Stereoselective Cyclisation Cascades Mediated by Carbon Electrophiles to Access Novel Polycyclic Scaffolds



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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2020 until December 2023. All of the work is entirely my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Daniya Aynetdinova

December 2023



Abstract

The research outlined in this thesis describes the progress achieved in carbon electrophile-triggered cationic cyclisation cascades. The cation-initiated polyene cyclisation to form carbocyclic rings, as well as heterocyclisation to form novel lactones, has been explored. High levels of diastereoselectivity in setting up new stereocentres during the cyclisation were achieved. Furthermore, initial studies to control the absolute configuration of products were conducted. The results and all the experimental data are discussed in detail in the corresponding chapters.

Chapter 1 provides a literature overview of the current stereoselective polyene cyclisation and heterocyclisation methodologies. Different modes of initiating a cascade cyclisation are discussed. In addition, the role of HFIP solvent in facilitating cationic transformations, such as carbocation generation, is described.

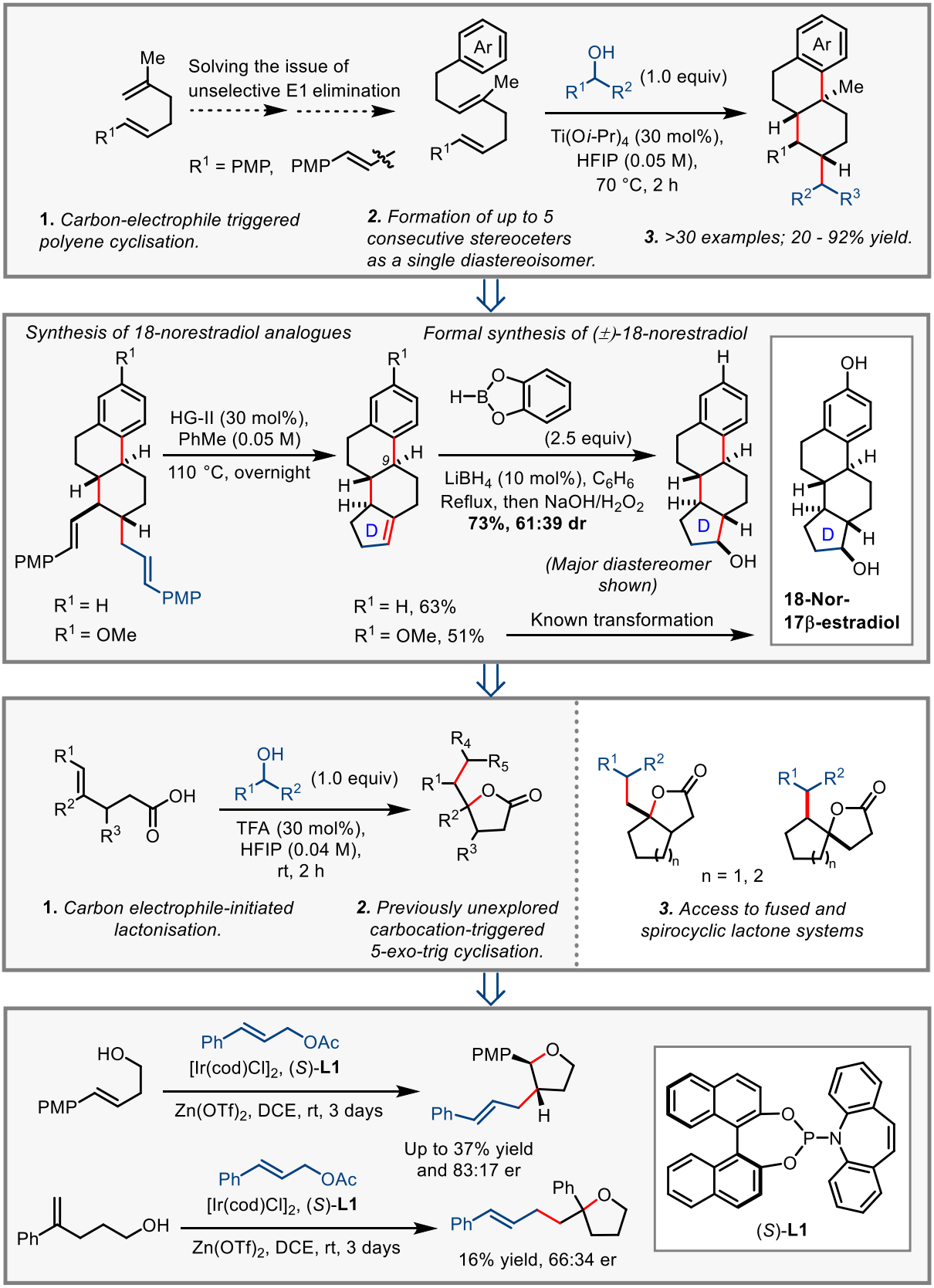
Chapter 2 describes the development of a novel cation-triggered polyene cyclisation cascade. First, the formation of single ring systems is explored. The results from this part are then used to achieve the formation of multiple carbocyclic rings in a single step bearing a new exocyclic C-C bond. Finally, the developed methodology is applied for the synthesis of steroid-like compounds, including the formal synthesis of (±)-nor-estradiol.

Chapter 3 outlines the progress achieved in alkylative lactonisation *via* previously an unexplored *5/6-exo-trig* cyclisation pathway. The synthesis of fused and spiro-lactones using HFIP-alcohol system is detailed, accompanied by control experiments and mechanistic studies aimed at elucidating the reaction mechanism.

Chapter 4 details the initial studies on enantioselective Ir-catalysed polyene cyclisation and heterocyclisation *via* asymmetric allylic substitution.

Chapter 5 provides the summary and major conclusions of the conducted research. Furthermore, potential future work is discussed.

Chapter 6 lists all the experimental procedures and analytical data for all the compounds discussed in this work.



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And to myself (since I will read it again) – always be yourself and never change – it is never worth it. Just be yourself and keep going, Dana!

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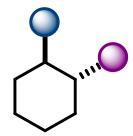
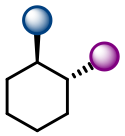
Stereochemistry

Throughout the text in this thesis, straight bonds (unwedged) are used to denote relative stereochemistry in racemic compounds, whereas wedged bonds are used to denote absolute and relative configuration in enantioenriched compounds. Where the absolute stereochemistry could not be determined in enantioenriched compounds, a nominal absolute assignment has been given for ease of discussion.



Racemic



Enantioenriched

Abbreviations and Acronyms

α	alpha
A	allylic
Ac	acetyl
Ar	aryl/aromatic
ax	axial
[α]	specific rotation
β	beta
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
n-Bu	*normal*-butyl
t-Bu	*tert*-butyl
°C	degrees celsius
Cbz	carboxylbenzyl
CDSC	chlorodiethyl sulfonium salts
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
d	doublet
DBDMH	1,3- dibromo-5,5-dimethylhydantoin
DIBAL-H	diisobutylaluminium hydride
DCE	dichloroethane
DCDMH	1,3-dichloro-5,5-dimethylhydantoin
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dqd	double quartet of doublets

dqt	double quartet of triplets
dr	diastereomeric ratio
ee	enantiomeric excess
ent	enantioenriched
eq	equatorial
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
g	grams
h	hours
hept	heptet
HMDS	bis(trimethylsilyl)amine
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
in situ	in place (latin)
in vacuo	in a vacuum (latin)
IR	infrared
IDSI	iododiethyl sulfonium salts
J	coupling constant
L	litre
LBA	Lewis and Brønsted acid system
LDA	lithium diiospropylamide
m	*meta*
m	multiplet
M	molar
Me	methyl

MeCN	acetonitrile
mg	milligrams
min	minute(s)
mL	millilitre(s)
mol%	molar percent
NBS	N-bromosuccinamide
NIS	N-iodosuccinamide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
p	*para*
p	pentet
Ph	phenyl
PMP	*para*-methoxyphenyl
PMB	*para*-methoxybenzyl
PhMe	toluene
ppm	parts per million
i-Pr	*iso*-propyl
q	quartet
qd	quartet of doublets
^{q}NMR	quantitative NMR
(±)	racemic
rr	regioisomeric ratio
rt	room temperature
s	singlet
SM	starting material
SFC	supercritical fluid chromatography
TBCO	2,4,4,6-tetrabromocyclohexa-2,5-dienone
t/*tert*	tertiary
Ts	tosyl

THF	tetrahydrofuran
TMS	trimethylsilyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
t	triplet
TLC	thin layer chromatography
t_r	retention time
UV	ultraviolet
UPLC	ultra performance liquid chromatography
via	by way of (latin)

Chapter 1: Introduction

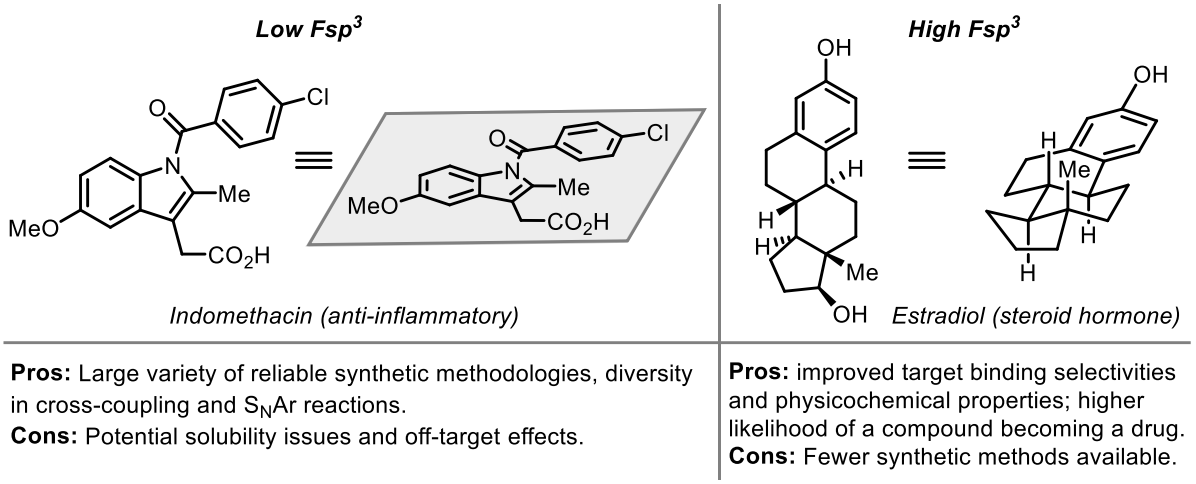
1.1 The need for methodologies to access three-dimensional (3D) scaffolds

The stereoselective construction of 3D molecules is an important but challenging area in synthetical and medicinal chemistry. In 2016 Boström and coworkers published a review in which they analysed chemical reactions used in medicinal chemistry in 2014.[1] The top 20 most employed synthetic transformations included amide bond formation, Suzuki–Miyaura reactions, S_NAr, phenol alkylations and Buchwald–Hartwig aminations. All of these transformations focus on making or functionalising sp^2-rich carbon skeletons. Indeed, Boström and coworkers report that amides, biphenyls and anilines, functionalities that could be accessed with the aforementioned reactions, are common in medicinal compound libraries. On the other hand, sp^3-rich and more natural product-like chemical space, available for medical chemists, remain underexplored.[2]

In 2009 Lovering and coworkers introduced Fsp^3 parameter, a fraction of sp^3 hybridized carbons to a total number of carbons in the molecule: $Fsp^3 = \frac{\mathrm{N}\,(sp^3)}{\mathrm{N}\,(\mathrm{total})}$.[3] The analysis of GVK BIO (now Aragen Life Sciences) drug database by Lovering and coworkers revealed that the average Fsp^3 increased through every stage of drug development: from discovery to drug. This trend illustrates that compounds with higher saturation are more likely to progress through drug development stages. In addition, the same report demonstrates that Fsp^3 parameter affects physical properties of compounds. Aqueous solubility, measured by LogS, was found to increase with Fsp^3, while higher melting point was associated with lower average Fsp^3. Both higher aqueous solubility and lower melting point are important physicochemical parameters of drug candidates, which are often associated with an improved oral bioavailability.[4] Therefore, increasing molecular complexity and sp^3 character has a positive impact on physicochemical properties as well. Furthermore, in 2013 Lovering showed that discovery compounds at Pfizer with higher Fsp^3 on average have lower Cyp450 inhibition and higher

target selectivity.[2] Cyp450 enzymes play a key role in drug metabolism and detoxification in humans, thus any drug candidate must be optimised to reduced Cyp450 inhibition.[5]

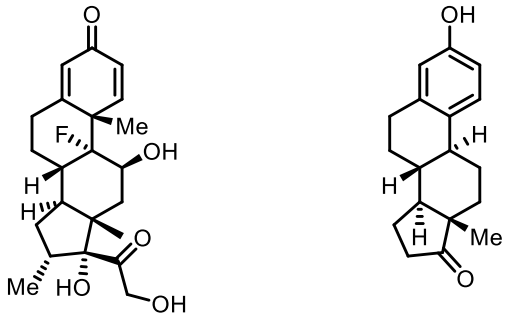
The increasing evidence for lower toxicity and off-target binding of sp^3-rich drug candidates, as well as the improved physicochemical parameters, should facilitate pharmaceutical industries to explore diverse chemical space outside flat sp^2-rich scaffolds (Scheme **1**). However, the opposite trend is seen. As reported by Walters and coworkers in 2011, Fsp^3 in compounds published in the Journal of Medicinal Chemistry steadily decreased in the period from 1995 to 2009.[6] Interestingly, the median Fsp^3 was found to be higher in approved drugs between 2005–2009 versus discovery compounds published in the Journal of Medicinal Chemistry. This further suggests the lack of research to access sp^3-rich scaffolds in the pharmaceutical industry.



*Scheme **1***. Comparison of approved drugs with low and high Fsp^3.

To tackle this issue, it is important to continue new reaction development to access structures with multiple stereocenters in a controlled and efficient way. Furthermore, the stereoselective synthesis of 3D compounds from achiral precursors is of particular interest to medicinal chemistry, and hence, the synthetic community.[7] Indeed, based on data from major pharmaceutical companies, Roughley and coworkers conclude that in up to 87% cases stereocenters in drugs and drug candidates were introduced through modification of chiral pool starting materials.[8]

Formation of saturated hetero- or carbocycles through stereoselective cyclisation of achiral starting materials provides a versatile platform to rapidly increase molecular complexity and form new stereocenters. In addition, saturated cyclic scaffolds have reduced numbers of rotational degrees of freedom and often possess unique 3D shapes, which are important for target binding.[9] Corticosteroids and gonadal steroids are examples of biologically active saturated carbocycles with important anti-inflammatory properties (Scheme **2**).[10]



Dexamethazone
Corticosteroid

Estrone
Gonadal steroid

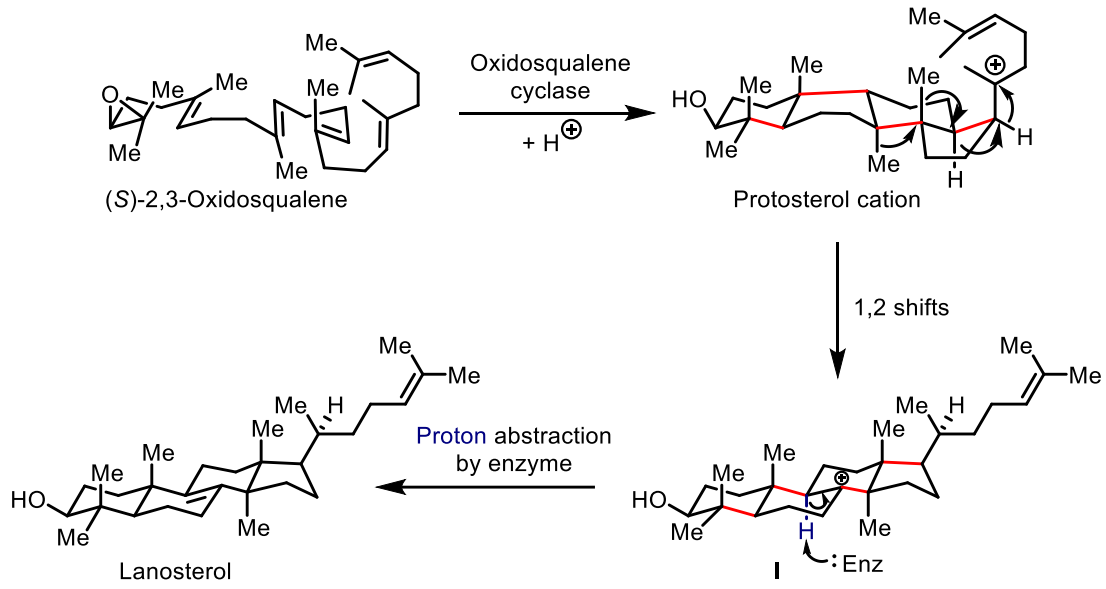
*Scheme **2***. Examples of biologically active corticosteroids and gonadal steroids.

Consequently, the stereoselective synthesis of hetero- and carbocycles has received a growing attention from the synthetic community. In this introductory chapter, the recent developments in the area of stereoselective cyclisation to access sp^3-rich scaffolds will be discussed. The discussion will be divided into sections, detailing the progress made in polyene cyclisation towards carbocycles, followed by heterocyclisation to access saturated heterocycles. In the last section of the introduction, the role of carbocations in C-C bond forming reactions as well as the unique properties of HFIP solvent will be discussed.

1.2 Recent developments in polyene cyclisation

Polyene cyclisations are highly efficient and versatile biomimetic transformations which allow us to set up multiple stereocenters in a single step from a linear polyene precursor.[11] Polyene cyclisation rapidly generates molecular complexity by forming new C(sp^3)-C(sp^3) bonds. In Nature, these reactions are catalysed by a series of enzymes called terpenoid cyclases.[12]

These enzymes bind linear polyene terpene precursor in the active site and preorganise the substrate in a defined way. This allows for a stereocontroled cyclisation from a precise conformation of an otherwise flexible terpene precursor, generating a specific stereoisomer of the terpene product. For example, the cationic cyclisation of squalene oxide, catalysed by oxidosqualene cyclase, proceeds with the formation of a single stereoisomer of lanosterol, an intermediate in the biosynthesis of cholesterol (Scheme **3**).[12,13] The polyene cyclisation is initiated by protonation of the epoxide in the enzyme active site and proceeds *via* chair-boat-chair conformation, controlled by the enzyme. This generates a single stereoisomer of an intermediate protesterol cation, which then undergoes a series of 1,2-methyl and hydride shifts to generate tertiary carbocation **I**. Finally, a proton abstraction by the enzyme affords lanosterol.



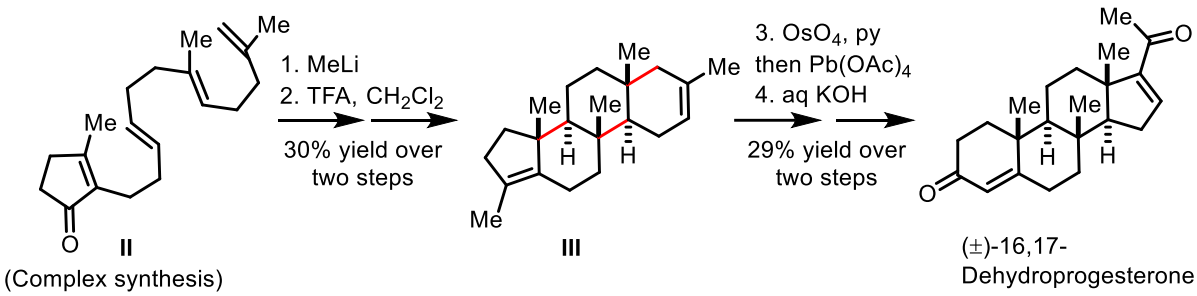
*Scheme **3***. Biosynthesis of Lanosterol *via* an enzyme-controlled polyene cyclisation.

Polyene cyclisation cascades can be broadly divided into three steps: initiation, propagation and termination. Each step has its own set of challenges and requirements. Given the efficiency of polyene cyclisation reactions in forming new C-C bonds and stereocenters, these transformations have been explored by the synthetic community as well.[11] Several cationic and radical polyene cyclisation methodologies have been developed, with cationic cyclisation

mode being more broadly explored.[11,14] Given the nature of this DPhil project and broadness of the field, only cationic polyene cyclisation strategies will be discussed in the introduction. The discussion will be divided based on the initiator type. To date, the most explored initiators to trigger polyene cyclisation cascades in literature are Lewis and Brønsted acids, halonium ions and sulfonium ions.[11,14,15]

1.2.1 Overview of cationic polyene cylisations initiated by Lewis and Brønstead acids

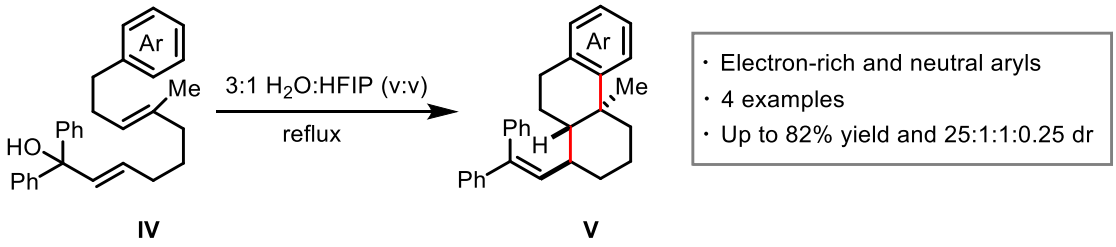
Inspired by the biosynthesis of Lanosterol in Nature, organic chemists have studied polyene cyclisation cascades, expanding the substrate scopes and developing new reaction methodologies. The first reports on synthetic polyene cyclisations come in late 1960, after Stork and Eschenmoser developed a set of rules to explain the regio- and stereoselectivity observed in enzyme-catalysed polyene cyclisations.[16] One of the first reports, was the total synthesis of (±)-16,17-dehydroprogesterone by Johnson and coworkers completed in 1968 (Scheme **4**).[17] The key reaction was polyene cyclisation of tertiary allylic alcohol, formed after the addition of MeLi to ketone **II**. The tertiary allylic alcohol was unstable and was subjected to cationic polyene cyclisation under acidic conditions without purification. The reaction proceeded with a high diastereoselectivity to form alkene **III** in 30% yield over two steps. In this case, regioselective E1 elimination served as a termination event. The synthesis of (±)-16,17-dehydroprogesterone was completed in two steps from alkene **III** *via* oxidative alkene cleavage followed by intramolecular aldol reaction.



II (Complex synthesis) **III** (±)-16,17-Dehydroprogesterone

*Scheme **4***. Total synthesis of (±)-16,17-dehydroprogesterone *via* cationic polyene cyclisation.

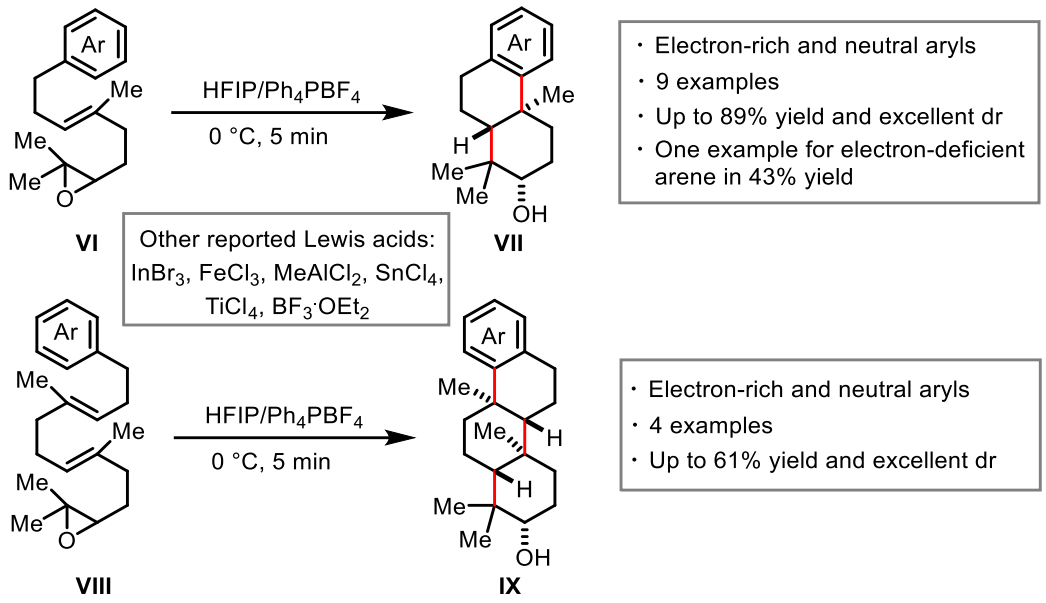
Following early reports, the field of cationic polyene cyclisation initiated by Lewis or Brønsted acids has rapidly expanded. While the early reports mostly covered individual reactions applied to total synthesis, the recent work focused on developing more general polyene cyclisation methodologies. In 2015, Qu and coworkers reported polyene cyclisation of π-activated alcohols, a general methodology conceptually similar to the Johnson's key step polyene cyclisation (Scheme **5**).[18] In this work, 3:1 H_2O:HFIP solvent mixture was used to trigger ionisation of an allylic alcohol within substrate **IV**, which then initiated cascade cyclisation. Substrates with neutral and electron-rich aryl groups were engaged in up to 82% yield and 25:1:1:0.25 dr. Two new C-C bonds were made during the polyene cyclisation, setting up an exocyclic alkene. The presence of HFIP as a minor component in the solvent mixture with water was essential, as no conversion was otherwise observed.



*Scheme **5***. Qu's polyene cyclisation of π-activated alcohols.

A biomimetic polyene cyclisation initiated by epoxide ring opening was later published by the same group in 2016 (Scheme **6**).[19] In this work, the authors utilized the combination of HFIP and Ph_4PBF_4 to trigger highly diastereoselective cyclisation cascades. It was proposed that solvolysis of Ph_4PBF_4 in HFIP generated HF *in situ* which then triggered polyene cyclisation of substrates **VI** and **VIII** by epoxide protonation. In addition, the authors comment that any carbocationic intermediates are further stabilized by non-nucleophilic BF_4^- anions. For substrate **VI**, 9 examples bearing electron-rich and neutral aryls were obtained in up to 89% yield and excellent diastereoselectivity. Only one example of electron deficient *para*-fluoro-substituted arene was demonstrated, furnishing the corresponding product **VII** in reduced 43% yield. This highlights the common limitation of polyene cyclisation methodologies in engaging

substrates with electron-deficient terminating groups. In addition, polyene **VIII** could be engaged in the cyclisation to form product **IX** with three new C-C bonds in up to 61% yield.

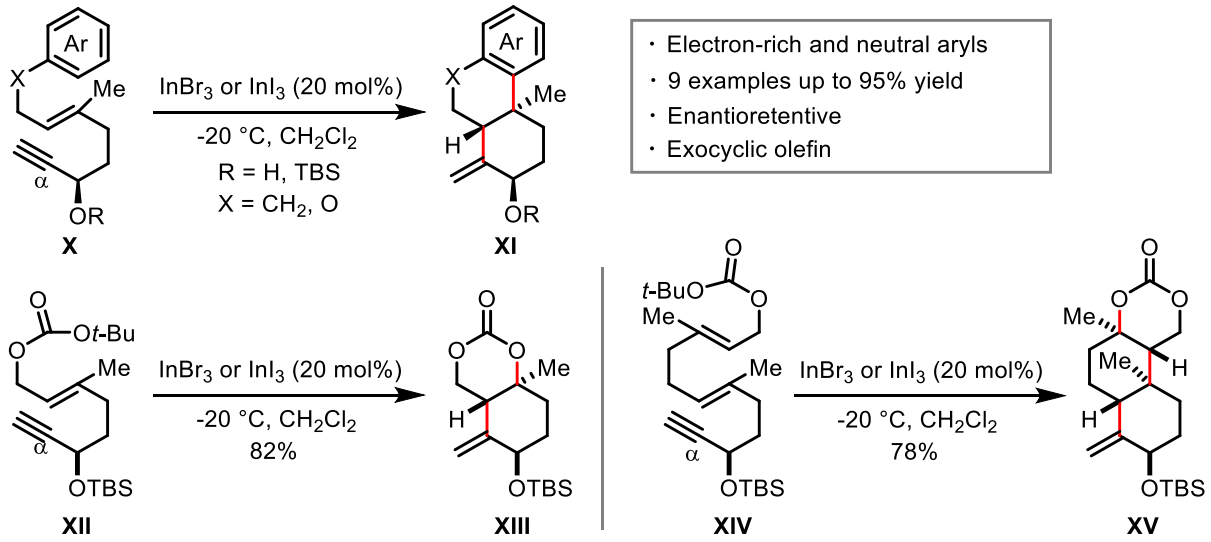


Scheme ***6***. Qu's biomimetic polyene cyclisation using Ph_4PBF_4 and the summary of other Lewis acids employed.

Prior to the use of Ph_4PBF_4, several different Lewis and Brønsted acids have been used to trigger polyene cyclisations by coordination to epoxides. In 2008 Loh and coworkers reported $InBr_3$ promoted polyene cyclisation of substrate **VI** in up to 77% yield.[20] However, the reaction efficiency was reduced by the formation of monocyclised side-products. Following the literature reports, $FeCl_3$ Lewis acid was used by Baran and coworkers in 2013 during the total synthesis of (±)-Steviol.[21] In Baran's work, the polyene cyclisation of substrate related to compound **VI** was achieved in 52% yield. The use of other Lewis acids, such as $MeAlCl_2$,[22] $SnCl_4$,[23] and $BF_3{\cdot}OEt_2$[24] has been also demonstrated for similar scaffolds. It appears that the exact choice of a Lewis or Brønsted acid depends on the reaction conditions as well as the precise structure of the polyene cyclisation substrate.

A different mode of activation was reported by Corey and coworkers in 2011 (Scheme **7**).[25] In their work, the authors used $InBr_3$ or InI_3 Lewis acids to trigger polyene cyclisations from propargylic alcohol substrates **X**, **XII** and **XIV**. The reaction proceeded *via* coordination of In(III)

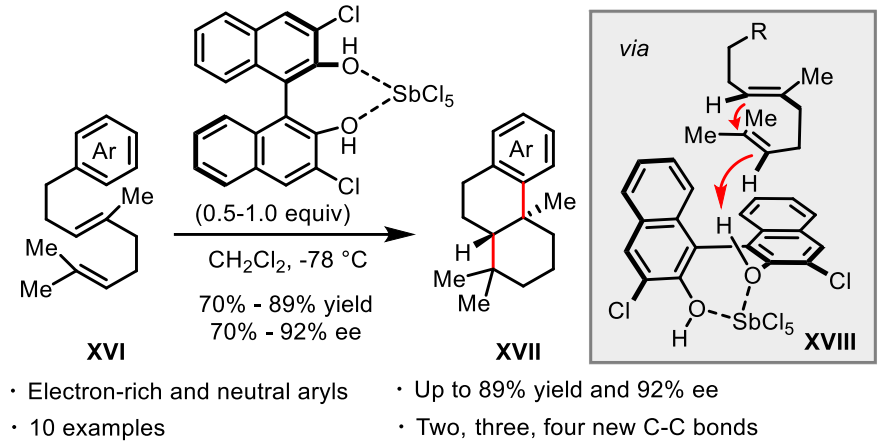
to the alkyne, directed by the neighbouring oxygen. This increased the build-up of a positive charge on α-carbon, triggering polyene cyclisation. For substrate **X**, the reaction was enantioretentive, with a single chiral centre controlling the absolute configuration of the product. Electron-rich and neutral aryls could be used and the polyene cyclisation proceeded with a high stereoselectivity forming up to four new C-C bonds. Interestingly, racemic carbonate substrates **XII** and **XIV** could also be engaged, forming products **XIII** and **XV** in good yields. This proceeded with carbonate oxygen acting as an intramolecular nucleophile.



Scheme ***7***. Corey's enantioretentive $InBr_3$ or InI_3 polyene cyclisation.

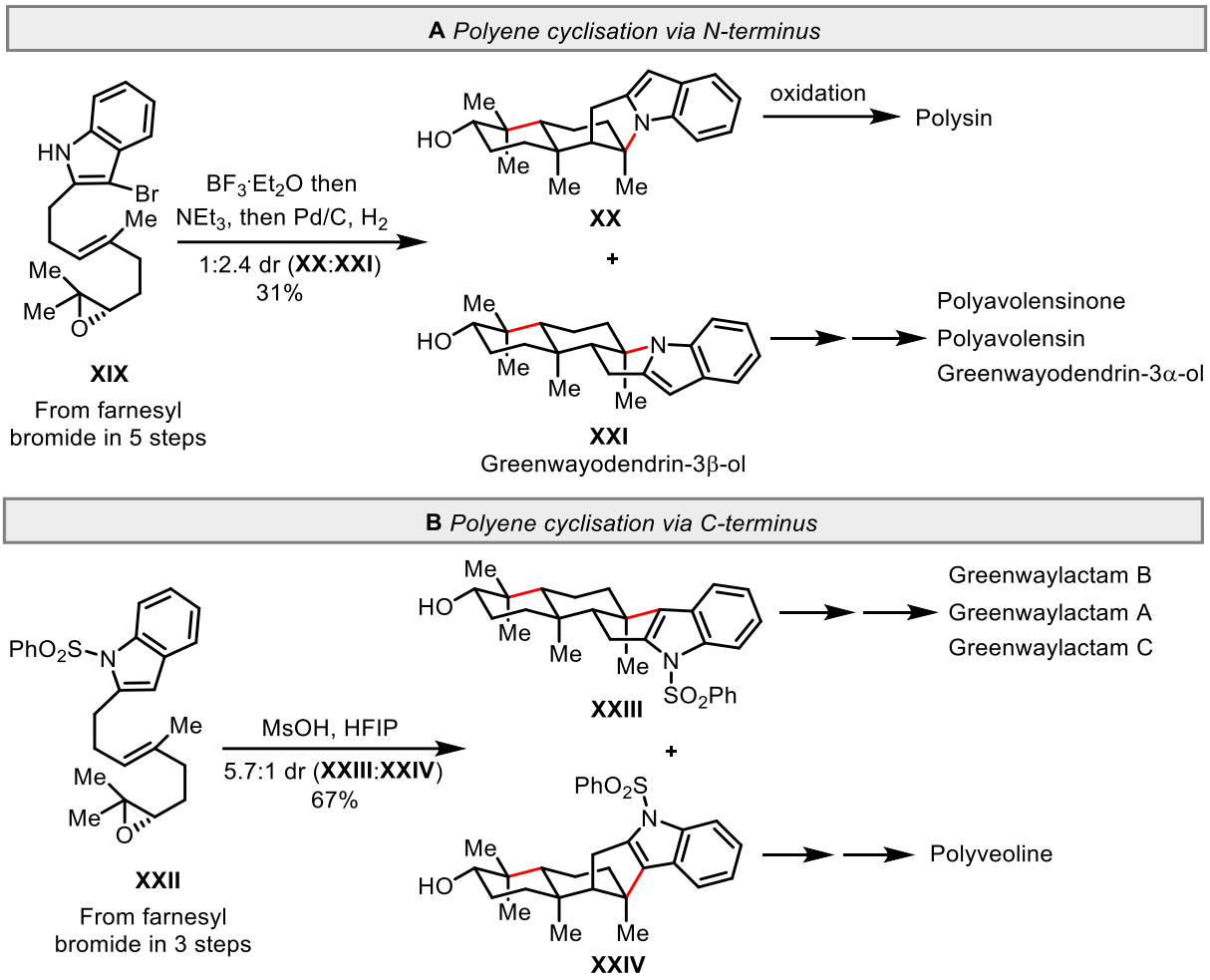
The same group later published enantioselective proton-initiated polyene cyclisation.[26] The reaction concept was inspired by the early work of Yamamoto and coworkers from 1999.[27] Yamamoto's group were the first to show that combining $SnCl_4$ Lewis acid and monoether binol derivative (LBA system) increases the acidity of the Brønsted acid and can trigger enantioselective proton-catalysed polyene cyclisations. While conceptually important, the early work suffered from the modest levels of enantioselectivity and, in some cases, diastereoselectivity. Corey and coworkers improved the reactivity of the combined Lewis and Brønsted acid system by using bulkier and more Lewis acidic $SbCl_5$, instead of $SnCl_4$, and a more acidic binol derivative (Scheme **8**).[26] With these changes, up to 92% ee and 89% yield could be achieved. Electron-rich and neutral arenes, as well as one example of *para*-bromo-

substituted arene were engaged with the formation of up to four new endocyclic C-C bonds. The authors suggested that 1:1 complex between the binol derivative and $SbCl_5$ restricts the access to the proton, forcing pre-transition-state assembly **XVIII**. Protonation of the polyene then proceeds with π-face-selectivity with the build-up of a positive charge on the tertiary carbon being stabilized by π-π interactions with the binol naphthyl subunit.



*Scheme **8***. Corey's enantioselective proton-catalysed polyene cyclisation.

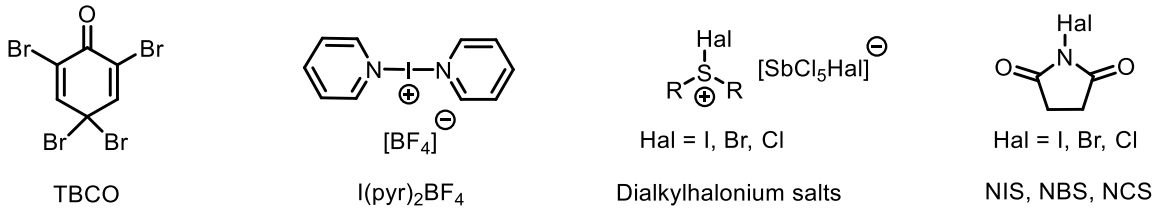
Lewis or Brønsted acid catalysed polyene cyclisation methodologies are widely used as key steps to rapidly build-up molecular complexity in total synthesis. For example, in 2023 Magauer and coworkers reported a divergent polyene cyclisation initiated by epoxide ring opening to access nine natural products and biologically active compounds (Scheme **9**).[28] Two different polyene cyclisation reactions have been employed to set-up polycyclic scaffolds. In the first type, the cascade cyclisation was terminated with nitrogen of the indole ring, while in the second type the termination was achieved with a formation of a C-C bond. Substrate **XIX** was prepared in five steps from farnesyl bromide and then subjected to polyene cyclisation using $BF_3{\cdot}OEt_2$ Lewis acid (Scheme **9**, A). Diastereomers **XX** and **XXI** were isolated in 31% combined yield as a separable 1:2.4 diastereomeric mixture. Diastereomers **XX** and **XXI** were then used to access four different sesquiterpenoid alkaloid scaffolds. Polyene cyclisation of substrate **XXII** catalysed by MsOH Brønsted acid, proceeded in an improved 67% yield and diastereoselectivity (Scheme **9**, B). Diastereomers **XXIII** and **XXIV** were formed in 5.7:1 ratio and then used to access additional natural product structures.



Scheme ***9***. Magauer's polyene cyclisation cascade as a key step in divergent total synthesis.

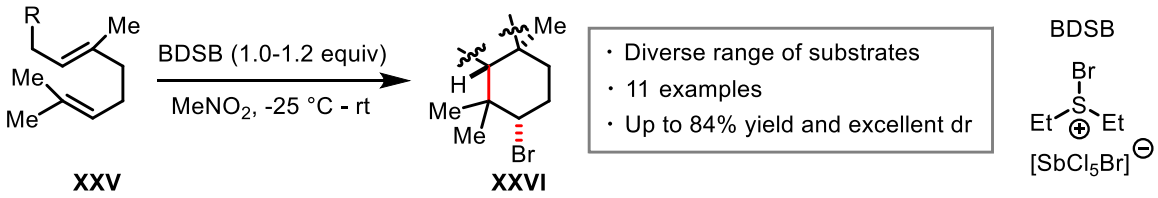
1.2.2 Overview of cationic polyene cyclisations initiated by halonium ions

Halonium ion induced polyene cyclisation is another biomimetic type of cascade reaction that has received a lot of attention from the scientific community.[14(b)] In addition to allowing the synthesis of several halogenated terpenoid natural products, these transformations set-up a synthetically versatile C-Hal bond with a high degree of stereocontrol. Several halogenating reagents have been developed to initiate synthetic polyene cyclisations (Scheme **10**). Examples include 2,4,4,6-Tetrabromocyclohexa-2,5-dienone (TBCO),[29] bis(pyridine)iodonium tetrafluoroborate,[30] halodialkyl sulfonium salts[31] and N-haloamides.[32] While there are several protocols for iodo-, bromo- and even chloro-induced polyene cascades, only isolated literature examples are available for the cyclisations initiated by C-F bond formation.[33]



*Scheme **10***. Common halogenation reagents.

The use of TBCO brominating agent, pioneered by Kato and coworkers in 1975,[29(a)] has commonly suffered from low yields and selectivity in polyene cyclisations. An important breakthrough was the 2009 work from Snyder and coworkers on developing bromodialkyl sulfonium salts, such as $[Et_2SBr]^+[SbCl_5Br]^-$ (BDSB).[34] These salts proved to be powerful and general reagents for bromo-induced polyene cyclisations to form **XXVI** (Scheme **11**). With BDSB reagent, 11 examples in up to 84% yield were obtained using a diverse range of polyene substrates.

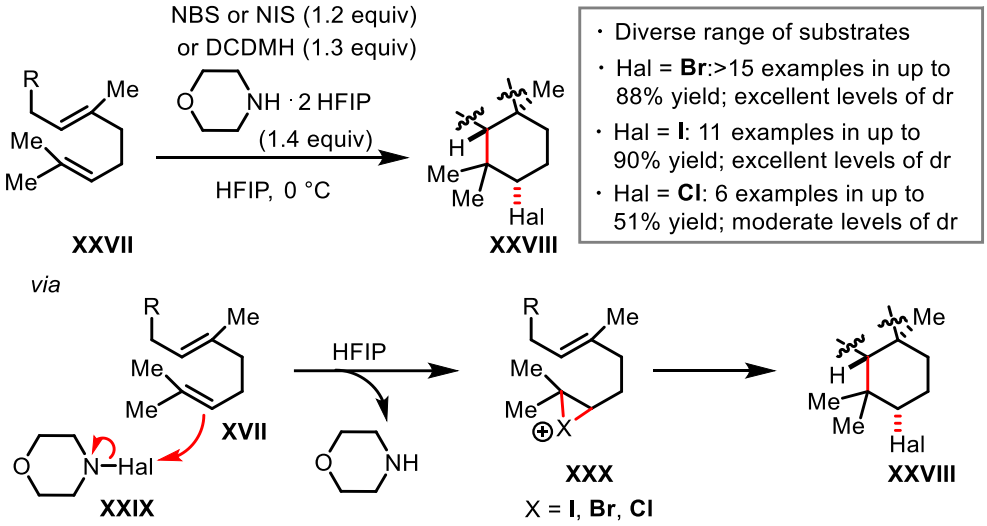


*Scheme **11***. Snyder's bromonium induced polyene cyclisation.

Later, the same group has extended their methodology to allow iodo- and chloro-induced polyene cyclisations using iododiethyl sulfonium salts (IDSI) and chlorodiethyl sulfonium salts (CDSC) respectively.[35] Excellent yields in up to 93% of polycyclic products with IDSI could be achieved. Chloro-induced polyene cyclisations with CDSC, on the other hand, suffered from low selectivities with yields up to 46% of inseparable product diastereomers. Mechanistically, halodialkyl sulfonium salts first form three-membered halonium ion after reacting with the most accessible olefin of the substrate, followed by cationic polyene cyclisation.

Another breakthrough came from the group of Gulder. The use of N-haloamides in polyene cyclization has been explored before, however, additives such as phosphines and phosphites, were required to form more reactive halophosphonium ions *in situ*.[32] In 2018 Gulder and

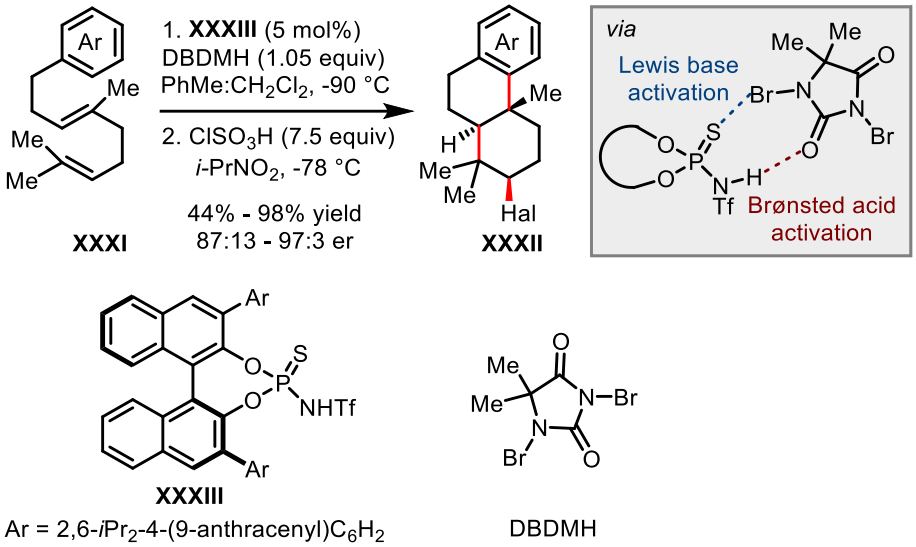
coworkers demonstrated that superior results could be obtained using N-haloamides, such as NBS, NIS or DCDMH (1,3-dichloro-5,5-dimethylhydantoin), together with morpholine-HFIP salt in HFIP (Scheme **12**).[36] The reaction proceeds *via* the formation of halomorpholine species **XXIX** which then generates halonium ions **XXX**, followed by polyene cyclisation to form products **XXVIII**. Excellent yields and dr were achieved for bromo- and iodo-induced cyclisations, while chloro-induced cationic cascades suffered from low to moderate yields and dr.



*Scheme **12***. Gulder's halonium ion-induced polyene cyclisation using N-haloamides in HFIP.

N-haloamides have been a halogenation reagent of choice in several asymmetric halonium ion-induced polyene cyclisations.[14(b)] One of the most recent developments in this field is the 2017 work from Yamamoto's research group.[37] The enantioselective bromocyclization of polyenes was achieved using 1,3- dibromo-5,5-dimethylhydantoin (DBDMH) under binol-derived chiral thiophosphoramide catalysis (Scheme **13**). The concept was similar to early work from Ishihara and coworkers on asymmetric halocyclization, which relied on the use of phosphoramidite or phosphite-urea bifunctional catalysts.[32(a),32(b),38] Yamamoto's work has enabled general bromonium-induced polyene cyclisations by changing the Lewis base of the catalyst from phosphorus to sulfur. Yamamoto and coworkers propose that dual Brønsted acid and Lewis base activation of DBDMH occurs, allowing enantioselective polyene cyclisation cascade. Under the optimised conditions, treatment of the crude reaction mixture with $ClSO_3H$

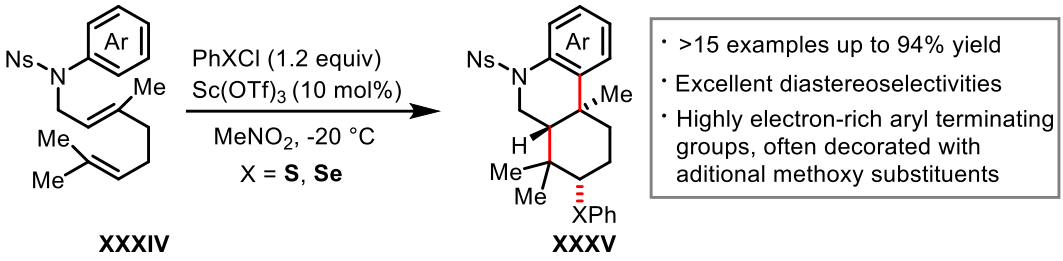
was necessary to achieve the second cyclisation. With substrates **XXXI**, 7 examples of products **XXXII** in up to 98% yield and 97:3 er were obtained.



*Scheme **13***. Yamamoto's enantioselective bromocyclization of polyenes.

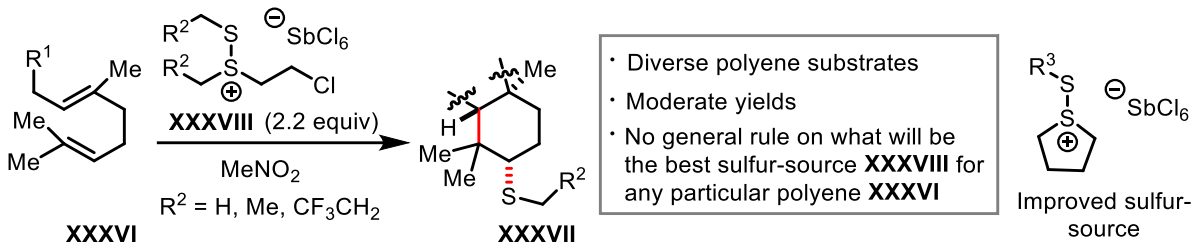
1.2.3 Overview of cationic polyene cyclisations initiated by sulfenium ions

Polyene cyclisation with the formation of an exocyclic C-S bond is an emerging mode of triggering cationic cascades.[15(a)] Following early reports from the Livinghouse research group,[39] Shaw and coworkers developed a diastereoselective polyene cyclisation of N-geranyl anilines **XXXIV** initiated by PhSCl (Scheme **14**).[40] Excellent yields and diastereoselectivities could be achieved, however, the reaction relied on the use of highly electron-rich aryls. Only one substrate without additional electron-donating groups was employed, resulting in a significant decrease in the reaction yield.



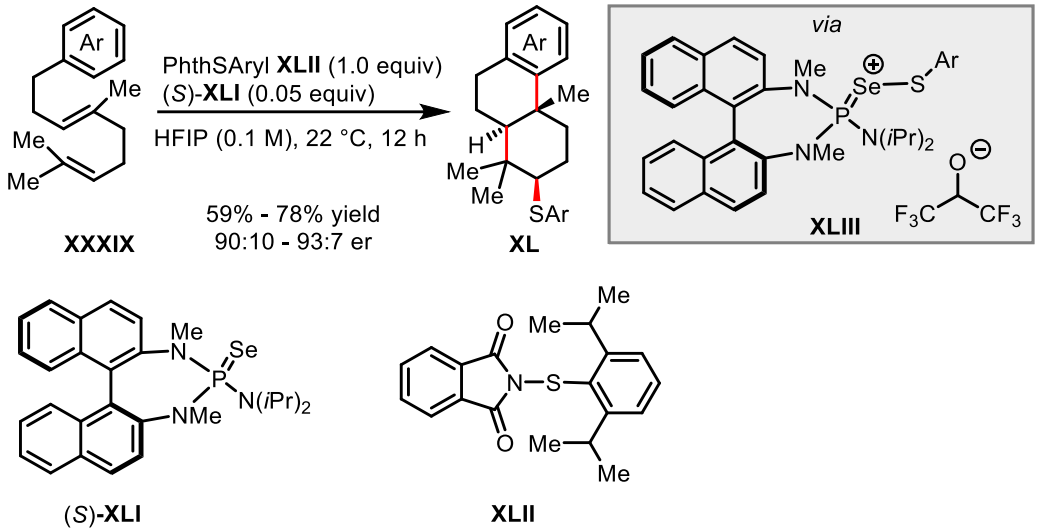
*Scheme **14***. Shaw's sulfur and selenium-induced polyene cyclisation.

In 2017, Snyder reported an alternative reagent for sulfur-promoted polyene cyclisation.[41] Following their previous work on halodialkyl sulfonium salts,[34,35] Snyder's group developed alkyldisulfanium salts **XXXVIII** to initiate polyene cyclisations with the formation of an exocyclic C-S bond (Scheme **15**). Although the reaction no longer required electron-rich aryl terminating groups, this protocol suffered from moderate yields and the requirement to test different reagents **XXXVIII** to find the most optimum sulfur-source for each substrate **XXXVI**. Later, Snyder's group have improved their sulfur source by developing tetrahydrothiophene-based disulfanium salts.[42] The cyclic sulfur-derived activating group afforded higher yields for the same reactions.



*Scheme **15***. Snyder's sulfur-induced polyene cyclisation using alkyldisulfanium salts.

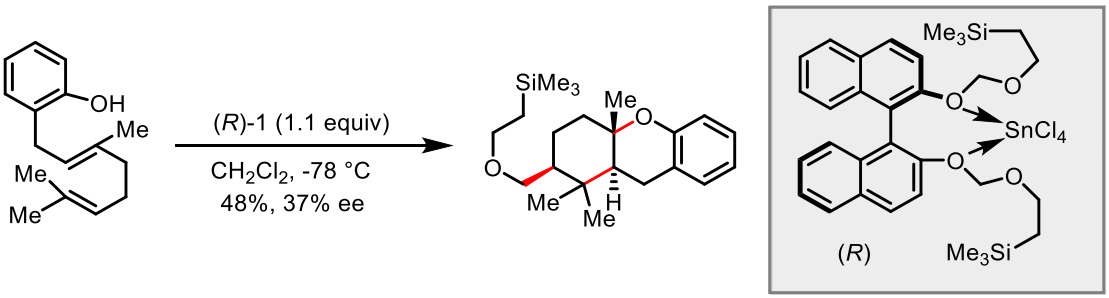
Perhaps, one of the most exciting developments in sulfenocyclisation of polyenes is the work from Denmark and coworkers reported in 2018.[43] By employing S-arylthiophthalimide **XLII** with chiral binol-derived thiophosphoramide Lewis base catalyst **XLI**, the group was able to achieve enantioselective polyene cyclisation triggered by sulfenium ions (Scheme **16**). Products **XL** in up to 78% yield and 93:7 er could be obtained using this method. The authors propose that the reaction proceeds *via* the formation of chiral cationic complex **XLIII**, which then reacts with the most accessible alkene of substrate **XXXIX** to transfer sulfur group in asymmetric fashion.



*Scheme **16***. Denmark's sulfenium-induced polyene cyclisation.

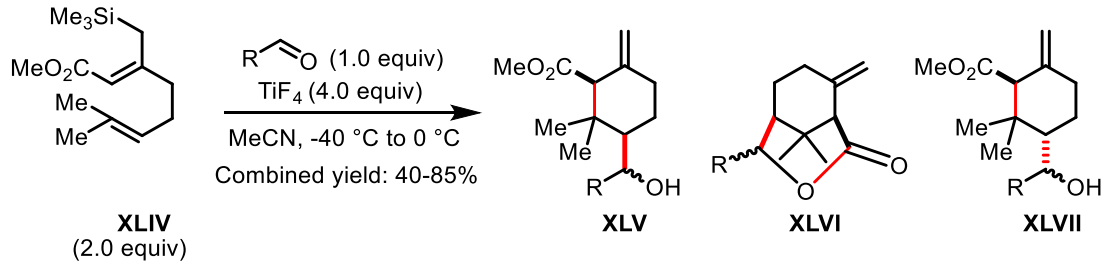
1.2.4 Overview of cationic polyene cyclisations initiated by carbon electrophiles

Compared to other types of initiators, the use of carbon-electrophiles to trigger cationic polyene cyclisations has been largely underexplored. This mode of initiating allows to set up an exocyclic C-C bond which could be used to further build up molecular complexity. The pioneering example of the polyene cyclisation triggered by the formation of an exocyclic C-C bond comes from the Yamamoto's research group.[44] In 2000, Yamamoto and coworkers demonstrated that chiral binol-derived acetals in combination with $SnCl_4$ can be used as an enantioselective hydroxymethylating reagent for trisubstituted alkenes. Although only one example of cascade cyclisation in 48% yield and 37% ee was reported, this work paved the way for the future acetal or aldehyde-induced cationic polyene cyclisations (Scheme **17**).



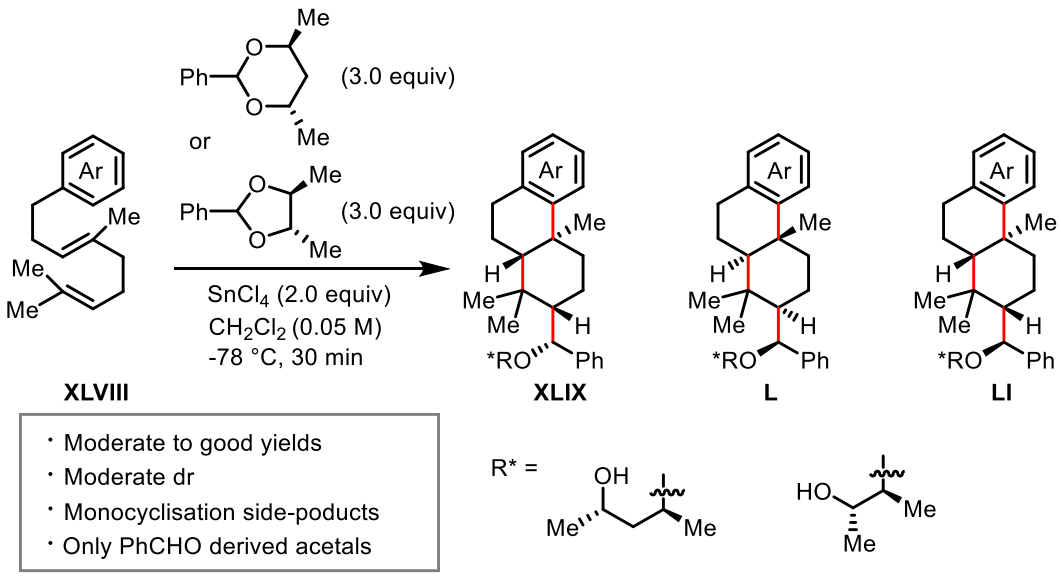
*Scheme **17***. Yamamoto's carbon-electrophile induced polyene cyclisation.

Vidari and coworkers later reported TiF_4-mediated biomimetic alkylation–cyclization cascade with aldehydes (Scheme **18**).[45] Limitations of this work were poor to moderate levels of dr, as well as complex mixtures of *cis*-ester **XLV**, lactone **XLVI** and *trans*-ester **XLVII** being formed.



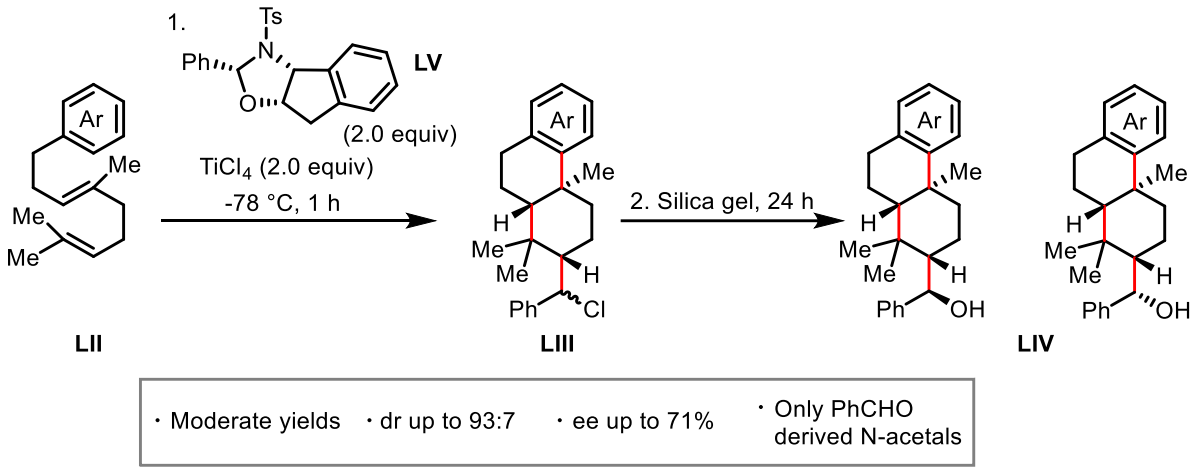
*Scheme **18***. Vidari's carbon-electrophile induced polyene cyclisation using aldehydes.

The most general methodology for polyene cyclisation initiated by carbon-electrophiles was developed by Loh's research group. In 2007 the group reported intermolecular acetal-initiated cationic cyclisation of polyenes promoted by $SnCl_4$ (Scheme **19**).[46] The group tested different benzaldehyde-derived acetals and found that cyclic 5- and 6-membered acetals give the best results in terms of minimising monocyclised side-products. Loh and coworkers then used chiral cyclic acetals in the presence of $SnCl_4$ to trigger polyene cyclisation with the formation of an exocyclic C-C bond. Up to 89% combined yield and 73:14:13 dr for **XLIX**, **L** and **LI** respectively could be achieved.



*Scheme **19***. Loh's intermolecular acetal-initiated polyene cyclisation.

Later, the group extended their methodology to include chiral N-acetals to trigger intermolecular cationic cascades (Scheme **20**).[47] Interestingly, with chiral N-acetal **LV** the reaction proceeded *via* the formation of exocyclic benzylic chloride **LIII**, which upon exposure to silica gel generated diastereomeric alcohols **LIV** in up to 93:7 dr. Levels of enantioselectivity were determined after oxidising the exocyclic alcohol to a ketone to remove the benzylic chiral centre. Up to 71% ee could be achieved. Although Loh's acetal- and N-acetal-promoted polyene cyclisation serves as a proof of concept that carbon electrophiles could act as intermolecular initiators, the work suffers from limited scope and moderate diastereoselectivities. In addition, only benzaldehyde-derived acetals and N-acetals were employed.

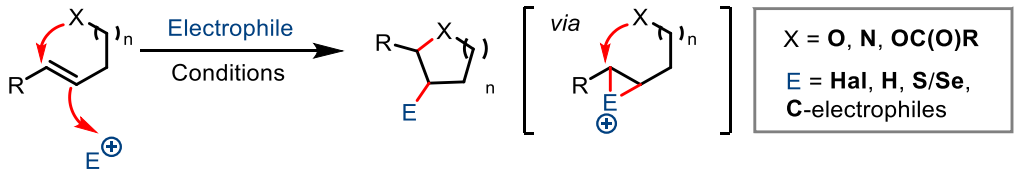


*Scheme **20***. Loh's enantioselective N-acetal induced polyene cyclisation.

To conclude, it is important to explore carbon electrophiles that are not derived from carbonyl species to trigger a polyene cyclisation with the stereoselective formation of an exocyclic C-C bond.

1.3 Recent developments in heterocyclisation cascades and the role of HFIP solvent in carbocation generation

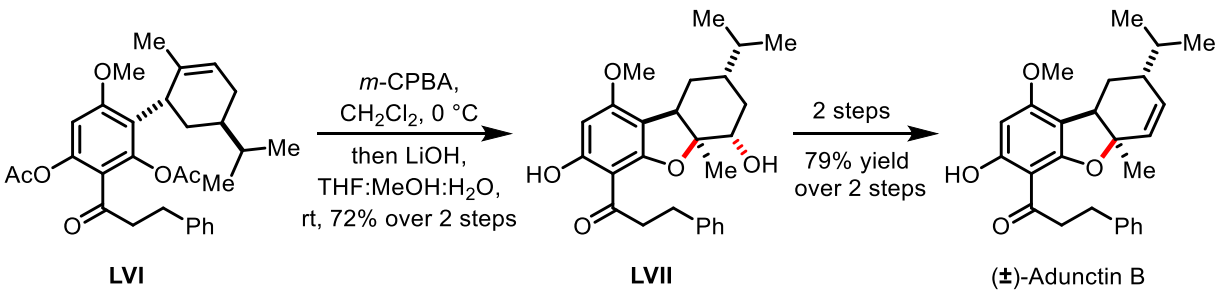
In this section, recent breakthroughs in cationic heterocyclisation which involve olefin activation will be discussed (Scheme **21**). Generally, such heterocyclisation cascades could be divided in a similar way to polyene cyclisations, i.e. based on the initiator type.



*Scheme **21***. General reaction design.

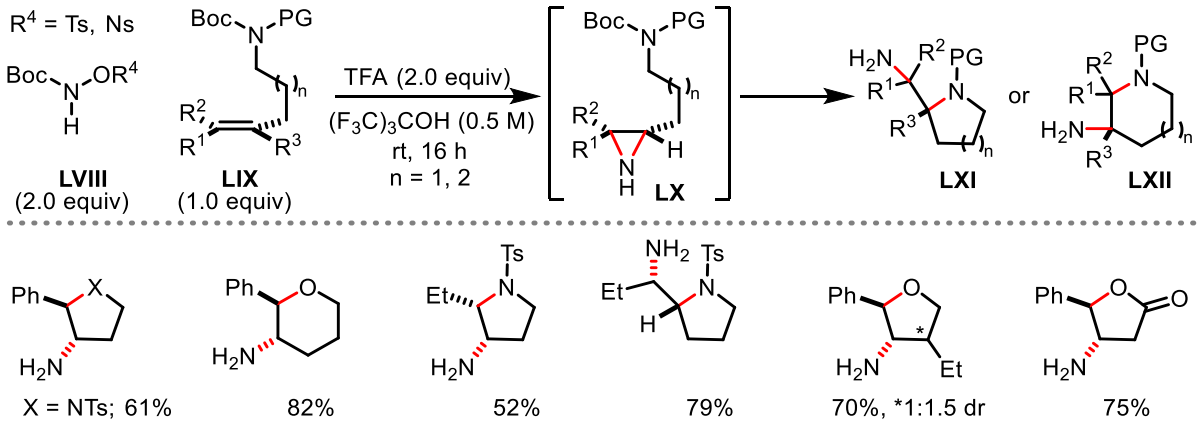
1.3.1 Overview of the recent reactions to form saturated heterocycles

Heterocyclisation *via* an intramolecular attack on an epoxide is one of the most common reactions to set up stereocenters in the synthesis of saturated heterocycles.[48] Following initial studies on the cyclisation selectivity and kinetics,[49] epoxidation as a strategy to activate an alkene has been extensively used in total synthesis.[48(c)] From the recent literature reports, Dethe and coworkers used this method to achieve the total synthesis of Adunctin B (Scheme **22**).[50] *m*-CPBA epoxidation *trans* to the neighbouring aryl group of intermediate **LVI**, followed by acetate hydrolysis and intramolecular nucleophilic attack on the epoxide furnished tetrahydrofuran **LVII** in 72% yield over two steps; (±)-Adunctin B was then synthesised in two steps from alcohol **LVII**.



*Scheme **22***. Dethe's total synthesis of (±)-Adunctin B.

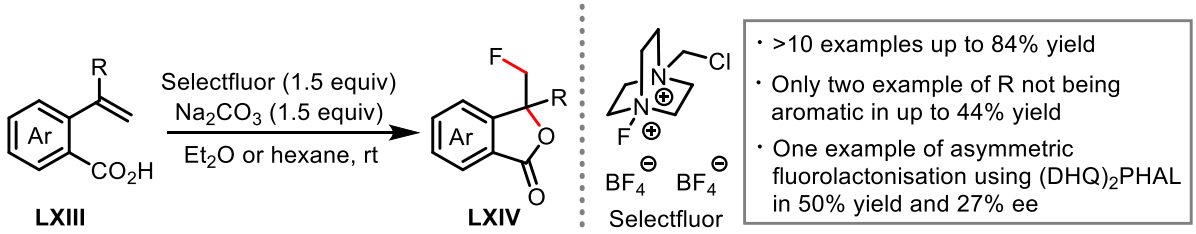
While heterocyclisation *via* epoxide ring opening is a common strategy, the nitrogen variation *via* an aziridinium is much less explored. One of the recent breakthroughs in heterocyclisation with the formation of an exocyclic C-N bond came from Bower's research group in 2023.[51] Bower and coworkers achieved a one step aminative cyclisation triggered by intermolecular Aza-Prilezhaev alkene aziridination (Scheme **23**). The reaction proceeds *via* aziridine **LX** followed by intramolecular nucleophilic attack of alcohols, amines or carboxylic acids. Using this method, the diastereoselective synthesis of piperidines **LXII** or pyrrolidines **LXI** bearing an exocyclic free amine could be achieved. In addition, substituted tetrahydrofurans, tetrahydropyrans and lactones could be accessed in high yields.



*Scheme **23***. Bower's aminative heterocyclisation using RNH-LG **LVIII**.

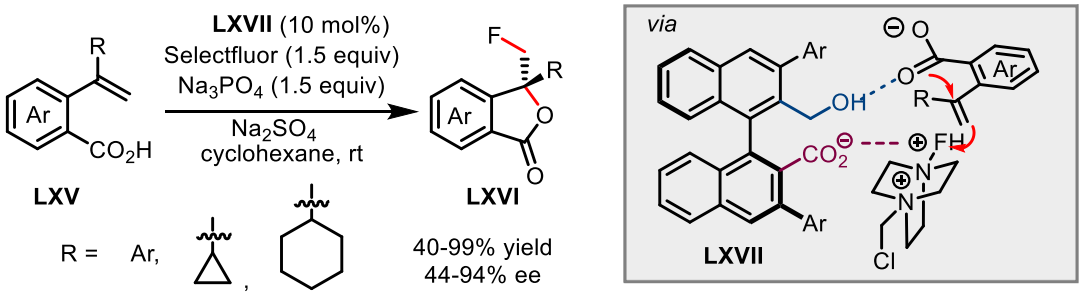
While one-step cyclisation *via* an intramolecular attack on an aziridinium is an emerging mode of heterocycle synthesis, heterocyclisation triggered by halonium ions is well-explored.[52] In particular, halolactonisation has been extensively studied to build-up molecular complexity and form new stereocenters.[53] As with polyene cyclisation, various electrophilic reagents have been used to initiate halolactonisations with the formation of a new exocyclic C-Hal bond.[52,53] Within this class of reactions, fluorolactonisations have been underexplored. Recent progress was achieved in 2014 when Rueping and coworkers reported the Selectfluor® mediated fluorolactonisation of carboxylic acids (Scheme **24**).[54] Using Selectfluor® as an electrophilic source of fluorine, the group achieved cyclisation of carboxylic acids **LXIII** to form fluorolactones **LXIV** possessing an exocyclic C-F bond in up to 84% yield. Only two examples

of substrates bearing non-aromatic R group were demonstrated with the highest yield being 44%. Furthermore, Rueping and coworkers showed that the addition of 20 mol% of $(DHQ)_2PHAL$ afforded the enantioenriched fluorolactone in 50% yield and 27% ee.



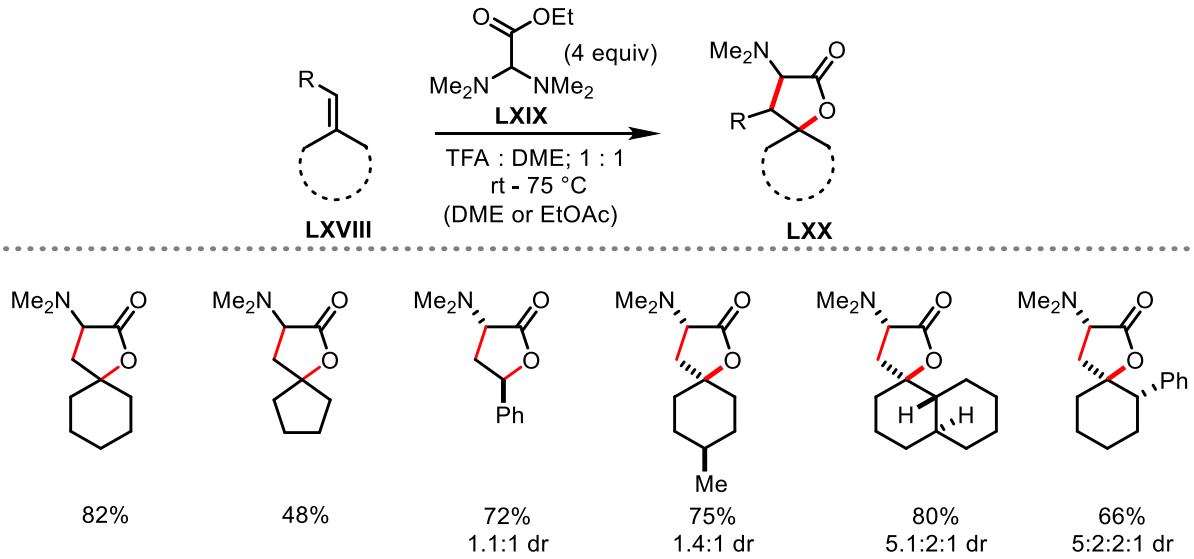
*Scheme **24***. Rueping's fluorolactonisation using Selectfluor®

Hamashima and coworkers later developed a general methodology to access enantioenriched fluorolactone scaffolds.[55] The reaction design was similar to the work of Rueping and coworkers but relied on the use of chiral bifunctional hydroxyl carboxylate catalyst **LXVII** (Scheme **25**). Selectfluor® was chosen as a fluorine source based on a report from Toste and coworkers that chiral phosphonates can act as phase-transfer catalysts to solubilise Selectfluor® in non-polar solvents.[56] Using 10 mol% of catalyst **LXVII**, enantioenriched fluorolactones **LXVI** were made in up to 99% yield and 94% ee. As with Rueping's work, carboxylic acids **LXV** bearing non-aromatic R groups afforded fluorolactones in diminished yields and er. The authors proposed that asymmetric induction was achieved through the chiral ternary complex. The carboxylate group of catalyst **LXVII** forms an ion pair with Selectfluor®, while the hydroxy group hydrogen-bonds deprotonated substrate **LXV**, thus controlling the absolute configuration upon fluorine transfer within the chiral pocket.



*Scheme **25***. Hamashima's enantioselective fluorolactonisation using Selectfluor® and catalyst **LXVII**.

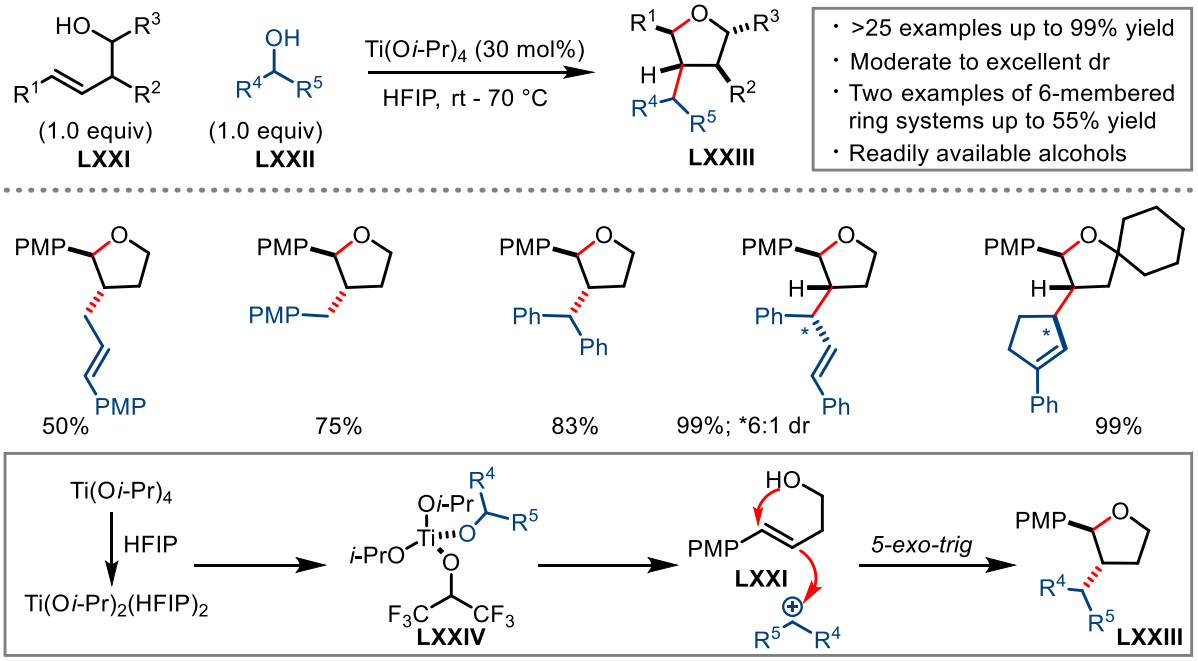
Similar to polyene cyclisation, examples of heterocyclisation initiated by the formation of new exocyclic C-C bonds are rare. Recently, Maulide and coworkers reported a synthesis of aminolactones **LXX** from unactivated alkenes **LXVIII** using aminal **LXIX** with a Brønsted acid as a cosolvent (Scheme **26**).[57] The reaction design differs from the pathway outlined in Scheme **21**, since the nucleophile is not part of the alkene substrate. Instead, the reaction follows an aza-Prins-type pathway, followed by cyclisation of the ester onto the carbocation. Spirocyclic aminolactones were formed in up to 89% yield with low to moderate dr around the ring system.



Scheme **26**. Maulide's aminolactonisation using aminals as carbon electrophiles.

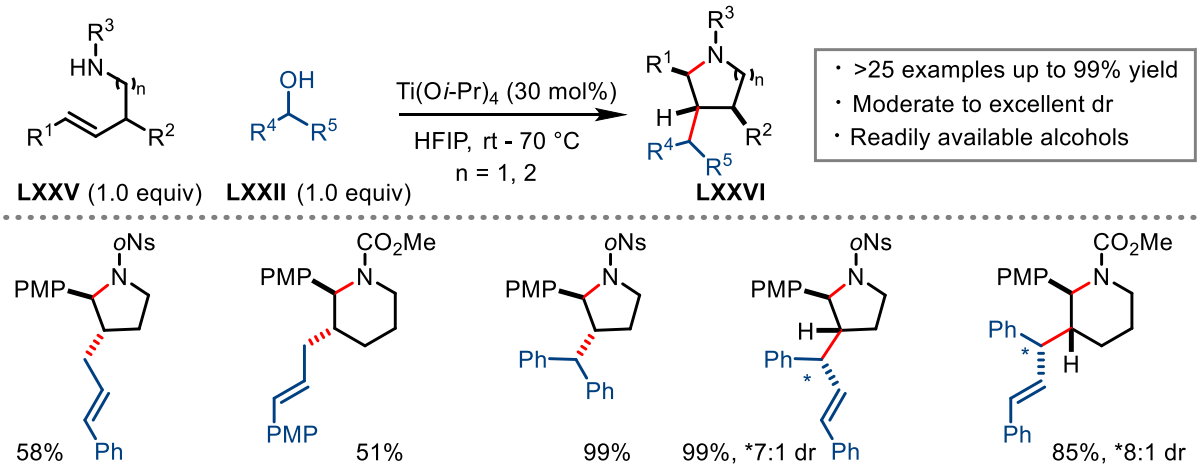
A significant development in the field of carbon electrophile-induced heterocyclisation occured in 2018, when the Donohoe group reported a diasatereoselective carbocation-triggered synthesis of tetrahydrofurans L**XXIII** (Scheme **27**).[58] To generate carbocations *in situ*, the group utilised the unique properties of HFIP solvent to enable ionisation of benzylic or allylic alcohols in the presence of Ti(O*i*-Pr)$_4$ Lewis acid. A broad range of alcohols could be engaged in up to 99% yield and excellent dr at the exocyclic position. Ti(O*i*-Pr)$_4$ Lewis acid was important for achieving high yields in this transformation. The authors explained this observation by the formation of Ti(O*i*-Pr)$_2$HFIP, after two isopropoxide ligands are displaced by HFIP molecules. Alcohol substrate then displaces one of the HFIP ligands, affording

complex **LXXIV**. Ionisation of alcohol substrate can then occur, generating reactive carbocation species *in situ*. Due to the low nucleophilicity of HFIP solvent,[59] carbocation intermediates are not trapped and can trigger *5-endo-trig* cyclisation of substrate L**XXI**, reacting first with the electron-rich alkene. This affords substituted *trans*-tetrahydrofurans, such as L**XXIII**, with an exocyclic C-C bond. Two examples of tetrahydropyran products were also demonstrated, albeit in lower yields.



Scheme **27**. Donohoe's cation-triggered synthesis of substituted tetrahydrofurans.

Later, Donohoe and coworkers have extended their cation-triggered heterocyclisation to access pyrrolidines and piperidines **LXXVI** (Scheme **28**).[60] The reaction proceeded with a high diastereoselectivity and afforded saturated N-heterocycles in up to 99% yield.



*Scheme **28***. Donohoe's cation-triggered synthesis of substituted pyrrolidines and piperidines.

In both cation-triggered heterocyclisation methodologies, the Donohoe group note that HFIP solvent was essential to achieve the desired reactivity. During the optimisation studies to access substituted tetrahydrofuran rings, the use of any other solvent apart from HFIP and nonafluoro-*tert*-butyl alcohol completely shut down the reaction. With nonafluoro-*tert*-butyl alcohol solvent a much lower yield of tetrahydrofuran formation was observed. The crucial role of HFIP in these transformations was explained by the unique properties of the solvent, which allow effective generation of carbocation species.[59] Furthermore, HFIP is commonly seen as a solvent of choice for cationic polyene cyclisations.[61] In the next section, the properties of HFIP solvent which enable it to facilitate generation of carbocation species and promote cationic reaction pathways will be discussed.

1.3.2 HFIP solvent and its applications in the reactions involving carbocation species

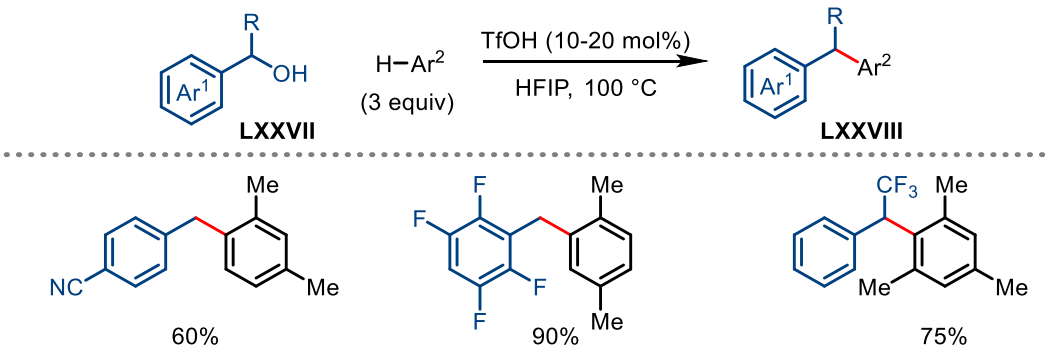
Starting from 1950, the number of articles featuring HFIP solvent in organic reactions has rapidly increased.[62] This was facilitated by the early studies on the physical parameters of polyfluorinated solvents, which suggested that their unique properties could be used in organic synthesis.[63] Within polyfluorinated solvents, HFIP is one of the most commonly employed to date.[62] The strong inductive electron-withdrawing effect of two CF_3 groups is responsible for the enhanced Brønsted acidity (pKa = 9.3) and polarity of HFIP solvent compared to *i*-PrOH (Table **1**).[62(b)] In addition, HFIP possesses reduced nucleophilicity and enhanced hydrogen-

bond donor ability.[62(b)] These factors contribute to the high ionising power of HFIP solvent and enable it to facilitate reactions that proceed *via* a cationic pathway.

Physical properties	*i*-PrOH	HFIP
pKa[64]	17.1	9.3
Polarity (E_T^N)[65]	0.546	1.068
Nucleophilicity ($N_{t\text{-BuCl}}$)[66]	0.09	−3.93
Ionizing power ($Y_{t\text{-BuCl}}$)[66]	−2.73	2.46
Dipole moment (μ)[67]	1.68	2.05
Hydrogen-bond acidity (α_1)[68]	0.53	1.86

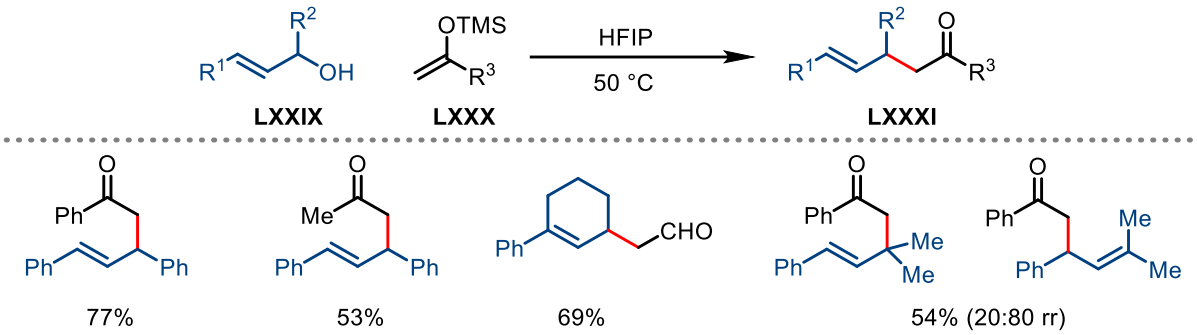
*Table **1***. Comparison between the key properties of HFIP and *i*-PrOH.[62(b)]

Indeed, HFIP is commonly employed for challenging S_N1 type transformations. In 2017 Moran and coworkers reported the Friedel–Crafts reactions of electronically deactivated benzylic alcohols L**XXVII** (Scheme **29**).[69] The authors proposed that interactions between TfOH and HFIP generate catalytically active aggregates that enable ionization of electron-deficient alcohols. The formation of the aggregates was enabled by the strong hydrogen-bond accepting ability of HFIP solvent. The reaction was shut down completely in non-fluorinated solvents. The use of TFE and nonafluoro-*tert*-butyl alcohol afforded some product formation *via* the Friedel–Crafts reaction, however HFIP was found to be superior.



*Scheme **29***. The use of HFIP solvent to enable ionisation of electron-deficient alcohols.

Another example of the C-C bond formation enabled by HFIP solvent comes from Baeza's group. Baeza and coworkers reported HFIP-promoted direct allylation of silyl enol ethers **LXXX** with allylic alcohols **LXXIX** under metal-free conditions (Scheme **30**).[70] The reaction proceeded in up to 90% yield and did not require any Lewis or Brønsted acid catalyst. For unsymmetrical allylic alcohols, however, mixtures of regioisomers were obtained.



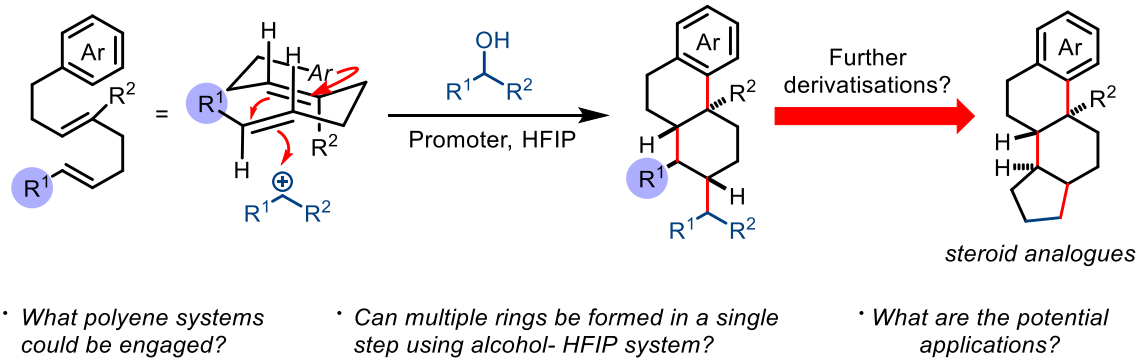
*Scheme **30***. HFIP-promoted metal free allylation of silyl enol ethers with allylic alcohols.

To summarise, the unique properties of HFIP solvent enable generation of carbocation species and intermediates, while also minimising any undesired trapping. These properties can facilitate future discoveries in C-C bond forming reactions *via in situ* generation of reactive species from readily available precursors.

1.4 Summary and research aims

After analysing the *state of the art* literature for polyene cyclisation reactions, it is clear that the current limitation lies in the lack of methodologies to use intermolecular carbon electrophiles to trigger cascade cyclisations. This type of initiation would allow diastereoselective formation of an exocyclic C-C bond, which could be used as an additional vector to build-up molecular complexity. Since polyene cyclisation allows us to efficiently set up two new carbocyclic rings, an exocyclic C-C bond could be used to construct an additional ring to access steroid-like scaffolds. Furthermore, the ability to use readily available intermolecular carbon-based initiators will allow rapid access to various interesting structures.

Therefore, the first research objective described in this thesis is to develop a general diastereoselective polyene cyclisation methodology initiated by carbon electrophiles (Scheme **31**). Through reviewing the literature and the previous work done in the Donohoe group, it was decided to further explore the alcohol-HFIP system as a source of carbon electrophiles. The following challenges and questions needed to be addressed: a) what type of polyene substrates could be engaged in the cation-triggered cyclisation; b) is it possible to form multiple rings in a single step using HFIP system; c) what type of molecules could be accessed using the cation-triggered polyene cyclisation.



*Scheme **31***. Research objective for carbon electrophile-initiated polyene cyclisation.

Next, carbon electrophile-induced lactonisation reactions would be explored. As with polyene cyclisation, lactonisations initiated by the formation of new C-C bond are underexplored. Attention would then be turned to broaden the scope of alkene systems which could be engaged in alkylative heterocyclisation using alcohol-HFIP system.

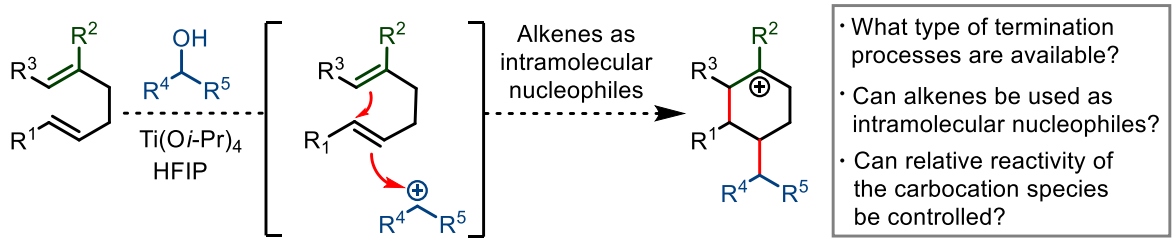
For both objectives, the main focus would be to optimise carbon electrophile-triggered cyclisation reactions to achieve high diastereoselectivity upon forming new chiral centers. Furthermore, the possibility of controlling the absolute stereochemistry would be addressed.

Chapter 2: The Cation-Triggered Polyene Cyclisation in HFIP

2.1 Chapter overview and origin of the project

In this chapter the development of a cation-triggered polyene cyclisation will be detailed. First, the studies towards a cyclohexene ring formation *via 6-endo-trig cyclisation* will be presented. The results from this part were crucial for the project development and prompted substrate tuning to avoid the issue of unselective E1 elimination as a termination process. Then, the optimisation and substrate scope of the cation-triggered polyene cyclisation to form multiple carbocyclic rings will be outlined. The last part of this chapter details the derivatisation and functionalisation strategies of the scaffolds prepared using the developed carbon electrophile-initiated polyene cyclisation. The emphasis is directed towards derivatising the newly formed exocyclic C-C bond to either install versatile synthetic functionalities, or to access streroid-like compounds.

As was outlined in Section **1.4**, the origin of the project traces back to the previous work from the Donohoe group, wherein the HFIP-alcohol system was used to enable heterocyclisation.[58,60] The use of alkenes as intramolecular nucleophiles was unexplored due to the challenges in quenching the second carbocation formed upon cyclisation (Scheme **32**). Furthermore, the formation of another reactive carbocation species could trigger multiple unselective side-reactions. On the other hand, a cation-triggered polyene cyclisation would substantially expand the chemical space accessible with this strategy. It was therefore decided to explore the use of alkenes as intramolecular nucleophiles in HFIP promoted cyclisations.

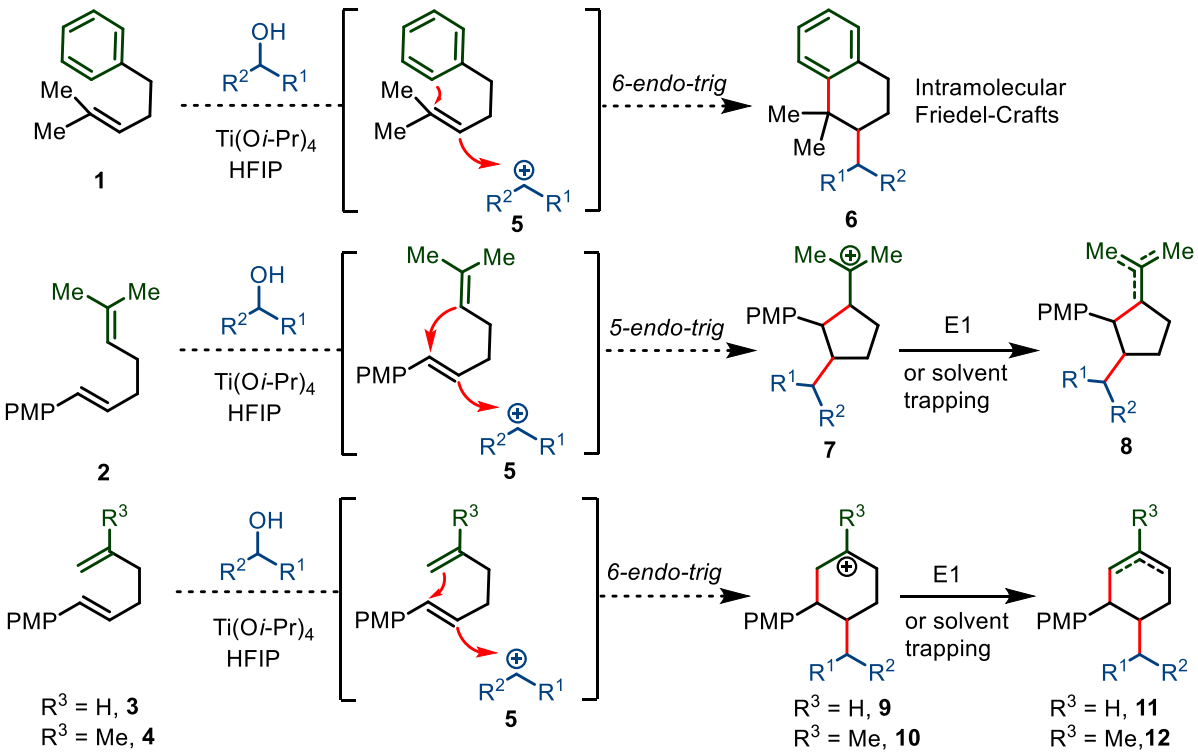


*Scheme **32***. The project origin.

2.2 System development for the cation-triggered polyene cyclisation cascade

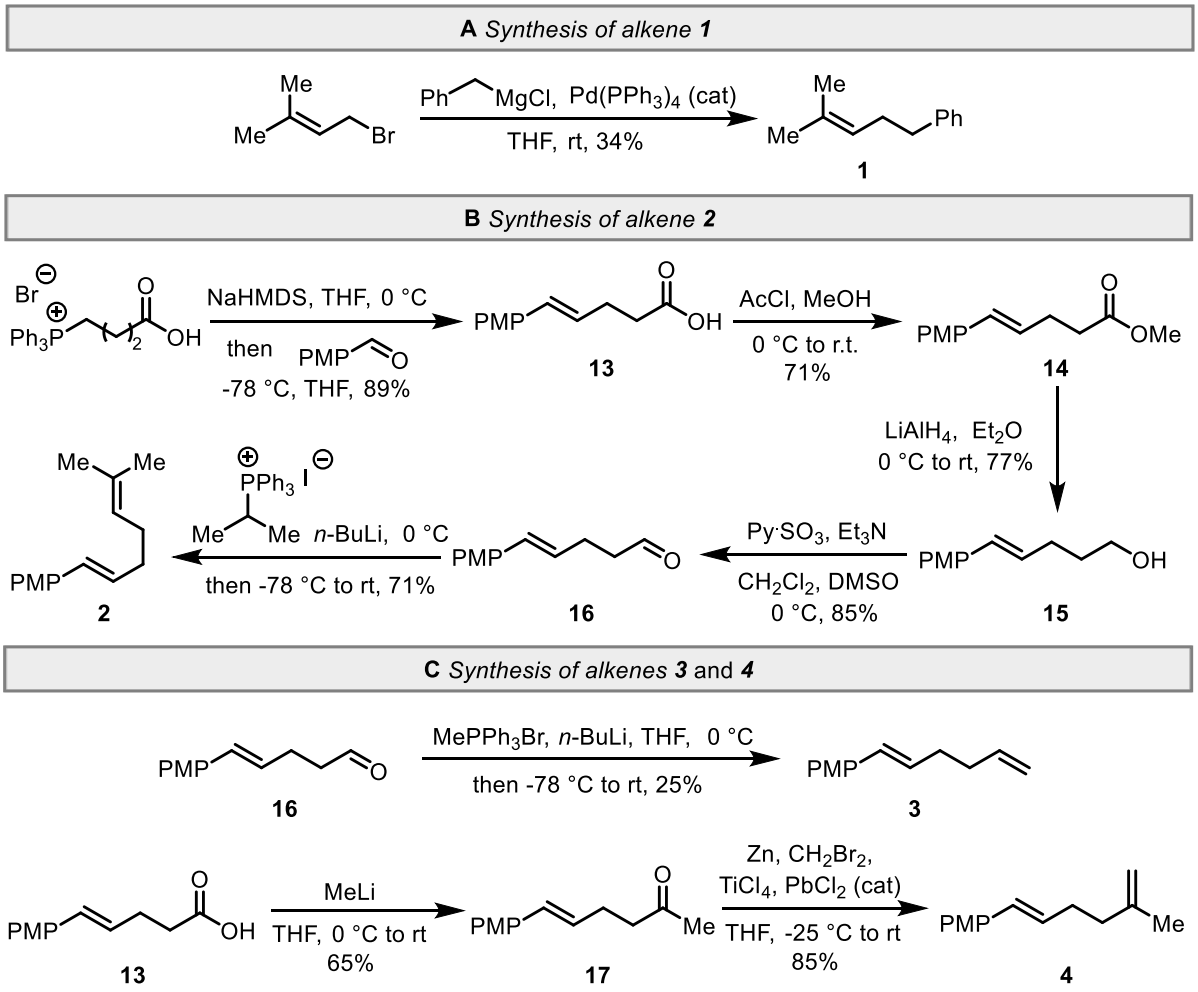
2.2.1 Studies in a single ring formation *via* the cation-triggered carbocyclisation

First, it was decided to explore which alkene systems can undergo cyclisation reactions triggered by carbocation generation in HFIP solvent, and which cyclisation modes are possible. To this end, four different alkene-substrate classes were chosen to be prepared (Scheme **33**). Alkene **1** has a Ph group positioned to trap a build-up of a positive charge by intramolecular Friedel–Crafts reaction to form a 6-membered ring **6**. For alkene **2**, a *5-endo-trig* cyclisation pathway was thought to be possible in which a trisubstituted alkene cyclises onto a benzylic carbon to form **7.** An alternative *5-endo-trig* cyclisation pathway in which carbocation **5** reacts with the trisubstituted alkene first could not be excluded. The feasibility of a *6-endo-trig* cyclisation using alkenes as intramolecular nucleophiles could be explored with substrates **3** and **4**. For alkenes **2**, **3** and **4**, E1 elimination or solvent trapping, following generation of cyclic carbocations **7**, **9** and **10** respectively, was predicted to be a termination event.



*Scheme **33***. Overview of different cyclisation modes predicted for alkenes **1**-**4**.

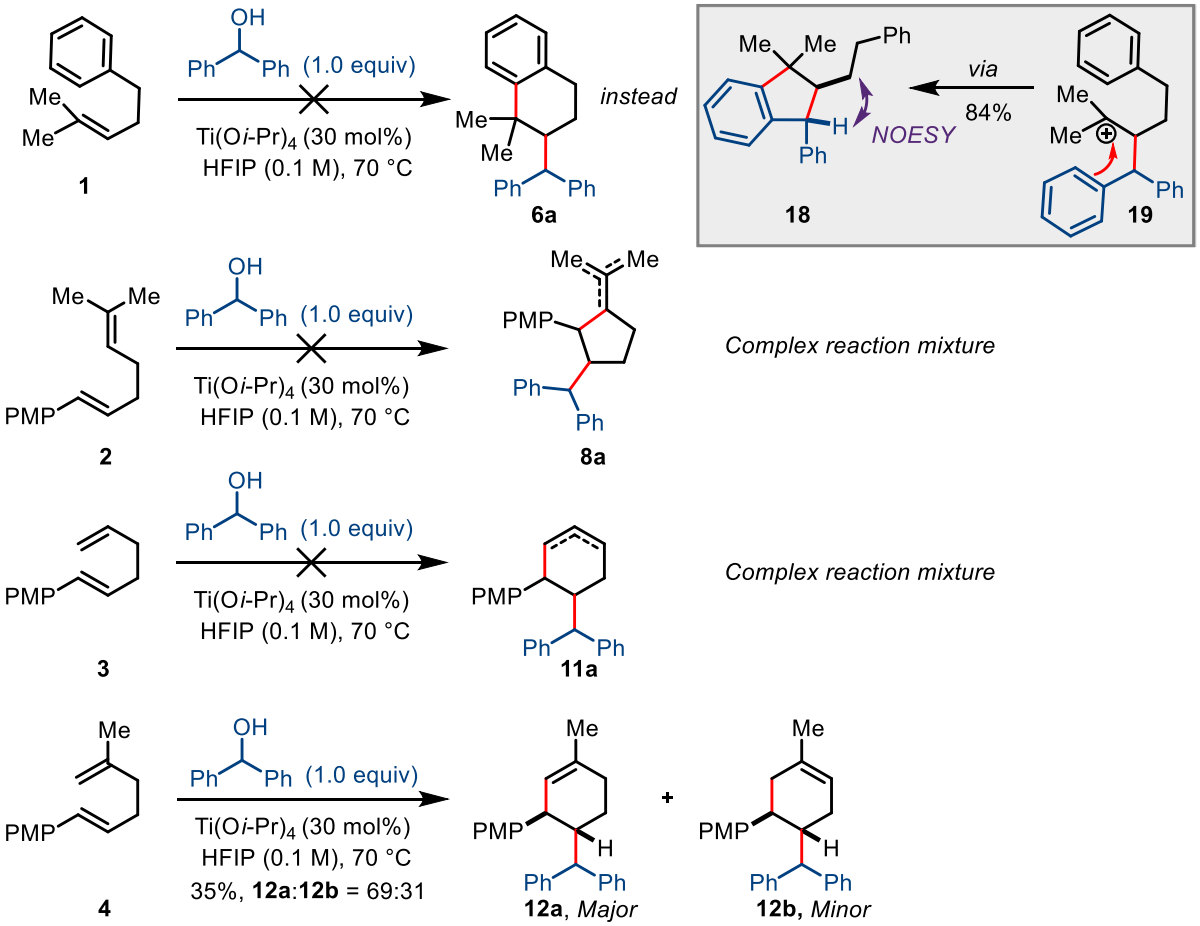
Alkene **1** was prepared in 34% yield in a single step from commercially available 1-bromo-3-methylbut-2-ene using a Pd-catalysed Tsuji–Trost reaction (Scheme **34**, A).[71] A five-step sequence was used to prepare alkene **2** in 29% overall yield (Scheme **34**, B). First, a Wittig reaction between commercially available (3-carboxypropyl)triphenylphosphonium bromide and 4-anisaldehyde furnished carboxylic acid **13** in 89% as a single *E*-isomer as evidenced by an alkene coupling constant of 15.9 Hz.[72] This result contradicts the conventional *Z*-selectivity commonly observed for non-stabilised ylides.[73] Several explanations were proposed to account for unconvential *E*-selectivity observed for some ylides bearing an anionic group.[74] It is possible that the formation of oxaphosphetane and betaine intermediates becomes reversible in the presence of an intramolecular carboxylate nucleophile, thus the more thermodynamically stable (*E*)-betaine predominates which leads to (*E*)-isomer of **13**. Methyl ester formation using AcCl in MeOH proceeded smoothly to give ester **14** in 71% yield. $LiAlH_4$ reduction gave alcohol **15** in 77% which was then subjected to a Parikh–Doering oxidation to furnish aldehyde **16** in 85% yield.[75] Aldehyde **16** was then used to synthesise alkene **2** in 71% yield and alkene **3** in 25% yield using *iso*propyltriphenylphosphonium iodide and methyltriphenylphosphonium bromide respectively under Wittig conditions (Scheme **34**, C).[76] Alkene **4** was obtained in two steps from carboxylic acid **13**. Addition of MeLi proceeded smoothly to furnish ketone **17** in 65% yield. No conversion was observed when ketone **17** was subjected to a Wittig reaction with methyltriphenylphosphonium bromide, even at elevated temperatures. The use of more forcing Lombardo olefination conditions, on the other hand, furnished alkene **4** in 85% yield.[77]



*Scheme **34***. Synthesis of alkenes **1**, **2**, **3** and **4**.

With alkenes **1**, **2**, **3** and **4** in hand, HFIP mediated carbocyclisation reactions were attempted using previously published conditions (Scheme **35**).[58] It was decided to use benzhydrol as an electrophile due to the high yields reported for this alcohol in previous work. The reaction between alkene **1** and benzhydrol in HFIP in the presence of Ti(O*i*-Pr)$_4$ as a Lewis acid at 70 °C furnished carbocycle **18**, instead of the desired product **6a**, as a single diastereomer in 84% yield. It was proposed that product **18** is formed from the intermediate **19** after the tertiary carbocation is trapped by a Ph group which was part of a benzhydrol molecule. This outcompetes the initially proposed 6-membered ring formation *via* Friedel–Crafts reaction with a Ph group of the substrate **1**. When alkene **2** was subjected to the same reaction conditions, a complex reaction mixture was obtained. The same outcome was observed for alkene **3**. Fortunately, the reaction between alkene **4** and benzhydrol furnished the desired 6-membered

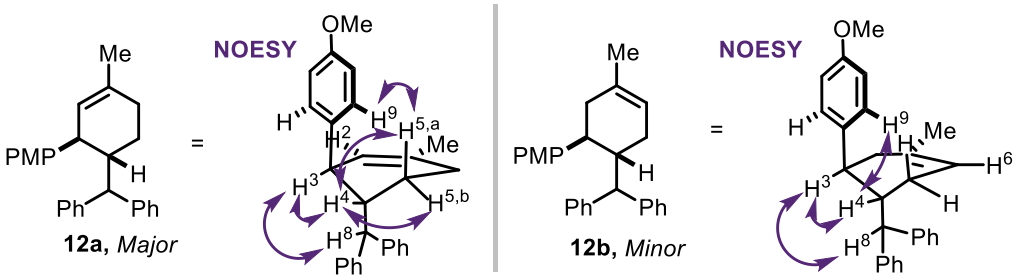
carbocyclic product **12** in 35% yield as a 69:31 mixture of alkene regioisomers, both as a single diastereomer. The difference in reactivities observed for substrates **3** and **4** in the alkylative cyclization cascade was explained by a higher electron density of the gem-substituted terminal alkene in **4** compared to the mono-substituted alkene in **3**. Consequently, a more efficient trapping of a build-up of a positive charge on a benzylic carbon was possible in substrate **4**.



Scheme 35. The cation-triggered cyclisation of alkenes **1**, **2**, **3** and **4**.

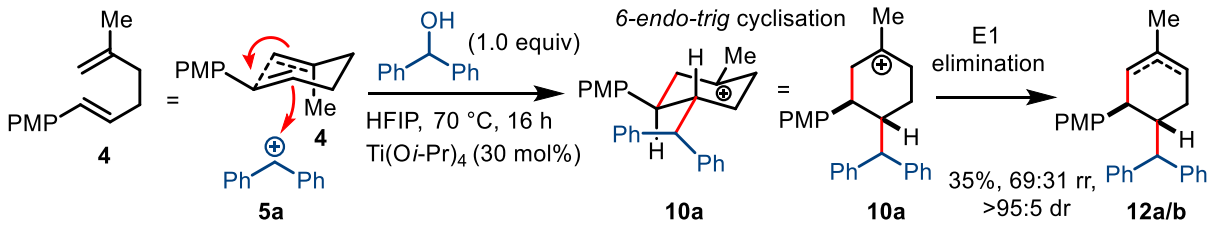
The successful formation of cyclohexene products **12a** and **12b** demonstrated that a cation-triggered diastereoselective polyene cyclisation to set up 6-membered rings was feasible. As such, it was decided to explore this reaction further. Surprisingly, the NOESY analysis of the mixture of cycloxenes **12a** and **12b** indicated a *trans*-diaxial arrangement between PMP and diphenylmethyl groups for both regioisomers (Scheme **36**). The unusual *trans*-diaxial

conformation could be a result from a severe $A^{1,3}$ strain if a PMP group would occupy an equatorial position.[78]



*Scheme **36***. Stereochemical analysis of the mixture of cyclohexenes **12a** and **12b** using NOESYs.

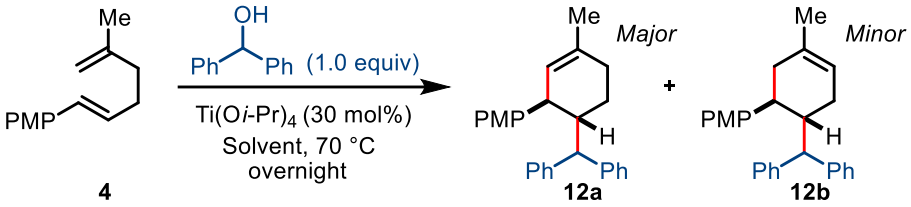
The following mechanism for the cyclisation of **4** was proposed (Scheme **37**). First, benzhydrol is ionised under the reaction conditions to form species **5a**. The carbocation **5a** then triggers a *6-endo-trig* cyclisation cascade of diene **4** by first interacting with the electron-rich alkene in conjugation with a PMP group. The terminal alkene of substrate **4** quenches the build-up of a positive charge on a benzylic carbon, most likely in a concerted mechanism *via* a chair-like transition state. The concerted pathway is further supported by the previous work from Vidari and co-workers on TiF_4-mediated biomimetic alkylation–cyclization cascades with aldehydes (see Scheme **18**).[79] In the report, the authors exclude the possibility of a stepwise mechanism. The cyclisation of **4** generates tertiary carbocation **10a** with PMP and diphenylmethyl groups *trans* to each other. Finally, unselective E1 elimination generates a mixture of cyclohexenes **12a** and **12b**. A ring-flip of a carbocation **10a** prior to E1 elimination, or of alkenes **12a** and **12b**, brings the two substituents into a *trans*-diaxial arrangement. The formation of a common intermediate **10a** is consistent with the observed identical relative stereochemistry of regioisomers **12a** and **12b**.



*Scheme **37***. Proposed reaction mechanism for *6-endo-trig* cyclisation of the substrate **4.**

2.2.2 Optimisation of the reaction conditions

The next goal was to optimise the *6-endo-trig* cyclisation of substrate **4** with respect to yield and ratio of regioisomers (Table **2**). Application of the reaction conditions from the previous work in the group,[58] furnished the desired product **12** in 35% isolated yield as a 69:31 mixture of alkene regioisomers (Table **2**, entry 1). Performing the cyclisation at room temperature instead of 70 °C resulted in a complex reaction mixture with only 12% of product **12** isolated. (Table **2**, entry 2). When the concentration was reduced to 0.05 M, the yield of **12** increased to 49% (Table **2**, entry 3); a slight increase in regioselectivity was also observed. Further dilution to 0.02 M improved yield of **12** to 55%, although with a drop in regioselectivity (Table **2**, entry 4). It was decided to keep concentration at 0.02 M and explore if co-solvents can further improve the combined yield and ratio of **12a** and **12b**. No conversion was observed when THF was used as a co-solvent in 1:1 volume ratio with HFIP (Table **2**, entry 5). The use of MeCN as a co-solvent also resulted in a low conversion with only 12% of product **12** formed (Table **2**, entry 6). CH_2Cl_2 was found to be a promising co-solvent. When the reaction was performed in 1:1 HFIP and CH_2Cl_2 solvent mixture, 58% yield of product **12** was isolated in 63:37 ratio (Table **2**, entry 7). A slight decrease in yield and rr of product **12** was observed when CH_2Cl_2 was used in a 2:1 ratio with HFIP (Table **2**, entry 8). The reaction did not proceed in CH_2Cl_2 or IPA without HFIP present (Table **2**, entries 9-10). This observation is consistent with previous work from the group which suggests that HFIP solvent is essential for cation-triggered cyclisation cascades.[58,60] Finally, increasing the loading of Ti(O*i*-Pr)$_4$ to 50 mol% and using 1:1 CH_2Cl_2 and HFIP solvent mixture furnished product **12** in 62% yield as a 57:43 mixture of alkene regioisomers (Table **2**, entry 11).

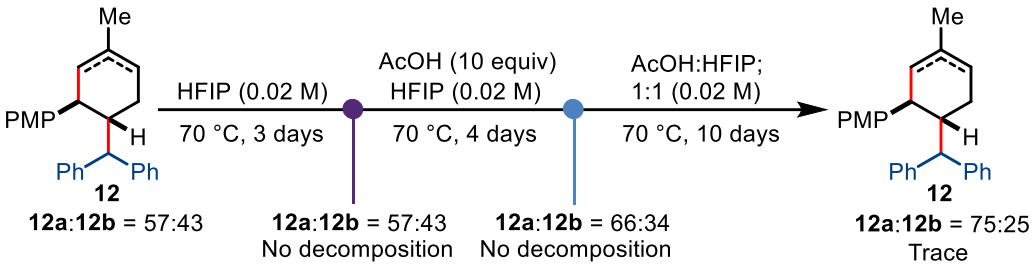


Entry	Solvent	Concentration (M)	T (°C)	Ti(O*i*-Pr)$_4$ (mol%)	Yield[a] of **12a** and **12b**	rr[b]
1	HFIP	0.1	70	30	35%	69:31
2	HFIP	0.1	rt	30	12%	71:29
3	HFIP	0.05	70	30	49%	73:27
4	HFIP	0.02	70	30	55%	62:38
5	HFIP : THF; 1 : 1	0.02	70	30	NR	ND
6	HFIP: MeCN; 1 : 1	0.02	70	30	(12%)[c]	60:40
7	HFIP : CH_2Cl_2; 1 : 1	0.02	70	30	58%	63:37
8	HFIP : CH_2Cl_2; 1 : 2	0.02	70	30	52%	57:43
9	CH_2Cl_2	0.02	70	30	NR	ND
10	IPA	0.02	70	30	NR	ND
11	**HFIP : CH_2Cl_2; 1 : 1**	**0.02**	**70**	**50**	**62%**	**57:43**

Table **2**. Optimisation of the *6-endo-trig* cyclisation of the substrate **4.** [a] Isolated yields are reported; [b] ratio of alkene regioisomers is calculated based on crude ^{1}H NMR; [c] NMR yield using 1,3,5-trimethoxybenzene as a standard.

Although it was possible to improve yield of the reaction from 35% to 62%, the ratio between cyclohexene regioisomers **12a** and **12b** remained low. To check if longer exposure to HFIP can lead to a higher ratio between regioisomers, the mixture of alkenes **12a** and **12b** in a 57:43 ratio was heated in HFIP at 70 °C for 3 days (Scheme **38**). However, the ratio did not change. It was then decided to use more acidic conditions to facilitate reversible protonation of a cyclohexene mixture **12**. Resubjecting a mixture of alkenes **12a** and **12b** in a 57:43 ratio to 10 equivalents of AcOH in HFIP (0.02 M) at 70 °C improved ratio to 66:34 with no decomposition

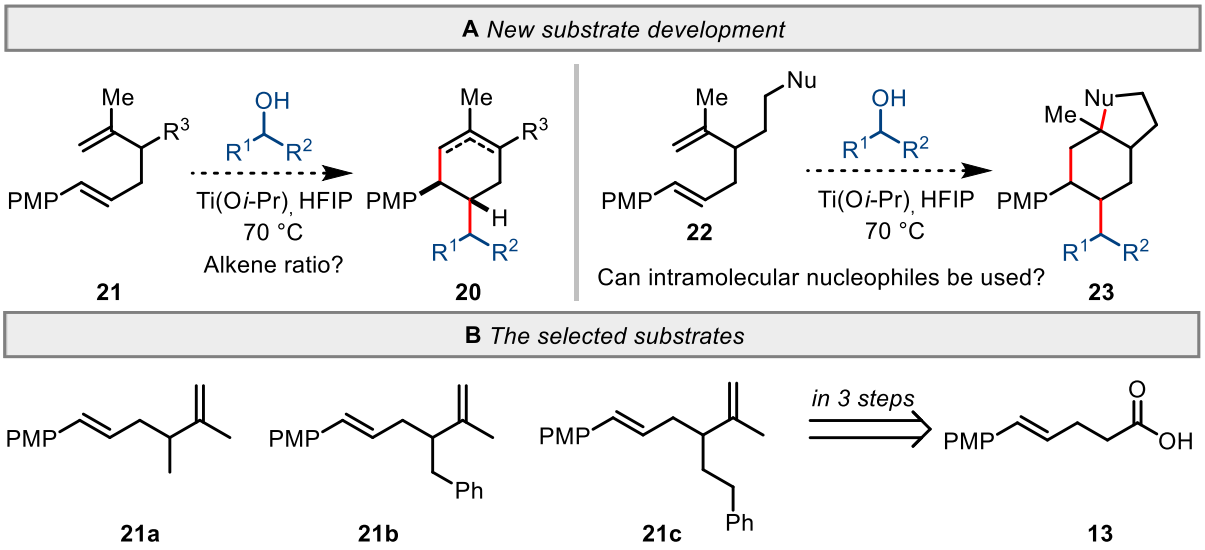
observed. The use of more forcing conditions, AcOH as a co-solvent with HFIP in 1:1 volume ratio and heating the mixture for 10 days, led to decomposition of alkenes **12a** and **12b** with trace product remaining in 75:25 ratio. It was therefore concluded that the ratio between cyclohexenes **12a** and **12b** could not be significantly improved by subjecting the mixture to acidic conditions and that a different approach to solve the issue of unselective E1 elimination was required.



*Scheme **38***. Resubjection of the cyclohexene mixture **12** to HFIP and AcOH.

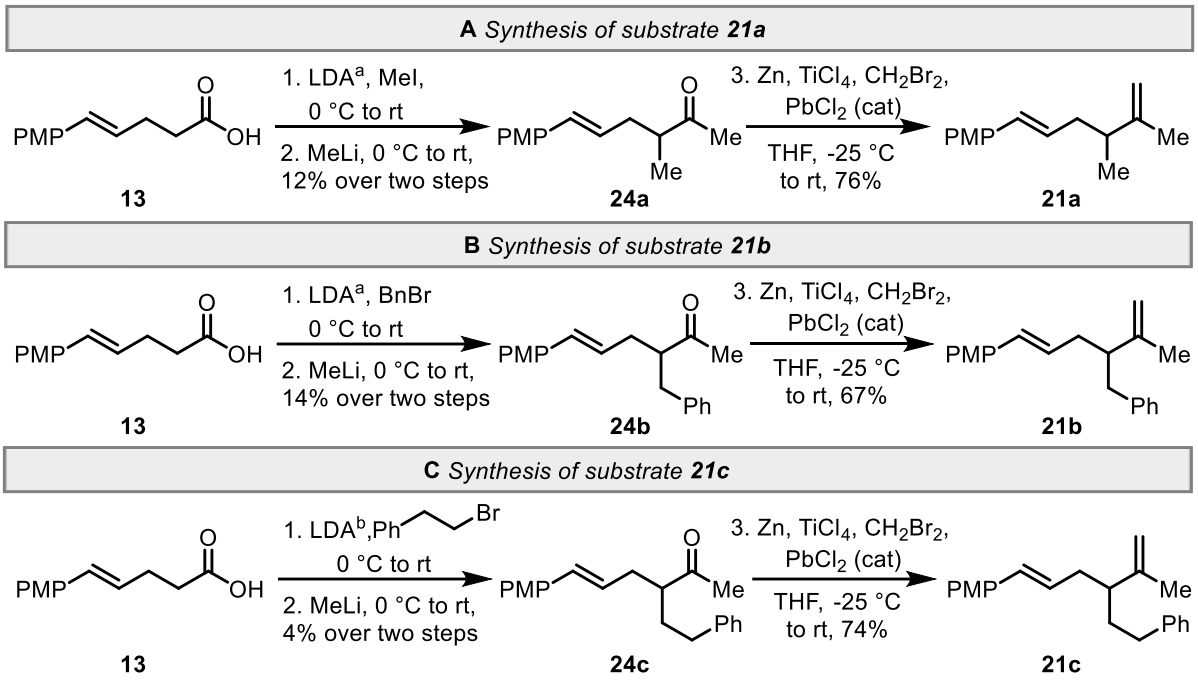
2.2.3 Substrate tuning to avoid the issue of unselective E1 elimination

It was decided to explore if the regioselectivity of E1 elimination following a *6-endo-trig* cyclisation could be controlled by the substrate structure (Scheme **39**, A). For example, the presence of an allylic substituent, such as in substrate **21**, might favour the formation of a more substituted double bond at the thermodynamic equilibrium. On the other hand, a severe $A^{1,3}$ strain between Me and R^3 would have an opposing effect and favour a less substituted alkene of **20**. Alternatively, it was proposed that the intermediate carbocation formed after *6-endo-trig* cyclisation could undergo intramolecular trapping with a suitably positioned nucleophile, preventing E1 elimination. This would remove the issue of alkene regioisomers and set up a polycyclic ring structure **23**, preferably with a high level of diastereocontrol. Given the importance of steroidal-compounds in medicinal chemistry and the abundance of polycyclic carbocycles amongst natural products,[80] it was decided to install an aromatic ring as an intramolecular nucleophile. With these approaches in mind, substrates **21a**, **21b** and **21c** were chosen to be synthesised from carboxylic acid **13** in three steps to test their suitability in a cation-triggered *6-endo-trig* cyclisation (Scheme **39**, B).



*Scheme **39***. Substrate optimisation to solve the issue of low regioselectivity in product formation**.**

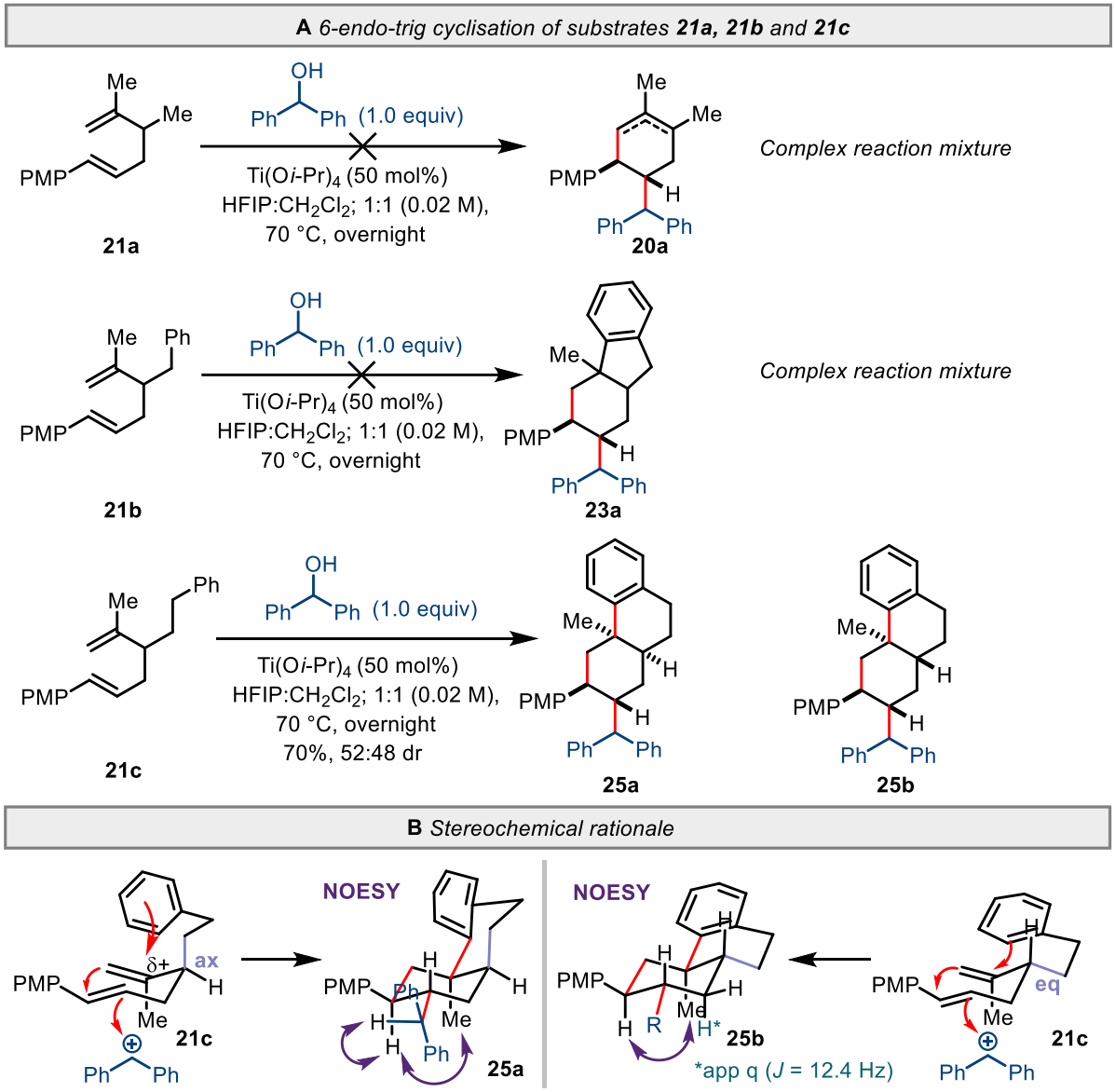
Synthesis of substrate **21a** commenced with alkylation of carboxylic acid **13** using MeI (Scheme **40**, A). The reaction did not go to completion and α-substituted carboxylic acid and acid **13** could not be fully separated by column chromatography. The mixture was treated with MeLi to furnish ketone **24a** and ketone **17** which could be separated at this stage. The desired ketone **24a** was isolated in 12% yield over two steps. The subsequent Lombardo olefination furnished substrate **21a** in 76% yield. Low conversion was also observed when carboxylic acid **13** was alkylated with BnBr and (2-bromoethyl)benzene (Scheme **40**, B and C). Increasing the equivalents of alkylating agents did not improve the conversion. In both cases mixtures of carboxylic acids were taken through to the next step after which separation was possible. Following the reaction with MeLi, ketone **24b** was obtained in 14% yield and ketone **24c** in 4% yield over two steps. Lombardo olefination of ketone **24b** furnished diene **21b** in 67% yield and diene **21c** in 74% yield. The decision was made to first try substrates **21a**, **21b** and **21c** in cyclisation reactions and then to develop a more efficient synthetic route to access the desired substrate, if necessary.



*Scheme **40***. Synthesis of substrates **21a**, **21b**, and **21c**. [a] Reaction performed with 2.5 equiv of LDA; [b] Reaction performed with 3.0 equiv of LDA.

Substrates **21a**, **21b** and **21c** were then subjected to the reaction conditions, previously optimised for *6-endo-trig* cyclisation of a diene **4** (Scheme **41**). Reaction of substrate **21a** and benzhydrol resulted in a complex reaction mixture. No desired product was observed with substrate **21b** either. This result is consistent with the previous observation that 5-membered carbocyclic rings could not be accessed with the cation-triggered cyclisation reaction in HFIP. Fortunately, substrate **21c** with a longer side-chain furnished the desired polycyclic product **25** in 70% yield as a 52:48 mixture of diastereomers at a 6-membered ring fusion. It was proposed that a diphenylmethyl carbocation initiates polyene cyclisation of diene **21c** with a build-up of a positive charge on the tertiary carbon. This triggers intramolecular Friedel–Crafts reaction, which could proceed in a concerted fashion. NOESY analysis of the mixture of diastereomers **25a** and **25b** indicates the same relative configuration of the substituents apart from the C-H centre at the 6-membered ring fusion. The PMP and the diphenylmethyl group are *trans* to each other and occupy equatorial positions, whereas Me group is axial for both diastereomers **25a** and **25b**. It appears that the alkyl chain bearing a Ph group can occupy pseudo-axial or pseudo-equatorial positions with almost no preference during the cyclisation, hence there is

no control at the C-H centre of the 6-membered ring fusion in the product. Alternatively, a stepwise mechanism with the formation of intermediate carbocation could not be excluded.

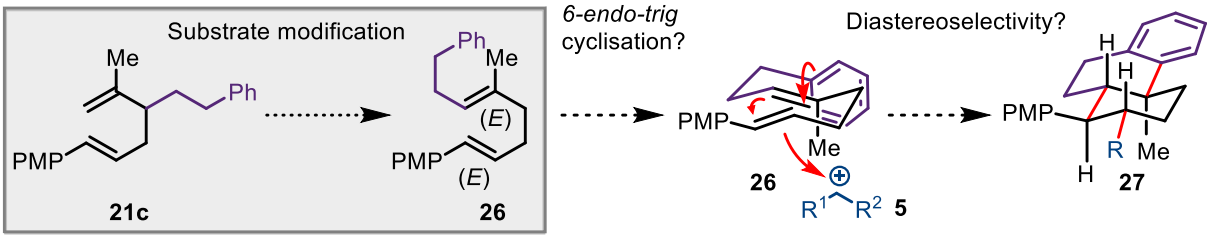


*Scheme **41***. The cation-triggered cyclisation of alkenes **21a**, **21b**, and **21c**.

2.2.4 Substrate tuning to avoid the diastereoselectivity issue

Despite the lack of diastereocontrol, cation-triggered polyene cyclisation of substrate **21c** proceeded in a good yield and has solved the issue of alkene regioisomers by utilising an intramolecular Friedel–Crafts reaction as a termination event. The reaction also set two new ring systems and three new C-C bonds, all in a single step. It was therefore decided to keep

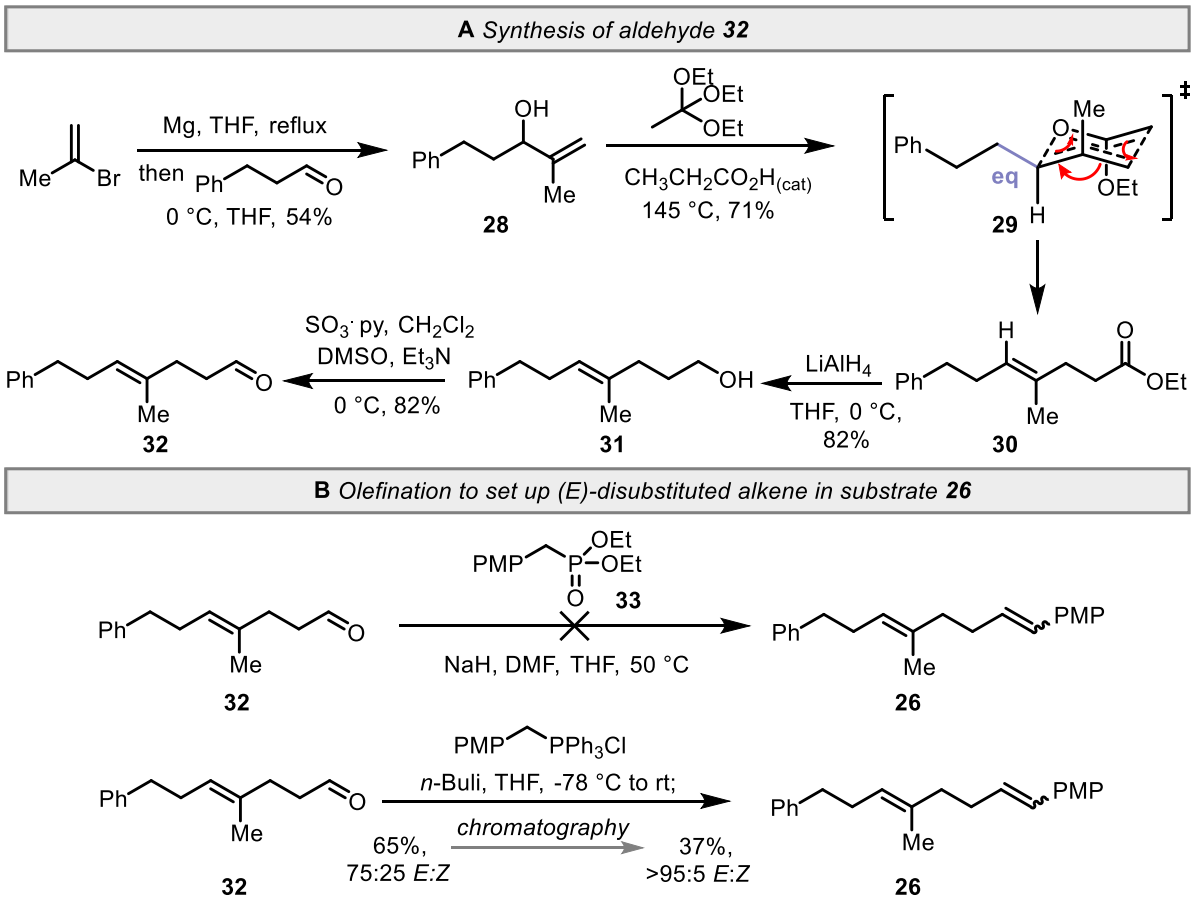
an ethylbenzene group and concentrate on solving the issue of a poor diastereoselectivity (Scheme **42**). It was proposed that attaching an alkyl group bearing an aromatic ring to the alkene, such as in diene **26**, will improve the diastereoselectivity of the reaction. Provided the cation-triggered *6-endo-trig* cyclisation cascade proceeds in a concerted fashion, the geometry of the trisubstituted double bond in diene **26** would dictate stereochemistry at the ring fusion in product **27**. This approach requires a highly diastereoselective synthesis of diene **26** since both alkenes need to be set-up in a high *E*/*Z* ratio. Taking this into account a synthetic route towards diene **26** was investigated.



