

Synthesis of Furanocycloalkanes from Furans and Non-aromatic Precursors

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Abstract

Synthesis of Furanocycloalkanes from Furans and Non-aromatic Precursors

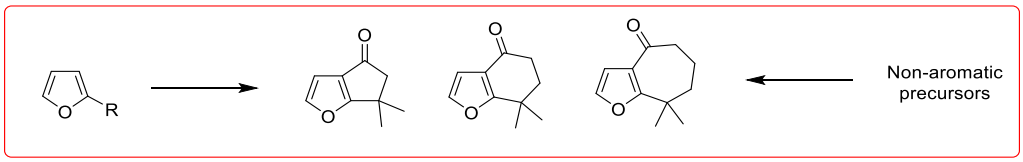
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This thesis describes synthetic studies toward furano[*b*]cycloalkanes from both furans and non-aromatic ring systems, with the aim of establishing short and efficient synthetic methods from inexpensive starting materials.

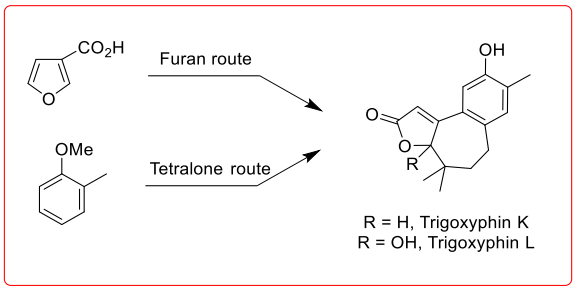
The **Introduction** summarises the reactivity of furans and the established synthetic methods for the furan ring system and annulated furan derivatives. It also briefly discusses the chemistry of two furan-related unsaturated heterocycles, 2(5*H*)-furanone and 2,3-dihydrofuran.

Chapter 1 details methodology studies on the synthesis of furano[*b*]cycloalkanones with fully alkylated furfurylic carbons and the carbonyl group conjugated to the furan ring. The targeted molecules were 5/5-, 5/6- and 5/7-ring fused furans with dimethylated furfurylic positions, whose synthesis was attempted from both 2-substituted furans and a variety of acyclic furan precursors.

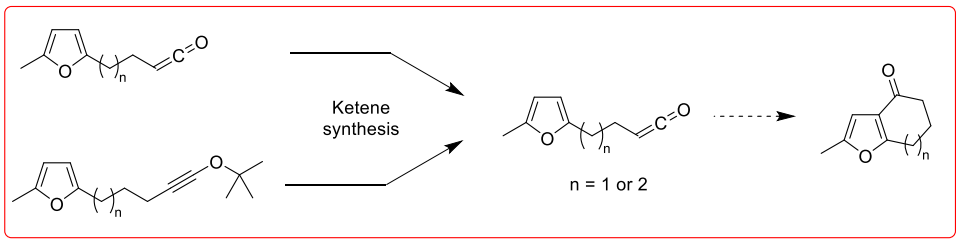


Chapter 2 describes two total syntheses of furanone-derived diterpenoids trigoxyphins K and L. The first synthetic route uses furan derivatives as synthetic intermediates and accesses the furanone ring through late-stage photochemical furan oxidation, while the second route

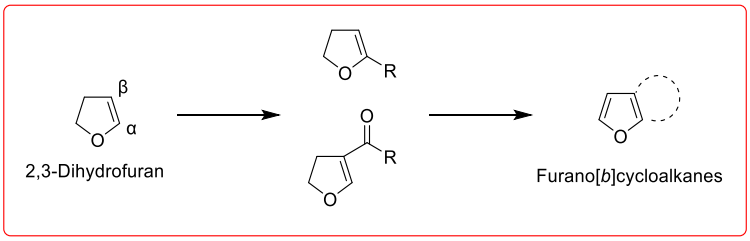
constructs the tricyclic skeleton from *o*-methylanisole *via* derivatives of α-tetralone, with no involvement of furan derivatives.



Chapter 3 discusses research on ω-(fur-2-yl)alkyl ketenes as a potential source of furano[*b*]cycloalkanones. The two types of ketene precursors used were carboxylic acids and ynol ethers derived from 2-methylfuran. Subsequently, both precursors were converted to the corresponding ketenes, whose reactivity was investigated accordingly.



Chapter 4 outlines an investigation of 2,3-dihydrofuran and its derivatives as potential precursors to furano[*b*]cycloalkanes. Efforts focused on the α- and β-functionalisation of 2,3-dihydrofuran, and annulation was attempted through lithium-halogen exchange, cross-coupling or cycloaddition reactions.



Abbreviations

°C	Degree celsius
ν_{max}	Absorption maximum
Ac	Acetyl
aq.	Aqueous
AIBN	Azobisisobutyronitrile
Ar	Aryl
BAIB	Bis(acetoxy)iodobenzene
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
Biphep	2,2’-Bis(diphenylphosphino)-1,1’-biphenyl
br	Broad
Bu	Butyl
calcd	Calculated
cat.	Catalytic
conc.	Concentrated
COSY	Correlation Spectroscopy
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*’-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHF	2,3-Dihydrofuran
DIBAL	Diisobutylaluminium hydride

DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisoproylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMP	Dess−Martin periodinane
DMPU	*N*,*N*′-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
DPPB	1,4-Bis(diphenylphosphino)butane
DTBP	Di-*tert*-butyl peroxide
eq.	Equivalent
ESI+	Electrospray ionisation
Et	Ethyl
et al.	*et alia*
FGI	Functional group interconversion
g	Grams
g	Relative centrifugal force
GC	Gas chromatography
GDH	Glucose dehydrogenase
h	Hour
Hz	Hertz (s^{-1})
HFIP	1,1,1,3,3,3-Hexafluoropropan-2-ol
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMPA	Hexamethylphorphoramide
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy

i	*Iso*
IPA	Isopropanol
IR	Infra-red
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amine
m	Multiplet; medium
m-	*meta*
m/z	Mass to charge ratio
m-CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
min	Minute
mmol	Millimole
MO	Molecular orbital
mol	Mole
mp	Melting point
Ms	Methanesulfonyl
MVK	Methyl vinyl ketone
n	*Normal*
$NADP^+$	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
o-	*ortho*
p-	*para*
PCC	Pyridinium chlorochromate
Ph	Phenyl

PPA	Polyphosphoric acid
ppm	Parts per million
Pr	Propyl
PTSA	*p*-Toluenesulfonic acid monohydrate
q	Quartet
quant.	Quantitative
quin	Quintet
R_f	Retention factor
RT	Room temperature
R_t	Retention time
s	Strong / Singlet
sat.	Saturated
sept	Septet
SET	Single-electron transfer
S_N2	Bimolecular nucleophilic substitution
t	Triplets
t	*Tertiary*
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

$P450_{BM3}$ variant abbreviations

The haem domain of the $P450_{BM3}$ wildtype has 477 amino acid residues; 40 out of the 43 variants included in this thesis are mutated. When the n^{th} residue (X) has been mutated into a different amino acid (Z), the mutation is denoted XnZ. For example, in the wildtype the 74^{th} amino acid is alanine (A); the mutation A74G denotes that the alanine has been mutated into a glycine (G).

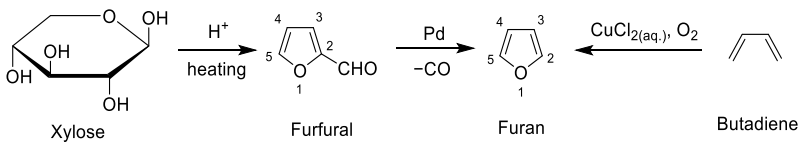
Abbreviation	Relationship to subset abbreviations	Mutations
GLQ	-	A74G/F87L/L188Q
GV	-	A74G/F87V
GVQ	**GV** + L188Q	A74G/F87V/L188Q
RLYF	-	R47L/Y51F
K19	-	H171L/Q307H/N319Y
R19	-	R47L/Y51F/H171L/Q307H/N319Y
KSK19	-	F87A/H171L/Q307H/N319Y
RK	**RLYF** + **KSK** / **R19** + F87A	R47L/Y51F/F87A/H171L/Q307H/N319Y
KU3	-	N239H/I259V/A276T
RT2	**KU3** + R47L/Y51F/A191T/L353I	R47L/Y51F/A191T/N239H/I259V/A276T /L353I
RP	-	R47L/Y51F/I401P

Table: Mutations present in common $P450_{BM3}$ variant abbreviations.

Introduction

Chemistry and reactivity of furans

As one of the most fundamental heterocyclic aromatic systems, the furan ring system is found widely in natural products and synthetic compounds alike. The parent compound furan is a flammable and volatile liquid sensitive to light and air. It is a versatile building block with great utility to the material and pharmaceutical industries, and first synthesised by Limpricht and co-workers in 1870 through base-mediated decarboxylation of barium 2-furoate,[1] 90 years after Scheele's discovery of the first furan derivative 2-furoic acid.[2] Industrially, it is produced from palladium-catalysed decarbonylation of 2-furfuraldehyde (furfural), an agricultural by-product obtained from the dehydration of polysaccharides in materials such as sawdust and bran (*Scheme 1*).[3] The oxygenation of butadiene in aqueous $CuCl_2$ solution has been reported as an alternative method for large-scale production.[4]



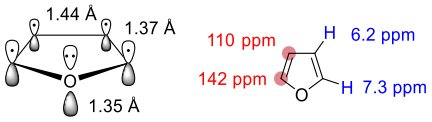
Scheme 1: Industrial production of furan from agricultural by-products, with xylose as an example of sugars that can be converted into furfural.

With six fully-conjugated π-electrons, furan is aromatic and has a higher electron density than the isoelectric benzene, since the six π-electrons are delocalised over five atoms. Its aromaticity is reflected by the similar bond lengths of its skeleton as well as the observed chemical shifts in its ^{1}H and ^{13}C NMR spectra (*Scheme 2*).[5] On the other hand, furan is much less aromatic than benzene as measured by its significantly lower resonance energy (68 $kJmol^{-1}$ compared

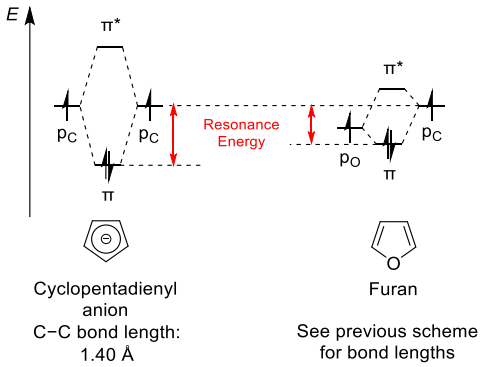
with 152 kJmol^{-1} for benzene), which is defined as the difference between the theoretical and observed standard enthalpy of formation:[6]

$$\text{Resonance Energy} = \Delta H_f^{\ominus}\ (\text{theoretical}) - \Delta H_f^{\ominus}\ (\text{observed})$$

Heterocyclic aromatic compounds have lower resonance energies than the isoelectric carbocycles, as the electronegativity difference between carbon and heteroatoms causes a mismatch in the energy of their p-orbitals (*Scheme 3*). This leads to poor orbital overlap and reduced stabilisation, reflected also by the different bond lengths of their ring systems.[7] Consequently, the chemical properties of furans resemble both benzene derivatives and conjugate dienes, and there are three principal types of reactions characteristic to furan and its derivatives.



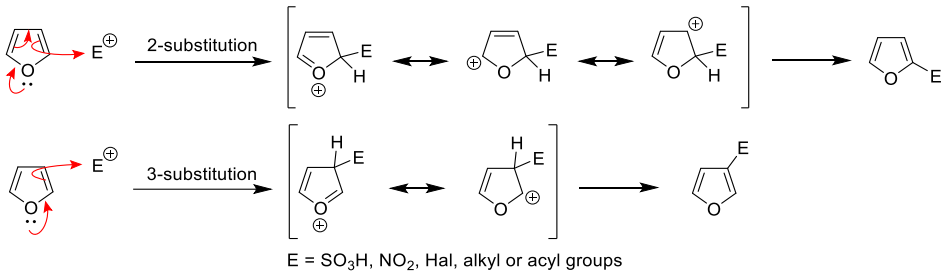
Scheme 2: Key bond length and NMR data observed in furan that demonstrate its aromaticity. For reference, the approximate average C−C, C=C and C−O bond lengths are 1.54 Å, 1.34 Å and 1.43 Å respectively.[7]



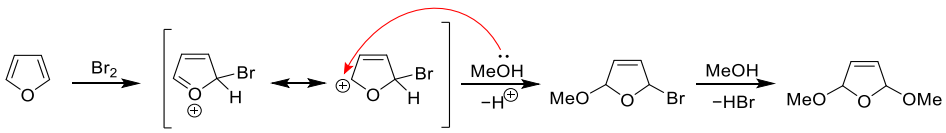
Scheme 3: Illustrative MO diagrams of cyclopentadienyl anion (left) and isoelectric furan (right), with C−C bond length data of the former. The resonance energies of these two systems are indicated in red.

Substitution reactions

The most common substitution reaction of furan derivatives is electrophilic aromatic substitution. Compared with benzene derivatives, furans are generally more reactive and more likely to give multi-substituted products. Substitution is regioselective and occurs on the α-(namely 2- and 5-) positions if vacant, as this creates cationic intermediates with better delocalisation (*Scheme 4*).[8] It is worth noting that the outcome of halogenation reactions depends on the solvent used. This is because particularly at low temperatures, the cationic intermediate generated by electrophilic attack has a sufficiently long lifespan to allow nucleophilic trapping by solvents such as methanol (*Scheme 5*). The net result is an electrophilic 1,4-addition, and further substitution could follow.[9]



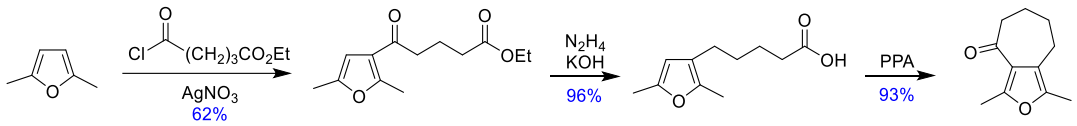
Scheme 4: Mechanisms and resonance structures of the two possible types of electrophilic substitution of furan.



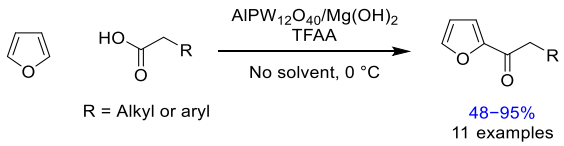
Scheme 5: Solvent inference (methanol, for instance) in the reaction of furan with bromine, leading to 1,4-addition products.

As a powerful tool for carbon-carbon bond formation, the Friedel−Crafts reaction is among the most useful electrophilic substitutions of furans. Furans readily undergo Friedel−Crafts acylation with carboxylic acids and their derivatives at ambient temperature,[10] and the products are stabilised by the electron-withdrawing acyl substituents. Intramolecular Friedel−Crafts

furan acylation is a useful way to access bicyclic ring systems, as for instance in Strübe's synthesis of a furano[*c*]cycloheptanone derivative from 2,5-dimethylfuran (*Scheme 6*).[11] Conventional acylation catalysts such as $AlCl_3$ are used[8] but generally not considered suitable for electron-rich furan derivatives, as decomposition and polymerisation can result. Acid catalysts such as $SnCl_4$ and TFAA are popular choices and generally give good yields.[12–13] Moreover, the Friedel–Crafts acylation of furans could proceed with air- and moisture-stable heterogeneous catalysts such as zeolites and heteropolyacids.[14–15] For example, Opietnik and co-workers reported that the catalyst couple $AlPW_{12}O_{40}/Mg(OH)_2$ delivered excellent yields for the reaction between furan and carboxylic acids (*Scheme 7*).[15] The $Mg(OH)_2$ additive was believed to prevent the deactivation of the heteropolyacid catalyst, yet the mechanism was not fully understood. Using this protocol, reactions can take place in neat conditions with minimal work-up procedures required.



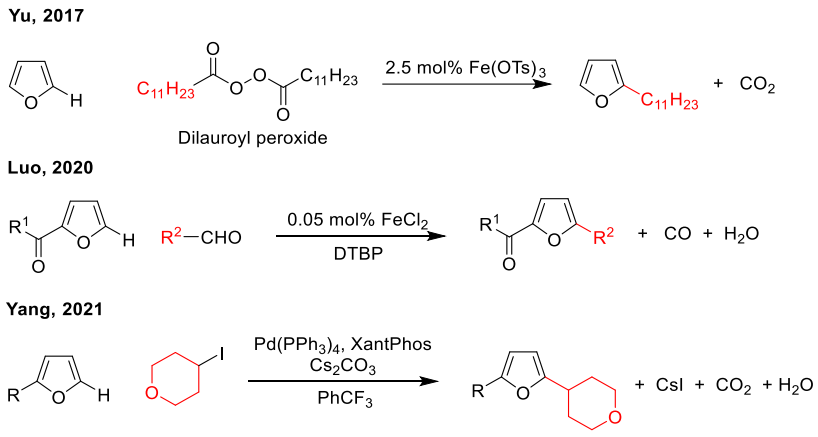
Scheme 6: Strübe's synthesis of a furano[*c*]cycloheptanone as an example of intramolecular Friedel–Crafts furan acylation.



Scheme 7: Opietnik's Friedel–Crafts furan acylation protocol using heterogeneous catalysts $AlPW_{12}O_{40}$ and $Mg(OH)_2$.

The Friedel–Crafts alkylation is predominantly seen in electron-deficient furan derivatives, which tolerate strong Lewis acid catalysts. For instance, methyl 2-furoate reacts with alkyl chlorides in the presence of stoichiometric or excess amounts of $AlCl_3$, and upon subsequent

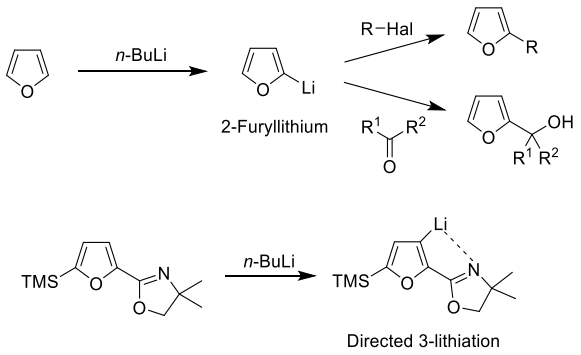
hydrolysis, 5-alkyl-2-furoic acids may be obtained with good yields.[10a] Recent advances have led to new alkylation protocols with significantly lower catalyst loading (*Scheme 8*). To illustrate, Yu and co-workers reported an iron(III)-catalysed alkylation protocol with dilauroyl peroxide.[16] A variation of this protocol was developed by Luo and co-workers that alkylated furans through oxidative decarbonylation of aldehydes.[17] More recently, Yang *et al.* achieved the alkylation of 2-substituted furans using alkyl iodides and $Pd(PPh_3)_4$. The protocol was compatible with both electron-rich and electron-deficient substrates.[18]



Scheme 8: Examples of transition metal-catalysed alkylation of furan or 2-substituted furans.

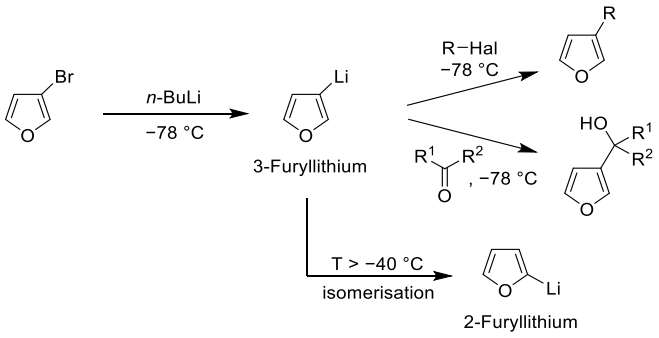
Besides electrophilic substitution, furans undergo metallation through either deprotonation or metal-halogen exchange. Effective metallation reagents include sodium metal, organolithium reagents (butyllithium isomers, LDA) and organomercury reagents (diethylmercury, diphenylmercury and dibenzylmercury).[19] Taking as example *n*-butyllithium, deprotonation of furan predominantly occurs on the 2-position, while 3-lithiation can occur only with the directing effect of Lewis basic 2-substituents.[20] The nucleophilic furyllithium intermediates readily undergo nucleophilic substitution or addition to generate various 2-functionalised furans (*Scheme 9*).[19,21] The alkylation of 2-furyllithium is a reliable and acid-free alternative to Friedel−Crafts furan alkylation, yet only primary alkyl halides have been used as reagents. This

is likely because furyllthium is a powerful nucleophile, secondary and tertiary alkyl halides are unsuitable, giving rise instead to elimination products.



Scheme 9: Examples of furan lithiation through deprotonation.

3-Furyllithium itself is synthesised from 3-bromofuran and *n*-butyllithium at −78 °C and would undergo isomerisation to give 2-methylfuran at temperatures higher than −40 °C.[22] Therefore, electrophilic trapping at −78 °C or similarly low temperatures is necessary for access of 3-substituted furans.

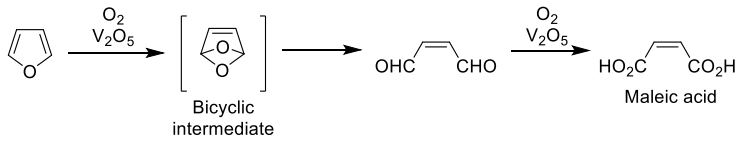


Scheme 10: Synthesis and reactivity of 3-furyllithium.

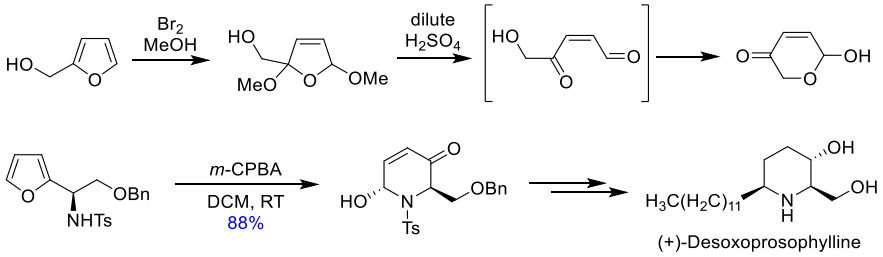
Oxidation and reduction reactions

Furans are highly sensitive to oxidisers and form explosive peroxides on standing in air.[23] Catalysed oxidation of furan has been studied since the 1930s. To illustrate, Milas and Walsh

synthesised maleic acid through V_2O_5-mediated furan oxidation and postulated that the ring opening succeeded the formation of a 4/5-ring fused intermediate (*Scheme 11*).[24] Subsequent investigations using metal oxide catalysts found that a wide variety of products, including maleic anhydride and oxalic acid, could result from the oxidation.[25] Oxidation techniques developed since have achieved better chemoselectivity and targeted non-aromatic cyclic systems. The classic Achmatowicz reaction generates dihydropyran derivatives from furyl carbinols *via* bromination in methanol and acid-mediated rearrangement (*Scheme 12*).[26] Peroxy acids and their salts have since been reported as alternative oxidants.[27] This reaction has since contributed to divergent organic synthesis and natural product synthesis alike, such as the established total synthesis of the fungal metabolite (+)-desoxoprosophylline.[27a]



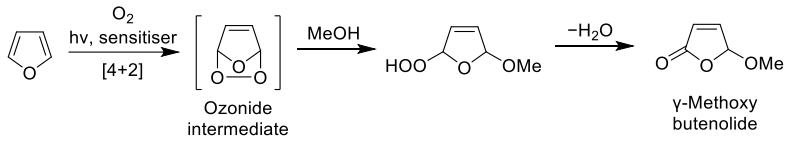
Scheme 11: Outcome of the V_2O_5-mediated oxygenation of furan and proposed mechanism by Milas and Walsh.



Scheme 12: The classic Achmatowicz reaction (upper) and its application in the total synthesis of (+)-desoxoprosophylline by Yang and co-workers (lower).

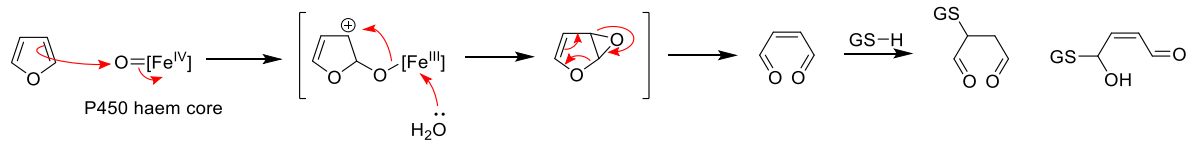
Schroeter and co-workers in 1966 reported the photochemical oxygenation of furan into γ-hydroxy butenolide derivatives in the presence of methanol and a photosensitiser such as rose Bengal.[28] The reaction mechanism is believed to be a [4+2] cyclisation, since the ozonide intermediate was successfully isolated at low temperatures (*Scheme 13*). The photooxygenation

was employed by previous DPhil student O'Hanlon of our group in the attempted synthesis of trigoxyphin L, as discussed in **Chapter 2**.[29]



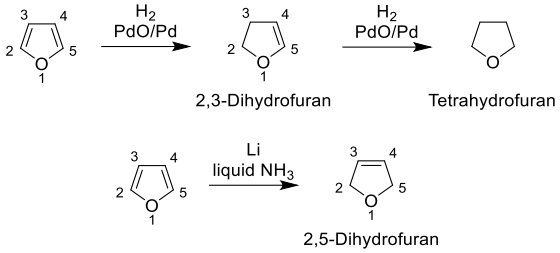
Scheme 13: Outcome and proposed mechanism of photosensitised furan oxidation.

Furthermore, furan oxidation is achievable with enzyme catalysis. Cytochrome P450 enzymes, which are responsible for various metabolic processes in living organisms and whose mechanism is detailed in **Chapter 1**, initially oxidise furan into *cis*-2-butene-1,4-dialdehyde, which may then be trapped by glutathione (GSH) *en route* to give toxic metabolites (*Scheme 14*).[30–31] According to Peterson,[30] the oxidation mechanism involves the formation of an epoxide species through coordination of the enzyme. This metabolic process is deemed responsible for the manifestation of hepatotoxic and carcinogenic properties of furan-containing organic compounds.[31]



Scheme 14: Simplified mechanism proposed for the metabolic oxidation of furan by Cytochrome P450 enzymes.

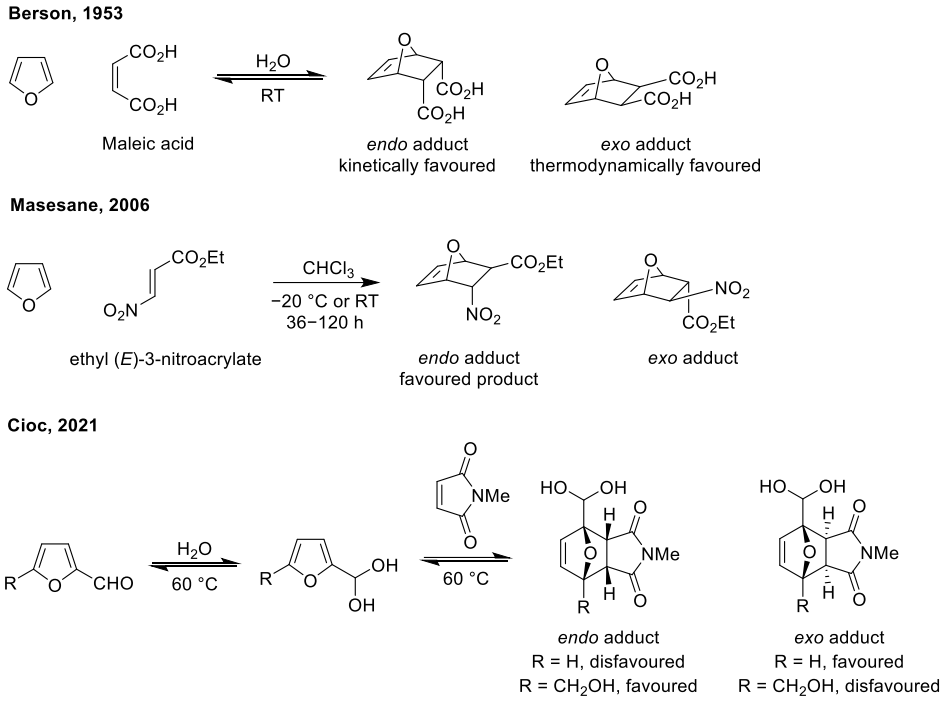
There are two main reduction pathways for furan (*Scheme 15*): catalytic hydrogenation with PdO/palladium black generates tetrahydrofuran *via* 2,3-dihydrofuran,[32] whereas reduction with lithium in liquid ammonia gives 2,5-dihydrofuran.[33] With the exception of 2,5-dihydrofuran, the hydrofurans are not normally synthesised from furan. The synthesis and reactivity of 2,3-dihydrofuran is a key focus of this thesis and will be discussed in due course.



Scheme 15: The reduction products of furan.

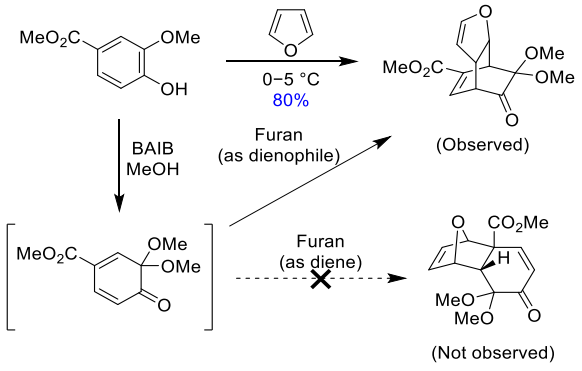
Cycloaddition reactions

As an electron-rich diene, furan can participate in Diels−Alder reactions under very mild conditions; the stereoselectivity and thermodynamics of these reactions vary greatly with specific cases. For instance, the cycloaddition with maleic acid in water is reversible and poorly diastereoselective,[34] while the reaction with ethyl (*E*)-3-nitroacrylate favours *endo* addition with respect to the nitro group.[35] Kinetically, furan derivatives with electron-donating substituents are favoured for [4+2] cycloadditions and constitute the majority of Diels−Alder substrates. A good example is the Diels−Alder reaction of furfurals with maleimides in water, where the substrates are hydrated into much less electron-deficient *geminal* diols;[36] the results also show that the electron-donating 5-hydroxymethyl group alters the stereoselectivity of the reaction in favour of *endo* adduct (*Scheme 16*).



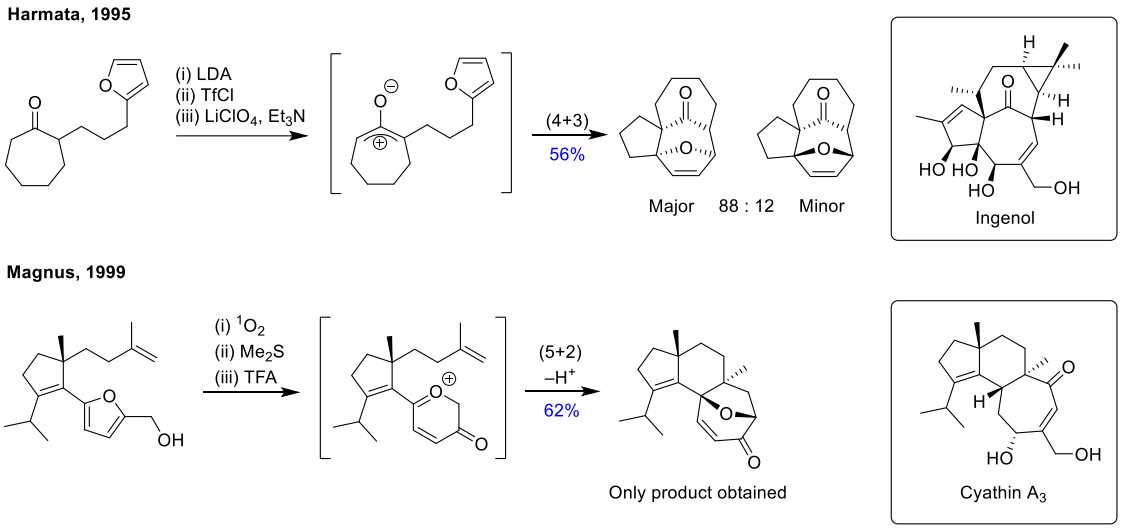
Scheme 16: Examples of Diels−Alder reactions of furans.

On the other hand, furans rarely serve as dienophiles in cycloadditions reactions; inverse-demand Diels−Alder reactions with electron-deficient dienes are precedented but low yields are a consistent issue. A remarkable breakthrough was achieved by Liao *et al.* who obtained unexpectedly high yields of an inverse-demand Diels−Alder adduct from furan and a masked *o*-benzoquinone species (*Scheme 17*).[37] The authors found that the reaction occurred in a direct manner with no involvement of cycloaddition reactions where furan acted as a diene.



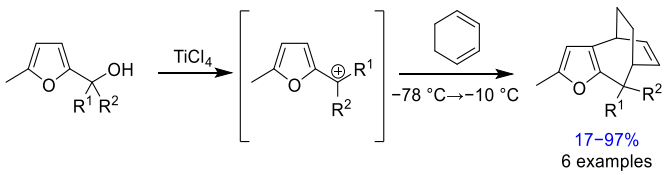
Scheme 17: The Diels−Alder reaction of furan with a benzoquinone derivative demonstrated by Liao, where furan was observed to exclusively serve as a dienophile.

In addition to neutral dienophiles, oxyallyl cations and are known to undergo (4+3) cycloaddition with furan. For example, Harmata synthesised a model compound for the total synthesis of ingenol.[38] Furans can also be transformed into oxidopyrylium ions capable of (5+2) cycloadditions, as demonstrated by Magnus and co-workers in their efforts toward the tricyclic skeleton of cyathin A_3 (*Scheme 18*).[39]



Scheme 18: The (4+3) cycloaddition of furan with oxyallyl (upper) and the (5+2) cycloaddition of an oxidopyryllium derivative synthesised from a 5-substituted furfuryl alcohol.

Last but not least, cycloaddition reactions with furfurylic cations have been observed. For example, furyl carbinols undergo cationic (4+3) cycloaddition with dienes such as isoprene, giving 5/7-fused products (*Scheme 19*).[40] Effective cycloaddition was only observed from carbinols derived from 2-methylfuran, presumably because they are stable toward the catalyst ($TiCl_4$) and the shielding effect of the methyl group in these molecules prevents side reactions.



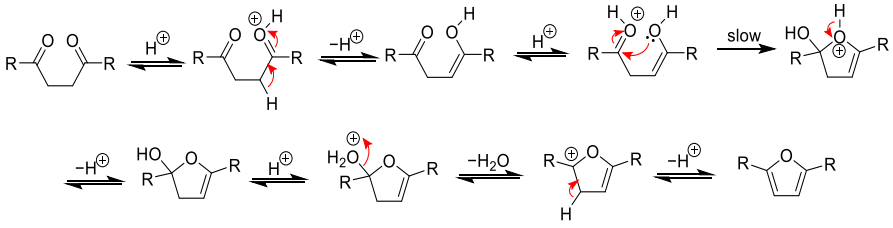
Scheme 19: The (4+3) cycloaddition of furyl carbinols with dienes such as 1,3-cyclohexadiene.

Synthesis of the furan ring system

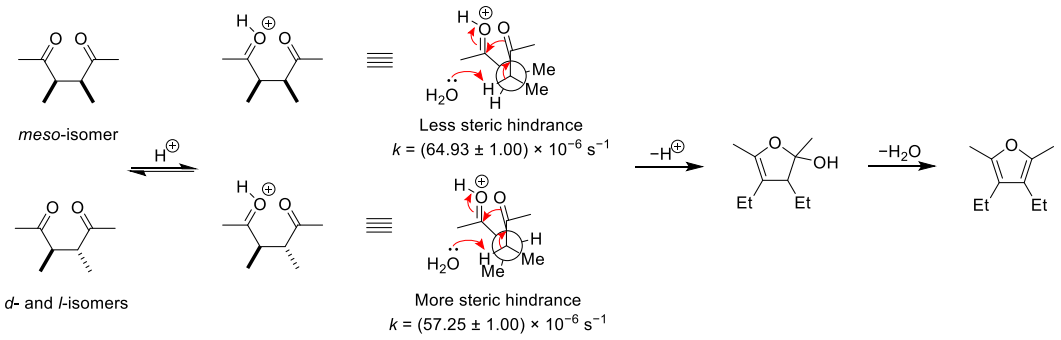
In organic synthesis, establishment of the furan ring system *in situ* is often necessary due to the sensitivity of furans to acids, oxidants and reducing reagents. The good accessibility of furan derivatives from non-aromatic precursors has facilitated the development of a wide range of furan synthesis protocols, the most notable of which are outlined below. In addition, furan synthesis is achievable through the oxidation or reduction of related five-membered ring systems such as dihydrofurans and furanones, which will be discussed in the next section.

Paal−Knorr synthesis

Reported in 1884, the Paal−Knorr synthesis is the first known synthetic method for substituted furans, pyrroles and thiophenes.[41] Using 1,4-diketones as substrates, the Paal−Knorr furan synthesis delivers 2,5-disubsituted furans through Brønsted acid-catalysed condensation. Despite its 140-year history, the mechanism of the Paal−Knorr furan synthesis was elucidated only in recent decades. It involves the rate-determining cyclisation step that generates a hemiacetal intermediate, which subsequently ejects water to give the furan ring (*Scheme 20*).[42] Moreover, Amarnath observed that the reaction rate of 2,3-disubstituted substrates varies with the stereochemistry of the substituents.[43] The authors proposed accordingly that the steric hindrance of the substituents can influence the rate-determining cyclisation step (*Scheme 21*).

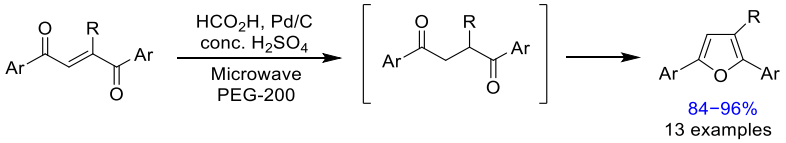


Scheme 20: The commonly accepted mechanism of the Paal−Knorr furan synthesis.



Scheme 21: Amarnath's demonstration of the different rates of cyclisation observed for instance in different stereoisomers of 3,4-dimethylhexane-2,5-dione. The reactions were carried out in water.

The Paal−Knorr furan synthesis is widely used in modern synthetic chemistry and renowned for its high efficiency. However, a number of substrates for the Paal−Knorr synthesis, most notably aryl ketones, require elevated temperatures for good conversion, which, upon treatment of conventional acidic catalysts for prolonged periods of time, can result in significant degradation of the products.[44] This problem may be overcome in microwave-mediated reactions, such as the one developed by Rao and Jothilingam. Reactions typically reach completion within minutes and can be conducted in open vessels (*Scheme 22*).[45]



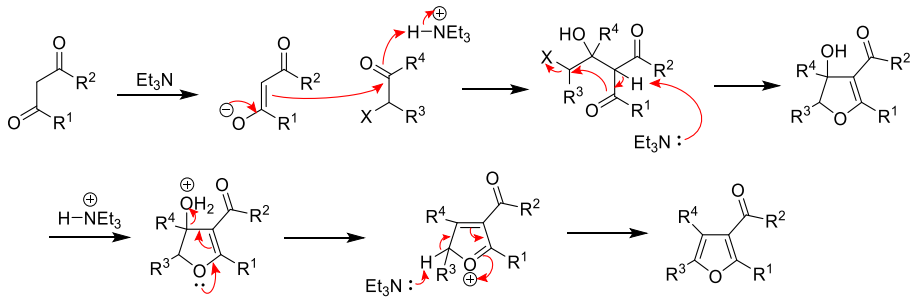
Scheme 22: Rao and Jothilingam's microwave-mediated Paal−Knorr furan synthesis. PEG-200 signifies the solvent poly(ethylene glycol)-200.

The main limitation of the Paal−Knorr furan synthesis is that the 1,4-diketone substrates are difficult to prepare and are susceptible to oxidation and nucleophilic substitution reactions. Nevertheless, with general effectiveness and simple reaction conditions, the Paal−Knorr synthesis remains a popular method for access of furan derivatives. Moreover, a number of

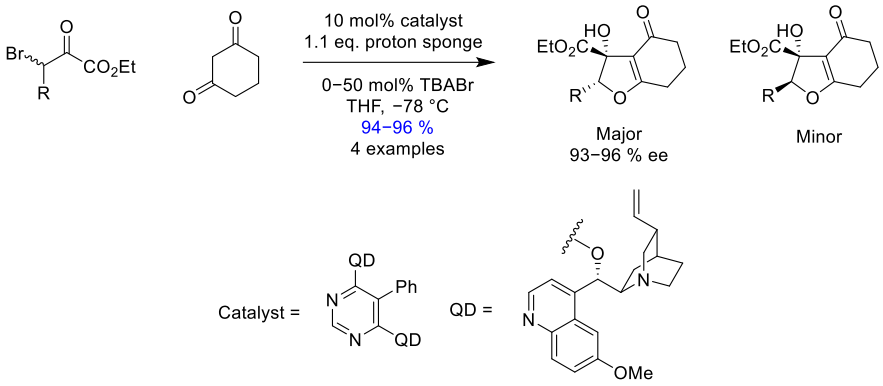
new furan synthesis pathways developed since, which will be discussed in due course, can be regarded as variations of the Paal−Knorr synthesis.

Feist−Benary synthesis

Independently developed and reported by Feist (1902)[46] and Benary (1911),[47] this classical synthetic method is dedicated to furan derivatives and provides a base-mediated alternative to the Paal−Knorr synthesis. The Feist−Benary synthesis combines an α-halo ketone and a 1,3-dicarbonyl compound in a process similar to the Knoevenagel condensation, and the intermediate ejects a water molecule to form the furan ring (*Scheme 23*).[48] The mechanism has been supported by the isolation of the dihydrofuran intermediates from the so-called 'interrupted' Feist−Benary reactions (see *Scheme 24* for example).[49] As only one carbonyl group in the 1,3-dicarbonyl compound is directly involved in this transformation, the product is a 3-acylated furan derivative; the 'surviving' carbonyl group is, however, vital to the furan synthesis because it facilitates the initial deprotonation of the 1,3-dicarbonyl compound.



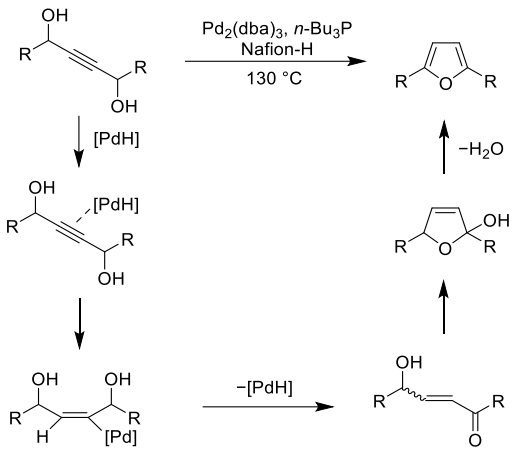
Scheme 23: The mechanism of the Feist−Benary furan synthesis.



Scheme 24: Calter's 'interrupted' Feist−Benary synthesis which generates dihydrofuran intermediates.

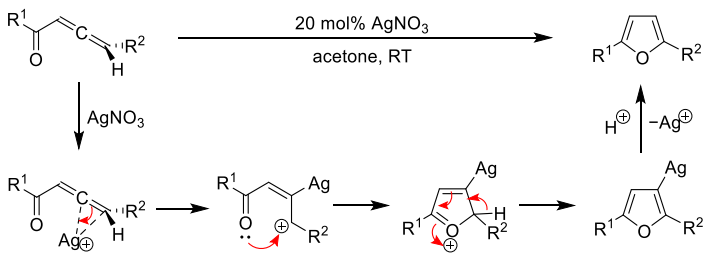
Cyclisation of other non-aromatic motifs

With the development of transition metal catalysis, a wide variety of other non-aromatic compounds have been demonstrated as viable furan precursors. Most of these compounds contain acyclic, four-carbon fragments with two carbon-carbon π-bonds and two C−O bonds capable of cyclising *via* rearrangement or condensation. To illustrate, the conversion of 2-yne-1,4-diols into furans has been achieved with ruthenium[50] and palladium[51] catalysts or Brønsted acids such as PTSA.[52] The mechanism of this furan synthesis, as understood by Ji and Lu who developed a palladium catalysis protocol (*Scheme 25*), involves the rearrangement of the alkyne diol substrates into γ-hydroxy-α,β-unsaturated carbonyl compounds, which then cyclise to give furans.[51] Thus, it is essentially a variation of the Paal−Knorr furan synthesis.

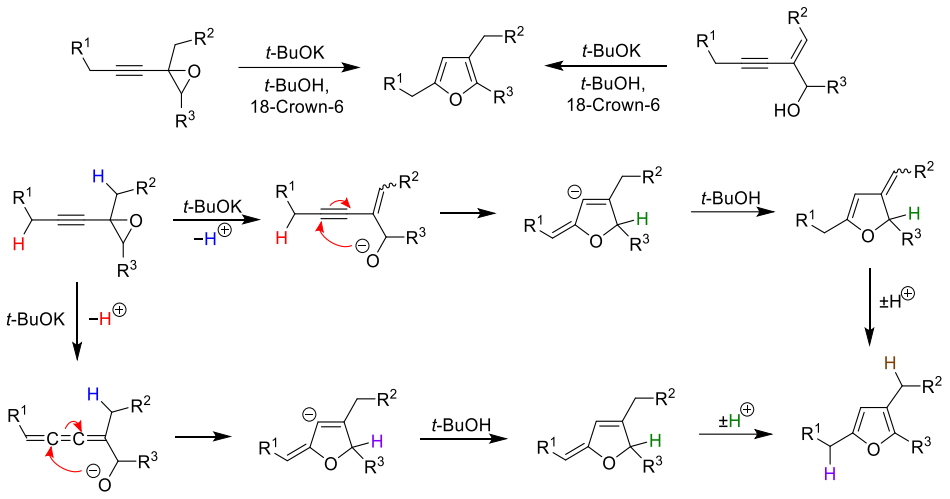


Scheme 25: Ji and Lu's proposed mechanism for the Pd-catalysed cyclisation of 2-yne-1,4-diols into furans.

Marshall *et al.* in the 1990s conducted pioneering research on the rearrangement of allenyl ketones (allenones) into furans using silver(I) and rhodium(I) catalysts.[53] Protocols with gold catalysts have also been reported.[54] The reactions proceeded with high efficiency and good tolerance of functional groups. They also required only a simple work-up that removed the catalyst and solvent. The proposed mechanism with $AgNO_3$-impregnated silica as catalyst indicates that the silver cation coordinates with the unconjugated C−C double bond, generating the cationic intermediate capable of cyclisation (*Scheme 26*).[53c] The major drawback of this method is that the allenone synthesis used dangerous reagents such as organotin compounds and diazomethane. Marshall also reported the furan synthesis of alkynyloxiranes and alkynyl allylic alcohols, both of which are structurally isomeric to allenyl ketones (*Scheme 27*).[55] Crucially, their cyclisation is achievable without recourse to transition metal catalysts.

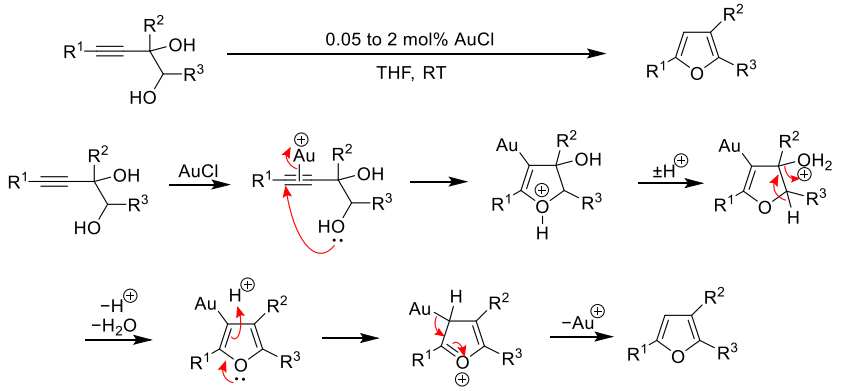


Scheme 26: Marshall's proposed mechanism of the $AgNO_3$-mediated furan synthesis from allenyl ketones.



Scheme 27: Marshall's synthesis of 2,3,5-trisubstituted furans from alkynyloxiranes (upper) and alkynyl allylic alcohols (lower), along with the proposed mechanism.

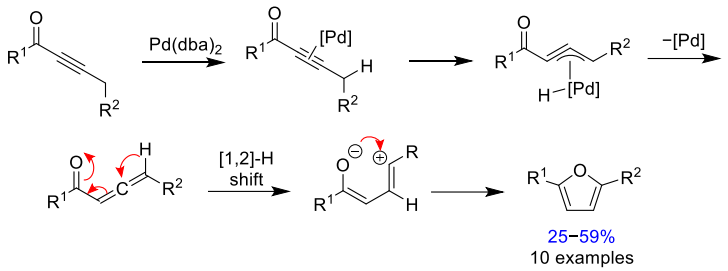
3-Yne-1,2-diols are also established as viable furan precursors. Similar to allenyl ketones, their conversion into furan can be catalysed by palladium,[56] silver[57] or gold[58] catalysts. The mechanism below (*Scheme 28*)[58a] proposed by Iqbal for the AuCl-catalysed process bears resemblance to the one shown in *Scheme 26*, with both processes starting from the π-coordination of the catalysts.



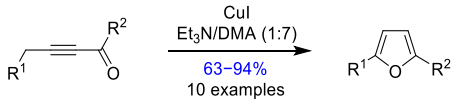
Scheme 28: Iqbal's proposed mechanism of the AuCl-catalysed cyclisation of 3-yne-1,2-diols.

Conjugate ynones give furans when treated with transition metal catalysts such as copper(I) iodide or bis(dibenzylideneacetone)palladium. The furan synthesis requires elevated temperatures and tolerates alkenes, esters and alcohols. Huang *et al.* proposed that the catalyst

(Pd(dba)$_2$ in their instance) facilitates the isomerisation of ynones into allenyl ketones, which then cyclises to give the furan ring (*Scheme 29*).[59] Gevorgyan reported improved yields with CuI and triethylamine (*Scheme 30*).[60] The allenyl ketone intermediates have so far not been isolated; nevertheless, this transformation provides a good alternative to Marshall's method due to the ready availability of ynones.



Scheme 29: Outcome and proposed mechanism of the palladium-catalysed rearrangement of ynones into furans by Huang and co-workers.

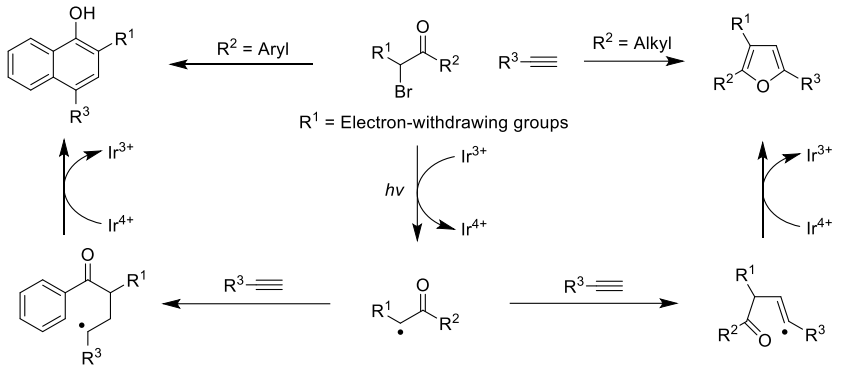


Scheme 30: Gevorgyan's copper-catalysed ynone-to-furan transformation.

Photochemical synthesis

Photochemical reactions function with high-energy intermediates that can be difficult to access from thermal transformations, therefore offering fast, effective and often atom-efficient alternatives to traditional synthetic methods. The reactive intermediates can arise from compounds otherwise inert under thermal conditions as the reactivity threshold is significantly lowered by photoactivation. This is particularly beneficial for furan synthesis given the labile nature of the furan ring system. For instance, Jiang and co-workers found that unfunctionalised terminal alkynes react with α-brominated alkyl ketones in the presence of iridium catalysts to

give furans.[61] With aryl ketones, the products are naphthols instead. The reaction is understood to be radical-based and initiated by the activated Ir(III) form of the catalyst (*Scheme 31*). Overall, photochemical furan synthesis remains a relatively new field in furan chemistry, and future development of highly efficient photoactivated processes could significantly improve the synthetic availability of furan derivatives.

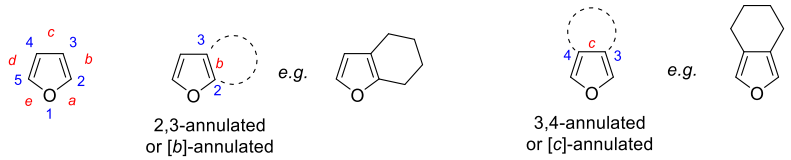


Scheme 31: Jiang's photochemical furan synthesis from α-brominated alkyl ketones and terminal alkynes (transformation on the right-hand side).

Synthesis of annulated furan derivatives

Bicyclic and polycyclic furan derivatives occupy a prominent status both in nature and in the field of furan chemistry. The annulated furan ring is found in various sesqui- and diterpenes with distinct biological activities, for instance furodysin and furanonaphthaquinones; it also constitutes polycyclic aromatic skeletons such as benzofurans.[62] This thesis focuses on alicyclic-annulated furans, since polycyclic aromatics such as benzo[*b*]furan have significantly different reactivities and are not considered furan derivatives. There are two types of annulated furans (*Scheme 32*); the 2,3- (or [*b*]-) annulation involves both the α- and β-positions of the furan ring features in the majority of annulated furan derivatives. Arguably for these reasons, it has been the focus of most synthetic efforts toward annulated furans to date; efforts discussed

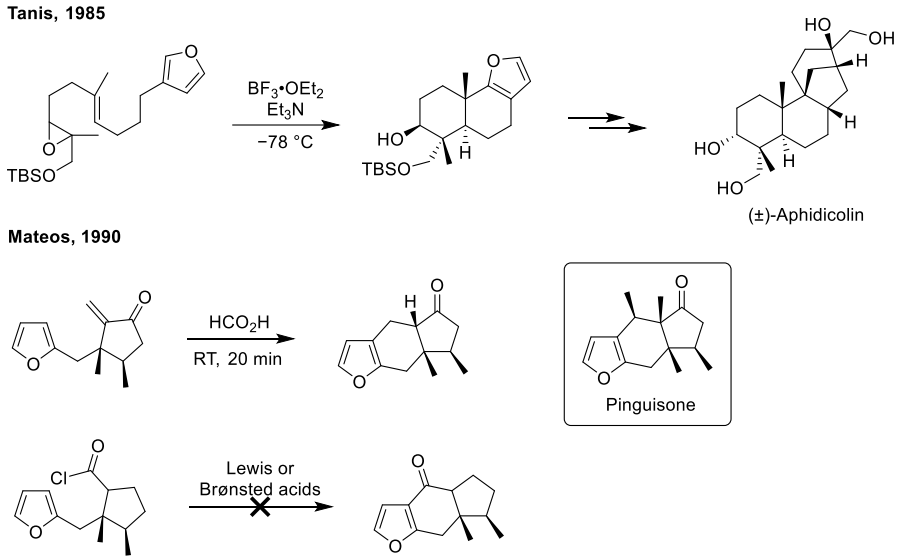
in this thesis also exclusively targeted [*b*]-annulated furans. The 260-year history of furan chemistry has witnessed the development of various synthetic methods for annulated furans, the most prominent of which are outlined below.



Scheme 32: Illustration of the positions (numbers in blue) and faces (italicised letters in red) of the furan ring, and the two types of annulated furans.

Alkene hydroarylation

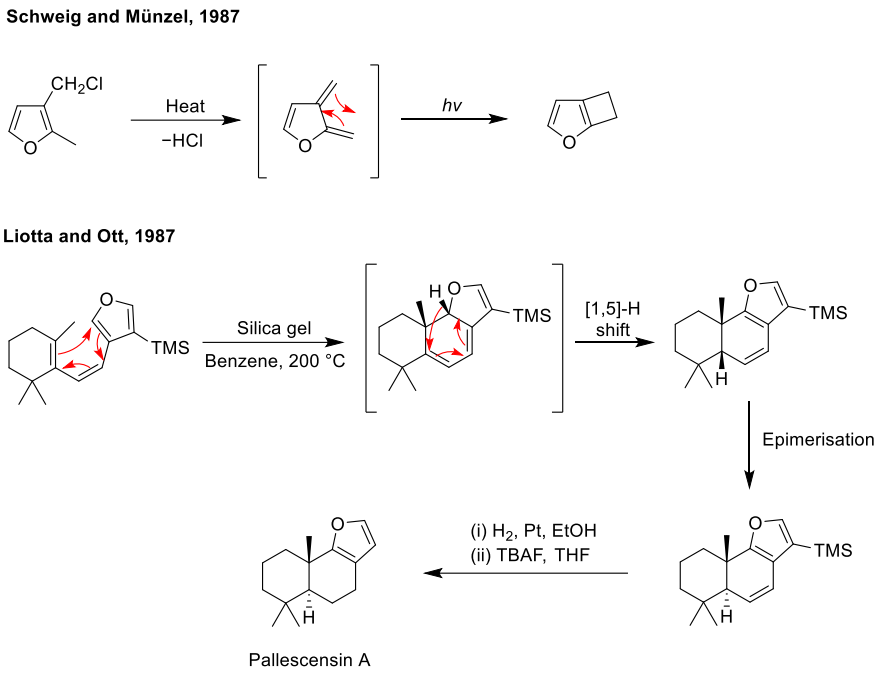
Alkene principally forms addition products with electrophiles; however, in alkene hydroarylation reactions, they are converted into electrophilic cationic species and react with electron-rich aromatic systems. The furan ring, despite its lability, is found compatible with many Lewis and Brønsted acids used in alkene hydroarylation reactions. To illustrate (*Scheme 33*), Tanis reported the BF_3-mediated [*b*]-annulation of a 3-substituted furan intermediate, which coincided with the epoxide ring-opening and delivered a 5/6/6 tricycle.[63] Mateos *et al.* used formic acid to facilitate the cationic cyclisation of a terminal enone which gave a homologue of antifeedant natural product pinguisone.[64] The reactions in both examples required no heating and achieved good chemoselectivity. Moreover, Mateo attempted without success the synthesis of a structural isomer *via* Friedel−Crafts acylation and attributed the lack of substrate reactivity to steric factors. This demonstrates the better compatibility of the cationic cyclisation method for furan-derived substrates.



Scheme 33: Examples of furan [*b*]-annulation using Lewis or Brønsted acid-mediated alkene hydroarylation, compared with the unsuccessful attempt of Friedel−Crafts acylation.

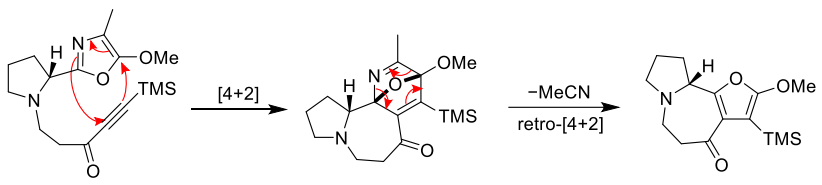
Pericyclic reactions

Electrocyclic reactions and cycloadditions are the main types of pericyclic reactions used in furan annulation. Thermal pericyclic reactions can proceed in the absence of added catalysts or with just weak Lewis acids such as silica, which proves advantageous in the synthesis of acid-sensitive furan derivatives (*Scheme 34*). Schweig and Münzel conducted pioneering studies and observed the highly labile furano[*b*]cyclobutene from thermolysis and ultraviolet irradiation of 3-(chloromethyl)-2-methylfuran.[65] More recently, Liotta and Ott initiated a thermal 6π-electrocyclisation of a conjugated diene intermediate whose product was then hydrogenated to give the natural product pallescensin A.[66] The annulation step used silica gel and high pressures, with quantitative yields achieved after 6 days; the authors also noted the importance of temperature control, as the reaction performed best at 195−200 °C but large amounts of side products were produced when the temperature exceeded 210 °C.



Scheme 34: Furan annulation examples achieved *via* photochemical (upper) or thermal (lower) cycloaddition reactions.

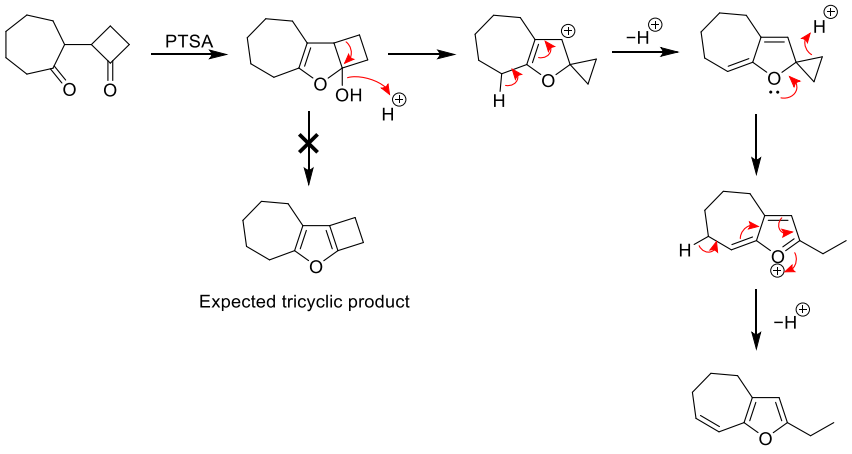
In addition, annulated furans are also accessible from the cycloaddition of other heterocyclic ring systems. A relatively widely-used example is the thermolysis of alkyne-tethered 2-substituted 4-methyloxazoles, in which the alkyne moiety participates in a Diels−Alder reaction with the oxazole ring then a retro-[4+2] cycloaddition follows (*Scheme 35*).[67] The driving force is understood to be the formation of stable C−N triple bond as well as the positive entropy change afforded by the expulsion of by-product acetonitrile. This cascade reaction is a powerful tool to generate [*b*]-annulated furans and has been used in efforts toward sesquiterpenes and alkaloids.



Scheme 35: Synthesis of [*b*]-annulated furans from an alkyne-tethered 2-substituted 4-methyloxazole.

Furan synthesis techniques

Although most annulated furans are synthesised from furan derivatives, late-stage installation of the furan ring provides an alternative pathway toward some annulated furans. Many furan synthesis methodologies outlined earlier can be adopted for this purpose with cyclic substrates. For example, based on Schweig and Münzel's report outlined earlier, Spencer and co-workers attempted to transform γ-ketocyclobutanones into furano[*b*]cyclobutanes using PTSA-mediated Paal−Knorr furan synthesis (*Scheme 36*).[68] Although their intention did not materialise, the authors succeeded in accessing [*b*]-annulated furans as the other carbonyl group of the substrates formed part of the cycloheptanone ring system.

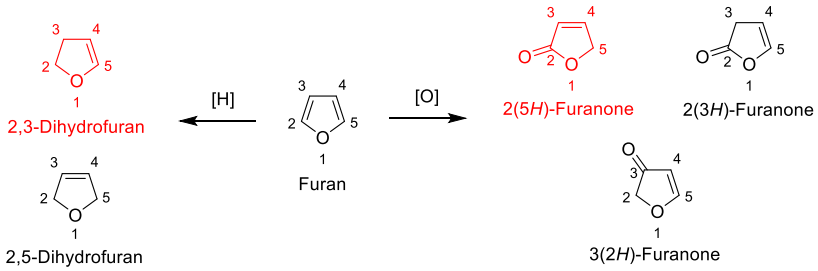


Scheme 36: Spencer's attempted synthesis of a furano[*b*]cyclobutene derivative using the Paal−Knorr synthesis.

