Pericyclic and Related Rearrangements for the Synthesis of Nitrogen Heterocyclic Ring Systems

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ASLIB Abstract

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The thesis describes synthesis and reactions of allene azides tethered to various functional groups and the application of the discovered cascade transformations towards the synthesis of radianspene J model system.

Chapter 1 covers reactions of simple allene azides containing alkyl and cycloalkyl substituents. Thermal rearrangements of these substrates delivered isocyanides and azadienes via the proposed azatrimethylenemethane (ATMM) intermediates.

On the other hand, vinylidenecyclopropanes (VDCPs) gave dramatically different products, as described in Chapter 2. A phenyl-substituted VDCP was transformed into an unstable polycyclic compound by a divinylcyclopropane rearrangement.

Chapter 3 discusses allene azides tethered to furan, *N*-substituted pyrroles, and *E*- and *Z*-dienes. Depending on the structure of the starting material, products of formal (3+4)- or (2+3)-cycloaddition were formed.

Finally, an application of the discovered cyclisation cascade towards total synthesis is described in Chapter 4. A model system of radianspene J was assembled using a key transannular cycloaddition of a macrocyclic allene.

Contents

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Above all I want to express my deepest gratitude to my parents who brought me up and gave all they had—and then let me go so far away.

Abbreviations

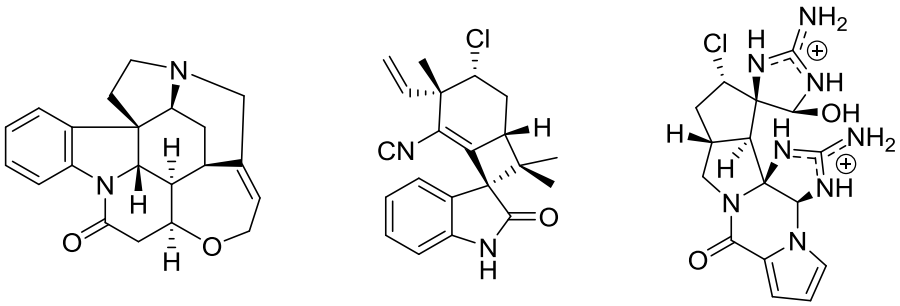
)))	sonication
Å	Ångström, 10^{-10} m
µm	micrometre, 10^{-6} m
µW	microwave irradiation
Ac	acetyl
ADMP	2-azido-1,3-dimethylimidazolinium hexafluorophosphate
ATMM	azatrimethylenemethane
aq.	aqueous
Bn	benzyl
b.r.s.m.	based on recovered starting material
Bu	butyl
Bz	benzoyl
ca.	circa (approximately)
cat.	catalytic amount, catalyst
CDI	carbonyl diimidazole
CI	chemical ionisation
COSY	correlation spectroscopy
Cp	cyclopentadienyl
d	day
dba	dibenzylideneacetone
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
d.r.	diastereomeric ratio
eq.	equivalent

ESI	electrospray ionisation
Et	ethyl
et al.	and others
FI	field ionisation
g	gram
GC	gas chromatography
hν	(ultraviolet) irradiation
H_a	axial proton
Hal	halide
H_e	equatorial proton
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
hr	hour
HSQC	heteronuclear single-quantum coherence
i-	iso-
imid.	imidazole
IR	infrared
J	coupling constant
L	litre
LDA	lithium diisopropylamide
LHMDS	lithium *bis*-(trimethylsilyl)amide
lit.	literature value
LUMO	lowest unoccupied molecular orbital
M	mole/litre
m/z	mass/charge ratio
MA	methylene aziridine
m-CPBA	3-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
mL	millilitre
mmol	millimole

mol	mole
m.p.	melting point
MS	molecular sieves, mass spectrometry
Ms	methanesulfonyl
MVK	methyl vinyl ketone (3-buten-2-one)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
oct	octyl, octanoate
Ph	phenyl
PMB	4-methoxybenzyl
Pr	propyl
PTSA	4-toluenesulfonic acid
RCM	ring-closing metathesis
R_f	retention factor
rpm	repetitions per minute
RT	room temperature
s-	sec-
sat.	saturated
SM	starting material
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEBA	benzyltriethylammonium chloride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMM	trimethylenemethane
TMS	trimethylsilyl
tol.	toluene
Ts	4-toluenesulfonyl
vs.	versus
v/v	volume-to-volume ratio
W	Watt

Introduction

Heterocycles are undoubtedly one of the most important classes of organic compounds. They constitute an essential part of our lives through the variety of their chemical and physical properties. In fact, heterocycles *are* us—all nucleic acids, cyclic sugars, and many proteins contain a variety of heterocyclic units. Heterocycles amounted for ca. 65% of the top-100 non-enzymatic drugs in 2012.[1,2] They are also important in agrochemistry and often found in natural products (Scheme 1), and thus they have always attracted significant attention from the synthetic community.[3] Nitrogen-containing heterocycles often pose an added challenge due to the high reactivity of the nitrogen atoms and numerous side reactions at these centres.

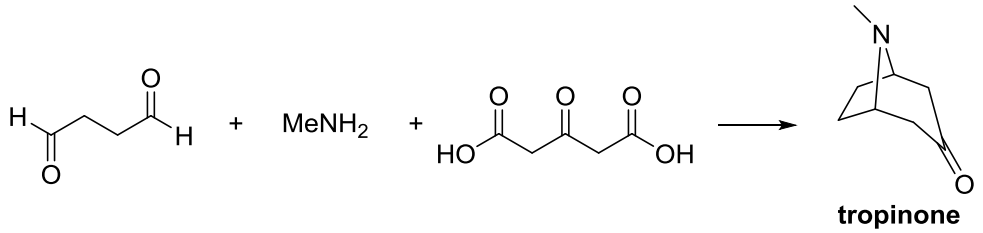


Scheme 1. Some of the challenging natural products with nitrogen heterocyclic moieties and their first total syntheses.

One of the popular ways for the rapid assembly of complex structures is by cascade (tandem)* reaction sequences.[4–7] In these processes, a product of the first reaction participates immediately in the next step without the need to be isolated. This addresses the potential instability of the intermediates and reduces the amount of waste and the total number of purification steps. In addition, tandem reactions increase the compound diversity because even small changes in the starting materials often lead

* The terms "cascade" and "tandem" will be used interchangeably in this thesis. However, one should be aware of the ongoing debate[5] on the exact definition of these concepts.

to vastly different products. Robinson's synthesis of tropinone[8] is often acknowledged[5,9] as the first example of a cascade reaction (Scheme 2).



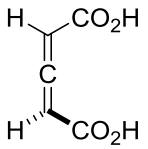
Scheme 2. Robinson's synthesis of tropinone.

Clearly, organic chemistry has advanced on many fronts since then and modern cascade processes allow the construction of fascinatingly complex structures in a highly efficient and concise manner, thus bringing us closer to the "ideal synthesis".[10]

This thesis describes cascade reactions of tethered allene azides and the products generated therein. In the introduction, general reactivity of allenes and azides is reviewed, followed by more specific allene–azide interactions including relevant work in the Robertson group. The thesis body consists of 4 chapters, each of which deals with a specific allene azide subclass. At the end, a synthesis of a radianspene J model system is used to showcase the synthetic utility of the discovered reactions.

Allene synthesis and reactivity

For many years, allenes were viewed as curiosities but thought to be synthetically useless, difficult to prepare and to work with.[11,12] Reportedly,[13] the first synthesis of an allene, glutinic acid, was performed in an attempt to prove the non-existence of this class of compounds.[14,15]



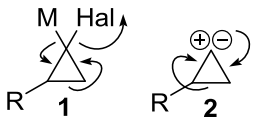
glutinic acid

The situation began to change in the 1950s, and more than 300 papers on allenes have been published in 2012 alone.* These compounds are not just interesting intermediates but synthetically valuable targets themselves; for example, over 150 natural products are known with an allene or cumulene fragment.[13]

* Data from the Web of Science database.

The chemistry of allenes has been reviewed in a number of books[11,16–18] and journal articles.[12,19–27] It is impossible to give a full account on the topic in this introduction, and thus only the most important reactions will be covered.

Some key approaches towards allenes are outlined in Scheme 3.[28–31] One of the older methods is the Skattebøl rearrangement[28,32–37] (also called the Doering–Moore–Skattebøl or Doering–LaFlamme[32,38,39] rearrangement), in which a *gem*-dihalocyclopropane **3** is treated with an organolithium compound (or dissolving metal) and the presumed intermediate **1**[37] rearranges into an allene either directly or via carbene-like species **2**.* Notably, even

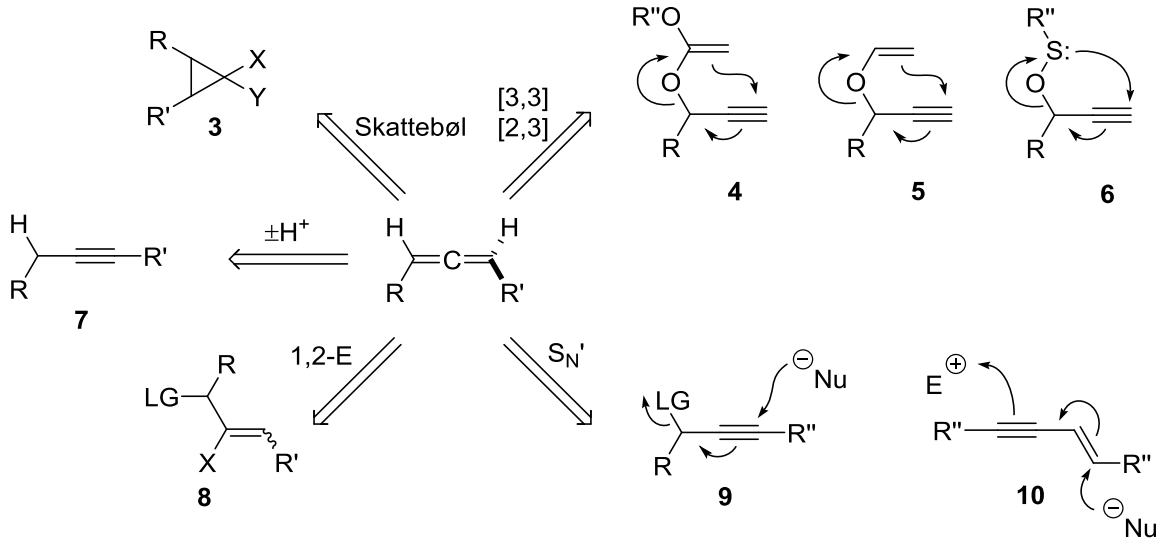


strained allenes can be generated by this procedure.[40] Modifications involving leaving groups of different nature are also known.[28]

Arguably, the most convenient modern method of allene synthesis is by sigmatropic rearrangement of propargylic substrates.[29–31] Johnson–Claisen[31,41] and Ireland–Claisen[42] rearrangements of ketene acetals **4** have been used a number of times to prepare allenic esters and acids. Interestingly, the latter reaction was originally developed in Oxford—by Baldwin[43,44]—and then rediscovered and greatly improved by Brummond in Pittsburgh.[45,46] Reactions of vinyl ethers **5** (the Saucy–Marbet rearrangement) give allene aldehydes,[47,48] while propargylic sulfenates **6** give allene sulfoxides.[49,50]

Allenes can also be prepared by nucleophilic substitution in **9** and **10** (Nu^- can be a hydride anion), 1,2-elimination from **8**, proton transfer in **7**, and other, less general, methods.[29,30]

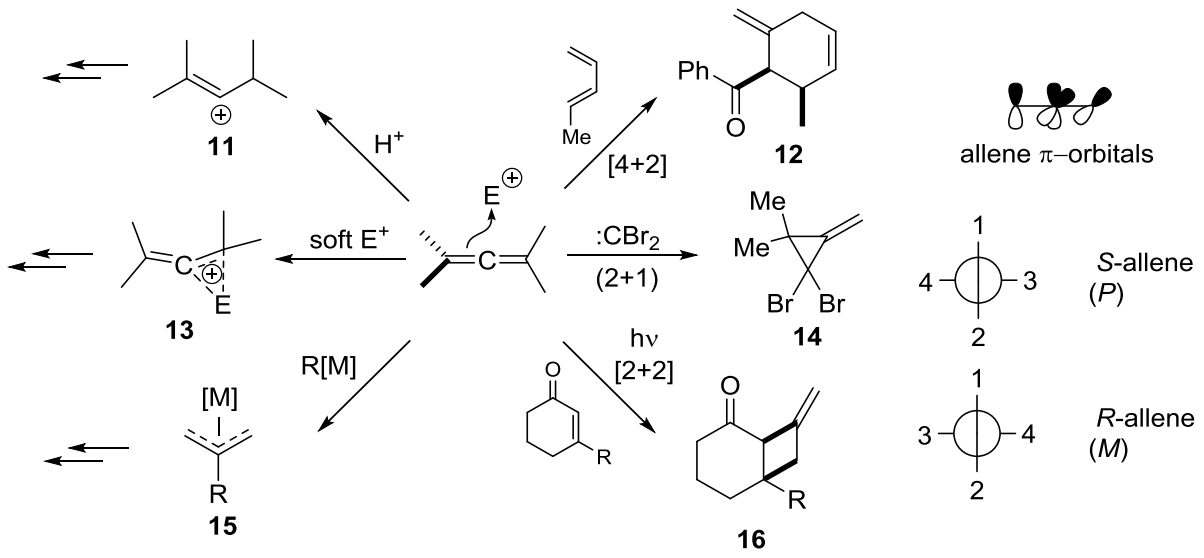
* It should be noted that the formation of a free carbene in this reaction has been disputed.



Scheme 3. Overview of the most common allene syntheses.

The reactivity of allenes is very rich and opens wide possibilities for discovery.[19,21,22,51,52] The two π-bonds are located at the 90° angle to each other (Scheme 4), and thus require a reagent to approach from somewhat different directions. With an appropriate substitution pattern, allenes exhibit axial chirality as predicted by van't Hoff in 1875.[53] Such compounds are now extensively investigated.[51,54,55]

Protonation of allenes gives cations **11** that undergo further transformations.[56] Reactions with soft electrophiles (e.g. Br^+) deliver positively charged onium ions **13**.[19] Transition-metal-catalysed reactions proceed via allylic intermediates **15** and have attracted significant interest in recent years.[57,58] Numerous cycloadditions are also known, including [4+2]-, (2+1)-, and [2+2]-variants, which deliver, e.g., **12**, **14**, and **16**, respectively. [19,59–61]



Scheme 4. Overview of allene reactivity.

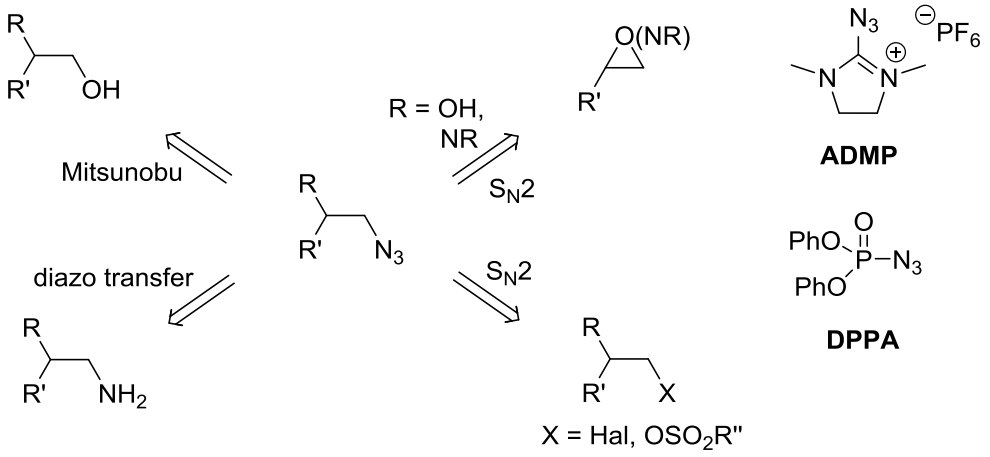
Azide synthesis and reactivity

In 2014, the chemistry of organic azides celebrates its 150th anniversary: the first representative of the class, phenyl azide ("diazoamidobenzol"), was reported in 1864 by a German chemist Peter Griess.[62,63] The field was later taken over by another German, Theodor Curtius, who obtained hydrazoic acid, HN_3,[64] and discovered the well-known Curtius rearrangement in the 1890s,[65] among many other accomplishments. Rolf Huisgen dominated this area since the 1960s, exploring the mechanisms of many azide reactions, including the eponymous 1,3-dipolar cycloaddition.[66–68]

The interest in azides among organic chemists has been relatively modest due to the reported instability of these compounds.[69] The situation has changed dramatically with the discovery by Sharpless *et al*. of Cu-catalysed (3+2)-cycloadditions between organic azides and terminal alkynes.[70,71] The azido- and the alkyne groups are "bioorthogonal", which means they do not interact with living systems, and at the same time they undergo an impressively fast and selective coupling. This type of formal 1,3-dipolar cycloaddition became the most famous example of so-called "click

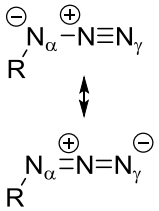
chemistry"[72,73] (perhaps, the only one known to a non-specialist), and the field of organic azides exploded.

Some common methods for the synthesis of alkyl azides are outlined in Scheme 5.[69,74–80] Undoubtedly, simple nucleophilic substitution of a suitable leaving group with an azide anion remains the method of choice. The leaving group can be halide,[81] sulfonate,[82,83] and others. The azide source is most often NaN_3, although LiN_3, $TMSN_3$, and Bu_3SnN_3 have all been used.[69] Microwave[84] and enantioselective[85] modifications of the reaction are also known. Alcohols can be converted into azides in one step using 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[86,87] or under Mitsunobu conditions with diphenylphosphoryl azide (DPPA).[88] Hydroxy- and amino-azides are accessible by the epoxide and aziridine ring cleavage, respectively.[89,90] Diazo transfer onto amines using TfN_3 and TsN_3 has been reported.[91] In recent years, direct hydroazidation of alkenes has become increasingly popular.[92]



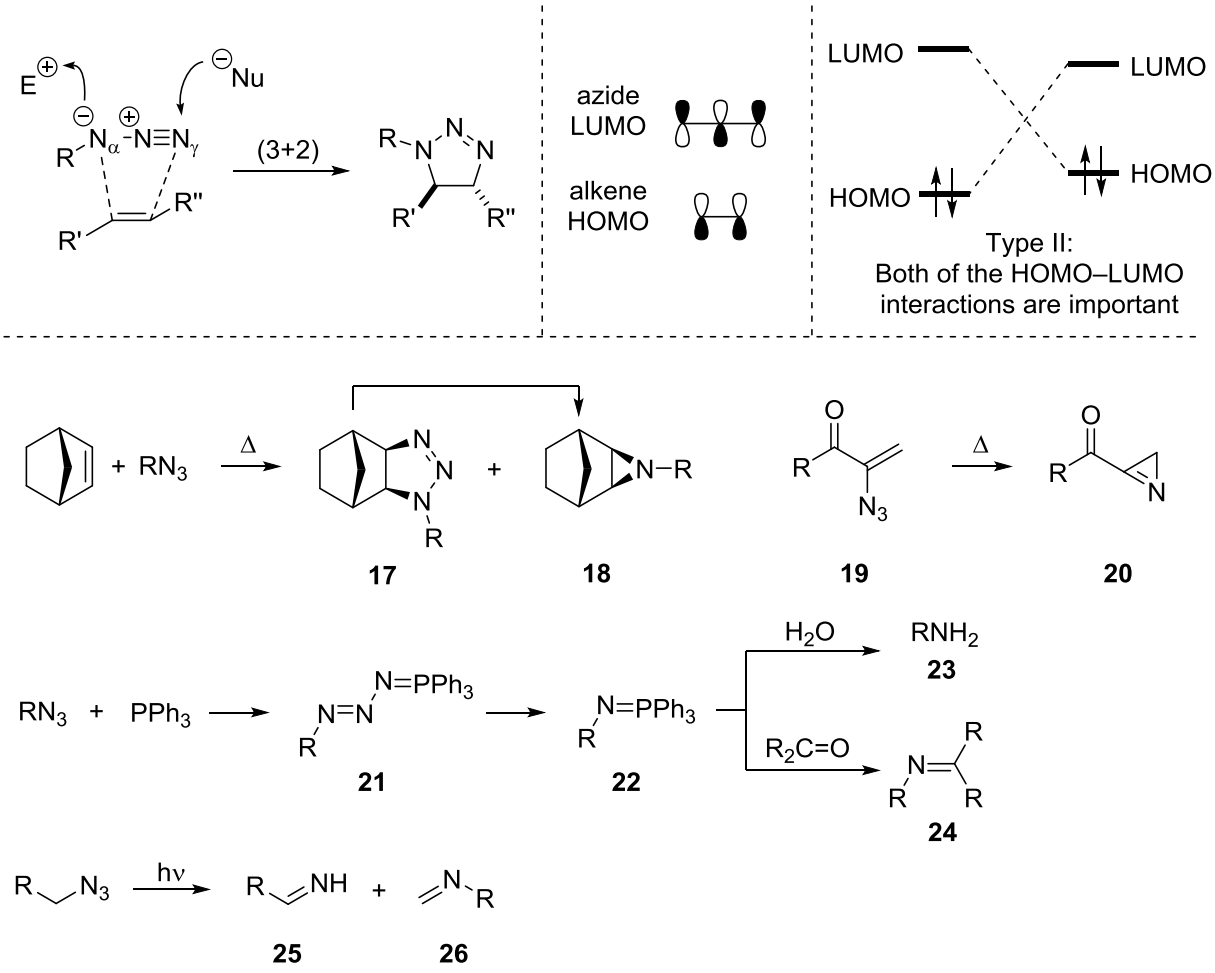
Scheme 5. Brief overview of alkyl azide synthesis.

The number of research papers on azide reactivity grows rapidly.* Some of the most important reactions, relevant to this project, are shown in Scheme 6. Generally, nucleophiles attack the azide at the terminal nitrogen N_γ, while electrophiles react at the internal atom N_α.[69] Probably the most famous is the reaction with phosphines, which leads to iminophosphoranes **22**; these can be hydrolysed into primary amines **23** (the Staudinger reaction),[93,94] react with carbonyl compounds to give imines **24** (the aza-Wittig reaction),[95–98] or undergo other transformations. Thermal decomposition of azides gives nitrenes, which participate in a variety of reactions; vinyl azides **19** decompose into 2*H*-azirines **20**.[69,99] Alkyl azides with low nitrogen-content ($[n_C + n_O]/n_N \geq 3$) are relatively stable and decompose only above ca. 175 °C.[74]



Direct photochemical decomposition of alkyl azides leads almost exclusively to imines (e.g. **25** and **26**).[69] It is proposed that the azide group is promoted to the singlet excited state and then undergoes concerted rearrangement without the intermediacy of nitrenes. The presence of triplet sensitisers, however, may change the reaction mechanism and result in the formation of triplet nitrenes. The latter were observed directly by ESR spectroscopy at −269 °C[100] as well as inferred in some photolyses.[101] Triplet methyl nitrene is 31 kJ/mol more stable than its singlet form, and thus is most likely the ground state.[69,102]

* Number of papers per year in the Web of Science database with the topic keyword “azide”: 800 in 2000, 1,400 in 2009, 2,100 in 2010, and 2,600 in 2012.

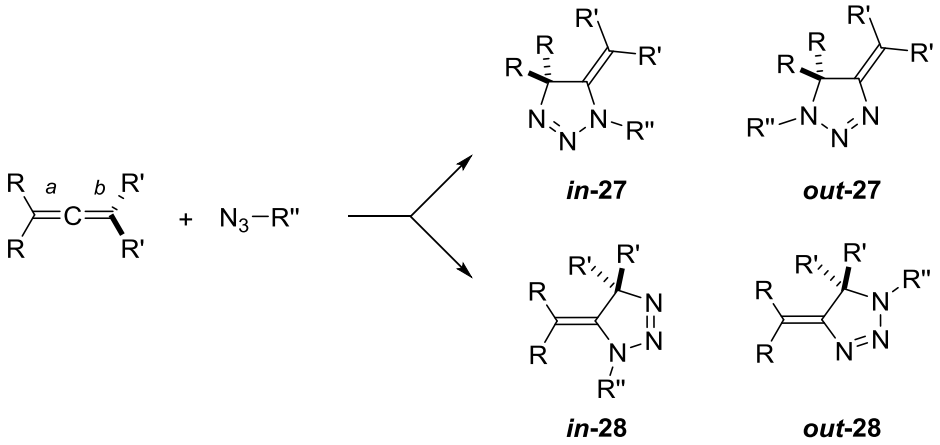


Scheme 6. Brief overview of azide reactivity.

The (3+2)-cycloaddition of azides to double or triple bonds is one of the most utilised cycloadditions in organic chemistry and affords triazolines (e.g. **17**) or triazoles, respectively.[66,76,103,104] The uncatalysed reaction is a concerted pericyclic process,[67] in which the configuration of the alkene component is transferred to the triazoline product. The Woodward–Hoffmann denomination is $[_{\pi}4_{s}+_{\pi}2_{s}]$ and the reaction is symmetry-allowed. According to Sustmann, this is a Type II cycloaddition, which means the two HOMOs and the two LUMOs have comparable energies, and thus both electron-withdrawing and electron-donating substituents may lead to an increase in the reaction rate.[105,106] The reaction is generally free from significant solvent effects because both the reactants and the transition state (TS) are non-polar.[107]

Previous work on allene azides

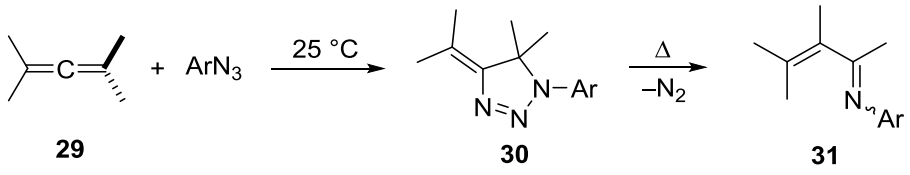
Reactions of allenes with various dipoles were reviewed recently by Pinho e Melo.[108] From a purely geometrical point of view, the *intermolecular* cycloaddition between an allene and azide can lead to the formation of either *out*- or *in*-triazolines **27**–**28**, as defined in Scheme 7. Importantly, the *out*-isomers but not the *in*-ones have conjugated C=C and N=N bonds.



Scheme 7. Possible products of allene–azide (3+2)-cycloadditions.

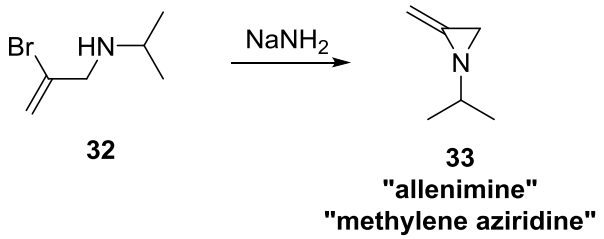
When the substituents R and R' differ, chemoselectivity issues (bond *a* vs. *b*) can arise to further complicate the process. As mentioned earlier, the two bonds of the allene require the reagent to approach in two different planes that are oriented at 90° to each other.

The seminal report on allene–azide cycloadditions was published by Bleiholder and Schechter in 1968.[109] They found that tetramethylallene **29** reacts with electron-deficient azides at RT to give crystalline *out*-triazolines **30** as the only products (Scheme 8). Heating of the latter produced azadienes **31**.



Scheme 8. First example of the allene–azide (3+2)-cycloaddition.

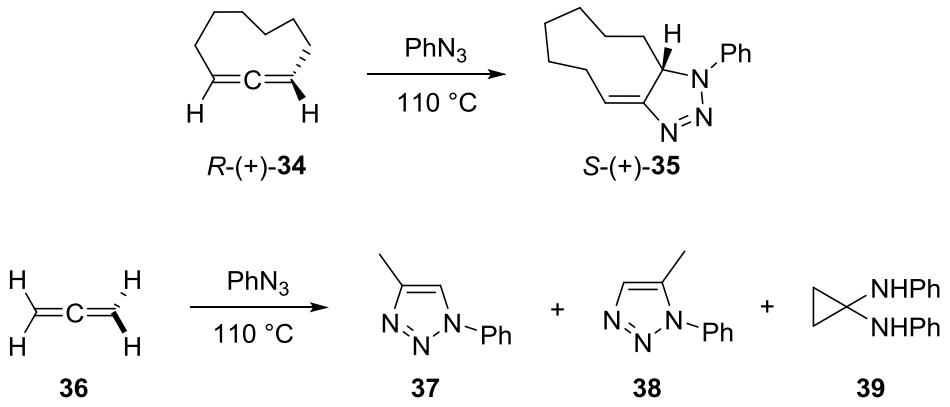
It was known at the time of Bleiholder and Schechter's report that treatment of **32** with strong bases gives “allenimines" **33** (later dubbed methylene aziridines, MAs; Scheme 9)[110] but, despite the expectations, these compounds were not observed in photochemical or thermal reactions of the aforementioned triazolines **30**.



Scheme 9. Formation of methylene aziridine **33.**

The rate and regiochemistry of allene–azide reactions are highly sensitive to steric factors. For example, chiral macrocyclic allene *R*-(+)-**34** was converted enantio- and regioselectively into the *out*-triazoline *S*-(+)-**35**, whereas more sterically accessible allene **36** gave a mixture of three products: **37**, **38**, and **39** (Scheme 10).[111]

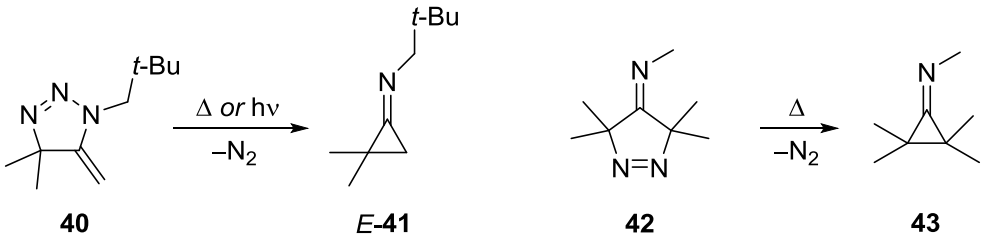
As can be seen from these examples, intermolecular reactions between allenes and azides generally favour the *out*-triazoline products with conjugated C=C and C=N bonds. High levels of stereocontrol as well as quantum chemical computations support the concerted cycloaddition mechanism.[112]



Scheme 10. Differences in reactivity of allenes **34** and **36** with phenyl azide.

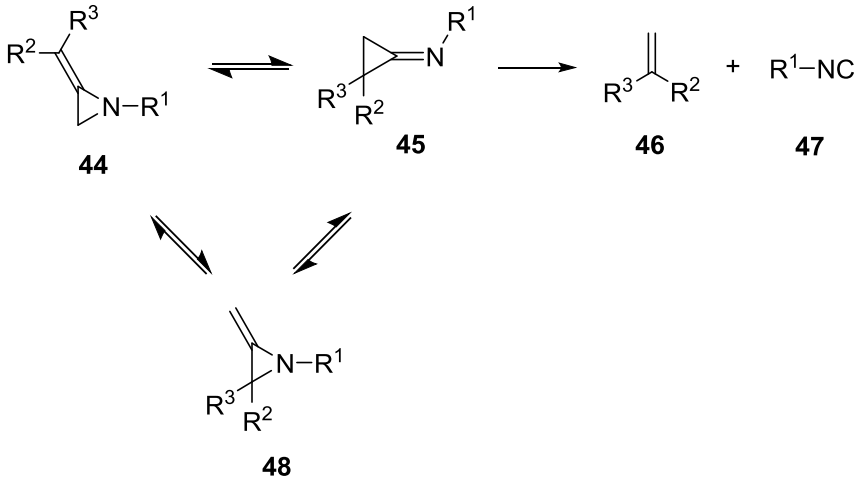
In-depth studies on unstable azoles and aziridines were performed by the group of Quast[113–123] who demonstrated that non-conjugated *in*-triazoles, such as **40**, undergo

thermal or photochemical decomposition into *E*-imine **41** (Scheme 11).[113,115] Related species **43** was isolated from the reaction of pyrazole derivative **42**.



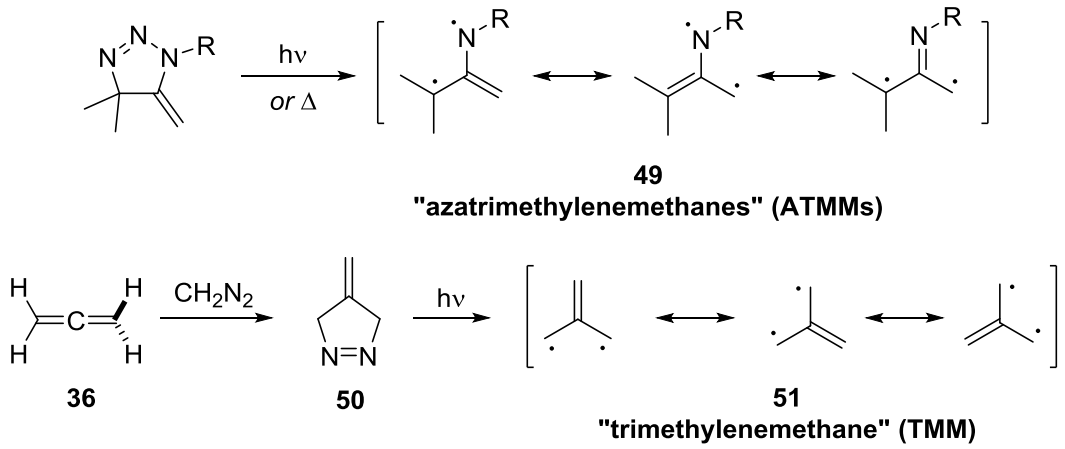
Scheme 11. Formation of MAs from triazoline **40** and pyrazoline **42**.

It was shown that various MAs **44** undergo valence isomerisation into **45** and **48** at increased temperatures (Scheme 12).[114,123] Further reaction afforded isocyanides **47** and alkenes **46**; these are thought to arise from the (2+1)-cycloreversion of cyclopropane imine **45**.[113–116] Similar products were also reported more recently by Huisgen.[124]



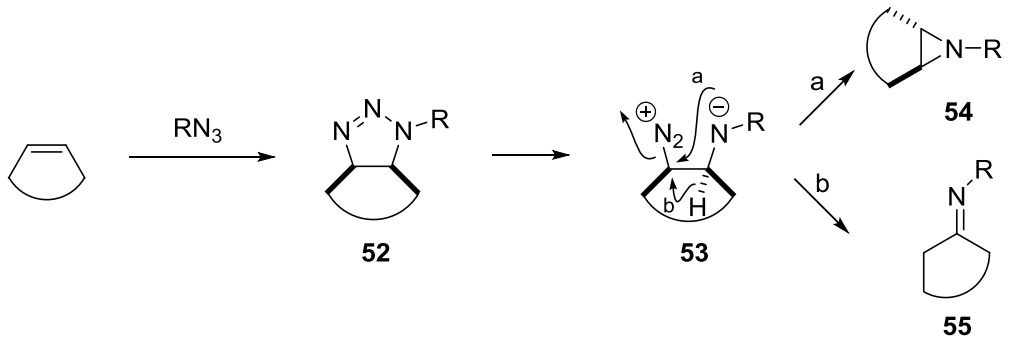
Scheme 12. Formation of isocyanides from MAs.

The mechanisms of these remarkable reactions have been extensively investigated by Quast who proposed the formation of delocalised diradical species **49** (Scheme 13), dubbed "azatrimethylenemethanes" (ATMMs).[115,123] These are related to the better known trimethylenemethane (TMM), **51**, first obtained by Dowd by the photolysis of Δ_1-pyrazoline **50**.[125]



Scheme 13. Formation of ATMMs and TMM.

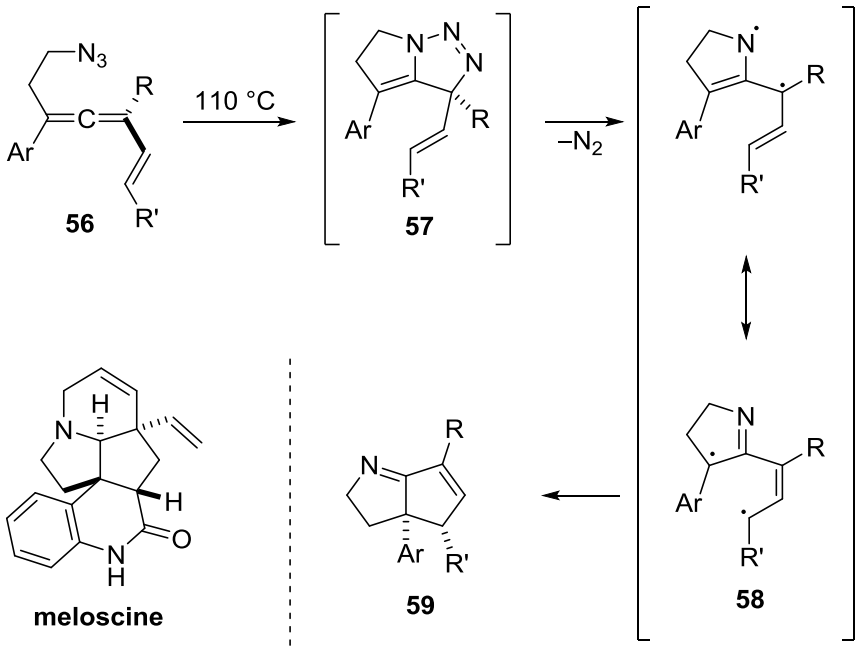
Interestingly, while Quast and others (see below) advocate the diradical structure for the products of nitrogen elimination, several studies have been published that postulate ionic intermediates.[126,127] Shea investigated the decomposition of polycyclic adducts **52** into compounds **54** and **55** and proposed zwitterionic species **53** (Scheme 14).[128] High-level computations on various aza-analogs of TMM indicated inherent computational issues with ATMMs and the intermediate nature of these species between purely diradical TMM (**51**) and zwitterionic 2-oxyallyl species.[129]



Scheme 14. Proposed cleavage of triazolines via ionic intermediates.

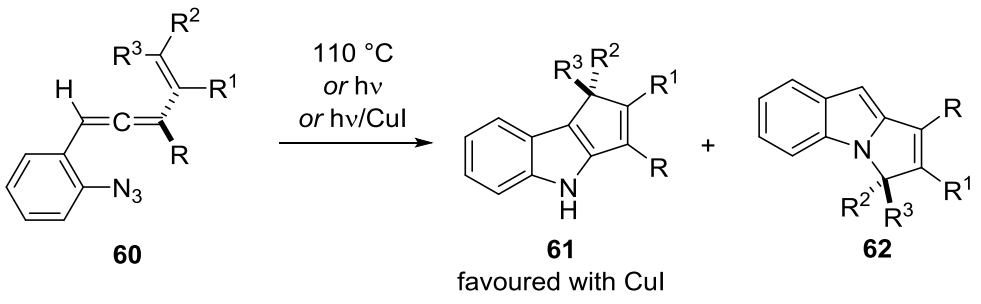
As of 2013, the group of Feldman is the most active in the field of allene–azide cycloadditions.[112,130–137] This group showed that conjugated allene azides **56** can be transformed into bicyclic products **59**, presumably via triazolines **57** and diradical intermediates **58** (Scheme 15).[136] Extensive quantum chemical computations were performed to support the proposed diradical mechanism.[112,135] Azadienes **59** were

rather unstable and had to be immediately hydrogenated[136] or trapped in situ with TMSCN.[130] Functionalised azadiene (not shown), related to **59**, was later elaborated into the natural product meloscine.[137]



Scheme 15. Cascade cyclisations of tethered allene azides by the group of Feldman.

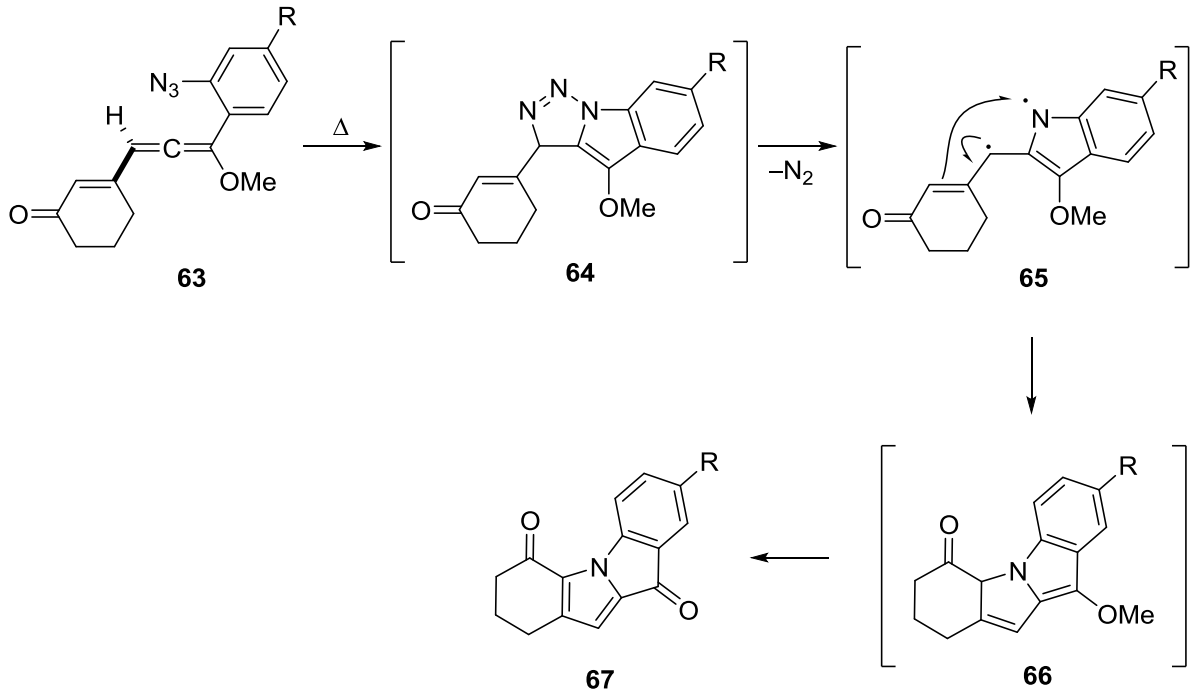
In a related project, fully conjugated allene azides **60** were transformed into indoles **61** and **62** (Scheme 16).[134] The reactions could be induced thermally (110 °C) or photochemically. Interestingly, Cu^{I} catalysis favoured the formation of indole compounds **61**.



Scheme 16. Cyclisation of conjugated allene azides.

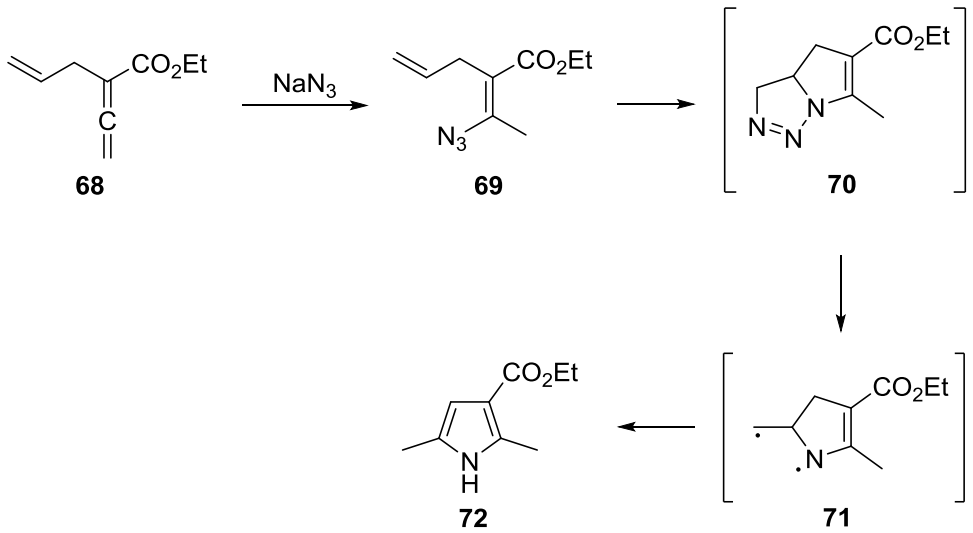
Huang *et al*. developed a conceptually related cascade synthesis of oxindoles.[138] Allene azides **63**, obtained by the Pd-catalysed coupling between 3-iodocyclohexen-2-

one and a propargylic ether, were transformed in situ into ATMM **65**; ring closure and hydrolysis afforded oxindoles **67** in 49–76% yield (Scheme 17).



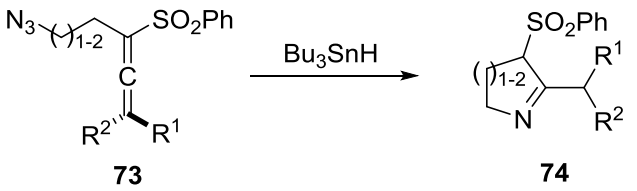
Scheme 17. Formation of oxindoles from tethered allene azides.

Reactions of inorganic azides with electronically biased allenes often give Michael addition products. For example, the reaction of electron-deficient allene **68** with NaN_3 delivered conjugated azide **69** (Scheme 18).[139] The latter was converted into substituted pyrrole **72** by gentle heating (80 °C).



Scheme 18. Michael addition of azide anion to allenes and subsequent pyrrole formation.

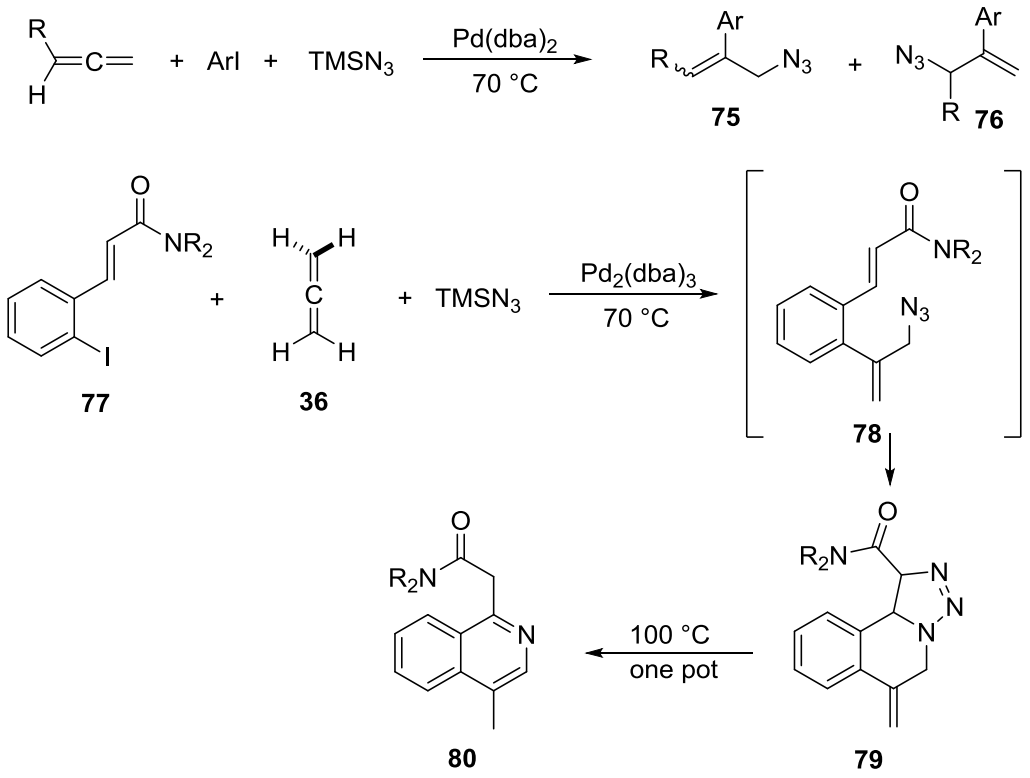
Reactions of sulfonyl allene azides **73** with Bu_3SnH at RT furnished 1-pyrrolines **74** in good to excellent yields, presumably by the 1,4-addition of the in situ formed amine (Scheme 19).[49]



73 **74**

Scheme 19. Cyclisations of allene azides in the presence of tin reagents.

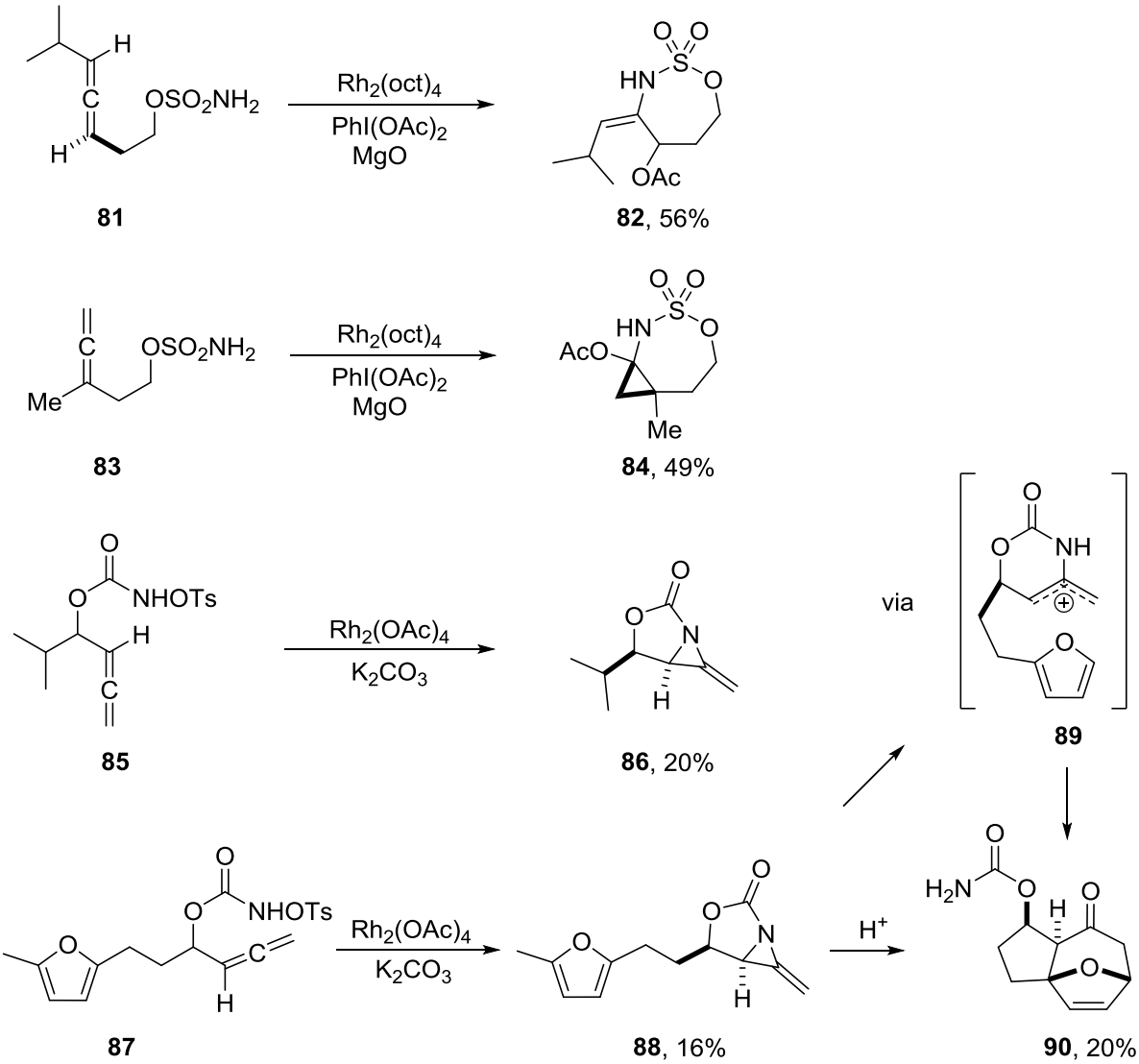
Transition-metal-catalysed reactions are also reported (Scheme 20).[140,141] Cheng obtained allylic azides **75** and **76** by a three-component coupling between terminal allenes, aryl iodides, and $TMSN_3$, in the presence of $Pd(dba)_2$ complex.[141] Grigg developed a cascade process, in which the intermediate azides **78** are trapped by nearby C=C bond to give triazolines **79**. An increase in the reaction temperature from 70 to 100 °C led to the concomitant loss of N_2 and formation of isoquinolines **80**.[140]



Scheme 20. Transition-metal catalysed reactions of allenes with azides.

Previous research in the Robertson group

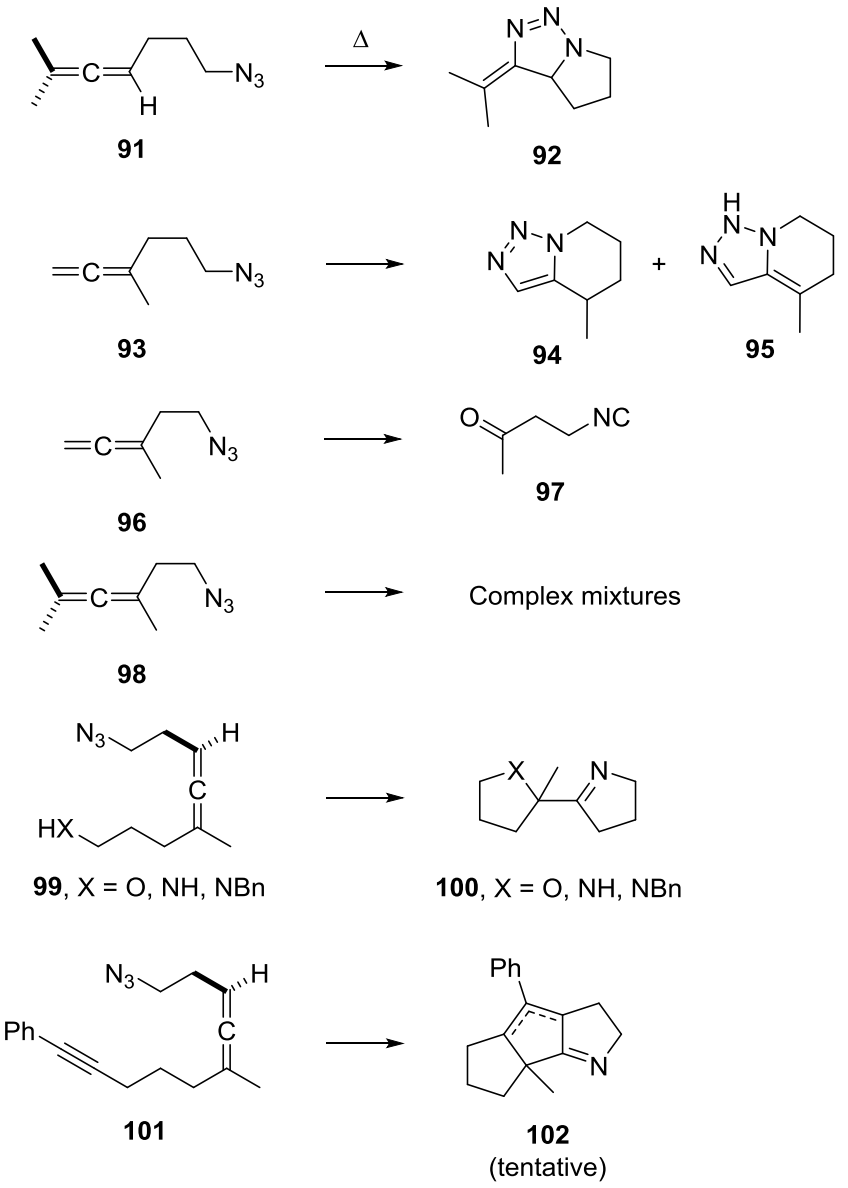
The Robertson group has been long interested in the synthesis of saturated oxa- and azaheterocycles. Cyclisations of rhodium nitrenoids with allenes were explored as means to access small and normal nitrogen rings.[142,143] Reactions of allenic substrates **81** and **83** under Du Bois conditions[144] delivered cyclic sulfamates **82** and **84**, respectively (Scheme 21).[145] Tosyl carbamates **85** and **87** were transformed into MAs **86** and **88** under $Rh_2(OAc)_4$ catalysis.[146–148] Treatment of **88** with acids gave tricyclic ketone **90** in low yields via the proposed aza-allyl intermediate **89**.[148]



Scheme 21. Rh-catalysed aziridination of allenes in the Robertson group.

Since these aziridinations are thought to proceed via Rh-bound nitrenoids, RN=[M], presumably obtained from RN[M]X species, it was of interest to probe other nitrene analogues. Azides were viewed as good surrogates because they have a similar resonance structure, $RN^{(-)}–N_2^{(+)}$.

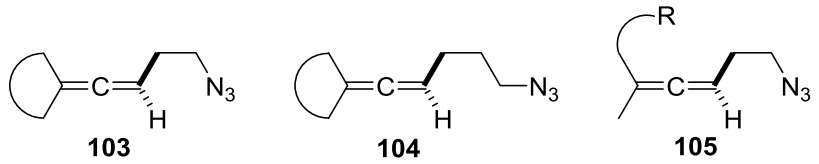
Several subprojects were run in parallel to the one described in this thesis (Scheme 22). Thermal reactions of allene azides **91** and **93** gave the expected triazole and triazoline products **92**, **94** and **95**.[147] At the same time, allene azide **96** with a shorter carbon tether was transformed into isocyano ketone **97**.[149] Tetrasubstituted allene **98** underwent decomposition and formed complex mixtures of products. Allene azides **99** tethered to nucleophiles gave products **100** of trapping in situ. Finally, compound **101** with a phenylacetylene moiety gave interesting tricyclic derivative **102** as a mixture of alkene regioisomers.[150]



Scheme 22. Concurrent work on allene azides in the Robertson group.

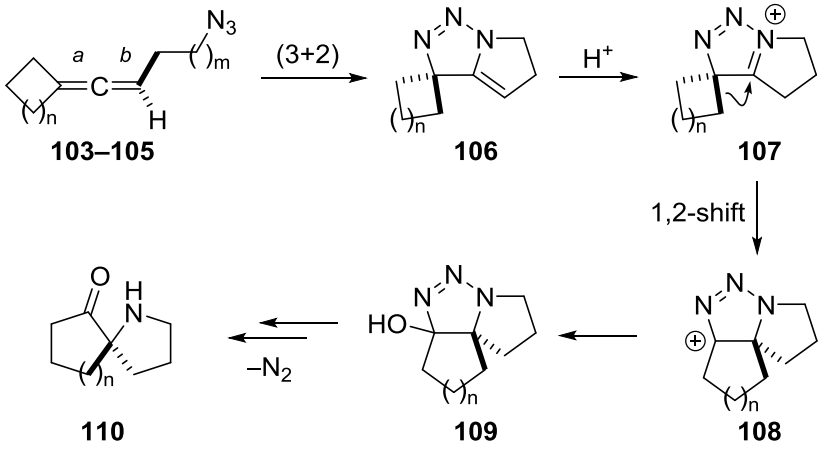
Scope and aims of the project

Clearly, reactions of appropriately substituted allene azides go beyond simple cycloadditions. In this project, we wanted to investigate the reactivity of allene azides having different tether lengths (**103** vs. **104**, Scheme 23) and substituents R (**105**).



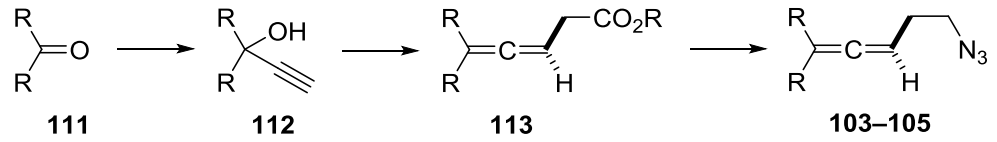
Scheme 23. Proposed starting materials for cascade transformations.

The original research proposal, outlined in Scheme 24, was based on expectations that substrates and conditions could be found that would allow isolation of the first-formed triazolines **106**. The intention was then to effect, for example, acid-catalysed ring expansion to form spirocyclic compounds **109**. The chemoselectivity of the initial cycloaddition in **103**–**105** (*a* vs. *b*) would depend on the tether length *m*, while the 1,2-alkyl shift in **107** would be driven by the release in ring strain (if *n* = 0 or 1). Substituents R, present in allene azides **105**, could react with these intermediates, leading to a variety of other *N*-heterocyclic structures.



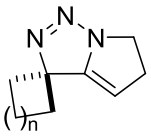
Scheme 24. Original research proposal: synthesis of spirocycles from tethered allene azides.

It was proposed to install the required allene unit in **103**–**105** by the Johnson–Claisen rearrangement of propargylic alcohols **112** (Scheme 25). The latter would come from ketones **111** by treatment with organolithium or organomagnesium reagents. Straightforward reduction and azidation would convert esters **113** into azides.



Scheme 25. Proposed synthetic route towards the test substrates.

In the event, we found that none of the tested allene azides delivered the desired spirocyclic triazolines **106**. Structures that we obtained instead were sometimes unexpected and often much more interesting. These results are presented below.



106

Chapter 1. Reactions of Simple Alkyl Allenes with Azides

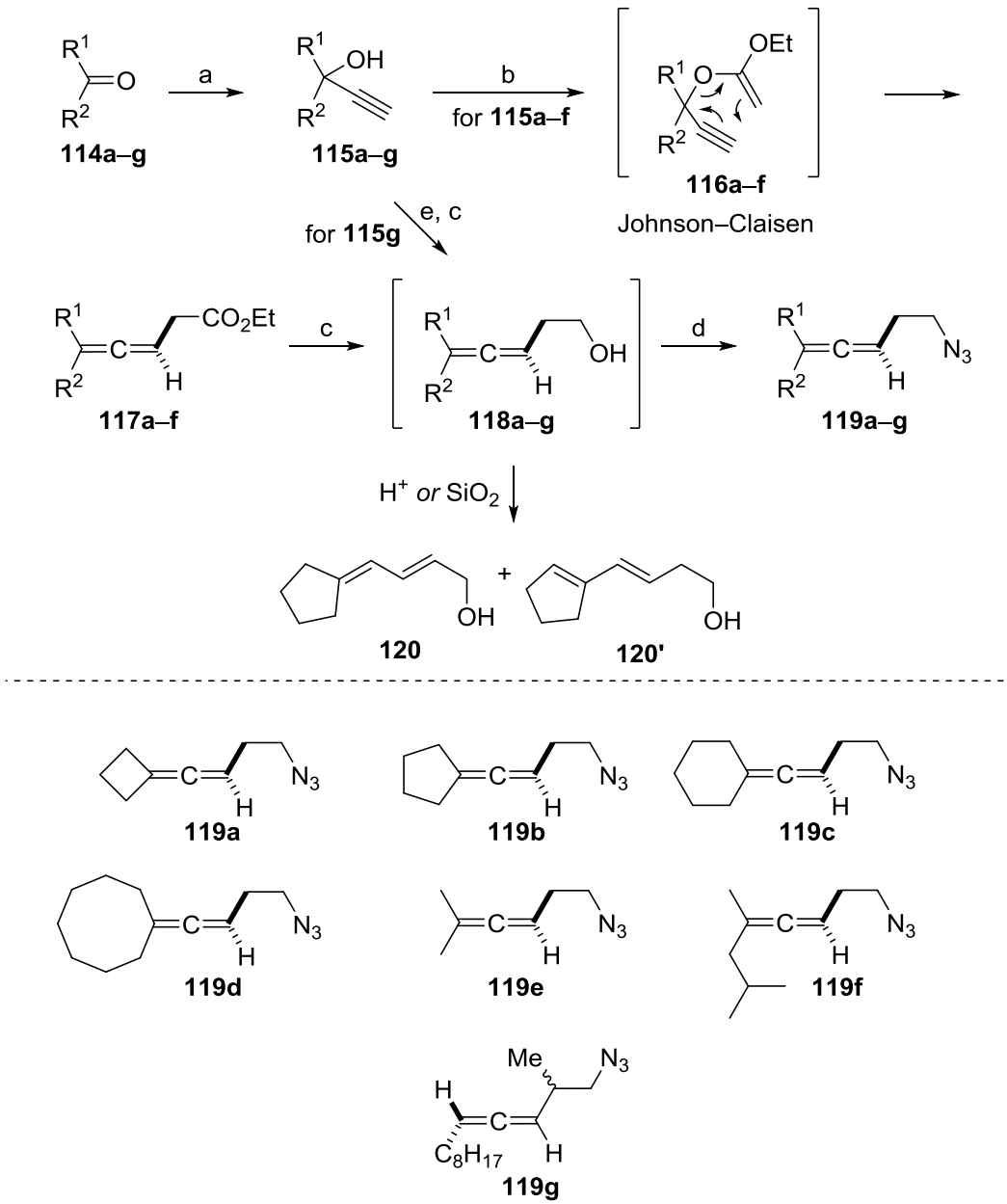
Synthesis of the test substrates

Two-carbon-tethered allene azides

In order to test the research hypothesis (page 18), we first approached the simplest non-functionalised tethered allene azides **119a**–**g**. The syntheses of **119a**–**f** were based on the Johnson–Claisen orthoester rearrangement as the key step* (Scheme 26).[41,151] In this reaction, propargylic alcohols are heated with triethyl orthoacetate in the presence of an acid catalyst, and the initially formed ketene acetals (such as **116a**–**f**) undergo a [3,3] sigmatropic rearrangement into the desired allene esters.

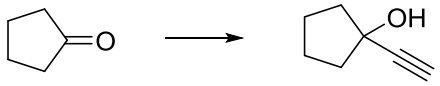
First, the required propargylic alcohols **115a**–**g** had to be obtained in reasonable quantities. Cyclopentanone (**114b**) was chosen as a test substrate to optimise this and subsequent steps, and the optimised protocols were then applied to other ketones. Addition of one equivalent of lithium acetylide–ethylenediamine complex to cyclopentanone under reported conditions[152] gave alcohol **115b** in very low yields (Table 1); however, degassing the solvent and adding the organolithium in two portions improved the yield to a more acceptable 46%. Chromatographic separation of **115b** from the unreacted starting material proved to be difficult but we later found that the use of HC≡CMgBr solution[153] led to the clean formation of desired propargylic alcohols **115a**–**g** in reproducibly high yields (typically above 80%).

* Compound **119g** was prepared using the Ireland–Claisen rearrangement. This reaction will be discussed in Chapters 3 and 4.



Scheme 26. Synthesis of two-carbon-tethered allene azides. Reagents and conditions: a) HC≡CMgBr, THF, reflux, 60–91%;b) triethyl orthoacetate, $EtCO_2H$ (cat.), 140 °C, 60–90%; c) $LiAlH_4$, Et_2O, 0 °C, 95–100%; d) PPh_3, CBr_4, DMF, *then* NaN_3, 63–100%; e) TEA, TIPSOTf, PhH, 50%.
Note: compound **119g** was prepared using the Ireland–Claisen rearrangement (Chapters 3 and 4).

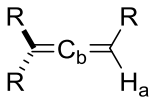
Table 1. Optimization of the acetylide addition step.



114b **115b**

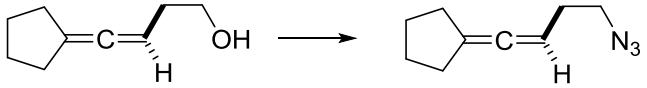
No.	Conditions	Isolated yield
1	LiC≡CH·en (1 eq), THF, 0 °C → RT, 2 hr	7%
2	LiC≡CH·en (1 eq), THF, 35 °C → RT, 3.5 hr	29%
3	LiC≡CH·en (2×1 eq), THF, RT, 15 hr	46%
4	HC≡CMgBr (1.1 eq), THF, reflux, 5 hr	85%

The Johnson–Claisen rearrangement of **115a–f** and subsequent $LiAlH_4$ reduction of so-formed allene esters **117a–f** gave alcohols **118a–f**. Many of these alcohols were unstable in a protic environment and underwent rapid isomerisation into an inseparable mixture of 1,3-dienes, such as **120** and **120'**. Attempts to purify **118b** by flash chromatography led to significant loss of the product; therefore, **118a–f** were used immediately in the following step without purification. The allene moiety in these and subsequent compounds was confirmed by IR ($\tilde{\nu}$ 1960–1970 cm^{-1}) and NMR (H_a δ 5.0–5.2 ppm; C_b δ 195–205 ppm) spectroscopy.[12,154,155]



Conversion of alcohol **118b** into azide **119b** was initially achieved by the procedure from Bose,[156] which involved treatment with a PPh_3/DIAD/DPPA system (Table 2). Later, we switched to a tandem Appel reaction/azide S_N2 protocol[157] to allow for easier product isolation. We found that premixing of CBr_4, NaN_3, and PPh_3 led to noticeable yield deterioration (presumably due to Staudinger-type side reactions). This was overcome either by using an excess of reagents or by adding NaN_3 *after* most of PPh_3 had been consumed in the Appel reaction. In this way, azides **119a–g** were prepared in yields varying from good to quantitative. Some of the more sensitive substrates (Chapter 3) partially decomposed under these conditions and alcohol activation via the mesylate was required (Table 2, entry 6).

Table 2. Optimisation of the ROH → RN_3 step.



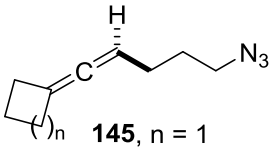
118b **119b**

No.	Conditions	Isolated yield
1	PPh_3 (1.1 eq), DIAD (1.1 eq), DPPA (1.1 eq), THF, 0 °C → RT, 15 hr	49% + 49% SM
2	PPh_3 (2 eq), DIAD (2 eq), DPPA (2 eq), THF, 0 °C → RT, 15 hr	75%
3	PPh_3 (1.5 eq), CBr_4 (1.5 eq), NaN_3 (2 eq), DMF, RT, 24 hr	70% + 20% SM
4	PPh_3 (2.5 eq), CBr_4 (2.5 eq), NaN_3 (3 eq), DMF, RT, 24 hr	74–100%
5	PPh_3 (2 eq), CBr_4 (2 eq); *then* NaN_3 (3 eq), DMF, RT, 24 hr	84–100%
6	MsCl (1.5 eq), TEA (1.8 eq), DCM, 0 °C, 2 hr; *then* NaN_3 (3 eq), DMF, 31 °C, 26 hr*	79%

*Note: entry 6 was performed on deprotected alcohol **269** (Chapter 3). These conditions are given for comparison.

Three-carbon-tethered allene azides

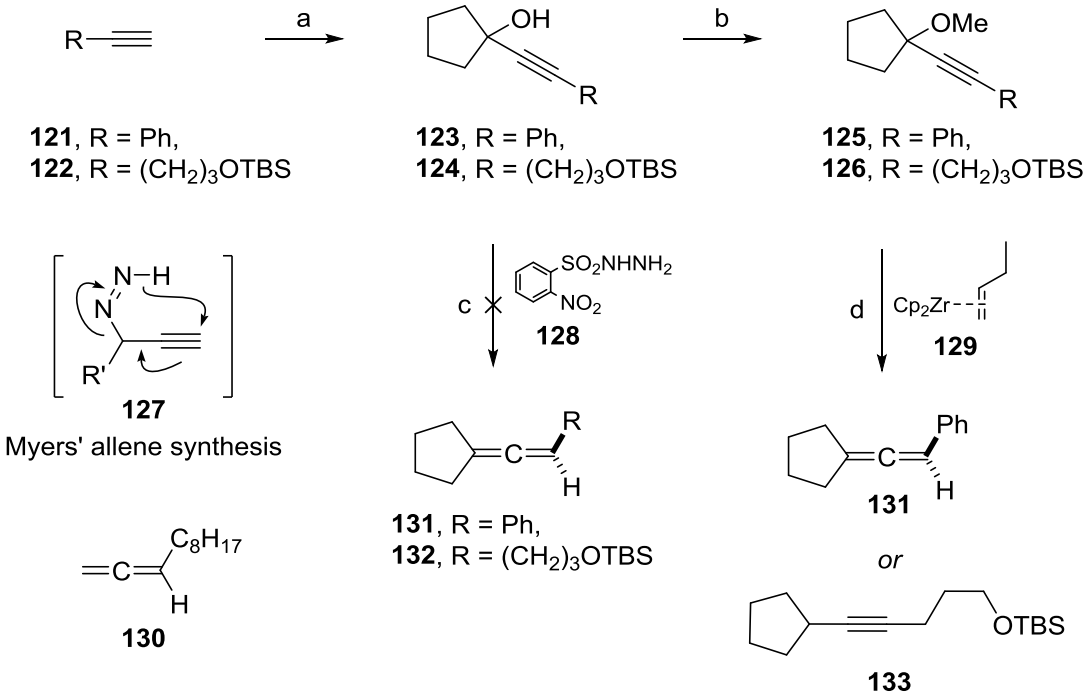
Allene azides **145**/**146**, with a three-carbon tether, could not be prepared conveniently by the Johnson–Claisen orthoester rearrangement; thus, a number of alternative approaches were tried (Schemes 27, 28): Myers' 2-nitrobenzenesulfonyl hydrazide (NBSH, **128**) protocol;[158–161] S_N2' reduction of propargylic methyl ethers **125**/**126** with Negishi reagent (**129**);[162,163] S_N2' reactions between propargylic acetate **115b** and organocopper/cuprate reagents.[164–166]



145, n = 1
146, n = 2

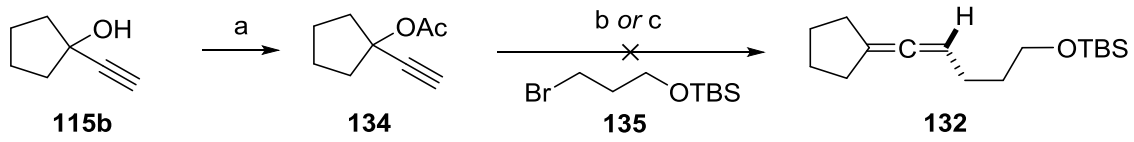
Myers' protocol for allene synthesis relies on the conversion of propargylic alcohols into unstable diazene derivatives **127** under Mitsunobu conditions,[167] and subsequent retro-ene reaction (Scheme 27).[160] Allene **130** was successfully obtained in a test reaction in 45% yield (unoptimised). However, treatment of alcohols **123**/**124** with **128** resulted in no appreciable conversion; presumably, these tertiary alcohols are too hindered for the initial Mitsunobu reaction.

Liu, Li *et al.* reported[163] that treatment of propargylic methyl ethers (including hindered ones) with Negishi reagent (**129**)[162] leads to the formation of either allenes or deoxygenated alkynes depending on the structure of the ether. Reaction of model substrate **125** under the reported conditions did indeed generate allene **131**, whereas the actual system **126** gave only the alkyne product **133**.



Scheme 27. Attempted allene synthesis from the preformed propargylic substrates. Reagents and conditions: a) BuLi, 0 °C, THF, *then* cyclopentanone; b) NaH, THF, *then* Me_2SO_4, yield over 2 steps: 60% of **125**, 33% of **126**; c) DEAD, PPh_3, **128**, THF, −15 °C *or* RT; d) BuLi, Cp_2ZrCl_2, THF, −78 °C → RT, 79% of **133**, the yield of **131** not measured.

In an alternative approach (Scheme 28), propargylic acetate **134** was treated with organocopper/cuprate reagents derived from bromide **135**. The anticipated S_N2' substitution did not take place; instead, mixtures of the starting material and decomposition products were isolated. Most likely, the source of the problem lay in the alkyl cuprate generation step, as these reagents are known to have a narrow window of stability.[168,169] The nature of the copper source is also important.[170]

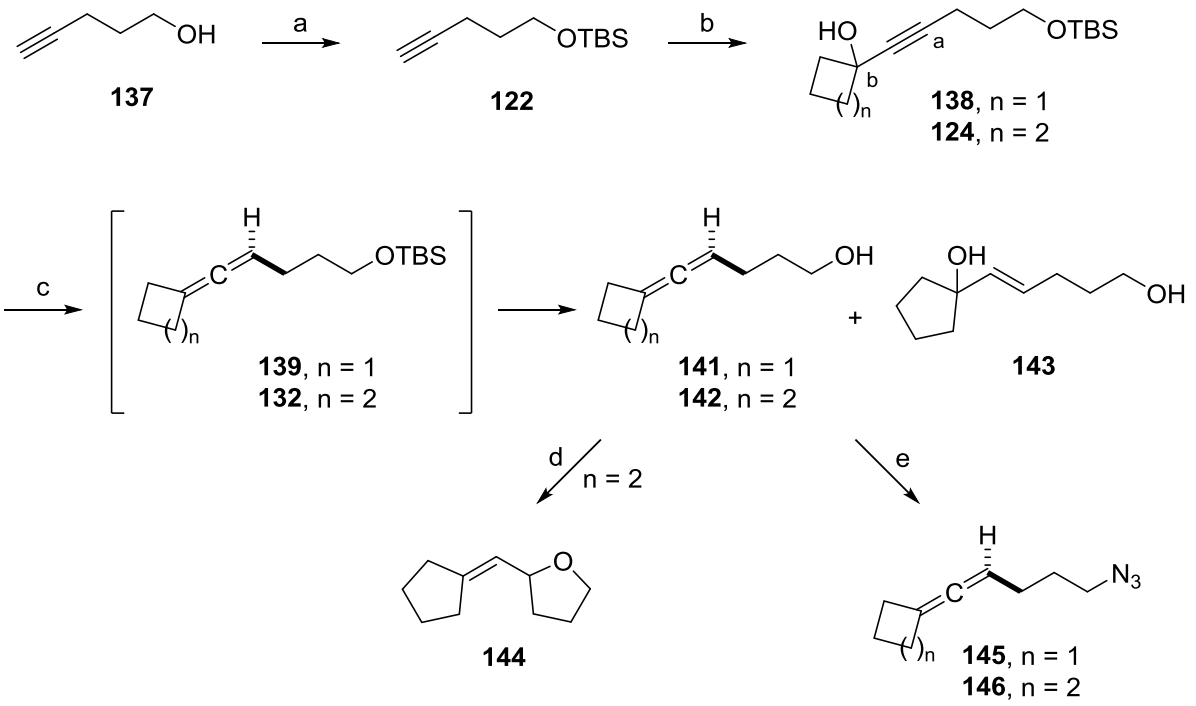


115b **134** **135** **132**

Scheme 28. Attempted allene synthesis by S_N2' substitution. Reagents and conditions: a) Ac_2O, H_3PO_4 (cat.), 50 °C → RT, 53%; b) **135**, Mg, *then* CuBr, **134**; c) **135**, *t*-BuLi, *then* CuBr, **134**.

The successful synthesis of allenes **145** and **146** was eventually achieved by an S_N2' reduction[171] of propargylic alcohols **138** and **124**, respectively, with AlH_3, generated in situ (Scheme 29). In this method, concentrated H_2SO_4 is slowly added to a mixture of the alcohol and $LiAlH_4$ and the reaction is brought to reflux until completion. It is believed[29] that the Al atom coordinates to the C_b-OH to activate the alcohol as a leaving group, while the hydride attacks the more accessible carbon C_a (Scheme 29). In our case, this reaction was accompanied by (a) desired concomitant deprotection of silyl ethers **132**/**139** into alcohols **141** and **142**, respectively, and (b) undesired *trans*-selective reduction of the triple bond in **124** to give allylic alcohol **143**. In addition, prolonged contact of **142** with silica during flash chromatography led to the acid-catalysed cyclisation into tetrahydrofuran **144**.* Build-up of **144** was also observed in $CDCl_3$ solutions of **142**. Therefore, alcohols **141** and **142** had to be purified by passing through short silica plugs. Appel reaction followed by azide substitution delivered the target allene azides **145** and **146** in reasonable yields without issues.

* Asymmetric cyclisation of **142** into **144**, using gold catalysis, was reported while this work was in progress.[310] For related research, see ref.[361]

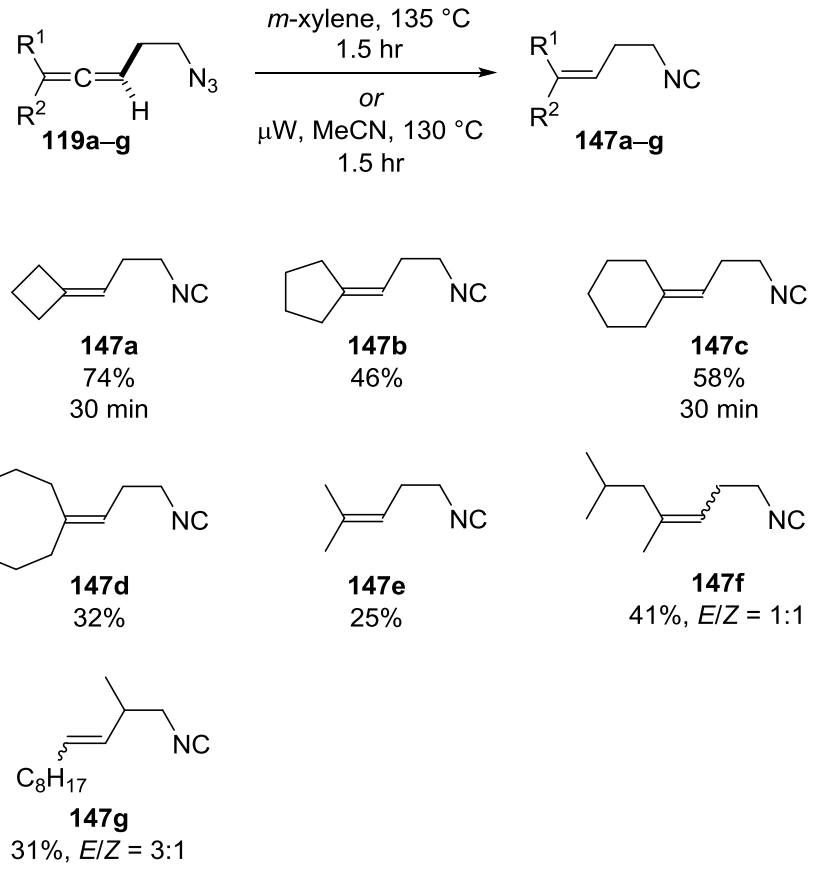


Scheme 29. Preparation of three-carbon-tethered allene azides. Reagents and conditions: a) TBSCl, imid., DCM, 98%; b) BuLi *or i*-PrMgCl, *then* cyclopentanone *or* cyclobutanone, 98% of **138**, 37% of **124**; c) $LiAlH_4$, H_2SO_4 (conc.), THF, RT → reflux, 72% of **141**, 30% of **142** and 58% of **143**; d) SiO_2 chromatography; e) PPh_3, CBr_4, DMF, *then* NaN_3, 60% of **145**, 74% of **146**.

Reactivity of two-carbon-tethered allene azides. Formation of isocyanides.

Thermal reactions of two-carbon-tethered allene azides **119a**–**g** led to the formation of alkene isocyanides **147a**–**g**; no triazoles or spirocyclic products were isolated (Scheme 30). This was unexpected at the time and implied that the substrates underwent extensive rearrangement along the course of the reaction.

The isocyanide products possessed a characteristic disagreeable smell[172,173] and required handling inside a fume hood. Since compounds **147a**–**g** were unfunctionalised and had relatively low molecular weights, most of them were volatile. Accordingly, we assume that the low yields of isocyanides **147b** and **147e** are at least in part explained by this volatility.



Scheme 30. Formation of isocyanides from two-carbon-tethered allene azides.

The NMR spectra of isocyanides **147a–g** exhibited an interesting feature (Figure 1): both ^{1}H and ^{13}C resonances of the nuclei next to the nitrogen had an additional 1:1:1 triplet splitting ($^{2}J_{NH}$ = 2.0 Hz, $^{1}J_{NC}$ = 6.0–6.5 Hz). This phenomenon was earlier explained as a consequence of the axial symmetry of the electron cloud surrounding the isocyanide nitrogen,[174,175] which decreases the normally strong electric field gradient near the quadrupolar ^{14}N nucleus. This field gradient, present in other nitrogen-containing compounds, would normally lead to local spin decoupling but is absent in this case.

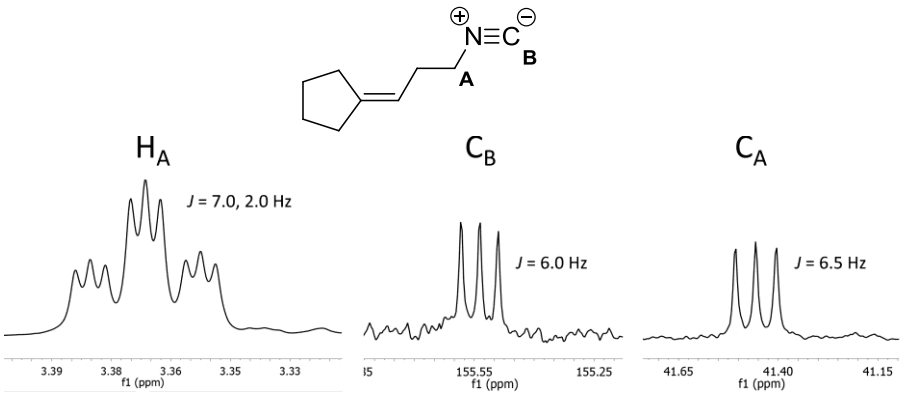
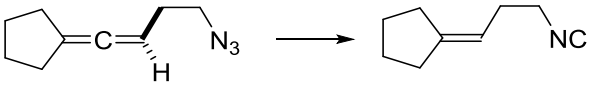


Figure 1. Additional triplet splitting in the NMR spectra of isocyanides.

The results of screening experiments for the isocyanide formation are shown in Table 3. The optimised reactions were carried out at 130–135 °C over 90 min, either in *m*-xylene with conventional heating or in acetonitrile under microwave irradiation. For more functionalised allene azides (Chapters 2–4), unreactive aromatic solvents (*m*-xylene, toluene, benzene) were preferred. Addition of K_2CO_3, which was beneficial for related enol ether/azide cycloadditions,[176] led to diminished yields in this reaction.

Table 3. Screening experiments for the rearrangement of **119b**.



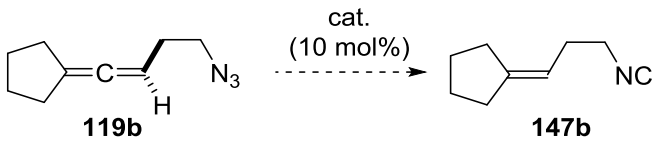
119b **147b**

No.	Solvent, additive	t, °C	Time, hr	Result
1	C_6D_6	60	2	No reaction
2	C_6D_6	80	50	50% conversion
3	$CDCl_3$	23	2	No reaction
4	$CDCl_3$	60	5	Deconjugation of allene
5	tol.-d_8	110	12	Decomposition
6	CD_3CN	83	3	No reaction
7	CD_3CN	130 (μW)	1–1.5	**40% isocyanide**
8	CH_3CN, K_2CO_3	130 (μW)	1.5	7% isocyanide
9	*m*-xylene	135	1–1.5	**40% isocyanide**
10	*m*-xylene, K_2CO_3	135	1.5	17% isocyanide

Because reactions of both allenes and azides can be catalysed by transition metals,[20,52,58,133] we screened several of the most common catalysts with allene azide

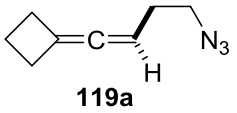
119b (Table 4). Surprisingly, this compound was essentially inert under all of the conditions tried; even CuI catalysis or irradiation with short-wave light, earlier reported by Feldman as the effective means to trigger allene azide cascades,[133] led to no appreciable conversion. At the moment, the best method to activate these allene azides remains simple heating in an inert solvent.

Table 4. Attempted catalysis of the rearrangement of **119b.**

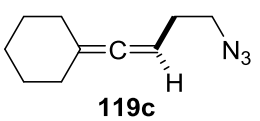


119b **147b**

No.	Catalyst	Conditions	Result
1	$AuCl{\cdot}PPh_3$	DCM, MS 4Å	No reaction
2	$AuCl{\cdot}PPh_3/AgOTf$	DCM	—
3	$Rh_2(OAc)_4$	DCM	—
4	$Rh_2(Oct)_4$	tol.	—
5	$AgNO_3/SiO_2$	MeCN	—
6	$AuCl_3$	DCM	—
7	$PdCl_2$	C_6D_6, 60 °C	—
8	$PtCl_2$	C_6D_6, 60 °C	—
9	CuI	CD_3CN	—
10	CuI	C_6D_6, RT → 60 °C	—
11	None	hν, MeCN	Decomposition



119a

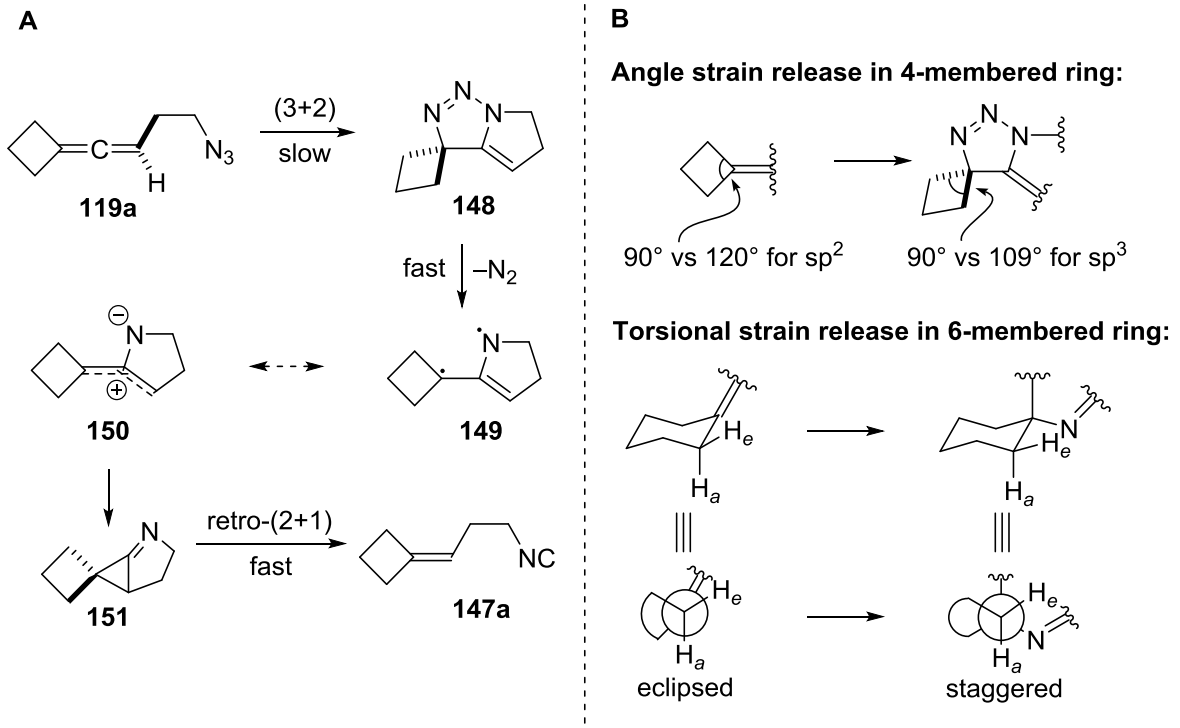


119c

Cyclobutyl- and cyclohexyl-containing derivatives, **119a** and **119c**, were more reactive than other allenes, undergoing clean "spot-to-spot" conversion into the corresponding isocyanides within 30 min at 135 °C (Scheme 30). This paralleled the increased reactivity of the corresponding starting ketones **114a** and **114c** towards HC≡CMgBr. We attribute these trends to angle strain release in the transition states for cyclobutane derivatives and torsional strain release[177] in the transition states for cyclohexane compounds (see Scheme 31B and discussion below). Similarities in the

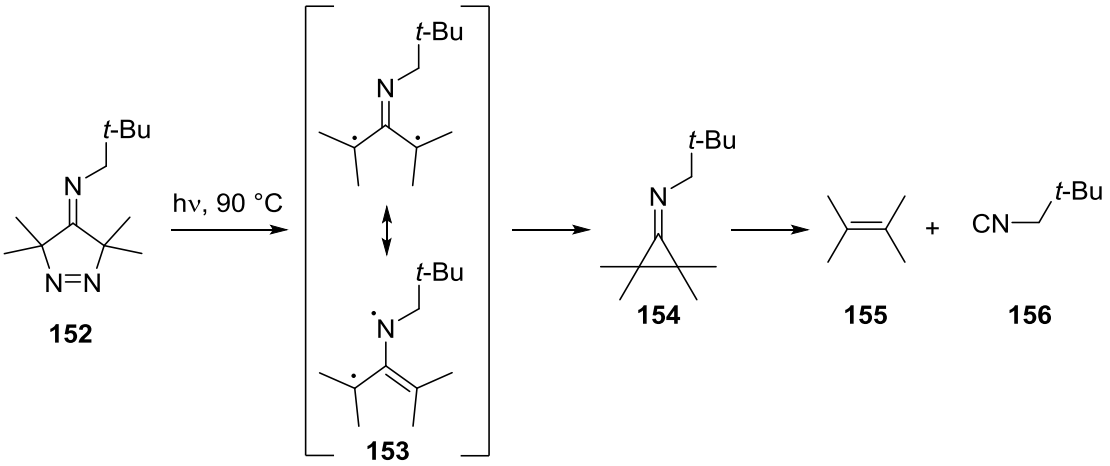
reaction rates for cyclobutane and cyclohexane derivatives, and the relative sluggishness of cyclopentane compounds, are well documented.[178,179]

Based on the experimental and literature data, we propose the following mechanism for the conversion of allene azides into isocyanides (Scheme 31). The reaction starts with a rate-limiting (3+2)-cycloaddition between the distal allene bond and the azide. This process is slow because: (a) the distal double bond is sterically encumbered with two substituents; (b) the LUMO is located on the proximal double bond (Hückel calculations), whereas the distal alkene corresponds to [LUMO+1], much higher in energy; and (c) *both* of the reaction partners are electron-rich. Subsequent elimination of N_2 from triazoline **148** generates either a diradical **149** (advocated by Quast[115] and Feldman[132]) or a zwitterion **150** similar to oxyallyl ions. Recombination of this species gives a strained iminocyclopropane **151**, which undergoes cheletropic (2+1)-cycloreversion to generate the final product, **147**. Based on the fact that none of these intermediates could be isolated or observed by NMR in our experiments, we assume that these steps are fast compared with the initial allene–azide cycloaddition.



Scheme 31. **A**. Proposed mechanism for the conversion of two-carbon-tethered allene azides into isocyanides. **B**. Proposed rationale for the increased reactivity of allenes **119a** and **119c**.

This reaction pathway is further supported by the studies of Schechter,[109] Gilbert,[180] Feldman,[132,135] and, especially, Quast.[113–116] Quast has shown that ATMM **153** can be formed by photolysis or flash vacuum pyrolysis of suitable starting materials (e.g. **152**, Scheme 32) and undergoes further transformations into isolable iminocyclopropanes **154** and/or isocyanides **156**.



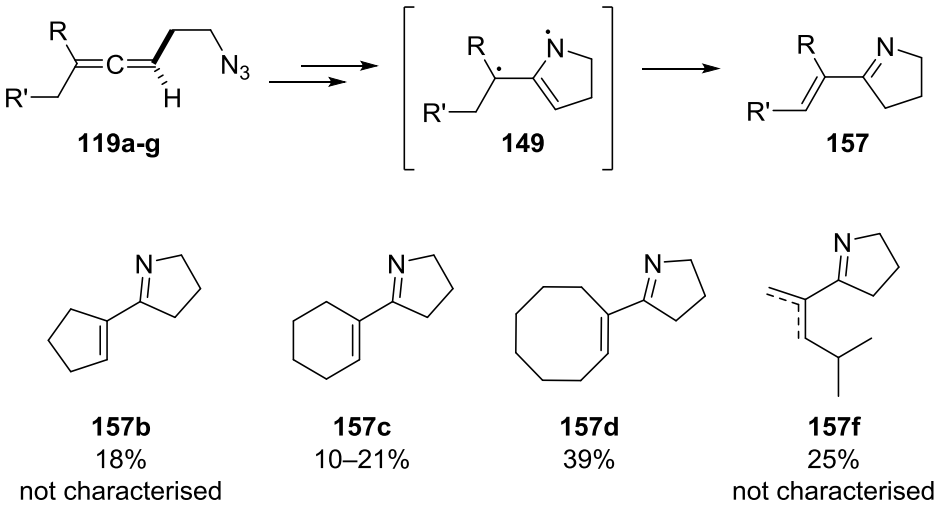
Scheme 32. An example of the formation of isocyanides from ATMM.[116]

Since the initial (3+2)-cycloaddition between the allene and the azide in **119a–g** is presumably slow and rate-determining, any factors facilitating this step should greatly accelerate the overall rate of the reaction, as indeed observed in the case of cyclobutane and cyclohexane derivatives, **119a** and **119c**.

Side products: imines and ketones

Our results show (Scheme 30) that the isocyanide formation does not account for the majority of the mass balance. The rest of the starting material is converted into highly polar side products that were assigned as conjugated azadienes **157** (Scheme 33). These compounds were often unstable and only cyclohexene and cyclooctene derivatives, **157c** and **157d**, were isolated in pure form. Most of the time, the imine side products amounted for ca. 20–40% of the crude product (NMR data). Reactions performed in a polar solvent, such as acetonitrile, generally contained a larger proportion of these azadienes.

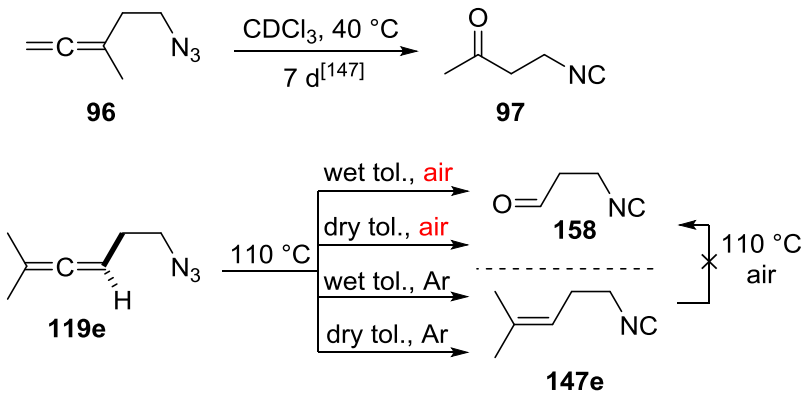
Formation of imines, related to **157**, in the reactions of ATMM species has been described earlier.[109,113,134]



Scheme 33. Identified side products from thermal rearrangements of allene azides. *Note:* the numbers refer to the isolated yields.

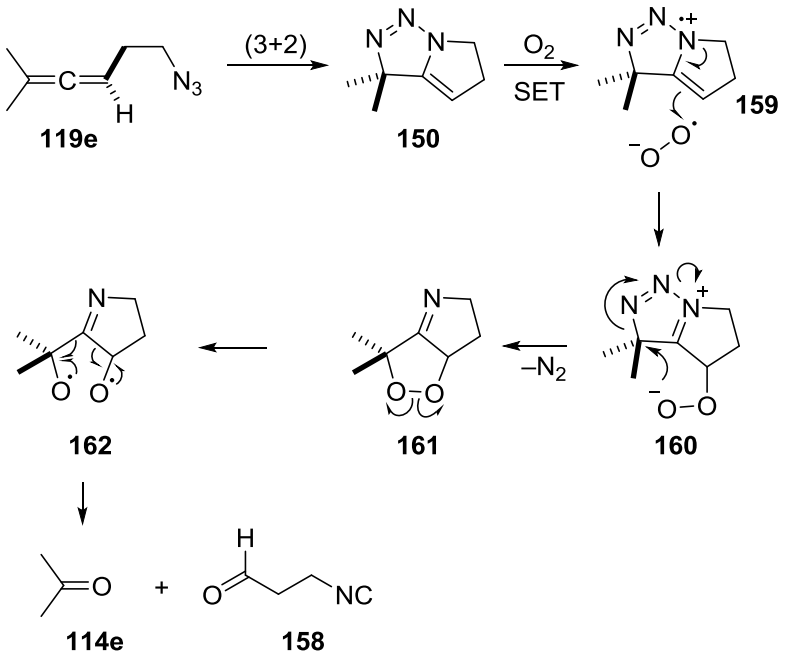
It was observed previously in our laboratory that the thermal reactions of allene azides **96** and **119e** delivered isocyanide ketone **97** and aldehyde **158**, respectively

(Scheme 34).[147,149] This change in reactivity was originally attributed to the structural peculiarities of the starting allenes; however, compounds **97** and **158** actually arise from oxidative cleavage of allene azides or intermediates of their cycloaddition. Thus, heating allene **119e** under air delivered aldehyde **158** as the major product, whereas the same reaction under an atmosphere of argon delivered alkene isocyanide **147e** exclusively. The presence or absence of small amounts of water in the solvent did not affect the course of the reaction. A separate experiment confirmed that alkene **147e**, once formed, did not convert into aldehyde **158**.



Scheme 34. Alternative oxidative pathways for the reaction of allene azides.

We propose that the initially formed triazoline **150** is oxidised with air oxygen into peroxide **159**, which then undergoes cleavage into the final carbonyl-containing products (Scheme 35).



Scheme 35. Proposed mechanism for the oxidative cleavage of allenes.

In order to suppress this oxidative side reaction, all subsequent transformations of allene azides were performed with thorough exclusion of air.

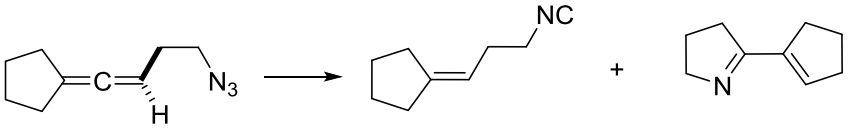
Flow chemistry

Conducting reactions in a flow system is well-established for large-scale industrial production, however, the technique is becoming increasingly popular in the academic laboratory setting.[181,182] Proponents of the method appeal to such advantages as rapid conditions screening, safe handling of superheated and pressurised reaction mixtures, scalability and in-flow reaction monitoring. It was therefore of interest to test the discovered allene azide cycloaddition cascade in flow. The results of our experiments, using a Uniqsis FlowSyn reactor, are presented in Table 5.

