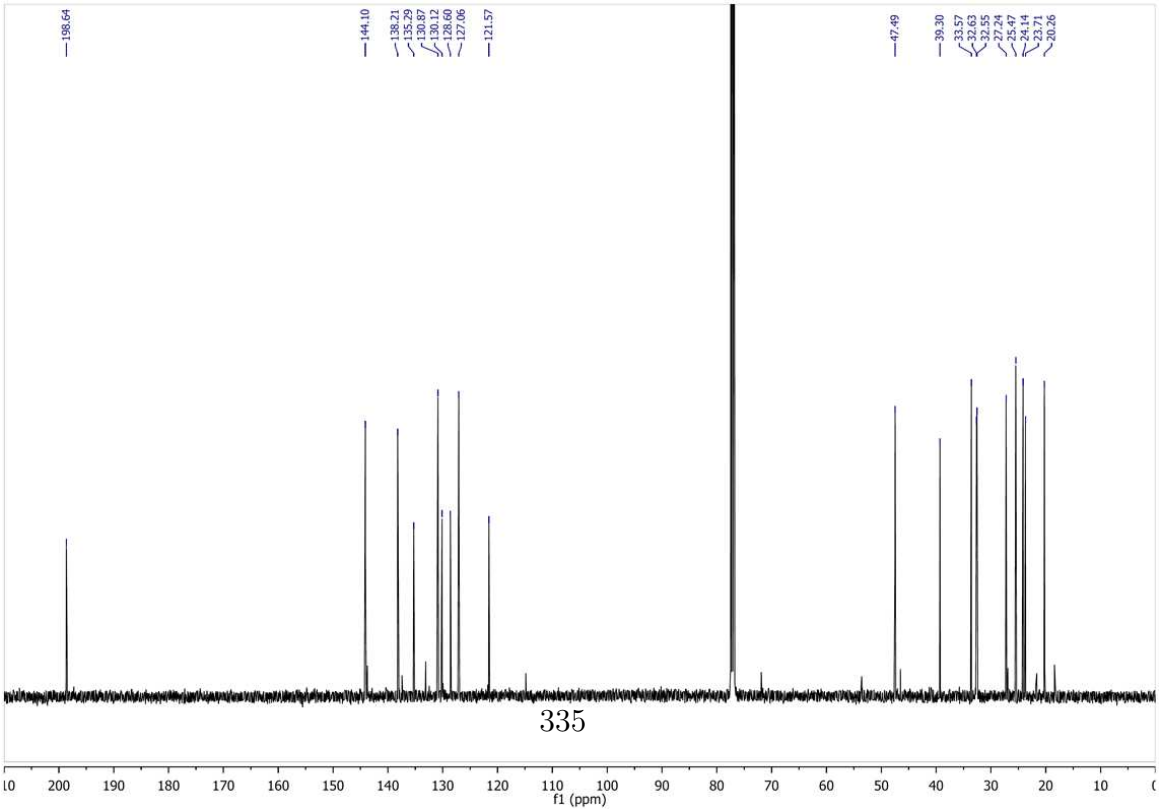
FT-IR thin film, neat (ATR): 2921, 2360, 1667, 1604, 1577, 1251, 995 cm^{-1};

HRMS (ESI^+): calculated for $C_{19}H_{27}O^{79}Br^{35}Cl$, $[M+H]^{+\bullet}$: 385.09283 found 385.09216 (Δ = -1.74 ppm);

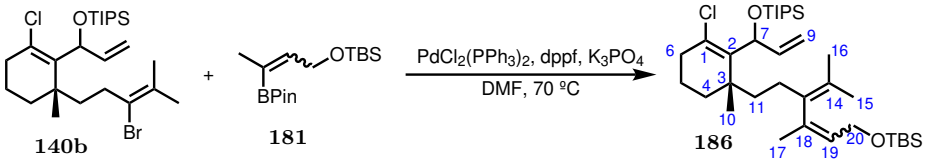
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 28° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR


7.25
7.24
7.23
7.22
7.21
6.39
6.37
6.36
6.34
6.19
6.16
2.50
2.48
2.47
2.46
2.45
2.44
2.43
2.42
2.41
2.37
2.37
2.37
2.35
2.35
2.34
2.34
2.33
2.30
2.26
1.84
1.75
1.59
1.59
1.59
1.58
1.57
1.56
1.55
1.55
1.54
1.53
1.52
1.52
1.50
1.49
1.48
1.47
1.47
1.46
1.45
1.44
1.43
1.43
1.42
0.96
1.72
0.93
0.77
1.83
1.72
3.34
0.34
3.00
2.59
3.87
2.64
f1 (ppm)


198.64
144.10
138.21
135.29
130.87
130.12
128.60
127.06
121.57
47.49
39.30
33.57
32.63
32.55
27.24
25.47
24.14
23.71
20.26
f1 (ppm)

5.3.1.47 Silylated diol 186



$PdCl_2(PPh_3)_2$ (53 mg, 0.075 mmol, 0.098 mol equiv), 1,1'-Bis(diphenylphosphinoferrocene) (dppf) (43 mg, 0.078 mmol, 0.10 mol equiv) and K_3PO_4 (491 mg, 2.32 mmol, 3.0 mol equiv) were added to a flame dried 7 mL vial, equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were then performed. Bromide **140b** (387 mg, 0.769 mmol, 1.00 mol equiv) and *Z*-boronic ester **181** (265 mg, 0.851 mmol, 1.10 mol equiv) were dissolved in dry, degassed (splarged with N_2 for 30min) DMF (1.5 mL) before being added to the solid reagents by syringe. The vial was placed in a 70 °C oil bath, fitted with a N_2 balloon and allowed to stir until the reaction was judged complete by TLC (elution with pentane, approx. 23 hours). The reaction mixture was allowed to cool to room temperature. An equal volume of benzene was added followed by water (1 mL) and the biphasic mixture stirred vigorously. The aqueous phase was extracted (3x) with benzene, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a clear oil (415 mg, 0.683 mmol, 89% yield).

The *E* isomer was prepared in the same manner as described above using the *E*-boronic ester.

Z-isomer data

R_f = 0.73 (10% Et_2O/*n*-pentane, stains purple with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (dddd, J = 16.9, 10.4, 4.3, 2.0 Hz, 1H, 8), 5.46 (td, J = 4.3, 2.2 Hz, 1H, 7), 5.38 – 5.34 (m, 1H, 19), 5.39 – 5.04 (m, 2H, 9), 3.96 – 3.90 (m, 2H, 20), 2.40 – 1.83 (m, 6H, alkyl-H), 1.73(1.72) (m, 3H, 17), 1.67(1.66) (s, 3H, 15), 1.54(1.53) (s, 3H, 16), 1.43 – 1.26 (m, 4H, alkyl-H), 1.15 – 1.07 (m, 3H, TIPS-^{i}Pr-H), 1.09 – 1.02 (m, 18H, TIPS-^{i}Pr-Me), 0.92(0.87) (s, 3H, 10), 0.89(0.88) (s, 9H, TBS-^{t}Bu), 0.05(0.04) (s, 6H, TBS-Me) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7 18, 138.4(138.3) 8, 133.8(133.7) 1, 133.4(133.3) 14, 126.3(126.2) 19, 126.2(126.1) 13, 125.0(124.9) 2, 113.5 9, 72.3(72.2) 7, 61.5(61.4) 20, 46.4 (CH_2), 39.8 (CH_2), 33.9 3, 33.0(bs) (CH_2), 26.2 TBS-^{t}Bu, 25.4(25.3) (CH_2), 24.0(23.9) 10, 23.3(23.2) 17, 21.7 16, 21.4 TBS-^{t}Bu(C) 21.05 (CH_2), 19.4(19.3) 15, 18.2(18.16)(18.1)(18.0) TIPS-^{i}Pr-Me, 12.4 TIPS-^{i}Pr-H, −4.9 TBS-Me ppm;

FT-IR thin film, neat (ATR): 2928, 2866, 2360, 1463, 1254, 1101, 1065, 836 cm^{-1};

HRMS (EI^+): calculated for $C_{35}H_{65}O_2{}^{35}Cl^{23}Na^{28}Si_2$, $[M+Na]^{+\bullet}$: 631.41038 found 631.41028 (Δ = -0.17 ppm);

$[\alpha]_D^{25}$ = + 3.8° (*c* = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

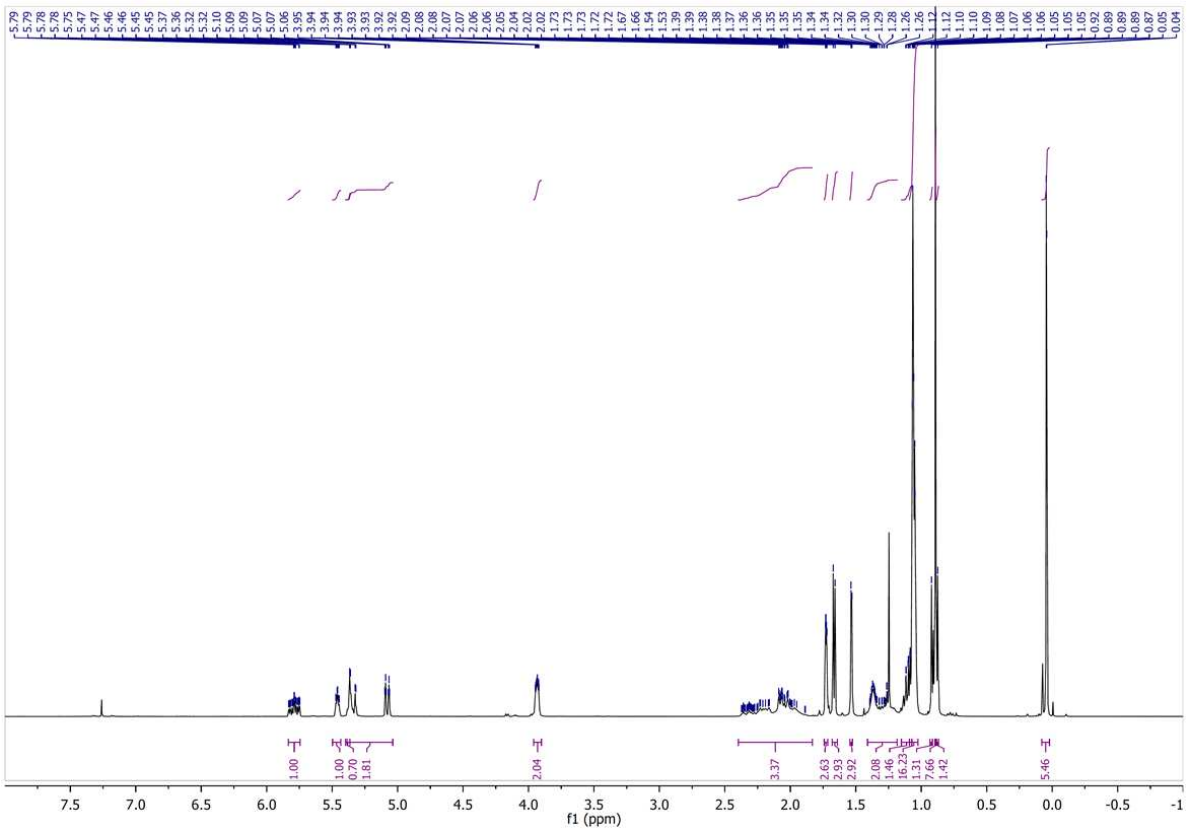
E-isomer NMR data

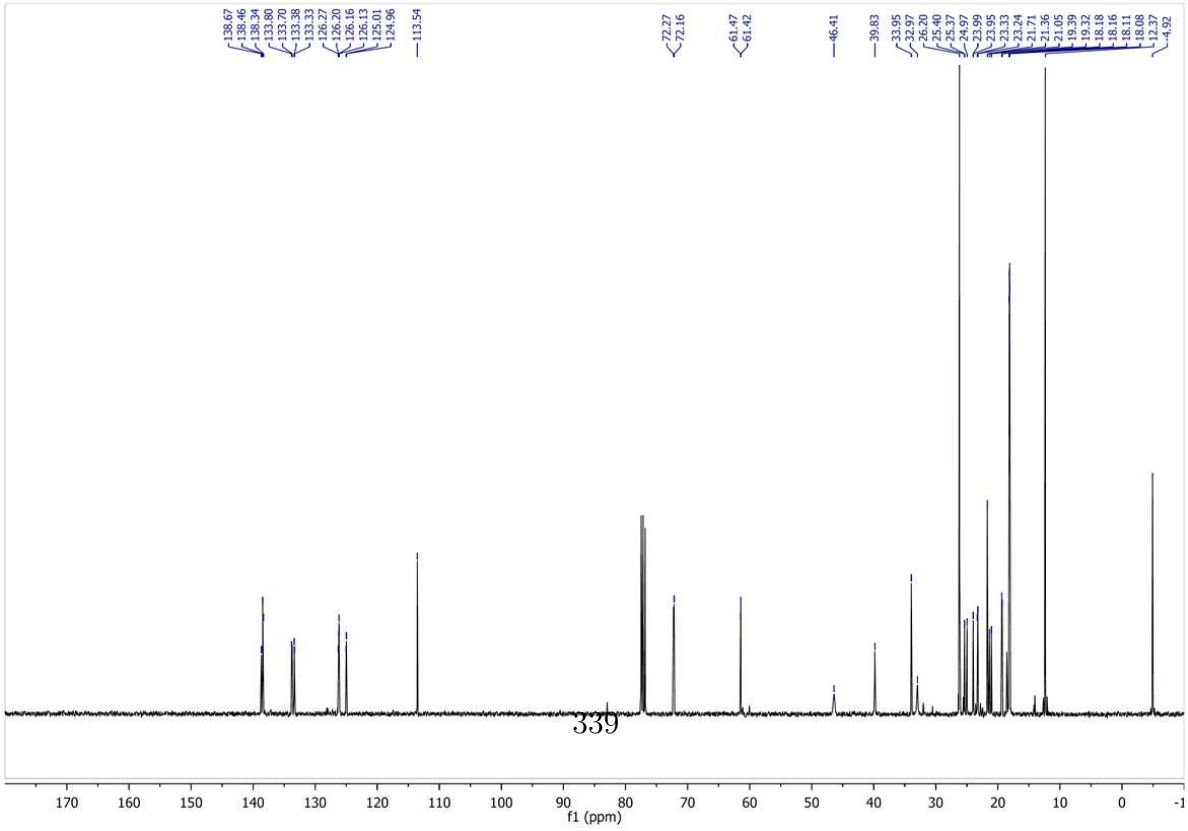
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (dddd, J = 17.0, 10.4, 4.3, 2.2 Hz, 1H, 8), 5.45 (td, J = 4.3, 2.1 Hz, 1H, 7), 5.34 (dq, J = 17.1, 2.1 Hz, 1H, 9-*trans*), 5.15

(tdd, J = 6.2, 2.8, 1.6 Hz, 1H, 19), 5.08 (dt, J = 10.4, 1.8 Hz, 1H, 9-*cis*), 4.24 (ddd, J = 6.2, 3.5, 0.9 Hz, 2H, 20), 2.39 – 1.91 (m, 6H, alkyl-H), 1.66 – 1.60 (m, 9H, 3xCH_3), 1.40 – 1.17 (m, 4H, alkyl-H), 1.14 – 1.06 (m, 3H, TIPS-^{i}Pr-H), 1.05 (m, 18H, TIPS-^{i}Pr-Me), 0.91(0.86) (s, 3H, 10), 0.90 (s, 9H, TBS-^{t}Bu), 0.08(0.07) (s, 6H, TBS-Me) ppm;

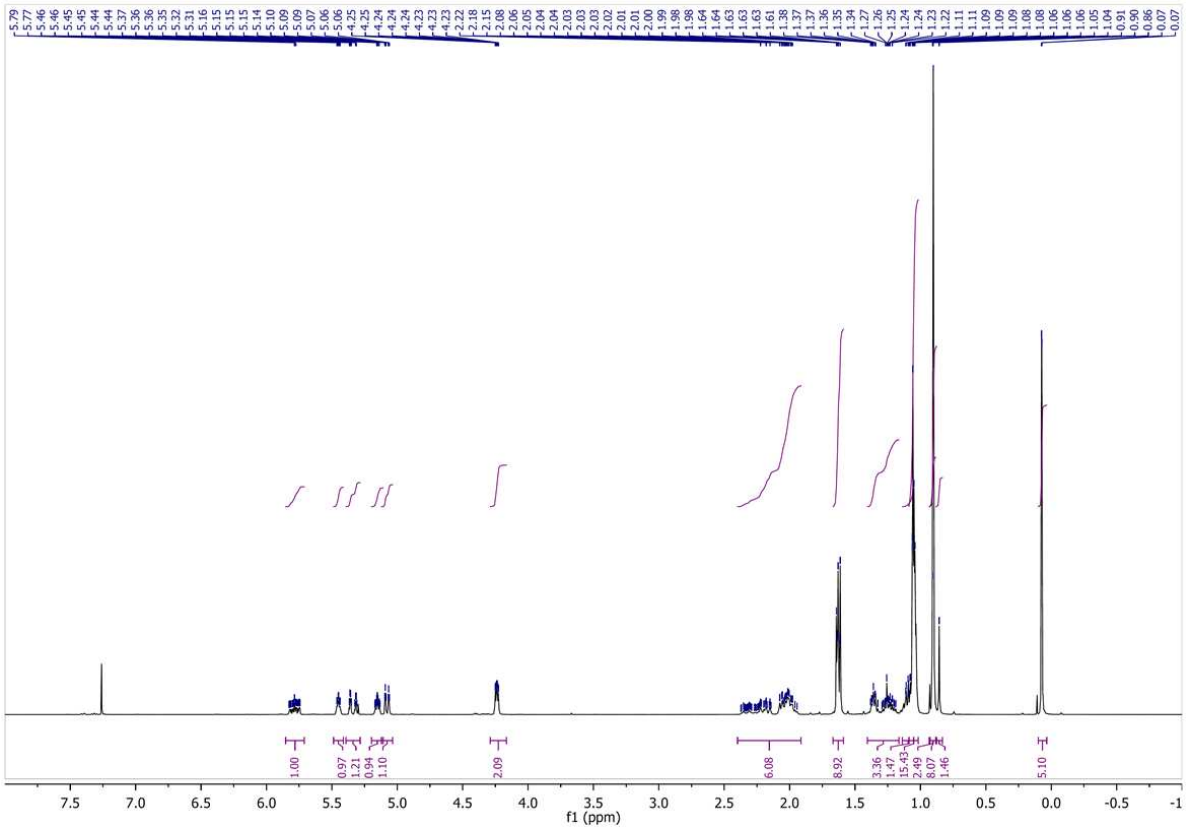
^{13}C NMR (101 MHz, $CDCl_3$): δ 138.5(138.4) 8, 137.8(137.8) 18, 137.6(137.6) 1, 133.8(133.7) 14, 127.76 19, 125.1(125.0) 13, 125.0(124.9) 2, 113.53 9, 72.3(72.2) 7, 60.46 20, 46.4(46.3) (CH_2), 40.0(39.9) (CH_2), 33.94 3, 33.1(33.0) (CH_2), 26.2(26.1) TBS-^{t}Bu, 25.4(25.3) (CH_2), 24.0(23.9) 10, 21.85 CH_3, 21.37 TBS-^{t}Bu(C), 21.06 (CH_2), 19.7(19.6) (CH_3), 18.2(18.1) TIPS-^{i}Pr-Me, 16.8(16.7) CH_3, 12.4 TIPS-^{i}Pr-H, −4.8 TBS-Me ppm;

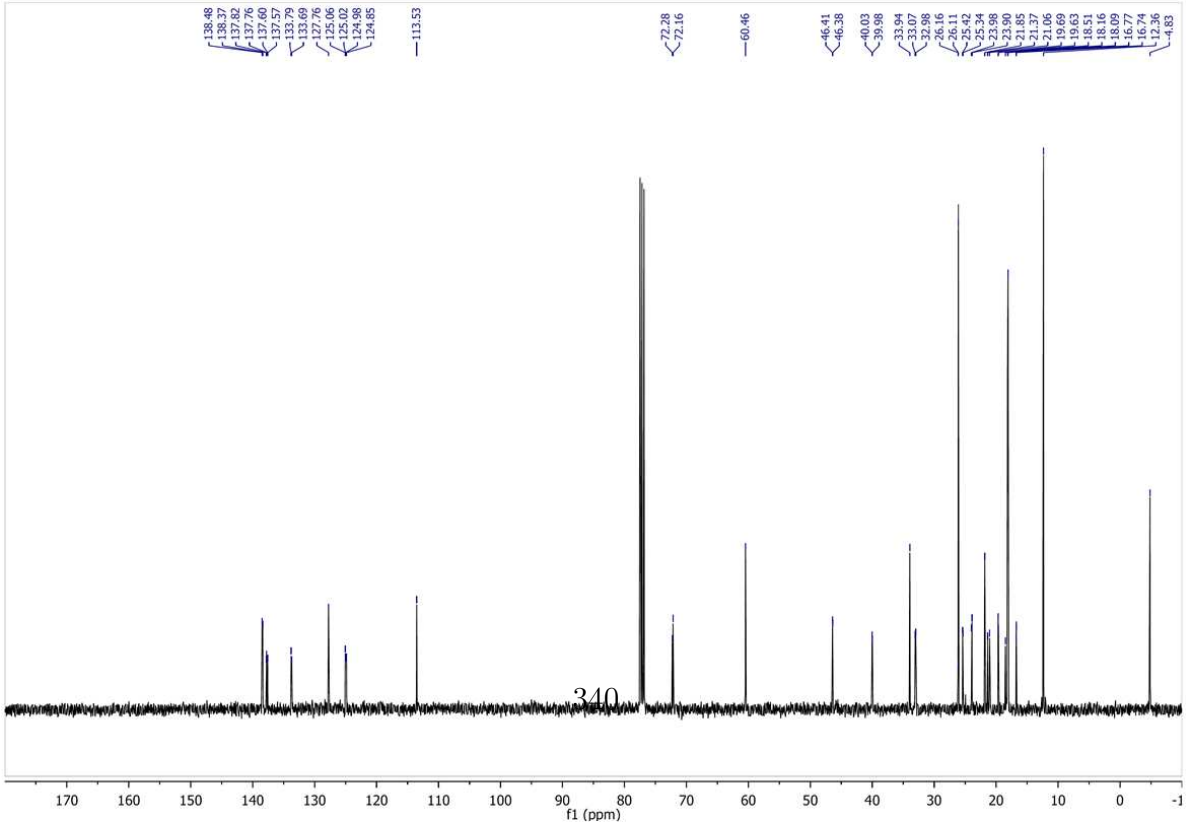
$^{1}H/^{13}C$ NMR (*Z* isomer)



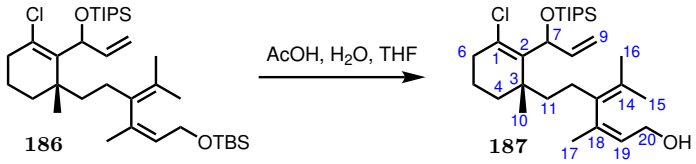


$^{1}H/^{13}C$ NMR (*E* isomer)





5.3.1.48 Allylic alcohol 187



Doubly protected alcohol **186** (578 mg, 0.949 mmol, 1.00 mol equiv), dionised water (4.7 mL) and tetrahydrofuran (4.7 mL) were added to a round bottom flask equipped with a stirrer bar. Glacial acetic acid (14.6 mL) was added and the solution was stirred for 2 days or until the disappearance of the starting material was observed (TLC control). When the reaction was judged to be complete, the reaction was poured into a 250 mL separatory funnel and quenched with saturated $NaHCO_{3(aq)}$ until gas evolution ceased. The aqueous phase was extracted (3x) with dichloromethane, the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product containing acetic acid was purified by flash chromatography (0–30% Et_2O/*n*-pentane, silica column) and dried under an oil pump (to remove traces of acetic acid) to furnish the desired product as a pale yellow oil (375 mg, 0.758 mmol, 80% yield).