*Scheme **42***. New substrate design.

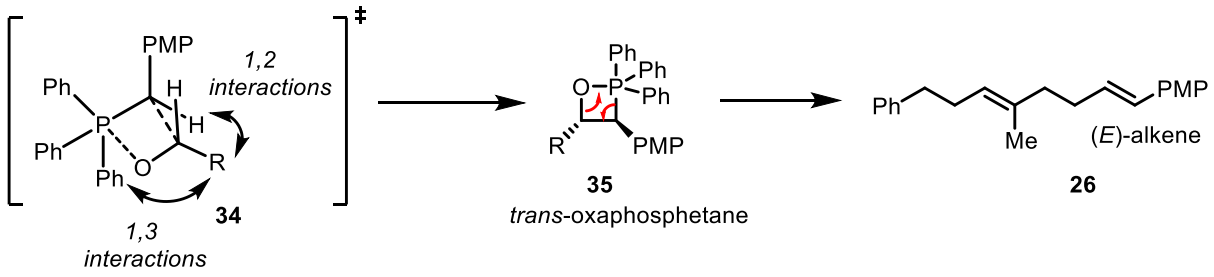
Based on reports from the literature, it was decided to use a Johnson–Claisen rearrangement to set up a trisubstituted alkene in an *E*-configuration.[81] This rearrangement typically proceeds *via* a well-defined chair-like transition state, leading to high levels of *E*/*Z*-selectivity observed in products.[81] A disubstituted alkene which is conjugated to a PMP group was planned to be installed using aldehyde olefination. To access the required allylic alcohol **28**, the Grignard reagent derived from 2-bromoprop-1-ene was added to commercially available 3-phenylpropanal in 54% yield (Scheme **43**, A). A subsequent Johnson–Claisen rearrangement using triethyl orthoacetate and a catalytic amount of propionic acid furnished the desired ester **30** in 71% yield as a single detectable (*E*)-isomer. Such a high (*E*)-selectivity for the Johnson–Claisen rearrangement was explained based on a chair-like transition state **29** in which the alkyl chain occupies a pseudo-equatorial position. Interestingly, when 8 mol% of propionic acid was replaced with AcOH, a complex reaction mixture was obtained. The subsequent $LiAlH_4$ reduction delivered alcohol **31** in 82% yield with a Parikh–Doering oxidation furnishing aldehyde **32** in 82% yield. Next, different olefination reactions were tested for their suitability

to make the required disubstituted alkene (Scheme **43**, B). Benzylic phosphonate **33** was made in one step from 4-methoxybenzyl alcohol and triethyl phosphite in the presence of ZnI_2 in 61% yield.[82] Unfortunately, the attempted Horner–Wadsworth–Emmons reaction between phosphonate **33** and aldehyde **32** failed. No desired product **26** or aldehyde **32** was observed by crude NMR and only phosphonate **33** was present, suggesting decomposition of aldehyde **32** under the reaction conditions. A Wittig reaction between aldehyde **32** and commercially available (4-methoxybenzyl)(triphenyl)phosphonium chloride was then pursued. The desired diene **26** was formed in 65% yield as a 75:25 mixture of alkene isomers, in favour of (*E*)-isomer **26**. Alkene isomers (*E*)-**26** and (*Z*)-**26** could be partially separated by column chromatography; (*E*)-**26** with >95:5 *E*:*Z* could be obtained in 37% yield after consecutive chromatography purifications. The stereochemistry of (*E*)-**26** was assigned based on an alkene coupling constant of 15.8 Hz and that of (*Z*)-**26** based on an 11.7 Hz coupling constant.



*Scheme **43***. Synthesis of substrate **26**.

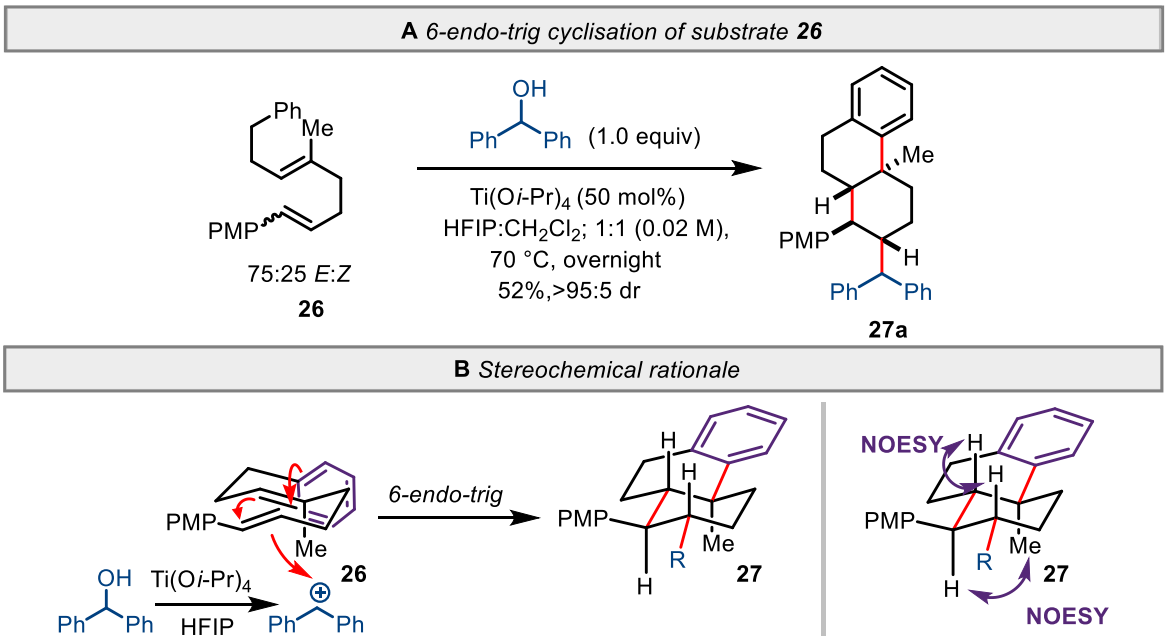
The (*E*/*Z*)- selectivity of a Wittig reaction with semi-stabilized ylides is not well understood.[73(b),83] The computational study from Aggarwal and Harvey suggests non-reversible formation of oxaphosphetane species either through a puckered *cis*-transition state or a planar *trans*-transition state.[773(b)] The authors claim that the exact preference depends on multiple factors including the structure of the aldehyde and the reaction conditions. Given that the observed selectivity for a Wittig reaction between aldehyde **32** and 4-(methoxybenzyl)(triphenyl)phosphonium chloride was 75:25 in favour of the (*E*)-isomer, it is believed that the reaction proceeds predominantly *via* a planar transition state **34** (Scheme **44**). To minimise 1,2 and 1,3-interactions, the PMP and R groups are positioned *trans* to each other in transition state **34**, leading to a *trans*-oxaphosphetane **35**. This decomposes to furnish an (*E*)-double bond in product **26**, as the major alkene stereoisomer.



*Scheme **44***. Rationalisation of the observed (*E*)-selectivity for a Wittig reaction to form diene **26**.

With substrate **26** in hand, the cation-triggered polyene cyclisation was attempted under the previously optimised conditions (Scheme **45**, A). Using benzhydrol as an alkylating agent, the product **27a** was obtained in 52% yield as a single detectable diastereomer. Given that the diene **26** was used as a 75:25 *E*:*Z* mixture, the formation of a single diastereomer **27a** was unexpected and prompted additional mechanistic experiments in the future (see Chapter **2.3.5**). At the current stage of the project, it was proposed that the diphenylmethylcation triggers *6-endo-trig* cyclisation of diene **26** which proceeds *via* a concerted pathway to furnish product **27a** (Scheme **45**, B). The relative stereochemistry of the product **27a** was confirmed by NOESY analysis and was found to be consistent with a concerted cyclisation of (*E*)-**26**. Since the yield of the cyclisation was only 52%, it was uncertain if (*Z*)-**26** follows the same

mechanistic pathway or if a minor diastereomer of product **27a** decomposes under the reaction conditions. Nevertheless, formation of a carbocycle **27** possessing three new C-C bonds with complete diastereocontrol in four consecutive stereocenters was an exciting example of a carbon-electrophile initiated polyene cyclisation. In addition, the polycyclic skeleton of product **27** is a privileged structural element in a number of natural products and biologically active steroidal compounds. [80(c),84] It was therefore decided to further explore the cation-triggered cyclisation of the developed polyene system.



*Scheme **45***. Cation-triggered polyene cyclisation of substrate **26**.

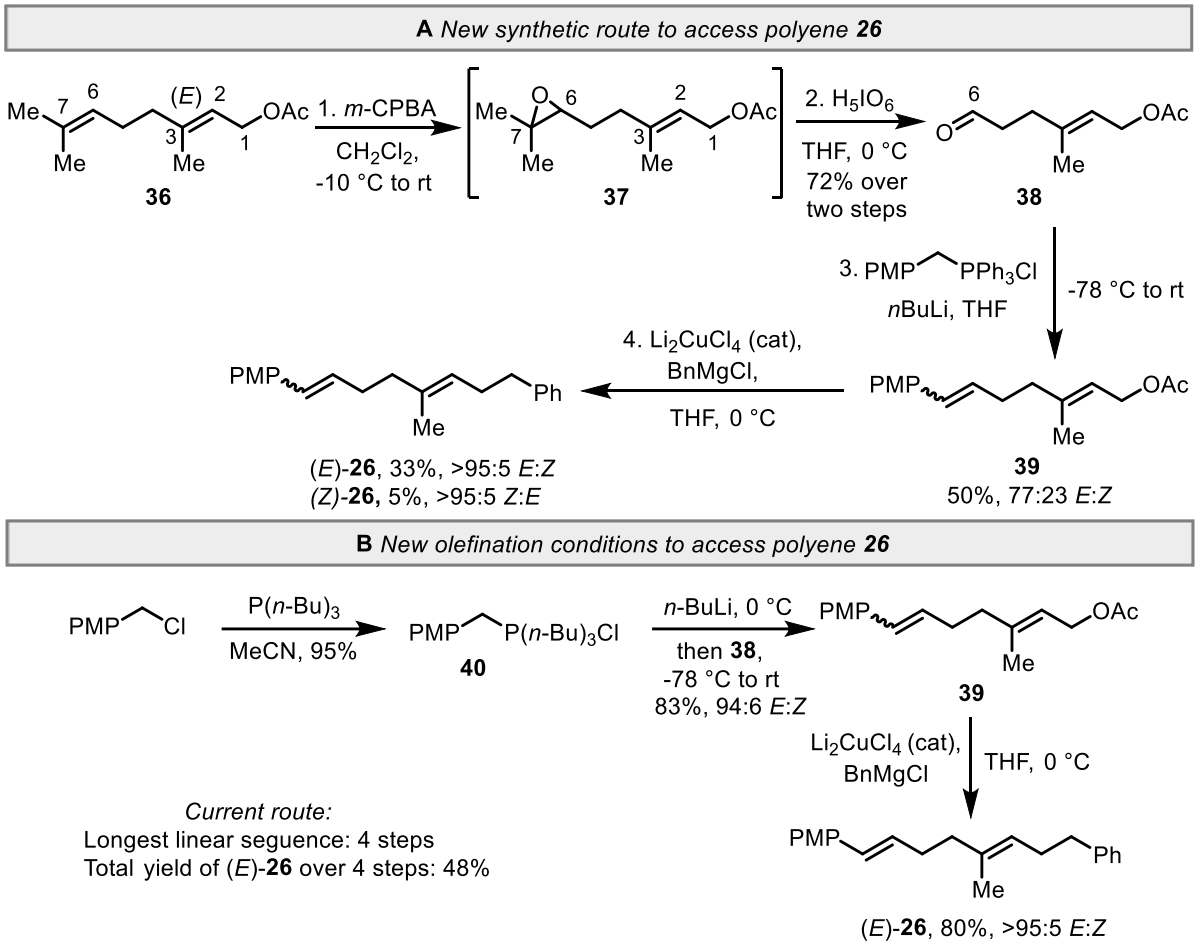
2.3 Studies in the cation-triggered polyene cyclisation cascade

2.3.1 New synthetic route to access polyene 26

To carry out further studies on the cation-triggered polyene cyclisation, a more efficient approach to access substrate **26**, preferably as a single (*E*)-isomer, was required. The previous synthetic route had several issues, such as a long step count and an introduction of a Ph group in the first step (see Scheme **43**). Thus, the entire sequence would need to be repeated to synthesise a substrate with a different aryl terminating group. In addition, difficult separation of (*E*/*Z*)-isomers of **26** further reduced the total yield of (*E*)-**26**. For the second-

generation route, it was decided to use geranyl acetate **36**, a commercially available monoterpene which exists as a *trans*-alkene isomer at C-3 (Scheme **46**, A). In this way, the stereochemistry of the trisubstituted alkene in polyene **26** was already set-up in the starting material. The synthesis commenced with epoxidation of **36** using *m*-CPBA which proceeded exclusively at C-6,7 to furnish epoxide **37**. The alkene at C-2,3 was found to be chemically inert to epoxidation under the reaction conditions which was explained by the inductive electron-withdrawing effect of the acetate group at C-1. Epoxide **37** was telescoped to the next step and subjected to a hypervalent-iodine promoted cleavage at C-6.[85] This formed aldehyde **38** in 72% yield over two steps. Repeating the sequence on 18 g scale of geranyl acetate **36** furnished aldehyde **38** in 65% yield, demonstrating the reliability of this transformation. The consecutive Wittig reaction with the triphenylphosphonium chloride salt furnished acetate **39** in a moderate 77:23 *E*:*Z* ratio, in favour of (*E*)-**39**. Finally, a Ph-group was installed *via* a Cu-catalysed acetate displacement with BnMgCl.[86] At this stage the (*E*/*Z*)-isomers could be separated to furnish (*E*)-**26** in 33% yield and (*Z*)-**26** in 5% yield.

Although this synthetic approach to access (*E*)-**26** is shorter than the previous route *via* a Johnson–Claisen rearrangement, the efficiency was still limited by a moderate *E:Z* ratio of acetate **39** and a difficult separation of alkene isomers by column chromatography. To further improve the synthetic sequence, different olefination conditions were tried. It is known in the literature that replacing the Ph groups on phosphorus with alkyl groups usually increases the (*E*)-selectivity for semi-stabilized ylides in a Wittig reaction.[773(c),87] To test this, tributylphosphonium salt **40** was prepared in 95% from 4-methoxybenzyl chloride and tributylphosphine (Scheme **46**, B). A Wittig reaction between aldehyde **38** and the tributylphosphorane derived from salt **40** furnished acetate **39** in 83% yield in an excellent stereoisomeric ratio of 94:6 in favour of (*E*)-**39**. As before, the acetate group was then displaced with BnMgCl to form polyene **26** in 80% yield and in >95:5 *E*:*Z* ratio after a single purification. Overall, substrate **26** could be obtained in 48% yield over four steps with only three purifications. This synthesis was a significant improvement from the previous six step sequence and 10% overall yield and allowed large amounts of diene (*E*, *E*)-**26** to be prepared.

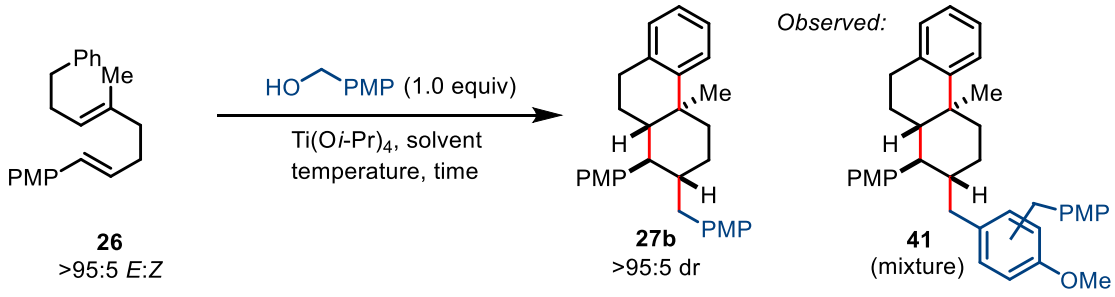


*Scheme **46***. 2nd Generation route to access polyene **26**.

2.3.2 Optimisation of the reaction conditions

With the efficient synthetic route to access polyene **26** in hand, optimisation of the reaction conditions was pursued. From the previous work it was known that benzhydrol-type alcohols tend to give higher yields which do not typically translate well when other alcohols are used.[58] It was therefore decided to optimise the cation-triggered polyene cyclisation using a more challenging primary benzylic alcohol. The starting point were the optimum conditions from the cyclohexene system **12**. Repeating the reaction under these conditions with substrate **26** and 4-methoxybenzyl alcohol furnished product **27b** in 45% and >95:5 dr (Table **3**, entry 1). In addition, a mixture of polyalkylated species **41** was observed by crude NMR. Increasing the concentration to 0.05 M did not affect the reaction yield (Table **3**, entry 2), so future experiments were performed at 0.05 M to minimise solvent use. Complete conversion was

observed after 2 h and product **27b** was isolated in the same yield as after 18 h (Table **3**, entry 3). When the cyclisation was repeated in HFIP alone, the yield of **27b** slightly increased to 52% (Table **3**, entry 4). Reducing the amount of Ti(O*i*-Pr)$_4$ to 30 mol% increased the yield of **27b** to 65% (Table **3**, entry 5). Further reduction in the Lewis acid loading, however, was counterproductive (Table **3**, entry 6). Increasing the concentration in HFIP or decreasing temperature, were detrimental to the reaction yield (Table **3**, entries 7-8). Finally, only 25% of product **27b** was isolated when alcohol was used in excess (Table **3**, entry 9). In this case a complex reaction mixture was observed as a result of extensive polyalkylation.

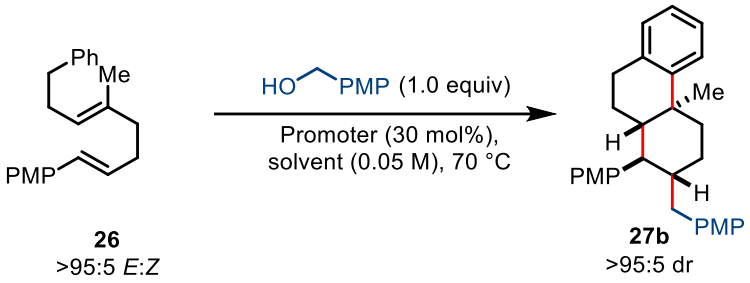


Entry	Solvent	Concentration (M)	T (°C)	Ti(O*i*-Pr)$_4$ (mol%)	Time (h)	Yield[a] of **27b**
1	HFIP : CH_2Cl_2; 1 : 1	0.02	70	50	18	45%
2	HFIP : CH_2Cl_2; 1 : 1	0.05	70	50	18	47%
3	HFIP : CH_2Cl_2; 1 : 1	0.05	70	50	2	48%
4	HFIP	0.05	70	50	2	52%
5	**HFIP**	**0.05**	**70**	**30**	**2**	**65%**
6	HFIP	0.05	70	20	2	53%
7	HFIP	0.1	70	30	2	48%
8	HFIP	0.05	40	30	2	37%
9	HFIP	0.05	70	30	2	25%[b]

Table 3. Optimisation of the reaction with respect to concentration, time, temperature and loading of Ti(O*i*-Pr)$_4$**.** [a] Isolated yields are reported; [b] The reaction was performed using 1.5 equiv of alcohol.

Next, Lewis and Brønsted acids were screened (Table **4**). The use of Ph_4PBF_4, a salt which was reported to improve the cation stabilizing ability of HFIP, was not beneficial for the reaction and furnished product **27b** in 38% yield (Table **4**, entry 2).[88] Other divalent and trivalent Lewis acids furnished product **27b** in low to moderate yields (Table **4**, entries 3-5). The use of TFA, a Brønsted acid, was detrimental to yield. (Table **4**, entry 6). Since complete conversion was observed in all cases, the low yields were explained by varying amounts of aforementioned Friedel–Crafts polyalkylation. Interestingly, when cyclisation was performed without a Lewis or a Brønsted acid, 49% of product **27b** was still isolated (Table **4**, entry 7). This result demonstrates that 4-methoxybenzyl alcohol can ionise to form a carbocation species in HFIP without a promoter present. To conclude, Ti(O*i*-Pr)$_4$ was found to be the optimum Lewis acid. This is consistent with the previous work on HFIP promoted heterocyclisation.[58,60] In the study it was shown that the addition of Ti(O*i*-Pr)$_4$ to HFIP generates Ti(O*i*-Pr)$_2$(OHFIP)$_2$ complex. This complex activates alcohols towards nucleophilic attack by an electron-rich alkene. It is possible that the same process happens in the polyene cyclisation as well, although this would only account for a small increase in yield.

Finally, a range of common solvents with Ti(O*i*-Pr)$_4$ additive were tested for their suitability in the cation-triggered polyene cyclisation of substrate **26** (Table **4**, entries 8-14). The reaction was shut down completely when HFIP was replaced with different solvents which are known to promote S_N1 or S_N2 type processes.[89] Only starting material was observed after 2 h and 24 h. These results highlight the unique properties of HFIP solvent, such as relatively high dielectric constant (ε = 15.7) and low nucleophilicity, in facilitating reactions that involve the generation of cationic species.[90] In addition, it is possible that HFIP, as a highly polar medium, induces a pre-organisation of a non-polar polyene **26**. This results in a reactive conformation which also minimises the surface area of substrate **26** exposed to solvent. A similar effect of HFIP on polyene reactivity has been reported by several groups in the literature.[88,91]



26
>95:5 *E*:*Z*

27b
>95:5 dr

Entry	Solvent	Lewis acid (30 mol%)	Time (h)	Yield[a] of **27b**
1	**HFIP**	**Ti(O*i*-Pr)$_4$**	**2**	**65%**
2	HFIP	Ph_4PBF_4	2	38%
3	HFIP	$Zn(OTf)_2$	2	34%
4	HFIP	$Zn(OAc)_2$	2	45%
5	HFIP	$AlCl_3$	2	15%
6	HFIP	TFA	2	31%
7	HFIP	-	2	49%
8	*i*-PrOH	Ti(O*i*-Pr)$_4$	2	0%[b]
9	DMF	Ti(O*i*-Pr)$_4$	2/24	0%[b]
10	MeOH	Ti(O*i*-Pr)$_4$	2/24	0%[b]
11	MeCN	Ti(O*i*-Pr)$_4$	2/24	0%[b]
12	EtOAc	Ti(O*i*-Pr)$_4$	2/24	0%[b]
13	PhMe	Ti(O*i*-Pr)$_4$	2/24	0%[b]
14	DCE	Ti(O*i*-Pr)$_4$	2/24	0%[b]

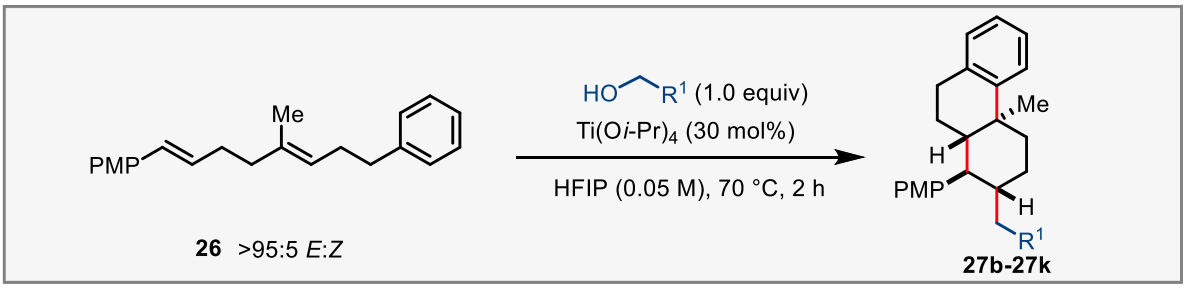
*Table **4***. Screen of Lewis/Brønsted acids and solvents**.** [a] Isolated yields are reported; [b] No conversion over 2 and 24 h.

2.3.3 Alcohol substrate scope for diene 26

After determining the optimum conditions for the cation-triggered polyene cyclisation, attention was turned to obtain the scope of this transformation. First, it was decided to explore which alcohols can be engaged to trigger the cyclisation cascade of substrate **26**.

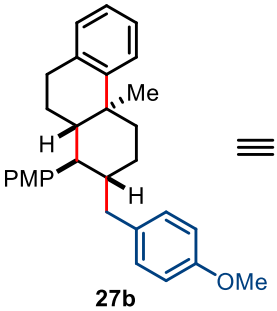
Primary benzylic alcohols furnished products **27b**-**27k** in moderate yields as single diastereomers (Scheme **47**). The relative stereochemistry of the products was confirmed by NOESY analysis as well as single crystal X-ray structures obtained for compounds **27b** and **27e**. Free hydroxyl (**27c**), amine (**27d**) and halogen (**27f**) functional groups could be tolerated under the reaction conditions. Benzylic alcohols with *ortho*-substituents could be engaged but resulted in lower yields of products **27f** and **27e**. An indole-derived alcohol worked well and furnished product **27g** in 56%, demonstrating that heterocycles could also be tolerated. This reaction was performed at rt to minimise decomposition of (1-methyl-1*H*-indol-3-yl)methanol in HFIP. In all cases complete conversion was achieved after 2 h. Low yields were explained by the observed formation of complex mixtures of polyalkylated species *via* a Friedel–Crafts side-reaction.[92] Primary allylic alcohols could also be engaged in the cation-triggered polyene cyclisation to install a synthetically versatile exocyclic alkene. Electron-rich cinnamyl alcohols furnished products **27h** and **27i** in 41% and 39% yield respectively. Low yield of product **27j** was explained by the slower rate of ionisation of a non-activated cinnamyl alcohol and thus increased amount of background decomposition of substrate **26** (see Chapter **2.3.5**). Finally, a non-cinnamyl derived allylic alcohol was also engaged to furnish product **27k** in 19% yield.

Next, the use of secondary allylic and benzylic alcohols in the cation-triggered polyene cyclisation was explored (Scheme **48**). As a general trend, secondary alcohols were more effective than primary alcohols in triggering the cyclisation of substrate **26**. For secondary alcohols, the Friedel–Crafts polyalkylation side-reaction was not observed, hence higher yields were obtained. In addition to the previously mentioned functionalities, ester (**27o**), acetal (**27m**) and thiophene heterocycle (**27p**) were tolerated under the reaction conditions. 1-Arylethan-1-ol alcohols worked well furnishing products **27l-o** in up to 92% yield. The reaction with 1-(thiophen-2-yl)ethan-1-ol furnished product **27p** in 40% yield. In this case a complex mixture of unidentified side-products was also isolated which might be due to uncontrolled alkylation of the thiophene ring. Cyclic secondary alcohols could also be engaged to generate product **27q** in 77% yield. Products **27l-q** and **27w** were formed with moderate to excellent dr at the exocyclic position and with the same relative stereochemistry around the ring system.



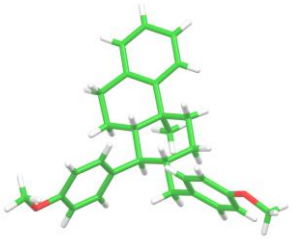
26 >95:5 *E*:*Z*

27b-27k

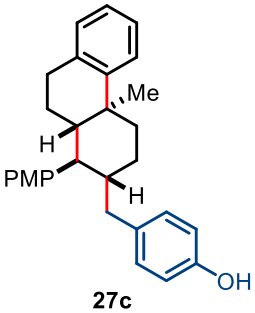


27b
65%[a]; dr>95:5

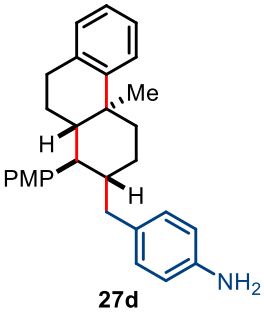
≡



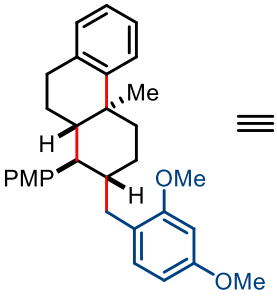
[X-ray]



27c
66%; dr>95:5

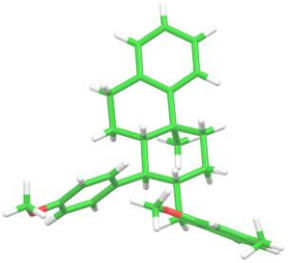


27d
62%; dr>95:5



27e
33%; dr>95:5

≡



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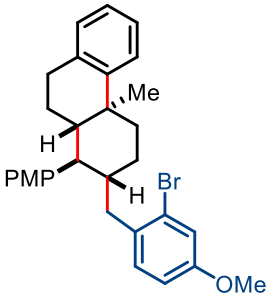
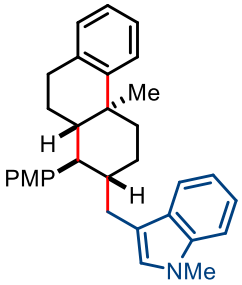
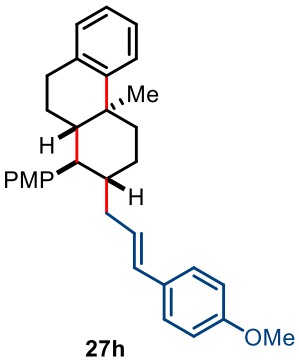


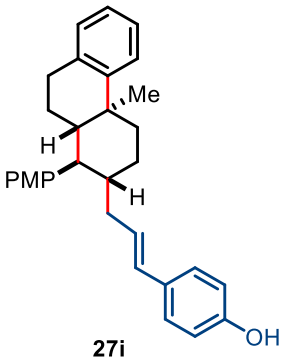
27f
34%; dr>95:5



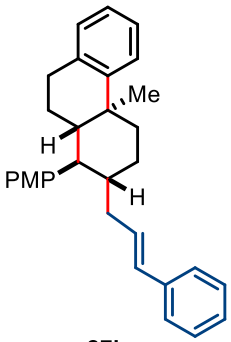
27g
56%[b]; dr>95:5



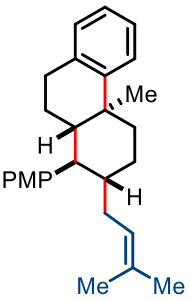
27h
41%; dr>95:5



27i
39%; dr>95:5

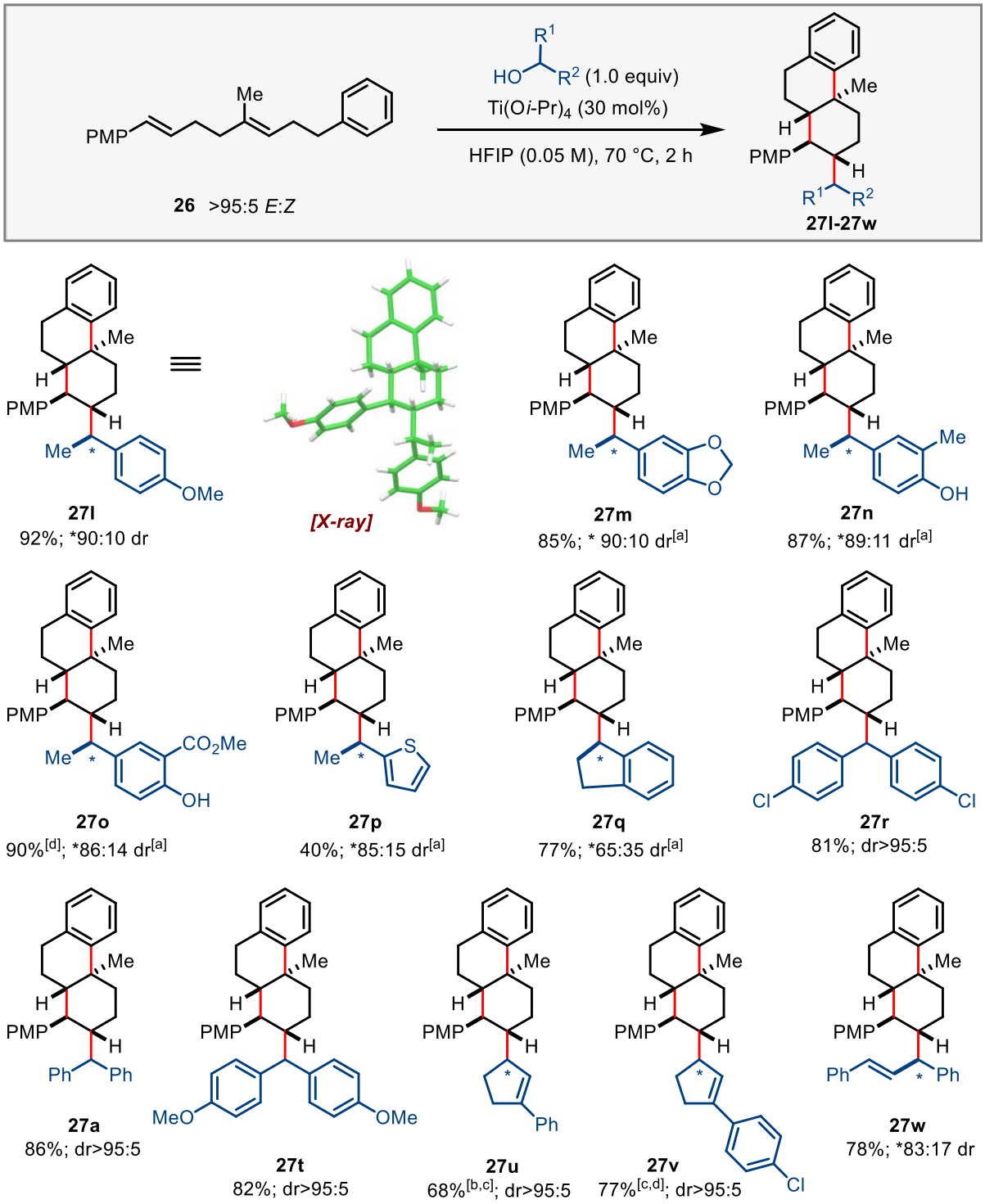


27j
19%; dr>95:5



27k
19%[c]; dr>95:5

*Scheme **47***. Cation-triggered polyene cyclisation of substrate **26** using primary alcohols. Reactions were performed on 0.1 mmol scale unless otherwise stated. [a] Reaction performed on 0.082 mmol scale (25 mg); [b] reaction performed at rt for 2.5 h; [c] Reaction performed with 2.0 equiv of alcohol and for 50 min.

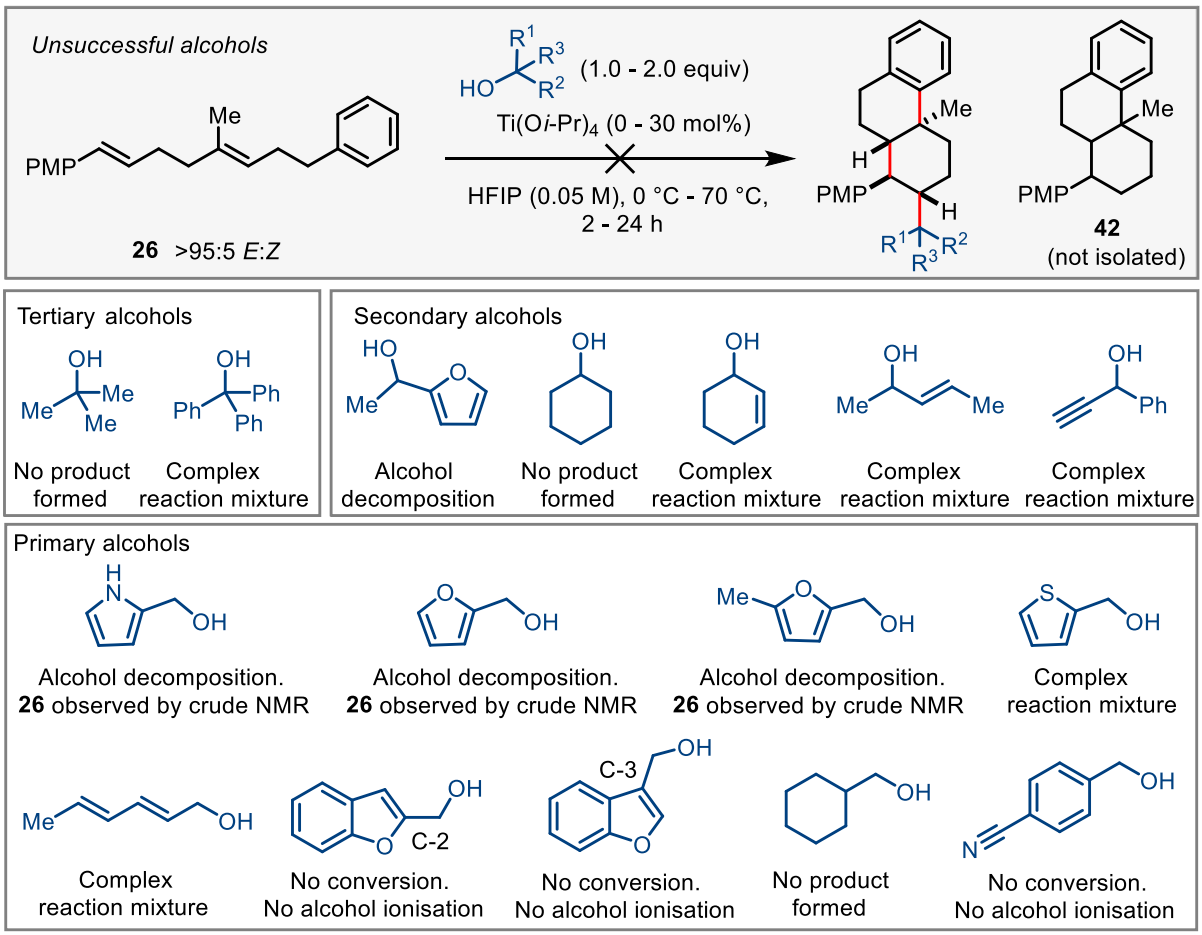


*Scheme **48***. Cation-triggered polyene cyclisation of substrate **26** using secondary alcohols. Reactions were performed on 0.1 mmol scale unless otherwise stated. dr determined by ^{1}H NMR spectroscopy of the crude reaction mixture unless otherwise stated. [a] dr determined after column chromatography; [b] Reaction performed at rt for 4 h; [c] The exocyclic stereochemistry of **27u** and **27v** could not be determined unambiguously; [d] Reaction performed at rt for 1.5 h.

The levels of diastereoselectivity at the exocyclic centre were found to depend on the stabilization of the carbocation formed *in situ*. The more stable the carbocation, the higher the observed diastereoselectivity (**27l** to **27q**). The relative stereochemistry of products **27m-q** and **27w** was assigned in analogy to compound **27l**, for which a crystal structure was obtained. Benzhydrol-type alcohols furnished products **27r**, **27a** and **27t** in excellent yields. Electron-withdrawing (**27r**), neutral (**27a**) and electron-rich (**27t**) substituents on the aromatic rings were well tolerated. Finally, cyclic and acyclic allylic alcohols were engaged to furnish compounds **27u-w** in good yields. Notably, products **27u** and **27v** were formed as single diastereomers with five newly formed contiguous stereocenters.

Inspired by the good yields and moderate to excellent diastereoselectivities obtained for secondary and primary alcohols, the use of tertiary alcohols was then examined (Scheme **49**). Unfortunately, no product formation was observed over 24 h when *t*-BuOH and triphenylmethanol were subjected to the reaction conditions. Instead, a complex reaction mixture was formed in both cases. When *t*-BuOH was used, formation of species **42** was also observed by NMR, although any attempt to isolate compound **42** in sufficient purity failed. Species **42** could be formed when a proton from HFIP, instead of a carbocation, triggers cyclisation of substrate **26**. The absence of desired reactivity of tertiary alcohols was explained by the steric hindrance of tertiary carbocations which prevents the key C-C forming step that triggers the cyclisation cascade. Thus, background side-reactions are more prevalent and decomposition of substrate **26** can occur. It was found that the right balance between carbocation stability, reactivity and the rate of ionisation is required for an efficient cation-triggered polyene cyclisation cascade. Within secondary alcohols, the use of 1-(furan-2-yl)ethan-1-ol resulted in the alcohol decomposition/polymerisation with only remaining starting material **26** being observed by crude NMR. The same result was obtained when the reaction was conducted at room temperature. No desired product was formed when cyclohexanol was used. Instead, a mixture containing polyene **26**, species **42** and unidentified side-products was observed. In the case of cyclohex-2-en-1-ol, (*E*)-pent-3-en-2-ol and 1-phenylprop-2-yn-1-ol, complex reaction mixtures were formed. Repeating the reaction with (*E*)-pent-3-en-2-ol at rt

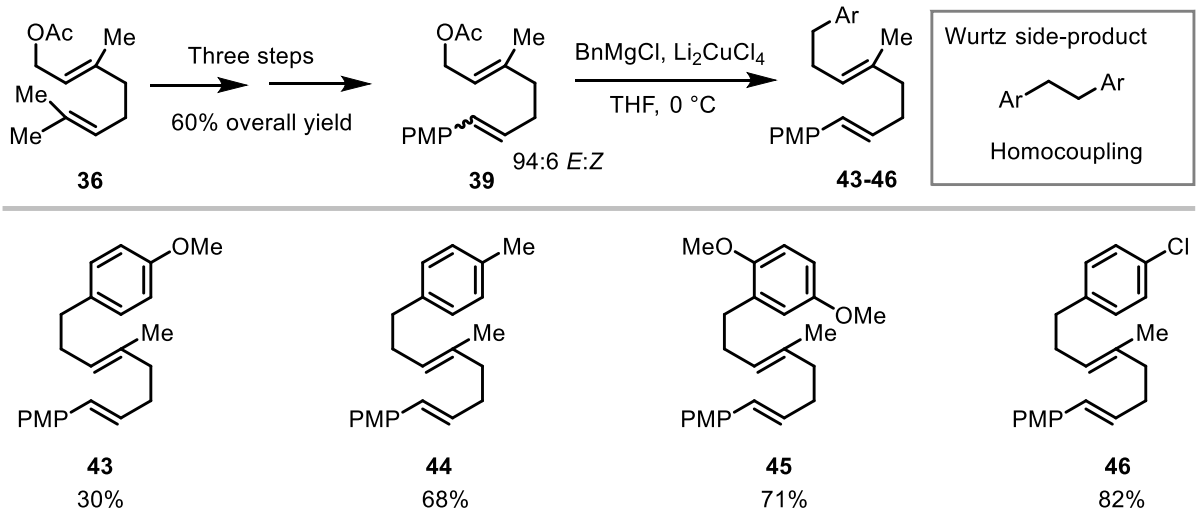
and 0 °C, with a view to minimise unwanted side-reactions or alcohol decomposition, yielded similar results. It was concluded that primary alcohols bearing 5-membered aromatic heterocycles such as pyrrole, furan and thiophene are not compatible with the reaction conditions, even when reactions are conducted at room temperature and without Ti(O*i*-Pr)$_4$ Lewis acid. In the case of thiophen-2-ylmethanol and (2*E*,4*E*)-hexa-2,4-dien-1-ol, complex mixtures were obtained. Interestingly, no conversion was observed with benzofurans substituted at either the C-2 or C-3 position with a -CH_2OH group. In both cases, the alcohol was still observed by crude NMR, indicating no ionisation under the reaction conditions. Similarly, with cyclohexylmethanol and 4-cyanobenzyl alcohol no conversion was observed. Instead, mixtures containing unreacted starting material **26** and species **42** were formed. 4-Cyanobenzyl alcohol was isolated in quantitative yield after the reaction, hence no ionisation of the electron-deficient benzylic alcohol had occurred under the reaction conditions.



*Scheme **49***. Unsuccessful alcohols.

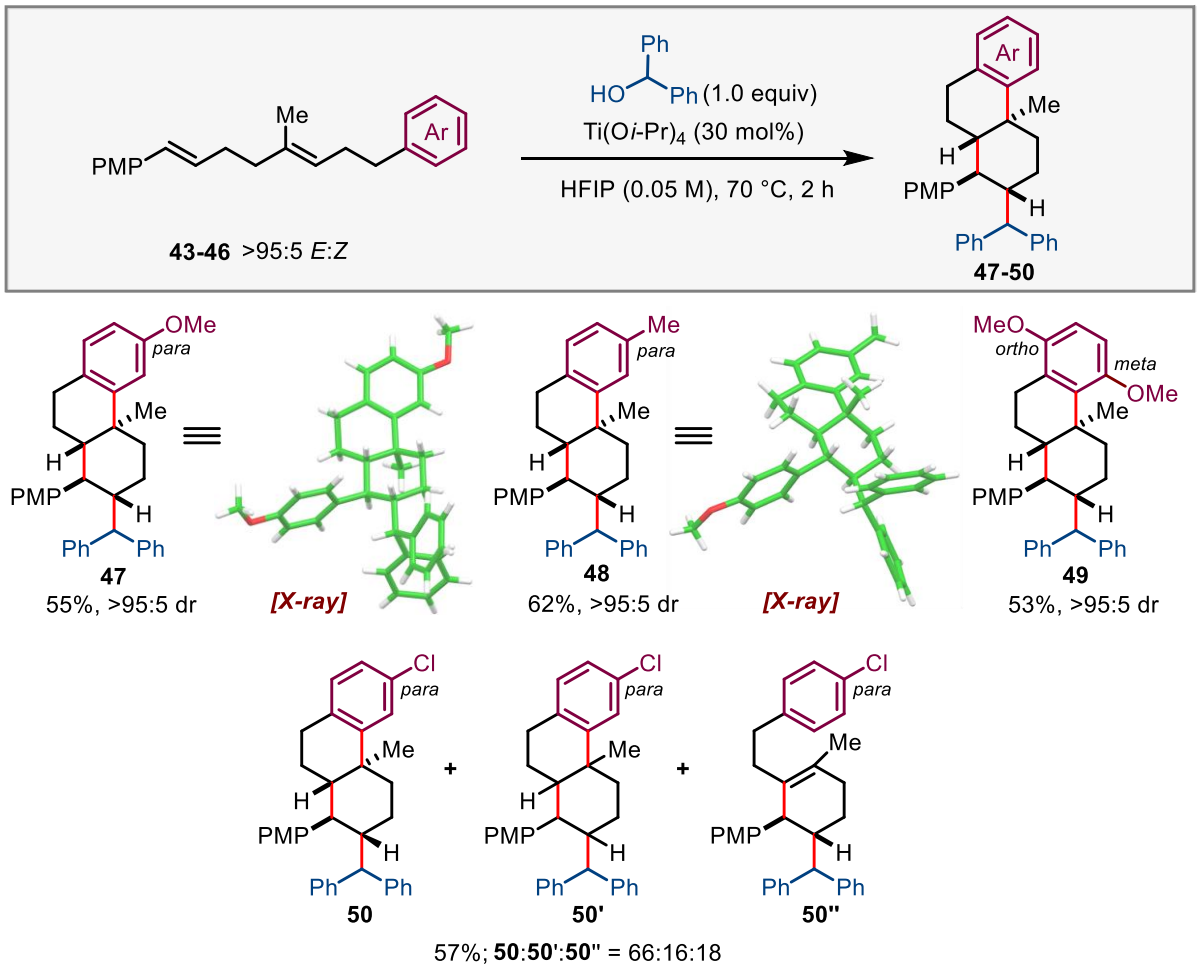
2.3.4 Substrate scope of the terminating aryl group

After investigating the alcohol substrate scope, attention was turned to explore which aryl terminating groups can be used in the cation-triggered polyene cyclisation. It was decided to synthesise substrates bearing electron-rich and electron-deficient arenes to examine a range of reactivities. With the second-generation route to access polyene **26**, the aryl group is installed in the last step, making this approach ideal for the synthesis of a variety of the polyene structures (see Scheme **46**). The acetate precursor **39** was synthesised from commercially available geranyl acetate in 60% yield over three steps (Scheme **50**). Then, copper-catalysed acetate displacement with Grignard reagents was used to install the desired aryl group. During the preparation of the required Grignard reagents in THF, the formation of homocoupled side-products *via* a Wurtz reaction was observed.[93] In the case of 4-methoxybenzyl magnesium chloride, this resulted in a significant decrease in yield of product **43**. Polyenes **44** and **45**, on the other hand, were isolated in 68% yield and 71% respectively. In an attempt to prepare 4-chlorobenzyl magnesium chloride in THF only the Wurtz coupling side-product was formed; hence no reaction was observed upon the addition of the mixture to acetate **39** in the presence of Li_2CuCl_4. Preparing 4-chlorobenzyl magnesium chloride in Et_2O instead of THF minimised the undesired Wurtz coupling and furnished product **46** in 82% yield.



*Scheme **50***. Synthesis of polyenes **43**-**46**.

With polyenes **43-46** in hand, the cation-triggered polyene cyclisation cascade was attempted using benzhydrol as an electrophile (Scheme **51**). Substrates **43** and **44** furnished products **47** and **48** in 55% yield and 62% yield as single diastereomers respectively. Similarly, product **49** was obtained in 53% yield with excellent diastereoselectivity. These results demonstrate that electron-rich arenes with substituents at *para*-, *ortho*- and *meta*-positions are tolerated under the reaction conditions. The relative stereochemistry of products **47**-**49** was confirmed by NOESY analysis as well as X-ray crystal structures obtained for compounds **47** and **48**. The reaction between polyene **46,** which bears an electron-withdrawing group at the *para*-position, with benzhydrol, on the other hand, furnished a complex mixture consisting of major diastereomer **50**, minor diastereomer **50'** and cyclohexene **50"** in 66:16:18 ratio. This was explained by the reduced propensity of an electron-deficient aromatic ring to participate in

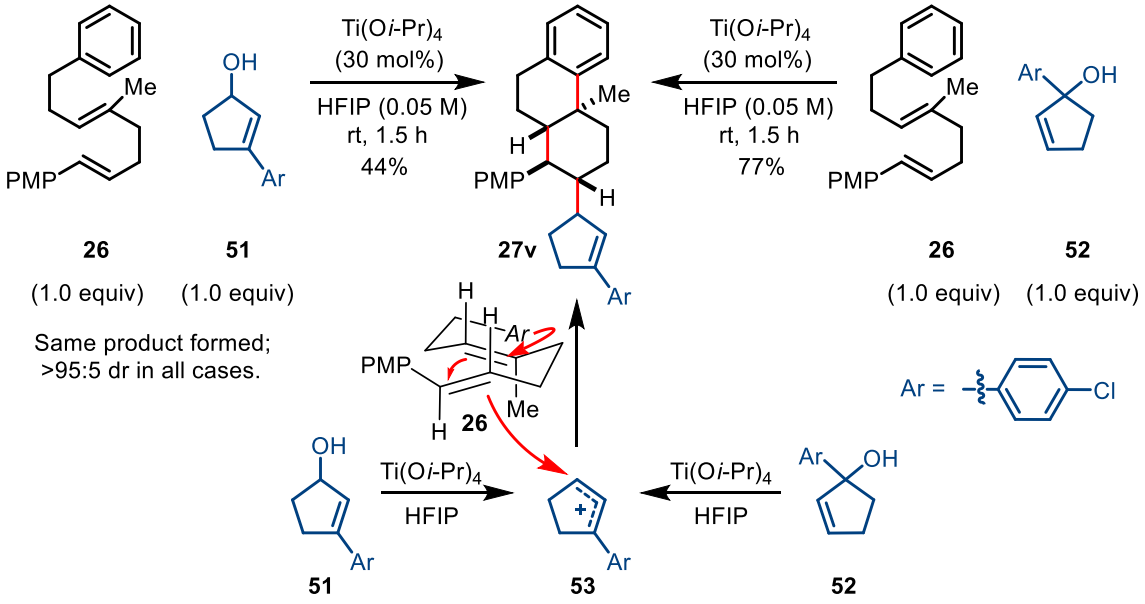


*Scheme **51***. Substrate scope with respect to aryl group.

cyclisation, resulting in the formation of an intermediate carbocation which undergoes unselective cyclisation and E1 elimination (see Scheme **37**). Hence, electron-deficient arenes are not a suitable terminating group for the cation-triggered polyene cyclisation.

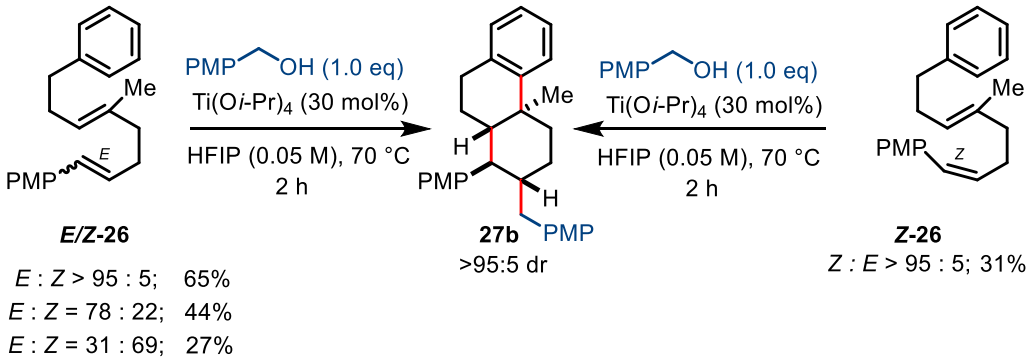
2.3.5 Mechanism of the alkylative polyene cyclisation of substrate 26

Having investigated both the scope of aryl terminating groups and the scope of alcohols, mechanistic experiments were performed to investigate the cyclisation mode of substrate **26**. First, the evidence for carbocation formation in HFIP was obtained using the reaction between polyene **26** and transposed isomers of an allylic alcohol **52** and **51** (Scheme **52**). Both reactions furnished the same regioisomer and diastereomer of the product **27v**. In the case of a tertiary alcohol **52**, product **27v** was formed in 77% yield, while secondary alcohol **51** furnished product **27v** in 44% yield. This is consistent with the formation of the delocalised carbocation species **53** *in situ* which then triggers the polyene cyclisation cascade of substrate **26**. The reaction proceeds exclusively through the least hindered end of the delocalised cation **53**, forming product **27v** as a single regioisomer. The lower reaction yield with alcohol **51** could arise from the different rate of ionisation of alcohols **51** and **52** under the reaction conditions to form species **53** and may also be impacted by the variance in alcohol stability.



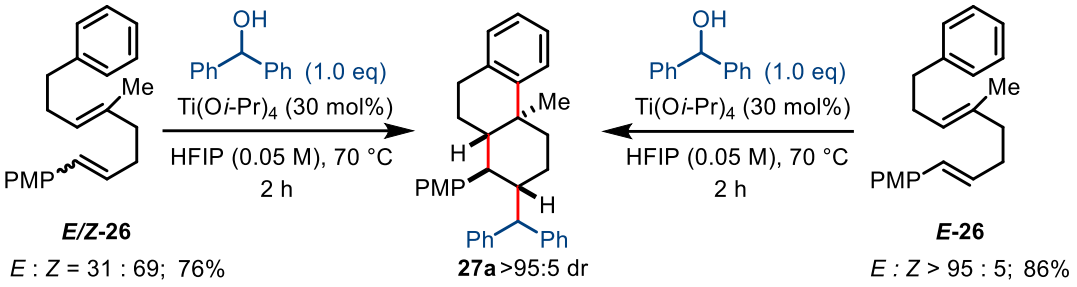
*Scheme **52***. Evidence for carbocation formation.

Next, the effect of (*E*/*Z*)-geometry of the double bond in conjugation with the PMP group of substrate **26** was investigated (Scheme **53**). It was previously observed that the reaction between polyene **26** as a 75:25 *E*:*Z* alkene mixture and benzhydrol furnished product **27a** in 52% as a single diastereomer (see Scheme **45**). To explore this further, (*Z*)-**26** which was formed as a minor isomer *via* a Wittig reaction using (4-methoxybenzyl)(triphenyl)phosphonium chloride was subjected to the optimised reaction conditions together with 4-methoxybenzyl alcohol (Scheme **53**, right). This furnished product **27b** in 31% yield as a single diastereomer having the same relative stereochemistry as product **27b** obtained from the identical reaction of (*E*)-**26** with 4-methoxybenzyl alcohol (Scheme **53**, left). In addition, subjecting (*E*/*Z*)-mixtures of a polyene **26** with different proportions of (*Z*)-isomer resulted in the formation of a single diastereomer of the product **27b**. Generally, the higher the proportion of (*E*)-**26** in the mixture, the higher was isolated yield of product **27b**.



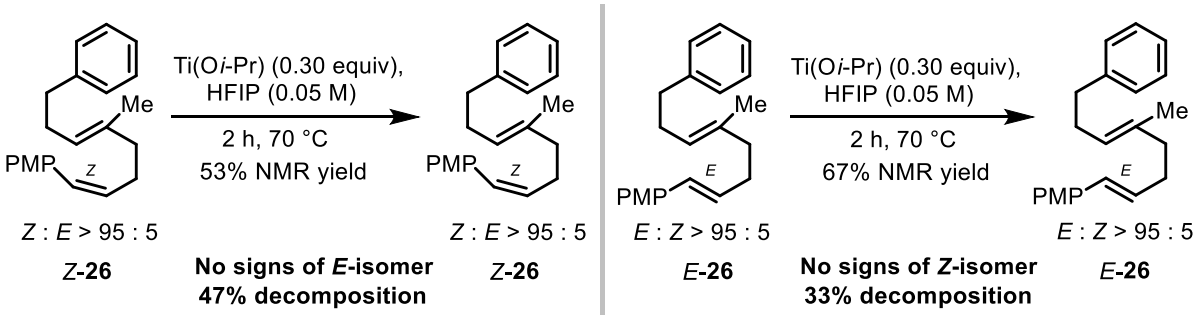
*Scheme **53***. The reaction of (*E*/*Z*)-**26** with 4-methoxybenzyl alcohol.

The stereoconvergent mode of cyclisation of substrate **26** was also observed for secondary alcohols (Scheme **54**). The reaction of (*E*/*Z*)-**26** in 31:69 ratio, in favour of the (*Z*)-isomer, with benzhydrol furnished product **27a** in 76% yield as a single diastereomer with the same relative stereochemistry as obtained from the reaction of (*E*)-**26**. Again, the yield of the cation-triggered cyclisation was higher when (*E*)-**26** was used. In all cases, the stereoconvergent formation of product **27a** was first confirmed by comparing crude ^{1}H and ^{13}C NMR data from the reactions of (*E*)-**26** and (*Z*)-**26** mixtures with alcohols, following by product isolation and detailed NOESY analysis.



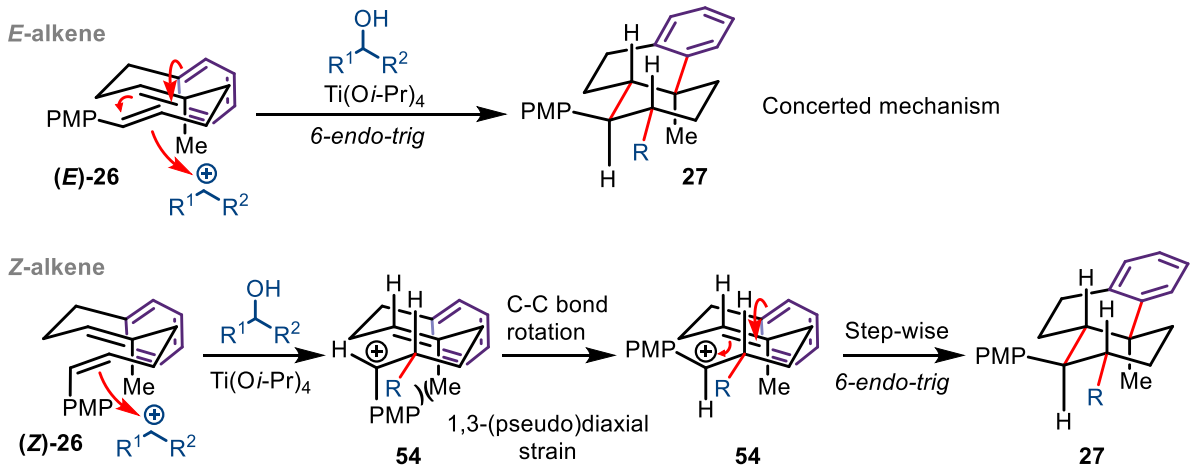
*Scheme **54***. The reaction of (*E/Z*)-**26** with benzhydrol.

To check if (*Z*)-isomer **26** isomerises to the more thermodynamically stable (*E*)-**26** prior to the cation-triggered cyclisation cascade, both isomers were subjected to the reaction conditions but without alcohol present (Scheme **55**). In the case of (*Z*)-**26**, significant decomposition was observed after 2 h with only 53% of substrate remaining by NMR analysis of the crude mixture (Scheme **55**, left). However, no sign of (*E*)-isomer **26** was observed. It was proposed that (*Z*)-isomer **26** could isomerise to (*E*)-**26** which then undergoes fast decomposition. To check if that is possible, the stability of (*E*)-**26** under the reaction conditions was examined (Scheme **55**, right). Heating the solution of (*E*)-**26** in HFIP (0.05 M) in the presence of Ti(O*i*-Pr)$_4$ (30 mol%) at 70 °C resulted in 33% decomposition. Since (*E*)-**26** was found to be more stable than (*Z*)-**26** under the reaction conditions, isomerisation of (*Z*)-**26** into (*E*)-**26** followed by fast decomposition is unlikely. These findings elucidate why yields of cation-triggered polyene cyclisation are higher for (*E*)-**26** than for (*Z*)-**26**. In addition, the limited stability of both isomers of substrate **26** under the reaction conditions explains why more activated alcohols are generally more efficient in the cation-triggered polyene cyclisation cascade.



*Scheme **55***. Stability of (*E*)-**26** and (*Z*)-**26** under the reaction conditions. NMR yields were calculated using 1,1,2,2,-tetrachloroethane as an internal standard.

To explain the results obtained from the mechanistic experiments, the following stereoconvergent mechanism for the cation-triggered cyclisation of substrate **26** was proposed (Scheme **56**). For (*E*)-**26**, it is believed that the reaction proceeds in a concerted fashion *via* a chair-like transition state to furnish product **27**. (*Z*)-**26**, however, undergoes a stepwise cyclisation. In the first step, a C-C bond is formed between the carbocation generated *in situ* and the electron-rich alkene of substrate **26** to furnish intermediate cation **54**. Due to unfavourable 1,3-(pseudo)diaxial strain between the PMP and axial methyl groups, cyclisation does not occur until the C-C bond rotates to bring the PMP group into an equatorial position in intermediate **54**. The subsequent cyclisation furnishes product **27** with the same relative stereochemistry as from the reaction of (*E*)-**26**. It is not possible to exclude that the (*E*)-isomer of substrate **26** undergoes a stepwise mechanism as well. However, based on the difference in reaction yields for (*E*)-**26** and (*Z*)-**26**, as well as more complex reaction mixtures generally obtained with (*Z*)-**26** substrate, it is likely that different mechanisms are being followed. For substrate **46** bearing an electron-deficient arene, a stepwise mechanism occurs as a result of the reduced nucleophilicity of the *para*-chloro-substituted arene.

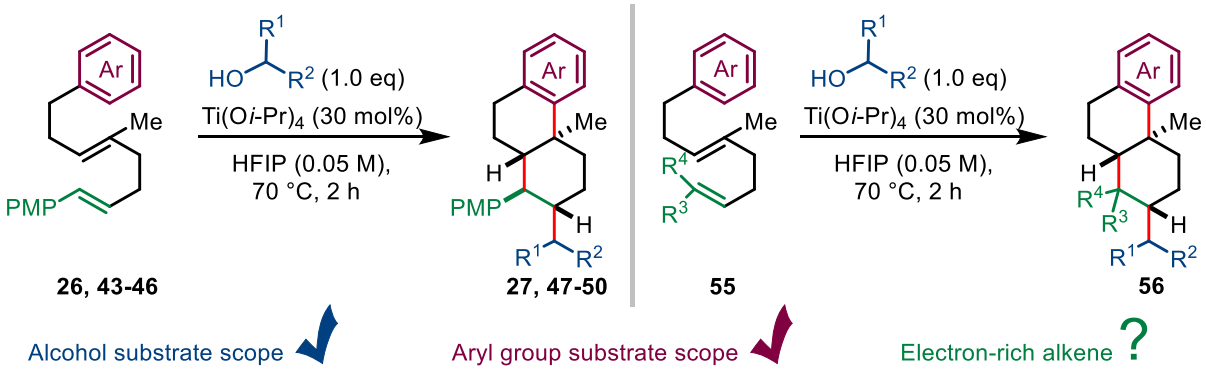


*Scheme **56***. The proposed stereoconvergent reaction mechanism for (*E*/*Z*)-**26**.

2.3.6 Reactivity of other conjugated alkene systems in the polyene cyclisation

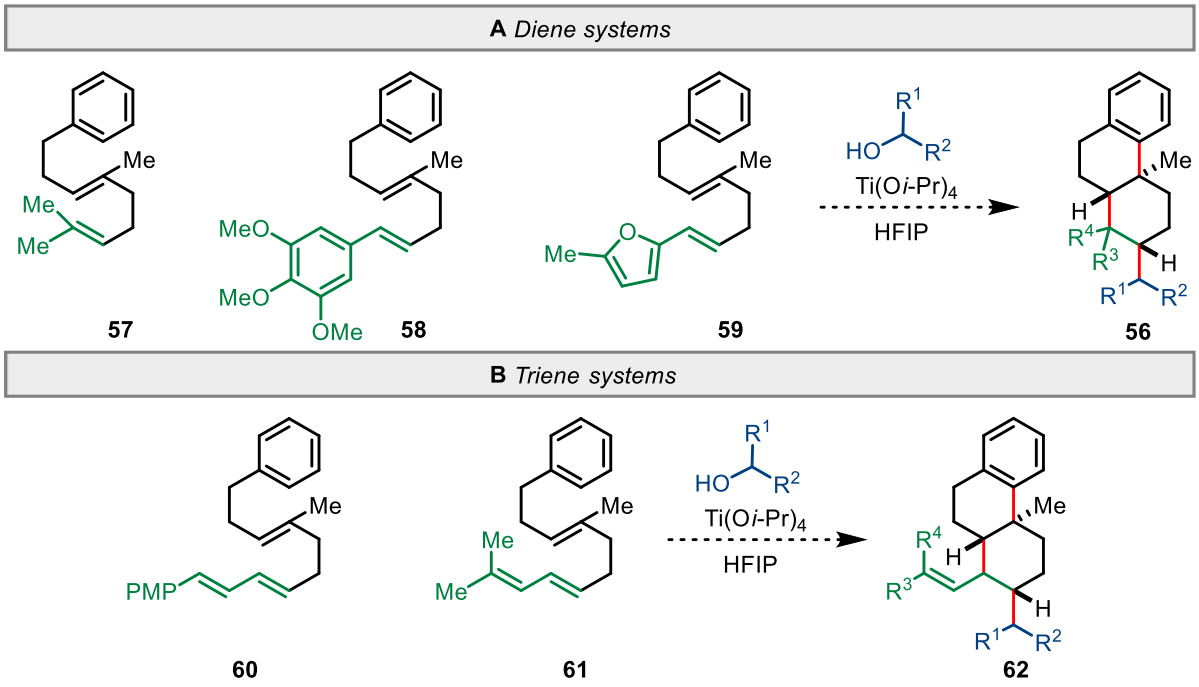
After studying the reaction mechanism and obtaining substrate scopes with respect to alcohol and aryl terminating group, attention was turned to explore which alkene systems can be used

in the cation-triggered cyclisation cascade (Scheme **57**). Installing different alkenes in substrate **55** which control the first C-C bond forming event with carbocations formed *in situ*, could generate a library of products **56**. Furthermore, the use of R^3/R^4 groups in substrate **55** that could be further derivatised after formation of product **56** was particularly desirable.



*Scheme **57***. New substrate design: variation of electron-rich alkene.

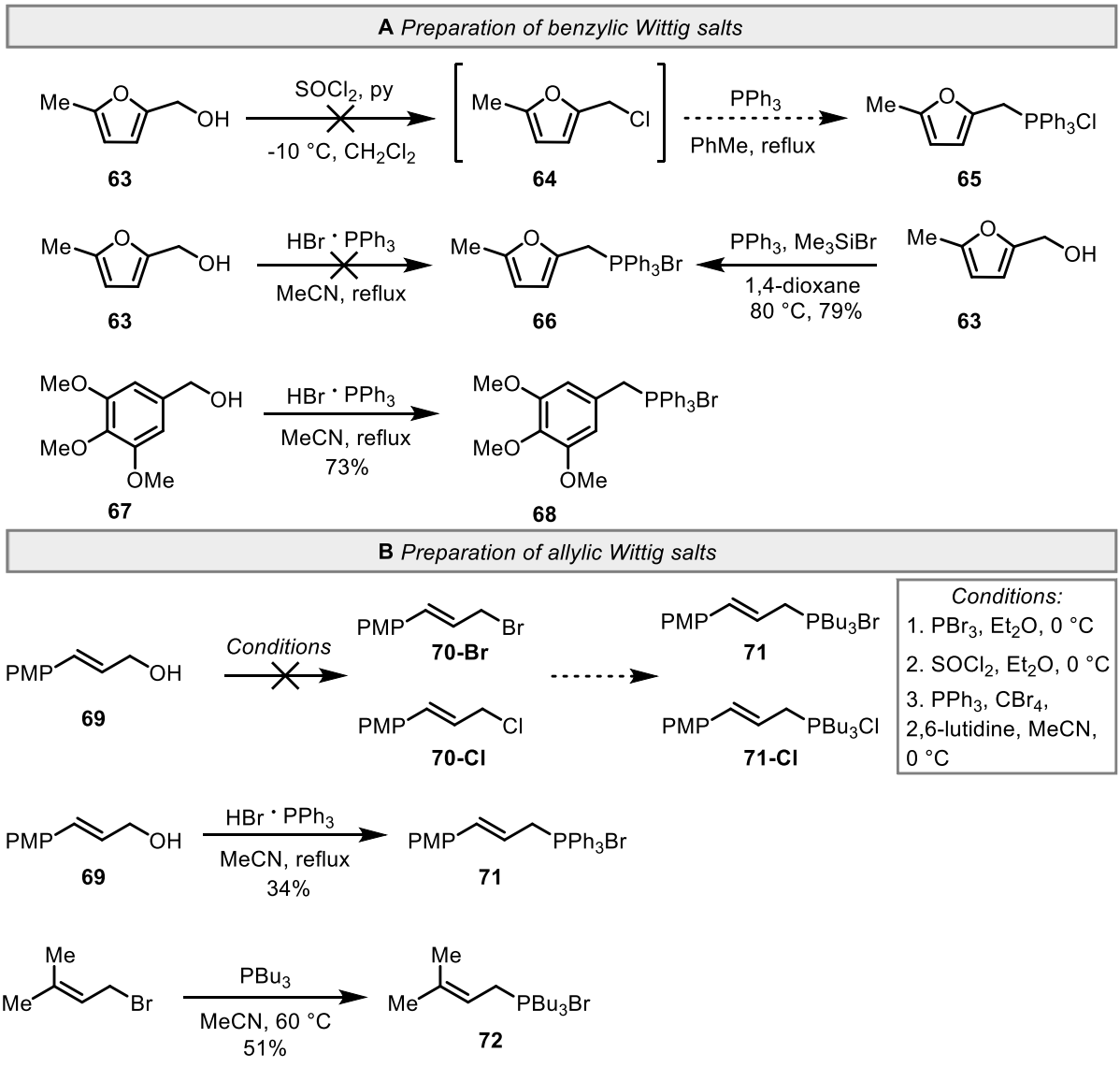
With this in mind, it was decided to prepare a series of diene and triene substrates to explore their suitability in the cation-triggered polyene cyclisation (Scheme **58**). Diene **57** is a common substrate employed in the polyene cyclisation methodologies due to the number of natural products containing a gem-dimethyl substituted carbon at this position (Scheme **58**, A).[94] Therefore, it was interesting to examine if it could be engaged in the alkylative cyclisation cascade as well. Dienes **58** and **59** contain a highly electron-rich alkene and so were predicted to perform well under the reaction conditions. In addition, there are several literature reports on oxidising furan group to a carboxylic acid using $RuCl_3$, as well as ring-opening procedures.[95] Thus, a furan ring at the exocyclic position of product **56** could be used as a synthetic handle for further derivatisations. Similarly, *6-endo-trig* cyclisation of triene substrates **60** and **61** would install an exocyclic alkene in scaffold **62** which could also be derivatised using ozonolysis or other alkene oxidation methodologies (Scheme **58**, B).[96] Here, a conjugated diene system could introduce an additional regioselectivity issue upon carbocation attack on an alkene. Furthermore, controlling diastereoselectivity of the transformation in this system might be challenging.



*Scheme **58***. New alkene systems.

Diene **57** could be prepared in one step from commercially available geranyl acetate. The synthesis of other substrates **58**-**61** commenced with preparation of corresponding Wittig salts required for aldehyde olefination (Scheme **59**). First, salt **66** was made from (5-methylfuran-2-yl)methanol **63** (Scheme **59**, A). This synthesis proved to be challenging as the attempts to install a halogen at the benzylic position of a furan failed. The reaction with $SOCl_2$ at -10 °C furnished a complex reaction mixture. The use of HBr·PPh_3 salt which enables synthesis of triphenylphosphonium salts from alcohols in a single step, led to decomposition of alcohol **63** with only trace amount of **66** being formed.[97] Fortunately, a mild methodology from Abaev and co-workers which enables one-pot generation of triphenylphosphonium salts for acid-sensitive substrates, furnished the desired salt **66** in 79% yield after trituration with pentane.[98] Wittig salt **68** was prepared from benzylic alcohol **67** using HBr·PPh_3 in 73% yield. This reaction proceeds *via* S_N1 ionisation of alcohol to form carbocation species which are intercepted with a bromide nucleophile, followed by another substitution with a phosphine. The synthesis of triene substrates began with attempts to make Wittig salts **71** (Scheme **59**, B). As observed for alcohol **63**, synthesis of allylic chloride **70-Cl** or allylic bromide **70-Br** from alcohol **69** could

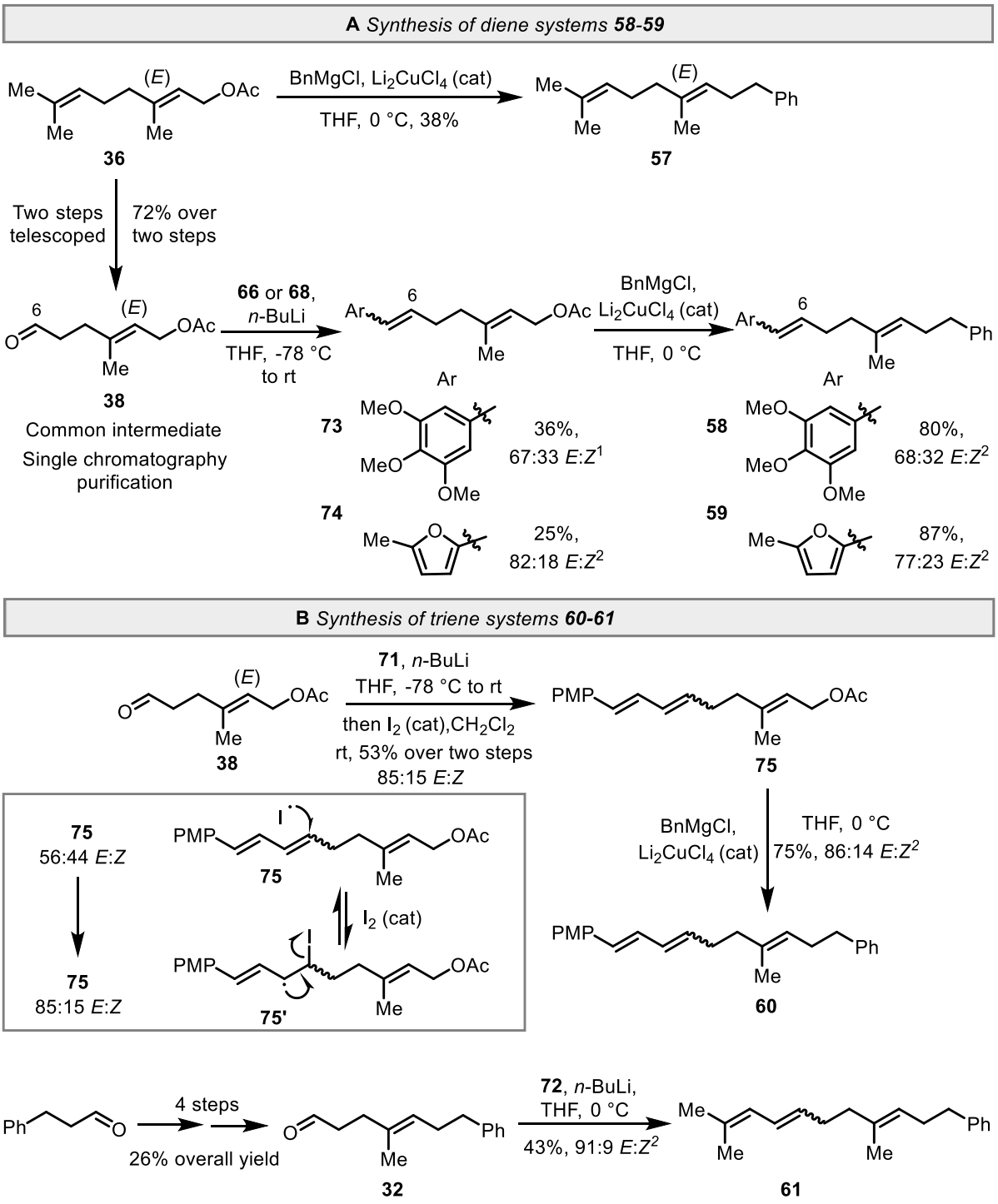
not be achieved under a variety of conditions. Instead, triphenylphosphonium salt **71** was formed *via* a one-pot procedure using HBr·PPh_3 in 34% yield after recrystallisation from CH_2Cl_2 and Et_2O at -20 °C. Since 1-bromo-3-methylbut-2-ene is commercially available, it was decided to synthesise tributylphosphonium salt **72** instead of a triphenylphosphonium salt to maximise the (*E*:*Z*)-ratio of an alkene after Wittig olefination. Salt **72** was prepared in 51% yield from 1-bromo-3-methylbut-2-ene after trituration with pentane.



*Scheme **59***. Synthesis of Wittig salts

With the required Wittig salts in hand, synthesis of substrates **57**-**61** was explored further. Diene **57** was prepared in 38% yield from geranyl acetate **36** in one step (Scheme **60**, A). Low

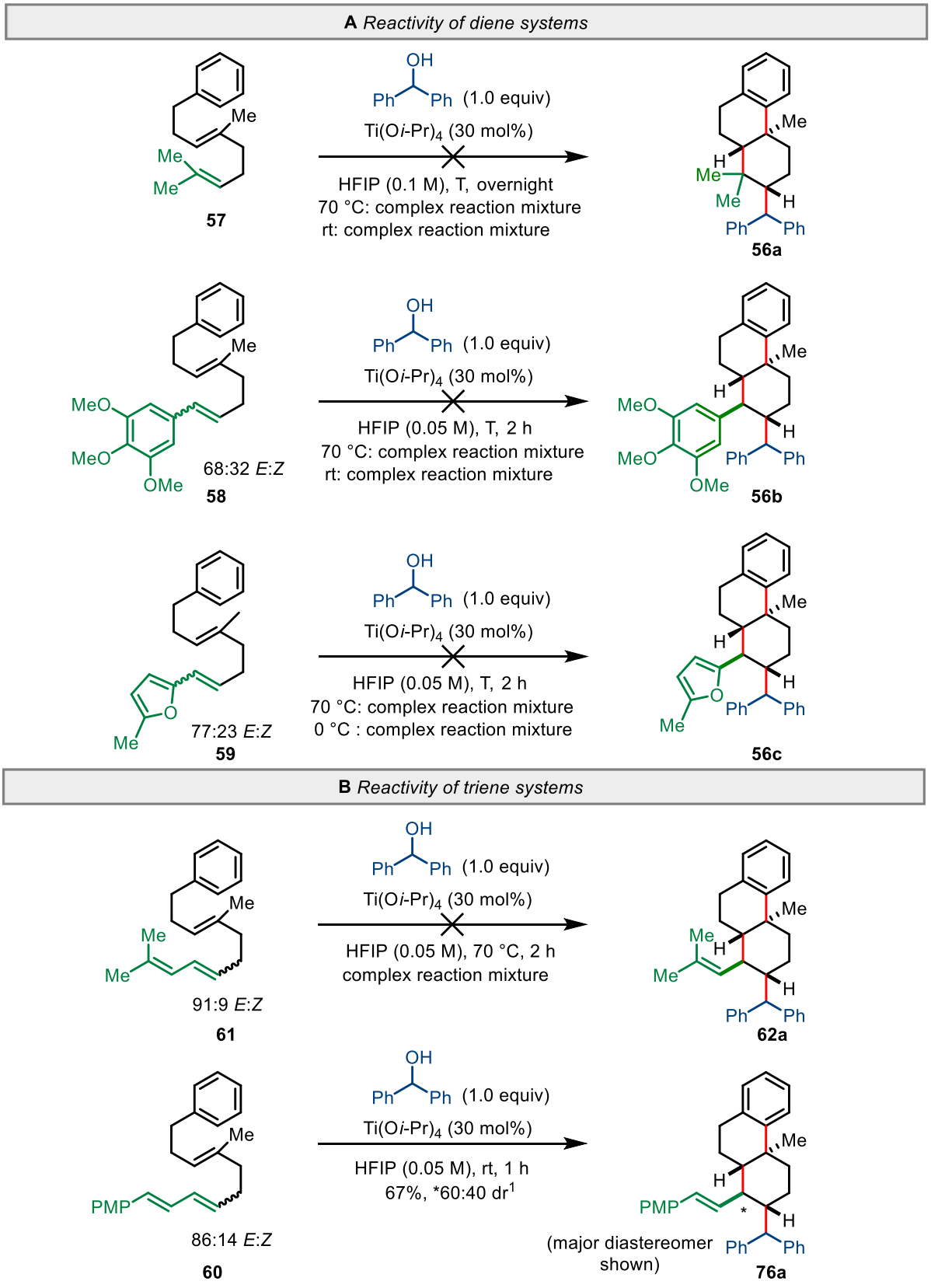
conversion was explained by the formation of significant amounts of Wurtz side-product from dimerization of BnMgCl under the reaction conditions.[93] The same starting material **36** was used to synthesise aldehyde **38** in 72% yield over two steps and single chromatography purification. Aldehyde **38** is a common intermediate *en route* to substrates **58**, **59** and **60**. Wittig olefination between aldehyde **38** and triphenylphosphonium bromide **68** furnished acetate **73** as an inseparable mixture of alkene stereoisomers with 67:33 *E*:*Z* ratio in 36% yield. The subsequent Cu-catalysed acetate displacement using excess of BnMgCl furnished diene **58** in 80% yield as a mixture of alkene isomers in 68:32 ratio. Similarly, Wittig reaction between aldehyde **38** and triphenylphosphonium salt **66** furnished acetate **74** in 25% yield in 82:18 *E*:*Z* ratio. Diene **59** was then prepared in 87% yield as an inseparable 77:23 *E*:*Z* mixture of alkene isomers using excess of BnMgCl. To synthesise triene **60**, triphenylphosphonium salt **71** was used (Scheme **60**, B). Initially, Wittig reaction between aldehyde **38** and salt **71** furnished acetate **75** as an inseparable mixture of alkene isomers with 56:44 *E*:*Z* ratio in 55% yield. It was then found that subjecting the mixture of alkenes **75** to a catalytic amount of iodine at room temperature for 30 minutes improved the *E*:*Z* ratio from 56:44 to 85:15.[99] No column chromatography was required after this stage and product **75** could be isolated in 53% over two steps in improved 85:15 *E*:*Z* ratio. Unfortunately, resubjecting an 85:15 *E*:*Z* mixture of **75** to the same conditions did not improve the alkene ratio further. Iodine-catalysed olefin isomerisation to a thermodynamically more stable alkene is known in the literature and is believed to proceed *via* a radical process.[99] For the triene system **75**, it is proposed that iodine radical adds to an electron-rich alkene within a conjugated diene system forming an allylic radical **75'**. This scrambles (*E*/*Z*)-geometry of the double bond and upon elimination of iodine radical reforms the olefin in predominantly (*E*)-configuration. With triene **75** in hand, Cu-catalysed acetate displacement using excess of BnMgCl afforded substrate **60** in 75% yield and 86:14 *E*:*Z* ratio. For the synthesis of final substrate **61**, aldehyde **32** which was previously made in 4 steps and 26% overall yield from 3-phenylpropanal (see Scheme **43**) was employed. Wittig reaction with tributylphosphonium salt **72** furnished triene **61** in 43% yield and an excellent 91:9 *E*:*Z* ratio.



*Scheme **60***. Synthesis of substrates **57**-**61**; [1] *E*:*Z* ratio determined using crude NMR before column chromatography; [2] *E*:*Z* ratio determined after column chromatography.

Having completed the synthesis of substrates **57**-**61**, attention was turned to examine reactivity of new systems in the cation-triggered polyene cyclisation cascade (Scheme **61**). Since (*E*/*Z*)-isomers of substrates **58**-**61** could not be separated, these compounds were used

as mixtures. Given that polyenes (*E*)-**26** and (*Z*)-**26** afforded products with the same relative stereochemistry, it was hoped that the (*E*/*Z*)-ratio of dienes **58**-**61** would not affect the diastereoselectivity of the cation-triggered polyene cyclisation. All trial experiments were performed using benzhydrol as the alkylating agent due to high yields observed for this alcohol in the previous work. Unfortunately, subjecting diene **57** to the reaction conditions at 70 °C afforded complex reaction mixture in which all starting material **57** was consumed (Scheme **61**, A). Repeating the reaction at room temperature did not change the outcome. Surprisingly, the reaction between diene (*E*/*Z*)-**58** with a highly electron-rich conjugated alkene and benzhydrol at 70 °C also furnished a complex reaction mixture with no starting material present. Product **56b** could be identified by crude NMR, however any attempt to isolate compound **56b** in sufficient purity failed. Repeating the reaction at room temperature did not improve the desired reactivity. Complex reaction mixture was instead observed by crude NMR with only trace amount of product **56b**. No desired product **56c** was isolated or observed when the polyene cyclisation was attempted using furan containing diene **59** both at 70 °C and 0 °C. A triene system **61** was not successful either (Scheme **61**, B). Fortunately, the reaction between triene **60** in 86:14 *E*:*Z* ratio and benzhydrol furnished the desired product **76a** in 67% yield and 60:40 dr at the exocyclic allylic position. The reaction was carried out at room temperature and monitored by TLC with complete conversion observed after 1 h. It is unclear why only PMP containing substrates, such as diene **26** and triene **60,** could be engaged in the cation-triggered polyene cyclisation cascade. For diene **57** it was originally thought that both trisubstituted alkenes have similar nucleophilicity and thus the initial C-C bond forming step is not selective, leading to a complex reaction mixture. However, this does not explain why other diene and triene systems were not successful. It appears that the cation-triggered cyclisation is very sensitive to a nucleophilicity of the reacting alkene with any change leading to a complex reaction mixture. Nevertheless, formation of product **76a** with an exocyclic double bond which can be used as a synthetic handle for further derivatisations was an exciting result. Thus, more studies to explore the cation-triggered cyclisation of triene **60** were commenced.



*Scheme **61***. Reactivity of new diene and triene systems. [1] dr determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Even though major and minor diastereomers of **76** were not separable, NOESY NMR analysis of the mixture provided strong evidence to assign relative stereochemistry of both diastereomers (Scheme **62**). For major diastereomer **76** NOESY between H-11 and H-5, H-2 and H-4, H-2 and Me, H-4 and Me indicate a *trans*-decalin ring system with allyl and alkyl groups in equatorial positions. The relative stereochemistry of minor diastereomer **76** was found to be the same apart from the allyl group which occupies axial position, as indicated by NOESY between H-11 and a Me group.



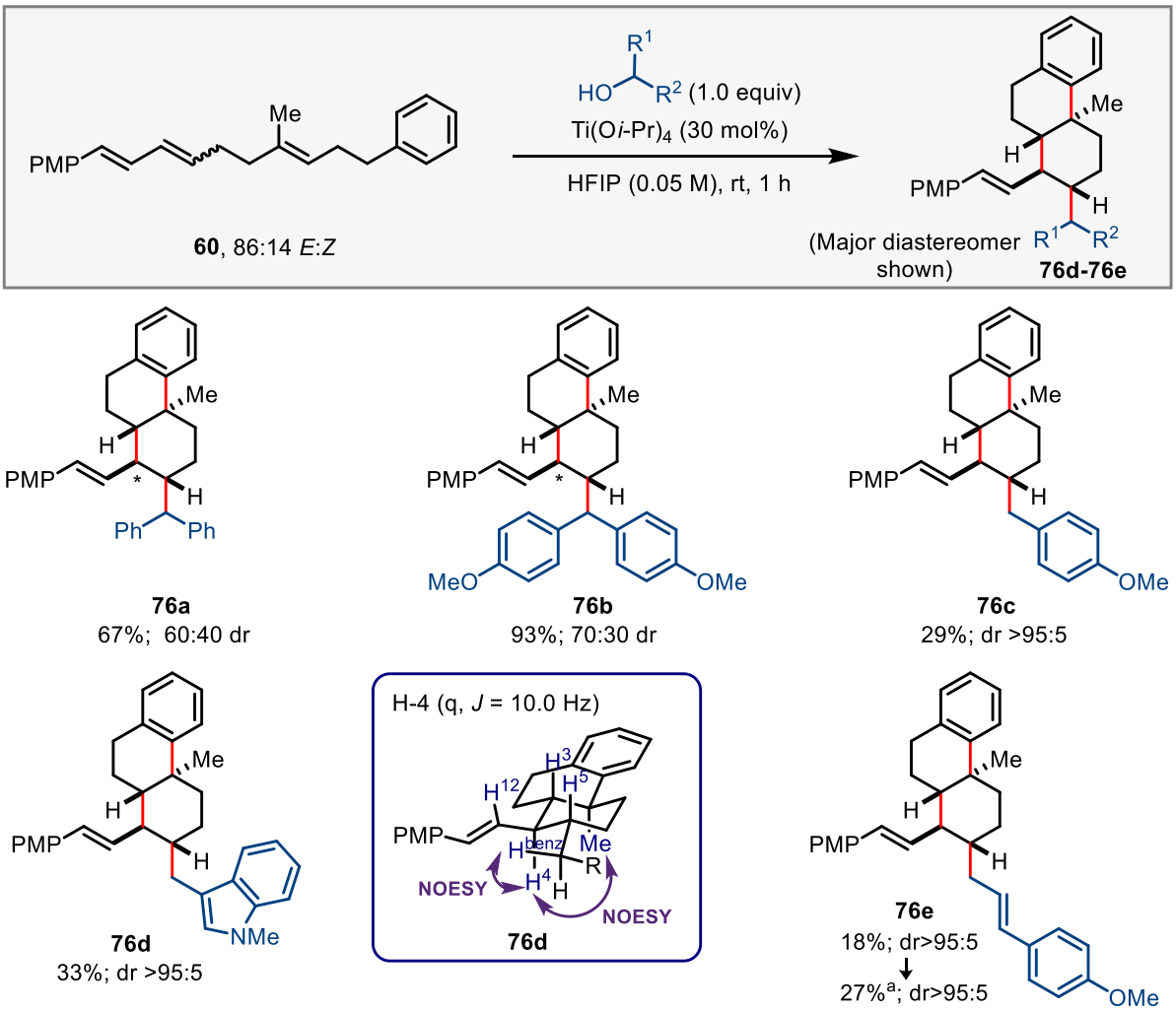
76, *Major* **76,** *Minor*

*Scheme **62***. Stereochemical analysis of the major and minor diastereoisomers **76** by NOESY.

2.3.7 Alcohol substrate scope for triene 60

The reliability of the cation-triggered cyclisation of substrate **60** was examined using secondary and primary alcohols (Scheme **63**). Yields varied from 18% to 93% depending on the alcohol used. As observed for diene **26**, secondary alcohols were more efficient in triggering a cyclisation cascade. When bis(4-methoxyphenyl)methanol was used, product **76b** was obtained in an excellent 93% yield and moderate 70:30 dr. Although yields for primary benzylic and allylic alcohols were lower, products **76c-e** were isolated as single diastereomers with no minor diastereomer observed by crude NMR. 4-Methoxybenzyl alcohol furnished product **76c** in 29% yield, which is much lower compared to product **76b** with bis(4-methoxyphenyl)methanol. An indole ring could be tolerated, although product **76d** was isolated only in 33% yield. 4-Methoxycinnamyl alcohol furnished product **76e** in low 18% yield. In all cases complete conversion of triene **60** was observed after 1 h. The relative stereochemistry of products **76a-e** was confirmed by NOESY analysis and ^{3}J coupling

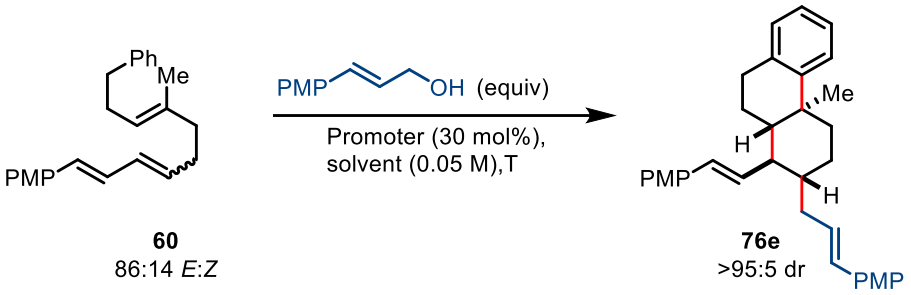
constants. For example, the appearance of ^{1}H NMR signal for H-4 in product **76d** as an apparent quartet with ^{3}J = 10 Hz is indicative of a *trans*-diaxial arrangement between H-4 and H-12, H-4 and H-3, H-4 and H-5. This, together with NOESY between H-4 and Me group confirms the relative stereochemistry in all four stereocenters.



Scheme 63. Alcohol substrate scope for triene **60**. dr determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [a] After optimisation: reaction performed without Ti(O*i*-Pr)$_4$ and overnight.

Product **76e** bears two exocyclic alkenes that could be further derivatised. In addition, excellent diastereoselectivity in all four newly formed stereocenters meant that compound **76e** can be a useful synthetic intermediate which would be difficult to form using other methods. Therefore, it was decided to carry out additional experiments in attempt to improve the reaction (Table **5**). It was found that isolated yield of product **76e** varied from 16% to 23% under the

same conditions depending on the run (Table **5**, entry 1). It could be that the reaction has some minor reproducibility issues under these conditions, however the difference could also arise from the experimental error upon isolation of product **76e**. Increasing temperature to 40 °C, using CH_2Cl_2 as a co-solvent or increasing the equivalents of 4-methoxycinnamyl alcohol did not improve the reaction (Table **5**, entries 2-4). Finally, removing Ti(O*i*-Pr)$_4$ and leaving the reaction mixture overnight might have had a slight beneficial effect on the yield of product **76e** (Table **5**, entry 5). In all cases near complete conversion of triene **60** was observed with no remaining alcohol present. Thus, it could be that background decomposition processes are responsible for low isolated yields of product **76e**.



60
86:14 *E*:*Z*

76e
>95:5 dr

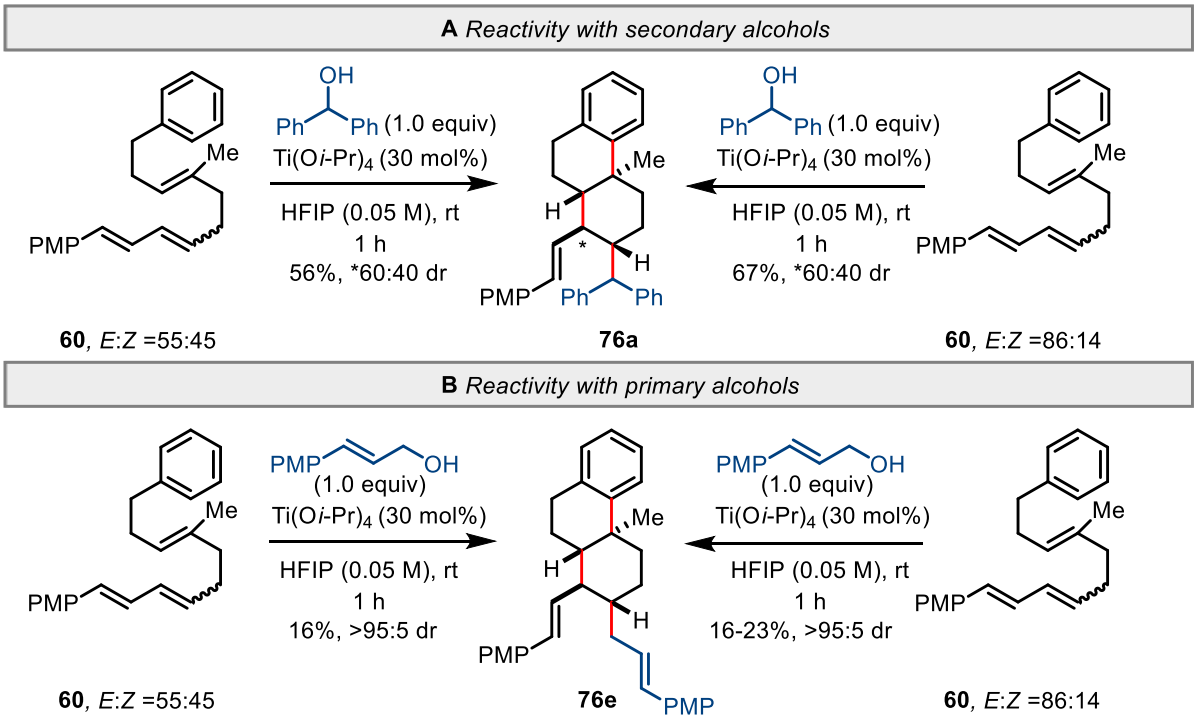
Entry	Solvent	Alcohol equivalents	T (°C)	Ti(O*i*-Pr)$_4$ (mol%)	Time (h)	Yield[a] of **76e**
1	HFIP	1	rt	30	1	16-23%
2	HFIP	1	40	30	1	17%
3	HFIP : CH_2Cl_2; 1 : 1	1	rt	30	1	19%
4	HFIP	3	rt	30	1	22%
5	**HFIP**	**1**	**rt**	**-**	**overnight**	**26-27%**

*Table **5***. Additional experiments to increase yield of product **76e**. All reactions performed on 0.10 mmol scale of **60** (33.2 mg). [a] Isolated yields are reported.

2.3.8 Mechanism of the alkylative polyene cyclisation of substrate 60

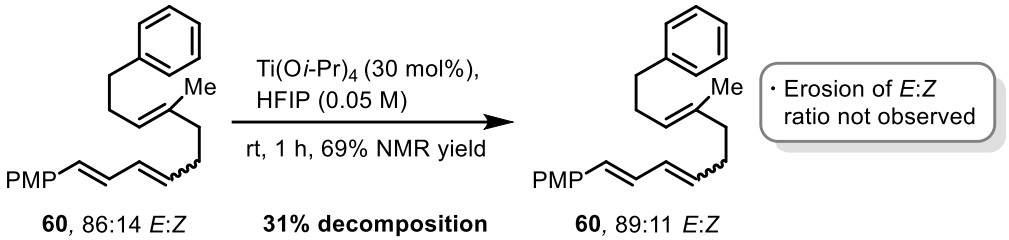
Next, control experiments were performed to get more understanding on the mechanism of the cation-triggered cyclisation of substrate **60**. When polyene **60** in 86:14 *E*:*Z* ratio and

benzhydrol were subjected to the reaction conditions, product **76a** was isolated in 67% yield with 60:40 dr calculated for the crude reaction mixture (Scheme **64,** A). Cyclisation of substrate **60** in 55:45 *E*:*Z* ratio under the same conditions furnished product **76a** in a slightly lower 56% yield but with identical dr at the exocyclic allylic position. When primary allylic alcohol was used, product **76e** was isolated in similar yields with excellent diastereoselectivity which was independent on the *E*:*Z* ratio of the starting material **60**.



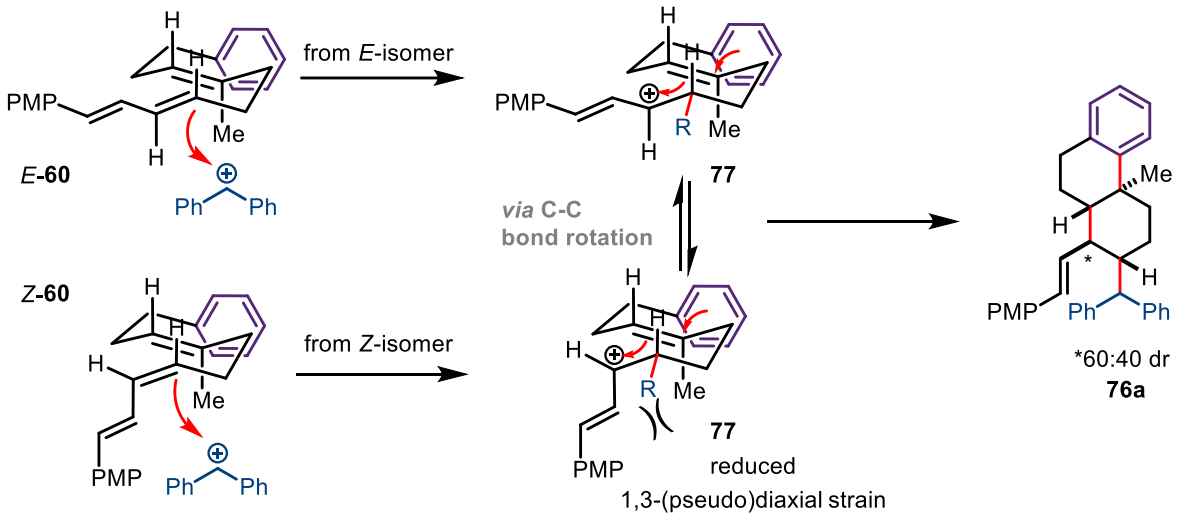
Scheme ***64***. The reaction of (*E*/*Z*)-**60** with secondary and primary alcohols.

To check if the *E*:*Z* ratio of triene **60** changes in HFIP prior to the cyclisation cascade, an 86:14 (*E*:*Z*)-mixture was subjected to the reaction conditions, but without alcohol present. After 1 h, only 69% of substrate **60** remained as calculated by NMR analysis with an internal standard. Erosion of *E*:*Z* ratio was not observed. Limited stability of triene **60** under the reaction conditions likely contributes to the low cyclisation yields observed in some cases. In addition, it is consistent with the fact that more activated secondary alcohols for which fast carbocation generation is expected, afford products in much higher yields.



Scheme ***65***. Control experiment using (*E*/*Z*)-**60**. NMR yield is calculated using 1,1,2,2,-tetrachloroethane as an internal standard.

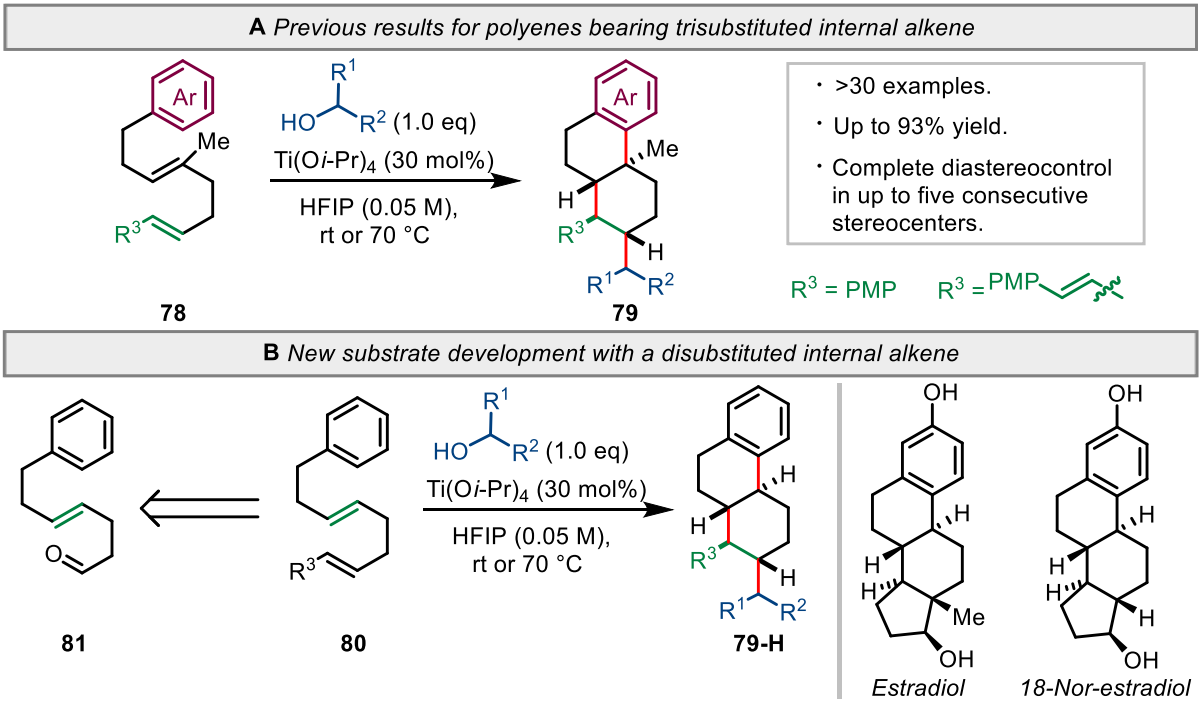
To explain the obtained results from the control experiments, the following mechanistic rational was proposed (Scheme **66**). For secondary alcohols, such as benzhydrol, cyclisation is stepwise. The first C-C bond forming event furnishes allylic cation **77** which is highly stabilized due to a conjugation with an electron-rich styrene system. Cation **77** can undergo a C-C bond rotation that scrambles any *E* or *Z* stereochemistry from the former alkene. For the (*Z*)-**60** conformation 1,3-(pseudo)diaxial strain is significantly reduced compared to diene **26**, since a PMP group is moved away from the pseudo-axial Me group. Thus, the cyclisation of the *cis*-configured intermediate **77** can proceed, rationalising the loss of stereoselectivity. It is not clear why excellent diastereoselectivity is observed when primary alcohols are used. However, with low yields obtained for primary alcohols it could be that the minor diastereomer decomposes under the reaction conditions.



Scheme ***66***. Mechanistic rationale for cyclisation of triene **60**.

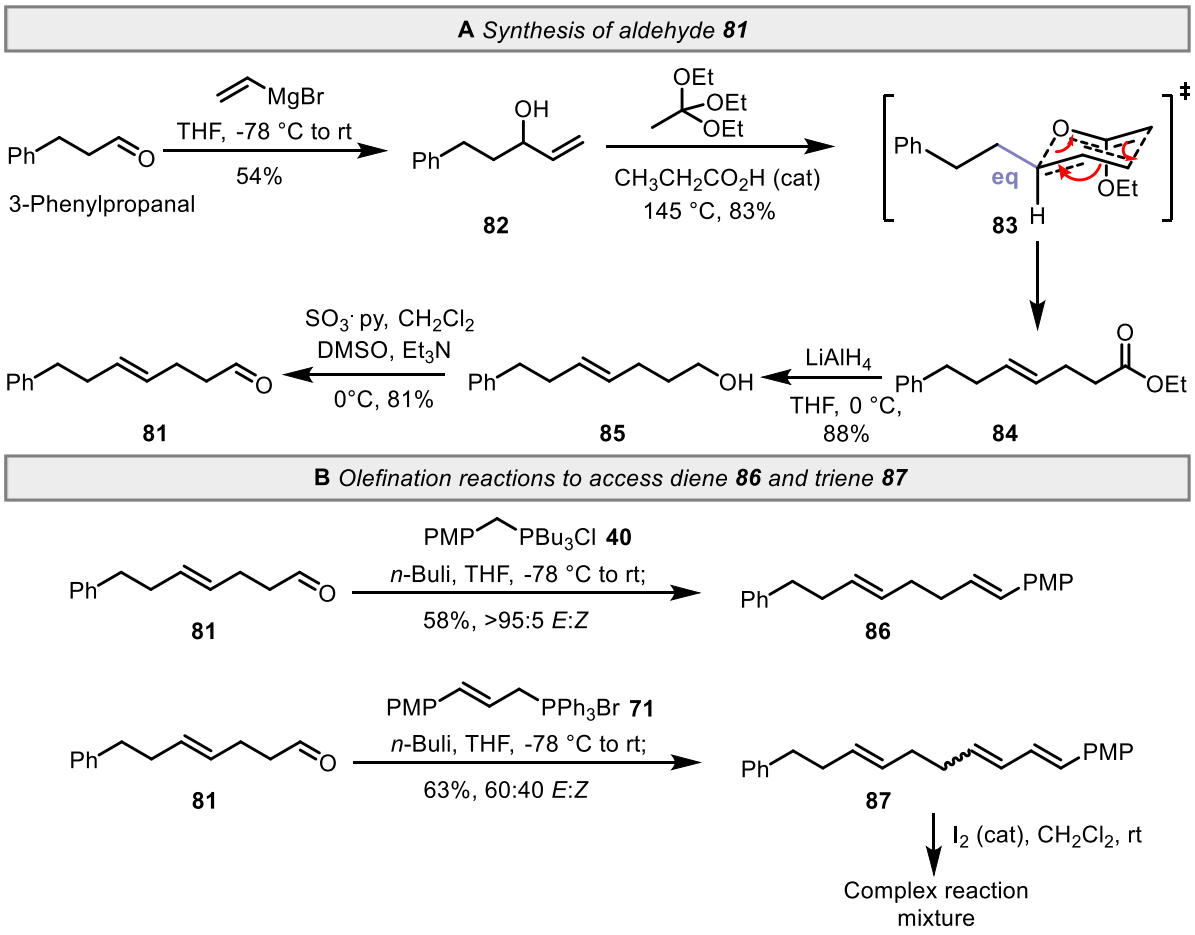
2.3.9 Other internal alkene systems in the cation-triggered polyene cyclisation

So far, all the polyene systems which have been tried possess a trisubstituted internal alkene (Scheme **67**, A). As a result, products formed, such as **79**, contain a tetrasubstituted benzylic carbon, which is a common structural element in several terpenoid natural products.[94,100] More than 30 examples of products **79** were obtained in up to 93% yield. Moderate to excellent diastereoselectivity was observed depending on the substrate and alcohol used. While many terpenoids possess a tetrasubstituted benzylic carbon, steroids, a pharmacologically active subclass of terpenoid compounds, often have a trisubstituted carbon at this position.[101] Estradiol, estrone, estriol and 18-nor-estradiol are examples of estrogen hormones and steroid-derived compounds which possess a trisubstituted benzylic carbon (Scheme **67**, B).[101,102] Given the importance of steroid hormones in all aspects of human life, it was decided to explore if substrates with a disubstituted internal alkene, such as **80**, could be engaged in the cation-triggered polyene cyclisation. This would furnish products **79-H** possessing the desired trisubstituted carbon. Retrosynthesis of substrate **80** led to aldehyde **81**, which was proposed to be made *via* a Johnson–Claisen rearrangement to install (*E*)-alkene.



Scheme ***67***. New substrate class with a disubstituted internal alkene.

Forward synthesis of aldehyde **81** commenced with the addition of vinyl magnesium bromide to commercially available 3-phenylpropanal in 54% yield (Scheme **68**, A). Allylic alcohol **82** was subjected to a Johnson–Claisen rearrangement to afford ester **84** as a single (*E*)-isomer in a good 83% yield. Excellent selectivity for the alkene formation was explained by the chair-like transition-state **83** in which alkyl group occupies pseudo-equatorial position. $LiAlH_4$ reduction of ester **84** furnished alcohol **85** in 88% yield which was oxidised under Parikh–Doering conditions to afford aldehyde **81** in 81% yield. This synthetic sequence allowed large amounts of aldehyde **81** to be reliably prepared in 32% yield over four steps. With aldehyde **81** in hand, Wittig olefination to access diene **86** and triene **87** were performed (Scheme **68**, B). The use of tributylphosphonium chloride **40** afforded diene **86** in 58% yield as a single (*E*)-isomer after a column chromatography. Wittig reaction between aldehyde **81** and allyl triphenylphosphonium bromide **71** furnished triene **87** in 63% yield and 60:40 *E*:*Z* ratio.

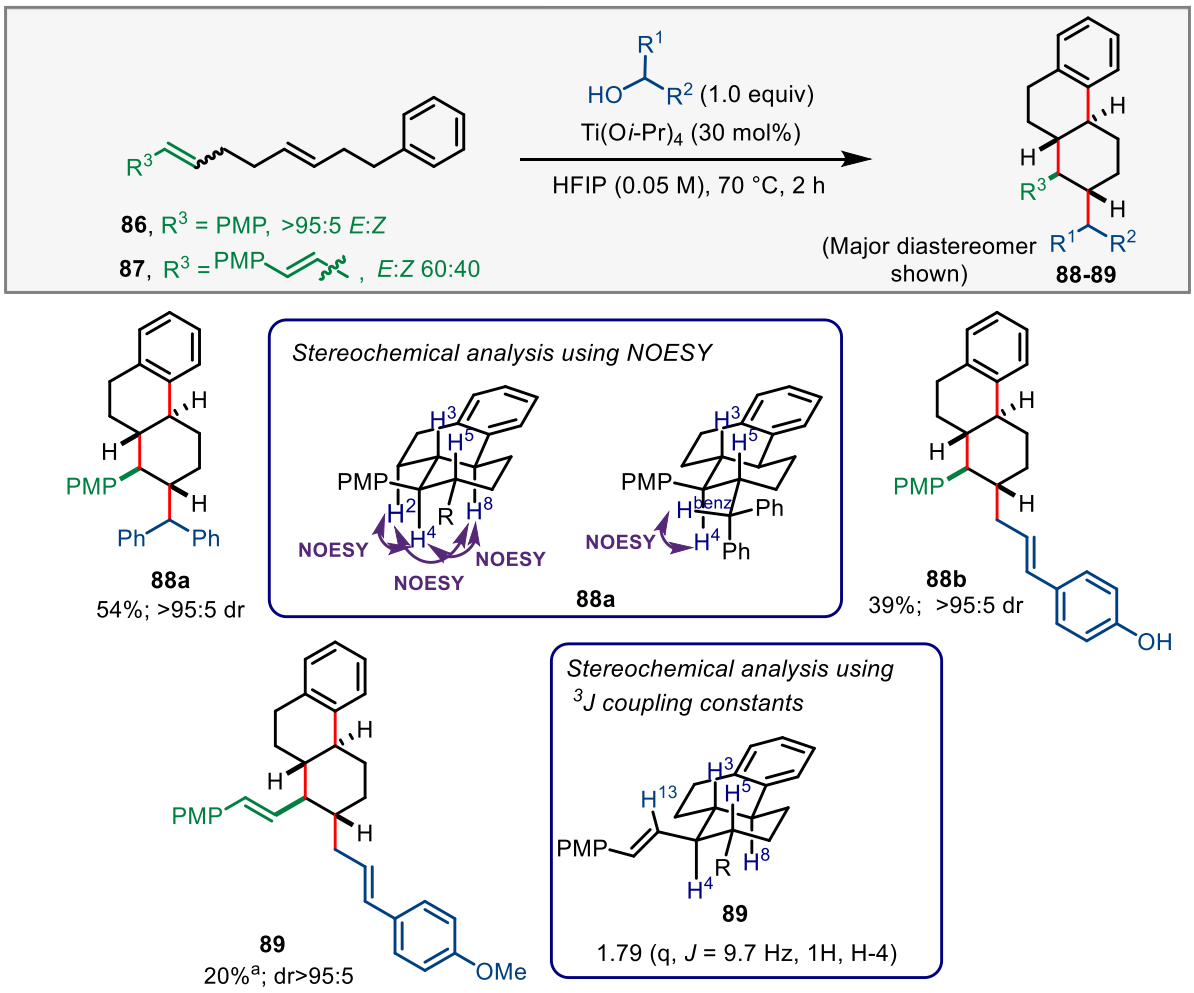


*Scheme **68***. Synthesis of diene **86** and triene **87**.

Unfortunately, when the iodine-catalysed olefin isomerisation to enrich the proportion of (*E*)-isomer **87** was attempted, a complex reaction mixture was observed. It was proposed that the reduced selectivity for the iodine-catalysed isomerisation of triene **87** is most likely due to unwanted side-reactions with an internal disubstituted alkene. For triene **75**, on the other hand, the inductive electron-withdrawing effect of an allylic acetate decreases the nucleophilicity of the internal trisubstituted alkene, thus allowing selective iodine-catalysed olefin isomerisation (see Scheme **60**).

Having completed the synthesis of substrates **86** and **87**, the cation-triggered polyene cyclisation was attempted (Scheme **69**). When benzhydrol was used, diene **86** furnished product **88a** in 54% as a single diastereomer. With 4-hydroxycinnamyl alcohol product **88b** was formed in 39% yield and with excellent diastereoselectivity. The relative stereochemistry of products **88a** and **88b** was confirmed by NOESY analysis. For example, NOESYs between H-2 and H-4, H-2 and H-8, H-4 and H-8, H-4 and H^{benz} confirm that PMP and alkyl groups occupy equatorial positions, whereas H-3 and H-5 are axial. Interestingly, in the ^{13}C NMR spectra some of the C^{Ar}-H signals for an equatorial PMP group were missing due to a coalescence and extreme peak broadening. This indicates that the substituent at the benzylic centre, i.e H-8 or Me-8, has a strong conformational effect. All PMP-carbons were inequivalent for products arising from the cyclisation of diene **26** with the X-ray crystal structures confirming the orthogonal position of the PMP group with respect to the decalin ring system. The removal of a Me-group allows for some rotation of the PMP group, resulting in the observed coalescence in ^{13}C NMR spectra for products **88a** and **88b**. Finally, the cation triggered cyclisation of triene **87** in 60:40 *E*:*Z* ratio using 4-methoxycinnamyl alcohol afforded product **89** in 20% yield as a single diastereomer. Different reaction conditions were screened, with the slightly higher yield of 20% obtained with 10 mol% of Ti(O*i*-Pr)$_4$ over 1 h. The relative stereochemistry at C-4, C-5 and C-3 was assigned on the basis of a ^1H NMR signal for H-4 which appears as an apparent quartet with ^3J = 9.7 Hz. The relative stereochemistry at C-8 was assigned by analogy to products **88a** and **88b**. Yields for the cation-triggered cyclisation of substrates **86** and **87** were generally lower compared to the cyclisation of Me-analogues **26**

and **60**. Nevertheless, products **88-89** were still isolated in useful synthetic yields with excellent diastereoselectivity, forecasting that the cation triggered polyene cyclisation could be used for the synthesis of steroid-analogues.



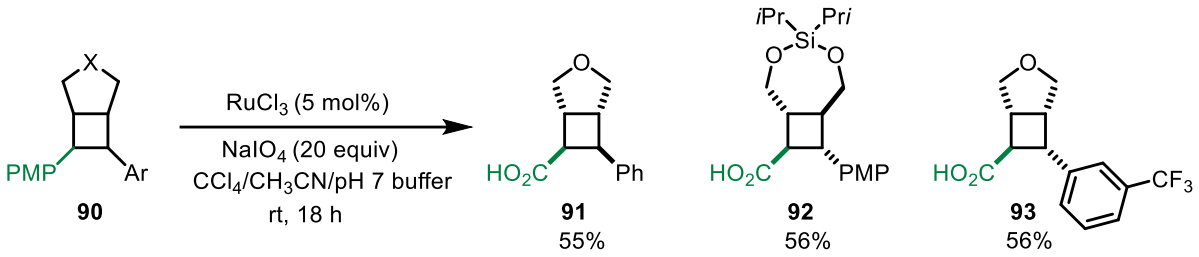
Scheme ***69***. The cation-triggered polyene cyclisation of diene **86** and triene **87**. [a] The reaction was conducted using 10 mol% of Ti(O*i*-Pr)$_4$ at rt for 1 h.

2.4 Applications of the cation-triggered polyene cyclisation

2.4.1 Attempts at the oxidative cleavage of a PMP group

Diene substrates, such as **26** and **43-46**, possessing a PMP-conjugated alkene were found to be the most high yielding in the cation-triggered polyene cyclisation. The corresponding products all bear the equatorial exocyclic PMP group. It was therefore decided to explore if a PMP group could be converted into other functionalities. An interesting literature precedent is

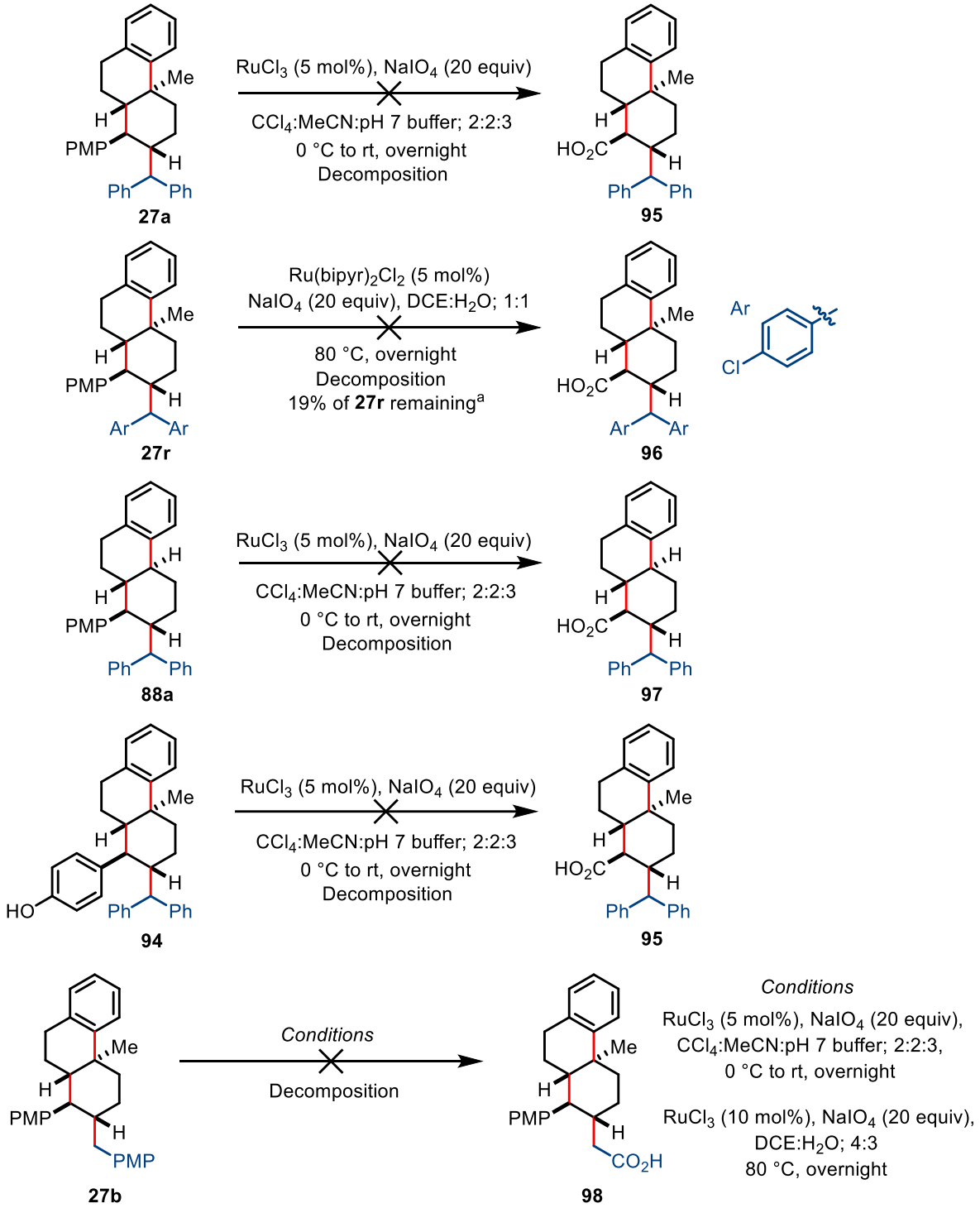
the $RuCl_3$ and $NaIO_4$ mediated oxidation of a PMP group to a carboxylic acid, which is believed to proceed *via* oxidative cleavage of unsaturated double bonds by RuO_4 formed *in situ*.[103] In previous work the Donohoe group has shown that such oxidations can be in principle carried out in the presence of neutral and electron-deficient arenes (Scheme **70**).[104] For example, $RuCl_3$ and $NaIO_4$ oxidation of cyclobutane substrates **90** furnished carboxylic acids **91**, **92** and **93** in moderate yields.



*Scheme **70***. Examples of previous work in the Donohoe group on $RuCl_3$ and $NaIO_4$ mediated PMP oxidation.[104] All experiments were carried out by Yuxiang Zhu and Ignacio Colomer.

It was therefore decided to attempt $RuCl_3$ and $NaIO_4$ mediated oxidations using the polycyclic products obtained from the cation-triggered polyene cyclisation (Scheme **71**). Unfortunately, subjecting compound **27a** to the reaction conditions, previously used by the Donohoe group for a PMP group cleavage furnished a complex reaction mixture. At 0 °C no conversion was observed and upon warming to room temperature overnight unspecific decomposition occurred. A different set of conditions with $Ru(bipyr)_2Cl_2$, previously employed by the Magauer group for a challenging oxidation of electron-rich aromatics within a polycyclic ring system, did not lead to the desired product **96**.[105] For this reaction substrate **27r** with an electron-deficient aryl groups was used with the view to avoid potential unproductive oxidation of the aromatic rings. A complex reaction mixture was obtained with 19% of starting material **27r** remained by ^1H NMR analysis with an internal standard. It was proposed that the absence of the desired reactivity is due to steric hindrance within a polycyclic ring system, which is presumably also responsible for the observed restricted rotation of a PMP group. Therefore, it was decided to attempt to cleave the PMP group of substrate **88a**. The observed coalescence in ^{13}C NMR of

decalin **88a** was attributed to the increased rotation of the PMP group relative to substrate **27a** due to a reduced steric crowdedness. Unfortunately, unspecific decomposition was observed upon warming to room temperature overnight, with no conversion at 0 °C by TLC analysis.



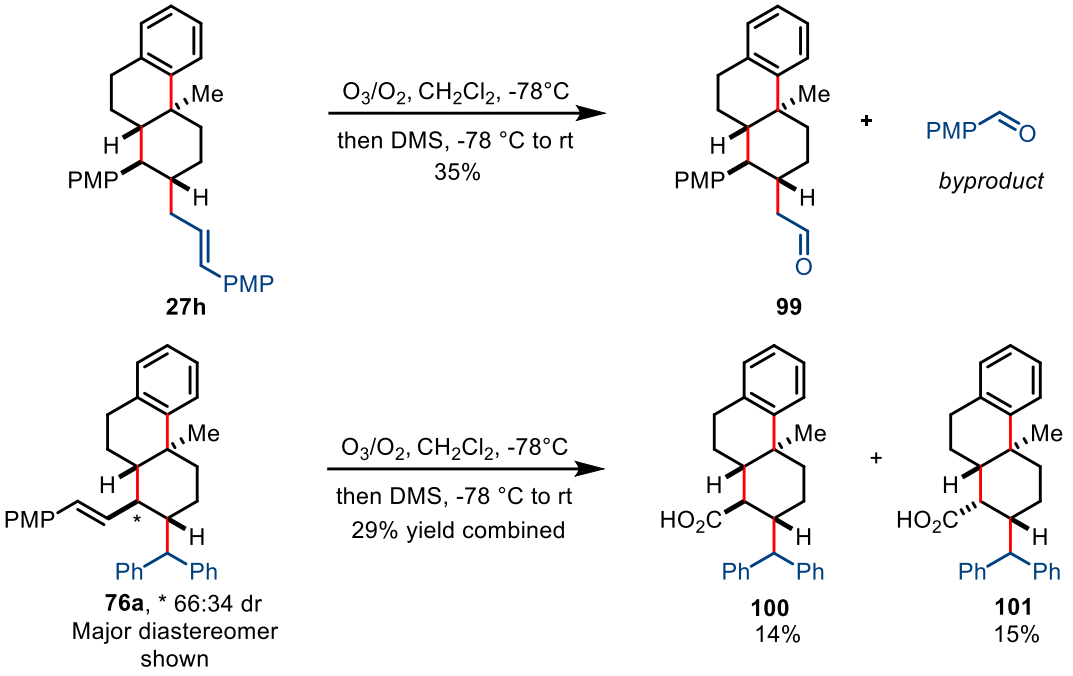
*Scheme **71***. Attempts for the oxidative cleavage of a PMP group. [a] NMR yield using quantitative ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

It was then decided to use phenol **94** which is more electron-rich and could perhaps coordinate RuO_4 to initiate oxidative cleavage. Phenol **94** was obtained in one step from substrate **27a** by BBr_3 mediated deprotection in 58% yield. Unfortunately, subjecting phenol **94** to the reaction conditions afforded a complex reaction mixture with no desired carboxylic acid **95** isolated or observed. Finally, it was decided to use substrate **27b** with an exocyclic PMB group to check if extreme steric hindrance around the PMP group slows down oxidation, allowing background undesired oxidations to occur. However, even in this position the PMP group could not be oxidatively cleaved using different sets of conditions. It was concluded that the selective oxidation of a PMP group within the scaffold obtained from the cation-triggered polyene cyclisation is extremely challenging using the literature reported RuO_4 mediated conditions. It could be that integral 'top' aromatic ring, which is doubly substituted with alkyl groups, is too electron-rich and more accessible, so it undergoes undesired oxidation first. The substrates with electron-deficient terminating arenes did not perform well in the cation-triggered polyene cyclisation (see Scheme **51**). It was therefore decided against trying them for the PMP group cleavage and instead concentrate on other derivatisation reactions.