As expected, the increased temperatures achievable in this setup greatly accelerated the reactions. It was found that performing the rearrangement at 160 °C allowed for the complete consumption of the starting material **119b** within 12 min (Table 5, entry 4). A further increase of the temperature to 190 °C led to a truly "flash" reaction that finished in 2 min (entry 5). The yields of isocyanide **147b** remained

within the 40–60% range, as in the case of conventional heating, but the proportion of polar side products, such as **157b**, diminished greatly. Other solvents were screened at increased temperatures; both acetonitrile (entry 3) and THF (entry 6) gave no improvement in yield, confirming our earlier observations that the reaction preferred non-polar solvents. Cyclohexane was screened but abandoned due to the problems with solvent removal. DMF was also tried but, predictably, decomposed at 160 °C.

Table 5. Rearrangement of allene azide **119b** under flow and batch conditions



119b **147b** **157b**

No.	Conditions	Temp.	Time	Isolated yield	
				147b	**157b**
1	Conventional heating, *m*-xylene	135 °C	90 min	25–46%	38%
2	μW, MeCN	135 °C	70 min	40%	Not measured
3	Flow, MeCN	160 °C	10 min	10–25%	35%
4	**Flow, tol.**	**160 °C**	**12 min**	**38–65%**	**trace**
5	**Flow, tol.**	**190 °C**	**2 min**	**45%**	**trace**
6	Flow, THF	160 °C	16 min	10%	Not measured
7	Flow, DMF	160 °C	11 min	Solvent decomposition	
8	Flow, cyclohexane	160 °C	11 min	Solvent removal issues	

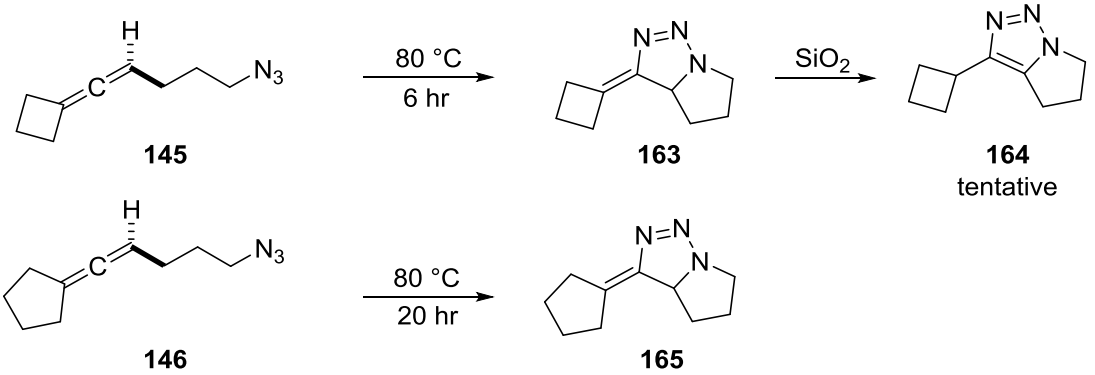
To summarise, conducting these reactions under flow conditions can be highly useful, allowing the use of more volatile solvents, shorter reaction times, and better control over the potentially explosive azides at large scales. Results of the flow chemistry tests on more sophisticated allene azide systems are discussed in Chapter 2.

Reactivity of three-carbon-tethered substrates. Formation of triazoles

Allene azides with a three-carbon tether between the two moieties reacted in a different way than their two-carbon counterparts (Scheme 36). For example,

heating **146** in C_6D_6 at 80 °C led to the formation of triazoline **165** in moderate yields by (3+2)-cycloaddition of the azide to the proximal double bond of the allene. In contrast with the previous observations,[183] this product did not isomerise spontaneously into the corresponding triazole. The strained allene azide **145** was more reactive than **146**, undergoing conversion into triazoline **163** approximately 3 times faster. This is noteworthy, because, in principle, the proximal double bond of the allene should not be activated by ring strain. Both **145** and **146** underwent essentially "spot to spot" conversion at 80 °C. Microwave heating in acetonitrile at 130 °C was too harsh and led to decomposition of the reaction mixtures.

Triazoline **163** was relatively unstable and converted into a single highly polar product upon prolonged contact with silica (TLC data). We assumed that the product most likely was triazole **164** but no further analysis was performed at the time.

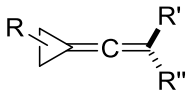


Scheme 36. Reactivity of three-carbon-tethered allene azides. Reagents and conditions: C_6D_6, 80 °C, 20 hr, 58% of **163**, 6 hr, 65% of **165**.

Eventually, the breadth of reactivity of two-carbon-tethered allene azides consumed all our effort, and thus we stopped investigating substrates **145**–**146**, which possessed lesser novelty.

Chapter 2. Intramolecular Cycloadditions of Azides with VDCPs

As mentioned in Chapter 1, cyclobutylidene allene azides **119a** and **145** were much more reactive in the (3+2)-cycloaddition cascade than most of the larger rings and open-chain analogs, which we attribute to strain release in the rate-determining step. It was therefore of interest to probe the ultimate case of strain activation by studying the reactivity of cyclopropane derivatives.



vinylidenecyclopropanes (VDCPs)

Compounds, in which a three-membered ring is appended to an allene unit, are known as vinylidenecyclopropanes (VDCPs). They are highly strained and undergo a variety of unusual chemical transformations. However, being somewhat exotic and difficult to prepare, VDCPs do not belong to the realm of mainstream organic chemistry and research in this area is mostly confined to photochemical reactions, flash vacuum pyrolysis and other transformations of mostly mechanistic interest.[40]

Difficulties with the synthesis of azido-VDCPs

It was expected that VDCPs would be more difficult to prepare than their less strained allenes. Still, the amount of chemistry that did not work was astonishing (Scheme 37). The following approaches[40] were tried without success until we found conditions that worked:

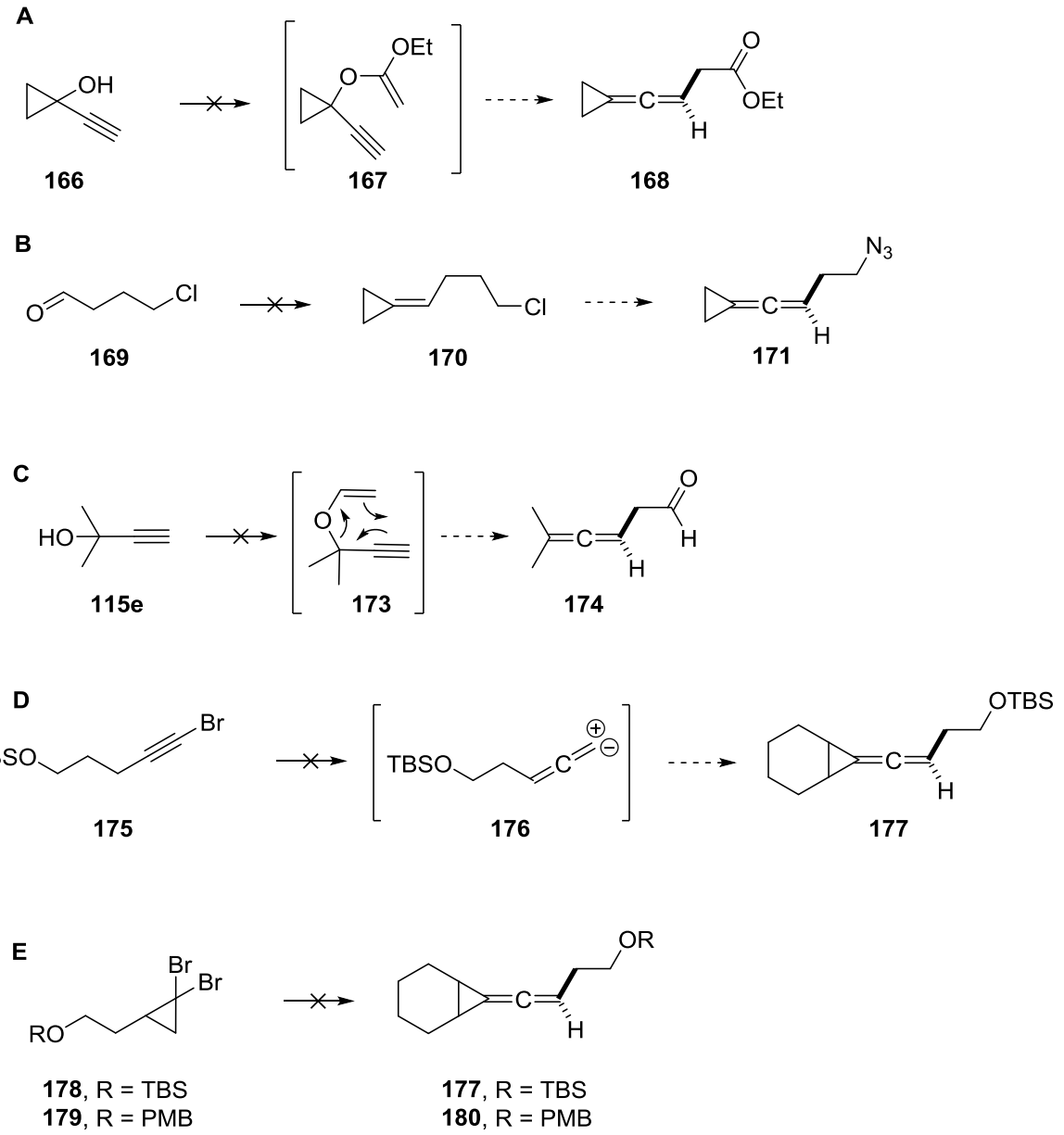
A. Johnson–Claisen rearrangement[29,151] of cyclopropane alcohol **166**

B. Preparation of alkylidene cyclopropane **170** for the subsequent Doering–Moore–Skattebøl rearrangement[28,33–37] (also known as the Doering–LaFlamme rearrangement[32,38,39])

C. Saucy–Marbet rearrangement[47,48,184] of model vinyl ether **173**

D. Carbene generation from terminal bromoalkyne **175**[40,185–187]

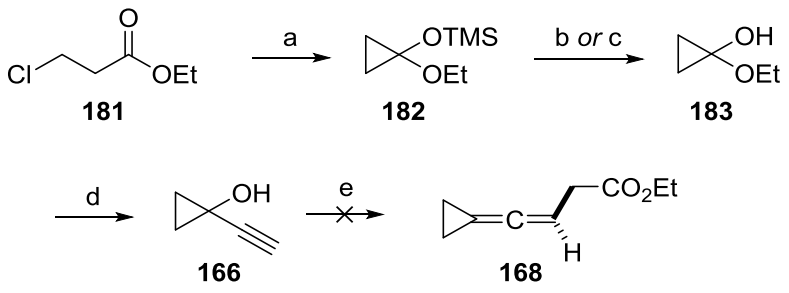
E. VDCP synthesis via *gem*-dibromocyclopropanes **178**–**179**.[188]



Scheme 37. Unsuccessful approaches towards VDCPs.

Attempted Johnson–Claisen rearrangement of cyclopropane alcohol 166

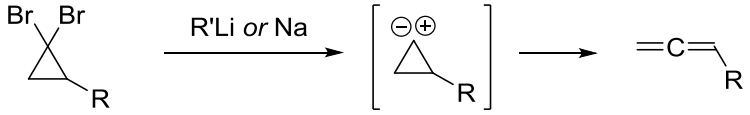
The first approach that we explored relied on the "classical" Johnson–Claisen rearrangement. Known monosilylated cyclopropanone acetal **182** was prepared from ethyl 2-chloropropionate (**181**) on a large scale by the action of sodium sand in the presence of TMSCl (Scheme 38). The yield of this reaction was rather low but sufficient to provide enough material for the subsequent steps. All attempts to cleave the silyl group by the reported protocol (stirring in methanol for several hours)[189] were unsuccessful; however, addition of catalytic amounts of aq. HCl (1 M) facilitated the transformation and delivered acetal **183** in seconds. The product was prone to decomposition in acidic methanol but stable in acidic THF, and thus we switched to the latter as the reaction solvent. Treatment of **183** with HC≡CMgBr gave desired propargylic alcohol **166** in high yield; this product was surprisingly stable and could be purified by chromatography on silica gel without significant weight loss. Indeed, **166** was so unreactive that it resisted all attempts to effect its Johnson–Claisen rearrangement and starting material was recovered from the reaction mixtures. Ultimately, this route was abandoned.



Scheme 38. Preparation of cyclopropane-containing alcohol **166** and attempted Johnson–Claisen rearrangement. Reagents and conditions: a) Na (sand), TMSCl, Et_2O, reflux, 25%; b) aq. HCl (cat.), MeOH, 36%; c) aq. HCl (cat.), THF, 100%; d) HC≡CMgBr, THF, reflux, 75%; e) $MeC(OMe)_3$, $EtCO_2H$ (cat.), 115 °C, no reaction.

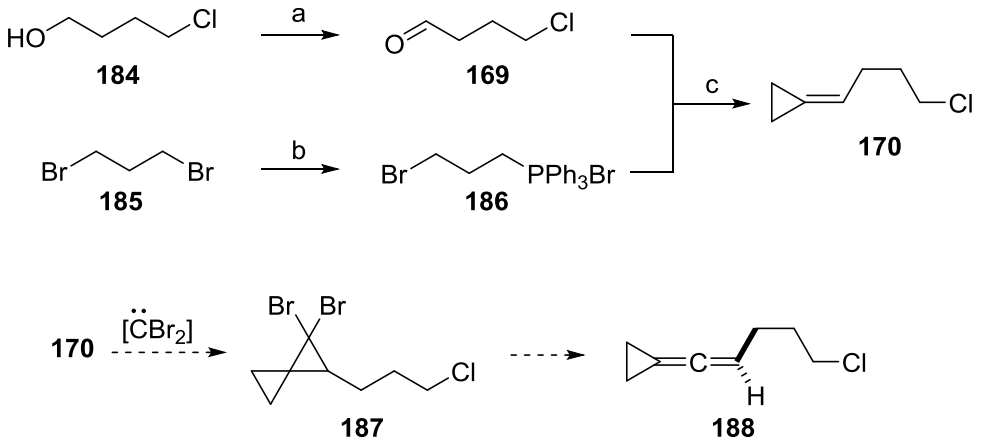
Preparation of alkylidene cyclopropane 170 for subsequent Skattebøl rearrangement

The Skattebøl rearrangement (Scheme 39) has been successfully used in the past to access strained substrates.[40]



Scheme 39. Skattebøl rearrangement.

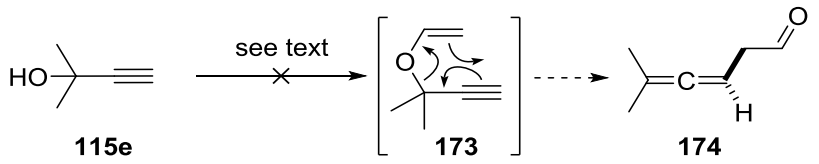
Application of this reaction to bicyclic derivative **187** could potentially furnish desired VDCP **188** (Scheme 40). Compound **187**, in turn, would be formed from alkylidene cyclopropane **170** by treatment with dibromocarbene generated in situ.[190,191] Thus, known aldehyde **169**[192] and phosphonium salt **186**[193] were prepared from 4-chlorobutan-1-ol (**184**) and 1,3-dibromopropane (**185**), respectively. Tandem Witting reaction/alkylation[194] between the two substrates was then attempted. The crude reaction mixtures contained only traces of the desired product, **170**, which proved hard to isolate, and thus other approaches were considered.



Scheme 40. Attempted synthesis of alkylidene cyclopropane **170**. Reagents and conditions: a) TEMPO, aq. NaOCl, KBr, $NaHCO_3$, DCM/H_2O, 0 °C, 65%; b) PPh_3, tol., 70 °C, 72%; c) KO*t*-Bu, DMSO, RT → 75 °C.

Saucy–Marbet rearrangement of a vinyl ether

Next, we explored the Saucy–Marbet rearrangement[47,48,184] of vinyl propargylic ethers as a route to the allene. Alcohol **115e** was chosen as a test substrate (Scheme 41). It was conceived that transition-metal catalysed etherification of **115e** would be accompanied by a [3,3]-rearrangement to deliver allene aldehyde **174**.



Scheme 41. Attempted synthesis of allenes using Saucy–Marbet rearrangement of vinyl propargylic ethers.

A number of conditions were tried (Table 6) but all of them led to decomposition of the starting material.

Table 6. Attempted approaches for the synthesis of enol ether **173**

No.	Conditions	Result
1	$Hg(OAc)_2$, butyl vinyl ether, 110 °C	Decomposition
2	$Hg(OAc)_2$, ethyl vinyl ether, RT	—
3	$Pd(OAc)_2$, BPhen, butyl vinyl ether, 80 °C	—
4	$Pd(tfa)_2$, BPhen, butyl vinyl ether, 75 °C	—
5	$Pd(tfa)_2$, BPhen, butyl vinyl ether, 75 °C, sealed tube	—

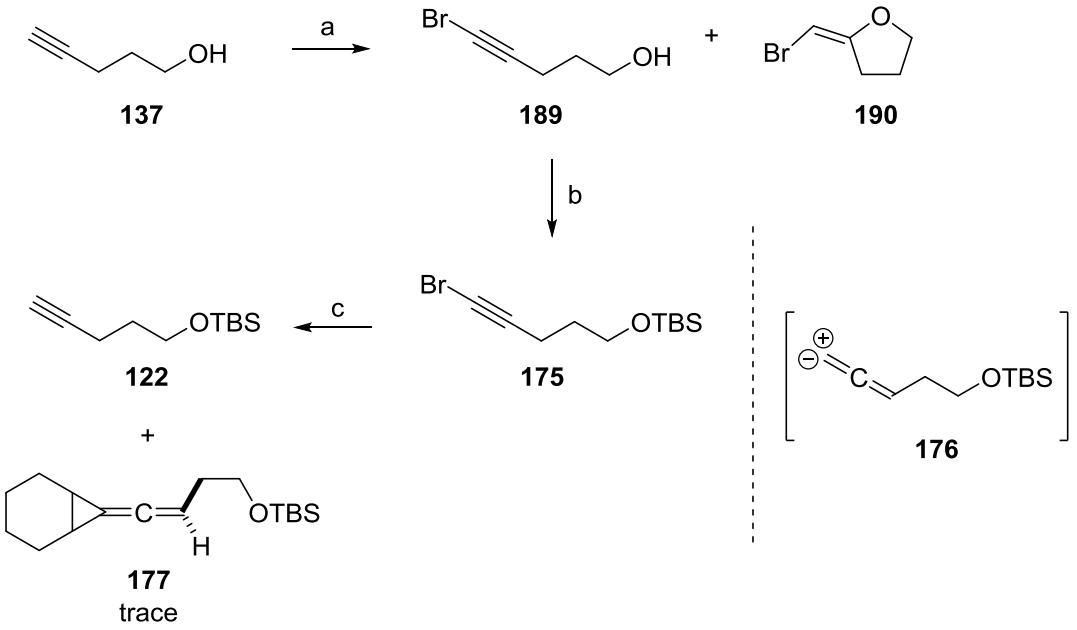
Failure to generate an allene under these conditions may be attributed to several factors, such as: (a) high intrinsic reactivity of aldehydes and their propensity to decomposition;* (b) the initial ether formation did not proceed and alternative catalysts should have been tried; (c) the rather volatile reagents occupied overhead space of the reaction vessel and did not interact with the catalyst.

* In the seminal work by Saucy and Marbet, aldehydes were distilled off the reaction mixtures upon formation.

Attempted carbene generation from terminal bromoalkyne 175

Yet another reported way for the preparation of VDCPs relies on terminal bromoalkynes, such as that shown in Scheme 42,[185,186] treatment of which with a strong base (usually KO*t*-Bu) generates unusual "allenylidene carbenes" (e.g. **176**).[186,187] Such carbenes are known to react with C=C-bonds to generate cyclopropanes.

The desired bromoalkyne **175** was obtained uneventfully from commercially available alkyne **137** by bromination and TBS-protection. Heating compound **175** in the presence of a strong base and excess of cyclohexene as the trapping reagent gave only trace amounts of the desired cyclopropane **177**. The major product of this reaction was debrominated alkyne **122**.

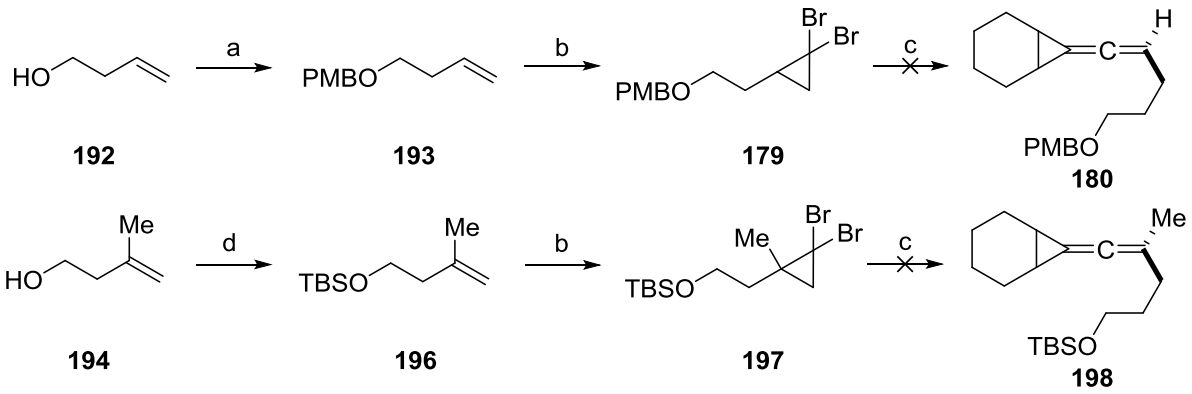


Scheme 42. Attempted VDCP synthesis via bromoalkyne **175**. Reagents and conditions: a) Br_2, KOH, H_2O, 0 °C, 52% of **189**, 25% of **190**; b) TBSCl, imid., DCM, 98%; c) KO*t*-Bu, cyclohexene, reflux, 53% of **122**, trace of **177**.

Based on our subsequent success with allenylidene carbenes (see below), we assume that this reaction could potentially be optimised, most likely by finding the right combination of alkene, solvent and reaction temperature; however, at the time we switched to other methods.

Attempted VDCP synthesis from *gem*-dibromocyclopropanes

A further attempted route was based on the reported conversion[188] of *gem*-dibromocyclopropanes into allenylidene carbenes upon treatment with a base under phase-transfer conditions followed by trapping with alkenes (Scheme 43). *Gem*-dibromides **179** and **197** were obtained from commercial alkenyl alcohols **192** and **194** by protection and subsequent reaction with dibromocarbene (generated in situ from bromoform and NaOH).[191,195] Notably, reactions of monosubstituted alkene **193** delivered only 6% of desired product **179**, whereas disubstituted substrate **196** gave 76% of dibromide **197**. Treatment of compounds **179** and **197** with the reported combination of reagents (NaOH, TEBA, cyclohexene) resulted in decomposition and not the formation of desired VDCPs **180**/**198**. In light of our later results with the carbene trapping (see below), we assume that a switch in the trapping agent from cyclohexene to styrene or 1-methylcyclohexene would have been beneficial.

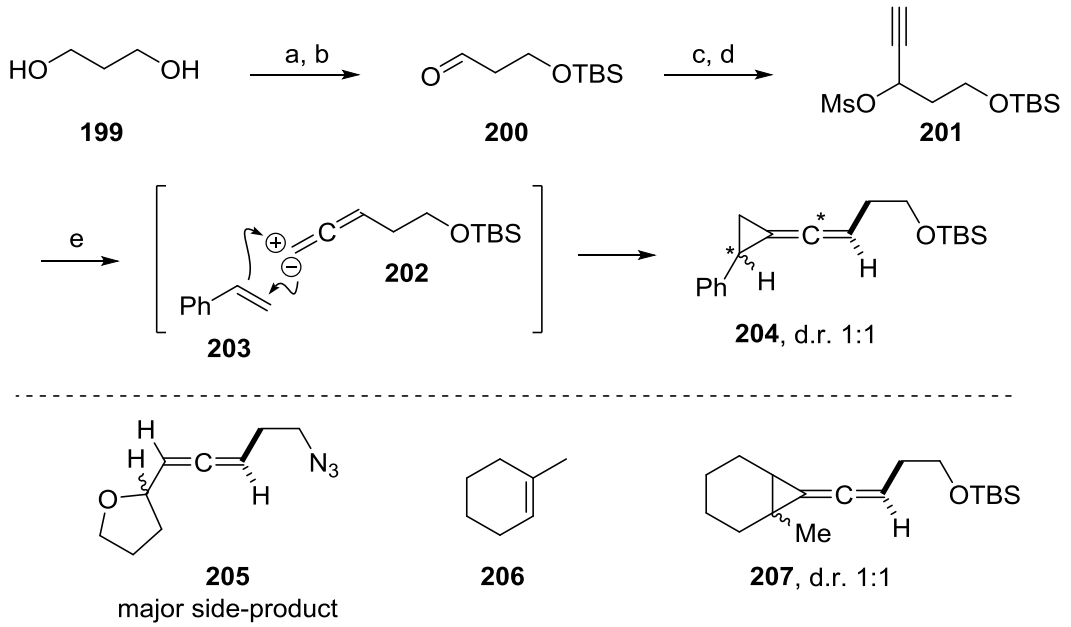


Scheme 43. Attempted synthesis of VDCP via *gem*-dibromocyclopropanes. Reagents and conditions: a) NaH, PMBCl, DMF, 0 °C → RT, 98%; b) $CHBr_3$, NaOH, TEBA, H_2O, 6% of **179**, 76% of **197**; c) NaOH, TEBA, cyclohexene; d) TBSCl, imid., DCM, 100%.

Successful synthesis of VDCPs via "allenylidene carbene"

After many unproductive attempts, we were almost ready to abandon the pursuit of cyclopropyl derivatives, but success came eventually. One of the final approaches towards VDCPs via an "allenylidene carbene" resulted in the formation of

desired products in reasonable yields (Scheme 44). First, 1,3-propanediol (**199**) was monoprotected using McDougal's procedure[196] and the remaining hydroxyl group was elaborated into propargylic mesylate **201**.[197,198] Treatment of this compound with KO*t*-Bu in THF led to the formation of allenylidene carbene **202**,[*cf.*199–201] which reacted quickly with conjugated (styrene, **203**) or electron-rich (1-methylcyclohexene, **206**) alkenes to give the products of (2+1)-cycloaddition, **204** and **207**. The reaction is stereospecific (suprafacial addition)[202] but not diastereoselective and thus the products were formed as inseparable 1:1 mixtures of allene diastereomers. In early runs, allene **205** was generated as a major side product arising from C–H insertion into THF (up to 16%).[199] The formation of **205** was suppressed by careful optimisation of the reaction conditions: starting alkenes **203** and **206** were purified immediately before use, the initial temperature was lowered to 0 °C, and the amount of THF was reduced to the minimum (ca. 1:1 v/v with the alkene).

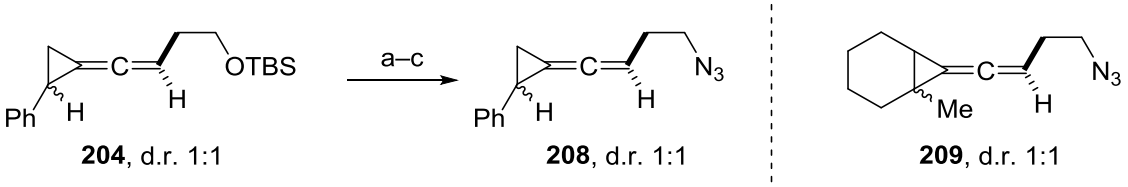


Scheme 44. Successful synthesis of VDCPs **204** and **207**. Reagents and conditions: a) NaH, THF, *then* TBSCl, 100%; b) $(COCl)_2$, DMSO, TEA, DCM, −78 °C → RT, 90–98%; c) HC≡CMgBr, THF, 0 °C, 92%; d) MsCl, TEA, DCM, 0 °C, 66–84%; e) KO*t*-Bu, THF, 0 °C → RT, 67% of **204**, 60% of **207**.

The reaction of allenylidene carbene **202** with unsubstituted cyclohexene was disappointing and gave only trace amounts of the desired cycloadduct, **177**.

As expected, the NMR spectra of the diastereomeric mixtures of allenes **204** and **207** (and all their derivatives) contained two sets of signals; these were highly similar and could not always be assigned to a particular isomer.

TBS-protected alcohols **204** and **207** were transformed into the corresponding azides **208** and **209** (Scheme 45). First, the silicon protecting group was cleaved by HF·py in pyridine-buffered THF. This method was very mild and allowed to avoid side reactions at the cyclopropane ring. The alcohol was then activated with MsCl and substituted by an azide under S_N2 conditions to give compounds **208** and **209** in 75% and 70% yields, respectively, over 3 steps.



204, d.r. 1:1 **208**, d.r. 1:1 **209**, d.r. 1:1

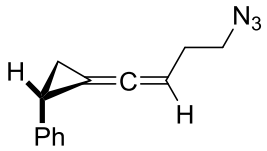
Scheme 45. Synthesis of strained allene azides **208** and **209**. Reagents and conditions: a) HF·py, THF/py; b) MsCl, TEA, DCM, 0 °C → RT; c) NaN_3, DMF, 35 °C. Yields over 3 steps: 75% of **208**, 70% of **209**.

With two VDCPs, **208** and **209**, finally in hand, we were ready to test cycloaddition cascades of the strained systems. The compounds did indeed benefit from strain-activation but in a rather unexpected way.

Reactivity of aryl-VDCP 208 under thermal conditions

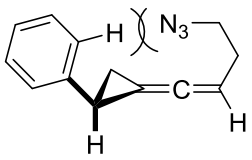
The first surprise came when aryl-VDCP **208** was heated. The strained cyclopropyl ring activated the allene, and the starting material was consumed at an appreciable rate (2–3 days) even at 80 °C, delivering unexpected polycyclic compound **210** as the major product (Scheme 46). One diastereomer of **208** reacted notably faster than the other but the rate difference between the two compounds did not permit a

complete kinetic resolution, and thus the relative reactivities could not be assigned unambiguously. Based on steric grounds, we assume that the *anti*-isomer of **208** reacts more rapidly.

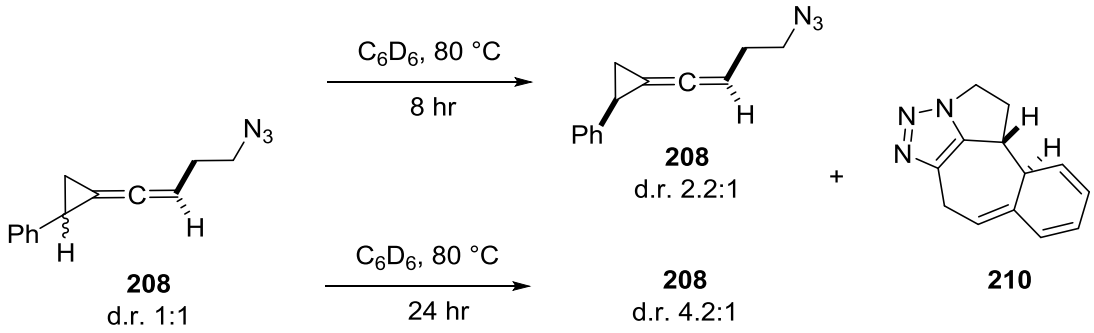


***anti*-208**

Compound *anti*-**208** generally reacted within 30 min at 135 °C, while the complete consumption of the other isomer required prolonged heating over 3 hr. This, however, did not have any beneficial effect on the yield. The reactions invariably delivered ca. 50% of highly unstable compound **210**. Whether this is explained by the reaction mechanism or the simultaneous decomposition of **210**, remains unknown. In the end, we identified the following optimised conditions: temperature—110 °C, and reaction time—2 hr.

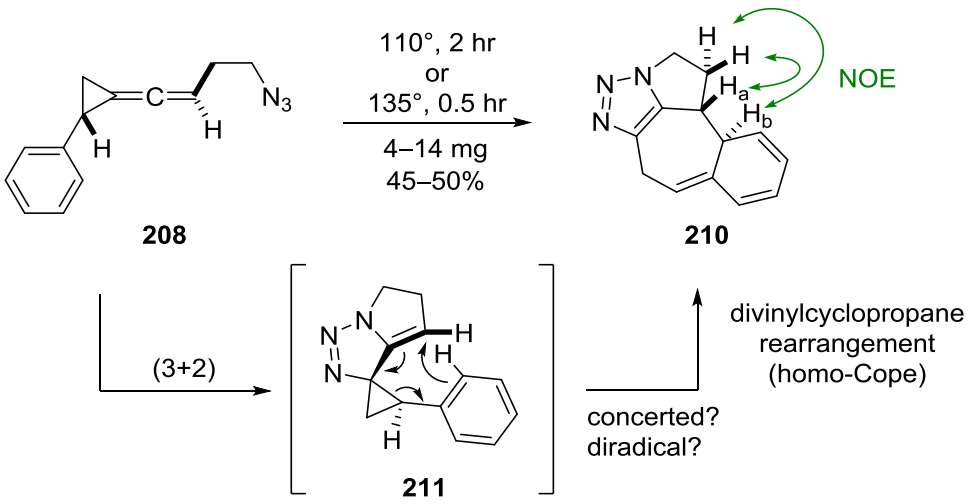


***syn*-208**



Scheme 46. Attempted kinetic resolution of the two isomers of **208.**

Polycyclic product **210** was unstable and thus hard to identify: it decomposed within one day in $CDCl_3$, and even benzene solutions became cloudy after 1–2 days. The structure of **210** was eventually established by extensive NMR studies of freshly prepared solutions in DMSO-d_6 (this solvent separated the overlapped signals), and protons H_a and H_b were assigned as *trans* to each other based on NOE data (Scheme 47; also see Appendix).



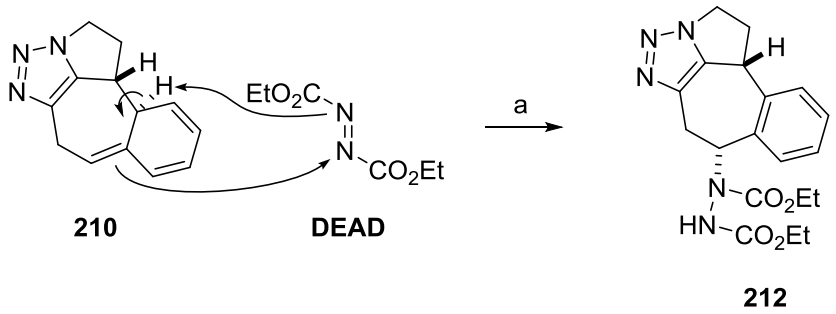
Scheme 47. Rearrangement of aryl-VDCP **208.**

We propose that the reaction proceeds via intermediate **211**, arising from the initial (3+2)-cycloaddition between the azide and allene. As with the cycloadditions discussed in Chapter 1, this is presumably the rate-determining step, which benefits greatly from strain activation by the adjacent ring. The intermediate then undergoes divinylcyclopropane ("*homo*-Cope") rearrangement into seven-membered product **210**. This reaction results in the dearomatisation of the benzene ring and formation of the reactive triene unit in **210**.

Based on the relative stereochemistry of compound **210** and presumed steric interactions in *syn*-**208** vs. *anti*-**208**, we propose the relative configuration of intermediate **211** as the one shown in Scheme 47. Even though the divinylcyclopropane rearrangement has been extensively studied over many years, the mechanistic details of the reaction are unclear and the major debate is whether it proceeds by a diradical or a concerted pathway.[203] Equally, we have no data to conclude if only one isomer of **208** reacts productively or whether it is the decomposition of the product that diminishes the yield.

We expected compound **210** to be an excellent participant in intermolecular ene reaction, and thus it was treated with diethyl azodicarboxylate (DEAD), a well-known

enophile.[204–206] The reaction was very fast indeed and gave the aromatised product **212** in 50–63% yield within 5 min (under anhydrous conditions; Scheme 48). This adduct was reasonably stable and allowed for complete characterisation. An attempt to "telescope" the azide rearrangement/ene-reaction offered no improvement and **212** was isolated in only 21% over 2 steps (ca. 50% per step).



Scheme 48. Ene-reaction of triene **210**. Reagents and conditions: a) diethyl azodicarboxylate, PhH, 63%.

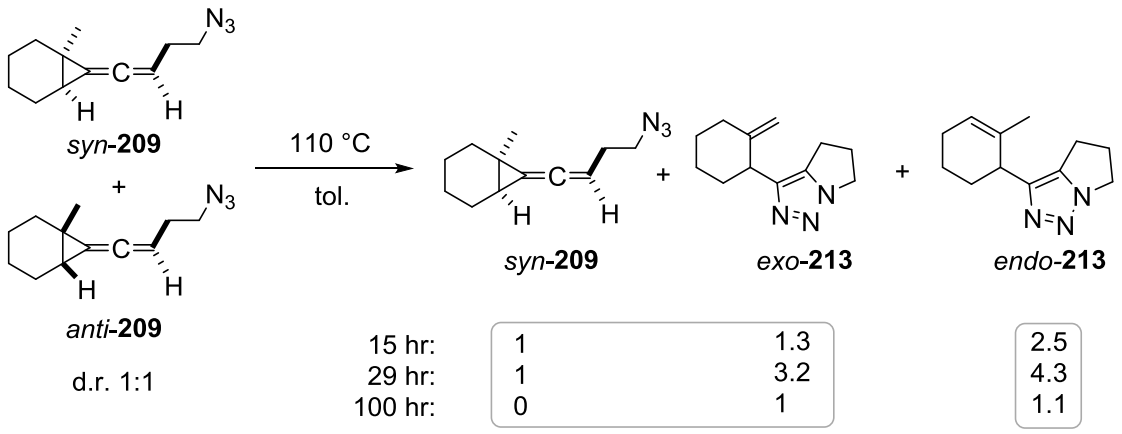
Reactivity of alicyclic VDCP 209 under thermal conditions

Strained allene azide **209** was also found to be rather reactive under thermal conditions but the reaction delivered distinctly different products, triazoles **213**, in yields and isomer ratios that depended on the reaction time and temperature (Scheme 49). For example, by heating azide **209** in *m*-xylene at 135 °C for 30 min, **213** was produced as the 6.5:1 mixture of *endo*/*exo*-double bond isomers in 63% combined yield, along with some recovered *syn*-**209** (the relative stereochemistry was assigned based on a mechanistic proposal, see below). The same reaction performed over 3 hr—until complete consumption of starting material—gave a 1.6:1 ratio of *endo*-/*exo*-**213** in 80% combined yield.

Comparison of NMR traces of this reaction at 110 °C revealed that the two isomers of starting azide **209** react with different rates and give different products. The ratio of *endo*-**213** to (*exo*-**213** + **209**) remained very close to 1:1 over the course of the

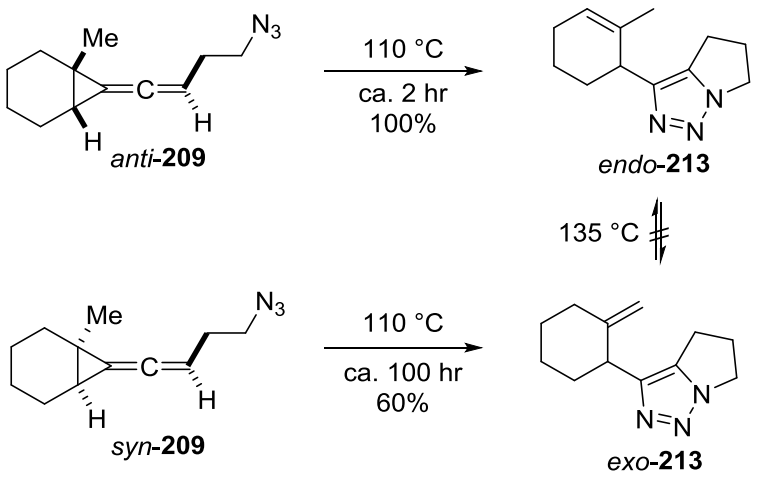
reactions (Scheme 49), suggesting that products *endo*-**213** and *exo*-**213** are indeed formed from the different isomers of starting material.

The *anti*-isomer of **209** reacts very quickly (ca. 2 hr at 110 °C) to give the endocyclic double bond product *endo*-**213** in essentially quantitative yield (Scheme 49). The *syn*-isomer of **209** undergoes transformation much more sluggishly (ca. 100 hr at 110 °C) and delivers *exo*-**213**, with noticeably inferior yields (about 60-80%). The superposition of these two processes defines the overall reaction yield and product ratio.



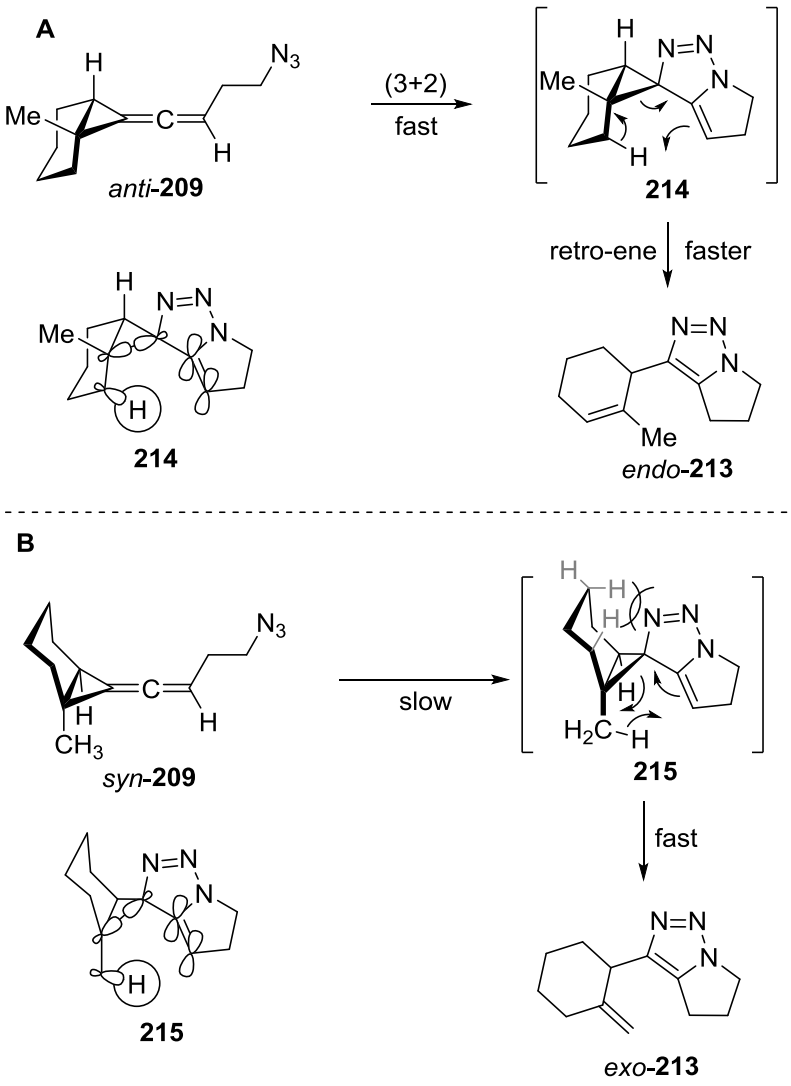
Scheme 49. Product ratios for the rearrangement of allene azide **209**.

Here, it was possible to perform kinetic resolution of the two VDCP diastereomers and isolate *syn*-**209** as a single isomer, albeit in only 10% yield; this compound gave exclusively *exo*-**213** upon heating in *m*-xylene. In a separate experiment, prolonged heating of a purified *endo*-/*exo*-**213** mixture led to no noticeable interconversion (Scheme 50).



Scheme 50. Estimated conversion times and products for *syn*- and *anti*-VDCP azides **209**.

Based on these experiments, we propose the reaction mechanisms shown in Scheme 51. The process starts with a rate-determining (3+2)-cycloaddition between the azide and the distal bond of the allene; this reaction is much faster for *anti*-**209** than for the *syn*-isomer due to the absence of unfavourable steric interactions in the former. The intermediate triazolines **214** and **215** then undergo rapid retro-ene reaction to give the *endo*- and *exo*-**213**, respectively. The triazoline intermediates, however, were never observed in the NMR traces and are presumably consumed immediately upon formation. The orbital overlap dictates that only the endocyclic methylene proton may migrate in **214**, whereas the methyl proton is involved in the rearrangement of **215**.



Scheme 51. Proposed mechanisms for the formation of *exo*- and *endo*-**213.**

In principle, this mechanistic proposal can be verified by isotope labelling experiments. For example, labelling of the exocyclic methyl group as $-CD_3$ should result in specific deuteration as $=CD_2$ and CD_3 in *exo*- and *endo*-**213**, respectively. Moreover, there are literature examples for the successful use of ene-reaction to construct labelled compounds stereospecifically.[207] We did not perform these experiments due to the lower apparent utility of substrates **213**.

The results obtained with VDCPs **208** and **209** are highly interesting from the mechanistic point of view and worthy of further research. However, we pursued an exploratory project and aimed to investigate a wide variety of allene azides, and thus moved on to other derivatives.

Chapter 3. ATMMs in Cycloaddition Reactions

Previous reports on aminoallyl and oxyallyl (3+4)-cycloadditions

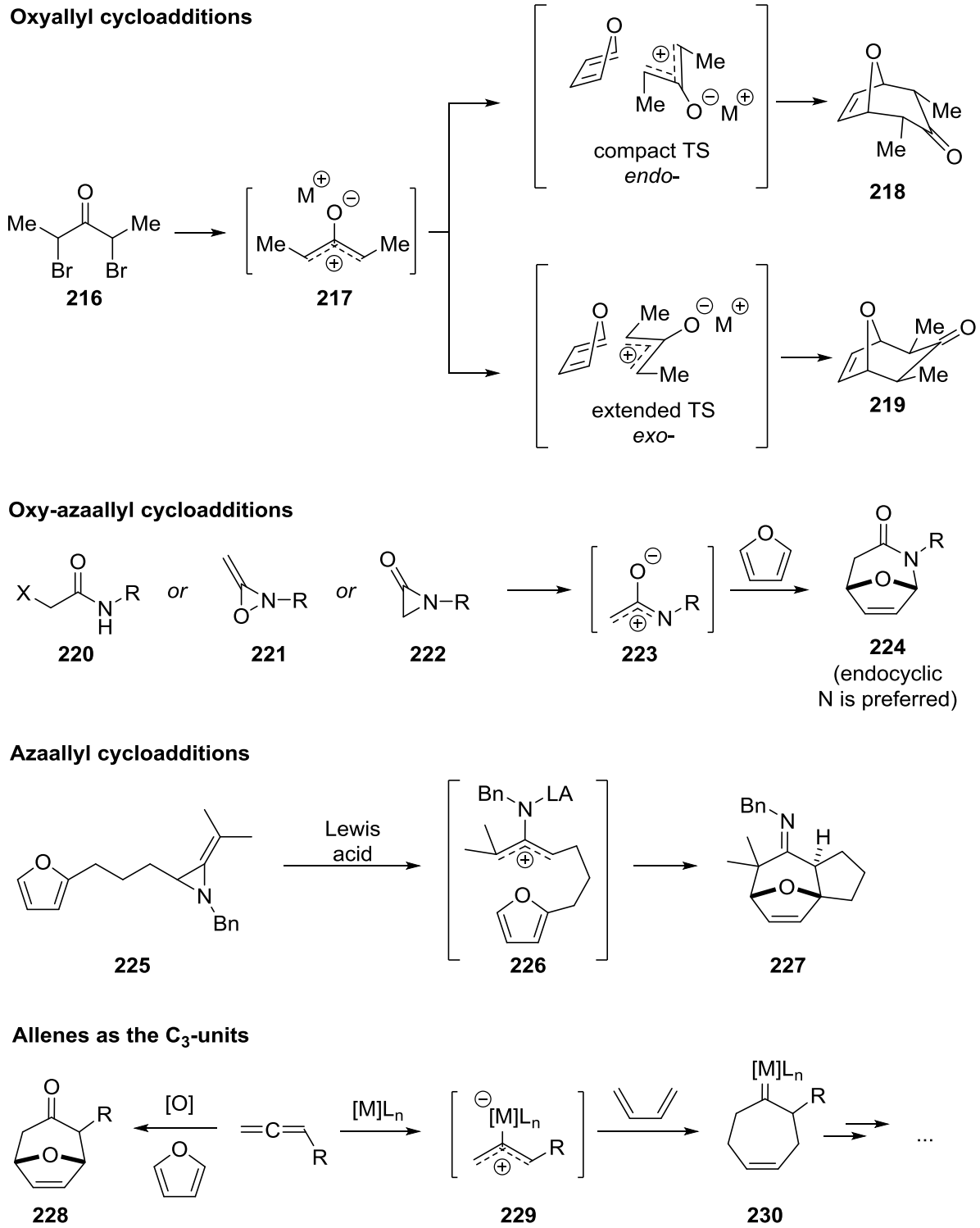
The (4+3)-cycloadditions between an allylic species and a diene have become a useful reaction since the original discovery by Fort in 1962.[208] This reaction is particularly well-suited for the synthesis of 7-membered carbocycles (e.g. **218**, **219**) often found in natural products, and thus has been extensively reviewed.[209–211] Mechanistically, this is a $[_{\pi}4_{s}+_{\pi}2_{s}]$-process, isoelectronic with the Diels–Alder reaction, and involves similar terminology (e.g. *exo*-/*endo*-) and orbital considerations. The diene is almost universally a furan, while the most common dienophile is an oxyallyl zwitterion (e.g. **217**, Scheme 52).

The (4+3)-cycloaddition is a concerted process and can proceed via either a compact (*endo*-) or extended (*exo*-) TS.[211] The well-known preference of the Diels–Alder reaction for the *endo*-TS is much less pronounced here. In some cases, products arising from a stepwise reaction have also been isolated.

While the required allyl species are most often generated from α-haloketones (such as **216**), several examples involving allenes are known. For example, Gung *et al.* used allenes as the three-carbon unit in his synthesis of cortistatins by transannular (4+3)-cycloaddition.[212,213] Allene-alkene cycloadditions catalysed by gold(I), platinum(II), and other late transition metals have been studied by the groups of Mascareñas[25,214–216] and Gung.[217,218]

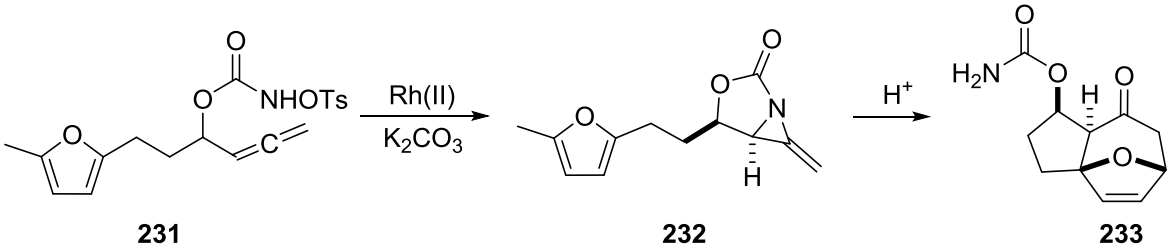
At the same time, reactions of azaallyl dienophiles[148,219,220] in the (4+3)-cycloadditions are rather under-investigated. In these reactions, the aza-species (**226**) are commonly generated from strained alkylidene aziridines (e.g. **225**) by treatment with Lewis acids. Interestingly, zwitterionic intermediates are proposed here, whereas

the conceptually related ATMM species, discussed in Chapter 1, are thought to be diradical.



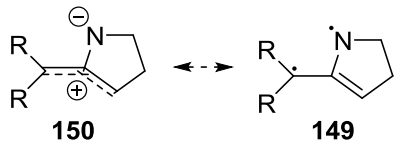
Scheme 52. Literature examples of (4+3)-cycloadditions in allylic systems. References: oxyallyl cycloadditions,[211] oxy-azaallyl cycloadditions,[220] azaallyl cycloadditions,[219] allenes as the C_3-units.[25,213]

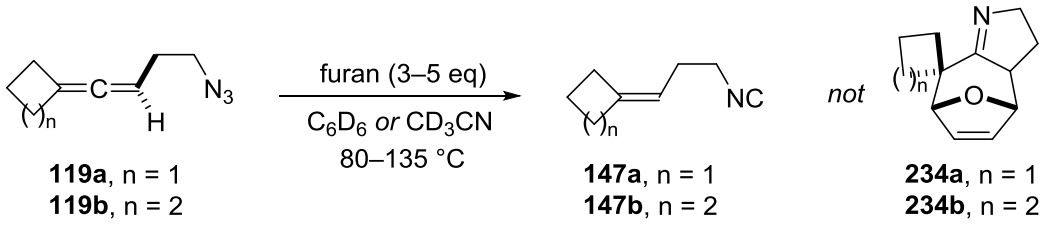
Earlier, our group studied strained aziridine **232** in acid-catalysed reactions with a tethered furan (Scheme 53).[148] Tricyclic product **233** was isolated, arising from the (4+3)-cycloaddition of the intermediate azaallyl species followed by hydrolysis. The starting aziridine **232** was obtained from allenyl carbamate **231** under Rh^{II} catalysis.[145,148]



Scheme 53. Earlier work on azaallyl (4+3)-cycloadditions in the Robertson lab.

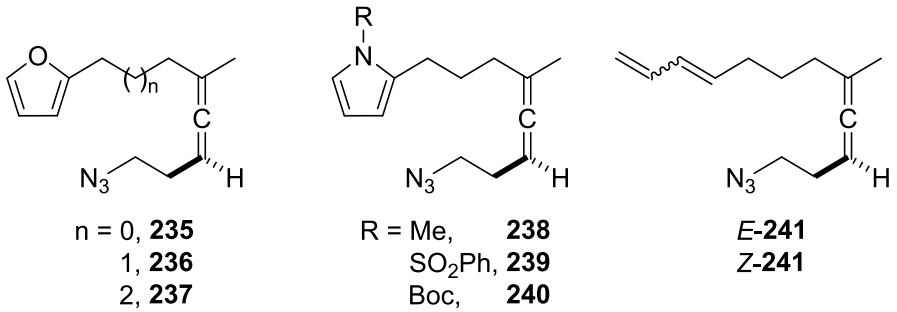
At this point of the project, we wanted to test if the azaallyl intermediates **149/150** proposed in Chapter 1 (whether these were zwitterionic or diradical) would react with dienes in (4+3)-cycloadditions. Initial attempts to react azides **119a/119b** with furan *intermolecularly* showed no cycloaddition products **234a** or **234b** and only isocyanides **147a** and **147b** were isolated (Scheme 54).





Scheme 54. Attempted intermolecular reactions of allene azides **119a**–**b** with furan.

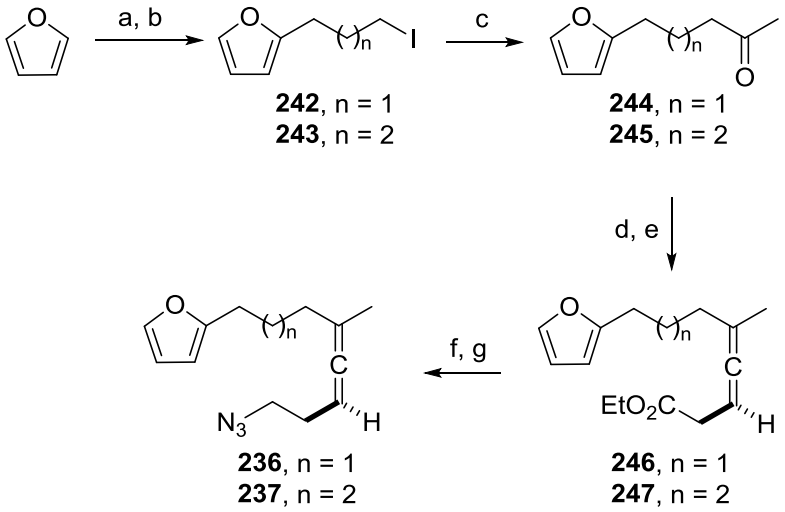
Therefore, *intramolecular* reactions had to be approached, and a series of allene azides tethered to furan, *N*-substituted pyrroles, and 1,3-dienes (Scheme 55) was devised and synthesised.



Scheme 55. Allene azides discussed in this chapter.

Synthesis of allene azides tethered to furans

The synthesis of allene azides with a two or three-carbon tether to a furan started with known 2-(ω-iodoalkyl)furans **242** and **243**, easily accessible from the parent heterocycle (Scheme 56).[221–225] The side-chain was homologated into a methyl ketone using the procedure of Baldwin *et al.*[226] Ketones **244** and **245**[227,228] were then converted into allene azides **236** and **237** uneventfully using the Johnson–Claisen rearrangement to install the allene.

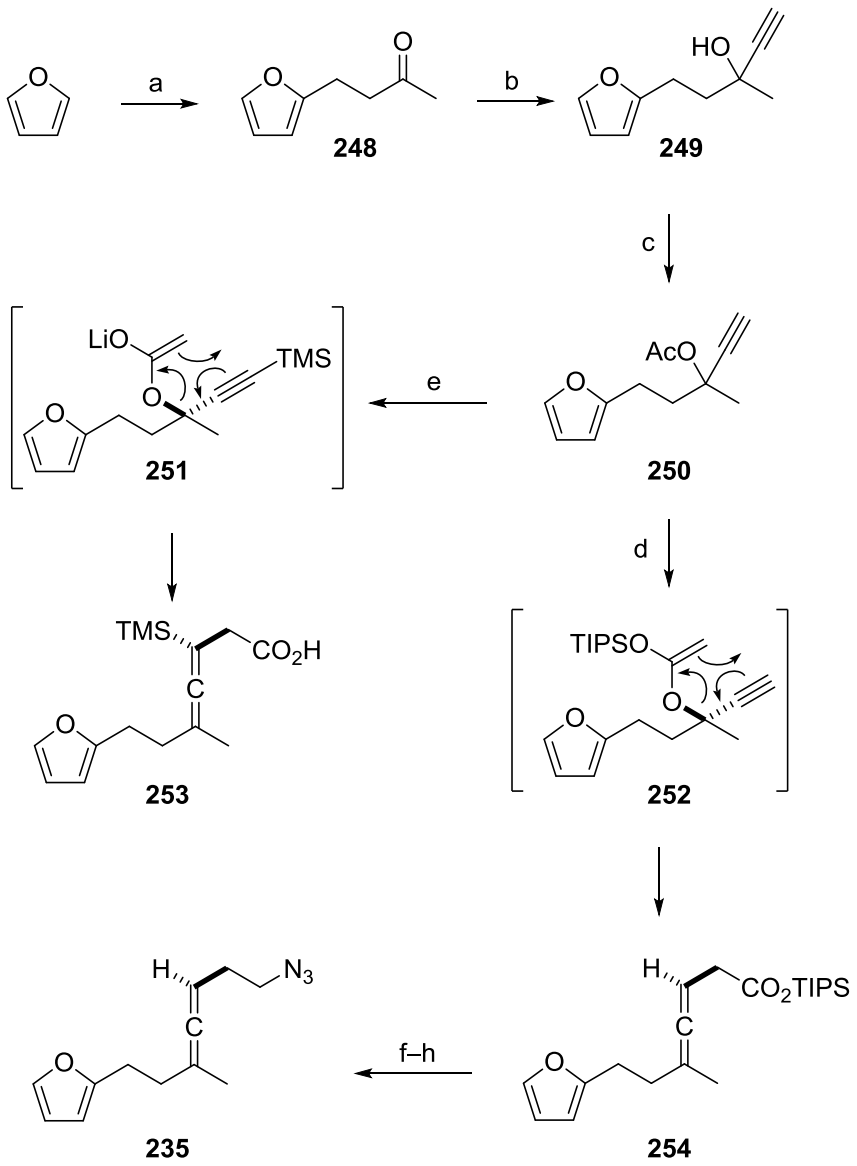


Scheme 56. Synthesis of allene azides with a three- and four-carbon tether to furan. Reagents and conditions: a) BuLi, THF, −78 °C, *then* 1-chloro-3-iodopropane *or* 1-chloro-4-iodobutane, −78 °C → RT, 100%; b) NaI, butanone, reflux, 82% of **242**, 94% of **243**; c) ethyl vinyl ether, BuLi, THF, −78 °C → RT, *then* PTSA·H_2O, ether, 84% of **244**, 89% of **245**; d) HC≡CMgBr, THF, reflux; e) triethyl orthoacetate, $EtCO_2H$, 140 °C, yield over 2 steps: 39% of **246**, 59% of **247**; f) $LiAlH_4$, Et_2O, 0 °C; g) CBr_4, PPh_3, DMF, *then* NaN_3, yield over 2 steps: 98% of **236**, 78% of **237**.

Allene azide **235**, with a two-carbon tether to the furan, had to be assembled in a different way (Scheme 57). Furan was alkylated with methyl vinyl ketone under acid

catalysis to give ketone **248** in moderate yields.[229] The ketone was easily converted into propargylic acetate **250** by Grignard addition[230] and acetylation. An attempted Ireland–Claisen rearrangement of acetate **250** under the conditions of Baldwin (by treatment with excess LiHMDS and TMSCl at low temperatures)[43,44] gave silylated allene **253** in yields around 30%. An alternative procedure by Brummond,[46] relying on the "soft enolisation"[231] with TIPSOTf and TEA,* gave better yields and delivered almost 70% of TIPS-ester **254**. Subsequent reduction with $LiAlH_4$, alcohol activation via the mesylate, and azide substitution delivered the desired two-carbon-tethered allene azide **235** in 73% over 3 steps.

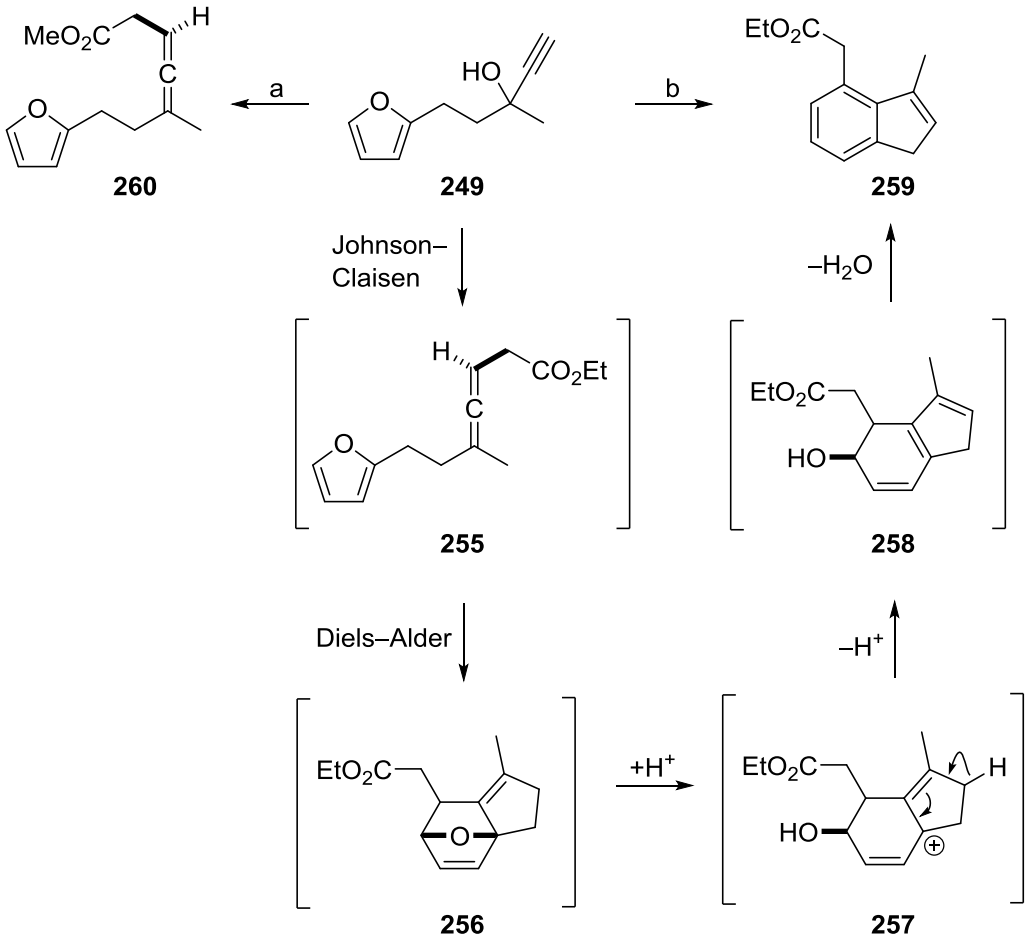
* The mechanism of this reaction is discussed in Chapter 4.



Scheme 57. Synthesis of allene azide **235** with a two-carbon tether to furan. Reagents and conditions: a) methyl vinyl ketone, PTSA (cat.), reflux, 39%; b) HC≡CMgBr, THF, reflux, 75%; c) Ac_2O, TEA, DMAP, DCM, 91%; d) TIPSOTf, TEA, PhH, 40 °C, 68%; e) LiHMDS, TMSCl, THF, −78 °C → RT, 30%; f) $LiAlH_4$, Et_2O, 0 °C → RT; g) MsCl, TEA, DCM, 0 °C → RT; h) NaN_3, DMF, 35 °C, 73% over 3 steps.

Our earlier attempt to synthesise allenyl ester **255** by the Johnson–Claisen rearrangement led to the unexpected formation of indene **259** as the major product (63% yield, Scheme 58). We assume that the initially formed allene **255** undergoes a proximity-driven Diels–Alder reaction with the furan moiety and the resulting 1,4-epoxide **256** fragments into the final product. This process is facilitated by the rather harsh conditions used in the Johnson–Claisen reaction (140 °C, acid catalyst).

Performing the rearrangement at lower temperatures (110 °C, trimethyl orthoacetate) allowed the isolation of the desired allenyl furan **260** in just 6% yield.



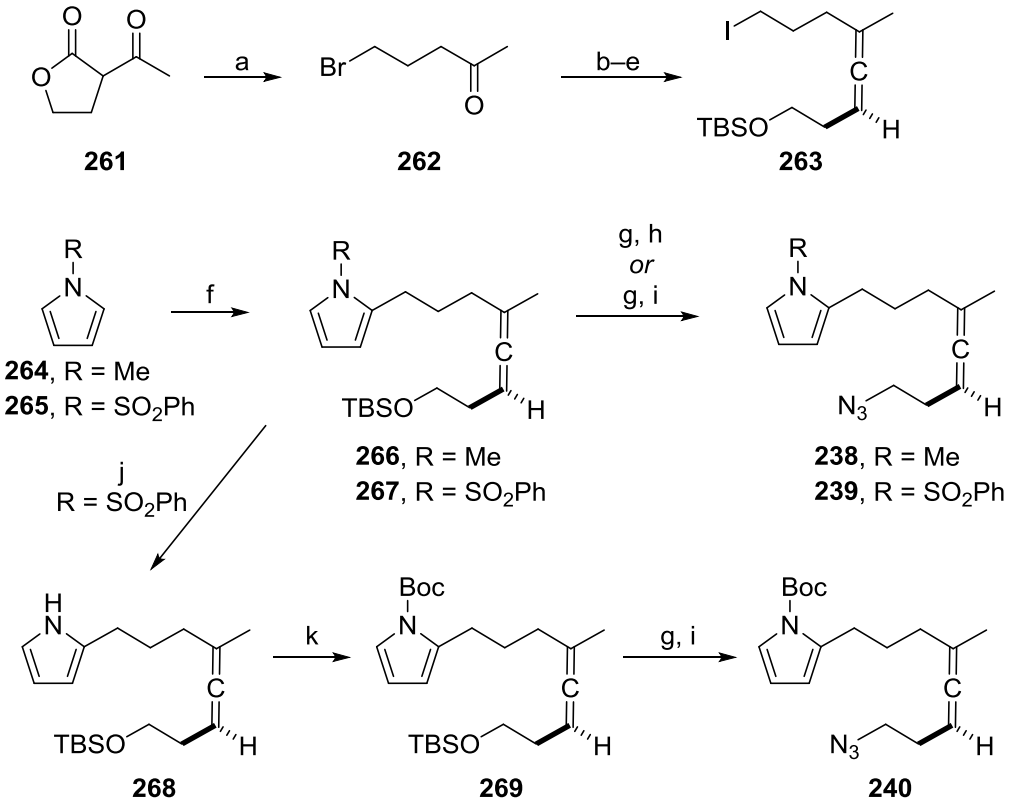
Scheme 58. Unexpected formation of indene **259** from alcohol **249**. Reagents and conditions: a) trimethyl orthoacetate, $EtCO_2H$, 105 °C, 6%; b) triethyl orthoacetate, $EtCO_2H$, 140 °C, 63%.

Synthesis of allene azides tethered to pyrroles

Pyrroles are electron-rich heterocycles that easily undergo a number of reactions, such as electrophilic substitution and oxidation (often undesired).[3] Many of them are unstable towards acids and heating, and thus our synthetic strategy had to be significantly revised. We decided to prepare a complete side-chain in the form of iodide **263**, and then append the pyrrole at the final stage of the synthesis (Scheme 59).

5-Bromopentan-2-one (**262**) was prepared in bulk from commercially available 2-acetylbutyrolactone (**261**) by refluxing with aq. HBr in toluene.[232] This compound

was then converted into functionalised iodide **263** in a straightforward manner.* *N*-protected pyrroles **264** and **265** were deprotonated, then alkylated with iodide **263**. The reactions were very temperature- and moisture-sensitive and required the use of DMPU as co-solvent. The hydroxyl group in compounds **266** and **267** was deprotected with pyridine-buffered HF and the alcohols were converted into azides **238**/**239** as before.



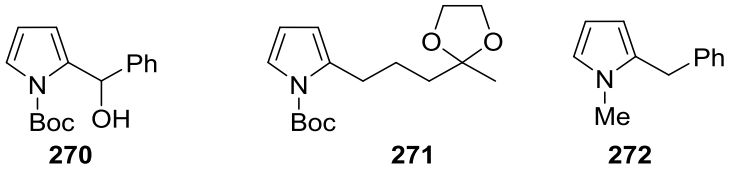
Scheme 59. Preparation of allene azides tethered to *N*-substituted pyrroles. Reagents and conditions: a) aq. HBr, tol., 80 °C, 78%; b) HC≡CMgBr, THF, 0 °C, 93%; c) triethyl orthoacetate, $EtCO_2H$, 140 °C, 55%; d) $LiAlH_4$, Et_2O, 0 °C, *then* TBSCl, imid., DCM, 78%; e) NaI, acetone, 72–90%; f) LiTMP *or* BuLi, THF, −78 °C, *then* **263**, THF/DMPU, −78 °C → RT, 72% of **266**, 67% of **267**; g) HF·py, THF/py, 68% for R = SO_2Ph, 98% for R = Me, 93% for R = Boc; h) PPh_3, CBr_4, DMF, *then* NaN_3, 61% of **239**; i) MsCl, TEA, DCM, 0 °C → RT, *then* NaN_3, DMF, 71% of **238**, 79% of **240**; j) Mg, MeOH,)), 88%; k) Boc_2O, DMAP, MeCN, 90%.

N-Boc-protected pyrrole **269** was not accessible by alkylation of the parent heterocycle and had to be obtained from *N*-phenylsulfonyl derivative **267** by deprotection (Mg, MeOH, sonication)[233] and acylation (Boc_2O, DMAP).[234,235] The

* Allenic iodide **263** could also be synthesised from commerically available 5-chloropentan-2-one using a similar reaction sequence.[150]

protected alcohol moiety of **269** was then converted into the azide in **240** by deprotection (HF·py), mesylation and azide substitution.

While investigating the synthesis and reactivity of C_2-subsituted pyrroles, we prepared a variety of other heterocyclic substrates. Some of these are presented in Scheme 60 but not otherwise discussed.



270 **271** **272**

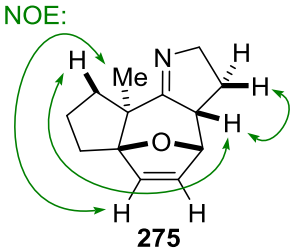
Scheme 60. Some test substrates prepared on the way to pyrrole allene azides.

Cascade cycloadditions of tethered allene azides

Cycloadditions of furan-tethered allene azides **235**–**237** were investigated first (Scheme 61), followed by evaluation of pyrrole derivatives **238**–**240**. Two important features were discovered: (1) the importance of the tether length, and (2) the influence of electron density of the heteroaromatic ring.

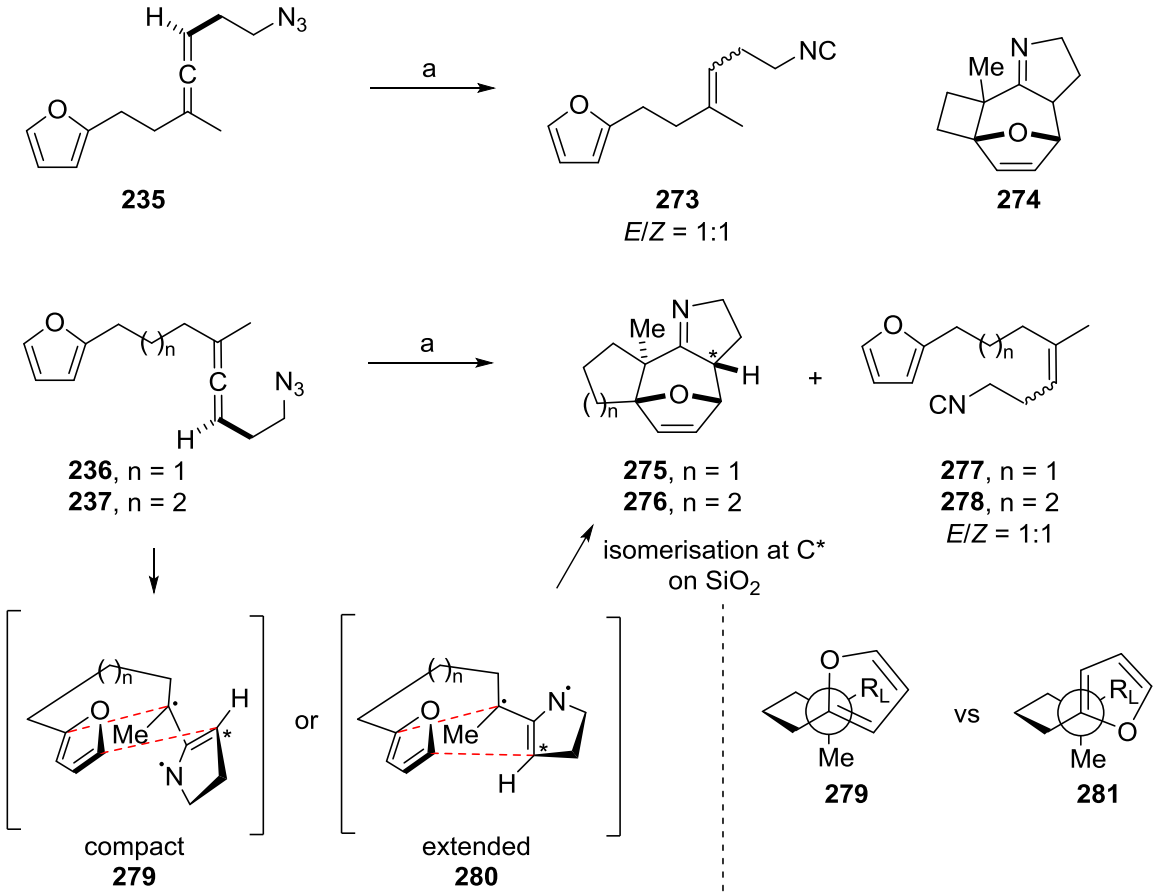
Azide **235**, with a short two-carbon tether, gave only the corresponding isocyanide **273** in low yields when heated, with the majority of the starting material undergoing unproductive decomposition. Presumably, cycloadduct **274** would have been excessively strained due to the presence of a cyclobutane ring.

Reactions of the three-carbon tethered allene azide **236** were the most successful. Heating **236** at 135 °C in *m*-xylene over 90 min reproducibly delivered the desired tetracyclic product **275** in 40% yield. The selectivity of this process was remarkable: compound **275** was formed exclusively with the oxa bridge and the methyl group being *trans* to each other (NOE data, see Appendix). The imine subunit was initially formed as a 3:1–5:1 mixture of diastereomers at C* (with the imine hydrogen being "up" in the major isomer), as indicated by NMR analysis of the crude



275

mixtures, but isomerised into a single product on a silica column when eluted with a MeOH-containing eluent. Presumably, "up"-**275** is both the kinetic and thermodynamic product. Overall, this reaction selectively delivered three new rings and four stereocentres with an average yield of 75% per ring. Isocyanide side product **277** was formed in 6% yield as a 1:1 mixture of alkene stereoisomers.



Scheme 61. Cycloaddition cascade of furan-tethered allene azides. Reagents and conditions: a) *m*-xylene, 135 °C, 11% of **273**, 29–40% of **275**, 8% of **276**, 6% of **277**, 26% of **278**.

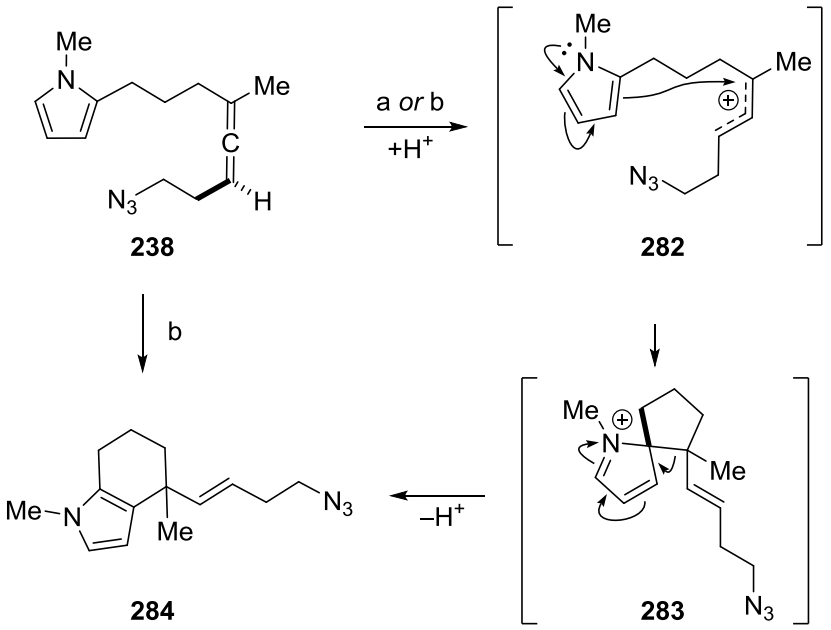
The cycloaddition cascade of four-carbon-tethered allene azide **237** was much less effective and resulted in the formation of tetracycle **276** as a mixture of unassigned diastereomers in 31% yield. The major isomer of **276** (depicted in Scheme 61) was isolated by repeated chromatography on silica in 8% yield. The major product of the reaction was isocyanide **278** (19–26%) isolated as a 1:1 mixture of alkene stereoisomers.

The proposed reaction intermediates are ATMMs **279**/**280**. The "up" (major) and "down" imine diastereomers can either be formed directly from the compact (**279**) and the extended (**280**) pre-TS conformations of the formal (4+3)-cycloaddition, respectively, or result from post-reaction tautomerisation. The orientation of the epoxy-bridge is determined by the position of the furan moiety (**279** vs. **281**). Further investigations are required to establish whether a concerted cycloaddition or a stepwise process is operating.

It should be noted that the relative configuration of the seven-membered ring in **275**/**276** is the same as the one observed[148] in the acid-catalysed cycloaddition of methylene aziridine **232** (Scheme 53).

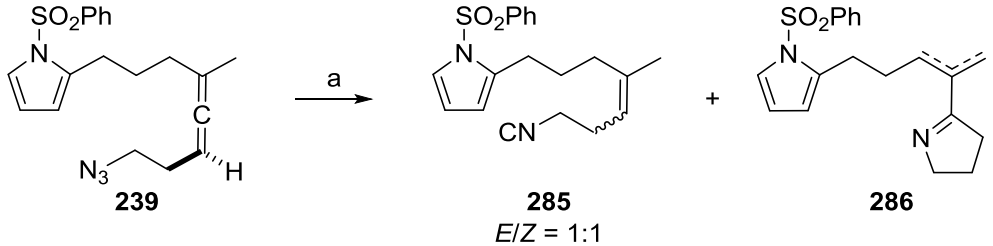
These results suggest that the optimal tether length between the allene and the furan moieties is three methylene units. A longer tether leads to greatly diminished reactivity and diastereoselectivity, whereas a shorter link prevents the cycloaddition altogether. Having established this, we were ready to continue by testing the pyrrole-containing substrates with the optimal, three-carbon, tether.

Reactions of *N*-methyl pyrrole derivative **238** were investigated first. Surprisingly, heating of **238** delivered not the (4+3)-cycloadduct, nor even the isocyanide, but tetrahydroindole product **284** (Scheme 62). The same reaction could also be performed at lower temperatures (80 °C, C_6D_6, ≤30 min, 100% conversion) under acid catalysis (ethereal HCl). We propose the following sequence for the formation of **284**: C_2-alkylation of the electron-rich heteroaromatic ring gives intermediate **283**, which then undergoes a $C_2 \rightarrow C_3$ migration common in pyrrole systems.[3] A highly similar reaction under transition-metal catalysis was reported by the group of Nelson in their synthesis of rhazinilam.[236]



Scheme 62. Undesired S_EAr alkylation of electron-rich pyrrole **238** with a tethered allene unit. Reagents and conditions: a) *m*-xylene, 135 °C, 15%; b) ethereal HCl (cat.), C_6D_6, 80 °C, 0.5 hr, 100% conversion, yield not measured.

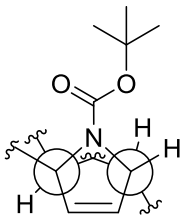
This undesired alkylation indicated that the pyrrole ring had to be somewhat deactivated by a suitable electron-withdrawing group; therefore, we tested *N*-phenylsulfonyl pyrrole **239** next. It was found that thermal rearrangements of **239** led to isocyanide **285** in low yields, accompanied by a mixture of azadienes **286**. It appears that the sulfonamide group decreased the electron density on the heteroaromatic ring too much, rendering the latter unreactive in cycloadditions. Clearly, a more moderate EWG on the nitrogen was required.



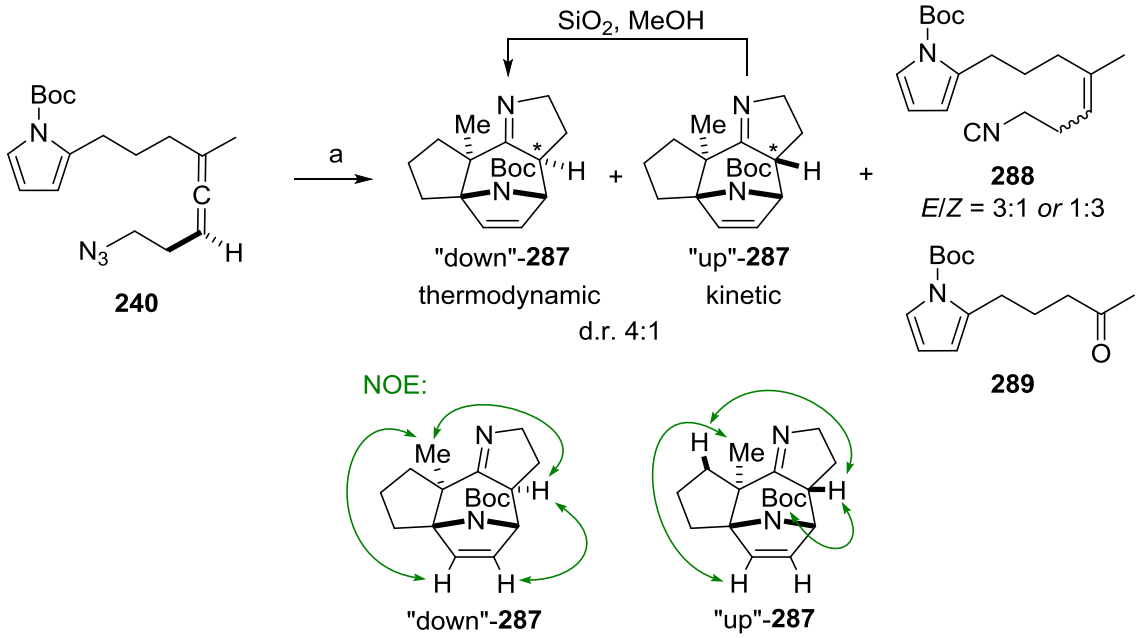
Scheme 63. Products of thermal rearrangement of allene azide tethered to electron-poor pyrrole. Reagents and conditions: a) *m*-xylene, 135 °C, 10% of **285**, 18% of **286**.

And this group was found to be a Boc carbamate. Heating *N*-Boc-protected pyrrole **240** delivered the desired tetracyclic product **287** as a 4:1 mixture of imine

diastereomers (NOE data, Scheme 64, also see Appendix), albeit in only 23% isolated yield. The relative configuration of the aza-bridge and the methyl group is identical to that in oxy-products **275** and **276**. NMR traces of the reaction mixtures and isolated compounds indicate that the "up" C*–H isomer is the kinetic product and the "down" isomer is the thermodynamic one. Furthermore, the reprotonation of the enamine tautomer occurs preferentially from the bottom side, since the approach from the top is hindered by the bulky Boc group.



The identified side products were isocyanide **288** (12%, E/Z = 3:1 or 1:3) and ketone **289** (7%, arises from the oxidative cleavage discussed in Chapter 1).



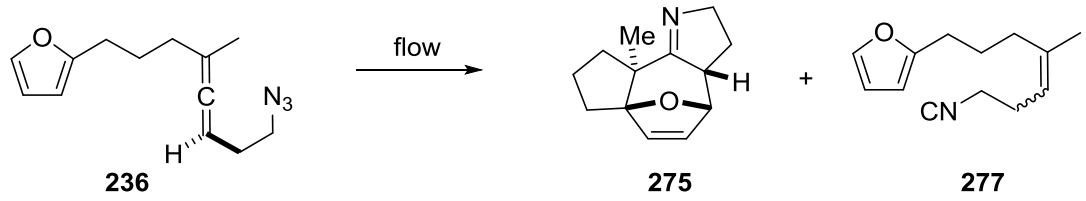
Scheme 64. Cycloaddition cascade of allene azide **240** tethered to *N*-Boc pyrrole. Reagents and conditions: a) *m*-xylene, 135 °C, *then* silica column, 23% of **287**, d.r. 5:1, 12% of **288**, E/Z = 3:1 (or 1:3), 7% of **289**.

Reactions of furan-tethered allene azide 236 in flow

Allene azide **236** with a three-carbon-tether to furan was also tested under flow conditions (Scheme 65). As expected, the increase in reaction temperatures led to much faster conversions: experiments conducted at 160 °C (tol.) were finished in 15–20 min, and those performed at 180 °C (MeCN) were complete in just 10 min.

However, there was no improvement in efficiency and the cycloaddition product was obtained in 30–40% isolated yields. In addition, the selectivity of the reaction diminished with the increase in temperature; trace amounts of unidentified diastereomers were detected in the 160 °C runs and these became a significant component at 180 °C (d.r. 3:1, inseparable; Scheme 65, entry 1).

In summary, the application of flow conditions did not lead to significant improvement of the cascade (4+3)-cycloadditions.



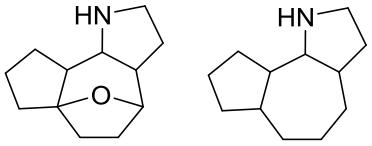
236 **275** **277**

1. MeCN, 180 °C, 10 min	d.r. 3:1 (major isomer shown) 38%	27%
2. tol, 160 °C, 15 min	29% (35% b.r.s.m.)	4%

Scheme 65. Thermal rearrangements of allene azide **236** in flow.

Aminoallyl intermediates in formal (3+2)-cycloadditions

The developed (4+3)-cycloaddition cascades of tethered allene azides opened a concise approach towards tetracyclic cores **290**. However, simpler tricyclic frameworks **291** would be potentially more useful in applied research;* therefore, we attempted a synthesis of allene azides tethered to 1,3-dienes.



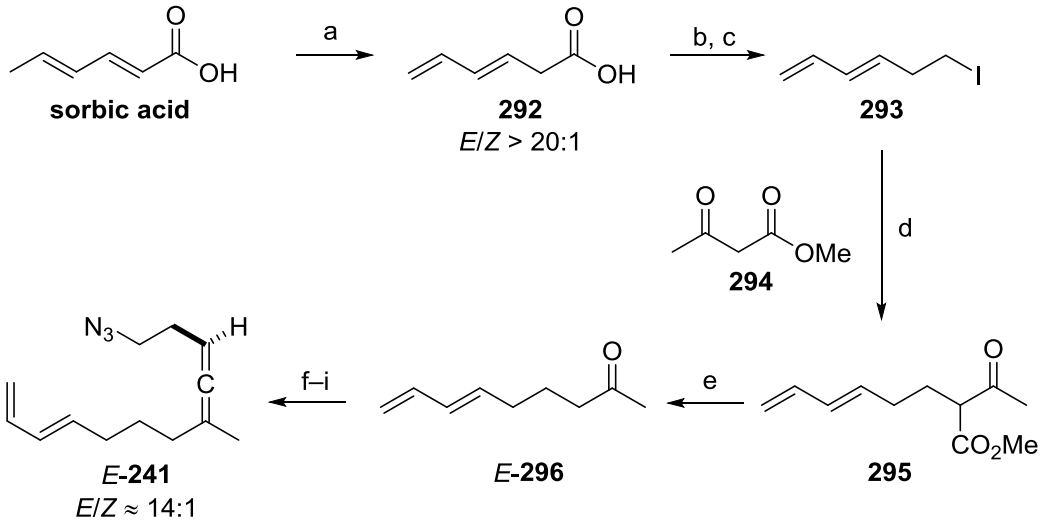
290 **291**

Synthesis of *E*-diene-tethered allene azide *E*-241

Synthesis of allene azide *E*-**241** was relatively straightforward (Scheme 66). Deconjugation of sorbic acid[6] delivered the required *E*-diene **292** in nearly quantitative yield with only trace amounts of the *Z*-isomer (NMR data). Acid **292** was converted into iodide **293**[6] and the latter was used to alkylate the enolate of methyl acetoacetate **294**

* A search in the Reaxys database delivered 8 hits for the substructure **291** and none for **290**.

to give ketoester **295**.[227] Krapcho decarboxylation[237] of **295** delivered *E*-dienyl methyl ketone *E*-**296**,[227,238] which was transformed into allene azide *E*-**241** in the usual way. The final product was formed as a 14:1 mixture of *E*/*Z*-isomers as indicated by ^{1}H NMR spectroscopy.

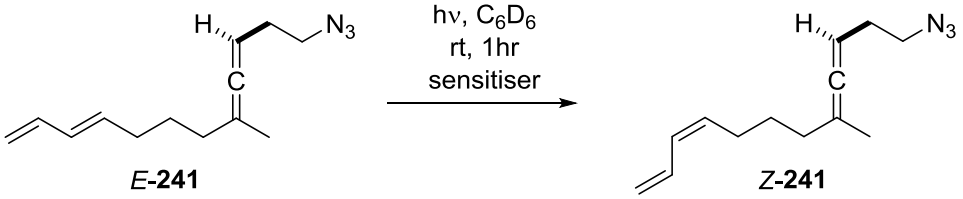


Scheme 66. Synthesis of *E*-diene-tethered allene azide *E*-**241**. Reagents and conditions: a) LDA, THF, −10 °C → RT, *then* aq. HCl, THF, 0 °C, 100%; b) $LiAlH_4$, THF, reflux, 71%; c) PPh_3, I_2, imid., DCM, 10 °C → RT, 82%; d) **294**, NaH, THF/DMF, RT → 60 °C, 72%; e) LiCl, H_2O, DMSO, 160 °C, 77%; f) HC≡CMgBr, THF, reflux, 96%; g) triethyl orthoacetate, $EtCO_2H$ (cat.), 140 °C, 72%; h) $LiAlH_4$, Et_2O, 0 °C, 76%; i) CBr_4, PPh_3, DMF, *then* NaN_3, 99%.

Synthesis of *Z*-diene-tethered allene azide *Z*-241

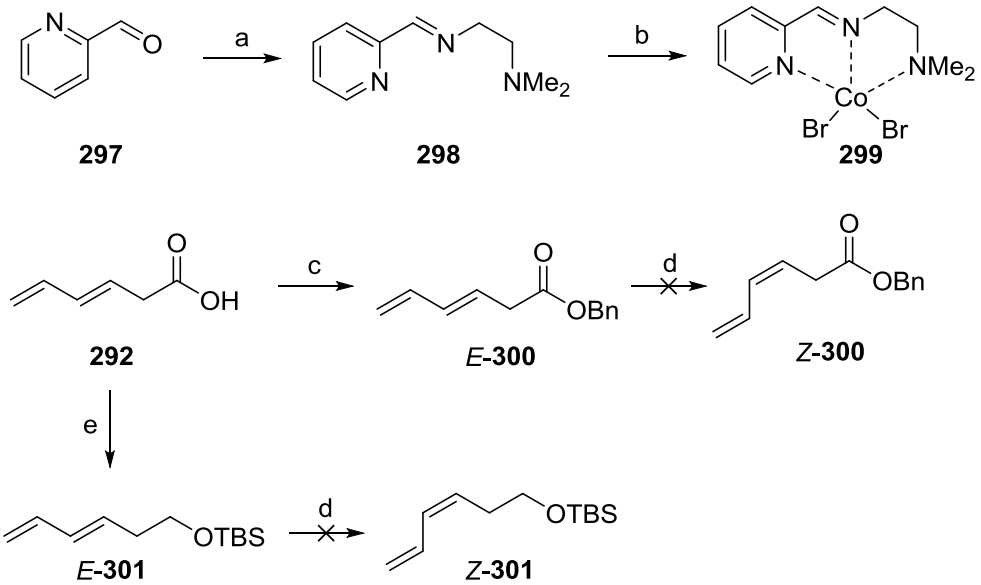
The easiest way to obtain *Z*-**241** was envisaged to be through a light-induced double-bond isomerisation of *E*-**241**.[239] We screened several of the most common sensitisers using an Exo-Terra PT-2056 200 Watt lamp as the light source and a quartz flask as the reaction vessel (Table 7). Benzophenone was found to be the most effective sensitiser, producing 0.7:1 *Z*/*E*-mixtures. This translates into just 40% of the desired *Z*-isomer, the major component remaining the starting *E*-**241**. The two isomers could not be separated by chromatography (using both normal and $AgNO_3$-impregnated silica) and the overall yield was very low; therefore, this approach was abandoned and alternatives were sought.

Table 7. *E/Z*-Photoisomerisation studies.



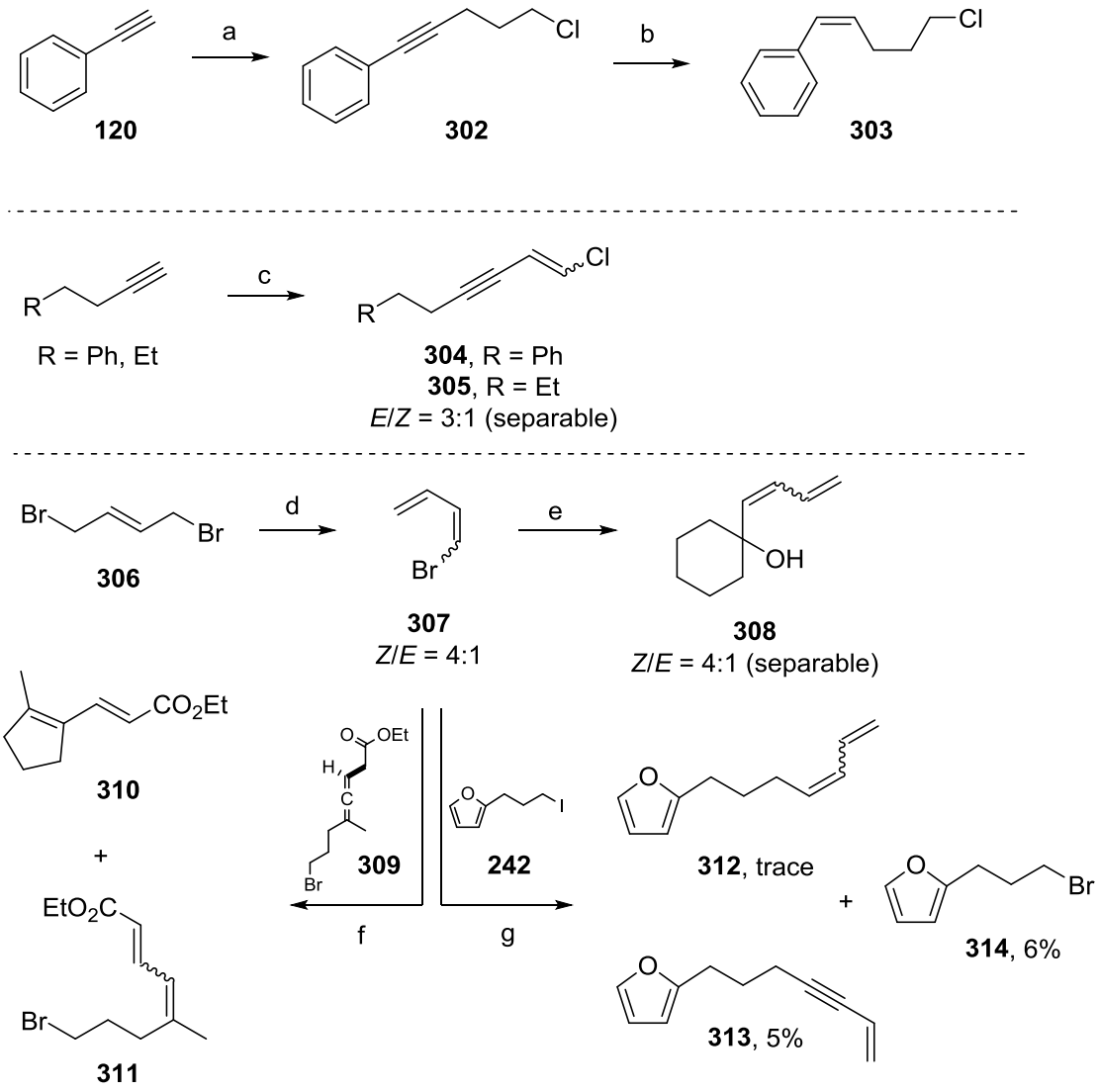
No.	Sensitiser	*Z/E*
1	Acetophenone	0.56:1
2	**Benzophenone**	**0.71:1**
3	**Benzophenone (CD_3CN)**	**0.70:1**
4	Benzil	0.40:1
5	Pyrene	1:15 (no reaction)
6	Fluorenone (CD_3CN)	1:4.2

Hilt and co-workers recently reported *E/Z*-isomerisation of dienes using Co^{II} catalysis.[240] We synthesised the required catalyst **299** and ran tests on the reported[241] substrate *E*-**300** as well as silyl ether *E*-**301** but no isomerisation was observed and we repeatedly re-isolated the starting materials (Scheme 67). The use of degassed solvents and different batches of the reagents had no effect on the reactions; therefore, other approaches were tried.



Scheme 67. Studies towards Hilt's *E/Z*-diene isomerisation. Reagents and conditions: a) *N,N*-dimethylethylenediamine, EtOH, $MgSO_4$, 99%; b) $CoBr_2$, THF, 91%; c) BnOC(O)Cl, TEA, DMAP(cat.), DCM, 0 °C, 84%; d) **299**, Zn, ZnI_2, DCM, no reaction; e) $LiAlH_4$, THF, 60 °C; *then* TBSCl, imid., DMAP (cat.), DCM, 0 °C → RT, 51%.

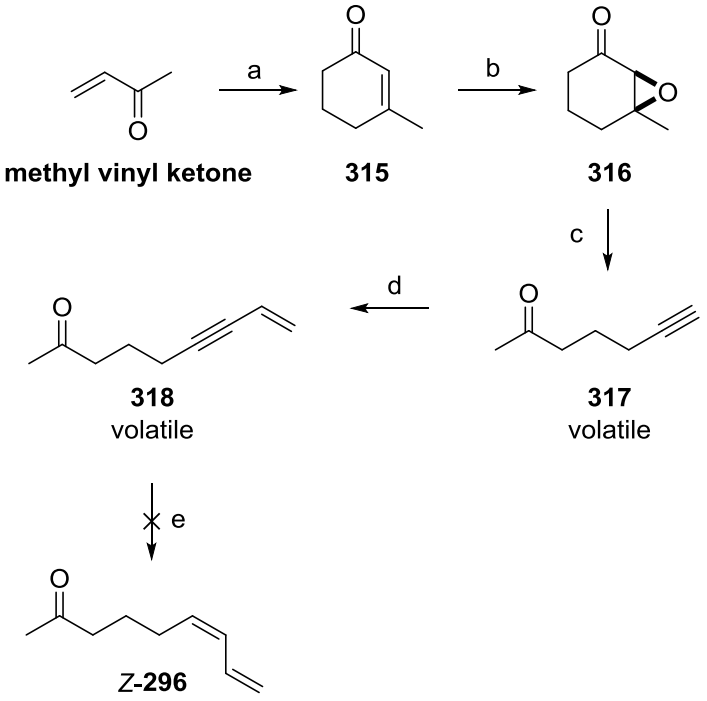
We then expended a significant effort to prepare the desired *Z*-diene by partial reduction[242] of a suitable enyne or by alkylation of *(Z)*-1-bromobuta-1,3-diene, **307**. Some of the test substrates prepared during these trials are shown in Scheme 68 and not discussed further.



Scheme 68. Studies towards the *Z*-diene subunit. Reagents and conditions: a) BuLi, THF, −78 °C → RT, *then* $Cl(CH_2)_3Br$, RT → reflux, 100%; b) $Pd/CaCO_3$/[Pb],* quinoline, EtOAc, H_2 (1 atm), 100%; c) 1,2-dichloroethylene (*E*/*Z* = 3:1), $Pd(OAc)_2$, *i*-Pr_2NH, CuI, 40 °C *or* RT, 20% of *E*-**305**, 7% of *Z*-**305**, 25% of *E*-**304**, 7% of *Z*-**304**; d) KOH, $C_{14}H_{30}$, reflux, yield not measured; e) *t*-BuLi, THF, −78 °C, *then* cyclohexanone, −78 °C → RT, 63% of *Z*-**308**, 19% of *E*-**308**; f) *t*-BuLi, THF, −78 °C, then **309**, −78 °C → RT, 18% of **310**, 4% of **311**; g) *t*-BuLi, Et_2O, −78 °C, *then* **242**, DMPU/THF, −78 °C → RT.