Z-isomer data

R_f = 0.12 (10% Et_2O/*n*-pentane, stains purple with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (dddd, J = 16.8, 10.4, 4.4, 1.6 Hz, 1H, 8), 5.50 – 5.41 (m, 2H, 7/19), 5.34 (dt, J = 17.1, 1.9 Hz, 1H, 9-*trans*), 5.08 (dt, J = 10.4, 1.9 Hz, 1H, 9-*cis*), 3.93 (ddd, J = 7.1, 4.4, 1.2 Hz, 2H, 20), 2.38 – 1.85 (m, 6H, alkyl-H), 1.75(1.74) (s, 3H, CH_3), 1.68(1.66) (s, 3H, CH_3), 1.55(1.54) (s, 3H,

CH_3), 1.40 – 1.33 (m, 2H, alkyl-H), 1.29 – 1.15 (m, 2H, alkyl-H), 1.14 – 1.06 (m, 3H, TIPS-^{i}Pr-H), 1.08 – 1.02 (m, 18H, TIPS-^{i}Pr-Me), 0.92(0.88) (s, 3H, 10) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 138.4(138.3) 8, 133.8(133.7), 133.2(133.1), 126.5(126.3), 125.3(125.2) 19, 124.8, 113.6 9, 72.2(72.1) 7, 61.1 20, 46.3 (CH_2), 39.7 (CH_2), 33.9 3, 33.0 (CH_2), 25.3 (CH_2), 24.1 10, 23.3 CH_3, 21.7 CH_3, 21.3(21.0) (CH_2), 19.4(19.3) CH_3, 18.2(18.1) TIPS-^{i}Pr-Me 12.3 TIPS-^{i}Pr-H ppm;

FT-IR thin film, neat (ATR): 3344, 2941, 2886, 2360, 1464, 1130, 1029, 1014, 883 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{29}H_{51}O_2{}^{35}Cl^{23}Na^{28}Si$, $[M+Na]^{+\bullet}$: 517.32391 found 517.32397 (Δ = 0.13 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 5.6° (c = 1.0, CH_2Cl_2), based on a sample of 90% *ee*;

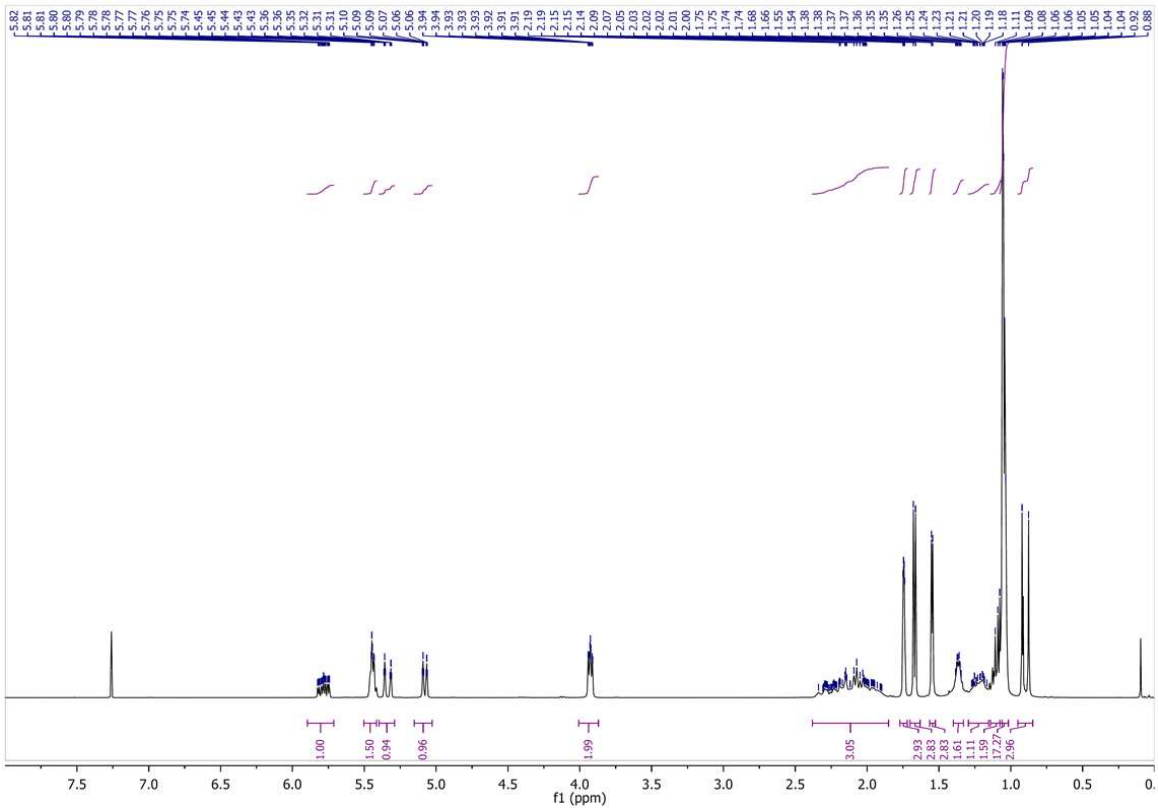
E-isomer NMR data

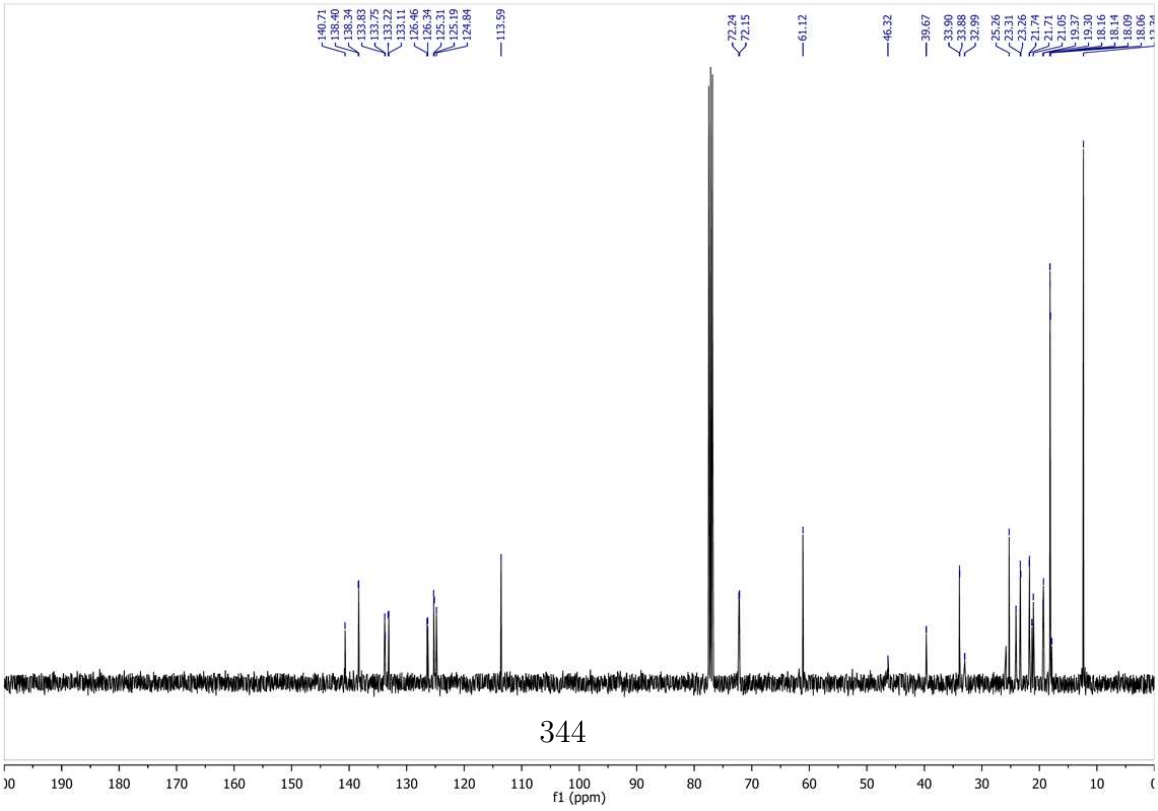
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (dddd, J = 17.4, 10.4, 4.4, 2.9 Hz, 1H, 8), 5.51 – 5.42 (m, 1H, 7), 5.33 (dq, J = 17.4, 1.7 Hz, 1H, 9-*trans*), 5.25 (tt, J = 6.8, 1.5 Hz, 1H, 19), 5.07 (dt, J = 10.4, 1.9 Hz, 1H, 9-*cis*), 4.20 (dd, J = 6.8, 5.6 Hz, 2H, 20), 2.38 – 1.93 (m, 6H, alkyl-H), 1.69 (dd, J = 2.8, 1.4 Hz, 3H, CH_3), 1.65(1.63) (s, 3H, CH_3), 1.61 (d, J = 2.0 Hz, 3H, CH_3), 1.40 – 1.33 (m, 2H, alkyl-H), 1.23 (dtd, J = 12.7, 11.2, 10.6, 6.0 Hz, 2H, alkyl-H), 1.14 – 1.06 (m, 3H, TIPS-^{i}Pr-H), 1.07 – 1.02 (m, 18H, TIPS-^{i}Pr-Me), 0.91(0.86) (s, 3H, 10) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.6(140.5), 138.4(138.3) 8, 137.6(137.5), 133.8(133.7), 126.4(126.3) 19, 125.2(125.1), 124.9, 113.5 9, 72.2(72.1) 7, 59.63(59.60) 20, 46.4 (CH_2), 39.8(39.7) (CH_2), 33.92(33.8)9 3, 33.0(32.9) (CH_2), 25.43(25.36) (CH_2), 24.1(24.0) 10, 21.84(21.81) CH_3, 21.3(21.1) (CH_2), 19.7(19.6) CH_3,

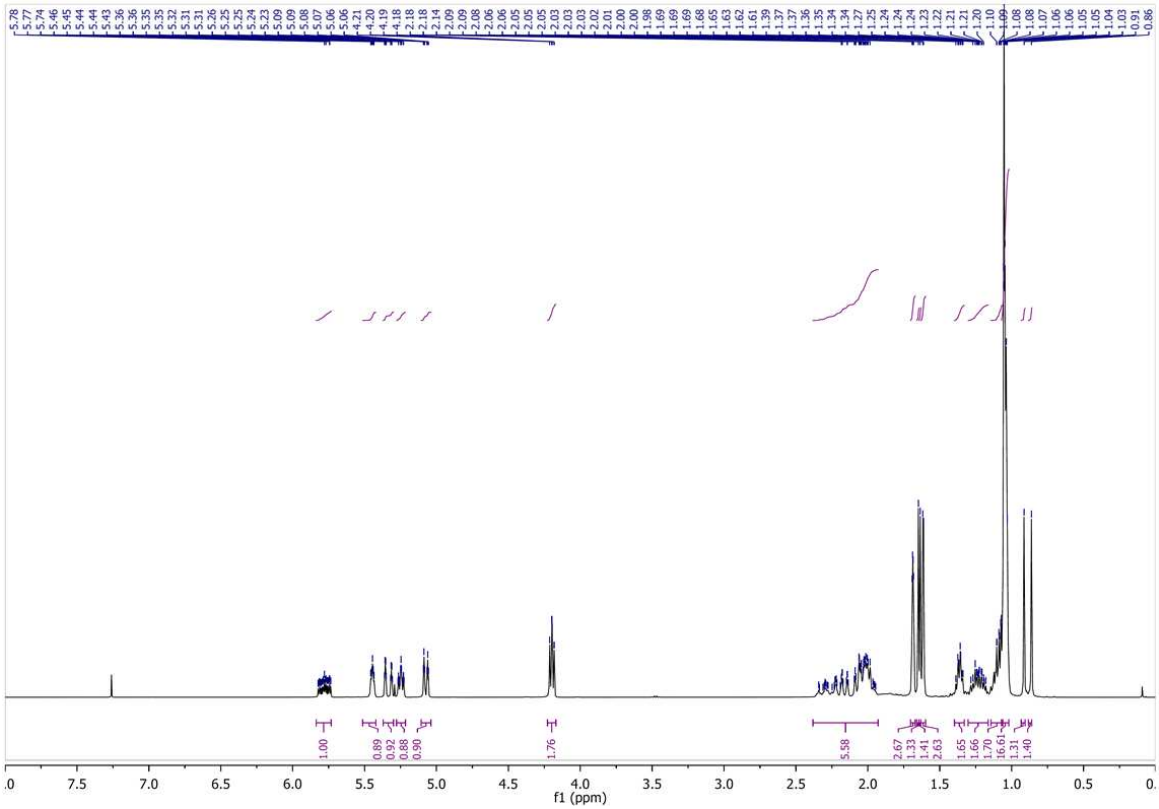
18.14(18.12)(18.07)(18.04) TIPS-^{i}Pr-Me, 16.7 CH_3, 12.3 TIPS-^{i}Pr-H ppm;

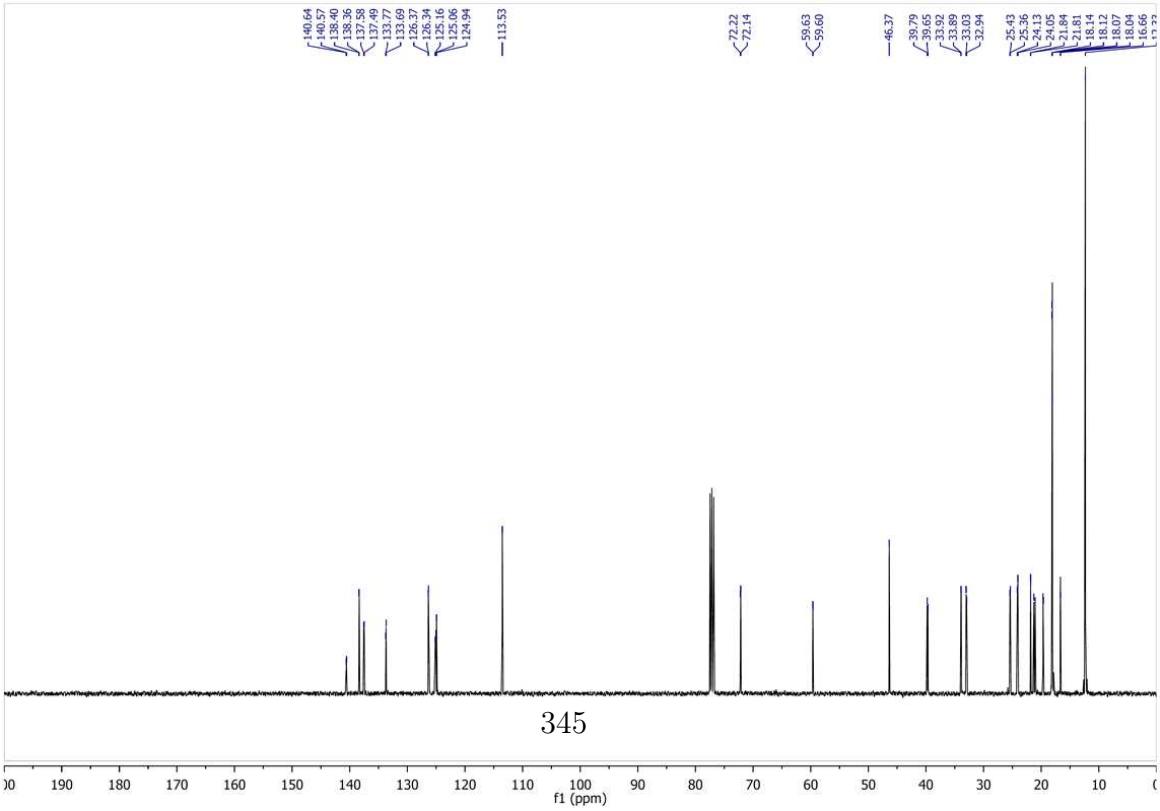
$^{1}H/^{13}C$ NMR (*Z* isomer)



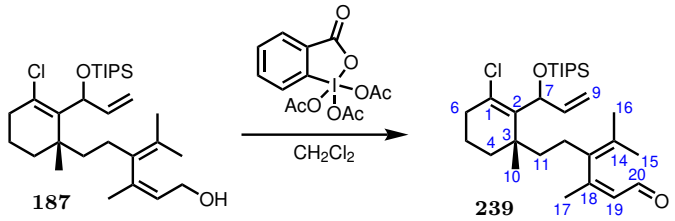


$^{1}H/^{13}C$ NMR (*E* isomer)





5.3.1.49 Allylic aldehyde 239



Allylic alcohol **187** (122 mg, 0.19 mmol, 1.0 mol equiv) was dissolved in dry CH_2Cl_2 (1.3 mL) in a 7 mL vial, equipped with a stirrer bar. Dess-Martin periodinane (96 mg, 0.23 mmol, 1.2 mol equiv) was added and the mixture stirred vigorously until the reaction was judged complete (TLC control, approx. 10 – 30 min). The reaction was quenched with 1.3 mL each of 10% $Na_2S_2O_3$ and saturated $NaHCO_{3(aq)}$. The organic layer was extracted (3x) with Et_2O, dried (Na_2SO_4) and concentrated *in vacuo*. The product is shown to be unstable and decomposes under ambient conditions (an additional spot forms with R_f = 0.74 30% Et_2O, stains pink with *p*-anisaldehyde stain). The crude product is purified by flash chromatography (0–20% Et_2O/*n*-pentane, silica column) to give the title compound as a clear oil (58 mg, 0.12 mmol, 65% yield).

R_f = 0.53 (30% Et_2O/*n*-pentane, stains purple with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (dd, J = 8.3, 2.2 Hz, 1H, 20), 5.95 – 5.88 (m, 1H, 19), 5.86 – 5.70 (m, 1H, 8), 5.45 (dq, J = 6.1, 2.2 Hz, 1H, 8), 5.33 (ddd, J = 17.1, 4.0, 2.1 Hz, 1H, 9-*trans*), 5.08 (ddd, J = 10.4, 3.1, 1.5 Hz, 1H, 9-*cis*), 2.40 – 2.02 (m, 6H, alkyl-H), 1.99(1.98) (s, 3H, CH_3), 1.75(1.73) (s, 3H, CH_3), 1.67(1.65) (s, 3H, CH_3), 1.61(1.60) (s, 3H, CH_3), 1.35(1.34) (s, 3H, CH_3), 1.45 – 1.19 (m, 4H, alkyl-H), 1.17 – 1.00 (m, 21H, TIPS-^{i}Pr-Me/TIPS-^{i}Pr-H), 0.98

– 0.86 (m, 6H, 10) ppm;

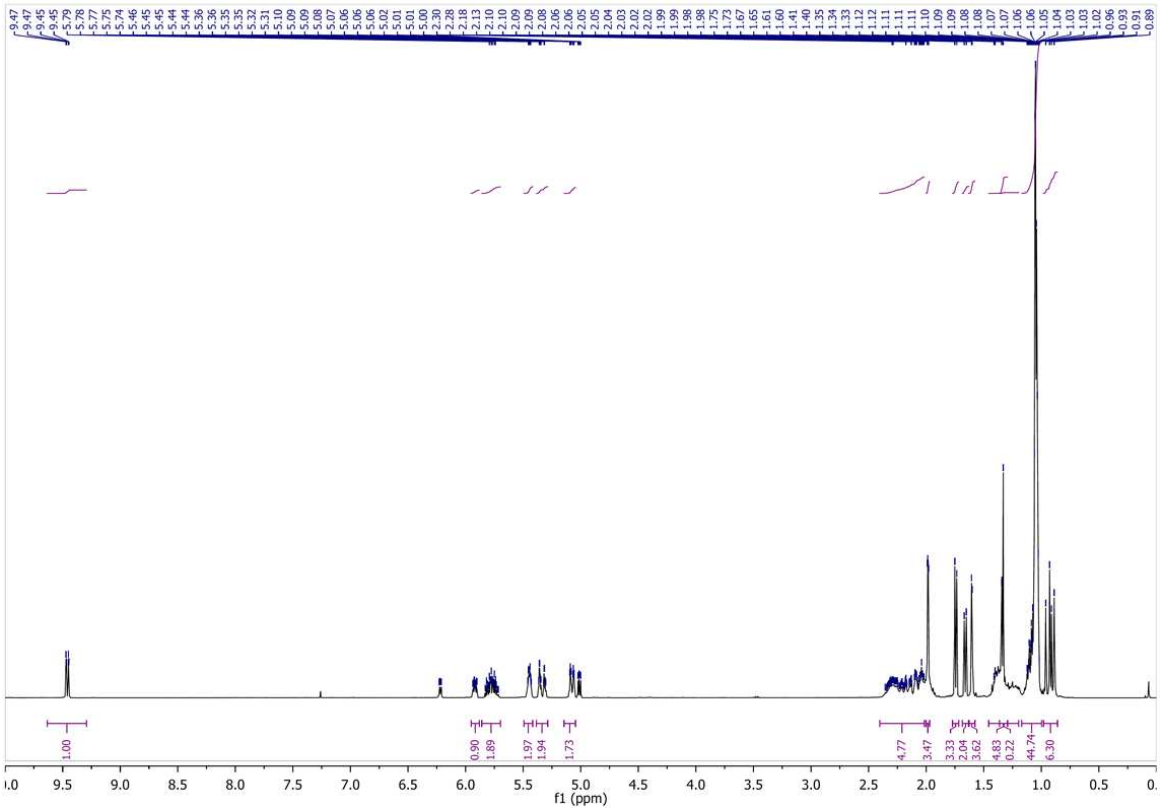
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1(194.0) 20, 138.4(138.3)(138.3)(138.2) 8, 133.9(133.8), 131.8(131.7), 129.6(129.5) 19, 128.5, 124.7(124.5), 113.7(113.6) 9, 72.2(72.1) 7, 46.2(46.1) (CH_2), 40.9(40.4) (CH_2), 39.3 (CH_2), 34.3(34.2)(33.9) 3, 33.0 (CH_2), 25.7(25.6) (CH_2), 25.6(25.5) CH_3, 24.4 CH_3, 24.2(24.0) CH_3, 22.5(22.4)(22.2) CH_3, 21.3(21.1)(21.0) (CH_2), 19.7(19.6) CH_3, 18.14(18.07) TIPS-^{i}Pr-Me, 17.0(16.9) CH_3, 12.3 TIPS-^{i}Pr-H ppm;

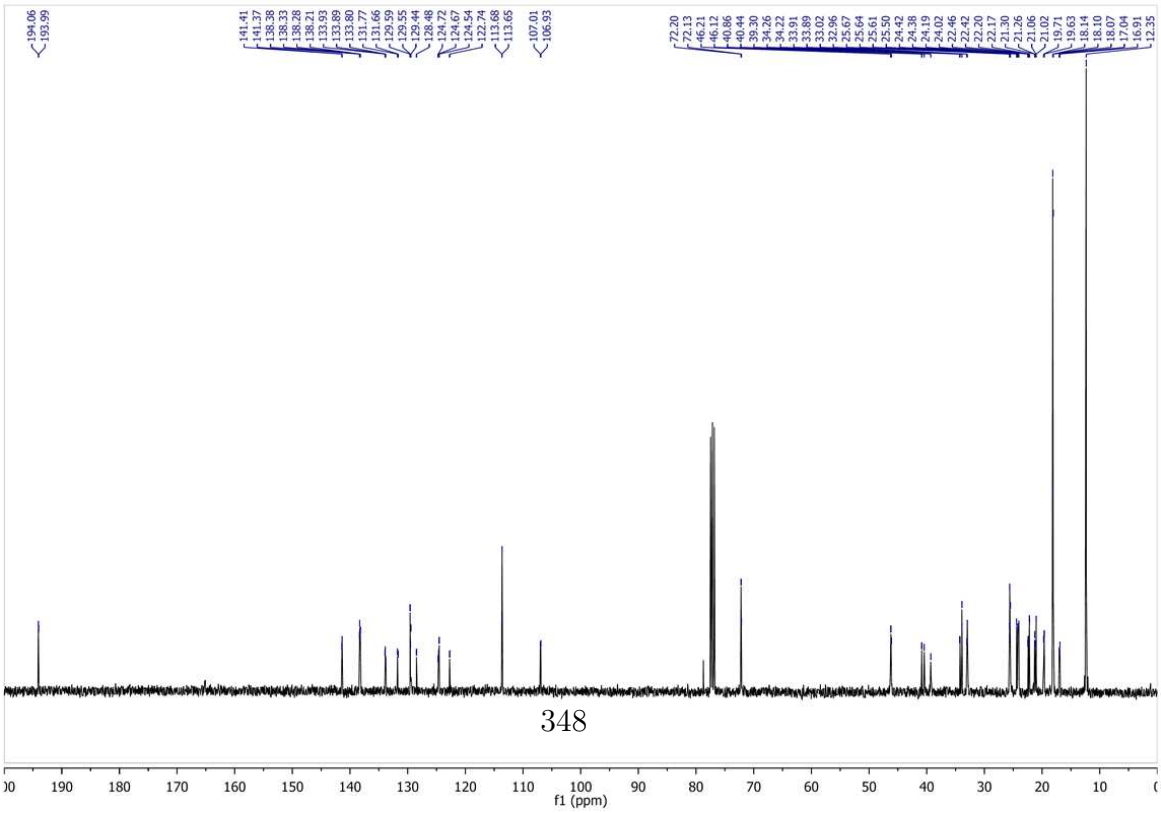
FT-IR thin film, neat (ATR): 2942, 2866, 1681, 1463, 1245, 1130, 1015, 882, 683 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{29}H_{49}O_2{}^{35}Cl^{23}Na^{28}Si$, $[M+Na]^{+\bullet}$: 515.30826 found 515.30848 (Δ = 0.44 ppm);

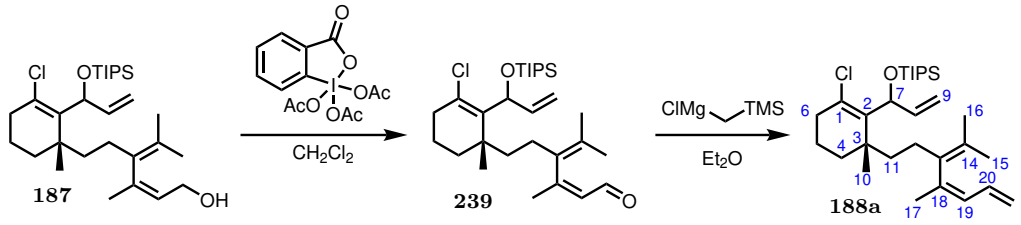
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 8.9° (c = 1.0, CH_2Cl_2), based on a sample of 90% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.50 Triene (from allylic alcohol 187) 188a



The oxidation step of **187** was carried out in an analogous fashion to the preparation of **239** (0.083 mmol alcohol). The crude aldehyde was transferred to a 7 mL vial, equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were then performed and dry Et_2O (0.40 mL) was added. ((Trimethylsilyl)methyl)magnesium chloride (0.18 mL of a 1.9M solution in Et_2O, 0.34 mmol, 4.1 mol equiv) was added dropwise. When the reaction was judged complete by TLC, the solution was cooled in an ice-bath and 3 drops of saturated $NH_4Cl_{(aq)}$ solution were added. After diluting the mixture to twice its volume with Et_2O, 5 drops of concentrated $HCl_{(aq)}$ and 0.4 mL 1M $HCl_{(aq)}$ were added and the biphasic mixture was stirred at room temperature for 1 hour. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–2% Et_2O/*n*-pentane, silica column) to give the title compound as a clear oil (13.7 mg, 0.028 mmol, 34% yield over 2 steps).

