Novel Synthesis of Highly Functionalised Furans and Investigation into a Cope Rearrangement of Furylvinylcyclopropanes

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The best way out is always through. (Robert Frost)

for myself

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One last advice: ‘When the spirits are low, when the day appears dark, when work becomes monotonous, when hope hardly seems worth having, just mount a bicycle and go out for a spin down the road, without thought on anything but the ride you are taking.’

Declaration

I herby declare that the substance of this thesis has not been submitted, nor is being concurrently submitted, in candidature for any other degree.

I also declare that the work presented in this thesis is the result of my own investigations and when the work of other investigators has been used, this has been fully acknowledged in the text.

Verena Klaus

Professor J. S. Clark

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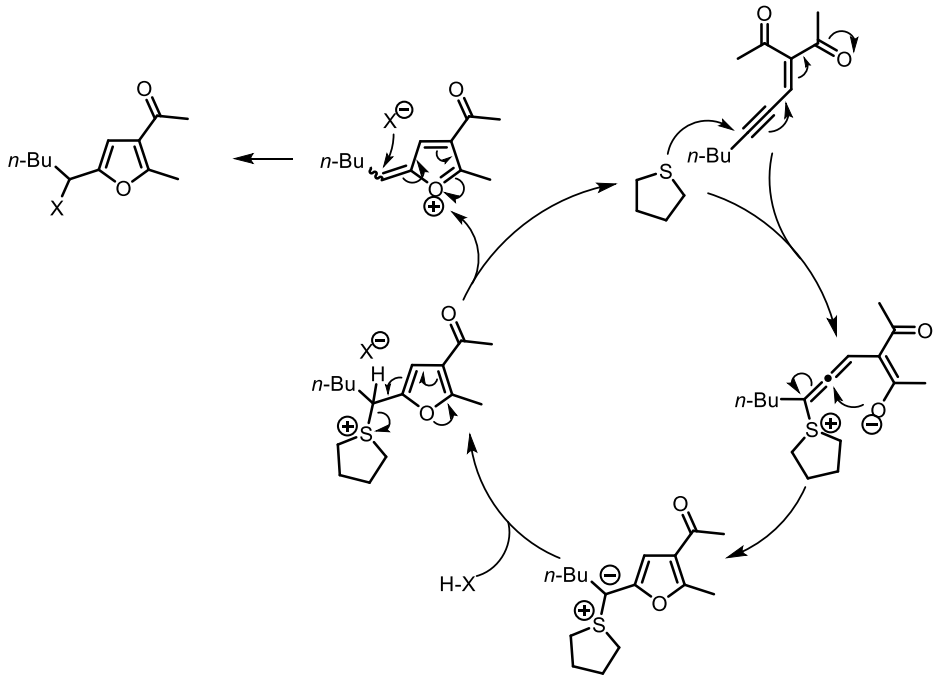
Abstract

Furans are important heteroaromatic units that occur as subunits in various complex natural products, biologically active compounds and pharmaceuticals. Due to their pharmacophoric properties they find widespread application *e.g.* in the drug discovery process. In contrast to the classical condensation based-methods and metal-mediated approaches, organocatalytic methods for construction of furan have been relatively unexplored.

As a result of their importance the Clark group developed a new organocatalytic method for the construction of highly functionalized furans using an organosulfur catalyst. It was observed that treatment of the ynenedione with an acidic nucleophile delivered the highly functionalised furan using sub-stoichiometric amount of tetrahydrothiophene (THT).

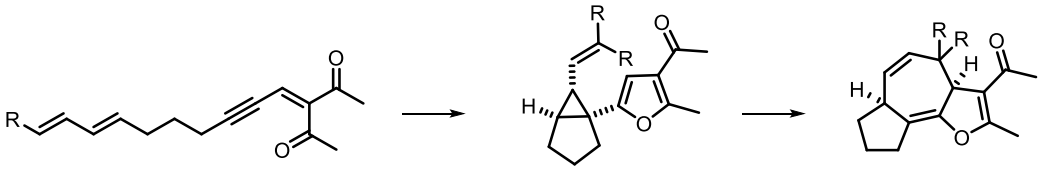


The opening chapter details investigation undertaken into furan formation methodology developed within the Clark group. It was determined that the choice of the acid species was vital for proton transfer to ensure clean and effective conversion of the substrates into the desired furans. Studies were carried out using a chiral acid in an attempt to

deliver the furan product in an enantioselective manner. Since the formation of a new stereocentre is achieved in this process, we investigated the potential development of a diastereoselective reaction using substrates bearing an existing stereocentre. The original organocatalytic furan synthesis using THT and ynenedione with nucleophiles was successfully expanded by designing a substrate with a tethered nucleophile that initiates a second cyclization to form polycyclic systems.

Cyclohepta[*b*]furans are an important class of organic compounds found in many natural products, pharmaceuticals, bioactive compounds and functional materials. The development of efficient routes for their formation is therefore of great interest to the synthetic chemist.

The second chapter details research undertaken towards a new methodology for the construction of cyclohepta[*b*]furans. Starting from a simple linear ynenedione the cascade reaction affords furans containing a fused bicyclic system which rearrange to cycloheptadienes. Since it has been observed that the cyclisation and rearrangement occurred successfully it was hypothesised that it may be possible to carry out furan formation followed by Cope rearrangement in a one-pot fashion without isolation of the furan intermediate.



Abbreviations

Ac	acetyl
ACDC	asymmetric counteranion-directed catalysis
aq.	aqueous
Ar	aryl
ATR	attenuated total reflectance
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinone
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
CI	chemical ionisation
CSA	camphorsulfonic acid
decomp.	decomposition
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DOSP	tetrakis[1-[[4-alkyl(C_{11}-C_{13})phenyl]sulonyl]-pyrrolidinecarboxylate
dr	diastereomeric ratio
ee	enantiomeric ratio
DVCPR	divinylcyclopropane rearrangement
ESI	electrospray ionisation
EI	electron ionisation
Et	ethyl
EWG	electron withdrawing group
FTIR	fourier transform infrared spectroscopy
GSK	GlaxoSmithKline

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMRS	high-resolutions mass spectrometry
HPLC	high performance liquid chromatography
i	*iso*
IPr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]
leu	leucine
Me	methyl
MDR	multiple-drug resistant
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
n	normal (e.g. unbranched alkyl chain)
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
p	*para*
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTC	phase-transfer catalyst
Pyr	pyridine
R	generalised group
R_f	retention factor in chromatography
rt	room temperature
SES	2-(Trimethylsilyl)ethanesulfonyl
SM	starting material
t	tert
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
Tc	trichloro
TEBAC	benzyltriethylammonium chloride
TES	triethylsilyl

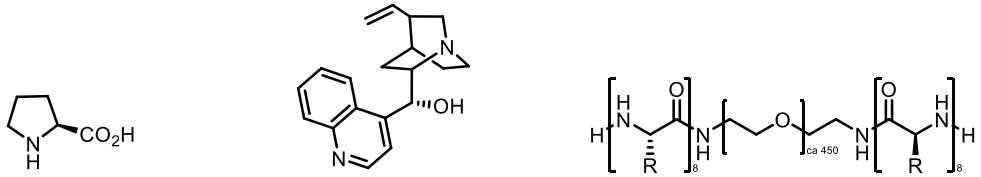
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THT	tetrahydrothiophene
TIPB	triisopropylbenzene
TLC	thin layer chromatography
TMS	trimethylsilyl
TRIP-H	3,3’-bis(2,4,6-triisopropylphenyl)-1,1’-binaphthyl-2,2’-diyl hydrogenphosphate
Ts	tosyl
UV	ultraviolet

1 Introduction

1.1 Organocatalysis

For many years there were two classes of efficient catalysts: biocatalysts, such as enzymes, and metal complexes.[1] Recently, the catalysis of chemical reactions using a sub-stoichiometric amount of a purely organic, metal-free small molecule has emerged, termed organocatalysis.[2] Many transformations, even originally transition metal-mediated cross couplings, can now be carried out under metal-free conditions by employing organocatalysts.[2]

Some of the most widely used organocatalysts are L-proline (**1**), quinine (**2**) and peptides such as oligo-L-leu (**3**) (*Figure 1*). L-Proline (**1**) is probably the most widely used organocatalyst for aldol reactions, Mannich reactions and Michael additions, through iminium or enamine pathways. Alkylation reactions[3], cyclopropanation reactions[4] and epoxidation of enones[5] are just a few of the various reactions which can be performed asymmetrically by the use of quinine (**2**) or its derivatives. The peptide oligo-L-leu (**3**) is used in the asymmetric epoxidation of enones.[6]



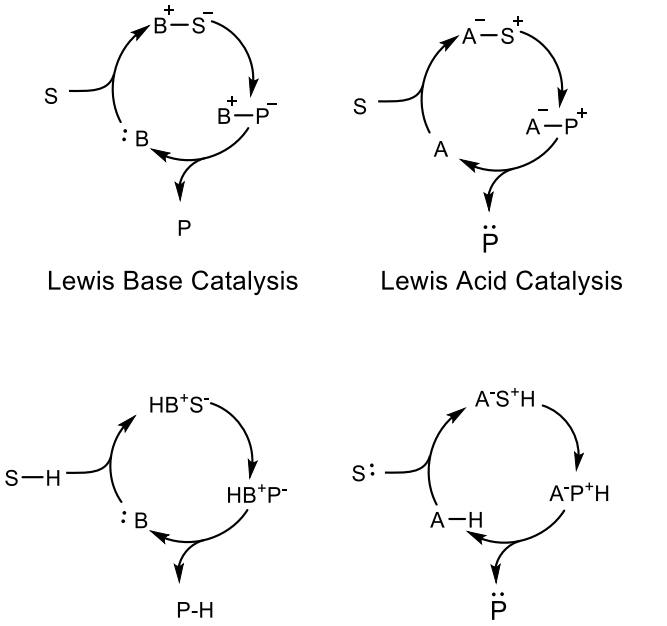
L-proline (**1**) quinine (**2**) oligo-L-leu (R = *i*-butyl) (**3**)

Figure 1

The operational simplicity of reactions catalysed by organocatalysis makes them attractive for organic synthesis. The catalysts are generally non-toxic compounds that are readily available and easy to synthesise. The non-toxicity of organocatalysts makes them attractive for the preparation of pharmaceutical compounds or drug intermediates, especially considering their ability to produce such products with high enantiomeric excess.[7] Their tolerance towards water and air make them an attractive alternative to enzymes or bioorganic catalysts.[8] For these reasons, the interest particularly in enantioselective organocatalysis has increased enormously in the last few years.

In 2005, List introduced a system to classify organocatalysis into four main types based on their reactivity.[9] These four categories are Lewis Base, Lewis Acid, Brønsted Base

and Brønsted Acid catalysts (*Scheme 1*). The catalytic cycles are initiated by electron donation to or acceptance by the substrate for Lewis bases and acids, and by proton donation or proton acceptance for Brønsted acids and bases.[9a]

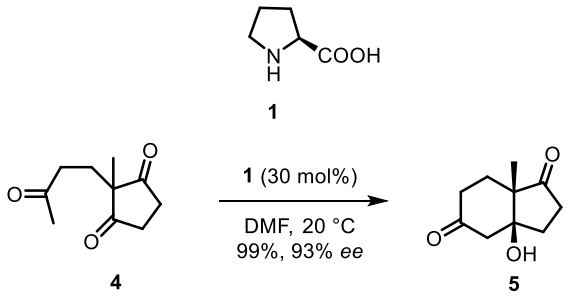


Scheme 1[10]

1.1.1 Asymmetric Organocatalysis

Asymmetric organocatalysis describes the acceleration of an enantioselective transformation with a sub-stoichiometric amount of a chiral organic molecule, which does not contain a metal element.[11] The field has had a great impact on chemical synthesis through the development of new asymmetric catalytic methodology and is now routinely used in organic synthesis for the construction of chiral molecules.

In the 1970s, Hajos[12] and Wiechert[13] made a seminal contribution to the field of asymmetric organocatalysis. Both research groups independently reported the first highly enantioselective intramolecular aldol reaction. Starting with achiral triketones **4** using proline (**1**) as the catalyst, aldol adduct **5** was formed in good yield and with good enantioselectivity (*Scheme 2*)[12].

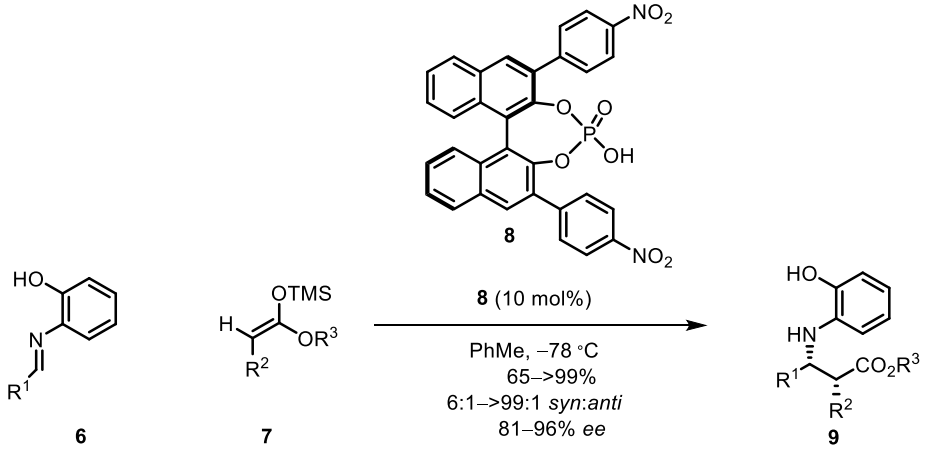


Scheme 2

1.1.2 Brønsted Acid Catalysis

Brønsted acid catalysts have not, until recently, attracted much attention in organic synthesis, but they have been shown to be excellent catalysts for achieving asymmetric induction in many cases. These catalysts have found widespread application in other asymmetric procedures, such as Friedel-Crafts reactions, reductive aminations and cycloaddition reactions.[14]

The first reports that strong Brønsted acids could be used as efficient catalysts were made by Akiyama[15] and Terada[8] in 2004, and their observations were a significant contribution to the field of organocatalysis (*Scheme 3*). The reaction between aldimines **6** and silyl enolethers **7** is catalysed by chiral phosphate Brønsted acid **8** to provide the chiral β-amino esters **9** in good yield and with both high diastereoselectivity for the *syn* product and high enantioselectivity.

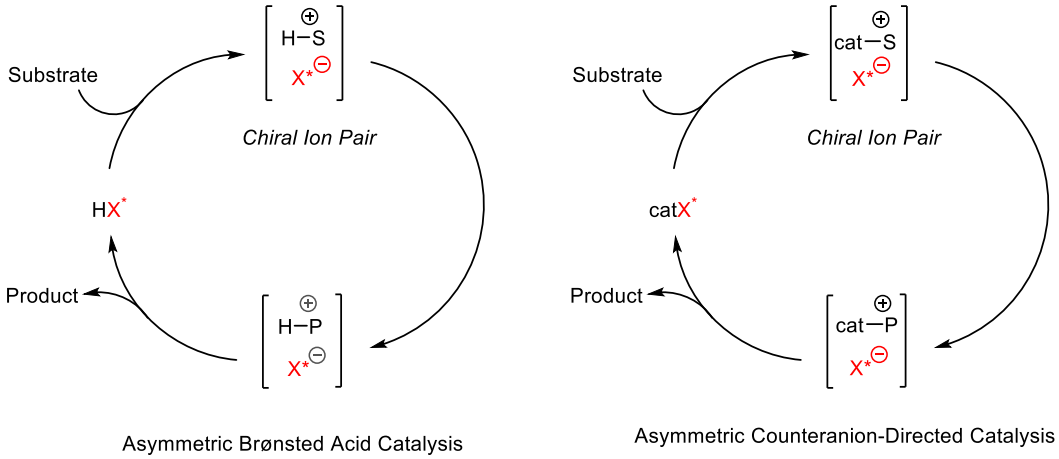


Scheme 3

These Brønsted acid catalysts have bifunctional properties as they can act as both as a Brønsted acid, or as a Lewis base, using the phosphoryl oxygen as the electron donor.

1.1.3 Asymmetric Counteranion-Directed Catalysis

Taking inspiration from the established concept using binol phosphates in asymmetric Brønsted acid catalysis, the List group hypothesised that any reaction that proceeds *via* a cationic intermediate could be rendered enantioselective (*Scheme 4*).[16] The term 'asymmetric counteranion-directed catalysis' (ACDC) in general describes reactions *proceeding via a charged intermediate in which the chiral information is induced by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst.*[16] According to this definition, Brønsted acid catalysis can be classified as a specific case. Since the introduction of ACDC by List, the concept has found widespread application in both organocatalysis and transition-metal catalysis.[16]

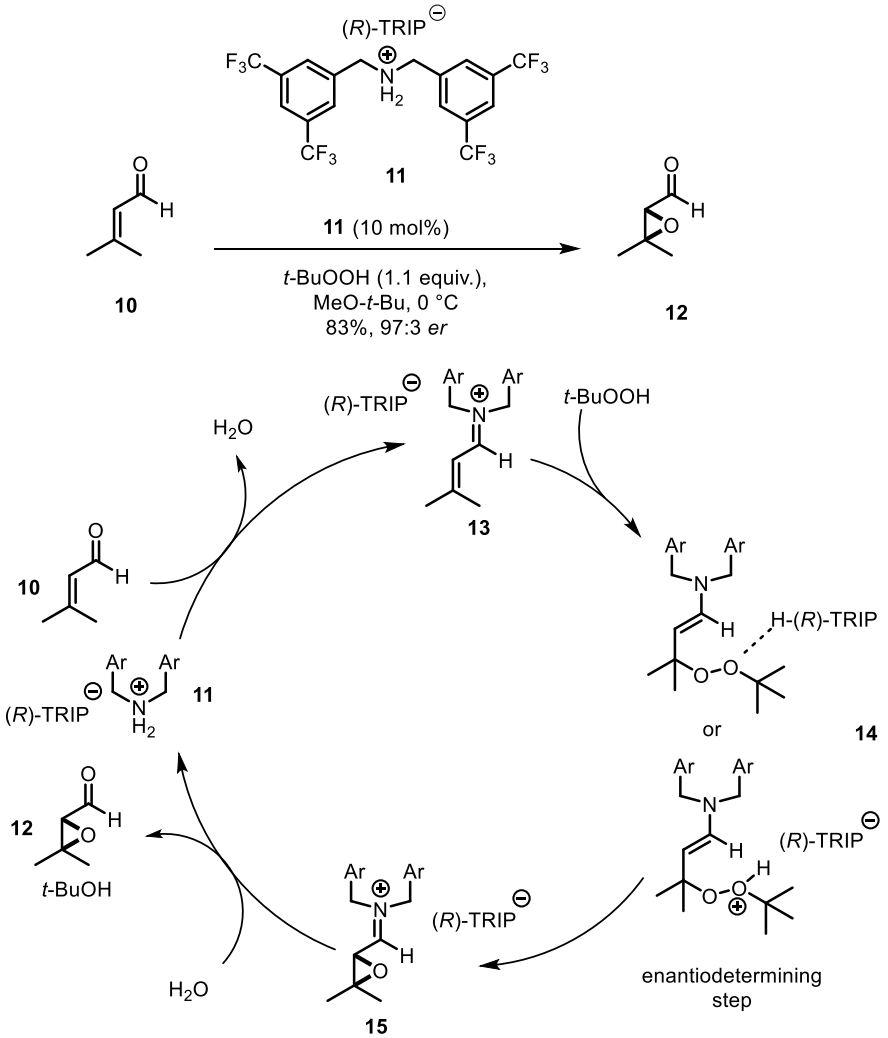


Scheme 4

In 2005, Jørgensen described an enantioselective epoxidation reaction of enals using a diarylproline silylether as organocatalyst.[17] However, high enatioselectivites (95:5) were limited to 1,2-disubstituted enals, while reactions of trisubstituted enals generally gave inferior results. The reaction proceeds *via* a cationic quaternary iminium ion and so List and co-workers proposed the use of their recently developed concept of ACDC to overcome these limitations (*Scheme 5*).[18] Use of the dibenzylamine salt of TRIP-H

11 and *t*-butyl hydroperoxide as the oxidant delivered the best results for converting the aldehyde **10** into the desired 2,3-epoxyaldehyde **12**.

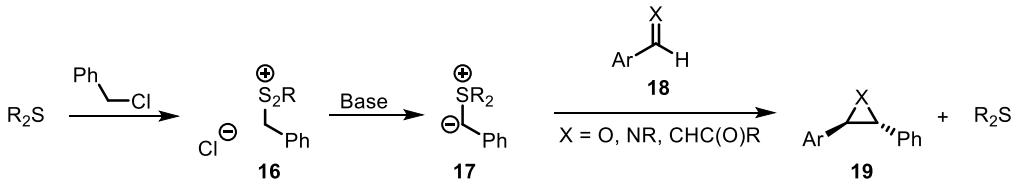
The catalytic asymmetric epoxidation of β,β-disubstituted enal **10** is postulated to proceed by condensation between the dibenzylamine salt **11** of the catalyst and the enal **10**. The iminium ion **13** is generated as a transient intermediate and this then undergoes conjugate addition with *t*-butyl hydroperoxide thus delivering the achiral addition product **14**. Finally, C-O bond formation leads to the iminium ion **15** and subsequent hydrolysis affords the epoxide **12**. The intermediate **14** could lead to both enantiomers of **12**, hence the researchers proposed that enantioselectivity results from a '*TRIP-assisted cyclisation'*. The ACDC concept could be applied to a broader scope of substrates to access synthetically valuable motifs in highly stereoselective manner.



Scheme 5

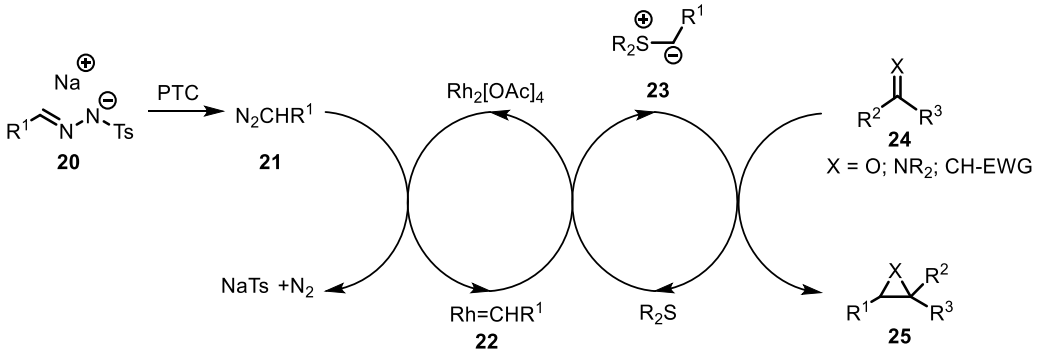
1.2 Synthesis and Use of Sulfur Ylides

Due to their reactivity and synthetic diversity, sulfur ylides have proven to be useful reagents in organic synthesis especially in the development of new cascade reactions[19], [20] that allow access to structurally complex molecules from relative simple starting materials.[21] Ylides are zwitterions and can be considered to be composed of a positively charged heteroatom directly tethered to a carbanion.[22] Phosphorus ylides that are utilised in Wittig olefination reactions are the most widely used ylides in synthesis. However, the use of sulfur ylides has led to great achievements ranging from dearomatisation[23] and ring expansion,[24] to rearrangement reactions to form substituted indoles[25]. This diversity of use means that sulfur ylides are important intermediates in synthesis. The most common known way to construct a sulfur ylide involves sulfonium salt formation by alkylation of a thioether with an organic halide and subsequent treatment of the sulfonium salt with a base. The ylide can be trapped by an aldehyde, enone or imine to yield the corresponding epoxide, cyclopropane or aziridine (*Scheme 6*).[22]



Scheme 6

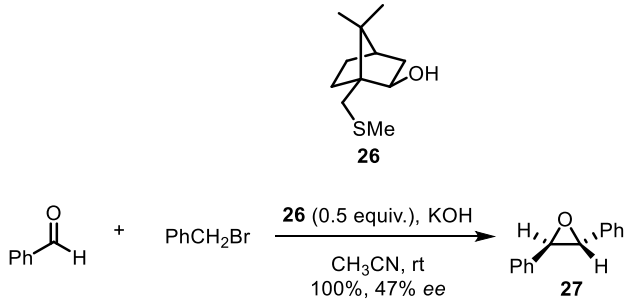
A second method has been demonstrated by Aggarwal for the formation of sulfur ylides through reaction of a sulfide and a diazo compound with a metal catalyst (e.g. $Rh_2[OAc]_4$) (*Scheme 7*).[26] A significant improvement of this method was reported, in which the diazocompound is generated *in situ* from a tosylhydrazone. This methodology presents some advantages to the synthetic chemist as it is performed under neutral conditions allowing it to be used with base-sensitive compounds. Additionally, less reactive sulfides can be employed because the intermediate metal carbene should be more reactive than the alkyl halide.[27]



Scheme 7

1.2.1 Sulfur Ylide Mediated Epoxidation

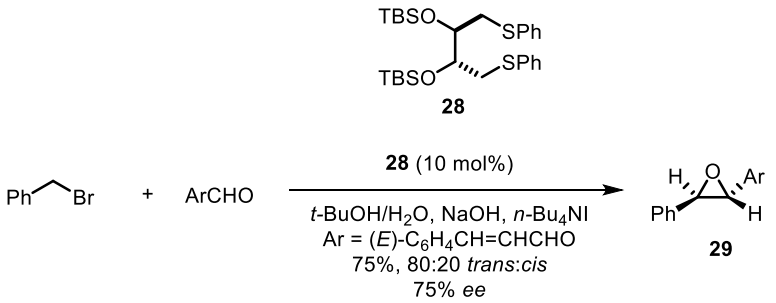
Suflur ylide mediated epoxidation represents a convenient one-step method for the formation of epoxides. Furthermore the reaction is an alternative to the general approach to the formation of an epoxide by olefination of an aldehyde followed by alkene oxidation. The first sulfur ylide mediated epoxidation was carried out by Johnson and LaCount in 1958.[28] In 1987, Furukawa reported the first example of epoxide formation from an aldehyde mediated by a sub-stoichiometric amount of a sulfur ylide.[29] The first asymmetric example of the reaction was described in 1989 and in this case a chiral sulfur ylide, derived from (+)-camphorsulfonic acid in three steps, was employed (*Scheme 8*).[30] Reaction of benzaldehyde and benzyl bromide in the presence of a sub-stoichiometric amount of sulfide **26** led to the *trans* epoxide **27** in excellent yield and with 47% *ee*.



Scheme 8

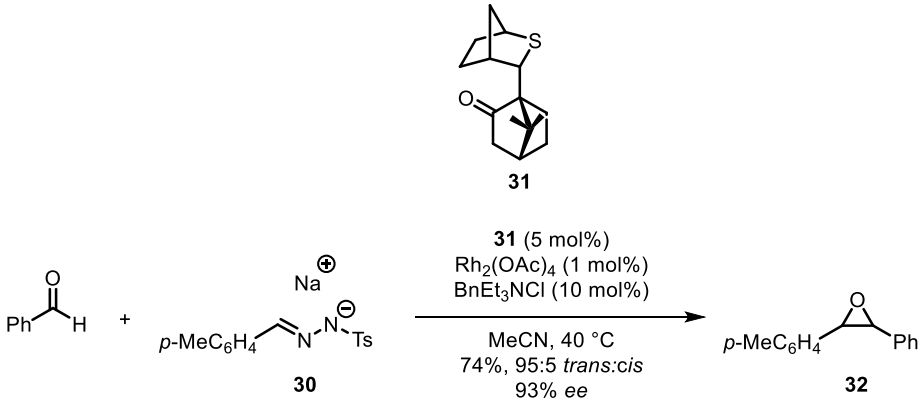
Other examples of the use of chiral sulfur ylides were reported in 2002 by Ishizaki and Hoshino who used a C_2-symmetric sulfide for the asymmetric epoxidation of aldehydes (*Scheme 9*).[31] The best results for the epoxidation reaction were obtained with *bis*-

sulfide **28** derived from (*R*,*R*)-tartaric acid. Applying the optimised reaction conditions to a wide variety of aldehydes, *trans* cinnamaldehyde was shown to be the most effective substrate with the *trans* epoxide **27** being obtained in 75% isolated yield and with an enantiomeric excess of 75%.



Scheme 9

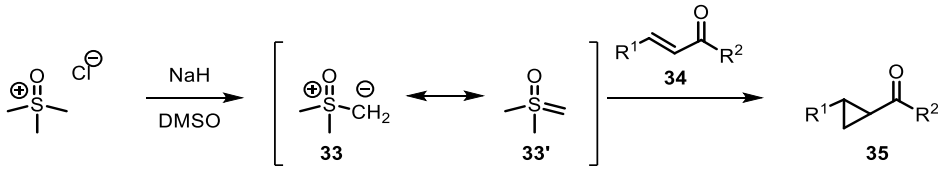
In 2003, Aggarwal and co-workers applied their previously described strategy to the enantioselective synthesis of epoxides using optimised chiral sulfur ylides (*Scheme 10*). These new semi-stabilised sulfides were found to be sufficiently stable to be recovered quantitatively in most cases. The asymmetric epoxidation reaction proceeds in good yield and high enantioselectivity and diastereoselectivity with an array of aldehydes ranging from aromatic and α,β-unsaturated to aliphatic. Aggarwal began evaluating different tosylhydrazone salts in order to determine their effectiveness for epoxidation reactions. It was found that electron-rich aromatic tosyl hydrazone salts delivered the epoxides with highest enantiomeric excesses (>93% *ee*) and with high diasteroselectivities.



Scheme 10

1.2.2 Sulfur Ylide Mediated Cyclopropanation

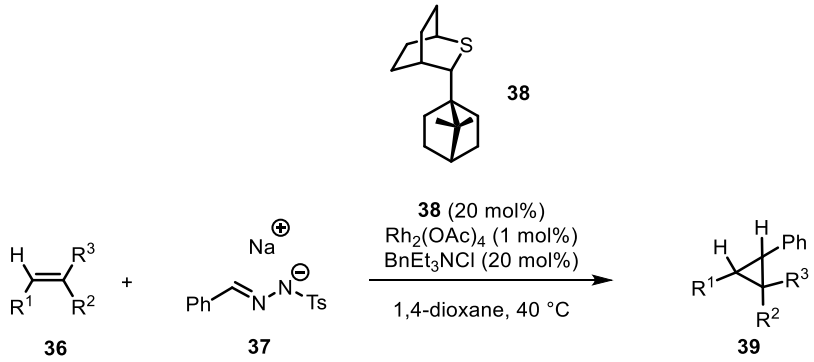
The cyclopropane ring is a common sub-unit in many natural products, bioactive compounds and synthetic drugs. One of the classical protocols employed for the preparation of cyclopropanes was reported in 1962 by Corey and Chaykovsky using reactive dimethylsulfoxonium methylide (*Scheme 11*).[32] The Corey-Chaykovsky reaction employs deprotonation of trimethylsulfoxonium halide to deliver the reactive ylide **33** required for the reaction. The reaction proceeds by conjugate addition of the sulfur ylide **33** to the α,β-unsaturated carbonyl compound **34** which affords the cyclopropane **35** after intramolecular cyclisation and loss of dimethyl sulfoxide.



Scheme 11

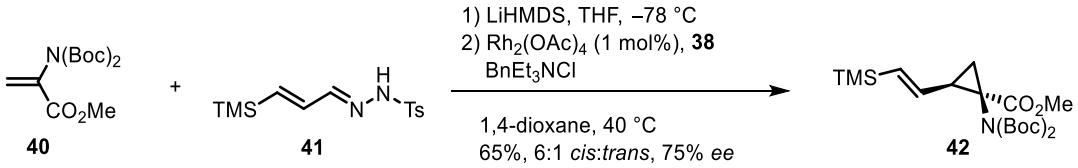
One notable drawback to this reaction is that it is not possible to synthesise other trialkylsulfonium salts and therefore the reaction is limited to the methylide. Nevertheless, substituted methylene units could be installed onto carbonyl compounds from various sulfur ylides derived from sulfoximines.[33]

Aggarwal and co-workers demonstrated the versatility of their methodology by applying it to the enantioselective formation of cyclopropanes **39** from electron-deficient alkenes **36** by means of a chiral sulfur ylide derived from the thioether **38** (*Scheme 12*).[34] The best results were obtained using a phenyl ketone (R^3 = COPh) as the Michael acceptor; the desired cyclopropane product was obtained in good yield and with high enantioselectivity.



Scheme 12

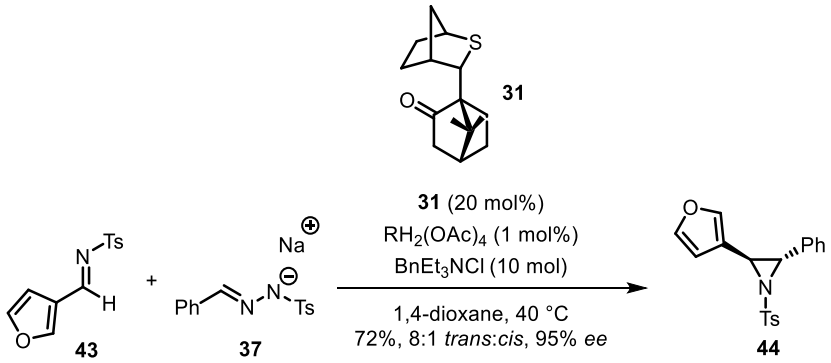
The utility of this methodology was demonstrated in the synthesis of vinylcyclopropane **42** (*Scheme 13*).[34] The diazo-compound was generated *in situ* from tosylhydrazone **41** and subsequent reaction with the α-substituted amino acrylate **40** afforded the vinylcyclopropane **42** in 65% yield as 6:1 *cis*:*trans* mixture of diastereomers. The major isomer (*cis*) was obtained with 75% enantiomeric excess. With the vinylsilane group in place, further functionalisation is possible to give access to a range of conformationally-locked amino acids.



Scheme 13

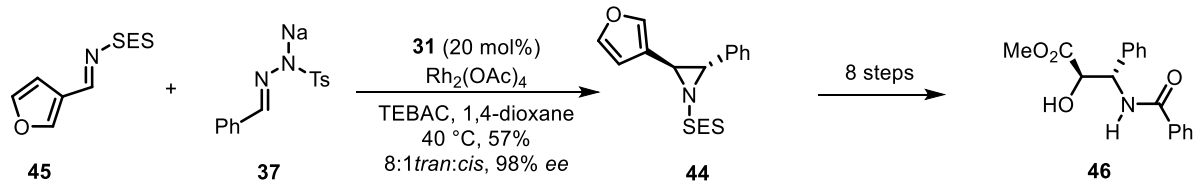
1.2.3 Sulfur Ylide Mediated Aziridination

Aziridines are useful intermediates for organic synthesis and can be transformed into α-amino alcohols[35] by ring opening, or can undergo ring expansion to either β- or γ-lactams. In 2001, Aggarwal and co-workers adapted their epoxidation method to the asymmetric synthesis of the *trans* aziridine **44** using imine **43** and the tosyl hydrazone salt **37** in the presence of a catalytic amount of chiral sulfide **31** (*Scheme 14*).[34] Evaluating different *N*-activating groups revealed that best results were obtained using sulfonyl- or TcBoc-activated imines for the synthesis of aziridines. However, sulfonyl-substituted imines are easier to prepare, more stable under the reaction conditions and the sulfonyl group is more readily removed. Subsequently, the reaction was studied with a wide range of different sulfonyl-activated imines prepared from aromatic, heteroaromatic, unsaturated and aliphatic aldehydes. The corresponding aziridines were obtained in good yields and with high enantioselectivties. Good levels of diasterocontrol could be achieved but were dependent on the imine substituent. Cinnamaldehyde and 3-furfural derived imines were shown to deliver the product with the best *trans*:*cis* diasteromeric ratio.



Scheme 14

Aggarwal and co-workers applied their promising methodology to the synthesis of *syn*-α-amino alcohol **46**, found in the side chain of taxol (*Scheme 15*).[35] The *N*-SES-activated imine **45** was treated with tosylhydrazone salt **37** in the presence of a sub-stoichiometric amount of chiral sulfide **31**, a phase-transfer catalyst and [$Rh_2(OAc)_4$]. The reaction delivered aziridine **44** in good yield and high enantioselectivity for the *trans* isomer. The *syn*-α-amino alcohol **46** was obtained in 8 steps from aziridine **44**.



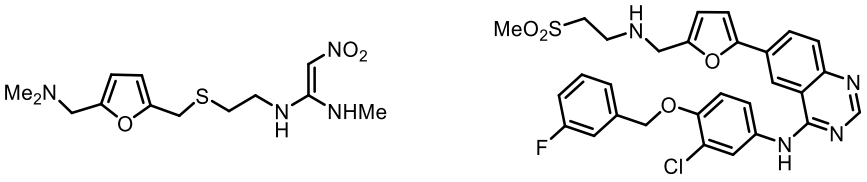
45 37 44 46

Scheme 15

1.3 Furans

Furans are common sub-units in organic molecules such as pharmaceutical compounds (*Figure 2*) and complex natural products[36] (*Figure 3*). They also serve as important intermediates for the synthesis of various heterocyclic and acyclic compounds.[37] Ranitidine (**47**) is one of these furan-containing synthetic drugs, which is marketed by GSK under the name Zantac® and is one of the biggest selling drugs in history. It is used as a histamine H2-receptor antagonist for the treatment of stomach ulcers.[38]

Lapatinib (**48**) is another example of a pharmaceutical drug possessing a furan ring. The drug is marked by GSK under the name Tyberb® and is used in the treatment of breast cancer and other solid tumours.[39]

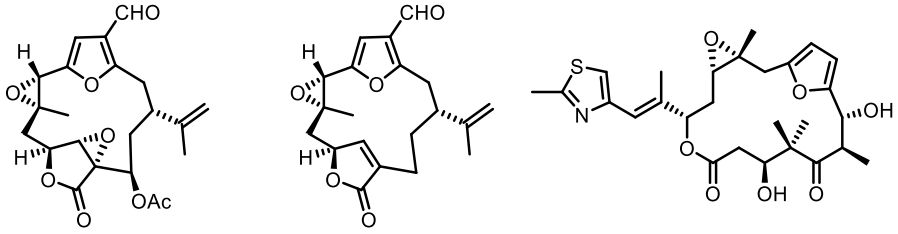


Ranitidine (**47**) Lapatinib (**48**)

Figure 2

The furan motif is commonly found in many natural products, ranging from acetogenins and terpenes, to complex alkaloids.[40] The cembranolides lophotoxin (**49**) and pukalide (**50**)[41] are among those bioactive natural products. Both of these macrocyclic marine products contain a highly-substituted furan as part of their macrocyclic core structures. Members of this natural product family have some interesting bioactive properties, ranging from neutrotoxic to anti-inflammatory and anti-feedant activities.[41] The neurotoxin lophotoxin (**49**) is known to be an irreversible inhibitor of the nicotinic acetylcholine receptors, which are ligand-gated ion channels in nerve and muscle cells.[42] A further example of a furan-containing bioactive compound is the bacterial

macrolide furano ephithilone B (**51**), which is highly potent against multiple-drug resistant (MDR) human carcinoma cell lines.[43]



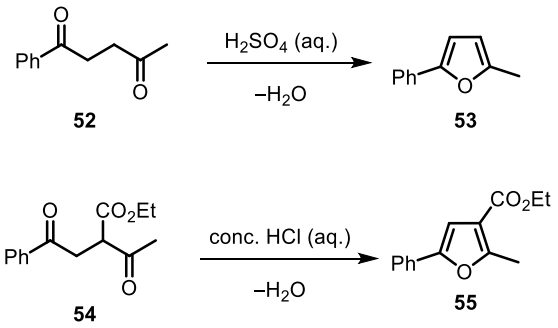
lophotoxin (**49**) pukalide (**50**) furano epothilone B (**51**)

Figure 3

Furan-containing compounds have attracted extensive synthetic interest. Considerable ingenuity has been displayed in the development of routes to these compounds in addition to the classical approaches involving condensation-based methods.[37] These new approaches range from Diels-Alder cycloaddition to alkene cross-metathesis, and metal-mediated furan syntheses are also becoming more common.[44] In contrast, the use of organocatalytic methodology for the construction of furans is rare.

1.3.1 Classic synthetic routes to form furans

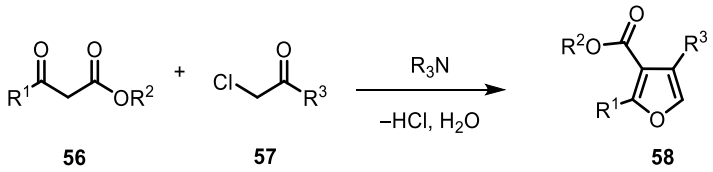
Furans can be synthesised by various routes, but many of the methods are based on the Paal-Knorr synthesis which was described independently by Carl Paal and Ludwig Knorr in 1884.[45] In this synthetically valuable method, substituted furans are formed by acid-catalysed cyclocondensation of 1,4-diketones (*Scheme 16*).



Scheme 16

However, the Paal-Knorr reaction has two major drawbacks. First the limited availability of 1,4-dicarbonyl compounds and second, the restrictive tolerance of many functionalities towards the harsh acidic conditions that are usually required.

In 1902, the Feist-Benary synthesis for the formation of highly-substituted furans **58** was reported. This method proceeds by the condensation of an α-halo ketone **57** and a β-ketoester **56** under basic conditions (*Scheme 17*).[46]



Scheme 17

The synthesis of functionalised furans has been an important research area since the 1990s. Due to the importance of these heterocycles, research is nowadays focused on milder and more versatile approaches that allow the introduction of more functionality during formation of the furan ring.

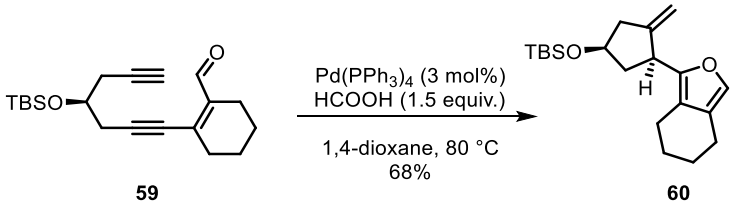
1.3.2 Metal Mediated Methods of Forming Furans

Developments in the area of transition metal-catalysed processes can lead to highly efficient and selective synthetic procedures. Thus, metal catalysis is an important tool for the synthesis of valuable organic compounds.[47]

In recent years, metal-catalysed processes have been developed to produce substituted furans under mild conditions. The use of a large variety of metal complexes has been reported, especially those of palladium, copper, gold, silver and zinc, and some representative examples are presented in the following discussion.

1.3.2.1 Palladium-Catalysed Synthesis of Furans

Thus far, palladium complexes alongside gold complexes are some of the most commonly used catalysts for furan synthesis.[48] In 2007, Oh and co-workers reported a protocol for the stereocontrolled formation of 2-(2-methylenecycloalkyl)-furan derivatives **60**.[49] The tandem cyclisation procedure is based on cycloreduction of conjugated enynals **59** using a palladium(0) complex as the catalyst (*Scheme 18*). Treatment of enynals **59** with $Pd(PPh_3)_4$ and formic acid was found to afford the complex furan **60** in high yield and as single isomer. Evaluation of the reaction using an array of substrates showed that product yields were highest when substrates bearing a *gem*-diester were employed and that the yield improved when the tether length was increased so that a cycloheptane was produced instead of cyclopentane. Furthermore, it was found that for a substrate bearing a benzyl protected alcohol the corresponding furan product was obtained in good yield and with a 3:1 *cis*:*trans* isomer ratio. However, the reaction was completely selective for the *cis* isomer when a more bulky protecting group was used.

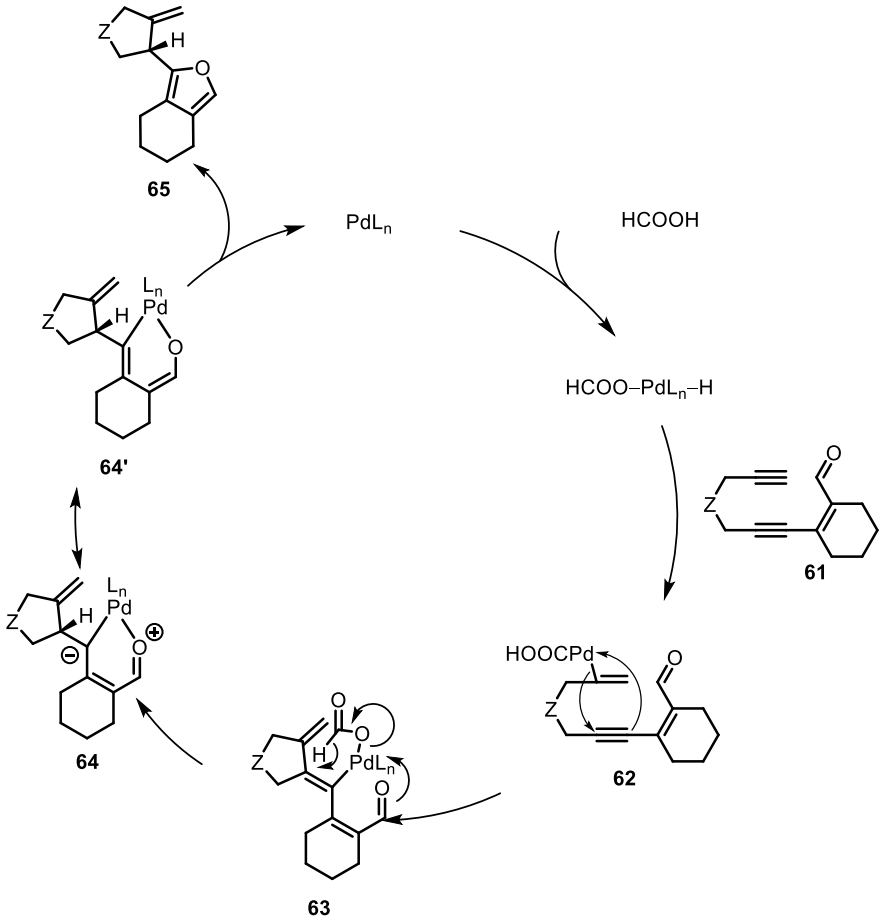


59 **60**

Scheme 18

The cycloisomerisation reaction is proposed to proceed according to the mechanism shown in Scheme 19.[49] Firstly a Pd(II) species is generated *in situ* through oxidative

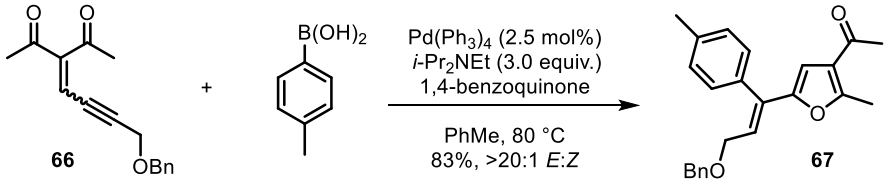
addition of the palladium into the formic acid. Subsequently, hydropalladation of alkyne **61** occurs to form the vinylpalladium **62** species and then cyclisation through carbopalladation of the triple bond to produces the intermediate **63**. Attack of the palladium centre by the carbonyl oxygen with the extrusion of CO_2, followed by hydrogen transfer generates the intermediate **64** which evolves into **64'** by electron delocalisation. Finally, reductive elimination regenerates the catalyst and delivers the furan product **65**.



Scheme 19

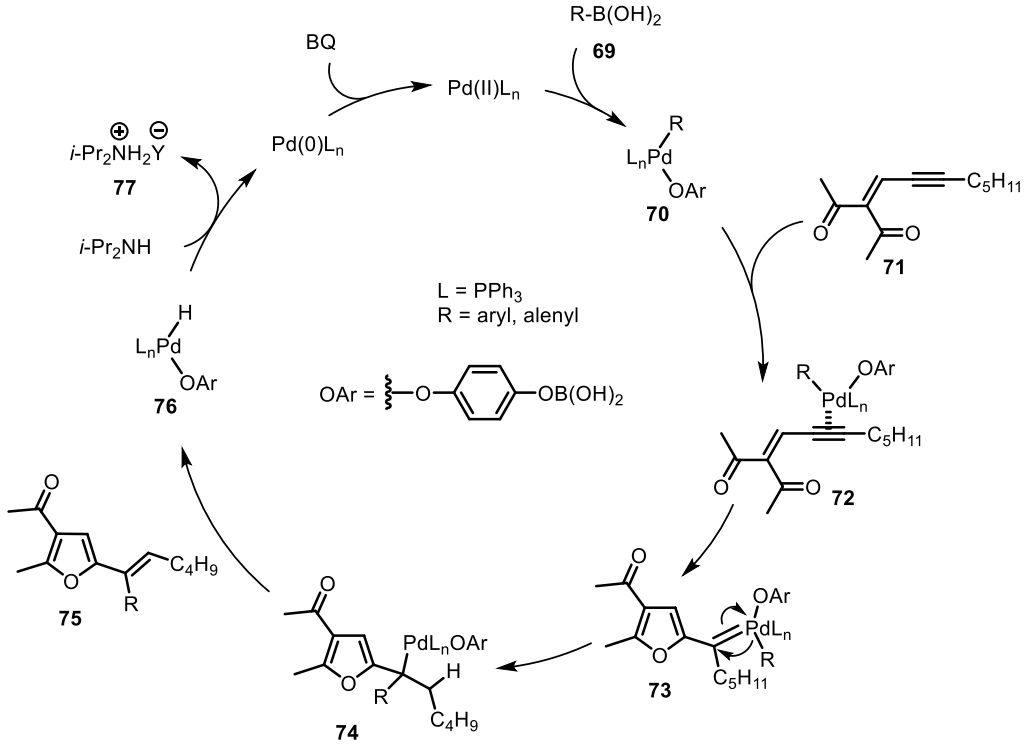
Wang and co-workers recently reported a novel method for the formation of 2-alkenyl substituted furans **67** with high (*E*)-selectivity, in which classical palladium cross coupling reaction was combined with carbene chemistry (*Scheme 20*).[50] The palladium-catalysed oxidative cross coupling of enynone **66** with *p*-tolylboronic acid proceeds in good yield and with high stereoselectivity. Studies revealed that many

arylboronic acids and alkenylboronic acids are suitable substrates for the transformation.



Scheme 20

The proposed mechanism proceeds by oxidation of Pd(0) with benzoquinone and subsequent oxidative addition of organoboronic acid **69** to generated palladium species **70** (*Scheme 21*). Activation of the alkyne is followed by the key step: nucleophilic addition of the carbonyl oxygen onto alkyne. The resulting (2-furyl)carbene **73** undergoes migratory insertion to afford intermediate **74** and β-hydride elimination then occurs to form the furyl-substituted olefin **75**. Finally, reaction of the palladium hydride intermediate with base regenerates the reactive Pd species.

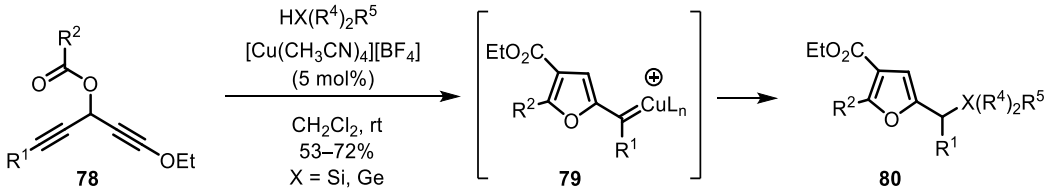


Scheme 21

1.3.2.2 Copper-Catalysed Synthesis of Furans

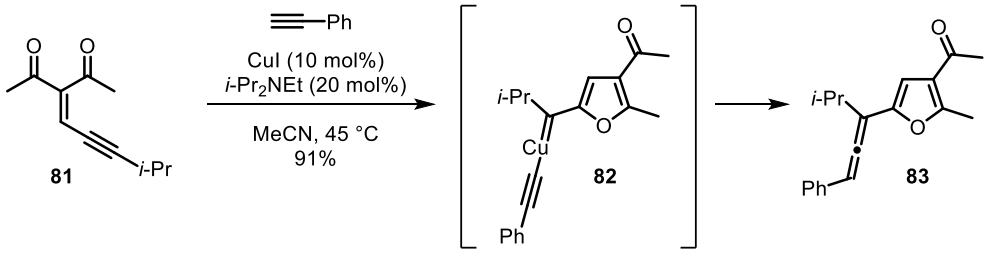
Other metal complexes such as those of copper have also been employed for the synthesis of furans. Barluenga described a copper(I)-catalysed regioselective

synthesis of tri- and tetra-substituted furans **80** from *bis*-propargylic esters **78** (*Scheme 22*).[51] The formation of 2-furyl copper(I) carbene complex **79** allows further functionalisation to create either a new carbon-carbon double bond or a carbon-heteroatom double bond. By investigating the scope of the reaction, it was found that the terminal alkyne and the ester could be substituted with various groups to provide the furan **80** in good yield.



Scheme 22

In early 2016, Wang and co-workers reported a new approach to the synthesis of furan-substituted allenes employing a copper-catalysed carbene migration insertion (*Scheme 23*).[52] It was observed that reaction between eneynedione **81** and an alkyne with catalytic amounts of CuI produced the corresponding furan **83** in good yields. The conditions accommodated a wide range of electron-rich, electron-deficient, polycyclic aryl and alkyl terminal alkynes. The highest yields were observed with alkyl-substituted eneynediones.

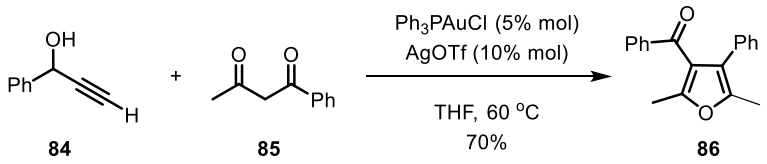


Scheme 23

1.3.2.3 Gold-Catalysed Synthesis of Furans

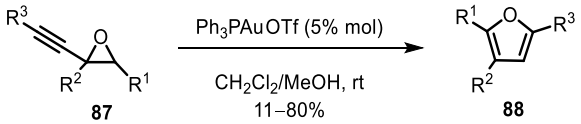
Gold catalysts have proven to be particularly suitable for the construction of furans because of the bifunctional properties of the late transition metal. Cationic gold species possess strong σ Lewis acid abilities and are also able to activate alkynes and allenes through complexation. Some recent examples of gold-catalysed furan formation are described below.

Arcadi demonstrated the coupling between the propargylic alcohol **84** and a 1,3-diketone **85** in a tandem process to form tetrasubstituted furan **86** using a gold-based catalyst (*Scheme 24*).[53]



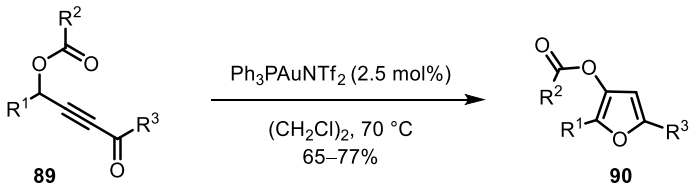
Scheme 24

In 2009, Pale described a procedure for the synthesis of highly substituted furans **88** from alkynyl oxiranes **87** employing (triphenylphosphine)gold triflate as the catalyst (*Scheme 25*).[54] The presence of an alcohol that serves as an external nucleophile is required for the gold-catalysed isomerisation reaction to take place.



Scheme 25

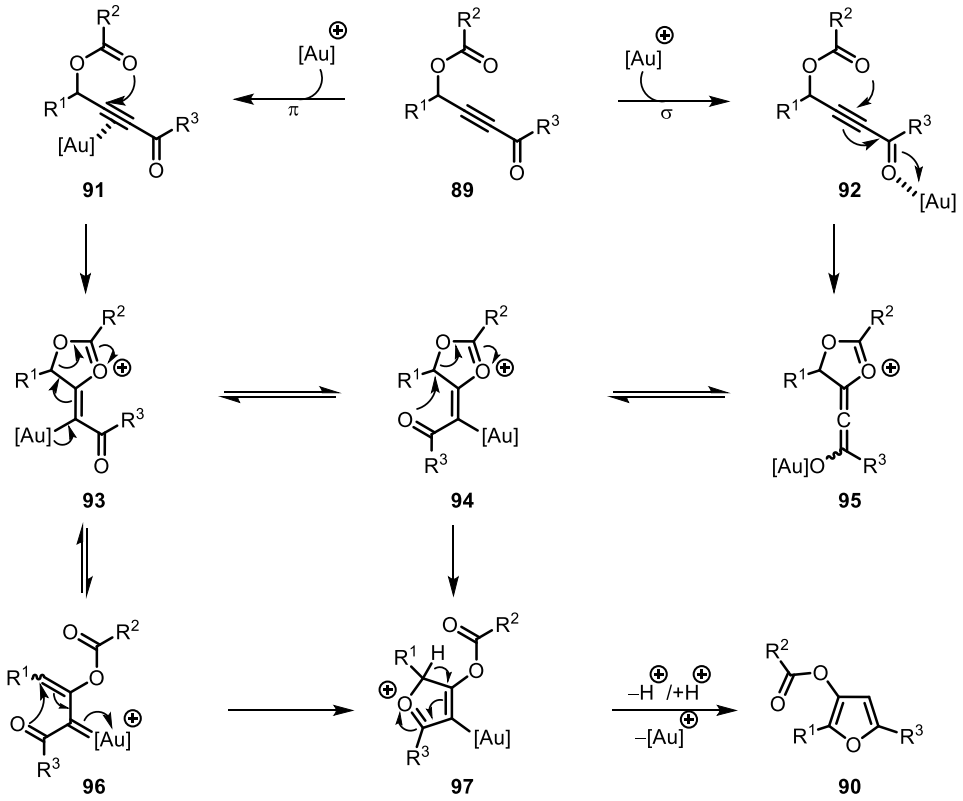
Several furan-forming reactions, catalysed by either gold(I) or gold(III) complexes, have been reported in the past few years. A range of substrates can be employed, such as allenyl ketones, enynes, alkynes or alkynyl alcohols. In 2013, Pale reported the formation of functionalized furans **90** from various precursors such as γ-acyloxyalkynyl ketones **89** using a gold(I) complex as the catalyst (*Scheme 26*).[55] After identification of the optimal conditions, furan formation was successful for substrates containing various R^3 substituents, such as methyl, propyl, 2-phenylethyl and 3-benzyloxypropyl.



Scheme 26

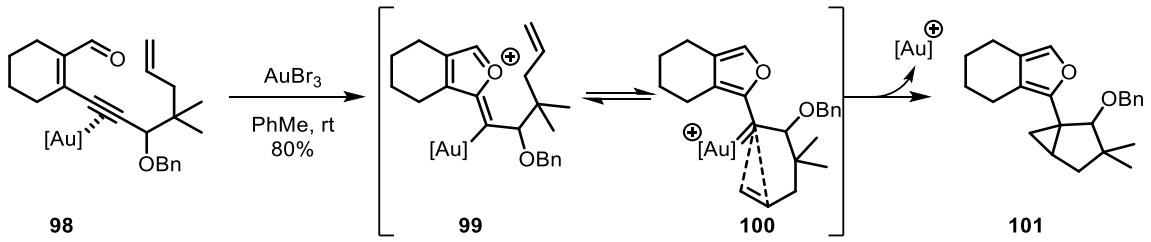
Pale proposed a viable mechanism for the rearrangement of γ-acyloxyalkynyl ketones **89**, which is based on the bifunctionality of gold cations to behave as either π or σ Lewis acids (*Scheme 27*).[55] If the gold catalyst functions as a σ Lewis acid, $[Au]^+$ firstly

operates as an oxophilic activator by complexing to the oxygen of the carbonyl function of the ketone **92**. Complexation is followed by [1,4]-addition of the nucleophilic acyloxy group to the carbon-carbon triple bond to form gold allenolate **95**, which is in equilibrium with *Z* and *E* vinylgold intermediates **94** and **93**. Intermediate **93** could also be formed by carbophilic activation of the triple bond by co-ordination of the metal, followed by nucleophilic attack of the carbonyl oxygen onto the electron-poor carbon-carbon bond. Formation of the carbenoid species **96** followed by intramolecular attack of the carbonyl function on to the alkene bond generates the oxygenated five-membered ring **97**. The final furan product **90** is obtained by tautomerisation and regeneration of the catalyst.



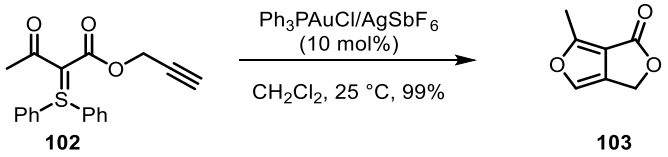
Scheme 27

Oh and co-workers developed a procedure for the gold-catalysed construction of furans containing a fused bicyclic system that incorporates a cyclopropane (*Scheme 28*).[56] Exposure of the cycloalkenecarbaldehyde **98** to $AuBr_3$ led to intramolecular 5-*exo*-dig cyclisation of the gold-complex through nucleophilic attack of the carbonyl oxygen onto the alkyne moiety, to afford the alkenyl gold intermediate **99**. The intermediate **99** evolves into the carbenoid **100** which cyclopropanates the pendant alkene to afford the cyclopropyl-substituted furan **101** as the sole product in 80% yield.



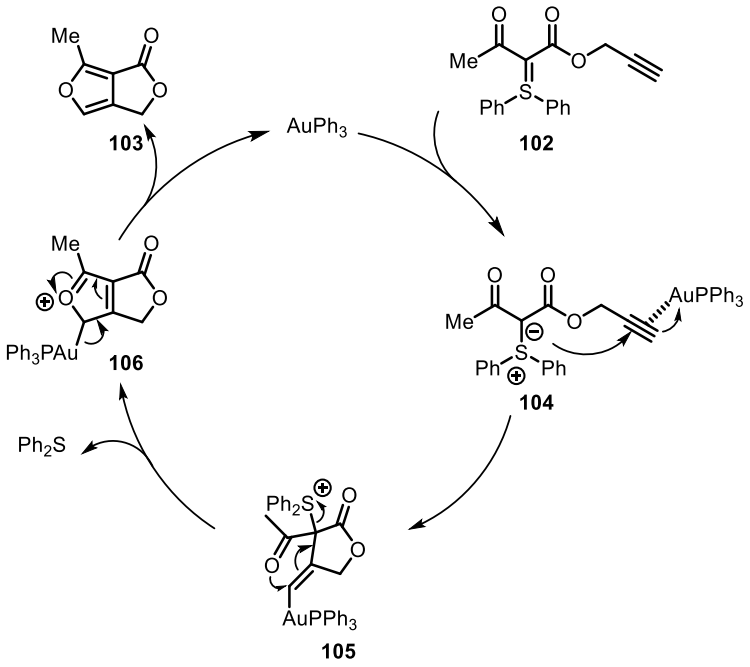
Scheme 28

In 2012, Maulide and co-workers described an efficient approach for the intramolecular construction of bicyclofurans from doubly stabilised sulfur ylides employing gold catalysis (*Scheme 29*).[57] Treatment of the sulfonium ylide **102,** which is easily accessible from the corresponding ketoester by ylide transfer, with PPh_3AuCl and $AgSbF_6$ yielded the 3-carboxyfuran **103** in excellent yield.



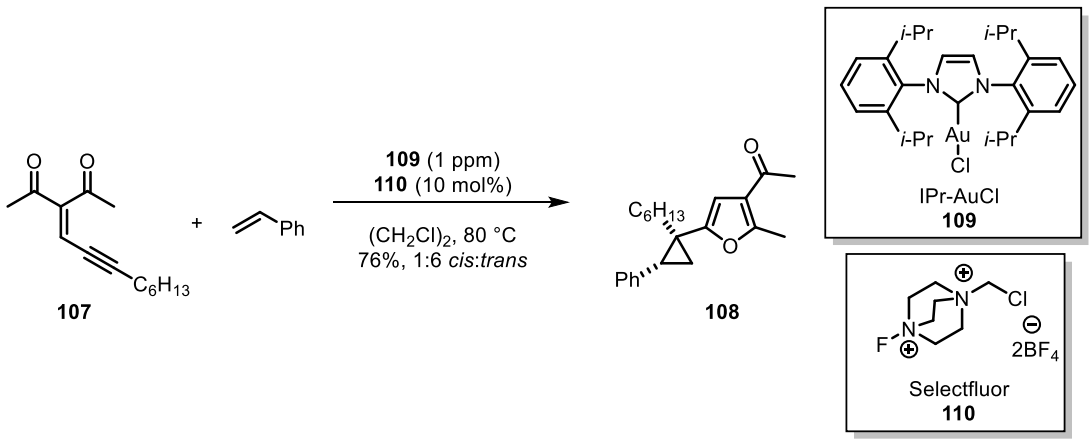
Scheme 29

Maulide proposed that the mechanism for this transformation proceeds firstly by activation of the alkyne **102** through coordination of the metal catalyst which acts as a π Lewis acid to form the gold complex **104** (*Scheme 30*).[57] Next, cyclisation by intramolecular nucleophilic attack of the ylide onto the activated alkyne produced the vinyl gold intermediate **105**. Intramolecular attack of the vinylic gold by the carbonyl oxygen and subsequent loss of Ph_2S afforded the complex **106**. Finally, the bicyclic furan product is formed by regeneration of the gold catalyst to restart the catalytic cycle by forming the π complex **104**. Computational studies completed by the group support the proposed mechanism and suggest that a gold carbene intermediate is not involved in the mechanistic pathway.