* Sigma–Aldrich does not specify the source of Pb in the catalyst, describing the lot as "palladium deposited on calcium carbonate and treated with various forms of lead".

One of the more successful routes relied on the partial reduction of known enyne ketone **318** (Scheme 69).[243,244] In the first-generation approach, enyne **318** was prepared by the Eschenmoser–Tanabe fragmentation of epoxy ketone **316**[245,246] followed by the Sonogashira reaction with vinyl bromide. Both enyne **318** and alkyne **317** have low molecular weight and are volatile; therefore, significant precautions had to be taken when working on a small scale. Initial attempts to reduce **318** using Lindlar catalyst[247,248] were unsuccessful (cf. ref.[249,250]) and the overall protocol had to be extensively modified.



Scheme 69. Initial studies towards ketone *Z*-**296**. Reagents and conditions: a) ethyl acetoacetate, KO*t*-Bu, *t*-BuOH, 0 °C → reflux; b) aq. H_2O_2, NaOH, MeOH, 38% over 2 steps; c) *p*-$MeC_6H_4SO_2NHNH_2$, AcOH, DCM, −40 °C → RT, 42%; d) vinyl bromide, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, 15%; e) $Pd/CaCO_3$/[Pb], quinoline, H_2, petrol, no reaction.

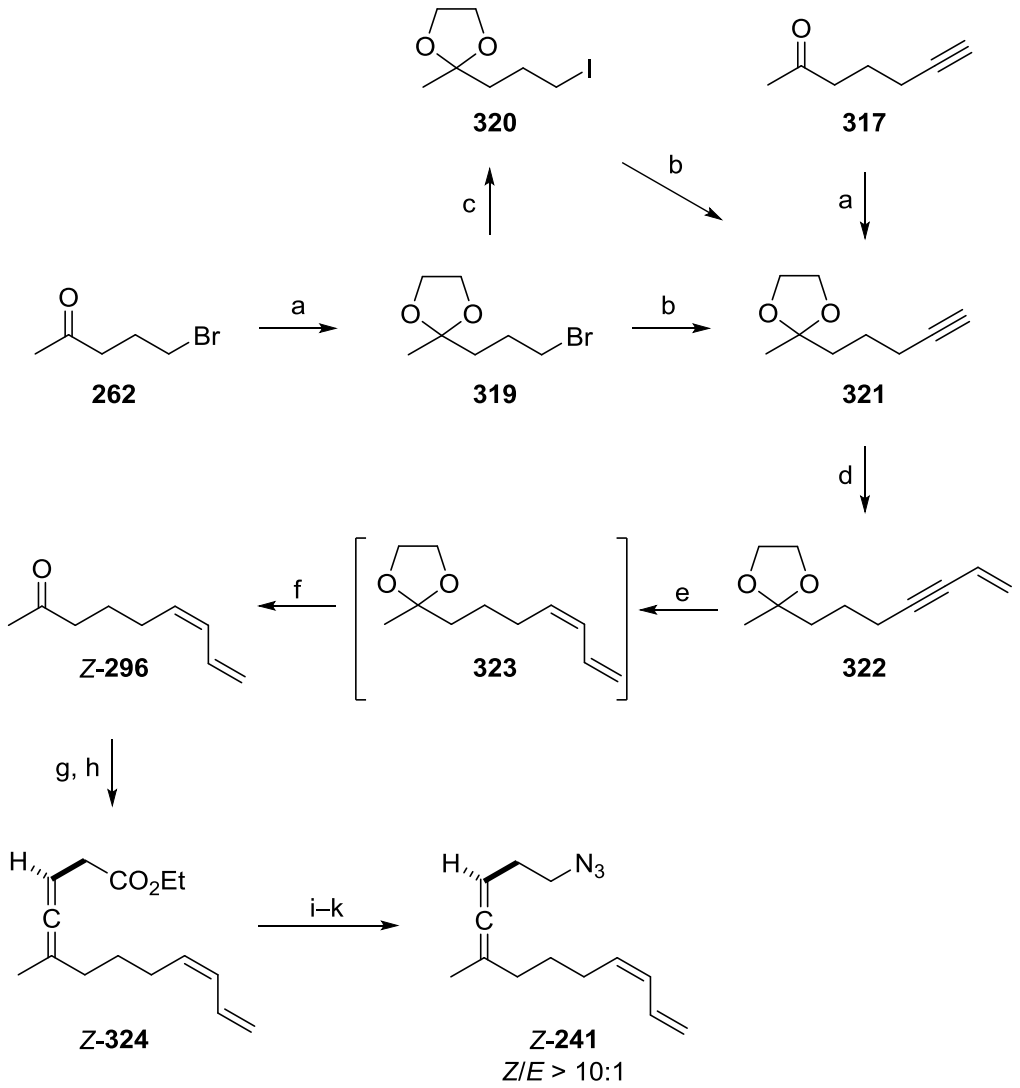
In the second-generation approach (Scheme 70), protected ketone **321** was first synthesised using a number of routes, of which the best one was then chosen. In the optimal protocol (**262**→**319**→**321**), later performed on a multi-gram scale, bromoketone **262** was protected as acetal **319** and treated with LiC≡CH·en in DMSO. The rather unusual solvent choice was essential for fast and high-yielding alkylation.

This reaction, originally reported by Novis Smith and Beumel, Jr,[251] was extremely convenient for the installation of the required alkyne unit. Both bromide **319** and iodide **320** afforded high yields of **321**.

The acetal in compounds **319**–**321** served two functions: first, it protected the ketone from the reactions with organolithium; second, and more importantly, it rendered all the intermediates in this route heavier and less volatile.

Alkyne **321** was converted into enyne **322** by the Sonogashira reaction with vinyl bromide. Selective reduction of the conjugated triple bond was achieved by treatment with Zn powder activated with $Cu(OAc)_2$ and $AgNO_3$,[249,250] which was the only method that did not lead to over-reduction or decomposition of **322**. The reaction was rather slow (8 days) and the product was indistinguishable from the starting material by TLC; therefore, aliquots of the reaction mixtures were analysed periodically by ^{1}H NMR spectroscopy. Diene acetal **323** was used as received and deprotected into ketone *Z*-**296** immediately.

Compound *Z*-**296** was converted into diene-tethered allene azide *Z*-**241** using the standard route, in which the allene bond (*Z*-**324**) was installed by the Johnson–Claisen rearrangement. The final product was formed as a >10:1 mixture of *Z*/*E*-isomers (NMR data).



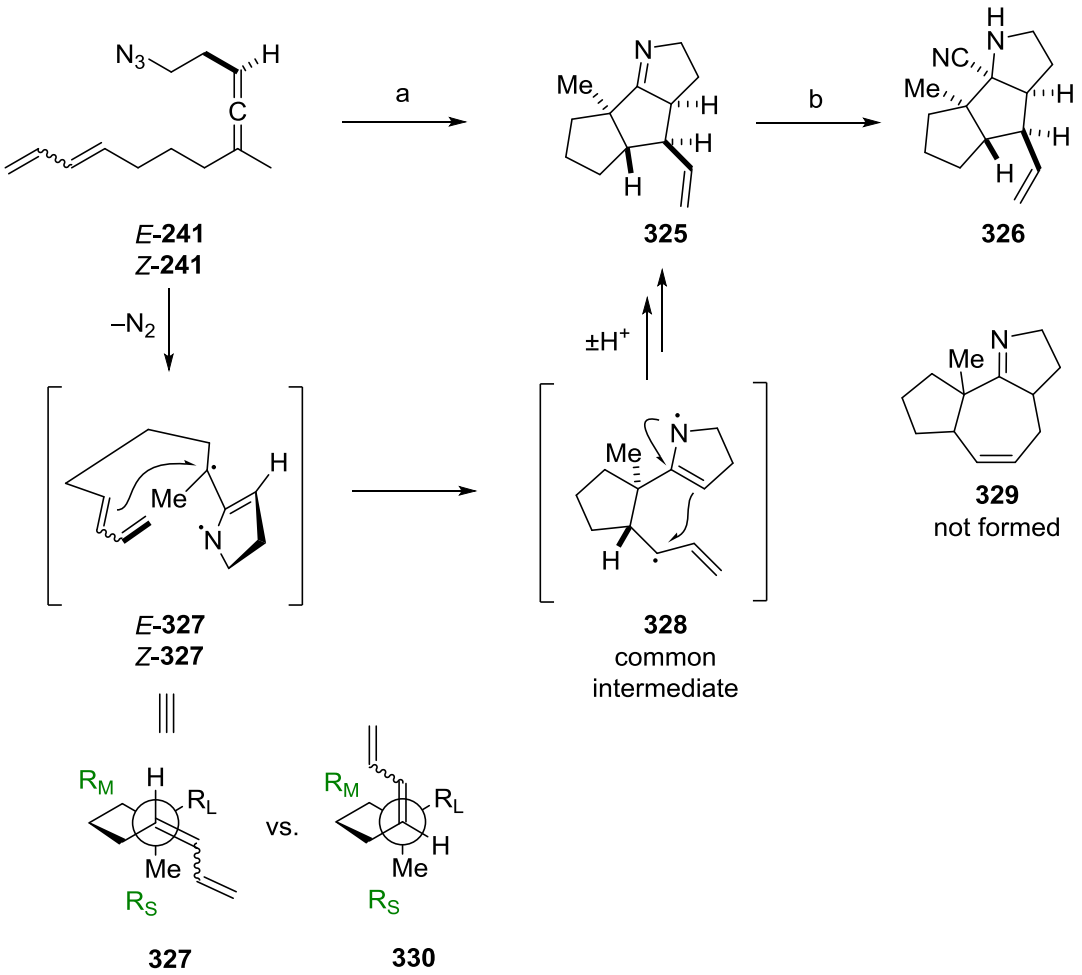
Scheme 70. Synthesis of *Z*-diene-tethered allene azide *Z*-**241**. Reagents and conditions: a) ethylene glycol, trimethyl orthoformate, PTSA·H_2O, 3Å MS, 89% of **319**, 71% of **321**; b) LiC≡CH·en, DMSO, 5 °C → RT, 82% from **319**, 88% from **320**; c) NaI, acetone, 98%; d) $Pd(OAc)_2$, CuI, *i*-Pr_2NH, vinyl bromide, 78%; e) $Zn/Cu(OAc)_2/AgNO_3$, aq. MeOH, 35 °C → RT; f) aq. HCl, acetone, 78% over 2 steps; g) HC≡CMgBr, THF, 92%; h) triethyl orthoacetate, $EtCO_2H$, 140 °C, 63%; i) $LiAlH_4$, Et_2O, 0 °C; j) MsCl, TEA, DCM, 0 °C → RT, 65% over 2 steps; k) NaN_3, DMSO, 30 °C → RT, 90%.

Reactions and mechanisms

The two isomers of **241** were subjected to the standard rearrangement conditions (135 °C, *m*-xylene). Surprisingly, no expected tricycle **329** was formed (Scheme 71). Both *Z*- and *E*-dienyl allene azides transformed into the same tricyclic system **325** (40% from *E*-**241** and 25% from *Z*-**241**). As in the case with (4+3)-

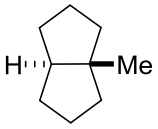
cycloadditions, the two imine diastereomers of **325** underwent isomerisation into a single product during chromatography on silica.

The proposed reaction mechanism is as follows. First, the azaallyl intermediate **327** cyclises onto the internal carbon atom of the diene. This step presumably proceeds via an open-chain TS and is directed by the minimisation of the steric repulsion between the diene moiety and the two larger substituents at the reaction centre (**327** vs. **330**). The allylic intermediate **328** must be sufficiently long-lived to allow equilibration and convergence to the same species from both *E*- and *Z*-isomer of **241**. Subsequent recombination of the radicals (or ions) delivers the third and final ring in **325**.



Scheme 71. Formal (3+2)-cycloadditions of allene azide tethered to diene. Reagents and conditions: a) *m*-xylene, 135 °C, 40% from *E*-**241**, 25% from *Z*-**241**; b) TMSCN, MeCN *or m*-xylene (for in situ reactions), 75% from **325**, 30% from Z-**241**, 25% from *E*-**241**.

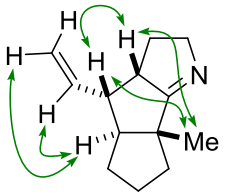
Notably, this reaction delivers a highly strained *trans*-bicyclo[3.3.0]octane unit. PM3 computations indicate that *trans*-**331** is almost 46 kJ/mol higher in energy than the corresponding *cis*-isomer. Such *trans*-junctions are not trivial to assemble and often require exhaustive trial-and-error effort.[252,253] The discovered cascade of diene-tethered azides may be a useful reaction for those working with such polycyclic systems.



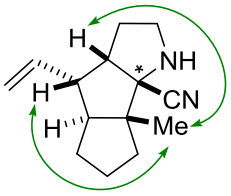
331

$\Delta G_{trans/cis}$ = 45.6 kJ/mol

Finally, we attempted to stabilise the reactive imine group in **325** by converting it into a cyanide adduct (*cf.* Feldman *et al*).[130] Treatment of pre-purified **325** with TMSCN quickly delivered cyanide **326** as a single isomer, which was less polar and much more stable than the starting imine. The relative configuration of the stereocentres on the central ring was reconfirmed by NOE studies (see Appendix). The configuration of the C* in **326** is uncertain and was inferred from molecular modelling.



325



326

Trapping of **325** from crude mixtures of allene azide cycloadditions led to the formation of **326** as 3:1–4:1 mixtures of unassigned diastereomers; direct comparison of the crude ^{1}H NMR spectra with those of a single isomer of **326** was not performed at the time due to the differences in NMR solvent. We ascribe the formation of multiple products to the fact that the initially formed imine diastereomers of **325** are trapped with TMSCN before isomerisation can take place.

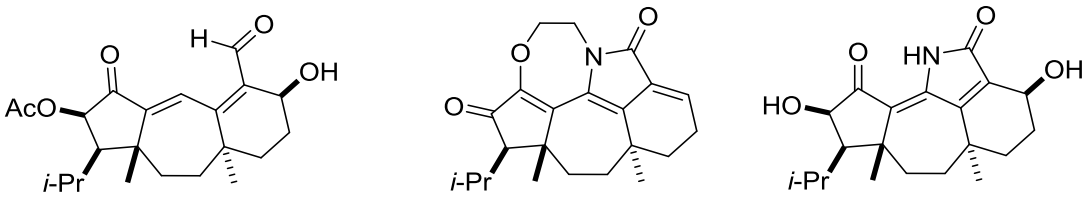
Future work in this area requires a detailed study of the reaction mechanisms, including the relative rates for the formation of various isomers of **325**, and optimisation of the reaction yields.

Chapter 4. Synthesis of Radianspene J Model System

At this point in the project, we wanted to explore the potential of the cascade cycloadditions in the complex setting of natural product total synthesis.

We selected radianspene J, a member of the recently reported radianspene family (Scheme 72). These are guanacastepene-type diterpenoids isolated from the endophytic fungus *Coprinus radians*, which lives within *Amanita* mushrooms from China.[254] The parent family, the guanacastepenes, was identified in 2001 by Clardy who showed that endophytic fungi are a rich and underexplored source of novel structures.[255–257] Some of radianspenes are cytotoxic against MDA-MB-435 cells but a more extensive study of their biological activity has not yet been reported.

Structurally, these compounds are characterised by a 5-7-6-tricyclic core, to which additional rings may be appended.



guanacastepene A **guanacastepene D** **radianspene J**

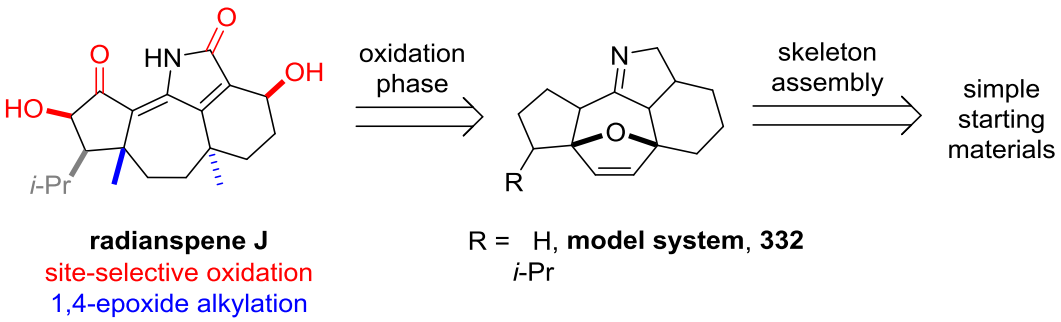
Scheme 72. Examples of guanacastepene diterpenoids.

No synthetic approaches to the radianspenes have been reported to date, despite active research in the terpene field. Carreira published highly interesting studies towards related guanacastepenes, in which he described the 5-7-6-ring framework as "non-trivial and formidable as a test of a number of cyclization strategies and reactions."[258]

However, this four-ring core of radianspene J is particularly well suited for synthesis by the cascade azide-allene-furan cycloaddition: the only nitrogen in this

compound is attached to the seven-membered ring, reminiscent of compounds **275**, **276** and **287** (Chapter 3).

We decided to approach the synthesis using a two-stage strategy (Scheme 73).[10,259,260] First, a non-functionalised carbon-rich core would be assembled; then, the correct oxygenation pattern would be installed by late-stage site-selective oxidations accompanied by further elaboration of the structure. This way, we would focus on the key cyclisation without being hampered by the potential instability and high polarity of polyoxygenated intermediates. The isopropyl group of radianspene J was temporarily neglected in this first-generation synthesis and we targeted simpler model system **332**.



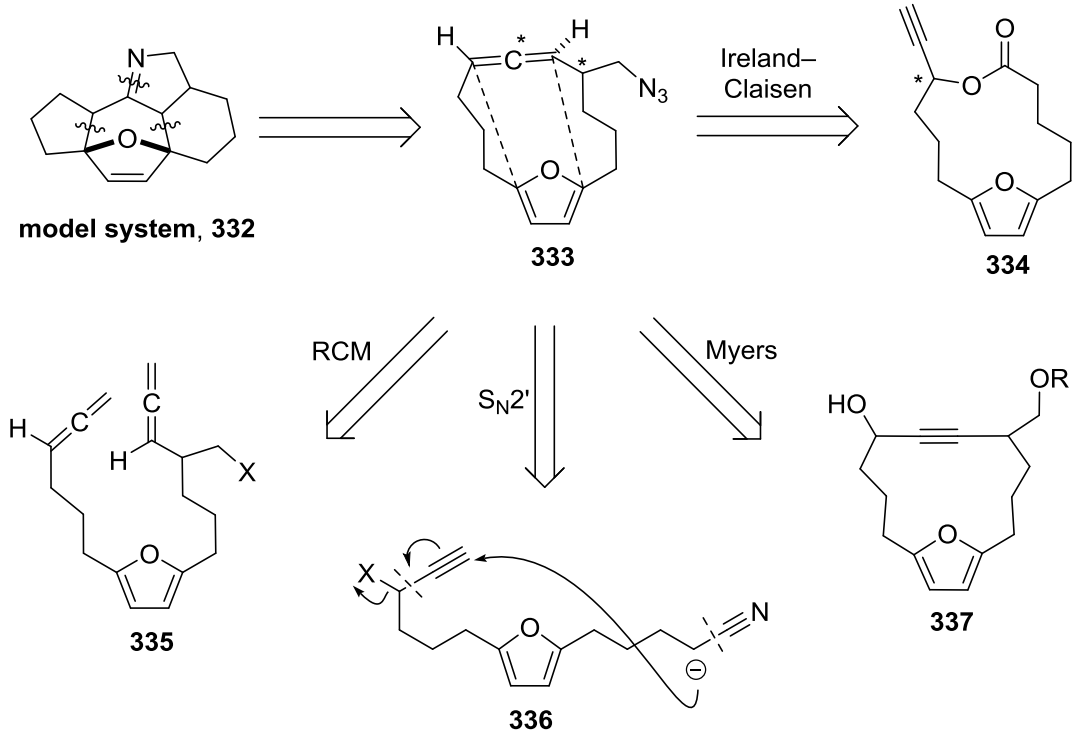
Scheme 73. Model system for the two-stage approach towards radianspene J.

Retrosynthetic analysis

Model system **332** was subjected to further retrosynthetic analysis as shown in Scheme 74. The pentacyclic core of the model system would be formed in a key transannular cycloaddition of macrocyclic allene **333**.[cf. 212,213] The latter compound can exist as a pair of diastereomers but at the time of the analysis we were not concerned about this point. In turn, a number of approaches were considered for the allene unit:

- Grubbs' ring-closing allene/allene metathesis (RCM) of precursor **335**[213]
- S_N2' substitution of propargylic derivative **336**
- one-step rearrangement of propargylic alcohol **337** under Myers' conditions[158,159]

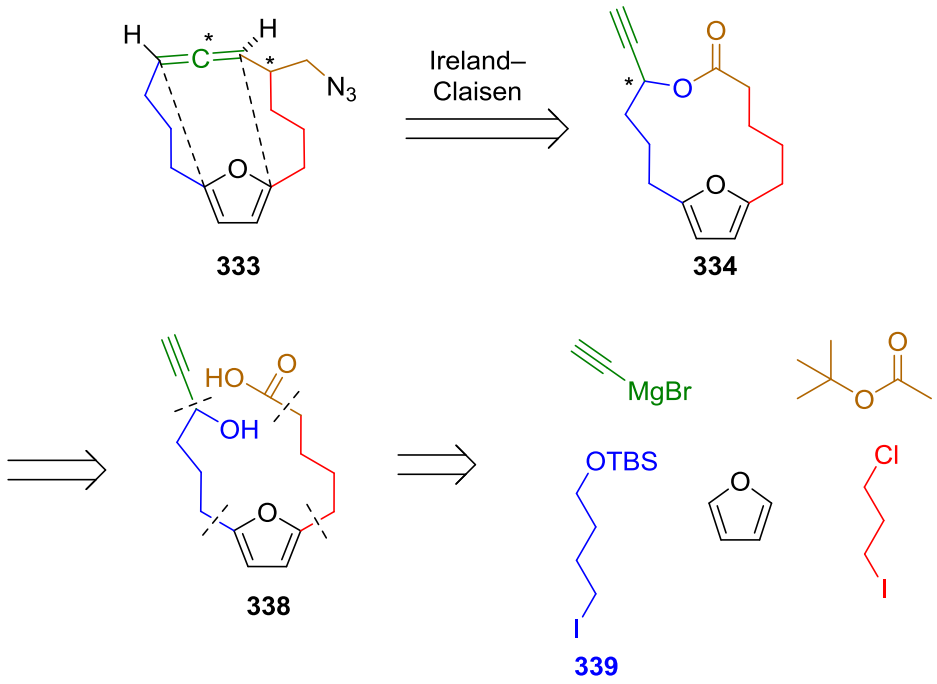
- Ireland–Claisen rearrangement of lactone **334**[43–46]



Scheme 74. Retrosynthetic analysis of the radianspene J model system.

All these methods, apart from the last one, required either a complex starting material or relied on risky or poorly-precedented transformations, and were not pursued. On the other hand, the synthesis of allenes by the Ireland–Claisen rearrangement seemed a reliable reaction both from our experience (Chapter 3) and literature evidence.[43–46]

With numerous methods available for the assembly of macrolides,[261–265] we did not envisage problems with the synthesis of **334** (Scheme 75). The corresponding seco-acid **338** was dissected retrosynthetically into simple building blocks of approximately equal size and complexity.

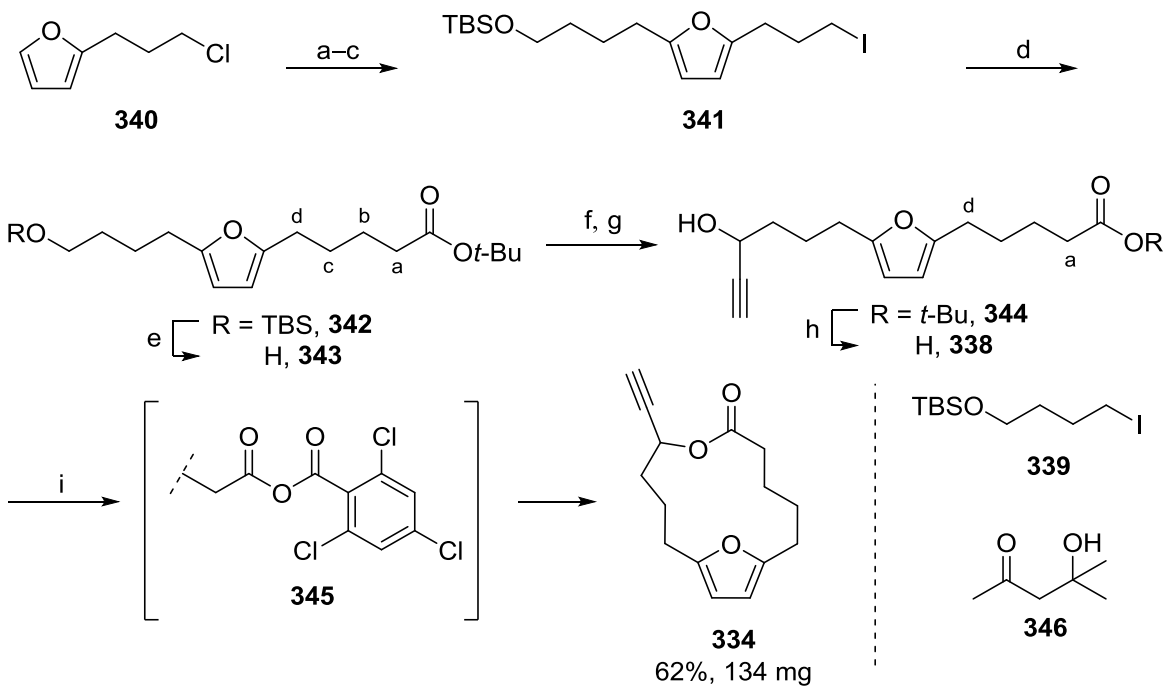


Scheme 75. Retrosynthetic analysis of macroallene **333** via macrolactone **334.**

Synthesis

The forward synthesis started with known 2-(3-chloropropyl)furan, **340** (Scheme 76), which was deprotonated, then alkylated with *O*-TBS-4-iodobutan-1-ol, **339**. The resulting alkyl chloride was activated by the Finkelstein reaction, giving iodide **341**. In this process, some TBS cleavage occurred and the crude product was immediately reprotected with TBSCl.

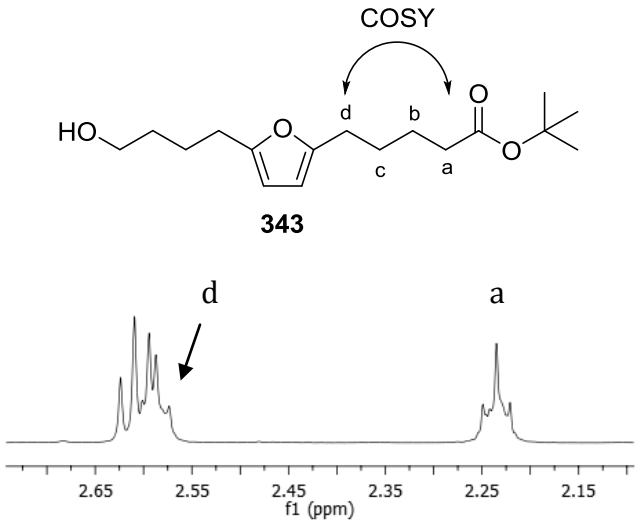
Next, we had to elongate the "right-hand" side chain by two carbons in the correct oxidation state. This was conveniently achieved by treating iodide **341** with the enolate of *t*-butyl acetate in THF/DMSO. In this reaction, originally reported by Rathke,[266] the enolate is generated with a somewhat exotic base, lithium isopropyl cyclohexyl amide (LICA), in pure THF at −78 °C. The choice of base prevents self-condensation of the enolate. Dropwise addition of this enolate to a DMSO solution of alkyl iodide **341** at RT allows for extremely fast (20 min) and high-yielding reactions (>90% of **342** on gram-scale).



Scheme 76. Reagents and conditions: a) BuLi, THF, −25 °C, *then* **339**, THF, −25 °C → RT, 86%; b) NaI, acetone, reflux; *then* c) TBSCl, imid., DCM, 87% over 2 steps; d) *t*-BuOAc, LICA, THF, −78 °C, *then* **341**, DMSO/THF, −78 °C → RT, 99%; e) HF·py, THF/py, 95%; f) $(COCl)_2$, DMSO, TEA, DCM, −78 → 0 °C, 93%; g) HC≡CMgBr, THF, −78 → 0 °C, 91%; h) LiOH, acetone/H_2O, 65 °C, 64% (91% on small scale); i) 2,4,6-trichlorobenzoyl chloride, TEA, THF, *then* DMAP, tol., 85 °C, 62%.

Deprotection of **342** with HF·py afforded alcohol **343**; subsequent Swern oxidation and Grignard addition gave propargylic substrate **344**. Hydrolysis of the ester in **344** required prolonged heating in aqueous acetone under basic conditions[267] (acid-catalysed hydrolysis led to decomposition). The resulting seco-acid **338** was formed as an inseparable mixture with diacetone alcohol (**346**, 92:8 mol%), arising from self-condensation of acetone. This was inconsequential and addressed by taking a slight excess of the reagents in the following step.

Interestingly, compounds **342**, **338** and all of the intermediates exhibited curious ^{1}H NMR spectra, in which the signals for H_a and H_d were broadened and showed mutual cross-peaks in the COSY spectrum (Figure 2). We attribute these features to the second-order effects[268] arising from the fact that H_a/H_d are coupled to H_b/H_c, respectively, while the latter are strongly coupled and behave as a unit ($J_{b,c} \gg \Delta\delta_{b-c}$).



Fugure 2. Unusual signal shapes in the ^{1}H NMR spectrum of compound **343**.

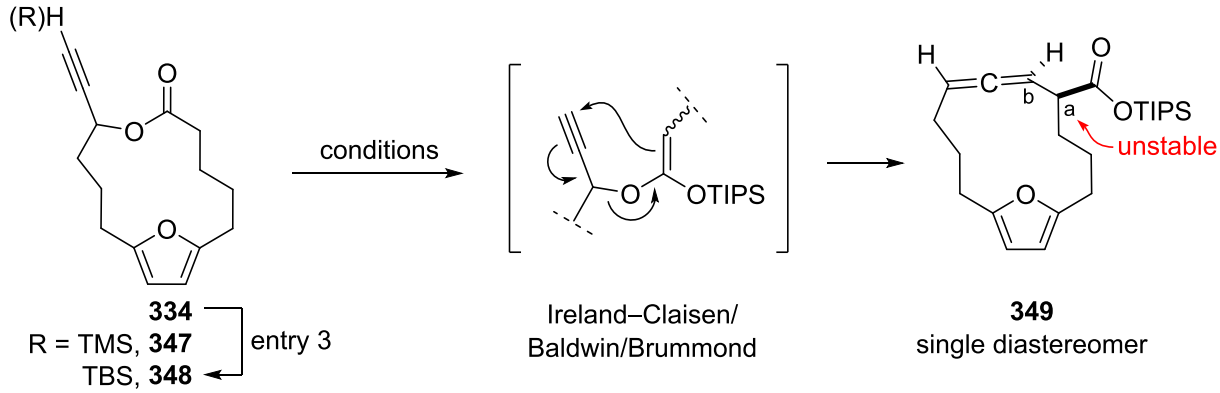
Macrolactonisation of seco-acid **338** was performed under Yamaguchi conditions.[269] In this reaction, the acid is first activated with 2,4,6-trichlorobenzoyl chloride at room temperature and this mixed anhydride is slowly added to a hot solution of DMAP in toluene or benzene. The original Yamaguchi protocol, involving the isolation of the intermediate **345**, did not work for us. The problem was solved by the Carreira modification of this reaction,[270] in which the intermediate isolation step was simply omitted. This reaction routinely generated over 100 mg (62–67%) of macrolactone **334** per batch.

Synthesis of macrocyclic allene 333

Conversion of lactone **334** into allene **349** was surprisingly problematic, despite our earlier successful synthesis of TIPS-ester **254** (Chapter 3). Treatment of **334** (or its TMS-derivative **347**) with various combinations of base and silyl source led either to recovery of the starting materials, unproductive silylation or decomposition (Table 8). After weeks of frustration, we realised that the only critical difference between this and earlier reactions was concentration. Since macrolactone **334** was very precious, we had used minimal quantities of it (10–20 mg, ca. 0.04 M), whereas allenes **118g** and **254** were synthesised on larger scale (300–500 mg, 0.2–0.7 M). When we risked doing the

transformation of **334** at 0.7 M, the desired product **349** was formed in up to 81% yield (along with some recovered SM).

Table 8. Synthesis of macrocyclic allene **349** by the Ireland–Claisen rearrangement of macrolactone **334**.



No.	Conditions	Product
1	TIPSOTf (1.3 eq), TEA (1.4 eq), PhH, 40 °C, 14 hr	No reaction
2	TIPSOTf (1.5 eq), TEA (1.7 eq), PhH, 60 → 80 °C, 18+3 hr	No reaction
3	TBSCl (1.2 eq), LHMDS (1.1 eq), THF, 0 °C, 14 hr	**348** (50%)
4	TBSCl (1 eq), LHMDS (2 eq), THF, 0 °C, 14 hr	Decomposition
5	TIPSOTf (1.5 eq), TEA (1.7 eq), C_6D_6, 60 → 80 °C, 18+3 hr, R = TMS	No reaction
6	LHMDS (1.2 eq), TIPSOTf (1.2 eq), THF/HMPA, −78 °C → RT, R = TMS	Decomposition
7	TIPSOTf (1.5 eq), TEA (2 eq), $BF_3{\cdot}OEt_2$ (2 eq), PhH, 60 °C, 14 hr	No reaction
8	**TIPSOTf (1.5 eq), TEA (2 eq), PhH, 0.7 M, RT, 45 hr**	**349 (81%)**

NMR data indicated that macroallene **349** was formed as a single diastereomer. This product, however, was configurationally unstable, presumably due to the increased acidity of H_a flanked by a carboxyl group and a C=C-bond; therefore, TIPS ester **349** was reduced immediately with $LiAlH_4$ into alcohol **351** (Scheme 79).

The relative configuration of the C_a–C_b unit was established by single crystal X-ray crystallography of tosylate **350** (Figure 3).

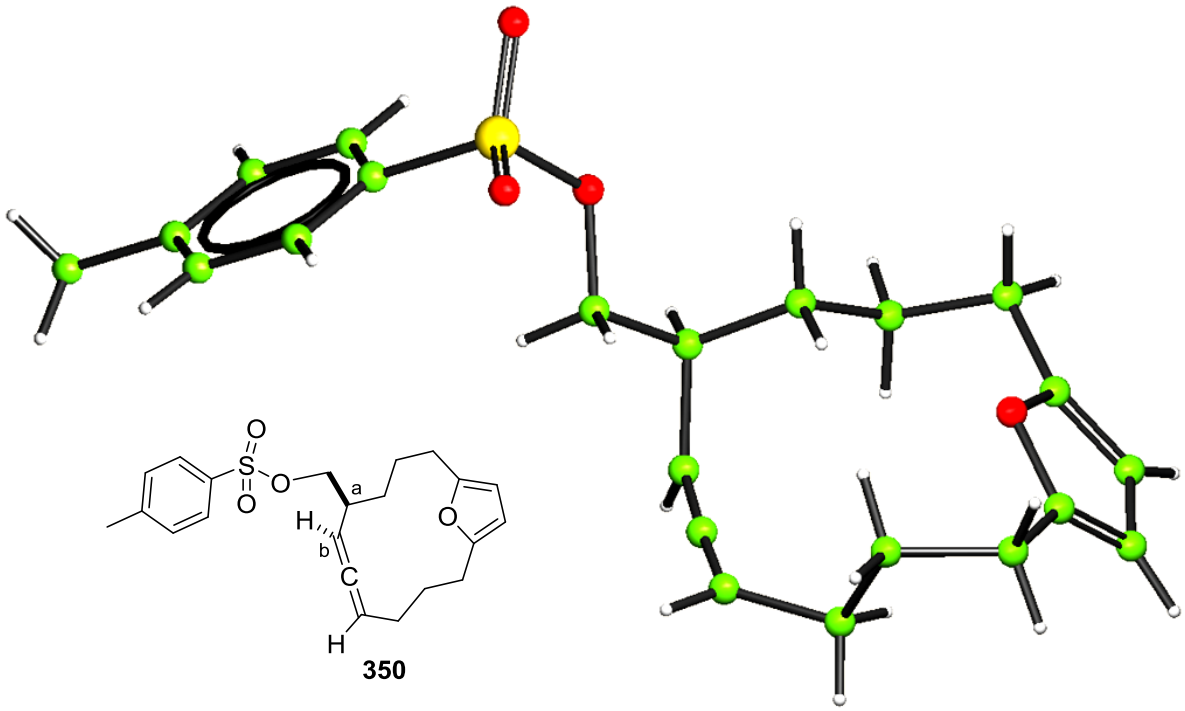


Figure 3. Single crystal X-ray crystallography structure of tosylate **350**.

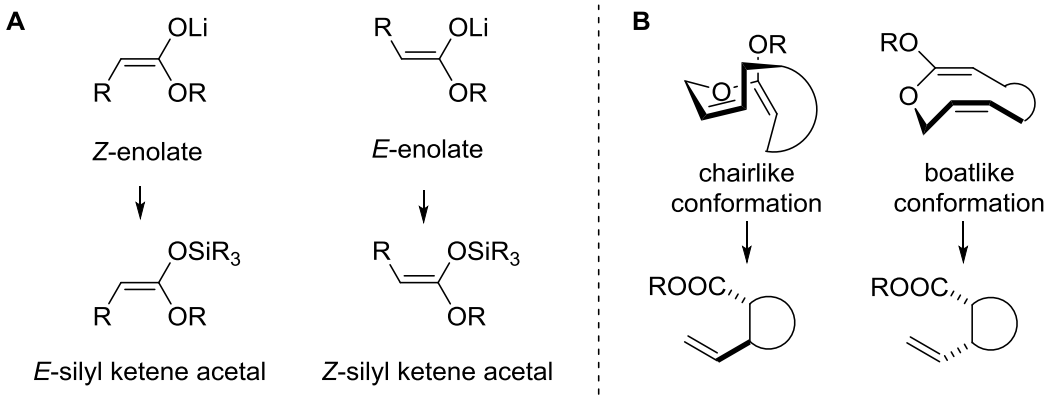
The excellent diastereoselectivity of the allene formation is noteworthy and deserves special discussion.

Extensive studies of alicyclic Ireland–Claisen rearrangements have been performed by the groups of Funk,[271–275] Magriotis,[276,277] and others. Both Funk and Magriotis, however, investigated reactions of lactones derived from allylic, rather than propargylic alcohols. Funk has shown that, for 7- to 14-membered lactones, the preferred *E*-silyl ketene acetal (formed from *Z*-enolate, Scheme 77)* undergoes the rearrangement exclusively in a boatlike transition state. For larger rings (15-membered or more), the internal asymmetric induction[278] erodes as a result of greater flexibility of the ring. Interestingly, the presence of an additional *trans*-double bond inside the macrocycle inverted the selectivity of the reaction.[272]

On the other hand, Magriotis showed that 14- and 15-membered poly-unsaturated lactones could form both *E*- and *Z*-silyl ketene acetals under different

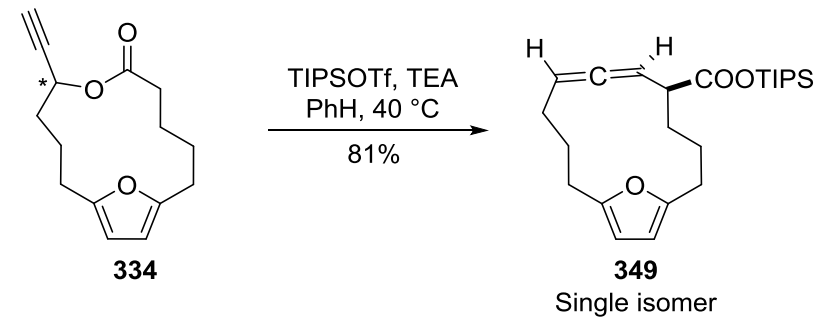
* *E*/*Z*-denominations as proposed by Ireland,[42] Funk, and Magriotis are used throughout this thesis. One should be aware of an alternative nomenclature by Evans and others.[362]

reaction conditions (THF vs. THF/HMPA, respectively). The preference of the subsequent Ireland–Claisen rearrangement for a boatlike or chairlike TS depended on minor structural differences in starting compounds.[276,277]



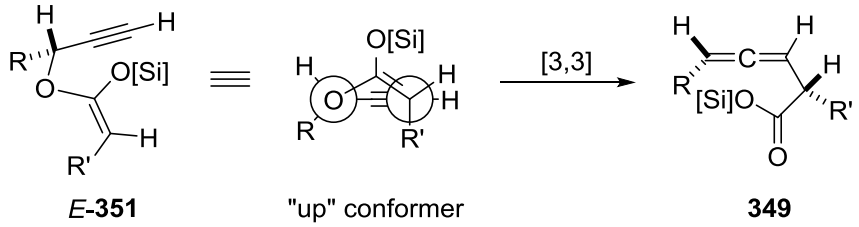
Scheme 77. A) *E*/*Z*-denominations of ester enolates and silyl ketene acetals as used in this thesis.[279] B) Chairlike vs. boatlike pre-TS conformations for the Ireland–Claisen rearrangement.[272]

The chairlike/boatlike treatment is inapplicable to the propargylic Ireland–Claisen rearrangement due to the presence of a linear alkyne fragment. Based on the relative configuration of allene **349**, we propose that the observed product could form from either *E*- or *Z*-acetal **351** depending on the relative orientation of the silyl substituent with respect to the rest of macrocycle (Scheme 78). *E*-silyl acetal *E*-**351** must react as the "up" isomer to account for the product, while *Z*-**352** can lead to the same isomer of **349** only if reacts as its "down" isomer. Preliminary molecular modelling, performed in our group,[280] showed that the TS corresponding to *E*-**351** was lower in energy, but these results require further refinement and are not discussed here.



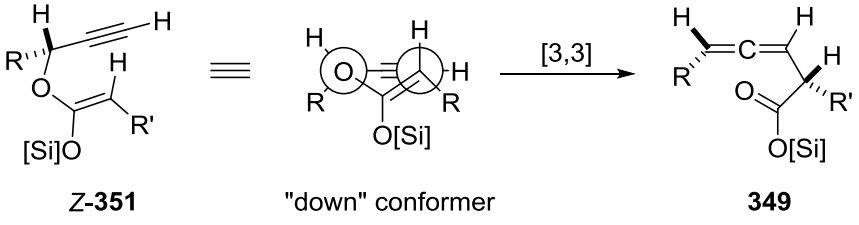
334 **349**
Single isomer

From *E*-acetal:



E-**351** "up" conformer **349**

From *Z*-acetal:

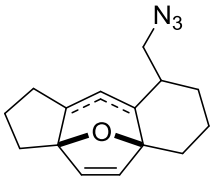


Z-**351** "down" conformer **349**

Scheme 78. Synthesis of macrocyclic allene **349** by Ireland-Claisen rearrangement of macrolactone **334**.

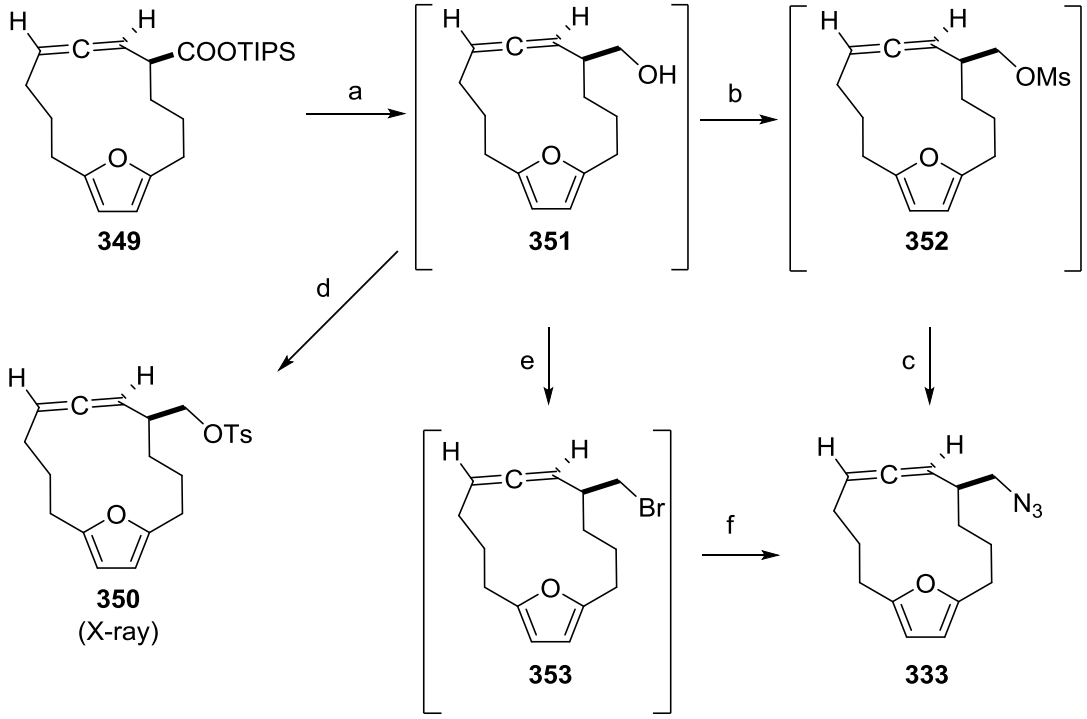
Completion of the synthesis. Transannular cycloaddition

TIPS ester **349** was initially converted into desired azide **333** by a three-step sequence: reduction, mesylation, and azide substitution (a–c, Scheme 79). The last reaction was slow and required prolonged heating at 35 °C. This led to the formation of detectable amounts (3 mg, 5%) of unidentified side products, tentatively assigned as isomeric azides **354** arising from acid catalysed transannular cycloaddition. The IR-spectrum of the mixture **354** exhibited a strong absorption at 2097 cm^{-1} indicating the presence of the intact azide group,[281] whereas its ^1H NMR spectrum was reminiscent of that for tricyclic compounds **275–276** (Chapter 3). Despite the loss in yield, we were



354

encouraged by these findings, since they suggested macroallene **333** was potentially higly reactive.



Scheme 79. Synthesis of macrocyclic allene azide **333**. Reagents and conditions: a) $LiAlH_4$, Et_2O, 0 °C; b) MsCl, TEA, DCM, 0 °C → RT; c) NaN_3, DMF, 35 °C, 5 d → RT, 2 d, 30% over 3 steps; d) TsCl, TEA, DMAP, DCM, 67% over 2 steps; e) CBr_4, PPh_3, DMF, 15 °C → RT; f) NaN_3, DMF, 35 °C, 1 d, *then* RT, 2 d, 70–81% over 3 steps.

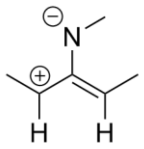
In a second round of optimisation, we developed a slightly modified sequence: reduction of the TIPS ester, Appel reaction, and azide substitution on the bromide (a→e→f, Scheme 79). Bromide **353** was much more reactive than mesylate **352**, thus allowing for cleaner conversion into azide **333** (70–81% over 3 steps).

We were most pleased to find out that reactions of allene azide **333** were indeed straightforward (Scheme 80). When compound **333** was heated in toluene at 110 °C (as opposed to 135 °C for open-chain systems), the desired pentacyclic model system **332** was formed in 70% on a small scale (from 8 mg of the azide). Initial scale-up attempts met with a rapid drop in yields to 15%, presumably arising from decomposition of **332** during purification: the upscaled-reaction mixtures were passed through longer columns and had greater contact time with silica and methanol-based eluent. We

considered that the imine unit may be unstable under these conditions. When the reactions were performed at higher dilution (to prevent possible intermolecular side reactions), and the crude mixture was quickly passed through a very short, 5 mm, silica plug, the yields increased again to 60–70% on a 15–20 mg scale.

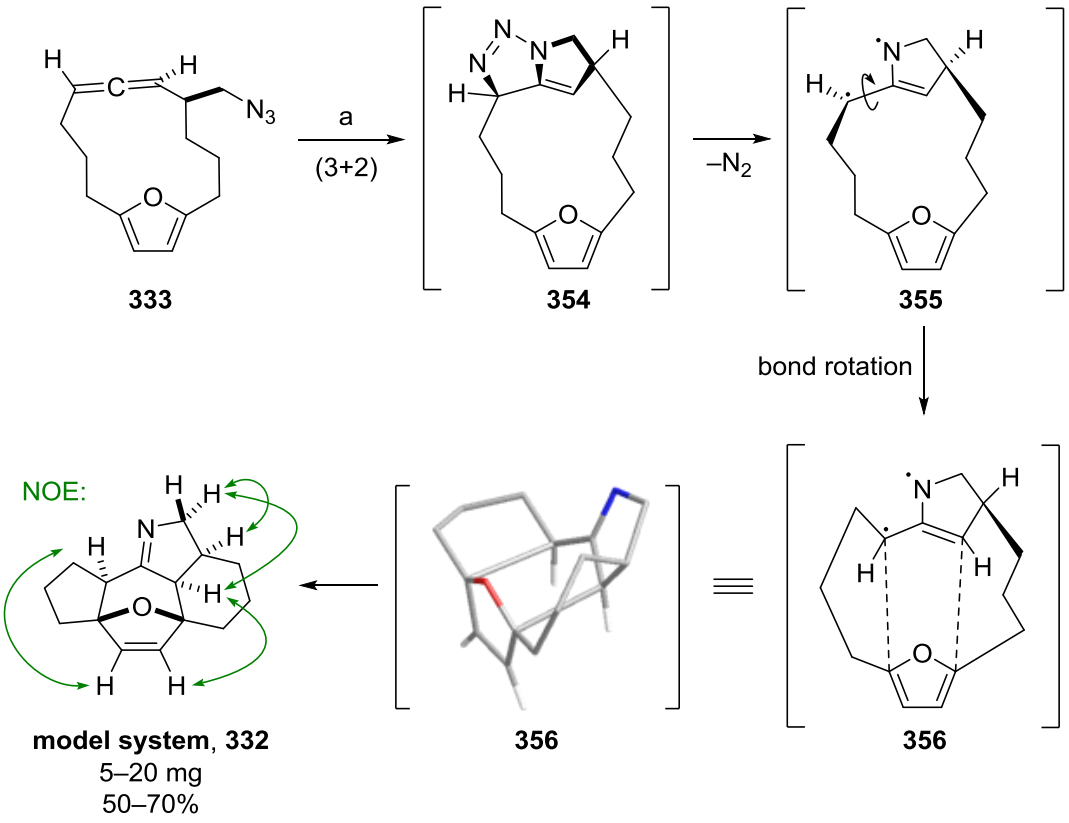
It is noteworthy that this reaction forms a pentacyclic product with five stereocenters *as a single diastereomer*. The relative configuration of **332** was established by NOE studies (Scheme 80, also see Appendix).

The proposed reaction sequence is shown in Scheme 80. The initial (3+2)-cycloaddition gives triazoline **354**, which then loses N_2 to form ATMM species **355**. Bond rotation in **355** produces conformer **356**, which is reminiscent of aminoallyl zwitterions in a W-shaped conformation. Subsequent formal (3+4)-cycloaddition proceeds via an arrangement similar to that of the extended TS (cf. Scheme 61) and affords final product **332**. It should be noted that at the moment we have not enough experimental data to differentiate between the concerted and the stepwise (3+4)-addition. The nature of **335**/**356**—singlet radical, triplet radical or zwitterionic—is still to be established.



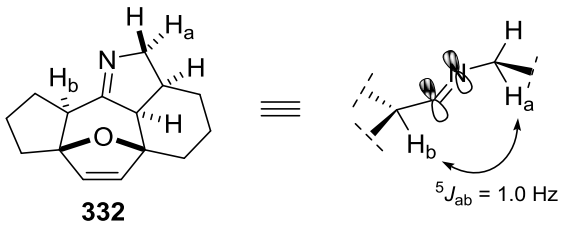
aminoallyl zwitterion
W-shaped conformation

The observed high selectivity could be attributed to pre-organisation in polycyclic starting material **333**, which limits rotational freedom and the number of possible reactive conformations.[cf. 213,282,283]



Scheme 80. Formation of model system **332** from macrocyclic allene azide **333**. Reagents and conditions: a) 110 °C, tol., 70 min, 50–70%. *Note: some hydrogens are omitted for clarity*.

The ^{1}H NMR spectrum of compound **332** exhibited an interesting long-range coupling between H_a and H_b ($^{5}J_{ab}$ = 1.0 Hz), which may be explained by favourable orbital overlap in the rigid polycyclic structure. Presumably, σ_{C-Ha}, σ_{C-Hb}, and $\pi_{C=N}$ are reasonably parallel to each other. This hypothesis was supported by molecular modelling.



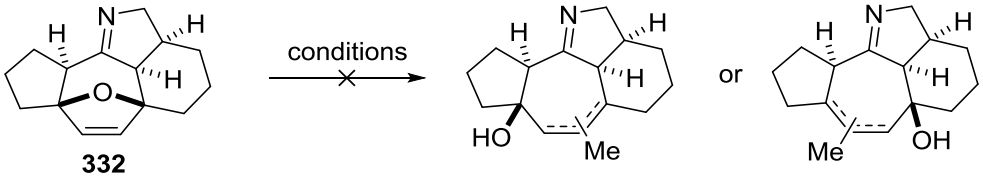
Most likely, all stereochemical information in model system **332** is derived from the single stereocentre in macrolactone **334** (Scheme 75), although one cannot exclude the potential atropisomerism of the furan subunit.

Studies towards functionalisation of the model system

Having established access to model system **332**, we were ready to test its potential in further modifications, although only limited quantities of **332** were available.

First, we attempted to open the 1,4-epoxy bridge with methylating agents. Methylative cleavage of unsaturated 1,2- and 1,4-epoxides has been reported with cuprates[284] or, better, cyanocuprates.[285–287] Additionally, combinations of alkylating agents with appropriate Lewis acids have been reported.[288–290] To our surprise, compound **332** was completely resistant towards organocuprates or $AlMe_3$ (Table 9). Only starting material was invariably returned from these reactions.

Table 9. Attempts to methylate model system **332**

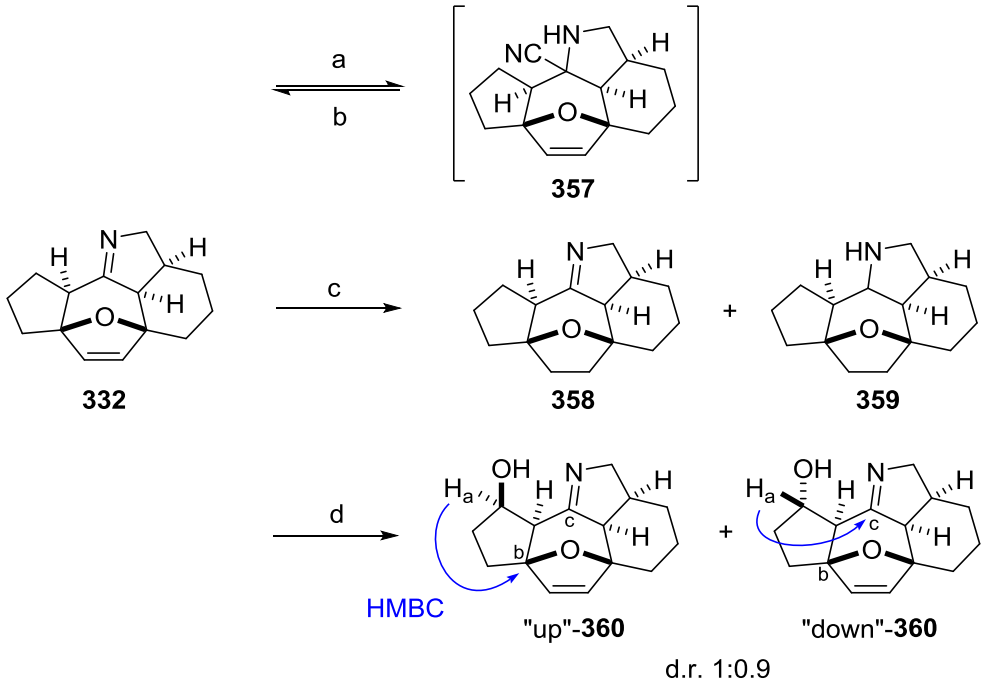


332

No.	Conditions	Result
1	$AlMe_3$ (1.3 eq), pentane/hexane, 0 °C → RT	No reaction
2	$AlMe_3$ (2.2 eq), DCM/pentane, −30 °C → RT	—
3	$LiCuMe_2$ (2 eq), $BF_3{\cdot}OEt_2$ (excess), THF/Et_2O, −30 °C → RT	—
4	$Me_2Cu(CN)Li_2$ (2 eq), THF/Et_2O, 0 °C → RT	—

Puzzled by this inertness, we sampled some reactions of **332** with less sterically demanding reagents (Scheme 81). However, even TMSCN, successfully employed by Feldman to stabilise polycyclic imines,[132] reacted very sluggishly. The product **357**, though detectable in the NMR spectrum of the crude mixture, reverted back to starting material during chromatography on silica. Some success was achieved in Pd-catalysed hydrogenation of **332**, which afforded saturated polycyclic products **358/359**. In this

reaction, the C=C-bond was reduced first but the selectivity was rather low, resulting a 1:1.4 mixture of **358** and **359** in ca. 60% yield after 2.5 hr.



Scheme 81. Functionalisation of model system, **332**. Reagents and conditions: a) TMSCN (excess), $CDCl_3$; b) SiO_2 column; c) H_2 (1 atm), Pd/C, EtOH, 60% combined yield; d) $P450_{BM3}$ RP/FV/EV, DMSO, pH 8.0, 15%.

In a separate series of experiments, model system **332** was subjected to enzyme oxidations with P450 mutants.* First, 16 enzymes were screened in small scale reactions (0.1 mg of the substrate) and the crude mixtures were analysed by GC. The $P450_{BM3}$ RP/FV/EV mutant[291] was then chosen for a preparative scale reaction (14 mg of **332**). We were pleased to isolate monooxygenated product **360** in 15% yield as a 1:0.9 mixture of the "up" and "down" diastereomers (Scheme 81). The relative configuration of the newly oxygenated stereocentre was established by the analysis of the $^{1}H-^{13}C$ HMBC spectrum and relating it to the predicted dihedral angles in the two isomers (See Appendix).

The result of the biocatalysed oxygenation is encouraging; however, much more work is to be done before this reaction becomes synthetically useful.

* Enzyme oxidations were performed by Xinkun (Tony) Ren from Dr. Luet Wong's lab, University of Oxford.

Conclusions and future work

We have synthesised a model system, **332**, for radianspene J in 12 steps and 15% overall yield (85% per step), based on a transannular formal (3+4)-cycloaddition of a furan with an aminoallyl species generated in situ. This reaction allowed for rapid complexity build-up and in one step generated a compound with five stereocentres and four new rings. The route also featured a two-stage skeleton-building/oxidation strategy, allowing work with stable non-polar intermediates for most of the sequence.

The future work will focus on:

- enantioselective installation of the isopropyl group in the cyclisation precursor early in the sequence;
- cleavage of the 1,4-epoxy bridge with methylating agents;
- site-selective C–H oxidations of the carbocyclic core.

Overall, the discovered (3+4)-cycloaddition of aminoallyl species appears promising and worthy of further investigation and development.

Experimental

General experimental

Atom numbering. The atom numbering in schemes reflects NMR peak assignments and *does not* necessarily correspond to the IUPAC nomenclature.

Solvents and reagents. All reactions were performed using oven-dried reaction vessels under an atmosphere of argon unless stated otherwise. "Petrol" refers to the fraction of petroleum ether boiling in the range 30–40 °C. Dry diethyl ether (ether), dichloromethane (DCM), and tetrahydrofuran (THF) were obtained from solvent dispenser units having been passed through an activated alumina column under argon. Pyridine, triethylamine (TEA), *m*-xylene, and benzaldehyde were distilled prior to use and stored over KOH (pyridine) or 4Å MS (other compounds)[292]. CuBr[293], CuI, and CBr_4 were purified using standard procedures[292]. Other reagents were used as supplied.

Chromatography. Thin layer chromatography (TLC) was carried out using Merck aluminium-backed DC60 F_{254} precoated plates (particle size 0.2 mm). Spots were visualised by the quenching of ultraviolet light (λ_{max} = 254 nm) and then stained and heated with anisaldehyde, potassium permanganate as appropriate. Retention factors (R_f) are reported along with the solvent system used in parenthesis. Flash column chromatography[294] was performed using Merck 60 silica gel (particle size 40-63 μm) and the solvent system used is reported in parentheses.

Microwave assisted reactions. Microwave assisted reactions were run in a CEM Discover S-class manual single-node reactor (150 W) in specialised oven-dried thick-walled glass vessels.

Reactions in flow. Reactions under flow conditions were performed using a bench top Uniqsis FlowSyn reactor with plastic (up to 160 °C) or metal (up to 190 °C) coils.

Melting points. Melting points were determined using a Griffin MFB-700-010U melting point apparatus and are uncorrected.

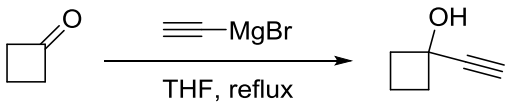
NMR spectroscopy. Proton (^{1}H) and carbon-13 (^{13}C) spectra were recorded on Bruker AVC-500 (500/125 MHz), Bruker DPX-400 (400/100 MHz), Bruker DPX-200 (200 MHz), or Bruker AVC-700 (700 MHz) spectrometers in deuterated solvents. ^{1}H and ^{13}C NMR spectra were referenced to the solvent residual peak ($CDCl_3$, δ 7.26 and 77.16 ppm respectively; C_6D_6, 7.15 and 128.06 ppm respectively; $C\underline{D}_3OD$, 3.34 and 49.00 ppm respectively; CD_3CN, 1.94 and 118.26 ppm respectively).[295,296] Peak assignments were made on the basis of chemical shifts, integrations and coupling constants, using COSY, DEPT, HSQC and NOE experiments where appropriate. The NOE spectra are presented in Appendices. Multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quitet (quit), sextet (sext), septet (sept), multiplet (m), apparent (app.), and broad (br). Coupling constants (*J*) are rounded to the nearest 0.5 Hz.

Infrared spectroscopy. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer on neat samples. Absorption maxima ($\tilde{\nu}$) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w), and broad (br).

Mass spectrometry. Low resolution mass spectra were recorded on a Micromass LCT Premier spectrometer (ESI). High resolution mass spectra (HRMS) were recorded either by the author on a GCMS spectrometer (CI) or by the staff of the Chemistry Research Laboratory mass-spec facilities on a Bruker Daltronics MicroTOF spectrometer (ESI or FI). Mass to charge ratios (m/z) are reported in Daltons.

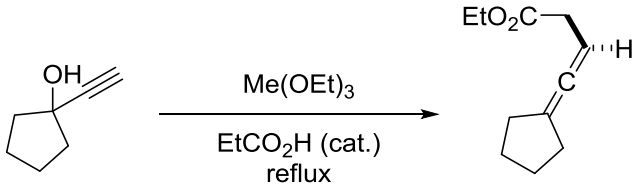
General procedures

General method A



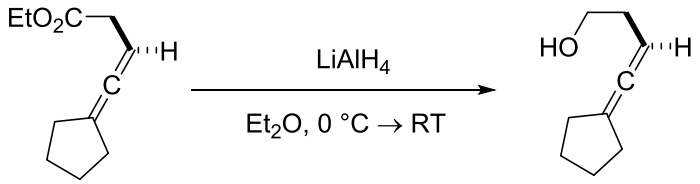
Following a procedure reported in ref.[153], 1-ethynylcyclobutanol was prepared by the addition of cyclobutanone (0.50 g, 7.1 mmol; dissolved in 2 + 2 mL of THF) to a solution of HC≡CMgBr (0.5 M in THF, 15.8 mL, 7.9 mmol) and heating at reflux for 5 hr. The reaction mixture was quenched by the addition of wet ether (10 mL), sat. aq. NH_4Cl (10 mL), and water (5 mL). The aq. layer was extracted with ether (2×7 mL). Combined ethereal layers were dried over $MgSO_4$, and concentrated. Flash chromatography (25:75, ether/petrol) yielded the desired product as a colourless volatile oil.

General method B



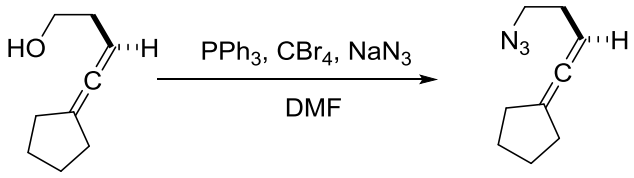
To a solution of 1-ethynylcyclopentanol (1.50 g, 13.6 mmol) in neat $MeC(OEt)_3$ (12.0 mL, 10.6 g, 65 mmol) was added propanoic acid (ca. 0.4 mL). The resulting solution was stirred at reflux for 5 hr (oil bath temp. 145 °C) with distillative removal of ethanol. The reaction mixture was cooled to RT, diluted with ether (50 mL) and washed sequentially with aq. HCl (1 M, 2×25 mL), sat. aq. $NaHCO_3$ (25 mL), and brine (20 mL), then dried over $MgSO_4$, and concentrated. Flash chromatography on the crude mixture (5:95, ethyl acetate/petrol) yielded the desired product.

General method C



The starting ester (0.60 g, 3.3 mmol) was dissolved in Et_2O (40 mL) and cooled to 0 °C. $LiAlH_4$ (0.22 g, 5.77 mmol) was then added, the ice bath removed and the mixture then stirred at RT. After 2 hr, the reaction was carefully quenched with sat. aq. Na_2SO_4 at 0 °C *(caution: gas evolution)*. Solid by-products were removed by filtration, washing with large amounts of ether. The combined organic layer was washed with brine (2×15 mL), dried over Na_2SO_4 and concentrated.

General method D

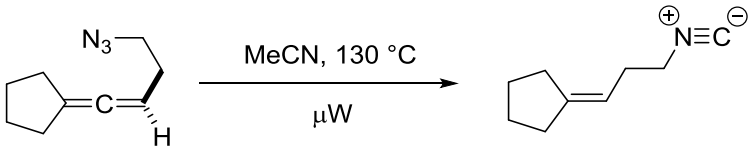


The starting alcohol (50 mg, 0.36 mmol) was dissolved in dry DMF (2 mL; *note:* the reaction does not work in wet solvents; freshly opened commercial DMF is suitable). The following reagents were added in sequence: NaN_3 (71 mg, 1.09 mmol), PPh_3 (236 mg, 0.90 mmol), and CBr_4 (298 mg, 0.90 mmol; *note:* the commercial reagent must be recrystallized from EtOH and dried in vacuo prior to use). The reaction mixture turned yellow after the addition of CBr_4. The stirring was continued for 13 hr. The reaction mixture was extracted with petrol (2×10 mL). The combined petrol layers were washed sequentially with water (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated (230 Torr, RT). The product was purified by flash chromatography (1:30, ether/petrol). The compound was spectroscopically and chromatographically identical to that obtained by Method E.

General method E

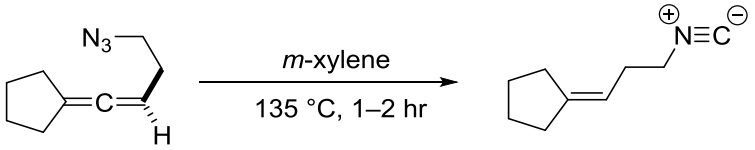
Identical to the General method D, but NaN_3 was added 30 min *after* addition of the other reagents.

General method F



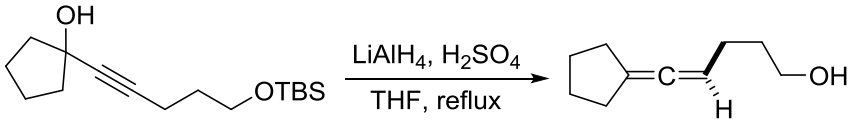
The starting azide (115 mg, 0.70 mmol) was dissolved in freshly distilled MeCN (3 mL) and heated in a microwave reactor at 130 °C for 70 min. The volatiles were removed *in vacuo* (80 Torr) and the crude residue (*note: disagreeable odour)* was purified by flash chromatography (5:95, ether/petrol) .

General method G



The starting azide (100 mg, 0.65 mmol) was dissolved in freshly distilled *m*-xylene (2 mL) in a thick-walled glass tube. The tube was tightly sealed and heated in an oil bath at 135 °C for 1–2 hr until all starting material has been consumed (TLC monitoring). The crude reaction mixture *(note: disagreeable odour)* was loaded directly into a short silica column and eluted with an ether/petrol mixture of appropriate polarity. The product was identical to that obtained by General method F.

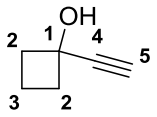
General method H



1-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclopentanol (0.974 g, 3.45 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. To this *vigorously* stirred solution, $LiAlH_4$ (786 mg, 20.7 mmol) was added in four portions *(warning: gas evolution)*. Then, concentrated H_2SO_4 (98%, 1.01 g, 10.3 mmol) was carefully added dropwise *(caution: intense gas evolution!)* The resulting mixture was heated and kept at reflux for 3 hr. The reaction mixture was cooled to 0 °C, then sat. aq. Na_2SO_4 was carefully added dropwise *(warning: gas evolution)*. When the addition of Na_2SO_4 did not cause bubbling, the mixture was allowed to warm to RT. The addition of aq. Na_2SO_4 was continued until most of Al-containing species were complexed into a dense white precipitate. The resulting mixture was dried with anhydrous Na_2SO_4 and filtered through Celite, the solids being thoroughly washed with ether. The solution was concentrated and purified by flash chromatography with a *short* silica column (1:3 → 1:1, ether/petrol).

Compounds

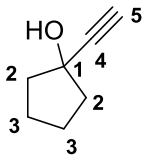
1-ethynylcyclobutanol (115a)[153]



Prepared by general method A from cyclobutanone (0.50 g, 7.1 mmol; dissolved in 2 + 2 mL THF) and HC≡CMgBr (0.5 M in THF, 15.8 mL, 7.9 mmol). Flash chromatography (25:75, ether/petrol) afforded the title product as a colourless volatile oil (0.59 g, 86%).

R_f 0.31 (25:75, ether/petrol); δ_H (400 MHz, $CDCl_3$) 2.55 (1H, s, H-5), 2.40–2.50 (2H, m, H-2), 2.20–2.35 (3H, m, H-2,OH), 1.80–1.90 (2H, m, H-3); δ_C (101 MHz, $CDCl_3$) 84.7 (C-4), 71.5 (C-5), 67.7 (C-1), 38.3 (C-2), 12.7 (C-3).

1-Ethynylcyclopentanol (115b)[152]

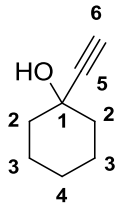


A 250 mL flask was charged with THF (100 mL). The solvent was degassed by bubbling argon with stirring for 1 hr *(note: the product yields were lower without degassing)*. Cyclopentanone (3.00 g, 35.7 mmol) was dissolved in this THF and the solution was cooled to ca. 15 °C using an ice/water bath; then, LiC≡CH·en (7.30 g, 71.3 mmol) was added to the vigorously stirred reaction mixture. The ice bath was removed and the mixture was stirred overnight (14 hr). The reaction was diluted with ether (20 mL) and quenched with the mixture of sat. aq. NH_4Cl (15 mL) and water (50 mL). The aq. layer was neutralized with aq. HCl (1 M, ca. 60 mL) and extracted with ether (2×50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated at 180 Torr *(note: the product is moderately volatile)*.

Kugelrohr distillation of the crude residue (40–50 °C, 15 Torr) gave the desired product as a clear colourless oil (1.79 g, 46%).

R_f 0.28 (25:75, ether/petrol); ν_{max}/cm^{-1} 3400br.s (OH), 3301s (≡C–H), 2110w (C≡C); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, br.s, OH), 2.49 (1H, s, H-5), 2.06 – 1.63 (8H, m, H-2,3); δ_C (101 MHz, $CDCl_3$) 87.7 (C-4), 74.3 (C-1), 71.1 (C-5), 42.4 (C-2), 23.4 (C-3).

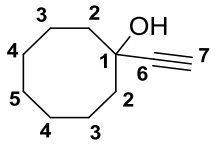
1-Ethynylcyclohexanol (115c)[297,298]



Cyclohexanone (0.94 mL, ca. 0.89 g, 9.1 mmol) was added dropwise to a stock solution of HC≡CMgBr (0.5 M in THF, 20 mL, 10 mmol). The resulting mixture was stirred at RT for 1 hr. The reaction was quenched at 0 °C with sat. aq. NH_4Cl (20 mL) and water (2 mL). The layers were separated and the aq. layer was extracted with ether (2×20 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$, and concentrated. The crude mixture was purified by Kugelrohr distillation (80 → 120 °C, 18 Torr) to afford the product as a white, easy-melting, solid (1.03 g, 91%).

R_f 0.39 (DCM); mp 30–31 °C (lit.[298] 31–33 °C); ν_{max}/cm^{-1} 3389br.s (OH), 3306m (≡C–H), 2251w (C≡C); δ_H (400 MHz, $CDCl_3$) 2.48 (1H, s, H-6), 2.08 (1H, s, OH), 1.97 – 1.83 (2H, m, H-2a), 1.70 (2H, m, H-3a), 1.64 – 1.47 (5H, m, H-2b,3b, 4a), 1.31 – 1.17 (1H, m, H-4b); δ_C (101 MHz, $CDCl_3$) 87.7 (C-5), 72.1 (C-6), 68.5 (C-1), 39.7 (C-2), 25.1 (C-4), 23.1 (C-3).

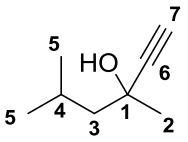
1-Ethynylcyclooctanol (115d)[299]



Prepared by General method A from cyclooctanone (1.89 g, 15.0 mmol) and HC≡CMgBr (33 mL, 0.5 M in THF, 16.5 mmol). Purified by flash chromatography (1:5 → 1:4, ether/petrol). The product is a yellow oil that solidifies into a waxy pale yellow solid upon standing in freezer. Slow crystallization from melt yields white needles (1.72 g, 75%).

R_f 0.25 (25:75, ether/petrol); ν_{max}/cm^{-1} 3304s (OH), 3283s (≡C–H), 2106w (C≡C); δ_H (400 MHz, $CDCl_3$) 2.43 (1H, s, H-7), 2.03 – 1.82 (7H, m, 7H, OH, 3×CH_2), 1.74 – 1.41 (8H, m, 4×CH_2); δ_C (100 MHz, $CDCl_3$) 88.6 (C-6), 71.2 (C-1), 71.0 (C-7), 38.0 (C-2), 27.8 (C-4), 24.4 (C-5), 21.9 (C-3).

3,4-Dimethylpent-1-yn-3-ol (115f)[300]

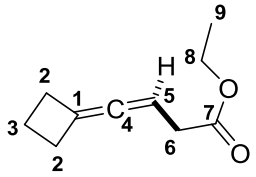


The title compound was prepared from methyl isobutyl ketone (1.50 g, 15.0 mmol) and HC≡CMgBr (0.5 M, 36 mL, 18.0 mmol) using a modification of General method A: the reaction was started at 0 °C, then continued at RT over 14 hr. Flash chromatography (25:75, ether/petrol) provided the product as a yellow oil (1.72 g, 91%).

R_f 0.39 (25:75, ether/petrol); ν_{max}/cm^{-1} 3403br.s (OH), 3310s (≡C–H), 2109w (C≡C); δ_H (400 MHz, $CDCl_3$) 2.44 (1H, s, H-7), 2.03 (1H, s, OH), 1.95 (1H, app. sept, *J* = 6.5 Hz, H-4), 1.59 (2H, d, *J* = 6.5 Hz, H-3), 1.50 (3H, s, H-2), 1.00 (6H, app. t, *J* = 6.5 Hz, H-

5); δ_C (101 MHz, $CDCl_3$) 88.3 (C-6), 71.6 (C-7), 66.0 (C-1), 51.7 (C-3), 31.0 (C-2), 24.4 (C-5), 24.2 (C-5), 15.4 (C-4).

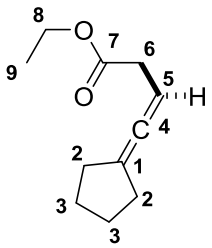
Ethyl 4-cyclobutylidenebut-3-enoate (117a)



The allene ester was synthesized according to general method B from 1-ethynylcyclobutanone (0.40 g, 4.2 mmol), $MeC(OEt)_3$ (4 mL), and a catalytic amount of propanoic acid (0.2 mL). The reaction mixture was diluted with ether (30 mL) and sequentially washed with aq. HCl (1 M, 2×8 mL), sat. aq. $NaHCO_3$ (8 mL), and brine (8 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (1:20 → 1:10, ether/petrol) yielded the product as a colourless oil (0.42 g, 60%).

R_f 0.39 (5:95, ethyl acetate/petrol); ν_{max}/cm^{-1} 1968w (C=C=C), 1738s (C=O); δ_H (500 MHz, $CDCl_3$) 5.28 – 5.21 (1H, m, H-5), 4.15 (2H, q, *J* = 7.0 Hz, H-8), 3.01 (2H, d, *J* = 7.0 Hz, H-6), 2.86 (4H, ddd, *J* = 11.0, 8.0, 3.5 Hz, H-2), 1.93 (2H, quint., *J* = 8.0 Hz, H-3), 1.26 (3H, t, *J* = 7.0 Hz, H-9); δ_C (126 MHz, $CDCl_3$) 196.6 (C-4), 171.7 (C-8), 102.3 (C-1), 86.3 (C-5), 60.6 (C-8), 35.6 (C-6), 29.7 (C-2), 17.5 (C-9), 14.8 (C-3); HRMS (TOF ESI+), m/z: calcd for $C_{10}H_{14}NaO_2$ [M+Na^+] 189.0886, found 189.0892.

Ethyl 4-cyclopentylidenebut-3-enoate (117b)[41,301]

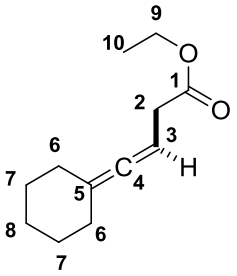


Prepared by General method B from 1-ethynylcyclopentanol (1.50 g, 13.6 mmol), $MeC(OEt)_3$ (12.0 mL, 10.6 g, 65 mmol), and propanoic acid (ca. 0.4 mL). Flash

chromatography on the crude mixture (5:95, ethyl acetate/petrol) afforded the title product as a colourless oil (2.21 g, 90%).

R_f 0.50 (10:90, ether/petrol); ν_{max}/cm^{-1} 1960w (C=C=C), 1730s (C=O); δ_H (400 MHz, $CDCl_3$) 5.24 – 5.13 (1H, m, H-5), 4.14 (2H, q, *J* = 7.0 Hz, H-8), 2.98 (2H, d, *J* = 7.0 Hz, H-6), 2.38 – 2.30 (4H, m, H-2), 1.65 (4H, app. ddd, *J* = 7.5, 4.0, 3.0 Hz, H-3), 1.26 (3H, t, *J* = 7.0 Hz, H-9); δ_C (101 MHz, $CDCl_3$) 198.5 (C-4), 172.1 (C-7), 105.0 (C-1), 84.5 (C-5), 60.7 (C-8), 35.6 (C-6), 31.2 (C-2), 27.1 (C-3), 14.3 (C-9).

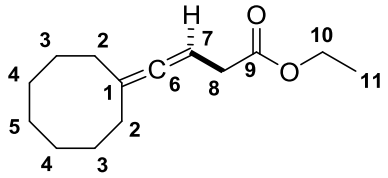
Ethyl 4-cyclohexylidenebut-3-enoate (117c)[41]



Prepared by General method B by heating 1-ethynyl cyclooctanol (0.90 g, 7.2 mmol), $MeC(OEt)_3$ (6.0 mL), and propanoic acid (0.2 + 0.2 mL) at 140 °C for 8 hr. Flash chromatography(5:95 → 15:85 → 50:50, ether/petrol) afforded the title compound as a colourless oil with an "acrylic" odour (1.18 g, 84%).

R_f 0.43 (10:90, ether/petrol); ν_{max}/cm^{-1} 1968w (C=C=C), 1736s (C=O); δ_H (400 MHz, $CDCl_3$) 5.14 – 5.05 (1H, m, H-3), 4.15 (2H, q, *J* = 7.0 Hz, H-9), 2.99 (2H, d, *J* = 7.0 Hz, H-2), 2.18 – 2.04 (4H, m, H-6), 1.65 – 1.45 (6H, m, H-7,8), 1.27 (3H, t, *J* = 7.0 Hz, H-10); δ_C (101 MHz, $CDCl_3$) 199.6 (C-4), 172.0 (C-1), 103.6 (C-5), 81.8 (C-3), 60.6 (C-9), 35.7 (C-2), 31.3 (C-6), 27.3 (C-7), 26.0 (C-8), 14.2 (C-10).

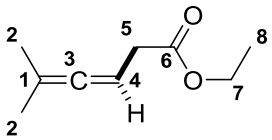
Ethyl 4-cyclooctylidenebut-3-enoate (117d)



Prepared by General method B from 1-ethynylcyclooctanol (1.05 g, 6.89 mmol), $MeC(OEt)_3$ (6 mL, ca. 33 mmol), and propanoic acid (3×0.2 mL). Flash chromatography (1:19 → 1:5, ether/petrol,) afforded the target material as a yellowish oil (0.99 g, 65%).

R_f 0.58 (10:90, ether/petrol); ν_{max}/cm^{-1} 1960w (C=C=C), 1736s (C=O); δ_H (400 MHz, $CDCl_3$) 5.14 – 5.07 (1H, m, H-7), 4.14 (2H, q, *J* = 7.0 Hz, H-10), 2.97 (2H, d, *J* = 7.0 Hz, H-8), 2.21 – 2.09 (4H, m, H-2), 1.72 – 1.45 (10H, m, H-3,4,5), 1.26 (3H, t, *J* = 7.0 Hz, H-11); δ_C (101 MHz, $CDCl_3$) 203.1 (C-6), 172.1 (C-9), 105.6 (C-1), 82.2 (C-7), 60.6 (C-10), 35.0 (C-8), 31.5 (C-2), 26.8 (C-3), 26.7 (C-4), 26.1 (C-5), 14.2 (C-11); HRMS (TOF FI^+), m/z: calcd for $C_{14}H_{22}NaO_2$ $[M+Na^+]$ 245.1512, found 245.1509.

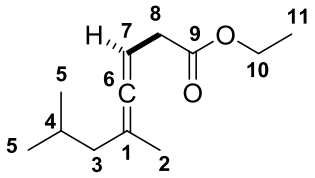
Ethyl 5-methylhexa-3,4-dienoate (117e)[149,302]



Prepared according to General method B from 1,1-dimethylprop-2-yn-1-ol (2.00 g, 23.8 mmol), $MeC(OEt)_3$ (22 mL, 120 mmol), and propanoic acid (0.36 mL, 0.5 mmol). Flash chromatography (5:95, ether/petrol) afforded the target material as colourless volatile oil (2.82 g, 77%).

R_f 0.59 (10:90, ether/petrol); ν_{max}/cm^{-1} 1971w (C=C=C), 1736s (C=O); δ_H (400 MHz, $CDCl_3$) 5.11 – 5.04 (2H, m, H-4), 4.14 (2H, q, *J* = 7.0 Hz, H-7), 2.96 (2H, d, *J* = 7.0 Hz, H-5), 1.68 (6H, d, *J* = 3.0 Hz, H-2), 1.26 (3H, t, *J* = 7.0 Hz, H-8); δ_C (101 MHz, $CDCl_3$) 203.1 (C-3), 172.1 (C-6), 96.5 (C-1), 82.1 (C-4), 60.7 (C-7), 35.5 (C-5), 20.5 (C-2), 14.3 (C-8).

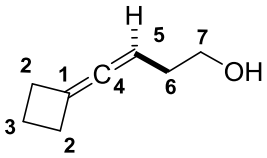
Ethyl 5,6-dimethylhepta-3,4-dienoate (117f)



Prepared by General method B from 3,4-dimethylpent-1-yn-3-ol (1.26 g, 10.0 mmol), $MeC(OEt)_3$ (10 mL, ca. 52 mmol), and propanoic acid (0.30 + 0.15 mL). Flash chromatography (7:93, ether/petrol) afforded the target material as a yellow oil (1.25 g, 64%).

R_f 0.37 (10:90, ether/petrol); ν_{max}/cm^{-1} 1969w (C=C=C), 1737s (C=O); δ_H (400 MHz, $CDCl_3$)* δ 5.11 (1H, app. dqt, *J* = 7.5, 5.5, 2.5 Hz, H-7), 4.13 (2H, app. quint, *J* = 7.0 Hz, H-10), 2.97 (2H, d, *J* = 7.5 Hz, H-8), 1.81 (2H, 2×d, *J* = 7.0 Hz, H-3), 1.77 – 1.66 (1H, m, H-4), 1.65 (3H, 2×s, H-2), 1.25 (3H, 2×t, *J* = 7.0 Hz, H-11), 0.88 (6H, d, *J* = 6.5 Hz, H-5); δ_C (101 MHz, $CDCl_3$)* 203.1 (C-6), 171.9 (C-9), 99.5 (C-1), 82.5 (C-7), 60.5 (C-10), 43.5 (C-3), 35.4 (C-8), 26.2 (C-4), 22.5 (C-5), 22.4 (C-5), 18.9 (C-2), 14.2 (C-11); HRMS (TOF FI+), m/z: calcd for $C_{12}H_{20}O_2$ $[M^+]$ 196.1463, found 196.1468.

4-Cyclobutylidenebut-3-en-1-ol (118a)

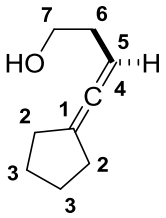


Prepared according to General method C from ethyl 4-cyclobutylidenebut-3-enoate (0.28 g, 1.7 mmol) and $LiAlH_4$ (91 mg, 2.4 mmol) in Et_2O (20 mL). The reaction mixture was diluted with ether (20 mL) and quenched with sat. aq. Na_2SO_4 (ca. 2 mL) at 0 °C. The solids were filtered off, thoroughly washing with ether (50 mL). The combined organic extracts were washed with brine (2×20 mL), dried over $MgSO_4$, and concentrated. The target material, a colourless oil, was used as received (0.20 g, 95%).

* Note: two rotamers can be seen in the spectrum.

R_f 0.25 (1:1, ether/petrol); ν_{max}/cm^{-1} 3332br.s (OH), 1965w (C=C=C); δ_H (500 MHz, C_6D_6) 5.19 – 5.09 (1H, m, H-5), 3.48 (2H, t, *J* = 6.5 Hz, H-7), 2.81 – 2.65 (4H, m, H-2), 2.12 (2H, app. q, *J* = 6.5 Hz, H-6), 1.65 (2H, quint., *J* = 8.0 Hz, H-3), 1.26 (1H, br.s, OH); δ_C (126 MHz, C_6D_6) 196.9 (C-4), 101.4 (C-1), 90.5 (C-5), 62.1 (C-7), 33.5 (C-6), 30.2 (C-2), 17.7 (C-3); HRMS (TOF FI^+), m/z: calcd for $C_8H_{12}O$ $[M^+]$ 124.0888, found 124.0885.

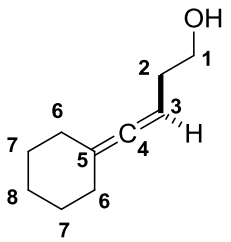
4-Cyclopentylidenebut-3-en-1-ol (118b)[303]



Prepared by General method C from ethyl 4-cyclopentylidenebut-3-enoate (0.60 g, 3.3 mmol) and $LiAlH_4$ (0.22 g, 5.77 mmol). The product is an acid-sensitive colourless oil that was used without purification (0.38 g, 83%).

R_f 0.51 (ether); ν_{max}/cm^{-1} 3330br.s (OH), 1965w (C=C=C); δ_H (400 MHz, C_6D_6) 5.16 – 5.03 (1H, m, H-5), 3.51 (2H, t, *J* = 6.5 Hz, H-7), 2.40 – 2.21 (4H, m, H-2), 2.14 (2H, q, *J* = 6.5 Hz, H-6), 1.48 – 1.38 (5H, m, H-3,OH); δ_C (101 MHz, C_6D_6) 198.5 (C-4), 104.1 (C-1), 88.4 (C-5), 62.2 (C-7), 33.4 (C-6), 31.5 (C-2), 27.3 (C-3); HRMS (GCMS CI^+), m/z: calcd for $C_9H_{15}O$ $[M+H^+]$ 139.1124, found 139.1123.

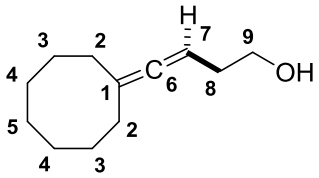
4-Cyclohexylidenebut-3-en-1-ol (118c)[41]



Prepared by General method C from ethyl 4-cyclohexylidenebut-3-enoate (1.05 g, 5.4 mmol) and $LiAlH_4$ (205 mg, 5.4 mmol) in 40 mL of ether. The product, a clear colourless oil, was used immediately without further purification (0.78 g, 95%).

R_f 0.41 (50:50, ether/petrol); ν_{max}/cm^{-1} 3325br.s (OH), 1964w (C=C=C); δ_H (400 MHz, C_6D_6) 5.15 – 5.04 (1H, m, H-3), 3.60 (2H, td, *J* = 6.0, 5.5 Hz, H-1), 2.25 – 2.16 (6H, m, H-2,6), 1.64 – 1.51 (4H, m, H-7), 1.48 – 1.37 (2H, m, H-8), 1.26 (t, *J* = 5.5 Hz, 1H, OH); δ_C (101 MHz, C_6D_6) 199.6 (C-4), 102.8 (C-5), 85.8 (C-3), 62.2 (C-1), 33.2 (C-2/6), 31.9 (C-2/6), 27.7 (C-7), 26.3 (C-8).

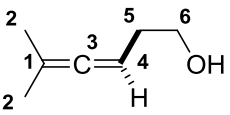
4-Cyclooctylidenebut-3-en-1-ol (118d)



Prepared by General method C from ethyl 4-cyclooctylidenebut-3-enoate (0.766 g, 3.45 mmol) and $LiAlH_4$ (0.170 g, 4.48 mmol). The target material, a colourless oil, was used as received (0.605 g, 97%).

R_f 0.37 (1:1, ether/petrol); ν_{max}/cm^{-1} 3333br.s (OH), 1956w (C=C=C); δ_H (400 MHz, C_6D_6) 5.03 – 4.92 (1H, m, H-7), 3.50 (2H, t, *J* = 6.5 Hz, H-9), 2.20 – 2.06 (6H, m, H-2,8), 1.70 – 1.40 (10H, m, H-3,4,5), 1.29 (1H, br.s, OH); δ_C (101 MHz, C_6D_6) 203.3 (C-6), 104.7 (C-1), 86.0 (C-7), 62.4 (C-9), 33.1 (C-8), 32.3 (C-2), 27.3 (C-3), 27.1 (C-4), 26.5 (C-5); HRMS (TOF FI$^+$), m/z: calcd for $C_{12}H_{20}O$ [M^+] 180.1514, found 180.1520.

5-Methylhexa-3,4-dien-1-ol (118e)[149,302]

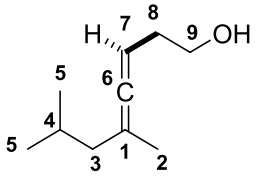


Prepared according to General method C from ethyl 5-methylhexa-3,4-dienoate (2.50 g, 16.2 mmol) and $LiAlH_4$ (0.738 g, 19.5 mmol). The target material, a colourless volatile oil, was used as received (1.82 g, 100%).

R_f 0.38 (1:1, ether/petrol); ν_{max}/cm^{-1} 3330br.s (OH), 1969w (C=C=C); δ_H (400 MHz, C_6D_6) 4.94 (1H, app. qt, *J* = 6.5, 3.0 Hz, H-4), 3.46 (app.q, *J* = 6.5 Hz, 2H, H-6), 2.07

(2H, app. q, *J* = 6.5 Hz, H-5), 1.57 (6H, d, *J* = 3.0 Hz, H-2), 0.95 (1H, t, *J* = 7.0 Hz, OH); δ_C (101 MHz, C_6D_6) 203.1 (C-3), 95.2 (C-1), 85.9 (C-3), 62.2 (C-6), 33.2 (C-5), 20.7 (C-2).

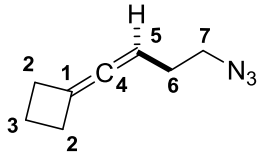
5,6-Dimethylhepta-3,4-dien-1-ol (118f)



Prepared by general method C from ethyl 5,6-dimethylhepta-3,4-dienoate (1.04 g, 5.3 mmol) and $LiAlH_4$ (0.260 g, 6.9 mmol). The target material, a colourless oil, was used as received (0.81 g, 100%).

R_f 0.24 (25:75, ether/petrol); ν_{max}/cm^{-1} 3333br.m (OH), 1962w (C=C=C); δ_H (400 MHz, C_6D_6)* δ 5.03 – 4.95 (1H, m, H-7), 3.50 (2H, br.t, *J* = 6.5 Hz, H-9), 2.12 (2H, app. q, *J* = 6.5 Hz, H-8), 1.80 – 1.75 (2H, m, H-3), 1.74 – 1.64 (1H, m, H-4), 1.59 (3H, 2×s's, H-2), 1.46 (1H, br.s, OH), 0.90 (6H, overlapped d, *J* = 6.5 Hz, H-5); δ_C (101 MHz, C_6D_6)* 203.3 (C-6), 98.5 (C-1), 86.4 (C-7), 62.4 (C-9), 44.1 (C-3), 33.4 (C-8), 26.6 (C-4), 22.73 (C-5), 22.71 (C-5), 19.4 (C-2); HRMS (TOF FI^+), m/z: calcd for $C_{10}H_{18}O$ $[M^+]$ 154.1358, found 154.1358.

(4-Azidobut-1-en-1-ylidene)cyclobutane (119a)

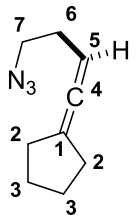


Prepared according to General method D from 4-cyclobutylidenebut-3-en-1-ol (120 mg, 0.97 mmol), NaN_3 (190 mg, 2.9 mmol), PPh_3 (630 mg, 2.4 mmol), and CBr_4 (796 mg, 2.4 mmol). Purified by flash chromatography (1:200, ether/petrol,). The target material is a colourless oil (145 mg, 100%).

* Note: two rotamers can be seen in the spectrum.

R_f 0.63 (5:95, ether/petrol); ν_{max}/cm^{-1} 2091s (N_3), 1966w (C=C=C); δ_H (500 MHz, C_6D_6) 5.04 – 4.93 (1H, m, H-5), 2.86 – 2.65 (6H, t *over* m, *J* = 6.5 Hz, H-7,2), 1.91 (2H, app. q, *J* = 6.5 Hz, H-6), 1.75 – 1.60 (2H, m, H-3); δ_C (126 MHz, C_6D_6) 196.7 (C-4), 102.4 (C-1), 90.2 (C-5), 50.5 (C-7), 30.1 (C-2), 29.4 (C-6), 17.8 (C-3); HRMS (TOF FI$^+$), m/z: calcd for $C_8H_{11}N_3$ [M$^+$] 149.0953, found 149.0956.

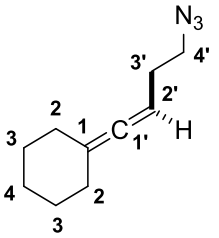
(4-Azidobut-1-en-1-ylidene)cyclopentane (119b)



Prepared by General method D from 4-cyclopentylidenebut-3-en-1-ol (50 mg, 0.36 mmol), NaN_3 (71 mg, 1.09 mmol), PPh_3 (236 mg, 0.90 mmol), and CBr_4 (298 mg, 0.90 mmol). The product was purified by flash chromatography (1:30, ether/petrol) as a colourless oil (47 mg, 80%).

R_f 0.77 (25:75, ether/petrol); ν_{max}/cm^{-1} 2097s (N_3), 1964w (C=C=C); δ_H (400 MHz, C_6D_6) 5.04 – 4.88 (1H, m, H-5), 2.81 (2H, t, *J* = 7.0 Hz, H-7), 2.46 – 2.21 (4H, m, H-2), 1.94 (2H, q, *J* = 7.0 Hz, H-6), 1.53 – 1.37 (4H, m, H-3); δ_C (101 MHz, C_6D_6) 198.4 (C-4), 105.0 (C-1), 88.3 (C-5), 50.7 (C-7), 31.5 (C-2), 29.2 (C-6), 27.3 (C-3); HRMS (TOF FI$^+$), m/z: calcd for $C_9H_{13}N_3$ [M$^+$] 163.1109, found 163.1111.

(4-Azidobut-1-en-1-ylidene)cyclohexane (119c)

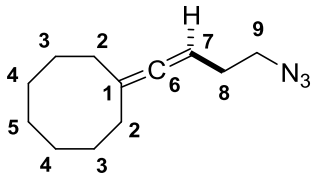


Prepared by General method E from 4-cyclohexylidenebut-3-en-1-ol (0.75 g, 4.9 mmol), PPh_3 (3.22 g, 12.3 mmol), CBr_4 (4.08 g, 12.3 mmol), and NaN_3 (1.28 g, 19.7

mmol) in 35 mL of DMF. Flash chromatography (petrol → 1:99 → 2:98 → 3:97, ether/petrol) afforded the title compound as a colourless oil (0.80 g, 92%).

R_f 0.36 (1:99, ether/petrol); ν_{max}/cm^{-1} 3025w (=C−H), 2094s (N_3), 1953w (C=C=C); δ_H (400 MHz, $CDCl_3$) 5.06 – 4.91 (1H, m, H-2'), 3.32 (t2H,, *J* = 7.0 Hz, H-4'), 2.26 (2H, td, *J* = 7.0, 6.5 Hz, H-3'), 2.18 – 2.06 (4H, m, H-2), 1.66 – 1.47 (6H, m, H-3,4); δ_C (101 MHz, $CDCl_3$) 199.0 (C-1'), 103.8 (C-1), 84.8 (C-2'), 50.7 (C-4'), 31.5 (C-3'), 28.8 (C-2/3), 27.4 (C-3/2), 26.1 (C-4); HRMS (TOF FI+), m/z: calcd for $C_{10}H_{15}N_3$ [M+] 177.1266, found 177.1266.

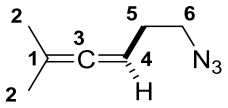
(4-Azidobut-1-en-1-ylidene)cyclooctane (119d)



Prepared by General method D from 4-cyclooctylidenebut-3-en-1-ol (100 mg, 0.55 mmol), NaN_3 (107 mg, 1.65 mmol), PPh_3 (362 mg, 1.38 mmol), and CBr_4 (458 mg, 1.38 mmol). Flash chromatography (petrol → 1:50, ether/petrol) afforded the target material as a colourless oil (92 mg, 81%).

R_f 0.64 (3:97, ether/petrol); ν_{max}/cm^{-1} 2094s (N_3), 1957w (C=C=C); δ_H (400 MHz, C_6D_6) 4.91 – 4.78 (1H, m, H-7), 2.81 (2H, t, *J* = 7.0 Hz, H-9), 2.21 – 2.08 (4H, m, H-2), 1.93 (2H, app. q, *J* = 7.0 Hz, H-8), 1.66 – 1.41 (10H, m, H-3,4,5); δ_C (101 MHz, C_6D_6) 203.1 (C-6), 105.6 (C-1), 85.9 (C-7), 50.8 (C-9), 31.9 (C-2), 28.9 (C-8), 27.2 (C-3), 27.0 (C-4), 26.4 (C-5); HRMS (TOF FI+): m/z: calcd for $C_{12}H_{19}N_3$ [M+] 205.1579, found 205.1547.

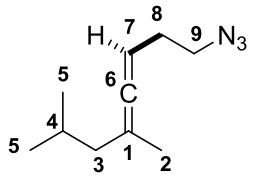
6-Azido-2-methylhexa-2,3-diene (119e)[149,304]



Prepared according to General method E from 5-methylhexa-3,4-dien-1-ol (0.500 g, 4.45 mmol), PPh_3 (2.33 g, 8.90 mmol), CBr_4 (2.95 g, 8.90 mmol), and NaN_3 (0.87 g, 13 mmol). The product, a colourless volatile oil, was purified by flash chromatography (petrol → 2:98, ether/petrol) (490 mg, 80%).

R_f 0.53 (7:93, ether/petrol); ν_{max}/cm^{-1} 2096s (N_3), 1970w (C=C=C); δ_H (400 MHz, $CDCl_3$) 4.99 – 4.93 (1H, m, H-4), 3.32 (2H, t, *J* = 7.0 Hz, H-6), 2.25 (2H, app.q, *J* = 7.0 Hz, H-5), 1.71 (6H, d, *J* = 3.0 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 202.4 (C-3), 96.4 (C-1), 85.0 (C-4), 50.8 (C-6), 28.7 (C-5), 20.5 (C-2).

1-Azido-5,6-dimethylhepta-3,4-diene (119f)



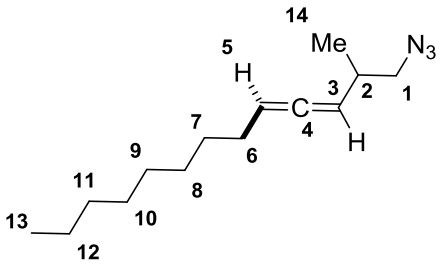
Prepared by General method D from 5,6-dimethylhepta-3,4-dien-1-ol (308 mg, 2.0 mmol), NaN_3 (650 mg, 10.0 mmol), PPh_3 (1.31 g, 5.0 mmol), and CBr_4 (1.66 g, 5.0 mmol). Flash chromatography (1:200, ether/petrol) afforded the target material as a colourless oil (225 mg, 63%).