2.4.2 Olefin ozonolysis as a derivatisation strategy

Next, ozonolysis of substrates **27h** and **76a** bearing exocyclic alkenes was attempted. Decalin **27h**, formed upon the cation-triggered polyene cyclisation using 4-methoxycinnamyl alcohol, afforded aldehyde **99** in 35% yield. The reaction yield was lower than expected partially due to a difficult separation of the desired aldehyde **99** from 4-methoxybenzaldehyde byproduct. Nevertheless, this reaction demonstrates that products, obtained using allylic alcohols as initiators in the polyene cyclisation, could be derivatised to install synthetically versatile functional groups. Then, ozonolysis of alkene substrate **76a**, formed upon the benzhydrol-triggered cyclisation of triene **60**, was attempted. Interestingly, the reaction furnished a complex mixture from which diastereomeric carboxylic acids **100** and **101** were isolated in 14% yield and 15% respectively. The relative stereochemistry of each compound was proven by NOESY analysis. It is unclear why overoxidation occurred during ozonolysis even though

the reaction was quenched with DMS. It could be that the residual oxygen in the system oxidised an aldehyde formed *in situ* after DMS addition. Furthermore, even though formation of diastereomeric carboxylic acids **100** and **101** is not surprising, the 1:1 ratio observed upon isolation does not represent exocyclic dr of 66:34 of the starting material **76a**. However, with a low combined yield of 29%, it could be that aromatic rings in substrate **76a** or carboxylic acids **100** and **101** undergo unselective oxidation with ozone/oxygen.[106]

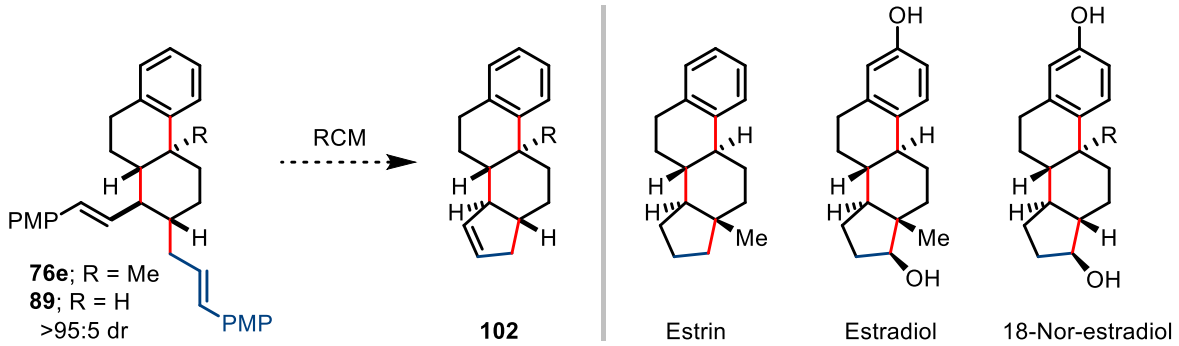


Scheme **72**. Ozonolysis of substrates **27h** and **76a**.

2.4.3 Ring-closing metathesis as a derivatisation strategy

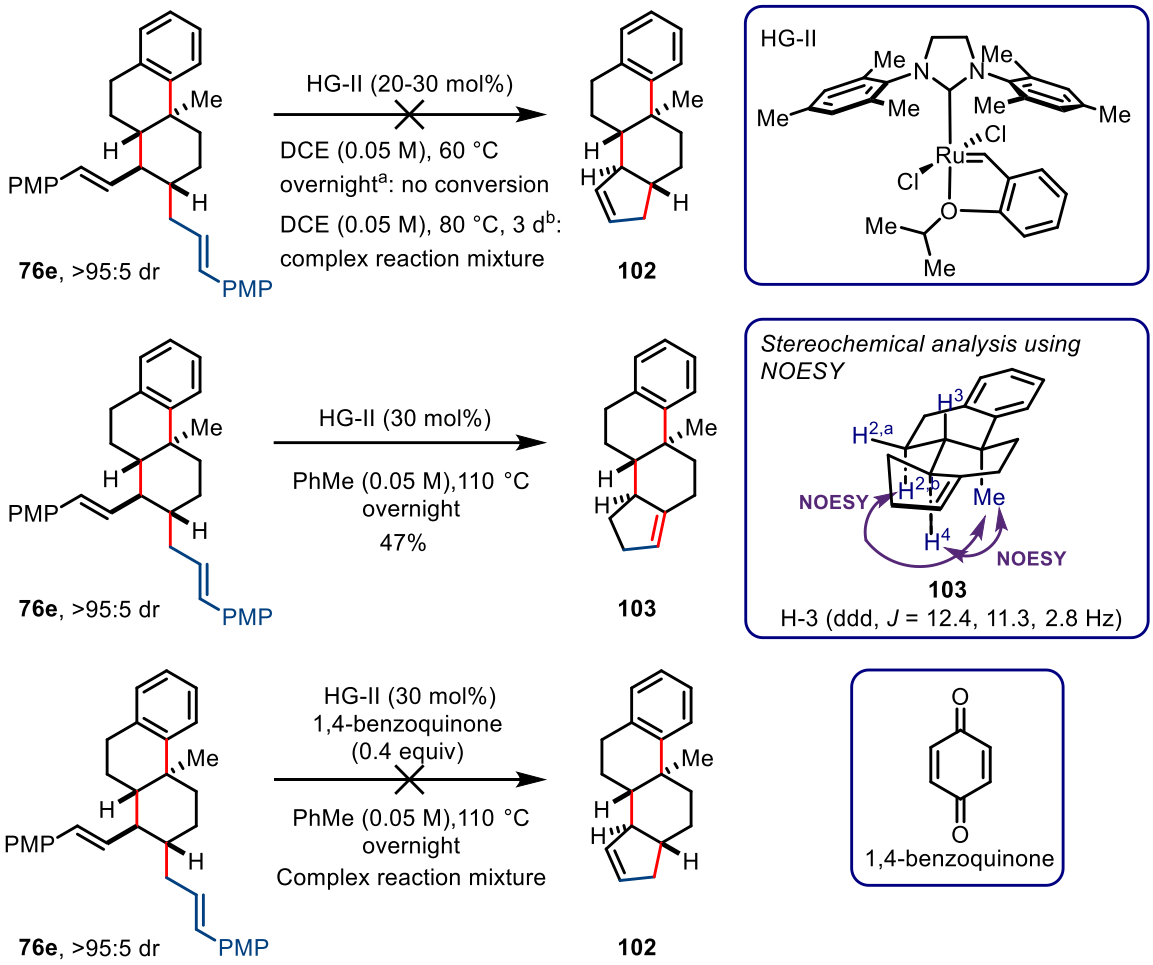
After investigating ozonolysis as a derivatisation protocol, attention was turned to explore ring-closing metathesis of compounds containing two exocyclic alkenes (Scheme **73**). It was noted that connecting the two exocyclic alkenes of substrates **76e** and **89** would form an additional 5-membered ring. The so-formed products **102** would possess the carbon skeleton of important steroid hormones and steroid-derived compounds with the correct relative stereochemistry, such as estrin, estradiol and 18-nor-estradiol.[101,102] It has been shown that disubstituted alkenes could be tolerated, affording products with a desired trisubstituted carbon at the benzylic position. In addition, since alkenes **76e** and **89** were formed as single

diastereomers, ring-closing metathesis strategy could be an efficient way to synthesise the desired polycyclic scaffolds.



*Scheme **73***. Ring-closing metathesis strategy.

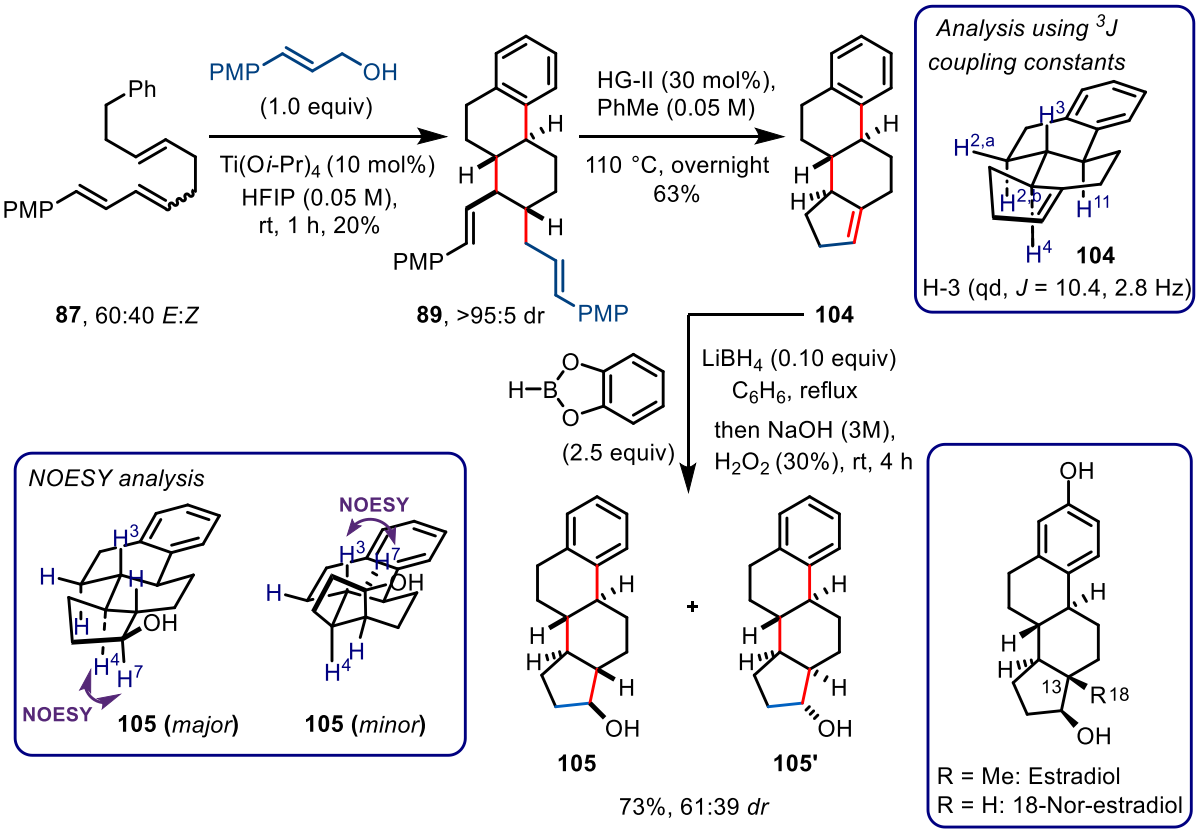
First, ring-closing metathesis was attempted using 20 mol% of 2nd Generation Hoveyda–Grubbs (HG-II) catalyst in DCE at 60 °C overnight (Scheme **74**). Only starting material **76e** was observed by crude NMR. Increasing the catalyst loading to 30 mol% and performing the reaction at 80 °C over 3 days afforded a complex mixture. Fortunately, when solvent was changed to PhMe which allowed the reaction to be performed at 110 °C overnight, the desired product **103** was isolated in 47% yield. Interestingly, ring-closing metathesis proceed with a double bond migration to the more substituted position to afford a trisubstituted alkene **103**. It is proposed that the observed isomerisation happens as a result of Ru-H species formed *in situ* which catalyse the formation of a more thermodynamically stable alkene.[107] Nevertheless, formation of product **103** demonstrates that steroid-like skeletons could be accessed by ring-closing metathesis of substrates obtained from the cation-triggered cyclisation of triene **60**. Relative stereochemistry of product **103** was confirmed by NOESY analysis as well as ^{3}J coupling constants. Finally, ring-closing metathesis of compound **76e** was attempted in the presence of 1,4-benzoquinone, an efficient scavenger of Ru-H species.[107(b)] In this case a complex reaction mixture was obtained under otherwise identical conditions.



*Scheme **74***. Ring-closing metathesis strategy. [a] Reaction performed with 20 mol% HG-II; [b] Reaction performed with 30 mol% HG-II.

Inspired by these results obtained for a ring-closing metathesis of substrate **76e** bearing a benzylic methyl group, the sequence was repeated for the analogues compound **89** with a trisubstituted carbon at this position (Scheme **75**). First, substrate **89** was prepared from the cation-triggered cyclisation of triene **87** with 4-methoxycinnamyl alcohol in 20% yield with excellent diastereoselectivity. Compound **89** was then subjected to ring-closing metathesis conditions using HG-II catalyst to afford product **104** in 63% yield. As observed before, ring-closing metathesis proceeded with an alkene migration to the more substituted position. Relative stereochemistry of product **104** was confirmed using ^{3}J coupling constants. It was noted that the olefin migration was in fact desirable since the alkene at this position could be used to install a hydroxy group at the same centre as observed for estradiol-like steroids. In

1999 Kreiser and co-workers reported an interesting hydroboration procedure which relies on the use of catecholborane in combination with catalytic amount of $LiBH_4$.[102(c)] Although the mechanism of action of $LiBH_4$ is not understood, it has been previously reported to promote challenging hydroboration reactions employing 1,3,2-benzodioxaborole complexes.[108] Following these reports, Kreiser and co-workers discovered that hydroboration with catecholborane in the presence of 10 mol% of $LiBH_4$ provided the best results in a very similar steroid-like system (see Scheme **76,** Chapter **2.4.4**). Application of this hydroboration procedure with alkene **104** furnished diastereomeric alcohols **105** and **105'** in 73% combined yield and 61:39 dr in favour of the desired *trans* diastereomer **105**. This result is intriguing since the major diastereomer **105** is formed *via* the addition of borane from the concave face of the compound **104**, which is consistent with the result obtained by Kreiser and co-workers. Overall, this synthetic sequence demonstrates that the developed cation-triggered cyclisation can be applied in the *de-novo* synthesis of unnatural steroid-like structures.



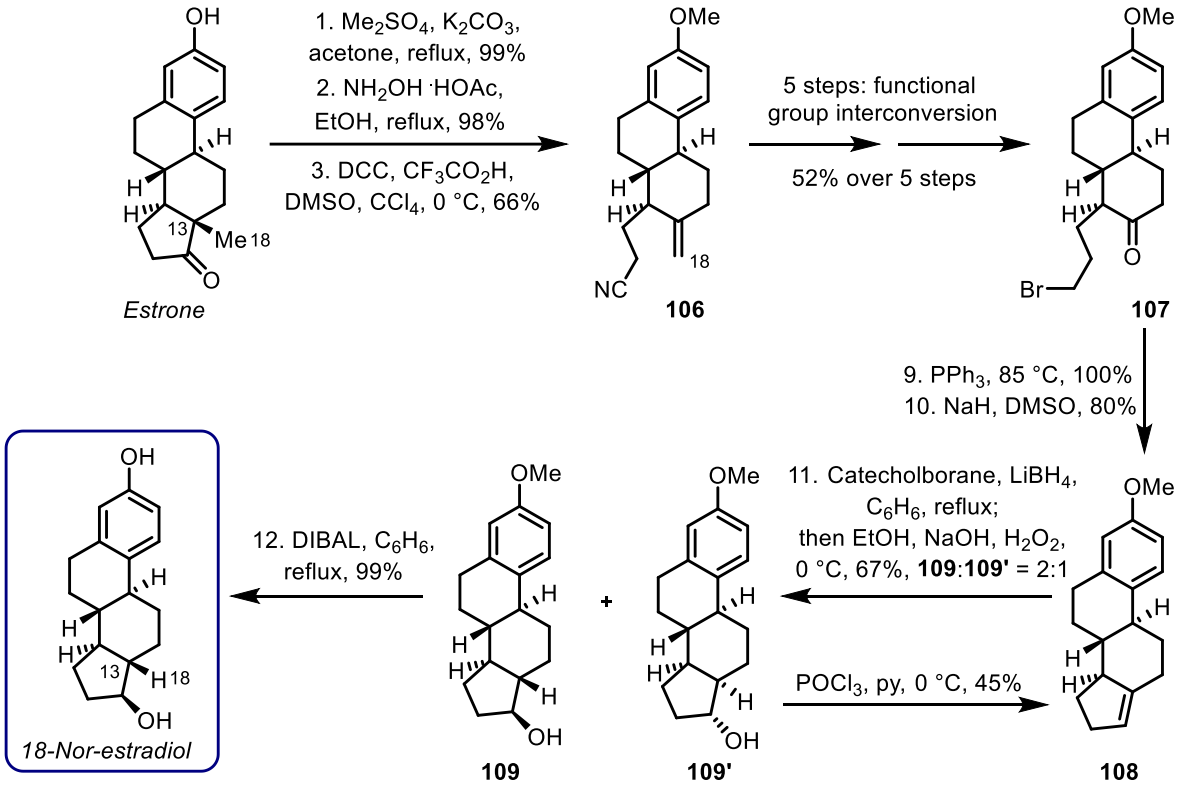
*Scheme **75***. Synthesis of steroidal scaffolds *via* RCM of substrate **89**.

The ability to synthesise steroid-like compounds *de-novo* is noteworthy since the majority of the total synthesis reports rely on chemical modifications of naturally occurring steroids.[102(c),109] Although this approach has important advantages, such as employing starting materials with pre-formed stereocenters, it often relies on lengthy degradation sequences. In addition, it often possesses challenges in the synthesis of structurally diverse steroid-like libraries. The cation-triggered polyene cyclisation approach, on the other hand, could be used to introduce structural elements which could be difficult to access *via* steroid degradation.

2.4.4 Formal synthesis of 18-nor-estradiol

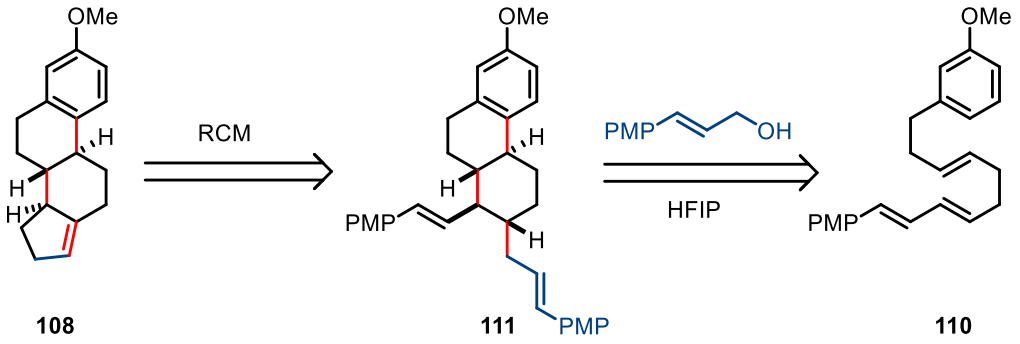
Finally, the developed cation-triggered polyene cyclisation methodology was applied in the formal synthesis of 18-nor-estradiol, a steroid analogue with interesting biological properties.[110] 18-Norsteroids possess a hydrogen at C-13, which distinguishes them from steroids bearing a Me group at C-13 (Scheme **75**). Structural modifications to the group at C-13 have been shown to alter the pharmacological properties of the steroid-derived compounds, so the synthesis of 18-norsteroids has received a lot of attention from the scientific community.[110] In the previously mentioned report, Kreiser and co-workers achieved a synthesis of 18-nor-estradiol from the parent steroid estrone in 12 steps (Scheme **76**).[102(c)] The synthesis was based on estrone degradation *via* a Beckmann fragmentation to enable functionalization of the angular Me group at C-13. With this approach, compound **106** was obtained in 64% over three steps after optimisation. Then, functional group interconversion involving reduction of the nitrile to an alcohol, formation of a primary bromide and ozonolysis to remove C-18, furnished bromide **107** in 5 steps and 52% overall yield. Triphenylphosphonium salt was prepared by melting a neat mixture of bromide **107** and PPh_3 at 85 °C. The subsequent intramolecular Wittig reaction furnished key intermediate **108** in 80% yield over two steps. As described above, Kreiser and co-workers used catecholborane as a hydroboration reagent in the presence of $LiBH_4$ to achieve diastereoselective syntheses of alcohols **109** and **109'** in 2:1 ratio in favour of the desired diastereomer **109**. Interestingly, the use of more standard hydroboration reagents, such as B_2H_6 or $BH_3{\cdot}Me_2S$ afforded

diastereomer **109'** as a major species. The mixture of alcohols **109** and **109'** was separated by reversed-phase HPLC. Minor diastereomer **109'** could be transformed back to alkene **108** by dehydration using $POCl_3$ in 45% yield. Finally, the desired alcohol **109** was readily deprotected with DIBAL in 99% yield to afford 18-nor-estradiol in 12 steps.



*Scheme **76***. Synthesis of 18-nor-estradiol from estradiol reported by Kreiser and co-workers.

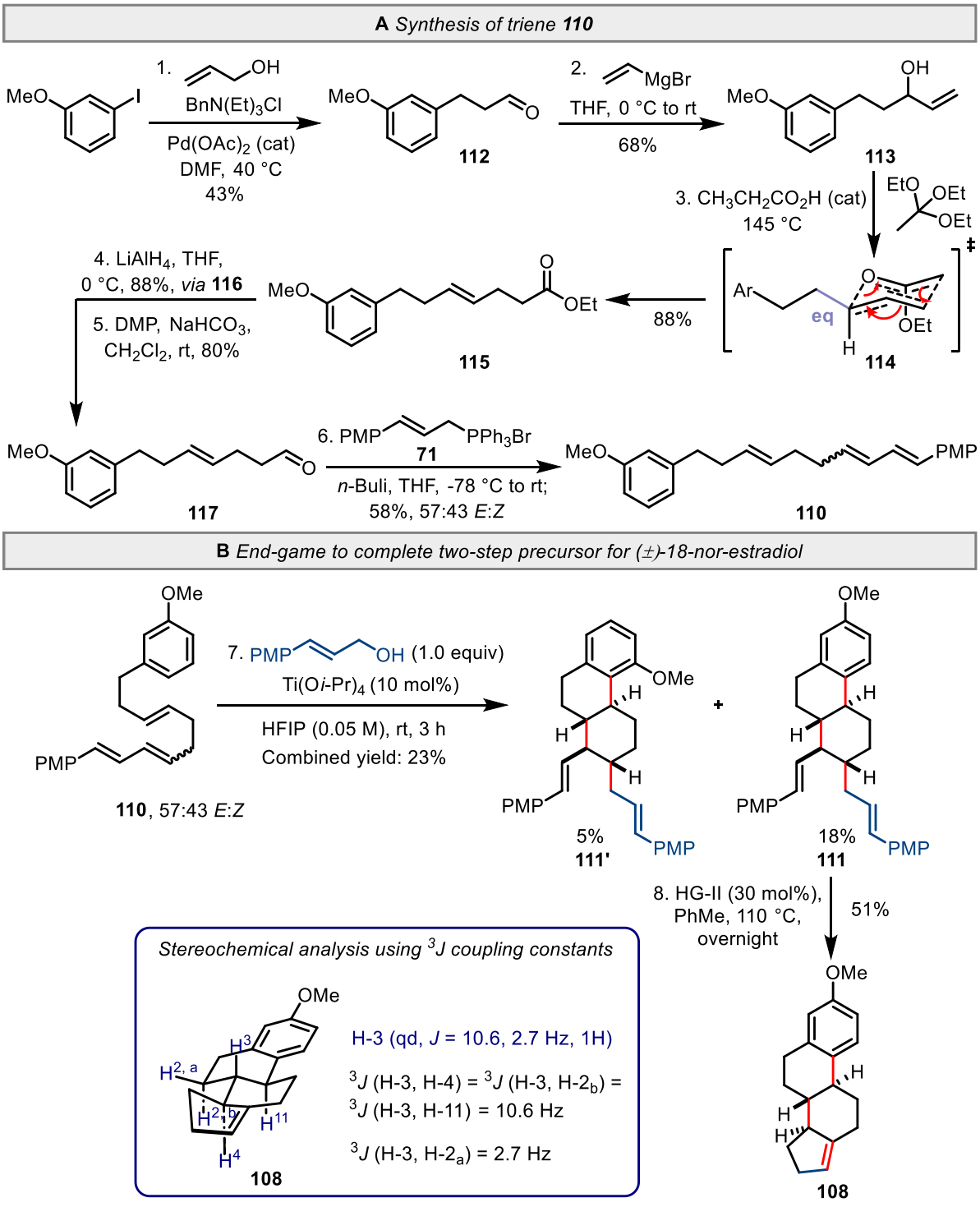
It was proposed that the crucial intermediate **108** could be instead prepared *via* the developed cation-triggered polyene cyclisation of the corresponding triene substrate. Since the hydroboration/oxidation protocol had previously been successfully executed on a steroidal framework **104** (see Scheme **75**), focus shifted towards synthesizing alkene **108**. Retrosynthetic analysis of alkene **108** led to diene **111**, a product from the polyene cyclisation of triene **110** triggered by allylic carbocation (Scheme **77**). Triene **110** possesses an electron-rich terminating aryl group, so the polyene cyclisation was predicted to afford a single diastereomer of product **111**. However, with a non-symmetrical aryl group, a mixture of regioisomers was expected upon cyclisation.



Scheme **77**. Retrosynthetic analysis of 18-nor-estradiol precursor **108**.

The forward syntheses commenced with a Heck reaction involving commercially available 1-iodo-3-methoxybenzene and prop-2-en-1-ol to furnish aldehyde **112** in 43% yield (Scheme **78**, A).[111] Addition of vinyl magnesium bromide to aldehyde **112** afforded allylic alcohol **113** in 68% yield. The subsequent Johnson–Claisen rearrangement in triethyl orthoacetate proceeded smoothly and furnished ester **115** in good 88% yield as a single (*E*)-isomer. As before, excellent alkene diastereoselectivity was explained by chair-like transition state **114**, in which the alkyl group adopts an equatorial position. Reduction of ester **115** using $LiAlH_4$ to obtain alcohol **116**, followed by Dess-Martin periodinane oxidation afforded aldehyde **117** in 70% yield over two steps. Aldehyde **117** was then subjected to a Wittig reaction with allyl triphenylphosphonium salt **71** to furnish the desired triene substrate **110** as an inseparable mixture of (*E*/*Z*)-isomers in poor 57:43 ratio, in favour of (*E*)-**110**, in 58% yield. Given that the cyclisation of triene (*E*/*Z*)-**87** in 60:40 ratio triggered by a primary allylic alcohol afforded single diastereomer **89** (see Scheme **69**), it was decided to use triene **110** as a 57:43 (*E*/*Z*)-mixture without further separation. Indeed, the cation-triggered polyene cyclisation of (*E*/*Z*)-**110** with 4-methoxycinnamyl alcohol afforded separable regioisomers **111'** and **111** as single diastereomers in 5% yield and 18% yield respectively (Scheme **78**, B). The best result of 23% combined yield was obtained with 10 mol% of $Ti(O\textit{i}\text{-}Pr)_4$. The desired major regioisomer **111** was formed *via* intramolecular Friedel–Crafts reaction at the more accessible *para*-position of the aryl group. Finally, ring-closing metathesis of major regioisomer **111** proceeded with olefin isomerisation to afford a two-step (±)-18-nor-estradiol precursor **108** in 51% yield, completing

a formal synthesis of this steroid-analogue in 8 steps. Although certain steps in this synthesis are less efficient than the Kreiser's route *via* estardiol deconstruction, it further highlights the potential applicability of the developed polyene cyclization for the *de-novo* synthesis of important steroid analogues.

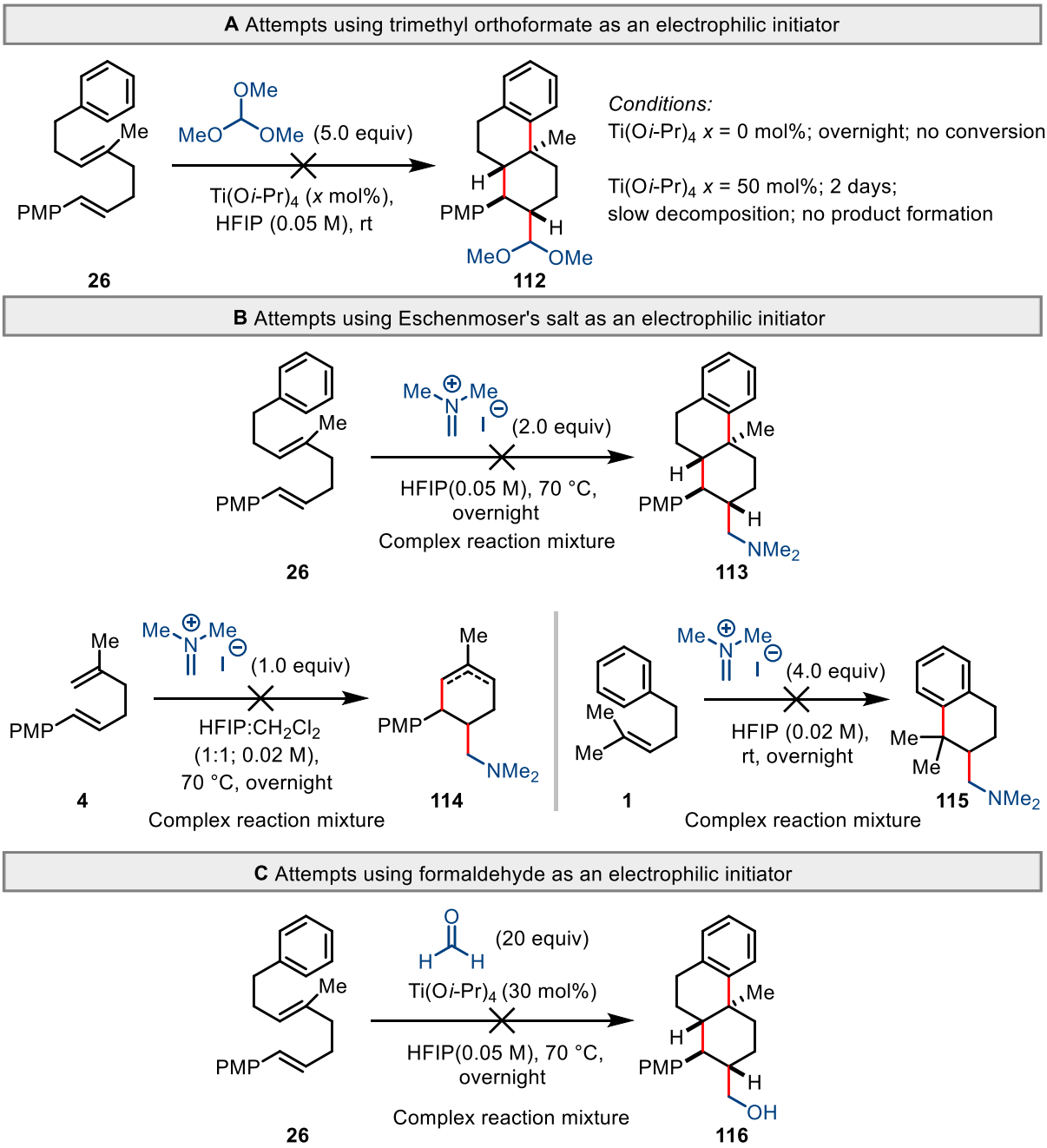


Scheme ***78***. Formal synthesis of (±)-18-nor-estradiol *via* the cation-triggered polyene cyclisation.

2.5 The use of alternative carbon-electrophiles in the polyene cyclisation

To complete the studies on the alkylative polyene cyclisation, the use of other carbon-electrophiles, distinct from carbocations, was explored. Electrophilic species, such as ortho esters that can form oxonium species under acidic conditions, iminium ions and formaldehyde, were chosen to be examined as potential initiators to trigger the cascade cyclisation. These electrophiles have been reported to react with activated alkenes in different settings.[112,113,114] Moreover, Donohoe and co-workers have previously shown that both orthoformate and formaldehyde could initiate heterocyclisation of homoallylic alcohols in HFIP to form substituted THF-scaffolds.[58,60]

First, the use of trimethyl orthoformate as an electrophilic partner was explored (Scheme **79**, A). The reaction between diene **26** and excess of trimethyl orthoformate in HFIP without $Ti(O\textit{i}\text{-}Pr)_4$ Lewis acid led to no conversion. It was proposed that without the additive the formation of oxonium species in HFIP is negligible or highly reversible, resulting in no conversion. The addition of 50 mol% of $Ti(O\textit{i}\text{-}Pr)_4$, unfortunately, afforded a complex reaction mixture, with trace starting material **26** and no trimethyl orthoformate observed by crude NMR. The complex mixture was likely a result of a decomposition of substrate **26** under the reaction conditions. Then, Eschenmoser's salt was tried as an electrophilic initiator (Scheme **79**, B). Different alkene substrate classes **1**, **4** and **26** were employed using various sets of conditions, however, in all cases a complex reaction mixture was afforded. Finally, the cyclisation was attempted using an excess of formaldehyde (Scheme **79**, C). The desired product **116** was not isolated or observed. It is unclear why these non-carbocation electrophiles did not generate any of the desired product. It was previously noted that even within carbocation species generated *in situ* from alcohols there is a large difference in reactivity profiles and product yields. Therefore, it could be that the polyene system is extremely sensitive to the nature of an electrophilic partner used, with any deviation from the ideal conditions leading to unspecific decomposition or complex mixture.



Scheme ***79***. Attempts to use other electrophiles in the alkylative polyene cyclisation.

2.6 Summary and outlook

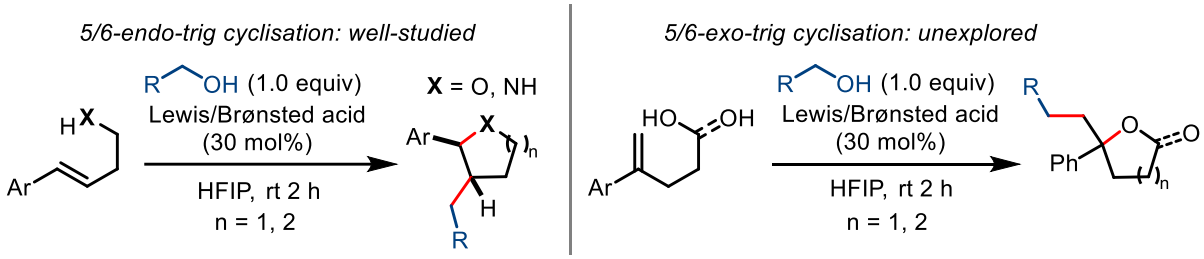
A new mode of polyene cyclisation has been developed, proceeding *via* the *in situ* generation of carbocations as intermolecular initiators. The reaction is highly diastereoselective with the formation of up to five contiguous stereocenters as a single diastereomer. Readily available alcohol starting materials could be used to form carbocations in HFIP solvent and trigger the

cascade cyclisations with the formation of new exocyclic C-C bond. Furthermore, the products formed from the cyclisation with allylic alcohols possess an exocyclic alkene, which could be used to install other functional groups or to access steroid-like compounds. It is anticipated that this methodology will broaden the scope of intermolecular carbon electrophiles that could trigger polyene cyclisations, extending it beyond acetal or carbonyl species. The use of other carbon-electrophiles, such as iminium ions and orthoesters under HFIP conditions, has so far being unsuccessful. Future work could therefore focus on extending the scope of intermolecular carbon electrophiles to initiate polyene cyclisations.

Chapter 3: The Cation-Triggered Lactonisation

3.1 Chapter overview and origin of the project

In this chapter, to date progress on the cation-triggered *5-exo-trig* lactonisation will be detailed. The prior heterocyclisation methodologies from the Donohoe group, as well as the polyene cyclisation described in the previous chapter, solely focus on exploring *5/6-endo-trig* cyclisation cascades. Other cyclisation modes were unexplored. In addition, while the use of alcohols,[58] amines[60] and now alkenes[115] as intramolecular nucleophiles in the cation-triggered cyclisation is well studied, no in-depth investigation was conducted for lactonisations.



*Scheme **80***. Cyclisation modes.

It was therefore decided to explore an alkylative *5/6-exo-trig* lactonisation reaction to access γ- and δ-lactones. The first part of this chapter outlines the initial work in collaboration with Megan Jaschinski to establish a *5-exo-trig* heterocyclisation system. The later sections focus on optimising the reaction conditions for the lactonisation reaction, as well as broadening the substrate scope to access novel fused and sprirocyclic lactone scaffolds.

3.2 System development for the cation-triggered lactonisation

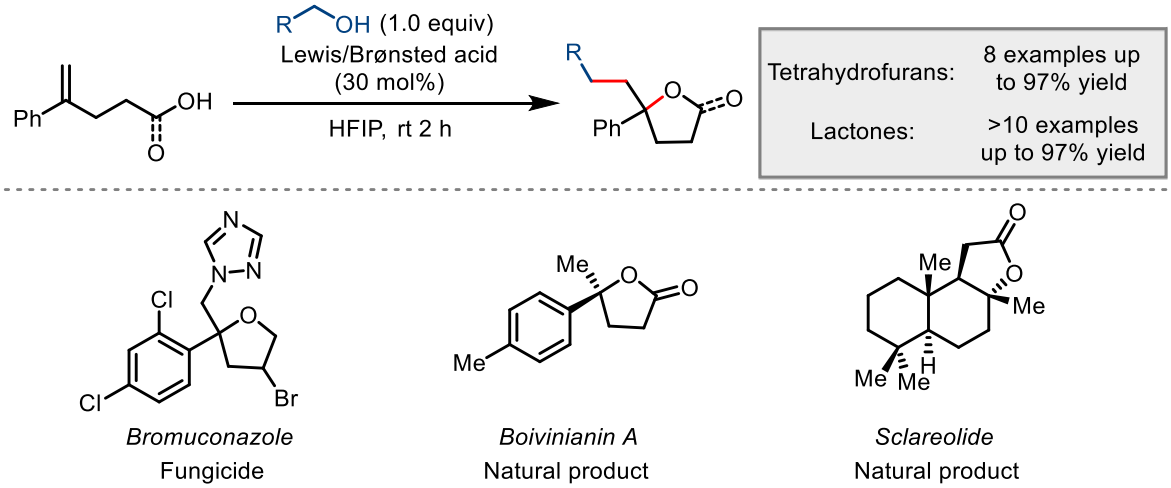
3.2.1 A note on collaboration

Work outlined in Section **3.2.2** (Preliminary work on *5-exo-trig* cyclisations and substrate scopes) was carried out by Megan Jaschinski, a Part II (Master's) student in the group of Prof. Timothy Donohoe. My involvement in this part was to provide a project guidance and

supervision to Megan Jaschinski during her Part II year and her work is included for completeness and context. I continued the project when Megan Jaschinski has left the group, as described from Section **3.2.3** (Further studies on the reaction conditions). From Section **3.2.3** onwards is my work unless specifically stated.

3.2.2 Preliminary work on *5-exo-trig* cyclisation and substrate scopes

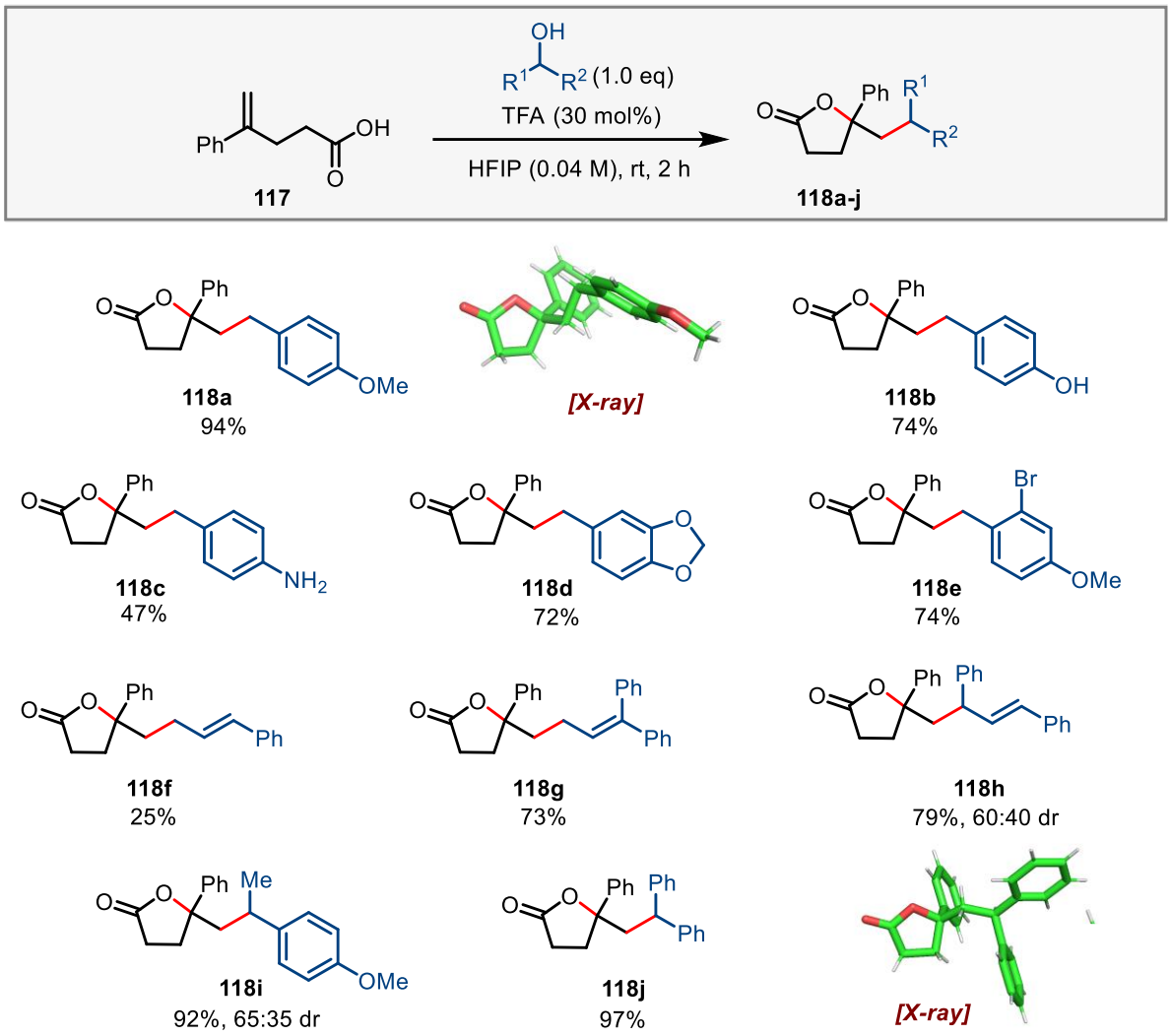
Megan Jaschinski had shown that *5-exo-trig* cyclisation is feasible using alcohols and carboxylic acids as intramolecular nucleophiles (Scheme **81**).[116] The new mode of cyclisation allows the synthesis of quaternary stereocenters which has been underexplored in the previous HFIP promoted heterocyclisation methodologies developed in the Donohoe group.[58,60,115] In addition, quaternary stereocenters within 5-membered heterocycles are a common structural motif in a variety of natural products and biologically active compounds.[117] It was therefore decided to explore *5-exo-trig* cyclisation further.



*Scheme **81***. Previous work by Megan Jaschinski. Supervised by Daniya Aynetdinova.

It was found that the scope for tetrahydrofuran ring formation was limited, even after comprehensive reaction optimisation. Allylic alcohols could not be productively engaged, resulting in complex mixtures. On the other hand, lactonisation of aryl-substituted carboxylic acids was more reliable. To further demonstrate this, Megan Jaschinski obtained the scope with respect to alcohol component which could be employed in the alkylative lactonisation

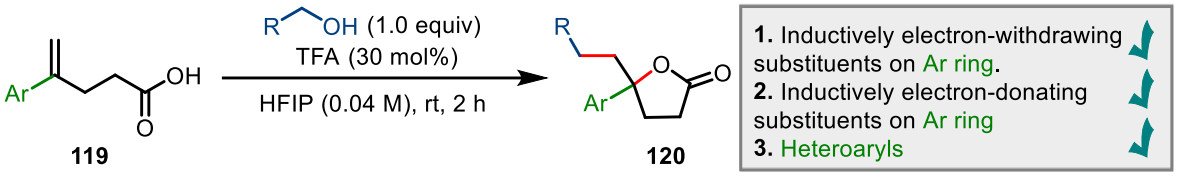
(Scheme **82**). Primary and secondary alcohols could be engaged in the reaction furnishing products in high yield. An acetal (**118d**), amine (**118c**), free hydroxyl (**118b**), halogen (**118e**) and alkene (**118f-h**) were tolerated under the reaction conditions. Allylic alcohols could be engaged as well, but with variable yields.



Scheme ***82***. Reaction scope with respect to alcohol. All experiments were performed by Megan Jaschinski. See Megan Jaschinski's Part II Thesis 2023.

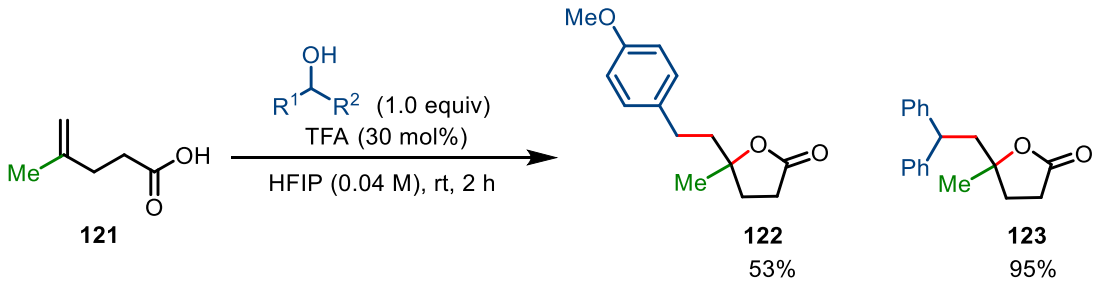
In addition to engaging different alcohols in the alkylative lactonisation, Megan Jaschinski also explored the scope with respect to the aryl group of the carboxylic acid substrate **119** (Scheme **83**). High yields were obtained for inductively electron-withdrawing, inductively electron-donating and some heteroaryl substrates. Mesomerically electron-donating and electron-withdrawing substituents on the aromatic ring, on the other hand, were not tolerated well. For

electron-rich aryl substrates complex reaction mixtures were obtained, whereas resonance electron-withdrawing aryl substituents resulted in no conversion.



*Scheme **83***. The scope with respect to aryl substituents. All experiments were performed by Megan Jaschinski. See Megan Jaschinski's Part II Thesis 2023.

Furthermore, Megan Jaschinski has shown that aliphatic carboxylic acids could also be engaged. For example, 4-methylpent-4-enoic acid **121** was reacted with benzhydrol and 4-methoxybenzyl alcohol to furnish products **122** and **123** in 53% yield and 95% yield respectively (Scheme **84**). These encouraging results prompted additional experiments to explore new substrate classes for the alkylative lactonisation in the future (see Section **3.3.2**).

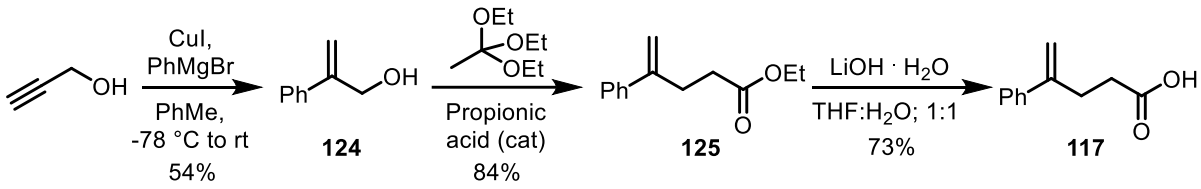


*Scheme **84***. Initial work on aliphatic substrates. All experiments were performed by Megan Jaschinski. See Megan Jaschinski's Part II Thesis 2023.

3.2.3 Further studies on the exocyclic reaction conditions

Inspired by the results obtained in collaboration with Megan Jaschinski, it was decided to further explore the alkylative lactonisation reaction. The initial optimisation experiments were performed on a different system to access substituted THF-rings (see Megan Jaschinski's Part II Thesis 2023). The best set of conditions was then used for the lactonisation reaction. Thus, before exploring more challenging substrates in the alkylative lactonisation, it was decided to conduct further studies on the reaction parameters and conditions.

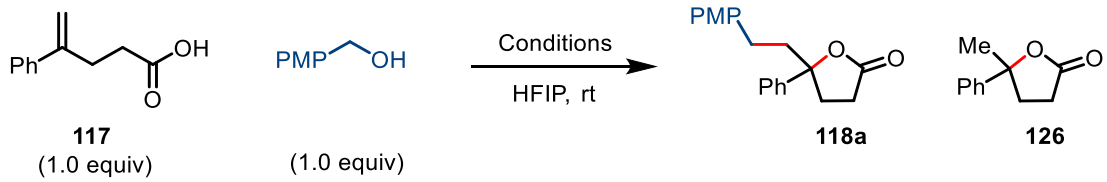
Carboxylic acid **117** was synthesised in 33% yield over three steps from commercially available propargyl alcohol (Scheme **85**). In the first step the addition of PhMgBr in the presence of substoichiometric CuI furnished allylic alcohol **124** in 54% yield. A subsequent Johnson–Claisen rearrangement afforded ester **125** in an excellent 84% yield. Hydrolysis of ester **125** furnished the desired carboxylic acid **117** in 73% yield. With this synthetic sequence, large quantities of carboxylic acid **117** could be reliably prepared.



*Scheme **85***. Synthesis of carboxylic acid **117**.

With substrate **117** in hand, a screen of reaction conditions was performed (Table **6**). First, the reaction between carboxylic acid **117** and 4-methoxybenzyl alcohol was conducted at 0.1 M in HFIP using Ti(O*i*-Pr)$_4$ Lewis acid (Table **6**, entry 1). Low conversion was observed with only 6% of product **118a** formed after 2 h. In addition, formation of side-product **126** in 4% NMR yield was observed. Side-product **126** was proposed to be formed when a proton from carboxylic acid **117**, instead of a carbocation, triggers the cyclisation. It was later found that separation of side-product **126** and lactone **118a** by chromatography was very challenging, so it was necessary to minimize the formation of lactone **126**. Since reducing the concentration was found to be beneficial for the cyclohexene system **12** (see Table **2**, Chapter **2.2.2**), it was decided to run the experiment at 0.04 M (Table **6**, entry 2). Indeed, the formation of lactone **118a** was observed in slightly improved 10% NMR yield over 2 h. Leaving the reaction overnight improved conversion and afforded the desired lactone **118a** in 40% yield and side-product **126** in 37% yield (Table **6**, entry 3). At this point the effect of different Lewis and Brønsted acids was explored (Table **6**, entries 4-10). The ratio between the desired lactone **118a** and side-product **126** was found to strongly depend on the promoter employed. For example, while the use of Sc(OTf)$_3$ afforded undesired lactone **126** as a major species, $ZnCl_2$

furnished exclusively product **118a** in an excellent 98% yield by NMR spectroscopy. AcOH afforded product **118a** in 58% yield overnight, which improved to 90% when more acidic TFA was employed. Finally, when the lactonisation was conducted without any promoter, product **118a** was formed in 53% NMR yield.



117 (1.0 equiv) (1.0 equiv) **118a** **126**

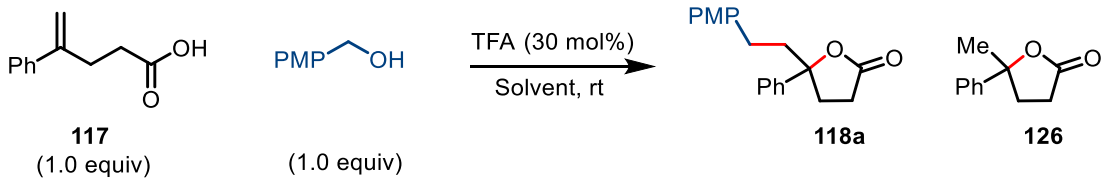
Entry	Concentration (M)	Time (h)	Promoter (30 mol%)	**118a** yield[a]	**126** yield[a]
1	0.1	2	Ti(O*i*-Pr)$_4$	6%	4%
2	0.037	2	Ti(O*i*-Pr)$_4$	10%	8%
3	0.037	overnight	Ti(O*i*-Pr)$_4$	40%	37%
4	0.037	overnight	$AlCl_3$	50%	45%
5	0.037	overnight	Sc(OTf)$_3$	27%	66%
6	0.037	overnight	$ZnCl_2$	98%	none
7	0.037	overnight	Zn(OAc)$_2$	82%	Trace
8	0.037	overnight	AcOH	58%	14%
9	0.037	overnight	TFA	90%	11%
10	0.037	overnight	none	53%	18%

Table ***6***. Optimisation of the reaction with respect to concentration, time and promoter used**.** [a] Yield was determined by quantitative crude NMR using 1,1,2,2-tetrachloroethane as an internal standard.

From the promoter screen the two best additives were identified as $ZnCl_2$ and TFA. For practical reasons it was decided to continue with TFA since $ZnCl_2$ was found to be extremely hydroscopic, making weighing small amounts of this Lewis acid unreliable.

Next, a solvent screen was performed using TFA as an additive (Table **7**). As observed for the polyene cyclisation, the use of non-fluorinated solvents failed to give any conversion with only

starting materials **117** and *para*-methoxybenzyl observed by crude NMR spectroscopy (Table **7**, entries 1-6). When TFE was used, the desired lactone **118a** was formed in 91% NMR yield overnight (Table **7**, entry 7). Reducing the reaction time to 2 h resulted in lower conversion with 60% of product **118a** being formed (Table **7**, entry 8). With HFIP as a reaction medium, the reaction was found to be complete within 2 h under otherwise identical conditions (Table **7**, entry 10).



117 (1.0 equiv) (1.0 equiv) **118a** **126**

Entry	Concentration (M)	Time (h)	Solvent	**118a** yield[a]	**126** yield[a]
1	0.037	overnight	IPA	0%	0%
2	0.037	overnight	MeCN	0%	0%
3	0.037	overnight	CH_2Cl_2	0%	0%
4	0.037	overnight	EtOH	0%	0%
5	0.037	overnight	DMF	0%	0%
6	0.037	overnight	Et_2O	0%	0%
7	0.037	overnight	TFE	91%	Trace
8	0.037	2 h	TFE	60%	Trace
9	0.037	overnight	HFIP	90%	11%
10	0.037	2 h	HFIP	94%	6%

Table **7**. Optimisation of the reaction with respect to solvent and time. [a] Yield was determined by quantitative crude NMR using 1,1,2,2-tetrachloroethane as an internal standard.

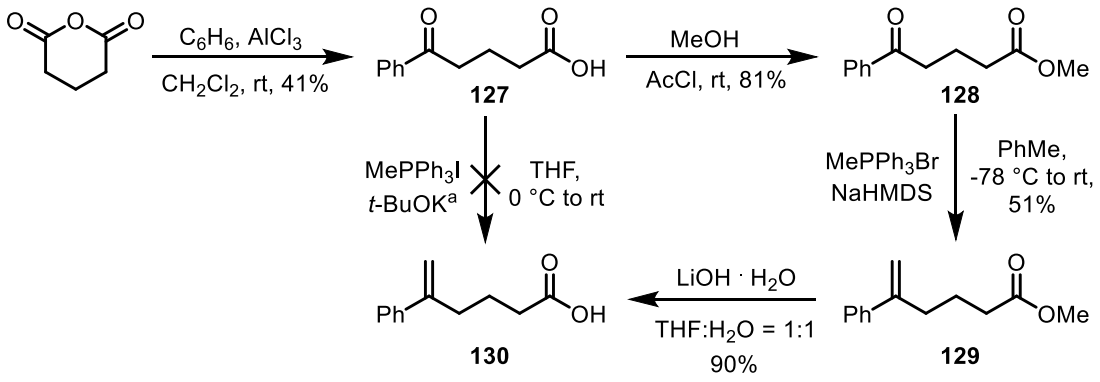
The improved reaction efficiency in HFIP could be due to lower pKa and higher polarity of HFIP when compared to TFE.[118] Given that full conversion was observed in HFIP over 2 h

and an increased toxicity of TFE compared to HFIP, it was decided to continue further experiments using HFIP as the reaction solvent.

3.3 Expansion of the substrate scope

3.3.1 Synthesis of δ-lactones

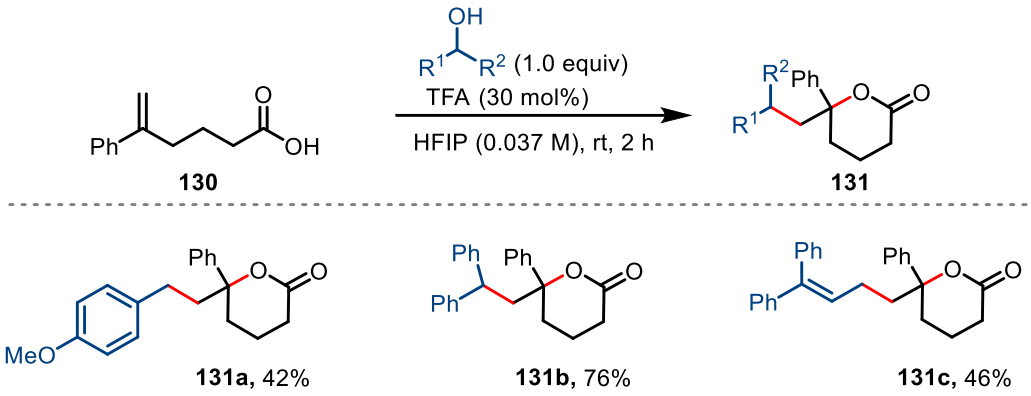
So far, only 5-membered lactones had been prepared using the cation-triggered lactonisation strategy. To explore if 6-membered lactones could be accessed, the synthesis of carboxylic acid **130** was commenced (Scheme **86**). Friedel–Crafts reaction between benzene and glutaric anhydride furnished ketone **127** in 41% yield after purification. Unfortunately, no conversion was observed when ketone **127** was subjected to a Wittig reaction with an excess of base. It was therefore decided to use ester **128** instead, which was prepared in 81% yield from acid **127**. Wittig reaction using ester **128** and $MePPh_3Br$ afforded alkene **129** in 51% yield. The subsequent ester hydrolysis furnished the desired carboxylic acid **130** in 90% yield.



*Scheme **86***. Synthesis of carboxylic acid **130**. [a] Wittig reaction was attempted using 3.2 equivalents of base and 2.1 equivalents of $MePPh_3I$.

With carboxylic acid **130** in hand, the cation-triggered cyclisation to access δ-lactones was conducted. The reaction was performed using three different alcohols: primary, secondary and allylic (Scheme **87**). 4-Methoxybenzyl alcohol furnished lactone **131a** in 42% yield. Benzhydrol afforded lactone **131b** in good 76% yield, while 3,3-diphenylprop-2-en-1-ol furnished lactone **131c** in 46% yield. When the same alcohols were used to access γ-lactones, the

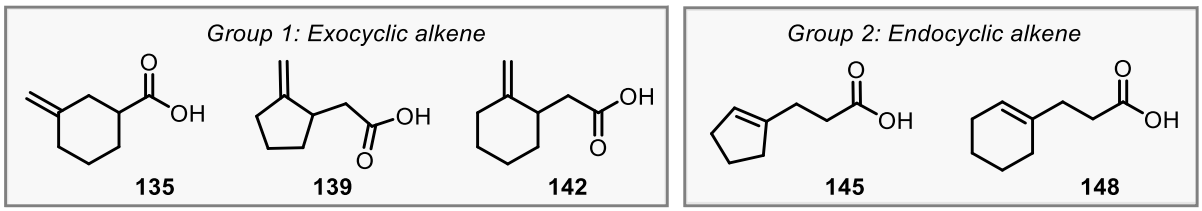
corresponding products were isolated in higher yields. This is consistent with the previous observation from the Donohoe group that the cation-triggered heterocyclisation woks better for 5-membered systems versus 6-membered.[58,60,115]



*Scheme **87***. Examples of δ-lactones prepared *via* a cation-triggered lactonisation.

3.3.2 Synthesis of novel aliphatic substrates

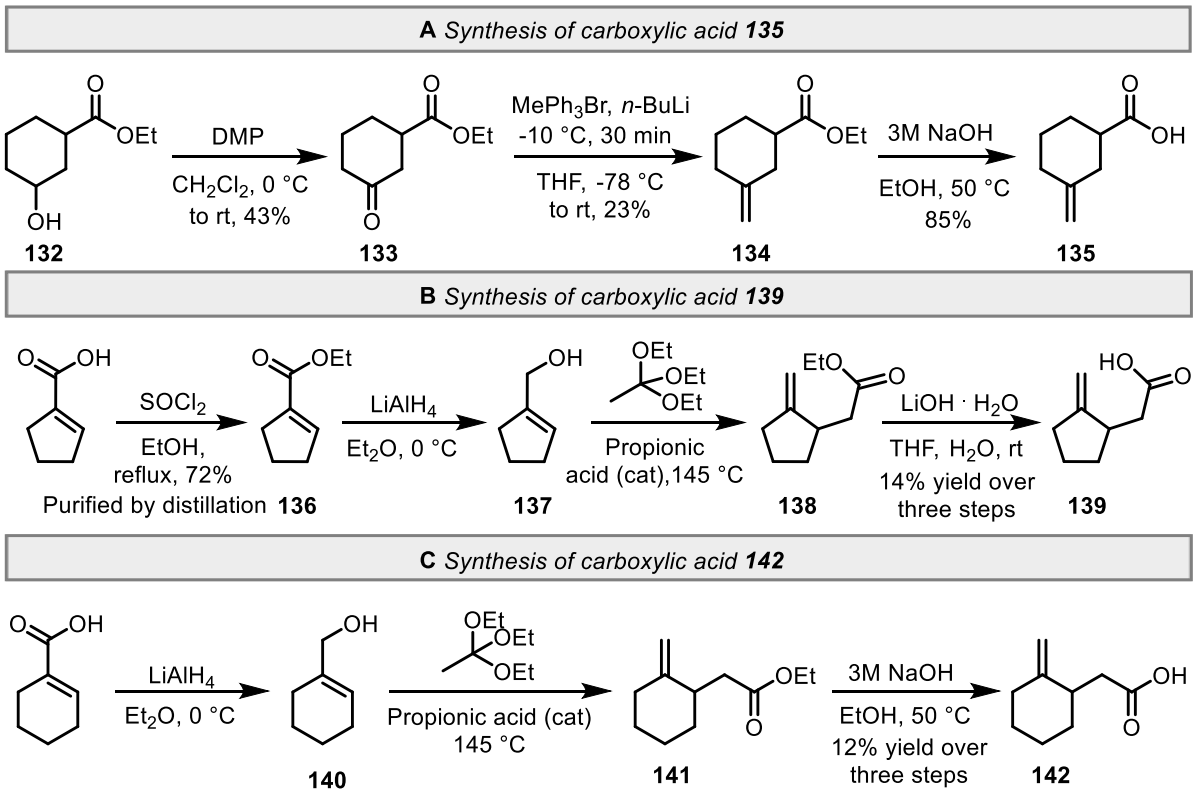
Next, attention moved to explore new aliphatic substrates, which upon lactonisation would set up interesting polycyclic scaffolds. For this purpose, the substrates to be synthesised were separated into two different groups (Scheme **88**). In the first group carboxylic acids containing exocyclic alkenes were placed, which upon cyclisation would generate fused or bridged ring systems. The second group consists of substrates with endocyclic alkenes, which after lactonisation would form spirocyclic scaffolds.



*Scheme **88***. New aliphatic substrates

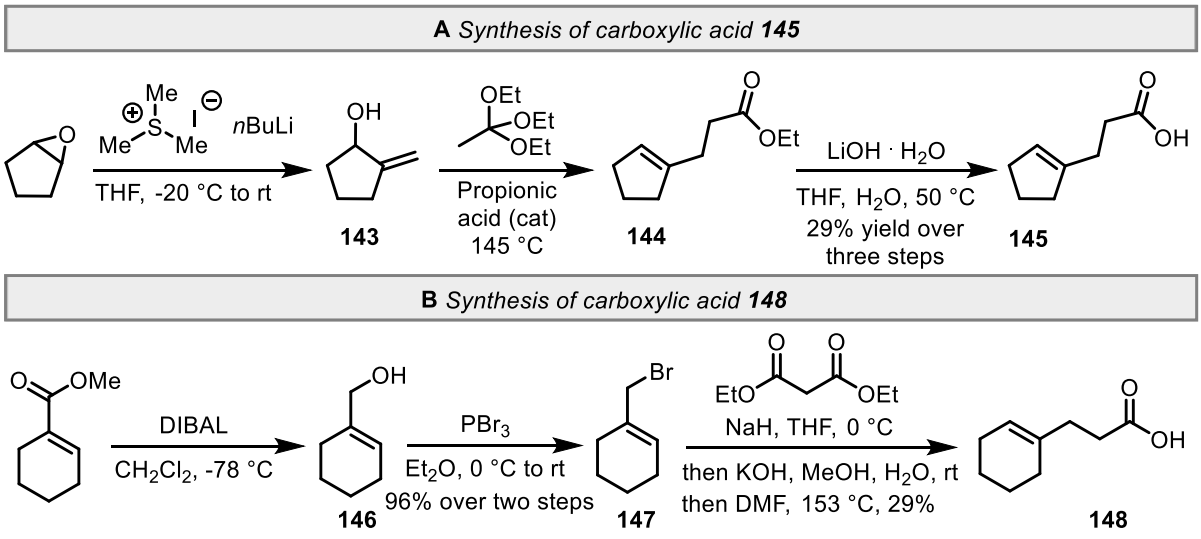
The synthesis of substrates from group 1 commenced with the route used to access carboxylic acid **135** (Scheme **89**, A). In the first step commercially available alcohol **132** was oxidised to ketone **133** using Dess–Martin periodinane in 43% yield. The reduced yield was due to

incomplete conversion and challenging separation afterwards. Wittig reaction on ketone **133** furnished volatile alkene **134** in 23% yield. The subsequent ester hydrolysis afforded carboxylic acid **135** in 85% yield. Synthesis of carboxylic acid **139** commenced with formation of ethyl ester **136** in 72% yield which was purified by distillation (Scheme **89**, B). Given the volatility issues which were observed for ester **134**, it was decided against isolating intermediate allylic alcohol **137** and ester **138**. Instead $LiAlH_4$ reduction of ester **136** followed by Johnson–Claisen rearrangement afforded ester **138** which was then subjected to ester hydrolysis to furnish carboxylic acid **139** in 14% over three steps. A similar synthetic sequence was used to access analogous carboxylic acid **142** (Scheme **89**, C). $LiAlH_4$ reduction of cyclohex-1-ene-1-carboxylic acid afforded allylic alcohol **140** which was immediately subjected to the next step to afford ester **141**. The subsequent hydrolysis furnished carboxylic acid **142** in 12% yield over three steps. Reduced yields for substrates **139** and **142** may arise from the intermediate Johnson–Claisen rearrangement step which involves heating the reaction at 145 °C over 24 h, contributing to a loss of material.



*Scheme **89***. Synthesis of new aliphatic substrates from group 1.

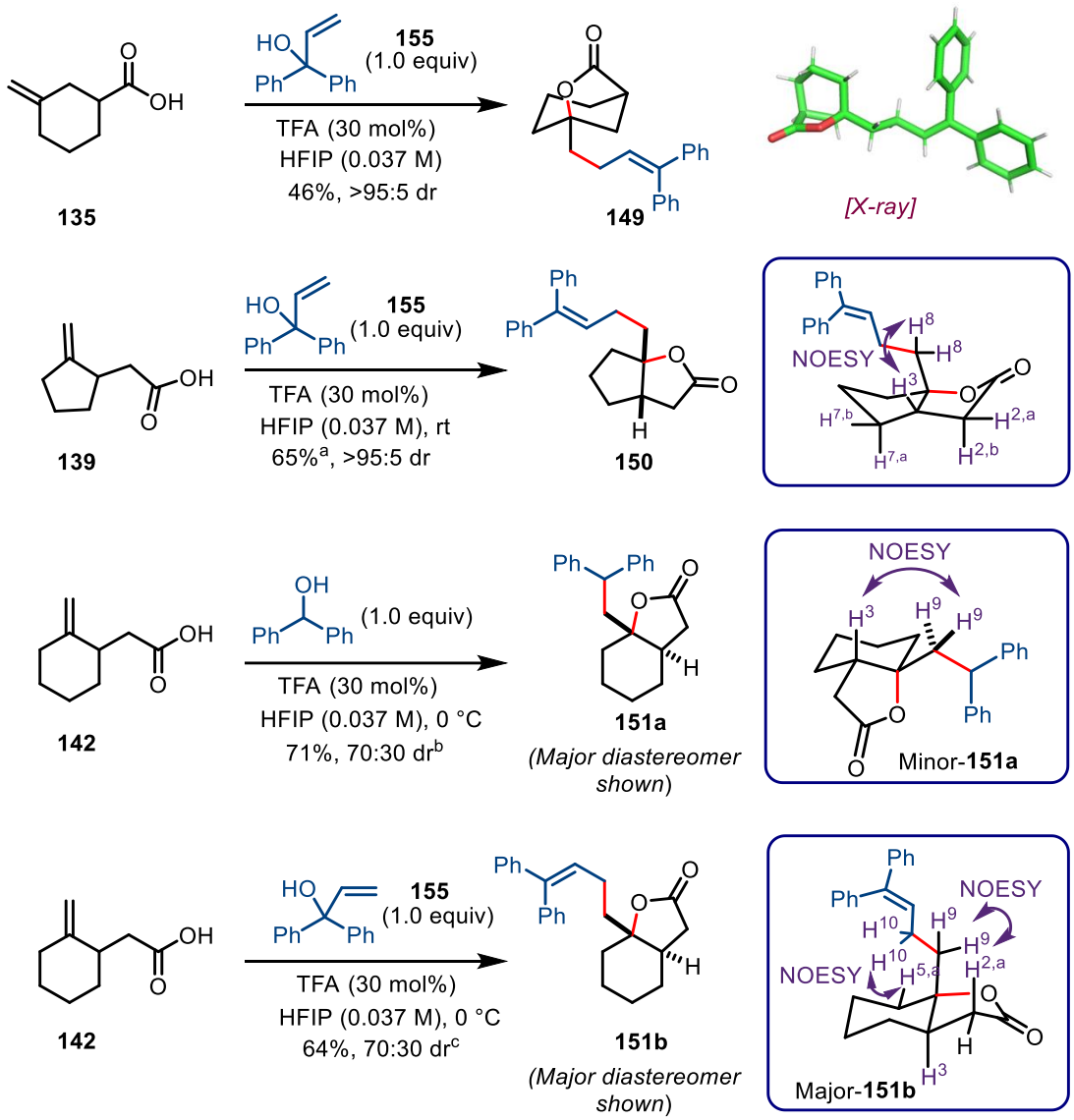
The synthesis of substrates from group 2 commenced with carboxylic acid **145** (Scheme **90**, A). In the first step epoxide ring opening with trimethylsulfonium ylide followed by *in situ* elimination of dimethylsulfide furnished allylic alcohol **143**. Due to volatility concerns, allylic alcohol **143** was subjected to the next step without purification. Johnson–Claisen rearrangement afforded ester **144** and subsequent ester hydrolysis furnished carboxylic acid **145** in 29% yield over three steps. To synthesise carboxylic acid **148**, commercially available methyl cyclohex-1-ene-1-carboxylate was subjected to DIBAL reduction to afford allylic alcohol **146** (Scheme **90**, B). After a careful solvent swap, alcohol **146** was brominated using PBr_3 to furnish allylic bromide **147** in 96% yield over two steps which did not require any purification. Then, a three-step telescoped procedure from Bower and coworkers was used to obtain carboxylic acid **148**.[119] Thus, alkylation of diethyl malonate with bromide **147**, ester hydrolysis and decarboxylation in DMF at 153 °C afforded carboxylic acid **148** in 29% yield over three steps with a single chromatography purification.



*Scheme **90***. Synthesis of new aliphatic substrates from group 2.

With the desired carboxylic acids in hand, the cation-triggered lactonisation using 1,1-diphenylprop-2-en-1-ol **155** was conducted (Scheme **91A**). The bridged lactone **149** was isolated in 46% yield as a single diastereomer. Excellent diastereoselectivity was also observed with carboxylic acid **139**. *Cis*-fused [5,5] bicyclic lactone **150** was formed in 65%

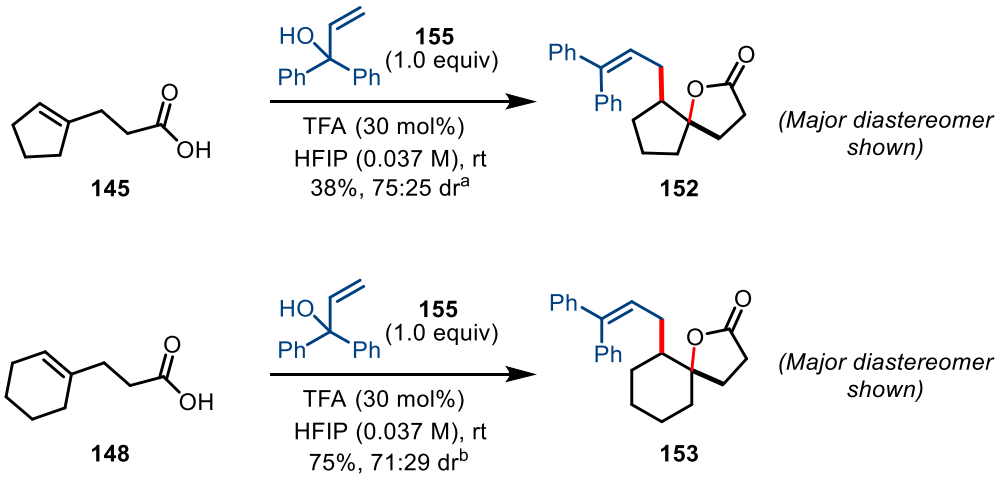
yield with >95:5 dr. The relative stereochemistry was proved by a NOESY between H-3 and H-8, as well as the absence of NOESYs between H-8 and H-7[a/b], H-8 and H-2[a/b]. Formation of *cis*-fused [5,5] bicyclic system was also expected since the diastereomeric *trans*-fused [5,5] lactone would be more strained. Unfortunately, the levels of diastereoselectivity dropped for lactonisation of carboxylic acid **142**, even when it was conducted at 0 °C. Lactones **151a** and **151b** were formed in good yields but as a mixture of diastereomers in around 70:30 ratio.



Scheme ***91A***. The cation-triggered lactonisation of substrates from group 1. [a] The reaction was conducted by Megan Jaschinski; [b] dr calculated after column chromatography; [c] dr was calculated of the crude reaction mixture.

NOESY analysis of the mixture of lactones **151a** revealed weak NOESY between H-3 and H-9 for minor diastereomer **151a**, suggesting the *cis*-fused [5,6] bicyclic system for minor diastereomer. Furthermore, analytical amounts of the major diastereomer of lactone **151b** were isolated for NOESY analysis to confirm relative stereochemistry. NOESYs between H-9 and H-2_a, H-5_a and H-10 as well as the absence of NOESY between H-$9^{a/b}$ and H-3 was used to assign the major diastereomer as a *trans*-fused [5,6] bicyclic lactone system.

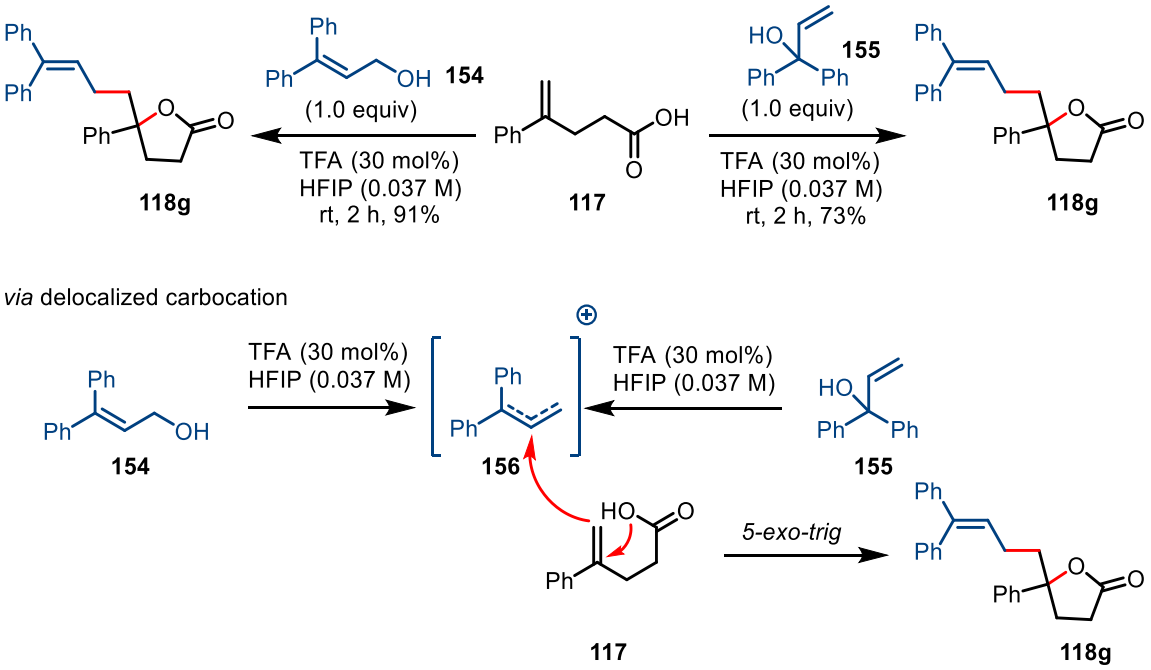
Next, the cation-triggered lactonisation of carboxylic acids from group 2 was conducted (Scheme **91B**). The use of substrate **145** furnished [5,5] spirocyclic lactone **152** in 38% yield and 75:25 dr. Carboxylic acid **148** afforded [6,6] spirocyclic system **153** in good 75% yield and similar 71:29 dr. In both cases, the diastereomers could not be separated by column chromatography. The relative stereochemistry of **153** was assigned based on NMR analysis of aldehyde **166** which was obtained after ozonolysis (see Scheme **97**). The relative stereochemistry of [5,5] spirocyclic lactone **152** was assigned by analogy to product **153**. The observed configuration of the major diastereomers of spirocyclic lactones **152** and **153** is consistent with *trans* addition of a carbocation electrophile and carboxylate nucleophile across the alkene.



*Scheme **91B***. The cation-triggered lactonisation of substrates from group 2. [a] dr was calculated of the crude reaction mixture; [b] dr was calculated after column chromatography.

3.4 Mechanistic studies

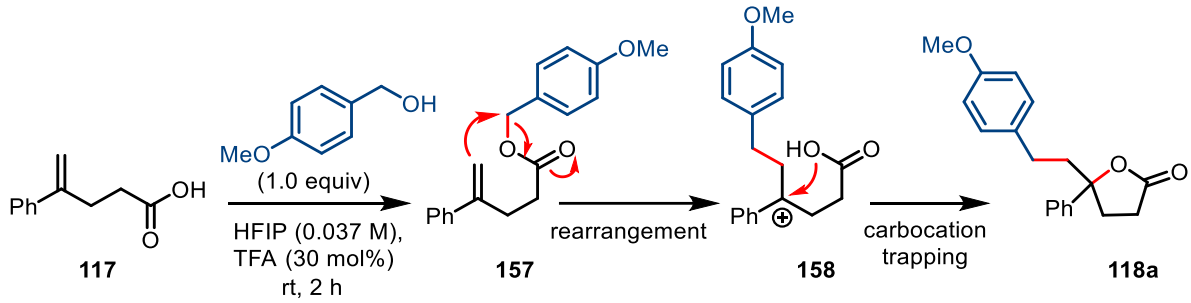
After expanding the substrate scope, attention was turned to further explore the mechanism of this cation-triggered lactonisation. First, evidence for the carbocation formation was obtained using transposed isomers of allylic alcohol **155** and **154** (Scheme **92**). With the primary allylic alcohol **154**, lactone **118g** was formed in an excellent 91% yield. Tertiary allylic alcohol **155** furnished the same regioisomer of lactone **118g** in good 73% yield. This is consistent with an *in situ* ionisation of allylic alcohols **154** and **155** to form the same delocalised carbocation **156** which then triggers lactonisation of carboxylic acid **117**. As observed in the polyene cyclisation system, the carbocation reacts with an alkene at the least hindered end. The small difference in reaction yields for alcohols **154** and **155** could arise from the different rates of ionisation of **154** and **155** to form delocalised carbocation **156**.



*Scheme **92***. Evidence for the *in situ* carbocation formation using transposed isomers **155** and **154**.

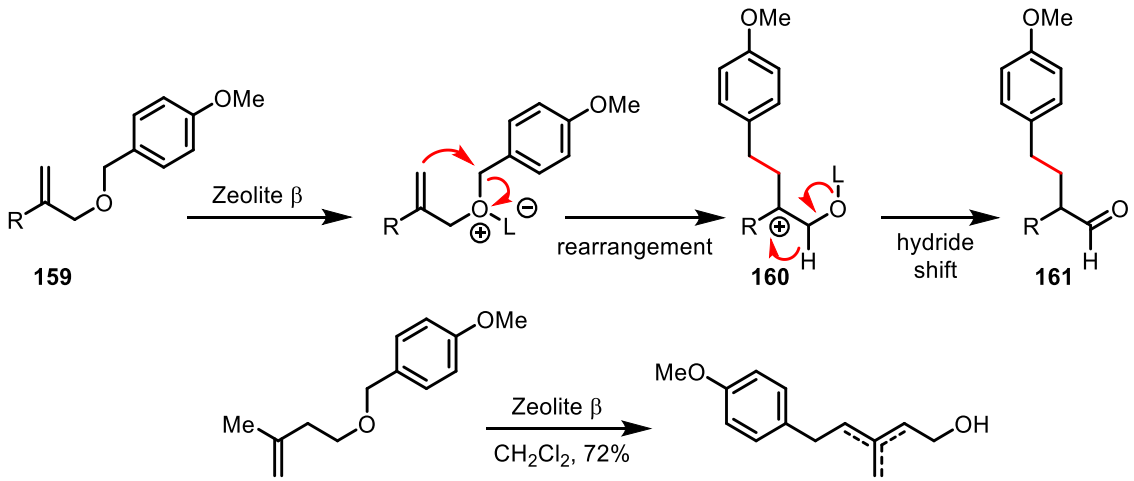
It was proposed that, in the presence of a heteroatom-based functional group, the carbocation formed *in situ* from alcohol ionisation could first be trapped by a nucleophilic carboxylic acid to form ester **157** (Scheme **93**). Ester **157** could then undergo intramolecular rearrangement *via* attack of an alkene on newly formed C-O bond, either in a concerted or stepwise fashion.

This would furnish benzylic carbocation **158** which could then be trapped by a carboxylic acid to form lactone **118a**.



*Scheme **93***. An alternative mechanistic pathway for lactonisation.

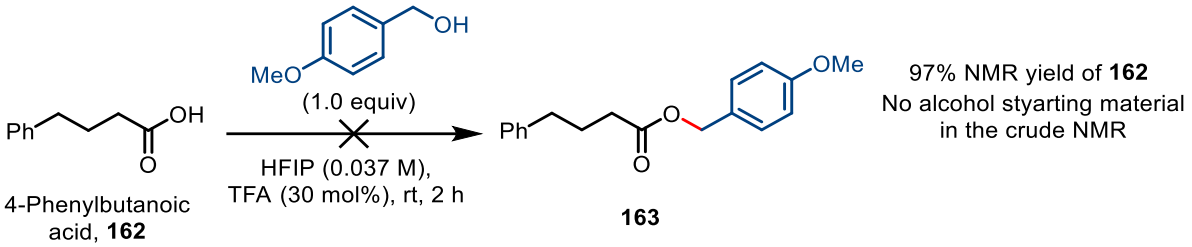
Similar rearrangements have been reported in the literature, although for a shorter carbon-chain length and employing ethers as substrates.[120] For example, Frejd and co-workers have reported a zeolite-induced rearrangement of alkoxybenzyl allyl ethers **159** to carbonyl compounds **161** (Scheme **94**).[120b] In this work, carbocation **160** formed after rearrangement either triggers an intramolecular hydride shift from alkoxide or undergoes E1 elimination as a termination event.



*Scheme **94***. Literature precedent for an intramolecular rearrangement pathway.

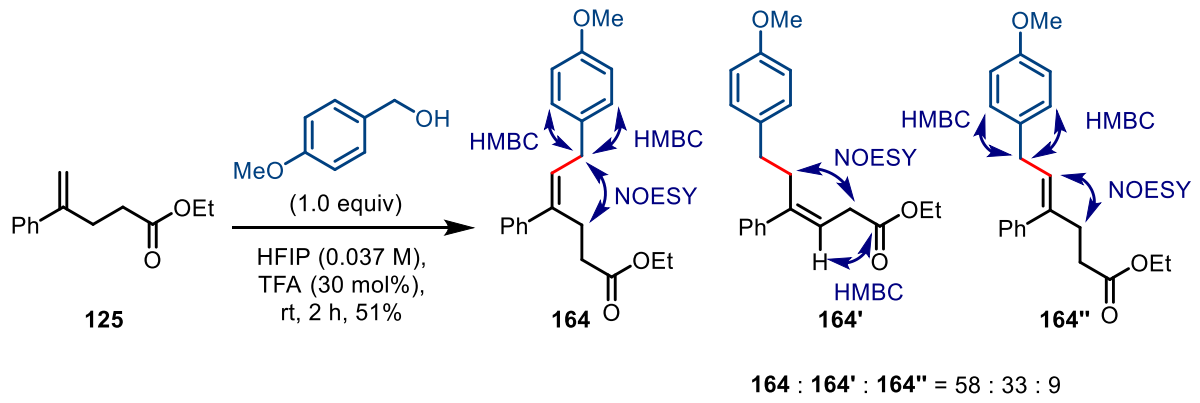
To shed light on whether the C-O or C-C bond is formed first during the cation-triggered lactonisation, a serious of control experiments was designed. First, 4-phenylbutanoic acid lacking an alkene functional group and 4-methoxybenzyl alcohol were subjected to the

reaction conditions (Scheme **95**). No ester **163** was observed or isolated. Instead, analysis of the crude reaction mixture indicated that 97% of 4-phenylbutanoic acid was remaining but that no alcohol starting material was present.



*Scheme **95***. Control experiment using 4-phenylbutanoic acid. NMR yield calculated using quantitative ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

Next, ester **125** bearing an alkene functionality and a protected carboxylic acid was used (Scheme **96**). When reacted with 4-methoxybenzyl alcohol, an inseparable mixture of alkenes **164**, **164'** and **164"** was isolated in combined 51% yield and in a 58:33:9 ratio. (*E*)-Alkene **164** was the major species in the mixture with (*Z*)-**164"** being the minor. Thus, in the absence of an intramolecular nucleophile, the electrophile is still trapped by the alkene followed by E1 elimination of the so-formed carbocation as a termination event.



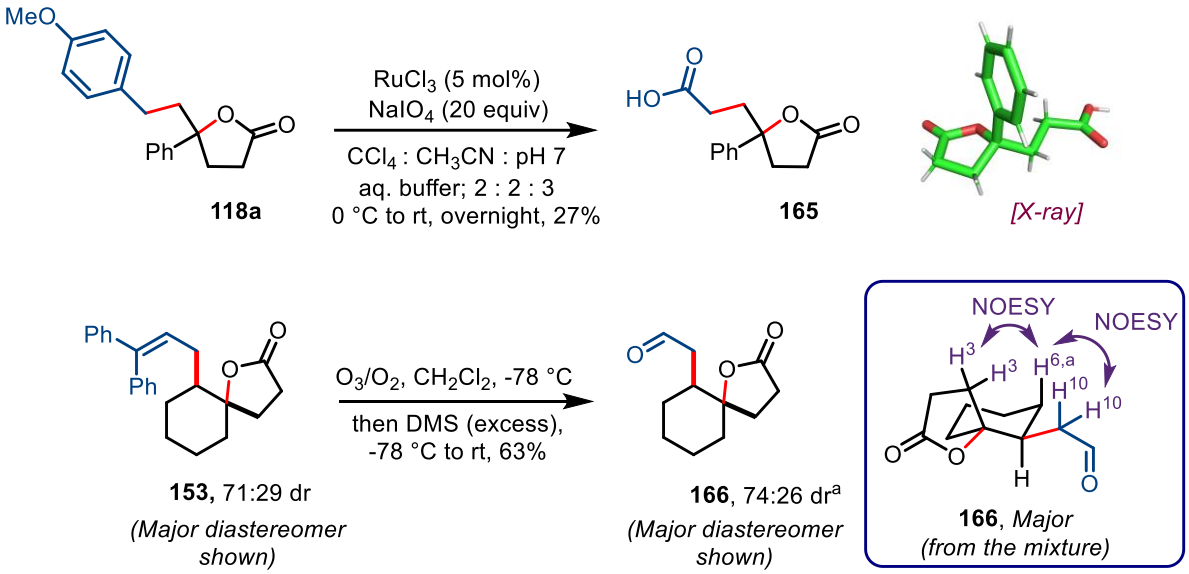
*Scheme **96***. Control experiment using ester **125**.

Given that no ester **163** was formed when 4-phenylbutanoic acid was subjected to the reaction conditions and that no alcohol starting material was remaining, it was concluded that carbocation species generated *in situ* decomposes in the absence of a suitable nucleophile.

On the other hand, if an alkene nucleophile is present, trapping of carbocation species still happens followed by unselective E1 elimination. These findings suggest that the C-C bond between the alkene and an electrophile is formed first, followed by cyclisation and C-O bond formation. Thus, mechanism outlined in Scheme **93** *via* an ester rearrangement is unlikely. Furthermore, the formation of alkene mixture **164** suggests that lactonisation could proceed *via* a stepwise mechanism, instead of a concerted *5-exo-trig* cyclisation. The degree of concertedness, however, might depend on the exact carboxylic acid substrate employed. The stepwise mechanism is further supported by moderate diastereoselectivities observed for spirocycles **152** and **153**.

3.4 Derivatisations

Finally, representative derivatisation experiments were carried out on some of the lactone products (Scheme **97**). First, it was shown that an electron-rich aryl group could be oxidised to a carboxylic acid using RuO_4 mediated cleavage. Carboxylic acid **165** was isolated in 27% yield after a cleavage of a PMP group in the presence of a Ph group. Given that this reaction did not give any desired product in the polyene system under a variety of conditions (see Scheme **71**), it could be that the RuO_4 mediated cleavage is strongly substrate dependent. To show that products obtained from the reaction with allylic alcohols could be derivatised, ozonolysis of lactone **153** was conducted. Aldehyde **166** was isolated in 63% yield as an inseparable mixture of diastereomers in 74:26 ratio. 2D NMR analysis of the major diastereomer from the mixture indicated NOESY interactions between H-6_a and H-3, as well as NOESY interactions between H-6_a and H-10. Thus, the major diastereomer was assigned to have a *cis*-configuration of the two exocyclic C-C bonds. The relative stereochemistry of the major and minor diastereomers of lactone **153** was assigned using data for aldehyde **166** and then extrapolating to lactone **152** by analogy.



*Scheme **97***. Derivatisation experiments. [a] dr determined after column chromatography.

3.5 Summary and outlook

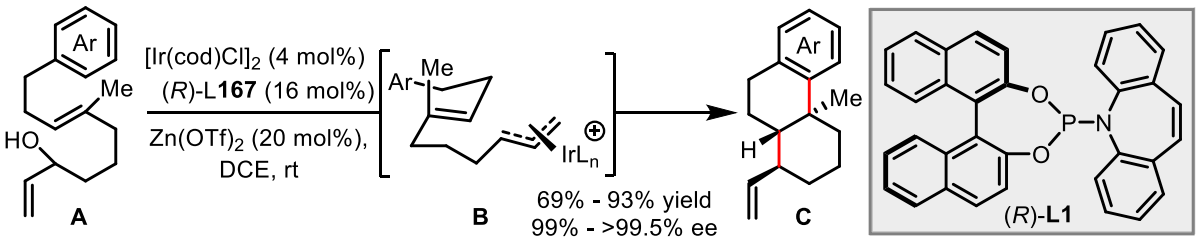
To summarise, the cation-triggered *5/6-exo-trig* lactonisation was achieved in good yields with moderate to excellent diastereoselectivity. Fused and spirocyclic lactones possessing an exocyclic C-C bond could be accessed using the alcohol-HFIP system. Moderate dr for spirocyclic lactones **152** and **153**, as well as the results from the mechanistic experiments suggest that the lactonisation might proceed through a stepwise mechanism. The future work could focus on further expanding the substrate scope, improving diastereoselectivities for multiple ring formation and exploring other types of carbon-electrophiles.

Chapter 4: Studies Towards Asymmetric Ir-Catalysed Cyclisation

4.1 Introduction and key literature precedent for asymmetric cyclisation *via* Ir-catalysed allylic substitution

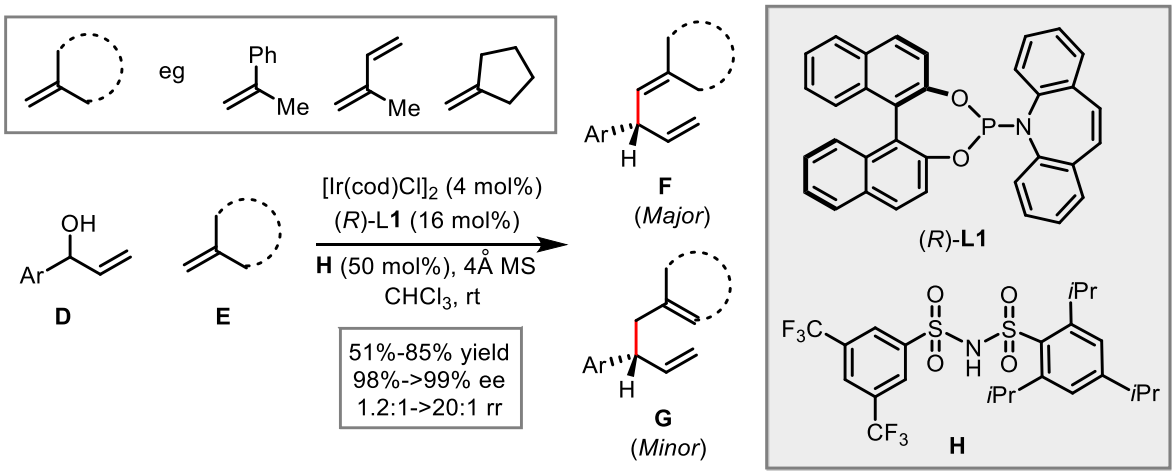
After developing methodologies for diastereoselective cyclisation cascades, attention was turned to explore strategies to control the absolute configuration of newly formed chiral centres. In this chapter, studies towards enantioselective polyene cyclisations, as well as heterocyclisations, will be described. Through a literature review, it became clear that enantioselective Ir-catalysed allylic substitution reactions could be applied for asymmetric carbo- and heterocyclisation.[121] Some other transition metal-free strategies to achieve enantioselective cyclisations have been discussed in chapter **1**. This introductory chapter will instead focus on the key literature precedents in asymmetric Ir-catalysed transformations to explain why this approach has been chosen for the studies.

In 2012 Carreira and coworkers reported an enantioselective Ir-catalysed polyene cyclisation (Scheme **98**).[122] (*R*)-Phosphoramidite **L1**, known as the Carreira ligand, was employed. Allylic alcohol substrates **A** bearing electron-rich aryl groups could be engaged in up to 93% yield and >99.5% ee. The authors proposed that the polyene cyclisation proceeded *via* the formation of complex **B**, in which chiral ligand (*R*)-**L1** controls the absolute configuration in all three newly formed chiral centres. Although only eight examples of products **C** with electron-rich aryl terminating groups were shown, this work serves as a proof-of-concept that allyl-metal species could be used in enantioselective polyene cyclisation.



*Scheme **98***. Carreira's enantioselective polyene cyclisation.

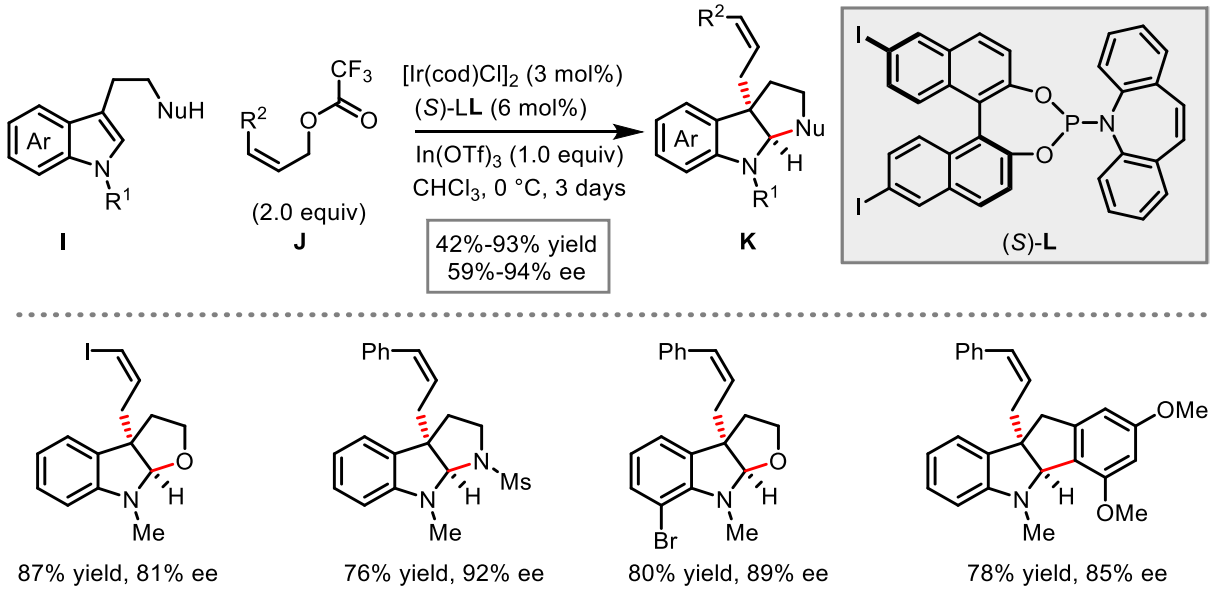
Two years later, the same group published an enantioselective allyl-alkene coupling (Scheme **99**).[123] Even though this work did not utilise polyene substrates, it showed that electron-rich alkenes could be used as intermolecular nucleophiles to trap allyl-metal species. Carreira and coworkers achieved excellent yields and levels of enantioselectivity by using terminal disubstituted alkenes **E** with secondary allylic alcohols **D**. As with polyene cyclisation, Ir-catalysis with ligand (*R*)-**L1** was employed. Since alkene substrates did not possess any internal nucleophilic group, E1 elimination served as a termination event with various levels of regioselectivity. A broad scope of alkene substrates was presented bearing aromatic and aliphatic substituents.



*Scheme **99***. Carreira's enantioselective allyl-alkene coupling.

Another important precedent was published by You's research group. In 2021 the group reported an asymmetric Ir-catalysed (*Z*)-retentive heterocyclisation of indole derived substrates **I** (Scheme **100**).[124] Using a similar reaction design based on phosphoramidite ligand (*S*)-**L** and [Ir(cod)Cl]$_2$, You and coworkers achieved highly enantioselective heterocyclisation with a variety of intramolecular nucleophiles. Alcohol, amine and aryl nucleophiles could be engaged in up to 93% yield and 94% ee. Most importantly, the alkene substrates **I** utilized by You and coworkers resemble the substrates employed in the HFIP promoted work described in this thesis. In the polyene system described in chapter **2**, as well as in the Donohoe's cation-triggered heterocyclisation,[58,60] the nucleophilic partner possesses

an electron-rich alkene conjugated with a PMP group. In Donohoe's system, the build-up of a positive-charge upon new C-C bond formation initiates the *5-endo-trig* cyclisation, which is similar to the overall transformation reported by You and coworkers. It was therefore concluded that the application of Ir-catalysis in Donohoe's system could in principle enable enantioselective heterocyclisations. Interestingly, You and coworkers exclusively carried out the heterocyclisation of indole-derived substrates.[124] Therefore, the prospect of substituting indole with an alternative electron-rich aryl group, such as PMP, was yet to be explored.



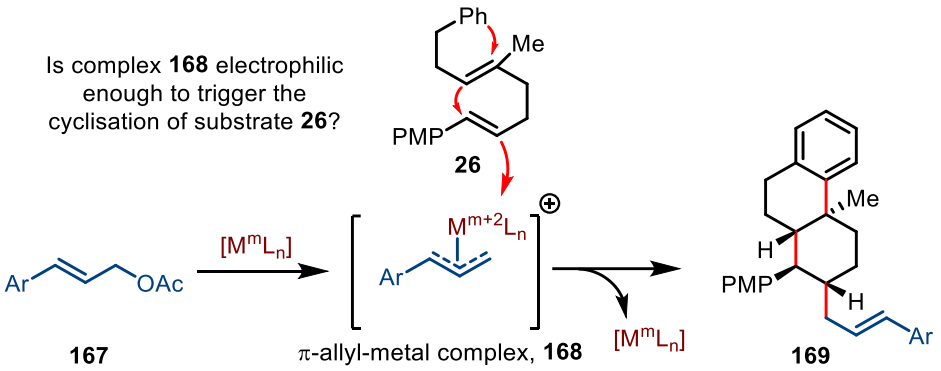
*Scheme **100***. You's Ir-catalysed heterocyclisation.

4.2 Studies on enantioselective iridium-catalysed polyene cyclisation *via* asymmetric allylic substitution

4.2.1 System development during an industrial placement at Vertex Pharmaceuticals

Based on an extensive literature search, it was decided to explore transition metal catalysed asymmetric allylic substitution as a strategy for the enantioselective cyclization cascade. Phosphoramidite ligands, and in particular Carreira ligand **L1**, are widely used in related metal catalysis methodologies.[125] Consequently, the preliminary screening of the reaction parameters at Vertex Pharmaceuticals was conducted using phosphoramidite ligands.

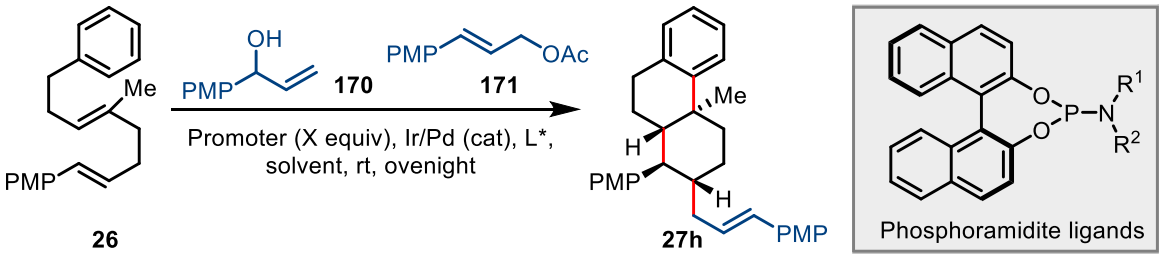
First, the enantioselective polyene cyclisation using substrate **26** was studied. It was proposed that chiral π-allyl-metal complex **168**, generated *via* oxidative insertion of a metal-ligand complex into allylic acetate **167**, could initiate the enantioselective cyclisation of polyene **26** (Scheme **101**). The proposed idea is conceptually similar to the work by Carreira and coworkers on Ir-catalysed enantioselective polyene cyclisation (see Scheme **98**).[122] The key difference is that in this work π-allyl-metal complex **168** would act as an intermolecular initiator in a two-component reaction, whereas Carreira's method proceeds solely in an intramolecular fashion.



*Scheme **101***. Mechanistic proposal for the transition-metal catalysed polyene cyclisation of **26**.

Several challenges with the proposed approach were identified. First, it was unclear if π-allyl-metal complex **168** would be electrophilic enough to trigger the cyclisation of polyene **26**. Secondly, the use of several ligand classes, including phosphoramidite ligands, would not be compatible with HFIP solvent. HFIP had proved to be essential for the cation-triggered diastereoselective cyclisation of polyene **26** (see Chapter **2**), so it remained to be seen if it could be replaced with another solvent when a different electrophile is employed. Lastly, it was envisioned that the regioselectivity of a metal-catalysed nucleophilic substitution using the polyene system could be challenging to control. Under HFIP conditions, the polyene cyclisation was highly selective for the least hindered site of a delocalised carbocation, while the opposite regioselectivity is commonly observed for Ir-catalysed allylic substitutions.[121,125] Thus, the reactivity mismatch between the intrinsic system preference and a metal catalysed pathway was likely to possess a challenge for the reaction optimisation.

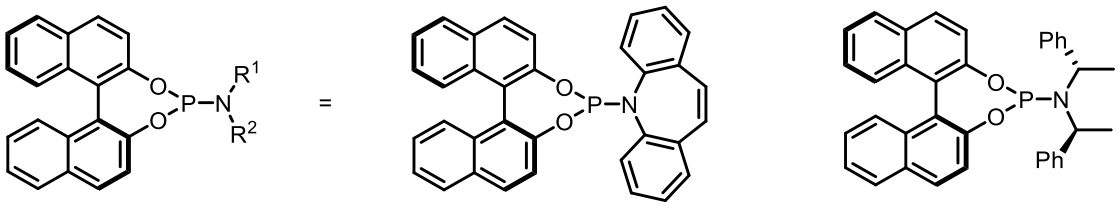
With the outlined challenges in mind, a screen of reaction conditions employing different metal catalysts was performed (Table **8**). First, the focus was set on trying a variety of literature known transition metal-catalysed conditions for asymmetric allylic substitution involving alkenes to get an initial hit.[126] No conversion was observed with Pd metal and phosphoramidite ligands **L1** and **L2** (Table **8**, entries 1-2). The use of $[Ir(cod)Cl]_2$ together with (*S*)-Carreira ligand **L1** and $In(OTf)_3$ Lewis acid furnished a complex reaction mixture in which a trace amount of the desired product **27h** could be identified (Table **8**, entry 3). The same result was observed when **L2** was used (Table **8**, entry 4). When loadings of $[Ir(cod)Cl]_2$ and phosphoramidite ligand **L1** were increased and TFA was employed as a promoter, an initial positive result was obtained (Table **8**, entry 5). Product **27h** was isolated in around 38% mass recovery, however, it could not be fully separated from minor unidentified impurities. The sample was first subjected to analytical SFC separation followed by chiral SFC analysis which indicated 17% ee. Reducing the equivalents of TFA improved the ee to 39%, measured after analytical SFC separation (Table **8**, entry 6). The reaction, however, was slower and required 3 days to reach similar conversion by UPLC analysis as with 1 equivalent of TFA. When a different phosphonamidite ligand **L2** was used, no conversion was observed (Table **8**, entry 7). It was then decided to conduct the polyene cyclisation with secondary allylic alcohol **170** (Table **8**, entry 8). Interestingly, more selective conversion to product **27h** was observed. Compound **27h** was isolated in 23% yield but with reduced 12% ee. Finally, using primary allylic acetate **171** and increased catalyst loadings, product **27h** was formed with 47% ee, measured after analytical SFC separation (Table **8**, entry 9).



Entry	**171/170** (equiv)	catalyst	Ligand[a] (mol%)	Promoter (equiv)	Solvent (M)	**27h** Isolated	ee[b]
1	**171** (1.2 equiv)	$(PdallylCl)_2$ (22.5 mol%)	**L1** (45 mol%)	K_2CO_3 (1.2 equiv)	PhMe (0.1 M)	0%[c]	ND
2	**171** (1.3 equiv)	Pd_2dba_3 (2.5 mol%)	**L2** (11 mol%)	none	CH_2Cl_2 (0.1 M)	0%[c]	ND
3	**171** (2 equiv)	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	$In(OTf)_3$ (1.0 equiv)	DCE (0.25 M)	Trace[d]	ND
4	**171** (2 equiv)	$[Ir(cod)Cl]_2$ (3 mol%)	**L2** (6 mol%)	$In(OTf)_3$ (1.0 equiv)	DCE (0.25 M)	Trace[d]	ND
5	**171** (1 equiv)	$[Ir(cod)Cl]_2$ (5 mol%)	**L1** (16 mol%)	TFA (1.0 equiv)	DCE (0.25 M)	38%[e] (24 h)	17%
6	**171** (1 equiv)	$[Ir(cod)Cl]_2$ (5 mol%)	**L1** (16 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	24%[e] (3 days)	39%
7	**171** (1 equiv)	$[Ir(cod)Cl]_2$ (5 mol%)	**L2** (16 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	Trace[c]	ND
8	**170** (1 equiv)	$[Ir(cod)Cl]_2$ (5 mol%)	**L1** (16 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	23% (24 h)	12%
9	**171** (1 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	42%[e] (5 days)	47%

*Table **8***. Initial screening of different reaction conditions. All experiments were set up in a purge box and conducted during an industrial placement at Vertex Pharmaceuticals. [a] Commercial ligands were used; [b] Determined by normal phase SFC using a chiral stationary phase; [c] No conversion by UPLC

and NMR; [d] Complex reaction mixture was formed; [e] Product was contaminated with unknown minor impurities which could not be fully separated by column chromatography. Levels of enantioselectivity were determined after analytical normal phase SFC separation.



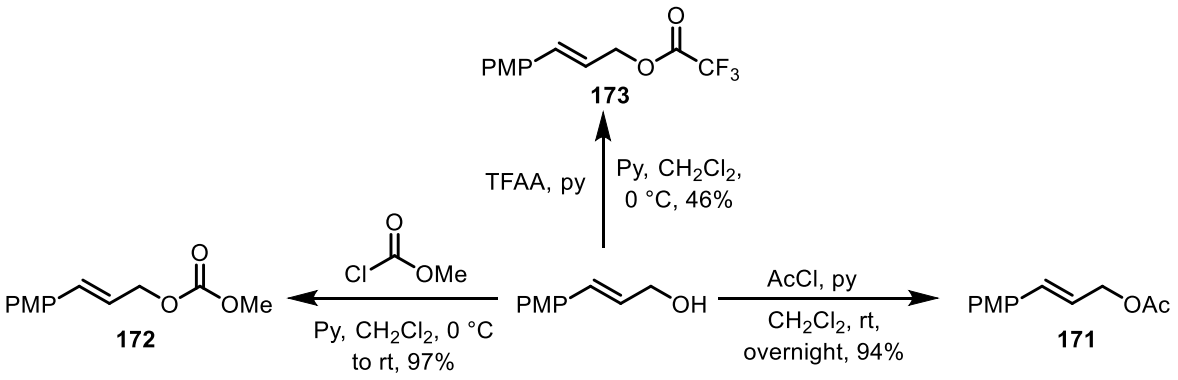
Phosphoramidite ligands

(*S*)-Carreira ligand, **L1**

(*S*, *S*, *S*)-**L2**

4.2.2 Further studies conducted at the University of Oxford

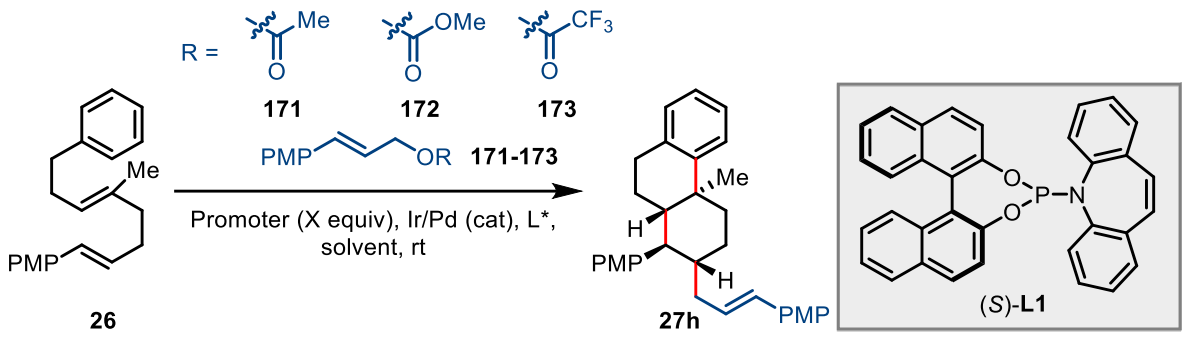
Upon completion of the industrial placement at Vertex Pharmaceuticals, further optimisation experiments were continued at the University of Oxford. It was decided to explore if a leaving group on the allylic alcohol could influence the reactivity. For this purpose, different alkylating reagents were prepared (Scheme **102**). 4-Methoxycinnamyl alcohol was converted to acetate **171** using acetyl chloride in an excellent 94% yield. Similarly, carbonate **172** was formed in 97% yield using methyl chloroformate. To form trifluoroacetate **173**, 4-methoxycinnamyl alcohol was reacted with TFAA in 46% yield. Quick column chromatography was necessary to minimise decomposition of acid sensitive trifluoroacetate **173**.



*Scheme **102***. Synthesis of different alkylating reagents.

With different alkylating reagents in hand, further system optimisation was continued (Table **9**). First, it was decided to repeat the best set of conditions identified at Vertex Pharmaceuticals

(Table **9**, entry 1). When conducted at the University of Oxford, 65:35 er and lower yield of product **27h** was obtained over 5 days. As before, product **27h** could not be fully separated from minor impurities even after multiple column chromatography purifications. An analytical sample of pure alkene **27h** was used to measure ee which was 17% lower than that obtained at Vertex Pharmaceuticals under identical conditions. The reason for the discrepancy between the results is unclear, however, it could be that the change in experimental set up has negatively impacted both the mass recovery and er of product **27h**. All experiments conducted at Vertex Pharmaceuticals were set up in a purge box, while the experiments conducted at the University of Oxford were done under the inert atmosphere created by purging. In addition, different batches of a commercially available ligand (*S*)-**L1** were used. When the reaction was performed using carbonate **172** (Table **9**, entry 2), no conversion was observed. On the other hand, with trifluoroacetate **173** a complex reaction mixture was afforded (Table **9**, entry 3). This could be explained by the instability of reactive trifluoroacetate **173** under the acidic conditions. Pd catalysis was also attempted under the new set of conditions using acetate **171** and carbonate **172**, however, in both cases no conversion was observed (Table **9**, entries 4-5). Finally, a control experiment using acetate **171** in the absence of Ir catalyst and ligand was conducted. Interestingly, similar conversion to product **27h** was observed over 5 days, suggesting that the racemic background reaction likely proceeds under Ir conditions as well.



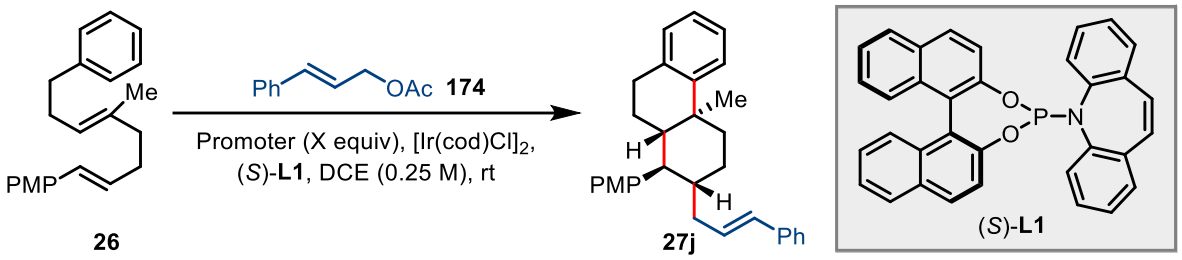
Entry	Electrophile (equiv)	catalyst	Ligand[a] (mol%)	Promoter (equiv)	Solvent (M)	**27h** Isolated	er[b]
1	**171** (1 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	29%[c] (5 days)	65:35
2	**172** (1 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	Trace[d]	ND
3	**173** (1 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	0%[e] (3 days)	ND
4	**171** (2 equiv)	$Pd_2(dba)_3$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	0%[d] (3 days)	ND
5	**172** (1 equiv)	$Pd_2(dba)_3$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	DCE (0.25 M)	0%[d] (3 days)	ND
6	**171** (1 equiv)	-	-	TFA (0.5 equiv)	DCE (0.25 M)	24%[c] (3 days)	ND

Table ***9***. Further reaction optimisation. [a] Commercial ligand from Sigma-Aldrich (Product number: 744646) was used; [b] er was calculated using normal phase HPLC with a chiral stationary phase; [c] Product was contaminated with unknown minor impurities which could not be fully separated by column chromatography. Levels of enantioselectivity were determined using analytical sample of **27h** isolated in sufficient purity; [d] No conversion; [e] Complex reaction mixture.

It was decided to change the system to minimise any racemic background reaction. It was hoped that this could improve er as well as give a cleaner conversion to product **169**. For this purpose, cinnamyl acetate **174** was prepared in 88% yield from cinnamyl alcohol. The control

experiment using acetate **174** and substrate **26** in the absence of Ir catalyst and (*S*)-**L1** ligand, did not afford alkene **27j** (Table **10,** entry 1). Thus, the removal of an electron-donating methoxy group from acetate **167** reduced its propensity for S_N1 type ionisation. Using acetate **174** under the most optimum conditions afforded product **27j** in low yield but with improved 83:17 er (Table **10**, entry 2). Unfortunately, isolation of pure alkene **27j** remained challenging with an analytical sample being used for er determination. Increasing the temperature to 60 °C improved the conversion and resulted in only slight drop in er (Table **10**, entry 3). Finally, it was found that $Zn(OTf)_2$ was more active promoter under the reaction conditions, furnishing higher conversion to product **27j** which was formed in 79:21 er (Table **10**, entry 4).

Although enantioselectivity levels with acetate **27j** were promising, the isolation issues were a significant drawback for the efficient screening of the reaction conditions and data analysis. Peak separation in crude ^{1}H NMR was poor, making NMR yields with an internal standard unreliable. Multiple chromatography purifications were necessary to isolate an analytical sample of the desired product for HPLC analysis. With product **27j** bearing four stereocenters, it could be that multiple diastereomers being formed as well as side-products from monocyclisation, which was hard to separate. It was therefore decided to simplify the system to avoid the issues associated with the polyene cyclisation cascade.



Entry	Electrophile (equiv)	catalyst	Ligand[a] (mol%)	Promoter (equiv)	T	**27j** Isolated	er[b]
1	**174** (1.5 equiv)	-	-	TFA (0.5 equiv)	rt	0%[c] (4 days)	ND
2	**174** (1.5 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	rt	17%[d] (4 days)	83:17
3	**174** (1.5 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	TFA (0.5 equiv)	60 °C	31%[d] (4 days)	80:20
4	**174** (1.5 equiv)	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	57%[d] (3 days)	79:21

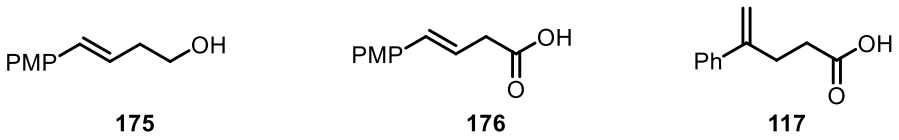
*Table **10***. Further reaction optimisation. [a] Commercial ligand from Sigma-Aldrich (Product number: 744646) was used; [b] er was calculated using normal phase HPLC with a chiral stationary phase; [c] No conversion; [d] Product was contaminated with unknown minor impurities which could not be fully separated by column chromatography. Levels of enantioselectivity were determined using analytical sample of **27j**.

4.3 Studies on enantioselective Ir-catalysed heterocyclisation *via* asymmetric allylic substitution

4.3.1 System development for the asymmetric heterocyclisation

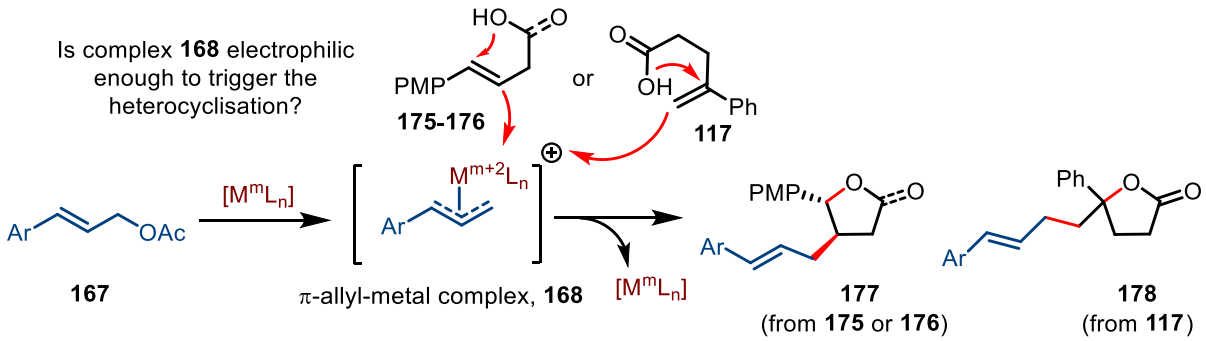
The attention was then turned to heterocyclisation reactions, in which a single ring is formed with up to two new stereocenters. It was decided to use the most optimum conditions for several different substrates with the aim to identify the most suitable system. Three different substrate classes were identified (Scheme **103**). Given that heterocyclisation was less efficient

for 6-membered ring formation, only 5-membered ring systems were considered. The cation-triggered cyclisation of homoallylic alcohol **175** and carboxylic acid **176** was previously studied in the Donohoe group,[58] while HFIP promoted cyclisation of carboxylic acid **117** was described in the previous chapter.



Scheme **103**. Substrates for heterocyclisation.

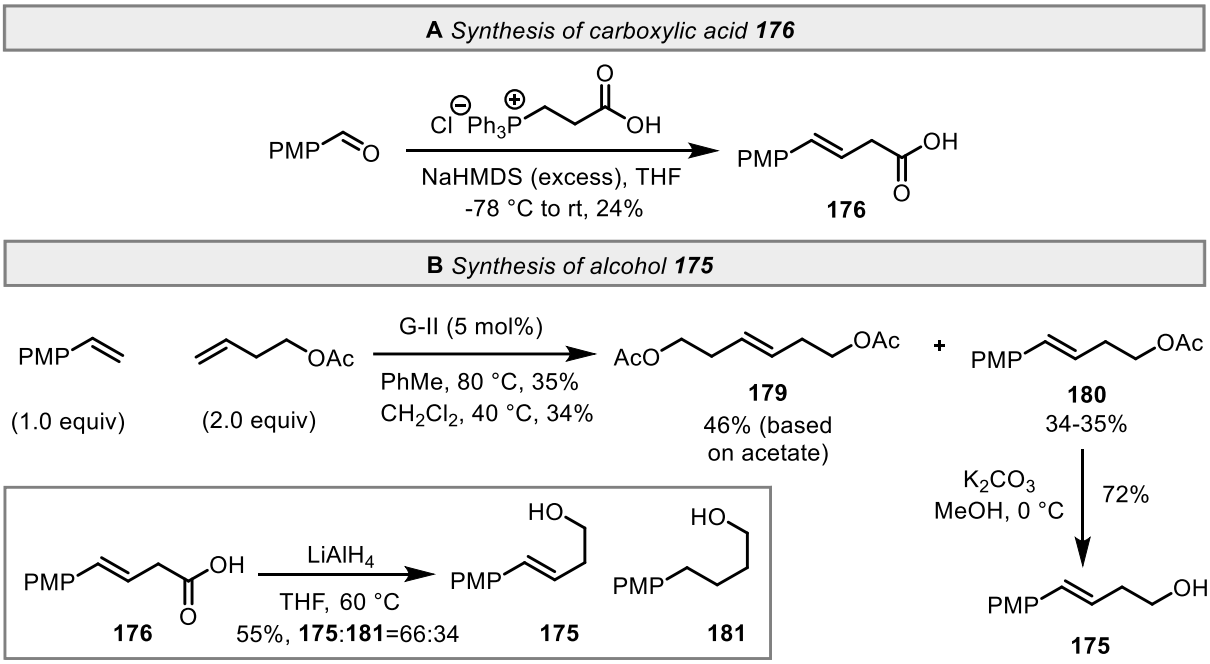
The proposed mechanistic pathway involves the formation of chiral π-allyl-metal complex **168** after the oxidative insertion of [M^mL_n] into allylic acetate **167** (Scheme **104**). π-Allyl-metal complex **168** could then trigger enantioselective heterocyclisation of substrates **175**-**176** and **117** to furnish products **177** or **178**.



*Scheme **104***. Proposed mechanistic pathway.

The synthesis of alcohol **175** and carboxylic acid **176** was achieved according to the reported literature procedures.[58] Wittig reaction between 4-methoxybenzaldehyde and (2-carboxyethyl)triphenylphosphonium chloride afforded carboxylic acid **176** in 24% yield as a single (*E*)-**176** isomer, consistent with the literature (Scheme **105**, A). Unfortunately, $LiAlH_4$ reduction of carboxylic acid **176** furnished an inseparable mixture between alcohol **175** and alcohol **181** in 55% combined yield (Scheme **105**, B). Therefore, a different approach was used to synthesise alcohol **175**. Cross-metathesis between 4-vinylanisole and but-3-en-1-yl

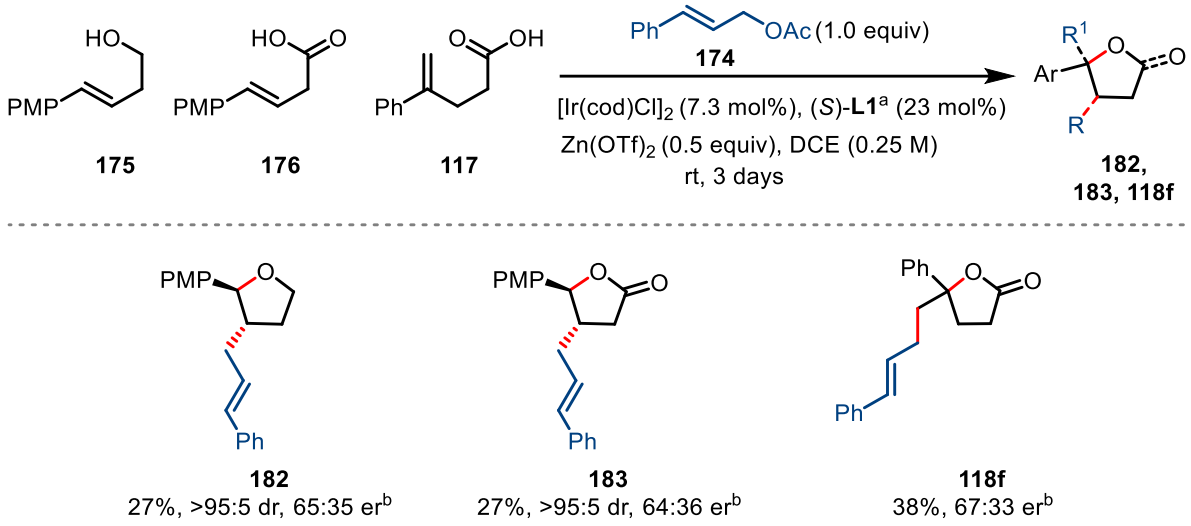
acetate using Grubbs 2nd generation catalyst afforded separable alkene **179** in 46% yield and alkene **180** in 34-35% yield depending on conditions. Excess of but-3-en-1-yl acetate was required to avoid dimerization of 4-vinylanisole. Finally, acetate hydrolysis proceeded smoothly to afford alcohol **175** in 72% yield. Synthesis of carboxylic acid **117** was achieved using the route described in the previous chapter (see Scheme **85**).



*Scheme **105***. Substrate synthesis.

With substrates **175**, **176** and **117** in hand, enantioselective Ir-catalysed heterocyclisation was attempted using the optimum conditions identified for the polyene system (Scheme **106**). Homoallylic alcohol **175** furnished tetrahydrofuran **182** in 27% yield and 65:35 er. Carboxylic acid **176** afforded lactone **183** in similar 27% yield and 64:36 er. Products **182** and **183** were formed as single *trans*-diastereomers. When carboxylic acid **117** was used under the reaction conditions, lactone **118f** was formed in 38% yield and 67:33 er. Most importantly, the isolation issues experienced in the polyene system were not encountered for heterocycles **182**, **183** and **118f**. Analysis of the ^{1}H crude NMR for all three reactions indicated low conversion with unreacted starting material being present. Furthermore, due to good peak separation in all three systems it would have been possible to use NMR yields for the reaction optimisation. To

conclude, enantioselective Ir-catalysed heterocyclisation appeared to be a more suitable system for the reaction optimisation then the polyene cyclisation cascade.



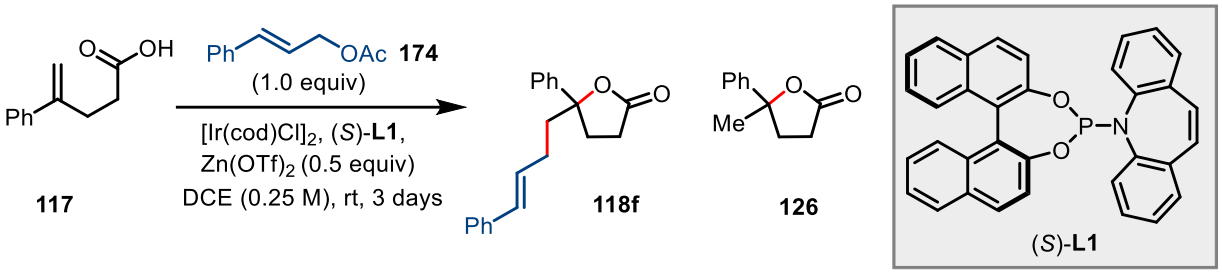
*Scheme **106***. Initial results for Ir-catalysed enantioselective heterocyclisation of substrates **175**, **176, 117**. Racemic samples of **182** and **183** were prepared according to the reported literature procedures.[58] Racemic sample for **118f** was synthesised as described in Chapter **3**. [a] Commercial ligand from Sigma-Aldrich (Product number: 744646) was used; [b] er was calculated using normal phase HPLC with a chiral stationary phase.

It was decided to first explore enantioselective lactonisation of carboxylic acid **117** given the slightly higher 37% yield and 67:33 er. Thus, further reaction optimisation was commenced.

4.3.2 Further studies on enantioselective lactonisation of substrate 117

First, a control experiment without Ir catalyst and ligand (*S*)-**L1** was conducted (Table **11**, entry 2). A trace amount of the desired lactone **118f** and side-product **126** was formed, suggesting that the racemic background reaction is not significant in this system. Increasing the temperature to 60 °C was detrimental to the reaction, lowering the er of the product **118f** to 58:42 and forming 56% of side-product **126** (Table **11**, entry 3). Then, the attention was turned to lower catalyst loadings before exploring the ligand scope. Conducting the reaction with 3 mol% of $[Ir(cod)Cl]_2$ and 6 mol% of (*S*)-**L1** afforded product **118f** in 10% isolated yield and 52:48 er (Table **11**, entry 4). Increasing the equivalents of ligand (*S*)-**L1** to 12 mol% significantly

improved the isolated yield to 50% and er to 65:35. This result might suggest that two phosphoramidite ligands are bound to one Ir metal in the active form of a catalyst, which is consisted with the literature reports.[121(b)]

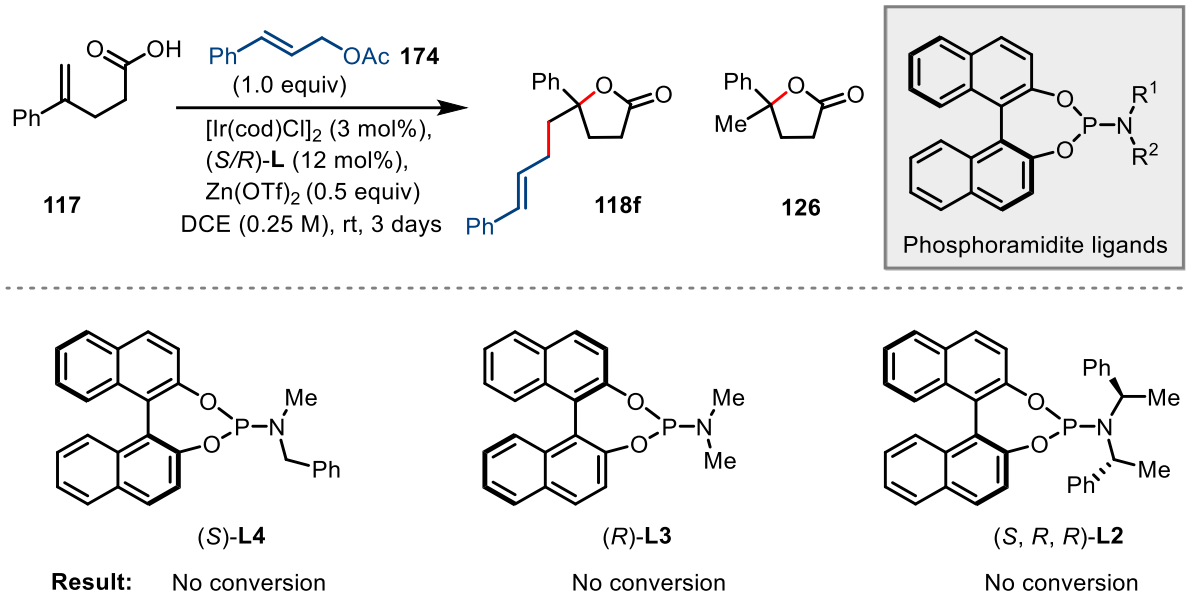


Entry	catalyst	Ligand[a] (mol%)	Promoter (equiv)	T	**118f** yield	**126** yield	er[b]
1	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	38%	Trace	67:33
2	-	-	$Zn(OTf)_2$ (0.5 equiv)	rt	Trace	Trace	ND
3	$[Ir(cod)Cl]_2$ (7.3 mol%)	**L1** (23 mol%)	$Zn(OTf)_2$ (0.5 equiv)	60 °C	(40%)	56%	58:42
4	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	10% (15%)	Trace	52:48
5	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	50% (67%)	Trace	65:35

*Table **11***. Further optimisation for enantioselective lactonisation of substrate **117**. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. [a] Commercial ligand from Sigma-Aldrich (Product number: 744646) was used; [b] er was calculated using normal phase HPLC with a chiral stationary phase.