2(5*H*)-Furanone and 2,3-dihydrofuran

Five unsaturated five-membered heterocyclic compounds are accessible from the hydroxylation or partial hydrogenation of furan (*Scheme 37*); namely, the three isomers of furanone (2(5*H*)-furanone, 2(3*H*)-furanone and 3(2*H*)-furanone) and the two isomers of dihydrofuran (2,3- and 2,5-dihydrofuran). This section outlines the synthesis and reactivity of

2(5*H*)-furanone and 2,3-dihydrofuran, because their derivatives were investigated during the research described in this thesis.

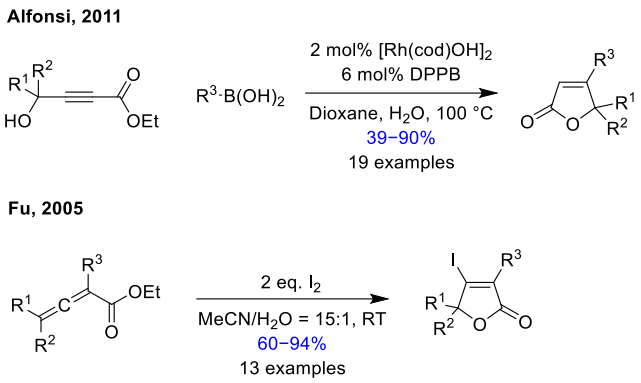


Scheme 37: Structures of all unsaturated five-membered heterocyclic compounds related to furan. The two compounds discussed in this thesis are highlighted in red.

2(5*H*)-Furanone

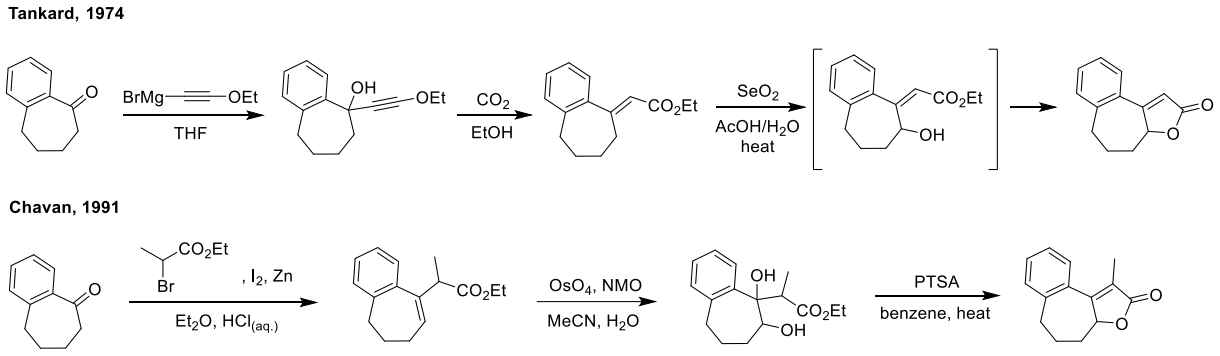
This five-membered heterocycle, known colloquially as 'butenolide', is an α,β-unsaturated γ-lactone. As an electron-deficient molecule, butenolides are markedly more stable than furans toward strong acids and oxidising agents. 2(5*H*)-Furanone itself is accessible from the reaction of furfural with hydrogen peroxide,[69] and its conversion into furan can be achieved with DIBAL.[70]

Many examples of butenolide synthesis from acyclic precursors resemble furan synthesis protocols (*Scheme 38*). To begin with, Alfonsi reported the rhodium-catalysed addition-lactonisation of alkyl 4-hydroxy-2-alkynoates with organoboron reagents; the adduct can be regarded as an oxidised version of 2-yne-1,4-diols discussed in the furan synthesis section.[71] Fu and Ma reported butenolide formation through iodolactonisation of ethyl 2,3-allenoates,[72] which can be regarded as oxidised derivatives of allenyl ketones.



Scheme 38: Examples of butenolide synthesis from acyclic precursors.

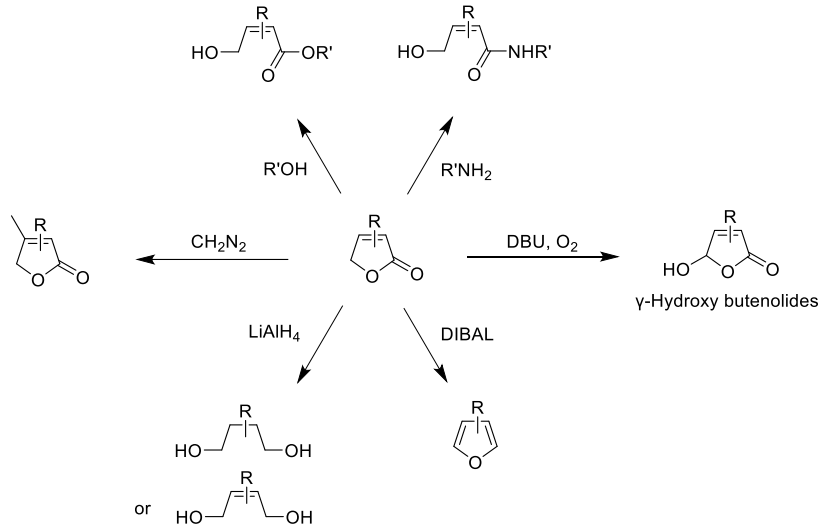
In addition, the butenolide ring system can be developed from alicyclic systems (*Scheme 39*). Tankard and Whitehurst demonstrated the butenolide synthesis from ethoxyethynyl alcohols via rearrangement into α,β-unsaturated esters and subsequent allylic oxidation.[73] Chavan *et al.*, by comparison, used a β,γ-unsaturated ester as an intermediate for the total synthesis of heritol.[74] These precedents provided useful guidance for the efforts toward the total synthesis of trigoxyphins K and L as outlined in **Chapter 2**.



Scheme 39: Examples of butenolide synthesis from alicyclic compounds.

The reactivity of butenolides is overall similar to that of lactones (*Scheme 40*); for instance, it reacts with alcohols to give ester exchange products and with amines to give amides. Reduction with $LiAlH_4$ yields acyclic diols, while the products with DIBAL are furans.[75] Among reactions characteristic to butenolides, base-mediated oxygenation gives γ-hydroxy butenolides.[76] The

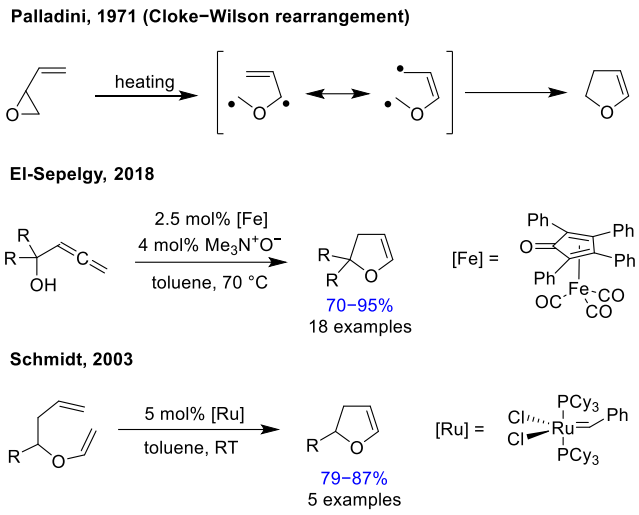
oxidation proceeds under mild conditions and can reach completion within hours. In addition, the reaction with diazomethanes would give β-methylation products.[75]



Scheme 40: Overview of characteristic oxidation, reduction and substitution reactions of butenolides.

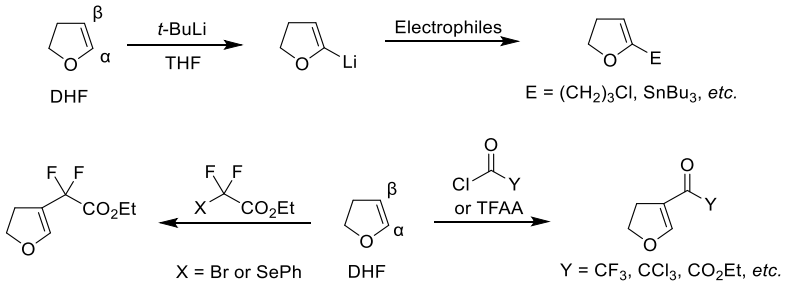
2,3-Dihydrofuran

The term 'dihydrofuran' (DHF) normally refers to 2,3-dihydrofuran, the cyclic enol ether among whose derivatives are biologically active natural products found in many plant species. The compound can be accessed from the incomplete hydrogenation of furan,[32] yet its derivatives are normally accessed from acyclic precursors (*Scheme 41*). For example, the Cloke−Wilson rearrangement of vinyl epoxides, which likely proceeds *via* diradical intermediates, is a classical method to access the DHF ring system.[77] Dihydrofurans are also prepared from the rearrangement of α-allenyl alcohols,[78] which are the reduction products of allenyl ketones used in Marshall's furan synthesis.[53c] Other pathways toward DHF derivatives included ring-closing metathesis and catalysed cycloaddition reactions.[79−80]



Scheme 41: Examples of 2,3-dihydrofuran synthesis from non-aromatic precursors.

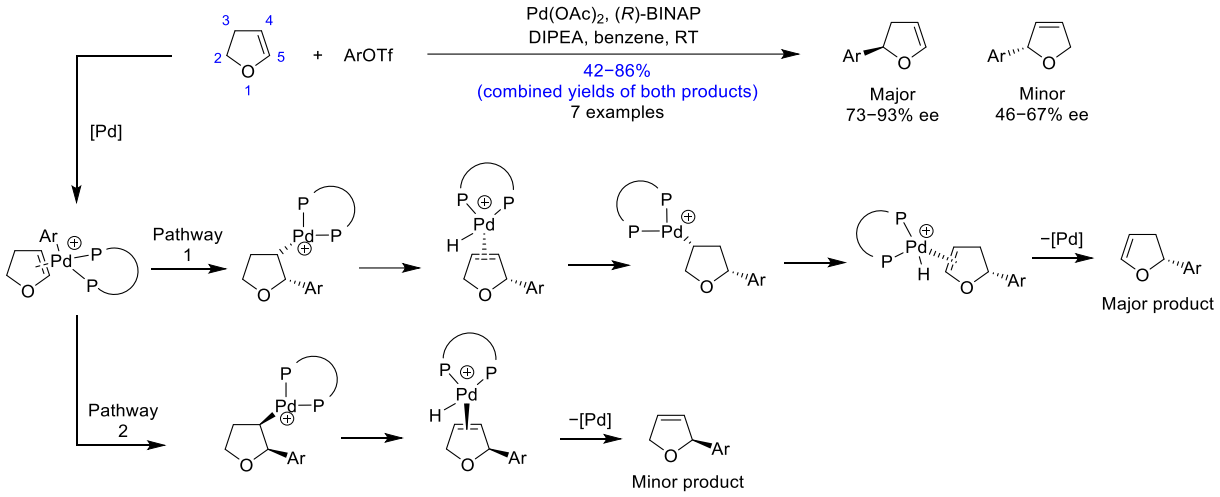
The dihydrofuran ring system is known for its substitution and addition reactions. Substitution mostly occurs on the α- and β-positions (*Scheme 42*). The α-deprotonation of 2,3-dihydrofuran is most effectively performed with *tert*-butyllithium;[81] subsequent electrophilic trapping is known to give alkylation, acylation and metallation products.[81c,82] By comparison, β-substitution to date has only been achieved using strong electrophiles such as trichloroacetyl chloride or fluorinated compounds.[83] The β-acylation products can either be aromatised to give 3-substituted furans[83a] or undergo addition reactions that produce derivatives of tetrahydrofuran.[84]



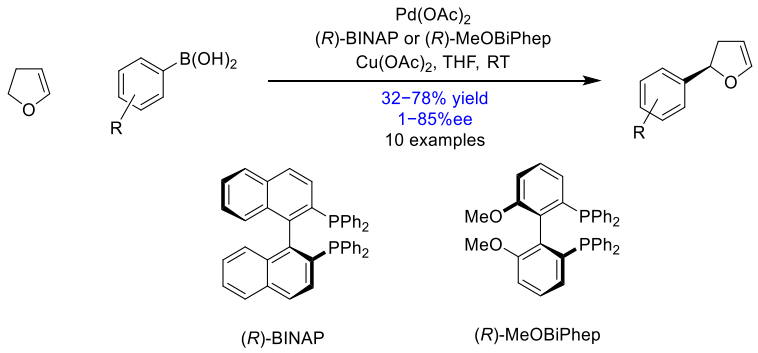
Scheme 42: Overview of the α- and β-functionalisation of 2,3-dihydrofuran.

The ‘saturated’ side of the DHF ring can be functionalised by cross-coupling reactions. In fact, the first reported example of asymmetric Heck coupling used 2,3-dihydrofuran with aryl

triflates in the presence of palladium(II) acetate and (*R*)-BINAP.[85] As the proposed mechanism shows, the position is the α-position, as the catalyst undergoes several insertion and β-hydride elimination processes during the reaction (*Scheme 43*). It is noteworthy that double-bond isomerisation was observed which generated 2,5-dihydrofuran derivatives with opposite configuration to the desired products. This can be explained by the catalyst-induced kinetic resolution through its stereoselective re-insertion of the 2,5-dihydrofuran intermediates. Apart from aryl triflates, enantioselective 2-functionalisation is achievable also with arylboronic acids, although the yields and stereoselectivity are both found to vary greatly with choice of substrate and ligand (*Scheme 44*).[86]



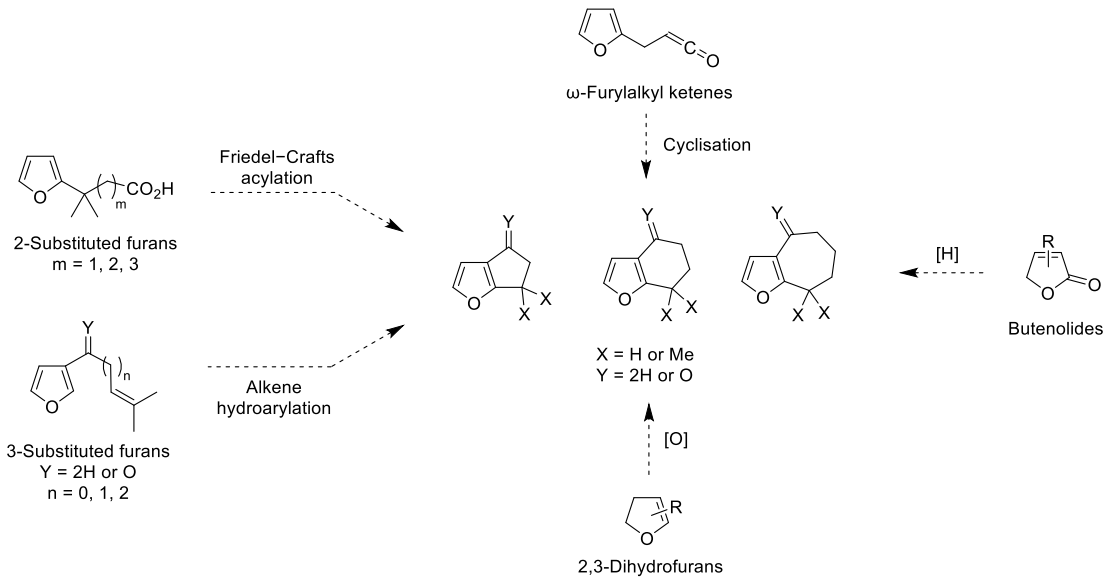
Scheme 43: Outcome and proposed mechanism of the palladium-catalysed enantioselective 2-arylation of DHF by aryl triflates.



Scheme 44: Outcome of the palladium-catalysed enantioselective 2-arylation of DHF by arylboronic acids.

Aims and proposed work

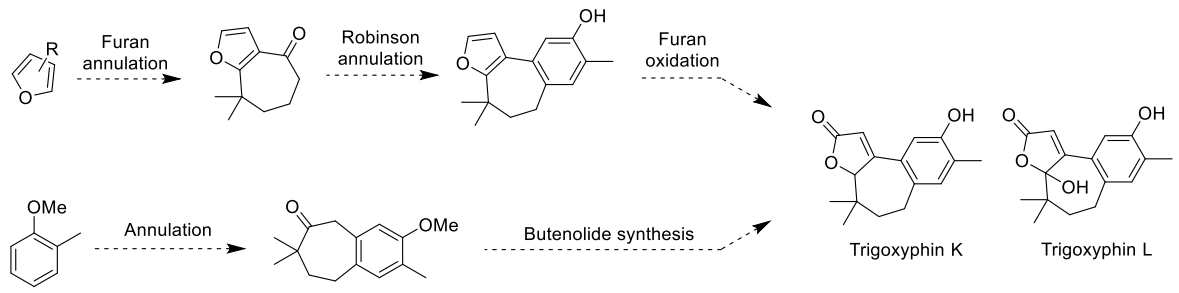
This thesis describes efforts toward short and efficient synthetic methodologies for furano[*b*]cycloalkanes. Two types of starting materials were investigated, which represent different pathways to establish the bicyclic skeleton of the target molecules (*Scheme 45*). The first type is 2- and 3-substituted furan derivatives, in particular those with fully substituted furfurylic carbons as their synthesis is rarely achieved *via* Friedel−Crafts acylation. Furan annulation efforts also examined ω-furylalkyl ketenes, highly reactive species which were expected to achieve spontaneous and atom-efficient furan annulation. The non-aromatic furan precursors to be discussed included the acyclic furan synthesis 'motifs' discussed above and the derivatives of 2,3-dihydrofuran (DHF) and 2(5*H*)-furanone (butenolide).



Scheme 45: Overview of proposed synthetic routes toward furano[*b*]cycloalkanes.

Furthermore, it was planned for the synthetic efforts on furanocycloalkanones to contribute to the total synthesis of trigoxyphins K and L, two tricyclic diterpenoids derived from 2(5*H*)-furanone (*Scheme 46*). Initial efforts used monosubstituted furans to construct the tricyclic core that deliver the butenolide ring *via* late-stage furan oxidation; this was envisaged to involve a

furano[*b*]cycloalkanone intermediate. In parallel, a second route was developed where the tricyclic structure is constructed from the benzene ring without recourse to furan derivatives. As this route predominantly employed conventional synthetic methods, it was hoped that improved overall yields could be achieved within fewer steps.



Scheme 46: Overview of the two synthetic routes envisaged for trigoxyphins K and L.

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Chapter 1: Synthesis of Furano[*b*]cycloalkanones with Fully Alkylated Furfurylic Carbons

1.1 Background

As a prominent class of [*b*]-annulated furans, furano[*b*]cycloalkanones are present in several biologically active natural products, many of which feature carbonyl groups adjacent to the 3-position of the furan ring (*Figure 1*).[1–4] The synthesis of these compounds dates back to 1959, when Taylor and co-workers achieved the Friedel–Crafts acylation of γ-(5-methylfuran-2-yl)butyric acid with PCl_5 and $SnCl_4$.[5] Riedel and Maier later used the same protocol to achieve quantitative yields at gram scale.[6] More recently, TFAA has gained in popularity as a mild alternative which obviates the need for a Lewis acid catalyst.[7–8] Although furan annulation *via* Friedel–Crafts acylation can usually achieve good yields, a new generation of non-acylating ring fusion protocols have been established, notably those using Feist–Benary synthesis or cycloaddition reactions. These new methodologies are well suited for acid-sensitive furan derivatives which decompose under Friedel–Crafts conditions.

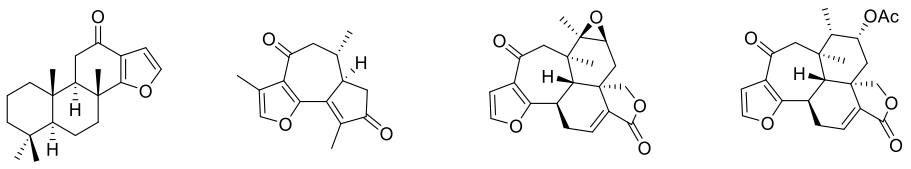
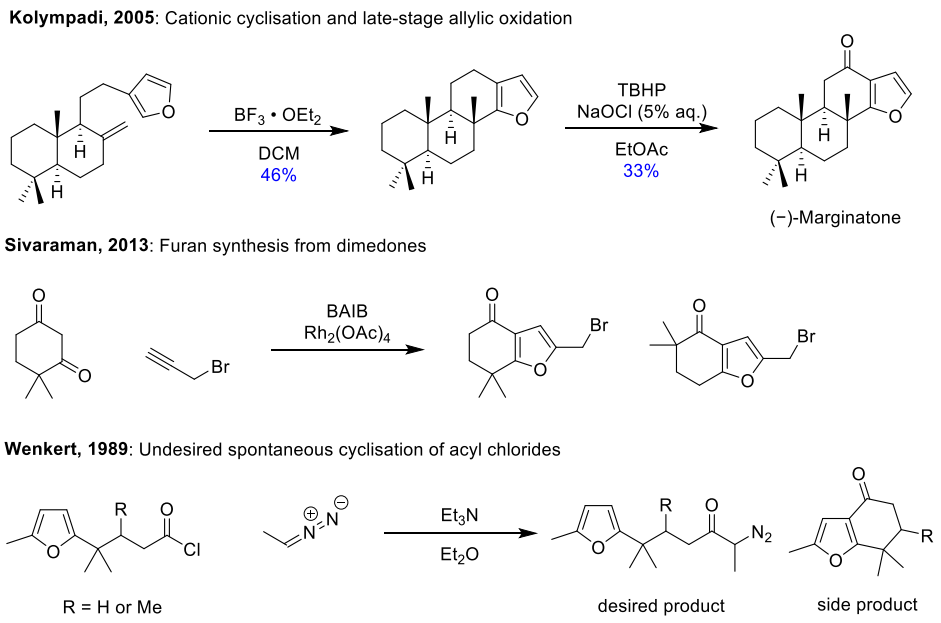


Figure 1: Selected examples of natural products belonging to the family of [*b*]-annulated furans.

The focus of this chapter is on furano[*b*]cycloalkane-1-ones in which the 2-furyl α-position (furfurylic position) is fully substituted. The challenges with their synthesis arise primarily from the difficulty in accessing furan precursors bearing these sterically encumbered furfurylic carbons or by connecting such quaternary carbons to the 2-position of the furan ring. Many

reported syntheses use either expensive and relatively inaccessible 3-substituted furans as cyclisation precursors or rearrange non-aromatic compounds into furan derivatives.[1,9] Kolympadi and co-workers, for example, used Lewis acid-mediated alkene hydroarylation followed by allylic oxidation in their total synthesis of (−)-marginatone (*Scheme 1*). There are very few reported syntheses of furano[*b*]cycloalkan-1-ones with fully substituted furfurylic carbons achieved by cyclisation through Friedel−Crafts acylation; a notable example was reported by Wenkert in which 5/6-fused bicyclic furans were obtained as side products from the undesired cyclisation of acyl chloride substrates.[10]

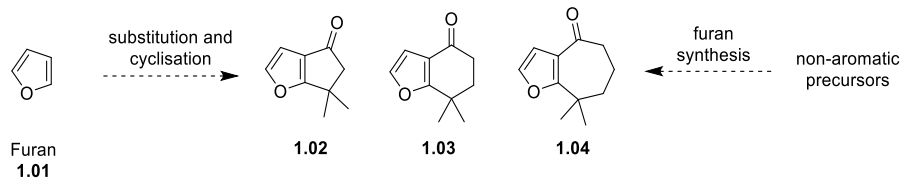


Scheme 1: Examples of established syntheses of furano[*b*]cycloalkan-1-ones with fully-substituted 2α-positions.

1.2 Aims of this project

The project sought to establish short (≤ 5 steps) and efficient synthetic routes toward 5/5-, 5/6- and 5/7-ring fused furano[*b*]cycloalkan-1-ones bearing fully substituted 2α-carbons, ideally using furan (**1.01**) or 2-substituted furans as starting materials (*Scheme 2*). Ketones **1.02**, **1.03**

and **1.04**, with the geminal dimethyl functionality at their 2α-positions, were chosen as representative target molecules for this work. Efforts were primarily aimed at establishing viable routes beginning with furan itself; in parallel, furan synthesis strategies using non-aromatic starting materials were also developed.



Scheme 2: Overview of the proposed work to be discussed in this chapter.

1.3 The Friedel−Crafts acylation pathway

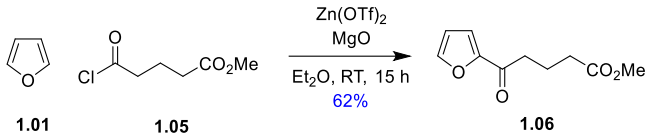
To date, the Friedel−Crafts acylation remains the most thoroughly studied and frequently used reaction for the cyclisation of substituted aromatic compounds, and it was the principal means of cyclisation onto the furan ring studied in this work. Efforts exclusively used trifluoroacetic anhydride (TFAA) as acylation reagent owing to its efficiency and clean reactions, and a variety of synthesis strategies for 2α,2α-dimethylated furan substrates were investigated.

1.3.1 The carbonyl *gem*-dimethylation strategy

The conversion of ketones into geminal dimethyl functionality was first reported in 1974 by Meisters and Mole with trimethylaluminum.[11] Over the following decades new methylation protocols have been established, many of which use organozinc and organotitanium complexes.[12–13] The reported substrates are predominantly simple alkyl and aryl ketones

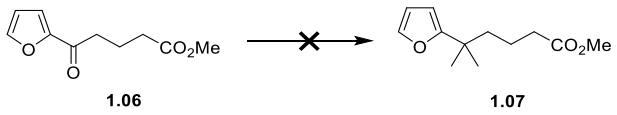
containing at most alkoxy groups, and it is not reported whether the geminal dimethylation reaction tolerates other functional groups.

Initial efforts targeted the synthesis of 5/7-ring fused **1.04** *via* keto ester **1.06**, prepared directly from furan with acyl chloride **1.05**.[14] Magnesium oxide was used in the Friedel−Crafts acylation reaction as a scavenger of the HCl by-product which if not scavenged was found to negatively affect the yields (*Scheme 3*).



Scheme 3: Preparation of keto ester **1.06** through Friedel−Crafts furan acylation

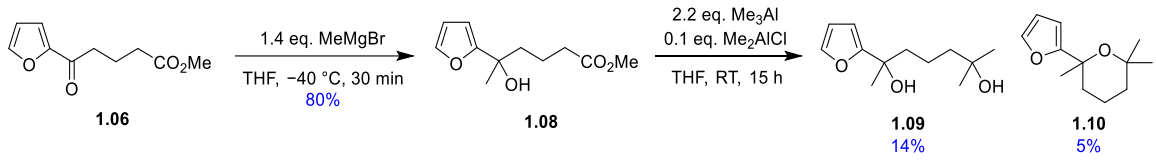
To begin with, a variety of organometallic complexes were screened for the geminal dimethylation of keto ester **1.06**, ranging from strongly Lewis acidic Me_2TiCl_2 to the milder organoaluminium and organozinc complexes (*Scheme 4*).[12,13,15] Complicated mixtures were obtained from all trials, and it was unclear if any nucleophilic addition occurred on the substrate.



Scheme 4: Attempted one-pot geminal dimethylation of **1.06** by organometallic complexes. The conditions used included: (a) $TiCl_4$, Me_2Zn, DCM, −78 °C; (b) Me_3Al, Me_2AlCl, DCM, 0 °C; (c) Me_3Al, TMSOTf, DCM, 0 °C.

Zefirova proposed that the carbonyl *geminal* dimethylation could be achieved stepwise, where a tertiary alcohol is generated from a Grignard reaction in the first step.[16] Nucleophilic addition of keto ester **1.06** gave alcohol **1.08** where the ester group was unaffected. While Zefirova's method with $TiCl_4$ and Me_2Zn only resulted in the decomposition of **1.08**, a new attempt using Kim's protocol (*Scheme 5*)[15] delivered small amounts of diol **1.09** and ether **1.10**. This

indicated preferential nucleophilic attack on the ester group of **1.08**, followed by partial self-condensation of the diol product **1.09**. However, control experiments with 2-acetylfuran and 2-(furan-2-yl)propan-2-ol as substrates only resulted in the decomposition of both compounds. It was thus concluded that the organometallic reagents used were not suitable for 2-acyl furan substrates.

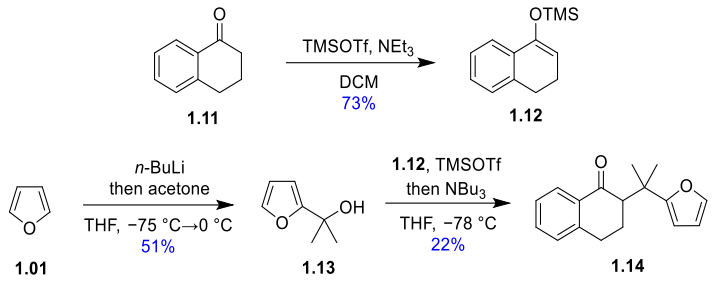


Scheme 5: Attempted stepwise geminal dimethylation of keto ester **1.06**.

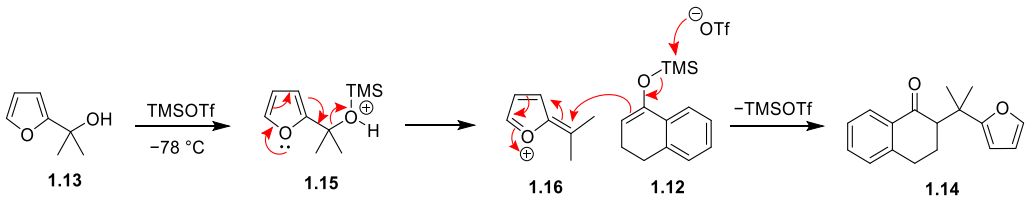
1.3.2 The Lewis acid-catalysed coupling strategy

The challenge of incorporating a quaternary centre at the furfurylic carbon has inspired us to evaluate a new coupling strategy that takes advantage of furan's electron richness. Through their studies on indolyl carbinols, Martin *et al.* developed a TMSOTf-mediated coupling protocol with silyl ketene acetals.[17] With 0.9 equivalents of the Lewis acid, substrates derived from indole, benzo[*b*]furan, pyrrole, furan and thiophene were reported to generate β-heteroaryl propionates efficiently. Through extensive research on the reaction of furan carbinol **1.13** with acetophenone-derived silyl enol ethers, DPhil student Harwood of our group found that the products tended to decompose shortly after being generated, and that quenching the reaction mixture after 5−10 minutes was necessary for satisfactory results.[18] Following Harwood's precedent, the TMS enol ether of 1-tetralone was converted into ketone **1.14**, which remained stable in the reaction mixture for up to an hour (*Scheme 6*). Mechanistically, we believe that the Lewis acid reacts with the furyl carbinol to produce an oxonium species (**1.16** in *Scheme 7*), which is then trapped *in situ* by the silyl enol ether. The silyl group then detached

to re-form the silyl triflate catalyst, completing the catalytic cycle. Owing to its fast progress and convenient work-up, this coupling reaction is very useful for electron-rich aromatic compounds bearing quaternary α-carbons.



Scheme 6: The TMSOTf-mediated coupling of furan carbinol **1.13** with tetralone-derived TMS enol ether **1.12**.

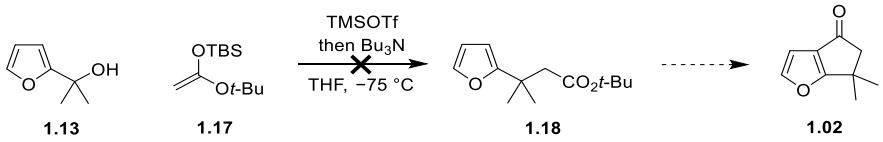


Scheme 7: Proposed mechanism of the aforementioned TMSOTf-mediated coupling reaction.

1.3.2.1 Toward the 5/5- and 5/7-ring fused systems

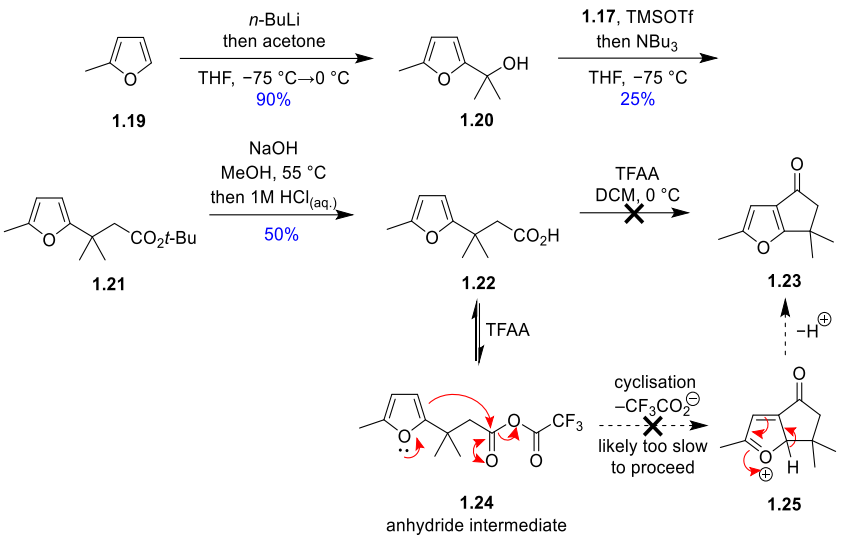
Silyl ketene acetals are more nucleophilic than silyl enol ethers due to the presence of an additional electron-releasing alkoxy group. They are normally prepared by formation of the ester enolate with a strong non-nucleophilic base, then trapping by reactive silylating agents. The coupling reactions with silyl ketene acetals give ester products, whose derived carboxylic acids would serve as Friedel−Crafts acylation substrates. Because silyl ketene acetals, and the extended dienyl variants, provide donor synthons with two and four carbon units respectively, this strategy could be used to access 5/5- and 5/7-ring fused systems.

The synthesis of the 5/5-ring fused ketone **1.02** required the silyl ketene acetal derived from acetic acid, the selected candidate being **1.17**, in which the TBS and *tert*-butyl substituents were expected to enhance its reactivity and stabilise the cationic intermediate (*Scheme 7*). Trials with furan carbinol **1.13** produced no desired product whatsoever. The silyl ketene acetal hydrolysed during the reaction, and the crude product mixtures contained predominantly residual silane and tributylamine.



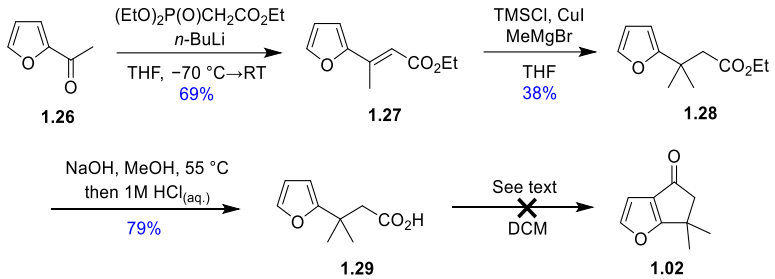
Scheme 8: Attempted coupling of carbinol **1.13** with silyl ketene acetals **1.17**.

By contrast, carbinol **1.20** derived from 2-methylfuran **1.19** was successfully coupled to give the ester product **1.21**, albeit in a low yield (*Scheme 9*). The 5-methyl substituent of **1.20** likely contributed to the improved result through shielding the 5-position from nucleophilic attack by the silyl ketene acetal. Hydrolysis of ester **1.21** afforded carboxylic acid **1.22**, whose annulation into bicyclic compound **1.23** was attempted using TFAA. The mechanism of the cyclisation step is assumed to involve the formation of a mixed anhydride intermediate (**1.24**, *Scheme 9*), as its good trifluoroacetate leaving group should facilitate nucleophilic attack from the furan ring. Nevertheless, it transpired that **1.22** decomposed extensively in the reaction mixture and no annulation product was detected. The failure of the annulation step was likely attributed to the short lifespan of the anhydride intermediate with regard to the rate of ring closure, as the sterically hindered carbon centre next to the furan ring likely made it difficult for the formation of a relatively small five-membered ring.



Scheme 9: Preparation of *tert*-butyl ester **1.21** and attempted annulation of the derived acid **1.22**, with a proposed mechanism for the intended cyclisation step.

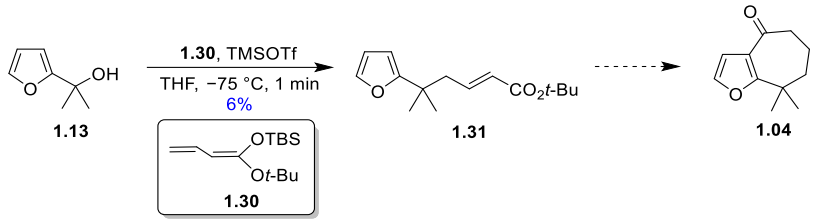
A new attempt on 5/5-fused systems through Friedel−Crafts acylation was undertaken using monosubstituted furan **1.29**, as the compound was more synthetically accessible and would lead to the desired target **1.02**. The carboxylic acid was prepared from 2-acetylfuran with an overall yield over three steps of 21%. Like its analogue **1.22**, decomposition resulted when **1.29** was treated with TFAA or Lewis acids (*Scheme 10*); consequently, no further pursuits of 5/5-ring fused systems were undertaken.



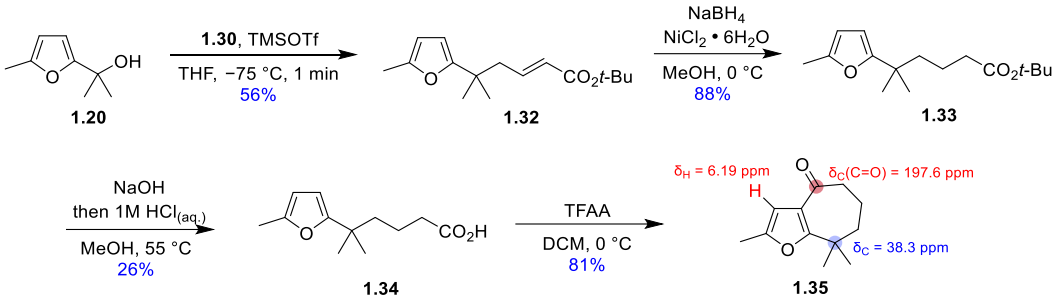
Scheme 10: Synthesis of carboxylic acid **1.29** and its attempted cyclisation. Reagents and conditions used: (a) TFAA, DCM, 0 °C; (b) BF_3•OEt_2, DCM, 0 °C; (c) $SnCl_4$, DCM, −30 °C.

The synthesis of 5/7-ring fused ketone **1.04** required an alkene-extended silyl ketene acetal – derived from an α,β-unsaturated ester – and **1.30** was targeted in analogy to the simpler silyl

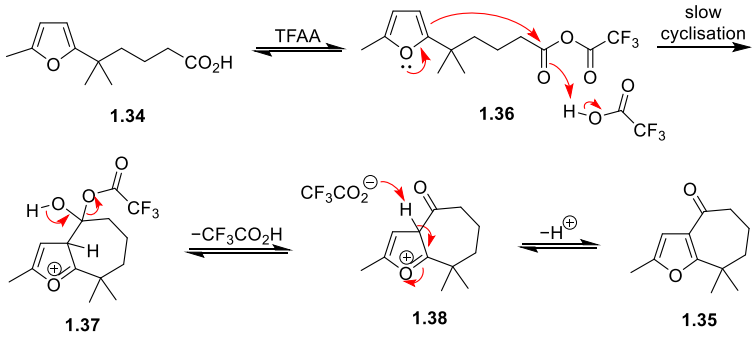
ketene acetal **1.17**. Attempted couplings with the simplest furan carbinol (**1.13**) produced only traces of the desired product **1.31**, with significant amounts of silane residues detected in the crude mixture (*Scheme 11*). In addition, ester **1.31** was found to have a short lifespan in the reaction mixtures, and the 'highest' yield of 6% was obtained from a one-minute reaction. Markedly higher yields of coupling product **1.32** were obtained using alcohol **1.20** as substrate (*Scheme 12*). Reduction of **1.32** and subsequent ester hydrolysis gave carboxylic acid **1.34**, which cyclised efficiently in the presence of excess TFAA to deliver exclusively the 5/7-ring fused ketone **1.35**. It is believed that the distance between the carbonyl group of anhydride intermediate **1.36** (*Scheme 13*) and its bulky *geminal* dimethyl group contributed to its fast and successful cyclisation. The 1H NMR spectrum of **1.35** showed only one signal (δ_H = 6.19 ppm) in the olefinic region, confirming the tri-substituted nature of the furan ring. Furthermore, the ^{1}H-^{13}C HMBC spectrum of **1.35** indicated the correlation of furan proton (δ_C = 197.6 ppm) with the carbonyl carbon (δ_C = 197.6 ppm) but not the quaternary centre (highlighted in blue, δ_C = 38.3 ppm). This confirms that the carbonyl group of **1.35** is adjacent to the unsubstituted furan carbon, which could not be deduced from one-dimensional NMR or IR spectroscopy alone.



Scheme 11: Outcome of the coupling reaction of **1.13** with silyl ketene acetal **1.30**. The low yield obtained for **1.31** made impractical further reactions toward annulated furan **1.04**.

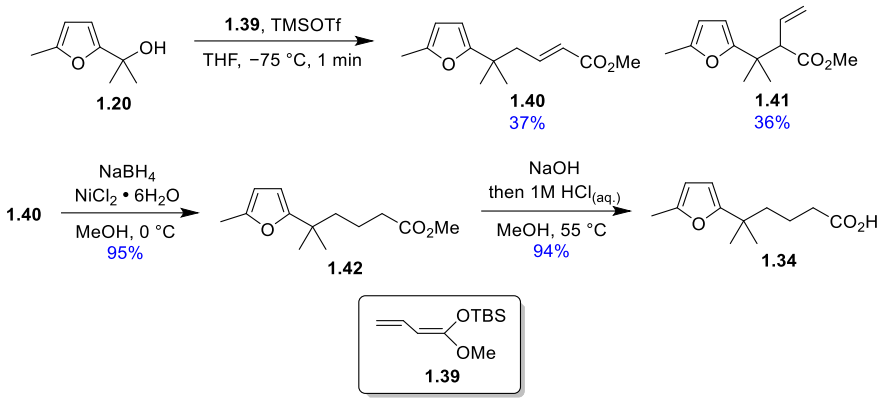


Scheme 12: Outcome of the coupling reaction of **1.20** with silyl ketene acetal **1.30**, whose product **1.32** was converted into 5/7-ring fused ketone **1.35**. The identity of **1.35** was confirmed by HMBC spectroscopy where the atoms in red showed correlation with each other.



Scheme 13: The proposed mechanism of the cyclisation step (**1.34**→**1.35**).

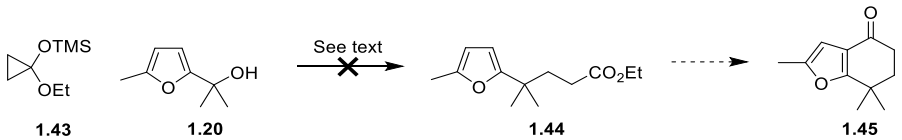
It was postulated that the low yield of the hydrolysis resulted from the stability of *tert*-butyl esters, and thus the coupling reaction was repeated using TBS−methyl ketene acetal **1.39** (*Scheme 14*). The reaction gave markedly better yields but chemoselectivity was poor; ^{1}H NMR suggested that the desired product **1.40** and its branched isomer **1.41** were present in approximately equal amounts. By contrast, the *tert*-butyl ester **1.32** had been the only product detected. Nevertheless, the two products were easily isolated and subsequent reduction and hydrolysis reactions **1.42** gave acid **1.34** in 94% yield. With this optimisation, the synthesis of ketone **1.35** was achieved in five steps from 2-methylfuran with an overall yield of 21%.



Scheme 14: Alternative synthesis of carboxylic acid **1.34** using silyl ketene acetal **1.39** for the coupling reaction with alcohol **1.20**.

1.3.2.2 Toward the 5/6-ring fused system

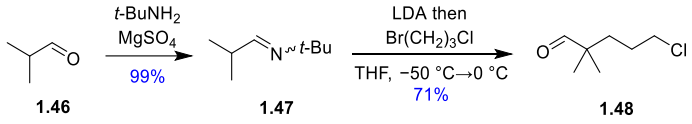
The 5/6-ring fused ring system requires a three-carbon donor synthon for the coupling reaction. As providers of even-numbered carbon synthons, silyl ketene acetals are unfit for this purpose. Instead, cyclopropane derivative **1.43** was proposed as the nucleophilic component, its reactions with diaryl- and triaryl-substituted methanols having been extensively studied by Zhang and co-workers.[19] Although it is commercially available, it could be prepared by treating ethyl acrylate with sodium metal and TMSCl. In practice, the silyl acetal did not effectively trap the cationic intermediate generated from **1.20**; the total loss of the substrate resulted in all trials conducted (*Scheme 15*). Since the activation of **1.20** was achievable using TMSOTf, we believe that silyl acetal **1.43** was not sufficiently nucleophilic to trap the oxonium intermediate from **1.20** effectively, resulting in the oligomerisation of the furyl carbinol.



Scheme 15: Attempted coupling of silyl acetal **1.43** with alcohol **1.20**. Reagents and conditions used: (a) TMSOTf, THF, −78 °C; (b) $TiCl_4$, DCM, −78 °C; (c) BF_3•OEt_2, DCM; (d) BBr_3, DCM, −78 °C.

1.3.3 The furan synthesis strategy

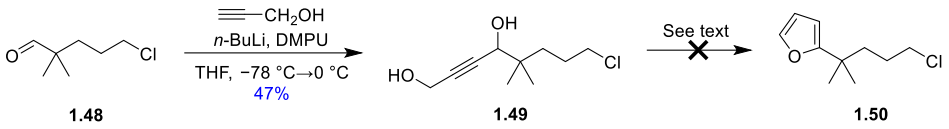
Faced with a limited range of viable synthetic methods from furans, attention turned to furan synthesis protocols with non-aromatic starting materials. The key objective was the development of a non-aromatic 'motif' that could rearrange itself into a furan derivative, which would subsequently give a carboxylic acid for cyclisation through Friedel−Crafts acylation. The investigation of these four non-aromatic structural motifs started from the preparation of their common precursor **1.48** using alkylation of imine **1.47**; which served to introduce the crucial *gem*-dimethyl functionality (*Scheme 16*).



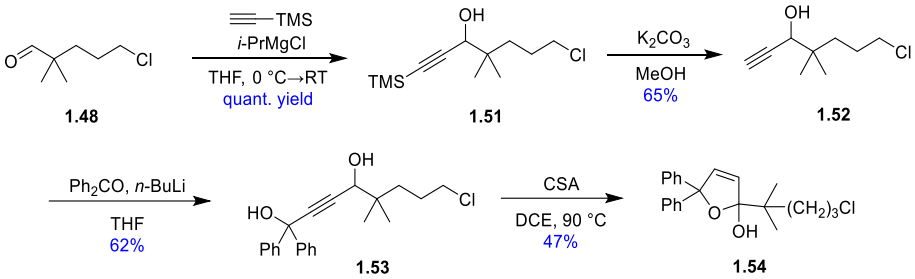
Scheme 16: Preparation of aldehyde **1.48** from isobutyraldehyde.

1.3.3.1 From 1,4-diol-2-ynes

Alkyne diol **1.49**, the first substrate examined, was prepared from aldehyde **1.48**, yet in the subsequent furan synthesis trials it remained stable to all conditions tested (*Scheme 17*).[20–22] For comparison purposes, alkyne diol **1.53** was subjected to Mothe's cycloisomerisation protocol for 2,3,5-trisubstituted furans (*Scheme 18*).[22] The reaction stalled at compound **1.54** and, despite prolonged heating at elevated temperatures, this intermediate did not progress to the furan (by loss of water and phenyl [1,2]-shift). The successful production of intermediate **1.54** indicated, however, that the aryl substituents were influential in the cyclisation step.



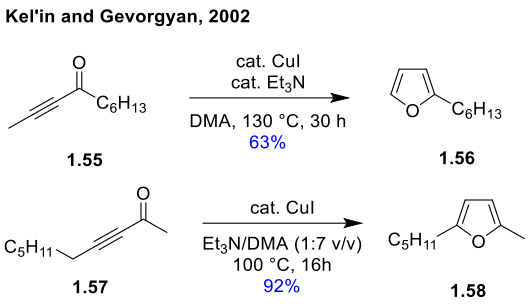
Scheme 17: Preparation of ynediol **1.49** and its attempted cyclisation. Reagents and conditions tested for the second step: (a) CSA, DCE, 90 °C, 16 h; (b) $Pd_2(dba)_3$, *n*-Bu_3P, $CHCl_3$, 80 °C, 24 h; (c) $Ru(PPh_3)_4Cl_2$, toluene, reflux, 36 h.



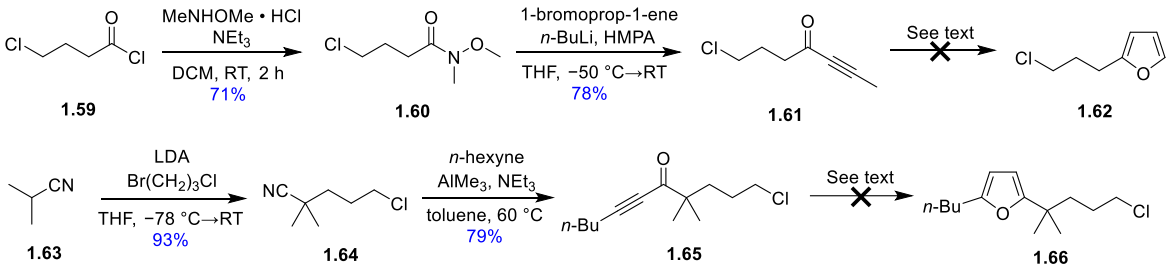
Scheme 18: Preparation of ynediol **1.53** and its conversion into 2,5-dihydrofuran-2-ol **1.54**.

1.3.3.2 From conjugate ynones

In 2002, Kel'in and Gevorgyan[23] presented the successful furan synthesis from a variety of ynones using copper(I) iodide and triethylamine. Among the substrates used were mono- and di-substituted furans with alkyl side chains such as **1.55** and **1.57** (*Scheme 19*). Accordingly, efforts examined structurally analogous ynones **1.61** and **1.65** as potential furan precursors, which had similar structural features to aldehyde **1.48** and whose synthesis from commercially available starting materials was short and efficient (*Scheme 20*). The former was derived from acyl chloride **1.59** through Weinreb ketone synthesis, while the latter was prepared from nitrile **1.63** and *n*-hexyne using Korbad's protocol.[24] Unfortunately, in the furan synthesis attempts,[23,25] both substrates remained stable to the reaction conditions applied and were recoverable from the reaction mixtures.



Scheme 19: Gevorgyan's examples of CuI-catalysed rearrangements of ynones **1.55** and **1.57**.

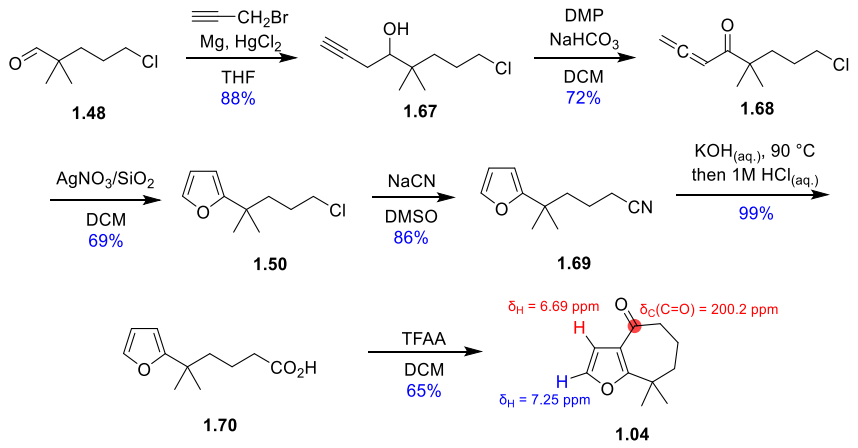


Scheme 20: Synthesis of ynone substrates **1.61** and **1.65** and their attempted rearrangement to furans. Reagents and conditions tested: (a) CuI (10 mol%), Et_3N/DMA (1:7 v/v), 100 °C, 24 h; (b) CuI (10 mol%), Et_3N (5 mol%), DMA, 100 °C, 24 h; (c) $Pd(dba)_2$, PPh_3, RT, 16 h.

1.3.3.3 From allenyl ketones

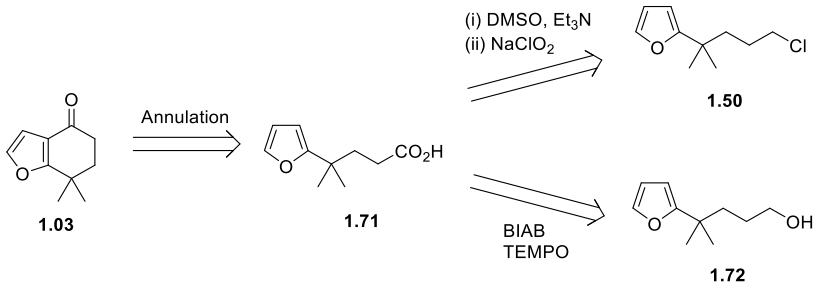
The silver(I)-mediated rearrangement of allenyl ketones features mild conditions and a simple filtration work-up. A synthesis of 5/7-ring fused ketone **1.04** was achieved, based on this methodology, developing from isobutyraldehyde to allenyl ketone **1.68** *via* imine alkylation, propargylation and oxidation (*Scheme 21*). In the oxidation step from alcohol **1.67**, both PCC and the Swern oxidation conditions resulted in varying degrees of substrate decomposition. Marshall's protocol applied to the rearrangement of allenone **1.68** reached completion within 4 hours to give furan derivative **1.50** in 69% yield.[26] Completion of the synthesis by homologation and TFAA-mediated cyclisation gave the target compound **1.04**. This was

reflected by ^{1}H-^{13}C HMBC data, where the carbonyl carbon showed correlation with the furan proton at the β- position but not the α-position.

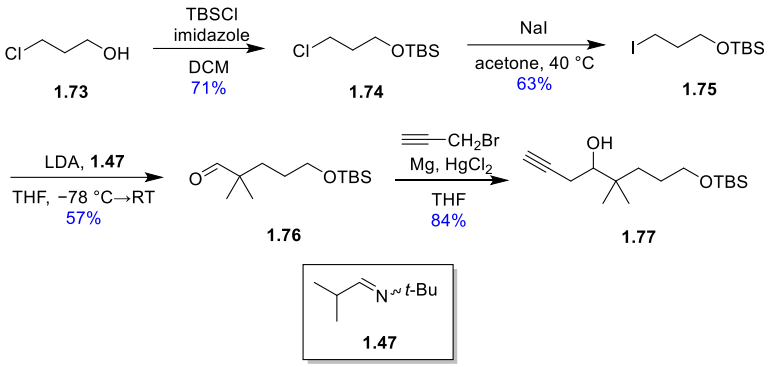


Scheme 21: Synthesis of ketone **1.04** from aldehyde **1.48**, *via* rearrangement of allenyl ketone **1.68**. The identity of **1.04** was confirmed by HMBC where the atoms in red showed correlation with each other.

Efforts targeted 5/6-ring fused ketone **1.03** next. Its precursor **1.71** could in principle be obtained from chloride **1.50** using Kornblum and Pinnick oxidations, yet Epp's protocol with BIAB/TEMPO would allow a one-step alternative from alcohol **1.72** (*Scheme 22*).[27] The synthesis of **1.72** required a different electrophile for the imine alkylation; unlike the 1,3-dihalide used to access aldehyde **1.48**, 1,2-dihalides are prone to E2-type elimination under strongly basic conditions and were deemed unsuitable for the alkylation of imine **1.47**. The silyl ether of 3-iodopropan-1-ol was used instead, providing a masked alcohol from which later desilylation and oxidation would give a carboxylic acid. The TBS ether of 3-iodopropan-1-ol gave the expected alkylation product **1.76** and subsequent treatment with propargylmagnesium bromide delivered homopropargylic alcohol **1.77** (*Scheme 22*).

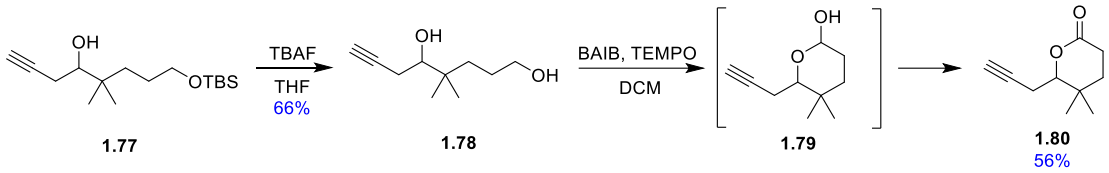


Scheme 22: Comparison of the prospective synthetic routes to carboxylic acid **1.71**, precursor to **1.03**.

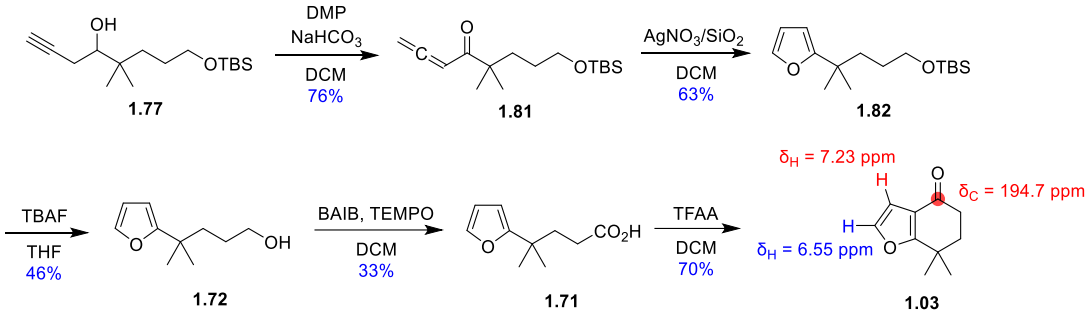


Scheme 23: Preparation of homopropargylic alcohol **1.77** from 3-chloropropan-1-ol and imine **1.47**.

At this stage, efforts proceeded with the desilylation of **1.77**, intending that the product **1.78** would be directly oxidised by BAIB and TEMPO into a ketocarboxylic acid. In reality, the oxidation reaction gave δ-lactone **1.80**, indicating initial oxidation of the 1° alcohol then cyclisation (→ lactol **1.79**) before oxidation of the 2° alcohol, the latter being slowed by the bulky *geminal* dimethyl functionality which might also promote the formation of the lactol (*Scheme 24*). Retaining the TBS group until after the furan synthesis gave significantly better results, delivering the desired carboxylic acid **1.71**. No optimisation of the desilylation and oxidation steps were conducted, given that the amount of **1.71** generated from an 8-step synthesis was sufficient for the subsequent Friedel−Crafts acylation. In the presence of excess TFAA, the cyclisation of **1.71** proceeded smoothly and delivered ketone **1.03** (*Scheme 25*).

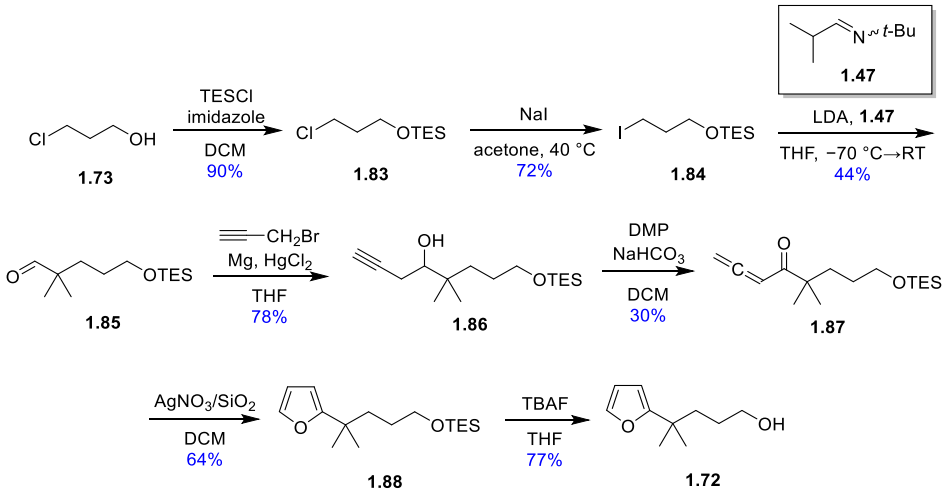


Scheme 24: Attempted route diversion with diol **1.77**, resulting in lactone **1.80**.



Scheme 25: Completion of the synthesis of furano[*b*]cyclohexanone **1.03** from **1.77**. ^{1}H-^{13}C correlation was shown by atoms of **1.03** highlighted in red.

The route was repeated with TES in place of TBS in the hope of improving the yield for the desilylation step. While the intended purpose was fulfilled (77% for **1.88** → **1.72** *vs.* 46% for **1.82** → **1.72**), the yields were reduced in most of the preceding steps (*Scheme 26*) which demonstrated the susceptibility of this less sterically-hindered silyl protecting group to the reaction conditions applied.

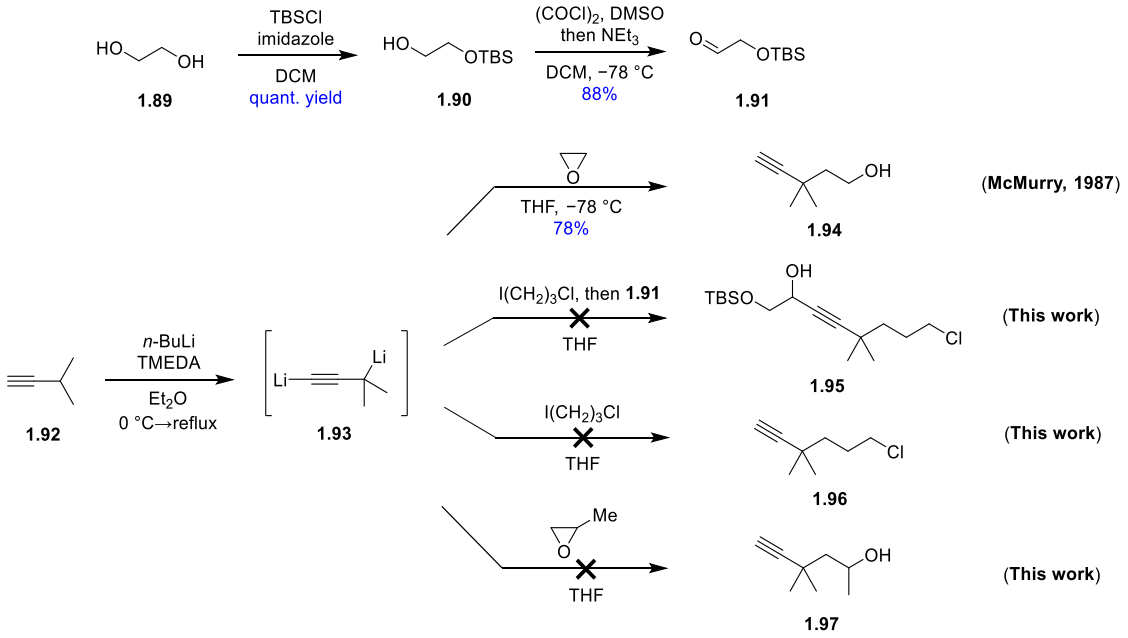


Scheme 26: Preparation of furyl alcohol **1.72** *via* TES ether intermediates.

1.3.3.4 From 3-yne-1,2-diols

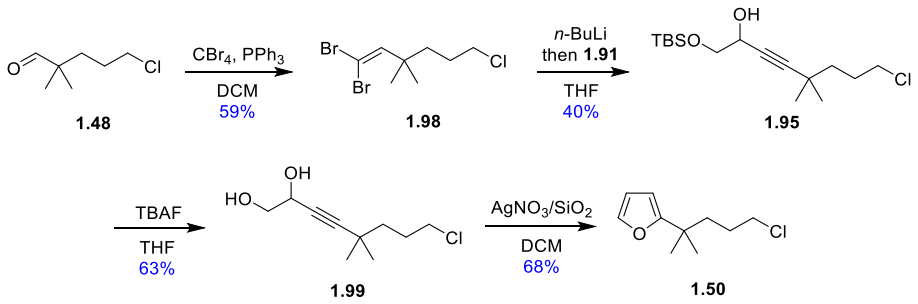
Isomeric to 2-yne-1,4-diols, 3-yne-1,2-diols are also proven furan precursors. As discussed in **Introduction**, their conversion into furans may be achieved with the same catalysts used for the rearrangement of allenyl ketones.[28] In principle, then, 3-yne-1,2-diols could be better alternatives to allenyl ketones if their synthesis are shorter and more efficient.