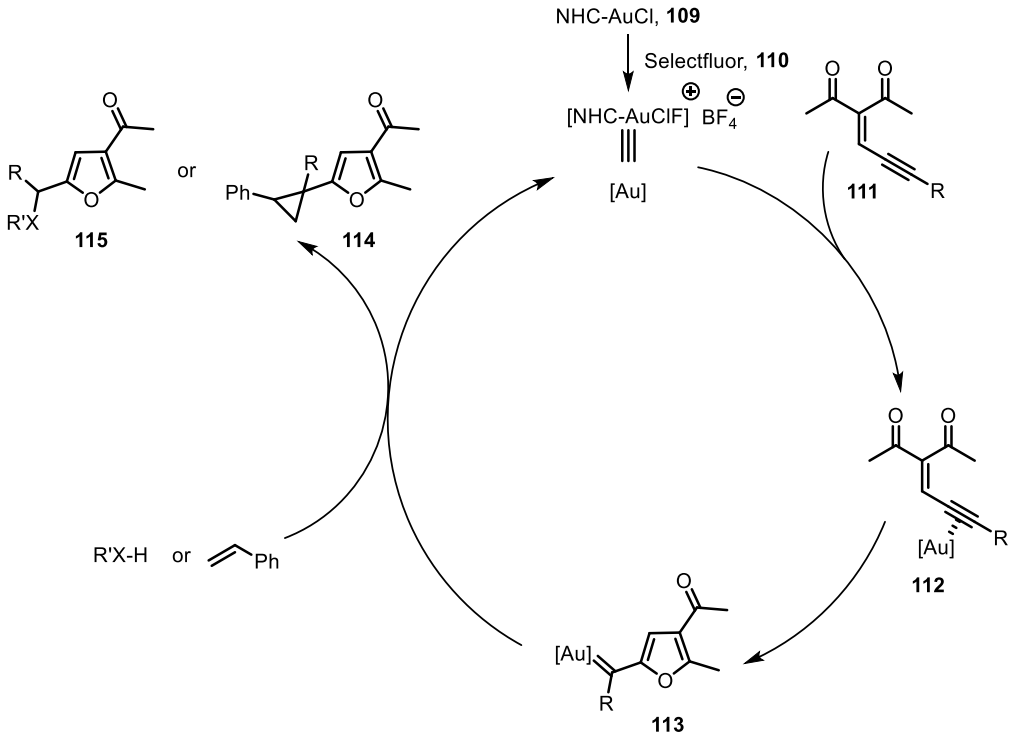
Scheme 30

Zhu and co-workers reported a highly efficient method for the synthesis of cyclopropyl subsituted furans using *N*-heterocyclic carbene (NHC) suppported cationic $[Au]^+$ complexes with Selectfluor® **110** (*Scheme 31*).[58] Initial studies revealed that IPrAuCl **109** in combination with Selectfluor® **110** gave the best results for the cyclopropanation reaction. When the enynone **107** and styrene were reacted under optimised conditions, the furan **108** was obtained in good yield. The reaction proceeded best when the alkene substrate was electron-rich, but only low levels of diastereocontrol were observed. The best diastereomeric ratio was achieved when alkyl enynones were employed as substrates. In addition, the methodology proved to be highly versatile for different insertion reactions. By using imidazole, benzyl alcohol or Et_3SiH instead of styrene derivatives, the corresponding X-H insertion product was obtained in high yield.



Scheme 31

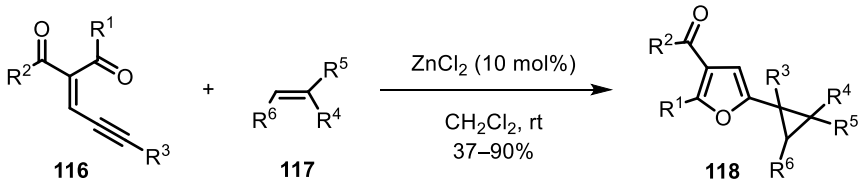
The mechanism for the transformation of enyonone **111** into the corresponding furan products is proposed to proceed by firstly the generation of [NHC-Au(III)ClF]$^{+}$ through oxidation of IPr-AuCl **109** with Selectfluor® **110** (*Scheme 32*). This is followed by activation of the triple bond of the enynone **112** through coordination of the *in situ* generated gold species. Subsequent nucleophilic attack of the carbonyl oxygen onto the electron-poor triple bond, produces the gold furyl carbene **113**. Either an alkene or HX-R' is used to trap the carbenoid formed, leading to the formation of furan **114** or **115**.



Scheme 32

1.3.2.4 Zinc-Catalysed Synthesis of Furans

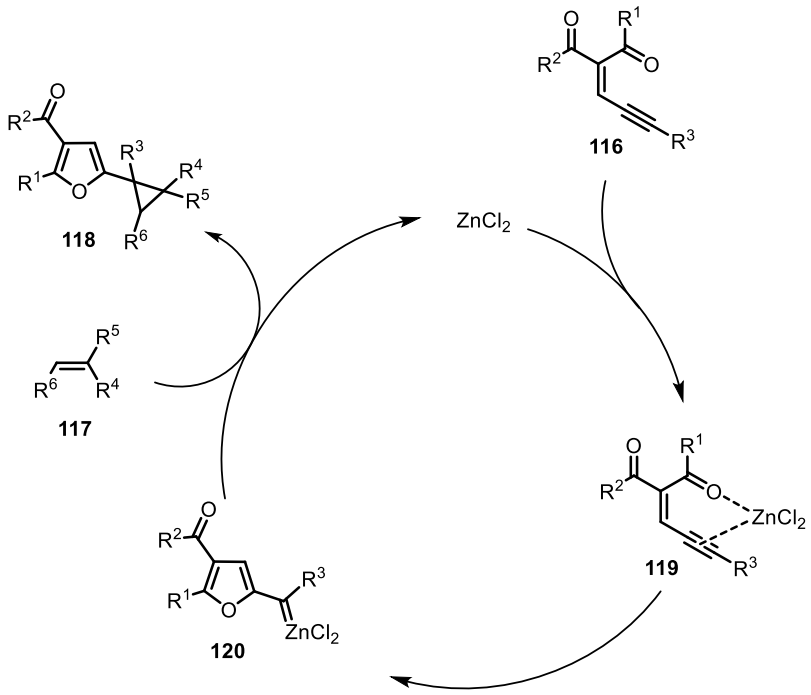
Vicente and Lopez have developed a procedure for the synthesis of highly substituted furans using zinc salts in sub-stoichiometric amounts.[59] The reaction proceeds by treatment of readily available ynenedione **116** with zinc chloride to form what is presumed to be a zinc carbenoid species. This cyclopropanating intermediate is trapped by an alkene **117** to deliver the cyclopropyl furan **118** in good yield (*Scheme 33*).



Scheme 33

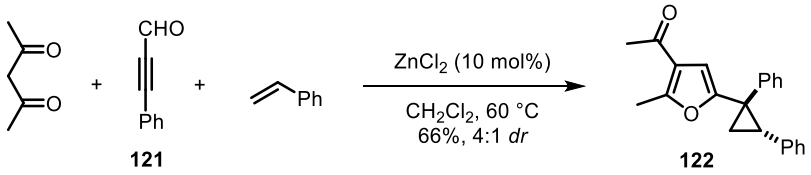
Experiments involving alkenes bearing a variey of substituents (R^4, R^5 and R^6) demonstrated that the reaction could be applied to a large variety of compounds, ranging from monosubstituted to disubstituted alkenes, to yield furans in respectable yield but with moderate levels of diastereocontrol. Furthermore, changing the enyne substituent R^3 to aryl or alkyl, afforded the corresponding cyclopropane in good yields and with higher levels of diastereocontrol in the case of alkyl substituents.

Vincente proposed a mechanism in which coordination of $ZnCl_2$ to the carbonyl group and the alkyne of enyne **116** affords the zinc complex **119** (*Scheme 34*).[59] Nucleophilic attack of the carbonyl oxygen onto the alkyne results in 5-*exo*-dig cyclisation to yield the intermediate **120**. The zinc furyl carbene **120** then reacts with the alkene **117** to afford the furan **118**.



Scheme 34

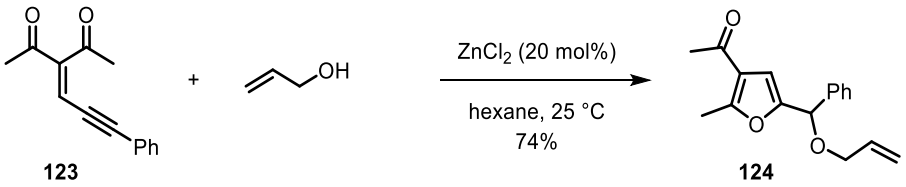
Using their knowledge of $ZnCl_2$-catalysed Knoevenagel condensation reactions, these researchers explored the possibility of accessing the furan product **122** in a one-pot procedure and starting from acetylacetone, propynal **121** and styrene (*Scheme 35*).[59]



Scheme 35

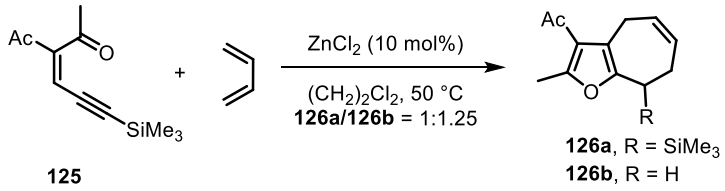
In 2013, Vincente and co-workers published an extension to this work and applied the methodology to a wider range of substrates.[60] Under the previously established conditions, they performed a zinc-catalysed cyclisation followed by C-O or C-N bond formation when treating enynes with alcohols or azoles. Several simple primary alcohols were employed as reactants under optimised reaction conditions, leading to the formation of the expected furan derivatives in good to moderate yield (*Scheme 36*). Furan formation proceeded best when alkyne substrates bearing electron-rich arenes were used but alkynes bearing alkyl groups or electron-poor arenes were found to be unsuitable. Amines or amides were used to study a possible zinc-catalysed cyclisation

and C-N bond formation sequence.[60] Monocyclic azoles such as pyrazole, imidazole and triazole proved to be suitable reactants and products resulting from N-H bond insertion were obtained from these reactions.



Scheme 36

In 2015, Vicente and co-workers once again proved the versatility of their zinc methodology by creating the fused cycloheptafurans **126a** and **126b** (*Scheme 37*).[61] Treatment of silyl substituted enyne **125** with a catalytic amount of zinc chloride resulted in formation of a zinc silylcarbenoid intermediate which reacted with butadiene to deliver the fused bicyclic furans **126a** and **126b**. Partial desilylation occurred as a consequence of the reaction conditions employed. The furan products are most likely formed by a formal [4+3] cycloaddition reaction, but formation of cyclopropane and subsequent Cope rearrangement cannot be ruled out.



Scheme 37

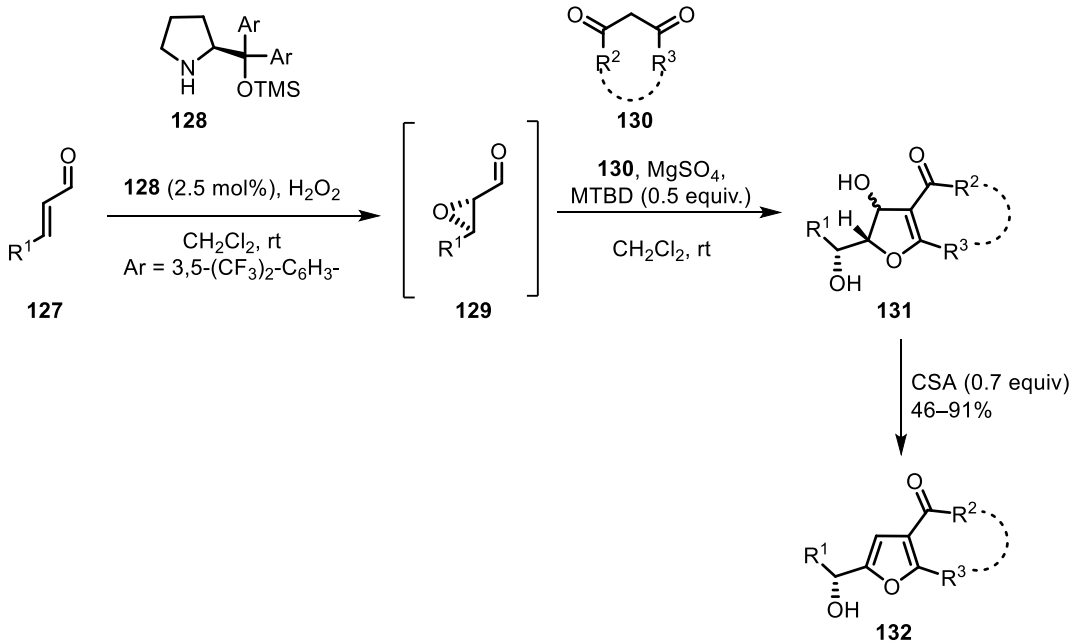
1.3.3 Organocatalysed Furan Formation

Due to the importance of furans, the development of new methodology for their construction has received considerable attention. Their construction *via* metal-mediated procedures has been the subject of numerous investigations over the years. However, organocatalytic methods for the construction of furans have been relatively unexplored until recently.[62] A few recent protocols for furan formation focussing on organocatalysis are described in the following section.

1.3.3.1 Organocatalytic Approach to 2-Hydroxyalkyl Furans

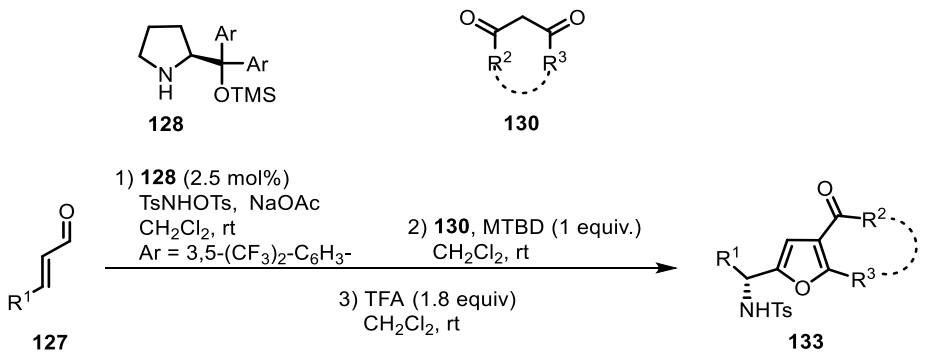
In 2010, Jørgensen reported an enantioselective method for the synthesis of electron-poor 2-hydroxyalkyl and 2-aminoalkyl furans based on an improved Feist-Benary synthesis (*Scheme 38*).[62] The pyrrolidine **128** was employed to catalyse the enantioselective epoxidation of the α,β-unsaturated *trans* alkenal **127**. The resulting 2,3-epoxy aldehyde **129** underwent a Feist-Benary reaction with 1,3-dicarbonyl compound **130** to furnish 2-hydroxyalkyl-2,3-dihydrofuran **131** as single product. Dehydration under acidic conditions yielded the 2-hydroxyalkyl furan **132**. The reaction was carried out with *trans* 2-hexenal and methyl acetoacetate as model substrates. Further screening revealed that the use of MTBD as base to form the dihydrofuran and camphorsulfonic acid as acid to accomplish dehydration was optimal to deliver the product in good yield and with high enantiomeric excess.

The reaction was viable with a wide range of γ-branched aliphatic and aromatic α,β-unsaturated aldehydes **127**. Further studies revealed, that a large variety of 1,3-diketones **130** could be used, leading to the formation of furans **132** in good yield and with high enantiomeric excess. An economic benefit of this organocatalytic approach is that a relatively low catalyst loading is required.



Scheme 38

Using the same methodology, Jørgensen succeeded in synthesising the corresponding furylamines **133** *via* 2,3-aziridinyl aldehydes (*Scheme 39*).

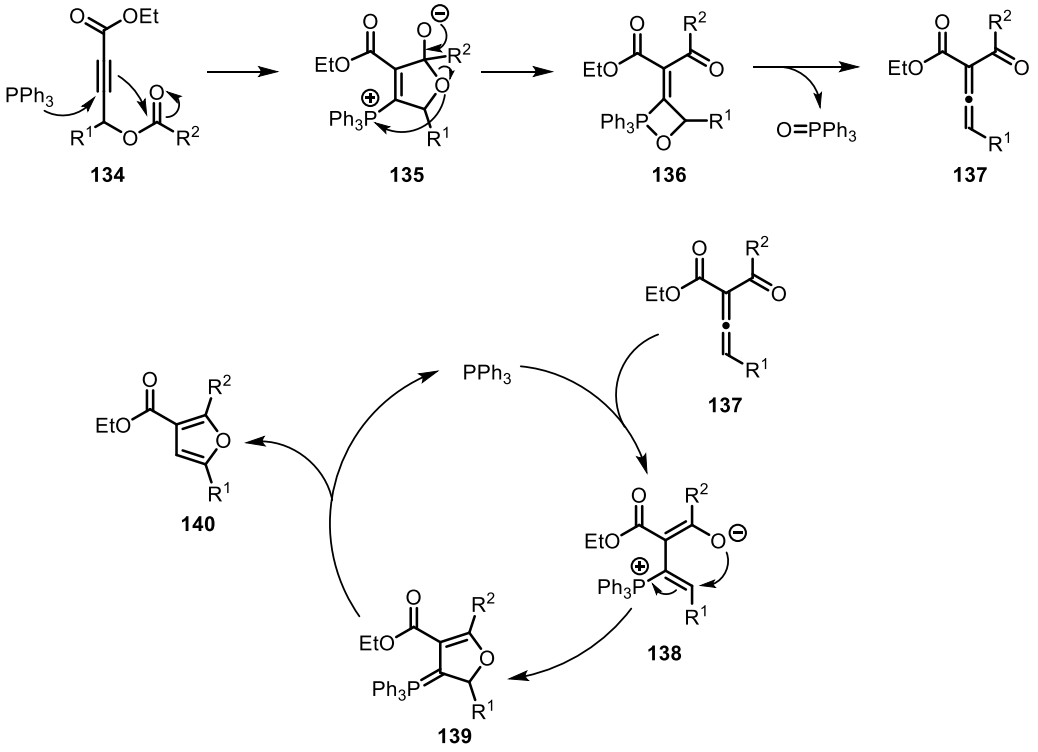


Scheme 39

In summary, Jørgensen reported an enantioselective method for the synthesis of the 2-hydroxyalkyl furans **132** and the 2-aminoalkyl furans **133**. The furan products are formed under mild conditions and with low catalyst loadings to give motifs found in many biologically active products.

1.3.3.2 Organocatalytic Approach to 2-Hydroxyalkyl Furans

Another strategy for the construction of substituted furans was reported by Krische.[63] In this protocol, a *γ*-acyloxy butynoate **134** is exposed to a stoichiometric quantity of a triarylphosphine, which induces an intramolecular reductive cyclisation reaction to yield a substituted furan **140** through the formation of the allenic ester **137** (*Scheme 40*). In the postulated reaction mechanism, exposure of butynoate species **134** to triphenylphosphine leads to tandem conjugate addition/acyl substitution to afford intermediate **136**. Extrusion of triphenylphosphine oxide from the betaine **136** affords the allenic ester **137**. The ester **137** is transformed into the corresponding furan **140** by nucleophilic attack of a second equivalent of triphenylphosphine.

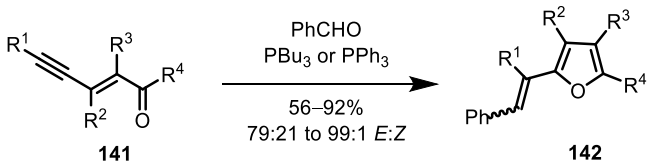


Scheme 40

Under optimised conditions (1.2 equiv. PPh_3 at 110 °C in EtOAc), studies were carried out by the group to assess the feasibility of the proposed transformation. Screening of various γ-acyloxy butynoates led to the formation of substituted furans in 60–86% yield and revealed that furan formation was most efficient when the γ-acyloxy substituent (R^2) of the butynoate is electron-deficient.

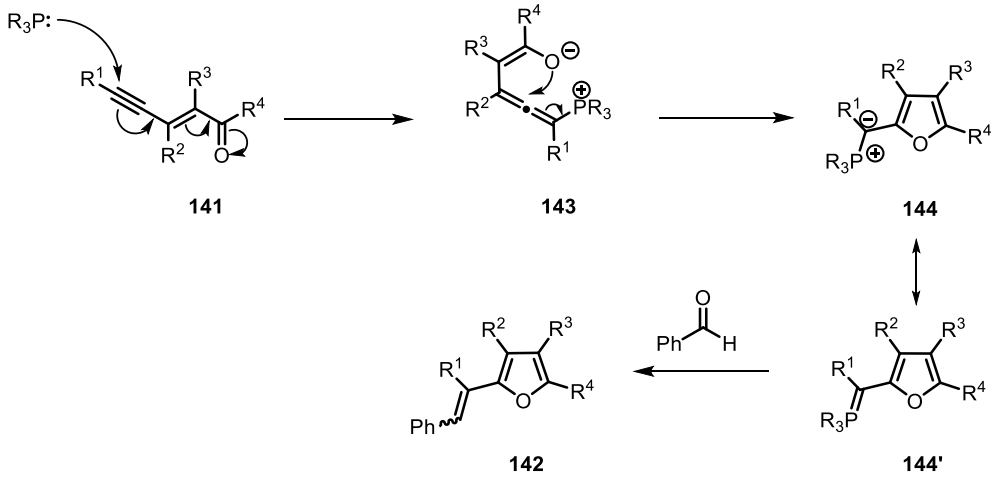
1.3.3.3 Phosphine-Mediated Synthesis of Furans form Enynes

In 1991, Kuroda reported a method for the preparation of furans by a phosphine-initiated reaction of substituted enynes.[64] In 2004, he applied this method to the synthesis of more highly-substituted furans **142** from ynenones **141** (*Scheme 41*).[65]



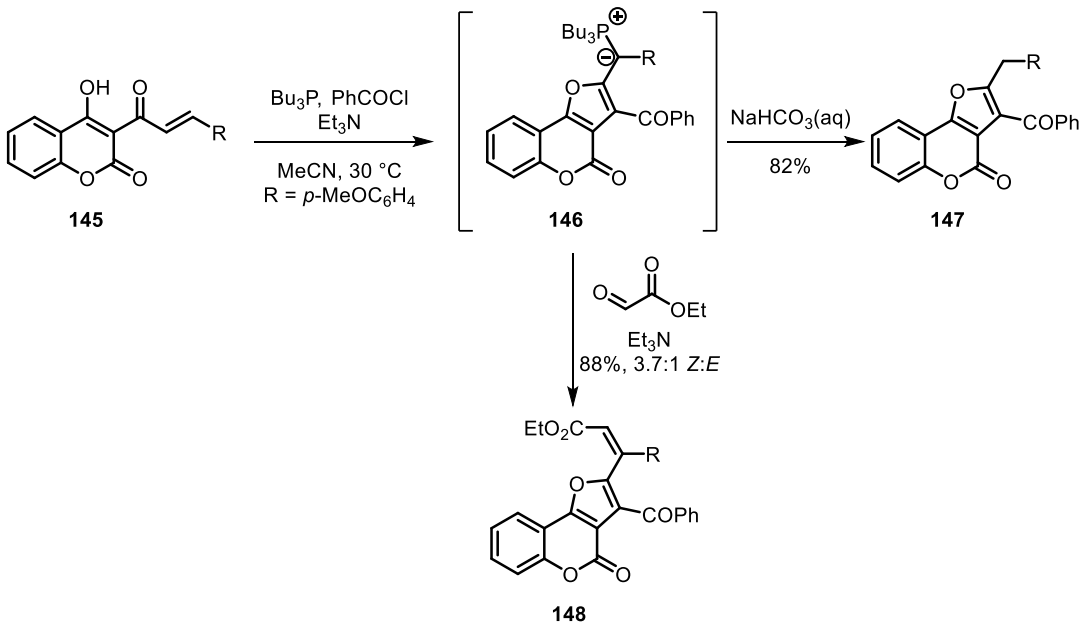
Scheme 41

The reaction was performed in the presence of stoichiometric amounts of triphenylphosphine or tributylphosphine and promising results were obtained. The use of a sub-stoichiometric amount of phosphine results in a reduction of the yield by half. In accord with these observations, the authors proposed that the reaction proceeds by 1,6-addition of the nucleophilic phosphine to the alkyne **141** to form intermediate **143** (*Scheme 42*). Subsequent internal cyclisation to give the intermediate phosphonium ylide **144** and a Wittig reaction with an aldehyde delivers the α-vinyl furan **142** and triphenylphosphine oxide. Stoichiometric equivalents of nucleophilic phosphine are required in order to give good yields. Exploration of the versatility of the reaction by screening of substrates possessing various substituents, revealed that the yields are remarkably influenced by alkyne substituent (R^1) rather than by the carbonyl substituent (R^4). If an aromatic substituent is present on the alkyne, poor results are obtained. Additionally, unknown side reactions occur when R^3 is an alkyl substituent.



Scheme 42

Lin and co-workers recently reported a novel phosphine-promoted *C*-acylation/cyclisation reaction to furnish coumarin derivatives **147** and **148** in moderate to good yields using a similar approach as Kuroda (*Scheme 43*). The protocol involves reaction of a chromen-2-one **145** with an acyl chloride and Bu_3P in the presence of Et_3N to access the phosphorus ylide **146**. The *in situ* generated ylide can either be quenched with aqueous $NaHCO_3$ to generate the corresponding furo[3,2-c]coumarin derivative **147** or trapped with a carbonyl electrophile to afford the corresponding Wittig product **148**.[66]

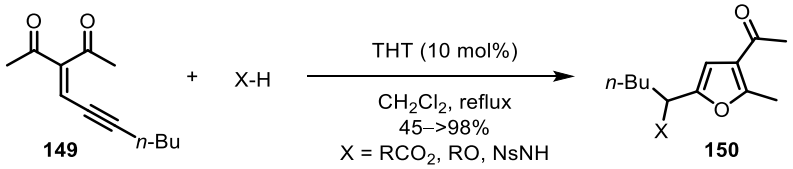


Scheme 43

1.3.3.4 Organosulfur-catalysed Synthesis of Furans from Ynenones

Drawing inspiration from the work of Kuroda, the Clark group proposed that a similar cascade reaction could be triggered by an organosulfur catalyst rather than a phosphine. The sulfur catalyst should initiate a similar reaction sequence *via* a sulfonium ylide intermediate and the group assumed that the resulting sulfur ylide could be adapted to allow introduction of a variety of substituents to the ring, leading to the synthesis of highly substituted furans. In 2012, Clark and co-workers reported a new approach to the formation of substituted furans using a simple thioether as the organocatalyst.[67]

Starting from ynenone **149**, treatment with a sub-stoichiometric amount of tetrahydrothiophene (THT) and an acidic nucleophile was observed to generate the furan products **150** in excellent yields (*Scheme 44*).



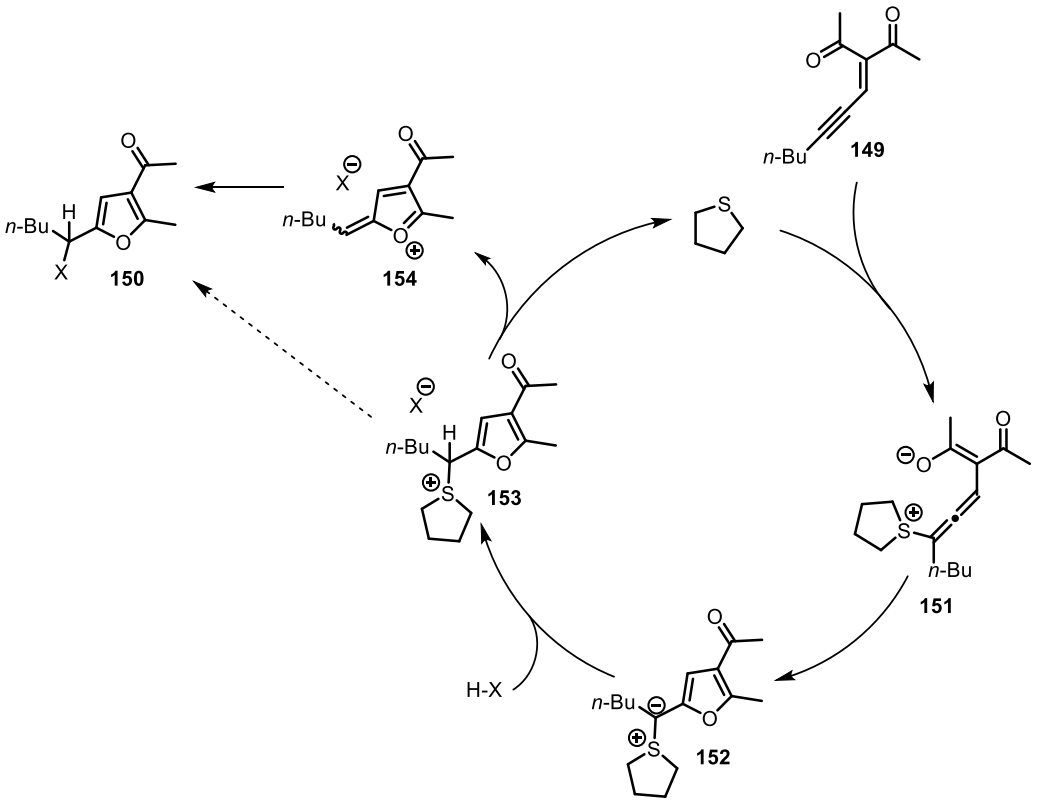
Scheme 44

The optimised reaction conditions were employed to incorporate a diverse set of nucleophiles. Electron-rich and electron-poor aryl carboxylic acids were screened as well as a variety of alcohols, such as methanol and *t*-butyl alcohol, to yield the corresponding furans in excellent yields. However, yields were slightly lower for bulky alcohols. The conclusion was that highly acidic nucleophiles are not required in order to accomplish the reaction. It was also found that sulfonamides can function successfully as nucleophiles.

The conditions were found to be compatible with a diverse set of alkyne substituents. Furan formation was successful when alkyl, aryl or trialkylsilyl substituted alkynes were employed. The reaction proceeds well, even in a case where a tetrasubstituted carbon was located adjacent to the site of nucleophilic attack.

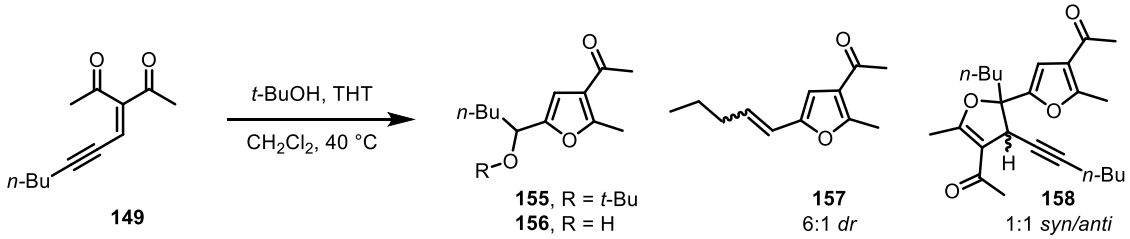
Additionally, the reaction was examined with substrates bearing an electron-withdrawing substituent instead of one of the ketone carbonyl groups. In the case of ester, phosphonate, sulfone and nitrile groups, the cyclisation reaction was found to give furan products in good yield.

The proposed reaction pathway proceeds by conjungate addition of the sulfur nucleophile onto the alkyne **149** (*Scheme 45*). The resulting enolate **151** undergoes intramolecular cyclisation to furnish the intermediate **152**, in which the furan is tethered to a sulfur ylide. In the presence of an appropriate acidic nucleophile, the ylide **152** undergoes protonation to afford the sulfonium salt **153**. The reaction most likely proceeds to give the final product *via* an S_N1 pathway rather than a concerted S_N2 process, thereby releasing the tetrahydrothiophene back into the catalytic cycle to generate the oxocarbenium ion **154**. The final step involves attack of the nucleophile to yield the final furan **150**.



Scheme 45

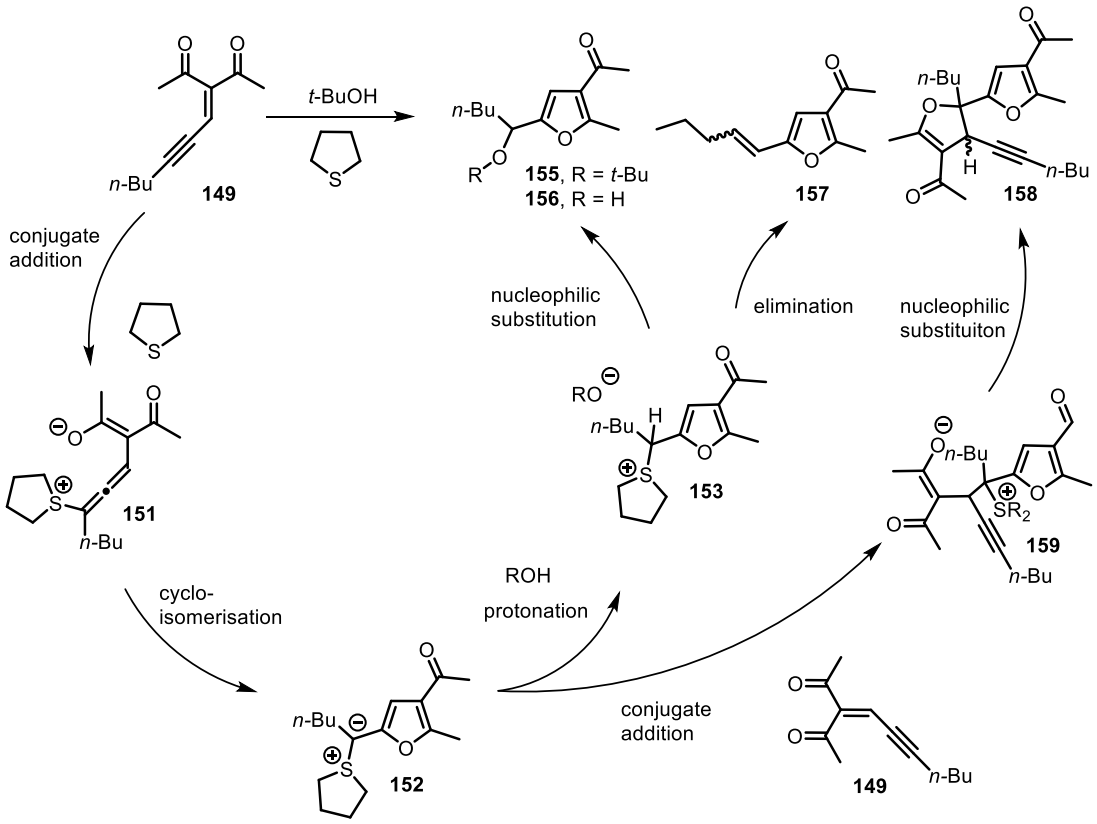
Further investigations by the group concerning the furan formation methodology have shown that when the reaction is carried out with electrophilic ynenone **149** and *t*-butyl alcohol as nucleophile, three side products are formed along with the desired product **155** (*Scheme 46*). These compounds have been isolated and characterised.[68]



Scheme 46

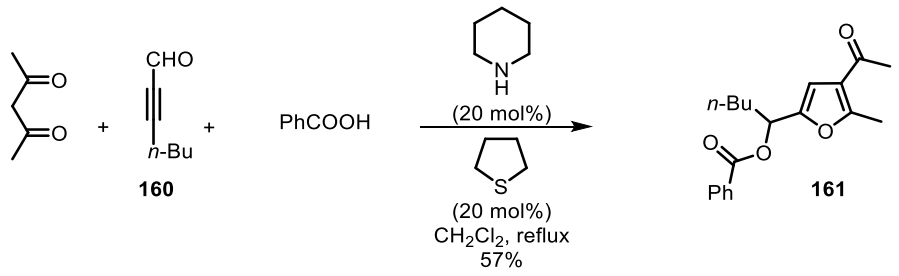
Formation of these side products is proposed to proceed by a mechanism in which the organosulfur catalyst undergoes conjugate addition onto the ynenone **149** to produce the **151** (*Scheme 47*). Cyclisation of the intermediate **151** affords sulfonium ylide **152**. Protonation by *t*-butyl alcohol yields sulfonium salt **153** and subsequent nucleophilic

substitution affords the desired product **155** (R = *t*-Bu). The 'water addition product' **156** (R = H) results from a competing reaction with water as nucleophile. Elimination of THT and proton abstraction leads to the formation of vinyl furan **157**. On the other hand, conjugate addition of ynenone **149** to sulfur ylide **152** followed by cyclisation affords dimer **158**.



Scheme 47

As a final test of the power of this methodology the Clark group was able to combine the condensation reaction and the furan-forming reaction in a one-pot procedure, as it was reasoned that these two reactions would be independent from each other.[67] One-pot organic transformations have some advantages: they significantly reduce chemical waste and improve synthetic efficiency. Consequently, their design and application has increased in the last few decades.[20] The final compound **161** was constructed from acetylacetone, the aldehyde **160** and benzoic acid in the presence of THT and piperidine (*Scheme 48*). This one-pot procedure delivered yields that were comparable to those obtained when the reactions were performed separately.



Scheme 48

In summary, this method allows organocatalytic formation of highly decorated furans under mild conditions and in good yield. The reaction operates with various substrates and nucleophiles and has the potential to be extended to more complex cascade systems.

1.3.3.5 Brønsted Acid Promoted Cascade to form Cyclopropanated Furans

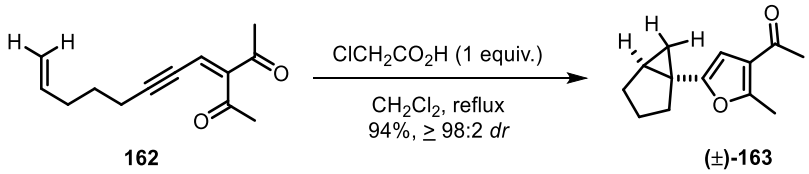
Following the success of the thioether-catalysed furan formation, it was of interest to extend the methodology to afford complex polycyclic furans.

The Clark group applied the previously established organosulfur methodology, using a stoichiometric amount of acid as the nucleophile, to a wider range of substrates bearing an unsaturated side chain, such as **162** (*Scheme 49*).[69] Surprisingly the reaction of the alkene **162** yielded the trisubstituted furan **163** bearing a fused bicyclic system that contains a cyclopropane, as a single diastereoisomer. Further studies demonstrated that THT is not needed for this transformation, instead cyclisation is promoted by the presence of a Brønsted acid. Optimisation studies revealed that chloroacetic acid delivered the best yields and that the use of weaker acids such as benzoic acid or acetic acid necessitated longer reaction times.

A wide range of readily accessible ynenediones could be transformed into the corresponding cyclopropyl-substituted furans in excellent yield and with high diastereocontrol when optimised reaction conditions were employed. Spirocyclic products could be isolated in good yields when the ynenone was tethered to a methylenecyclopentane or methylenecyclohexane. The reaction was also performed on substrates with various lengths of carbon tether and relevant bicyclic systems with fused cyclopentane or cyclohexane rings were constructed in good yield. The incorporation of heteroatoms such as oxygen or nitrogen into the chain linking the

alkene to the ynenone was also successful and reactions of these substrates delivered the corresponding oxa- and aza-bicyclic products in reasonable yields.

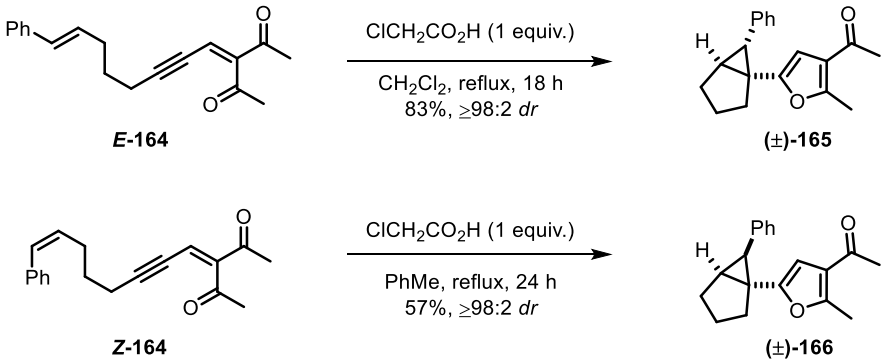
Additionally the reaction was examined with substrates bearing an electron-withdrawing substituent instead of the carbonyl group. In the case of substrates containing an ester, phosphonate or sulfone group, cyclisation to give the furan products was observed.



162 **(±)-163**

Scheme 49

Additionally, the effect of the geometry ot the tethered alkene on the stereochemical outcome of the reaction was investigated (*Scheme 50*).[69] The *E*-alkene ***E*-164** and the *Z*-alkene ***Z*-164** were synthesised and their cyclisation reactions to give the furan-containing tricyclic ketone products were explored. Carrying out the reactions under optimised conditions resulted in conversion of the substrate ***E*-164** into the cyclopropane **165**, with *syn* relationship between the two aryl substuents, as a single diastereoisomer and in good yield. When substrate ***Z*-164** was employed, the rate was much slower and therefore the reaction was carried out in toluene at reflux. In this case, the *Z* configuration of the alkene ***Z*-164** was translated into an *anti* relationship between the two aryl substuents in the cyclopropane **166**.



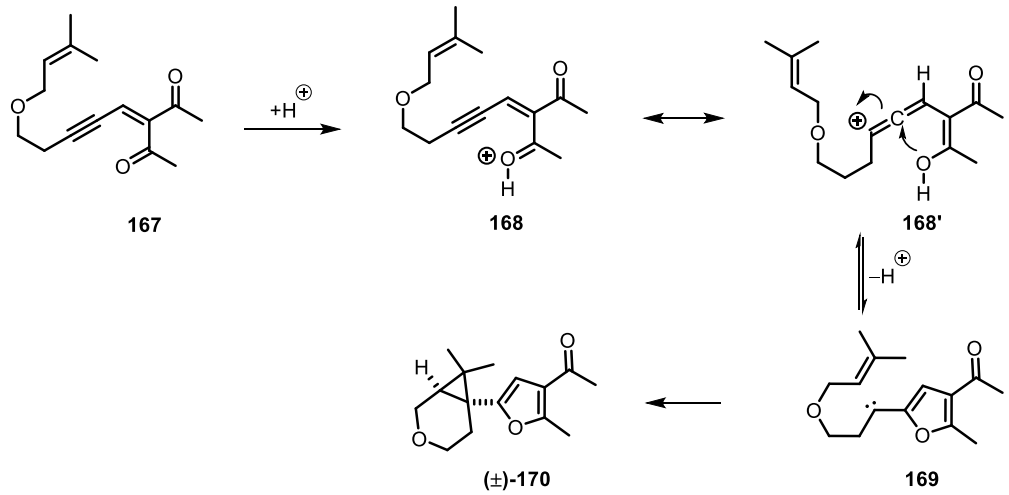
***E*-164** **(±)-165**

***Z*-164** **(±)-166**

Scheme 50

In the proposed mechanism, the cascade reaction is initiated by protonation of one of the carbonyl groups (*Scheme 51*).[69] The resulting protonated compound **168** can be

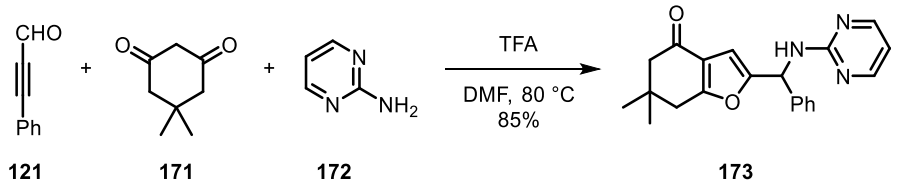
drawn in the resonance form **168'** which then undergoes internal cyclisation through nucleophilic attack of the oxygen onto the allenic carbon. Cyclopropanation of the pendant alkene by the resulting carbene **169** then leads to the final product **170**.



Scheme 51

In summary, a simple, new and highly stereoselective synthesis of furans was developed, delivering furan products in excellent yields. The reaction proceeds under mild conditions and has the potential to be extended to more complex polycyclic systems.

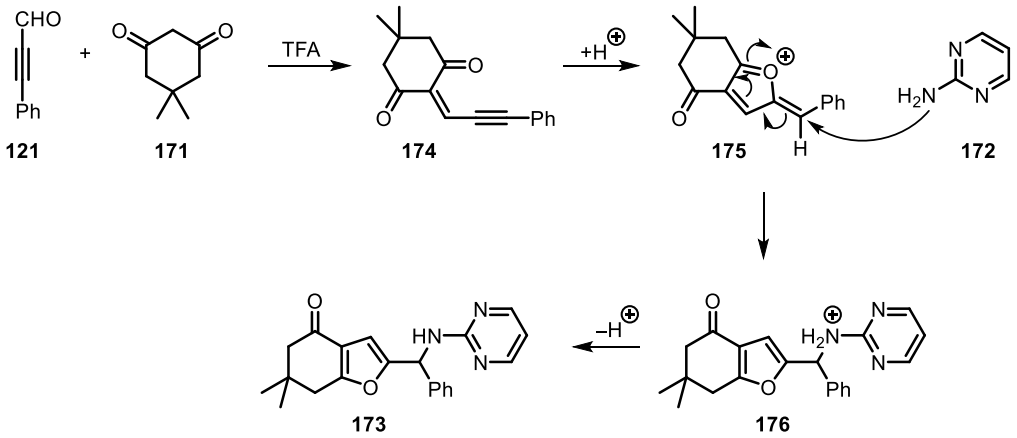
An approach to the construction of furan rings in which a three-component domino process is employed has been reported by Cao and co-workers (*Scheme 52*).[70] The reaction between propargylic aldehyde **121**, cyclohexanedione **171** and pyrazine-2-amine **172** in the presence of a catalytic amount of TFA delivered the corresponding furan **173** in good yield. It was found that the reaction could be applied to a wide variety of amine partners and that also open-chain 1,3-dicarbonyl compounds were suitable.



Scheme 52

It is proposed that aldehyde **121** and diketone **171** undergo Knoevenagel condensation to generate intermediate **171** in the presence of TFA (*Scheme 53*). The condensation reaction is followed by intramolecular cyclisation to generate the electrophilic

intermediate **175**. Finally conjugate addition of the nucleophilic amine **172** furnishes the furan product **173**.



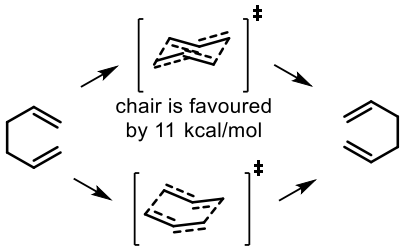
Scheme 53

1.4 Cycloheptane

The cycloheptane system is present in various natural products, bioactive compounds and pharmaceuticals. Despite its recurrance as a structural unit in nature, the cycloheptane framework has been less extensively studied then the cyclohexane system. Traditional approaches to the construction of cycloheptanes range from transition metal-catalysed cycloadditions[71] and ring-closing methathesis[72], to one-carbon ring expansion of cyclohexanones. The development of new, efficient and stereoselective reactions to form these frameworks remains an important goal.

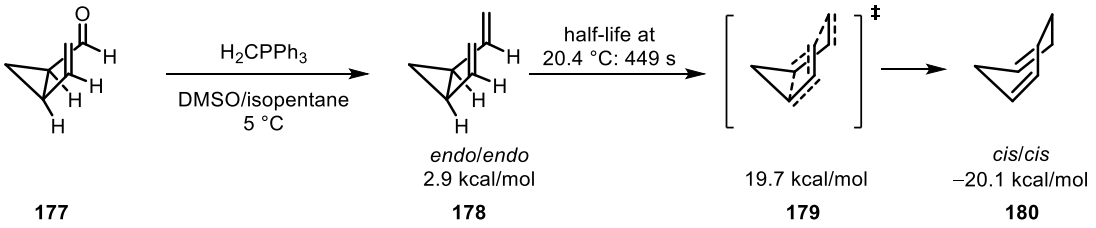
1.4.1 Cope Rearrangement of *cis* Divinylcyclopropane

The Cope rearrangement of *cis* divinylcyclopropane has been recognised as an efficient procedure for the synthesis of cycloheptane-containing systems. The Cope rearrangement is a [3,3]-sigmatropic rearrangement which involves the thermal rearrangement of a 1,5-diene. The concerted transformation generally proceeds through the favoured chair-like transition state (*Scheme 54*).



Scheme 54

The *cis* divinylcyclopropane rearrangement (DVCPR) to give 1,4-cycloheptadiene was first reported by Vogel in 1960 in his studies on small carbocycles.[73] However, Vogel was not able to isolate the labile *cis* 1,2-divinylcyclopropane as it immediately rearranged to the more stable cyclohepta-1,4-diene under the reaction conditions that were employed. In 1973, Brown and co-workers were finally able to prove the structure using a low temperature Wittig reaction (*Scheme 55*).[74] On the basis of mechanistic studies concerning this thermolysis reaction, it has been concluded that rearrangement of *cis* divinylcyclopropane **178** proceeds *via* a concerted pathway involving the only possible boat-like transition state **179**, in which both divinyl groups are in the endo position, to provide cycloheptadiene **180** with the favoured (*Z*)-geometry as a single isomer.



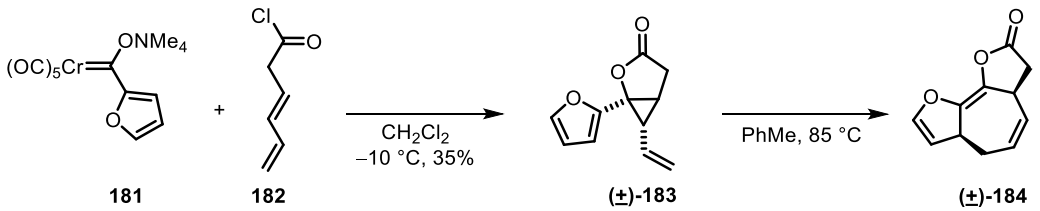
Scheme 55

The *trans* isomer is also suitable for the reaction, because isomerisation to the corresponding *cis* divinylcyclopropane takes place beforehand. This process normally proceeds at temperatures above 190 °C but the reaction temperature can be reduced for more highly conjugated systems. The isomerisation reaction is followed by the concerted rearrangement of the *cis* isomer. It has been suggested that the isomerisation from *trans* to *cis* proceeds through either a one-centre epimerisation reaction or *via* a diradical intermediate.

1.4.2 Synthetic Application of the Divinylcyclopropane Rearrangement

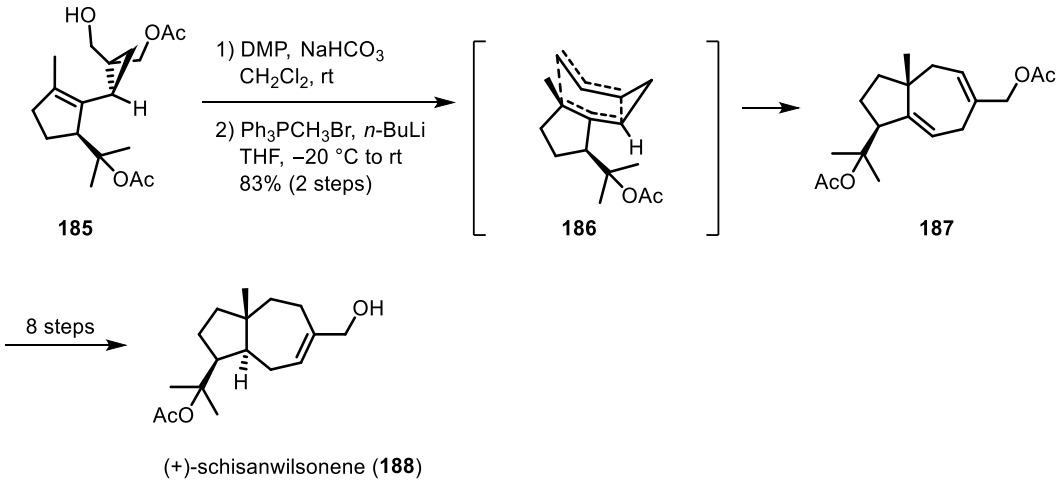
The *cis* divinylcyclopropane rearrangement reaction is an important method for the formation of seven-membered rings and it has found widespread application in the synthesis of many natural products and other complex molecules.

In 2002, Barluenga and co-workers utilised the DVCPR to prepare cycloheptane-fused γ-lactones **184** by thermolysis of arylvinylcyclopropanes **183** (*Scheme 56*).[75] Preparation of vinyl cyclopropane **183,** in which the furan and vinyl group are *syn*, was accomplished with high diastereoselectivity by reaction of the chromium carbene complex **181** with butenoyl chloride **182**. At temperatures above 85 °C, rearrangement results in dearomatisation of the furyl-substituted cyclopropane **183** and delivers the corresponding cycloheptadiene **184** as a single isomer.



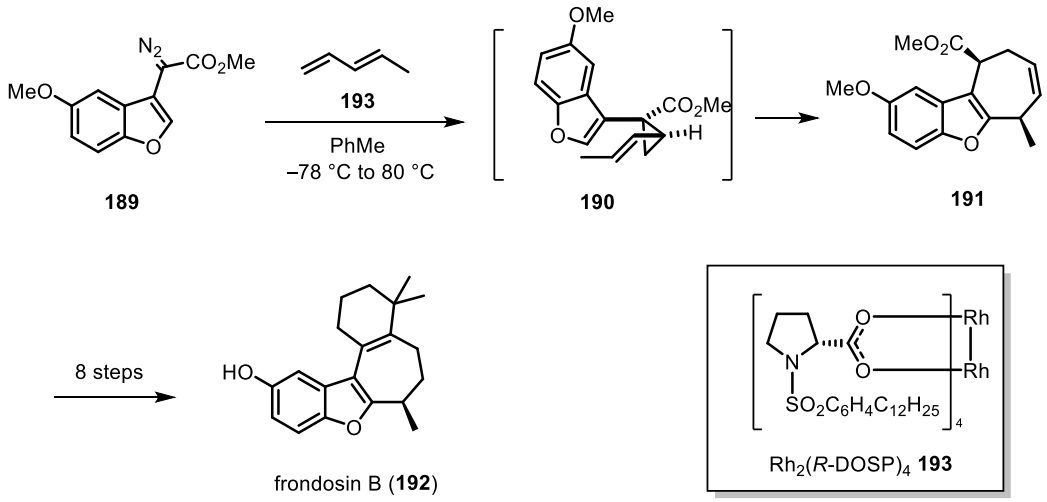
Scheme 56

Echavarren successfully applied the rearrangement of divinylcyclopropanes to deliver the key intermediate for the first enantioselective synthesis of (+)-schisanwilsonene A (**188**) (*Scheme 57*).[76] In this case, the cyclopropane **185** was subjected to oxidation, using DMP followed by Wittig reaction of the aldehyde to install the methylene group. The resulting highly reactive *cis* divinylcyclopropane then underwent rearrangement at room temperature to form the bicyclic hexahydroazulene **187**. The intermediate bicyclic diene **187** was converted into the natural product (**188**) in eight additional steps.



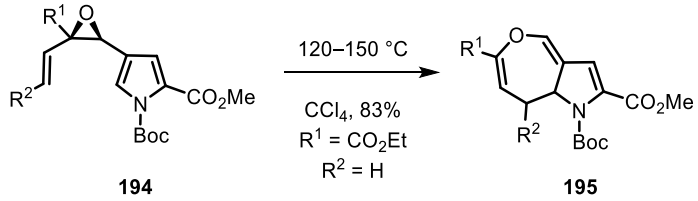
Scheme 57

The group of Davies used this specific type of Cope rearrangement reaction to prepare the sequiterpene-hydroquinone derivative frondosin B (**192**) (*Scheme 58*).[77] Enantioselective cyclopropanation of piperylene using diazocompound **189** in the presence of Rh_2(*R*-DOSP)$_4$ **193** gave the *cis* divinylcyclopropane **190**. Under the reaction conditions, the intermediate **190** underwent *in situ* DVCPR and subsequent rearomatisation to furnish the benzofuran **191** which can be converted into the desired natural product (**192**) in eight additional steps.



Scheme 58

There are several possible heteroatom variations of the DVCPR in which the heteroatom is incorporated either in the three-membered ring or as part of the vinyl moiety. The heteroatom that is incorporated can either be oxygen, nitrogen, phosphorus or sulfur. For example, rearrangement of a divinyloxirane to the seven-membered cyclic ether has been investigated extensively by White[78] and Smith[78b]. Rizzacasa and co-workers recently utilised the epoxy-Cope rearrangement for the synthesis of the dihydrooxepino[4,3-b]pyrrole **195** (*Scheme 59*).[79] Rearrangement of the readily accessible vinyl pyrrole epoxide **194** to the dihydrooxepine was carried out in carbon tetrachloride in a sealed tube at 150 °C. Studies revealed that the epoxide substituent (R^1) plays an important role in the Cope rearrangement. If a substituent is not present on the epoxide (R^1 = H) but an unsaturated ester is tethered to the alkene, the epoxide decomposes slowly. In contrast, if the epoxide is substituted with an carboxylate ester (R^1 = CO_2Et) but the vinyl group is unsubstituted, rearrangement takes place to furnish the fused heterocycle **195** in good yield.



194 **195**

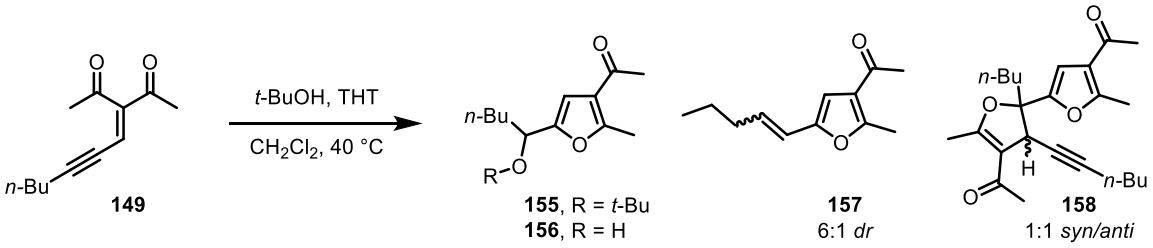
Scheme 59

2 Results and Discussion

2.1 Role of Acid in THT-Mediated Furan Formation

2.1.1 Previous Work

Recently the Clark group has reported a novel organocatalytic route for the synthesis of functionalised furans.[67] In this reaction, an ynenone was treated with a nucleophile to give the furan. Many nucleophiles can participate in this transformation, and high acidity is not necessary. However, when bulky *t*-butyl alcohol was employed as the nucleophile, the furan **155** was obtained in reduced yield along with three side products. In previous work these were isolated and characterised (*Scheme 60*).[68]



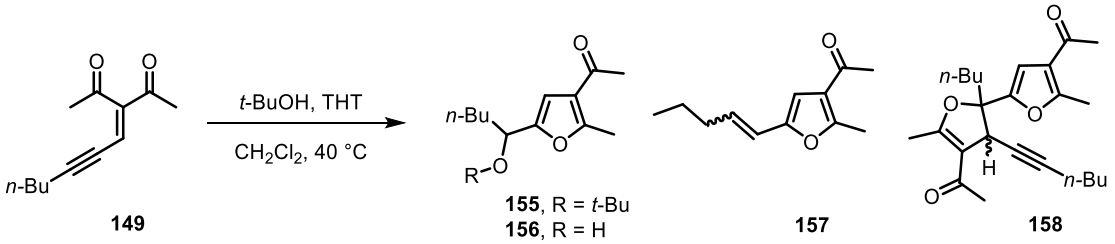
Scheme 60

Efforts are now focussed on the optimisation of the reaction by alteration of the conditions in order to suppress the undesired side reactions and improve the yield of furan **155**.

2.1.2 Influence of Acidic Additives

The effects of acid additives on both the yield of the desired product and the selectivity of the furan forming reaction was studied (*Table 1*). When no acid was used the desired product was isolated in 60% yield but various side products were formed as well (*Entry 1*). The formation of the alcohol **156** could be suppressed in nearly all experiments by using dry solvents and reagents or by addition of $MgSO_4$ (0.1 equiv.). Experiments with various acids showed that with lower pK_a, the vinyl furan **157** could be obtained as a single product (*Entries 2–4*). The stronger acids chlorosulfonic acid and HBF_4 delivered the vinyl furan **157** in only 47% and 33% yield respectively because the ynenone **149** is unstable under these conditions (*Entries 2 and 3*). When *p*-toluenesulfonic acid was used, **157** was obtained in 57% yield (*Entry 4*). The use of additives with slightly higher pK_a resulted in isolation of the furan **155** but various side products were also formed (*Entries 5 and 6*). Interestingly, camphorsulfonic acid, which has a higher pK_a than TFA and sulfamic acid, afforded the elimination product **157** as the sole isolable in 89% isolated yield (*Entry 7*). In contrast, phenylphosphonic acid, which has a similar pK_a as camphorsulfonic acid, was optimal and the furan **155** was isolated in 71% yield (*Entry 8*). Molybdic acid, 4-nitrophenol and 2-bromo-4,5-difluorophenol delivered similar results but with lower yields of the desired product (*Entries 9–11*). Acids with $pK_a \geq 8$ were shown to be inferior to phenylphosphonic acid due to the formation of various side products (*Entries 12 and 13*).

Table 1



149

155, R = *t*-Bu
156, R = H

157

158

Entry	Additive[a]	155	156	157	158	others	pK*a*
1	none	67 (60%)[b]	6	7	13	7	
2	chlorosulfonic acid	-	-	53 (47%)[b]	-	-	−6.0[80]
3	HBF_4	-	-	41 (33%)[b]	-	-	−4.9[81]
4	*p*-toluenesulfonic acid	trace	-	63 (57%)[b]	-	trace	−2.8[80]
5	TFA	54 (43%)[b]	6	12	-	28	0.5[82]
6	sulfamic acid	23 (17%)[b]	-	25	trace	52	1.0[83]
7	CSA	-	-	95 (89%)[b]	-	-	1.2[84]
8	phenylphosphonic acid	76 (71%)[b]	-	15	-	9	1.3[85]
9	molybdic acid	64 (58%)[b]	6	6	12	12	~3.8[86]
10	4-nitrophenol	66 (64%)[b]	6	6	trace	21	7.2[87]
11	2-bromo-4,5-difluorophenol	58 (56%)[b]	6	12	-	24	~7.9[87]
12	phenylboronic acid	45 (37%)[b]	15	5	-	35	8.8[88]
13	4-fluorophenol	11 (5%)[b]	-	-	23	66	9.9[87]

149 (1.0 equiv.), *t*-butyl alcohol (3.0 equiv.), THT (0.1 equiv.), 1 M in CH_2Cl_2; ratios determined by ^1H NMR; [a] additive (0.1 equiv.); [b] isolated yield after column chromatography.

As described, beside the previously identified by-products **156**, **157** and **158** various other furan products were formed. After careful NMR studies three of these could be identified (*Figure 4*). Furans **196**, **197** and **198** were generated from a THT catalysed furan-formation between ynenone **149** and the phenol derived additive.

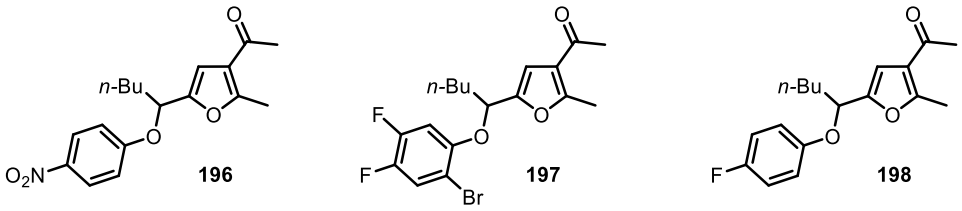


Figure 4

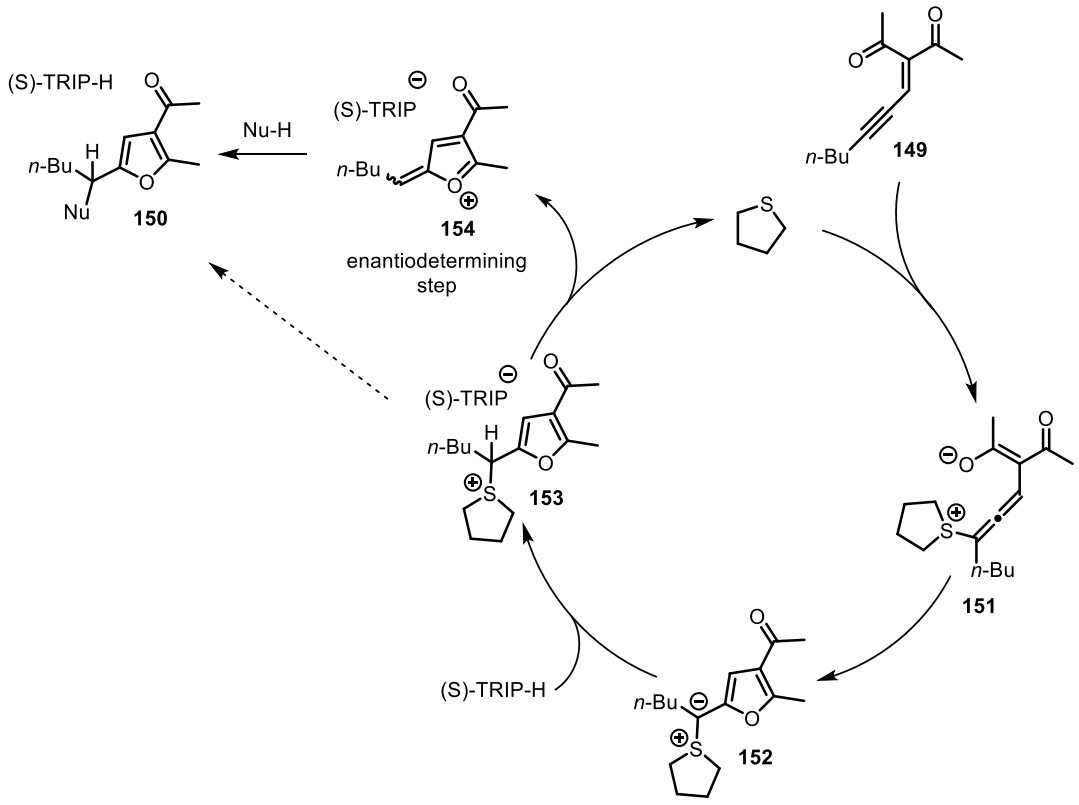
In these optimisation studies it was shown that the furan formation was dependent on the type of acid additive employed. Phenylphosphonic acid delivered the best results as it was acidic enough to promote the desired reaction but not acidic enough to catalyse the side reaction leading to formation of the vinyl furan and not nucleophilic enough to be trapped by the cationic species and be incorporated into the final product.