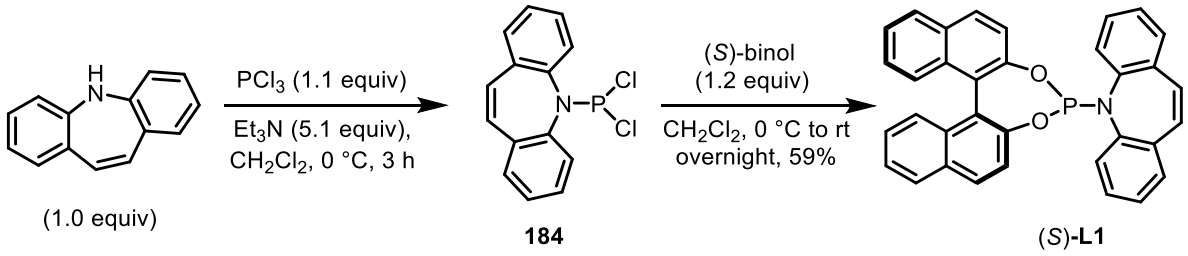
With lower catalyst loadings, different commercially available phosphoramidite ligands were tested in the enantioselective alkylative lactonisation of substrate **117** (Scheme **107**).

Unfortunately, the use of (*S*)-**L4**, (*R*)-**L3** and (*S*, *R*, *R*)-**L2** did not afford any conversion with only unreacted starting material **117** and **174** being observed by ^{1}H crude NMR in a 1:1 ratio.



*Scheme **107***. Ligand scope. All phosphoramidite ligands were purchased from commercial suppliers.

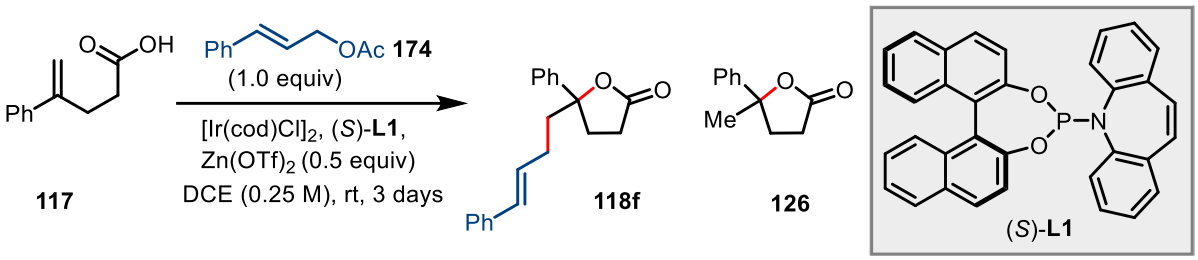
It was then decided to repeat the reaction using self-made phosphoramidite ligand (*S*)-**L1** as a control experiment. For this purpose, phosphoramidite (*S*)-**L1** was prepared following the two-step one pot literature procedure.[127] The reaction proceed *via in situ* formation of dibenzazepinyl dichlorophosphine **184**, followed by the addition of (S)-binol which afforded phosphoramidite (*S*)-**L1** in 59% yield. (Scheme **108**).



*Scheme **108***. Synthesis of phosphoramidite (*S*)-**L1**.

The enantioselective Ir-catalysed lactonisation of carboxylic acid **117** was then repeated using self-made ligand (*S*)-**L1** (Table **12**). Surprisingly, only trace conversion was observed under otherwise identical conditions with unreacted starting material **117** and **174** present by ^{1}H NMR

analysis (Table **12**, entry 1). The reaction using self-made ligand (*S*)-**L1** was repeated with the same outcome. After conducting the reaction with commercial (*S*)-**L1** ligand several times, reproducibility issues were encountered (Table **12**, entry 2); yield and er were found to vary depending on the experiment as well as batch of the commercial ligand purchased from the same supplier.



Entry	catalyst	Ligand (mol%)	**118f** yield	**126** yield	er[b]
1	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%) Self-made	Trace No conversion	Trace	ND
2	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%) commercial[a]	30% (37%)-50% (67%)	Trace	65:35-70:30

Table ***12***. Reproducibility issues with self-made and commercial (*S*)-**L1** ligand in the lactonisation system. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. [a] Different batches of commercial ligand were purchased from Sigma-Aldrich (Product number: 744646); [b] er was calculated using normal phase HPLC with a chiral stationary phase.

4.3.3 Reproducibility issues for asymmetric lactonisation of substrate 117

After a new batch of commercial (*S*)-**L1** ligand from Sigma-Aldrich had arrived, its ^{1}H and ^{31}P NMR was compared to self-made (*S*)-**L1** ligand (Figure **1**). Comparison of ^{1}H NMR data collected in C_6D_6 immediately upon the arrival of the commercial ligand indicated that the commercial (*S*)-**L1** ligand was impure. Purity level of self-made (*S*)-**L1** was calculated to be 98% using quantitative ^{1}H NMR analysis in C_6D_6 with an internal standard. For commercial

(*S*)-**L1** ligand, NMR yield in C_6D_6 calculated immediately upon arrival using the same method, technique and on the same scale was only 79%.

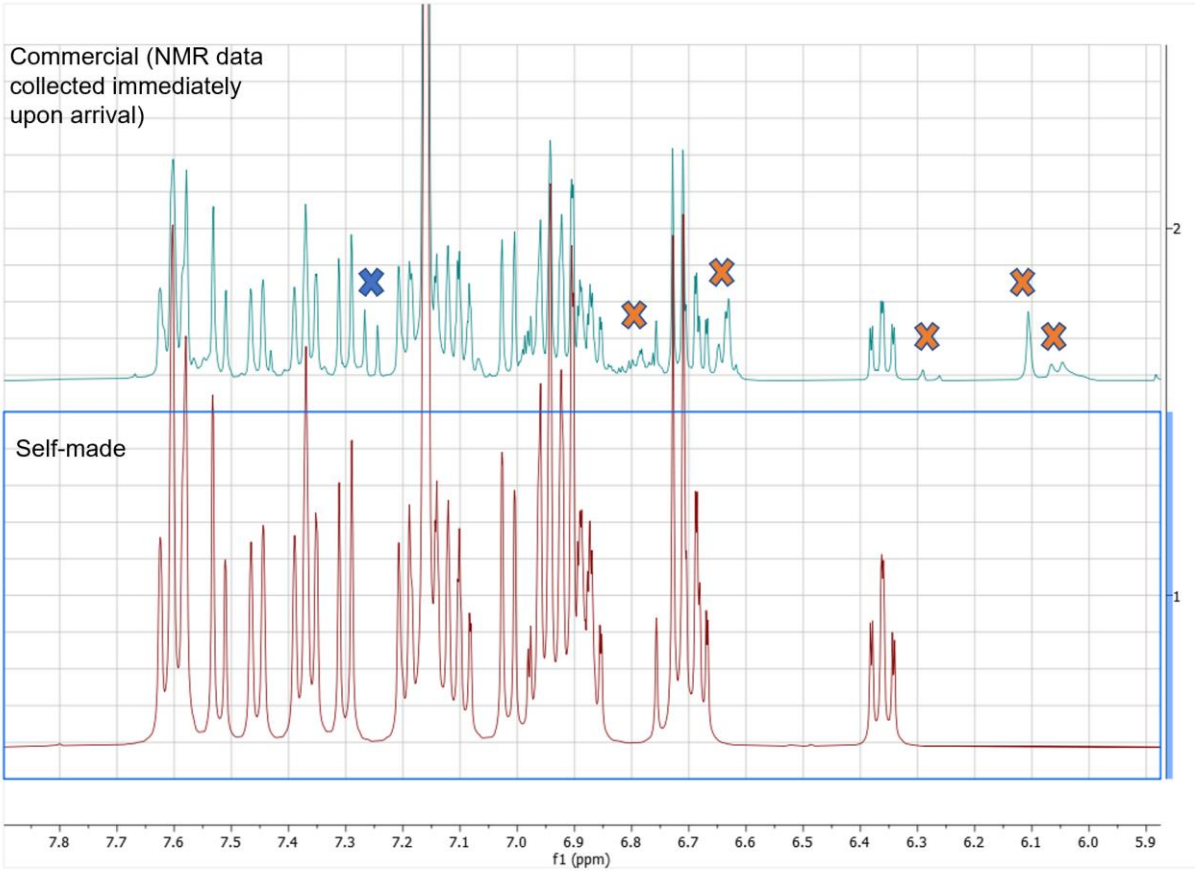


*Figure **1***. Comparison of ^{1}H NMR data collected in C_6D_6 for commercial (*S*)-**L1** ligand from Sigma-Aldrich (Product number: 744646; top, green) and self-made (*S*)-**L1** ligand (bottom, red). NMR data for commercial ligand was collected immediately upon the arrival.

Analysis of ^{31}P NMR data collected in C_6D_6 indicated that the commercial (*S*)-**L1** ligand contained other ^{31}P signals in addition to the desired signal at 138.4 ppm. Furthermore, while self-made ligand (*S*)-**L1** was stable in C_6D_6 over a two-week period, the commercial sample of (*S*)-**L1** rapidly decomposed with purity dropping to 33% after only 1 day in C_6D_6 (Figure **2**). After 1 day the major signal in ^{31}P NMR for the commercial (*S*)-**L1** ligand was at 13.3 ppm while the desired phosphoramidite ^{31}P signal completely disappeared over a two-week period.

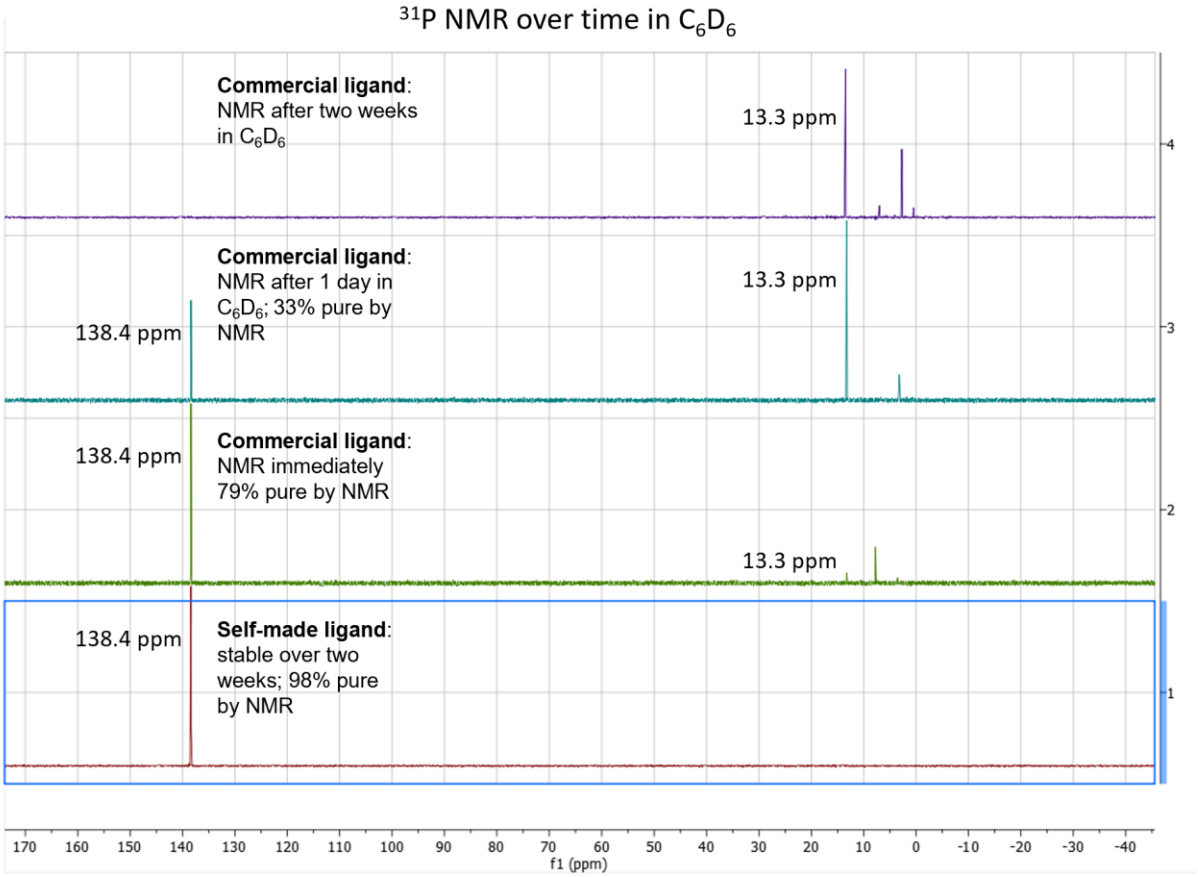
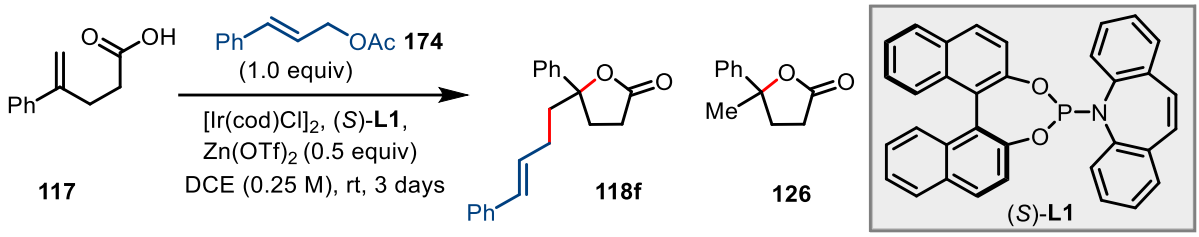


Figure **2**. Comparison of ^{31}P NMR data collected in C_6D_6 for commercial (*S*)-**L1** ligand from Sigma-Aldrich (Product number: 744646) and self-made (*S*)-**L1** ligand.

It was proposed that commercial (*S*)-**L1** ligand purchased from Sigma-Aldrich (Product number: 744646) contained some unidentified minor impurities that were beneficial for the reaction. To test this hypothesis, commercial (*S*)-**L1** ligand was purified by chromatography to afford pure sample of commercial (*S*)-**L1** ligand in 65% yield together with 11% of iminostilbene. The purified sample had identical ^{1}H and ^{31}P NMR to self-made (*S*)-**L1** ligand and was stable in C_6D_6. When a purified sample of commercial (*S*)-**L1** ligand was used in the reaction, only trace amounts of the desired lactone **118f** was detected by crude NMR with unreacted starting material **117** and **174** being the major species (Table **13**, entry 2). Since optimisation of ligand to Ir ratio was performed using unpurified commercial ligand (*S*)-**L1**, it was suggested to lower equivalents of pure self-made ligand (*S*)-**L1** to 9 mol% (Table **13**, entry 4). This resulted in improved 10% isolated yield of lactone **118f**, although the material was

nearly racemic. A further decrease in self-made (*S*)-**L1** ligand loading shut down the reaction. It was therefore concluded that the most likely explanation for the observed reproducibility issues are the impurities in the commercial sample of (*S*)-**L1** ligand. Finally, since iminostilbene was isolated after purifying the commercial sample, it was decided to spike the reaction with 4 mol% iministilbene and 4 mol% of (S)-binol when using self-made (*S*)-**L1** ligand (Table **13**, entry 5). Unfortunately, this did not improve the conversion to lactone **118f**.



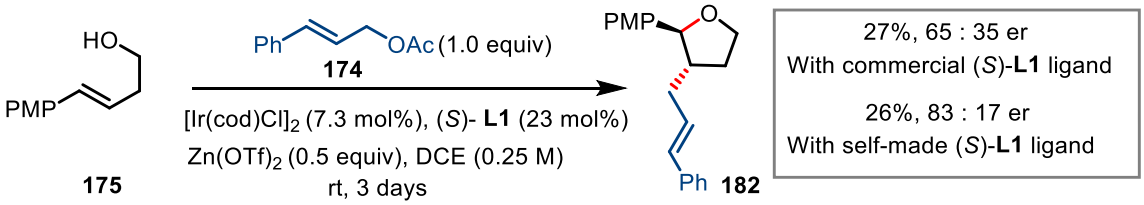
Entry	catalyst	Ligand (mol%)	Comment on (*S*)-**L1**	Additives	**118f** yield	**126** yield	er[a]
1	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%)	Commercial; unpurified	none	30-50%	Trace	65:35-70:30
2	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%)	Commercial; purified	none	Trace	Trace	ND
3	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%)	Self-made	none	Trace	Trace	ND
4	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (9 mol%)	Self-made	none	10% (11%)	Trace	52:48
5	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%)	Self-made	S-Binol (4 mol%) Iminostilbene (4 mol%)	0%	0%	ND

*Table **13***. Reproducibility issues with self-made and commercial (*S*)-**L1** ligand. Yields in brackets are NMR yields. Commercial ligand was purchased from Sigma-Aldrich (Product number: 744646); [a] er was calculated using normal phase HPLC with a chiral stationary phase.

Consequently, it was decided against further system optimisation for the enantioselective lactonisation of substrate **117**.

4.3.4 Studies on the enantioselective formation of tetrahydrofuran rings

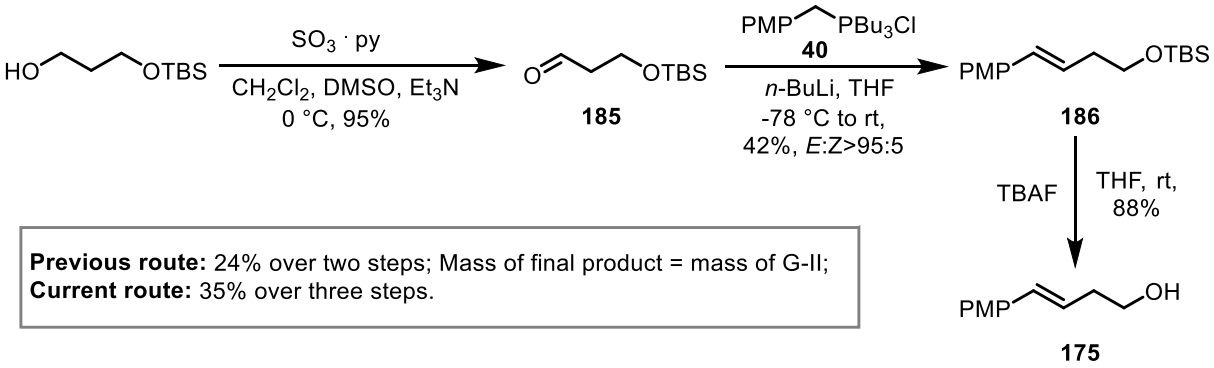
Following the reproducibility issues in the alkylative lactonisation of substrate **117**, it was decided to repeat Ir-catalysed heterocyclization in a different system. From this point in the project only self-made (*S*)-**L1** ligand was used. Attention was turned to the asymmetric synthesis of substituted tetrahydrofurans. Repeating Ir-catalysed heterocyclisation of homoallylic alcohol **175** with a self-made (*S*)-**L1** ligand furnished tetrahydrofuran **182** in 26% yield and 83:17 er (Scheme **109**). Although the yield of product **182** was similar to the one obtained with commercial (*S*)-**L1** ligand, a much higher er was encouraging. Thus, further studies on enantioselective cyclisation of homoallylic alcohol **175** commenced.



*Scheme **109***. Enantioselective formation of tetrahydrofuran **182** using self-made (*S*)-**L1** ligand.

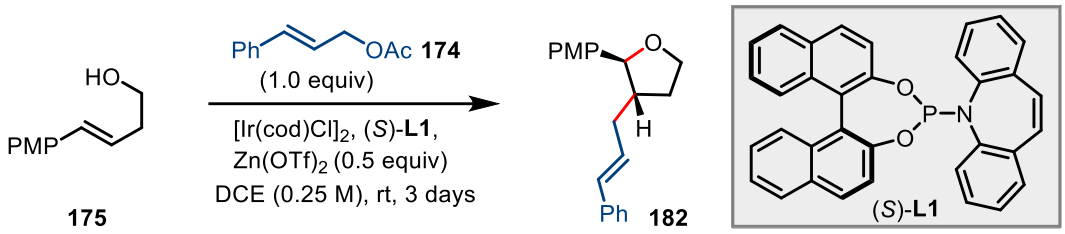
First, it was necessary to find a more efficient synthetic route towards homoallylic alcohol **175**. The previous approach *via* cross metathesis suffered from a few drawbacks (see Scheme **105**). The major being that mass of product **175** at the end of the sequence was found to be roughly equal to the mass of 2nd generation Grubbs catalyst required in step 1. Thus, this approach was considered unscalable. To solve this problem, a different synthetic route to access homoallylic alcohol **175** was designed (Scheme **110**). First, commercially available 3-[[*tert*-butyl(dimethyl)silyl]oxy]-1-propanol was oxidised to aldehyde **185** in 95% yield under Parikh–Doering conditions. A Wittig reaction between aldehyde **185** and tributylphosphonium salt **40** afforded alkene **186** in 42% yield with an excellent (*E*)-selectivity. Finally, TBS deprotection furnished the desired alcohol **175** in 88% yield. Overall, substrate **175** was

obtained in 35% yield over three steps, an improvement from the previous result of 24% yield over two steps.



*Scheme **110***. Synthetic route to access homoallylic alcohol **175**.

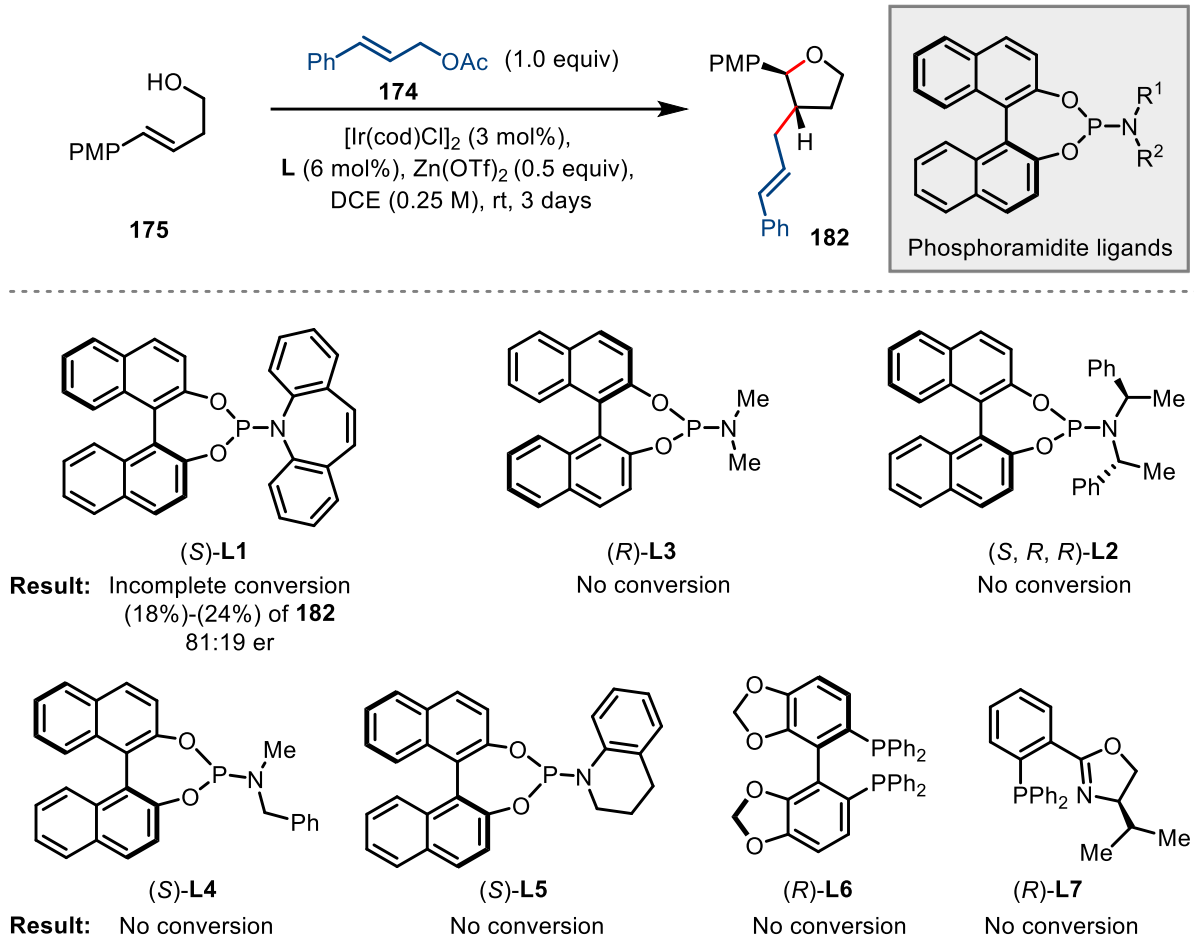
With the scalable route to access homoallylic alcohol **175** in hand, optimisation of the reaction conditions was continued. First, the effect of the ligand to Ir ratio was investigated (Table **14**). For this system the optimum ratio was found to be 1:1 between Ir metal and (*S*)-**L1** ligand (Table **14**, entry 1). With 3 mol% of $[Ir(cod)Cl]_2$ and 6 mol% of (*S*)-**L1** ligand product **182** was formed in 24% yield by NMR and with 81:19 er. This experiment was repeated several times and the results were found to be consistent, with yields varying between 18% and 24%. Increasing the amount of ligand was detrimental for the conversion (Table **14**, entries 2-3). When the reaction was repeated at 60 °C, a complex reaction mixture was formed with 15% of the desired product **182** by NMR (Table **14**, entry 5). In addition, it was shown that under the conditions from entry 1, the conversion to product **182** slowly increased over the course of 3 days with 10% NMR yield of product **182** being formed after 24 hours. However, leaving the reaction longer did not improve the conversion to product **182** above 24%.



Entry	catalyst	Ligand[a] (mol%)	Promoter (equiv)	T	**182** yield	**174** remaining	er[b]
1	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	(18%)-(24%)	(41%)-(37%)	81:19-83:17
2	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (9 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	(11%)	(73%)	83:17
3	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (12 mol%)	$Zn(OTf)_2$ (0.5 equiv)	rt	(6%)	(89%)	ND
5	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	$Zn(OTf)_2$ (0.5 equiv)	60 °C	(15%)	Trace	ND

Table ***14***. Initial reaction optimisation. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. [a] self-made (*S*)-**L1** ligand was used for all experiments; [b] er was calculated using normal phase HPLC with a chiral stationary phase. Analytical samples required for er determination were isolated using semi-prep TLC.

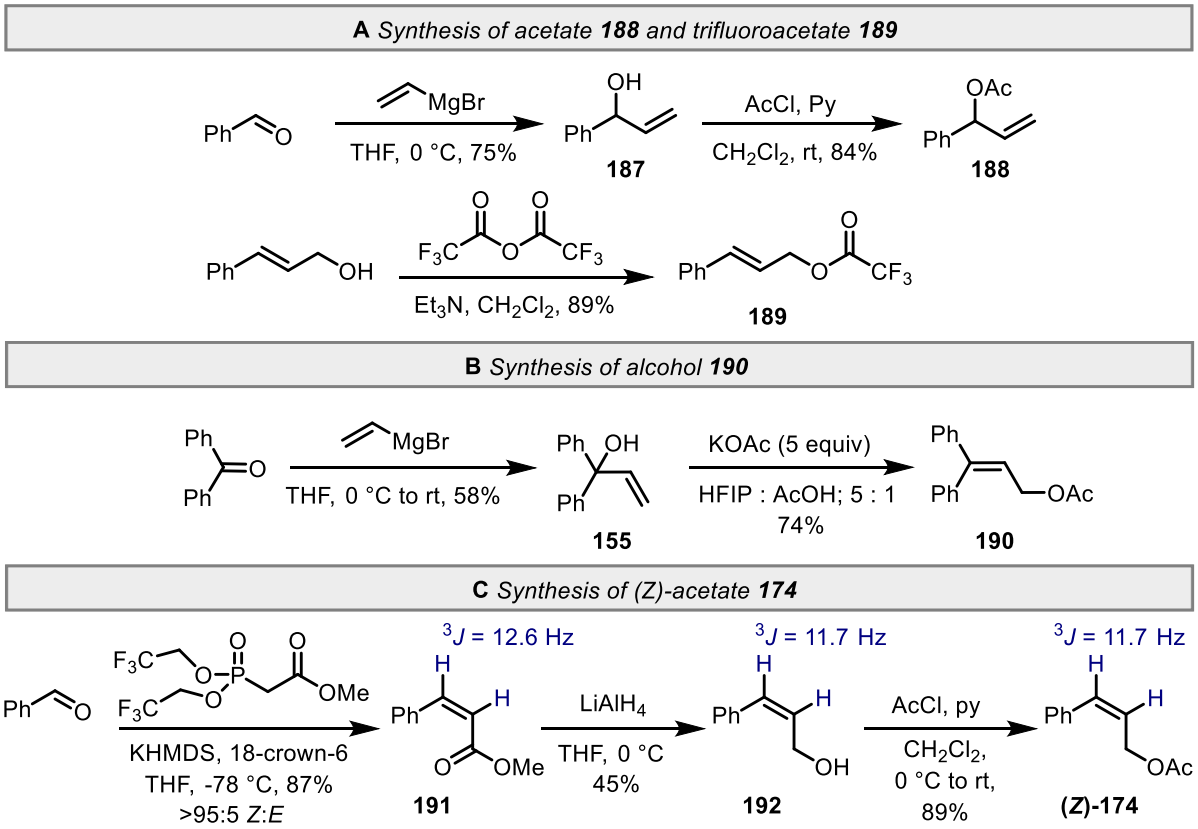
Next, ligands, previously shown to be highly efficient in Ir-catalysed enantioselective allylic substitution reactions were tested (Scheme **111**).[121] Unfortunately, the use of other phosphoramidite ligands, as well as (*R*)-SEGPHOS **L6** and phosphinooxazoline ligand **L7**, did not afford any of the desired product **182**, with no conversion observed in all cases. These results highlight the unique role of (*S*)-**L1** ligand in enantioselective Ir-catalysed allylic substitutions, an observation commonly reported in the literature.[121,125]



*Scheme **111***. Ligand scope. All ligands except for (*S*)-L**1** were purchased from the commercial suppliers. Purity of commercial ligands have been confirmed by ^{1}H and ^{31}P NMR analysis prior to use.

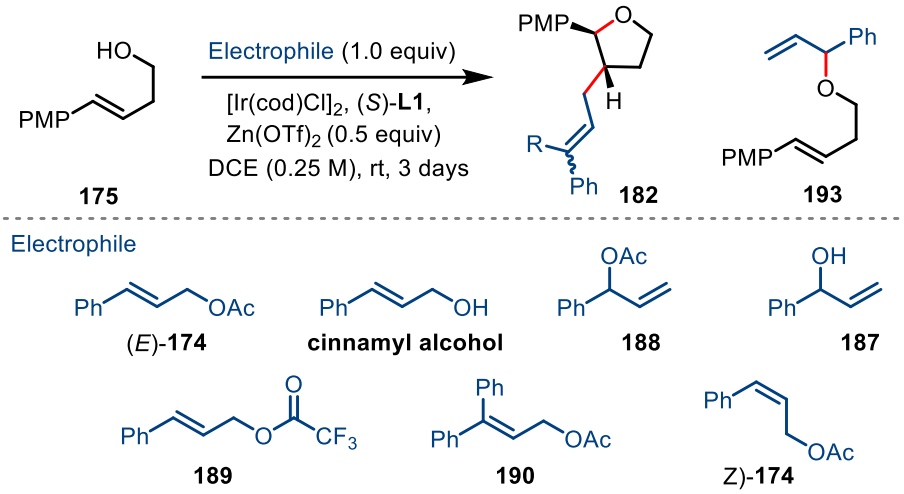
The attention was then turned to different alkylating agents, with the hope to improve conversion. At this point it was thought that if the yield of product **182** could be improved, then derivatives of (*S*)-**L1** ligand would be synthesised with the aim to further improve the reaction yield and enantioselectivity. It was decided to change the leaving group on cinnamyl alcohol, as well as trying other allylic alkylating reagents. In the previous work, 3,3-diphenylallyl alcohol **154** was found to be an efficient initiator for the heterocyclisation reactions, so 3,3-diphenylallyl acetate **190** was considered to be a promising electrophile in the asymmetric system. It was also decided to use (*Z*)-cinnamyl acetate **174** in the enantioselective heterocycliation, following the reports from You and coworkers on Ir-catalysed (*Z*)-retentive asymmetric allylic substitution *via* indole dearomatisation.[124] Synthesis of alkylating reagents then commenced

with cinnamyl alcohol derivatives **188** and **189** (Scheme **112**, A). The addition of vinyl magnesium bromide to benzaldehyde afforded secondary alcohol **187** in 75% yield. Acetate **188** was then readily obtained in 84% by acetylation of alcohol **187** with AcCl. Trifluoroacetate **189** was synthesised in one step in 89% yield using TFAA. To access acetate **190**, vinyl magnesium bromide was added to benzophenone in 58% yield, followed by rearrangement in HFIP in the presence of KOAc to afford acetate **190** in 74% yield (Scheme **112**, B). Finally, the synthesis of (*Z*)-acetate **174** commenced with a Still–Gennari olefination of benzaldehyde to furnish ester **191** in 87% yield with an excellent (*Z*)-selectivity (Scheme **112**, C).[128] The alkene stereochemistry was proven by ^{3}J coupling constant of 12.6 Hz. $LiAlH_4$ reduction proceeded in 45% yield followed by acetylation to afford (*Z*)-acetate **174** in 89% yield.



*Scheme **112***. Synthesis of electrophiles.

With these new alkylating reagents in hand, the Ir-catalysed enantioselective heterocyclisation of homoallylic alcohol **175** was attempted (Table **15**). When cinnamyl alcohol was used as an electrophile, 12% of the desired product **182** with 85:15 er was formed (Table **15**, entry 2).

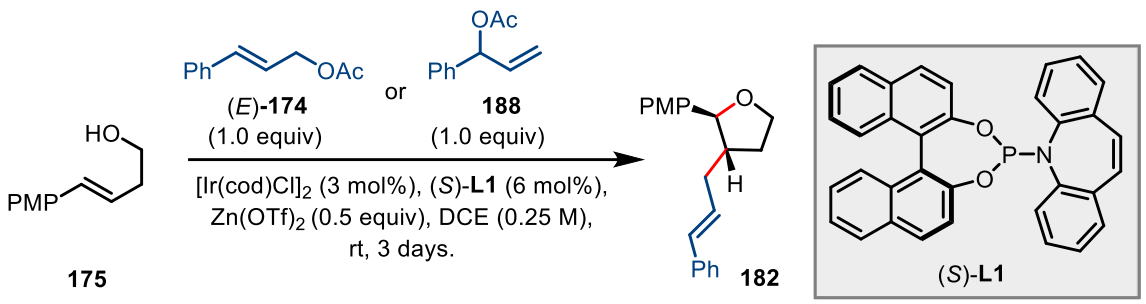


Entry	catalyst	Ligand[a] (mol%)	Electrophile	**182** yield	**193** yield	er[b]
1	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	(*E*)-**174**	(18%)-(24%)	0%	81:19-83:17
2	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	**Cinnamyl alcohol**	(12%)	0%	85:15
3	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	**188**	(24%)	0%	53:47
4	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	**187**	0%	23%	ND
5	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	**189**	19%	0%	75:25
6	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	**190**	0%	0%	ND
7	$[Ir(cod)Cl]_2$ (3 mol%)	**L1** (6 mol%)	(*Z*)-**174**	0%	0%	ND

Table ***15***. Electrophile scope. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. [a] self-made (*S*)-**L1** ligand was used for all experiments; [b] er was calculated using normal phase HPLC with a chiral stationary phase. Analytical samples required for er determination were isolated using semi-prep TLC.

With secondary acetate **188**, a higher yield of product **182** was observed, however the er of tetrahydrofuran **182** was much lower (Table **15**, entry 3). Interestingly, secondary alcohol **187** afforded 23% of ether **193** with no desired product **182** being formed (Table **15**, entry 4). The use of trifluoroacetate **189** furnished tetrahydrofuran **182** in 19% isolated yield but lower 75:25 er, compared to acetate (*E*)-**174** (Table **15**, entry 5). In all cases, low conversion was observed after 3 days with significant amount of starting material **175** and the corresponding electrophile remaining. Finally, the use of acetate **190** and (*Z*)-**174** did not lead to any product **182** formation (Table **15**, entries 6-7). Instead, no conversion was observed for both reactions. When Ir-catalysed cyclisation of substrate **175** with (*Z*)-**174** was heated to 60 °C instead of being conducted at room temperature, a complex reaction mixture was furnished. Therefore, only allylic acetate (*E*)-**174** was found to be a suitable electrophile for the Ir-catalysed asymmetric heterocyclisation of alcohol **175**.

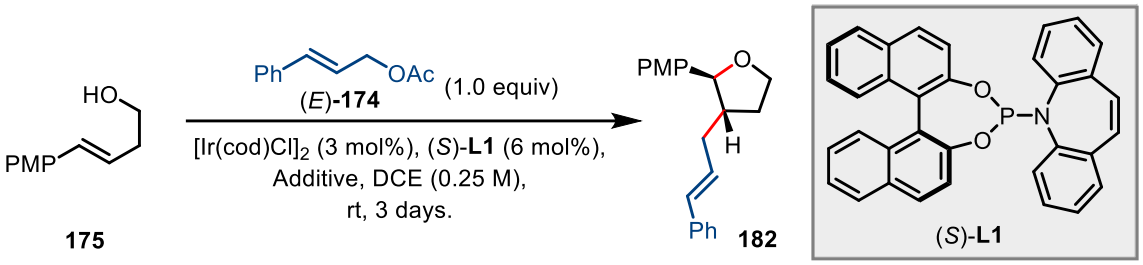
To explain why product **182** from the reaction with secondary acetate **188** was formed in much lower er, control experiments without Ir catalyst and (*S*)-**L1** ligand were conducted (Table **16**). With primary acetate (*E*)-**174**, no racemic background reaction proceeds in the absence of a catalyst, hence higher er (Table **16**, entry 2). With secondary acetate **188**, on the other hand, 23% of product **182** was isolated when the reaction was conducted in the absence of $[Ir(cod)Cl]_2$ and (*S*)-**L1** ligand (Table **16**, entry 4). The yield of racemic reaction is similar to the yield of Ir-catalysed reaction when acetate **188** is used (Table **16**, entries 3 and 4). Therefore, a significant background reaction proceeds with secondary acetate **188**, explaining nearly racemic material.



Entry	catalyst	Ligand[a] (mol%)	Electrophile	**182** yield	er[b]
1	[Ir(cod)Cl]$_2$ (3 mol%)	**L1** (6 mol%)	(*E*)-**174**	(18%)-(24%)	81:19
2	-	-	(*E*)-**174**	0%[c]	ND
3	[Ir(cod)Cl]$_2$ (3 mol%)	**L1** (6 mol%)	**188**	(24%)	53:47
4	-	-	**188**	23% (25%)	ND

Table ***16***. Control experiments. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. [a] self-made (*S*)-**L1** ligand was used for all experiments; [b] er was calculated using normal phase HPLC with a chiral stationary phase. Analytical samples required for er determination were isolated using semi-prep TLC; [c] No conversion.

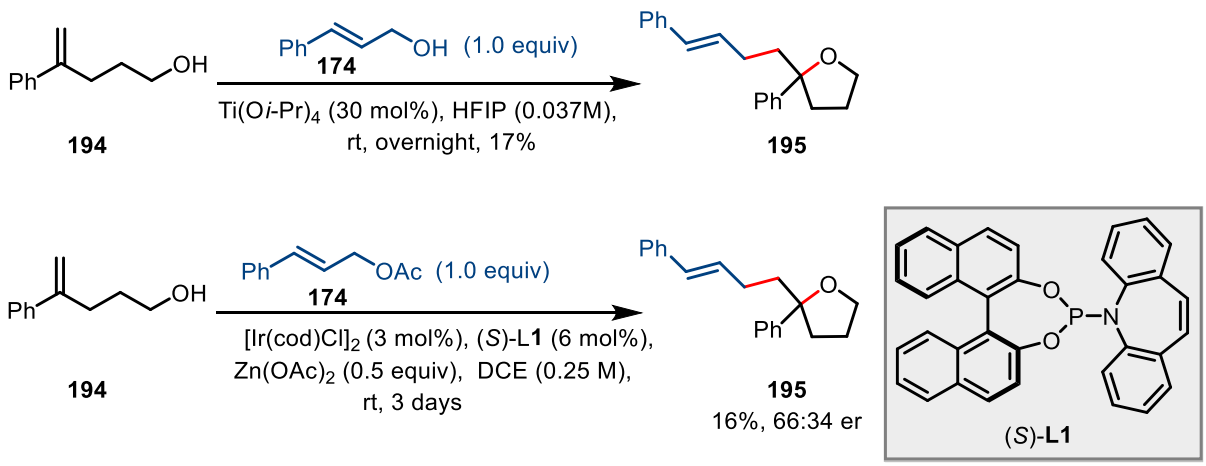
An extensive literature search indicated that additives play a significant role in many Ir-catalysed asymmetric allylic substitution reactions and can enhance conversion and reaction yield.[121,125,129] Thus, a screen of different Lewis and Brønsted acids was performed (Table **17**). Conducting the reaction with 100 mol% of Zn(OTf)$_2$ or with reduced loading of 20 mol%, was not beneficial (Table **17**, entries 2-3). Without additive, no conversion was observed (Table **17**, entry 4). The same result was obtained with Brønsted acids as well as monovalent Lewis acids (Table **17**, entries 5-9). Interestingly, the use of AgOTf furnished product **182** in 23% isolated yield but with a lower 76:24 er (Table **17**, entry 10). Divalent and trivalent Lewis acids afforded a complex reaction mixture with trace amounts of product **182**, alcohol starting material **175** and acetate (*E*)-**174** remaining (Table **17**, entries 11-14). It therefore appears that Zn(OTf)$_2$ and AgOTf Lewis acids balance the reactivity of the system to some extent, enabling some product formation in similar yields and in 81:19 er and 76:24 er respectively.



Entry	Additive	Loading of additive	**182** yield	er[a]
1	$Zn(OTf_{)2}$	50 mol%	(24%)	81:19
2	$Zn(OTf)_2$	100 mol%	(11%)	83:17
3	$Zn(OTf_{)2}$	25 mol%	(14%)	ND
4	-	-	0%[b]	ND
5	AcOH	50 mol%	0%[b]	ND
6	TFA	50 mol%	Trace[b]	ND
7	LiCl	50 mol%	0%[b]	ND
8	LiOTf	50 mol%	0%[b]	ND
9	$Cu(OTf)\cdot C_6H_6$	50 mol%	0%[b]	ND
10	AgOTf	50 mol%	23%	76:24
11	$Cu(OTf)_2$	50 mol%	7%[c]	50:50
12	$Sc(OTf)_3$	50 mol%	Trace[c]	ND
13	$Fe(OTf)_3$	50 mol%	Trace[c]	ND
14	$In(OTf)_3$	50 mol%	Trace[c]	ND

Table ***17***. Additive scope. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. Self-made (*S*)-**L1** ligand was used for all experiments. [a] er was calculated using normal phase HPLC with a chiral stationary phase. Analytical samples required for er determination were isolated using semi-prep TLC; [b] No conversion; [c] Complex reaction mixture.

It was then decided to change the system and try the most optimum conditions using substrate **194**, designed for *5-exo-trig* cyclisation (Scheme **113**). The racemic reaction between substrate **194** and primary allylic alcohols using the cation-triggered methodology did not work well (see Megan Jaschinski's Part II thesis; 2023). However, by changing the Lewis acid it was possible to isolate racemic material in 17% yield. Unfortunately, under the Ir-catalysed conditions, complex reaction mixture was afforded from which product **195** was isolated in low 16% yield and 66:34 er.

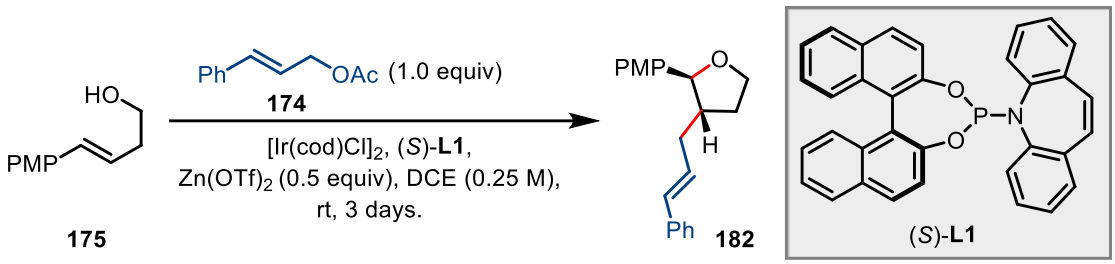


*Scheme **113***. Enantioselective cyclisation of substrate **194** under the optimised conditions. Substrate **194** was synthesised by Megan Jaschinski (see Megan Jaschinski's part II thesis **2023**). Self-made (*S*)-**L1** ligand was used.

As a final study on Ir-catalysed asymmetric heterocyclisation of substrate **175**, the effect of elevated catalyst loadings was explored (Table **18**). Indeed, increasing catalyst loadings improved yield of product **182** while the er did not change significantly. However, even with 6 mol% of Ir dimer, incomplete conversion was observed with only 37% of product **182** isolated in 83:17 er (Table **18**, entry 3). These findings might suggest that the catalyst deactivation under the reaction conditions is partially responsible for incomplete conversion and low yields observed.

At this point the decision was made to cease further attempts to optimise the Ir catalysed enantioselective heterocyclisation to access tetrahydrofuran scaffolds. Challenging reaction

optimisation and potential Ir catalyst deactivation in the tetrahydrofuran system deterred us from pursuing additional efforts to improve the reaction. It was also decided against optimising other systems, given the limited time left for the DPhil project.



Entry	catalyst	Ligand[a] (mol%)	**182** yield	er[b]
1	$[Ir(cod)Cl]_2$ (3 mol%)	(*S*)-**L1** (6 mol%)	(18%)-(24%)	81:19-83:17
2	$[Ir(cod)Cl]_2$ (5 mol%)	(*S*)-**L1** (10 mol%)	23% (28%)	84:16
3	$[Ir(cod)Cl]_2$ (6 mol%)	(*S*)-**L1** (12 mol%)	37%	83:17

*Table **18***. The use of elevated catalyst loadings. Yields in brackets are NMR yields calculated using 1,1,2,2-tetrachloroethane as an internal standard. [a] self-made (*S*)-**L1** ligand was used for all experiments. [b] er was calculated using normal phase HPLC with a chiral stationary phase. Analytical samples required for er determination were isolated using semi-prep TLC.

4.4 Summary and outlook

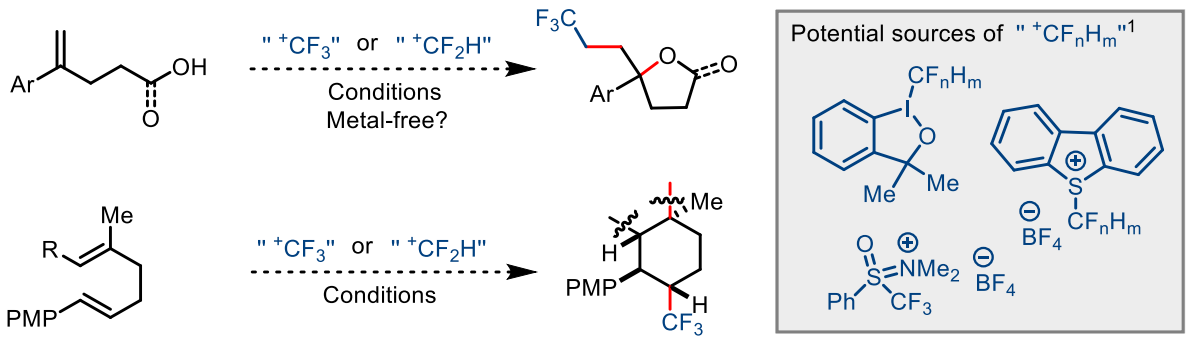
An asymmetric polyene cyclisation using Ir catalysis under the conditions described in this chapter could not be fully explored due to the isolation problems. Reproducibility issues were encountered when employing carboxylic acids as intramolecular nucleophiles, with the problem most likely stemming from the utilization of the commercial (S)-Carreira ligand **L1**. Although the initial results for the asymmetric synthesis of substituted tetrahydrofuran rings were promising, the extensive reaction optimisation did not improve the reaction. Potential catalyst deactivation might suggest that a more specialised reaction set-up, such as a glove box, is required to do this transformation. Alternatively, the substrate could be made more

reactive by substituting a PMP group with a more electron-rich aryl group, thus increasing nucleophilicity of the adjacent alkene. This could lower the reaction time and improve the conversion before the catalyst gets deactivated. Finally, other strategies to control the absolute configuration upon cyclisation could be explored.

Chapter 5: Conclusion and Future Work

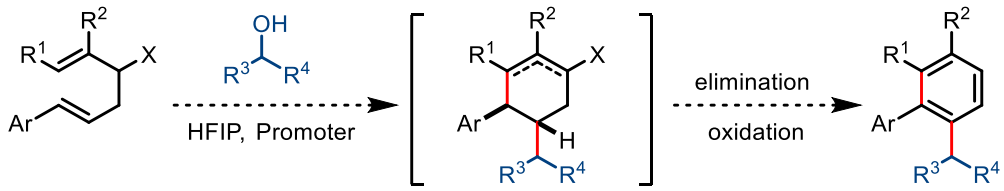
This thesis describes the successful development of carbocation-induced polyene cyclisation and lactonisation transformations. The key aim of achieving high diastereoselectivity upon forming new chiral centres has been accomplished. The diastereoselective polyene cyclisation methodology enables the use of readily available alcohols as precursors to trigger cascade cyclisations which set up a new exocyclic C-C bond. The application of this methodology has been demonstrated by synthesizing steroid analogies and completing formal synthesis of (±)-18-nor-estradiol. The alcohol-HFIP strategy was then applied to achieve novel *5/6-exo-trig* alkylative lactonisation with the formation of quaternary stereocenters. This transformation allows us to explore new chemical space, unavailable with the previously described cation-triggered *5/6-endo-trig* heterocyclisation protocols.

While the developed transformations enable underexplored carbon electrophile-induced cascade processes, significant progress remains to be achieved in this area. The use of other intermolecular carbon-based initiators could be explored in the future work. The application of fluorine-containing carbon electrophiles, such as CF_3-X or CF_2H-X could be particularly interesting (Scheme **114**).[130] The polyene cyclisation described in this thesis has been briefly attempted using Eschenmoser's salts, aldehydes and orthoesters as intermolecular initiators, however with no success. This might suggest that different set of conditions are required.



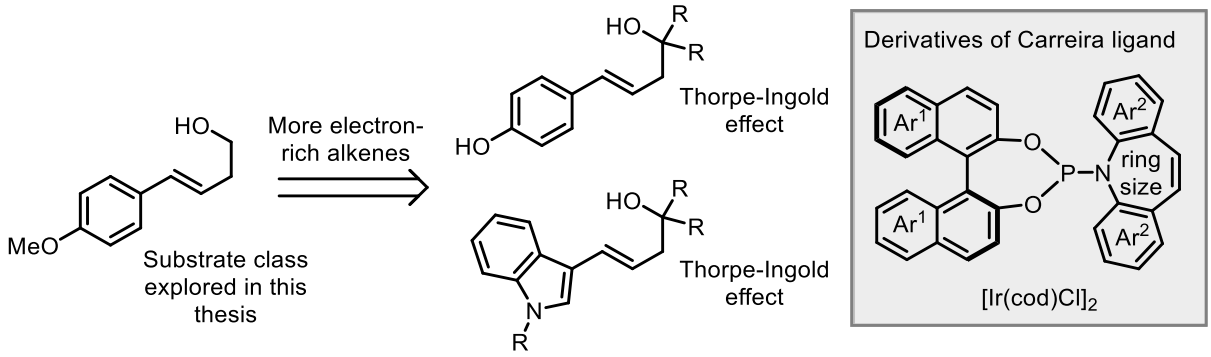
*Scheme **114***. Potential use of fluorine-containing carbon-electrophiles.

Furthermore, it could be interesting to combine the cation-triggered carbocyclisation with other reactions. For example, at the beginning of the project synthesis of cyclohexenes **12** was pursued. The issue of unselective E1 elimination was solved by introducing an intramolecular nucleophile, capable of trapping the build-up of a positive charge. Another option could be to aromatise the system to access polysubstituted aromatic rings (Scheme **115**). While this sequence would remove the 3D aspect of the cation-triggered cyclisation, it could enable the synthesis of densely substituted aryl rings that are difficult to form using other methods.



*Scheme **115***. Combining the cation-triggered cyclisation with oxidation.

The research described in this thesis concluded with the preliminary studies towards enantioselective Ir-catalysed carbo- and heterocyclisation. For the asymmetric synthesis of substituted tetrahydrofurans, promising levels of enantioselectivity were achieved using (*S*)-Carreira ligand. To improve conversion and the reaction yield, it might be necessary to change the system (Scheme **116**). Alkenes could be made more nucleophilic by changing to an electron-rich aromatic group. In addition, substituents on the carbon skeleton could be introduced to facilitate the cyclisation through the Thorpe–Ingold effect.[131] In addition, the ligand scope could be expanded to include derivatives of Carreira's ligand. Finally, other strategies to control the absolute configuration of newly formed carbon centers upon carbon-electrophile-triggered cyclisation could be explored.



Scheme **116**. Future work for Ir-catalysed enantioselective heterocyclisation.

Chapter 6: Experimental Data and Procedures

Supporting information

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6.1 General remarks

Reaction Setup: Microwave vials and vial caps (containing a resealing Silicone/PTFE septum) were purchased from Kinesis (Cole-Palmer) and were used without flame-drying. Unless otherwise stated, all other reactions were performed in flame-dried glassware equipped with a stir bar using standard Schlenk techniques under an atmosphere of N_2. Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of –17 °C were obtained using a salt/ice bath. Temperatures of –78 °C were obtained using a dry ice/acetone bath. Reflux conditions were obtained using an oil bath equipped with a contact thermometer. Other temperatures were obtained using a Julabo FT902 immersion cooler.

Reagents and solvents: Unless detailed below or otherwise stated, all reagents and solvents were purchased and used as supplied from Sigma-Aldrich (now Merck KGaA), Thermo Fisher Scientific (including Alfa Aesar and Acros Organics), Fluorochem, Honeywell, Tokyo Chemical Industry, Apollo Scientific, Manchester Organics (part of Navin Fluorine Int. Ltd.) and Strem Chemicals.

Anhydrous DMSO and Et_3N were purchased from Sigma-Aldrich in Sure/SealTM bottles. Anhydrous Et_2O, CH_2Cl_2, MeOH, THF and toluene were obtained from MBRAUN SPS-5 solvent purification system by passage through double filtration columns under N_2. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) was purchased from Fluorochem. Ti(O*i*-Pr)$_4$ (≥97%) was purchased from Sigma-Aldrich. Alcohols were purchased from commercial suppliers or prepared using standard literature procedures unless otherwise stated.

Chromatography: Thin layer chromatography (TLC) was performed on pre-coated aluminium (200 μm) Merck Kieselgel 60 F254 plates, visualised using UV irradiation (λ = 254 nm) and/or staining with potassium permanganate (KMnO4), vanillin, or phosphomolybdic acid (PMA) solutions. Purification by flash column chromatography was performed with Merck Kieselgel 60 (40– 63 μm) or (15–40 μm) silica gel using head pressure by means of a nitrogen line. All solvents used for chromatography were HPLC grade or equivalent and supplied by Honeywell, Sigma-Aldrich or Thermo Fisher Scientific.

Nomenclature: Systematic names were generated by the software ChemDraw according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). Conventional names are also provided for reference where applicable. All compounds reported are racemates, and stereodescriptors drawn in the structures are relative. For *meso* and other symmetric achiral cyclic compounds, the prefixes *cis* and *trans* are used for clarity where appropriate.

Compound Numbering: Where applicable, atom numbering shown does not follow IUPAC numbering and is therefore different to the compound name.

Melting points: Melting points (M.p.) were obtained using a Eisco Melting Point Apparatus 230V, 50-60Hz and are uncorrected. Melting points were measured on a mixture when compounds could not be separated by column chromatography.

Infrared spectroscopy: Fourier-transform infrared (FT-IR) spectra were recorded from evaporated films on a Bruker Tensor 27 spectrometer equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers (ν_{max}) with units of cm^{-1} and for the range of 3600–600 cm^{-1}. IR spectra were measured on a mixture when compounds could not be separated by column chromatography.

NMR spectroscopy: ^{1}H and ^{13}C NMR experiments were carried out using Bruker NMR spectrometers (400, 500, 600 or 700 MHz for ^{1}H NMR) in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted to the nearest 0.1 hertz (Hz) and are presented as observed. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet), dd (double of doublets), dt (doublet of triplets), dq (doublet of quartets), td (triplet of doublets), tt (triplet of triplets), tq (triplet of quartets), ddd (doublet of doublets of doublets), ddt (doublet of doublets of triplets), dddd (doublet of doublet of doublet of doublets), qd (quartet of doublets) and m (multiplet). ^{1}H and ^{13}C NMR peaks for diastereomers were assigned major or minor. Assignments were made with the assistance of gCOSY, gHSQC, gHMBC or NOESY NMR spectra. For unseparable mixtures of diastereomers (>70:30 dr) both isomers are reported separately. When ^{1}H and ^{13}C NMR data for the major diastereoisomer is reported, any signals that overlap with the minor isomer have been integrated without the contribution from the minor isomer being included. In such a case, signals of the minor isomer are not reported. For equimolar mixtures of diastereomers (dr ≤ 70:30) ^{1}H NMR data for isomers is reported together. Unless otherwise stated, dr or rr was calculated based on crude NMR analysis. When the use of crude NMR was not possible due to poor peak separation, dr or rr was calculated after column chromatography. In these cases, no partial separation was observed unless specifically stated.

Mass spectrometry (MS): High resolution mass spectrometry (HRMS) under ESI conditions were recorded on a Thermo Exactive Orbitrap mass spectrometer equipped with a Waters Equity LC system, a Bruker MicroToF mass spectrometer equipped with an Agilent 1100 HPLC pump and autosampler, or on a Waters Xevo Quadrupole Time of Flight (Q-ToF) mass spectrometer. The Thermo Exactive system employs a flow rate of 0.2 mL min–1 using H_2O:MeOH:HCOOH (10:89.9:0.1) as eluent, with a heated electrospray ionisation (HESI-II)

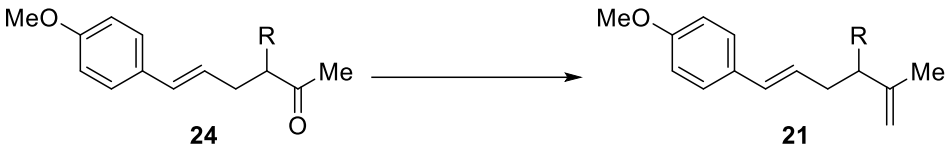
probe and has a resolution of 50,000 FWHM. The Bruker system uses the built-in electrospray source, while the Waters system runs on a lock-mass mode with ESI performed by a secondary electrospray source, both using conditions identical to the Thermo Exactive system. Instrument control and data processing were performed using the softwares Thermo Xcalibur for the Thermo Exactive system, Compass DataAnalysis 4.0 for the Bruker system, and MassLynx for the Waters system. Atmospheric pressure chemical ionisation (APCI) HRMS were recorded on the abovementioned Thermo Exactive spectrometer under identical conditions using N_2 as the reagent gas. Electron impact ionisation (EI) HRMS were performed on an Agilent 7200 Quadrupole Q-ToF mass spectrometer equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using the software Agilent MassHunter. All HRMS conditions were adjusted for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. Unless otherwise specified, the mass reported for HRMS is the mass-to-charge ratio containing the most abundant isotopes, with each value to 4 or 5 decimal places and within 5 ppm of the calculated mass. HRMS data was collected on a mixture when compounds could not be separated by column chromatography.

X-Ray Crystallography: Single crystal X-ray diffraction was performed by Dr. Kirsten E. Christensen on a (Rigaku) Oxford Diffraction/Agilent Supernovae A diffractometer using Cu-K_α radiation (λ = 1.54184 Å) and a graphite monochromator. Samples were mounted on perfluoropoly-ethyl ether oil and cooled by a Cryostream N_2 open-flow cooling device to 150 K throughout the data collection process. The diffraction patterns were integrated and reduced using the software CrysAlisPro. The software CRYSTALS for Microsoft Windows was used to obtain ab initio solutions (using SuperFlip embedded within CRYSTALS) and carry out structure refinement. The images of the solved structures were generated with the softwares Mercury and Ortep3 and represent displacement ellipsoid plots of the best-fit model drawn at 50% probability level.

Optical rotations: Optical rotations were recorded on a Schmidt Haensch Unipol L2000 polarimeter in a cell with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C. Chiral normal phase HPLC was performed on an Agilent 1260 Series HPLC unit equipped with UV-vis diodearray detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø × 25 cm) along with the corresponding guard column (0.4 cm ø × 1 cm). Wavelengths (λ) are reported in nm, retention times (tR) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

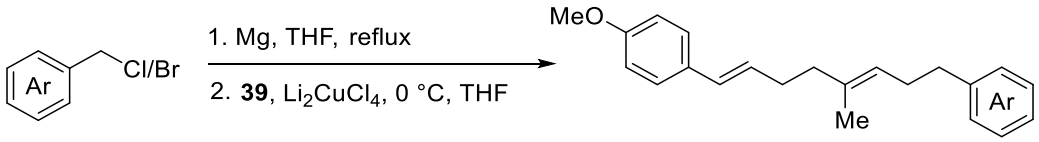
6.2 General procedures

General procedure A: *Synthesis of terminal alkenes from methyl ketones.*



According to a literature procedure,[1] zinc (25 equiv) and $PbCl_2$ (cat) were weighed into a round bottom flask which was then subjected to three evacuate-refill cycles with N_2. THF (*approx*. 17 mL/mmol ketone) and CH_2Br_2 (8.3 equiv) were then added and the obtained suspension was cooled to -25 °C. $TiCl_4$ (4.8 equiv) was then added dropwise and the mixture was allowed to warm to -10 °C and then stirred at the same temperature for 2 h. Ketone **24** (1.0 equiv) dissolved in THF (approx. 6 mL/mmol ketone) was added dropwise and the reaction mixture was warmed to 0 °C and stirred at the same temperature for 0.5 h. Mixture was poured onto ice cold aq. 1 M HCl, diluted with water and extracted with Et_2O. The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (see specific conditions) to furnish the desired product.

General procedure B: *Synthesis of* **43**-**46** *by Cu-catalysed acetate displacement.*



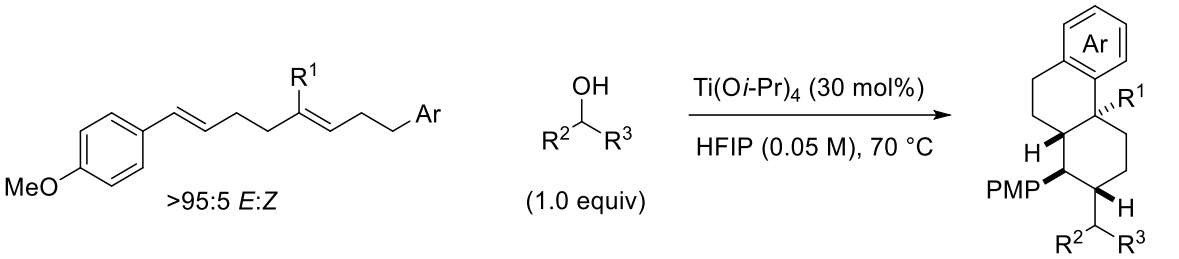
A flame-dried round-bottomed flask was charged with magnesium turnings (18 equiv) and catalytic amount of iodine. THF (0.42 M wrt benzyl chloride) was added followed by the dropwise addition of benzyl chloride (9.0 equiv) at such a rate to maintain gentle reflux. After the addition was complete the resulting suspension was stirred at rt for 2 h. The prepared benzyl magnesium chloride solution was used in the next step immediately.

A mixture of acetates (*E*)-**39** and (*Z*)-**39** (1.0 equiv, 94:6 *E*:*Z*) was dissolved in THF (0.03 M) and cooled to 0 °C. To the obtained solution Li_2CuCl_4 (0.10 M in THF, 0.20 equiv) was added in one portion followed by the dropwise addition of the corresponding benzyl magnesium chloride (3.0 equiv). The reaction was allowed to stir at 0 °C for 1 h and then progress was monitored by TLC. If starting material was present, an additional portion of benzyl magnesium

[1] L. Lombardo, *Tetrahedron Lett.* **1982**, *23*, 4293–4296.

chloride (3.0 equiv) was added dropwise, and the solution was allowed to stir for another 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (5 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography using the appropriate mixture of eluents.

General procedure C: *The cation triggered diene cyclisation.*

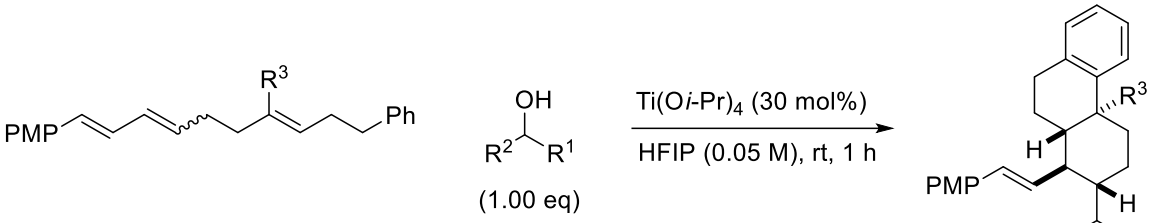


26, 43-46 R^1 = Me (1.0 equiv)
86 R^1 = H (1.0 equiv)

27, 47-50 R^1 = Me (1.0 equiv)
88 R^1 = H (1.0 equiv)

Diene substrate (1.00 equiv) and the corresponding alcohol (1.00 equiv) were transferred to a microwave vial which was then purged with nitrogen. The balloon of nitrogen was removed and HFIP followed by a stock solution of Ti(O*i*-Pr)$_4$ in HFIP (0.30 equiv, 0.066 M) were added to obtain an overall 0.050 M solution of the diene substrate. The solution was heated at 70 °C in an oil bath for 2 h, then cooled to rt and diluted with water (3 mL). The obtained suspension was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 4 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography using the appropriate mixture of eluents.

General procedure D: *The cation-triggered triene cyclisation.*



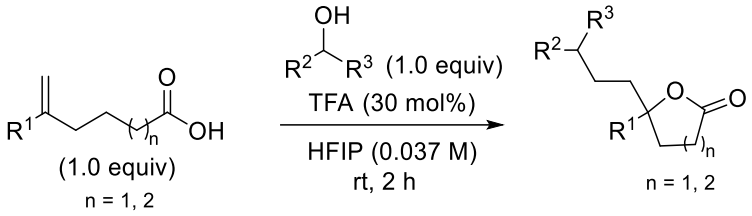
60 R^3=Me; 86:14 *E*:*Z;* (1.00 equiv)
87 R^3=H; 60:40 *E*:*Z;* (1.00 equiv)

76 R^3 = Me
89 R^3 = H
(Major dr)

Triene substrate (1.00 equiv) and the corresponding alcohol (1.00 equiv) were transferred to a microwave vial which was then purged with nitrogen. The balloon of nitrogen was removed and HFIP followed by a stock solution of Ti(O*i*-Pr)$_4$ in HFIP (0.30 equiv, 0.066 M) were added

to obtain an overall 0.050 M solution of a polyene substrate. The solution was stirred at rt for 1 h and then diluted with water (3 mL). The obtained suspension was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 4 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography using the appropriate mixture of eluents.

General procedure E: *Alkylative lactonisation in HFIP.*

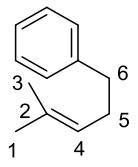


Corresponding carboxylic acid (1.0 equiv) and alcohol (1.0 equiv) were transferred to a microwave vial, which was caped and purged with N_2 for 15 min. HFIP (0.037 M) followed by TFA (0.30 equiv) were added and the reaction mixture was stirred at rt for 2 h. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography using the appropriate mixture of eluents.

6.3 Experimental procedures

*6.3.1 Experimental procedures for chapter **2***

(4-Methylpent-3-en-1-yl)benzene 1.



1

$C_{12}H_{16}$

160.26 g mol^{-1}

BnMgCl (1.6 mL, 3.3 mmol, 1.4 equiv, 2.0 M in THF) was added dropwise to a solution of 1-bromo-3-methylbut-2-ene (0.28 mL, 2.4 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (145 mg, 0.125 mmol, 0.0523 equiv, 5.23 mol%) in THF (2 mL) at 0 °C. The obtained solution was warmed to rt, stirred overnight and then quenched with sat. aq. NH_4Cl (1 mL). The mixture was diluted with water (10 mL) and Et_2O (10 mL). The organic layer was separated, and the aqueous layer

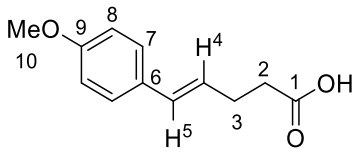
was extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane) to furnish the alkene **1** as a colourless oil (0.130 g, 34%).[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.12 (m, 5H, H-Ph), 5.18 (tdt, *J* = 7.1, 2.9, 1.5 Hz, 1H, H-4), 2.64 (dd, *J* = 9.1, 6.7 Hz, 2H, H-6), 2.30 (q, *J* = 7.6 Hz, 2H, H-5), 1.69 (d, *J* = 1.4 Hz, 3H, H-1/H-3), 1.57 (s, 3H, H-3/H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.6 (C-2/C-Ph), 132.3 (C-Ph/C-2), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.8 (C-Ph), 123.9 (C-4), 36.3 (C-6), 30.2 (C-5), 25.8 (C-1/C-3), 17.8 (C-3/C-1).

The data are consistent with the literature[3]

(*E*)-5-(4-Methoxyphenyl)pent-4-enoic acid 13.



13
$C_{12}H_{14}O_3$
206.24 g mol^{-1}
$^3J_{H\text{-}4,\ H\text{-}5}$ = 15.9 Hz

According to a literature procedure,[2] to a solution of (3-carboxypropyl)triphenylphosphonium bromide (5.67 g, 13.2 mmol, 1.19 equiv) in THF (130 mL) NaHMDS (13.3 mL, 2.00 M in THF, 26.6 mmol, 2.40 equiv) was added dropwise at 0 °C. The solution was stirred for 30 min at the same temperature and then cooled to -78 °C. 4-Methoxybenzaldehyde (1.35 mL, 11.1 mmol, 1.00 equiv) was added dropwise and the reaction was allowed to warm to rt overnight. Water (70 mL) and Et_2O (70 mL) were added. The aqueous layer was separated, acidified with 1.0 M aq. HCl to pH = 1 and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was washed with pentane (3 × 20 mL) to afford carboxylic acid **13** as a white solid (2.03 g, 89%).

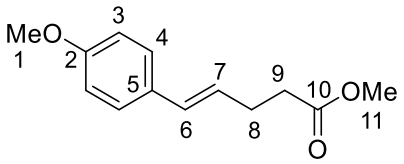
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 2H, H-7), 6.84 (d, *J* = 8.8 Hz, 2H, H-8), 6.39 (d, *J* = 15.9 Hz, 1H, H-5), 6.12 – 5.99 (m, 1H, H-4), 3.80 (s, 3H, H-11), 2.55 – 2.50 (m, 4H, H-2 and H-3). The carboxylic acid proton was not found.

[2] Product **1** is volatile.
[3] G. Sudhakar Reddy, E. J. Corey, *Org. Lett.* **2023**, *25*, 1872–1877.

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.0 (C-1), 159.1 (C-9), 130.7 (C-5), 130.3 (C-6), 127.4 (2C, C-7), 126.0 (C-4), 114.1 (2C, C-8), 55.4 (C-10), 33.9 (C-3), 28.1 (C-2).

The analytical data are consistent with those previously reported in the literature.[4]

Methyl (*E*)-5-(4-methoxyphenyl)pent-4-enoate 14.



14
$C_{13}H_{16}O_3$
220.27 g mol^{-1}

Acetyl chloride (5.0 equiv, 12 mmol, 0.86 mL) was added dropwise to a solution of carboxylic acid **13** (1.0 equiv, 1.2 mmol, 0.25 g) in MeOH (6 mL) at 0 °C. The reaction was allowed to warm to room temperature. The reaction was monitored by TLC until completion, and the solvent was evaporated *in vacuo* to give the crude product that was purified by flash column chromatography (SiO_2; pentane:Et_2O; 4:1) to furnish the ester **14** as a white solid (0.24 g, 89%).

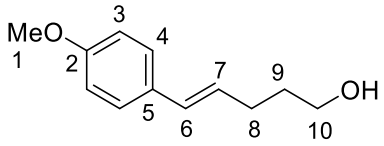
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.8 Hz, 2H, H-4), 6.88 (d, *J* = 8.8 Hz, 2H, H-3), 6.42 (d, *J* = 15.9, 1H, H-6), 6.10 (dt, *J* = 15.9, 6.6 Hz, 1H, H-7), 3.85 (s, 3H, H-1), 3.73 (s, 3H, H-11), 2.71 – 2.37 (m, 4H, H-8, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6 (C-10), 159.0 (C-2), 130.5 (C-6), 130.3 (C-5), 127.3 (2C, C-4), 126.3 (C-7), 114.0 (2C, C-3), 55.5 (C-1), 51.7 (C-11), 34.1 (C-9), 28.4 (C-8).

Analytical data are consistent with those previously reported.[4]

[4] I. Colomer, R. C. Barcelos, K. E. Christensen, T. J. Donohoe, *Org. Lett.* **2016**, *18*, 5880–5883.

(*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol 15.



15
$C_{12}H_{16}O_2$
192.26 g mol^{-1}

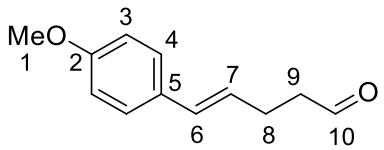
Ester **14** (1.00 equiv, 1.07 mmol, 0.236 g) was dissolved in THF (5 mL) and the obtained solution was cooled to 0 °C. $LiAlH_4$ (2.1 equiv, 2.3 mmol, 86 mg) was added portion-wise at the same temperature and the mixture was allowed to stir at rt for 4h followed by the subsequent addition of water (87 µL), NaOH (15% aq, 87 µL) and water (0.26 mL). The obtained suspension was stirred for 20 min, diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:EtOAc = 9:1) to furnish alcohol **15** as a white solid (0.16 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.9 Hz, 2H, H-4), 6.82 (d, *J* = 8.9 Hz, 2H, H-3), 6.35 (d, *J* = 15.8 Hz, 1H, H-6), 6.06 (dt, J = 15.8, 7.0 Hz, 1H, H-7), 3.78 (s, 3H, H-1), 3.75 – 3.67 (m, 2H, H-10), 2.33 – 2.25 (m, 2H, H-8), 1.78 – 1.66 (m, 2H, H-9), 1.30 (brs, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9 (C-2), 130.6 (C-5), 129.9 (C-6), 128.0 (C-7), 127.2 (2C, C-4), 114.1 (2C, C-3), 62.7 (C-10), 55.5 (C-1), 32.6 (C-9), 29.5 (C-8).

Analytical data are consistent with those previously reported.[5]

(*E*)-5-(4-Methoxyphenyl)pent-4-enal 16.



16
$C_{12}H_{14}O_2$
190.24 g mol^{-1}

Alcohol **15** (1.0 equiv, 0.16 g, 0.82 mmol) was dissolved in a mixture of CH_2Cl_2 (1.6 mL), DMSO (1.6 mL) and Et_3N (0.56 mL) at 0 °C. To the obtained solution $SO_3 \cdot$ py complex (2.8

[5] D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc*. **2012**, *45*, 18577–18580.

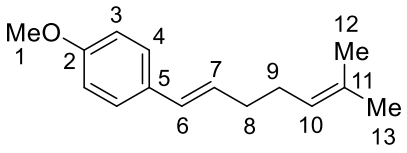
equiv, 2.3 mmol, 0.37 g) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 2 h and then diluted with water (5 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:EtOAc; 4:1) to furnish aldehyde **16** as a colourless oil (0.13 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (t, *J* = 6.8 Hz, 1H, H-10), 7.26 (d, *J* = 8.8 Hz, 2H, H-4), 6.84 (d, *J* = 8.8 Hz, 2H, H-3), 6.38 (d, *J* = 15.6 Hz, 1H, H-6), 6.06 (dt, *J* = 6.4, 15.6 Hz, 1H, H-7), 3.80 (s, 1H, H-1), 2.65 – 2.59 (m, 2H, H-9), 2.49 − 2.58 (m, 2H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.1 (C-10), 159.1 (C-2), 130.7 (C-6), 130.2 (C-5), 127.3 (2C, C-4), 126.1 (C-7), 114.1 (2C, C-3), 55.4 (C-1), 43.6 (C-9), 25.7 (C-8).

Analytical data are consistent with those previously reported.[6]

(*E*)-1-Methoxy-4-(5-methylhexa-1,4-dien-1-yl)benzene 2.



2
$C_{15}H_{20}O$
216.32 g mol^{-1}

Isopropyltriphenylphosphonium iodide (1.2 equiv, 0.84 mmol, 0.37 g) was suspended in THF (4.5 mL) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.77 mmol, 0.31 mL) was added dropwise and the obtained suspension was stirred at 0 °C for 15 min before being cooled to -78 °C. Aldehyde **16** (1.0 equiv, 0.70 mmol, 0.13 g) in THF (0.7 mL) was added dropwise and the reaction mixture was allowed to warm to rt over 30 min. Saturated aqueous NH_4Cl (1 mL) was then added followed by water (3 mL) and Et_2O (5 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 9:1) to furnish alkene **2** as a colourless oil (0.11 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (d, *J* = 8.8 Hz, 2H, H-4), 6.83 (d, *J* = 8.8 Hz, 2H, H-3), 6.34 (dt, *J* = 15.9, 1.5 Hz, 1H, H-6), 6.09 (dt, *J* = 15.8, 6.7 Hz, 1H, H-7), 5.20 – 5.13 (m,

[6] T. Itoh, H. Ishikawa, Y. Hayashi, *Angew. Chem. Int. Ed*. **2011**, *50*, 3920–3924.

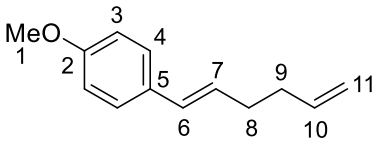
1H, H-10), 3.80 (s, 3H, H-1), 2.26 – 2.09 (m, 4H, H-8, H-9), 1.74 – 1.68 (m, 3H, H-13/H-12), 1.62 (m, 3H, H-12/H-13).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-2), 132.1 (C-11), 130.9 (C-5) 129.4 (C-6), 128.8 (C-7), 127.1 (2C, C-4), 124.0 (C-10), 114.1 (2C, C-3), 55.4 (C-1), 33.4 (C-8), 28.3 (C-9), 25.9 (C-12/C-13), 17.9 (C-13/C-12).

IR (film) ν_{max}: 2981, 1608, 1510, 1379, 1247, 1174, 1037, 964, 762 cm^{-1}.

HRMS (APCI): calculated for $C_{15}H_{21}O$ $[M+H]^+$ requires m/z 217.1587, found m/z 217.1587 (*p* = 0.19).

(*E*)-1-(Hexa-1,5-dien-1-yl)-4-methoxybenzene 3.



3
$C_{13}H_{16}O$
188.27 g mol^{-1}

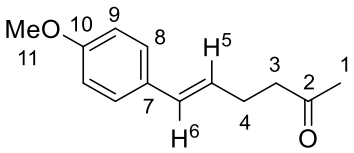
Methyltriphenylphosphonium bromide (1.2 equiv, 0.84 mmol, 0.30 g) was suspended in THF (4.5 mL) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.77 mmol, 0.31 mL) was added dropwise and the obtained suspension was stirred at 0 °C for 15 min before being cooled to -78 °C. Aldehyde **16** (1.0 equiv, 0.70 mmol, 0.13 g) in THF (0.7 mL) was added dropwise and the reaction mixture was allowed to warm to rt overnight. Saturated aqueous NH_4Cl (1 mL) was then added followed by water (3 mL) and Et_2O (5 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2 pentane:Et_2O; 19:1) to furnish alkene **3** as a colourless oil (33 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H, H-4), 6.88 – 6.79 (m, 2H, H-3), 6.39 – 6.31 (m, 1H, H-6), 6.09 (dt, *J* = 15.8, 6.6 Hz, 1H, H-7), 5.93 – 5.80 (m, 1H, H-10), 5.14 – 4.94 (m, 2H, H-11_a, H-11_b), 3.80 (s, 3H, H-1), 2.34 – 2.18 (m, 4H, H-8, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-2), 138.4 (C-10), 130.8 (C-5), 129.7 (C-6), 128.1 (C-7), 127.2 (2C, C-4), 115.0 (C-11), 114.1 (2C, C-3), 55.5 (C-1), 33.9 (C-9), 32.6 (C-8).

Analytical data are consistent with those previously reported.[7]

(*E*)-6-(4-Methoxyphenyl)hex-5-en-2-one 17.



17
$C_{13}H_{16}O_2$
204.27 g mol^{-1}
$^3J_{H\text{-}5,\ H\text{-}6}$ = 15.8 Hz

Carboxylic acid **13** (2.43 g, 11.8 mmol, 1.00 equiv) was suspended in THF (58 mL) and cooled to 0 °C. MeLi (19 mL, 1.6 M in Et_2O, 30 mmol**,** 2.5 equiv) was then added dropwise at the same temperature and the obtained suspension was allowed to warm to rt overnight. The mixture was poured into a solution of conc. HCl (3.5 mL) in water (110 mL) and extracted with Et_2O (3 × 100 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2) to furnish the ketone **17** as a yellow oil (1.51 g, 63%).

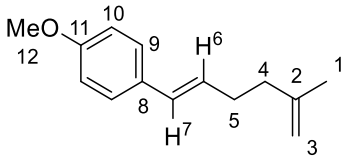
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.8 Hz, 2H, H-8), 6.83 (d, *J* = 8.8 Hz, 2H, H-9), 6.35 (d, *J* = 15.8 Hz, 1H, H-6), 6.04 (dt, *J* = 15.8, 6.8 Hz, 1H, H-5), 3.80 (s, 3H, H-11), 2.64 – 2.56 (m, 2H, H-3), 2.50 – 2.41 (m, 2H, H-4), 2.17 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.4 (C-2), 159.0 (C-10), 130.4 (C-7), 130.3 (C-5), 127.3 (2C, C-8), 126.7 (C-6), 114.1 (2C, C-9), 55.4 (C-11), 43.5 (C-3), 30.2 (C-1), 27.3 (C-4).

The analytical data are consistent with those previously reported in the literature.[8]

[7] H. Y. Wang, L. J. Zhong, G. F. Lv, Y. Li, J. H. Li, *Org. Biomol. Chem*. **2020**, *18*, 5589–5593.
[8] P. Calleja, Ó. Pablo, B. Ranieri, M.Gaydou, A. Pitaval, M. Moreno, M. Raducan, A. M. Echavarren, *Chem. Eur. J*. **2016**, *22*, 13613–13618.

(*E*)-1-Methoxy-4-(5-methylhexa-1,5-dien-1-yl)benzene 4.



4

$C_{14}H_{18}O$

202.30 g mol^{-1}

$^{3}J_{\text{H-6, H-7}}$ = 15.8 Hz

According to a literature procedure,[9] zinc (3.43 g, 52.5 mmol, 25.0 equiv) and $PbCl_2$ (cat) were weighed into a round bottom flask which was then subjected to three evacuate-refill cycles with N_2. THF (35 mL) and CH_2Br_2 (1.21 mL,17.4 mmol, 8.29 equiv) were then added and the obtained suspension was cooled to -25 °C. $TiCl_4$ (1.10 mL, 10.0 mmol, 4.76 equiv) was then added dropwise and the mixture was allowed to warm to -10 °C and then stirred at the same temperature for 2 h. Ketone **17** (0.429 g, 2.10 mmol, 1.00 equiv) dissolved in THF (12 mL) was added dropwise and the reaction mixture was warmed to 0 °C and stirred at the same temperature for 0.5 h. The mixture was poured onto ice cold aq. HCl (1 M, 12 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O = 9:1) to furnish alkene **4** as a colourless oil (0.361 g, 85%).

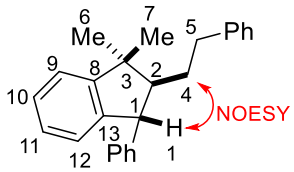
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.8 Hz, 2H, H-9), 6.83 (d, *J* = 8.8 Hz, 2H, H-10), 6.35 (dt, *J* = 15.8, 1.5 Hz, 1H, H-7), 6.08 (dt, *J* = 15.8, 6.8 Hz, 1H, H-6), 4.78 – 4.69 (m, 2H, H-3), 3.80 (s, 3H, H-12), 2.38 – 2.29 (m, 2H, H-5), 2.21 – 2.14 (m, 2H, H-4), 1.76 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-11), 145.5 (C-2), 130.8 (C-8), 129.4 (C-7), 128.4 (C-6), 127.2 (2C, C-9), 114.1 (2C, C-10), 110.3 (C-3), 55.4 (C-12), 37.8 (C-4), 31.3 (C-5), 22.7 (C-1).

The analytical data are consistent with those previously reported in the literature.[10]

[9] L. Lombardo, *Tetrahedron Lett.* **1982**, *23*, 4293–4296.
[10] Y. Sumida, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 1629–1632.

(±)-(2*S*,3*R*)-1,1-dimethyl-2-phenethyl-3-phenyl-2,3-dihydro-1H-indene 18.



18

$C_{25}H_{26}$

326.48 g mol^{-1}

Alkene **1** (35.0 mg, 0.218 mmol, 1.00 equiv) and benzhydrol (40.4 mg, 0.219 mmol, 1.00 equiv) were transferred to a microwave vial which was then purged with N_2 for 10 min. The balloon of nitrogen was removed and HFIP (1.2 mL) followed by a stock solution of Ti(O*i*-Pr)$_4$ (66 µmol, 0.30 equiv) in HFIP (0.066 M, 1.0 mL, 0.30 equiv) were added. The reaction mixture was heated at 70 °C overnight, cooled to rt and diluted with CH_2Cl_2 (5 mL). The solution was washed with H_2O (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane) to furnish carbocycle **18** as a colourless oil (59.7 mg, 84%, >95:5 dr).

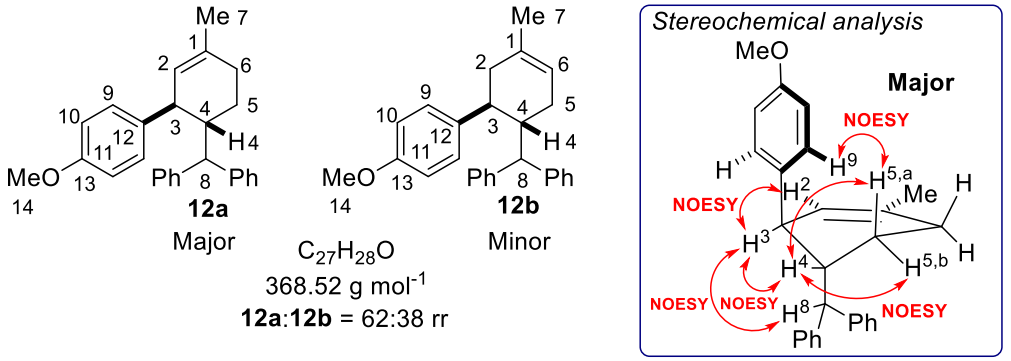
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.11 (m, 11H, H-Ph, H-9, H-10, H-11), 7.08 – 7.03 (m, 2H, H-Ph), 6.79 (dd, *J* = 7.3, 1.2 Hz, 1H, H-12), 4.03 (d, *J* = 10.6 Hz, 1H, H-1), 2.53 – 2.38 (m, 2H, H-5), 2.27 (ddd, *J* = 10.5, 7.7, 5.4 Hz, 1H, H-2), 2.08 – 1.84 (m, 2H, H-4), 1.49 (s, 3H, H-6), 1.19 (s, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (C-8), 145.7 (C-13), 144.6 (C-Ph), 142.9 (C-Ph), 129.3 (2C, C-Ph), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 128.3 (2C, C-Ph), 127.0 (C-10), 126.7 (2C, C-11, C-Ph), 125.7 (C-Ph), 124.8 (C-12), 121.8 (C-9), 59.9 (C-2), 56.5 (C-1), 45.4 (C-3), 35.2 (C-5), 31.8 (C-4), 27.5 (C-6), 24.0 (C-7).

IR (film) ν_{max}: 3025, 2956, 2863, 1494, 1477, 1452, 1261, 1074, 1028, 804, 752, 698 cm^{-1}.

HRMS (ESI): A stable molecular ion could not be detected by ESI, APCI or EI.

(±)-(1*R*,2*S*)-2-Benzhydryl-4'-methoxy-5-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (major)-12a and (±)-(1*S*,2*S*)-2-Benzhydryl-4'-methoxy-5-methyl-1,2,3,6-tetrahydro-1,1'-biphenyl (minor)-12b.



$C_{27}H_{28}O$
368.52 g mol^{-1}
12a:**12b** = 62:38 rr

Diene **4** (32.2 mg, 0.159 mmol, 1.00 equiv), benzhydrol (29.3 mg, 0.159 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (14.5 µL, 49.0 µmol, 0.308 equiv) in HFIP (8.1 mL, 0.020 M) were subjected to the general procedure **C** except the reaction was performed at 70 °C overnight and at 0.02 M. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 99:1 to 49:1) to furnish compounds **12a** and **12b** as an inseparable mixture of alkene regioisomers as a colourless oil (32.1 mg, 55%, 62:38 rr).[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 748 – 7.39 (m, 2H$_{maj}$, 2H$_{min}$, H-Ph$_{maj}$, H-Ph$_{min}$), 7.37 – 7.11 (m, 8H$_{maj}$, 8H$_{min}$, H-Ph$_{maj}$, H-Ph$_{min}$), 7.08 (d, *J* = 8.7 Hz, 2H$_{min}$, H-9$_{min}$), 7.04 (d, *J* = 8.6 Hz, 2H$_{maj}$, H-9$_{maj}$), 6.86 – 6.80 (m, 2H$_{maj}$, 2H$_{min}$, H-10$_{maj}$, H-10$_{min}$), 5.39 – 5.33 (m, 1H$_{min}$, H-6$_{min}$), 5.31 (d, *J* = 3.7 Hz, 1H$_{maj}$, H-2$_{maj}$), 3.98 – 3.90 (m, 1H$_{maj}$, 1H$_{min}$, H-8$_{maj}$, H-8$_{min}$), 3.81 – 3.78 (m, 3H$_{maj}$, 3H$_{min}$, H-14$_{maj}$, H-14$_{min}$), 3.21 – 3.10 (m, 1H$_{maj}$, H-3$_{maj}$), 2.84 (dt, *J* = 6.3, 2.8 Hz, 1H$_{min}$, H-3$_{min}$), 2.68 – 2.54 (m, 1H$_{maj}$, 1H$_{min}$, H-4$_{maj}$, H-4$_{min}$), 2.37 (dd, *J* = 17.5, 6.4 Hz, 1H$_{min}$, H-2$_{a,\ min}$), 2.09 – 1.95 (m, 1H$_{maj}$, 1H$_{min}$, H-6$_{a,\ maj}$, H-2$_{b,\ min}$), 1.90 – 1.78 (m, 4H$_{maj}$, 4H$_{min}$, H-7$_{maj}$, H-6$_{b,\ maj}$, H-7$_{min}$, H-5$_{a,\ min}$), 1.74 – 1.63 (m, 1H$_{maj}$, 1H$_{min}$, H-5$_{a,\ maj}$, H-5$_{b,\ min}$), 1.38 – 1.26 (m, 1H$_{maj}$, H-5$_{b,\ maj}$).

^{13}C NMR (101 MHz, $CDCl_3$) **for the major regioisomer** (from the mixture): δ 158.0 (C-11), 145.1 (C-Ph), 144.1 (C-Ph), 138.5 (C-12), 135.0 (C-1), 129.4 (2C, C-9), 128.7 (2C, C-Ph), 128.5 (2C, C-Ph), 128.4 (2C, C-Ph), 128.3 (2C, C-Ph), 126.3 (C-Ph), 126.2 (C-Ph), 121.7 (C-2), 113.6 (2C, C-10), 55.4 (C-14), 53.4 (C-8), 43.6 (C-4), 42.3 (C-3), 26.3 (C-6), 24.0 (C-7), 19.8 (C-5). **Selected peaks for the minor regioisomer** (from the mixture): δ 157.8 (C-11), 144.6 (C-Ph), 144.5 (C-Ph), 139.2 (C-12), 132.6 (C-1), 128.5 (C-Ph), 128.4 (C-Ph), 128.3 (C-9), 128.2 (C-Ph), 126.2 (C-Ph), 120.0 (C-6), 113.7 (C-10), 55.4 (C-14), 53.6 (C-8), 42.1 (C-4), 38.5 (C-3), 31.5 (C-2), 23.9 (C-5), 23.7 (C-7).

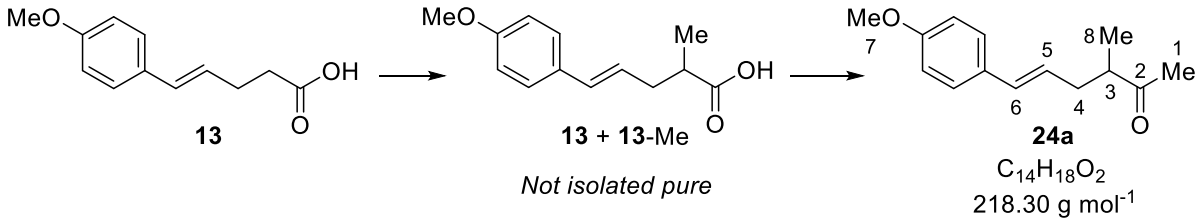
[11] Ratio of alkene regioisomers was determined after column chromatography.

NOESY (600 MHz, $CDCl_3$): between H-2_{maj} and H-3_{maj}, between H-3_{maj} and H-4_{maj}, between H-3_{maj} and H-8_{maj}, between H-4_{maj} and H-$5_{a,\ maj}$, between H-4_{maj} and H-$5_{b,\ maj}$, between H-9_{maj} and H-$5_{a,\ maj}$.

IR (film) ν_{max}: 2910, 1509, 1493, 1450, 1246, 1178, 1034, 829, 757, 747, 703 cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{29}O$ $[M+H]^+$ requires m/z 369.2213, found m/z 369.2215 (Δ = 0.51 ppm).

(*E*)-6-(4-methoxyphenyl)-3-methylhex-5-en-2-one 24a.



Carboxylic acid **13** (0.40 g, 1.9 mmol, 1.0 equiv) was dissolved in THF (22 mL) and cooled to 0 °C. To the solution, LDA (2.4 mL, 4.8 mmol, 2.5 equiv, 2.0 M in THF/Heptane/Ethylbenzene) was added dropwise and the obtained suspension was stirred at the same temperature for 15 min. MeI (0.18 mL, 2.9 mmol, 1.5 equiv) was added dropwise and the reaction mixture was allowed to slowly warm to rt overnight and then quenched with water (20 mL). The obtained suspension was washed with Et_2O (20 mL), the aqueous layer was acidified to pH = 1 with 2 M HCl and then extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (60 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:EtOAc; 7:3; 1% HCO_2H) to furnish carboxylic acid **13**-Me as a white solid which was used in the next step with minor impurities (0.206 g).[12]

Crude carboxylic acid from the previous step (0.206 g) was suspended in THF (4.2 mL) and cooled to 0 °C. MeLi (1.5 mL, 2.3 mmol, 1.6 M in Et_2O) was then added dropwise at the same temperature and the obtained suspension was allowed to warm to rt overnight. The mixture was poured into a solution of conc. HCl (0.65 mL) in water (13 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 4:1) to furnish the ketone **24a** as a yellow oil (51.6 mg, 12% over two steps).

[12] Impurities could not be separated by column chromatohraphy.

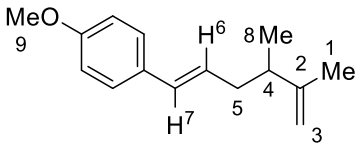
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 2H, H-Ar), 6.87 – 6.77 (m, 2H, H-Ar), 6.35 (dt, *J* = 15.8, 1.5 Hz, 1H, H-6), 5.98 (ddd, *J* = 15.7, 7.5, 6.9 Hz, 1H, H-5), 3.80 (s, 3H, H-7), 2.65 (h, *J* = 6.9 Hz, 1H, H-3), 2.53 (dtd, *J* = 13.6, 6.8, 1.5 Hz, 1H, H-4_a), 2.24 (dtd, *J* = 14.1, 7.3, 1.3 Hz, 1H, H-4_b), 2.17 (s, 3H, H-1), 1.14 (d, *J* = 7.0 Hz, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7 (C-2), 159.1 (C-Ar), 131.6 (C-6), 130.3 (C-Ar), 127.3 (2C, C-Ar), 125.2 (C-5), 114.1 (2C, C-Ar), 55.4 (C-7), 47.4 (C-3), 36.4 (C-4), 28.6 (C-1), 16.2 (C-8).

IR (film) ν_{max}: 2967, 1710, 1608, 1511, 1247, 1175, 1111, 1034, 968, 840 cm^{-1}.

HRMS: A stable molecular ion could not be detected.

(*E*)-1-(4,5-Dimethylhexa-1,5-dien-1-yl)-4-methoxybenzene 21a.



21a
$C_{15}H_{20}O$
216.32 g mol^{-1}

Zinc (0.353 g, 5.40 mmol, 25.1 equiv), $PbCl_2$ (cat), CH_2Br_2 (0.13 mL, 1.9 mmol, 8.3 equiv), $TiCl_4$ (0.11 mL, 1.0 mmol, 4.8 equiv) and ketone **24a** (46.7 mg, 0.214 mmol, 1.00 equiv) in THF (4.8 mL) were subjected to the general procedure **A**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish alkene **21a** as a colourless oil (35.0 mg, 76%).

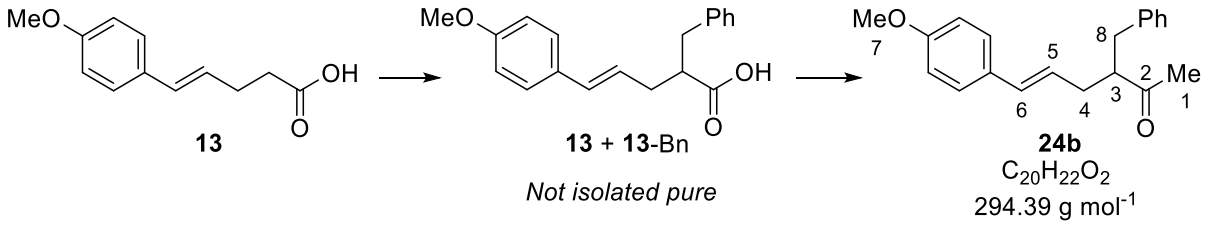
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 2H, H-Ar), 6.88 – 6.77 (m, 2H, H-Ar), 6.32 (dd, *J* = 15.6, 1.7 Hz, 1H, H-7), 6.11 – 5.94 (m, 1H, H-6), 4.72 (q, *J* = 1.3 Hz, 2H, H-3), 3.80 (s, 3H, H-9), 2.36 – 2.23 (m, 2H, H-5_a, H-4), 2.21 – 2.10 (m, 1H, H-5_b), 1.72 (t, *J* = 1.2 Hz, 3H, H-1), 1.05 (d, *J* = 6.7 Hz, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 149.9 (C-2), 130.9 (C-Ar), 130.2 (C-7), 127.4 (C-6), 127.2 (2C, C-Ar), 114.1 (2C, C-Ar), 109.6 (C-3), 55.4 (C-9), 41.4 (C-4), 38.9 (C-5), 19.9 (C-1), 19.4 (C-8).

IR (film) ν_{max}: 2961, 1608, 1510, 1441, 1246, 1174, 1037, 965, 888, 838, 801 cm^{-1}.

HRMS (APCI): calculated for $C_{15}H_{21}O$ $[M+H]^+$ requires m/z 217.1587, found m/z 217.1589 (*Δ* = 0.81 ppm).

(*E*)-3-Benzyl-6-(4-methoxyphenyl)hex-5-en-2-one 24b.



Carboxylic acid **13** (0.40 g, 1.9 mmol, 1.0 equiv) was dissolved in THF (22 mL) and cooled to 0 °C. To the solution, LDA (2.4 mL, 4.8 mmol, 2.5 equiv, 2.0 M In THF/Heptane/Ethylbenzene) was added dropwise and the obtained suspension was stirred at the same temperature for 15 min. Benzyl bromide (0.28 mL, 2.3 mmol, 1.2 equiv) was added dropwise and the reaction mixture was allowed to slowly warm to rt overnight and then quenched with water (20 mL). The obtained suspension was washed with Et_2O (20 mL), the aqueous layer was acidified to pH = 1 with 2 M HCl and then extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (60 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude mixture was purified by flash column chromatography (SiO_2; 60 Å; 15–40 µm; pentane:EtOAc; 7:3; 1% HCO_2H) to furnish carboxylic acid **13**-Bn contaminated with carboxylic acid **13** as a white solid which was used in the next step without further purification (0.230 g).[13]

Crude carboxylic acid from the previous step (0.230 g) was suspended in THF (3.5 mL) and cooled to 0 °C. MeLi (1.2 mL, 1.9 mmol, 1.6 M in Et_2O) was then added dropwise at the same temperature and the obtained suspension was allowed to warm to rt overnight. The mixture was poured into a solution of conc. HCl (0.65 mL) in water (13 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 4:1) to furnish the ketone **24b** as a yellow oil (80.0 mg, 14% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.11 (m, 7H, H-Ar, H-Ph), 6.87 – 6.76 (m, 2H, H-Ar), 6.34 (dt, *J* = 15.7, 1.5 Hz, 1H, H-6), 5.96 (dt, *J* = 15.7, 7.3 Hz, 1H, H-5), 3.80 (s, 3H, H-7), 3.02 – 2.87 (m, 2H, H-3, H-8_a), 2.81 – 2.68 (m, 1H, H-8_b), 2.49 (dtd, *J* = 14.2, 7.5, 1.4 Hz, 1H, H-4_a), 2.35 (dddd, *J* = 14.2, 7.1, 5.5, 1.5 Hz, 1H, H-4_b), 2.01 (s, 3H, H-1).

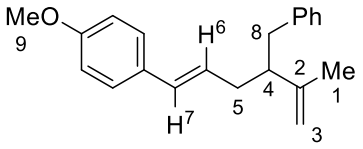
^{13}C NMR (101 MHz, $CDCl_3$): δ 211.8 (C-2), 159.1 (C-Ar), 139.6 (C-Ph), 132.0 (C-6), 130.2 (C-Ar), 129.1 (2C, C-Ar/C-Ph), 128.7 (2C, C-Ar/C-Ph), 127.4 (2C, C-Ar/C-Ph), 126.5 (C-Ph), 124.6 (C-5), 114.1 (2C, C-Ar), 55.4 (C-7), 54.8 (C-3), 37.6 (C-8), 35.1 (C-4), 30.8 (C-1).

[13] Carboxylic acids **13** and **13**-Bn could not be fully separated by column chromatography.

IR (film) ν_{max}: 2981, 2890, 1710, 1607, 1511, 1382, 1248, 1175, 967, 701 cm^{-1}.

HRMS: A stable molecular ion could not be detected.

(*E*)-1-(4-Benzyl-5-methylhexa-1,5-dien-1-yl)-4-methoxybenzene 21b.



21b
$C_{21}H_{24}O$
290.41 g mol^{-1}

Zinc (0.64 g, 9.7 mmol, 25 equiv), $PbCl_2$ (cat), CH_2Br_2 (0.23 mL, 3.2 mmol, 8.4 equiv), $TiCl_4$ (0.20 mL, 1.8 mmol, 4.7 equiv) and ketone **24b** (0.114 g, 0.388 mmol, 1.00 equiv) in THF (8.7 mL) were subjected to the general procedure **A**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 99:1) to furnish alkene **21b** as a colourless oil (75.4 mg, 67%).

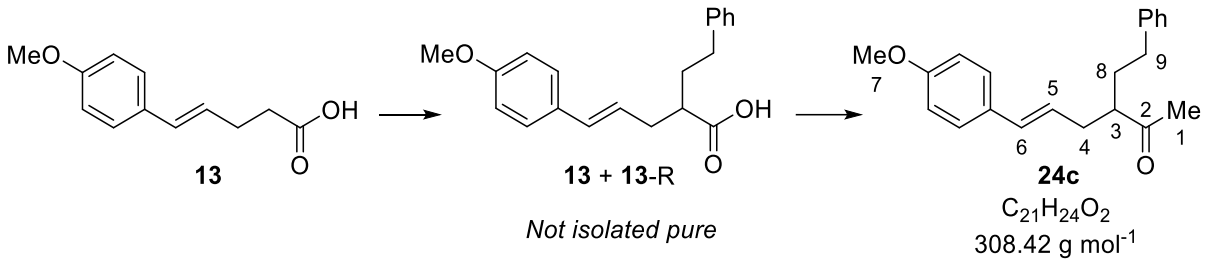
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.11 (m, 7H, H-Ar, H-Ph), 6.87 – 6.79 (m, 2H, H-Ar), 6.30 (dt, *J* = 15.8, 1.5 Hz, 1H, H-7), 5.99 (dt, *J* = 15.7, 7.1 Hz, 1H, H-6), 4.77 – 4.72 (m, 1H, H-3_a), 4.68 – 4.61 (m, 1H, H-3_b), 3.80 (s, 3H, H-9), 2.80 – 2.65 (m, 2H, H-8), 2.50 (qd, *J* = 7.6, 5.9 Hz, 1H, H-4), 2.35 – 2.20 (m, 2H, H-5), 1.70 (dd, *J* = 1.5, 0.8 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 146.9 (C-2), 141.0 (C-Ph), 130.8 (C-Ar), 130.4 (C-7), 129.2 (2C, C-Ph/C-Ar), 128.2 (2C, C-Ph/C-Ar), 127.2 (2C, C-Ph/C-Ar), 126.9 (C-6), 125.9 (C-Ph), 114.0 (2C, C-Ar), 112.0 (C-3), 55.4 (C-9), 49.3 (C-4), 40.1 (C-8), 36.5 (C-5), 19.7 (C-1).

IR (film) ν_{max}: 2981, 2361, 1607, 1510, 1381, 1248, 1174, 1036, 965, 699 cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{25}O$ $[M+H]^+$ requires m/z 293.1900, found m/z 293.1900 (*Δ* = 0.08 ppm).

(*E*)-6-(4-Methoxyphenyl)-3-phenethylhex-5-en-2-one 24c.



n-BuLi (2.3 mL, 5.8 mmol, 3.0 equiv, 2.5 M in hexanes) was added dropwise to asolution of DIPA (0.90 mL, 6.4 mmol, 3.3 equiv) in THF (15 mL) at -78 °C. The obtained solution was warmed to 0 °C and stirred for 15 min. The solution was then transferred dropwise via a cannula to a solution of carboxylic acid **13** (0.40 g, 1.9 mmol, 1.0 equiv) in THF (22 mL) at0 °C and stirred for 15 min. (2-Bromoethyl)benzene (0.53 mL, 3.9 mmol, 2.0 equiv) was added dropwise and the reaction mixture was allowed to slowly warm to rt overnight and was then quenched with water (20 mL). The obtained suspension was washed with Et_2O (20 mL), the aqueous layer was acidified to pH = 1 with 2 M HCl and then extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (60 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude mixture was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:EtOAc; 1:1) to furnish carboxylic acid **13**-R contaminated with carboxylic acid **13** as a white solid which was used in the next step without further purification (0.117 g).[14]

Crude carboxylic acid from the previous step (0.117 g) was suspended in THF (3.1 mL) and cooled to 0 °C. MeLi (0.58 mL, 0.93 mmol, 1.6 M in Et_2O) was then added dropwise at the same temperature and the obtained suspension was allowed to warm to rt overnight. The mixture was poured into a solution of conc. HCl (0.32 mL) in water (6 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 3:1) to furnish the ketone **24c** as a yellow oil (23.2 mg, 4% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.14 (m, 7H, H-Ar, H-Ph), 6.87 – 6.79 (m, 2H, H-Ar), 6.34 (dt, *J* = 15.8, 1.5 Hz, 1H, H-6), 5.94 (dt, *J* = 15.7, 7.2 Hz, 1H, H-5), 3.80 (s, 3H, H-7), 2.70 – 2.44 (m, 4H, H-3, H-4_a, H-9_a, H-9_b), 2.36 (dddd, *J* = 13.9, 7.4, 6.1, 1.4 Hz, 1H, H-4_b), 2.15 (s, 3H, H-1), 2.01 (dddd, *J* = 14.1, 9.5, 8.3, 6.2 Hz, 1H, H-8_a), 1.79 (dddd, *J* = 13.8, 9.8, 6.6, 5.3 Hz, 1H, H-8_b).

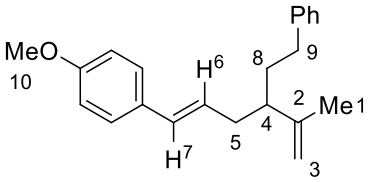
[14] Carboxylic acids **13** and **13**-R could not be fully separated by column chromatography.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.8 (C-2), 159.1 (C-Ar), 141.7 (C-Ph), 131.7 (C-6), 130.2 (C-Ar), 128.6 (2C, C-Ph/C-Ar), 128.5 (2C, C-Ph/C-Ar), 127.4 (2C, C-Ph/C-Ar), 126.2 (C-Ph), 124.8 (C-5), 114.1 (2C, C-Ar), 55.4 (C-7), 52.5 (C-3), 35.2 (C-4), 33.6 (C-9), 32.8 (C-8), 29.6 (C-1).

IR (film) ν_{max}: 2981, 2361, 1709, 1607, 1511, 1382, 1250, 1153, 1073, 955 cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{25}O_2$ $[M+H]^+$ requires m/z 309.1849, found m/z 309.1850 (*Δ* = 0.20 ppm).

(*E*)-1-Methoxy-4-(5-methyl-4-phenethylhexa-1,5-dien-1-yl)benzene 21c.



21c
$C_{22}H_{26}O$
306.45 g mol^{-1}

Zinc (0.27 g, 4.2 mmol, 25 equiv), $PbCl_2$ (cat), CH_2Br_2 (0.10 mL, 1.4 mmol, 8.4 equiv), $TiCl_4$ (90 µL, 0.82 mmol, 4.9 equiv) and ketone **24c** (51.2 mg, 0.166 mmol, 1.00 equiv) in THF (3.7 mL) were subjected to the general procedure **A**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish alkene **21c** as a colourless oil (37.7 mg, 74%).

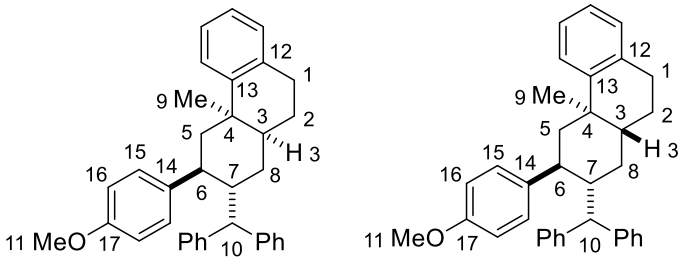
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.12 (m, 7H, H-Ar, H-Ph), 6.91 – 6.79 (m, 2H, H-Ar), 6.32 (d, *J* = 15.7 Hz, 1H, H-7), 6.01 (dt, *J* = 15.7, 6.8 Hz, 1H, H-6), 4.89 – 4.83 (m, 1H, H-3_a), 4.81 – 4.76 (m, 1H, H-3_b), 3.81 (s, 3H, H-10), 2.67 – 2.57 (m, 1H, H-9_a), 2.56 – 2.46 (m, 1H, H-9_b), 2.33 – 2.18 (m, 3H, H-5_a, H-5_b, H-4), 1.83 – 1.64 (m, 5H, H-8_a, H-8_b, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 147.0 (C-2), 142.9 (C-Ph), 130.8 (C-Ar), 130.2 (C-7), 128.5 (2C, C-Ar/C-Ph), 128.4 (2C, C-Ar/C-Ph), 127.2 (2C, C-Ar/C-Ph), 127.1 (C-6), 125.8 (C-Ph), 114.0 (2C, C-Ar), 112.2 (C-3), 55.4 (C-10), 47.3 (C-4), 37.5 (C-5), 34.7 (C-8), 33.8 (C-9), 18.8 (C-1).

IR (film) ν_{max}: 2981, 2361, 1607, 1510, 1382, 1249, 1152, 1073, 965 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{27}O$ $[M+H]^+$ requires m/z 307.2056, found m/z 307.2057 (*Δ* = 0.32 ppm).

(±)-(2*S*,3*S*,4*aR*,10*aS*)-2-benzhydryl-3-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 25a and (±)-(2*S*,3*S*,4*aR*,10*aR*)-2-benzhydryl-3-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 25b.



25a **25b**

$C_{35}H_{36}O$
472.67 g mol^{-1}
25a:**25b**=52:48

Alkene **21c** (35.5 mg, 0.116 mmol, 1.00 equiv) and benzhydrol (21.4 mg, 0.116 mmol, 1.00 equiv) were transferred to a microwave vial and purged with nitrogen for 10 min. The balloon of nitrogen was removed, and CH_2Cl_2 (2.9 mL), a stock solution of Ti(O*i*-Pr)$_4$ (0.50 equiv) in HFIP (0.068 M, 0.9 mL) and HFIP (2 mL) were added sequentially to obtain a 0.02 M solution of alkene **21c**. The reaction mixture was stirred at 70 °C overnight and then water (5 mL) and CH_2Cl_2 (2 mL) were added. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic layers were combined, washed with brine (15 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 49:1) to furnish product **25** as an inseparable mixture of diastereomers as a colourless oil (38.2 mg, 52:48 dr, 70%)[15]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.04 (m, 16H$_{maj}$, 16H$_{min}$, H-Ar$_{maj}$, H-15$_{maj}$, H-Ar$_{min}$, H-15$_{min}$), 6.97 – 6.82 (m, 2H$_{maj}$, 2H$_{min}$, H-16$_{maj}$, H-16$_{min}$), 4.12 (d, *J* = 3.0 Hz, 1H$_{maj}$, H-10$_{maj}$), 4.08 (d, *J* = 2.7 Hz, 1H$_{min}$, H-10$_{min}$), 3.87 (m, 3H$_{min}$, H-11$_{min}$), 3.83 (m, 3H$_{maj}$, H-11$_{maj}$), 3.05 – 2.82 (m, 3H$_{maj}$, 2H$_{min}$, H-1$_{a, maj}$, H-1$_{b, maj}$, H-7$_{maj}$, H-1$_{a, min}$, H-1$_{b, min}$), 2.80 – 2.61 (m, 1H$_{maj}$, 2H$_{min}$, H-6$_{maj}$, H-6$_{min}$, H-7$_{min}$), 2.45 – 2.24 (m, 2H$_{min}$, H-5$_{a, min}$, H-2$_{a, min}$), 2.01 – 1.62 (m, 7H$_{maj}$, 4H$_{min}$, H-2$_{a, maj}$, H-2$_{b, maj}$, H-8$_{a, maj}$, H-8$_{b, maj}$, H-5$_{a, maj}$, H-5$_{b, maj}$, H-3$_{maj}$, H-3$_{min}$, H-8$_{a, min}$, H-2$_{b, min}$, H-5$_{b, min}$), 1.58 – 1.45 (m, 1H$_{min}$, H-8$_{b, min}$), 1.35 (s, 3H$_{maj}$, H-9$_{maj}$), 1.03 (s, 3H$_{min}$, H-9$_{min}$).

^{3}C NMR (101 MHz, $CDCl_3$): **Selected peaks for the major diastereomer** (from the mixture) δ 158.1 (C-17), 146.7 (C-13), 144.7 (C-Ph), 141.8 (C-Ph), 137.9 (C-14), 135.6 (C-12), 114.1 (2C, C-16), 55.4 (C-11), 50.8 (C-10), 48.6 (C-5), 44.1 (C-6), 40.8 (C-3), 39.0 (C-7), 37.9 (C-4), 31.2 (C-1), 30.7 (C-8), 26.5 (C-9), 25.7 (C-2). **Selected peaks for the minor diastereomer** (from the mixture) δ 158.0 (C-17), 147.3 (C-13), 144.5 (C-Ph), 141.7 (C-Ph), 137.7 (C-14),

[15] dr was calculated after column chromatography.

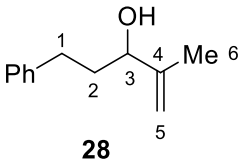
135.5 (C-12), 114.2 (2C, C-16), 55.4 (C-11), 51.5 (C-10), 49.1 (C-5), 46.3 (C-7), 43.4 (C-6), 42.4 (C-3), 37.6 (C-4), 30.6 (C-8), 29.6 (C-1), 26.0 (C-2), 22.6 (C-9). **Peaks in the aromatic region that could not be unambiguously assigned** (from the mixture) δ 130.9, 129.4, 129.1, 128.5, 128.4, 128.1, 127.9, 127.8, 127.1, 126.4, 126.3, 126.0, 125.7, 125.6, 125.6, 125.4, 124.9.

IR (film) ν_{max}: 2928, 1610, 1510, 1494, 1447, 1243, 1177, 1034, 907, 729, 701, 649 cm^{-1}.

HRMS (APCI): calculated for $C_{35}H_{37}O$ $[M+H]^+$ requires m/z 473.2839, found m/z 473.2833 (*Δ* = -1.26 ppm).

First generation route to substrate 26

2-Methyl-5-phenylpent-1-en-3-ol 28.



28
$C_{12}H_{16}O$
176.26 g mol^{-1}

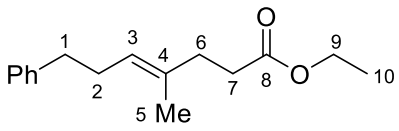
2-Bromoprop-1-ene (1.0 equiv, 9.0 mmol, 0.80 mL) was added dropwise to a suspension of magnesium turnings (1.2 equiv, 11 mmol, 0.26 g) and catalytic amount of iodine in THF (12 mL). The mixture was heated at reflux for 1h and then cooled to 0 °C. 3-phenylpropanal (1.1 equiv, 9.9 mmol, 1.3 mL) was then added dropwise and the obtained mixture was stirred at the same temperature for 0.5 h. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 4:1) to furnish allylic alcohol **28** as a colourless oil (0.76 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.25 (m, 2H, H-Ph), 7.24 – 7.17 (m, 3H, H-Ph), 4.99 – 4.95 (m, 1H, H-5_a), 4.89 – 4.86 (m, 1H, H-5_b), 4.15 – 4.04 (m, 1H, H-3), 2.78 – 2.57 (m, 2H, H-1), 1.93 – 1.83 (m, 2H, H-2), 1.75 (s, 3H, H-6). The OH proton was not found

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.6 (C-Ph/C-4), 142.1 (C-4/C-Ph), 128.6 (2C, C-Ph), 128.5 (2C, C-Ph), 126.0 (C-Ph), 111.4 (C-5), 75.4 (C-3), 36.7 (C-2), 32.0 (C-1), 17.8 (C-6).

The analytical data are consistent with those previously reported.[16]

Ethyl (*E*)-4-methyl-7-phenylhept-4-enoate 30.



30
$C_{16}H_{22}O_2$
246.35 g mol^{-1}

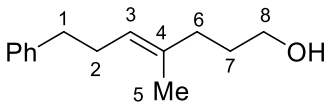
A solution of the allylic alcohol **28** (1.0 equiv, 4.3 mmol, 0.76 g) and propanoic acid (25 µL) in triethyl orthoacetate (10 ml) was heated with stirring at 145 °C for 24 h. The solution was cooled to room temperature, poured into water (10 mL) and extracted with Et_2O (3 X 15 mL). Organic layers were combined, washed successively with 1M $HCl_{(aq)}$ (2 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 19:1) to furnish ester **30** as a colourless oil (0.75 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H, H-Ph), 7.21 – 7.14 (m, 3H, H-Ph), 5.26 – 5.17 (m, 1H, H-3), 4.12 (q, *J* = 7.1 Hz, 2H, H-9), 2.63 (t, *J* = 7.5, 2H, H-1), 2.42 – 2.23 (m, 6H, H-2, H-6, H-7), 1.55 (s, 3H, H-5), 1.25 (t, *J* = 7.1 Hz, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6 (C-8), 142.3 (C-Ph/C-4), 134.3 (C-4/C-Ph), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.9 (C-Ph), 124.5 (C-3), 60.4 (C-9), 36.1 (C-1), 34.8 (C-2/C-6), 33.4 (C-7), 30.0 (C-6/C-2), 16.0 (C-5), 14.4 (C-10).

Analytical data are consistent with those previously reported.[17]

(*E*)-4-Methyl-7-phenylhept-4-en-1-ol 31.



31
$C_{14}H_{20}O$
204.31 g mol^{-1}

[16] W.-B. Xu, M. Sun, M. Shu, C. Li, , *J. Am. Chem. Soc*. **2021**, *143*, 8255–8260.
[17] R. O. McCourt, E. M. Scanlan, *Org. Lett*. **2019**, *21*, 3460–3464.

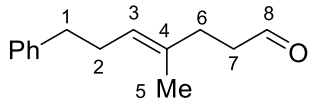
Ester **30** (1.0 equiv, 3.0 mmol, 0.74 g) in THF (3 mL) was added dropwise to a suspension of $LiAlH_4$ (1.2 equiv, 3.7 mmol, 0.14 g) in THF (15 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 2h followed by the subsequent addition of water (0.14 mL), NaOH (15% aq; 0.14 mL) and water (0.14 mL). The obtained suspension was stirred at room temperature for 20 min, transferred to a separatory funnel, diluted with an additional amount of water (15 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2) to furnish alcohol **31** as a colourless oil (0.51 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 2H, H-Ph), 7.22 – 7.14 (m, 3H, H-Ph), 5.26 – 5.18 (m, 1H, H-3), 3.60 (q, *J* = 6.0 Hz, 2H, H-8), 2.64 (t, *J* = 7.5 Hz, 2H, H-1), 2.37 – 2.26 (m, 2H, H-2), 2.06 (t, *J* = 7.3 Hz, 2H, H-6), 1.72 – 1.61 (m, 2H, H-7), 1.56 (s, 3H, H-5). The exchangeable OH proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.4 (C-Ph/C-4), 135.6 (C-4/C-Ph), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.9 (C-Ph), 124.3 (C-3), 62.9 (C-8), 36.2 (C-1), 36.1 (C-6), 30.9 (C-7), 30.0 (C-2), 16.0 (C-5).

The analytical data are consistent with those previously reported.[18]

(*E*)-4-Methyl-7-phenylhept-4-enal 32.



32
$C_{14}H_{18}O$
202.30 g mol^{-1}

Alcohol **31** (1.0 equiv, 0.25 g, 1.2 mmol) was dissolved in a mixture of CH_2Cl_2 (2.4 mL), DMSO (2.4 mL) and Et_3N (0.8 mL) at 0 °C. To the obtained solution $SO_3 \cdot$ py complex (2.9 equiv, 3.5 mmol, 0.55 g) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 2.5 h and then diluted with water (5 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 4:1) to furnish aldehyde **32** as a colourless oil (0.20 g, 81%).

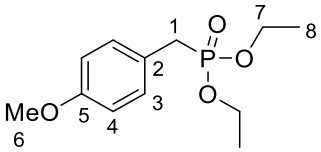
[18] H. Xu, H. Tang, H. Feng, Y. Li, *Tetrahedron Lett*. **2014**, *55*, 7118–7120.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, *J* = 2.0 Hz, 1H, H-8), 7.41 – 7.11 (m, 5H, H-Ph), 5.23 (t, *J* = 7.2 Hz, 1H, H-3), 2.66 (t, *J* = 7.6 Hz, 2H, H-1), 2.52 (td, *J* = 7.5, 2.0 Hz, 2H, H-7), 2.41 – 2.26 (m, 4H, H-2, H-6), 1.58 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.7 (C-8), 142.2 (C-Ph/C-4), 133.9 (C-4/C-Ph), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.9 (C-Ph), 124.9 (C-3), 42.3 (C-7), 36.0 (C-1), 32.0 (C-2/C-6), 30.0 (C-6/C-2), 16.2 (C-5).

Analytical data are consistent with those previously reported.[19]

Diethyl (4-methoxybenzyl)phosphonate 33.



33

$C_{12}H_{19}O_4P$

258.3 g mol^{-1}

According to a literature procedure,[20] ZnI_2 (1.7 g, 5.4 mmol, 1.5 equiv) was suspended in PhMe (10 mL) and triethyl phosphite (1.9 mL, 11 mmol, 3.1 equiv) was added in one portion at rt. 4-Methoxybenzyl alcohol (0.50 g, 3.6 mmol, 1.0 equiv) was added and the obtained solution was heated at reflux overnight. The solution was cooled to rt and volatiles were removed *in vacuo*. The residue was redissolved in Et_2O (10 mL), washed with 2M aq. NaOH (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane:EtOAc; 1:1 to EtOAc:MeOH; 49:1) to afford phosphonate **33** as a colourless oil (0.573 g, 61%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.11 (m, 2H, H-3), 6.94 – 6.73 (m, 2H, H-4), 4.08 – 3.91 (m, 4H, H-7), 3.77 (s, 3H, H-6), 3.07 (d, *J* = 21.2 Hz, 2H, H-1), 1.23 (t, *J* = 7.1 Hz, 6H, H-8).

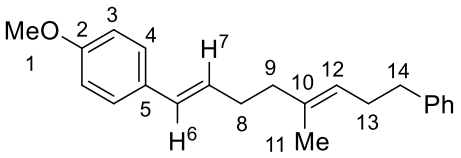
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7 (d, *J* = 3.5 Hz, C-5), 130.8 (d, *J* = 6.6 Hz, 2C, C-3), 123.5 (d, *J* = 9.2 Hz, C-2), 114.1 (d, *J* = 3.1 Hz, 2C, C-4), 62.2 (d, *J* = 6.8 Hz, 2C, C-7), 55.3 (C-6), 32.8 (d, *J* = 139.1 Hz, C-1), 16.47 (d, *J* = 6.0 Hz, 2C, C-8).

^{31}P NMR {^{1}H} (162 MHz, $CDCl_3$) δ 26.9.

[19] J. F. Zhao, T. P. Loh, *Angew. Chem. Int. Ed*. **2009**, *48*, 7232–7235.
[20] R. M. Richardson, D. F. Wiemer, *Org. Synth.* **2013**, *90*, 145–152.

The analytical data are consistent with those previously reported.[21]

1-Methoxy-4-((1*E*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)benzene *E*-26.



(*E*)-**26**
$C_{22}H_{26}O$
306.45 g mol^{-1}
$^{3}J_{\text{H-6, H-7}}$ = 15.8 Hz

(4-Methoxybenzyl)triphenylphosphonium chloride (1.48 equiv, 3.70 mmol, 1.55 g) was suspended in THF (10 mL) and cooled to -78 °C. *n*-BuLi (2.5 M in hexanes; 1.5 equiv, 3.8 mmol, 1.5 mL) was added dropwise and the obtained suspension was stirred at -78 °C for 0.5 h. Aldehyde **32** (1.0 equiv, 2.5 mmol, 0.50 g) in THF (3 mL) was added and the reaction mixture was allowed to warm to rt overnight. Saturated $NH_4Cl_{(aq)}$ (3 mL) was then added followed by water (10 mL) and Et_2O (10 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product (*E*:*Z*=75:25) was purified by flash column chromatography (SiO_2; 60 Å, 15–40 μm; pentane:Et_2O; 49:1) to furnish alkene (*E*)-**26** as a white solid (*E*:*Z*>95:5; 0.28 g, 37%) and alkene (*Z*)-**26** as a colourless oil (*Z*:*E*>95:5; 37 mg, 5%).

Data for (*E*)-26:

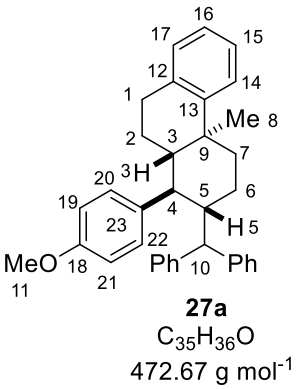
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.22 (m, 4H, H-Ph), 7.21 – 7.14 (m, 3H, H-4, H-Ph), 6.84 (d, *J* = 8.8 Hz, 2H, H-3), 6.33 (d, *J* = 15.8 Hz, 1H, H-6), 6.06 (dt, *J* = 15.8, 6.8 Hz, 1H, H-7), 5.27 – 5.19 (m, 1H, H-12), 3.80 (s, 3H, H-1), 2.68 – 2.59 (m, 2H, H-14), 2.37 – 2.23 (m, 4H, H-8, H-13), 2.17 – 2.08 (m, 2H, H-9), 1.58 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-2), 142.5 (C-10), 135.4 (C-Ph), 130.9 (C-5), 129.3 (C-6), 128.7 (C-7), 128.6 (2C, C-4), 128.4 (2C, C-Ph), 127.1 (2C, C-Ph), 125.8 (C-Ph), 124.2 (C-12), 114.1 (2C, C-3), 55.4 (C-1), 39.7 (C-9), 36.3 (C-14), 31.8 (C-8), 30.1 (C-13), 16.2 (C-11).

The analytical data for (*E*)-**26** and (*Z*)**-26** are consistent with the reported for this compound obtained *via* a different method, see page **179** and **182**.

[21] H. Huang, J. Denne, C.-H. Yang, H. Wang, J. Y. Kang, *Angew. Chem. Int. Ed*. **2018**, *57*, 6624–6628.

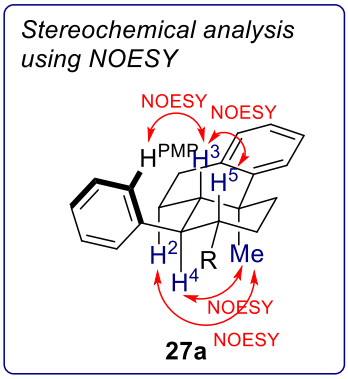
(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-benzhydryl-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27a.



27a

$C_{35}H_{36}O$

472.67 g mol^{-1}



Diene **26** (30.6 mg 0.100 mmol, 1.00 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish compound **27a** as a colourless sticky foam (40.5 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.19 (m, 7H, H-14, H-20/H-21, H-Ph), 7.17 – 7.05 (m, 7H, H-15, H-16, H-Ph), 7.03 – 6.98 (m, 1H, H-11), 6.95 – 6.88 (m, 2H, H-19/H-18, H-21/H-20), 6.84 (dd, *J* = 8.3, 2.8 Hz, 1H, H-18/H-19), 3.95 (d, *J* = 3.1 Hz, 1H, H-10), 3.84 (s, 3H, H-11), 2.77 – 2.53 (m, 3H, H-1, H-5), 2.43 – 2.33 (m, 2H, H-7$_a$, H-4), 1.99 – 1.89 (m, 1H, H-6$_a$), 1.78 – 1.61 (m, 3H, H-3, H-7$_b$, H-6$_b$), 1.39 – 1.27 (m, 1H, H-2$_a$), 1.22 – 1.13 (m, 1H, H-2$_b$), 1.01 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-18), 147.8 (C-13), 144.7 (C-Ph), 141.8 (C-Ph), 136.0 (C-23), 135.6 (C-12), 133.3 (C-20/C-22), 131.0 (2C, C-Ph), 129.3 (C-17), 128.4 (2C, C-Ph), 128.1 (2C, C-Ph), 127.9 (2C, C-Ph), 126.3 (C-Ph), 126.1 (C-22/C-20), 125.7 (2C, C-15, C-Ph), 125.6 (C-16), 124.6 (C-14), 115.1 (C-19/C-21), 112.8 (C-21/C-19), 55.3 (C-11), 51.8 (C-10), 49.1 (C-3), 47.9 (C-4), 47.4 (C-5), 37.9 (C-7), 37.6 (C-9), 29.6 (C-1), 23.9 (C-6), 22.9 (C-8), 22.7 (C-2).