Targeting monosilylated alkyne diol **1.95**, the initially proposed route began from 3-methyl-1-butyne, whose 1,3-dilithiation and alkylation was reported by McMurry to deliver alcohol **1.94**.[29] This distinct reactivity is likely specific to ethylene oxide, because attempts with either 1-chloro-3-iodopropane or propylene oxide as electrophiles generated no isolable products whatsoever (*Scheme 27*).



Scheme 27: Outcome of attempted 3-alkylation reactions of 3-methyl-1-butyne **1.92**.

The preparation of **1.95** was achieved by a new route that featured the Corey−Fuchs methodology from aldehyde **1.48**, then cyclisation of ynediol **1.99** using $AgNO_3$-impregnated silica, as before, to deliver furan **1.50** (*Scheme 28*). This route was not an improvement on the allenyl ketone route, as it delivered furan **1.50** in 10% yield over four steps from aldehyde **1.48**, compared with 44% yield over three steps achieved by the allenyl route. Furthermore, the cyclisation of **1.99** took 8–16 hours to complete while, under the same conditions, the conversion of allenyl ketone **1.68** into furan **1.50** reached completion within 4 hours.

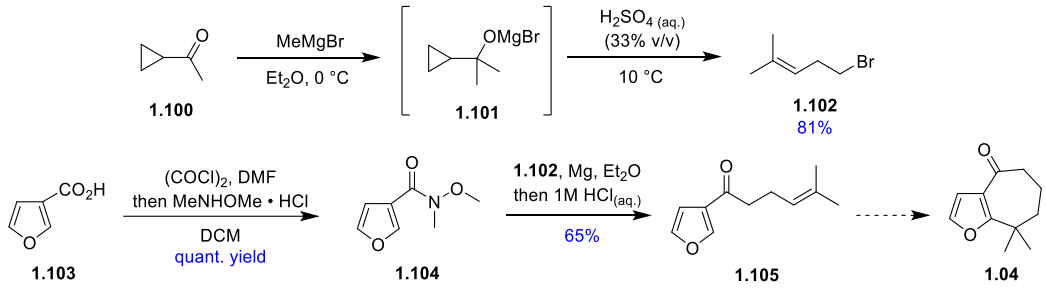


Scheme 28: Synthesis of furan **1.50** through rearrangement of 3-yne-1,2-diol **1.99**.

1.4 The alkene hydroarylation route

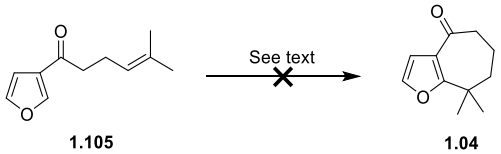
The Friedel−Crafts pathway proved capable of delivering the 2α,2α-dimethylated furanocycloalkanone targets, although the need to access the carboxylic acid precursors prolonged the synthesis and reduced its efficiency. As an alternative cyclisation method, alkene hydroarylation features mild reaction conditions and dispenses with the need to prepare labile ω-furylcarboxylic acid substrates. Originating from Spivey's report on the hydroarylation of styrene derivatives,[30] the alkene hydroarylation route sought to explore the viability of 3-acyl furans as possible precursors to the bicyclic target molecules.

The investigation of this methodology started with the preparation of ketone **1.105** which, upon successful cyclisation, would deliver the 5/7-fused bicyclic ketone **1.04** (*Scheme 29*). This necessitated a Weinreb ketone synthesis from 3-furoic acid **1.103**, achieved through the treatment of Weinreb amide **1.101** with the Grignard reagent derived from bromide **1.104**. The alkyl bromide was, in turn, prepared from the nucleophilic addition and acid-catalysed ring-opening of cyclopropyl methyl ketone.

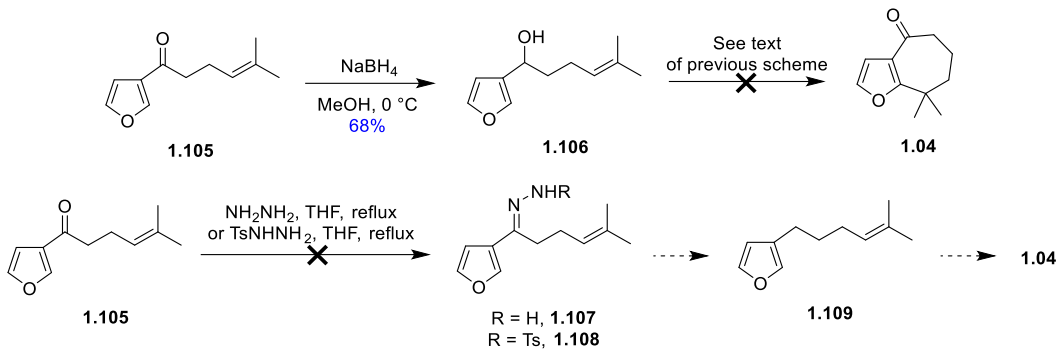


Scheme 29: Preparation of 3-acyl furan **1.105** using the Weinreb ketone synthesis of 3-furoic acid.

The preparation of ketone **1.105** required just two steps from commercially available 3-furoic acid; therefore, this route benefited from efficient assembly of all the required carbons but the intramolecular alkene hydroarylation of this 3-furyl ketone was not achieved (*Scheme 30*). No reactions occurred with catalytic PTSA, while all other catalysts trialled gave complicated mixtures.[1,30,31] The electron-deficiency of the substrate likely contributed to the low reactivity and so the derived alcohol **1.106** was employed under the same alkene hydroarylation conditions but this resulted merely in decomposition. The cyclisation of fully-reduced derivative **1.109** could not be tested, because its attempted synthesis using Wolff–Kishner reduction of **1.105** failed in the hydrazone formation step where the ketone remained stable to the conditions applied (*Scheme 31*).



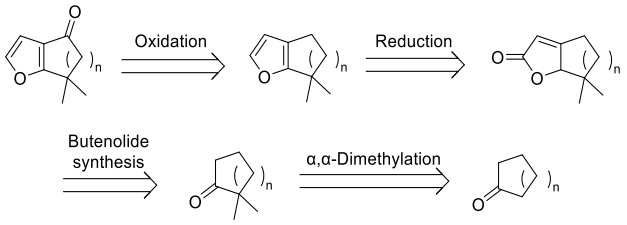
Scheme 30: Attempted cyclisation of ketone **1.105**. Reagents and conditions tested: (a) PTSA (10 mol%), HFIP/$CHCl_3$ (1:4 v/v), RT, 16 h; (b) BF_3•OEt_2, DCM, 0 °C, 30 min; (c) $RuCl_3$, AgOTf, DCM, 0 °C, 1 h; (d) $TiCl_4$, DCM, −78 °C, 10 min; (e) $SnCl_4$, DCM, −78 °C, 10 min.



Scheme 31: Reduction attempts from ketone **1.105** and outcome of attempted cationic cyclisation of alcohol **1.106**. The reagents and conditions tested with alcohol **1.106** were as specified in *Scheme 30*.

1.5 The butenolide route

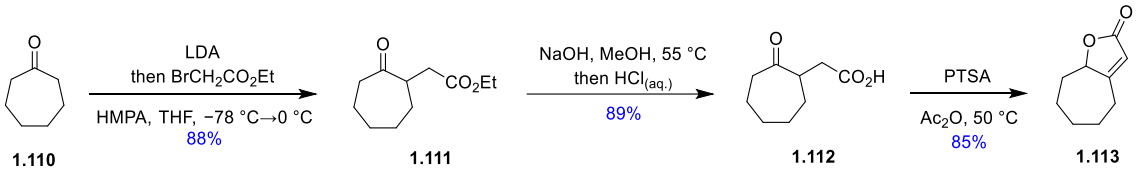
The synthetic methodologies discussed above all endeavoured to achieve cyclisation of a pre-formed furan derivative. Consequently, the overall yields were affected by either the lengthy synthesis of cyclisation precursors or the acid sensitivity of the furan ring. Starting from an alicyclic compound, on the other hand, would allow strongly acidic or oxidising conditions to be used with the furan ring being established in the late stages of the synthesis. Retrosynthetic analysis suggested that cycloalkanones as starting materials could facilitate the installation of the *geminal* dimethyl functionality through their α-alkylation reactions (*Scheme 32*). This approach would create furano[*b*]cycloalkanes, whose conversion into the ring fused ketone targets would then require a further oxidation step.



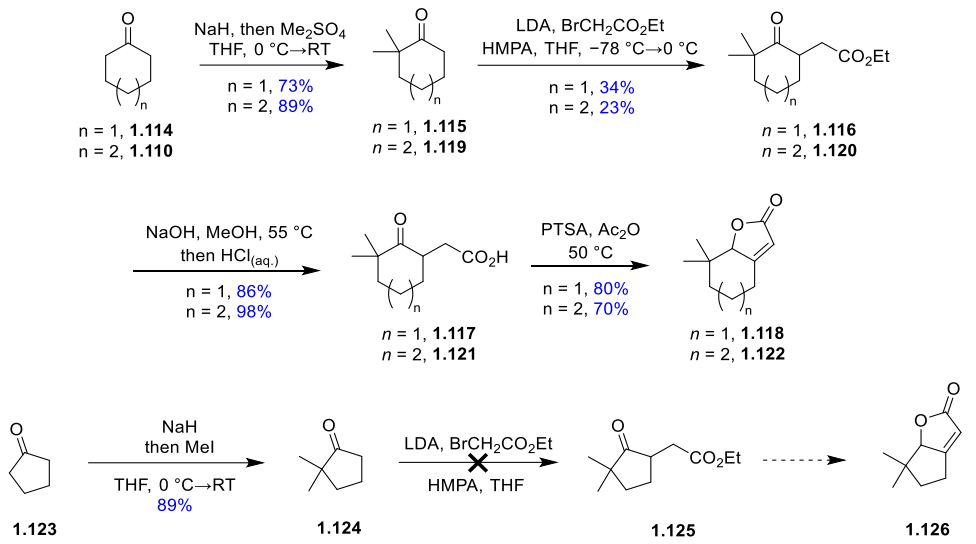
Scheme 32: Retrosynthetic analysis of the butenolide route (n = 5, 6 or 7).

1.5.1 Synthesis and functionalisation of alicyclic [*b*]-annulated butenolides

To begin with, the 'unmethylated' model butenolide **1.113** was prepared from cycloheptanone *via* γ-keto acid **1.112**, which underwent a PTSA-mediated condensation following literature precedent (*Scheme 33*).[32] For the synthesis of 'dimethylated' butenolide **1.122**, cycloheptanone was treated with excess sodium hydride and iodomethane. Subsequent steps followed those used in the preparation of **1.122** with, notably, the alkylation step with ethyl bromoacetate achieving a markedly lower yield. This synthetic route was also applicable to 5/6-ring fused butenolide **1.118** but not the 5/5-ring fused **1.126**, because the alkylation of 2,2-dimethylcyclopentan-1-one (**1.124)** was not successful and the substrate did not react (*Scheme 34*). The steric hindrance imparted by the *geminal* dimethyl group in **1.115**, **1.119** and **1.124** presumably contributes to the reduced yields or failure of the alkylation reactions.



Scheme 33: Preparation of fused bicyclic butenolide **1.113** from cycloheptanone.

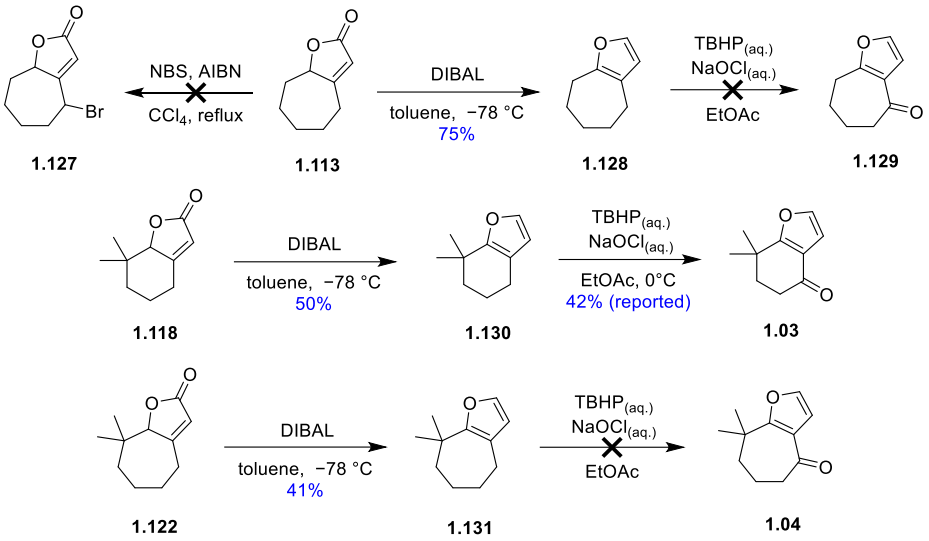


Scheme 34: The attempted synthesis of 'dimethylated' fused bicyclic butenolides **1.118**, **1.122** and **1.126**.

1.5.2 Reduction of bicyclic butenolides and subsequent allylic oxidation

Butenolides **1.113**, **1.118** and **1.122** were readily reduced by DIBAL into their corresponding furan derivatives at temperatures as low as −78 °C (*Scheme 35*).[33] No purification of the products was necessary, because the furano[*b*]cycloalkanes were produced with sufficiently high purity and were found to have limited stability towards chromatography on silica. The furanocycloalkanes were also somewhat volatile, because overlong exposure to vacuum led to reduced yields.

Furfurylic oxidation of the furanocycloalkanes constituted the final step in accessing the bicyclic ketone targets. The one-step oxidation of **1.130** into ketone **1.03** was reported by Kolympadi and co-workers,[1] yet their protocol resulted in complete decomposition of furanocycloalkanes **1.128** and **1.131**. As might be expected, the butenolides **1.113**, **1.118** and **1.122** did not respond to these conditions. Besides, the bromination of butenolide **1.113** was attempted with bromine or NBS, but this resulted in a complicated mixture containing just traces of the starting material.



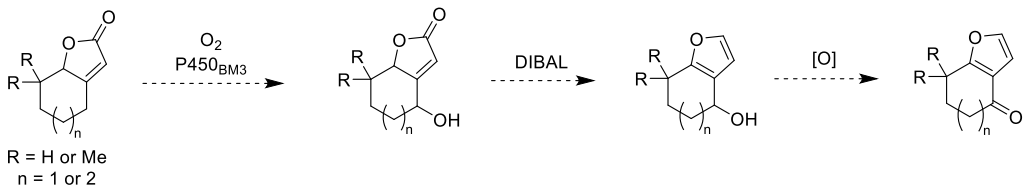
Scheme 35: Reduction of butenolides **1.113**, **1.118** and **1.122** as well as the outcome of subsequent furfurylic functionalisation attempts.

1.5.3 Furfurylic enzymatic hydroxylation of bicyclic butenolides

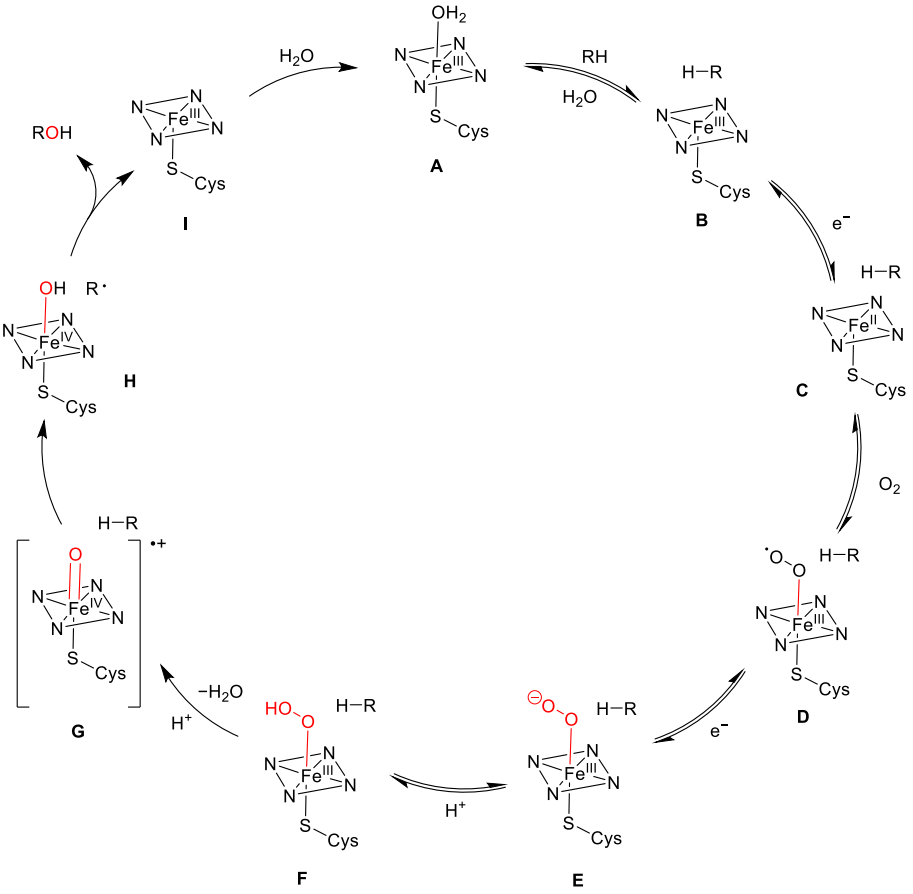
Following unsuccessful chemical oxidation and bromination attempts, enzymatic butenolide hydroxylation was evaluated out with evolved cytochrome $P450_{BM3}$ variants. This effort aimed to achieve allylic hydroxylation of the butenolide substrates, which, following subsequent redox reactions, would give furano[*b*]cycloalkanones (*Scheme 36*). The P450 enzymes are an important class of oxidases responsible for the biosynthesis, cell respiration and detoxification processes in many living organisms. The name P450 is short for 'Pigment 450' and is derived from the absorption wavelength characteristic of the iron(II)-carbon monoxide complex of the haem group in the enzyme active site. The subscript 'BM3' signifies that the enzyme is the third P450 variant isolated from the bacterium species *Bacillus megaterium*.[34] The haem group of P450 enzymes consists of a hexacoordinate iron centre and a proto-porphyrin ligand and is responsible for the function of the enzymes as oxygenation catalysts. The catalytic cycle (*Scheme 37*)[35] starts with the displacement of water by the substrate (Structure **A**→**B**); then,

the Fe(III) was reduced so that it could coordinate with molecular oxygen and reduce the dioxygen ligand into a peroxide anion (Structure **E**). Subsequent protonation and elimination of water generates the active radical cation form (Structure **G**) with an Fe(IV) centre capable of hydrogen abstraction from sp^3-C−H bonds. The alkyl radical thus generated bites back onto the hydroxyl ligand on Structure **H** and forms the alcohol product. The Fe(III) centre is meanwhile regenerated and captures a water molecule to close the catalytic cycle. Hence the overall process can be summarised as:

$$RH + O_2 + 2\ e^- + 2\ H^+ \rightarrow ROH + H_2O$$

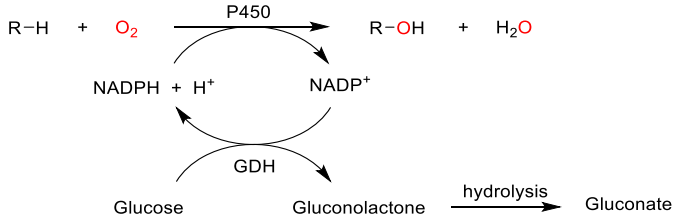


Scheme 36: Aim of the enzymatic butenolide hydroxylation.



Scheme 37: Catalytic cycle of cytochrome P450 enzymes, with simplified structures of haem groups.

While other P450 enzymes typically require a redox partner for their operation, $P450_{BM3}$ variants only need an NADPH co-factor[36] available from the reduction of $NADP^+$ by glucose in the presence of glucose dehydrogenase (GDH) (*Scheme 38*). Phosphate buffer is used in these reactions to both maintain a weakly basic environment and sustain the action of the enzyme and to ensure the hydrolysis of gluconolactone into gluconate.



Scheme 38: Source of protons and electrons in the P450 catalytic cycle.

All three synthesised butenolides **1.113**, **1.118** and **1.122** were screened against libraries of pre-harvested $P450_{BM3}$ enzymes with a diverse range of sequence variations. Reactions were carried out at ~5 μmol scale with 500:1 substrate-to-enzyme ratio, using enzyme plates that contain 13, 16 or 24 enzyme variants. Overall, the screening used 43 mutants that are derived from 10 base variants shown in the abbreviations section. Mutagenesis previously developed by the group had introduced between two and five additional mutations at active site residues S72, V78, F81, A82, F87, A184, I263, A264, A328, P329 and A330 (*Figure 1*).[37] Then, one active P450 variant with good activity and product selectivity was selected from each library for preparative-scale reactions of each substrate.

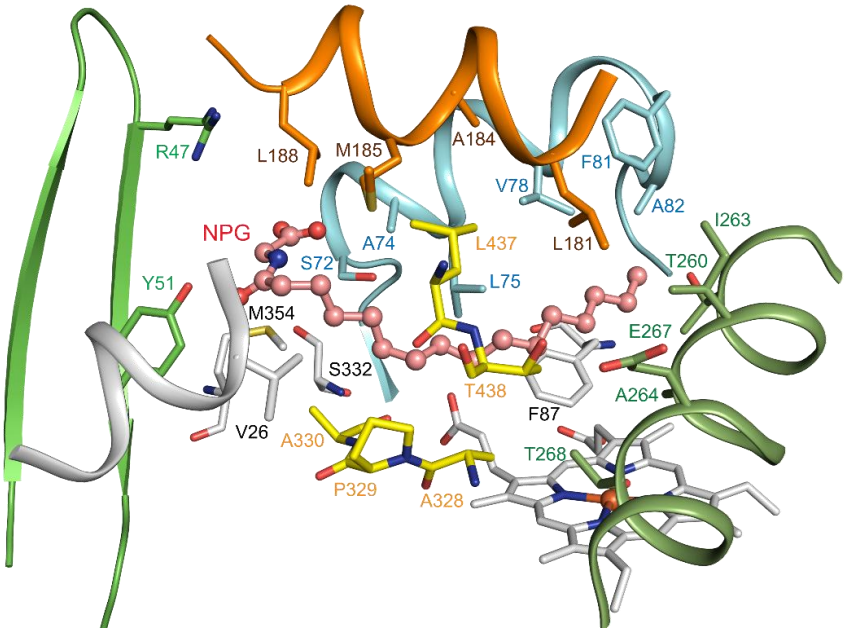
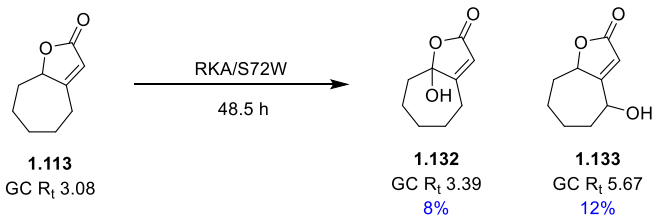


Figure 1: The active site of wildtype $P450_{BM3}$ with the natural substrate *N*-palmitoylglycine ('NPG', shown in pale red) bound, and labelling of key amino acids.

A total of 16 P450 variants were screened for the 'unmethylated' 5/7-ring fused bicyclic butenolide **1.113**, yet substrate conversion was low and achieved by only seven mutants (*Table 1*; See **Appendix 1** for full list of variants). The four mutants with the lowest conversions (Entries 4−7) all exclusively delivered one product each; enzyme RKA/S72W was chosen for

preparative-scale reaction, as it was among the three variants initially assumed to have generated the desired allylic alcohol **1.133** despite the low conversion. In reality, GC analysis of the scaled-up reaction revealed that the screening product with RKA/S72W was γ-hydroxy butenolide **1.132**, while GVQ delivered allylic alcohol **1.133** selectively in the screening (*Scheme 39*). Because the scaled-up run lasted 48 hours, substrate conversion was higher (about 33%) and both hydroxylation products were observed. Furthermore, the two products were the only species obtained in significant amounts, which indicated impressive regioselectivity of the hydroxylation. Given that the substrate **1.113** was obtained as a racemate from ketocarboxylic acid **1.112**, the enzyme likely reacted selectively with one of its stereoisomers; however, no further stereoselectivity studies were conducted since all hydroxylation products would be subsequently converted into achiral furano[*b*]cycloalkanones.



1.113
GC R_t 3.08

1.132
GC R_t 3.39
8%

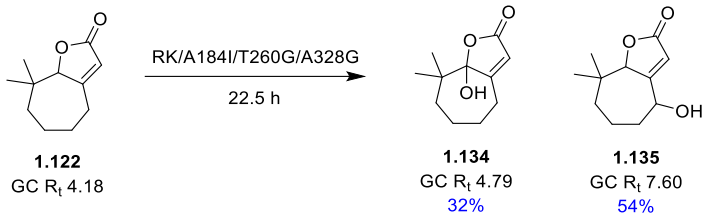
1.133
GC R_t 5.67
12%

Scheme 39: Outcome of the hydroxylation of butenolide **1.113** by P450 enzyme RKA/S72W, with 33% substrate conversion.

Entry	Enzyme variant	Conversion	1.132	1.133	Others
1	GVQ/A328G	12%	9%	71%	20%
2	K19/F87V/E267V/V78I	8%	13%	87%	0%
3	K19/F87V/E267V	6%	9%	91%	0%
4	GVQ	4%	0%	100%	0%
5	RKA/S72W	1%	100%	0%	0%
6	RK/F81W/TG/A328G	1%	100%	0%	0%
7	RLYF/KSK19/A184I	1%	100%	0%	0%

Table 1: Outcome of the P450 screening of butenolide **1.113**, listed in descending order of substrate conversion. Selectivity (percentage data in columns headed by the compound number) is calculated by peak area [(single metabolite/all metabolites) × 100]. Product **1.133** was isolated as a single unassigned diastereomer.

The screening outcome of 5/7-ring fused butenolide **1.122** was dramatically different to that of its 'unmethylated' analogue **1.113** (*Table 2*). The enzyme library presented below registered positive substrate conversion with all mutants, where rates higher than 70% were observed in six variants. The screening outcome suggested that mutations A82M (by comparison of Entries 1, 7 and 13) and A328G (Entries 2 and 5) were likely critical to high activity of the enzymes, and mutant RK/A184I/T260G/A328G was used for the scaled-up run because it achieved the highest substrate conversion without giving an observable amount of **1.134**. NMR spectroscopic analysis of products from the preparative-scale reaction (*Scheme 40*) confirmed the assignment of the γ-hydroxy butenolide. Last but not least, the steric hindrance engendered by the *geminal* dimethyl functionality in substrate **1.122** resulted in reduced accessibility of its γ-carbon, which was likely responsible for the low yields of γ-hydroxy butenolide **1.134** observed in both the screening and the scaled-up run.



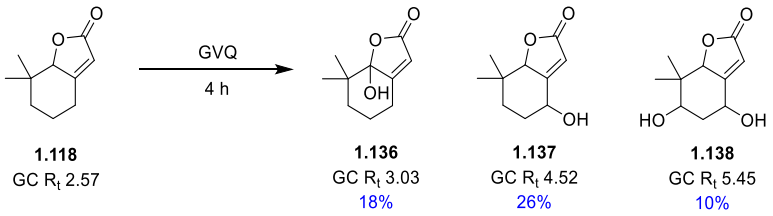
Scheme 40: Outcome of the hydroxylation of butenolide **1.122** by P450 enzyme RK/A184I/T260G/A328G, with complete substrate conversion. Product **1.135** was isolated as a single unassigned diastereomer.

Entry	Enzyme variant	Conversion	1.134	1.135	Others
1	KSK19/A82M	97%	26%	43%	31%
2	RK/A328G	91%	29%	52%	19%
3	KSK19/A82M/I263G	87%	8%	42%	50%
4	RK/A184I/T260G/A328G	83%	0%	27%	73%
5	RK	76%	36%	57%	7%
6	R19/F87I	73%	0%	12%	71%
7	KSK19/I263A	37%	4%	63%	33%
8	GV/A184I	32%	0%	35%	65%
9	KU3/A330P/I263G	16%	0%	81%	19%
10	R19/A330W	11%	0%	82%	18%
11	RK/I263G	10%	0%	61%	39%
12	RK/A328L	9%	0%	75%	25%
13	KSK19/I264G	6%	0%	69%	31%

Table 2: Outcome of the P450 screening of butenolide **1.122**, listed in descending order of substrate conversion.

Finally, the screening of 'dimethylated' 5/6-ring fused butenolide **1.118** revealed good overall substrate conversion and low yields of γ-hydroxy butenolide **1.136** (*Table 3*). Cross comparison of the results suggested that mutation E267V (Entries 1 and 2) was likely conducive to effective hydroxylation of **1.118** into **1.137**, while mutations Q403P (Entries 2 and 5), I263G, V78L (Entries 4 and 7) and A328V (Entries 2 and 14) would suppress enzyme activity. The scale-up reaction with enzyme GVQ was highly efficient and delivered complete conversion within 4

hours, yielding desired alcohol **1.137** as the major product alongside γ-hydroxy butenolide **1.136**. Moreover, a new species (**1.138**) was observed in all trials and is believed to be the dihydroxylation product (*Scheme 41*). It is worth noting that **1.138** dominated in crude products with low substrate conversion yet were only present in very small amounts when conversion was high (Entries 15−24 of *Table 3*). This might suggest that the compound was predominantly generated in the early stages of the hydroxylation process when the enzyme was highly active, while monohydroxylation products **1.136** and **1.137** were the main products after enzyme activity declined subsequently.



Scheme 41: Outcome of the hydroxylation of butenolide **1.118** by P450 enzyme GVQ. Complete conversion of substrate was achieved. Products **1.137** and **1.138** were both isolated as single unassigned diastereomers.

Entry	Enzyme variant	Conversion	1.136	1.137	1.138	Others
1	K19/F87V/E267V	100%	8%	69%	6%	17%
2	K19/F87V	88%	13%	63%	2%	22%
3	RP/H171L/I263G	86%	2%	66%	11%	21%
4	GVQ	78%	8%	70%	10%	12%
5	K19/F87V/Q403P	71%	18%	60%	5%	17%
6	RLYF/KSK19	61%	36%	41%	0%	22%
7	GVQ/I263G/V78L	60%	2%	82%	14%	2%
8	GV/A184I	59%	3%	74%	6%	17%
9	KSK19IG	48%	12%	62%	0%	26%
10	RT2/S72G/A330W	33%	0%	56%	27%	17%
11	RLYF/KSK19/A184I	31%	6%	62%	0%	32%
12	KSK19/F81W	28%	20%	47%	0%	34%

13	RK/A184I/T260G/A328G	28%	18%	48%	0%	34%
14	K19/F87V/A328V	24%	0%	67%	33%	0%
15	R19/A328L/A184I	14%	2%	36%	53%	9%
16	RK/A328G	13%	7%	29%	0%	64%
17	RT2/A330P/V78I/A184I	10%	0%	22%	74%	4%
18	R19FI	10%	0%	24%	76%	0%
19	KSK19/I263A	9%	0%	24%	76%	0%
20	KSK19/A82M/I263G	9%	0%	31%	57%	12%
21	KU3/AP/IA	9%	0%	14%	76%	10%
22	R19/A330W	7%	0%	0%	92%	8%
23	KU3/AP/S72W	7%	0%	0%	100%	0%
24	RLYF/K19	7%	0%	0%	100%	0%

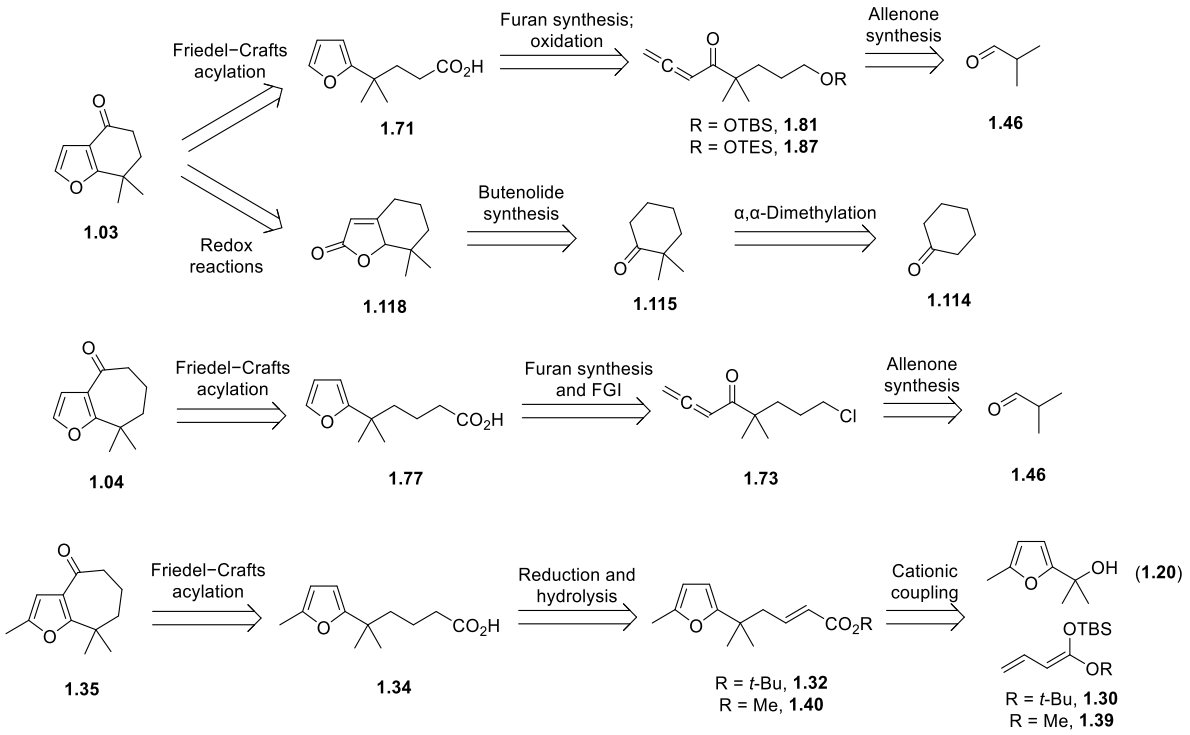
Table 3: Outcome of the P450 screening of butenolide **1.118**, listed in descending order of substrate conversion.

Lastly, the reduction of allylically hydroxylated butenolides **1.133**, **1.135** and **1.137** was carried out with DIBAL, yet all the crude mixtures were void of organic material. In view of the absence of substrates in all crude mixtures and the low yields obtained from the reduction of non-hydroxylated butenolides **1.113**, **1.118** and **1.122**, we believe that the reduction occurred as expected but the small scales and likely low yields of the reactions contributed to the apparent zero yields of the products.

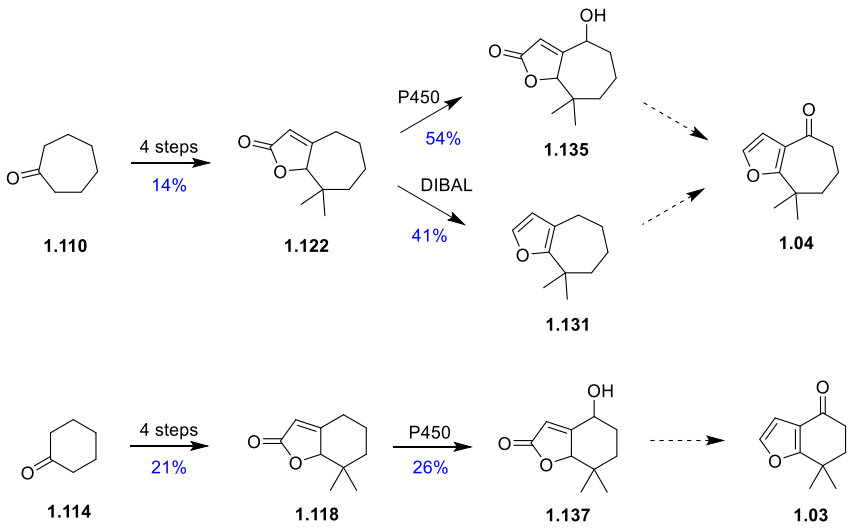
1.6 Conclusions and future work

This work achieved the synthesis of 5/6-ring fused bicyclic ketone **1.03** and two 5/7-ring fused bicyclic ketones **1.04** and **1.35** (*Scheme 42*); all three [*b*]-annulated furans have fully substituted furfurylic carbons and were produced from late-stage Friedel−Crafts acylation of ω-furylcarboxylic acids. The synthesis of original target compound **1.04** used furan synthesis

techniques, while **1.03** could be accessed from allenyl ketone **1.81** and **1.87** or butenolide **1.118**. 2-Methylfuran derivative **1.35**, on the other hand, resulted from a much shorter synthesis featuring TMSOTf-mediated coupling of furyl carbinol **1.20**. Meanwhile, the butenolide route delivered cycloalkano[*b*]furan **1.131** and hydroxylation products **1.135** and **1.137**, all of which could in principle lead to the corresponding furano[*b*]cycloalkanones **1.03** and **1.04** (*Scheme 43*). Furthermore, efforts on the alkene hydroarylation route provided guidance to the total synthesis of trigoxyphins K and L presented in the next chapter. The unsuccessful attempts of furan synthesis, oxidation reactions and cyclisation of furan derivatives demonstrated the synthetic challenges associated with furan derivatives.



Scheme 42: Summary of achieved syntheses for furano[*b*]cycloalkan-1-ones **1.03**, **1.04** and **1.35**.



Scheme 43: The synthesis of compounds **1.131**, **1.135** and **1.137** in the butenolide route, which were potential precursor to furano[*b*]cycloalkan-1-ones **1.03** and **1.04**.

The synthetic routes investigated could provide guidance and serve as the basis of future methodology development for fused bicyclic furans. To begin with, the coupling protocol for furyl carbinols and silyl acetals could be optimised with different Lewis acid catalysts to improve its compatibility with 2-substituted furan substrates. The furan synthesis outcome with ynones and 2-yne-1,4-diols was found to vary with substrate but the underlying causes are not fully understood, necessitating in-depth investigations of the rearrangement reactions. Last but not least, the synthesis of 5/5-ring fused bicyclic furan **1.02** and its homologue **1.34** have not been achieved to date. As this work showed the Friedel−Crafts and butenolide routes to be unsuccessful, it is suggested that future efforts use furano[*b*]cyclopentanes as intermediates, whose electron-rich nature will likely allow their access *via* cationic cyclisation of 3-alkyl furans.

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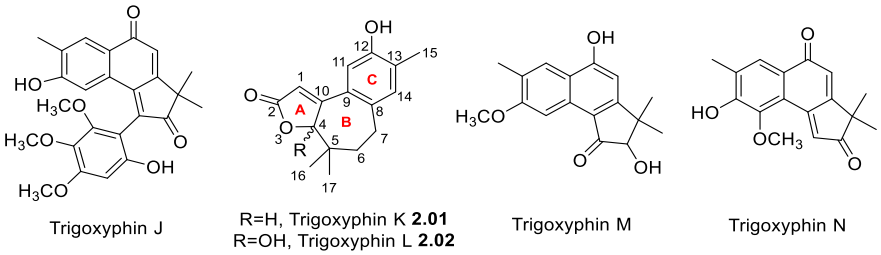
Chapter 2: Total Synthesis of Trigoxyphins K and L

2.1 Background and aims

2.1.1 Origin and structural traits of the target molecules

The genus *Trigonostemon*, part of the Euphorbiaceae family, is native to tropical and subtropical Asia. It consists of approximately 50 species and is a rich source of various biologically active natural products. Among these are daphnane diterpenoids that possess 5,7,6-fused tricyclic structures and manifest cytotoxic, insecticidal and enzyme inhibiting activities.[1] The plant species *Trigonostemon xyphophylloides* grows in China's southernmost Hainan province and finds its use in Chinese folk medicine. It is the source of the trigoxyphin family of diterpenoids and to date, 24 compounds of this family with varying structural complexity have been discovered and named in alphabetical order.[1–4]

The target compounds, trigoxyphins K (**2.01**) and L (**2.02**), were isolated from the twigs of this species and fully characterised along with three other molecules of the family by Wu and co-workers in 2013 (*Scheme 1*).[1] The two natural products have demonstrated promising anti-tumour and anti-inflammatory potential in relevant pharmacological studies.[5–6] These molecules share a high degree of structural similarity and are derivatives of butenolide and γ-hydroxy butenolide, respectively. Notable features of the molecules include the oxidation-prone phenol moiety, the seven-membered B-ring, and the geminal dimethyl group adjacent to the butenolide ring. Moreover, the chirality originating at C5 in both molecules may bring about the need for enantioselective synthesis, although the hydroxybutenolide moiety of trigoxyphin L is expected to rapidly racemise due to its reversible ring-opening.

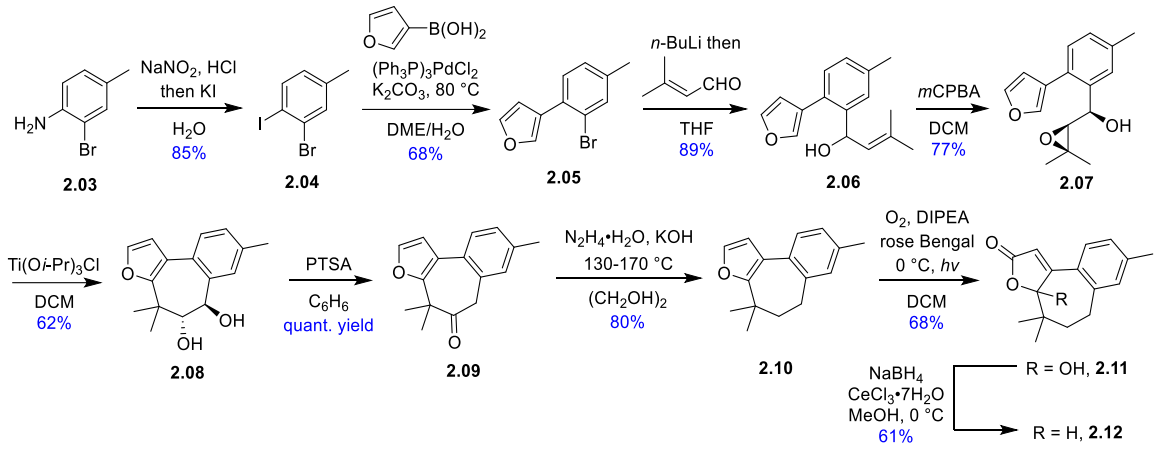


Scheme 1: Structures of trigoxyphins J–N, all having tricyclic scaffolds.

2.1.2 Earlier efforts toward the trigoxyphin ring system

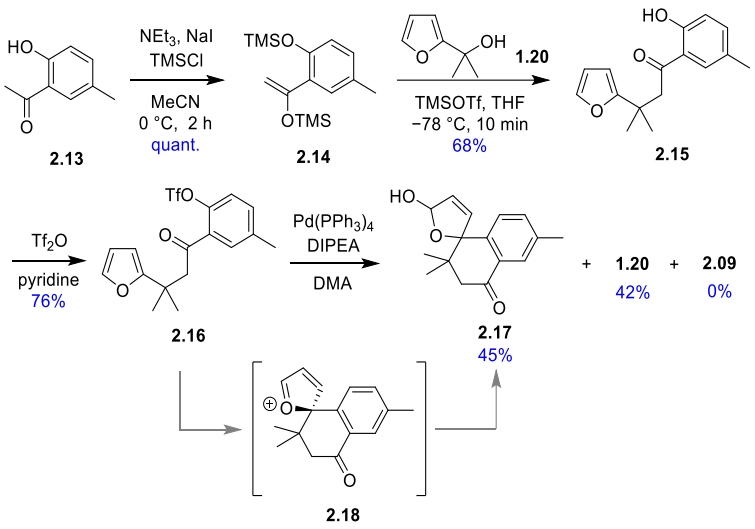
The Robertson group has primarily anchored its trigoxyphin synthesis studies in furan chemistry, owing to well-established butenolide synthesis protocols using singlet oxygen oxidation of furans.[7–8] Previous studies targeted the des-oxy-trigoxyphins **2.11** and **2.12**, from which the phenol was expected to be accessible by late-stage enzymatic aryl hydroxylation using cytochrome $P450_{BM3}$ enzymes.[9–10]

Previous DPhil student O'Hanlon pioneered the studies with aniline derivative **2.03** (*Scheme 2*).[9] His route, further optimised by Part II student Pickford,[10] used Suzuki coupling to connect the two aromatic rings. The bromobenzene was prenylated *via* lithium-halogen exchange, then epoxidation paved the way for Lewis acid-catalysed formation of the seven-membered ring. Functional-group interconversion and Wolff−Kishner reduction completed the furan-based tricyclic core, from which photochemical oxidation and Luche reduction gave des-oxy-trigoxyphins L (**2.11**) and K (**2.12**) respectively. In addition, furan tricycles **2.09** and **2.10** were used as substrates for enzymatic screenings with $P450_{BM3}$ variants in a bid for late-stage arene oxidation. Unfortunately, none of the trials were capable of clean and selective C−H oxidation, and it was not possible to isolate the products formed.

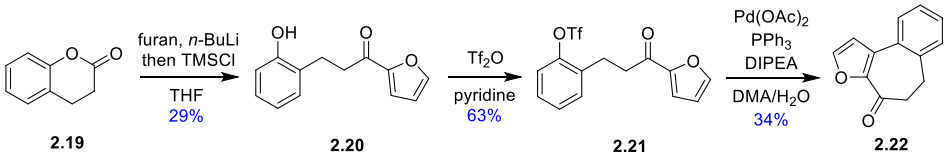


Scheme 2: First synthesis of des-oxy-trigoxyphins K and L by O'Hanlon.

Later, DPhil student Harwood conducted optimisation research on the formation of tricycle **2.10**,[11] inspired by Martin's carbinol coupling protocols outlined in **Chapter 1** (*Scheme 3*). The silyl enol ether of acetylcresol derivative **2.13** was used for the TMSOTf-mediated coupling with furyl carbinol **1.24**, and the product was triflated in anticipation of ring formation through electrophilic arylation and rearrangement. In practice, the arylation reaction succeeded, but the spirocyclic intermediate could not be induced to re-arrange as desired to give the intended tricycle. The only substrates found capable of an equivalent overall process were 2-acylfurans such as **2.21**, produced from lactone **2.19** (*Scheme 4*). No attempts were made to convert the carbonyl to the *geminal* dimethyl group, although this was considered.



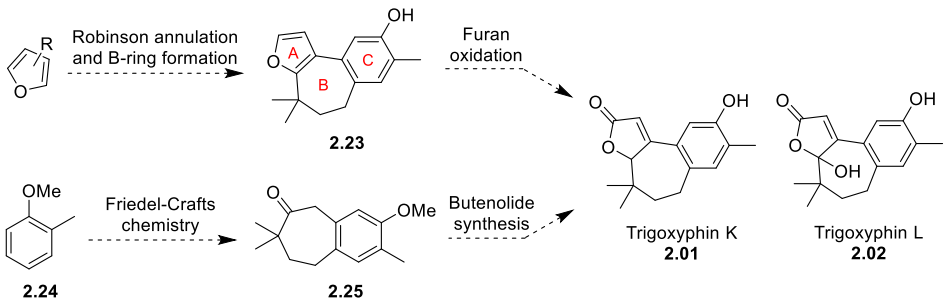
Scheme 3: Harwood's research on TMSOTf-mediated coupling of silyl enol ether **2.14** *en route* to des-oxy trigoxyphins **2.11** and **2.12**.



Scheme 4: Harwood's successful synthesis of tricycle **2.22**, starting from lactone **2.19**.

2.1.3 Aims of this project

Two total synthesis routes toward trigoxyphins K and L were proposed based on different disconnection strategies (*Scheme 5*).[12] The first 'furan route' followed in the footsteps of earlier efforts and aimed to establish the tricyclic core from a furan derivative. The 'tetralone route', on the other hand, sought to begin with conventional benzene derivatives and build the butenolide ring with a non-furan approach. Both routes were designed to avoid cross-coupling reactions and late-stage enzymatic C-H oxidation, which had limited progress and efficiency in previous studies.



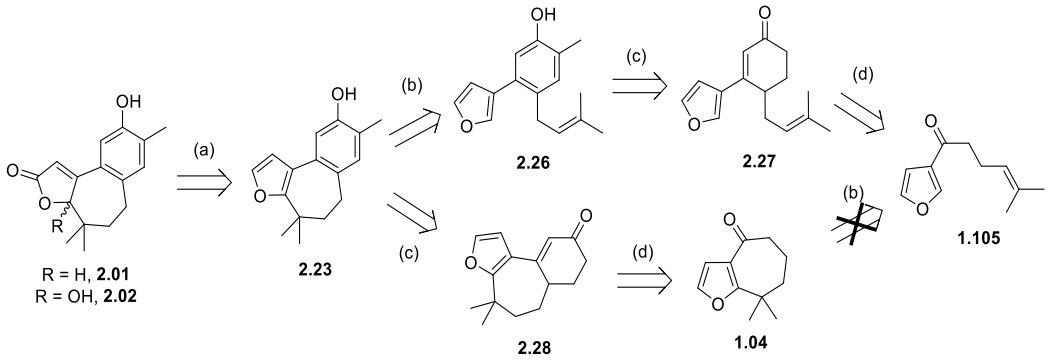
Scheme 5: Summary of the two synthesis routes toward trigoxyphins K and L.

2.2 The 'furan route' *via* Robinson annulation

2.2.1 Retrosynthesis

The first route to trigoxyphins K and L, the 'furan route' sought to construct the tricyclic core structure from the furan ring, followed by late-stage furan oxidation to establish the butenolide moiety. It was envisaged that Robinson annulation followed by cyclohexenone aromatisation would be an effective method to build the phenol moiety.

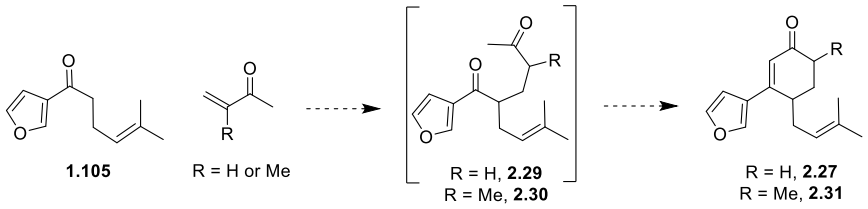
Four possible route variations were identified which met these preconditions: the starting material could be a 2- or 3-substituted furan, and formation of the seven-membered B-ring could either precede or succeed the C-ring. Crucially, the furan cyclisation efforts discussed in the previous chapter showed that furanocycloheptanone **1.04** could not be synthesised from **1.105**. Hence, it was decided that the 'furan route' would begin with Robinson annulation of **1.105**, whose product **2.27** would undergo aromatisation to provide the electron-rich phenol system that facilitates ring closure through acid-catalysed alkene hydroarylation (*Scheme 6*). O'Hanlon's photo-oxidation and Luche reduction would follow to convert tricycle **2.20** into trigoxyphins L and K respectively.[9]



Scheme 6: Retrosynthetic analysis for the 'furan route'. Key steps indicated in this scheme: (a) furan oxidation; (b) alkene hydroarylation; (c) aromatisation; and (d) Robinson annulation.

2.2.2 Robinson annulation of ketone 1.105

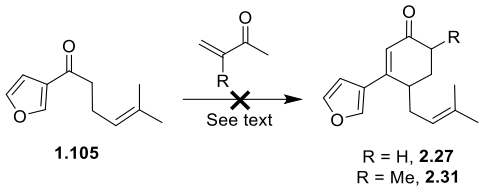
The total synthesis started from ketone **1.105**, which was featured in the alkene hydroarylation study and prepared from Weinreb amide **1.104** in 65% yield. The subsequent Robinson annulation was tested primarily with methyl vinyl ketone (MVK), a highly reactive enone prone to polymerisation. The less reactive methyl isopropenyl ketone was also investigated because, if successful, there would be no need for ketone α-methylation (*Scheme 7*).



Scheme 7: Envisaged Robinson annulation of ketone **1.105**.

2.2.2.1 One-pot Robinson annulation

It was envisaged, based on literature precedent, that synthesis of cyclohexenone **2.27** could proceed *via* a one-pot multistep process. Both basic and acidic reagents were used for the screening with established protocols (*Scheme 8*).[13–15] Neither the desired product nor the 1,4-diketone intermediate **2.29** was found in any of the conditions used. Treatment with LDA or sodium methoxide resulted in MVK polymerisation, while acid catalysts resulted in degradation or no reactions. Replacement of MVK with methyl isopropenyl ketone did not lead to improvements, as this enone lacked reactivity and was left unaffected in all trials.

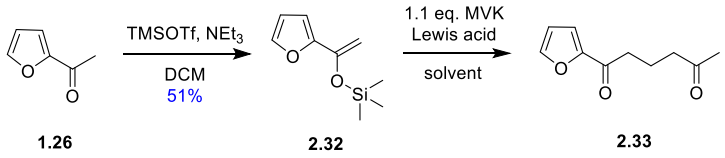


Scheme 8: Condition screening for attempted direct Robinson annulation of ketone **1.105**. Reagents and conditions tested: (a) NaOMe, MeOH, 50 °C, 16 h; (b) $BF_3{\cdot}OEt_2$, 0 °C, 2 h; (c) $SnCl_4$, −78 °C, 20 min.

2.2.2.2 Mukaiyama−Michael addition and subsequent aldol condensation

The Mukaiyama−Michael addition uses silyl enol ethers as nucleophiles. Unlike the enamine alkylation protocol, enones like MVK are pre-mixed with a Lewis acid catalyst to increase their reactivity.[16] The trimethylsilyl enol ether of 2-acetylfuran **1.26** was used in the screening of conditions. When it was treated with different Lewis acid catalysts (*Table 1*),[16–18] strong Lewis acids gave complicated mixtures containing decomposition products and traces of 2-acetylfuran. Success was only achieved with the pre-mixing MVK and the weakly Lewis-acidic $InCl_3$ prior to the addition of the silyl enol ether. Catalyst loading and reaction temperature were found to significantly alter the outcome. The optimal conditions were found to be 3 mol%

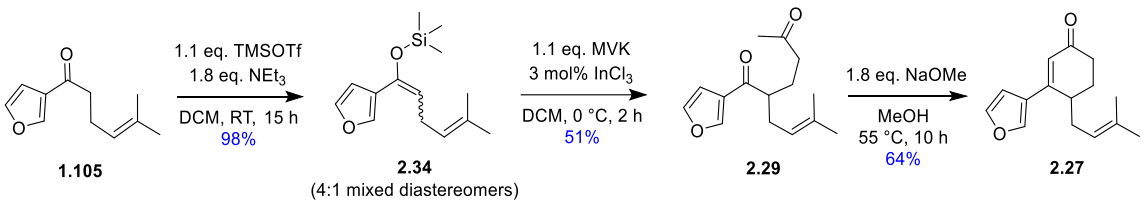
$InCl_3$ and 0 °C, which gave diketone **2.33** in 62% isolated yield. No reaction was observed with less catalyst and lower temperatures, while more than 10 mol% of $InCl_3$ resulted in markedly reduced yield.



Lewis acid	mol%	Solvent	Concentration of 1.26	Temperature	Time	Yield of 2.33 /%
$TiCl_4$	70	DCM	0.1 M	-78 °C	10 min	n/a
I_2	10	MeCN	0.1 M	20 °C	1 h	53
$InCl_3$	5	DCM	0.1 M	20 °C	30 min	16
$InCl_3$	5	DCM	0.1 M	0 °C	2 h	45
$InCl_3$	3	DCM	0.04 M	0 °C	3 h	65

Table 1: Lewis acid screening for Mukaiyama-Michael reaction of 2-acetylfuran. All yields were isolated yields.

The Mukaiyama−Michael reaction was then applied to the real system (**1.105**), achieving isolated yields of up to 51% for **2.29**. Subsequent sodium methoxide-mediated condensation proceeded smoothly, with 64% isolated yield achieved for enone **2.27** (*Scheme 9*).[19] Complete conversion of **2.27** would take up to 50 hours at room temperature but only 10 hours at 55 °C, above which yields began to decrease significantly due to decomposition (*Table 2*).



Scheme 9: Three-step Robinson annulation of **1.105** achieved *via* the Mukaiyama−Michael reaction of intermediate **2.34**.

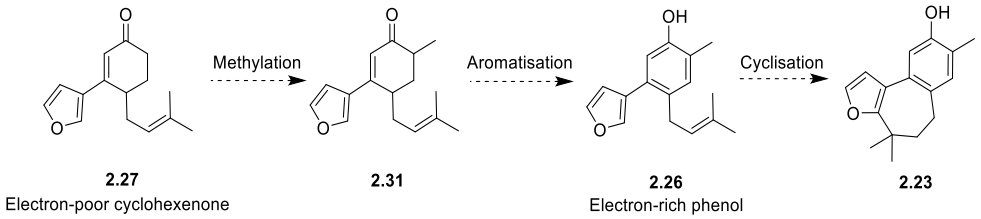
Temperature	Time /h	Conversion of diketone 2.29 /%	Yield of enone 2.27 /%
RT	20	48	n/a
RT	50	100	67
40 °C	16	88	n/a
55 °C	10	100	64
60 °C	8	100	55
Reflux	8	100	45

Table 2: Conversion of **2.29** and isolated yields of its condensation product **2.27** recorded at different temperatures. The reactions were conducted with 0.1 mmol of substrate **2.29**.

The success with MVK and $InCl_3$ could not be replicated when methyl isopropenyl ketone was used instead. No reaction could be observed, and the silyl enol ether **2.34** was recoverable when distilled water was used for the work-up. Augmenting the strength of the Lewis acid led to the hydrolysis and partial degradation of **2.34**, while methyl isopropenyl ketone remained stable.

2.2.3 Aromatisation of cyclohexenone intermediate and completion of synthesis

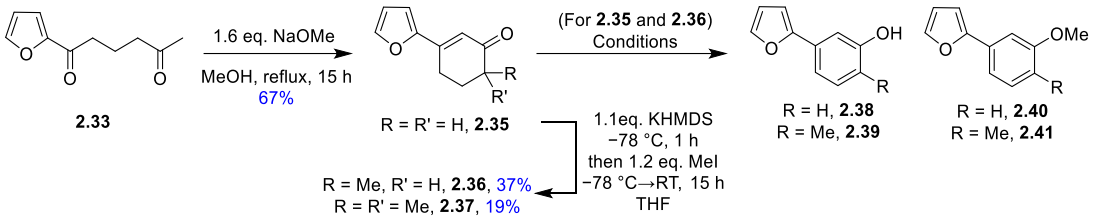
Cyclohexenone derivative **2.27** was still not considered to be a viable substrate for the seven-membered ring formation, because the furan ring is still electron-deficient owing to the electron-withdrawing conjugative effect of the enone carbonyl. Aromatisation therefore became the necessary step, as the phenol product would equip the molecule with sufficient electron density for the seven-membered ring formation (*Scheme 10*). The structure of the target molecules also demanded the methylation of **2.27**, and that this should precede aromatisation to ensure regiocontrol.



Scheme 10: Initial route proposed for the synthesis of tricycle **2.23** from **2.27**.

2.2.3.1 Oxidative aromatisation

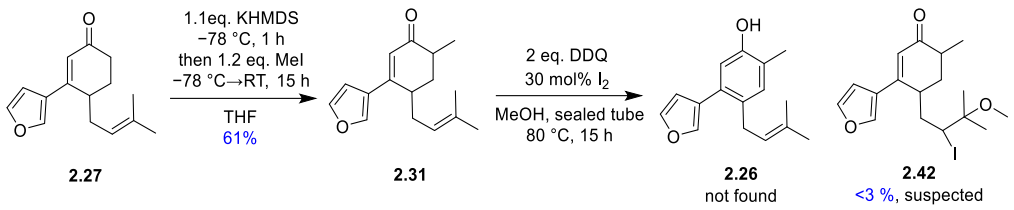
Enone **2.35** prepared from diketone **2.33** was used as the model compound to determine the optimal aromatisation condition (*Table 3*). Aromatisation was conducted on both **2.35** and its methylation product **2.36** using either Kikushima's copper(II)-catalysed method[20] or Jiang's DDQ method.[21] None of the desired aromatic product was observed when Kikushima's method was used; with Jiang's protocol, the products were anisole derivatives instead of phenols. Reactions with stoichiometric DDQ and 30 mol% of iodine achieved the best results, with isolated yields of 44% for **2.40** and 37% for **2.41**. Furthermore, extending the reaction duration resulted in reduced yields even with a lower iodine loading. The *O*-methylated products were likely prone to decomposition in the reaction mixture over time with the applied reaction conditions.



Substrate	Reagents	Conditions	Target product	Isolated yield /%
2.35	$CuBr_2$ (5 mol%) 48 wt% aq. HBr (20 mol%)	O_2 (1 bar) 1,4-dioxane, RT, 20 h	**2.38**	n/a
2.35	DDQ (1.0 eq.) I_2 (30 mol%)	MeOH, sealed tube 80 °C, 6 h	**2.40**	37
2.35	DDQ (1.0 eq.) I_2 (5 mol%)	MeOH, sealed tube 80 °C, 16 h	**2.40**	16
2.36	$CuBr_2$ (3 mol%) 48 wt% aq. HBr (5 mol%)	O_2 (1 bar) 1,4-dioxane, RT, 20 h	**2.39**	n/a
2.36	DDQ (1.0 eq.) I_2 (30 mol%)	MeOH, sealed tube 80 °C, 6 h	**2.41**	44

Table 3: Screening of conditions for the oxidative aromatisation in the model system.

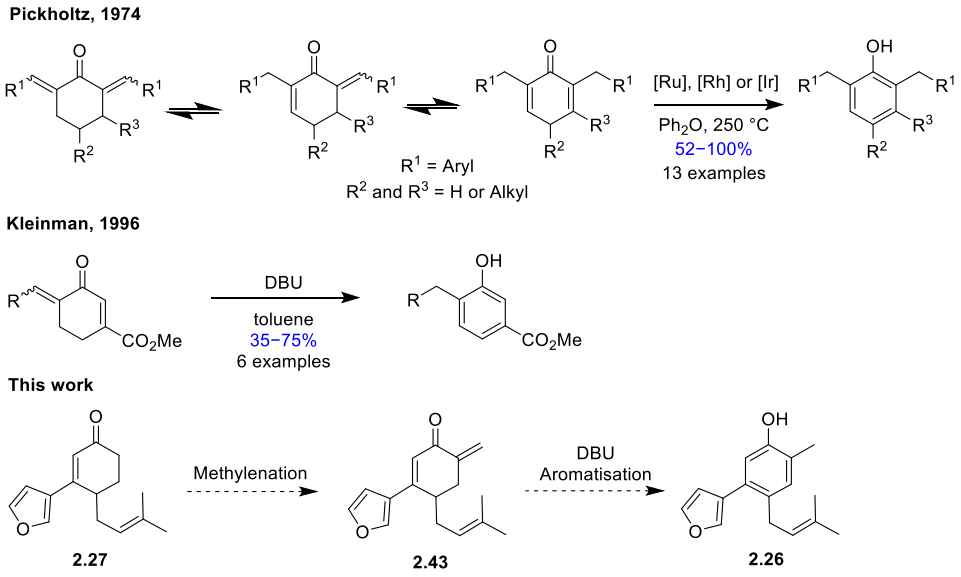
Aromatisation of the real system (**2.31**, produced from the methylation of **2.27**) resulted in more complication (*Scheme 11*). Mass recovery averaged 16% and there was no starting material remaining in the crude product. In the ^{1}H NMR spectrum, the enone olefinic peak remained, indicating no effective aromatisation. Crucially, the characteristic prenyl proton peak disappeared, and a new multiplet at 3.90 ppm (OC**H**$_3$) as well as a 3.50 ppm (C**H**I) singlet were found. It was believed that the reaction produced compound **2.42** through iodo-methoxylation of the prenyl side chain of **2.31**, yet **2.42** was generated in traces only and could not be isolated as a pure compound.