R_f = 0.74 (10% Et_2O/*n*-pentane, stains purple with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 (dtd, J = 17.0, 10.5, 3.3 Hz, 1H, 20), 5.88 (ddd, J = 10.9, 7.5, 1.5 Hz, 1H, 19), 5.78 (dddd, J = 17.1, 10.6, 9.2, 4.3 Hz, 1H, 8), 5.45 (ddd, J = 6.0, 4.1, 2.0 Hz, 1H, 7), 5.33 (ddt, J = 17.1, 4.9, 1.9 Hz,

1H, 9-*trans*), 5.11 – 5.02 (m, 2H, 9-*cis*/21), 4.91 – 4.85 (m, 1H, 21), 2.35 – 1.89 (m, 6H, alkyl-H), 1.78(1.77) (s, 3H, CH_3), 1.70(1.69) (s, 3H, CH_3), 1.53(1.52) (s, 3H, CH_3), 1.46 – 1.15 (m, 4H, alkyl-H), 1.16 – 1.07 (m, 3H, TIPS-^{i}Pr-H), 1.05 (m, 18H, TIPS-^{i}Pr-Me), 0.91(0.87) (s, 3H, 10) ppm;

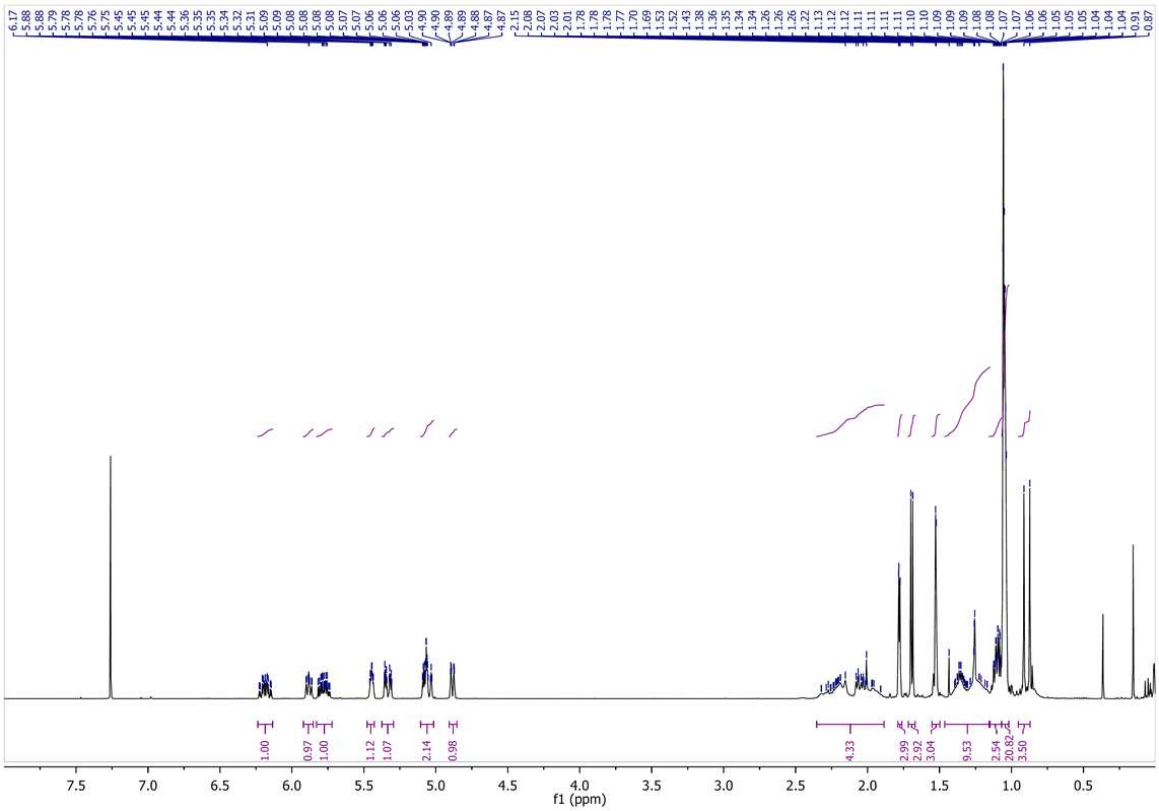
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 138.4(138.3) 8, 135.5 20, 133.8, 133.5(133.4), 127.7(127.6) 19, 126.3(126.2), 124.9, 114.3 21, 113.5 9, 72.2 7, 46.4 (CH_2), 39.6(39.4) (CH_2), 33.9 3, 32.9 (CH_2), 25.3 (CH_2), 24.0 10, 23.3 CH_3, 21.7 CH_3, 21.3 CH_3, 21.1 (CH_2), 19.5(19.4) CH_3, 18.2(18.1) TIPS-^{i}Pr-Me, 12.4 TIPS-^{i}Pr-H ppm;

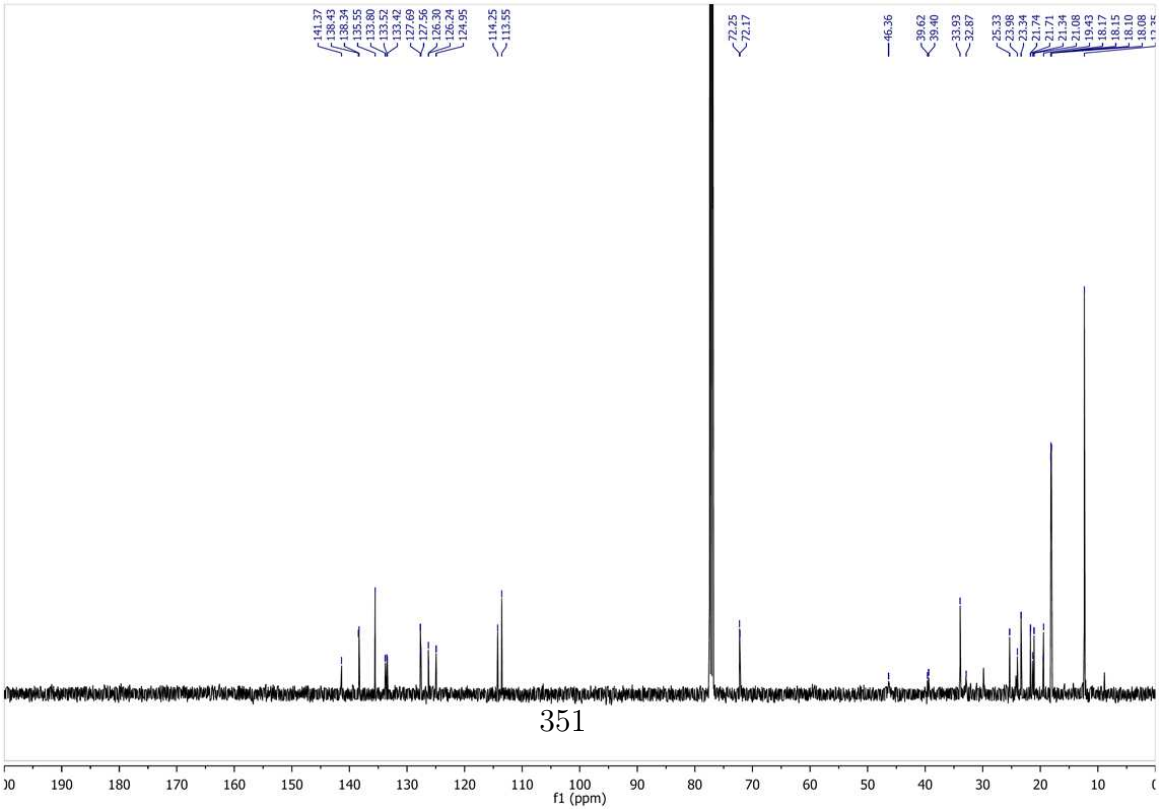
FT-IR thin film, neat (ATR): 2925, 2866, 2359, 1638, 1463, 1130, 1030, 895, 683 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{30}H_{52}O^{35}Cl^{28}Si$, $[M+H]^{+\bullet}$: 491.34705 found 491.34702 (Δ = -0.06 ppm);

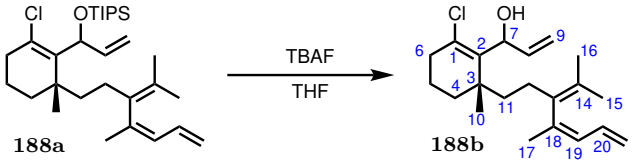
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 5.4° (c = 1.0, CH_2Cl_2), based on a sample of 90% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.51 Free alcohol 188b



Triene **188a** (11.3 mg, 0.023 mmol, 1.0 mol equiv) and THF (0.23 mL) were added to a flame dried 7 mL vial, equipped with a rubber septum and stirrer bar. Tetrabutylammonium fluoride (44 μL of a 1M solution in THF, 0.044 mmol, 1.9 mol equiv) was added and the reaction stirred for 2 hours. The reaction was quenched with saturated $NaHCO_{3(aq)}$ solution and the biphasic mixture was extracted (3x) Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–30% Et_2O/*n*-pentane, silica column) to give the title compound as a 1:1 mixture of diastereomers (7.4 mg clear oil, 0.022 mmol, quantitative yield).

R_f = 0.43, 0.51 (30% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 (ddt, J = 17.0, 13.2, 10.4 Hz, 1H, 20), 5.93 – 5.79 (m, 2H, 19/8), 5.38 (d, J = 4.5 Hz, 1H, 7), 5.31 (ddt, J = 17.1, 8.7, 1.6 Hz, 1H, 9-*trans*), 5.16 (ddt, J = 10.5, 5.0, 1.6 Hz, 1H, 9-*cis*), 5.05 (ddd, J = 17.0, 5.3, 2.0 Hz, 1H, 21-*trans*), 4.89 (ddd, J = 10.4, 4.9, 2.0 Hz, 1H, 21-*cis*), 2.31 – 1.88 (m, 6H, alkyl-H), 1.79(1.77) (d, J = 1.3 Hz, 3H, 17), 1.69(1.70) (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.45 – 1.36 (m, 2H, alkyl-H), 1.32 – 1.14 (m, 2H, alkyl-H), 0.93(0.89) (s, 3H, 10) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.4 18, 137.5 19, 135.5 12, 133.3 1, 132.3 2, 127.6 8, 127.2 13, 126.4 14, 114.9(114.7) 9, 114.3(114.2) 21, 71.9(71.8) 7, 46.5(46.4)

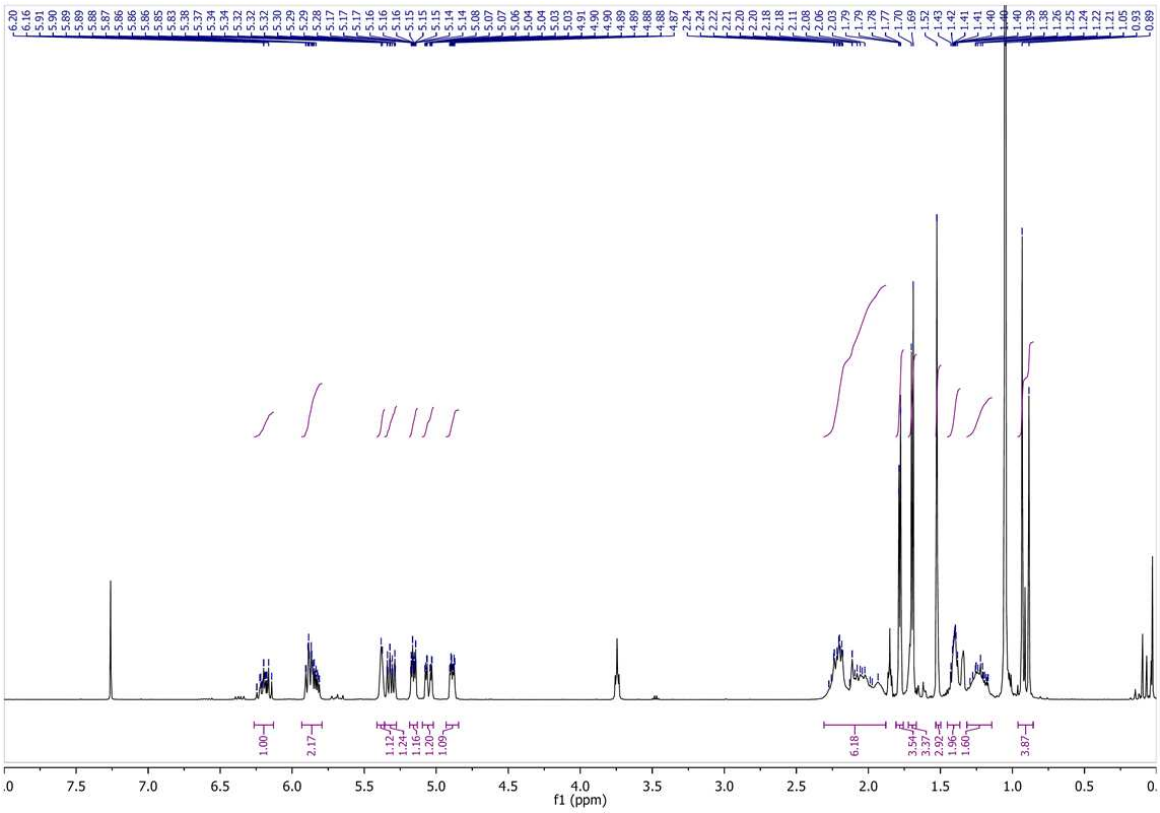
(CH_2), 39.3 (CH_2), 33.8 3, 32.9 (CH_2), 25.4(25.3) (CH_2), 24.0 10, 23.36(23.31) 17, 21.69 (CH_2), 21.68 CH_3, 19.5(19.4) CH_3, ppm;

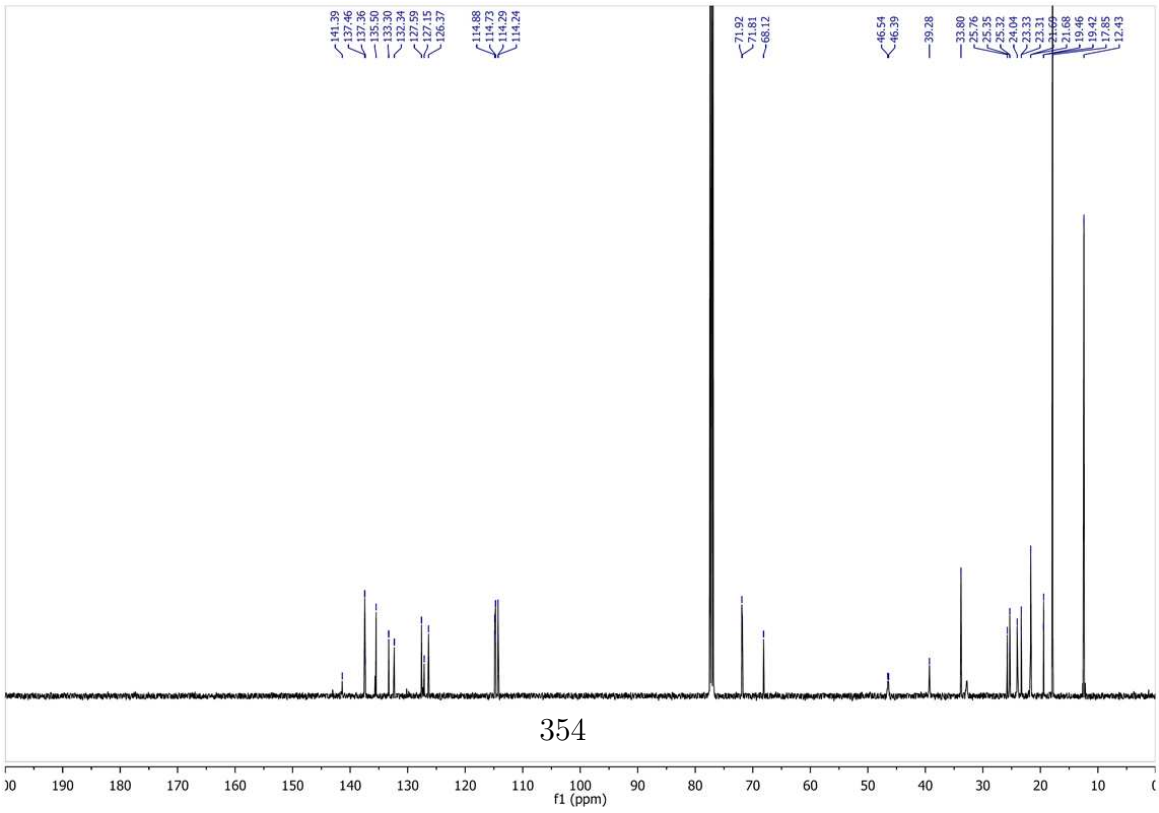
FT-IR thin film, neat (ATR): 3393, 2925, 1432, 1375, 995, 897 cm^{-1};

HRMS (ESI^+): calculated for $C_{21}H_{31}O^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 357.19556 found 357.19537 (Δ = -0.53 ppm);

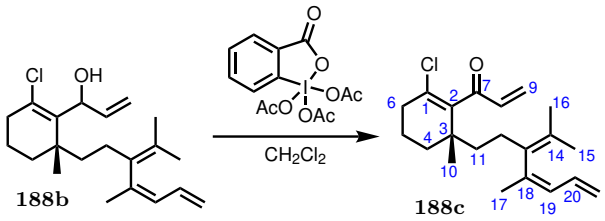
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 17° (c = 0.44, CH_2Cl_2), based on a sample of 90% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.52 Ketone 188c



Allylic alcohol **188b** (29 mg 77% pure by ^{1}H NMR , 0.067 mmol, 1.0 mol equiv) was dissolved in dry CH_2Cl_2 (2.2 mL) in a flame dried 22 mL vial, equipped with a stirrer bar. Dess-Martin periodinane (34 mg, 0.080 mmol, 1.2 mol equiv) was added and the mixture stirred vigorously until the reaction was judged complete (TLC control, approx. 10 – 30 min). The reaction was quenched with 1 mL each of saturated $Na_2S_2O_3$ and saturated $NaHCO_{3(aq)}$. The organic layer was extracted (3x) with Et_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product is purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a cloudy oil (22 mg, 0.065 mmol, quantitative yield).

R_f = 0.43 (10% Et_2O/*n*-pentane, stains green with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.50 (dd, J = 17.5, 10.4 Hz, 1H, 8), 6.19 (d, J = 16.8 Hz, 1H, 9-*trans*), 6.25 – 6.14 (m, 1H, 20), 5.95 (d, J = 10.4 Hz, 1H, 9-*cis*), 5.90 (d, J = 10.4 Hz, 1H, 19), 5.06 (dd, J = 17.1, 2.0 Hz, 1H, 21-*trans*), 4.90 (dd, J = 10.2, 2.0 Hz, 1H, 21-*cis*), 2.35 – 1.88 (m, 6H, alkyl-H), 1.79 (s, 3H, 17), 1.71 (s, 3H, 16), 1.54 (s, 3H, 15), 1.47 (q, J = 5.8, 5.0 Hz, 2H, alkyl-H), 1.38 – 1.19 (m, 2H, alkyl-H), 0.98 (s, 3H, 10) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9 7, 141.2 18, 135.8 8, 135.4 20, 133.4 1, 133.0 13, 130.9 2, 130.7 9, 127.7 19, 126.6 14, 114.5 21, 46.3(bs) (CH_2), 39.3(bs) (CH_2), 34.0 3, 32.2(bs) (CH_2), 25.9 (CH_2), 25.2 (CH_2), 24.1 10, 23.3 17, 21.7 16,

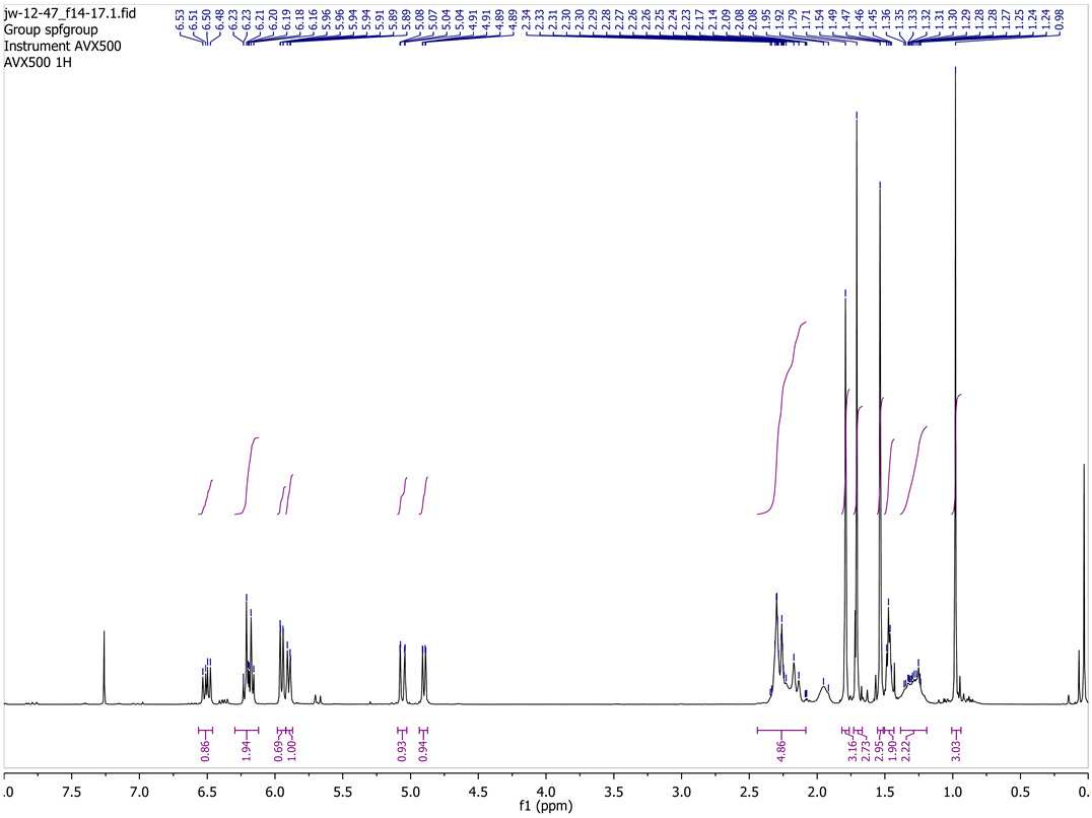
19.5 15 ppm;