2.2 Stereoselective THT-Mediated Furan Formation: Introducing Enantioselectivity

The previous findings suggested that furan formation is mediated by an acidic additive. It was hypothesised that the new stereocentre could be introduced in an enantioselective fashion using a chiral acid, through asymmetric counteranion-directed catalysis (ACDC).

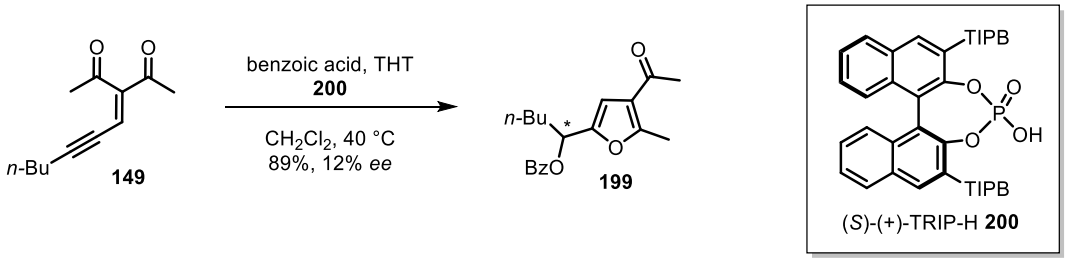
2.2.1 Study on Enantioselectivity Using Analysis by Chiral HPLC

According to the mechanism for the furan transformation, the reaction proceeds through a cationic intermediate **154** (*Scheme 61*). Therefore, it was proposed to apply the concept of ACDC and to use a chiral counterion to influence the stereochemical outcome of the reaction.[16] The catalyst most often employed in ACDC consist of a chiral BINOL backbone which is substituted in 3,3'-positon. For these studies the chiral phosphoric acid (*S*)-(+)-TRIP-H was chosen, because several literature examples of reactions in which high levels of asymmetric induction have achieved using this catalyst.[18] The catalyst is readily available and can be synthesised from *S*-BINOL in five steps.[89]



Scheme 61

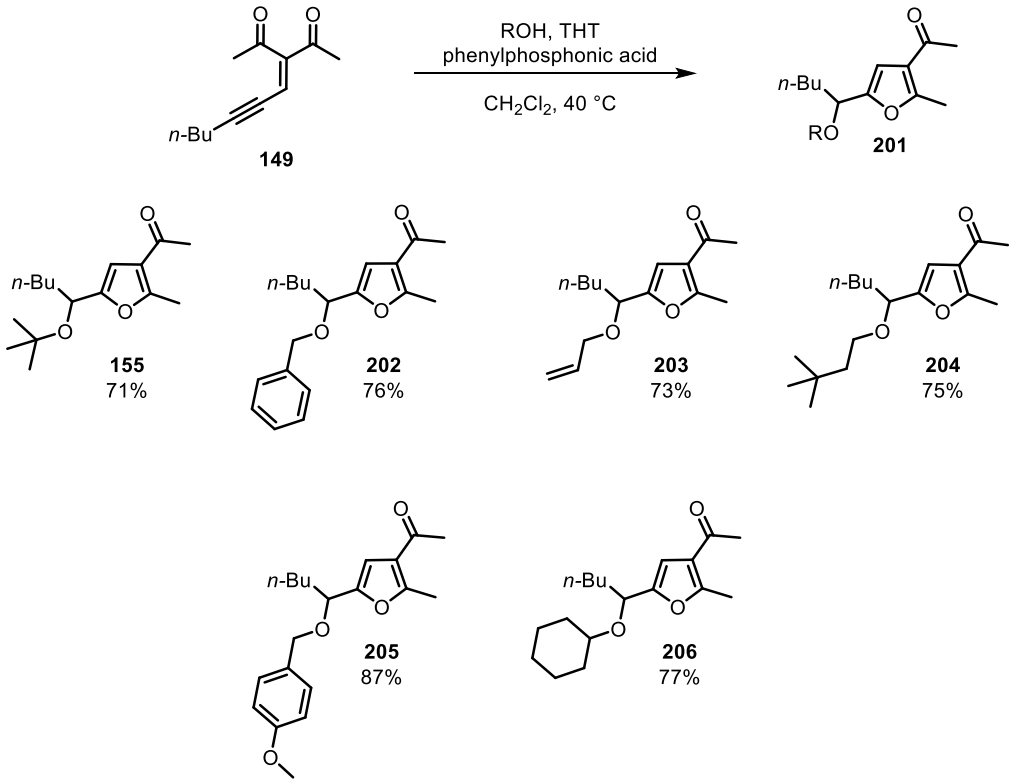
A preliminary experiment with ynenone **149** and benzoic acid as nucleophile was carried out in the presence of (*S*)-(+)-TRIP-H **200** (*Scheme 62*). The applied conditions afforded the furfuryl benzoate **199** in 89% yield and 12% *ee* (HPLC analysis).



Scheme 62

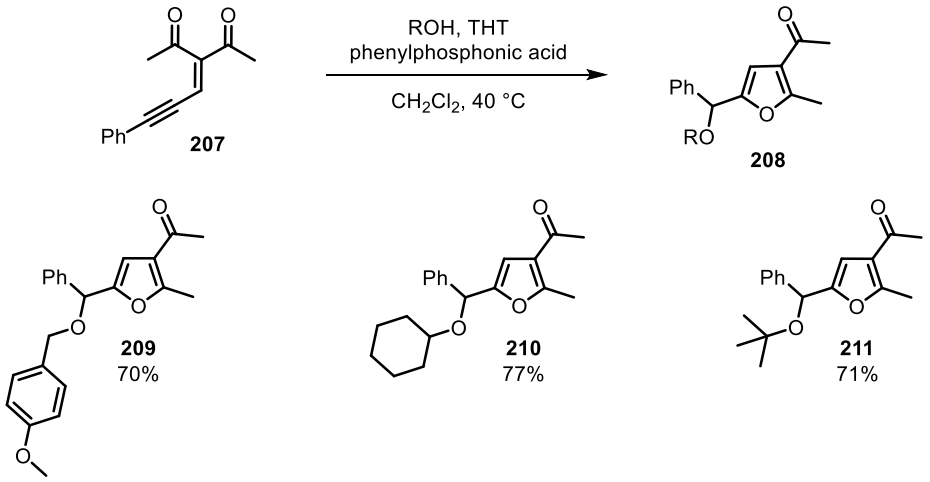
It should be noted, that (*S*)-TRIP-H **200** was purified on silica gel chromatography therefore it is suggested that the actual catalyst was not the phosphoric acid, but the corresponding calcium salt formed as an impurity during the purification.

It was reasoned that by examining various nucleophiles their effect on enantioselectivity and yield could be investigated. Therefore, reactions involving various alcohols were investigated. However, conditions that would deliver enantiomer separation by chiral HPLC could not be found and so the study using the chiral catalyst was not performed (*Scheme 63*).



Scheme 63

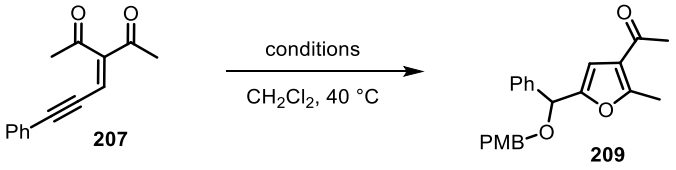
In order to facilitate analysis of the reaction outcome by HPLC, the phenyl substituted ynenone **207** was used (*Scheme 64*). A screen of various alcohols revealed that in the reaction with anisyl alcohol the racemic mixture of the furan **209** could be separated by chiral HPLC.



Scheme 64

However, the reaction catalysed by (*S*)-(+)-TRIP-H **200** gave only low levels of asymmetric induction (*Tabel 2*, *Entry 1*). Surprisingly, when no organosulfur catalyst was present, a trace amount of product **209** was formed with 16% *ee* (*Entry 2*). The formation of **209** in the absence of THT was unexpected and it was assumed that impurities in the solvent or reagent enabled the reaction.

Table 2

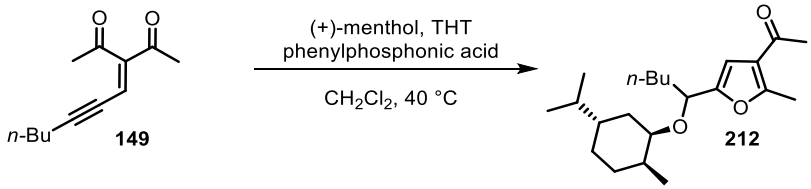


Entry	Nucleophile[a]	Catalyst	Additive[c]	*ee*[d]	Yield[e]
1	anisyl alcohol	THT[b]	(*S*)-TRIP-H	4%	70%
2	anisyl alcohol	-	(*S*)-TRIP-H	16%	7%

207 (1.0 equiv.), 1 M in CH_2Cl_2; [a] nucleophile (3.0 equiv.); [b] catalyst (0.1 equiv.); [c] additive (0.1 equiv.); [d] determined by chiral HPLC; [e] isolated yield after column chromatography.

2.2.2 Study on Enantioselectivity Using Analysis by ^{1}H NMR

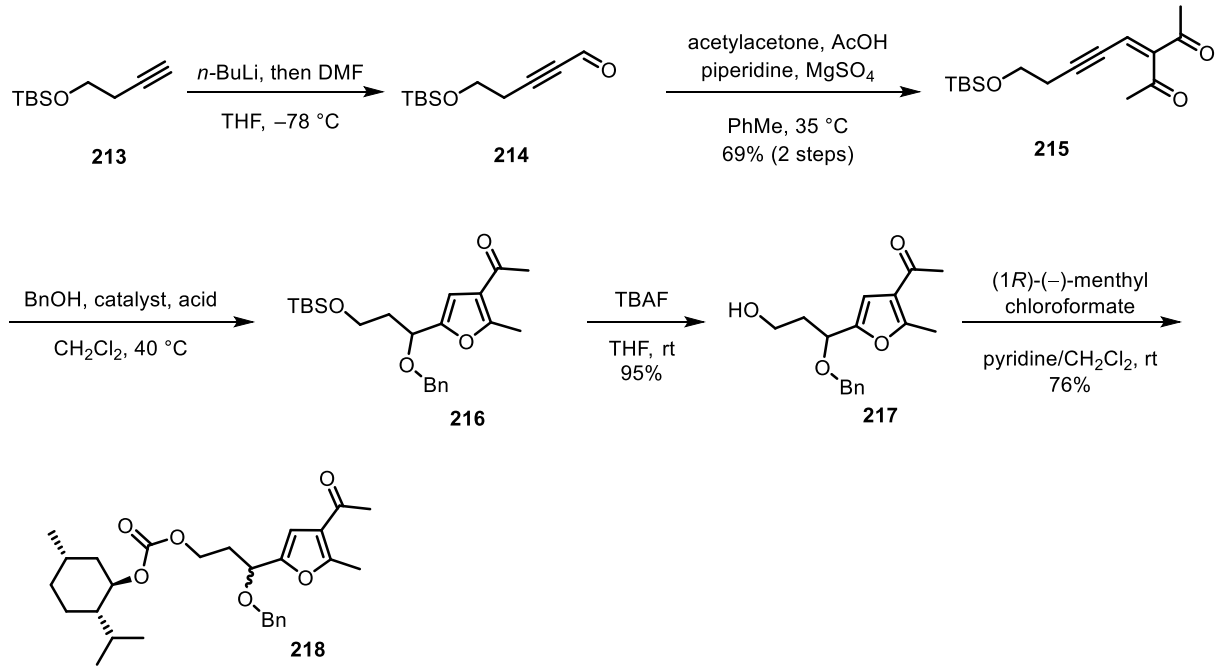
In order to study the effect of the chiral phosphate based catalyst by ^{1}H NMR, enantiomerically pure (+)-menthol was used as the nucleophile in the furan-forming reaction so that a mixture of diastereoisomers would be produced. However, even with prolonged reaction time (4 days) the starting material was not completely consumed and various side products were formed. NMR analysis of the crude mixture confirmed formation of **212** but the two diastereoisomers were not distinguishable by ^{1}H NMR (*Scheme 65*).



Scheme 65

To facilitate the analysis of the enantiomeric excess of the product from the reaction using a chiral catalyst, a substrate was designed that could be coupled to a chiral compound after furan formation in order to generate a mixture of diastereoisomers whose ratio can be measured by ^{1}H NMR. Thus, ynenone **215** was synthesised (*Scheme 66*).

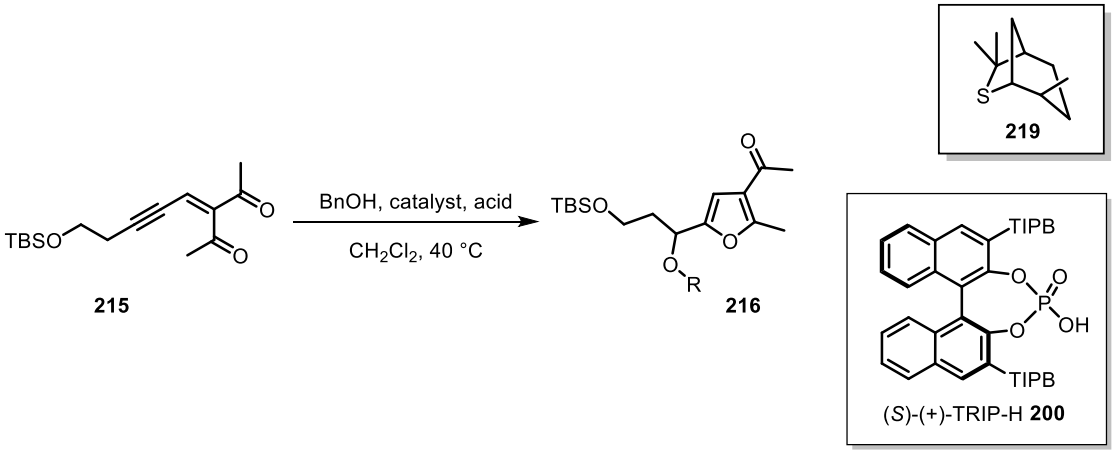
The synthesis started by formylation of alkyne **213**, using DMF to afford the alkynyl-aldehyde **214**. The aldehyde was treated with acetylacetone under Knoevenagel condensation conditions to provide ynenone **215** in 69% yield over 2 steps. Ynenone **215** was exposed to various reaction conditions using benzyl alcohol as the nucleophile; in all cases *O*-benzyl furfuryl alcohol **216** was obtained in good yield (*Table 3*). Deprotection using TBAF yielded alcohol **217** and finally acylation with menthyl chloroformate afforded a chromatographically inseparable mixture of diastereoisomers whose ratio could be measured by ^{1}H NMR.



Scheme 66

When the previously established reaction conditions were employed, the *O*-benzyl furfuryl alcohol **216** was obtained in 62% yield as a 1:1 mixture of diastereoisomers (*Table 3*, *Entry 1*). It is interesting to note that when the chiral thioether (1*R*,4*R*,5*R*)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane **219** was used as the catalyst , incomplete conversion of the starting material was observed even after prolonged reaction times and that no diastereocontrol was observed (*Entry 2*). When THT was used in combination with the BINOL derived phosphoric acid (*S*)-(+)-TRIP-H **200**, a low level of diastereocontrol was obtained (*Entry 3*).

Table 3



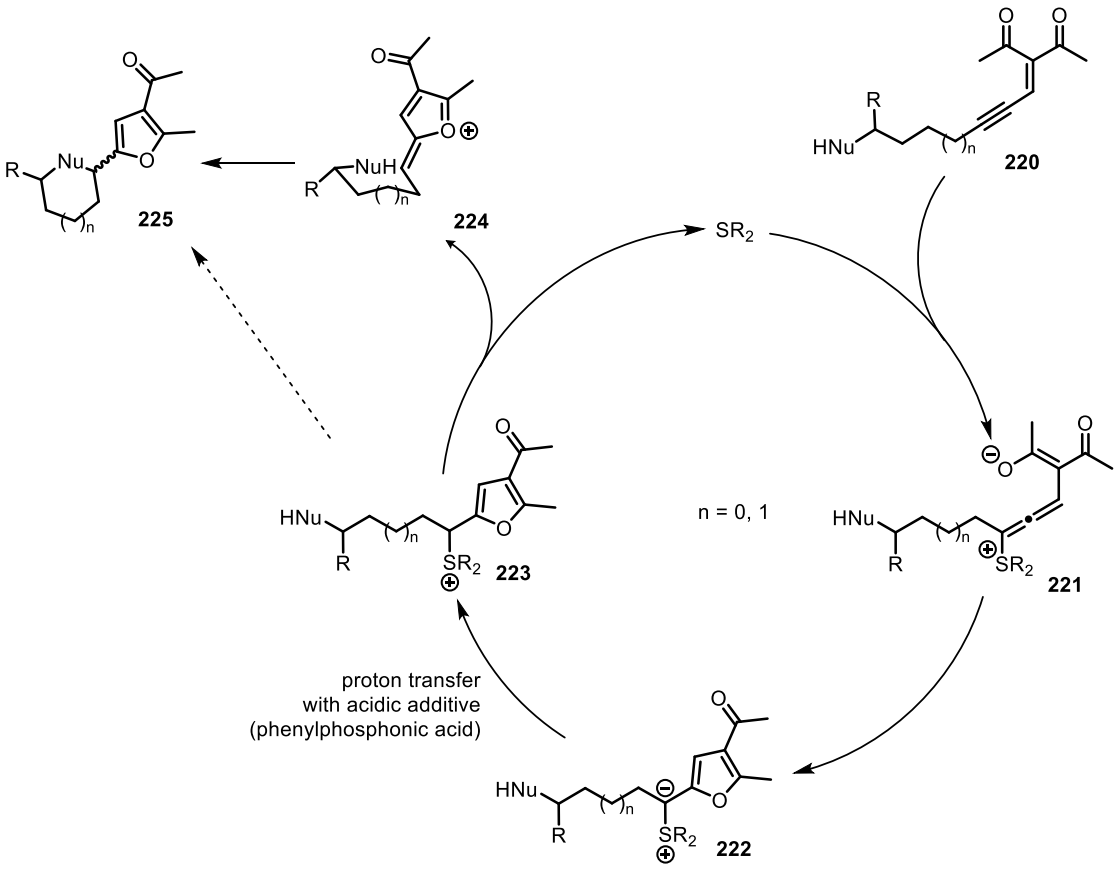
Entry	Catalyst[a]	Acid[b]	Time	*de*[c]	Yield[d]
1	THT	phenylphosphonic acid	2 d	0%	62%
2	**219**	phenylphosphonic acid	2 weeks	0%	41%
3	THT	**200**	1 d	9%	74%

215 (1.0 equiv.), benzyl alcohol (3.0 equiv.), 0.5 M in CH_2Cl_2; [a] catalyst (0.5 equiv.); [b] acid (0.1 equiv.); [c] determined by ^{1}H NMR of crude product; [d] isolated yield after column chromatography.

The selectivity matches that which has been observed previously (*Scheme 62*). Even the level of asymmetric induction was low, this observation suggests that the reaction proceeds through an S_N1 mechanism *via* an ion pair between furonium species and (*S*)-(+)-TRIP **200**.

2.3 Setereoselective THT-Mediated Furan Formation: Introducing Diastereoselectivity

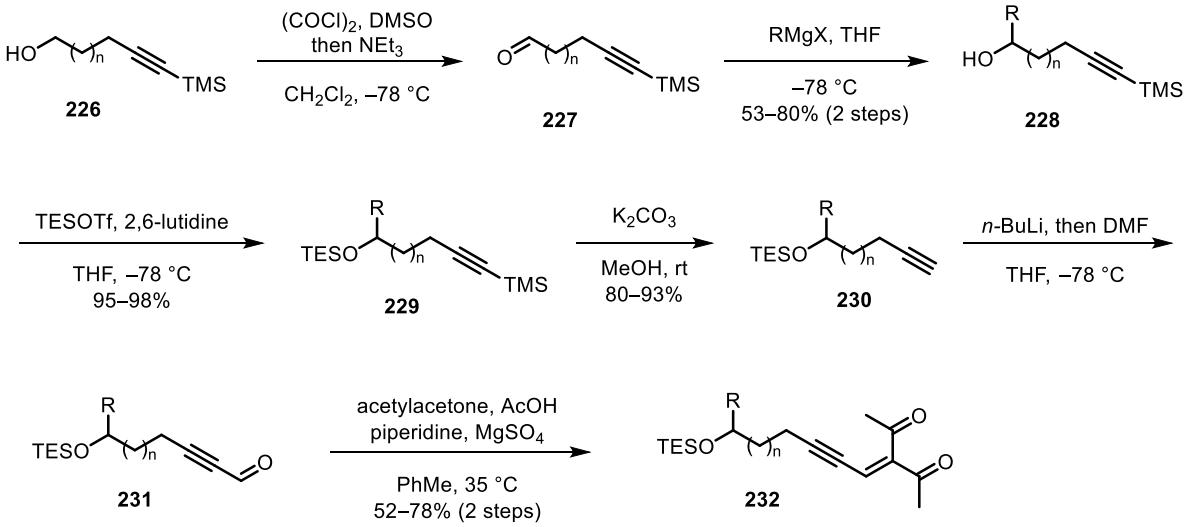
It was hypothesised that using previously established conditions, the ynenone substrate **220**, in which the nucleophile is tethered to the alkyne, would undergo a similar cascade to form a cyclic ether **225** (*Scheme 67*). The proposed mechanism involves formation of the allene **221** through nucleophilic attack of the catalyst to the ynenone **220**. Cyclisation to give the furan affords ylide **222** and subsequent protonation enhanced by an acidic additive provides the sulfonium salt **223**. According to the proposed mechanism it was assumed that the tethered carbon side chain of the oxocarbenium ion **224** would arrange in a chair or chair-like conformation with the bulky substituent in equatorial position. The aim of this study was to explore if the new stereocentre could be formed in a diastereoselective manner.



Scheme 67

2.3.1 Preparation of Substrates 233

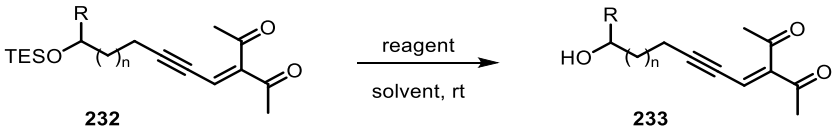
A series of ynenone substrates bearing a tethered oxygen nucleophile were designed. The general synthetic route started with oxidation of alcohols **226** to give the aldehyde **227** using standard Swern conditions (*Scheme 68*). Previous studies had shown that silyl protection of the alkyne is essential in order to suppress side reactions and to ensure high yields.[69] Grignard reactions with various reagents were performed to yield the corresponding alcohols **228**. Silyl protection of the alcohols and deprotection of the alkynes provided the terminal alkynes **230**. Alkyne formylation was accomplished by lithiation and treatment with DMF to deliver the alkynyl aldehydes **231**. Treatment of the aldehydes with acetylacetone under Knoevenagel condensation conditions provided the dimethyl substituted ynenones **232** in good yield.



Scheme 68

The choice of the triethylsilyl protecting group and conditions for its removal were crucial because the ynenone systems are fragile and some deprotection conditions (e.g., 1 M HCl, HF•pyridine, TBAF or TFA) led to decomposition (*Table 4*, *Entries 1–4*). The use of weak acids such as PPTS did not deliver the desired deprotected alcohols (*Entry 5*) but the use of a sub-stoichiometric amount of CSA was found to be optimal and delivered the alcohols **233** in good yield (*Entry 6*).

Table 4

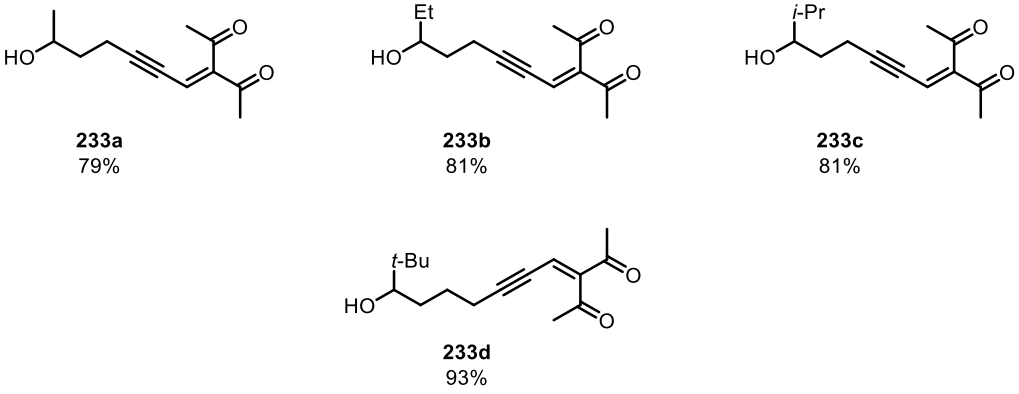


232 **233**

Entry	Reagent	Solvent[c]	Yield	Result
1	TBAF[a]	THF	-	decomp.
2	HF•pyr	MeCN	-	decomp.
3	1 M HCl	THF	-	decomp.
4	TFA[a]	MeCN	-	decomp.
5	PPTS[b]	EtOH	-	SM
6	CSA[b]	MeOH	79−93%[d]	product

232 (1.0 equiv.); [a] reagent (1.0 equiv.); [b] reagent (0.1 equiv.); [c] 0.2–0.5 M solution; [d] isolated yield after column chromatography.

The discovery of an efficient and robust route for the synthesis of the ynenone substrates, meant that various substrates could be prepared (*Figure 5*).



233a 79%

233b 81%

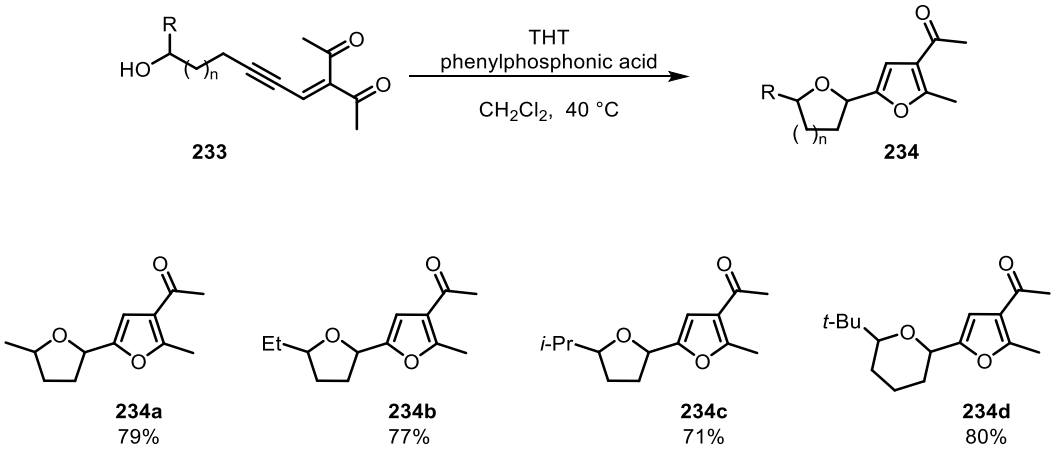
233c 81%

233d 93%

Figure 5

2.3.2 Cyclisation of Substrates 233

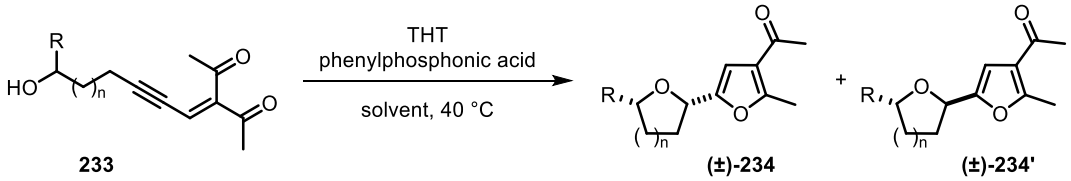
The successful preparation of the ynenone precursors meant that the cyclisation reactions could be investigated using the methodology previously developed to afford bicyclic furans **234** (*Scheme 69*).



Scheme 69

The reaction provided the furans **234** as an inseparable mixtures of diastereoisomers and their ratio was determined by ^{1}H NMR analysis of the crude reaction mixture in each case (*Table 5*). Investigations showed that a catalytic amount of THT was necessary to promote the formation of furan. The yield could be improved by the addition of phenylphosphonic acid to enhance the proton transfer step. However, with all of the substrates that were tested, the products were obtained with modest diastereoselectivity. Interestingly, during the formation of the 5-membered ether a reversal of the selectivity was observed depending on the substituent. With the methyl and ethyl substituents the *trans* disubstituted ether was favoured (*Entries 1 and 2*). However, for *i*-propyl the *cis* ether was formed in slight excess (*Entry 3*). Formation of the 6-membered ether with a *t*-butyl substituent resulted in slight improvement in the level of diastereocontrol (*Entry 4*).

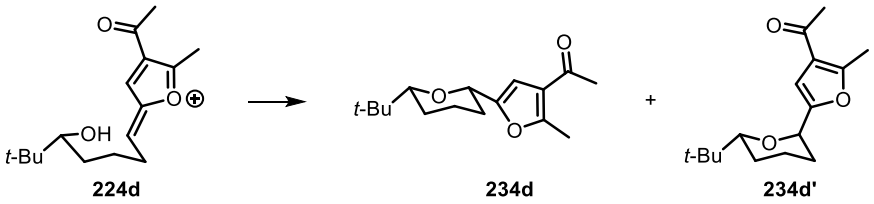
Table 5



Entry	Furan	n	R	Yield[a]	234:234'[b]
1	**234a**	1	Me	79%	1:1.2
2	**234b**	1	Et	77%	1:1.1
3	**234c**	1	*i*-Pr	71%	1.2:1
4	**234d**	2	*t*-Bu	80%	2.7:1

233 (1.0 equiv.), THT (0.5 equiv.), phenylphosphonic acid (0.1 equiv.), 1 M in CH_2Cl_2; [a] isolated yield after column chromatography; [b] determined by ^{1}H NMR of crude product.

It should be expected that formation of *anti* **234d'** is faster because no rotation of the substituent is necessary (kinetic product). However the formation of *syn* **234d** is favoured because of the lower in energy equatorial orientation of the two substituents (thermodynamic prodcut, *Scheme 70*).

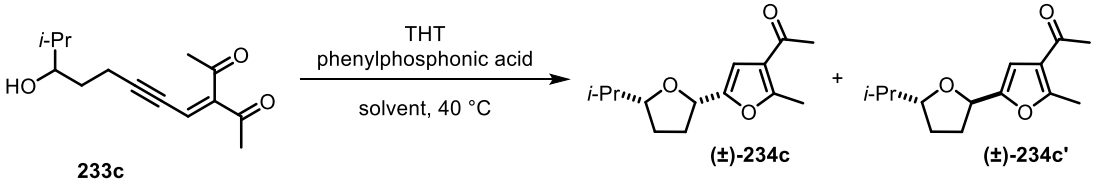


Scheme 70

In an effort to improve the stereochemical outcome of the reaction various reaction conditions for furan formation were investigated. First, a brief solvent screen was undertaken to test the effect of solvent polarity on the stereoselectivity of the reaction (*Table 6*). Protic polar solvents were not included because these would undergo reaction with the sulfur ylide **222** (*Scheme 67*) to afford substituted furan side products. In general, the reaction was robust and the desired furan **234c** was formed in good yield with all the solvents tested. However, there was little variation in the diastereselectivity of the reactions and no real correlation with the solvent polarity was observed. For the least polar solvents – *n*-hexane and cyclohexane – the

diastereoselectivity was 1.3:1 and 1.4:1 respectively (*Entries 1 and 2*). Switching to slightly more polar solvents, the stereoselective ratio ranged from 1.2:1 to 1.3:1. (*Entries 3–7 and 10*). The use of THF, $CHCl_3$ or 1,4-dioxane as solvent led to equal mixtures of products (*Entries 8, 9 and 11*). The level of diastereoselectivity rose when more polar solvents were used and the highest levels of diastereocontrol were obtained when acetone, DMF or DMSO was used as the solvent (*Entries 12, 14 and 15*). In contrast, a ratio of 1.2:1 was obtained from the reaction performed in MeCN (*Entry 13*).

Table 6



233c (±)-234c (±)-234c'

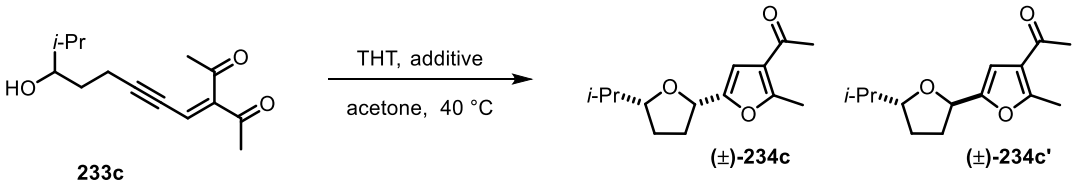
Entry	Solvent[a]	Yield[b]	234c:234c'[c]	Increasing Polarity[90]
1	*n*-hexane	47%	1.3:1	
2	cyclohexane	65%	1.4:1	
3	PhMe	65%	1.2:1	
4	PhH	68%	1.3:1	
5	Et_2O	73%	1.3:1	
6	CH_2Cl_2	71%	1.2:1	
7	1,2-dichloroethane	77%	1.3:1	
8	THF	61%	1.1:1	
9	$CHCl_3$	66%	1.1:1	
10	EtOAc	70%	1.3:1	
11	1,4-dioxane	73%	1:1	
12	acetone	72%	1.7:1	
13	MeCN	75%	1.2:1	
14	DMF	65%	1.6:1	
15	DMSO	42%	1.5:1	

233c (1.0 equiv.), THT (0.5 equiv.), phenylphosphonic acid (0.1 equiv.); [a] 1 M solution; [b] isolated yield after column chromatography; [c] determined by ^{1}H NMR of crude product.

In an attempt to improve the diastereomeric ratio of the products, the effect of various acidic additives and Lewis acids was investigated. In general, all the additives tested,

with the exception of $AlCl_3$ and $FeCl_3$, were able to promote the formation of the desired furan **234c** (*Table 7*, *Entries 7 and 8*). In the absence of an acidic additive, a ratio of 1.5:1 was obtained (*Entry 1*). The use of *p*-tolylboronic acid (pK_a = 9.3) delivered the same result (*Entry 2*). On the other hand, with camphorsulfonic acid (pK_a = 1.2) the ratio dropped significantly to 1.1:1 (*Entry 3*). The Lewis acids tested were mostly ineffective and 1:1 mixtures of the diastereomeric products were obtained (*Entry 4, 5*) or decomposition occurred (*Entries 6 and 7*). However, better results were obtained with tributyltin chloride and $AlMe_3$ (*Entries 8 and 9*). Previous experiments had shown that the rate of furan formation was dependent on the acid employed. This finding could not be applied to improve the diastereoselectivity because there was little correlation between the acid used and the level of diastereocontrol.

Table 7



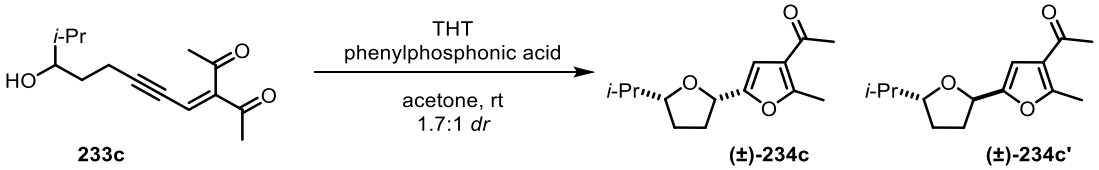
233c **(±)-234c** **(±)-234c'**

Entry	Additive[a]	234c:234c'[b]
1	-	1.5:1
2	*p*-tolylboronic acid	1.5:1
3	CSA	1.1:1
4	$InCl_3$	1.1:1
5	$InBr_3$	1:1
6	$AlCl_3$	decomp
7	$FeCl_3$	decomp
8	$(n\text{-Bu})_3SnCl$	1.5:1
9	$Al(Me)_3$	1.3:1

233c (1.0 equiv.), THT (0.5 equiv.), 1 M in acetone; [a] additive (0.1 equiv.); [b] determined by ^1H NMR of crude product.

It was suggested that an increase in the diastereoselectivity could be achieved by decreasing the reaction temperature to prolong the reaction time. However, when alcohol **233c** was stirred in acetone at rt until full consumption of the starting material

was achieved (3 d), the diastereoselectivity was consistent with that obtained when the reaction was performed at 40 °C (*Scheme 71*).



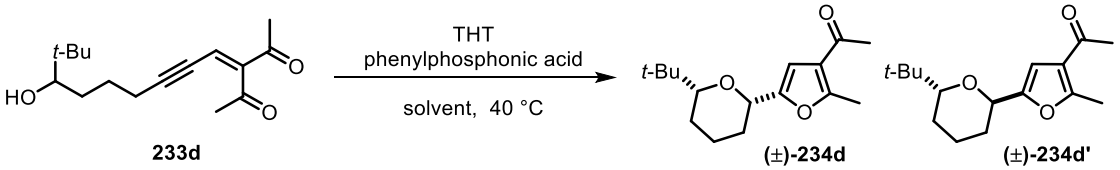
233c **(±)-234c** **(±)-234c'**

Scheme 71

Although nearly all reaction conditions allowed the furan **234c** to be obtained in good yield, high levels of diastereoselective control proved to be difficult to achieve. The best result was obtained when the reaction was performed in acetone with phenylphosphonic acid as additive (1.7:1).

When ynenone **233d** was exposed to the established cyclisation conditions, a diastereomeric mixture of the furan **234d** bearing a 6-membered ring ether was obtained as the sole product (*Table 8*). A study was carried out to investigate the correlation between solvent polarity and diastereomeric ratio. In all cases, the product was obtained with modest selectivity and no correlation with solvent polarity was observed. Diastereoselectivities of <2.0 were obtained when 1,2-dichloroethane, THF, 1,4-dioxane, DMF or DMSO was used as the solvent (*Entries 7, 8, 11, 14, and 15*). For reactions performed in the other solvents tested, the product ratio ranged from 2.0:1 to 2.8:1 (*Entries 1–6, 9, 10 and 12*). Among the various solvents investigated, the highest yield and diastereoselectivity (3.1:1 ratio) was obtained when MeCN was used as the solvent (*Entry 13*).

Table 8



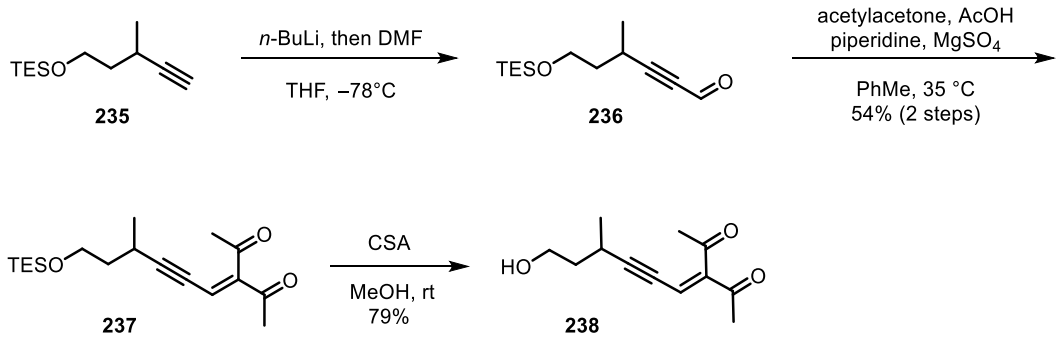
233d (±)-234d (±)-234d'

Entry	Solvent[a]	Yield[b]	234d:234d'[c]	Increasing Polarity [90]
1	*n*-hexane	78%	2.5:1	
2	cyclohexane	71%	2.1:1	
3	PhMe	79%	2.6:1	
4	PhH	79%	2.8:1	
5	Et_2O	87%	2.1:1	
6	CH_2Cl_2	80%	2.7:1	
7	1,2-dichloroethane	72%	1.7:1	
8	THF	73%	1.8:1	
9	$CHCl_3$	73%	2.3:1	
10	EtOAc	51%	2.1:1	
11	1,4-dioxane	68%	1.8:1	
12	acetone	83%	2.2:1	
13	MeCN	89%	3.1:1	
14	DMF	75%	1.4:1	
15	DMSO	55%	1.4:1	

233d (1.0 equiv.), THT (0.5 equiv.), phenylphosphonic acid (0.1 equiv.); [a] 1 M solution; [b] isolated yield after column chromatography; [c] determined by ^{1}H NMR of crude product.

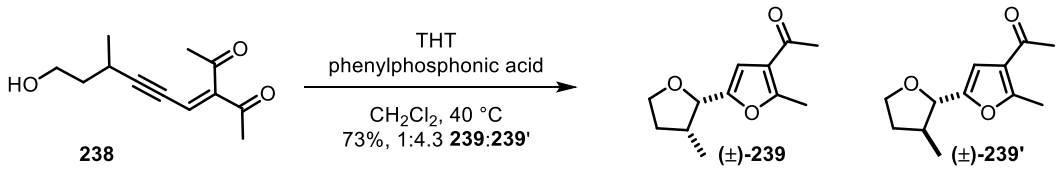
2.3.3 Preparation and Cyclisation of Substrate 238

The influence of the substituent on the diastereoselectivity was explored further. The ynenone **238**, which has the substituent at a different position on the carbon side chain, was synthesised (*Scheme 72*). The synthesis commenced with formylation of alkyne **235** using DMF. The resulting aldehyde **236** was transformed into the dimethyl substituted ynenone **237** by Knoevenagel condensation with acetylacetone. Subsequent deprotection delivered alcohol **238** in 79% yield.



Scheme 72

With ynenone **238** in hand, the stage was set for furan formation. In the absence of a catalyst, the desired product was not formed. The alcohol was transformed into the corresponding furan **239** by treatment with THT and phenylphosphonic acid because better results had been obtained when the reaction was performmed in the presence of an acidic additive (*Scheme 73*). The method delivered the furan product **239** as a 1:4.3 mixture of diastereoisomers, as determined by ^{1}H NMR analysis of the crude mixture. Although the position of the substituent influenced the isomer ratio further experiments were not carried out because previous results showed that changing the reaction conditions did not lead to a major improvement in the stereoselectivity.



Scheme 73

In conclusion, the viability of an organocatalytic tandem furan formation and ether synthesis was investigated. The overall process enabled the efficient synthesis of highly functionalised furans, by use of the readily available, inexpensive and non-toxic THT, as the organocatalyst. The products were obtained in high yield and with low to medium levels of diastereoselectivity. Unfortunately, the diastereoselectivity could not be improved in spite of extensive optimisation studies.

2.4 Expansion of Furan Formation Scope – Syntheses of Complex Polycyclic Systems

Promising results were obtained during the formation of bicyclic systems containing both a furan and a cyclic ether from ynenone systems bearing an alcohol function tethered to the alkyne. It was reasoned that other nucleophiles, such as carboxylic acids or phenols, could be used to trigger the cascade reaction. This could open up a pathway for the construction of a wide variety of polycyclic furan products (*Figure 6*) whose synthesis will be described in the following section.

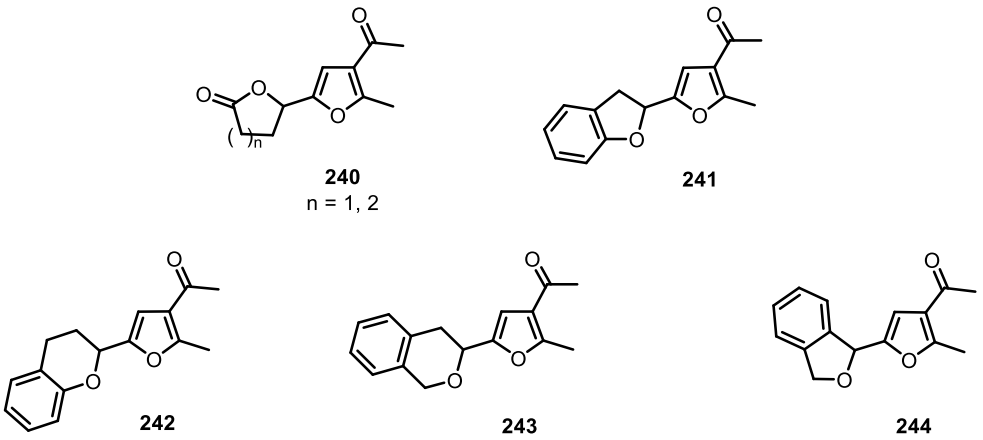


Figure 6

Some of these frameworks represent key ring systems found within a wide range of natural products, bioactive molecules, pharmaceuticals and can be used as building blocks for the syntheses of various heterocyclic compounds (*Figure 7*).[91] As a consequence, new methods for the construction of such motifs are constantly sought after.

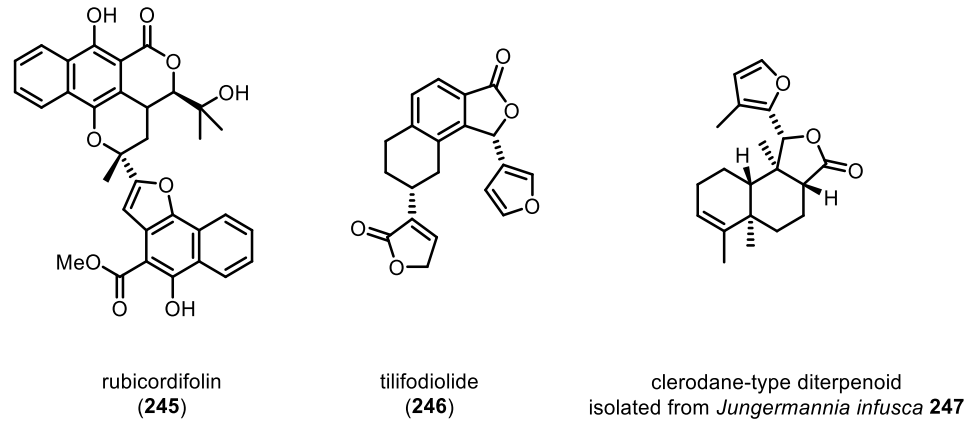
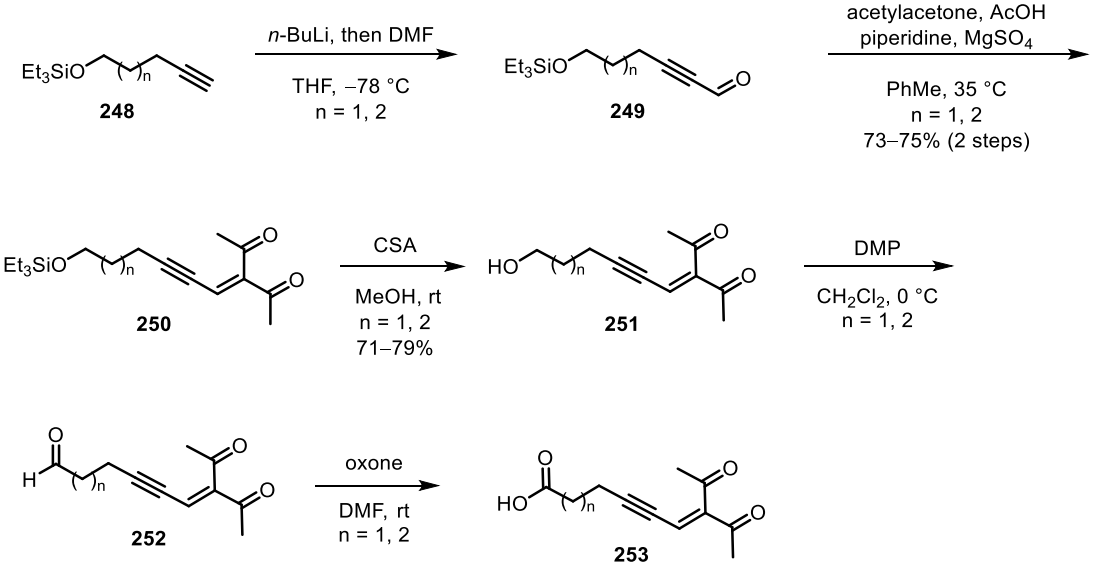


Figure 7

2.4.1 Syntheses of Ynenone Substrates

2.4.1.1 Syntheses of Ynenone Substrates with Aliphatic Side Chain

The approach used to prepare the furanolactones **240** was inspired by previous work in the group where it had been found that benzoic acid was a suitable nucleophile during furan formation promoted by a sub-stoichiometric amount of THT.[67] It was reasoned that an intramolecular cyclisation cascade reaction could be triggered by a carboxylic acid tethered to the alkyne. The syntheses of the ynenone precursors started with formylation of alkynes **248**, which was followed by Knoevenagel condensation and subsequent deprotection to afford primary alcohols **251** in good yield (*Scheme 74*). Alcohols **251** were oxidised to the corresponding carboxylic acids by use of a two-step procedure. Thus, DMP oxidation of alcohols **251** to provide aldehydes **252** was followed by further oxidation to give the carboxylic acids **253** using oxone. Surprisingly, attempted oxidation of the aldehydes **252** under conventional Pinnick conditions was not successful. Both the aldehydes and the carboxylic acids were found to be unstable and therefore were used in the next step without further purification.

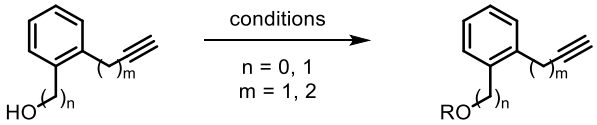


Scheme 74

2.4.1.2 Syntheses of Ynenone Substrates with Aromatic Side Chain

The reaction scope was expanded to include more complex systems such as furans bearing a 5-benzofuran or 5-benzopyran substituent at the position 5 (*see Figure 6*). The syntheses of the corresponding ynenone precursors started by protection of the free hydroxyl group[92] to deliver alkynes **255** in excellent yield (*Table 9*).

Table 9

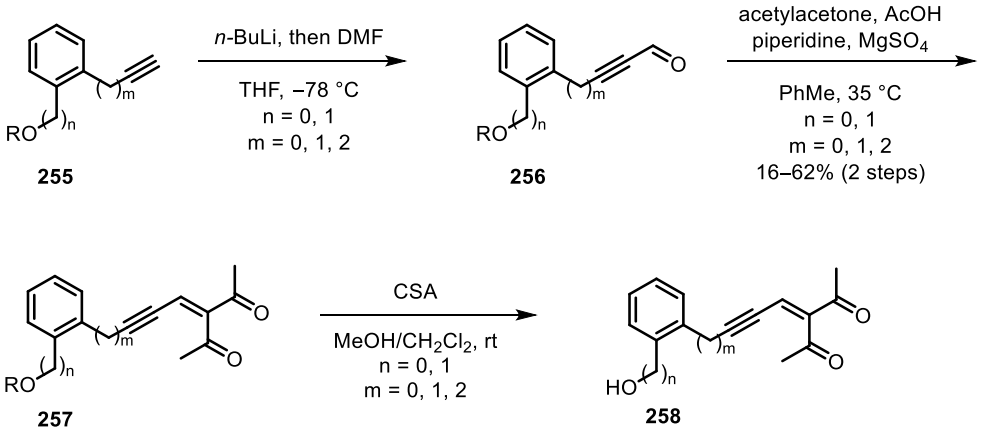


254 **255**

Entry	Alkyne	n	m	Reagents			Solvent	Yield[f]
1	**255a**	0	1	TESCl[a]	DMAP[b]	NEt_3[a]	CH_2Cl_2[d]	95%
2	**255b**	0	2	TESCl[a]	DMAP[b]	NEt_3[a]	CH_2Cl_2[d]	98%
3	**255c**	1	1	TBSCl[a]		imidazole[c]	DMF[e]	95%

254 (1.0 equiv.); [a] (1.2 equiv.); [b] (2 mol%); [c] (1.5 equiv.); [d] 0.2 M solution; [e] 0.5 M solution; [f] isolated yield after column chromatography.

Formylation of the alkynes **255**[93] by lithiation and treatment with DMF was expected to furnish aldehydes **256** (*Scheme 75*). However, after full consumption of the starting alkyne (TLC analysis) and application of the previously established quenching conditions only decomposed material was obtained. Further experimentation showed that pouring the reaction into a mixture of 10% aqueous KH_2PO_4 solution and Et_2O then vigorous stirring was successful. The aldehydes were found to be unstable and were used immediately in the next step without further purification. Subjecting aldehydes **256** to Knoevenagel condensation with acetylacetone afforded ynenones **257**. The desired ynenone precursors **258** were obtained thereafter by silylether cleavage using camphorsulfonic acid. The precursors were found to be unstable and therefore were used in the next step without further purification.



Scheme 75

Having succeeded in developing an efficient route to complex ynenone systems the scope and limitation of the reaction was examined further and the syntheses of various substrates shown below were carried out (*Figure 8*). The successful preparation of these precursors meant that the organocatalytic furan formation using THT as the catalyst could now be explored.

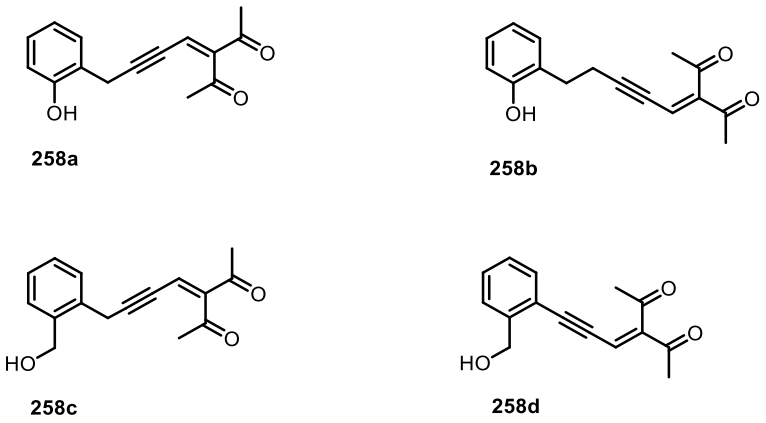


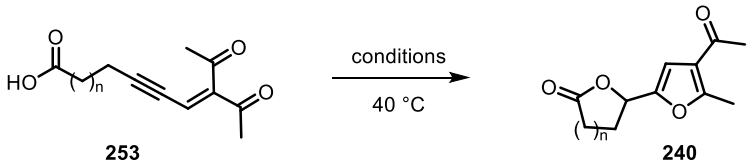
Figure 8

2.4.2 Cyclisation Cascade of Ynenone Substrates

2.4.2.1 Cyclisation of Ynenone Substrates with Aliphatic Side Chain

The successful synthesis of the carboxylic acids **253** meant that attention could be turned to exploration of furan and lactone formation by the cascade reaction (*Table 10*). Furan formation was not observed in the absence of the sulfur catalyst (*Entries 1 and 3*). Investigations showed that a catalytic amount of THT was necessary to promote the reaction (*Entries 2 and 4*). The THT-promoted reactions delivered the furanolactones **240** in yields of 38% and 47% respectively.

Table 10



253 **240**

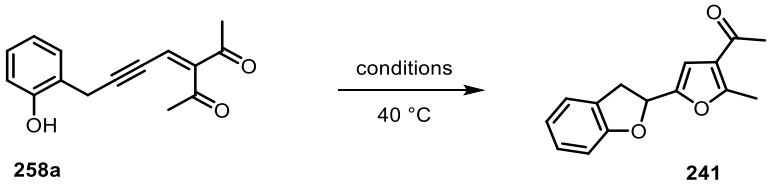
Entry	Furan	n	Catalyst	Solvent[b]	Yield
1	**240a**	1	-	CH_2Cl_2	-
2	**240a**	1	THT[a]	CH_2Cl_2	38%[c]
3	**240b**	2	-	CH_2Cl_2	-
4	**240b**	2	THT[a]	CH_2Cl_2	47%[c]

253 (1.0 equiv.); [a] catalyst (0.5 equiv.); [b] 1 M solution; [c] isolated yield after column chromatography calculated over 3 steps.

2.4.2.2 Cyclisation of Ynenone Substrates with Phenol Side Chain

Studies were performed concerning the transformation of phenol **258a** into furan **241**. Interestingly, when no THT catalyst was present a very small amount of the product was formed (*Table 11*, *Entries 1 and 2*). The reason for this is that small amounts of impurities in the solvent most likely catalysed the formation of **241**. Due to the limited quantities produced, it was not possible to carry out further test reactions. Transformation of the alcohol into the corresponding furan **241** in the presence of THT delivered the product in 32% yield over two steps (*Entry 3*). Under the optimal conditions, using THT and phenylphosphonic acid, better results were obtained and furan **241** could be isolated in 60% yield over two steps (*Entry 4*).

Table 11



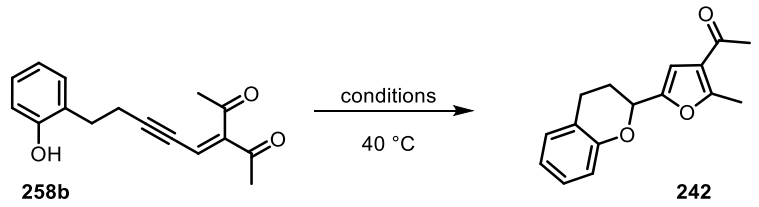
258a **241**

Entry	Catalyst	Additive	Solvent[c]	Yield[d]
1	-	-	CH_2Cl_2	6%
2	-	phenylphosphonic acid[b]	CH_2Cl_2	10%
3	THT[a]	-	CH_2Cl_2	32%
4	THT[a]	phenylphosphonic acid[b]	CH_2Cl_2	60%

258a (1.0 equiv.); [a] catalyst (0.5 equiv.); [b] additive (0.1 equiv.); [c] 1 M solution; [d] isolated yield after column chromatography calculated over 2 steps.

The successful preparation of phenol **241** meant that the furan transformation could be explored further (*Table 12*). When ynenone **258b** was subjected to conditions in the absence of catalyst, formation of the desired product was not observed (*Entries 1 and 2*). It is interesting to mention, that the product was not obtained in the absence of an acidic additive. Instead, an unidentified by-product was formed in this case (*Entry 3*). Transformation of the alcohol into the corresponding furan **242** with a catalytic amount of THT and phenylphosphonic acid was found to be optimal and under these conditions the polycyclic product was obtained in good yield (*Entry 4*).

Table 12



258b **242**

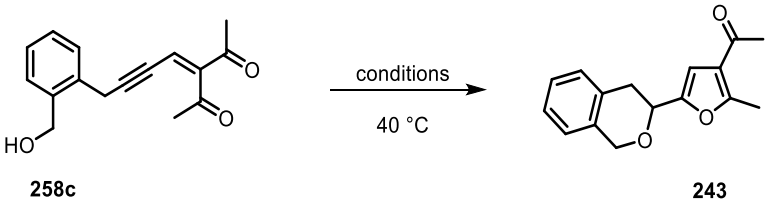
Entry	Catalyst	Additive	Solvent[c]	Yield
1	-	-	CH_2Cl_2	-
2	-	phenylphosphonic acid[b]	CH_2Cl_2	-
3	THT[a]	-	CH_2Cl_2	-
4	THT[a]	phenylphosphonic acid[b]	CH_2Cl_2	57%[d]

258b (1.0 equiv.); [a] catalyst (0.5 equiv.); [b] additive (0.1 equiv.); [c] 1 M solution; [d] isolated yield after column chromatography calculated over 2 steps.

2.4.2.3 Cyclisation of Ynenone Substrates with Alcohol Side Chain

After successful synthesis of the the homologated substrate **258c**, furan formation was investigated (*Table 13*). The cyclisation reaction was achieved by the use of sub-stoichiometric amount of THT to give the targeted benzopyran **243** in 47% yield (*Entry 2*). Again, it was found, that the transformation did not take place in the absence of THT (*Entry 1*).

Table 13



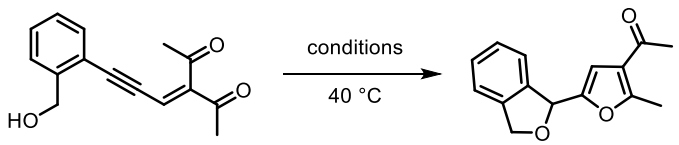
258c **243**

Entry	Catalyst	Additive[b]	Solvent[c]	Yield
1	-	phenylphosphonic acid	CH_2Cl_2	-
2	THT[a]	phenylphosphonic acid	CH_2Cl_2	47%[d]

258c (1.0 equiv.); [a] catalyst (0.5 equiv.); [b] additive (0.1 equiv.); [c] 1 M solution; [d] isolated yield after column chromatography calculated over 2 steps.

Based on the successful furan synthesis with phenol **258a**, the isomeric alcohol **258d** was also subjected to the reaction. When analytical grade CH_2Cl_2 was used for the transformation of alcohol **258d**, a small amount of furan **244** was isolated (*Table 14*, *Entries 1 and 2*). However, when purified CH_2Cl_2 was used as the solvent formation of the desired product **244** was not observed in the absence of THT (*Entries 2 and 3*). This confirms that impurities within analytical grade CH_2Cl_2 were catalysing furan formation. When ynenone **258d** was exposed to the established cyclisation conditions, the furan **244** was isolated in 60% yield (*Entry 5*). It was noted, that when a sub-stoichiometric amount of phenylphosphonic acid was added, a slight increase in yield was observed (*Entry 6*). Thus, exposure of the substrate to THT and phenylphosphonic acid was found to be optimal for transformation of the alcohol into the corresponding furan **244**.

Table 14



258d **244**

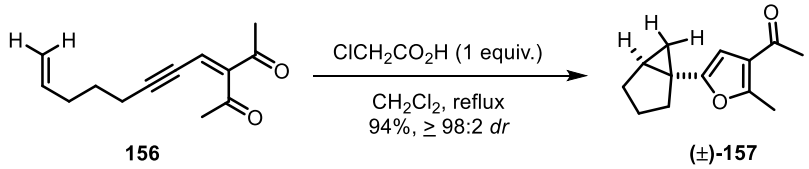
Entry	Catalyst	Additive	Solvent[c]	Yield
1	-	-	analytical CH_2Cl_2	8%[d]
2	-	phenylphosphonic acid[b]	analytical CH_2Cl_2	6%[d]
3	-	-	CH_2Cl_2	-
4	-	phenylphosphonic acid[b]	CH_2Cl_2	-
5	THT[a]	-	CH_2Cl_2	60%[d]
6	THT[a]	phenylphosphonic acid[b]	CH_2Cl_2	62%[d]

258d (1.0 equiv.); [a] catalyst (0.5 equiv.); [b] additive (0.1 equiv.); [c] 1 M solution; [d] isolated yield after column chromatography.

In conclusion, the tandem cyclisation methodology was adapted to the synthesis of various polycyclic furan frameworks. Sub-stoichiometric amount of THT and an acidic additive were used to convert nucleophile-bearing ynenones into highly functionalised furans.

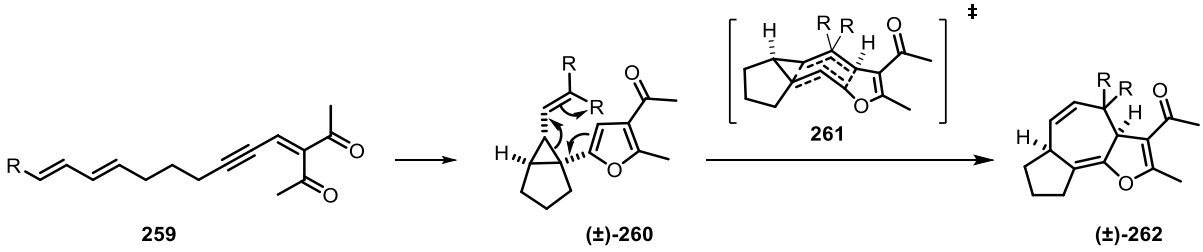
2.5 Cascade Cyclohepta[*b*]furan Synthesis

The aim of this work was to develop new synthetic methodology for the construction of cycloheptanes. This project would be a continuation of the work previously undertaken in the Clark group on furan formation employing a Brønsted acid catalyst (*Scheme 76*).[69] It had been shown that the highly functionalised furan **157** containing a fused bicyclic system which incorporates a cyclopropane could be accessed from ynenone **156** using this reaction.



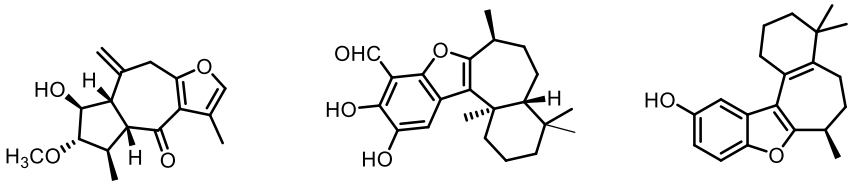
Scheme 76

It was envisioned that exposure of diene **259** to the standard cyclisation conditions would lead to the formation of furan **260**. The resulting vinyl-substituted cyclopropane would be able to undergo a Cope rearrangement to give the corresponding cycloheptadiene **262** (*Scheme 77*). It was proposed that this sequence could be adapted to give a cascade process in which furan formation would be followed by immediate ring expansion in a one-pot process.