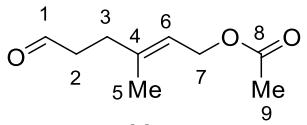
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me, between H-5 and H-3, between H-2 and Me, between H^{PMP} and H-3, between H^{PMP} and H-5.

IR (film) ν_{max}: 2935, 1610, 1510, 1494, 1148, 1245, 1177, 1035, 908, 731, 702 cm^{-1}.

HRMS (APCI): calculated for $C_{35}H_{36}ONa$ [M+Na]$^+$ requires m/z 495.2658, found m/z 495.2656 (*Δ* = -0.47 ppm).

Second generation route to substrate 26

(*E*)-3-Methyl-6-oxohex-2-en-1-yl acetate 38.



38

$C_9H_{14}O_3$

170.21 g mol^{-1}

According to a literature procedure,[1] to a solution of geranyl acetate **36** (0.41 g, 2.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at -10 °C was added *m*-CPBA (77% wt, 0.46 g, 2.1 mmol, 1.0 equiv) portionwise. The resulting slurry was warmed to rt, stirred for 2 h and then poured into 2 M NaOH (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was used in the next step without further purification. The crude product was redissolved in THF (1.5 mL) and then added dropwise to a solution of H_5IO_6 (0.47 g, 2.1 mmol, 1.0 equiv) in THF (1 mL) at 0 °C. The suspension was stirred at the same temperature for 1.5 h, poured into sat. aq. $NaHCO_3$ solution (5 mL) and then extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and volatiles were removed *in vacuo*. The residue was purified by flash chromatography (SiO_2; pentane:Et_2O; 4:1) to furnish aldehyde **38** as a colourless oil (0.25 g, 69% over two steps).

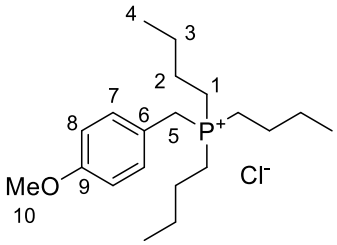
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (t, *J* = 1.7 Hz, 1H, H-1), 5.36 (tq, *J* = 7.0, 1.3 Hz, 1H, H-6), 4.58 (d, *J* = 7.0 Hz, 2H, H-7), 2.58 (td, *J* = 7.7, 1.6 Hz, 2H, H-2), 2.38 (t, *J* = 7.5 Hz, 2H, H-3), 2.05 (s, 3H, H-9), 1.72 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.8 (C-1), 171.2 (C-8), 140.1 (C-4), 119.5 (C-6), 61.2 (C-7), 41.9 (C-2), 31.6 (C-3), 21.2 (C-9), 16.7 (C-5).

The analytical data are consistent with those previously reported in the literature.[22]

[22] S. J. Partridge, D. M. Withall, J. C. Caulfield, J. A. Pickett, R. A. Stockman, N. J. Oldham, M. A. Birkett, *Chem. Eur. J*. **2021**, *27*, 7231–7234.

Tributyl(4-methoxybenzyl)phosphonium chloride 40.



40
$C_{20}H_{36}OPCl$
358.93 g mol^{-1}

4-Methoxybenzyl chloride (2.07 mL, 15.3 mmol, 1.05 equiv) and tri-*n*-butylphosphine (3.60 mL, 14.6 mmol, 1.00 equiv) were dissolved in MeCN (6 mL) and the solution was heated at 60 °C overnight. Volatiles were removed *in vacuo* and the residue was washed with pentane (3 × 10 mL). The remaining solid was dried under vacuum to obtain tri-*n*-butylphosphonium salt **40** as a white waxy solid (4.96 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.31 (m, 2H, H-7), 6.95 – 6.85 (m, 2H, H-8), 4.17 (d, *J* = 14.6 Hz, 2H, H-5), 3.80 (s, 3H, H-10), 2.49 – 2.31 (m, 6H, H-1), 1.55 – 1.36 (m, 12H, H-2 and H-3), 0.94 (t, *J* = 6.9 Hz, 9H, H-4).

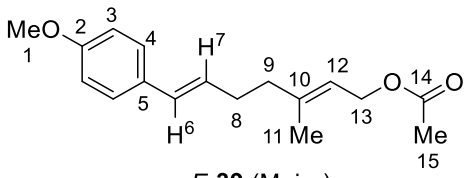
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7 (d, *J* = 3.6 Hz, C-9), 131.3 (d, *J* = 4.8 Hz, 2C, C-7), 120.1 (d, *J* = 8.7 Hz, C-6), 114.9 (d, *J* = 2.8 Hz, 2C, C-8), 55.4 (C-10), 26.2 (d, *J* = 45.3 Hz, C-5), 24.0 (d, *J* = 15.5 Hz, 3C, C-2), 23.8 (d, *J* = 4.8 Hz, 3C, C-3), 18.6 (d, *J* = 46.5 Hz, 3C, C-1), 13.5 (3C, C-4).

^{31}P (162 MHz, $CDCl_3$): δ 31.4.

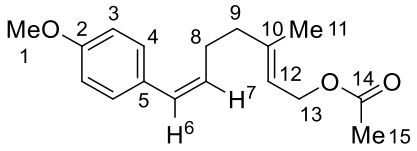
IR (film) ν_{max}: 3386, 2960, 2934, 2873, 2360, 1611, 1514, 1465, 1250, 1181, 1030, 844 cm^{-1}.

HRMS (ESI): calculated for $C_{20}H_{36}OP$ $[M]^+$ requires m/z 323.2498, found m/z 323.2500 (*Δ* = 0.62 ppm).

(2*E*,6*E*)-7-(4-Methoxyphenyl)-3-methylhepta-2,6-dien-1-yl acetate *E*-39 and (2*E*,6*Z*)-7-(4-Methoxyphenyl)-3-methylhepta-2,6-dien-1-yl acetate *Z*-39.



E-**39** (Major)
$C_{17}H_{22}O_3$
274.36 g mol^{-1}
$^3J_{H\text{-}6,\ H\text{-}7}$ = 15.8 Hz



Z-**39** (Minor)
$C_{17}H_{22}O_3$
274.36 g mol^{-1}
$^3J_{H\text{-}6,\ H\text{-}7}$ = 11.6 Hz

Tributyl(4-methoxybenzyl)phosphonium chloride **40** (5.06 g, 14.1 mmol, 1.50 equiv) was suspended in THF (200 mL) and cooled to 0 °C. *n*-BuLi (5.6 mL, 2.5 M in hexanes, 14 mmol, 1.5 equiv) was then added dropwise and the obtained suspension was allowed to stir at 0 °C for 30 min. After that the mixture was cooled to -78 °C and aldehyde **38** (1.60 g, 9.41 mmol, 1.00 equiv) in THF (18 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm to rt overnight and then quenched with sat. aq. NH_4Cl (20 mL). The mixture was diluted with water (100 mL) and extracted with Et_2O (3 × 100 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 9:1) to furnish an inseparable mixture of alkenes *E*-**39** and *Z*-**39** as a colourless oil (2.14 g, 83%, 94:6 *E*:*Z*).

Major *E*-39 (from the mixture)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H, H-4), 6.83 (d, *J* = 8.7 Hz, 2H, H-3), 6.33 (d, *J* = 15.8 Hz, 1H, H-6), 6.04 (dt, *J* = 15.8, 6.8 Hz, 1H, H-7), 5.39 (tq, *J* = 7.1, 1.3 Hz, 1H, H-12), 4.59 (d, *J* = 7.1 Hz, 2H, H-13), 3.80 (s, 3H, H-1), 2.36 – 2.28 (m, 2H, H-8), 2.24 – 2.15 (m, 2H, H-9), 2.04 (s, 3H, H-15), 1.74 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C-14), 158.9 (C-2), 141.9 (C-10), 130.7 (C-5), 129.7 (C-6), 127.9 (C-7), 127.2 (2C, C-4), 118.9 (C-12), 114.1 (2C, C-3), 61.5 (C-13), 55.4 (C-1), 39.5 (C-9), 31.3 (C-8), 21.2 (C-15), 16.6 (C-11).

Characteristic peaks for the minor *Z*-39 (from the mixture):

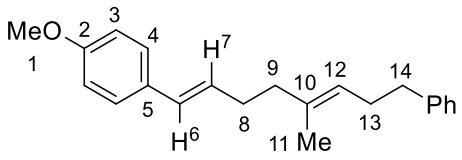
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.7 Hz, 2H, H-4), 6.87 (d, *J* = 8.7 Hz, 2H, H-3), 5.53 (dt, *J* = 11.6, 7.2, Hz, 1H, H-7), 3.81 (s, 3H, H-1), 2.50 – 2.42 (m, 2H, H-8), 2.05 (s, 3H, H-15), 1.69 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$): δ 130.0 (C-4), 113.8 (C-3).

IR (film) ν_{max}: 2935, 1735, 1608, 1510, 1366, 1232, 1175, 1033, 964, 844 cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{22}O_3Na$ $[M+Na]^+$ requires m/z 297.1461, found m/z 297.1463 (Δ = 0.62 ppm).

1-Methoxy-4-((1*E*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)benzene *E*-26.



***E*-26**
$C_{22}H_{26}O$
306.45 g mol^{-1}
$^3J_{H\text{-}6,\ H\text{-}7}$ = 15.8 Hz

A mixture of alkenes *E*-**39** and *Z*-**39** (0.170 g, 0.620 mmol, 1.00 equiv, 94:6 *E*:*Z*) was dissolved in THF (10 mL) and cooled to 0 °C. Li_2CuCl_4 (1.9 mL, 0.10 M in THF, 0.19 mmol, 0.30 equiv) was then added at the same temperature. To the obtained solution BnMgCl (2.8 mL, 2.0 M in THF, 5.6 mmol, 9.0 equiv) was added dropwise over 15 min keeping the temperature at 0 °C. The reaction mixture was allowed to stir at the same temperature for 3 h, quenched with sat. aq. NH_4Cl (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish compound (*E*)-**26** as a colourless oil which solidified on standing (0.151 g, 80%, >95:5 *E:Z*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.22 (m, 4H, H-Ph), 7.21 – 7.14 (m, 3H, H-4, H-Ph), 6.84 (d, *J* = 8.8 Hz, 2H, H-3), 6.33 (d, *J* = 15.8 Hz, 1H, H-6), 6.06 (dt, *J* = 15.8, 6.8 Hz, 1H, H-7), 5.27 – 5.19 (m, 1H, H-12), 3.80 (s, 3H, H-1), 2.68 – 2.59 (m, 2H, H-14), 2.37 – 2.23 (m, 4H, H-8, H-13), 2.17 – 2.08 (m, 2H, H-9), 1.58 (s, 3H, H-11).

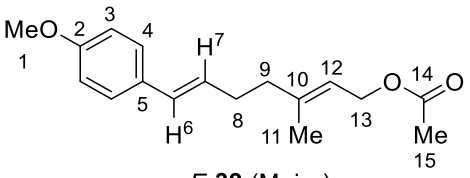
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-2), 142.5 (C-10), 135.4 (C-Ph), 130.9 (C-5), 129.3 (C-6), 128.7 (C-7), 128.6 (2C, C-4), 128.4 (2C, C-Ph), 127.1 (2C, C-Ph), 125.8 (C-Ph), 124.2 (C-12), 114.1 (2C, C-3), 55.4 (C-1), 39.7 (C-9), 36.3 (C-14), 31.8 (C-8), 30.1 (C-13), 16.2 (C-11).

M.p. 34-35 °C.

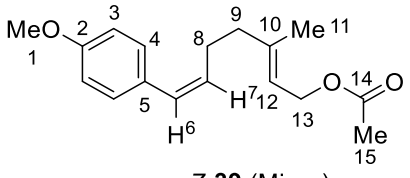
IR (film) ν_{max}: 2915, 2361, 1608, 1511, 1248, 1175, 1038, 965 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{27}O$ $[M+H]^+$ requires m/z 307.2056, found m/z 307.2057 (Δ = 0.25 ppm).

(2*E*,6*E*)-7-(4-Methoxyphenyl)-3-methylhepta-2,6-dien-1-yl acetate *E*-39 and (2*E*,6*Z*)-7-(4-methoxyphenyl)-3-methylhepta-2,6-dien-1-yl acetate *Z*-39.



E-**39** (Major)
$C_{17}H_{22}O_3$
274.36 g mol^{-1}
$^3J_{\text{H-6, H-7}}$ = 15.8 Hz



Z-**39** (Minor)
$C_{17}H_{22}O_3$
274.36 g mol^{-1}
$^3J_{\text{H-6, H-7}}$ = 11.6 Hz

(4-Methoxybenzyl)(triphenyl)phosphonium chloride (0.628 g, 1.50 mmol, 1.50 equiv) was suspended in THF (5 mL) and cooled to -78 °C. *n*-BuLi (0.600 mL, 2.5 M in hexanes, 1.50 mmol, 1.50 equiv) was then added dropwise and the obtained suspension was allowed to stir at -78 °C for 30 min. Aldehyde **38** (0.171 g, 1.00 mmol, 1.00 equiv) in THF (1.5 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm to rt overnight and then quenched with sat. aq. NH_4Cl (10 mL). The mixture was diluted with water (5 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 9:1) to furnish an inseparable mixture of alkenes *E*-**39** and *Z*-**39** as a colourless oil (0.138 g, 50%, 77:23 *E*:*Z*).

Major *E*-39 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H, H-4), 6.83 (d, *J* = 8.7 Hz, 2H, H-3), 6.33 (d, *J* = 15.8 Hz, 1H, H-6), 6.04 (dt, *J* = 15.8, 6.8 Hz, 1H, H-7), 5.39 (tq, *J* = 7.1, 1.3 Hz, 1H, H-12), 4.59 (d, *J* = 7.1 Hz, 2H, H-13), 3.80 (s, 3H, H-1), 2.36 – 2.28 (m, 2H, H-8), 2.24 – 2.15 (m, 2H, H-9), 2.04 (s, 3H, H-15), 1.74 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2 (C-14), 158.9 (C-2), 141.9 (C-10), 130.7 (C-5), 129.7 (C-6), 128.0 (C-7), 127.2 (2C, C-4), 118.9 (C-12), 114.1 (2C, C-3), 61.5 (C-13), 55.4 (C-1), 39.6 (C-9), 31.3 (C-8), 21.2 (C-15), 16.6 (C-11).

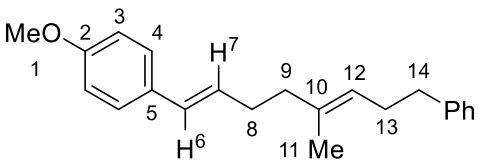
Characteristic peaks for the minor *Z*-39 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.7 Hz, 2H, H-4), 6.87 (d, *J* = 8.7 Hz, 2H, H-3), 5.53 (dt, *J* = 11.6, 7.2, Hz, 1H, H-7), 3.81 (s, 3H, H-1), 2.50 – 2.42 (m, 2H, H-8), 2.05 (s, 3H, H-15), 1.69 (s, 3H, H-11).

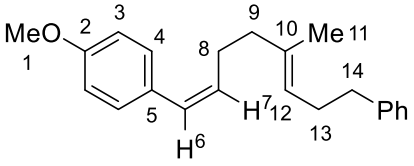
^{13}C NMR (101 MHz, $CDCl_3$): δ 141.7 (C-10), 130.4 (C-4), 113.7 (C-3), 39.7 (C-9).

The analytical data are consistent with the data for the previously reported mixture of *E*-**39** and *Z*-**39** mixture (94:6 *E*:*Z*).

1-Methoxy-4-((1*E*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)benzene *E*-26 and 1-Methoxy-4-((1Z,5E)-5-methyl-8-phenylocta-1,5-dien-1-yl)benzene *Z*-26.



E-**26** (Major)
$C_{22}H_{26}O$
306.45 g mol^{-1}
$^{3}J_{\text{H-6, H-7}}$ = 15.8 Hz



Z-**26** (Minor)
$C_{22}H_{26}O$
306.45 g mol^{-1}
$^{3}J_{\text{H-6, H-7}}$ = 11.7 Hz

A mixture of alkenes (*E*)-**39** and (*Z*)-**39** (0.120 g, 0.437 mmol, 1.00 equiv, 77:23 *E*:*Z*) was dissolved in THF (15 mL) and cooled to 0 °C. Li_2CuCl_4 (0.44 mL, 0.10 M in THF, 44 µmol, 0.10 equiv) was then added at the same temperature. To the obtained solution BnMgCl (0.66 mL, 2.0 M in THF, 1.3 mmol, 3.0 equiv) was added dropwise over 5 min keeping the temperature at 0 °C. The reaction mixture was allowed to stir at the same temperature for 3 h, quenched with sat. aq. NH_4Cl (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish compound *E*-**26** as a colourless oil which solidified on standing (44.3 mg, 33%, >95:5 *E:Z*) and *Z*-**26** as a colourless oil (7.0 mg, 5%,>95:5 *Z:E*).

Data for *E*-26:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.22 (m, 4H, H-Ph), 7.21 – 7.14 (m, 3H, H-4, H-Ph), 6.84 (d, *J* = 8.8 Hz, 2H, H-3), 6.33 (d, *J* = 15.8 Hz, 1H, H-6), 6.06 (dt, *J* = 15.8, 6.8 Hz, 1H, H-7), 5.27 – 5.29 (m, 1H, H-12), 3.80 (s, 3H, H-1), 2.64 (t, *J* = 7.5, 6.8 Hz, 2H, H-14), 2.37 – 2.23 (m, 4H, H-8, H-13), 2.17 – 2.08 (m, 2H, H-9), 1.58 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-2), 142.5 (C-10), 135.4 (C-Ph), 130.9 (C-5), 129.3 (C-6), 128.7 (C-7), 128.6 (2C, C-4), 128.4 (2C, C-Ph), 127.1 (2C, C-Ph), 125.8 (C-Ph), 124.2 (C-12), 114.1 (2C, C-3), 55.4 (C-1), 39.7 (C-9), 36.3 (C-14), 31.8 (C-8), 30.1 (C-13), 16.2 (C-11).

The analytical data for *E*-**26** are consistent with the previously reported for this compound obtained *via* a different method, see page **179**.

Data for *Z*-26:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.14 (m, 7H, H-Ph, H-4), 6.87 (d, *J* = 8.9 Hz, 2H, H-3), 6.34 (dt, *J* = 11.7, 2.0 Hz, 1H, H-6), 5.53 (dt, *J* = 11.7, 7.1 Hz, 1H, H-7), 5.21 (tq, *J* = 7.2, 1.4 Hz, 1H, H-12), 3.82 (s, 3H, H-1), 2.64 (t, *J* = 7.0 Hz, 2H, H-14), 2.41 (dtd, *J* = 8.3, 7.1, 1.9 Hz, 2H, H-8), 2.35 – 2.25 (m, 2H, H-13), 2.11 (t, *J* = 7.70 Hz, 2H, H-9), 1.54 (s, 3H, H-11).

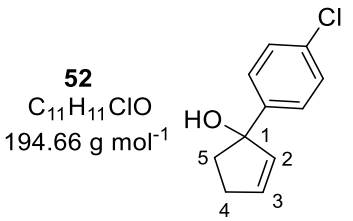
^{13}C NMR (151 MHz, $CDCl_3$) δ 158.3 (C-2), 142.5 (C-10), 135.3 (C-Ph), 131.1 (C-7), 130.6 (C-5), 130.1 (2C, C-4/C-Ph), 128.6 (2C, C-4/C-Ph), 128.4 (3C, C-6, C-4/C-Ph), 125.8 (C-Ph), 124.3 (C-12), 113.7 (2C, C-3), 55.4 (C-1), 39.9 (C-9), 36.2 (C-14), 30.1 (C-13), 27.2 (C-8), 16.1 (C-11).

IR (film) ν_{max}: 2917, 1608, 1510, 1247, 1176, 1026, 838, 698 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{27}O$ $[M+H]^+$ requires m/z 307.2056, found m/z 307.2057 (*Δ* = 0.35 ppm).

Electrophile synthesis

1-(4-Chlorophenyl)cyclopent-2-en-1-ol 52.



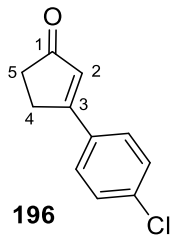
1-Bromo-4-chlorobenzene (0.23 g, 1.2 mmol, 1.0 equiv) was dissolved in THF (2.5 mL) and cooled to -78 °C. To the solution *n*-BuLi (0.53 mL, 2.5 M in hexanes, 1.3 mmol, 1.1 equiv) was added dropwise and the obtained suspension was allowed to stir at -78 °C for 30 min. Cyclopent-2-en-1-one (0.10 mL, 1.2 mmol, 1.0 equiv) in THF (0.5 mL) was then added dropwise at the same temperature and the suspension was allowed to stir at -78 °C for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (2 mL), diluted with water (5 mL) and Et_2O (5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 3:1) to get alcohol **52** as a colourless oil (0.161 g, 69%).

^{1}H NMR (400 MHz, C_6D_6): δ 7.21 – 7.11 (m, 4H, H-Ar), 5.64 (dt, *J* = 5.1, 2.4 Hz, 1H, H-2/H-3), 5.45 (dt, *J* = 5.7, 2.1 Hz, 1H, H-3, H-2), 2.19 (dddt, *J* = 15.7, 7.8, 4.9, 2.2 Hz, 1H, H-4_a), 2.06 – 1.85 (m, 3H, H-4_b, H-5_a, H-5_b), 1.26 – 1.14 (m, 1H, OH).

^{13}C NMR (101 MHz, C_6D_6): δ 146.4 (C-Ar), 137.0 (C-2/C-3), 134.4 (C-3/C-2), 132.7 (2C, C-Ar), 128.5 (2C, C-Ar), 126.9 (C-Ar), 86.3 (C-1), 42.5 (C-4/C-5), 31.5 (C-5/C-4).

The analytical data are consistent with those previously reported in the literature.[23]

3-(4-Chlorophenyl)cyclopent-2-en-1-one 196.



196
$C_{11}H_9ClO$
192.64 g mol^{-1}

1-Bromo-4-chlorobenzene (1.61 g, 8.40 mmol, 2.00 equiv) was dissolved in THF (12 mL) and cooled to -78 °C. *n*-BuLi (3.4 mL, 2.5 M in hexanes, 8.5 mmol, 2.0 equiv) was added dropwise and the obtained suspension was stirred at the same temperature for 30 min. The reaction mixture was warmed to 0 °C and 3-ethoxycyclopent-2-en-1-one (0.50 mL, 4.2 mmol, 1.0 equiv) in THF (3 mL) was then added dropwise. The obtained suspension was warmed to rt, stirred overnight and then quenched with sat. aq. NH_4Cl (3 mL). The mixture was diluted with water (15 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine (45 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 100:0 to 0:100) to obtain ketone **196** as a brown oil (0.375 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.53 (m, 2H, H-Ar), 7.48 – 7.39 (m, 2H, H-Ar), 6.55 (t, *J* = 1.8 Hz, 1H, H-2), 3.06 – 2.97 (m, 2H, H-5/H-4), 2.66 – 2.52 (m, 2H, H-4/H-5).

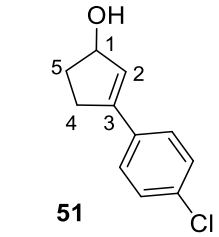
^{13}C NMR (101 MHz, $CDCl_3$): δ 209.2 (C-1), 172.5 (C-Ar/C-3), 137.4 (C-Ar/C-3), 132.7 (C-Ar/C-3), 129.4 (2C, C-Ar), 128.2 (2C, C-Ar), 128.0 (C-2), 35.4 (C-5/C-4), 28.8 (C-4/C-5).

IR (film) ν_{max}: 2919, 1704, 1687, 1599, 1490, 1408, 1188, 1092, 1013, 825, 717 cm^{-1}.

[23] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *39*, 9500–9512.

HRMS (ESI): calculated for $C_{11}H_9ClONa$ $[M+Na]^+$ requires m/z 215.0234, found m/z 215.0230 (Δ = -1.95 ppm).

3-(4-Chlorophenyl)cyclopent-2-en-1-ol 51.



51
$C_{11}H_{11}ClO$
194.66 g mol^{-1}

$CeCl_3 \times 7\ H_2O$ (0.677 g, 1.82 mmol, 1.03 equiv) was added in one portion to a solution of ketone **196** (0.340 g, 1.76 mmol, 1.00 equiv) in MeOH (6.3 mL) at 0 °C. To the obtained suspension $NaBH_4$ (69 mg, 1.8 mmol, 1.0 equiv) was added portionwise and the reaction mixture was stirred at the same temperature until judged to be complete by TLC. The mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; CH_2Cl_2:Et_2O; 9:1) to obtain allylic alcohol **51** as a pale yellow solid (0.219 g, 64%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.48 – 7.37 (m, 2H, H-Ar), 7.36 – 7.26 (m, 2H, H-Ar), 6.22 (q, *J* = 2.1 Hz, 1H, H-2), 5.02 – 4.90 (m, 1H, H-1), 2.92 – 2.79 (m, 1H, H-4_a), 2.67 – 2.55 (m, 1H, H-4_b), 2.44 (dddd, *J* = 13.5, 8.8, 7.3, 4.6 Hz, 1H, H-5_a), 1.83 (dddd, *J* = 13.8, 8.9, 5.1, 4.0 Hz, 1H, H-5_b), 1.65 (br, 1H, OH).

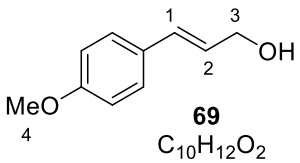
^{13}C NMR (101 MHz, CD_2Cl_2): δ 144.9 (C-Ar/C-3), 134.8 (C-Ar/C-3), 133.8 (C-Ar/C-3), 128.9 (3C, C-Ar, C-2), 127.8 (2C, C-Ar), 78.1 (C-1), 34.2 (C-5), 31.8 (C-4).

M.p: 91-93 °C.

IR (film) ν_{max}: 3317, 2971, 2360, 2341, 1775, 1493, 1335, 1094, 1050, 821 cm^{-1}.

HRMS (ESI): A stable molecular ion could not be detected by ESI, APCI or EI.

(*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol 69



69
$C_{10}H_{12}O_2$
164.20 g mol^{-1}

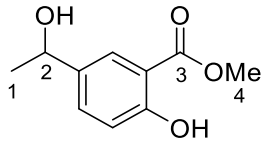
$NaBH_4$ (0.23 g, 6.2 mmol, 1.0 equiv) was added portionwise to the solution of (*E*)-3-(4-methoxyphenyl)acrylaldehyde (1.0 g, 6.2 mmol, 1.0 equiv) in MeOH (30 mL) at 0 °C. The obtained suspension was allowed to slowly warm to rt over 4 h and then cooled back to 0 °C. Water (20 mL) was slowly added and the mixture was extracted with Et_2O (4 × 30 mL). The organic layers were combined, washed with brine (60 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 1:1 to 3:7) to furnish alcohol **69** as a white solid (0.99 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H, H-Ar), 6.89 – 6.81 (m, 2H, H-Ar), 6.56 (dt, *J* = 15.7, 1.6 Hz, 1H, H-1), 6.24 (dt, *J* = 15.9, 5.9 Hz, 1H, H-2), 4.30 (td, *J* = 5.9, 1.5 Hz, 2H, H-3), 3.81 (s, 3H, H-4), 1.40 (t, *J* = 5.9 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (C-Ar), 131.2 (C-1), 129.6 (C-Ar), 127.8 (2C, C-Ar), 126.4 (C-2), 114.2 (2C, C-Ar), 64.1 (C-3), 55.4 (C-4).

The data are consistent with the literature[24]

Methyl 2-hydroxy-5-(1-hydroxyethyl)benzoate 198.



198
$C_{10}H_{12}O_4$
196.20 g mol^{-1}

Methyl 5-acetyl-2-hydroxybenzoate (0.300 g, 1.54 mmol, 1.00 equiv) was dissolved in MeOH (5 mL) and cooled to 0 °C. To the obtained solution $NaBH_4$ (0.117 g, 3.09 mmol, 2.00 equiv) was added portionwise and the obtained mixture was allowed to stir at 0 °C for 2 h. Water (10 mL) and Et_2O (10 mL) were then added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* to obtain methyl

[24] Y. Zhu, I. Colomer, A. L. Thompson, T. J. Donohoe, *J. Am. Chem. Soc*. **2019**, *141*, 6489−6493.

2-hydroxy-5-(1-hydroxyethyl)benzoate **198** as a colourless oil which did not require any further purification (0.271 g, 90%).

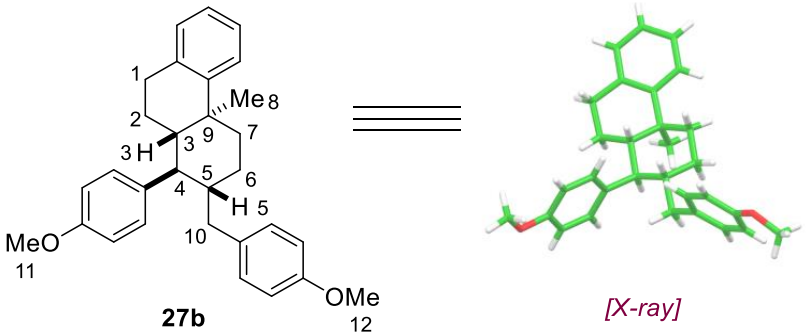
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H, OH), 7.85 (d, *J* = 2.1 Hz, 1H, H-Ar), 7.48 (dd, *J* = 8.6, 2.3 Hz, 1H, H-Ar), 6.97 (dd, *J* = 8.6, 1.2 Hz, 1H, H-Ar), 4.94 – 4.81 (m, 1H, H-2), 3.95 (s, 3H, H-4), 1.84 – 1.73 (br m, 1H, OH), 1.48 (d, *J* = 6.4 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6 (C-3), 161.1 (C-Ar), 136.7 (C-Ar), 133.3 (C-Ar), 126.8 (C-Ar), 117.9 (C-Ar), 112.2 (C-Ar), 69.8 (C-2), 52.4 (C-4), 25.3 (C-1).

The analytical data are consistent with those previously reported in the literature.[25]

The cation-triggered diene cyclisation

(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27b.



27b
$C_{30}H_{34}O_2$
426.60 g mol^{-1}

[X-ray]

Diene **26** (25.0 mg, 81.6 µmol, 1.00 equiv), 4-methoxybenzyl alcohol (11.3 mg, 81.6 µmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (7.4 µL, 25 µmol, 0.30 equiv) in HFIP (1.6 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm, pentane:Et_2O; 24:1) to furnish compound **27b** as a colourless oil which crystallised on standing (22.7 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 7.8, 1.5 Hz, 1H, H-Ar), 7.20 (dd, *J* = 8.7, 2.2 Hz, 1H, H-Ar), 7.16 – 6.95 (m, 5H, H-Ar), 6.91 (d, *J* = 8.6 Hz, 2H, H-Ar), 6.84 (dd, *J* = 8.3, 2.9 Hz, 1H, H-Ar), 6.77 (d, *J* = 8.6 Hz, 2H, H-Ar), 3.84 (s, 3H, H-11/H-12), 3.77 (s, 3H, H-12/H-11), 2.80 – 2.61 (m, 2H, H-1$_a$, H-1$_b$), 2.51 (dd, *J* = 13.4, 2.8 Hz, 1H, H-10$_a$), 2.38 – 2.25 (m, 2H, H-

[25] B. T. Cho, S. K. Kang, M. S. Kim, S. R. Ryu, D. K. An, *Tetrahedron* **2006**, *62*, 8164–8168.

7_a, H-4), 2.00 (dd, *J* = 13.4, 10.1 Hz, 1H, H-10_b), 1.78 – 1.65 (m, 3H, H-3, H-5, H-6_a), 1.55 – 1.34 (m, 3H, H-6_b, H-14_b, H-2_a), 1.31 – 1.22 (m, 1H, H-2_b), 1.19 (s, 3H, H-8).

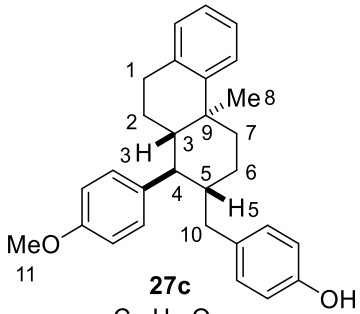
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-Ar), 157.7 (C-Ar), 148.1 (C-Ar), 136.7 (C-Ar), 135.7 (C-Ar), 133.6 (C-Ar), 132.7 (C-Ar), 130.1 (2C, C-Ar), 129.3 (C-Ar), 125.9 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.7 (C-Ar), 115.3 (C-Ar), 113.6 (2C, C-Ar), 112.8 (C-Ar), 55.4 (C-11/C-12), 55.3 (C-12/C-11), 50.5 (C-4), 47.8 (C-3), 46.1 (C-5), 40.4 (C-10), 37.6 (2C, C-7, C-9), 29.6 (C-1), 27.5 (C-6), 22.7 (2C, C-8, C-2).

M.p: 139 °C.

IR (film) ν_{max}: 2929, 2834, 1611, 1510, 1301, 1243, 1177, 1027, 829, 809, 761 cm^{-1}.

HRMS (ESI): calculated for $C_{30}H_{35}O_2$ $[M+H]^+$ requires m/z 427.2632, found m/z 427.2632 (*Δ* = 0.06 ppm).

(±)-4-(((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)methyl)phenol 27c.



27c
$C_{29}H_{32}O_2$
412.57 g mol^{-1}

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 4-(hydroxymethyl)phenol (12.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish compound **27c** as a sticky oil (27.3 mg, 66%).[26]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.24 – 6.92 (m, 6H, H-Ar), 6.90 – 6.80 (m, 3H, H-Ar), 6.69 (d, *J* = 8.3 Hz, 2H, H-Ar), 4.73 (br, 1H, OH), 3.84 (s, 3H, H-11), 2.82 – 2.61 (m, 2H, H-1), 2.50 (dd, *J* = 13.5, 2.7 Hz, 1H, H-10_a), 2.38 – 2.24 (m, 2H, H-4, H-7_a),

[26] Relative stereochemistry is determined by analogy to product **27b**.

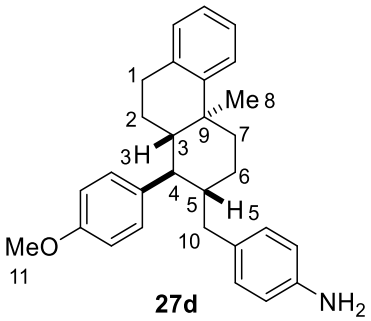
1.99 (dd, *J* = 13.5, 10.1 Hz, 1H, H-10_b), 1.78 – 1.63 (m, 3H, H-3, H-5, H-6_a), 1.56 – 1.35 (m, 3H, H-7_b, H-2_a, H-6_b), 1.32 – 1.22 (m, 1H, H-2_b), 1.19 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 153.5 (C-Ar), 148.1 (C-Ar), 136.7 (C-Ar), 135.7 (C-Ar), 133.7 (C-Ar), 132.6 (C-Ar), 130.2 (2C, C-Ar), 129.3 (C-Ar), 125.9 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.7 (C-Ar), 115.3 (C-Ar), 115.0 (2C, C-Ar), 112.8 (C-Ar), 55.4 (C-11), 50.5 (C-4), 47.8 (C-3), 46.1 (C-5), 40.4 (C-10), 37.5 (2C, C-7, C-9), 29.6 (C-1), 27.4 (C-6), 22.7 (2C, C-2, C-8).

IR (film) ν_{max}: 3400, 2923, 2853, 1611, 1511, 1447, 1240, 1177, 1037, 830, 763 cm^{-1}.

HRMS (ESI): calculated for $C_{29}H_{31}O_2$ $[M-H]^-$ requires m/z 411.2330, found m/z 411.2316 (*Δ* = -3.37 ppm).

(±)-4-(((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)methyl)aniline 27d.



27d
$C_{29}H_{33}NO$
411.59 g mol^{-1}

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (4-aminophenyl)methanol (12.3 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; CH_2Cl_2:Et_2O; 9:1) to furnish compound **27d** as a brown oil (25.4 mg, 62%).[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 7.8, 1.5 Hz, 1H, H-Ar), 7.22 – 6.94 (m, 6H, H-Ar), 6.83 (dd, *J* = 8.2, 2.8 Hz, 1H, H-Ar), 6.78 (d, *J* = 8.3 Hz, 2H, H-Ar), 6.57 (d, *J* = 8.3 Hz, 2H, H-Ar), 3.83 (s, 3H, H-11), 3.52 (br, 2H, NH_2), 2.80 – 2.61 (m, 2H, H-1), 2.46 (dd, *J* = 13.3, 2.8 Hz, 1H, H-10_a), 2.35 – 2.25 (m, 2H, H-7_a, H-4), 1.94 (dd, *J* = 13.4, 10.2 Hz, 1H, H-10_b), 1.79 –

[27] Relative stereochemistry is determined by analogy to product **27b**.

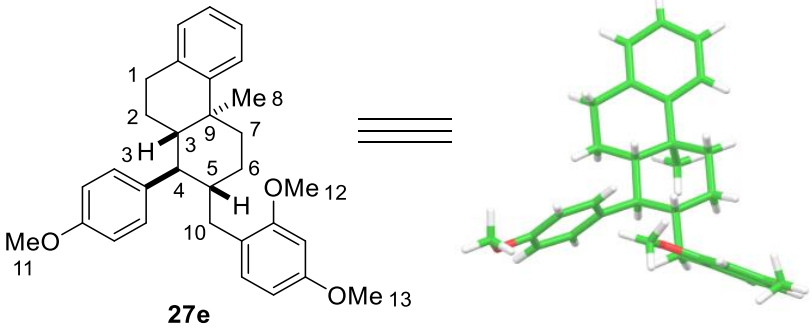
1.63 (m, 3H, H-3, H-5, H-6$_a$), 1.55 – 1.34 (m, 3H, H-7$_b$, H-6$_b$, H-2$_a$), 1.30 – 1.22 (m, 1H, H-2$_b$), 1.18 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 148.1 (C-Ar), 144.1 (C-Ar), 136.8 (C-Ar), 135.7 (C-Ar), 132.7 (C-Ar), 131.6 (C-Ar), 130.0 (2C, C-Ar)), 129.3 (C-Ar), 125.9 (C-Ar), 125.7 (C-Ar), 125.5 (C-Ar), 124.8 (C-Ar), 115.3 (C-Ar), 115.1 (2C, C-Ar), 112.7 (C-Ar), 55.4 (C-11), 50.5 (C-4), 47.8 (C-3), 46.1 (C-5), 40.5 (C-10), 37.6 (2C, C-9, C-7), 29.6 (C-1), 27.4 (C-6), 22.7 (2C, C-8, C-2).

IR (film) ν_{max}: 3369, 2925, 1611, 1512, 1267, 1243, 1178, 1037, 909, 829, 732 cm^{-1}.

HRMS (ESI): calculated for $C_{29}H_{34}NO$ $[M+H]^+$ requires m/z 412.2635, found m/z 412.2629 (*Δ* = -1.38 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-(2,4-Dimethoxybenzyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27e.



27e
$C_{31}H_{36}O_3$
456.63 g mol^{-1}

[X-ray]

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (2,4-dimethoxyphenyl)methanol (16.8 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 9:1) to furnish compound **27e** as a white solid (15.0 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 7.8, 1.4 Hz, 1H, H-Ar), 7.21 (dd, *J* = 8.6, 2.3 Hz, 1H, H-Ar), 7.16 – 7.04 (m, 3H, H-Ar), 7.03 – 6.92 (m, 2H, H-Ar), 6.89 – 6.78 (m, 2H, H-Ar), 6.42 – 6.31 (m, 2H, H-Ar), 3.84 (s, 3H, H-11/H-12/H-13), 3.77 (s, 3H, H-11/H-12/H-13), 3.69 (s, 3H, H-11/H-12/H-13), 2.80 – 2.60 (m, 2H, H-1), 2.46 (dd, *J* = 13.2, 2.9 Hz, 1H, H-10$_a$), 2.36 – 2.23 (m, 2H, H-4, H-7$_a$), 2.04 (dd, *J* = 13.2, 10.6 Hz, 1H, H-10$_b$), 1.86 – 1.63 (m, 3H, H-3, H-5, H-6$_a$), 1.53 – 1.35 (m, 3H, H-7$_b$, H-6$_b$, H-2$_a$), 1.32 – 1.19 (m, 4H, H-2$_b$, H-8).

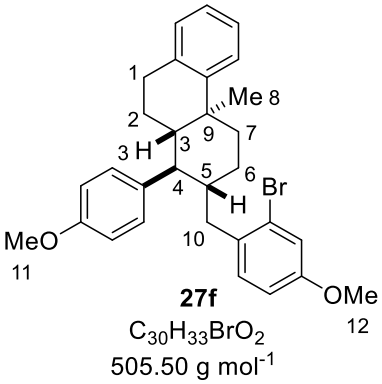
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (C-Ar), 158.6 (C-Ar), 158.0 (C-Ar), 148.3 (C-Ar), 136.8 (C-Ar), 135.8 (C-Ar), 132.5 (C-Ar), 130.9 (C-Ar), 129.2 (C-Ar), 126.4 (C-Ar), 125.6 (C-Ar), 125.5 (C-Ar), 124.8 (C-Ar), 122.5 (C-Ar), 115.0 (C-Ar), 112.4 (C-Ar), 103.7 (C-Ar), 98.5 (C-Ar), 55.4 (C-11/C-12/C-13), 55.3 (C-11/C-12/C-13), 55.2 (C-11/C-12/C-13), 50.9 (C-4), 47.9 (C-3), 44.3 (C-5), 37.7 (C-9), 37.6 (C-7), 35.0 (C-10), 29.7 (C-1), 27.5 (C-6), 22.8 (C-8), 22.7 (C-2).

M.p: 119-121 °C.

IR (film) ν_{max}: 2931, 1611, 1586, 1508, 1463, 1207, 1155, 1039, 909, 824, 761, 731 cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{37}O_3$ $[M+H]^+$ requires m/z 457.2737, found m/z 457.2737 (*Δ* = 0.05 ppm).

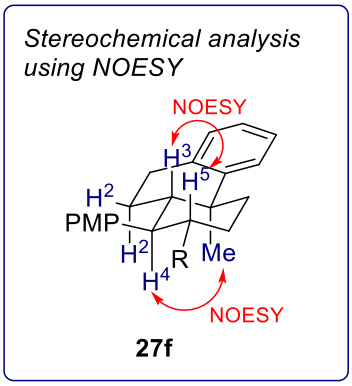
(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-(2-Bromo-4-methoxybenzyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27f.



27f

$C_{30}H_{33}BrO_2$

505.50 g mol^{-1}



Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (2-bromo-4-methoxyphenyl)methanol (21.6 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish compound **27f** as a colourless oil (17.4 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 7.8, 1.5 Hz, 1H, H-Ar), 7.24 (dd, *J* = 8.6, 2.2 Hz, 1H, H-Ar), 7.17 – 6.99 (m, 5H, H-Ar), 6.97 – 6.89 (m, 2H, H-Ar), 6.83 (dd, *J* = 8.2, 2.8 Hz, 1H, H-Ar), 6.74 (dd, *J* = 8.4, 2.6 Hz, 1H, H-Ar), 3.83 (s, 3H, H-11/H-12), 3.75 (s, 3H, H-12/H-11), 2.80 – 2.63 (m, 2H, H-1), 2.58 (dd, *J* = 13.5, 3.4 Hz, 1H, H-10$_a$), 2.40 – 2.27 (m, 2H, H-4, H-7$_a$), 2.23 (dd, *J* = 13.6, 11.0 Hz, 1H, H-10$_b$), 1.95 – 1.82 (m, 1H, H-5), 1.76 (ddd, *J* = 12.4, 11.3, 3.0 Hz, 1H, H-3), 1.67 – 1.36 (m, 4H, H-6$_a$, H-6$_b$, H-7$_b$, H-2$_a$), 1.32 – 1.18 (m, 4H, H-2$_b$, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2 (2C, C-Ar), 148.1 (C-Ar), 136.2 (C-Ar), 135.7 (C-Ar), 132.9 (C-Ar), 132.4 (C-Ar), 131.8 (C-Ar), 129.3 (C-Ar), 126.4 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 124.7 (C-Ar), 117.7 (C-Ar), 115.2 (C-Ar), 113.5 (C-Ar), 112.6 (C-Ar), 55.6 (C-11/C-12), 55.4 (C-12/C-11), 51.0 (C-4), 47.7 (C-3), 44.3 (C-5), 40.5 (C-10), 37.5 (2C, C-7, C-9), 29.6 (C-1), 27.3 (C-6), 22.8 (C-8), 22.7 (C-2).

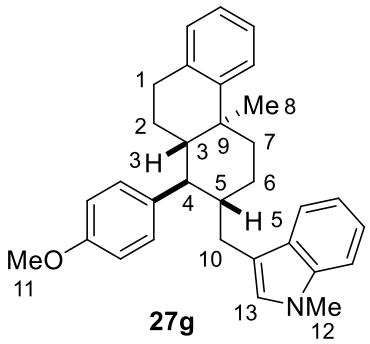
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me, between H-3 and H-5.

Note: the appearance of ^{1}H NMR signal for H-3: 1.76 (ddd, *J* = 12.4, 11.3, 3.0 Hz, 1H, H-3) is indicative of a *trans*-diaxial arrangement between H-3 and H-4, H-3 and H-2 and equatorial arrangement between H-3 and H-2.

IR (film) ν_{max}: 2932, 2361, 2343, 1606, 1511, 1492, 1241, 1178, 1038, 824, 761, 728 cm^{-1}.

HRMS (ESI): calculated for $C_{30}H_{34}O_2Br$ $[M+H]^+$ requires m/z 505.1737, found m/z 505.1738 (*Δ* = 0.25 ppm).

(±)-3-((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)methyl)-1-methyl-1H-indole 27g.



27g
$C_{32}H_{35}NO$
449.64 g mol^{-1}

Diene **26** (30.6 mg 0.100 mmol, 1.00 equiv), (1-methyl-1H-indol-3-yl)methanol[28] (16.1 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C** except that the reaction was performed at rt and for 2.5 h. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 19.1:0.9) to furnish compound **27g** as a colourless oil (25.1 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.23 (m, 4H, H-Ar), 7.22 – 6.99 (m, 7H, H-Ar), 6.88 (dd, *J* = 8.3, 2.6 Hz, 1H, H-Ar), 6.74 (s, 1H, H-13), 3.87 (s, 3H, H-11/H-12), 3.73 (s, 3H, H-12/H-

[28] M. A. J. Dubois, R. A. Croft, Y. Ding, C. Choi, D. R. Owen, J. A. Bulla, J. J. Mousseau, *RSC Med. Chem*. **2021**, *12*, 2045–2052.

11), 2.82 – 2.63 (m, 3H, H-1_a, H-1_b, H-10_a), 2.39 (t, *J* = 11.1 Hz, 1H, H-4), 2.34 – 2.15 (m, 2H, H-7_a, H-10_b), 1.94 – 1.71 (m, 3H, H-6_a, H-5, H-3), 1.54 – 1.39 (m, 3H, H-7_b, H-6_b, H-2_a), 1.35 – 1.28 (m, 1H, H-2_b), 1.23 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-Ar), 148.2 (C-Ar), 137.0 (2C, C-Ar), 135.7 (C-Ar), 132.7 (C-Ar), 129.3 (C-Ar), 128.4 (C-Ar), 127.0 (C-13), 126.1 (C-Ar), 125.7 (C-Ar), 125.5 (C-Ar), 124.7 (C-Ar), 121.3 (C-Ar), 119.4 (C-Ar), 118.5 (C-Ar), 115.3 (C-Ar), 114.0 (C-Ar), 112.7 (C-Ar), 109.1 (C-Ar), 55.4 (C-11), 50.7 (C-4), 47.8 (C-3), 45.0 (C-5), 37.6 (2C, C-7, C-9), 32.6 (C-12), 30.5 (C-10), 29.7 (C-1), 28.2 (C-6), 22.8 (C-8), 22.7 (C-2).

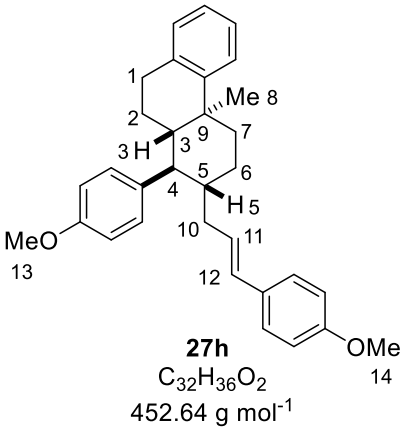
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Note: the appearance of ^{1}H NMR signal for H-4: 2.39 (t, *J* = 11.1 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

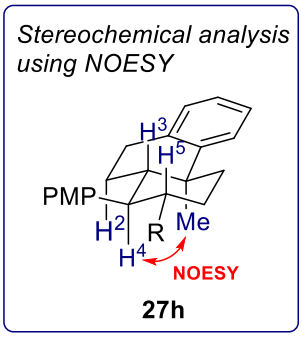
IR (film) ν_{max}: 2927, 1611, 1510, 1244, 1177, 1038, 908, 823, 761, 734 cm^{-1}.

HRMS (ESI): calculated for $C_{32}H_{36}ON$ $[M+H]^+$ requires m/z 450.2791, found m/z 450.2792 (*Δ* = 0.14 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)allyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27h.



27h
$C_{32}H_{36}O_2$
452.64 g mol^{-1}



Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol[24] (16.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 24:1) to furnish compound **27h** as a colourless oil (18.5 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.8, 1.4 Hz, 1H, H-Ar, H-Ar), 7.24 (d, *J* = 8.7 Hz, 2H, H-Ar), 7.18 – 6.99 (m, 5H, H-Ar), 6.97 – 6.89 (m, 1H, H-Ar), 6.87 – 6.77 (m, 3H, H-Ar),

6.17 (d, *J* = 15.7 Hz, 1H, H-12), 5.95 (ddd, *J* = 15.8, 8.2, 6.4 Hz, 1H, H-11), 3.83 (s, 3H, H-13/H-14), 3.80 (s, 3H, H-14/H-13), 2.80 – 2.60 (m, 2H, H-1), 2.44 – 2.36 (m, 1H, H-7_a), 2.32 (t, *J* = 11.0 Hz, 1H, H-4), 2.06 (dddd, *J* = 13.5, 6.1, 3.2, 1.5 Hz, 1H, H-10_a), 2.00 – 1.89 (m, 1H, H-6_a), 1.86 – 1.53 (m, 5H, H-10_b, H-3, H-5, H-7_b, H-6_b), 1.47 – 1.33 (m, 1H, H-2_a), 1.30 – 1.22 (m, 1H, H-2_b), 1.20 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 158.0 (C-Ar), 148.1 (C-Ar), 136.5 (C-Ar), 135.7 (C-Ar), 132.5 (C-Ar), 130.9 (C-Ar), 130.6 (C-12), 129.3 (C-Ar), 127.1 (3C, C-Ar,C-11), 126.0 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 115.1 (C-Ar), 114.0 (2C, C-Ar), 112.7 (C-Ar), 55.4 (C-13/C-14), 55.3 (C-14/C-13), 49.8 (C-4), 47.7 (C-3), 44.2 (C-5), 38.2 (C-10), 37.7 (C-7), 37.5 (C-7), 29.6 (C-1), 27.9 (C-6), 22.7 (C-8), 22.6 (C-2).

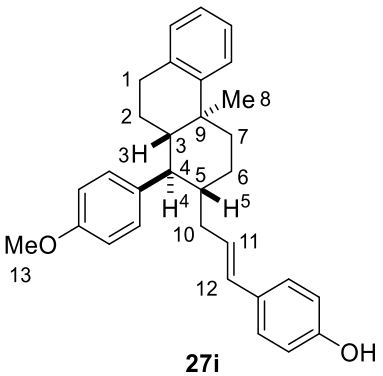
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Note: the appearance of ^{1}H NMR signal for H-4: 2.32 (t, *J* = 11.0 Hz, 1H, H-4) is indicative of a trans-diaxial arrangement between H-4 and H-3; H-4 and H-5.

IR (film) ν_{max}: 2925, 1608, 1510, 1464, 1245, 1176, 1037, 966, 909, 833, 760, 732 cm^{-1}.

HRMS (APCI): calculated for $C_{32}H_{37}O_2$ $[M+H]^+$ requires m/z 453.2788, found m/z 453.2785 (*Δ* = -0.69 ppm).

(±)-4-((*E*)-3-((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)prop-1-en-1-yl)phenol 27i.



27i
$C_{31}H_{34}O_2$
438.61 g mol^{-1}

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (*E*)-3-(4-hydroxyphenyl)prop-2-en-1-ol[29] (15.0 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL,

[29] C. Han, Z. Huang, C. Zheng, L. Wan, Y. Lai, S. Peng, K. Ding, H. Ji, Y. Zhang, *Eur. J. of Med. Chem*. **2013**, *66*, 82–90.

0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish compound **27i** as a colourless oil (17.3 mg, 39%).[30]

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.33 (dd, *J* = 7.9, 1.4 Hz, 1H, H-Ar), 7.22 – 6.97 (m, 7H, H-Ar), 6.93 (dd, *J* = 8.5, 2.8 Hz, 1H, H-Ar), 6.82 (dd, *J* = 8.2, 2.9 Hz, 1H, H-Ar), 6.74 (d, *J* = 8.6 Hz, 2H, H-Ar), 6.15 (d, *J* = 15.7 Hz, 1H, H-12), 5.95 (ddd, *J* = 15.7, 8.1, 6.4 Hz, 1H, H-11), 5.02 – 4.86 (m, 1H, OH), 3.80 (s, 3H, H-13), 2.79 – 2.58 (m, 2H, H-1), 2.39 (dd, *J* = 9.3, 3.2 Hz, 1H, H-7_a), 2.33 (t, *J* = 11.0 Hz, 1H, H-4), 2.07 – 1.99 (m, 1H, H-10_a), 1.97 – 1.90 (m, 1H, H-6_a), 1.86 – 1.53 (m, 5H, H-10b, H-6b, H-7b, H-5, H-3), 1.46 – 1.33 (m, 1H, H-2_a), 1.26 – 1.14 (m, 4H, H-8. H-2_b).

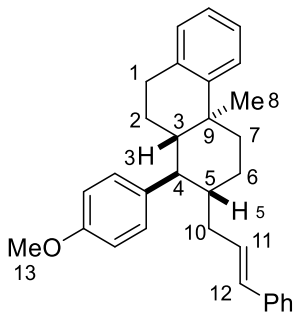
^{13}C NMR (101 MHz, CD_2Cl_2): δ 158.4 (C-Ar), 155.1 (C-Ar), 148.5 (C-Ar), 136.9 (C-Ar), 136.1 (C-Ar), 132.7 (C-Ar), 131.3 (C-Ar), 130.6 (C-12), 129.5 (C-Ar), 127.5 (2C, C-Ar), 127.4 (C-11), 126.4 (C-Ar), 125.9 (C-Ar), 125.7 (C-Ar), 125.0 (C-Ar), 115.6 (2C, C-Ar), 115.3 (C-Ar), 113.0 (C-Ar), 55.6 (C-13), 50.0 (C-4), 48.0 (C-3), 44.4 (C-5), 38.4 (C-10), 38.0 (C-7), 37.8 (C-9), 29.9 (C-1), 28.2 (C-6), 22.9 (C-2), 22.8 (C-8).

Note: the appearance of ^{1}H NMR signal for H-4: 2.33 (t, *J* = 11.0 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

IR (film) ν_{max}: 3386, 2917, 2849, 1610, 1511, 1241, 1177, 908, 731 cm^{-1}

HRMS (ESI): calculated for $C_{31}H_{33}O_2$ $[M-H]^-$ requires m/z 437.2486, found m/z 437.2470 (*Δ* = -3.78 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-Cinnamyl-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27j.



27j
$C_{31}H_{34}O$
422.61 g mol^{-1}

[30] Relative stereochemistry is determined by analogy to compound **2b**.

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (*E*)-3-phenylprop-2-en-1-ol (13.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 24:1) to furnish compound **27j** as a colourless oil (8.0 mg, 19%).

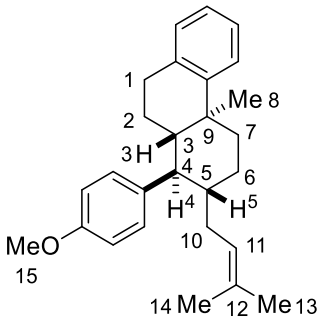
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 6.97 (m, 11H, H-Ar), 6.93 (dt, *J* = 8.8, 4.4 Hz, 1H, H-Ar), 6.86 – 6.77 (m, 1H, H-Ar), 6.22 (d, *J* = 15.8 Hz, 1H, H-12), 6.09 (ddd, *J* = 15.7, 8.2, 6.3 Hz, 1H, H-11), 3.82 (s, 3H, H-13), 2.81 – 2.58 (m, 2H, H-1$_a$, H-1$_b$), 2.43 – 2.24 (m, 2H, H-7$_a$, H-4), 2.08 (dddd, *J* = 13.6, 6.3, 3.5, 1.5 Hz, 1H, H-10$_a$), 1.99 – 1.90 (m, 1H, H-6$_a$), 1.89 – 1.79 (m, 1H, H-10$_b$), 1.78 – 1.50 (m, 4H, H-7$_b$, H-6$_b$, H-5, H-3), 1.48 – 1.33 (m, 1H, H-2$_a$), 1.30 – 1.13 (m, 4H, H-2$_b$, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (C-Ar), 148.1 (C-Ar), 138.0 (C-Ar), 136.5 (C-Ar), 135.7 (C-Ar), 132.5 (C-Ar), 131.2 (C-12), 129.3 (2C, C-Ar, C-11), 128.6 (2C, C-Ar), 126.9 (C-Ar), 126.0 (3C, C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 115.1 (C-Ar), 112.8 (C-Ar), 55.4 (C-13), 49.8 (C-4), 47.7 (C-3), 44.1 (C-5), 38.3 (C-10), 37.7 (C-7), 37.5 (C-9), 29.6 (C-1), 27.9 (C-6), 22.8 (C-8), 22.6 (C-2).

IR (film) ν_{max}: 3026, 2836, 2362, 1611, 1512, 1441, 1248, 1178, 1039, 967, 833, 762, 744, 695, 644 cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{35}O$ $[M+H]^+$ requires m/z 423.2682, found m/z 423.2680 (*Δ* = -0.58 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-2-(3-methylbut-2-en-1-yl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27k.



27k
$C_{27}H_{34}O$
374.57 g mol^{-1}

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 3-methylbut-2-en-1-ol (17.2 mg, 0.200 mmol, 2.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C** except that the reaction was performed with 2.00 equiv of alcohol and for 50 min. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 97:3) to furnish compound **27k** as a single detectable diastereomer as a colourless oil (7.0 mg, 19%).[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H, H-Ar), 7.18 – 7.05 (m, 3H, H-Ar), 7.05 – 6.94 (m, 2H, H-Ar), 6.93 – 6.85 (m, 1H, H-Ar), 6.84 – 6.75 (m, 1H, H-Ar), 5.05 (ddt, *J* = 8.1, 6.5, 1.5 Hz, 1H, H-11), 3.81 (s, 3H, H-15), 2.78 – 2.58 (m, 2H, H-1), 2.36 (dt, *J* = 12.2, 3.1 Hz, 1H, H-7$_a$), 2.27 (t, *J* = 10.8 Hz, 1H, H-4), 1.94 – 1.85 (m, 1H, H-6$_a$), 1.84 – 1.76 (m, 1H, H-10$_a$), 1.75 – 1.15 (m, 16H, H-2$_a$, H-2$_b$, H-3, H-5, H-6$_b$, H-7$_b$, H-8, H-10$_b$, H-14, H-13).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (C-Ar), 148.3 (C-Ar), 136.8 (C-Ar), 135.8 (C-Ar), 132.4 (C-Ar), 132.1 (C-12), 129.3 (C-Ar), 126.0 (C-Ar), 125.7 (C-Ar), 125.5 (C-Ar), 124.8 (C-Ar), 122.9 (C-11), 115.0 (C-Ar), 112.7 (C-Ar), 55.4 (C-15), 49.8 (C-4), 47.7 (C-3), 44.6 (C-5), 37.8 (C-7), 37.6 (C-9), 33.0 (C-10), 29.6 (C-1), 27.7 (C-6), 26.0 (C-14/C-13), 22.8 (C-8), 22.7 (C-2), 17.9 (C-13/C-14).

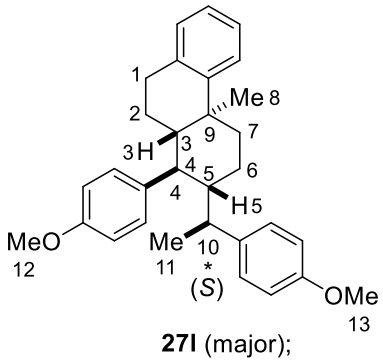
Note: the appearance of ^{1}H NMR signal for H-4: 2.27 (t, *J* = 10.8 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

IR (film) ν_{max}: 2925, 1611, 1511,1450, 1246, 1177, 1040, 909, 827, 733 cm^{-1}.

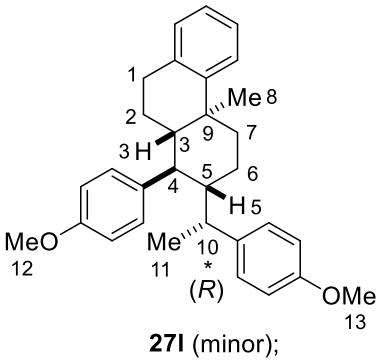
HRMS (ESI): calculated for $C_{27}H_{35}O$ $[M+H]^+$ requires m/z 375.2682, found m/z 375.2682 (*Δ* = -0.05 ppm).

[31] Relative stereochemistry is determined by analogy to compound **27h**.

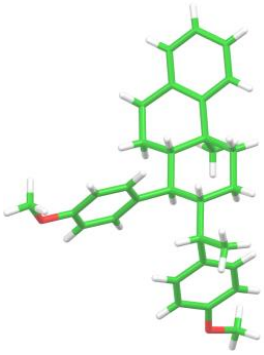
(±)-(1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-2-((*S*)-1-(4-methoxyphenyl)ethyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (major)-27l and (±)-(1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-2-((*R*)-1-(4-methoxyphenyl)ethyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (minor)-27l.



27l (major);



27l (minor);



[X-ray of the major diastereomer]

$C_{31}H_{36}O_2$
440.63 g mol^{-1}
*dr = 90:10

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 1-(4-methoxyphenyl)ethan-1-ol (15.2 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 24:1) to furnish compound **27l** as an inseparable mixture of two diastereomers at the exocyclic position as a pale yellow oil (40.3 mg, 92%, 90:10 dr).[32,33]

Major diastereomer (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 1H, H-Ar), 7.20 – 7.10 (m, 2H, H-Ar), 7.10 – 6.94 (m, 6H, H-Ar), 6.91 (dd, *J* = 8.2, 2.8 Hz, 1H, H-Ar), 6.84 (d, *J* = 8.6 Hz, 2H, H-Ar), 3.87 (s, 3H, H-12/H-13), 3.83 (s, 3H, H-13/H-12), 2.74 – 2.53 (m, 3H, H-1, H-10), 2.40 (dt, *J* = 12.6, 3.5 Hz, 1H, H-7$_a$), 2.21 (t, *J* = 11.2 Hz, 1H, H-4), 1.95 (dt, *J* = 13.0, 3.6 Hz, 1H, H-6$_a$), 1.85 (tt, *J* = 11.7, 3.0 Hz, 1H, H-5), 1.68 – 1.55 (m, 2H, H-7$_b$, H-3), 1.43 (td, *J* = 12.9, 4.2 Hz, 1H, H-6$_b$), 1.35 – 1.25 (m, 1H, H-2$_a$), 1.23 – 1.10 (m, 4H, H-11, H-2$_b$), 0.91 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 157.8 (C-Ar), 148.0 (C-Ar), 136.7 (C-Ar), 135.8 (C-Ar), 135.7 (C-Ar), 133.3 (C-Ar), 129.9 (2C, C-Ar), 129.2 (C-Ar), 126.3 (C-Ar), 125.6 (C-Ar), 125.5 (C-Ar), 124.7 (C-Ar), 115.1 (C-Ar), 113.0 (2C, C-Ar), 112.7 (C-Ar), 55.4 (C-12/C-13),

[32] Relative stereochemistry at the exocyclic benzylic position for the major diastereomer was determined by single crystal X-ray diffraction followed by ^{1}H NMR analysis of the single crystal used for the diffraction experiment.
[33] dr determined by ^{1}H NMR of the crude reaction mixture.

55.3 (C-13/C-12), 49.3 (C-5), 49.0 (C-3), 47.6 (C-4), 39.0 (C-10), 37.8 (C-7), 37.5 (C-9), 29.7 (C-1), 22.7 (C-8), 22.6 (C-2), 22.1 (C-6), 20.3 (C-11).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Note: the appearance of ^{1}H NMR signal for H-4: 2.21 (t, *J* = 11.2 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

Characteristic peaks for the minor diastereomer (from the mixture):

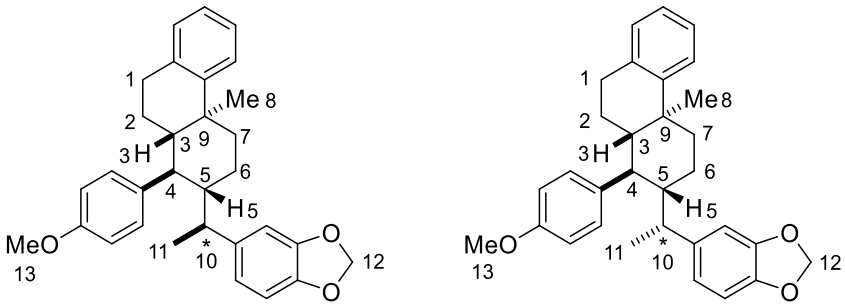
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, H-12/H-13), 3.79 (s, 3H, H-13/H-12).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.6 (C-Ar), 139.0 (C-Ar), 136.5 (C-Ar), 132.1 (C-Ar), 128.6 (C-Ar), 125.9 (C-Ar), 115.5 (C-Ar), 113.4 (C-Ar), 50.5 (C-5), 48.2 (C-3), 38.0 (C-10), 22.8 (C-8), 11.5 (C-11).

IR (film) ν_{max}: 2932, 1610, 1510, 1463, 1245, 1178, 1037, 908, 828, 761, 730 cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{37}O_2$ $[M+H]^+$ requires m/z 441.2788, found m/z 441.2787 (*Δ* = -0.18 ppm).

(±)-5-((*S*)-1-((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)ethyl)benzo[d][1,3]dioxole (major)-27m and (±)-5-((*R*)-1-((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)ethyl)benzo[d][1,3]dioxole (minor)-27m.



27m (major) **27m** (minor)

$C_{31}H_{34}O_3$
454.61 g mol^{-1}
*dr = 90:10

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 1-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol[34] (16.6 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column

[34] A. Joncour, A. Décor, J. M. Liu, M. E. Tran Huu Dau, O. Baudoin, *Chem. Eur. J.* **2007**, *13*, 5450–5465.

chromatography (SiO_2; pentane:Et_2O; 19:1) to furnish compound **27m** as an inseparable mixture of two diastereomers at the exocyclic position as a beige foam (38.5 mg, 85%, 90:10 dr)[35,36].

Major diastereomer (from the mixture)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 7.9, 1.4 Hz, 1H, H-Ar), 7.18 – 7.04 (m, 4H, H-Ar), 7.02 – 6.86 (m, 3H, H-Ar), 6.74 (d, *J* = 8.0 Hz, 1H, H-Ar), 6.64 (d, *J* = 1.7 Hz, 1H, H-Ar), 6.54 (dd, *J* = 8.0, 1.7 Hz, 1H, H-Ar), 5.95 (s, 2H, H-12), 3.86 (s, 3H, H-13), 2.75 – 2.51 (m, 3H, H-1, H-5), 2.40 (dt, *J* = 12.7, 3.5 Hz, 1H, H-7_a), 2.25 (t, *J* = 11.2 Hz, 1H, H-4), 1.97 – 1.78 (m, 2H, H-5, H-6_a), 1.67 – 1.54 (m, 2H, H-3, H-7_b), 1.43 (td, *J* = 13.1, 3.4 Hz, 1H, H-6_a), 1.38 – 1.24 (m, 1H, H-2_a), 1.19 – 1.08 (m, 4H, H-2_b, H-11), 0.94 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 147.9 (C-Ar), 147.0 (C-Ar), 145.5 (C-Ar), 137.7 (C-Ar), 136.6 (C-Ar), 135.7 (C-Ar), 133.3 (C-Ar), 129.2 (C-Ar), 126.3 (C-Ar), 125.6 (C-Ar), 125.5 (C-Ar), 124.7 (C-Ar), 122.0 (C-Ar), 115.2 (C-Ar), 112.7 (C-Ar), 109.3 (C-Ar), 107.5 (C-Ar), 100.8 (C-12), 55.3 (C-13), 49.3 (C-5), 49.0 (C-3), 47.5 (C-4), 39.6 (C-10), 37.8 (C-7), 37.5 (C-9), 29.6 (C-1), 22.8 (C-8), 22.6 (C-2), 22.3 (C-6), 20.3 (C-11).

Note: the appearance of ^{1}H NMR signal for H-4: 2.25 (t, *J* = 11.2 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

Characteristic peaks for the minor diastereomer (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (dd, *J* = 8.0, 1.8 Hz, 1H, H-Ar), 5.91 (s, 2H, H-12), 3.85 (s, 3H, H-13), 1.21 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 132.1 (C-Ar), 128.2 (C-Ar), 120.3 (C-Ar), 115.4 (C-Ar), 108.4 (C-Ar), 107.8 (C-Ar), 50.6 (C-5), 48.2 (C-3), 38.6 (C-10), 37.6 (C-7), 11.6 (C-11).

M.p: 75-81 °C

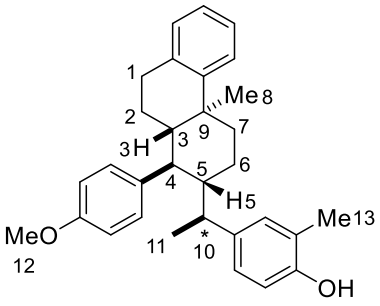
IR (film) ν_{max}: 3027, 2934, 1610, 1510, 1488, 1440, 1239, 1039, 909, 812, 762, 732 cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{35}O_3$ $[M+H]^+$ requires m/z 455.2581, found m/z 455.2583 (*Δ* = 0.44 ppm).

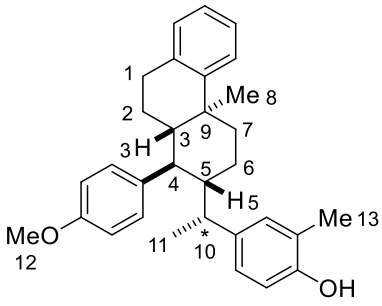
[35] Relative stereochemistry of the major and minor diastereomers is determined by analogy to compound **27l**

[36] dr determined by ^{1}H NMR after column chromatography due to the overlapping signals in the ^{1}H spectrum of the crude mixture.

(±)-4-((1*S*)-1-((1*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)ethyl)-2-methylphenol (major)-27n and (±)-4-((1*R*)-1-±)-((1*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)ethyl)-2-methylphenol (minor)-27n.

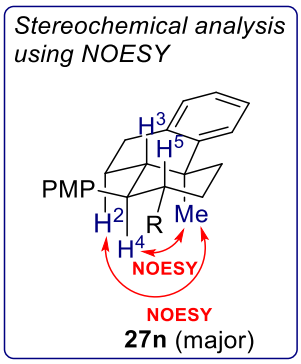


27n (major)



27n (minor)

$C_{31}H_{36}O_2$
440.63 g mol^{-1}
*dr = 89:11



Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 4-(1-hydroxyethyl)-2-methylphenol[37] (15.2 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish compound **27n** as an inseparable mixture of two diastereomers at the exocyclic position as a pale yellow oil (38.1 mg, 87%, 89:11 dr)[38,39].

Major diastereomer (from the mixture)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 7.8, 1.4 Hz, 1H, H-Ar), 7.18 – 6.88 (m, 7H, H-Ar), 6.86 – 6.79 (m, 2H, H-Ar), 6.69 (d, *J* = 7.9 Hz, 1H, H-Ar), 4.64 (br, 1H, OH), 3.87 (s, 3H, H-12), 2.76 – 2.51 (m, 3H, H-1, H-10), 2.40 (dt, *J* = 12.6, 3.4 Hz, 1H, H-7$_a$), 2.29 – 2.14 (m, 4H, H-13, H-4), 1.94 (dq, *J* = 13.3, 3.6 Hz, 1H, H-6$_a$), 1.84 (tt, *J* = 11.8, 3.2 Hz, 1H, H-5), 1.67 – 1.54 (m, 2H, H-7$_b$, H-3), 1.50 – 1.38 (m, 1H, H-6$_b$), 1.37 – 1.25 (m, 1H, H-2$_a$), 1.20 – 1.09 (m, 4H, H-2$_b$, H-11), 0.92 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (C-Ar), 151.9 (C-Ar), 148.0 (C-Ar), 136.7 (C-Ar), 135.9 (C-Ar), 135.7 (C-Ar), 133.4 (C-Ar), 131.7 (C-Ar), 129.2 (C-Ar), 127.5 (C-Ar), 126.3 (C-Ar), 125.6 (C-Ar), 125.5 (C-Ar), 124.7 (C-Ar), 122.5 (C-Ar), 115.0 (C-Ar), 114.2 (C-Ar), 112.7 (C-Ar), 55.4 (C-12), 49.2 (C-5), 49.0 (C-3), 47.5 (C-4), 39.1 (C-10), 37.8 (C-7), 37.5 (C-9), 29.6 (C-1), 22.8 (C-8), 22.6 (C-2), 22.2 (C-6), 20.3 (C-11), 16.1 (C-13).

[37] M. A. J. Dubois, R. A. Croft, Y. Ding, C. Choi, D. R. Owen, J. A. Bulla, J. J. Mousseau, *RSC Med. Chem.* **2021**, *12*, 2045–2052.
[38] Relative stereochemistry of the major and minor diastereomers is determined by analogy to compound **27l**.
[39] dr determined by ^{1}H NMR after column chromatography due to the overlapping signals in the ^{1}H spectrum of the crude mixture.

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me; between H-2 and Me.

Note: the appearance of ^{1}H NMR signal for H-5: 1.84 (tt, *J* = 11.8, 3.2 Hz, 1H, H-5) is indicative of a *trans*-diaxial arrangement between H-4 and H-5.

Characteristic peaks for the minor diastereomer (from the mixture):

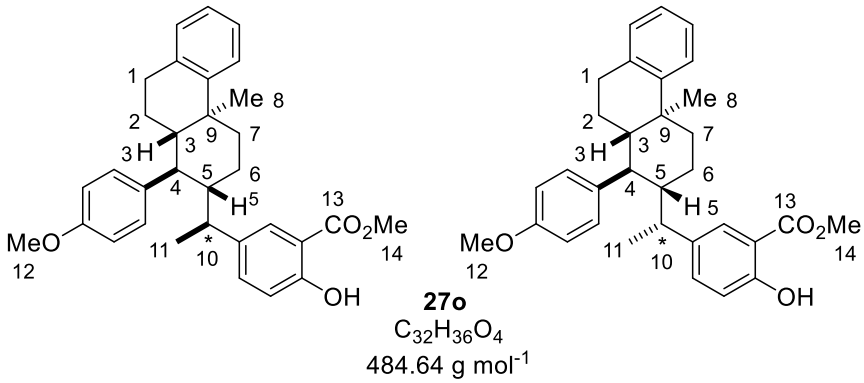
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, H-12), 1.21 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.7 (C-Ar), 139.0 (C-Ar), 136.5 (C-Ar), 132.1 (C-Ar), 130.3 (C-Ar), 115.5 (C-Ar), 114.4 (C-Ar), 50.4 (C-5), 48.2 (C-3), 38.0 (C-10), 11.6 (C-11).

IR (film) ν_{max}: 3426, 2932, 2361, 1510, 1243, 908, 825, 732 cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{36}O_2Na$ $[M+Na]^+$ requires m/z 463.2608, found m/z 463.2603 (*Δ* = -0.88 ppm).

(±)-Methyl 2-hydroxy-5-((*S*)-1-((1*R*,2*R*,4a*S*,10a*S*)-1-(4-methoxyphenyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)ethyl)benzoate (major)-27o and (±)-Methyl 2-hydroxy-5-((*R*)-1-((1*R*,2*R*,4a*S*,10a*S*)-1-(4-methoxyphenyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)ethyl)benzoate (minor)-27o.



27o
$C_{32}H_{36}O_4$
484.64 g mol^{-1}
*dr = 86:14

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), methyl 2-hydroxy-5-(1-hydroxyethyl)benzoate **198** (19.6 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C** except the reaction was performed overnight. The crude product was purified by flash column chromatography (SiO_2;

pentane:Et_2O; 83:17) to furnish compound **27o** as an inseparable mixture of two diastereomers as a colourless oil (43.5 mg, 90%, 86:14 dr).[40,41]

Major diastereomer (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (s, 1H, OH), 7.51 (d, *J* = 2.3 Hz, 1H, H-Ar), 7.29 (dd, *J* = 7.9, 1.5 Hz, 1H, H-Ar), 7.23 (dd, *J* = 8.6, 2.3 Hz, 1H, H-Ar), 7.16 – 6.84 (m, 8H, H-Ar), 4.00 (s, 3H, H-14), 3.85 (s, 3H, H-12), 2.75 – 2.52 (m, 3H, H-1, H-10), 2.40 (dt, *J* = 12.8, 3.5 Hz, 1H, H-7_a), 2.15 (t, *J* = 11.2 Hz, 1H, H-4), 1.95 (dq, *J* = 13.1, 3.6 Hz, 1H, H-6_a), 1.87 (tt, *J* = 11.8, 3.2 Hz, 1H, H-5), 1.66 – 1.54 (m, 2H, H-3, H-7_b), 1.46 – 1.08 (m, 6H, H-2_a, H-2_b, H-6_b, H-11), 0.91 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9 (C-13), 159.8 (C-Ar), 158.0 (C-Ar), 147.8 (C-Ar), 136.4 (C-Ar), 136.3 (C-Ar), 135.7 (C-Ar), 134.4 (C-Ar), 133.3 (C-Ar), 129.9 (C-Ar), 129.2 (C-Ar), 126.3 (C-Ar), 125.7 (C-Ar), 125.5 (C-Ar), 124.7 (C-Ar), 116.7 (C-Ar), 114.8 (C-Ar), 112.9 (C-Ar), 111.5 (C-Ar), 55.3 (C-12), 52.4 (C-14), 49.1 (C-3/C-5), 48.9 (C-5/C-3), 47.5 (C-4), 39.1 (C-10), 37.7 (C-7), 37.4 (C-9), 29.6 (C-1), 22.7 (C-8), 22.5 (C-2), 22.2 (C-6), 19.6 (C-11).

Note: the appearance of ^{1}H NMR signal for H-4: 2.15 (t, *J* = 11.2 Hz, 1H, H-4) is indicative of a trans-diaxial arrangement between H-4 and H-3; H-4 and H-5.

Characteristic peaks for the minor diastereomer (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, H-12/H-14).

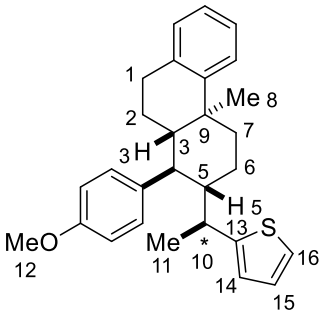
^{13}C NMR (101 MHz, $CDCl_3$): δ 137.5 (C-Ar), 135.7 (C-Ar), 132.0 (C-Ar), 127.9 (C-Ar), 117.2 (C-Ar), 115.5 (C-Ar), 112.8 (C-Ar), 50.3 (C-3/C-5), 48.2 (C-5/C-3), 47.6 (C-4), 38.0 (C-10), 37.6 (C-7), 20.1 (C-2/C-6), 11.5 (C-11).

IR (film) ν_{max}: 3203, 2935, 1677, 1511, 1490, 1441, 1248, 1212, 1039, 909, 735 cm^{-1}.

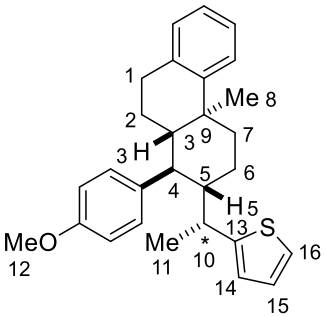
HRMS (ESI): calculated for $C_{32}H_{37}O_4$ $[M+H]^+$ requires m/z 485.2686, found m/z 485.2684 (*Δ* = -0.54 ppm).

[40] dr determined by ^{1}H NMR after column chromatography due to the overlapping signals in the ^{1}H spectrum of the crude mixture.
[41] Relative stereochemistry of the major and minor diastereomers is determined by analogy to compound **27l**.

(±)-2-((*S*)-1-((1*R*,2*S*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4a-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)ethyl)thiophene (major)-27p and (±)-2-((*R*)-1-((1*R*,2*S*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)ethyl)thiophene (minor)-27p.



27p (major)



27p (minor)

$C_{28}H_{32}OS$
416.62 g mol^{-1}
*dr = 85:15

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (*R*)-1-(thiophen-2-yl)ethan-1-ol (12.8 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish compound **27p** as an inseparable mixture of two diastereomers as a colourless oil (16.6 mg, 40%, 85:15 dr).[42,43]

Major diastereomer (from the mixture)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 1H, H-Ar), 7.19 – 6.84 (m, 9H, H-15, H-16, H-Ar), 6.73 – 6.68 (m, 1H, H-14), 3.85 (s, 3H, H-12), 2.98 (qd, *J* = 7.3, 2.5 Hz, 1H, H-10), 2.75 – 2.58 (m, 2H, H-1), 2.49 – 2.39 (m, 2H, H-4, H-7$_a$), 1.94 – 1.76 (m, 2H, H-6$_a$, H-5), 1.70 – 1.53 (m, 3H, H-7$_b$, H-6$_b$, H-3), 1.40 – 1.11 (m, 5H, H-2$_a$, H-2$_b$, H-11), 1.00 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-Ar), 147.9 (C-Ar), 147.2 (C-13), 136.2 (C-Ar), 135.7 (C-Ar), 133.4 (C-Ar), 129.3 (C-Ar), 126.1 (2C, C-Ar, C-15), 125.7 (C-Ar), 125.6 (C-Ar), 125.0 (C-14), 124.8 (C-Ar), 123.0 (C-16), 115.2 (C-Ar), 112.7 (C-Ar), 55.3 (C-12), 49.2 (C-5), 48.6 (C-3), 47.3 (C-4), 37.6 (C-7), 37.5 (C-9), 36.1 (C-10), 29.7 (C-11), 22.8 (C-8), 22.6 (C-2), 21.9 (C-11), 21.8 (C-6).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Characteristic peaks for the minor diastereomer (from the mixture):

[42] dr determined by ^{1}H NMR after column chromatography due to the overlapping signals in the ^{1}H spectrum of the crude mixture.
[43] Relative stereochemistry of the major and minor diastereomers is determined by analogy to compound **27l**.

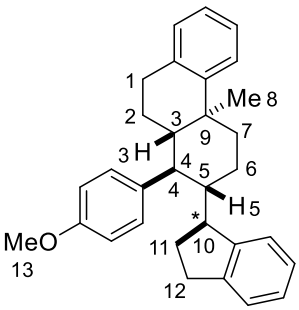
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H, H-12), 2.84 (dq, *J* = 7.1, 2.5 Hz, 1H, H-10), 1.21 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.0 (C-Ar), 132.0 (C-Ar), 126.5 (C-Ar), 125.9 (C-Ar), 125.6 (C-Ar), 124.7 (C-Ar), 122.9 (C-Ar), 122.4 (C-Ar), 115.5 (C-Ar), 113.0 (C-Ar), 51.1 (C-5), 48.2 (C-3), 47.3 (C-4), 35.3 (C-10), 29.6 (C-1), 22.5 (C-2), 20.7 (C-6), 13.3 (C-11).

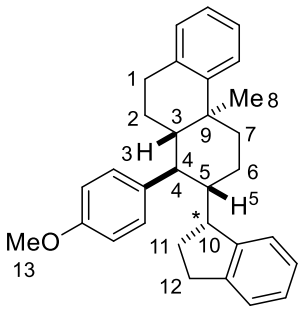
IR (film) ν_{max}: 2933, 1610, 1510, 1246, 1177, 1038, 908, 825, 731, 694 cm^{-1}.

HRMS (APCI): calculated for $C_{28}H_{33}OS$ $[M+H]^+$ requires m/z 417.2247, found m/z 417.2247 (*Δ* = -0.01 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-((*S*)-2,3-Dihydro-1H-inden-1-yl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (major)-27q and (±)-(1*R*,2*R*,4*aS*,10*aS*)-2-((*R*)-2,3-Dihydro-1H-inden-1-yl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (minor)-27q.



27q (major)



27q (minor)

$C_{31}H_{34}O$
422.61 g mol^{-1}
*dr = 65:35

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 2,3-dihydro-1H-inden-1-ol (13.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish compound **27q** as an inseparable mixture of two diastereomers as a white foam (32.6 mg, 77%, 65:35 dr).[44,45]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.2 Hz, 1H$_{maj}$, H-Ar$_{maj}$), 7.38 – 6.93 (m, 10H$_{maj}$, 11H$_{min}$, H-Ar$_{maj}$, H-Ar$_{min}$), 6.90 – 6.82 (m, 1H$_{maj}$, 1H$_{min}$, H-Ar$_{maj}$, H-Ar$_{min}$), 3.89 – 3.80 (m, 3H$_{maj}$, 3H$_{min}$, H-13$_{maj}$, H-13$_{min}$), 3.11 (ddd, *J* = 8.5, 5.4, 2.1 Hz, 1H$_{maj}$, H-10$_{maj}$), 3.02 – 2.87 (m, 2H$_{maj}$,

[44] dr determined after column chromatography due to the overlapping signals in the ^{1}H spectrum of the crude mixture.
[45] Relative stereochemistry of the major and minor diastereomers is determined by analogy to compound **27l**.

$2H_{min}$, H-4_{maj}, H-$12_{a,\ maj}$, H-10_{min}, H-$12_{a,\ min}$), 2.84 – 2.66 (m, $3H_{maj}$, $3H_{min}$, H-1_{maj}, H-$12_{b,\ maj}$, H-1_{min}, H-$12_{b,\ min}$), 2.54 (t, *J* = 11.3 Hz, $1H_{min}$, H-4_{min}), 2.40 – 2.30 (m, $1H_{maj}$, $1H_{min}$, H-$7_{a,\ maj}$, H-$7_{b,\ min}$), 2.26 – 2.20 (m, $1H_{min}$, H-5_{min}), 2.14 – 1.97 (m, $1H_{maj}$, $2H_{min}$, H-$11_{a,\ maj}$, H-$11_{a,\ min}$, H-$_{11b,\ min}$), 1.97 – 1.90 (m, $1H_{maj}$, H-5_{maj}), 1.88 – 1.78 (m, $1H_{maj}$, $1H_{min}$, H-$11_{b,\ maj}$, H-3_{min}), 1.77 – 1.69 (m, $2H_{maj}$, H-3_{maj}, H-$6_{a,\ maj}$), 1.67 – 1.42 (m, $2H_{maj}$, $4H_{min}$, H-$7_{b,\ maj}$, H-$2_{a,\ maj}$, H-$7_{b,\ min}$, H-$6_{a,\ min}$, H-$6_{b,\ min}$, H-$2_{a,\ min}$), 1.41 – 1.27 (m, $2H_{maj}$, $1H_{min}$, H-$6_{b,\ maj}$, H-$2_{b,\ maj}$, H-$2_{b,\ min}$), 1.23 (s, $3H_{min}$, H-8_{min}), 1.12 (s, $3H_{maj}$, H-8_{maj}).

^{13}C NMR (101 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 158.0 (C-Ar), 147.9 (C-Ar), 145.7 (C-Ar), 145.0 (C-Ar), 136.6 (C-Ar), 135.7 (C-Ar), 132.5 (C-Ar), 129.3 (C-Ar), 126.3 (2C, C-Ar), 125.9 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 125.2 (C-Ar), 124.8 (C-Ar), 124.7 (C-Ar), 115.4 (C-Ar), 112.8 (C-Ar), 55.3 (C-13), 49.8 (C-5), 48.5 (C-3), 47.7 (C-4), 45.8 (C-10), 37.7 (C-7), 37.6 (C-9), 32.3 (C-12), 31.6 (C-11), 29.7 (C-1), 22.9 (C-8), 22.8 (C-2), 22.0 (C-6). **Selected peaks for the minor diastereomer** (from the mixture): δ 158.1 (C-Ar), 148.0 (C-Ar), 146.3 (C-Ar), 144.4 (C-Ar), 136.4 (C-Ar), 132.1 (C-Ar), 129.3 (C-Ar), 126.1 (C-Ar), 126.0 (C-Ar), 125.9 (C-Ar), 125.6 (C-Ar), 124.7 (C-Ar), 124.3 (C-Ar), 123.4 (C-Ar), 115.2 (C-Ar), 112.9 (C-Ar), 55.3 (C-13), 48.0 (C-4/C-3), 47.9 (C-3/C-4), 46.8 (C-5), 46.3 (C-10), 37.6 (C-9), 37.5 (C-7), 32.0 (C-12), 29.6 (C-1), 25.1 (C-11), 22.9 (C-8), 22.8 (C-2), 21.0 (C-6).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4_{maj} and Me_{maj}, between H-4_{min} and Me_{min}.

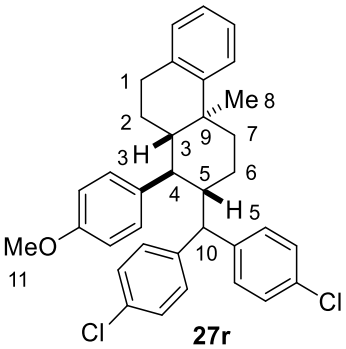
Note: the appearance of ^{1}H NMR signal for H-4_{min}: 2.54 (t, *J* = 11.3 Hz, 1H, H-4_{min}) is indicative of a *trans*-diaxial arrangement between H-4_{min} and H-3_{min}; H-4_{min} and H-5_{min}.

M.p. 67-77 °C

IR (film) ν_{max}: 2936, 1511, 1244, 1177, 1038, 908, 830, 757, 729 cm^{-1}.

HRMS (APCI): calculated for $C_{31}H_{35}O$ $[M+H]^+$ requires m/z 423.2682, found m/z 423.2681 (*Δ* = - 0.40 ppm).

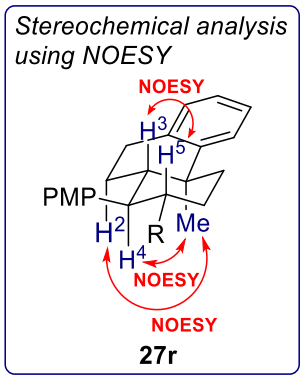
(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-(Bis(4-chlorophenyl)methyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27r.



27r

$C_{35}H_{34}Cl_2O$

541.56 g mol^{-1}



Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), bis(4-chlorophenyl)methanol (25.3 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish compound **27r** as a white foam (43.6 mg, 81%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.34 – 6.97 (m, 13H, H-Ar), 6.94 – 6.78 (m, 3H, H-Ar), 3.89 (d, *J* = 3.6 Hz, 1H, H-10), 3.81 (s, 3H, H-11), 2.76 – 2.49 (m, 3H, H-1, H-5), 2.43 – 2.31 (m, 2H, H-7$_a$, H-4), 1.91 – 1.80 (m, 1H, H-6$_a$), 1.74 (ddd, *J* = 12.4, 10.9, 2.7 Hz, 1H, H-3), 1.69 – 1.58 (m, 2H, H-6$_b$, H-7$_b$), 1.41 – 1.29 (m, 1H, H-2$_a$), 1.21 – 1.11 (m, 1H, H-2$_b$), 1.02 (s, 3H, H-8).

^{13}C NMR (101 MHz, CD_2Cl_2): δ 158.6 (C-Ar), 148.1 (C-Ar), 143.2 (C-Ar), 140.6 (C-Ar), 135.9 (2C, C-Ar), 133.5 (C-Ar), 132.5 (C-Ar), 132.4 (2C, C-Ar), 131.7 (C-Ar), 130.1 (2C, C-Ar), 129.5 (C-Ar), 128.5 (4C, C-Ar), 126.4 (C-Ar), 125.9 (C-Ar), 125.8 (C-Ar), 124.9 (C-Ar), 115.5 (C-Ar), 113.2 (C-Ar), 55.6 (C-11), 51.7 (C-10), 49.3 (C-3), 48.5 (C-4), 47.5 (C-5), 38.1 (C-7), 37.8 (C-9), 29.8 (C-1), 24.5 (C-6), 22.9 (2C, C-2, C-8).

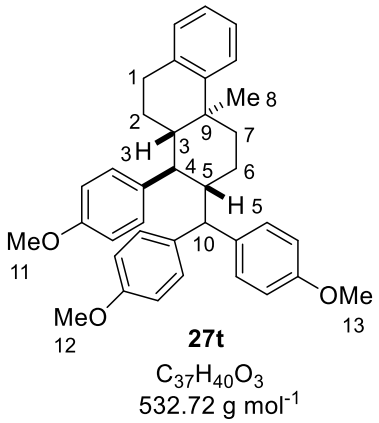
NOESY- 2D (600 MHz, CD_2Cl_2): between H-4 and Me, between H-5 and H-3**,** between H-2 and Me.

M.p: 95-97 °C

IR (film) ν_{max}: 2935, 1510, 1490, 1245, 1177, 1091, 1037, 1013, 953, 829, 761, 712 cm^{-1}.

HRMS (APCI): calculated for $C_{35}H_{35}Cl_2O$ $[M+H]^+$ requires m/z 541.2059, found m/z 541.2059 (*Δ* = - 0.07 ppm).

(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-(Bis(4-methoxyphenyl)methyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27t.



27t

$C_{37}H_{40}O_3$

532.72 g mol^{-1}

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), bis(4-methoxyphenyl)methanol (24.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 41:9) to furnish compound **27t** as a pink oil which crystallised on standing (43.5 mg, 82%).[46]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.24 (dd, *J* = 8.8, 2.1 Hz, 1H, H-Ar), 7.18 – 6.99 (m, 7H, H-Ar), 6.96 – 6.82 (m, 5H, H-Ar), 6.77 (d, *J* = 8.7 Hz, 2H, H-Ar), 3.88 – 3.81 (m, 7H, H-12, H-13, H-10), 3.77 (s, 3H, H-11), 2.78 – 2.57 (m, 2H, H-1), 2.51 (tt, *J* = 11.7, 3.4 Hz, 1H, H-5), 2.43 – 2.31 (m, 2H, H-7$_a$, H-4), 1.98 – 1.89 (m, 1H, H-6$_a$), 1.78 – 1.59 (m, 3H, H-6$_b$, H-3, H-7$_b$), 1.41 – 1.29 (m, 1H, H-2$_a$), 1.26 – 1.14 (m, 1H, H-2$_b$), 1.03 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (2C, C-Ar), 157.5 (C-Ar), 147.9 (C-Ar), 137.0 (C-Ar), 136.2 (C-Ar), 135.7 (C-Ar), 134.0 (C-Ar), 133.2 (C-Ar), 131.8 (2C, C-Ar), 129.2 (3C, C-Ar), 126.1 (C-Ar), 125.6 (2C, C-Ar), 124.6 (C-Ar), 115.1 (C-Ar), 113.4 (2C, C-Ar), 113.2 (2C, C-Ar), 112.8 (C-Ar), 55.3 (3C, C-11, C-12, C-13), 50.1 (C-10), 49.1 (C-3), 47.9 (C-4), 47.6 (C-5), 37.9 (C-7), 37.6 (C-9), 29.6 (C-1), 23.7 (C-6), 22.9 (C-8), 22.7 (C-2).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

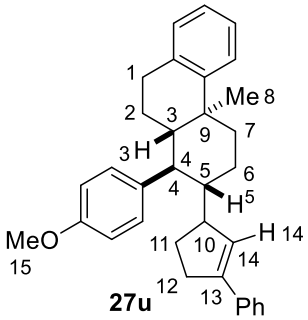
M.p: 81-85 °C

IR (film) ν_{max}: 2933, 1609, 1509, 1463, 1244, 1176, 1036, 909, 830, 761, 731 cm^{-1}.

[46] Relative stereochemistry is determined by analogy to compound **27a**.

HRMS (ESI): calculated for $C_{37}H_{40}O_3Na$ $[M+Na]^+$ requires m/z 555.2870, found m/z 555.2871 (Δ = 0.16 ppm).

(±)-(1*R*,2*R*,4a*S*,10a*S*)-1-(4-Methoxyphenyl)-4a-methyl-2-(3-phenylcyclopent-2-en-1-yl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene 27u.



27u
$C_{33}H_{36}O$
448.65 g mol^{-1}
*dr>95:5

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 1-phenylcyclopent-2-en-1-ol[24] (16.0 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C** except that the reaction was performed at rt and for 4 h. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish compound **27u** as a single detectable diastereomer as a pale brown foam (30.4 mg, 68%, >95:5 d.r.).[47]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.41 (m, 2H, H-Ph), 7.37 – 7.29 (m, 3H, H-Ar, H-Ph), 7.25 – 7.20 (m, 1H, H-Ph), 7.19 – 7.06 (m, 4H, H-Ar), 7.05 – 6.99 (m, 1H, H-Ar), 6.94 (dd, *J* = 8.6, 2.8 Hz, 1H, H-Ar), 6.80 (dd, *J* = 8.3, 2.8 Hz, 1H, H-Ar), 6.15 (d, *J* = 2.1 Hz, 1H, H-14), 3.81 (s, 3H, H-15), 2.81 – 2.48 (m, 6H, H-10, H-1, H-12, H-4), 2.44 – 2.35 (m, 1H, H-7$_a$), 1.98 – 1.88 (m, 1H, H-11$_a$), 1.87 – 1.79 (m, 1H, H-6$_a$), 1.79 – 1.52 (m, 5H, H-3, H-5, H-11$_b$, H-7$_b$, H-6$_b$), 1.47 – 1.35 (m, 1H, H-2$_a$), 1.31 – 1.23 (m, 1H, H-2$_b$), 1.18 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 148.1 (C-Ar), 143.0 (C-13), 137.0 (C-Ar/C-Ph), 136.8 (C-Ph/C-Ar), 135.8 (C-Ar), 132.3 (C-Ar), 129.3 (C-Ar), 128.4 (2C, C-Ph), 127.0 (C-Ph), 126.9 (C-14), 126.1 (C-Ar), 125.7 (3C, C-Ph, C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 115.3 (C-Ar), 112.7 (C-Ar), 55.4 (C-15), 48.5 (C-4/C-5), 48.4 (C-5/C-4), 48.0 (C-3/C-10), 47.9 (C-10/C-3), 37.7 (C-7), 37.6 (C-9), 33.2 (C-12), 29.6 (C-1), 27.9 (C-11), 22.9 (C-6), 22.8 (C-8), 22.7 (C-2).

[47] The exocyclic stereochemistry could not be unambiguously determined.

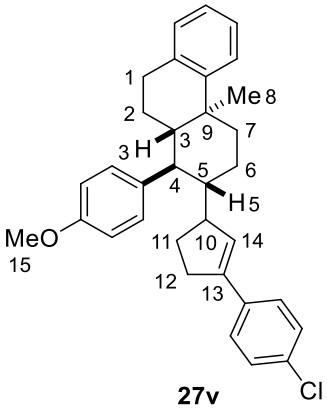
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me, between H-4 and H-14.

M.p: 85 °C.

IR (film) ν_{max}: 2932, 1511, 1244, 1177, 1038, 908, 827, 757, 731, 693 cm^{-1}.

HRMS (APCI): calculated for $C_{33}H_{37}O$ $[M+H]^+$ requires m/z 449.2839, found m/z 449.2837 (Δ = -0.46 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-(3-(4-chlorophenyl)cyclopent-2-en-1-yl)-1-(4-methoxyphenyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene 27v.



27v
$C_{33}H_{35}ClO$
483.09 g mol^{-1}
*dr>95:5

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 1-(4-chlorophenyl)cyclopent-2-en-1-ol **52** (19.5 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C** except that the reaction was performed at rt and for 1.5 h. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 24:1) to furnish compound **27v** as a single detectable diastereomer as a beige foam (37.4 mg, 77%, >95:5 d.r.).[48]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.22 (m, 5H, H-Ar), 7.20 – 6.99 (m, 5H, H-Ar), 6.95 (dd, *J* = 8.7, 2.8 Hz, 1H, H-Ar), 6.80 (dd, J = 8.2, 2.8 Hz, 1H, H-Ar), 6.17 – 6.08 (m, 1H, H-14), 3.81 (s, 3H, H-15), 2.82 – 2.60 (m, 4H, H-1, H-10, H-12$_a$), 2.59 – 2.45 (m, 2H, H-4, H-12$_b$), 2.40 (dt, *J* = 12.2, 3.3 Hz, 1H, H-7$_a$), 1.99 – 1.88 (m, 1H, H-11$_a$), 1.84 (dq, *J* = 13.2, 3.3 Hz, 1H, H-6$_a$), 1.79 – 1.35 (m, 6H, H-2$_a$, H-3, H-5, H-6$_b$, H-7$_b$, H-11$_b$), 1.32 – 1.23 (m, 1H, H-2$_b$), 1.19 (s, 3H, H-8).

[48] The exocyclic stereochemistry could not be unambiguously determined.

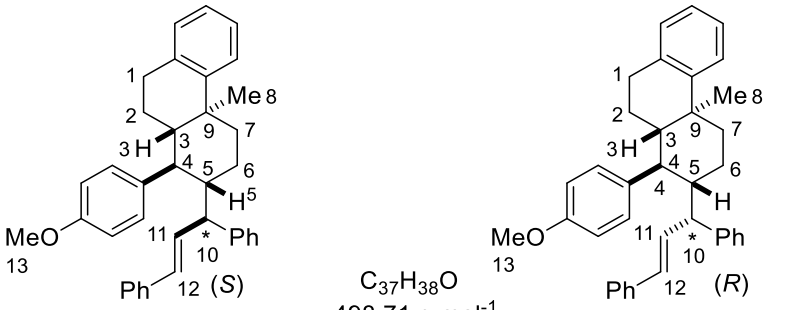
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 148.0 (C-Ar), 141.8 (C-13), 136.7 (C-Ar), 135.7 (C-Ar), 135.4 (C-Ar), 132.5 (C-Ar), 132.2 (C-Ar), 129.3 (C-Ar), 128.4 (2C, C-Ar), 127.8 (C-14), 127.0 (2C, C-Ar), 126.1 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 115.3 (C-Ar), 112.7 (C-Ar), 55.3 (C-15), 48.4 (C-4), 48.2 (2C, C-10, C-3/C-5), 47.9 (C-5/C-3), 37.6 (C-7), 37.5 (C-9), 33.1 (C-12), 29.6 (C-1), 27.8 (C-11), 23.1 (C-6), 22.8 (C-8), 22.6 (C-2).

IR (film) ν_{max}: 2937, 1511, 1491, 1245, 1177, 1093, 1038, 909, 818, 734 cm^{-1}.

M.p: 75-78 °C.

HRMS (ESI): calculated for $C_{33}H_{36}OCl$ $[M+H]^+$ requires m/z 483.2449, found m/z 483.2451 (*Δ* = 0.36 ppm).

(±)-(1*R*,2*R*,4*aS*,10*aS*)-2-((*S,E*)-1,3-Diphenylallyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (major)-27w and (±)-(1*R*,2*R*,4*aS*,10*aS*)-2-((*R,E*)-1,3-Diphenylallyl)-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (minor)-27w.



27w (major) **27w** (minor)

Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), (*E*)-1,3-diphenylprop-2-en-1-ol (21.0 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish compound **27w** as a an inseparable mixture of two diastereomers at the exocyclic benzylic position as a white foam (38.9 mg, 78%, 83:17 dr).[49,50]

Major diastereomer (from the mixture):

[49] dr determined by ^{1}H NMR of the crude reaction mixture.
[50] Relative stereochemistry of the major and minor diastereomers is determined by analogy to compound **27l**.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 6.87 (m, 18H, H-Ar, H-Ph), 6.51 (dd, *J* = 15.8, 7.7 Hz, 1H, H-11), 6.22 (dd, *J* = 15.8, 1.3 Hz, 1H, H-12), 3.86 (s, 3H, H-13), 3.46 (dd, *J* = 7.7, 2.9 Hz, 1H, H-10), 2.79 – 2.61 (m, 2H, H-1), 2.45 – 2.40 (m, 1H, H-7_a), 2.32 (t, *J* = 11.1 Hz, 1H, H-4), 2.29 – 2.22 (m, 1H, H-5), 2.07 – 2.01 (m, 1H, H-6_a), 1.72 – 1.64 (m, 3H, H-3, H-7_b, H-6_b), 1.39 – 1.29 (m, 1H, H-2_a), 1.23 – 1.17 (m, 1H, H-2_b), 0.99 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-Ar), 147.8 (C-Ar), 141.6 (C-Ph), 137.9 (C-Ph), 136.1 (C-Ar), 135.6 (C-Ar), 133.9 (C-11), 133.5 (C-Ar), 129.7 (2C, C-Ph), 129.6 (C-12), 129.2 (C-Ar), 128.5 (2C, C-Ph), 128.0 (2C, C-Ph), 127.0 (C-Ph), 126.4 (C-Ph), 126.3 (C-Ar), 126.2 (2C, C-Ph), 125.7 (C-Ar), 125.6 (C-Ar), 124.7 (C-Ar), 115.2 (C-Ar), 112.8 (C-Ar), 55.3 (C-13), 50.6 (C-10), 49.1 (C-3/C-5), 49.0 (C-5/C-3), 47.5 (C-4), 37.8 (C-7), 37.5 (C-9), 29.6 (C-1), 23.9 (C-6), 22.7 (C-8), 22.5 (C-2).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Note: the appearance of ^{1}H NMR signal for H-4: 2.32 (t, *J* = 11.1 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

Characteristic peaks for the minor diastereomer (from the mixture):

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 – 7.47 (m, 2H, H-Ar), 7.43 – 7.39 (m, 3H, H-Ar), 6.72 (dd, 1H, *J* = 15.7, 10.2 Hz, H-11), 6.31 (d, *J* = 15.7 Hz, 1H, H-12), 3.90 (s, 3H, H-13), 3.41 (dd, *J* = 10.2, 3.0 Hz, 1H, H-10), 1.21 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2 (C-Ar), 144.9 (C-Ar/C-Ph), 137.9 (C-Ar/C-Ph), 135.7 (C-Ar/C-Ph), 133.6 (C-12), 133.0 (C-Ar/C-Ph), 128.7 (C-Ar/C-Ph), 128.2 (C-Ar/C-Ph), 127.9 (C-Ar/C-Ph), 127.6 (C-11), 127.4 (C-Ar/C-Ph), 126.1 (C-Ar/C-Ph), 125.9 (C-Ar/C-Ph), 115.3 (C-Ar), 55.4 (C-13), 50.0 (C-5), 49.4 (C-10), 48.3 (C-3), 47.7 (C-4), 37.6 (C-7), 37.5 (C-9), 22.8 (C-8), 21.7 (C-6).

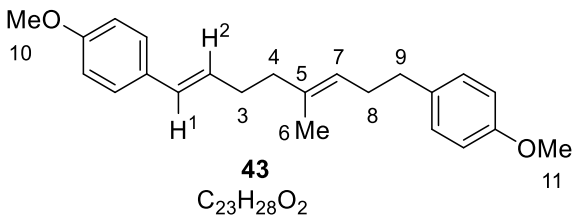
M.p: 88 °C.

IR (film) ν_{max}: 2933, 1510, 1244, 1177, 1037, 908, 760, 730, 699 cm^{-1}.

HRMS (APCI): calculated for $C_{37}H_{39}O$ $[M+H]^+$ requires m/z 499.2995, found m/z 499.2999 (*Δ* = 0.82 ppm).

Synthesis and the polyene cyclisation of dienes 43-46

4,4'-((1*E*,5*E*)-5-Methylocta-1,5-diene-1,8-diyl)bis(methoxybenzene) 43.



43

$C_{23}H_{28}O_2$

336.48 g mol^{-1}

$^3J_{H\text{-}1,\ H\text{-}2}$ = 15.8 Hz

4-Methoxybenzyl chloride (0.30 mL, 2.2 mmol, 9.0 equiv) was used to prepare the Grignard reagent which was reacted with (*E*/*Z*)-**39** (67.2 mg, 0.245 mmol, 1.00 equiv, 94:6 *E*:*Z*), Li_2CuCl_4 (0.49 mL, 0.10 M in THF, 49 µmol, 0.20 equiv) in THF (3.9 mL) according to the general procedure **B**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm, PhMe:pentane; 4:1) to obtain diene **43** as a colourless oil (24.5 mg, 30%, >95:5 *E:Z*).

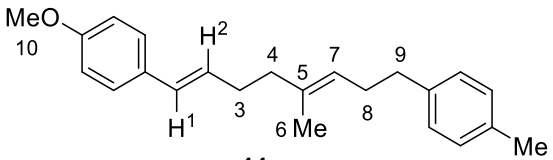
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 2H, H-Ar), 7.09 (d, *J* = 8.6 Hz, 2H, H-Ar), 6.88 – 6.78 (m, 4H, H-Ar), 6.33 (dd, *J* = 15.9, 1.6 Hz, 1H, H-1), 6.05 (dt, *J* = 15.8, 6.8 Hz, 1H, H-2), 5.26 – 5.14 (m, 1H, H-7), 3.80 (s, 3H, H-10/H-11), 3.78 (s, 3H, H-11/H-10), 2.58 (dd, *J* = 8.7, 6.7 Hz, 2H, H-9), 2.32 – 2.23 (m, 4H, H-3 and H-8), 2.16 – 2.08 (m, 2H, H-4), 1.58 (s, 3H, H-6).

^{13}C NMR (151 MHz, $CDCl_3$): δ 158.8 (C-Ar), 157.8 (C-Ar), 135.3 (C-5), 134.6 (C-Ar), 130.9 (C-Ar), 129.5 (2C, C-Ar), 129.3 (C-1), 128.7 (C-2), 127.1 (2C, C-Ar), 124.3 (C-7), 114.1 (2C, C-Ar), 113.8 (2C, C-Ar), 55.4 (2C, C-10 and C-11), 39.7 (C-4), 35.3 (C-9), 31.8 (C-3/C-8), 30.3 (C-8/C-3), 16.2 (C-6).

IR (film) ν_{max}: 2931, 2835, 1609, 1511, 1246, 1176, 1036, 828 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{29}O_2$ $[M+H]^+$ requires m/z 337.2162, found m/z 337.2161 (*Δ* = -0.33 ppm).

1-Methoxy-4-((1*E*,5*E*)-5-methyl-8-(p-tolyl)octa-1,5-dien-1-yl)benzene 44.



44
$C_{23}H_{28}O$
320.48 g mol^{-1}
$^{3}J_{\text{H-1, H-2}}$ = 15.7 Hz

4-Methylbenzyl chloride (0.65 mL, 4.9 mmol, 9.0 equiv) was used to prepare the Grignard reagent which was reacted with (*E*/*Z*)-**39** (0.150 g, 0.548 mmol, 1.00 equiv, 94:6 *E*:*Z*), Li_2CuCl_4 (1.1 mL, 0.10 M in THF, 0.11 mmol, 0.20 equiv) in THF (8.8 mL) according to the general procedure **B.** The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm, pentane:Et_2O; 49:1) to obtain diene **44** as a colourless oil (0.120 g, 68%, >95:5 *E:Z*).

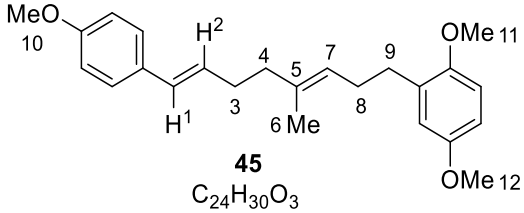
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 2H, H-Ar), 7.11 – 7.06 (m, 4H, H-Ar), 6.84 (d, *J* = 8.7 Hz, 2H, H-Ar), 6.33 (dt, *J* = 15.7, 1.4 Hz, 1H, H-1), 6.06 (dt, *J* = 15.7, 6.8 Hz, 1H, H-2), 5.23 (tq, *J* = 7.1, 1.3 Hz, 1H, H-7), 3.80 (s, 3H, H-10), 2.60 (dd, *J* = 8.9, 6.7 Hz, 2H, H-9), 2.36 – 2.24 (m, 7H, H-3, H-8 and H-11), 2.13 (dd, *J* = 8.9, 6.2 Hz, 2H, H-4), 1.60 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 139.4 (C-Ar), 135.3 (C-Ar), 135.2 (C-5), 130.9 (C-Ar), 129.3 (C-1), 129.0 (2C, C-Ar), 128.7 (C-2), 128.5 (2C, C-Ar), 127.1 (2C, C-Ar), 124.3 (C-7), 114.0 (2C, C-Ar), 55.4 (C-10), 39.7 (C-4), 35.8 (C-9), 31.8 (C-3/C-8), 30.2 (C-8/C-3), 21.2 (C-11), 16.2 (C-6).

IR (film) ν_{max}: 3029, 2360, 1608, 1511, 1248, 1175, 1037, 764 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{28}ONa$ $[M+Na]^+$ requires m/z 343.2032, found m/z 343.2031 (*Δ* = -0.44 ppm).

1,4-Dimethoxy-2-((3*E*,7*E*)-8-(4-methoxyphenyl)-4-methylocta-3,7-dien-1-yl)benzene 45.



45
$C_{24}H_{30}O_3$
366.50 g mol^{-1}
$^{3}J_{\text{H-1, H-2}}$ = 15.7 Hz

2,5-Dimethoxybenzyl chloride (0.92 g, 4.9 mmol, 9.0 equiv) was used to prepare the Grignard reagent which was reacted with (*E*/*Z*)-**39** (0.150 g, 0.548 mmol, 1.00 equiv, 94:6 *E*:*Z*), Li_2CuCl_4 (1.1 mL, 0.10 M in THF, 0.11 mmol, 0.20 equiv) in THF (8.8 mL) according to the general procedure **B**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm, pentane:Et_2O; 47:3) to obtain diene **45** as a colourless oil (0.143 g, 71%, 95:5 *E*:*Z*).

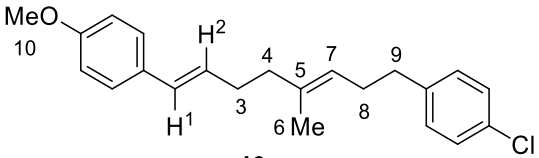
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H, H-Ar), 6.86 – 6.80 (m, 2H, H-Ar), 6.79 – 6.66 (m, 3H, H-Ar), 6.33 (dt, *J* = 15.6, 1.5 Hz, 1H, H-1), 6.07 (dt, *J* = 15.7, 6.8 Hz, 1H, H-2), 5.29 – 5.23 (m, 1H, H-7), 3.80 (s, 3H, H-10/11/12), 3.78 (s, 3H, H-10/11/12), 3.76 (s, 3H, H-10/11/12), 2.66 – 2.55 (m, 2H, H-9), 2.33 – 2.22 (m, 4H, H-3 and H-8), 2.13 (dd, *J* = 9.1, 6.2 Hz, 2H, H-4), 1.61 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ158.8 (C-Ar), 153.6 (C-Ar), 152.0 (C-Ar), 135.2 (C-5), 132.2 (C-Ar), 130.9 (C-Ar), 129.2 (C-1), 128.8 (C-2), 127.1 (2C, C-Ar), 124.6 (C-7), 116.5 (C-Ar), 114.0 (2C, C-Ar), 111.3 (C-Ar), 110.9 (C-Ar), 56.1 (C-10/11/12), 55.8 (C-10/11/12), 55.4 (C-10/11/12), 39.8 (C-4), 31.9 (C-3/C-8), 30.8 (C-9), 28.4 (C-8/C-3), 16.1 (C-6).

IR (film) ν_{max}: 2933, 1608, 1510, 1500, 1464, 1247, 1223, 1176, 1049, 1035, 800 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{30}O_3Na$ $[M+Na]^+$ requires m/z 389.2087, found m/z 389.2088 (*Δ* = 0.30 ppm).

1-Chloro-4-((3*E*,7*E*)-8-(4-methoxyphenyl)-4-methylocta-3,7-dien-1-yl)benzene 46.



46

$C_{22}H_{25}OCl$

340.89 g mol^{-1}

$^3J_{H\text{-}1,\ H\text{-}2}$ = 15.7 Hz

4-Chlorobenzyl chloride (0.79 g, 4.9 mmol, 9.0 equiv) was used to prepare the Grignard reagent which was reacted with (*E*/*Z*)-**39** (0.150 g, 0.548 mmol, 1.00 equiv, 94:6 *E*:*Z*), Li_2CuCl_4 (1.1 mL, 0.10 M in THF, 0.11 mmol, 0.20 equiv) in THF (8.8 mL) according to the general procedure **B**, except that the Grignard reagent was prepared in Et_2O instead of THF. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to obtain diene **46** as a colourless oil (0.154 g, 82%, >95:5 *E*:*Z*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.18 (m, 4H, H-Ar), 7.13 – 7.05 (m, 2H, H-Ar), 6.87 – 6.80 (m, 2H, H-Ar), 6.32 (dt, *J* = 15.9, 1.6 Hz, 1H, H-1), 6.04 (dt, *J* = 15.7, 6.8 Hz, 1H, H-2),

5.18 (tq, *J* = 7.2, 1.4 Hz, 1H, H-7), 3.80 (s, 3H, H-10), 2.60 (dd, *J* = 8.4, 6.9 Hz, 2H, H-9), 2.34 – 2.22 (m, 4H, H-3 and H-8), 2.12 (dd, *J* = 8.8, 6.3 Hz, 2H, H-4), 1.57 (s, 3H, H-6).

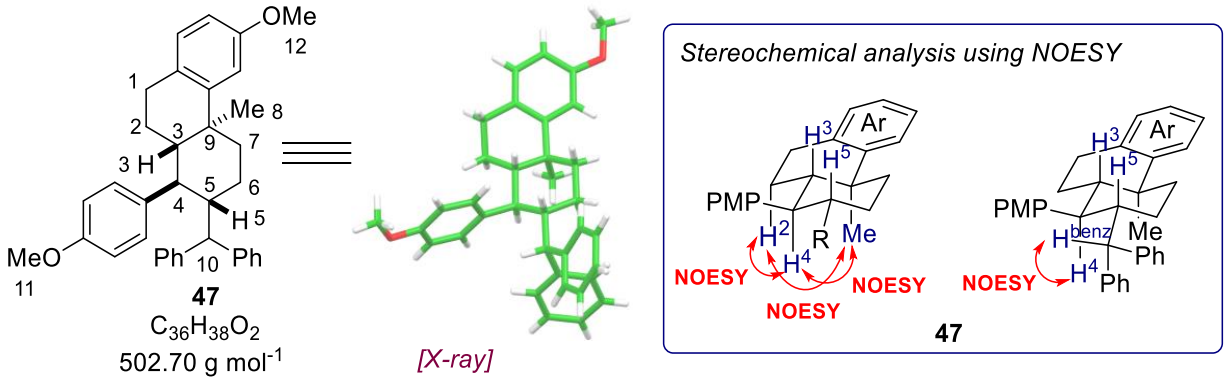
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 140.8 (C-5), 135.8 (C-Ar), 131.5 (C-Ar), 130.9 (C-Ar), 130.0 (2C, C-Ar)), 129.3 (C-1), 128.6 (C-2), 128.4 (2C, C-Ar), 127.1 (2C, C-Ar), 123.7 (C-7), 114.1 (2C, C-Ar), 55.4 (C-10), 39.7 (C-4), 35.5 (C-9), 31.7 (C-3), 29.8 (C-8), 16.2 (C-6).

M.p. 43 °C.

IR (film) ν_{max}: 2931, 2361, 2341, 1608, 1510, 1492, 1248, 1175, 1091, 1036, 965, 818 cm^{-1}.

HRMS: A stable molecular ion could not be detected by ESI, APCI or EI.

(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-Benzhydryl-6-methoxy-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 47.



Diene **43** (24.8 mg, 73.8 µmol, 1.00 equiv), benzhydrol (13.6 mg, 73.8 µmol, 1.00 equiv) and $Ti(O\textit{i}\text{-}Pr)_4$ (6.70 µL, 22.6 µmol, 0.306 equiv) in HFIP (1.5 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 24:1) to furnish compound **47** as a colourless foam (20.5 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.07 (m, 11H, H-Ar), 6.95 – 6.80 (m, 5H, H-Ar), 6.67 (dd, *J* = 8.3, 2.7 Hz, 1H, H-Ar), 3.94 (d, *J* = 3.1 Hz, 1H, H-10), 3.84 (s, 3H, H-11/H-12), 3.78 (s, 3H, H-12/H-11), 2.70 – 2.48 (m, 3H, H-1, H-5), 2.43 – 2.29 (m, 2H, H-4, H-7_a), 1.97 – 1.86 (m, 1H, H-6_a), 1.77 – 1.60 (m, 3H, H-3, H-6_b, H-7_b), 1.38 – 1.24 (m, 1H, H-2_a), 1.16 (ddt, *J* = 13.2, 7.7, 2.5 Hz, 1H, H-2_b), 1.00 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-Ar), 157.7 (C-Ar), 149.1 (C-Ar), 144.7 (C-Ar), 141.7 (C-Ar), 136.1 (C-Ar), 133.3 (C-Ar), 131.0 (2C, C-Ar), 130.0 (C-Ar), 128.4 (2C, C-Ar), 128.1 (2C, C-Ar), 127.9 (2C, C-Ar), 127.8 (C-Ar), 126.3 (C-Ar), 126.1 (C-Ar), 125.7 (C-Ar), 115.1 (C-

Ar), 112.8 (C-Ar), 110.9 (C-Ar), 110.6 (C-Ar), 55.4 (2C, C-11, C-12), 51.8 (C-10), 49.1 (C-3), 47.9 (C-4), 47.4 (C-5), 38.0 (C-7), 37.8 (C-9), 28.7 (C-1), 23.9 (C-6), 22.8 (2C, C-8, C-2).

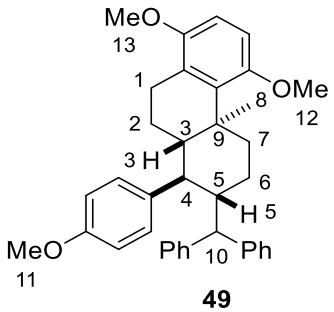
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me, between H-4 and H-2, between H-2 and Me, between H-4 and H^{benz}.

IR (film) ν_{max}: 2939, 1610, 1510, 1250, 1178, 1038, 908, 731, 704 cm^{-1}.

M.p. 168-170 °C

HRMS (ESI): calculated for $C_{36}H_{38}O_2Na$ $[M+Na]^+$ requires m/z 525.2764, found m/z 525.2767 (Δ = 0.63 ppm).

(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-Benzhydryl-5,8-dimethoxy-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 49.



49
$C_{37}H_{40}O_3$
532.72 g mol^{-1}

Diene **45** (36.6 mg, 0.100 mmol, 1.00 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 23:2) to furnish compound **49** as a sticky oil (28.4 mg, 53%).[51]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.08 (m, 11H, H-Ar), 6.96 – 6.81 (m, 3H, H-Ar), 6.68 (d, *J* = 9.0 Hz, 1H, H-Ar), 6.62 (d, *J* = 8.9 Hz, 1H, H-Ar), 3.93 (d, *J* = 3.0 Hz, 1H, H-10), 3.84 (s, 3H, H-11/H-13), 3.77 – 3.70 (m, 6H, H-12, H-13/H-11), 3.22 (dt, *J* = 13.0, 3.6 Hz, 1H, H-7_a), 2.70 – 2.44 (m, 3H, H-1_a, H-5, H-4), 2.35 – 2.18 (m, 1H, H-1_b), 1.85 – 1.64 (m, 3H, H-6_a, H-6_b, H-3), 1.44 – 1.31 (m, 1H, H-7_b), 1.23 – 1.04 (m, 5H, H-8, H-2_a, H-2_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 153.0 (C-Ar), 151.7 (C-Ar), 144.9 (C-Ar), 142.0 (C-Ar), 137.2 (C-Ar), 136.5 (C-Ar), 133.3 (C-Ar), 131.0 (2C, C-Ar), 128.5 (2C, C-Ar), 128.0 (2C, C-Ar), 127.8 (2C, C-Ar), 127.6 (C-Ar), 126.2 (2C, C-Ar), 125.5 (C-Ar), 115.1 (C-Ar), 112.8

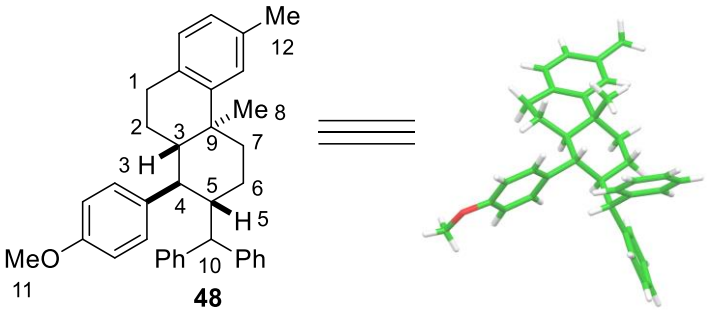
[51] Relative stereochemistry is determined by analogy to compounds **47** and **48**.

(C-Ar), 109.4 (C-Ar), 107.1 (C-Ar), 55.7 (C-11/C-12/C-13), 55.6 (C-11/C-12/C-13), 55.3 (C-11/C-12/C-13), 52.1 (C-10), 51.7 (C-3), 47.8 (C-5), 47.2 (C-4), 39.1 (C-9), 35.7 (C-7), 26.3 (C-1), 24.0 (C-6), 21.5 (C-2), 17.9 (C-8).

IR (film) ν_{max}: 2936, 1510, 1462, 1251, 1059, 1037, 909, 732, 703 cm^{-1}.

HRMS (ESI): calculated for $C_{37}H_{41}O_3$ $[M+H]^+$ requires m/z 533.3050, found m/z 533.3051 (*Δ* = 0.06 ppm).

(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-Benzhydryl-1-(4-methoxyphenyl)-4*a*,6-dimethyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 48.



Diene **44** (32 mg, 0.10 mmol, 1.0 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2 mL, 0.05 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish compound **48** as a colourless foam (30.3 mg, 62%).[52]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.19 (m, 6H, H-Ar), 7.16 – 7.08 (m, 6H, H-Ar), 6.95 – 6.80 (m, 5H, H-Ar), 3.94 (d, *J* = 3.2 Hz, 1H, H-10), 3.83 (s, 3H, H-11), 2.72 – 2.51 (m, 3H, H-1, H-5), 2.41 – 2.27 (m, 5H, H-4, H-7$_a$, H-12), 1.98 – 1.88 (m, 1H, H-6$_a$), 1.77 – 1.60 (m, 3H, H-7$_b$, H-3, H-6$_b$), 1.38 – 1.26 (m, 1H, H-2$_a$), 1.15 (ddt, *J* = 13.1, 7.8, 2.6 Hz, 1H, H-2$_b$), 1.00 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 147.7 (C-Ar), 144.7 (C-Ar), 141.8 (C-Ar), 136.1 (C-Ar), 134.9 (C-Ar), 133.3 (C-Ar), 132.5 (C-Ar), 131.0 (2C, C-Ar), 129.2 (C-Ar), 128.4 (2C, C-Ar), 128.1 (2C, C-Ar), 127.9 (2C, C-Ar), 126.5 (C-Ar), 126.3 (C-Ar), 126.1 (C-Ar), 125.6 (C-Ar), 125.2 (C-Ar), 115.1 (C-Ar), 112.8 (C-Ar), 55.3 (C-11), 51.8 (C-10), 49.2 (C-3), 47.9 (C-4), 47.4 (C-5), 37.9 (C-7), 37.5 (C-9), 29.1 (C-1), 23.9 (C-6), 22.9 (C-8), 22.8 (C-2), 21.4 (C-12).

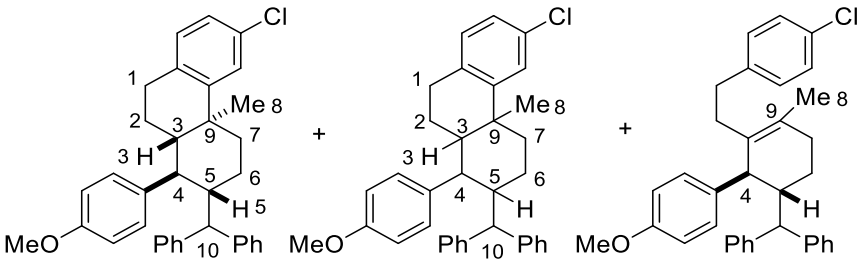
[52] Single crystal X-ray diffraction structure of enantiomer is shown.

M.p. 141-143 °C.

IR (film) ν_{max}: 2938, 1610, 1510, 1247, 1177, 1035, 909, 830, 732, 703 cm^{-1}.

HRMS (ESI): calculated for $C_{36}H_{38}ONa$ $[M+Na]^+$ requires m/z 509.2815, found m/z 509.2816 (Δ = 0.19 ppm).

(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-Benzhydryl-6-chloro-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 50 (from the mixture).



Diene **46** (34 mg, 0.10 mmol, 1.0 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish an inseparable mixture of compound **50**, diastereomer **50'** and alkene **50''** as a colourless oil (**50**:**50'**:**50''** = 66:16:18, 57% combined yield).[53,54]

Major diastereomer 50 (from the mixture)**:**

^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.42 – 6.76 (m, 17H, H-Ar), 3.92 (d, *J* = 3.4 Hz, 1H, H-10), 3.81 (s, 3H, H-11), 2.70 – 2.63 (m, 1H, H-1$_a$), 2.60 – 2.51 (m, 2H, H-1$_b$, H-5), 2.39 (t, *J* = 11.2 Hz, 1H, H-4), 2.33 – 2.28 (m, 1H, H-7$_a$), 1.96 – 1.89 (m, 1H, H-6$_a$), 1.72 – 1.59 (m, 3H, H-3, H-7$_b$, H-6$_b$), 1.36 – 1.28 (m, 1H, H-2$_a$), 1.19 – 1.09 (m, 1H, H-2$_b$), 0.98 (s, 3H, H-8).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.5 (C-Ar), 150.2 (C-Ar), 145.0 (C-Ar), 142.2 (C-Ar), 136.1 (C-Ar), 134.6 (C-Ar), 133.6 (C-Ar), 131.3 (C-Ar), 131.2 (2C, C-Ar), 130.9 (C-Ar), 128.7 (2C, C-Ar), 128.4 (2C, C-Ar), 128.2 (2C, C-Ar), 126.6 (C-Ar), 126.4 (C-Ar), 125.9 (C-Ar), 125.8 (C-Ar), 125.1 (C-Ar), 115.3 (C-Ar), 113.1 (C-Ar), 55.6 (C-11), 52.3 (C-10), 49.0 (C-3), 48.2 (C-4), 47.5 (C-5), 38.0 (2C, C-7, C-9), 29.2 (C-1), 24.4 (C-6), 22.8 (2C, C-2, C-8).

[53] **50**:**50'**:**50''** ratio was determined by ^{1}H NMR after column chromatography.
[54] Relative stereochemistry of the minor diastereomer could not be determined.

Characteristic peaks for minor diastereomer 50' (from the mixture):

^{1}H NMR (600 MHz, CD_2Cl_2): δ 3.76 (s, 3H, H-11), 3.68 (d, *J* = 4.6 Hz, H-10), 1.22 (s, 3H, H-8).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 34.9 (C-8)

Characteristic peaks for alkene 50'' (from the mixture):

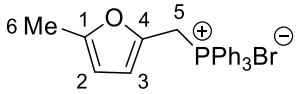
^{1}H NMR (600 MHz, CD_2Cl_2): δ 3.78 (s, 3H, H-11), 3.19 – 3.16 (m, 1H, H-4), 1.83 (s, 3H, H-8).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 138.3 (C-9), 46.0 (C-4), 19.1 (C-8).