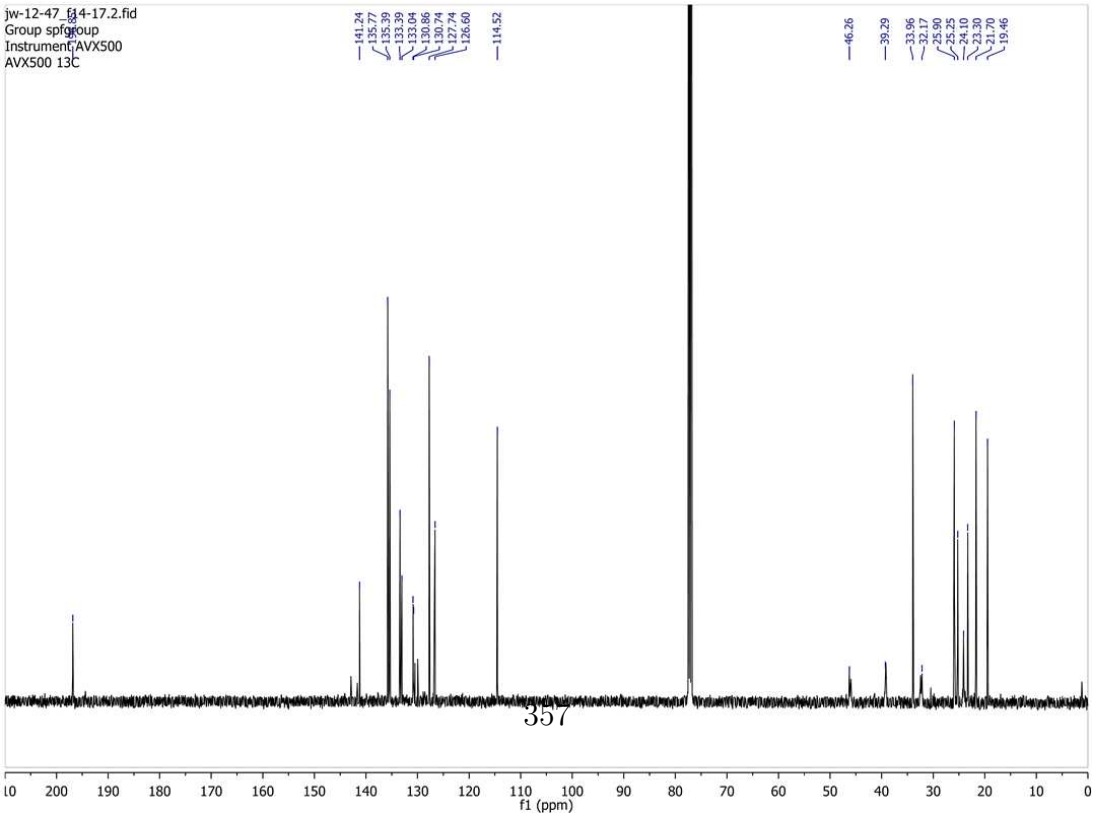
FT-IR thin film, neat (ATR): 2957, 2924, 2843, 1666, 1401 cm^{-1};

HRMS (APCI$^+$): calculated for $C_{21}H_{30}O^{35}Cl$, $[M+H]^{+\bullet}$: 333.19797 found 333.19809 (Δ = 0.36 ppm);

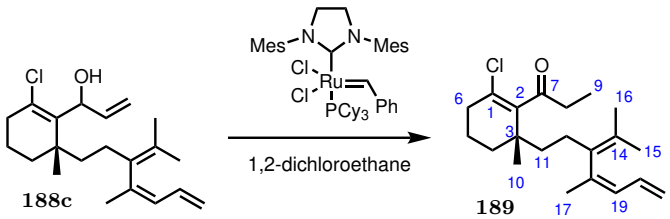
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -1.1^\circ$ (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


jw-12-47_f14-17.1.fid
Group spfgroup
Instrument AVX500
AVX500 1H
f1 (ppm)


jw-12-47_f14-17.2.fid
Group spfgroup
Instrument AVX500
AVX500 13C
f1 (ppm)

5.3.1.53 Transfer hydrogenation product 189



Allylic alcohol **188c** (0.046 mmol quantity determined by NMR, 1.0 mol equiv) and dry 1,2-dichloroethane (9.2 mL) were added to a flame dried round bottom flask equipped with a rubber septum and stirrer bar. Grubbs Second Generation Catalyst (25 μL of a freshly prepared 0.2M solution in dichloromethane, 0.0046 mmol, 0.10 mol equiv) was added in one portion, minimising exposure to the atmosphere. The flask was sealed with parafilm and heated to 80 °C. After stirring for 26 hours, starting material still remained but the reaction had stalled. After quenching with 0.4 mL 0.2M ethylvinyl ether in dichloromethane, the residue was concentrated and purified by preparative TLC (10% Et_2O/*n*-pentane) to furnish the desired product (1.0 mg, 0.0030 mmol, 6% yield).

R_f = 0.63 (30% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 (dt, J = 17.1, 10.3 Hz, 1H, 20), 5.93 – 5.86 (m, 1H, 19), 5.06 (dd, J = 17.1, 2.1 Hz, 1H, 21-*trans*), 4.89 (dd, J = 10.3, 2.1 Hz, 1H, 21-*cis*), 2.72 (q, J = 7.2 Hz, 2H, 8), 2.40 – 2.09 (m, 6H, alkyl-H), 1.79 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.47 – 1.26 (m, 4H, alkyl-H), 1.10 (t, J = 7.3 Hz, 3H, 9), 0.94 (s, 3H, 10) ppm;

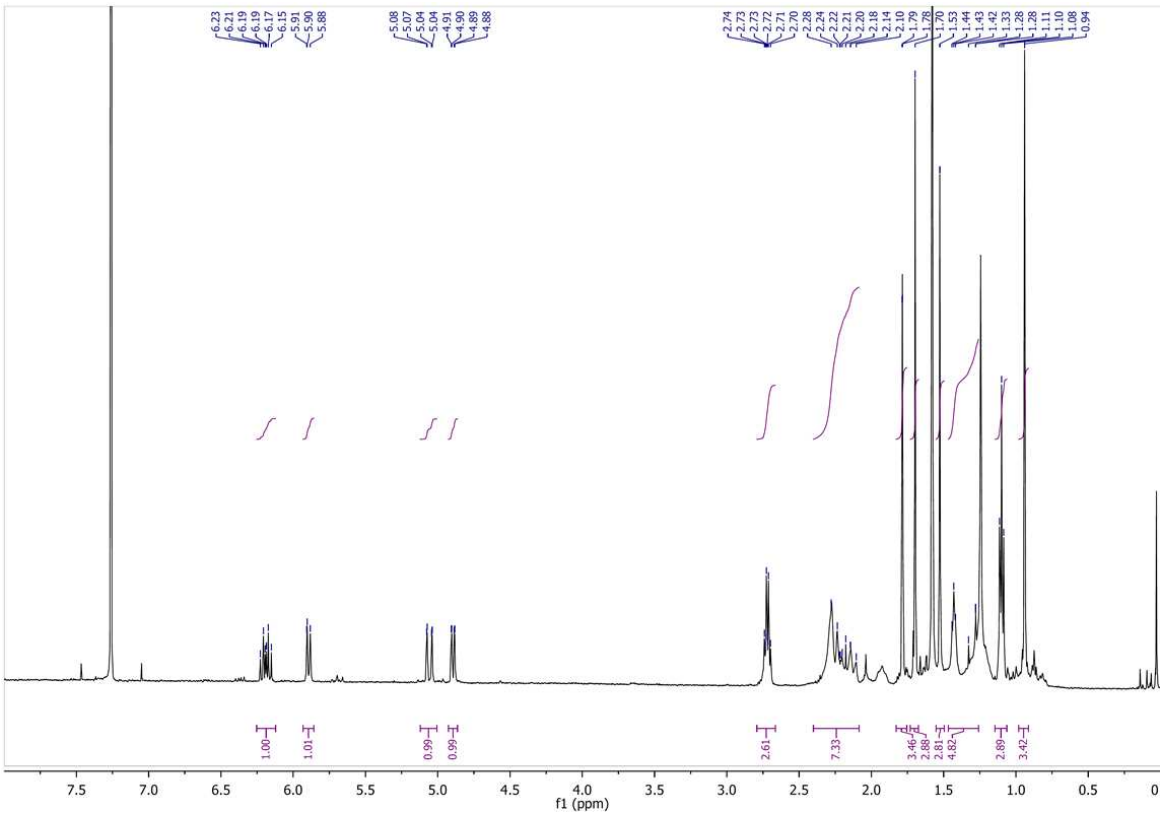
^{13}C NMR (126 MHz, $CDCl_3$): δ 206.7 7, 141.3, 135.4 20, 134.8, 133.0, 130.4, 127.6 19, 126.6, 114.5 21, 46.5(46.3) (CH_2), 39.1 (CH_2), 35.8 8, 33.8 3, 32.3(32.1) (CH_2), 25.5 (CH_2), 25.2 (CH_2), 23.9 10, 23.3 CH_3, 21.7 CH_3, 19.5 CH_3, 8.0 9 ppm;

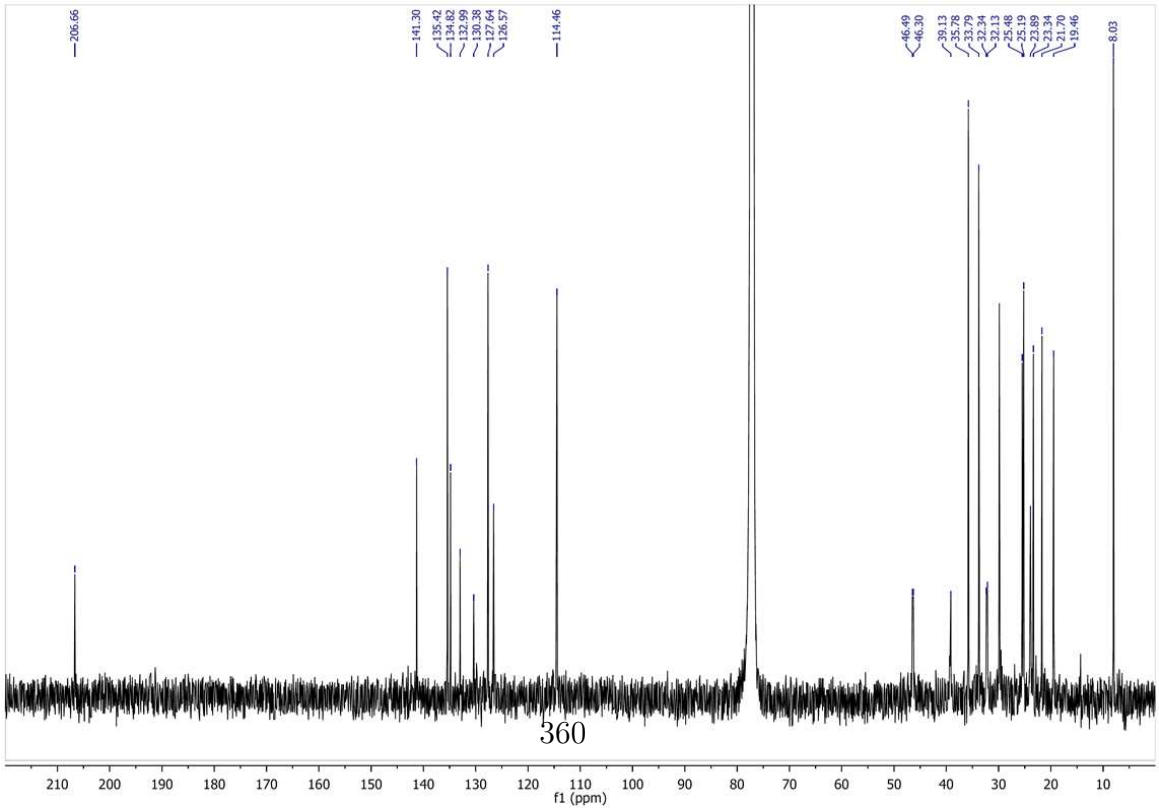
FT-IR thin film, neat (ATR): 2923, 2361, 2341, 1699, 1458, 1378 cm^{-1};

HRMS (ESI^+): calculated for $C_{21}H_{32}O^{35}Cl$, $[M+H]^{+\bullet}$: 335.21362 found 335.21387 (Δ = 0.74 ppm);

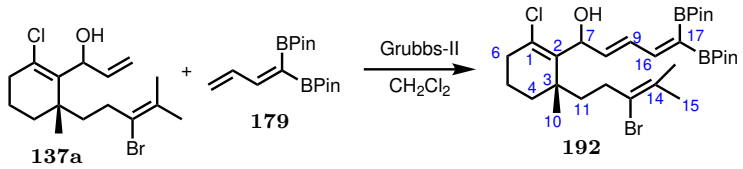
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 3.2° (c = 0.80, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR


6.23
6.21
6.19
6.17
6.15
5.91
5.90
5.88
5.08
5.07
5.04
5.04
4.91
4.90
4.89
4.88
2.74
2.73
2.73
2.72
2.71
2.70
2.28
2.24
2.22
2.21
2.20
2.18
2.14
2.10
1.79
1.78
1.70
1.53
1.44
1.43
1.42
1.33
1.28
1.28
1.11
1.10
1.08
0.94
1.00
1.01
0.99
0.99
2.61
7.33
3.46
2.88
2.81
4.82
2.89
3.42
f1 (ppm)


206.66
141.30
135.42
134.82
132.99
130.38
127.64
126.57
114.46
46.49
46.30
39.13
35.78
33.79
32.34
32.13
25.48
25.19
23.89
23.34
21.70
19.46
8.03
f1 (ppm)

5.3.1.54 diBPin alcohol 192



Alcohol **137a** (1.337 g, 4.18 mmol, 1.0 mol equiv) and diBPin[83] **179** (1.79 g, 5.85 mmol, 1.4 mol equiv) were added to a 100 mL flask equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were then performed. CH_2Cl_2 (21 mL) was added after which Grubbs catalyst 2nd generation (355 mg, 0.418 mmol, 0.10 mol equiv) was added in one portion and the reaction stirred at room temperature. When the reaction was deemed complete by TLC (approx. 24 hours), the reaction mixture was loaded directly onto celite and the product purified by flash chromatography (0–30% Et_2O/*n*-pentane, silica column) to give the title compound as an unstable, bright yellow oil (1.809 g, 2.44 mmol, 58% yield) (1:1 inseparable mixture of diastereomers).

R_f = 0.18 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 11.0 Hz, 1H, 16), 6.84 – 6.72 (m, 1H, 9), 5.94 (dd, J = 15.2, 5.5 Hz, 1H, 8), 5.52 – 5.44 (m, 1H, 7), 2.49 – 2.39 (m, 2H, alkyl-H), 2.36 – 1.96 (m, 4H, alkyl-H), 1.84(1.83) (s, 3H, CH_3), 1.74(1.73) (s, 3H, CH_3), 1.64 (bs, 1H, OH), 1.57 – 1.37 (m, 4H alkyl-H), 1.30(1.30) (s, 12H, BPin-CH_3), 1.24(1.24) (s, 12H, BPin-CH_3), 0.95(0.90) (s, 3H, 10) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.8(156.7) 9, 138.7 8, 132.5(132.4) 1, 131.6(131.5) 9, 130.0(129.9) 14, 127.1(127.0) 2, 121.8(121.7) 13, 83.5(83.4) C-B, 83.2(83.1) C-B, 71.5(71.3) 7, 46.5(46.4) (CH_2), 39.9(39.4) (CH_2), 33.6(33.5) 3,

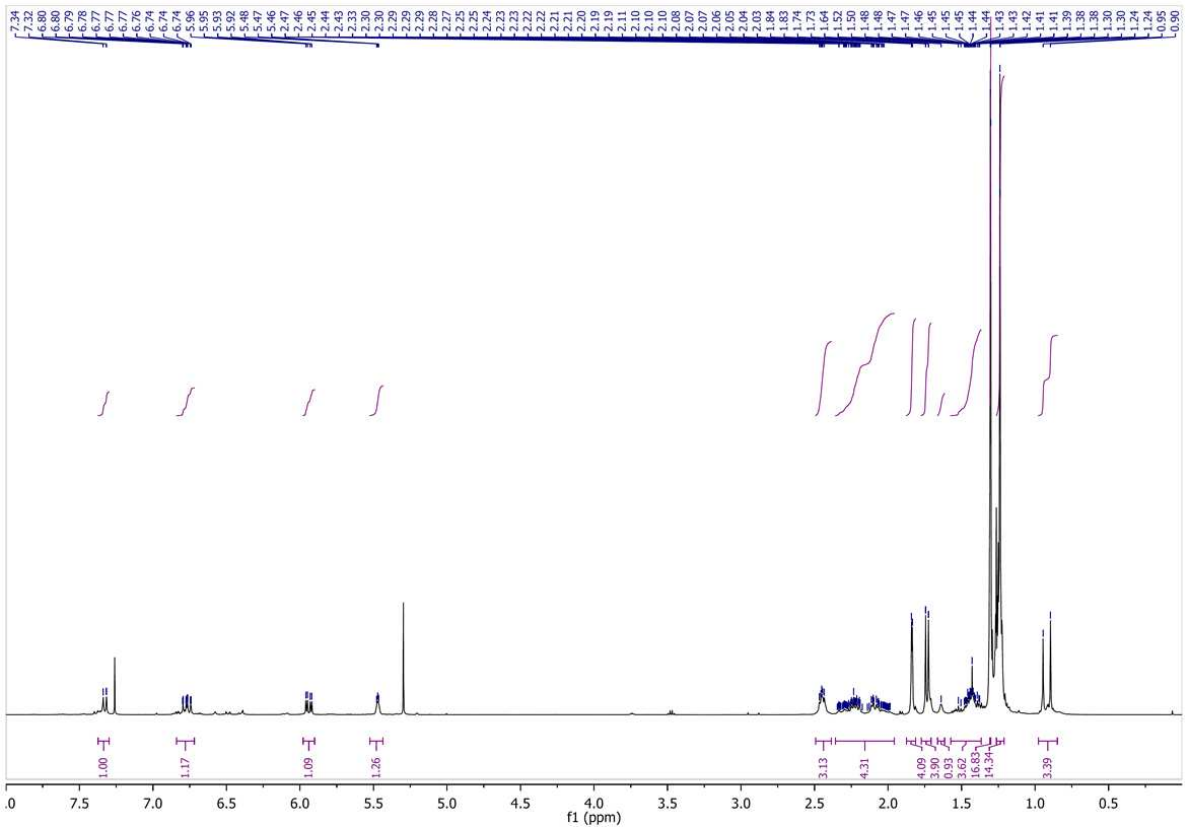
32.8(32.7) (CH_2), 32.5 (CH_2), 25.5 CH_3, 24.94(24.91) BPin-CH_3, 24.2(23.8) 10, 21.9(21.8) (CH_2), 20.3(20.2) CH_3 ppm;

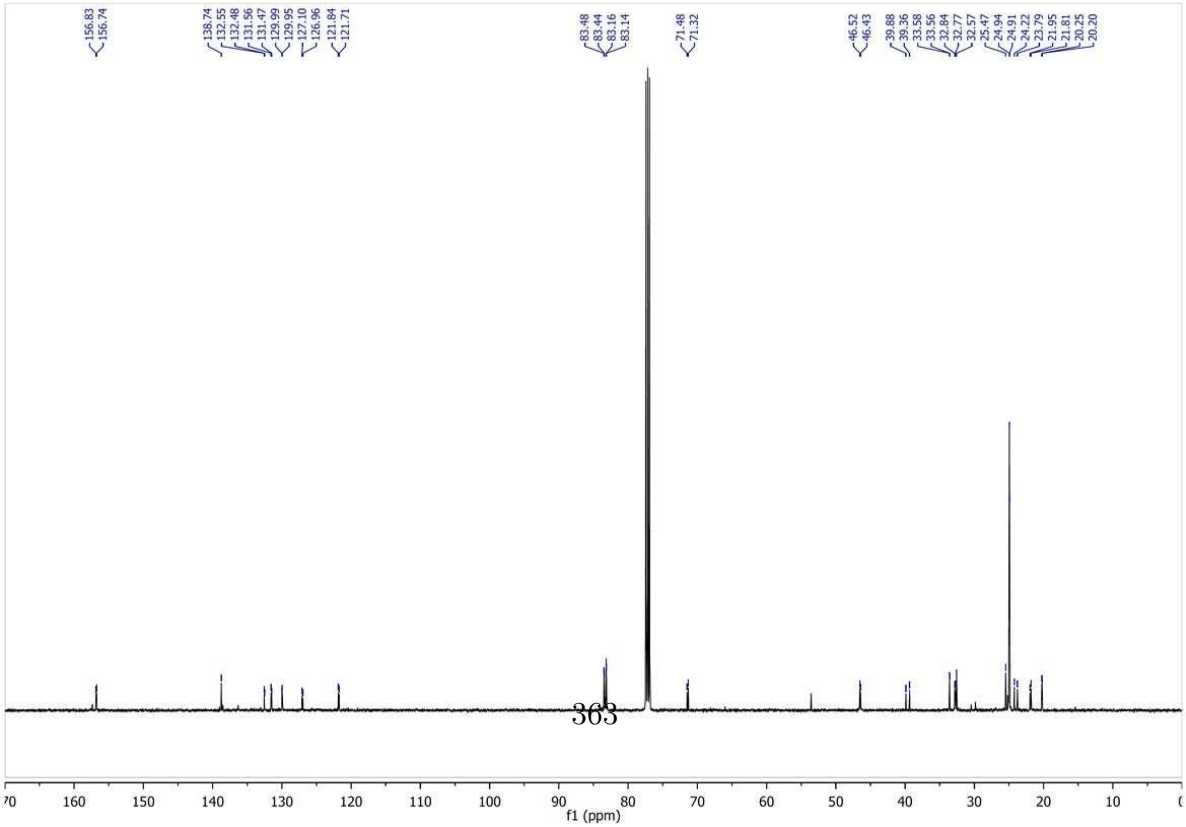
FT-IR thin film, neat (ATR): 3477, 2977, 2926, 2360, 1566, 1341, 1141, 987, 854 cm^{-1};

HRMS (ESI^+): calculated for $C_{30}H_{48}O_5{}^{10}B_2{}^{79}Br^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 645.25246 found 645.25256 (Δ = 0.16 ppm);

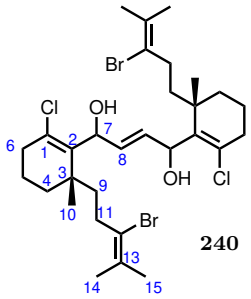
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 8.8° (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$





5.3.1.55 Allylic alcohol dimer 240



240

The product (128 mg, 0.22 mmol, 18% yield) was co-isolated with compound **192**.