Scheme 77

Seven-membered-ring-fused furans are important building blocks that are found in a wide range of natural products (*Figure 9*).[77a, 94] The construction of the cyclohepta[*b*]furan ring system has become a topic of great importance because of the interesting biological activities of many compounds that possess this ring system. These activities range from anti-inflammatory properties to potential application in anticancer and diabetes therapy.[95]



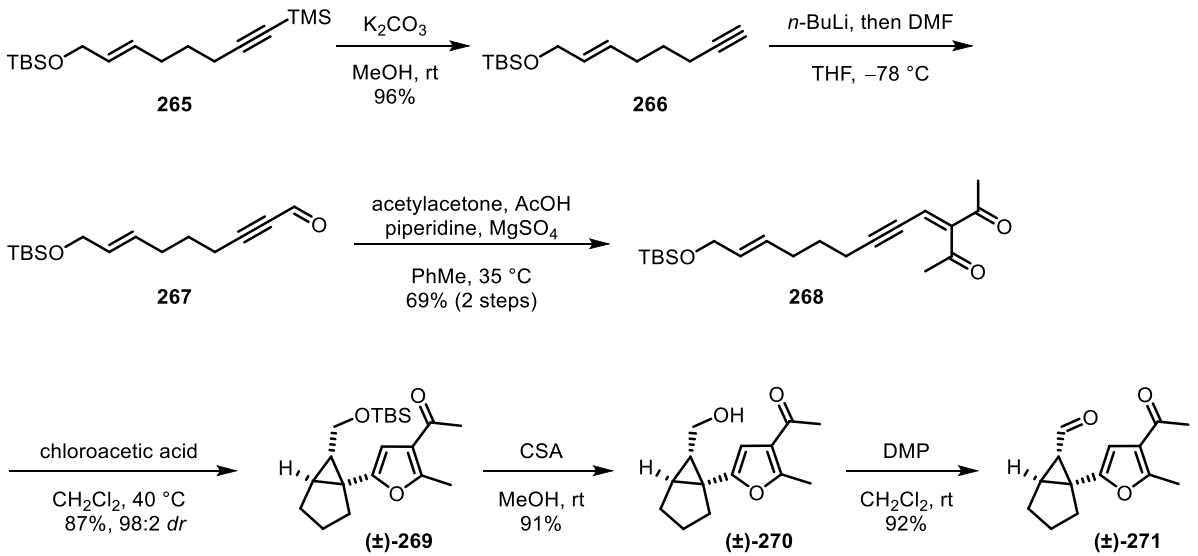
myrrhterpenoid H (**263**) liphagal (**264**) frondosin B (**192**)

Figure 9

2.5.1 Stepwise Approach

2.5.1.1 Synthesis and Rearrangement of Vinylcyclopropane 272

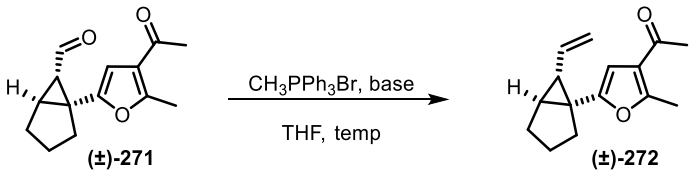
Studies concerning the new cascade reaction involved the separate investigation of the individual chemical steps. In this initial approach, the aldehyde **271** was envisioned as a common precursor for various vinyl-substituted cyclopropanes. The synthesis of this aldehyde began with cleavage of the TMS group from the compound **265** under basic conditions to afford the terminal alkyne **266** in high yield (*Scheme 78*). Formylation of the alkyne followed by Knoevenagel condensation with acetylacetone delivered ynenone **268** in 69% yield over two steps. Cyclopropyl substituted furan **269** was prepared using the previously established methodology,[69] subsequent deprotection of the alcohol using camphorsulfonic acid followed by oxidation with DMP gave the aldehyde **271** in high yield.



Scheme 78

Wittig methylenation of **271** proved to be more challenging than expected. The product was found to be acid labile and prone to decomposition during column chromatography using silica gel. Therefore, purification of the product was carried out on aluminium oxide (activated, basic, Brockmann I). Various Wittig olefination conditions were screened in order to deliver the product in good yield (*Table 15*). Only starting material was recovered using potassium *t*-butoxide as the base and the reaction carried out at 0 °C, possibly due to it being hygroscopic to be suitable for small scale reactions (*Entry 1*). Switching the base to LiHMDS (1 M in THF) and lowering the reaction temperature to −78 °C was not successful when aqueous NH_4Cl was used to quench the reaction (*Entry 2*). However, when water was used to quench the reaction, the required vinyl cyclopropane **272** was obtained in 33% yield (*Entry 3*). A similar result was obtained when *n*-BuLi was employed as the base, the reaction was performed at −78 °C and the reaction was quenched with pH 7 buffer (*Entry 4*). Other screening experiments were performed and the best result was obtained when the reaction temperature was increased to −10 °C, *n*-BuLi was employed as the base and pH 7 buffer was used to quench the reaction (*Entry 5*).

Table 15

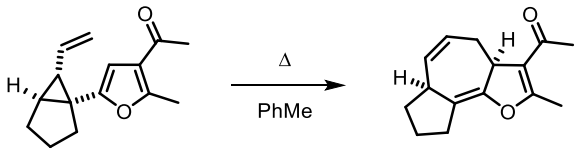


Entry	Base[a]	T	Method of Quenching	Yield[d]
1	*t*-BuOK	0 °C	filtered through SiO_2	SM
2	LiHMDS[b]	−78 °C	NH_4Cl	-
3	LiHMDS[b]	−78 °C	H_2O	33%
4	*n*-BuLi[c]	−78 °C	pH 7 buffer	34%
5	*n*-BuLi[c]	−10 °C	pH 7 buffer	69%

271 (1.0 equiv.) in THF (0.1–0.03 M solution), CH_3PPh_3Br (1.3–2.0 equiv.) in THF (0.08–0.1 M solution); [a] (1.1 equiv.); [b] 1 M in THF; [c] 2.3–2.5 M in hexanes; [d] isolated yield after column chromatography.

The successful synthesis of the vinylcyclopropane **272** meant that formation of cycloheptadiene **273** could be explored (*Table 16*). Optimisation studies of the cyclopropyl furan formation performed previously had revealed that CH_2Cl_2 and toluene were best solvents for this transformation.[69] Toluene was selected because it would allow the screening of higher temperatures for the Cope rearrangement reaction. When the substrate **272** was heated in toluene to 110 °C the fused tricyclic product **273** could be isolated in 36% yield (*Entry 1*). It was postulated that substrate **272** is thermally unstable and so underwent decomposition at a rate that is competitive with the rearrangement reaction to give the more stable cycloheptadiene **273**. Lowering the temperature to 80 °C resulted in an increase in yield to 61% (*Entry 2*). However, to be suitable for a cascade sequence, a lower temperature was more desirable. At 40 °C, the rearranged product **273** could be isolated in 63% yield under the conditions used (*Entry 3*).

Table 16

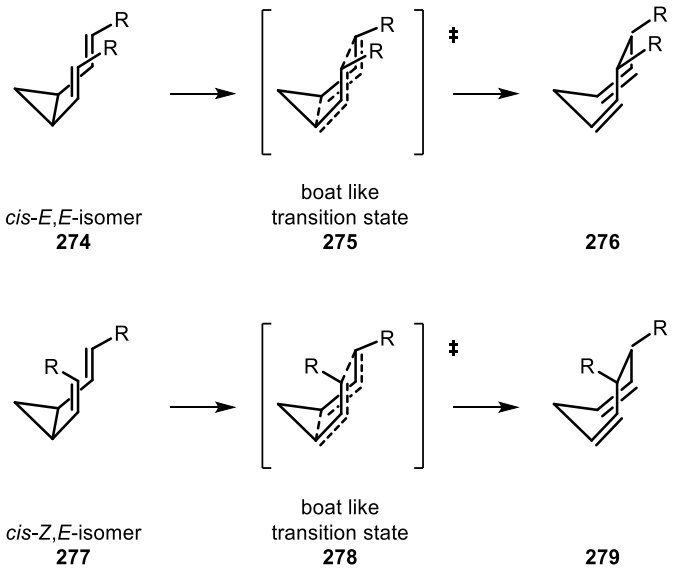


(±)-272 **(±)-273**

Entry	T	Time	Yield[a]
1	110 °C	1 h	36%
2	80 °C	5 h	61%
3	40 °C	16 h	63%

0.05–0.08 M in toluene; [a] isolated yield after column chromatography.

Excellent stereocontrol is possible because the rearrangement is stereospecific with respect to the configuration at the π-systems invovled (*Scheme 79*).[96] The furanylvinylcyclopropane undergoes a 3,3-sigmatropic rearrangement *via* a boat-like transition state in which both π-groups lie endo to the cyclopropane leading to formation of the corresponding cycloheptadiene.

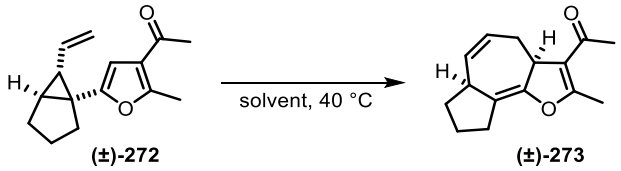


Scheme 79

In an attempt to improve the yield of the Cope rearrangement reaction, various solvents were screened (*Table 17*). When THF was employed as the solvent, the yield dropped to 30% (*Entry 1*). Dichloromethane facilitated the reaction, but the yield was still

significantly lower than that obtained from the reaction performed in toluene (*Entry 2*). Finally, a screening experiment was conducted using chloroacetic acid to discover whether an acid can influence the Cope rearrangement. Although full consumption of the starting material was observed, the cycloheptadiene was isolated with a slight reduction in yield (*Entry 3*).

Table 17



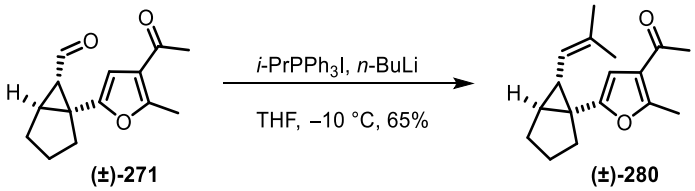
(±)-272 (±)-273

Entry	Solvent[a]	Additive	Yield[c]
1	THF	-	30%
2	CH_2Cl_2	-	38%
3	PhMe	$ClCH_2CO_2H$[b]	57%

[a] 0.05–0.08 M solution; [b] (0.1equiv.); [c] isolated yield after column chromatography.

2.5.1.2 Synthesis and Rearrangement of Vinylcyclopropane 280

Now that optimised conditions for the reaction had been established, the preparation and rearrangement of various substrates was investigated. Using the previously improved Wittig olefination conditions, *gem*-dimethyl substituted substrate **280** was prepared from aldehyde **271** in 65% yield (*Scheme 80*).



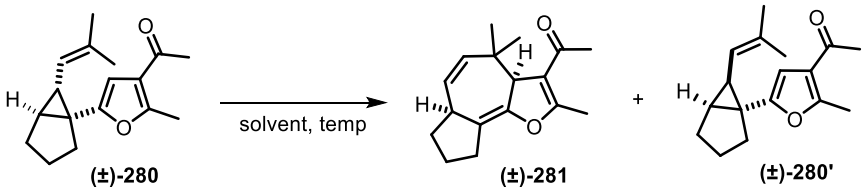
(±)-271 (±)-280

Scheme 80

However, when the Cope rearrangement of this substrate was attempted in toluene at 40 °C no reaction was observed (*Table 18*, *Entry 1*). Heating the mixture to 110 °C resulted in 32% conversion and cycloheptadiene **281** could be isolated in 27% yield (68% brsm, *Entry 2*). After careful NMR study, it was found that at this temperature a trace amount of the epimerised cyclopropane **280'** was formed. It is important to note

that this compound would undergo Cope rearrangement at a different rate than **280**. Prolonging the reaction time resulted in increased conversion, but the desired product was obtained in lower yield (*Entry 3 and 4*). The lower yield is attributed to the substrate **280** being thermally unstable and decomposing rather than undergoing the desired rearrangement reaction. When *p*-xylene was employed, the reaction temperature could be increased but this resulted in a decrease in yield (*Entry 5*).

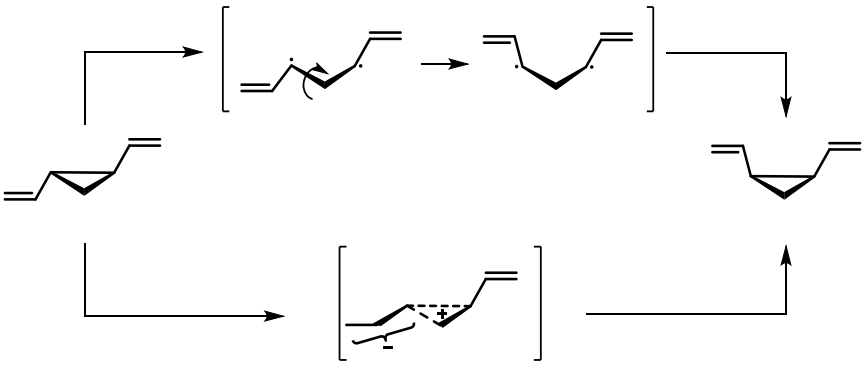
Table 18



Entry	Solvent[a]	T	Time	Conversion	Yield[b]
1	PhMe	40 °C	1 d	0%	-
2	PhMe	110 °C	1 d	32%	27% (68% brsm)
3	PhMe	110 °C	2 d	38%	20%
4	PhMe	110 °C	3 d	43%	15%
5	*p*-xylene	140 °C	1 d	33%	9%

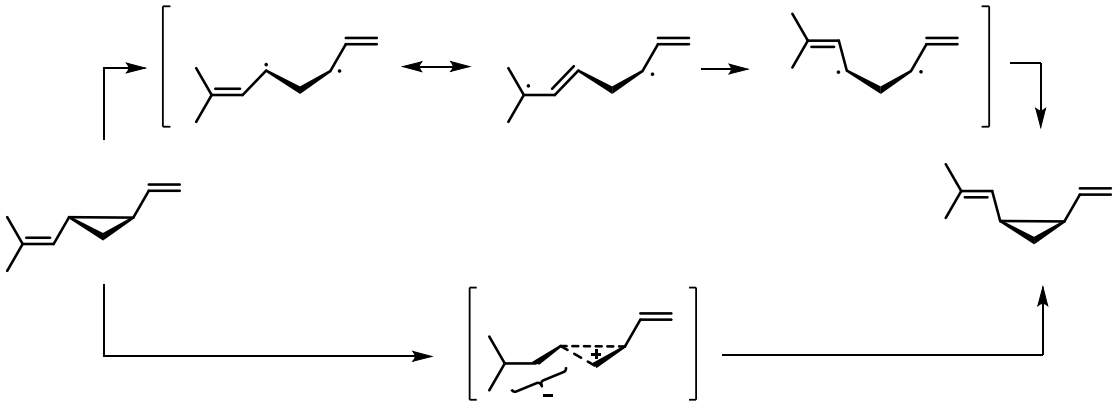
[a] 0.05–0.08 M solution; [b] isolated yield after column chromatography.

The observed epimerisation of vinylcyclopropane at 110 °C was rather unexpected because isomerisation normally only occurs at much higher temperatures of around 200 °C.[74] The mechanism for the formation of *trans*-divinylcyclopropane is proposed to proceed either through an intermediate diradical species or through a one-centre epimerisation pathway (*Scheme 81*).



Scheme 81

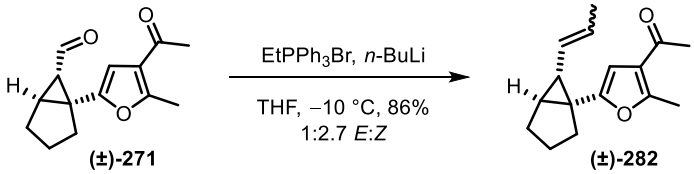
It is proposed that the increased stability of the dimethyl substituted cyclopropane transition state due to delocalisation leads to epimerisation at lower temperatures (*Scheme 81*).



Scheme 82

2.5.1.3 Synthesis and Rearrangement of Vinylcyclopropane 282

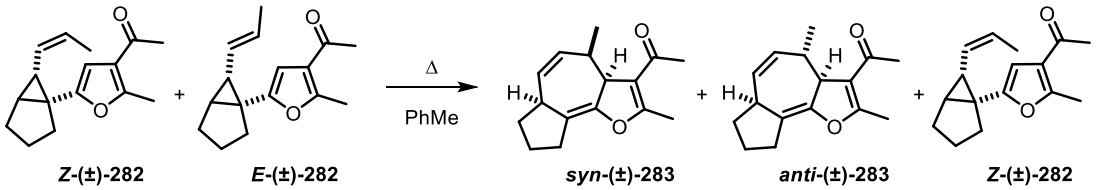
Optimisation studies showed that the rearrangement reaction is robust and so its scope was further expanded to explore the influence of the alkene geometry on the yield and stereochemical outcome of the reaction. Therefore, methyl substituted vinyl **282** was prepared by reaction of the aldehyde **271** with ethyltriphenylphosphonium bromide under Wittig conditions. The reaction afforded substrate **282** as an inseparable 1:2.7 mixture of alkene diastereoisomers (*Scheme 83*).



Scheme 83

To promote the Cope rearrangement, the mixture was stirred at 40 °C. Consumption of the *E*-isomer was completed after 16 h, but Cope rearrangement of the *Z*-isomer was not observed during this period of time (*Table 19*, *Entry 1*). When the reaction was performed at 110 °C, the cycloheptadiene ***syn*-283** was isolated in 17% yield and the *Z*-alkene ***Z*-282** was recovered in 25% yield. ^{1}H NMR studies suggested that only a trace amount of the cycloheptadiene ***anti*-283** was formed (*Entry 2*).

Table 19

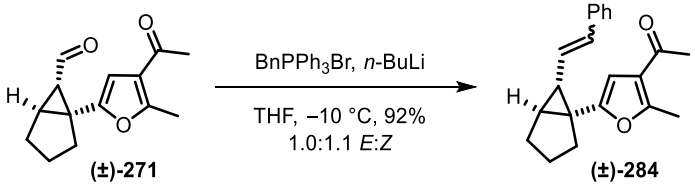


Entry	T	Time	*syn*-283[a]	*anti*-283	*Z*-282[a]
1	40 °C	18 h	23%	-	40%
2	110 °C	16 h	17%	trace	25%

0.05–0.08 M in toluene; [a] isolated yield after column chromatography.

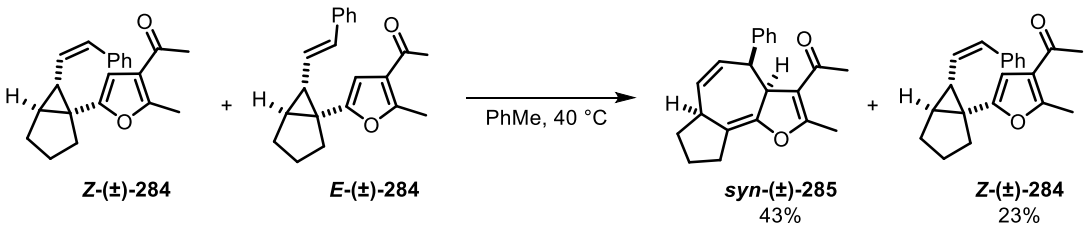
2.5.1.4 Synthesis and Rearrangement of Vinylcyclopropane 284

A final set of experiments was performed using a styrene-containing substrate. The Wittig reaction of aldehyde **271** with benzyltriphenylphosphonium bromide resulted in an inseparable mixture of *E* and *Z*-alkenes, albeit in excellent yield (*Scheme 84*). The stage was now set to investigate the Cope rearrangement of the phenyl-substituted substrate **284**.



Scheme 84

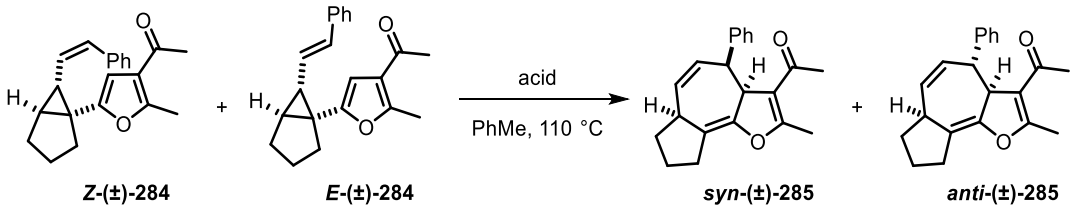
When the mixture of alkene isomers was heated at 40 °C in toluene, only the *E*-isomer rearranged to give the corresponding cycloheptadiene and some of the *Z*-isomer was recovered (*Scheme 85*).



Scheme 85

The propensity of the *Z*-isomer to undergo the Cope rearrangement was then examined. The temperature was increased and other acids were tested as promoters. Besides chloroacetic acid, 1,1,1,3,3,3-hexafluoro-2-propanol and benzoic acid were investigated (*Table 20*). The initial experiment in the study involved reaction of the isomeric mixture with a sub-stoichiometric amount of chloroacetic acid in toluene at 110 °C. Full consumption of the isomer ***E*-284** was observed and ^{1}H NMR analysis of the product suggested only traces of ***anti*-285** was formed. However, under these conditions the yield of ***syn*-285** was significantly lower because at high temperatures ***E*-284** and ***Z*-284** started to decompose (*Entry 1*). Addition of hexafluoro-2-propanol aided in decomposition of the starting material (*Entry 2*). The use of benzoic acid resulted in the formation of an unidentified by-product instead of the cycloheptadiene ***syn*-285** or ***anti*-285** (*Entry 3*).

Table 20



Entry	Acid[a]	pK_a	*syn*-285	*anti*-285	
1	$ClCH_2CO_2H$	2.9	21%[b]	trace	
2	$(CF_3)_2CHOH$	9.3	-	-	decomp
3	$PhCO_2H$	4.2	-	-	other

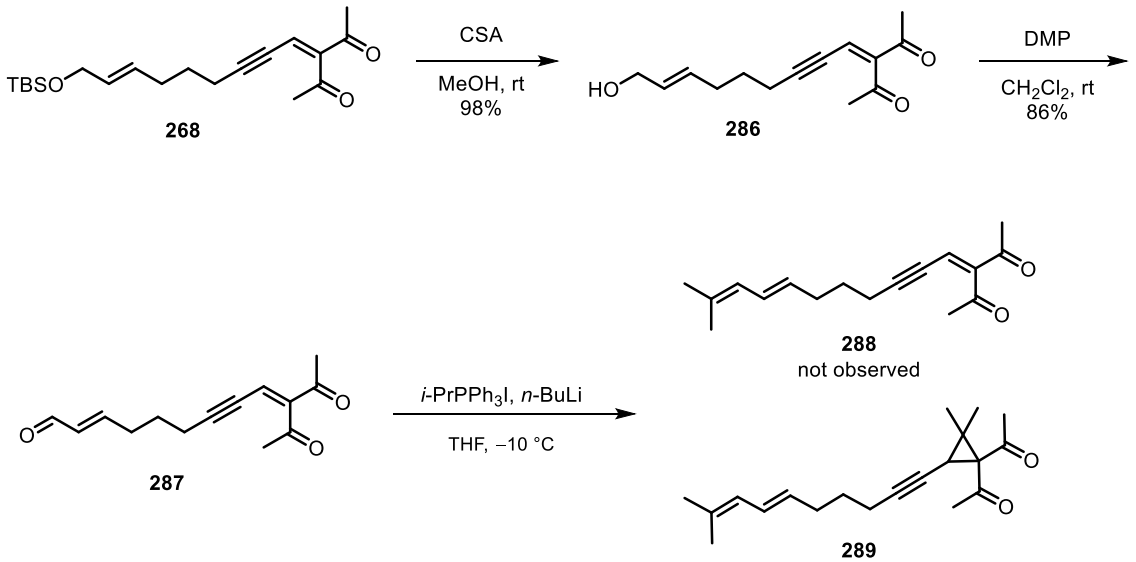
284 (1.0 equiv.), 0.05–0.08 M in toluene; [a] acid (0.1 equiv.); [b] isolated yield after column chromatography.

In summary, the vinylcyclopropane rearrangements were successful and an investigation of substrate scope was carried out. Studies have shown that the configuration on the alkene has a dramatic influence on the rate of the reaction. No conditions were found to promote efficient and high-yielding rearrangement of the *Z*-isomer.

2.5.2 Cascade Approach

2.5.2.1 First Generation Synthesis of Substrate for Cascade Approach

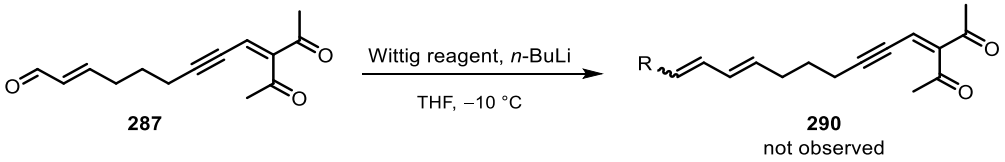
Following the independent study of the cyclopropanation and Cope rearrangement reactions, efforts were focused on developing a cascade process. Work was undertaken towards the synthesis of appropriate ynendione substrates for this transformation. The synthesis started with deprotection of ynenone starting material **268** with camphorsulfonic acid (*Scheme 86*). It is important to note that the resulting alcohol **286** is acid sensitive and prone to rearrange if exposed to camphorsulfonic acid for an extended period of time. Oxidation of alcohol **286** using DMP afforded the corresponding aldehyde **287** in 86% yield. Unfortunately, reaction of the aldehyde **287** with *i*-propyltriphenylphosphonium iodide using previously optimised Wittig reaction conditions did not afford the expected product **288** but an unknown by-product. Isolation of the by-product resulting from the Wittig reaction revealed that it appeared to be formed by Wittig olefination of the aldehyde and addition of the Wittig reagent to the alkene to form product **289**. It was hypothesised that the by-product was formed due to excess Wittig reagent being used. Therefore, the reaction was repeated with less than one equivalent of reagent. ^{1}H NMR analysis of the crude mixture showed, that **289** had been formed and unreacted aldehyde **287** was still present. However, formation of the desired diene **288** was not observed.



Scheme 86

When aldehyde **287** was treated with other Wittig reagents, the desired product **290** was not formed and only decomposition of the starting material occurred in all cases (*Table 21, Entries 1–3*).

Table 21



287 **290** not observed

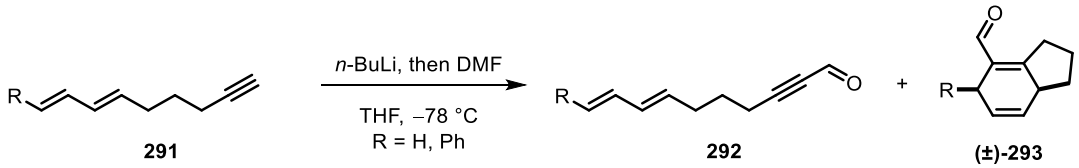
Entry	Wittig reagent[a]	R	Result
1	CH_3PPh_3Br	H	decomp.
2	$EtPPh_3Br$	Me	decomp.
3	$BnPPh_3Br$	Ph	decomp.

287 (1.0 equiv.) in THF (0.1 M solution), *n*-BuLi (1.1 equiv.); [a] Wittig reagent (1.3 equiv.) in THF (0.1 M solution).

Owing to the failure of this route, a different strategy was explored in which the olefin would be installed earlier in the synthesis.

2.5.2.2 Second Generation Synthesis of Diene for Cascade Approach

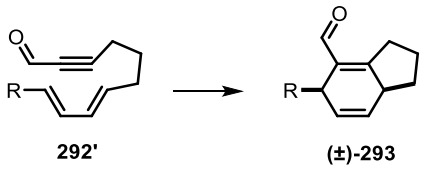
The desired ynenones were envisaged to derive from the dienes **291**.[97] Treatment with *n*-BuLi, followed by DMF afforded aldehydes **292**. However, ^{1}H NMR analysis of the crude reaction mixture revealed that an undesired by-product **293** was produced along with the required aldehydes **292** (*Scheme 87*).



291 **292** **(±)-293**

Scheme 87

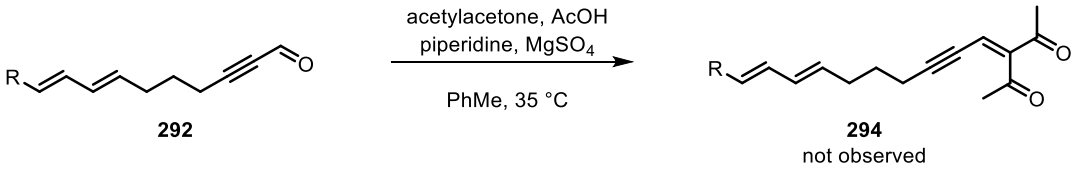
It was hypothesised that by-products such as **293** are generated from a Diels-Alder cycloaddition reaction between the electron-rich diene and the electron-deficient alkyne (*Scheme 88*).



292' **(±)-293**

Scheme 88

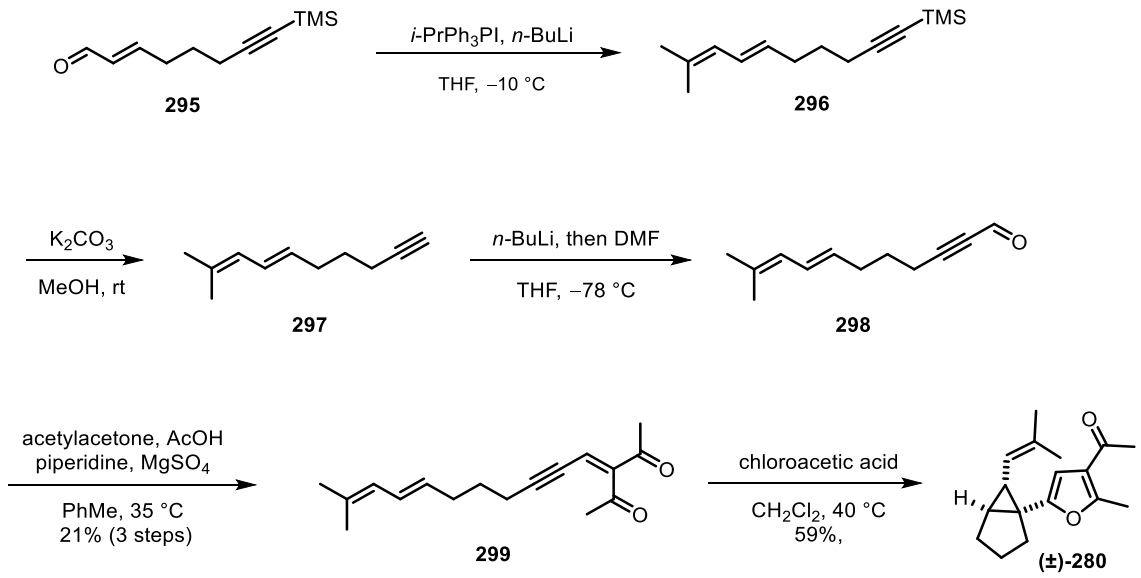
The aldehydes were unstable so the crude reaction mixtures were used immediately without further purification in each case. Although the aldehyde **292** was present, the expected Knoevenagel condensation product **294** could not be isolated from the reaction (*Scheme 89*). Instead only decomposition occurred. Several other reaction conditions were investigated but were not successful.



292 **294**
not observed

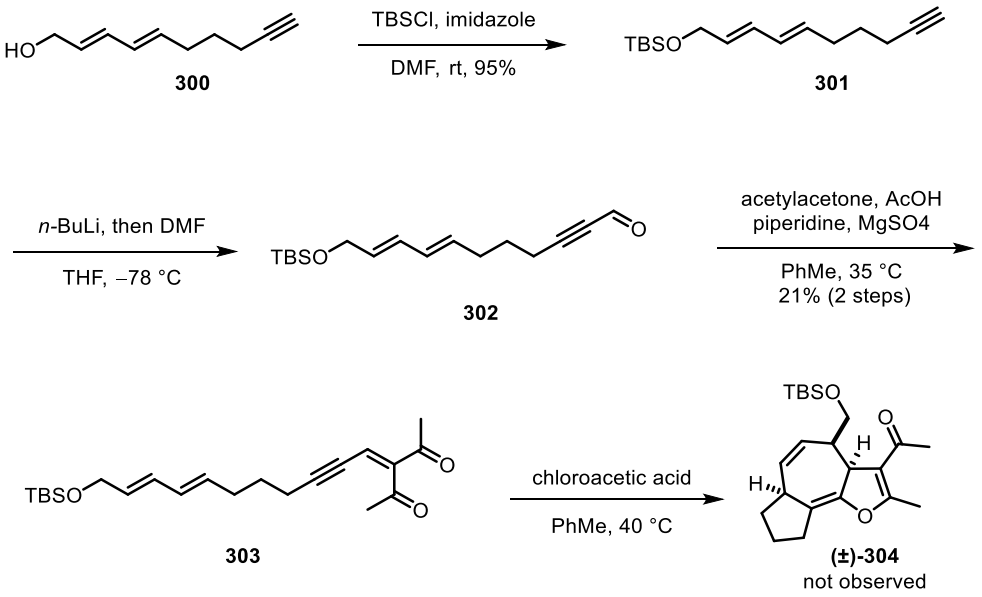
Scheme 89

The failure to obtain the required Knoevenagel condensation product prompted the synthesis of a different diene. The synthetic route started from aldehyde **295** which was then reacted with *i*-propyltriphenylphosphonium iodide under Wittig conditions to yield the corresponding diene **296** (*Scheme 90*). Deprotection of the alkyne moiety with potassium carbonate provided the terminal alkyne **297**. Substrate **299** was then accessed through a standard formylation and Knoevenagel condensation sequence. Treatment of ynenone **299** with chloroacetic acid at 40 °C resulted in formation of the furan **280** bearing a fused bicyclic system. As expected, this compound did not undergo Cope rearrangement at this temperature to give the cycloheptadiene (*Table 18*).



Scheme 90

However, with this promising result in hand, further investigation into the cascade process was undertaken. Alcohol **300** was protected as the TBS ether and the resulting intermediate **301** was subjected to formylation using *n*-BuLi and DMF (*Scheme 91*). It is interesting to note that formation of a Diels-Alder side product was not observed in this case. The aldehyde **302** was converted into the ynenone **303** by Knoevenagel condensation with acetylacetone. Unfortunately, treatment of the ynenone **303** with chloroacetic acid in toluene did not deliver cylcoheptane **304** and a rearranged product that did not correspond to the desired product was isolated instead. The structure of this unexpected by-product could not be elucidated.



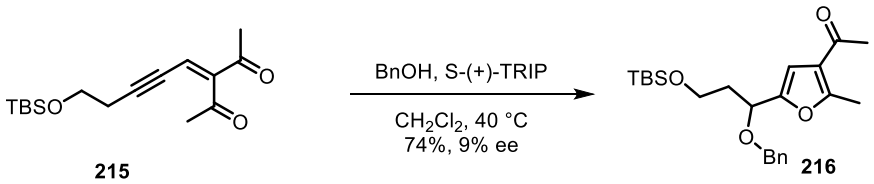
Scheme 91

In conclusion, new methodology for the formation of cycloheptadienes was investigated. The conditions for the Cope rearrangement of furylvinylcyclopropanes was successfully optimised. However, the synthesis of an appropriate substrate for a cascade process proved to be difficult.

3 Conclusions

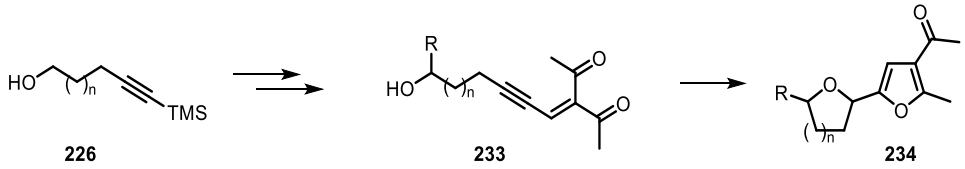
3.1 Furan Formation from Ynenones using THT

Furan formation from ynenones is dependent on an acid additive. However, applying this finding to asymmetric furan formation by use of a chiral acid only resulted in very low levels of enantiocontrol (*Scheme 92*). In future work, the use of a very strong chiral "super Brønsted acids" could be explored to improve the level of asymmetric induction during the reaction. Additionally, new types of TRIP ligand are being developed continually, so in future these also could be explored.



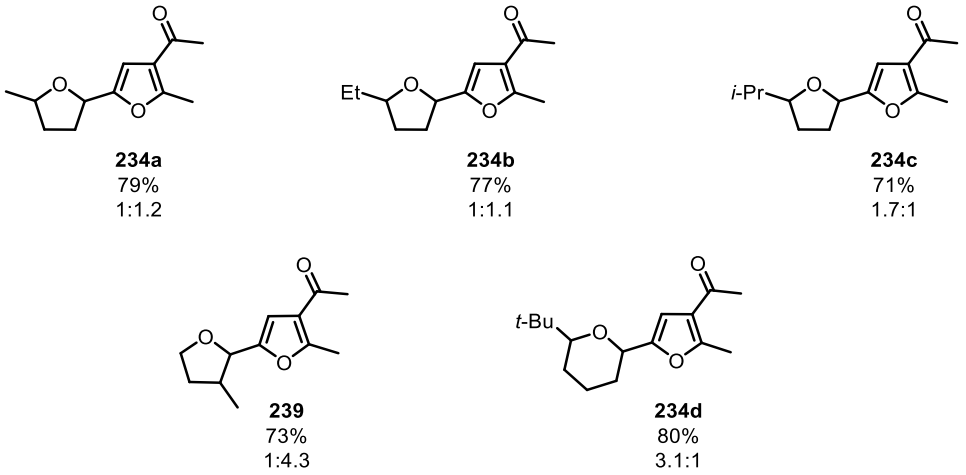
Scheme 92

The original organocatalytic furan synthesis using THT and ynenone in the presence of an oxygen nucleophile was successfully expanded to allow for additional ring formation. A general reaction that can be applied to a large range of substrates to provide furans furnished with a fused ether system was developed successfully (*Scheme 93*).



Scheme 93

Although these furan systems were synthesised in high yields, only low to medium levels of diastereocontrol were observed (*Figure 10*).



234a
79%
1:1.2

234b
77%
1:1.1

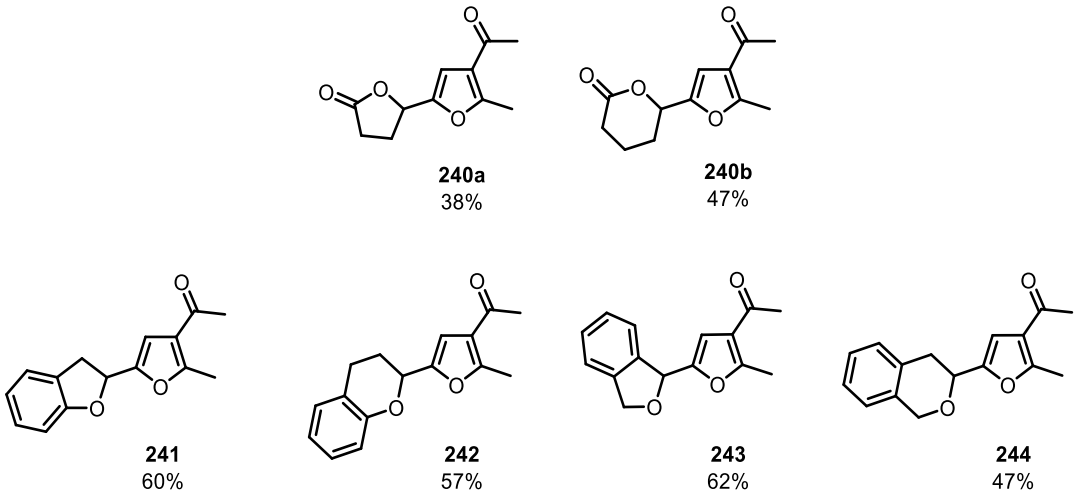
234c
71%
1.7:1

239
73%
1:4.3

234d
80%
3.1:1

Figure 10

The substrate scope of the polycyclic furan formation reaction was investigated, with all furans being obtained in good yield, demonstrating the versatility of the reaction (*Figure 11*).



240a
38%

240b
47%

241
60%

242
57%

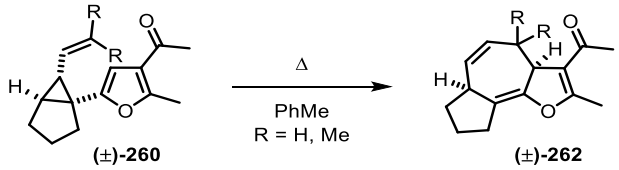
243
62%

244
47%

Figure 11

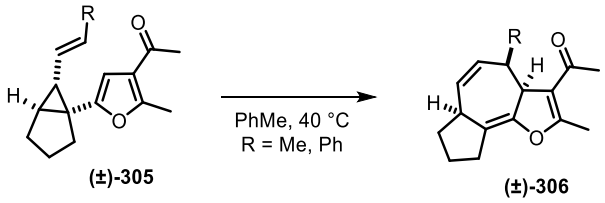
3.2 Cope Rearrangement of Vinylcyclopropanes

The second part of this thesis involved the investigation of a Cope rearrangement of furylvinylcyclopropane. The synthesis of substrate **260** allowed access to the complex tricyclic cycloheptadienes **262** (*Scheme 94*). Full optimisation studies were carried out and the rearrangement reaction was achieved in good yield.



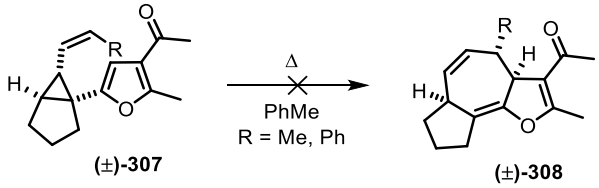
Scheme 94

The substrate scope of the DVCPR was investigated with various furylvinylcyclopropanes. Heating the *E*-vinyl substrate in toluene at 40 °C resulted in its smooth conversion into the cycloheptadiene **306** (*Scheme 95*).



Scheme 95

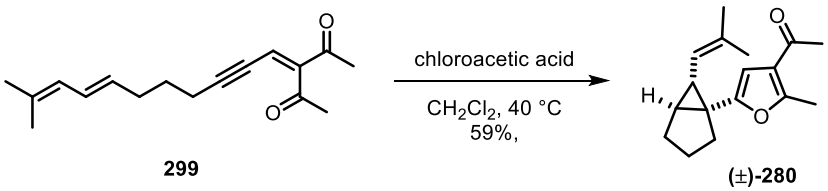
On attempted rearrangement of the *Z*-isomer **307**, difficulties were encountered and either rearrangement failed to occur or an unknown by-product was formed (*Scheme 96*).



Scheme 96

A cascade procedure for the direct formation of the tricyclic system containing a cycloheptadiene from an acyclic ynenone precursor was investigated. During the synthesis of the ynenone substrates, difficulties were encountered with competitive Diels-Alder cycloaddition of intermediate compounds. However, a promising

preliminary result was obtained with the formation of furan **280** derived from ynenone **299** (*Scheme 97*).



299 **(±)-280**

Scheme 97

4 Experimental Section

General Reaction Conditions

Air and/or moisture sensitive reactions were performed with the exclusion of air under an atmosphere of argon in flame dried glassware.

Solvents and Reagents

THF, PhMe, CH_2Cl_2 and Et_2O were dried using a Pure-Solv^{TM} solvent purification system. Other dry organic solvents and all reagents were purchased from commercial supplies and without further purification unless otherwise specified.

Chromatography

All reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 covered alumina plates. The TLC plates were visualised under UV light and stained with acidic ethanolic anisaldehyde solution or potassium permanganate solution.

Column chromatography was performed under pressure with silica gel (Fluorochem LC60A, 35-70 micron or Merck Geduran Si60, 40-63 micron) as solid. Petroleum ether used for column chromatography was the 40–60 °C fraction.

Apparatus

IR spectra were recorded on a Shimadzu FT IR-8400S ATR instrument. The IR spectrum of each compound was acquired directly on a thin film (liquid) or powder (solid) at room temperature.

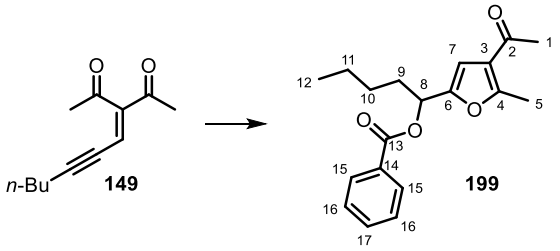
^{1}H NMR spectra were recorded using a Bruker Avance III 400 MHz or Bruker Avance III UltraShield 500 MHz spectrometer at ambient temperature. Data are recorded as

follows: chemical shifts in ppm relative to $CDCl_3$ (7.26) or C_6D_6 (7.16) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad, or a combination of these), coupling constant(s) *J* (Hz) and assignment. ^{13}C NMR spectra were recorded using a Bruker Avance III 400 MHz or Bruker Avance III UltraShield 500 MHz spectrometer at 100 MHz or 126 MHz at ambient temperature. Data are reported as follows: chemical shift in ppm, relative to $CDCl_3$ (77.16) or C_6D_6 (128.1) on the δ scale and assignment.

High resolution mass spectra (HRMS) were obtained by the analytical service of the University of Glasgow with an Jeol MStation JMS-700 instrument using positive chemical ionization (CI using isobutene) or a positive ion impact (EI) techniques, or on a Bruker micro TOFq High Resolution instrument using positive ion electrospray (ESI) techniques.

Melting points were recorded using an Electrothermal IA 9100 instrument.

Furan 199

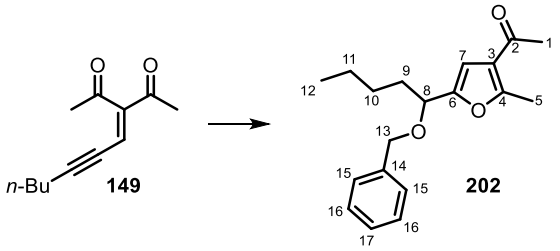


To a mixture of ynenone **149** (57 mg, 0.30 mmol), benzoic acid (37 mg, 0.30 mmol) and TRIP (19 mg, 25 μmol) was added a solution of tetrahydrothiophene (0.30 mL of a 0.50 M solution in CH_2Cl_2, 0.15 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford furan **199** (83 mg, 89%, 12% *ee*) as a pale yellow oil.

R_f = 0.11 (petroleum ether- EtOAc, 10:1); HPLC t_{1R} = 10.8 min, t_{2R} = 12.6 min, (Chiralcel AD-H ø 4.6 mm × 250 mm, 0.5 mL × min^{-1}, 90:10, detection: 189 nm, oven: 25.0 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 8.3 Hz, CH-C15), 7.56 (1H, t, *J* = 7.4 Hz, CH-C17), 7.44 (2H, dd, *J* = 8.3, 7.4 Hz, CH-C16), 6.61 (1H, s, CH-C7), 6.00 (1H, dd, *J* = 7.2, 7.2 Hz, CH-C8), 2.58 (3H, s, CH_3-C5), 2.39 (3H, s, CH_3-C1), 2.12–2.01 (2H, m, CH_2-C9), 1.43–1.28 (4H, m, CH_2-C10, CH_2-C11), 0.91 (3H, t, *J* = 6.9 Hz, CH_3-C12).

The analytical and spectroscopic data are in agreement with those reported in the literature.[67]

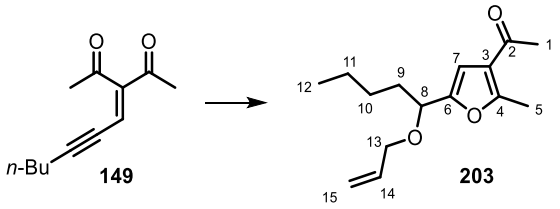
Furan 202



To a mixture of ynenone **149** (98 mg, 0.51 mmol), benzyl alcohol (0.16 mL, 1.6 mmol) and phenylphosphonic acid (8.1 mg, 51 μmol) was added a solution of tetrahydrothiophene (0.50 mL of a 0.50 M solution in CH_2Cl_2, 0.25 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford furan **202** (0.12 g, 76%) as a pale yellow oil.

R_f = 0.15 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m, Ph), 6.48 (1H, s, CH-C7), 4.54 (1H, d, *J* = 12.0 Hz, C*H*H-C13), 4.37 (1H, d, *J* = 12.0 Hz, CH*H*-C13), 4.26 (1H, dd, *J* = 7.0, 7.0 Hz, CH-C8), 2.59 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1), 1.98–1.89 (1H, m, C*H*H-C9), 1.84–1.75 (1H, m, CH*H*-C9), 1.42–1.19 (2H, m, CH_2-C10), 1.35–1.25 (2H, m, CH_2-C11), 0.88 (3H, t, *J* = 7.0 Hz, CH_3-12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3 (C-C2), 158.4 (C-C4), 152.8 (C-C6), 138.3 (C-C14), 128.5 (2C, CH-C16), 127.9 (2C, CH-C15), 127.8 (CH-C17), 122.0 (C-C3), 108.6 (CH-C7), 74.1 (CH-C8), 70.7 (CH_2-C13), 34.0 (CH_2-C9), 29.3 (CH_3-C1), 27.9 (CH_2-C10), 22.6 (CH_2-C11), 14.7 (CH_3-C5), 14.1 (CH_3-C12); ν_{max} (film) 2957, 1678, 1564, 1454, 1370, 1229, 1063, 1028 cm^{-1}; HMRS (ESI) calcd for $C_{19}H_{24}NaO_3$ $[M+Na]^+$ 323.1618, found 323.1604.

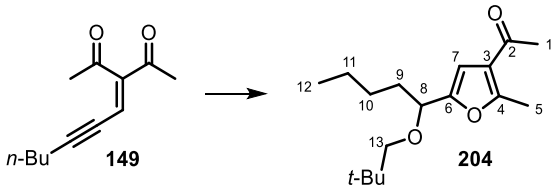
Furan 203



To a mixture of ynenone **149** (0.13 g, 0.69 mmol), allyl alcohol (0.14 mL, 2.1 mmol) and phenylphosphonic acid (11 mg, 69 μmol) was added a solution of tetrahydrothiophene (0.70 mL of a 0.50 M solution in CH_2Cl_2, 0.35 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 5:2) to afford furan **203** (0.13 g, 73%) as a pale yellow oil.

R_f = 0.22 (petroleum ether-Et_2O, 5:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, s, CH-C7), 5.88 (1H, dddd, *J* = 17.2, 10.4, 6.2, 5.2 Hz, CH-C14$_{trans}$), 5.26 (1H, br ddd, *J* = 17.2, 3.1, 1.5 Hz, C*H*H-C15$_{trans}$), 5.17 (1H, br ddd, *J* = 10.4, 3.1, 1.3 Hz, CH*H*-C15$_{cis}$), 4.23 (1H, dd, *J* = 7.0, 7.0 Hz, CH-C8), 3.99 (1H, dddd, *J* = 12.7, 5.2, 1.5, 1.5 Hz, C*H*H-C13), 3.85 (1H, dddd, *J* = 12.7, 6.2, 1.3, 1.3 Hz, CH*H*-C13), 2.58 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1), 1.94–1.85 (1H, m, C*H*H-C9), 1.83–1.74 (1H, m, CH*H*-C9), 1.40–1.19 (4H, m, CH_2-C10, CH_2-C11), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194. (C-C2), 158.3 (C-C4), 152.8 (C-C6), 134.8 (CH-C14), 122.0 (C-C3), 117.3 (CH-C15), 108.4 (CH-C7), 74.2 (CH-C8), 69.8 (CH_2-C13), 33.9 (CH_2-C9), 29.3 (CH_3-C1), 27.9 (CH_2-C10), 22.6 (CH_2-C11), 14.7 (CH_3-C5), 14.1 (CH_3-C12); ν_{max} (film) 2932, 1678, 1564, 1406, 1229, 1121, 1080 cm^{-1}; HMRS (ESI) calcd for $C_{15}H_{22}NaO_3$ $[M+Na]^+$ 273.1461, found 273.1451.

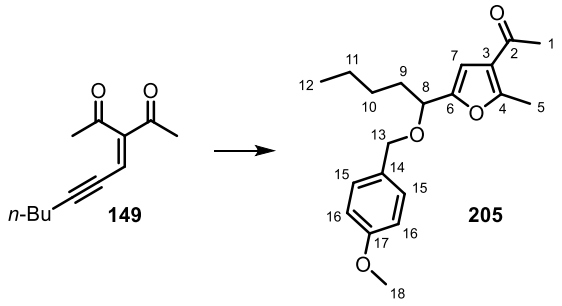
Furan 204



To a mixture of ynenone **149** (90 mg, 0.47 mmol), neopentyl alcohol (0.15 mL, 1.4 mmol) and phenylphosphonic acid (7.4 mg, 47 μmol) was added a solution of tetrahydrothiophene (0.45 mL of a 0.50 M solution in CH_2Cl_2 0.23 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 5:2) to afford furan **204** (98 mg, 75%) as a pale yellow oil.

R_f = 0.40 (petroleum ether-Et_2O, 5:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (1H, s, CH-C7), 4.12 (1H, dd, *J* = 7.7, 6.0 Hz, CH-C8), 3.06 (1H, d, *J* = 8.7 Hz, CH-C13), 2.94 (1H, d, *J* = 8.7 Hz, CH-C13), 2.57 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1), 1.91–1.82 (1H, m, C*H*H-C9), 1.77–1.68 (1H, m, CH*H*-C9), 1.46–1.23 (2H, m, CH_2-C10), 1.39–1.29 (2H, m, CH_2-C11), 0.90 (3H, t, *J* = 6.9 Hz, CH_3-C12), 0.88 (9H, s, CH_3-*t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4 (C-C2), 157.9 (C-C4), 153.8 (C-C6), 121.9 (C-C3), 107.5 (CH-C7), 79.6 (CH_2-C13), 75.6 (CH-C8), 34.2 (CH_2-C9), 32.3 (C-*t*-Bu), 29.3 (CH_3-C1), 27.9 (CH_2-C10), 26.8 (3C, CH_3-*t*-Bu), 22.6 (CH_2-C11), 14.6 (CH_3-C5), 14.2 (CH_3-C12); ν_{max} (film) 2957, 1680, 1566, 1362, 1229, 1092 cm^{-1}; HMRS (CI, isobutane) calcd for $C_{17}H_{29}O_3$ $[M+H]^+$ 281.2117, found 281.2113.

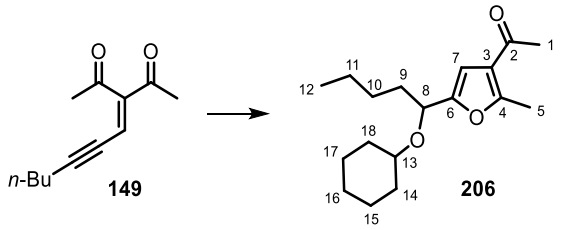
Furan 205



To a mixture of ynenone **149** (0.13 g, 0.69 mmol), *p*-methoxybenzyl alcohol (0.26 mL, 2.1 mmol) and phenylphosphonic acid (11 mg, 68 μmol) was added a solution of tetrahydrothiophene (0.70 mL of a 0.50 M solution in CH_2Cl_2, 0.35 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 10:3) to afford furan **205** (0.20 mg, 87%) as a pale yellow oil.

R_f = 0.12 (petroleum ether-Et_2O, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.6 Hz, CH-C16), 6.87 (2H, d, *J* = 8.6 Hz, CH-C15), 6.47 (1H, s, CH-C7), 4.47 (1H, d, *J* = 11.5 Hz, C*H*H-C13), 4.29 (1H, d, *J* = 11.5 Hz, CH*H*-C13), 4.23 (1H, dd, *J* = 7.2, 6.8 Hz, CH-C8), 3.80 (3H, s, CH_3-C18), 2.59 (3H, s, CH_3-C5), 2.41 (3H, s, CH_3-C1), 1.95–1.86 (1H, m, C*H*H-C9), 1.82–1.73 (1H, m, C*H*H-C9), 1.40–1.17 (2H, m, CH_2-C10), 1.34–1.23 (2H, m, CH_2-C11), 0.87 (3H, t, *J* = 7.1 Hz, CH_3-C12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3 (C-C2), 159.3 (C-C17), 158.3 (C-C4), 152.9 (C-C6), 130.4 (C-C14), 129.5 (2C, CH-C15), 122.0 (C-C3), 113.9 (2C, CH-C16), 108.4 (CH-C7), 73.7 (CH-C8), 70.3 (CH_2-C13), 55.4 (CH_3-C18), 34.0 (CH_2-C9), 29.3 (CH_3-C1), 27.9 (CH_2-C10), 22.6 (CH_2-C11), 14.7 (CH_3-C5), 14.1 (CH_3-C12); ν_{max} (film) 2956, 1676, 1560, 1512, 1246, 1172, 1080 cm^{-1}; HMRS (ESI) calcd for $C_{20}H_{26}NaO_4$ $[M+Na]^+$ 353.1723, found 353.1706.

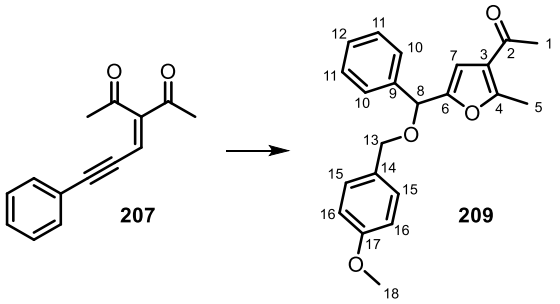
Furan 206



To a mixture of ynenone **149** (95 mg, 0.49 mmol), cyclohexanol (0.15 mL, 1.4 mmol) and phenylphosphonic acid (7.8 mg, 49 μmol) was added a solution of tetrahydrothiophene (0.50 mL of a 0.50 M solution in CH_2Cl_2, 0.25 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 5:2) to afford furan **206** (0.11 g, 77%) as a pale yellow oil.

R_f = 0.33 (petroleum ether-Et_2O, 5:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (1H, s, CH-C7), 4.30 (1H, dd, *J* = 7.7, 6.2 Hz, CH-C8), 3.25 (1H, dddd, *J* = 9.1, 9.1, 3.6, 3.6 Hz, CH-C13), 2.57 (3H, s, CH_3-C5), 2.39 (3H, s, CH_3-C1), 1.92–1.85 (1H, m, C*H*H-C14/C18), 1.85–1.78 (1H, m, C*H*H-C9), 1.76–1.70 (4H, m, CH*H*-C9, C*H*H-C14/C18, CH_2-C15/C17), 1.51–1.49 (1H, m, C*H*H-C16), 1.43–1.38 (1H, m, C*H*H-C10), 1.37–1.27 (2H, m, CH_2-C11), 1.28–1.19 (6H, m, CH*H*-C10, CH*H*-C14/C18, CH*H*-C14/C18, CH_2-C15/C17, CH*H*-C16), 0.89 (3H, t, *J* = 7.2 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4 (C-C2), 157.9 (C-C4), 154.3 (C-C6), 122.0 (C-C3), 107.2 (CH-C7), 75.8 (CH-C13), 72.1 (CH-C8), 34.8 (CH_2-C9), 33.5 (CH_2-C14/C18), 31.9 (CH_2-C14/C18), 29.3 (CH_3-C1), 28.1 (CH_2-C10), 25.9 (CH_2-C16), 24.5 (CH_2-C15/C17), 24.3 (CH_2-C15/C17), 22.6 (CH_2-C11), 14.7 (CH_3-C5), 14.2 (CH_3-C12); ν_{max} (film) 2932, 1678, 1566, 1451, 1356, 1229, 1080 cm^{-1}; HMRS (ESI) calcd for $C_{18}H_{28}NaO_3$ $[M+Na]^+$ 315.1931, found 315.1931.

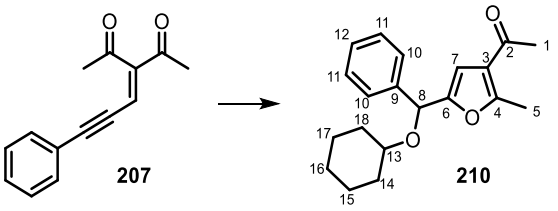
Furan 209



To a mixture of ynenone **207** (0.11 mg, 0.50 mmol), *p*-methoxybenzyl alcohol (0.18 mL, 1.5 mmol) and TRIP (38 mg, 50 μmol) was added a solution of tetrahydrothiophene (0.50 mL of a 0.50 M solution in CH_2Cl_2, 0.25 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 10:3) to afford furan **209** (0.12 g, 70%, 4% *ee*) as a pale yellow oil.

R_f = 0.20 (petroleum ether-Et_2O, 10:3); HPLC t_{1R} = 50.1 min, t_{2R} = 57.1 min, (Chiralcel AD-H ø 4.6 mm × 250 mm, 99:1, 0.5 mL × min^{-1} detection: 190 nm, oven 25.0 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.34 (5H, m, Ph), 7.27 (2H, d, *J* = 8.7 Hz, CH-C16), 6.89 (2H, d, *J* = 8.7 Hz, CH-C15), 6.31 (1H, s, CH-C7), 5.36 (1H, s, CH-C8), 4.52 (1H, d, *J* = 12.6 Hz, C*H*H-C13), 4.47 (1H, d, *J* = 12.6 Hz, CH*H*-C13), 3.81 (3H, s, CH_3-C18), 2.55 (3H, s, CH_3-C5), 2.33 (3H, s, CH_3-C1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (C-C2), 159.5 (C-C17), 158.8 (C-C4), 152.6 (C-C6), 138.8 (CH-C9), 129.9 (C-C14), 129.7 (2C, CH-C15), 128.7 (2C, CH-C11), 128.4 (CH-C12), 127.5 (2C, CH-C10), 122.1 (C-C3), 114.0 (2C, CH-C16), 109.2 (CH-C7), 75.6 (CH-C8), 70.5 (CH_2-C13), 55.5 (CH_3-C18), 29.3 (CH_3-C1), 14.7 (CH_3-C5); ν_{max} (film) 2936, 1676, 1564, 1513, 1248, 1173, 1034 cm^{-1}; HMRS (ESI) calcd for $C_{22}H_{22}NaO_4$ $[M+Na]^+$ 373.1410, found 373.1395.

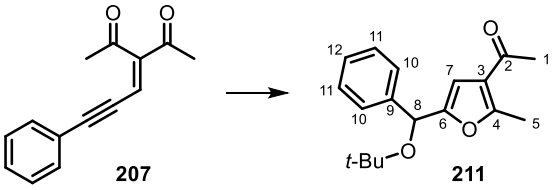
Furan 210



To a mixture of ynenone **207** (0.11 g, 0.50 mmol), cyclohexanol (0.16 mL, 1.5 mmol), and phenylphosphonic acid (8.7 mg, 55 μmol) was added a solution of tetrahydrothiophene (0.50 mL of a 0.50 M solution in CH_2Cl_2, 0.25 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 10:3) to afford furan **210** (0.12 g, 77%) as a pale yellow oil.

R_f = 0.08 (petroleum ether-Et_2O, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 7.0 Hz, CH-C10), 7.37 (2H, dd, *J* = 7.1, 7.0 Hz, CH-C11), 7.32 (1H, t, *J* = 7.1 Hz, CH-C12), 6.25 (1H, s, CH-C7), 5.48 (1H, s, CH-C8), 3.37 (1H, dddd, *J* = 9.5, 9.5, 3.8, 3.8 Hz, CH-C13), 2.55 (3H, s, CH_3-C5), 2.33 (3H, s, CH_3-C1), 1.99–1.96 (1H, m, C*H*H-C14/C18), 1.88-1.84 (1H, m, C*H*H-C14/C18), 1.81–1.69 (2H, m, CH_2-C15/C17), 1.53–1.50 (1H, m, C*H*H-C16), 1.47–1.34 (2H, m, CH*H*-C14/C18, CH*H*-C14/C18), 1.27–1.17 (3H, m, CH*H*-C16, CH_2-C15/C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3 (C-C2), 158.7 (C-C4), 153.5 (C-C6), 139.8 (C-C9), 128.6 (2C, CH-C11), 128.1 (CH-C12), 127.2 (2C, CH-C10), 122.1 (C-C3), 108.6 (CH-C7), 76.1 (CH-C8), 73.9 (CH-C13), 32.8 (CH_2-C14/C18), 32.2 (CH_2-C14/C18), 29.2 (CH_3-C1), 25.9 (CH_2-C16), 24.3 (CH_2-C15/C17), 24.3 (CH_2-C15/C17), 14.7 (CH_3-C5); ν_{max} (film) 2930, 1676, 1564, 1451, 1229, 1069, 1026 cm^{-1}; HMRS (ESI) calcd for $C_{20}H_{24}NaO_3$ $[M+Na]^+$ 335.1618, found 335.1606.

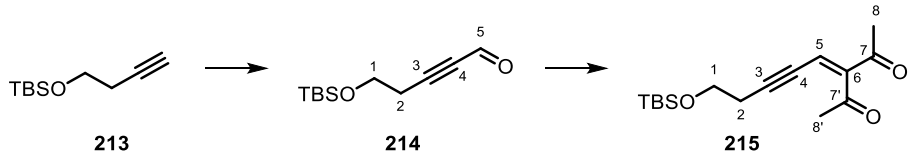
Furan 211



To a mixture of ynenone **207** (0.10 g, 0.49 mmol), *t*-butyl alcohol (0.14 mL, 1.5 mmol) and phenylphosphonic acid (8.2 mg, 52 μmol) was added a solution of tetrahydrothiophene (0.50 mL of a 0.50 M solution in CH_2Cl_2, 0.25 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 10:3) to afford furan **211** (0.10 g, 71%) as a pale yellow oil.

R_f = 0.27 (petroleum ether-Et_2O, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 7.0 Hz, CH-C10), 7.35 (2H, dd, *J* = 7.3, 7.0 Hz, CH-C11), 7.29 (1H, t, *J* = 7.3 Hz, CH-C12), 6.13 (1H, s, CH-C7), 5.55 (1H, s, CH-C8), 2.54 (3H, s, CH_3-C5), 2.30 (3H, s, CH_3-C1), 1.25 (9H, s, CH_3-*t*-Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4 (C-C2), 158.4 (C-C4), 154.8 (C-C6), 141.6 (C-C9), 128.4 (2C, CH-C11), 127.7 (CH-C12), 126.9 (2C, CH-C10), 122.1 (C-C3), 108.2 (CH-C7), 75.6 (CH-C8), 69.6 (C-*t*-Bu), 29.2 (CH_3-C1), 28.6 (3C, CH_3-*t*-Bu), 14.7 (CH_3-C5); ν_{max} (film) 2974, 1676, 1564, 1366, 1229, 1190, 1047, 1020 cm^{-1}; HMRS (EI) calcd for $C_{18}H_{22}O_3$ $[M]^+$ 286.1569, found 286.1568.