HRMS (ACI): calculated for $C_{35}H_{35}OClNa$ $[M+Na]^+$ requires m/z 529.2269, found m/z 529.2270 (*Δ* = 0.16 ppm).

Synthesis of substrates 57-61 *via* a Wittig reaction

((5-Methylfuran-2-yl)methyl)triphenylphosphonium bromide 66.



66

$C_{24}H_{22}BrOP$

437.3168 g mol^{-1}

According to a literature procedure,[55] (5-methylfuran-2-yl)methanol (0.507 g, 4.52 mmol, 1.00 equiv) was dissolved in 1,4-dioxane (9 mL) and PPh_3 (1.18 g, 4.50 mmol, 1.00 equiv) was added in one portion. Bromotrimethylsilane (0.71 mL, 5.4 mmol, 1.2 equiv) was then added dropwise. The resulting mixture was stirred at 80 °C overnight and then cooled using an ice bath. The precipitate formed upon cooling was filtered and triturated with pentane to afford triphenylphosphonium salt **66** as a brown solid (1.55 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.53 (m, 15H, H-Ph), 6.24 (t, *J* = 3.7 Hz, 1H, H-3), 5.76 (d, *J* = 3.1 Hz, 1H, H-2), 5.31 (d, *J* = 12.9 Hz, 2H, H-5), 1.96 (d, *J* = 2.7 Hz, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.1 (d, *J* = 4.1 Hz, C-1), 138.5 (d, *J* = 11.6 Hz, C-4), 135.1 (d, *J* = 3.2 Hz, 3C, C-Ph), 134.1 (d, *J* = 10.0 Hz, 6C, C-Ph), 130.2 (d, *J* = 12.7 Hz, 6C, C-Ph),

[55] P. N. Chalikidi, T. T. Magkoev, A. V. Gutnov, O. P. Demidov, M. G. Uchuskin, I. V. Trushkov, V. T. Abaev, *J. Org. Chem*. **2021**, *86*, 9838−9846.

117.9 (d, *J* = 85.9 Hz, 3C, C-Ph), 114.2 (d, *J* = 8.4 Hz, C-3), 107.4 (d, *J* = 3.5 Hz, C-2), 25.8 (d, *J* = 51.1 Hz, C-5), 13.3 (C-6).

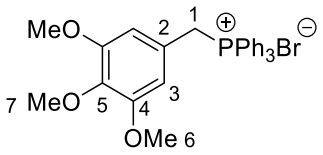
^{31}P NMR {^{1}H} (162 MHz, $CDCl_3$) δ 19.6.

M.p.: 182-184 °C.

IR (film) ν_{max}: 3058, 2358, 1716, 1439, 1113, 1025, 998, 746, 738, 692 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{22}OP$ $[M]^+$ requires m/z 357.1403, found m/z 357.1402 (*Δ* = -0.23 ppm).

Triphenyl(3,4,5-trimethoxybenzyl)phosphonium bromide 68.



68

$C_{28}H_{28}BrO_3P$

523.41 g mol^{-1}

(3,4,5-Trimethoxyphenyl)methanol (0.500 g, 2.52 mmol, 1.02 equiv) was dissolved in MeCN (6.6 mL) and to the obtained solution PPh_3·HBr (0.848 g, 2.47 mmol, 1.00 equiv) was added in one portion. The obtained solution was heated at reflux overnight and then cooled to rt. Volatiles were removed *in vacuo* and the crude product was triturated with pentane to afford triphenylphosphonium salt **68** as a white solid (0.964 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.50 (m, 15H, H-Ph), 6.51 – 6.38 (m, 2H, H-3), 5.31 (dd, *J* = 15.0, 4.1 Hz, 2H, H-1), 3.80 – 3.65 (m, 3H, H-7), 3.56 – 3.39 (m, 6H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.1 (3C, C-4, C-5), 134.9 (d, *J* = 3.0 Hz, 3C, C-Ph), 134.7 (d, *J* = 9.7 Hz, 6C, C-Ph), 130.1 (d, *J* = 12.6 Hz, 6C, C-Ph), 122.5 (d, *J* = 8.8 Hz, C-2), 117.9 (d, *J* = 85.7 Hz, 3C, C-Ph), 108.9 (d, *J* = 5.5 Hz, 2C, C-3), 60.9 (C-7), 56.3 (2C, C-6), 30.9 (d, *J* = 46.5 Hz, C-1).

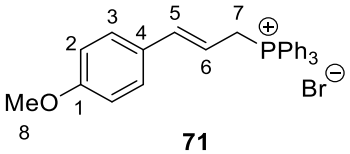
^{31}P NMR {^{1}H} (162 MHz, $CDCl_3$) δ 23.5.

M.p.: 194-196 °C.

IR (film) ν_{max}: 3401, 2935, 2360, 1509, 1467, 1231, 1038, 826, 735 cm^{-1}.

HRMS (ESI): calculated for $C_{28}H_{28}O_3P$ $[M]^+$ requires m/z 443.1771, found m/z 443.1778 (*Δ* = 1.66 ppm).

(*E*)-(3-(4-Methoxyphenyl)allyl)triphenylphosphonium bromide 71.



71
$C_{28}H_{26}OPBr$
489.39 g mol^{-1}

(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol (3.00 g, 18.3 mmol, 1.00 equiv) and triphenylphosphine hydrobromide (6.14 g, 17.9 mmol, 0.98 eq) were combined in MeCN (52 mL) and the obtained solution was heated under reflux overnight. The reaction mixture was allowed to cool to rt overnight and volatiles were removed *in vacuo.* The residue was washed with pentane (3 × 20 mL) and dried under vacuum. The obtained yellow solid **71** was used in the next step without purification (8.80 g, quant).[56]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.55 (m, 15H, H-Ph), 7.16 – 7.04 (m, 2H, H-3), 6.80 – 6.60 (m, 3H, H-2, H-5), 5.84 – 5.73 (m, 1H, H-6), 4.99 – 4.69 (m, 2H, H-7), 3.73 (s, 3H, H-8).

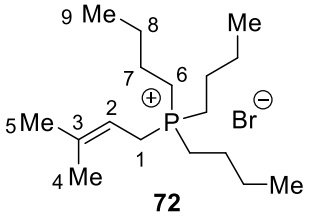
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9 (C-1), 139.8 (d, *J* = 13.5 Hz, C-5), 135.1 (d, *J* = 3.0 Hz, 3C, C-Ph), 134.1 (d, *J* = 9.8 Hz, 6C, C-Ph), 132.2 (C-4), 130.41 (d, *J* = 12.5 Hz, 6C, C-Ph), 127.9 (d, *J* = 2.3 Hz, 2C, C-3), 118.1 (d, *J* = 85.5 Hz, 3C, C-Ph), 114.1 (2C, C-2), 110.9 (d, *J* = 10.9 Hz, C-6), 55.4 (C-8), 28.41 (d, *J* = 48.9 Hz, C-7).

^{31}P (162 MHz, $CDCl_3$): δ 21.1.

HRMS (ESI): calculated for $C_{28}H_{26}OP$ $[M]^+$ requires m/z 409.1716, found m/z 409.1716 (*Δ* = 0.05 ppm).

[56] Product is impure but sufficient yields (53-63%) were achieved using unpurified **71**. Recrystallisation (Et_2O, CH_2Cl_2, -20 °C, **34%**) was performed to obtain clean sample of salt **71**, however, it did not improve the yield of the following Wittig reaction.

Tributyl(3-methylbut-2-en-1-yl)phosphonium bromide 72.



72

$C_{17}H_{36}PBr$

351.4 g mol^{-1}

1-Bromo-3-methylbut-2-ene (0.50 mL, 0.64 g, 4.3 mmol, 1.0 equiv) was dissolved in Et_2O (14 mL) and the obtained solution was cooled to 0°C. Tri-*n*-butylphosphine (2.75 mL, 2.26 g, 11.1 mmol, 2.59 equiv) was added dropwise and stirred at the same temperature for 15 min. The solution was allowed to warm to rt and stirred overnight. The formed solid was collected by filtration and washed with ice cold hexane (3 × 10 mL) to obtain tributylphosphonium salt **72** as a pale yellow solid (0.76 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.00 – 4.84 (m, 1H, H-2), 3.31 – 3.16 (m, 2H, H-1), 2.42 – 2.19 (m, 6H, H-6), 1.76 – 1.55 (m, 6H, H-4, H-5), 1.54 – 1.28 (m, 12H, H-7, H-8), 0.94 – 0.72 (m, 9H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.5 (d, *J* = 12.5 Hz, C-3), 108.9 (d, *J* = 9.3 Hz, C-2), 25.8 (d, *J* = 3.0 Hz, C-5/C-4), 24.0 – 23.4 (m, 6C, C-7, C-8), 20.3 (d, *J* = 48.0 Hz, C-1), 19.2 – 18.3 (m, 4C, C-6, C-4/C-5), 13.3 (3C, C-9).

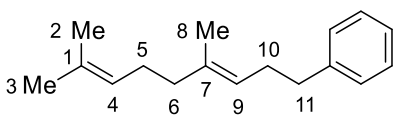
^{31}P NMR {^{1}H} (162 MHz, $CDCl_3$) δ 33.0.

M.p: 88-90 °C.

IR (film) ν_{max}: 2960, 2932, 2873, 1724, 1465, 1237, 1098, 970, 917, 815, 733 cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{36}P$ $[M]^+$ requires m/z 271.2549, found m/z 271.2557 (*Δ* = 2.88 ppm).

(*E*)-(4,8-dimethylnona-3,7-dien-1-yl)benzene 57.



57

$C_{17}H_{24}O$

228.38 g mol^{-1}

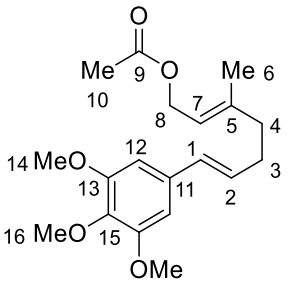
Geranyl acetate **36** (0.30 g, 1.5 mmol, 1.0 equiv), BnMgCl (2.0 M in THF, 1.5 mL, 3.0 mmol, 2.0 equiv) and Li_2CuCl_4 (0.10 M in THF, 1.5 mL, 0.15 mmol, 0.1 equiv) in THF were subjected to the general procedure **B** except the reaction was performed with 2.0 equiv of BnMgCl and 0.1 equiv of Li_2CuCl_4. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane) to furnish alkene **57** as a colourless oil (0.134 g, 38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 2H, H-Ph), 7.22 – 7.14 (m, 3H, H-Ph), 5.25 – 5.15 (m, 1H, H-9), 5.13 – 5.06 (m, 1H, H-4), 2.64 (dd, *J* = 8.9, 6.8 Hz, 2H, H-11), 2.31 (q, *J* = 7.5 Hz, 2H, H-10), 2.13 – 1.94 (m, 4H, H-5, H-6), 1.69 (s, 3H, H-2/H-3), 1.61 (s, 3H, H-3/H-2), 1.56 (s, 3H, H-8).

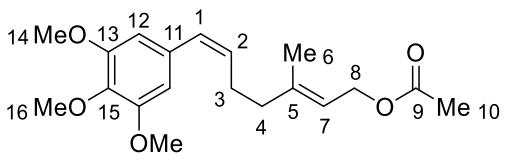
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.6 (C-1/C-7/C-Ph), 135.9 (C-1/C-7/C-Ph), 131.5 (C-1/C-7/C-Ph), 128.6 (2C, C-Ph), 128.3 (2C, C-Ph), 125.8 (C-Ph), 124.5 (C-4) 123.7 (C-9), 39.9 (C-6), 36.3 (C-11), 30.1 (C-10), 26.9 (C-5), 25.8 (C-2/C-3), 17.8 (C-3/C-2), 16.1 (C-8).

The data are consistent with the literature[57]

(2*E*,6*E*)-3-Methyl-7-(3,4,5-trimethoxyphenyl)hepta-2,6-dien-1-yl acetate *E*-73 major and (2*E*,6*Z*)-3-methyl-7-(3,4,5-trimethoxyphenyl)hepta-2,6-dien-1-yl acetate *Z*-73 minor.



Major-73
$C_{19}H_{26}O_5$
334.41 g mol^{-1}



Minor-73
$C_{19}H_{26}O_5$
334.41 g mol^{-1}

Triphenyl(3,4,5-trimethoxybenzyl)phosphonium bromide **68** (0.50 g, 0.96 mmol, 1.5 equiv) was suspended in THF (5 mL) and cooled to -78 °C. *n*-BuLi (0.38 mL, 2.5 M in hexanes, 0.96 mmol, 1.5 equiv) was added dropwise and the obtained suspension was allowed to stir at the same temperature for 30 min. Aldehyde **38** (0.11 g, 0.64 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise at -78 °C and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine (40 mL) and

[57] G. Sudhakar Reddy, E. J. Corey, *Org. Lett.* **2023**, *25*, 1872–1877.

volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 7:3) to furnish an inseparable mixture of alkenes (*E*)-**73** and (*Z*)-**73** as a colourless oil (77.7 mg, 36%, 67:33 *E*:*Z*).

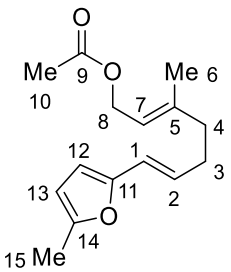
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, $2H_{maj}$, H-12_{maj}), 6.49 (s, $2H_{min}$, H-12_{min}), 6.40 – 6.26 (m, $1H_{maj}$, $1H_{min}$, H-1_{maj}, H-1_{min}), 6.10 (dt, *J* = 15.8, 6.8 Hz, $1H_{maj}$, H-2_{maj}), 5.59 (dt, *J* = 11.7, 7.2 Hz, $1H_{min}$, H-2_{min}), 5.43 – 5.30 (m, $1H_{maj}$, $1H_{min}$, H-7_{maj}, H-7_{min}), 4.64 – 4.52 (m, $2H_{maj}$, $2H_{min}$, H-8_{maj}, H-8_{min}), 3.95 – 3.74 (m, $9H_{maj}$, $9H_{min}$, H-14_{maj}, H-16_{maj}, H-14_{min}, H-16_{min}), 2.54 – 2.44 (m, $2H_{min}$, H-3_{min}), 2.39 – 2.28 (m, $2H_{maj}$, H-3_{maj}), 2.26 – 2.14 (m, $2H_{maj}$, $2H_{min}$, H-4_{maj}, H-4_{min}), 2.05 (s, $3H_{min}$, H-10_{min}), 2.03 (s, $3H_{maj}$, H-10_{maj}), 1.74 (s, $3H_{maj}$, H-6_{maj}), 1.69 (s, $3H_{min}$, H-6_{min}).

^{13}C NMR (101 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 171.2 (C-9), 153.4 (2C, C-13), 153.1 (C-15), 141.7 (C-5/C-11), 133.6 (C-11/C-5), 130.3 (C-1), 129.7 (C-2), 119.0 (C-7), 103.2 (2C, C-12), 61.5 (C-8), 61.1 (C-16), 56.2 (2C, C-14), 39.4 (C-4), 31.2 (C-3), 21.2 (C-10), 16.6 (C-6). **Selected peaks for the minor diastereomer** (from the mixture): δ 131.6 (C-2), 129.5 (C-1), 119.1 (C-7) 106.1 (2C, C-12), 39.6 (C-4), 26.9 (C-3).

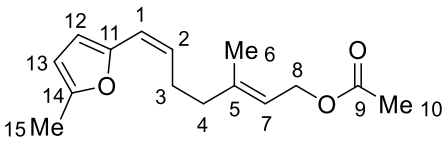
IR (film) ν_{max}: 2938, 1737, 1582, 1508, 1235, 1127, 1011, 964, 846 cm^{-1}.

HRMS (ESI): calculated for $C_{19}H_{27}O_5$ $[M+H]^+$ requires m/z 335.1853, found m/z 335.1864 (Δ = 3.27 ppm).

(2*E*,6*E*)-3-methyl-7-(5-methylfuran-2-yl)hepta-2,6-dien-1-yl acetate *E*-74 major and (2*E*,6*Z*)-3-methyl-7-(5-methylfuran-2-yl)hepta-2,6-dien-1-yl acetate *Z*-74 minor.



Major-74
$C_{15}H_{20}O_3$
248.32 g mol^{-1}



Minor-74
$C_{15}H_{20}O_3$
248.32 g mol^{-1}

((5-Methylfuran-2-yl)methyl)(phenyl)phosphonium bromide **66** (0.87 g, 2.0 mmol, 1.5 equiv) was suspended in THF (10 mL) and cooled to -78 °C. *n*-BuLi (0.80 mL, 2.5 M in hexanes, 2.0 mmol, 1.5 equiv) was added dropwise and the obtained suspension was allowed to stir at the same temperature for 30 min. Aldehyde **38** (0.228 g, 1.34 mmol, 1.00 equiv) in THF (5 mL) was added dropwise at -78 °C and the reaction mixture was allowed to warm to rt overnight.

The reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine (40 mL) and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 24:1) to furnish an inseparable mixture of alkenes (*E*)-**74** and (*Z*)-**74** as a pale yellow oil (83.7 mg, 25%, 82:18 *E*:*Z*).[58]

Major (*E*)-74 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 – 5.90 (m, 4H, H-12, H-13, H-1, H-2), 5.48 – 5.35 (m, 1H, H-7), 4.64 – 4.55 (m, 2H, H-8), 2.35 – 2.25 (m, 5H, H-15, H-3), 2.23 – 2.14 (m, 2H, H-4), 2.04 (s, 3H, H-10), 1.72 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C-9), 151.7 (C-14/C-11), 151.4 (C-11/C-14), 141.8 (C-5), 127.4 (C-2), 119.2 (C-1), 118.9 (C-7), 107.5 (C-12/C-13), 107.2 (C-13/C-12), 61.5 (C-8), 39.4 (C-4), 31.1 (C-3), 21.2 (C-10), 16.6 (C-6), 13.8 (C-15).

Characteristic peaks for minor (*Z*)-74 (from the mixture):

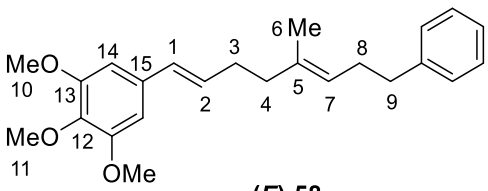
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 – 2.52 (m, 2H, H-3), 2.30 (s, 3H, H-15), 2.05 (s, 3H, H-10), 1.74 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 61.5 (C-8), 27.5 (C-3), 16.5 (C-6).

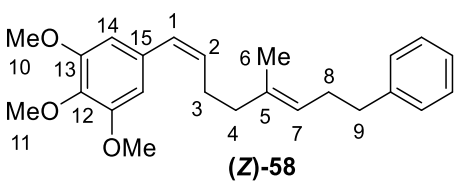
IR (film) ν_{max}: 2944, 1735, 1369, 1239, 1035, 740 cm^{-1}.

HRMS: A stable molecular ion could not be detected.

1,2,3-Trimethoxy-5-((1*E*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)benzene *E*-58 major and 1,2,3-Trimethoxy-5-((1*Z*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)benzene *Z*-58 minor.



(*E*)-58
$C_{24}H_{30}O_3$
366.50 g mol^{-1}
$^3J_{H\text{-}1,\ H\text{-}2}$ = 15.7 Hz



(*Z*)-58
$C_{24}H_{30}O_3$
366.50 g mol^{-1}
$^3J_{H\text{-}1,\ H\text{-}2}$ = 11.7 Hz

[58] *E*:*Z* ratio was determined after column chromatography.

Acetate **73** (74.3 mg, 0.222 mmol, 1.00 equiv, 67:33 *E*:*Z*), BnMgCl (2.0 M in THF, 1.0 mL, 2.0 mmol, 9.0 equiv) and Li_2CuCl_4 (0.10 M in THF, 0.67 mL, 67 µmol, 0.30 equiv) in THF were subjected to the general procedure **B**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish alkene **58** as an inseparable mixture of alkene diastereomers as a colourless oil (64.8 mg, 80%, 68:32 *E*:*Z*)[59].

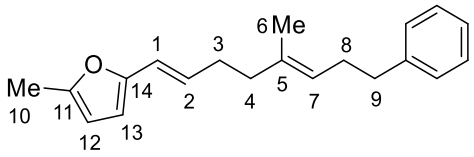
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.13 (m, $5H_{maj}$, $5H_{min}$, H-Ph_{maj}, H-Ph_{min}), 6.56 (s, $2H_{maj}$, H-14_{maj}), 6.50 (s, $2H_{min}$, H-14_{min}), 6.38 – 6.28 (m, $1H_{maj}$, $1H_{min}$, H-1_{maj}, H-1_{min}), 6.13 (dt, *J* = 15.7, 6.8 Hz, $1H_{maj}$, H-2_{maj}), 5.59 (dt, *J* = 11.7, 7.2 Hz, $1H_{min}$, H-2_{min}), 5.32 – 5.16 (m, $1H_{maj}$, $1H_{min}$, H-7_{maj}, H-7_{min}), 3.94 – 3.81 (m, $9H_{maj}$, $9H_{min}$, H-10_{maj}, H-11_{maj}, H-10_{min}, H-11_{min}), 2.70 – 2.58 (m, $2H_{maj}$, $2H_{min}$, H-9_{maj}, H-9_{min}), 2.44 (qd, *J* = 7.5, 1.8 Hz, $2H_{min}$, H-3_{min}), 2.38 – 2.24 (m, $4H_{maj}$, $2H_{min}$, H-3_{maj}, H-8_{maj}, H-8_{min}), 2.20 – 2.08 (m, $2H_{maj}$, $2H_{min}$, H-4_{maj}, H-4_{min}), 1.61 – 1.56 (m, $3H_{maj}$, $3H_{min}$, H-6_{maj}, H-6_{min}).

^{13}C NMR (101 MHz, $CDCl_3$): **for the major diastereomer** (from the mixture) δ 153.4 (2C, C-13), 153.0 (C-12) 142.4 (C-15/C-5/C-Ph), 135.3 (C-15/C-5/C-Ph), 133.9 (C-15/C-5/C-Ph), 130.4 (C-2), 129.9 (C-1), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.8 (C-Ph), 124.3 (C-7), 103.2 (2C, C-14), 61.1 (C-11), 56.2 (2C, C-10), 39.6 (C-4), 36.3 (C-9), 31.7 (C-3), 30.1 (C-8), 16.2 (C-6).**Selected peaks for the minor diastereomer** (from the mixture) δ 137.5 (C-15/C-5/C-Ph), 135.1 (C-15/C-5/C-Ph), 133.5 (C-15/C-5/C-Ph), 132.3 (C-2), 129.0 (C-1), 126.0 (C-Ph), 124.4 (C-7), 106.1 (C-14), 39.8 (C-4), 36.2 (C-9), 30.0 (C-8), 27.3 (C-3), 16.1 (C-6).

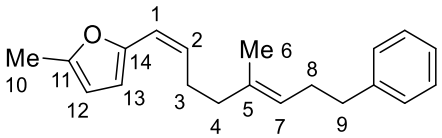
IR (film) ν_{max}: 2935, 2838, 1582, 1507, 1454, 1418, 1331, 1239, 1129, 1010, 700 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{30}O_3Na$ $[M+Na]^+$ requires m/z 389.2087, found m/z 389.2095 (*Δ* = 2.00 ppm).

2-Methyl-5-((1*E*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)furan *E*-59 major and 2-methyl-5-((1*Z*,5*E*)-5-methyl-8-phenylocta-1,5-dien-1-yl)furan *Z*-59 minor.



(*E*)-59
$C_{20}H_{24}O$
280.41 g mol^{-1}



(*Z*)-59
$C_{20}H_{24}O$
280.41 g mol^{-1}
$^3J_{H\text{-}1,\ H\text{-}2}$ = 11.7 Hz

[59] *E*:*Z* ratio was determined after column chromatography.

Acetate **74** (82.9 mg, 0.334 mmol, 1.00 equiv, 82:18 *E*:*Z*), BnMgCl (2.0 M in THF, 1.5 mL, 3.0 mmol, 9.0 equiv) and Li_2CuCl_4 (0.10 M in THF, 1.0 mL, 0.10 mmol, 0.3 equiv) in THF were subjected to the general procedure **B**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 99:1) to furnish alkene **59** as an inseparable mixture of alkene diastereomers as a colourless oil (81.5 mg, 87%, 77:23 *E*:*Z*)[60].

Major (*E*)-59 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.11 (m, 5H, H-Ph), 6.20 – 5.96 (m, 3H, H-1, H-2, H-13), 5.92 (dq, *J* = 3.2, 1.1 Hz, 1H, H-12), 5.27 – 5.17 (m, 1H, H-7), 2.69 – 2.56 (m, 2H, H-9), 2.37 – 2.19 (m, 7H, H-3, H-8, H-10), 2.17 – 2.06 (m, 2H, H-4), 1.57 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9 (C-11/C-14), 151.3 (C-14/C-11), 142.5 (C-5/C-Ph), 135.3 (C-Ph/C-5), 128.6 (2C, C-Ph), 128.3 (2C, C-Ph), 128.2 (C-1/C-2), 125.8 (C-Ph), 124.2 (C-7), 118.8 (C-2/C-1), 107.2 (2C, C-12, C-13), 39.5 (C-4), 36.2 (C-9), 31.6 (C-3), 30.1 (C-8), 16.1 (C-6), 13.8 (C-10).

Characteristic peaks for minor (*Z*)-59 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (dt, *J* = 11.7, 7.2 Hz, 1H, H-2), 2.50 (qd, *J* = 7.5, 1.8 Hz, 2H, H-3), 1.58 (s, 3H, H-6).

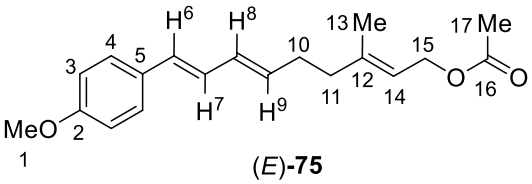
^{13}C NMR (101 MHz, $CDCl_3$): δ 39.4 (C-4), 30.1 (C-8), 16.0 (C-6), 13.8 (C-10).

IR (film) ν_{max}: 2972, 1452, 1384, 959, 910, 779, 734, 699 cm^{-1}.

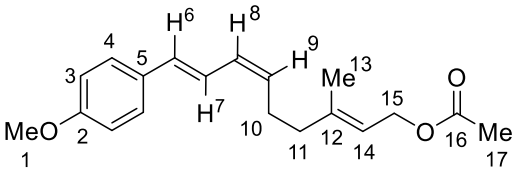
HRMS (ESI): calculated for $C_{20}H_{25}O$ $[M+H]^+$ requires m/z 281.1900, found m/z 281.1900 (*Δ* = 0.04 ppm).

[60] *E*:*Z* ratio was determined after column chromatography.

(2*E*,6*E*,8*E*)-9-(4-Methoxyphenyl)-3-methylnona-2,6,8-trien-1-yl acetate (*E*)-75 major and (2*E*,6*Z*,8*E*)-9-(4-Methoxyphenyl)-3-methylnona-2,6,8-trien-1-yl acetate (*Z*)-75 minor.



(*E*)**-75**
$C_{19}H_{24}O_3$
300.40 g mol^{-1}
$^3J_{\text{H-6, H-7}}$ = 15.5 Hz
$^3J_{\text{H-8, H-9}}$ = 14.8 Hz



(*Z*)**-75**
$C_{19}H_{24}O_3$
300.40 g mol^{-1}
$^3J_{\text{H-6, H-7}}$ = 15.6 Hz

(*E*)-(3-(4-Methoxyphenyl)allyl)triphenylphosphonium bromide **71** (2.15 g, 4.39 mmol, 1.50 equiv) was suspended in THF (21 mL) and cooled to -78 °C. *n*-BuLi (1.76 mL, 2.5 M in hexanes, 4.40 mmol, 1.50 equiv) was added dropwise and the obtained suspension was allowed to stir at the same temperature for 30 min. Aldehyde **38** (0.497 g, 2.92 mmol, 1.00 equiv) in THF (10 mL) was added dropwise at -78 °C and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (7 mL), diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 4:1) to furnish an inseparable mixture of alkenes (*E*)-**75** and (*Z*)-**75** as a pale yellow oil (0.482 g, 56:44 *E*:*Z*).

The mixture of alkenes (*E*)-**75** and (*Z*)-**75** (0.482 g, 1.61 mmol, 1.00 equiv, 56:44 *E*:*Z*) was dissolved in CH_2Cl_2 (3.3 mL) and I_2 (20.5 mg, 80.8 µmol, 0.0502 equiv) was added in one portion. The solution was stirred at rt for 30 min, quenched with sat. aq. $Na_2S_2O_3$ (1 mL), diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo* to obtain an inseparable mixture of alkenes (*E*)-**75** and (*Z*)-**75** as a yellow oil which did not require any further purification (0.469 g, 53% over two steps, 85:15 *E*:*Z*).[61]

Major (*E*)-75 (from the mixture)**:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.7 Hz, 2H, H-4), 6.84 (d, *J* = 8.7 Hz, 2H, H-3), 6.61 (dd, *J* = 15.5, 10.3 Hz, 1H, H-7), 6.40 (d, *J* = 15.7 Hz, 1H, H-6), 6.19 (ddt, *J* = 14.8, 10.3, 1.4 Hz, 1H, H-8), 5.73 (dt, *J* = 14.6, 6.9 Hz, 1H, H-9), 5.37 (tq, *J* = 7.0, 1.3 Hz, 1H, H-14), 4.59 (d, *J* = 7.1 Hz, 2H, H-15), 3.80 (s, 3H, H-1), 2.31 – 2.23 (m, 2H, H-10), 2.20 – 2.11 (m, 2H, H-11), 2.05 (s, 3H, H-17), 1.72 (s, 3H, H-13).

[61] E. E. Schultz, V. N. G. Lindsay, R. Sarpong, *Angew. Chem. Int. Ed*. **2014**, *53*, 9904–9908.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C-16), 159.1 (C-2), 141.8 (C-12), 133.5 (C-9), 131.2 (C-8), 130.5 (C-5), 130.1 (C-6), 127.5 (2C, C-4), 127.4 (C-7), 118.9 (C-14), 114.2 (2C, C-3), 61.5 (C-15), 55.4 (C-1), 39.4 (C-11), 31.1 (C-10), 21.2 (C-17), 16.6 (C-13).

Characteristic peaks for minor (*Z*)-75 (from the mixture)**:**

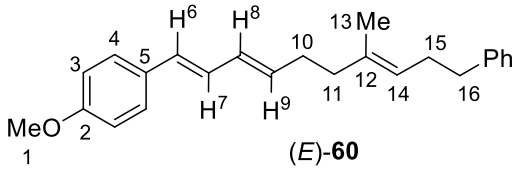
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.7 Hz, 2H, H-4), 6.48 (d, *J* = 15.6 Hz, 1H, H-6), 3.81 (s, 3H, H-1), 2.46 – 2.37 (m, 2H, H-11), 2.05 (s, 3H, H-17), 1.74 (s, 3H, H-13).

^{13}C NMR (101 MHz, $CDCl_3$): δ 127.7 (C-4), 114.2 (C-3), 26.3 (C-11).

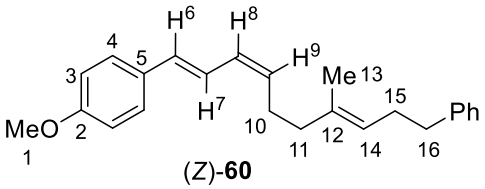
IR (film) ν_{max}: 2935, 1733, 1602, 1512, 1250, 1175, 1031, 911, 732 cm^{-1}.

HRMS (ESI): calculated for $C_{19}H_{25}O_3$ $[M+H]^+$ requires m/z 301.1798, found m/z 301.1795 (*Δ* = -1.0 ppm).

1-Methoxy-4-((1*E*,3*E*,7*E*)-7-methyl-10-phenyldeca-1,3,7-trien-1-yl)benzene (*E*)-60 and 1-Methoxy-4-((1E,3*Z*,7*E*)-7-methyl-10-phenyldeca-1,3,7-trien-1-yl)benzene (*Z*)-60.



(*E*)-**60**
$C_{24}H_{28}O$
332.49 g mol^{-1}
$^{3}J_{H\text{-}6,\ H\text{-}7}$ = 15.6 Hz
$^{3}J_{H\text{-}8,\ H\text{-}9}$ = 15.1 Hz



(*Z*)-**60**
$C_{24}H_{28}O$
332.49 g mol^{-1}
$^{3}J_{H\text{-}6,\ H\text{-}7}$ = 15.5 Hz
$^{3}J_{H\text{-}8,\ H\text{-}9}$ = 10.8 Hz

A mixture of alkenes *E*-**75** and *Z*-**75** (0.681 g, 2.27 mmol, 1.00 equiv, 85:15 *E*:*Z*) was dissolved in THF (35 mL) and cooled to 0 °C. Li_2CuCl_4 (6.8 mL, 0.10 M in THF, 0.68 mmol, 0.30 equiv) was then added at the same temperature. To the obtained solution BnMgCl (10.2 mL, 2.00 M in THF, 20.4 mmol, 8.99 equiv) was added dropwise over 5 min keeping the temperature at 0 °C. The reaction mixture was allowed to stir at the same temperature for 3 h, quenched with sat. aq. NH_4Cl (10 mL), diluted with water (30 mL) and extracted with Et_2O (3 × 40 mL). The organic layers were combined, washed with brine (100 mL) and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 97:3) to furnish an inseparable mixture of trienes (*E*)-**60** and (*Z*)-**60** as a colourless waxy solid (0.565 g, 75%, 86:14 *E*:*Z*).

Major (*E*)-60 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.25 (m, 4H, H-4, H-Ph), 7.22 – 7.17 (m, 3H, H-Ph), 6.84 (d, *J* = 8.8 Hz, 2H, H-3), 6.62 (dd, *J* = 15.6, 10.3 Hz, 1H, H-7), 6.39 (d, *J* = 15.6 Hz, 1H, H-6), 6.18 (dd, *J* = 15.1, 10.3 Hz, 1H, H-8), 5.74 (dt, *J* = 15.1, 6.9 Hz, 1H, H-9), 5.24 – 5.17 (m, 1H, H-14), 3.81 (s, 3H, H-1), 2.65 (dd, *J* = 8.8, 6.7 Hz, 2H, H-16), 2.36 – 2.28 (m, 2H, H-15), 2.26 – 2.19 (m, 2H, H-10), 2.12 – 2.05 (m, 2H, H-11), 1.57 (s, 3H, H-13).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1 (C-2), 142.5 (C-12), 135.3 (C-Ph), 134.3 (C-9), 130.9 (C-8), 130.7 (C-5), 129.8 (C-6), 128.6 (2C, C-Ph), 128.4 (2C, C-4), 127.6 (C-7), 127.4 (2C, C-Ph), 125.8 (C-Ph), 124.2 (C-14), 114.2 (2C, C-3), 55.4 (C-1), 39.6 (C-11), 36.2 (C-16), 31.6 (C-10), 30.0 (C-15), 16.1 (C-13).

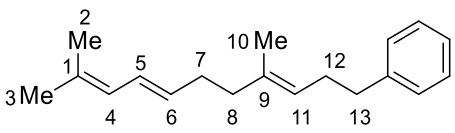
Characteristic peaks for minor (*Z*)-60 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.8 Hz, 2H, H-4), 6.48 (d, *J* = 15.5 Hz, 1H, H-6), 5.43 (dt, *J* = 10.8, 7.5 Hz, 1H, H-9), 3.82 (s, 3H, H-1), 1.59 (s, 3H, H-13).

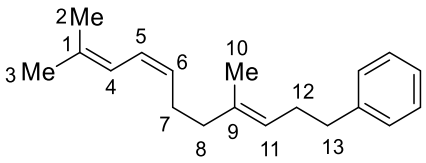
IR (film) ν_{max}: 2930, 1604, 1510, 1454, 1250, 1174, 1035, 986, 827, 748, 699 cm^{-1}.

HRMS (GC EI): calculated for $C_{24}H_{28}O$ $[M]^{\cdot+}$ requires 332.21347, found m/z 332.21309 (*Δ* = -1.1 ppm).

((3*E*,7*E*)-4,10-dimethylundeca-3,7,9-trien-1-yl)benzene (*E*)-61 and ((3*E*,7*Z*)-4,10-dimethylundeca-3,7,9-trien-1-yl)benzene (*Z*)-61.



(*E*)-**61**
$C_{19}H_{26}$
254.42 g mol^{-1}
$^{3}J_{H\text{-}5,\ H\text{-}6}$ = 15.2 Hz



(*Z*)-**61**
$C_{19}H_{26}$
254.42 g mol^{-1}

Tributyl(3-methylbut-2-en-1-yl)phosphonium bromide **72** (0.26 g, 0.74 mmol, 1.5 equiv) was dissolved in THF (20 mL) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 0.30 mL, 0.74 mmol, 1.5 equiv) was added dropwise, the obtained suspension was stirred at 0 °C for 30 min and then cooled to -78 °C. Aldehyde **32** (0.10 g, 0.49 mmol, 1.0 equiv) in THF (3 mL) was added dropwise, and the reaction mixture was allowed to warm to rt overnight. The solution was quenched with sat. aq. NH_4Cl (0.50 mL) and diluted with Et_2O (20 mL). The mixture was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane) to

furnish alkene **61** as an inseparable mixture of alkene diastereomers as a colourless oil (54.4 mg, 43%, 91:9 *E*:*Z*)[62].

Major (*E*)-61 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.2, 6.8 Hz, 2H, H-Ph), 7.19 (d, *J* = 7.4 Hz, 3H, H-Ph), 6.23 (ddt, *J* = 15.2, 10.7, 1.5 Hz, 1H, H-5), 5.78 (dq, *J* = 10.8, 1.3 Hz, 1H, H-4), 5.53 (dt, *J* = 15.2, 6.8 Hz, 1H, H-6), 5.20 (tq, *J* = 7.1, 1.4 Hz, 1H, H-11), 2.68 – 2.58 (m, 2H, H-13), 2.36 – 2.26 (m, 2H, H-12), 2.21 – 2.13 (m, 2H, H-7), 2.09 – 2.02 (m, 2H, H-8), 1.79 – 1.72 (m, 6H, H-3, H-2), 1.55 (d, *J* = 1.2 Hz, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (C-1/C-9/C-Ph), 135.5 (C-1/C-9/C-Ph), 133.0 (C-1/C-9/C-Ph), 131.6 (C-6), 128.6 (2C, C-Ph) 128.3 (2C, C-Ph), 126.9 (C-5), 125.8 (C-Ph), 125.2 (C-4), 124.0 (C-11), 39.8 (C-8), 36.3 (C-13), 31.6 (C-7), 30.1 (C-12), 26.0 (C-2/C-3), 18.3 (C-3/C-2), 16.1 (C-10).

Characteristic peaks for minor (*Z*)-61 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 – 6.03 (m, 1H, H-4), 5.34 – 5.25 (m, 1H, H-7), 1.81 (s, 3H, H-2/H-3).

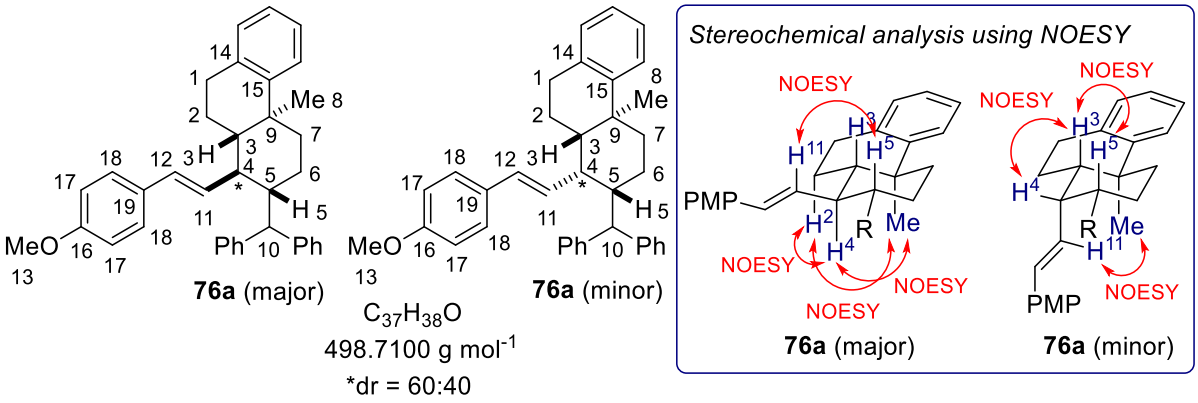
IR (film) ν_{max}: 2970, 2920, 1496, 1452, 1380, 1155, 1076, 1031, 986, 957, 747, 698 cm^{-1}.

HRMS (ESI): calculated for $C_{19}H_{27}$ $[M+H]^+$ requires m/z 255.2107, found m/z 255.2109 (*Δ* = 0.62 ppm).

[62] *E*:*Z* ratio was determined after column chromatography.

Polyene cyclisation of triene substrate 60

(±)-(1*R*,2S,4aS,10aS)-2-Benzhydryl-1-((*E*)-4-methoxystyryl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (major)-76a and (±)-(1*S*,2S,4aS,10aS)-2-Benzhydryl-1-((*E*)-4-methoxystyryl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (minor)-76a.



Triene **60** (33.2 mg, 0.100 mmol, 1.00 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **D**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 24:1) to furnish compound **76a** as an inseparable mixture of two diastereomers at the exocyclic allylic position as a colourless oil (33.2 mg, 67%, 60:40 dr).[63]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.03 (m, 16H$_{maj}$, 16H$_{min}$, H-Ar$_{maj}$, H-Ph$_{maj}$, H-Ar$_{min}$, H-Ph$_{min}$), 6.92 (d, *J* = 8.6 Hz, 2H$_{min}$, H-Ar$_{min}$), 6.88 (d, *J* = 8.6 Hz, 2H$_{maj}$, H-Ar$_{maj}$), 6.32 – 6.23 (m, 1H$_{maj}$, 1H$_{min}$, H-12$_{maj}$, H-11$_{min}$), 5.78 – 5.68 (m, 1H$_{maj}$, 1H$_{min}$, H-11$_{maj}$, H-12$_{min}$), 4.42 (d, *J* = 3.9 Hz, 1H$_{maj}$, H-10$_{maj}$), 3.85 (s, 3H$_{min}$, H-13$_{min}$), 3.84 (s, 3H$_{maj}$, H-13$_{maj}$), 3.66 (d, *J* = 11.8 Hz, 1H$_{min}$, H-10$_{min}$), 2.97 – 2.77 (m, 2H$_{maj}$, 2H$_{min}$, H-1$_{maj}$, H-1$_{min}$), 2.51 (tt, *J* = 11.5, 4.0 Hz, 1H$_{min}$, H-5$_{min}$), 2.42 (dt, *J* = 9.3, 4.2 Hz, 1H$_{min}$, H-4$_{min}$), 2.39 – 2.32 (m, 1H$_{maj}$, 1H$_{min}$, H-7$_{a, maj}$, H-7$_{a, min}$), 2.32 – 2.24 (m, 1H$_{maj}$, H-5$_{maj}$), 2.14 (q, *J* = 10.2 Hz, 1H$_{maj}$, H-4$_{maj}$), 1.94 (ddt, *J* = 13.0, 6.1, 2.8 Hz, 1H$_{maj}$, H-2$_{a, maj}$), 1.89 – 1.76 (m, 1H$_{maj}$, 2H$_{min}$, H-6$_{a, maj}$, H-2$_{a, min}$, H-3$_{min}$), 1.67 – 1.52 (m, 3H$_{maj}$, 3H$_{min}$, H-7$_{b, maj}$, H-3$_{maj}$, H-6$_{b, maj}$, H-7$_{b, min}$, H-6$_{a, min}$, H-6$_{b, min}$), 1.50 – 1.41 (m, 1H$_{maj}$, 1H$_{min}$, H-2$_{b, maj}$, H-2$_{b, min}$), 1.24 (s, 3H$_{min}$, H-8$_{min}$), 1.00 (s, 3H$_{maj}$, H-8$_{maj}$).

^{13}C NMR (151 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 159.0 (C-16), 147.8 (C-15), 144.9 (C-Ph), 142.5 (C-Ph), 135.7 (C-14), 132.2 (2C, C-12, C-11), 130.6 (2C, C-Ph), 130.5 (C-19), 129.3 (C-Ar), 128.7 (2C, C-Ph), 128.3 (2C, C-Ph), 128.0 (2C, C-Ph),

[63] dr determined by ^{1}H NMR of the crude reaction mixture.

127.3 (2C, C-18), 126.2 (C-Ar/C-Ph), 125.7 (2C, C-Ar/C-Ph), 125.6 (C-Ar/C-Ph), 124.7 (C-Ar/C-Ph), 114.1 (2C, C-17), 55.5 (C-13), 53.1 (C-10), 47.1 (C-4), 46.8 (C-3), 46.5 (C-5), 37.8 (C-7), 37.1 (C-9), 29.7 (C-1), 24.3 (C-6), 23.1 (C-8), 22.9 (C-2). **Selected peaks for the minor diastereomer** (from the mixture): 159.0 (C-Ar), 149.2 (C-15), 144.6 (C-Ph), 143.4 (C-Ph), 135.5 (C-14), 132.6 (C-12), 131.0 (C-19), 129.2 (C-Ar), 128.7 (C-Ph), 128.2 (C-Ph), 127.3 (C-18), 126.1 (2C, C-Ar/C-Ph), 125.8 (C-Ar/C-Ph), 125.6 (C-Ph/C-Ar), 125.5 (C-Ph/C-Ar), 124.5 (C-Ar/C-Ph), 114.1 (C-17), 56.4 (C-10), 47.4 (C-4), 46.4 (C-3), 45.2 (C-5), 38.8 (C-7), 37.4 (C-9), 29.8 (C-1), 26.1 (C-8), 24.7 (C-2), 23.7 (C-6).

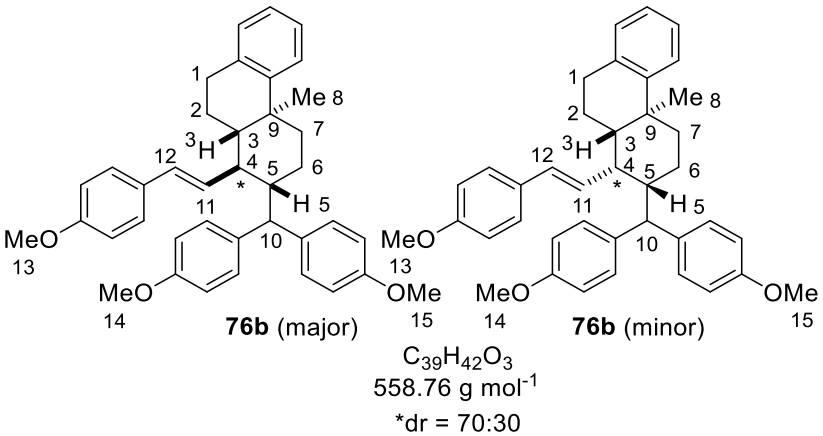
NOESY- 2D (600 MHz, $CDCl_3$): between H-4$_{maj}$ and Me$_{maj}$, between H-4$_{maj}$ and H-2$_{maj}$, between H-2$_{maj}$ and Me$_{maj}$, between H-5$_{maj}$ and H-11$_{maj}$, between H-4$_{maj}$ and H^{benz};

Between H-11$_{min}$ and Me$_{min}$, between H-4$_{min}$ and H-3$_{min}$, between H-3$_{min}$ and H-5$_{min}$.

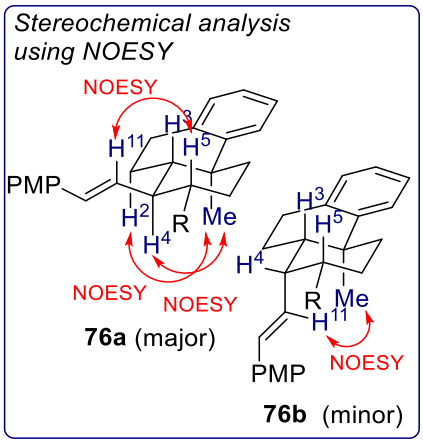
IR (film) ν_{max}: 3026, 2933, 2361, 1607, 1510, 1492, 1450, 1295, 1250, 1174, 1034, 970, 761, 737, 704 cm^{-1}.

HRMS (ESI): calculated for $C_{37}H_{39}O$ $[M+H]^+$ requires m/z 499.2995, found m/z 499.2992 (*Δ* = -0.70 ppm).

(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-(Bis(4-methoxyphenyl)methyl)-1-((*E*)-4-methoxystyryl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene (major)-76b and (±)-(1*S*,2*S*,4*aS*,10*aS*)-2-(Bis(4-methoxyphenyl)methyl)-1-((*E*)-4-methoxystyryl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren (minor)-76b.



$C_{39}H_{42}O_3$
558.76 g mol^{-1}
*dr = 70:30



Triene **60** (33.2 mg, 0.100 mmol, 1.00 equiv), bis(4-methoxyphenyl)methanol (24.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **D**. The crude product was purified by flash column

chromatography (SiO_2; pentane:Et_2O; 22:3) to furnish compound **76b** as an inseparable mixture of two diastereomers at the exocyclic allylic position as a colourless oil (52.0 mg, 93%, 70:30 dr).[64,65.]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, $3H_{maj}$, $3H_{min}$, H-Ar_{maj}, H-Ar_{min}), 7.25 – 7.04 (m, $7H_{maj}$, $7H_{min}$, H-Ar_{maj}, H-Ar_{min}), 6.98 – 6.79 (m, $6H_{maj}$, $6H_{min}$, H-Ar_{maj}, H-A_{rmin}), 6.33 – 6.22 (m, $1H_{maj}$, $1H_{min}$, H-12_{maj}, H-11_{min}), 5.83 – 5.70 (m, $1H_{maj}$, $1H_{min}$, H-11_{maj}, H-12_{min}), 4.33 (d, *J* = 3.9 Hz, $1H_{maj}$, H-10_{maj}), 3.89 – 3.83 (m, $6H_{maj}$, $3H_{min}$, H-14_{maj}, H-15_{maj}, H-14_{min}/H-15_{min}), 3.82 (s, $3H_{min}$, H-15_{min}/H-14_{min}), 3.79 – 3.75 (m, $3H_{maj}$, $3H_{min}$, H-13_{maj}, H-13_{min}), 3.58 (d, *J* = 11.7 Hz, $1H_{min}$, H-10_{min}), 2.99 – 2.79 (m, $2H_{maj}$, $2H_{min}$, H-1_{maj}, H-1_{min}), 2.46 – 2.32 (m, $1H_{maj}$, $3H_{min}$, H-$7_{a, maj}$, H-5_{min}, H-4_{min}, H-$7_{a, min}$), 2.26 – 2.18 (m, $1H_{maj}$, H-5_{maj}), 2.12 (q, *J* = 10.2 Hz, $1H_{maj}$, H-4_{maj}), 1.95 (ddt, *J* = 12.7, 6.2, 2.8 Hz, $1H_{maj}$, H-$2_{a, maj}$), 1.89 – 1.77 (m, $1H_{maj}$, $2H_{min}$, H-$6_{a, maj}$, H-3_{min}, H-$2_{a, min}$), 1.68 – 1.52 (m, $3H_{maj}$, $3H_{min}$, H-$6_{b, maj}$, H-$7_{b, maj}$, H-3_{maj}, H-$7_{b, min}$, H-$6_{a, min}$, H-$6_{b, min}$), 1.51 – 1.42 (m, $1H_{maj}$, $1H_{min}$, H-$2_{b, maj}$, H-$2_{b, min}$), 1.25 (s, $3H_{min}$, H-8_{min}), 1.02 (s, $3H_{maj}$, H-8_{maj}).

^{13}C NMR (101 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 158.9 (C-Ar), 157.9 (C-Ar), 157.5 (C-Ar), 147.8 (C-Ar), 137.2 (C-Ar), 135.7 (C-Ar), 134.8 (C-Ar), 132.4 (C-11), 132.0 (C-12), 131.4 (2C, C-Ar), 130.6 (C-Ar), 129.4 (2C, C-Ar), 129.3 (C-Ar), 127.2 (2C, C-Ar), 125.6 (C-Ar), 125.5 (C-Ar), 124.7 (C-Ar), 114.0 (2C, C-Ar), 113.6 (2C, C-Ar), 113.3 (2C, C-Ar), 55.5 (C-13/C-14/C-15), 55.3 (2C, C-13/C-14/C-15), 51.4 (C-10), 46.9 (C-4), 46.7 (2C, C-5, C-3), 37.8 (C-7), 37.1 (C-9), 29.7 (C-1), 24.0 (C-6), 23.1 (C-8), 22.9 (C-2). **Selected peaks for the minor diastereomer** (from the mixture): 158.9 (C-Ar), 157.8 (2C, C-Ar), 149.2 (C-Ar), 136.0 (C-Ar), 135.5 (C-Ar), 132.5 (C-12), 131.0 (C-Ar), 129.3 (C-Ar), 129.2 (C-Ar), 128.8 (C-Ar), 127.3 (C-Ar), 125.8 (2C, C-11, C-Ar), 125.4 (C-Ar), 124.5 (C-Ar), 114.1 (C-Ar), 114.0 (C-Ar), 113.6 (C-Ar), 54.5 (C-10), 47.4 (C-5/C-4), 46.4 (C-3), 45.6 (C-4/C-5), 38.8 (C-7), 37.4 (C-9), 29.8 (C-1), 26.0 (C-8), 24.7 (C-2), 23.7 (C-6).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4_{maj} and Me_{maj}, between H-5_{maj} and H-11_{maj}, between H-2_{maj} and Me_{maj}; Between H-11_{min} and Me_{min}.

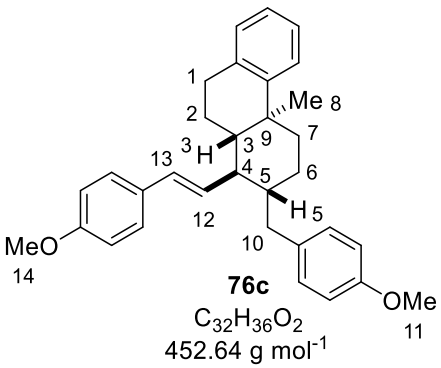
Note: the appearance of ^{1}H NMR signal for H-4_{maj}: 2.12 (q, *J* = 10.2 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4_{maj} and H-3_{maj}; H-4_{maj} and H-5_{maj}.

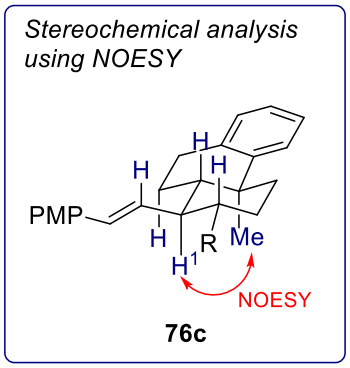
IR (film) ν_{max}: 2932, 2361, 2341, 1608, 1509, 1298, 1247, 1176, 1035, 835 cm^{-1}.

[64] dr determined by ^{1}H NMR of the crude reaction mixture.
[65] Relative stereochemistry of 7**6b** (minor) is assigned by analogy to **76a** (minor).

HRMS (ESI): calculated for $C_{39}H_{43}O_3$ $[M+H]^+$ requires m/z 559.3207, found m/z 559.3204 (Δ = -0.42 ppm).

(±)-(1*S*,2*R*,4*aS*,10*aS*)-2-(4-Methoxybenzyl)-1-((*E*)-4-methoxystyryl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 76c.





Triene **60** (33.2 mg, 0.100 mmol, 1.00 equiv), (4-methoxyphenyl)methanol (13.8 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **D**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 19:1) to furnish compound **76c** as a colourless oil (13.0 mg, 29%).[66]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 2H, H-Ar), 7.29 – 7.26 (m, 1H, H-Ar), 7.16 – 7.02 (m, 5H, H-Ar), 6.89 (d, *J* = 8.7 Hz, 2H, H-Ar), 6.81 (d, *J* = 8.6 Hz, 2H, H-Ar), 6.39 (d, *J* = 15.8 Hz, 1H, H-13), 5.80 (dd, *J* = 15.8, 9.4 Hz, 1H, H-12), 3.83 (s, 3H, H-14/H-11), 3.78 (s, 3H, H-11/H-14), 3.03 (dd, *J* = 13.6, 3.1 Hz, 1H, H-10$_a$), 2.91 – 2.74 (m, 2H, H-1), 2.31 – 2.22 (m, 1H, H-7$_a$), 2.15 (dd, *J* = 13.6, 9.6 Hz, 1H, H-10$_b$), 2.05 – 1.90 (m, 2H, H-4, H-2$_a$), 1.72 – 1.63 (m, 1H, H-6$_a$), 1.54 – 1.33 (m, 5H, H-2$_b$, H-7$_b$, H-5, H-3, H-6$_b$), 1.13 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 157.8 (C-Ar), 148.0 (C-Ar), 135.7 (C-Ar), 133.7 (C-Ar), 132.5 (C-12), 131.7 (C-13), 130.6 (C-Ar), 130.2 (2C, C-Ar), 129.3 (C-Ar), 127.3 (2C, C-Ar), 125.7 (C-Ar), 125.5 (C-Ar), 124.8 (C-Ar), 114.2 (2C, C-Ar), 113.6 (2C, C-Ar), 55.5 (C-14/C-11), 55.4 (C-11/C-14), 48.8 (C-4), 46.4 (C-3), 44.4 (C-5), 40.8 (C-10), 37.5 (C-7), 37.1 (C-9), 29.8 (C-1), 27.1 (C-6), 23.1 (C-2), 23.0 (C-8).

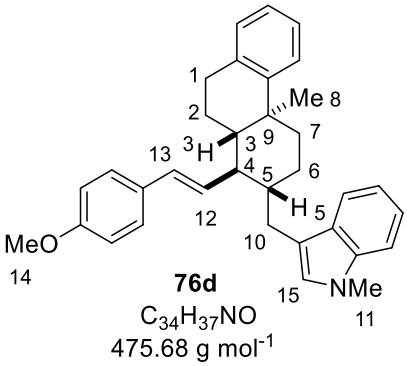
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

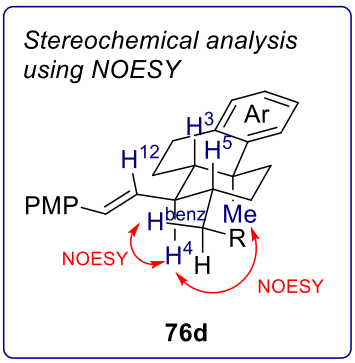
IR (film) ν_{max}: 2931, 2360, 1608, 1510, 1247, 1175, 1036, 969, 836, 761 cm^{-1}.

[66] Relative stereochemistry is assigned by analogy to compound **76d.**

HRMS (ESI): calculated for $C_{32}H_{37}O_2$ $[M+H]^+$ requires m/z 453.2788, found m/z 453.2787 (Δ = -0.13 ppm).

(±)-3-(((1*S*,2*R*,4a*S*,10a*S*)-1-((*E*)-4-Methoxystyryl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methyl)-1-methyl-1H-indole 76d.





Triene **60** (33.2 mg, 0.100 mmol, 1.00 equiv), (1-methyl-1H-indol-3-yl)methanol[67] (16.1 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **D**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 93:7) to furnish compound **76d** as a colourless oil (15.6 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 7.9, 1.1 Hz, 1H, H-Ar), 7.39 (d, *J* = 8.7 Hz, 2H, H-Ar), 7.30 – 7.25 (m, 2H, H-Ar), 7.21 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H, H-Ar), 7.15 – 7.01 (m, 4H, H-Ar), 6.91 (d, *J* = 8.7 Hz, 2H, H-Ar), 6.81 (s, 1H, H-15), 6.44 (d, *J* = 15.8 Hz, 1H, H-13), 5.89 (dd, *J* = 15.8, 9.4 Hz, 1H, H-12), 3.84 (s, 3H, H-14), 3.73 (s, 3H, H-11), 3.19 (dd, *J* = 14.2, 3.2 Hz, 1H, H-10$_a$), 2.93 – 2.74 (m, 2H, H-1), 2.38 (dd, *J* = 14.4, 9.8 Hz, 1H, H-10$_b$), 2.30 – 2.19 (m, 1H, H-7$_a$), 2.07 (q, *J* = 10.0 Hz, 1H, H-4), 2.02 – 1.92 (m, 1H, H-2$_a$), 1.90 – 1.80 (m, 1H, H-6$_a$), 1.63 – 1.35 (m, 5H, H-3, H-5, H-2$_b$, H-7$_b$, H-6$_b$), 1.16 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C-Ar), 148.1 (C-Ar), 137.1 (C-Ar), 135.8 (C-Ar), 132.7 (C-12), 131.5 (C-13), 130.7 (C-Ar), 129.3 (C-Ar), 128.5 (C-Ar), 127.3 (2C, C-Ar), 127.1 (C-15), 125.7 (C-Ar), 125.5 (C-Ar), 124.8 (C-Ar), 121.3 (C-Ar), 119.5 (C-Ar), 118.5 (C-Ar), 114.2 (2C, C-Ar), 114.1 (C-Ar), 109.2 (C-Ar), 55.5 (C-14), 49.0 (C-4), 46.4 (C-3), 43.5 (C-5), 37.6 (C-7), 37.1 (C-9), 32.7 (C-11), 30.7 (C-10), 29.9 (C-1), 27.9 (C-6), 23.1 (2C, C-2, C-8).

NOESY- 2D (600 MHz, CD_2Cl_2): between H-4 and Me, between H-1 and H^{benz}.

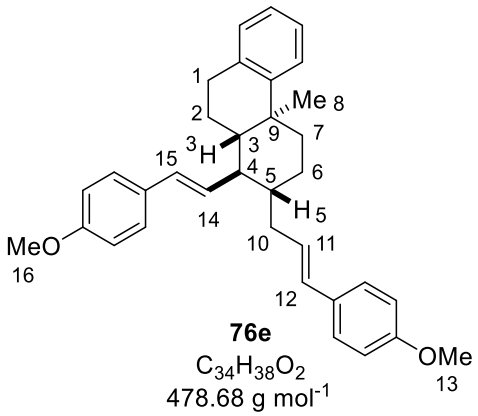
[67] M. A. J. Dubois, R. A. Croft, Y. Ding, C. Choi, D. R. Owen, J. A. Bulla, J. J. Mousseau, *RSC Med. Chem.* **2021**, *12*, 2045–2052.

Note: the appearance of ^{1}H NMR signal for H-4: 2.07 (q, *J* = 10.0 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5, H-4 and H-12.

IR (film) ν_{max}: 3054, 2931, 1607, 1510, 1468, 1249, 1175, 1035, 970, 835, 761, 739 cm^{-1}.

HRMS (ESI): calculated for $C_{34}H_{38}ON$ $[M+H]^+$ requires m/z 476.2948, found m/z 476.2945 (*Δ* = -0.62 ppm).

(±)-(1*S*,2*R*,4*aS*,10*aS*)-2-((*E*)-3-(4-Methoxyphenyl)allyl)-1-((*E*)-4-methoxystyryl)-4$_a$-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 76e.



76e
$C_{34}H_{38}O_2$
478.68 g mol^{-1}

Triene **60** (33.2 mg, 0.100 mmol, 1.00 equiv), (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (16.4 mg, 0.100 mmol, 1.00 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **D** except the reaction was performed overnight and without Ti(O*i*-Pr)$_4$. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 μm; pentane:Et_2O; 23:2) to furnish compound **76e** as a colourless oil (12.7 mg, 27%).[68]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H, H-Ar), 7.17 – 7.02 (m, 3H, H-Ar), 6.91 – 6.81 (m, 4H, H-Ar), 6.39 – 6.26 (m, 2H, H-15, H-12), 6.09 (ddd, *J* = 15.3, 8.1, 6.3 Hz, 1H, H-11), 5.74 (dd, *J* = 15.8, 9.4 Hz, 1H, H-14), 3.83 (s, 3H, H-16/H-13), 3.81 (s, 3H, H-13/H-16), 2.90 – 2.74 (m, 2H, H-1), 2.54 – 2.43 (m, 1H, H-10$_a$), 2.39 – 2.27 (m, 1H, H-7$_a$), 2.09 – 1.79 (m, 4H, H-2$_a$, H-4, H-6$_a$, H-10$_b$), 1.54 – 1.33 (m, 5H, H-3, H-7$_b$, H-6$_b$, H-2$_b$, H-5), 1.14 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C-Ar), 158.8 (C-Ar), 148.0 (C-Ar), 135.8 (C-Ar), 132.3 (C-14), 131.4 (C-15), 131.0 (C-Ar), 130.7 (C-12), 130.6 (C-Ar), 129.3 (C-Ar), 127.2 (3C, C-Ar, C-11), 127.1 (2C, C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.9 (C-Ar), 114.1 (4C, C-Ar), 55.5 (C-

[68] Relative stereochemistry is assigned by analogy to compound **76d.**

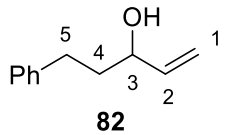
16/C-13), 55.4 (C-13/C-16), 48.1 (C-4), 46.3 (C-3), 42.6 (C-5), 38.4 (C-10), 37.6 (C-7), 37.1 (C-9), 29.8 (C-1), 27.4 (C-6), 23.0 (2C, C-2, C-8).

IR (film) ν_{max}: 2931, 1607, 1510, 1294, 1248, 1175, 1036, 967, 909, 761, 730 cm^{-1}.

HRMS (ESI): calculated for $C_{34}H_{39}O_2$ $[M+H]^+$ requires m/z 479.2945, found m/z 479.2944 (Δ = -0.12 ppm).

Synthesis and the polyene cyclisation of substrates 86 and 87

5-Phenylpent-1-en-3-ol 82.



82

$C_{11}H_{14}O$

162.23 g mol^{-1}

3-Phenylpropanal (1.33 mL, 10.1 mmol, 1.00 equiv) in Et_2O (10 mL) was added dropwise to a cooled to -78 °C solution of vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv). The reaction mixture was stirred at the same temperature for 3 h and then at rt for 0.5 h. The solution was quenched with aq. sat. NH_4Cl (5 mL) and diluted with water (15 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish allylic alcohol **82** as a pale yellow oil (0.882 g, 54%).

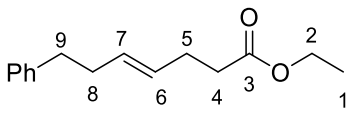
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 2H, H-Ph), 7.24 – 7.15 (m, 3H, H-Ph), 5.91 (ddd, *J* = 16.8, 10.4, 6.2 Hz, 1H, H-2), 5.25 (dt, *J* = 17.2, 1.4 Hz, 1H, H-1_a), 5.14 (dt, *J* = 10.4, 1.4 Hz, 1H, H-1_b), 4.19 – 4.08 (m, 1H, H-3), 2.84 – 2.63 (m, 2H, H-5), 1.94 – 1.77 (m, 2H, H-4). The OH was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.0 (C-Ph), 141.1 (C-2), 128.6 (4C, C-Ph), 126.0 (C-Ph), 115.1 (C-1), 72.6 (C-3), 38.7 (C-4), 31.8 (C-5).

The analytical data are consistent with those previously reported in the literature.[69]

[69] M. Lafrance, M. Roggen, E. M. Carreira, *Angew. Chem. Int. Ed*. **2012***, 51,* 3470–3473.

Ethyl (*E*)-7-phenylhept-4-enoate 84.



84

$C_{15}H_{20}O_2$

232.32 g mol^{-1}

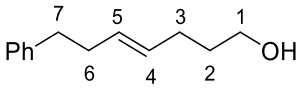
A solution of the allylic alcohol **82** (0.882 g, 5.44 mmol, 1.00 equiv) and propionic acid (31 µL, 0.41 mmol, 0.076 equiv) in triethyl orthoacetate (13 mL) was heated with stirring at 145 °C for 24 h. The solution was cooled to room temperature, poured into water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed successively with aq. HCl (1 M, 2 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 19:1) to furnish ester **84** as a colourless oil (1.05 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 2H, H-Ph), 7.22 – 7.13 (m, 3H, H-Ph), 5.59 – 5.36 (m, 2H, H-6, H-7), 4.13 (q, *J* = 7.1 Hz, 2H, H-2), 2.70 – 2.61 (m, 2H, H-9/H-4), 2.40 – 2.25 (m, 6H, H-8, H-5, H-4/H-9), 1.25 (t, *J* = 7.2 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C-3), 142.1 (C-Ph), 130.9 (C-6/C-7), 128.9 (C-7/C-6), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.9 (C-Ph), 60.4 (C-2), 36.1 (C-9/C-4), 34.5 (2C, C-4/C-9, C-8), 28.0 (C-5), 14.4 (C-1).

The analytical data are consistent with those previously reported in the literature.[70]

(*E*)-4-Methyl-7-phenylhept-4-en-1-ol 85.



85

$C_{13}H_{18}O$

190.29 g mol^{-1}

Ester **84** (0.500 g, 2.15 mmol, 1.00 equiv) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (81.6 mg, 2.15 mmol, 1.00 equiv) in THF (10 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 3 h followed by the subsequent addition of water (82 µL), 15% aq. NaOH (82 µL) and water (0.25 mL). The obtained suspension was stirred at rt for 30 min, transferred to a separatory funnel, diluted with an additional amount of water (15 mL) and

[70] C. U. Grunanger, B. Breit, *Angew. Chem. Int. Ed.* **2010***, 49,* 967–970.

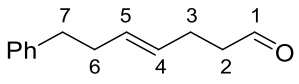
extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 1:1) to furnish alcohol **85** as a colourless oil (0.361 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H, H-Ph), 7.22 – 7.12 (m, 3H, H-Ph), 5.59 – 5.35 (m, 2H, H-4, H-5), 3.61 (t, *J* = 6.5 Hz, 2H, H-1), 2.70 – 2.62 (m, 2H, H-7), 2.37 – 2.24 (m, 2H, H-6), 2.12 – 2.01 (m, 2H, H-3), 1.66 – 1.56 (m, 2H, H-2). The OH was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.2 (C-Ph), 130.4 (C-5/C-4), 130.3 (C-4/C-5), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.9 (C-Ph), 62.7 (C-1), 36.2 (C-7), 34.5 (C-6), 32.5 (C-2), 29.0 (C-3).

The analytical data are consistent with those previously reported in the literature.[73]

(*E*)-7-Phenylhept-4-enal 81.



81

$C_{13}H_{16}O$

188.27 g mol^{-1}

Alcohol **85** (1.58 g, 8.30 mmol, 1.00 equiv) was dissolved in a mixture of CH_2Cl_2 (16 mL), DMSO (16 mL) and Et_3N (5.7 mL) at 0 °C. To the obtained solution $SO_3 \cdot$ py complex (3.77 g, 23.7 mmol, 2.86 equiv) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 2.5 h and then diluted with water (20 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 22:3) to furnish aldehyde **81** as a colourless oil (1.26 g, 81%).

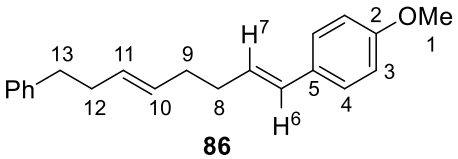
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.7 Hz, 1H, H-1), 7.31 – 7.23 (m, 2H, H-Ph), 7.21 – 7.12 (m, 3H, H-Ph), 5.58 – 5.36 (m, 2H, H-4, H-5), 2.66 (dd, *J* = 8.8, 6.6 Hz, 2H, H-7), 2.51 – 2.42 (m, 2H, H-2), 2.37 – 2.25 (m, 4H, H-3, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5 (C-1), 142.0 (C-Ph), 131.1 (C-5/C-4), 128.7 (C-4/C-5), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 125.9 (C-Ph), 43.6 (C-2), 36.0 (C-7), 34.4 (C-3/C-6), 25.3 (C-6/C-3).

IR (film) ν_{max}: 2922, 1725, 1496, 1454, 1276, 970, 749, 700 cm^{-1}.

HRMS (APCI): calculated for $C_{13}H_{17}O$ $[M+H]^+$ requires m/z 189.1274, found m/z 189.1274 (Δ= -0.18 ppm).

1-Methoxy-4-((1*E*,5E)-8-phenylocta-1,5-dien-1-yl)benzene 86.



86

$C_{21}H_{24}O$

292.42 g mol^{-1}

$^3J_{H\text{-}10,\ H\text{-}11}$ = 15.8 Hz

Tributyl(4-methoxybenzyl)phosphonium chloride **40** (0.400 g, 1.11 mmol, 1.50 equiv) was suspended in THF (16 mL) and cooled to 0 °C. *n*-BuLi (0.44 mL, 2.5 M in hexanes, 1.1 mmol, 1.5 equiv) was then added dropwise and the obtained suspension was allowed to stir at 0 °C for 30 min. After that the mixture was cooled to -78 °C and aldehyde **81** (0.14 g, 0.74 mmol, 1.0 equiv) in THF (1.4 mL) was added dropwise at the same temperature. The reaction mixture was allowed to warm to rt overnight and then quenched with sat. aq. NH_4Cl (5 mL). The mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 49:1) to furnish diene **86** as a white solid (0.126 g, 58%, >95:5 *E*:*Z*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 4H, H-4, H-Ph), 7.21 – 7.14 (m, 3H, H-Ph), 6.84 (d, *J* = 8.7 Hz, 2H, H-3), 6.32 (d, *J* = 15.8 Hz, 1H, H-6), 6.06 (dt, *J* = 15.8, 6.7 Hz, 1H, H-7), 5.55 – 5.43 (m, 2H, H-11, H-10), 3.80 (s, 3H, H-1), 2.67 (dd, *J* = 8.9, 6.6 Hz, 2H, H-13), 2.36 – 2.28 (m, 2H, H-12), 2.27 – 2.19 (m, 2H, H-8), 2.18 – 2.10 (m, 2H, H-9).

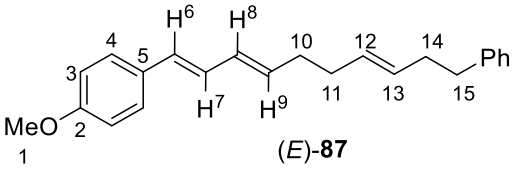
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-2), 142.3 (C-Ph), 130.8 (C-5), 130.4 (C-11/C-10), 130.1 (C-10/C-11), 129.5 (C-6), 128.6 (2C, C-Ph), 128.4 (3C, C-7, C-Ph/C-4), 127.1 (2C, C-4/C-Ph), 125.8 (C-Ph), 114.0 (2C, C-3), 55.4 (C-1), 36.2 (C-13), 34.6 (C-12), 33.2 (C-8), 32.7 (C-9).

IR (film) ν_{max}: 2915, 2360, 1608, 1511, 1454, 1248, 1175, 1036, 966, 909, 747, 699 cm^{-1}.

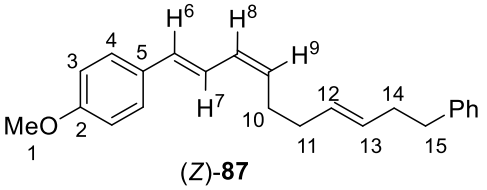
M.p. 45-47 °C.

HRMS (ESI): calculated for $C_{21}H_{25}O$ $[M+H]^+$ requires m/z 293.1900, found m/z 293.1900 (Δ = 0.03 ppm).

1-Methoxy-4-((1*E*,3*E*,7*E*)-10-phenyldeca-1,3,7-trien-1-yl)benzene (*E*)-87 and 1-Methoxy-4-((1*E*,3*Z*,7*E*)-10-phenyldeca-1,3,7-trien-1-yl)benzene (*Z*)-87.



(*E*)-**87**
$C_{23}H_{26}O$
318.46 g mol^{-1}
$^{3}J_{\text{H-6, H-7}}$ = 15.6 Hz
$^{3}J_{\text{H-8, H-9}}$ = 15.0 Hz



(*Z*)-**87**
$C_{23}H_{26}O$
318.46 g mol^{-1}
$^{3}J_{\text{H-6, H-7}}$ = 15.5 Hz

(*E*)-(3-(4-Methoxyphenyl)allyl)triphenylphosphonium bromide **71** (0.778 g, 1.59 mmol, 1.50 equiv) was suspended in THF (7.4 mL) and cooled to -78 °C. *n*-BuLi (0.64 mL, 2.5 M in hexanes, 1.6 mmol, 1.5 equiv) was added dropwise and the obtained suspension was allowed to stir at the same temperature for 30 min. Aldehyde **81** (0.200 g, 1.06 mmol, 1.00 equiv) in THF (3.8 mL) was added dropwise at -78 °C and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 24:1) to furnish an inseparable mixture of alkenes (*E*)-**87** and (*Z*)-**87** as a colourless waxy solid (0.211 g, 63%, 60:40 *E*:*Z*).

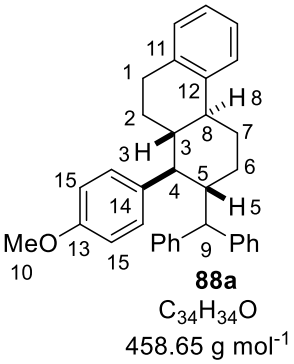
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.14 (m, 7H$_{maj}$, 7H$_{min}$, H-Ph$_{maj}$, H-4$_{maj}$, H-Ph$_{min}$, H-4$_{min}$), 6.97 – 6.82 (m, 2H$_{maj}$, 3H$_{min}$, H-3$_{maj}$, H-3$_{min}$, H-7$_{min}$), 6.63 (dd, *J* = 15.6, 10.3 Hz, 1H$_{maj}$, H-7$_{maj}$), 6.49 (d, *J* = 15.5 Hz, 1H$_{min}$, H-6$_{min}$), 6.40 (d, *J* = 15.6 Hz, 1H$_{maj}$, H-6$_{maj}$), 6.24 – 6.11 (m, 1H$_{maj}$, 1H$_{min}$, H-8$_{maj}$, H-8$_{min}$), 5.75 (dt, *J* = 15.0, 6.7 Hz, 1H$_{maj}$, H-9$_{maj}$), 5.59 – 5.37 (m, 2H$_{maj}$, 3H$_{min}$, H-12$_{maj}$, H-13$_{maj}$, H-12$_{min}$, H-13$_{min}$, H-9$_{min}$), 3.87 – 3.76 (m, 3H$_{maj}$, 3H$_{min}$, H-1$_{maj}$, H-1$_{min}$), 2.73 – 2.63 (m, 2H$_{maj}$, 2H$_{min}$, H-15$_{maj}$, H-15$_{min}$), 2.39 – 2.27 (m, 2H$_{maj}$, 4H$_{min}$, H-14$_{maj}$, H-14$_{min}$, H-11$_{min}$), 2.23 – 2.07 (m, 4H$_{maj}$, 2H$_{min}$, H-10$_{maj}$, H-11$_{maj}$, H-10$_{min}$).

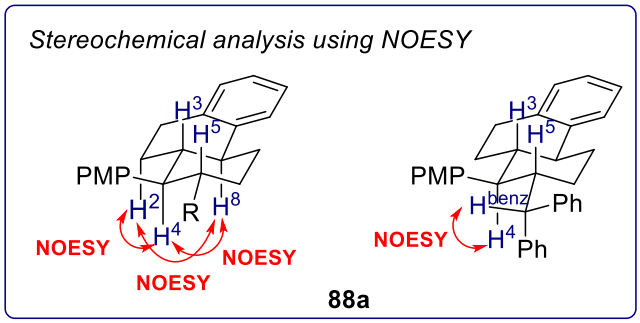
^{13}C NMR (101 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 159.1 (C-2), 142.2 (C-Ph), 134.0 (C-9), 131.1 (C-8), 130.6 (C-5), 130.3 (C-12/C-13), 130.2 (C-13/C-12), 129.8 (C-6), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 127.7 (C-7), 127.4 (2C, C-4), 125.8 (C-Ph), 114.2 (2C, C-3), 55.4 (C-1), 36.2 (C-15), 34.5 (C-14), 33.0 (C-10), 32.6 (C-11). **Selected peaks for the minor diastereomer** (from the mixture): δ 159.3 (C-2), 131.8 (C-6), 131.4 (C-9), 130.3 (C-13/C-12), 129.2 (C-8), 127.6 (C-4), 122.7 (C-7), 114.2 (C-3), 36.2 (C-15), 34.6 (C-14/C-11), 32.8 (C-10).

IR (film) ν_{max}: 2932, 2361, 2341, 1604, 1510, 1251, 1175, 1034, 986, 909, 732, 699 cm^{-1}.

HRMS calculated for $C_{23}H_{27}O$ $[M+H]^+$ requires m/z 319.2056, found m/z 319.2056 (Δ = -0.14 ppm).

(±)-(1*S*,2*S*,4*aS*,10*aR*)-2-Benzhydryl-1-(4-methoxyphenyl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 88a.





Diene **86** (29.2 mg, 0.100 mmol, 1.00 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 24:1) to furnish compound **88a** as a colourless foam (24.6 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.20 (m, 7H, H-Ar, H-Ph), 7.17 – 7.06 (m, 8H, H-Ar, H-Ph), 7.02 (dd, *J* = 7.2, 1.6 Hz, 1H, H-Ar/H-Ph), 6.94 – 6.86 (m, 2H, H-15), 3.99 (d, *J* = 2.9 Hz, 1H, H-9), 3.84 (s, 3H, H-10), 2.72 – 2.53 (m, 4H, H-1, H-5, H-7$_a$), 2.44 – 2.33 (m, 1H, H-8), 2.27 – 2.13 (m, 2H, H-6$_a$, H-4), 1.60 – 1.41 (m, 4H, H-7$_b$, H-3, H-6$_b$, H-2$_a$), 1.30 – 1.15 (m, 1H, H-2$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1 (C-13), 144.8 (C-Ph), 141.7 (C-Ph), 140.4 (C-12), 137.1 (C-11), 135.9 (C-14), 131.2 (2C, C-Ph), 129.0 (C-Ar), 128.4 (2C, C-Ph), 128.1 (2C, C-Ph), 127.8 (2C, C-Ph), 126.3 (C-Ph/C-Ar), 125.7 (3C, C-Ph, C-Ar), 125.6 (C-Ar/C-Ph), 114.0 (2C, C-15), 55.4 (C-10), 53.2 (C-4), 51.6 (C-9), 47.6 (C-3), 46.7 (C-5), 43.6 (C-8), 31.0 (C-7), 30.2 (C-1), 28.8 (C-6), 27.8 (C-2).[71]

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and H-2; between H-4 and H-8; between H-8 and H-2; between H-4 and H^{benz}.

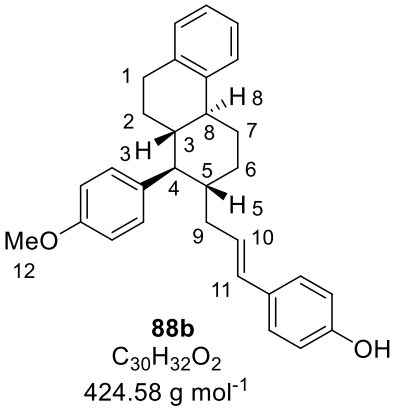
IR (film) ν_{max}: 2934, 1610, 1511, 1494, 1450, 1246, 1177, 1035, 909, 826, 732, 702 cm^{-1}.

[71] Two PMP carbons are missing due to coalescence in the ^{13}C NMR spectrum.

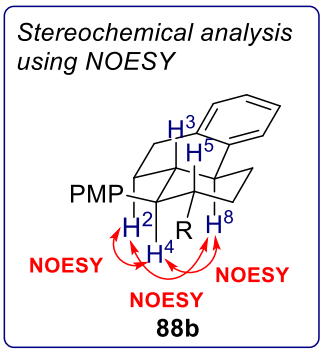
M.p: 136-139 °C.

HRMS (ESI): calculated for $C_{34}H_{34}ONa$ $[M+Na]^+$ requires m/z 481.2502, found m/z 481.2503 (Δ = 0.18 ppm).

(±)-4-((*E*)-3-((1*R*,2*R*,4a*S*,10a*R*)-1-(4-Methoxyphenyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)prop-1-en-1-yl)phenol 88b.



88b
$C_{30}H_{32}O_2$
424.58 g mol^{-1}



Diene **86** (29.2 mg, 0.100 mmol, 1.00 equiv), (*E*)-4-(3-hydroxyprop-1-en-1-yl)phenol[72] (15 mg, 0.10 mmol, 1.0 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 3:2) to furnish compound **88b** as a colourless oil (16.5 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.7 Hz, 1H, H-Ar), 7.22 – 7.01 (m, 7H, H-Ar), 6.96 – 6.82 (m, 2H, H-Ar), 6.79 – 6.72 (m, 2H, H-Ar), 6.14 (d, *J* = 15.7 Hz, 1H, H-11), 5.94 (ddd, *J* = 15.7, 7.9, 6.4 Hz, 1H, H-10), 4.75 (br, 1H, OH), 3.83 (s, 3H, H-12), 2.76 – 2.64 (m, 2H, H-1), 2.63 – 2.54 (m, 1H, H-7$_a$), 2.54 – 2.43 (m, 1H, H-8), 2.22 – 1.98 (m, 3H, H-6$_a$, H-4, H-9$_a$), 1.84 – 1.67 (m, 2H, H-9$_b$, H-5), 1.60 – 1.33 (m, 4H, H-2$_a$, H-3, H-7$_b$, H-6$_b$), 1.32 – 1.18 (m, 1H, H-2$_b$).

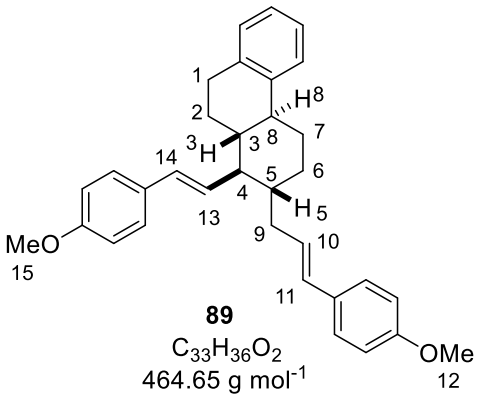
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (C-Ar), 154.6 (C-Ar), 140.5 (C-Ar), 137.2 (C-Ar), 136.4 (C-Ar), 131.1 (C-Ar), 130.5 (C-11), 129.0 (C-Ar), 127.3 (2C, C-Ar), 127.1 (C-10), 125.7 (3C, C-Ar), 115.5 (2C, C-Ar), 55.4 (C-12), 55.2 (C-4), 46.2 (C-3), 43.8 (C-3/C-5), 43.7 (C-5/C-3), 38.1 (C-9), 32.4 (C-6), 30.8 (C-7), 30.2 (C-1), 27.8 (C-2).[73]

[72] C. Han, Z. Huang, C. Zheng, L. Wan, Y. Lai, S. Peng, K. Ding, H. Ji, Y. Zhang, *Eur. J. Med. Chem*. **2013**, *66*, 82–90.
[73] Four PMP carbons are missing due to the coalescence in the ^{13}C NMR spectrum.

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and H-8; between H-2 and H-4; between H-2 and H-8.

HRMS (ESI): calculated for $C_{30}H_{33}O_2$ $[M+H]^+$ requires m/z 425.2475, found m/z 425.2475 (Δ = -0.09 ppm).

(±)-(1*S*,2*R*,4*aS*,10*aS*)-2-((*E*)-3-(4-Methoxyphenyl)allyl)-1-((*E*)-4-methoxystyryl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 89.



Triene **87** (31.8 mg, 0.100 mmol, 1.00 equiv), (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (16.4 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (3.0 µL, 10 µmol, 0.10 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **D** except the reaction was performed using 10 mol% (0.10 equiv) of Ti(O*i*-Pr)$_4$. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 23:2) to furnish compound **89** as a colourless oil (9.5 mg, 20%).[74]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H, H-Ar), 7.19 – 7.02 (m, 3H, H-Ar), 6.92 – 6.77 (m, 4H, H-Ar), 6.40 – 6.25 (m, 2H, H-14, H-11), 6.08 (ddd, *J* = 15.4, 8.2, 6.5 Hz, 1H, H-10), 5.80 (dd, *J* = 15.8, 9.6 Hz, 1H, H-15), 3.82 (s, 3H, H-15/H-12), 3.80 (s, 3H, H-12/H-15), 2.89 – 2.70 (m, 2H, H-1), 2.61 – 2.35 (m, 3H, H-7$_a$, H-8, H-9$_a$), 2.15 – 1.95 (m, 3H, H-6$_a$, H-2$_a$, H-9$_b$), 1.79 (q, *J* = 9.7 Hz, 1H, H-4), 1.51 – 1.41 (m, 1H, H-5), 1.38 – 1.22 (m, 4H, H-7$_b$, H-6$_b$, H-2$_b$, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 158.8 (C-Ar), 140.5 (C-Ar), 137.3 (C-Ar), 131.8 (C-13), 131.5 (C-14), 130.9 (C-Ar), 130.8 (C-11), 130.6 (C-Ar), 129.1 (C-Ar), 127.3 (2C, C-Ar), 127.2 (C-10), 127.1 (2C, C-Ar), 125.8 (C-Ar), 125.7 (2C, C-Ar), 114.1 (4C, C-Ar), 55.5

[74] Relative stereochemistry is assigned by analogy to compound **76d.**

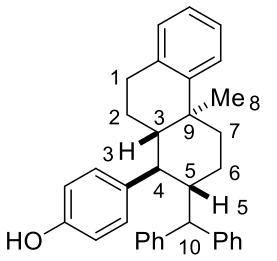
(2C, C-12, C-15), 53.4 (C-4), 44.5 (C-3), 43.2 (C-8), 42.3 (C-5), 38.4 (C-9), 31.8 (C-6), 30.8 (C-7), 30.3 (C-1), 28.0 (C-2).

IR (film) ν_{max}: 2913, 2836, 2360, 1608, 1464, 1248, 1175, 1036, 967, 909, 734 cm^{-1}.

HRMS (ESI): calculated for $C_{33}H_{37}O_2$ $[M+H]^+$ requires m/z 465.2788, found m/z 465.2785 (Δ = -0.59 ppm).

Derivatisations

(±)-4-((1*R*,2*S*,4*aS*,10*aS*)-2-benzhydryl-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-1-yl)phenol 94.



94
$C_{34}H_{34}O$
458.65 g mol^{-1}

Carbocycle **27a** (19.4 mg, 41.4 µmol, 1.00 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled to -78 °C. BBr_3 (1.0 M in CH_2Cl_2, 62 µL, 62 µmol, 1.5 equiv) was added dropwise and the obtained solution was stirred at the same temperature for 1 h 45 min. The solution was then slowly warmed to rt over 4 h. Then, the reaction mixture was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$ (1 mL). The mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (15 mL) and brine (15 mL). The organic phase was dried over Na_2SO_4 and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane:Et2O; 7:3) to furnish phenol **94** as a pale yellow oil (10.9 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 6.66 (m, 18H, H-Ar, H-Ph), 4.66 (s, 1H, OH), 3.93 (d, *J* = 3.2 Hz, 1H, H-10), 2.78 – 2.48 (m, 3H, H-1, H-5), 2.42 – 2.31 (m, 2H, H-4, H-7_a), 1.97 – 1.86 (m, 1H, H-6_a), 1.76 – 1.57 (m, 3H, H-3, H-6_a, H-7_b), 1.39 – 1.25 (m, 1H, H-2_a), 1.17 (ddt, *J* = 13.2, 7.8, 2.5 Hz, 1H, H-2_b), 1.00 (s, 3H, H-8).

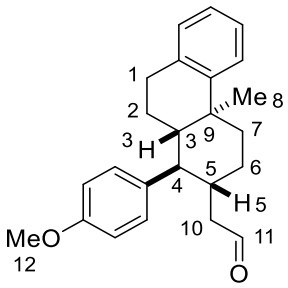
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (C-Ar), 147.8 (C-Ar), 144.6 (C-Ar), 141.7 (C-Ar), 136.3 (C-Ar), 135.6 (C-Ar), 133.5 (C-Ar), 131.0 (2C, C-Ar), 129.3 (C-Ar), 128.4 (2C, C-Ar), 128.1 (2C, C-Ar), 127.9 (2C, C-Ar), 126.4 (C-Ar), 126.3 (C-Ar), 125.7 (2C, C-Ar), 125.6 (C-Ar), 124.6

(C-Ar), 116.5 (C-Ar), 114.4 (C-Ar), 51.9 (C-10), 49.1 (C-3), 48.0 (C-4), 47.5 (C-5), 37.9 (C-7), 37.6 (C-9), 29.6 (C-1), 24.0 (C-6), 22.9 (C-8), 22.7 (C-2).

IR (film) ν_{max}: 3446, 2917, 1612, 1513, 1494, 1449, 1249, 1174, 910, 830, 734, 704 cm^{-1}.

HRMS (ESI): calculated for $C_{34}H_{33}O$ $[M-H]^-$ requires m/z 457.2537, found m/z 457.2550 (Δ = 2.88 ppm).

(±)-2-((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4a-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)acetaldehyde 99.



99
$C_{24}H_{28}O_2$
348.49 g mol^{-1}

Alkene **27h** (27.6 mg, 61.0 µmol, 1.00 equiv) was dissolved in CH_2Cl_2 (20 mL) and the obtained solution was cooled to -78 °C. O_3/O_2 was bubbled through the solution for 5 min until blue colour was observed and then left to bubble through the solution for an additional 2 min. O_2 was bubbled until the blue colour disappeared and then N_2 for the additional 10 min. The reaction mixture was quenched with DMS (1.8 mL) at -78 °C, left stirring at the same temperature for 30 min, warmed to rt and stirred for 4 h. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 21:4) to afford aldehyde **99** as a colurless oil (7.5 mg, 35%).

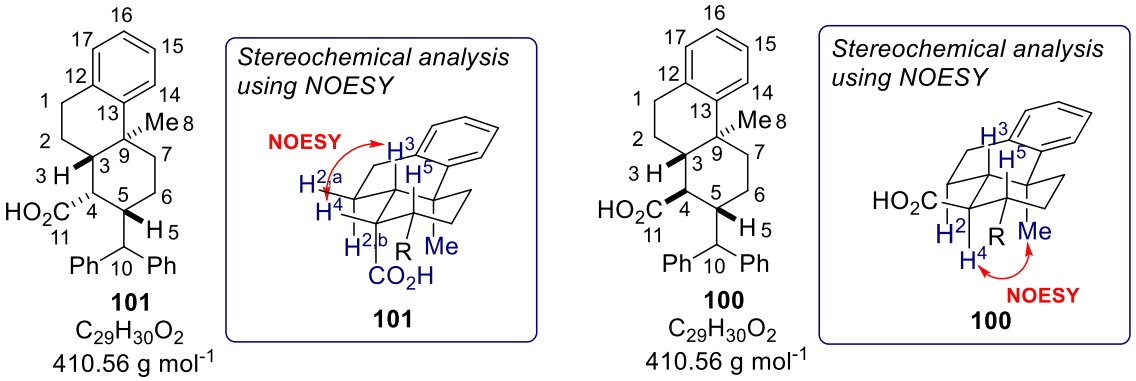
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (dd, *J* = 2.5, 1.6 Hz, 1H, H-11), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H, H-Ar), 7.19 – 6.96 (m, 5H, H-Ar), 6.91 (dd, *J* = 8.5, 2.8 Hz, 1H, H-Ar), 6.80 (dd, *J* = 8.3, 2.8 Hz, 1H, H-Ar), 3.81 (s, 3H, H-12), 2.80 – 2.63 (m, 2H, H-1), 2.42 – 2.28 (m, 2H, H-4, H-7_a), 2.28 – 2.20 (m, 1H, H-10_a), 2.18 – 2.06 (m, 2H, H-5, H-10_b), 1.95 – 1.87 (m, 1H, H-6_a), 1.79 (ddd, *J* = 12.5, 11.3, 3.0 Hz, 1H, H-3), 1.74 – 1.60 (m, 2H, H-6_b, H-7_b), 1.47 – 1.32 (m, 1H, H-2_a), 1.20 (m, 4H, H-2_b, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (C-11), 158.4 (C-Ar), 147.7 (C-Ar), 135.6 (C-Ar), 135.4 (C-Ar), 132.3 (C-Ar), 129.4 (C-Ar), 126.1 (C-Ar), 125.8 (C-Ar), 125.7 (C-Ar), 124.7 (C-Ar), 115.4 (C-Ar), 113.1 (C-Ar), 55.4 (C-12), 49.7 (C-4), 49.5 (C-10), 47.5 (C-3), 39.6 (C-5), 37.5 (C-7), 37.4 (C-9), 29.5 (C-1), 28.8 (C-6), 22.7 (C-8), 22.6 (C-2).

IR (film) ν_{max}: 2935, 2359, 1721, 1611, 1512, 1247, 1178, 1036, 830, 762 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{29}O_2$ $[M+H]^+$ requires m/z 349.2162, found m/z 349.2162 (Δ = -0.03 ppm).

(±)-(1*S*,2*R*,4*aS*,10*aS*)-2-benzhydryl-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-1-carboxylic acid 101 and (±)-(1*R*,2*R*,4*aS*,10*aS*)-2-benzhydryl-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-1-carboxylic acid 100.



Alkene **76a** (33.2 mg, 66.6 µmol, 1.00 equiv) was dissolved in CH_2Cl_2 (25 mL) and the obtained solution was cooled to -78 °C. O_3/O_2 was bubbled through the solution for 5 min until blue color was observed and then left to bubble through the solution for an additional 2 min. O_2 was bubbled until the blue color disappeared and then N_2 for an additional 10 min. The reaction mixture was quenched with DMS (2.0 mL) at -78 °C, left stirring at the same temperature for 30 min, warmed to rt and stirred for 4 h. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 9:1 to Et_2O) to afford carboxylic acid **101** as a pale yellow oil (4.2 mg, 15%) and carboxylic acid **100** as a pale yellow oil (3.9 mg, 14%)

(±)-(1*S*)-carboxylic acid 101:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.6 Hz, 2H, H-Ph), 7.28 – 7.21 (m, 7H, H-Ph, H-14), 7.17 – 7.12 (m, 2H, H-Ph), 7.12 – 7.09 (m, 1H, H-15), 7.08 – 7.04 (m, 1H, H-16), 7.02 (dd, *J* = 7.6, 1.5 Hz, 1H, H-17), 4.38 (d, *J* = 11.6 Hz, 1H, H-10), 2.92 – 2.81 (m, 2H, H-1), 2.49 – 2.45 (m, 1H, H-4), 2.37 (tt, *J* = 12.0, 3.7 Hz, 1H, H-5), 2.31 (dt, *J* = 13.1, 3.4 Hz, 1H, H-7_a), 2.20 (qd, *J* = 13.6, 3.8 Hz, 1H, H-6_a), 2.07 – 1.99 (m, 1H, H-2_a), 1.96 (ddd, *J* = 12.8, 5.3, 1.7 Hz, 1H, H-3), 1.82 – 1.76 (m, 1H, H-2_b), 1.57 – 1.51 (m, 1H, H-6_b), 1.46 (td, *J* = 13.3, 4.1 Hz, 1H, H-7_b), 1.18 (s, 3H, H-8). The carboxylic acid H was not found.

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.9 (C-11), 148.4 (C-13), 144.4 (C-Ph), 143.6 (C-Ph), 135.0 (C-12), 129.2 (C-17), 128.8 (2C, C-Ph), 128.7 (2C, C-Ph), 128.2 (2C, C-Ph), 128.2 (2C, C-Ph), 126.5 (C-Ph), 126.3 (C-Ph), 125.9 (C-15), 125.6 (C-16), 125.2 (C-14), 54.5 (C-10), 46.4 (C-3), 45.5 (C-4), 44.8 (C-5), 39.3 (C-7), 38.0 (C-9), 30.8 (C-1), 25.2 (C-2), 23.4 (C-6), 23.3 (C-8).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and H-3.

Note: the appearance of ^{1}H NMR signal for H-3: 1.96 (ddd, *J* = 12.8, 5.3, 1.7 Hz, 1H, H-3) is indicative of a *trans*-diaxial arrangement between H-3 and H-2^b and axial/equatorial arrangement between H-3 and H-2^a; H-3 and H-4.

IR (film) ν_{max}: 3400, 2918, 2360, 1710, 1490, 1450, 1192, 1047, 1025, 1002, 760, 706 cm^{-1}.

HRMS (ESI): calculated for $C_{29}H_{29}O_2$ $[M-H]^-$ requires m/z 409.2173, found m/z 409.2182 (*Δ* = 2.20 ppm).

(±)-(1*R*)-carboxylic acid 100:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.02 (m, 14H, H-Ph, H-Ar), 3.99 (d, *J* = 5.7 Hz, 1H, H-10), 2.92 – 2.84 (m, 2H, H-1), 2.76 (tdd, *J* = 12.5, 5.7, 4.1 Hz, 1H, H-5), 2.36 (t, *J* = 11.2 Hz, 1H, H-4), 2.25 (dt, *J* = 13.1, 3.7 Hz, 1H, H-7$_a$), 1.92 (td, *J* = 11.8, 3.1 Hz, 1H, H-3), 1.84 (dq, *J* = 14.2, 3.8 Hz, 1H, H-6$_a$), 1.71 – 1.53 (m, 3H, H-2$_a$, H-2$_b$, H-7$_b$), 1.40 – 1.32 (m, 1H, H-6$_b$), 0.93 (s, 3H, H-8). The carboxylic acid H was not found.

^{13}C NMR (151 MHz, $CDCl_3$) δ 180.6 (C-11), 146.7 (C-13), 143.0 (C-Ph), 142.3 (C-Ph), 135.0 (C-12), 129.9 (2C, C-Ph), 129.3 (C-17), 129.1 (2C, C-Ph), 128.3 (2C, C-Ph), 128.2 (2C, C-Ph), 126.6 (C-Ph), 126.5 (C-Ph), 125.9 (C-14/C-15), 125.8 (C-15/C-14), 124.8 (C-16), 56.0 (C-10), 50.4 (C-4), 45.0 (C-3), 42.7 (C-5), 37.1 (C-7), 36.6 (C-9), 29.5 (C-1), 24.8 (C-6), 23.0 (C-2), 22.5 (C-8).

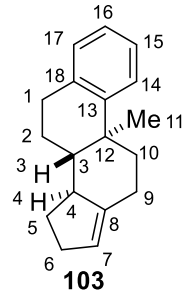
NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Note: the appearance of ^{1}H NMR signal for H-4: 2.36 (t, *J* = 11.2 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

IR (film) ν_{max}: 2926, 2361, 2341, 1701, 1493, 1451, 1276, 1261, 764, 750, 704 cm^{-1}.

HRMS (ESI): calculated for $C_{29}H_{29}O_2$ $[M-H]^-$ requires m/z 409.2173, found m/z 409.2173 (*Δ* = 0.00 ppm).

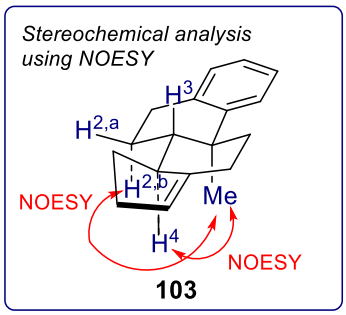
(±)-(8*S*,9*S*,14*S*)-9-Methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[*a*]phenanthrene 103.



103

$C_{18}H_{22}$

238.37 g mol^{-1}



Alkene **76e** (25.2 mg, 52.6 µmol, 1.00 equiv) and 2nd generation Hoveyda-Grubbs catalyst (9.8 mg, 15.6 µmol, 0.30 equiv) were transferred to a microwave vial and purged with nitrogen for 15 min. The balloon of nitrogen was removed and degassed PhMe (1.1 mL) was added. The solution was stirred at 110 °C overnight, cooled to rt and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane) to afford product **103** as a colourless oil (5.9 mg, 47%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 7.9, 1.4 Hz, 1H, H-14), 7.16 – 7.03 (m, 3H, H-15, H-16, H-17), 5.32 (t, *J* = 2.1 Hz, 1H, H-7), 2.92 – 2.83 (m, 2H, H-1), 2.53 – 2.43 (m, 2H, H-6$_a$, H-4), 2.40 – 2.31 (m, 2H, H-6$_b$, H-10$_a$), 2.31 – 2.24 (m, 2H, H-9), 2.23 – 2.16 (m, 1H, H-5$_a$), 1.83 – 1.77 (m, 1H, H-2$_a$), 1.67 – 1.58 (m, 1H, H-2$_b$), 1.46 – 1.37 (m, 2H, H-5$_b$, H-10$_b$), 1.25 (ddd, *J* = 12.4, 11.3, 2.8 Hz, 1H, H-3), 1.17 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (C-13), 145.2 (C-8), 135.7 (C-18), 129.5 (C-17), 125.8 (C-16/C-15/C-14), 125.5 (C-16/C-15/C-14), 125.4 (C-16/C-15/C-14), 121.2 (C-7), 50.9 (C-3), 46.3 (C-4), 38.0 (C-10), 37.7 (C-12), 31.2 (C-9), 30.2 (2C, C-1, C-5), 25.0 (C-6), 22.6 (C-2), 22.2 (C-11).

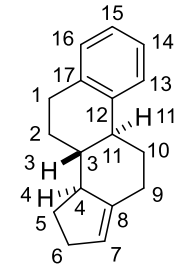
NOESY (600 MHz, $CDCl_3$): between H-4 and Me, between H-2$_b$ and Me.

Note: the appearance of ^{1}H NMR signal for H-3: 1.25 (ddd, *J* = 12.4, 11.3, 2.8 Hz, 1H, H-3) is indicative of a *trans*-diaxial arrangement between H-3 and H-4; H-3 and H-2$_b$ and equatorial/axial arrangement between H-2$_a$ and H-3.

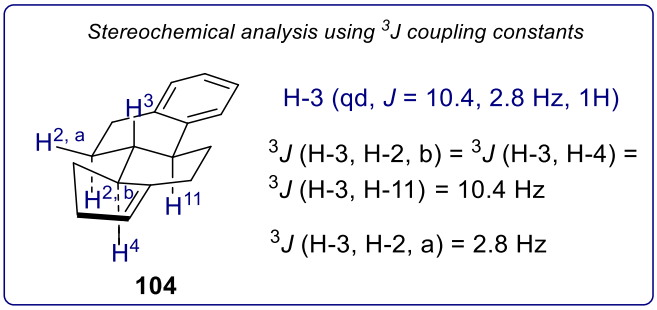
IR (film) ν_{max}: 2929, 2844, 1488, 1433, 1373, 797, 758, 726 cm^{-1}.

HRMS (APCI): calculated for $C_{18}H_{23}$ $[M+H]^+$ requires m/z 239.1794, found m/z 239.1794 (*Δ* = 0.07 ppm).

(±)-(8*S*,9*S*,14*S*)-7,8,9,11,12,14,15,16-Octahydro-6H-cyclopenta[*a*]phenanthrene 104.



104
$C_{17}H_{20}$
224.35 g mol^{-1}



Alkene **89** (9.2 mg, 20 µmol, 1.0 equiv) and 2nd generation Hoveyda-Grubbs catalyst (3.8 mg, 6.0 µmol, 0.30 equiv) were transferred to a microwave vial and purged with nitrogen for 15 min. The balloon of nitrogen was removed and degassed PhMe (0.42 mL) was added. The solution was stirred at 110 °C overnight, cooled to rt and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane) to afford product **104** as a colourless oil (2.8 mg, 63%).

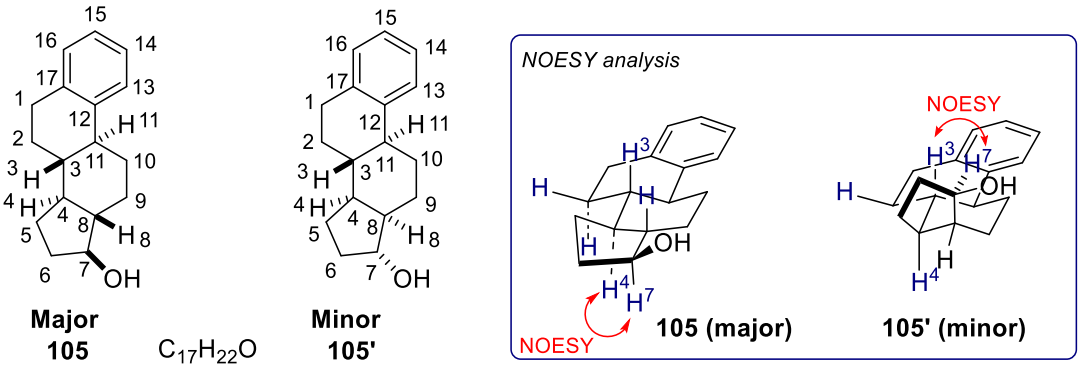
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 7.6 Hz, 1H, H-13), 7.21 – 7.01 (m, 3H, H-14, H-15, H-16), 5.34 – 5.29 (m, 1H, H-7), 2.92 – 2.77 (m, 2H, H-1), 2.66 (ddd, *J* = 14.1, 4.5, 2.2 Hz, 1H, H-9$_a$), 2.57 – 2.44 (m, 2H, H-11, H-10$_a$), 2.37 – 2.12 (m, 5H, H-6, H-4, H-5$_a$, H-9$_b$), 2.05 – 1.93 (m, 1H, H-2$_a$), 1.54 – 1.37 (m, 2H, H-2$_b$, H-5$_b$), 1.32 – 1.19 (m, 1H, H-10$_b$), 1.08 (qd, *J* = 10.4, 2.8 Hz, 1H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C-8), 140.0 (C-12), 137.3 (C-17), 129.2 (C-16), 126.4 (C-13), 125.8 (C-14/C-15), 125.7 (C-15/C-14), 121.1 (C-7), 51.4 (C-4), 49.0 (C-3), 42.9 (C-11), 31.8 (C-10), 31.5 (C-6), 30.3 (C-1), 29.2 (C-5), 28.8 (C-9), 27.8 (C-2).

IR (film) ν_{max}: 2925, 2854, 2360, 1489, 1450, 1433, 739 cm^{-1}.

HRMS (GC EI): calculated for $C_{17}H_{20}$ $[M]^+$ requires 224.15595, found m/z 224.15548 (*Δ* = -2.11 ppm).

(±)-(8*S*,9*S*,13*S*,14*S*,17*S*)-7,8,9,11,12,13,14,15,16,17-Decahydro-6H-cyclopenta[a]phenanthren-17-ol 105 (major) and (±)-(8*S*,9*S*,13*R*,14*S*,17*R*)-7,8,9,11,12,13,14,15,16,17-Decahydro-6H-cyclopenta[a]phenanthren-17-ol 105' (minor).



$C_{17}H_{22}O$
242.36 g mol^{-1}

According to a modified literature procedure[75], alkene **104** (6.1 mg, 27 µmol, 1.0 equiv) and $LiBH_4$ (cat) were transferred to a microwave vial which was then purged with nitrogen. Catecholborane (7.3 µL, 68 µmol, 2.5 equiv) as a stock solution in C_6H_6 (0.40 mL, 0.17 M) was then added in one portion and the obtained suspension was stirred at reflux for 24 h. The mixture was then cooled to rt and aq NaOH (3M, 0.2 mL) followed by aq H_2O_2 (30%, 0.2 mL) were added in one portion. The obtained mixture was vigorously stirred at rt for 4 h, diluted with water (3 mL) and CH_2Cl_2 (3 mL). The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2) to furnish an inseparable mixture of alcohols **105 (major)** and **105' (minor)** as a white solid (4.8 mg, 61:39 dr, 73%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 1H$_{maj}$, 1H$_{min}$, H-13$_{maj}$, H-13$_{min}$), 7.18 – 7.05 (m, 3H$_{maj}$, 3H$_{min}$, H-14$_{maj}$, H-15$_{maj}$, H-16$_{maj}$, H-14$_{min}$, H-15$_{min}$, H-16$_{min}$), 4.13 (td, *J* = 8.7, 6.7 Hz, 1H$_{min}$, H-7$_{min}$), 3.86 (td, *J* = 8.6, 6.1 Hz, 1H$_{maj}$, H-7$_{maj}$), 2.93 – 2.79 (m, 2H$_{maj}$, 2H$_{min}$, H-1$_{maj}$, H-1$_{min}$), 2.61 – 2.54 (m, 1H$_{maj}$, H-10$_{a, maj}$), 2.36 – 2.28 (m, 1H$_{maj}$, 2H$_{min}$, H-11$_{maj}$, H-9$_{a, min}$, H-11$_{min}$), 2.25 – 2.20 (m, 1H$_{maj}$, H-9$_{a, maj}$), 2.20 – 2.08 (m, 1H$_{maj}$, 1H$_{min}$, H-6$_{a, maj}$, H-6$_{a, min}$), 2.05 (dq, *J* = 14.0, 3.1 Hz, 1H$_{min}$, H-10$_{a, min}$), 2.01 – 1.89 (m, 1H$_{maj}$, 3H$_{min}$, H-2$_{a, maj}$, H-2$_{a, min}$, H-5$_{a, min}$, H-8$_{min}$), 1.89 – 1.76 (m, 1H$_{maj}$, 2H$_{min}$, H-5$_{a, maj}$, H-10$_{b, min}$, H-4$_{min}$), 1.64 – 1.49 (m, 1H$_{maj}$, 2H$_{min}$, H-6$_{b, maj}$, H-5$_{b, min}$, H-6$_{b, min}$), 1.46 – 1.20 (m, 6H$_{maj}$, 2H$_{min}$, H-2$_{b, maj}$, H-5$_{b, maj}$, H-10$_{b, maj}$, H-8$_{maj}$, H-9$_{b, maj}$, H-

[75] (a) A. Arase, Y. Nunokawa, Y. Masuda, M. Hoshi, *J. Chem. Soc., Chem. Commun*. **1991**, *4*, 205-206; (b) C. E. Garrett, G. C. Fu, *J. Org. Chem*. **1996**, *61*, 3224-3225; (c) Y. Suseela, M. Periasamy, *J. Organomet. Chem*. **1993**, *450*, 47-52; (d) A.-P. Schaffner, B. Becattini, C. Ollivier, V. Weber, P. Renaud, *Synthesis* **2003**, 2740–2742; (e) A. Kuhl, H. Karele, W. Kreiser, *Helv. Chim. Acta* **1999**, *82*, 30–34.

3_{maj}, H-$9_{b,\ min}$, H-$2_{b,\ min}$), 1.15 (qd, *J* = 10.8, 6.5 Hz, $1H_{maj}$, H-4_{maj}), 1.02 (qd, *J* = 11.1, 2.7 Hz, $1H_{min}$, H-3_{min}). The OH was not found.

^{13}C NMR (151 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 140.3 (C-12), 137.0 (C-17), 129.2 (C-16), 125.8 (C-15/C-14/C-13), 125.8 (C-15/C-14/C-13), 125.7 (C-15/C-14/C-13), 78.0 (C-7), 53.6 (C-8), 48.1 (C-4), 45.8 (C-3), 43.6 (C-11), 33.1 (C-6), 30.6 (C-10), 29.8 (C-1), 29.0 (C-9), 27.5 (C-2), 26.7 (C-5). **Peaks for the minor diastereomer** (from the mixture): δ 140.4 (C-12), 137.2 (C-17), 129.1 (C-16), 126.1 (C-13/C14/C-15), 125.8 (C-13/C-14/C-15), 125.7 (C-13/C-14/C-15), 74.3 (C-7), 47.6 (C-8), 44.0 (C-4), 42.7 (C-11), 41.7 (C-3), 33.0 (C-6), 30.3 (C-1), 28.1 (C-2), 26.8 (C-9), 26.5 (C-5), 24.9 (C-10).

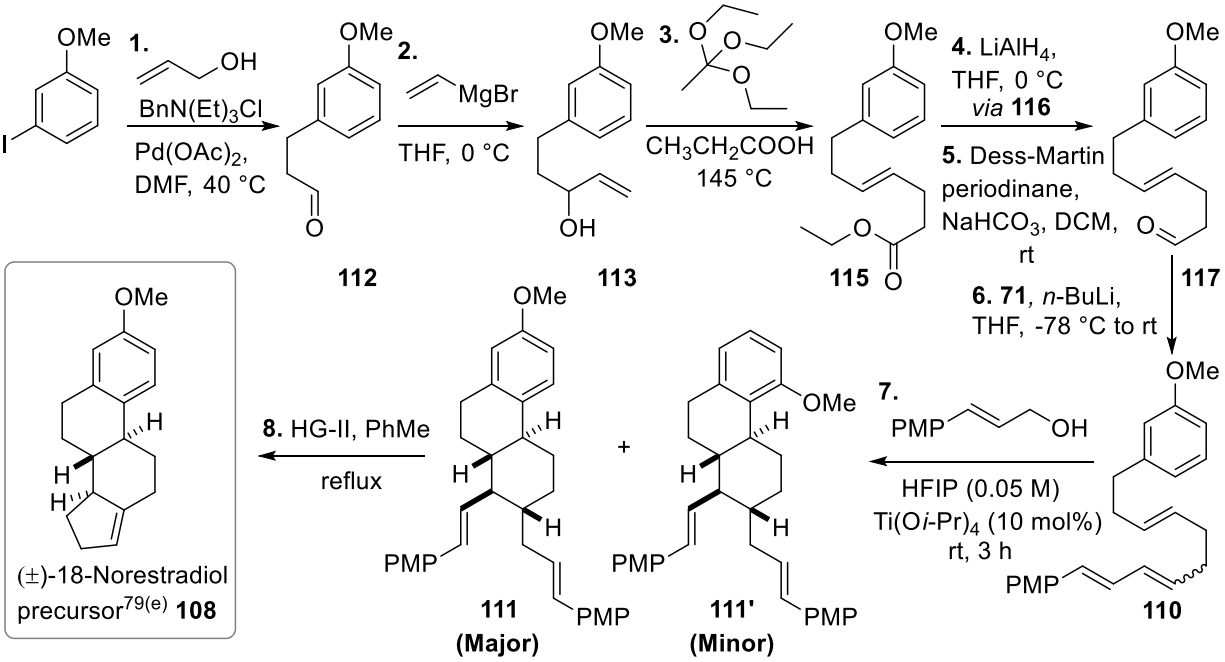
NOESY- 2D (600 MHz, $CDCl_3$): between H-4_{maj} and H-7_{maj}; between H-3_{min} and H-7_{min}.

M.p: 120-130 °C.

IR (film) ν_{max}: 3315, 2930, 2863, 2360, 2341, 1489, 1451, 1073, 912, 742 cm^{-1}.

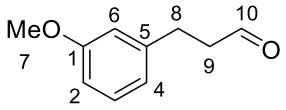
HRMS (GC EI): calculated for $C_{17}H_{22}O$ $[M]^+$ requires m/z 242.16652, found m/z 242.16707 (*Δ* = 3.21 ppm).

6.3.2 Experimental procedures for the formal synthesis of (±)-18-nor-estradiol



79(e) A. Kuhl, H. Karele, W. Kreiser, *Helv. Chim. Acta* **1999**, *82*, 30–34.

3-(3-Methoxyphenyl)propanal 112.



112

$C_{10}H_{12}O_2$

164.20 g mol^{-1}

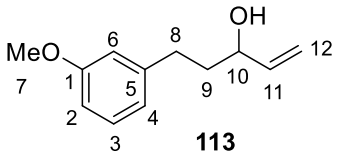
To a solution of 3-iodoanisole (2.00 mL, 16.8 mmol, 1.00 equiv) in DMF (30 mL) were added triethylbenzylammonium chloride (3.90 g, 17.1 mmol, 1.02 equiv), $NaHCO_3$ (2.88 g, 34.3 mmol, 2.04 equiv), allylalcohol (2.3 mL, 34 mmol, 2.0 equiv), and $Pd(OAc)_2$ (920 mg, 4.10 mmol, 0.240 equiv). The reaction mixture was stirred at 40°C for 12 h. After cooling to rt, the mixture was poured into ice-water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and volatiles were removed *in vacuo* to furnish the crude product, which was purified by flash column chromatography (SiO_2; pentane:EtOAc; 9:1) to afford the aldehyde **112** as a pale yellow oil (1.19 g, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (t, *J* = 1.6 Hz, 1H, H-10), 7.21 (td, *J* = 7.6, 1.0 Hz, 1H, H-3), 6.83 – 6.71 (m, 3H, H-2, H-4, H-6), 3.80 (s, 3H, H-7), 2.94 (t, *J* = 7.5 Hz, 2H, H-8), 2.84 – 2.73 (m, 2H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.7 (C-10), 159.9, (C-1), 142.1 (C-5), 129.7 (C-3), 120.7 (C-2/C-4), 114.3 (C-6), 111.7 (C-4/C-2), 55.3 (C-7), 45.3 (C-9), 28.3 (C-10).

The analytical data are consistent with those previously reported in the literature.[76]

5-(3-Methoxyphenyl)pent-1-en-3-ol 113.



113

$C_{12}H_{16}O_2$

192.26 g mol^{-1}

Aldehyde **112** (1.19 g, 7.25 mmol, 1.00 equiv) was dissolved in THF (45 mL) and cooled to 0 °C. To the obtained solution vinyl magnesium bromide (9.5 mL, 1.0 M in THF, 9.5 mmol, 1.3 equiv) was added dropwise. The reaction mixture was stirred at the same temperature for 2 h and then quenched with aq. sat. NH_4Cl (5 mL) and diluted with water (30 mL). The organic

[76] W. Ren, W. Chang, J. Dai, Y. Shi, J. Li, Y. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 14864–14867.

layer was separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish allylic alcohol **113** as a pale yellow oil (0.950 g, 68%).

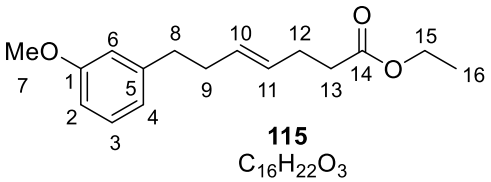
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.7 Hz, 1H, H-3), 6.85 – 6.69 (m, 3H, H-2, H-4, H-6), 5.91 (ddd, *J* = 16.9, 10.4, 6.1 Hz, 1H, H-11), 5.25 (dt, *J* = 17.1, 1.7 Hz, 1H, H-12$_a$), 5.14 (d, *J* = 10.3 Hz, 1H, H-12$_b$), 4.14 (q, *J* = 6.3 Hz, 1H, H-10), 3.80 (s, 3H, H-7), 2.79 – 2.61 (m, 2H, H-8), 1.92 – 1.77 (m, 2H, H-9). The OH was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8 (C-1), 143.7 (C-5), 141.1 (C-11), 129.5 (C-3), 121.0 (C-2/C-4), 115.1 (C-12), 114.3 (C-6), 111.3 (C-4/C-2), 72.6 (C-10), 55.3 (C-7), 38.5 (C-9), 31.8 (C-8).

IR (film) ν_{max}: 3395, 2944, 1602, 1585, 1489, 1261, 1153, 1042, 993, 924, 782, 696 cm^{-1}.

HRMS (ESI): A stable molecular ion could not be detected by ESI, APCI or EI.

Ethyl (*E*)-7-(3-methoxyphenyl)hept-4-enoate 115.



115
$C_{16}H_{22}O_3$
262.35 g mol^{-1}

A solution of the allylic alcohol **113** (0.937 g, 4.87 mmol, 1.00 equiv) and propionic acid (25 µL) in triethyl orthoacetate (12 mL) was heated with stirring at 145 °C for 24 h. The solution was cooled to room temperature, poured into water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed successively with aq. HCl (1 M, 2 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 23:2 to 9:1) to furnish ester **115** as a colourless oil (1.13 g, 88%).

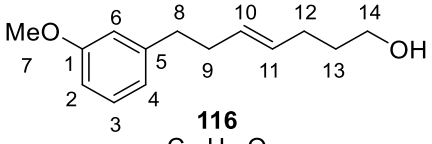
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.13 (m, 1H, H-3), 6.80 – 6.69 (m, 3H, H-2, H-4, H-6), 5.57 – 5.38 (m, 2H, H-10, H-11), 4.12 (q, *J* = 7.1 Hz, 2H, H-15), 3.80 (s, 3H, H-7), 2.63 (dd, *J* = 9.0, 6.6 Hz, 2H, H-8), 2.38 – 2.24 (m, 6H, H-9, H-12, H-13), 1.25 (t, *J* = 7.2 Hz, 3H, H-16).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C-14), 159.7 (C-1), 143.8 (C-5), 130.8 (C-10/C-11), 129.3 (C-3), 128.9 (C-11/C-10), 121.0 (C-2/C-4), 114.3 (C-6), 111.2 (C-4/C-2), 60.4 (C-15), 55.3 (C-7), 36.1 (C-8), 34.4 (2C, C-9, C-12), 28.0 (C-13), 14.4 (C-16).

IR (film) ν_{max}: 2938, 1735, 1602, 1490, 1455, 1261, 1166, 1153, 1044, 971, 780, 696 cm^{-1}.

HRMS (ESI): calculated for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ requires m/z 285.1461, found m/z 285.1462 (Δ = 0.28 ppm).

(*E*)-7-(3-Methoxyphenyl)hept-4-en-1-ol 116.



116
$C_{14}H_{20}O_2$
220.31 g mol^{-1}

$LiAlH_4$ (0.163 g, 4.30 mmol, 1.00 equiv) was added portion-wise to a solution of ester **115** (1.13 g, 4.31 mmol, 1.00 equiv) in THF (32 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 3 h followed by the subsequent addition of water (0.16 mL), 15% aq. NaOH (0.16 mL) and water (0.48 mL). The obtained suspension was stirred at rt for 30 min, transferred to a separatory funnel, diluted with an additional amount of water (30 mL) and extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2 to 2:3) to furnish alcohol **116** as a colourless oil (0.869 g, 92%).

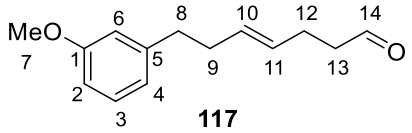
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.15 (m, 1H, H-3), 6.80 – 6.67 (m, 3H, H-2, H-4, H-6), 5.54 – 5.37 (m, 2H, H-10, H-11), 3.80 (s, 3H, H-7), 3.61 (t, *J* = 6.5 Hz, 2H, H-14), 2.65 (dd, *J* = 8.7, 6.7 Hz, 2H, H-8), 2.35 – 2.25 (m, 2H, H-9), 2.11 – 2.01 (m, 2H, H-12), 1.66 – 1.57 (m, 2H, H-13). The OH was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7 (C-1), 143.8 (C-5), 130.4 (C-10/C-11), 130.3 (C-11/C-10), 129.3 (C-3), 121.1 (C-2/C-4), 114.4 (C-6), 111.1 (C-4/C-2), 62.6 (C-14), 55.3 (C-7), 36.2 (C-8), 34.4 (C-9), 32.5 (C-13), 29.0 (C-12).

IR (film) ν_{max}: 3394, 2934, 2361, 2341, 1603, 1490, 1455, 1262, 1153, 1053, 870, 781 cm^{-1}.

HRMS (ESI): calculated for $C_{14}H_{20}O_2Na$ $[M+Na]^+$ requires m/z 243.1356, found m/z 243.1348 (Δ = -3.11 ppm).

(*E*)-7-(3-Methoxyphenyl)hept-4-enal 117.



117
$C_{14}H_{18}O_2$
218.30 g mol^{-1}

(*E*)-7-(3-Methoxyphenyl)hept-4-en-1-ol **116** (0.331 g, 1.50 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (25 mL) and to the obtained solution $NaHCO_3$ (2.4 g, 29 mmol, 7.4 equiv) and Dess-Martin Periodinane (0.96 g, 2.3 mmol, 1.5 equiv) were added sequentially in one portion. The obtained suspension was stirred at rt until the complete consumption of the starting material, then quenched with sat. aq. $Na_2S_2O_3$ (7 mL) and stirred for additional 15 min. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish aldehyde **117** as a colourless oil (0.263 g, 80%).

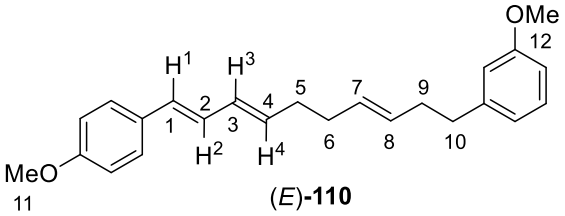
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.7 Hz, 1H, H-14), 7.23 – 7.14 (m, 1H, H-3), 6.82 – 6.68 (m, 3H, H-2, H-4, H-6), 5.57 – 5.37 (m, 2H, H-10, H-11), 3.80 (s, 3H, H-7), 2.63 (dd, *J* = 8.9, 6.7 Hz, 2H, H-8), 2.52 – 2.42 (m, 2H, H-13), 2.38 – 2.24 (m, 4H, H-9, H-12).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5 (C-14), 159.7 (C-1), 143.7 (C-5), 131.1 (C-10/C-11), 129.4 (C-3), 128.6 (C-11/C-10), 121.0 (C-2/C-4), 114.4 (C-6), 111.2 (C-4/C-2), 55.3 (C-7), 43.6 (C-13), 36.0 (C-8), 34.3 (C-9/C-12), 25.3 (C-12/C-9).

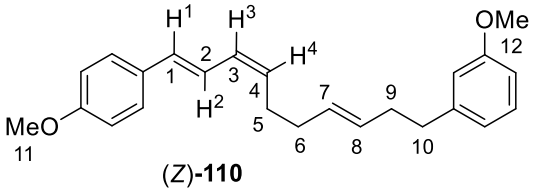
IR (film) ν_{max}: 2918, 2360, 1726, 1602, 1489, 1261, 1152, 1051, 970, 911, 733, 696 cm^{-1}.

HRMS (ESI): calculated for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ requires m/z 241.1199, found m/z 241.1193 (*Δ* = -2.51 ppm).

1-Methoxy-3-((3*E*,7*E*,9*E*)-10-(4-methoxyphenyl)deca-3,7,9-trien-1-yl)benzene (*E*)-110 and 1-methoxy-3-((3*E*,7*Z*,9*E*)-10-(4-methoxyphenyl)deca-3,7,9-trien-1-yl)benzene (*Z*)-110.



(*E*)-**110**
$C_{24}H_{28}O_2$
348.49 g mol^{-1}
$^3J_{\text{H-1, H-2}}$ = 15.6 Hz
$^3J_{\text{H-3, H-4}}$ = 14.4 Hz



(*Z*)-**110**
$C_{24}H_{28}O_2$
348.49 g mol^{-1}
$^3J_{\text{H-1, H-2}}$ = 15.6 Hz

(*E*)-(3-(4-Methoxyphenyl)allyl)triphenylphosphonium bromide **71** (0.884 g, 1.81 mmol, 1.50 equiv) was suspended in THF (9 mL) and cooled to -78 °C. *n*-BuLi (0.72 mL, 2.5 M in hexanes, 1.8 mmol, 1.5 equiv) was added dropwise and the obtained suspension was allowed to stir at the same temperature for 30 min. Aldehyde **117** (0.263 g, 1.20 mmol, 1.00 equiv) in THF (3 mL) was added dropwise at -78 °C and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 24:1) to furnish an inseparable mixture of alkenes (*E*)-**110** and (*Z*)-**110** as a colourless waxy solid (0.244 g, 58%, 57:43 *E*:*Z*).