R_f = 0.10 (30% Et_2O/*n*-pentane, stains with vanillin);

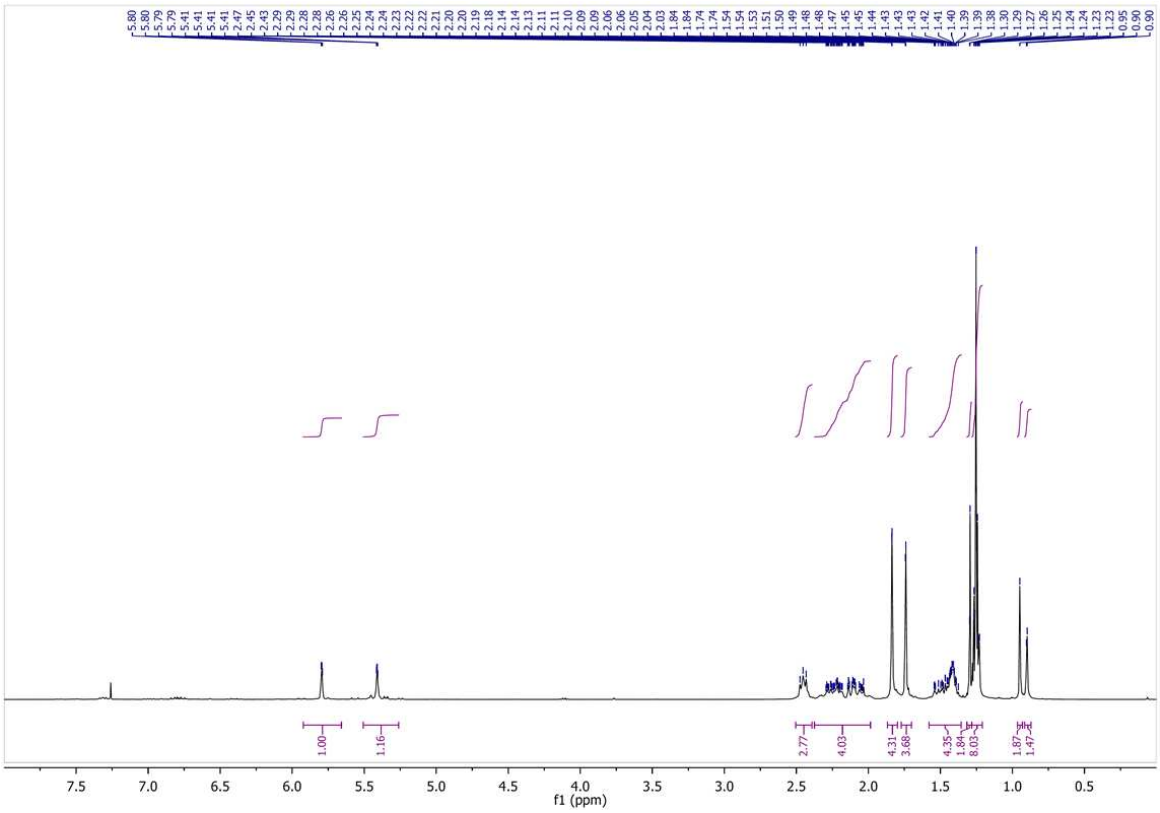
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (dd, J = 2.4, 1.2 Hz, 1H, 8), 5.51 – 5.26 (m, 1H, 7), 2.45 (m, 2H, alkyl-H), 2.37 – 1.98 (m, 4H, alkyl-H), 1.87 – 1.80 (m, 3H, CH_3), 1.74 (d, J = 1.6 Hz, 3H, CH_3), 1.58 – 1.36 (m, 4H, alkyl-H), 0.95(0.90) (m, 3H, 10) ppm;

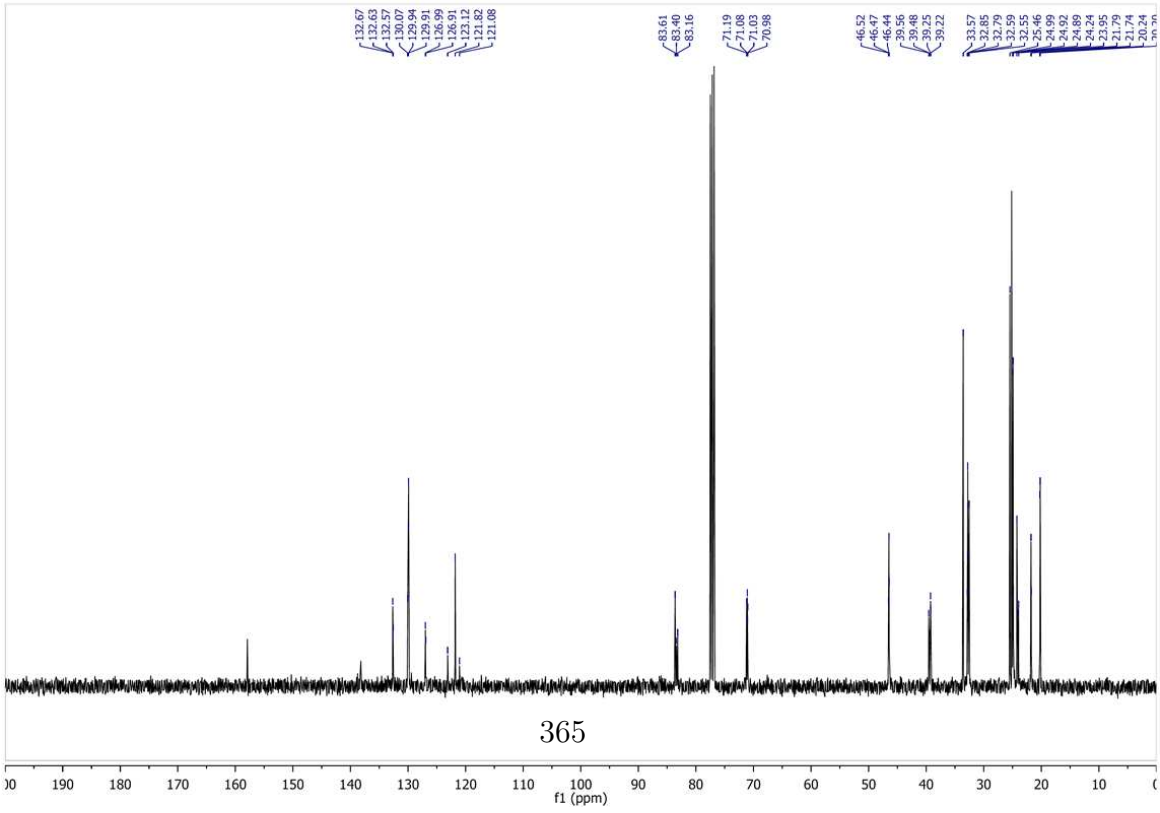
^{13}C NMR (126 MHz, $CDCl_3$) δ 132.7, 132.6, 132.6, 130.1, 129.9, 129.9, 127.0, 126.9, 123.1, 121.8, 121.1, 83.6, 83.4, 83.2, 71.2, 71.1, 71.0, 71.0, 46.5, 46.5, 46.4, 39.6, 39.5, 39.2, 39.2, 33.6, 32.8, 32.8, 32.6, 32.6, 25.5, 25.0, 24.9, 24.9, 24.2, 24.0, 24.0, 21.8, 21.7, 20.2, 20.2 ppm;

FT-IR thin film, neat (ATR): 3433, 2923, 2360, 1654, 1559, 1388, 1141, 1125 cm^{-1};

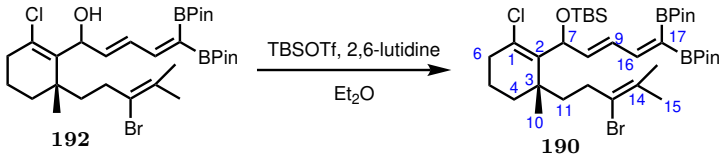
HRMS (ESI^+): calculated for $C_{30}H_{44}O_2Br_2Cl_2Na$, $[M+Na]^{+\bullet}$: 687.0977 found 687.0979 (Δ = 0.24 ppm);

$^{1}H/^{13}C$ NMR





5.3.1.56 TBS-protected diBPin alcohol 190



Alcohol **192** (78 mg of an 81% wt. solution in CH_2Cl_2, 0.10 mmol, 1.0 mol equiv) and dry Et_2O (0.30 mL) were added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. 2,6-lutidine (20 μL, 0.17 mmol, 1.7 mol equiv) was added by syringe and the solution was cooled to 0 °C. *Tert*-butyldimethylsilyl trifluoromethanesulfonate (40 μL, 0.17 mmol, 1.7 mol equiv) was added dropwise and upon completion of addition, the cooling bath was removed. When the reaction was deemed complete by TLC (approx. 3.5 hours), the mixture was diluted with Et_2O and quenched with saturated $NaHCO_{3(aq)}$ (0.5 mL). The aqueous phase was extracted (3 x 0.5 mL) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a yellow oil (31 mg, 0.042 mmol, 42% yield) (1:1 inseparable mixture of diastereomers).

R_f = 0.55 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 11.1 Hz, 1H, 16), 6.77 (ddt, J = 15.2, 11.1, 2.1 Hz, 1H, 9), 5.88 (ddt, J = 15.1, 4.3, 0.9 Hz, 1H, 8), 5.47 (td, J = 4.3, 1.7 Hz, 1H, 7), 2.45 (dd, J = 9.8, 6.8 Hz, 2H, alkyl-H), 2.30 – 1.91 (m, 4H, alkyl-H), 1.84(1.83) (s, 3H, CH_3), 1.74(1.72) (s, 3H, CH_3), 1.60 – 1.35 (m, 4H, alkyl-H), 1.30(1.29) (s, 12H, BPin-CH_3), 1.23(1.23) (s, 12H, BPin-CH_3), 0.92(0.91) (s, 3H, 10), 0.90(0.89) (s, 9H, TBS-^{t}Bu-Me), 0.06 (s, 3H, TBS-Me), 0.04(0.03) (s,

3H, TBS-Me) ppm;

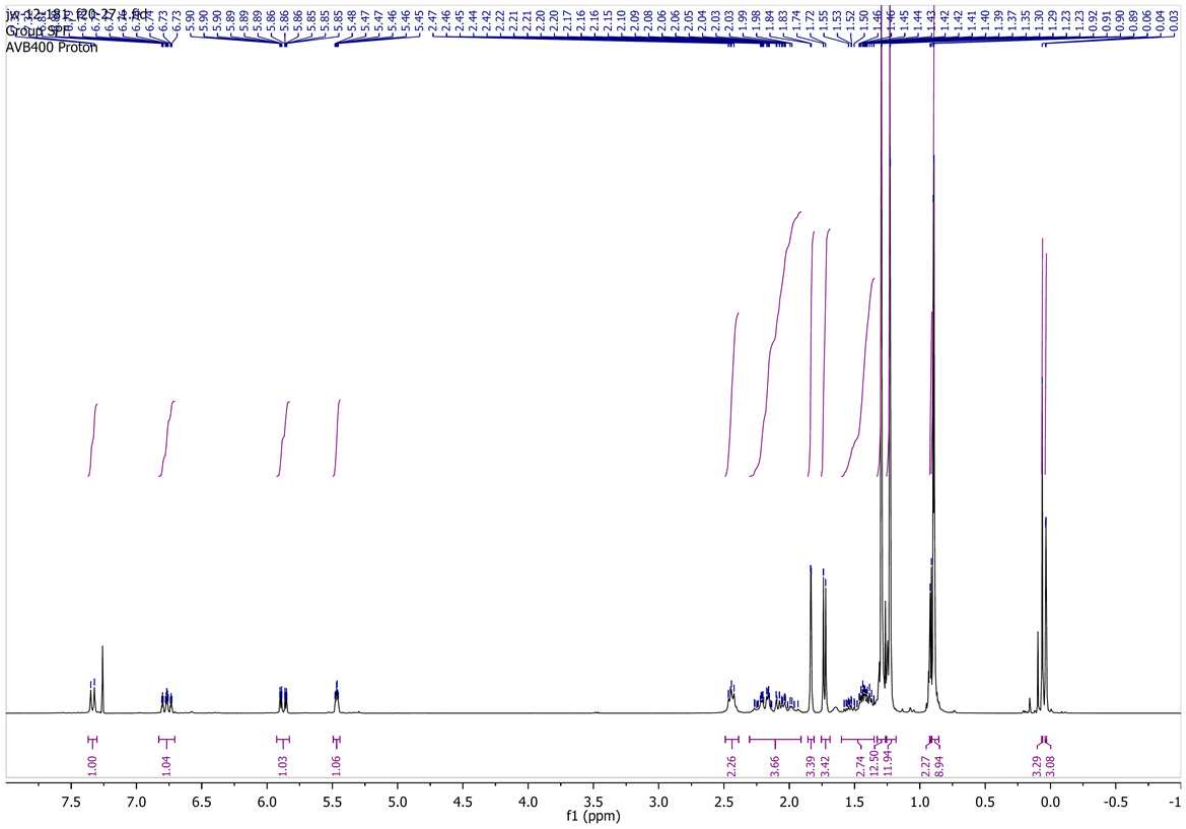
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.8(157.6) 9, 140.7(140.6) 8, 133.4(133.3) 1, 130.4 9, 130.0(129.8) 14, 125.1 2, 121.9(121.8) 13, 83.3(83.2) C-B, 83.04(83.00) C-B, 71.7(71.6) 7, 46.6(46.3) (CH_2), 40.3(38.7) (CH_2), 33.7(33.6) 3, 32.9(32.8) (CH_2), 32.6(32.6) (CH_2), 26.1(26.0) TBS-^{t}Bu-CH_3, 25.5 CH_3, 25.0(24.9) BPin-CH_3, 23.53 CH_3, 21.6(21.4) (CH_2), 20.3(20.2) CH_3, 18.44 TBS-^{t}Bu-C, −4.8(−4.9) TBS-Me ppm;

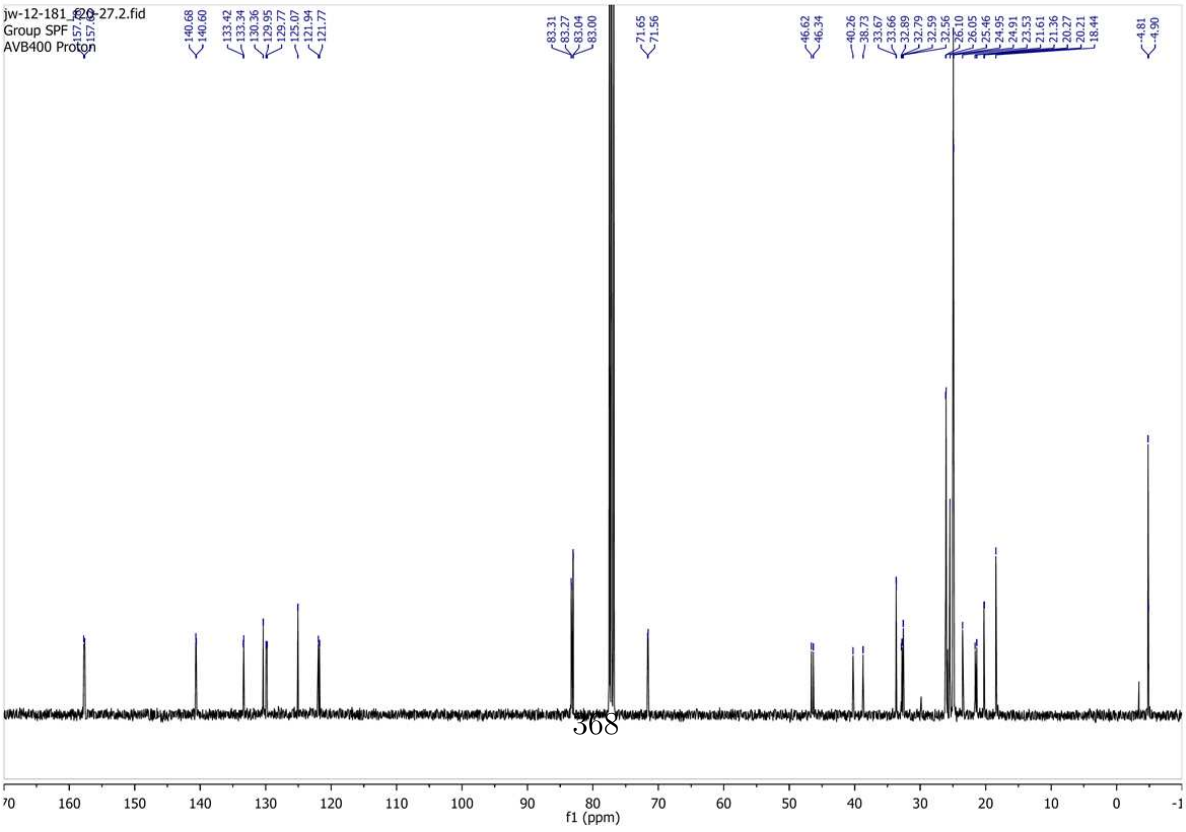
FT-IR thin film, neat (ATR): 2928, 2361, 1570, 1342, 1141 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{38}H_{61}O_5B_2{}^{79}Br^{35}Cl^{28}Si$, $[M+H]^{+\bullet}$: 759.3413 found 759.3395 (Δ = -2.38 ppm);

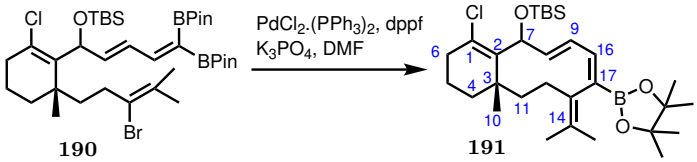
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +10^\circ$ (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR


jw-12-181_220-27.1.fid
Group SPF
AVB400 Proton
1.00
1.04
1.03
1.06
2.26
3.66
3.39
3.42
2.74
12.50
11.94
2.27
8.94
3.29
3.08
f1 (ppm)


jw-12-181_220-27.2.fid
Group SPF
AVB400 Proton
f1 (ppm)

5.3.1.57 ten-membered ring 191



$PdCl_2(PPh_3)_2$ (45 mg, 0.064 mmol, 1.0 mol equiv), dppf ligand (35 mg, 0.064 mmol, 1.0 mol equiv) and K_3PO_4 (68 mg, 0.32 mmol, 5.0 mol equiv) were added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were then performed, after which protected alcohol **190** (40 mg, 0.064 mmol, 1.0 mol equiv) was added in DMF, rinsing once (total volume DMF = 6.4 mL). The vial was sealed with parafilm and immersed in a 75 °C oil bath. When the reaction was deemed complete by TLC (approx. 2 hours), it was cooled to room temperature and quenched with with brine (equal volume to reaction solvent). The aqueous phase was extracted (3 x 1mL) with 1:1 pentane:Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–20% CH_2Cl_2/*n*-pentane then 10% Et_2O/*n*-pentane, silica column) to give the title compound as a yellow oil (6.7 mg, 0.013 mmol, 18% yield) (1:1 inseparable mixture of diastereomers).

R_f = 0.61 (10% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (d, J = 11.0 Hz, 1H, 16), 6.58 (ddd, J = 16.9, 11.0, 2.0 Hz, 1H, 9), 5.82 (dd, J = 16.9, 2.7 Hz, 1H, 8), 5.68 (d, J = 2.7 Hz, 1H, 7), 2.53 – 1.87 (m, 6H, alkyl-H), 1.83(1.69) (s, 3H, CH_3), 1.56(1.51) (s, 3H, CH_3), 1.42 – 1.30 (m, 4H), 1.27 – 1.17 (m, 12H, BPin-CH_3), 0.93(0.92) (s, 3H,

10), 0.89 (s, 9H, TBS-^{t}Bu-Me), 0.07(0.04) (s, 6H, TBS-Me) ppm;

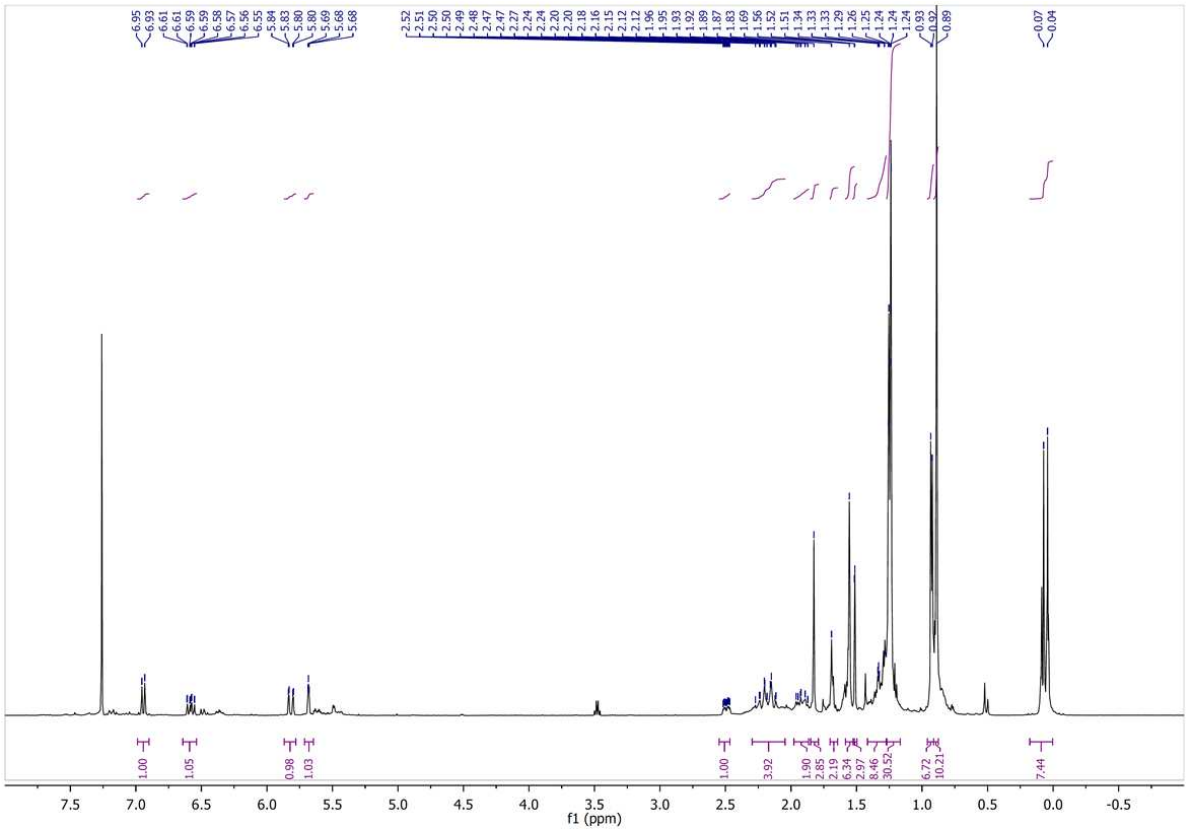
^{13}C NMR (126 MHz, $CDCl_3$): δ 141.7 1, 141.1 16, 137.8 8, 132.9 14, 131.8 9, 124.39 13, 124.00 2, 83.2(83.0) C-B, 72.94 7, 43.4 (CH_2), 34.8 (CH_2), 31.0 3, 28.60 10, 26.15(26.12) (CH_2), 26.04(25.99) TBS-^{t}Bu-CH_3, 24.9 (bs) BPin-CH_3, 24.7 (CH_2), 24.3 (CH_2), 22.3 CH_3, 20.6 CH_3, 18.3 TBS-^{t}Bu-C, −4.8(−4.9) TBS-Me ppm;

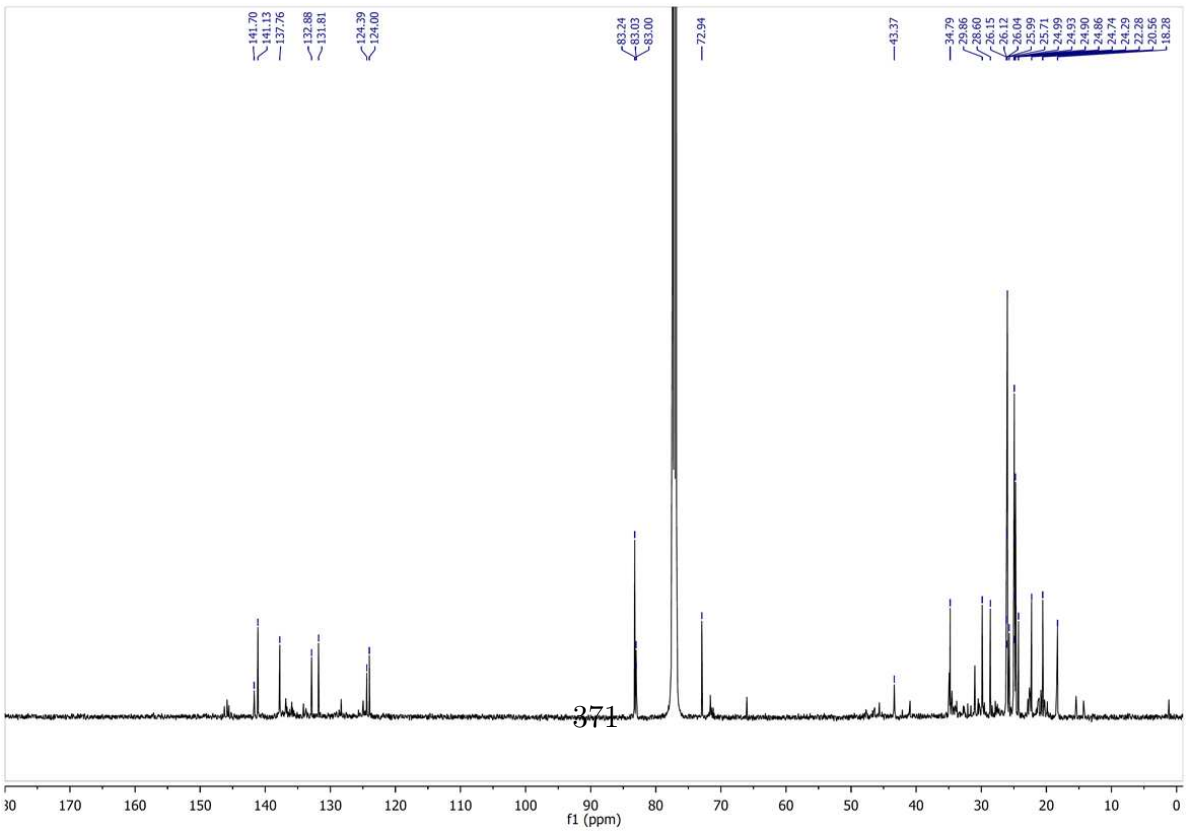
FT-IR thin film, neat (ATR): 2927, 2855, 2415, 2360, 1370, 1315, 1253, 1145, 1089, 867, 837 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{38}H_{61}O_5B_2{}^{79}Br^{35}Cl^{28}Si$, $[M+H]^{+\bullet}$: 532.3420 found 532.3417 (Δ = -0.45 ppm);

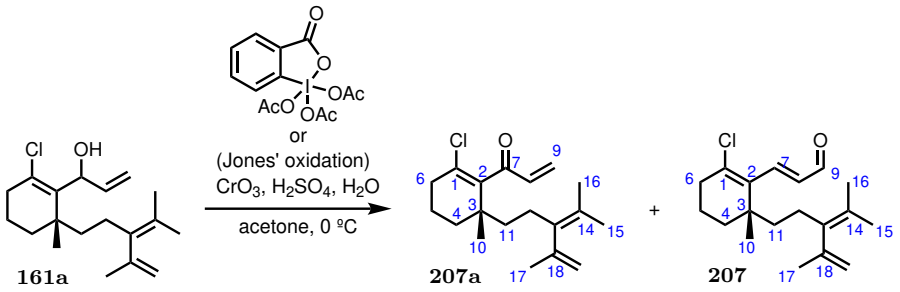
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = +11^\circ$ (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.58 Ketone 1st generation 207a



Jones' reagent

CrO_3 (142 mg, 1.42 mmol, 8.9 mol equiv) was added to a 7 mL vial equipped with a stirrer bar and cooled to 0 °C. Concentrated sulfuric acid (0.11 mL, ρ = 1.84 g.mL^{-1}, 2.1 mmol, 13 mol equiv) was added followed by distilled water (0.53 mL). The bright orange solution was stored at 0 °C in the dark until ready for use.