R_f 0.23 (petrol); ν_{max}/cm^{-1} 2092s (N_3), 1967w (C=C=C); δ_H (500 MHz, C_6D_6)* δ 4.96 (1H, app. qd, *J* = 6.0, 3.0 Hz, H-7), 2.91 (2H, app. td, *J* = 7.0, 1.2 Hz, H-9), 2.03 (2H, app. q, *J* = 7.0 Hz, H-8), 1.95 – 1.85 (2H, m, H-3), 1.80 (1H, app. sept, *J* = 6.5 Hz, H-4), 1.71 (2×s, 3H, H-2), 1.01 (6H, 2×d, *J* = 6.5 Hz, H-5); δ_C (126 MHz, C_6D_6)* 203.1 (C-6), 99.5

* Note: two rotamers can be seen in the spectrum.

(C-1), 86.2 (C-7), 50.8 (C-9), 43.9 (C-3), 29.2 (C-8), 26.5 (C-4), 22.7 (C-5), 22.6 (C-5), 19.1 (C-2); HRMS (TOF FI$^+$), m/z: calcd for $C_{10}H_{17}N$ [M−N_2^+] 151.1361, found 151.1363.

1-azido-2-methyltrideca-3,4-diene (119g)

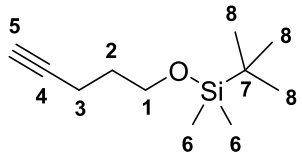


A solution of triisopropylsilyl 2-methyltrideca-3,4-dienoate (300 mg, 0.79 mmol) in ether (10 mL) was cooled to 0 °C. $LiAlH_4$ (30 mg, 0.79 mmol) was added and the resulting mixture was stirred at 0 °C for 30 min. The reaction was diluted with ether (10 mL) and carefully quenched by the slow addition of sat. aq. Na_2SO_4 at 0 °C (*caution: gas liberation)*. The cloudy mixture was stirred at RT for 30 min with periodic addition of sat. aq. Na_2SO_4, until a dense white precipitate of aluminium salts formed. The solution was dried with solid anhydrous Na_2SO_4, then filtered and concentrated. Flash chromatography (10:90 → 50:50, ether/petrol) afforded the intermediate alcohol as a clear colourless oil (R_f 0.40, 50:50, ether/petrol). The alcohol was immediately redissolved in DMF (3 mL) and the solution was cooled to 10 °C. To this, CBr_4 (561 mg, 1.7 mmol) and PPh_3 (443 mg, 1.7 mmol) were added; the ice bath was removed and the bright yellow mixture was stirred at RT for 3 hr. The reaction mixture was partitioned between water (5 mL) and petrol (5 mL). The layers were separated, and the aq. layer (*note: voluminous precipitate*) was extracted with petrol (3×4 mL). The combined organic layer was washed with brine (4 mL), dried over Na_2SO_4, filtered through a plug of silica (1 cm), and concentrated to yield the intermediate bromide as a clear colourless oil. The bromide was redissolved in DMF (4 mL). NaN_3 (69 mg, 1.1 mmol) was added and the resulting mixture was stirred under argon at 35 °C for 2 days

(additional 69 mg of NaN_3 were added after the first day). The reaction mixture was partitioned between water (20 mL) and petrol (20 mL). The layers were separated, and the aq. layer was extracted with petrol (3×10 mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (petrol → 1:99, ether/petrol) afforded the title material as a clear colourless oil (110 mg, 75% over 3 steps).

R_f 0.66 (10:90, ether/petrol); ν_{max}/cm^{-1} 2097s (N_3), 1962w (C=C=C); δ_H (500 MHz, $CDCl_3$) 5.21 (1H, qd, *J* = 6.5, 3.0 Hz, H-3), 5.08 (1H, tt, *J* = 6.0, 3.0 Hz, H-5), 3.26 (1H, dd, *J* = 12.0, 6.5 Hz, H-1a), 3.16 (1H, dd, *J* = 12.0, 7.0 Hz, H-1b), 2.41 (1H, m, H-2), 2.03 – 1.96 (2H, m, H-6), 1.44 – 1.22 (12H, m, H-7,8,9,10,11,12), 1.07 (3H, d, *J* = 6.5 Hz, H-14), 0.88 (3H, t, *J* = 7.0 Hz, H-13); δ_C (126 MHz, $CDCl_3$) 203.4 (C-4), 93.6 (C-5), 93.3 (C-3), 57.4 (C-1), 33.9 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.30 (CH_2), 29.0 (CH_2), 22.8 (CH_2), 18.0 (C-14), 14.3 (C-13); HRMS (TOF FI^+), m/z: calcd for $C_{14}H_{25}N$ $[M-N_2^+]$ 207.1982, found 207.1986.

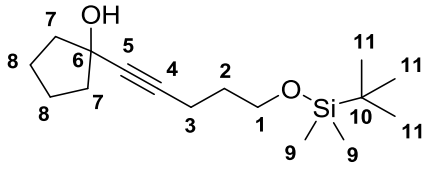
tert-Butyldimethyl(pent-4-yn-1-yloxy)silane (122)[305,306]



To a solution of 4-pentynol-1 (1.70 g, 20.2 mmol) and imidazole (2.40 g, 35.3 mmol) in DCM (15 mL) was added TBSCl (3.34 g, 22.2 mmol) at 0 °C. Formation of white precipitate was immediately observed. The resulting mixture was stirred at 0 °C for 1 hr. The mixture was diluted with DCM (30 mL) and washed with brine (20 mL). The aq. layer was extracted with DCM (15 mL). The combined organic layers were evaporated to the ¼ of the original volume and passed through a plug of silica (ca. 1 in; 1:1, DCM/petrol). Evaporation of the solution afforded the desired product as a colourless oil (4.00 g, 100%).

R_f 0.66 (10:90, ether/petrol); ν_{max}/cm^{-1} 3314m (≡C–H), 2121w (C≡C); δ_H (400 MHz, $CDCl_3$) 3.69 (2H, t, *J* = 6.0 Hz, H-1), 2.27 (2H, td, *J* = 7.0, 2.5 Hz, H-3), 1.92 (1H, t, *J* = 2.5 Hz, H-5), 1.78 – 1.67 (2H, tt, *J* = 7.0, 6.0 Hz, H-2), 0.90 (9H, s, H-8), 0.04 (6H, s, H-6); δ_C (101 MHz, $CDCl_3$) 84.4 (C-4), 68.4 (C-5), 61.6 (C-1), 31.7 (C-2), 26.1 (C-8), 18.5 (C-7), 15.0 (C-3), −5.2 (C-6).

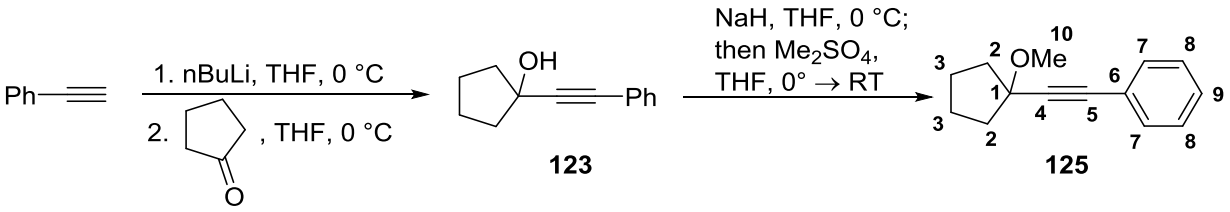
1-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclopentanol (124)



tert-Butyldimethyl(pent-4-yn-1-yloxy)silane (1.50 g, 7.6 mmol) was dissolved in THF (45 mL) and cooled to −78 °C. To this, BuLi (1.6 M in hexanes, 4.8 mL, 7.7 mmol) was added with a syringe. The mixture was stirred at −78 °C for 90 min, after which a solution of cyclopentanone (0.636 g, 7.6 mmol) in THF (5 mL) was added over 15 min. The solution was allowed to warm to RT and stirred for 17 hr. The reaction mixture was diluted with wet ether (5 mL), quenched with H_2O (10 mL), and neutralized with aq. HCl (1 M, ca. 5 mL). The aq. layer was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over $MgSO_4$, and concentrated. Two consecutive purifications by flash chromatography (25:75, ether/petrol) yielded the title compound as a colourless oil (0.80 g, 37%; b.r.s.m. 74%) along with some starting material.

R_f 0.42 (25:75, ether/petrol); ν_{max}/cm^{-1} 3600m (free OH), 3383br.s (H-bonded OH), 2237w (C≡C); δ_H (400 MHz, $CDCl_3$) 3.68 (2H, t, *J* = 6.0 Hz, H-1), 2.28 (2H, t, *J* = 7.0 Hz, H-3), 1.96 – 1.87 (4H, m, H-7), 1.87 – 1.63 (7H, m, H-2,8,OH), 0.89 (9H, s, H-11), 0.05 (6H, s, H-9); δ_C (101 MHz, $CDCl_3$) 84.3 (C-4), 83.3 (C-5), 74.8 (C-6), 61.7 (C-1), 42.7 (C-7), 31.9 (C-2), 26.1 (C-11), 23.5 (C-8), 18.5 (C-10), 15.3 (C-3), −5.2 (C-9); HRMS (ESI^+), m/z: calcd for $C_{16}H_{30}O_2SiNa$ [$M+Na^+$] 305.1913, found 305.1903.

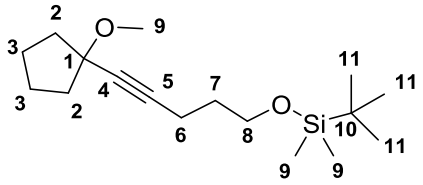
((1-Methoxycyclopentyl)ethynyl)benzene (125)[163]



Phenylacetylene (0.40 g, 3.9 mmol) was dissolved in THF (10 mL) at 0 °C. To this, BuLi (1.5 M, 2.3 mL, 3.5 mmol) was added. The solution was stirred at 0 °C for 1 hr. Cyclopentanone (0.295 g, 3.5 mmol) was added, and the resulting mixture was allowed to warm to RT and stirred overnight (16 hr). The cloudy mixture was diluted with ether (20 mL) and quenched with sat. aq. NH_4Cl (8 mL), then washed sequentially with aq. HCl (1 M, 3 mL), water (8 mL), and brine (8 mL). The organic layer was dried ($MgSO_4$) and evaporated, yielding 0.74 g of product **123**, which was used without purification. Crude propargylic alcohol **123** (0.44 g, 2.4 mmol) was dissolved in THF (10 mL) at 0 °C. Then, NaH (60% in oil, 144 mg, 3.6 mmol) was added and the mixture was stirred at 0 °C for 1 hr. Dimethyl sulfate (0.37 mL, 3.8 mmol) was added at 0 °C. The mixture was allowed to warm to RT and stirred for 2.5 hr. The cloudy solution was diluted with ether (10 mL) and quenched with sat. aq. NH_4Cl (10 mL). The aq. layer was extracted with ether (10 mL). The combined organic layers were washed with brine (8 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5:95, ether/petrol) afforded the title material as a pale yellow oil (0.30 g, 60% over 2 steps).

R_f 0.53 (10:90, ether/petrol); ν_{max}/cm^{-1} 3056w (=C–H), 2969m, 2941m, 2822m, 1598m, 1488m; δ_H (200 MHz, $CDCl_3$) 7.49 – 7.40 (2H, m, H-7), 7.36 – 7.25 (3H, m, H-8,9), 3.42 (3H, s, H-10), 2.18 – 1.89 (4H, m, H-2), 1.87 – 1.69 (4H, m, H-3); δ_C (126 MHz, $CDCl_3$) 131.7 (C-8), 128.2 (C-7), 128.1 (C-9), 123.4 (C-6), 90.4 (C-4), 84.9 (C-5), 81.1 (C-1), 52.1 (C-10), 39.1 (C-2), 23.4 (C-3).

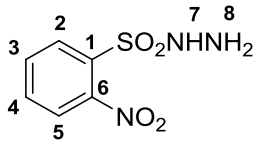
tert-Butyl((5-(1-methoxycyclopentyl)pent-4-yn-1-yl)oxy)dimethylsilane (126)



1-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclopentan-1-ol (0.323 g, 1.14 mmol) was dissolved in degassed THF (5 mL) and cooled to 0 °C. To this, NaH (60% in oil, 91 mg, 2.28 mmol) was added. The slurry was stirred at 0 °C for 1.5 hr. Then, MeI (0.485 g, 3.42 mmol) was added at 0 °C, the reaction mixture was allowed to warm to RT and stirred for 2.5 hr. The solution was diluted with ether (25 mL), washed with water (2×5 mL) and brine (5 mL), and dried over $MgSO_4$. Flash chromatography using a short silica column (1:19, ether/petrol) yielded spectroscopically pure target material as a yellow oil (0.318 g, 90%).

R_f 0.30 (petrol); ν_{max}/cm^{-1} 2235w (C≡C), 1471s, 1256s, 1106s; δ_H (400 MHz, $CDCl_3$) 3.69 (2H, t, *J* = 6.0 Hz, H-8), 3.31 (3H, s, H-9), 2.30 (2H, t, *J* = 7.0 Hz, H-6), 2.01 – 1.91 (2H, m, H-2a), 1.87 – 1.76 (2H, m, H-2b), 1.75 – 1.64 (6H, m, H-3,7), 0.89 (9H, s, H-11), 0.05 (6H, s, H-9); δ_C (101 MHz, $CDCl_3$) 85.0 (C-5), 81.5 (C-4), 81.0 (C-1), 61.8 (C-8), 51.9 (C-9), 39.3 (C-2), 32.0 (C-7), 26.1 (C-11), 23.4 (C-3), 18.5 (C-10), 15.3 (C-6), –5.2 (C-9); HRMS (ESI^+), m/z: calcd for $C_{17}H_{32}NaO_2Si$ [$M+Na^+$] 319.2064, found 319.2052.

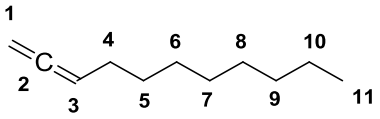
_o_-Nitrobenzenesulfonylhydrazide (128)[159]



_o_-Nitrobenzenesulfonyl chloride (2.00 g, 9.02 mmol) was dissolved in degassed THF (9 mL) and cooled to −30 °C. $N_2H_4 \cdot H_2O$ (1.12 g, 22.6 mmol) was added carefully, and the resulting mixture was stirred at −30 °C for 1 hr. Cold ethyl acetate (18 mL, 0 °C) was added to the reaction at 0 °C and the mixture was washed with cold aq. NaCl (10%, 0°C, 5×13 mL), then dried over Na_2SO_4 at 0°C and filtered. The resulting solution was slowly added to hexane (110 mL) at RT over 5 min. The off-white precipitate of _o_-nitrobenzenesulfonylhydrazide was filtered out, washed with hexane (2×5 mL), and dried at hi-vac for 14 hr (1.50 g, 77%).

M.p.: 87–88 °C (lit. 100–101 °C[159]); δ_H (500 MHz, CD_3CN) 8.11 – 8.03 (1H, m, H-5), 7.91 – 7.78 (3H, m, H-2,3,4), 6.92 (1H, br.s, NH), 2.98 (2H, br. s, NH_2); δ_C (126 MHz, CD_3CN) 149.6 (C-6), 135.6 (C-Ar), 133.5 (C-Ar), 133.3 (C-Ar), 131.0 (C-4), 125.9 (C-5).

_n_-Octyl allene (130)[36]

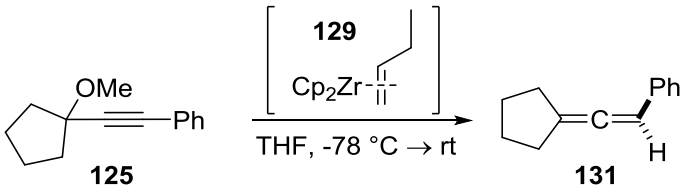


Prepared using Myers allenation protocol.[158] DEAD (0.10 mL, 0.65 mmol) was added to a solution of PPh_3 (170 mg, 0.65 mmol) in THF (2 mL) at −15 °C (external monitoring) and stirred for 10 min. Then, a solution of undec-1-yn-3-ol (84 mg, 0.50 mmol) in THF (1.5 mL) was added with a syringe. The mixture was stirred for another 10 min, followed by the addition of a solution of 2-nitrobenzenesulfonyl hydrazide (0.14 g, 0.65 mmol) in THF (2 mL) with a syringe. The mixture was stirred at −15 °C for 1 hr, then at RT for 20 hr. The cloudy yellow mixture was diluted with ether (2 mL) and filtered through a plug of silica (2 cm), washing with ether (4 mL). The resulting

solution was concentrated (100 Torr). Flash chromatography (petrol → 10:90, ether/petrol) afforded the title material as a clear colourless oil (30 mg, 45%).

R_f 0.82 (10:90, ether/petrol); ν_{max}/cm^{-1} 1956m (C=C=C); δ_H (400 MHz, $CDCl_3$) 5.09 (1H, app.quint, *J* = 6.5 Hz, H-3), 4.64 (2H, app. dt, *J* = 6.5, 3.0 Hz, H-1), 2.06 – 1.93 (2H, m, H-4), 1.47 – 1.21 (12H, m, H-5,6,7,8,9,10), 0.88 (3H, t, *J* = 7.0 Hz, H-11); δ_C (126 MHz, $CDCl_3$) 208.6 (C-2), 90.3 (C-3), 74.7 (C-1), 32.0 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.32 (CH_2), 29.30 (CH_2), 28.4 (C-4), 22.8 (CH_2), 14.3 (C-11).

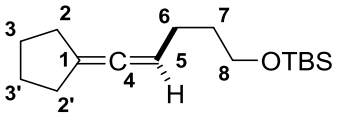
(2-Cyclopentylidenevinyl)benzene (131)[163]



Zirconocene dichloride (94 mg, 0.32 mmol) was dissolved in THF (1 mL) and cooled to −78 °C. BuLi (1.5 M in pentane, 0.43 mL, 0.64 mmol) was added with a syringe and the resulting yellow solution of Negishi reagent,[162] **129**, was stirred at −78 °C for 1 hr. A solution of ((1-methoxycyclopentyl)ethynyl)benzene (200 mg, 0.20 mmol) in THF (1 mL) was added. After 30 min, the dry ice bath was removed and the resulting mixture was stirred at RT for 2 hr. The reaction was diluted with ether (10 mL) and quenched with aq. HCl (1 M, 1 mL). The organic layer was washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated. Yield not measured.

ν_{max}/cm^{-1} 1960w (C=C=C). NMR data as reported.[163]

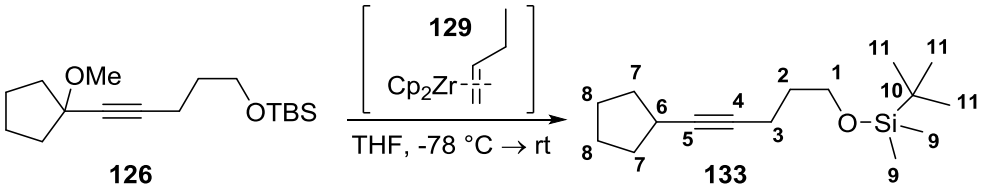
tert-Butyl((5-cyclopentylidenepent-4-en-1-yl)oxy)dimethylsilane (132)



Isolated as an intermediate in the synthesis of hydroxy allenes by General method H by quenching the reaction when some *O*-TBS-protected intermediate was still present. Flash chromatography (1:10→1:1, ether/petrol) yielded the product as the least polar compound. Yield not measured.

R_f 0.71 (10:90, ether/petrol); ν_{max}/cm^{-1} 1960w (C=C=C); MS (ESI^+), m/z: 289 (21%, $M+Na^+$), 330 (40%, $M+Na+MeCN^+$).

tert-Butyl((5-cyclopentylpent-4-yn-1-yl)oxy)dimethylsilane (133)

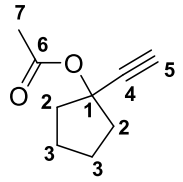


Zirconocene dichloride (88 mg, 0.30 mmol) was dissolved in THF (2 mL) and cooled to −78 °C. BuLi (1.5 M, 0.40 mL, 0.60 mmol) was added with a syringe and the resulting yellow solution of Negishi reagent,[162] **129**, was stirred at −78 °C for 1 hr. A solution of the propargylic ether (60 mg, 0.20 mmol) in THF (0.5 mL) was added. After 30 min, the dry ice bath was removed and the resulting mixture was stirred at RT over 14 hr. The reaction mixture was diluted with ether (50 mL), quenched with neutral phosphate buffer (15 mL, pH 7), and filtered. The organic layer was separated and washed with brine (20 mL), then dried ($MgSO_4$) and concentrated. Flash chromatography (3:97, ether/petrol) afforded the target material as a colourless oil (63 mg, 79%).

R_f 0.74 (10:90, ether/petrol); ν_{max}/cm^{-1} 2957s, 1471s, 1256s, 1104s, 835s; δ_H (400 MHz, $CDCl_3$) 3.70 (2H, t, *J* = 6.0 Hz, H-1), 2.61 – 2.51 (1H, m, H-6), 2.23 (2H, td, *J* =

7.0, 2.0 Hz, H-3), 1.95 – 1.82 (2H, m, H-7a), 1.74 – 1.63 (4H, m, H-2,7b), 1.59 – 1.48 (4H, m, H-8), 0.90 (9H, s, H-11), 0.07 (6H, s, H-9); δ_C (101 MHz, $CDCl_3$) 83.3 (C-5), 79.1 (C-4), 61.9 (C-1), 34.1 (C-7), 32.2 (C-2), 29.9 (C-6), 25.9 (C-11), 24.8 (C-8), 15.3 (C-3), −5.3 (C-9); HRMS (ESI^+), m/z: calcd for $C_{16}H_{30}NaOSi$ [$M+Na^+$] 289.1958, found 289.1935.

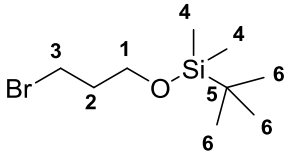
1-Ethynylcyclopentyl acetate (134)[307]



Acetic anhydride (3 mL, ca. 3.2 g, ca. 30 mmol) was added to 1-ethynylcyclopentanol (0.70 g, 6.4 mmol). To this, aq. H_3PO_4 was added dropwise (85%, ca. 7 mg, ca. 0.07 mmol). The mixture was heated with a reflux condenser for 1 hr at 50 °C, then allowed to cool down to RT and stirred overnight (16 hr). The reaction mixture was quenched with ice water (10 mL) and extracted with petrol (3×10 mL). The combined organic layers were washed with cold water (5×6 mL). Flash chromatography (10:90, ether/petrol) afforded the title product as a clear colourless oil. The compound is highly volatile (0.44 g, 53%).

R_f 0.48 (25:75, ether/petrol); ν_{max}/cm^{-1} 3287m (≡C–H), 2116w (C≡C), 1742s (C=O); δ_H (400 MHz, $CDCl_3$) 2.55 (1H, s, H-5), 2.25 – 2.10 (4H, m, H-2), 2.03 (3H, s, H-7), 1.79 – 1.68 (4H, m, H-3); δ_C (101 MHz, $CDCl_3$) 169.8 (C-6), 84.4 (C-4), 80.2 (C-1), 72.9 (C-5), 40.5 (C-2), 23.4 (C-3), 21.8 (C-7).

(3-Bromopropoxy)(tert-butyl)dimethylsilane (135)[308,309]

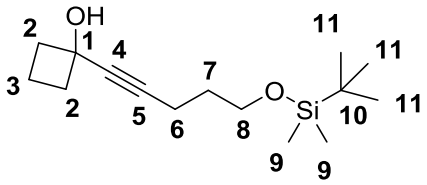


A solution of 3-bromopropanol-1 (1.46 g, 10.5 mmol) and imidazole (1.25 g, 18.4 mmol) in DCM (15 mL) was cooled to 0 °C. TBSCl (1.84 g, 12.6 mmol) was added to

the vigorously stirred mixture. The formation of voluminous white precipitate was observed immediately. The mixture was allowed to warm to RT and stirred for 3 hr. The reaction mixture was diluted with DCM (30 mL) and quenched with brine (20 mL). The aq. layer was extracted with DCM (10 mL). The combined organic layers were passed through a Phase Separator and evaporated to ca. ¼ of the initial volume. This solution was passed through a plug of silica (ca. 2.5 cm) eluting with DCM/petrol (1:1, 60 mL). Evaporation of the solvent yielded the title material as a colourless oil (2.65 g, 100%).

R_f 0.64 (10:90, ether/petrol); δ_H (400 MHz, $CDCl_3$) 3.73 (2H, t, *J* = 6.0 Hz, H-1), 3.51 (2H, t, *J* = 6.5 Hz, H-3), 2.17 – 1.91 (2H, m, H-2), 0.90 (9H, s, H-6), 0.07 (6H, s, H-4); δ_C (101 MHz, $CDCl_3$) 60.6 (C-1), 35.7 (C-2), 30.8 (C-3), 26.1 (C-6), 18.4 (C-5), −5.2 (C-4).

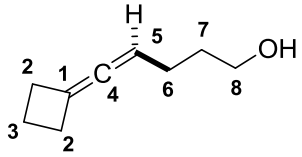
1-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclobutanol (138)



A solution of *O*-TBS-pent-4-yn-1-ol (920 mg, 4.64 mmol) in THF (18 mL) was cooled to 0 °C. To this, *i*-PrMgCl (2 M in THF, 2.3 mL, 4.6 mmol) was added over 2 min. The reaction was allowed to warm to RT and stirred for 2 hr. The mixture was cooled to 0 °C and solution of cyclobutanone (250 mg, 3.57 mmol) in THF (4 mL) was added. The reaction was allowed to warm to RT and stirred for 4 hr. The mixture was diluted with ether (50 mL) and quenched with sat. aq. NH_4Cl (15 mL). The aq. layer was extracted with ether (2×15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography on the crude residue (5:95 → 25:75, ether/petrol) afforded the title compound as a colourless oil (940 mg, 98%) along with some starting material.

R_f 0.30 (25:75, ether/petrol); ν_{max}/cm^{-1} 3348br.s (OH), 2240w (C≡C); δ_H (500 MHz, $CDCl_3$) 3.72 (2H, t, *J* = 6.0 Hz, H-8), 2.43 – 2.36 (2H, m, H-2), 2.33 (2H, t, *J* = 7.0 Hz, H-6), 2.25 (2H, qd, *J* = 9.0, 2.5 Hz, H-2), 2.11 (1H, s, OH), 1.84 – 1.77 (2H, m, H-3), 1.77 – 1.70 (2H, m, H-7), 0.92 (9H, s, H-11), 0.08 (6H, s, H-9) ;δ_C (126 MHz, $CDCl_3$) 84.0 (C-5), 83.7 (C-4), 68.3 (C-1), 61.7 (C-8), 38.9 (C-2), 31.8 (C-7), 26.1 (C-11), 18.5 (C-10), 15.3 (C-6), 13.0 (C-3), −5.2 (C-9); HRMS (ESI^+), m/z: calcd for $C_{15}H_{28}NaO_2Si$ [$M+Na^+$] 291.1751, found 291.1743.

5-Cyclobutylidenepent-4-en-1-ol (141)

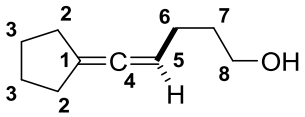


Prepared by a modification of General method H. A stock solution of $LiAlH_4$ (1 M in THF, 8.0 mL, 8.0 mmol) was cooled to 0 °C. To this vigorously stirred solution, concentrated H_2SO_4 (98%, 392 mg, 4.0 mmol) was added dropwise *(caution: intense gas evolution and self-heating; if H_2SO_4 is added too fast, black tar is formed)*. The resulting slurry was allowed to warm to RT and stirred for 1 hr. The mixture was allowed to settle for 30 min. The solids were discarded, while the solution of AlH_3 was transferred into a syringe. In a separate flask, 1-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclobutanol (536 mg, 2.0 mmol) was dissolved in THF (10 mL). To this, the solution of AlH_3 from the first step was added *(caution: moderate gas evolution is possible)* and the resulting mixture was heated at reflux for 1.5 hr. The mixture was cooled to 0 °C and diluted with wet ether (20 mL). Sat. aq. Na_2SO_4 was added dropwise *(caution: intense gas evolution! The rate of addition should be kept at 2-3 drops per minute)* until the gas evolution became moderate. The mixture was allowed to warm to RT and the addition of sat. Na_2SO_4 was continued until no additional white precipitate was formed. The solids were filtered off and thoroughly washed with ether. The

combined solution was dried ($MgSO_4$) and concentrated. Flash chromatography on a short silica column (10:90 → 25:75 → 50:50 → 75:25, ether/petrol) delivered the target material as a colourless volatile oil (178 mg, 72%).

R_f 0.13 (25:75, ether/petrol); ν_{max}/cm^{-1} 3321br.s (OH), 1965w (C=C=C); δ_H (500 MHz, C_6D_6)* 5.20 (1H, app.tquint, *J* = 6.5, 4.0 Hz, H-5), 3.37 (2H, t, *J* = 6.5 Hz, H-8), 3.31 (0.2×2H, t, *J* = 6.5 Hz, H-8_{rot}), 2.78 (4H, app.sept, *J* = 4.0 Hz, H-2), 2.02 (2H, dt, *J* = 7.5, 7.0 Hz, H-6), 1.69 (2H, quint, *J* = 8.0 Hz, H-3), 1.56 – 1.48 (2H, m,H-7), 0.58 (1H, br.s, OH); δ_C (126 MHz, C_6D_6)* 196.3 (C-4), 101.4 (C-1), 93.6 (C-5), 62.4 (C-8), 62.1 (C-8), 32.5 (C-7), 30.3 (C-2), 26.3 (C-6), 17.8 (C-3); HRMS (TOF FI+), m/z: calcd for $C_9H_{14}O$ [M+] 138.1045, found 138.1046.

5-Cyclopentylidenepent-4-en-1-ol (142)[310]

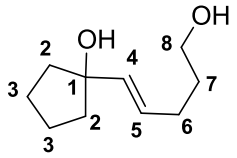


Prepared by General method H from 1-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclopentanol (0.974 g, 3.45 mmol), $LiAlH_4$ (786 mg, 20.7 mmol), and H_2SO_4 (98%, 1.01 g, 10.3 mmol). The target material was purified on a short silica column (1:3 → 1:1, ether/petrol) as a clear colourless oil (160 mg, 30%).

R_f 0.10 (25:75, ether/petrol); ν_{max}/cm^{-1} 3332br.s (OH), 1963w (C=C=C); δ_H (400 MHz, C_6D_6) 5.32 – 5.24 (1H, m, H-5), 3.50 (2H, td, *J* = 6.5, 4.5 Hz, H-8), 2.48 – 2.40 (4H, m, H-2), 2.13 (2H, app. q, *J* = 7.0 Hz, H-6), 1.69 – 1.59 (2H, m, H-7), 1.59 – 1.51 (4H, m, H-3), 0.91 (1H, t, *J* = 7.0 Hz, OH); δ_C (126 MHz, C_6D_6) 197.8 (C-4), 104.1 (C-1), 91.6 (C-5), 62.2 (C-8), 32.6 (C-7), 31.6 (C-2), 27.3 (C-3), 26.1 (C-6); HRMS (TOF FI+), m/z: calcd for $C_{10}H_{16}O$ [M+] 152.1201, found 152.1204.

* Note: two rotamers can be seen in the spectra.

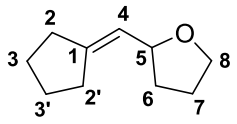
(*E*)-1-(5-Hydroxypent-1-en-1-yl)cyclopentanol (143)



The title compound was obtained as a side product in the synthesis of 5-cyclopentylidenepent-4-en-1-ol by General method H. Flash chromatography of the crude reaction mixture (1:1, ether/petrol) afforded the product as a clear colourless oil (0.14 g, 58%).

R_f 0.17 (1:1, ethyl acetate/petrol); ν_{max}/cm^{-1} 3331br.s (OH), 3033m (=C–H), 1668w (C=C); δ_H (200 MHz, C_6D_6) 5.84–5.59 (2H, m, H-4,5), 3.53 – 3.45 (2H, m, H-8), 2.20 – 2.08 (2H, m, H-6), 2.04 – 1.91 (2H, m, H-2a), 1.73 – 1.56 (m, 8H, H-2b,3,7), 0.68 (1H, t, *J* = 5.5 Hz, OH), 0.56 (1H, s, OH); HRMS (ESI^+), m/z: calcd for $C_{10}H_{18}NaO_2$ [$M+Na^+$] 193.1199, found 193.1192.

2-(cyclopentylidenemethyl)tetrahydrofuran (144)[310]

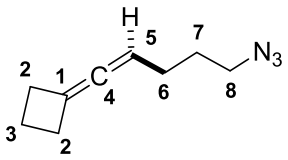


The title material was obtained as an undesired side-product when allene alcohol **143** was subjected to flash chromatography on silica (1:1, DCM/petrol). The compound is a clear colourless oil (0.17 g, 40%).

R_f 0.64 (50:50, ethyl acetate/petrol); ν_{max}/cm^{-1} 1681w (C=C), 1432s, 1371s, 1052s; δ_H (400 MHz, C_6D_6) 5.65 – 5.60 (1H, m, H-4), 4.53 (1H, td, *J* = 8.0, 6.5 Hz, H-5), 3.92 (1H, app. td, *J* = 8.0, 6.0 Hz, H-8a), 3.73 (1H, app. td, *J* = 8.0, 6.0 Hz, H-8b), 2.44 – 2.13 (4H, m, H-2,2'), 1.98 – 1.85 (1H, m, H-6a), 1.75 – 1.44 (m, 7H, H-6b,3,3',7); δ_C (101 MHz, C_6D_6) 145.3 (C-1), 122.9 (C-4), 77.7 (C-5), 67.6 (C-8), 34.0 (C-2), 32.7 (C-6), 29.0

(C-2'), 26.7 (C-3), 26.4 (C-3'), 26.4 (C-7); HRMS (ESI$^+$), m/z: calcd for $C_{10}H_{16}NaO$ [M+Na$^+$] 175.1093, found 175.1098.

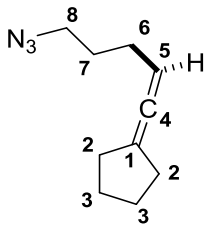
(5-Azidopent-1-en-1-ylidene)cyclobutane (145)



Prepared by General method E from 5-cyclobutylidenepent-4-en-1-ol (150 mg, 1.08 mmol), PPh_3 (635 mg, 2.42 mmol), CBr_4 (802 mg, 2.42 mmol), and NaN_3 (195 mg, 3.7 mmol). Flash chromatography (petrol → 1:99 → 3:97, ether/petrol) afforded the title compound as a colourless oil (107 mg, 60%).

R_f 0.58 (5:95, ether/petrol); ν_{max}/cm^{-1} 2095s (N_3), 1964w (C=C=C); δ_H (500 MHz, $CDCl_3$) 5.14 – 5.08 (1H, m, H-5), 3.30 (2H, t, *J* = 7.0 Hz, H-8), 2.92 – 2.79 (4H, m, H-2), 2.07 (2H, app.q, *J* = 7.0 Hz, H-6), 1.99 – 1.89 (2H, m, H-3), 1.71 (2H, quint, *J* = 7.0 Hz, H-7); δ_C (126 MHz, $CDCl_3$) 195.6 (C-4), 101.9 (C-1), 92.0 (C-5), 50.7 (C-8), 29.9 (C-2), 28.0 (C-6), 26.4 (C-7), 17.4 (C-3); HRMS (TOF, FI$^+$), m/z: calcd for $C_9H_{13}N_3$ [M$^+$] 163.1109, found 163.1106.

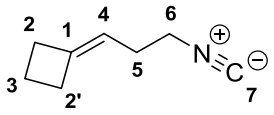
(5-Azidopent-1-en-1-ylidene)cyclopentane (146)



Prepared by General method D from 5-cyclopentylidenepent-4-en-1-ol (50 mg, 0.33 mmol), PPh_3 (215 mg, 0.82 mmol), CBr_4 (271mg, 0.82 mmol), and NaN_3 (64 mg, 1.0 mmol). Flash chromatography (1:100, ether/petrol) afforded the title compound as a colourless oil (42 mg, 74%).

R_f 0.60 (1:99, ether/petrol); ν_{max}/cm^{-1} 2095s (N_3), 1960w (C=C=C); δ_H (400 MHz, $CDCl_3$) 5.15 – 4.94 (1H, m, H-5), 3.31 (2H, t, *J* = 7.0 Hz, H-8), 2.33 (4H, m, H-6,2a), 2.06 (2H, m, H-2b), 1.82 – 1.58 (6H, m, H-3,7); δ_C (126 MHz, $CDCl_3$) 197.4 (C-4), 104.7 (C-1), 90.1 (C-5), 50.9 (C-8), 31.4 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 26.4 (CH_2); HRMS (FI^+), m/z: calcd for $C_{10}H_{15}N_3$ [M^+] 177.1266, found 177.1269.

(3-Isocyanopropylidene)cyclobutane (147a)



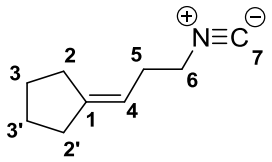
Method 1. Solution of the starting allene azide (5 mg) in C_6D_6 (0.6 mL) was placed into a dry NMR vial, thoroughly flushed with argon, and sealed. The vial was heated in an oil bath (83 °C) until all starting material was consumed (TLC and ^1H NMR monitoring). The average reaction time was 22 hr. The crude solution *(warning: disagreeable odour)* was loaded directly onto a pipette silica column (1:20, ether/petrol) to afford the title material a clear colourless oil with a disagreeable odour (2.4 mg, 58%).

R_f 0.33 (10:90, ether/petrol); ν_{max}/cm^{-1} 3096m (=C–H), 2147s (NC); δ_H (500 MHz, $CDCl_3$) 5.07 (1H, app. ddq, *J* = 9.5, 7.0, 2.5 Hz, H-4), 3.35 (2H, tt, *J* = 7.0, 1.5 Hz, H-6), 2.68 (4H, app. tdt, *J* = 8.0, 2.5, 1.5 Hz, H-2,2'), 2.30 – 2.23 (2H, m, H-5), 1.97 (2H, app. quint, *J* = 8.0 Hz, H-3); δ_C (126 MHz, $CDCl_3$) 155.8 (t, *J* = 5.7 Hz, C-7), 145.0 (C-1), 114.4 (C-4), 41.7 (t, *J* = 6.6 Hz, C-6), 31.1 (C-2), 29.4 (C-2'), 28.3 (C-5), 17.0 (C-3); HRMS (TOF FI^+), m/z: calcd for $C_8H_{10}N$ [M^+] 120.0813, found 120.0808.

Method 2. General method F. The starting azide (27 mg, 0.18 mmol) was dissolved in MeCN (2.0 mL), sealed in a microwave tube, and stirred at 130 °C under microwave irradiation for 60 min. The volatiles were removed in vacuo and the crude product was purified on a flash column (7:93, ether/petrol) to give the target

compound as a yellow oil. The material was chromatographically and spectroscopically identical with that obtained by Method H (17 mg, 74%).

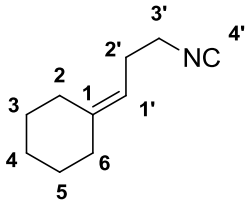
(3-Isocyanopropylidene)cyclopentane (147b)



Prepared by General method F from (4-azidobut-1-en-1-ylidene)cyclopentane (115 mg, 0.70 mmol) in MeCN (3 mL). The volatiles were removed in vacuo (RT, 80 Torr) and the crude residue (*note: disagreeable odour)* was purified on a flash column (5:95, ether/petrol) to afford the title compound as a colourless oil with a disagreeable odour (38 mg, 40%).

R_f 0.61 (5:95, ether/petrol); ν_{max}/cm^{-1} 3040w (=C−H), 2145s (NC); δ_H (400 MHz, C_6D_6) 5.10 – 5.01 (1H, m, H-4), 2.66 (2H, tt, *J* = 7.0, 2.0 Hz, H-6), 2.18 (2H, app. t, *J* = 6.5 Hz, H-2'), 2.01 (2H, app. t, *J* = 6.5 Hz, H-2), 1.91 (2H, br. q, *J* = 7.0 Hz, H-5), 1.60 – 1.47 (4H, m, H-3,3'); δ_H (500 MHz, $CDCl_3$) 5.28 – 5.22 (1H, m, H-4), 3.37 (2H, tt, *J* = 7.0, 2.0 Hz, H-6), 2.43 – 2.32 (2H, m, H-5), 2.31 – 2.25 (2H, m, H-2/2'), 2.25 – 2.20 (2H, m, H-2/2'), 1.73 – 1.59 (4H, m, H-3,3'); δ_C (101 MHz, C_6D_6) 147.2 (m, C-7), 127.9 (C-1), 114.7 (C-4), 41.0 (t, J = 6.5 Hz, C-6), 33.8 (C-2'), 29.8 (C-5), 28.8 (C-2), 26.6 (C-3'), 26.5 (C-3); δ_C (126 MHz, $CDCl_3$) 155.5 (t, *J* = 6.0 Hz, C-7), 147.9 (C-1), 113.9 (C-4), 41.46 (t, *J* = 6.5 Hz, C-6), 33.7 (C-2'), 29.7 (C-5), 28.8 (C-2), 26.3 (C-3'), 26.2 (C-3); HRMS (TOF FI^+), m/z: calcd for $C_9H_{13}N$ [M^+] 135.1048, found 135.1053.

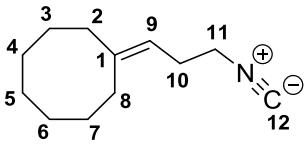
(3-Isocyanopropylidene)cyclohexane (147c)[311]



Prepared by General method G by heating (4-azidobut-1-en-1-ylidene)cyclohexane (29 mg, 0.16 mmol) in *m*-xylene (0.6 mL) at 135 °C for 1.5 hr. Flash chromatography (petrol → 10:90, ether/petrol → ether) afforded the title compound as a colourless oil with a disagreeable odour (14 mg, 58%).

R_f 0.50 (10:90, ether/petrol); ν_{max}/cm^{-1} 3054w (=C–H), 2145s (NC); δ_H (500 MHz, $CDCl_3$) 5.07 (1H, tquint, *J* = 7.5, 1.5 Hz, H-1'), 3.35 (2H, tt, *J* = 7.0, 2.0 Hz, H-3'), 2.44 – 2.34 (2H, m, H-2'), 2.19 – 2.05 (4H, m, H-2,6), 1.61 – 1.48 (6H, m, H-3,4,5); δ_C (126 MHz, $CDCl_3$) 155.6 (t, *J* = 6.0 Hz, C-4'), 144.2 (C-1), 115.1 (C-1'), 41.9 (t, *J* = 6.5 Hz, C-3'), 37.1 (C-6), 28.8 (CH_2), 28.5 (CH_2), 27.9 (CH_2), 27.3 (CH_2), 26.7 (CH_2).

(3-Isocyanopropylidene)cyclooctane (147d)

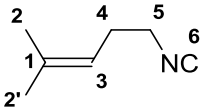


Prepared by General method G from (4-azidobut-1-en-1-ylidene)cyclooctane (25 mg, 0.12 mmol). The target material, a yellow oil with a disagreeable odour, was purified by flash chromatography (1:20, ether/petrol) (7 mg, 32%).

R_f 0.37 (10:90, ether/petrol); ν_{max}/cm^{-1} 2145m (NC); δ_H (500 MHz, $CDCl_3$) 5.16 (1H, app.t, *J* = 7.0 Hz, H-9), 3.38 (2H, tt, *J* = 7.0, 2.0 Hz, H-11), 2.42 (2H, br. app. q, *J* = 7.0 Hz, H-10), 2.24 – 2.16 (4H, m, H-2,8), 1.68 – 1.59 (4H, m, 2×CH_2), 1.54 – 1.46 (6H, m, 3×CH_2); δ_C (126 MHz, $CDCl_3$) 155.7 (t, *J* = 6.0 Hz, C-12), 145.7 (C-1), 119.0 (C-9), 41.5 (t, *J* = 6.5 Hz, C-11), 37.5 (C-2), 29.2 (CH_2), 28.0 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.23 (CH_2),

26.20 (CH_2), 26.0 (C-5); HRMS (TOF FI$^+$): m/z: calcd for $C_{12}H_{19}N$ [M$^+$] 177.1517, found 177.1519.

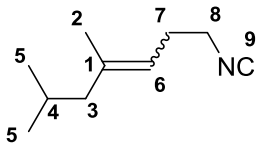
5-Isocyano-2-methylpent-2-ene (147e)



Prepared by General method G from 6-azido-2-methylhexa-2,3-diene (10 mg, 0.07 mmol). The target material was purified on a pipette silica column (5:95, ether/petrol). The compound is extremely volatile (evaporates at atmospheric pressure from an open vial). It has a very disagreeable odour (2 mg, 25%).

R_f 0.28 (10:90, ether/petrol); ν_{max}/cm^{-1} 2147s (NC); δ_H (500 MHz, $CDCl_3$) 5.16 – 5.10 (1H, m, H-3), 3.36 (2H, tt, *J* = 7.0, 2.0 Hz, H-5), 2.45 – 2.35 (2H, m, H-4), 1.74 (3H, s, H-2'), 1.66 (3H, s, H-2); δ_C (126 MHz, $CDCl_3$) 155.6 (t, *J* = 6.0 Hz, C-6), 136.1 (C-1), 118.5 (C-3), 41.5 (t, *J* = 6.5 Hz, C-5), 28.2 (C-4), 25.7 (C-2'), 17.9 (C-2); HRMS (TOF FI$^+$), m/z: calcd for $C_7H_{11}N$ [M$^+$] 109.0891, found 109.0889.

***EZ*-1-Isocyano-4,6-dimethylhept-3-ene (147f)**



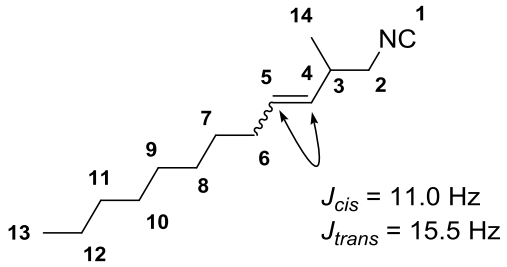
E/*Z* = 1:1

Prepared by General method G from 1-azido-5,6-dimethylhepta-3,4-diene (20 mg, 0.11 mmol). Flash chromatography (petrol → 5:95, ether/petrol) afforded the title compound as an inseparable mixture of alkene stereoisomers (*E*/*Z* = 1:1) as a clear colourless oil (7 mg, 41%).

R_f 0.30 (10:90, ether/petrol); ν_{max}/cm^{-1} 2146m (NC); δ_H (500 MHz, C_6D_6) 5.00 (1H, t, *J* = 7.0 Hz, H-6Z), 4.93 (1H, app. tq, *J* = 7.5, 1.5 Hz, H-6E), 2.66 (2H, tt, *J* = 7.0, 2.0 Hz, H-8E/8Z), 2.62 (2H, tt, *J* = 7.0, 1.5 Hz, H-8E/8Z), 1.97 (2H, br. q, *J* = 7.0 Hz, H-7Z),

1.91 (2H, br. q, *J* = 7.5 Hz, H-7E), 1.86 (2H, d, *J* = 7.5 Hz, H-3E), 1.80 (2H, d, *J* = 7.5 Hz, H-3Z), 1.76 – 1.65 (2H, m, H-4E,4Z), 1.63 (3H, d, *J* = 1.0 Hz, H-2Z), 1.46 (3H, s, H-3E), 0.94 (6H, d, *J* = 6.5 Hz, H-5E/5Z), 0.88 (6H, d, *J* = 6.5 Hz, H-5E/5Z); δ_C (126 MHz, C_6D_6) 159.6 (t, *J* = 5.0 Hz, C-9E/9Z), 159.5 (t, *J* = 5.0 Hz, C-9E/9Z), 138.4 (C-1E/1Z), 138.4 (C-1E/1Z), 120.7 (C-6Z), 120.3 (C-6E), 49.6 (C-3E), 41.2 (C-3Z), 41.0 (2×t, *J* = 6.5 Hz, C-8EZ), 28.12 (C-7E/7Z), 28.11 (C-7E/7Z), 26.6 (C-4E/4Z), 26.1 (C-4E/4Z), 23.7 (C-2Z), 22.49 (C-5E/5Z), 22.46 (C-5E/5Z), 15.9 (C-2E); HRMS (TOF FI$^+$), m/z: calcd for $C_{10}H_{17}N$ [M^+] 151.1361, found 151.1362.

1-isocyano-2-methyldodec-3-ene (147g)



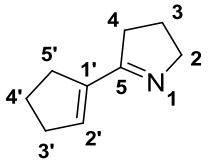
E/*Z* = 3:1

A solution of 1-azido-2-methyltrideca-3,4-diene (40 mg, 0.17 mmol) was dissolved in toluene (3.0 mL) and placed into a dry pressure tube (inner volume 10 mL) with a small stirbar. The tube was thoroughly flushed with argon and immersed into an oil bath (110 °C) so that the solvent level was lower than that of oil. The reaction was heated for 2.5 hr, until TLC showed complete consumption of the starting material. The contents was loaded directly onto a silica column and eluted with the following gradient: petrol → 5:95, ether/petrol. The product was isolated as a clear colourless oil with a weak disagreeable odour (11 mg, 31%).

R_f 0.49 (25:75, ether/petrol); ν_{max}/cm^{-1} 2146s (NC); δ_H (500 MHz, $CDCl_3$) 5.59 – 5.46 (1H, m, H-5), 5.30 (0.75×1H, ddt, *J* = 15.5, 7.5, 1.5 Hz, H-4E), 5.16 (0.25×1H, ddt, *J* = 11.0, 10.0, 1.5 Hz, H-4Z), 3.33 – 3.20 (2H, m, H-2), 2.89 – 2.79 (0.25×1H, m, H-3Z), 2.52 – 2.41 (0.75×1H, m, H-3E), 2.08 – 1.97 (2H, m, H-6), 1.40 – 1.20 (12H, m, H-

7,8,9,10,11,12), 1.11 (0.75×3H, d, *J* = 7.0 Hz, H-14E), 1.09 (0.25×3H, d, *J* = 7.0 Hz, H-14Z), 0.88 (3H, t, *J* = 7.0 Hz, H-13); δ_C (126 MHz, $CDCl_3$) 156.1 (t, *J* = 6.0 Hz, C-1Z), 156.0 (t, *J* = 6.0 Hz, C-1E), 132.6 (C-5E), 132.5 (C-5Z), 130.1 (C-4E), 129.8 (C-4Z), 47.8 (t, *J* = 6.0 Hz, C-2E), 47.6 (t, *J* = 6.0 Hz, C-2Z), 36.4 (C-3E), 32.5 (CH_2), 31.9 (CH_2), 31.7 (C-3Z), 29.6 (CH_2), 29.43 (CH_2), 29.40 (CH_2), 29.26 (CH_2), 29.25 (CH_2), 29.1 (CH_2), 27.6 (C-6Z), 22.6 (CH_2), 18.2 (C-14Z), 17.6 (C-14E), 14.1 (C-13EZ); HRMS (ESI^+), m/z: calcd for $C_{14}H_{25}NNa$ [$M+Na^+$] 230.1879, found 230. 1885.

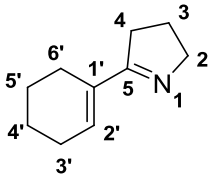
5-(Cyclopent-1-en-1-yl)-3,4-dihydro-2*H*-pyrrole (157b)



Prepared by General method G by heating (4-azidobut-1-en-1-ylidene)cyclopentane (30 mg, 0.17 mmol) in *m*-xylene (0.6 mL) at 135 °C for 1.5 hr. Flash chromatography (petrol → 10:90 → 25:75, ether/petrol → ether) afforded the title compound as a yellow oil (10 mg, 40%). The compound was too unstable to obtain reasonable NMR spectra.

R_f 0.07 (10:90, ether/petrol); ν_{max}/cm^{-1} 1638m (C=N), 1591w (C=N); HRMS (ESI^+), m/z: calcd for $C_9H_{14}N$ [$M+H^+$] 136.1121, found 136.1117.

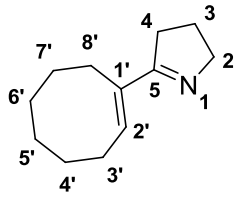
5-(cyclohex-1-en-1-yl)-3,4-dihydro-2*H*-pyrrole (157c)[312,313]



Prepared by General method G by heating (4-azidobut-1-en-1-ylidene)cyclohexane (29 mg, 0.16 mmol) in *m*-xylene (0.6 mL) at 135 °C for 1.5 hr. Flash chromatography (petrol → 10:90, ether/petrol → ether) afforded the title compound as a colourless oil with an earthy odour (3 mg, 10%).

R_f 0.03 (10:90, ether/petrol); ν_{max}/cm^{-1} 1637m (C=N), 1596m (C=N); δ_H (500 MHz, $CDCl_3$) 6.29 – 6.25 (1H, m, H-2'), 3.93 (2H, t, *J* = 7.0 Hz, H-2), 2.69 – 2.63 (2H, m, H-4), 2.43 – 2.37 (2H, m, H-3'/6'), 2.24 – 2.18 (2H, m, H-6'/3'), 1.92 – 1.84 (2H, m, H-3), 1.71 – 1.60 (4H, m, H-4',5'); δ_C (126 MHz, $CDCl_3$) 175.0 (C-5), 134.9 (C-1'), 134.4 (C-2'), 61.1 (C-2), 33.7 (C-4), 25.9 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.1 (CH_2); MS (ESI^+), m/z: 150 ($M+H^+$), 299 ($2M+H^+$).

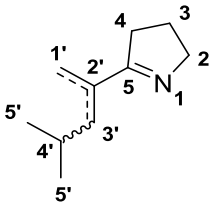
(*E*)-5-(cyclooct-1-en-1-yl)-3,4-dihydro-2*H*-pyrrole (157d)



Prepared by General method G by heating (4-azidobut-1-en-1-ylidene)cyclooctane (28 mg, 0.14 mmol) in *m*-xylene (0.6 mL) at 135 °C for 1.5 hr. Flash chromatography (petrol → 10:90 → 25:75, ether/petrol → ether) afforded the title compound as a colourless oil with an earthy odour (9 mg, 39%).

R_f 0.08 (10:90, ether/petrol); ν_{max}/cm^{-1} 1635m (C=N), 1592m (C=N); δ_H (500 MHz, $CDCl_3$) 6.21 (1H, t, *J* = 8.5 Hz, H-2'), 3.95 (2H, t, *J* = 7.5 Hz, H-2), 2.70 – 2.65 (2H, m, H-4), 2.65 – 2.61 (2H, m, H-8), 2.34 – 2.27 (2H, m, H-3'), 1.90 (2H, quint, *J* = 7.5 Hz, H-3), 1.63 – 1.55 (4H, m, ½×H H-4',5',6',7'), 1.52 – 1.42 (4H, m, ½×H-4',5',6',7'); δ_C (126 MHz, $CDCl_3$) 174.5 (C-5), 138.4 (C-1'), 136.9 (C-2'), 61.2 (C-2), 33.8 (C-4), 29.7 (CH_2), 29.1 (CH_2), 27.2 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 25.3 (CH_2), 22.7 (C-3); HRMS (ESI^+), m/z: calcd for $C_{12}H_{20}N$ [$M+H^+$] 178.1590, found 178.1586.

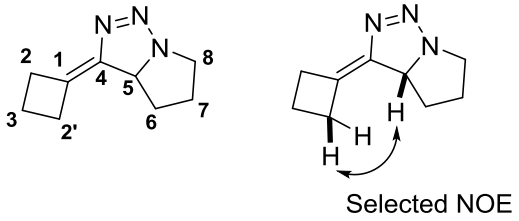
EZ-5-(4-methylpent-2-en-2-yl)-3,4-dihydro-2*H*-pyrrole (157f)



Prepared as an inseparable 1:1 mixture of unstable *E*- and *Z*-isomers by General method G by heating 1-azido-5,7-dimethylocta-3,4-diene (28 mg, 0.16 mmol) in *m*-xylene (0.6 mL) at 135 °C for 1.5 hr. Flash chromatography (petrol → 10:90 → 25:75, ether/petrol → ether) afforded the title compound as a clear yellowish oil with an unpleasant odour (6 mg, 25%). The compound was too unstable to obtain reasonable NMR spectra.

R_f 0.06 (10:90, ether/petrol); ν_{max}/cm^{-1} 1638m (C=N), 1595m (C=N); HRMS (TOF ESI$^+$), m/z: calcd for $C_{10}H_{18}N$ [M+H$^+$] 152.1434, found 152.1432.

3-Cyclobutylidene-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-c][1,2,3]triazole (163)

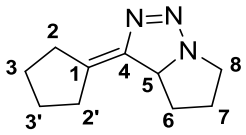


Prepared by a modification of General method G by heating 5-azidopent-1-en-1-ylidene)cyclobutane (12 mg, 0.06 mmol) in C_6D_6 (0.6 mL) for 7 hr. A pipette silica column (petrol → 10:90 → 50:50, ether/petrol) afforded the target material as a colourless oil that solidified in freezer (7 mg, 58%).

R_f 0.21 (25:75, ether/petrol); mp 24–25 °C; ν_{max}/cm^{-1} 2954s, 1421s, 1024s, 959s, 950s; δ_H (500 MHz, C_6D_6) 3.95 – 3.86 (1H, m, H-8a), 3.74 – 3.65 (1H, m, H-5), 3.13 – 2.93 (2H, m, H-2), 2.88 (1H, ddd, *J* = 12.0, 9.5, 6.0 Hz, H-8b), 2.51 – 2.36 (1H, m, H-2'a), 2.36 – 2.20 (1H, m, H-2'b), 1.81 – 1.68 (2H, m, H-3), 1.38 – 1.29 (1H, m, H-6a), 1.14 –

1.06 (2H, m, H-6b,7a), 1.04 – 0.97 (1H, m, H-7b); δ_C (126 MHz, C_6D_6) 153.2 (C-4), 136.1 (C-1), 59.0 (C-5), 50.9 (C-8), 31.4 (C-6), 30.5 (C-2/2'), 29.1 (C-2/2'), 24.4 (C-7), 18.3 (C-3); HRMS (TOF, FI^+), m/z: calcd for $C_9H_{13}N_3$ [M^+] 163.1109, found 163.1113.

3-Cyclopentylidene-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-c][1,2,3]triazole (165)

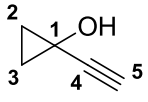


65%

(5-Azidopent-1-en-1-ylidene)cyclopentane (18 mg, 0.1 mmol) was dissolved in C_6D_6 (0.7 mL) and sealed in a dry NMR tube. The tube was immersed into an oil bath (83 °C), so that ca. 1 mm of the solution was above the oil level. The reaction was monitored by ^1H NMR spectroscopy until most of the starting material was consumed (total reaction time 20 hr). The solution was loaded directly onto a silica column (25:75, ether/petrol) and the target material was isolated as a colourless oil (12 mg, 65%).

R_f 0.25 (25:75, ether/petrol); ν_{max}/cm^{-1} 2958, 1425m, 1260s, 1124s, 1105s; δ_H (500 MHz, $CDCl_3$) 4.14 – 4.03 (2H, m, H-5,8a), 3.31 (1H, ddd, *J* = 12.0, 9.5, 6.5 Hz, H-8b), 2.85 – 2.72 (2H, m, H-2/2'), 2.40 – 2.23 (2H, m, H-2/2'), 2.07 – 1.93 (1H, m, H-6a), 1.87 – 1.70 (5H, m, H-3,3',7a), 1.37 – 1.24 (2H, m, H-6b,7b); δ_H (500 MHz, C_6D_6) 4.09 – 4.03 (1H, m, H-8a), 3.88 – 3.78 (1H, m, H-5), 3.04 (1H, ddd, *J* = 12.0, 9.5, 6.0 Hz, H-8b), 3.00 – 2.86 (2H, m, H-2/2'), 2.12 – 2.03 (½×2H, m, H-2/2'), 2.00 – 1.90 (½×2H, m, H-2/2'), 1.61 – 1.46 (5H, m, H-6a,3,3'), 1.29 – 1.11 (3H, m, H-7a,6b,7b); δ_C (126 MHz, $CDCl_3$) 151.6 (C-4), 139.2 (C-1), 60.3 (C-5), 51.2 (C-8), 31.2 (C-2'), 31.0 (C-2/2'), 30.8 (C-6), 26.5 (C-3'), 26.3 (C-3), 24.5 (C-7); δ_C (126 MHz, C_6D_6) 152.9 (C-4), 137.8 (C-1), 60.4 (C-5), 51.1 (C-8), 31.3 (C-2'), 31.0 (C-2), 30.8 (C-6), 26.7 (C-3'), 26.5 (C-3), 24.6 (C-7); HRMS (ESI^+), m/z: calcd for $C_{10}H_{15}N_3$ [$M+Na^+$] 200.1158, found 200.1158.

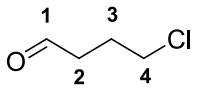
1-ethynylcyclopropanol (166)[314]



1-Ethoxycyclopropanol (86 mg, 1.0 mmol) was added to a stock solution of HC≡CMgBr (4.0 mL in THF, 0.5 M, 2.0 mmol). The mixture was stirred at reflux for 3 hr. The reaction mixture was cooled to RT and diluted with ether (6 mL), then quenched with sat. aq. NH_4Cl (4 mL). The aq. layer was extracted with ether (2×5 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (10:90 → 25:75, ether/petrol) afforded the target material as a colourless oil (52 mg, 75%).

R_f 0.49 (50:50, ether/petrol); ν_{max}/cm^{-1} 3300br.s (OH), 3288s (≡C–H), 2110w (C≡C).

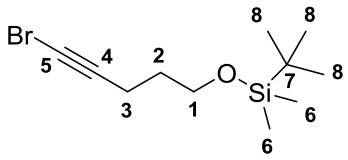
4-Chlorobutanal (169)[192]



4-Chlorobutanol (85%, 6.35 g, 50 mmol) was added to a rapidly stirred mixture of DCM (150 mL), water (150 mL), $NaHCO_3$ (7.5 g, 90 mmol), KBr (0.60 g, 5.0 mmol), and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO, 78 mg, 0.5 mmol) at 0 °C. Commercial bleach (approx. 6 wt%, 46 mL) was added dropwise. The reaction was stirred vigorously at 0 °C for 25 min, after which TLC analysis showed complete consumption of the starting material. The layers were separated. The aq. layer was extracted with DCM (3×50 mL). The combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), then dried over $MgSO_4$ and evaporated (25 °C, 300 → 240 Torr). The crude residue was purified by Kugelrohr distillation (80 → 110 °C, 30 Torr) to afford the title material as a colourless oil (3.44 g, 65%).

R_f 0.39 (50:50, ether/petrol); ν_{max}/cm^{-1} 2720m ($C_{aldehyde}$–H), 1721s (C=O); δ_H (400 MHz, $CDCl_3$) 11.32 (s, 0.02×2H, $OH_{gem\text{-}diol}$), 9.83 (1H, t, *J* = 1.0 Hz, H-1), 3.61 (2H, t, *J* = 6.5 Hz, H-4), 2.69 (2H, td, *J* = 7.0, 1.0 Hz, H-2), 2.11 (2H, tt, *J* = 7.0, 6.5 Hz, H-3); δ_C (101 MHz, $CDCl_3$) 200.9 (C-1), 44.1 (C-4), 40.9 (C-2), 24.8 (C-3).

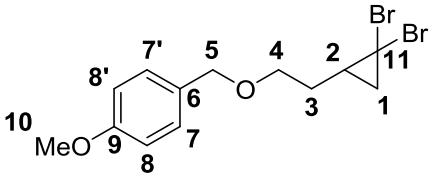
((5-Bromopent-4-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (175)[315]



The following reagents were dissolved in DCM (20 mL) under stirring in the following order: 5-bromopent-4-yn-1-ol (420 mg, 2.58 mmol), imidazole (350 mg, 5.16 mmol), and TBSCl (97%, 440 mg, 2.83 mmol). The mixture immediately turned cloudy white. The reaction was stirred at RT for 4 hr. The mixture was filtered through a silica plug (2 cm), eluting with DCM (50 mL). Evaporation of the volatiles afforded the target material as a colourless oil that was used without further purification (0.70 g, 98%).

R_f 0.67 (25:75, ether/petrol); ν_{max}/cm^{-1} 1104s, 834s; δ_H (400 MHz, $CDCl_3$) 3.69 (2H, t, *J* = 6.0 Hz, H-1), 2.31 (2H, t, *J* = 7.0 Hz, H-3), 1.72 (2H, tt, *J* = 7.0, 6.0 Hz, H-2), 0.90 (9H, s, H-8), 0.06 (6H, s, H-6); δ_C (101 MHz, $CDCl_3$) 80.0 (C-5), 61.4 (C-1), 37.7 (C-4), 31.3 (C-2), 25.9 (C-8), 18.3 (C-7), 16.1 (C-3), −5.4 (C-6).

1-((2-(2,2-Dibromocyclopropyl)ethoxy)methyl)-4-methoxybenzene (179)

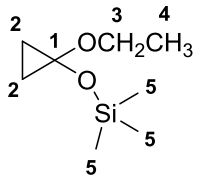


Ethanol-free $CHBr_3$ (2.27 g, 9.0 mmol; purified by washing with water four times, then dried over $MgSO_4$), 1-((but-3-en-1-yloxy)methyl)-4-methoxybenzene (534 mg, 3.0 mmol), and benzyltriethylammonium chloride (TEBA, 30 mg) were put into the flask and stirred vigorously. To this mixture was added dropwise aq. NaOH (0.48 g

NaOH in 0.6 mL H_2O). The resulting brown mixture was stirred at RT for 40 hr. The brown slurry was diluted with DCM (6 mL) and water (2 mL). The organic layer was washed sequentially with aq. HCl (1 M, 2 mL) and aq. K_2CO_3 (2 M, 1 mL), then filtered through a phase separator. The target compound was purified by flash chromatography (10:90, ether/petrol) as a colourless oil (65 mg, 6%; b.r.s.m. 10%).

R_f 0.20 (10:90, ether/petrol); ν_{max}/cm^{-1} 3060w, 2951m, 2856m, 1611s, 1511s, 1245s, 1097s, 1033s, 755s; δ_H (500 MHz, $CDCl_3$) 7.31 – 7.26 (2H, m, H-7,7'), 6.92 – 6.86 (2H, m, H-8,8'), 4.49 (2H, s, H-5), 3.81 (3H, s, H-10), 3.61 (2H, td, *J* = 6.0, 2.0 Hz, H-4), 1.99 – 1.89 (1H, m, H-3a), 1.80 – 1.69 (3H, m, H-1a,2,3b), 1.27 – 1.23 (1H, m, H-1b); δ_C (126 MHz, $CDCl_3$) 159.2 (C-9), 130.4 (C-6), 129.3 (C-7,7'), 113.8 (C-8,8'), 72.7 (C-5), 68.2 (C-4), 55.3 (C-10), 32.9 (C-3), 28.8 (C-11), 28.6 (C-1or2) , 28.3 (C-2or1); HRMS (ESI^+), m/z: calcd for $C_{13}H_{16}Br_2O_2$ [M+Na^+] 384.9409, found 384.9396.

_O_-TMS-1-ethoxycyclopropanol (182)[189]

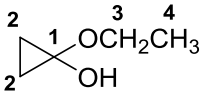


Preparation of sodium sand. A three-neck 100 mL flask with a reflux condenser was charged with toluene (50 mL) and sodium (5.3 g, 0.23 mol). The mixture was stirred vigorously at reflux for 4 hr. Stirring was stopped and the mixture was allowed to cool to RT. Toluene was removed using a cannula under the positive pressure of Ar. The sodium beads were carefully washed with ether (3×5 mL). *Reaction*. Ether (50 mL) was added to the sodium sand, followed by TMSCl (10.9 g, 0.10 mmol). Ethyl chloropropanoate (13.7 g, 0.10 mol) was added with a syringe over 0.5 hr. Deep blue colouration of sodium beads was observed. The reaction mixture was stirred at reflux overnight (14 hr). Solids were removed by careful filtration under a blanket of Ar and

washed with ether four times. Ether was then removed by distillation at normal pressure, and the residue was fractionally distilled under reduced pressure. The fraction boiling at 36–40 °C (10–13 Torr) was identified as the desired product, a colourless oil (4.35 g, 25%).

R_f 0.69 (50:50, ether/petrol); ν_{max}/cm^{-1} 2976m, 839s; δ_H (400 MHz, C_6D_6) 3.73 (2H, q, *J* = 7.0 Hz, H-3), 1.19 (3H, t, *J* = 7.0 Hz, H-4), 1.01 – 0.96 (2H, m, H-2), 0.96 – 0.91 (2H, m, H-2), 0.33 (9H, s, H-5); δ_C (101 MHz, C_6D_6) 86.65 (C-1), 61.67 (C-3), 15.39 (C-4), 14.08 (C-2), 0.78 (C-5).

1-ethoxycyclopropanol (183)[189]

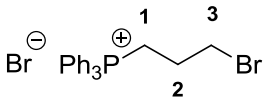


Method A. *O*-TMS-1-ethoxycyclopropanol (200 mg, 1.15 mmol) was dissolved in MeOH (1.8 mL) with a catalytic amount of aq. HCl (1 M, 1 drop) and the resulting solution was stirred at RT for 9 hr. The volatiles were then removed by slow evaporation (80 Torr, RT, 14 hr) and the residue was distilled in Kugelrohr (20 Torr, 100 °C). The product is a colourless oil (36 mg, 36%).

Method B. *O*-TMS-1-ethoxycyclopropanol (200 mg, 1.15 mmol) was dissolved in THF (8 mL). Two drops of aq. HCl (1M) was added and the resulting solution was stirred at RT for 2 hr (TLC monitoring). The volatiles were then removed under reduced pressure (80 → 20 Torr, RT, 30 min). The residue was spectroscopically identical with the material prepared by Method A (100 mg, 100%).

R_f 0.28 (50:50, ether/petrol); δ_H (500 MHz, C_6D_6) 3.73 (2H, q, *J* = 7.0 Hz, H-3), 1.22 (3H, t, *J* = 7.0 Hz, H-4), 1.09 – 0.85 (5H, m, H-2,OH); δ_C (126 MHz, C_6D_6) 85.6 (C-1), 61.8 (C-3), 15.7 (C-4), 14.5 (C-2).

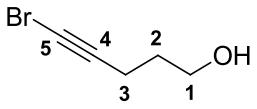
(3-Bromopropyl)triphenylphosphonium bromide (186)[193]



PPh_3 (5.0 g, 19 mmol) was added to a solution of 1,3-dibromopropane (9.6 mL, 95 mmol) in toluene (10 mL). The flask was equipped with a reflux condenser and the resulting mixture was stirred at 70 °C for 15 hr. The reaction was cooled to 0 °C and diluted with ether (50 mL). White precipitate of the product was filtered off, washed with cold ether (40 mL), and dried in vacuo (6 Torr) (6.31 g, 72%).

M.p.: 220–222 °C (lit. 217 °C,[316] 228–230 °C[317]); δ_H (400 MHz, $CDCl_3$) 7.92 – 7.76 (9H, m, H-Ph), 7.76 – 7.65 (6H, m, H-Ph), 4.20 – 4.05 (2H, m, H-1), 3.86 (t2H,, *J* = 6.1 Hz, H-3), 2.30 – 2.18 (2H, m, H-2); δ_C (101 MHz, $CDCl_3$) 135.2 (C-Ph), 133.7 (d, *J* = 10.0 Hz, C-Ph), 130.6 (d, *J* = 12.5 Hz, C-Ph), 117.9 (d, *J* = 86.5 Hz, C-Ph), 33.5 (C-3), 26.3 (d, *J* = 2.5 Hz, C-2), 21.6 (d, *J* = 52.5 Hz, C-1); δ_P (162 MHz, $CDCl_3$) 24.3 (s).

5-Bromopent-4-yn-1-ol (189)[318]

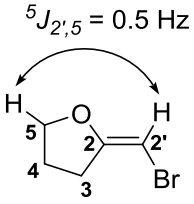


KOH (85%, 1.12 g, 16.7 mmol) was dissolved in water (20 mL) and cooled to 0 °C. Neat Br_2 (0.89 g, 5.6 mmol) was added. The flask was wrapped with foil and the yellow mixture was stirred at 0 °C until complete dissolution of bromine. Then, 4-pentynol-1 (420 mg, 5.0 mmol) was added. The reaction was stirred in dark at 0 °C for 3 hr. The cloudy white solution was extracted with ether (2×10 mL). The organic layer was dried over Na_2SO_4. Flash chromatography (1:3 → 1:1, ether/petrol) afforded the target material as a colourless oil, which turns brown over time (425 mg, 52%).

R_f 0.23 (50:50, ether/petrol); ν_{max}/cm^{-1} 3327br.s (OH), 2210w (C≡C); δ_H (400 MHz, $CDCl_3$) 3.76 (2H, td, *J* = 7.0, 5.0 Hz, H-1), 2.35 (2H, t, *J* = 7.0 Hz, H-3), 1.78 (2H,

quint, *J* = 7.0 Hz, H-2), 1.45 (1H, br.t, *J* = 5.0 Hz, OH); δ_C (101 MHz, $CDCl_3$) 79.5 (C-5), 61.4 (C-1), 38.3 (C-4), 30.9 (C-2), 16.2 (C-3).

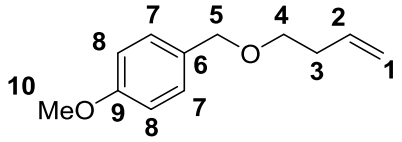
(E)-2-(bromomethylene)tetrahydrofuran (190)



Isolated as a side product in the synthesis of 5-bromopent-4-yn-1-ol. The compound is a colourless oil (205 mg, 25%).

R_f 0.53 (50:50, ether/petrol); ν_{max}/cm^{-1} 3106m (=C–H), 1660s (C=C); δ_H (400 MHz, $CDCl_3$) 4.89 (1H, td, *J* = 1.5, 0.5 Hz, H-2'), 4.27 (2H, td, *J* = 7.0, 0.5 Hz, H-5), 2.59 (2H, td, *J* = 7.0, 1.5 Hz, H-3), 2.12 (2H, quint, *J* = 7.0 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 158.3 (C-2), 71.9 (C-5), 70.8 (C-2'), 29.5 (C-3), 25.7 (C-4); HRMS (TOF FI^+), m/z: calcd for C_5H_7OBr [M^+] 161.9680, found 161.9679.

1-((But-3-en-1-yloxy)methyl)-4-methoxybenzene (193)[319]

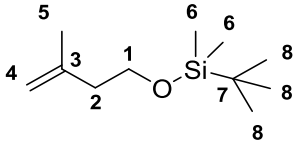


But-3-en-1-ol (1.00 g, 13.9 mmol) was dissolved in DMF (30 mL) and cooled to 0 °C. NaH (60% in oil, 640 mg, 16.7 mmol) was added in two portions *(caution: gas evolution)*. The mixture was stirred at 0 °C for 10 min. 4-Methoxybenzyl chloride (3.26 g, 20.8 mmol) was added. The mixture was allowed to warm to RT and stirred for 13 hr. The resulting solution was diluted with ether (100 mL), then washed sequentially with water (2×20 mL), aq. HCl (0.5 M, 2×20 mL), and brine (20 mL). The aq. layers were re-extracted with ether. The combined organic layers were dried

($MgSO_4$) and concentrated. Flash chromatography (5:95, ether/petrol) afforded the title compound as a colourless oil (2.38 g, 98%).

R_f 0.25 (10:90, ether/petrol); ν_{max}/cm^{-1} 3030w (=C–H), 1586s, 1246s; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* = 8.5 Hz, H-7), 6.89 (d, *J* = 8.5 Hz, 2H, H-8), 5.85 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, H-2), 5.15 – 5.05 (1H, m, H-1a), 5.11 – 5.02 (1H, m, H-1b), 4.47 (2H, s, H-5), 3.82 (3H, s, H-10), 3.51 (2H, td, *J* = 7.0, 1.0 Hz, H-4), 2.42 – 2.34 (2H, m, H-3); δ_C (101 MHz, $CDCl_3$) 159.3 (C-9), 135.5 (C-2), 130.7 (C-6), 129.4 (C-7), 116.4 (C-1), 113.9 (C-8), 72.7 (C-5), 69.4 (C-4), 55.4 (C-10), 34.4 (C-3).

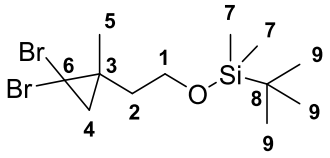
tert-Butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (196)[320,321]



A round-bottom flask was charged with DCM (8 mL), 3-methyl-but-3-en-1-ol (0.85 g, 10 mmol), TBSCl (1.66 g, 11 mmol), and imidazole (1.19 g, 17.5 mmol) at 0 °C. The solution was allowed to warm to RT and stirred for 25 hr. Volatiles were removed in vacuo, and the residue was filtered through a short silica plug (3×3 cm), eluting with petrol. The filtrate was concentrated and the flash chromatography on the crude residue (1:30, ether/petrol) afforded the target material as a colourless oil (2.09 g, 100%).

R_f 0.72 (10:90, ether/petrol); ν_{max}/cm^{-1} 3077w (=C–H), 2929m, 1650w, 1098s, 830s, 774s; δ_H (400 MHz, $CDCl_3$) 4.76 (1H, m, H-4a), 4.71 – 4.68 (1H, m, H-4b), 3.71 (2H, t, *J* = 7.0 Hz, H-1), 2.24 (2H, td, *J* = 7.0, 1.0 Hz, H-2), 1.77 – 1.70 (3H, app. t, *J* = 1.0 Hz, H-5), 0.89 (9H, s, H-8), 0.05 (6H, s, H-6); δ_C (101 MHz, $CDCl_3$) 143.3 (C-3), 111.6 (C-4), 62.3 (C-1), 41.3 (C-2), 26.1 (C-8), 23.0 (C-5), 18.5 (C-7), –5.2 (C-6).

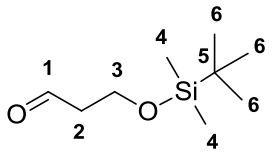
tert-Butyl(2-(2,2-dibromo-1-methylcyclopropyl)ethoxy)dimethylsilane (197)



To a *rapidly* stirred mixture of *tert*-butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (400 mg, 2.0 mmol) and aq. NaOH (1.20 g NaOH in 1.3 mL of water), cooled to 10 °C, was added dropwise ethanol-free $CHBr_3$ (750 mg, 3.0 mmol; purified by washing with water four times, then dried over $MgSO_4$) and the resulting brown suspension was stirred *rapidly* at RT for 48 hr. Water (10 mL) and ether (10 mL) were then added and the layers were separated. The aq. layer was extracted with ether (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (petrol → 5:95, ether/petrol) afforded the target material as a colourless oil (565 mg, 76%).

R_f 0.18 (petrol); ν_{max}/cm^{-1} 2955m, 1255s, 1099s, 834s, 774s; δ_H (500 MHz, C_6D_6) 3.68 – 3.56 (2H, m, H-1), 1.84 – 1.75 (1H, m, H-2a), 1.72 – 1.64 (1H, m, H-2b), 1.17 (1H, d, *J* = 7.5 Hz, H-4a), 1.16 (3H, s, H-5), 1.02 (1H, d, *J* = 7.5 Hz, H-4b), 0.96 (9H, s, H-9), 0.03 (6H, s, H-7); δ_C (126 MHz, C_6D_6) 60.8 (C-1), 41.2 (C-2), 39.6 (C-6), 34.7 (C-4), 28.0 (C-3), 26.1 (C-9), 22.8 (C-5), 18.4 (C-8), −5.2 (C-7), −5.3 (C-7); HRMS (TOF FI^+), m/z: calcd for $C_8H_{15}O^{79}Br_2Si$ [M−*t*-Bu^+] 312.9259, found 312.9253.

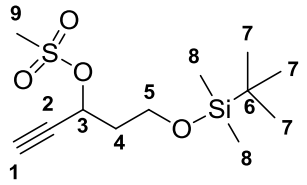
3-((*tert*-Butyldimethylsilyl)oxy)propanal (200)[322]



A solution of $(COCl)_2$ (1.80 mL, 20 mmol) in dry DCM (80 mL) was cooled to −78 °C. DMSO (2.80 mL, 40 mmol) was added dropwise with a syringe *(note: gas liberation; DMSO can freeze inside the needle if the flow is not sufficiently fast)*. The mixture was stirred at −78 °C for 25 min. Then, a solution of *O_1*-TBS-1,3-propanediol (1.90 g, 10 mmol) in dry DCM (20 mL) was added over 30 min using a syringe pump. The reaction was kept at −78 °C during the addition. The stirring was continued for another 20 min, followed by the addition of TEA (5.6 mL, 40 mmol). The mixture was stirred for 15 min at −78 °C, warmed to 0 °C, and stirred for another 40 min. The reaction was quenched with aq. $NaHSO_4$ (0.5 M, 50 mL) at 0 °C. The aq. layer was extracted with DCM (3×15 mL). The combined organic layers were washed with brine (15 mL), filtered through Phase Separator and concentrated (25 °C, 300 Torr). Spectroscopically pure target material could be obtained by flash chromatography (8:92, ether/petrol) as a colourless oil (0.88 g, 45%). This method, however, led to the significant decomposition of the product (large amounts of TBSOH were detected). Non-purified samples (ca. 90% yield) exhibited identical reactivity.

R_f 0.25 (10:90, ether/petrol); ν_{max}/cm^{-1} 2729m ($C_{aldehyde}$−H), 1727s (C=O); δ_H (400 MHz, $CDCl_3$) 9.81 (1H, t, *J* = 2.0 Hz, H-1), 4.00 (2H, t, *J* = 6.0 Hz, H-3), 2.61 (2H, td, *J* = 6.0, 2.0 Hz, H-2), 0.88 (9H, s, H-6), 0.07 (6H, s, H-4); δ_C (101 MHz, $CDCl_3$) 202.1 (C-1), 57.4 (C-3), 46.5 (C-2), 25.8 (C-6), 18.2 (C-5), −5.5 (C-4).

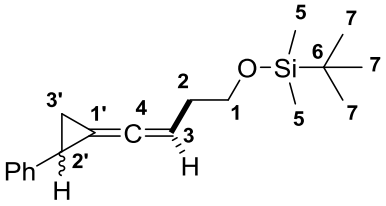
5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-3-yl methanesulfonate (201)[197]



5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-3-ol (3.37 g, 15.7 mmol) was dissolved in DCM (45 mL), followed by TEA (3.9 mL, ca. 28 mmol). The mixture was cooled to 0 °C, and neat MsCl (1.7 mL, ca. 22 mmol) was added with a syringe. The reaction was stirred at 0 °C for 1 hr, then transferred into a mixture of sat. aq. NH_4Cl (60 mL) and ether (50 mL). The reaction vessel was washed with ether (10 mL). The phases were combined, shaken and separated. The aq. layer was extracted with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The crude product was filtered through a 2×2 cm silica pad (1:1, ether/petrol). Evaporation afforded the target material as a viscous yellow oil (3.60 g, 78%). *Note:* attempts to perform standard column chromatography on the product invariably led to diminished yields.

R_f 0.28 (25:75, ether/petrol); ν_{max}/cm^{-1} 3305m (≡C–H), 2250m (C≡C), 1364s (SO), 1178s (SO); δ_H (400 MHz, $CDCl_3$) 5.38 (1H, ddd, *J* = 8.0, 6.0, 2.0 Hz, H-3), 3.77 (2H, t, *J* = 5.5 Hz, H-5), 3.14 (3H, s, H-9), 2.73 (1H, d, *J* = 2.0 Hz, H-1), 2.16 (1H, ddt, *J* = 13.5, 8.0, 5.5 Hz, H-4a), 2.05 (1H, ddt, *J* = 13.5, 6.0, 5.5 Hz, H-4b), 0.90 (9H, s, H-7), 0.07 (6H, s, H-8); δ_C (101 MHz, $CDCl_3$) 79.5 (C-2), 76.9 (C-1), 68.5 (C-3), 57.9 (C-5), 39.1 (C-9/4), 38.6 (C-9/4), 25.8 (C-7), 18.2 (C-6), −5.5 (C-8).

O-TBS-4-(2-Phenylcyclopropylidene)but-3-en-1-ol (204)



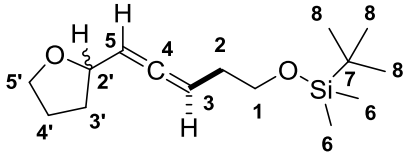
A mixture of KO*t*-Bu (480 mg, 4.3 mmol; *note:* the reaction appears to be sensitive to the quality of this reagent) and styrene (1.9 mL, 17 mmol; passed through a plug of neutral alumina immediately before use) in THF (4 mL) was cooled to 0 °C and stirred rapidly (*ca.* 600 rpm). A solution of 5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-3-yl methanesulfonate (0.50 g, 1.7 mmol) in 1.5 mL THF was added with a syringe. The mixture was stirred at 0 °C for 30 min and at RT for 1 hr. The crude reaction mixture was transferred into 30 mL of half-sat. aq. NH_4Cl, and extracted with ether (3×8 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, then concentrated. Flash chromatography (petrol → 5:95, ether/petrol) afforded the title compound as a clear colourless oil (often contaminated with a yellow impurity) (340 mg, 67%).

R_f 0.28 (petrol); ν_{max}/cm^{-1} 3060w (=C–H), 3029w (=C–H), 2020m (C=C=C); δ_H (500 MHz, $CDCl_3$)* 7.31 – 7.27 (2H, m, H-Ph), 7.22 – 7.17 (3H, m, H-Ph), 5.43 – 5.35 (1H, m, H-3), 3.72 (2×t, *J* = 7.0 Hz, 2H, H-1), 2.95 (app. tdd, *J* = 9.0, 5.5, 3.5 Hz, 1H, H-2'), 2.39 – 2.32 (2H, m, H-2), 2.10 – 2.04 (1H, m, H-3'a), 1.65 – 1.60 (1H, m, H-3'b), 0.90 (2×s, 9H, H-7), 0.08 – 0.05 (6H, m, H-5); δ_C (126 MHz, $CDCl_3$)* 190.21 (C-4), 190.20 (C-4), 140.99 (C-Ph), 140.85 (C-Ph), 128.36 (C-Ph), 128.33 (C-Ph), 126.51 (C-Ph), 126.42 (C-Ph), 126.16 (C-Ph), 91.29 (C-3), 91.12 (C-3), 82.72 (C-1'), 82.50 (C-1'), 63.02 (C-1), 62.94 (C-1), 33.16 (C-2), 33.14 (C-2), 25.92 (C-7), 24.44 (C-2'), 24.34 (C-2'), 18.33 (C-3'), 17.89

* Note: two diastereomers were detectable in the spectrum. We did not attempt to assign the doubled signals to any particular isomer.

(C-3'), 17.58 (C-6), −5.25 (C-5); HRMS (TOF FI$^+$), m/z: calcd for $C_{19}H_{28}OSi$ [M^+] 300.1909, found 300.1906.

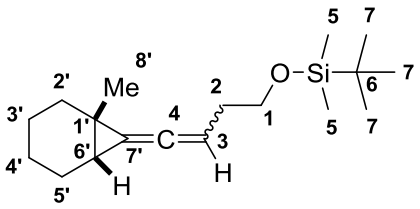
3*RS*-*O*-TBS- 5-(2*RS*-tetrahydrofuran-2-yl)penta-3,4-dien-1-ol (205)



Isolated as a side product in some syntheses of VDCPs **204**/**207** when THF was used as a solvent. The compound (clear colourless oil) formed as an inseparable mixture of diastereomers.

R_f 0.28 (10:90, ether/petrol); ν_{max}/cm^{-1} 1965w (C=C=C); δ_H (500 MHz, $CDCl_3$)* 5.29 – 5.21 (1H, m, H-3), 5.21 – 5.17 (1H, m, H-5), 4.39 (1H, app. td, *J* = 6.5, 2.0 Hz, H-2'), 3.92 – 3.85 (1H, m, H-5'a), 3.78 (1H, app. td, *J* = 8.0, 6.0 Hz, H-5'b), 3.67 (2H, 2×t, *J* = 7.0 Hz, H-1), 2.25 (2H, app. quint.d, *J* = 7.0, 3.0 Hz, H-2), 2.07 – 1.99 (1H, m, H-3'a), 1.98 – 1.84 (2H, m, H-4'), 1.80 – 1.70 (1H, m, H-3'b), 0.90 (9H, 2×s, H-8), 0.06 (6H, 2×s, H-6); δ_C (126 MHz, $CDCl_3$)* 204.0 (C-4), 203.9 (C-4), 93.2 (C-5), 93.1 (C-5), 89.5 (C-3), 89.4 (C-3), 77.2 (C-2'), 67.77 (C-5'), 67.68 (C-5'), 62.85 (C-1), 62.81 (C-1), 32.41 (C-2), 32.35 (C-2), 31.42 (C-3'), 31.40 (C-3'), 25.9 (C-8), 25.58 (C-4'), 25.52 (C-4'), 18.3 (C-7), −5.3 (C-6); HRMS (ESI$^+$), m/z: calcd for $C_{15}H_{28}NaO_2Si$ [M+Na^+] 291.1751, found 291.1746.

O-TBS-4-(1-methylbicyclo[4.1.0]heptan-7-ylidene)but-3-en-1-ol (207)



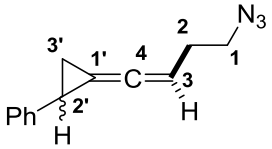
A slurry of KO*t*-Bu (420 mg, 3.75 mmol) in THF (4 mL) in a 25 mL flask was cooled to 0 °C and stirred vigorously (800 rpm). To this, 1-methylcyclohexene (1.8 mL,

* Note: two diastereomers were detectable in the spectrum. We did not attempt to assign the doubled signals to any particular isomer.

15 mmol) was added, followed by 5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-3-yl methanesulfonate (440 mg, 1.5 mmol) in THF (0.6 + 0.6 mL). The brown mixture was stirred at 0 °C for 2 hr. The reaction was quenched by the addition of half-sat. aq. NH_4Cl (30 mL), and the aq. layer was then extracted with ether (2×8 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Two consecutive pipette silica columns (5:95, ether/petrol; rapidly!) afforded the title material as a clear yellow oil (260 mg, 60%).

R_f 0.70 (10:90, ether/petrol); ν_{max}/cm^{-1} 2003m (C=C=C); δ_H (500 MHz, $CDCl_3$)* δ 5.18 – 5.13 (1H, m, H-3), 3.70 (2H, app.q, *J* = 7.5 Hz, H-1), 2.33 – 2.26 (2H, m, H-2), 2.01 – 1.83 (2H, m, CH_2), 1.77 – 1.50 (3H, m, H-6',CH_2), 1.47 – 1.14 (7H, m, H-8',CH_2,CH_2), 0.95 – 0.86 (9H, m, H-7), 0.11 – 0.02 (6H, m, H-5); δ_C (126 MHz, $CDCl_3$)* 187.6 (C-4), 187.5 (C-4), 91.1 (C-7'), 90.8 (C-7'), 88.9 (C-3), 88.8 (C-3), 63.6 (C-1), 63.3 (C-1), 33.4 (C-2), 33.3 (C-2), 30.3 (CH_2), 30.1 (CH_2), 26.8 (C-6'), 26.7 (C-6'), 26.1 (C-8'), 25.9 (C-7), 25.8 (C-8'), 25.7 (C-1'), 25.4 (C-1'), 23.6 (CH_2), 23.3 (CH_2), 21.44 (CH_2), 21.42 (CH_2), 21.41 (CH_2), 21.37 (CH_2), 18.39 (C-6), 18.36 (C-6), −5.22 (C-5), −5.25 (C-5); HRMS (TOF FI^+), m/z: calcd for $C_{18}H_{32}OSi$ [M^+] 292.2222, found 292.2214.

4-(2-Phenylcyclopropylidene)but-3-en-1-yl azide (208)



A solution of CBr_4 (663 mg, 2.0 mmol) in dry DMF (10 mL) was cooled to 10 °C. To this were added PPh_3 (524 mg, 2.0 mmol) and starting 4-(2-phenylcyclopropylidene)but-3-en-1-ol (182 mg, 0.98 mmol). The bright yellow mixture was stirred at RT for 1 hr. Then the reaction content was poured into a mixture of

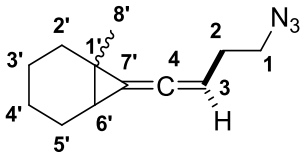
* Note: two diastereomers were detectable in the spectrum. We did not attempt to assign the doubled signals to any particular isomer.

petrol (10 mL) and water (20 mL). The layers were separated and the aq. layer was extracted with petrol (2×10 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$ and concentrated to ⅓ of the initial volume. The resulting solution of alkyl bromide was filtered through a plug of silica (1 cm, pipette), eluting with ether (5 mL), then concentrated. The residue was redissolved in DMF (5 mL), followed by the addition of NaN_3 (255 mg, 3.9 mmol), and stirred overnight (13 hr). The reaction mixture was diluted with water (15 mL) and extracted with petrol (3×8 mL). The combined petrol layers were washed with brine (8 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (petrol → 2:98, ether/petrol) afforded the title material as a yellow oil (155 mg, 75%).

R_f 0.56 (10:90, ether/petrol); ν_{max}/cm^{-1} 3436w, 3340w, 3233w, 3059w (=C–H), 3028w (=C–H), 2096s (N_3), 2018m (C=C=C); δ_H (500 MHz, C_6D_6)* δ 7.24 – 7.18 (4H, m, H-Ph), 7.18 – 7.10 (1H, m, H-Ph), 5.31 – 5.19 (1H, m, H-3), 2.92 – 2.83 (1½H, m, H-1,½×2'), 2.79 (½×1H, ddd, *J* = 8.5, 5.5, 3.5 Hz, H-2'), 2.12 (½×2H, q, *J* = 7.0 Hz, H-2), 2.07 (½×2H, qd, *J* = 7.0, 2.0 Hz, H-2), 1.90 (½×1H, ddd, *J* = 8.5, 7.0, 4.0 Hz, H-3'a), 1.85 (½×1H, ddd, *J* = 8.5, 7.0, 4.0 Hz, H-3'a), 1.62 (½×1H, ddd, *J* = 7.0, 5.5, 4.0 Hz, H-3'b), 1.58 (½×1H, ddd, *J* = 7.0, 5.5, 4.0 Hz, H-3'b); δ_C (126 MHz, C_6D_6)* 190.68 (C-4), 190.66 (C-4), 141.02 (C-Ph), 140.85 (C-Ph), 128.74 (C-Ph), 128.69 (C-Ph), 126.89 (C-Ph), 126.75 (C-Ph), 126.66 (C-Ph), 126.64 (C-Ph), 91.17 (C-3), 91.16 (C-3), 84.39 (C-1'), 84.10 (C-1'), 50.59 (C-1), 50.58 (C-1), 29.27 (C-2), 29.24 (C-2), 24.94 (C-2'), 24.88 (C-2'), 17.59 (C-3'); HRMS could not be obtained for this compound.

* Note: two diastereomers were detectable in the spectrum. We did not attempt to assign the doubled signals to any particular isomer.

7-((*RS*)-4-azidobut-1-en-1-ylidene)-1-methylbicyclo[4.1.0]heptane (209)

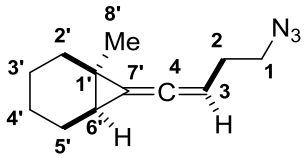


A solution of *O*-TBS-4-(1-methylbicyclo[4.1.0]heptan-7-ylidene)but-3-en-1-ol (230 mg, 0.79 mmol) in THF (2.5 mL) was placed into a plastic vial, and buffered with pyridine (0.80 mL). To this, HF·py (70 wt% of HF, 0.20 mL, 7.9 mmol) was added dropwise. The resulting solution was capped and stirred at RT for 3.5 hr. The reaction was partitioned between sat. aq. $NaHCO_3$ (30 mL; *caution: gas liberation*) and ether (10 mL). The layers were shaken until gas liberation ceased, then separated. The aq. layer was extracted with ether (2×10 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (2×10 mL) to remove pyridine, and brine (10 mL), then dried over $MgSO_4$, and concentrated. The crude alcohol was used immediately as received. To the solution of alcohol in DCM (8 mL) was added TEA (0.20 mL, 1.4 mmol). The resulting mixture was cooled to 0 °C. MsCl (86 μL, 1.1 mmol) was added dropwise. The resulting mixture was allowed to warm to RT over 1.5 hr. The reaction content was partitioned between water (30 mL) and petrol (20 mL). The layers were separated. The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The crude residue of mesylate was redissolved in dry DMF (1.5mL). To this was added NaN_3 (154 mg, 2.4 mmol) and the resulting slurry was stirred at 33 °C for 24 hr, then at RT for 24 hr. The reaction content was partitioned between water (15 mL) and petrol (10 mL). The layers were separated; the aq. layer was extracted with petrol (2×8 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography on a short column (3 cm; 5:95, ether/petrol) afforded the title material as a clear, slightly yellowish, oil (110 mg, 70% over 3 steps).

Note: the compound is unstable on silica. The use of a longer column (8 cm) led to the 47% yield.

R_f 0.80 (10:90, ether/petrol); ν_{max}/cm^{-1} 2097s (N_3), 2002m (C=C=C); δ_H (500 MHz, C_6D_6)* δ 5.11 (½×1H, td, *J* = 6.5, 4.0 Hz, H-3), 5.08 (½×1H, td, *J* = 6.5, 3.5 Hz, H-3), 2.87 (½×2H, t, *J* = 7.0 Hz, H-1), 2.85 (½×2H, t, *J* = 7.0 Hz, H-1), 2.10 – 2.02 (2H, m, H-2), 1.88 (1H, m, ½×CH_2), 1.80 – 1.69 (2H, m, H-5'), 1.68 – 1.63 (½×1H, m, H-6'), 1.63 – 1.58 (½×1H, m, H-6'), 1.46 – 1.23 (4H, m, H-4a,½CH_2,CH_2), 1.21 (½×3H, s, H-8'), 1.17 (½×3H, s, H-8'), 1.11 – 0.98 (1H, m, H-4b); δ_C (126 MHz, C_6D_6)* 188.4 (C-4), 188.3 (C-4), 92.32 (C-7'), 92.26 (C-7'), 89.3 (C-3), 50.83 (C-1), 50.79 (C-1), 30.6 (CH_2), 30.4 (CH_2), 29.6 (C-2), 29.5 (C-2), 27.33 (C-6'), 27.27 (C-6'), 26.3 (C-8'), 26.03 (C-8'), 25.97 (C-1'), 23.9 (CH_2), 23.7 (CH_2), 21.9 (C-4'), 21.8 (C-4'), 21.73 (CH_2), 21.69 (CH_2); HRMS could not be obtained for this compound.

(±)-(1*R*,6*R*)-7-((*S*)-4-azidobut-1-en-1-ylidene)-1-methylbicyclo[4.1.0]heptane (syn-209)

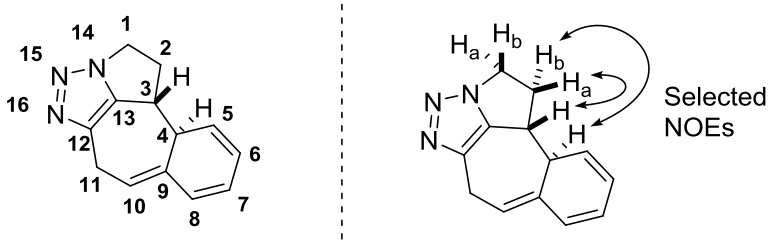


Prepared by kinetic resolution of the mixture of diastereomeric allenes. A solution of 7-((*RS*)-4-azidobut-1-en-1-ylidene)-1-methylbicyclo[4.1.0]heptane (d.r. 1:1, 22 mg, 0.11 mmol) in toluene (2 mL) was placed into a 4 mL pressure vial, equipped with a stirbar, flushed with argon, sealed and heated at 110 °C for 2 hr, then at 135 °C for 2 hr. The crude reaction mixture was loaded directly onto a silica column (petrol → 10:90, ether/petrol → 100% ether). The product was isolated at the first spot (R_f 0.80, 10:90, ether/petrol). Traces of toluene were removed in vacuo (8 mm) to give the title material as a colourless oil (2.5 mg, 11%).

* A mixture of 2 diastereomers was observed in the NMR.

δ_H (500 MHz, $CDCl_3$) 5.17 (1H, td, *J* = 6.5, 3.5 Hz, H-3), 3.36 (2H, t, *J* = 7.0 Hz, H-1), 2.37 (2H, q, *J* = 7.0 Hz, H-2), 2.00–1.87 (2H, m, CH_2), 1.81–1.71 (3H, m, 1½×CH_2), 1.62–1.56 (m, 1H, ½×CH_2), 1.47–1.19 (7H, m, H-8',CH_2,CH_2); δ_C (126 MHz, $CDCl_3$) 187.8 (C-4), 92.4 (C-7), 88.7 (C-3), 51.2 (C-1), 30.5 (CH_2), 29.4 (C-2), 27.5 (C-6'), 26.4 (C-1'), 26.1 (C-8'), 23.8 (CH_2), 21.73 (CH_2), 21.68 (CH_2).

3,4-*anti*-8a,8b,9,10-Tetrahydro-3*H*-1,2,10a-triazabenzo[f]cyclopenta[cd]azulene (210)

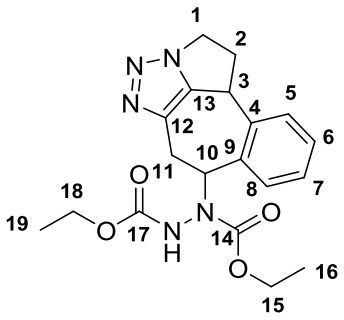


A solution of (2-(4-azidobut-1-en-1-ylidene)cyclopropyl)benzene (19 mg, 0.09 mmol) in toluene (2 mL) was placed into a dry pressure tube (4 mL) with a stirbar, sealed under argon, and heated at 110 °C for 90 min. The reaction content was loaded directly onto a short silica plug (0.5×1 cm) and eluted with an ether/petrol gradient (5:95, ether/petrol → ether). The target material is a white wax (sometimes white foam), unstable in acidic or protic environment (10 mg, 53%).