Ynenone 215



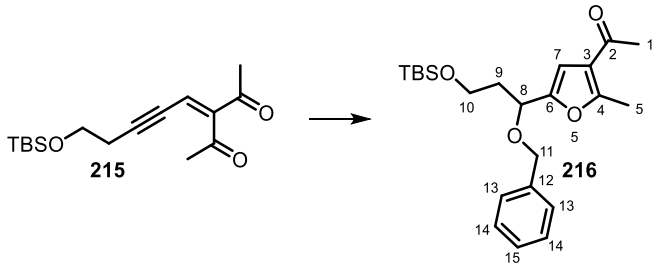
To a stirred solution of alkyne **213** (5.8 g, 31 mmol) in THF (160 mL) at −78 °C was added *n*-BuLi (18 mL of a 2.1 M solution in hexanes, 37 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (4.8 mL, 62 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 solution (160 mL) and diluted with Et_2O (60 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **214** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.50 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, t, *J* = 0.8 Hz, CH-C5), 3.80 (2H, t, *J* = 6.7 Hz, CH_2-C1), 2.63 (2H, td, *J* = 6.7, 0.8 Hz, CH_2-C2), 0.90 (9H, s, *t*-Bu-TBS), 0.08 (6H, s, CH_3-TBS).

To a stirred solution of crude acetylenic aldehyde **214** and acetylacetone (3.2 mL, 32 mmol) in toluene (310 mL) at rt were added $MgSO_4$ (0.75 g, 6.2 mmol), piperidine (0.15 mL, 1.5 mmol) and acetic acid (1.1 mL, 19 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (300 mL). The mixture was diluted with EtOAc (100 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:3) to afford ynenone **215** (6.3 g, 69% over 2 steps) as a pale yellow oil.

R_f = 0.31 (petroleum ether/EtOAc 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, t, *J* = 2.5 Hz, CH-C5), 3.71 (2H, t, *J* = 6.7 Hz, CH_2-C1), 2.60 (2H, td, *J* = 6.7, 2.5 Hz, CH_2-C2), 2.43 (3H, s, CH_3-C8'), 2.26 (3H, s, CH_3-C8), 0.84 (9H, s, CH_3-*t*-Bu-TBS), 0.02 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2 (C-C7'), 195.7 (C-C7), 149.8 (C-C6), 122.8 (CH-C5), 107.2 (C-C3), 77.7 (C-C4), 61.1 (CH_2-C1), 31.0 (CH_3-C8'), 27.3 (CH_3-C8), 25.9 (3C, CH_3-*t*-Bu-TBS), 24.7 (CH_2-C2), 18.3 (C-*t*-Bu-TBS), −5.3 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} (film) 2930, 1667, 1578, 1360, 1250 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{26}NaO_3Si$ $[M+Na]^+$ 317.1543, found 317.1531.

Furan 216



Method 1:

To a mixture of ynenone **215** (42 mg, 0.14 mmol), benzyl alcohol (0.45 mL, 0.44 mmol) and TRIP-H (11 mg, 15 μmol) was added a solution of tetrahydrothiophene (0.15 mL of a 0.50 M solution in CH_2Cl_2, 75 μmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford furan **216** (43 mg, 77%) as a pale yellow oil.

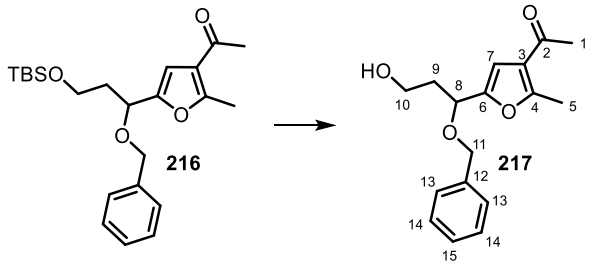
Method 2:

To a mixture of ynenone **215** (0.21 g, 0.71 mmol), benzyl alcohol (0.23 mL, 2.2 mmol) and phenylphosphonic acid (12 mg, 76 μmol) was added a solution of (1*R*,4*R*,5*R*)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane (0.70 mL of a 0.50 M solution in CH_2Cl_2, 0.35 mmol). The mixture was stirred at 40 °C for 2 weeks (conversion 1.0:1.2) and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford furan **216** (0.14 g, 49%) as a pale yellow oil.

R_f = 0.30 (petroleum ether-EtOAc, 5:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (5H, Ph), 6.49 (1H, s, CH-C7), 4.54 (1H, dd, *J* = 8.0, 5.8 Hz, CH-C8), 4.53 (1H, d, *J* = 11.7 Hz, C*H*H-C11), 4.39 (1H, d, *J* = 11.7 Hz, CH*H*-C11), 3.77 (1H, ddd, *J* = 10.3, 7.6, 5.1 Hz, C*H*H-C10), 3.61 (1H, ddd, *J* = 10.3, 5.7, 5.7 Hz, CH*H*-C10), 2.59 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1), 2.16 (1H, dddd, *J* = 13.7, 8.0, 5.7, 5.1 Hz, C*H*H-C9), 1.98 (1H, dddd, *J* = 13.7, 7.6, 5.8, 5.7 Hz, CH*H*-C9), 0.87 (9H, s, CH_3-*t*-Bu-TBS), 0.03 (3H, s,

CH_3-TBS), 0.02 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4 (C-C2), 157.5 (C-C4), 155.8 (C-C6), 138.3 (C-C12), 128.5 (2C, CH-C14), 127.9 (2C, CH-C13), 127.7 (CH-C15), 122.0 (C-C3), 108.8 (CH-C7), 70.9 (CH_2-C8), 70.9 (CH-C11), 59.3 (CH_2-C10), 37.4 (CH_2-C9), 29.3 (CH_3-C1), 26.0 (3C, CH_3-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 14.7 (CH_3-C5), −5.2 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} (film) 2928, 1680, 1564, 1252, 1092 cm^{-1}; HMRS (ESI) calcd for $C_{23}H_{34}NaO_4Si$ $[M+Na]^+$ 425.2119, found 425.2120.

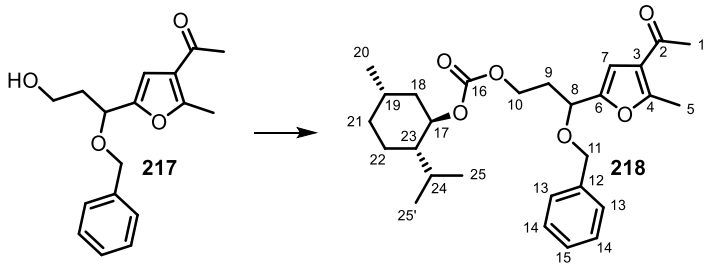
Alcohol 217



To a stirred solution of protected alcohol **216** (43 mg, 0.11 mmol) in MeOH/CH_2Cl_2 (v/v 5:2, 1.1 mL) at rt was added camphorsulfonic acid (4.9 mg, 21 μmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of water (10 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 3:2) to afford alcohol **217** (29 mg, 95%) as a colourless oil.

R_f = 0.13 (petroleum ether-EtOAc, 3:2); ^{1}H NMR (400M Hz, CDCl3) δ 7.37–7.27 (5H, m, Ph), 6.53 (1H, s, CH-C7), 4.58 (1H, d, *J* = 11.9 Hz, C*H*H-C11), 4.56 (1H, dd, *J* = 9.0, 4.5 Hz, CH-C8), 4.39 (1H, d, *J* = 11.9 Hz, CH*H*-C11), 3.85–3.79 (1H, m, C*H*H-C10), 3.75–3.69 (1H, m, CH*H*-C10), 2.60 (3H, s, CH_3-C5), 2.41 (3H, s, CH_3-C1), 2.23 (1H, dddd, *J* = 14.6, 9.0, 7.1, 4.5 Hz, C*H*H-C9), 2.03 (1H, br s, OH), 1.98 (1H, dddd, *J* = 14.6, 7.1, 4.5, 4.5 Hz, CH*H*-C9), ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1 (C-C2), 158.7 (C-C4), 151.8 (C-C6), 137.8 (C-C12), 128.7 (2C, CH-C14), 128.1 (3C, CH-C13, CH-C15), 122.1 (C-C3), 108.9 (CH-C7), 72.6 (CH-C8), 71.0 (CH_2-C11), 60.3 (CH_2-C10), 36.8 (CH_2-C9), 29.3 (CH_3-C1), 14.7 (CH-C5), ν_{max} (film) 3428 (br), 2928, 1676, 1562, 1231, 1055 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{20}NaO_4$ $[M+Na]^+$ 311.1254, found 311.1243.

Menthyl carbonate 218

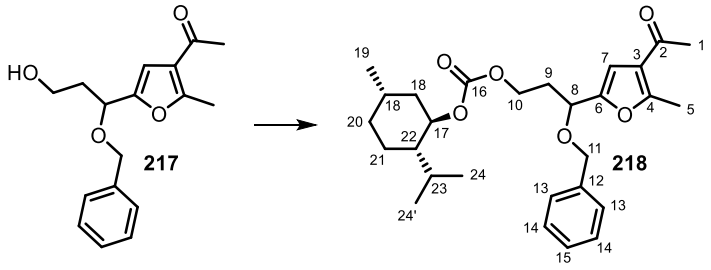


To a stirred solution of alcohol **217** (0.10 g, 0.39 mmol) in pyridine/CH_2Cl_2 (v/v 0.4:5, 0.50 mL) was added a solution of (1*R*)-(−)-menthyl chloroformate (0.10 g, 0.46 mmol,) in CH_2Cl_2 (0.50 mL). The mixture was stirred at room temperature for 18 h and then the reaction was quenched by addition of CH_2Cl_2 (5 mL) and 1 M HCl (3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford an inseparable mixture of furan **218** (0.14 g, 76%, 1:1 *dr*) as a colourless oil.

R_f = 0.17 (petroleum ether-Et_2O, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m, Ph), 7.35–7.25 (5H, m, Ph), 6.52 (1H, s, CH-C7), 6.51 (1H, s, CH-C7), 4.53 (1H, d, *J* = 11.4 Hz, C*H*H-C11), 4.53 (1H, d, *J* = 11.4 Hz, C*H*H-C11), 4.53–4.45 (2H, m, CH-C8, CH-C17), 4.53–4.45 (2H, m, CH-C8, CH-C17), 4.38 (1H, d, *J* = 11.4 Hz, CH*H*-C11), 4.38 (1H, d, *J* = 11.4 Hz, CH*H*-C11), 4.33–4.27 (1H, m, C*H*H-C10), 4.33–4.27 (1H, m, C*H*H-C10), 4.19 (1H, ddd, *J* = 11.0, 5.8, 5.8 Hz, CH*H*-C10), 4.16 (1H, ddd, *J* = 11.0, 5.8, 5.8 Hz, CH*H*-C10), 2.59 (3H, s, CH_3-C5), 2.59 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1), 2.40 (3H, s, CH_3-C1), 2.34 (1H, ddd, *J* = 9.6, 5.8, 5.8 Hz, C*H*H-C9), 2.30 (1H, ddd, *J* = 9.6, 5.8, 5.8 Hz, C*H*H-C9), 2.16 (1H, ddd, *J* = 7.9, 5.5, 5.5 Hz, CH*H*-C9), 2.12 (1H, ddd, *J* = 7.9, 5.5, 5.5 Hz, CH*H*-C9), 2.06 (1H, br d, *J* = 11.8 Hz, C*H*H-C18), 2.06 (1H, br d, *J* = 11.8 Hz, C*H*H-C18), 1.94 (1H, m, CH-C24), 1.94 (1H, m, CH-C24), 1.69–1.67 (2H, m, C*H*H-C21, C*H*H-C22), 1.69–1.67 (2H, m, C*H*H-C21, C*H*H-C22), 1.52–1.47 (1H, m, CH-C19), 1.52–1.47 (1H, m, CH-C19), 1.43–1.36 (1H, m, CH-C23), 1.43–1.36 (1H,

m, CH-C23), 1.10–0.98 (2H, m, CH*H*-C18, CH*H*-C22), 1.10–0.98 (2H, m, CH*H*-C18, CH*H*-C22), 0.93 (3H, d, *J* = 4.1 Hz, CH_3-C20), 0.91 (3H, d, *J* = 4.1 Hz, CH_3-C20), 0.91 (3H, d, *J* = 2.0 Hz, CH_3-C25/C25'), 0.90–0.88 (1H, m, CH*H*-C21), 0.90–0.88 (1H, m, CH*H*-C21), 0.89 (3H, d, *J* = 2.0 Hz, CH_3-C25/C25'), 0.80 (3H, d, *J* = 3.6 Hz, CH_3-C25/C25'), 0.78 (3H, d, *J* = 3.6 Hz, CH_3-C25/C25'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1 (C-C2), 194.1 (C-C2), 158.8 (C-C4), 158.8 (C-C4), 155.0 (C-C16), 154.9 (C-C16), 151.4 (C-C6), 151.4 (C-C6), 137.9 (C-C12), 137.9 (C-C12), 128.6 (2C, CH-C14), 128.5 (2C, CH-C14), 128.0 (2C, CH-C13), 127.9 (2C, CH-C13), 127.9 (CH-C15), 127.9 (CH-C15), 122.0 (C-C3), 122.0 (C-C3), 109.2 (CH-C7), 109.2 (CH-C7), 78.6 (CH-C8), 78.5 (CH-C8), 71.0 (CH_2-C11), 70.9 (CH_2-C11), 70.6 (CH-C17), 70.5 (CH-C17), 64.2 (CH_2-C10), 64.2 (CH_2-C10), 47.2 (CH-C23), 47.2 (CH-C23), 41.0 (CH_2-C18), 40.9 (CH_2-C18), 34.2 (CH_2-C21), 34.2 (CH_2-C21), 33.6 (CH_2-C9), 33.6 (CH_2-C9), 31.6 (CH-C19), 31.6 (CH-C19), 29.3 (CH_3-C1), 29.3 (CH_3-C1), 26.3 (CH-C24), 26.26 (CH-C24), 23.5 (CH_2-C22), 23.5 (CH_2-C22), 22.1 (CH_3-C20), 22.1 (CH_3-C20), 20.9 (CH_3-C25/C25'), 20.9 (CH_3-C25/C25'), 16.5 (CH_3-C25/C25'), 16.5 (CH_3-C25/C25'), 14.7 (CH_3-C5), 14.7 (CH_3-C5); ν_{max} (film) 2955, 1740, 1680, 1260, 1233, 1094 cm^{-1}HMRS (ESI) calcd for $C_{28}H_{38}NaO_6$ $[M+Na]^+$ 493.2561, found 493.2537.

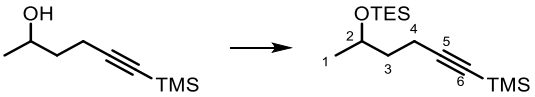
Menthyl carbonate 218



To a stirred solution of alcohol **217** (29 mg, 0.11 mmol) in pyridine/CH_2Cl_2 (v/v 0.8:10, 0.15 mL) was added a solution of (1*R*)-(−)menthyl chloroformate (29 mg, 0.13 mmol,) in CH_2Cl_2 (0.15 mL). The mixture was stirred at room temperature for 18 h and then the reaction was quenched by addition of CH_2Cl_2 (5 mL) and 1 M HCl (3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether-EtOAc, 5:1) to afford an inseparable mixture of furan **218** (37 mg, 78%, 1:1.2 *dr*) as a colourless oil.

The analytical and spectroscopic data are in agreement with those reported on pages 107–108

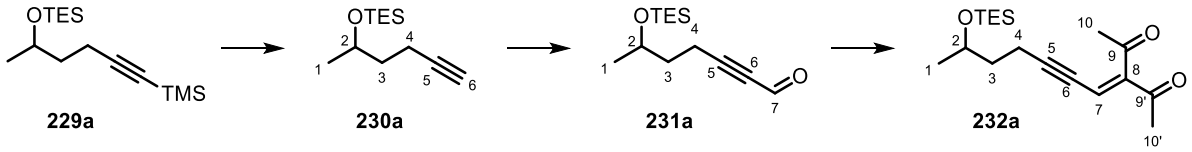
Protected alcohol 229a



To a stirred solution of alcohol **228a** (0.99 g, 5.8 mmol) in THF (60 mL) at 0 °C was added 2,6-lutidine (1.3 mL, 12 mmol). The mixture was cooled to −78 °C and triethylsilyl trifluoromethanesulfonate (1.6 mL, 6.9 mmol) was added slowly. The mixture was stirred at −78 °C for 1 h and then allowed to reach rt. The reaction was quenched by the addition of MeOH (5 mL), the mixture was diluted with EtOAc (50 mL) and then washed with saturated aqueous $NaHCO_3$ (40mL) and brine (40 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford protected alcohol **229a** (1.5 g, 91%) as a colourless oil.

R_f = 0.10 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (1H, dqd, *J* = 7.5, 6.1, 5.0 Hz, CH-C2), 2.30 (1H, dd, *J* = 7.7, 7.1 Hz, C*H*H-C4), 2.28 (1H, dd, *J* = 7.7, 7.1 Hz, CH*H*-C4), 1.66–1.56 (2H, m, CH_2-C3), 1.16 (3H, d, *J* = 6.1 Hz, CH_3-C1), 0.96 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.61 (6H, q, *J* = 8.0 Hz, CH_2-TES), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 107.5 (C-C6), 84.6 (C-C5), 67.01 (CH-C2), 38.4 (CH_2-C3), 23.9 (CH3-C1), 16.5 (CH_2-C4), 7.1 (3C, CH_3-TES), 5.1 (3C, CH_2-TES), 0.3 (CH_3-TMS); ν_{max} (film) 2955, 1248 cm^{-1}; HMRS (ESI) calcd for $C_{15}H_{32}NaOSi_2$ $[M+Na]^+$ 307.1884, found 307.1873.

Ynenone 232a



To a stirred solution of alcohol **229a** (1.5 g, 5.3 mmol) in MeOH (30 mL) at rt was added K_2CO_3 (0.77 g, 5.6 mmol) in one portion. The mixture was stirred for 16 h and then the reaction was quenched by addition of water (30 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 300:1) to afford alkyne **230a** as a colourless oil. The alkyne was used directly in the next step without further purification.

R_f = 0.10 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (1H, dqd, *J* = 7.3, 6.1, 4.9 Hz, CH-C2), 2.25 (2H, ddd, *J* = 7.4, 7.3, 2.7 Hz, CH_2-C4), 1.92 (1H, t, *J* = 2.7 Hz, CH-C6), 1.66–1.59 (2H, m, CH_2-C3), 1.16 (3H, d, *J* = 6.1 Hz, CH_3-C1), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-TES).

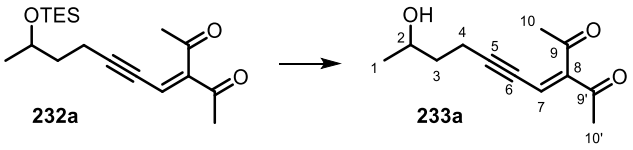
To a stirred solution of alkyne **230a** in THF (55 mL) at −78 °C was added *n*-BuLi (3.2 mL of a 2.1 M solution in hexanes, 6.7 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.86 mL, 11 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (55 mL). The mixture was diluted with EtOAc (20 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **231a** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.33 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (1H, t, *J* = 0.7 Hz, CH-C7), 3.92 (1H, dqd, *J* = 6.1, 6.1, 6.1 Hz, CH-C2), 2.48 (2H, ddd, *J* = 7.1, 7.1, 0.7 Hz, CH_2-C4), 1.69 (2H, td, *J* = 7.1, 6.1 Hz, CH_2-C3), 1.17 (3H, d, *J* = 6.1 Hz, CH_3-C1), 0.95 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.60 (6H, q, *J* = 8.0 Hz, CH_2-TES).

To a stirred solution of crude acetylenic aldehyde **231a** and acetylacetone (0.57 mL, 5.6 mmol) in toluene (55 mL) at rt were added $MgSO_4$ (0.14 g, 1.1 mmol), piperidine (55 μL, 0.56 mmol) and acetic acid (0.19 mL, 3.3 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (60 mL). The mixture was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **232a** (1.2 g, 72% over 3 steps) as a pale yellow oil.

R_f = 0.13 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, dd, *J* = 2.6 Hz, CH-C7), 3.88 (1H, dqd, *J* = 5.2, 6.1, 6.9 Hz, CH-C2), 2.51 (1H, ddd, *J* = 7.5, 7.5, 2.6 Hz, C*H*H-C4), 2.50 (1H, ddd, *J* = 7.3, 7.3, 2.6 Hz, CH*H*-C4), 2.47 (3H, s, CH_3-C10), 2.31 (3H, s, CH_3-C10'), 1.69–1.63 (2H, m, CH_2-C3), 1.16 (3H, d, *J* = 6.1 Hz, CH_3-C1), 0.96 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.60 (6H, q, *J* = 8.0 Hz, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4 (C-C9), 195.9 (C-C9'), 149.6 (C-C8), 123.3 (CH-C7), 110.5 (C-C5), 76.9 (C-C6) 67.1 (CH-C2), 37.9 (CH_2-C3), 31.1 (CH_3-C10), 27.4 (CH_3-C10'), 23.9 (CH_3-C1), 16.8 (CH_2-C4), 7.0 (3C, CH_3-TES), 5.1 (3C, CH_2-TES); ν_{max} (film) 2955, 1692 cm^{-1}; HMRS (ESI) calcd for $C_{18}H_{29}NaO_3Si$ $[M+Na]^+$ 344.1778, found 345.1858.

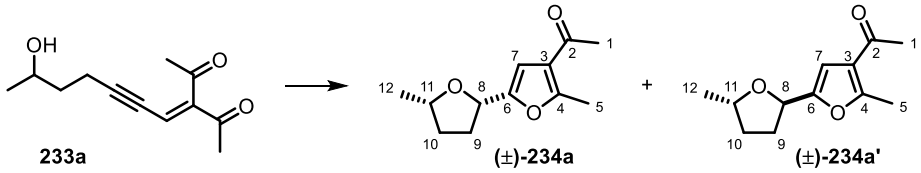
Alcohol 233a



To a stirred solution of protected alcohol **232a** (0.91 g, 2.8 mmol) in MeOH (28 mL) at rt was added camphorsulfonic acid (66 mg, 0.28 mmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of water (30 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **233a** (0.47 g, 79%) as a pale yellow oil.

R_f = 0.20 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, t, J = 2.5 Hz, CH-C7), 3.87 (1H, br dqd, J = 6.2, 6.2, 6.2 Hz, CH-C2), 2.54 (2H, ddd, J = 7.2, 7.2, 2.5 Hz, CH_2-C4), 2.42 (3H, s, CH_3-C10), 2.28 (3H, s, CH_3-C10'), 1.96 (1H, br s, OH), 1.69–1.63 (2H, m, CH_2-C3), 1.20 (3H, d, J = 6.2 Hz, CH_3-C1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (C-C9), 196.0 (C-C9'), 149.8 (C-C8), 123.2 (CH-C7), 109.9 (C-C5), 77.1 (C-C6), 66.7 (CH-C2), 37.1 (CH_2-C3), 31.0 (CH_3-C10), 27.2 (CH_3-C10'), 23.6 (CH_3-C1), 16.9 (CH_2-C4); ν_{max} (film) 3426 (br), 2967, 2210, 1662, 1588, 1578 cm^{-1}; HMRS (ESI) calcd for $C_{12}H_{16}NaO_3$ $[M+Na]^+$ 231.0992, found 231.0986.

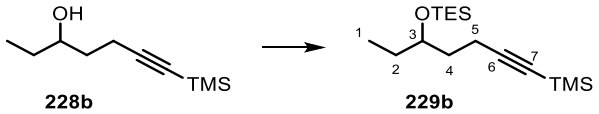
Furans 234a and 234a'



To a mixture of ynenone **233a** (0.12 g, 0.56 mmol) and phenylphosphonic acid (8.9 mg, 56 μmol) was added a solution of tetrahydrothiophene (0.56 mL of a 0.50 M solution in CH_2Cl_2, 0.28 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:3) to afford an inseparable mixture of furan **234a** and **234a'** (92 mg, 79%, 1.0:1.2 *dr*) as a colourless oil.

R_f = 0.22 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, s, CH-C7 **234a'**), 6.45 (1H, s, CH-C7 **234a**), 4.95 (1H, dd, *J* = 7.1, 6.9 CH-C8 **234a**), 4.80 (1H, dd, *J* = 7.1, 6.9 Hz, CH-C8 **234a'**), 4.25-4.17 (1H, tq, *J* = 8.0, 5.8 Hz, CH-C11 **234a**), 4.13-4.05 (1H, tq, *J* = 8.0, 5.8 Hz, CH-C11 **234a'**), 2.55 (3H, s, CH_3-C5 **234a**), 2.55 (3H, s, CH_3-C5 **234a'**), 2.36 (6H, s, CH_3-C1 **234a**), 2.36 (6H, s, CH_3-C1 **234a'**), 2.28–2.04 (6H, m, CH_2-9 **234a**, CH_2-C9 **234a'**, CH_2-C10 **234a**/**234a'**), 1.68–1.54 (2H, m, CH_2-10 **234a**/**234a'**), 1.30 (3H, d, *J* = 6.1 Hz, CH_3-C12 **234a'**), 1.26 (3H, d, *J* = 6.1 Hz, CH_3-C12 **234a**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (C-C2 **234a'**), 194.2 (C-C2 **234a**), 158.4 (C-C4 **234a**), 158.4 (C-C4 **234a'**), 153.5 (C-C6 **234a**), 153.2 (C-C6 **234a'**), 122.0 (C-C3 **234a'**), 122.0 (C-C3 **234a**), 107.3 (CH-C7 **234a'**), 107.2 (CH-C7 **234a**), 76.5 (CH-C11 **234a'**), 75.6 (CH-C11 **234a**), 73.9 (CH-C8 **234a'**), 73.3 (CH-C8 **234a**), 33.9 (CH_2-C10 **234a'**), 33.1 (CH_2-C10 **234a**), 30.9 (CH_2-C9 **234a'**), 30.6 (CH_2-C9 **234a**), 29.2 (CH_3-C1 **234a'**, 29.2 (CH_3-C1 **234a**), 21.3 (CH_3-C12 **234a'**), 21.1 (CH_3-C12 **234a**), 14.6 (CH_3-C5 **234a**), 14.6 (CH_3-C5 **234a'**); ν_{max} (film) 2970, 1676, 1566, 1404 cm^{-1}; HMRS (ESI) calcd for $C_{12}H_{16}NaO_3$ $[M+Na]^+$ 231.0992, found 231.0989.

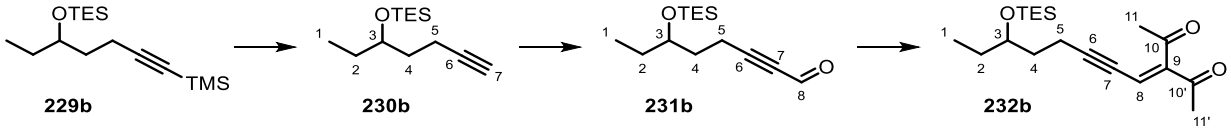
Protected alcohol 229b



To a stirred solution of alcohol **228b** (0.85 g, 4.6 mmol) in THF (45 mL) at 0 °C was added 2,6-lutidine (1.1 mL, 9.2 mmol). The mixture was cooled to −78 °C and then triethylsilyl trifluoromethanesulfonate (1.3 mL, 5.5 mmol) was added slowly. The mixture was stirring at −78 °C for 1 h and then allowed to reach rt. The reaction was quenched by the addition of MeOH (2 mL), the mixture was diluted with EtOAc (40 mL) and then washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford protected alcohol **229b** (1.3 g, 91%).

R_f = 0.29 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (1H, dddd, *J* = 6.6, 6.6, 5.6, 5.6 Hz, CH-C3), 2.28 (2H, t, *J* = 7.2 Hz, CH_2-C5), 1.69–1.55 (2H, m, CH_2-C4), 1.49 (1H, qd, *J* = 7.4, 6.6 Hz, C*H*H-C2), 1.47 (1H, qd, *J* = 7.4, 5.6 Hz, CH*H*-C2), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.88 (3H, t, *J* = 7.4 Hz, CH_3-C1), 0.61 (6H, q, *J* = 7.9 Hz, CH_2-TES), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.7 (C-C7), 84.6 (C-C6), 72.1 (CH-C3), 35.3 (CH_2-C4), 30.0 (CH_2-C2), 16.3 (CH_2-C5), 9.6 (CH_3-C1), 7.1 (3C, CH_3-TES), 5.2 (3C, CH_2-TES), 0.3 (3C, CH_3-TMS); ν_{max} (film) 2957, 1250, 1084, 1038, 1007 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{34}NaOSi_2$ $[M+Na]^+$ 321.2040, found 321.2032.

Ynenone 232b



To a stirred solution of alcohol **229b** (1.1 g, 3.6 mmol) in MeOH (18 mL) at rt was added K_2CO_3 (0.50 g, 3.6 mmol) in one portion. The mixture was stirred for 16 h and then the reaction was quenched by addition of water (20 mL). The mixture was diluted with Et_2O (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 300:1) to afford alkyne **230b** as a colourless oil. The alkyne was used directly in the next step without further purification.

R_f = 0.50 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (1H, dddd, *J* = 5.9, 5.9, 5.1, 5.1 Hz, CH-C3), 2.23 (2H, td, *J* = 7.3, 2.7 Hz, CH_2-C5), 1.91 (1H, t, *J* = 2.7 Hz, CH-C7), 1.70–1.57 (2H, m, CH_2-C4), 1.47 (2H, qd, *J* = 7.4, 5.9 Hz, CH_2-C2), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.87 (3H, t, *J* = 7.4 Hz, CH_3-C1), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-TES).

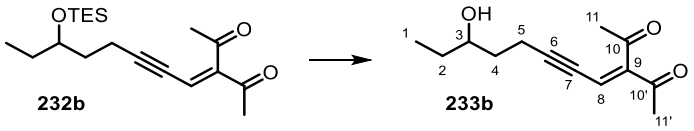
To a stirred solution of alkyne **230b** in THF (35 mL) at −78 °C was added *n*-BuLi (1.9 mL of a 2.3 M solution in hexanes, 4.4 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.55 mL, 7.1 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (35 mL). The mixture was diluted with EtOAc (10 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **231b** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.30 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, t, *J* = 0.7 Hz, CH-C8), 3.71 (1H, dddd, *J* = 6.2, 6.2, 5.5, 5.5 Hz, CH-C3), 2.48 (2H, td, *J* = 7.5, 0.7 Hz, CH_2-C5), 1.76–1.66 (2H, m, CH_2-C4), 1.51–1.46 (2H, m, CH_2-C2), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.88 (3H, t, *J* = 7.5 Hz, CH_3-C1), 0.61 (6H, q, *J* = 7.9 Hz, CH_2-TES).

To a stirred solution of of crude acetylenic aldehyde **231b** and acetylacetone (0.57 mL, 5.6 mmol) in toluene (55 mL) at rt were added $MgSO_4$ (0.14 g, 1.1 mmol), piperidine (55 μL, 0.56 mmol) and acetic acid (0.19 mL, 3.3 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (60 mL). The mixture was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **232b** (0.86 g, 46% over 3 steps) as a pale yellow oil.

R_f = 0.15 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, t, *J* = 2.3 Hz, CH-C8), 3.63 (1H, dddd, *J* = 6.0, 6.0, 5.7, 5.7 Hz, CH-C3), 2.45 (2H, td, *J* = 7.2, 2.3 Hz, CH_2-C5), 2.41 (3H, s, CH_3-C11), 2.25 (3H, s, CH_3-C11'), 1.69–1.55 (2H, m, CH_2-C4), 1.43 (2H, qd, *J* = 7.4, 5.7 Hz, CH_2-C2), 0.90 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.82 (3H, t, *J* = 7.4 Hz, CH_3-C1), 0.55 (6H, q, *J* = 7.9 Hz, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1 (C-C10), 195.7 (C-C10'), 149.5 (C-C9), 123.1 (CH-C8), 110.4 (C-C6), 76.8 (C-C7), 72.0 (CH-C3), 34.7 (CH_2-C4), 30.9 (CH_3-C11), 29.8 (CH_2-C2), 27.2 (CH_3-C11'), 16.4 (CH_2-C5), 9.4 (CH_3-C1), 6.9 (3C, CH_3-TES), 5.1 (3C, CH_2-TES); ν_{max} (film) 2956, 1692, 1667 cm^{-1}; HMRS (ESI) calcd for $C_{19}H_{32}NaO_3Si$ $[M+Na]^+$ 359.2013, found 359.1996.

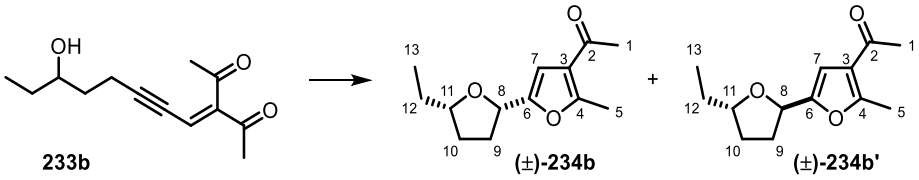
Alcohol 233b



To a stirred solution of protected alcohol **232b** (0.79 g, 2.3 mmol) in MeOH (23 mL) at rt was added camphorsulfonic acid (54 mg, 0.23 mmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of water (30 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc 1:1) to afford alcohol **233b** (0.42 g, 81%) as a pale yellow oil.

R_f = 0.21 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, t, *J* = 2.5 Hz, CH-C8), 3.57 (1H, m, CH-C3), 2.55 (2H, tdd, *J* = 7.0, 2.5, 1.0 Hz, CH_2-C5), 2.41 (3H, s, CH_3-C11), 2.27 (3H, s, CH_3-C11'), 2.05 (1H, br s, OH), 1.73–1.55 (2H, m, CH_2-C4), 1.51–1.39 (2H, m, CH_2-C2), 0.91 (3H, t, *J* = 7.5 Hz, CH_3-C1); ^{13}C NMR (126 MHz, $CDCl_3$) 201.5 (C-C10), 196.0 (C-C10'), 149.8 (C-C9), 123.3 (CH-C8), 110.1 (C-C6), 77.0 (C-C7), 71.9 (CH-C3), 35.0 (CH_2-C4), 31.0 (CH_3-C11), 30.3 (CH_2-C2), 27.2 (CH_3-C11'), 16.9 (CH_2-C5), 10.0 (CH_3-C1); ν_{max} (film) 3444 (br), 2924, 2210, 1662, 1587, 1422 cm^{-1}; HMRS (ESI) calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148, found 245.1142.

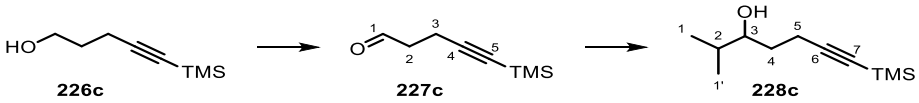
Furans 234b and 234b'



To a solution of ynenone **233b** (0.39 mg, 1.8 mmol) and phenylphosphonic acid (28 mg, 0.18 mmol) was added a solution of tetrahydrothiophene (1.7 mL of a 0.50 M solution in CH_2Cl_2, 0.85 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:3) to afford an inseparable mixture of furan **234b** and **234b'** (0.30 mg, 77% 1.0:1.1 *dr*) as a colourless oil.

R_f = 0.23 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, s, CH-C7 **234b**), 6.46 (1H, s, CH-C7 **234b'**), 4.92 (1H, t, *J* = 7.0 Hz, CH-C8 **234b**), 4.81 (1H, t, *J* = 7.0 Hz, CH-C8 **234b'**), 4.02 (1H, tt, *J* = 7.8 ,6.2 Hz, CH-C11 **234b**), 3.89 (1H, tt, *J* = 7.7, 6.3 Hz, CH-C11 **234b'**), 2.57 (3H, s, CH_3-C5 **234b**), 2.56 (3H, s, CH_3-C5 **234b'**), 2.37 (3H, s, CH_3-C1 **234b'**), 2.37 (3H,s, CH_3-C1 **234b**), 2.26–2.01 (6H, m, CH_2-C9 **234b**, CH_2-C9 **234b'**, CH_2-C10 **234b**/**234b'**), 1.77–1.42 (6H, m, CH_2-10 **234b**/**234b'**, CH_2-C12 **234b**, CH_2-C12 **234b'**), 0.95 (3H, t, *J* = 7.5 Hz, CH_3-C13 **234b'**), 0.94 (3H, t, *J* = 7.5 Hz, CH_3-C13 **234b**), ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3 (C-C2 **234b'**), 194.3 (C-C2 **234b**), 158.4 (C-C4 **234b**), 158.3 (C-C4 **234b'**), 153.5 (C-C6 **234b**), 153.4 (C-C6 **234b'**), 122.0 (C-C3 **234b'**), 122.0 (C-C3 **234b**), 107.3 (CH-C7 **234b'**), 107.3 (CH-C7 **234b**), 82.0 (CH-C11 **234b'**), 81.1 (CH-C11 **234b**), 73.7 (CH-C8 **234b'**), 73.3 (CH-C8 **234b**), 31.6 (CH_2-C9 **234b**/**234b'**), 30.8 (CH_2-C10 **234b**/**234b'**), 30.8 (CH_2-C9 **234b**/**234b''**), 30.5 (CH_2 C10 **234b**/**234b'**), 29.2 (CH_3-C1 **234b**), 29.2 (CH_3-C1 **234b'**), 28.7 (CH_2-C12 **234b'**), 28.6 (CH_2-C12 **234b**), 14.6 (CH_3-C5 **234b**), 14.6 (CH_3-C5 **234b'**), 10.5 (CH_3-C13 **234b'**), 10.3 (CH_3-C13 **234b**); ν_{max} (film) 2965, 1676, 1566, 1406 cm^{-1}; HMRS (ESI) calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148, found 2245.1143.

Alcohol 228c



To a stirred solution of oxalyl chloride (6.0 mL, 71 mmol) in CH_2Cl_2 (320 mL) at −78 °C was added DMSO (9.9 mL, 0.14 mol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **226c** (9.1 g, 58 mmol) in CH_2Cl_2 (15 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h. Et_3N (43 mL, 0.31 mmol) was added, the mixture was allowed to reach rt and then the reaction was quenched by addition of water (320 mL). The phases were separated and the organic phase was washed with 1 M HCl (3 × 80 mL), saturated aqueous $NaHCO_3$ (80 mL) and brine (80 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde **227c** as a yellow oil. The aldehyde was used directly in the next step without further purification.

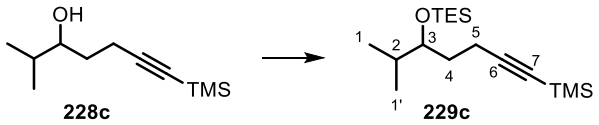
R_f = 0.26 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.2 Hz, CH-C1), 2.67 (2H, m, CH_2-C2), 2.54 (2H, m, CH_2-C3), 0.14 (9H, s, CH_3-TMS).

To a stirred solution of crude aldehyde **227c** in THF (500 mL) at −78 °C was added *i*-propylmagnesium chloride (58 mL of a 2.0 M solution in Et_2O, 0.12 mol). The mixture was allowed to reach rt, stirred for 16 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (500 mL). The mixture was diluted with Et_2O (200 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford alcohol **228c** (9.2 g, 80% over 2 steps) as a colourless oil.

R_f = 0.16 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (1H, dddd, *J* = 9.0, 9.0, 5.1, 2.5 Hz, CH-C3), 2.39 (1H, ddd, *J* = 17.0, 6.9, 6.9 Hz, C*H*H-C5), 2.34 (1H, ddd, *J* = 17.0, 7.2, 7.2 Hz, CH*H*-C5), 1.76 (1H, br s, OH), 1.73–1.66 (1H, m, C*H*H-

C4), 1.70 (1H, septd, *J* = 6.9, 5.1 Hz, CH-C2), 1.57 (1H, dddd, *J* = 16.1, 9.0, 7.2, 6.9 Hz, CH*H*-C4), 0.92 (3H, d, *J* = 6.9 Hz, CH_3-C1), 0.92 (3H, d, *J* = 6.9 Hz, CH_3-C1'), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.4 (C-C7), 85.3 (C-C6), 76.2 (CH-C3), 33.7 (CH-C2), 32.9 (CH_2-C4), 18.8 (CH_3-C1/C1'), 17.5 (CH_3-C1/C1'), 17.1 (CH_2-C5), 0.3 (3C, CH_3-TMS); ν_{max} (film) 2959, 1248, 1053 cm^{-1}; HMRS (ESI) calcd for $C_{11}H_{22}NaOSi$ $[M+Na]^+$ 221.1332, found 221.1328.

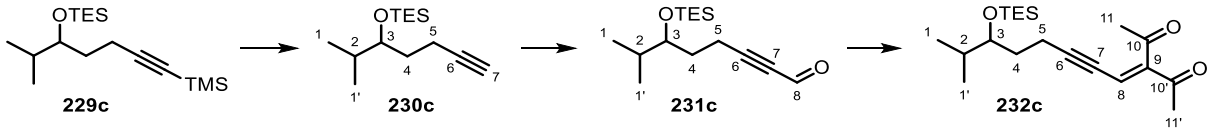
Protected alcohol 229c



To a stirred solution of alcohol **228c** (4.9 g, 26 mmol) in THF (250 mL) at 0 °C was added 2,6-lutidine (5.7 mL, 49 mmol). The mixture was cooled to −78 °C and then triethylsilyl trifluoromethanesulfonate (6.7 mL, 30 mmol) was added slowly. The mixture was stirred at −78 °C for 1 h and then allowed to reach rt. The reaction was quenched by the addition of MeOH (10 mL), the mixture was diluted with EtOAc (200 mL) and then washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford protected alcohol **229c** (7.4 g, 92%) as a colourless oil.

R_f = 0.35 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (1H, ddd, *J* = 6.6, 5.1, 4.4 Hz, CH-C3), 2.30 (1H, ddd, *J* = 17.1, 7.0, 7.0 Hz, C*H*H-C5), 2.24 (1H, ddd, *J* = 17.1, 7.6, 7.6 Hz, CH*H*-C5), 1.74 (1H, septd, *J* = 6.9, 4.4 Hz, CH-C2), 1.59–1.54 (2H, m, CH_2-C4), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.88 (3H, d, *J* = 6.9 Hz, CH_3-C1/C1'), 0.86 (3H, d, *J* = 6.9 Hz, CH_3-C1/C1'), 0.61 (6H, q, *J* = 7.9 Hz, CH_2-TES), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.8 (C-C7), 84.7 (C-C6), 75.6 (CH-C3), 33.3 (CH-C2), 31.6 (CH_2-C4), 18.1 (CH_3-C1/C1'), 17.5 (CH_3-C1/C1'), 16.5 (CH_2-C5), 7.2 (3C, CH_3-TES), 5.4 (3C, CH_2-TES), 0.3 (3C, CH_3-TMS); ν_{max} (film) 2957, 2176, 1250, 1080, 1055 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{36}NaOSi_2$ $[M+Na]^+$ 335.2197, found 335.2184.

Ynenone 232c



To a stirred solution of alcohol **229c** (9.5 g, 31 mmol) in MeOH (150 mL) at rt was added K_2CO_3 (5.1 g, 37 mmol) in one portion. The mixture was stirred for 16 h and then the reaction was quenched by addition of water (150 mL). The mixture was diluted with Et_2O (70 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 300:1) to afford alkyne **230c** as a colourless oil. The alkyne was used directly in the next step without further purification.

R_f = 0.52 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (1H, ddd, *J* = 6.0, 6.0, 4.5 Hz, CH-C3), 2.31–2.15 (2H, m, CH_2-C5), 1.93 (1H, t, *J* = 2.7 Hz, CH-C7), 1.73 (1H, septd, *J* = 7.0, 4.5 Hz, CH-C2), 1.60 (2H, ddd, *J* = 7.0, 7.0, 6.0 Hz, CH_2-C4), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.88 (3H, d, *J* = 7.0 Hz, CH_3-C1/C1'), 0.86 (3H, d, *J* = 7.0 Hz, CH_3-C1/C1'), 0.61 (6H, q, *J* = 7.9 Hz, CH_2-TES).

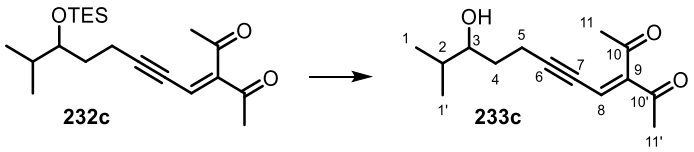
To a stirred solution of alkyne **230c** in THF (300 mL) at −78 °C was added *n*-BuLi (15 ml of a 2.4 M solution in hexanes, 36 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (4.5 mL, 58 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (300 mL). The mixture was diluted with EtOAc (150 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **231c** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.33 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (1H, t, *J* = 0.9 Hz, CH-C8), 3.56 (1H, ddd, *J* = 6.8, 4.9, 4.9 Hz, CH-C3), 2.54–2.39 (2H, m, CH_2-C5), 1.73 (1H, septd, *J* = 6.8, 4.9 Hz, CH-C2), 1.69–1.64 (2H, m, CH_2-C4), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.87 (3H, d, *J* = 6.8 Hz, CH_3-C1/C1'), 0.86 (3H, d, *J* = 6.8 Hz, CH_3-C1/C1'), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-TES).

To a stirred solution of crude acetylenic aldehyde **231c** and acetylacetone (2.7 mL, 26 mmol) in toluene (250 mL) at rt were added $MgSO_4$ (0.610 g, 5.07 mmol), piperidine (0.13 mL, 1.3 mmol) and acetic acid (880 μL, 15.4 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (250 mL). The mixture was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 80 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **232c** (8.0 g, 75% over 3 steps) as a pale yellow oil.

R_f = 0.16 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, t, *J* = 2.4 Hz, CH-C8), 3.54 (1H, ddd, *J* = 7.0, 7.0, 4.6 Hz, CH-C3), 2.57–2.41 (2H, m, CH_2-C5), 2.47 (3H, s, CH_3-C11), 2.32 (3H, s, CH_3-C11'), 1.73 (1H, septd, *J* = 6.9, 4.6 Hz, CH-C2), 1.66–1.60 (2H, m, CH_2-C4), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.87 (3H, d, *J* = 6.9 Hz, CH_3-C1/C1'), 0.86 (3H, d, *J* = 6.9 Hz, CH_3-C1/C1'), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4 (C-C10), 196.0 (C-C10'), 149.6 (C-C9), 123.4 (CH-C8), 110.8 (C-C6), 77.0 (C-C7), 75.7 (CH-C3), 33.4 (CH-C2), 31.1 (CH_2-C4), 31.1 (CH_3-C11), 27.4 (CH_3-C11'), 18.4 (CH_3-C1/C1'), 17.3 (CH_3-C1/C1'), 16.8 (CH_2-C5), 7.1 (3C, CH_3-TES), 5.3 (3C, CH_2-TES); ν_{max} (film) 2958, 1666, 1424 cm^{-1}; HMRS (ESI) calcd for $C_{20}H_{34}NaO_3Si$ $[M+Na]^+$ 373.2169, found 373.2152.

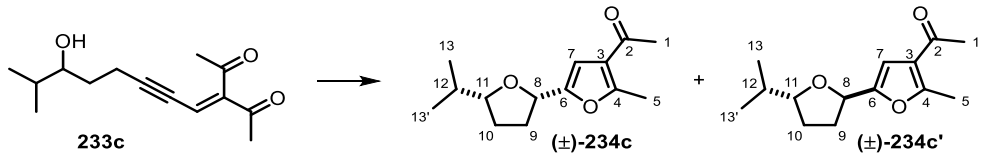
Alcohol 233c



To a stirred solution of protected alcohol **232c** (8.0 g, 23 mmol) in MeOH (115 mL) at rt was added camphorsulfonic acid (0.27 g, 1.2 mmol) in one portion. The mixture was stirred 1 h and then the reaction was quenched by addition of water (120 mL) and saturated aqueous $NaHCO_3$ (20 mL). The mixture was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 80 mL) and the combined organic extracts were washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **233c** (4.4 g, 81%) as a pale yellow oil.

R_f = 0.23 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (1H, t, *J* = 2.5 Hz, CH-C8), 3.46 (1H, dddd, *J* = 8.3, 5.3, 2.9, 2.9 Hz, CH-C3), 2.62–2.58 (2H, m, CH_2-C5), 2.46 (3H, s, CH_3-C11), 2.32 (3H, s, CH_3-C11'), 1.76–1.70 (1H, qd, *J* = 6.9, 2.9 Hz, CH-C2), 1.69–1.59 (2H, m, CH_2-C4), 1.55 (1H, br s, OH), 0.94 (3H, d, *J* = 6.9 Hz, CH_3-C1/C1'), 0.94 (3H, d, *J* = 6.9 Hz, CH_3-C1/C1'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5 (C-C10), 196.0 (C-C10'), 149.9 (C-C9), 123.3 (CH-C8), 110.1 (C-C6), 77.2 (C-C7), 75.5 (CH-C3), 33.9 (CH-C2), 32.5 (CH_2-C4), 31.1 (CH_3-C11), 27.3 (CH_3-C11'), 18.8 (CH_3-C1/C1'), 17.4 (CH_3-C1/C1'), 17.3 (CH_2-C5); ν_{max} (film) 3600 (br), 2962, 1771, 1677, 1606 cm^{-1}; HMRS (ESI) calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$ 259.1305, found 259.1309.

Furans 234c and 234c'

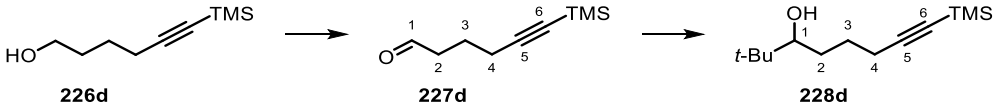


To a solution of ynenone **233c** (0.11 g, 0.46 mmol) and phenylphosphonic acid (8.2 mg, 52 μmol) was added a solution of tetrahydrothiophene (0.50 mL of a 0.50 M solution in CH_2Cl_2, 0.25 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:2) to afford an inseparable mixture of furan **234c** and **234c'** (78 mg, 71%, 1.2:1 *dr*) as a colourless oil.

R_f = 0.45 (petroleum ether-EtOAc, 5:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (1H, s, CH-C7 **234c**), 6.46 (1H, s, CH-C7 **234c'**), 4.89 (1H, t, *J* = 6.9 Hz, CH-C8 **234c**), 4.82 (1H, t, *J* = 6.9 Hz, CH-C8 **234c'**), 3.81 (1H, ddd, *J* = 8.6, 6.8, 6.1 Hz, CH-C11 **234c**), 3.67 (1H, ddd, *J* = 6.8, 6.8, 8.0 Hz, CH-C11 **234c'**), 2.57 (3H, s, CH_3-C5 **234c**), 2.57 (3H, s, CH_3-C5 **234c'**), 2.38 (3H, s, CH_3-C1 **234c**), 2.38 (3H, s, CH_3-C1 **234c'**), 2.24–2.07 (4H, m, CH_2-C9 **234c'**, CH_2-C9 **234c**), 2.07–1.95 (2H, m, CH_2-C10 **234c'**/**234c**), 1.80–1.72 (2H, m, CH-C12 **234c'**, CH-C12 **234c**), 1.72–1.64 (2H, m, CH_2-C10 **234c'**/**234c**), 0.99 (3H, d, *J* = 6.6 Hz, CH_3-C13/C13' **234c'**), 0.98 (3H, d, *J* = 6.6 Hz, CH_3-C13/C13' **234c**), 0.90 (3H, d, *J* = 6.6 Hz, CH_3-C13/C13' **234c'**), 0.89 (3H, d, *J* = 6.6 Hz, CH_3-C13/C13' **234c**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4 (C-C2 **234c'**), 194.3 (C-C2 **234c**), 158.4 (C-C4 **234c'**), 158.3 (C-C4 **234c**), 153.5 (C-C6 **234c'**), 153.4 (C-C6 **234c**), 122.0 (C-C3 **234c'**), 122.0 (C-C3 **234c**), 107.3 (CH-C7 **234c'**), 107.2 (CH-C7 **234c**), 86.0 (CH-C11 **234c**), 85.1 (CH-C11 **234c'**), 73.7 (CH-C8 **234c**), 73.5 (CH-C8 **234c'**), 33.2 (CH-C12 **234c**), 33.1 (CH-C12 **234c'**), 31.0 (CH_2-C9 **234c'**), 30.7 (CH_2-C9 **234c**), 29.3 (CH_2-C10 **234c'**), 29.3 (CH_3-C1 **234c'**), 29.3 (CH_3-C1 **234c**), 28.7 (CH_2-C10 **234c**), 19.6 (CH_3-C13/C13' **234c**), 19.5 (CH_3-C13/C13' **234c'**), 18.6 (CH_3-C13/C13' **234c**), 18.3 (CH_3-C13/C13' **234c'**), 14.7 (CH_3-C5 **234c'**), 14.7 (CH_3-C5 **234c**);ν_{max} (film) 2959, 1676,

1566, 1406 cm^{-1}; HMRS (ESI) calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$ 259.1305, found 259.1296.

Alcohol 228d



To a stirred solution of oxalyl chloride (2.3 mL, 27 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added DMSO (3.8 mL, 33 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **226d** (3.8 g, 23 mmol) in CH_2Cl_2 (7 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h. Et_3N (17 mL, 0.12 mol) was added, the mixture was allowed to reach rt and then the reaction was quenched by addition of water (200 mL). The phases were separated and the organic phase was washed with 1 M HCl (3 × 70 mL), saturated aqueous $NaHCO_3$ (70 mL) and brine (70 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde **227d** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.40 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (1H, t, *J* = 1.4 Hz, CH-C1), 2.59 (2H, td, *J* = 7.2, 1.4 Hz, CH_2-C2), 2.30 (2H, t, *J* = 6.9 Hz, CH_2-C4), 1.84 (2H, tt, *J* = 7.2, 6.9 Hz, CH_2-C3), 0.14 (9H, s, CH_3-TMS).

To a stirred solution of crude aldehyde **227d** in THF (210 mL) at −78 °C was added *t*-butylmagnesium chloride (21 mL of a 2.0 M solution in Et_2O, 42 mmol). The mixture was allowed to reach rt, stirred for 16 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (200 mL). The mixture was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 70 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford alcohol **228d** (3.2 g, 62% over 2 steps) as a colourless oil.

R_f = 0.10 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (1H, br dd, *J* = 10.7, 1.8 Hz, CH-C1), 2.22 (2H, dd, *J* = 6.7, 6.4 Hz, CH_2-C4), 1.84–1.65 (2H, m, *CH*H-C2, C*H*H-C3), 1.61–1.50 (1H, m, CH*H*-C3), 1.47 (1H, br s, OH), 1.41–1.28 (1H, m, CH*H*-C2), 0.90 (9H, s, CH_3-*t*-Bu), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 107.6 (C-C6), 85.0 (C-C5), 79.5 (CH-C1), 35.2 (C-*t*-Bu), 30.5 (CH_2-C2), 26.0 (CH_2-C3), 25.8 (3C, CH_3-*t*-Bu), 19.8 (CH_2-C4), 0.3 (3C, CH_3-TMS); ν_{max} (film) 2957, 2174, 1248, 1076 cm^{-1}; HMRS (ESI) calcd for $C_{13}H_{26}NaOSi$ $[M+Na]^+$ 249.1645, found 249.1635.

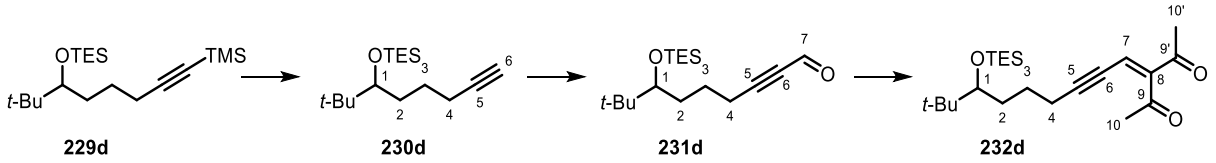
Protected alcohol 229d

228d **229d**

To a stirred solution of alcohol **228d** (3.2 g, 14 mmol) in THF (140 mL) at 0 °C was added 2,6-lutidine (3.2 mL, 28 mmol). The mixture was cooled to −78 °C and then triethylsilyl trifluoromethanesulfonate (3.8 mL, 17 mmol) was added slowly. The mixture was stirred at −78 °C for 1 h and then allowed to reach rt. The reaction was quenched by addition of MeOH (5 mL), the mixture was diluted with EtOAc (150 mL) and then washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford protected alcohol **229d** (4.4 g, 93%) as a colourless oil.

R_f = 0.79 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.26 (1H, dd, *J* = 7.7, 2.7 Hz, CH-C1), 2.22 (2H, dd, *J* = 6.6, 6.6 Hz, CH_2-C4), 1.74–1.61 (2H, m, C*H*H-C2, C*H*H-C3), 1.49–1.33 (2H, m, CH*H*-C2, CH*H*-C3), 0.97 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.86 (9H, s, CH_3-*t*-Bu), 0.61 (6H, q, *J* = 7.9 Hz, CH_2-TES), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 107.6 (C-C6), 84.8 (C-C5), 80.8 (CH-C1), 36.0 (C-*t*-Bu), 32.4 (CH_2-C2), 26.7 (CH_2-C3), 26.4 (3C, CH_3-*t*-Bu), 20.3 (CH_2-C4), 7.3 (3C, CH_3-TES), 5.8 (3C, CH_2-TES), 0.3 (3C, CH_3-TMS); ν_{max} (film) 2955, 2176, 1250, 1099, 1009 cm^{-1}; HMRS (ESI) calcd for $C_{19}H_{40}NaOSi_2$ $[M+Na]^+$ 363.2510, found 363.2494.

Ynenone 232d



To a stirred solution of alcohol **229d** (4.4 g, 13 mmol) in MeOH (65 mL) at rt was added K_2CO_3 (1.9 g, 14 mmol) in one portion. The mixture was stirred for 16 h and then the reaction was quenched by addition of water (65 mL). The mixture was diluted with Et_2O (40 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 300:1) to afford alkyne **230d** as a colourless oil. The alkyne was used directly in the next step without further purification.

R_f = 0.67 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (1H, dd, *J* = 8.0, 2.7 Hz, CH-C1), 2.19 (2H, td, *J* = 6.7, 2.6 Hz, CH_2-C4), 1.94 (1H, t, *J* = 2.6 Hz, CH-C6), 1.77–1.59 (2H, m, CH_2-C3), 1.51–1.34 (2H, m, CH_2-C2), 0.97 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.85 (9H, s, CH_3-*t*-Bu), 0.62 (6H, q, *J* = 8.0 Hz, CH_2-TES).

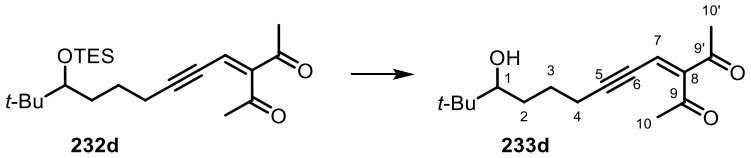
To a stirred solution of alkyne **230d** in THF (100 mL) at −78 °C was added *n*-BuLi (5.3 mL of a 2.3 M solution in hexanes, 12 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (1.6 mL, 20 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (100 mL). The mixture was diluted with EtOAc (70 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **231d** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.36 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, t, *J* = 0.7 Hz, CH-C7), 3.27 (1H, dd, *J* = 8.1, 2.7 Hz, CH-C1), 2.41 (2H, td, *J* = 6.9, 0.7 Hz, CH_2-C4), 1.65–1.50 (2H, m, CH_2-C3) 1.45–1.37 (2H, m, CH_2-C2), 0.97 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.86 (9H, s, CH_3-*t*-Bu), 0.62 (6H, q, *J* = 8.0 Hz, CH_2-TES).

To a stirred solution of crude acetylenic aldehyde **231d** and acetylacetone (0.97 mL, 9.5 mmol) in toluene (95 mL) at rt were added $MgSO_4$ (0.23 g, 1.9 mmol), piperidine (46 μL, 0.47 mmol) and acetic acid (0.32 mL, 5.6 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (95 mL). The mixture was diluted with Et_2O (60 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **232d** (2.6 g, 54% over 3 steps) as a pale yellow oil.

R_f = 0.15 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, t, *J* = 2.5 Hz), 3.26 (1H, dd, *J* = 8.4, 2.6 Hz), 2.47 (3H, s, CH_3-C10), 2.44 (2H, td, *J* = 7.0, 2.5 Hz, CH_2-C4), 2.31 (3H, s, CH_3-C10'), 1.79–1.71 (1H, m, C*H*H-C3), 1.61–1.55 (1H, m, C*H*H-C2), 1.54-1.45 (1H, m, CH*H*-C3), 1.42–1.34 (1H, m, CH*H*-C2), 0.97 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.85 (9H, s, CH_3-*t*-Bu), 0.61 (6H, q, *J* = 8.0 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4 (C-C9), 196.0 (C-C9'), 149.6 (C-C8), 123.4 (CH-C7), 110.3 (C-C5), 80.8 (CH-C1), 77.1 (C-C6), 35.9 (C-*t*-Bu), 32.6 (CH_2-C2), 31.1 (CH_3-C10), 27.5 (CH_3-C10'), 26.4 (3C, CH_3-*t*-Bu), 26.3 (CH_2-C3), 20.8 (CH_2-C4), 7.3 (3C, CH_3-TES), 5.8 (3C, CH_2-TES); ν_{max} (film) 2955, 1692, 1667 cm^{-1}; HMRS (ESI) calcd for $C_{22}H_{38}NaO_3Si$ $[M+Na]^+$ 401.2482, found 401.2493.

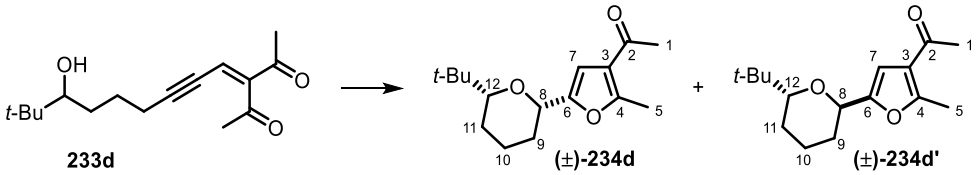
Alcohol 233d



To a stirred solution of protected alcohol **232d** (2.6 g, 6.8 mmol) in MeOH (35 mL) at rt was added camphorsulfonic acid (80 mg, 0.34 mmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of water (40 mL) and saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (30 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford ynenone **233d** (1.7 g, 93%) as a pale yellow oil.

R_f = 0.29 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (1H, t, *J* = 2.3 Hz, CH-C7), 3.16 (1H, br d, *J* = 10.4 Hz, CH-C1), 2.46 (2H, td, *J* = 6.6, 2.3 Hz, CH_2-C4), 2.43 (3H, s, CH_3-C10), 2.28 (3H, s, CH_3-C10'), 1.87–1.78 (1H, m, C*H*H-C2), 1.66 (1H, br s, OH), 1.64–1.53 (2H, m, CH_2-C3), 1.36–1.26 (1H, m, CH*H*-C2), 0.87 (9H, s, CH_3-*t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (C-C9), 195.9 (C-C9'), 149.8 (C-C8), 123.3 (CH-C7), 110.4 (C-C5), 79.5 (CH-C1), 77.1 (C-C6), 35.1 (C-*t*-Bu), 31.0 (CH_2-C2), 30.7 (CH_3-C10), 27.2 (CH_3-C10'), 25.8 (3C, CH_3-*t*-Bu), 25.7 (CH_2-C3) , 20.4 (CH_2-C4); ν_{max} (film) 3600 (br), 2955, 2211, 1665, 1578 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$ 287.1618, found 287.1608.

Furans 234d and 234d'

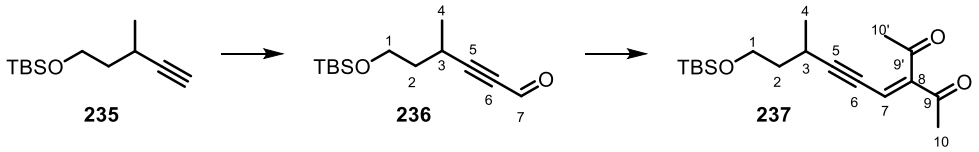


To a solution of ynenone **233d** (88 mg, 0.33 mmol) and phenylphosphonic acid (5.2 mg, 33 μmol) was added a solution of tetrahydrothiophene (0.33 mL of a 0.50 M solution in CH_2Cl_2, 0.17 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford an inseparable mixture of furan **234d** and **234d'** (70 mg, 80%, 2.7:1 *dr*) as a colourless oil.