Scheme 11: Outcome of the oxidative aromatisation pathway in the real system.

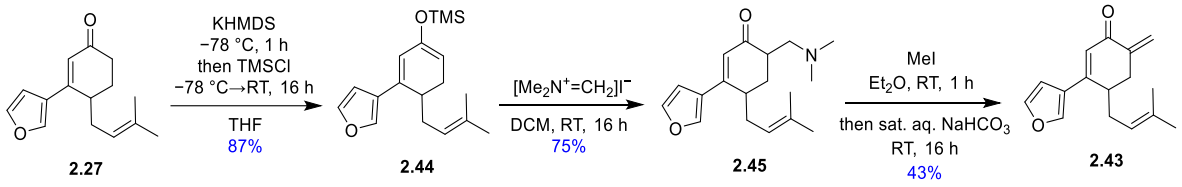
2.2.3.2 Aromatisation *via* isomerisation of methylenation product

The *ortho* relationship between the methyl and hydroxyl groups on the target molecule's C-ring made possible an alternative phenol synthesis strategy (*Scheme 12*). The rearrangement of 6-alkylidenecyclohex-2-en-1-ones to 2-alkylphenols has for instance been thoroughly studied by Pickholtz, who reported success with iridium and rhodium catalysts.[22] The complex $IrCl(CO)(PPh_3)_2$ in particular was found highly efficient and achieved near quantitative yields within 3 hours at 250 °C. More recently, Kleinman *et al.* reported a much simpler protocol with DBU in toluene.[23] The exo-methylene cyclohexenone substrates in their study were conveniently prepared from the condensation of methyl 1-cyclohexene-1-carboxylate with aldehydes.



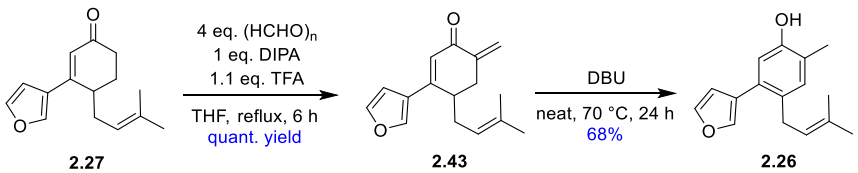
Scheme 12: Literature background of the isomerisation pathway and overview of its application to enone **2.27**.

In consideration of furan's instability toward acidic reagents, DBU was preferred as the isomerisation catalyst. As shown in *Scheme 13*, methylenation of enone **2.27** was initially pursued using the classical Mannich−Mentschukin−Hofmann elimination sequence. Formation of Mannich base intermediate **2.45** proceeded efficiently *via* aminomethylation of the silyl enol ether.[24–25] The yield-limiting step in the sequence was the Hofmann elimination, which achieved a yield of 43%. The aqueous layer during work-up was turbid and difficult to separate, suggesting the presence of significant amounts of the unreacted ammonium salt.



Scheme 13: Synthesis of dienone **2.43** *via* Mannich base **2.45**.

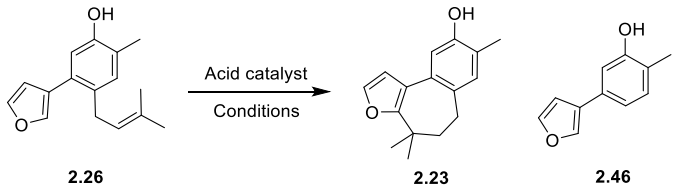
Fortunately, an alternative method − reported by Bugarin in 2010 − proved to be operationally simple and highly efficient (*Scheme 14*).[26] Thus, using excess paraformaldehyde and stoichiometric DIPA•TFA in refluxing THF, the enone **2.27** was methylenated to **2.43** in quantitative yields. The reaction required minimal work-up and no further purification, while also achieving high atomic efficiency. The DBU-mediated isomerisation of **2.43** was found to be slow and could only proceed in neat conditions at elevated temperatures. With 10 equivalents of DBU, phenol **2.26** was obtained in 68% yield.



Scheme 14: Optimised synthesis of **2.43** and its subsequent isomerisation into **2.26**.

2.2.3.3 Formation of the seven-membered ring and furan oxidation

Upon completion of the aromatisation, Spivey's alkene hydroarylation protocol was applied to phenol **2.26** (*Table 4*).[27] The reaction achieved completion within 6 hours giving tricycle **2.23** in yields up to 56%. The main side product in this reaction was de-prenylation product **2.46**, arising from retro Friedel−Crafts alkylation of **2.26**. Yields of this side product were found to be higher with longer reaction times and larger proportions of HFIP in the solvent system, whereas the use of CAS instead of PTSA gave marginally better chemoselectivity for **2.23**. Also tested as a proton source was the $RuCl_3$/AgOTf system,[28] from which a complicated and uncharacterisable mixture resulted.



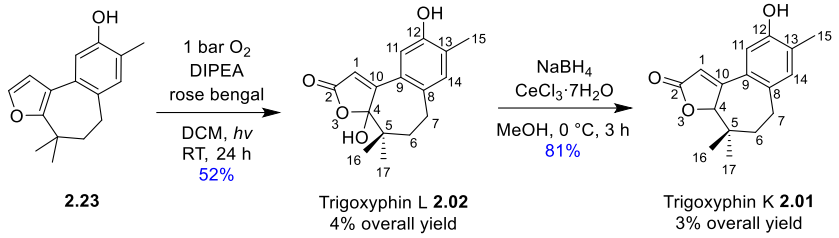
2.26 **2.23** **2.46**

Catalysts	mol%	Conditions	Yield 2.23 /%	Yield 2.46 /%
$TsOH{\cdot}H_2O$	10	HFIP-$CHCl_3$ (1:4 v/v), RT, 1 h	11†	< 2†
$TsOH{\cdot}H_2O$	10	HFIP-$CHCl_3$ (1:4 v/v), RT, 16 h	34†	10†
CSA	10	HFIP-$CHCl_3$ (1:4 v/v), RT, 16 h	38†	8†
CSA	5	HFIP-$CHCl_3$ (1:4 v/v), RT, 10 h	56‡	0†
CSA	5	HFIP-$CHCl_3$ (1:1 v/v), RT, 10 h	46‡	21‡
$RuCl_3$/AgOTf (1:3)	5	HFIP-$CHCl_3$ (1:4 v/v), RT, 30 min	0†	0†

Table 4: Screening for the Brønsted acid catalyst for the cyclisation of **2.26**. †: yields by crude NMR analysis; ‡: isolated yields.

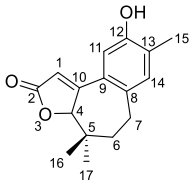
With the tricyclic core constructed, the final steps toward the natural products followed those in O'Hanlon's deoxy-trigoxyphin synthesis (*Scheme 15*).[9] Photochemical furan oxidation in

the presence of rose Bengal proceeded with good tolerance of the phenol moiety achieving 52% yield for trigoxyphin L. Compared with O'Hanlon's model system, this step progressed markedly more slowly and required overnight irradiation for complete conversion. Lastly, Luche reduction of trigoxyphin L at 0 °C delivered trigoxyphin K in 81% yield.



Scheme 15: Completion of synthesis for trigoxyphins K and L from furan tricycle **2.23**.

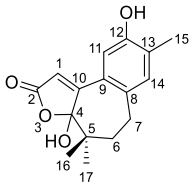
The spectroscopic data of the synthesised natural products were in good accordance with literature values provide by Wu and co-workers.[1] For trigoxyphin K in chloroform-*d* (*Table 5*), the characteristic proton peaks were the aromatic and vinyl protons at δ_H 6.94, 6.86 and 6.15 (literature δ_H 6.93, 6.88 and 6.16, respectively), the crucial C4 proton peak at δ_H 4.88 (δ_H 4.89 in literature) as well as methyl peaks on C15, C16 and C17 at δ_H 2.25, 1.27 and 0.91 (literature δ_H 2.24, 1.27 and 0.90, respectively). For trigoxyphin L in methanol-d_4 (*Table 6*), there was no C4 proton as expected, and aromatic and vinyl protons appeared at δ_H 6.89, 6.79 and 6.05 (literature δ_H 6.89, 6.78 and 6.05, respectively). All ^{13}C NMR resonances also accorded with the literature values, notably the C4 carbon peak in trigoxyphin K (at δ_C 90.7; literature value 90.5), which became barely visible in trigoxyphin L (as in literature). There is no reported information on the absolute configuration – including specific rotation – for these natural products but trigoxyphin L will racemise rapidly *via* reversible ring-opening, and trigoxyphin K could also racemise through its equilibrium with the hydroxyfuran tautomer.



Trigoxyphin K
2.01

Carbon	Observed δ_H (mult., *J*)	Literature δ_H (mult., *J*)	Observed δ_C	Literature δ_C
1	6.15 (s)	6.16 (s)	115.7	115.1
2	n/a	n/a	174.1	173.7
4	4.88 (s)	4.89 (s)	90.7	90.5
5	n/a	n/a	38.2	38.2
6	1.95 – 1.88 (m), 1.74 – 1.62 (m)	1.91 (m), 1.68 (m)	40.3	40.3
7	2.85 (dd, 16.0 Hz, 8.0 Hz), 2.66 (dd, 16.0 Hz, 8.0 Hz)	2.86 (dd, 16.0 Hz, 8.0 Hz), 2.66 (dd, 16.0 Hz, 8.0 Hz)	30.3	30.3
8	n/a	n/a	133.5	134.0
9	n/a	n/a	128.6	128.8
10	n/a	n/a	169.8	169.3
11	6.86 (s)	6.88 (s)	114.8	115.7
12	n/a	n/a	153.2	152.9
13	n/a	n/a	128.2	127.8
14	6.94 (s)	6.93 (s)	133.9	133.5
15	2.25 (s)	2.24 (s)	15.9	15.8
16	1.27 (s)	1.27 (s)	29.8	29.8
17	0.91 (s)	0.90 (s)	19.1	18.9

Table 5: Observed and literature ^{1}H and ^{13}C NMR data of Trigoxyphin K in chloroform-*d*.



Trigoxyphin L
2.02

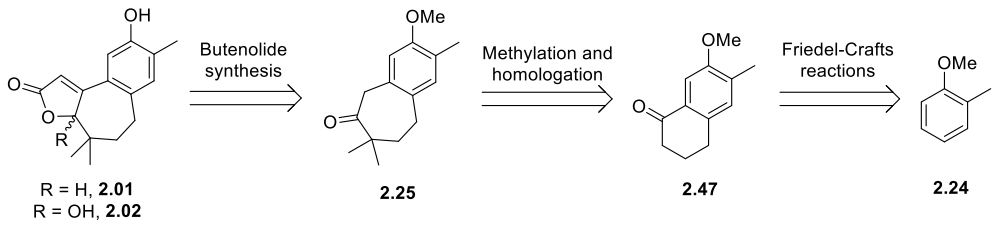
Carbon	Observed δ_H (mult., *J*)	Literature δ_H (mult., *J*)	Observed δ_C	Literature δ_C
1	6.05 (s)	6.05 (s)	117.6	116.9
2	n/a	n/a	173.3	173.2
4	n/a	n/a	112.4	112.7
5	n/a	n/a	42.0	42.0
6	2.23 (t, 12.5 Hz), 1.52 (dd, 12.5 Hz, 5.5 Hz)	2.20 (m), 1.48 (m)	39.7	39.7
7	2.89 (d, 14.5 Hz), 2.62 (dd, 14.5 Hz, 5.5 Hz)	2.87 (m), 2.61 (m)	31.6	31.5
8	n/a	n/a	133.3	133.3
9	n/a	n/a	133.0	129.9
10	n/a	n/a	172.3	172.3
11	6.79 (s)	6.78 (s)	117.6	117.5
12	n/a	n/a	154.9	154.9
13	n/a	n/a	128.8	128.7
14	6.89 (s)	6.89 (s)	134.0	133.9
15	2.18 (s)	2.16 (s)	16.0	16.0
16	1.03 (s)	1.03 (s)	21.5	21.5
17	1.22 (s)	1.21 (s)	25.6	25.6

Table 6: Observed and literature ^{1}H and ^{13}C NMR data of Trigoxyphin L in methanol-d_4.

2.3 The ‘tetralone route’ *via* oxidative ring expansion

The ‘furan route’, despite delivering the first total synthesis of trigoxyphins K and L, is flawed with limited yields and choices of reactions due to the sensitivity of furan derivatives toward oxidants and Lewis acids. The starting material, 3-furoic acid, is also expensive and difficult to prepare. Constructing the tricyclic core structure from the benzene ring, on the other hand, would benefit from cheaper starting materials and a wide range of applicable reactions.

As the name suggests, the ‘tetralone route’ aimed to synthesise an α-tetralone derivative *en route* to the target molecules, ideally without recourse to acid-labile furan derivatives (*Scheme 16*). The synthesis would start with the preparation of tetralone derivative **2.47** using Friedel–Crafts chemistry. After methylation, the newly formed ring would be expanded through an appropriate homologation, and subsequent butenolide synthesis from **2.25** would deliver the trigoxyphin natural products.

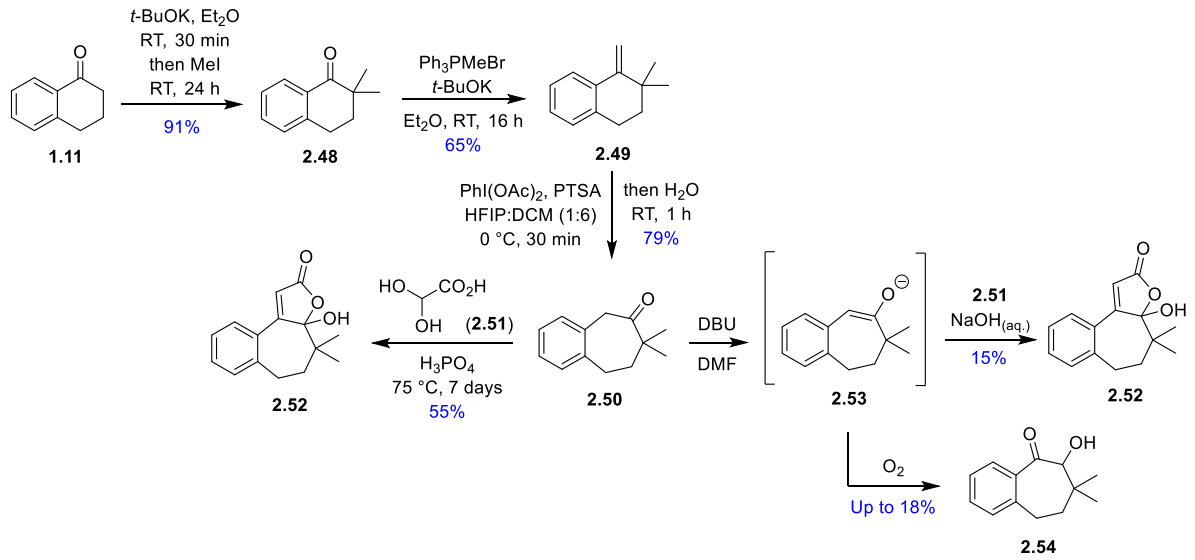


Scheme 16: Retrosynthetic analysis of the ‘tetralone route’.

2.3.1 Earlier research within the Robertson Group

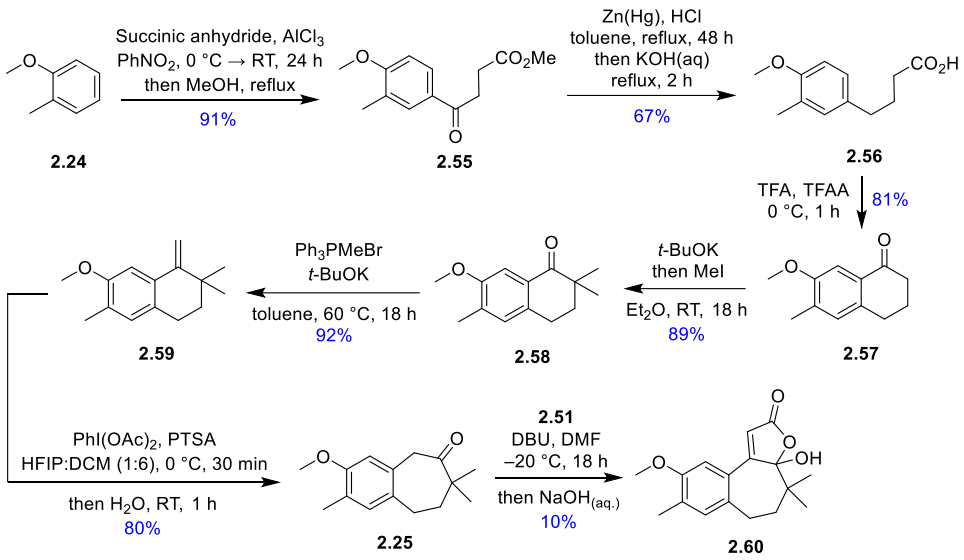
Studies on the ‘tetralone route’ were pioneered by former Part II student Mattimoe, who prepared benzosuberone derivative **2.50** from α-tetralone **1.11** (*Scheme 17*).[29] The route enabled efficient installation of the geminal dimethyl moiety through α-methylation, then Wittig reaction gave olefin **2.49**, which was converted into **2.50** by an oxidative ring-expansion

process. A one-step butenolide synthesis was evaluated, where **2.50** was treated with glyoxylic acid monohydrate (**2.51**) and phosphoric acid. The reaction gave **2.52** in 55% yield, but proceeded slowly and required one week of heating at 75 °C for complete conversion of the starting material. A new trial was conducted using DBU, which gave up to 15% yield of **2.52** provided that the reaction mixtures were strictly oxygen-free, as the α-hydroxylation product **2.54** was found alongside **2.52** in initial trials.



Scheme 17: Mattimoe's synthesis of γ-hydroxy butenolide **2.52** from α-tetralone.

Then, when working on the real system leading to the trigoxyphins (*Scheme 18*), Mattimoe noted that all the reactions of intermediates were slower and more complicated as a result of electron donation from the aryl methyl and methoxy substituents. Ketone **2.25**, formed from oxidative ring expansion of **2.59**, was also found labile to acidic and oxidising conditions. When the H_3PO_4-mediated condensation protocol was tested on **2.25**, extensive decomposition was observed and none of the desired product was isolated. The DBU method only delivered very low yields of *O*-methyl trigoxyphin L **2.60**.

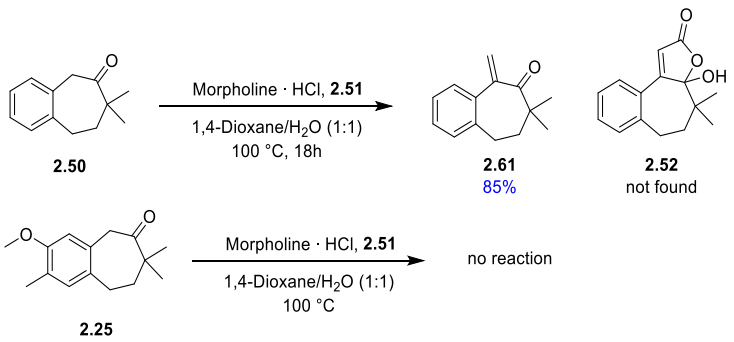


Scheme 18: Mattimoe's attempted synthesis of *O*-methyl trigoxyphin L **2.60**.

2.3.2 Optimisation of the final steps in the 'tetralone route'

2.3.2.1 New attempts to effect a one-pot butenolide synthesis

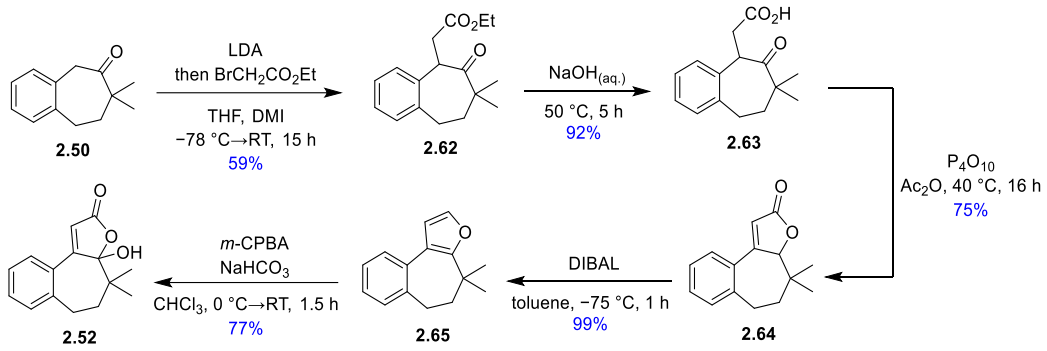
In light of unsatisfactory outcomes from strongly acidic and basic conditions, a new attempt to achieve a one-pot formation of γ-hydroxy butenolide was carried out using Chan's protocol (*Scheme 19*).[30] Substrate **2.25** remained stable to the conditions; by contrast, **2.50** underwent methylenation reaction and yielded enone **2.61**. The desired butenolide product **2.52** was not found from the trials.



Scheme 19: Attempted butenolide synthesis on benzosuberone derivatives **2.50** and **2.25** using Chen's protocol.

2.3.2.2 Butenolide synthesis *via* condensation of γ-keto carboxylic acid

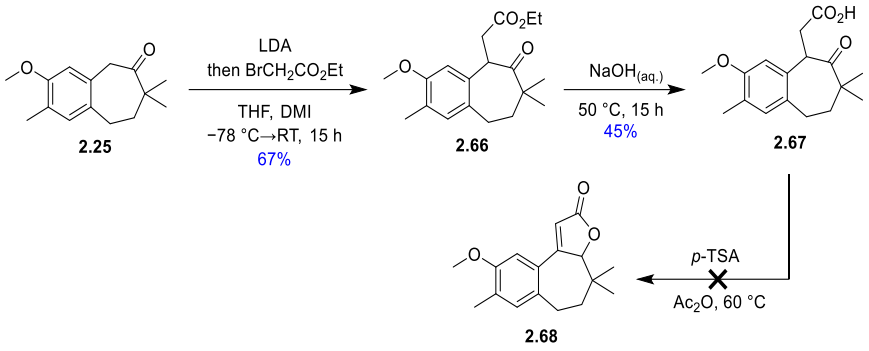
The cycloalkanone route for fused furan synthesis as detailed in the previous chapter paved the way to a two-step butenolide synthesis through γ-keto ester intermediates (*Scheme 20*). Ketone **2.50** was deprotonated and alkylated with ethyl bromoacetate to give intermediate **2.62**, whose parent carboxylic acid **2.63** was expected to cyclise in the presence of acetic anhydride.[31] Using this protocol, keto-acid **2.63** was converted into butenolide **2.64**, then DIBAL reduction (→ **2.65**) and oxidation by *m*-CPBA gave γ-hydroxy butenolide **2.52**.[32] Despite adding extra steps, this protocol completed the trigoxyphin L model (**2.52**) synthesis in acceptable overall yield (31% from **2.50**).



Scheme 20: Synthesis of butenolide **2.64** and γ-hydroxy butenolide **2.52**.

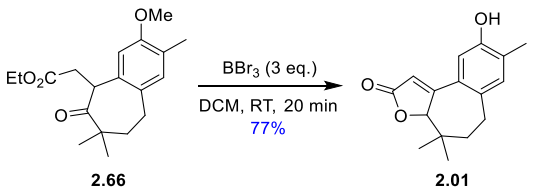
When the alkylation protocol was applied to ketone **2.25** (*Scheme 21*), residual substrate was found in the crude product mixture. The starting ketone **2.25** and alkylation product **2.66** were similarly polar and separation with silica gel chromatography was difficult. The incomplete reaction was not resolved by using excess LDA or bromoacetate, but by an excess of DMI. This indicated that the lithium enolate of **2.25** was not sufficiently reactive and needed a strong solvating agent such as DMI for effective alkylation. Furthermore, attempted cyclocondensation of γ-keto acid **2.67** only led to its decomposition. At this point, efforts

focused on a more promising alternative pathway and no further transformations of γ-keto acid **2.67** were attempted.



Scheme 21: Attempted synthesis of *O*-methylated trigoxyphin K via γ-ketocarboxylic acid **2.67**.

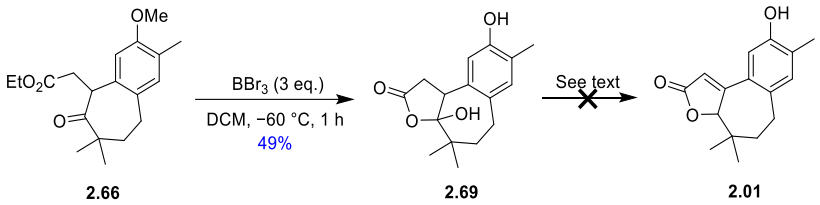
One of the necessary steps in the 'tetralone route' was *O*-demethylation to reveal the free phenolic group and work towards this end led to the discovery of an efficient one-step butenolide synthesis. A widely-used reagent for this type of ether cleavage is boron tribromide (BBr_3), a strong Lewis acid known for its effectiveness in activating the aryl ether and cleaving the Me–O bond.[33] In a test run, γ-keto ester **2.66** was treated with three molar equivalents of BBr_3 at room temperature, aiming to achieve both ether and ester cleavage. In practice, these conditions both fulfilled the intended purpose and, as a bonus, resulted in the direct synthesis of trigoxyphin K (**2.01**, *Scheme 22*). This outcome showed that BBr_3 also facilitated the cyclocondensation,[34] and that trigoxyphin K remained stable in the reaction mixture.



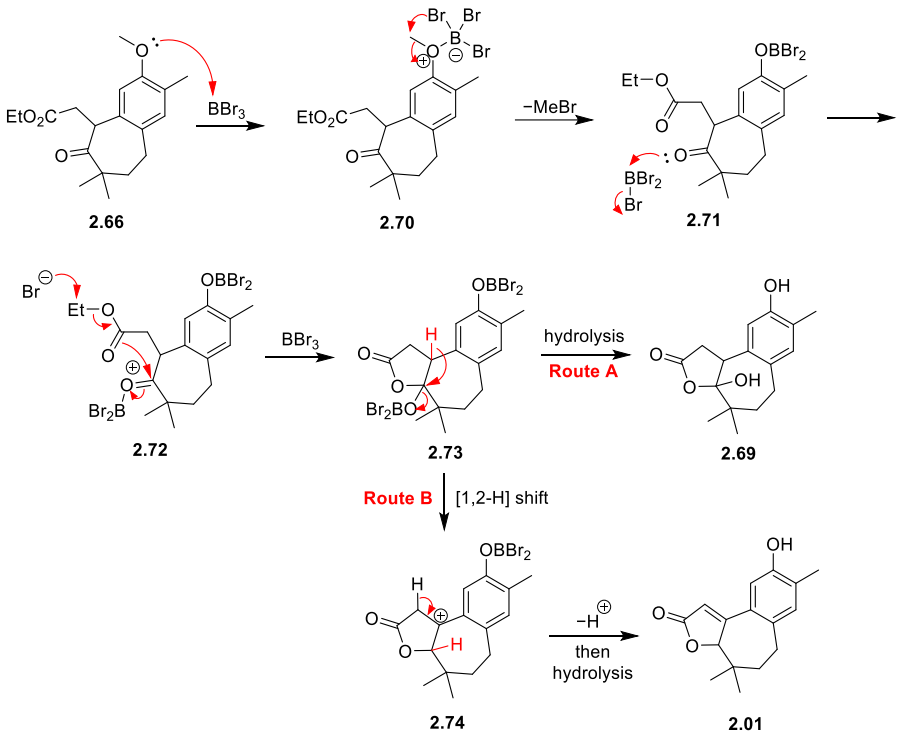
Scheme 22: One-step synthesis of trigoxyphin K by BBr_3 treatment of γ-keto ester **2.66**.

Attempts to repeat the BBr_3-mediated condensation demonstrated the special reactivity of substrate **2.66**. It was thought that lower temperatures and dropwise addition of BBr_3 would

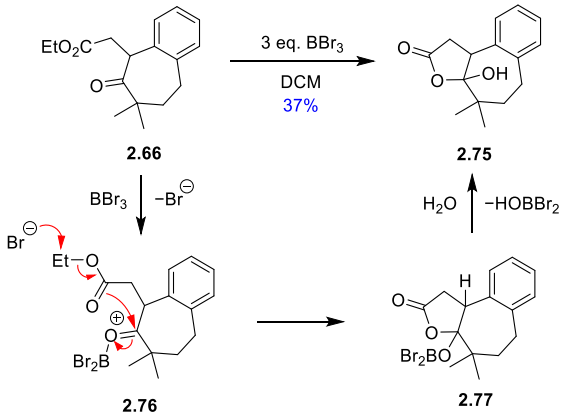
further reduce the possibility of side reactions; however, running the reaction slowly at temperatures up to 0 °C exclusively produced γ-hydroxy butanolide **2.69**. Reducing the amount of BBr_3 while keeping the reaction temperature unchanged only reduced the overall conversion rate. The butanolide showed good stability to acidic and basic conditions, and once produced it could not be subsequently converted into trigoxyphin K (*Scheme 23*).[35,36] By comparison, treating ketone **2.66** of the model system with excess BBr_3 at both −60 °C and room temperature gave hydroxy-butanolide **2.75** as the only product. To rationalise the different outcomes from the two substrates, it is proposed (*Schemes 24 and 25*) that following ring formation and ether cleavage, the rate-limiting is the elimination of Br_2BO^- from the γ-carbon of the newly-formed lactone. This is more likely to occur in the electron-rich real system, where a possible 1,2-hydride shift could create a stabilised benzylic cation following departure of Br_2BO^-, which loses a proton to give the butenolide ring. This process is presumably much less likely to occur in the less electron-rich model system, and the intermediate **2.77** remained stable in the reaction mixture until its hydrolysis.



Scheme 23: Synthesis of γ-hydroxy butanolide **2.69** through BBr_3 treatment of **2.66** at −60 °C, and attempted conversion of **2.69** to trigoxyphin K (**2.01**). Reagents used (**2.69** → **2.01**): HCl in THF and PTSA/Ac_2O.



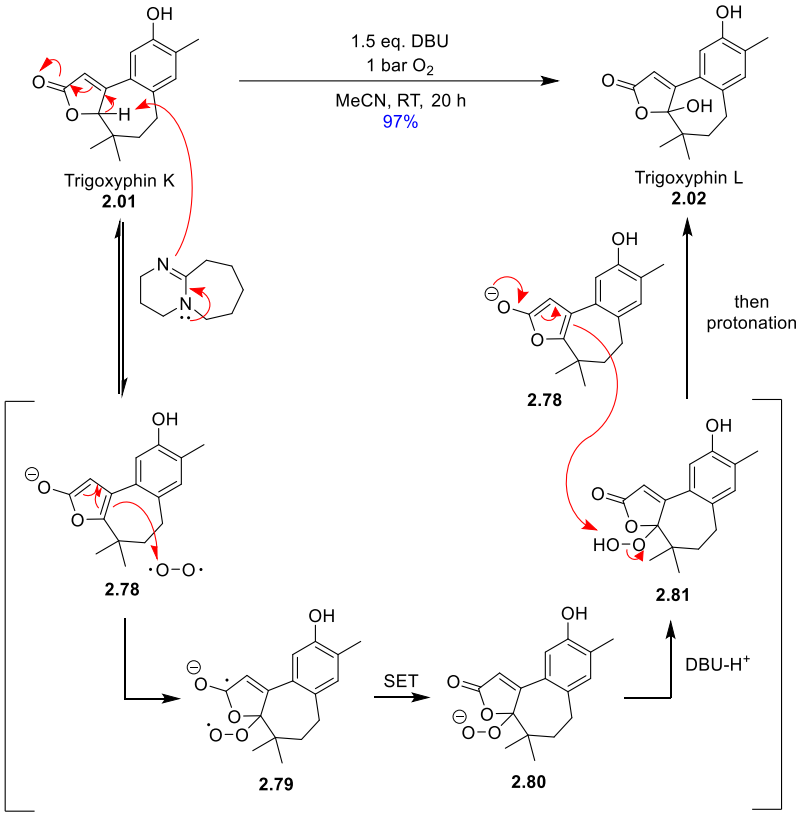
Scheme 24: Proposed mechanism of the reaction of **2.66** with BBr_3 at −60 °C (Route A) and at room temperature (Route B).



Scheme 25: Proposed mechanism for the conversion of **2.66** into γ-hydroxy-γ-lactone **2.75**.

In consideration of phenol's vulnerability to strong oxidisers, the oxidation of trigoxyphin K to trigoxyphin L was achieved using DBU and oxygen gas following Boukouvalas' precedent.[37] The reaction likely involved O_2 capture by the enolate through a SET mechanism following γ-deprotonation of the butenolide. This concluded the 'tetralone route' (*Scheme 26*),

which compared with the ‘furan route’ had the same number of steps but achieved much better overall yields for trigoxyphin K (28%) and trigoxyphin L (27%) respectively. The spectral data obtained from this synthesis were identical to those from the ‘furan route’ (see **Section 2.2.3.3**).

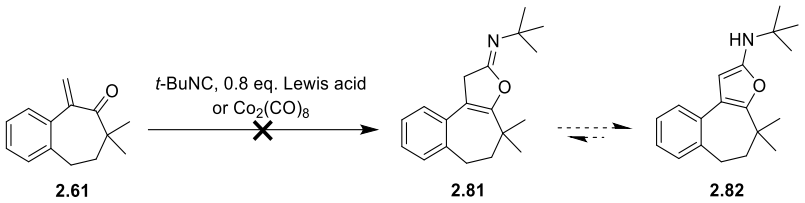


Scheme 26: Outcome and proposed mechanism of DBU-mediated oxidation of trigoxyphin K.

2.4 Attempted furan synthesis from side product 2.61

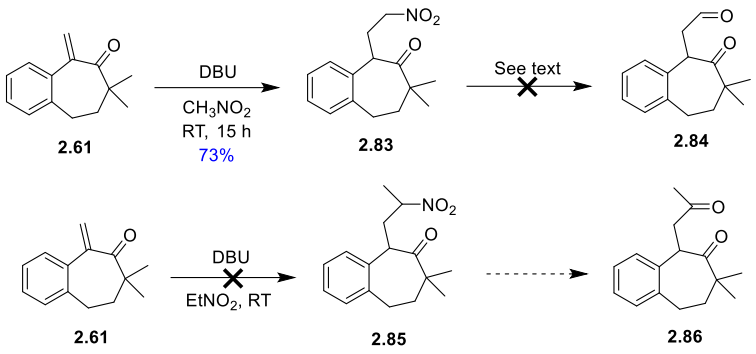
A side project originating from the total synthesis efforts was the conversion of the exo-methylene compound **2.61** to a furan derivative. The first explored pathway was overall (4+1)-cycloaddition with a one-carbon synthon. The low HOMO energy level of enones means that an electron-rich counterpart is required to initiate the process; carbon monoxide and its derivatives which bear negative formal charge on the carbon terminus would meet this demand.

Following Saegusa's γ-butyrolactone synthesis protocol with isocyanides, **2.61** was treated with *tert*-butyl isocyanide and a variety of Lewis acid catalysts (*Scheme 27*).[38–40] In each case, the starting material was recovered unaffected; this reflected the careful selection of the enone substrates in the original study which all had β-alkyl substituents with the majority β,β-disubstituted. Clearly, the terminal enone **2.61** was not suited for this cycloaddition, perhaps because it could not be adequately polarised by the Lewis acid.



Scheme 27: Attempted Lewis acid-mediated (4+1) cycloaddition of **2.61** with *tert*-butyl isocyanide. The Lewis acids used included $GaCl_3$, $AlCl_3$ and Et_2AlCl.

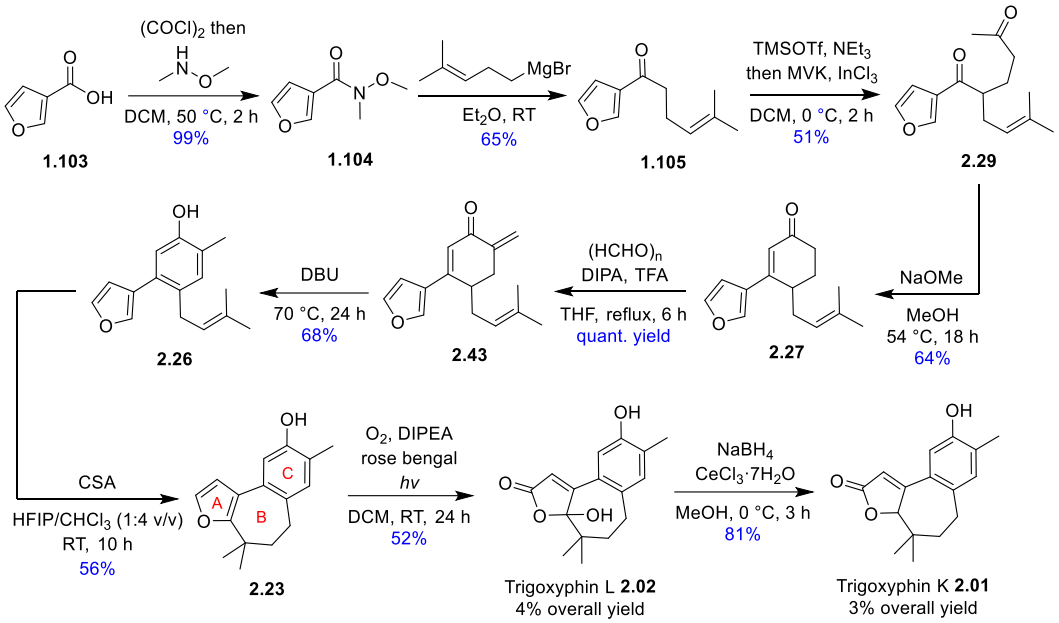
Then, **2.61** was converted into nitroketone **2.83**, which upon a Nef reaction would give 1,4-dicarbonyl compound **2.84** for the Paal−Knorr synthesis. In practice, the substrate remained stable to the conditions tested except basic permanganate, which resulted in its decomposition.[41–43] It is also worth noting that there were no precedents of Nef reactions on primary γ-nitro ketones. Besides, the preparation of secondary γ-nitro ketone was attempted but only a complicated mixture resulted.



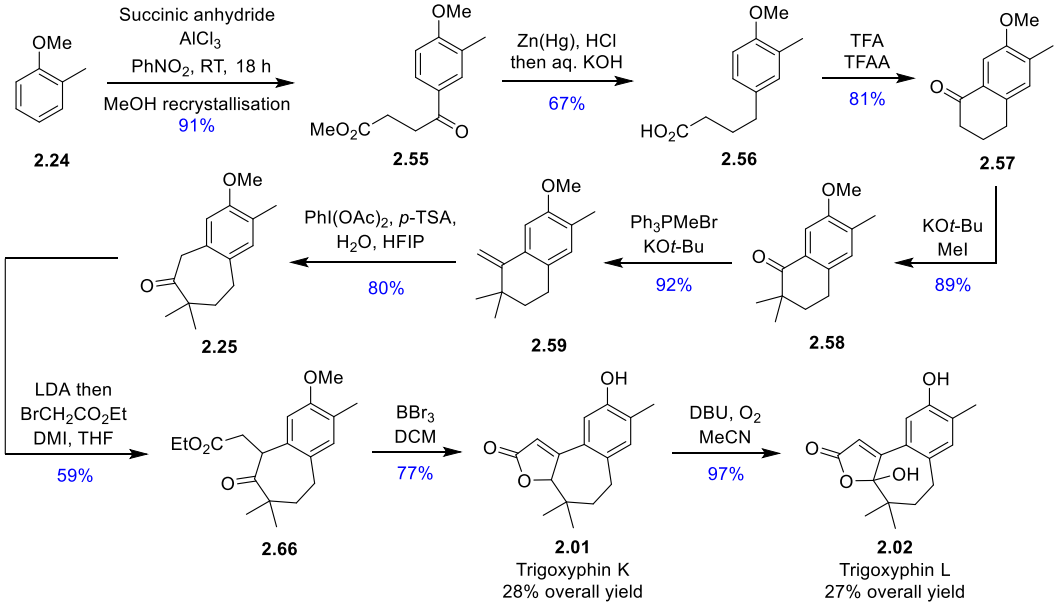
Scheme 28: Synthesis and attempted Nef reaction of nitroketones **2.83** and **2.85**, and the attempted Nef reaction of **2.83**. Reagents and conditions tested for **2.83**→**2.84**: (a) $KMnO_4$, 1M $KOH_{(aq.)}$, $MgSO_4$, 0 °C, 1 h; (b) $PhCH_2Br$, 1M $KOH_{(aq.)}$, Bu_4NI, RT, 20 h; (c) DBU, O_2, DCM, RT, 16 h, then 1M $HCl_{(aq.)}$.

2.5 Conclusion and future work

Research on the total synthesis of trigoxyphins K and L established two routes that used different ring construction strategies.[12] The 'furan route' advanced the study on furan chemistry to deliver the target molecules from 3-furoic acid with two key achievements (*Scheme 29*). Firstly, it established the phenolic system with Robinson annulation and dienone aromatisation, thereby by-passing the difficult late-stage arene hydroxylation required for routes developed previously. Secondly, closure of the seven-membered B-ring was subsequently achieved through acid-catalysed alkene hydroarylation. The 'tetralone route' gave significantly better yields than the 'furan route' as it took advantage of commercially available benzene derivatives and good stability of its synthetic intermediates (*Scheme 30*). It provided an example of one-pot butenolide synthesis from γ-keto esters with the use of boron tribromide. This route would be suitable for large-scale production of the natural products, as well as analogues.



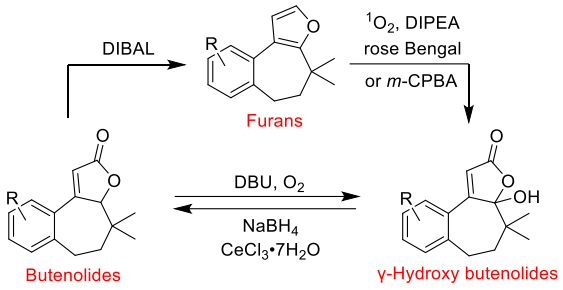
Scheme 29: Overview of the 'furan route'.



Scheme 30: Overview of the 'tetralone route'.

In a broader context, this successful total synthesis marks the first total synthesis of compounds within the trigoxyphin family, paving the way for further medicinal and synthesis studies on structurally related compounds. It also demonstrates the interconvertible nature of three mutually related five-membered ring systems, namely furans, butenolides and γ-hydroxy

butenolides (*Scheme 31*). The ‘tetralone route’ in particular could facilitate further research on effective furan synthesis from ketones and conjugate enones.



Scheme 31: The interconversions between furans, butenolides and γ-hydroxy butenolides.

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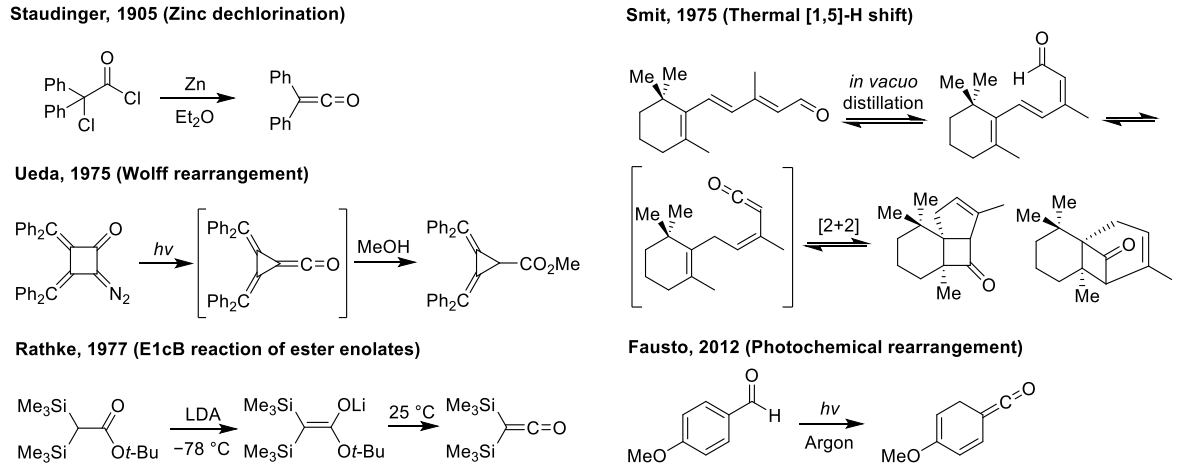
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Chapter 3: The Ketene Approach to [*b*]-Annulated Furanocycloalkanones

3.1 Introduction

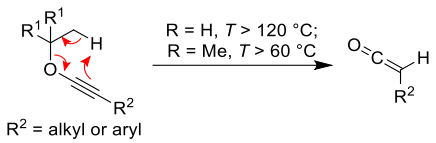
3.1.1 Background

Owing to their high electrophilicity, ketenes are commonly used in the synthesis of carboxylic acid derivatives.[1–3] As most ketenes are transient and highly reactive species, they are almost always generated and used *in situ* through nucleophilic trapping. Wedekind in 1901 proposed[4] that ketenes could be generated from base-mediated elimination reaction of acyl chlorides, which later proved to be one of the most frequently used ketene synthesis methods. Although the Wolff rearrangement discovered one year later involves ketene intermediates,[5] the first preparation and isolation of ketenes was achieved by Staudinger in 1905 through zinc-mediated dechlorination of chlorodiphenylacetyl chloride.[6] The simplest ketene, by contrast, can be generated from thermal pyrolysis of acetone or acetic acid.[7] Many new synthetic methods have been discovered since, including E1cB reaction of ester enolates as well as thermal or photochemical pericyclic reactions (*Scheme 1*).[8–10]



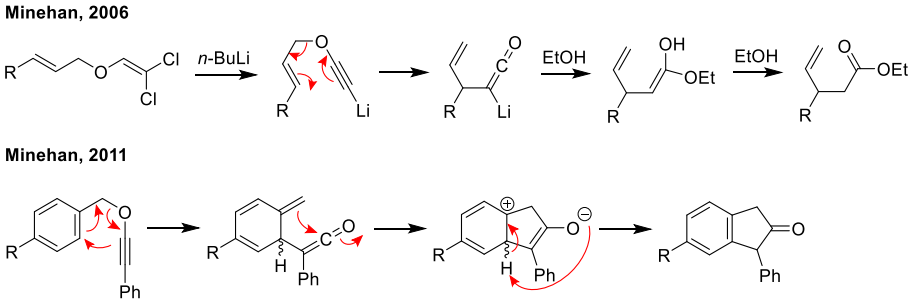
Scheme 1: Selected examples of ketene synthesis from electron-deficient precursors.

The majority of ketene precursors are electron-deficient species such as carboxylic acid derivatives and diazo ketones;[5,6,8,11,12] a notable exception is the ynol ether functionality, which owes its distinct reactivity to the polarising effect of the oxygen atom conjugated with the carbon-carbon triple bond.[13] First reported by Ficini and Arens, ethyl alkynyl ethers undergo thermal decompositions at temperatures exceeding 100 °C, producing ethylene and a ketene.[14–15] In later research, the temperature threshold was found to be much lower for *tert*-butyl alkynyl ethers.[16] It is believed that these transformations are retro-ene reactions (*Scheme 3.02*);[17] as the reactions require only an inert solvent and an elevated temperature, they are powerful tools of *in situ* ketene generation and have been used in the synthesis of lactones, lactams and cyclic imides.[17–19]



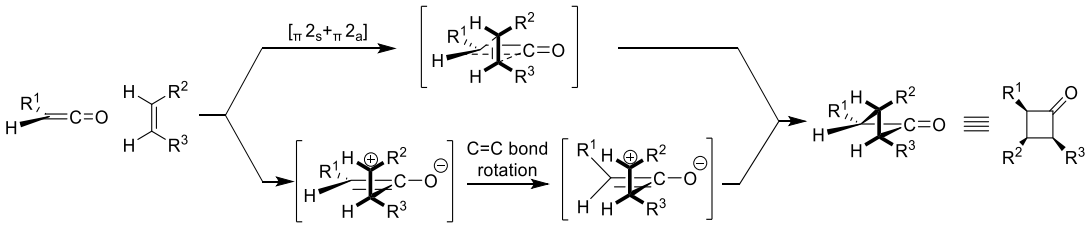
Scheme 2: Retro-ene reaction of (substituted) ethyl alkynyl ethers.

In addition, some alkenyl ynol ethers are capable of producing ketenes *via* [3,3]-sigmatropic processes related to the Claisen rearrangement. Observed in allyl and benzyl ynol ethers, such rearrangements can proceed spontaneously at temperatures below 0 °C, and find use in, for example, the synthesis of 2-indanones (*Scheme 3*).[13]

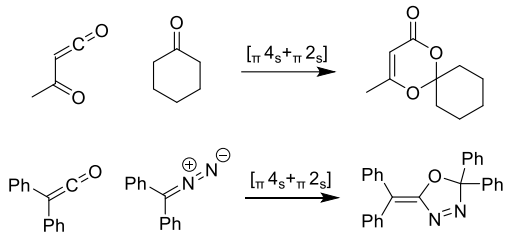


Scheme 3: Minehan's ketene synthesis *via* [3,3]-sigmatropy of allyl and benzyl ynol ethers.

Ketenes are prone to spontaneous dimerisation *via* overall [2+2] cycloaddition; the same mechanism underlies their reaction with unsaturated C−C, C−O and C−N bonds.[7] The [2+2] cycloaddition of ketenes with olefins, a useful way to access cyclobutanones, is understood to proceed with either a concerted or stepwise mechanism (*Scheme 4*).[20] The [4+2] cycloaddition of ketenes is much less common and typically across the C−O double bond. The products are predominantly 5- or 6-membered heterocycles (*Scheme 5*).[21−22]

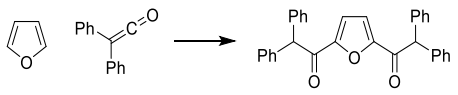


Scheme 4: Overall [2+2] cycloaddition of ketenes and olefins with either a concerted (upper) or stepwise (lower) reaction mechanism.



Scheme 5: Reported examples of [4+2] cycloadditions of ketenes, with the ketene being either the 4π component (top) or the 2π component (bottom).

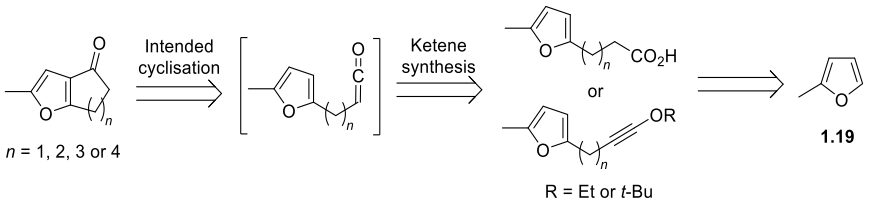
Furthermore, unlike carbenes, ketenes are not known to engage in pericyclic reactions with aromatic systems such as furans. One of the very few precedented reactions of furans and ketenes is the acylation of furan with diphenylketene which produces a diketone product (*Scheme 6*).[23] This example shows that the high reactivity of ketenes could offer an acid-free alternative to the Friedel−Crafts acylation reaction for electron-rich aromatic compounds.



Scheme 6: The 2,5-diacylation of furan by diphenylketene.

3.1.2 Project aims

This study, inspired by the thermal retro-ene reaction of alkyl alkynyl ethers, aimed to explore synthetic methodology based on furan-derived ketenes and investigate the viability of achieving ring fusion to furan with tethered ketenes. This study served as a complementary project to the studies discussed in **Chapter 1**, in that it sought to establish a short and atom-efficient pathway to furano[*b*]cycloalkanones. All the ketene targets in this project were ω-(5-methylfuran-2-yl)alkyl ketenes with varying chain lengths, whose precursors would be a carboxylic acid or an ynol ether (*Scheme 7*). Mechanistically, the intended cyclisation step is proposed as either direct or *via* a spirocyclic intermediate and [1,2]-shift of the acyl group. 2-Methylfuran (**1.19**) was chosen as the parent compound of the substrates because it was believed that the chemically inert methyl group would shield the 5-position of the furan ring from possibly reacting with ketenes, thus increasing the regioselectivity of any cyclisation reactions that might occur.

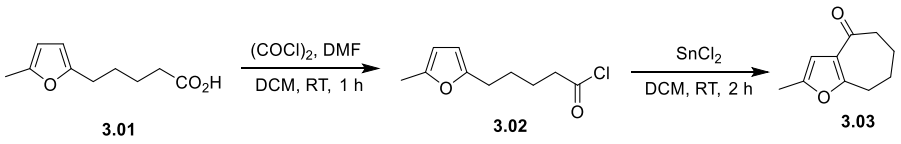


Scheme 7: Retrosynthetic analysis of furanocycloalkanone synthesis *via* ω-(5-methylfuran-2-yl) ketenes.

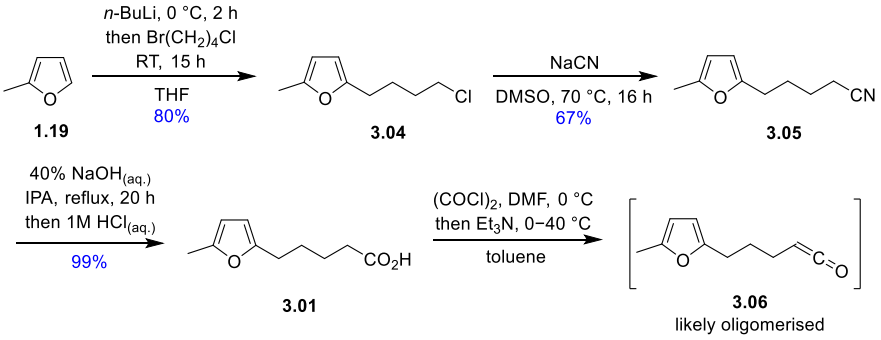
3.2 Preparation of furyl ketene species from carboxylic acids

3.2.1 Ketene synthesis *via* acyl chloride

Acyl chlorides are the most frequently used ketene source, being readily generated from the corresponding carboxylic acid and used *in situ* for the synthesis of esters and amides. Liu et al. reported the conversion of carboxylic acid **3.01** into furano[*b*]cycloheptanone **3.03** through Friedel−Crafts acylation of its corresponding acyl chloride **3.02** (*Scheme 8*).[24] Following this precedent, the said acid was prepared from a three-step synthesis from 2-methylfuran (*Scheme 9*). With Cremonesi's ketene synthesis protocol, a one-pot conversion of **3.01** into ketene **3.06** *via* the acyl chloride intermediate was then carried out.[25] To analyse the outcomes, the reaction mixtures were directly concentrated *in vacuo* and analysed by IR and ^{1}H NMR spectroscopy. It was not clear whether **3.06** had been produced as the analysis data on the crude material only showed the presence of acid **3.01** and acyl chloride **3.02**. Repeating this process using LDA or LHMDS made no difference to the reaction outcome. Efforts subsequently moved on to other methods for generating the furyl ketene intermediates.



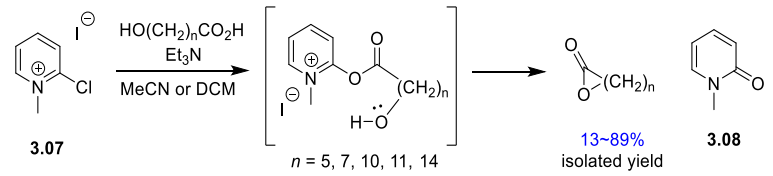
Scheme 8: Cremonesi's reported two-step cyclisation of **3.01** through $SnCl_2$-mediated Friedel−Crafts acylation.



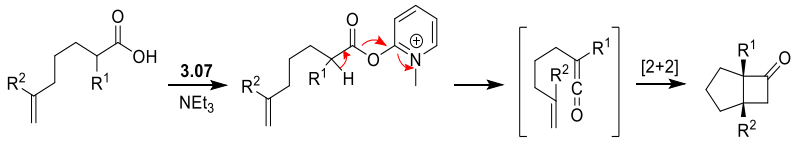
Scheme 9: Synthesis of acid substrate **3.01** and the outcome of the acyl chloride pathway.

3.2.2 Ketene synthesis with Mukaiyama reagent

The Mukaiyama reagent, namely *N*-methyl-2-chloropyridinium iodide (**3.07**), is a mild condensation reagent for alcohols and carboxylic acids.[26] It is frequently used in tandem with a base such as triethylamine to form cationic ester adducts with carboxylic acids, which then react with alcohols and amines to give esters and amides, respectively (*Scheme 10*).[26–28] Mechanistically, Kohl-Mines and Hansen proposed that the Mukaiyama reagent likely converts the acid substrates into ketenes.[29] This hypothesis was investigated and substantiated by Funk and co-workers, who demonstrated the formation of *cis*-fused cyclobutanones from alkenoic acids (*Scheme 11*).[30] Moreover, the Mukaiyama reagent is always used together with an amine base such as triethylamine, making it compatible with acid-labile furan derivatives.

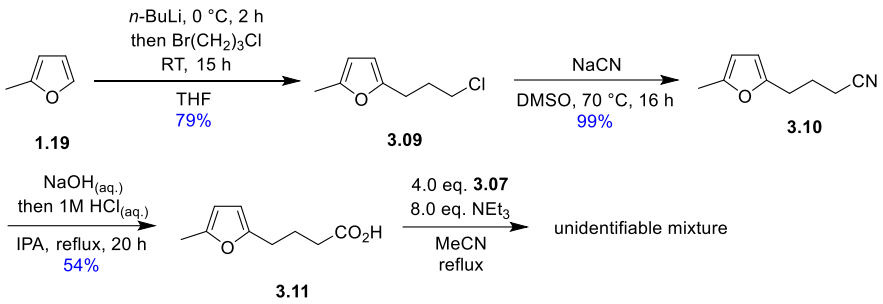


Scheme 10: Mukaiyama's lactone synthesis from hydroxycarboxylic acids.



Scheme 11: Funk's synthesis of cyclobutanones from ω-alkenyl acids with the Mukaiyama reagent (**3.07**).

As a test substrate, carboxylic acid **3.11** was pre-mixed with triethylamine before being added to a refluxing solution of **3.07** (*Scheme 12*). the ^{1}H NMR data for the crude product, which was absent of substrate **3.11**, revealed a series of products with similar structural features, but no substantial information could be retrieved. It was thus concluded that an alternative type of ketene precursor was needed.



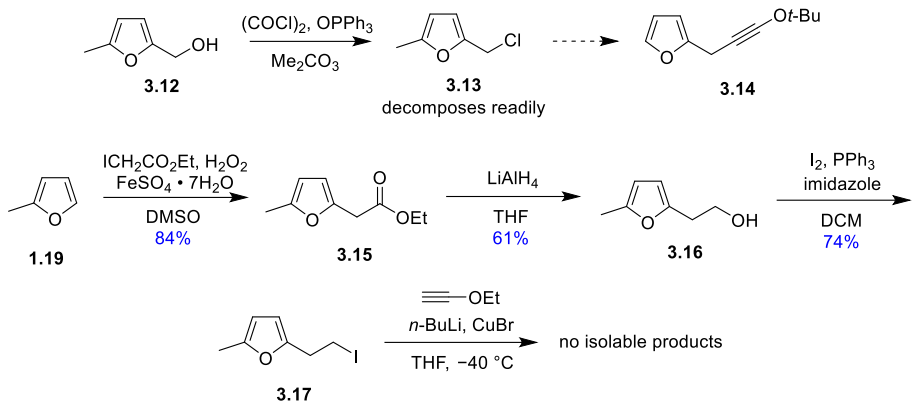
Scheme 12: Preparation of carboxylic acid substrate **3.11**, which only gave uncharacterisable products upon treatment with the Mukaiyama reagent (**3.07**).

3.3 Preparation of furyl ketenes from ynol ethers

3.3.1 Synthesis of ω-(fur-2-yl)alkyl ynol ethers

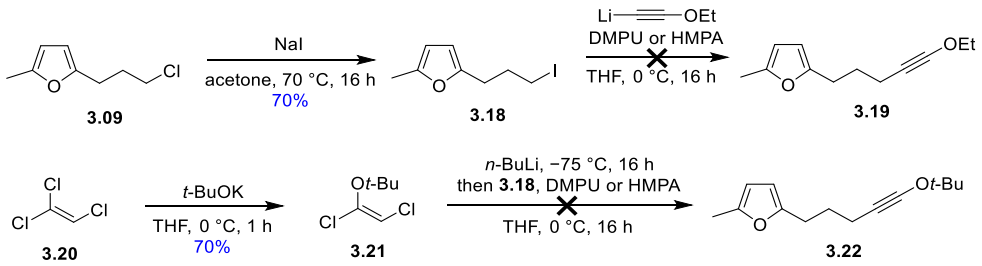
Ynol ethers are accessible from 1,1- and 1,2-dichlorovinyl ethers by treatment with an excess of butyllithium; Minehan *et al.* demonstrated that lithium-halogen exchange precedes the elimination of lithium halide.[13] Although Muthusamy and co-workers developed an alternative method that used α-alkoxy ketones,[31] 1,1-dihalovinyl ethers are the most frequently used ynol ether precursors and were used for the preparation of the substrates in this study.[13]

Efforts sought to prepare the ω-(fur-2-yl)alkyl ynol ether substrates through direct installation of the ynol ether moiety by alkylation of alkoxyacetylene organolithiums with a suitable furan electrophile. A screening of the furan-based alkylation substrates revealed that a minimum of three methylene groups was necessary to separate the furan and the leaving group (*Scheme 13*).[32–33] Furfuryl chloride **3.13** was too unstable to be evaluated effectively; the homologous iodide **3.17**, prepared from ester **3.15**, yielded no characterisable product after the attempted alkylation. It was believed that elimination of **3.17** occurred instead, generating volatile 2-vinylfuran.



Scheme 13: Attempted preparation of ynol ethers from halides **3.13** and **3.17**.

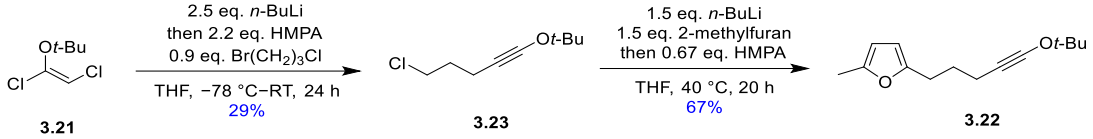
Efforts subsequently targeted ynol ethers **3.19** and **3.22** (*Scheme 14*) but alkylation attempts with iodide **3.18** did not succeed and the substrate was recoverable; this result persisted even when DMPU or HMPA were used to enhance the reactivity of the acetylide.



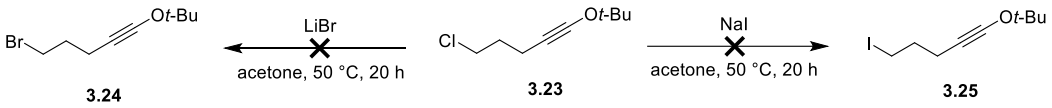
Scheme 14: Attempted synthesis of ynol ethers **3.19** and **3.22** from alkyl iodide **3.18**.

A breakthrough was achieved by inverting the C–C bond forming steps in which ω-chlorinated ynol ether **3.23** was alkylated with 5-methyl-2-furyllithium in the presence of HMPA as activator. This achieved up to 67% isolated yield for **3.22** (*Scheme 15*). Temperature, substrate concentration, and reagent ratios were all key parameters for this reaction. Reaction mixtures with a concentration of 0.2 M for the substrate, 1.5 mole equivalents of furyllithium and 67 mol% of HMPA gave the best result after overnight stirring at 40 °C. Yields declined significantly when higher temperatures were used due to the thermal instability of both the product **3.22** and the reagent **3.23**. The reaction did not proceed without HMPA, while smaller

relative quantities of furyllthium and lower temperatures both led to incomplete conversion. It is also noteworthy that the Finkelstein reactions of **3.23** for the preparation of the corresponding bromide and iodide were attempted without success (*Scheme 16*). These reactions did not progress at room temperature, and the instability of **3.23** led to its degradation when heated.