R_f 0.16 (ether); ν_{max}/cm^{-1} 3426br.s, 3035m, 1626m, 1425m, 1303m, 1155s; δ_H (700 MHz, DMSO-d_6) 6.11 (1H, d, *J* = 9.5 Hz, H-8), 5.99 (1H, dddd, *J* = 9.5, 5.5, 2.0, 1.0 Hz, H-6), 5.94–5.91 (1H, m, H-10), 5.75 (1H, ddt, *J* = 9.5, 5.5, 1.0 Hz, H-7), 5.71 (1H, dd, *J* = 9.5, 4.5 Hz, H-5), 4.37 (1H, ddd, *J* = 11.0, 9.0, 1.0 Hz, H-1a), 4.31 (1H, td, *J* = 11.0, 6.0 Hz, H-1b), 3.56 (1H, ddt, *J* = 21.0, 8.0, 1.0 Hz, H-11a), 3.48 (1H, dt, *J* = 21.0, 4.0 Hz, H-11b), 3.32–3.29 (1H, br.m, H-4), 3.21 (1H, td, *J* = 9.5, 6.5 Hz, H-3), 2.78 (1H, dtd, *J* = 12.0, 6.5, 1.0 Hz, H-2a), 2.64–2.56 (1H, m, H-2b); δ_C (126 MHz, DMSO-d_6) 144.0 (C-9/12/13), 139.2 (C-9/12/13), 135.5 (C-9/12/13), 131.9 (C-8), 128.2 (C-5), 127.7 (C-10), 122.8 (C-

6), 120.2 (C-7), 46.8 (C-1), 43.6 (C-4), 38.0 (C-3), 35.1 (C-2), 24.4 (C-11); HRMS (TOF FI$^+$), m/z: calcd for $C_{13}H_{13}N_3$ [M^+] 234.1002, found 234.0997.

***Ene-reaction product* (212)**

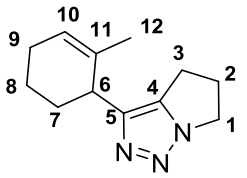


To a solution of freshly prepared 3,4-*anti*-8a,8b,9,10-tetrahydro-3*H*-1,2,10a-triazabenzo[f]cyclopenta[cd]azulene (14 mg, 0.06 mmol) in benzene (0.7 mL) was added DEAD (11 μL, ca. 0.07 mmol). The clear orange solution was stirred at RT. After 10 min, voluminous precipitation was observed, and TLC indicated complete consumption of the starting material. The mixture was stirred overnight (14 hr). The reaction content was diluted with 3 mL of DCM and loaded directly onto a 2 cm pipette silica column (packed with 10:90 ether/petrol, eluted with the following gradient: 10:90, ether/petrol → ether → 6:94, MeOH/ether). The product is a clear reddish oil that precipitates as white solid from ethereal solutions. It is well-soluble in chlorinated solvents (15 mg, 63%).

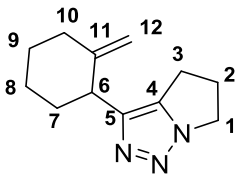
R_f 0.23 (6:94, MeOH/ether); ν_{max}/cm^{-1} 3290br.m (NH), 3200br.m (NH), 3067w (=C–H), 1747s (C=O), 1711s (C=O); δ_H (700 MHz, $CDCl_3$) 7.48–7.22 (3H, m, H-Ph), 7.22–7.06 (1H, m, H-Ph), 7.04–6.79 (1H, br.s, NH), 5.79–5.49 (1H, br.s, H-10), 4.72–4.60 (1H, m, H-3), 4.57–4.41 (2H, m, H-1), 4.35–4.23 (2H, m, H-15/18), 4.20–4.02 (2H, m, H-15/18), 3.55 (1H, d, *J* = 13.0 Hz, H-11a), 3.30–3.10 (2H, m, H-2), 3.05 (1H, t, *J* = 13.0 Hz, H-11b), 1.33 (3H, t, *J* = 7.0 Hz, H-16/19), 1.37–0.82 (3H, br.m, H-16/19); δ_C (175 MHz, $CDCl_3$) 157.1 (C-14/17), 155.6 (C-14/17), 141.6 (C-4/9/12/13), 141.5 (C-4/9/12/13), 138.4 (C-4/9/12/13), 136.9 (C-4/9/12/13), 127.6 (C-5/6/7/8), 127.4 (C-5/6/7/8),

125.1 (C-5/6/7/8), 124.5 (C-5/6/7/8), 62.8 (C-15/18), 65.5 (C-15/18), 59.6 (C-10), 47.3 (C-1), 35.2 (C-2), 34.6 (C-3), 27.9 (C-11), 14.5 (C-16/19), 14.3 (C-16/19); HRMS (ESI^+), m/z: calcd for $C_{19}H_{23}N_5O_4Na$ [$M+Na^+$] 408.1642, found 408.1628.

Triazoles from alicyclic cyclopropylidene allene azides (*endo*-213, *exo*-213)



endo-**213**



exo-**213**

Method 1 (gives *endo*-**213** as the major isomer).

A 1:1 diastereomeric mixture of 7-((*RS*)-4-azidobut-1-en-1-ylidene)-1-methylbicyclo[4.1.0]heptane (30 mg, 0.15 mmol) was dissolved in *m*-xylene (2.0 mL), transferred into a dry pressure tube (4 mL volume), equipped with a stirbar, flushed with argon, sealed, and heated at 135 °C for 0.5 hr. The crude reaction mixture was loaded straight onto a short pipette silica column (0.5×1 cm, 10:90, ether/petrol → ether), collecting the spot with R_f 0.12 (ether), which was an inseparable mixture of alkene stereoisomers. The product is a clear yellowish oil (16 mg, 53%), *endo*/*exo* = 6.5:1 (NMR).

Method 2 (gives *exo*-**213** as the major isomer).

A solution of (±)-(1R,6R)-7-((S)-4-azidobut-1-en-1-ylidene)-1-methyl-bicyclo[4.1.0]heptane (ca. 4:1 mixture with its allene diastereomer; 10 mg) in degassed toluene (2 mL) was placed into a 4 mL pressure tube with a stirbar, flushed with argon, sealed, and heated at 135 °C for 2 hr. The crude reaction mixture was loaded directly onto a short silica column (0.5×1 cm, 10:90, ether/petrol → ether), collecting the spot with R_f 0.12 (ether), as an inseparable 4.7:1 mixture of the alkene stereoisomers. The product is a clear yellowish oil (3 mg, 30%), *endo*/*exo* = 1:4.7 (NMR).

Method 3 (gives the highest overall yield).

A 1:1 diastereomeric mixture of 7-((*RS*)-4-azidobut-1-en-1-ylidene)-1-methylbicyclo[4.1.0]heptane (30 mg, 0.15 mmol) was dissolved in *m*-xylene (2.0 mL), transferred into a dry pressure tube (4 mL volume), equipped with a stirbar, flushed with argon, sealed, and heated at 135 °C for 3 hr. The crude reaction mixture was loaded straight onto a pipette silica column (0.5×1 cm, 10:90, ether/petrol → ether), collecting the spot with R_f 0.12 (ether), as an inseparable 1.6:1 mixture of the alkene stereoisomers. The product is a clear orange oil (24 mg, 80%), *endo*/*exo* = 1.6:1 (NMR). Yield of *endo*-**213** – 100% of theoretical. Yield of *exo*-**213** – 60% of theoretical.

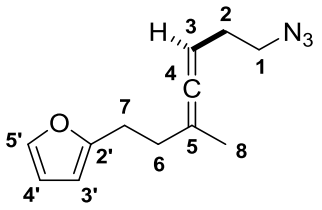
3-(2-Methylcyclohex-2-en-1-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-c][1,2,3]triazole, A (*endo*-213)

R_f 0.12 (ether); ν_{max}/cm^{-1} 2931s, 1572w, 1446s, 1316m, 1169m, 910m, 893m; δ_H (500 MHz, C_6D_6) 5.62 – 5.59 (1H, m, H-10), 3.82 (1H, br.s, H-6), 3.54 – 3.46 (2H, m, H-1), 2.25 – 2.12 (3H, m, H-3,7), 2.10 – 1.95 (3H, m, H-7,9), 1.78 – 1.69 (5H, m, H-2,12), 1.61 – 1.52 (2H, m, H-8); δ_H (500 MHz, $CDCl_3$) 5.61–5.55 (1H, m, H-10), 4.30–4.26 (2H, m, H-1), 3.49–4.44 (1H, m, H-6), 2.79–2.69 (4H, m, H-2,3), 2.07–1.99 (2H, m, H-9), 1.89–1.82 (2H, m, H-7), 1.58–1.55 (3H, m, H-12), 1.56–1.51 (1H, m, H-8), 1.47–1.37 (1H, m, H-8); δ_C (126 MHz, C_6D_6) 142.2 (C-4/5), 138.5 (C-4/5), 133.9 (C-11), 123.8 (C-10), 45.6 (C-1), 37.2 (C-6), 30.8 (C-7), 27.9 (C-3), 25.7 (C-9), 23.0 (C-12), 20.8 (C-2), 19.4 (C-8); δ_C (126 MHz, $CDCl_3$) 143.0 (C-4/5), 138.8 (C-4/5), 133.2 (C-11), 123.9 (C-10), 46.0 (C-1), 36.8 (C-6), 30.4 (C-7), 28.3 (C-3), 25.2 (C-9), 22.7 (C-12), 20.9 (C-2), 18.9 (C-8); HRMS (ESI^+), m/z: calcd for $C_{12}H_{18}N_3$ $[M+H^+]$ 204.1495, found 204.1497.

3-(2-Methylenecyclohexyl)-5,6-dihydro-4*H*-pyrrolo[1,2-c][1,2,3]triazole, B (*exo*-213)

R_f 0.12 (ether); δ_H (500 MHz, $CDCl_3$) 4.75 (1H, s, H-12a), 4.33 (1H, s, H-12b), 4.33–4.28 (2H, m, H-1), 3.60–3.50 (1H, t, *J* = 6.0 Hz, H-6), 2.90–2.68 (4H, m, H-2,3), 2.36–2.28 (1H, m, H-10a), 2.22–2.13 (1H, m, H-10b), 1.99–1.89 (2H, m, H-7), 1.83–1.75 (1H, m, H-8a), 1.75–1.69 (1H, m, H-9a), 1.61–1.47 (2H, m, H-8b,9b); δ_C (126 MHz, $CDCl_3$) 150.2 (C-11), 141.5 (C-4/5), 139.2 (C-4/5), 108.3 (C-12), 46.1 (C-1), 41.4 (C-6), 34.9 (C-10), 32.6 (C-7), 28.3 (C-3), 28.2 (C-9), 24.9 (C-8), 21.3 (C-2).

7-(furan-2-yl)-5-methylhepta-3,4-dienyl azide (235)

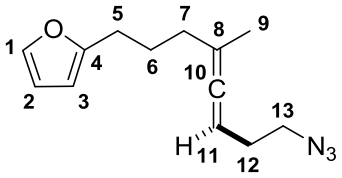


Tri-*tert*-butylsilyl 7-(furan-2-yl)-5-methylhepta-3,4-dienoate (350 mg, 0.97 mmol) was dissolved in ether (10 mL) in a 50 mL flask. The solution was cooled to 0 °C and $LiAlH_4$ (73 mg, 1.93 mmol) was added in one portion. The grey mixture was allowed to warm to RT and stirred for 15 min, until TLC showed the complete consumption of the starting material. Sat. aq. Na_2SO_4 was added dropwise to the vigorously stirred reaction *(caution: gas evolution)*, with 1-2 minute intervals between drops. When 5-6 drops were added this way, the addition of Na_2SO_4 was continued in larger portions (*ca* 0.1 mL), with 10 min intervals between the additions. When the most of the grey precipitate converted into dense white solid, a scoopula tip of anhydrous Na_2SO_4 was added and the mixture was stirred for additional 15 min. The solids were removed by filtration, thoroughly washing with ether. The resulting solution was concentrated. Crude allenic alcohol was used immediately without further purification. The alcohol was redissolved in DCM (5 mL) and cooled to 0 °C. To the mixture were added TEA (0.47 mL, 3.4 mmol) and MsCl (0.21 mL, 2.7 mmol). The ice bath was removed and the cloudy white reaction mixture was stirred at RT for 100

min, upon which its colour changed to yellow. The reaction was diluted with DCM (15 mL) and quenched with sat. aq. NH_4Cl (30 mL). The layers were separated and the aq. layer was extracted with DCM (2×10 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4) and concentrated. The residue was filtered through a 4 cm plug of silica, eluting with 50:50, ether/petrol. Evaporation of the filtrate yielded crude allene mesylate that was used without further purification. The mesylate was dissolved in DMF (7 mL). NaN_3 (270 mg, 4.2 mmol) was added and the resulting mixture was stirred at 35 °C for 14 hr, until TLC showed complete consumption of the starting material. The crude reaction mixture was partitioned between ether (50 mL) and water (50 mL). The aq. layer was separated and extracted with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (petrol → 1.5:98.5, ether/petrol) afforded the title material as a a clear colourless oil (163 mg, 73% over 3 steps). *Note: the major side product in this protocol was assigned as TIPSOAc (R_f 0.57, 3:97, ether/petrol).*

R_f 0.47 (3:97, ether/petrol); ν_{max}/cm^{-1} 3116w (=C–H), 2097s (N_3), 1969w (C=C=C); δ_H (500 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.99 (1H, dd, *J* = 3.0, 1.0 Hz, H-3'), 5.09 – 5.02 (1H, m, H-3), 3.24 (2H, t, *J* = 7.0 Hz, H-1), 2.75 (2H, t, *J* = 7.5 Hz, H-7), 2.29 (2H, td, *J* = 7.5, 3.0 Hz, H-6), 2.20 (2H, q, *J* = 7.0 Hz, H-2), 1.72 (3H, d, *J* = 3.0 Hz, H-8); δ_C (126 MHz, $CDCl_3$) 202.0 (C-4), 155.9 (C-2'), 140.9 (C-5'), 110.3 (C-4'), 105.0 (C-3'), 100.2 (C-5), 87.5 (C-3), 50.9 (C-1), 32.2 (C-6), 28.8 (C-2), 26.3 (C-7), 19.3 (C-8); HRMS (TOF FI^+), m/z: calcd for $C_{12}H_{15}N_3O$ $[M^+]$ 217.1215, found 217.1212.

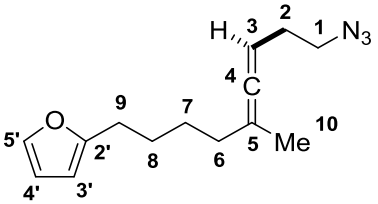
2-(8-Azido-4-methylocta-4,5-dien-1-yl)furan (236)



The target azide was prepared by General method E from 8-(furan-2-yl)-5-methylocta-3,4-dien-1-ol (206 mg, 1.00 mmol), PPh_3 (656 mg, 2.5 mmol), CBr_4 (829 mg, 2.5 mmol), and NaN_3 (195 mg, 3.0 mmol). Flash chromatography (petrol → 2:98, ether/petrol) afforded the title product as a clear colourless oil (0.236 g, 100%).

R_f 0.61 (5:95, ether/petrol); ν_{max}/cm^{-1} 2096s (N_3), 1960w (C=C=C); δ_H (500 MHz, C_6D_6) 7.25 (1H, d, *J* = 2.0, 1.0 Hz, H-1), 6.24 (1H, dd, J = 3.0, 2.0 Hz, H-2), 6.02 (1H, dd, J = 3.0, 1.0 Hz, H-3), 4.99 – 4.95 (1H, m, H-11), 2.88 (2H, t, *J* = 7.0 Hz, H-13), 2.65 (2H, t, *J* = 7.5 Hz, H-5), 1.98 (2H, app. q, *J* = 7.0 Hz, H-12), 1.96 – 1.91 (2H, m, H-7), 1.88 – 1.83 (2H, m, H-6), 1.68 (3H, d, *J* = 3.0 Hz, H-9); δ_C (126 MHz, C_6D_6) 202.3 (C-10), 156.3 (C-4), 141.1 (C-1), 110.5 (C-2), 105.3 (C-3), 100.3 (C-8), 87.4 (C-11), 50.7 (C-13), 33.4 (C-7), 29.1 (C-12), 27.8 (C-5), 26.4 (C-6), 19.1 (C-9); HRMS could not be obtained for this compound.

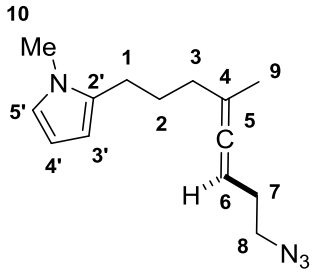
2-(9-Azido-5-methylnona-5,6-dien-1-yl)furan (237)



Prepared by General method E by stirring 9-(furan-2-yl)-5-methylnona-3,4-dien-1-ol (0.62 g, 2.8 mmol), CBr_4 (2.32 g, 7.0 mmol), PPh_3 (1.83 g, 7.0 mmol), and NaN_3 (730 mg, 11.2 mmol) in DMF (20 mL) for 24 hr (10 °C → RT). Flash chromatography (petrol → 1:99 → 2:98, petrol/ether) afforded the target material as a colourless oil (534 mg, 78%).

R_f 0.25 (petrol); ν_{max}/cm^{-1} 3113w (=C–H), 2097s (N_3), 1966w (C=C=C); δ_H (400 MHz, $CDCl_3$) 7.31 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.98 (1H, dt, *J* = 3.0, 1.0 Hz, H-3'), 5.07 – 4.99 (1H, m, H-3), 3.31 (2H, t, *J* = 7.0 Hz, H-1), 2.64 (2H, t, *J* = 7.5 Hz, H-9), 2.25 (2H, td, *J* = 7.0, 7.0 Hz, H-2), 1.99 (2H, td, *J* = 7.5, 3.0 Hz, H-6), 1.69 (3H, d, *J* = 3.0 Hz, H-10), 1.68 (2H, tt, *J* = 7.5, 7.5 Hz, H-8), 1.48 (2H, tt, *J* = 7.5, 7.5 Hz, H-7); δ_C (101 MHz, $CDCl_3$) 201.9 (C-4), 156.3 (C-2'), 140.7 (C-5'), 110.0 (C-4'), 104.6 (C-3'), 100.6 (C-5), 86.4 (C-3), 50.9 (C-1), 33.5 (C-6), 28.8 (C-2), 27.8 (C-7/8), 27.6 (C-7/8), 26.9 (C-9), 19.0 (C-10); HRMS could not be obtained for this compound.

2-(8-Azido-4-methylocta-4,5-dien-1-yl)-1-methyl-1*H*-pyrrole (238)

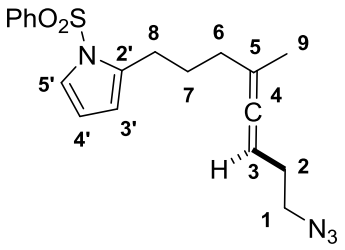


A solution of 5-methyl-8-(1-methyl-1*H*-pyrrol-2-yl)octa-3,4-dien-1-ol (53 mg, 0.24 mmol) and TEA (0.06 mL, ca. 0.4 mmol) in DCM (2 mL) was cooled to 0 °C, followed by the dropwise addition of MsCl (26 µL, 0.34 mmol) using a microsyringe. The yellowish reaction mixture was stirred at 0 °C for 5 min, then the ice bath was removed and the reaction was stirred at RT for 2 hr (note: the starting material and the product are indistinguishable by TLC in ether/petrol based eluents). The mixture was diluted with DCM (5 mL), washed with water (2×1 mL), then filtered through Phase Separator, and concentrated (300 → 60 Torr, 20 °C). The crude yellow residue of mesylate was redissolved in DMF (1.5 mL); NaN_3 (47 mg, 0.72 mmol) was added. The suspension was stirred at RT for 72 hr. The reaction contents was diluted with ether (12 mL), washed with water (2×4 mL) and brine (2×4 mL), then dried over $MgSO_4$ and

concentrated. Flash chromatography (petrol → 5:95, ether/petrol) afforded the title compound as a clear colourless oil (42 mg, 71%).

R_f 0.78 (10:90, ether/petrol); ν_{max}/cm^{-1} 3090w (=C−H), 2097s (N_3), 1950w (C=C=C); δ_H (500 MHz, $CDCl_3$) 6.55 (1H, dd, *J* = 2.5, 2.0 Hz, H-5'), 6.06 (1H, dd, *J* = 3.5, 2.5 Hz, H-4'), 5.89 (1H, ddt, *J* = 3.5, 2.0, 0.5 Hz, H-3'), 5.06 (1H, tsext, *J* = 6.5, 3.0 Hz, H-6), 3.54 (3H, s, H-10), 3.32 (2H, t, *J* = 6.5 Hz, H-8), 2.62 – 2.51 (2H, m, H-1), 2.26 (2H, q, *J* = 6.5 Hz, H-7), 2.11 – 1.99 (2H, m, H-3), 1.76 (2H, quint, *J* = 7.5 Hz, H-2), 1.72 (3H, d, *J* = 3.0 Hz, H-9); δ_C (126 MHz, $CDCl_3$) 201.9 (C-5), 133.2 (C-2'), 120.9 (C-5'), 106.5 (C-4'), 105.5 (C-3'), 100.5 (C-4), 86.7 (C-6), 50.8 (C-8), 33.52 (C-3/10), 33.48 (C-3/10), 28.9 (C-7), 26.6 (C-2), 25.8 (C-1), 19.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{14}H_{20}N_4Na$ $[M+Na^+]$ 267.1580, found 267.1582.

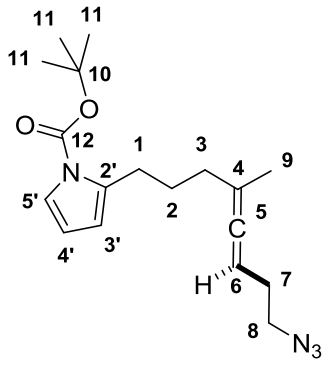
5-Methyl-8-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)octa-3,4-dien-1-yl azide (239)



To a solution of 5-methyl-8-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)octa-3,4-dien-1-ol (ca. 25 mg, 0.072 mmol) in DMF (1 mL) were added CBr_4 (47 mg , 0.14 mmol) and PPh_3 (37 mg, 0.14 mmol). The mixture immediately turned yellow. The reaction was stirred at RT for 1 hr, followed by the addition of NaN_3 (19 mg, 0.29 mmol). The mixture was rapidly stirred overnight (14 hr). The reaction contents was partitioned between water (5 mL) and petrol (10 mL). The aq. layer was separated and extracted with ether (2×5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (10:90 → 20:80, ether/petrol) afforded the title material as a viscous colourless oil (14 mg, 61% over two steps).

R_f 0.31 (25:75, ether/petrol); ν_{max}/cm^{-1} 3155w (=C–H), 3066w (=C–H), 2097s (N_3), 1967w (C=C=C), 1366s (sulfamide), 1177s (sulfamide); δ_H (500 MHz, $CDCl_3$) 7.77 – 7.73 (2H, m, H-Ph), 7.62 – 7.58 (1H, m, H-Ph), 7.53 – 7.48 (2H, m, H-Ph), 7.30 (1H, dd, *J* = 3.0, 2.0 Hz, H-5'), 6.22 (1H, t, *J* = 3.0 Hz, H-4'), 6.01 (1H, ddt, *J* = 3.0, 2.0, 1.0 Hz, H-3'), 5.01 (1H, tsext, *J* = 7.0, 3.0 Hz, H-3), 3.29 (2H, t, *J* = 7.0 Hz, H-1), 2.68 (2H, t, *J* = 7.5 Hz, H-8), 2.23 (2H, q, *J* =7.0 Hz, H-2), 1.99 – 1.93 (2H, m, H-6), 1.70 (2H, quint, *J* = 7.5 Hz, H-7), 1.66 (3H, d, *J* = 3.0 Hz, H-9); δ_C (126 MHz, $CDCl_3$) 201.9 (C-4), 139.5 (C-2'), 135.6 (C-Ph), 133.6 (C-Ph), 129.3 (C-Ph), 126.6 (C-Ph), 122.4 (C-5'), 112.0 (C-3'), 111.4 (C-4'), 100.2 (C-5), 86.7 (C-3), 50.8 (C-1), 33.3 (C-6), 28.8 (C-2), 26.7 (C-7/8), 26.4 (C-7/8), 19.0 (C-9); HRMS (ESI^+), m/z: calcd for $C_{19}H_{22}N_4NaO_2S$ [$M+Na^+$] 393.1356, found 393.1354.

tert-Butyl 2-(8-azido-4-methylocta-4,5-dien-1-yl)-1*H*-pyrrole-1-carboxylate (240)

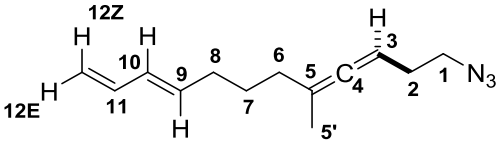


A solution of 5-methyl-8-(1-Boc-1*H*-pyrrol-2-yl)octa-3,4-dien-1-ol (76 mg, 0.25 mmol) and TEA (0.06 mL, ca. 0.4 mmol) in DCM (2 mL) was cooled to 0 °C, followed by the dropwise addition of MsCl (27 μL, 0.35 mmol) using a microsyringe. The yellowish reaction mixture was stirred at 0 °C for 5 min, then the ice bath was removed and the reaction was stirred at RT for 2 hr (note: the starting material and the product are indistinguishable by TLC in ether/petrol based eluents). The mixture was diluted with DCM (5 mL), washed with water (3×1 mL), then filtered through Phase Separator, and concentrated (300 → 60 Torr, 20 °C). The crude yellow oil of mesylate was redissolved

in DMF (1.5 mL), and NaN_3 (49 mg, 0.75 mmol) was added. The suspension was stirred at 31–32 °C for 26 hr. The reaction content was diluted with ether (12 mL), washed with water (4 mL) and brine (2×4 mL), then dried over $MgSO_4$, and concentrated. Flash chromatography using a pipette silica column (petrol → 5:95, ether/petrol) afforded the title compound as a clear colourless oil (65 mg, 79%).

R_f 0.73 (10:90, ether/petrol); ν_{max}/cm^{-1} 2097s (N_3), 1964w (C=C=C), 1741s (C=O); δ_H (500 MHz, $CDCl_3$) 7.19 (1H, dd, *J* = 3.5, 2.0 Hz, H-5'), 6.08 (1H, t, *J* = 3.5 Hz, H-4'), 5.99 – 5.94 (1H, m, H-3'), 5.05 (1H, tsext, *J* = 7.0, 3.0 Hz, H-6), 3.31 (2H, t, *J* = 7.0 Hz, H-8), 2.87 (2H, t, *J* = 7.5 Hz, H-1), 2.25 (2H, q, *J* = 7.0 Hz, H-7), 2.06 – 1.98 (2H, m, H-3), 1.75 (2H, quint, *J* = 7.5 Hz, H-2), 1.71 (3H, d, *J* = 3.0 Hz, H-9), 1.59 (9H, s, H-11); δ_C (126 MHz, $CDCl_3$) 202.1 (C-5), 149.7 (C-12), 136.2 (C-2'), 120.9 (C-5'), 111.1 (C-3'), 110.0 (C-4'), 100.8 (C-4), 86.7 (C-6), 83.4 (C-10), 51.0 (C-8), 33.7 (C-3), 28.9 (C-7), 28.6 (C-1), 28.2 (C-11), 26.9 (C-2), 19.3 (C-9); HRMS (ESI^+), m/z: calcd for $C_{18}H_{26}N_4NaO_2$ $[M+Na^+]$ 353.1948, found 353.1942.

(*E*)-12-Azido-8-methyldodeca-1,3,8,9-tetraene (*E*-241)

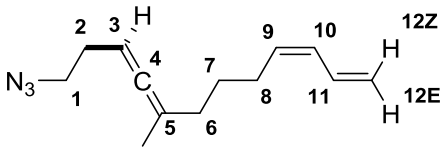


Prepared by General method E by stirring (*E*)-5-methyldodeca-3,4,9,11-tetraen-1-ol (0.18 g, 0.94 mmol), CBr_4 (776 mg, 2.34 mmol), PPh_3 (613 mg, 2.34 mmol), and NaN_3 (247 mg, 3.8 mmol) in DMF (7 mL) at RT for 24 hr. Flash chromatography (petrol → 1:99, petrol/ether) afforded the target material as a colourless oil (200 mg, 99%). *E*/*Z* > 14:1 (NMR).

R_f 0.54 (5:95, ether/petrol); ν_{max}/cm^{-1} 3039w (=C–H), 2096s (N_3), 1963w (C=C=C); δ_H (400 MHz, $CDCl_3$) 6.32 (1H, app. dt, *J* = 17.0, 10.5 Hz, H-11), 6.06 (1H, dd, *J* = 15.0, 10.5 Hz, H-10), 5.77 – 5.66 (1H, m, H-9), 5.10 (1H, d, *J* = 17.0 Hz, H-12Z), 5.07 –

5.01 (1H, m, H-3), 4.97 (1H, d, *J* = 10.5 Hz, H-12E), 3.32 (2H, t, *J* = 7.0 Hz, H-1), 2.26 (2H, app.q, *J* = 7.0 Hz, H-2), 2.12 (2H, app. q, *J* = 7.0 Hz, H-8), 2.00 – 1.92 (2H, m, H-6), 1.70 (3H, d, *J* = 3.0 Hz, H-5'), 1.57 – 1.49 (2H, m, H-7); δ_C (101 MHz, $CDCl_3$) 201.9 (C-4), 137.2 (C-11), 135.0 (C-9), 131.2 (C-10), 114.8 (C-12), 100.6 (C-5), 86.5 (C-3), 50.9 (C-1), 33.3 (C-6), 32.1 (C-8), 28.9 (C-2), 27.0 (C-7), 19.1 (C-5'); HRMS (TOF FI$^+$), m/z: calcd for $C_{13}H_{19}N_3$ [M$^+$] 217.1579, found 217.1598.

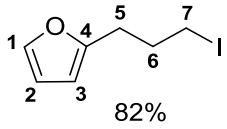
(*Z*)-12-Azido-8-methyldodeca-1,3,8,9-tetraene (*Z*-241)



To a solution of (*Z*)-5-methyldodeca-3,4,9,11-tetraen-1-yl methanesulfonate (**392**, 182 mg, 0.67 mmol) in DMSO (4 mL) was added NaN_3 (131 mg, 2.0 mmol) and the mixture was stirred at 30 °C for 24 hr, then at RT for 24 hr. The mixture was diluted with ether (40 mL), washed with half-brine (2×12 mL) and brine (12 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (1:99, ether/petrol) afforded the title material as a clear colourless oil (132 mg, 90%; *Z*/*E* > 10:1 (NMR)

R_f 0.66 (10:90, ether/petrol); ν_{max}/cm^{-1} 3085w (=C–H), 3008w (=C–H), 2097s (N_3), 1965w (C=C=C); δ_H (500 MHz, $CDCl_3$) 6.63 (1H, dtd, *J* = 16.5, 10.5, 1.0 Hz, H-11), 6.01 (1H, t, *J* = 10.5 Hz, H-10), 5.45 (1H, dt, *J* = 10.5, 7.5 Hz, H-9), 5.19 (1H, dd, *J* = 16.5, 2.0 Hz, H-12Z), 5.09 (1H, d, *J* = 10.0 Hz, H-12E), 5.04 (1H, tsext, *J* = 7.0, 3.0 Hz, H-3), 3.31 (2H, t, *J* = 7.0 Hz, H-1), 2.25 (2H, q, *J* = 7.0 Hz, H-2), 2.24 – 2.14 (2H, m, H-8), 1.96 (2H, tt, *J* = 7.5, 3.0 Hz, H-6), 1.69 (3H, d, *J* = 3.0 Hz, H-13), 1.51 (2H, quint, *J* = 7.5 Hz, H-7); δ_C (126 MHz, $CDCl_3$) 202.1 (C-4), 132.6 (C-9), 132.4 (C-11), 129.7 (C-10), 117.1 (C-12), 100.7 (C-5), 86.6 (C-3), 51.0 (C-1), 33.5 (C-6), 29.0 (C-2), 27.5 (C-7/8), 27.4 (C-7/8), 19.3 (C-13); HRMS (TOF FI$^+$), m/z: calcd for $C_{13}H_{19}N_3$ [M$^+$] 217.1579, found 217.1577.

2-(3-Iodopropyl)furan (242)[221,222]

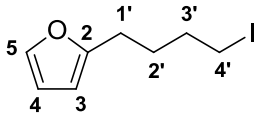


82%

NaI (15.55 g, 10.4 mmol) was added to a solution of 2-(3-chloropropyl)furan in butanone-2 (80 mL). This mixture was stirred at reflux for 15 hr. The volatiles were removed *in vacuo* (80 Torr). The residue was partitioned between half-sat. aq. NaCl (50 mL) and pentane (100 mL). The organic layer was separated and washed with aq. $Na_2S_2O_3$ (10%, 2×25 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated. The residue was a chromatographically inseparable mixture of the target material and 1,3-diiodopropane (85:15 mol% by ^1H NMR analysis). It was used as received (7.65 g, 82%).

R_f 0.34 (petrol); ν_{max}/cm^{-1} 3114w (=C–H), 2933m, 2869m, 1596m, 1506m, 1429m, 1010s, 727s; δ_H (250 MHz, $CDCl_3$) 7.31 (1H, dd, *J* = 2.0, 1.0 Hz, H-1), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H-2), 6.05 (1H, dd, *J* = 3.0, 1.0 Hz, H-3), 3.20 (2H, t, *J* = 7.0 Hz, H-7), 2.76 (2H, t, *J* = 7.0 Hz, H-5), 2.14 (2H, app. quint, *J* = 7.0 Hz, H-6); δ_C (101 MHz, $CDCl_3$) 154.0 (C-4), 141.2 (C-1), 110.1 (C-2), 105.8 (C-3), 31.7 (C-6), 28.6 (C-5), 5.8 (C-7).

2-(4-iodobutyl)furan (243)[223]

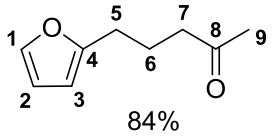


To a solution of 2-(4-chlorobutyl)furan (1.40 g, 11.5 mmol) in butanone (27 mL) was added NaI (5.19 g, 34.6 mmol). The resulting mixture was kept under reflux overnight (13 hr). The volatiles were removed at 80 Torr (RT). The brown residue was mixed with petrol (50 mL), washed sequentially with brine (30 mL) and aq. $Na_2S_2O_3$ (sat., 2×10 mL), then dried over $MgSO_4$ and concentrated. The residue was distilled in a

Kugelrohr apparatus (60 → 90 °C, 0.1 Torr) to yield the target material as a yellowish oil (2.09 g, 94%).

R_f 0.26 (petrol); ν_{max}/cm^{-1} 3115w (=C–H); δ_H (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* = 2.0 Hz, H-5), 6.29 (1H, dd, *J* = 3.0, 2.0 Hz, H-4), 6.01 (1H, dd, *J* = 3.0, 0.5 Hz, H-3), 3.21 (3H, t, *J* = 7.0 Hz, H-4'), 2.67 (2H, t, *J* = 7.5 Hz, H-1'), 1.93 – 1.83 (2H, m, H-3'), 1.82 – 1.72 (2H, m, H-2'); δ_C (101 MHz, $CDCl_3$) 155.4 (C-2), 140.9 (C-5), 110.1 (C-4), 105.1 (C-3), 32.8 (C-3'), 28.9 (C-2'), 26.8 (C-1'), 6.4 (C-4').

5-(Furan-2-yl)pentan-2-one (244)[226,227]

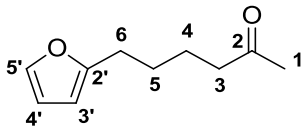


84%

Ethyl vinyl ether (1.96 g, 27.2 mmol) was dissolved in THF (14 mL) and cooled to −78 °C. A solution of *t*-BuLi (1.7M, 10 mL, 17.0 mmol) was added dropwise. The resulting yellow mixture was stirred at −78 °C for 30 min, then warmed to 0 °C, stirred for additional 25 min, and re-cooled to −78 °C. A solution of 2-(3-iodopropyl)furan (1.87 g, 86:14 mol% with 1,3-diiodopropane, 6.8 mmol) was slowly added. The resulting mixture was stirred at −78 °C for 30 min (overnight stirring is also acceptable). The reaction was quenched with a mixture of sat. aq. NH_4Cl (10 mL) and water (3 mL) at 0 °C. The aq. layer was separated and extracted with ether (2×8 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was redissolved in dry ether (15 mL). To this, PTSA·H_2O (1.29 g, 6.8 mmol) was added and the mixture was stirred at RT for 5 min (timing is essential as the product is acid-labile). The reaction was quenched with water (10 mL). The aq. layer was extracted with ether (10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (1:9 → 1:3, petrol/ether) afforded the product as a yellow oil that solidifies in freezer (0.844 g, 84%).

R_f 0.38 (25:75, ether/petrol); ν_{max}/cm^{-1} 1713s (C=O); δ_H (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, H-1), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, H-2), 5.99 (1H, br.dd, *J* = 3.0, 1.0 Hz, H-3), 2.64 (2H, t, *J* = 7.5 Hz, H-7), 2.46 (2H, t, *J* = 5.0 Hz, H-5), 2.12 (3H, s, H-9), 2.00 – 1.83 (2H, m, H-6); δ_C (101 MHz, $CDCl_3$) 208.5 (C-8), 155.3 (C-4), 141.0 (C-1), 110.1 (C-2), 105.3 (C-3), 42.6 (C-7), 30.0 (C-5), 27.1 (C-9), 22.1 (C-6).

6-(Furan-2-yl)hexan-2-one (245)[228]

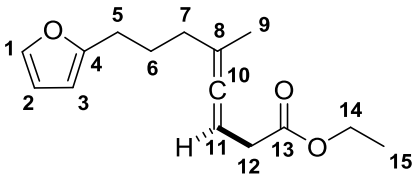


Ethyl vinyl ether (2.25 g, 31.2 mmol) was dissolved in freshly distilled THF (16 mL) and cooled to −78 °C. *t*-BuLi (11.8 mL, 1.6 M, 19 mmol) was added dropwise over 10 min. The resulting yellow solution was stirred at −78 °C for 30 min, then at 0 °C for 30 min. Upon warming the solution became colourless. The mixture was cooled down to −78 °C, followed by the dropwise addition of 2-(4-iodobutyl)furan (1.90 g, 7.6 mmol) in THF (10 mL). The mixture was stirred at −78 °C for 10 min, then the ice bath was removed and the stirring was continued for another 3.5 hr. The reaction was quenched at 0 °C with sat. aq. NH_4Cl (12 mL) and water (3 mL). The aq. layer was extracted with ether (2×10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was redissolved in dry ether (20 mL), followed by the addition of PTSA·H_2O (1.445 g, 7.6 mmol). The mixture was stirred for 6 min, then quenched with water (12 mL). The aq. layer was extracted with ether (2×12 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (5:95 → 20:80, ether/petrol) afforded the target material as a colourless oil (1.12 g, 89%).

R_f 0.35 (25:75, ether/petrol); ν_{max}/cm^{-1} 3116w (=C−H), 1713s (C=O); δ_H (400 MHz, $CDCl_3$) 7.28 (1H, dd, *J* = 2.0, 0.5 Hz, $H_{5'}$), 6.26 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.98

(1H, ddd, *J* = 3.0, 1.5, 0.5 Hz, H-3'), 2.63 (3H, br.t, *J* = 7.0 Hz, H-6), 2.44 (3H, br.t, *J* = 7.0 Hz, H-3), 2.12 (s, 3H, H-1), 1.69 – 1.57 (4H, m, H-5,4); δ_C (101 MHz, $CDCl_3$) 208.8 (C-2), 155.8 (C-2'), 140.8 (C-5'), 110.1 (C-4'), 104.8 (C-3'), 43.3 (C-3), 29.8 (C-1), 27.7 (C-6), 27.5 (C-5), 23.2 (C-4).

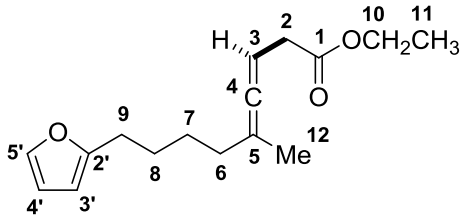
Ethyl 8-(furan-2-yl)-5-methylocta-3,4-dienoate (246)



Prepared by General method B from 6-(furan-2-yl)-3-methylhex-1-yn-3-ol (1.05 g, 5.31 mmol), $MeC(OEt)_3$ (14 mL), and propanoic acid (0.3 mL). Flash chromatography (5:95 → 15:85 → 25:75, ether/petrol) afforded the target material as a colourless oil along with some starting material (0.58 g, 44%; 75% b.r.s.m.).

R_f 0.56 (10:90, ether/petrol); ν_{max}/cm^{-1} 1968w (C=C=C), 1734s (C=O); δ_H (400 MHz, $CDCl_3$) 7.30 (1H, d, *J* = 1.0 Hz, H-1), 6.30 – 6.26 (1H, m, H-2), 5.99 (1H, d, *J* = 3.0 Hz, H-3), 5.19 (1H, app. ddt, *J* = 9.5, 7.0, 3.0 Hz, H-11), 4.15 (2H, q, *J* = 7.0 Hz, H-14), 2.99 (2H, d, *J* = 7.0 Hz, H-12), 2.64 (2H, t, *J* = 7.5 Hz, H-5), 1.99 (2H, td, *J* = 7.5, 3.0 Hz, H-7), 1.82 – 1.72 (2H, m, H-6), 1.69 (3H, d, *J* = 3.0 Hz, H-9), 1.29 – 1.22 (3H, m, H-15); δ_C (101 MHz, $CDCl_3$) 202.5 (C-10), 171.9 (C-13), 156.1 (C-4), 140.7 (C-1), 110.0 (C-2), 104.8 (C-3), 100.3 (C-8), 83.7 (C-11), 60.6 (C-14), 35.4 (C-12), 33.1 (C-7), 27.4 (C-5), 25.8 (C-6), 19.0 (C-9), 14.2 (C-15); HRMS (TOF FI+), m/z: calcd for $C_{15}H_{20}O_3$ [M^+] 248.1412, found 248.1415.

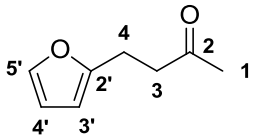
Ethyl 9-(furan-2-yl)-5-methylnona-3,4-dienoate (247)



To a solution of 7-(furan-2-yl)-3-methylhept-1-yn-3-ol (1.00 g, 5.2 mmol) in $MeC(OEt)_3$ (20 mL) was added propanoic acid (0.3 mL) and the resulting solution was stirred at reflux with distillative removal of ethanol for 8 hr. The reaction mixture was diluted with ether (60 mL) and washed sequentially with aq. HCl (0.5 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (7:93 → 25:75, ether/petrol) afforded the title compound as a clear yellowish oil with acrylic odour (0.85 g, 65%).

R_f 0.39 (10:90, ether/petrol); ν_{max}/cm^{-1} 3116w (=C–H), 1968w (C=C=C), 1735s (C=O); δ_H (400 MHz, $CDCl_3$) 7.29 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.97 (1H, dd, *J* = 3.0, 1.0 Hz, H-3'), 5.20 – 5.10 (1H, m, H-3), 4.15 (2H, q, *J* = 7.0 Hz, H-10), 2.98 (2H, d, *J* = 7.0 Hz, H-2), 2.62 (2H, t, *J* = 7.5 Hz, H-9), 1.97 (2H, td, *J* = 7.5, 3.0 Hz, H-6), 1.68 (3H, d, *J* = 3.0 Hz, H-12), 1.70 – 1.61 (2H, m, H-8), 1.48 (2H, tt, *J* = 7.5, 7.5 Hz, H-7), 1.27 (3H, t, *J* = 7.0 Hz, H-11); δ_C (101 MHz, $CDCl_3$) 202.5 (C-4), 171.9 (C-1), 156.4 (C-2'), 140.6 (C-5'), 110.0 (C-4'), 104.6 (C-3'), 100.5 (C-5), 83.4 (C-3), 60.6 (C-10), 35.4 (C-2), 33.4 (C-6), 27.8 (C-7/8/9), 27.5 (C-7/8/9), 26.8 (C-7/8/9), 18.9 (C-11), 14.2 (C-12); HRMS (ESI^+), m/z: calcd for $C_{16}H_{22}O_3Na$ [$M+Na^+$] 285.1461, found 285.1463.

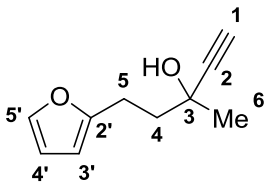
4-(Furan-2-yl)butan-2-one (248)[229]



Methyl vinyl ketone (1.40 g, 20 mmol) was added to a refluxing mixture of furan (15 mL) and PTSA (20 mg) over 3 hr using a syringe pump (note: the slow addition is essential to minimize dialkylation). The reaction was cooled to RT and stirred overnight (13 hr). Volatiles were then evaporated. Flash chromatography of the residue (15:85 → 25:75, ether/petrol → ether) afforded the title material as a colourless oil (1.08 g, 39%) along with dialkylated side product **374**.

R_f 0.41 (25:75, ether/petrol); ν_{max}/cm^{-1} 3148w (=C–H), 3118w (=C–H), 1716s (C=O); δ_H (400 MHz, $CDCl_3$) 7.29 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.99 (1H, ddd, *J* = 3.0, 1.5, 1.0 Hz, H-3'), 2.91 (2H, tm, *J* = 7.5 Hz, H-4), 2.78 (2H, tm, *J* = 7.5 Hz, H-3), 2.17 (3H, s, H-1); δ_C (101 MHz, $CDCl_3$) 207.3 (C-2), 154.5 (C-2'), 141.1 (C-5'), 110.2 (C-4'), 105.2 (C-3'), 41.7 (C-3), 29.9 (C-1), 22.1 (C-4); MS (ESI^+), m/z: 161.1 ($M+Na^+$).

5-(Furan-2-yl)-3-methylpent-1-yn-3-ol (249)[230]

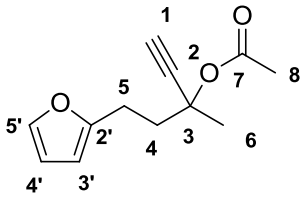


4-(Furan-2-yl)butan-2-one (0.75 g, 5.4 mmol) was added to a stock solution of HC≡CMgBr (0.5 M in THF, 12 mL, 6.0 mmol) with a syringe, and the mixture was heated at reflux for 3 hr. The reaction mixture was cooled down, diluted with ether (20 mL), and quenched with sat. aq. NH_4Cl (15 mL) and water (2 mL). The layers were separated and the aq. layer was extracted with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. Flash

chromatography (20:80, ether/petrol) afforded the title compound as a clear colourless oil (0.667 g, 75%).

R_f 0.31 (25:75, ether/petrol); ν_{max}/cm^{-1} 3403br.s (OH), 3291s (≡C−H), 3118w (=C−H), 2110w (C≡C); δ_H (400 MHz, $CDCl_3$) 7.35 – 7.30 (1H, m, H-5'), 6.33 – 6.26 (1H, m, H-4'), 6.07 – 6.01 (1H, m, H-3'), 2.99 – 2.82 (2H, m, H-5), 2.50 (1H, s, H-1), 2.11 (1H, br.s, OH), 2.07 – 2.00 (2H, m, H-4), 1.55 (3H, s, H-6); δ_C (101 MHz, $CDCl_3$) 155.3 (C-2'), 140.9 (C-5'), 110.2 (C-4'), 104.9 (C-3'), 86.9 (C-2), 71.9 (C-1), 67.6 (C-3), 41.3 (C-4), 29.9 (C-6), 23.5 (C-5).

5-(furan-2-yl)-3-methylpent-1-yn-3-yl acetate (250)

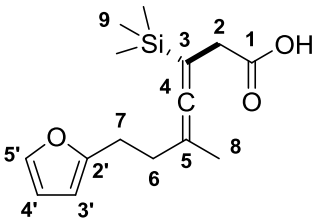


A solution of 5-(furan-2-yl)-3-methylpent-1-yn-3-ol (330 mg, 2.0 mmol) in DCM (4 mL) was cooled to 10 °C. To this were added in sequence: TEA (0.39 mL, 2.8 mmol), acetic anhydride (0.28 mL, 3.0 mmol), and DMAP (24 mg, 0.2 mmol). The ice bath was removed and the solution was stirred at RT for 16 hr. The crude reaction mixture was partitioned between DCM (20 mL) and water (15 mL). The aq. layer was extracted with DCM (10 mL). The combined organic layers were washed with brine (10 mL), dried by passing through a Phase Separator and concentrated. Flash chromatography (1:9, ether/petrol) afforded the title compound as a clear colourless oil that freezes between −20 °C and RT (374 mg, 91%).

R_f 0.43 (25:75, ether/petrol); ν_{max}/cm^{-1} 3290m (≡C−H), 2117w (C≡C), 1744s (C=O); δ_H (500 MHz, $CDCl_3$) 7.31 (1H, dd, *J* = 2.0, 0.5 Hz, H-5'), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 6.01 (1H, dd, *J* = 3.0, 0.5 Hz, H-3'), 2.92 – 2.79 (2H, m, H-5), 2.60 (1H, s, H-1), 2.35 – 2.23 (1H, m, H-4a), 2.20 – 2.08 (1H, m, H-4b), 2.03 (3H, s, H-8), 1.73 (3H, s, H-6);

δ_C (126 MHz, $CDCl_3$) 169.5 (C-7), 155.1 (C-2'), 141.1 (C-5'), 110.3 (C-4'), 105.1 (C-3'), 83.3 (C-2), 74.3 (C-3), 73.9 (C-1), 39.8 (C-4), 26.5 (C-6), 23.2 (C-5), 21.9 (C-8); HRMS (ESI^+), m/z: calcd for $C_{12}H_{14}O_3$ [M+Na^+] 229.0835, found 229.0829.

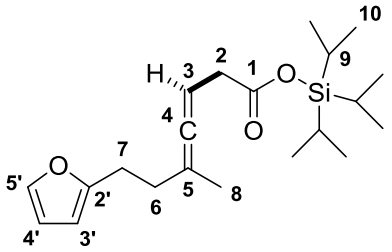
7-(Furan-2-yl)-5-methyl-3-(trimethylsilyl)hepta-3,4-dienoic acid (253)



Prepared according to the procedure by Baldwin and Bennett.[43,44] A stock solution of LiHMDS (0.6 mL, 1 M in THF, 0.6 mmol) was placed into a 5 mL flask and cooled to −78 °C. To this, TMSCl (76 μL, 0.6 mmol) was added using a microsyringe. The mixture was stirred for 5 min. Then, a solution of 5-(furan-2-yl)-3-methylpent-1-yn-3-yl acetate (42 mg, 0.2 mmol) in THF (0.5 mL) was added dropwise. The reaction was allowed to warm to RT and stirred for 2 days. The mixture was diluted with ether (10 mL) and quenched with brine (6 mL)/citrate buffer (4 mL, pH 3). The organic layer was separated, dried over $MgSO_4$ and concentrated. Flash chromatography (5:95 → 25:75, ether/petrol) afforded the title compound as a clear yellowish oil (17 mg, 30%).

R_f 0.34 (50:50, ether/petrol); ν_{max}/cm^{-1} 3100br.s (OH), 1944m (C=C=C), 1707s (C=O); δ_H (500 MHz, $CDCl_3$) 10.52 (1H, br.s, OH), 7.29 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.98 (1H, dd, *J* = 3.0, 1.0 Hz, H-3'), 2.96 (2H, s, H-2), 2.78 – 2.66 (2H, m, H-7), 2.27 (2H, t, *J* = 8.0 Hz, H-6), 1.70 (3H, s, H-8), 0.09 (9H, s, H-9); δ_C (126 MHz, $CDCl_3$) 206.1 (C-4), 177.9 (C-1), 155.9 (C-2'), 140.7 (C-5'), 110.1 (C-4'), 104.7 (C-3'), 94.9 (C-5), 90.5 (C-3), 36.1 (C-2), 31.6 (C-6), 26.4 (C-7), 18.3 (C-8), −1.4 (C-9); HRMS (ESI^+), m/z: calcd for $C_{15}H_{22}O_3SiNa$ [M+Na^+] 301.1230, found 301.1228.

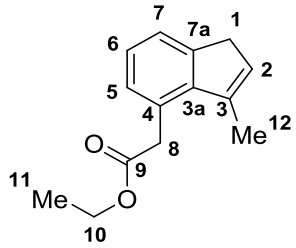
Tri-*tert*-butylsilyl 7-(furan-2-yl)-5-methylhepta-3,4-dienoate (254)



Prepared using a procedure by Brummond *et al.*[45,46] 5-(furan-2-yl)-3-methylpent-1-yn-3-yl acetate (312 mg, 1.5 mmol) was dissolved in dry benzene (7 mL) and transferred using a cannula into a dry 25 mL flask under argon. To this were added TEA (0.46 mL, 3.3 mmol) and TIPSOTf (0.65 mL, 2.4 mmol). After the mixture was stirred for 5 min, the septum was exchanged for a glass stopper, the flask was thoroughly sealed with parafilm and heated at 40 °C for 20 hr. The reaction content was then diluted with ether (50 mL), washed sequentially with water (15 mL) and brine (10 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (petrol → 1:99 → 10:90, ether/petrol) afforded the title product a clear yellowish oil (373 mg, 68%). *Note: one of the side products in this reaction is tentatively assigned as TIPSOAc and is rather difficult to separate by flash chromatography (R_f 0.63, 10:90, ether/petrol). It, however, does not interfere in the subsequent steps.*

R_f 0.57 (10:90, ether/petrol); ν_{max}/cm^{-1} 3116w (=C–H), 1967w (C=C=C), 1710s (C=O); δ_H (500 MHz, $CDCl_3$) 7.28 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 6.01 – 5.94 (1H, m, H-3'), 5.27 – 5.15 (1H, m, H-3), 2.98 (2H, dd, *J* = 7.5, 1.0 Hz, H-2), 2.73 (2H, m, H-7), 2.27 (2H, td, *J* = 8.0, 3.0 Hz, H-6), 1.70 (3H, d, *J* = 3.0 Hz, H-8), 1.30 (3H, hept, *J* = 7.5 Hz, H-9), 1.08 (18H, d, *J* = 7.5 Hz, H-10); δ_C (126 MHz, $CDCl_3$) 202.4 (C-4), 171.9 (C-1), 155.9 (C-2'), 141.0 (C-5'), 110.2 (C-3'), 104.9 (C-2'), 100.0 (C-5), 84.9 (C-3), 37.1 (C-2), 32.1 (C-6), 26.3 (C-7), 19.2 (C-8), 17.9 (C-10), 12.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{21}H_{34}O_3SiNa$ [M+Na^+] 385.2169, found 385.2169.

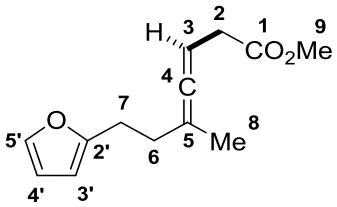
Ethyl 2-(3-methyl-1*H*-inden-4-yl)acetate (259)



5-(Furan-2-yl)-3-methylpent-1-yn-3-ol (0.62 g, 3.8 mmol) was dissolved in $MeC(OEt)_3$ (5 mL). Propanoic acid (0.15 mL) was added, and the mixture was stirred at 140 °C for 9 hr with distillative removal of ethanol. The reaction mixture was cooled to RT, diluted with ether (40 mL), washed with aq. HCl (0.5 M, 10 mL), sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL), then dried ($MgSO_4$) and concentrated. Flash chromatography (5:95 → 10:90, ether/petrol) afforded the title material as a colourless oil (0.52 g, 63%).

R_f 0.50 (25:75, ether/petrol); ν_{max}/cm^{-1} 3056w (=C–H), 1733s (C=O); δ_H (400 MHz, C_6D_6) 7.30 – 7.23 (2H, m, H-Ph), 7.21 – 7.15 (1H, m, H-Ph), 6.05 (1H, s, H-2), 3.97 (2H, q, *J* = 7.0 Hz, H-10), 3.87 (2H, s, H-8), 3.06 (2H, s, H-1), 2.38 (3H, s, H-12), 0.97 (3H, t, *J* = 7.0 Hz, H-11); δ_C (101 MHz, C_6D_6) 171.4 (C-9), 146.2 (C-7a), 141.1 (C-3a), 131.1 (C-2), 129.5 (C-5/6/7), 124.9 (C-5/6/7), 123.1 (C-5/6/7), 60.5 (C-10), 38.8 (C-8), 37.3 (C-1), 17.2 (C-12), 14.1 (C-11), *note:* the signals for C-3 and C-4 are presumably hidden under the solvent residual peak; HRMS (ESI^+), m/z: calcd for $C_{14}H_{16}NaO_2$ [$M+Na^+$] 239.1043, found 239.1036.

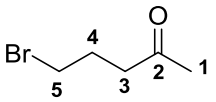
Methyl 7-(furan-2-yl)-5-methylhepta-3,4-dienoate (260)



5-(Furan-2-yl)-3-methylpent-1-yn-3-ol (0.10 g, 0.61 mmol) was dissolved in $HC(OMe)_3$ (3 mL). Propanoic acid (0.10 mL) was added, and the mixture was stirred at 105 °C for 7 hr with distillative removal of methanol. The reaction mixture was cooled to RT and diluted with ether (20 mL), then washed sequentially with aq. HCl (0.5 M, 5 mL), sat. aq. $NaHCO_3$ (5 mL), and brine (5 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (5:95 → 10:90 → 25:75, ether/petrol) afforded the title compound as a clear colourless oil (7 mg, 6%). *Note:* the product elutes closely to side products.

R_f 0.42 (10:90, ether/petrol); ν_{max}/cm^{-1} 3116w (=C–H), 1969w (C=C=C), 1740s (C=O); δ_H (400 MHz, $CDCl_3$) 7.33 – 7.28 (1H, m, H-5'), 6.31 – 6.26 (1H, m, H-4'), 6.01 – 5.96 (1H, m, H-3'), 5.24 – 5.15 (1H, m, H-3), 3.70 (3H, s, H-9), 2.96 (2H, d, *J* = 7.0 Hz, H-2), 2.78 – 2.70 (2H, m, H-7), 2.32 – 2.23 (2H, m, H-6), 1.72 (3H, d, *J* = 2.5 Hz, H-8); δ_C (101 MHz, $CDCl_3$) 202.4 (C-4), 172.3 (C-1), 155.7 (C-2'), 140.7 (C-5'), 110.1 (C-4'), 104.8 (C-3'), 100.0 (C-5), 84.2 (C-3), 51.8 (C-9), 35.3 (C-2), 31.9 (C-6), 26.1 (C-7), 18.9 (C-8); HRMS (ESI^+), m/z: calcd for $C_{13}H_{16}NaO_3$ $[M+Na^+]$ 243.0992, found 243.0988.

5-Bromopentan-2-one (262)[232]

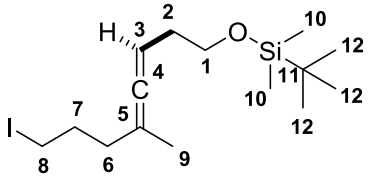


Prepared according to a modified procedure by Allemann *et al.*[232] A 250 mL flask was charged with reagent grade toluene (80 mL) and 2-acetylbutyrolactone (13 mL, 120 mmol). A reflux condenser was attached. To this rapidly stirred solution was added aq. HBr (48%, 20.5 mL, 180 mmol). The mixture was vigorously stirred under

argon at 80 °C for 14 hr. The reaction was cooled to RT and diluted with water (60 mL) and ether (60 mL). The layers were separated and the aq. layer was extracted with ether (2×40 mL). The combined organic extracts were washed sequentially with water (40 mL) and brine (40 mL), then dried over $MgSO_4$ and concentrated in vacuo (40 °C, 300→50 Torr). The brown residue was fractionally distilled with a Vigreux column, collecting the fraction that came out at 100–120 °C/10 Torr (oil bath temp). The product is a clear, slightly yellow oil that turns brown over time (15.44 g, 78%).

R_f 0.37 (25:75, ether/petrol); ν_{max}/cm^{-1} 1711s (C=O); δ_H (400 MHz, $CDCl_3$) 3.45 (2H, t, *J* = 6.5 Hz, H-5), 2.64 (2H, t, *J* = 7.0 Hz, H-3), 2.17 (3H, s, H-1), 2.12 (2H, tt, *J* = 7.0, 6.5 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 207.6 (C-2), 41.6 (C-3), 33.5 (C-5), 30.3 (C-1), 26.5 (C-4).

tert-Butyl((8-iodo-5-methylocta-3,4-dien-1-yl)oxy)dimethylsilane (263)

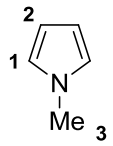


To a solution of *O*-TBS-8-bromo-5-methylocta-3,4-dien-1-ol (180 mg, 0.54 mmol) in acetone (6 mL) was added NaI (270 mg, 1.8 mmol). The mixture was stirred at RT for 6 hr. The reaction mixture was diluted with water (60 mL) and extracted with DCM (3×15 mL). The combined organic layers were dried through a Phase Separator and concentrated. Flash chromatography on a short column (1:99, ether/petrol) afforded the title material as a colourless oil (147 mg, 72%). The yield can be increased to 85-90% if the chromatography step is omitted (acceptable for the most of batches).

R_f 0.50 (2:98, ether/petrol); ν_{max}/cm^{-1} 1966w (C=C=C); δ_H (400 MHz, $CDCl_3$) 5.11 – 4.99 (1H, m, H-3), 3.66 (2H, t, *J* = 7.0 Hz, H-1), 3.22 (2H, t, *J* = 6.5 Hz, H-8), 2.19 (2H, td, *J* = 7.5, 7.0 Hz, H-2), 2.06 – 1.99 (2H, m, H-6), 1.99 – 1.89 (2H, m, H-7), 1.68 (3H,

s, H-9), 0.91 (9H, s, H-12), 0.07 (6H, s, H-10); δ_C (101 MHz, $CDCl_3$) 201.7 (C-4), 97.5 (C-5), 87.6 (C-3), 63.2 (C-1), 34.5 (C-6), 33.1 (C-2), 31.4 (C-7), 25.9 (C-12), 19.3 (C-9), 18.4 (C-11), 6.6 (C-8), −5.2 (C-10); HRMS (TOF FI^+), m/z: calcd for $C_{15}H_{29}OSiI$ [M^+] 380.1032, found 380.1031.

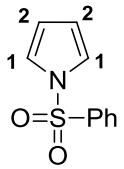
_N_-Methyl-1_H_-pyrrole (264)[323]



Pyrrole (3.00 g, 44.7 mmol) and KOH (5.00 g, 67.1 g) were mixed in a 50 mL flask, followed by the addition of tetrabutylammonium bromide (1.45 g, 4.5 mmol). The mixture was sonicated for 1 hr. The flask was placed into a water bath (RT); MeI (9.5 g, 67.1 mmol) was then added slowly (*warning:* due to the intense self-heating, the first few drops should be added very slowly). The mixture was stirred at RT for 24 hr. The reaction contents was diluted with DCM (50 mL). The solids were separated by filtration through a plug of Florisil (ca. 2 cm), washing with DCM (70 mL). The solution was concentrated (300 → 200 Torr, 20 °C) and the residue was distilled in Kugelrohr (150 Torr, 100 °C; the receiver was cooled with dry ice/acetone). Finally, DCM leftovers were removed by evaporation (150 Torr, 20 °C) (2.43 g, 68%).

R_f 0.56 (10:90, ether/petrol); ν_{max}/cm^{-1} 3100w (=C−H), 1286s; δ_H (400 MHz, $CDCl_3$) 6.65 (2H, t, *J* = 2.0 Hz, H-1), 6.19 (2H, t, *J* = 2.0 Hz, H-2), 3.71 (3H, s, H-3). δ_C (101 MHz, $CDCl_3$) 121.7 (C-1), 108.2 (C-2), 36.1 (C-3).

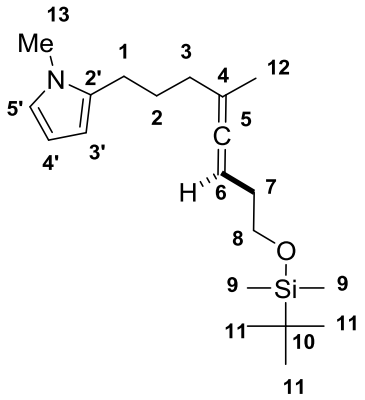
1-(Phenylsulfonyl)-1*H*-pyrrole (265)[233,324]



Following a modified literature procedure,[233] pyrrole (0.53 g, 7.9 mmol) was dissolved in DCM (10 mL), followed by tetrabutylammonium hydrogen sulfate (0.27 g, 0.79 mmol) and aq. NaOH (4.9 g in 8 mL H_2O). The biphasic mixture was cooled to 0 °C and stirred rapidly (ca. 1000 rpm). $PhSO_2Cl$ (2.10 g, 11.9 mmol) was added fairly quickly. The ice bath was removed and the slurry was stirred at RT for 20 hr. The reaction mixture was filtered through a Celite pad (ca. 1 cm), and the cake was thoroughly washed with DCM (ca. 40 mL). The organic layer was washed with water (4×10 mL) and brine (10 mL), passed through Whatman Phase Separator, and concentrated. Flash chromatography (20:80, ether/petrol) afforded the title compound as a white solid (1.38 g, 84%). *Note:* the mixture is better loaded into the column as a concentrated solution in DCM.

R_f 0.40 (25:75, ether/petrol); m.p.: 86–88 °C (lit.[233] 88–89 °C); ν_{max}/cm^{-1} 3137w, 1451m, 1366s, 1189s, 1169s; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, app.d, *J* = 7.5 Hz, H-Ph), 7.61 (1H, app.t, *J* = 7.0 Hz, H-Ph), 7.51 (1H, app.t, *J* = 7.0 Hz, H-Ph), 7.18 (1H, s, H-1), 6.31 (1H, s, H-2); δ_C (101 MHz, $CDCl_3$) 139.1 (C-Ar), 133.8 (C-Ar), 129.4 (C-Ar), 126.8 (C-Ar), 120.8 (C-1), 113.7 (C-2).

2-(8-((*tert*-Butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-1-methyl-1*H*-pyrrole (266)

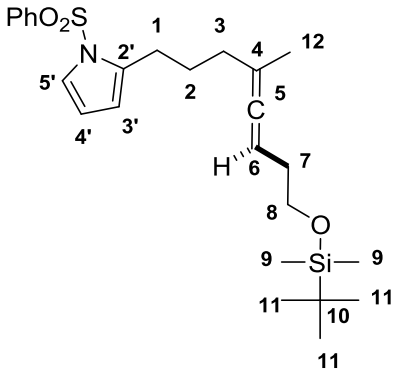


Following a modified literature procedure,[325] *N*-methylpyrrole (325 mg, 4.0 mmol) was dissolved in THF (8 mL; degassed by bubbling argon for 30 min) and cooled to −78 °C. BuLi was added dropwise (1.6 M, 2.5 mL, 4.0 mmol). The resulting yellowish solution was stirred at −78 °C for 10 min, then the ice bath was removed and the reaction was allowed to warm to RT and stirred overnight (14 hr). *Note: the solution of ArLi should be pale yellow at this point, with a bit of cloudiness.* To this solution was added neat *O*-TBS-8-iodo-5-methylocta-3,4-dien-1-ol (380 mg, 1.0 mmol) at −78 °C, the bath was removed and the reaction was stirred at RT for ca. 24 hr. The reaction was then diluted with ether (50 mL), washed with sat. aq. NH_4Cl (2×15 mL) and brine (2×15 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (3:97, ether/petrol) afforded the title compound as a colourless oil (240 mg, 72%).

R_f 0.61 (10:90, ether/petrol); ν_{max}/cm^{-1} 3102w (=C−H), 1965w (C=C=C); δ_H (500 MHz, $CDCl_3$) 6.54 (1H, dd, *J* = 2.5, 2.0 Hz, H-5'), 6.06 (1H, dd, *J* = 3.5, 2.5 Hz, H-4'), 5.89 (1H, ddt, *J* = 3.5, 2.0, 1.0 Hz, H-3'), 5.04 (1H, tsext, *J* = 7.0, 3.0 Hz, H-6), 3.66 (2H, m, H-8), 3.54 (3H, s, H-13), 2.56 (2H, m, H-1), 2.20 (2H, q, *J* = 7.0 Hz, H-7), 2.05 – 2.00 (2H, m, H-3), 1.75 (2H, quint, *J* = 7.5 Hz, H-2), 1.69 (3H, d, *J* = 3.0 Hz, H-12), 0.91 (9H, s, H-11), 0.07 (6H, s, H-9); δ_C (126 MHz, $CDCl_3$) 202.2 (C-5), 133.5 (C-2'), 121.1 (C-5'), 106.6 (C-4'),

105.6 (C-3'), 98.9 (C-4), 87.1 (C-6), 63.4 (C-8), 33.8 (C-3/13), 33.7 (C-3/13), 33.4 (C-7), 26.9 (C-2), 26.1 (C-1/11), 25.9 (C-1/11), 19.5 (C-12), 18.5 (C-10), −5.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{20}H_{36}NOSi$ $[M+H]^+$ 334.2561, found 334.2551.

2-(8-((*tert*-Butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrole (267)

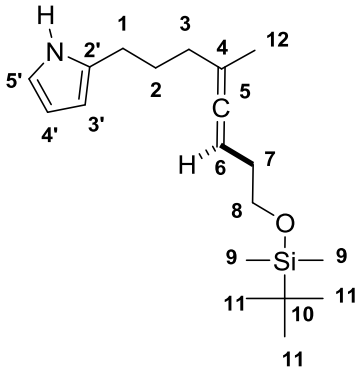


A solution of 2,2,6,6-tetramethylpiperidine (245 mg, 1.74 mmol) in THF (6 mL) was cooled to 0 °C, followed by the addition of BuLi (1.1 mL, 1.6M, 1.7 mol). The mixture was stirred at 0 °C for 30 min, then cooled to −78 °C. To this was added dropwise a solution of 1-(phenylsulfonyl)-1*H*-pyrrole (360 mg, 1.74 mmol) in THF (3 mL) in 3×1.0 mL portions every 2 minutes. The reaction was stirred −78 °C for 60 min. Then, a solution of *O*-TBS-8-iodo-5-methylocta-3,4-dien-1-ol (330 mg, 0.87 mmol) in DMPU (6 mL) was added over 30 min using a syringe pump. The cooling bath was covered in foil and the reaction was allowed to slowly warm up to RT overnight (ca. 16 hr), followed by additional 5 hr of stirring at RT. *Note*: *the reaction is extremely sensitive to moisture and overheating. Precautions should be made to exclude air and moisture (freshly distilled THF and DMPU, properly sealed flasks, etc.). The intermediate aryl lithium appears to decompose above −78 °C (cf. N-Boc-2-pyrrolyl lithium*[326]*). The yield dropped to 18-23% if alkyl iodide was not added slowly enough to allow temperature equilibration with the ice bath.* The reaction was diluted with ether (50 mL), washed with citrate buffer (3×15 mL, pH 3) and brine (2×15 mL), then dried ($MgSO_4$) and

concentrated. Flash chromatography (10:90, ether/petrol) afforded the title compound as a colourless oil (260 mg, 67%), along with the excess of the starting pyrrole.

R_f 0.43 (10:90 ether/petrol); ν_{max}/cm^{-1} 3067w (=C−H), 1975w (C=C=C), 1369s, 1186s, 1093s; δ_H (500 MHz, $CDCl_3$) 7.77 – 7.73 (2H, m, H-Ph), 7.62 – 7.57 (1H, m, H-Ph), 7.53 – 7.48 (2H, m, H-Ph), 7.30 (1H, dd, *J* = 3.5, 2.0 Hz, H-5'), 6.22 (1H, d, *J* = 3.5 Hz, H-4'), 6.01 (1H, ddt, *J* = 3.5, 2.0, 1.0 Hz, H-3'), 4.99 (1H, tsext, *J* = 7.0, 3.0 Hz, H-6), 3.63 (2H, m, H-8), 2.67 (2H, t, *J* = 7.5 Hz, H-1), 2.16 (2H, q, *J* = 7.0, H-7), 1.92 (2H, td, *J* = 7.5, 3.0 Hz, H-3), 1.68 (2H, quint, *J* = 7.5 Hz, H-2), 1.63 (3H, d, *J* = 3.0 Hz, H-12), 0.90 (9H, s, H-11), 0.05 (6H, s, H-9); δ_C (126 MHz, $CDCl_3$) 201.8 (C-5), 139.5 (C-Ph), 135.7 (C-2'), 133.6 (C-Ph), 129.3 (C-Ph), 126.6 (C-Ph), 122.3 (C-Ph), 112.0 (C-3'), 111.4 (C-4'), 98.6 (C-4), 86.9 (C-6), 63.3 (C-8), 33.4 (C-3/7), 33.1 (C-3/7), 26.6 (C-1/2), 26.5 (C-1/2), 25.9 (C-11), 19.2 (C-12), 18.3 (C-10), −5.3 (C-9); HRMS (ESI^+), m/z: calcd for $C_{25}H_{37}NNaO_3SSi$ $[M+Na^+]$ 482.2156, found 482.2152.

2-(8-((*tert*-Butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-1H-pyrrole (268)

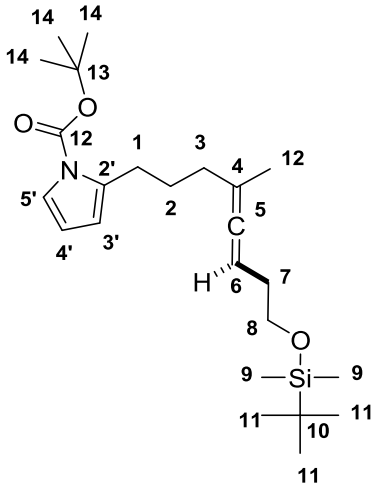


Following a modified literature procedure,[327] 2-(8-((*tert*-butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrole (260 mg, 0.57 mmol) was dissolved in dry MeOH (ca. 12 mL), followed by Mg powder (50 mesh, 69 mg, 2.8 mmol). The reaction was sonicated (Kerry Pulsatron) for 4 hr, keeping the bath close to RT (ca. 18-25 °C) by the periodic addition of ice. *Note: the*

reaction does not work in commercial grade methanol or with large Mg turnings. Solvent, freshly dried by passing through an activated alumina column, and commercial Mg powder (50 mesh) are sufficient. The reaction mixture was filtered through a cotton plug, eluting with ether (note: this process is extremely slow, the use of filter aid is advised), then evaporated. The residue was dissolved in ether (ca. 20 mL) and washed with sat. aq. NH_4Cl. The aq. layer was separated and extracted with ether (2×15 mL). The combined organic layers were washed with brine (2×10 mL), dried over $MgSO_4$, and filtered through a 3 cm silica plug. The residue was evaporated to afford spectroscopically pure target material as a colourless oil that turns brown over time (159 mg, 88%). *Note: the product is chromatographically indistinguishable from the starting material (ether/petrol-based eluents)*.

R_f 0.63 (25:75, ether/petrol); ν_{max}/cm^{-1} 3389br.m (NH), 1960w (C=C=C); δ_H (500 MHz, $CDCl_3$) 7.99 (1H, br.s, NH), 6.67 (1H, td, *J* = 3.0, 1.5 Hz, H-5'), 6.13 (1H, app.q, *J* = 3.0 Hz, H-4'), 5.95 – 5.89 (1H, m, H-3'), 5.04 (1H, tsext, *J* = 7.0, 3.0 Hz, H-6), 3.67 (2H, t, *J* = 7.0 Hz, H-8), 2.63 (2H, t, *J* = 7.5 Hz, H-1), 2.20 (2H, q, *J* = 7.0 Hz, H-7), 1.98 (2H, td, *J* = 7.5, 3.0 Hz, H-3), 1.75 (2H, quint, *J* = 7.5 Hz, H-2), 1.68 (3H, d, *J* = 3.0 Hz, H-12), 0.91 (9H, s, H-11), 0.07 (6H, s, H-9); δ_C (126 MHz, $CDCl_3$) 202.1 (C-5), 132.7 (C-2), 116.2 (C-5'), 108.4 (C-4'), 105.2 (C-3'), 98.9 (C-4), 87.2 (C-6), 63.4 (C-8), 33.41 (C-3/7), 33.35 (C-3/7), 27.7 (C-2), 27.2 (C-1), 26.1 (C-11), 19.5 (C-12), 18.5 (C-10), −5.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{19}H_{33}NNaOSi$ [$M+Na^+$] 342.2224, found 342.2211.

2-(8-OTBS-4-methylocta-4,5-dien-1-yl)-1-Boc-1*H*-pyrrole (269)

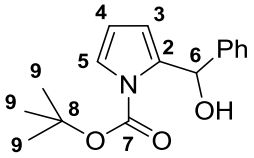


Following a modified literature procedure,[234,235] 2-(8-((*tert*-butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-1*H*-pyrrole (155 mg, 0.48 mmol) was dissolved in MeCN (ca. 8 mL), followed by Boc_2O (127 mg, 0.58 mmol) and DMAP (6 mg, 0.048 mmol). The solution was stirred at RT for 20 hr. TLC showed that the reaction was incomplete; therefore, additional 52 mg of Boc_2O were added and the mixture was stirred for 8 hr, after which TLC indicated complete consumption of the starting material. The reaction content was partitioned between ether (50 mL) and sat. aq. $NaHCO_3$ (10 mL). The aq. layer was extracted with ether (10 mL), and the combined organic layers were washed with brine (2×10 mL), dried over $MgSO_4$, and concentrated. Flash chromatography on a short silica column (5 cm; 10:90, ether/petrol) afforded the target material as a clear slightly yellowish oil (183 mg, 90%).

R_f 0.67 (10:90, ether/petrol); ν_{max}/cm^{-1} 1965w (C=C=C), 1744s (C=O); δ_H (500 MHz, $CDCl_3$) 7.19 (1H, dd, *J* = 3.5, 2.0 Hz, H-5'), 6.08 (1H, t, *J* = 3.5 Hz, H4'), 5.98 – 5.93 (1H, m, H3'), 5.02 (1H, tsext, *J* = 7.0, 3.0 Hz, H-6), 3.70 – 3.60 (2H, m, H-8), 2.85 (2H, t, *J* = 7.5 Hz, H-1), 2.19 (2H, q, *J* = 7.0 Hz, H-7), 1.99 (2H, td, *J* = 7.5, 3.0 Hz, H-3), 1.73 (2H, quint, *J* = 7.5 Hz, H-2), 1.68 (3H, d, *J* = 3.0 Hz, H-12), 1.59 (9H, s, H-14), 0.90 (9H, s, H-

11), 0.05 (6H, s, H-9); δ_C (126 MHz, $CDCl_3$) 202.0 (C-5), 149.7 (C-12), 136.2 (C-2'), 120.9 (C-5'), 111.1 (C-3'), 110.0 (C-4'), 99.1 (C-4), 86.9 (C-6), 83.4 (C-13), 63.5 (C-8), 33.7 (C-7), 28.6 (C-1), 28.2 (C-14), 27.0 (C-2), 26.1 (C-11), 19.5 (C-12), 18.5 (C-10), −5.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{24}H_{41}NNaO_3Si$ [$M+Na^+$] 442.2748, found 442.2731.

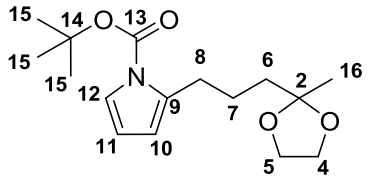
(*N*-Boc-1*H*-pyrrol-2-yl)(phenyl)methanol (270)[326]



2,2,6,6-Tetramethylpiperidine (0.20 mL 1.2 mmol) was dissolved in freshly distilled THF (2 mL) and cooled to −78 °C. BuLi solution (1.6 M, 0.74 mL, 1.2 mmol) was added dropwise. The yellow mixture was stirred at −78 °C for 5 min, at 0 °C for 5 min, then cooled back to −78 °C. *N*-Boc-1*H*-pyrrole (0.20 mL, 1.2 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 hr. Neat benzaldehyde (150 mg, 1.4 mmol) was added dropwise. The resulting pale brown mixture was stirred at −78 °C for 1 hr. The reaction mixture was quenched with aq. NaOH (3 M, 1 mL) at −78 °C, then warmed to RT. The mixture was diluted with ether (5 mL), the layers were separated, and the organic layer was washed with a citrate buffer (3×4 mL, pH 3), brine (2 mL), then dried over $MgSO_4$, and concentrated. Flash chromatography (1:9, ether/petrol) afforded the target material as a viscous lime-green oil (170 mg, 66%).

R_f 0.42 (25:75, ether/petrol); ν_{max}/cm^{-1} 3480br.s (OH), 1719s (C=O); δ_H (400 MHz, $CDCl_3$) 7.45 – 7.39 (2H, m, H-Ph), 7.39 – 7.33 (2H, m, H-Ph), 7.33 – 7.26 (1H, m, H-Ph), 7.21 (1H, dd, *J* = 3.5, 2.0 Hz, H-5), 6.06 (1H, m, H-3), 6.04 (1H, d, *J* = 6.0 Hz, H-6), 5.73 (1H, dd, *J* = 2.5, 2.0 Hz, H-4), 4.55 (1H, d, *J* = 6.0 Hz, OH), 1.58 (9H, s, H-9); δ_C (101 MHz, $CDCl_3$) 150.3 (C-7), 141.5 (C-2/Ph), 137.9 (C-2/Ph), 128.0 (C-Ph), 127.3 (C-Ph), 126.7 (C-Ph), 122.4 (C-5), 114.7 (C-4), 110.2 (C-3), 84.8 (C-8), 69.0 (C-6), 27.9 (C-9).

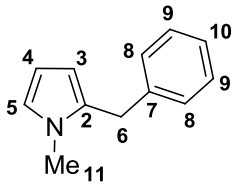
2-(3-(2-Methyl-1,3-dioxolan-2-yl)propyl)-*N*-Boc-1*H*-pyrrole (271)



2,2,6,6-Tetramethylpiperidine (85 mg, 0.6 mmol) was dissolved in freshly distilled THF (1 mL) and cooled to −78 °C. The solution was stirred for 5 min; *N*-Boc-pyrrole (100 mg, 0.6 mmol) was then added. The brown mixture was stirred at −78 °C for 45 min. A solution of 2-(3'-iodopropyl)-2-methyl-1,3-dioxolane (154 mg, 0.6 mmol) in THF (1 mL) was added. After 30 min at −78 °C, the solution was allowed to warm to RT and stirred overnight (14 hr). The reaction was quenched with aq. NaOH (3 M, 2 mL), diluted with ether (10 mL) and washed with a citrate buffer (3×2 mL, pH 3), then dried over $MgSO_4$ and concentrated. Flash chromatography (1:9 → 1:5, ether/petrol) delivered target material as a brown oil (14 mg, 9%).

R_f 0.13 (25:75, ether/petrol); ν_{max}/cm^{-1} 1674s (C=O); δ_H (500 MHz, $CDCl_3$) 6.94 – 6.90 (1H, m, H-12), 6.86 – 6.83 (1H, m, H-11), 6.26 – 6.23 (1H, m, H-10), 4.02 – 3.87 (4H, m, H-4,5), 3.22 (2H, t, *J* = 7.0 Hz, H-8), 2.01 – 1.91 (2H, m, H-6), 1.79 – 1.73 (2H, m, H-7), 1.57 (9H, s, H-15), 1.33 (3H, s, H-16); δ_C (126 MHz, $CDCl_3$) 160.5 (C-13), 124.4 (C-9), 121.9 (C-12), 114.5 (C-11), 110.2 (C-10), 109.4 (C-2), 80.8 (C-14), 64.7 (C-4,5), 43.8 (C-8), 39.8 (C-7), 28.4 (C-15), 28.2 (C-6), 23.9 (C-16); HRMS could not be obtained for this compound.

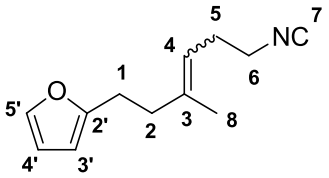
2-Benzyl-1-methyl-1*H*-pyrrole (272)[325]



N-Methyl-1*H*-pyrrole (81 mg, 1.0 mmol) was dissolved in THF (2.0 mL) and cooled to −78 °C. BuLi (0.63 mL, 1.6M in hexanes, 1.0 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 10 min, then allowed to warm to RT and stirred overnight (ca. 14 hr). Neat benzyl bromide (171 mg, 1.0 mmol) was added to the reaction at −78 °C. The reddish mixture was stirred at −78 °C for 10 min, then allowed to warm to RT and stirred for 6 hr. The reaction was diluted with ether (6 mL), then washed with water (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (petrol → 5:95, ether/petrol) to afford a colourless oil (34 mg, 20%).

R_f 0.46 (10:90, ether/petrol); ν_{max}/cm^{-1} 3084w (=C–H), 3061w (=C–H), 3026w (=C–H), 1493s, 697s; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.29 (2H, m, H-Ph), 7.28 – 7.17 (3H, m, H-Ph), 6.62 (1H, dd, *J* = 2.5, 2.0 Hz, H-5), 6.12 (1H, dd, *J* = 3.5, 2.5 Hz, H-4), 5.99 – 5.93 (1H, m, H-3), 3.99 (2H, s, H-6), 3.47 (3H, s, H-11); δ_C (101 MHz, $CDCl_3$) 139.5 (C-7), 131.4 (C-2), 128.5 (C-Ph), 126.2 (C-Ph), 121.8 (C-5), 107.9 (C-3), 106.6 (C-4), 33.8 (C-11), 32.9 (C-6).

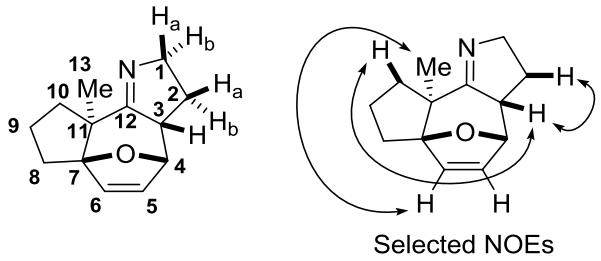
EZ-2-(6-isocyano-3-methylhex-3-en-1-yl)furan (273)



A solution of 7-(furan-2-yl)-5-methylhepta-3,4-dienyl azide (20 mg, 0.09 mmol) in degassed *m*-xylene (0.7 mL) was transferred into a dry NMR vial, thoroughly flushed with argon, sealed and heated in an oil bath at 135 °C for 2 hr. The crude reaction mixture was loaded directly onto a pipette silica column and eluted with the following gradient: petrol → 5:95, ether/petrol. The title material was isolated as a clear volatile oil with a disagreeable odour (2 mg, 11%, *E*/*Z* = 1:1).

R_f 0.25 (5:95, ether/petrol); ν_{max}/cm^{-1} 3110w (=C−H), 2148s (NC); δ_H (500 MHz, $CDCl_3$) 7.30 (1H, m, H-5'), 6.29 – 6.25 (1H, m, H-4'), 6.00 – 5.97 (1H, m, H-3'), 5.18 – 5.11 (1H, m, H4), 3.32 (1H, tt, *J* = 7.0, 2.0 Hz, H-6E/6Z), 3.22 (1H, tt, *J* = 7.0, 2.0 Hz, H-6E/6Z), 2.74 (½×2H, t, *J* = 7.5 Hz, H-1E/1Z), 2.73 (½×2H, t, *J* = 7.5 Hz, H-1E/1Z), 2.42 – 2.24 (4H, m, H-2,5E,5Z), 1.74 (½×3H, d, *J* = 1.0 Hz, H-8E), 1.68 (½×3H, s, H-8Z); δ_C (126 MHz, $CDCl_3$) 155.9 (t, *J* = 6.0 Hz, C-7E/7Z), 155.8 (t, *J* = 6.0 Hz, C-7E/7Z), 155.7 (C-2'E/2'Z), 155.4 (C-2'E/2'Z), 141.1 (C-5'E/5'Z), 140.9 (C-5'E/5'Z), 138.8 (C-3E/3Z), 138.3 (C-3E/3Z), 120.4 (C-4E/4Z), 119.4 (C-4E/4Z), 110.4 (C-4'E/4'Z), 110.2 (C-4'E/4'Z), 105.5 (C-3'E/3'Z), 105.1 (C-3'E/3'Z), 41.7 (t, *J* = 6.5 Hz, C-6E/6Z), 41.6 (t, *J* = 6.5 Hz, C-6E/6Z), 38.0 (C-2E), 30.7 (C-2Z), 28.2 (C-5E/5Z), 27.9 (C-5E/5Z), 26.9 (C-1E/1Z), 26.5 (C-1E/1Z), 23.3 (C-8E), 16.27 (C-8Z); HRMS (TOF FI^+), m/z: calcd for $C_{12}H_{15}NO$ [M^+] 189.1154, found 189.1152.

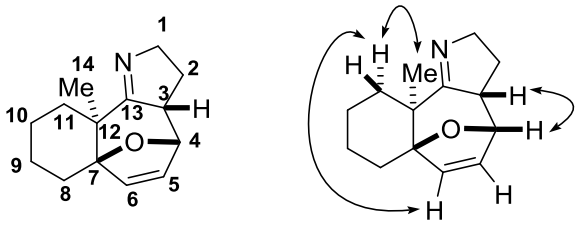
9a-Methyl-2,3,3a,4,7,8,9,9a-octahydro-4,6a-epoxyazuleno[4,5-b]pyrrole (275)



Prepared by General method G from 2-(8-azido-4-methylocta-4,5-dien-1-yl)furan (100 mg, 0.43 mmol) and freshly distilled *m*-xylene (3 mL) in a glass bomb. The crude reaction mixture was loaded directly onto a silica column (petrol → 10:90 → 25:75 → 50:50, ether/petrol → ether → 5:95, methanol/ether). The product is a yellow oil with an unpleasant odour (25 mg, 29%; 40% b.r.s.m.)

R_f 0.24 (5:95, methanol/ether); ν_{max}/cm^{-1} 3073w (=C–H), 1632s (C=N), 1305m, 1004s; δ_H (500 MHz, $CDCl_3$) 6.21 (1H, d, *J* = 6.0 Hz, H-6), 6.18 (1H, dd, *J* = 6.0, 1.5 Hz, H-5), 4.86 (1H, dd, *J* = 5.0, 1.5 Hz, H-4), 3.92 – 3.86 (1H, m, H-1a), 3.55 – 3.46 (1H, m, H-1b), 3.17 – 3.10 (1H, br. m, H-3), 2.23 – 2.14 (2H, m, H-8a,10a), 2.07 – 1.93 (3H, m, H-2a,9ab), 1.86 (1H, ddd, *J* = 14.0, 9.5, 3.5 Hz, H-10b), 1.56 – 1.50 (1H, ddd, *J* = 12.0, 8.0, 2.5 Hz, H-8b), 1.28 – 1.19 (1H, m, H-2b), 1.08 (3H, s, H-13); δ_C (126 MHz, $CDCl_3$) 181.5 (C-12), 135.1 (C-6), 131.7 (C-5), 97.4 (C-7), 80.4 (C-4), 58.8 (C-1), 54.3 (C-11), 48.4 (C-3), 33.7 (CH_2), 29.7 (CH_2), 26.0 (CH_2), 21.3 (CH_2), 19.5 (C-13); HRMS (TOF ESI^+), m/z: calcd for $C_{13}H_{18}NO$ [$M+H^+$] 204.1383, found 204.1383.

(3a*S*,4*S*,6a*R*,10a*S*)-10a-Methyl-3,3a,4,7,8,9,10,10a-octahydro-2*H*-4,6a-epoxybenzo[6,7]cyclohepta[1,2-*b*]pyrrole (276)

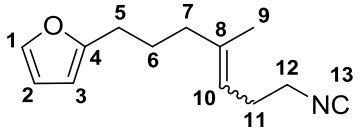


Selected NOEs

2-(9-Azido-5-methylnona-5,6-dien-1-yl)furan (30 mg, 0.12 mmol) was dissolved in degassed xylene (0.6 mL) in a dry NMR tube, thoroughly flushed with argon and sealed. The reaction was heated at 135 °C for 100 min. The mixture was cooled down and loaded directly onto a pipette silica column, eluting with the following gradient: petrol → 2:98 → 10:90 → 25:75 → 50:50, ether/petrol → ether → 3:97, MeOH/ether, to afford the unstable title compound as a colourless oil (2 mg, 8%).

R_f 0.25 (5:95, MeOH/ether); ν_{max}/cm^{-1} 3075w (=C–H), 1633 (C=N); δ_H (500 MHz, $CDCl_3$) 6.13 (1H, dd, *J* = 6.0, 2.0 Hz, H-5), 6.06 (1H, d, *J* = 6.0 Hz, H-6), 4.91 (1H, dd, *J* = 5.0, 2.0 Hz, H-4), 3.86 (1H, ddt, *J* = 15.0, 9.0, 1.0 Hz, H-1a), 3.52 – 3.45 (1H, m, H-1b), 3.28 – 3.22 (1H, m, H-3), 2.10 (1H, td, *J* = 13.0, 5.5 Hz, H-8a), 2.01 (1H, dddd, *J* = 12.5, 8.5, 7.0, 1.0 Hz, H-2a), 1.98 – 1.91 (1H, m, H-11a), 1.76 – 1.59 (5H, m, H-11b,9ab,10ab), 1.37 – 1.31 (1H, m, H-8b), 1.20 (4H, s over m, H-14,2b); δ_C (126 MHz, $CDCl_3$) 183.0 (C-13), 137.7 (C-6), 131.1 (C-5), 87.7 (C-7), 81.1 (C-4), 58.9 (C-1), 49.2 (C-3), 46.0 (C-12), 32.2 (C-8), 28.5 (C-11), 25.6 (C-2), 20.9 (C-9/10), 20.5 (C-9/10), 18.2 (C-14); HRMS (TOF ESI^+), m/z: calcd for $C_{14}H_{20}NO$ $[M+H^+]$ 218.1539, found 218.1536.

EZ-2-(7-Isocyano-4-methylhept-4-en-1-yl)furan (277)

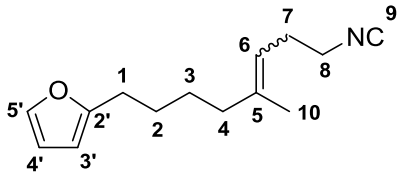


E/*Z* = 1:1

Prepared by General method G from 2-(8-azido-4-methylocta-4,5-dien-1-yl)furan (100 mg, 0.43 mmol) and freshly distilled *m*-xylene (3 mL) in a tightly sealed glass bomb. The crude reaction mixture was loaded onto a silica column (petrol → 10:90 → 25:75 → 50:50, ether/petrol → ether → 5:95, methanol/ether). The product is a yellow oil with an unpleasant odour (5 mg, 6%).

R_f 0.40 (10:90, ether/petrol); ν_{max}/cm^{-1} 2148s (NC); δ_H (500 MHz, $CDCl_3$) 7.31 (1H, dd, *J* = 5.5, 1.0 Hz, H-1E,1Z), 6.31 – 6.27 (1H, m, H-2E,2Z), 6.00 (1H, 2×dd, *J* = 3.0, 1.0 Hz, H-3E,3Z), 5.16 (1H, app. tp, *J* = 7.0, 1.0 Hz, H-10E,10Z), 3.35 (2H, 2×tt, *J* = 7.0, 2.0 Hz, H-12E,12Z), 2.62 (2H, app. q, *J* = 7.5 Hz, H-5E,5Z), 2.44 – 2.31 (2H, m, H-11E,11Z), 2.08 (2H, app. q, *J* = 8.0 Hz, H-7E,7Z), 1.81 – 1.75 (2H, m, H-6E,6Z), 1.74 (d, *J* = 1.0 Hz, ½×3H, H-9Z), 1.66 (s, ½×3H, H-9E); δ_C (126 MHz, $CDCl_3$) 156.0 (C-4E/Z), 155.8 (C-4E/4Z), 155.7 (m, C-13E,13Z), 140.8 (C1E/1Z), 140.7 (C-1E/1Z), 139.3 (C-8E/8Z), 139.2 (C-8E/8Z), 119.5 (C-10E/10Z), 118.9 (C-10E/10Z), 110.1 (C-2E/2Z), 110.0 (C-2E/2Z), 104.9 (C-3E/3Z), 104.8 (C-3E/3Z), 41.7 (t, *J* = 6.5 Hz, C-12E/12Z), 41.5 (t, *J* = 6.5 Hz, C-12E/12Z), 38.9 (C-7E), 31.2 (C-7Z), 28.0 (C-11E/11Z), 27.8 (C-11E/11Z), 27.6 (C-5E/5Z), 27.4 (C-5E/5Z), 26.2 (C-6E/6Z), 26.0 (C-6E/6Z), 23.3 (C-9Z), 16.1 (C-9E); HRMS (TOF ESI^+), m/z: calcd for $C_{13}H_{17}NNaO$ [$M+Na^+$] 226.1202, found 226.1196.

EZ-2-(8-Isocyano-5-methyloct-5-en-1-yl)furan (278)

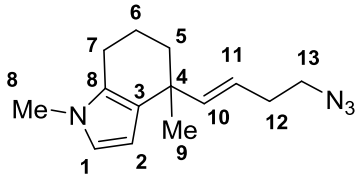


E/*Z* = 1:1

2-(9-Azido-5-methylnona-5,6-dien-1-yl)furan (30 mg, 0.12 mmol) was dissolved in degassed xylene (0.6 mL) in a dry NMR tube, thoroughly flushed with argon and sealed. The reaction was heated at 135 °C for 100 min. The mixture was cooled down and loaded directly onto a pipette silica column, eluting with the following gradient: petrol → 2:98 → 10:90 → 25:75 → 50:50, ether/petrol → ether → 3:97, MeOH/ether. The product was isolated as an inseparable 1:1 mixture of the alkene stereoisomers. It is a colourless oil with a disagreeable odour (7 mg, 26%; b.r.s.m. 28%).

R_f 0.30 (10:90, ether/petrol); ν_{max}/cm^{-1} 3090w (=C−H), 2147s (NC); δ_H (500 MHz, $CDCl_3$) 7.30 (1H, 2×dd, *J* = 2.0, 1.0 Hz, H-5'), 6.31 – 6.26 (1H, m, H-4'), 6.00 – 5.97 (1H, m, H-3'), 5.16 – 5.10 (1H, m, H-6), 3.36 – 3.32 (2×tt, *J* = 7.0, 2.0 Hz, 2H, H-8E,8Z), 2.65 (2H, 2×t, *J* = 7.0 Hz, H-1E,1Z), 2.44 – 2.35 (2H, m, H-7), 2.07 (2H, 2×t, *J* = 8.0 Hz, H-4E,4Z), 1.72 (½×3H, m, H-10Z), 1.64 (½×3H, s, H-10E), 1.68 – 1.58 (2H, m, H-2), 1.50 – 1.41 (2H, m, H-3); δ_C (126 MHz, $CDCl_3$) 156.3 (C-2'E/2'Z), 156.1 (C-2'E/2'Z), 155.74 (t, *J* = 6.0 Hz, C-9E/9Z), 155.69 (t, *J* = 6.0 Hz, C-9E/9Z), 140.74 (C-5'E/5'Z), 140.66 (C-5'E/5'Z), 139.8 (C-5E/5Z), 139.6 (C-5E/5Z), 119.1 (C-6E/6Z), 118.4 (C-6E/6Z), 110.04 (C-4'E/4'Z), 110.02 (C-4'E/4'Z), 104.74 (C-3'E/3'Z), 104.64 (C-3'E/3'Z), 41.7 (t, *J* = 6.5 Hz, C-8E/8Z), 41.5 (t, *J* = 6.5 Hz, C-8E/8Z), 39.2 (C-4E), 31.6 (C-4Z), 28.0 (C-1/2/3/7), 27.89 (C-1/2/3/7), 27.88 (C-1/2/3/7), 27.8 (C-1/2/3/7), 27.5 (CH_2), 27.4 (CH_2), 27.2 (CH_2), 23.4 (C-10Z), 16.1 (C-10E); HRMS (ESI^+), m/z: calcd for $C_{14}H_{19}NNaO$ [$M+Na^+$] 240.1359, found 240.1360.

(*E*)-4-(4-Azidobut-1-en-1-yl)-1,4-dimethyl-4,5,6,7-tetrahydro-1*H*-indole (284)

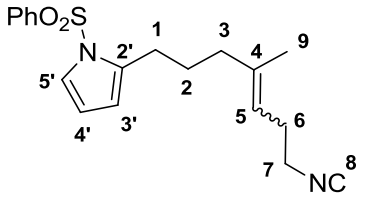


Method A. A solution of 2-(8-azido-4-methylocta-4,5-dien-1-yl)-1-methyl-1*H*-pyrrole (10 mg, 0.041 mmol) in *m*-xylene (0.6 mL) was placed into a dry NMR vial, flushed with argon, and sealed. The solution was heated at 135 °C for 1.5 hr. The solids were filtered off and the yellow solution was loaded directly onto a pipette silica column (petrol → 5:95, ether/petrol). The product is a yellow oil (1.5 mg, 15%).

Method B. A solution of 2-(8-azido-4-methylocta-4,5-dien-1-yl)-1-methyl-1*H*-pyrrole (4 mg, 0.016 mmol) in C_6D_6 (0.75 mL) was placed into a dry NMR vial, flushed with argon. Anhydrous HCl (1 M in Et_2O, 2 drops) was added. The tube was capped and heated at 80 °C for 30 min, until the starting material has been consumed (^{1}H NMR data). The product was spectroscopically and chromatographically identical with the one formed by Method A. Yield not measured.

R_f 0.56 (10:90, ether/petrol); ν_{max}/cm^{-1} 2096s (N_3); δ_H (500 MHz, $CDCl_3$) 6.50 (1H, d, *J* = 2.0 Hz, H-12), 5.93 (1H, d, *J* = 2.0 Hz, H-11), 5.65 (1H, dt, *J* = 15.5, 1.5 Hz, H-4), 5.20 (1H, dt, *J* = 15.5, 7.0 Hz, H-3), 3.47 (3H, s, H-13), 3.29 – 3.18 (2H, m, H-1), 2.53 – 2.40 (2H, m, H-8), 2.36 – 2.26 (2H, m, H-2), 1.91 – 1.72 (2H, m, H-7), 1.68 (1H, ddd, *J* = 13.0, 6.5, 3.0 Hz, H-6a), 1.55 – 1.48 (1H, m, H-6b), 1.27 (3H, s, H-14); δ_C (126 MHz, $CDCl_3$) 143.9 (C-4), 127.6 (C-9), 123.7 (C-10), 122.6 (C-3), 119.8 (C-12), 104.8 (C-11), 51.3 (C-1), 37.4 (C-6), 37.2 (C-5), 32.9 (C-13), 32.3 (C-2), 28.7 (C-14), 21.6 (C-8), 19.6 (C-7); HRMS (ESI^+), m/z: calcd for $C_{14}H_{20}N_4Na$ [M+Na^+] 267.1580, found 267.1572.