R_f = 0.35 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (1H, d, *J* = 1.2 Hz, CH-C7 **234d'**), 6.41 (1H, s, CH-C7 **234d**), 4.98 (1H, d, *J* = 5.9 Hz, CH-C8 **234d'**), 4.30 (1H, dd, *J* = 10.7, 2.0 Hz, CH-C8 **234d**), 3.05 (1H, dd, *J* = 11.2, 1.7 Hz, CH-C12 **234d**), 2.98 (1H, dd, *J* = 11.4, 1.9 Hz, CH-C12 **234d'**), 2.57 (3H, s, CH_3-C5 **234d'**), 2.55 (3H, s, CH_3-C5 **234d**), 2.40 (3H, s, CH_3-C1 **234d'**), 2.38 (3H, s, CH_3-C1 **234d**), 2.02–1.96 (1H, m, C*H*H-C9 **234d**), 2.02–1.90 (1H, m, C*H*H-C10 **234d**), 1.96–1.75 (1H, m, CH*H*-C9 **234d**), 1.88–1.75 (1H, m, C*H*H-C9 **234d'**), 1.79–1.61 (2H, m, CH_2-C10 **234d'**), 1.66–1.51 (2H, m, CH_2-C11 **234d'**/**234d**), 1.61–1.51 (2H, m, CH*H*-C9 **234d'**, CH*H*-C10 **234d**), 1.37–1.24 (2H, m, CH_2-C11 **234d**/**234d'**), 0.90 (9H, s, CH_3-*t*-Bu **234d**), 0.88 (9H, s, CH_3-*t*-Bu **234d'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4 (C-C2 **234d**), 194.3 (C-C2 **234d'**), 157.8 (C-C4 **234d'**), 157.5 (C-C4 **234d**), 154.3 (C-C6 **234d**), 152.8 (C-C6 **234d'**), 122.2 (C-C3 **234d'**), 122.0 (C-C3 **234d**), 108.3 (C-C7 **234d'**), 106.0 (C-C7 **234d**), 86.2 (CH-C8 **234d**), 78.8 (CH-C8 **234d'**), 73.5 (CH-C12 **234d**), 69.38 (CH-C12 **234d'**), 34.4 (C-*t*-Bu **234d**), 34.1 (C-*t*-Bu **234d'**), 30.0 (CH_2-C9 **234d'**), 29.2 (CH_3-C1 **234d'**), 29.2 (CH_3-C1 **234d**), 26.2 (3C, CH_3-*t*-Bu **234d'**), 26.2 (3C CH_3-*t*-Bu **234d**), 26.0 (CH_2-C9 **234d**), 25.4 (CH_2-C11 **234d'**), 25.1 (CH_2-C11 **234d**), 23.9 (CH_2-C10 **234d**), 20.3 (CH_2-C10 **234d'**), 14.6 (CH_3-C5 **234d'**), 14.6 (CH_3-C5

234d); ν_{max} (film) 2951, 1678, 1568 cm^{-1}; HMRS (EI) calcd for $C_{16}H_{24}O_3$ $[M]^+$ 264.1725, found 264.1725.

Ynenone 237



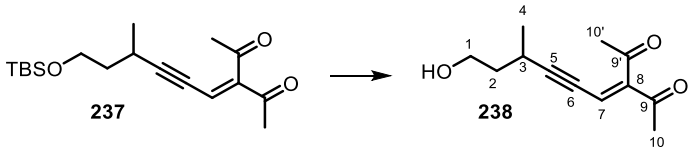
To a stirred solution of alkyne **235** (0.20 g, 0.92 mmol) in THF (9 mL) at −78 °C was added *n*-BuLi (0.60 mL of a 2.3 M solution in hexanes, 1.4 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.14 mL, 1.8 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (20 mL). The mixture was diluted with EtOAc (10 mL), stirred for 30 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **236** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.32 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (1H, d, *J* = 0.8 Hz, CH-C7), 3.73 (2H, t, *J* = 6.1 Hz, CH_2-C1), 2.93-2.85 (1H, qtd, *J* = 7.2, 7.0, 0.8 Hz, CH-C3), 1.72 (2H, dt, *J* = 7.2, 6.1 Hz, CH_2-C2), 1.27 (3H, d, *J* = 7.0 Hz, CH_3-C4), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.06 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS).

To a stirred solution of crude acetylenic aldehyde **236** and acetylacetone (80 μL, 0.78 mmol) in toluene (8 mL) at rt were added $MgSO_4$ (22 mg, 0.18 mmol), piperidine (4.0 μL, 41 μmol) and acetic acid (30 μL, 0.52 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (10 mL). The mixture was diluted with Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **237** (0.16 g, 54%) as a pale yellow oil.

R_f = 0.08 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (1H, d, *J* = 2.2 Hz, CH-C7), 3.73–3.65 (2H, m, CH_2-C1), 2.89 (1H, qddd, *J* = 7.0, 6.8, 6.8, 2.2 Hz, CH-C3), 2.46 (3H, s, CH_3-C10'), 2.30 (3H, s, CH_3-C10), 1.73–1-62 (2H, m, CH_2-C2), 1.23 (3H, d, *J* = 7.0 Hz, CH_3-C4), 0.88 (9H, s, CH_3-t-Bu-TBS), 0.04 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2 (C-C9'), 195.8 (C-C9), 149.6 (C-C8), 123.2 (CH-C7), 114.3 (C-C5), 77.3 (C-C6), 60.7 (CH_2-C1), 39.4 (CH_2-C2), 31.1 (CH_3-C10'), 27.4 (CH_3-C10), 26.0 (3C, CH_3-*t*-Bu-TBS), 24.0 (CH-C3), 20.4 (CH_3-C4), 18.4 (C-*t*-Bu-TBS), −5.2 (CH_3-TBS), −5.2 (CH_3-TBS); ν_{max} (film) 2955, 1692, 1578 cm^{-1}; HMRS (ESI) calcd for $C_{18}H_{30}NaO_3Si$ $[M+Na]^+$ 345.1856, found 345.1849.

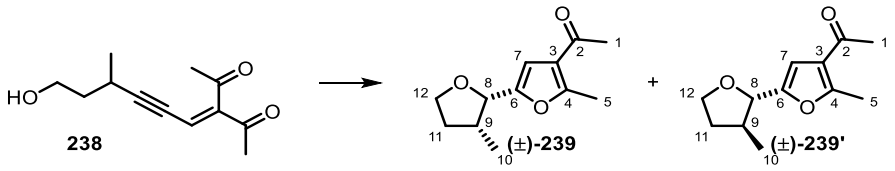
Alcohol 238



To a stirred solution of protected alcohol **237** (0.17 g, 0.51 mmol) in MeOH (5 mL) at rt was added camphorsulfonic acid (5.9 mg, 26 μmol) in one portion. The mixture was stirred for 1 h and then filtered through a pad of silica and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **238** (84 mg, 79%) as a pale yellow oil.

R_f = 0.18 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (1H, d, *J* = 2.2 Hz, CH-C7), 3.78 (2H, dt, *J* = 6.5, 5.3 Hz, CH_2-C1), 2.91 (1H, ddqd, *J* = 7.3, 7.3, 7.0, 2.2 Hz, CH-C3), 2.46 (3H, s, CH_3-C10'), 2.32 (3H, s, CH_3-C10'), 1.81–1.73 (1H, m, C*H*H-C2), 1.75–1.67 (1H, m, CH*H*-C2), 1.54 (1H, t, *J* = 5.3 Hz, OH), 1.26 (3H, d, *J* = 7.0 Hz, CH_3-C4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3 (C-C9'), 195.9 (C-C9), 149.9 (C-C8), 123.1 (CH-C7), 113.5 (C-C5), 77.5 (C-C6), 60.7 (CH_2-C1), 39.1 (CH_2-C2), 31.1 (CH_3-C10'), 27.3 (CH_3-C10), 24.3 (CH-C3), 20.5 (CH_3-C4); ν_{max} (film) 3600 (br), 2932, 1665, 1577 cm^{-1}; HMRS (ESI) calcd for $C_{12}H_{16}NaO_3$ $[M+Na]^+$ 231.0992, found 231.0996.

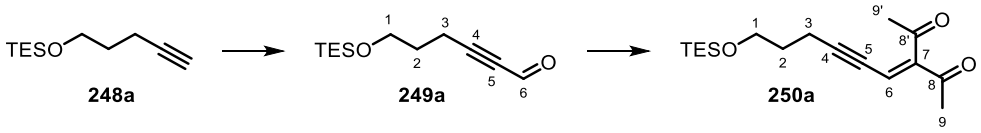
Furans 239 and 239'



To a mixture of ynenone **238** (49 mg, 0.24 mmol) and phenylphosphonic acid (3.6 mg, 23 μmol) was added a solution of tetrahydrothiophene (0.23 mL of a 0.50 M solution in CH_2Cl_2, 0.12 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford an inseparable mixture of furan **239** and **239'** (36 mg, 73%, 1.0:4.3 *dr*) as pale yellow oil.

R_f = 0.46 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (1H, s, CH-C7 **239'**), 6.36 (1H, s, CH-C7 **239**), 4.80 (1H, d, *J* = 7.4 Hz, CH-C8 **239**), 4.22 (1H, d, *J* = 8.2 Hz, CH-C8 **239'**), 4.07 (1H, ddd, *J* = 8.2, 8.2, 3.7 Hz, C*H*H-C12 **239**), 3.95–3.88 (2H, m, CH_2-C12 **239'**), 3.79 (1H, ddd, *J* = 8.3, 8.3, 7.0 Hz, CH*H*-C12 **239**), 2.51 (3H, s, CH_3-C5 **239'**), 2.50 (3H, s, CH_3-C5 **239**), 2.47–2.43 (1H, m, CH-C9 **239**), 2.39–2.32 (1H, m, CH-C9 **239'**), 2.32 (3H, s, CH_3-C1 **239**), 2.32 (3H, s, CH_3-C1 **239'**), 2.17 (1H, ddd, *J* = 7.0, 7.0, 4.4 Hz, C*H*H-C11 **239'**), 1.76–1.71 (1H, m, CH*H*-C11 **239**), 1.62 (1H, ddd, *J* = 12.0, 8.5, 8.5 Hz, C*H*H-C11 **239'**), 2.09–2.03 (1H, m, CH*H*-C11 **239**), 1.04 (3H, d, *J* = 6.7 Hz, CH_3-C10 **239'**), 0.78 (3H, d, *J* = 6.9 Hz, CH_3-C10 **239**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1 (C-C2 **239'**), 158.5 (C-C4 **239'**), 152.0 (C-C6 **239'**), 121.9 (C-C3 **239'**), 107.9 (CH-C7 **239'**), 80.5 (CH-C8 **239'**), 67.8 (CH_2-C12 **239'**), 38.4 (CH-C9 **239'**), 34.7 (CH-C11 **239'**), 29.1 (CH_3-C1 **239'**), 16.9 (CH_3-C10 **239'**), 14.5 (CH_3-C5 **239'**); ν_{max} (film) 2928, 1678, 1567, 1407, 1359, 1230, 1034 cm^{-1}; HMRS (ESI) calcd for $C_{12}H_{16}NaO_3$ $[M+Na]^+$ 231.0992, found 231.0995.

Ynenone 250a



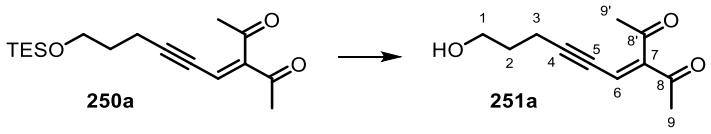
To a stirred solution of alkyne **248a** (1.8 g, 9.1 mmol) in THF (90 mL) at −78 °C was added *n*-BuLi (4.5 mL of a 2.4 M solution in hexanes, 9.1 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (1.4 mL, 18 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (90 mL). The mixture was diluted with EtOAc (45 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **249a** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.32 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (1H, t, *J* = 0.8 Hz, CH-C6), 3.70 (1H, t, *J* = 6.0 Hz, CH_2-C1), 2.53 (2H, td, *J* = 7.0, 0.8 Hz, CH_2-C3), 1.80 (2H, tt, *J* = 7.0, 6.0 Hz, CH_2-C2), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-TES).

To a stirred solution of crude acetylenic aldehyde **249a** and acetylacetone (0.89 mL, 8.7 mmol) in toluene (85 mL) at rt were added $MgSO_4$ (0.20 g, 1.7 mmol), piperidine (40 μL, 0.41 mmol) and acetic acid (0.29 mL, 5.1 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (90 mL). The mixture was diluted with Et_2O (40 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:3) to afford ynenone **250a** (2.1 g, 75% over 2 steps) as a pale yellow oil.

R_f = 0.45 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, *J* = 2.2 Hz, CH-C6), 3.66 (2H, t, *J* = 6.1 Hz, CH_2-C1), 2.53 (2H, td, *J* = 6.8, 2.2 Hz, CH_2-C3), 2.45 (3H, s, CH_3-C9'), 2.30 (3H, s, CH_3-C9), 1.76 (2H, tt, *J* = 6.8, 6.1 Hz, CH_2-C2), 0.94 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.58 (6H, q, *J* = 7.9 Hz, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (C-C8'), 195.9 (C-C8), 149.7 (C-C7), 123.3 (CH-C6), 110.1 (C-C4), 77.0 (C-C5), 61.1 (CH_2-C1), 31.3 (CH_2-C2), 31.0 (CH_3-C9'), 27.4 (CH_3-C9), 16.9 (CH_2-C3) 6.9 (CH_3-TES), 4.5 (CH_2-TES); ν_{max} (film) 2954, 2360, 1691, 1577, 1374, 1363, 1245 cm^{-1}; HMRS (CI, isobutane) calcd for $C_{17}H_{29}O_3Si$ $[M+H]^+$ 309.1886, found 309.1888.

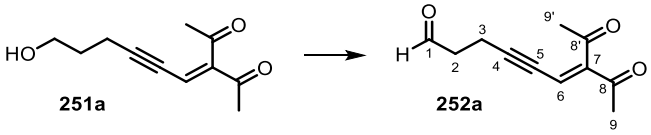
Alcohol 251a



To a stirred solution of protected alcohol **250a** (0.21 mg, 0.69 mmol) in MeOH (7 mL) at rt was added camphorsulfonic acid (8.0 mg, 34 μmol) in one portion. The mixture was stirred for 1 h and then filtered through a pad of silica and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **251a** (95 mg, 71%) as a pale yellow oil.

R_f = 0.08 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, t, *J* = 2.5 Hz, CH-C6), 3.70 (2H, br t, *J* = 6.1 Hz, CH_2-C1), 2.6 (2H, td, *J* = 6.9, 2.5 Hz, CH_2-C3), 2.43 (3H, s, CH_3-C9'), 2.29 (3H, s, CH_3-C9), 2.06 (1H, br s, OH), 1.79 (2H, tt, *J* = 6.9, 6.1 Hz, CH_2-C2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (C-C8'), 195.9 (C-C8), 149.8 (C-C7), 123.1 (CH-C6), 109.5 (C-C4), 77.1 (C-C5), 61.1 (CH_2-C1), 30.9 (CH_3-C9'), 30.7 (CH_2-C2), 27.1 (CH_3-C9), 16.8 (CH_2-C3); ν_{max} (film) 3420 (br), 2955, 1740, 1362, 1252, 1182 cm^{-1}; HMRS (CI, isobutane) calcd for $C_{11}H_{15}O_3$ $[M+H]^+$ 195.1021, found 195.1020.

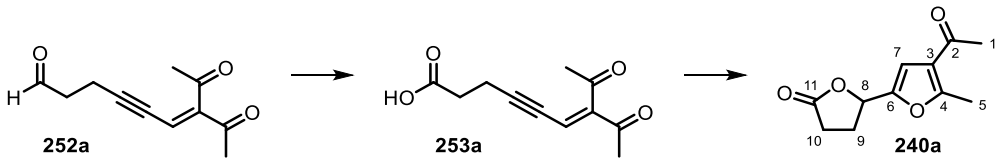
Aldehyde 252a



To a stirred solution of alcohol **251a** (82 mg, 0.42 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added DMP (0.32 g, 0.75 mmol) in small portions. The mixture was stirred at rt for 1 h and then the reaction was quenched by sequential addition of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL), stirred until two clear layers were obtained (*ca.* 30 min) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 1:1) to afford aldehyde **252a** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.27 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, t, *J* = 0.7 Hz, CH-C1), 6.58 (1H, t, *J* = 2.3 Hz, CH-C6), 2.70–2.69 (4H, m, CH_2-C2, CH_2-C3), 2.37 (3H, s, CH_3-C9'), 2.25 (3H, s, CH_3-C9).

Lactone 240a

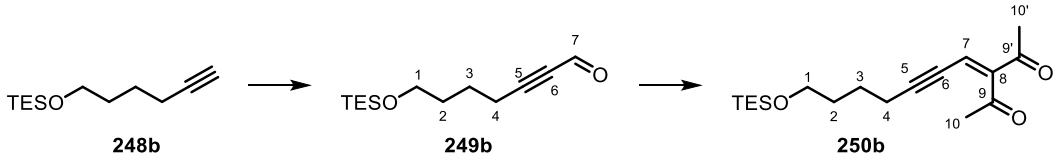


To a stirred solution of crude aldehyde **252a** in DMF (6 mL) at rt was added oxone (0.32 g, 0.52 mmol) in one portion. The mixture was stirred for 16 h and then the reaction was quenched by addition of 1 M HCl (10 mL). The mixture was diluted with EtOAc (10 mL) and the phases were separated. The organic phase was washed with brine (2 × 10 mL) and the organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude carboxylic acid **253a** as yellow oil. The carboxylic acid was used directly in the next step without further purification.
R_f = 0.19 (EtOAc).

To ynenone **253a** was added a solution of tetrahydrothiophene (0.42 mL of a 0.50 M solution in CH_2Cl_2, 0.21 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford lactone **240a** (17 mg, 38% over 3 steps) as a colourless solid.

R_f = 0.18 (petroleum ether-EtOAc, 1:1); m.p. = 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, s, CH-C7), 5.41 (1H, t, *J* = 7.2 Hz, CH-C8), 2.76–2.57 (2H, m, CH_2-C9/C10), 2.56 (3H, s, CH_3-C5), 2.54–2.42 (2H, m, CH_2-C9/C10), 2.37 (3H, s, CH_3-C1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7 (C-C2), 176.2 (C-C11), 159.4 (C-C4), 148.8 (C-C6), 122.2 (C-C3), 110.0 (CH-C7), 74.0 (CH-C8), 29.2 (CH_3-C1), 28.5 (CH_2-C9/C10), 26.5 (CH_2-C9/C10), 14.5 (CH_3-C5); ν_{max} (film) 1767, 1674, 1231, 1146 cm^{-1}; HMRS (ESI) calcd for $C_{11}H_{12}NaO_4$ $[M+Na]^+$ 231.0628, found 231.0619.

Ynenone 250b



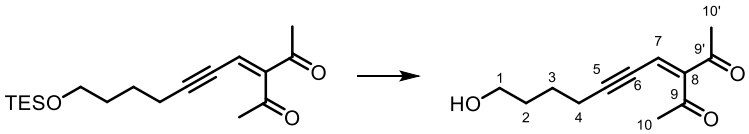
To a stirred solution of alkyne **248b** (2.7 g, 13 mmol) in THF (125 mL) at −78 °C was added *n*-BuLi (6.3 mL of a 2.4 M solution in hexanes, 15 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (1.9 mL, 25 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (130 mL). The mixture was diluted with EtOAc (60 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **249b** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.43 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (1H, t, *J* = 1.1 Hz, CH-C7), 3.65–3.61 (2H, m, CH_2-C1), 2.47–2.43 (2H, m, CH_2-C4), 1.71–1.57 (4H, m, CH_2-C2, CH_2-C3), 0.95 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.59 (6H, q, *J* = 7.9 Hz, CH_2-TES).

To a stirred solution of crude acetylenic aldehyde **249b** and acetylacetone (1.3 mL, 13 mmol) in toluene (125 mL) at rt were added $MgSO_4$ (0.30 g, 2.5 mmol), piperidine (60 μL, 0.61 mmol) and acetic acid (0.44 mL, 7.7 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (130 mL). The mixture was diluted with Et_2O (60 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:3) to afford ynenone **250b** (2.9 g, 73% over 2 steps) as a pale yellow oil.

R_f = 0.40 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, *J* = 2.4 Hz, CH-C7), 3.61 (2H, t, *J* = 5.6 Hz, CH_2-C1), 2.47–2.44 (2H, m, CH_2-C4), 2.45 (3H, s, CH_3-C10), 2.30 (3H, s, CH_3-C10'), 1.65–1.58 (4H, m, CH_2-C2, CH_2-C3), 0.94 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.58 (6H, q, *J* = 8.0 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4 (C-C9), 195.9 (C-C9'), 149.7 (C-C8), 123.3 (CH-C7), 110.3 (C-C5), 77.1 (C-C6), 62.2 (CH_2-C1), 32.0 (CH_2-C2/C3), 31.0 (CH_3-C10), 27.4 (CH_3-C10'), 24.9 (CH_2-C2/C3), 20.2 (CH_2-C4), 6.9 (3C, CH_3-TES), 4.5 (3C, CH_2-TES); ν_{max} (film) 2954, 2360, 1715, 1374, 1236, 1102 cm^{-1}; HMRS (CI, isobutane) calcd for $C_{18}H_{31}O_3Si$ $[M+H]^+$ 323.2042, found 323.2043.

Alcohol 251b

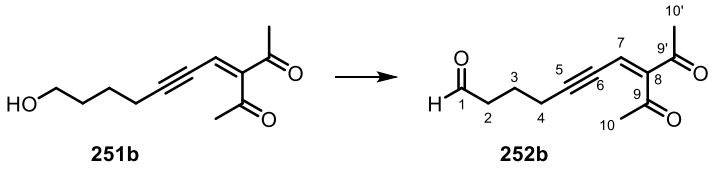


250b **251b**

To a stirred solution of protected alcohol **250b** (1.3 g, 4.2 mmol) in MeOH (42 mL) at rt was added camphorsulfonic acid (48 mg, 0.21 mmol) in one portion. The mixture was stirred for 1 h and then filtered through a pad of silica and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **251b** (0.68 mg, 79%) as a pale yellow oil.

R_f = 0.15 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, *J* = 2.4 Hz, CH-C7), 3.70–3.66 (2H, m, CH_2-C1), 2.51–2.47 (2H, m, CH_2-C4), 2.46 (3H, s, CH_3-C10), 2.32 (3H, s, CH_3-C10'), 1.68 (4H, m, CH_2-C2, CH_2-C3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8 (C-C9), 196.0 (C-C9'), 149.6 (C-C8), 123.2 (CH-C7), 110.1 (C-C5), 76.9 (C-C6), 61.8 (CH_2-C1), 31.6 (CH_2-C2/C3), 30.9 (CH_3-C10), 27.0 (CH_3-C10'), 24.4 (CH_2-C2/C3), 19.9 (CH_2-C4); ν_{max} (film) 3415 (br), 2941, 1695, 1355, 1247, 1183 cm^{-1}; HMRS (CI, isobutane) calcd for $C_{12}H_{17}O_3$ $[M+H]^+$ 209.1178, found 209.1176.

Aldehyde 252b

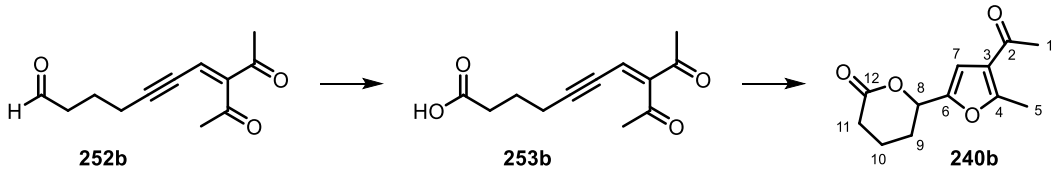


251b **252b**

To a stirred solution of alcohol **251b** (0.16 g, 0.76 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added DMP (0.53 g, 1.3 mmol) in small portions. The mixture was stirred at rt for 1 h and then the reaction was quenched by sequential addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (20 mL), then stirred until two clear layers were obtained (*ca.* 30 min) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 1:1) to afford aldehyde **252b** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.30 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.1 Hz, CH-C1), 6.64 (1H, t, *J* = 2.4 Hz, CH-C7), 2.60 (2H, td, *J* = 7.1, 1.1 Hz, CH_2-C2), 2.51 (2H, td, *J* = 6.9, 2.4 Hz, CH_2-C4), 2.43 (3H, s, CH_3-C10), 2.31 (3H, s, CH_3-C10'), 1.88 (2H, tt, *J* = 7.1, 6.9 Hz, CH_2-C3).

Lactone 240b

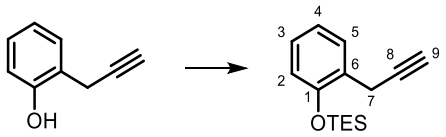


To a stirred solution of crude aldehyde **252b** in DMF (8 mL) at rt was added oxone (0.47 g, 0.76 mmol) in one portion. The mixture was stirred for 16 h and then the reaction was quenched by addition of 1 M HCl (20 mL). The mixture was diluted with EtOAc (10 mL) and the phases were separated. The organic phase was washed with brine (2 × 10 mL) and the organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude carboxylic acid **253b** as yellow oil. The carboxylic acid was used directly in the next step without further purification.
R_f = 0.19 (EtOAc).

To ynenone **253b** was added a solution of tetrahydrothiophene (0.80 mL of a 0.50 M solution in CH_2Cl_2, 0.40 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford lactone **240b** (82 mg, 47% over 3 steps) as a thick colourless gum.

R_f = 0.27 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (1H, s, CH-C7), 5.31 (1H, dd, J = 9.6, 4.2 Hz, CH-C8), 2.69–2.50 (2H, m, CH_2-C11), 2.56 (3H, s, CH_3-C5), 2.37 (3H, s, CH_3-C1), 2.19–1.87 (4H, m, CH_2-C9, CH_2-C10); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0 (C-C2), 170.4 (C-C12), 158.9 (C-C4), 149.5 (C-C6), 122.1 (C-C3), 108.9 (CH-C7), 74.6 (CH-C8), 29.6 (CH_2-C11), 29.2 (CH_3-C1), 26.2 (CH_2-C9), 18.4 (CH_2-C10), 14.5 (CH_3-C5); ν_{max} (film) 1732, 1674, 1564 cm^{-1}; HMRS (ESI) calcd for $C_{12}H_{14}O_4$ $[M+Na]^+$ 245.0784, found 245.0781.

Alkyne 255a

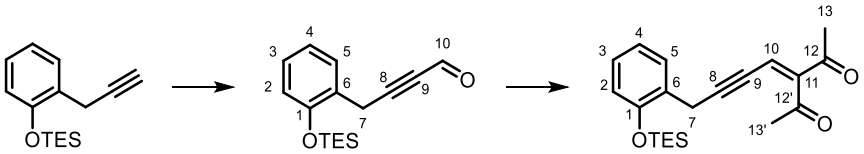


254a **255a**

To a stirred solution of phenol **254a** (0.80 g, 6.1 mmol) in CH_2Cl_2 (25 mL) at rt were sequentially added DMAP (15 mg, 0.12 mmol), Et_3N (1.0 ml, 7.3 mmol) and TESCl (1.2 mL, 7.3 mmol). The mixture was stirred for 16 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (25 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford protected phenol **255a** (1.56 g, 95%) as a pale yellow oil.

R_f = 0.36 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* =7.6, 1.7 Hz, CH-C5), 7.14 (1H, ddd, *J* = 8.0, 7.5, 1.7 Hz, CH-C3), 6.96 (1H, ddd, *J* = 7.6, 7.5, 1.1 Hz, CH-C4), 6.80 (1H, dd, *J* = 8.0, 1.1 Hz, CH-C2), 3.58 (2H, d, *J* = 2.7 Hz, CH_2-C7), 2.17 (1H, t, *J* = 2.7 Hz, CH-C9), 1.02 (9H, t, *J* = 8.1 Hz, CH_3-TES), 0.80 (6H, q, *J* = 8.1 Hz, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (C-C1), 129.2 (CH-C5), 127.9 (CH-C3), 126.8 (C-C6), 121.3 (CH-C4), 118.1 (CH-C2), 82.2 (C-C8), 70.3 (CH-C9), 19.8 (CH_2-C7), 6.8 (3C, CH_3-TES), 5.5 (3C, CH_3-TES); ν_{max} (film) 2957, 1489, 1454 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}NaOSi$ $[M+Na]^+$ 269.1332, found 269.1328.

Ynenone 257a



255a **256a** **257a**

To a stirred solution of alkyne **255a** (0.39 mg, 1.6 mmol) in THF (16 mL) at −78 °C was added *n*-BuLi (1.1 mL of a 2.1 M solution in hexanes, 2.3 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.24 mL, 3.1 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by pouring the solution into a mixture of 10% aqueous KH_2PO_4 (40 mL) and EtOAc (15 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **256a** as a yellow oil. The aldehyde was used immediately in the next step without further purification.

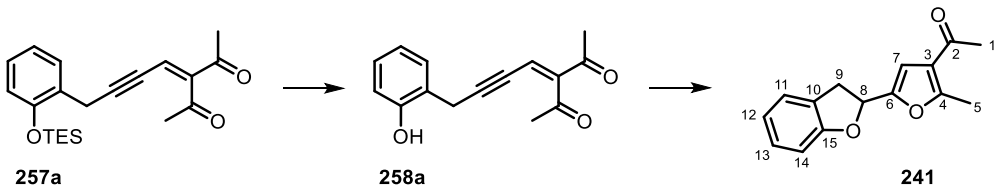
R_f = 0.30 (petroleum ether-EtOAc, 10:1).

To a stirred solution of crude acetylenic aldehyde **256a** and acetylacetone (0.16 mL, 1.6 mmol) in toluene (16 mL) at rt were added $MgSO_4$ (38 mg, 0.32 mmol), piperidine (15 μL, 0.15 mmol) and acetic acid (53 μL, 0.93 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (30 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **257a** (0.18 g, 32% over 2 steps) as a pale yellow oil.

R_f = 0.11 (petroleum ether-EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 7.6, 1.7 Hz, CH-C5), 7.14 (1H, ddd, *J* = 7.9, 7.7, 1.7 Hz, CH-C3), 6.94 (1H, ddd, *J* =

7.7, 7.6, 1.1 Hz, CH- C4), 6.80 (1H, dd, *J* = 7.9, 1.1 Hz, CH-C2), 6.75 (1H, t, *J* = 2.5 Hz, CH-C10), 3.80 (2H, d, *J* = 2.5 Hz, CH_2-C7), 2.45 (3H, s, CH_3-C13'), 2.32 (3H, s, CH_3-C13), 1.02–0.98 (9H, m, CH_3-TES), 0.81–0.75 (6H, m, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4 (C-C12'), 195.9 (C-C12), 153.2 (C-C1), 149.9 (C-C11), 129.3 (CH-C5), 128.3 (CH-C3), 125.7 (C-C6), 123.1 (CH-C10), 121.4 (CH-C4), 118.2 (CH-C2), 107.8 (C-C8), 78.4 (C-C9), 31.1 (CH_3-C13'), 27.5 (CH_3-C13), 21.5 (CH_2-C7), 6.8 (3C, CH_3-TES), 5.5 (3C, CH_2-TES); ν_{max} (film) 2957, 1717, 1692, 1667, 1584, 1489, 1452, 1416 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{28}O_3Si$ $[M]^+$ 356.1808 ,found 356.1810.

Furan 241



257a **258a** **241**

To a stirred solution of protected phenol **257a** (98 mg, 0.28 mmol) in MeOH (5 mL) at rt was added camphorsulfonic acid (13 mg, 56 μmol) in one portion. The mixture was stirred until consumption of the starting material was complete (TLC analysis). The reaction was quenched by pouring the solution into a mixture of water (20 mL), saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL). The mixture was stirred for 10 min and then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL) dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude ynenone **258a** as a yellow oil. The ynenone was used immediately in the next step without further purification.

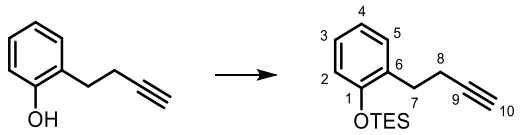
R_f = 0.12 (petroleum ether-EtOAc, 5:1).

To a mixture of ynenone **258a** and phenylphosphonic acid (4.3 mg, 27 μmol) was added a solution of tetrahydrothiophene (0.30 mL of a 0.50 M solution in CH_2Cl_2, 0.15 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced

pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford furan **241** (39 mg, 59%).

R_f = 0.07 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 7.5, 0.8 Hz, CH-C11), 7.15 (1H, ddd, *J* = 7.9, 7.5, 0.8 Hz, CH-C13), 6.90 (1H, ddd, *J* = 7.5, 7.5, 0.8 Hz, CH-C12), 6.82 (1H, br d, *J* = 7.9 Hz, CH14), 6.64 (1H, s, CH-C7), 5.68 (1H, dd, *J* = 9.2, 8.6 Hz, CH-C8), 3.51 (1H, dd, *J* = 15.6, 9.2 Hz, C*H*H-C9), 3.47 (1H, dd, *J* = 15.6, 8.6 Hz, CH*H*-C9), 2.59 (3H, s, CH_3-C5), 2.39 (3H, s, CH_3-C1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0 (C-C2), 159.3 (C-C4), 158.9 (C-C6), 151.0 (C-C15), 128.5 (CH-C13), 126.0 (C-C10), 124.9 (CH-C11), 122.2 (C-C3), 121.1 (CH-C12), 109.8 (CH-C14), 109.0 (CH-C7), 76.7 (CH-C8) 34.3 (CH_2-C9), 29.3 (CH_3-C1), 14.7 (CH_3-C5); ν_{max} (film) 1676, 1599, 1564, 1479, 1460 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{14}NaO_3$ $[M+Na]^+$ 265.0835, found 265.0830.

Alkyne 255b

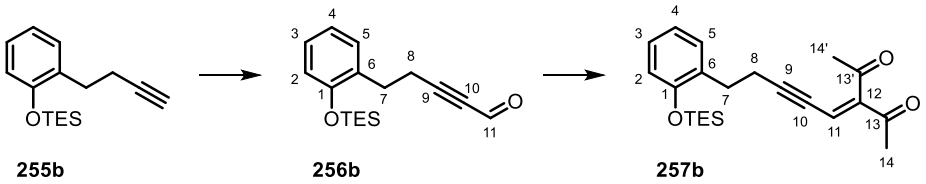


254b **255b**

To a stirred solution of phenol **254b** (0.10 g, 0.71 mmol) in CH_2Cl_2 (3 mL) at rt were sequentially added DMAP (1.7 mg, 0.014 mmol), Et_3N (0.12 ml, 0.86 mmol) and TESCl (0.14 mL, 0.83 mmol). The mixture was stirred for 16 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford the protected phenol **255b** (0.18 mg, 98%) as a colourless oil.

R_f = 0.17 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (1H, dd, *J* = 7.4, 1.7 Hz, CH-C5), 7.09 (1H, ddd, *J* = 7.9, 7.6, 1.7 Hz, CH-C3), 6.88 (1H, ddd, *J* = 7.6, 7.4, 1.1 Hz, CH-C4), 6.78 (1H, dd, *J* = 7.9, 1.1 Hz, CH-C2), 2.83 (2H, t, *J* = 7.8 Hz, CH_2-C7), 2.46 (2H, td, *J* = 7.8, 2.6 Hz, CH_2-C8), 1.95 (1H, t, *J* = 2.6 Hz, CH-C10), 1.03–0.99 (9H, m, CH_3-TES), 0.82–0.75 (6H, m, CH_2-TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (C-C1), 130.9 (C-C6), 130.4 (CH-C5), 127.6 (CH-C3), 121.0 (CH-C4), 118.3 (CH-C2), 84.5 (C-C9), 68.5 (CH-C10), 30.4 (CH_2-C7), 19.0 (CH_2-C8), 6.9 (3C, CH_3-TES), 5.5 (3C, CH_2-TES); ν_{max} (film) 2956, 1490, 1454 cm^{-1}; HMRS (EI) calcd for $C_{16}H_{24}OSi$ $[M]^+$ 260.1596, found 260.1584.

Ynenone 257b



To a stirred solution of alkyne **255b** (0.45 mg, 1.7 mmol) in THF (17 mL) at −78 °C was added *n*-BuLi (1.4 mL of a 2.3 M solution in hexanes, 3.2 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.29 mL, 3.8 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by pouring the solution into a mixture of 10% aqueous KH_2PO_4 (50 mL) and Et_2O (20 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **256b** as a yellow oil. The aldehyde was used immediately in the next step without further purification.

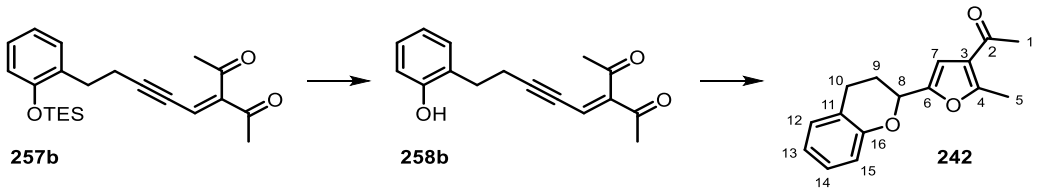
R_f = 0.38 (petroleum ether-EtOAc, 10:1).

To a stirred solution of crude acetylenic aldehyde **256b** and acetylacetone (0.18 mL, 1.8 mmol) in toluene (17 mL) at rt were added $MgSO_4$ (42 mg, 0.35 mmol), piperidine (16 μL, 0.16 mmol) and acetic acid (58 μL, 1.0 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (30 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford ynenone **257b** (0.31 g, 48% over 2 steps) as a pale yellow oil.

R_f = 0.33 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (2H, dd, *J* = 7.6, 1.7 Hz, CH-C5), 7.10 (1H, ddd, *J* = 7.9, 7.8, 1.7 Hz, CH-C3), 6.88 (1H, ddd, *J* =

7.9, 7.6, 1.1 Hz, CH-C4), 6.78 (1H, dd, *J* = 7.8, 1.1 Hz, CH-C2), 6.69 (1H, t, *J* = 2.5 Hz, CH-C11), 2.85 (2H, t, *J* = 7.5 Hz, CH-C7), 2.73 (2H, td, *J* = 7.5, 2.5 Hz, CH-C8), 2.38 (3H, s, CH_3-C14'), 2.30 (3H, s, CH_3-C14), 1.02–0.98 (9H, m, CH_3-TES), 0.81–0.75 (6H, m, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4 (C-C13'), 195.9 (C-C13), 153.9 (C-C1), 149.5 (C-C12), 130.4 (CH-C5), 130.2 (C-C6), 127.9 (CH-C3), 123.3 (CH-C11), 121.2 (CH-C4), 118.3 (CH-C2), 110.1 (C-C9), 77.3 (C-C10), 31.0 (CH_3-C14'), 30.0 (CH_2-C7), 27.5 (CH_3-C14), 20.6 (CH_2-C8), 6.8 (3C, CH_3-TES), 5.5 (3C, CH_2-TES); ν_{max} (film) 2957, 1717, 1691, 1666, 1582, 1490, 1454, 1416, 1359, 1248, 1153, 1106 cm^{-1}; HMRS (ESI) calcd for $C_{22}H_{30}NaO_3Si$ $[M+Na]^+$ 393.1856, found 393.1839.

Furan 242



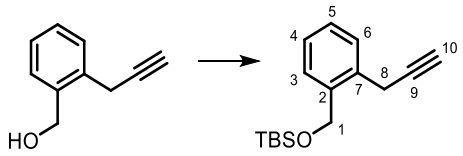
To a stirred solution of protected phenol **257b** (0.50 mg, 0.14 mmol) in MeOH (14 mL) at rt was added camphorsulfonic acid (6.5 mg, 28 μmol) in one portion. The mixture was stirred until consumption of the starting material was complete (TLC analysis). The reaction was quenched by pouring the solution into a mixture of water (60 mL), saturated aqueous $NaHCO_3$ (15 mL) and CH_2Cl_2 (20 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine (3 × 20 mL) dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude ynenone **258b** as a yellow oil. The ynenone was used immediately in the next step without further purification.
R_f = 0.10 (petroleum ether-EtOAc, 10:1)

To ynenone **258b** and phenylphosphonic acid (2.0 mg, 13 μmol) was added a solution of tetrahydrothiophene (0.14 mL of a 0.50 M solution in CH_2Cl_2, 0.070 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford furan **242** (20 mg, 54% over 2 steps) as a colourless oil.

R_f = 0.28 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.07 (2H, m, CH-C12, CH-C14), 6.90–6.86 (2H, m, CH-C13, CH-C15), 6.60 (1H, s, CH-C7), 5.05 (1H, dd, *J* = 8.1, 4.3 Hz, CH-C8), 2.96 (1H, ddd, *J* = 16.6, 8.4, 8.4 Hz, C*H*H-C10), 2.85 (1H, ddd, *J* = 16.6, 4.7, 4.7 Hz, CH*H*-C10), 2.60 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1), 2.30–2.24 (2H, m, CH_2-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2 (C-C2), 158.5 (C-C4), 154.4 (C-C6), 151.7 (C-C16), 129.7 (CH-C12), 127.6 (CH-C14), 122.2 (C-C3), 121.5 (C-C11), 120.9 (CH-C13), 117.1 (CH-C15), 108.1 (CH-C7), 71.0 (CH-C8), 29.3 (CH_3-

C1), 26.0 (CH_2-C9), 24.6 (CH_2-C10), 14.6 (CH_3-C5); ν_{max} (film) 2925, 1679, 1583, 1566, 1488, 1457 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{16}NaO_3$ $[M+Na]^+$ 279.0992, found 279.0986.

Alkyne 255c

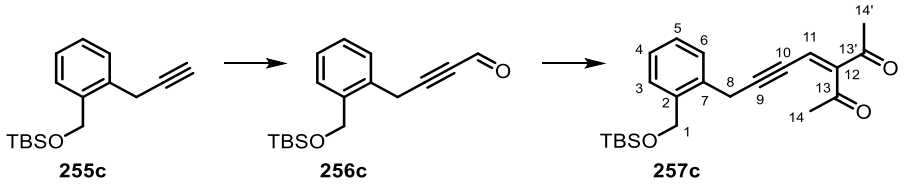


254c **255c**

To a stirred solution of alcohol **254c** (0.40 g, 2.8 mmol) in DMF (5.5 mL) at rt were sequentially added imidazole (0.28 g, 4.1 mmol) and TBSCl (0.50 g, 3.3 mmol). The mixture was stirred for 2 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was diluted with Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford protected alcohol **255c** (0.68 g, 95%) as a pale yellow oil.

R_f = 0.05 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (1H, m, CH-C6), 7.46–7.44 (1H, m, CH-C3), 7.32–7.29 (2H, m, CH-C4, CH-C5), 4.81 (2H, s, CH_2-C1), 3.65 (2H, d, *J* = 2.7 Hz, CH_2-C8), 2.21 (1H, t, *J* = 2.7 Hz, CH-C10), 0.99 (9H, s, CH_3-*t*-Bu-TBS), 0.14 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7 (C-C2), 133.7 (C-C7), 128.6 (CH-C6), 127.6 (CH-C3), 127.3 (CH-C5), 127.1 (CH-C4), 81.7 (C-C9), 70.8 (CH-C10), 63.3 (CH_2-C1), 26.1 (3C, CH_3-*t*-Bu-TBS), 22.0 (CH_2-C8), 18.5 (C-*t*-Bu-TBS), −5.1 (CH_3-TBS), −5.1 (CH_3-TBS); ν_{max} (film) 2928, 1253, 1117, 1047 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{24}NaOSi$ $[M+Na]^+$ 283.1489, found 283.1482.

Ynenone 257c



To a stirred solution of alkyne **255c** (0.21 g, 0.81 mmol) in THF (8 mL) at −78 °C was added *n*-BuLi (0.54 mL of a 2.3 M solution in hexanes, 1.2 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.12 mL, 1.6 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by pouring the solution into a mixture of 10% aqueous KH_2PO_4 (20 mL) and Et_2O (10 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **256c** as a yellow oil. The aldehyde was used immediately in the next step without further purification.

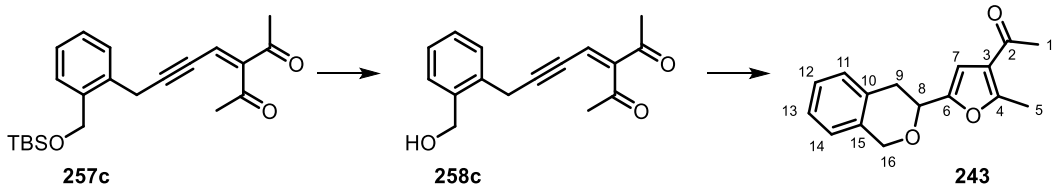
R_f = 0.44 (petroleum ether-EtOAc, 10:1).

To a stirred solution of crude acetylenic aldehyde **256c** and acetylacetone (42 μL, 0.41 mmol) in toluene (4 mL) at rt were added $MgSO_4$ (10 mg, 83 μmol), piperidine (4.0 μL, 41 μmol) and acetic acid (14 μL, 0.25 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (10 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **257c** (49 mg, 16%) as a pale yellow oil.

R_f = 0.13 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.36 (2H, m, CH-C3, CH-C6), 7.30–7.27 (2H, m, CH-C4, CH-C5), 6.72 (1H, t, *J* = 2.5 Hz, CH-

C11), 4.74 (2H, s, CH_2-C1), 3.88 (2H, d, J = 2.5 Hz, CH_2-C8), 2.42 (3H, s, CH_3-C14), 2.32 (3H, s, CH_3-C14'), 0.92 (9H, s, CH_3-*t*-Bu-TBS), 0.09 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (C-C13'), 195.8 (C-C13), 150.1 (C-C12), 138.6 (C-C2), 132.0 (C-C7), 128.7 (CH-C5/C6), 127.9 (CH-C5/C6), 127.8 (CH-C3/C4), 127.4 (CH-C3/C4), 122.8 (CH-C11), 106.9 (C-C9), 78.8 (C-C10), 63.5 (CH_2-C1), 31.1 (CH_3-C14'), 27.4 (CH_3-C14), 26.1 (3C, CH_3-*t*-Bu-TBS), 23.6 (CH_2-C8), 18.5 (C-*t*-Bu-TBS), −5.1 (CH_3-TBS), −5.1 (CH_3-TBS); ν_{max} (film) 2932, 1667, 1373, 1250 cm^{-1}; HMRS (ESI) calcd for $C_{22}H_{30}NaO_3Si$ $[M+Na]^+$ 393.1856, found 393.1838.

Furan 243



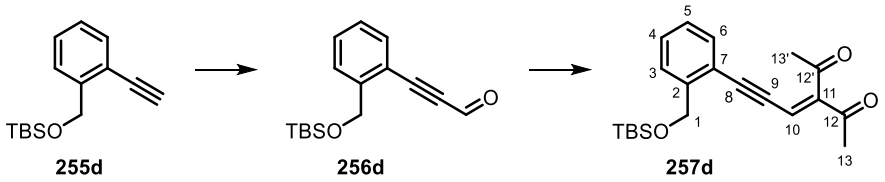
To a stirred solution of protected alcohol **257c** (43 mg, 0.12 mmol) in MeOH/CH_2Cl_2 (v/v 5:2, 1.2 mL) at rt was added camphorsulfonic acid (5.4 mg, 23 μmol) in one portion. The mixture was stirred until consumption of the starting material was complete (TLC analysis). The reaction was quenched by pouring the solution into a mixture of water (15 mL), saturated aqueous $NaHCO_3$ (3 mL) and CH_2Cl_2 (5 mL). The mixture was stirred for 10 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (3 × 5 mL) dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude ynenone **258c** as a yellow oil. The ynenone was used immediately in the next step without further purification.
R_f = 0.16 (petroleum ether-EtOAc, 3:2).

To a mixture of ynenone **258c** and phenylphosphonic acid (1.8 mg, 12 mmol) was added a solution of tetrahydrothiophene (0.12 mL of a 0.50 M solution in CH_2Cl_2, 60 μmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford furan **243** (14 mg, 47% over 2 steps) as a colourless oil.

R_f = 0.20 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.16 (3H, m, CH-C11, CH-C12, CH-C13), 7.05–7.03 (1H, m, CH-C14), 6.60 (1H, s, CH-C7), 4.98 (1H, d, *J* = 15.2 Hz, C*H*H-C16), 4.92 (1H, d, *J* = 15.2 Hz, CH*H*-C16), 4.77 (1H, dd, *J* = 10.7, 3.5 Hz, CH-C8), 3.30 (1H, dd, *J* = 16.2, 10.7 Hz, C*H*H-C9), 3.00 (1H, dd, *J* = 16.2, 3.5 Hz, CH*H*-C9), 2.62 (3H, s, CH_3-C5), 2.40 (3H, s, CH_3-C1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (C-C2), 158.7 (C-C4), 152.0 (C-C6), 134.1 (C-C10), 132.3 (C-C15),

129.0 (CH-C11), 126.8 (CH-C12/C13), 126.6 (CH-C12/C13), 124.4 (CH-C14), 122.1 (C-C3), 108.1 (CH-C7), 69.8 (CH-C8), 68.3 (CH_2-C16), 31.7 (CH_2-C9), 29.3 (CH_3-C1), 14.6 (CH_3-C5); ν_{max} (film) 2928, 1676, 1566, 1230, 1086 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{16}NaO_3$ $[M+Na]^+$ 279.0992, found 279.0984.

Ynenone 257d



To a stirred solution of alkyne **255d** (2.0 g, 8.12 mmol) in THF (80 mL) at −78 °C was added *n*-BuLi (6.0 mL of a 2.0 M solution in hexanes, 12 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (1.2 mL, 16 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by pouring the solution into a mixture of 10% aqueous KH_2PO_4 (160 mL) and Et_2O (40 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with brine (2 × 40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **256d** as a yellow oil. The aldehyde was used immediately in the next step without further purification.

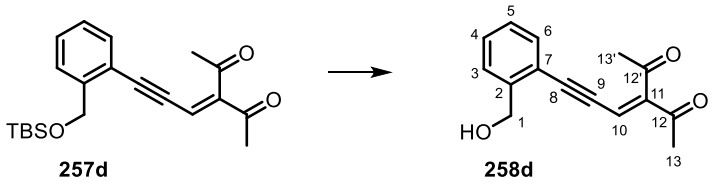
R_f = 0.43 (petroleum ether-EtOAc, 5:1).

To a stirred solution of crude acetylenic aldehyde **256d** and acetylacetone (0.84 mL, 8.1 mmol) in toluene (80 mL) at rt were added $MgSO_4$ (0.20 g, 1.6 mmol), piperidine (40 μL, 0.41 mmol) and acetic acid (0.28 mL, 4.9 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (80 mL). The mixture was diluted with Et_2O (40 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford ynenone **257d** (1.8 g, 62% over 2 steps) as a pale yellow oil.

R_f = 0.22 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 7.6 Hz, CH-C3), 7.43 (1H, dd, *J* = 7.6, 7.5 Hz, CH-C5), 7.43 (1H, d, *J* = 7.6 Hz, CH-

C6), 7.24 (1H, dd, *J* = 7.6, 7.5 Hz, CH-C4), 6.93 (1H, s, CH-C10), 4.85 (2H, s, CH_2-C1), 2.53 (3H, s, CH_3-C13'), 2.37 (3H, s, CH_3-C13), 0.96 (9H, s, CH_3-*t*-Bu-TBS), 0.14 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.8 (C-C12'), 195.7 (C-C12), 149.5 (C-C11), 144.5 (C-C2), 132.6 (CH-C6), 130.6 (CH-C5), 126.8 (CH-C4), 126.2 (CH-C3), 122.2 (CH-C10), 118.4 (C-C7), 104.5 (C-C8), 89.7 (C-C9), 63.1 (CH-C1), 31.1 (CH_3-C13'), 27.3 (CH_3-C13), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), −5.2 (CH_3-TBS), −5.2 (CH_3-TBS); ν_{max} (film) 2929, 1692, 1665, 1578 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{28}NaO_3Si$ $[M+Na]^+$ 379.1700, found 379.1682.

Alcohol 258d

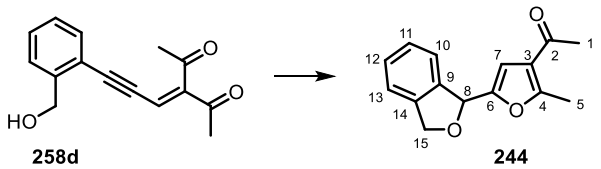


To a stirred solution of protected alcohol **257d** (1.8 g, 5.0 mmol) in MeOH/CH_2Cl_2 (v/v 5:2, 50 mL) at rt was added camphorsulfonic acid (23 mg, 1.0 mmol) in one portion. The mixture was stirred until consumption of the starting material was complete (TLC analysis). The mixture was filtered through a pad of silica and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **258d** (0.94 g, 77%) as a pale yellow solid.

R_f = 0.27 (petroleum ether-EtOAc, 1:1); m.p. = 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.47 (2H, m, CH-C3, CH-C6), 7.43 (1H, ddd, *J* = 7.6, 7.5, 1.1 Hz, CH-C4/C5), 7.30 (1H, ddd, *J* = 7.6, 7.5, 1.1 Hz, CH-C4/C5), 6.92 (1H, s, CH-C10), 4.79 (2H, d, *J* = 6.4 Hz, CH_2-C1), 2.76 (1H, t, *J* = 6.4 Hz, OH), 2.51 (3H, s, CH_3-C13'), 2.40 (3H, s, CH_3-C13); ν_{max} (film) 3439 (br), 2187, 1707, 1663, 1601, 1582 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{14}NaO_3$ $[M+Na]^+$ 265.0835, found 265.0830.

The ^{13}C NMR could not be obtained.

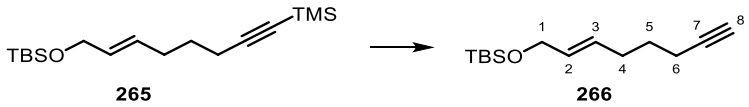
Furan 244



To a mixture of ynenone **258d** (84 mg, 0.35 mmol) and phenylphosphonic acid (5.5 mg, 35 μmol) was added a solution of tetrahydrothiophene (0.35 mL of a 0.50 M solution in CH_2Cl_2, 0.18 mmol). The mixture was stirred at 40 °C for 48 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford furan **244** (52 mg, 61%) as a pale yellow oil.

R_f = 0.17 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (3H, m, CH-C11, CH-C12, CH-C13/C10), 7.21 (1H, dd, *J* = 7.4, 0.8 Hz, CH-C13/C10), 6.44 (1H, s, CH-C7), 6.17 (1H, dd, *J* = 2.4, 2.2 Hz, CH-C8), 5.26 (1H, dd, *J* = 12.1, 2.4 Hz, C*H*H-C15), 5.16 (1H, d, *J* = 12.1, 2.2 Hz, CH*H*-C15), 2.56 (3H, s, CH_3-C5), 2.36 (3H, s, CH_3-C1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1 (C-C2), 159.3 (C-C4), 152.2 (C-C6), 139.8 (C-C9), 138.2 (C-C14), 128.4 (CH-C12/C11), 127.7 (CH-C12/C11), 122.4 (CH-C13/C10), 122.1 (C-C3), 121.3 (CH-C13/C10), 108.7 (CH-C7), 78.9 (CH-C8), 73.1 (CH_2-15), 29.2 (CH_3-C1), 14.7 (CH_3-C5); ν_{max} (film) 1675, 1561, 1229, 1020 cm^{-1}; HMRS (ESI) calcd for $C_{15}H_{14}NaO_3$ $[M+Na]^+$ 265.0835, found 265.0822.

Alkyne 266

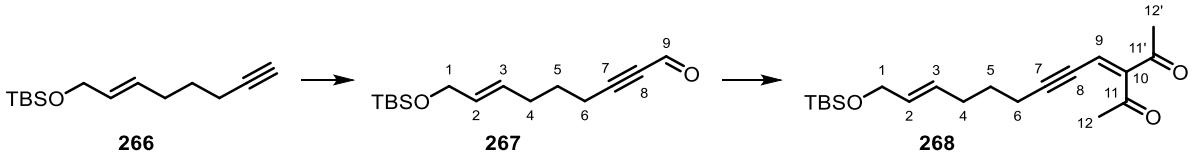


To a stirred solution of alkene **265** (2.0 g, 6.5 mmol) in MeOH (65 mL) at rt was added K_2CO_3 (0.99 g, 7.2 mmol) in one portion. The mixture was stirred for 12 h and then the reaction was quenched by addition of water (70 mL). The mixture was diluted with Et_2O (30 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford alkyne **266** (1.5 g, 96%) as a colourless oil.

R_f = 0.04 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66–5.54 (2H, m, CH-C2, CH-C3), 4.13–4.12 (2H, m, CH_2-C1), 2.20 (2H, td, *J* = 7.2, 2.7 Hz, CH_2-C6), 2.17–2.12 (2H, m, CH_2-C4), 1.95 (1H, t, *J* = 2.7 Hz, CH-C8), 1.61 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C5), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.3 (CH-C2/C3), 130.0 (CH-C2/C3), 84.4 (C-C7), 68.5 (CH-C8), 64.0 (CH_2-C1), 31.2 (CH_2-C4), 28.1 (CH_2-C5), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.0 (CH_2-C6), −5.0 (CH_3-TBS), −5.0 (CH_3-TBS); ν_{max} (film) 2930, 1472, 1250, 1096, 1059 cm^{-1}.

The mass could not be obtained.

Ynenone 268



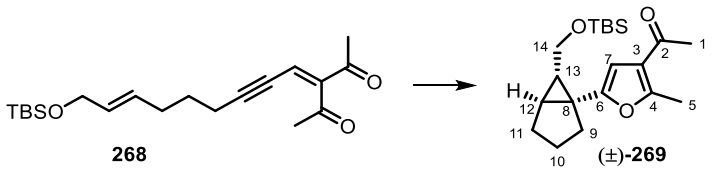
To a stirred solution of alkyne **266** (2.3 g, 9.7 mmol) in THF (96 mL) at −78 °C was added *n*-BuLi (6.6 mL of a 2.2 M solution in hexanes, 15 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (1.5 mL, 19 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (100 mL). The mixture was diluted with EtOAc (50 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **267** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.29 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (H, t, *J* = 0.8 Hz, CH-C9), 5.63–5.56 (2H, m, CH-C2, CH-C3), 4.13–4.12 (2H, m, CH_2-C1), 2.42 (2H, td, *J* = 7.2, 0.8 Hz, CH_2-C6), 2.18–2.09 (2H, m, CH_2-C4), 1.69 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C5), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (6H, s, CH_3-TBS).

To a stirred solution of crude acetylenic aldehyde **267** and acetylacetone (0.99 mL, 9.6 mmol) in toluene (10 mL) at rt were added $MgSO_4$ (0.23 g, 1.9 mmol) and EDDA (0.17 g, 0.99 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (30 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **268** (2.3 g, 69%) as a pale yellow oil.

R_f = 0.09 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (1H, t, *J* = 2.5 Hz, CH-C9), 5.62–5.53 (2H, m, CH-C2, CH-C3), 4.11 (2H, d, *J* = 3.7 Hz, CH_2-C1), 2.45 (3H, s, CH_3-C12), 2.43 (2H, td, *J* = 7.2, 2.5 Hz, CH_2-C6), 2.30 (3H, s, CH_3-C12'), 2.13 (2H, dt, *J* = 6.9, 7.1 Hz, CH_2-C4), 1.64 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C5), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4 (C-C11), 195.9 (C-C11'), 149.7 (C-C10), 130.7 (CH-C2/C3), 129.4 (CH-C2/C3), 123.3 (CH-C9), 110.1 (C-C7), 77.2 (C-C8), 63.9 (CH_2-C1), 31.3 (CH_2-C4), 31.1 (CH_3-C12), 27.7 (CH_2-C5), 27.3 (CH_3-C12'), 26.1 (3C, CH_3-t-Bu-TBS), 19.7 (CH_2-C6), 18.6 (C-*t*-Bu-TBS), −5.0 (CH_3-TBS), −5.0 (CH_3-TBS); ν_{max} (film) 2957, 2362, 1677, 1572 cm^{-1}; HMRS (ESI) calcd for $C_{20}H_{32}NaO_3Si$ $[M+Na]^+$ 371.2013, found 371.1997.

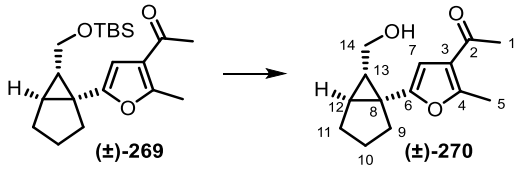
Furan 269



To a stirred solution of ynenone **268** (2.0 g, 5.8 mmol) in CH_2Cl_2 (23 mL) at rt was added chloroacetic acid (0.55 g, 5.8 mmol) in one portion. The mixture was stirred at 40 °C for 4 d and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford furan **269** (1.8 g, 87%) as a pale yellow oil.

R_f = 0.45 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (1H, s, CH-C7), 3.60 (1H, dd, *J* = 11.0, 6.4 Hz, C*H*H-C14), 3.44 (1H, dd, *J* = 11.0, 7.8 Hz, CH*H*-C14), 2.53 (3H, s, CH_3-C5), 2.36 (3H, s, CH_3-C1), 2.13 (1H, dd, *J* = 12.5, 8.0 Hz, C*H*H-C9), 1.89–1.81 (3H, m, CH_2-C11, CH*H*-C9), 1.71 (1H, ddd, *J* = 12.5, 8.0, 8.0 Hz, C*H*H-C10), 1.53 (1H, dd, *J* = 4.0, 4.0 Hz, CH-C12), 1.38–1.30 (2H, m, CH*H*-C10, CH-C13); 0.84 (9H, s, CH_3-*t*-Bu-TBS), −0.03 (3H, s, CH_3-TBS), −0.04 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5 (C-C2), 157.0 (C-C4), 154.6 (C-C6), 122.0 (C-C3), 106.4 (CH-C7), 62.8 (CH_2-C14), 33.0 (CH_2-C9), 30.7 (C-C8), 29.3 (CH_3-C1), 29.0 (CH-C12), 27.8 (CH-C13), 27.5 (CH_2-C11), 26.0 (3C, CH_3-*t*-Bu-TBS), 22.0 (CH_2-C10), 18.4 (C-*t*-Bu-TBS) 14.6 (CH_3-C5), −5.1 (CH_3-TBS), −5.2 (CH_3-TBS); ν_{max} (film) 2928, 1678, 1570 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{32}O_3Si$ $[M]^+$ 348.2121, found 348.2125.

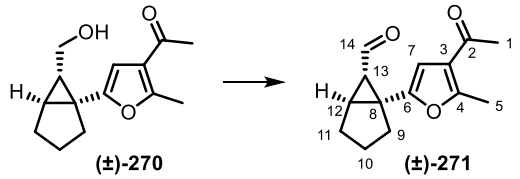
Alcohol 270



To a stirred solution of protected alcohol **269** in (0.25 g, 0.71 mmol) in MeOH/CH_2Cl_2 (v/v 5:2, 7 mL) at rt was added camphorsulfonic acid (32 mg, 0.14 mmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of water (20 mL) and saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 2:1) to afford alcohol **270** (0.15 g, 91%) as a colourless oil.

R_f = 0.08 (petroleum ether-EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (1H, s, CH-C7), 3.69 (1H, ddd, *J* = 12.0, 6.5, 6.5 Hz, C*H*H-C14), 3.36 (1H, ddd, *J* = 12.0, 8.8, 3.3 Hz, CH*H*-C14), 2.55 (3H, s, CH_3-C5), 2.37 (3H, s, CH_3-C1), 2.16 (1H, dd, *J* = 12.4, 8.0 Hz, C*H*H-C9), 1.90–1.82 (3H, m, CH*H*-C9, CH_2-C11), 1.74 (1H, ddd, *J* = 13.2, 8.1, 8.0 Hz, C*H*H-C10), 1.59 (1H, dd, *J* = 4.0, 4.0 Hz, CH-C12), 1.44–1.40 (1H, m, CH-C13), 1.39–1.32 (2H, m, CH*H*-C10, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3 (C-C2), 157.2 (C-C4), 154.5 (C-C6), 122.2 (C-C3), 106.9 (CH-C7), 62.8 (CH_2-C14), 33.1 (CH_2-C9), 30.6 (C-C8), 29.3 (CH_3-C1), 29.2 (CH-C12), 27.8 (CH-C13), 27.4 (CH_2-C11), 22.1 (CH_2-C10), 14.6 (CH_3-C5); ν_{max} (film) 3410 (br), 2928, 1663, 1566 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_3$ $[M]^+$ 234.1256, found 234.1257.

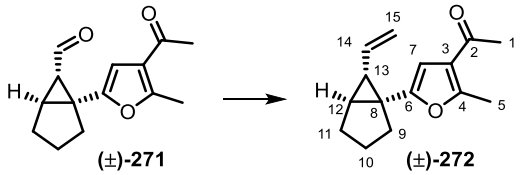
Aldehyde 271



To a stirred solution of alcohol **270** (0.15 g, 0.64 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added DMP (0.45 g, 1.1 mmol) in small portions. The mixture was stirred at rt for 16 h and then the reaction was quenched by sequential addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (10 mL), stirred until two clear layers were obtained (*ca.* 30 min) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:3) to afford aldehyde **271** (0.14 g, 92%) as a pale yellow oil.

R_f = 0.16 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (1H, d, *J* = 6.5 Hz, CH-C14), 6.37 (1H, s, CH-C7), 2.55 (1H, dd, *J* = 3.9, 3.9 Hz, CH-C12), 2.53 (3H, s, CH_3-C5), 2.36 (3H, s, CH_3-C1), 2.26 (1H, dd, *J* = 13.2, 8.1 Hz, C*H*H-C9), 2.10–1.97 (2H, m, CH_2-C11), 2.05 (1H, dd, *J* = 6.5, 3.9 Hz, CH-C13), 1.96 (1H, dd, *J* = 13.2, 7.9 Hz, CH*H*-C9), 1.81 (1H, ddd, *J* = 13.5, 7.9, 7.9 Hz, C*H*H-C10), 1.33 (1H, ddddd, *J* = 13.5, 8.1, 8.1, 3.1, 3.1 Hz, CH*H*-C10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7 (CH-C14), 194.0 (C-C2), 157.6 (C-C4), 151.3 (C-C6), 122.2 (C-C3), 107.9 (CH-C7), 37.5 (CH-C13), 36.6 (C-C8), 33.5 (CH_2-C9), 32.4 (CH-C12), 29.3 (CH_3-C1), 27.3 (CH_2-C11), 20.9 (CH_2-C10), 14.6 (CH_3-C5); ν_{max} (film) 2959, 1701, 1674, 1568, 1414 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}NaO_3$ $[M+Na]^+$ 255.0992, found 255.0991.

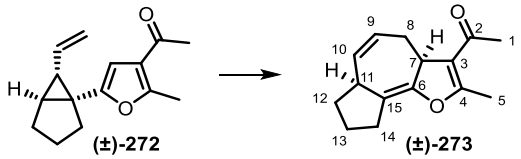
Vinylcyclopropane 272



To a stirred solution of methyltriphenylphosphonium bromide (0.21 g, 0.59 mmol) in THF (8 mL) at −10 °C was added *n*-BuLi (0.16 mL of a 2.3 M solution in hexanes, 0.37 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **271** (71 mg, 0.31 mmol) in THF (10 mL) at −10 °C. The mixture was stirred at rt for 2 h and then the reaction was quenched by pouring the solution into a mixture of pH 7 buffer (50 mL) and Et_2O (20 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I, petroleum ether-EtOAc, 10:1) to afford vinylcyclopropane **272** (57 mg, 81%) as a colourless oil.