Scheme 15: Preparation of **3.22** from ω-chlorinated ynol ether **3.23**.



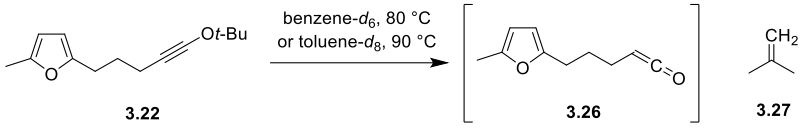
Scheme 16: Attempted Finkelstein reactions of **3.23**.

3.3.2 Thermal retro-ene reaction of ynol ethers

Ynol ether **3.22** could not be purified by column chromatography due to its instability to silica; therefore, it was directly used for retro-ene tests in NMR tubes with an inert deuterated solvent because an elevated temperature was the only prerequisite for the retro-ene reaction, and reaction progress could be monitored by NMR spectroscopy in real time. The *tert*-butyl (rather than an ethyl) ynol ether **3.22** was also expected to require a lower temperature threshold for its retro-ene reaction.

Both benzene-d_6 and toluene-d_8 were used as solvent for these reactions (*Scheme 17*). The loss of isobutylene from **3.22** proceeded at a similar rate in both solvents at 80 °C, reaching completion within 5 hours. Elevating the reaction temperature to 90 °C markedly increased the reaction rate, as expected. In the time-sequenced ^{1}H NMR spectra, resonances arising from the

isobutylene were clearly visible, indicating successful ketene generation (*Figure 1*, Region B). As the reaction progressed, the CH_2 peaks of the substrate at 2.8 ppm, 2.2 ppm (Region C) and 1.8 ppm (Region D) gradually disappeared as expected, giving way to more complicated multiplets. However, the number of peaks in furan region (5.7−6.0 ppm) increased. This was in contrast to the expected emergence of only one furan signal, as annulation would give a trisubstituted furan. Assuming that only one product was generated, the product was evidently still a disubstituted furan; however, it could not be identified with certainty due to the limited reaction scale and complexity in the 1.00−2.50 ppm region of the ^{1}H NMR spectrum.



Scheme 17: Envisaged thermal decomposition of *tert*-butyl alkynyl ether **3.22**.

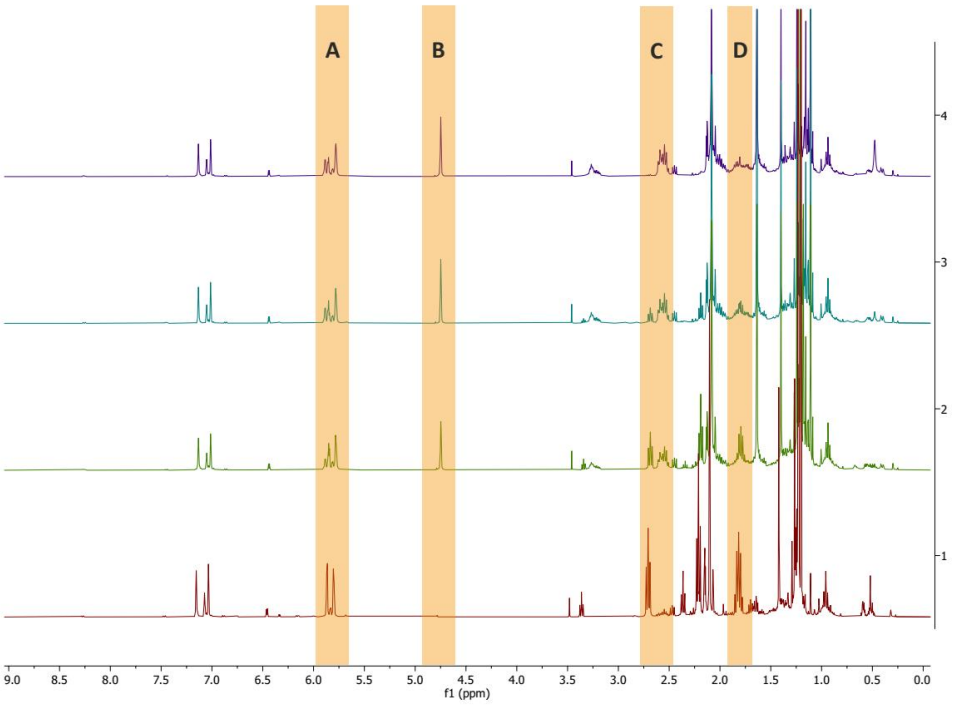


Figure 1: Time-sequenced ^{1}H NMR spectra of the thermal retro-ene reaction of **3.22** in toluene-d_8, with main regions of interest highlighted in orange. Spectrum 1 was recorded from the starting material, whereas spectra 2–4 were recorded from the reaction mixture after 0.5 h, 1 h and 2.5 h, respectively, of heating at 80 °C.

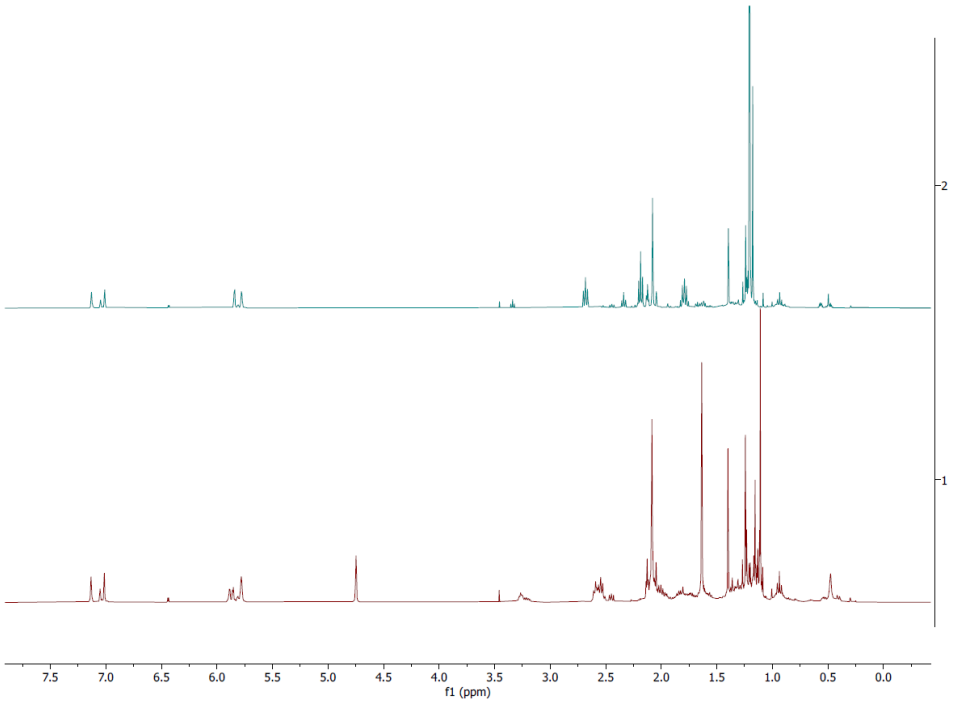


Figure 2: Stacked ^{1}H NMR spectra of ynol ether **3.22** (green) and the crude thermolysis product (crimson) in toluene-d_8.

To facilitate product characterisation, the reaction was repeated on 2-mmol scale at 90 °C using a 0.1 M toluene solution of the **3.22**, with ^{1}H NMR spectroscopic data appearing identical to those of the NMR-scale reactions. Subsequent analysis revealed that the reaction indeed produced one major product, responsible for the two aromatic peak clusters observed in the spectrum. Furthermore, the NMR spectrum showed a pair of CH_2 triplets at 2.54 and 2.59 ppm with approximately the same intensity. It was concluded from these observations that following the retro-ene reaction, the ketene intermediate did not react with the furan ring but prompted a dimerisation reaction (*Scheme 18*). Other evidence in the ^{1}H NMR spectrum, notably the CH multiplet at 3.27 ppm and its relative intensity to the strong singlets at 2.06 and 1.02 ppm, suggested that the product was *tert*-butyl ester **3.30** (*Figure 3*). The singlet at 1.07 ppm is attributed to a solvent impurity peak.

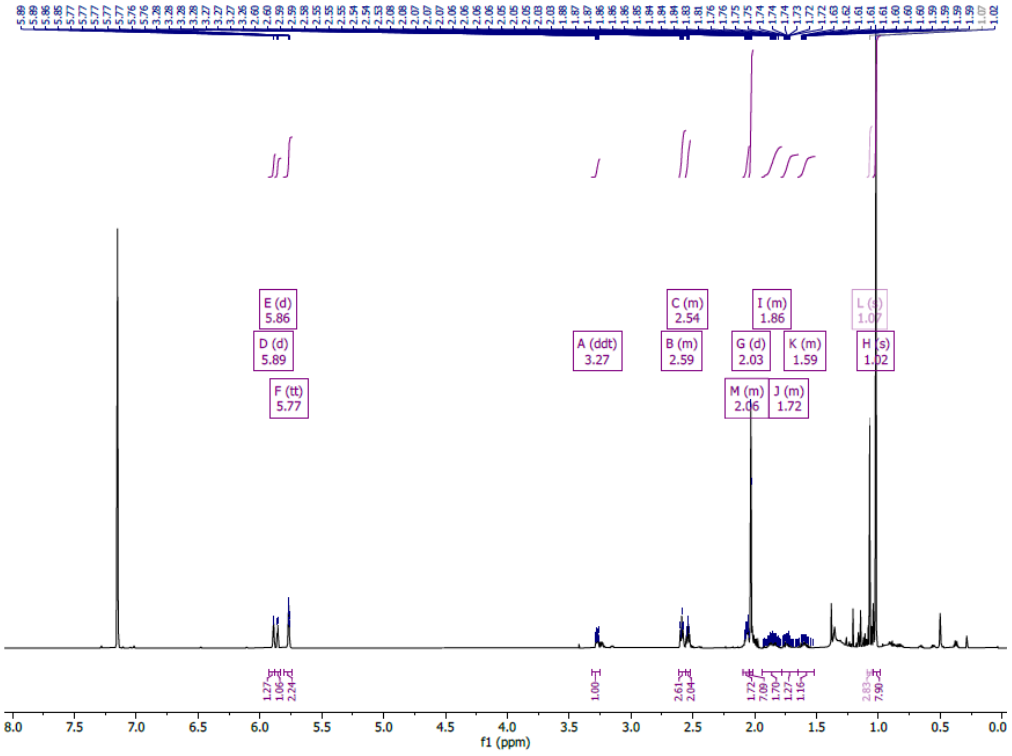
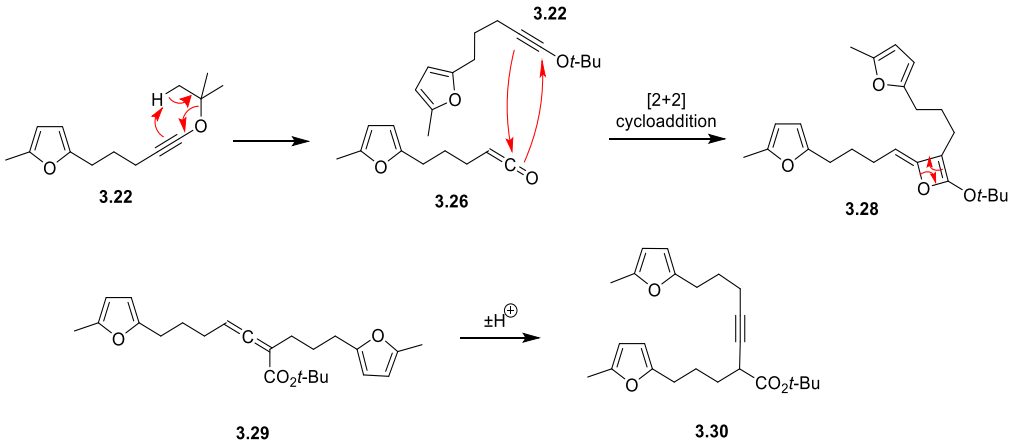


Figure 3: ^{1}H NMR spectrum of the thermolysis product **3.30**.



Scheme 18: Proposed mechanism for the synthesis of the thermolysis product **3.30**.

This structural assignment is backed by the ^{1}H-^{1}H COSY spectrum (*Figure 4*), in which the 3.27 ppm multiplet shows strong interaction with multiplets upfield while the two furyl-CH_2 triplets correlated with different peak clusters.

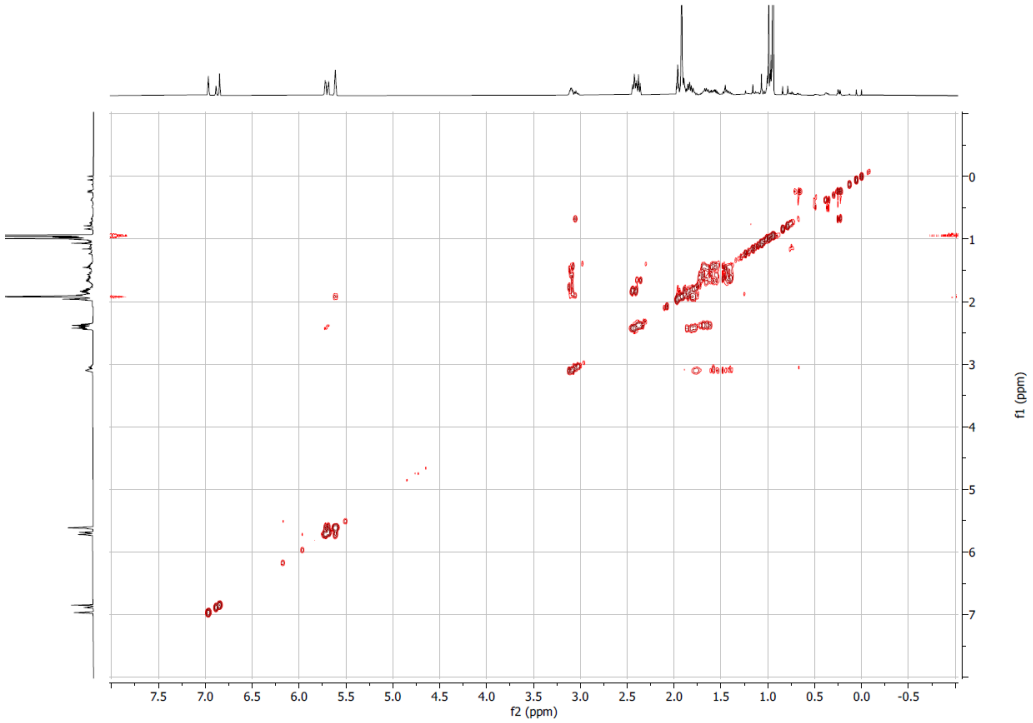
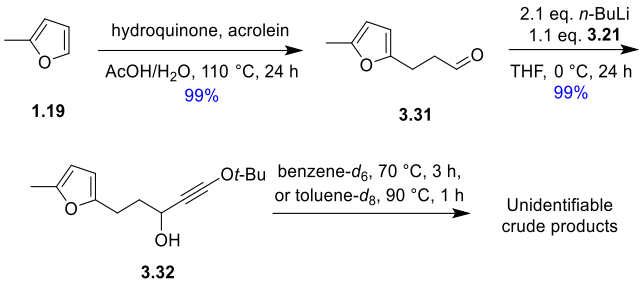


Figure 4: COSY spectrum of the thermolysis product **3.30**.

3-Hydroxy ynol ether **3.32** was also subjected to the retro-ene reaction conditions (*Scheme 19*). As expected, the presence of the nucleophilic hydroxyl group in **3.32** markedly accelerated its decomposition: the substrate was completed consumed within an hour at 90 °C or 3 hours at 70 °C (*Figure 5*). The confirmed formation of isobutene (by NMR, as evidenced in Region B of *Figure 5*) signified successful ketene production but the noise in the ^{1}H NMR spectrum of this micromolar-scale reaction complicated the structural assignment. Identical outcomes were obtained with a 2-mmol scale reaction. It was hence concluded that the remaining mass balance from this reaction most likely comprised a variety of ketene oligomers, which together gave poorly resolved signals in the ^{1}H NMR spectrum.



Scheme 19: Synthesis of 3-hydroxy ynol ether **3.32** and the outcome of its attempted retro-ene reaction.

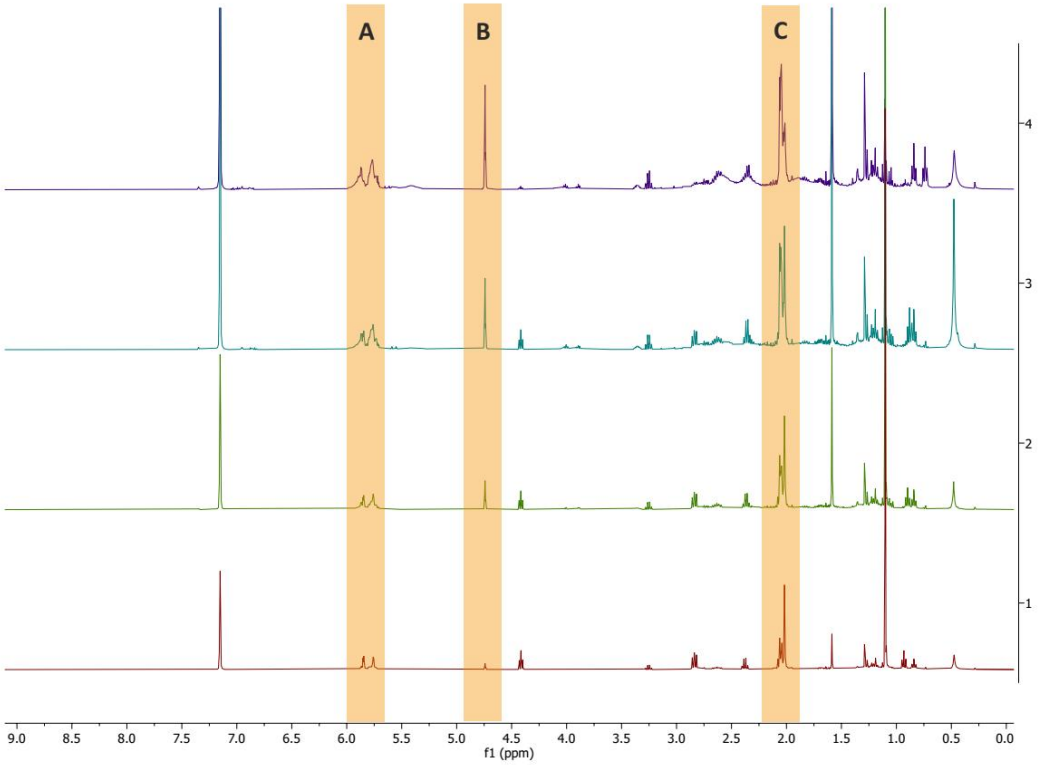
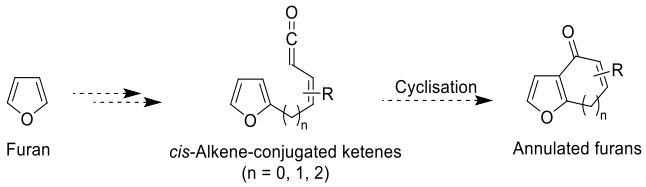


Figure 5: Time-sequenced ^{1}H NMR spectra of the thermal retro-ene reaction of 3-hydroxy ynol ether **3.32** in benzene-d_6, with main regions of interest highlighted in orange. Spectrum 1 (in crimson) was recorded from the starting material, whereas spectra 2–4 were recorded from the reaction mixture after 0.5 h, 1 h and 2.5 h, respectively, of heating at 70 °C.

3.4 Conclusions and future work

The research on furyl ketenes discussed in this chapter showed that fused oxocycloalkyl furans could not be synthesised by spontaneous cyclisation of furan-tethered ketenes under the conditions tested. Owing to the characterisation data of the obtained products, all three of the attempted methods likely resulted in successful ketene synthesis but, in the absence of effective nucleophilic trapping functionality, these intermediates tended to form oligomers. When generated gradually, as in the retro-ene reaction of ynol ether **3.22**, the ketenes preferred to react with their precursor molecules rather than cyclise.

This work focused on the reactivity of ketene precursors **3.01**, **3.11**, **3.22** and **3.32** owing to the good accessibility of these compounds. It is assumed that the distance of the ketene functionality to the furan ring in any successfully generated ketene intermediates likely hindered their interactions. Furan-tethered ketenes with shorter side chains (such as one or two methylene units) may be more reactive, yet they are more likely to react intermolecularly as cyclisation would give small and highly strained ring systems. A potentially viable solution is the introduction of *cis*-double bonds in the substrates, which would bring the furan ring and the ketene functionality in close proximity (*Scheme 20*) and thus facilitate the formation of annulated systems. The rigidity of unsaturated bonds would also reduce the loss of entropy during cyclisation. Furthermore, a wider range of reaction conditions could be applied to the furan-tethered ketene substrates, for the use of transition metal complexes[34] or Lewis acids.[35] These conditions may activate the ketene functionalities more effectively and facilitate their reactions with electron-rich aromatic systems.



Scheme 20: Proposed annulated furan synthesis from furan-tethered ketene substrates with conjugate *cis*-alkene functionalities.

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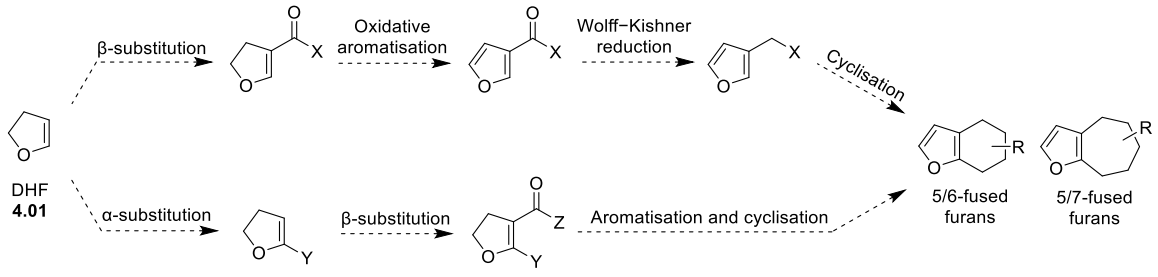
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Chapter 4: Synthesis of Furano[*b*]cycloalkanes from 2,3-Dihydrofuran

4.1 Aims of this project

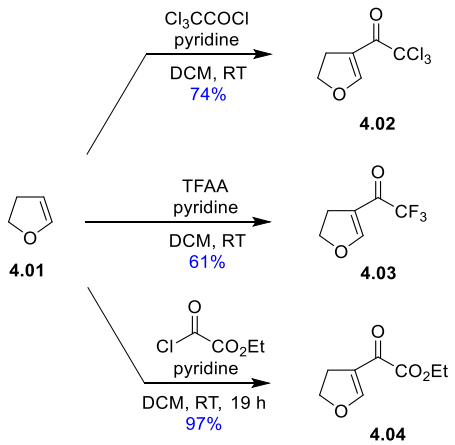
Although 2,3-Dihydrofuran (DHF, **4.01**) is inexpensive and structurally analogous to furan, it is not often used as a furan precursor but as an electron-rich alkene.[1] To date, the aromatisation and cyclisation of DHF derivatives as a route to bicyclic furan derivatives remain a poorly explored field of heterocyclic chemistry. The conversion of dihydrofurans to furans has mostly been achieved using elimination reactions, with the exception of NBS-[3] or MnO_2-mediated[4] oxidative aromatisation. The furan derivatives thus synthesised were not used for cyclisation purposes; plus, there is no precedent for the synthesis of annulated DHF derivatives[5] from 2,3-dihydrofuran itself. This project therefore aimed to evaluate this strategy as an approach to furano[*b*]cycloalkanes, beginning with both α- and β-substituted DHFs. The target ring systems of this project were 5/6- and 5/7-ring fused (*Scheme 1*). Apart from the main objective of accessing fused furans, it was hoped that the project would broaden the scope of dihydrofuran chemistry and the range of 3-substituted furans that can be accessed from inexpensive DHF.



Scheme 1: Overview of the project aims.

4.2 β-Functionalised dihydrofurans as intermediates

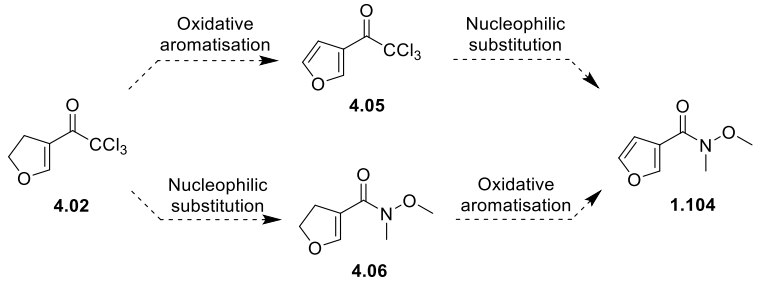
As an electron-rich enol ether, 2,3-dihydrofuran undergoes β-substitution reactions when exposed to strong electrophiles. There are currently few known studies on the synthetic utility of β-substituted dihydrofurans; compounds in this category hitherto made are mostly 2,3-dihydrofuran-4-carboxamides, which were among the compounds researched as potential inhibitors of soluble epoxide hydrolase in a study related to treatment of Alzheimer's disease.[6] Structurally simpler compounds are also known, among which ketone **4.02** is a precursor to 3-substituted furans through oxidative aromatisation.[3] To date, the β-functionalisation of DHF has been achieved with a limited range of acylating reagents; namely, those bearing strongly electron-withdrawing groups (e.g. CCl_3, CF_3 and CO_2Et) (*Scheme 2*).[3,7,8,9] As such, this work focused on ketone **4.02** as well as its structural analogues **4.03** and **4.04**; the key objective was to convert the β-acylated dihydrofurans into substituted furans capable of annulation. In addition, α-lithiation of unsubstituted 2,3-dihydrofuran is known,[10] while α-lithiation attempts with all three acylated dihydrofurans were unsuccessful and resulted in substrate decomposition. Hence, ring formation would only be achieved through cyclisation of the β-substituent on the α-carbon of the dihydrofuran or furan ring.



Scheme 2: Preparation of β-acylated dihydrofurans **4.02**, **4.03** and **4.04**.

4.2.1 From halomethyl ketones 4.02 and 4.03

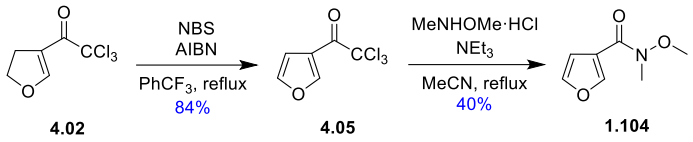
The reactivity of trihalomethyl ketones **4.02** and **4.03** is similar to each other but significantly different from that of typical ketones. Reduction using $LiBH_4$ or $NaBH_4$ resulted in decomposition,[11] while treatment with organolithium (*e.g. n*-butyllithium) or Grignard reagents (*e.g.* methylmagnesium bromide) gave traces of monodehalogenation products. On the other hand, **4.02** is known to undergo oxidative aromatisation in the presence of NBS.[3] Given the apparently limited range of transformations open to these ketones, it was decided that efforts toward 3-substituted furans should first achieve the preparation of Weinreb amide **1.104**. As **4.02** and **4.03** have similar reactivities, this attempt only used **4.02** as the starting material. In principle, the two necessary steps in this synthesis, aromatisation and nucleophilic substitution, could be fulfilled in either order (*Scheme 3*).



Scheme 3: Overview of the two-pronged approach toward Weinreb amide **1.104** from **4.02**.

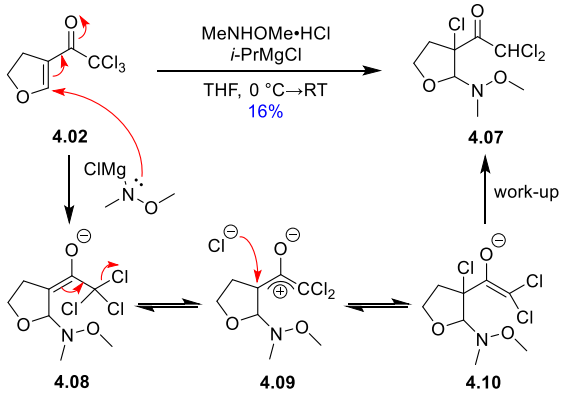
Efforts started with the reported oxidative aromatisation of **4.02** into furan derivative **4.05**. Nucleophilic displacement of the CCl_3 group in **4.05** with water and alcohols is known to give derivatives of 3-furoic acid.[12] This prompted an attempt to achieve a one-step synthesis of Weinreb amide **1.104** through the reaction of these halomethyl ketones with a source of *N*,*O*-dimethylhydroxylamine. It was found that the transformation was successful when ketone **4.05**

was heated with the amine in acetonitrile at reflux, delivering Weinreb amide **1.104** in 40% isolated yield (*Scheme 4*).



Scheme 4: The two-step synthesis of Weinreb amide **1.104** from DHF derivative **4.02**.

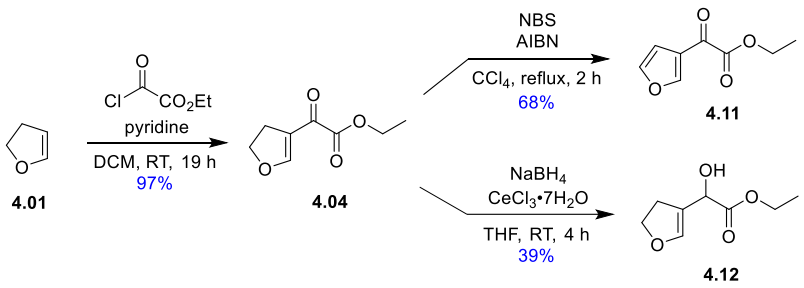
The synthesis was attempted anew by direct reaction of **4.02** with *N*,*O*-dimethylhydroxylamine hydrochloride. Interestingly, when isopropylmagnesium chloride as base, THF derivative **4.06**, obtained in low yields. A conjugate addition mechanism (*Scheme 5*) was proposed for the generation of this side-product, where nucleophilic attack by the amide anion on the α-carbon of the dihydrofuran ring generated enolate **4.07**. As the product bore a chloride group on the β-carbon of the THF ring, it was postulated that the enolate subsequently ejected a chloride anion to give dipolar oxyallyl intermediate **4.09** which then captured chloride ion to effect overall isomerisation of intermediate **4.08** into **4.10**. Accordingly, **4.08** and **4.10** might be in equilibrium and the isolation of **4.07** may reflect a greater proportion of **4.09** at equilibrium.



Scheme 5: Conditions and proposed mechanism for the synthesis of THF derivative **4.07** from **4.02**.

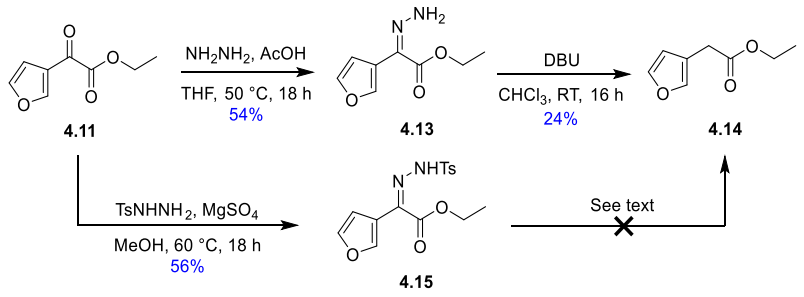
4.2.2 From keto ester 4.04

Unlike halomethyl ketones **4.02** and **4.03**, alpha-keto ester **4.04** was reactive towards 1,2-addition as exemplified by its Luche reduction to α-hydroxy ester **4.11** (*Scheme 6*). The outcome of the oxidative aromatisation varied significantly with the solvent, reaction temperature and the amount of NBS, the most efficient reaction being achieved with 50% excess NBS in CCl_4 at reflux. Using, for example, DCE as solvent, a lower temperature and less NBS gave only mixtures of unidentifiable products.



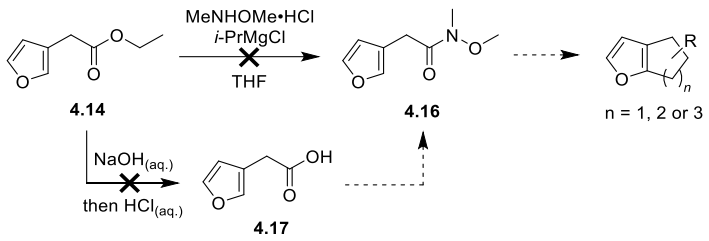
Scheme 6: Conversion of keto ester **4.04** to furan derivative **4.11** and α-hydroxy ester **4.12**.

Efforts then used the aromatisation product **4.11** to prepare 3-alkyl furans *via* a stepwise Wolff−Kishner reaction (*Scheme 7*). Base-mediated elimination of hydrazone intermediate **4.13** gave ester **4.14** exclusively,[13] although with only a low yield of 24% and significant mass loss was observed in this step. Tosylhydrazone **4.15** was also tested, but it did not proceed with the elimination step and remained stable to the conditions tested.



Scheme 7: Outcome of the Wolff−Kishner reduction of **4.11** *via* hydrazones **4.13** or **4.15**. The conditions applied to **4.15** were: (a) DBU, $CHCl_3$, RT, 16 h; (b) $NaBH_3CN$, THF−MeOH (1:1 v/v), 60 °C, 18 h.

Attempts were made to convert ester **4.14** into Weinreb amide **4.16**, a potential intermediate for further elaboration and cyclisation leading to bicyclic furan derivatives (*Scheme 8*) but both direct and indirect conversions were ultimately unsuccessful. Strikingly, the hydrolysis attempt with **4.14** delivered no carboxylic acid **4.17** while the substrate also decomposed. This outcome, combined with the low yield recorded in the synthesis of **4.14** discussed earlier, indicated that the lability of both **4.14** and **4.17** are labile species contributed to the failed attempts. To sum up, this multi-step synthesis of 3-alkyl furan **4.14** from 2,3-dihydrofuran achieved an overall yield of 8.5% over four steps, with the DBU-mediated hydrazone reduction as the yield-limiting step.



Scheme 8: Attempted conversion of ester **4.14** into Weinreb amide **4.16** directly or *via* carboxylic acid **4.17**.

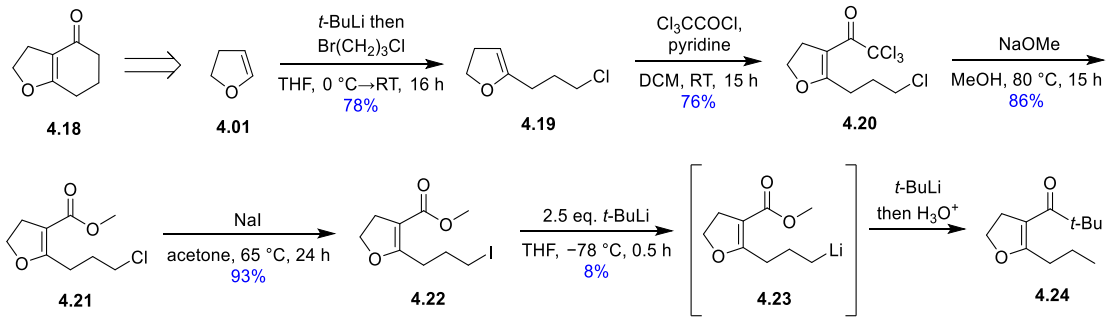
4.3 α-Functionalised dihydrofurans as intermediates

In contrast to the limited range of synthesis methods and reactions known for β-substituted dihydrofurans, α-functionalised DHF derivatives are much more diverse, in part because of their ease of lithiation with *tert*-butyllithium followed by subsequent electrophilic substitution.[10,14,15] Based on this precedent, efforts sought to elaborate α-functionalised dihydrofuran intermediates in the synthesis of annulated ring systems.

4.3.1 Ring formation through lithium-halogen exchange

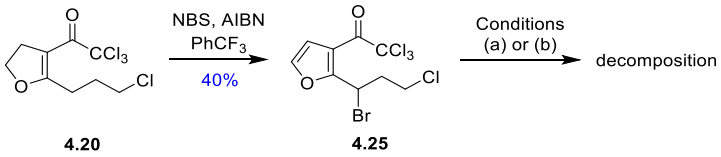
The ability of α-substituted dihydrofurans to undergo β-acylation reactions inspired the first synthetic approach, which aimed to access fused ring systems from α,β-disubstituted dihydrofurans. In principle, to facilitate ring closure, the two substituents needed to bear complementary synthons and β-dihydrofuranyl carboxylic acid derivatives bearing ω-haloalkyl α-substituents were proposed initially as viable substrates for lithium-halogen exchange and cyclisation.

The target compound chosen was cyclic ketone **4.18**, with the route beginning with α-alkylation then β-acylation of 2,3-dihydrofuran.[3,10] The product of these two steps (**4.20**) was treated with sodium methoxide to give ester **4.21**, and a Finkelstein reaction with sodium iodide gave the intended cyclisation substrate **4.22**. In the subsequent metal-halogen exchange toward **4.18**, magnesium metal did not result in any change in the substrate while SmI_2 gave an uncharacterisable mixture. *tert*-Butyllithium, meanwhile, reacted with **4.22** to produce ketone **4.24** (*Scheme 9*), the product of protodehalogenation and substitution at the ester. This outcome is attributed to the carbonyl group's conjugation with the dihydrofuran enol ether. While *t*-BuLi effected lithium-halogen exchange, the intermediate (proposed as **4.23**) failed to cyclise and only the highly reactive (external) *t*-BuLi was able to react with the ester.



Scheme 9: Preparation and attempted cyclisation of **4.22** by a lithium-halogen exchange reaction, with the intention to synthesise bicyclic compound **4.18**.

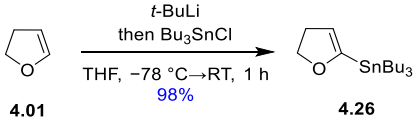
Trichloromethyl ketone **4.20** was also heated with NBS in CCl_4 as a prelude to attempting lithium-halogen exchange on the corresponding furan derivatives for comparison purposes. The dihydrofuran ring of **4.20** was successfully aromatised but bromination also occurred on the α-substituent, at a faster rate than the aromatisation stage to yield **4.25** as the only identifiable product (*Scheme 10*). This compound was found labile to reaction conditions applied subsequently.



Scheme 10: Outcome of the oxidative aromatisation of **4.20** with NBS. The conditions subsequently applied to product **4.25** were: (a) NaI, acetone, 40 °C, 2 h; (b) NaOMe, MeOH, RT, 4 h.

4.3.2 Cross-coupling attempts

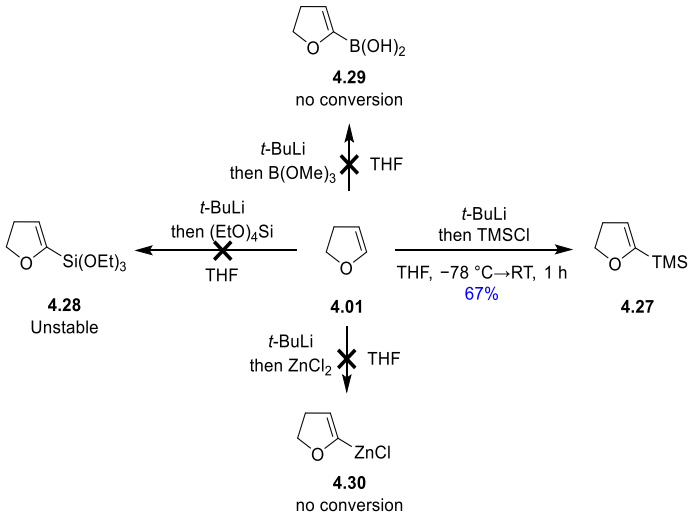
Lithiation of DHF followed by treatment with tributyltin chloride gives stannane **4.26**, first synthesised in 1993 by Zhang and co-workers (*Scheme 11*).[15] Its Stille coupling reactions has been extensively studied,[16] and as these reactions allow α-functionalisation of DHF with sp^2-hybridised carbons, they could open up new opportunities to access bicyclic systems.



Scheme 11: Preparation of stannane **4.26** from 2,3-dihydrofuran.

Aiming to broaden the scope of accessible cross-coupling substrates beyond **4.26**, 2,3-dihydrofuran was treated with a variety of relevant electrophiles following α-lithiation (*Scheme*

12). Silylation with trimethylsilyl chloride is a known reaction and our attempt gave silylation product **4.27** in up to 67% yield;[17] on the other hand, there are no literature precedents on the attempts to access silicate **4.28** as well as precursors for Suzuki and Negishi couplings, and all three reactions were unproductive. No organic material was retrievable from the synthesis attempts toward **4.29** and **4.30**, while treatment of lithiated DHF with tetraethyl orthosilicate to generate silane **4.28** produced an oil that rapidly hydrolysed on standing in air. It was concluded from these observations that the target compounds (**4.28**, **4.29**, **4.30**) were either not generated from the reactions or were too unstable to be isolated and characterised.

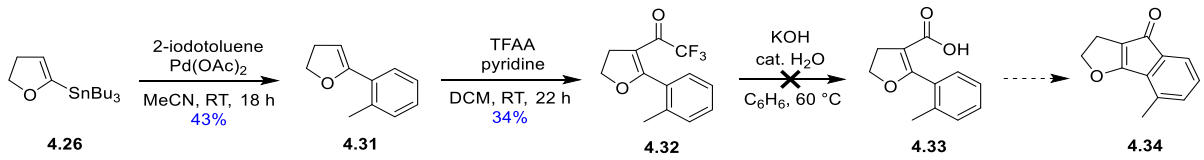


Scheme 12: Outcome of attempted silylation and metallation reactions from 2-lithio-2,3-dihydrofuran.

Accordingly, this work developed itself with two objectives. First, it sought to investigate the viability and scope of the Stille coupling of stannane **4.26** with relevance to the subsequent conversion of the coupling products to fused ring systems. Second, it aimed to explore the viability of Hiyama coupling reactions with silane **4.27** and cyclisation reactions of its derivatives.

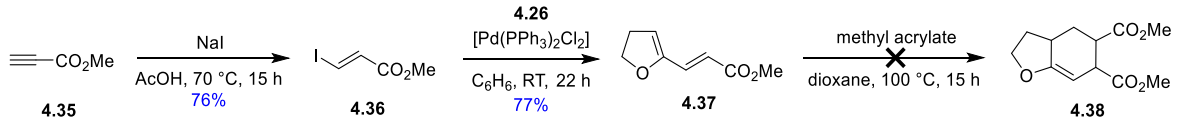
4.3.2.1 Stille coupling

Efforts began with an attempt to use the Stille reaction of **4.26** or its derivatives for the synthesis of a bicyclic ring system. The first target compound was benzene derivative **4.31**, prepared from 2-iodotoluene in moderate yields.[16a] This product was acylated by TFAA to give ketone **4.32**, whose subsequent hydrolysis was expected to lead to carboxylic acid **4.33** and thence to tricycle **4.34** (*Scheme 13*). In the event, none of the carboxylic acid was detected from the hydrolysis trial and the low level of substrate recovery from the reaction mixture (≤ 17%) indicated that decomposition occurred either during the hydrolysis step or the acidic work-up.



Scheme 13: Sequential Stille coupling and acylation of stannane **4.26**, and attempted synthesis of tricycle **4.34**.

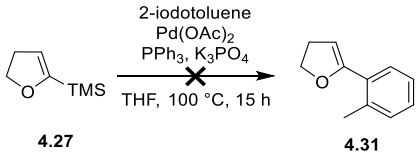
Another synthesis target was conjugated ester **4.37** (*Scheme 14*), due to its structural similarity to azepene derivatives investigated by Bassler and co-workers for [4+2] cycloaddition with electron-deficient dienophiles.[18] The Stille coupling of stannane **4.26** with methyl β-iodoacrylate gave ester **4.37** efficiently but this diene was unreactive when heated with methyl acrylate.



Scheme 14: Outcomes for the Stille coupling of **4.26** with vinyl iodide derivative **4.36**, and the attempted [4+2] cycloaddition of cross-coupling product **4.37**.

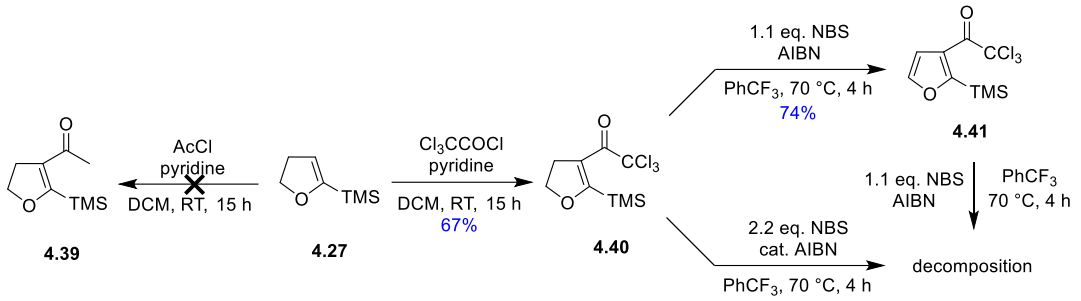
4.3.2.2 Chemistry of silane 4.27 and its derivatives

The Hiyama coupling discovered in 1988 uses organosilanes as substrates and works best with fluoro- and alkoxysilanes.[19] It has become popular after its discovery owing to the good stability and low toxicity of the organosilicon reagents, but few precedents use simple trialkylsilyl substrates, *i.e.* those lacking silicon-halogen bonds. The Hiyama coupling protocol developed for such alkyl(triorgano)silanes uses an expensive ferrocene ligand,[20] without which the coupling was attempted without success as confirmed in the case of substrate **4.27** (*Scheme 15*).



Scheme 15: Attempted Hiyama coupling of **4.27** with triphenylphosphine replacing a ferrocenyl ligand.

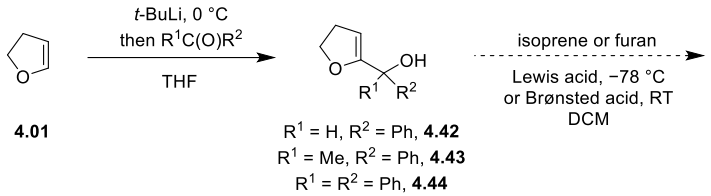
Showing a similar reactivity pattern to 2,3-dihydrofuran, silane **4.27** underwent β-acylation with trichloroacetyl chloride to give ketone **4.40**, but it did not react with acetyl chloride under analogous conditions. Oxidative aromatisation of **4.40** with a small excess of NBS delivered furan **4.41** as expected (*Scheme 16*). In an attempt to replace the TMS group of **4.40** with bromide, the reaction as attempted anew with 2.2 equivalents of NBS. This only led to the complete decomposition of **4.40**, and furan **4.41** gave the same result when treated with 1.1 equivalents of NBS. It was unclear if any bromination reactions had occurred; these results also indicated that silane **4.27** was unable to deliver any product that could contribute to bicyclic systems and merited no further investigation. Besides, Hiyama coupling was attempted on both silanes **4.40** and **4.41** using the same protocol as detailed on *Scheme 15*, and both compounds remained stable.



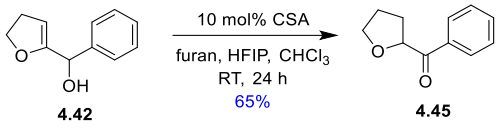
Scheme 16: Overview of β-acylation and aromatisation attempts on silane **4.27**.

4.3.3 Cationic cycloaddition

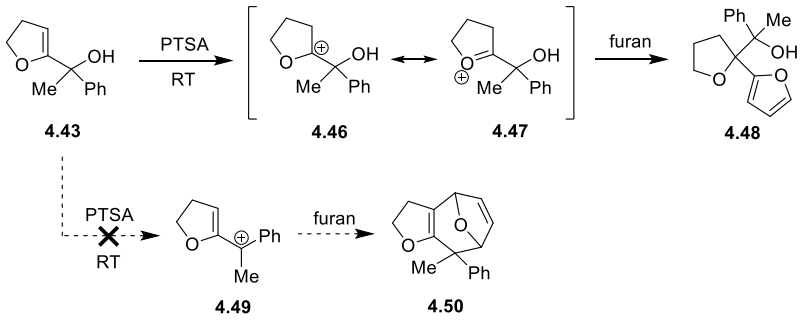
Finally, efforts to elaborate DHF examined the reactivity of 1-(4,5-dihydrofuran-2-yl)carbinols in the presence of Lewis or Brønsted acids. Inspired by reported (4+3) cycloadditions of furfuryl cations,[21] the readily-prepared alcohol substrates were treated with acid catalysts in the presence of an excess of isoprene or furan (*Scheme 17*). With all the Lewis acids tested, substrate degradation resulted. Under protic acid catalysis (CSA), in the presence of an excess of furan, alcohols **4.44** decomposed unproductively, while **4.42** isomerised to yield ketone **4.45** as a result of enol ether protonation and [1,2]-H migration or an equivalent elimination/tautomerisation process (*Scheme 18*). Only alcohol **4.43** was found to react intermolecularly, although not as intended; a reaction in which the alcohol was stirred with an excess of furan in the presence of PTSA yielded adduct **4.48** rather than the desired cycloaddition product **4.50**. This result indicated that the acid catalyst did not activate the hydroxyl group of **4.43** but facilitated overall alkene hydroarylation instead (*Scheme 19*).



Scheme 17: Attempted (4+3) cycloaddition of DHF-carbinols. Lewis acids: $TiCl_4$ (5 mol% and 1.0 eq.), $SnCl_4$ (5 mol%) and BF_3•OEt_2 (5 mol%). Brønsted acids: PTSA (1 mol%) and CSA (1 mol%).



Scheme 18: Acid-mediated rearrangement of allylic alcohol **4.42** into ketone **4.45**.



Scheme 19: Outcome of the PTSA-mediated reaction of alcohol **4.43** with furan, yielding compound **4.48**. This was in contrast to the intended (4+3) cycloaddition (→ **4.50**).

4.4 Conclusions and future work

This work focused on accessing [*b*]-annulated furans and dihydrofurans from 2,3-dihydrofuran by utilising two groups of DHF derivatives arising from substitution reactions on the α- and β-positions of dihydrofuran. Efforts with β-substituted dihydrofurans demonstrated three main limitations of these compounds. First, the compounds in this family directly accessible from DHF are predominantly β-acylated DHF derivatives with a limited scope of further structural

modifications. Second, α-functionalisation was difficult without disruption of the dihydrofuran ring system, as demonstrated by the unintended synthesis of THF derivative **4.07** (see *Scheme 5*). Third, the only known reagent for effective aromatisation of β-acylated dihydrofurans is NBS, whose reaction with keto ester **4.04** was prone to side-product formation.

By contrast, through α-functionalisation of 2,3-dihydrofuran, a wide range of mono- and disubstituted DHF and furan derivatives were obtained. The α-metallation products in particular allowed for synthetic routes based on cross-coupling reactions and subsequent cyclisation endeavours. Nevertheless, the compounds covered in this work were not found to be viable precursors to fused ring systems. They either did not offer a synthetic advantage for accessing prospective substrates for ring formation (**4.27** and derivatives, for instance, *Scheme 16*), or lacked sufficient reactivity for subsequent cyclisation (**4.22** → **4.18**, *Scheme 9*) or cycloaddition (**4.43** → **4.50**, *Scheme 14*) reactions.

Despite the challenges encountered in both routes, this work demonstrated the accessibility of 3-substituted furans from inexpensive 2,3-dihydrofuran; in particular, ester **4.14** made from the Wolff−Kishner reduction of **4.12** (*Scheme 7*) is a gateway to more 3-alkyl furans that could be used to access alicyclic [*b*]-annulated furans. The studies also showed that the reactions with dihydrofurans were more likely to give side products than those with furan derivatives. Future efforts are therefore recommended to focus on the development of new dihydrofuran aromatisation protocols compatible with a greater range of substrates than β-acylated dihydrofurans.

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Chapter 5: Experimental

5.1 General Experimental

All experiments, unless otherwise stated, were conducted under an atmosphere of dry nitrogen or dry argon using oven (80 °C) dried glassware. All solvents used were either commercially available or supplied by the communal Grubbs drying columns in the Chemistry Research Laboratory, University of Oxford. Unless specifically stated otherwise, all reagents were purchased from commercial suppliers and used directly without further purification.

The chemical structures of each compound discussed in the thesis are depicted above the relevant preparative procedure. Novel compounds have their proton (^{1}H) and carbon (^{13}C) NMR and IR spectroscopic data, and high-resolution mass spectrometric data reported. Literature precedented compounds have at least proton (^{1}H) and carbon (^{13}C) NMR and IR spectroscopic data. Boiling points and melting points are reported where appropriate.

^{1}H and ^{13}C NMR spectra were recorded using Bruker AVG400 (400/101 MHz), AVH400 (400/101 MHz) and NEO600 (600/151 MHz) spectrometers. ^{1}H and ^{13}C chemical shifts (δ_H, δ_C) are quoted in ppm relative to tetramethylsilane ($\delta = 0$) and referenced to the solvent during processing within MestReNova. Coupling constants (*J*) are quoted as observed and rounded to the nearest 0.5 Hz. All ^{1}H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons, assignment). All ^{13}C NMR spectra are reported as follows: ppm (assignment). Peak assignments were made based on chemical shifts, coupling constants, two-dimensional NMR (COSY, HSQC, HMBC and NOESY) data, and by comparison with spectra of related compounds. Atom numbering reflects NMR peak assignments and does not necessarily correspond to the IUPAC nomenclature. Where an assignment could not be made unambiguously, possible assignments are listed.

Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer as a thin film on a diamond ATR module. Only selected absorption maxima (ν_{max}) are reported, in wavenumbers (cm^{-1}), and these are identified as strong (s), medium (m), weak (w) and/or broad (br) as a measure of relative peak intensity. Gas chromatography (GC) analysis was performed on a ThermoFisher Scientific TRACE 1300 equipped with a flame ionisation detector (FID) and an AS3000 autosampler with hydrogen as the carrier gas (3.0 mL/min) using a DB-1 MS fused silica column (30 m × 0.25 mm, 0.25 μm film thickness, Agilent Technology). High resolution mass spectra (HRMS) data were obtained from either Thermo Exactive High Resolution Orbitrap FTMS or Agilent 7200 Accurate Mass Q-TOF GC-MS. Melting points were recorded in degrees Celsius (°C), using a Griffin melting point apparatus.

Silica gel chromatography was carried out using Merck Geduran® Silicagel 60 SiO_2, particle size 40–63 μm, and the solvent system used is recorded in parentheses. Thin-layer chromatography (TLC) was performed using Merck aluminium-backed Silicagel 60 F254 fluorescent treated silica; visualisation was enabled by UV light (λ_{max} = 254 nm) and staining with either potassium permanganate or phosphomolybdic acid solution. Retention factors (R_f) are quoted with the solvent system in parentheses.

Compound names are as generated by PerkinElmer ChemDraw Professional 23.0.

Procedures are organised in numerical order as they appear in the thesis, and subsequently in order of synthesis.

5.2 Enzymatic Oxidation of Butenolide Substrates in Chapter 1

The $P450_{BM3}$ enzymes were produced in *Escherichia coli* BL21 (DE3) and purified by addition of $(NH_4)_2SO_4$ to a concentration of 40% w/v and centrifugation at 37,500 *g* for 10 min at 4 °C; the residue was discarded and $(NH_4)_2SO_4$ was added to a concentration of 60% w/v. The solution was submitted to centrifugation at 37,500 g for 10 min at 4 °C, the supernatant was discarded and the residue was resuspended in phosphate buffer. The enzymes were stored as stock solutions in 1.0 mL aliquots at –20 °C and thawed at RT before use.

5.2.1 General Procedure 1 − Initial Screening of Substrates

Small scale screens of the substrates were conducted on a 1.0 mL scale in a 24-well plate containing 13, 16 or 24 $P450_{BM3}$ variants (1 per well). These reactions were performed using 200 mM phosphate buffer (pH 7.9) containing 100 mM glucose, 3 mg/mL $NADP^+$, 8 mg/mL GDH, 5 mM substrate and 10 μM enzyme. The solvent used to make the stock solutions was 200 mM phosphate buffer, and the substrate solutions (0.2 M, stock concentration) were in methanol. The screening plates were prepared by adding 900 μL of the mixture detailed in *Table 1* to each well containing 100 μL of enzyme.

The reactions were shaken at 120 rpm and 20 °C for 16 h. Each reaction mixture was then transferred into a 1.5 mL microcentrifuge tube and extracted with 300 μL of Ethyl acetate. The biphasic mixtures were vortexed and centrifuged at 1,330 rpm for 1 minute. 180 μL of the organic layer from each tube was separated and transferred into a 200 μL glass GC insert. This was analysed by a ThermoFisher TRACE 1300 gas chromatograph equipped with a flame ionisation detector, an AS3000 autosampler and a DB-1 MS fused silica column. Hydrogen was used as the carrier gas (3.0 mL/min). The injector temperature was 250 °C. For all substrates, the oven temperature was held at 150 °C for 1 min and increased at a rate of 1 °C

min^{-1} to 155 °C, then 4 °C min^{-1} to 165 °C, 25 °C min^{-1} to 220 °C, 4 °C min^{-1} to 260 °C and finally 75 °C min^{-1} to 300 °C, and the temperature was held for 30 seconds. Retention times determined by GC for the substrates and all identified products were then recorded.

Substance	Stock concentration	Volume/µL	Final concentration
Phosphate buffer	n/a	337.5	135 mM
Glucose	1 M	50	100 µM
$NADP^+$	4 mM	5	40 µM
GDH	200 U/mL	5	2 U/mL
Enzyme	10 µM	100	2 µM
Substrate	200 mM (in methanol)	2.5	1 mM

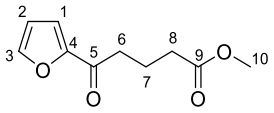
Table 1: Components for the screening of substrates.

5.2.2 General Procedure 2 − Preparative Scale Reactions

All preparative scale reactions were performed in a conical (Erlenmeyer) flask at 20 °C using the same ratios of reagents as in **General Procedure 1**, with a total volume of 203 mL each. The mixture was left to stir and monitored by GC at regular intervals, with reaction durations ranging from 4 to 48.5 hours. Afterwards, the reaction mixture was split into six 50 mL falcon tubes with approximately 34 mL in each tube. Then, 10 mL of Ethyl acetate was added to each tube, and the tubes were shaken and centrifuged at 13,300 *g* for 3 minutes. The organic layers were pipetted off and the process repeated twice more, and the combined organic layers were concentrated *in vacuo*. The residues were purified by silica gel chromatography with Geduran silica gel 60 (40–63 µm) as the stationary phase and pentane and Ethyl acetate as the mobile phase. The purified compounds were characterised by NMR spectroscopy, IR spectrometry and HRMS.

5.3 Synthesis and characterisation of compounds

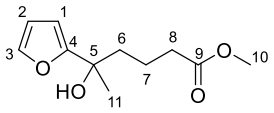
Methyl 5-(furan-2-yl)-5-oxopentanoate, 1.06



To a solution of methyl 5-chloro-5-oxopentanoate (3.45 mL, 25.0 mmol) in acetonitrile (20 mL) was added $Zn(OTf)_2$ (2.72 g, 6.25 mmol) followed by MgO (1.21 g, 30.0 mmol). The resulting suspension was stirred for 5 minutes and a solution of furan (3.25 mL, 45.0 mmol) in acetonitrile (5 mL) was dropwise added. Vigorous stirring was continued for another 15 h before the mixture was quenched by sat. aq. $NaHCO_3$ (30 mL) and filtered through a pad of celite. The aqueous phase of the filtrate was extracted with ethyl acetate (3 × 20 mL), and the organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a dark brown oil. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 1:1) to give compound **1.06** (3.05 g, 62%) as a colourless crystalline solid.

R_f 0.62 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 3124 (w), 1722 (s), 1665 (s), 1293 (s), 1169 (m), 987 (m), 813 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.65 (dd, *J* = 2.0 Hz, 1.5 Hz, 1H, H3), 7.22 (dd, *J* = 3.5 Hz, 1.5 Hz, 1H, H1), 7.15 (dd, *J* = 3.5 Hz, 1.5 Hz, 1H, H2), 3.70 (s, 3H, H10), 2.93 (t, *J* = 7.5 Hz, 2H, H6), 2.44 (t, *J* = 7.5 Hz, 2H, H8), 2.07 (quin, *J* = 7.5 Hz, 2H, H7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 189.1 (C5), 169.4 (C9), 154.1 (C4), 146.3 (C3), 117.0 (C1), 112.2 (C2), 51.6 (C10), 37.3 (C6), 33.1 (C8), 19.7 (C7); **mp** 41−43 °C. Spectroscopic data in agreement with literature.[1]

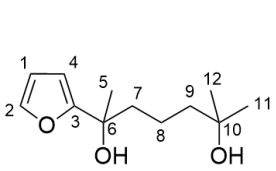
Methyl 5-(furan-2-yl)-5-hydroxyhexanoate, 1.08

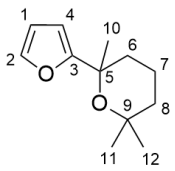


To a solution of **1.06** (3.05 g, 15.5 mmol) in THF (15 mL) at −40 °C under N_2 was added methyl magnesium bromide (7.25 mL, 3.0 M, 21.8 mmol) dropwise. The mixture was stirred for 30 min, quenched by sat. aq. Na_2CO_3 (15 mL), and filtered through a pad of celite. The filtrate was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **1.08** (2.66 g, 80%) as a colourless oil.

R_f 0.53 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 3444 (br w), 2980 (w), 1734 (s), 1262 (s), 1171 (s), 739 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H3), 6.24 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H1), 6.14 (dd, *J* = 3.5 Hz, 1.0 Hz, 1H, H2), 3.59 (s, 3H, H10), 2.23 (t, *J* = 7.5 Hz, 2H, H8), 1.80 (m, 2H, H6), 1.55 (m, 2H, H7), 1.48 (s, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 173.6 (C9), 158.2 (C3), 141.2 (C2), 109.9 (C1), 105.5 (C4), 68.8 (C10), 51.6 (C5), 37.3 (C6), 33.1 (C8), 23.5 (C7), 19.3 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_4$, 213.1127; found, 213.1127.

2-(Furan-2-yl)-6-methylheptane-2,6-diol, 1.09; 2-(Furan-2-yl)-2,6,6-trimethyltetrahydro-2H-pyran, 1.10



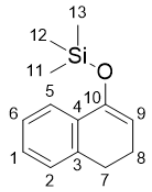


To a solution of keto ester **1.08** (0.414 g, 2.00 mmol) in DCM (15 mL) at 0 °C was added trimethylaluminium solution (2.20 mL, 2.0 M in hexanes, 4.40 mmol) followed dropwise by dimethylaluminium chloride solution (0.200 mL, 1.0 M in hexanes, 0.20 mmol). The mixture was allowed to warm to RT and stirring was continued for 15 h. Then, sat. aq. $NaHCO_3$ (25 mL) was slowly added. The two layers of liquid were separated, and the aqueous layer was extracted by ethyl acetate (3 × 10 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a yellow oil. The product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **1.09** (0.0575 g, 14%) as a yellow oil and **1.10** (0.0186 g, 5.0%) as a yellow oil.

Data for **1.09**: $\mathbf{R_f}$ 0.16 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 3379 (br w), 2969 (w), 1375 (w), 1161 (s), 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (m, 1H, H2), 6.22 (m, 1H, H4), 6.11 (m, 1H, H1), 1.75 (m, 2H, H7), 1.46 (s, 3H, H5), 1.36 (dd, *J* = 9.5 Hz, 7.0 Hz, 2H, H9), 1.25 (m, 2H, H8), 1.09 (s, 6H, H11, H12); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 159.7 (C3), 141.4 (C2), 110.0 (C1), 104.4 (C4), 71.6 (C6), 71.0 (C10), 43.9 (C9), 42.0 (C7), 29.2 (C11), 26.6 (C12), 18.9 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{21}O_3$, 213.1491; found, 213.1485.