Oxidation (Jones' reagent)

Alcohol **161a** (50 mg, 0.16 mmol, 1.0 mol equiv) was dissolved in 'HPLC grade' acetone (2.7 mL) in a 22 mL vial, equipped with a stirrer bar. The solution was cooled to 0 °C and Jones' reagent prepared above, was added dropwise resulting in a bright orange solution. After stirring for 10min, TLC indicated complete consumption of the starting material. Isopropyl alcohol was added (0.3 mL) and the reaction stirred for an additional 10 minutes. The contents of the vial were then transferred to a separatory funnel containing water (8 mL) and EtOAc (8 mL). The organic phase was drawn off and the aqueous phase was extracted (2x5 mL) with EtOAc. The combined organic extracts were washed with water (8 mL),

brine (8 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–20% Et_2O/*n*-pentane, silica column) to give compound **207a** as a yellow oil (44 mg, 0.14 mmol, 90% yield).

Oxidation (Dess-Martin periodinane)

Alcohol **161a** (67.4 mg, 0.22 mmol, 1.0 mol equiv) was dissolved in dry CH_2Cl_2 (7.3 mL) in a 22 mL vial, equipped with a stirrer bar. Dess-Martin periodinane (111 mg, 0.26 mmol, 1.2 mol equiv) was added and the mixture stirred vigorously until the reaction was judged complete (TLC control, approx. 10 – 30 min). The reaction was quenched with 1.5 mL each of saturated $Na_2S_2O_{3(aq)}$ and saturated $NaHCO_{3(aq)}$. The organic layer was extracted (3x) with Et_2O, dried (Na_2SO_4), filtered through celite and concentrated *in vacuo*. The crude product is purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give **207a** (40 mg, 0.13 mmol) and **207** (21 mg, 0.069 mmol) (combined yield 90%, 0.20 mmol, 1.5:1 **207a :207**).

207a

$\mathbf{R_f}$ = 0.47 (10% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (dd, J = 17.5, 10.4 Hz, 1H, 8), 6.21 (dd, J = 17.5, 1.2 Hz, 1H, 9-*trans*), 5.96 (dd, J = 10.4, 1.2 Hz, 1H, 9-*cis*), 4.91 (dq, J = 2.9, 1.5 Hz, 1H, 19), 4.60 – 4.51 (m, 1H, 19), 2.35 – 2.13 (m, 4H, alkyl-H), 2.09 – 2.02 (m, 2H, alkyl-H), 1.76 (dd, J = 1.5, 0.9 Hz, 3H, 17), 1.66 (s, 6H, 15/16), 1.51 – 1.46 (m, 2H, alkyl-H), 1.32 (dt, J = 9.9, 8.4 Hz, 2H, alkyl-H), 0.99 (s, 3H,

10) ppm;

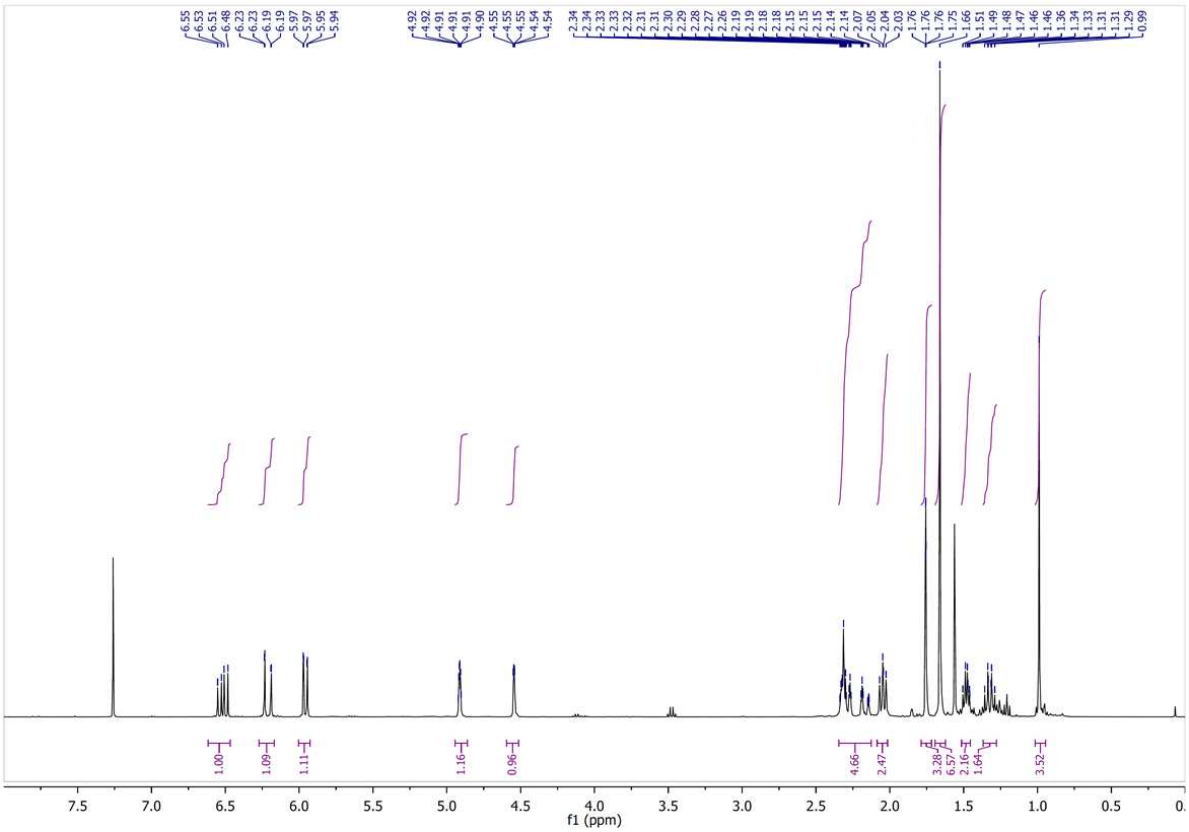
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 146.6, 136.4, 135.8 8, 133.4, 130.9, 130.6 9, 125.2, 113.3 19, 46.2 (CH_2), 39.5 (CH_2), 34.0 3, 32.4 (CH_2), 25.9 (CH_2), 25.2 (CH_2), 24.2 10, 22.9 17, 21.9 CH_3, 19.6 CH_3 ppm;

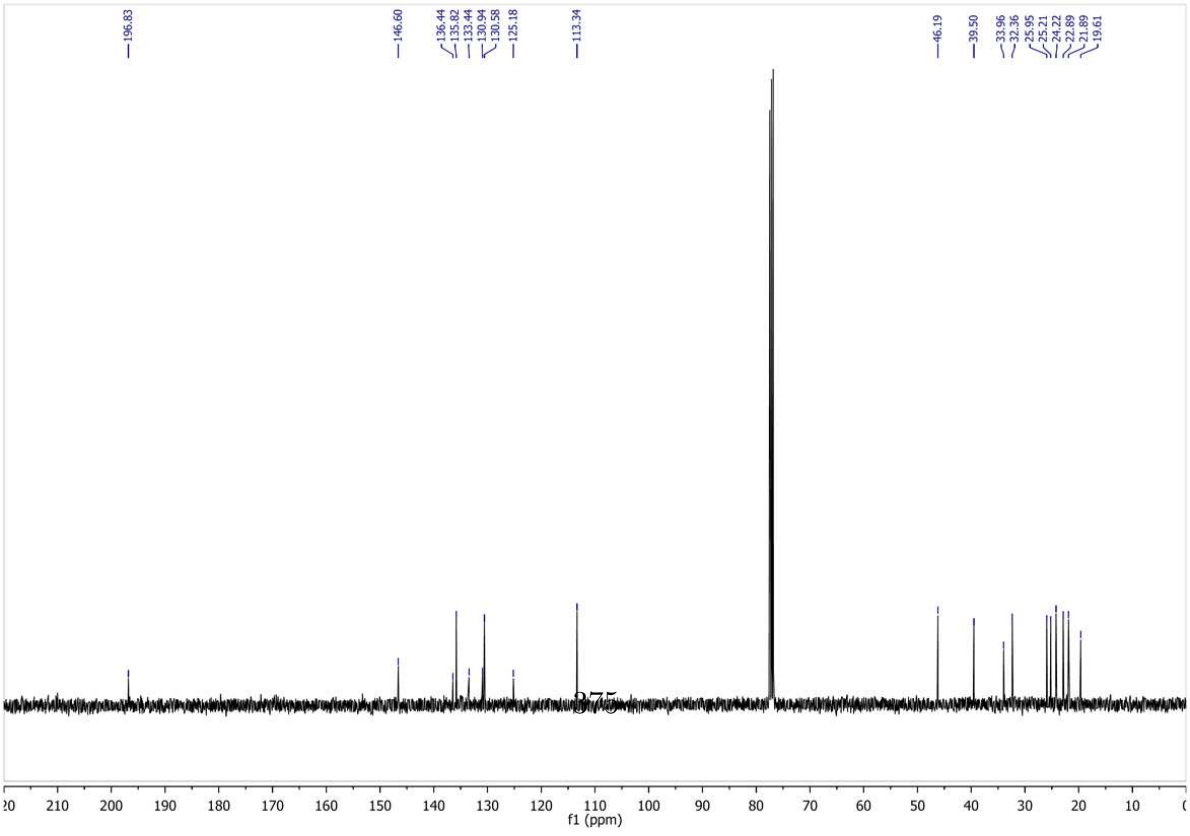
FT-IR thin film, neat (ATR): 2920, 1666, 1444, 1401 cm^{-1};

HRMS (ESI^+): calculated for $C_{19}H_{27}O^{35}ClNa$, $[M+Na]^{+\bullet}$: 329.16426 found 329.16434 (Δ = 0.22 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 20° (c = 0.7, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR


6.55
6.53
6.51
6.48
6.23
6.23
6.19
6.19
5.97
5.97
5.95
5.94
4.92
4.92
4.91
4.91
4.91
4.90
4.55
4.55
4.55
4.54
4.54
2.34
2.34
2.33
2.33
2.32
2.31
2.31
2.30
2.29
2.28
2.27
2.26
2.19
2.19
2.18
2.18
2.15
2.15
2.15
2.14
2.14
2.07
2.05
2.04
2.03
1.76
1.76
1.76
1.75
1.66
1.51
1.49
1.48
1.47
1.46
1.46
1.36
1.34
1.33
1.31
1.31
1.29
0.99
1.00
1.09
1.11
1.16
0.96
4.66
2.47
3.28
6.57
2.16
1.64
3.52
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
f1 (ppm)


196.83
146.60
136.44
135.82
133.44
130.94
130.58
125.18
113.34
46.19
39.50
33.96
32.36
25.95
25.21
24.22
22.89
21.89
19.61
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

207

R_f = 0.33 (10% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (d, J = 7.8 Hz, 1H, 9), 7.78 (d, J = 15.8 Hz, 1H, 7), 6.22 – 6.14 (dd, J = 15.8, 7.8 Hz, 1H, 8), 4.90 (dd, J = 2.7, 1.5 Hz, 1H, 19), 4.53 (dd, J = 2.7, 1.1 Hz, 1H, 19), 2.48 – 2.27 (m, 4H, alkyl-H), 2.07 – 2.01 (m, 2H, alkyl-H), 1.75 (t, J = 1.1 Hz, 3H, 17), 1.65 (s, 7H, 15/16), 1.55 – 1.50 (m, 2H, alkyl-H), 1.35 – 1.23 (m, 2H, alkyl-H), 0.96 (s, 3H, 10) ppm;

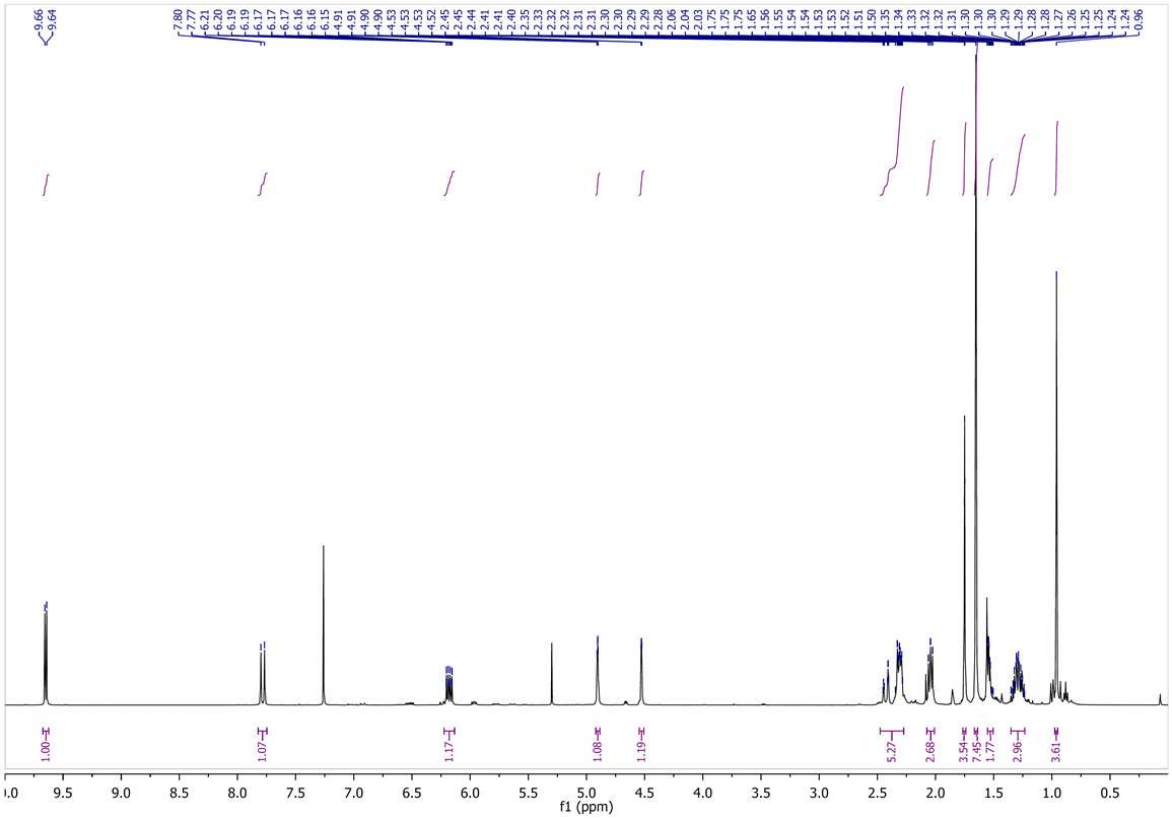
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4 9, 149.0 7, 146.5 13, 140.8 1, 136.4 18 128.9 8, 128.2 2, 125.2 14, 113.3 19, 47.9 (CH_2), 39.5 (CH_2), 33.8 3, 32.5 (CH_2), 25.2 (CH_2), 24.0 10, 23.8 (CH_2), 22.9 17, 21.9 16 19.6 15 ppm;

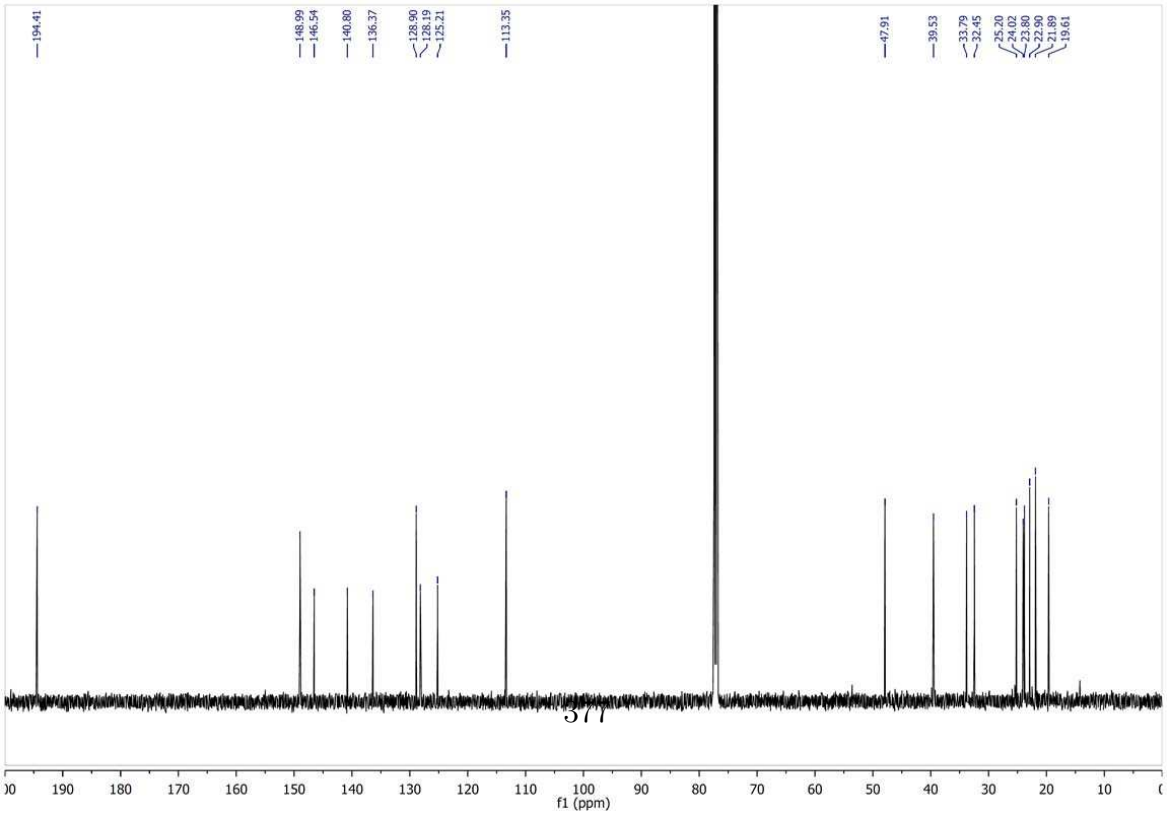
FT-IR thin film, neat (ATR): 2960, 2921, 2361, 1686, 1616, 1126 cm^{-1};

HRMS (ESI^+): calculated for $C_{19}H_{28}O^{35}Cl$, $[M+H]^{+\bullet}$: 307.18232 found 307.18237 (Δ = 0.17 ppm);

$[\alpha]_D^{25}$ = + 30° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


9.66
9.64
7.80
7.77
6.21
6.20
6.19
6.19
6.17
6.17
6.17
6.16
6.16
6.15
4.91
4.91
4.90
4.90
4.53
4.53
4.53
4.52
2.45
2.45
2.44
2.41
2.41
2.40
2.35
2.33
2.32
2.32
2.31
2.31
2.30
2.30
2.29
2.29
2.28
2.06
2.04
2.03
1.75
1.75
1.75
1.65
1.56
1.55
1.54
1.54
1.53
1.53
1.52
1.51
1.50
1.35
1.34
1.33
1.32
1.32
1.31
1.30
1.30
1.30
1.29
1.29
1.29
1.28
1.28
1.27
1.26
1.25
1.25
1.24
1.24
0.96
1.00
1.07
1.17
1.08
1.19
5.27
2.68
3.54
7.45
1.77
2.96
3.61
f1 (ppm)


194.41
148.99
146.54
140.80
136.37
128.90
128.19
125.21
113.35
47.91
39.53
33.79
32.45
25.20
24.02
23.80
23.60
21.89
19.61
f1 (ppm)

5.3.1.59 Taxol core 208



207a **208**

$TiCl_4$ (14 μL, ρ = 1.15 g.mL^{-1}, 0.13 mmol, 1.1 mol equiv) was dissolved in dry CH_2Cl_2 (11 mL) in a flame dried round bottom flask equipped with a stirrer bar under N_2. The flask was cooled to −40 °C and ketone **207a** (35 mg, 0.11 mmol, 1.0 mol equiv), dissolved in dry CH_2Cl_2 (11 mL), was added via syringe pump over 1 hour. At this point, complete consumption of starting material was observed by TLC (10% Et_2O, $KMnO_4$) and the reaction was quenched with $NaHCO_{3(aq)}$ (6 mL) and warmed to room temperature. The aqueous phase was extracted (3x) with dichloromethane and the combined organic extracts washed with water, dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was dry loaded onto celite, then purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a white foam in an inseparable 1:1 diastereomeric mixture C1 epimer (12 mg, 0.039 mmol, 35% yield).

R_f = 0.31 and 0.23 (mixture of diastereomers 30% Et_2O/*n*-pentane, CAM);
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.65 (dd, J = 12.4, 2.7 Hz, 1H, 1), 2.80 (dd, J = 12.2, 2.8 Hz, 1H, 1), 2.76 – 2.20 (m, 6H, alkyl-H), 2.13 (m, 8H, alkyl-H), 2.06 – 1.62 (m, 8H, alkyl-H), 1.60 (s, 3H, 12-CH_3), 1.58 (s, 3H, 12-CH_3), 1.51 – 1.29 (m, 2H, alkyl-H), 1.24 (s, 3H, 14-CH_3), 1.19 (s, 3H, 14-CH_3), 1.15 – 0.96 (m, 4H, alkyl-H), 1.04 (s, 3H, 14-CH_3), 1.00 (s, 3H, 14-CH_3), 0.94 (s, 3H, 8-CH_3), 0.85 (s, 3H, 8-CH_3) ppm;

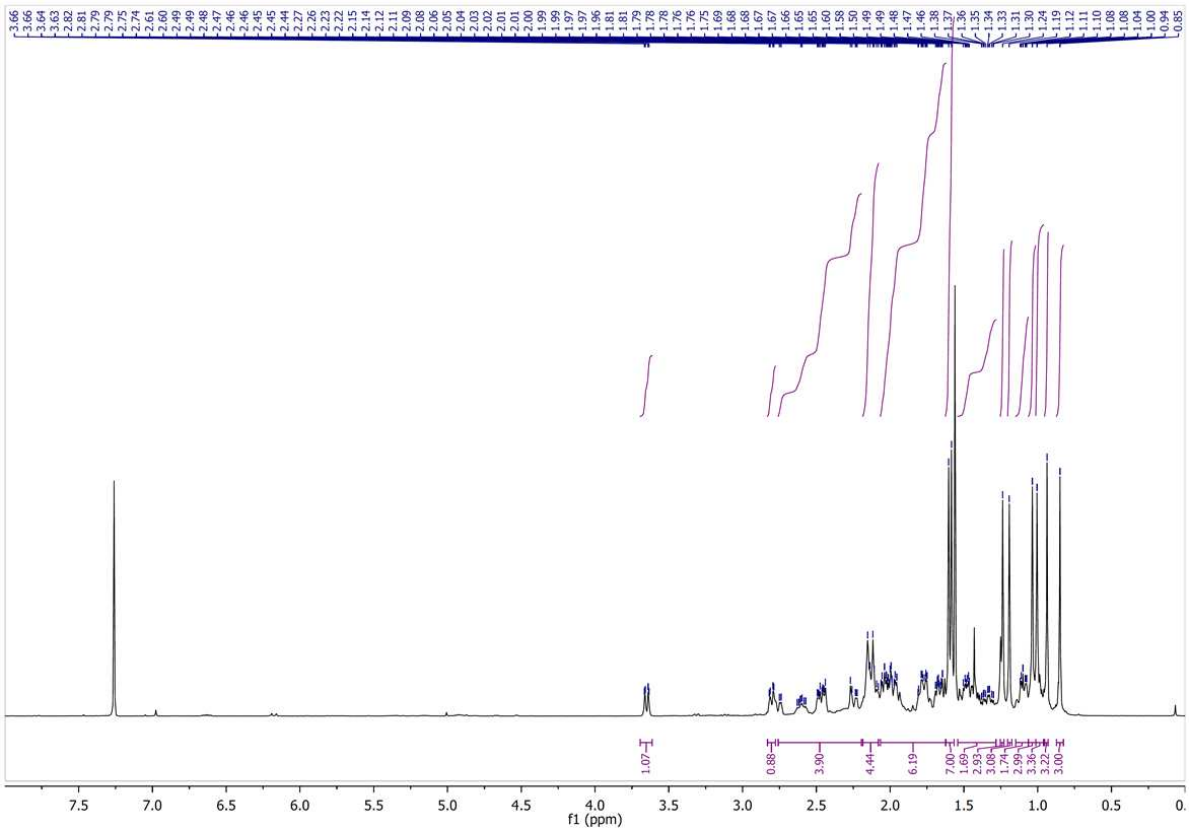
^{13}C NMR (126 MHz, $CDCl_3$) δ 209.7, 206.3, 136.7, 136.5, 136.5, 134.0, 133.8, 133.4, 127.0, 126.9, 56.4, 53.1, 51.4, 44.5, 39.0, 38.9, 37.6, 37.0, 36.2, 33.9, 33.9, 31.6, 31.5, 30.0, 29.3, 27.1, 27.0, 27.0, 26.9, 25.0, 23.4, 23.2, 22.2, 22.1, 21.7, 20.5, 20.0, 19.9 ppm;