R_f = 0.13 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (1H, s, CH-C7), 5.39 (1H, ddd, *J* = 17.1, 10.2, 9.3 Hz, CH-C14), 5.08 (1H, dd, *J* = 17.1, 1.8 Hz, C*H*H-C15$_{trans}$), 4.88 (1H, dd, *J* = 10.2, 1.8 Hz, CH*H*-C15$_{cis}$), 2.54 (3H, s, CH_3-C5), 2.37 (3H, s, CH_3-C1), 2.16 (1H, dd, *J* = 12.7, 8.4 Hz, C*H*H-C9), 1.94 (1H, dd, *J* = 12.7, 8.4 Hz, CH*H*-C9), 1.93–1.88 (2H, m, CH_2-C11), 1.80–1.78 (1H, m, CH-C13), 1.77–1.71 (1H, m, C*H*H-C10), 1.75 (1H, dd, *J* = 4.1, 9.1 Hz, CH-C12), 1.43–1.32 (1H, m, CH*H*-C10); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5 (C-C2), 157.1 (C-C4), 154.4 (C-C6), 137.1 (CH-C14), 122.1 (C-C3), 113.9 (CH_2-C15), 106.5 (CH-C7), 33.4 (C-C8), 32.7 (CH_2-C9), 32.4 (CH-C12), 30.2 (CH-C13), 29.3 (CH_3-C1), 27.5 (CH_2-C11), 21.7 (CH_2-C10), 14.6 (CH_3-C5); ν_{max} (film) 2926, 1678, 1570 cm^{-1}; HMRS (ESI) calcd for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1199, found 253.1187.

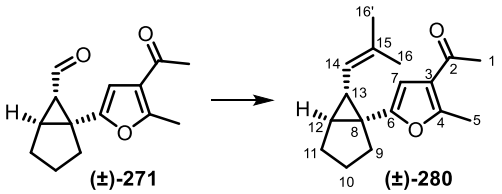
Cycloheptadiene 273



A solution of vinylcyclopropane **272** (70 mg, 0.30 mmol) in toluene (6 mL) was stirred at 40 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford cycloheptadiene **273** (44 mg, 63%) as a pale yellow oil.

R_f = 0.49 (petroleum ether-EtOAc, 10:3); ^{1}H NMR (400 MHz, C_6D_6) δ 5.50–5.47 (2H, m, CH-C9, CH-C10), 4.18 (1H, br d, *J* = 11.5 Hz, CH-C7), 3.19 (1H, m, CH-C11), 2.76–2.69 (1H, m, C*H*H-C8), 2.57–2.50 (1H, m, C*H*H-C14), 2.44–2.33 (1H, m, CH*H*-C14), 2.08–1.98 (1H, m, CH*H*-C8), 1.89 (3H, d, *J* = 1.4 Hz, CH_3-C5), 1.85 (3H, s, CH_3-C1), 1.84–1.79 (1H, m, C*H*H-C12), 1.59–1.53 (1H, m, C*H*H-C13), 1.32–1.23 (2H, m, CH*H*-C12, CH*H*-C13); ^{13}C NMR (126 MHz, C_6D_6) δ 192.0 (C-C2), 164.8 (C-C4), 150.4 (C-C6), 131.2 (CH-C9/C10), 126.4 (CH-C9/C10), 118.6 (C-C3), 117.1 (C-C15), 44.2 (CH-C7), 42.0 (CH-C11), 36.4 (CH_2-C12), 32.0 (CH_2-C8), 29.4 (CH_2-C14), 29.2 (CH_3-C1), 25.0 (CH_2-C13), 14.7 (CH_3-C5); ν_{max} (film) 2953, 1618, 1387, 1204, 1020 cm^{-1}; HMRS (ESI) calcd for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1199, found 253.1187.

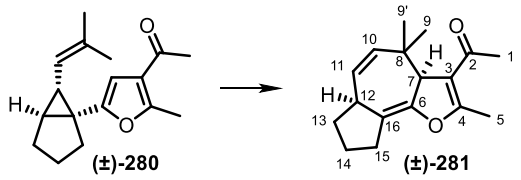
Vinylcyclopropane 280



To a stirred solution of *i*-propyltriphenylphosphonium iodide (0.72 mg, 1.7 mmol) in THF (30 mL) at −10 °C was added *n*-BuLi (0.55 mL of a 2.3 M solution in hexanes, 2.4 mmol). The mixture was stirred at −10 °C for 2 h and then added to a stirred solution of aldehyde **271** (0.19 mg, 0.83 mmol) in THF (60 mL) at −10 °C. The mixture was stirred for 16 h at −10 °C and then the reaction was quenched by pouring the solution into a mixture of pH 7 buffer (90 mL) and Et_2O (40 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I, petroleum ether-EtOAc, 10:1) to afford vinylcyclopropane **280** (0.14 mg, 65%) as a colourless oil.

R_f = 0.48 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 6.19 (1H, s, CH-C7), 4.99 (1H, dsept, *J* = 8.7, 1.3 Hz, CH-C14), 2.38 (3H, s, CH_3-C5), 2.13 (1H, dd, *J* = 12.5, 8.4 Hz, C*H*H-C9), 2.01 (3H, s, CH_3-C1), 1.91 (1H, ddd, *J* = 12.5, 11.4, 8.4 Hz, CH*H*-C9), 1.81 (1H, dd, *J* = 8.7, 4.1 Hz, CH-C13), 1.75–1.72 (2H, m, CH_2-C11), 1.68–1.66 (1H, m, CH-C12), 1.64 (3H, d, *J* = 1.3 Hz, CH_3-C16/C16'), 1.59 (3H, d, *J* = 1.3 Hz, CH_3-C16/C16'), 1.54–1.47 (1H, m, C*H*H-C10), 1.26–1.13 (1H, m, CH*H*-C10); ^{13}C NMR (101 MHz, C_6D_6) δ 192.6 (C-C2), 156.6 (C-C4), 154.9 (C-C6), 132.1 (C-C15), 123.3 (CH-C14), 122.6 (C-C3), 106.7 (CH-C7), 33.3 (C-C8), 33.1 (CH_2-C9), 33.0 (CH-C12), 28.8 (CH_3-C1), 27.9 (CH_2-C11), 25.8 (CH_3-C16/C16'), 25.7 (CH-C13), 22.2 (CH_2-C10), 18.5 (CH_3-C16/C16'), 14.3 (CH_3-C5); ν_{max} (film) 2926, 1677, 1570 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{22}NaO_2$ $[M+Na]^+$ 281.1512, found 281.1499.

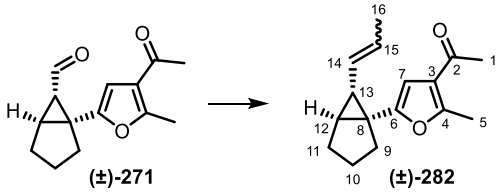
Cycloheptadiene 281



A solution of vinylcyclopropane **280** (48 mg, 0.19 mmol) in toluene (4 mL) was stirred at 110 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford cycloheptadiene **281** (13 mg, 27%, 68% brsm) as a colourless gum.

R_f = 0.45 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 5.35 (1H, dd, *J* = 12.3, 2.0 Hz, CH-C10/C11), 5.27 (1H, dd, *J* = 12.3, 2.5 Hz, CH-C10/C11), 4.20–4.19 (1H, m, CH-C7), 3.12–3.07 (1H, m, CH-C12), 2.58–2.51 (1H, m, C*H*H-C15), 2.44–2.33 (1H, m, CH*H*-C15), 2.05 (3H, d, *J* = 1.3 Hz, CH_3-C5), 2.04 (3H, s, CH_3-C1), 1.85–1.78 (1H, m, C*H*H-C13), 1.71–1.64 (1H, m, C*H*H-C14), 1.43–1.26 (2H, m, CH*H*-C13, CH*H*-C14), 1.11 (3H, s, CH_3-C9/C9'), 1.05 (3H, s, CH_3-C9/C9'); ^{13}C NMR (101 MHz, C_6D_6) δ 193.6 (C-C2), 164.0 (C-C4), 149.3 (C-C6), 139.3 (CH-C10/11), 128.6 (CH-C10/C11), 117.6 (C-C3), 117.1 (C-C16), 53.0 (CH-C7), 41.1 (CH-C12), 38.6 (C-C8), 36.2 (CH_2-C13), 30.2 (CH_3-C9/C9'), 29.3 (CH_3-C1), 29.2 (CH_2-C15), 25.3 (CH_2-C14), 24.2 (CH_3-C9/C9'), 14.1 (CH_3-C5); ν_{max} (film) 2955, 1607, 1377, 1360, 1204, 1022 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{22}NaO_2$ $[M+Na]^+$ 281.1512, found 281.1501.

Vinylcyclopropanes *E*-282 and *Z*-282

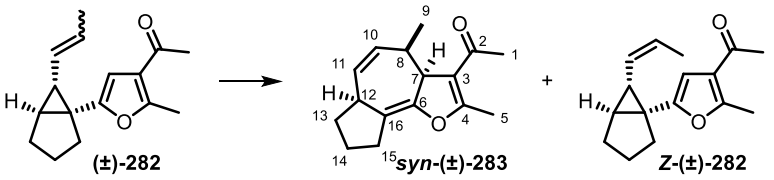


To a stirred solution of ethyltriphenylphosphonium bromide (0.14 mg, 0.38 mmol) in THF (5 mL) at −10 °C was added *n*-BuLi (0.13 mL of a 2.2 M solution in hexanes, 0.29 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **271** (60 mg, 0.26 mmol) in THF (9 mL) at −10 °C. The mixture was stirred at rt for 2 h and then the reaction was quenched by pouring the solution into a mixture of pH 7 buffer (20 mL) and Et_2O (10 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I, petroleum ether-EtOAc, 10:1) to afford an inseparable mixture of *E*-vinylcyclopropane ***E*-282** and *Z*-vinylcyclopropane ***Z*-282** (0.62 g, 86%, 1:2.7 *E*:*Z*) as a colourless oil.

R_f = 0.16 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 6.18 (1H, s, CH-C7 ***E*-282**), 6.18 (1H, s, CH-C7 ***Z*-282**), 5.50 (1H, dq, *J* = 15.2, 6.5 Hz, CH-C15$_{trans}$ ***E*-282**), 5.44 (1H, dqd, *J* = 10.8, 6.8, 1.0 Hz, CH-C15$_{cis}$ ***Z*-282**), 5.25–5.21 (1H, m, CH-C14$_{trans}$ ***E*-282**), 5.19 (1H, ddq, *J* = 10.8, 9.5, 1.7 Hz, CH-C14$_{cis}$ ***Z*-282**), 2.37 (3H, s, CH_3-C5 ***Z*-282**), 2.37 (3H, s, CH_3-C5 ***E*-282**), 2.11 (1H, ddd, *J* = 12.5, 8.2, 0.6 Hz, C*H*H-C9 ***Z*-282**), 2.08 (1H, dd, *J* = 8.0, 4.5, 1.0 Hz, C*H*H-C9 ***E*-282**), 1.94–1.84 (4H, m, CH*H*-C9 ***E*-282**, CH*H*-C9 ***Z*-282**, CH-C13 ***E*-282**, CH-C13 ***Z*-282**), 2.02 (3H, s, CH_3-C1 ***Z*-282**), 2.02 (3H, s, CH_3-C1 ***E*-282**), 1.73–1.67 (6H, m, CH_2-C11 ***E*-282**, CH_2-C11 ***Z*-282**, CH-C12 ***E*-282**, CH-C12 ***Z*-282**), 1.64 (3H, dd, *J* = 6.8, 1.7 Hz, CH_3-C16 ***Z*-282**), 1.54 (3H, dd, *J* = 6.5, 1.6 Hz, CH_3-C16 ***E*-282**), 1.51–1.43 (1H, m, C*H*H-C10 ***E*-282**), 1.51 – 1.43 (1H, m, C*H*H-C10 ***Z*-282**), 1.22–1.07 (1H, m, CH*H*-C10 ***E*-282**), 1.22–1.07 (1H, m, CH*H*-C10 ***Z*-282**); ^{13}C NMR (126 MHz, C_6D_6) δ 192.6 (C-C2 ***Z*-282**), 192.6 (C-C2 ***E*-

282), 156.7 (C-C4 ***Z*-282**), 156.6 (C-C4 ***E*-282**), 154.7 (C-C6 ***E*-282**), 154.6 (C-C6 ***Z*-282**), 129.8 (CH-C14 ***E*-282**), 129.2 (CH-C14 ***Z*-282**), 125.0 (CH-C15 ***E*-282**), 123.9 (CH-C15 ***Z*-282**), 122.6 (C-C3 ***E*-282**), 122.5 (C-C3 ***Z*-282**), 106.9 (CH-C7 ***Z*-282**), 106.8 (CH-C7 ***E*-282**), 33.6 (C-C8 ***Z*-282**), 33.2 (C-C8 ***E*-282**), 33.2 (CH-C12 ***Z*-282**), 33.0 (CH_2-C9 ***Z*-282**), 33.0 (CH_2-C9 ***E*-282**), 32.1 (CH-C12 ***E*-282**), 29.5 (CH_3-C1 ***E*-282**), 28.9 (CH_3-C1 ***Z*-282**), 27.8 (CH_2-C11 ***Z*-282**), 27.7 (CH_2-C11 ***E*-282**), 24.7 (CH-C13 ***E*-282**), 24.7 (CH-C13 ***Z*-282**), 22.1 (CH_2-C10 ***Z*-282**), 22.0 (CH_2-C10 ***E*-282**), 18.2 (CH_3-C16 ***E*-282**), 14.3 (CH_3-C5 ***E*-282**), 14.3 (CH_3-C5 ***Z*-282**), 13.5 (CH_3-C16 ***E*-282**) 13.5 (CH_3-C16 ***Z*-282**); ν_{max} (film) 1676, 1569, 1393, 1229 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{20}NaO_2$ $[M+Na]^+$ 267.1356, found 267.1343.

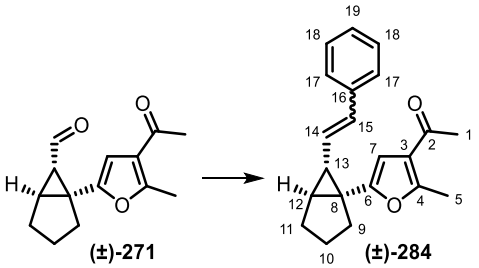
Cycloheptadiene *syn*-283



A mixture of *E* and *Z*-vinylcyclopropane **282** (35 mg, 0.14 mmol, 1:2.7 *E*:*Z*) in toluene (4 mL) was stirred at 40 °C for 18 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford cycloheptadiene ***syn*-283** (7.9 mg, 23%) as a colourless gum and recovered *Z*-vinylcyclopropane ***Z*-282** (14 mg, 40%).

R_f = 0.45 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 5.45 (1H, ddd, *J* = 12.2, 2.5, 2.5 Hz, CH-C10/C11), 5.29 (1H, ddd, *J* = 12.2, 2.3, 2.3 Hz, CH-C10/C11), 3.97 (1H, br d, *J* = 10.3 Hz, CH-C7), 3.17–3.11 (1H, m, CH-C12), 2.57–2.50 (1H, m, C*H*H-C15), 2.44–2.32 (2H, m, CH-C8, CH*H*-C15), 1.93 (3H, d, *J* = 1.3 Hz, CH_3-C5), 1.91 (3H, s, CH_3-C1), 1.85–1.80 (1H, m, C*H*H-C13), 1.60–1.55 (1H, m, C*H*H-C14), 1.31–1.25 (2H, m, CH*H*-C13, CH*H*-C14), 0.94 (3H, d, *J* = 7.4 Hz, CH_3-C9); ^{13}C NMR (101 MHz, C_6D_6) δ 193.3 (C-C2), 164.0 (C-C4), 150.7 (C-C6), 134.3 (C-C10/C11), 130.6 (C-C10/C11), 118.7 (C-C3), 116.9 (C-C16), 49.8 (CH-C7), 41.5 (CH-C12), 39.3 (CH-C8), 36.1 (CH_2-C13), 29.4 (CH_2-C15), 29.3 (CH_3-C1), 25.2 (CH_2-C14), 21.4 (CH_3-C9), 14.3 (CH_3-C5); ν_{max} (film) 2928, 1670, 1610 cm^{-1} ; HMRS (ESI) calcd for $C_{16}H_{20}NaO_2$ $[M+Na]^+$ 267.1356, found 267.1345.

Vinylcyclopropanes *E*-284 and *Z*-284

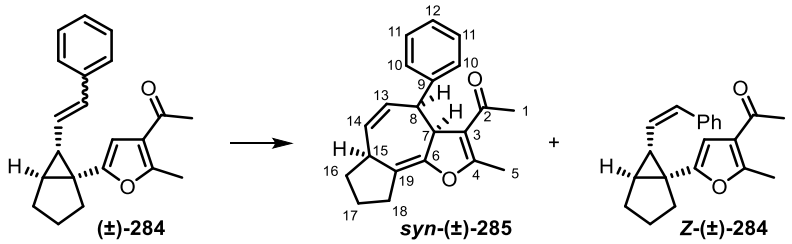


To a stirred solution of benzyltriphenylphosphonium bromide (0.14 g, 0.32 mmol) in THF (4 mL) at −10 °C was added *n*-BuLi (0.12 mL of a 2.2 M solution in hexanes, 0.26 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **271** (50 mg, 0.22 mmol) in THF (7 mL) at −10 °C. The mixture was stirred for 2 h at −10 °C and then the reaction was quenched by pouring the solution into a mixture of pH 7 buffer (50 mL) and Et_2O (20 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I, petroleum ether-EtOAc, 5:1) to afford an inseparable mixture of *E*-vinylcyclopropane ***E*-284** and *Z*-vinylcyclopropane ***Z*-284** (60 mg, 92%, 1.0:1.1 *E*:*Z*) as a colourless oil.

R_f = 0.32 (petroleum ether-EtOAc); ^{1}H NMR (400 MHz, C_6D_6) δ 7.43 (2H, d, *J* = 7.6 Hz, CH-C17 ***Z*-284**), 7.23 (2H, d, *J* = 7.9, CH-C17 ***E*-284**), 7.22 (2H, dd, *J* = 7.6, 7.9 Hz, CH-C18 ***Z*-284**), 7.10–7.07 (3H, m, CH-C18 ***E*-284**, CH-C19 ***Z*-284**), 6.98 (1H, t, *J* = 7.4 Hz, CH-C19 ***E*-284**), 6.45 (1H, d, *J* = 15.8 Hz, CH-C15$_{trans}$ ***E*-284**), 6.44 (1H, d, *J* = 11.4 Hz, CH-C15$_{cis}$ ***Z*-284**), 6.23 (1H, s, CH-C7 ***Z*-284**), 6.22 (1H, s, CH-C7 ***E*-284**), 6.00 (1H, dd, *J* = 15.8, 9.2 Hz, CH-C14$_{trans}$ ***E*-284**), 5.43 (1H, dd, *J* = 11.4, 9.3 Hz, CH-C14$_{cis}$ ***Z*-284**), 2.28 (3H, s, CH_3-C5 ***Z*-284**), 2.36 (3H, s, CH_3-C5 ***E*-284**), 2.18 (1H, dd, *J* = 9.3, 4.2 Hz, CH-C13 ***Z*-284**), 2.09 (1H, ddd, *J*= 12.6, 8.2, 5.6 Hz, C*H*H-C9 ***E*-284**), 2.08 (1H, ddd, *J* = 12.6, 8.2, 5.6 Hz, CH*H*-C9 ***Z*-284**), 2.03 (3H, s, CH_3-C1 ***Z*-284**), 1.99 (3H, s, CH_3-C1 ***E*-284**), 1.90 (1H, ddd, *J* = 12.6, 11.5, 8.6 Hz, CH*H*-C9 ***E*-284**), 1.88 (1H, ddd,

J = 12.6, 11.5, 8.6 Hz, CH*H*-C9 ***Z*-284**), 1.79–1.76 (2H, m, CH-C12 ***E*-284**, CH-C13 ***E*-284**), 1.75–1.71 (3H, m, CH-C12 ***Z*-284**, C*H*H-C11 ***Z*-284**, C*H*H-C11 ***E*-284**), 1.69–1.64 (2H, m, CH*H*-C11 ***Z*-284**, CH*H*-C11 ***E*-284**), 1.52–1.46 (1H, m, C*H*H-C10 ***E*-284**), 1.43–1.37 (1H, m, C*H*H-C10 ***E*-284**), 1.21–1.12 (1H, m, CH*H*-C10 ***Z*-284**), 1.07–0.98 (1H, m, CH*H*-C10 ***Z*-284**); ^{13}C NMR (101 MHz, C_6D_6) δ 192.6 (C-C2 ***Z*-284**), 192.5 (C-C2 ***E*-284**), 156.8 (C-C4 ***Z*-284**), 156.7 (C-C4 ***E*-284**), 154.3 (C-C6 ***E*-284**), 154.2 (C-C6 ***Z*-284**), 138.2 (C-C16 ***Z*-284**), 138.2 (C-C16 ***E*-284**), 130.9 (CH-C14 ***Z*-284**), 130.1 (CH-C15 ***E*-284**), 129.6 (CH-C15 ***Z*-284**), 129.4 (CH-C14 ***E*-284**), 129.2 (2C, CH-C17 ***Z*-284**), 128.9 (2C, CH-C18 ***E*-284**), 128.6 (2C, CH-C18 ***Z*-284**), 127.1 (CH-C19 ***E*-284**), 127.0 (CH-C19 ***Z*-284**), 126.1 (2C, CH-C17 ***E*-284**), 122.6 (C-C3 ***Z*-284**), 122.6 (C-C3 ***E*-284**), 107.2 (CH-C7 ***E*-284**), 107.0 (CH-C7 ***Z*-284**), 34.5 (C-C8 ***E*-284/*Z*-284**), 34.3 (C-C8 ***E*-284/*Z*-284**), 34.1 (CH-C12 ***Z*-284**), 33.2 (CH_2-C9 ***E*-284**), 33.1 (CH-C12 ***E*-284**), 32.6 (CH_2-C9 ***Z*-284**), 30.2 (CH-C13 ***E*-284**), 28.9 (CH_3-C1 ***Z*-284**), 28.84 (CH_3-C1 ***E*-284**), 27.8 (CH_2-C11 ***E*-284**), 27.6 (CH_2-C11 ***Z*-284**), 26.7 (CH-C13 ***Z*-284**), 21.9 (CH_2-C10 ***Z*-284**), 21.9 (CH_2-C10 ***E*-284**), 14.2 (CH_3-C5 ***Z*-284**), 14.2 (CH_3-C5 ***E*-284**); ν_{max} (film) 2957, 1676, 1568 cm^{-1}; HMRS (ESI) calcd for $C_{21}H_{22}NaO_2$ $[M+Na]^+$ 329.1512, found 329.1502.

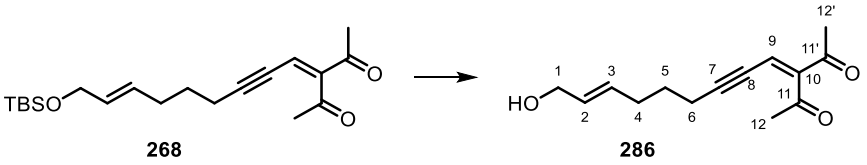
Cycloheptadiene *syn*-285



A mixture of *E* and *Z*-vinylcyclopropane **284** (60 mg, 0.20 mmol, 1.0:1.1 *E*:*Z*) in toluene (6 mL) was stirred at 40 °C for 18 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford cycloheptadiene ***syn*-285** (26 mg, 43%) as a colourless gum and recovered *Z*-vinylcyclopropane ***Z*-284** (14 mg, 23 %).

R_f = 0.45 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 7.27 (2H, dd, *J* = 7.9, 1.3 Hz, CH10), 7.14 (2H, dd, *J* = 7.9, 7.5 Hz, CH-C11), 7.06 (1H, tt, *J* = 7.5, 1.3 Hz, CH-C12), 5.66 (1H, ddd, *J* = 12.3, 6.0, 2.5 Hz, CH-C13), 5.61 (1H, dd, *J* = 12.3, 1.7 Hz, CH-C14), 4.66 (1H, ddq, *J* = 5.2, 2.5, 1.4 CH-C7), 4.35 (1H, m, CH-C8), 3.24–3.21 (1H, m, CH-C15), 2.56–2.51 (1H, m, C*H*H-C18), 2.45–2.36 (1H, m, CH*H*-C18), 1.93 (3H, s, CH_3-C1), 1.88–1.84 (1H, m, C*H*H-C16), 1.63–1.58 (1H, m, C*H*H-C17), 1.47 (3H, d, *J* = 1.4 Hz, CH_3-C5), 1.35–1.25 (2H, m, CH*H*-C16, CH*H*-C17); ^{13}C NMR (126 MHz, C_6D_6) δ 191.9 (C-C2), 164.6 (C-C4), 147.8 (C-C6), 140.9 (C-C9), 131.0 (C-C14), 130.0 (2C, C-C10), 129.8 (C-C13), 127.9 (2C, C-C11), 126.9 (C-C12), 117.6 (C-C3), 117.3 (C-C19), 49.4 (CH-C7), 44.3 (CH-C8), 41.8 (CH-C15), 36.5 (CH_2-C16), 29.4 (CH_2-C18), 29.4 (CH_3-C1), 25.2 (CH_2-C17), 14.4 (CH_3-C5); ν_{max} (film) 2924, 1620, 1387, 1202, 1049, 1022 cm^{-1}; HMRS (EI) calcd for $C_{21}H_{22}O_2$ $[M]^+$ 306.1620, found 306.1623.

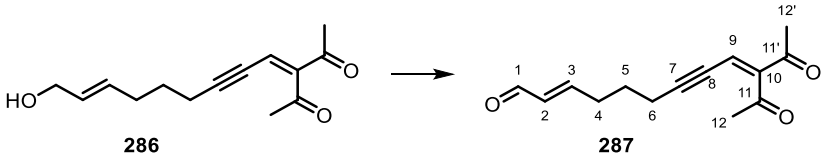
Alcohol 286



To a stirred solution of protected alcohol **268** in (0.58 g, 1.7 mmol) in MeOH/CH_2Cl_2 (v/v 5:2, 17 mL) at rt was added camphorsulfonic acid (77 mg, 0.33 mmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of water (20 mL) and saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford alcohol **286** (0.38 g, 98%) as a pale yellow oil.

R_f = 0.13 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, t, *J* = 2.4 Hz, CH-C9), 5.66–5.63 (2H, m, CH-C2, CH-C3), 4.08-4.07 (2H, d, *J* = 4.1 Hz, CH_2-C1), 2.44 (3H, s, CH_3-C12), 2.43 (2H, td, *J* = 7.1, 2.4 Hz, CH_2-C6), 2.29 (3H, s, CH_3-C12'), 2.16-2.11 (2H, m, CH_2-C4), 1.69 (1H, br s, OH), 1.64 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (C-C11), 195.9 (C-C11'), 149.8 (C-C10), 131.1 (CH-C2/C3), 130.5 (CH-C2/C3), 123.2 (CH-C9), 109.9 (C-C7), 77.2 (C-C8), 63.5 (CH_2-C1), 31.3 (CH_2-C4), 31.0 (CH_3-C12), 27.5 (CH_2-C5), 27.2 (CH_3-C12'), 19.7 (CH_2-C6); ν_{max} (film) 2211, 1663, 1587, 1422 cm^{-1}; HMRS (ESI) calcd for $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1139.

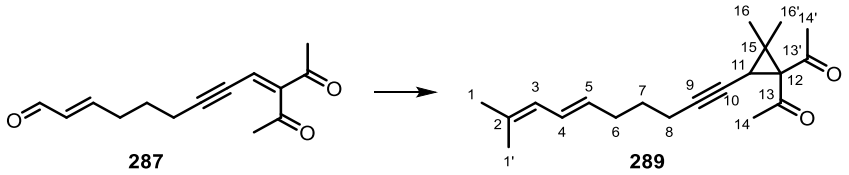
Aldehyde 287



To a stirred solution of alcohol **286** (0.36 g, 1.5 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added DMP (1.0 g, 2.4 mmol) in small portions. The mixture was stirred at rt for 16 h and then the reaction was quenched by sequential addition of saturated aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The mixture was diluted with Et_2O (20 mL), stirred until two clear layers were obtained (*ca.* 30 min) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to afford aldehyde **287** (0.31 g, 86%) as a pale yellow oil.

R_f = 0.24 (petroleum ether-EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (1H, d, *J* = 7.8 Hz, CH-C1), 6.81 (1H, dt, *J* = 15.7, 6.9 Hz, CH-C3), 6.63 (1H, t, *J* = 2.4 Hz, CH-C9), 6.12 (1H, ddt, *J* = 15.7, 7.8, 1.5 Hz, CH-C2), 2.49 (2H, td, *J* = 7.0, 2.4 Hz, CH_2-C6), 2.44 (2H, tdd, *J* = 7.7, 6.9, 1.5 Hz, CH_2-C4), 2.42 (3H, s, CH_3-C12), 2.29 (3H, s, CH_3-C12'), 1.77 (2H, tt, *J* = 7.7, 7.0 Hz, CH_2-C5), ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3 (C-C11), 195.8 (C-C11'), 193.8 (CH-C1), 156.6 (CH-C2), 150.2 (C-C10), 133.7 (CH-C3), 122.6 (CH-C9), 108.2 (C-C7), 77.6 (C-C8), 31.6 (CH_2-C4), 31.0 (CH_3-C12), 27.1 (CH_2-C5), 26.3 (CH_3-C12'), 19.7 (CH_2-C6); ν_{max} (film) 2211, 1684, 1375, 1248, 1165, 1125 cm^{-1}; HMRS (ESI) calcd for $C_{14}H_{16}NaO_3$ $[M+Na]^+$ 255.0992, found 255.0987.

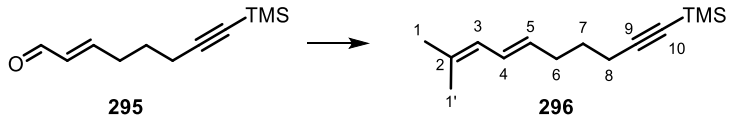
Diene 289



To a stirred solution of *i*-propyltriphenylphosphonium iodide (0.92 g, 2.1 mmol) in THF (26 mL) at −10 °C was added *n*-BuLi (0.69 mL of a 2.3 M solution in hexanes, 1.59 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **287** (0.245 g, 1.06 mmol) in THF (35 mL) at −10 °C. The mixture was stirred for 16 h at rt and then the reaction was quenched by pouring the solution into a mixture of buffer pH 7 (90 mL) and Et_2O (50 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford cyclopropane **289** (0.19 g, 61%) as a colourless oil.

R_f = 0.33 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (500 MHz, C_6D_6) δ 6.35 (1H, ddt, *J* = 15.0, 10.9, 1.3 Hz, CH-C4), 5.88 (1H, d, *J* = 10.9 Hz, CH-C3), 5.43 (1H, dt, *J* = 15.0, 7.1 Hz, CH-C5), 2.63 (1H, t, *J* = 2.1 Hz, CH-C11), 2.12 (3H, s, CH_3-C14'), 2.07 (2H, tdd, *J* = 7.2, 7.1, 1.3 Hz, CH_2-C6), 1.98 (2H, td, *J* = 7.1, 2.1 Hz, CH_2-C8), 1.85 (3H, s, CH_3-C14), 1.66 (3H, s, CH_3-C1/C1'), 1.64 (3H, s, CH_3-C1/C1'), 1.42 (3H, s, CH_3-C16'), 1.41 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C7), 0.82 (3H, s, CH_3-C16); ^{13}C NMR (126 MHz, C_6D_6) δ 201.4 (C-C13'), 198.9 (C-C13), 132.7 (C-C2), 130.51 (CH-C5), 128.4 (CH-C4), 125.9 (CH-C3), 84.1 (C-C9/C10), 76.8 (C-C9/C10), 59.3 (C-C12), 32.9 (C-C15), 32.2 (CH_2-C6), 30.6 (CH_3-C14'), 29.5 (CH_3-C14), 29.2 (CH_2-C7), 26.0 (CH_3-C1/C1'), 23.8 (CH-C11), 20.5 (CH_3-C16), 20.4 (CH_3-C16'), 18.4 (CH_2-C8), 18.2 (CH_3-C1/C1'); ν_{max} (film) 1695, 1358, 1213, 1188 cm^{-1}; HMRS (ESI) calcd for $C_{20}H_{28}NaO_2$ $[M+Na]^+$ 323.1982, found 323.1979.

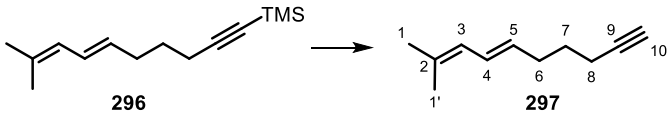
Alkyne 296



To a stirred solution of *i*-propyltriphenylphosphonium iodide (1.4 g, 3.3 mmol) in THF (20 mL) at −10 °C was added *n*-BuLi (1.1 mL of a 2.2 M solution in hexanes, 2.4 mmol). The mixture was stirred at −10 °C for 2 h and then added to a stirred solution of aldehyde **295** (0.33 g, 1.70 mmol) in THF (20 mL) at −10 °C. The mixture was stirred for 1 h and then the reaction was quenched by addition of brine (40 mL). The mixture was diluted with Et_2O (30 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 300:1) to afford diene **296** (0.62 g, 86%) as a pale yellow oil.

R_f = 0.43 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (1H, ddt, *J* = 15.0, 10.8, 1.3 Hz, CH-C4), 5.78 (1H, d, *J* = 10.8 Hz, CH-C3), 5.50 (1H, dt, *J* = 15.0, 7.2 Hz, CH-C5), 2.22 (2H, t, *J* = 7.2 Hz, CH_2-C8), 2.18 (2H, br dt, *J* = 7.2, 7.1 Hz, CH_2-C6), 1.75 (3H, s, CH_3-C1/C1'), 1.73 (3H, s, CH_3-C1/C1'), 1.60 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C7) 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.0 (C-C2), 130.5 (CH-C5), 127.7 (CH-C4), 125.1 (CH-C3), 107.3 (C-C10), 84.7 (C-C9), 31.9 (CH_2-C6), 28.5 (CH_2-C7), 26.0 (CH_3-C1/C1'), 19.3 (CH_2-C8), 18.2 (CH_3-C1/C1'), 0.3 (3C, CH_3-TMS); ν_{max} (film) 2174, 1248 cm^{-1}; HMRS (CI) calcd for $C_{14}H_{25}Si$ $[M+H]^+$ 221.1726, found 221.1726.

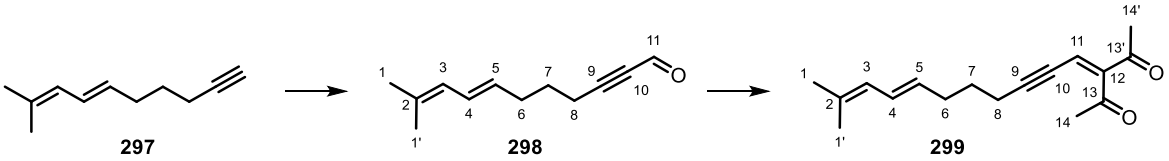
Alkyne 297



To a stirred solution of protected alkyne **296** (0.58 g, 2.6 mmol) in MeOH (13 mL) at rt was added K_2CO_3 (0.36 g, 2.6 mmol) in one portion. The mixture was stirred for 12 h and then the reaction was quenched by addition of water (20 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a small pad of silica gel (petroleum ether-EtOAc, 300:1) to afford alkyne **297** as a colourless oil. The alkyne was used directly in the next step without further purification.

R_f = 0.33 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (1H, ddt, *J* = 15.0, 10.8, 1.2 Hz, CH-C4), 5.79 (1H, d, *J* = 10.8 Hz, CH-C3), 5.51 (1H, dt, *J* = 15.0, 7.1 Hz, CH-C5), 2.23–2.17 (2H, m, CH_2-C6), 2.20 (2H, td, *J* = 7.1, 2.7 Hz, CH_2-C8), 1.95 (1H, t, *J* = 2.7 Hz, CH-C10), 1.76 (3H, s, CH_3-C1/C1'), 1.74 (3H, s, CH_3-C1/C1'), 1.62 (2H, tt, *J* = 7.2, 7.1 Hz, CH_2-C7).

Ynenone 299



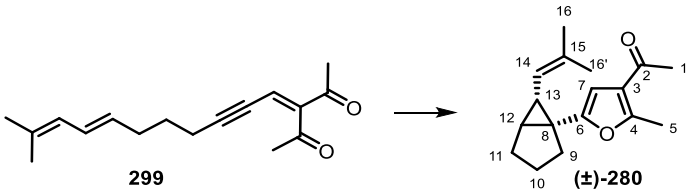
To a stirred solution of alkyne **297** in THF (24 mL) at −78 °C was added *n*-BuLi (2.6 mL of a 2.1 M solution in hexanes, 3.6 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.37 mL, 4.8 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 solution (50 mL). The mixture was diluted with Et_2O (20 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **298** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.39 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (1H, t, *J* = 0.8 Hz, CH-C11), 6.27 (1H, ddt, *J* = 15.1, 10.8, 1.2 Hz, CH-C4), 5.79 (1H, d, *J* = 10.8 Hz, CH-C3), 5.48 (1H, dt, *J* = 15.1, 7.1 Hz, CH-C5), 2.42 (2H, td, *J* = 7.2, 0.8 Hz, CH_2-C8), 2.21 (2H, dt, *J* = 7.2, 7.1 Hz, CH_2-C6), 1.76 (3H, s, CH_3-C1/C1'), 1.74 (3H, s, CH_3-C1/C1'), 1.69 (2H, tt, *J* = 7.2, 7.2 Hz, CH_2-C7).

To a stirred solution of crude acetylenic aldehyde **298** and acetylacetone (0.23 mL, 2.4 mmol) in toluene (24 mL) at rt were added $MgSO_4$ (58 mg, 0.48 mmol), piperidine (21 μL, 0.24 mmol), acetic acid (0.10 mL, 1.4 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (50 mL). The mixture was diluted with EtOAc (25 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford ynenone **299** (0.47g, 76% over 3 steps) as a pale yellow oil.

R_f = 0.13 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, t, *J* = 2.4 Hz, CH-C11), 6.24 (1H, ddt, *J* = 15.0, 10.8, 1.2 Hz, CH-C4), 5.78 (1H, d, *J* = 10.8 Hz, CH-C3), 5.48 (1H, dt, *J* = 15.0, 7.2 Hz, CH-C5), 2.46 (3H, s, CH_3-C14), 2.44 (2H, td, *J* = 7.1, 2.4 Hz, CH_2-C8), 2.31 (3H, s, CH_3-C14'), 2.18 (2H, dtd, *J* = 7.2, 7.1, 1.2 Hz, CH_2-C6), 1.75 (3H, s, CH_3-C1/C1'), 1.73 (3H, s, CH_3-C1/C1'), 1.65 (2H, tt, *J* = 7.1, 7.1 Hz, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4 (C-C13), 195.9 (C-C13'), 149.7 (C-C12), 133.8 (C-C2), 129.8 (C-C5), 128.2 (C-C4), 124.9 (C-C3), 123.3 (CH-C11), 110.2 (C-C9), 77.2 (C-C10), 32.0 (CH_2-C6), 31.1 (CH_3-C14), 28.1 (CH_2-C7), 27.4 (CH_3-C14'), 26.0 (CH_3-C1/C1'), 19.8 (CH_2-C8), 18.4 (CH_3-C1/C1'); ν_{max} (film) 2928, 2211, 1665, 1576 m^{-1}; HMRS (ESI) calcd for $C_{17}H_{22}NaO_2$ $[M+Na]^+$ 281.1512, found 281.1501.

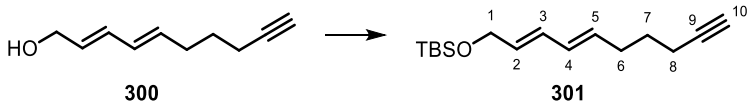
Vinylcyclopropane 280



To a stirred solution of ynenone **299** (42 mg, 0.16 mmol) in CH_2Cl_2 (0.60 mL) at rt was added chloroacetic acid (15 mg, 0.16 mmol) in one portion. The mixture was stirred at 40 °C for 24 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to afford vinylcyclopropane **280** (25 mg, 59%) as a colourless oil.

The analytical and spectroscopic data are in agreement with those reported on page 174.

Protected alcohol 301

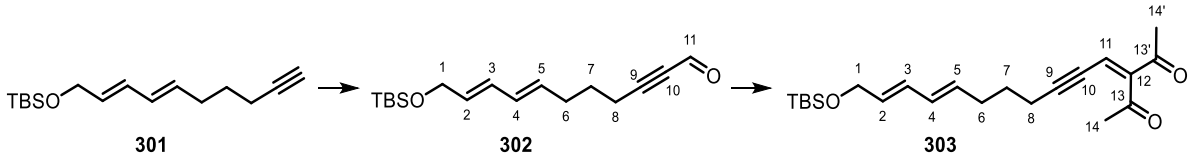


300 **301**

To a solution of alcohol **300** (0.24 g, 1.6 mmol) in DMF (2 mL) at rt were sequentially added imidazole (0.22 g, 3.2 mmol) and TBSCl (0.37 g, 2.5 mmol). The mixture was stirred for 2 h and then the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was diluted with Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 200:1) to afford silane **301** (0.41 g, 95%) as a colourless oil.

R_f = 0.10 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (1H, ddt, *J* = 15.3, 10.5, 1.3 Hz, CH-C3), 6.07 (1H, dd, *J* = 15.3, 10.5 Hz, CH-C4), 5.66 (1H, dt, *J* = 15.3, 5.2 Hz, CH-C2), 5.62 (1H, dt, *J* = 15.3, 7.0 Hz, CH-C5), 4.19 (2H, d, *J* = 5.2, 1.3 Hz, CH_2-C1), 2.21–2.17 (4H, m, CH_2-C6, CH_2-C8), 1.94 (1H, t, *J* = 2.6 Hz, CH-C10), 1.62 (2H, tt, *J* = 7.3, 7.2 Hz, CH_2-C7), 0.91 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.0 (CH-C5), 130.8 (CH-C2), 130.7 (CH-C4), 130.1 (CH-C3), 84.3 (C-C9), 68.6 (CH-C10), 63.7 (CH_2-C1), 31.6 (CH_2-C6), 28.1 (CH_2-C7), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 17.9 (CH_2-C8), −5.1 (CH_3-TBS), −5.1 (CH_3-TBS); ν_{max} (film) 2930, 1254, 1109 cm^{-1}; HMRS (ESI) calcd for $C_{16}H_{28}NaOSi$ $[M+Na]^+$ 287.1802, found 287.1798.

Ynenone 303



To a stirred solution of alkyne **301** (0.29 g, 1.1 mmol) in THF (11 mL) at −78 °C was added *n*-BuLi (0.71 mL of a 2.3 M solution in hexanes, 1.6 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.17 mL, 2.2 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (20 mL). The mixture was diluted with EtOAc (10 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **302** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.23 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, t, *J* = 0.8 Hz, CH-C11), 6.19 (1H, ddt, *J* = 14.7, 10.7, 1.5 Hz, CH-C4), 6.07 (1H, dd, *J* = 15.0, 10.7 Hz, CH-C3), 5.68 (1H, dt, *J* = 15.0, 5.2 Hz, CH-C2), 5.59 (1H, dt, *J* = 14.7, 7.1 Hz, CH-C5), 4.20 (2H, d, *J* = 5.2 Hz, CH_2-C1), 2.42 (2H, td, *J* = 7.2, 0.8 Hz, CH_2-C8), 1.70 (2H, tt, *J* = 7.3, 7.2 Hz, CH_2-C7), 2.23–2.18 (2H, m, CH_2-C6), 0.91 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (6H, s, CH_3-TBS).

To a stirred solution of crude acetylenic aldehyde **302** and acetylacetone (0.10 mL, 0.97 mmol) in toluene (10 mL) at rt were added $MgSO_4$ (26 mg, 0.22 mmol), piperidine (10 μL, 0.10 mmol), acetic acid (45 μL, 0.79 mmol). The mixture was stirred at 35 °C for 1 h and then the reaction was quenched by addition of water (300 mL). The mixture was diluted with EtOAc (100 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was

purified by flash column chromatography on silica gel (petroleum ether-EtOAc 10:3) to afford ynenone **303** (0.31 g, 75% over 2 steps) as a pale yellow oil.

R_f = 0.13 (petroleum ether-EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 6.43 (1H, t, *J* = 2.4 Hz, CH-C11), 6.41 (1H, dd *J* = 14.7, 10.5 Hz, CH-C4), 6.17 (1H, dd, *J* = 15.1, 10.5 Hz, CH-C3), 5.77 (1H, dt, *J* = 15.1, 5.1 Hz, CH-C2), 5.51 (1H, dt, *J* = 14.7, 7.1 Hz, CH-C5), 4.22 (2H, dd, *J* = 5.1 Hz, CH_2-C1), 2.35 (3H, s, CH_3-C14), 2.10 (2H, td, *J* = 7.1, 2.4 Hz, CH_2-C8), 2.05 (2H, dt, *J* = 7.1, 7.1 Hz, CH_2-C6), 1.92 (3H, s, CH_3-C14'), 1.41 (2H, tt, *J* = 7.1, 7.1 Hz, CH_2-C7), 1.08 (9H, s, CH_3-*t*-Bu-TBS), 0.16 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, C_6D_6) δ 200.1 (C-C13), 194.9 (C-C13'), 150.7 (C-C12), 132.3 (CH-C5), 131.6 (CH-C2/C3), 131.5 (CH-C2/C3), 130.0 (CH-C4), 122.0 (CH-C11), 108.7 (C-C9), 77.7 (C-C10), 63.6 (CH_2-C1), 31.8 (CH_2-C6), 30.8 (CH_3-C14), 27.9 (CH_2-C7), 26.6 (CH_3-C14'), 26.2 (3C, CH_3-*t*-Bu-TBS), 19.5 (CH_2-C8), 18.6 (C-*t*-Bu-TBS), −5.0 (CH_3-TBS), −5.0 (CH_3-TBS); ν_{max} (film) 2955, 1674, 1560 cm^{-1}; HMRS (ESI) calcd for $C_{22}H_{34}NaO_3Si$ $[M+Na]^+$ 397.2169, found 397.2151.

5 References

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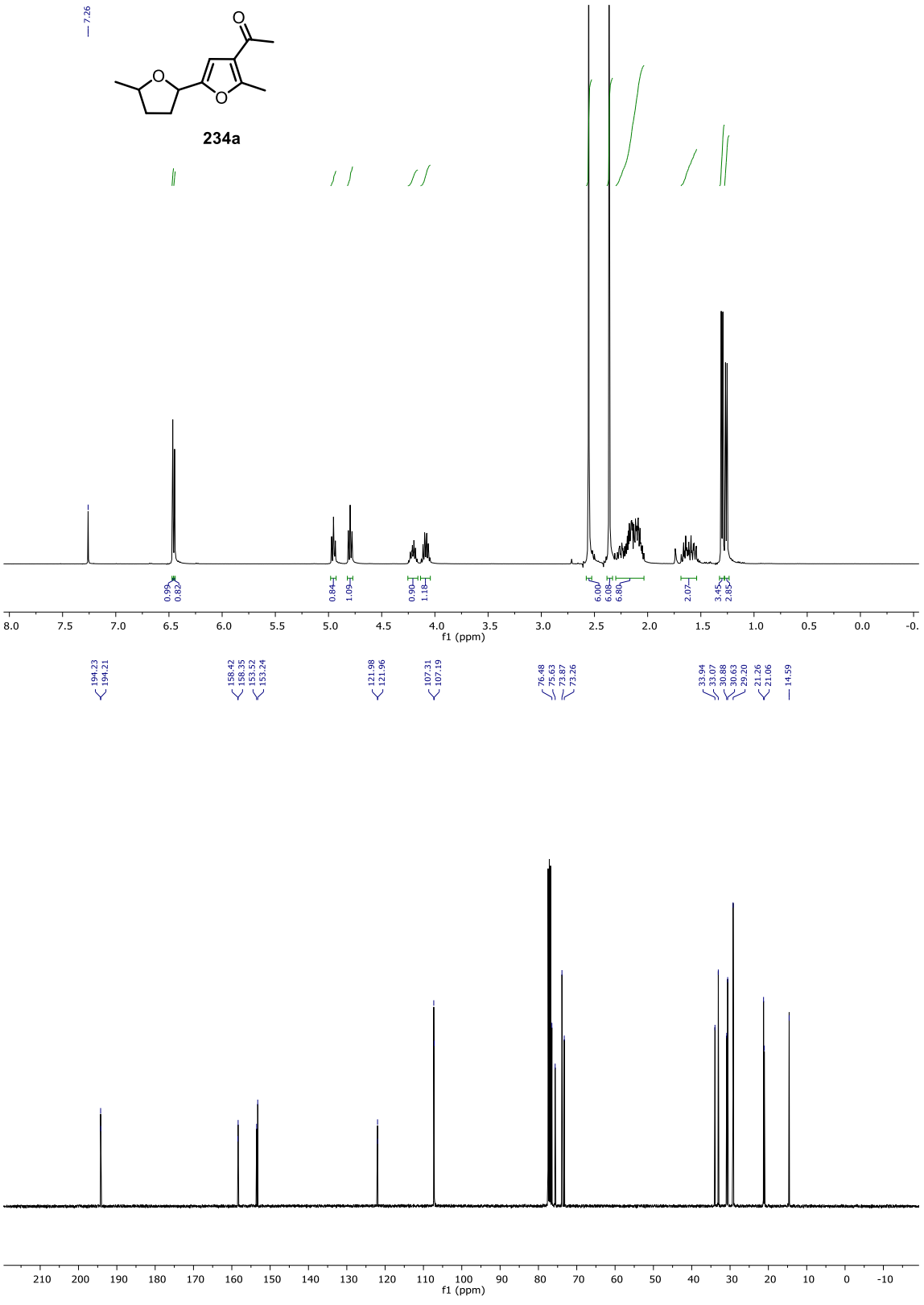
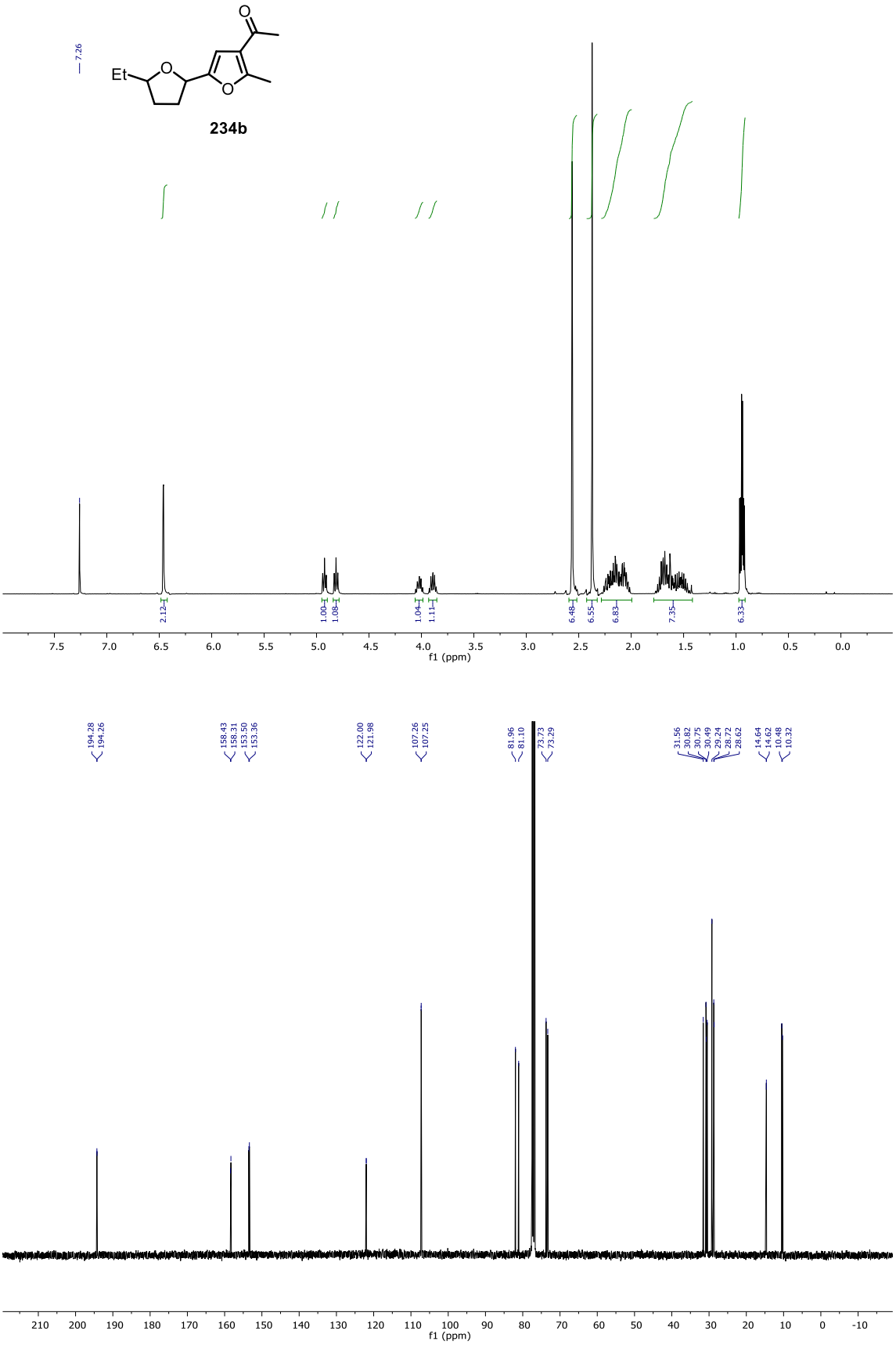
6 Appendices