Data for **1.10**: $\mathbf{R_f}$ 0.94 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 2974 (w), 1084 (s), 993 (s), 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H2), 6.22 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H4), 6.02 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H1), 2.13 (m, 1H, H6a), 1.83 (m, 1H, H6b), 1.57 (m, 1H, H8a), 1.46 (m, 1H, H8b), 1.39 (m, 2H, H7), 1.36 (s, 3H, H10), 1.15 (s, 3H, H11), 0.69 (s, 3H, H12); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 159.3 (C2), 140.9 (C2), 110.0 (C1), 104.6 (C4), 77.3 (C5), 77.0 (C9), 36.7 (C8), 33.9 (C6), 32.7 (C11), 31.9 (C12), 24.2 (C10), 17.5 (C7); **HRMS** (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{12}H_{18}O_2Na$, 217.1204; found, 217.1204.

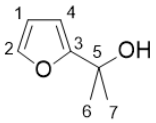
((3,4-Dihydronaphthalen-1-yl)oxy)trimethylsilane, 1.12



1-Tetralone **1.11** (0.146 g, 10.0 mmol) was mixed with triethylamine (2.79 mL, 20.0 mmol) and DCM (20 mL). TMSOTf (2.00 mL, 11.0 mmol) was dropwise added, and stirring was continued for 21 h. Five drops of methanol were added, and the mixture was concentrated on a rotary evaporator. The residue was diluted with acetonitrile (10 mL) and extracted with 2% ether in pentane (3 × 15 mL). The extracts were combined and its solvents removed under reduced pressures to yield silyl enol ether **1.12** (1.68 g) as a light brown oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2957 (m), 2832 (w), 1686 (w), 1639 (s), 1252 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, H6), 7.22 – 7.14 (m, 1H, H1), 7.08 (ddd, *J* = 15.0 Hz, 7.5 Hz, 1.5 Hz, 2H, H2, H5), 5.17 (t, *J* = 4.5 Hz, 1H, H9), 2.75 (t, *J* = 8.0 Hz, 2H, H7), 2.31 (td, *J* = 8.0 Hz, 4.5 Hz, 2H, H8), 0.22 (s, 9H, H11, H12, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 150.8 (C10), 144.5 (C3), 133.4 (C1), 132.6 (C6), 128.8 (C4), 127.2 (C2), 126.6 (C5), 105.3 (C9), 29.7 (C7), 23.2 (C8), 0.2 (C11, C12, C13). Spectroscopic data in agreement with literature.[2]

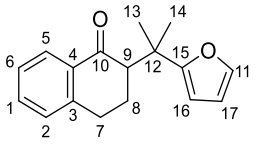
2-(Furan-2-yl)-propan-2-ol, 1.13



To a solution of furan **1.01** (0.730 mL, 10.0 mmol) in diethyl ether (10 mL) at −78 °C under N_2 was added *n*-butyllithium (6.25 mL, 1.6 M in hexanes, 10.0 mmol). The resulting solution was allowed to warm to 0 °C for 30 minutes before it was cooled back to −78 °C, and acetone (0.810 mL, 11.0 mmol) was dropwise added. Stirring was continued for another 1 h, and the resulting mixture was warmed to 0 °C, quenched with sat. aq. $NaHCO_3$ (10 mL), and then filtered on a pad of celite. The aqueous phase of the filtrate was extracted with diethyl ether (3 × 10 mL), and the combined ethereal phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 4:1) to give compound **1.13** (0.633 g, 51%) as a colourless oil.

R_f 0.28 (pentane/diethyl ether, 7:3); **IR** ν_{max}/cm^{-1} 3368 (br m), 2981 (w), 1364 (m), 1158 (s), 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H2), 6.31 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H4), 6.18 (m, 1H, H1), 1.95 (s, 1H, OH), 1.59 (s, 6H, H6, H7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 160.2 (C3), 141.5 (C2), 110.0 (C1), 103.6 (C4), 68.9 (C5), 28.7 (C6, C7). Spectroscopic data in agreement with literature.[3]

2-(2-(Furan-2-yl)propan-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one, 1.14

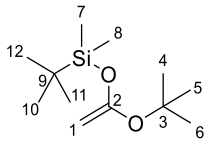


Alcohol **1.13** (0.252 g, 2.00 mmol) and silyl ketene acetal **1.12** (0.756 g, 3.60 mmol) were dissolved in THF (6 mL). The solution was cooled to −78 °C before trimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.40 mmol) was dropwise added, generating a bright red mixture. Stirring was continued for 8 minutes and tributylamine (0.95 mL) was added, after which the red colour disappeared. This mixture was concentrated under reduced pressures. The

residue was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The extracts were combined, washed by brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:4) to yield compound **1.14** (0.112 g, 22%) as a colourless oil.

R_f 0.87 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2971 (w), 1689 (s), 1221 (s), 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.89 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, H5), 7.35 (td, *J* = 7.5 Hz, 1.5 Hz, 1H, H1), 7.23 – 7.19 (m, 2H, H6, H11), 7.14 – 7.07 (m, 1H, H2), 6.21 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H17), 5.96 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H16), 2.91 – 2.79 (m, 3H, H7, H9), 1.82 – 1.77 (m, 2H, H8), 1.50 (s, 3H, H13), 1.33 (s, 3H, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 198.8 (C10), 162.8 (C15), 143.6 (C3), 140.5 (C11), 134.2 (C4), 132.8 (C1), 128.3 (C2), 127.3 (C5), 126.5 (C6), 109.9 (C17), 103.6 (C16), 54.9 (C9), 38.5 (C12), 29.5 (C7), 26.2 (C13), 25.9 (C14), 22.8 (C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{19}O_2$, 255.1385; found, 255.1385.

((1-(*tert*-Butoxy)vinyl)oxy)(*tert*-butyl)dimethylsilane, 1.17

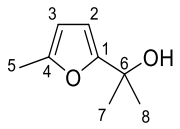


To a solution of DIPA (1.70 mL, 12.1 mmol) in THF under N_2 at −20 °C was added *n*-BuLi (7.56 mL, 1.6 M in hexanes, 5.50 mmol) dropwise. After stirring for 30 min, the mixture was cooled to −78 °C; HMPA (1.20 mL, 6.90 mmol) was added, followed dropwise by *tert*-butyl acetate (1.61 mL, 5.00 mmol). Stirring was continued for another hour, then a solution of *tert*-butyldimethylsilyl chloride (1.84 g, 12.2 mmol) in THF (2 mL) was slowly added. The mixture was allowed to slowly warm to RT over 30 minutes with vigorous stirring and then concentrated *in vacuo*. The residue was washed by cold sat. aq. $NaHCO_3$ (15 mL), extracted

with pentane (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give compound **1.17** (1.535 g, 56%) as a yellow oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2932 (w), 1651 (s), 1254 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.47 (d, J = 1.5 Hz, 1H, H1a), 3.45 (d, J = 1.5 Hz, 1H, H1b), 1.34 (s, 9H, H4, H5, H6), 0.93 (s, 9H, H10, H11, H12), 0.18 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.7 (C2), 78.0 (C3), 72.7 (C1), 28.5 (C4, C5, C6), 25.7 (C10, C11, C12), 18.0 (C9), −4.8 (C7, C8). Spectroscopic data in agreement with literature.[4]

2-(5-Methylfuran-2-yl)propan-2-ol, 1.20

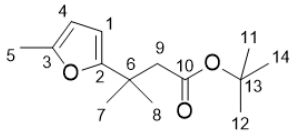


To a solution of 2-methylfuran **1.19** (2.69 mL, 30.0 mmol) in THF (10 mL) at −78 °C under N_2 was added *n*-butyllithium (2.62 mL, 11 M in hexanes, 28.8 mmol). The resulting solution was allowed to warm to 0 °C for 30 minutes before it was cooled back to −78 °C, and acetone (2.67 mL, 36.0 mmol) was dropwise added. Stirring was continued for another 1 h, and the resulting mixture was warmed to 0 °C, quenched with sat. aq. $NaHCO_3$ (10 mL), and then filtered on a pad of celite. The aqueous phase of the filtrate was extracted with diethyl ether (3 × 10 mL), and the combined ethereal phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 4:1) to give alcohol **1.20** (3.26 g, 90%) as a colourless oil.

R_f 0.77 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3388 (s, br), 2978 (s), 1664 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.04 (d, J = 3.0 Hz, 1H, H2), 5.86 (dq, J = 3.0 Hz, 1.0 Hz, 1H, H3), 2.27

(d, J = 1.0 Hz, 3H, H5), 2.01 (s, 1H, OH), 1.56 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 158.4 (C1), 151.2 (C4), 105.8 (C2), 104.2 (C3), 68.6 (C6), 28.6 (C7, C8), 13.5 (C5). Spectroscopic data in agreement with literature.[3]

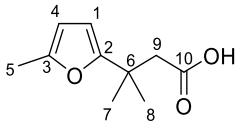
***tert*-Butyl 3-methyl-3-(5-methylfuran-2-yl)butanoate, 1.21**



Alcohol **1.20** (0.140 g, 1.00 mmol) and silyl ketene acetal **1.17** (0.346 g, 1.50 mmol) were dissolved in THF (4 mL) under argon. This solution was cooled to −78 °C before a solution of TMSOTf (72.6 μL, 0.400 mmol) in THF (1 mL) was dropwise added. The mixture was stirred for 1 minute and quenched *in situ* by tributylamine (0.480 mL, 2.00 mmol). The solvent was removed *in vacuo*, and to the residue was added diethyl ether (5 mL) and water (5 mL). The aqueous layer was isolated and extracted with ether (3 × 5 mL); the extracts were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressures. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to yield compound **1.21** (58.7 mg, 25%) as a pale-yellow oil.

R_f 0.85 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2977 (w), 1728 (s), 1368 (s), 1167 (s), 752 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.71 (d, J = 3.0 Hz, 1H, H1), 5.69 (dt, J = 3.0 Hz, 1.0 Hz, 1H, H4), 2.34 (s, 2H, H9), 2.12 (s, 3H, H5), 1.22 (s, 6H, H7, H8), 1.21 (s, 9H, H11, H12, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.9 (C10), 159.7 (C2), 150.2 (C3), 105.5 (C1), 103.8 (C4), 79.9 (C13), 47.5 (C9), 35.1 (C6), 28.1 (C11, C12, C14), 26.9 (C7, C8), 13.6 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{23}O_3$, 239.1642; found, 239.1638.

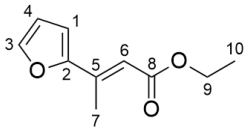
3-Methyl-3-(5-methylfuran-2-yl)butanoic acid, 1.22



Sodium hydroxide pellets (0.566 g, 1.42 mmol) were ground into a powder form using a mortar and pestle, and dissolved in a mixture of methanol (1 mL) and water (2 mL) in a 50 mL round-bottom flask. To this solution was added ester **1.21** (0.139 g, 0.708 mmol). The mixture was placed under a nitrogen atmosphere, heated to 50 °C and stirred for 17 hours. After cooling to 0 °C, the mixture was carefully acidified by dropwise addition of 1.0 M HCl until its pH reached 3−4. ethyl acetate (3 × 10 mL) was used to extract the mixture, and the organics were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures to yield acid **1.22** (0.113 g, 99%) as a yellow oil, which was used without further purification.

R_f 0.32 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3125 (br w), 2978 (w), 1709 (s), 1164 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.88 (d, J = 3.0 Hz, 1H, H1), 5.83 (dq, J = 3.0 Hz, 1.0 Hz, 1H, H4), 2.61 (s, 2H, H9), 2.24 (d, J = 1.0 Hz, 3H, H5), 1.39 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.8 (C10), 159.3 (C2), 150.5 (C3), 105.7 (C4), 103.8 (C1), 45.6 (C9), 34.8 (C6), 26.7 (C7, C8), 13.5 (C5). Spectroscopic data in agreement with literature.[5]

Ethyl (*E*)-3-(furan-2-yl)but-2-enoate, 1.27

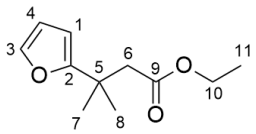


Under argon atmosphere, butyllithium (1.6 M in hexanes, 13.0 mmol, 8.13 mL) was dropwise added to a solution of triethyl phosphonoacetate (13.0 mmol, 2.92 g) in THF (20 mL) at −40 °C.

After 15 minutes of stirring, 2-acetylfuran **1.26** (1.10 g, 10.0 mmol) was added. The mixture was warmed to RT with stirring continued for another 16 hours, before being concentrated under reduced pressures. Distilled water (15 mL) was added to the residue, and the resulting mixture was extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to yield compound **1.27** (1.24 g, 69%) as a colourless oil.

R_f 0.75 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2952 (w), 1737 (s), 1169 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 (d, *J* = 2.0 Hz, 1H, H3), 6.63 (d, *J* = 3.5 Hz, 1H, H1), 6.46 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H4), 5.73 (q, *J* = 1.5 Hz, 1H, H6), 4.21 – 4.09 (q, *J* = 7.5 Hz, 2H, H9), 2.21 (d, *J* = 1.5 Hz, 3H, H7), 1.28 (t, *J* = 7.5 Hz, 3H, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.2 (C8), 151.4 (C2), 142.9 (C3), 138.6 (C5), 114.5 (C6), 111.7 (C4), 111.7 (C1), 60.0 (C9), 22.7 (C7), 14.3 (C10). Spectroscopic data in agreement with literature.[6]

Ethyl 3-(furan-2-yl)-3-methylbutanoate, 1.28

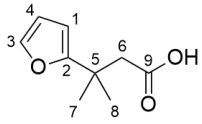


Copper(I) iodide (0.229 g, 1.20 mmol) was suspended in a solution of **1.27** (0.541 g, 3.00 mmol) in THF (3 mL) under nitrogen atmosphere. This mixture was cooled to −20 °C, then TMSCl (0.391 g, 3.60 mmol) followed by methylmagnesium bromide (3.0 M in THF, 1.20 mL, 3.60 mmol). The acetone cooling bath was removed, and the mixture was stirred for 18 hours. Saturate ammonium chloride solution (10 mL) was added, and the mixture was filtered *in vacuo*. The two layers of the filtrate were separated, and the aqueous layer extracted by diethyl ether

(3 × 10 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to yield compound **1.28** (0.223 g, 38%) as a colourless oil.

R_f 0.67 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2976 (w), 1734 (s), 1179 (s), 1077 (s), 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H3), 6.26 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H1), 5.99 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H4), 4.03 (q, *J* = 7.0 Hz, 2H, H10), 2.59 (s, 2H, H6), 1.39 (s, 6H, H7, H8), 1.16 (t, *J* = 7.0 Hz, 3H, H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.9 (C9), 159.8 (C2), 150.2 (C3), 105.5 (C1), 103.8 (C4), 60.6 (C10), 47.4 (C5), 35.0 (C6), 27.4 (C7, C8), 13.6 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_3$, 197.1178; found, 197.1178.

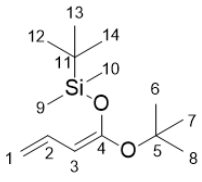
3-(Furan-2-yl)-3-methylbutanoic acid, 1.29



Sodium hydroxide pellets (0.566 g, 1.42 mmol) were ground into a powder form using a mortar and pestle, and dissolved in a mixture of methanol (1 mL) and water (2 mL) in a 50 mL round-bottom flask. To this solution was added **1.28** (0.139 g, 0.708 mmol). The mixture was placed under a nitrogen atmosphere, heated to 50 °C and stirred for 17 hours. After cooling to 0 °C, the mixture was carefully acidified by dropwise addition of 1.0 M HCl until its pH reached 3−4. ethyl acetate (3 × 10 mL) was used to extract the mixture, and the organics were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures to yield compound **1.29** (0.113 g, 99%) as a yellow oil, which was used without further purification.

R_f 0.30 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3100 (br w), 2976 (w), 1708 (s), 1159 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H3), 6.19 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H1), 5.95 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H4), 2.57 (s, 2H, H6), 1.34 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.9 (C9), 161.0 (C2), 141.1 (C3), 109.9 (C1), 103.3 (C4), 45.5 (C6), 34.9 (C5), 26.8 (C7, C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}O_3$, 169.0865; found, 169.0865.

(*Z*)-((1-(*tert*-Butoxy)buta-1,3-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane, 1.30



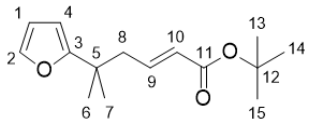
To a solution of crotonic acid (2.58 g, 30.0 mmol) in DCM (20 mL) under N_2 was added oxalyl chloride (2.75 mL, 32.0 mmol) dropwise. After the addition the mixture was heated under reflux for another 30 min with vigorous stirring. Then it was allowed to cool to 0 °C, and *tert*-butyl alcohol (2.224 g, 30.0 mmol) was added, followed dropwise by NEt_3 (5.58 mL, 40.0 mmol). The mixture was stirred for another 30 min before diluted by ethyl acetate (20 mL) and water (30 mL). The resulting phases were separated, the aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic phase was washed by brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 9:1) to give *tert*-butyl crotonate (2.50 g, 59%) as a colourless liquid. **R_f** 0.75 (pentane/diethyl ether, 9:1); **IR** ν_{max}/cm^{-1} 2975 (w), 1716 (s), 1658 (w), 1292 (w), 1154 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.85 (dq, *J* = 15.5 Hz, 7.0 Hz, 1H, H2), 5.75 (dq, *J* = 15.5 Hz, 1.5 Hz, 1H, H3), 1.83 (dd, *J* = 7.0 Hz, 1.5 Hz, 3H, H1),

1.46 (s, 9H, H6, H7, H8); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 166.0 (C4), 143.1 (C2), 124.5 (C3), 79.9 (C5), 28.0 (C6, C7, C8), 17.7 (C1). Spectroscopic data in agreement with literature.[7]

To a solution of DIPA (0.770 mL, 5.50 mmol) in THF under N_2 at −20 °C was added *n*-BuLi (3.44 mL, 1.6 M in hexanes, 5.50 mmol) dropwise. After stirring for 30 min, the mixture was cooled further to −78 °C; DMPU (0.720 mL, 6.00 mmol) was added, followed dropwise by *tert*-butyl crotonate (0.800 mL, 5.00 mmol). Stirring was continued for another hour, then a solution of *tert*-butyldimethylsilyl chloride (0.829 g, 5.50 mmol) in THF (2 mL) was slowly added. The mixture was allowed to slowly warm to RT over 15 h with vigorous stirring and concentrated *in vacuo*. The residue was washed by cold sat. aq. Na_2CO_3 (15 mL), extracted with pentane (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give compound **1.30** (0.922 g, 72%) as a yellow oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2944 (w), 1711 (s), 1662 (s), 1280 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.66 (m, 1H, H2), 4.81 (m, 2H, H1), 4.66 (dddd, *J* = 10.0 Hz, 8.0 Hz, 2.0 Hz, 0.5 Hz, 1H, H3), 1.37 (s, 9H, H6, H7, H8), 0.96 (s, 9H, H12, H13, H14), 0.23 (s, 6H, H9, H10); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 154.2 (C4), 133.2 (C2), 108.2 (C3), 95.4 (C3), 79.7 (C5), 29.1 (C6, C7, C8), 25.6 (C12, C13, C14), 18.1 (C11), −4.7 (C9, C10). Spectroscopic data in agreement with literature.[8]

***tert*-Butyl (*E*)-5-(furan-2-yl)-5-methylhex-2-enoate, 1.31**

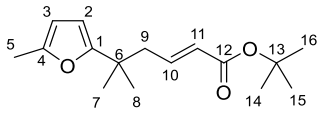


To a solution of alcohol **1.13** (0.172 mL, 1.00 mmol) in THF (6 mL) was added silyl ketene acetal **1.30** (0.462 g, 1.80 mmol), and the mixed solution was cooled to −78 °C before TMSOTf

(0.127 mL, 0.700 mmol) was added dropwise. Stirring was continued for 1 min, and the mixture was quenched by tributylamine (0.250 mL, 1.05 mmol) and warmed to RT. All volatile material was removed *in vacuo*, and to the residue was added diethyl ether (15 mL) and water (10 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined ethereal phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 4:1) to give compound **1.31** (15.1 mg, 6.0%) as a colourless oil.

R_f 0.65 (pentane/diethyl ether, 4:1); **IR** ν_{max}/cm^{-1} 2977 (w), 1753 (w), 1715 (s), 1159 (s), 850 (s), 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H2), 6.67 (dt, *J* = 15.5 Hz, 7.5 Hz, 1H, H9), 6.25 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H1), 5.97 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H4), 5.70 (dt, *J* = 15.5 Hz, 1.5 Hz, 1H, H10), 2.44 (dd, *J* = 7.5 Hz, 1.5 Hz, 2H, H8), 1.45 (s, 9H, H13, H14, H15), 1.26 (s, 6H, H6, H7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 165.1 (C11), 161.7 (C3), 142.5 (C9), 141.6 (C2), 122.9 (C10), 111.1 (C1), 108.6 (C4), 80.7 (C12), 45.4 (C7), 39.5 (C5), 28.1 (C13, C14, C15), 25.7 (C6, C7); **HRMS** (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{22}O_3Na$, 273.1466; found, 273.1467.

tert-Butyl (_E_)-5-methyl-5-(5-methylfuran-2-yl)hex-2-enoate, 1.32

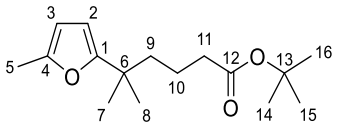


Alcohol **1.20** (0.140 g, 1.00 mmol) and silyl ketene acetal **1.30** (0.410 g, 1.60 mmol) were dissolved in THF (5 mL) under argon. The solution was cooled to −78 °C before a solution of TMSOTf (36.3 μL, 0.200 mmol) in THF (1 mL) was dropwise added. The mixture was stirred for 3 minutes and quenched *in situ* by tributylamine (0.480 mL, 2.00 mmol). The solvent was

removed *in vacuo*, and to the residue was added diethyl ether (5 mL) and water (5 mL). The aqueous layer was separated and extracted with ether (3 × 5 mL); the extracts were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressures. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to yield compound **1.32** (17 mg, 6.4%) as a pale-yellow oil.

R_f 0.86 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2973 (w), 2928 (w), 1713 (s), 1150 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.70 (dt, *J* = 15.5 Hz, 7.5 Hz, 1H, H10), 5.87 – 5.78 (m, 2H, H2, H3), 5.72 (dt, *J* = 15.5 Hz, 1.5 Hz, 1H, H11), 2.43 (dd, *J* = 7.5 Hz, 1.5 Hz, 2H, H9), 2.25 (d, *J* = 1.0 Hz, 3H, H5), 1.46 (s, 9H, H14, H15, H16), 1.24 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.9 (C12), 160.0 (C1), 150.4 (C4), 144.7 (C10), 125.1 (C11), 105.6 (C2), 104.1 (C3), 80.0 (C13), 44.4 (C9), 35.8 (C6), 28.2 (C14, C15, C16), 26.7 (C7, C8), 13.6 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{25}O_3$, 265.1804; found, 265.1804.

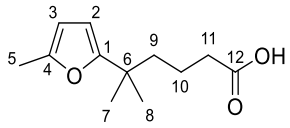
***tert*-Butyl 5-methyl-5-(5-methylfuran-2-yl)hexanoate, 1.33**



Nickel(II) chloride hexahydrate (99.8 mg, 0.0420 mmol) was suspended in methanol (2 mL) under nitrogen. The suspension was cooled to 0 °C, to which substrate **1.32** (110 mg, 0.420 mmol) was added, followed by sodium borohydride (31.8 mg, 0.840 mmol) in ~2 mg portions. Stirring was continued at 0 °C for 12 hours, after which the mixture was quenched with sat. aq. $NaHCO_3$ (10 mL). The organic layer was separated and extracted with ether (3 × 5 mL); the extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures to yield compound **1.33** (99 mg, 88%) as a pale-yellow oil.

R_f 0.91 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2971 (w), 1730 (s), 1156 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.92 – 5.86 (m, 2H, H2, H3), 2.31 (s, 3H, H5), 2.21 (t, *J* = 7.0 Hz, 2H, H11), 1.69 – 1.58 (m, 2H, H9), 1.50 (s, 9H, H14, H15, H16), 1.40 – 1.31 (m, 2H, H10), 1.29 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.2 (C12), 160.9 (C1), 150.0 (C4), 105.4 (C2), 103.8 (C3), 80.0 (C13), 41.4 (C9), 36.0 (C11), 35.5 (C6), 28.12 (C14, C15, C16), 26.8 (C7, C8), 20.5 (C10), 13.6 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{27}O_3$, 267.1960; found, 267.1960.

5-Methyl-5-(5-methylfuran-2-yl)hexanoic acid, 1.34

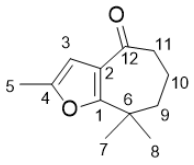


Method 1 (from **1.33**): Ester **1.33** (266 mg, 1.00 mmol) was dropwise added to a solution of NaOH (0.140 g, 3.50 mmol) in methanol (1.5 mL) at RT. The mixture was then heated to 60 °C and stirred at this temperature for 18 h. After cooling to RT, it was acidified with 1M HCl until pH reached 3−4. The mixture was diluted by 10 mL water and extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressures to give acid **1.34** (54.6 mg, 26%) as an orange oil, which was used without further purification.

Method 2 (from **1.42**): Ester **1.42** (224 mg, 1.00 mmol) was dropwise added to a solution of NaOH (0.140 g, 3.50 mmol) in methanol (1.5 mL) at RT. The mixture was then heated to 60 °C and stirred at this temperature for 18 h. After cooling to RT, it was acidified with 1M HCl until pH reached 3−4. The mixture was diluted by 10 mL water and extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressures to give acid **1.34** (0.198 g, 94%) as an orange oil, which was used without further purification.

R_f 0.91 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 3504 (br w), 2943 (w), 1708 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.72 – 5.61 (m, 2H, H2, H3), 2.11 (d, J = 7.5 Hz, 2H, H11), 2.08 (s, 3H, H5), 1.48 – 1.37 (m, 2H, H9), 1.37 – 1.26 (m, 2H, H10), 1.06 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.1 (C12), 160.7 (C1), 150.2 (C4), 104.8 (C2), 103.9 (C3), 41.3 (C9), 35.5 (C11), 34.3 (C6), 26.8 (C7, C8), 20.1 (C10), 13.6 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{19}O_3$, 211.1329; found, 211.1329.

2,8,8-Trimethyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan-4-one, 1.35

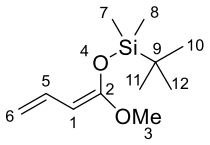


To a stirred solution of 5-(furan-2-yl)-5-methylpentanoic acid (0.392 g, 2.00 mmol) in DCM (30 mL) at 0 °C was dropwise added trifluoroacetic anhydride (0.47 mL). Stirring was continued for 4 h at the same temperature, then the mixture was quenched with ice-cold sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted by ethyl acetate (3 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown oil, which was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give compound (0.206 g, 58%) as a yellow oil.

R_f 0.51 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2973 (w), 1645 (s), 1152 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.19 (t, J = 1.0 Hz, 1H, H3), 2.67 – 2.52 (m, 2H, H11), 2.16 (t, J = 1.0 Hz, 3H, H5), 1.92 – 1.73 (m, 4H, H9, H10), 1.27 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 197.6 (C12), 165.2 (C1), 150.48 (C4), 122.2 (C2), 105.8 (C3), 44.7 (C11), 41.4 (C9), 38.3 (C6),

29.1 (C7, C8), 18.7 (C10), 13.2 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{17}O_2$, 193.1223; found, 193.1221.

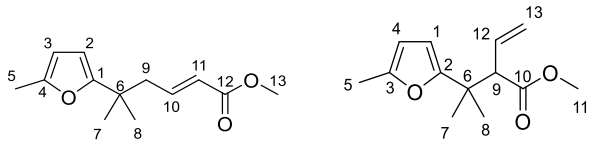
(*Z*)-*tert*-Butyl((1-methoxybuta-1,3-dien-1-yl)oxy)dimethylsilane, 1.39



To a solution of DIPA (0.770 mL, 5.50 mmol) in THF under N_2 at −20 °C was added *n*-BuLi (3.44 mL, 1.6 M in hexanes, 5.50 mmol) dropwise. After stirring for 30 min, the mixture was cooled further to −78 °C; DMPU (0.720 mL, 6.00 mmol) was added, followed dropwise by methyl crotonate (0.501 mL, 5.00 mmol). Stirring was continued for another hour, then a solution of *tert*-butyldimethylsilyl chloride (0.829 g, 5.50 mmol) in THF (2 mL) was slowly added. The mixture was allowed to slowly warm to RT over 15 h with vigorous stirring and concentrated *in vacuo*. The residue was washed by cold sat. aq. Na_2CO_3 (15 mL), extracted with pentane (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give compound **1.39** (0.943 g, 88%) as a yellow oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2958 (w), 2860 (w), 1648 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.60 – 6.47 (m, 1H, H-5), 4.84 (dd, *J* = 17.0 Hz, 2.5 Hz, 1H, H6a), 4.60 (dd, *J* = 10.5 Hz, 2.5 Hz, 1H, H6b), 4.48 (d, *J* = 10.5 Hz, 1H, H1), 3.57 (s, 3H, H3), 0.95 (s, 9H, H10, H11, H12), 0.18 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 158.8 (C2), 132.4 (C5), 106.7 (C6), 80.3 (C1), 54.8 (C3), 25.6 (C10, C11, C12), 18.2 (C9), −4.8 (C7, C8). Spectroscopic data in agreement with literature.[9]

Methyl (*E*)-5-methyl-5-(5-methylfuran-2-yl)hex-2-enoate, 1.40; Methyl 2-(2-(5-methylfuran-2-yl)propan-2-yl)but-3-enoate, 1.41



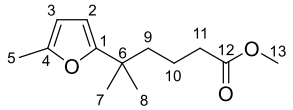
Alcohol **1.20** (0.841 g, 6.00 mmol) and silyl ketene acetal **1.39** (1.93 g, 9.00 mmol) were dissolved in THF (5 mL) under argon. This solution was cooled to −78 °C before a solution of TMSOTf (0.650 mL, 3.60 mmol) in THF (1 mL) was dropwise added. The mixture was stirred for 3 minutes and quenched *in situ* by tributylamine (1.71 mL, 7.20 mmol). The solvent was removed *in vacuo*, and to the residue was added diethyl ether (15 mL) and water (15 mL). The aqueous layer was separated and extracted with ether (3 × 10 mL); the extracts were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressures. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:9) to yield compound **1.40** (361 mg, 36%) as a pale-yellow oil and compound **1.41** (364 mg, 37%) as a pale-yellow oil.

Data for **1.40**: $\mathbf{R_f}$ 0.57 (pentane/diethyl ether, 4:1); **IR** ν_{max}/cm^{-1} 2974 (w), 1713 (s), 1155 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.64 (dt, *J* = 15.5 Hz, 7.5 Hz, 1H, H10), 5.72 – 5.61 (m, 3H, H2, H3, H11), 3.54 (s, 3H, H13), 2.30 (dd, *J* = 7.5 Hz, 1.5 Hz, 2H, H9), 2.08 (s, 3H, H5), 1.08 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.9 (C12), 159.8 (C1), 150.5 (C4), 146.3 (C10), 123.1 (C11), 105.6 (C2), 104.2 (C3), 51.4 (C13), 44.6 (C9), 35.9 (C6), 26.7 (C7, C8), 13.6 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{19}O_3$, 223.1334; found, 223.1334.

Data for **1.41**: $\mathbf{R_f}$ 0.72 (pentane/diethyl ether, 4:1); **IR** ν_{max}/cm^{-1} 2976 (w), 1735 (s), 1118 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.87 – 5.82 (m, 2H, H1, H4), 5.79 (dt, *J* = 3.0 Hz, 1.0 Hz, 1H, H12), 5.11 (dd, *J* = 10.0 Hz, 1.5 Hz, 1H, H13a), 5.00 (ddd, *J* = 17.0 Hz, 1.5 Hz, 1.0 Hz, 1H, H13b), 3.55 (s, 3H, H11), 3.30 (d, *J* = 9.5 Hz, 1H, H9), 2.24 (s, 3H, H5), 1.30 (d, *J* = 1.0 Hz,

6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.0 (C9), 158.7 (C2), 150.7 (C3), 133.5 (C12), 118.9 (C13), 105.7 (C1), 105.3 (C4), 59.5 (C9), 51.5 (C11), 38.7 (C6), 24.3 (C7, C8), 13.7 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{19}O_3$, 223.1334; found, 223.1334.

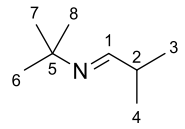
Methyl 5-methyl-5-(5-methylfuran-2-yl)hexanoate, 1.42



Nickel(II) chloride hexahydrate (71.3 mg, 0.300 mmol) was suspended in methanol (5 mL) under nitrogen. The suspension was cooled to 0 °C, to which substrate **1.40** (110 mg, 0.420 mmol) was added, followed by sodium borohydride (0.227 g, 6.00 mmol) in ~20 mg portions. Stirring was continued at 0 °C for 1.5 hours, after which the mixture was quenched with sat. aq. $NaHCO_3$ (20 mL). The organic layer was separated and extracted with ether (3 × 5 mL); the extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures to yield compound **1.42** (0.633 g, 94%) as a pale-yellow oil.

R_f 0.88 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2974 (w), 1732 (s), 1152 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.86 – 5.80 (m, 2H, H2, H3), 3.55 (s, 3H, H11), 2.24 (s, 3H, H5), 2.14 (t, *J* = 7.0 Hz, 2H, H11), 1.62 – 1.51 (m, 2H, H9), 1.33 – 1.24 (m, 2H, H10), 1.22 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.2 (C12), 160.9 (C1), 150.0 (C4), 105.4 (C2), 103.8 (C3), 51.6 (C13), 41.5 (C9), 36.2 (C11), 35.6 (C6), 26.9 (C7, C8), 20.8 (C10), 13.7 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{21}O_3$, 225.1491; found, 225.1491.

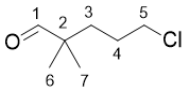
***N*-(*tert*-Butyl)-2-methylpropan-1-imine, 1.47**



To a stirred suspension of anhydrous $MgSO_4$ (16.0 g, 0.133 mol) in *tert*-butylamine (12.6 mL, 0.120 mol) was slowly added isobutyraldehyde (9.13 mL, 0.100 mol). The resulting mixture was stirred for another 15 h before being filtered *in vacuo*. The filtrate was distilled at 70 °C and 60 mbar to give compound **1.47** (10.4 g, 82%) as a colourless liquid.

IR ν_{max}/cm^{-1} 2945 (w), 1671 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 (d, J = 4.0 Hz, 1H, H1), 2.37 (heptd, J = 7.0 Hz, 4.0 Hz, 1H, H2), 1.14 (s, 9H, H6, H7, H8), 1.01 (d, 6H, H3, H4); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 161.5 (C1), 34.0 (C5), 32.2 (C2), 29.5 (C6, C7, C8), 19.1 (C3, C4). Spectroscopic data in agreement with literature.[10]

5-Chloro-2,2-dimethylpentanal, 1.48

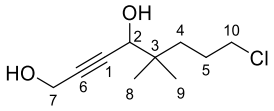


To a stirred solution of DIPA (7.56 mL, 54.0 mmol) in 30 mL THF was dropwise added *n*-butyllithium solution (27.0 mL, 1.6 M in hexanes, 43.2 mmol) at –10 °C. The mixture was stirred for 15 min before imine **1.47** (4.58 g, 36.0 mmol) was dropwise added. Stirring was continued for another 30 min, then the mixture was cooled to –50 °C and 1-bromo-3-chloropropane (6.23 g, 39.6 mmol) was dropwise added. The resulting suspension was slowly warmed to 0 °C over 15 min and was quenched with 20 mL sat. aq. ammonium chloride solution. The aqueous layer was separated and extracted with diethyl ether (3 × 20 mL). The

organic extracts were combined, washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified with silica gel chromatography (diethyl ether/pentane, 1:4) to give aldehyde **1.48** (8.63 g, 71%) as a colourless liquid.

R_f 0.45 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2963 (w), 1725 (s), 1471 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.46 (s, 1H, H1), 3.52 (t, *J* = 6.0 Hz, 2H, H5), 1.74 – 1.68 (m, 2H, H3), 1.66 – 1.59 (m, 2H, H4), 1.08 (s, 6H, H6, H7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 205.7 (C1), 45.2 (C5), 34.3 (C3), 27.6 (C4), 21.4 (C6, C7). Spectroscopic data in agreement with literature.[11]

8-Chloro-5,5-dimethyloct-2-yne-1,4-diol, 1.49

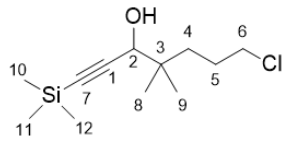


To a stirred solution of propargyl alcohol (0.130 mL, 2.20 mmol) in THF (8 mL) at −78 °C was dropwise added *n*-butyllithium (2.63 mL, 1.6 M in hexanes, 4.20 mmol) under argon. The mixture was stirred for 20 min, to which DMPU (0.482 mL, 4.00 mmol) and aldehyde **1.48** (0.297 g, 2.00 mmol) were then added. Stirring was continued for another 5 min, then the mixture was warmed to 0 °C and quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified with silica gel chromatography (ethyl acetate/pentane, 2:3) to give compound **1.49** (192 mg, 47%) as a colourless liquid.

R_f 0.36 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 3371 (br w), 2962 (w), 2251 (w), 1471 (w), 1011 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.26 (d, *J* = 1.5 Hz, 2H, H7), 4.11 – 3.99 (m, 1H, H2), 3.46 (t, *J* = 6.5 Hz, 2H, H10), 1.78 – 1.65 (m, 2H, H4), 1.48 – 1.38 (m, 2H, H5), 0.91 (s,

6H, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 85.3 (C1), 84.6 (C6), 70.5 (C2), 51.3 (C7), 45.9 (C10), 38.2 (C3), 35.6 (C4), 27.6 (C5), 22.8 (C8, C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{18}ClO_2$, 205.0995; found, 205.0995.

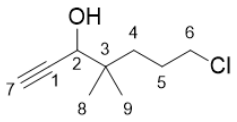
7-Chloro-4,4-dimethyl-1-(trimethylsilyl)hept-1-yn-3-ol, 1.51



Isopropylmagnesium chloride (2.0 M solution in THF, 5.00 mL, 10.0 mmol) was dropwise added to a 0 °C solution of ethynyltrimethylsilane (1.70 mL, 12.0 mmol) in THF (2 mL). After an hour of stirring, aldehyde **1.48** (1.20 g, 8.06 mmol) was slowly added. The mixture was stirred at RT for 17 h then poured onto saturate ammonium chloride solution (15 mL). The aqueous layer was separated and extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield compound **1.51** (1.97 g, 99%) as a pale-yellow oil, which was used without further purification.

IR ν_{max}/cm^{-1} 3469 (br w), 2961 (w), 2172 (w), 1251 (s), 844 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.95 (d, *J* = 6.0 Hz, 1H, H2), 3.42 (t, *J* = 7.0 Hz, 2H, H6), 1.88 – 1.57 (m, 2H, H4), 1.48 – 1.32 (m, 2H, H5), 0.89 (s, 3H, H8), 0.86 (s, 3H, H9), 0.06 (s, 9H, H10, H11, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 105.2 (C1), 91.1 (C7), 70.8 (C2), 45.9 (C6), 38.1 (C3), 35.6 (C4), 27.6 (C5), 22.8 (C8), 22.5 (C9), 0.0 (C10, C11, C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{24}ClOSi$, 247.1280; found, 247.1275.

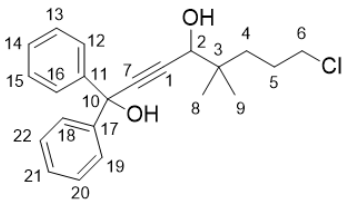
7-Chloro-4,4-dimethylhept-1-yn-3-ol, 1.52



Potassium carbonate (0.768 g, 5.56 mmol) was mixed with methanol (10 mL) at RT, resulting in a white suspension. To this was added **1.151** (0.413 g, 2.75 mmol). The mixture was stirred at RT, and thin layer chromatography was used to indicate the reaction progress. After 2 h of stirring with the completion of the reaction, water (30 mL) and diethyl ether (20 mL) were added, and the two layers were separated. The aqueous layer was extracted with ether (3 × 10 mL) and then discarded. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressures to yield compound **1.152** (0.115 g, 65%) as a colourless oil, which was used without further purification.

IR ν_{max}/cm^{-1} 3438 (br w), 3300 (s), 2963 (s), 2114 (w), 1473 (s), 1062 (s), 1024 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.06 (dtt, *J* = 11.5 Hz, 4.5 Hz, 1.5 Hz, 1H, H6a), 4.00 – 3.89 (m, 1H, H2), 3.53 (dddd, *J* = 11.0 Hz, 9.5 Hz, 3.0 Hz, 1.0 Hz, 1H, H6b), 2.53 (dd, *J* = 2.5 Hz, 1.0 Hz, 1H, H7), 1.90 – 1.62 (m, 2H, H4), 1.61 – 1.36 (m, 2H, H5), 1.11 (dd, *J* = 25.7, 1.1 Hz, 6H, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 76.2 (C1), 74.3 (C7), 67.1 (C2), 35.8 (C6), 33.5 (C3), 26.7 (C8), 22.2 (C4), 21.6 (C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{16}ClO$, 175.0890; found, 175.0890.

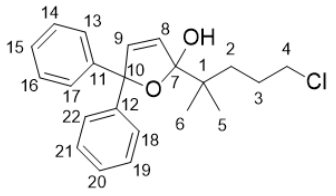
8-Chloro-5,5-dimethyl-1,1-diphenyloct-2-yne-1,4-diol, 1.53



Under argon at −78 °C, compound **1.52** (87.3 mg, 0.500 mmol) was dissolved in THF (3 mL). Butyllithium (1.6 M in hexanes, 0.660 mL, 1.05 mmol) was added dropwise to the solution with vigorous stirring. The mixture was stirred for 90 minutes while being slowly warmed to −50 °C. A solution of benzophenone (85.6 mg, 0.470 mmol) was dissolved in THF (*ca.* 0.2 mL) was added, then the mixture was warmed to RT with stirring continued for 3 h. Saturated aqueous ammonium chloride solution (10 mL) was added, and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The extracts were combined, washed by brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:4) to yield compound **1.53** (0.110 g, 62%) as a colourless oil.

R_f 0.64 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3062 (w), 1659 (m), 1318 (s), 1275 (s), 699 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60 (m, 4H, H12, H16, H18, H19), 7.34 – 7.28 (m, 4H, H13, H15, H20, H22), 7.27 – 7.19 (m, 2H, H14, H21), 4.03 (s, 1H, H2), 3.98 (dtd, *J* = 11.5 Hz, 4.5 Hz, 1.5 Hz, 1H, H6a), 3.47 (ddd, *J* = 11.5 Hz, 9.5 Hz, 3.5 Hz, 1H, H6b), 2.83 (s, 1H, OH), 1.80 – 1.56 (m, 2H, H4), 1.55 – 1.24 (m, 2H, H5), 1.06 (s, 3H, H8), 0.99 (s, 3H, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.0 (C11, C17), 128.2 (C13, C15, C20, C22), 127.6 (C14, C21), 126.0 (C12, C16, C18, C19), 89.1 (C7), 84.8 (C1), 76.5 (C2), 74.5 (C10), 67.2 (C6), 36.0 (C5), 34.1 (C4), 26.9 (C9), 22.3 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}ClO_2$, 357.1616; not found.

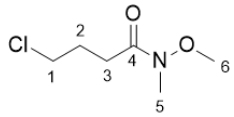
2-(5-Chloro-2-methylpentan-2-yl)-5,5-diphenyl-2,5-dihydrofuran-2-ol, 1.54



In a glass pressure tube, *p*-toluenesulfonic acid monohydrate (7.61 mg, 40.0 μmol) was dissolved in 1,2-dichloroethane (0.5 mL) under a nitrogen atmosphere. diol **1.53** (71.4 mg, 0.200 mmol) was added, then the tube was sealed and heated to 80 °C for 2 h. After cooling to RT, the contents were poured into 5 mL of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL). The extracts were combined, washed by brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:4) to yield compound **1.54** (33.9 mg, 47%) as a colourless oil.

R_f 0.49 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 3060 (w), 1659 (s), 1318 (s), 1277 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 – 7.25 (m, 4H, H13, H17, H18, H22), 7.25 – 7.21 (m, 2H, H15, H20), 7.21 – 7.07 (m, 4H, H15, H17, H19, H21), 6.56 (t, *J* = 6.0 Hz, 1H, H9), 5.87 (d, *J* = 6.0 Hz, 1H, H8), 4.07 (m, 1H, H4a), 3.82 – 3.51 (m, 1H, H4b), 1.91 – 1.77 (m, 2H, H2a, H3a), 1.42 – 1.30 (m, 1H, H2b), 1.25 (m, 1H, H3b), 1.02 (s, 3H, H5), 0.50 (s, 3H, H6**); ^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.8 (C11), 144.5 (C12), 137.0 (C8, C9), 128.0 (C14, C16, C19, C21), 127.0 (C15), 126.9 (C13, C17), 126.8 (C20), 126.5 (C18, C22), 115.9 (C7), 95.2 (C10), 62.1 (C4), 36.4 (C1), 33.9 (C2), 26.5 (C3), 24.0 (C5), 22.0 (C6); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}ClO_2$, 357.1616; found, 357.1616.

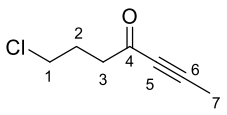
4-Chloro-*N*-methoxy-*N*-methylbutanamide, 1.60



N,*O*-Dimethylhydroxylamine hydrochloride (0.750 g, 8.00 mmol) and 4-chlorobutanoyl chloride (0.89 mL, 8.00 mmol) were mixed in DCM (6 mL) at RT. Then triethylamine (1.67 mL, 12.0 mmol) was dropwise added. The resulting mixture was stirred for 2 h before being quenched by water (20 mL). The two layers were separated, and the aqueous layer was extracted by ethyl acetate (3 × 10 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified with silica gel chromatography (2:3 ethyl acetate-pentane) to give compound **1.60** (0.939 g, 71%) as a yellow oil.

IR ν_{max}/cm^{-1} 2966 (w), 2940 (w), 1666 (s), 1000 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.69 (d, *J* = 2.0 Hz, 3H), 3.69 – 3.61 (m, 2H), 3.17 (d, *J* = 2.0 Hz, 3H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.16 – 2.06 (m, 2H, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.4 (C4), 61.4 (C6), 44.8 (C1), 32.3(C5), 28.9 (C3), 27.4 (C2). Spectroscopic data in agreement with literature.[12]

7-Chlorohept-2-yn-4-one, 1.61

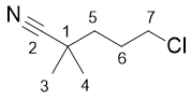


To a stirred solution of 1-bromo-1-propene (mixed isomers, 1.28 mL, 15.0 mmol) in THF (15 mL) at −50 °C was dropwise added *n*-butyllithium (18.8 mL, 1.6 M in hexanes, 30.0 mmol) under argon. The mixture was stirred for 20 min, to which HMPA (1.04 mL, 6.00 mmol) and Weinreb amide **1.60** (0.297 g, 2.00 mmol) were then added. Stirring was continued for another

5 min, then the mixture was warmed to 0 °C and quenched with sat. aq. NH_4Cl (20 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:2) to give ynone **1.61** (1.69 g, 78%) as a colourless liquid.

R_f 0.87 (ethyl acetate/pentane, 1:2); **IR** ν_{max}/cm^{-1} 2969 (w), 2221 (s), 1675 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.51 (t, *J* = 6.5 Hz, 2H, H1), 2.67 (t, *J* = 7.0 Hz, 2H, H3), 2.04 (tt, *J* = 7.0 Hz, 6.5 Hz, 2H, H2), 1.96 (s, 3H, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 186.5 (C4), 90.6 (C6), 80.1 (C5), 44.0 (C1), 41.6 (C3), 26.5 (C2), 4.1 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_7H_{10}ClO$, 145.0420; found, 145.0420.

5-Chloro-2,2-dimethylpentanenitrile, 1.64

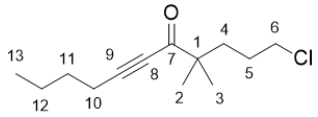


To a stirred solution of DIPA (4.20 mL, 30.0 mmol) in THF (4 mL) at –20 °C was added *n*-butyllithium (13.8 mL, 1.60 M solution in hexanes, 22.0 mmol), and this mixture was stirred for 15 minutes before being cooled to –75 °C. Isobutyronitrile **1.63** (1.79 mL, 20.0 mmol) was added dropwise to the mixture, which was stirred for a further 2 h before 1-bromo-3-chloropropane (2.18 mL) was slowly added. Stirring was allowed to continue for 15 h while the mixture was warmed slowly back to RT. Saturated NH_4Cl solution (20 mL) was added to quench this mixture, and the two layers were separated. The aqueous layer was extracted by diethyl ether (3 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered and

concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:19) to give compound **1.64** (2.71 g, 93%) as a pale-yellow oil.

R_f 0.36 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2980 (m), 1619 (w), 1470 (s), 1035 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.58 (t, *J* = 6.5 Hz, 2H, H7), 2.01 – 1.94 (m, 2H, H6), 1.71 – 1.67 (m, 2H, H5), 1.37 (s, 6H, H3, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 124.4 (C2), 44.2 (C7), 38.1 (C5), 31.7 (C1), 28.2 (C6), 26.4 (C3, C4). Spectroscopic data in agreement with literature.[11]

1-Chloro-4,4-dimethylundec-6-yn-5-one, 1.65

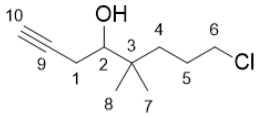


To a mixture of triethylamine (60.0 µL, 0.471 mmol) and toluene (3 mL) under argon was added trimethylaluminium solution (2.0 M in hexanes, 7.06 mL, 14.1 mmol) followed by 1-hexyne (1.61 mL, 14.1 mmol). The resulting mixture was stirred at 60 °C for 6 h; after cooling back to RT, **1.64** (0.686 g, 4.71 mmol) was dropwise added. This mixture was heated to 60 °C again and stirred for another 15 hours. It was then quenched at 0 °C with sat. aq. $NaHCO_3$ (10 mL), and the two layers were separated. The aqueous layer was extracted by diethyl ether (3 × 5 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:19) to give compound **1.65** (0.847 g, 79%) as a yellow oil.

R_f 0.49 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2958 (w), 2224 (s), 1673 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.58 (t, *J* = 6.0 Hz, 2H, H6), 2.46 (t, *J* = 7.0 Hz, 2H, H10), 1.81 – 1.70 (m, 4H, H4, H5), 1.70 – 1.58 (m, 2H, H11), 1.58 – 1.46 (m, 2H, H12), 1.24 (s, 6H, H2, H3), 1.00

(t, *J* = 7.5 Hz, 3H, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.7 (C7), 95.9 (C9), 75.9 (C8), 47.6 (C1), 45.4 (C6), 36.9 (H4), 29.8 (C11), 27.9 (C5), 24.0 (C2, C3), 22.0 (C12), 18.7 (C10), 13.0 (C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{22}ClO$, 229.1359; found, 229.1356.

8-Chloro-5,5-dimethyloct-1-yn-4-ol, 1.67

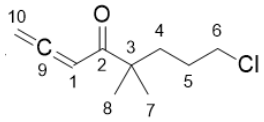


To a stirred suspension of magnesium turnings (1.10 g, 45.3 mmol) and mercury(II) chloride (0.184 g, 0.680 mmol) in 8 mL diethyl ether was dropwise added propargyl bromide solution (4.21 mL, 80 wt%, 22.6 mmol) at RT. The resulting mixture was stirred for 1 h before being cooled to –30 °C, and a solution of aldehyde **1.48** (2.16 g, 18.1 mmol) in 2 mL diethyl ether was added dropwise. After stirring for 5 min, the mixture was quenched with ice-cold sat. aq. ammonium chloride (20 mL) followed by 10 mL 1.0 M HCl. The aqueous layer was separated and extracted with diethyl ether (3 × 10 mL). The ethereal layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **1.67** (2.32 g, 68%) as a yellow oil.

R_f 0.51 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3566 (br, w), 2961 (s), 1473 (w), 1071 (s), 647 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.51 (m, 3H, H2, H6), 2.42 (dt, *J* = 16.5 Hz, 3.0 Hz, 1H, H1a), 2.27 (ddd, *J* = 16.5 Hz, 10.0 Hz, 2.5 Hz, 1H, H1b), 2.09 (d, *J* = 3.0 Hz, 1H, OH), 2.06 (t, *J* = 2.5 Hz, 1H, H10), 1.78 (m, 2H, H5), 1.49 (m, 1H, H4a), 1.33 (m, 1H, H4b), 0.90 (s, 3H, H7), 0.88 (s, 3H, H8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 82.1 (C9), 76.1 (C2), 70.8 (C10),

45.8 (C6), 36.8 (C3), 36.3 (C4), 27.4 (C5), 23.0 (C8), 22.6 (C7), 22.4 (C1); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{18}ClO$, 189.1046; found, 189.1046.

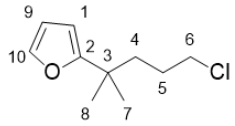
8-Chloro-5,5-dimethylocta-1,2-dien-4-one, 1.68



To a stirred suspension of Dess-Martin periodinane (1.34 g, 3.17 mmol) and $NaHCO_3$ (0.840 g, 10.0 mmol) in 10 mL DCM at RT was dropwise added alcohol **1.67** (0.599 g, 3.17 mmol). The resulting mixture was stirred for 15 h before being poured into 100 mL 1:4 diethyl ether-pentane and filtered under reduced pressure. The filtrate was concentrated *in vacuo* to give an orange oil, which was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give allenyl ketone **1.68** (0.426 g, 72%) as an orange oil.

R_f 0.54 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2970 (w), 1962 (w), 1679 (s), 851 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.07 (t, *J* = 6.5 Hz, 1H, H1), 5.14 (d, *J* = 6.5 Hz, 2H, H10), 3.45 (td, *J* = 5.5 Hz, 1.0 Hz, 2H, H6), 1.64 (m, 4H, H4, H5), 1.12 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 215.5 (C9), 198.9 (C2), 90.9 (C1), 79.2 (C10), 47.4 (C3), 45.4 (C6), 37.2 (C4), 28.0 (C5), 24.6 (C7, C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{16}ClO$, 187.0889; found, 187.0891.

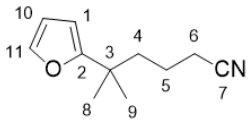
2-(5-Chloro-2-methylpentan-2-yl)furan, 1.50



To a stirred suspension of $AgNO_3$-impregnated silica (2.226 g, 5 wt%, 0.655 mmol) in 10 mL DCM was added allenyl ketone **1.68** (1.223 g, 6.55 mmol). The mixture was stirred in the dark under a nitrogen atmosphere for 2 h before being filtered with suction. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **1.50** (0.840 g, 69%) as a pale-yellow oil.

R_f 0.94 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2966 (w), 1012 (s), 730 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (dd, J = 2.0 Hz, 1.0 Hz, 1H, H10), 6.26 (dd, J = 3.0 Hz, 2.0 Hz, 1H, H9), 5.96 (dd, J = 3.0 Hz, 1.0 Hz, 1H, H1), 3.42 (t, J = 6.5 Hz, 2H, H6), 1.69 (m, 2H, H5), 1.59 (m, 2H, H4), 1.26 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.2 (C2), 140.8 (C10), 109.7 (C9), 103.5 (C1), 45.5 (C6), 39.4 (C3), 35.4 (C5), 28.3 (C4), 26.8 (C7, C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{16}ClO$, 187.0890; found, 187.0889.

5-(Furan-2-yl)-5-methylhexanenitrile, 1.69

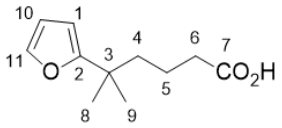


To a sealed tube containing sodium cyanide (0.441 g, 9.00 mmol) and DMSO (4 mL) was added compound **1.50** (0.840 g, 4.50 mmol). The resulting mixture was heated to 70 and stirred under N_2 for 16 h, cooled back to RT and poured into 50 mL water. The product was extracted by diethyl ether (3 × 10 mL), and the aqueous solution after extraction was treated with

sufficient amounts of 5% H_2O_2 solution before being discarded so that all remaining cyanide was destroyed. The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give nitrile **1.69** (0.685 g, 86%) as a yellow oil.

R_f 0.71 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2968 (w), 1508 (w), 734 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 (dd, *J* = 2.0, 1.0 Hz, 1H, H11), 6.25 (dd, *J* = 3.0, 2.0 Hz, 1H, H10), 5.97 (dd, *J* = 3.0, 1.0 Hz, 1H, H1), 2.21 (t, *J* = 7.0 Hz, 2H, H6), 1.71 (m, 2H, H5), 1.48 (m, 2H, H4), 1.27 (s, 6H, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 161.7 (C2), 141.0 (C11), 119.7 (C7), 109.8 (C10), 103.7 (C1), 41.1 (C6), 35.5 (C3), 26.8 (C5), 21.2 (C4), 17.5 (C8, C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{16}NO$, 178.1232; found, 178.1235.

5-(Furan-2-yl)-5-methylpentanoic acid, 1.70

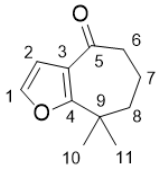


To a stirred solution of NaOH (4.00 g) in 6 mL water were added nitrile **1.69** (2.23 g, 12.6 mmol) and 3 mL isopropyl alcohol, and the mixture was heated under reflux for 20 h. After being cooled to 0 °C, the mixture was acidified by adding 40% H_3PO_4 slowly whilst ensuring that its temperature did not exceed 5 °C. After the pH reached 3, the product was extracted by ethyl acetate (3), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 3:7) to give compound **1.70** (2.47 g, 99%) as a colourless oil.

R_f 0.42 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2970 (w), 1713 (s), 732 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.41 (*J* = 2.0, 1.0 Hz, 1H, H11), 6.36 (dd, *J* = 3.0, 2.0 Hz, 1H, H10), 6.07 (dd,

J = 3.0, 1.0 Hz, 1H, H1), 2.37 (m, 2H, H6), 1.71 (m, 2H, H5), 1.57 (m, 2H, H4), 1.36 (s, 6H, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 181.1 (C7), 162.4 (C2), 140.7 (C11), 109.7 (C10), 103.4 (C1), 41.3 (C6), 35.6 (C5), 34.2 (C3), 26.8 (C4), 20.1 (C8, C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_3$, 197.1178; found, 197.1180.

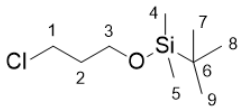
8,8-Dimethyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan-4-one, 1.04



To a stirred solution of acid **1.70** (0.392 g, 2.00 mmol) in DCM (30 mL) at 0 °C was dropwise added trifluoroacetic anhydride (0.470 mL, 3.38 mmol). Stirring was continued for 4 h at the same temperature, then the mixture was quenched with ice-cold sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted by ethyl acetate (3 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown oil, which was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give ketone **1.04** (0.206 g, 58%) as a colourless crystalline solid.

R_f 0.45 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2970 (w), 1643 (s), 1157 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 (d, *J* = 2.0 Hz, 1H, H1), 6.76 (d, *J* = 2.0 Hz, 1H, H2), 2.76 (m, 2H, H6), 1.96 (m, 4H, H7, H8), 1.42 (s, 6H, H10, H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 200.2 (C5), 162.4 (C4), 140.8 (C1), 126.3 (C3), 110.3 (C2), 44.7 (C6), 41.3 (C8), 38.3 (C9), 28.9 (C10, C11), 18.6 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{15}O_2$, 179.1072; found, 179.1072; **mp** 51–53 °C.

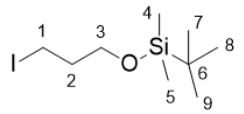
***tert*-Butyl(3-chloropropoxy)dimethylsilane, 1.74**



3-Chloro-1-propanol (1.66 mL, 20.0 mmol) and imidazole (4.09 g, 60.0 mmol) were dissolved in DCM (30 mL) at RT. To this solution was slowly added a solution of *tert*-butyldimethylsilyl chloride (3.92 g, 26.0 mmol) in DCM (3 mL). The mixture was stirred at RT for 2 h before being poured into 50 mL of ice-cold water. The resulting layers were separated, and the aqueous layer was extracted with ether (3 × 5 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified by silica gel chromatography (pentane) to give compound **1.74** (2.96 g, 71%) as a colourless oil.

IR ν_{max}/cm^{-1} 2958 (w), 1255 (s); **^{1}H NMR** (400 MHz, $CDCl_3$); δ_H 3.75 (2H, t, J = 6.0 Hz, H1), 3.65 (2H, t, J = 6.0 Hz, H3), 1.95 (2H, quin, J = 6.0 Hz, H2), 0.89 (9H, s, H7, H8, H9), 0.06 (6H, s, H4, H5); **^{13}C NMR** (101 MHz, $CDCl_3$); δ_C 59.3 (C1), 41.7 (C3), 35.3 (C2), 25.8 (C7, C8, C9), 18.2 (C6), −5.6 (C4, C5). Spectroscopic data in agreement with literature.[13]

***tert*-Butyl(3-iodopropoxy)dimethylsilane, 1.75**

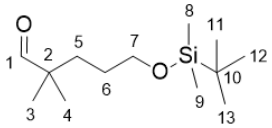


Sodium iodide (0.450 g, 3.00 mmol) was dissolved in acetone (7 mL) at RT. This was followed by the addition of **1.74** (0.209 g, 1.00 mmol). The mixture was heated to 60 °C for 15 h. After being cooled to RT, it was poured into pentane (50 mL) and filtered under reduced pressures.

The filtrate was concentrated *in vacuo* to give compound **1.75** (0.231 g, 77%) as a colourless oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2957 (w), 2930 (w), 1472 (s), 1257 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.67 (t, *J* = 5.5 Hz, 2H, H3), 3.29 (t, *J* = 6.5 Hz, 2H, H1), 1.99 (ddd, *J* = 12.0 Hz, 6.5 Hz, 5.5 Hz, 2H, H2), 0.90 (s, 9H, H7, H8, H9), 0.07 (s, 6H, H4, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 62.5 (C3), 36.3 (C1), 26.1 (C2), 18.5 (C7, C8, C9), 3.9 (C6), −5.2 (C4, C5). Spectroscopic data in agreement with literature.[14]

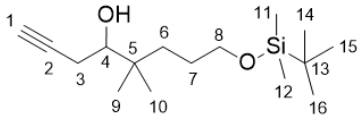
5-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylpentanal, 1.76



DIPA (0.550 mL, 3.00 mmol) was dissolved in THF (5 mL) at –30 °C under argon. Then *n*-butyllithium solution (2.25 mL, 1.60 M solution in hexanes, 3.60 mmol) was slowly added. The mixture was stirred for 15 min before imine **1.47** (0.382 g, 3.00 mmol) was dropwise added. The mixture was warmed to 0 °C with stirring continued for another 2 h, then it was cooled to –75 °C and compound **1.84** (0.634 g, 3.00 mmol) was dropwise added. The resulting suspension was slowly warmed to RT, stirred over 15 h and was quenched with 20 mL sat. aq. NH_4Cl solution. The aqueous layer was separated and extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified with silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **1.76** (1.00 g, 57%) as a colourless oil.