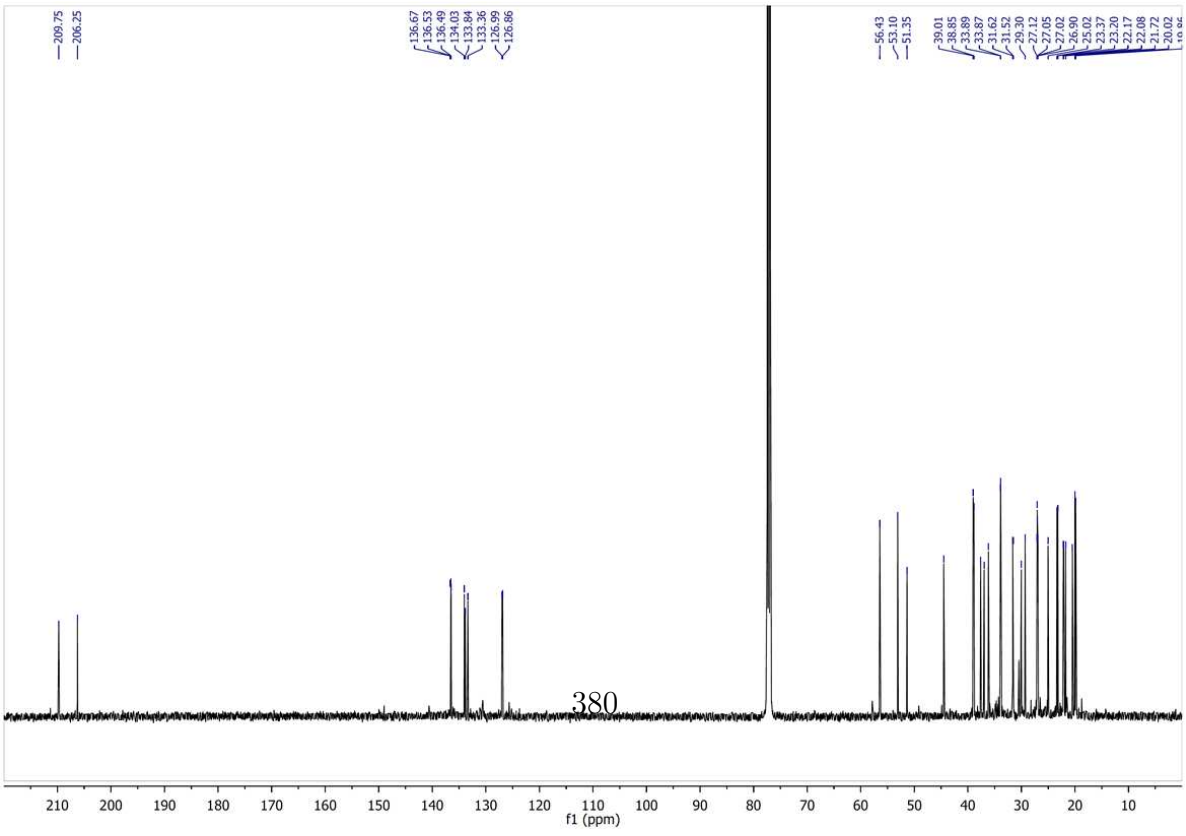
FT-IR thin film, neat (ATR): 2925, 1685. 1431, 1366, 780, 737 cm^{-1};

HRMS ($APCI^+$): calculated for $C_{19}H_{28}O^{35}Cl$, $[M+H]^{+\bullet}$: 307.18232 found 307.18201 (Δ = -1.02 ppm);

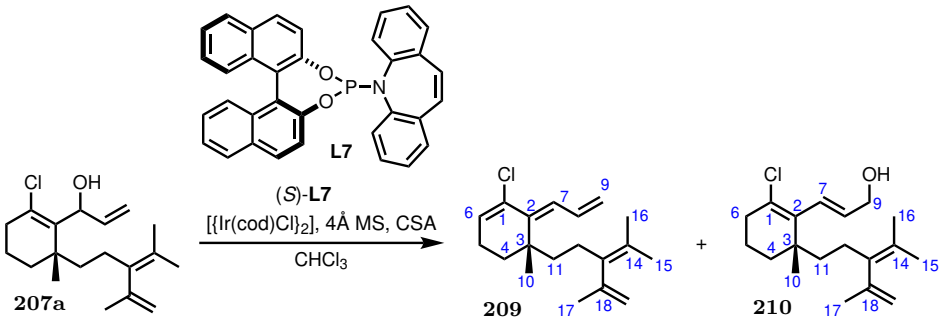
$[\alpha]_{\mathbf{D}}^{\mathbf{25}} = -10\ ^\circ$ (c = 1.0, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.60 Attempted allyl-alkene coupling of triene 207a



The reaction was conducted according to an existing literature procedure.[104] The desired cyclised allyl-alkene coupled product was not observed.

[{Ir(cod)Cl}$_2$] (5.4 mg, 0.0087 mmol, 0.040 mol equiv) and phosphoramidite ligand **L7** (18 mg, 0.036 mmol, 0.17 mol equiv) were added to a 7 mL vial equipped with a stirrer bar. $CHCl_3$ (0.40 mL) was added and the solution was stirred vigorously for 15 minutes. Trienol **207a** (67 mg, 0.22 mmol, 1.0 mol equiv) was then added (as a solution in 0.2 mL $CHCl_3$ then rinsed with an additional 0.2 mL $CHCl_3$) followed by powdered 4A molecular sieves (22 mg) and camphorsulfonic acid (25 mg, 0.11 mmol, 0.50 mol equiv). After stirring for 23 hours or when complete consumption of starting material was observed (TLC control), the the reaction was filtered through a short plug of silica, eluting with CH_2Cl_2 before volatiles were removed *in vacuo*. The residue was purified directly using flash chromatography (0-40% Et_2O/*n*-pentane gradient, silica column) to give **209** as a pungent yellow oil (47 mg, 0.16 mmol, 74% yield) and **210** as yellow residue (5.6 mg, 0.018 mmol, 8% yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

Compound 209

$\mathbf{R_f}$ = 0.76 (30% Et_2O/*n*-pentane, stains blue with *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (ddd, J = 16.5, 11.3, 10.0 Hz, 1H, 8), 6.54 (d, J = 11.3 Hz, 1H, 7), 5.86 (s, 1H, 6), 5.37 (dd, J = 16.5, 1.9 Hz, 1H, 9-*trans*), 5.23 (dd, J = 10.0, 1.9 Hz, 1H, 9-*cis*), 4.91 (dd, J = 2.8, 1.3 Hz, 1H, 19), 4.54 (dd, J = 2.8, 1.1 Hz, 1H, 19), 2.72 – 2.48 (m, 2H, alkyl-H), 2.11 – 1.98 (m, 2H, alkyl-H), 1.75 (t, J = 1.3 Hz, 3H, 17), 1.66 (d, J = 1.5 Hz, 6H, 15/16), 1.70 – 1.44 (m, 2H, alkyl-H), 1.43 – 1.33 (m, 2H, alkyl-H), 1.06 (s, 3H, 10) ppm;

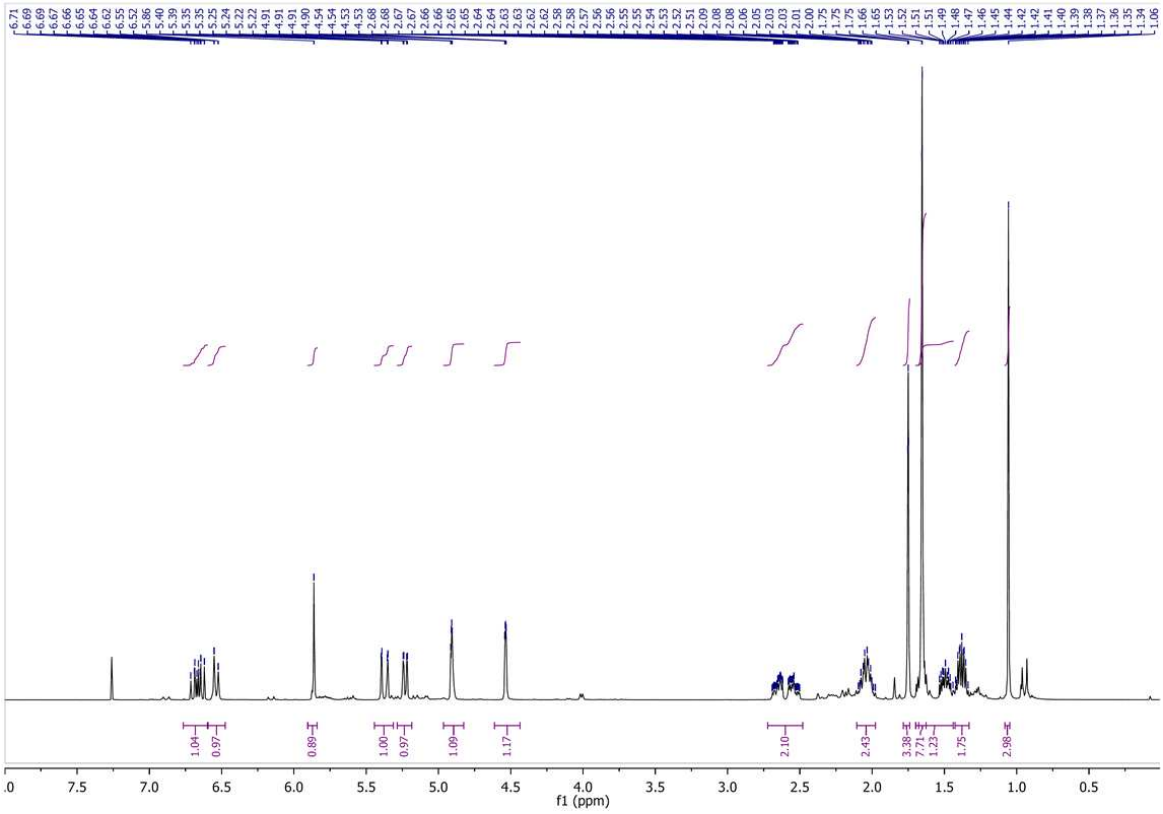
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 13, 138.3 6, 136.5 18, 132.9 8, 132.48 1, 130.8 2, 126.8 7, 125.2 14, 119.5 9, 113.3 19, 40.2 (CH_2), 37.6 3, 33.4 (CH_2), 25.9 10, 25.7 (CH_2), 23.5 (CH_2), 22.9 17, 21.9 16, 19.6 15 ppm;

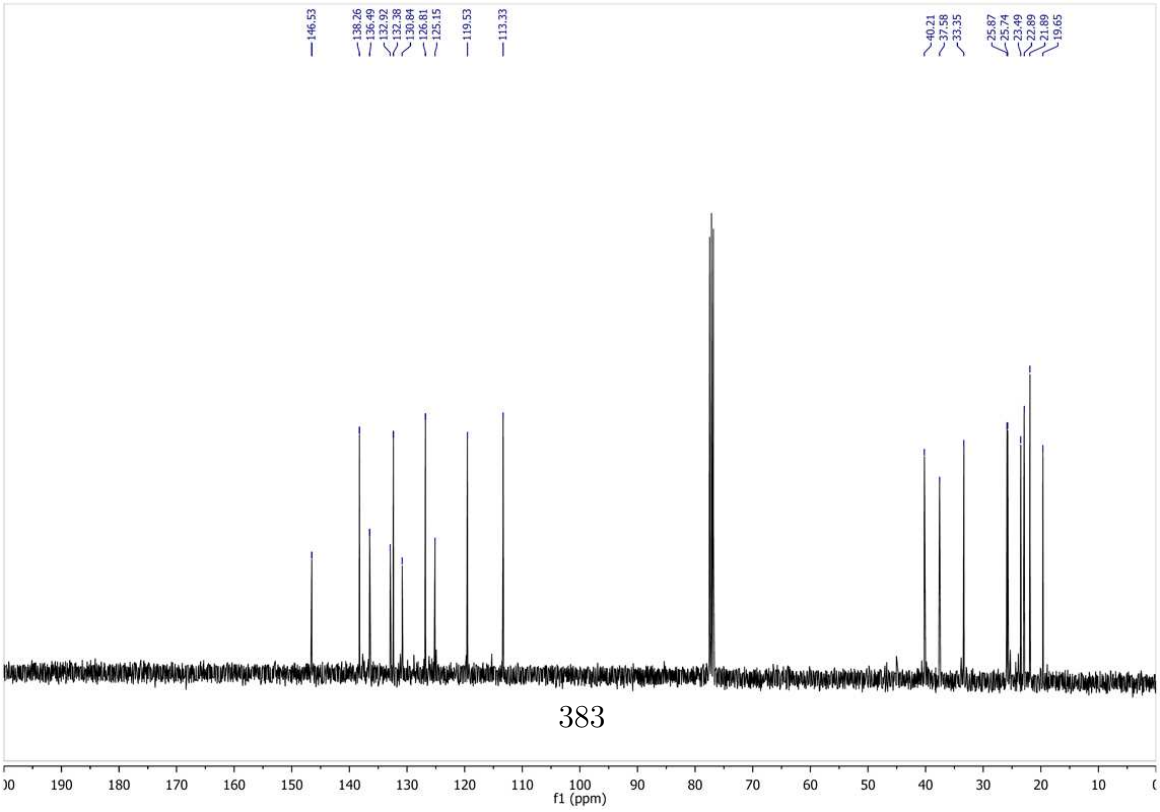
FT-IR thin film, neat (ATR): 3076, 2959, 2364, 1631, 1444, 1373, 985, 903 cm^{-1};

HRMS (ESI^+): calculated for $C_{19}H_{28}O^{35}Cl$, $[M+H]^{+\bullet}$: 291.18741 found 291.18743 (Δ = 0.07 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 49° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





Compound 210

$\mathbf{R_f}$ = 0.11 (30% Et_2O/*n*-pentane, stains with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, J = 15.8 Hz, 1H, 7), 5.91 – 5.80 (m, 1H, 8), 4.90 (dd, J = 2.8, 1.5 Hz, 1H, 19), 4.56 – 4.44 (m, 1H, 19), 4.26 (d, J = 5.8 Hz, 2H, 9), 2.37 – 2.14 (m, 4H, alkyl-H), 2.09 – 2.00 (m, 2H, alkyl-H), 1.75 (t, J = 1.2 Hz, 3H, 17), 1.65 (s, 6H, CH_3), 1.50 – 1.46 (m, 2H, alkyl-H), 1.34 – 1.21 (m, 2H, alkyl-H), 0.93 (s, 3H, 10) ppm;

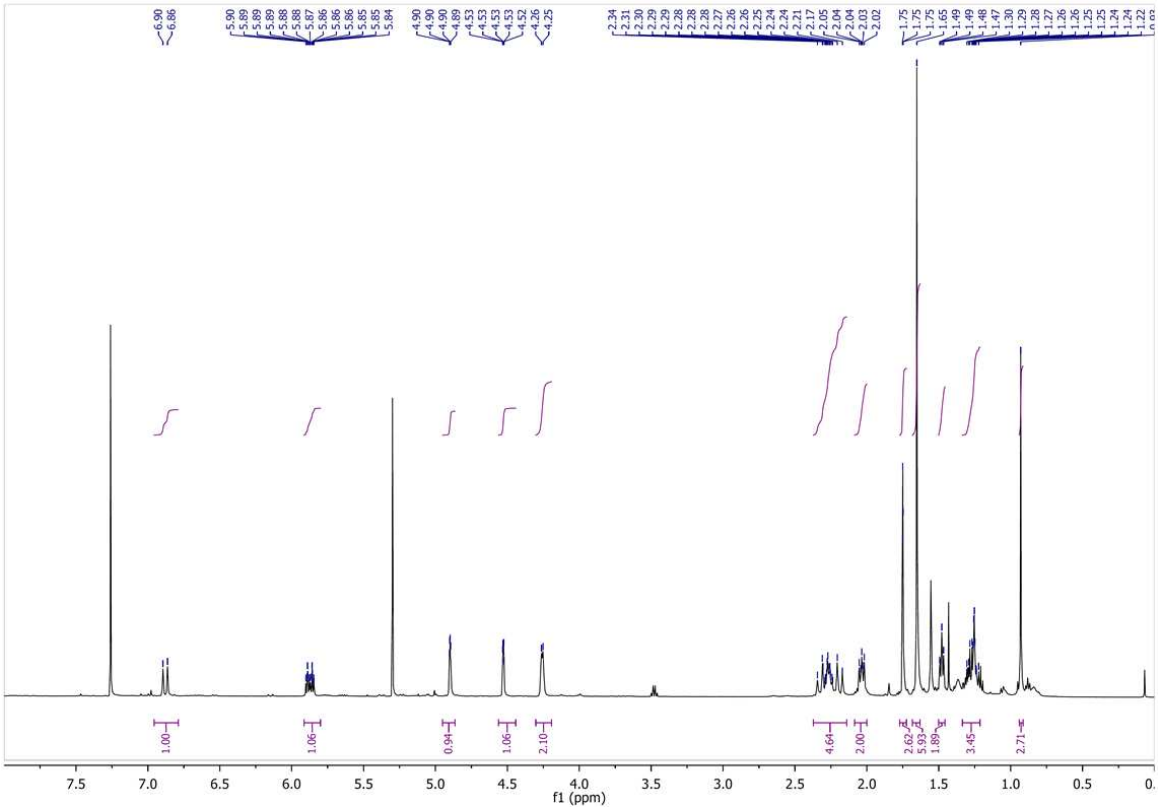
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.7 13, 136.7 18, 131.1 1, 128.9 7, 128.6 8, 127.8 2, 125.0 14, 113.2 19, 64.2 9, 47.1 (CH_2), 39.8 (CH_2), 33.8 3, 32.9 (CH_2), 25.3 (CH_2), 24.0 10, 23.9 (CH_2), 22.9 17, 21.9 CH_3, 19.6 CH_3 ppm;

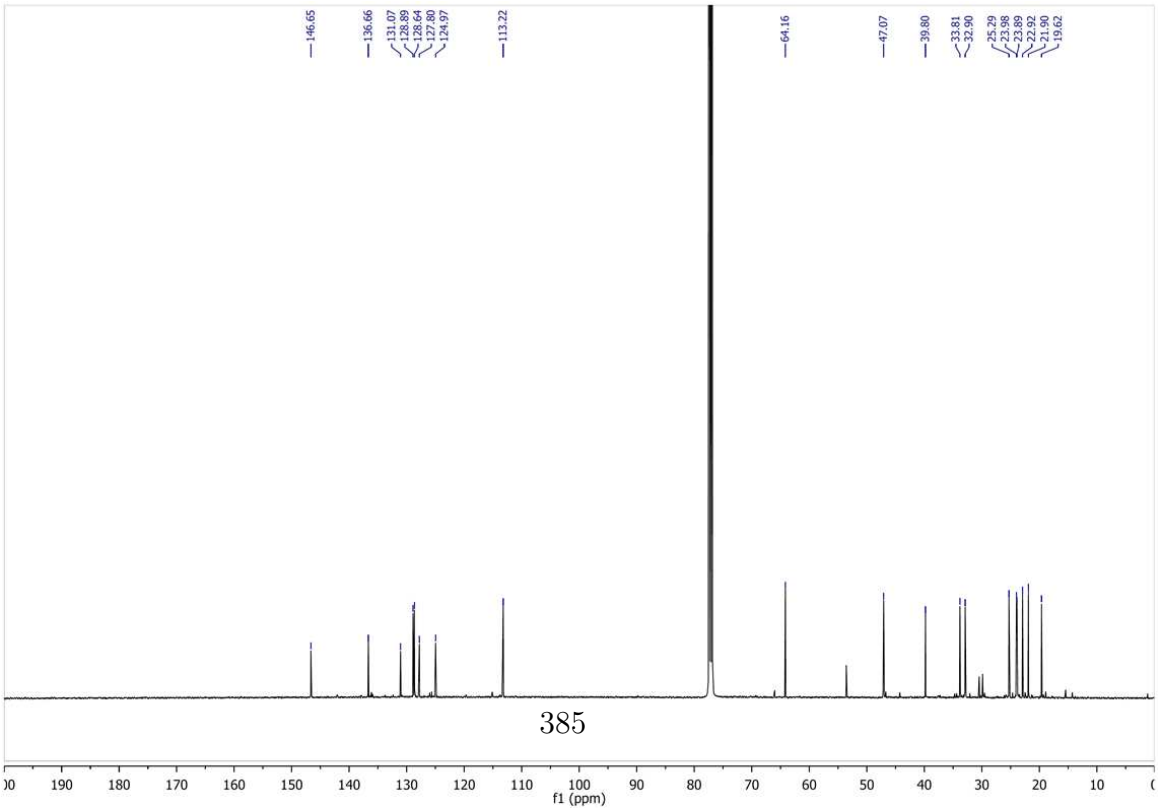
FT-IR thin film, neat (ATR): 3356, 2921, 2360, 1445, 1376, 968 cm^{-1};

HRMS (ESI^+): calculated for $C_{19}H_{27}{}^{35}Cl$, $[M\text{-}H_2O+H]^{+\bullet}$: 291.18741 found 291.187533 (Δ = 0.44 ppm);

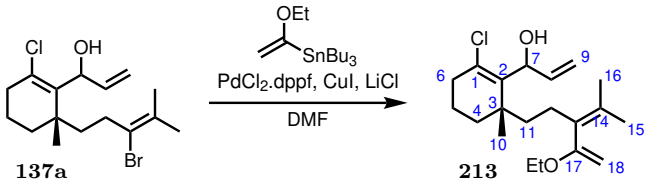
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 41° (c = 0.50, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR





5.3.1.61 Vinyl ether 213



$PdCl_2$dppf (73 mg, 0.0.10 mmol, 0.10 mol equiv), CuI (19 mg, 0.10 mmol, 0.10 mol equiv), and anhydrous LiCl (225 mg, 5.3 mmol, 5.3 mol equiv) were added to a flame dried 22 mL vial equipped with a rubber septum and stirrer bar. Three cycles of vacuum and back filling with N_2 were performed and the vial was fitted with a N_2 balloon. Bromide **137a** (320 mg, 1.0 mmol, 1.0 mol equiv) was added as a solution in dry, degassed DMF (10 mL). Stannane[105] (0.50 mL, 1.5 mmol, 1.5 mol equiv) was injected and the reaction mixture was immersed in a 75 °C oil bath for 3 days or until TLC showed complete consumption of starting material. When the reaction was deemed to be complete, it was cooled to room temperature and quenched with an equal volume of brine. The aqueous phase was extracted (3x) with 1:1 pentane:Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (pentane then 10% Et_2O/*n*-pentane, 10% wt K_2CO_3/silica column) to give the title compound as a colorless oil (133 mg, 0.39 mmol, 39% yield) (1:1 mixture of diastereomers). The compound is unstable on silica and thus the column should be as performed as fast possible in order to maximize yield.