(*EZ*)-2-(7-Isocyano-4-methylhept-4-en-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrole (285)

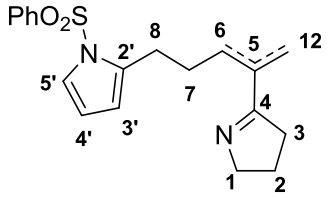


5-Methyl-8-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)octa-3,4-dien-1-yl azide (12 mg, 0.032 mmol) was dissolved in *m*-xylene (0.6 mL) in a dry NMR tube, flushed with argon, and sealed. The reaction was kept at 135 °C for 100 min. The mixture was cooled down and loaded directly onto a pipette silica column, eluting with the following gradient: 5:95 → 10:90 → 25:75 → 50:50, ether/petrol → ether → 5:95, MeOH/ether. The product was collected as an inseparable 1:1 mixture of *E*- and *Z*-isomers as a colourless oil (1.0 mg, 10%).

R_f 0.68 (ether); ν_{max}/cm^{-1} 2148m (NC), 1365s (sulfamide), 1177s (sulfamide); δ_H (500 MHz, $CDCl_3$) 7.77 – 7.71 (2H, m, H-Ph), 7.64 – 7.57 (1H, m, H-Ph), 7.55 – 7.48 (2H, m, H-Ph), 7.30 (½×1H, dd, *J* = 3.5, 2.0 Hz, H-5'E/5'Z), 7.29 (½×1H, dd, *J* = 3.5, 2.0 Hz, H-5'E/5'Z), 6.23 (½×1H, t, *J* = 3.5 Hz, H-4'E/4'Z), 6.22 (½×1H, t, *J* = 3.5 Hz, H-4'E/4'Z), 6.04 – 5.99 (1H, m, H-3'), 5.17 – 5.08 (1H, m, H-5), 3.36 (½×2H, tt, *J* = 7.0, 2.0 Hz, H-7E/7Z), 3.33 (½×2H, tt, *J* = 7.0, 2.0 Hz, H-7E/7Z), 2.63 (2H, t, *J* = 7.7 Hz, H-1), 2.43 – 2.30 (2H, m, H-6), 2.10 – 2.00 (2H, m, H-3), 1.72 – 1.64 (3½H, m, H-2,9Z), 1.62 (½×3H, s, H-9E). δ_C (126 MHz, $CDCl_3$) 155.9 (t, *J* = 5.5 Hz, C-8_8), 139.7 (C-Ar/4), 139.6 (C-Ar/4), 139.4 (C-Ar/4), 135.8 (C-Ar), 135.5 (C-Ar), 133.9 (C-Ar), 133.8 (C-Ar), 129.6 (C-Ar), 129.5 (C-Ar), 126.8 (C-Ar), 122.6 (C-5'E/5'Z), 122.5 (C-5'E/5'Z), 119.7 (C-5E/5Z), 118.9 (C-5E/5Z), 112.3 (C-3'E/3'Z), 112.2 (C-3'E/3'Z), 111.6 (C-4'), 41.8 (t, *J* = 6.5 Hz, H-7E/7Z), 41.7 (t, *J* = 6.5 Hz, H-7E/7Z), 39.2 (C-3E), 31.5 (C-3Z), 28.2 (H-6E/6Z), 28.0 (H-6E/6Z), 27.9 (H-1E/1Z/2E/2Z), 27.06 (C-1E/1Z/2E/2Z), 27.05 (C-2E/2Z), 26.8 (C-1),

23.4 (C-9Z), 16.3 (C-9E); HRMS (TOF FI$^+$), m/z: calcd for $C_{19}H_{22}N_2O_2S$ [M$^+$] 342.1402, found 342.1406.

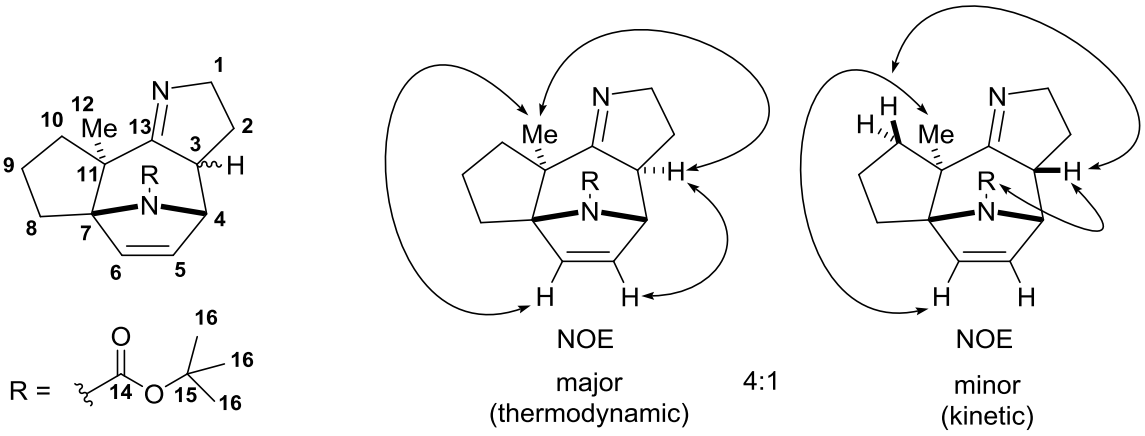
2-(4-(3,4-dihydro-2*H*-pyrrol-5-yl)pent-4-en-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrole (286)



5-Methyl-8-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)octa-3,4-dien-1-yl azide (12 mg, 0.032 mmol) was dissolved in *m*-xylene (0.6 mL) in a dry NMR tube, flushed with argon, and sealed. The reaction was kept at 135 °C for 100 min. The mixture was cooled down and loaded directly onto a pipette silica column, eluting with the following gradient: 5:95 → 10:90 → 25:75 → 50:50, ether/petrol → ether → 5:95, MeOH/ether. The product was collected as an inseparable mixture of the alkene isomers as a colourless oil (2 mg, 18%). It was too unstable to obtain reasonable NMR spectra.

R_f 0.30 (ether); ν_{max}/cm^{-1} 1633m (C=N), 1365s (sulfonamide), 1177s (sulfonamide); HRMS (ESI$^+$), m/z: calcd for $C_{19}H_{23}N_2O_2S$ [M+H$^+$] 343.1475, found 343.1463.

(±)-*tert*-butyl (*4S,6aR,9aR*)-9*a*-methyl-2,3,3a,4,7,8,9,9a-octahydro-4,6a-epiminoazuleno[4,5-b]pyrrole-10-carboxylate (287)

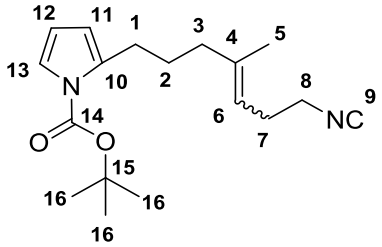


A solution of 2-(8-azido-4-methylocta-4,5-dien-1-yl)-*N*-Boc-1*H*-pyrrole (20 mg, 0.061 mmol) in *m*-xylene (6 mL) was placed into a thick-walled tube, thoroughly flushed with argon, and sealed. The solution was heated at 135 °C for 2.5 hr, until TLC showed almost complete consumption of the starting material. The crude reaction mixture was cooled to RT and loaded directly onto a silica column (2.5×8 cm), eluting with the following gradient: petrol → 5:95 → 20:80, petrol/ether → 5:95, MeOH/ether. The product was collected as a colourless oil, which was an inseparable mixture of the two C-3 diastereomers (4.2 mg, 23%, d.r. = 4:1, ^{1}H NMR). The NMR data is given for the major isomer.

R_f 0.50 (ether); ν_{max}/cm^{-1} 1747m, 1702s, 1677m, 1390s; δ_H (500 MHz, $CDCl_3$) 6.31 (1H, dd, *J* = 6.0, 2.5 Hz, H-5), 5.96 (1H, d, *J* = 6.0 Hz, H-6), 4.81 (1H, d, *J* = 2.5 Hz, H-4), 3.81 (1H, dd, *J* = 14.5, 8.5 Hz, H-1a), 3.36 (1H, dddd, *J* = 14.5, 11.0, 6.5, 2.5 Hz, H1b), 2.94 (1H, ddd, *J* = 15.5, 10.0, 6.5 Hz, H-10a), 2.61 (1H, ddd, *J* = 11.0, 8.0, 2.5 Hz, H-3), 2.33 – 2.17 (2H, m, H-8a,2a), 2.16 – 1.75 (5H, m, H-10b,8b,9a,2b,9b), 1.45 – 1.39 (9H, m, H-16), 1.08 (3H, s, H-12); δ_C (126 MHz, $CDCl_3$) 185.5 (C-13), 152.0 (C-14), 137.9 (C-6), 134.6 (C-5), 79.7 (C-15), 76.5 (C-7), 62.3 (C-4), 57.8 (C-11), 56.7 (C-1), 45.8 (C-3), 38.1

(C-8), 29.9 (C-2), 29.2 (C-10), 28.4 (C-16), 22.7 (C-9), 20.9 (C-12); HRMS (ESI$^+$), m/z: calcd for $C_{18}H_{27}N_2O_2$ [M+H$^+$] 303.2067, found 303.2054.

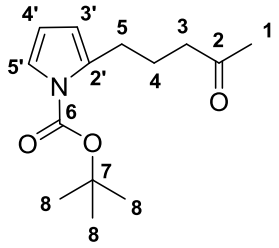
***tert*-Butyl (*EZ*)-2-(7-isocyano-4-methylhept-4-en-1-yl)-1*H*-pyrrole-1-carboxylate (288)**



Isolated as a side product in the synthesis of compound **287**. Flash chromatography afforded the title compound as a colourless oil (2.1 mg, 12%; E/Z = 3:1 or 1:3, ^{1}H NMR).

R_f 0.73 (50:50, ether/petrol); ν_{max}/cm^{-1} 2147s (NC), 1741s (C=O); δ_H (500 MHz, $CDCl_3$) 7.21 – 7.15 (1H, m, H-13), 6.10 – 6.05 (1H, m, H-12), 5.99 – 5.91 (1H, m, H-11), 5.20 – 5.09 (1H, m, H-6), 3.35 (2H, 2×tt, J = 7.0, 2.0 Hz, H-8E/8Z), 2.89 – 2.78 (2H, m, H-1), 2.45 – 2.31 (2H, m, H-7), 2.17 – 2.04 (2H, m, H-3), 1.79 – 1.67 (5H, m, H-2,5), 1.61 – 1.57 (9H, m, H-16); δ_C (126 MHz, $CDCl_3$) 155.7 (m, C-9E/9Z), 149.4 (C-Ar), 139.7 (C-Ar), 135.9 (C-Ar), 120.87 (C-13E/13Z), 120.82 (C-13E/13Z), 119.2 (C-6E/6Z), 110.89 (C-11E/11Z), 110.77 (C-11E/11Z), 109.8 (C-12), 83.2 (C-15), 41.7 (t, J = 6.0 Hz, C-8E,8Z), 39.0 (C-3E/3Z), 31.6 (C-3E/3Z), 28.6 (CH_2), 28.1 (CH_2), 27.9 (C-16), 27.2 (CH_2), 23.4 (C-2); HRMS (TOF FI$^+$), m/z: calcd for $C_{18}H_{26}N_2O$ [M$^+$] 302.1994, found 302.1996.

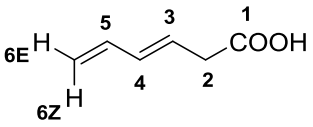
tert-Butyl 2-(4-oxopentyl)-1*H*-pyrrole-1-carboxylate (289)



Isolated as an oxidation side product in the synthesis of compound **287**. Flash chromatography afforded the title compound as a colourless oil (1 mg, 7%).

R_f 0.25 (25:75, ether/petrol); ν_{max}/cm^{-1} 1740s (C=O), 1717s (C=O); δ_H (500 MHz, $CDCl_3$) 7.19 (1H, dd, *J* = 3.5, 2.0 Hz, H-5'), 6.07 (1H, t, *J* = 3.5 Hz, H-4'), 5.97 – 5.95 (1H, m, H-3'), 2.86 (2H, t, *J* = 7.5 Hz, H-5), 2.50 (2H, t, *J* = 7.5 Hz, H-3), 2.14 (3H, s, H-1), 1.91 (2H, quint, *J* = 7.5 Hz, H-4), 1.59 (9H, s, H-8); δ_C (126 MHz, $CDCl_3$) 208.8 (C-2), 149.4 (C-6), 135.2 (C-2'), 121.0 (C-5'), 111.3 (C-4'), 109.9 (C-3'), 83.3 (C-7), 43.1 (C-3), 29.9 (C-1), 28.04 (C-5), 28.01 (C-8), 22.8 (C-4); HRMS (ESI^+), m/z: calcd for $C_{14}H_{21}NNaO_3$ [$M+Na^+$] 274.1414, found 274.1406.

(*E*)-Hexa-3,5-dienoic acid (292)[6]

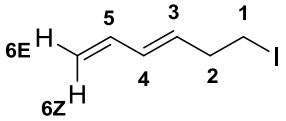


A solution of *i*-Pr_2NH (2.02 g, 20 mmol) in freshly distilled THF (20 mL) was cooled to −10 °C. BuLi (12.5 mL, 1.6 M, 20 mmol) was added with a syringe. The resulting orange-brown solution was stirred for 30 min. A solution of sorbic acid (1.0 g, 8.9 mmol) in THF (5 mL) was added. The orange mixture was allowed to warm to RT and stirred for 1 hr. The flask was then equipped with a reflux condenser and put into an ice bath (0 °C). The reaction was quenched with aq. HCl (3 M, 20 mL), added over the top of the condenser *(caution: heat liberation)*. The layers were separated and the product was extracted with ether (3×20 mL), washed with brine (20 mL) and dried

over $MgSO_4$. Concentration of the crude residue afforded the target material as a colourless oil (1.0 g, 100%). E/Z > 20:1 (^{1}H NMR).

R_f 0.56 (ethyl acetate); ν_{max}/cm^{-1} 3500br.s (OH), 3085w (=C–H), 1710s (C=O); δ_H (400 MHz, $CDCl_3$) 10.96 (1H, br.s, OH), 6.33 (1H, dt, *J* = 17.0, 10.0 Hz, H-5), 6.16 (1H, dd, *J* = 15.0, 10.0 Hz, H-4), 5.77 (1H, dtd, *J* = 15.0, 7.0, 0.5 Hz, H-3), 5.18 (1H, d, *J* = 17.0 Hz, H-6Z), 5.07 (1H, d, *J* = 10.0 Hz, H-6E), 3.16 (2H, dd, *J* = 7.0, 1.0 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 177.6 (C-1), 136.2 (C-5), 134.8 (C-4), 124.7 (C-3), 117.3 (C-6), 37.6 (C-2).

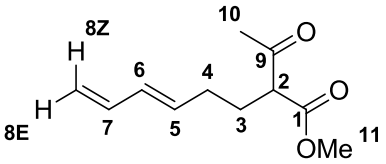
(*E*)-6-Iodohexa-1,3-diene (293)[6]



PPh_3 (1.97 g, 7.5 mmol) and imidazole (710 mg, 7.5 mmol) were dissolved in DCM (25 mL). The solution was cooled to 10 °C, followed by the addition of I_2 (1.91 g, 7.5 mmol). The resulting orange mixture was stirred at 10 °C for 5 min. (*E*)-hexa-3,5-dien-1-ol (0.55 g, 5.6 mmol) was added as a solution in DCM (5 mL), the reaction was allowed to warm to RT and stirred for 20 min. The mixture was filtered through a 5 cm silica plug, eluting with petrol. The resulting brown-yellow solution was washed sequentially with sat. aq. $Na_2S_2O_3$ (2×20 mL) and brine (10 mL), then dried over $MgSO_4$. Concentration of the resulting solution provided the target material as a pale yellow oil (0.95 g, 82%).

R_f 0.47 (petrol); ν_{max}/cm^{-1} 3085 (=C–H), 1001s; δ_H (400 MHz, $CDCl_3$) 6.32 (1H, dt, *J* = 17.0, 10.0 Hz, H-5), 6.13 (1H, dd, *J* = 15.0, 10.0 Hz, H-4), 5.70 – 5.59 (1H, m, H-3), 5.19 (1H, d, *J* = 17.0 Hz, H-6Z), 5.08 (1H, d, *J* = 10.0 Hz, H-6E), 3.18 (2H, t, *J* = 7.0 Hz, H-1), 2.67 (2H, dt, *J* = 7.0, 7.0 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 136.6 (C-5), 133.2 (C-4), 132.6 (C-3), 116.7 (C-6), 36.6 (C-2), 4.8 (C-1).

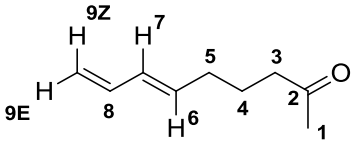
Methyl (*E*)-2-acetylocta-5,7-dienoate (295)[227]



Methyl acetoacetate (0.58 g, 5.0 mmol) was dissolved in freshly distilled THF (5 mL), followed by NaH (60% in oil, 200 mg, 5.0 mmol; *warning: intense bubbling*) and DMF (360 mg, 5.0 mmol). The solution was stirred at RT for 15 min. (*E*)-6-iodohexa-1,3-diene (1.25 g, 6.0 mmol) was added and the resulting yellow solution was stirred at 60 °C for 5 hr. The reaction was quenched with water (10 mL), neutralized to pH 7 with aq. HCl (1 M), and extracted with ether (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (1:100 → 1:5, ether/petrol) afforded the target material as a colourless oil (0.71 g, 72%; 98% b.r.s.m.), along with the excess of (*E*)-6-iodohexa-1,3-diene.

R_f 0.22 (25:75, ether/petrol); ν_{max}/cm^{-1} 3100w (=C–H), 1743s (C=O), 1716s (C=O); δ_H (400 MHz, $CDCl_3$) 12.71 (0.1×1H, s, OH_{enol}), 6.28 (1H, dt, *J* = 17.0, 10.5 Hz, H-7), 6.04 (1H, dd, *J* = 15.0, 10.5 Hz, H-6), 5.61 (1H, dt, *J* = 15.0, 7.0 Hz, H-5), 5.10 (1H, d, *J* = 17.0 Hz, H-8Z), 4.98 (1H, d, *J* = 10.5 Hz, H-8E), 3.72 (3H, s, H-11), 3.45 (1H, t, *J* = 7.0 Hz, H-2), 2.21 (3H, s, H-10), 2.14 – 2.04 (2H, m, H-4), 2.02 – 1.90 (2H, m, H-3); δ_C (101 MHz, $CDCl_3$) 202.9 (C-9), 170.1 (C-1), 136.8 (C-7), 132.8 (C-5), 132.4 (C-6), 115.8 (C-8), 58.7 (C-2), 52.4 (C-11), 30.2 (C-4), 29.0 (C-10), 27.4 (C-3).

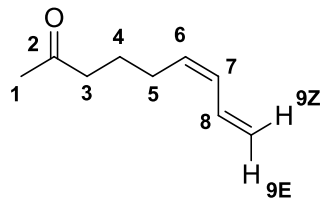
(E)-Nona-6,8-dien-2-one (*E*-296)[227,238]



Methyl *(E)*-2-acetylocta-5,7-dienoate (0.80 g, 4.1 mmol) was dissolved in DMSO (20 mL), followed by LiCl (0.35 g, 8.2 mmol) and H_2O (74 mg, 4.1 mmol). The mixture was heated with a reflux condenser at 160 °C for 5 hr. The reaction was cooled to RT and quenched with brine (50 mL). The product was extracted with petrol (3×50 mL). The combined organic layers were washed with brine (30 mL), then dried ($MgSO_4$), and concentrated. Flash chromatography (1:6, ether/petrol) afforded the target material as a yellowish oil (436 mg, 77%). $E/Z \approx 14:1$ (^{1}H NMR).

R_f 0.40 (25:75, ether/petrol); ν_{max}/cm^{-1} 3086w (=C–H), 1715s (C=O); δ_H (400 MHz, $CDCl_3$) 6.28 (1H, dt, *J* = 17.0, 10.0 Hz, H-8), 6.04 (1H, dd, *J* = 15.0, 10.0 Hz, H-7), 5.63 (1H, dt, *J* = 15.0, 7.0 Hz, H-6), 5.08 (1H, d, *J* = 17.0 Hz, H-9Z), 4.96 (1H, d, *J* = 10.0 Hz, H-9E), 2.42 (2H, t, *J* = 7.5 Hz, H-3), 2.11 (3H, s, H-1), 2.08 (2H, app. q, *J* = 7.5 Hz, H-5), 1.67 (2H, quint, *J* = 7.5 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 208.9 (C-2), 137.1 (C-8), 134.2 (C-7), 131.9 (C-6), 115.3 (C-9), 42.9 (C-3), 31.9 (C-5), 30.1 (C-1), 23.2 (C-4).

(*Z*)-Nona-6,8-dien-2-one (*Z*-296)[328]

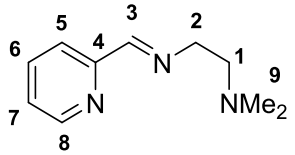


Crude (*Z*)-2-(hepta-4,6-dien-1-yl)-2-methyl-1,3-dioxolane (ca. 3.6 mmol) was dissolved in acetone (20 mL). Then, aq. HCl (1 M, 7 mL, 7 mmol) was added, and the opalescent white mixture was stirred at RT for 75 min. The reaction content was poured into a mixture of sat. aq. $NaHCO_3$ (15 mL) and brine (80 mL). The product was

extracted with ether (3×30 mL), dried over $MgSO_4$, and concentrated (note: a biphasic mixture was formed at this stage). Flash chromatography (10:90, ether/petrol) afforded the title material as a colourless oil with a pleasant fruity smell (392 mg, 78% over two steps). $Z/E \approx 15:1$ (^{1}H NMR).

R_f 0.47 (25:75, ether/petrol); ν_{max}/cm^{-1} 3095w (=C–H), 3025w (=C–H), 1714s (C=O); δ_H (400 MHz, $CDCl_3$) 6.53 (1H, dtd, *J* = 16.5, 10.5, 1.0 Hz, H-8), 5.97 (1H, t, *J* = 10.5 Hz, H-7), 5.34 (1H, dt, *J* = 10.5, 7.5 Hz, H-6), 5.13 (1H, dd, *J* = 16.5, 1.5 Hz, H-9Z), 5.04 (1H, d, *J* = 10.5 Hz, H-9E), 2.37 (2H, t, *J* = 7.5 Hz, H-3), 2.14 (2H, qd, *J* = 7.5, 1.3 Hz, H-5), 2.06 (3H, s, H-1), 1.61 (2H, quint, *J* = 7.5 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 208.9 (C-2), 132.0 (C-8), 131.6 (C-6), 130.2 (C-7), 117.4 (C-9), 42.7 (C-3), 30.0 (C-1), 26.9 (C-5), 23.4 (C-4).

N^1,*N*^{1}-Dimethyl-*N*^{2}-(pyridin-2-ylmethylene)ethane-1,2-diamine (298)[329]

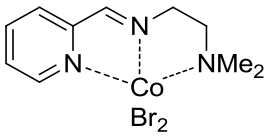


Following a reported procedure, 2-pyridyl carboxaldehyde (1.90 mL, ca. 20.0 mmol) was dissolved in absolute EtOH (18 mL), followed by the addition of $MgSO_4$ (3.6 g, 30 mmol) and *N*^{1},*N*^{1}-dimethylethylenediamine (2.17 mL, ca. 20.0 mmol). The mixture was stirred rapidly at RT for 72 hr. The solids were filtered off using a fritted filter and washed thoroughly with DCM (ca. 3×10 mL; *note:* this process is slow). The solution was concentrated under reduced pressure (300 → 10 Torr, 20 °C) to yield the title compound as a pale brown oil that was used without further purification (3.51 g, 99%).

R_f 0.03 (1:1, ether/petrol); ν_{max}/cm^{-1} 3054w (=C–H), 1649s (C=N); δ_H (400 MHz, $CDCl_3$) 8.64 (1H, dt, *J* = 5.0, 1.5 Hz, H-8), 8.41 (1H, t, *J* = 1.5 Hz, H-3), 7.99 (1H, dt, *J* = 7.5, 1.5 Hz, H-5), 7.73 (1H, td, *J* = 7.5, 1.5 Hz, H-6), 7.31 (1H, ddd, *J* = 7.5, 5.0, 1.5 Hz, H-7), 3.80 (2H, td, *J* = 7.0, 1.5 Hz, H-2), 2.67 (2H, t, *J* = 7.0 Hz, H-1), 2.31 (6H, s, H-9); δ_C (101

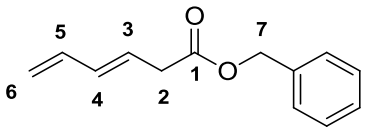
MHz, $CDCl_3$) 162.8 (C-3), 154.4 (C-4), 149.4 (C-8), 136.5 (C-6), 124.7 (C-7), 121.4 (C-5), 59.9 (C-1), 59.5 (C-2), 45.8 (C-9).

$CoBr_2$ – *N*¹,*N*¹-dimethyl-*N*²-(pyridin-2-ylmethylene)ethane-1,2-diamine complex (299)[330]



To a solution of *N*¹,*N*¹-dimethyl-*N*²-(pyridin-2-ylmethylene)ethane-1,2-diamine (0.50 g, 2.8 mmol) in THF (33 mL) was added $CoBr_2$ (0.62 g, 2.8 mmol; *note:* the compound is extremely moisture-sensitive and should be weighed under argon atmosphere). The reaction mixture turned brown, and precipitation was observed. Over time, the colour of the reaction mixture changed to deep green. The mixture was stirred rapidly for 20 hr. The dark green precipitate of the product was filtered out using a fritted filter, washing with ca. 100 mL of petrol (*note:* the filter cake should not be exposed to air), then dried in vacuum (0.01 Torr, 20 °C) and used without further purification. The product was stored under argon (1.02 g, 91%).

(*E*)-Benzyl hexa-3,5-dienoate (*E*-300)[241]

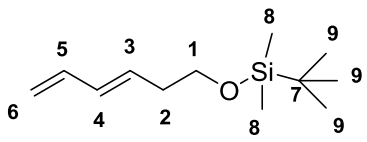


Prepared using a general procedure by Kim *et al.*[331] To a solution of (*E*)-hexa-3,5-dienoic acid (150 mg, 1.34 mmol) in DCM (6 mL) was added distilled TEA (150 mg, 1.47 mmol). The clear solution was cooled to 0 °C and stirred for 5 min, then benzyl chloroformate (250 mg, 1.47 mmol) was added dropwise with a syringe. The solution turned yellow. The mixture was stirred at 0 °C for 5 min (precipitation observed), then DMAP (49 mg, 0.4 mmol) was added in one portion. The colour of the reaction shifted to reddish-orange. The stirring was continued at 0 °C for 15 min. The crude reaction

mixture was poured into a mixture of sat. aq. NH_4Cl (15 mL) and water (2 mL). The layers were separated, and the aq. layer was extracted with ether (2×10 mL). The combined organic layers were washed with brine (2×8 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (1:9, ether/petrol) afforded the title material as a clear colourless oil (227 mg, 84%).

R_f 0.35 (10:90, ether/petrol); ν_{max}/cm^{-1} 3089w (=C–H), 3066w (=C–H), 3034w (=C–H), 1733s (C=O); δ_H (400 MHz, $CDCl_3$) 7.35 – 7.22 (5H, m, H-Ph), 6.27 (1H, dt, *J* = 17.0, 10.5 Hz, H-5), 6.08 (1H, dd, *J* = 15.0, 10.5 Hz, H-4), 5.73 (1H, dt, *J* = 15.0, 7.0 Hz, H-3), 5.09 (1H, d, *J* = 17.0 Hz, H-6Z), 5.06 (2H, s, H-7), 5.00 (1H, d, *J* = 10.5 Hz, H-6E), 3.10 (2H, dd, *J* = 7.0, 1.0 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 171.4 (C-1), 136.3 (C-5), 135.8 (C-8), 134.5 (C-4), 128.6 (C-Ph), 128.33 (C-Ph), 128.31 (C-Ph), 125.4 (C-3), 117.1 (C-6), 66.6 (C-7), 37.9 (C-2).

(*E*)-*tert*-Butyl(hexa-3,5-dien-1-yloxy)dimethylsilane (*E*-301)[332]

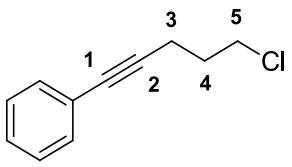


To a rapidly stirred solution of *E*-hexa-3,5-dienoic acid (200 mg, 1.79 mmol) in THF (7 mL) was added $LiAlH_4$ (56 mg, 1.46 mmol; *warning: gas evolution and self-heating*). The mixture was heated at 60 °C with a reflux condenser for 2 hr, then cooled to RT. The reaction content was diluted with ether (7 mL) and cooled to 0 °C. To this mixture were added in succession: water (0.05 mL), aq. NaOH (3 M, 0.05 mL), and water (0.15 mL). The ice bath was removed and the mixture was stirred at RT for 20 min. The solids were filtered off on a pad of silica (ca. 1 cm), washing with ether. The organic layer was concentrated under reduced pressure (150 Torr, 20 °C) to give colourless (*E*)-hexa-3,5-dien-1-ol, which was immediately used in the next step. (*E*)-hexa-3,5-dien-1-ol was redissolved in DCM (7 mL), followed by the addition of

imidazole (244 mg, 3.58 mmol). The solution was cooled to 0 °C and TBSCl (297 mg, 1.97 mmol) was added. A spatula tip of DMAP was added, the cooling was removed, and the reaction was stirred at RT for 15 min. The mixture was filtered through a plug of silica (1 cm), washing with a 1:9, ether/petrol mixture, then concentrated under reduced pressure. Flash chromatography (5:95, ether/petrol) afforded the title compound as a clear colourless oil (193 mg, 51% over two steps).

R_f 0.70 (10:90, ether/petrol); ν_{max}/cm^{-1} 3085w (=C–H), 3036w (=C–H); δ_H (400 MHz, $CDCl_3$) 6.26 (1H, dt, *J* = 17.0, 10.5 Hz, H-5), 6.05 (1H, dd, *J* = 15.0, 10.5 Hz, H-4), 5.65 (1H, dt, *J* = 15.0, 7.0 Hz, H-3), 5.06 (1H, d, *J* = 17.0 Hz, H-6Z), 4.93 (1H, d, *J* = 10.5 Hz, H-6E), 3.60 (2H, t, *J* = 7.0 Hz, H-1), 2.26 (2H, qd, *J* = 7.0, 1.0 Hz, H-2), 0.84 (9H, s, H-9), 0.00 (6H, s, H-8); δ_C (101 MHz, $CDCl_3$) 137.2 (C-5), 132.7 (C-4), 131.4 (C-3), 115.3 (C-6), 62.8 (C-1), 36.2 (C-2), 25.9 (C-9), 18.4 (C-7), −5.3 (C-8).

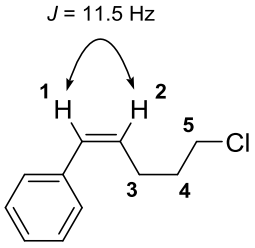
(5-Chloropent-1-yn-1-yl)benzene (302)[333]



Phenylacetylene (2.0 g, 19.6 mmol) was dissolved in freshly distilled THF and cooled to −78 °C. BuLi (12.4 mL, 1.6 M, 19.6 mmol) was added over 5 min. The resulting mixture was stirred at −78 °C for 10 min, then allowed to warm up slowly to RT. Upon warming, the colour of the mixture changed from pale green to black. Neat 1-bromo-3-chloropropane (3.40 g, 21.6 mmol) was added with a syringe and the resulting solution was stirred at RT for 15 min, then brought to gentle reflux for 21 hr. Volatiles were evaporated under reduced pressure (80 Torr). The residue was dissolved in ethyl acetate (20 mL), washed with water (15 mL), then brine (5 mL), dried ($MgSO_4$), filtered through a silica plug (1 in), and concentrated. The product was a brown oil that was used without further purification (3.50 g, 100%).

R_f 0.45 (3:97, ether/petrol); ν_{max}/cm^{-1} 3080w (=C-H), 2233w (C≡C); δ_H (400 MHz, $CDCl_3$) 7.43 – 7.38 (2H, m, H-Ph), 7.31 – 7.26 (3H, m, H-Ph), 3.73 (2H, t, *J* = 6.5 Hz, H-5), 2.62 (2H, t, *J* = 6.5 Hz, H-3), 2.07 (2H, quint, *J* = 6.5 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 131.6 (C-Ph), 128.2 (C-Ph), 127.8 (C-Ph), 123.6 (C-Ph), 88.1 (C-2), 81.5 (C-1), 43.7 (C-5), 31.5 (C-4), 16.9 (C-3).

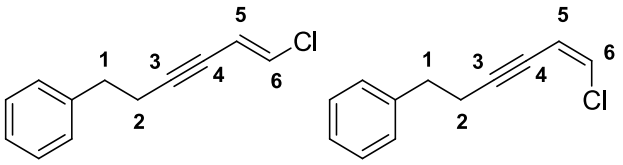
(*Z*)-(5-Chloropent-1-en-1-yl)benzene (303)[334,335]



(5-Chloropent-1-yn-1-yl)benzene (1.78 g, 10.0 mmol) was dissolved in ethyl acetate (18 mL), followed by the addition of quinoline (95 mg) and Lindlar's catalyst (5% $Pd/CaCO_3$ poisoned with lead, 18 mg) under argon. The atmosphere was exchanged for H_2 (1 atm) using a series of five pump–refill cycles. The mixture was stirred for 13 hr. The atmosphere was exchanged back to argon by a series of five pump-refill cycles. The reaction mixture was filtered through a silica/Celite plug (2 cm of silica, 1 cm of Celite), washing with 30 mL of ether *(note: the solids should not let dry).* The organic layer was washed with aq. HCl (0.5 M, 20 mL), brine (15 mL), then dried over $MgSO_4$. Concentration of the resulting solution afforded the title compound as a yellow oil that was used without further purification (1.80 g, 100%).

R_f 0.42 (1:99, ether/petrol); ν_{max}/cm^{-1} 3081m (=C–H), 3058m (=C–H), 3025m (=C–H); δ_H (400 MHz, $CDCl_3$) 7.41 – 7.18 (5H, m, H-Ph), 6.51 (1H, dt, *J* = 11.5, 2.0 Hz, H-1), 5.65 (1H, dt, *J* = 11.5, 7.5 Hz, H-2), 3.57 (2H, t, *J* = 7.0 Hz, H-5), 2.51 (2H, qd, *J* = 7.5, 2.0 Hz, H-3), 1.95 (2H, tt, *J* = 7.5, 7.0 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 137.3 (C-Ph), 130.8 (C-2), 130.2 (C-1), 128.7 (C-Ph), 128.2 (C-Ph), 126.7 (C-Ph), 44.5 (C-5), 32.8 (C-4), 25.9 (C-3).

(*E*)-(6-Chlorohex-5-en-3-yn-1-yl)benzene, (*Z*)-(6-chlorohex-5-en-3-yn-1-yl)benzene (304)



4-Phenylbutyne-1 (65 mg, 0.50 mmol) was dissolved in dry *i*-Pr_2NH (3 mL), followed by the addition of PPh_3 (13 mg, 0.05 mmol), *EZ*-1,2-dichloroethylene (*E*/*Z* ≈ 3:1; 240 mg, 2.5 mmol), CuI (10 mg, 0.05 mmol), and $Pd(OAc)_2$ (6 mg, 0.025 mmol). The mixture was stirred at RT for 3 days (ca. 68 hr). The reaction mixture was filtered through a pad of Celite, washing with ether. The volatiles were evaporated and the products were purified by flash chromatography, eluting with petrol (*E*-**304**, 24 mg, 25%; *Z*-**304**, 7 mg, 7%).

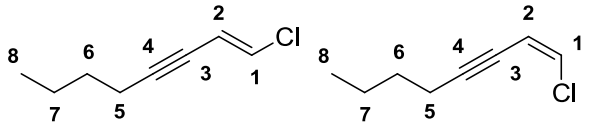
***E*-304 (major)**

R_f 0.49 (petrol); ν_{max}/cm^{-1} 3071m (=C–H), 3027m (=C–H), 2218m (C≡C); δ_H (500 MHz, $CDCl_3$) 7.35 – 7.29 (2H, m, H-Ph), 7.26 – 7.19 (3H, m, H-Ph), 6.43 (1H, d, *J* = 13.5 Hz, H-6), 5.91 (1H, dt, *J* = 13.5, 2.0 Hz, H-5), 2.85 (2H, t, *J* = 7.5 Hz, H-1), 2.60 (2H, td, *J* = 7.5, 2.0 Hz, H-2); δ_C (126 MHz, $CDCl_3$) 140.4 (C-Ph), 129.1 (C-6), 128.4 (C-Ph), 126.4 (C-Ph), 114.1 (C-5), 92.4 (C-3), 76.4 (C-4), 34.8 (C-1), 21.6 (C-2).

***Z*-304 (minor)**

R_f 0.23 (petrol); ν_{max}/cm^{-1} 3085m (=C–H), 3064m (=C–H), 3028m (=C–H), 2214m (C≡C); δ_H (500 MHz, $CDCl_3$) 7.36 – 7.19 (5H, m, H-Ph), 6.31 (1H, d, *J* = 7.5 Hz, H-6), 5.85 (1H, dt, *J* = 7.5, 2.0 Hz, H-5), 2.91 (2H, t, *J* = 7.5 Hz, H-1), 2.70 (2H, td, *J* = 7.5, 2.0 Hz, H-2); δ_C (126 MHz, $CDCl_3$) 140.4 (C-Ph), 128.5 (C-Ph), 128.4 (C-Ph), 127.1 (C-6), 126.3 (C-Ph), 112.3 (C-5), 98.3 (C-3), 75.3 (C-4), 34.9 (C-1), 21.9 (C-2).

(*E*)-1-Chlorooct-1-en-3-yne,[336] **(*Z*)-1-chlorooct-1-en-3-yne (305)**[336]



1-Hexyne (82 mg, 1.0 mmol) was dissolved in *i*-Pr_2NH (6 mL), followed by PPh_3 (26 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and *EZ*-1,2-dichloroethylene (*E*/*Z* ≈ 3:1, 0.49 g, 5.0 mmol). The mixture was placed into an oven-dried pressure tube, thoroughly flushed with argon, sealed, and heated at 40 °C for 22 hr. The reaction content was cooled to RT, filtered through a pad of Celite, and concentrated (80 Torr, 30 °C). Flash chromatography (petrol) afforded ***E*-305** as the less polar fraction (27 mg, 20%), and ***Z*-305** as the more polar one (10 mg, 7%). The latter was isolated as an inseparable mixture with dodeca-5,7-diyne (dimerization side product).

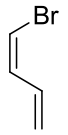
***E*-305 (major)**

R_f 0.58 (petrol); ν_{max}/cm^{-1} 3075w (=C–H), 2222w (C≡C); δ_H (400 MHz, $CDCl_3$) 6.43 (1H, d, *J* = 13.5 Hz, H-1), 5.91 (1H, dt, *J* = 13.5, 2.0 Hz, H-2), 2.30 (2H, td, *J* = 7.0, 2.0 Hz, H-5), 1.57 – 1.46 (2H, m, H-6), 1.47 – 1.35 (2H, m, H-7), 0.92 (3H, t, *J* = 7.0 Hz, H-8); δ_C (101 MHz, $CDCl_3$) 128.7 (C-1), 114.3 (C-2), 93.4 (C-4), 75.6 (C-3), 30.5 (C-6), 21.9 (C-7), 19.1 (C-5), 13.6 (C-8).

***Z*-305 (minor)**

R_f 0.47 (petrol); ν_{max}/cm^{-1} 3085w (=C–H), 2215w (C≡C); δ_H (400 MHz, $CDCl_3$) 6.30 (1H, d, *J* = 7.5 Hz, H-1), 5.86 (1H, dt, *J* = 7.5, 2.0 Hz, H-2), 2.40 (2H, td, *J* = 7.0, 2.0 Hz, H-5), 1.63 – 1.35 (4H, m, H-6,7), 0.98 – 0.86 (3H, m, H-8); δ_C (101 MHz, $CDCl_3$) 126.7 (C-1), 112.5 (C-2), 99.4 (C-4), 74.6 (C-3), 30.4 (C-6), 21.9 (C-7), 18.9 (C-5), 13.5 (C-8).

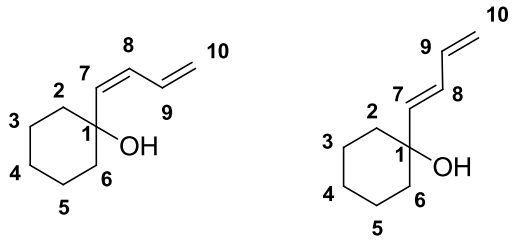
(*Z*)-1-Bromobuta-1,3-diene (307)[337]



A 500 mL flask was charged with 62 g of freshly powdered KOH (4 portions of 15.5 g) under argon. Tetradecane (38 mL) was added, followed by 10.7 g (50 mmol) of *E*-1,4-dibromobutene-2. The flask was equipped with a 30 cm Vigreux column, a distillation Still head with a thermometer and a double-jacketed condenser, 3-way adapter and a 50 mL receiving flask. The system was attached to vacuum pump and evacuated (ca. 10 Torr), and the receiving flask was immersed into dry ice bath. The reaction was vigorously stirred and heated gently with a heat gun, until intense bubbling and reflux were observed. The heating was temporarily stopped for 5 min, then renewed for another 20 min. The product is not directly observable during distillation, but it solidifies directly in the receiving flask. During the course of the reaction, the KOH/tetradecane mixture aggregates and forms a big chunk of solids. Next, both heating and cooling were removed, the system was refilled with argon and allowed to warm to RT. The product, yellow oil, was stored in dark under argon at −20 °C and used without further purification. Yield not measured. $Z/E \approx 4{:}1$ (^{1}H NMR).

δ_C (101 MHz, $CDCl_3$) 133.1, 132.6, 121.3, 108.7.

1-(Buta-1,3-dien-1-yl)cyclohexanol (308)[338]



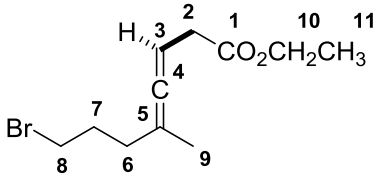
A solution of 1-bromobutadiene-1,3 (Z/E ≈ 4:1, 43 mg, 0.32 mmol) in ether (2.5 mL) was cooled to −78° C. To this, *t*-BuLi (1.4 M in pentane, 0.23 mL, 0.32 mmol) was

added dropwise. The bright yellow solution was stirred at −78° C for 2 hr. Then, neat cyclohexanone (21 mg, 0.21 mmol) was added using a microsyringe. The solution immediately turned clear and colourless. The reaction was allowed to warm to RT overnight (14 hr). The mixture was poured into sat. aq. NH_4Cl (2 mL) and water (2 mL) and diluted with ether (3 mL). The layers were separated and the aq. layer was extracted with ether (2×2 mL). The combined organic layers were washed with brine (2×2 mL), dried over $MgSO_4$, and concentrated. The products were separated by flash chromatography (8:92, ether/petrol).

***Z*-308.** Clear colourless oil (20 mg, 63%). R_f 0.25 (25:75, ether/petrol); ν_{max}/cm^{-1} 3435br.s (OH), 3084w (=C−H), 3008w (=C−H); δ_H (400 MHz, $CDCl_3$) 7.18 (1H, m, H-9), 5.91 (1H, tt, *J* = 11.5, 1.0 Hz, H-8), 5.46 (1H, dtd, *J* = 11.5, 1.5, 1.0 Hz, H-7), 5.13 – 5.05 (2H, m, H-10), 1.65 – 1.34 (10H, m, H-2,3,4,5,6), 1.27 (1H, br.s, OH); δ_C (101 MHz, $CDCl_3$) 137.7 (C-7), 133.8 (C-9), 130.2 (C-8), 118.7 (C-10), 72.9 (C-1), 39.4 (CH_2), 25.3 (CH_2), 22.3 (CH_2).

***E*-308.** Clear colourless oil with a strong pleasant odour (6 mg, 19%). R_f 0.17 (25:75, ether/petrol); ν_{max}/cm^{-1} 3370br.s (OH), 3086w (=C−H), 3037w (=C−H); δ_H (400 MHz, $CDCl_3$) 6.34 – 6.16 (2H, m, H-9,7), 5.76 (1H, d, *J* = 14.5 Hz, H-8), 5.18 – 5.11 (1H, m, H-10a), 5.04 – 4.98 (1H, m, H-10b), 1.67 – 1.39 (10H, m, H-2,3,4,5,6), 1.25 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 141.7 (C-8), 136.8 (C-9), 127.9 (C-7), 117.0 (C-10), 71.4 (C-1), 37.9 (C-2,6), 25.5 (CH_2), 22.1 (CH_2).

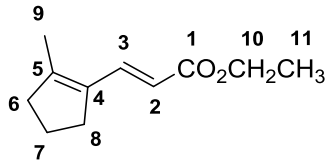
Ethyl 8-bromo-5-methylocta-3,4-dienoate (309)



6-Bromo-3-methylhex-1-yn-3-ol (1.44 g, 7.5 mmol) was dissolved in $MeC(OEt)_3$ (12 mL), followed by propanoic acid (0.15 mL). The resulting mixture was kept at reflux (140 °C) for 9 hr with a Dean-Stark trap to remove the forming ethanol. The reaction was then cooled to RT. Ether (35 mL) was added and the resulting solution was washed with aq. HCl (1 M, 2×10 mL), sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL); then dried ($MgSO_4$) and concentrated. Flash chromatography (1:19 → 1:4, ether/petrol) afforded the target material as a colourless oil (1.07 g, 55%; 64% b.r.s.m.) along with recovered starting material.

R_f 0.40 (petrol); ν_{max}/cm^{-1} 1968w (C=C=C), 1734s (C=O); δ_H (400 MHz, $CDCl_3$) 5.24 – 5.16 (1H, m, H-3), 4.15 (2H, q, *J* = 7.0 Hz, H-10), 3.43 (2H, t, *J* = 6.5 Hz, H-8), 2.98 (2H, d, *J* = 7.0 Hz, H-2), 2.12 – 2.06 (2H, m, H-6), 1.99 (2H, tt, *J* = 6.5, 6.5 Hz, H-7), 1.70 (3H, d, *J* = 3.0 Hz, H-9), 1.27 (3H, t, *J* = 7.0 Hz, H-11); δ_C (101 MHz, $CDCl_3$) 202.4 (C-4), 171.8 (C-1), 99.6 (C-5), 84.5 (C-3), 60.8 (C-10), 35.5 (C-2), 33.5 (C-8), 32.2 (C-6), 30.6 (C-7), 19.2 (C-9), 14.4 (C-11); HRMS (ESI^+), m/z: calcd for $C_{11}H_{17}Br^{81}NaO_2$ $[M+Na^+]$ 285.0284, found 285.0282.

(*E*)-Ethyl 3-(2-methylcyclopent-1-en-1-yl)acrylate (310)

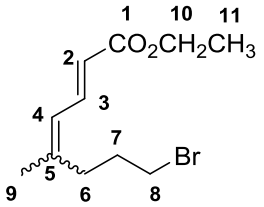


Z-1-bromobutadiene-1,3 (54 mg, 0.41 mmol) was dissolved in THF (2.5 mL) and cooled to −78° C. BuLi was added dropwise (1.6 M, 0.26 mL, 0.41 mmol). The solution was stirred at −78° C for 10 min. Neat ethyl 8-bromo-5-methylocta-3,4-dienoate (100

mg, 0.38 mmol) was added using a microsyringe. The mixture was allowed to warm slowly to RT and stirred overnight (16 hr). The reaction mixture was diluted with ether (3 mL) and quenched with sat. aq. NH_4Cl (3 mL) and water (1 mL). The layers were separated and the aq. layer was extracted with ether (2×3 mL). The combined organic layers were washed with brine (2×2 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (7:93, ether/petrol) afforded the title compound as a clear colourless oil (14 mg, 18%).

R_f 0.40 (10:90, ether/petrol); ν_{max}/cm^{-1} 3061w (=C–H), 1709s (C=O), 1631m, 1612m; δ_H (500 MHz, $CDCl_3$) 7.64 (d, *J* = 15.5 Hz, 1H, H-3), 5.70 (1H, d, *J* = 15.5 Hz, H-2), 4.22 (2H, q, *J* = 7.0 Hz, H-10), 2.48 (4H, app.t, *J* = 7.5 Hz, H-6,8), 1.90 (3H, s, H-9), 1.88 (2H, quint, *J* = 7.5 Hz, H-7), 1.31 (3H, t, *J* = 7.0 Hz, H-11); δ_C (126 MHz, $CDCl_3$) 167.9 (C-1), 149.4 (C-5), 138.4 (C-3), 132.9 (C-4), 116.7 (C-2), 60.1 (C-10), 39.9 (C-8), 32.4 (C-6), 21.4 (C-7), 14.6 (C-9/11), 14.3 (C-9/11); HRMS (ESI^+), m/z: calcd for $C_{11}H_{16}NaO_2$ $[M+Na^+]$ 203.1043, found 203.1039.

(2*E*,4*EZ*)-Ethyl 8-bromo-5-methylocta-2,4-dienoate (311)

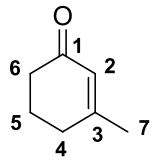


The compound was isolated as a side product in the synthesis of (*E*)-ethyl 3-(2-methylcyclopent-1-en-1-yl)acrylate. Flash chromatography (7:93, ether/petrol) afforded the title compound as a clear colourless oil (4 mg, 4%; *Z*/*E* = 2:1, ^1H NMR).

R_f 0.27 (10:90, ether/petrol); ν_{max}/cm^{-1} 1710s (C=O), 1636m; δ_H (500 MHz, $CDCl_3$) 7.57 (1H, 2×dd, *J* = 15.0, 11.5 Hz, H-3E,3Z), 6.04 (1H, 2×d, *J* = 11.5 Hz, H-4E,4Z), 5.81 (1H, 2×d, *J* = 15.0 Hz, H-2E,2Z), 4.21 (2H, 2×q, *J* = 7.0 Hz, H-10E,10Z), 3.40 (2H, 2×t, *J* = 6.5 Hz, H-8E,8Z), 2.45 (0.66×2H, t, *J* = 7.5 Hz, H-6E/6Z), 2.33 – 2.27 (0.33×2H, m, H-

6E/6Z), 2.02 (2H, 2×quint, *J* = 7.0 Hz, H-7E,7Z), 1.90 (1H, d, *J* = 1.0 Hz, H-9E/9Z), 1.89 (2H, s, H-9E/9Z), 1.30 (3H, t, *J* = 7.1 Hz, H-11); δ_C (126 MHz, $CDCl_3$) 167.52 (C-1E/1Z), 167.50 (C-1E/1Z), 147.6 (C-5E/5Z), 147.3 (C-5E/5Z), 140.4 (C-3E/3Z), 140.0 (C-3E/3Z), 125.1 (C-4E/4Z), 124.2 (C-4E/4Z), 119.70 (C-2E/2Z), 119.68 (C-2E/2Z), 60.2 (C-10), 38.3 (C-6E), 32.9 (C-8E/8Z), 32.8 (C-8E/8Z), 31.2 (C-7/6Z), 31.1 (C-7/6Z), 24.2 (C-9Z), 17.2 (C-9E), 14.3 (C-11); MS (ESI^+), m/z: 283.0 ($M^{79}Br+Na^+$), 285.0 ($M^{81}Br+Na^+$).

3-Methylcyclohex-2-enone (315)[245,339]

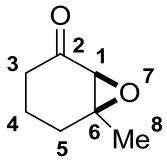


Methyl vinyl ketone (5.0 g, 71 mmol) was added to a solution of ethyl acetoacetate (9.20 g, 71 mmol) in *t*-BuOH (70 mL). The solution was cooled to 0 °C, followed by the addition of KO*t*-Bu (0.60 g, 5.3 mmol). The mixture was stirred at 0 °C for 30 min, then allowed to warm to RT. More KO*t*-Bu (1.60 g, 14.3 mmol) was added and the reaction was heated at reflux for 21 hr. The mixture was cooled to 0 °C, diluted with ether (50 mL), and quenched with aq. HCl (1 M, 30 mL) and water (50 mL). The layers were separated and the aq. layer was extracted with ether (4×35 mL). The combined organic layers were reduced to ca. ½ of the initial volume, diluted with benzene, washed with aq. NaOH (1 M, 4×20 mL), and concentrated (40 °C, 80 → 20 Torr). The product was used as received (yield not measured). Flash chromatography on a small sample (40:60, ether/petrol) afforded a spectroscopically pure material for characterisation.

R_f 0.29 (40:60, ether/petrol); ν_{max}/cm^{-1} 3496br.m (OH_{enol}), 3030w (=C–H), 1736m (C=O), 1663s, 1626m; δ_H (400 MHz, $CDCl_3$) 5.88 – 5.85 (1H, m, H-2), 2.33 (2H, app. dd, *J* = 7.5, 6.0 Hz, H-6), 2.27 (2H, app. t, *J* = 6.0 Hz, H-4), 2.03 – 1.92 (5H, m, H-5,7);

δ_C (101 MHz, $CDCl_3$) 199.8 (C-1), 162.8 (C-3), 126.7 (C-2), 36.9 (C-6), 30.9 (C-4), 24.5 (C-5), 22.5 (C-7).

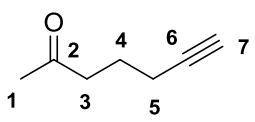
6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (316)[245]



3-Methylcyclohex-2-enone, **315**, (ca. 70 mmol) was dissolved in MeOH (70 mL) and cooled to 0 °C. Aq. H_2O_2 (~35% w/w, 20 mL, 0.21 mol) was added over 5 min with a syringe. The mixture was treated with sat. aq. NaOH (ca. 1.2 g in 5 mL of water) dropwise, maintaining the internal temperature below 10 °C. The solution was stirred in an ice bath for 3 hr. The mixture was quenched with ice water (ca. 50 mL) and the aq. layer was extracted with DCM (4×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The product was purified by Kugelrohr distillation (100 → 150 °C, 20 Torr) as a clear colourless oil (3.30 g, 38% over 2 steps, unoptimised).

R_f 0.50 (50:50, ether/petrol); ν_{max}/cm^{-1} 1707s (C=O); δ_H (400 MHz, $CDCl_3$) 3.08 (1H, s, H-1), 2.55 – 2.44 (1H, m, H-3a), 2.19 – 1.81 (4H, m, H-3b,4a,5), 1.70 – 1.60 (1H, m, H-4b), 1.45 (3H, s, H-8); δ_C (101 MHz, $CDCl_3$) 206.8 (C-2), 62.4 (C-6), 61.9 (C-1), 35.7 (C-3), 28.4 (C-5), 22.2 (C-8), 17.1 (C-4).

Hept-6-yn-2-one (317)[245,246]

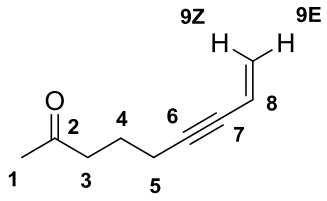


To 6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (60 mg, 0.48 mmol) was added DCM (0.70 mL) and glacial acetic acid (0.35 mL). The mixture was cooled to −40 °C, followed by slow addition of a solution of $TsNHNH_2$ (90 mg) in a mixture of DCM (0.70 mL) and AcOH (0.35 mL). The reaction was allowed to warm to RT slowly and stirred

overnight (20 hr). The reaction was quenched by careful addition of anhydrous Na_2CO_3 (ca. 0.6 g) and water (ca. 3 mL). The aq. layer was extracted with ether (2×4 mL) and the combined organic layers were washed with brine (2 mL), dried ($MgSO_4$), and evaporated (30 °C, 400 → 300 Torr). Flash chromatography using a short column (20:80, ether/petrol) afforded the title material as a highly volatile colourless oil (22 mg, 42%).

R_f 0.28 (25:75, ether/petrol); ν_{max}/cm^{-1} 3133w (≡C–H), 2200w (C≡C), 1767m (C=O); δ_H (500 MHz, $CDCl_3$) 2.59 (2H, t, *J* = 7.0 Hz, H-3), 2.23 (2H, td, *J* = 7.0, 2.5 Hz, H-5), 2.16 (3H, s, H-1), 1.96 (1H, t, *J* = 2.5 Hz, H-7), 1.79 (2H, quint, *J* = 7.0 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 208.2 (C-2), 83.5 (C-6), 69.0 (C-7), 41.9 (C-3), 30.0 (C-1), 22.2 (C-4), 17.7 (C-5).

Non-8-en-6-yn-2-one (318)[243,244]

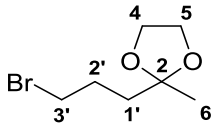


A suspension of $Pd(PPh_3)_2Cl_2$ (7 mg, 0.0095 mmol) and CuI (4 mg, 0.019 mmol) in *i*-Pr_2NH (1.3 mL) was stirred at RT for 5 min. Then, a stock solution of vinylmagnesium bromide was added (1 M in THF, 0.25 mL, 0.25 mmol), followed by a solution of hept-6-yn-2-one (21 mg, 0.19 mmol) in *i*-Pr_2NH (0.5 mL). The reaction mixture was stirred at RT for 22 hr. Ether (2 mL) was then added and the resulting slurry was filtered through a plug of Celite in a pipette, thoroughly washing with ether. The solution was diluted with ether (total volume 30 mL) and washed sequentially with aq. HCl (1 M, 3×5 mL), sat. aq. $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography (pipette, 10:90,

ether/petrol) afforded the title material as a colourless oil (4 mg, 15%). *Note: $Pd(OAc)_2$ as the Pd^{II} source led to much faster reactions (15 min).*

R_f 0.15 (10:90, ether/petrol); ν_{max}/cm^{-1} 3085w (≡C–H), 2226w (C≡C), 2200w (C≡C), 1716s (C=O); δ_H (500 MHz, $CDCl_3$) 5.77 (1H, ddt, *J* = 17.5, 11.0, 2.0 Hz, H-8), 5.56 (1H, dd, *J* = 17.5, 2.0 Hz, H-9Z), 5.40 (1H, dd, *J* = 11.0, 2.0 Hz, H-9E), 2.58 (2H, t, *J* = 7.0 Hz, H-3), 2.36 (2H, td, *J* = 7.0, 2.0 Hz, H-5), 2.17 (3H, s, H-1), 1.81 (2H, quint, *J* = 7.0 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 208.3 (C-2), 125.9 (C-9), 117.4 (C-8), 89.9 (C-6), 80.1 (C-7), 42.2 (C-3), 30.0 (C-1), 22.5 (C-5), 18.6 (C-4).

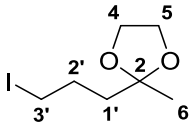
2-(3'-Bromopropyl)-2-methyl-1,3-dioxolane (319)[340]



A 25 mL flask was charged with 5-bromopentan-2-one (0.50 g, 3.0 mmol), ethylene glycol (1.86 g, 30 mmol), $HC(OMe)_3$ (1.22 g, 11.5 mmol), PTSA·H_2O (57 mg, 0.3 mmol), and 3Å molecular sieves (0.25 g). The mixture was stirred at RT for 4 hr. In a separate flask, NaH_2PO_4 (1 g) and pyridine (0.05 mL) were dissolved in 20 mL of water. A 5 mL aliquot of this solution was used to quench the reaction, followed by 5 mL of ether. The aq. layer was separated and extracted with ether (ca. 6 mL). The combined organic layers were washed with brine (ca. 2 mL), dried over $MgSO_4$, and concentrated. Kugelrohr distillation (110–130 °C, 10 Torr) afforded the target material as a colourless oil (0.60 g, 89%).

R_f 0.48 (25:75, ether/petrol); ν_{max}/cm^{-1} 2982m, 1046s; δ_H (400 MHz, $CDCl_3$) 3.99 – 3.90 (4H, m, H-4,5), 3.44 (2H, t, *J* = 7.0 Hz, H-3'), 2.04 – 1.91 (2H, m, H-1'), 1.84 – 1.74 (2H, m, H-2'), 1.32 (3H, s, H-6); δ_C (101 MHz, $CDCl_3$) 109.7 (C-2), 64.9 (C-4,5), 37.7 (C-2'), 34.1 (C-3'), 27.7 (C-1'), 24.1 (C-6).

2-(3'-Iodopropyl)-2-methyl-1,3-dioxolane (320)[341]

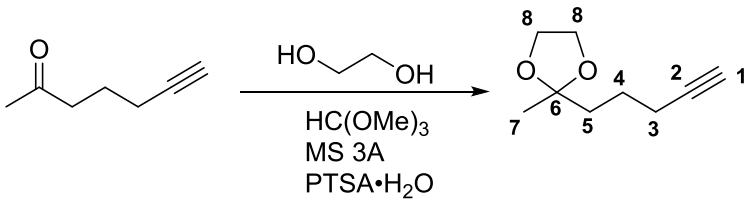


2-(3'-Bromopropyl)-2-methyl-1,3-dioxolane (220 mg, 1.05 mmol) was dissolved in dry acetone (3 mL). Then, NaI (450 mg, 3 mmol) was added and the solution was stirred at RT overnight (16 hr). Volatiles were removed in vacuo and the oily residue was partitioned between petrol (15 mL) and water (3 mL). The organic layer was separated and washed sequentially with $Na_2S_2O_3$ (1 M, 3 mL) and brine (2 mL), then dried over $MgSO_4$ and concentrated (RT, 150 Torr). The product is a colourless oil, which turns brown over time (250 mg, 98%).

R_f 0.47 (25:75, ether/petrol); ν_{max}/cm^{-1} 2981m, 2878m, 1041s; δ_H (400 MHz, $CDCl_3$) 3.99 – 3.90 (4H, m, H-4,5), 3.22 (2H, t, *J* = 7.0 Hz, H-3'), 2.00 – 1.90 (2H, m, H-2'), 1.79 – 1.72 (2H, m, H-1'), 1.32 (3H, s, H-6); δ_C (101 MHz, $CDCl_3$) 109.4 (C-2), 64.7 (C-4,5), 39.8 (C-1'), 28.3 (C-2'), 24.0 (C-6), 7.0 (C-3').

2-methyl-2-(pent-4-yn-1-yl)-1,3-dioxolane (321)[342,343]

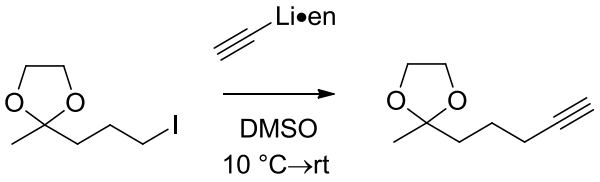
Method A.



The following reagents were mixed successively: hept-6-yn-2-one (300 mg, 2.73 mmol), ethylene glycol (1.69 g, 27.3 mmol), $HC(OMe)_3$ (1.02 g, 9.6 mmol), 3Å molecular sieves (0.15 g), and $PTSA{\cdot}H_2O$ (50 mg, 0.27 mmol). The mixture was stirred at RT for 1.5 hr. In a separate flask, $NaH_2PO_4{\cdot}H_2O$ (1.1 g) was dissolved in water (20 mL) followed by pyridine (0.05 mL); 5 mL of this mixture were used to quench the acetal formation. The aq. layer was then extracted with ether (3×5 mL). The combined

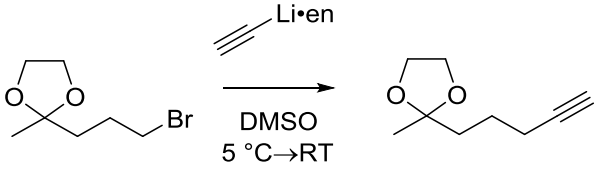
organic layers were washed with sat. aq. $CuSO_4$ (3 mL) and brine (2×3 mL), then dried over $MgSO_4$ and carefully concentrated under reduced pressure until constant weight (RT, 300 → 180 Torr). The product is a clear golden-brown oil that was used as received (300 mg, 71%).

Method B.



Adapted from the procedure by Novis Smith and Beumel, Jr.[251] LiC≡CH·en (90%, 0.58 g, 5.9 mmol) was suspended in DMSO (3.5 mL; dried by stirring over powdered CaH_2 for 15 hr). This mixture was cooled to 10 °C, and neat 2-(3-iodopropyl)-2-methyl-1,3-dioxolane (0.75 g, 2.9 mmol) was added dropwise over 10 min. The reaction was stirred at 10 °C for 10 min, then at RT for 50 min. The mixture was then cooled to 5° C, diluted with ether (4 mL) and quenched carefully with sat. aq. NH_4Cl (4 ml; *caution: gas evolution*) with vigorous stirring. After 5 min, the ice bath was removed and the reaction content was partitioned between sat. aq. NH_4Cl (40 mL) and ether (40 mL). The layers were separated and the aq. layer was extracted with ether (3×15 mL). The combined organic layers were washed with water (2×15 mL) and brine (2×15 mL), then dried over $MgSO_4$, and carefully concentrated under reduced pressure (RT, 300 → 200 Torr). The product is a clear yellow oil that was used as received (0.395 g, 88%).

Method C.

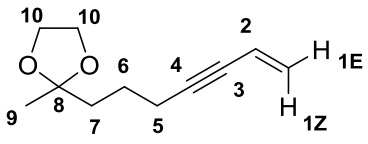


Similar to Method B but 2-(3-bromopropyl)-2-methyl-1,3-dioxolane was used as the starting material. A solution of 2-(3-bromopropyl)-2-methyl-1,3-dioxolane (1.35 g,

6.0 mmol) in DMSO (7.0 mL, dried by stirring over powdered CaH_2 for 15 hr) was cooled to 5 °C. Then, LiC≡CH·en (90%, 1.10 g, 12 mmol) was added slowly to the rapidly stirred (800 rpm) reaction mixture. The colour of the reaction changed to dark brown. The ice bath was removed and stirring was continued for 100 min. The reaction was diluted with ether (4 mL) and transferred portionwise into a separating funnel containing sat. aq. NH_4Cl (40 mL) and ether (40 mL). *Caution: intense gas evolution.* The reaction flask was washed with water (4 mL), the mixture was shaken and the layers were separated. The aq. layer was extracted with ether (3×15 mL). The combined organic layers were washed with water (2×15 mL) and brine (2×15 mL), then dried over Na_2SO_4, and concentrated carefully (300 → 150 Torr, RT). The crude yellow residue was distilled in Kugelrohr (9 Torr, 110 → 120 °C). The product is a clear colourless oil (0.754 g, 82%).

R_f 0.38 (25:75, ether/petrol); ν_{max}/cm^{-1} 3292m (≡C–H), 2117w (C≡C); δ_H (400 MHz, C_6D_6) 3.51 – 3.42 (4H, m, H-8), 1.98 2H, (td, *J* = 7.0, 2.5 Hz, H-3), 1.77 (1H, t, *J* = 2.5 Hz, H-1), 1.72 – 1.65 (2H, m, H-5), 1.64 – 1.54 (2H, m, H-4), 1.22 (3H, s, H-7). δ_C (101 MHz, C_6D_6) 109.5 (C-6), 83.9 (C-2), 68.7 (C-1), 64.3 (C-8), 38.2 (C-5), 23.7 (C-7), 23.2 (C-4), 18.4 (C-3).

2-(hept-6-en-4-yn-1-yl)-2-methyl-1,3-dioxolane (322)

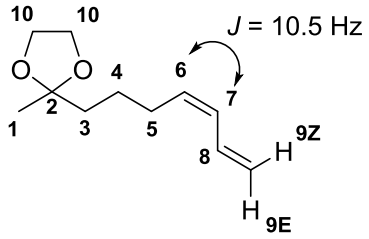


PPh_3 (150 mg, 0.57 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), and CuI (55 mg, 0.29 mmol) were put into a flask under argon. Distilled *i*-Pr_2NH (6 mL) was added, quickly followed by a stock solution of vinyl bromide (1 M in THF, 9.6 mL, 9.6 mmol) and neat 2-methyl-2-(pent-4-yn-1-yl)-1,3-dioxolane (0.75 g, 4.8 mmol). The resulting yellow solution was stirred at RT for 5 hr (*note:* the product and starting material are

indistinguishable by TLC in ether/petrol based systems). Over the course of reaction, the solution turned darker yellow and voluminous precipitation was observed. The reaction was diluted with ether (55 mL) and quenched with half-sat. aq. NH_4Cl (50 mL). The blue aq. layer was separated and extracted with ether (5×15 mL). The organic layer was washed with water (15 mL) and brine (2×15 mL); the aqueous washes were re-extracted with ether (15 mL). The combined ether extracts were dried over $MgSO_4$ and carefully concentrated (150 Torr, 20 °C). The crude product (yellow oil) was contaminated predominantly with $Ph_3P{=}O$. The pure target compound was obtained by Kugelrohr distillation (9 Torr, 120 → 150 °C) as a colourless oil (674 mg, 78%). *Note:* Attempts to purify the title compound by flash chromatography on silica (10:90 → 20:80, ether/petrol) invariably led to the significant loss of the material (average yield: 41% in 3 attempts).

R_f 0.40 (25:75, ether/petrol); ν_{max}/cm^{-1} 3099w (=C–H); δ_H (500 MHz, C_6D_6) 5.74 (1H, ddt, *J* = 17.5, 11.0, 2.5 Hz, H-2), 5.53 (1H, dd, *J* = 17.5, 2.5 Hz, H-1Z), 5.10 (1H, dd, *J* = 11.0, 2.5 Hz, H-1E), 3.52 – 3.44 (4H, m, H-10), 2.17 (2H, td, *J* = 7.0, 2.5 Hz, H-5), 1.75 – 1.69 (2H, m, H-7), 1.69 – 1.60 (2H, m, H-6), 1.23 (3H, s, H-9); δ_C (126 MHz, C_6D_6) 125.4 (C-1), 118.3 (C-2), 109.9 (C-8), 91.4 (C-4), 80.3 (C-3), 64.7 (C-10), 38.7 (C-7), 24.1 (C-9), 23.8 (C-6), 19.8 (C-5); HRMS (TOF FI^+), m/z: calcd for $C_{11}H_{16}O_2$ [M^+] 180.1150, found 180.1144.

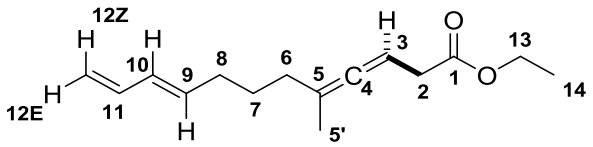
(Z)-2-(hepta-4,6-dien-1-yl)-2-methyl-1,3-dioxolane (323)



Prepared using a general procedure by Avignon-Tropis[249] and Boland.[250] *Activation of zinc.* Argon was bubbled through a suspension of Zn dust (8.25 g) in deionized water (50 mL) in a 250 mL flask for 30 min. Then, $Cu(OAc)_2$ (0.83 g) was added with rapid stirring (1000 rpm). The stirring was continued for 15 min, followed by the addition of $AgNO_3$ (0.83 g; *caution: exotherm*). At this point, the metal suspension turned deeper black. The mixture was stirred vigorously for 15 min, then let settle for 5 min. Water was carefully syringed out, and the metals were washed sequentially with water (2×50 mL), methanol (50 mL), acetone (50 mL), and ether (2×50 mL), while keeping the surface under argon. *Reduction of enyne.* To the freshly prepared ether-wet cake of activated Zn was added methanol (16 mL) and water (16 mL), followed by 2-(hept-6-en-4-yn-1-yl)-2-methyl-1,3-dioxolane (660 mg, 3.67 mmol) in methanol (5 mL). The reaction flask was equipped with an air-cooled reflux condenser and gently heated at 35 °C with vigorous stirring. The heating was continued for 4 days, followed by 4 days of stirring at RT, until NMR analysis showed complete consumption of the starting material *(note: the product and the starting material co-elute on TLC)*. The solids were filtered off on Celite, thoroughly washing with methanol (30 mL), water (20 mL) and ether (100 mL). The washes were diluted with brine (20 mL) and shaken. The layers were separated and the aq. layer was extracted with ether (2×25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and carefully concentrated (20 °C, 150 → 120 Torr). The product, a colourless oil, was used immediately in the next step. Yield not measured.

R_f 0.50 (25:75, ether/petrol); ν_{max}/cm^{-1} 3085w (=C–H); δ_H (500 MHz, C_6D_6) 6.65 (1H, dtd, *J* = 17.0, 10.5, 1.0 Hz, H-8), 6.05 (1H, app. tsept, *J* = 10.5, 1.0 Hz, H-7), 5.39 (1H, dt, *J* = 10.5, 7.5 Hz, H-6), 5.13 (1H, dd, *J* = 17.0, 2.0 Hz, H-9Z), 5.02 (1H, app. d, *J* = 10.5 Hz, H-9E), 3.53 – 3.49 (4H, m, H-10), 2.10 (2H, qd, *J* = 7.5, 1.5 Hz, H-5), 1.68 – 1.63 (2H, m, H-3), 1.58 – 1.50 (2H, m, H-4), 1.27 (3H, s, H-1); δ_C (126 MHz, C_6D_6) 132.8 (C-6/8), 132.7 (C-6/8), 130.1 (C-7), 117.0 (C-9), 110.1 (C-2), 64.7 (C-10), 39.1 (C-3), 28.1 (C-5), 24.5 (C-4), 24.1 (C-1); HRMS (TOF FI$^+$), m/z: calcd for $C_{11}H_{18}O_2$ [M^+] 182.1307, found 182.1306.

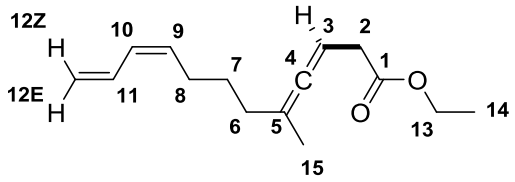
(E)-Ethyl 5-methyldodeca-3,4,9,11-tetraenoate (*E*-324)



Prepared by General method B from *(E)*-3-methyldeca-7,9-dien-1-yn-3-ol (*E*-**389**, 0.353 g, 2.15 mmol), $MeC(OEt)_3$ (10 mL), and propanoic acid (0.10 mL). Flash chromatography (5:95 → 20:80, ether/petrol) afforded the target material as a colourless oil (360 mg, 72%).

R_f 0.48 (10:90, ether/petrol); ν_{max}/cm^{-1} 3084w (=C–H), 1967w (C=C=C), 1738s (C=O); δ_H (400 MHz, $CDCl_3$) 6.31 (1H, dt, *J* = 17.0, 10.0 Hz, H-10), 6.05 (1H, dd, *J* = 15.0, 10.0 Hz, H-11), 5.70 (1H, dt, *J* = 15.0, 7.0 Hz, H-9), 5.20 – 5.13 (1H, m, H-3), 5.10 (1H, d, *J* = 17.0 Hz, H-12Z), 4.96 (1H, d, *J* = 10.0 Hz, H-12E), 4.15 (2H, q, *J* = 7.0 Hz, H-13), 2.98 (2H, d, *J* = 7.0 Hz, H-2), 2.10 (2H, app. q, *J* = 7.0 Hz, H-8), 1.95 (2H, td, *J* = 7.5, 3.0 Hz, H-6), 1.68 (3H, d, *J* = 3.0 Hz, H-5'), 1.58 – 1.48 (2H, m, H-7), 1.27 (3H, t, *J* = 7.0 Hz, H-14); δ_C (126 MHz, $CDCl_3$) 202.5 (C-4), 171.9 (C-1), 137.2 (C-10), 135.0 (C-9), 131.2 (C-11), 114.8 (C-12), 100.5 (C-5), 83.5 (C-3), 60.6 (C-13), 35.4 (C-2), 33.2 (C-6), 32.0 (C-8), 26.8 (C-7), 18.9 (C-5), 14.2 (C-14); HRMS (ESI$^+$), m/z: calcd for $C_{15}H_{22}NaO_2$ [$M+Na^+$] 257.1512, found 257.1513.

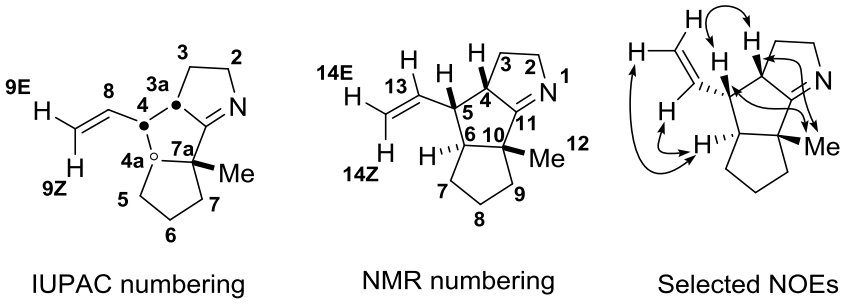
(*Z*)-Ethyl 5-methyldodeca-3,4,9,11-tetraenoate (*Z*-324)



Prepared by General method B from (*Z*)-3-methyldeca-7,9-dien-1-yn-3-ol (*Z*-**389**, 289 mg, 1.76 mmol), $MeC(OEt)_3$ (5.8 mL) and propanoic acid (0.1 mL) by heating at 140 °C for 5 hr. The cooled reaction mixture was diluted with ether (50 mL), washed sequentially with aq. HCl (0.5M, 12 mL), sat. aq. $NaHCO_3$ (12 mL) and brine (12 mL). The aqueous washes were re-extracted with ether (10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (3:97 → 20:80, ether/petrol) afforded the title material as a clear colourless oil with a weak acrylic smell (0.26 g, 63%; b.r.s.m. 85%).

R_f 0.61 (25:75, ether/petrol); ν_{max}/cm^{-1} 3085w (=C–H), 1969w (C=C=C), 1736s (C=O); δ_H (500 MHz, $CDCl_3$) 6.62 (1H, dtd, *J* = 16.5, 10.5, 10.5, 1.0 Hz, H-11), 6.00 (1H, t, *J* = 10.5 Hz, H-10), 5.44 (1H, dt, *J* = 10.5, 7.5 Hz, H-9), 5.21 – 5.12 (2H, m, H-12Z,3), 5.08 (1H, d, *J* = 10.5 Hz, H-12E), 4.14 (2H, q, *J* = 7.0 Hz, H-13), 2.98 (2H, d, *J* = 7.0 Hz, H-2), 2.23 – 2.16 (2H, m, H-8), 1.97 – 1.91 (2H, m, H-6), 1.67 (3H, d, *J* = 3.0 Hz, H-15), 1.50 (2H, quint, *J* = 7.5 Hz, H-7), 1.26 (3H, t, *J* = 7.0 Hz, H-14); δ_C (126 MHz, $CDCl_3$) 202.5 (C-4), 172.1 (C-1), 132.7 (C-9), 132.4 (C-11), 129.6 (C-10), 117.1 (C-12), 100.6 (C-5), 83.7 (C-3), 60.8 (C-13), 35.6 (C-2), 33.3 (C-6), 27.31 (C_{7or8}), 27.29 (C_{8or7}), 19.2 (C-15), 14.4 (C-14); HRMS (ESI^+), m/z: calcd for $C_{15}H_{22}NaO_2$ [$M+Na^+$] 257.1512, found 257.1510.

(±)-(3a*S*,4*S*,4a*S*,7a*R*)-7a-Methyl-4-vinyl-3,3a,4,4a,5,6,7,7a-octahydro-2*H*-pentaleno[1,2-*b*]pyrrole (325)



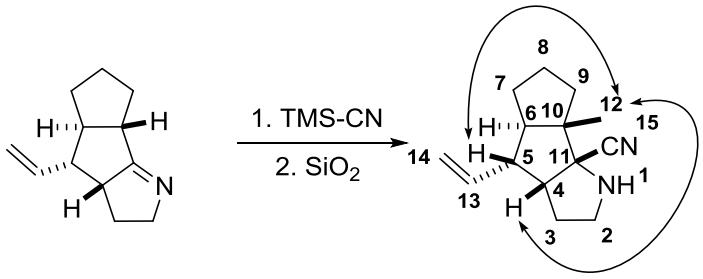
(E)-12-azido-8-methyldodeca-1,3,8,9-tetraene (29 mg, 0.13 mmol; E/Z>13:1) was dissolved in distilled *m*-xylene (0.7 mL) and placed into a dry NMR tube, thoroughly flushed with argon. The tube was sealed and heated at 135 °C for 1.5 hr. The crude mixture was loaded onto a silica column and eluted with a gradient (petrol → 10:90 → 25:75 → 50:50, ether/petrol → ether → 5:95, methanol/ether), affording the title compound as a colourless oil with an earthy odour (10 mg, 40%).

R_f 0.50 (5:95, MeOH/ether); ν_{max}/cm^{-1} 1650m (C=N); δ_H (700 MHz, $CDCl_3$) 5.73 (1H, ddd, *J* = 14.0, 10.0, 7.0 Hz, H-13), 5.06 – 4.99 (2H, m, H-14), 3.91 (1H, dd, *J* = 13.5, 8.0 Hz, H-2a), 3.67 – 3.58 (2H, m, H-2b,4), 2.78 (1H, td, *J* = 11.0, 7.0 Hz, H-5), 2.16 – 2.01 (2H, m, H-8ab/9ab), 1.92 – 1.83 (2H, m, H-3a,6), 1.65 – 1.55 (3H, m, H-3b,7a,8a-or-9a), 1.45 (1H, dd, *J* = 12.5, 10.5 Hz, H-8b/9b), 1.40 – 1.33 (1H, m, H-7b), 1.09 (3H, s, H-12); δ_H (500 MHz, C_6D_6) 5.57 (1H, ddd, *J* = 17.0, 10.5, 7.0 Hz, H-13), 4.97 (1H, ddd, *J* = 10.5, 1.5, 1.0 Hz, H-14E), 4.92 (1H, ddd, *J* = 17.0, 2.0, 1.5 Hz, H-14Z), 3.95 (1H, dd, *J* = 13.5, 8.0 Hz, H-2a), 3.58 (1H, dddd, *J* = 13.5, 11.0, 5.0, 2.0 Hz, H-2b), 3.20 (1H, dddd, *J* = 10.5, 10.0, 8.0, 2.0 Hz, H-4), 2.53 – 2.45 (1H, m, H-5), 1.92 – 1.73 (3H, m, H-8a,8b,9a), 1.69 (1H, app.td, *J* = 12.5, 6.5 Hz, H-6), 1.59 (1H, ddd, *J* = 12.0, 8.0, 5.0 Hz, H-3a), 1.47 – 1.31 (3H, m, H-7a,3b,9b), 1.19 – 1.11 (1H, m, H-7b), 0.86 (3H, d, *J* = 0.5 Hz, H-12); δ_C (126 MHz, $CDCl_3$) 188.9 (C-11), 138.1 (C-13), 115.1 (C-14), 62.3 (C-2), 60.2 (C-6), 57.5 (C-4), 51.9

(C-10), 39.9 (C-5), 29.2 (C-3), 28.0 (C-8/9), 26.6 (C-8/9), 20.6 (C-7), 15.6 (C-12); HRMS (ESI$^+$), m/z: calcd for $C_{13}H_{20}N$ [M+H$^+$]190.1590, found 190.1585.

(±)-(3a*R*,4*R*,4a*R*,7a*S*,7b*R*)-7a-methyl-4-vinyldecahydro-1*H*-pentaleno[1,2-*b*]pyrrole-7b-carbonitrile (326)

Method A. From imine 325



To a solution of the starting imine (6 mg, 0.034 mmol) in $CDCl_3$ (0.6 mL) was added neat TMSCN (1 drop) at RT. TLC showed complete consumption of the starting material after 10 min of stirring. The solvent was evaporated and the residue was purified on a pipette silica column (0.5×3 cm, ether/petrol, 15:85 → 25:75) to afford the title compound as a clear colourless oil with an unpleasant odour (4.5 mg, ca. 75%).

Method B. One-pot cyclization/addition from *Z*-241

A solution of (*Z*)-12-azido-8-methyldodeca-1,3,8,9-tetraene (10 mg) in *m*-xylene (0.70 mL) was transferred into a dry NMR tube, thoroughly flushed with argon, sealed and heated at 135 °C for 110 min. The reaction mixture was cooled to RT and transferred into a 2.5 mL vial. The NMR tube was washed with ether (0.7 mL) into the same vial. Neat TMSCN (3 drops) was added and the mixture was stirred at RT for 1 hr. The mixture was reduced to *ca*. ½ of the initial volume under reduced pressure (250 → 50 Torr, 35 °C) and the residue was loaded directly onto a silica column. Elution with a gradient (15:85 → 25:75, ether/petrol → ether) afforded the target material as the major product (3 mg, 30% over 2 steps), accompanied by an unassigned diastereomer

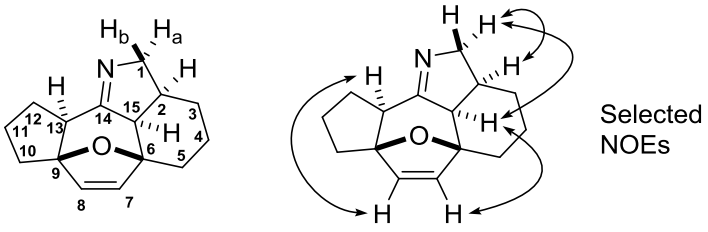
(1 mg, 10% over 2 steps). The title compound was chromatographically and spectroscopically identical with that obtained by Method A.

Method C. One-pot cyclization/addition from *E*-241

Identical to Method B but (*E*)-12-azido-8-methyldodeca-1,3,8,9-tetraene (24 mg) was used instead. Flash chromatography afforded the title compound (6 mg, 25% over 2 steps) along with a mixture of unassigned diastereomers (1.5 mg, 6% over 2 steps). The title compound was chromatographically and spectroscopically identical with that obtained by Method A.

The relative configuration of C_{11} was assigned tentatively based on ΔH_f calculations. The relative configuration of C_6 was assigned based on the configuration of the starting material and further confirmed by the absence of NOE to H_5, H_4 and H_{12} in the product. R_f 0.14 (25:75, ether/petrol); ν_{max}/cm^{-1} 3334m (NH), 3080w (=C–H), 2218w (CN); δ_H (500 MHz, $CDCl_3$) 5.72 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz, H-13), 5.11 – 5.01 (2H, m, H-14), 3.36 (td, *J* = 9.0, 7.5 Hz, 1H, H-4), 3.20 – 3.14 (1H, m, H-2a), 3.09 – 3.01 (1H, m, H-2b), 2.57 – 2.48 (1H, m, H-5), 2.17 (1H, td, *J* = 12.5, 7.0 Hz, H-6), 2.13 – 2.04 (2H, m, H-9), 1.89 (1H, br.s, NH), 1.86 – 1.77 (1H, m, H-3a), 1.73 – 1.63 (1H, m, H-3b), 1.56 – 1.45 (2H, m, H-7a,8a), 1.34 – 1.18 (2H, m, H-7b,8b), 1.10 (3H, s, H-12); δ_C (126 MHz, $CDCl_3$) 137.5 (C-13), 123.7 (C-15), 116.6 (C-14), 66.6 (C-11), 59.7 (C-4), 56.1 (C-10), 52.1 (C-6), 48.1 (C-2), 42.8 (C-5), 28.2 (C-7), 27.4 (C-3/9), 27.2 (C-3/9), 20.8 (C-8), 19.1 (C-12); HRMS (ESI^+), m/z: calcd for $C_{14}H_{21}N_2$ [$M+H^+$] 217.1699, found 217.1692.

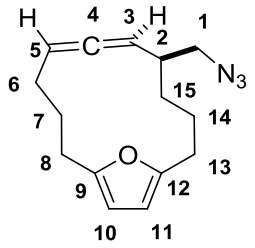
Radianspene J Model System (332)



A solution of 5-(azidomethyl)-15-oxabicyclo[10.2.1]pentadeca-1(14),6,7,12-tetraene (8 mg, 0.03 mmol) in distilled toluene (0.7 mL) was placed into a dry NMR tube, thoroughly flushed with argon, sealed, and heated at 110 °C for 70 min. The reaction content was loaded directly onto a short (0.5 cm, pipette) silica column, eluting with a minimal amount of solvent (10:90, ether/petrol → ether → 5:95, MeOH/ether). The product is a clear colourless oil (5 mg, 70%).

R_f 0.44 (5:95, MeOH/ether); ν_{max}/cm^{-1} 3067w (=C–H), 1638s (C=N); δ_H (500 MHz, $CDCl_3$) 6.16 (1H, d, *J* = 5.5 Hz, H-7/8), 6.00 (1H, d, *J* = 5.5 Hz, H-7/8), 3.61 (1H, dddd, *J* = 14.5, 6.0, 4.0, 2.5 Hz, H-1a), 3.43 (1H, dq, *J* = 14.5, 1.0 Hz, H-1b), 2.61 – 2.55 (1H, tdt, *J* = 8.5, 4.0, 1.0 Hz, H-13), 2.52 (1H, br.d, *J* = 7.5 Hz, H-15), 2.35 – 2.26 (1H, m, H-2), 2.11 – 1.99 (3H, m, H-12,½CH_2), 1.93 – 1.49 (7H, m, 3½×CH_2), 1.45 – 1.28 (2H, m, CH_2); δ_C (126 MHz, $CDCl_3$) 179.6 (C-14), 138.9 (C-7/8), 136.9 (C-7/8), 93.7 (C-9), 84.1 (C-6), 63.5 (C-1), 50.5 (C-13/15), 49.4 (C-13/15), 36.0 (C-2), 35.2 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 25.3 (CH_2), 22.8 (CH_2), 16.8 (CH_2); HRMS (ESI^+), m/z: calcd for $C_{15}H_{20}NO$ [$M+H^+$] 230.1539, found 230.1542.

5-(Azidomethyl)-15-oxabicyclo[10.2.1]pentadeca-1(14),6,7,12-tetraene (333)

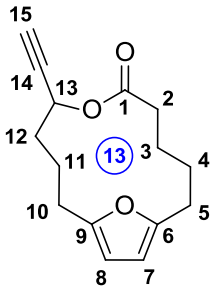


A solution of *O*-TIPS-15-oxabicyclo[10.2.1]pentadeca-1(14),6,7,12-tetraene-5-carboxylic acid (100 mg, 0.25 mmol) in ether (4 mL) was cooled to 0 °C. To this, $LiAlH_4$ (10 mg, 0.25 mmol) was added and the resulting mixture was stirred at 0 °C for 40 min. The reaction was carefully quenched by the dropwise addition of sat. aq. Na_2SO_4 (~1 drop/min), then stirred at RT for 30 min. The solution was dried with anhydrous Na_2SO_4, filtered and concentrated. The alcohol was unstable on silica and therefore used as received. The alcohol was redissolved in DMF (1.5 mL) and the vial was placed into a water bath (10 °C) to absorb any excessive heat (important!). To this, CBr_4 (209 mg, 0.63 mmol) and PPh_3 (165 mg, 0.63 mmol) were added and the mixture was stirred at RT overnight (14 hr). The reaction was cooled to 0 °C and partitioned between petrol (10 mL) and a water/brine mixture (10+10 mL). The layers were separated and the aq. layer was extracted with petrol (2×5 mL). The combined organic layers were washed with brine (2×5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (1.5:98.5, ether/petrol) afforded the intermediate bromide as a clear colourless oil (R_f 0.75, 1.5:98.5, ether/petrol). It was used immediately as received. The bromide was redissolved in DMF (1.5 mL). NaN_3 (49 mg, 0.75 mmol) was added and the mixture was stirred at 35 °C for 24 hr, then at RT for 2 days. The reaction was partitioned between petrol (10 mL) and a water/brine mixtre (10+5 mL). The layers were separated and the aq. layer was extracted with petrol (3×5 mL). The combined

organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (0.5:99.5 → 1.5:98.5, ether/petrol) afforded the title material as a clear colourless oil (52 mg, 81% over 3 steps).

R_f 0.66 (10:90, ether/petrol); ν_{max}/cm^{-1} 3099w (=C–H), 2096s (N_3), 1954w (C=C=C); δ_H (500 MHz, $CDCl_3$) 5.88 (1H, d, *J* = 3.0 Hz, H-10/11), 5.85 (1H, d, *J* = 3.0 Hz, H-10/11), 5.20 (1H, app.q, *J* = 6.0 Hz, H-3), 5.05 (1H, dddd, *J* = 10.0, 6.0, 4.0, 2.0 Hz, H-5), 3.26 (1H, dd, *J* = 12.0, 6.5 Hz, H-1a), 3.13 (1H, dd, *J* = 12.0, 7.5 Hz, H-1b), 2.78 – 2.70 (1H, m, H-13a), 2.69 – 2.62 (2H, m, H-8), 2.53 – 2.44 (1H, m, H-13b), 2.21 – 2.09 (2H, m, 1½CH_2), 2.02 – 1.88 (2H, m, CH_2), 1.86 – 1.77 (m, 1H, ½CH_2), 1.75 – 1.48 (3H, 1½CH_2); δ_C (126 MHz, $CDCl_3$) 204.0 (C-4), 154.3 (C-9/12), 153.9 (C-9/12), 106.0 (C-10/11), 105.9 (C-10/11), 94.6 (C-5), 91.7 (C-3), 57.0 (C-1), 38.4 (C-2), 31.0 (CH_2), 29.0 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 26.5 (CH_2); HRMS (TOF FI^+), m/z: calcd for $C_{15}H_{19}N_3O$ [M^+] 257.1528, found 257.1534.

5-Ethynyl-6,15-dioxabicyclo[10.2.1]pentadeca-1(14),12-dien-7-one (334)

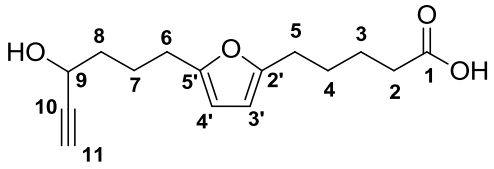


Prepared using a modified Yamaguchi macrolactonisation[269] protocol by Carreira *et al.*[270] Freshly distilled THF (90 mL) was placed into a 250 mL flask. The starting seco-acid (232 mg, 0.88 mmol) was added as a solution in THF (2×5 mL), followed by TEA (0.74 mL, 5.3 mmol) and 2,4,6-trichlorobenzoyl chloride (0.69 mL, 4.4 mmol). The solution was stirred at RT for 90 min. White precipitate formed over the course of reaction. The resulting solution of the mixed anhydride was diluted with more THF (50 mL), before being used in the next step. In a separate 500 mL flask,

equipped with a reflux condenser, a solution of DMAP (1.07 g, 8.8 mmol) in toluene (250 mL) was heated at 85 °C (oil bath temp.) To this, the solution of the activated seco-acid was added slowly with a syringe pump, using 5×20 mL syringes, over the top of reflux condenser, so that the drops did not touch the condenser. The rate of addition was adjusted to result in ca. 7 hr addition time. When all seco-acid was added, the heating was turned off and the reaction was stirred at RT overnight (15 hr). Volatiles were evaporated (30 °C, 120 → 30 Torr). The solid residue was dissolved in DCM (20 mL) and filtered through a plug of silica (2 cm), eluting with 100 mL of DCM. The solution was concentrated and the resulting yellow oil was purified by flash chromatography (1:10, ether/petrol) to afford the title product as a white solid (134 mg, 62%).

R_f 0.37 (10:90, ether/petrol); m. p.: 52–54 °C; δ_H (500 MHz, $CDCl_3$) 5.87 (1H, d, *J* = 3.0 Hz, H-7/8), 5.84 (1H, d, *J* = 3.0 Hz, H-7/8), 5.59 – 5.55 (1H, m, H-1), 2.77 – 2.66 (2H, m, CH_2), 2.59 – 2.43 (3H, m, 1½×CH_2), 2.43 (1H, d, *J* = 2.5 Hz, H-15), 2.24 – 2.15 (1H, m, ½×CH_2), 2.07 – 1.87 (2H, m, CH_2), 1.83 – 1.60 (6H, m, 3×CH_2); δ_C (126 MHz, $CDCl_3$) 172.3 (C-1), 154.3 (C-6/9), 153.4 (C-6/9), 106.6 (C-7/8), 106.0 (C-7/8), 80.9 (C-14), 73.6 (C-15), 62.8 (C-13), 34.8 (CH_2), 32.7 (CH_2), 27.2 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 24.1 (CH_2), 22.1 (CH_2); ν_{max}/cm^{-1} 3307m (≡C–H), 3101w (=C–H), 2124w (C≡C), 1732s (C=O); HRMS (ESI^+), m/z: calcd for $C_{15}H_{18}O_3Na$ [$M+Na^+$] 269.1148, found 269.1142.

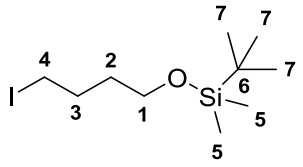
5-(5-(4-hydroxyhex-5-yn-1-yl)furan-2-yl)pentanoic acid (338)



tert-Butyl 5-(5-(4-hydroxyhex-5-yn-1-yl)furan-2-yl)pentanoate (340 mg, 1.06 mmol) was dissolved in a mixture of reagent grade acetone (5 mL) and water (5 mL) in a thick-walled tube (inner volume ca. 30 mL) containing a small stirbar. $LiOH{\cdot}H_2O$ (222 mg, 5.3 mmol) was then added. The tube was thoroughly flushed with argon, sealed, and heated in an oil bath at 76 °C for 8 hr, keeping the solution ca. 5 mm higher than the oil level. The reaction content was cooled and partitioned between ether (50 mL), water (30 mL) and citrate buffer (20 mL, pH 3). The aq. layer was separated (pH ~5-6) and extracted with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (1:1, ether/petrol) afforded an inseparable mixture of the target material (92 wt%) and diacetone alcohol (8 wt%). The product is a yellow oil that solidifies upon standing into a white solid (278 mg, 92% purity, 91% yield).

R_f 0.45 (ether); m. p.: 46–49 °C; ν_{max}/cm^{-1} 3290s (OH), 3200br.s (OH), 3101w (=C–H), 2117w (C≡C), 1706s (C=O); δ_H (500 MHz, $CDCl_3$) 5.87 (2H, app.q, *J* = 3.0 Hz, H-4',3'), 4.39 (1H, td, *J* = 6.0, 2.0 Hz, H-9), 2.66 – 2.57 (4H, m, H-5,6), 2.47 (1H, d, *J* = 2.0 Hz, H-11), 2.40 – 2.34 (2H, m, H-2), 1.85 – 1.72 (4H, m, H-7,8), 1.71 – 1.63 (4H, m, H-3,4), *note: the OH signals were not observable*; δ_C (126 MHz, $CDCl_3$) 178.5 (C-1), 154.03 (C-2'/5'), 154.00 (C-2'/5'), 105.63 (C-3'/4'), 105.62 (C-3'/4'), 84.8 (C-10), 73.2 (C-11), 62.3 (C-9), 37.1 (C-8), 33.7 (C-2), 27.8 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 24.3 (CH_2), 23.8 (C-7); HRMS (ESI^+), m/z: calcd for $C_{15}H_{20}O_4Na$ [$M+Na^+$] 287.1254, found 287.1258.

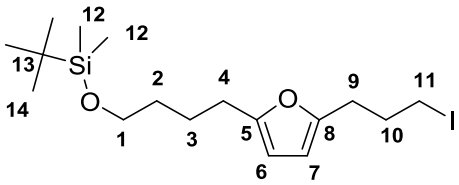
4-Iodo-1-(*tert*-butyldimethylsilyloxy)butane (339)[344]



Anhydrous $CaCO_3$ (167 mg, 1.66 mmol) and NaI (dried at 70 °C/hi-vac for 14 hr; 2.49 g, 16.6 mmol) were mixed in THF (11 mL). Next, TBSCl (2.50 g, 16.6 mmol) was added. The mixture was kept at reflux for 48 hr. The reaction was cooled to RT and quenched with sat. aq. $Na_2S_2O_3$ (ca. 8 mL). The aq. layer was extracted with ether (3×8 mL). The combined organic layers were washed with brine (8 mL) and dried ($MgSO_4$). The resulting solution was filtered through a silica pad (ca. 1 in), washing with petrol. Evaporation of the resulting solution provided the pure target material as a colourless oil (5.01 g, 96%).

R_f 0.25 (petrol); ν_{max}/cm^{-1} 2953m, 2929m, 2856m, 1471m, 1264m, 1101s, 835s, 775s; δ_H (400 MHz, $CDCl_3$) 3.64 (2H, t, *J* = 6.0 Hz, H-1), 3.23 (2H, t, *J* = 7.0 Hz, H-4), 1.96 – 1.87 (2H, m, H-3), 1.67 – 1.58 (2H, m, H-2), 0.89 (9H, s, H-7), 0.05 (6H, s, H-5); δ_C (101 MHz, $CDCl_3$) 61.9 (C-1), 33.5 (C-2), 30.2 (C-3), 25.9 (C-7), 18.3 (C-6), 7.1 (C-4), −5.3 (C-5).

***tert*-Butyl(4-(5-(3-iodopropyl)furan-2-yl)butoxy)dimethylsilane (341)**

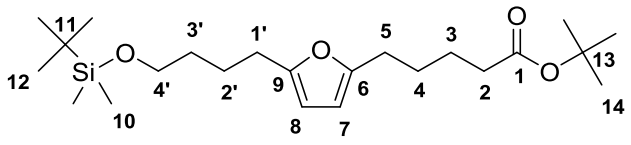


To a solution of *O*-TBS-4-(5-(3-chloropropyl)furan-2-yl)butan-1-ol (2.58 g, 7.8 mmol) in reagent grade acetone (25 mL) was added NaI (3.51 g, 23.3 mmol), and this mixture was stirred at reflux for 24 hr. The resulting yellow solution with white precipitate was diluted with ether (30 mL) and water (150 mL). The layers were

separated and the aq. layer was extracted with ether (3×30 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (20 mL), brine (20 mL), then dried over $MgSO_4$, and concentrated. ^1H NMR analysis of the crude mixture indicated a 3:2 mol/mol mixture of the TM and deprotected alcohol, respectively. The crude residue was redissolved in DCM (10 mL), followed by imidazole (1.06 g, 15.6 mmol) and TBSCl (1.21 g, 8.0 mmol). The mixture was stirred at RT until all alcohol has been consumed (ca. 2 hr). The reaction was diluted with ether (40 mL) and quenched with sat. aq. NH_4Cl (40 mL). The layers were separated and the aq. layer was extracted with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (petrol → 1:99, ether/petrol) afforded the title material as a clear colourless oil (2.86 g, 87%).