R$_f$ 0.68 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2956 (w), 2925 (w), 1726 (s), 1701 (m), 1470 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.40 (s, 1H, H1), 3.60 (t, *J* = 6.0 Hz, 2H, H7), 1.51 – 1.34 (m, 4H, H5, H6), 1.15 (s, 6H, H3, H4), 0.85 (s, 9H, H11, H12, H13), 0.04 (s, 6H, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 206.2 (C1), 63.1 (C7), 45.4 (C2), 33.4 (C6), 27.6 (C5), 25.9 (C11, C12, C13), 21.2 (C3, C4), 18.3 (C10), −5.3 (C8, C9). Spectroscopic data in agreement with literature.[15]

8-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethyloct-1-yn-4-ol, 1.77

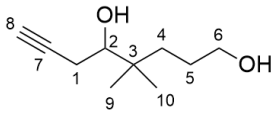


Under a nitrogen atmosphere, magnesium turnings (0.135 g, 5.60 mmol) and mercury(II) chloride (27.1 mg, 0.100 mmol) were suspended in diethyl ether (8 mL) at RT. With vigorous stirring, a solution of propargyl bromide (80 wt% in toluene, 0.260 mL, 2.40 mmol) was dropwise added. Stirring was continued for another hour after the addition; then the resulting mixture was cooled to 0 °C, and a solution of aldehyde **1.76** (0.489 g, 2.00 mmol) in ether (2 mL) was added dropwise. The mixture was warmed back to RT and stirred for another 30 min, then saturated aqueous ammonium chloride solution (20 mL) was added. The layers were separated, and the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified with silica gel chromatography (1:4 diethyl ether-pentane) to give compound **1.77** (0.475 g, 84%) as a colourless oil.

R$_f$ 0.80 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 3550 (br, w), 2959 (s), 2226 (w), 1074 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.65 – 3.55 (m, 1H, H-), 3.54 (ddd, *J* = 10.0 Hz, 3.5 Hz, 3.0

Hz, 1H), 2.43 (dt, *J* = 16.5 Hz, 3.0 Hz, 1H), 2.28 (ddd, *J* = 16.5 Hz, 10.0 Hz, 3.0 Hz, 1H), 2.15 (dd, *J* = 3.5 Hz, 1.0 Hz, 1H, OH), 2.06 (t, *J* = 3.0 Hz, 1H), 1.63 – 1.44 (m, 2H), 1.44 – 1.17 (m, 2H), 0.90 (d, *J* = 1.0 Hz, 12H), 0.87 (s, 3H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 82.6 (C2), 76.3 (C4), 70.5 (C1), 64.0 (C8), 36.9 (C5), 34.9 (C6), 27.2 (C7), 26.1 (C14, C15, C16), 22.8 (C3), 22.4 (C11, C12), 18.5 (C13), −5.1 (C11, C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{33}O_2Si$, 285.2250; found, 285.2250.

4,4-Dimethyloct-7-yne-1,5-diol, 1.78

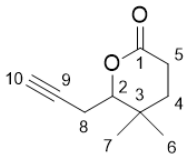


To a 50 mL round-bottom flask containing TBAF (1.0 M in THF, 1.50 mL, 1.50 mmol) at RT was dropwise added **1.77** (0.142 g, 0.500 mmol). The mixture was stirred for 16 h then quenched with water (20 mL). The layers were separated, and the aqueous layer extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 3:2) to give compound **1.78** (56.4 mg, 66%) as a yellow oil.

R_f 0.31 (ethyl acetate/pentane, 3:2); **IR** ν_{max}/cm^{-1} 3308 (br w), 2964 (s), 2119 (w), 1474 (w), 1057 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.57 – 3.51 (m, 2H, H6), 3.46 (dd, *J* = 10.0 Hz, 3.0 Hz, 1H, H2), 2.71 (br s, 1H, OH on C2), 2.57 (br s, 1H, OH on C6), 2.34 (dt, *J* = 16.5 Hz, 2.5 Hz, 1H, H1a), 2.19 (ddd, *J* = 16.5 Hz, 10.0 Hz, 2.5 Hz, 2H, H1b), 1.99 (t, *J* = 2.5 Hz, 1H, H8), 1.63 – 1.31 (m, 3H, H4a, H5), 1.23 – 1.08 (m, 1H, H4b), 0.81 (s, 3H, H9), 0.79 (s, 3H, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 82.7 (C7), 76.0 (C2), 70.3 (C8), 63.4 (C6), 36.8 (C3), 34.9

(C4), 26.8 (C5), 23.0 (C9), 22.5 (C10), 22.2 (C1); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{19}O_2$, 171.1380; found, 171.1378.

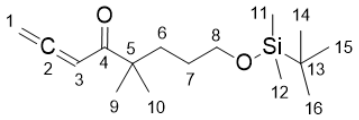
5,5-Dimethyl-6-(prop-2-yn-1-yl)tetrahydro-2*H*-pyran-2-one, 1.80



4,4-Dimethyloct-7-yne-1,5-diol (85.1 mg, 0.500 mmol) was dissolved in a mixture of DCM (1.5 mL) and water (0.5 mL) at 0 °C. TEMPO (15.6 mg, 0.100 mmol) and BAIB (0.483 g, 1.15 mmol) were added to this mixture. The mixture was stirred at RT for 16 h. Saturated aqueous sodium thiosulfate (10 mL) was used to quench this mixture, and the aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL). The extracts were combined, washed by brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:4) to yield compound **1.80** (46.4 mg, 56%) as a colourless oil.

R_f 0.21 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3248 (w), 2971 (w), 1724 (s), 1050 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.23 (ddd, *J* = 8.0 Hz, 4.5 Hz, 1.0 Hz, 1H, H2), 2.69 – 2.46 (m, 4H, H5, H8), 2.09 (td, *J* = 2.5 Hz, 1.0 Hz, 1H, H10), 1.85 – 1.65 (m, 2H, H4), 1.12 (d, *J* = 1.5 Hz, 3H, H6), 1.03 (d, *J* = 1.5 Hz, 3H, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.8 (C1), 85.3 (C2), 80.2 (C9), 70.7 (C10), 34.2 (C4), 32.2 (C3), 27.3 (C5), 26.6 (C6), 21.0 (C8), 19.5 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_2$, 167.1067; found, 167.1067.

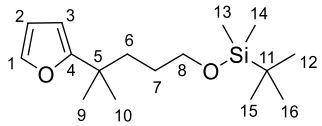
8-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethylocta-1,2-dien-4-one, 1.81



To a stirred suspension of Dess-Martin periodinane (0.255 g, 0.600 mmol) and $NaHCO_3$ (84.0 mg, 1.00 mmol) in 10 mL DCM at RT was dropwise added alcohol **1.77** (0.142 g, 0.500 mmol). The resulting mixture was stirred for 15 h before being poured into 100 mL 1:4 diethyl ether-pentane and filtered under reduced pressure. The filtrate was concentrated *in vacuo* to give an orange oil, which was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **1.81** (0.108 g, 76%) as an orange oil.

R_f 0.64 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2955 (w), 2858 (w), 1765 (s), 1683 (w), 1101 (s), 836 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.21 (t, J = 6.5 Hz, 1H, H3), 5.24 (d, J = 6.5 Hz, 2H, H1), 3.73 – 3.53 (m, 2H, H8), 1.72 – 1.54 (m, 2H, H6), 1.54 – 1.39 (m, 2H, H7), 1.22 (s, 6H, H9, H10), 0.95 (d, J = 1.0 Hz, 9H, H14, H15, H16), 0.10 (s, 6H, H11, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 215.6 (C4), 203.9 (C2), 90.9 (C3), 79.2 (C1), 63.4 (C8), 47.6 (C5), 36.4 (C7), 28.3 (C6), 26.1 (C14, C15, C16), 24.6 (C9), 24.4 (C10), 18.8 (C13), −5.2 (C11, C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{31}O_2Si$, 283.2093; found, 283.2093.

***tert*-Butyl((4-(furan-2-yl)-4-methylpentyl)oxy)dimethylsilane, 1.82**

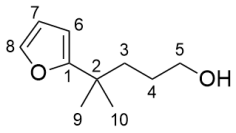


To a stirred suspension of $AgNO_3$-impregnated silica (8.53 mg, 10 wt%, 0.0502 mmol) in 5 mL DCM was added allenyl ketone **1.81** (71.0 g, 0.251 mmol). The mixture was stirred in the

dark under a nitrogen atmosphere for 3 h before being filtered with suction. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (diethyl ether/pentane, 1:19) to give compound **1.82** (45.0 g, 63%) as a pale-yellow oil.

R_f 0.89 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2956 (w), 2858 (w), 1765 (w), 1628 (w), 1099 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (dd, J = 2.0 Hz, 1.0 Hz, 1H, H1), 6.29 (dd, J = 3.0 Hz, 2.0 Hz, 1H, H3), 5.99 (dd, J = 3.0 Hz, 1.0 Hz, 1H, H2), 3.56 (t, J = 6.5 Hz, 2H, H8), 1.68 – 1.60 (m, 2H, H6), 1.44 – 1.35 (m, 2H, H7), 1.29 (s, 6H, H9, H10), 0.92 (s, 9H, H12, H15, H16), 0.06 (s, 6H, H13, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.9 (C4), 140.6 (C1), 109.6 (C3), 103.2 (C2), 63.7 (C8), 38.1 (C6), 35.5 (C5), 28.3 (C7), 26.9 (C9, C10), 26.0 (C12, C15, C16), 18.36 (C11), −5.26 (C13, C14); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{31}O_2Si$, 283.2093; found, 283.2093.

4-(Furan-2-yl)-4-methylpentan-1-ol, 1.72

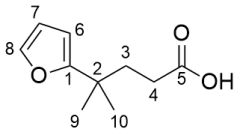


From **1.82**: Silyl ether **1.82** (96.2 mg, 0.400 mmol) was dissolved in THF (1 mL) under a nitrogen atmosphere. To this solution was added TBAF (1.0 M in THF, 0.640 mL, 0.640 mmol). The mixture was stirred for 2.5 h before being poured onto saturated ammonium chloride solution (5 mL). The two layers of liquid were separated, and the aqueous layer extracted by ethyl acetate (3 × 5 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give alcohol **1.72** (39.4 mg, 46%) as a yellow oil.

From **1.88**: Silyl ether **1.88** (0.120 g, 0.500 mmol) was dissolved in THF (1 mL) under a nitrogen atmosphere. To this solution was added TBAF (1.0 M in THF, 0.640 mL, 0.640 mmol). The mixture was stirred for 2.5 h before being poured onto saturated ammonium chloride solution (5 mL). The two layers of liquid were separated, and the aqueous layer extracted by ethyl acetate (3 × 5 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give alcohol **1.72** (66.0 mg, 77%) as a yellow oil.

R_f 0.51 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 3466 (br w), 2956 (w), 2875 (w), 1725 (s), 1460 (w), 1073 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H8), 6.31 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H6), 6.03 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H7), 3.61 (t, *J* = 6.5 Hz, 2H, H5), 1.74 – 1.66 (m, 2H, H3), 1.55 – 1.42 (m, 2H, H4), 1.33 (s, 6H, H9, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.8 (C1), 140.8 (C8), 109.8 (C6), 103.5 (C7), 63.5 (C5), 38.2 (C3), 35.6 (C2), 28.3 (C4), 26.9 (C9, C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{17}O_2$, 169.1229; found, 169.1229.

4-(Furan-2-yl)-4-methylpentanoic acid, 1.71

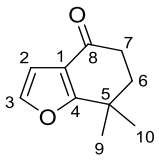


Iodobenzene diacetate (0.143 g, 0.443 mmol) and TEMPO (4.62 mg, 29.5 μmol) were dissolved in DCM (2 mL) and water (0.6 mL). To this was added a solution of **1.72** (49.7 mg, 0.295 mmol) in DCM (1 mL). The mixture was stirred at RT for 18 hours before being quenched by sat. aq. $Na_2S_2O_3$ (10 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined, dried

(Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give compound **1.71** (22.5 mg, 42%) as a yellow oil.

R_f 0.46 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 3564 (br w), 2972 (w), 1709 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H8), 6.32 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H7), 6.06 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, H6), 2.37 – 2.16 (m, 2H, H4), 2.11 – 1.96 (m, 2H, H3), 1.33 (s, 6H, H9, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.1 (C5), 161.5 (C1), 141.2 (C8), 109.9 (C7), 104.1 (C6), 36.6 (C3), 35.4 (C2), 29.9 (C4), 26.8 (C9, C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_3$, 183.1021; found, 183.1021.

7,7-Dimethyl-6,7-dihydrobenzofuran-4(5*H*)-one, 1.03

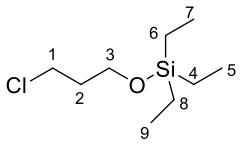


To a stirred solution of acid **1.71** (4.40 mg, 24.1 µmol) in DCM (30 mL) at 0 °C was dropwise added TFAA (6.09 mg, 29.0 µmol). Stirring was continued for 4 h at the same temperature, then the mixture was quenched with ice-cold sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted by ethyl acetate (3 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give ketone **1.03** (2.78 mg, 70%) as a yellow oil.

R_f 0.41 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2973 (m), 2933 (w), 1683 (s); **^{1}H NMR** (600 MHz, CDCl3) δ_H 7.32 (d, *J* = 2.0 Hz, 1H, H3), 6.63 (d, *J* = 2.0 Hz, 1H, H2), 2.68 – 2.53 (m, 2H, H7), 2.00 (m, 2H, H6), 1.38 (s, 6H, H9, H10); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 194.6 (C8),

172.9 (C1), 142.5 (C2), 118.8 (C4), 106.5 (C3), 37.9 (C5), 35.4 (C7), 26.3 (C6), 25.9 (C9, C10). Spectroscopic data in agreement with literature.[16]

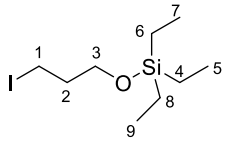
(3-Chloropropoxy)triethylsilane, 1.83



3-Chloro-1-propanol (1.66 mL, 20.0 mmol) and imidazole (4.09 g, 60.0 mmol) were dissolved in DCM (30 mL) at RT. To this solution was slowly added a solution of triethylsilyl chloride (3.92 g, 26.0 mmol) in DCM (3 mL). The mixture was stirred at RT for 2 h before being poured into 50 mL of ice-cold water. The resulting layers were separated, and the aqueous layer was extracted with ether (3 × 5 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressures. The residue was purified by silica gel chromatography (pentane) to give compound **1.83** (3.75 g, 90%) as a colourless oil.

IR ν_{max}/cm^{-1} 2960 (w), 1253 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.75 (t, J = 6.0 Hz, 2H, H1), 3.65 (t, J = 6.0 Hz, 2H, H3), 1.96 (quin, J = 6.0 Hz, 2H, H2), 0.96 (t, 9H, H5, H7, H9), 0.60 (q, 6H, H4, H6, H8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 59.2 (C3), 41.9 (C1), 35.6 (C2), 6.9 (C5, C7, C9), 4.5 (C4, C6, C8). Spectroscopic data in agreement with literature.[17]

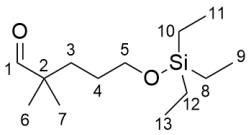
(3-Iodopropoxy)triethylsilane, 1.84



Sodium iodide (0.450 g, 3.00 mmol) was dissolved in acetone (7 mL) at RT. This was followed by the addition of **1.83** (0.209 g, 1.00 mmol). The mixture was heated to 60 °C for 15 h. After being cooled to RT, it was poured into pentane (50 mL) and filtered under reduced pressures. The filtrate was concentrated *in vacuo* to give compound **1.84** (0.216 g, 72%) as a colourless oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2962 (w), 1477 (s), 1249 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.67 (t, *J* = 6.0 Hz, 2H, H3), 3.28 (t, *J* = 6.0 Hz, 2H, H1), 2.00 (quin, *J* = 6.0 Hz, 2H, H2), 0.96 (t, *J* = 6.0 Hz, 9H, H5, H7, H9), 0.61 (q, *J* = 6.0 Hz, 6H, H4, H6, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 62.3 (C3), 36.4 (C1), 6.9 (C2), 4.5 (C5, C7, C9), 3.7 (C4, C6, C8). Spectroscopic data in agreement with literature.[17]

2,2-Dimethyl-5-((triethylsilyl)oxy)pentanal, 1.85

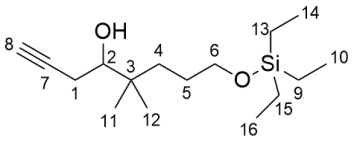


DIPA (1.10 mL, 6.00 mmol) was dissolved in THF (5 mL) at –30 °C under argon. Then *n*-butyllithium solution (3.75 mL, 1.60 M solution in hexanes, 6.00 mmol) was slowly added. The mixture was stirred for 15 min before aldehyde **1.47** (0.891 g, 7.00 mmol) was dropwise added. The mixture was warmed to 0 °C with stirring continued for another 2 h, then it was cooled to –75 °C and compound **1.84** (1.50 g, 5.79 mmol) was dropwise added. The resulting suspension was slowly warmed to RT, stirred over 15 h and was quenched with 20 mL sat. aq. NH_4Cl solution. The aqueous layer was separated and extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was

purified with silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **1.85** (0.758 g, 54%) as a colourless oil.

R_f 0.80 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2955 (w), 1731 (s), 1101 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.46 (s, 1H, H1), 3.59 (t, *J* = 6.0 Hz, 2H, H5), 1.59 – 1.41 (m, 4H, H3, H4), 1.06 (s, 6H, H6, H7), 0.96 (t, *J* = 8.0 Hz, 9H, H9, H11, H13), 0.71 – 0.56 (q, *J* = 8.0 Hz, 6H, H8, H10, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 206.4 (C1), 62.9 (C5), 45.5 (C2), 33.4 (C3), 27.7 (C4), 21.3 (C6, C7), 6.8 (C9, C11, C13), 4.4 (C8, C10, C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{29}O_2Si$, 245.1937; found, 245.1937.

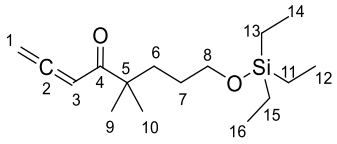
5,5-Dimethyl-8-((triethylsilyl)oxy)oct-1-yn-4-ol, 1.86



Under a nitrogen atmosphere, magnesium turnings (0.633 g, 25.9 mmol) and mercury(II) chloride (9.37 mg, 0.0345 mmol) were suspended in diethyl ether (8 mL) at RT. With vigorous stirring, a solution of propargyl bromide (80 wt% in toluene, 0.513 g, 3.45 mmol) was dropwise added. Stirring was continued for another hour after the addition; then the resulting mixture was cooled to 0 °C, and a solution of aldehyde **1.85** (0.489 g, 2.00 mmol) in ether (2 mL) was added dropwise. The mixture was warmed back to RT and stirred for another 30 min, then saturated aqueous ammonium chloride solution (20 mL) was added. The layers were separated, and the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified with silica gel chromatography (1:4 diethyl ether-pentane) to give compound **1.86** (0.375 g, 66%) as a colourless oil.

R_f 0.67 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 3541 (br, w), 2960 (s), 2224 (w), 1080 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.58 (t, *J* = 6.5 Hz, 2H, H6), 3.53 (dd, *J* = 10.0 Hz, 3.0 Hz, 1H, H2), 2.42 (dt, *J* = 16.5 Hz, 2.5 Hz, 1H, H1a), 2.27 (ddd, *J* = 16.5 Hz, 10.0 Hz, 2.5 Hz, 1H, H1b), 2.05 (dd, *J* = 3.0 Hz, 2.0 Hz, 1H, H8), 1.62 – 1.43 (m, 2H, H5), 1.38 (ddd, *J* = 13.5 Hz, 10.5 Hz, 5.5 Hz, 1H, H4a), 1.29 – 1.17 (m, 1H, H4b), 0.95 (t, *J* = 8.0 Hz, 9H, H10, H14, H16), 0.88 (d, *J* = 10.5 Hz, 6H, H11, H12), 0.60 (q, *J* = 8.0 Hz, 6H, H9, H13, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 82.5 (C7), 76.1 (C2), 70.4 (C8), 63.6 (C6), 36.8 (C3), 34.8 (C4), 27.1 (C5), 22.8 (C11, C12), 22.3 (C1), 6.8 (C10, C14, C16), 4.4 (C9, C13, C15); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{33}O_2Si$, 285.2250; found, 285.2250.

5,5-Dimethyl-8-((triethylsilyl)oxy)octa-1,2-dien-4-one, 1.87

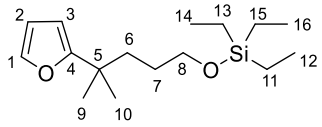


To a stirred suspension of Dess-Martin periodinane (0.255 g, 0.600 mmol) and $NaHCO_3$ (84.0 mg, 1.00 mmol) in 10 mL DCM at RT was dropwise added alcohol **1.86** (0.142 g, 0.500 mmol). The resulting mixture was stirred for 15 h before being poured into 100 mL 1:4 diethyl ether-pentane and filtered under reduced pressure. The filtrate was concentrated *in vacuo* to give an orange oil, which was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give allenyl ketone **1.87** (42.3 mg, 30%) as an orange oil.

IR ν_{max}/cm^{-1} 2958 (w), 2852 (w), 1767 (s), 1685 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.22 (t, *J* = 6.5 Hz, 1H, H3), 5.25 (d, *J* = 6.5 Hz, 2H, H1), 3.63 (td, *J* = 6.5 Hz, 3.0 Hz, 2H, H8), 1.73 – 1.58 (m, 2H, H7), 1.49 (dddd, *J* = 12.0 Hz, 10.0 Hz, 5.0 Hz, 3.0 Hz, 2H, H7), 1.23 (s, 6H, H9, H10), 1.02 (t, *J* = 8.0 Hz, 9H, H12, H14, H16), 0.65 (q, *J* = 8.0 Hz, 6H, H11, H13, H15);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 215.4 (C2), 203.8 (C4), 90.9 (C3), 79.0 (C1), 63.0 (C8), 47.5 (C5), 36.2 (C6), 28.1 (C7), 24.5 (C9, C10), 6.8 (C12, C14, C16), 4.5 (C11, C13, C15); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{31}O_2Si$, 283.2088; found, 283.2083.

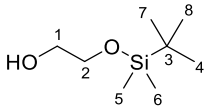
Triethyl((4-(furan-2-yl)-4-methylpentyl)oxy)silane, 1.88



To a stirred suspension of $AgNO_3$-impregnated silica (8.53 mg, 10 wt%, 0.0502 mmol) in 5 mL DCM was added allenyl ketone **1.87** (71.0 g, 0.251 mmol). The mixture was stirred in the dark under a nitrogen atmosphere for 3 h before being filtered with suction. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (diethyl ether/pentane, 1:19) to give compound **1.88** (45.7 g, 64%) as a pale-yellow oil.

R_f 0.89 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2955 (w), 1759 (w), 1628 (w), 1099 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (dt, *J* = 2.0 Hz, 1.0 Hz, 1H, H1), 6.21 (ddd, *J* = 3.0 Hz, 2.0 Hz, 1.0 Hz, 1H, H3), 5.92 (dt, *J* = 3.0 Hz, 1.0 Hz, 1H, H2), 3.50 (td, *J* = 7.0 Hz, 1.0 Hz, 2H, H8), 1.70 – 1.53 (m, 2H, H6), 1.42 – 1.31 (m, 2H, H7), 1.22 (s, 6H, H9, H10), 0.93 (t, *J* = 8.0 Hz, 9H, H12, H14, H16), 0.62 – 0.47 (m, 6H, H11, H13, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.7 (C4), 140.7 (C1), 109.7 (C3), 103.3 (C2), 63.3 (C8), 38.1 (C6), 35.5 (C5), 28.2 (C7), 26.8 (C9, C10), 6.8 (C11, C13, C15); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{31}O_2Si$, 283.2088; found, 283.2088.

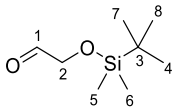
2-((*tert*-Butyldimethylsilyl)oxy)ethan-1-ol, 1.90



To a solution of ethylene glycol **1.89** (5.48 mL, 100 mmol) and imidazole (2.04 g, 30 mmol) in DCM (20 mL) at RT was added TBSCl (3.01 g, 20 mmol) dropwise. The mixture was stirred for 2 h before sat. aq. $NaHCO_3$ (10 mL) and ether (15 mL) were added. The phases were separated and the aqueous layer was extracted twice with ether (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give monosilyl ether **1.90** (3.52 g, quant.) as a colourless oil, which was used without further purification.

IR ν_{max}/cm^{-1} 3387 (br w), 1464 (s), 1390 (s), 1256 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.73 – 3.70 (m, 2H, H1), 3.66 – 3.62 (m, 2H, H2), 2.05 (t, J = 6.0 Hz, 1H, OH), 0.91 (s, 9H, H4, H7, H8), 0.08 (s, 6H, H5, H6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 64.3 (C2), 63.9 (C1), 26.1 (C4, C7, C8), 18.5 (C3), –5.1 (C5, C6). Spectroscopic data in agreement with literature.[18]

2-((*tert*-Butyldimethylsilyl)oxy)acetaldehyde, 1.91

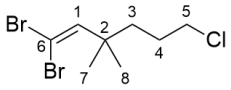


To a solution of oxalyl chloride (2.00 mL, 23.5 mmol) in DCM (30 mL) at −78 °C was added DMSO (3.30 mL, 47.0 mmol). After 30 min, a solution of compound **1.90** (3.45 g, 19.6 mmol) in DCM (10 mL) was added dropwise. After an hour, triethylamine (13.6 mL, 97.8 mmol) was added, and the stirring was continued while warming up to RT over 1 h. The mixture was

quenched upon addition of water (15 mL) and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under vacuo to give the corresponding aldehyde **1.91** (3.01 g, 88%) as a yellow oil, which was used directly without further purification.

IR ν_{max}/cm^{-1} 2917 (w), 2849 (w), 2365 (w), 1739 (s), 1267 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.70 (s, 1H, H1), 4.20 (d, 2H, *J* = 1.0 Hz, H2), 0.93 (s, 9H, H4, H7, H8), 0.11 (s, 6H, H5, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.3 (C1), 69.6 (C2), 25.7 (C4, C7, C8), 18.3 (C3), –5.4 (C5, C6). Spectroscopic data in agreement with literature.[19]

1,1-Dibromo-6-chloro-3,3-dimethylhex-1-ene, 1.98

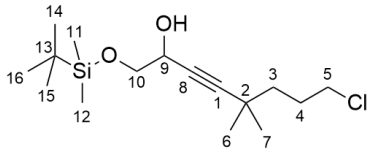


A 50 mL round-bottom flask was charged with aldehyde **1.48** (1.38 g, 9.28 mmol), triphenylphosphine (9.76 g, 37.2 mmol) and DCM (10 mL). The flask was cooled to 0 °C and with vigorous stirring, a solution of carbon tetrabromide (6.16 g, 18.6 mmol) in DCM (18 mL) was added dropwise over 5 minutes. Stirring was continued for 30 minutes, then silica gel (5 g) was added to the mixture and dichloromethane was removed by vacuum using a rotary evaporator. The residue was filtered on a pad of celite and the filtrate was concentrated under reduced pressure to give compound **1.98** (1.57 g, 59%) as a colourless oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2961 (s), 2871 (m), 1471 (w), 810 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.52 (s, 1H, H1), 3.54 (t, *J* = 6.5 Hz, 2H, H5), 1.81 – 1.71 (m, 2H, H3), 1.70 – 1.59 (m, 2H, H4), 1.19 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.7 (C1), 85.9 (C6), 45.5 (C5), 39.0 (C3),

38.7 (C2), 28.2 (C4), 27.3 (C7, C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_8H_{14}Br_2Cl$, 302.9151; not found.

1-((*tert*-Butyldimethylsilyl)oxy)-8-chloro-5,5-dimethyloct-3-yn-2-ol, 1.96

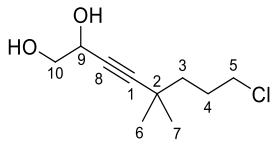


Under an argon atmosphere, compound **1.98** (0.305 g, 1.00 mmol) was dissolved in THF (4 mL). The solution was cooled to −70 °C and *n*-butyllithium (1.6 M in hexanes, 0.800 mL, 2.00 mmol) was added dropwise *via* a syringe. Stirring was continued for 30 minutes then DMPU (0.120 mL, 1.00 mmol) was added, which resulted in a white slurry. A solution of aldehyde **1.91** (0.305 g, 1.00 mmol) in THF (1 mL) was added to the mixture, then the cooling bath was removed and the mixture was stirred for another 3 hours. Saturate ammonium chloride solution (10 mL) was added, and the mixture was filtered *in vacuo*. The two layers of the filtrate were separated, and the aqueous layer extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressures. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to yield compound **1.96** (0.375 g, 40%) as a colourless oil.

R_f 0.59 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 3379 (br w), 2970 (w), 2241 (w), 1081 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.30 (ddd, J = 14.5 Hz, 7.5 Hz, 4.0 Hz, 1H, H9), 3.62 (dd, J = 10.0 Hz, 4.0 Hz, 1H, H10a), 3.55 – 3.41 (m, 3H, H5, H10b), 1.87 − 1.78 (m, 2H, H3), 1.47 – 1.36 (m, 2H, H4), 1.10 (s, 6H, H6, H7), 0.82 (s, 9H, H14, H15, H16), 0.00 (s, 6H, H11, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 92.3 (C1), 78.3 (C8), 67.3 (C10), 63.2 (C9), 45.5 (C5), 40.5

(C3), 30.7 (C2), 29.2 (C6, C7), 28.8 (C4), 25.9 (C14, C15, C16), 18.3 (C13), −5.3 (C11, C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{32}ClO_2Si$, 319.1855; found, 319.1852.

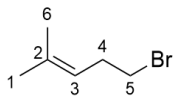
8-Chloro-5,5-dimethyloct-3-yne-1,2-diol, 1.99



Monosilyl ether **1.96** (127.4 mg, 0.400 mmol) was dissolved in THF (1 mL) under a nitrogen atmosphere. To this solution was added TBAF (1.0 M in THF, 1.20 mL, 1.20 mmol). The mixture was stirred for 2.5 h before being poured onto saturated ammonium chloride solution (10 mL). The two layers of liquid were separated, and the aqueous layer extracted by ethyl acetate (3 × 5 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 3:2) to give ynediol **1.99** (51.0 mg, 62%) as a yellow oil.

R_f 0.53 (ethyl acetate/pentane, 3:2); **IR** ν_{max}/cm^{-1} 3383 (br s), 2969 (w), 2239 (w), 1080 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.37 (dd, *J* = 7.5 Hz, 3.5 Hz, 1H, H9), 3.62 (dd, *J* = 11.5 Hz, 3.5 Hz, 1H, H10a), 3.55 (d, *J* = 7.5 Hz, 1H, H10b), 3.50 (t, *J* = 6.5 Hz, 2H, H5), 1.92 – 1.78 (m, 2H, H3), 1.52 – 1.40 (m, 2H, H4), 1.14 (s, 6H, H6, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 93.3 (C8), 77.9 (C1), 66.9 (C9), 63.3 (C10), 45.4 (C5), 40.4 (C4), 30.8 (C2), 29.1 (C3), 28.8 (C6, C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{18}ClO_2$, 205.0995; found, 205.0995.

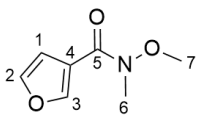
5-Bromo-2-methylpent-2-ene, 1.102



To a 0 °C solution of methyl magnesium bromide (11.0 mL, 3.0 M, 33.0 mmol) in diethyl ether (15 mL) under N_2 was slowly added cyclopropyl methyl ketone **1.100** (2.97 mL, 30.0 mmol). The resulting mixture was added to a pre-cooled (0 °C) aqueous solution of H_2SO_4 (33%, 60 mL) at a steady rate whilst keeping the temperature below 10 °C. Stirring was continued for another 30 min while the mixture was allowed to warm to RT. The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined ethereal phase was washed with sat. aq. $NaHCO_3$ (20 mL) followed by brine (20 mL), dried over $MgSO_4$, and filtered, and concentrated under reduced pressure to a colourless liquid. The crude product was purified by silica gel chromatography (pentane) to give compound **1.102** (3.96 g, 81%) as a colourless oil.

R_f 0.82 (pentane); **IR** ν_{max}/cm^{-1} 2968 (w), 2916 (w), 1439 (s), 1375 (s), 1268 (s), 831 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.13 (ddquin, J = 8.5 Hz, 6.0 Hz, 1.5 Hz, 1H, H3), 3.34 (t, J = 7.5 Hz, 2H, H5), 2.56 (q, J = 7.0 Hz, 2H, H4), 1.72 (m, 3H, H1), 1.63 (m, 3H, H6); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 135.2 (C2), 121.1 (C3), 33.0 (C5), 32.0 (C4), 25.8 (C1), 18.1 (C6). Spectroscopic data in agreement with literature.[20]

***N*-Methoxy-*N*-methylfuran-3-carboxamide, 1.104**

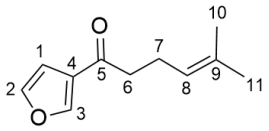


Method 1 (from **1.103**): To a solution of 3-furoic acid **1.103** (2.24 g, 20.0 mmol) in THF (25 mL) under N_2 was added oxalyl chloride (1.88 mL, 22.0 mmol) dropwise. After the addition the mixture was heated under reflux for another 30 min with vigorous stirring. Then it was allowed to cool to RT, and *N*-methoxy-*N*-methylhydroxylamine hydrochloride (2.34 g, 24.0 mmol) was added, followed dropwise by NEt_3 (8.36 mL, 30.0 mmol). The mixture was stirred for another 30 min before diluted by ethyl acetate (20 mL) and water (30 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 15 mL), and the combined organic phase was washed by brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give Weinreb amide **1.104** (3.10 g, quant.) as a white crystalline solid.

Method 2 (from **4.05**): Ketone **4.05** (3.20 g, 15 mmol) was added into a suspension of *N*-methoxy-*N*-methylhydroxylamine hydrochloride (1.95 g, 20.0 mmol) in acetonitrile (10 mL) at RT. To this was dropwise added triethylamine (5.58 g, 40.0 mmol). The reaction mixture was heated to reflux for 16 h, then cooled and diluted with water (15 mL) and ethyl acetate (15 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 15 mL), and the combined organic phase was washed by brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give Weinreb amide **1.104** (1.24 g, 40%) as a white crystalline solid.

R_f 0.44 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 3099 (w), 1620 (s), 1570 (s), 1340 (s), 1155 (s), 875 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.01 (dd, J = 1.5 Hz, 1.0 Hz, 1H, H3), 7.42 – 7.38 (m, 1H, H2), 6.88 – 6.82 (m, 1H, H1), 3.69 (s, 3H, H7), 3.31 (s, 3H, H6); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 163.0 (C5), 146.4 (C3), 142.5 (C2), 119.6 (C4), 111.2 (C1), 61.0 (C7), 32.6 (C6); **mp** 34−36 °C. Spectroscopic data in agreement with literature.[21]

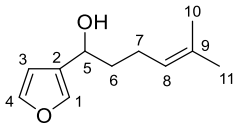
1-(Furan-3-yl)-5-methylhex-4-en-1-one, 1.105



To a suspension of magnesium turnings (0.758 g, 31.2 mmol) in diethyl ether (3 mL) was added iodine (0.127 g, 0.500 mmol). The mixture was heated and stirred gently until the brown colour disappeared. A solution of bromide **1.102** (2.30 mL, 17.1 mmol) in diethyl ether (15 mL) was then added dropwise to the suspension with vigorous stirring. The resulting mixture was heated to a gentle reflux for another 1 h before being cooled to 0 °C, and a solution of Weinreb amide **1.104** (2.42 g, 15.6 mmol) in diethyl ether (3 mL) was slowly added. Afterwards, the mixture was quenched by 1.0 M HCl (5 mL) and diluted by water (20 mL). The resulting two liquid phases were separated, and the aqueous phase was extracted by diethyl ether (3 × 20 mL). The combined ethereal phase was washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a yellow oil. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 4:1) to give compound **1.105** (1.77 g, 65%) as a colourless oil.

R_f 0.87 (pentane/diethyl ether, 3:1); **IR** ν_{max}/cm^{-1} 3130 (w), 2967 (w), 1673 (s), 1563 (s), 1510 (s), 1154 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.01 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H3), 7.43 (m, 1H, H2), 6.77 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H1), 5.13 (tdt, *J* = 7.0 Hz, 3.0 Hz, 1.5 Hz, 1H, H8), 2.76 (dd, *J* = 8.0 Hz, 7.0 Hz, 2H, H6), 2.39 (m, 2H, H7), 1.68 (q, *J* = 1.5 Hz, 3H, H11), 1.63 (d, *J* = 1.5 Hz, 3H, H10); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 194.9 (C5), 147.2 (C3), 144.2 (C2), 133.0 (C9), 127.9 (C4), 122.8 (C8), 108.8 (C1), 40.7 (C6), 25.8 (C7), 23.0 (C11), 17.8 (C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{15}O_2$, 179.1067; found, 179.1066. Spectroscopic data in agreement with literature.[22]

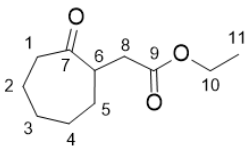
1-(Furan-3-yl)-5-methylhex-4-en-1-ol, 1.106



Sodium borohydride (30.3 mg, 0.800 mmol) was added in methanol (1 mL) at 0 °C under nitrogen. Then, ketone **1.105** (89.1 mg, 0.500 mmol) was dropwise added. Stirring was continued at 0 °C for 90 minutes, after which the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined ethereal phase was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give alcohol **1.106** (61.0 mg, 68%) as a colourless oil, which was used without further purification.

R_f 0.42 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 3374 (br w), 2924 (w), 1449 (s), 1161 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56 – 7.41 (m, 2H, H1, H4), 6.47 (d, *J* = 1.5 Hz, 1H, H3), 5.21 (ddq, *J* = 7.5 Hz, 4.0 Hz, 1.5 Hz, 1H, H8), 4.73 (t, *J* = 6.5 Hz, 1H, H5), 2.26 – 2.07 (m, 2H, H7), 1.99 – 1.81 (m, 2H, H6), 1.77 (s, 3H, H10), 1.67 (s, 3H, H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 142.3 (C4), 139.2 (C1), 130.1 (C9), 129.4 (C2), 124.5 (C8), 108.3 (C3), 68.0 (C5), 36.1 (C6), 24.9 (C7), 23.7 (C10), 20.6 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_2$, 181.1229; found, 181.1229.

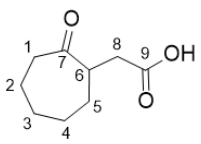
Ethyl 2-(2-oxocycloheptyl)acetate, 1.111



DIPA (0.630 mL, 4.50 mmol) was dissolved in THF (5 mL) at –40 °C under argon. After 5 min of stirring, *n*-butyllithium solution (2.63 mL, 1.60 M solution in hexanes, 4.20 mmol) was slowly added. The mixture was stirred for 15 min before cycloheptanone (0.360 mL, 3.00 mmol) was dropwise added. The mixture was warmed to 0 °C with stirring continued for another 2 h, then it was cooled to –75 °C and ethyl bromoacetate (0.330 mL, 3.00 mmol) was dropwise added. The resulting suspension was slowly warmed to RT, stirred over 15 h and was quenched with 20 mL saturated ammonium chloride solution. The aqueous layer was separated and extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **1.111** (0.525 g, 88%) as a colourless oil, which was used without further purification.

R_f 0.58 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2827 (w), 1800 (s), 1705 (s), 1185 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.12 (q, *J* = 7.0 Hz, 2H, H10), 3.10 (dtd, *J* = 11.0 Hz, 6.0 Hz, 3.0 Hz, 1H, H6), 2.80 (dd, *J* = 16.5 Hz, 8.5 Hz, 1H, H8a), 2.64 (m, 1H, H1a), 2.49 – 2.45 (m, 2H, H1b), 2.29 (dd, *J* = 16.5 Hz, 6.0 Hz, 1H, H8b), 1.93 – 1.58 (m, 4H, H2, H5), 1.57 – 1.38 (m, 2H, H4), 1.37 – 1.27 (m, 2H, H3), 1.24 (t, *J* = 7.0 Hz, 3H, H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 214.2 (C7), 172.5 (C9), 60.4 (C10), 47.4 (C6), 43.3 (C1), 36.7 (C8), 31.2 (C5), 29.3 (C3), 28.9 (C4), 23.5 (C2), 14.1 (C11). Spectroscopic data in agreement with literature.[23]

2-(2-Oxocycloheptyl)acetic acid, 1.112

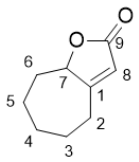


Sodium hydroxide pellets (0.300 g, 7.50 mmol) were ground into a powder using a mortar and pestle and then dissolved in methanol-water (1:2 v/v, 6 mL). To the resulting solution, **1.111**

(0.175 g, 0.898 mmol) was slowly added. The mixture was heated to 50 °C and stirred for 20 h under a nitrogen atmosphere. Hydrochloric acid (3 M) was used to acidify the mixture until the aqueous pH reached 4. Subsequently, the mixture was extracted by ethyl acetate (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 3:2) to give compound **1.112** (0.515 g, 73%) as a viscous orange oil.

R_f 0.32 (ethyl acetate/pentane, 1:1); **IR** ν_{max}/cm^{-1} 3642 (br w), 3095 (s), 1699 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.33 (br s, 1H, OH), 3.12 – 3.04 (m, 1H, H6), 2.85 (dd, *J* = 17.0 Hz, 8.5 Hz, 1H, H8a), 2.63 (dt, *J* = 9.0 Hz, 4.0 Hz, 1H, H1a), 2.50 – 2.40 (m, 1H, H1b), 2.34 (dd, *J* = 17.0 Hz, 6.5 Hz, 1H, H8b), 1.96 – 1.68 (m, 5H, H2, H4, H5a), 1.62 – 1.50 (m, 1H, H5b), 1.44 – 1.23 (m, 2H, H3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 214.3 (C7), 178.4 (C9), 47.2 (C6), 43.3 (C1), 36.4 (C8), 31.1 (C5), 29.3 (C3), 29.0 (C4), 23.4 (C2). Spectroscopic data in agreement with literature.[24]

4,5,6,7,8,8a-Hexahydro-2*H*-cyclohepta[*b*]furan-2-one, 1.113

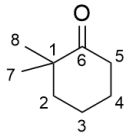


To a 50 mL round-bottom flask was charged *p*-toluenesulfonic acid monohydrate (0.283 g, 1.50 mmol) and acetic anhydride (3 mL). Then keto acid **1.112** (0.340 g, 2.00 mmol) was dropwise added. This mixture was heated to 60 °C for 15 min then cooled to 55 °C and stirred for 10 h. It was quenched at RT by saturated $NaHCO_3$ solution (20 mL). The two layers of liquid were separated, and the aqueous layer extracted by diethyl ether (3 × 10 mL). The

extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give lactone **1.113** (0.116 g, 38%) as a yellow oil.

R_f 0.23 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2937 (s), 2856 (s), 1756 (s), 1011 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.82 (q, *J* = 1.5 Hz, 1H, H8), 5.00 (ddt, *J* = 8.5 Hz, 4.0 Hz, 1.5 Hz, 1H, H7), 2.85 – 2.68 (m, 2H, H2), 2.42 – 2.33 (m, 1H, H1a), 1.96 – 1.80 (m, 3H, H2, H3a), 1.68 – 1.38 (m, 3H, H1b, H5), 1.35 – 1.14 (m, 1H, H3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.0 (C9), 173.5 (C1), 115.6 (C8), 85.1 (C7), 33.3 (C6), 29.6 (C3), 28.6 (C2), 26.0 (C4), 25.7 (C5). Spectroscopic data in agreement with literature.[25]

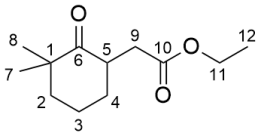
2,2-Dimethylcyclohexan-1-one, 1.115



Sodium hydride (43% suspension in mineral oil, 2.19 g, 39.2 mmol) was suspended in 20 mL THF at RT under an argon atmosphere. To this was slowly added cyclohexanone (1.47 g, 15.0 mmol), and the mixture was heated to 60 °C for 90 minutes. Afterwards, the reaction mixture was cooled to 0 °C and dimethyl sulfate (4.94 g, 39.2 mmol) was dropwise added. The cooling bath was removed, and stirring was continued for another 16 hours. The mixture was quenched by sat. aq. $NaHCO_3$ (15 mL) and extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane) to give compound **1.115** (1.38 g, 73%) as a colourless oil.

R$_f$ 0.85 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2931 (s), 1713 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.55 – 2.49 (m, 2H, H5), 2.01 – 1.92 (m, 2H, H2), 1.90 – 1.83 (m, 2H, H4), 1.81 – 1.76 (m, 2H, H3), 1.24 (s, 6H, H7, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 216.4 (C6), 45.4 (C1), 41.3 (C2), 38.5 (C5), 27.8 (C4), 25.4 (C7, C8), 21.6 (C3). Spectroscopic data in agreement with literature.[26]

Ethyl 2-(3,3-dimethyl-2-oxocyclohexyl)acetate, 1.116

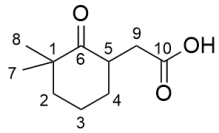


DIPA (1.96 mL, 4.50 mmol) was dissolved in THF (8 mL) at –40 °C under argon. After 5 min of stirring, *n*-butyllithium solution (7.50 mL, 1.60 M solution in hexanes, 12.0 mmol) was slowly added. The mixture was stirred for 15 min before HMPA (1.79 g, 10.0 mmol) was dropwise added, followed by ketone **1.115** (1.26 g, 10.0 mmol). The mixture was warmed to 0 °C with stirring continued for another 2 h, then it was cooled to –75 °C and ethyl bromoacetate (0.330 mL, 3.00 mmol) was dropwise added. The resulting suspension was slowly warmed to RT, stirred over 15 h and was quenched with 20 mL saturated ammonium chloride solution. The aqueous layer was separated and extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **1.116** (0.728 g, 34%) as a colourless oil, which was used without further purification.

R$_f$ 0.61 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2977 (s), 1736 (s), 1708 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.21 (q, *J* = 7.5 Hz, 2H, H11), 3.23 (ddt, *J* = 13.0 Hz, 7.5 Hz, 6.0 Hz, 1H, H5), 2.81 (dd, *J* = 16.5 Hz, 7.5 Hz, 1H, H9a), 2.21 (dd, *J* = 16.5 Hz, 6.0 Hz, 1H, H9b), 2.05 – 1.96 (m, 1H, H4a), 1.93 – 1.81 (m, 1H, H3a), 1.82 – 1.73 (m, 1H, H2a), 1.64 (td, *J* = 13.0 Hz,

4.0 Hz, 1H, H4b), 1.47 (td, *J* = 13.0 Hz, 3.9 Hz, 1H, H3b), 1.35 (t, *J* = 7.0 Hz, 3H, H12), 1.32 (s, 3H, H6, H7), 1.31 – 1.19 (m, 1H, H2b), 1.14 (s, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 215.2 (C6), 172.8 (C10), 60.4 (C11), 45.3 (C1), 42.9 (C5), 41.7 (C2), 34.8 (C9), 34.3 (C4), 25.5 (C7), 25.0 (C8), 21.4 (C3), 14.2 (C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{21}O_3$, 213.1491; found, 213.1491.

2-(3,3-Dimethyl-2-oxocyclohexyl)acetic acid, 1.117

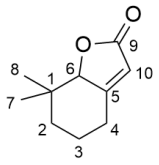


Sodium hydroxide pellets (0.360 g, 9.00 mmol) were ground into a powder using a mortar and pestle and then dissolved in methanol-water (1:2 v/v, 6 mL). To the resulting solution, keto ester **1.116** (0.637 g, 3.00 mmol) was slowly added. The mixture was heated to 60 °C and stirred for 22 h under a nitrogen atmosphere. Hydrochloric acid (1 M) was used to acidify the mixture until the aqueous pH reached 3−4. Subsequently, the mixture was extracted by ethyl acetate (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **1.117** (0.474 g, 86%) as a viscous orange oil, which was used without further purification.

R_f 0.34 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3673 (br w), 2934 (s), 1706 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.19 (ddt, *J* = 13.5 Hz, 7.5 Hz, 5.5 Hz, 1H, H5), 2.85 (dd, *J* = 16.5 Hz, 7.5 Hz, 1H, H9a), 2.27 (dd, *J* = 16.5 Hz, 5.5 Hz, 1H, H9b), 2.20 (dddd, *J* = 12.5 Hz, 6.5 Hz, 3.5 Hz, 2.0 Hz, 1H, H4a, H3a), 1.98 (tt, *J* = 13.5 Hz, 4.0 Hz, 1H, H3a), 1.80 (ddt, *J* = 13.5 H\, 4.0 Hz, 3.0 Hz, 1H, H2a), 1.69 (dtt, *J* = 13.5 Hz, 4.0 Hz, 2.8 Hz, 1H, H4b), 1.56 (td, *J* = 13.5 Hz, 4.0 Hz, 1H, H3b), 1.40 (td, *J* = 13.5 Hz, 4.0 Hz, 1H, H2b), 1.22 (s, 3H, H7), 1.06 (s, 3H,

H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 215.3 (C6), 177.5 (C10), 45.3 (C1), 42.8 (C5), 41.6 (C2), 34.6 (C9), 34.3 (C4), 25.4 (C7), 24.9 (C8), 21.3 (C3); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{17}O_3$, 185.1178; found, 185.1178.

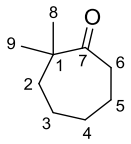
7,7-Dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, 1.118



Under a nitrogen atmosphere, PTSA (0.114 g, 0.600 mmol) was mixed with acetic anhydride (2.5 mL). Then acid **1.117** (0.369 g, 2.00 mmol) was dropwise added. This mixture was heated to 60 °C for 15 min then cooled to 50 °C and stirred for 24 h. It was quenched at RT by saturated aqueous $NaHCO_3$ solution (20 mL) with vigorous stirring. The two layers of liquid were separated, and the aqueous layer extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give compound **1.118** (0.267 g, 80%) as a yellow oil.

R$_f$ 0.57 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 2941 (s), 1754 (s), 1656 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.72 (t, *J* = 2.0 Hz, 1H, H10), 4.46 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H6), 2.79 (ddt, *J* = 14.0 Hz, 4.0 Hz, 2.0 Hz, 1H, H4a), 2.31 – 2.16 (m, 1H, H4b), 1.87 – 1.75 (m, 1H, H2a), 1.72 – 1.53 (m, 3H, H2b, H3), 1.21 (s, 3H, H7), 0.71 (s, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.9 (C9), 169.7 (C5), 113.3 (C10), 88.9 (C6), 38.6 (C1), 37.1 (C2), 29.0 (C7), 27.6 (C4), 21.8 (C3), 16.8 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_2$, 167.1067; found, 167.1065.

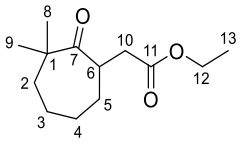
2,2-Dimethylcycloheptan-1-one, 1.119



Sodium hydride (43% suspension in mineral oil, 2.19 g, 39.2 mmol) was suspended in 20 mL THF at RT under an argon atmosphere. To this was slowly added cycloheptanone (1.68 mL, 15.0 mmol), and the mixture was heated to 60 °C for 90 minutes. Afterwards, the reaction mixture was cooled to 0 °C and dimethyl sulfate (4.94 g, 39.2 mmol) was dropwise added. The cooling bath was removed, and stirring was continued for another 16 hours. The mixture was quenched by sat. aq. $NaHCO_3$ (15 mL) and extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (100% pentane) to give compound **1.119** (1.87 g, 89%) as a colourless oil.

R_f 0.88 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2931 (s), 1717 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.45 (2H, m, H6), 1.60 – 1.53 (6H, m, H2, H4, H5), 1.41 (2H, m, H3), 1.00 (6H, s, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 218.1 (C7), 47.4 (C1), 39.9 (C6), 39.2 (C2), 30.5 (C4), 26.4 (C5), 25.7 (C8, C9), 24.8 (C3). Spectroscopic data in agreement with literature.[27]

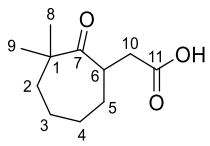
Ethyl 2-(3,3-dimethyl-2-oxocycloheptyl)acetate, 1.120



DIPA (1.96 mL, 4.50 mmol) was dissolved in THF (8 mL) at –40 °C under argon. After 5 min of stirring, *n*-butyllithium solution (7.50 mL, 1.60 M solution in hexanes, 12.0 mmol) was slowly added. The mixture was stirred for 15 min before HMPA (1.79 g, 10.0 mmol) was dropwise added, followed by **1.119** (1.40 g, 10.0 mmol). The mixture was warmed to 0 °C with stirring continued for another 2 h, then it was cooled to –78 °C and ethyl bromoacetate (0.330 mL, 3.00 mmol) was dropwise added. The resulting suspension was slowly warmed to RT, stirred over 15 h and was quenched with 20 mL saturated ammonium chloride solution. The aqueous layer was separated and extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **1.120** (0.520 g, 23%) as a colourless oil, which was used without further purification.

R_f 0.64 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2930 (s), 1737 (s), 1703 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.07 (q, *J* = 7.0 Hz, 2H, H12), 3.33 (dddd, *J* = 12.0 Hz, 9.5 Hz, 5.0 Hz, 2.5 Hz, 1H, H6), 2.85 (dd, *J* = 17.0 Hz, 9.5 Hz, 1H, H10a), 2.25 (dd, *J* = 17.0 Hz, 5.0 Hz, 1H, H10b), 1.86 – 1.52 (m, 4H, H2, H3, H4, H5), 1.22 (t, *J* = 7.2 Hz, 3H, H13), 1.14 (s, 3H, H8), 1.10 (s, 3H, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 217.8 (C7), 172.4 (C11), 60.4 (C12), 47.7 (C1), 43.8 (C6), 38.8 (C9), 37.3 (C10), 33.2 (C5), 29.9 (C4), 28.4 (C8), 24.4 (C3), 23.5 (C9), 14.2 (C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{23}O_3$, 227.1647; found, 227.1647.

2-(3,3-Dimethyl-2-oxocycloheptyl)acetic acid, 1.121

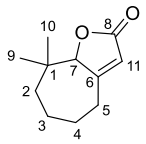


Sodium hydroxide pellets (0.360 g, 9.00 mmol) were ground into a powder using a mortar and pestle and then dissolved in methanol-water (1:2 v/v, 6 mL). To the resulting solution, ester

1.120 (0.678 g, 3.00 mmol) was slowly added. The mixture was heated to 60 °C and stirred for 22 h under a nitrogen atmosphere. Hydrochloric acid (1 M) was used to acidify the mixture until the aqueous pH reached 3−4. Subsequently, the mixture was extracted by ethyl acetate (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **1.121** (0.583 g, 98%) as a viscous orange oil, which was used without further purification.

R_f 0.34 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3546 (br w), 2930 (s), 1704 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.31 (dddd, *J* = 12.0 Hz, 9.5 Hz, 5.0 Hz, 2.5 Hz, 1H, H6), 2.89 (dd, *J* = 17.0 Hz, 9.5 Hz, 1H, H10a), 2.32 (dd, *J* = 17.0 Hz, 5.0 Hz, 1H, H10b), 1.92 – 1.59 (m, 4H, H2, H3, H4, H5), 1.11 (d, *J* = 1.0 Hz, 6H, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 217.9 (C7), 177.8 (C11), 47.7 (C1), 43.7 (C6), 38.8 (C9), 37.0 (C10), 33.0 (C5), 29.8 (C4), 28.3 (C8), 24.4 (C3), 23.5 (C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{19}O_3$, 199.1334; found, 199.1334.

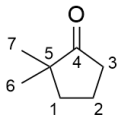
8,8-Dimethyl-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one, 1.122



Under a nitrogen atmosphere, PTSA (0.114 g, 0.600 mmol) was mixed with acetic anhydride (2.5 mL). Then acid **1.121** (0.396 g, 2.00 mmol) was dropwise added. This mixture was heated to 60 °C for 15 min then cooled to 50 °C and stirred for 24 h. It was quenched at RT by saturated aqueous $NaHCO_3$ solution (20 mL) with vigorous stirring. The two layers of liquid were separated, and the aqueous layer extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give compound **1.122** (0.252 g, 70%) as a yellow oil.

R_f 0.62 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 2940 (s), 1756 (s), 1658 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.80 (q, *J* = 2.0 Hz, 1H, H11), 4.77 (t, *J* = 2.0 Hz, 1H, H7), 3.00 – 2.88 (m, 1H, H5a), 2.57 (dddt, *J* = 19.5 Hz, 12.5 Hz, 3.5 Hz, 2.0 Hz, 1H, H5b), 1.94 – 1.79 (m, 2H, H2), 1.59 – 1.33 (m, 4H, H3, H4), 1.20 (d, *J* = 1.5 Hz, 3H, H9), 0.72 (d, *J* = 1.5 Hz, 3H, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 182.0 (C8), 170.6 (C6), 116.9 (C11), 91.1 (C7), 42.8 (C2), 38.5 (C1), 29.7 (C5), 29.1 (C4), 25.5 (C9), 22.2 (C3), 18.1 (C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_2$, 181.1229; found, 181.1228.

2,2-Cyclopentan-1-one, 1.124

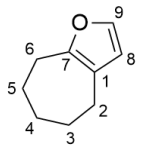


Sodium hydride (43% suspension in mineral oil, 3.30 g, 60.0 mmol) was suspended in 20 mL THF at RT under an argon atmosphere. To this was slowly added cyclopentanone (2.10 g, 25.0 mmol), and the mixture was heated to 60 °C for 90 minutes. Afterwards, the reaction mixture was cooled to 0 °C and dimethyl sulfate (7.57 g, 60.0 mmol) was dropwise added. The cooling bath was removed, and stirring was continued for another 22 hours. The mixture was quenched by sat. aq. NH_4Cl (15 mL) and extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (100% pentane) to give compound **1.124** (2.50 g, 89%) as a colourless oil.

R_f 0.93 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2934 (s), 1718 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.26 (t, *J* = 7.5 Hz, 2H, H3), 1.80 (t, *J* = 6.5 Hz, 2H, H1), 1.50 (quin, *J* = 7.5 Hz,

2H, H2), 1.04 (s, 6H, H6, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 123.8 (C4), 44.9 (C5), 38.5 (C3), 37.1 (C2), 23.8 (C1), 18.7 (C6, C7). Spectroscopic data in agreement with literature.[28]

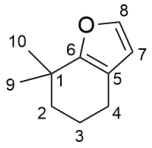
5,6,7,8-Tetrahydro-4*H*-cyclohepta[*b*]furan, 1.128



To a 50 mL round-bottom flask was charged lactone **1.113** (0.163 g, 1.07 mmol) and THF (1.5 mL). The resulting solution was cooled to −78 °C and diisobutylammonium hydride (1.2 M in toluene, 1.34 mL, 1.60 mmol). The mixture was warmed to 0 °C over 15 minutes and stirred for 2.5 hours. It was quenched by 15 mL saturated Rochelle's salt solution. The two layers of liquid were separated, and the aqueous layer extracted by diethyl ether (3 × 5 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give furan derivative **1.128** (0.205 g, 75%) as a yellow oil.

R_f 0.90 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2927 (s), 2853 (s), 1446 (s), 1006 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 (d, J = 2.0 Hz, 1H, H9), 6.13 (d, J = 2.0 Hz, 1H, H8), 2.79 – 2.71 (m, 2H, H2), 2.50 – 2.43 (m, 2H, H6), 1.76 (m, 2H, H5), 1.73 – 1.62 (m, 4H, H3, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.3 (C7), 138.4 (C9), 120.5 (C1), 113.1 (C8), 30.8 (C2), 28.9 (C4), 28.7 (C6), 26.6 (C3), 26.1 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}O$, 137.0961; found, 137.0961.

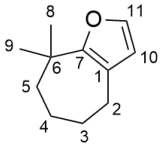
7,7-Dimethyl-4,5,6,7-tetrahydrobenzofuran, 1.130



Butenolide **1.118** (0.267 g, 1.61 mmol) was dissolved in THF (2 mL) under nitrogen. The solution was cooled to −78 °C and DIBAL (1.2 M in hexanes, 1.31 mL, 1.57 mmol) was dropwise added. This mixture was then warmed to 0 °C over 10 minutes and stirring was continued for an hour. An aqueous solution prepared beforehand by mixing 1M NaOH (10 mL) and saturated Rochelle's salt (10 mL) was used to quench the reaction mixture at 0 °C. The two layers of liquid were separated, and the aqueous layer extracted by diethyl ether (3 × 5 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:9) to give furan **1.130** (0.118 g, 50%) as a yellow oil.

R_f 0.87 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2934 (s), 2853 (m), 1503 (s), 1457 (s), 1160 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 (d, J = 2.0 Hz, 1H, H8), 6.11 (d, J = 2.0 Hz, 1H, H7), 2.51 – 2.37 (m, 2H, H4), 1.83 – 1.76 (m, 2H, H2), 1.75 – 1.59 (m, 2H, H3), 1.25 (s, 6H, H9, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.6 (C6), 140.0 (C8), 115.0 (C5), 110.1 (C7), 39.4 (C2), 39.4 (C1), 30.3 (C9), 27.7 (C10), 22.7 (C4), 20.5 (C3). Spectroscopic data in agreement with literature.[16]

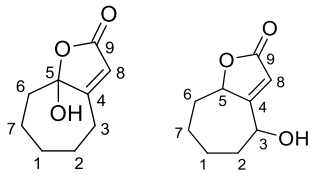
8,8-Dimethyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan, 1.131



A 50 mL round-bottom flask was charged with butenolide **1.122** (87.5 mg, 0.485 mmol) and THF (1.5 mL). The resulting solution was cooled to −78 °C and DIBAL (1.2 M in toluene, 0.648 mL, 0.777 mmol). The mixture was warmed to 0 °C over 15 minutes and stirred for 2.5 hours. It was quenched by 15 mL saturated Rochelle's salt solution. The two layers of liquid were separated, and the aqueous layer extracted by diethyl ether (3 × 5 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give compound **1.131** (64.3 g, 75%) as a yellow oil.

R_f 0.90 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2923 (s), 1454 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.13 (d, *J* = 1.5 Hz, 1H, H11), 6.08 (d, *J* = 1.5 Hz, 1H, H10), 2.52 – 2.44 (m, 2H, H2), 1.80 (m, 1H, H5a), 1.75 – 1.66 (m, 1H, H5b), 1.65 – 1.45 (m, 2H, H3), 1.25 (s, 6H, H8, H9), 1.04 (m, 2H, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.9 (C7), 138.2 (C11), 121.0 (C1), 113.2 (C10), 41.7 (C5), 41.6 (C6), 29.4 (C2), 28.0 (C3), 27.7 (C8, C9), 22.5 (C4); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O$, 165.1279; found, 165.1280.

8a-Hydroxy-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one, 1.132; 4-Hydroxy-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one, 1.133



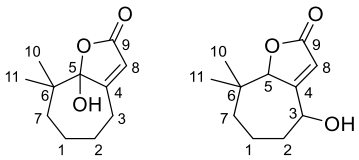
To a conical flask 200 mM phosphate buffer (pH 7.9, 174.51 mL) were added a solution of butenolide **1.114** (30.7 mg in 0.5 mL MeOH, 0.203 mmol), glucose (20.3 mL of a 1.0 M solution in phosphate buffer, pH 7.9, 20.3 mmol), GDH (2.03 mL of a 2.0 U/μL solution in

phosphate buffer, pH 7.9) and $NADP^+$ monosodium salt (2.03 mL of a 4.0 mM solution in water), followed by $P450_{BM3}$ enzyme variant RKA/S72W (6.37 mL of a 63.7 μM solution in phosphate buffer, pH 7.9). The mixture was swirled under air for 48.5 h. After this time, it was split into six ~34 mL portions; ethyl acetate (10 mL) was added to each portion, and the mixture was centrifuged at 13,300 *g* for 3 min. The layers were separated and the aqueous phases in each portion was re-extracted twice with ethyl acetate through the same procedure. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:1) to give γ-hydroxy butenolide **1.132** (2.75 mg, 8%) as a white foam and alcohol **1.133** (4.03 mg, 12%) as a pale-yellow foam.