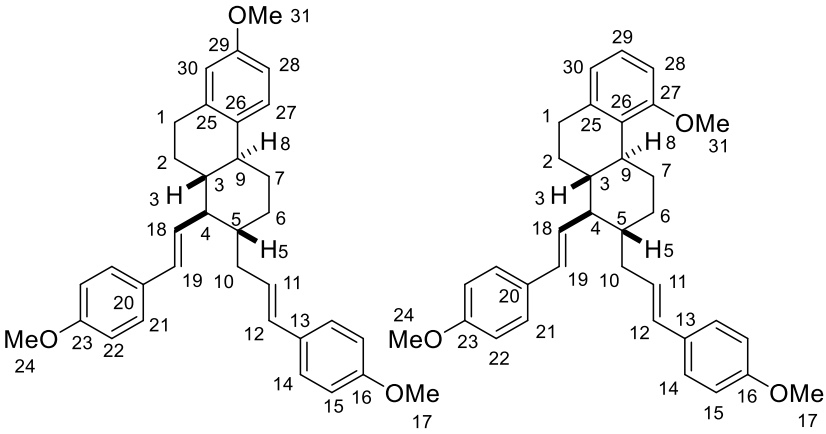
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 2H$_{maj}$, 2H$_{min}$, H-Ar$_{maj}$, H-Ar$_{min}$), 7.23 – 7.16 (m, 1H$_{maj}$, 1H$_{min}$, H-Ar$_{maj}$, H-Ar$_{min}$), 6.97 – 6.70 (m, 5H$_{maj}$, 6H$_{min}$, H-Ar$_{maj}$, H-Ar$_{min}$, H-2$_{min}$), 6.63 (dd, *J* = 15.6, 10.4 Hz, 1H$_{maj}$, H-2$_{maj}$), 6.52 – 6.36 (m, 1H$_{maj}$, 1H$_{min}$, H-1$_{maj}$, H-1$_{min}$), 6.23 – 6.07 (m, 1H$_{maj}$, 1H$_{min}$, H-3$_{maj}$, H-3$_{min}$), 5.75 (dt, *J* = 14.4, 6.7 Hz, 1H$_{maj}$, H-4$_{maj}$), 5.57 – 5.38 (m, 2H$_{maj}$, 3H$_{min}$, H-7$_{maj}$, H-8$_{maj}$, H-7$_{min}$, H-8$_{min}$, H-4$_{min}$), 3.85 – 3.76 (m, 6H$_{maj}$, 6H$_{min}$, H-11$_{maj}$, H-12$_{maj}$, H-11$_{min}$, H-12$_{min}$), 2.69 – 2.61 (m, 2H$_{maj}$, 2H$_{min}$, H-10$_{maj}$, H-10$_{min}$), 2.39 – 2.26 (m, 2H$_{maj}$, 4H$_{min}$, H-9$_{maj}$, H-5$_{min}$, H-9$_{min}$), 2.23 – 2.06 (m, 4H$_{maj}$, 2H$_{min}$, H-5$_{maj}$, H-6$_{maj}$, H-6$_{min}$).

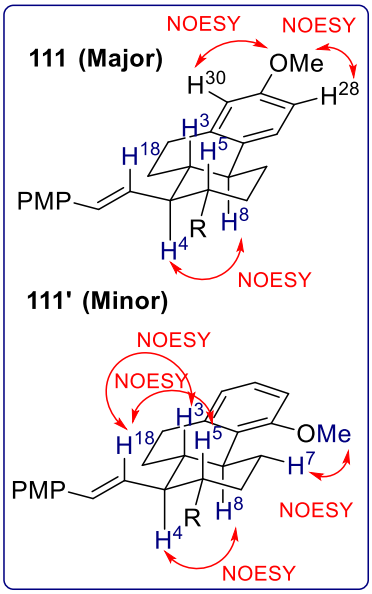
^{13}C NMR (101 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 159.7 (C-Ar), 159.0 (C-Ar), 143.9 (C-Ar), 134.0 (C-4), 131.1 (C-3), 130.6 (C-Ar), 130.3 (C-7/C-8), 130.1 (C-8/C-7), 129.8 (C-1), 129.3 (C-Ar), 127.5 (C-2), 127.4 (2C, C-Ar), 121.1 (C-Ar), 114.4 (C-Ar), 114.2 (2C, C-Ar), 111.1 (C-Ar), 55.4 (C-11/C-12), 55.3 (C-12/C-11), 36.3 (C-10), 34.4 (C-9), 33.0 (C-5/C-6), 32.6 (C-6/C-5). **Selected peaks for the minor diastereomer** (from the mixture): δ 159.2, 131.8 (C-1), 131.4 (C-4), 130.6 (C-Ar), 127.7, 122.7 (C-2), 114.3, 114.2, 34.5 (C-9), 32.8 (C-6), 28.1 (C-5).

IR (film) ν_{max}: 2935, 2360, 1604, 1510, 1252, 1174, 1152, 1037, 987, 736, 696 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{29}O_2$ $[M+H]^+$ requires m/z 349.2162, found m/z 349.2166 (Δ = 1.12 ppm).

(±)-(1*S*,2*R*,4a*S*,10a*S*)-7-Methoxy-2-((*E*)-3-(4-methoxyphenyl)allyl)-1-((*E*)-4-methoxystyryl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene 111 (major) and (±)-(1*S*,2*R*,4a*S*,10a*S*)-5-methoxy-2-((*E*)-3-(4-methoxyphenyl)allyl)-1-((*E*)-4-methoxystyryl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene 111' (minor).





Triene **(*EIZ*)-110** (40.0 mg, 0.115 mmol, 1.00 equiv, 57:43 *E*:*Z*) and *trans*-4-methoxycinnamyl alcohol (18.9 mg, 0.115 mmol, 1.00 equiv) were transferred to a microwave vial which was then purged with nitrogen. The balloon of nitrogen was removed, and HFIP (2.1 mL), followed by $Ti(O\textit{i}\text{-}Pr)_4$ (3.40 µL, 11.5 µmol, 0.100 equiv) as a stock solution in HFIP (0.17 mL, 0.067 M), were added to obtain a 0.05 M solution of a triene **(*EIZ*)-110**. The solution was stirred at rt for 3 h, then diluted with water (3 mL). The obtained suspension was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 4 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 22:3) to furnish alkene **111'** (minor, 3.0 mg, 5%) as a colourless oil and alkene **111** (major, 10.1 mg, 18%) as a colourless oil.

Major regioisomer 111:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 2H, H-14/H-21), 7.28 – 7.26 (m, 2H, H-21/H-14), 7.25 – 7.21 (m, 1H, H-27), 6.92 – 6.79 (m, 4H, H-15, H-22), 6.72 (dd, *J* = 8.7, 2.8 Hz, 1H,

H-28), 6.64 – 6.59 (m, 1H, H-30), 6.36 (d, *J* = 15.9 Hz, 1H, H-19), 6.30 (d, *J* = 15.8 Hz, 1H, H-12), 6.09 (ddd, *J* = 15.4, 8.2, 6.5 Hz, 1H, H-11), 5.80 (dd, *J* = 15.9, 9.6 Hz, 1H, H-18), 3.85 – 3.79 (m, 6H, H-17/H-24/H-31, H-17/H-24/H-31), 3.77 (s, 3H, H-17/H-24/H-31), 2.85 – 2.70 (m, 2H, H-1), 2.53 – 2.43 (m, 2H, H-7_a, H-10_a), 2.39 – 2.29 (m, 1H, H-8), 2.14 – 2.06 (m, 2H, H-2_a, H-6_a), 2.05 – 1.97 (m, 1H, H-10_b), 1.79 (q, *J* = 10.0 Hz, 1H, H-4), 1.50 – 1.39 (m, 1H, H-5), 1.35 – 1.20 (m, 4H, H-2_b, H-7_b, H-6_b, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (C-29/C-23/C-16), 158.8 (C-29/C-23/C-16), 157.6 (C-29/C-23/C-16), 138.5 (C-25), 132.8 (C-26), 131.8 (C-18), 131.5 (C-19), 131.0 (C-13/C-20), 130.7 (C-12), 130.6 (C-20/C-13), 127.3 (2C, C-14/C-21), 127.2 (C-11), 127.1 (2C, C-21/C-14), 126.8 (C-27), 114.1 (4C, C-15, C-22), 113.6 (C-30), 111.8 (C-28), 55.5 (C-17/C-24/C-31), 55.4 (C-17/C-24/C-31), 55.3 (C-17/C-24/C-31), 53.3 (C-4), 44.8 (C-3), 42.6 (C-9), 42.3 (C-5), 38.5 (C-10), 31.8 (C-6), 31.0 (C-7), 30.6 (C-1), 28.1 (C-2).

NOESY- 2D (500 MHz, $CDCl_3$): between H-4 and H-8; between OMe and H-28; between OMe and H-30.

Note: the appearance of ^{1}H NMR signal for H-4: 1.79 (q, *J* = 10.0 Hz, 1H, H-4) is indicative of a *trans*-diaxial arrangement between H-4 and H-3, H-4 and H-5, H-4 and H-18.

IR (film) ν_{max}: 2919, 1608, 1510, 1249, 1175, 1037, 968, 838 cm^{-1}.

HRMS (ESI): calculated for $C_{34}H_{39}O_3$ $[M+H]^+$ requires m/z 495.2894, found m/z 495.2893 (*Δ* = - 0.12 ppm).

Minor regioisomer 111':

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H, H-14/H-21), 7.29 – 7.22 (m, 2H, H-21/H-14), 7.10 – 7.02 (m, 1H, H-29), 6.90 – 6.80 (m, 4H, H-22, H-15), 6.73 – 6.64 (m, 2H, H-28, H-30), 6.40 – 6.22 (m, 2H, H-12, H-19), 6.09 (ddd, *J* = 15.4, 8.2, 6.5 Hz, 1H, H-11), 5.82 (dd, *J* = 15.9, 9.6 Hz, 1H, H-18), 3.84 – 3.78 (m, 9H, H-17, H-24, H-31), 2.98 (dd, *J* = 12.6, 2.8 Hz, 1H, H-7_a), 2.83 – 2.63 (m, 2H, H-1), 2.56 – 2.43 (m, 2H, H-8, H-10_a), 2.09 – 1.85 (m, 4H, H-10_b, H-2_a, H-4, H-6_a), 1.53 – 1.46 (m, 1H, H-5), 1.42 – 1.30 (m, 2H, H-3, H-6_b), 1.17 – 1.00 (m, 2H, H-2b, H-7_b).

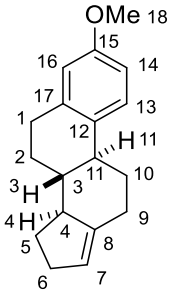
^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (C-23/C-16/C-27), 158.9 (C-23/C-16/C-27), 158.7(C-23/C-16/C-27), 140.2 (C-25), 132.2 (C-18), 131.2 (C-19), 131.0 (C-20/C-13), 130.7 (C-13/C-20), 130.6 (C-12), 129.1 (C-26), 127.4 (C-11), 127.2 (2C, C-21/C-14), 127.1 (2C, C-14/C-21), 126.2 (C-29), 121.8 (C-30), 114.1 (4C, C-22, C-15), 108.2 (C-28), 55.5 (2C, C-24/C-17/C-31, C-24/C-17/C-31), 55.1 (C-17/C-31/C-24), 53.5 (C-4), 47.7 (C-3), 43.3 (C-5), 42.9 (C-9), 38.5 (C-10), 32.8 (C-6), 32.1 (C-1), 31.3 (C-7), 26.9 (C-2).

NOESY- 2D (500 MHz, $CDCl_3$): between H-4 and H-8; between H-18 and H-3; between H-18 and H-5; between H-7_a and OMe.

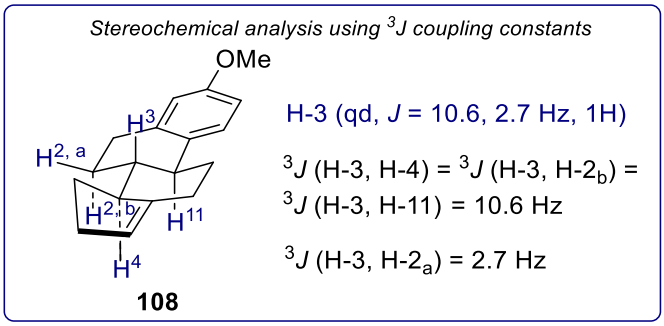
IR (film) ν_{max}: 2981, 2918, 2360, 1510, 1465, 1248, 1174, 967 cm^{-1}.

HRMS (ESI): calculated for $C_{34}H_{39}O_3$ $[M+H]^+$ requires m/z 495.2894, found m/z 495.2892 (Δ = -0.35 ppm).

(±)-(8*S*,9*S*,14*S*)-3-Methoxy-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[*a*]phenanthrene 108.



108
$C_{18}H_{22}O$
254.37 g mol^{-1}



Alkene **111** (20.0 mg, 40.4 µmol, 1.00 equiv) and 2nd generation Hoveyda-Grubbs catalyst (7.60 mg, 12.1 µmol, 0.300 equiv) were transferred to a microwave vial and purged with nitrogen for 15 min. Balloon of nitrogen was removed and degassed PhMe (0.81 mL) was added. The solution was stirred at 110 °C overnight, cooled to rt and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane to pentane:Et_2O; 100:0 to 98:2) to afford product **108** as a colurless oil (5.3 mg, 51%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 1H, H-13), 6.72 (dd, *J* = 8.7, 2.8 Hz, 1H, H-14), 6.62 (d, *J* = 2.8 Hz, 1H, H-16), 5.34 – 5.28 (m, 1H, H-7), 3.78 (s, 3H, H-18), 2.88 – 2.76 (m, 2H, H-1), 2.64 (ddd, *J* = 14.2, 4.2, 2.0 Hz, 1H, H-9_a), 2.50 – 2.40 (m, 2H, H-11, H-10_a), 2.35 – 2.25 (m, 3H, H-4, H-6), 2.25 – 2.13 (m, 2H, H-5_a, H-9_b), 1.98 (ddt, *J* = 12.8, 5.4, 2.8 Hz, 1H, H-2_a), 1.52 – 1.38 (m, 2H, H-5_b, H-2_b), 1.21 (qd, *J* = 11.9, 4.3 Hz, 1H, H-10_b), 1.04 (qd, *J* = 10.6, 2.7 Hz, 1H, H-3).

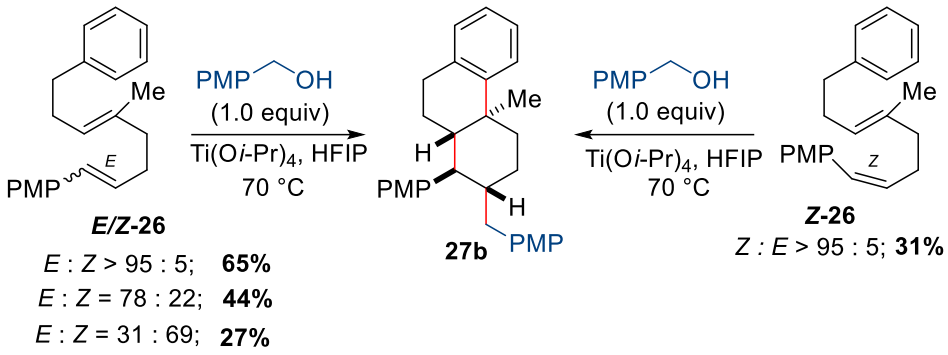
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4 (C-15), 145.3 (C-8), 138.5 (C-17), 132.3 (C-12), 127.4 (C-13), 121.1 (C-7), 113.8 (C-16), 111.9 (C-14), 55.3 (C-18), 51.3 (C-4), 49.2 (C-3), 42.3 (C-11), 32.0 (C-10), 31.5 (C-6), 30.6 (C-1), 29.2 (C-5), 28.7 (C-9), 27.9 (C-2).

IR (film) ν_{max}: 2927, 2854, 2360, 1611, 1501, 1254, 1237, 1048, 909, 802, 735 cm^{-1}.

HRMS (ESI): calculated for $C_{18}H_{23}O$ $[M+H]^+$ requires m/z 255.1743, found m/z 255.1744 (Δ = 0.35 ppm).

Control and mechanistic experiments

Stereoconvergent synthesis of **27b**.



***E*/*Z*-26**

E : *Z* > 95 : 5; **65%**

E : *Z* = 78 : 22; **44%**

E : *Z* = 31 : 69; **27%**

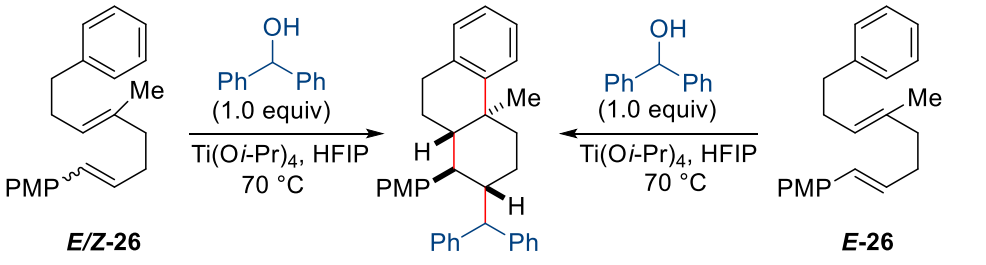
27b

***Z*-26**

Z : *E* > 95 : 5; **31%**

Experimental procedure: E/*Z*-**26** (0.100 mmol, 1.00 equiv), *E*-**26** (0.0816 mmol, 1.00 equiv) or *Z*-**26** (0.0816 mmol, 1.00 equiv), 4-methoxybenzyl alcohol (1.00 equiv) and Ti(O*i*-Pr)$_4$ (0.30 equiv) in HFIP (0.050 M) were subjected to the general procedure **C**. The crude mixture was analysed by NMR and purified by flash column chromatography (SiO_2; 60 Å, 15–40 μm, pentane:Et_2O; 24:1) to furnish compound **27b** as a colourless oil which crystallised on standing. Only a single diastereomer of **27b** could be detected in the crude ^{1}H and ^{13}C NMR prior to column chromatography.

Stereoconvergent synthesis of **27a**.



***E*/*Z*-26**

E : *Z* = 31 : 69; **76%**

27a

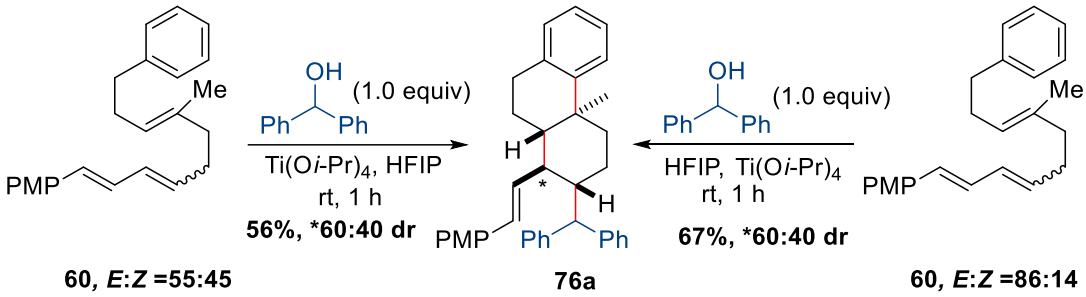
***E*-26**

E : *Z* > 95 : 5; **86%**

Experimental procedure: E/*Z*-**26** (0.100 mmol, 1.00 equiv) or *E*-**26** (0.100 mmol, 1.00 equiv), benzhydrol (1.00 equiv) and Ti(O*i*-Pr)$_4$ (0.30 equiv) in HFIP (0.050 M) were subjected to the general procedure **C**. The crude mixture was analysed by NMR and purified by flash column

chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish compound **27a** as a foam. Only a single diastereomer of **27a** could be detected in the crude prior to column chromatography.

Stereoconvergent synthesis of **76a**.

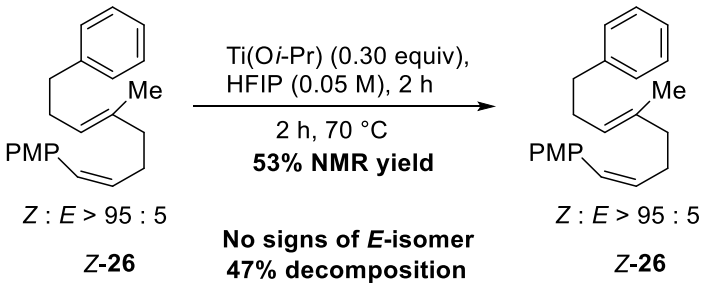


60, *E*:*Z* =55:45 **76a** **60, *E*:*Z* =86:14**

Experimental procedure: E/Z-**60** (0.100 mmol, 1.00 equiv), benzhydrol (0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (0.30 equiv) in HFIP (0.050 M) were subjected to the general procedure **D**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 24:1) to furnish compound **76a** as an inseparable mixture of two diastereomers at the exocyclic allylic position as a colourless oil (60:40 dr).[77] dr of the crude reaction mixture was found to be independent of the *E*/*Z* ratio of the triene **60**.

Stability of *Z*-**26**, *E*-**26**, *E/Z*-**60** under the reaction conditions

Z-**26** stability/interconversion.



Z : *E* > 95 : 5 **No signs of *E*-isomer** *Z* : *E* > 95 : 5

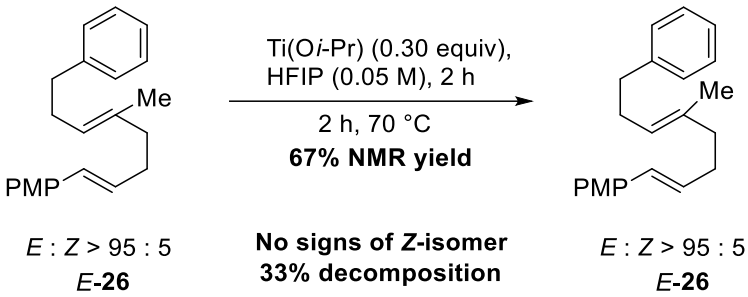
Z-**26** **47% decomposition** *Z*-**26**

Experimental procedure: Z-**26** (1.00 equiv) and Ti(O*i*-Pr)$_4$ (0.30 equiv) in HFIP (0.050 M) were subjected to the general procedure **C** but without electrophile present. NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard indicated the

[77] dr determined by ^{1}H NMR of the crude reaction mixture.

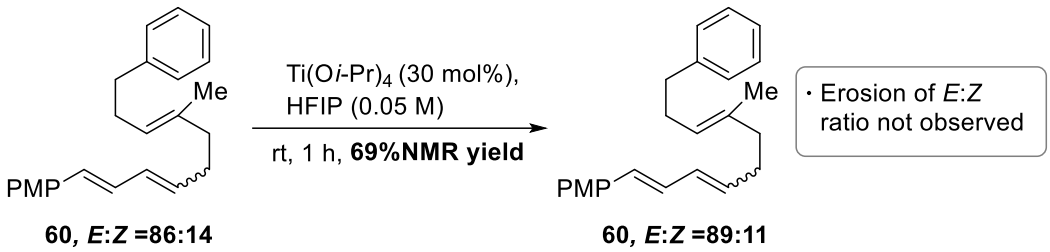
presence of *Z*-**26** (53% NMR yield) together with complex mixture of unidentified decomposition products. No *E*-isomer was detected.

E-**26** stability/interconversion.



Experimental procedure: E-**26** (1.00 equiv) and Ti(O*i*-Pr)$_4$ (0.30 equiv) in HFIP (0.050 M) were subjected to the general procedure **C** but without electrophile present. NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard indicated the presence of *E*-**26** (67% NMR yield) together with complex mixture of unidentified decomposition products. No *Z*-isomer was detected.

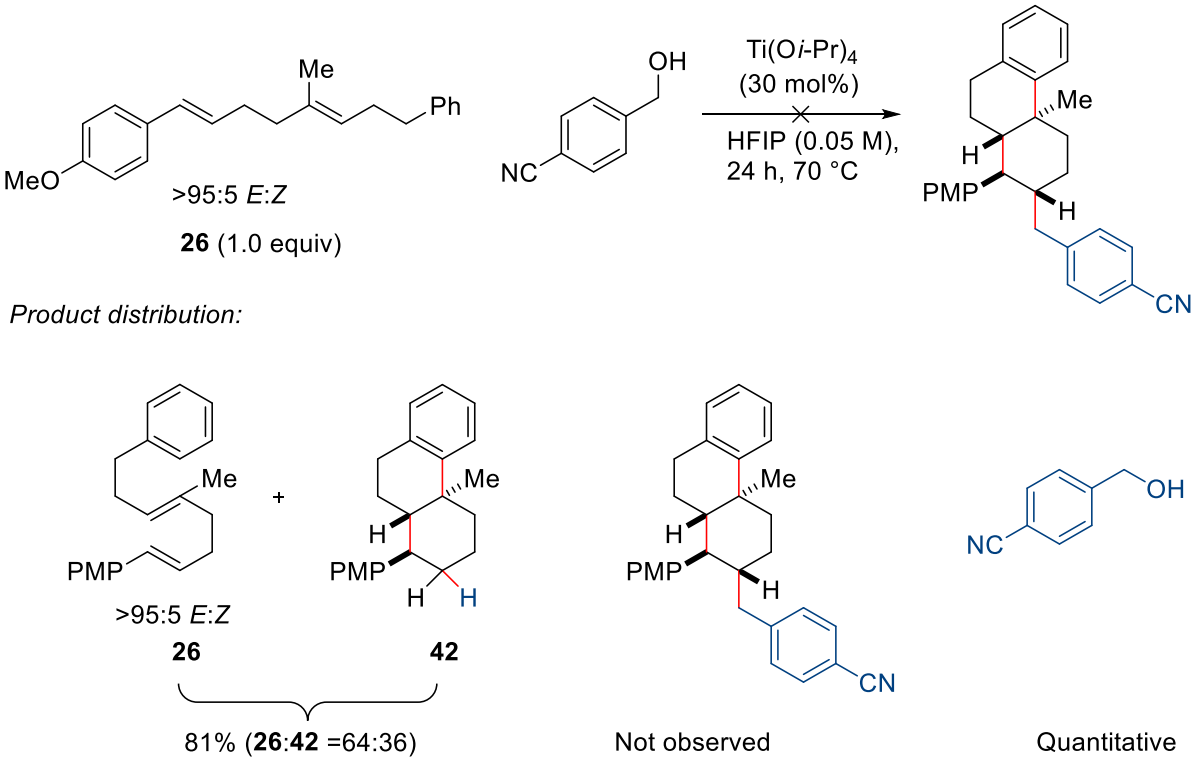
E/Z-**60** stability/interconversion.



Experimental procedure: E/Z-**60** (1.00 equiv, 86:14 *E*/*Z*) and Ti(O*i*-Pr)$_4$ (0.30 equiv) in HFIP (0.050 M) were subjected to the general procedure **D** but without electrophile present. NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard indicated the presence of *E/Z*-**60** (67% NMR yield, 89:11 *E*/*Z*) together with complex mixture of unidentified decomposition products.

Reaction with electron-deficient benzyl alcohol

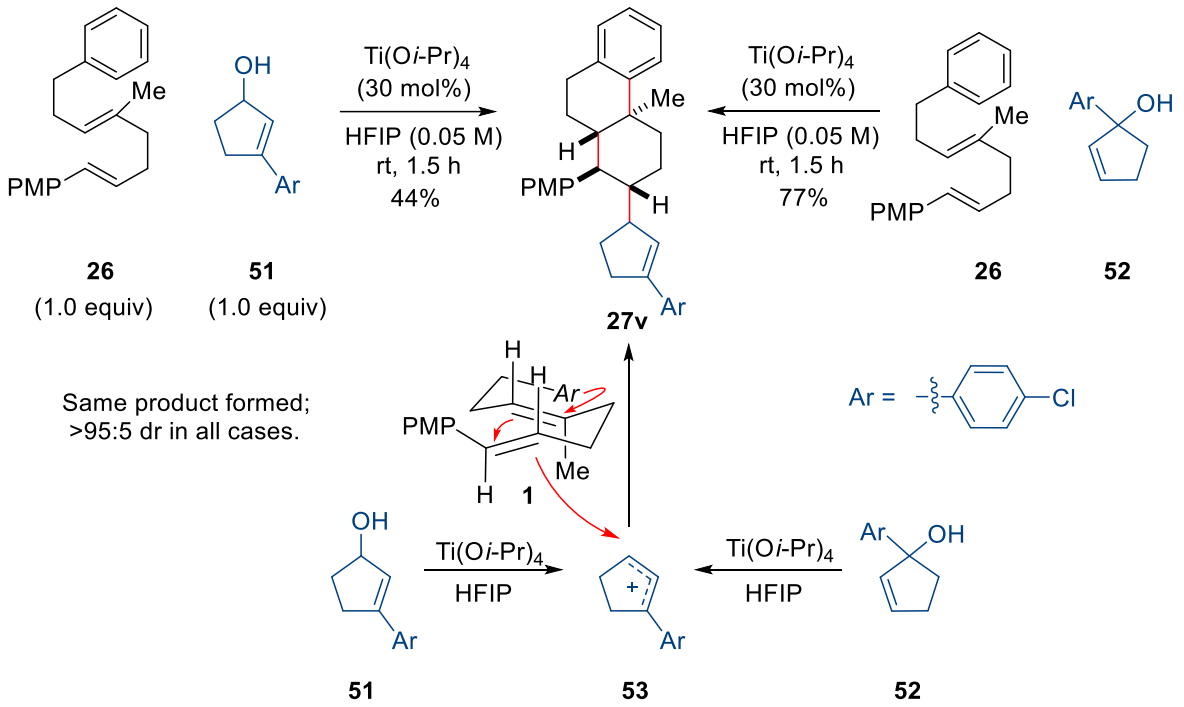
When 4-cyanobenzyl alcohol was used in the reaction, no desired product was isolated or observed. Instead, the alcohol was isolated in quantitative yield after column chromatography together with the mixture of starting material **26** and protonated carbocycle **42**. This is consistent with S_N1 mechanism: 4-cyanobenzyl alcohol does not ionise under the reaction conditions as it cannot form sufficiently stabilised carbocation. Instead, cyclisation proceeds by protonation of a diene **26** catalysed by HFIP solvent.



Experimental procedure: Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), 4-cyanobenzyl alcohol (13.3 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm, pentane:Et_2O; 24:1 to 0:100) to furnish an inseparable mixture of **26** and **42'** (24.9 mg, 81%, **1**:**1'** = 64:36) as a colourless oil and 4-cyanobenzyl alcohol (quant) as a colourless oil.

Reaction with transposed isomers of unsymmetrical allylic alcohol

The use of transposed isomers **52** and **51** of unsymmetrical allylic alcohol furnished the same product **27V** in 77% and 44% yield respectively. This is consistent with S_N1 reaction mechanism: **52** and **51** ionise under the reaction conditions to form the same delocalised carbocation **53** which then initiates polyene cyclisation. The external C-C bond is formed at the least hindered (secondary) end of a delocalised system **53**. This is consistent with our previous observation that a new exocyclic C-C bond could not be formed using tertiary carbocations, possibly due to steric hindrance.

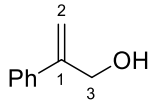


Experimental procedure: Diene **26** (30.6 mg, 0.100 mmol, 1.00 equiv), alcohol **51** or **52** (19.5 mg, 0.100 mmol, 1.00 equiv) and Ti(O*i*-Pr)$_4$ (9.0 µL, 30 µmol, 0.30 equiv) in HFIP (2.0 mL, 0.050 M) were subjected to the general procedure **C** except the reaction was performed at rt and for 1.5 h. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm, pentane:Et_2O; 24:1) to furnish compound **27v** as a single detectable diastereomer as a beige foam (77%, >95:5 d.r. for **52** and 44%, >95:5 d.r. for **51**).[78]

[78] The exocyclic stereochemistry could not be unambiguously determined.

*6.3.3 Experimental procedures for chapter **3***

2-Phenylprop-2-en-1-ol 124.



124
$C_9H_{10}O$
134.18 g mol^{-1}

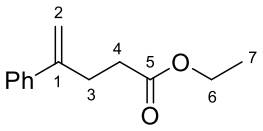
Copper (I) iodide (1.28 g, 6.72 mmol, 0.517 equiv) was suspended in PhMe (16 mL) and cooled to -78 °C. To the solution, propargyl alcohol (0.78 mL, 13 mmol, 1.0 equiv) was added. PhMgBr (40.0 mL, 40.0 mmol, 3.08 equiv, 1.00 M solution in THF) was then added dropwise, and the obtained suspension was allowed to stir at rt for 24 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL), diluted with water (20 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with brine (60 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 3:2) to get 2-phenylprop-2-en-1-ol **124** as a colourless oil (0.966 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H, H-Ar), 7.40 – 7.28 (m, 3H, H-Ar), 5.51 – 5.42 (m, 1H, H-2_a), 5.36 (q, *J* = 1.4 Hz, 1H, H-2_b), 4.56 (t, *J* = 1.1 Hz, 2H, H-3). The OH was not found.

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C-Ar/C-1), 138.6 (C-1/C-Ar), 128.7 (2C, C-Ar), 128.1 (C-Ar), 126.2 (2C, C-Ar), 112.8 (C-2), 65.2 (C-3).

The data are consistent with the literature[79]

Ethyl 4-phenylpent-4-enoate 125.



125
$C_{13}H_{16}O_2$
204.27 g mol^{-1}

[79] L. Koser, V. M. Lechner, T. Bach, *Angew. Chem. Int. Ed*. **2021**, *60*, 20269 –2027.

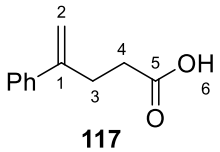
Allylic alcohol **124** (0.857 g, 6.39 mmol, 1.00 equiv) was dissolved in triethyl orthoacetate (6 mL) and to the obtained solution propionic acid (50 µL, 0.67 mmol, 0.10 equiv) was added in one portion. The reaction mixture was stirred at 140 °C overnight, cooled to rt and diluted with Et_2O (10 mL). The mixture was washed with water (20 mL), 2 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2; pentane:Et_2O; 19:1) to furnish ester **125** as a colourless oil (1.09 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 5H, H-Ar), 5.31 – 5.28 (m, 1H, H-2_a), 5.09 (q, *J* = 1.4 Hz, 1H, H-2_b), 4.12 (q, *J* = 7.2 Hz, 2H, H-7), 2.89 – 2.80 (m, 2H, H-3), 2.52 – 2.41 (m, 2H, H-4), 1.24 (t, *J* = 7.2 Hz, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C-5), 147.1 (C-1/C-Ar), 140.8 (C-Ar/C-1), 128.5 (2C, C-Ar), 127.7 (C-Ar), 126.3 (2C, C-Ar), 112.9 (C-2), 60.5 (C-6), 33.4 (C-4), 30.6 (C-3), 14.4 (C-7).

The data are consistent with the literature[80]

4-Phenylpent-4-enoic acid 117.



117

$C_{11}H_{12}O_2$

176.22 g mol^{-1}

LiOH × H_2O (2.24 g, 53.3 mmol, 9.98 equiv) was added in one portion to the solution of ester **125** (1.09 g, 5.34 mmol, 1.00 equiv) in THF/water (42 mL, 1:1). The obtained suspension was stirred at rt overnight and then diluted with Et_2O (20 mL). The aqueous phase was separated, washed with Et_2O (15 mL) and acidified with 3 M aq. HCl (20 mL) to pH=1. The obtained suspension was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to obtain carboxylic acid **117** as a white solid (0.689 g, 73%)

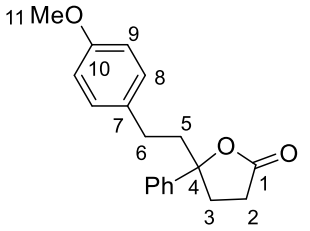
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (br, 1H, H-6), 7.57 – 7.12 (m, 5H, H-Ar), 5.33 (s, 1H, H-2_a), 5.11 (s, 1H, H-2_b), 2.85 (t, *J* = 7.8 Hz, 2H, H-3), 2.54 (dd, *J* = 9.0, 6.6 Hz, 2H, H-4).

[80] C. Jing, B. T. Jones, R. J. Adams, J. F. Bower, *J. Am. Chem. Soc.* **2022**, *144*, 16749–16754.

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9 (C-5), 146.6 (C-Ar/C-1), 140.5 (C-1/C-Ar), 128.6 (2C, C-Ar), 127.8 (C-Ar), 126.1 (2C, C-Ar), 113.1 (C-2), 33.1 (C-4), 30.2 (C-3).

The data are consistent with the literature[81]

5-(4-Methoxyphenethyl)-5-phenyldihydrofuran-2(3H)-one 118a.



118a
$C_{19}H_{20}O_3$
296.37 g mol^{-1}

4-Phenylpent-4-enoic acid **117** (17.6 mg, 0.100 mmol, 1.00 equiv), 4-methoxybenzyl alcohol (13.8 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 µL, 0.030 mmol, 0.30 equiv) in HFIP (2.7 mL) were subjected to general procedure **E**. The crude product was purified by flash column chromatography (SiO2, pentane:Et_2O; 7:3) to obtain lactone **118a** as a pale yellow oil which crystallised on standing (22.4 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.27 (m, 5H, H-Ph), 7.03 – 6.95 (m, 2H, H-8), 6.83 – 6.72 (m, 2H, H-9), 3.76 (s, 3H, H-11), 2.69 – 2.41 (m, 5H, H-2_a, H-2_b, H-3_a, H-3_b, H-6_a), 2.35 – 2.15 (m, 3H, H-5_a, H-5_b, H-6_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7 (C-1), 157.9 (C-10), 142.7 (C-Ph), 133.4 (C-7), 129.2 (2C, C-8), 128.8 (C-Ph), 127.8 (C-Ph), 124.7 (C-Ph), 113.9 (2C, C-9), 89.2 (C-4), 55.4 (C-11), 44.8 (C-5), 35.6 (C-3), 29.4 (C-6), 28.7 (C-2).

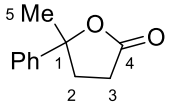
M.p: 70-71 °C.

IR (film) ν_{max}: 2953, 2360, 1780, 1513, 1247, 1179, 1039, 939, 704 cm^{-1}.

HRMS (ESI): calculated for $C_{19}H_{20}O_3Na$ $[M+Na]^+$ requires m/z 319.1305, found m/z 319.1305 (Δ = 0.09 ppm).

[81] D. von der Heiden, F. B. Németh, M. Andreasson, D. Sethio, I. Pápai, M. Erdelyi, *Org. Biomol. Chem*. **2021**, *19*, 8307–8323.

5-Methyl-5-phenyldihydrofuran-2(3H)-one 126.



126

$C_{11}H_{12}O_2$

176.22 g mol^{-1}

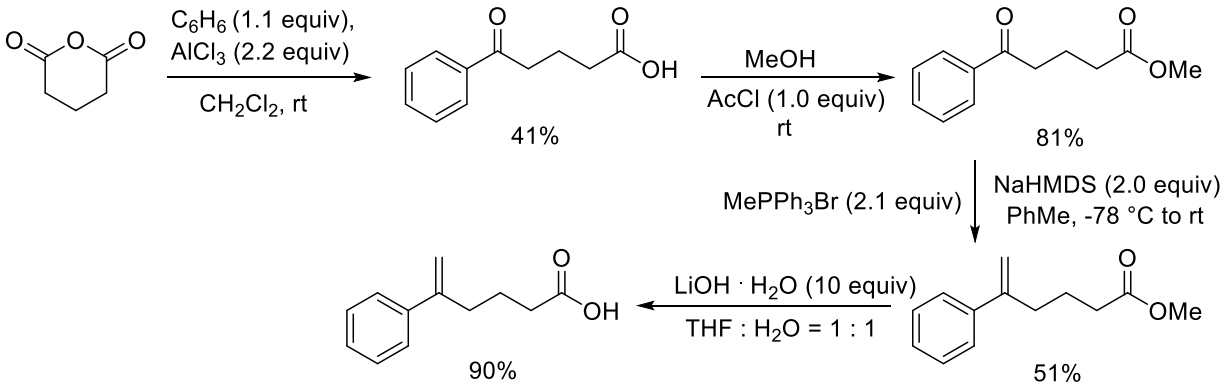
Carboxylic acid **117** (35.2 mg, 0.200 mmol, 1.00 equiv) and *N*, *N*-dimethylmethaniminium iodide (0.148 g, 0.800 mmol, 4.00 equiv) were transferred to a microwave vial which was capped and purged with argon for 15 min. The balloon of argon was removed and HFIP (0.33 mL) was added. The reaction mixture was stirred at rt overnight and then diluted with Et_2O (5 mL). The obtained solution was washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and volatiles were removed *in vacuo* to obtain lactone **126** as a colourless oil which did not require any purification (35.5 mg, quantitative).[82]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H, H-Ph), 2.71 – 2.32 (m, 4H, H-2 and H-3), 1.72 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6 (C-4), 144.4 (C-Ph), 128.7 (2C, C-Ph), 127.8 (C-Ph), 124.2 (2C, C-Ph), 87.1 (C-1), 36.3 (C-2/C-3), 29.6 (C-5), 29.1 (C-3/C-2).

The data are consistent with the literature[83]

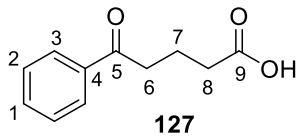
Synthesis and lactonisation reactions of 5-phenylhex-5-enoic acid 130



[82] The desired amine containing product was not observed or isolated.

[83] R. Maji, S. Ghosh, O. Grossmann, P. Zhang, M. Leutzsch, N. Tsuji, B. List, *J. Am. Chem. Soc.* **2023**, *145*, 8788–8793.

5-Oxo-5-phenylpentanoic acid 127.



127

$C_{11}H_{12}O_3$

192.21 g mol^{-1}

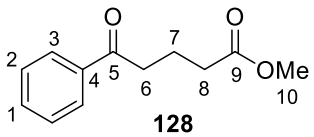
According to the modified literature procedure,[84] benzene (0.86 mL, 9.6 mmol, 1.1 equiv) was added in one portion to a solution of glutaric anhydride (1.00 g, 8.76 mmol, 1.00 equiv) in CH_2Cl_2 (30 mL). To the obtained solution, $AlCl_3$ (2.57 g, 19.3 mmol, 2.20 equiv) was added portion-wise at rt. The obtained suspension was stirred at rt overnight, cooled to 0°C and aq. NaOH (3 M, 20 mL) was slowly added. The organic phase was separated, and the aqueous phase was acidified with aq. HCl (3 M) to ph = 1. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:EtOAc; 1:1 to EtOAc) to furnish carboxylic acid **127** as a pale yellow solid (0.687 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 – 7.91 (m, 2H, H-2/H-3), 7.61 – 7.51 (m, 1H, H-1), 7.51 – 7.40 (m, 2H, H-3/H-2), 3.09 (t, *J* = 7.1 Hz, 2H, H-6/H-8), 2.51 (t, *J* = 7.1 Hz, 2H, H-8/H-6), 2.09 (p, *J* = 7.1 Hz, 2H, H-7). The carboxylic acid proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (C-5), 178.9 (C-9) 136.9 (C-4), 133.3 (C-1), 128.8 (2C, C-3/C-2), 128.2 (2C, C-2/C-3), 37.4 (C-6/C-8), 33.1 (C-8/C-6), 19.1 (C-7).

The analytical data are consistent with those previously reported in the literature.[88]

Methyl 5-oxo-5-phenylpentanoate 128.



128

$C_{12}H_{14}O_3$

206.24 g mol^{-1}

According to the literature procedure,[85] AcCl (74 µL, 1.0 mmol, 1.0 equiv) was added dropwise to the solution of acid **127** (0.20 g, 1.0 mmol, 1.0 equiv) in MeOH (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt overnight and then diluted with CH_2Cl_2 (10 mL). The solution

[84] Y.-Y. Hua, H.-Y Bin, T. Wei, H.-A. Cheng, Z.-P. Lin, X.-F. Fu, Y.-Q. Li, J.-H. Xie, P.-C. Yan, Q.-L. Zhou, *Org. Lett*. **2020**, *22*, 818−822.
[85] A. B. Pulipaka, S. C. Bergmeier, *J. Org. Chem*. **2008**, *73*, 1462–1467.

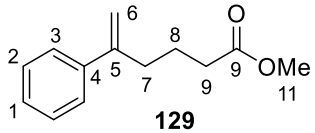
was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), brine (10 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 4:1 to 7:3) to furnish ester **128** as a colourless oil (0.174 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.90 (m, 2H, H-2/H-3), 7.61 – 7.51 (m, 1H, H-1), 7.51 – 7.40 (m, 2H, H-3/H-2), 3.68 (s, 3H, H-10), 3.06 (t, *J* = 7.2 Hz, 2H, H-6/H-8), 2.45 (t, *J* = 7.2 Hz, 2H, H-8/H-6), 2.08 (p, *J* = 7.1 Hz, 2H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (C-5), 173.9 (C-9), 136.9 (C-4), 133.2 (C-1), 128.7 (2C, C-3/C-2), 128.2 (2C, C-2/C-3), 51.7 (C-10), 37.6 (C-6/C-8), 33.3 (C-8/C-6), 19.5 (C-7).

The analytical data are consistent with those previously reported in the literature.[86]

Methyl 5-phenylhex-5-enoate 129.



129

$C_{13}H_{16}O_2$

204.27 g mol^{-1}

According to the literature procedure,[87] to the suspension of $MePPh_3Br$ (0.632 g, 1.77 mmol, 2.10 equiv) in PhMe (7 mL) was added NaHMDS (1.0 M in THF, 1.7 mL, 1.7 mmol, 2.0 equiv) at -78 °C. The resulting mixture was stirred at the same temperature for 30 min. Ester **128** (0.174 g, 0.844 mmol, 1.00 equiv) in toluene (2 mL) was then added dropwise at -78 °C and the obtained suspension was allowed to warm to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and diluted with Et_2O (10 mL). The mixture was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 19:1 to 9:1) to furnish ester **129** as a pale yellow oil (88.5 mg, 51%).

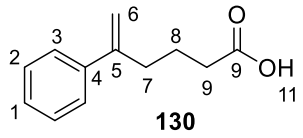
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.23 (m, 5H, H-1, H-2, H-3), 5.30 (d, *J* = 1.4 Hz, 1H, H-6_a), 5.07 (q, *J* = 1.3 Hz, 1H, H-6_b), 3.66 (s, 3H, H-11), 2.55 (td, *J* = 7.5, 1.2 Hz, 2H, H-7/H-9), 2.34 (t, *J* = 7.5 Hz, 2H, H-9/H-7), 1.79 (p, *J* = 7.5 Hz, 2H, H-8).

[86] A. B. Pulipaka, S. C. Bergmeier, *J. Org. Chem*. **2008**, *73*, 1462–1467.
[87] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed*. **2010**, *49*, 9174 –9177.

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1 (C-9), 147.6 (C-4/C-5), 141.0 (C-5/C-4), 128.5 (2C, C-2/C-3), 127.6 (C-1), 126.3 (2C, C-3/C-2), 113.1 (C-6), 51.6 (C-11), 34.7 (C-7/C-9), 33.5 (C-9/C-7), 23.5 (C-8).

The analytical data are consistent with those previously reported in the literature.[88]

5-Phenylhex-5-enoic acid 130.



130

$C_{12}H_{14}O_2$

190.24 g mol^{-1}

According to a modified literature procedure,[89] $LiOH \cdot H_2O$ (0.33 g, 7.9 mmol, 10 equiv) was added in one portion to a solution of ester **129** (0.161 g, 0.788 mmol, 1.00 equiv) in THF:H_2O (6 mL, 1:1) at rt. The suspension was stirred overnight and Et_2O (10 mL) was added. The mixture was washed with water (3 × 10 mL), the aqueous phases were combined, washed with Et_2O (30 mL) and acidified with aq. HCl (3 M) to ph = 1. The aqueous phase was extracted with EtOAc (3 × 40 mL), the organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to give carboxylic acid **130** as white solid which did not require any further purification (0.135 g, 90%).

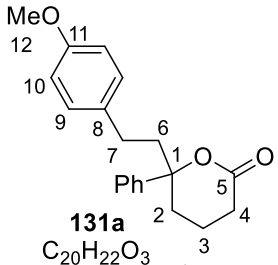
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.20 (m, 5H, H-1, H-2, H-3), 5.31 (d, *J* = 1.4 Hz, 1H, H-6_a), 5.08 (q, *J* = 1.3 Hz, 1H, H-6_b), 2.58 (td, *J* = 7.5, 1.3 Hz, 2H, H-7), 2.38 (t, *J* = 7.4 Hz, 2H, H-9), 1.80 (p, *J* = 7.5 Hz, 2H, H-8). The carboxylic acid proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.3 (C-9), 147.5 (C-4/C-5), 140.9 (C-5/C-4), 128.5 (2C, C-2/C-3), 127.6 (C-1), 126.2 (2C, C-3/C-2), 113.2 (C-6), 34.6 (C-7), 33.3 (C-9), 23.2 (C-8).

The analytical data are consistent with those previously reported in the literature.[90]

[88] X.-G. Liu, C.-J. Zhou, E. Lin, X.-L. Han, S.-S. Zhang, Q. Li, H. Wang, *Angew. Chem. Int. Ed*. **2018**, *57*, 13096–13100.
[89] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed*. **2010**, *49*, 9174 –9177.
[90] L. Song, Y. Zhou, H. Liang, H. Li, Y. Lai, H. Yao, R. Lin, R. Tong, *J. Org. Chem*. **2023**, *88*, 504−512.

6-(4-Methoxyphenethyl)-6-phenyltetrahydro-2H-pyran-2-one 131a.



131a
$C_{20}H_{22}O_3$
310.39 g mol^{-1}

Carboxylic acid **130** (24.2 mg, 0.127 mmol, 1.00 equiv), 4-methoxybenzyl alcohol (17.5 mg, 0.127 mmol, 1.00 equiv) and TFA (2.9 µL, 38 µmol, 0.30 equiv) were subjected to the general procedure **E**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 1:1) to furnish lactone **131a** as a colourless oil (16.5 mg, 42%).

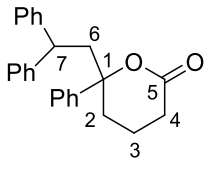
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.25 (m, 5H, H-Ph), 7.08 – 6.95 (m, 2H, H-9), 6.84 – 6.71 (m, 2H, H-10), 3.76 (s, 3H, H-12), 2.79 – 2.67 (m, 1H, H-7$_a$), 2.55 – 2.41 (m, 2H, H-4), 2.37 – 2.11 (m, 4H, H-2$_a$, H-6$_a$, H-6$_b$, H-7$_b$), 2.05 (ddd, *J* = 14.1, 12.2, 4.3 Hz, 1H, H-2$_b$), 1.82 – 1.71 (m, 1H, H-3$_a$), 1.63 – 1.50 (m, 1H, H-3$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C-5), 157.8 (C-11), 142.8 (C-8/C-Ph), 133.7 (C-Ph/C-8), 129.2 (2C, C-9), 128.8 (2C, C-Ph), 127.4 (C-Ph), 125.0 (2C, C-Ph), 113.8 (2C, C-10), 87.4 (C-1), 55.3 (C-12), 46.1 (C-6), 33.3 (C-2), 29.3 (C-4), 28.5 (C-7), 16.3 (C-3).

IR (film) ν_{max}: 2981, 2888, 1732, 1513, 1382, 1245, 1178, 1050, 952, 824, 735, 703 cm^{-1}.

HRMS (ESI): calculated for $C_{20}H_{22}O_3Na$ $[M+Na]^+$ requires m/z 333.1461, found m/z 333.1464 (*Δ* = 0.84 ppm).

6-(2,2-Diphenylethyl)-6-phenyltetrahydro-2H-pyran-2-one 131b.



131b
$C_{25}H_{24}O_2$
356.47 g mol^{-1}

Carboxylic acid **130** (19.1 mg, 0.100 mmol, 1.00 equiv), benzhydrol (18.4 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 µL, 0.030 mmol, 0.30 equiv) were subjected to the general procedure **E**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2) to furnish lactone **131b** as a colourless oil (27.1 mg, 76%).

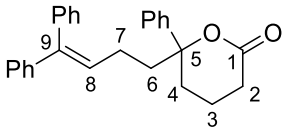
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.00 (m, 15H, H-Ph), 4.14 (t, *J* = 6.5 Hz, 1H, H-7), 2.79 (d, *J* = 6.6 Hz, 2H, H-6), 2.44 – 2.26 (m, 2H, H-4), 2.07 (dt, *J* = 14.3, 4.2 Hz, 1H, H-2_a), 1.82 (ddd, *J* = 14.3, 12.2, 4.5 Hz, 1H, H-2_b), 1.69 – 1.56 (m, 1H, H-3_a), 1.54 – 1.38 (m, 1H, H-3_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C-5), 145.3 (C-Ph), 144.9 (C-Ph), 142.9 (C-Ph), 128.7 (2C, C-Ph), 128.6 (2C, C-Ph), 128.4 (2C, C-Ph), 127.9 (2C, C-Ph), 127.8 (2C, C-Ph), 127.5 (C-Ph), 126.3 (C-Ph), 126.0 (C-Ph), 125.3 (2C, C-Ph), 87.7 (C-1), 49.7 (C-6), 46.6 (C-7), 32.4 (C-2), 29.2 (C-4), 16.4 (C-3).

IR (film) ν_{max}: 2980, 2361, 1733, 1599, 1494, 1449, 1256, 1236, 1047, 912, 735, 701 cm^{-1}.

HRMS (ESI): calculated for $C_{25}H_{25}O_2$ $[M+H]^+$ requires m/z 357.1849, found m/z 357.1849 (*Δ* = -0.03 ppm).

6-(4,4-Diphenylbut-3-en-1-yl)-6-phenyltetrahydro-2H-pyran-2-one 131c.



131c

$C_{27}H_{26}O_2$

382.50 g mol^{-1}

Carboxylic acid **130** (19.1 mg, 0.100 mmol, 1.00 equiv), 1,1-diphenylprop-2-en-1-ol **155** (21.0 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 µL, 0.030 mmol, 0.30 equiv) were subjected to the general procedure **E**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 3:2 to 1:1) to furnish lactone **131c** as a colourless oil (17.7 mg, 46%).

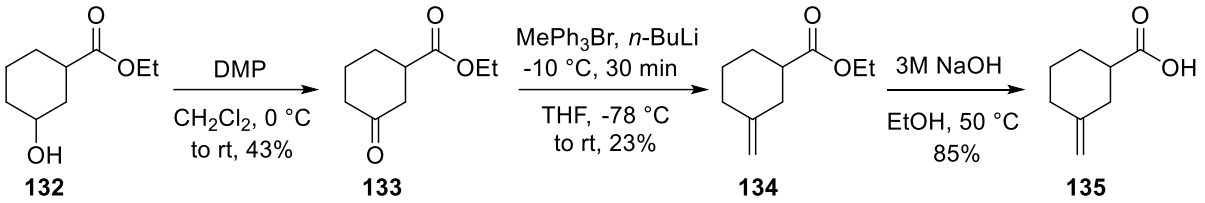
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 6.96 (m, 15H, H-Ph), 5.96 (t, *J* = 7.3 Hz, 1H, H-8), 2.50 – 2.33 (m, 2H, H-2), 2.28 – 2.17 (m, 2H, H-7_a, H-4_a), 2.14 – 1.89 (m, 4H, H-6_a, H-6_b, H-7_b, H-4_b), 1.78 – 1.67 (m, 1H, H-3_a), 1.59 – 1.45 (m, 1H, H-3_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C-1), 142.8 (C-Ph/C-9), 142.7 (C-Ph/C-9), 142.4 (C-Ph/C-9), 139.9 (C-Ph/C-9), 129.8 (2C, C-Ph), 128.7 (2C, C-Ph), 128.7 (C-8), 128.3 (2C, C-Ph), 128.2 (2C, C-Ph), 127.4 (C-Ph), 127.3 (2C, C-Ph), 127.1 (C-Ph), 127.0 (C-Ph), 125.1 (2C, C-Ph), 87.5 (C-5), 43.7 (C-6), 32.7 (C-4), 29.3 (C-2), 23.9 (C-7), 16.4 (C-3).

IR (film) ν_{max}: 3025, 2359, 1735, 1495, 1446, 1241, 1047, 912, 764, 735, 701 cm^{-1}.

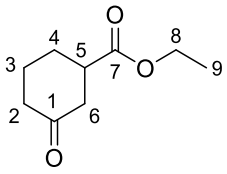
HRMS (ESI): calculated for $C_{27}H_{27}O_2$ $[M+H]^+$ requires m/z 383.2006, found m/z 383.2002 (Δ = -0.94 ppm).

Synthesis of 3-methylenecyclohexane-1-carboxylic acid 135



132 **133** **134** **135**

Ethyl 3-oxocyclohexane-1-carboxylate 133.



133
$C_9H_{14}O_3$
170.21 g mol^{-1}

Ethyl 3-hydroxycyclohexane-1-carboxylate **132** (0.50 g, 0.47 mL, 2.9 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (11 mL) and cooled to 0 °C. To the solution, DMP (2.4 g, 5.7 mmol, 2.0 equiv) was added portionwise and the obtained suspension was allowed to warm to rt overnight. Then sat. aq. $NaHCO_3$ (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo*, and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 7:3 to 3:2) to afford ketone **133** as a colourless oil (0.213 g, 43%).

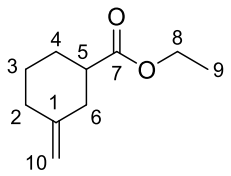
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, *J* = 7.1 Hz, 2H, H-8), 2.84 – 2.72 (m, 1H, H-5), 2.60 – 2.50 (m, 2H, H-6), 2.42 – 2.25 (m, 2H, H-2), 2.16 – 2.01 (m, 2H, H-3_a, H-4_a), 1.90 – 1.65 (m, 2H, H-3_b, H-4_b), 1.26 (t, *J* = 7.1 Hz, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.4 (C-1), 173.8 (C-7), 61.0 (C-8), 43.4 (C-5/C-6), 43.3 (C-6/C-5), 41.1 (C-2), 27.9 (C-4), 24.6 (C-3), 14.3 (C-9).

The analytical data are consistent with those previously reported in the literature.[91]

[91] R. Membrat, A. Vasseur, A. Martinez, L. Giordano, D. Nuel, *Eur. J. Org. Chem.* **2018**, 5427–5434.

Ethyl 3-methylenecyclohexane-1-carboxylate 134.



134
$C_{10}H_{16}O_2$
168.24 g mol^{-1}

n-BuLi (0.80 mL, 2.0 mmol, 1.6 equiv, 2.5 M in hexanes) was added dropwise to a suspension of $MePPh_3Br$ (0.71 g, 2.0 mmol, 1.6 equiv) in THF (5 mL) at -10 °C. The suspension was stirred at the same temperature for 30 min and then cooled to -78 °C. Ketone **133** (0.213 g, 1.25 mmol, 1.00 equiv) in THF (2 mL) was then added dropwise at -78 °C and the suspension was stirred at the same temperature for 10 minutes. The cooling bath was removed, and the mixture was warmed to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (0.5 mL) and then diluted with Et_2O (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo*, and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 49:1 to 7:3) to afford alkene **134** as a colourless oil (48.9 mg, 23%).[92]

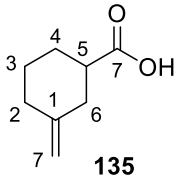
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68 (t, *J* = 1.6 Hz, 2H, H-10), 4.13 (q, *J* = 7.1 Hz, 2H, H-8), 2.49 (ddt, *J* = 12.9, 3.6, 1.7 Hz, 1H, H-6_a), 2.37 (tt, *J* = 11.3, 3.8 Hz, 1H, H-5), 2.30 – 2.16 (m, 2H, H-2_a, H-6_b), 2.05 – 1.92 (m, 2H, H-2_b, H-4_a), 1.91 – 1.80 (m, 1H, H-3_a), 1.63 – 1.49 (m, 1H, H-4_b), 1.44 – 1.29 (m, 1H, H-3_b), 1.25 (t, *J* = 7.1 Hz, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5 (C-7), 147.2 (C-1), 108.8 (C-10), 60.4 (C-8), 44.5 (C-5), 37.4 (C-6), 34.5 (C-2), 28.8 (C-4), 26.7 (C-3), 14.4 (C-9).

The analytical data are consistent with those previously reported in the literature.[93]

[92] Alkene **134** is volatile.
[93] E. W. Della, A. M. Knill, *J. Org. Chem.***1995***, 60,* 3518–3522.

3-Methylenecyclohexane-1-carboxylic acid 135.



135
$C_8H_{12}O_2$
140.18 g mol^{-1}

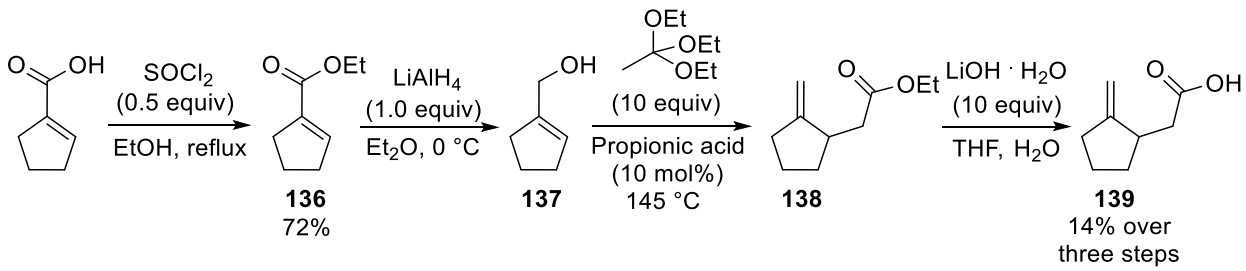
According to a modified literature procedure,[94] ester **134** (43.1 mg, 0.256 mmol, 1.00 equiv) was dissolved in the mixture of EtOH (1mL) and 3 M aq. NaOH (1 mL). The solution was heated at 50 °C for 3 h, cooled to rt and diluted with H_2O (5 mL). The mixture was washed with Et_2O (3 × 5 mL), and the aqueous layer was acidified to pH = 1 with 3 M aq. HCl. The obtained suspension was extracted with EtOAc (3 × 10 mL), the organic layers were combined, washed with brine (20 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to afford carboxylic acid **135** as a yellow oil which did not require any further purification (30.4 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 – 4.65 (m, 2H, H-10), 2.57 – 2.49 (m, 1H, H-6$_a$), 2.43 (tt, *J* = 11.2, 3.8 Hz, 1H, H-5), 2.32 – 2.17 (m, 2H, H-2$_a$, H-6$_b$), 2.07 – 1.95 (m, 2H, H-4$_a$, H-2$_b$), 1.93 – 1.82 (m, 1H, H-3$_a$), 1.67 – 1.51 (m, 1H, H-4$_b$), 1.47 – 1.31 (m, 1H, H-3$_b$). The carboxylic acid proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.3 (C-7), 146.6 (C-1), 109.2 (C-8), 44.1 (C-5), 37.1 (C-6), 34.4 (C-2), 28.6 (C-4), 26.6 (C-3).

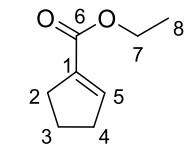
The analytical data are consistent with those previously reported in the literature.[95]

Synthesis of 2-(2-Methylenecyclopentyl)acetic acid 139



[94] Y. Tsuda, A. Ishiura, S. Takamura, S. Hosoi, K. Isobe, K. Mohri, *Chem. Pharm. Bull*. **1991**, *39*, 2797–2802.
[95] N. Pérez-Hernández, M. Febles, C. Pérez, R. Pérez, M. L. Rodríguez, C. Foces-Foces, J. D. Martín, *J. Org. Chem.* **2006***, 71,* 1139–1151.

Ethyl cyclopent-1-ene-1-carboxylate 136.



136
$C_8H_{12}O_2$
140.18 g mol^{-1}

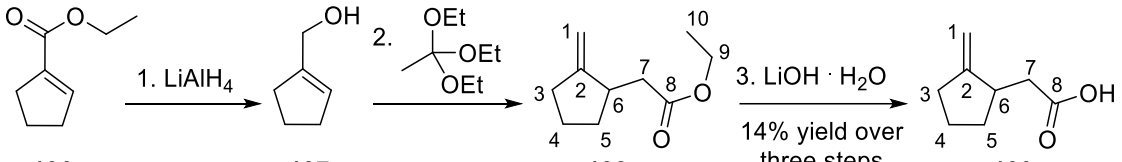
According to the literature procedure,[96] $SOCl_2$ (0.27 mL, 3.7 mmol, 1.0 equiv) was added dropwise to a solution of cyclopent-1-ene-1-carboxylic acid (0.83 g, 7.4 mmol, 1.0 equiv) in EtOH (15 mL) at rt. The reaction mixture was heated under reflux for 4 h and solvent was removed *in vacuo*. The crude product was purified by short path vacuum distillation (b.p. 95 °C/47 mbar) to afford ester **136** as a colourless oil (0.75 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 – 6.74 (m, 1H, H-5), 4.19 (q, *J* = 7.1 Hz, 2H, H-7), 2.60 – 2.45 (m, 4H, H-2, H-4), 2.01 – 1.89 (m, 2H, H-3), 1.29 (t, *J* = 7.1 Hz, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6 (C-6), 143.6 (C-4), 136.9 (C-1), 60.2 (C-7), 33.5 (C-4), 31.5 (C-2), 23.3 (C-3), 14.5 (C-8).

The analytical data are consistent with those previously reported in the literature.[100]

2-(2-Methylenecyclopentyl)acetic acid 139.



136 **137** **138** **139**
$C_8H_{12}O_2$
140.18 g mol^{-1}

$LiAlH_4$ (0.20 g, 5.3 mmol, 0.98 equiv) was added portion-wise to the solution of ester **136** (0.75 g, 5.4 mmol, 1.0 equiv) in Et_2O (40 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h and then quenched by dropwise addition of water (0.2 mL), 15% aq. NaOH (0.2 mL) and water (0.6 mL). The obtained suspension was allowed to warm to rt over 1 h, washed with water (40 mL), brine (40 mL) and the organic phase was dried over Na_2SO_4.

[96] X.-H. Hu, J. Zhang, X.-F. Yang, Y.-H. Xu, T.-P. Loh, *J. Am. Chem. Soc.* **2015**, *137*, 3169–3172.

Volatiles were removed *in vacuo* and the crude alcohol **137** was subjected to the next step without purification (0.525 g).[97,98]

The crude alcohol **137** (0.525 g) was dissolved in triethyl orthoacetate (10 mL) and propionic acid (40 µL, 0.53 mmol) was added. The solution was stirred at 145 °C for 24 h, cooled to rt and then diluted with Et_2O (20 mL). The mixture was washed with water (20 mL), 2 M aq. HCl (2 × 20 mL), brine (20 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to furnish the crude product which was purified by flash column chromatography (SiO_2, pentane:Et_2O; 47:3) to furnish ester **138** as a colourless oil (0.311 g).[99,100]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 – 4.85 (m, 1H, H-1_a), 4.80 – 4.74 (m, 1H, H-1_b), 4.14 (q, *J* = 7.2 Hz, 2H, H-9), 2.85 – 2.70 (m, 1H, H-6), 2.56 (dd, *J* = 15.2, 5.4 Hz, 1H, H-7_a), 2.43 – 2.19 (m, 3H, H-3, H-7_b), 2.06 – 1.91 (m, 1H, H-5_a), 1.79 – 1.65 (m, 1H, H-4_a), 1.65 – 1.50 (m, 1H, H-4_b), 1.39 – 1.23 (m, 4H, H-5_b, H-10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2 (C-8), 155.3 (C-2), 105.0 (C-1), 60.4 (C-9), 40.6 (C-6), 39.4 (C-7), 33.2 (C-3/C-5), 33.0 (C-5/C-3), 24.1 (C-4), 14.4 (C-10).

According to a modified literature procedure,[101] LiOH · H_2O (0.770 g, 18.4 mmol, 9.90 equiv) was added in one portion to a solution of ester **138** (0.311 g, 1.85 mmol, 1.00 equiv) in THF:H_2O (14 mL, 1:1) at rt. The suspension was stirred overnight and Et_2O (20 mL) was added. The mixture was extracted with water (3 × 20 mL), the aqueous phases were combined, washed with Et_2O (50 mL) and acidified with 3 M aq. HCl until pH = 1. The obtained suspension was extracted with EtOAc (3 × 70 mL), the organic layers were combined, washed with brine (200 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to afford carboxylic acid **139** as a colourless solid which did not require any further purification (0.100 g, 14% over three steps).

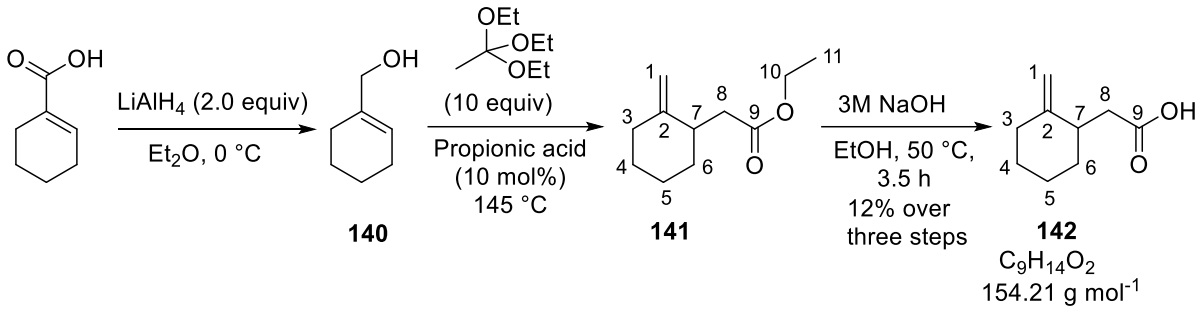
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (q, *J* = 2.3 Hz, 1H, H-1_a), 4.81 (q, *J* = 2.3 Hz, 1H, H-1_b), 2.86 – 2.74 (m, 1H, H-6), 2.63 (dd, *J* = 15.7, 5.3 Hz, 1H, H-7_a), 2.44 – 2.26 (m, 3H, H-3, H-7_b), 2.11 – 1.95 (m, 1H, H-5_a), 1.80 – 1.67 (m, 1H, H-4_a), 1.66 – 1.52 (m, 1H, H-4_b), 1.43 – 1.30 (m, 1H, H-5_b). The carboxylic acid proton was not found.

[97] Y. Xu, Y. J. Hong, D. J. Tantillo, M. Kevin Brown, *Org. Lett*. **2017**, *19*, 3703–3706.
[98] The presence of the product in the crude was confirmed by ^{1}H and ^{13}C NMR data. Due to volatility concern, the crude material was taken to the next step without purification.
[99] R. G. Salomon, S. Ghosh, M.I G. Zagorski, M. Reitz, *J. Org. Chem.* **1982***, 47, 829–836.*
[100] The identity of the product was confirmed by ^{1}H and ^{13}C NMR data. Due to volatility concern, the product was not fully dried and contained residual solvent peaks.
[101] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed*. **2010**, *49*, 9174 –9177.

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.9 (C-8), 155.0 (C-2), 105.3 (C-1), 40.3 (C-6), 39.0 (C-7), 33.2 (C-5), 33.0 (C-3), 24.1 (C-4).

The analytical data are consistent with those previously reported in the literature.[102]

Synthesis of 2-(2-methylenecyclohexyl)acetic acid 142



$LiAlH_4$ (0.38 g, 10 mmol, 1.3 equiv) was suspended in Et_2O (25 mL) and cooled to 0 °C. To the suspension, cyclohex-1-ene-1-carboxylic acid (1.0 g, 7.9 mmol, 1.0 equiv) in Et_2O (20 mL) was added dropwise, and the obtained mixture was stirred at the same temperature for 1 h. The reaction was quenched by sequential dropwise addition of water (0.38 mL), 15% aq. NaOH (0.38 mL) and water (1.1 mL) at 0 °C. The suspension was allowed to warm to rt and diluted with water (40 mL). The organic layer was separated, and the aqueous layer washed with Et_2O (2 × 40 mL). The organic layers wee combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude alcohol **140** was subjected to the next step without purification (0.402 g).[103,104]

The crude alcohol **140** (0.402 g) was dissolved in triethyl orthoacetate (6.5 mL) and propionic acid (26 µL, 0.35 mmol) was added. The solution was stirred at 145 °C for 24 h, cooled to rt and then diluted with Et_2O (15 mL). The mixture was washed with water (15 mL), 2 M aq. HCl (15 mL), brine (15 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 97:3) to furnish ester **141** as a colourless oil (0.233 g).[105,106]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 – 4.61 (m, 1H, H-1$_a$), 4.55 – 4.50 (m, 1H, H-1$_b$), 4.17 – 4.08 (m, 2H, H-10), 2.64 – 2.50 (m, 2H, H-7, H-8$_a$), 2.35 – 2.23 (m, 2H, H-3$_a$, H-8$_b$), 2.10 – 1.98 (m,

[102] K.-T. Yip, D. Yang, *Org. Lett.* **2011***, 13,* 2134–2137.
[103] Y. Xu, Y. J. Hong, D. J. Tantillo, M. Kevin Brown, *Org. Lett*. **2017**, *19*, 3703–3706.
[104] The presence of the product in the crude was confirmed by ^{1}H and ^{13}C NMR data. Due to volatility concern, the crude material was taken to the next step without purification.
[105] W.-H. Chiou, Y.-W. Wang, C.-L. Kao, P.-C. Chen, C.-C. Wu, *Organometallics* **2014***, 33,* 4240–4244.
[106] The identity of the product was confirmed by ^{1}H and ^{13}C NMR data. Due to volatility concern, the product was not fully dried and contained residual solvent peaks.

1H, H-3_b), 1.83 – 1.63 (m, 3H, H-4_a, H-5_a, H-6_a), 1.54 – 1.35 (m, 2H, H-4_b, H-5_b), 1.28 – 1.17 (m, 4H, H-11, H-6_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2 (C-9), 151.7 (C-2), 105.4 (C-1), 60.4 (C-10), 40.0 (C-7), 38.2 (C-8), 35.7 (C-3), 34.2 (C-6), 28.6 (C-4), 25.2 (C-5), 14.4 (C-11).

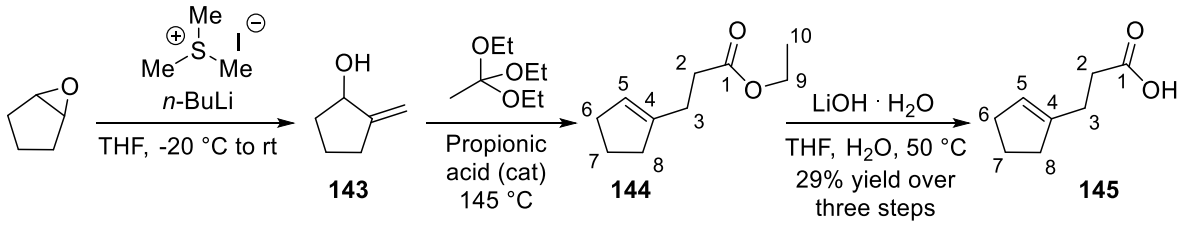
According to a modified literature procedure,[107] ester **141** (0.233 g) was dissolved in a mixture of EtOH (5 mL) and 3 M aq. NaOH (5 mL). The solution was heated at 50 °C for 3.5 h, cooled to rt and diluted with H_2O (10 mL). The mixture was washed with Et_2O (3 × 10 mL), and the aqueous layer was acidified to pH = 1 with 3 M aq. HCl. The obtained suspension was extracted with EtOAc (3 × 25 mL), the organic layers were combined, washed with brine (70 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to afford carboxylic acid **142** as a colourless oil which did not require any further purification (0.1474 g, 12% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (s, 1H, H-1_a), 4.55 (s, 1H, H-1_a), 2.71 – 2.61 (m, 1H, H-8_a), 2.60 – 2.50 (m, 1H, H-7), 2.42 – 2.23 (m, 2H, H-3_a, H-8_b), 2.13 – 1.98 (m, 1H, H-3_b), 1.91 – 1.78 (m, 1H, H-6_a), 1.78 – 1.65 (m, 2H, H-4_a, H-5_a), 1.57 – 1.32 (m, 2H, H-4_b, H-5_b), 1.29 – 1.13 (m, 1H, H-6_b). The carboxylic acid proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.4 (C-2), 105.6 (C-1), 39.7 (C-7), 37.9 (C-8), 35.8 (C-3), 34.2 (C-6), 28.6 (C-4), 25.2 (C-5).[108]

The analytical data are consistent with those previously reported in the literature.[109]

Synthesis of 3-(cyclopent-1-en-1-yl)propanoic acid 145



According to a literature procedure,[110] trimethylsulfonium iodide (6.0 g, 0.029 mol, 3.9 equiv) was dissolved in THF (37 mL) and cooled to -20 °C. *n*-BuLi (9.7 mL, 0.024 mol, 3.2 equiv) was added dropwise at the same temperature, and the solution was stirred for 30 min. 6-

[107] Y. Tsuda, A. Ishiura, S. Takamura, S. Hosoi, K. Isobe, K. Mohri, *Chem. Pharm. Bull*. **1991**, *39*, 2797–2802.
[108] Note: ^{13}C NMR signal for a carboxylic acid functional group (C-9) is missing.
[109] K.-T. Yip, D. Yang, *Org. Lett.* **2011***, 13,* 2134–2137.
[110] R. Kato, H. Saito, S. Uda, D. Domon, K. Ikeuchi, T. Suzuki, K. Tanino, *Org. Lett*. **2021**, *23*, 8878–8882.

Oxabicyclo[3.1.0]hexane (0.62 g, 7.4 mmol, 1.0 equiv) in THF (6 mL) was then added, and the reaction mixture was warmed to rt over 1 h and then stirred for additional 2 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and then diluted with Et_2O (40 mL). The mixture was washed with H_2O (40 mL), 1 M aq. NaOH (40 mL), brine (40 mL), and the organic phase was dried over Na_2SO_4. Volatiles were removed *in vacuo* to obtain crude allylic alcohol **143** which was used in the next step without purification (0.7325 g).[111,112]

The crude alcohol **143** (0.70 g) was dissolved in triethyl orthoacetate (9 mL) and propionic acid (54 µL, 0.72 mmol) was added. The solution was stirred at 145 °C for 24 h, cooled to rt and then diluted with Et_2O (25 mL). The mixture was washed with water (25 mL), 2 M aq. HCl (25 mL), brine (25 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 49:1) to furnish ester **144** as a colourless oil (0.527 g).[113,114]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 – 5.29 (m, 1H, H-5), 4.13 (q, *J* = 7.2 Hz, 2H, H-9), 2.50 – 2.43 (m, 2H, H-2), 2.42 – 2.34 (m, 2H, H-3), 2.33 – 2.19 (m, 4H, H-6, H-8), 1.93 – 1.79 (m, 2H, H-7), 1.25 (t, *J* = 7.1 Hz, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6 (C-1), 143.1 (C-4), 124.0 (C-5), 60.4 (C-9), 35.3 (C-6/C-8), 33.0 (C-2), 32.6 (C-8/C-6), 26.6 (C-3), 23.5 (C-7), 14.4 (C-10).

According to a modified literature procedure,[115] LiOH (0.375 g, 15.7 mmol, 5.02 equiv) was added in one portion to the solution of ester **144** (0.527 g, 3.13 mmol, 1.00 equiv) in THF:H_2O (10.6 mL, 1:1) at rt. The suspension was stirred at 50 °C overnight and then cooled to rt. Et_2O (20 mL) was added. The mixture was extracted with water (3 × 20 mL), the aqueous phases were combined, washed with Et_2O (50 mL) and acidified with 3 M aq. HCl until pH = 1. The obtained suspension was extracted with EtOAc (3 × 50 mL), the organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* to afford carboxylic acid **145** as a colourless oil which did not require any further purification (0.301 g, 29% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 – 5.33 (m, 1H, H-5), 2.59 – 2.47 (m, 2H, H-2), 2.44 – 2.35 (m, 2H, H-3), 2.34 – 2.20 (m, 4H, H-6, H-8), 1.86 (m, 2H, H-7).

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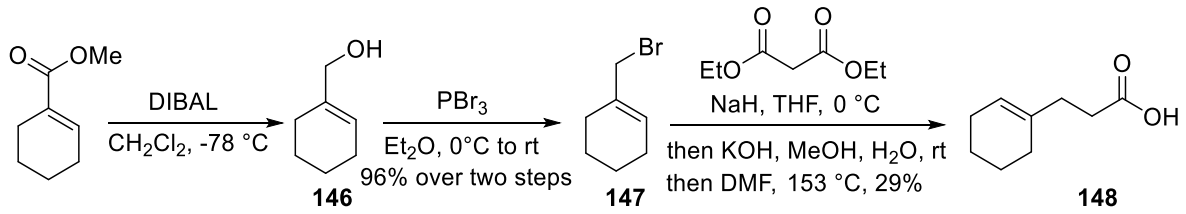
[111] The presence of the product in the crude was confirmed by ^{1}H and ^{13}C NMR data. Due to volatility concern, the crude material was taken to the next step without purification.
[112] L. Alcaraz, A. Cridland, E. Kinchin, *Org. Lett.* **2001**, *3*, 4051–4053.
[113] The identity of the product was confirmed by ^{1}H and ^{13}C NMR data. Due to volatility concern, the product was not fully dried and contained residual solvent peaks.
[114] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed*. **2010**, *49*, 9174–9177.
[115] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed*. **2010**, *49*, 9174–9177.

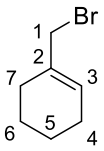
^{13}C NMR (101 MHz, $CDCl_3$): δ 179.4 (C-1), 142.8 (C-4), 124.3 (C-5), 35.3 (C-8), 32.66 (C-2/C-6), 32.61 (C-6/C-2), 26.2 (C-3), 23.5 (C-7).

The analytical data are consistent with those previously reported in the literature.[116]

Synthesis of 3-(cyclohex-1-en-1-yl)propanoic acid 148



1-(Bromomethyl)cyclohex-1-ene 147.



147
$C_7H_{11}Br$
175.07 g mol^{-1}

Methyl cyclohex-1-ene-1-carboxylate (2.0 g, 14 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78 °C. DIBAL-H (31 mL, 31 mmol, 2.2 equiv, 1.0 M in CH_2Cl_2) was then added dropwise, and the obtained solution was stirred at the same temperature for 3.5 h. The mixture was quenched by dropwise addition of MeOH (25 mL) at -78 °C, warmed to 0 °C and sat. aq. Rochelle salt (25 mL) was added. The obtained mixture was allowed to warm to rt overnight and was then diluted with water (40 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The organic layers were combined, washed with brine (100 mL) and then dried over Na_2SO_4. The solvent was carefully removed *in vacuo* and crude allylic alcohol **146** was subjected to the next step without purification (1.59 g).[117]

Crude allylic alcohol **146** (1.59 g) was dissolved in Et_2O (70 mL) and cooled to 0 °C. PBr_3 (0.67 mL, 7.1 mmol, 0.51 equiv) was added dropwise at the same temperature, and the reaction mixture was allowed to warm to rt over 3 h. The solution was poured onto sat. aq. Na_2CO_3 (30 mL), and the organic layer was separated. The aqueous layer was extracted with

[116] Q. Liu, E. M. Ferreira, B. M. Stoltz, *J. Org. Chem*. **2007**, *72*, 7352–7358.
[117] Due to volatility concern, the product from this step was not purified by chromatography.

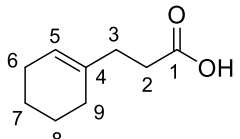
Et_2O (2 × 30 mL), the organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. The solvent was carefully removed *in vacuo* to obtain bromide **147** as a colourless oil which did not require purification (2.35 g, 96% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 – 5.82 (m, 1H, H-3), 3.94 (s, 2H, H-1), 2.17 – 2.08 (m, 2H, H-7), 2.08 – 1.99 (m, 2H, H-4), 1.72 – 1.50 (m, 4H, H-6, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.8 (C-2), 128.3 (C-3), 40.0 (C-1), 26.5 (C-7), 25.6 (C-4), 22.5 (C-6), 22.0 (C-5).

The analytical data are consistent with those previously reported in the literature.[118]

3-(Cyclohex-1-en-1-yl)propanoic acid 148.



148
$C_9H_{14}O_2$
154.21 g mol^{-1}

According to a modified literature procedure,[121] to a suspension of NaH (0.536 g, 13.4 mmol, 2.00 equiv, 60% weight in mineral oil) in THF (40 mL) at 0 °C was added diethyl malonate (2.0 mL, 13 mmol, 2.0 equiv) dropwise. The reaction mixture was stirred at 0 °C for 1 hour before dropwise addition of bromide **147** (0.91 mL, 1.2 g, 6.7 mmol, 1.0 equiv). The reaction mixture was warmed to room temperature and monitored by TLC. Upon completion, the reaction mixture was poured into a solution of KOH (4.5 g, 80 mmol, 12 equiv) in water:MeOH (20 mL, 1:1) and stirred for 40 minutes at rt. The reaction mixture was acidified with 10 M aq. HCl to pH = 1, concentrated to an aqueous solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and volatiles were removed *in vacuo*. The obtained crude mixture of malonic acids was dissolved in DMF (14 mL) and heated at reflux for 3 h. Solvent was removed *in vacuo* and the crude product was redissolved in THF (10 mL). 3M aq. NaOH (10 mL) was added, and the solution was stirred for 10 min at rt. The mixture was washed with Et_2O (3 × 10 ml), and the aqueous phase was then acidified with 3M aq. HCl to pH = 1. The mixture was extracted with EtOAc (3 × 15 mL), the organic layers were combined, washed with brine (40 mL) and dried over Na_2SO_4. Volatiles were removed *in*

[118] I. R. Hazelden, R. C. Carmona, T. Langer, P. G. Pringle, J. F. Bower, *Angew. Chem. Int. Ed.* **2018**, *57*, 5124–5128.

vacuo, and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 3:2) to afford carboxylic acid **148** as a colourless oil (0.2971 g, 29%).

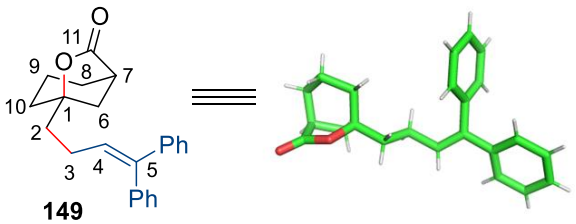
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 – 5.40 (m, 1H, H-5), 2.46 (dd, *J* = 8.8, 6.7 Hz, 2H, H-2), 2.32 – 2.20 (m, 2H, H-3), 2.03 – 1.87 (m, 4H, H-6, H-9), 1.69 – 1.48 (m, 4H, H-7, H-8). The carboxylic acid proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.7 (C-1), 135.9 (C-4), 121.9 (C-5), 32.76 (C-2/C-3), 32.68 (C-3/C-2), 28.4 (C-9), 25.3 (C-6), 23.0 (C-8), 22.5 (C-7).

The analytical data are consistent with those previously reported in the literature.[121]

The cation-triggered lactonisation of aliphatic substrates

(±)-(1*R*,5*R*)-5-(4,4-Diphenylbut-3-en-1-yl)-6-oxabicyclo[3.2.1]octan-7-one 149.



149

$C_{23}H_{24}O_2$

332.44 g mol^{-1}

[X-ray]

Carboxylic acid **135** (29.0 mg, 0.207 mmol, 1.00 equiv), 1,1-diphenylprop-2-en-1-ol **155** (43.5 mg, 0.207 mmol, 1.00 equiv) and TFA (4.8 µL, 0.062 mmol, 0.30 equiv) were subjected to the general procedure **E**, except the reaction was performed in a round bottomed flask, instead of a microwave vial. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 7:3) to furnish lactone **149** as a colourless oil (31.7 mg, 46%).

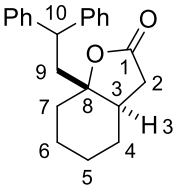
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.11 (m, 10H, H-Ph), 6.06 (t, *J* = 7.4 Hz, 1H, H-4), 2.74 – 2.65 (m, 1H, H-7), 2.28 – 2.15 (m, 2H, H-3), 2.11 – 2.02 (m, 1H, H-6$_a$), 1.94 – 1.56 (m, 7H, H-2$_a$, H-2$_b$, H-6$_b$, H-8$_a$, H-9$_a$, H-9$_b$, H-10$_a$), 1.55 – 1.40 (m, 2H, H-8$_b$, H-10$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.5 (C-11), 142.5 (2C, C-5, C-Ph), 140.0 (C-Ph), 129.8 (2C, C-Ph), 128.5 (C-4), 128.4 (2C, C-Ph), 128.2 (2C, C-Ph), 127.3 (2C, C-Ph), 127.3 (C-Ph), 127.1 (C-Ph), 86.9 (C-1), 41.3 (C-7/C-6), 41.2 (C-6/C-7), 38.9 (C-2), 32.5 (C-10), 26.3 (C-8), 24.0 (C-3), 19.4 (C-9).

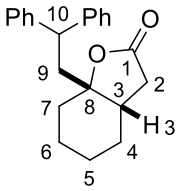
IR (film) ν_{max}: 2944, 2874, 1773, 1494, 1444, 1286, 1134, 917, 765, 733, 701 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{25}O_2$ $[M+H]^+$ requires m/z 333.1849, found m/z 333.1857 (Δ = 2.37 ppm).

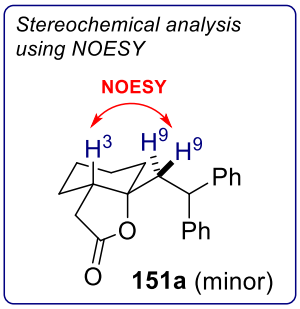
(±)-(3*aR*,7*aR*)-7*a*-(2,2-Diphenylethyl)hexahydrobenzofuran-2(3H)-one 151a-major and (±)-(3*aS*,7*aR*)-7*a*-(2,2-diphenylethyl)hexahydrobenzofuran-2(3H)-one 151a-minor.



Major-151a
$C_{22}H_{24}O_2$
320.43 g mol^{-1}



Minor-151a
$C_{22}H_{24}O_2$
320.43 g mol^{-1}



Carboxylic acid **142** (30.8 mg, 0.200 mmol, 1.00 equiv), benzhydrol (36.8 mg, 0.200 mmol, 1.00 equiv) and TFA (4.6 µL, 0.060 mmol, 0.30 equiv) were subjected to the general procedure **E**, except that the rection was performed at 0 °C. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish lactone **151a** as an inseparable mixture of diastereomers as a colourless oil (45.6 mg, 71%, 70:30 dr).[119]

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.43 – 6.98 (m, 10H$_{maj}$, 10H$_{min}$, H-Ph$_{maj}$, H-Ph$_{min}$), 4.34 – 4.22 (m, 1H$_{maj}$, 1H$_{min}$, H-10$_{maj}$, H-10$_{min}$), 2.72 (dd, *J* = 14.6, 8.9 Hz, 1H$_{maj}$, H-9$_{a,\ maj}$), 2.61 – 2.51 (m, 2H$_{min}$, H-9$_{min}$) 2.47 – 2.32 (m, 2H$_{maj}$, 2H$_{min}$, H-2$_{maj}$, H-2$_{min}$), 2.26 – 2.19 (m, 1H$_{min}$, H-3$_{min}$), 2.13 – 2.05 (m, 2H$_{maj}$, H-9$_{b,\ maj}$, H-3$_{maj}$), 1.82 – 1.72 (m, 3H$_{maj}$, H-4$_{a,\ maj}$, H-5$_{a,\ maj}$, H-7$_{a,\ maj}$), 1.71 – 1.64 (m, 1H$_{min}$, H-7$_{a,\ min}$) 1.55 – 1.18 (m, 5H$_{maj}$, 7H$_{min}$, H-6$_{a,\ maj}$, H-6$_{b,\ maj}$, H-4$_{b,\ maj}$, H-5$_{b,\ maj}$, H-7$_{b,\ maj}$, H-5$_{a,\ min}$, H-5$_{b,\ min}$, H-4$_{a,\ min}$, H-4$_{b,\ min}$, H-6$_{a,\ min}$, H-6$_{b,\ min}$, H-7$_{b,\ min}$).

^{13}C NMR (176 MHz, $CDCl_3$) **for the major diastereomer** (from the mixture): δ 176.3 (C-1), 145.9 (C-Ph), 144.8 (C-Ph), 128.8 (2C, C-Ph), 128.8 (2C, C-Ph), 128.2 (2C, C-Ph), 127.6 (2C, C-Ph), 126.6 (C-Ph), 126.3 (C-Ph), 87.6 (C-8), 48.8 (C-3), 46.5 (C-10), 35.3 (C-9), 33.6 (C-7), 33.2 (C-2), 25.4 (C-4), 24.3 (C-5), 22.5 (C-6). **Selected peaks for the minor diastereomer** (from the mixture): δ 176.7 (C-1), 145.4 (C-Ph), 145.2 (C-Ph), 128.8 (2C, C-Ph), 128.8 (2C, C-Ph), 127.9 (2C, C-Ph), 127.7 (2C, C-Ph), 126.50 (C-Ph), 126.48 (C-Ph), 87.4 (C-8), 46.8 (C-10), 43.2 (C-9), 38.7 (C-3), 34.5 (C-2), 25.8 (C-4), 21.8 (C-6), 20.6 (C-5).

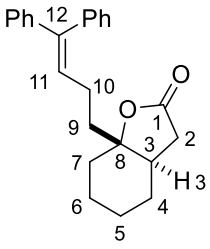
NOESY-2D (700 MHz, $CDCl_3$): between H-3$_{min}$ and H-9$_{min}$.

IR (film) ν_{max}: 2981, 2884, 1776, 1494, 1452, 1382, 1202, 1146, 966, 910, 734, 704 cm^{-1}.

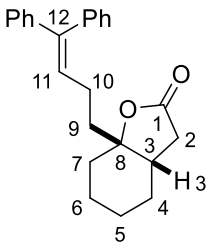
[119] dr was calculated after column chromatography.

HRMS (ESI): calculated for $C_{22}H_{24}O_2Na$ $[M+Na]^+$ requires m/z 343.1669, found m/z 343.1683 (Δ = 4.21 ppm).

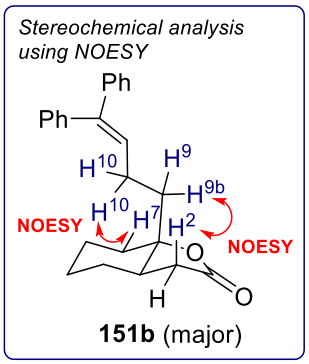
(±)-(3*aR*,7*aR*)-7*a*-(4,4-Diphenylbut-3-en-1-yl)hexahydrobenzofuran-2(3H)-one 151b-major and (±)-(3*aS*,7*aR*)-7a-(4,4-diphenylbut-3-en-1-yl)hexahydrobenzofuran-2(3H)-one 151b-minor.



Major-151b
$C_{24}H_{26}O_2$
346.47 g mol^{-1}



Minor-151b
$C_{24}H_{26}O_2$
346.47 g mol^{-1}



Carboxylic acid **142** (15.4 mg, 0.100 mmol, 1.00 equiv), 1,1-diphenylprop-2-en-1-ol **155** (21.0 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 µL, 0.030 mmol, 0.30 equiv) were subjected to the general procedure **E**, except that the rection was performed at 0 °C. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; pentane:Et_2O; 7:3) to furnish lactone **151b** as an inseparable mixture of diastereomers as a colourless oil (22.3 mg, 64%, 70:30 dr).[120] Analytical amount of the major diastereomer was separated to assist the data analysis.

Data for major diastereomer 151b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.05 (m, 10H, H-Ph), 6.08 (dd, *J* = 8.1, 7.0 Hz, 1H, H-11), 2.42 – 2.32 (m, 2H, H-2), 2.29 – 1.97 (m, 4H, H-10$_a$, H-10$_b$, H-3, H-7$_a$), 1.92 – 1.64 (m, 4H, H-9$_a$, H-4$_a$, H-5$_a$, H-6$_a$), 1.56 – 1.20 (m, 5H, H-4$_b$, H-5$_b$, H-6$_b$, H-7$_b$, H-9$_b$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (C-1), 142.8 (C-Ph/C-12), 142.5 (C-Ph/C-12), 139.9 (C-Ph/C-12), 129.8 (2C, C-Ph), 128.6 (C-11), 128.4 (2C, C-Ph), 128.3 (2C, C-Ph), 127.3 (3C, C-Ph), 127.1 (C-Ph), 87.3 (C-8), 47.8 (C-3), 33.3 (C-2/C-7), 33.2 (C-7/C-2), 29.5 (C-9), 25.4 (C-5), 24.6 (C-4), 23.3 (C-10), 22.6 (C-6).

NOESY-2D (600 MHz, $CDCl_3$) δ between H-2 and H-9$_b$, between H-7$_a$ and H-10.

IR (film) ν_{max}: 2981, 1778, 1657, 1383, 1072, 966, 909, 732, 703 cm^{-1}.

[120] dr was determined of the crude reaction mixture (700 MHz, THF-d8).

HRMS (ESI): calculated for $C_{24}H_{26}O_2Na$ $[M+Na]^+$ requires m/z 369.1825, found m/z 369.1826 (Δ = 0.26 ppm).

Selected peaks for the minor diastereomer (from the mixture):

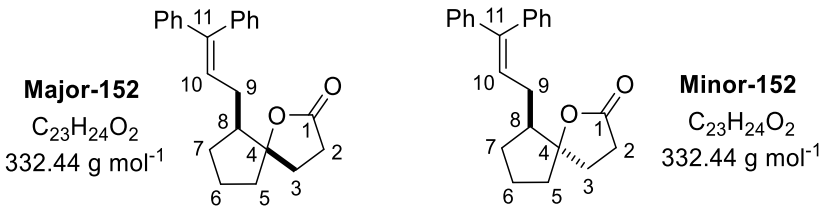
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (t, *J* = 7.4 Hz, 1H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7 (C-1), 142.6 (C-12/C-Ph), 140.0 (C-12/C-Ph), 129.8 (C-Ph), 128.5 (C-11), 86.8 (C-8), 38.6 (C-3), 37.6, 34.8, 32.2, 26.2, 24.1, 21.8, 20.9.[121]

IR (film) ν_{max}: 2980, 2884, 1778, 1444, 1382, 1146, 1073, 966, 905, 764, 733, 701 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{26}O_2Na$ $[M+Na]^+$ requires m/z 369.1825, found m/z 369.1841 (Δ = 4.32 ppm).

(±)-(5*S*,6*S*)-6-(3,3-Diphenylallyl)-1-oxaspiro[4.4]nonan-2-one 152-major and (±)-(5*R*,6*S*)-6-(3,3-diphenylallyl)-1-oxaspiro[4.4]nonan-2-one 152-minor.



Carboxylic acid **145** (14.0 mg, 0.100 mmol, 1.00 equiv), 1,1-diphenylprop-2-en-1-ol **155** (21.0 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 µL, 0.030 mmol, 0.30 equiv) were subjected to the general procedure **E**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 µm; PhMe:Et_2O; 47:3) to furnish lactone **152** as an inseparable mixture of diastereomers as a colourless oil (12.6 mg, 38%, 75:25 dr).[122]

Major diastereomer 152 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.10 (m, 10H, H-Ph), 6.04 (dd, *J* = 8.1, 6.2 Hz, 1H, H-10), 2.61 – 2.36 (m, 2H, H-2), 2.33 – 2.17 (m, 2H, H-8, H-9_a), 2.14 – 1.89 (m, 4H, H-7_a, H-3_a, H-9_b, H-6_a), 1.88 – 1.69 (m, 2H, H-3_b, H-5_a), 1.69 – 1.51 (m, 2H, H-5_b, H-6_b), 1.50 – 1.37 (m, 1H, H-7_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7 (C-1), 143.1 (C-Ph/11), 142.5 (C-Ph/C-11), 140.0 (C-Ph/C-11), 129.9 (2C, C-Ph), 128.4 (2C, C-Ph), 128.3 (2C, C-Ph), 127.32 (3C, 2×C-Ph, C-

[121] $\underline{C}H_2$ carbons for the minor diastereomer could not be unambiguously assigned from the mixture.
[122] Relative stereochemistry of the major diastereomer assigned in analogy to lactone **153**.

Ph/C-10), 127.28 (C-10/C-Ph), 127.2 (C-10/C-Ph), 96.2 (C-4), 47.6 (C-8), 37.2 (C-6), 30.5 (C-9), 29.6 (C-2), 28.9 (C-7), 28.0 (C-3), 20.5 (C-5).

Characteristic peaks for minor diastereomer 152 (from the mixture):

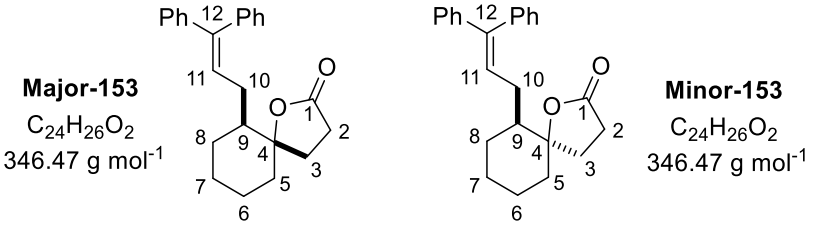
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dd, *J* = 8.0, 7.1 Hz, 1H, H-10)

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9 (C-1), 142.9 (C-Ph/C-11), 139.9 (C-Ph/C-11), 129.9 (C-Ph), 128.3 (C-Ph), 127.8 (C-Ph/C-10), 127.1 (C-Ph/C-10), 95.2 (C-4), 49.7 (C-8), 39.3 (C-6), 30.14 (C-2/C-3/C-7/C-9), 30.09 (C-2/C-3/C-7/C-9), 29.5 (C-2/C-3/C-7/C-9), 28.7 (C-2/C-3/C-7/C-9), 21.4 (C-5).

IR (film) ν_{max}: 2980, 2362, 1771, 1444, 1382, 1243, 1152, 1074, 949, 914, 771, 702 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{24}O_2Na$ $[M+Na]^+$ requires m/z 355.1669, found m/z 355.1676 (*Δ* = 2.10 ppm).

(±)-(5*S*,6*S*)-6-(3,3-Diphenylallyl)-1-oxaspiro[4.5]decan-2-one 153-major and (±)-(5*R*,6*S*)-6-(3,3-diphenylallyl)-1-oxaspiro[4.5]decan-2-one 153-minor .



Carboxylic acid **148** (30.0 mg, 0.195 mmol, 1.00 equiv), 1,1-diphenylprop-2-en-1-ol **155** (40.9 mg, 0.195 mmol, 1.00 equiv) and TFA (4.5 µL, 0.059 mmol, 0.30 equiv) were subjected to the general procedure **E**. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3 to 3:2) to furnish lactone **153** as an inseparable mixture of diastereomers as a colourless oil (50.8 mg, 75%, 71:29 dr).[123, 124]

Major diastereomer 153 (from the mixture):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.08 (m, 10H, H-Ph), 6.05 (dd, *J* = 8.0, 6.0 Hz, 1H, H-11), 2.64 – 2.47 (m, 1H, H-2_a), 2.45 – 2.26 (m, 2H, H-2_b, H-10_a), 2.09 – 1.43 (m, 9H, H-3_a, H-3_b, H-5_a, H-6_a, H-6_b, H-7_a, H-8_a, H-9, H-10_b), 1.39 – 1.23 (m, 2H, H-5_b, H-7_b), 1.07 (dtd, *J* = 14.6, 10.8, 4.0 Hz, 1H, H-8_b).

[123] dr was calculated after column chromatography.
[124] Relative stereochemistry of the major diastereomer assigned based on aldehyde **166**.

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7 (C-1), 143.0(C-Ph/C-12), 142.5 (C-Ph/C-12), 140.0 (C-Ph/C-12), 129.9 (2C, C-Ph), 128.3 (2C, C-Ph), 128.2 (2C, C-Ph), 127.7 (C-11), 127.3 (2C, C-Ph), 127.13 (C-Ph), 127.09 (C-Ph), 89.3 (C-4), 45.6 (C-9), 37.1 (C-6), 29.3 (C-10), 29.0 (C-2), 28.2 (C-8), 26.5 (C-3), 24.1 (C-5/C-7), 23.1 (C-7/C-5).

Characteristic peaks for minor diastereomer 153 (from the mixture):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (dd, *J* = 8.1, 6.9 Hz, 1H, H-11).

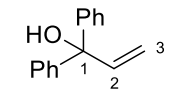
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0 (C-1), 143.1 (C-Ph/C-12), 142.5 (C-Ph/C-12), 139.9 (C-Ph/C-12), 129.8 (C-Ph), 128.4 (C-Ph), 127.7 (C-11), 127.2 (C-Ph), 88.0 (C-4), 45.9 (C-9), 38.1 (C-6), 31.4 (C-3), 29.1 (C-2/10), 28.8 (C-10/C-2), 27.8 (C-5/C-7/C-8), 22.4 (C-5/C-7/C-8).

IR (film) ν_{max}: 2981, 1769, 1494, 1446, 1382, 1148, 1131, 966, 952, 912, 762, 733, 702 cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{27}O_2$ $[M+H]^+$ requires m/z 347.2006, found m/z 347.2003 (*Δ* = -0.75 ppm).

Mechanistic experiments

1,1-Diphenylprop-2-en-1-ol 155.



155

$C_{15}H_{14}O$

210.28 g mol^{-1}

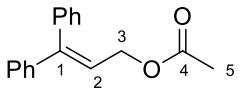
Benzophenone (0.300 g, 1.65 mmol, 1.00 equiv) was dissolved in THF (10 mL) and cooled to 0 °C. Vinyl magnesium bromide (1.0 M in THF, 1.8 mL, 1.8 mmol, 1.1 equiv) was added dropwise at the same temperature and the obtained solution was allowed to slowly warm to rt overnight. Additional vinyl magnesium bromide (1.0 M in THF, 1.0 mL, 1.0 mmol, 0.61 equiv) was then added and the solution was stirred at rt for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl (2 mL) and diluted with Et_2O (10 mL) and water (10 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (40 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 19:1 to 9:1) to obtain alcohol **155** as a colourless oil (0.202 g, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.19 (m, 10H, H-Ph), 6.58 – 6.45 (m, 1H, H-2), 5.41 – 5.27 (m, 2H, H-3). The OH proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (2C, C-Ph), 143.6 (C-2), 128.3 (4C, C-Ph), 127.4 (2C, C-Ph), 127.0 (4C, C-Ph), 114.2 (C-3), 79.5 (C-1).

The data are consistent with the literature[125]

1,1-Diphenylprop-2-en-1-ol 190.



190

$C_{17}H_{16}O_2$

252.31 g mol^{-1}

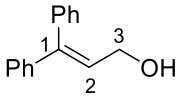
1,1-Diphenylprop-2-en-1-ol **155** (0.165 g, 0.787 mmol, 1.00 equiv) was dissolved in HFIP (8 mL) and KOAc (0.386 g, 3.94 mmol, 5.01 equiv) followed by AcOH (1.6 mL) were added in one portion at rt. The reaction mixture was heated at 50 °C for 4 h, cooled to rt and quenched with H_2O (8 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL), the organic layers were combined, washed with brine and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 47:3 to 9:1) to obtain acetate **190** as a colourless oil (0.146 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.08 (m, 10H, H-Ph), 6.18 (t, *J* = 7.1 Hz, 1H, H-2), 4.64 (d, *J* = 7.1 Hz, 2H, H-3), 2.08 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C-4), 146.5 (C-Ph/C-1), 141.6 (C-Ph/C-1), 138.8 (C-Ph/C-1), 129.8 (2C, C-Ph), 128.5 (2C, C-Ph), 128.3 (2C, C-Ph), 128.0 (C-Ph), 127.9 (C-Ph), 127.8 (2C, C-Ph), 122.5 (C-2), 62.8 (C-3), 21.2 (C-5).

The data are consistent with the literature[126]

3,3-Diphenylprop-2-en-1-ol 154.



154

$C_{15}H_{14}O$

210.28 g mol^{-1}

[125] A. Boelke, B. J. Nachtsheim, *Adv. Synth. Catal.* **2020**, *362*, 184–191.
[126] Z. Zhang, C. Li, S. H. Wang, F. M. Zhang, X. Han, Y. Q. Tu, X. M. Zhang, *Org. Biomol. Chem*. **2017**, *15*, 3239–3247.

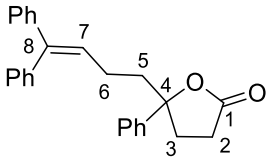
According to the modified literature procedure,[127] acetate **190** (0.116 g, 0.460 mmol, 1.00 equiv) was dissolved in MeOH (4.7 mL) and to the obtained solution K_2CO_3 (0.32 g, 2.3 mmol, 5.0 equiv) was added in one portion. The solution was stirred at rt overnight and then diluted with Et_2O (5 mL) and H_2O (5 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic layers were combined, washed with brine (20 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 7:3) to furnish alcohol **154** as a colourless solid (89.4 mg, 92%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.04 (m, 10H, H-Ph), 6.24 (t, *J* = 6.8 Hz, 1H, H-2), 4.21 (dd, *J* = 6.8, 5.5 Hz, 2H, H-3), 1.46 – 1.34 (m, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.4 (C-Ph/C-1), 141.9 (C-Ph/C-1), 139.2 (C-Ph/C-1), 129.9 (2C, C-Ph), 128.4 (2C, C-Ph), 128.3 (2C, C-Ph), 127.8 (3C, C-Ph), 127.7 (C-Ph/C-2), 127.6 (C-2/C-Ph), 60.9 (C-3).

The analytical data are consistent with those previously reported in the literature.[128]

5-(4,4-diphenylbut-3-en-1-yl)-5-phenyldihydrofuran-2(3H)-one 118g



118g

$C_{26}H_{24}O_2$

368.48 g mol^{-1}

Carboxylic acid **117** (15.4 mg, 0.100 mmol, 1.00 equiv), tertiary alcohol **155** or primary alcohol **154** (21.0 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 µL, 0.030 mmol, 0.30 equiv) were subjected to the general procedure **E.** The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2) to furnish lactone **118g** as a colourless oil (33.4 mg, 91% with **154** and 73% with **155**).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.12 (m, 13H, H-Ph), 7.11 – 6.98 (m, 2H, H-Ph), 5.97 (t, *J* = 7.3 Hz, 1H, H-7), 2.60 – 2.27 (m, 4H, H-2_a, H-2_b, H-3_a, H-3_b), 2.24 – 2.03 (m, 3H, H-5_a, H5_b, H-6_a), 2.03 – 1.92 (m, 1H, H-6_b).

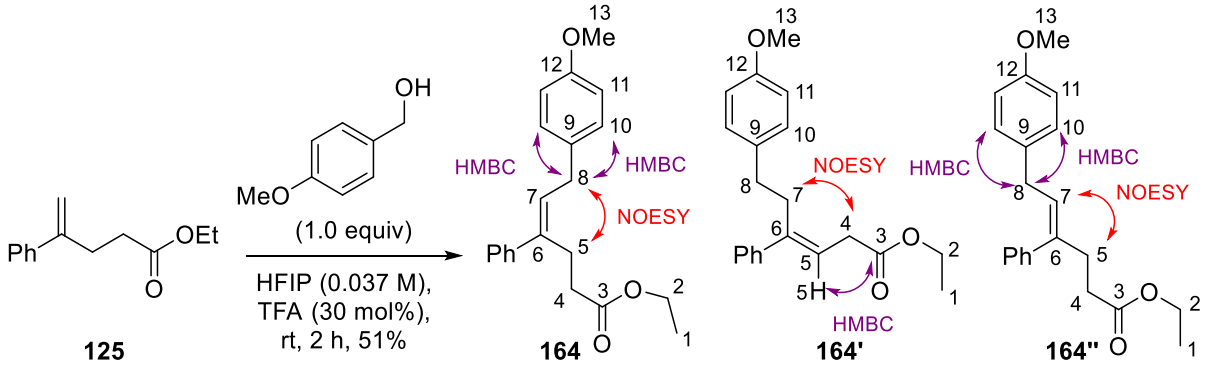
[127] Y. Ishizuka, H. Fujimori, T. Noguchi, M. Kawasaki, M. Kishida, T. Nagai, N. Imai, M. Kirihara, *Chem. Lett*. **2013**, *42*, 1311–1313.
[128] J. Li, C. Tan, J. Gong, Z. Yang, *Org. Lett*. **2014**, *16*, 5370–5373.

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.5 (C-1), 142.51 (C-Ph or C-8), 142.49 (C-Ph or C-8), 142.47 (C-Ph or C-8), 139.7 (C-Ph or C-8), 129.7 (2C, C-Ph), 128.6 (2C, C-Ph), 128.3 (2C, C-Ph), 128.16 (2C, C-Ph) 128.15 (C-7), 127.7 (C-Ph), 127.3 (2C, C-Ph), 127.1 (C-Ph), 127.1 (C-Ph), 124.7 (2C, C-Ph), 89.2 (C-4), 42.3 (C-5), 35.0 (C-3), 28.7 (C-2), 24.5 (C-6).

IR (film) ν_{max}: 2980, 2360, 1777, 1193, 916, 763, 701 cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{25}O_2$ $[M+H]^+$ requires m/z 369.1849, found m/z 369.1858 (Δ = 2.41 ppm).

Control experiment using ester 125



164 : **164'** : **164"** = 58 : 33 : 9

Ester **125** (20.4 mg, 0.100 mmol, 1.00 equiv), 4-methoxybenzyl alcohol (13.8 mg, 0.100 mmol, 1.00 equiv) and TFA (2.3 μL, 0.030 mmol, 0.30 equiv) were subjected to the general procedure **E**. The crude product was purified by flash column chromatography (SiO_2; 60 Å, 15–40 μm; pentane:Et_2O; 9:1 to 17:3) to furnish inseparable mixture of esters **164**, **164'** and **164"** as a colourless oil (16.7 mg, 51%, **164**:**164'**:**164"** = 58:33:9).

Characteristic peaks for major ester 164 (from the mixture):

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 – 7.14 (m, 2H, H-10), 6.88 – 6.84 (m, 2H, H-11), 5.89 – 5.84 (m, 1H, H-7), 4.09 (q, *J* = 7.2 Hz, 2H, H-2), 3.80 (s, 3H, H-13), 3.54 (d, *J* = 7.4 Hz, 2H, H-8), 2.98 – 2.92 (m, 2H, H-5), 2.40 – 2.33 (m, 2H, H-4), 1.22 (t, *J* = 7.2 Hz, 3H, H-1).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2 (C-3), 158.1 (C-12), 139.0 (C-6), 129.4 (2C, C-10), 128.9 (C-7), 114.1 (2C, C-11), 60.5 (C-2), 55.4 (C-13), 33.9 (C-8), 33.5 (C-4), 25.3 (C-5), 14.3 (C-1).

NOESY-2D (600 MHz, $CDCl_3$): between H-8 and H-5.

HMBC-2D (600 MHz -151 MHz, $CDCl_3$): between C-10 and H-8.

Characteristic peaks for ester 164' (from the mixture):

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 – 7.05 (m, 2H, H-10), 6.83 – 6.79 (m, 2H, H-11), 5.89 – 5.84 (m, 1H, H-5), 4.14 (q, *J* = 7.2 Hz, 2H, H-2), 3.79 (s, 3H, H-13), 3.05 (d, *J* = 7.2 Hz, 2H, H-4), 2.78 (dd, *J* = 9.0, 6.7 Hz, 2H, H-7), 2.59 (dd, *J* = 8.9, 6.7 Hz, 2H, H-8), 1.27 (t, *J* = 7.2 Hz, 3H, H-1).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.9 (C-3), 158.0 (C-12), 129.5 (2C, C-10), 120.7 (C-5), 113.9 (2C, C-11), 60.8 (C-2), 55.4 (C-13), 34.3 (C-4), 33.7 (C-8), 32.6 (C-7).

NOESY-2D (600 MHz, $CDCl_3$): between H-7 and H-4.

HMBC-2D (600 MHz -151 MHz, $CDCl_3$): between C-3 and H-5.

Characteristic peaks for ester 164" (from the mixture):

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 – 7.02 (m, 2H, H-10), 5.70 – 5.64 (m, 1H, H-7), 3.78 (s, 3H, H-13), 3.21 (d, *J* = 7.5 Hz, 2H, H-8), 2.74 – 2.69 (m, 2H, H-5).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0 (C-12), 129.3 (2C, C-10), 126.9 (C-7), 114.0 (2C, C-11), 34.7 (C-5), 34.3 (C-8).

NOESY-2D (600 MHz, $CDCl_3$): between H-7 and H-5.

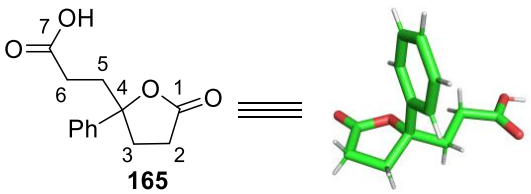
HMBC-2D (600 MHz -151 MHz, $CDCl_3$): between C-10 and H-8.

IR (film) ν_{max}: 2981, 2890, 1733, 1512, 1374, 1246, 1176, 1155, 1036, 826, 766, 700 cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{25}O_3$ $[M+H]^+$ requires m/z 325.1798, found m/z 325.1808 (Δ = 3.00 ppm).

Derivatisations

3-(5-Oxo-2-phenyltetrahydrofuran-2-yl)propanoic acid 165.



165

$C_{13}H_{14}O_4$

234.25 g mol^{-1}

[X-ray]

Lactone **118a** (19.0 mg, 64.1 μmol, 1.00 equiv) was dissolved in CCl_4:CH_3CN:pH 7 buffer (2:2:3; 0.7 mL) and cooled to 0 °C. $NaIO_4$ (271 mg, 1.27 mmol, 19.8 equiv) was added in one

portion and the obtained suspension was cooled to 0 °C and stirred at the same temperature for 15 min. $RuCl_3$ (0.6 mg, 3 µmol, 0.05 equiv) was added at 0 °C in one portion and the reaction mixture was allowed to slowly warm to rt overnight. Then water (3 mL) and Et_2O (3 mL) were added. The organic layer was separated and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; EtOAc to EtOAc:MeOH; 9:1) to furnish carboxylic acid **165** as a pale yellow oil (4.0 mg, 27%).

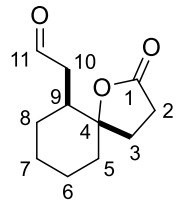
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H, H-Ph), 2.69 – 2.55 (m, 1H, H-2_a), 2.55 – 2.39 (m, 4H, H-2_b, H-3_a, H-3_b, H-5_a), 2.31 (t, *J* = 7.8 Hz, 2H, H-6), 2.09 (dt, *J* = 15.8, 7.1 Hz, 1H, H-5_b). The carboxylic acid proton was not found.

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3 (C-7), 176.3 (C-1), 141.8 (C-Ph), 128.9 (2C, C-Ph), 128.1 (C-Ph), 124.7 (2C, C-Ph), 88.3 (C-4), 36.9 (C-6), 35.8 (C-3), 29.0 (C-5), 28.6 (C-2).

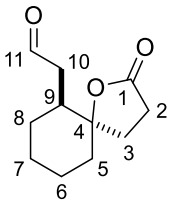
IR (film) ν_{max}: 2918, 2362, 1780, 1714, 1198, 1056, 943, 913, 769, 737, 705, 640, 630 cm^{-1}.

HRMS (ESI): calculated for $C_{13}H_{13}O_4$ $[M-H]^-$ requires m/z 233.0819, found m/z 233.0828 (Δ = 3.73 ppm).

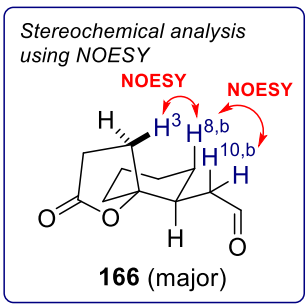
(±)-2-((5*S*,6*S*)-2-oxo-1-oxaspiro[4.5]decan-6-yl)acetaldehyde 166-major and (±)-2-((5*R*,6*S*)-2-oxo-1-oxaspiro[4.5]decan-6-yl)acetaldehyde 166-minor.



Major-166
$C_{11}H_{16}O_3$
196.25 g mol^{-1}



Minor-166
$C_{11}H_{16}O_3$
196.25 g mol^{-1}



Lactone **153** (45.3 mg, 0.230 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (25 mL) and cooled to -78 °C. O_3/O_2 was bubbled through the solution until blue colour was observed and then left for an additional 2 min. O_2 was then bubbled through the solution until the blue colour was no longer seen, followed by N_2 for an additional 15 min. The reaction was then quenched by dropwise addition of DMS (4.5 mL) at -78 °C. The mixture was stirred at the same temperature for 30 min and then slowly warmed to rt overnight. The solution was washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O;

1:1) to obtain aldehyde **166** as an inseparable mixture of diastereomers as a colourless oil (16.1 mg, 63%, 74:26 dr).[129]

Major diastereomer 166 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 – 9.66 (m, 1H, H-11), 2.69 – 2.47 (m, 3H, H-2_a, H-2_b, H-10_a), 2.46 – 2.33 (m, 1H, H-9), 2.28 – 2.16 (m, 1H, H-10_b), 2.03 – 1.94 (m, 2H, H-3), 1.85 – 1.47 (m, 5H, H-8_a, H-5_a, H-5_b, H-7_a, H-6_a), 1.45 – 1.29 (m, 2H, H-7_b, H-6_b), 1.11 (dtd, *J* = 15.0, 11.2, 3.8 Hz, 1H, H-8_b).

^{13}C NMR (151 MHz, $CDCl_3$) δ 200.8 (C-11), 176.2 (C-1), 88.1 (C-4), 44.2 (C-10), 39.4 (C-9), 37.1 (C-5), 29.1 (C-8), 28.7 (C-2), 26.0 (C-3), 24.3 (C-7), 23.2 (C-6).

NOESY-2D (600 MHz, $CDCl_3$): between H-8_b and H-3, between H-8_b and H-10_b.

Characteristic peaks for minor diastereomer 166 (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 – 9.76 (m, 1H, H-11), 2.16 – 2.06 (m, 1H, H-3_a), 1.94 – 1.86 (m, 1H, H-5_a).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.1 (C-11), 176.5 (C-1), 87.2 (C-4), 38.3 (C-9), 36.8 (C-5), 31.4 (C-3), 28.9 (C-8), 28.7 (C-2), 22.2 (C-6).

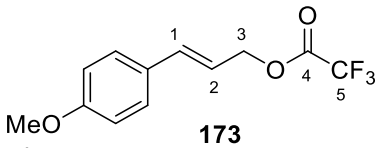
IR (film) ν_{max}: 2981, 1771, 1722, 1453, 1383, 1205, 1150, 956, 913 cm^{-1}.

HRMS (ESI): calculated for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ requires m/z 219.0992, found m/z 219.1000 (Δ = 3.79 ppm).

*6.3.4 Experimental procedures for chapter **4***

Enantioselective polyene cyclisation

(*E*)-3-(4-methoxyphenyl)allyl 2,2,2-trifluoroacetate 173.



173

$C_{12}H_{11}F_3O_3$

260.21 g mol^{-1}

[129] dr was calculated after column chromatography.

trans-4-Methoxycinnamyl alcohol (0.20 g, 1.2 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Pyridine (0.30 mL, 3.7 mmol, 3.1 equiv) followed by TFAA (0.26 mL, 1.8 mmol, 1.5 equiv) were added dropwise at the same temperature and the reaction mixture was stirred at the same temperature until judged to be complete by TLC analysis. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:2) to furnish trifluoroacetate **173** as a colourless oil (0.143 g, 46%).[130]

^{1}H NMR (400 MHz, C_6D_6) δ 7.05 – 6.96 (m, 2H, H-Ar), 6.73 – 6.63 (m, 2H, H-Ar), 6.24 (d, *J* = 15.8 Hz, 1H, H-1), 5.70 (dt, *J* = 15.8, 7.0 Hz, 1H, H-2), 4.32 (dd, *J* = 7.0, 1.1 Hz, 2H, H-3), 3.25 (s, 3H, H-6).

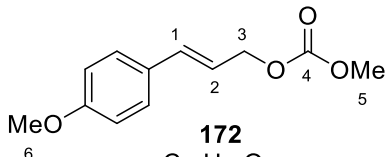
^{13}C NMR (101 MHz, C_6D_6) δ 160.6 (C-Ar), 137.0 (C-1), 128.6 (2C, C-Ar), 117.8 (C-2), 114.4 (2C, C-Ar), 69.0 (C-3), 54.8 (C-6). Note: C-4 and C-5 not observed due to the strong coupling with ^{19}F.

^{19}F NMR (377 MHz, C_6D_6) δ -74.9 (3F, CF_3).

IR (film) ν_{max}: 3001, 2838, 1788, 1609, 1515, 1255, 1226, 1176, 1036, 971, 917, 732 cm^{-1}.

HRMS (ESI): calculated for $C_{10}H_{11}O$ $[M\text{-}CO_2CF_3]^+$ requires m/z 147.0804, found m/z 147.0807 (*Δ* = 1.73 ppm).

(*E*)-3-(4-Methoxyphenyl)allyl methyl carbonate 172.



172
$C_{12}H_{14}O_4$
222.24 g mol^{-1}

trans-4-Methoxycinnamyl alcohol (0.20 g, 1.2 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Pyridine (0.30 mL, 3.7 mmol, 3.1 equiv) was added and the solution was stirred at the same temperature for 15 min. Then methyl chloroformate (0.20 mL, 2.4 mmol, 2.0 equiv) was added dropwise and the reaction mixture was allowed to warm to rt overnight. The solution was quenched with sat. aq. NH_4Cl (2 mL), diluted with water (8 mL) and CH_2Cl_2 (5 mL). The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine (30 mL) and dried over

[130] (*E*)-3-(4-methoxyphenyl)allyl 2,2,2-trifluoroacetate **173** was found to be unstable on silica and so the exposure to silica should be minimised during column chromatography.

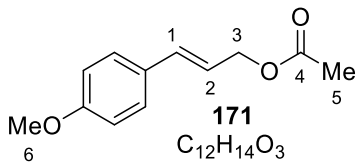
Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 7:3) to furnish carbonate **172** as a white solid (0.264 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H, H-Ar), 6.89 – 6.81 (m, 2H, H-Ar), 6.67 – 6.59 (dt, *J* = 15.9, 1.4 Hz, 1H, H-1), 6.16 (dt, *J* = 15.8, 6.7 Hz, 1H, H-2), 4.77 (dd, *J* = 6.7, 1.3 Hz, 2H, H-3), 3.84 – 3.78 (m, 6H, H-5 and H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C-4), 155.8 (C-Ar), 134.8 (C-1), 128.9 (C-Ar), 128.1 (2C, C-Ar), 120.2 (C-2), 114.1 (2C, C-Ar), 68.9 (C-3), 55.4 (C-5/C-6), 55.0 (C-6/C-5).

The data are consistent with the literature[131]

(*E*)-3-(4-methoxyphenyl)allyl acetate 171.



171

$C_{12}H_{14}O_3$

206.24 g mol^{-1}

trans-4-Methoxycinnamyl alcohol (0.32 g, 2.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and pyridine (0.24 mL, 3.0 mmol, 1.5 equiv) was added in one portion. Then acetyl chloride (0.21 mL, 3.0 mmol, 1.5 equiv) was added dropwise and the obtained solution was stirred at rt overnight. Water (20 mL) was added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2; pentane:Et_2O; 4:1) to obtain ester **171** as a colourless oil (0.382 g, 94%).

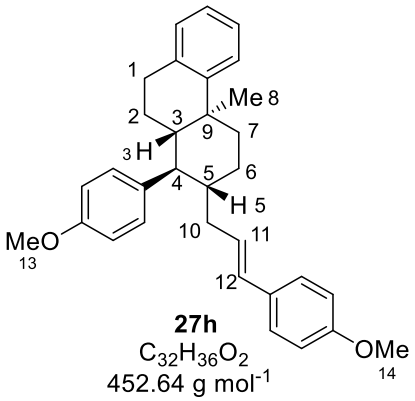
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H, H-Ar), 6.90 – 6.81 (m, 2H, H-Ar), 6.60 (dt, *J* = 15.9, 1.2 Hz, 1H, H-1), 6.15 (dt, *J* = 15.8, 6.7 Hz, 1H, H-2), 4.70 (dd, *J* = 6.6, 1.2 Hz, 2H, H-3), 3.81 (s, 3H, H-6), 2.09 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C-4), 159.7 (C-Ar), 134.2 (C-1), 129.1 (C-Ar), 128.0 (2C, C-Ar), 120.9 (C-2), 114.1 (2C, C-Ar), 65.5 (C-3), 55.4 (C-6), 21.2 (C-5).

The data are consistent with the literature[132]

[131] M. Ohkoshi, J. Michinishi, S. Hara, H. Senboku, *Tetrahedron* **2010**, *66*, 7732–7737.
[132] T. Katsina, S. P. Sharma, R. Buccafusca, D. J. Quinn, T. S. Moody, S. Arseniyadis, *Org. Lett.* **2019***, 21,* 9348–9352.

(1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-2-((*E*)-3-(4-methoxyphenyl)allyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27h.



27h
$C_{32}H_{36}O_2$
452.64 g mol^{-1}

Alkene **26** (20 mg, 65 µmol, 1.0 equiv), acetate **174** (13.4 mg, 65.0 µmol, 1.00 equiv), $[Ir(cod)Cl]_2$ (3.2 mg, 4.8 µmol, 0.074 equiv, 7.4 mol%) and (*S*)-**L1** Carreira ligand[133] (7.6 mg, 15 µmol, 0.23 equiv, 23 mol%) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.26 mL, 0.25 M) followed by TFA (2.5 µL, 33 µmol, 0.50 equiv) were added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 5 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 24:1) to furnish alkene **27h** together with an inseparable mixture of impurities as a colourless oil (8.5 mg, 29%).[134] An analytical sample in sufficient purity was isolated and subjected to chiral HPLC analysis (35:65 er).[135]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.8, 1.4 Hz, 1H, H-Ar), 7.24 (d, *J* = 8.7 Hz, 2H, H-Ar), 7.18 – 6.99 (m, 5H, H-Ar), 6.97 – 6.89 (m, 1H, H-Ar), 6.87 – 6.77 (m, 3H, H-Ar), 6.17 (d, *J* = 15.7 Hz, 1H, H-12), 5.95 (ddd, *J* = 15.8, 8.2, 6.4 Hz, 1H, H-11), 3.83 (s, 3H, H-14/H-13), 3.80 (s, 3H, H-13/H-14), 2.80 – 2.60 (m, 2H, H-1_a, H-1_b), 2.44 – 2.36 (m, 1H, H-7_a), 2.32 (t, *J* = 11.0 Hz, 1H, H-4), 2.06 (dddd, *J* = 13.5, 6.1, 3.2, 1.5 Hz, 1H, H-10_a), 2.00 – 1.89 (m, 1H, H-6_a), 1.86 – 1.53 (m, 5H, H-10_b, H-3, H-5, H-7_b, H-6_b), 1.47 – 1.33 (m, 1H, H-2_a), 1.30 – 1.22 (m, 1H, H-2_b), 1.20 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C-Ar), 158.0 (C-Ar), 148.1 (C-Ar), 136.5 (C-Ar), 135.7 (C-Ar), 132.5 (C-Ar), 130.9 (C-Ar), 130.6 (C-12), 129.3 (C-Ar), 127.1 (3C, C-Ar, C-11), 126.0 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 115.1 (C-Ar), 114.0 (2C, C-Ar), 112.7 (C-Ar),

[133] (*S*)-Carreira ligand was purchased from Sigma-Aldrich (Merck). Product number: 744646
[134] Nonpolar impurities could not be fully separated even after multiple chromatography purifications.
[135] The absolute stereochemistry of the major enantiomer is not known. Nominal absolute stereochemistry is assigned.

55.4 (C-14/C-13), 55.3 (C-13/C-14), 49.8 (C-4), 47.7 (C-3), 44.2 (C-5), 38.2 (C-10), 37.7 (C-7), 37.5 (C-9), 29.6 (C-1), 27.9 (C-6), 22.7 (C-8), 22.6 (C-2).

NOESY- 2D (600 MHz, $CDCl_3$): between H-4 and Me.

Note: the appearance of ^{1}H NMR signal for H-4: 2.32 (t, *J* = 11.0 Hz, 1H, H-1) is indicative of a *trans*-diaxial arrangement between H-4 and H-3; H-4 and H-5.

IR (film) ν_{max}: 2925, 1608, 1510, 1464, 1245, 1176, 1037, 966, 909, 833, 760, 732 cm^{-1}.

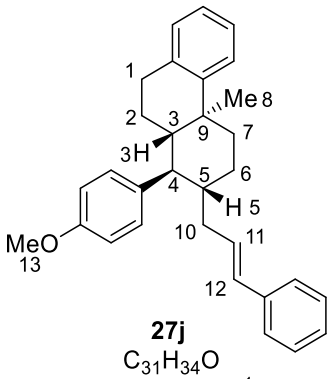
HRMS (APCI): calculated for $C_{32}H_{37}O_2$ $[M+H]^+$ requires m/z 453.2788, found m/z 453.2785 (Δ = -0.69 ppm).

[α] $\frac{25}{D}$ **=** +24.2 (c = 0.3, $CHCl_3$).

HPLC: Enantiomeric ratio was determined by HPLC with a Chiralpak® IA column (99:1 hexane:IPA, 1.0 mL min^{-1}, 254 nm, rt); tr (major) = 29.4 min, tr (minor) = 21.0 min; 38:62 er.

The analytical data is consistent to the racemic sample of **27h** - see page **192**.

(1*R*,2*R*,4*aS*,10*aS*)-2-Cinnamyl-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27j.