R_f 0.55 (3:97, ether/petrol); ν_{max}/cm^{-1} 3103w (=C–H), 1101s, 834s, 774s; δ_H (500 MHz, $CDCl_3$) 5.91 (1H, d, *J* = 3.0 Hz, H-7), 5.85 (1H, d, *J* = 3.0 Hz, H-6), 3.63 (2H, t, *J* = 6.5 Hz, H-1), 3.19 (2H, t, *J* = 7.0 Hz, H-11), 2.70 (2H, t, *J* = 7.0 Hz, H-9), 2.58 (2H, t, *J* = 7.5 Hz, H-4), 2.12 (2H, quint, *J* = 7.0 Hz, H-10), 1.70 – 1.61 (2H, m, H-3), 1.60 – 1.50 (2H, m, H-2), 0.89 (9H, s, H-14), 0.05 (6H, s, H-12); δ_C (126 MHz, $CDCl_3$) 155.2 (C-5/8), 152.2 (C-5/8), 106.3 (C-7), 105.3 (C-6), 63.0 (C-1), 32.5 (C-2), 31.9 (C-10), 28.9 (C-9), 27.9 (C-4), 26.1 (C-14), 24.6 (C-3), 18.5 (C-13), 6.2 (C-11), −5.1 (C-12); HRMS (TOF FI^+), m/z: calcd for $C_{17}H_{31}O_2ISi$ $[M^+]$ 422.1138, found 422.1132.

tert-Butyl 5-(5-(4-((_tert_-butyldimethylsilyl)oxy)butyl)furan-2-yl)pentanoate (342)

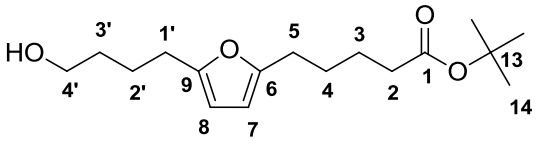


Prepared using a modified procedure of Rathke.[266] Isopropylcyclohexylamine (1.07 mL, 6.5 mmol; distilled over 10 wt% CaH_2/10 Torr) was dissolved in freshly

distilled THF (5 mL) and cooled to 0 °C. To this, BuLi (2.5 M, 2.6 mL, 6.5 mmol) was added dropwise with a syringe. The solution was stirred at 0 °C for 15 min, then cooled to −78 °C. Neat *t*-BuOAc (0.87 mL, 6.5 mmol) was added with a syringe. The resulting enolate solution was stirred at −78 °C for 1 hr, then transferred via cannula to a solution (RT) of the starting *O*-TBS-4-(5-(3-iodopropyl)furan-2-yl)butan-1-ol (2.15 g, 5.1 mmol) in 25 mL of DMSO (freshly dried by stirring over 10 wt% CaH_2 for 5 hr and filtering through a syringe filter directly into the reaction flask). The resulting mixture was stirred at RT for 20 min, until TLC showed complete consumption of starting iodide. The reaction was quenched with sat. aq. NH_4Cl (100 mL) and ether (50 mL). The layers were separated and the aq. layer was extracted with ether (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (petrol → 1:99 → 2:98 → 4:96, ether/petrol) afforded the title material as a clear colourless oil (2.10 g, 99%).

R_f 0.40 (8:92, ether/petrol); ν_{max}/cm^{-1} 3103w (=C–H), 1732s (C=O); δ_H (500 MHz, $CDCl_3$) 5.86 – 5.83 (2H, m, H-7,8), 3.62 (2H, t, *J* = 6.5 Hz, H-4'), 2.58 (4H, app.t, *J* = 7.5 Hz, H-1',5), 2.26 – 2.20 (2H, m, H-2), 1.70 – 1.61 (6H, m, H-2',3,4), 1.60 – 1.52 (2H, m, H-3'), 1.44 (9H, s, H-14), 0.89 (9H, s, H-11), 0.04 (6H, s, H-10), n*ote: the H-2 peak appears as a distorted triplet, suggesting some secondary interactions*; δ_H (400 MHz, acetone-d_6) δ 5.93 – 5.87 (2H, $m_{7,8}$), 3.66 (t, *J* = 6.0 Hz, 2H, H-4'), 2.580 (t, *J* = 7.5 Hz, 2H, $H_{1'or5}$), 2.575 (t, *J* = 7.0 Hz, 2H, $H_{5or1'}$), 2.22 (br.t, *J* = 7.0 Hz, 2H, H-2), 1.73 – 1.50 (m, 8H, $H_{3,4,2',3'}$), 1.42 (9H, s, H-14), 0.89 (9H, s, H-12), 0.05 (6H, s, H-10), *note: the H-2 signal is much sharper in acetone-D_6*; δ_C (126 MHz, $CDCl_3$) 173.2 (C-1), 154.6 (C-6/9), 154.2 (C-6/9), 105.3 (C-7/8), 105.2 (C-7/8), 80.2 (C-13), 63.1 (C-4'), 35.5 (C-2), 32.5 (C-3'), 28.3 (C-14), 28.0 (C-1'), 27.9 (C-5), 27.7 (C-3), 26.1 (C-12), 24.8 (C-4), 24.6 (C-2'), 18.5 (C-10); HRMS (ESI^+), m/z: calcd for $C_{23}H_{42}O_4SiNa$ [$M+Na^+$] 433.2745, found 433.2751.

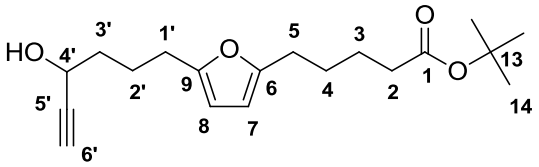
tert-Butyl 5-(5-(4-hydroxybutyl)furan-2-yl)pentanoate (343)



Pyridine (0.3 mL) was dissolved in THF (4 mL) in a plastic vial, followed HF·py (70wt% HF, 0.16 mL, 6.5 mmol). The mixture was stirred for 5 min. Then, a solution of *tert*-butyl 5-(5-(*O*-TBS-4-hydroxybutyl)furan-2-yl)pentanoate (0.54 g, 1.3 mmol) in THF (6 mL) was added. The resulting solution was capped and stirred under air for 30 hr. *Note: use of 6 eq of HF·py, instead of 5 eq, allows to shorten the reaction time to 14 hr without compromising the yield.* The reaction mixture was transferred into sat. aq. $NaHCO_3$ (30 mL) in a separating funnel *(caution: gas evolution)*. The reaction vessel was washed with ether (10 mL) into the same funnel. The mixture was shaken until gas evolution ceased. The layers were separated and the aq. layer was extracted with ether (4×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (40:60, ether/petrol) afforded the title material as a clear colourless oil; traces of pyridine were removed by prolonged evaporation at 20 °C/8 Torr (370 mg, 95%).

R_f 0.52 (ether); ν_{max}/cm^{-1} 3417br.s (OH), 3103w (=C–H), 1729s (C=O); δ_H (500 MHz, $CDCl_3$) 5.87 – 5.83 (2H, m, H-7,8), 3.65 (2H, t, *J* = 6.5 Hz, H-4'), 2.63 – 2.55 (4H, m, H-1',5), 2.26 – 2.19 (2H, br.t, *J*= 7.0 Hz, H-2), 1.73 – 1.58 (8H, m, H-2',3',3,4), 1.51 (1H, br.s, OH), 1.43 (9H, s, H-14); δ_C (126 MHz, $CDCl_3$) 173.2 (C-1), 154.3 (C-6/9), 154.2 (C-6/9), 105.4 (C-7/8), 105.3 (C-7/8), 80.2 (C-13), 62.8 (C-4'), 35.5 (C-2), 32.4 (C-3'), 28.3 (C-14), 27.9 (C-1'/2'/3/4/5), 27.9 (C-1'/2'/3/4/5), 27.7 (C-1'/2'/3/4/5), 24.7 (C-1'/2'/3/4/5), 24.5 (C-1'/2'/3/4/5); HRMS (ESI^+), m/z: calcd for $C_{17}H_{28}O_4Na$ [$M+Na^+$] 319.1880, found 319.1876.

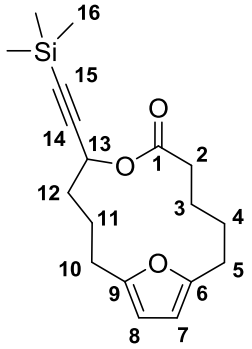
tert-Butyl 5-(5-(4-hydroxyhex-5-yn-1-yl)furan-2-yl)pentanoate (344)



A solution of the starting aldehyde **398** (1.30 g, 4.4 mmol) in THF (20 mL) was cooled to −78 °C. To this, a stock solution of HC≡CMgBr (0.5M in THF, 9.7 mL, 4.9 mmol) was added dropwise over 20 min using a syringe pump. The mixture was stirred for 1 hr at −78 °C, then at 0 °C for 15 min. The reaction was quenched at 0 °C with sat. aq. NH_4Cl (30 mL) and water (10 mL), then allowed to warm to RT. The mixture was diluted with ether (20 mL). The layers were separated and the aq. layer was extracted with ether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The product was purified by filtration through a silica plug (2×2 cm), eluting with ether, to afford the title material as a clear yellow oil (1.29 g, 91%).

R_f 0.46 (50:50, ether/petrol); ν_{max}/cm^{-1} 3425br.s (OH), 3295s (≡C−H), 3103w (=C−H), 1727s (C=O); δ_H (500 MHz, $CDCl_3$) 5.87 (1H, d, *J* = 3.0 Hz, H-7/8), 5.85 (1H, d, *J* = 3.0 Hz, H-7/8), 4.38 (1H, td, *J* = 6.0, 2.0 Hz, H-4'), 2.63 (2H, t, *J* = 7.0 Hz, H-1'/5), 2.58 (2H, t, *J* = 6.5 Hz, H-1'/5), 2.46 (1H, d, *J* = 2.0 Hz, H-6'), 2.26 – 2.20 (2H, br.t, *J* = 7.0, H-2), 1.85 – 1.71 (5H, m, H-3',2',OH), 1.67 – 1.60 (4H, m, H-3,4), 1.44 (9H, s, H-14); δ_C (126 MHz, $CDCl_3$) 173.3 (C-1), 154.4 (C-6/9), 153.9 (C-6/9), 105.6 (C-7/8), 105.4 (C-7/8), 84.9 (C-5'), 80.3 (C-13), 73.1 (C-6'), 62.2 (C-4'), 37.2 (C-3'), 35.5 (C-2), 28.3 (C-14), 27.9 (C-1'/3/4/5), 27.8 (C-1'/3/4/5), 27.7 (C-1'/3/4/5), 24.7 (C-3/4), 23.8 (C-2'); HRMS (ESI^+), m/z: calcd for $C_{19}H_{28}O_4Na$ [$M+Na^+$] 343.1880, found 343.1885.

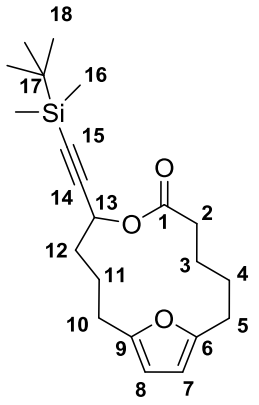
5-((Trimethylsilyl)ethynyl)-6,15-dioxabicyclo[10.2.1]pentadeca-1(14),12-dien-7-one (347)



5-Ethynyl-6,15-dioxabicyclo[10.2.1]pentadeca-1(14),12-dien-7-one (20 mg, 0.08 mmol) was dissolved in THF (2 mL). The mixture was cooled to −78 °C. A stock solution of LiHMDS (0.24 mL, 1M in THF, 0.24 mmol) was added with a microsyringe, quickly followed by neat TMSCl (31 μL, 0.24 mmol). The reaction mixture was stirred for 1.5 hr, then the ice bath was removed and stirring was continued at RT for additional 30 min. The reaction was quenched with a mixture of sat. aq. NH_4Cl (3 mL) and brine (3 mL), then diluted with ether (5 mL). The layers were separated. The organic layer was dried over Na_2SO_4 and concentrated. The crude yellow residue was purified on a pipette silica column (petrol → 3:97, ether/petrol) to afford the title compound as a clear colourless oil (26 mg, 100%).

R_f 0.42 (10:90, ether/petrol); ν_{max}/cm^{-1} 3102w (=C–H), 2180w (C≡C), 1735s (C=O); δ_H (400 MHz, $CDCl_3$) 5.87 (1H, d, *J* = 3.0 Hz, H-7/8), 5.83 (1H, d, *J* = 3.0 Hz, H-7/8), 5.59 (1H, dd, *J* = 5.0, 3.0 Hz, H-13), 2.70 (2H, m, CH_2), 2.50 (3H, m, 1½×CH_2), 2.15 (1H, m, ½×CH_2), 2.0–1.60 (8H, m, 4×CH_2), 0.18 (9H, s, H-16); HRMS (ESI^+), m/z: calcd for $C_{18}H_{26}O_3SiNa$ [$M+Na^+$] 341.1543, found 341.1558.

5-((*tert*-Butyldimethylsilyl)ethynyl)-6,15-dioxabicyclo[10.2.1]pentadeca-1(14),12-dien-7-one (348)

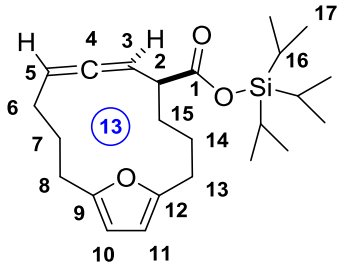


5-Ethynyl-6,15-dioxabicyclo[10.2.1]pentadeca-1(14),12-dien-7-one (15 mg, 0.06 mmol) was dissolved in THF (0.5 mL) and cooled to 0 °C. To this, TBSCl (11 mg, 0.07 mmol) was added. The solution was stirred for 5 min, followed by the addition of stock solution of LiHMDS (1 M in THF, 0.06 mL, 0.06 mmol). The reaction was stirred at 0 °C for 1 hr, then at RT for 22 hr. *Note: the use of 2 eq. of LiHMDS under the same conditions led to the complete decomposition of the reaction mixture.* The reaction mixture was partitioned between ether (12 mL) and sat. aq. NH_4Cl (3 mL). The organic layer was separated, washed with brine (5 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (5:95, ether/petrol) afforded the title material as a clear colourless oil (11 mg, 50%).

R_f 0.41 (10:90, ether/petrol); ν_{max}/cm^{-1} 3102w (=C–H), 2179m (C≡C), 1736s (C=O); δ_H (500 MHz, $CDCl_3$) 5.86 (1H, d, *J* = 3.0 Hz, H-7/8), 5.83 (1H, d, *J* = 3.0 Hz, H-7/8), 5.60 (1H, dd, *J* = 5.0, 3.0 Hz, H-13), 2.77 – 2.66 (2H, m, CH_2), 2.56 – 2.40 (3H, m, 1½×CH_2), 2.20 – 2.11 (1H, m, ½×CH_2), 2.05 – 1.84 (2H, m, CH_2), 1.81 – 1.59 (6H, m, 3×CH_2), 0.92 (9H, s, H-18), 0.10 (3H, s, H-16), 0.09 (3H, s, H-16); δ_C (126 MHz, $CDCl_3$) 172.4 (C-1), 154.2 (C-6/9), 153.6 (C-6/9), 106.4 (C-7/8), 105.9 (C-7/8), 103.0 (C-14), 88.7 (C-15), 63.4 (C-13), 34.9 (CH_2), 33.0 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 26.2

(C-18), 24.3 (CH_2), 22.2 (CH_2), 16.6 (C-17), −4.6 (C-16); HRMS (ESI^+), m/z: calcd for $C_{21}H_{32}O_3SiNa$ [$M+Na^+$] 383.2013, found 383.1995.

_O_-TIPS-15-Oxabicyclo[10.2.1]pentadeca-1(14),6,7,12-tetraene-5-carboxylic acid (349)

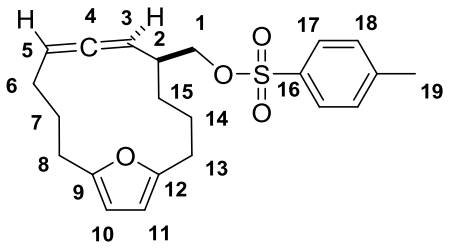


Note: the following reaction does not proceed unless highly concentrated. To a solution of the starting macrolactone (5-ethynyl-6,15-dioxabicyclo[10.2.1]pentadeca-1(14),12-dien-7-one, 80 mg, 0.32 mmol) in benzene (0.25 mL) were added TEA (90 µL, 0.65 mmol) and TIPSOTf (132 µL, 0.49 mmol). The reaction was stirred rapidly (800 rpm) at RT for 2 days. Two phases formed over the course of the reaction. The reaction contents was partitioned between ether (10 mL) and aq. NH_4Cl (4 mL sat. aq. NH_4Cl + 1 mL water). The layers were separated and the aq. layer was extracted with ether (2×4 mL). The organic layer was washed with brine (3 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (2:98 → 10:90, ether/petrol) afforded the title compound as a clear colourless oil (106 mg, 81%), along with recovered starting lactone (10 mg, 13%). *Note: the compound is moderately unstable in $CDCl_3$ (half-life ca. 4 weeks at RT). The relative configuration of the TM was inferred from the single-crystal analysis of a tosyl derivative **350**.*

R_f 0.74 (10:90, ether/petrol); ν_{max}/cm^{-1} 3101w (=C−H), 1958w (C=C=C), 1715s (C=O); δ_H (500 MHz, C_6D_6) 5.77 (2H, s, H-10,11), 5.56 (1H, tdd, *J* = 6.0, 4.5, 2.0 Hz, H-3), 4.99 (1H, dddd, *J* = 9.5, 6.5, 4.5, 3.0 Hz, H-5), 3.01 (1H, ddt, *J* = 9.0, 6.0, 3.5 Hz, H-2), 2.55 (1H, ddd, *J* = 15.0, 8.0, 3.0 Hz, ½CH_2), 2.47 – 2.33 (3H, m, 1½CH_2), 2.17 – 2.07 (1H, m, H-

15a), 2.06 – 1.90 (3H, m, H-6,15b), 1.87 – 1.77 (1H, m, ½CH_2), 1.76 – 1.66 (1H, m, ½CH_2), 1.50 – 1.38 (2H, m, ½CH_2,½CH_2), 1.31 (3H, hept, *J* = 7.5 Hz, H-16), 1.12 (18H, app.dd, *J* = 7.5, 1.0 Hz, H-17); δ_C (126 MHz, C_6D_6) 204.3 (C-4), 173.4 (C-1), 154.6 (C-9/12), 153.9 (C-9/12), 106.4 (C-10/11), 106.2 (C-10/11), 95.1 (C-5), 90.5 (C-3), 45.2 (C-2), 29.6 (C-15), 28.8 (CH_2), 27.4 (CH_2), 27.1 (CH_2), 27.02 (CH_2), 27.01 (CH_2), 18.1 (C-17), 12.3 (C-16); HRMS (ESI^+), m/z: calcd for $C_{24}H_{38}O_3SiNa$ [$M+Na^+$] 425.2482, found 425.2464.

***O*-Tosyl-5-(hydroxymethyl)-15-oxabicyclo[10.2.1]pentadeca-1(14),6,7,12-tetraene (350)**



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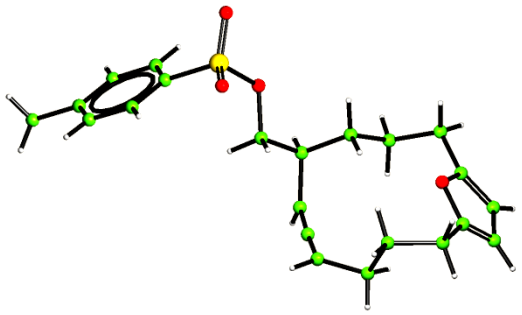
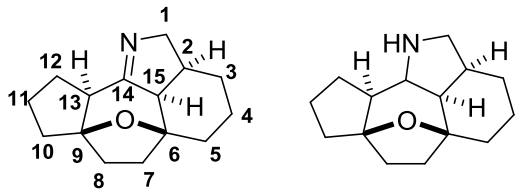


To a solution of the starting alcohol, 5-(hydroxymethyl)-15-oxabicyclo[10.2.1]pentadeca-1(14),6,7,12-tetraene (9 mg, 0.04 mmol), in DCM (1 mL), were added in sequence: TEA (10 µL, 0.07 mmol), TsCl (11 mg, 0.06 mmol), and DMAP (spatula tip). The solution was stirred at RT for 4 hr. The reaction content was partitioned between water (6 mL) and ether (2 mL). The layers were separated, and the aq. layer was extracted with ether (2×2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (10:90, ether/petrol) afforded the title material as a clear colourless oil that solidified upon standing (10 mg, 67%). Single crystals suitable for X-ray analysis were grown by slow evaporation of the MTBE/hexane solutions (1:1 v/v, 10 mg/mL).

R_f 0.56 (25:75, ether/petrol); m.p.: 68–71 °C; ν_{max}/cm^{-1} 3100w (=C–H), 3065w (=C–H), 1955w (C=C=C), 1350s, 1220s; δ_H (500 MHz, $CDCl_3$) 7.79 (d, *J* = 8.0 Hz, 2H, H-

17), 7.35 (d, *J* = 8.0 Hz, 2H, H-18), 5.86 (d, *J* = 3.0 Hz, 1H, H-10/11), 5.82 (1H, d, *J* = 3.0 Hz, H-10/11), 5.08 (1H, m, H-3), 4.94 (1H, m, H-5), 3.89 (1H, dd, *J* = 9.0, 6.0 Hz, H-1a), 3.78 (1H, dd, *J* = 9.0, 8.0 Hz, H-1b), 2.70 (1H, m, H-13a), 2.63 (2H, m, H-8), 2.46 (3H, s, H-19), 2.42 (1H, m, H-13b), 2.25 (1H, m, H-2), 2.10 (1H, m, H-6a), 1.90 (2H, m, H-6b,7a), 1.75 (2H, m, H-7b,14a), 1.50 (3H, m, H-14b,15 – under the water peak); δ_C (126 MHz, $CDCl_3$) 204.1 (C-4), 154.1 (C-9/12), 153.7 (C-9/12), 144.6 (C-16), 133.1 (C-19), 129.8 (C-18), 127.9 (C-17), 105.8 (C-10/11), 105.7 (C-10/11), 94.6 (C-5), 89.8 (C-3), 76.7 (C-4), 73.7 (C-1), 37.4 (C-2), 29.4 (C-15), 28.7 (C-7), 26.90 (C-8/13), 26.87 (C-8/13), 26.4 (C-6), 26.1 (C-14), 21.6 (C-4); HRMS (ESI^+), m/z: calcd for $C_{22}H_{26}O_4SNa$ $[M+Na^+]$ 409.1444, found 409.1433.

(±)-(*3aS,3b1R,5aS,8aS,10aR*)-tetradecahydro-8a,10a-epoxyazuleno[4,5,6-cd]isoindole (358, 359)



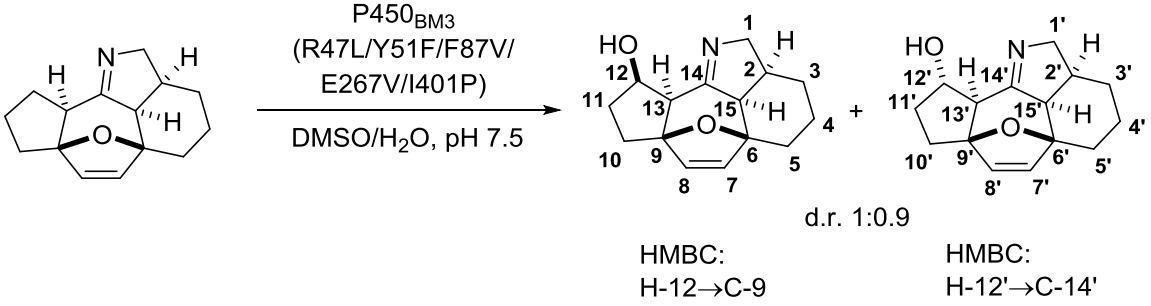
358 1.4:1 **359**

A solution of the starting alkene **332** (5 mg, 0.02 mmol) in ethanol (0.6 mL) was placed into a 1 mL flask, followed by Pd/C (10% Pd, 1 mg). The flask was equipped with a 3-way stopcock and the atmosphere was exchanged first for argon, and then for hydrogen using a balloon (1 atm). The mixture was stirred at RT for 2.5 hr (prolonged stirring did not led to appreciable conversion as judged by ^1H NMR). The atmosphere was switched back to argon. The crude reaction mixture was filtered through a short pad of Celite (5×3 mm), washing with 3×0.5 mL of ethanol. The volatiles were evaporated and the white greasy residue was analysed by NMR (3 mg, 60%).

R_f 0.30 (85:15, $CHCl_3$/2 M NH_3 in EtOH); δ_H (400 MHz, $CDCl_3$) 3.69 – 3.61 (1H, m, H-1a-imine), 3.47 (1H, dd, *J* = 14.5, 1.0 Hz, H-1b-imine), 3.33 (1.4×1H, dd, *J* = 6.0, 5.5 Hz,

H-14-amine), 2.82 (1.4×1H, dd, *J* = 11.0, 9.5 Hz, H-1a-amine), 2.72 (1.4×1H, dd, *J* = 11.0, 8.5 Hz, H-1a-amine), 2.51 – 1.20 (m, H-2-13).

Enzyme-catalysed oxidation of radianspene J Model System (360)



Substrate oxidation (Part 1) was performed by Xinkun (Tony) Ren from Dr. Luet Wong's group, University of Oxford. Purification of the products and structural assignment (Part 2) was performed by the author.

Part 1. Determination of enzyme concentrations. Four $P450_{BM3}$ variants were quantitated using ($\varepsilon_{450}-\varepsilon_{490}$) = 91 $mM^{-1}\cdot cm^{-1}$ for the ferrous CO-bound form. CO was bubbled gently though a solution of the protein to pre-saturate the buffer, after which small quantities of $Na_2S_2O_4$ were added to reduce the haem iron to the ferrous state. Additional CO was bubbled through until absorbance at 450 nm was maximised. **Assays of organic compounds using an NADPH regeneration system**. Assays using an NADPH regeneration system were performed with organic substrates using P450 enzyme (1 μM) in phosphate buffer (0.5 mL, 200 mM, pH 7.5). The substrate was added as a solution in DMSO (2 mM), followed by glucose dehydrogenase (2 units/mL), and glucose (final concentration 100 mM). $NADP^+$ was added (final concentration 0.2 mg/mL) and the reactions were shaken at 200 rpm at RT overnight (15 hr). The reaction mixture was extracted with ethyl acetate (200 μL) and analysed by gas chromatography. **Preparatory scale P450 reaction**. The prep-scale reaction was performed on the substrate (14 mg, 0.06 mmol) using the $P450_{BM3}$ R47L/Y51F/F87V/E267V/I401P mutant by stirring at RT overnight (15 hr) in

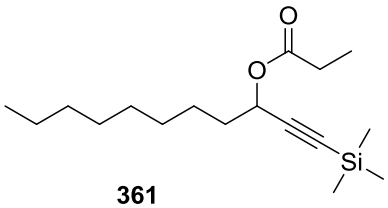
phosphate buffer (50 mL, 200 mM, pH 7.5) in a 100 mL round bottom flask using the same concentration of the components as in the 0.5 mL scale assays.

Part 2. Isolation and characterisation. The ether extract, obtained from the Wong group, was dried over Na_2SO_4, then filtered and concentrated. The resulting crude brown oil was loaded onto a pipette silica column (25:75 → 50:50, ethyl acetate/petrol → ethyl acetate → 5:95, NH_3/MeOH(2 M)/ethyl acetate). Four fractions were separated and analysed by NMR and MS. The unstable title product was obtained as a clear colourless oil as a 1:0.9 mixture of C-12 diastereomers (3 mg, 15%). *Note: the relative configuration of the two isomers was assigned based on molecular modelling (dihedral angles) and HMBC correlations.*

R_f 0.28 (5:95, NH_3/MeOH(2 M)/ethyl acetate); ν_{max}/cm^{-1} 3360br.s (OH), 1700m, 1638s; δ_H (500 MHz, $CDCl_3$) 6.41 (1H, d, *J* = 6.0 Hz, H-7/8), 6.18 (1H, d, *J* = 5.5 Hz, H-7'/8'), 6.08 (1H, d, *J* = 6.0 Hz, H-7/8), 6.02 (1H, d, *J* = 5.5 Hz, H-7'/8'), 4.40 (1H, ddd, *J* = 9.0, 7.0, 6.0 Hz, H-12'), 4.19 (1H, t, *J* = 5.5 Hz, H-12), 3.64 – 3.57 (2H, m, H-1a,1'a), 3.46 – 3.40 (2H, m, H-1b,1'b), 2.79 – 2.72 (1H, m, H-13), 2.52 (2H, app. d, *J* = 7.5 Hz, H-15,15'), 2.46 – 2.41 (1H, m, H-13'), 2.35 – 2.22 (2H, m, H-2,2'), 2.21 – 2.03 (4H, m), 1.93 – 1.47 (12H, m), 1.39 – 1.28 (4H, m, H-3,3'); δ_C (126 MHz, $CDCl_3$) 179.2 (C-14/14'), 178.8 (C-14/14'), 139.7 (C-7/8), 139.4 (C-7'/8'), 136.8 (C-7/8), 133.2 (C-7'/8'), 96.3 (C-9), 91.5 (C-9'), 84.63 (C-6/6'), 84.60 (C-6/6'), 77.6 (C-12), 75.2 (C-12'), 63.6 (C-1/1'), 63.5 (C-1/1'), 57.2 (C-13'), 49.5 (C-15/15'), 49.4 (C-15/15'), 48.8 (C-13), 36.0 (C-2/2'), 35.7 (C-2/2'), 33.6 (C-11'), 32.1 (CH_2), 31.3 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 24.9 (C-11), 22.8 (C-3/3'), 22.6 (C-3/3'), 16.8 (C-4,4'); HRMS (ESI^+), m/z: calcd for $C_{15}H_{20}NO_2$ $[M+H^+]$ 246.1489, found 246.1489.

Additional compounds

The following compounds were prepared at various stages of this work but have not been explicitly discussed in the thesis body.



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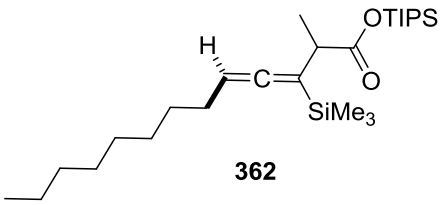

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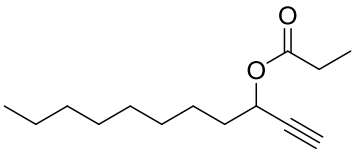

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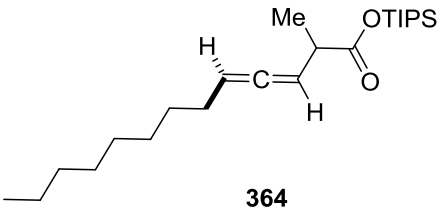

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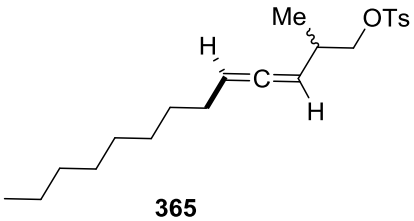

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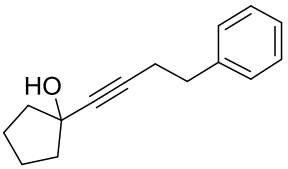

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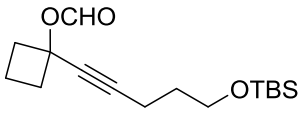

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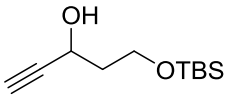

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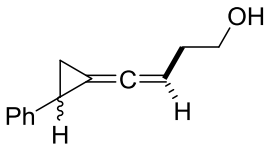

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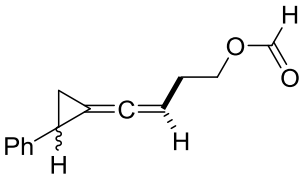

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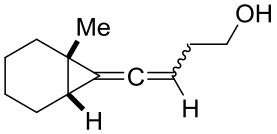

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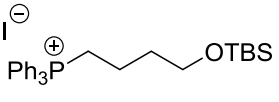

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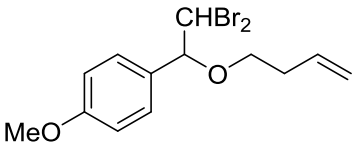

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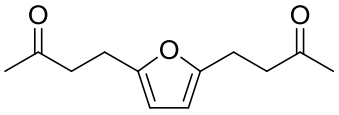

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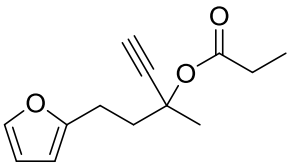

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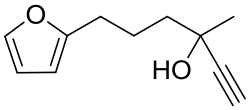

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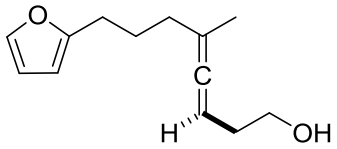

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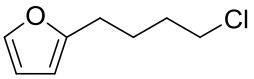

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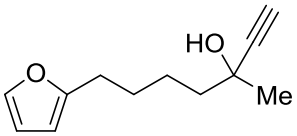

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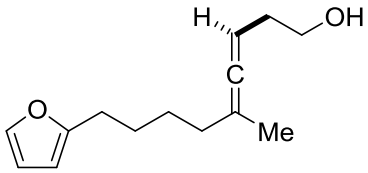

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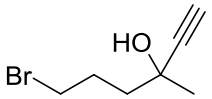

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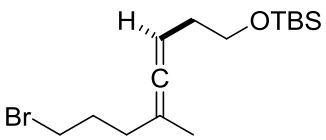

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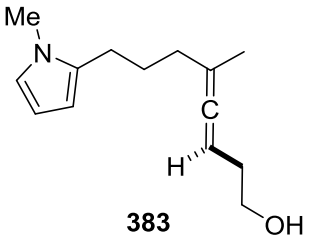

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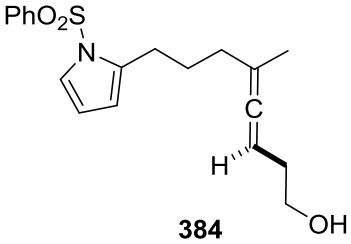

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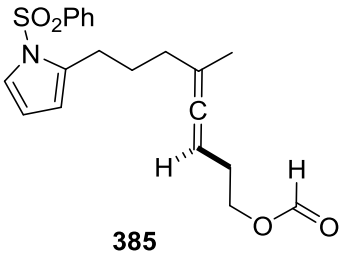

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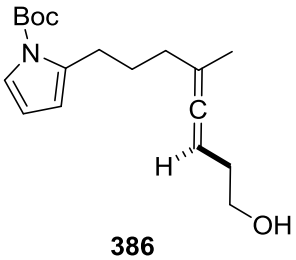

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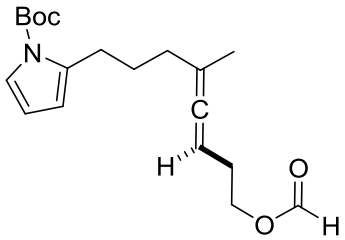

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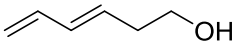
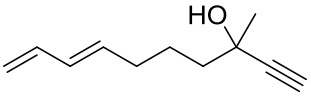


E-**388**



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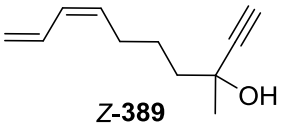

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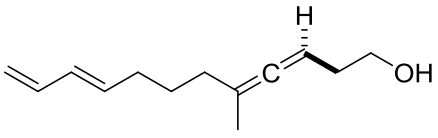

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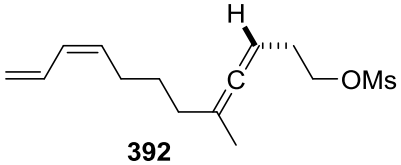

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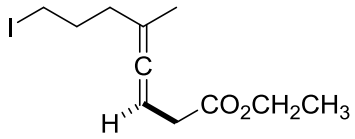

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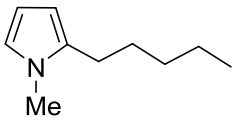

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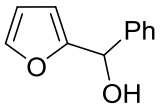

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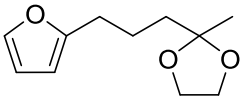

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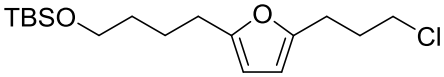

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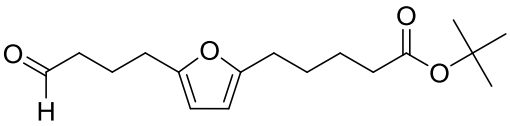

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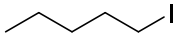

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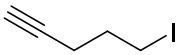

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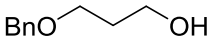

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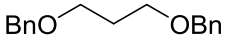

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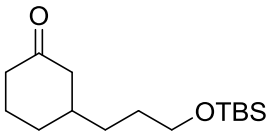

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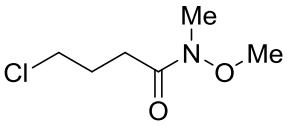

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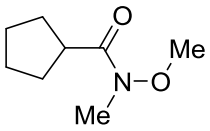

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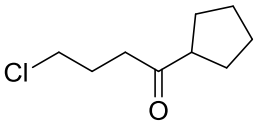

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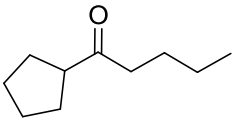

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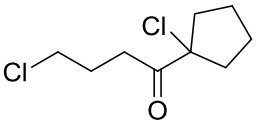

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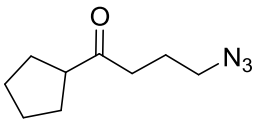

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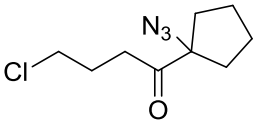

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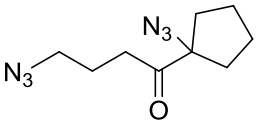
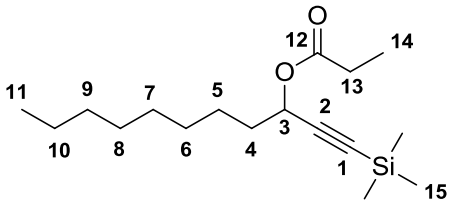


411

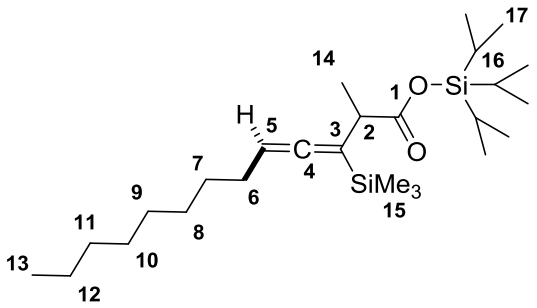
1-(trimethylsilyl)undec-1-yn-3-yl propionate (361)



THF (20 mL) was cooled to −78 °C. A stock solution of LiHMDS (3.0 mL, 1 M in THF, 3.0 mmol) was added, quickly followed by neat TMSCl (0.49 mL, 3.0 mmol). The mixture was stirred for 5 min, after which undec-1-yn-3-yl propionate (224 mg, 1.0 mmol) was added as a solution in THF (2×0.5 mL) with a syringe. The reaction was stirred at −78 °C for 1 hr, then allowed to warm to RT over 1 hr and stirred for additional 2 hr. The reaction mixture was partitioned between ether (30 mL), sat. aq. NH_4Cl (20 mL), and brine (10 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated. Flash chromatography (petrol → 1:99 → 3:97, ether/petrol) afforded the title product as a clear colourless oil (233 mg, 79%).

R_f 0.57 (10:90, ether/petrol); δ_H (200 MHz, $CDCl_3$) 5.40 (1H, t, *J* = 6.5 Hz, H-3), 2.36 (2H, q, *J* = 7.5 Hz, H-13), 1.75 (2H, m, H-4), 1.50–1.20 (15H, m, H-5,6,7,8,9,10,14), 0.90 (br. t, *J* = 7.5 Hz, 3H, H-11), 0.25 (9H, m, H-15); HRMS (ESI^+), m/z: calcd for $C_{17}H_{32}O_2SiNa$ [$M+Na^+$] 319.2064, found 319.2063.

Triisopropylsilyl 2-methyl-3-(trimethylsilyl)trideca-3,4-dienoate (362)

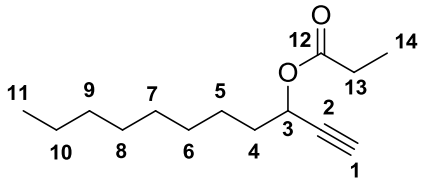


To a solution of 1-(trimethylsilyl)undec-1-yn-3-yl propionate (41 mg, 0.14 mmol) in PhH (0.7 mL) were added sequentially TEA (34 μL, 0.24 mmol) and

TIPSOTf (50 μL, 0.19 mL). The resulting mixture was stirred at 60 °C for 36 hr. The reaction contents was partitioned between ether (10 mL) and brine (5 mL). The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography (petrol → 1:99, ether/petrol) afforded the title material as a clear colourless oil (30 mg, 50%).

R_f 0.55 (5:95, ether/petrol); ν_{max}/cm^{-1} 1938m (C=C=C), 1714m (C=O); δ_H (500 MHz, $CDCl_3$) 4.98 (1H, td, *J* = 7.0, 2.0 Hz, H-5), 3.00 (1H, qd, *J* = 7.0, 2.0 Hz, H-2), 1.96 (2H, qd, *J* = 7.0, 1.0 Hz, H-6), 1.40 – 1.22 (18H, m, H-7,8,9,10,11,12,14,16), 1.08 (18H, app.dd, *J* = 7.5, 1.0 Hz, H-17), 0.88 (3H, t, *J* = 7.0 Hz, H-13), 0.11 (9H, s, H-15); δ_C (126 MHz, $CDCl_3$) 206.8 (C-4), 174.9 (C-1), 97.3 (C-3), 88.5 (C-5), 41.3 (C-2), 32.1 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 28.5 (C-6), 22.8 (CH_2), 18.2 (C-14), 17.99 (C-17), 14.3 (C-13), 12.2 (C-16), −0.9 (C-15); HRMS (ESI^+), m/z: calcd for $C_{26}H_{52}O_2Si_2Na$ $[M+Na^+]$ 475.3398, found 475.3378.

Undec-1-yn-3-yl propionate (363)

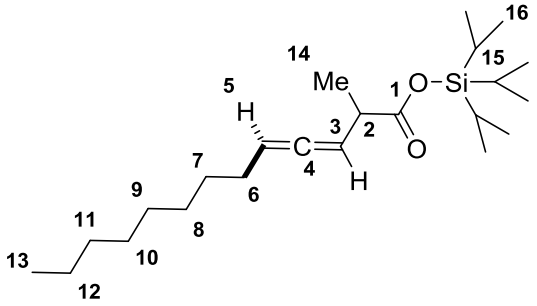


A stock solution of HC≡CMgBr (22 mL, 0.5M in THF, 11 mmol) was cooled to −78 °C. To this, a solution of nonanal (1.42 g, 10 mmol) in THF (3 mL) was added with a syringe. The mixture was stirred at −78 °C for 1 hr, then at 0 °C for 2 hr. The reaction was quenched at 0 °C with sat. aq. NH_4Cl (30 mL) and diluted with ether (30 mL). The layers were separated and the aq. layer was further extracted with ether (20 mL). The combined organic layers were dried over $MgSO_4$, filtered through a pad of silica (1 cm), and concentrated. The crude yellow oil of propargylic alcohol (1.52 g) was used immediately as received. The alcohol was redissolved in DCM (20 mL). To this were

added DMAP (110 mg, 0.9 mmol) and TEA (1.9 mL, 13.5 mmol). The solution was cooled to 0 °C. Propanoic anhydride (1.7 mL, 13.5 mmol) was added. The reaction mixture was stirred at 0 °C for 1 hr, then at RT for 45 min. The mixture was partitioned between 50 mL of DCM and 100 mL of water. The layers were separated and the aq. layer was extracted with DCM (20 mL). The combined organic layers were dried by passing through Phase Separator and concentrated. Flash chromatography (5:95, ether/petrol) afforded the title product as a clear yellowish oil (1.28 g, 57% over 2 steps).

R_f 0.47 (10:90, ether/petrol); ν_{max}/cm^{-1} 3318m (≡C–H), 2121w (C≡C), 1745s (C=O); δ_H (400 MHz, $CDCl_3$) 5.35 (1H, td, *J* = 7.0, 2.0 Hz, H-3), 2.44 (1H, d, *J* = 2.0 Hz, H-1), 2.36 (2H, q, *J* = 7.5 Hz, H-13), 1.81 – 1.72 (2H, m, H-4), 1.48 – 1.38 (2H, m, H-5), 1.36 – 1.20 (10H, m, H-6,7,8,9,10), 1.15 (3H, t, *J* = 7.5 Hz, H-14), 0.88 (3H, br.t, *J* = 7.0 Hz, H-11); δ_C (126 MHz, $CDCl_3$) 173.6 (C-12), 81.6 (C-2), 73.4 (C-1), 63.8 (C-3), 34.7 (C-4), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.7 (C-13), 25.0 (C-5), 22.8 (CH_2), 14.3 (C-11), 9.1 (C-14); HRMS (ESI^+), m/z: calcd for $C_{14}H_{24}O_2Na$ [$M+Na^+$] 247.1669, found 247.1663.

Triisopropylsilyl 2-methyltrideca-3,4-dienoate (364)

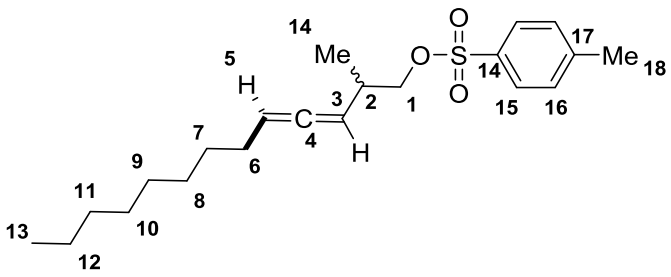


Note: this reaction does not proceed when diluted. To a solution of undec-1-yn-3-yl propionate (0.65 g, 2.77 mmol) in PhH (2.1 mL) were added sequentially TEA (0.77 mL, 5.54 mmol) and TIPSOTf (1.1 mL, 4.15 mmol). The resulting mixture was stirred at RT for 22 hr. Two phases formed over the course of the reaction. The bottom

layer (ca. 0.8 mL) was separated and extracted twice with benzene. The benzene extracts were combined with the top reaction layer and concentrated. Flash chromatography (petrol → 2:98, ether/petrol) afforded the title product as a clear colourless oil (0.54 g, 50%).

R_f 0.64 (10:90, ether/petrol); ν_{max}/cm^{-1} 1965w (C=C=C), 1719s (C=O); δ_H (500 MHz, $CDCl_3$) 5.32 (1H, tt, *J* = 6.5, 3.0 Hz, H-3), 5.23 (1H, qd, *J* = 6.5, 3.0 Hz, H-5), 3.10 (1H, qdd, *J* = 7.0, 6.5, 3.0 Hz, H-2), 1.99 (2H, qd, *J* = 7.5, 6.5, 3.0 Hz, H-6), 1.43 – 1.22 (18H, m, H-7,8,9,10,11,12,14,15), 1.08 (18H, d, *J* = 7.5 Hz, H-16), 0.88 (3H, t, *J* = 7.0 Hz, H-13); δ_C (126 MHz, $CDCl_3$) 203.7 (C-4), 174.7 (C-1), 93.7 (C-5), 91.8 (C-3), 41.1 (C-2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 22.8 (CH_2), 17.9 (C-16), 16.7 (C-14), 14.3 (C-13), 12.1 (C-15); HRMS (ESI^+), m/z: calcd for $C_{23}H_{44}O_2SiNa$ [$M+Na^+$] 403.3003, found 403.2989.

_O_-Tosyl 2-methyltrideca-3,4-dien-1-ol (365)

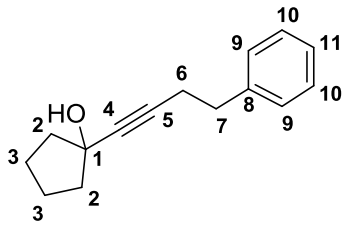


To a solution of triisopropylsilyl 2-methyltrideca-3,4-dienoate (30 mg, 0.08 mmol) in dry ether (1 mL) was added $LiAlH_4$ (4 mg, 0.08 mmol). The mixture was stirred at RT for 20 min. The reaction was carefully quenched by the dropwise addition of sat. aq. Na_2SO_4 (*caution: gas liberation)*, followed by the addition of anhydrous Na_2SO_4. The solids were filtered off, and the clear solution of allene alcohol was concentrated in vacuo. The alcohol was redissolved in pyridine (1 mL) and cooled to 0 °C. To this, TsCl (13 mg, 0.16 mmol) was added. The mixture was allowed to warm to RT and stirred overnight (15 hr). The reaction content was poured into the mixture of

water (3 mL), aq. HCl (1 M, 3 mL) and ether (5 mL). The layers were separated. The organic layer was washed sequentially with sat. aq. $NaHCO_3$ (3 mL) and brine (3 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (10:90, ether/petrol) afforded the title material as a clear colourless oil (15 mg, 53% over 2 steps).

R_f 0.44 (25:75, ether/petrol); ν_{max}/cm^{-1} 1963w (C=C=C), 1363s, 1189s, 1177s; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz, H-15), 7.27 (2H, d, *J* = 8.0 Hz, H-16), 5.08 (1H, qd, *J* = 6.5, 3.0 Hz, H-3/5), 4.94 – 4.88 (1H, m, H-3/5), 3.87 (1H, dd, *J* = 9.5, 6.0 Hz, H-1a), 3.75 (1H, dd, *J* = 9.5, 7.5 Hz, H-1b), 2.46 – 2.39 (1H, m, H-2), 2.38 (3H, s, H-18), 1.91 – 1.82 (2H, m, H-6), 1.30 – 1.11 (12H, m, H-7,8,9,10,11,12), 0.93 (3H, d, *J* = 7.0 Hz, H-14), 0.81 (3H, t, *J* = 7.0, 7.0 Hz, H-13); δ_C (101 MHz, $CDCl_3$) 203.5 (C-4), 144.6 (C-14), 133.2 (C-17), 129.8 (C-16), 127.9 (C-15), 93.3 (C-3/5), 91.8 (C-3/5), 74.4 (C-1), 32.9 (C-2), 31.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.13 (CH_2), 29.10 (CH_2), 28.7 (CH_2), 22.7 (CH_2), 21.8 (C-18), 16.6 (C-14), 14.1 (C-13); HRMS (ESI^+), m/z: calcd for $C_{21}H_{32}O_3SNa$ [$M+Na^+$] 387.1972, found 387.1964.

1-(4-Phenylbut-1-yn-1-yl)cyclopentanol (366)

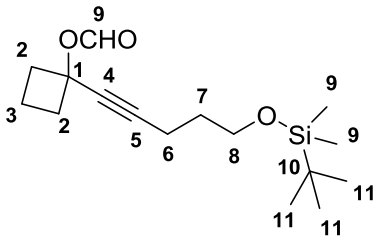


To a solution of 4-phenylbut-1-yne (100 mg, 0.77 mmol) in THF (1 mL) was added stock solution of *i*-PrMgCl (2 M in Et_2O, 0.39 mL, 0.77 mmol) over 2 min at 0 °C. The reaction mixture was allowed to warm to RT over 90 min. Cyclopropanone (59 mg, 0.70 mmol) was dissolved in THF (0.5 mL) and added at −10 °C. The resulting solution was allowed to warm to RT and stirred overnight (13 hr). The reaction was quenched with wet Et_2O (2 mL) and water (2 mL). The aq. layer was neutralized with aq. HCl (1 M) and extracted with Et_2O (2×3 mL). The combined organic layers were dried over

$MgSO_4$ and concentrated. Flash chromatography (30:70, ether/petrol) yielded the title compound as a colourless oil (81 mg, 54%).

R_f 0.20 (25:75, ether/petrol); δ_H (400 MHz, $CDCl_3$) 7.37 – 7.15 (5H, m, H-9,10,11), 2.83 (2H, t, *J* = 7.5 Hz, H-7), 2.50 (2H, t, *J* = 7.5 Hz, H-6), 1.96 – 1.55 (m, 8H, H-2,3); δ_C (101 MHz, $CDCl_3$) 139.0 (C-8), 128.5 (C-10), 128.3 (C-9), 126.3 (C-11), 84.8 (C-5), 82.8 (C-4), 74.6 (C-1), 42.5 (C-2), 35.1 (C-7), 23.4 (C-3), 21.0 (C-6); HRMS (ESI^+), m/z: calcd for $C_{15}H_{18}NaO$ [$M+Na^+$] 237.1250, found 237.1250.

1-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclobutyl formate (367)

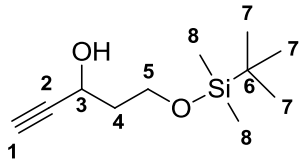


Prepared using a modified procedure from Sawamura. [345] Pyridone-2 (53 mg, 0.56 mmol) and DCC (138 mg, 0.67 mmol) were dissolved in DCM (1.5 mL) and cooled to 0 °C. Next, formic acid (28 mg, 0.62 mmol) was added and the mixture was stirred at 0 °C for 1.5 hr. A solution of 1-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)cyclobutanol (0.150 g, 0.56 mmol) in DCM (0.8 mL) was added at 0 °C. The reaction was allowed to warm to RT and stirred overnight (15 hr). The mixture was diluted with DCM (3 mL) and filtered through Celite, thoroughly washing the solids with DCM (ca. 4 mL). Volatiles were evaporated. Flash chromatography (10:90 → 25:75, ether/petrol) afforded the product as a colourless oil (67 mg, 40%; 83% b.r.s.m.)

R_f 0.43 (10:90, ether/petrol); ν_{max}/cm^{-1} 2240w (C≡C), 1734s (C=O), 1157s; δ_H (400 MHz, $CDCl_3$) 8.02 (1H, s, H-9), 3.69 (2H, t, *J* = 6.0 Hz, H-8), 2.61 – 2.51 (2H, m, H-2a), 2.50 – 2.40 (2H, m, H-2b), 2.34 (2H, t, *J* = 7.0 Hz, H-6), 2.01 – 1.88 (2H, m, H-3), 1.77 – 1.67 (2H, m, H-7), 0.90 (9H, s, H-11), 0.07 (6H, s, H-9); δ_C (101 MHz, $CDCl_3$) 159.6 (C-

9), 86.0 (C-4,5), 72.9 (C-1), 61.5 (C-8), 37.0 (C-2), 31.5 (C-7), 25.9 (C-11), 17.7 (C-10), 15.1 (C-6), 14.5 (C-3), −5.4 (C-9); HRMS (TOF ESI$^+$), m/z: calcd for $C_{16}H_{28}NaO_3Si$ [M+Na$^+$] 319.1700, found 319.1694.

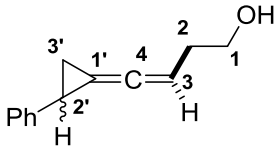
5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-3-ol (368)[346,347]



3-((*tert*-Butyldimethylsilyl)oxy)propanal (0.400 g, 2.13 mmol) was dissolved in THF (1+1 mL) and added to a stock solution of HC≡CMgBr (0.5 M, 4.25 mL, 2.15 mmol) at 0 °C. The mixture was stirred at this temperature for 2 hr. The reaction was diluted with ether (20 mL) and quenched with sat. aq. NH_4Cl (4 mL) and water (1 mL), then neutralized to pH 7 with aq. HCl (1 M, 1 drop). The organic layer was washed with water (2×5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated. The product, a colourless oil, was used directly in the next step (0.42 g, 92%). Analytically pure samples could be obtained, with a significant loss of material, by flash chromatography on silica (25:75, ether/petrol).

R_f 0.34 (25:75, ether/petrol); ν_{max}/cm^{-1} 3400br.s (OH), 3312s (≡C−H); δ_H (400 MHz, $CDCl_3$) 4.63 (1H, ddd, *J* = 6.5, 4.0, 2.0 Hz, H-3), 4.07 (1H, ddd, *J* = 10.5, 8.0, 3.5 Hz, H-5a), 3.85 (1H, ddd, *J* = 10.5, 6.0, 4.0 Hz, H-5b), 3.55 (1H, br.s, OH), 2.47 (1H, d, *J* = 2.0 Hz, H-1), 2.09 – 1.96 (1H, m, H-4a), 1.94 – 1.82 (1H, m, H-4b), 0.91 (9H, s, H-7), 0.10 (6H, s, H-8); δ_C (101 MHz, $CDCl_3$) 84.4 (C-2), 72.8 (C-1), 61.8 (C-3), 61.1 (C-5), 38.3 (C-4), 25.8 (C-7), 18.1 (C-6), −5.6 (C-8).

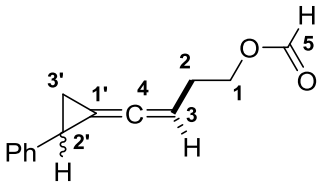
4-(2-Phenylcyclopropylidene)but-3-en-1-ol (369)



Pyridine (2 mL) was dissolved in THF (5 mL) in a plastic vial. To this, HF·py was added (70% of HF, 0.36 mL, 14 mmol) with a syringe. (3*RS*)-*O*-TBS-4-(2*RS*-2-Phenylcyclopropylidene)but-3-en-1-ol (335 mg, 1.11 mmol) was dissolved in 3 mL of THF and added to this mixture. The reaction was stirred at RT for 19 hr. The reaction content was transferred into sat. aq. $NaHCO_3$ (30 mL). The reaction vessel was thoroughly washed with ether (10 ml) and the washes were mixed with the aq. layer. The latter was extracted with ether (2×10 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (15 mL) to remove pyridine, then with brine (10 mL), and finally dried over $MgSO_4$. Evaporation of the volatiles afforded the target material as a viscous yellow oil that was used as received (196 mg, 95%).

R_f 0.38 (50:50, ether/petrol); ν_{max}/cm^{-1} 3352br.s (OH), 3059m (=C−H), 3027m (=C−H), 2018s (C=C=C); δ_H (500 MHz, $CDCl_3$)* 7.33 – 7.25 (2H, m, H-Ph), 7.24 – 7.16 (3H, m, H-Ph), 5.42 – 5.35 (1H, m, H-3), 3.74 (2H, dt, *J* = 11.0, 6.0 Hz, H-1), 3.02 – 2.94 (1H, m, H-2'), 2.39 (2H, qd, *J* = 6.5, 1.5 Hz, H-2), 2.14 – 2.06 (1H, m, H-3'a), 1.73 – 1.63 (1H, m, H-3'b); δ_C (126 MHz, $CDCl_3$)* 190.3 (C-4), 190.2 (C-4), 140.7 (C-Ph), 140.6 (C-Ph), 128.5 (C-Ph), 128.4 (C-Ph), 126.5 (C-Ph), 126.3 (C-Ph), 90.86 (C-3), 90.85 (C-3), 83.5 (C-1'), 83.1 (C-1'), 62.1 (C-1), 62.0 (C-1), 32.78 (C-2), 32.75 (C-2), 24.7 (C-2'), 24.5 (C-2'), 17.76 (C-3'), 17.74 (C-3'); HRMS (ESI^+), m/z: calcd for $C_{13}H_{14}NaO$ $[M+Na^+]$ 209.0937, found 209.0941.

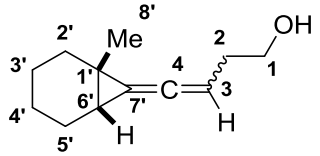
4-(2-Phenylcyclopropylidene)but-3-en-1-yl formate (370)



Isolated as a side product in the synthesis of azide **208** from alcohol **369** on a 20 mg scale (1 mg, 5%).

R_f 0.33 (10:90, ether/petrol); ν_{max}/cm^{-1} 3059w (=C–H), 3028w (=C–H), 2019m (C=C=C), 1724s (C=O); δ_H (500 MHz, $CDCl_3$)* 8.08 (½×1H, s, H-5), 7.96 (½×1H, 1H, s, H-5), 7.34 – 7.25 (2H, m, H-Ph), 7.24 – 7.16 (3H, m, H-Ph), 5.41 – 5.33 (1H, m, H-3), 4.32 – 4.21 (2H, m, H-1), 3.02 – 2.94 (1H, m, H-2'), 2.52 – 2.44 (2H, m, H-2), 2.13 – 2.06 (1H, m, H-3'a), 1.72 – 1.63 (1H, m, H-3'b); δ_C (126 MHz, $CDCl_3$)* 190.27 (C-4), 190.25 (C-4), 161.01 (C-5), 160.98 (C-5), 140.60 (C-Ph), 140.49 (C-Ph), 128.43 (C-Ph), 128.39 (C-Ph), 126.48 (C-Ph), 126.39 (C-Ph), 126.31 (C-Ph), 89.99 (C-3), 89.94 (C-3), 83.81 (C-1'), 83.52 (C-1'), 63.14 (C-1), 63.08 (C-1), 28.71 (C-2), 28.59 (C-2), 24.71 (C-2'), 24.58 (C-2'), 17.78 (C-3'), 17.72 (C-3'); HRMS (TOF ESI^+), m/z: calcd for $C_{14}H_{14}NaO_2$ $[M+Na^+]$ 237.0886, found 237.0896.

4-(1-Methylbicyclo[4.1.0]heptan-7-ylidene)but-3-en-1-ol (371)

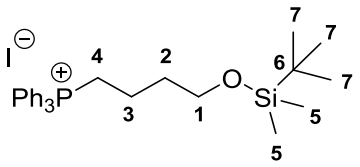


The title compound could be isolated as in intermediate in the synthesis of 7-(4-azidobut-1-en-1-ylidene)-1-methylbicyclo[4.1.0]heptane.

* Note: two diastereomers were detectable in the spectrum. We did not attempt to assign the doubled signals to any particular isomer.

R_f 0.35 (50:50, ether/petrol); ν_{max}/cm^{-1} 3333br.s (OH), 2002s (C=C=C); δ_H (500 MHz, $CDCl_3$)* δ 5.22 – 5.12 (1H, m, H-3), 3.80 – 3.66 (2H, m, H-1), 2.41 – 2.29 (2H, m, H-2), 2.03 – 1.85 (2H, m, H-5'a,2'a), 1.83 – 1.68 (2H, m, H-6',5'b), 1.64 (1H, t, *J* = 6.0 Hz, OH), 1.59 – 1.52 (1H, m, H-2'b), 1.47 – 1.17 (7H, m, H-3',4',8'); δ_C (126 MHz, $CDCl_3$)* 187.53 (C-4), 187.50 (C-4), 91.77 (C-7'), 91.60 (C-7'), 88.52 (C-3), 88.46 (C-3), 62.10 (C-1), 62.04 (C-1), 32.88 (C-2), 32.75 (C-2), 30.29 (C-2'), 30.05 (C-2'), 27.16 (C-6'), 27.00 (C-6'), 26.07 (C-1'), 26.01 (C-1'), 25.84 (C-8'), 23.56 (C-5'), 23.28 (C-5'), 21.43 (C-3'/4'), 21.41 (C-3'/4'), 21.33 (C-3'/4'); HRMS (ESI^+), m/z: calcd for $C_{12}H_{18}NaO$ $[M+Na^+]$ 201.1250, found 201.1255.

4-(*tert*-Butyldimethylsilyloxy)butyltriphenylphosphonium iodide (372)[348]

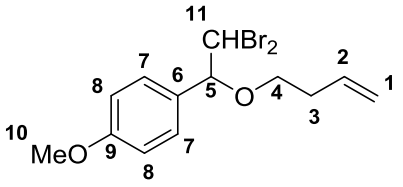


PPh_3 (1.10 g, 4.2 mmol) and 4-iodo-1-(*tert*-butyldimethylsilyloxy)butane (0.942 g, 3.0 mmol) were dissolved in THF (12 mL) and heated at reflux for 18 hr. The mixture was cooled to RT, poured into 50 mL of petrol, and stirred over 10 min. The off-white precipitate was filtered off, washed with petrol, and dried at hi-vac (0.70 g, 40%).

ν_{max}/cm^{-1} 3053w (=C–H), 2952m, 2855m, 1435s, 1253m, 1110s, 834s, 689s; δ_H (400 MHz, $CDCl_3$) 7.90 – 7.78 (9H, m, H-Ph), 7.75 – 7.68 (6H, m, H-Ph), 3.85 – 3.73 (2H, m, H-4), 3.66 (2H, t, *J* = 5.5 Hz, H-1), 1.99 – 1.85 (2H, m, H-3), 1.85 – 1.70 (2H, m, H-2), 0.78 (9H, s, H-7), −0.05 (6H, s, H-5); δ_C (101 MHz, $CDCl_3$) 135.1 (C-Ph), 133.8 (C-Ph), 133.7 (C-Ph), 130.6 (C-Ph), 130.5 (C-Ph), 60.1 (C-1), 31.8 (CH_2), 25.9 (C-7), 19.8 (CH_2), 19.2 (C-6), −5.5 (C-5).

* Note: two diastereomers were detectable in the spectrum. We did not attempt to assign the doubled signals to any particular isomer.

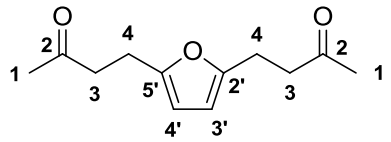
1-(2,2-Dibromo-1-(but-3-en-1-yloxy)ethyl)-4-methoxybenzene (373)



Isolated as a side product in the synthesis of 1-((but-3-en-1-yloxy)methyl)-4-methoxybenzene on a 3.0 mmol scale. Flash chromatography (10:90, ether/petrol) afforded the title compound as a clear colourless oil (35 mg, 10%).

R_f 0.30 (10:90, ether/petrol); ν_{max}/cm^{-1} 3076w, 1610m, 1511s, 1250s; δ_H (500 MHz, $CDCl_3$) 7.35 – 7.30 (2H, m, H-7), 6.93 – 6.89 (2H, m, H-8), 5.84 (1H, m, H-2), 5.65 (1H, d, *J* = 5.5 Hz, H-11), 5.09 (1H, m, H-1a), 5.06 – 5.02 (1H, m, H-1b), 4.57 (1H, d, *J* = 5.5 Hz, H-5), 3.83 (3H, s, H-10), 3.51 (2H, td, *J* = 6.5, 1.0 Hz, H-4), 2.38 (2H, m, H-3); δ_C (126 MHz, $CDCl_3$) 160.0(C-9), 134.8 (C-2), 129.2 (C-7), 129.0 (C-6), 116.6 (C-1), 113.7 (C-8), 85.6 (C-5), 69.6 (C-4), 55.2 (C-10), 48.5 (C-11), 34.0 (C-3); HRMS (ESI^+), m/z: calcd for $C_{13}H_{12}Br_2O_2$ [M^+] 384.9409, found 384.9397.

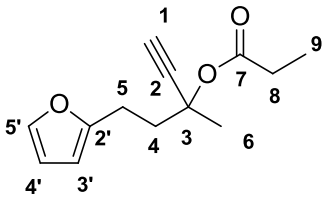
4,4'-(Furan-2,5-diyl)*bis*(butan-2-one) (374)[349]



Formed as a dialkylated side product in the synthesis of ketone **248**. Flash chromatography (15:85 → 25:75, ether/petrol → ether) afforded the title compound as a clear colourless oil that solidifies in freezer (0.95 g, 23%).

R_f 0.09 (25:75, ether/petrol); ν_{max}/cm^{-1} 3106w (=C–H), 1714s (C=O); δ_H (400 MHz, $CDCl_3$) 5.85 (2H, s, H-4',3'), 2.85 (4H, tm, *J* = 7.5 Hz, H-4), 2.75 (4H, tm, *J* = 7.5 Hz, H-3), 2.16 (6H, s, H-2); δ_C (101 MHz, $CDCl_3$) 207.4 (C-2), 152.9 (C-2',5'), 105.7 (C-3',4'), 41.8 (C-3), 29.9 (C-1), 22.2 (C-4); MS (ESI^+), m/z: 231.1 ($M+Na^+$).

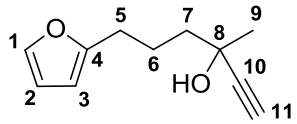
5-(furan-2-yl)-3-methylpent-1-yn-3-yl propionate (375)



To a solution of 5-(furan-2-yl)-3-methylpent-1-yn-3-ol (100 mg, 2.0 mmol) in DCM (3 mL) were added in sequence: TEA (0.13 mL, 0.91 mmol), propionic anhydride (120 μL, 0.91 mmol), and DMAP (7 mg, 0.06 mmol). The solution was stirred at RT for 25 hr. The crude reaction mixture was partitioned between DCM (20 mL) and water (15 mL). The aq. layer was extracted with DCM (10 mL). The combined organic layers were dried by passing through a Phase Separator and concentrated. Flash chromatography (1:9, ether/petrol) afforded the title compound as a clear colourless oil (110 mg, 84%).

R_f 0.44 (25:75, ether/petrol); ν_{max}/cm^{-1} 3291s (≡C–H), 3151w (=C–H), 3118w (=C–H), 2119w (C≡C), 1746s (C=O); δ_H (500 MHz, $CDCl_3$) 7.31 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 6.02 – 6.00 (1H, m, H-3'), 2.90 – 2.82 (2H, m, H-5), 2.59 (1H, s, H-1), 2.34 – 2.25 (3H, m, H-8,4a), 2.18 – 2.10 (1H, m, H-4b), 1.73 (3H, s, H-6), 1.13 (3H, t, *J* = 7.5 Hz, H-9); δ_C (126 MHz, $CDCl_3$) 172.9 (C-7), 155.1 (C-2'), 141.1 (C-5'), 110.3 (C-4'), 105.1 (C-3'), 83.4 (C-2), 74.0 (C-3), 73.8 (C-1), 39.9 (C-4), 28.4 (C-8), 26.6 (C-6), 23.2 (C-5), 9.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{13}H_{16}O_3Na$ $[M+Na^+]$ 243.0992, found 243.0997.

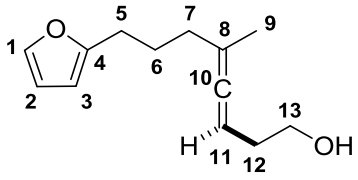
6-(Furan-2-yl)-3-methylhex-1-yn-3-ol (376)



Prepared according to General method A from 5-(furan-2-yl)pentan-2-one (0.800 g, 5.25 mmol) and HC≡CMgBr (0.5 M in THF, 11.6 mL). Flash chromatography (1:5, ether/petrol) afforded the target material as a pale yellow oil (0.823 g, 88%).

R_f 0.33 (25:75, ether/petrol); ν_{max}/cm^{-1} 3390br.s (OH), 3293m (≡C–H), 2111w (C≡C); δ_H (400 MHz, $CDCl_3$) 7.31 – 7.29 (1H, m, H-1), 6.29 – 6.26 (1H, m, H-2), 6.03 – 6.00 (1H, m, H-3), 2.68 (2H , t, *J* = 7.5 Hz, H-5), 2.44 (1H, s, H-11), 2.12 (1H, s, OH), 1.94 – 1.81 (2H, m, H-6), 1.76 – 1.67 (2H, m, H-7), 1.50 (3H, s, H-9); δ_C (100 MHz, $CDCl_3$) 155.8 (C-4), 140.8 (C-1), 110.1 (C-2), 104.9 (C-3), 87.5 (C-10), 71.5 (C-8), 67.9 (C-11), 42.8(C-7), 29.8 (C-5), 27.9 (C-9), 23.2 (C-6); HRMS (TOF FI^+), m/z: calcd for $C_{11}H_{14}O_2$ $[M^+]$ 178.0994, found 178.0995.

8-(Furan-2-yl)-5-methylocta-3,4-dien-1-ol (377)

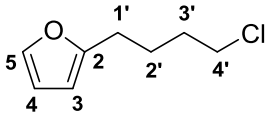


Prepared by General method C from ethyl 8-(furan-2-yl)-5-methylocta-3,4-dienoate (0.580 g, 2.33 mmol) and $LiAlH_4$ (106 mg, 2.80 mmol). The target material, a colourless oil, was used as received (468 mg, 98%).

R_f 0.43 (1:1, ether/petrol); ν_{max}/cm^{-1} 3337br.s (OH), 3115w, 1964w (C=C=C); δ_H (500 MHz, C_6D_6) 7.13 (1H, dd, *J* = 2.0, 1.0 Hz, H-1), 6.12 (1H, dd, *J* = 3.0, 2.0 Hz, H-2), 5.90 (1H, dd, *J* = 3.0, 1.0 Hz, H-3), 4.98 (1H, app. qd, *J* = 6.5, 3.0 Hz, H-11), 3.44 (2H, t, *J* = 6.5 Hz, H-13), 2.54 (2H, t, *J* = 7.5 Hz, H-5), 2.06 (2H, app. q, *J* = 6.5 Hz, H-12), 1.85 – 1.78 (2H, m, H-7), 1.78 – 1.70 (2H, m, H-6), 1.55 (3H, d, *J* = 3.0 Hz, H-9), 1.00 (1H, br.s, OH);

δ_C (126 MHz, C_6D_6) 202.5 (C-10), 156.4 (C-4), 141.1 (C-1), 110.5 (C-2), 105.3 (C-3), 99.3 (C-8), 87.6 (C-11), 62.3 (C-13), 33.4 (C-12), 33.3 (C-7), 27.8 (C-5), 26.4 (C-6), 19.4 (C-9); HRMS (TOF FI$^+$), m/z: calcd for $C_{13}H_{18}O_2$ [M^+] 206.1307, found 206.1308.

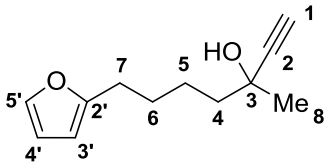
2-(4-Chlorobutyl)furan (378)[224,225]



Furan (1.21 g, 17.8 mmol) was dissolved in freshly distilled THF and cooled to −78 °C. BuLi (5.6 mL, 1.6 M, 8.9 mmol) was added over 5 min. The resulting mixture was stirred at −78 °C for 10 min, then at 0 °C for 2.5 hr. The solution was cooled to −78 °C and neat 1-chloro-4-iodobutane (97%, 2.0 g, 8.88 mmol) was added with a syringe. The mixture was stirred at −78 °C for 10 min, then allowed to warm up to RT slowly and stirred for 3 hr. The reaction was diluted with ether (50 mL) and quenched with a mixture of sat. aq. NH_4Cl (40 mL), water (2 mL), and aq. HCl (1 M, 2 mL). The organic layer was separated and washed sequentially with sat. aq. $Na_2S_2O_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated. The product was obtained as a brown oil and used without further purification (1.41 g, 100%).

R_f 0.72 (10:90, ether/petrol); ν_{max}/cm^{-1} 3100 w (=C−H); δ_H (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* = 2.5 Hz, H-5), 6.29 (1H, t, *J* = 2.5 Hz, H-4), 6.01 (1H, d, *J* = 2.5 Hz, H-3), 3.56 (2H, t, *J* = 6.0 Hz, H-4'), 2.67 (2H, t, *J* = 7.0 Hz, H-1'), 1.84 – 1.79 (4H, m, H-2',3'); δ_C (101 MHz, $CDCl_3$) 155.5 (C-2), 140.9 (C-5), 110.1 (C-4), 105.0 (C-3), 44.7 (C-4'), 31.9 (C-3'), 27.2 (C-1'), 25.3 (C-2').

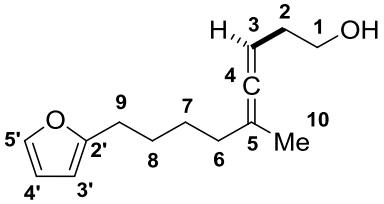
7-(Furan-2-yl)-3-methylhept-1-yn-3-ol (379)[350]



Prepared by General method A by stirring 6-(furan-2-yl)hexan-2-one (1.06 g, 6.39 mmol) and a stock solution of HC≡CMgBr (0.5 M, 14 mL, 7.0 mmol) at reflux for 3 hr. Flash chromatography (25:75, ether/petrol) afforded the target material as a yellow oil (1.12 g, 91%).

R_f 0.22 (25:75, ether/petrol); ν_{max}/cm^{-1} 3675m (OH), 3532br.s (OH), 3386s (≡C–H), 3150w (=C–H), 2146w (C≡C); δ_H (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, H-5'), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 5.99 (1H, dtd, *J* = 3.0, 1.5, 1.0 Hz, H-3'), 2.67 (2H, t, *J* = 7.5 Hz, H-7), 2.44 (1H, s, H-1), 1.98 (1H, s, OH), 1.76 – 1.65 (4H, m, H-6,4), 1.63 – 1.52 (2H, m, H-5), 1.50 (3H, s, H-8); δ_C (101 MHz, $CDCl_3$) 156.1 (C-2'), 140.7 (C-5'), 110.1 (C-4'), 104.7 (C-3'), 87.6 (C-2), 71.4 (C-1), 68.0 (C-3), 43.1 (C-4), 29.7 (C-8), 28.1 (C-6/7), 27.9 (C-6/7), 24.1 (C-5).

9-(Furan-2-yl)-5-methylnona-3,4-dien-1-ol (380)

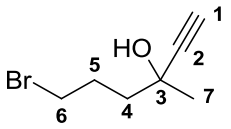


(Ethyl 9-(furan-2-yl)-5-methylnona-3,4-dienoate (850 mg, 3.24 mmol) was dissolved in dry ether (30 mL) and cooled to 0 °C. $LiAlH_4$ (0.123 g, 3.24 mmol) was added carefully and the mixture was stirred for 35 min. The reaction was quenched at 10 °C by careful addition of sat. aq. Na_2SO_4 *(caution: gas liberation)* until a white precipitate formed. The solution was dried with anhydrous Na_2SO_4. The solids were filtered off and washed with ether. Concentration of the organic layer afforded the

target material as a colourless oil that was used without further purification (0.62 g, 87%).

R_f 0.13 (25:75, ether/petrol); ν_{max}/cm^{-1} 3336br.s (OH), 3315w (=C–H), 1965w (C=C=C); δ_H (400 MHz, C_6D_6) 7.24 (1H, dd, *J* = 1.8, 1.0 Hz, H-5'), 6.24 (1H, dd, *J* = 3.0, 2.0 Hz, H-4'), 6.00 (1H, dp, *J* = 3.0, 1.0 Hz, H-3'), 5.13 – 5.05 (1H, m, H-3), 3.57 (2H, br.td, *J* = 6.5, 6.0 Hz, H-1), 2.61 (2H, t, *J* = 7.5 Hz, H-9), 2.18 (2H, q, *J* = 6.5 Hz, H-2), 1.90 (2H, td, *J* = 7.5, 3.0 Hz, H-6), 1.68 (2H, quint, *J* = 7.5 Hz, H-8), 1.67 (3H, dd, *J* = 3.0, 0.5 Hz, H-10), 1.49 (2H, quint, *J* = 7.5 Hz, H-7), 1.13 (1H, t, *J* = 5.5 Hz, OH); δ_C (101 MHz, C_6D_6) 202.5 (C-4), 156.5 (C-2'), 140.9 (C-5'), 110.4 (C-4'), 105.1 (C-3'), 99.5 (C-5), 87.2 (C-3), 62.2 (C-1), 33.8 (C-2/6), 33.2 (C-2/6), 28.1 (C-7/8/9), 27.9 (C-7/8/9), 27.2 (C-7/8/9), 19.2 (C-10); HRMS (TOF FI^+), m/z: calcd for $C_{14}H_{20}O_2$ [M^+] 220.1463, found 220.1470.

6-Bromo-3-methylhex-1-yn-3-ol (381)[351]

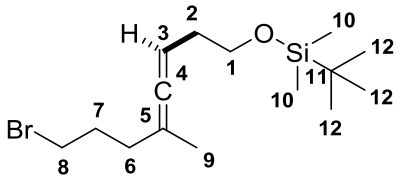


A 100 mL flask was charged with a stock solution of HC≡CMgBr (0.5 M in THF, 35.2 mL, 16.2 mmol) and cooled to 0 °C. A solution of 5-bromopentan-2-one (1.34 g, 8.13 mmol) in degassed THF (4 mL) was added and the resulting mixture was stirred at 0 °C for 4 hr. The reaction mixture was diluted with ether (40 mL), quenched with sat. aq. NH_4Cl (15 mL) and water (3 mL), then neutralized with aq. HCl (1 M, ca. 5 mL). The layers ware separated and the aq. layer was extracted with ether (2×20 mL). The combined ether extracts were washed with brine (15 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (1:4, ether/petrol) afforded the target material as a reddish oil that turned brown over time (1.44 g, 93%).

R_f 0.35 (25:75, ether/petrol); ν_{max}/cm^{-1} 3377br.s (OH), 3291s (≡C–H), 2109w (C≡C); δ_H (400 MHz, $CDCl_3$) 3.51 – 3.44 (2H, m, H-6), 2.47 (1H, s, H-1), 2.19 – 2.04 (2H,

m, H-5), 1.81 (2H, t, *J* = 8.0 Hz, H-4), 1.53 (3H, s, H-7); δ_C (101 MHz, $CDCl_3$) 87.0 (C-2), 71.9 (C-1), 67.5 (C-3), 41.8 (C-4), 33.7 (C-6), 30.1 (C-7), 28.1 (C-5).

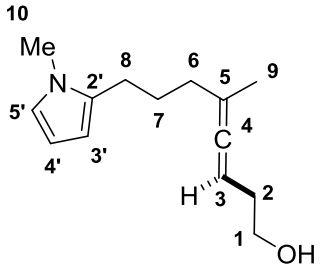
((8-Bromo-5-methylocta-3,4-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane (382)



A solution of ethyl 8-bromo-5-methylocta-3,4-dienoate (200 mg, 0.77 mmol) in ether (10 mL) was cooled to 0 °C. $LiAlH_4$ (29 mg, 0.77 mmol) was added and the resulting mixture was stirred at 0 °C for 10 min. The reaction was diluted with ether (10 mL), quenched with sat. aq. Na_2SO_4 *(caution: gas evolution)*, dried over $MgSO_4$, and filtered through cotton. The volatiles were removed in vacuo. The colourless oily residue was redissolved in DCM. Imidazole (104 mg, 1.53 mmol) and TBSCl (130 mg, 0.84 mmol) were added sequentially. The reaction was stirred at RT overnight (16 hr). The mixture was diluted with DCM, filtered through a plug of silica (1:1, ether/petrol), and evaporated to give a colourless oil (203 mg, 78%).

R_f 0.35 (petrol); ν_{max}/cm^{-1} 1970w (C=C=C); δ_H (500 MHz, $CDCl_3$) 5.06 (1H, tsext, *J* = 7.0, 3.0 Hz, H-3), 3.66 (2H, m, H-1), 3.44 (2H, t, *J* = 7.0, H-8), 2.19 (2H, q, *J* = 7.0, Hz, H-2), 2.10 – 2.04 (2H, m, H-6), 2.01 – 1.95 (2H, m, H-7), 1.69 (3H, d, *J* = 3.0, H-9), 0.90 (9H, s, H-12), 0.07 (6H, s, H-10); δ_C (126 MHz, $CDCl_3$) 201.7 (C-4), 97.7 (C-5), 87.7 (C-3), 63.1 (C-1), 33.5 (C-8/2), 33.1 (C-8/2), 32.2 (C-6), 30.6 (C-7), 25.9 (C-12), 19.4 (C-9), 18.4 (C-11), −5.3 (C-10); HRMS (ESI^+), m/z: calcd for $C_{15}H_{29}Br^{81}NaOSi$ [$M+Na^+$] 357.1043, found 357.1045.

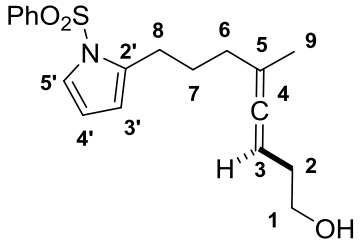
5-Methyl-8-(1-methyl-1*H*-pyrrol-2-yl)octa-3,4-dien-1-ol (383)



To a solution of 2-(8-((*tert*-butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-11-pyrrole (86 mg, 0.26 mmol) in THF (3 mL) was added a stock solution of TBAF (1 M in THF, 0.26 mL, 0.26 mmol). The reaction was stirred at RT for 3 hr. The reaction content was partitioned between ether (20 mL) and sat. aq. NH_4Cl (4 mL). The organic layer was separated and washed sequentially with sat. aq. NH_4Cl (4 mL) and brine (2×4 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (30:70, ether/petrol → ether) afforded the title material as a clear colourless oil (58 mg, 98%).

R_f 0.19 (1:1, ether/petrol); ν_{max}/cm^{-1} 3370br.s (OH), 3101w (=C–H), 1964w (C=C=C); δ_H (500 MHz, $CDCl_3$) 6.55 (1H, dd, *J* = 2.5, 2.0 Hz, H-5'), 6.06 (1H, dd, *J* = 3.5, 2.5 Hz, H-4'), 5.89 (ddt, *J* = 3.5, 2.0, 0.5 Hz, 1H, H-3'), 5.06 (1H, tsext, *J* = 6.5, 3.0 Hz, H-3), 3.74 – 3.65 (2H, m, H-1), 3.54 (3H, s, H-10), 2.59 – 2.54 (2H, m, H-8), 2.24 (2H, q, *J* = 6.5 Hz, H-2), 2.08 – 2.02 (2H, m, H-6), 1.76 (2H, quint, *J* = 7.5 Hz, H-7), 1.72 (3H, d, *J* = 3.0 Hz, H-9), 1.52 (1H, t, *J* = 6.0 Hz, OH); δ_C (126 MHz, $CDCl_3$) 202.1 (C-4), 133.2 (C-2'), 120.9 (C-5'), 106.5 (C-4'), 105.5 (C-3'), 99.7 (C-5), 86.7 (C-3), 62.2 (C-1), 33.6 (C-6/10), 33.5 (C-6/10), 32.7 (C-2), 26.6 (C-7), 25.8 (C-8), 19.3 (C-9); HRMS (ESI^+), m/z: calcd for $C_{14}H_{21}NNaO$ [$M+Na^+$] 242.1515, found 242.1511.

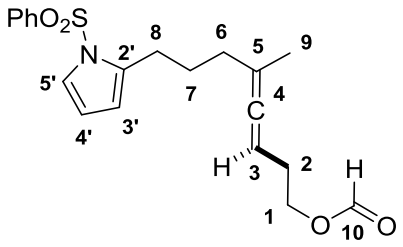
5-Methyl-8-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)octa-3,4-dien-1-ol (384)



HF·py (0.13 mL, 70% as HF) was dissolved in a mixture of THF (0.8 mL) and pyridine (0.2 mL). An aliquot of this solution (0.40 mL) was added to a solution of 2-(8-((*tert*-butyldimethylsilyl)oxy)-4-methylocta-4,5-dien-1-yl)-1-(phenylsulfonyl)-1*H*-pyrrole (55 mg, 0.12 mmol) in THF (2 mL) in a plastic vial. The reaction was stirred at RT for 3.5 hr, then an additional aliquot of the HF·py solution (0.2 mL) was added. The mixture was stirred for 2 hr. The reaction mixture was poured into of sat. aq. $NaHCO_3$ (15 mL). The aq. layer was extracted with DCM (3×8 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (2×5 mL) to remove pyridine, then passed through Phase Separator and concentrated. Flash chromatography (50:50, ether/petrol → ether) afforded the title compound as a colourless oil (28 mg, 68%).

R_f 0.41 (ether); ν_{max}/cm^{-1} 3377br.s (OH), 3151w (=C−H), 3067w (=C−H), 1963w (C=C=C), 1365s (sulfamide), 1177s (sulfamide); δ_H (500 MHz, $CDCl_3$) 7.77 – 7.73 (2H, m, H-Ph), 7.62 – 7.58 (1H, m, H-Ph), 7.53 – 7.49 (2H, m, H-Ph), 7.30 (1H, dd, *J* = 3.0, 1.8 Hz, H-5'), 6.22 (1H, t, *J* = 3.0 Hz, H-4'), 6.01 (1H, ddt, *J* = 3.0, 1.8, 1.1 Hz, H-3'), 5.00 (1H, tsext, *J* = 6.5, 3.0 Hz, H-3), 3.67 (2H, t, *J* = 6.5 Hz, H-1), 2.74 – 2.62 (2H, m, H-8), 2.21 (2H, q, *J* = 6.5 Hz, H-2), 1.96 (2H, td, *J* = 8.0, 3.0 Hz, H-6), 1.70 (2H, quint, *J* = 8.0 Hz, H-7), 1.66 (3H, d, *J* = 3.0 Hz, H-9), 1.58 (1H, br.s, OH); δ_C (126 MHz, $CDCl_3$) 202.1 (C-4), 139.5 (C-Ph), 135.6 (C-2'), 133.6 (C-Ph), 129.3 (C-Ph), 126.6 (C-Ph), 122.4 (C-5'), 112.0 (C-3'), 111.5 (C-4'), 99.4 (C-5), 86.7 (C-3), 62.2 (C-1), 33.4 (C-6), 32.6 (C-2), 26.6 (C-8), 26.4 (C-7), 19.2 (C-9); HRMS (ESI^+), m/z: calcd for $C_{19}H_{23}NO_3SNa^+$ [M+Na^+] 368.1291, found 368.1279.

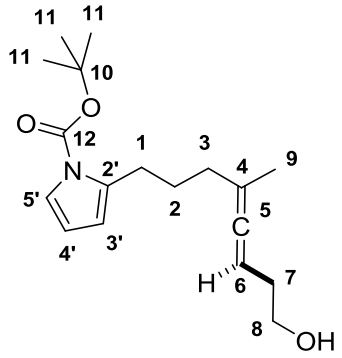
5-Methyl-8-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)octa-3,4-dien-1-yl formate (385)



The title compound was isolated as a side product in the synthesis 5-methyl-8-(1-(phenylsulfonyl)-1H-pyrrol-2-yl)octa-3,4-dien-1-yl azide (**384**) on a 0.072 mmol scale. The compound is a colourless oil (3 mg, 11%).

R_f 0.26 (25:75, ether/petrol); ν_{max}/cm^{-1} 3149w (=C–H), 3066w (=C–H), 1966w (C=C=C), 1724s (C=O), 1366s (sulfonamide), 1177s (sulfonamide); δ_H (500 MHz, $CDCl_3$) 8.02 (1H, s, H-10), 7.76 – 7.73 (2H, m, H-Ph), 7.62 – 7.58 (1H, m, H-Ph), 7.53 – 7.48 (2H, m, H-Ph), 7.30 (1H, dd, *J* = 3.5, 2.0 Hz, H-5'), 6.22 (1H, t, *J* = 3.5 Hz, H-4'), 6.01 (1H, ddt, *J* = 3.0, 2.0, 1.0 Hz, H-3'), 4.99 (1H, tsext, *J* = 6.5, 3.0 Hz, H-3), 4.19 (2H, t, *J* = 6.5 Hz, H-1), 2.68 (2H, t, *J* = 7.5 Hz, H-8), 2.30 (2H, q, *J* = 6.5 Hz, H-2), 1.97 – 1.91 (2H, m, H-6), 1.69 (2H, quint, *J* = 7.5 Hz, H-7), 1.65 (3H, d, *J* = 3.0 Hz, H-9); δ_C (126 MHz, $CDCl_3$) 201.9 (C-4), 161.0 (C-10), 139.5 (C-2'), 135.6 (C-Ph), 133.6 (C-Ph), 129.3 (C-Ph), 126.6 (C-Ph), 122.4 (C-5'), 112.0 (C-3'), 111.4 (C-4'), 100.0 (C-5), 85.9 (C-3), 63.3 (C-1), 33.2 (C-6), 28.5 (C-2), 26.7 (C-7/8), 26.4 (C-7/8), 19.1 (C-9); HRMS (ESI^+), m/z: calcd for $C_{20}H_{23}NNaO_4S$ $[M+Na^+]$ 396.1240, found 396.1226.

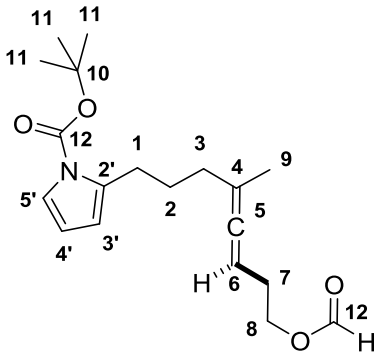
2-(4-Methylocta-4,5-dien-1-yl)-1-Boc-1*H*-pyrrole (386)



To a solution of 2-(8-*O*-TBS-4-methylocta-4,5-dien-1-yl)-1-Boc-1*H*-pyrrole (170 mg, 0.41 mmol) in THF (4 mL) was added stock solution of TBAF (1 M in THF, 0.41 mL, 0.41 mmol). The reaction was stirred at RT for 2 hr. The reaction content was partitioned between ether (30 mL) and sat. aq. NH_4Cl (8 mL). The organic layer was separated and washed sequentially with sat. aq. NH_4Cl (8 mL) and brine (2×8 mL), then dried over $MgSO_4$ and concentrated. Flash chromatography (40:60, ether/petrol → ether), afforded the title material as a viscous yellow oil (115 mg, 93%), along with recovered starting material (10 mg, 6%).

R_f 0.39 (1:1, ether/petrol); ν_{max}/cm^{-1} 3350br.m (OH), 1965w (C=C=C), 1741s (C=O); δ_H (500 MHz, $CDCl_3$) 7.19 (1H, dd, *J* = 3.5, 2.0 Hz, H-5'), 6.08 (1H, t, *J* = 3.5 Hz, H-4'), 5.98 – 5.94 (1H, m, H-3'), 5.04 (1H, tsext, *J* = 6.5, 3.0 Hz, H-6), 3.69 (2H, q, *J* = 6.0 Hz, H-8), 2.93 – 2.80 (2H, m, H-1), 2.24 (2H, q, *J* = 6.5 Hz, H-7), 2.03 (2H, td, *J* = 7.5, 3.0 Hz, H-3), 1.75 (2H, quint, *J* = 7.5 Hz, H-2), 1.71 (3H, d, *J* = 3.0 Hz, H-9), 1.61 (1H, t, *J* = 6.5 Hz, OH), 1.59 (9H, s, H-11); δ_C (126 MHz, $CDCl_3$) 202.4 (C-5), 149.7 (C-12), 136.2 (C-2'), 120.9 (C-5'), 111.0 (C-3'), 110.0 (C-4'), 99.9 (C-4), 86.7 (C-6), 83.4 (C-10), 62.3 (C-8), 33.8 (C-3), 32.8 (C-7), 28.5 (C-1), 28.2 (C-11), 26.8 (C-2), 19.4 (C-9); HRMS (ESI^+), m/z: calcd for $C_{18}H_{27}NNaO_3$ [$M+Na^+$] 328.1883, found 328.1878.

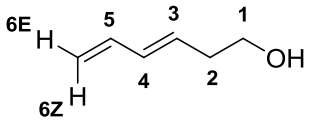
tert-Butyl 2-(8-(formyloxy)-4-methylocta-4,5-dien-1-yl)-1*H*-pyrrole-1-carboxylate (387)



Isolated as a side product in the synthesis of 2-(8-azido-4-methylocta-4,5-dien-1-yl)-*N*-Boc-1*H*-pyrrole (**240**) on a 0.11 mmol scale. Flash chromatography (petrol → 5:95, ether/petrol) afforded the title compound as a clear colourless oil (1.5 mg, 4%).

R_f 0.49 (10:90, ether/petrol); ν_{max}/cm^{-1} 1963w (C=C=C), 1729s (C=O); δ_H (400 MHz, $CDCl_3$) 8.02 (1H, s, H-12), 7.21 – 7.13 (1H, m, H-5'), 6.08 (1H, t, *J* = 3.5 Hz, H-4'), 6.01 – 5.91 (1H, m, H-3'), 5.10 – 4.97 (1H, m, H-6), 4.26 – 4.14 (2H, m, H-8), 2.86 (2H, t, *J* = 7.5 Hz, H-1), 2.33 (2H, q, *J* = 7.0 Hz, H-7), 2.01 (2H, td, *J* = 7.5, 3.0 Hz, H-3), 1.80 – 1.65 (5H, m, H-2,9), 1.59 (9H, s, H-11).

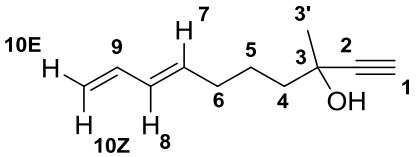
(*E*)-Hexa-3,5-dien-1-ol (*E*-388)[6]



(*E*)-Hexa-3,5-dienoic acid (1.0 g, 8.9 mmol) was dissolved in freshly distilled THF (25 mL), followed by $LiAlH_4$ (277 mg, 7.3 mmol). The mixture was brought to gentle reflux (oil bath 60 °C) and stirred for 1 hr. The reaction was then cooled to 0 °C and quenched by the sequential addition of water (0.3 mL), 15% aq. NaOH (0.3 mL), and water (0.9 mL). The resulting mixture was stirred at RT for 15 min, then filtered through a 5 cm silica pad, eluting with ether. Concentration of the crude solution afforded the target material as a colourless oil (0.62 g, 71%).

R_f 0.37 (50:50, ethyl acetate/petrol); ν_{max}/cm^{-1} 3328br.s (OH), 3086w (=C–H); δ_H (400 MHz, $CDCl_3$) 6.32 (1H, dt, *J* = 17.0, 10.0 Hz, H-5), 6.15 (1H, dd, *J* = 15.0, 10.0 Hz, H-4), 5.68 (1H, dt, *J* = 15.0, 7.0 Hz, H-3), 5.13 (1H, d, *J* = 17.0 Hz, H-6Z), 5.01 (1H, d, *J* = 10.0 Hz, H-6E), 3.67 (2H, t, *J* = 7.0 Hz, H-1), 2.35 (2H, dt, *J* = 7.0, 7.0 Hz, H-2), 1.82 (1H, br.s, OH); δ_C (101 MHz, $CDCl_3$) 136.8 (C-5), 133.7 (C-4), 130.6 (C-3), 115.9 (C-6), 61.8 (C-1), 35.9 (C-2).

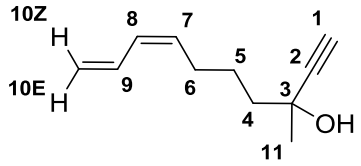
***(E)*-3-methyldeca-7,9-dien-1-yn-3-ol (*E*-389)**



Prepared by General method A by stirring (*E*)-nona-6,8-dien-2-one (0.43 g, 3.1 mmol) in a stock solution of HC≡CMgBr (0.5 M in THF, 6.8 mL, 3.4 mmol) at reflux for 2.5 hr. Flash chromatography (1:4, ether/petrol) afforded the title product as a yellowish oil (490 mg, 96%). E/Z ≈ 13:1 (^{1}H NMR).

R_f 0.36 (25:75, ether/petrol); ν_{max}/cm^{-1} 3400br.s (OH), 3300s (≡C–H), 3085w (=C–H), 3036w (=C–H), 2108w (C≡C); δ_H (400 MHz, $CDCl_3$) 6.32 (1H, dt, *J* = 17.0, 10.0 Hz, H-9), 6.08 (1H, dd, *J* = 15.0, 10.0 Hz, H-8), 5.71 (1H, dt, *J* = 15.0, 7.0 Hz, H-7), 5.10 (1H, d, *J* = 17.0 Hz, H-10Z), 4.97 (1H, d, *J* = 10.0 Hz, H-10E), 2.44 (1H, s, H-1), 2.18 – 2.11 (2H, m, H-6), 2.04 (1H, s, OH), 1.72 – 1.59 (4H, m, H-4,5), 1.50 (3H, s, H-3'); δ_C (101 MHz, $CDCl_3$) 137.2 (C-9), 134.7 (C-7), 131.4 (C-8), 115.0 (C-10), 87.6 (C-2), 71.4 (C-1), 67.9 (C-3), 42.9 (C-4), 32.4 (C-6), 29.8 (C-3'), 24.1 (C-5); HRMS (TOF FI^+), m/z: calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found 164.1206.

(*Z*)-3-methyldeca-7,9-dien-1-yn-3-ol (*Z*-389)

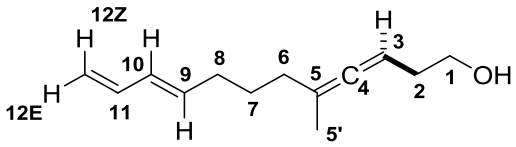


Prepared by General method A from (*Z*)-nona-6,8-dien-2-one (390 mg, 2.8 mmol) in THF (2×0.5 mL) and a stock solution of HC≡CMgBr (0.5M in THF, 6.2 mL, 3.1 mmol) by stirring the mixture at RT for 3.5 hr. The reaction mixture was diluted with ether (10 mL) and quenched with sat. aq. NH_4Cl (10 mL) and water (1 mL). The aq. layer was extracted with ether (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (10:90 → 20:80, ether/petrol) afforded the title material as a clear yellowish oil (424 mg, 92%).

R_f 0.26 (25:75, ether/petrol); ν_{max}/cm^{-1} 3380br.s (OH), 3300s (≡C–H), 3086w (=C–H), 3008w (=C–H), 2114w (C≡C); δ_H (500 MHz, $CDCl_3$) 6.64 (1H, dtd, *J* = 16.5, 10.5, 1.0 Hz, H-9), 6.03 (1H, tm, *J* = 10.5 Hz, H-8), 5.46 (1H, dt, *J* = 10.5, 7.5 Hz, H-7), 5.20 (1H, dd, *J* = 16.5, 2.0 Hz, H-10Z), 5.10 (1H, d, *J* = 10.5 Hz, H-10E), 2.44 (1H, s, H-1), 2.26 (2H, qd, *J* = 7.5, 1.5 Hz, H-6), 1.93 (1H, s, OH), 1.73 – 1.59 (4H, m, H-4,5), 1.50 (3H, s, H-11); δ_C (126 MHz, $CDCl_3$) 132.32 (C-7/9), 132.30 (C-7/9), 129.8 (C-8), 117.3 (C-10), 87.7 (C-

2), 71.6 (C-1), 68.1 (C-3), 43.0 (C-4), 29.9 (C-11), 27.7 (C-6), 24.7 (C-5); HRMS (TOF FI$^+$), m/z: calcd for $C_{11}H_{16}O$ [M$^+$] 164.1201, found 164.1199.