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O
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1.00
1.08
1.04
1.11
6.48
6.55
6.83
7.35
6.33
f1 (ppm)
194.28
194.26
158.43
158.31
153.50
153.36
122.00
121.98
107.26
107.25
81.96
81.10
73.73
73.29
31.56
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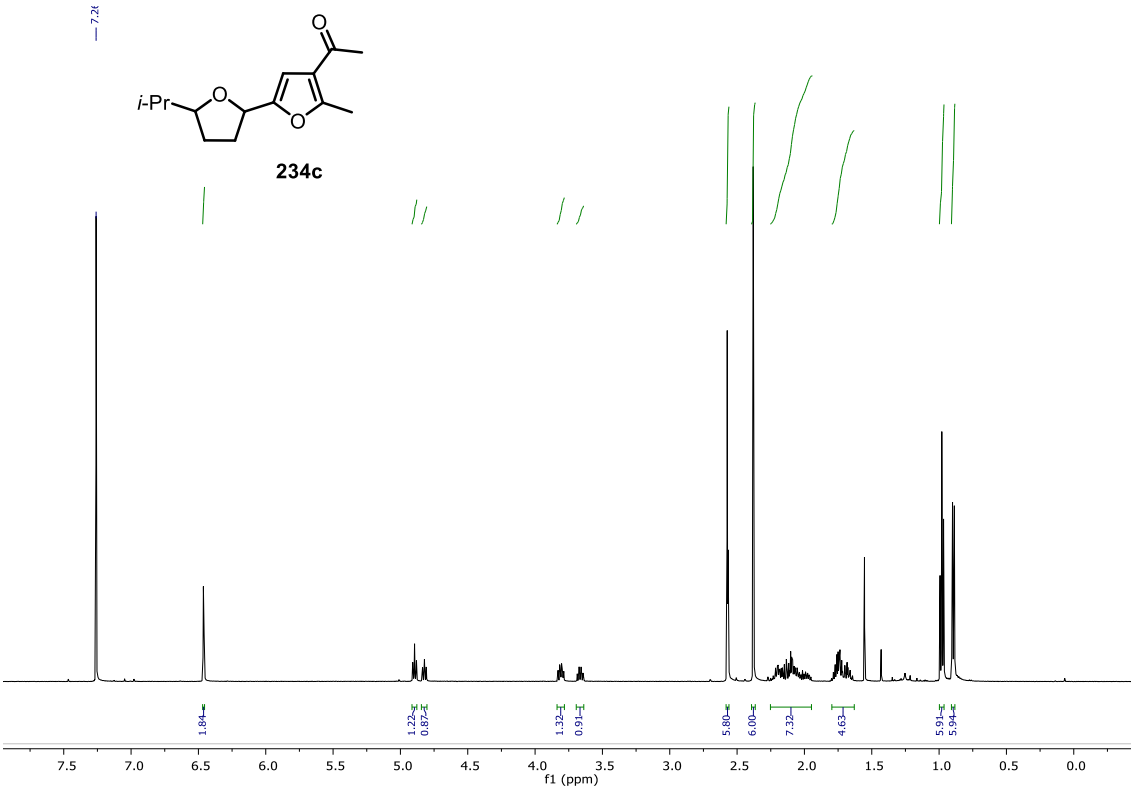
30.75
30.49
29.24
28.72
28.62
14.64
14.62
10.48
10.32
f1 (ppm)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O
O
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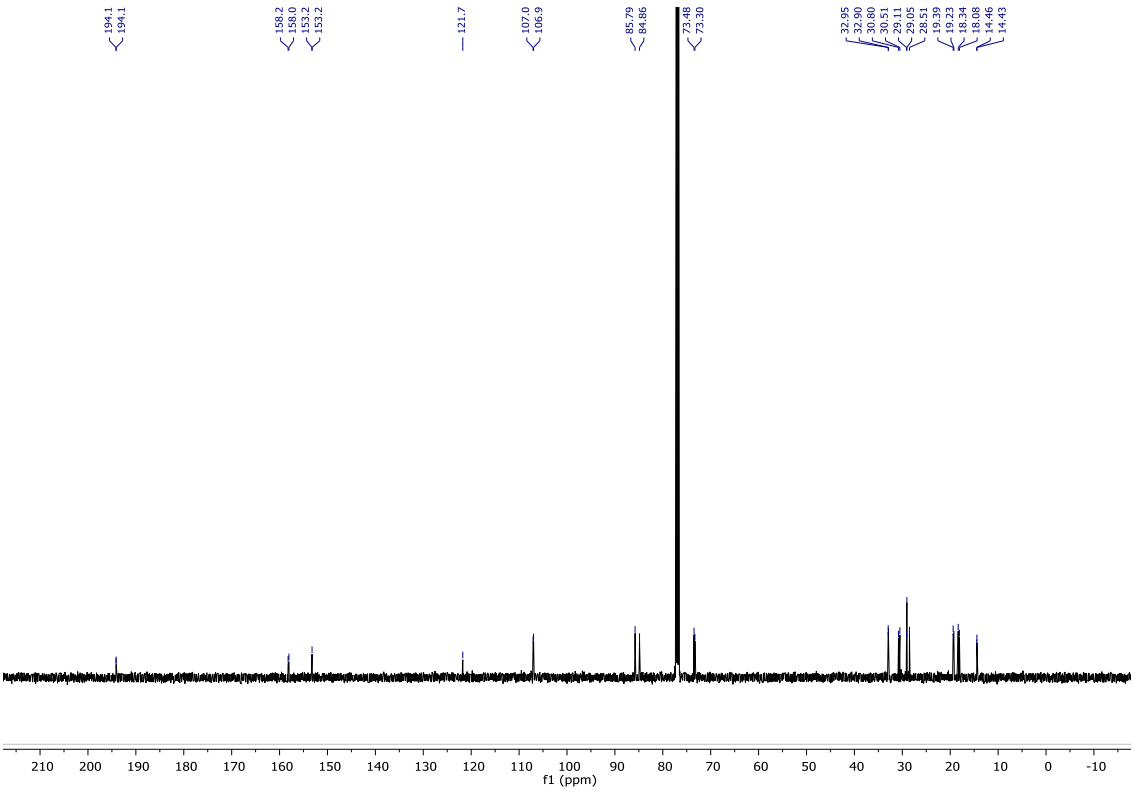
7.32
4.63
5.91
5.94
f1 (ppm)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194.1
158.2
158.0
153.2
153.2
121.7
107.0
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85.79
84.86
73.48
73.30
32.95
32.90
30.80
30.51
29.11
29.05
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19.39
19.23
18.34
18.08
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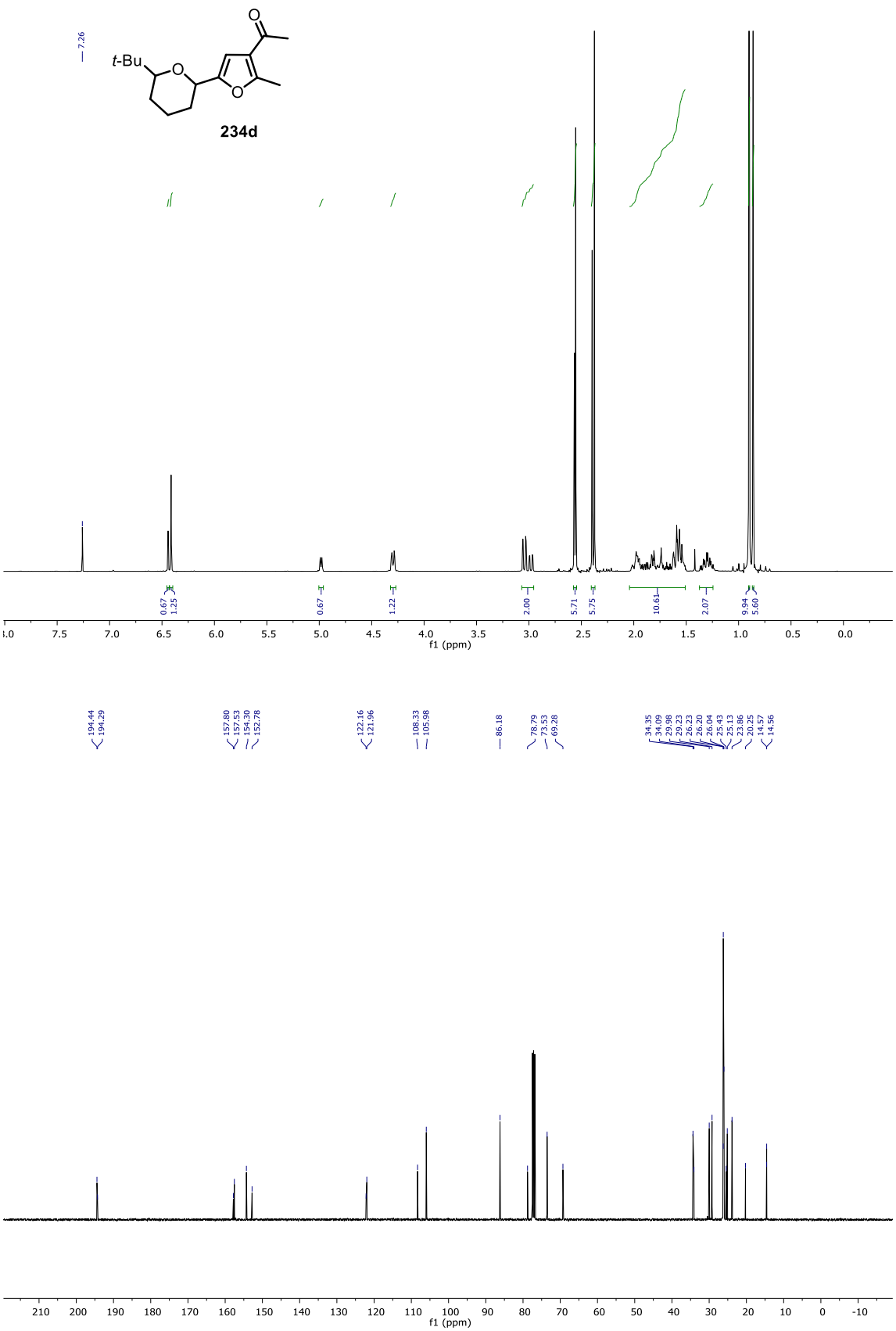
14.43
f1 (ppm)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t-Bu
O
O
O
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10.61
2.07
9.94
5.60
f1 (ppm)
194.44
194.29
157.80
157.53
154.30
152.78
122.16
121.96
108.33
105.98
86.18
78.79
73.53
69.28
34.35
34.09
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26.23
26.20
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20.25
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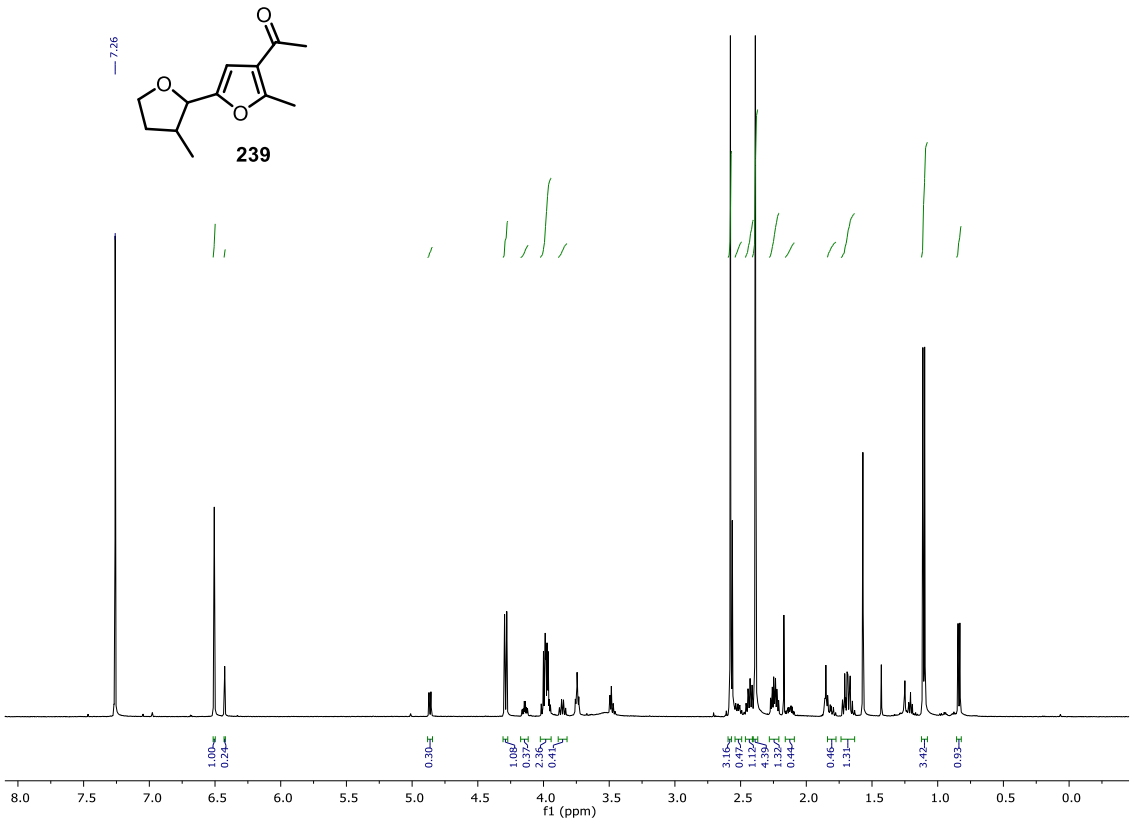
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1.32
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0.46
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3.42
0.93
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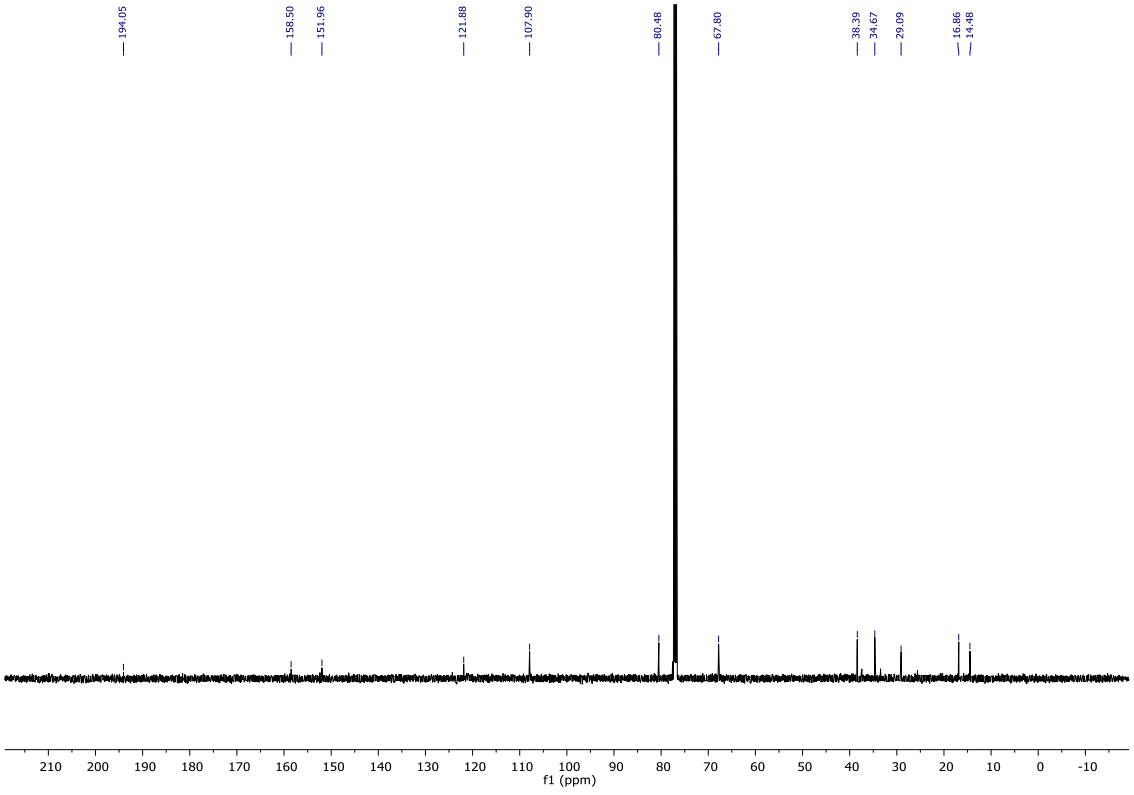
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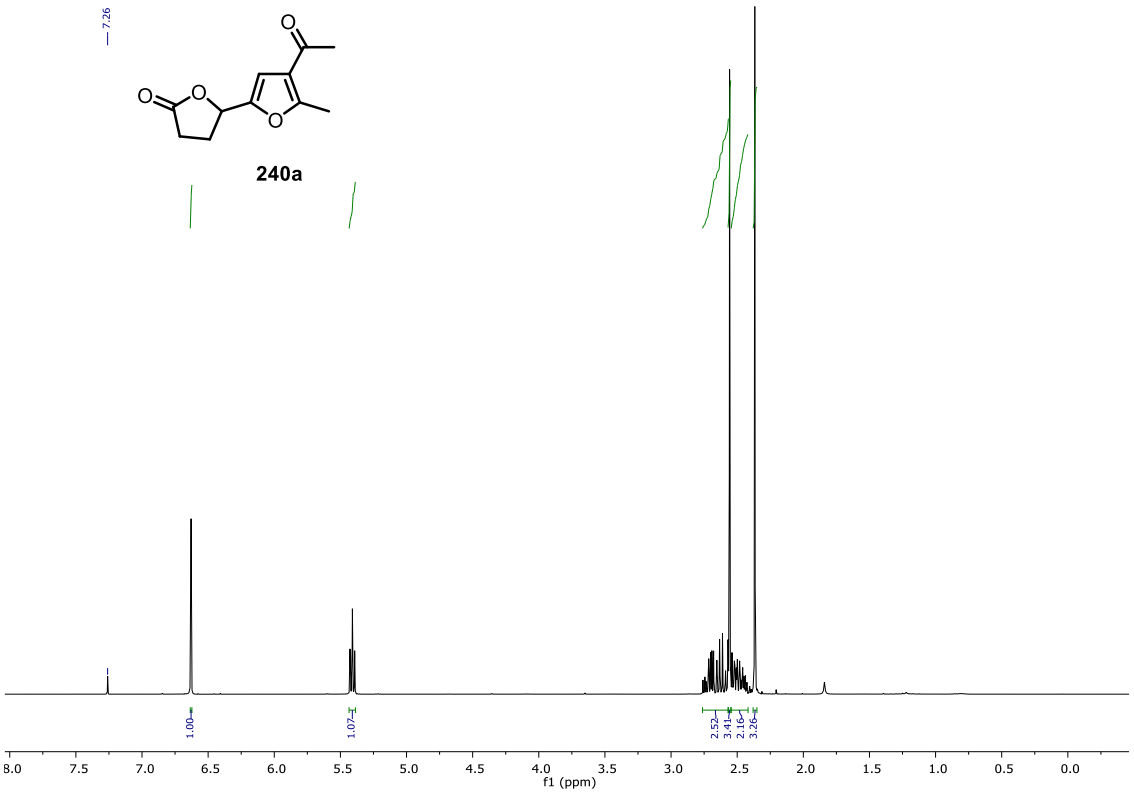
f1 (ppm)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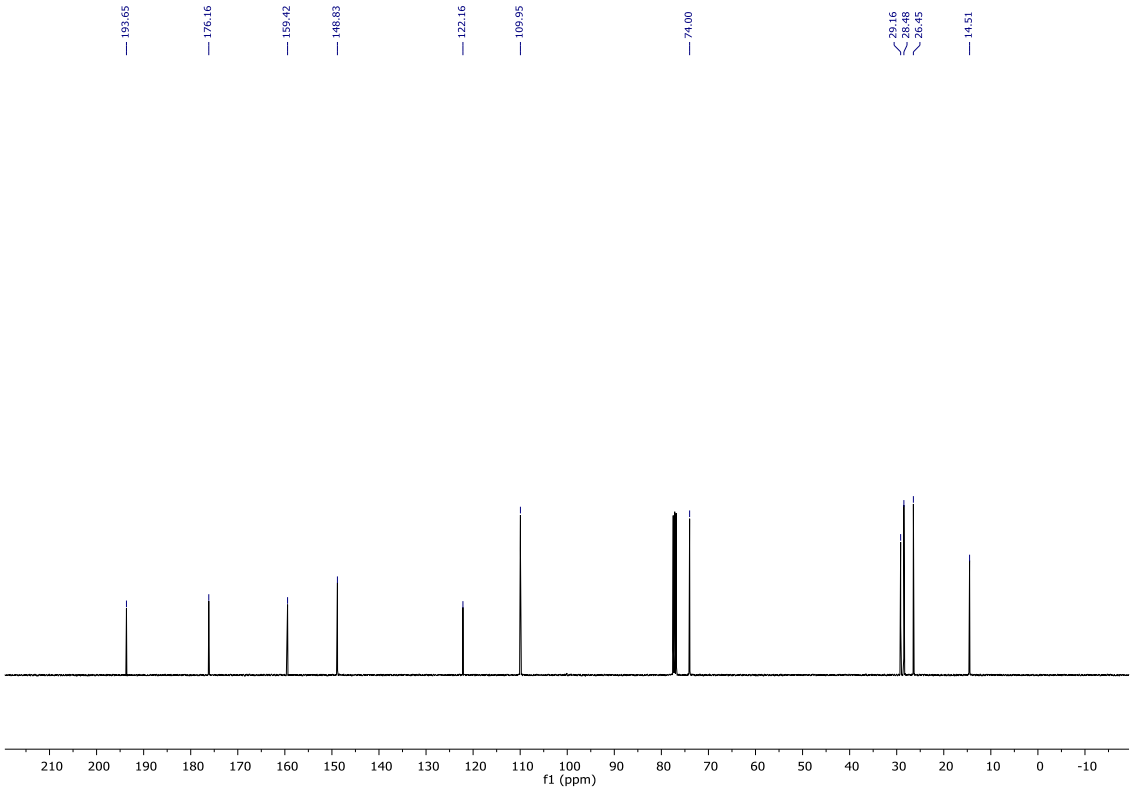
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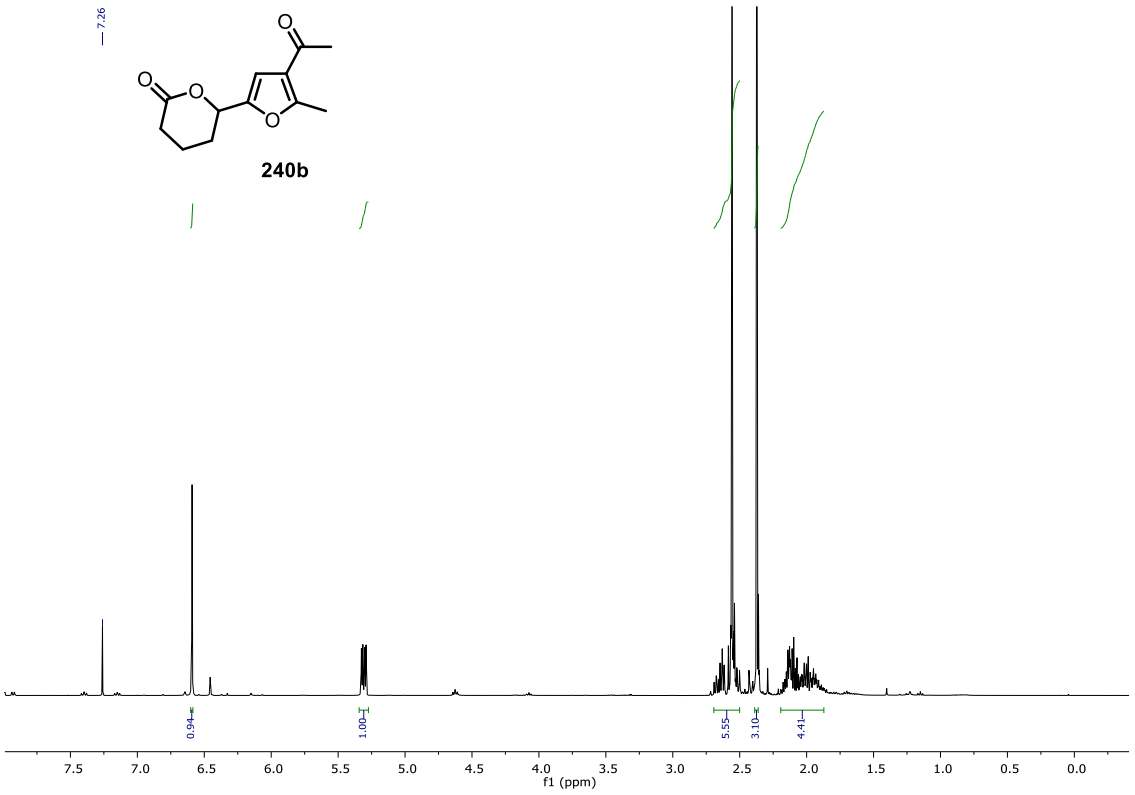
14.51
f1 (ppm)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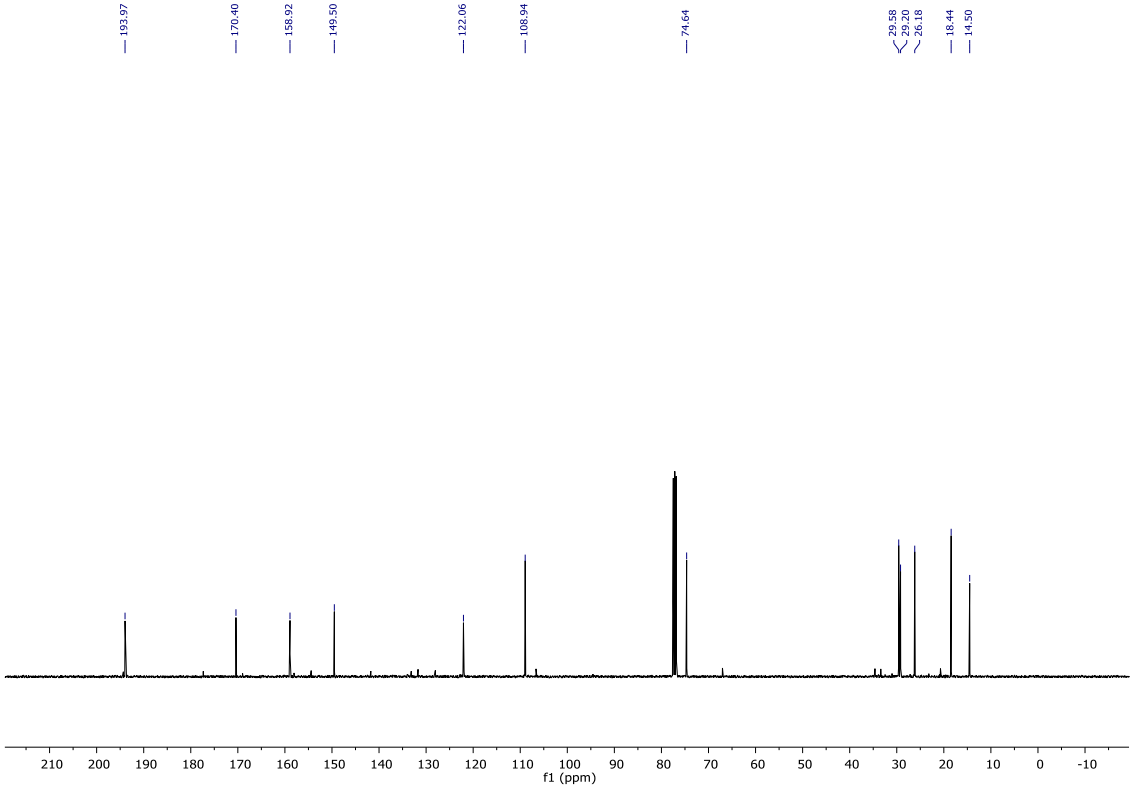
3.10
4.41
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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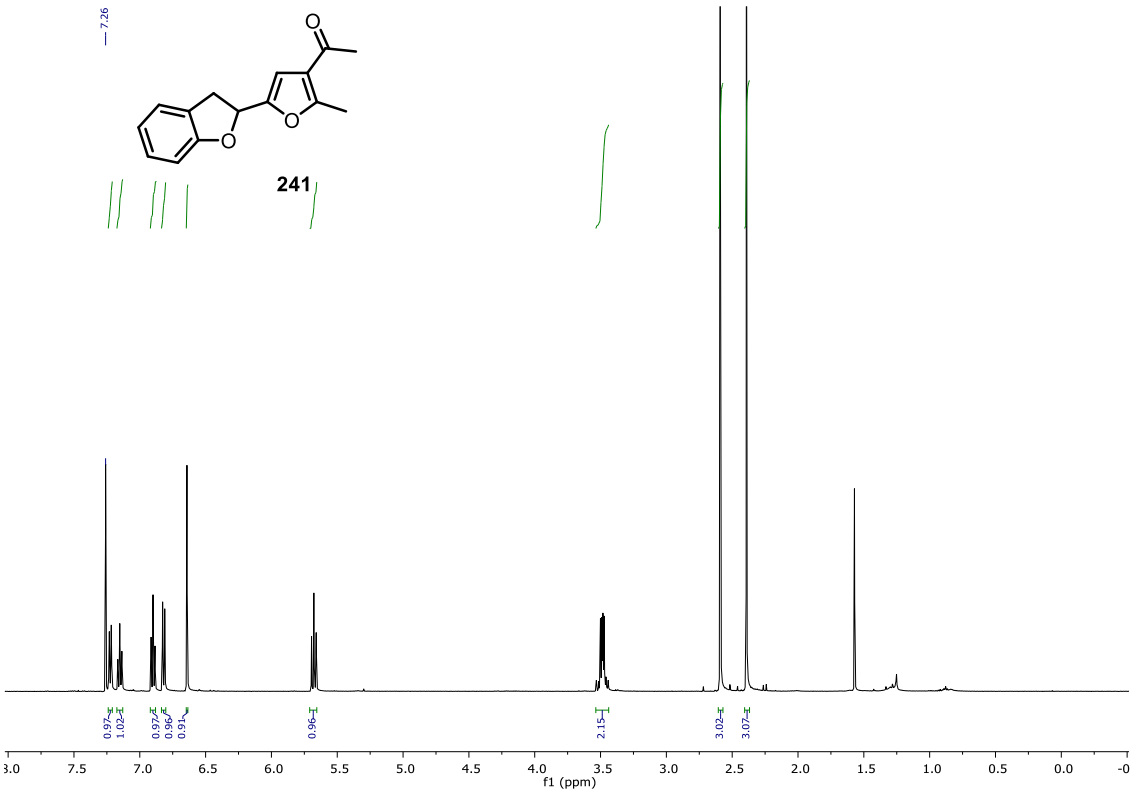
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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0.91
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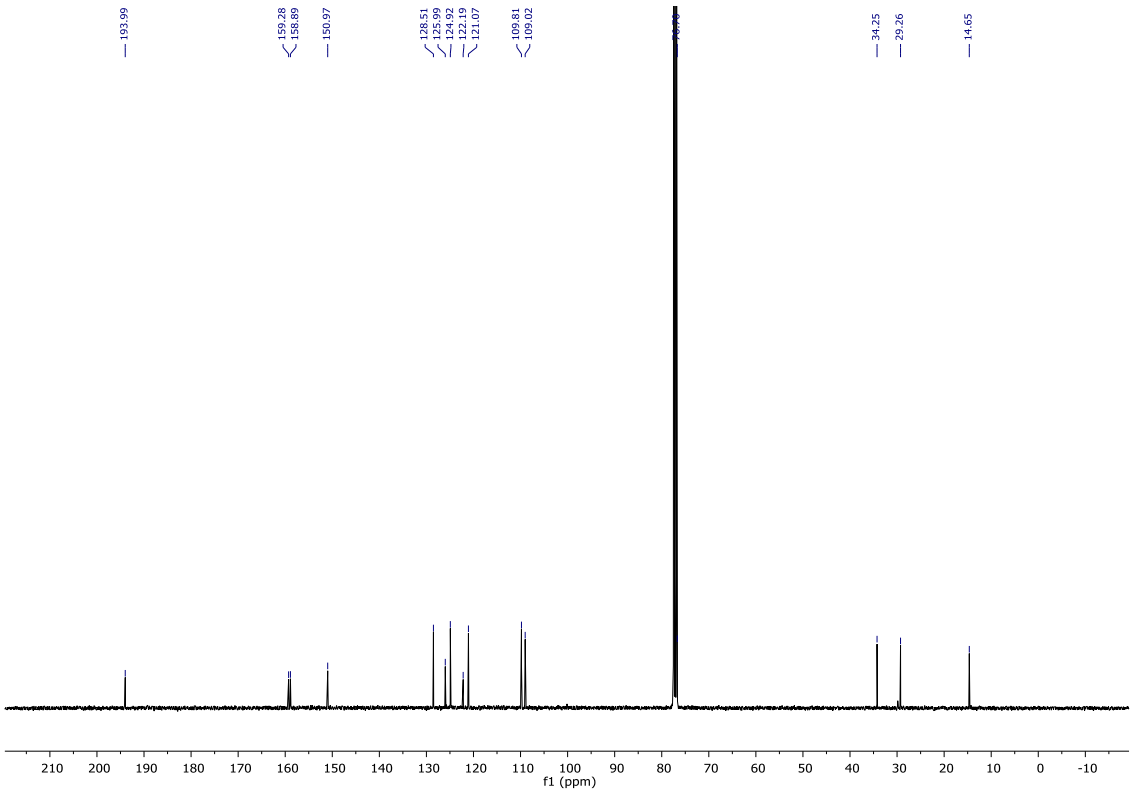
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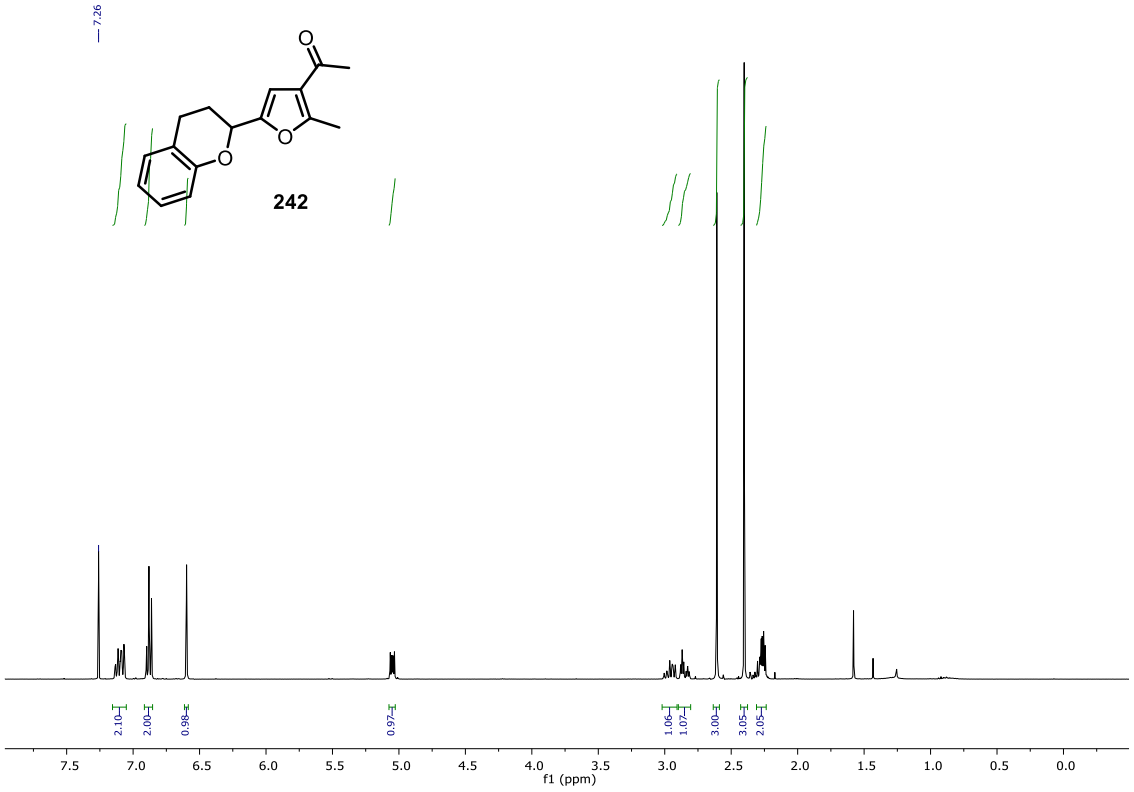
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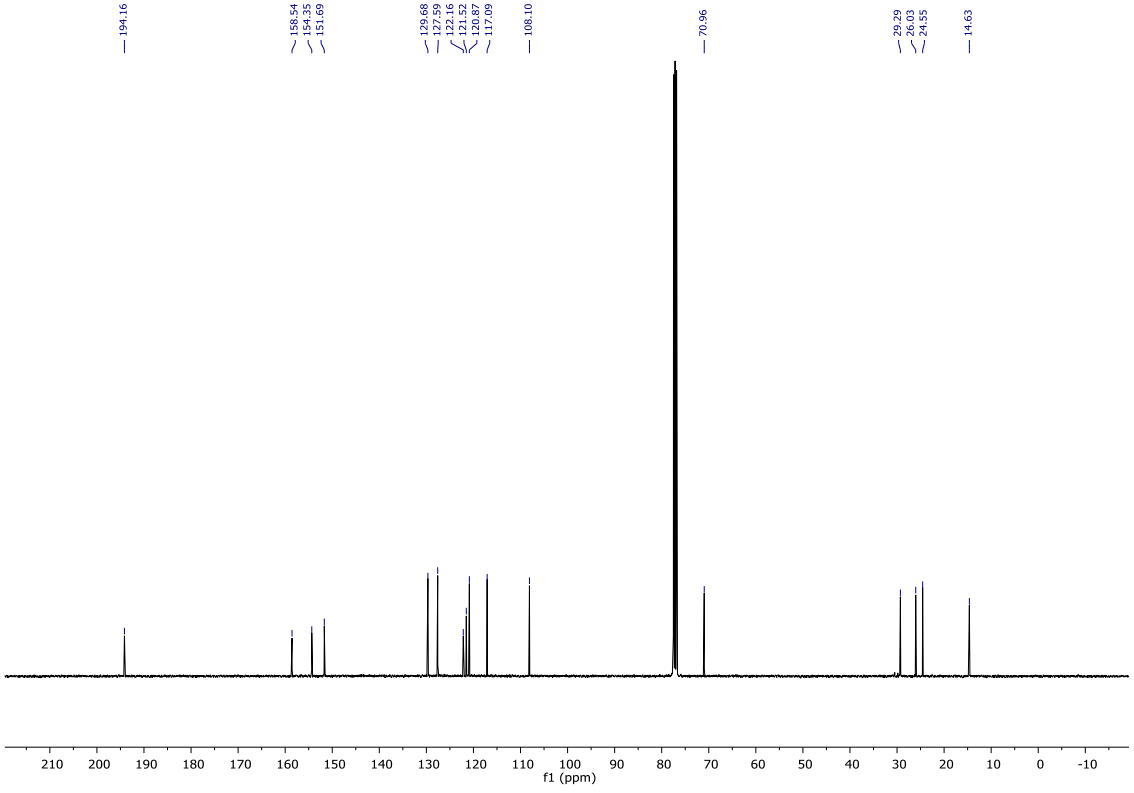
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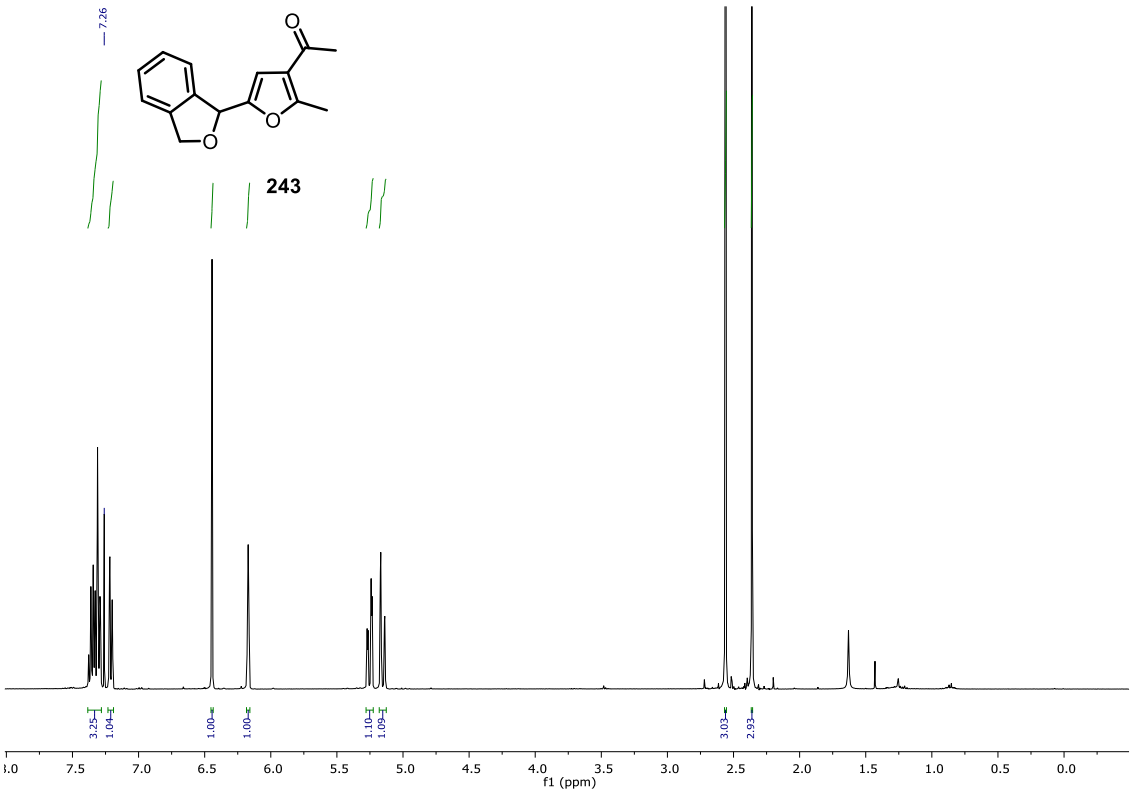
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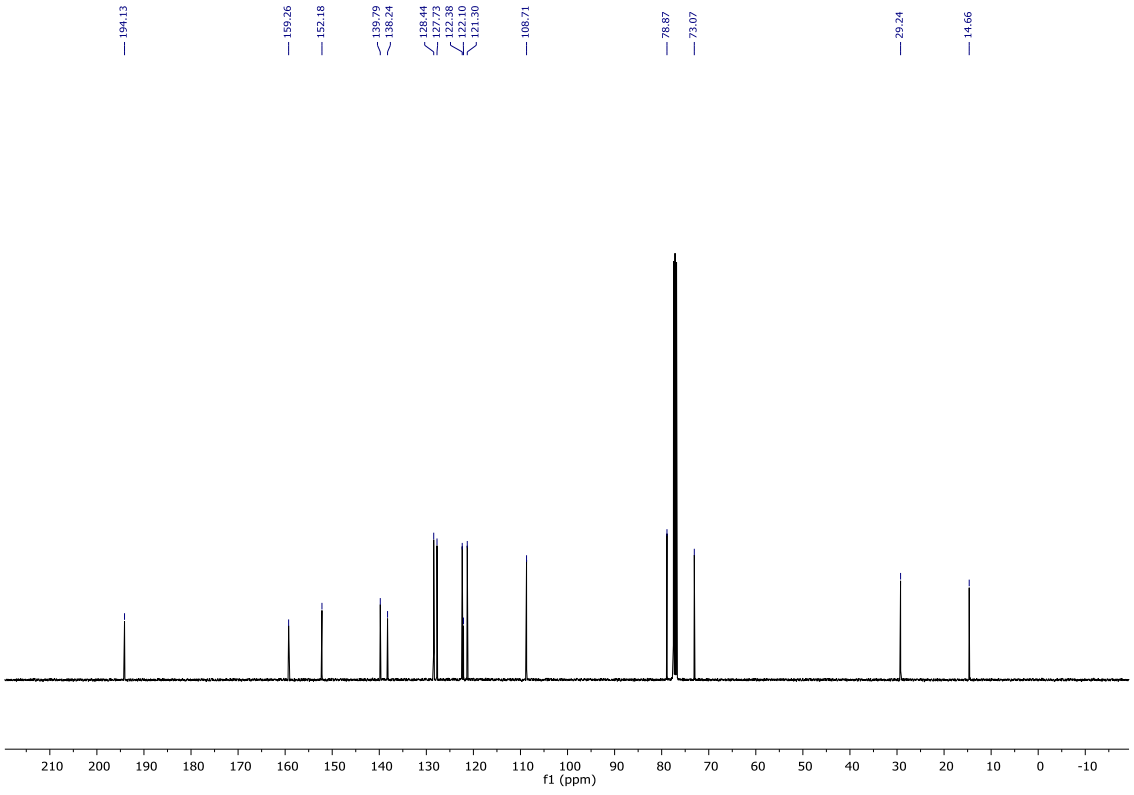
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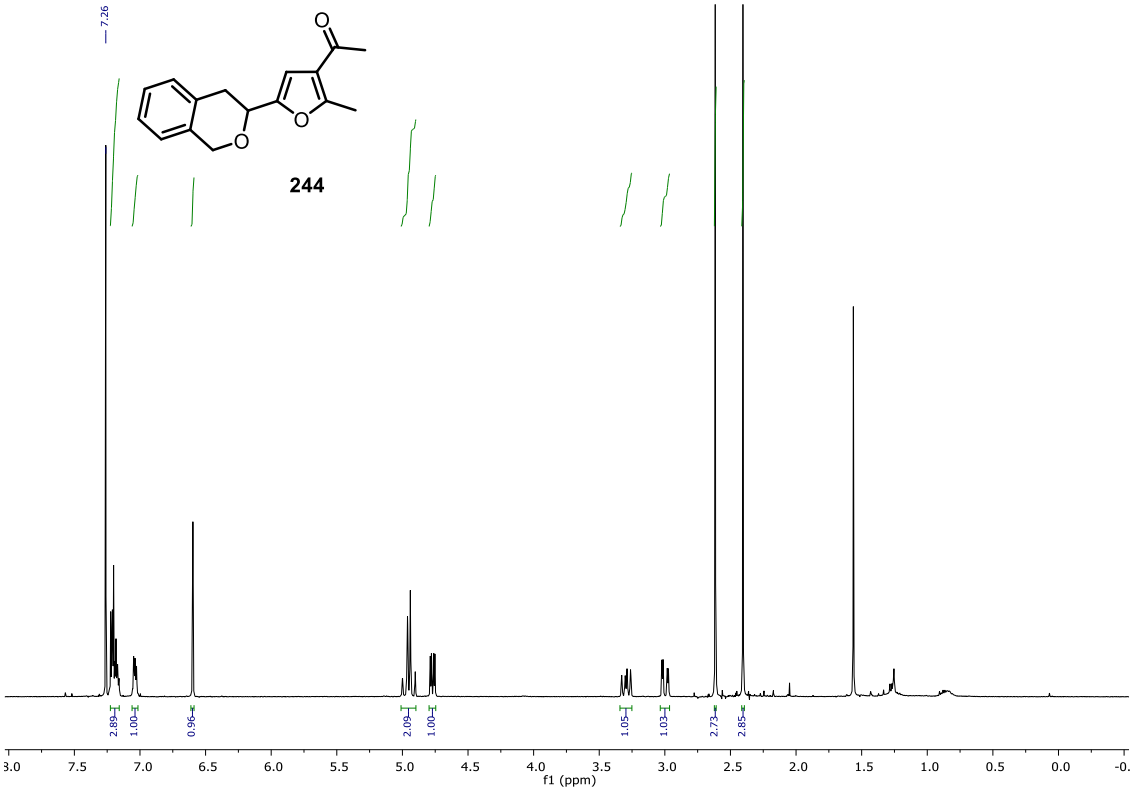
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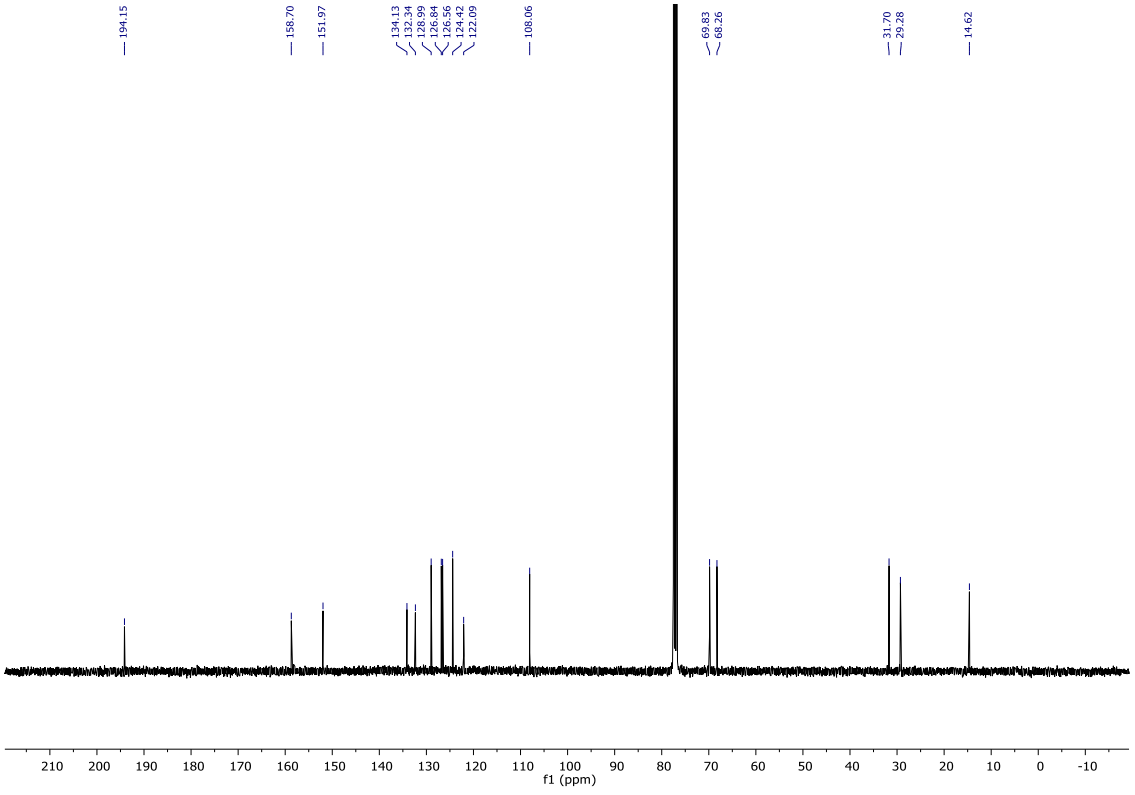
244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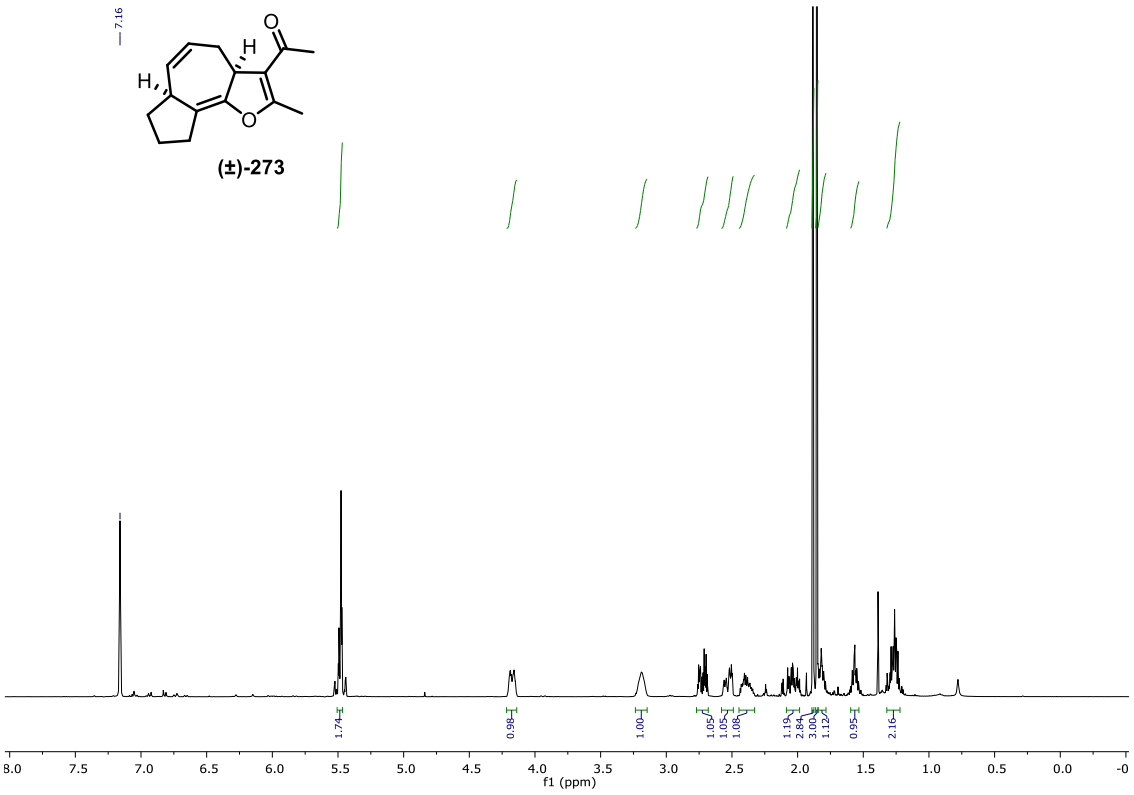
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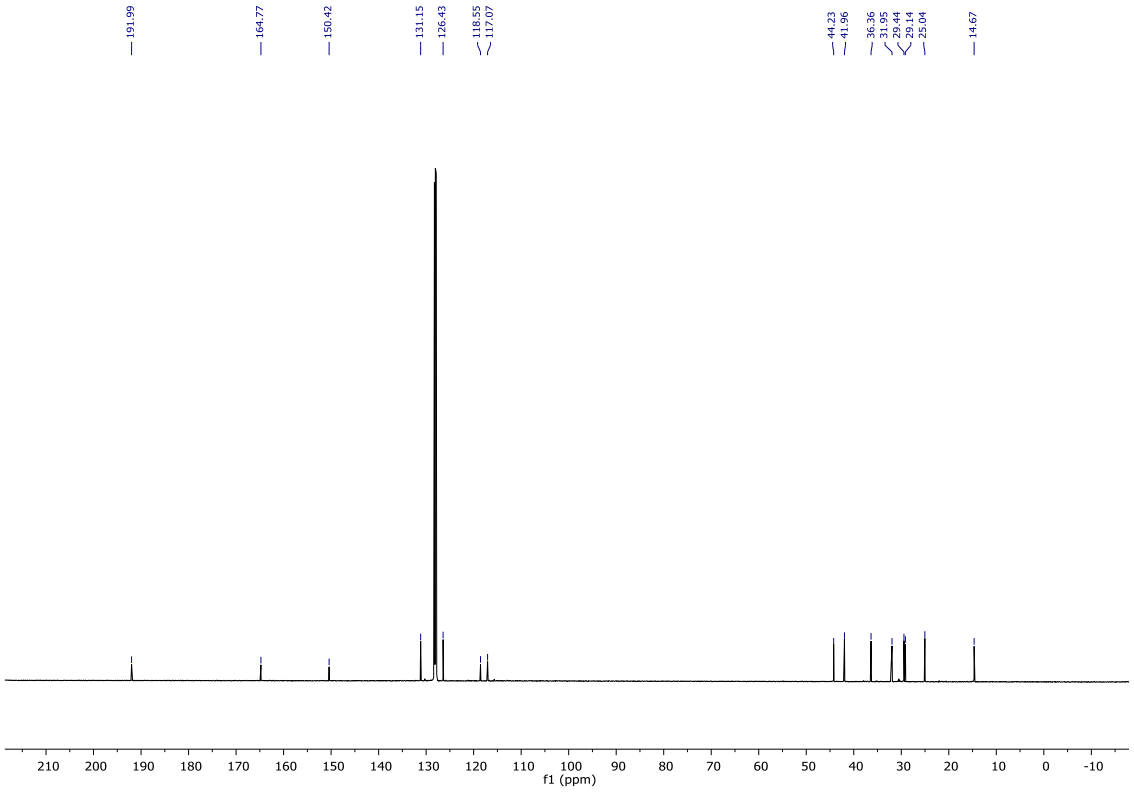
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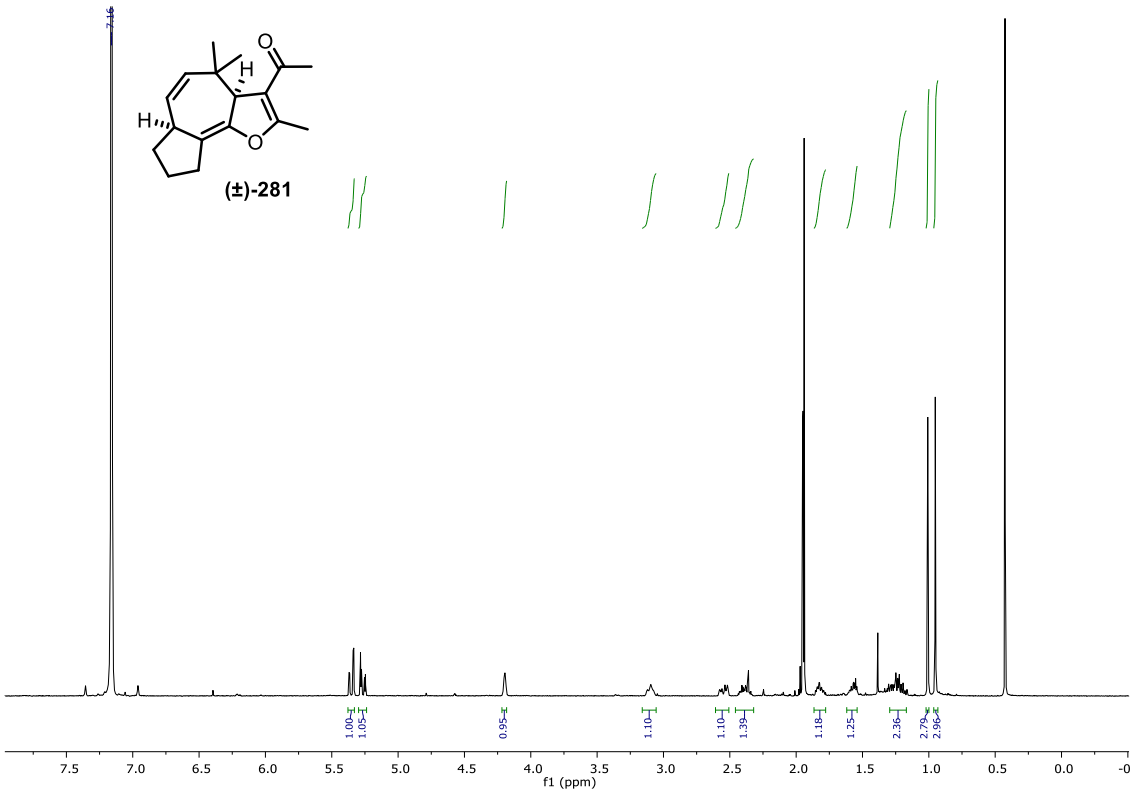
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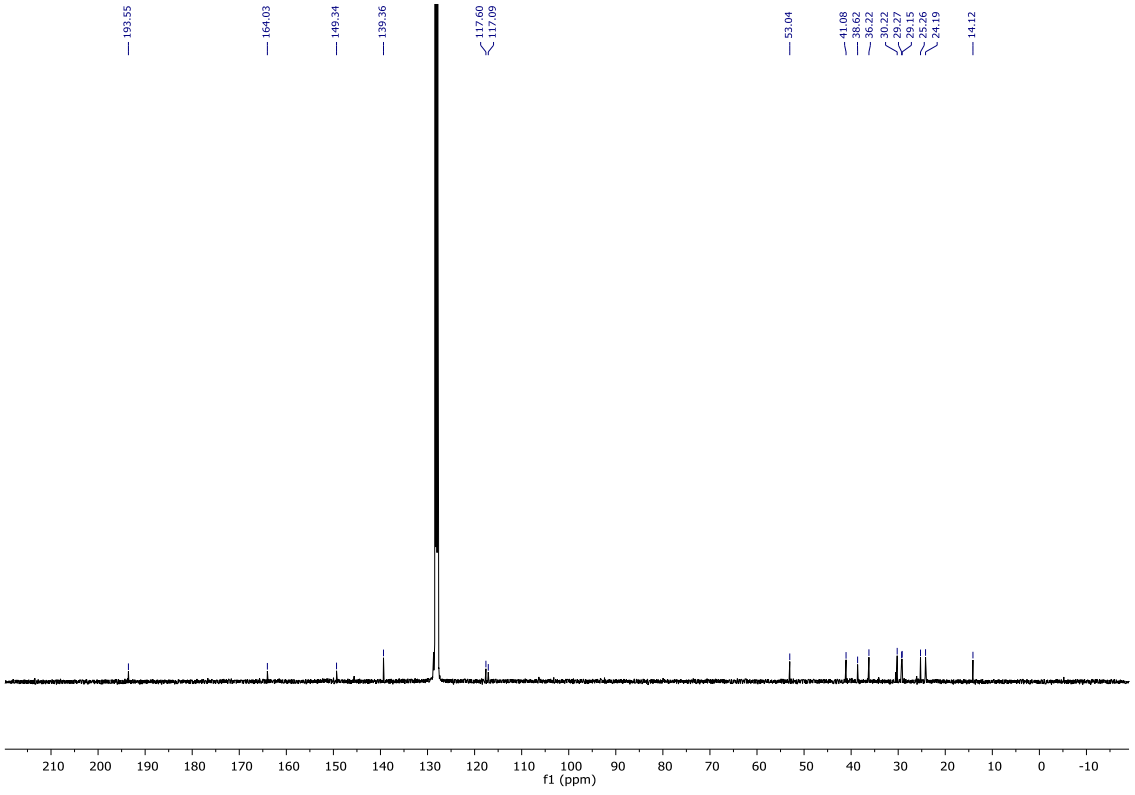
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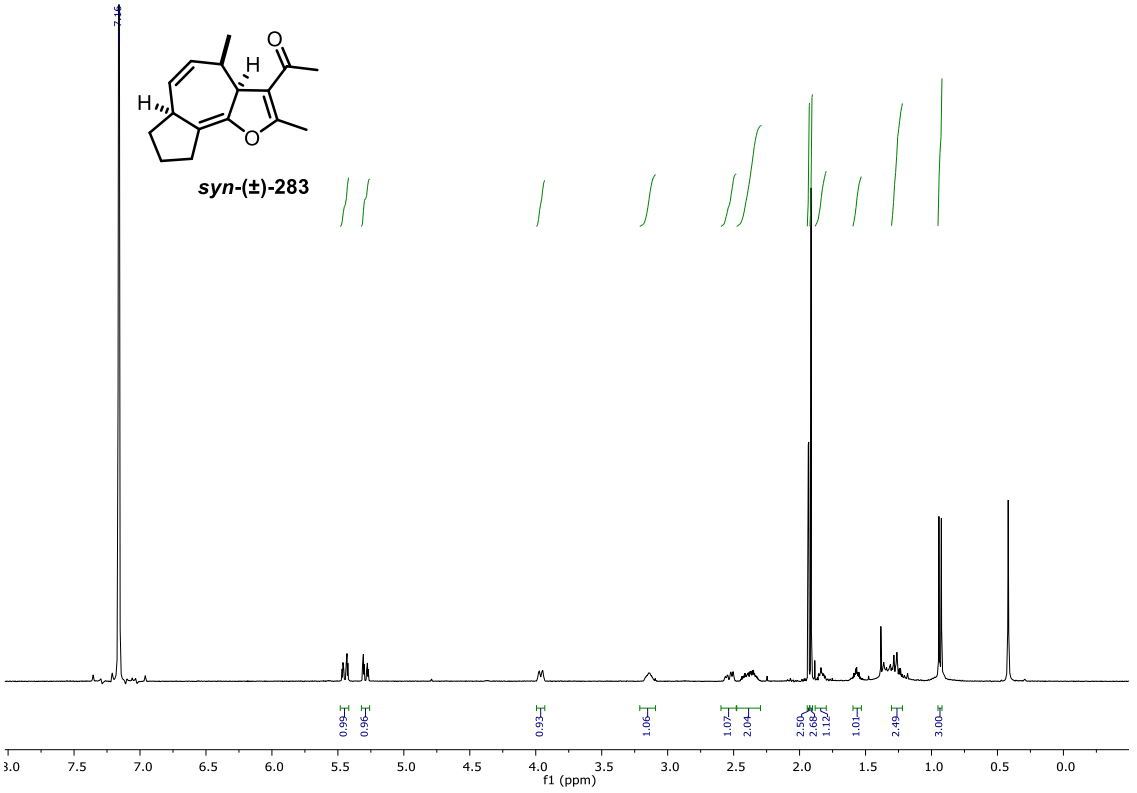
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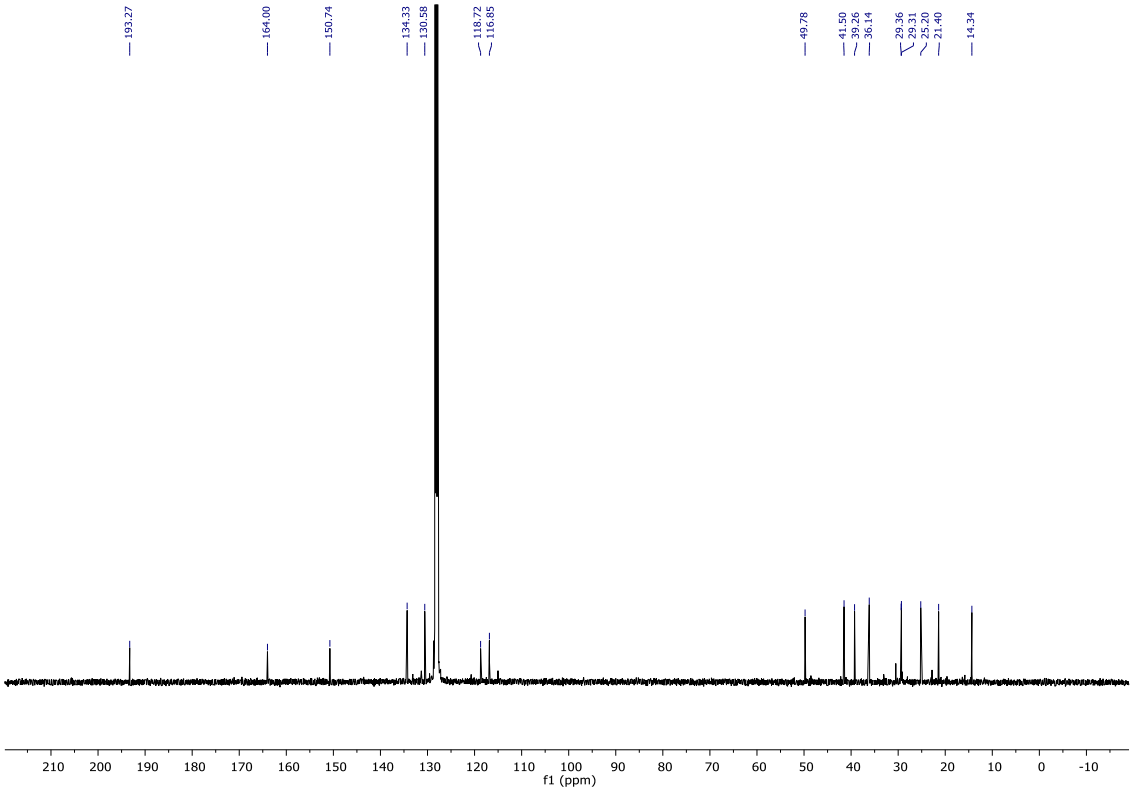
3.00
f1 (ppm)

***syn*-(±)-283**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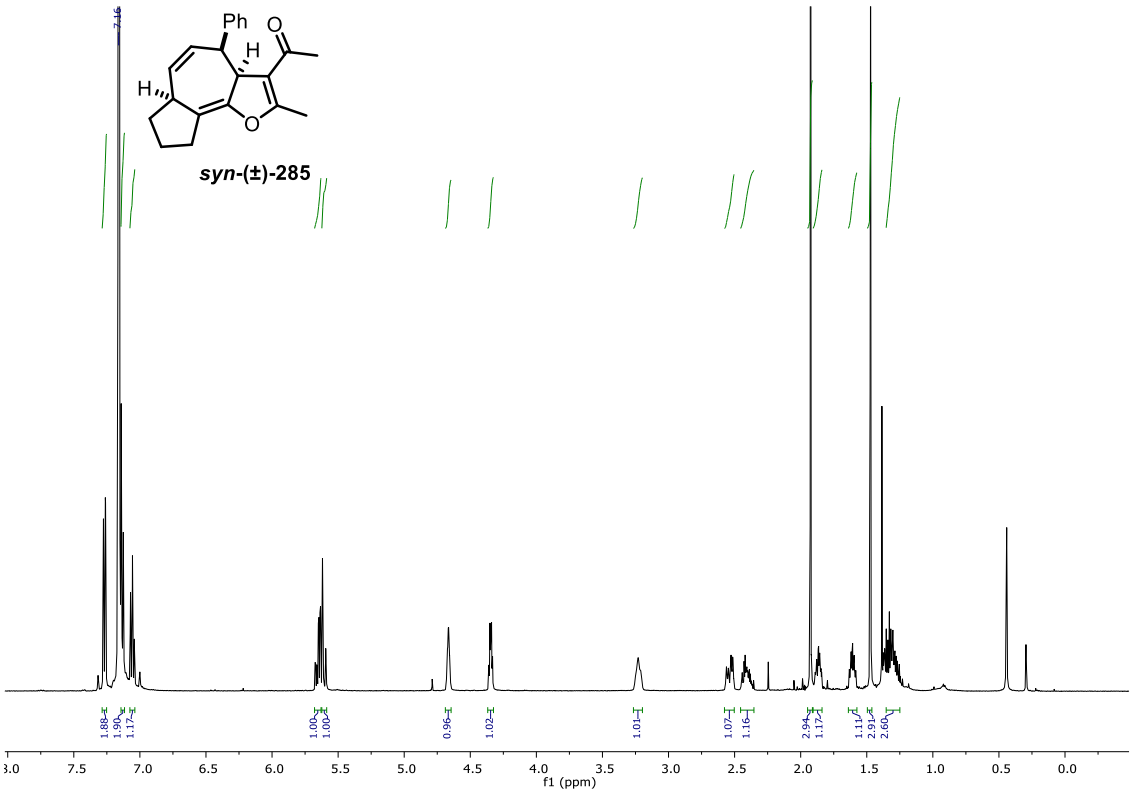
14.34
f1 (ppm)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H
O
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1.01
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2.94
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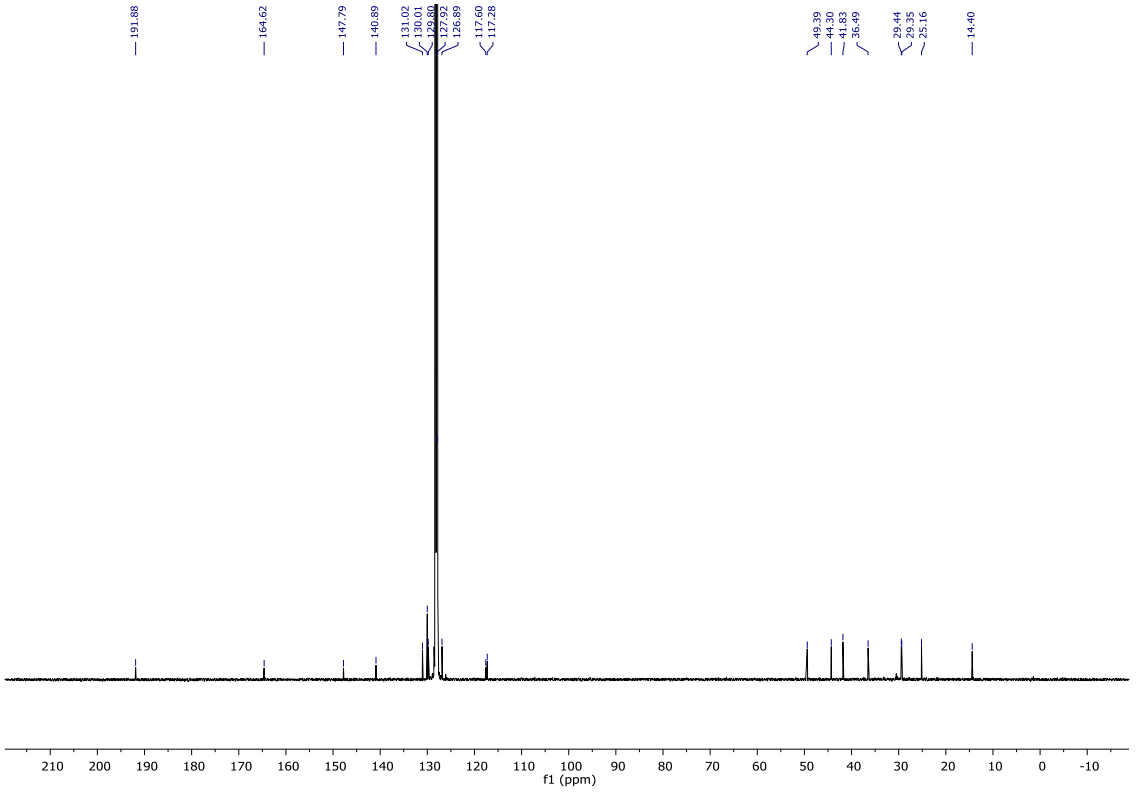
f1 (ppm)


191.88
164.62
147.79
140.89
131.02
130.01
129.80
127.92
126.89
117.60
117.28
49.39
44.30
41.83
36.49
29.44
29.35
25.16
14.40
f1 (ppm)

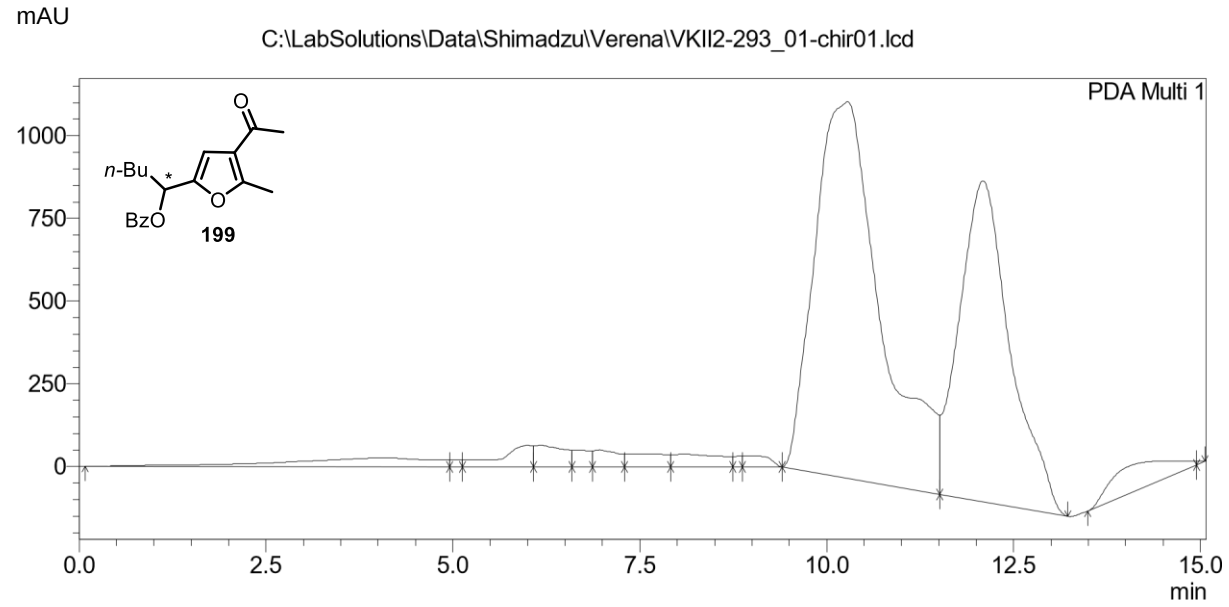
18/11/2016 16:23:01 1 / 1

HPLC Report

Sample Name	: VKII2-293_1; 1;	Injection Volume	: 20 uL
Data File Name	: VKII2-293_01-chir01.lcd		
Method File Name	: 2pcB-1mlMin.lcm		
Acquired	: 23/08/2013 18:17:53;	Data Processed	: 23/08/2013 18:33:02

0.5mL/min
10% IPA in Hexane
Colum AD-H
Oven 25 C
Chiralcel OD-H
Oven 25 C

<Chromatogram>



1 PDA Multi 1/254nm 4nm

<Results>

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.106	3793572	26646	2.823	1.041
2	5.077	210059	20547	0.156	0.803
3	5.985	2002624	65030	1.490	2.541
4	6.172	1795760	65537	1.336	2.561

5	6.645	829507	50922	0.617	1.990
6	6.958	1160618	51205	0.864	2.001
7	7.525	1425644	39142	1.061	1.529
8	8.098	1747791	38364	1.301	1.499
9	8.839	247547	32932	0.184	1.287
10	8.964	790302	32927	0.588	1.287
11	10.272	69984876	1137450	52.077	44.444
12	12.086	45893966	969866	34.151	37.896
13	14.863	4464701	19350	3.322	0.756
14	14.965	40261	9372	0.030	0.366
Total		134387228	2559289	100.000	100.000

C:\LabSolutions\Data\Shimadzu\Verena\VKII2-293_01-chir01.lcd