R_f = 0.35 (30% Et_2O/*n*-pentane, stains grey with *p*-anisaldehyde);

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (dddd, J = 17.1, 10.5, 6.5, 4.9 Hz, 1H, 8), 5.38 (d, J = 4.6 Hz, 1H, 7), 5.32 (ddq, J = 17.1, 4.2, 1.6 Hz, 1H, 9-*trans*),

5.17 (dtd, J = 10.5, 3.8, 1.6 Hz, 1H, 9-*cis*), 4.11 (dd, J = 6.1, 1.6 Hz, 1H, 18), 3.83 (dd, J = 4.6, 1.6 Hz, 1H, 18), 3.73 (qd, J = 7.0, 5.2 Hz, 2H, OEt-CH_2), 2.34 – 1.92 (m, 6H, alkyl-H), 1.77(1.76) (s, 3H, CH_3), 1.69(1.68) (s, 3H, CH_3), 1.49 – 1.18 (m, 6H, alkyl-H), 1.31 (td, J = 7.0, 2.6 Hz, 3H, OEt-CH_3), 0.94(0.89) (s, 3H, 10) ppm;

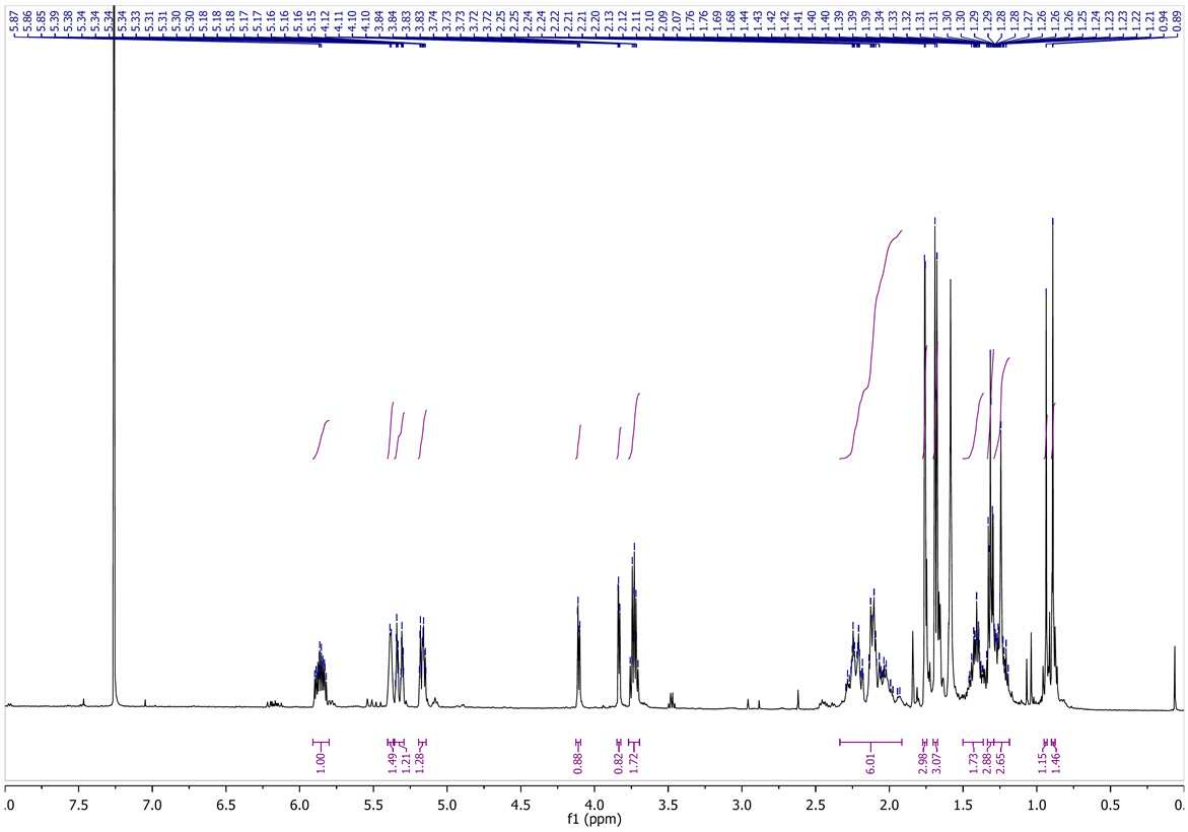
^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4(161.3), 137.3(137.2) 8, 132.2(132.1), 131.94, 130.73(130.71), 127.4(127.2), 114.8(114.7) 9, 84.55 18, 71.8(71.7) 7, 62.73(62.70) OEt-CH_2, 46.39 (CH_2), 39.3(39.1) (CH_2), 33.7 3, 32.6 (CH_2), 25.3(25.2) (CH_2), 24.1(23.9) 10, 22.5(22.4) CH_3, (21.6)21.5 (CH_2), 19.9(19.8) CH_3, 14.61 CH_3 ppm;

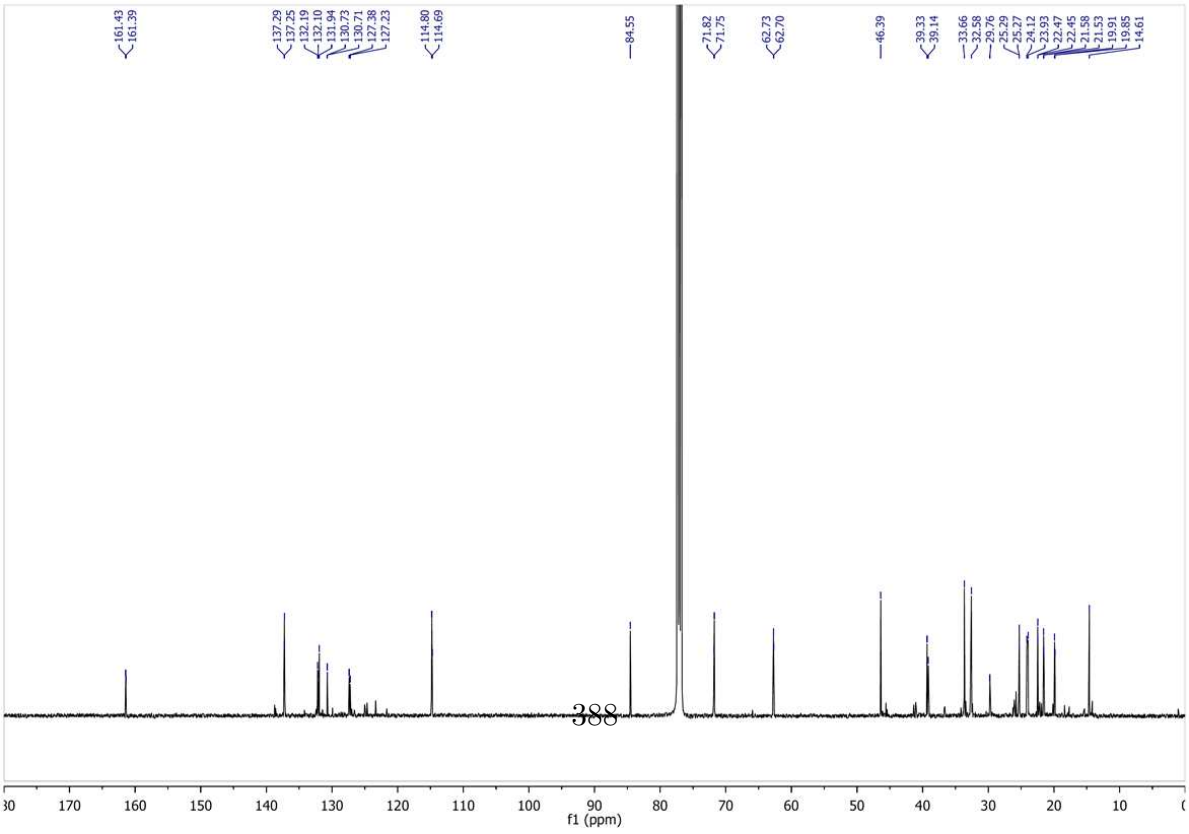
FT-IR thin film, neat (ATR): 3401, 2922, 2360, 1662, 1603, 1457, 1298, 1078, 809 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{20}H_{31}O_2{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 361.1905 found 361.1906 (Δ = 0.37 ppm);

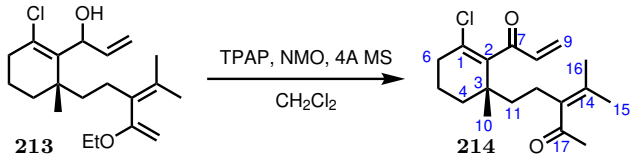
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 7.0° (c = 0.27, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$





5.3.1.62 Diketone 214



Vinyl ether **213** (15 mg, 0.044 mmol, 1.0 mol equiv), *N*-methylmorpholine *N*-oxide (7.7 mg, 0.066 mmol, 1.5 mol eq), activated 4A molecular sieves (30 mg) and dry CH_2Cl_2 (0.50 mL) were added to a flame dried 7 mL vial equipped with a rubber septum and stirrer bar. After stirring for 1 hour at room temperature, TPAP (1.0 mg, 0.0028 mmg, 0.060 mol equiv) was added in one portion. The vial was sealed with a cap and stirred at room temperature. After 24 hours, the mixture was diluted with CH_2Cl_2, filtered through celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (0–10% Et_2O/*n*-pentane, silica column) to give the title compound as a colourless oil (2.0 mg, 0.0065 mmol, 15% yield or 17% brsm).

R_f = 0.60 (30% Et_2O/*n*-pentane, $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.53 (dd, J = 17.5, 10.4 Hz, 1H, 8), 6.22 (dd, J = 17.5, 1.2 Hz, 1H, 9-*trans*), 5.97 (dd, J = 10.4, 1.2 Hz, 1H, 9-*cis*), 2.40 – 2.16 (m, 6H, alkyl-H), 2.26 (s, 3H, 17), 1.83 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.50 (t, J = 6.3 Hz, 2H, alkyl-H), 1.39 – 1.31 (m, 2H, alkyl-H), 1.01 (s, 3H, 10) ppm;

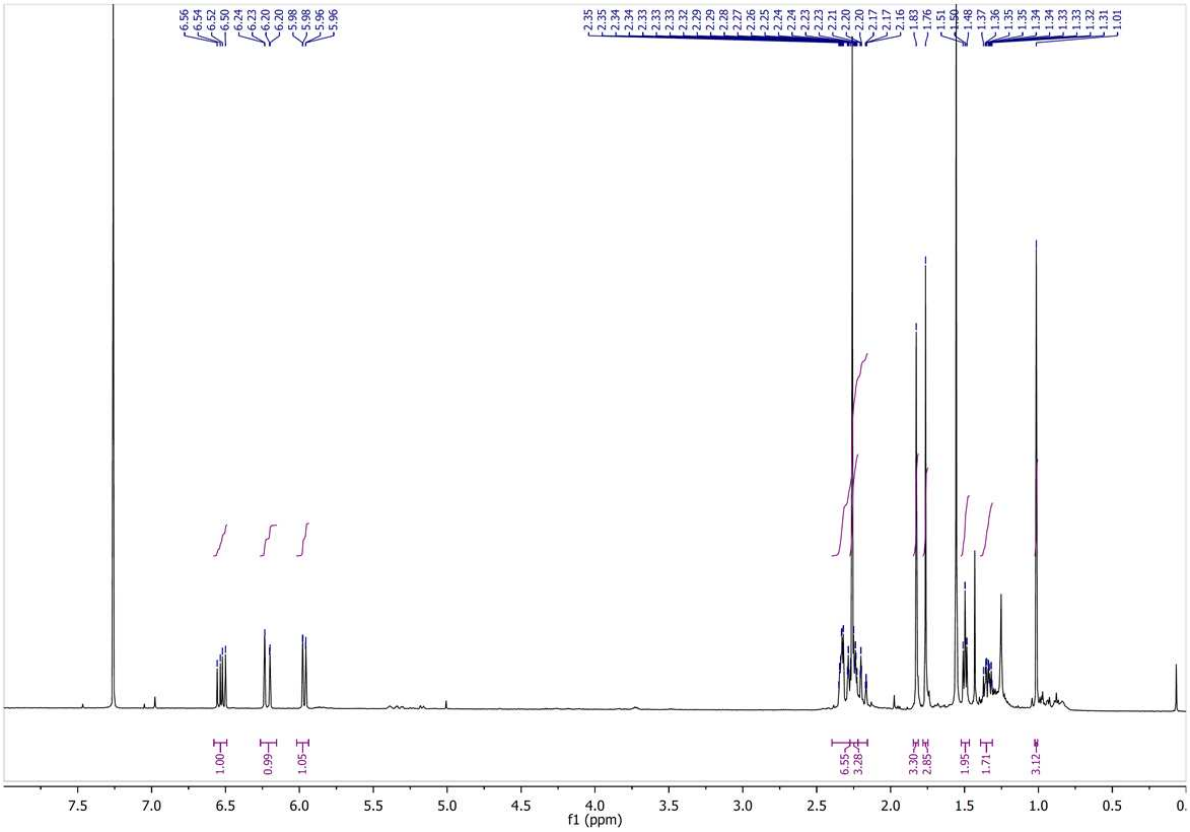
^{13}C NMR (126 MHz, $CDCl_3$): δ 206.0 17, 196.6 7, 137.1 14, 136.7 13, 135.7 8, 133.5 1, 130.7 9, 130.6 2, 45.9 (CH_2), 40.1 (CH_2), 34.0 3, 32.3 (CH_2), 30.7 18, 25.8 (CH_2), 24.1 (CH_2), 24.0 10, 22.8 CH_3, 21.1 CH_3 ppm;

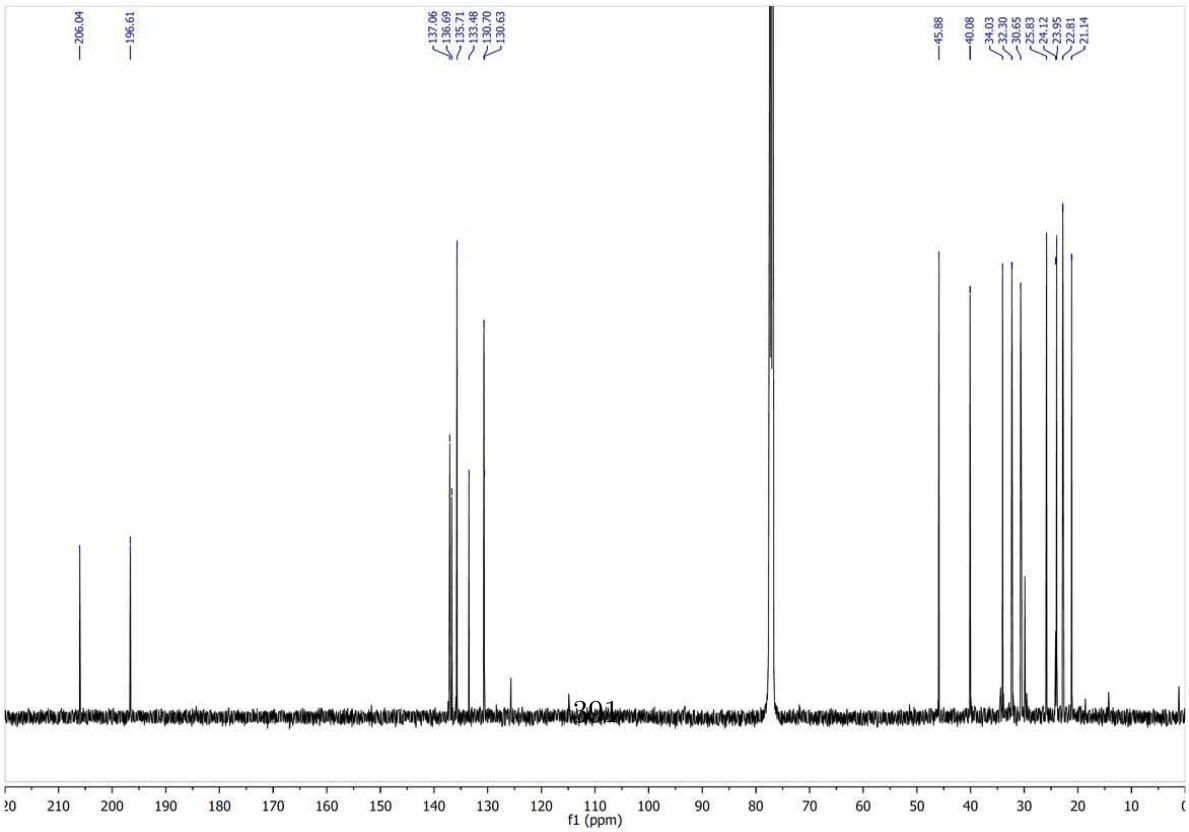
FT-IR thin film, neat (ATR): 2922, 2361, 1668 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{18}H_{26}O_2{}^{35}Cl$, $[M+H]^{+\bullet}$: 309.1616 found 309.1617 (Δ = 0.22 ppm);

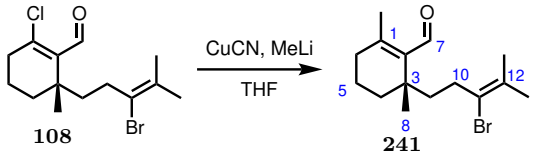
$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 11° (c = 0.28, CH_2Cl_2), based on a sample of 93% *ee*;

$^{1}H/^{13}C$ NMR


6.56
6.54
6.52
6.50
6.24
6.23
6.20
6.20
5.98
5.98
5.96
5.96
2.35
2.35
2.34
2.34
2.33
2.33
2.32
2.32
2.29
2.28
2.27
2.26
2.25
2.24
2.24
2.23
2.23
2.21
2.20
2.20
2.17
2.17
2.16
1.83
1.76
1.51
1.50
1.48
1.37
1.36
1.35
1.35
1.34
1.34
1.33
1.33
1.32
1.31
1.01
1.00
0.99
1.05
6.55
3.28
3.30
2.85
1.95
1.71
3.12
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
f1 (ppm)


206.04
196.61
137.06
136.69
135.71
134.48
130.70
130.63
45.88
40.08
34.03
32.30
30.65
25.83
24.12
23.95
22.81
21.14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

5.3.1.63 (*S*)-6-(3-bromo-4-methylpent-3-en-1-yl)-2,6-dimethylcyclohex-1-ene-1-carbaldehyde 241



Copper(I) cyanide (41 mg, 0.46 mmol, 1.2 mol equiv) was added to a flame dried round bottom flask equipped with a stirrer bar and rubber septum. Three cycles of vacuum and back filling with N_2 were performed. THF (2 mL) was added and the mixture was cooled to −78 °C. Methyllithium (0.57 mL of a 1.6M solution in Et_2O, 0.91 mmol, 2.4 mol equiv) was added dropwise, the solution was immediately warmed to −12 °C (20% MeOH/H_2O and dry ice) and a clear reaction mixture was obtained after 5 minutes. After 40 minutes, the cuprate was cooled to −78 °C again and was added dropwise (down the sides of the flask) to a solution of chloroaldehydes **108** (120 mg, 0.38 mmol, 1.0 mol equiv) in THF (2 mL) also at −78 °C. The solution became yellow and after stirring for 30 minutes, the reaction was quenched with saturated ammonium chloride solution (1 mL) and warmed to room temperature. The aqueous phase was extracted (3x) with Et_2O, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (30–50% CH_2Cl_2/*n*-pentane then 30% EtOAc/*n*-pentane, silica column) to give the title compound as a colourless oil (20 mg, 0.068 mmol, 18% yield).

R_f = 0.17 (50% CH_2Cl_2/*n*-pentane, stains with $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.16 (s, 1H, 7), 2.55 – 2.38 (m, 2H, alkyl-H),

2.24 (m, 2H, alkyl-H), 2.13 (d, J = 1.0 Hz, 3H, 1-Me), 2.12 – 1.94 (m, 2H, alkyl-H), 1.84 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.51 – 1.40 (m, 4H, alkyl-H), 0.91 (s, 3H, 8) ppm;

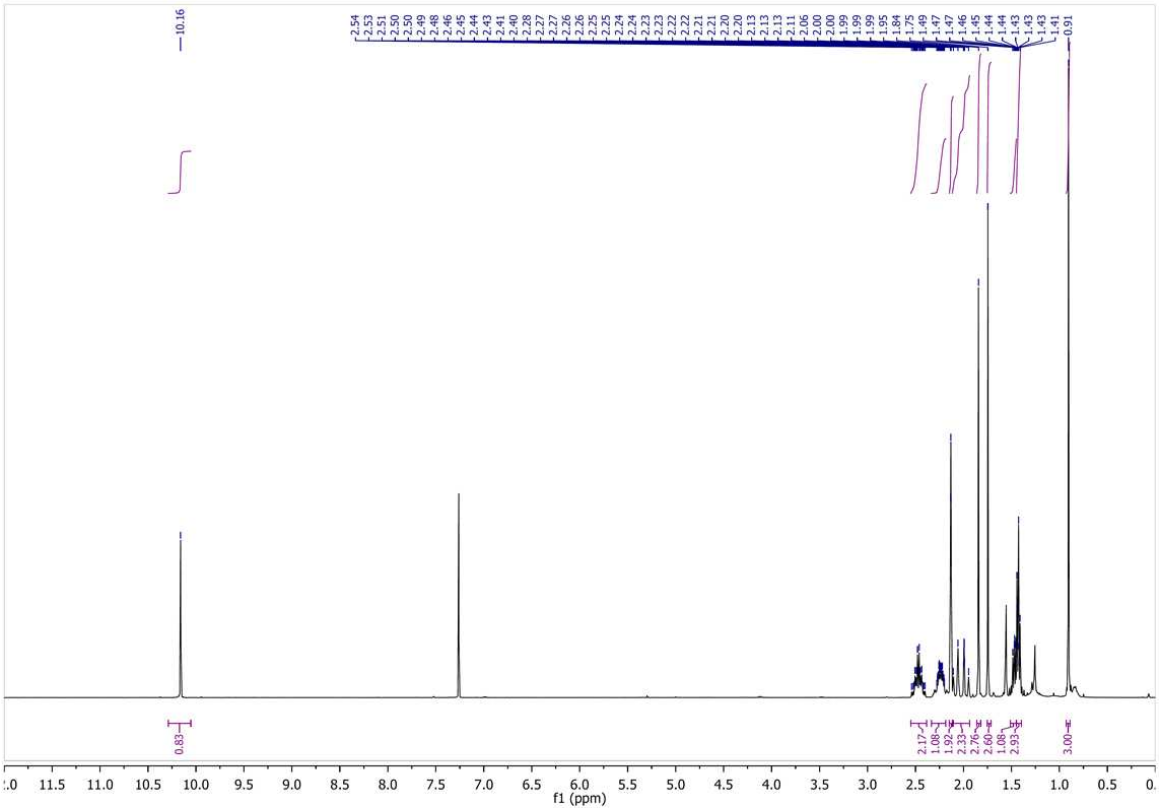
^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9 7, 154.7, 132.7, 129.9, 122.0, 47.1 (CH_2), 39.4 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 31.4 3, 25.5 CH_3, 24.6 8, 20.2 CH_3, 19.8 (CH_2), 18.7 1-CH_3 ppm;

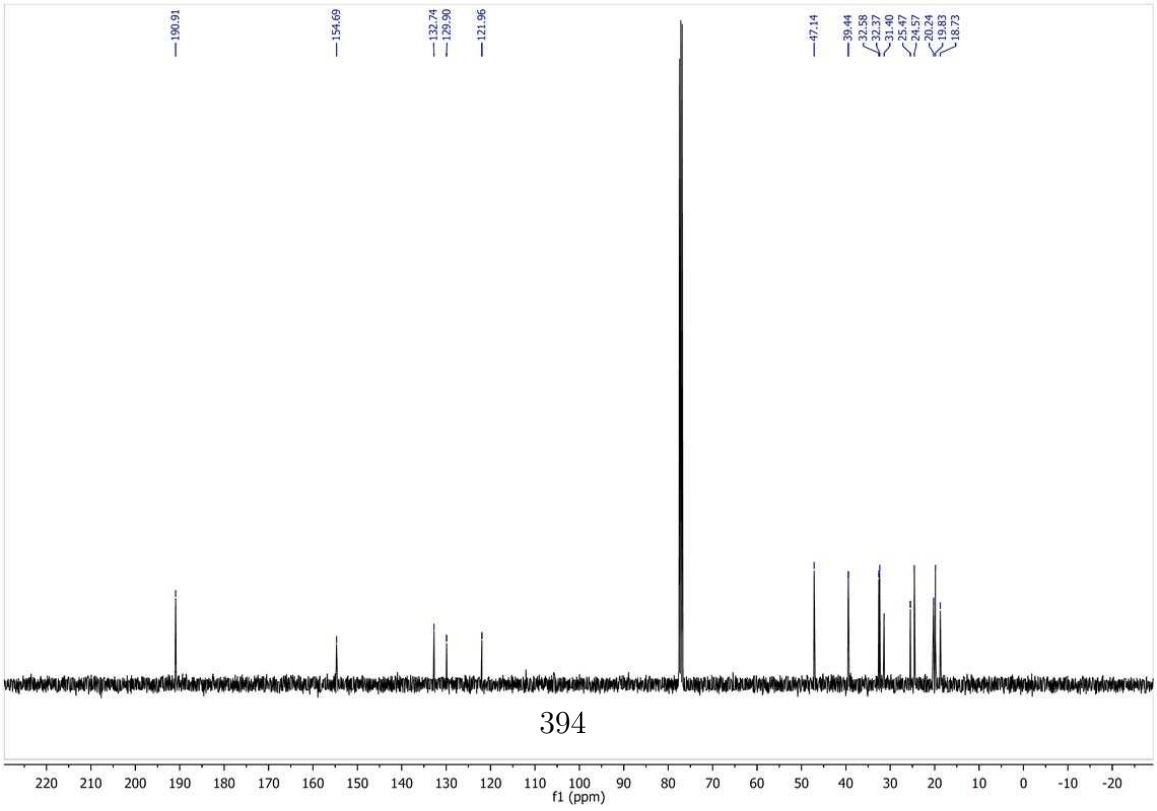
FT-IR thin film, neat (ATR): 2953, 2856, 1667, 1638, 1378, 1246 cm^{-1};

HRMS (ESI$^+$): calculated for $C_{15}H_{24}O^{79}Br$, $[M+H]^{+\bullet}$: 299.10050 found 299.10065 (Δ = 0.48 ppm);

$[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ = + 26° (c = 1.0, CH_2Cl_2), based on a sample of 92% *ee*;

$^{1}H/^{13}C$ NMR


10.16
0.91
0.83
3.00
f1 (ppm)


190.91
154.69
132.74
129.90
121.96
47.14
39.44
32.58
32.37
31.40
25.47
24.57
20.24
19.83
18.73
f1 (ppm)

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