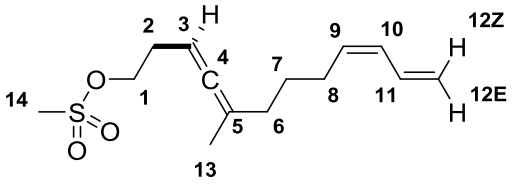
***(E)*-5-methyldodeca-3,4,9,11-tetraen-1-ol (*E*-390)**



(E)-ethyl 5-methyldodeca-3,4,9,11-tetraenoate (*E*-**324**, 310 mg, 1.32 mmol) was dissolved in dry ether (13 mL) and cooled to 0 °C. $LiAlH_4$ (50 mg) was added in one portion and the mixture was stirred for 40 min. The reaction was quenched at ca. 10 °C by careful addition of sat. aq. Na_2SO_4 *(caution: gas evolution)* until a white precipitate formed. The mixture was additionally dried with anhydrous Na_2SO_4. The solids were filtered off and washed with ether. Concentration of the washes afforded the target material as a colourless oil that was used immediately without further purification (190 mg, 76%). E/Z ≈ 14:1 (^{1}H NMR).

R_f 0.43 (50:50, ether/petrol); ν_{max}/cm^{-1} 3320br.s (OH), 3085w (=C–H), 1966w (C=C=C); δ_H (500 MHz, C_6D_6) 6.32 (1H, app. dt, *J* = 17.0, 10.0 Hz, H-11), 6.07 (1H, dd, *J* = 15.0, 10.0 Hz, H-10), 5.61 – 5.53 (1H, m, H-9), 5.09 (1H, d, *J* = 17.0 Hz, H-12Z), 5.04 – 4.97 (1H, m, H-3), 4.94 (1H, d, *J* = 10.0 Hz, H-12E), 3.46 (2H, td, *J* = 6.5, 6.0 Hz, H-1), 2.08 (2H, app. q, *J* = 6.5 Hz, H-2), 1.99 (2H, app. q, *J* = 7.5 Hz, H-8), 1.82 (2H, td, *J* = 7.5, 3.0 Hz, H-6), 1.58 (3H, d, *J* = 3.0 Hz, H-5'), 1.47 (2H, quint, *J* = 7.5 Hz, H-7), 0.93 (1H, t, *J* = 6.0 Hz, OH); δ_C (126 MHz, C_6D_6) 202.6 (C-4), 137.8 (C-11), 135.1 (C-9), 131.9 (C-10), 114.9 (C-12), 99.6 (C-5), 87.4 (C-3), 62.3 (C-1), 33.6 (C-2/6), 33.3 (C-2/6), 32.5 (C-8), 27.5 (C-7), 19.4 (C-5); HRMS (TOF FI$^+$), m/z: calcd for $C_{13}H_{20}O$ [M$^+$] 192.1514, found 192.1516.

(*Z*)-5-methyldodeca-3,4,9,11-tetraen-1-yl methanesulfonate (392)

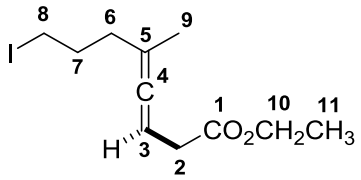


To a solution of (*Z*)-ethyl 5-methyldodeca-3,4,9,11-tetraenoate (*Z*-**324**, 0.26 g, 1.1 mmol) in ether was added $LiAlH_4$ (42 mg, 1.1 mmol) at 0 °C (*caution:* gas evolution). The mixture was stirred at 0 °C for 80 min, then diluted with ether (10 mL), and quenched by careful dropwise addition of sat. aq. Na_2SO_4 over 30 min (0 °C → RT; *ca*. 15 drops) until a dense white precipitate formed. The mixture was dried with anhydrous Na_2SO_4. The solids were filtered off and thoroughly washed with ether. The organic solution was concentrated and the crude alcohol (a colourless oil) was used immediately in the next step. The alcohol was redissolved in DCM (4 mL) and cooled to 0 °C. TEA (0.23 mL, 2.0 mmol) and MsCl (120 μL, 1.6 mmol) were added. The ice bath was removed and the clear yellow mixture was stirred for 1.5 hr. The reaction was diluted with DCM (40 mL) and quenched with sat. aq. NH_4Cl (25 mL). The aq. layer was separated and extracted with DCM (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (25:75 → 50:50, ether/petrol), afforded the title material as a colourless oil (196 mg, 65% over 2 steps).

R_f 0.35 (1:1, ether/petrol); ν_{max}/cm^{-1} 3083w (=C–H), 1966w (C=C=C), 1354s (sulfonyl), 1174s (sulfonyl); δ_H (400 MHz, $CDCl_3$) 6.56 (1H, dddd, *J* = 17.0, 11.0, 10.0, 1.1 Hz, H-11), 5.95 (1H, tm, *J* = 11.0 Hz, H-10), 5.38 (1H, dt, *J* = 11.0, 7.5 Hz, H-9), 5.12 (1H, dd, *J* = 17.0, 2.0 Hz, H-12Z), 5.02 (1H, dm, *J* = 10.0 Hz, H-12E), 4.98 – 4.92 (1H, m, H-3), 4.18 (2H, t, *J* = 7.0 Hz, H-1), 2.94 (3H, s, H-14), 2.34 (2H, q, *J* = 7.0 Hz, H-2), 2.14 (2H, app.qt, *J* = 7.5, 1.5 Hz, H-6), 1.92 – 1.84 (2H, m, H-8), 1.61 (3H, d, *J* = 3.0 Hz, H-13), 1.44 (2H, quint, *J* = 7.5 Hz, H-7); δ_C (101 MHz, $CDCl_3$) 202.3 (C-4), 132.4 (C-9/11), 132.2 (C-

9/11), 129.6 (C-10), 117.0 (C-12), 100.9 (C-5), 84.9 (C-3), 69.1 (C-1), 37.5 (C-14), 33.2 (C-8), 29.2 (C-2), 27.3 (C-6/7), 27.2 (C-6/7), 19.2 (C-13); HRMS (ESI$^+$), m/z: calcd for $C_{14}H_{22}O_3SNa$ [M+Na$^+$] 293.1182, found 293.1189.

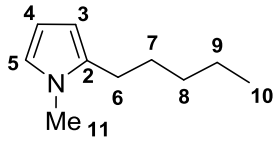
Ethyl 8-iodo-5-methylocta-3,4-dienoate (393)



To a solution of ethyl 8-bromo-5-methylocta-3,4-dienoate (33 mg, 0.13 mmol) in acetone (1 mL) was added NaI (59 mg, 0.39 mmol), and the reaction was stirred for 3 days at RT. White precipitate was formed. The volatiles were then removed in vacuo. The residue was partitioned between ether (5 mL) and water (5 mL). The aq. layer was separated and extracted with ether (2×5 mL). The combined organic layers were dried over $MgSO_4$, then concentrated to yield the title material as a colourless oil (16 mg, 40%). Note: the compound co-elutes with the starting bromide.

R_f 0.28 (10:90, ether/petrol); ν_{max}/cm^{-1} 1970w (C=C=C), 1733s (C=O); δ_H (500 MHz, $CDCl_3$) 5.24 – 5.16 (1H, m, H-3), 4.16 (2H, q, *J* = 7.0 Hz, H-10), 3.22 (2H, td, *J* = 7.0, 1.5 Hz, H-8), 2.99 (2H, d, *J* = 7.0 Hz, H-2), 2.06 (2H, td, *J* = 7.0, 3.0 Hz, H-6), 1.95 (2H, q, *J* = 7.0 Hz, H-7), 1.70 (3H, d, *J* = 3.0 Hz, H-9), 1.28 (3H, t, *J* = 7.0 Hz, H-11); δ_C (126 MHz, $CDCl_3$) 202.3 (C-4), 171.7 (C-1), 99.2 (C-5), 84.2 (C-3), 60.7 (C-10), 35.3 (C-2), 34.4 (C-6), 31.1 (C-7), 19.0 (C-9), 14.2 (C-11), 6.4 (C-8); MS (ESI$^+$), m/z: 309 (27%, M+H$^+$), 331 (100%, M+Na$^+$).

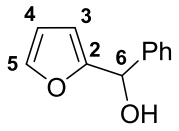
1-Methyl-2-pentyl-1*H*-pyrrole (394)



N-Methyl-1*H*-pyrrole (81 mg, 1.0 mmol) was dissolved in THF (2.0 mL) and cooled to −78 °C. BuLi (0.63 mL, 1.6M in hexanes, 1.0 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 10 min, then allowed to warm to RT and stirred overnight (13 hr). Neat pentyl iodide (100 mg, 0.5 mmol) was added at −78 °C. The reddish mixture was stirred at −78 °C for 10 min, then allowed to warm to RT and stirred for 6 hr. The reaction was diluted with ether (6 mL), then washed with water (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (petrol → 5:95, ether/petrol) to afford a colourless oil (20 mg, 27%).

R_f 0.66 (10:90, ether/petrol); ν_{max}/cm^{-1} 3101w (=C−H), 1494m, 1088m, 697s; δ_H (400 MHz, $CDCl_3$) 6.59 – 6.54 (1H, m, H-5), 6.08 (1H, t, *J* = 3.1 Hz, H-4), 5.94 – 5.88 (1H, m, H-3), 3.55 (3H, s, H-11), 2.55 (2H, t, *J* = 8.0 Hz, H-6), 1.72 – 1.60 (2H, m, H-7), 1.45 – 1.35 (4H, m, H-8,9), 0.98 – 0.90 (3H, m, H-10). δ_C (101 MHz, $CDCl_3$) 133.8 (C-2), 120.9 (C-5), 106.4 (C-4), 105.3 (C-3), 33.5 (C-11), 31.7 (C-8), 28.5 (C-7), 26.3 (C-6), 22.5 (C-9), 14.1 (C-10).

Furan-2-yl(phenyl)methanol (395)[352]

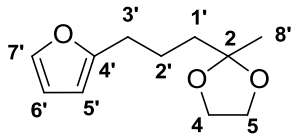


Furan (68 mg 1.0 mmol) was dissolved in freshly distilled THF (4 mL) and cooled to 0 °C. Solution of BuLi (1.6 M, 0.63 mL, 1.0 mL) was added dropwise. The mixture was stirred at 0 °C for 1 hr. The resulting yellow solution was cooled to −78 °C; benzaldehyde (95 mg, 0.9 mmol) was then added dropwise. After 30 min, the solution

was allowed to warm to RT and stirred for 2.5 hr. The reaction mixture was diluted with ether (3 mL) and quenched with sat. aq. NH_4Cl (4 mL) and aq. HCl (1 M, 0.5 mL). The layers were separated and the aq. layer was extracted with ether (2×2 mL). The combined organic extracts were washed with brine (2 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (25:75, ether/petrol) afforded the target material as a colourless oil (100 mg, 66%).

R_f 0.40 (50:50, ether/petrol); ν_{max}/cm^{-1} 3350br.s (OH); δ_H (400 MHz, $CDCl_3$) 7.47 – 7.31 (6H, m, H-Ar), 6.33 (1H, dd, *J* = 3.0, 2.0 Hz, H-4), 6.13 (1H, d, *J* = 3.0 Hz, H-3), 5.83 (1H, s, H-6), 2.54 (1H, br.s, OH); δ_C (101 MHz, $CDCl_3$) 156.0 (C-2), 142.6 (C-5), 140.8 (C-Ph), 128.5 (C-Ph), 128.1 (C-Ph), 126.6 (C-Ph), 110.2 (C-4), 107.4 (C-3), 70.1 (C-6).

2-(3-(Furan-2-yl)propyl)-2-methyl-1,3-dioxolane (396)

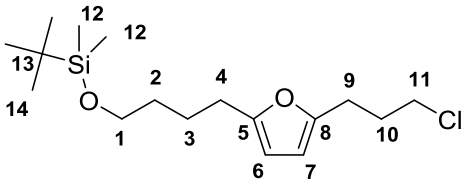


Furan (20 mg, 0.5 mmol) was dissolved in freshly distilled THF (1 mL) and cooled to −78 °C, followed by BuLi (0.16 mL, 1.6 M, 0.25 mmol). The mixture was warmed up to 0 °C and stirred for 2 hr. A solution of 2-(3'-Iodopropyl)-2-methyl-1,3-dioxolane (65 mg, 0.25 mmol) in THF (0.5 mL) was then added at 0 °C. The resulting mixture was stirred at RT for 3 hr. The reaction mixture was quenched with a citrate buffer (2 mL, pH 3), followed by the extraction with ether (12 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (1:4, ether/petrol) afforded the target material as a colourless oil (48 mg, 98%).

R_f 0.19 (25:75, ether/petrol); ν_{max}/cm^{-1} 3080w (=C−H), 1057s; δ_H (500 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, H-7'), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H-6'), 5.99 (1H, dd, *J* = 3.0, 1.0 Hz, H-5'), 3.98 – 3.90 (4H, m, H-4,5), 2.65 (2H, t, *J* = 7.0 Hz, H-3'), 1.80 – 1.72

(2H, m, H-1'), 1.72 – 1.67 (2H, m, H-2'), 1.33 (3H, s, H-8'); δ_C (126 MHz, $CDCl_3$) 156.1 (C-4'), 140.7 (C-7'), 110.0 (C-6'), 109.9 (C-2), 104.8 (C-5'), 64.6 (C-4,5), 38.5 (C-1'), 28.0 (C-3'), 23.8 (C-8'), 22.6 (C-2').

tert-Butyl(4-(5-(3-chloropropyl)furan-2-yl)butoxy)dimethylsilane (397)

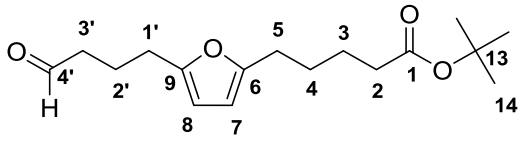


A solution of 2-(3-chloropropyl)furan (1.61 g, 11.1 mmol) in freshly distilled THF (11 mL) was cooled to −25 °C (ice bath temp.) and stirred for 15 min. Then, BuLi (1.6 M in hexanes, 7.0 mL, 11.1 mmol) was added dropwise over 10 min with a syringe, while the temperature was maintained below −20 °C. The mixture was allowed to warm to −15 °C and stirred at this temperature for 4 hr (the colour of the solution gradually changed to yellow). A solution of *O*-TBS-4-iodopropanol-1 (2.87 g, 9.1 mmol) in freshly distilled THF (8.5 mL) was added over 15 min with a syringe. The resulting mixture was stirred at −15 °C for 1 hr, then at RT for 19 hr. The clear orange solution was diluted with ether (50 mL) and quenched with sat. aq. NH_4Cl (30 mL). The layers were separated and the aq. layer was extracted with ether (2×10 mL). The combined organic layers were washed with brine (2×20 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (petrol → 1:99, ether/petrol) afforded the title product as a clear yellow oil (2.58 g, 86%) along with recovered starting material (205 mg).

R_f 0.27 (2:98, ether/petrol); ν_{max}/cm^{-1} 3104w (=C−H), 1614w, 1255m, 1103s, 836s, 776s; δ_H (400 MHz, $CDCl_3$) 5.90 (1H, d, *J* = 3.0 Hz, H-7), 5.86 (1H, d, *J* = 3.0 Hz, H-6), 3.63 (2H, t, *J* = 6.5 Hz, H-1), 3.56 (2H, t, *J* = 7.0 Hz, H-11), 2.75 (2H, t, *J* = 7.0 Hz, H-9), 2.58 (2H, t, *J* = 7.5 Hz, H-4), 2.08 (2H, quint, *J* = 7.0 Hz, H-10), 1.72 – 1.61 (2H, m, H-3), 1.61 – 1.51 (2H, m, H-2), 0.89 (9H, s, H-14), 0.05 (6H, s, H-12); δ_C (101 MHz, $CDCl_3$)

155.1 (C-5/8), 152.5 (C-5/8), 106.1 (C-7), 105.3 (C-6), 63.0 (C-1), 44.4 (C-11), 32.5 (C-2), 31.2 (C-10), 27.9 (C-4), 26.1 (C-14), 25.4 (C-9), 24.6 (C-3), 18.5 (C-13), −5.2 (C-12); HRMS (ESI$^+$), m/z: calcd for $C_{17}H_{31}ClO_2SiNa$ [M+Na$^+$] 353.1674, found 353.1664.

tert-Butyl 5-(5-(4-oxobutyl)furan-2-yl)pentanoate (398)

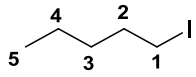


$(COCl)_2$ (0.32 mL, 3.8 mmol) was dissolved in DCM (13 mL) in a dry 50 mL flask, and cooled to −78 °C. DMSO (0.53 mL, 7.5 mmol) was added dropwise over 5 min (note: gas liberation). The mixture was stirred at −78 °C for 15 min, then a solution of *tert*-butyl 5-(5-(4-hydroxybutyl)furan-2-yl)pentanoate (557 mg, 1.9 mmol) in DCM (5 mL) was added over 20 min using a syringe pump. The cloudy mixture was stirred for additional 15 min at −78 °C. TEA (1.05 mL, 7.5 mmol) was added dropwise. The mixture was stirred at −78 °C for 15 min, then at 0 °C for 30 min. The reaction mixture was diluted with DCM (10 mL) and quenched with aq. $NaHSO_4$ (0.5 M, 15 mL) and water (5 mL). The layers were shaken and separated. The aq. layer was extracted with DCM (4×10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by passing through a short silica plug (2×5 cm), eluting with 25:75, ether/petrol, to yield the title material as a clear yellow oil (505 mg, 91%).

R_f 0.35 (25:75, ether/petrol); ν_{max}/cm^{-1} 3104w (=C−H), 2723w ($C_{aldehyde}$−H), 1727s (C=O); δ_H (500 MHz, $CDCl_3$) 9.75 (1H, t, *J* = 1.5 Hz, H-4'), 5.88 (1H, d, *J* = 3.0 Hz, H-7/8), 5.86 (1H, d, *J* = 3.0 Hz, H-7/8), 2.63 (2H, t, *J* = 7.5 Hz, H-1'), 2.59 (2H, br.t, *J* = 7.0 Hz, H-5), 2.48 (2H, td, *J* = 7.5, 1.5 Hz, H-3'), 2.27 – 2.20 (2H, m, H-2), 1.96 (2H, quint, *J* = 7.5 Hz, H-2'), 1.66 – 1.61 (4H, m, H-3,4), 1.45 (9H, s, H-14); δ_C (126 MHz, $CDCl_3$) 202.3 (C-4'), 173.2 (C-1), 154.7 (C-6/9), 153.1 (C-6/9), 106.1 (C-7/8), 105.4 (C-7/8), 80.2 (C-

13), 43.2 (C-3'), 35.4 (C-2), 28.3 (C-14), 27.9 (C-1/3/5), 27.7 (C-1/3/5), 27.4 (C-1/3/5), 24.8 (C-4), 20.9 (C-2'); HRMS (ESI$^+$), m/z: calcd for $C_{17}H_{26}O_4Na$ [M+Na$^+$] 317.1723, found 317.1710.

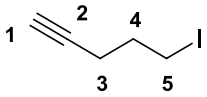
1-Iodopentane (399)[353]



Pentan-1-ol (2.81 g, 31.8 mmol) was dissolved in aq. HI (57%, 7 mL) and the mixture was stirred at reflux at 120 °C for 4 hr. Formation of two immiscible layers was observed. The cooled reaction mixture was diluted with ether (20 mL) and water (5 mL) and shaken vigorously. The organic layer was separated and washed sequentially with water (2× 5 mL) and sat. aq. $Na_2S_2O_3$ (3 mL). The organic layer was filtered through a 5 cm silica plug, eluting with petrol. Concentration of the residue afforded the target material as a colourless oil.

R_f 0.67 (petrol); ν_{max}/cm^{-1} 2956s, 2927s, 2871m, 2858m, 1228s, 723m; δ_H (400 MHz, $CDCl_3$) 3.20 (2H, t, *J* = 7.0 Hz, H-1), 1.85 (2H, quint, *J* = 7.0 Hz, H-2), 1.45 – 1.20 (4H, m, H-3,4), 0.9 (3H, t, *J* = 7.0 Hz, H-5); δ_C (101 MHz, $CDCl_3$) 34.1 (C-2), 33.3 (C-3), 21.7 (C-4), 13.9 (C-5), 7.3 (C-1).

5-Iodopent-1-yne (400)[354]

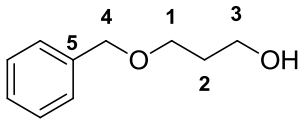


To a solution of PPh_3 (73 mg, 0.28 mmol) in DCM (1.0 mL) were added imidazole (19 mg, 0.28 mmol) and I_2 (71 mg, 0.28 mmol). The mixture was stirred at RT for 35 min. A solution of 4-pentyn-1-ol (20 mg, 0.24 mmol) in DCM (0.35 mL) was added. The reaction mixture was stirred for 1.5 hr. The mixture was then filtered through a cotton plug, and partitioned between water (2 mL) and petrol (5 mL). The organic layer was dried over $MgSO_4$, evaporated, then filtered through a small plug of

silica (0.5×1 cm), eluting with petrol. Concentration of the filtrate (RT, 150 Torr) afforded the title material as a colourless volatile oil (28 mg, 61%).

R_f 0.42 (petrol); ν_{max}/cm^{-1} 3294m (≡C–H), 2118w (C≡C); δ_H (400 MHz, $CDCl_3$) 3.32 (2H, t, *J* = 6.5 Hz, H-5), 2.35 (2H, td, *J* = 6.5, 6.5, 2.5 Hz, H-3), 2.07 – 1.96 (3H, m, H-4,1); δ_C (101 MHz, $CDCl_3$) 82.3 (C-2), 69.4 (C-1), 31.8 (C-4), 19.4 (C-3), 5.1 (C-1).

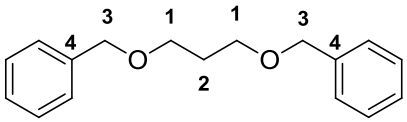
3-(Benzyloxy)propan-1-ol (401)[355]



1,3-Propanediol (76 mg, 1.0 mmol) was dissolved in THF (5 mL). To this were added DMPU (25 mg, 0.2 mmol) and NaH (60% in oil, 40 mg, 1.0 mmol). The mixture was stirred at RT for 1 hr. Then, a solution of benzyl bromide (170 mg, 1.0 mmol) and tetrabutylammonium iodide (74 mg, 0.2 mmol) in THF (1 mL) was added and the resulting mixture was stirred overnight (13 hr). The crude reaction mixture was partitioned between sat. aq. NH_4Cl (5 mL) and ether (15 ml). The organic layer was separated and dried over $MgSO_4$, then evaporated. Flash chromatography (1:3 → 1:1, ether/petrol → ether) afforded the title compound as a colourless oil (73 mg, 44%), along with some dialkylated side product.

R_f 0.15 (25:75, ether/petrol); ν_{max}/cm^{-1} 3391br.s (OH), 3088w (=C–H), 3064w (=C–H), 3030w (=C–H); δ_H (400 MHz, $CDCl_3$) 7.41 – 7.27 (5H, m, H-Ph), 4.54 (2H, s, H-4), 3.80 (2H, t, *J* = 5.5 Hz, H-3), 3.68 (2H, t, *J* = 5.5 Hz, H-1), 2.23 (1H, s, OH), 1.88 (2H, quint, *J* = 5.5 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 138.1 (C-5), 128.5 (C-Ph), 127.72 (C-Ph), 127.65 (C-Ph), 73.3 (C-4), 69.4 (C-1), 61.9 (C-3), 32.1 (C-2).

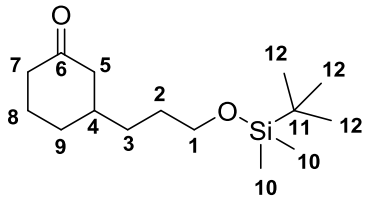
1,3-Bis(benzyloxy)propane (402)[355]



Isolated as a side product in the synthesis of 3-(benzyloxy)propan-1-ol on a 1 mmol scale. The compound is a colourless oil (10 mg, 4%).

R_f 0.78 (50:50, ether/petrol); ν_{max}/cm^{-1} 3087w (=C–H), 3063w (=C–H), 3030w (=C–H); δ_H (400 MHz, $CDCl_3$) 7.43 – 7.23 (10H, m, H-Ph), 4.51 (4H, s, H-3), 3.61 (4H, t, *J* = 6.5 Hz, H-1), 1.95 (2H, quint, *J* = 6.5 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 138.5 (C-4), 128.4 (C-Ph), 127.7 (C-Ph), 127.5 (C-Ph), 72.9 (C-3), 67.3 (C-1), 30.2 (C-2).

3-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)cyclohexanone (403)[356]

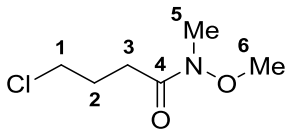


(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (253 mg, 1.0 mmol) was dissolved in ether (2 mL) in a 10 mL vial and cooled to −78 °C. A solution of *t*-BuLi (1.6 M, 1.25 mL, 2.0 mmol) was added dropwise and the resulting solution was stirred at −78 °C for 15 min, warmed to RT, then stirred for another 15 min. Meanwhile, freshly purified CuI (95 mg, 0.50 mmol) was suspended in ether (2 mL) in another 10 mL vial and cooled to −50 °C. The solution of 3-(OTBS)propyllithium was transferred into this vessel with a syringe, and the resulting suspension was stirred at −50 °C for 15 min. Then, a solution of cyclohexanone (24 mg, 0.25 mmol) in ether (0.5 mL) was added. After 10 min at −50 °C, the reaction was quenched with MeOH (ca. 0.06 mL) and warmed to RT. Sat. aq. NH_4Cl was added (3 mL) and the resulting mixture was shaken until intense blue colour indicated the formation of copper amino complexes. The aq. layer was extracted with ether (3×2 mL). The combined organic layers were dried

($MgSO_4$) and concentrated. Flash chromatography (15:85, ether/petrol) afforded the title material as a clear colourless oil (68 mg, 100%).

R_f 0.50 (25:75, ether/petrol); ν_{max}/cm^{-1} 1714s (C=O); δ_H (400 MHz, $CDCl_3$) 3.60 (2H, t, *J* = 6.5 Hz, H-1), 2.43 (1H, ddt, *J* = 13.5, 4.0, 2.0 Hz, H-5a), 2.40 – 2.31 (1H, m, H-7a), 2.30 – 2.24 (1H, m, H-7b), 2.11 – 1.97 (2H, m, ½×CH_2 + H-5b), 1.97 – 1.87 (1H, m, ½×CH_2), 1.84 – 1.72 (1H, m, H-4), 1.71 – 1.18 (6H, m, 3×CH_2), 0.89 (9H, s, H-12), 0.05 (6H, s, H-10); δ_C (101 MHz, $CDCl_3$) 211.9 (C-6), 63.1 (C-1), 48.2 (C-5), 41.5 (C-7), 38.9 (C-4), 32.8 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 25.9 (C-12), 25.3 (CH_2), 18.3 (C-11), −5.3 (C-10).

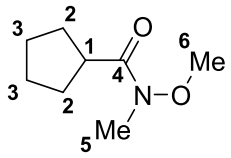
4-Chloro-*N*-methoxy-*N*-methylbutanamide (404)[357]



4-Chlorobuturyl chloride (385 mg, 2.73 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. To this, dimethylhydroxylamine hydrochloride (293 mg, 3.00 mmol) was added, followed by freshly distilled pyridine (0.49 ml, 6.0 mmol). The ice bath was removed after 15 min and the solution was stirred at RT for 5 hr. The reaction mixture was diluted with ether (20 mL) and washed with a brine/water mixture (10 + 2 mL, respectively), dried ($MgSO_4$), and concentrated. Flash chromatography (2:3, ethyl acetate/petrol) afforded the target compound as a colourless oil (0.444 g, 98%).

R_f 0.41 (ether); ν_{max}/cm^{-1} 1658s (C=O); δ_H (200 MHz, $CDCl_3$) 3.73 (3H, s, H-6), 3.65 (2H, t, *J* = 6.0 Hz, H-1), 3.20 (3H, s, H-5), 2.63 (2H, t, *J* = 6.0 Hz, H-3), 2.10 (2H, app. quint, *J* = 6.0 Hz, H-2); δ_C (126 MHz, $CDCl_3$) 173.3 (br. s, C-4), 61.2 (C-6), 44.7 (C-1), 32.1 (br.s, C-5), 28.7 (C-3), 27.2 (C-2).

_N_-Methoxy-_N_-methylcyclopentanecarboxamide (405)[358]

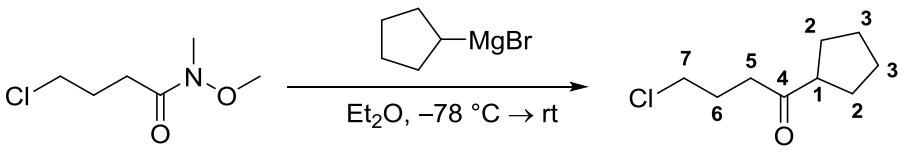


To a solution of cyclopentanecarboxylic acid (95 mg, 0.84 mmol) in benzene (10 mL) was added $(COCl)_2$ (0.75 mL, 8.8 mmol) with a syringe. The solution was stirred at RT for 15 min, then heated at reflux for 1 hr. Volatiles were removed in vacuo and the residue was redissolved in dry DCM (ca. 8 mL). The solution was cooled to 0 °C. To this were sequentially added methoxymethylamine hydrochloride (90 mg, 0.92 mmol) and dry pyridine (0.10 mL, ca. 1.7 mmol). The ice bath was removed and the stirring was continued overnight (14 hr). The reaction mixture was diluted with ether (10 mL), washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (40:60, ether/petrol) to afford the target material as a colourless oil (110 mg, 84%).

R_f 0.28 (50:50, ether/petrol); ν_{max}/cm^{-1} 1659s (C=O); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, H-6), 3.18 (3H, s, H-5), 3.00–3.16 (1H, m, H-1), 1.65–1.90 (6H, m, H-2,3a), 1.50–1.65 (2H, m, H-3b); δ_C (125 MHz, $CDCl_3$) 178.0 (br.s, C-4, *note:* this signal is shifted compared to the reported value of 168 ppm[358]), 61.5 (C-6), 40.4 (C-1), 32.5 (br.s, C_5), 30.2 (C-2), 26.2 (C-3).

4-Chloro-1-cyclopentylbutan-1-one (406)[359]

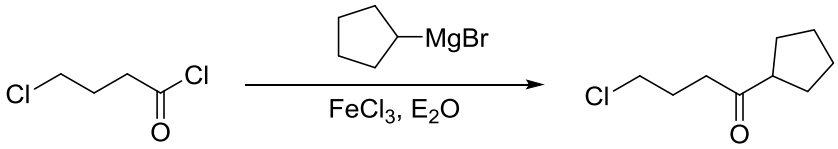
Method 1. From Weinreb amide.



Cyclopentylmagnesium bromide (1 M, 8.4 mL, 8.4 mmol) was added to a solution of 4-chloro-_N_-methoxy-_N_-methylbutanamide (1.15 g, 6.9 mmol) in ether

(40 mL) at −78 °C. The reaction mixture was allowed to warm to RT and stirred overnight (15 hr). The reaction was quenched with a water-brine mixture (5 + 5 mL) at 0 °C. The aq. layer was neutralized with aq. HCl (1 M) and extracted with ether (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (1:9, ether/petrol) afforded the target material as a colourless oil (0.32 g, 26%).

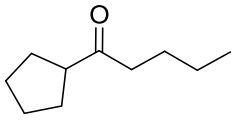
Method 2. From acyl chloride.



4-Chlorobutyryl chloride (1.35 g, 9.6 mmol) was dissolved in ether (5 mL). $FeCl_3$ (38 mg, 0.24 mmol) was added. To this, a solution of cyclopentylmagnesium bromide (0.96 *M*, 5 mL, 4.8 mmol) was added dropwise, and the resulting mixture was stirred at RT for 2 hr. Note: the colour of the solution gradually changed upon the addition of the reagents and subsequent reaction: red → greenish black → reddish brown. The reaction was quenched with cold aq. NH_4Cl (8 mL) and water (10 mL), then extracted with ether (3×15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (7:93, ether/petrol) afforded the target material identical with that obtained by Method 1 (368 mg, 44%).

R_f 0.51 (25:75, ether/petrol); ν_{max}/cm^{-1} 1706 s (C=O); δ_H (400 MHz, $CDCl_3$) 3.57 (2H, t, *J* = 6.5 Hz, H-7), 2.87 (1H, q, *J* = 8.0 Hz, H-1), 2.64 (2H, t, J = 6.5 Hz, H-5), 2.04 (2H, app. quint, J = 6.5 Hz, H-6), 1.88 – 1.51 (8H, m, H-2,3); δ_C (100 MHz, $CDCl_3$) 212.1 (C-4), 51.2 (C-1), 44.6 (C-7), 38.2 (C-5), 28.9 (C-2), 26.4 (C-6), 26.0 (C-3).

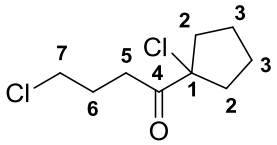
1-Cyclopentylpentan-1-one (407)[360]



A solution of *N*-methoxy-*N*-methylcyclopentanecarboxamide (43 mg, 0.27 mmol) in ether (1 mL) was cooled to 0 °C. To this was slowly added BuLi (1.6 M, 0.19 mL, 0.30 mmol). The mixture was stirred at 0 °C for 5 min, then diluted with wet ether (3 mL) and quenched with water (2 mL). The organic layer was separated, washed with brine (1 mL), dried ($MgSO_4$), and concentrated to give the title material as a colourless oil (40 mg, 100%).

R_f 0.66 (25:75, ether/petrol); ν_{max}/cm^{-1} 1710s (C=O). NMR data as reported.[360]

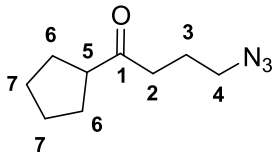
4-Chloro-1-(1-chlorocyclopentyl)butan-1-one (408)



4-Chloro-1-cyclopentylbutan-1-one (365 mg, 2.1 mmol) was dissolved in DCM (3 mL). To this, SO_2Cl_2 (0.34 mL, 4.2 mmol) was added dropwise and the resulting solution was stirred overnight. The reaction was diluted with ether (5 mL) and carefully quenched with water (1 mL) and aq. K_2CO_3 (2 M, ca. 2 mL, *caution: gas evolution*). The organic layer was separated, washed with brine (1 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5:95, ether/petrol) afforded the title material as a colourless oil (140 mg, 67%).

R_f 0.51 (1:4, ether/petrol); ν_{max}/cm^{-1} 1713s (C=O); δ_H (400 MHz, $CDCl_3$) 3.60 (2H, t, *J* = 6.5 Hz, H-7), 3.01 (2H, t, *J* = 7.0 Hz, H-5), 2.30 – 2.19 (2H, m, H-2a), 2.15 – 2.06 (4H, m, H-2b,6), 2.05 – 1.92 (2H, m, H-3a), 1.85 – 1.73 (2H, m, H-3b); δ_C (101 MHz, $CDCl_3$) 205.6 (C-4), 81.0 (C-1), 44.2 (C-7), 39.4 (C-2), 34.8 (C-5), 26.8 (C-6), 23.4 (C-3).

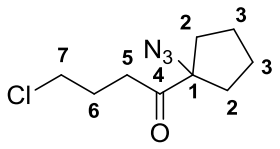
4-Azido-1-cyclopentylbutan-1-one (409)



4-Chloro-1-cyclopentylbutan-1-one (200 mg, 1.1 mmol) was dissolved in dry DMF (7 mL), followed by the addition of NaN_3 (150 mg, 2.2 mmol). The resulting suspension was stirred at 50 °C (oil bath) for 24 hr. The reaction mixture was cooled to RT and diluted with ether (20 mL) and water (10 mL). The aq. layer was extracted with ether (3×20 mL). The combined organic layers were washed with brine (15 ml) and dried over $MgSO_4$. Flash chromatography (1:9 → 1:3, ether/petrol) provided the target material as a colourless oil (192 mg, 95%).

R_f 0.29 (25:75, ether/petrol); ν_{max}/cm^{-1} 2092s (N_3), 1708s (C=O); δ_H (500 MHz, $CDCl_3$) 3.32 (2H, t, *J* = 6.5 Hz, H-4), 2.87 (1H, app. td, *J* = 8.0, 7.0 Hz, H-5), 2.56 (2H, t, *J* = 7.0 Hz, H-2), 1.85 (4H, t over m, *J* = 7.0 Hz, H-3,6), 1.77 – 1.54 (6H, m, H-6,7); δ_C (126 MHz, $CDCl_3$) 212.0 (C-1), 51.5 (C-5), 50.8 (C-4), 38.2 (C-2), 28.9 (C-6), 25.9 (C-7), 22.9 (C-3); HRMS (TOF FI^+), m/z: calcd for $C_9H_{15}N_3O$ [M^+] 181.1215, found 181.1213.

1-(1-Azidocyclopentyl)-4-chlorobutan-1-one (410)

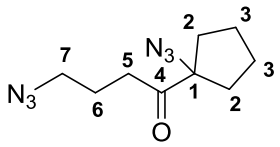


4-Chloro-1-(1-chlorocyclopentyl)butan-1-one (21 mg, 0.1 mmol) and NaN_3 (20 mg, 0.3 mmol) were dissolved in DMSO-d_6 (0.30 mL) and stirred overnight at RT. The reaction mixture turned into a yellow viscous solid. It was diluted with small amount of fresh DMSO-d_6 (ca. 0.1 mL) and loaded directly onto a pipette silica column (3:97, ether/petrol), collecting the mixed fraction with R_f 0.34 (5:95, ether/petrol). This

fraction was further separated on another pipette column (3:97, ether/petrol). The less polar compound, a yellowish oil, was the title monoazide (7 mg, 33%).

R_f 0.36 (5:95, ether/petrol); ν_{max}/cm^{-1} 2101s (N_3), 1714s (C=O); δ_H (500 MHz, $CDCl_3$) 3.59 (2H, t, *J* = 6.0 Hz, H-7), 2.83 (2H, t, *J* = 7.0 Hz, H-5), 2.12 – 2.01 (4H, m, H-2), 1.92 – 1.77 (6H, m, H-6,3); δ_C (126 MHz, $CDCl_3$) 208.4 (C-4), 79.1 (C-1), 44.4 (C-7), 35.6 (C-2), 35.2 (C-5), 26.5 (C-6), 24.7 (C-3).

4-Azido-1-(1-azidocyclopentyl)butan-1-one (411)



Isolated as a more polar side product in the synthesis of 1-(1-azidocyclopentyl)-4-chlorobutan-1-one. Flash chromatography (3:97, ether/petrol) afforded the title compound as a clear colourless oil (5 mg, 23%).

R_f 0.26 (5:95, ether/petrol); ν_{max}/cm^{-1} 2101s (N_3), 1714m (C=O); δ_H (500 MHz, $CDCl_3$) 3.35 (2H, t, *J* = 6.5 Hz, H-7), 2.74 (2H, t, *J* = 7.0 Hz, H-5), 2.13 – 1.99 (3H, m, H-2a), 1.95 – 1.77 (7H, m, H-2b,3,6); δ_C (126 MHz, $CDCl_3$) 208.2 (C-4), 78.9 (C-1), 50.6 (C-7), 35.4 (C-2), 35.0 (C-5), 24.6 (C-3), 22.9 (C-6).

References

(1) Vitaku, E.; Ilardi, E. A.; Njarðarson, J. T. Top 200 Pharmaceutical Products by US Retail Sales in 2012 http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012.

(2) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348–1349.

(3) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; 5th ed.; Wiley–Blackwell, 2010; p. 718.

(4) Anderson, E. A. *Org. Biomol. Chem.* **2011**, *9*, 3997–4006.

(5) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

(6) Brodney, M. A.; O'Leary, J. P.; Hansen, J.; Giguere, R. *Synth. Commun.* **1995**, *25*, 521–531.

(7) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

(8) Robinson, R. *J. Chem. Soc., Trans.* **1917**, *111*, 762–768.

(9) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: Weinheim, Cambridge, 1996; p. 821.

(10) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657–4673.

(11) *The Chemistry of the Allenes (vol. 1–3)*; Landor, S. R., Ed.; Academic Press: London, 1982.

(12) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317–359.

(13) Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216.

(14) Burton, B. S.; von Pechman, H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145–149.

(15) Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3208–3212.

(16) *The chemistry of ketenes, allenes, and related compounds (vol. 1–2)*; Patai, S., Ed.; Wiley: Chichester, New York, 1980.

(17) Coppola, G. M.; Schuster, H. F. *Allenes in Organic Synthesis*; Wiley: NY, 1984; p. 358.

(18) Brandsma, L. *Synthesis of acetylenes, allenes, cumulenes*; Elsevier: Amsterdam, 2003; p. 286.

(19) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805–2827.

(20) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3126.

(21) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91–102.

(22) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679–1688.

(23) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783–816.

(24) Pinho e Melo, T. M. V. D. *Monatsh. Chem.* **2011**, *142*, 681–697.

(25) López, F.; Mascareñas, J. L. *Chem. Eur. J.* **2011**, *17*, 418–428.

(26) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954–1993.

(27) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009.

(28) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150.

(29) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795–818.

(30) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384–5418.

(31) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García-Tellado, F. *Chem. Soc. Rev.* **2013**, *42*, 458–471.

(32) Doering, W. von E.; LaFlamme, P. M. *Tetrahedron* **1958**, *2*, 75–79.

(33) Skattebøl, L. *Acta Chem. Scand.* **1963**, *17*, 1683–1693.

(34) Skatteböl, L. *Tetrahedron Lett.* **1961**, *2*, 167–172.

(35) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1960**, *25*, 2073–2073.

(36) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1962**, *27*, 4179–4181.

(37) Skattebøl, L. *J. Org. Chem.* **1966**, *31*, 2789–2794.

(38) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099–1132.

(39) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier, 2005; p. 758.

(40) Shi, M.; Shao, L.-X.; Lu, J.-M.; Wei, Y.; Mizuno, K.; Maeda, H. *Chem. Rev.* **2010**, *110*, 5883–5913.

(41) Trost, B. M.; Pinkerton, A.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466–12476.

(42) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

(43) Bennett, P. A. R. Synthetic Approaches to the Alkaloid Himbacine. DPhil Thesis, University of Oxford, 1988.

(44) Baldwin, J. E.; Bennett, P. A. R.; Forrest, A. K. *J. Chem. Soc., Chem. Commun.* **1987**, 2–3.

(45) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186–15187.

(46) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180–6185.

(47) Saucy, G.; Marbet, R. *Helv. Chim. Acta* **1967**, *50*, 1158–1167.

(48) Kurtz, K. C. M.; Frederick, M. O.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 3928–3938.

(49) Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 2128–2136.

(50) Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867–6873.

(51) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074–3112.

(52) Ma, S. *Chem. Rev* **2005**, *105*, 2829–2872.

(53) Van 't Hoff, J. H. *La Chimie dans l'Espace*; P.M. Bazendijk, 1875; p. 43.

(54) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25–36.

(55) Lowe, G. *Chem. Commun. (London)* **1965**, 411–413.

(56) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions: Reference Edition*; Wiley, 2010; p. 526.

(57) Ma, S. *Pure Appl. Chem.* **2006**, *78*, 197–208.

(58) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12–21.

(59) Rahman, W.; Kuivila, H. G. *J. Org. Chem.* **1966**, *31*, 772–776.

(60) Wiesner, K. *Tetrahedron* **1975**, *31*, 1655–1658.

(61) Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 9019–9022.

(62) Griess, P. *Proc. R. Soc. London* **1864**, *13*, 375–384.

(63) Griess, P. *Justus Liebigs Ann. Chem.* **1866**, *137*, 39–91.

(64) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023–3033.

(65) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 778–781.

(66) Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–632.

(67) Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633–696.

(68) Geittner, J.; Huisgen, R. *Tetrahedron Lett.* **1977**, *18*, 881–884.

(69) *Organic Azides: Syntheses and Applications*; Bräse, S.; Banert, K., Eds.; Wiley, 2010; p. 507.

(70) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950.

(71) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

(72) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791–1815.

(73) Rostovtsev, V. V; Green, L. G.; Fokin, V. V; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.

(74) *The chemistry of the azido group*; Patai, S., Ed.; Interscience Publishers: London, 1971; p. 626.

(75) *Azides and Nitrenes—Reactivity and Utility*; Scriven, E. F. V, Ed.; Academic Press, Inc: Orlando, FL, 1984; p. 542.

(76) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; Wiley: New York, USA, 2002; Vol. 59, p. 940.

(77) Wolff, H. *Org. React.* **1946**, *3*, 337–349.

(78) Boyer, J.; Canter, F. *Chem. Rev.* **1954**, *45*, 1–57.

(79) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

(80) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.

(81) Righi, G.; D'Achille, C.; Pescatore, G.; Bonini, C. *Tetrahedron Lett.* **2003**, *44*, 6999–7002.

(82) Baran, P. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc* **2004**, *126*, 3726–3727.

(83) Shaffer, K. J.; Taylor, C. M. *Org. Lett.* **2006**, *8*, 3959–3962.

(84) Singh, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdottir, A. D. *Tetrahedron Lett.* **2003**, *44*, 9169–9171.

(85) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898.

(86) Kitamura, M.; Koga, T.; Yano, M.; Okauchi, T. *Synlett* **2012**, *23*, 1335–1338.

(87) Kitamura, M.; Yano, M.; Tashiro, N.; Miyagawa, S.; Sando, M.; Okauchi, T. *Eur. J. Org. Chem.* **2011**, 458–462.

(88) Lee, S.-H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139–2145.

(89) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343–345.

(90) Saito, S.; Bunyat, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309–5312.

(91) Titz, A.; Radic, Z.; Schwardt, O.; Ernst, B. *Tetrahedron Lett.* **2006**, *47*, 2383–2385.

(92) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712.

(93) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646.

(94) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.

(95) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197–1218.

(96) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1–17.

(97) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523–575.

(98) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112–8113.

(99) Alvares, Y. S. P.; Alves, M. J.; Azoia, N. G.; Bickley, J. F.; Gilchrist, T. L. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1911–1919.

(100) Wasserman, E.; Smolinsky, G.; Yager, W. A. *J. Am. Chem. Soc.* **1964**, *86*, 1963–1964.

(101) Klima, R. F.; Gudmundsdóttir, A. D. *J. Photochem. Photobiol., A* **2004**, *162*, 239–247.

(102) Travers, M. J.; Cowles, D. C.; Clifford, E. P.; Ellison, G. B.; Engelking, P. C. *J. Chem. Phys.* **1999**, *111*, 5349–5360.

(103) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805–816.

(104) Tarabara, I. N.; Kas'yan, A. O.; Yarovoi, M. Y.; Shishkina, S. V.; Shishkin, O. V.; Kas'yan, L. I. *Russ. J. Org. Chem.* **2004**, *40*, 992–998.

(105) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717–2720.

(106) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569–593.

(107) Geittner, J.; Huisgen, R.; Reissig, H.-U. *Heterocycles* **1978**, *11*, 109–120.

(108) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2009**, *13*, 1406–1431.

(109) Bleiholder, R. F.; Shechter, H. *J. Am. Chem. Soc.* **1968**, *90*, 2131–2137.

(110) Bottini, A. T.; Olsen, R. E. *J. Am. Chem. Soc.* **1962**, *84*, 195–199.

(111) Wedegaertner, D. K.; Kattak, R. K.; Harrison, I.; Cristie, S. K. *J. Org. Chem.* **1991**, *95*, 4463–4467.

(112) López, C. S.; Faza, O. N.; Feldman, K. S.; Iyer, M. R.; Hester II, D. K. *J. Am. Chem. Soc.* **2007**, *129*, 7638–7646.

(113) Quast, H.; Meichsner, G. *Chem. Ber.* **1987**, *120*, 1049–1058.

(114) Quast, H.; Risler, W. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 414–415.

(115) Quast, H.; Fuß, A.; Heublein, A.; Jakobi, H.; Seiferling, B. *Chem. Ber.* **1991**, *124*, 2545–2554.

(116) Quast, H.; Fuss, A.; Heublein, A. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 49–50.

(117) Quast, H.; Vélez, C. A. W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 213–214.

(118) Kindermann, M. K.; Poppek, R.; Rademacher, P.; Fuß, A.; Quast, H. *Chem. Ber.* **1990**, *123*, 1161–1168.

(119) Quast, H.; Jakobi, H. *Chem. Ber.* **1991**, *124*, 1619–1626.

(120) Quast, H.; Frank, R.; Heublein, A.; Schmitt, E. *Liebigs Ann. Chem.* **1980**, 1814–1835.

(121) Quast, H.; Frank, R. *Liebigs Ann. Chem.* **1980**, 1939–1945.

(122) Quast, H.; Schmitt, E.; Frank, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 651–652.

(123) Quast, H.; Schmitt, E. *Chem. Ber.* **1970**, *103*, 1234–1249.

(124) Giera, H.; Huisgen, R.; Polborn, K. *Eur. J. Org. Chem.* **2005**, 3781–3790.

(125) Dowd, P. *J. Am. Chem. Soc.* **1966**, *88*, 2587–2589.

(126) De Kimpe, N.; Boeykens, M. *J. Org. Chem.* **1994**, *59*, 5189–5191.

(127) Hassner, A.; Amarasekara, A. S.; Andisik, D. *J. Org. Chem.* **1988**, *53*, 27–30.

(128) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 4846–4855.

(129) Li, J.; Worthington, S. E.; Cramer, C. J. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1045–1051.

(130) Feldman, K. S.; Iyer, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 4590–4591.

(131) Feldman, K. S.; Iyer, M. R.; Hester II, D. K. *Org. Lett.* **2006**, *8*, 3113–3116.

(132) Feldman, K. S.; Iyer, M. R.; Silva López, C.; Nieto Faza, O. *J. Org. Chem.* **2008**, *73*, 5090–5099.

(133) Feldman, K. S.; Hester, D. K.; López, C. S.; Faza, O. N. *Org. Lett.* **2008**, *10*, 1665–1668.

(134) Feldman, K. S.; Hester II, D. K.; Iyer, M. R.; Munson, P. J.; Lopez, C. S.; Faza, O. N. *J. Org. Chem.* **2009**, *74*, 4958–4974.

(135) Faza, O. N.; Feldman, K. S.; López, C. S. *Curr. Org. Chem.* **2010**, *14*, 1646–1657.

(136) Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934–937.

(137) Feldman, K. S.; Antoline, J. F. *Tetrahedron* **2013**, *69*, 1434–1445.

(138) Huang, X.; Zhu, S.; Shen, R. *Adv. Synth. Catal.* **2009**, *351*, 3118–3122.

(139) Huang, X.; Shen, R.; Zhang, T. *J. Org. Chem.* **2007**, *72*, 1534–1537.

(140) Gai, X.; Grigg, R.; Rajviroongit, S.; Songarsa, S.; Sridharan, V. *Tetrahedron Lett.* **2005**, *46*, 5899–5902.

(141) Chang, H.-M.; Cheng, C.-H. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3799–3807.

(142) Unsworth, W. P.; Robertson, J.; Lamont, S. *Abstr. Pap. Am. Chem. Soc.* **2009**, *239*, 75–ORGN.

(143) Unsworth, W. P. Rhodium(II) Catalysed Oxyamination Reactions. DPhil Thesis, University of Oxford, 2010.

(144) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598–600.

(145) Feast, G. C.; Page, L. W.; Robertson, J. *Chem. Commun.* **2010**, *46*, 2835–2837.

(146) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198–14199.

(147) Feast, G. C. Aziridinations of tethered allenes. DPhil. Thesis, University of Oxford, 2010.

(148) Robertson, J.; Feast, G. C.; White, L. V; Steadman, V. A.; Claridge, T. D. W. *Org. Biomol. Chem.* **2010**, *8*, 3060–3063.

(149) Brown, C. Intramolecular allene and azide cycloadditions. Part II Thesis, University of Oxford, 2011.

(150) Ungureanu, A. Cascade reactions of azidoalkyl allenes: generation and trapping of azatrimethylenemethane intermediates. Part II Thesis, University of Oxford, 2013.

(151) Crandall, J. K.; Tindell, G. L. *Chem. Commun.* **1970**, 1411–1412.

(152) Beumel Jr, O. F.; Harris, R. F. *J. Org. Chem.* **1964**, *29*, 1872–1876.

(153) Takeshi, N.; Ichiro, Y.; Hidenori, M.; Ikuo, K.; Akihiro, I.; Tetsuyuki, N. Antiulcer compounds having a substituted alkynyl or quinoxaline nucleus and methods of making thereof. U.S. Patent 5,583,227 A1,. 5583227, 1996.

(154) Wotiz, J. H.; Celmer, W. D. *J. Am. Chem. Soc.* **1952**, *74*, 1860–1861.

(155) Wotiz, J. H.; Mancuso, D. E. *J. Org. Chem.* **1957**, *22*, 207–211.

(156) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977–1980.

(157) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110–7113.

(158) Myers, A.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492–4493.

(159) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507–7507.

(160) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208–8210.

(161) Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *30*, 5747–5750.

(162) Negishi, E.; Cederbaum, F.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.

(163) Zhang, H.; Fu, X.; Chen, J.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 9351–9358.

(164) Pasto, D. J.; Chou, S. K.; Fritzen, E.; Shults, R. H.; Waterhouse, A.; Hennion, G. F. *J. Org. Chem.* **1978**, *43*, 1389–1394.

(165) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928–3938.

(166) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289–3292.

(167) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(168) Gilman, H.; Straley, J. M. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 821.

(169) *Organocopper Reagents*; Taylor, R. K., Ed.; Oxford University Press: Oxford, 1994; p. 362.

(170) Bertz, S.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251–4254.

(171) Hung, S.-C.; Wen, Y.-F.; Chang, J.-W.; Liao, C.-C.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1308–1313.

(172) Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316–321.

(173) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 472–484.

(174) Kuntz Jr, I. D.; Schleyer, P. von R.; Allerhand, A. *J. Chem. Phys.* **1961**, *35*, 1533–1534.

(175) Stephany, R. W.; de Bie, M. J. A.; Drenth, W. *Org. Magn. Reson.* **1974**, *6*, 45–47.

(176) Liddon, J. T. R.; Robertson, J. Unpublished results.

(177) Schneider, H.; Thomas, F. *J. Am. Chem. Soc.* **1980**, *102*, 1424–1425.

(178) Finiels, A.; Geneste, P. *J. Org. Chem.* **1979**, *44*, 1577–1578.

(179) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; 3rd ed.; Plenum Press: London, 1990; p. 802.

(180) Ringham, E. M.; Gilbert, J. C. *J. Org. Chem.* **1975**, *40*, 224–228.

(181) Ley, S. V; Baxendale, I. R. In *Systems Chemistry*; Bozen, 2008; pp. 65–86.

(182) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.

(183) Feast, G. C.; Robertson, J. Unpublished results.

(184) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945–1955.

(185) Beard, C. D.; Craig, J. C.; Solomon, M. D. *J. Am. Chem. Soc.* **1974**, *96*, 7944–7949.

(186) Craig, J. C.; Beard, C. D. *Chem. Commun.* **1971**, 691–692.

(187) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383–405.

(188) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2283–2285.

(189) Salaun, J.; Marguerite, J. *Org. Synth.* **1985**, *63*, 147–179.

(190) Skell, P. S.; Garner, A. Y. *J. Am. Chem. Soc.* **1956**, *78*, 5430–5433.

(191) Doering, W. von E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.

(192) Witiak, D. T.; Tomita, K.; Patch, R. J. *J. Med. Chem.* **1981**, *24*, 788–794.

(193) Corey, E.; Desai, M. *Tetrahedron Lett.* **1985**, *26*, 5747–5748.

(194) Kopp, R.; Hanack, M. *Angew. Chem. Int. Ed.* **1975**, *15*, 821–822.

(195) Harwood, L. M.; Moody, C. J. *Experimental Organic Chemistry*; Blackwell Scientific: Oxford, 1994; p. 778.

(196) McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390.

(197) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Fujii, N.; Tanaka, T. *Eur. J. Chem.* **2007**, *13*, 1692–1708.

(198) Yoshida, Y.; Okamoto, S.; Sato, F. *J. Org. Chem.* **1996**, *61*, 7826–7831.

(199) Katsuhira, T.; Harada, T.; Oku, A. *J. Org. Chem.* **1994**, *59*, 4010–4014.

(200) Hartzler, H. D. *J. Am. Chem. Soc.* **1959**, *81*, 48–49.

(201) Hartzler, H. D. *J. Am. Chem. Soc.* **1961**, *83*, 4990–4996.

(202) Hartzler, H. D. *J. Am. Chem. Soc.* **1961**, *83*, 4997–4999.

(203) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1–40.

(204) Hoffmann, H. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 556–577.

(205) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.

(206) Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476–486.

(207) Townsend, C. A.; Scholl, T.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1975**, 921–922.

(208) Fort, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 4979–4981.

(209) Chidgey, R.; Hoffmann, H. *Tetrahedron Lett.* **1977**, *18*, 2633–2636.

(210) Foley, D. a.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 1131–1175.

(211) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904–8922.

(212) Gung, B. W.; Craft, D. T.; Bailey, L. N.; Kirschbaum, K. *Chem. Eur. J.* **2010**, *16*, 639–644.

(213) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934.

(214) Montserrat, S.; Faustino, H.; Lledós, A.; Mascareñas, J. L.; López, F.; Ujaque, G. *Chem. Eur. J.* **2013**, *19*, 15248–15260.

(215) Fernández, I.; Mascareñas, J. L. *Org. Biomol. Chem.* **2012**, *10*, 699–704.

(216) Alonso, I.; Faustino, H.; López, F.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11496–11500.

(217) Gung, B. W.; Bailey, L. N.; Wonser, J. *Tetrahedron Lett.* **2010**, *51*, 2251–2253.

(218) Gung, B. W.; Craft, D. T. *Tetrahedron Lett.* **2009**, *50*, 2685–2687.

(219) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6517–6519.

(220) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 7688–7691.

(221) Rogers, C.; Keay, B. *Can. J. Chem.* **1992**, *70*, 2929–2947.

(222) Nash, B. S. Oxidative Cyclisation of 2-(omega-Aminoalkyl)furan Derivatives. Part II Thesis, University of Oxford, 2007.

(223) Hashmi, A.; Schwarz, L. *Chem. Ber./ Recl.* **1997**, *130*, 1449–1456.

(224) Föhlisch, B.; Herter, R. *Chem. Ber.* **1984**, *117*, 2580–2596.

(225) Ryoichi, A.; Toshiro, S.; Yasuhiro, M.; Chizuko, T.; Yoshikuni, T. Alpha-aminoketone derivatives. U.S. Patent 5,422,359,, 1995.

(226) Baldwin, J. E.; Hoefle, G. A.; Lever, O. W. J. *J. Am. Chem. Soc.* **1974**, *96*, 7125–7127.

(227) Harmata, M.; Fletcher, V. R.; Claassen II, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9861–9862.

(228) Hinz, A.; Meyer, G.; Schucking, G. *Chem. Ber.* **1943**, *76*, 676–689.

(229) Zeelen, F. J.; Groen, M. B. Cyclosation substrates and related 11alpha-equatorially-substituted steroids. U.S. Patent 4,221,713,, 1980.

(230) Chudinov, Y. B.; Gashev, S. B.; Chernysheva, N. B.; Semenov, V. V. *Russ. Chem. Bull.* **2006**, *55*, 123–136.

(231) Evans, D. A.; Shaw, J. T. Soft Enolization : A Powerful Method for Diastereoselective Carbon-Carbon Bond Formation.

http://www.researchgate.net/publication/228539940_Soft_Enolization_A_Powerful_Method_for_Diastereoselective_Carbon-Carbon_Bond_Formation/file/9c9605216456a53e78.pdf.

(232) Yu, F.; Miller, D. J.; Allemann, R. K. *Chem. Commun.* **2007**, 4155–4157.

(233) Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; Mcdonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896–902.

(234) Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. *Org. Lett.* **2010**, *12*, 5740–5743.

(235) Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 296–301.

(236) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352–10353.

(237) Krapcho, A. P.; Lovey, A. J. *Synthesis* **1982**, 893–914.

(238) Collonges, F.; Descotes, G. *Bull. Chem. Soc. Fr.* **1973**, 3491–3493.

(239) Mori, T.; Inoue, Y. In *Synthetic Organic Photochemistry*; Taylor & Francis, 2005; pp. 417–452.

(240) Pünner, F.; Schmidt, A.; Hilt, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1270–1273.

(241) Berges, D. A.; Snipes, E. R.; Chan, G. W. *Tetrahedron Lett.* **1981**, *22*, 3557–3560.

(242) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313–1350.

(243) Gevorgyan, V.; Tando, K.; Uchiyama, N.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7022–7025.

(244) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391–6402.

(245) Trost, B. M.; Bartlett, M. J. *Org. Lett.* **2012**, *14*, 1322–1325.

(246) Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalvoda, J.; Kaufmann, H.; Wieland, P.; Anner, G. *Helv. Chim. Acta* **1967**, *50*, 2101–2108.

(247) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446–450.

(248) Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89–93.

(249) Avignon-Tropis, M.; Pougny, J. R. *Tetrahedron Lett.* **1989**, *30*, 4951–4952.

(250) Boland, W.; Shroer, N.; Sieler, C. *Helv. Chim. Acta* **1987**, *70*, 1025–1040.

(251) Novis Smith, W.; Beumel Jr, O. F. *Synthesis* **1974**, 441–442.

(252) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586–6594.

(253) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1095–1098.

(254) Ou, Y.; Li, Y.; Qian, X.; Shen, Y. *Phytochemistry* **2012**, *78*, 190–196.

(255) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901.

(256) Singh, M.; Janso, J.; Luckman, S.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256–261.

(257) Brady, S.; Singh, M.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2117.

(258) Gampe, C. M.; Carreira, E. M. *Chem. Eur. J.* **2012**, *18*, 15761–15771.

(259) Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738–4744.

(260) Ishihara, Y.; Baran, P. *Synlett* **2010**, 1733–1745.

(261) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev.* **2013**, *113*, PR1–PR40. DOI:10.1021/cr300129n.

(262) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 585–607.

(263) Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273.

(264) Ferraz, H. M. C.; Bombonato, F. I.; Longo Jr, L. S. *Synthesis* **2007**, 3261–3285.

(265) Back, T. G. *Tetrahedron* **1977**, *33*, 3041–3059.

(266) Rathke, M.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318–2320.

(267) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603–4614.

(268) Jacobsen, N. E. *NMR Spectroscopy Explained*; Wiley: Hoboken, NJ, 2007; p. 668.

(269) Inanaga, J.; Hirata, K.; H, S.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(270) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283.

(271) Funk, R. L.; Awlman, M. M.; Munger, J. D. J. *Tetrahedron* **1986**, *42*, 2831–2846.

(272) Abelman, M. M.; Funk, R. L.; Munger, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 4030–4032.

(273) Funk, R.; Munger, J. *J. Org. Chem.* **1984**, *49*, 4319–4320.

(274) Funk, R.; Munger, J. *J. Org. Chem.* **1985**, *50*, 707–709.

(275) Funk, R.; Abelman, M. *J. Org. Chem.* **1986**, *51*, 3247–3248.

(276) Magriotis, P. A.; Kim, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2912–2913.

(277) Vourloumis, D.; Kim, K. D.; Petersen, J. L.; Magriotis, P. A. *J. Org. Chem* **1996**, *61*, 4848–4852.

(278) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–72.

(279) Kobayashi, S.; Manabe, K.; Ishitani, H.; Matsuo, J.-I. In *Science of Synthesis*; 2002; pp. 317–370.

(280) Robertson, J. Unpublished results.

(281) Lieber, E.; Rao, C. N. R.; Chao, T. S.; Hoffman, C. W. W. *Anal. Chem.* **1957**, *29*, 916–918.

(282) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831–1847.

(283) Holub, J. M.; Jang, H.; Kirshenbaum, K. *Org. Lett.* **2007**, *9*, 3275–3278.

(284) Barbosa, L.; Rubinger, M.; Mann, J.; Mansell, H. *Tetrahedron* **1996**, *52*, 11297–11306.

(285) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467–4468.

(286) Kitching, W.; Penman, K. G.; Laycock, B.; Maynard, I. *Tetrahedron* **1988**, *44*, 3819–3831.

(287) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, *20*, 675–678.

(288) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978–979.

(289) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Lett.* **2009**, *11*, 5034–5037.

(290) Arjona, O.; Iradier, F.; Medel, R.; Plumet, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3431–3442.

(291) Whitehouse, C. J. C.; Bell, S. G.; Wong, L.-L. *Chem. Soc. Rev.* **2012**, *41*, 1218–1260.

(292) W.L.F. Armarego; Chai, C. *Purification of Laboratory Chemicals*; 6th ed.; Butterworth-Heinemann: Oxford, 2009; p. 760.

(293) Keller, R.; Wycoff, H. *Inorg. Synth.* **1946**, *2*, 1–4.

(294) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(295) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.

(296) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.

(297) Iwasaki, T.; Agura, K.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Chem. Eur. J.* **2010**, *16*, 11567–11571.

(298) Midland, M. *J. Org. Chem.* **1975**, *40*, 2250–2252.

(299) Carlson, R.; Cox, W. *J. Org. Chem.* **1977**, *42*, 2382–2386.

(300) Schneekloth Jr., J. S.; Pucheault, M.; Crews, C. M. *Eur. J. Org. Chem.* **2007**, 40–43.

(301) Fu, C.; Ma, S. *Org. Lett.* **2005**, *7*, 1707–1709.

(302) Jonasson, C.; Horvath, A.; Bäckwall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600–9609.

(303) Lalonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 598–601.

(304) Crandall, J. K.; Reix, T. *J. Org. Chem.* **1992**, *57*, 6759–6764.

(305) Kleinbeck, F.; Toste, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 9178–9179.

(306) Corey, E.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(307) Ghosh, N.; Nayak, S.; Sahoo, A. K. *J. Org. Chem.* **2011**, *76*, 500–511.

(308) Yotsu-Yamashita, M.; Yasumoto, T.; Rawal, V. H. *Heterocycles* **1998**, *48*, 79–93.

(309) Wilson, S. R.; Zucker, P. A. *J. Org. Chem.* **1988**, *53*, 4682–4693.

(310) Aikawa, K.; Kojima, M.; Mikami, K. *Adv. Synth. Catal.* **2010**, *352*, 3131–3135.

(311) Hughes, D. J.; Livinghouse, T. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2373–2374.

(312) Morimoto, T.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 1758–1759.

(313) Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7014–7018.

(314) Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375–2376.

(315) Stefani, H. A.; Menezes, P. H.; Costa, I. M.; Silva, D. O.; Petragnani, N. *Synlett* **2002**, 1335–1337.

(316) Salaun, J.; Hanack, M. *J. Org. Chem.* **1975**, *40*, 1994–1998.

(317) Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K. *Chem. Commun.* **2002**, 724–725.

(318) Montierth, J. M.; Demario, D. R.; Kurth, M. J.; Schore, N. E. *Tetrahedron* **1998**, *54*, 11741–11748.

(319) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2008**, *10*, 4489–4492.

(320) Kao, C.; Kittleman, W.; Zhang, H.; Seto, H.; Liu, H. *Org. Lett.* **2005**, *7*, 5677–5680.

(321) Alonso, F.; Rodríguez-Fernández, M.; Sánchez, D.; Yus, M. *Synthesis* **2010**, 3013–3020.

(322) Smith III, A. B.; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099–3102.

(323) Diez-Barra, E.; de la Hoz, A.; Loupy, A.; Sanchez-Migallon, A. *J. Heterocycl. Chem.* **1994**, *31*, 1715–1717.

(324) Levchenko, E. S. .; Bal'on, Y. G. *Zhurnal Org. Khimii [in Russian]* **1967**, *3*, 1509–1512.

(325) Brittain, J. M.; Jones, R. A.; Arques, J. S.; Saliente, T. A. *Synth. Commun.* **1982**, *12*, 231–248.

(326) Hasan, I.; Marinelli, E. R.; Lin, L. C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157–164.

(327) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017–1018.

(328) Wuts, P.; Jung, Y.-W. *J. Org. Chem.* **1991**, *56*, 365–372.

(329) Taillefer, M.; Cristau, H.-J.; Cellier, P.-P. Method of forming a carbon-carbon or carbon-heteroatom linkage. U.S. Patent 2005/0234239,. US 2005/0234239 A1, 2005.

(330) Hilt, G.; Lüers, S. *Synthesis* **2002**, 609–618.

(331) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1984**, *50*, 560–565.

(332) Haynes, R. K.; Lam, K.-P.; Wu, K.-Y.; Williams, I. D.; Yeung, L.-L. *Tetrahedron* **1999**, *55*, 89–118.

(333) Baker, M. V.; Brown, D. H.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **2000**, 4607–4616.

(334) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223–6225.

(335) Ashikari, Y.; Nokami, T.; Yoshida, J. *Org. Lett.* **2012**, *14*, 938–941.

(336) Chemin, D.; Linstrumelle, G. *Tetrahedron* **1994**, *50*, 5335–5344.

(337) Keegstra, M. A.; Verkruijsse, H. D.; Andringa, H.; Brandsma, L. *Synth. Commun.* **1991**, *21*, 721–726.

(338) Bloch, R.; Abecassis, J.; Hassan, E. T. D. *Can. J. Chem.* **1984**, *62*, 2019–2024.

(339) Koo, S.; Chong, B.; Ji, Y.; Oh, S.; Yang, J.; Baik, W. *J. Org. Chem.* **1997**, *62*, 9323–9325.

(340) Audin, P.; Doutheau, A.; Gore, J. *Bull. Chem. Soc. Fr.* **1984**, 297–306.

(341) Cornish, C. A.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2585–2598.

(342) Johnston, B.; Oehlschlager, A. *J. Org. Chem.* **1982**, *47*, 5384–5386.

(343) Kohda, A.; Nagayoshi, K.; Maemoto, K.; Sato, T. *J. Org. Chem.* **1983**, *48*, 425–432.

(344) Nyström, J.-E.; McCanna, T. D.; Helquist, P.; Amouroux, R. *Synthesis* **1988**, 56–58.

(345) Ohmiya, H.; Yang, M.; Yamauchi, Y.; Ohtsuka, Y.; Sawamura, M. *Org. Lett.* **2010**, *12*, 1796–1799.

(346) Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, I. Y.; Kampf, J. W. *J. Org. Chem.* **2007**, *72*, 4135–4148.

(347) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662–5671.

(348) Merlic, C. A.; Aldrich, C. C.; Albaneze-walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297–1309.

(349) Poirier, J.-M.; Dujardin, G. *Heterocycles* **1987**, *25*, 399–407.

(350) Vereshchagin, L. I.; Korshunov, S. P.; Skoblikova, V. I.; Aleksandrova, S. L. *Zh. Obshch. Khim.* **1964**, *34*, 1419–1427.

(351) Joung, M. J.; Ahn, J. H.; Yoon, N. M. *J. Org. Chem.* **1996**, *61*, 4472–4475.

(352) Karthikeyan, J.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2010**, *16*, 8989–8992.

(353) Klein, S. M.; Zhang, C.; Jiang, Y. L. *Tetrahedron Lett.* **2008**, *49*, 2638–2641.

(354) Mancini, I.; Cavazza, M.; Guella, G.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2181–2185.

(355) Bartels, B.; Hunter, R. *J. Org. Chem.* **1993**, *58*, 6756–6765.

(356) Enholm, E. J.; Whitley, P. E.; Xie, Y. *J. Org. Chem.* **1996**, *61*, 5384–5390.

(357) Selvamurugan, V.; Aidhen, I. S. *Synthesis* **2001**, 2239–2246.

(358) White, J. M.; Tunoori, A. R.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2004**, *69*, 2573–2576.

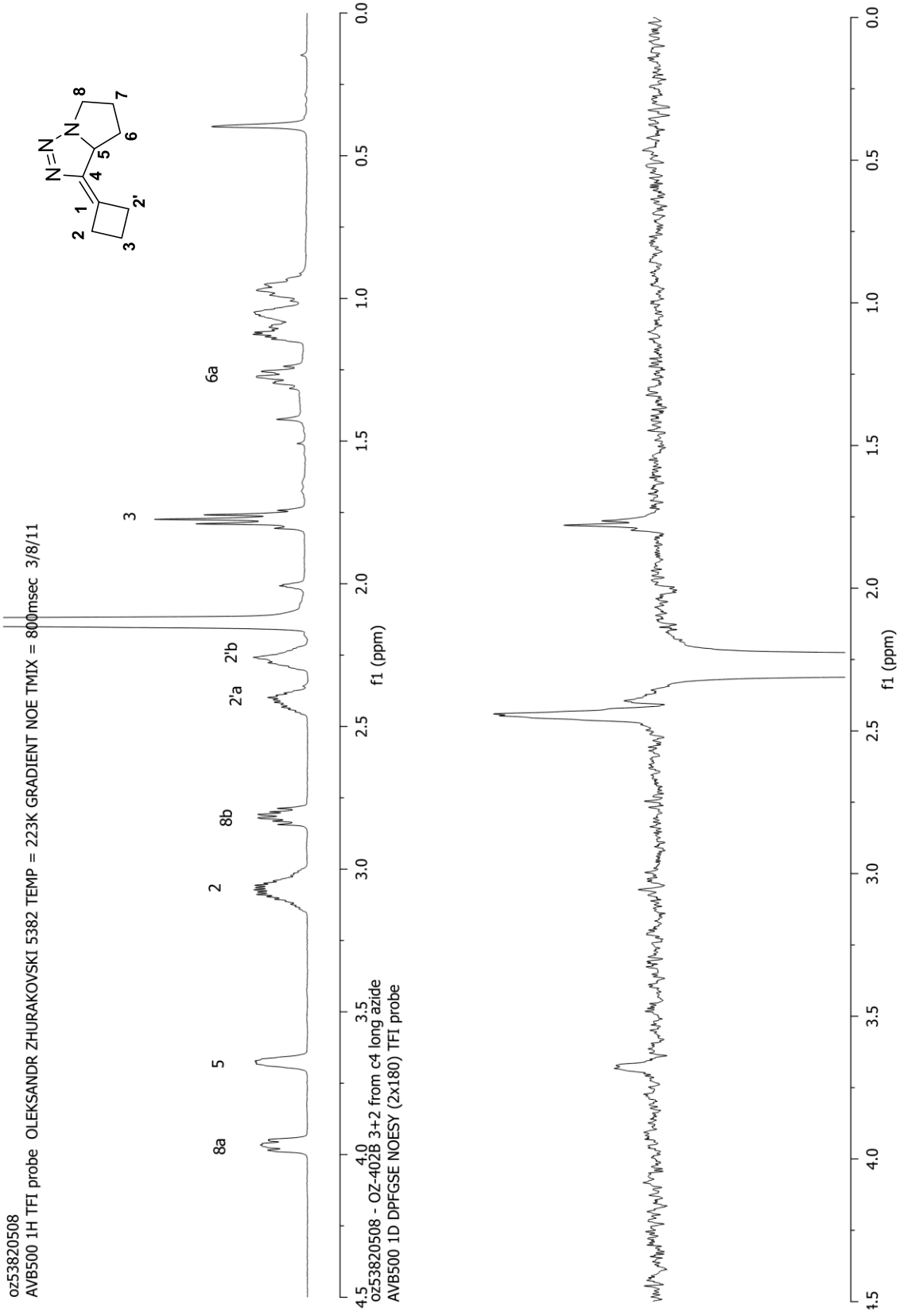
(359) Uchida, M.; Komatsu, M.; Morita, S.; Kanbe, T.; Yamasaki, K.; Nakagawa, K. *Chem. Pharm. Bull.* **1989**, *37*, 958–961.

(360) Yamamoto, Y.; Kondo, K.; Moritani, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3682–3685.

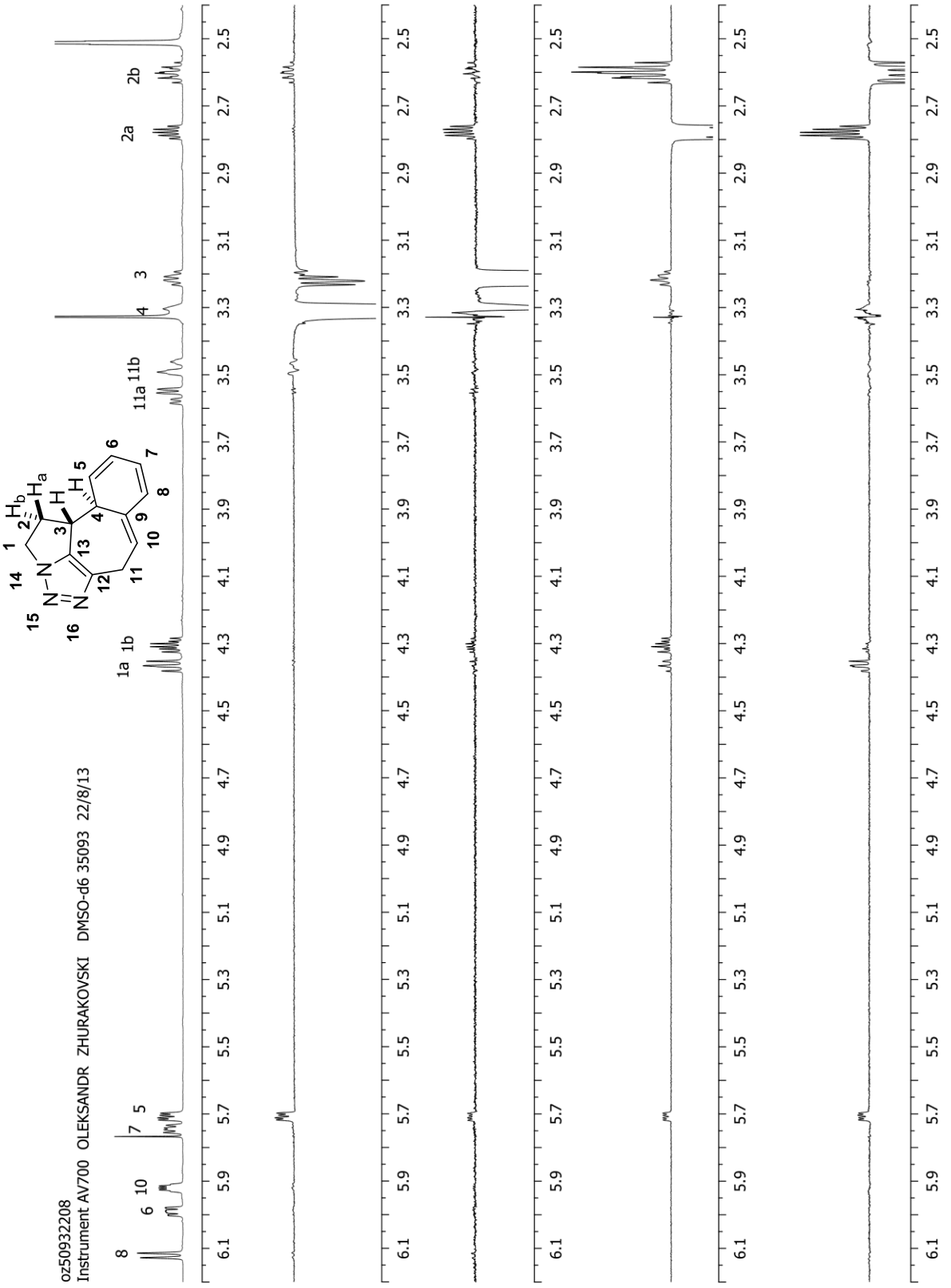
(361) Wang, Z. J.; Brown, C. J.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 7358–7360.

(362) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

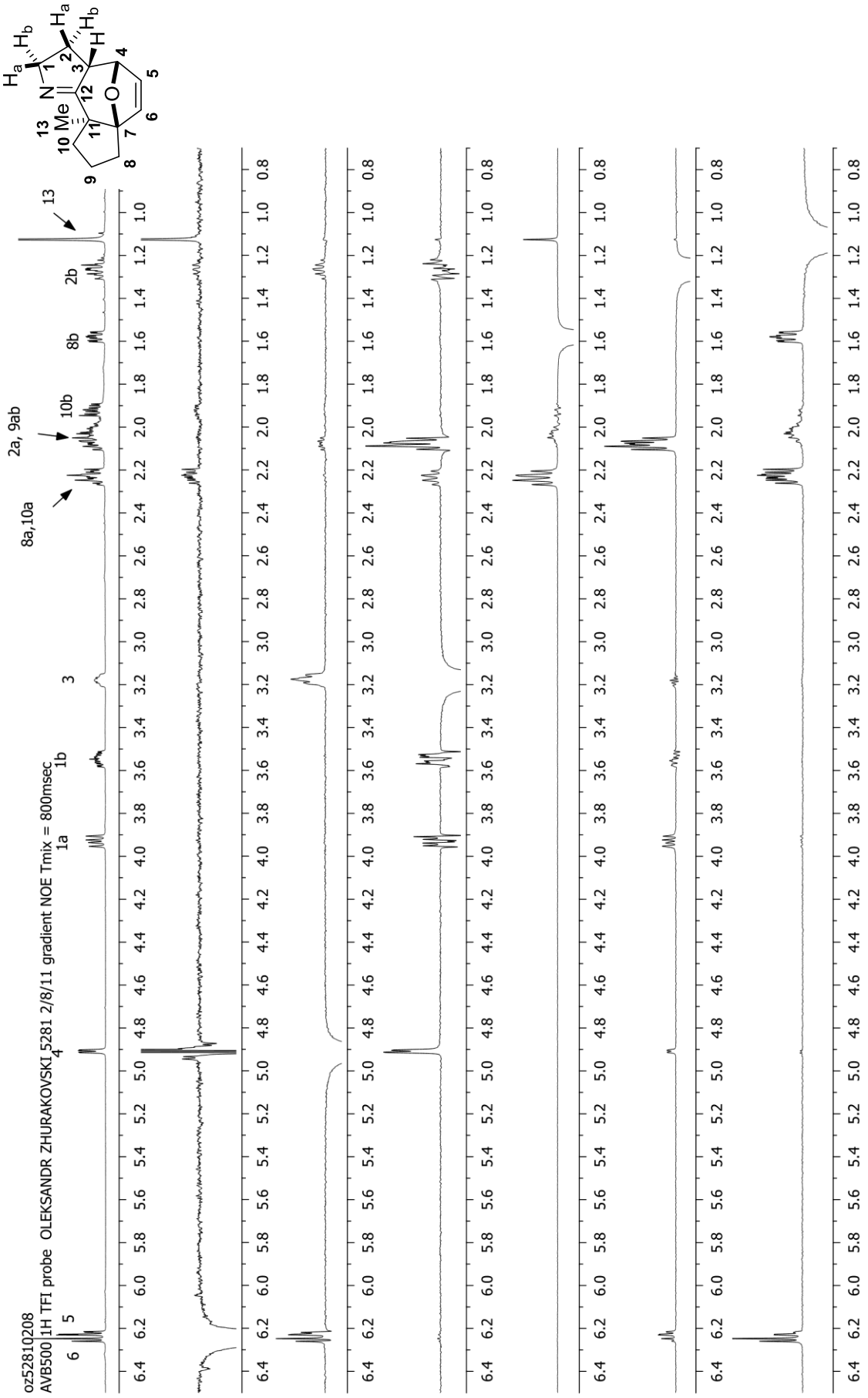
Appendix 1. NOE Spectrum of Compound 163



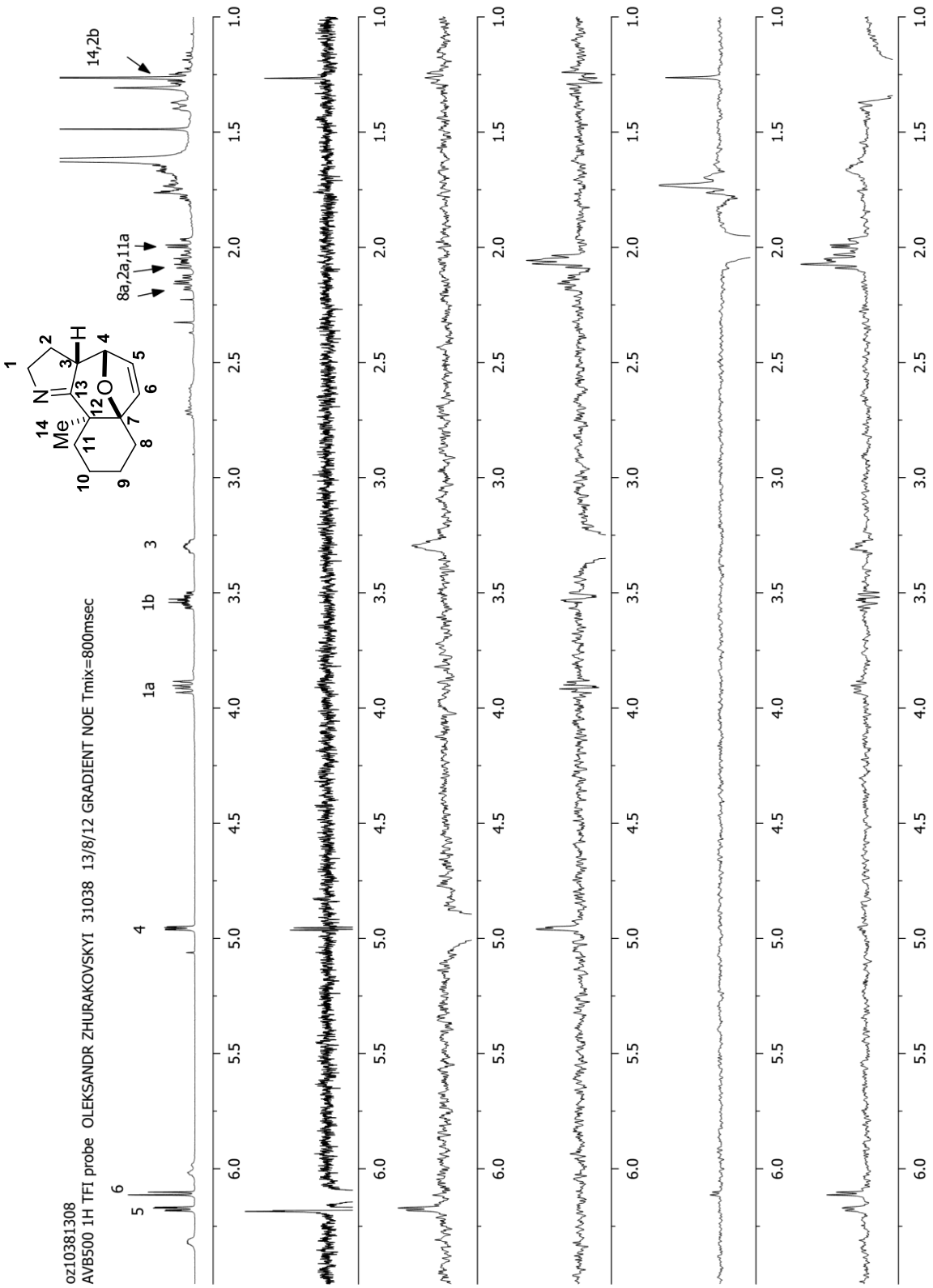
Appendix 2. NOE Spectra of Compound 210



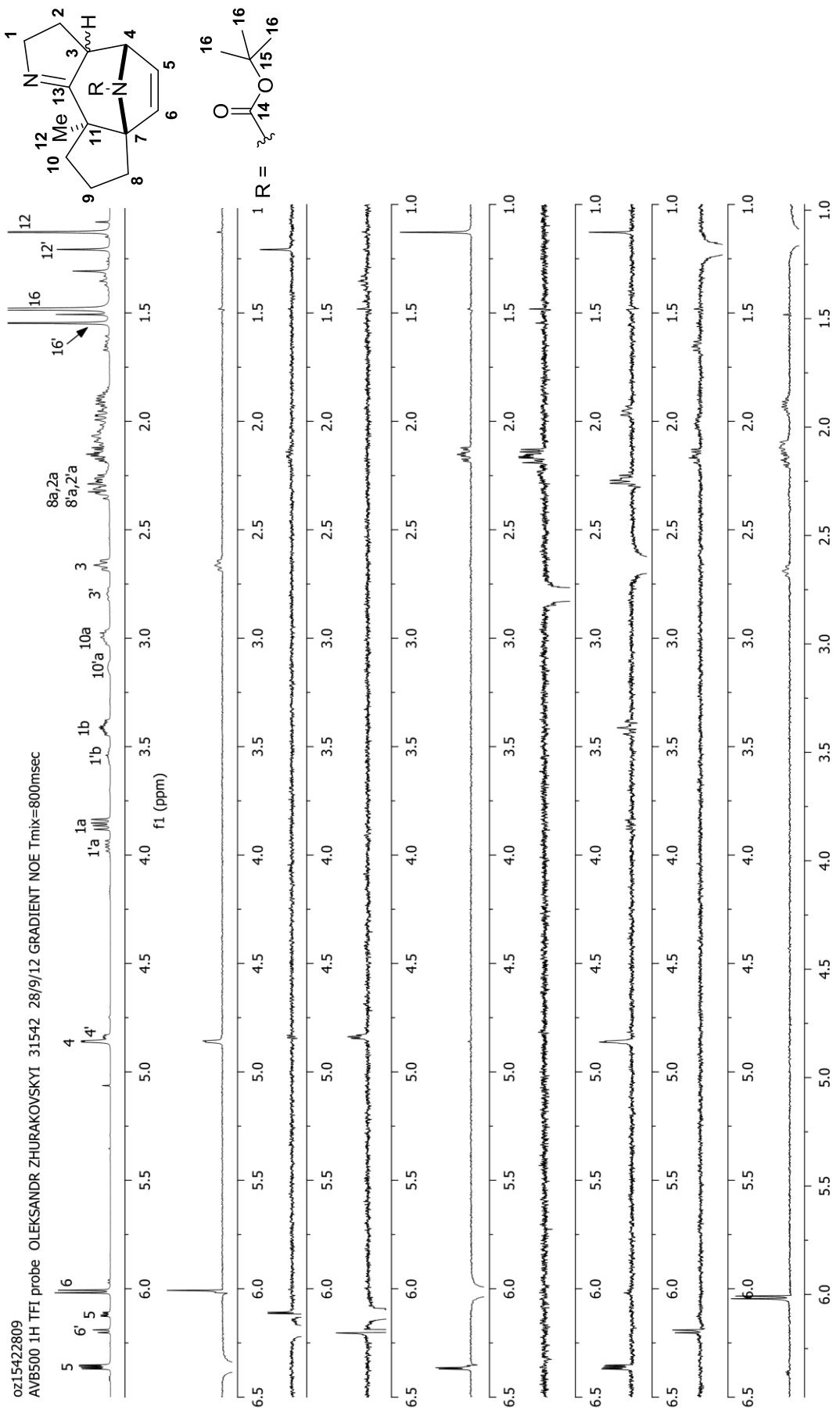
Appendix 3. NOE Spectra of Compound 275



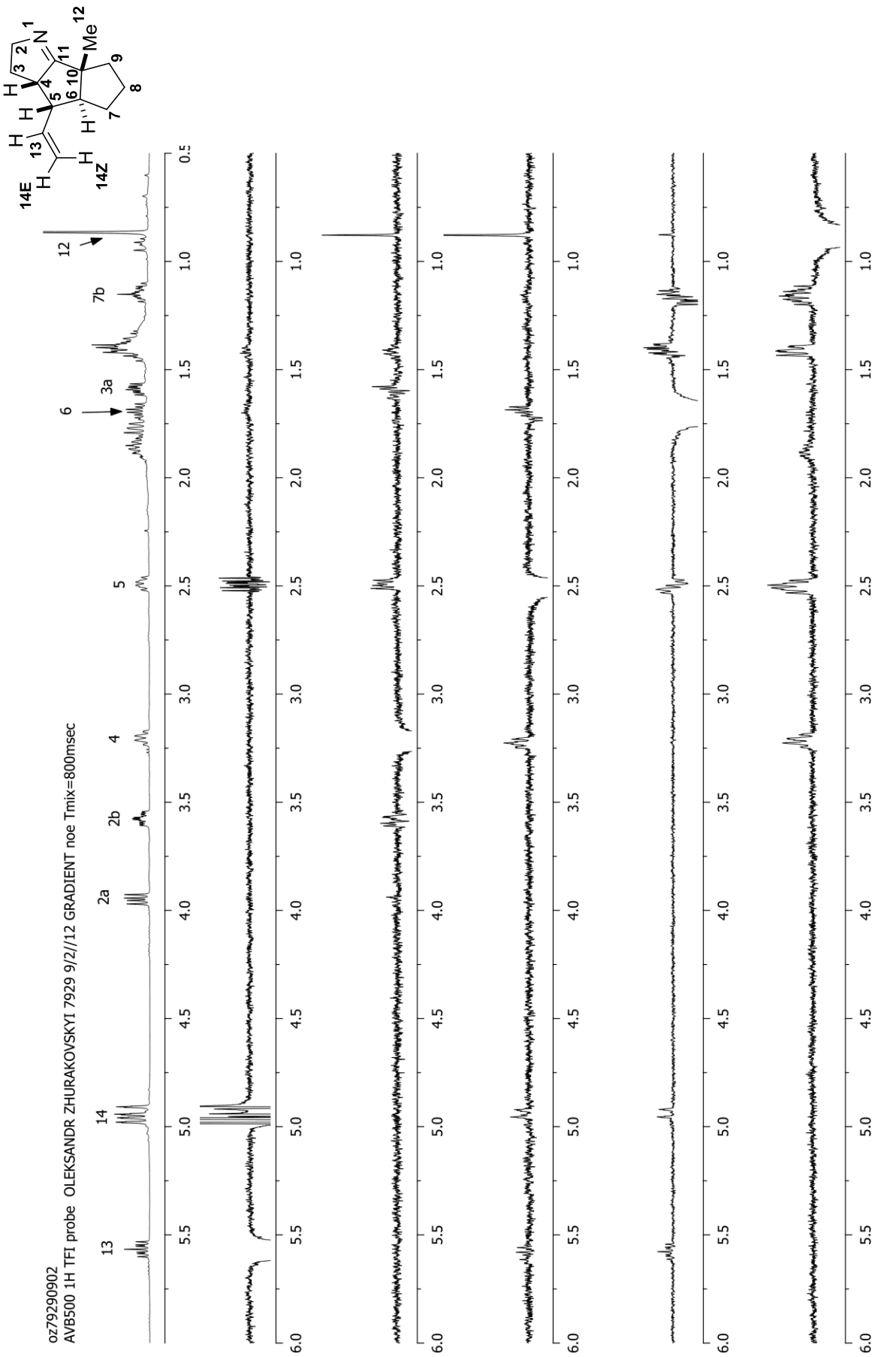
Appendix 4. NOE Spectra of Compound 276



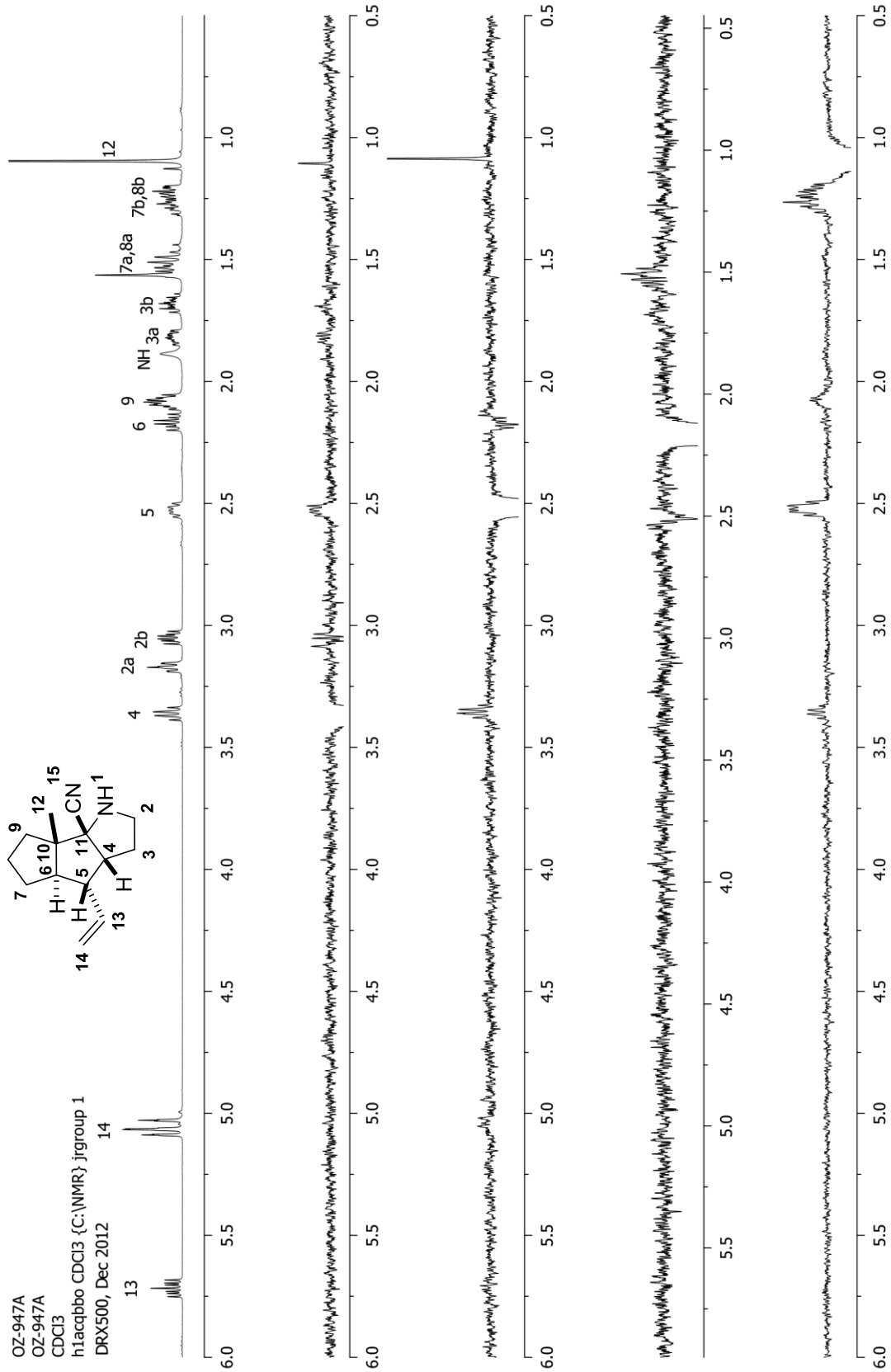
Appendix 5. NOE Spectra of Compound 287



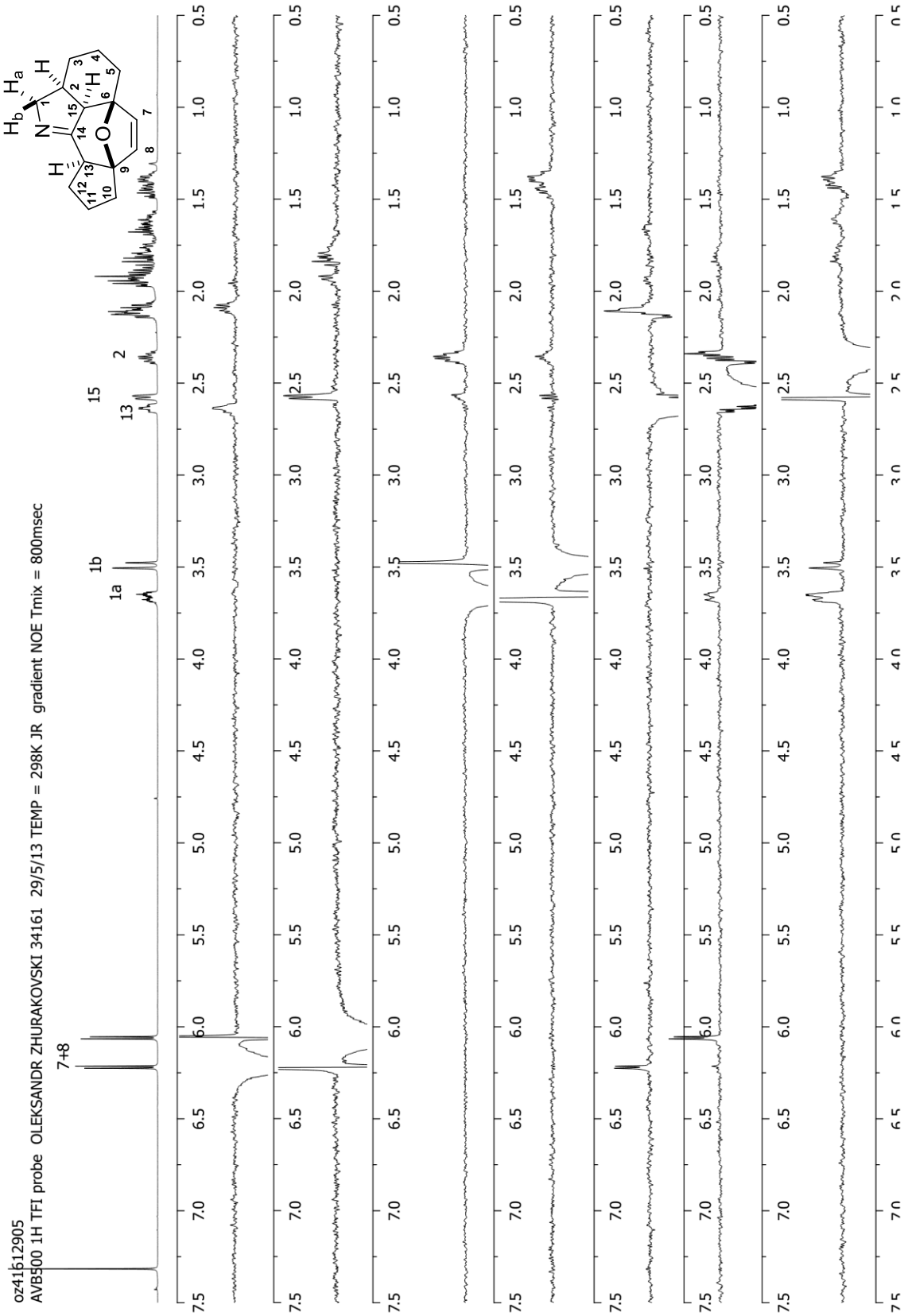
Appendix 6. NOE Spectra of Compound 325



Appendix 7. NOE Spectra of Compound 326



Appendix 8. NOE Spectra of Compound 332



Appendix 9. HMBC Spectrum of Compound 360