27j
$C_{31}H_{34}O$
422.61 g mol^{-1}

Diene **26** (20 mg, 65 µmol, 1.0 equiv), acetate **174** (17.6 mg, 1.00 mmol, 1.50 equiv), $[Ir(cod)Cl]_2$ (3.2 mg, 4.8 µmol, 0.074 equiv, 7.4 mol%), (*S*)-**L1** Carreira ligand[136] (7.6 mg, 15 µmol, 0.23 equiv, 23 mol%) and $Zn(OTf)_2$ (11.8 mg, 32.5 µmol, 0.500 equiv) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.26 mL, 0.25 M) was added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 3 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column

[136] (*S*)-Carreira ligand was purchased from Sigma-Aldrich (Merck). Product number: 744646

chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 49:1) to furnish alkene **27j** together with an inseparable mixture of impurities as a colourless oil (15.6 mg, 57%).[137] Analytical sample in sufficient purity was isolated and subjected to chiral HPLC analysis (79:21 er).[138]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 6.97 (m, 11H, H-Ar), 6.93 (dt, *J* = 8.8, 4.4 Hz, 1H, H-Ar), 6.86 – 6.77 (m, 1H, H-Ar), 6.22 (d, *J* = 15.8 Hz, 1H, H-12), 6.09 (ddd, *J* = 15.7, 8.2, 6.3 Hz, 1H, H-11), 3.82 (s, 3H, H-13), 2.81 – 2.58 (m, 2H, H-1_a, H-1_b), 2.43 – 2.24 (m, 2H, H-7_a, H-4), 2.08 (dddd, *J* = 13.6, 6.3, 3.5, 1.5 Hz, 1H, H-10_a), 1.99 – 1.90 (m, 1H, H-6_a), 1.89 – 1.79 (m, 1H, H-10_b), 1.78 – 1.50 (m, 4H, H-7_b, H-6_b, H-5, H-3), 1.48 – 1.33 (m, 1H, H-2_a), 1.30 – 1.13 (m, 4H, H-2_b, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (C-Ar), 148.1 (C-Ar), 138.0 (C-Ar), 136.5 (C-Ar), 135.7 (C-Ar), 132.5 (C-Ar), 131.2 (C-12), 129.3 (2C, C-Ar, C-11), 128.6 (2C, C-Ar), 126.9 (C-Ar), 126.0 (3C, C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 124.8 (C-Ar), 115.1 (C-Ar), 112.8 (C-Ar), 55.4 (C-13), 49.8 (C-4), 47.7 (C-3), 44.1 (C-5), 38.3 (C-10), 37.7 (C-7), 37.5 (C-9), 29.6 (C-1), 27.9 (C-6), 22.8 (C-8), 22.6 (C-2).

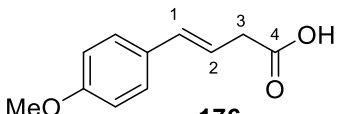
[α] $\frac{25}{D}$ **=** +35.8 (c = 0.4, $CHCl_3$).

HPLC: Enantiomeric ratio was determined by HPLC with a Chiralcel® OD column (99.5:0.5 hexane:IPA, 1.0 mL min^{-1}, 254 nm, rt); tr (major) = 21.8 min, tr (minor) = 26.6 min; 79:21 er.

The analytical data is consistent to the racemic sample of **27j** - see page **194.**

Enantioselective heterocyclisation

(*E*)-4-(4-Methoxyphenyl)but-3-enoic acid 176.



176

$C_{11}H_{12}O_3$

192.21 g mol^{-1}

NaHMDS (24 mL, 24 mmol, 3.6 equiv, 1.0 M solution in THF) was added dropwise to a solution of (2-carboxyethyl)(triphenyl)phosphonium chloride (3.0 g, 8.1 mmol, 1.2 equiv) in THF (4 mL) at 0 °C. The solution was then stirred for 30 min. After cooling to -78 °C, 4-

[137] Nonpolar impurities could not be fully separated even after multiple chromatography purifications.
[138] The absolute stereochemistry of the major enantiomer is not known. Nominal absolute stereochemistry is assigned.

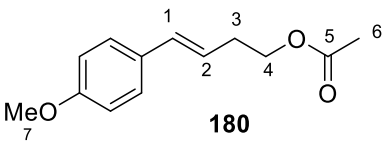
methoxybenzaldehyde (0.82 mL, 6.7 mmol, 1.0 equiv) was added dropwise. The reaction was allowed to warm to rt overnight and then water (20 mL) and Et_2O (20 mL) were added. The aqueous phase was separated and then acidified with 3 M aq. HCl (10 mL) to pH=1. The obtained suspension was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:EtOAc:HCO_2H; 100:100:1) to furnish acid **176** as a yellow solid (0.32 g, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H, H-Ar), 6.88 – 6.81 (m, 2H, H-Ar), 6.47 (dt, *J* = 15.8, 1.5 Hz, 1H, H-1), 6.14 (dt, *J* = 15.9, 7.1 Hz, 1H, H-2), 3.81 (s, 3H, H-5), 3.28 (dd, *J* = 7.3, 1.5 Hz, 2H, H-3). The carboxylic acid proton was not found.

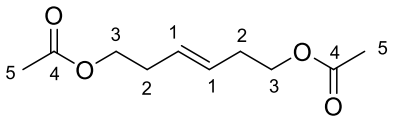
^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3 (C-4), 159.4 (C-Ar), 133.6 (C-1), 129.6 (C-Ar), 127.7 (2C, C-Ar), 118.7 (C-2), 114.1 (2C, C-Ar), 55.4 (C-5), 37.9 (C-3).

The data are consistent with the literature.[24]

(*E*)-4-(4-methoxyphenyl)but-3-en-1-yl acetate 180 and (*E*)-hex-3-ene-1,6-diyl diacetate 179.



180
$C_{13}H_{16}O_3$
220.27 g mol^{-1}



179
$C_{10}H_{16}O_4$
200.23 g mol^{-1}

1-Methoxy-4-vinylbenzene (0.50 g, 3.7 mmol, 1.0 equiv) and but-3-en-1-yl acetate (0.85 g, 7.5 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (10 mL, degassed by purging N_2 for 30 min) and the obtained solution was added dropwise to G-II (0.15 g, 0.18 mmol, 0.049 equiv) dissolved in CH_2Cl_2 (5 mL, degassed by purging N_2 for 30 min). The reaction mixture was stirred under reflux overnight and then cooled to rt. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O 4:1) to furnish acetate **180** as a brown oil (0.282 g, 35%) and acetate **179** as a brown oil (0.340 g, 46%)[139]

Data for acetate **180**:

[139] Yield is calculated based on but-3-en-1-yl acetate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H, H-Ar), 6.90 – 6.77 (m, 2H, H-Ar), 6.41 (dt, *J* = 15.9, 1.6 Hz, 1H, H-1), 6.02 (dt, *J* = 15.8, 7.0 Hz, 1H, H-2), 4.17 (t, *J* = 6.8 Hz, 2H, H-4), 3.80 (s, 3H, H-7), 2.52 (qd, *J* = 6.8, 1.4 Hz, 2H, H-3), 2.06 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C-5), 159.1 (C-Ar), 131.9 (C-1), 130.2 (C-Ar), 127.3 (2C, C-Ar), 123.5 (C-2), 114.1 (2C, C-Ar), 64.0 (C-4), 55.4 (C-7), 32.5 (C-3), 21.2 (C-6).

The data are consistent with the literature.[24]

Data for acetate **179**:

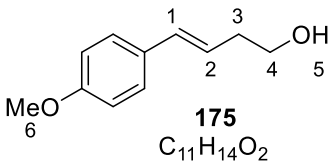
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (ddt, *J* = 5.3, 3.7, 2.3 Hz, 2H, H-1), 4.06 (t, *J* = 6.9 Hz, 4H, H-3), 2.43 – 2.27 (m, 4H, H-2), 2.04 (d, *J* = 1.7 Hz, 6H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (2C, C-4), 128.4 (2C, C-1), 63.9 (2C, C-3), 32.1 (2C, C-2), 21.1 (2C, C-5).

IR (film) ν_{max}: 2981, 2891, 2361, 1739, 1385, 1366, 1237, 1035, 970 cm^{-1}.

HRMS (ESI): calculated for $C_{10}H_{16}O_4Na$ $[M+Na]^+$ requires m/z 223.0941, found m/z 223.0934 (*Δ* = -3.07 ppm).

(*E*)-4-(4-methoxyphenyl)but-3-en-1-ol 175.



175

$C_{11}H_{14}O_2$

178.23 g mol^{-1}

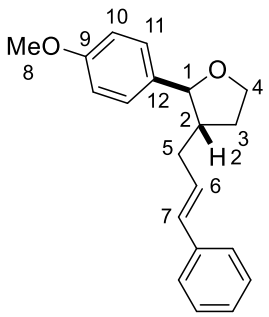
K_2CO_3 (0.89 g, 6.4 mmol, 5.0 equiv) was added in one portion to a solution of acetate **180** (0.284 g, 1.29 mmol, 1.00 equiv) in MeOH (13 mL) at 0 °C. The obtained suspension was stirred at the same temperature for 3 h and then filtered. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 3:7) to furnish alcohol **175** as a colourless solid (0.165 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H, H-Ar), 6.91 – 6.79 (m, 2H, H-Ar), 6.50 – 6.39 (m, 1H, H-1), 6.06 (dt, *J* = 15.8, 7.2 Hz, 1H, H-2), 3.81 (s, 3H, H-6), 3.74 (q, *J* = 6.1 Hz, 2H, H-4), 2.47 (dtd, *J* = 7.6, 6.2, 1.4 Hz, 2H, H-3), 1.46 (t, *J* = 5.8 Hz, 1H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (C-Ar), 132.5 (C-1), 130.2 (C-Ar), 127.3 (2C, C-Ar), 124.1 (C-2), 114.1 (2C, C-Ar), 62.2 (C-4), 55.4 (C-6), 36.6 (C-3).

The data are consistent with the literature.[24]

(±)-(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)tetrahydrofuran 182.



182
$C_{20}H_{22}O_2$
294.39 g mol^{-1}

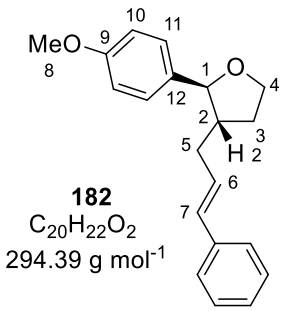
According to the literature procedure,[24] a microwave vial was charged with a stirring bar, alcohol **175** (17.8 mg, 0.100 mmol, 1.00 equiv) and (*E*)-3-phenylprop-2-en-1-ol (13.4 mg, 0.100 mmol, 1.00 equiv). The vial was purged with nitrogen for 15 min. Balloon of nitrogen was removed and HFIP (1.0 mL) followed by Ti(O*i*-Pr)$_4$ (9.0 µL, 0.030 mmol, 0.30 equiv, 30 mol%) were added in one portion. The reaction mixture was stirred at 70 °C overnight and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 4:1) to furnish tetrahydrofuran **182** as a colourless oil (9.9 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 7H, H-Ph, H-11), 6.95 – 6.79 (m, 2H, H-10), 6.40 (dt, *J* = 15.8, 1.3 Hz, 1H, H-7), 6.12 (dt, *J* = 15.7, 6.9 Hz, 1H, H-6), 4.42 (d, *J* = 7.1 Hz, 1H, H-1), 4.11 (dt, *J* = 8.5, 7.2 Hz, 1H, H-4$_a$), 4.01 (td, *J* = 8.3, 4.6 Hz, 1H, H-4$_b$), 3.81 (s, 3H, H-8), 2.48 – 2.36 (m, 1H, H-5$_a$), 2.30 – 2.12 (m, 3H, H-5$_b$, H-3$_a$, H-2), 1.87 – 1.73 (m, 1H, H-3$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2 (C-9), 137.6 (C-12/C-Ph), 134.3 (C-Ph/C-12), 131.4 (C-7), 128.61 (2C, C-Ph/C-11), 128.57 (C-6), 127.8 (2C, C-11/C-Ph), 127.2 (C-Ph), 126.1 (2C, C-Ph/C-11), 113.9 (2C, C-10), 85.9 (C-1), 67.9 (C-4), 55.4 (C-8), 48.0 (C-2), 35.6 (C-5), 32.5 (C-3).

The data are consistent with the literature.[24]

(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)tetrahydrofuran 182.



182
$C_{20}H_{22}O_2$
294.39 g mol^{-1}

Alcohol **175** (17.8 mg, 0.100 mmol, 1.00 equiv), acetate **174** (17.6 mg, 0.100 mmol, 1.00 equiv), $[Ir(cod)Cl]_2$ (4.9 mg, 7.3 µmol, 0.073 equiv, 7.3 mol%), (*S*)-**L1** Carreira ligand[140] (11.7 mg, 23.0 µmol, 0.23 equiv, 23 mol%) and $Zn(OTf)_2$ (18.2 mg, 0.0500 mmol, 0.500 equiv) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.40 mL, 0.25 M) was added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 3 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 4:1) to furnish tetrahydrofuran **182** as a colourless oil (7.7 mg, 26%, 17:83 er).[141]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 7H, H-Ph, H-11), 6.95 – 6.79 (m, 2H, H-10), 6.40 (dt, *J* = 15.8, 1.3 Hz, 1H, H-7), 6.12 (dt, *J* = 15.7, 6.9 Hz, 1H, H-6), 4.42 (d, *J* = 7.1 Hz, 1H, H-1), 4.11 (dt, *J* = 8.5, 7.2 Hz, 1H, H-4$_a$), 4.01 (td, *J* = 8.3, 4.6 Hz, 1H, H-4$_b$), 3.81 (s, 3H, H-8), 2.48 – 2.36 (m, 1H, H-5$_a$), 2.30 – 2.12 (m, 3H, H-5$_b$, H-3$_a$, H-2), 1.87 – 1.73 (m, 1H, H-3$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2 (C-9), 137.6 (C-12/C-Ph), 134.3 (C-Ph/C-12), 131.4 (C-7), 128.61 (2C, C-Ph/C-11), 128.57 (C-6), 127.8 (2C, C-11/C-Ph), 127.2 (C-Ph), 126.1 (2C, C-Ph/C-11), 113.9 (2C, C-10), 85.9 (C-1), 67.9 (C-4), 55.4 (C-8), 48.0 (C-2), 35.6 (C-5), 32.5 (C-3).

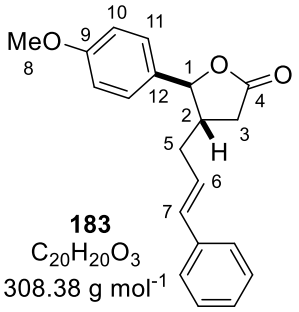
[α] $\frac{25}{D}$ **=** +9.5 (c = 0.2, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (97:3 hexane:IPA, 1.0 mL min^{-1}, 254 nm, rt); tr (major) = 21.0 min, tr (minor) = 17.9 min; 17:83 er.

The data are consistent with the literature.[24]

[140] (*S*)-Carreira ligand was synthesised in house according to the literature procedure – see page **310**.
[141] The absolute stereochemistry of the major enantiomer is not known. Nominal absolute stereochemistry is assigned.

(±)-(4*S*,5*S*)-4-Cinnamyl-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one 183.



183
$C_{20}H_{20}O_3$
308.38 g mol^{-1}

According to the literature procedure,[24] a microwave vial was charged with a stirring bar, carboxylic acid **176** (19.2 mg, 0.100 mmol, 1.00 equiv) and (*E*)-3-phenylprop-2-en-1-ol (13.4 mg, 0.100 mmol, 1.00 equiv). The vial was purged with nitrogen for 15 min. Balloon of nitrogen was removed and HFIP (1.0 mL) followed by Ti(O*i*-Pr)$_4$ (9.0 µL, 0.030 mmol, 0.30 equiv, 30 mol%) were added in one portion. The reaction mixture was stirred at 70 °C overnight and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 1:1) to furnish lactone **183** as a colourless oil (13 mg, 40%, 93:7 dr).

Data for the major *trans*-diastereomer (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.18 (m, 7H, H-11, H-Ph), 6.98 – 6.88 (m, 2H, H-10), 6.45 (dt, *J* = 15.8, 1.4 Hz, 1H, H-7), 6.05 (dt, *J* = 15.8, 7.2 Hz, 1H, H-6), 5.10 (d, *J* = 7.5 Hz, 1H, H-1), 3.82 (s, 3H, H-8), 2.81 (dd, *J* = 17.2, 7.9 Hz, 1H, H-3$_a$), 2.67 – 2.32 (m, 4H, H-3$_b$, H-2, H-5$_a$, H-5$_b$).

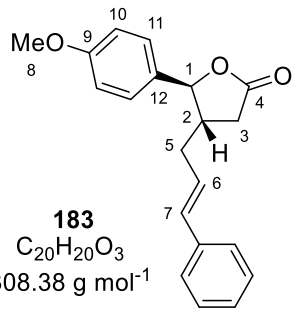
^{13}C NMR (101 MHz, $CDCl_3$): δ 176.1 (C-4), 160.1 (C-9), 136.9 (C-12/C-Ph), 133.1 (C-7), 130.2 (C-Ph/C-12), 128.7 (2C, C-Ph/C-11), 127.8 (2C, C-Ph/C-11), 127.7 (C-Ph), 126.3 (2C, C-Ph/C-11), 125.9 (C-6), 114.3 (2C, C-10), 86.1 (C-1), 55.5 (C-8), 44.6 (C-2), 35.5 (C-5), 35.0 (C-3).

Data for the minor *cis*-diastereomer (from the mixture):

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 15.9, 1.4 Hz, 1H, H-7), 5.86 (ddd, *J* = 15.9, 8.1, 6.3 Hz, 1H, H-6), 5.62 (d, *J* = 6.5 Hz, 1H, H-1).

The data are consistent with the literature.[24]

(4*S*,5*S*)-4-Cinnamyl-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one 183.



183
$C_{20}H_{20}O_3$
308.38 g mol^{-1}

Carboxylic acid **176** (19.2 mg, 0.100 mmol, 1.00 equiv), acetate **174** (17.6 mg, 0.100 mmol, 1.00 equiv), $[Ir(cod)Cl]_2$ (4.9 mg, 7.3 µmol, 0.073 equiv, 7.3 mol%), (*S*)-Carreira ligand[142] (11.7 mg, 23.0 µmol, 0.23 equiv, 23 mol%) and $Zn(OTf)_2$ (18.2 mg, 0.0500 mmol, 0.500 equiv) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.40 mL, 0.25 M) was added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 3 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 1:1) to furnish lactone **183** as a colourless oil (8.4 mg, 27%, 97:3 dr, 64:36 er).[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.18 (m, 7H, H-11, H-Ph), 6.98 – 6.88 (m, 2H, H-10), 6.45 (dt, *J* = 15.8, 1.4 Hz, 1H, H-7), 6.05 (dt, *J* = 15.8, 7.2 Hz, 1H, H-6), 5.10 (d, *J* = 7.5 Hz, 1H, H-1), 3.82 (s, 3H, H-8), 2.81 (dd, *J* = 17.2, 7.9 Hz, 1H, H-3$_a$), 2.67 – 2.32 (m, 4H, H-3$_b$, H-2, H-5$_a$, H-5$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.1 (C-4), 160.1 (C-9), 136.9 (C-12/C-Ph), 133.1 (C-7), 130.2 (C-Ph/C-12), 128.7 (2C, C-Ph/C-11), 127.8 (2C, C-Ph/C-11), 127.7 (C-Ph), 126.3 (2C, C-Ph/C-11), 125.9 (C-6), 114.3 (2C, C-10), 86.1 (C-1), 55.5 (C-8), 44.6 (C-2), 35.5 (C-5), 35.0 (C-3).

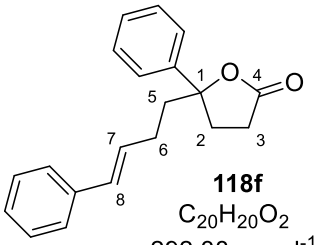
[α]$_D^{25}$ = +8.8 (c = 0.57, $CHCl_3$).

HPLC: Enantiomeric ratio was determined by HPLC with a Chiralpak® IA column (85:15 hexane:IPA, 1.0 mL min^{-1}, 254 nm, rt); tr (major) = 20.0 min, tr (minor) = 21.8 min; 65:35 er.

The data are consistent with the literature.[24]

[142] (*S*)-Carreira ligand was purchased from Sigma-Aldrich (Merck). Product number: 744646
[143] The absolute stereochemistry of the major enantiomer is not known. Nominal absolute stereochemistry is assigned.

(*E*)-5-Phenyl-5-(4-phenylbut-3-en-1-yl)dihydrofuran-2(3H)-one 118f.



118f
$C_{20}H_{20}O_2$
292.38 g mol^{-1}

Carboxylic acid **117** (17.6 mg, 0.100 mmol, 1.00 equiv), acetate **174** (17.6 mg, 0.100 mmol, 1.00 equiv), $[Ir(cod)Cl]_2$ (2.0 mg, 3.0 µmol, 0.030 equiv, 3.0 mol%), (*S*)-Carreira ligand[144] (6.0 mg, 12 µmol, 0.12 equiv, 12 mol%) and $Zn(OTf)_2$ (18.2 mg, 0.0500 mmol, 0.500 equiv) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.40 mL, 0.25 M) was added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 3 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:EtOAc; 4:1) to furnish lactone **118f** as a colourless oil (10.4 mg, 36%, 70:30 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.04 (m, 10H, H-Ph), 6.30 (dt, *J* = 15.8, 1.4 Hz, 1H, H-8), 6.08 (dt, *J* = 15.8, 6.7 Hz, 1H, H-7), 2.67 – 2.37 (m, 4H, H-2_a, H-2_b, H-3_a, H-3_b), 2.34 – 2.05 (m, 3H, H-5_a, H-5_b, H-6_a), 2.06 – 1.90 (m, 1H, H-6_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.6 (C-4), 142.7 (C-Ph), 137.6 (C-Ph), 130.6 (C-8), 129.3 (C-7), 128.8 (2C, C-Ph), 128.6 (2C, C-Ph), 127.8 (2C, C-Ph), 127.2 (C-Ph), 126.1 (C-Ph), 124.8 (2C, C-Ph), 89.2 (C-1), 42.2 (C-5), 35.5 (C-2), 28.7 (C-3), 27.7 (C-6).

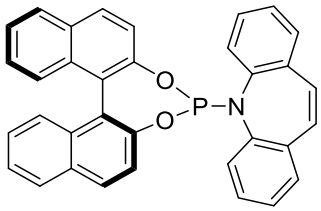
[α]$_D^{25}$ = -25.6 (c = 0.5, $CHCl_3$).

HPLC: Enantiomeric ratio was determined by HPLC with a Chiralpak® IG column (90:10 hexane:IPA, 1.0 mL min^{-1}, 254 nm, rt); tr (major) = 26.3 min, tr (minor) = 37.8 min; 70:30 er.

The analytical data is consistent to the racemic sample of **118f**- see Megan Jaschinski's Part II thesis 2023.

[144] (*S*)-Carreira ligand was purchased from Sigma-Aldrich (Merck). Product number: 744646

5-((11b*S*)-Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)-5H-dibenzo[b,f]azepine *(S)*-L1.



Carreira ligand (*S*)-**L1**
$C_{34}H_{22}NO_2P$
507.53 g mol^{-1}

According to the literature procedure[145], iminostilbene (0.273 g, 1.41 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (5.5 mL) in a schlenk tube and cooled to 0 °C. To the solution Et_3N (1.0 mL, 7.2 mmol, 5.1 equiv) was added in one portion followed by dropwise addition of PCl_3 (0.13 mL, 1.6 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 3 h. A solution of (*S*)-binol (0.47 g, 1.6 mmol, 1.2 equiv) in CH_2Cl_2 (6.0 mL) was then added dropwise and the reaction mixture was allowed to slowly warm to rt overnight. Et_2O (5 mL) was added, and the suspension was stirred at rt for 1 h. The mixture was filtered through the pad of Celite® and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:PhMe; 1:1) to furnish phosphonamidite (*S*)-**L1** as a colourless solid (0.424 mg, 59%).

^{1}H NMR (400 MHz, C_6D_6) δ 7.65 – 7.56 (m, 3H, H-Ar), 7.52 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.46 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.37 (t, *J* = 7.6 Hz, 2H, H-Ar), 7.30 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.24 – 7.07 (m, 3H, H-Ar), 7.02 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.00 – 6.84 (m, 6H, H-Ar), 6.77 – 6.65 (m, 3H, H-Ar), 6.36 (td, *J* = 7.7, 1.7 Hz, 1H, H-Ar).

^{13}C NMR (101 MHz, C_6D_6) δ 150.7 (d, *J* = 8.0 Hz, C-Ar), 149.4 (C-Ar), 143.5 (d, *J* = 23.7 Hz, C-Ar), 143.2 (C-Ar), 137.0 (d, *J* = 3.5 Hz, C-Ar), 135.8 (C-Ar), 133.5 (d, *J* = 1.8 Hz, C-Ar), 132.8 (C-Ar), 132.0 (C-Ar), 131.8 (HC-Ar), 131.7 (HC-Ar), 130.9 (HC-Ar), 130.8 (C-Ar), 129.7 – 129.5 (m, 2C, HC-Ar), 129.4 (HC-Ar), 129.3 – 129.2 (m, 2C, HC-Ar), 129.0 – 128.8 (m, 2C, HC-Ar), 128.7 (HC-Ar), 128.2 (HC-Ar), 127.6 (HC-Ar), 127.4 (HC-Ar), 126.9 (HC-Ar), 126.5 (HC-Ar), 126.4 (HC-Ar), 126.2 (HC-Ar), 125.1 (HC-Ar), 124.8 (d, *J* = 5.3 Hz, C-Ar), 124.7 (HC-Ar), 122.42 (d, *J* = 1.9 Hz, HC-Ar), 122.1 (HC-Ar), 121.9 (d, *J* = 2.8 Hz, C-Ar).

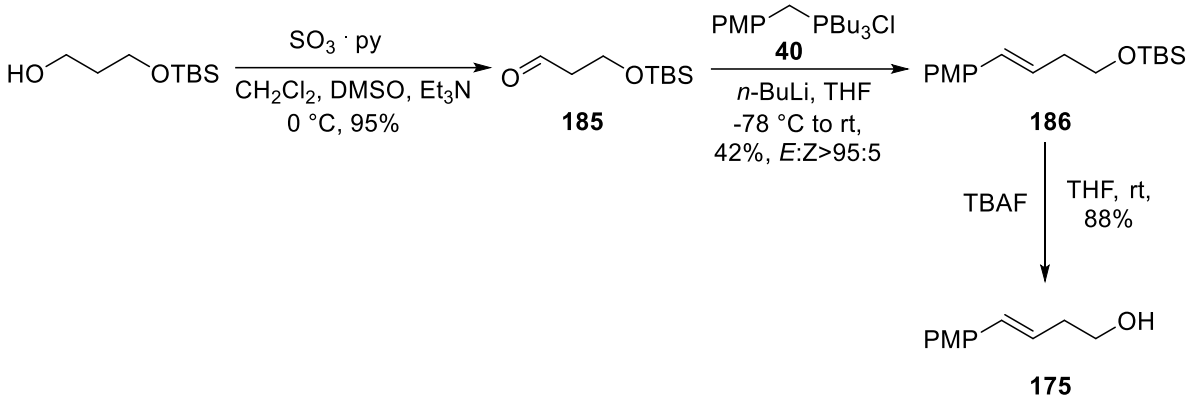
^{31}P NMR (162 MHz, C_6D_6) δ 138.38.

[α] $\frac{25}{D}$ = +296 (c = 0.21, $CHCl_3$).

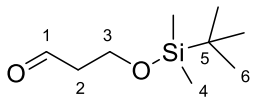
[145] D. Albat, A. Köcher, J. Witt, H. G. Schmalz, *Eur.J. Org. Chem*. **2022**, e202200188.

The data are consistent with the literature[146]

Improved route to homoallylic alcohol 175



3-((*Tert*-butyldimethylsilyl)oxy)propanal 185.



185
$C_9H_{20}O_2Si$
188.34 g mol^{-1}

SO_3 · py (12 g, 77 mmol, 2.8 equiv) was added in one portion to a solution of 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (5.17 g, 27.2 mmol, 1.00 equiv) in CH_2Cl_2 (53 mL), DMSO (53 mL) and Et_3N (18.6 mL, 0.133 mol, 4.89 equiv) at 0 °C. The reaction mixture was stirred at the same temperature for 4 h and then poured into water (100 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with brine (150 mL), dried over Na_2SO_4 and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 9:1) to furnish aldehyde **185** as a colourless oil (4.88 g, 95%).

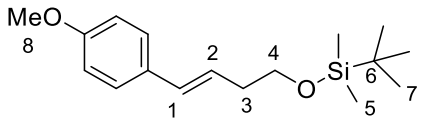
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.1 Hz, 1H, H-1), 3.99 (t, *J* = 6.1 Hz, 2H, H-3), 2.60 (td, *J* = 6.0, 2.1 Hz, 2H, H-2), 0.88 (s, 9H, H-6), 0.06 (s, 6H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2 (C-1), 57.6 (C-3), 46.7 (C-2), 26.0 (3C, C-6), 18.4 (C-5), -5.3 (2C, C-4).

The data are consistent with the literature[147]

[146] L. J. Hilpert, B. Breit, *Angew. Chem. Int. Ed.* **2019**, *58*, 9939–9943; C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem. Int. Ed*. **2007**, *46*, 3139–3143.
[147] O. Hartmann, M. Kalesse, *Org. Lett.* **2012**, *14*, 3064–3067.

(*E*)-*Tert*-butyl((4-(4-methoxyphenyl)but-3-en-1-yl)oxy)dimethylsilane 186.



186
$C_{17}H_{28}O_2Si$
292.49 g mol^{-1}

Tributyl(4-methoxybenzyl)phosphonium chloride **40** (2.86 g, 7.96 mmol, 1.50 equiv) was suspended in THF (113 mL) and cooled to 0 °C. *n*-BuLi (3.2 mL, 8.0 mL, 1.5 equiv, 2.5 M in hexanes) was added dropwise at the same temperature. The obtained suspension was allowed to stir at 0 °C for 30 min, then cooled to -78 °C and aldehyde **185** (1.00 g, 5.31 mmol, 1.00 equiv) in THF (10 mL) was added dropwise. The reaction mixture was allowed to slowly warm to rt overnight and quenched with sat. aq. NH_4Cl (10 mL). Water (50 mL) and Et_2O (50 mL) were added, and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 50 mL), the organic phases were combined, washed with brine (200 mL), dried over Na_2SO_4 and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 49:1) to furnish alkene **186** as a colourless oil (0.66 g, 42%, *E*:*Z*>95:5).

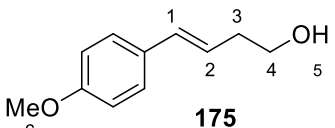
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H, H-Ar), 6.96 – 6.76 (m, 2H, H-Ar), 6.38 (dt, *J* = 15.9, 1.4 Hz, 1H, H-1), 6.07 (dt, *J* = 15.9, 7.1 Hz, 1H, H-2), 3.80 (s, 3H, H-8), 3.71 (t, *J* = 6.8 Hz, 2H, H-4), 2.41 (qd, *J* = 6.9, 1.4 Hz, 2H, H-3), 0.90 (s, 9H, H-7), 0.06 (s, 6H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C-Ar), 131.1 (C-1), 130.7 (C-Ar), 127.2 (2C, C-Ar), 125.1 (C-2), 114.0 (2C, C-Ar), 63.3 (C-4), 55.4 (C-8), 36.8 (C-3), 26.1 (3C, C-7), 18.5 (C-6), -5.1 (2C, C-5).

IR (film) ν_{max}: 2955, 2858, 2362, 1610, 1512, 1251, 1175, 1104, 1039, 838, 777 cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{28}O_2SiNa$ $[M+Na]^+$ requires m/z 315.1751, found m/z 315.1754 (*Δ* = 1.00 ppm).

(*E*)-4-(4-methoxyphenyl)but-3-en-1-ol 175.



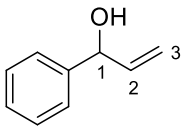
175
$C_{11}H_{14}O_2$
178.23 g mol^{-1}

Alkene **186** (0.655 g, 2.24 mmol, 1.00 equiv) was dissolved in THF (5 mL) and TBAF (3.4 mL, 3.4 mmol, 1.0 equiv, 1.0 M in THF) was added dropwise. The reaction was stirred at rt for 1 h 20 min and then quenched with H_2O (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), the organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:EtOAc; 1:1) to furnish alkene **175** as a colourless oil (0.351 g, 88%, *E*:*Z*>95:5).

The analytical data is consistent with those obtained for product **175** synthesised via a different route (see page **304**).

Electrophile synthesis

1-Phenylprop-2-en-1-ol 187.



187
$C_9H_{10}O$
134.18 g mol^{-1}

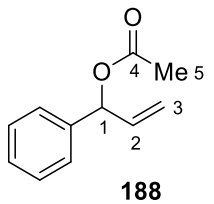
Vinyl magnesium bromide (23 mL, 23 mmol, 1.2 equiv, 1 M solution in THF) was added dropwise to a solution of benzaldehyde (2.0 g, 19 mmol, 1.0 equiv) in THF (54 mL) at 0 °C. The solution was stirred at the same temperature for 30 min and quenched with sat. aq. NH_4Cl (10 mL). Water (30 mL) and Et_2O (40 mL) were added, and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 × 40 mL), the organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 4:1 to 7:3) to furnish compound allylic alcohol **187** as a colourless oil (1.89 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H, H-Ph), 6.06 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 1H, H-2), 5.42 – 5.31 (m, 1H, H-3_a), 5.25 – 5.17 (dq, *J* = 9.0, 1.6 Hz, 2H, H-3_b, H-1), 2.00 – 1.92 (m, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (C-Ph), 140.4 (C-2), 128.7 (2C, C-Ph), 127.9 (C-Ph), 126.4 (2C, C-Ph), 115.3 (C-3), 75.5 (C-1).

The data are consistent with the literature[148]

1-Phenylallyl acetate 188.



188
$C_{11}H_{12}O_2$
176.22 g mol^{-1}

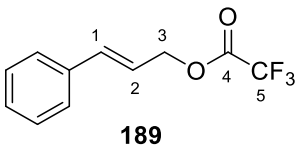
Allylic alcohol **187** (0.20 g, 1.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (14 mL) and pyridine (0.18 mL, 2.2 mmol, 1.5 equiv) was added in one portion. Then acetyl chloride (0.16 mL, 2.2 mmol, 1.5 equiv) was added dropwise and the obtained solution was stirred at rt overnight. Water (15 mL) was added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2; pentane:Et_2O; 47:3 to 9:1) to obtain ester **188** as a colourless oil (0.222 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 5H, H-Ph), 6.17 (dt, *J* = 5.9, 1.4 Hz, 1H, H-1), 5.92 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, H-2), 5.24 – 5.12 (m, 2H, H-3$_a$, H-3$_b$), 2.02 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C-4), 139.0 (C-Ph), 136.4 (C-2), 128.7 (2C, C-Ph), 128.3 (C-Ph), 127.3 (2C, C-Ph), 117.0 (C-3), 76.3 (C-1), 21.4 (C-5).

The data are consistent with the literature[149]

Cinnamyl 2,2,2-trifluoroacetate 189.



189
$C_{11}H_9F_3O_2$
230.19 g mol^{-1}

[148] L. Zhou, N. Zanda, M. Chaudhari, M. F. Da Silva, M. A. Pericàs, *J. Org. Chem.* **2023**, *88*, 2166–2173.
[149] R. Tomita, K. Mantani, A. Hamasaki, T. Ishida, M. Tokunaga, *Chem. Eur. J.* **2014**, *20*, 9914–9917.

Cinnamyl alcohol (0.50 g, 3.8 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Et_3N (1.0 mL, 7.1 mmol, 1.9 equiv) followed by TFAA (0.70 mL, 4.9 mmol, 1.3 equiv) were added dropwise at the same temperature and the reaction mixture was allowed to warm to rt overnight. Then aq. HCl (1 M, 10 mL) and water (10 mL) were added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), the organic layers were combined, washed with brine (60 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane:Et_2O; 24:1 to 47:3) to furnish trifluoroacetate **189** as a colourless oil (0.433 g, 50%).

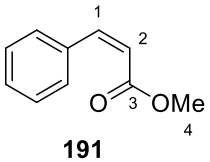
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 5H, H-Ph), 6.81 – 6.68 (dt, *J* = 15.8, 1.4 Hz, 1H, H-1), 6.30 (dt, *J* = 15.8, 6.8 Hz, 1H, H-2), 4.99 (dd, *J* = 6.7, 1.2 Hz, 2H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3 (C-1), 135.6 (C-Ph), 128.9 (3C, C-Ph), 127.0 (2C, C-Ph), 120.2 (C-2), 68.7 (C-3). Note: C-4 and C-5 not observed due to the strong coupling with ^{19}F.

^{19}F NMR (377 MHz, $CDCl_3$) δ -75.0 (3F, CF_3).

The data are consistent with the literature[150]

Methyl (*Z*)-3-phenylacrylate 191.



191

$C_{10}H_{10}O_2$

162.19 g mol^{-1}

Methyl P, P-bis(2,2,2-trifluoroethyl)phosphonoacetate (0.83 mL, 4.0 mmol, 1.4 equiv) and 18-crown-6 (1.86 g, 7.08 mmol, 2.50 equiv) in THF (10 mL) was treated with KHMDS (0.7 M in toluene, 5.7 mL, 4.0 mmol, 1.4 equiv) at -78 °C and the obtained suspension was stirred at the same temperature for 30 min. A solution of benzaldehyde (0.29 mL, 2.8 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise, and the reaction mixture was stirred at -78 °C for 2 h and then slowly allowed to warm to rt overnight. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and diluted with Et_2O (15 mL) and water (10 mL). The organic phase was separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The organic layers were combined, washed with brine (40 mL) and dried over Na_2SO_4. Volatiles were removed

[150] E. Lee, D.V. Yandulov, *J. Fluor. Chem.* **2009**, *130*, 474–483.

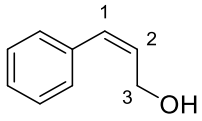
in vacuo and the crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O; 24:1) to furnish ester **191** as a colourless oil (0.400 g, 87%, *Z*:*E*>95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.53 (m, 2H, H-Ph), 7.42 – 7.30 (m, 3H, H-Ph), 6.96 (d, *J* = 12.7 Hz, 1H, H-1), 5.96 (d, *J* = 12.6 Hz, 1H, H-2), 3.72 (s, 3H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C-3), 143.6 (C-1), 134.9 (C-Ph), 129.8 (2C, C-Ph), 129.2 (C-Ph), 128.2 (2C, C-Ph), 119.4 (C-2), 51.5 (C-4).

The data are consistent with the literature[151]

(*Z*)-3-Phenylprop-2-en-1-ol 192.



192

$C_9H_{10}O$

134.18 g mol^{-1}

Ester **191** (0.400 g, 2.46 mmol, 1.00 equiv) was dissolved in THF (22 mL) and cooled to 0 °C. $LiAlH_4$ (94 mg, 2.5 mmol, 1.0 equiv) was added portionwise and the obtained suspension was stirred at 0 °C for 2 h. Water (0.09 mL), aq. NaOH (15 wt.%, 0.09 mL) and water (0.27 mL) were added sequentially at the same temperature and the obtained suspension was allowed to slowly warm to rt over 30 min. The mixture was diluted with Et_2O (20 mL), washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 7:3) to furnish alcohol **192** as a colourless oil (0.148 g, 45%, *Z*:*E*>95:5).

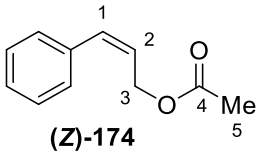
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.13 (m, 5H, H-Ph), 6.58 (dt, *J* = 11.7, 1.8 Hz, 1H, H-1), 5.88 (dt, *J* = 11.7, 6.5 Hz, 1H, H-2), 4.44 (dd, *J* = 6.5, 1.7 Hz, 2H, H-3). The OH was not found.

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6 (C-Ph), 131.3 (C-1/C-2), 131.2 (C-2/C-1), 128.9 (2C, C-Ph), 128.4 (2C, C-Ph), 127.4 (C-Ph), 59.9 (C-3).

The data are consistent with the literature[152]

[151] T. Gatzenmeier, P. S. J. Kaib, J. B. Lingnau, R. Goddard, B. List, *Angew. Chem. Int. Ed.* **2018**, *57*, 2464–2468.
[152] B. Y. Park, M. S. Han, *Adv. Synth.Catal.* **2023**, *365*, 1505–1513.

(*Z*)-3-Phenylallyl acetate 174.



(*Z*)-174

$C_{11}H_{12}O_2$

176.22 g mol^{-1}

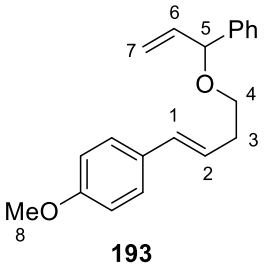
(*Z*)-3-phenylprop-2-en-1-ol **192** (0.139 g, 1.04 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (9 mL) and pyridine (0.13 mL, 1.6 mmol, 1.5 equiv) was added in one portion. Then acetyl chloride (0.11 mL, 1.6 mmol, 1.5 equiv) was added dropwise and the obtained solution was stirred at rt overnight. Water (10 mL) was added, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine and volatiles were removed *in vacuo* to obtain the crude product which was purified by flash column chromatography (SiO_2; pentane:Et_2O; 47:3) to obtain ester **(*Z*)-174** as a colourless oil (0.163 g, 89%, *Z*:*E*>95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 5H, H-Ph), 6.67 (dt, *J* = 11.7, 1.8 Hz, 1H, H-1), 5.82 (dt, *J* = 11.7, 6.6 Hz, 1H, H-2), 4.85 (dd, *J* = 6.6, 1.7 Hz, 2H, H-3), 2.09 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C-4), 136.2 (C-Ph), 133.1 (C-1), 128.9 (2C, C-Ph), 128.5 (2C, C-Ph), 127.7 (C-Ph), 125.9 (C-2), 61.6 (C-3), 21.1 (C-5).

The data are consistent with the literature[153]

(*E*)-1-methoxy-4-(4-((1-phenylallyl)oxy)but-1-en-1-yl)benzene 193.



193

$C_{20}H_{22}O_2$

294.39 g mol^{-1}

Alcohol **175** (17.8 mg, 0.100 mmol, 1.00 equiv), allylic alcohol **187** (13.4 mg, 0.100 mmol, 1.00 equiv), $[Ir(cod)Cl]_2$ (2.0 mg, 3.0 µmol, 0.030 equiv, 3.0 mol%), *S*-Carreira ligand[154]

[153] D. Orr, J. M. Percy, T. Tuttle, A. R. Kennedy, Z. A. Harrison, *Chem. Eur. J*. **2014**, *20*, 14305–14316.
[154] *S*-Carreira Ligand was self-made according to a literature procedure – see page **310.**

(3.0 mg, 6.0 µmol, 0.060 equiv, 6.0 mol%) and $Zn(OTf)_2$ (18.2 mg, 0.0500 mmol, 0.500 equiv) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.40 mL, 0.25 M) was added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 3 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 19:1) to furnish ether **193** as a colourless oil (6.7 mg, 23%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 7H, H-Ar), 6.88 – 6.77 (m, 2H, H-Ar), 6.39 (dt, *J* = 15.6, 1.5 Hz, 1H, H-1), 6.09 (dt, *J* = 15.8, 7.0 Hz, 1H, H-2), 5.96 (ddd, *J* = 17.0, 10.3, 6.6 Hz, 1H, H-6), 5.34 – 5.11 (m, 2H, H-7), 4.77 (dt, *J* = 6.6, 1.2 Hz, 1H, H-5), 3.80 (s, 3H, H-8), 3.64 – 3.41 (m, 2H, H-4), 2.51 (qd, *J* = 6.9, 1.5 Hz, 2H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C-Ar), 141.3 (C-Ar), 139.2 (C-6), 131.0 (C-1), 130.6 (C-Ar), 128.6 (2C, C-Ar), 127.7 (C-Ar), 127.2 (2C, C-Ar), 127.0 (2C, C-Ar), 125.0 (C-2), 116.3 (C-7), 114.0 (2C, C-Ar), 83.2 (C-5), 68.5 (C-4), 55.4 (C-8), 33.7 (C-3).

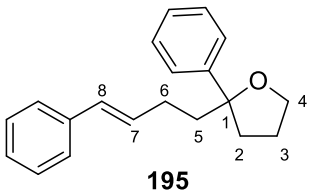
IR (film) ν_{max}: 3029, 2836, 1609, 1512, 1304, 1250, 1176, 1088, 1037, 928, 762, 702 cm^{-1}.

[α] $\frac{25}{D}$ = +4.5 (c = 3.0 mg × ml^{-1}, $CHCl_3$).

HRMS (ESI): calculated for $C_{20}H_{22}O_2Na$ $[M+Na]^+$ requires m/z 317.1512, found m/z 317.1514 (*Δ* = 0.61 ppm).

Enantioselective heterocyclisation of substrate 194

(±)-((*E*)-2-Phenyl-2-(4-phenylbut-3-en-1-yl)tetrahydrofuran 195.



195

$C_{20}H_{22}O$

278.40 g mol^{-1}

Alcohol **194** (16.2 mg, 0.100 mmol, 1.00 equiv),[155] (*E*)-3-phenylprop-2-en-1-ol (13.4 mg, 0.100 mmol, 1.00 equiv), Ti(O*i*-Pr)$_4$ (8.9 µL, 0.030 mmol, 0.30 equiv, 30 mol%) in HFIP (2.7 mL) were subjected to the general procedure **E**, except the reaction was conducted using

[155] Alcohol **194** was provided by Megan Jaschinski. See Megan Jaschinski's Part II thesis **2023**.

Ti(O*i*-Pr)$_4$ instead of TFA and overnight. The crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:Et_2O; 47:3) to furnish tetrahydrofuran **195** as a colourless oil (4.7 mg, 17%).

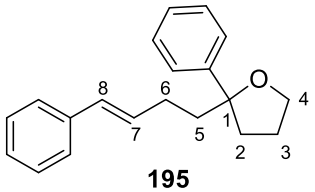
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.09 (m, 10H, H-Ph), 6.34 – 6.23 (m, 1H, H-8), 6.19 – 6.08 (m, 1H, H-7), 4.03 – 3.95 (m, 1H, H-4$_a$), 3.92 (td, *J* = 8.1, 5.7 Hz, 1H, H-4$_b$), 2.30 – 2.16 (m, 2H, H-2$_a$, H-6$_a$), 2.15 – 1.86 (m, 5H, H-3$_a$, H-2$_b$, H-5$_a$, H-5$_b$, H-6$_b$), 1.79 (dqd, *J* = 12.1, 7.9, 6.5 Hz, 1H, H-3$_b$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.6 (C-Ph), 138.0 (C-Ph), 131.0 (C-7), 129.7 (C-8), 128.6 (2C, C-Ph), 128.2 (2C, C-Ph), 126.9 (C-Ph), 126.5 (C-Ph), 126.0 (2C, C-Ph), 125.4 (2C, C-Ph), 86.6 (C-1), 67.7 (C-4), 42.2 (C-5), 38.7 (C-2), 28.3 (C-6), 25.7 (C-3).

IR (film) ν_{max}: 3025, 2980, 2358, 1600, 1494, 1446, 1057, 966, 746, 704, 645 cm^{-1}.

HRMS (ESI) calculated for $C_{20}H_{22}ONa$ $[M+Na]^+$ requires 301.1563 m/z, found 301.1570 m/z (Δ = 2.36 ppm).

((*E*)-2-Phenyl-2-(4-phenylbut-3-en-1-yl)tetrahydrofuran 195.



195

$C_{20}H_{22}O$

278.40 g mol^{-1}

Alcohol **194**[156] (16.2 mg, 0.100 mmol, 1.00 equiv), acetate **174** (17.6 mg, 0.100 mmol, 1.00 equiv), $[Ir(cod)Cl]_2$ (2.0 mg, 3.0 µmol, 0.030 equiv, 3.0 mol%), (*S*)-**L1** Carreira ligand[157] (3.0 mg, 6.0 µmol, 0.060 equiv, 6.0 mol%) and $Zn(OTf)_2$ (18.2 mg, 0.0500 mmol, 0.500 equiv) were transferred into a GC vial equipped with a stirring bar. The vial was closed and purged with argon for 15 min. The balloon of argon was removed and 1,2-dichloroethane (0.40 mL, 0.25 M) was added. The vial was additionally sealed with parafilm and the suspension was stirred at rt for 3 days. Volatiles were removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 60 Å, 15–40 µm; pentane:EtOAc; 19:1 to 9:1) to furnish ether **195** as a colourless oil (4.4 mg, 16%, 66:34 er).

[156] Alcohol **194** was provided by Megan Jaschinski. See Megan Jaschinski's Part II thesis **2023.**
[157] (*S*)-Carreira **L1** ligand was synthesised in house according to the literature procedure – see page **310**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.09 (m, 10H, H-Ph), 6.34 – 6.23 (m, 1H, H-8), 6.19 – 6.08 (m, 1H, H-7), 4.03 – 3.95 (m, 1H, H-4_a), 3.92 (td, *J* = 8.1, 5.7 Hz, 1H, H-4_b), 2.30 – 2.16 (m, 2H, H-2_a, H-6_a), 2.15 – 1.86 (m, 5H, H-3_a, H-2_b, H-5_a, H-5_b, H-6_b), 1.79 (dqd, *J* = 12.1, 7.9, 6.5 Hz, 1H, H-3_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.6 (C-Ph), 138.0 (C-Ph), 131.0 (C-7), 129.7 (C-8), 128.6 (2C, C-Ph), 128.2 (2C, C-Ph), 126.9 (C-Ph), 126.5 (C-Ph), 126.0 (2C, C-Ph), 125.4 (2C, C-Ph), 86.6 (C-1), 67.7 (C-4), 42.2 (C-5), 38.7 (C-2), 28.3 (C-6), 25.7 (C-3).

[α] $\frac{25}{D}$ **=** +15.7 (c = 0.1, $CHCl_3$)

HPLC: Enantiomeric ratio was determined by HPLC with a Chiralpak® IC column (99.5:0.5 hexane:IPA, 1.0 mL min^{-1}, 254 nm, rt); tr (major) = 5.3 min, tr (minor) = 5.9 min; 66:34 er.

The analytical data is consistent to the racemic sample of **195.**

6.4 Single crystal X-ray diffraction for compounds 27b, 27e, 27l, 47, 48, 149, 165

Single Crystal Data for 27l

C_{248} H_{288} O_{16}

M_r 3525.00

150 K

Monoclinic

C 2/c

a = 23.5285(2) Å, b = 23.8965(2) Å, c = 34.6674(4) Å

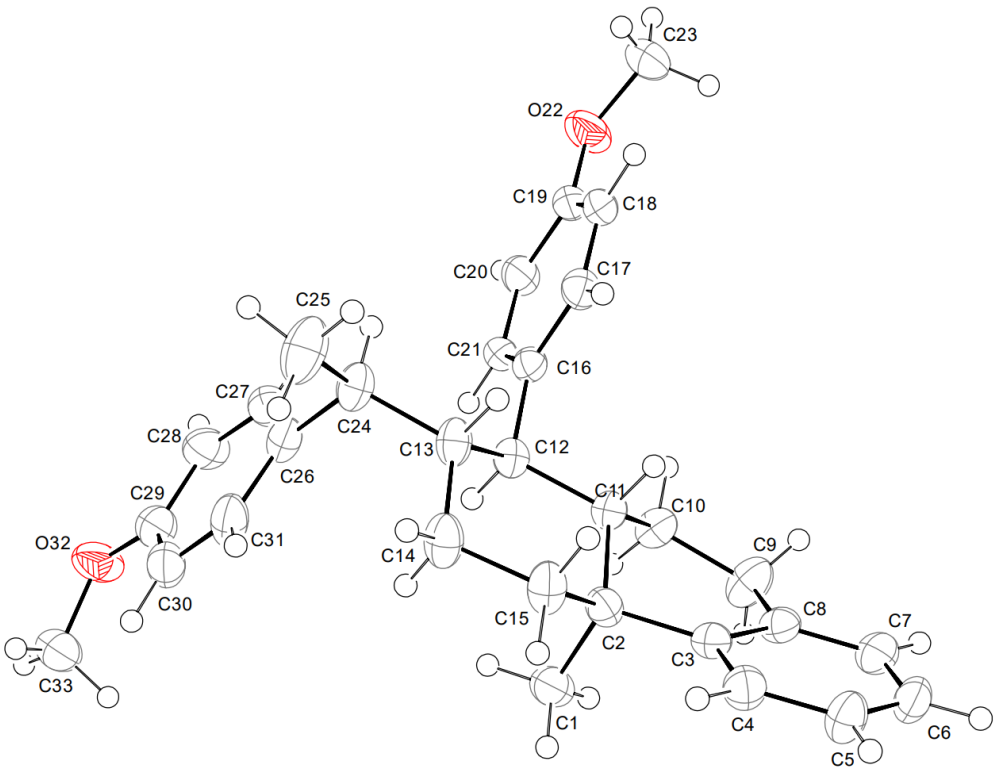
α= 90° β= 97.2217(9)° γ = 90°

V = 19337.1(3) Å^3

Data/restraints/parameters – 16043/ 313/1373

[R(int) = 0.058

Final R1 = 0.0921, wR2 = 0.2392 [I>2sigma(I)]



This structure contains four molecules in the asymmetric unit. For clarity only one molecule is shown. Additional molecules are off-set in the numbering scheme by 50 and any disorder is off-set by 500.

Single Crystal Data for 27e

C_{31} H_{36} O_3

M_r 456.62

150 K

Monoclinic

P $2_1/n$

a = 5.75750(10) Å, b = 31.6859(6) Å, c = 13.7088(3) Å

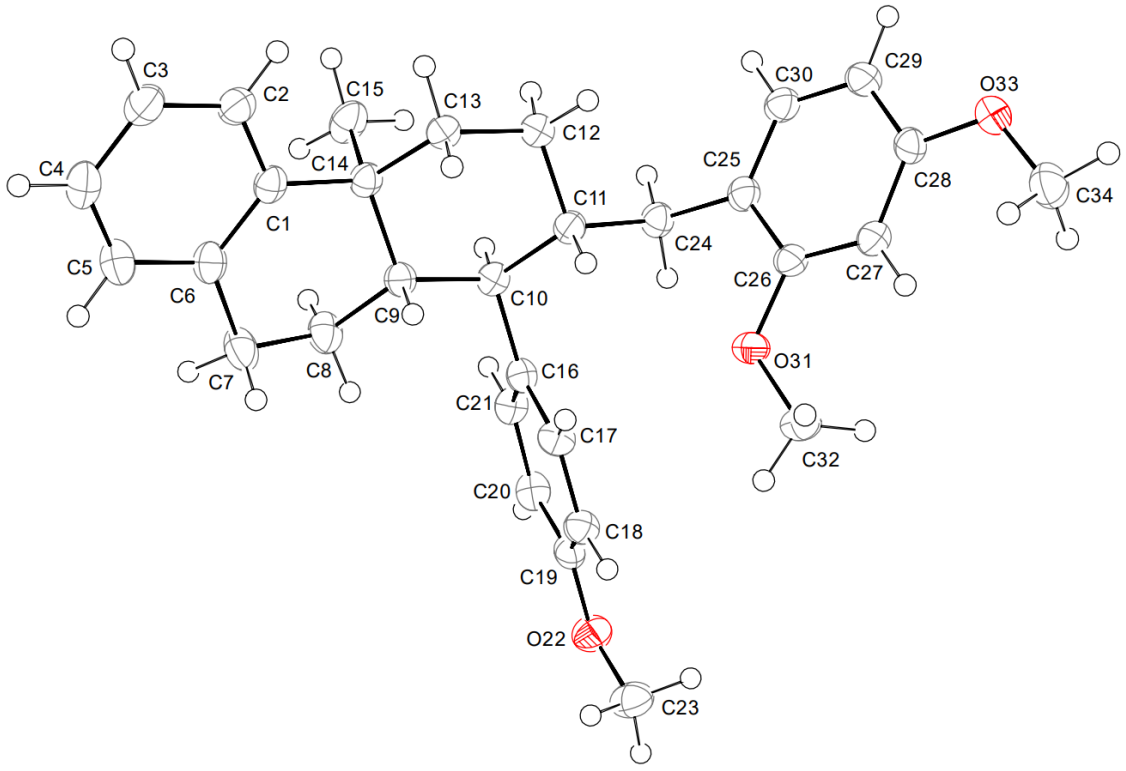
α= 90° β= 94.198(2)° γ = 90°

V = 2494.21(8) Å^3

Data/restraints/parameters – 5158/ 0/ 307

R(int) = 0.034

R1 = 0.0397, wR2 = 0.0962 [I>2sigma(I)]



Single Crystal Data for 27b

C_{30} H_{34} O_2

M_r 426.60

150 K

Monoclinic

P $2_1/c$

a = 10.0874(5) Å, b = 15.3761(6) Å, c = 15.3706 (6) Å

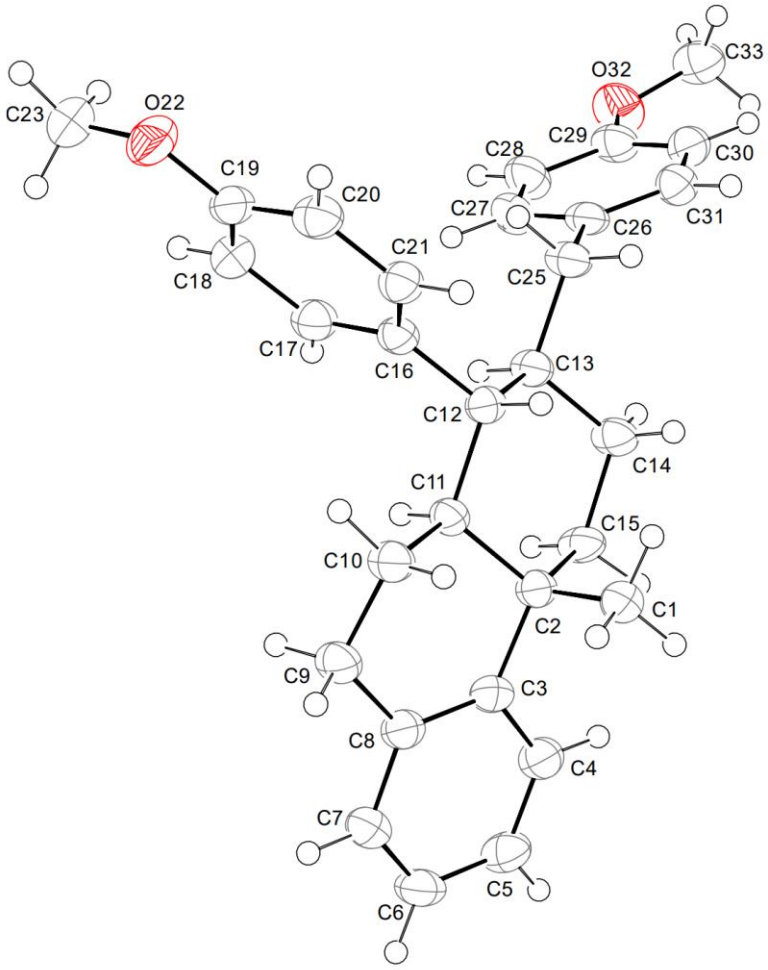
α= 90° β= 101.820(5)° γ = 90°

V = 2333.50(18) Å^3

Data/restraints/parameters – 4864/0/ 289

R(int) = 0.097

R1 = 0.0676, wR2 = 0.1701 [I>2sigma(I)]



Single Crystal Data for 47

C_{36} H_{38} O_2

M_r 502.70

150 K

Triclinic

P -1

a = 10.1264(3) Å, b = 10.8819(3) Å, c = 13.4382(4) Å

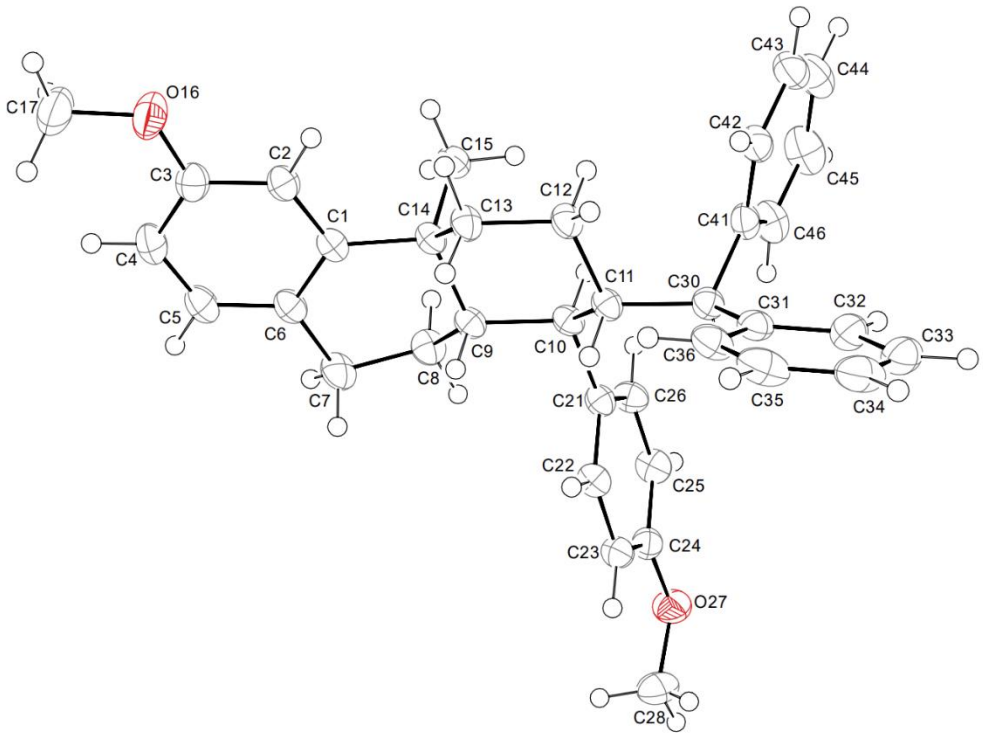
α= 88.808(3)° β= 77.853(3)° γ = 76.137(3)°

V = 1404.81(7) Å^3

Data/restraints/parameters – 5813/0/343

R(int) = 0.025

R1 = 0.0359, wR2 = 0.0960 [I>2sigma(I)]



Single Crystal Data for 48

$C_{36}H_{38}O$

M_r 486.70

150 K

Triclinic

P -1

a = 10.0988(3) Å, b = 11.1576(4) Å, c = 12.6763(3) Å

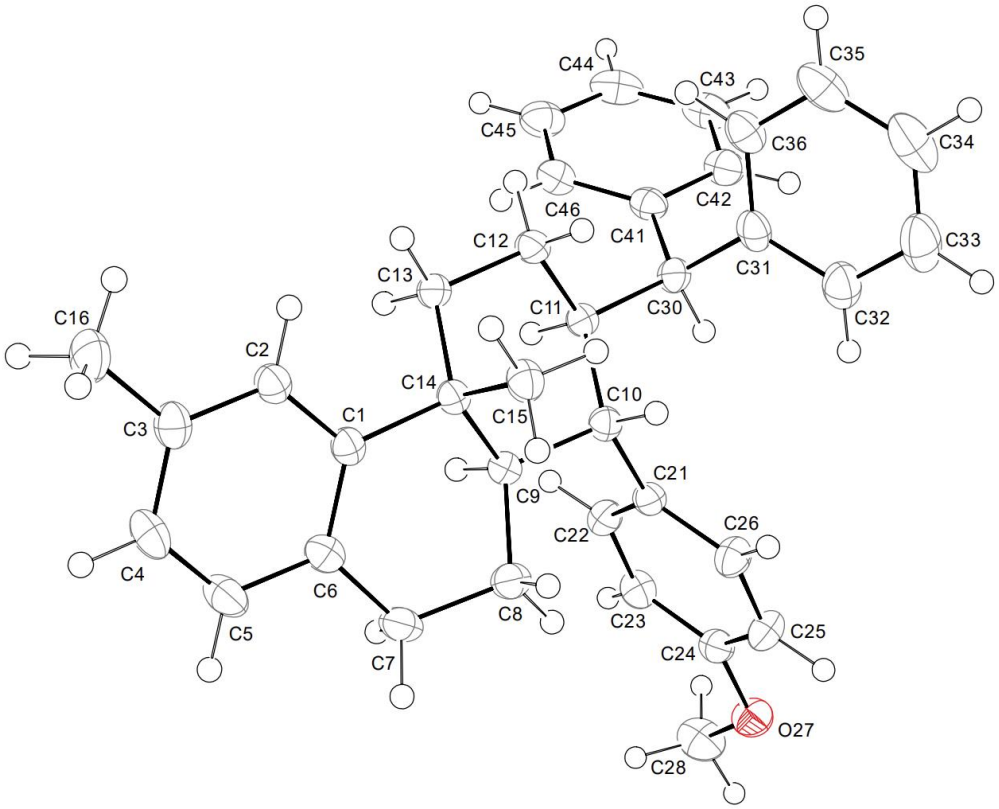
α= 89.681(2)° β= 77.820(2)° γ = 76.018(3)°

V = 1353.27(7) Å^3

Data/restraints/parameters – 5521/0/335

R(int) = = 0.024

R1 = 0.0415, wR2 = 0.0970 [I>2sigma(I)]



Single Crystal Data for 149

$C_{23}H_{24}O_2$

M_r 332.44

150 K

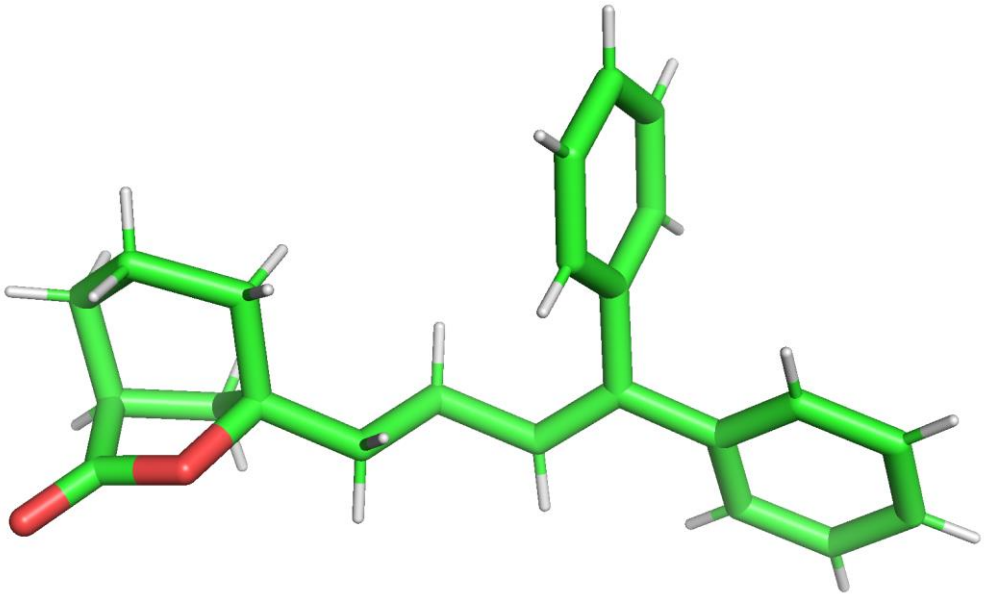
Monoclinic

P $2_1/n$

a = 6.11840(10) Å, b = 33.9883(5) Å, c = 8.72550(10) Å

α= 90° β= 90.5312(15)° γ = 90°

V = 1814.43(4) $Å^3$



Single Crystal Data for 165

C_{13} $H_{14}O_4$

M_r 234.25

150 K

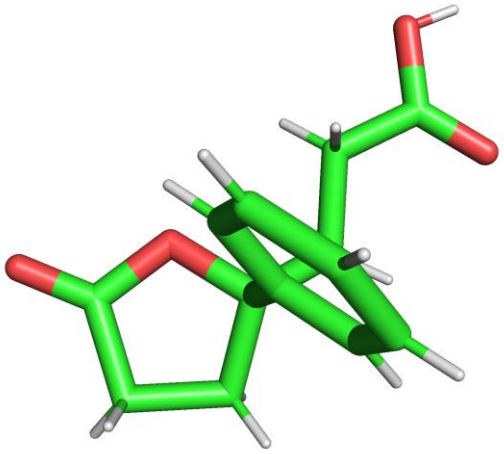
Monoclinic

P $2_1/c$

a = 5.76180(10) Å, b = 7.2943(2) Å, c = 27.0456(7) Å

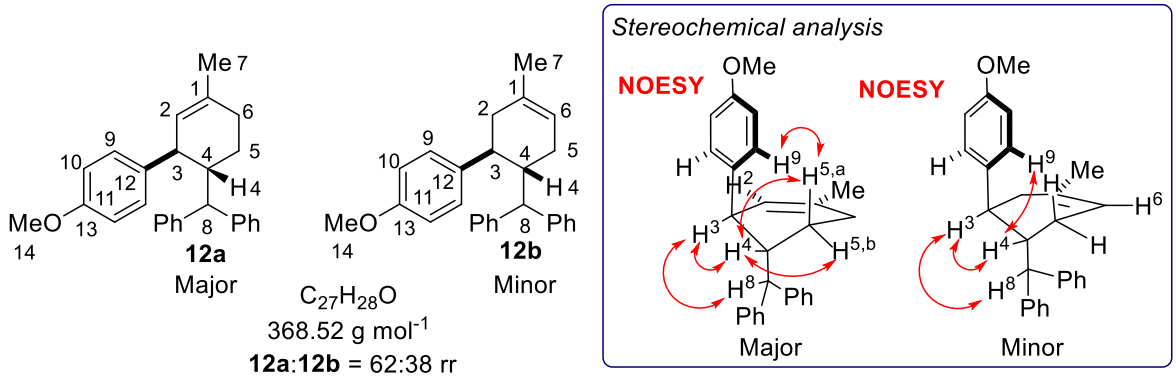
α= 90° β= 93.910(2)° γ = 90°

V = 1134.03(5) $Å^3$

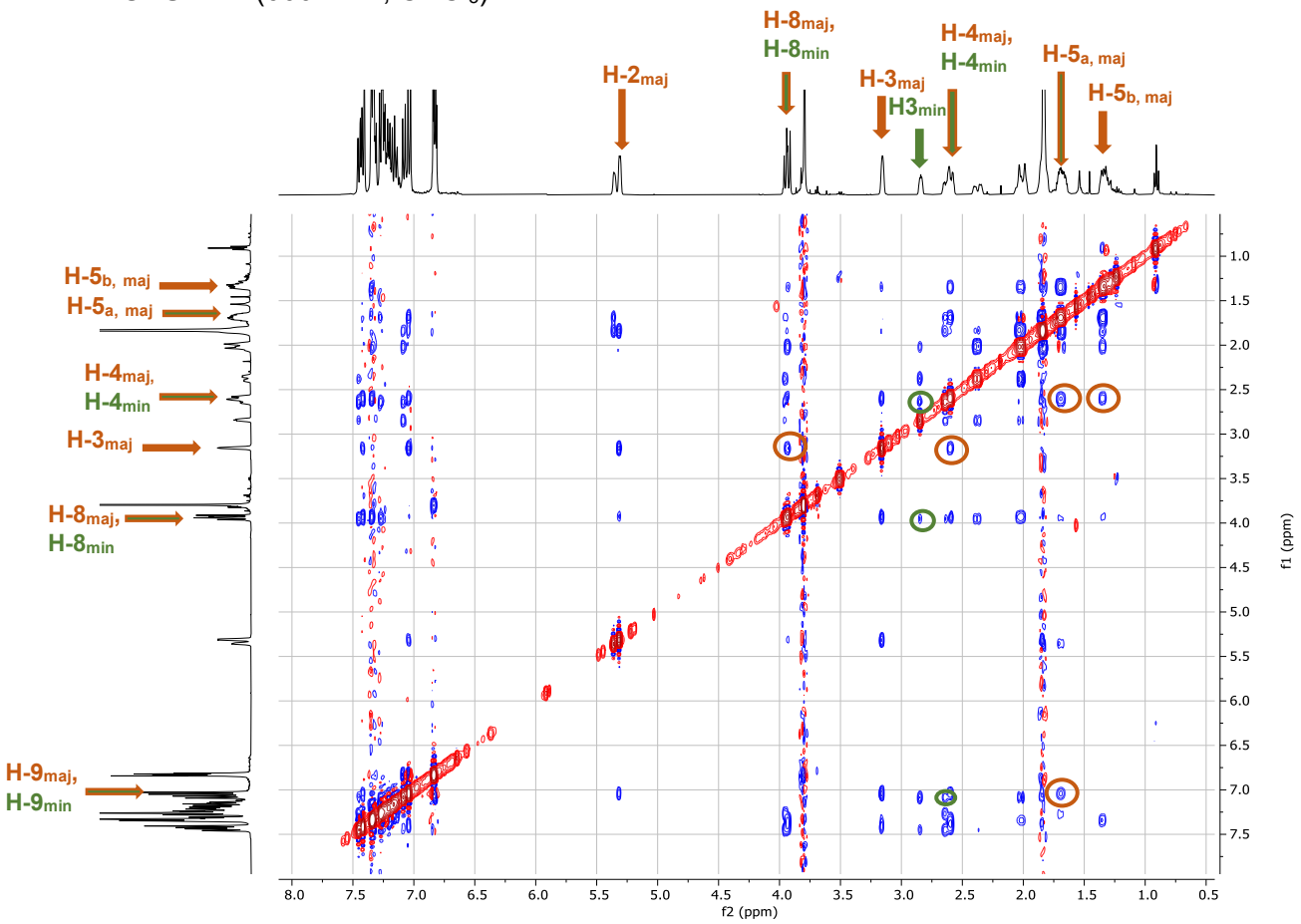


6.5 NOESY data for representative compounds

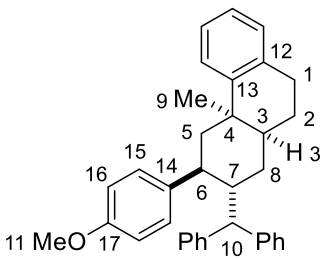
(±)-(1*R*,2*S*)-2-Benzhydryl-4'-methoxy-5-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (major)-12a and (±)-(1*S*,2*S*)-2-Benzhydryl-4'-methoxy-5-methyl-1,2,3,6-tetrahydro-1,1'-biphenyl (minor)-12b.



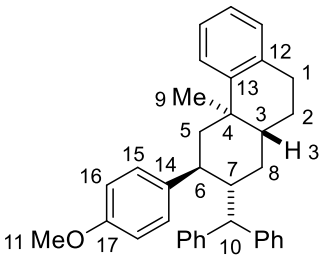
NOESY-2D (600 MHz, $CDCl_3$)



(±)-(2*S*,3*S*,4*aR*,10*aS*)-2-benzhydryl-3-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 25a and (±)-(2*S*,3*S*,4*aR*,10*aR*)-2-benzhydryl-3-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 25b.

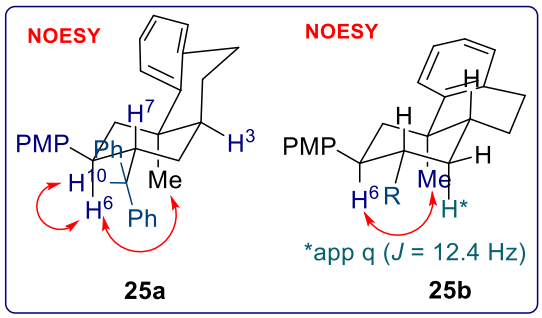


25a

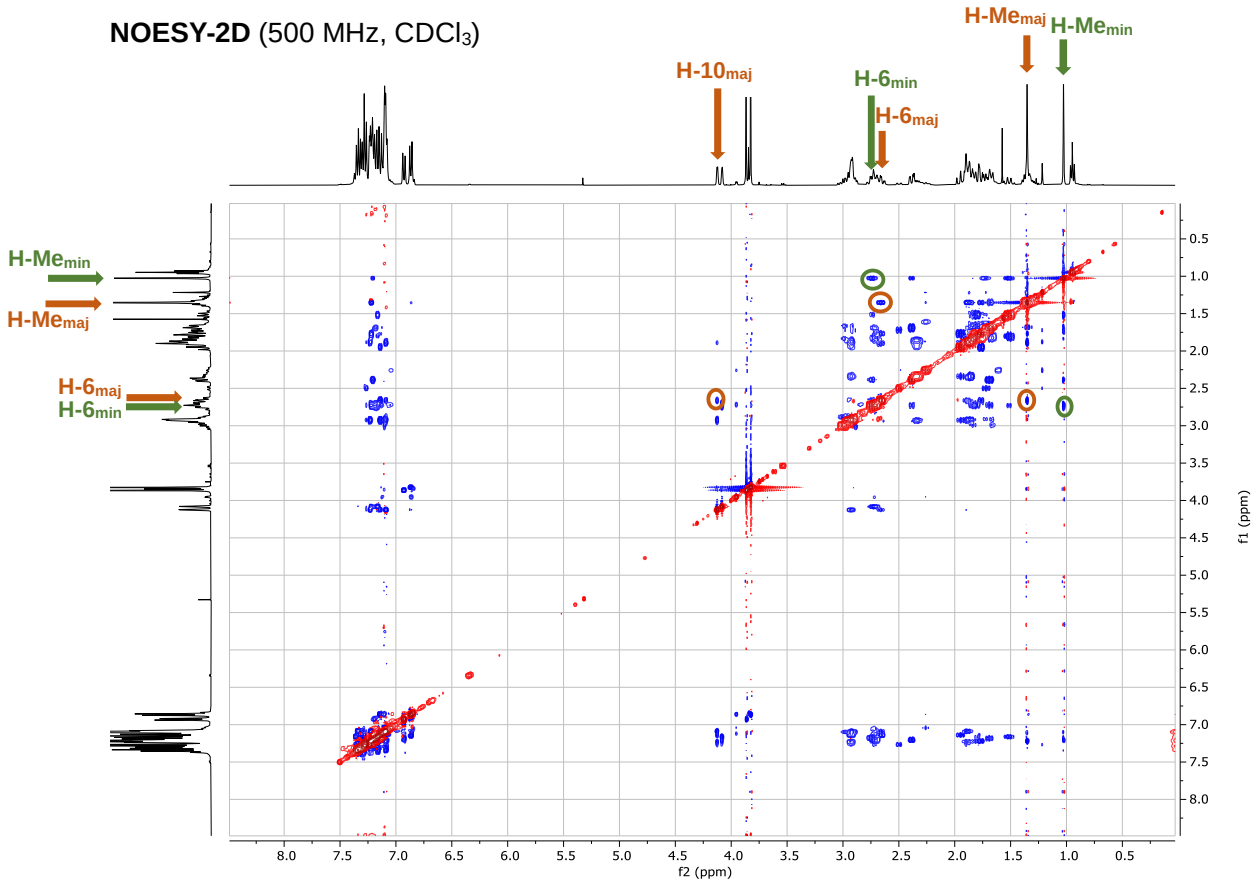


25b

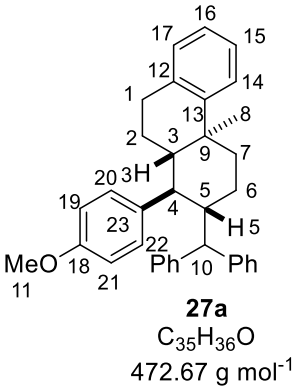
$C_{35}H_{36}O$
472.67 g mol^{-1}
25a:**25b**=52:48



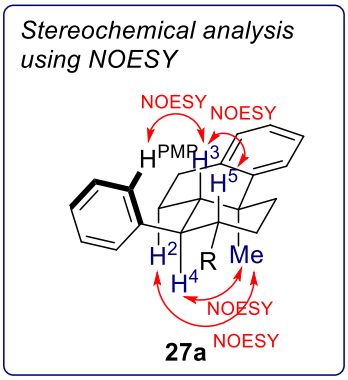
25a **25b**



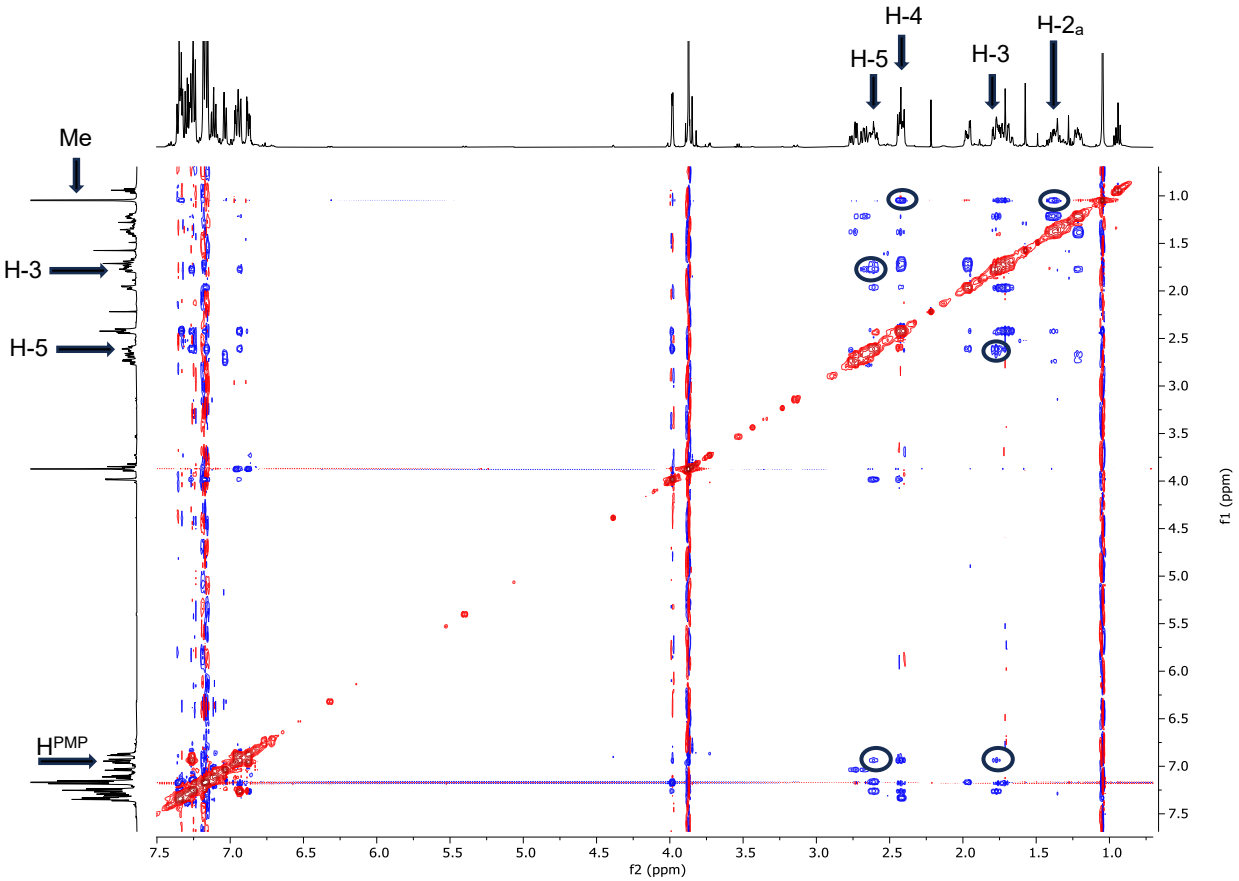
(±)-(1*R*,2*S*,4*aS*,10*aS*)-2-benzhydryl-1-(4-methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 27a.



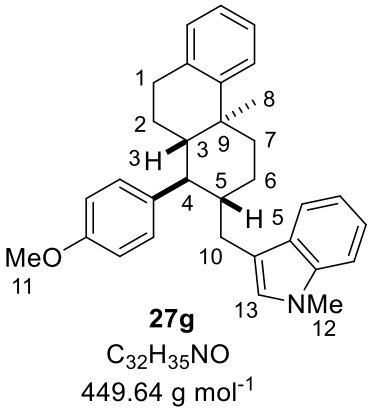
27a
$C_{35}H_{36}O$
472.67 g mol^{-1}



NOESY-2D (600 MHz, $CDCl_3$)



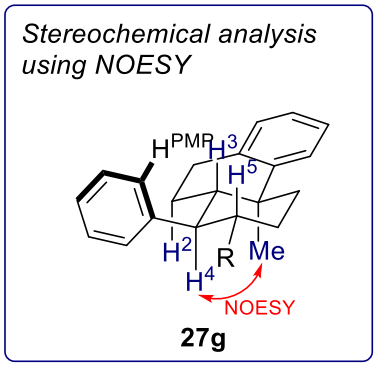
(±)-3-((1*R*,2*R*,4*aS*,10*aS*)-1-(4-Methoxyphenyl)-4*a*-methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-2-yl)methyl)-1-methyl-1H-indole 27g.



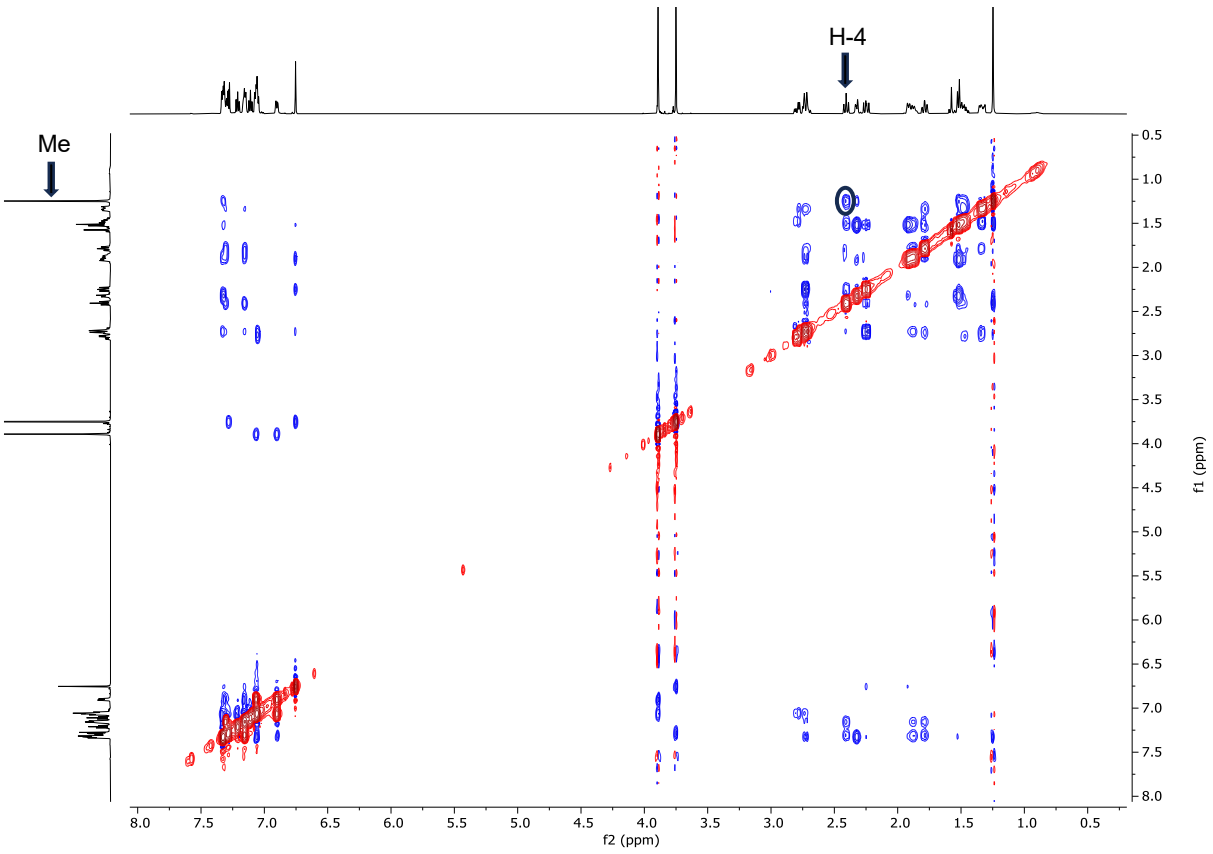
27g

$C_{32}H_{35}NO$

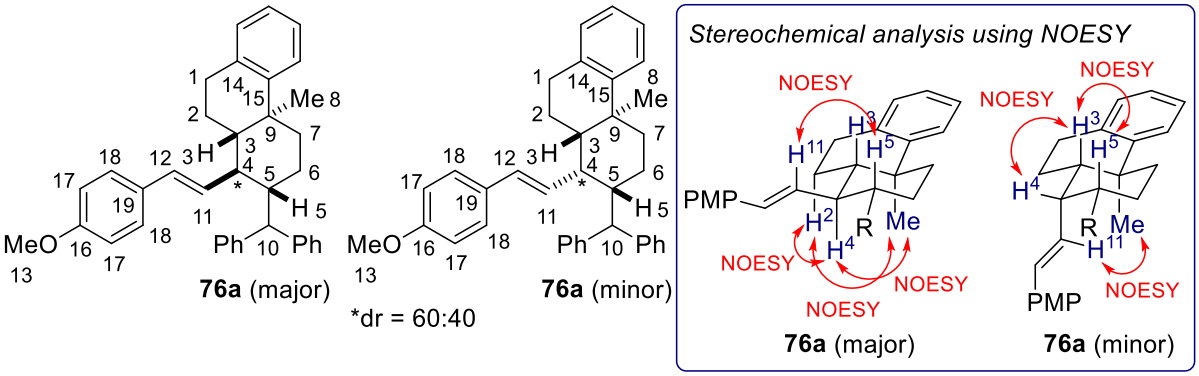
449.64 g mol^{-1}



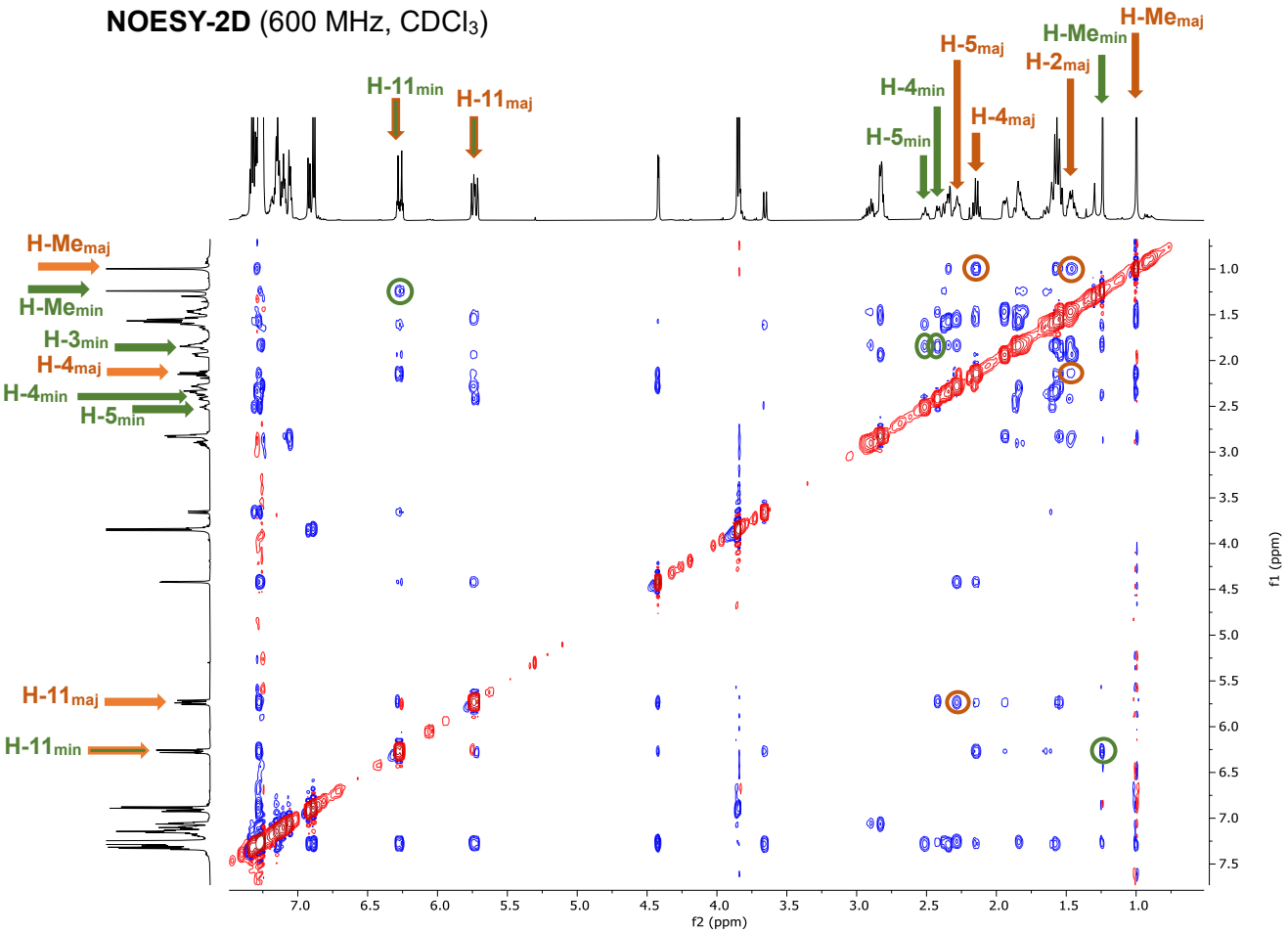
NOESY-2D (600 MHz, $CDCl_3$)



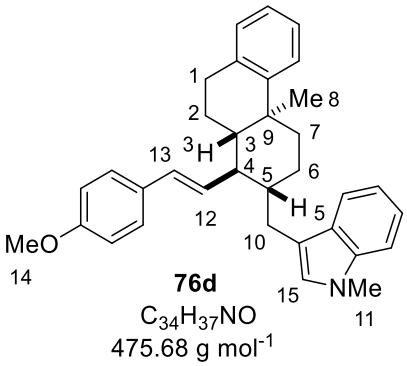
(±)-(1*R*,2S,4aS,10aS)-2-Benzhydryl-1-((*E*)-4-methoxystyryl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (major)-76a and (±)-(1*S*,2S,4aS,10aS)-2-Benzhydryl-1-((*E*)-4-methoxystyryl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (minor)-76a.



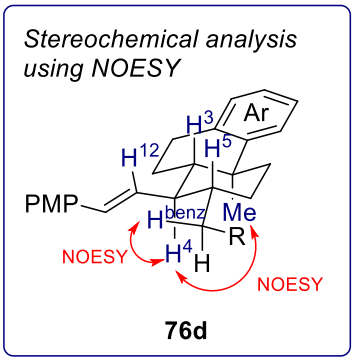
NOESY-2D (600 MHz, $CDCl_3$)



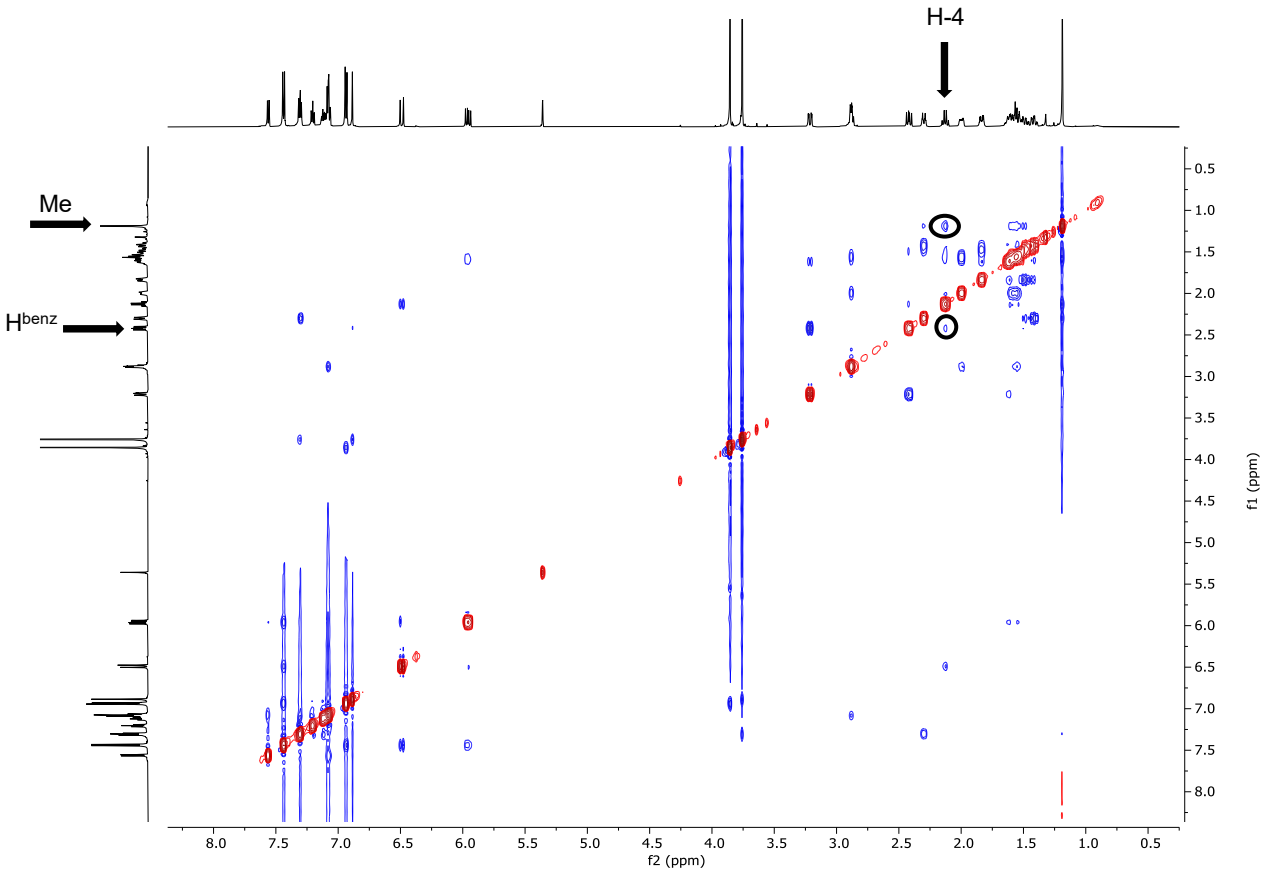
(±)-3-(((1*S*,2*R*,4*aS*,10*aS*)-1-((*E*)-4-Methoxystyryl)-4*a*-methyl-1,2,3,4,4$_a$,9,10,10*a*-octahydrophenanthren-2-yl)methyl)-1-methyl-1H-indole 76d.



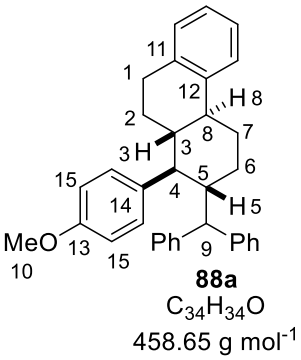
76d
$C_{34}H_{37}NO$
475.68 g mol^{-1}



NOESY-2D (600 MHz, $CDCl_3$)



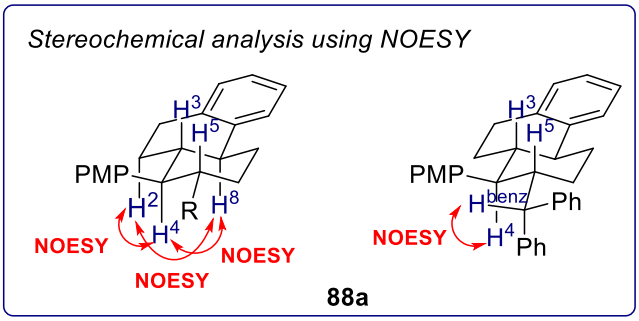
(±)-(1*S*,2*S*,4*aS*,10*aR*)-2-Benzhydryl-1-(4-methoxyphenyl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene 88a.



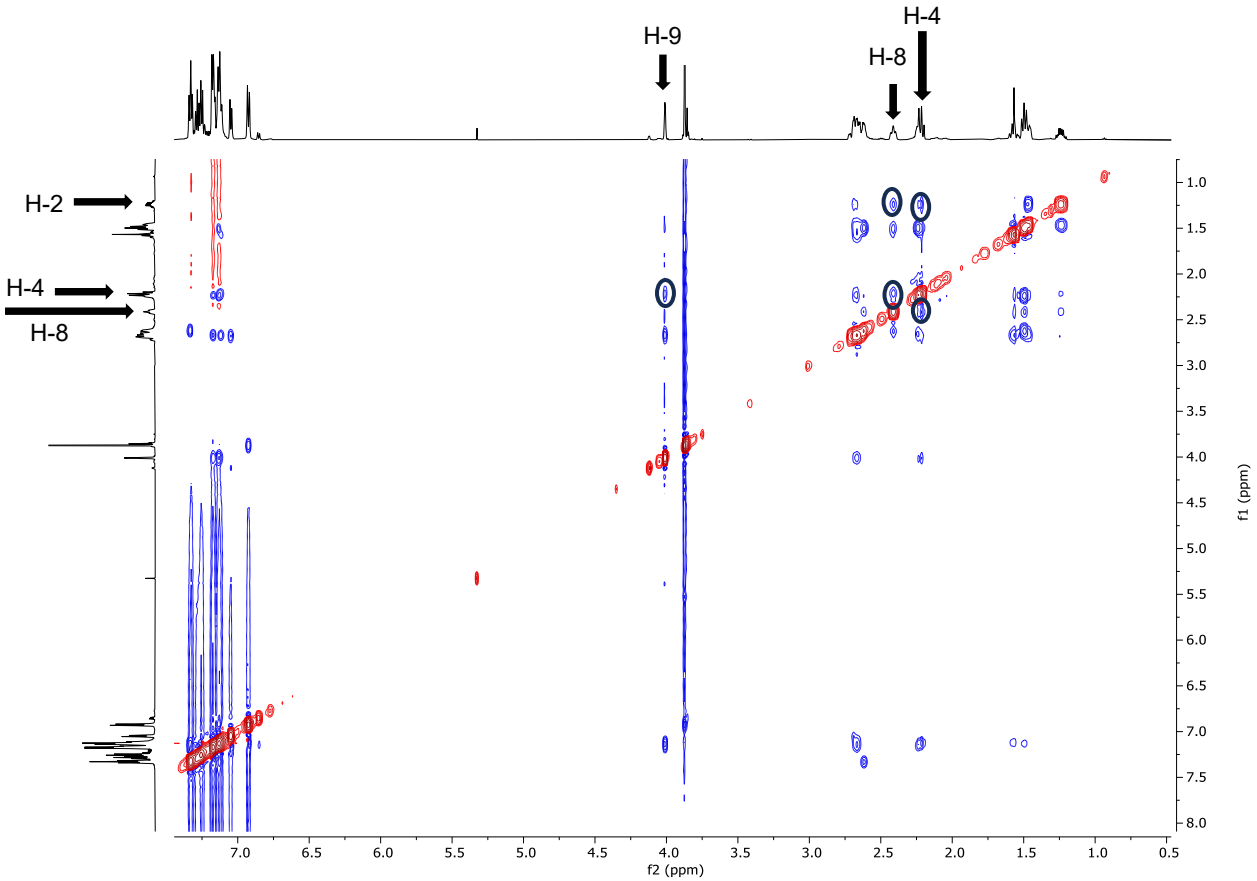
88a

$C_{34}H_{34}O$

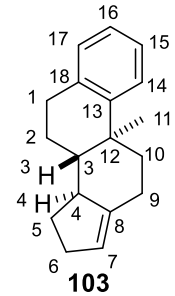
458.65 g mol^{-1}



NOESY-2D (600 MHz, $CDCl_3$)



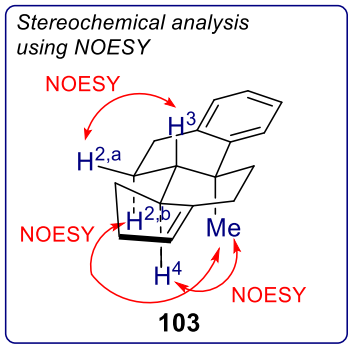
(±)-(8*S*,9*S*,14*S*)-9-Methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[*a*]phenanthrene 103.



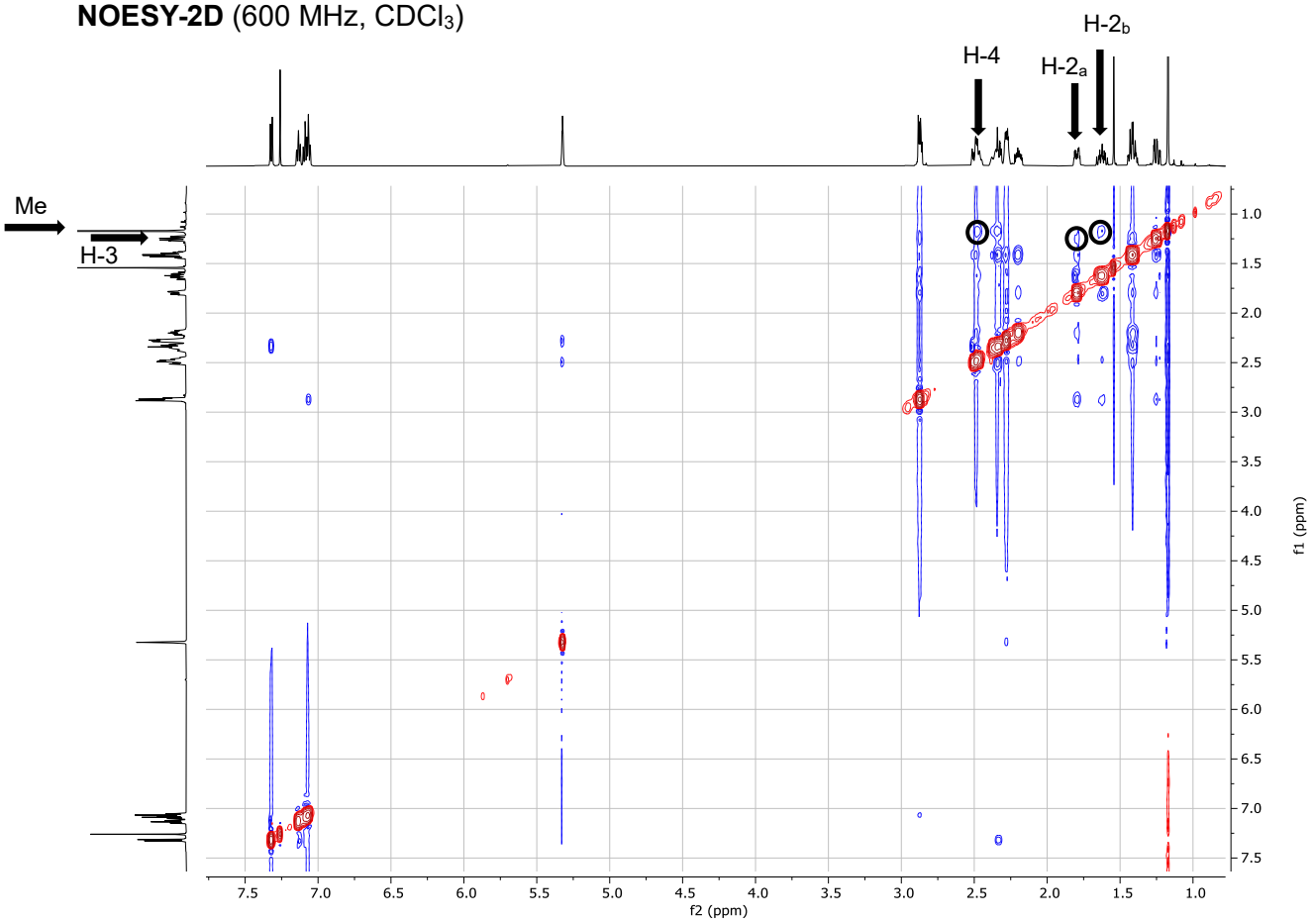
103

$C_{18}H_{22}$

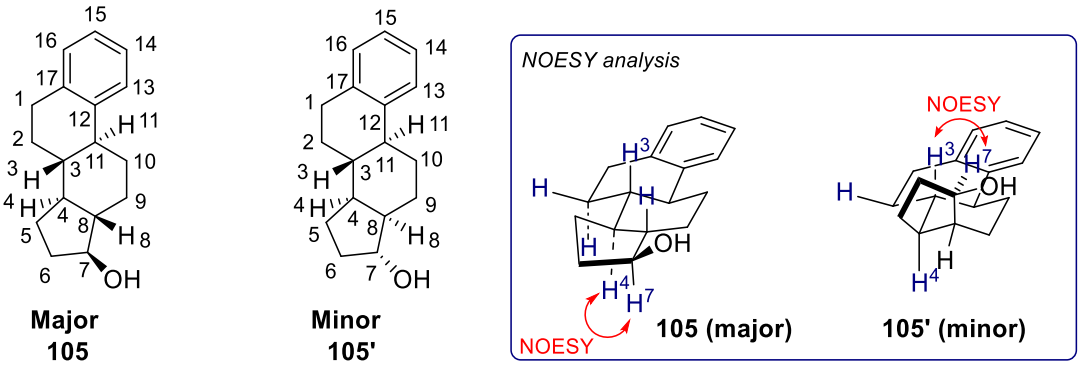
238.37 g mol^{-1}



NOESY-2D (600 MHz, $CDCl_3$)

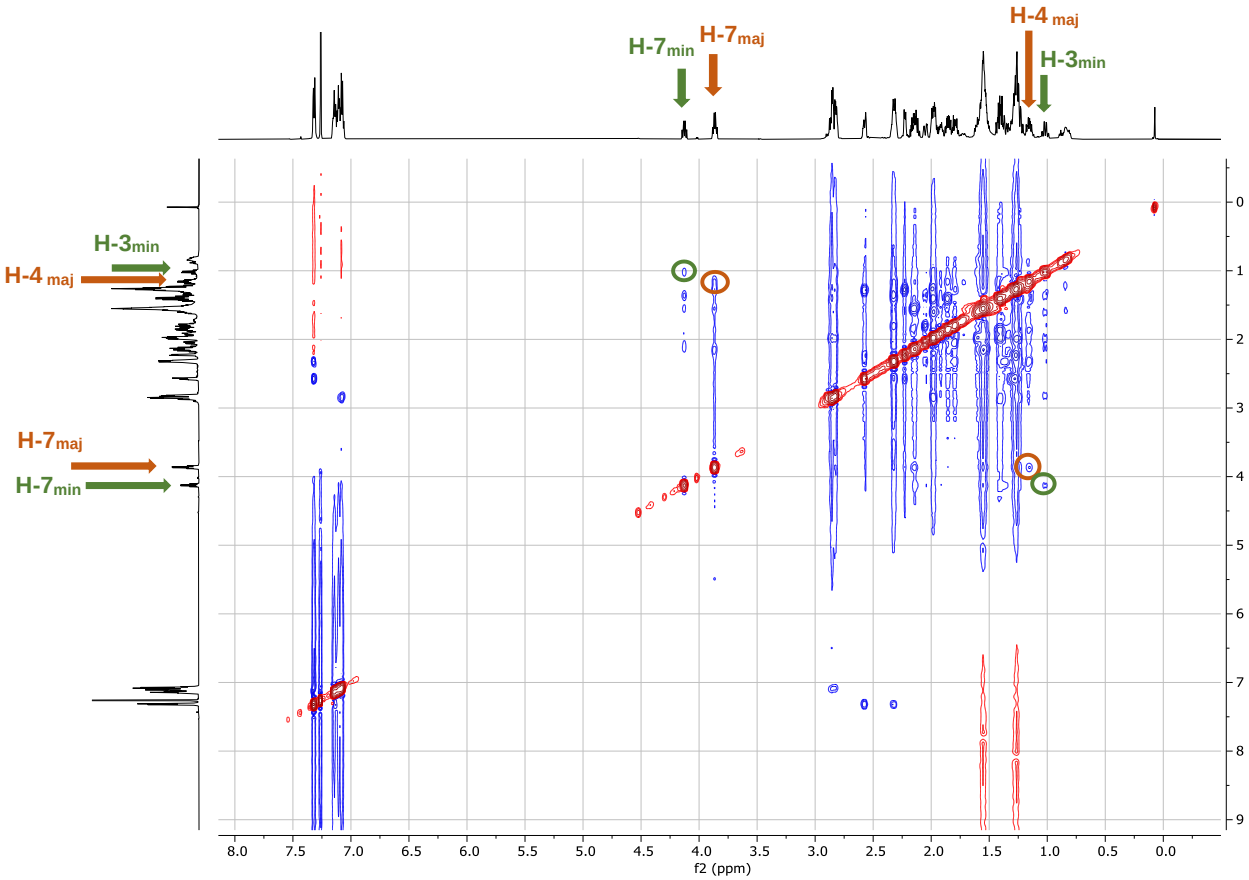


(±)-(8*S*,9*S*,13*S*,14*S*,17*S*)-7,8,9,11,12,13,14,15,16,17-Decahydro-6H-cyclopenta[a]phenanthren-17-ol 105 (major) and (±)-(8*S*,9*S*,13*R*,14*S*,17*R*)-7,8,9,11,12,13,14,15,16,17-Decahydro-6H-cyclopenta[a]phenanthren-17-ol 105' (minor).

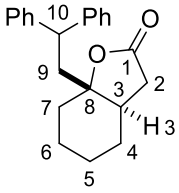


$C_{17}H_{22}O$
242.36 g mol^{-1}

NOESY-2D (600 MHz, $CDCl_3$)



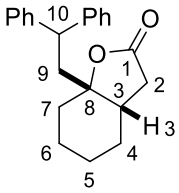
(±)-(3*aR*,7*aR*)-7*a*-(2,2-Diphenylethyl)hexahydrobenzofuran-2(3H)-one 151a-major and (±)- (3*aS*,7*aR*)-7*a*-(2,2-diphenylethyl)hexahydrobenzofuran-2(3H)-one 151a-minor.



Major-151a

$C_{22}H_{24}O_2$

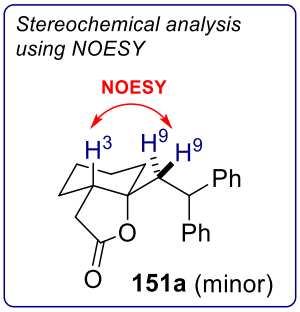
320.43 g mol^{-1}



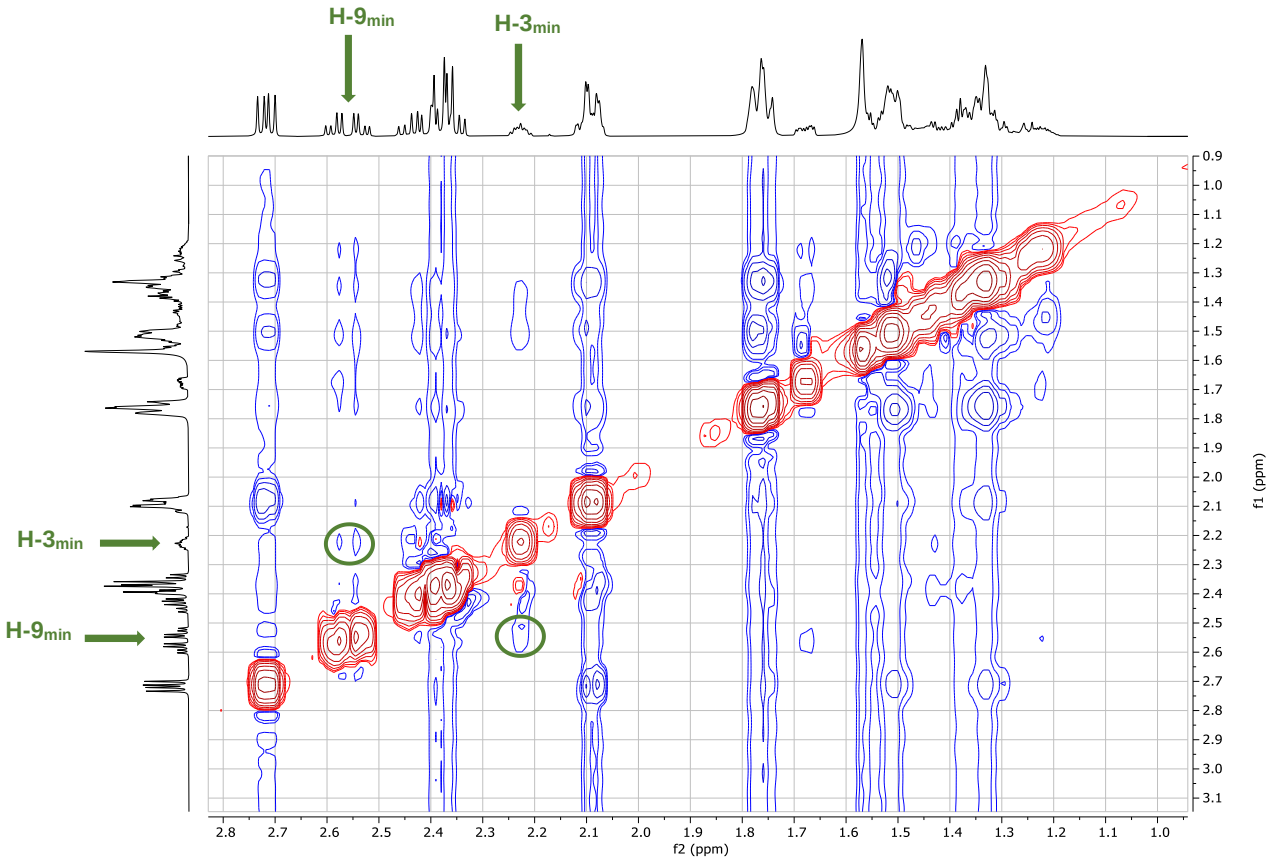
Minor-151a

$C_{22}H_{24}O_2$

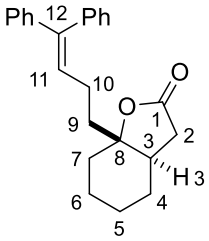
320.43 g mol^{-1}



NOESY-2D (600 MHz, $CDCl_3$)



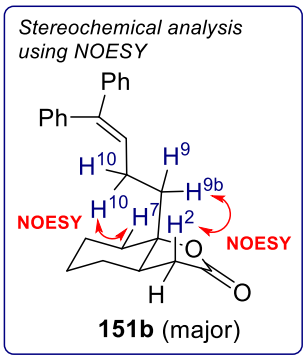
(±)-(3*aR*,7*aR*)-7*a*-(4,4-Diphenylbut-3-en-1-yl)hexahydrobenzofuran-2(3H)-one 151b-major



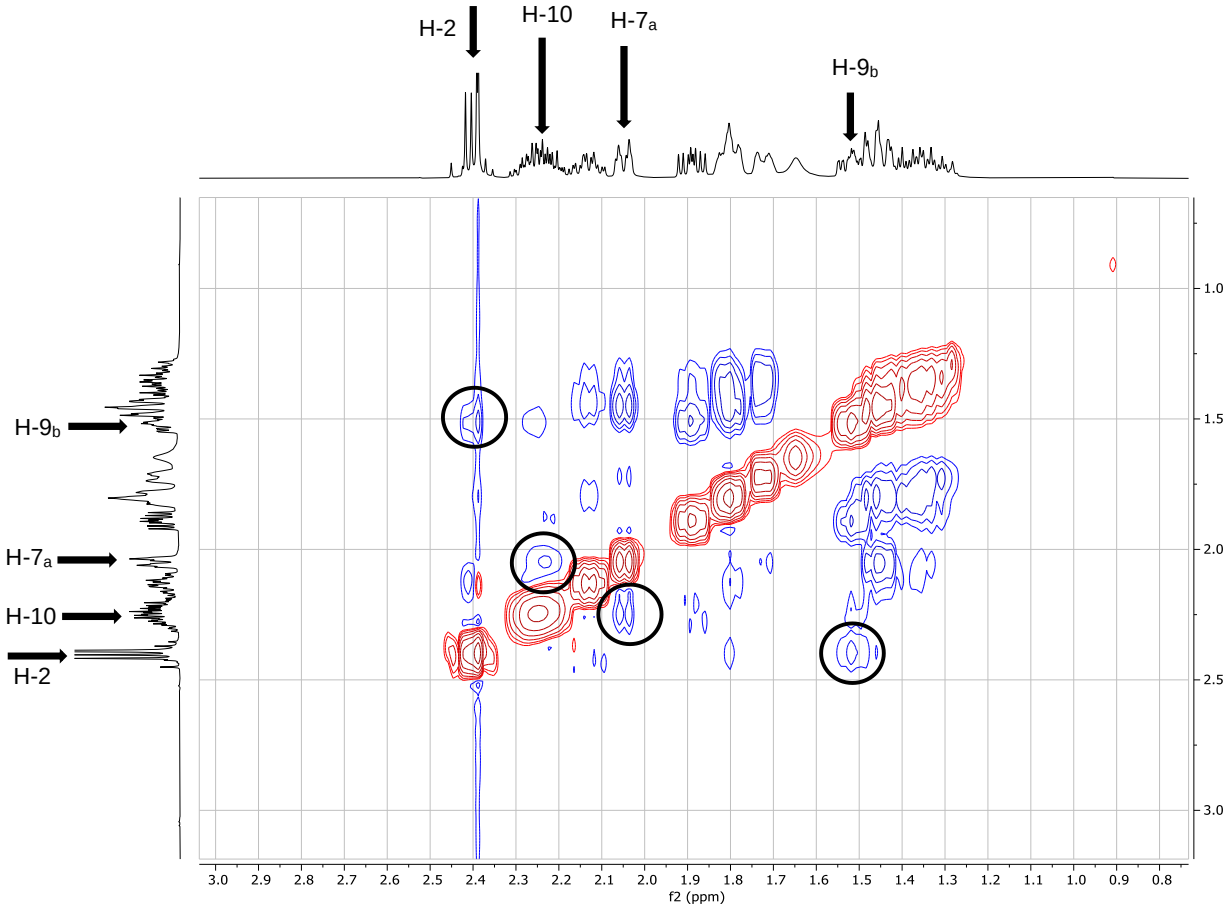
Major-151b

$C_{24}H_{26}O_2$

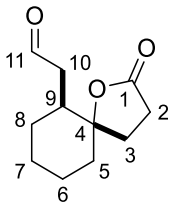
346.47 g mol^{-1}



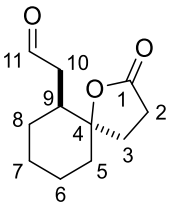
NOESY-2D (600 MHz, $CDCl_3$)



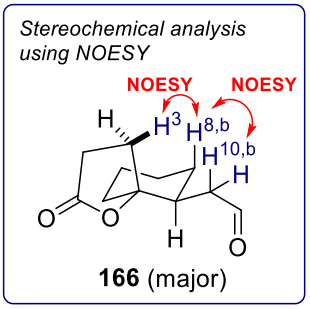
(±)-2-((5*S*,6*S*)-2-oxo-1-oxaspiro[4.5]decan-6-yl)acetaldehyde 166-major and (±)-2-((5*R*,6*S*)-2-oxo-1-oxaspiro[4.5]decan-6-yl)acetaldehyde 166-minor.



Major-166
$C_{11}H_{16}O_3$
196.25 g mol^{-1}

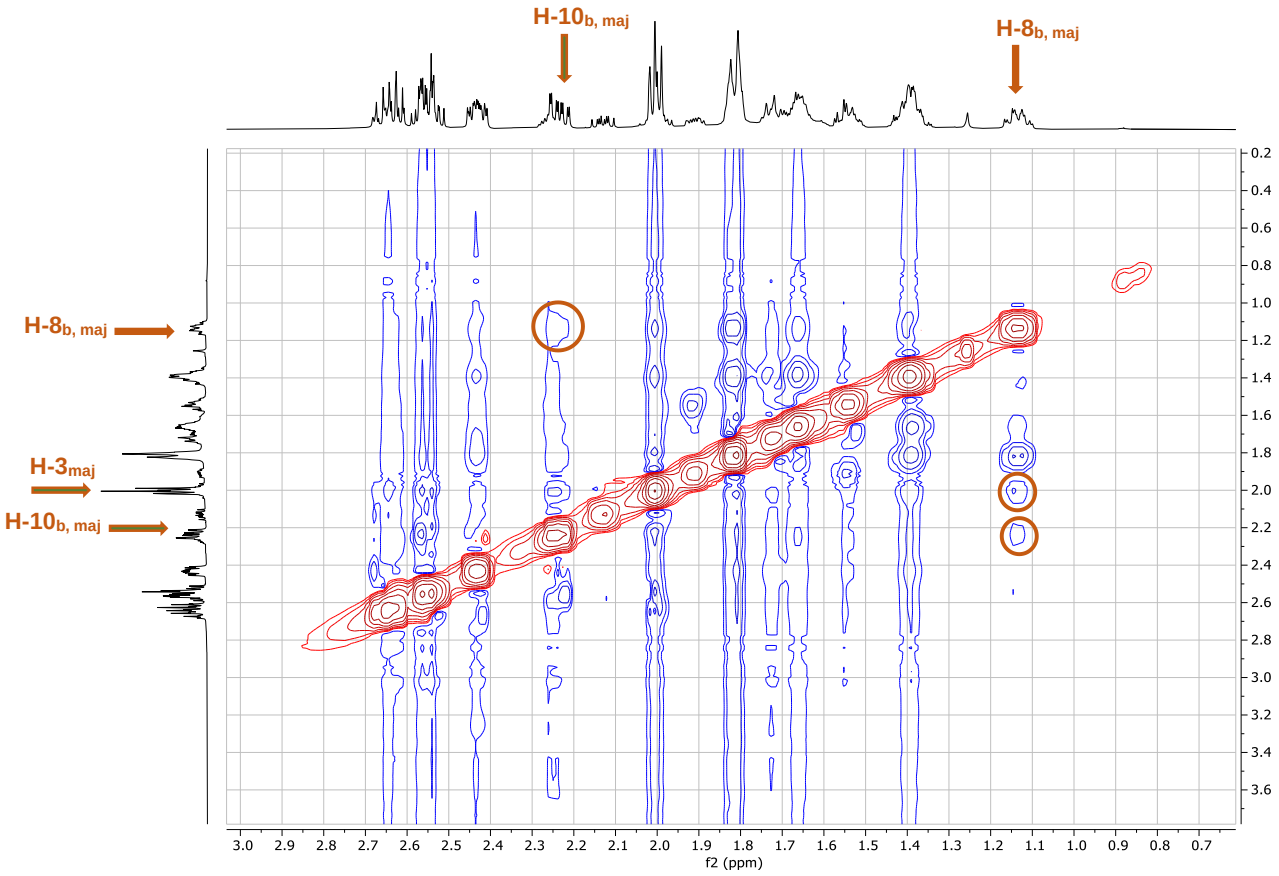


Minor-166
$C_{11}H_{16}O_3$
196.25 g mol^{-1}

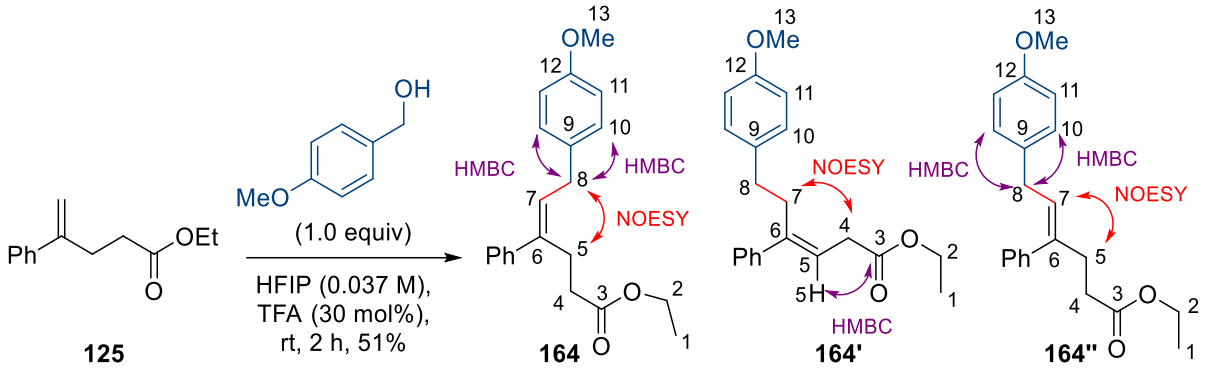


166 (major)

NOESY-2D (600 MHz, $CDCl_3$)

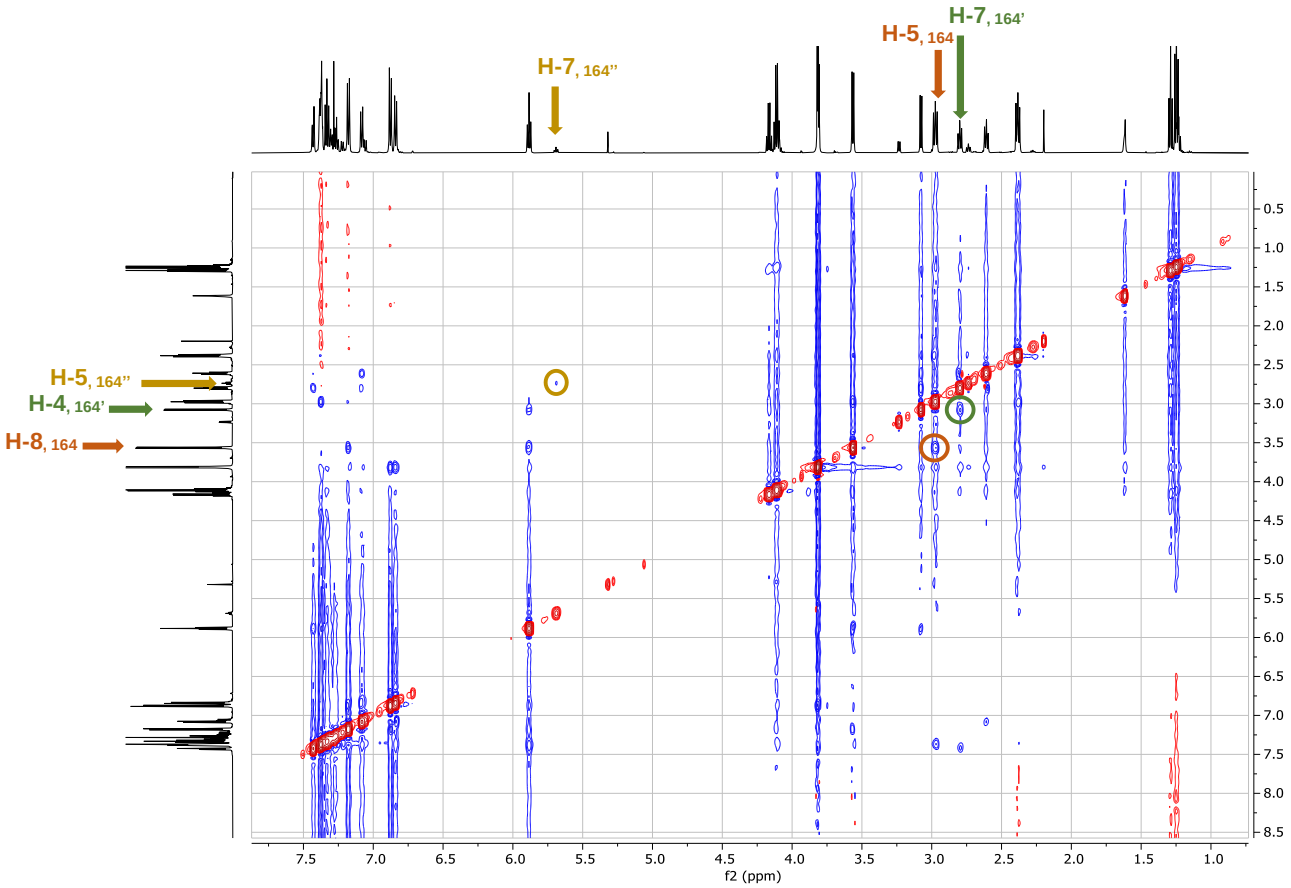


Control experiment using ester 125.



164 : **164'** : **164"** = 58 : 33 : 9

NOESY-2D (600 MHz, $CDCl_3$)



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