Data for **1.132**: **R_f** 0.71 (ethyl acetate/pentane, 2:1); **IR** ν_{max}/cm^{-1} 3366 (br w), 2933 (s), 1752 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.78 – 5.43 (m, 1H, H8), 3.42 (s, 1H, OH), 2.71 – 2.49 (m, 2H, H3), 2.32 – 2.13 (m, 2H, H6), 1.88 – 1.61 (m, 2H, H2), 1.64 – 1.41 (m, 4H, H1, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.9 (C9), 164.8 (C4), 117.1 (C8), 115.7 (C5), 37.7 (C6), 28.7 (C1), 27.4 (C2), 25.6 (C3), 23.6 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}O_3$, 169.0865; found, 169.0865.

Data for **1.133**: **R_f** 0.48 (ethyl acetate/pentane, 2:1); **IR** ν_{max}/cm^{-1} 3437 (br w), 2933 (s), 1741 (s); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.98 (t, J = 2.0 Hz, 1H, H8), 5.20 (ddd, J = 7.0 Hz, 5.0 Hz, 2.0 Hz, 1H, H5), 4.90 (dd, J = 8.5 Hz, 3.0 Hz, 1H, H3), 2.29 – 1.90 (m, 4H, H2, H6), 1.87 – 1.43 (m, 4H, H1, H7); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 174.9 (C9), 173.1 (C4), 116.8 (C8), 83.3 (C5), 68.7 (C3), 36.3 (C2), 32.1 (C6), 24.6 (C1), 24.2 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}O_3$, 169.0865; found, 169.0864.

8a-Hydroxy-8,8-dimethyl-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one, 1.134; 4-Hydroxy-8,8-dimethyl-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one, 1.135



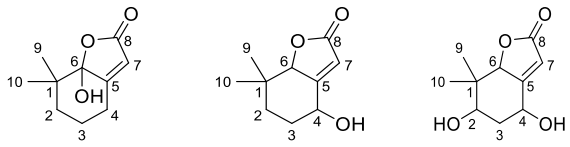
To a conical flask 200 mM phosphate buffer (pH 7.9, 174.73 mL) were added a solution of butenolide **1.122** (36.6 mg in 0.5 mL MeOH, 0.203 mmol), glucose (20.3 mL of a 1.0 M solution in phosphate buffer, pH 7.9, 20.3 mmol), GDH (2.03 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.9) and $NADP^+$ monosodium salt (2.03 mL of a 4.0 mM solution in water), followed by $P450_{BM3}$ enzyme variant RK/A184I/T260G/A328G (4.90 mL of a 139 μM solution in phosphate buffer, pH 7.9). The reaction mixture was swirled under air for 22.5 h. After this time, it was split into six ~34 mL portions; ethyl acetate (10 mL) was added to each portion, and the mixture was centrifuged at 13,300 *g* for 3 min. The layers were separated and the aqueous phases in each portion was re-extracted twice with ethyl acetate through the same procedure. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 3:1) to give γ-hydroxy butenolide **1.134** (12.8 mg, 32%) as a white foam and alcohol **1.135** (21.2 mg, 54%) as a pale-yellow foam.

Data for **1.134**: $\mathbf{R_f}$ 0.93 (ethyl acetate/pentane, 3:1); **IR** ν_{max}/cm^{-1} 3364 (br w), 2936 (s), 1751 (s); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.74 (t, J = 2.0 Hz, 1H, H8), 2.88 (ddt, J = 19.0 Hz, 4.5 Hz, 2.0 Hz, 1H, H3a), 2.62 (dddd, J = 19.0 Hz, 12.5 Hz, 4.5 Hz, 2.0 Hz, 1H, H3b), 2.05 – 1.62 (m, 4H, H2, H7), 1.47 – 1.29 (m, 2H, H1), 1.19 (s, 3H, H10), 0.85 (s, 3H, H11); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 171.5 (C9), 171.1 (C4), 118.0 (C8), 112.2 (C5), 40.6 (C6), 39.7 (C7),

28.3 (C3), 25.4 (C2), 24.9 (C1), 23.9 (C10), 21.1 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_3$, 197.1178; found, 197.1179.

Data for **1.135**: $\mathbf{R_f}$ 0.82 (ethyl acetate/pentane, 3:1); **IR** ν_{max}/cm^{-1} 3437 (br w), 2933 (s), 1741 (s); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 6.19 (t, *J* = 2.0 Hz, 1H, H10), 4.76 (dt, *J* = 7.0 Hz, 2.0 Hz, 1H, H5), 4.56 (ddt, *J* = 12.0 Hz, 4.0 Hz, 2.0 Hz, 1H, H3), 2.21 – 1.85 (m, 2H, H2), 1.87 – 1.44 (m, 4H, H1, H7), 0.77 (s, 3H, H10), 0.69 (s, 3H, H11); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 174.3 (C9), 173.0 (C4), 119.8 (C8), 90.2 (C5), 69.5 (C3), 42.2 (C7), 38.5 (C6), 33.9 (C2), 30.0 (C1), 18.4 (C10), 17.9 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}O_3$, 197.1178; found, 197.1179.

7a-Hydroxy-7,7-dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, 1.136; 4-Hydroxy-7,7-dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, 1.137; 4,6-Dihydroxy-7,7-dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, 1.138



To a conical flask 200 mM phosphate buffer (pH 7.9, 175.83 mL) were added a solution of butenolide **1.118** (33.6 mg in 0.5 mL MeOH, 0.203 mmol), glucose (20.3 mL of a 1.0 M solution in phosphate buffer, pH 7.9, 20.3 mmol), GDH (2.03 mL of a 2.0 U/μL solution in phosphate buffer, pH 7.9) and $NADP^+$ monosodium salt (2.03 mL of a 4.0 mM solution in water), followed by $P450_{BM3}$ variant GVQ (1.80 mL of a 229 μM solution in phosphate buffer, pH 7.9). The reaction mixture was swirled under air for 4 h. After this time, it was split into six ~34 mL portions; ethyl acetate (10 mL) was added to each portion, and the mixture was centrifuged at 13,300 *g* for 3 min. The layers were separated and the aqueous phases in each

portion was re-extracted twice with ethyl acetate through the same procedure. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:1) to give γ-hydroxy butenolide **1.136** (6.49 mg, 18%) as a white foam, alcohol **1.137** (9.51 mg, 26%) as a pale-yellow foam and **1.138** (3.50 mg, 10%) as a pale-yellow foam.

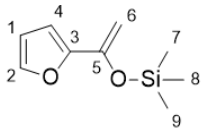
Data for **1.136**: **R_f** 0.88 (ethyl acetate/pentane, 2:1); **IR** ν_{max}/cm^{-1} 3409 (br w), 2941 (s), 1752 (s); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.73 (d, *J* = 2.0 Hz, 1H, H7), 2.71 (ddt, *J* = 14.0 Hz, 5.0 Hz, 2.0 Hz, 1H, H4a), 2.43 (tdd, *J* = 14.0 Hz, 6.0 Hz, 2.0 Hz, 1H, H4b), 1.86 – 1.76 (m, 2H, H3), 1.50 – 1.33 (m, 2H, H2), 1.19 (s, 3H, H9), 0.86 (s, 3H, H10); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 171.1 (C8), 168.9 (C5), 114.8 (C7), 107.5 (C6), 40.5 (C1), 35.8 (C2), 26.1 (C4), 22.9 (C3), 21.8 (C9), 20.3 (C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_3$, 183.1021; found, 183.1021.

Data for **1.137**: **R_f** 0.82 (ethyl acetate/pentane, 2:1); **IR** ν_{max}/cm^{-1} 3398 (br w), 2933 (s), 1733 (s); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.86 (d, *J* = 1.5 Hz, 1H, H7), 4.89 (d, *J* = 1.5 Hz, 1H, H6), 4.86 (q, *J* = 2.0 Hz, 1H, H5), 2.01 – 1.84 (m, 2H, H2), 1.79 – 1.64 (m, 1H, H3a), 1.45 – 1.33 (m, 1H, H3b), 1.23 (s, 3H, H9), 0.68 (s, 3H, H10); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 173.4 (C8), 168.8 (C5), 114.4 (C7), 86.7 (C6), 64.9 (C4), 39.3 (C6), 31.5 (C2), 29.9 (C3), 29.1 (C9), 16.6 (C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_3$, 183.1021; found, 183.1021.

Data for **1.138**: **R_f** 0.59 (ethyl acetate/pentane, 2:1); **IR** ν_{max}/cm^{-1} 3453 (br w), 2927 (s), 1737 (s); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.94 (d, *J* = 1.5 Hz, 1H, H7), 5.26 (d, *J* = 1.5 Hz, 1H, H6), 4.86 (dt, *J* = 6.5 Hz, 3.0 Hz, 1H, H4), 3.83 (dt, *J* = 6.0 Hz, 3.0 Hz, 1H, OH on C2), 3.57 (d, *J* = 7.5 Hz, 1H, H2), 2.80 (d, *J* = 6.0 Hz, 1H, OH on C4), 2.32 (dt, *J* = 15.5 Hz, 2.5 Hz, 1H, H3a), 2.06 – 1.96 (m, 1H, H3b), 1.27 (s, 6H, H9, H10); **^{13}C NMR** (151 MHz, $CDCl_3$) δ_C 173.1 (C8),

168.0 (C5), 114.7 (C7), 83.5 (C6), 77.5 (C2), 65.7 (C4), 43.7 (C1), 34.5 (C3), 29.4 (C9, C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_4$, 199.0970; not found.

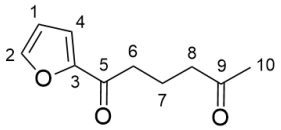
((1-(Furan-2-yl)vinyl)oxy)trimethylsilane, 2.32



2-Methylfuran **1.19** (2.20 g, 20.0 mmol) was dissolved in DCM (30 mL) at 0 °C under an argon atmosphere. To this solution was added triethylamine (5.02 mL, 36.0 mmol) followed dropwise by TMSOTf (3.99 mL, 22 mmol). The mixture was allowed to slowly warm to RT and stirred continuously for 15 h, after which the product was directly concentrated *in vacuo*. The two-phase residual liquid was separated, and the lower viscous layer was extracted with pentane (4 × 10 mL). All pentane used for the extraction was combined with the upper layer, which was concentrated *in vacuo* to give compound **2.32** (3.17 g, 87%) as a pale brown liquid, which was used without further purification.

R_f 0.81 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2962 (w), 1561 (w), 1254 (s), 1015 (s), 845 (s); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.34 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H2), 6.45 – 6.33 (m, 2H, H1, H4), 4.91 (d, *J* = 1.5 Hz, 1H, H6), 4.39 (d, *J* = 1.5 Hz, 1H, H6), 0.28 (s, 9H, H7, H8, H9); **^{13}C NMR** (C_6D_6, 101 MHz) δ_C 152.1 (C5), 147.5 (C3), 142.3 (C2), 111.0 (C1), 107.0 (C4), 90.3 (C6), −0.3 (C7, C8, C9). Spectroscopic data in agreement with literature.[29]

1-(Furan-2-yl)hexane-1,5-dione, 2.33



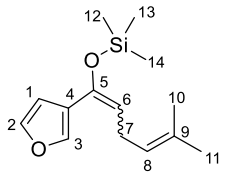
Method 1: To a 0 °C solution of silyl enol ether **2.32** (0.182 g, 1.00 mmol) in DCM (25 mL) under N_2 was dropwise added a mixture of $InCl_3$ (6.63 mg, 0.300 mmol) and MVK (0.0770 g, 1.10 mmol). The mixture was stirred at 0 °C for another hour, then water (5 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.33** (0.112 g, 62%) as a yellow oil.

Method 2: To a solution of silyl enol ether **2.32** (0.182 g, 1.00 mmol) in acetonitrile (10 mL) under N_2 was added a mixture of I_2 (10 mol%) and MVK (0.0770 g, 1.10 mmol), and the resulting mixture was stirred at RT for 3 hours before being quenched by sat. aq. $Na_2S_2O_3$ (10 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.33** (0.0955 g, 53%) as an orange oil.

R_f 0.63 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 3131 (m), 2942 (w), 1715 (s), 1681 (w), 1469 (s), 1018 (m), 767 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.68 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H2), 7.29 (dd, *J* = 3.5 Hz, 1.5 Hz, 1H, H4), 6.64 (dd, *J* = 3.5 Hz, 1.5 Hz, 1H, H1), 2.89 (t, *J* = 7.0 Hz, 2H, H6), 2.58 (t, *J* = 7.0 Hz, 2H, H8), 2.15 (s, 3H, H10), 2.00 (quin, *J* = 7.0 Hz, 2H, H7); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 207.7 (C9), 188.3 (C5), 152.0 (C3), 146.1 (C2), 116.7 (C4),

111.7 (C1), 41.9 (C8), 36.7 (C6), 29.4 (C10), 17.6 (C7). Spectroscopic data in agreement with literature.[30]

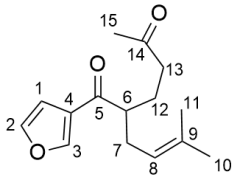
((1-(Furan-3-yl)-5-methylhexa-1,4-dien-1-yl)oxy)trimethylsilane, 2.34



Ketone **1.105** (2.01 mL, 11.3 mmol) was dissolved in DCM (30 mL) at 0 °C under an argon atmosphere. To this solution was added triethylamine (2.84 mL, 20.3 mmol) followed dropwise by TMSOTf (2.25 mL, 12.4 mmol). The mixture was allowed to slowly warm to RT and stirred continuously for 15 h, after which the product was directly concentrated *in vacuo*. The two-phase residual liquid was separated, and the lower layer was extracted with pentane (4 × 10 mL) and discarded. All pentane used for the extraction was combined with the upper layer, which was concentrated *in vacuo* to give compound **2.34** (2.63 g, 93%), a pale yellow oil as a 4:1 mixture of diastereomers, which was used in the next step without further purification.

IR ν_{max}/cm^{-1} 3121 (w), 1618 (s), 1150 (s), 797 (s); **^{1}H NMR** (400 MHz, C_6D_6) (major diastereomer) δ_H 7.44 (s, 1H, H3), 6.98 (t, J = 2.0 Hz, 1H, H2), 6.26 (dd, J = 2.0 Hz, 1.0 Hz, 1H, H1), 5.29 (tsept, J = 7.0 Hz, 1.5 Hz, 1H, H8), 5.09 (t, J = 7.0 Hz, 1H, H6), 3.00 (t, J = 7.0 Hz, 2H, H7), 1.67 – 1.65 (m, 3H, H10), 1.61 (br s, 3H, H11), 0.15 (s, 9H, H12, H13, H14); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 143.3 (C5), 142.9 (C2), 139.6 (C3), 131.9 (C9), 123.6 (C4), 123.4 (C8), 109.3 (C1), 108.5 (C6), 25.8 (C10), 25.4 (C11), 17.8 (C7), 0.6 (C12, C13, C14); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{23}O_2Si$, 251.1462; found, 251.1463. Spectroscopic data in agreement with literature.[22]

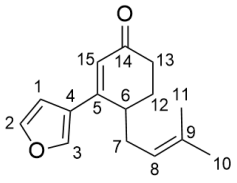
1-(Furan-3-yl)-2-(3-methylbut-2-en-1-yl)hexane-1,5-dione, 2.29



To a 0 °C solution of trimethylsilyl enol ether **2.34** (2.63 g, 10.5 mmol) in DCM (20 mL) under nitrogen was dropwise added a mixture of $InCl_3$ (46.4 mg, 0.210 mmol) and MVK (0.813 g, 11.6 mmol) with vigorous stirring. The mixture was stirred at 0 °C for another hour, then water (20 mL) was added. The aqueous phase was separated and extracted three times with 5 mL of ethyl acetate. The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 7:3) to give compound **2.29** (1.49 g, 57%) as a colourless oil.

R_f 0.61 (pentane/ethyl acetate, 7:3); **IR** ν_{max}/cm^{-1} 3134 (w), 2927 (w), 1713 (s), 1669 (s), 1561 (s), 1510 (s), 1153 (s), 872 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.97 (t, *J* = 1.0 Hz, 1H, H3), 7.37 (ddt, *J* = 2.0 Hz, 1.5 Hz, 0.5 Hz, 1H, H2), 6.70 (dq, *J* = 1.5 Hz, 0.5 Hz, 1H, H1), 4.98 (tsept, *J* = 7.5, 1.5 Hz, 1H, H8), 2.98 – 2.89 (1H, m, H6), 2.41 (ddd, *J* = 17.5 Hz, 8.5 Hz, 6.0 Hz, 1H, H13a), 2.34 – 2.21 (m, 2H, H13b, H7a), 2.15 – 2.05 (m, 1H, H7b), 2.01 (s, 3H, H15), 1.99 – 1.86 (m, 1H, H12a), 1.80 – 1.65 (m, 1H, H12b), 1.56 (d, *J* = 1.5 Hz, 3H, H10), 1.50 (d, *J* = 1.5 Hz, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 208.4 (C14), 198.3 (C5), 147.6 (C3), 144.4 (C2), 134.0 (C9), 128.2 (C4), 121.1 (C8), 108.8 (C1), 48.7 (C6), 40.9 (C13), 31.1 (C7), 30.0 (C15), 25.9 (C12), 25.8 (C10), 17.9 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{21}O_3$, 249.1485; found, 249.1491. Spectroscopic data in agreement with literature.[22]

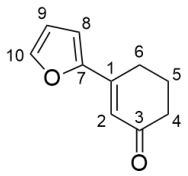
3-(Furan-3-yl)-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, 2.27



To a solution of **2.29** (1.44 g, 5.80 mmol) in methanol (10 mL) was added sodium methoxide (0.562 g, 10.4 mmol), and the resulting mixture was stirred at 54 °C for 16 h. After cooling to RT, the mixture was diluted with 0.1 M HCl (20 mL) and ethyl acetate (20 mL). The aqueous phase was separated and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.27** (0.863 g, 64%) as an orange oil.

R_f 0.82 (pentane/ethyl acetate, 7:3); **IR** ν_{max}/cm^{-1} 3121 (w), 2921 (w), 1658 (s), 1609 (s), 1161 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.71 (t, *J* = 1.5 Hz, 1H, H3), 7.46 (dd, *J* = 2.0 Hz, 1.5 Hz, 1H, H2), 6.59 (d, *J* = 2.0 Hz, 1H, H1), 6.20 (s, 1H, H15), 5.18 (tsept, *J* = 7.5 Hz, 1.5 Hz, 1H, H8), 2.72 – 2.64 (m, 1H, H6), 2.55 (dt, *J* = 17.0 Hz, 10.0 Hz, 1H, H13a), 2.39 (dt, *J* = 17.0 Hz, 3.0 Hz, 1H, H13b), 2.31 (t, *J* = 7.5 Hz, 2H, H7), 2.13 – 2.07 (m, 2H, H12), 1.73 (q, *J* = 1.5 Hz, 3H, H10), 1.62 (s, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 199.3 (C14), 155.7 (C5), 144.4 (C2), 142.2 (C3), 134.0 (C9), 125.1 (C4), 122.9 (C15), 122.2 (C8), 107.9 (C1), 37.0 (C6), 32.7 (C13), 30.6 (C7), 25.8 (C12), 25.4 (C10), 18.0 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{19}O_2$, 231.1380; found, 231.1380. Spectroscopic data in agreement with literature.[22]

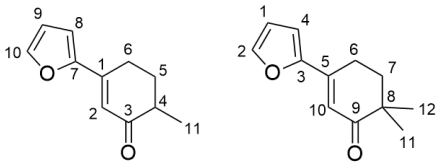
3-(Furan-2-yl)cyclohex-2-en-1-one, 2.35



To a solution of **2.33** (1.12 g, 6.21 mmol) in methanol (5 mL) was added sodium methoxide (0.604 g, 11.2 mmol), and the resulting mixture was stirred at 55 °C for 10 h. After cooling to RT, the mixture was diluted with 0.1 M HCl (20 mL) and ethyl acetate (20 mL). The aqueous phase was separated and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.35** (0.649 g, 64%) as a yellow oil.

R_f 0.56 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 2947 (w), 1656 (s), 1609 (s), 1249 (s), 745 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60 (s, 1H, H10), 6.80 (d, *J* = 3.5 Hz, 1H, H8), 6.50 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H9), 6.42 (s, 1H, H2), 2.59 (td, *J* = 6.0 Hz, 1.5 Hz, 2H, H6), 2.40 (dd, *J* = 7.5 Hz, 6.0 Hz, 2H, H4), 2.05 (m, 2H, H5); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 199.1 (C3); 151.9 (C1), 146.9 (C7), 144.7 (C10), 120.6 (C2), 112.3 (C8), 112.0 (C9), 37.2 (C4), 25.1 (C6), 22.1 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{11}O_2$, 163.0734; found, 163.0733. Spectroscopic data in agreement with literature.[30]

3-(Furan-2-yl)-6-methylcyclohex-2-en-1-one, 2.36; 3-(Furan-2-yl)-6,6-dimethylcyclohex-2-en-1-one, 2.37

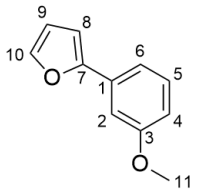


To a solution of enone **2.35** (0.222 g, 1.37 mmol) in THF (10 mL) under N_2 was added KHMDS (3.80 mL, 0.50 M, 1.92 mmol) at −78 °C, and the mixture was stirred for 1 h. Then, a solution of MeI (0.190 mL, 3.01 mmol) in THF (0.5 mL) was slowly added. The reaction mixture was allowed to gradually warm to RT over 15 h with vigorous stirring, and 0.1 M HCl (20 mL) was added. The two phases were separated, and the aqueous phase was extracted by ethyl acetate (3 × 10 mL). The combined ethereal phase was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a brown oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.36** (0.0895 g, 37%) as a white crystalline solid and compound **2.37** (0.0495 g, 19%) as a white crystalline solid.

Data for **2.36**: **R_f** 0.55 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 3112 (w), 2936 (w), 1656 (s), 1614 (s), 1205 (s), 966 (w), 882 (s), 762 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50 (dt, *J* = 4.0 Hz, 2.0 Hz, 1H), 6.70 (q, *J* = 3.0 Hz, 1H), 6.47 (tt, *J* = 3.5 Hz, 2.0 Hz, 1H), 6.41 (dt, *J* = 5.0 Hz, 2.0 Hz, 1H), 2.71 (m, 1H, H4), 2.62 (m, 1H, H6a), 2.40 (m, 1H, H6b), 2.15 (m, 1H, H5a), 1.78 (m, 1H, H5b), 1.17 (d, *J* = 6.5 Hz, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 199.5 (C3); 155.6 (C1), 152.2 (C7), 145.0 (C10), 121.0 (C2), 112.5 (C8), 112.3 (C9), 37.5 (C4), 25.3 (C6), 22.4 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{13}O_2$, 177.0916; found, 177.0917; **mp** 49−51 °C.

Data for **2.37**: **R$_f$** 0.76 (pentane/ethyl acetate, 3:2); **IR** ν_{max}/cm^{-1} 2969 (w), 1649 (s), 1612 (s), 1206 (s), 1165 (s), 889 (s), 774 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.51 (d, *J* = 2.0 Hz, 1H, H2), 6.71 (d, *J* = 3.5 Hz, 1H, H4), 6.48 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H1), 6.36 (d, *J* = 1.5 Hz, 1H, H10), 2.66 (td, *J* = 6.0 Hz, 1.5 Hz, 2H, H6), 1.92 (t, *J* = 6.0 Hz, 2H, H7), 1.13 (s, 6H, H11, H12); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 204.3 (C9), 152.2 (C2), 145.2 (C5), 144.8 (C2), 119.6 (C10), 112.2 (C4), 112.0 (C1), 40.7 (C8), 35.9 (C7), 24.3 (C6), 22.6 (C11, C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{15}O_2$, 191.1073; found, 191.1073; **mp** 42−44 °C.

2-(3-Methoxyphenyl)furan, 2.40

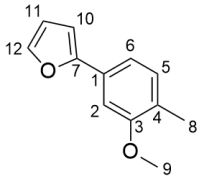


Enone **2.35** (0.220 g, 1.49 mmol), DDQ (0.338 g, 1.49 mmol) and I_2 (0.113 g, 0.447 mmol) were dissolved in methanol (3 mL) in a gastight glass pressure tube under a nitrogen atmosphere. The tube was sealed, and its content heated to 80 °C with vigorous stirring for 15 h. After cooling to RT, the mixture was diluted with sat. aq. $Na_2S_2O_3$ (10 mL) and ethyl acetate (5 mL). The aqueous phase was separated and extracted three times with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 4:1) to give compound **2.40** (0.116 g, 44%) as a colourless oil.

R$_f$ 0.82 (pentane/diethyl ether, 4:1); **IR** ν_{max}/cm^{-1} 2939 (w), 1606 (s), 1504 (s), 1291 (s), 1226 (s), 1038 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40 (d, *J* = 8.0 Hz, 1H, H10), 7.23 – 7.14 (m, 3H, H4, H5, H6), 6.75 – 6.73 (m, 1H, H2), 6.57 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H8), 6.39 (dd, *J*

= 3.5 Hz, 2.0 Hz, 1H, H9), 3.78 (s, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 160.0 (C3), 153.8 (C7), 142.2 (C10), 132.3 (C1), 129.8 (C5), 116.5 (C6), 113.3 (C4), 111.7 (C9), 109.2 (C2), 105.4 (C8), 55.4 (C11). Spectroscopic data in agreement with literature.[31]

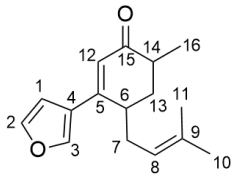
2-(3-Methoxy-4-methylphenyl)furan, 2.41



Enone **2.36** (0.241 g, 1.49 mmol), DDQ (0.338 g, 1.49 mmol) and I_2 (0.113 g, 0.447 mmol) were dissolved in methanol (3 mL) in a gastight glass pressure tube under a nitrogen atmosphere. The tube was sealed, and its contents were heated to 80 °C and vigorously stirred for 15 h. After cooling to RT, the mixture was diluted with sat. aq. $Na_2S_2O_3$ (10 mL) and ethyl acetate (5 mL). The aqueous phase was separated and extracted three times with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (pentane/diethyl ether, 3:2) to give compound **2.41** (0.0345 g, 37%) as a colourless oil.

R_f 0.96 (pentane/diethyl ether, 3:2); **IR** ν_{max}/cm^{-1} 2932 (w), 1610 (s), 1511 (s), 1288 (s), 1029 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H12), 7.14 (m, 3H, H2, H5, H6), 6.59 (d, *J* = 3.5 Hz, 1H, H10), 6.45 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H, H11), 3.88 (s, 3H, H9), 2.22 (s, 3H, H8); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 158.0 (C3), 154.3 (C7), 141.6 (C12), 130.8 (C5), 129.8 (C1), 126.1 (C4), 116.0 (C6), 111.6 (C11), 105.6 (C2), 104.4 (C10), 55.4 (C9), 16.1 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{13}O_2$, 189.0916; found, 189.0916.

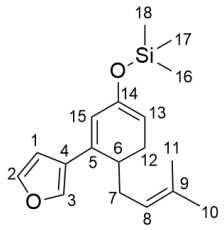
3-(Furan-3-yl)-6-methyl-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, 2.31



To a solution of **2.27** (0.0626 g, 0.272 mmol) in THF (10 mL) under N_2 was added KHMDS (0.810 mL, 0.5 M, 0.408 mmol) at −78 °C, and the mixture was stirred for 1 h. Then, a solution of MeI (0.0340 mL, 0.544 mmol) in THF (0.5 mL) was slowly added. The reaction mixture was allowed to gradually warm to RT over 15 h with vigorous stirring, and 0.1 M HCl (6 mL) was added. The two phases were separated, and the aqueous phase was extracted by ethyl acetate (3 × 10 mL). The combined ethereal phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a brown oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.31** (0.0747 g, 61%) as a yellow oil.

R_f 0.83 (pentane/diethyl ether, 3:2); **IR** ν_{max}/cm^{-1} 2926 (w), 1660 (s), 1609 (s), 1162 (s), 873 (s), 798 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.69 (m, 1H, H3), 7.45 (dt, *J* = 1.5 Hz, 1.0 Hz, 1H, H2), 6.58 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H1), 6.17 (d, *J* = 1.0 Hz, 1H, H12), 5.20 (tdt, *J* = 7.0 Hz, 3.0 Hz, 1.5 Hz, 1H, H8), 5.13 (m, 1H, H6), 2.67 (m, 1H, H14), 2.59 (m, 1H, H7a), 2.33 (m, 1H, H7b), 2.10 (m, 1H, H13a), 1.84 (m, 1H, H13b), 1.72 (s, 3H, H10), 1.61 (s, 3H, H11), 1.17 (d, *J* = 6.5 Hz, 3H, H16); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 154.7 (C15), 144.3 (C5), 142.3 (C3), 142.0 (C2), 134.0 (C9), 125.0 (C4), 122.6 (C12), 122.3 (C8), 108.0 (C1), 37.7 (C14), 36.1 (C13), 34.3 (C6), 30.8 (C7), 25.8 (C10), 17.9 (C11), 15.5 (C16); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{21}O_2$, 254.1542; found, 254.1540.

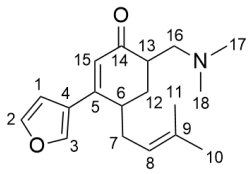
((5-(Furan-3-yl)-4-(3-methylbut-2-en-1-yl)cyclohexa-1,5-dien-1-yl)oxy)trimethylsilane, 2.44



To a solution of **2.27** (0.515 g, 2.24 mmol) in THF (10 mL) at −78 °C was added KHMDS (8.95 mL, 0.5 M, 4.47 mmol) dropwise. Stirring was continued for 1 h and TMSCl (0.340 mL, 2.68 mmol) was added. The mixture was then allowed to slowly warm to RT with vigorous stirring over 6 h, and sat. aq. Na_2CO_3 (15 mL) was added. The two phases were separated, and the aqueous phase was extracted by ethyl acetate (3 × 10 mL). The combined ethereal phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give compound **2.44** (0.589 g, 87%) as a brown oil, which was used without further purification.

IR ν_{max}/cm^{-1} 3119 (w), 1610 (s), 1164 (s), 794 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.57 (t, *J* = 1.0 Hz, 1H, H2), 7.48 (t, *J* = 1.5 Hz, 1H, H3), 6.64 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H1), 6.00 (d, *J* = 2.0 Hz, 1H, H15), 5.20 (dddt, *J* = 7.5 Hz, 6.0 Hz, 3.0 Hz, 1.5 Hz, 1H, H8), 4.87 (m, 1H, H13), 2.52 (m, 1H, H6), 2.40 (m, 2H, H7), 2.31 (m, 1H, H12a), 2.03 (m, 1H, H12b), 1.81 (s, 3H, H10), 1.69 (s, 3H, H11), 0.33 (s, 9H, H16, H17, H18); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 147.9 (C14), 143.4 (C2), 138.9 (C3), 135.3 (C5), 133.3 (C9), 128.0 (C4), 125.6 (C8), 122.5 (C8), 119.3 (C13), 107.5 (C1), 35.8 (C6), 28.5 (C7), 25.6 (C12), 25.2 (C10), 17.5 (C11), 0.0 (C16, C17, C18); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{27}O_2Si$, 303.1775; found, 303.1771.

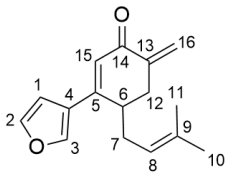
6-((Dimethylamino)methyl)-3-(furan-3-yl)-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, 2.45



To a solution of **2.44** (0.722 g, 2.39 mmol) in DCM (20 mL) under N_2 was added *N*,*N*-dimethylmethyleneiminium iodide (0.972 g, 5.25 mmol). The reaction mixture was stirred at RT for 16 h before aq. NaOH (1.0 M, 15 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give compound **2.45** (0.520 g, 75%) as a brown oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2929 (w), 2820 (w), 1660 (s), 1610 (s), 1162 (s), 873 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.69 (t, *J* = 1.0 Hz, 1H, H2), 7.43 (t, *J* = 1.5 Hz, 1H, H3), 6.58 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H1), 6.11 (t, *J* = 2.0 Hz, 1H, H15), 5.10 (tdd, *J* = 6.5 Hz, 3.0 Hz, 1.5 Hz, 1H, H8), 2.78 (m, 1H, H6), 2.74 (m, 1H, H13), 2.70 (m, 2H, H16), 2.22 (s, 6H, H17, H18), 2.20 (m, 1H, H7a), 2.17 (m, 1H, H7b), 1.68 (d, *J* = 1.0 Hz, 3H, H10), 1.60 (m, 2H, H12), 1.53 (d, *J* = 1.5 Hz, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 190.6 (C14), 155.7 (C5), 144.5 (C2), 142.2 (C3), 134.19 (C9), 126.4 (C4), 123.2 (C15), 121.9 (C8), 107.9 (C1), 55.3 (C16), 45.3 (C17, C18), 39.7 (C13), 38.7 (C6), 34.7 (C7), 32.6 (C12), 25.8 (C10), 18.0 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{26}NO_2$, 288.1958; found, 288.1955.

3-(Furan-3-yl)-4-(3-methylbut-2-en-1-yl)-6-methylenecyclohex-2-en-1-one, 2.43



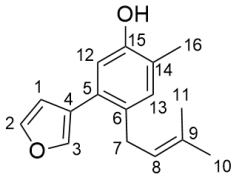
Method 1 (from **2.45**): To a solution of **2.45** (0.333 g, 1.16 mmol) in diethyl ether (15 mL) at RT was added MeI (0.440 mL, 6.94 mmol). The mixture was stirred continuously for 3 h, then sat. aq. $NaHCO_3$ (20 mL) was added. Stirring was continued for another 15 h before the aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a brown oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 3:2) to give compound **2.43** (0.119 g, 43%) as a white crystalline solid.

Method 2 (from **2.29**): Ketone **2.29** (115 mg, 0.500 mmol) was dissolved in a stirred suspension of diisopropylammonium trifluoroacetate (2.15 g, 10.0 mmol) in THF (8 mL) under N_2 then paraformaldehyde (45.0 mg, 1.50 mmol) and trifluoracetic acid (2.0 µL, 26 µmol) were added. This mixture was opened to the atmosphere and heated under reflux for 6 h, after which time it was cooled to RT and filtered. The filtrate was concentrated, dissolved in ether (10 mL), and hydrochloric acid (1 mL, 0.1 M) added. The layers were separated, and the ethereal layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (pentane/ether 9:1) to give title compound **2.43** (120 mg, 99%) as a colourless crystalline solid.

R_f 0.64 (pentane/diethyl ether, 3:2); **IR** ν_{max}/cm^{-1} 2913 (w), 1656 (s), 1602 (s), 1158 (s), 873 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 (t, *J* = 1.0 Hz, 1H, H3), 7.48 (dd, *J* = 2.0 Hz, 1.5 Hz, 1H, H2), 6.62 (d, *J* = 2.0 Hz, 1H, H1), 6.32 (s, 1H, H15), 6.15 (d, *J* = 2.0 Hz, 1H, H16a), 5.34 – 5.31 (m, 1H, H16b), 5.17–5.11 (m, 1H, H8), 2.88 – 2.70 (m, 3H, H6, H12), 2.29 – 2.13 (m,

2H, H7), 1.72 (s, 3H, H10), 1.56 (s, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 188.3 (C14), 155.8 (C5), 144.7 (C13), 142.4 (C3), 140.5 (C2), 134.5 (C9), 125.3 (C4), 123.3 (C15), 122.0 (C8), 121.7 (C16), 108.0 (C1), 38.9 (C6), 34.8 (C12), 32.7 (C7), 25.9 (C10), 18.1 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_2$, 243.1380; found, 243.1379; **mp** 59−61 °C. Spectroscopic data in agreement with literature.[22]

5-(Furan-3-yl)-2-methyl-4-(3-methylbut-2-en-1-yl)phenol, 2.26

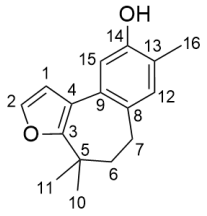


Enone **2.43** (0.754 g, 3.23 mmol) was added neat to DBU (4.84 mL, 32.3 mmol), and the mixture was heated to 50 °C for 24 h. The mixture was cooled to RT and treated with 1.0 M HCl (35 mL). The aqueous phase was separated, extracted with ethyl acetate (3 × 15 mL), and discarded. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to an orange oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 4:1) to give compound (0.537 g, 68%) as a yellow oil.

R_f 0.70 (pentane/ethyl acetate, 4:1); **IR** ν_{max}/cm^{-1} 3405 (br w), 2968 (w), 1512 (s), 1188 (s), 873 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46 – 7.44 (m, 2H, H2, H3), 6.99 (s, 1H, H13), 6.73 (s, 1H, H12), 6.50 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H1), 5.19 (tsept, *J* = 7.0 Hz, 1.5 Hz, 1H, H8), 4.64 (d, *J* = 3.5 Hz, 1H, OH), 3.28 (d, *J* = 7.0 Hz, 2H, H7), 2.25 (s, 3H, H16), 1.72 (q, *J* = 1.5 Hz, 3H, H10), 1.64 (s, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 151.9 (C15), 142.6 (C3), 140.0 (C2), 132.2 (C5), 132.1 (C9), 132.0 (C13), 130.8 (C6), 125.2 (C4), 124.3 (C14), 123.1 (C8), 116.1 (C12), 111.9 (C1), 31.6 (C7), 25.9 (C10), 18.0 (C11), 15.6 (C16); **HRMS** (ESI+)

m/z: $[M+H]^+$ calcd. for $C_{16}H_{19}O_2$, 243.1380; found, 243.1379. Spectroscopic data in agreement with literature.[22]

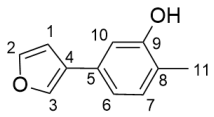
4,4,8-Trimethyl-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*b*]furan-9-ol, 2.23



To a solution of **2.26** (0.483 g, 1.993 mmol) in $CHCl_3$ (8 mL) at RT under N_2 was added a solution of CSA (7.00 mg, 0.0598 mmol) in HFIP (2 mL) dropwise. Stirring was continued for 16 h, then sat. aq. NH_4Cl was added. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL), and the combined organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a brown oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 4:1) to give compound **2.23** (0.269 g, 56%) as a white crystalline solid.

R_f 0.79 (pentane/ethyl acetate, 4:1); **IR** ν_{max}/cm^{-1} 3405 (br w), 2924 (w), 1512 (w), 1034 (s), 873 (s), 757 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (d, *J* = 2.0 Hz, 1H, H2), 6.93 (s, 1H, H12), 6.88 (m, 1H, H15), 6.53 (d, *J* = 2.0 Hz, 1H, H1), 2.73 – 2.69 (m, 2H, H7), 2.22 (s, 3H, H16), 1.83 – 1.78 (m, 2H, H6), 1.35 (s, 6H, H10, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 158.2 (C3), 152.1 (C14), 140.7 (C2), 134.3 (C12), 131.6 (C8), 130.8 (C9), 121.1 (C13), 117.6 (C4), 113.7 (C15), 110.1 (C1), 41.1 (C5), 38.1 (C6), 30.5 (C7), 29.6 (C10, C11), 15.4 (C16); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_2$, 243.1380; found, 243.1380; **mp** 86−89 °C. Spectroscopic data in agreement with literature.[22]

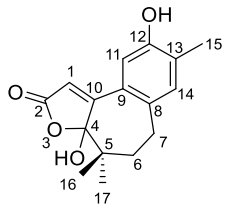
5-(Furan-3-yl)-2-methylphenol, 2.46



To a solution of compound **2.26** (41.6 mg, 0.172 mmol) in $CHCl_3$ (3 mL) at RT under N_2 was added a solution of CSA (2.00 mg, 0.00860 mmol) in HFIP (3 mL) dropwise. Stirring was continued for 6 h, then sat. aq. NH_4Cl was added. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL), and the combined organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a brown oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 4:1) to give compound **2.46** (6.20 mg, 21%) as a white crystalline solid.

R_f 0.55 (pentane/ethyl acetate, 4:1); **IR** ν_{max}/cm^{-1} 3303 (br w), 2927 (w), 1248 (s), 1199 (s), 1045 (s), 875 (s), 738 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.69 (d, *J* = 2.0 Hz, 1H, H3), 7.68 (d, *J* = 1.0 Hz, 1H, H2), 7.58 (d, *J* = 9.0 Hz, 1H, H6), 7.48 (dd, *J* = 9.0 Hz, 1.0 Hz, 1H, H7), 7.39 (s, 1H, H10), 7.12 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H1), 5.13 (s, 1H, OH), 2.44 (d, *J* = 1.0 Hz, 3H, H11); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 153.3 (C9), 143.7 (C3), 130.4 (C2), 127.7 (C5), 125.7 (C7), 124.4 (C4), 121.4 (C8), 110.1 (C6), 106.0 (C10), 105.4 (C1), 16.3 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{11}O_2$, 175.0759; found, 175.0755; **mp** 121−122 °C.

Trigoxyphin L, 2.02



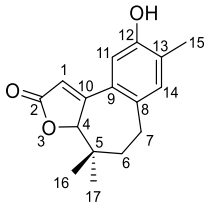
Method 1: To a solution of **2.23** (0.134 g, 0.555 mmol) in DCM (6 mL) was added DIPEA (0.290 mL, 1.664 mmol) followed by Rose Bengal (0.0270 g, 0.0275 mmol) at RT. O_2 was bubbled through the mixed solution for 15 minutes. Bubbling was then stopped, and the mixture was irradiated whilst being stirred at RT under an O_2 atmosphere (1 bar) for 18 h. The mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a pink oil. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 2:3) to give trigoxyphin L (75.4 mg, 52%) as a white crystalline solid.

Method 2: To a 25 mL round-bottom flask was added a solution of trigoxyphin K (11.0 mg, 4.26 µmol) and DBU (9.50 µL, 6.39 µmol) in acetonitrile (1 mL). O_2 was bubbled through this solution for 15 min, then the system was placed under an oxygen atmosphere (1 bar) for 18 hours. The reaction mixture was poured on sat. aq. NH_4Cl solution (5 mL) and acidified with 1.0 M HCl until the pH reached 4. Then, the layers were separated and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (pentane/ethyl acetate, 2:3) to give trigoxyphin L (7.8 mg, 67%) as an off-white solid.

R_f 0.58 (pentane/ethyl acetate, 2:3); **IR** ν_{max}/cm^{-1} 3370 (br w), 2980 (w), 1735 (s), 1618 (w), 1252 (s), 952 (s), 859 (s); **^{1}H NMR** (400 MHz, CD_3OD) δ_H 6.89 (s, 1H, H14), 6.79 (s, 1H,

H11), 6.05 (s, 1H, H1), 2.89 (t, *J* = 15.0 Hz, 1H, H7a), 2.62 (dd, *J* = 15.0 Hz, 6.5 Hz, 1H, H7b), 2.26 – 2.16 (m, 1H, H6a), 2.17 (overlaying s, 3H, H15), 1.50 (dd, *J* = 14.0 Hz, 6.0 Hz, 1H, H6b), 1.22 (s, 3H, H16), 1.03 (s, 3H, H17); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ_H 8.31 (1H, br s, OH), 6.93 (1H, s, H14), 6.81 (1H, s, H11), 6.19 (1H, br s, H1), 6.02 (1H, s), 2.90 (1H, t, *J* = 14.5 Hz, H7a), 2.62 (1H, dd, *J* = 14.5 Hz, 5.5 Hz, H7b), 2.23 (1H, t, *J* = 12.5 Hz, H6a), 2.18 (3H, s, H15), 1.52 (1H, dd, *J* = 12.5 Hz, 5.5 Hz, H6b), 1.22 (3H, s, H17), 1.03 (3H, s, H16); **^{13}C NMR** (101 MHz, CD_3OD) δ_C 173.3 (C2), 172.3 (C10), 154.9 (C12), 134.0 (C14), 133.3 (C8), 133.0 (C9), 128.8 (C13), 117.6 (C1), 117.0 (C11), 112.4 (C4), 42.0 (C5), 39.7 (C6), 31.6 (C7), 25.6 (C16), 21.5 (C17), 16.0 (C15); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) δ_C 170.6 (C2), 170.3 (C10), 154.4 (C12), 133.7 (C14), 132.8 (C8), 130.0 (C9), 127.7 (C13), 117.6 (C1), 117.5 (C11), 111.3 (C4), 41.7 (C5), 39.2 (C6), 31.2 (C7), 25.5 (C17), 21.3 (C16), 15.9 (C15); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_4$, 275.1278; not found; **mp** 197−199 °C. Spectroscopic data in agreement with literature.[22,32]

Trigoxyphin K, 2.01



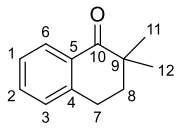
Method 1: To a solution of trigoxyphin L (25.0 mg, 0.0911 mmol) in methanol (3 mL) at 0 °C was added $NaBH_4$ (13.8 mg, 0.365 mmol) followed by $CeCl_3 \cdot 7H_2O$ (3.39 mg, 9.11 μmol). The solution was stirred at this temperature for 4 h before being quenched by 0.1 M HCl (8.0 mL). The solution was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with sat. NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a

light pink solid. The crude product was purified by flash chromatography (pentane/ethyl acetate, 2:3) to give trigoxyphin K (19.0 mg, 81%) as a white crystalline solid.

Method 2: To a stirred solution of ester **2.66** (31.0 mg, 0.100 mmol) in DCM (2 mL) was added BBr_3 (0.300 mL, 1.0 M in DCM, 0.300 mmol). The mixture was stirred for 15 h before being diluted by water (5 mL). The layers were separated, and the aqueous layer was extracted by DCM (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified using silica gel chromatography (pentane/ethyl acetate, 2:3) to give trigoxyphin K (19.0 mg, 74%) as a white crystalline solid.

R_f 0.73 (pentane/ethyl acetate, 2:3); **IR** ν_{max}/cm^{-1} 2971 (w), 1713 (s), 1597 (w), 949 (s), 873 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.94 (s, 1H, H11), 6.86 (s, 1H, H14), 6.15 (d, *J* = 1.5 Hz, 1H, H1), 5.11 (br s, 1H, OH), 4.88 (d, *J* = 1.5 Hz, 1H, H4), 2.85 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H, H7a), 2.66 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H, H7b), 2.25 (s, 3H, H15), 1.95 – 1.88 (m, 1H, H6a), 1.74 – 1.62 (m, 1H, H6b), 1.27 (s, 3H, H16), 0.91 (s, 3H, H17); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 174.1 (C2), 169.8 (C10), 153.3 (C12), 133.9 (C14), 133.5 (C8), 128.5 (C9), 128.3 (C13), 115.7 (C1), 114.8 (C11), 90.7 (C4), 40.3 (C6), 38.2 (C5), 30.3 (C7), 29.8 (C16), 19.1 (C17), 15.9 (C15); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_3$, 259.1383; not found; **mp** 146−148 °C. Spectroscopic data in agreement with literature.[22,32]

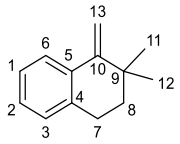
2,2-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-one, 2.48



Potassium *tert*-butoxide (3.36 g, 30.0 mmol) and 1-tetralone (1.33 mL, 10.00 mmol) were stirred under argon in dry ether (50 mL) for 30 minutes. Methyl iodide (2.18 mL, 17.5 mmol) was then added and the reaction was stirred for 24 h. The reaction was quenched with water (25 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water and then brine before being dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to give ketone **2.48** as a yellow oil (1.59 g, 91%).

IR ν_{max}/cm^{-1} 2559 (w), 1684 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.05 − 8.03 (m, 1H, H6), 7.47 − 7.43 (m, 1H, H1), 7.30 (t, *J* = 7.5 Hz, 1H, H2), 7.21 (d, *J* = 7.5 Hz, 1H, H3), 2.30 (t, *J* = 6.5 Hz, 2H, H7), 1.99 (t, *J* = 6.5 Hz, 2H, H8), 1.22 (s, 6H, H11, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 203.0 (C10), 143.4 (C4), 133.1 (C5), 131.5 (C2), 128.7 (C3), 128.0 (C6), 126.6 (C1), 41.7 (C9), 36.7 (C8), 25.8 (C7), 24.4 (C10, C11). Spectroscopic data in agreement with literature.[33]

2,2-Dimethyl-1-methylene-1,2,3,4-tetrahydronaphthalene, 2.49

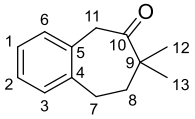


Potassium tert-butoxide (6.72 g, 60.0 mmol) and methyltriphenylphosphonium bromide (2.14 g, 6.00 mmol) were stirred under argon in dry ether (25 mL) for 1 hour. A solution of ketone **2.48** (6.96 g, 40.0 mmol) in dry ether (5 mL) was slowly added and the mixture was stirred for 16 h. The reaction was quenched with water (20 mL) and the mixture was extracted with DCM (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel

chromatography (ethyl acetate/pentane, 1:19) to give alkene **2.49** (448 mg, 65%) as a colourless oil.

IR ν_{max}/cm^{-1} 2959 (w), 1623 (s), 1449 (s), 1284 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.61 – 7.56 (m, 1H, H6), 7.20 – 7.08 (m, 3H, H1, H2, H3), 5.44 (s, 1H, H13a), 5.07 (s, 1H, H13b), 2.86 (t, *J* = 6.5 Hz, 2H, H7), 1.68 (t, *J* = 6.5 Hz, 2H, H8), 1.15 (s, 6H, H11, H12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 152.5 (C10), 136.2 (C4), 135.2 (C5), 128.8 (C2), 127.2 (C3), 125.9 (C1), 125.3 (C6), 106.2 (C13), 37.2 (C9), 34.8 (C8), 27.7 (C11, C12), 26.5 (C7). Spectroscopic data in agreement with literature.[34]

7,7-Dimethyl-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one, 2.50

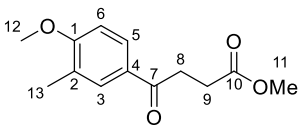


Iodobenzene (516 mg, 2.53 mmol), *m*-CPBA (70%) (436 mg, 2.53 mmol) and PTSA (480 mg, 2.53 mmol) were stirred in HFIP/DCM (1:6 v/v, 17.5 mL) for 30 min. The reaction mixture was cooled to 0 °C before adding water (0.5 mL) and alkene **2.49** (383 mg, 2.20 mmol). Stirring was continued for 1 h at RT, then sat. aq. $NaHCO_3$ (30 mL) was added and the mixture extracted with DCM (3 × 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 8:92) to give ketone **2.50** (149 mg, 79%) as a white solid.

R_f 0.54 (ethyl acetate/pentane, 8:92); **IR** ν_{max}/cm^{-1} 2970 (w), 2927 (w), 2360 (w), 2341 (w), 1702 (s), 1456 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 – 7.01 (4H, m, H(1–4)), 3.76 (2H, s, H(5)), 2.95 – 2.87 (2H, m, H(9)), 1.78 – 1.71 (2H, m, H(8)), 1.15 (6H, s, H(10)); **^{13}C NMR**

(101 MHz, $CDCl_3$) δ_C 210.1 (C(6)), 141.2 (C(4a)), 133.2 (C(9a)), 129.6 (C(4)), 129.1 (C(3)), 127.2 (C(1)), 127.0 (C(2)), 48.4 (C(7)), 46.4 (C(5)), 41.1 (C(8)), 30.7 (C(9)), 25.4 (C(10)); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{17}O$, 189.1274; found, 189.1275; **mp** 57–60 °C.

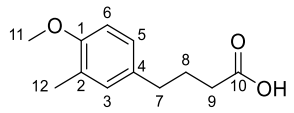
Methyl 4-(4-methoxy-3-methylphenyl)-4-oxobutanoate, 2.55



A solution of succinic anhydride (2.75 g, 27.5 mmol) and $AlCl_3$ (6.985 g, 52.5 mmol) in nitrobenzene (20 mL) was stirred at 0 °C. 2-methylanisole (3.10 mL, 25.0 mmol) was added slowly so that the reaction temperature did not exceed 5 °C. The mixture was stirred for 24 h at RT. Ice-cold 6M HCl (25 mL) was added and the mixture filtered. The solid obtained was washed with diethyl ether (3 × 20 mL) and then recrystallised from methanol to give ester **2.55** (5.36 g, 96%) as a white powder.

IR ν_{max}/cm^{-1} 2939 (w), 1740 (s), 1680 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.72 (s, 1H, H5). 6.90 (d, *J* = 9.0 Hz, 1H, H3), 7.80 (d, *J* = 9.0 Hz, 1H, H6), 3.83 (s, 3H, H12), 3.69 (s, 3H, H11), 3.19 (t, *J* = 7.0 Hz, 2H, H8), 2.72 (t, *J* = 7.0 Hz, 2H, H9), 2.21 (s, 2H, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 197.1 (C7), 173.2 (C10), 161.6 (C1), 130.5 (C3), 129.2 (C4), 128.1 (C5), 126.6 (C2), 109.4 (C6), 55.4 (C12), 51.6 (C11), 33.7 (C8), 29.1 (C9), 16.1 (C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{17}O_4$, 237.1127; found, 237.1125; **mp** 61–64 °C.

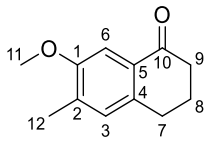
4-(4-Methoxy-3-methylphenyl)butanoic acid, 2.56



Zinc dust (2.28 g, 35.0 mmol), mercury (II) chloride (271 mg, 1.00 mmol), concentrated HCl (0.1 mL), and water (2.8 mL) were stirred for 30 mins to form a homogeneous solution. The supernatant liquid was then decanted and replaced with water (1.4 mL), conc. HCl (0.33 mL), and toluene (1.8 mL). After 3 mins of stirring, keto ester **2.55** (1.18 g, 5.00 mmol) was added and the mixture was refluxed at 115 °C for 48 h, during which time concentrated HCl (1.8 mL) was added every 6 hours. After cooling, the mixture was separated, and the aqueous layer was extracted by diethyl ether (3 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was refluxed in aq. 5% potassium hydroxide (60 mL) for 2 hours. After cooling, the mixture was brought to pH 4 by addition of 3M HCl. This aqueous mixture was then extracted with DCM (3 × 50 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to obtain the corresponding carboxylic acid **2.56** (0.698 g, 67%) as a white solid, which was used without further purification.

IR ν_{max}/cm^{-1} 2900 (br w), 1700 (s), 1610 (w), 1410(w), 1260(s), 1230(s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.9 (m, 2H, H3, H5), 6.77 (d, J = 8.0 Hz, 1H, H6), 3.77 (s, 3H, H11), 2.57 (t, J = 7.0 Hz, 2H, H7), 2.30 (t, J = 7.0 Hz, 2H, H9), 2.20 (s, 3H, H12), 1.93 (m, 2H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 177.7 (C10), 156.1 (C1), 133.2 (C4), 130.7 (C3), 126.7 (C5), 126.4 (C2), 110.1 (C6), 55.4 (C11), 34.7 (C7), 33.2 (C9), 26.2 (C8), 16.1 (C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{17}O_3$, 209.1178; found, 209.1177; **mp** 111–113 °C.

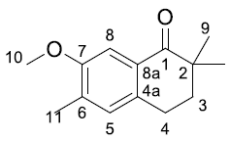
7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one, 2.57



Carboxylic acid **2.56** (2.78 g, 13.2 mmol) was added to a round-bottom flask fitted with an argon balloon and an exit needle. Then, a mixture of TFA (1.52 g, 13.2 mmol) and TFAA (10.4 g, 49.4 mmol) was added dropwise at 0 °C and the mixture was stirred at RT for 30 mins. The reaction was then quenched with 5% NaOH solution. The mixture was then separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to obtain a crude oil. The crude was purified by flash column chromatography (ethyl acetate/pentane, 1:4) to give ketone **2.57** (2.16 g, 85%) as an orange oil.

IR ν_{max}/cm^{-1} 2936 (w), 1680 (s), 1610 (w), 1350 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (s, 1H, H6), 6.90 (s, 1H, H3), 3.60 (s, 3H, H11), 2.70 (t, *J* = 5.5 Hz, 2H, H7), 2.55 (t, *J* = 5.5 Hz, 2H, H9), 2.17 (s, 3H, H12), 2.01 (m, 2H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 198.1 (C10), 156.4 (C1), 136.5 (C4), 133.3 (C2), 131.5 (C5), 130.2 (C3), 108.3 (C6), 55.9 (C11), 38.5 (C9), 29.4 (C7), 23.3 (C8), 15.8 (C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{15}O_2$, 191.1072; found, 191.1071.

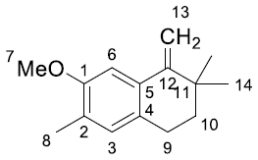
7-Methoxy-2,2,6-trimethyl-3,4-dihydronaphthalen-1(2*H*)-one, 2.58



Potassium *tert*-butoxide (1.82 g, 16.2 mmol) and ketone **2.57** (1.03 g, 5.41 mmol) were stirred in ether (30 mL) for 30 min. Iodomethane (1.18 mL, 19.0 mmol) was then added and the mixture was stirred for 14 h. The reaction was quenched with water (10 mL) and the mixture extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), and were then dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (pentane/ethyl acetate, 9:1), giving ketone **2.58** as a colourless solid (1.05 g, 89%).

R_f 0.64 (pentane/ethyl acetate, 9:1); **IR** ν_{max}/cm^{-1} 2923 (w), 2360 (w), 1678 (s), 1610 (m), 1499 (m), 1260 (s), 1032 (m), 882 (w), 763 (w); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45 (1H, s, H8), 6.98 (1H, s, H5), 3.85 (3H, s, H10), 2.87 (2H, t, *J* = 6.5 Hz, H4), 2.24 (3H, s, H11), 1.95 (2H, t, *J* = 6.5 Hz, H3), 1.20 (6H, s, H9); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 203.0 (C1), 156.8 (C7), 136.0 (C4a), 133.5 (C8a), 130.8 (C6) , 130.3 (C5), 107.6 (C8), 55.6 (C10), 41.4 (C2), 37.1 (C3), 25.0 (C4), 24.6 (C9), 16.7 (C11); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{19}O_2$, 219.1380; found, 219.1380; **mp** 48–52 °C. Spectroscopic data in agreement with literature.[22]

7-Methoxy-2,2,6-trimethyl-1-methylene-1,2,3,4-tetrahydronaphthalene, 2.59

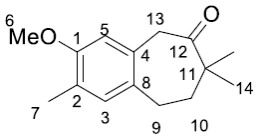


Potassium *tert*-butoxide (1.08 g, 9.62 mmol) and methyltriphenylphosphonium bromide (3.44 g, 9.63 mmol) were stirred in 1,4-dioxane (30 mL) for 1 h then a solution of ketone **2.58** (1.05 g, 4.81 mmol) in toluene (5 mL) was added, and the mixture was stirred at 60 °C for 14 h. The reaction was quenched with water (50 mL), the phases separated, and the aqueous phase was

extracted with DCM (3 × 30 mL). The combined organic portions were washed with water (20 mL) and brine (20 mL), and were then dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (pentane/ethyl acetate, 99:1), giving alkene **2.59** as a pale yellow oil (843 mg, 81%).

R_f 0.39 (pentane/ethyl acetate, 99:1); **IR** ν_{max}/cm^{-1} 2920 (w), 2851 (m), 2360 (w), 1501 (s), 1260 (s), 1209 (s), 1067 (m), 880 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.05 (1H, s, H6), 6.89 (1H, s, H3), 5.42 (1H, s, H13a), 5.06 (1H, s, H13b), 3.86 (3H, s, H7), 2.78 (2H, t, *J* = 6.5 Hz, H9), 2.21 (3H, s, H8), 1.68 (2H, t, *J* = 6.5 Hz, H10), 1.17 (6H, s, H14); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 156.2 (C12), 153.0 (C1), 133.5 (C5), 131.0 (C3), 128.2 (C4), 126.7 (C2), 106.3 (C13), 105.2 (C6), 55.5 (C7), 37.7 (C11), 34.8 (C10), 27.9 (C14), 25.8 (C9), 16.0 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{21}O$, 217.1587; found, 217.1588. Spectroscopic data in agreement with literature.[22]

3-Methoxy-2,7,7-trimethyl-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one, 2.25

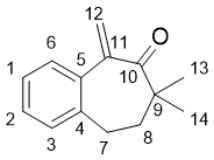


Iodobenzene diacetate (2.62 g, 8.13 mmol) and *p*-toluenesulfonic acid monohydrate (0.93 g, 4.89 mmol) were stirred in a mixture of HFIP and dichloromethane (1:6, 50 mL) for 30 min. The reaction mixture was cooled to 0 °C, water (1.5 mL) was added, followed by alkene **2.59** (1.60 g, 7.40 mmol), and stirring was continued for 10 min at 0 °C. Saturated aqueous $NaHCO_3$ solution (30 mL) was added, and the mixture extracted with DCM (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (50 mL) then dried

($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel chromatography (pentane/ethyl acetate, 92:8) to give ketone **2.25** as a white solid (1.50 g, 87%).

R_f 0.76 (ethyl acetate/pentane, 8:92); **IR** ν_{max}/cm^{-1} 2924 (m), 2360 (w), 2341 (w), 1696 (s), 1503 (m), 1206 (s), 1094 (s), 1067 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.86 (1H, s, H5), 6.63 (1H, s, H3), 3.80 (3H, s, H6), 3.77 (s, 2H, H13), 2.90 − 2.87 (2H, m, H9), 2.15 (3H, s, H7), 1.80 – 1.77 (2H, m, H10), 1.21 (6H, s, H14); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C 210.5 (C12), 156.6 (C1), 132.8 (C3), 131.7 (C4), 131.3 (C8), 125.1 (C2), 111.6 (C5), 55.6 (C6), 48.5 (C11), 46.6 (C13), 41.8 (C10), 29.8 (C9), 25.5 (C14), 15.8 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{21}O_2$, 233.1536; found 233.1537; **mp** 109–110 °C. Spectroscopic data in agreement with literature.[22]

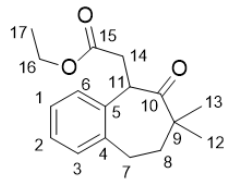
7,7-Dimethyl-5-methylene-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-7-one, 2.61



1,4-Dioxane (3 mL), water (3 mL), ketone **2.50** (47.5 mg, 0.300 mmol), glyoxylic acid monohydrate (0.141 g, 1.50 mmol) and morpholine hydrochloride (0.222 g, 1.80 mmol) were added to a sealed glass pressure tube under a nitrogen atmosphere. The tube was sealed and its contents were heated to 100 °C and stirred for 20 h; after cooling to RT, water (5 mL) was added, and the two layers were separated. The aqueous layer was extracted by diethyl ether (3 × 5 mL); the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **2.61** (51.7 mg, 86%) as a yellow oil.

IR ν_{max}/cm^{-1} 2926 (w); 1687 (s), 1052 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40 – 7.29 (m, 1H, H6), 7.27 – 7.17 (m, 2H, H1, H2), 7.14 – 7.03 (m, 1H, H3), 5.92 (d, *J* = 1.5 Hz, 1H, H12a), 5.58 (d, *J* = 1.5 Hz, 1H, H12b), 2.82 – 2.76 (m, 2H, H7), 1.93 – 1.82 (m, 2H), 1.06 (s, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 207.6 (C10), 149.6 (C11), 138.9 (C5), 136.6 (C4), 128.9 (C3), 128.6 (C6), 127.7 (C2), 127.1 (C1), 122.1 (C12), 46.5 (C9), 40.5 (C8), 31.7 (C7), 26.4 (C13, C14); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{17}O$, 201.1279; found, 201.1280.

Ethyl 2-(7,7-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)acetate, 2.62

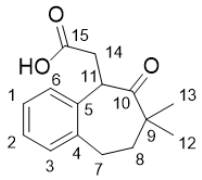


To a stirred solution of DIPA (0.110 mL, 0.834 mmol) in THF (4 mL) at –10 °C was added *n*-butyllithium solution (0.480 mL, 1.60 M solution in hexanes, 0.765 mmol), and this mixture was stirred for 15 minutes before being cooled to –78 °C. A solution of ketone **2.50** (0.110 g, 0.695 mmol) in 1 mL THF was added slowly, then the mixture was slowly warmed to 0 °C over 2 hours with stirring. Afterwards, ethyl bromoacetate (0.0769 mL, 0.695 mmol) and DMI (0.0751 mL, 0.695 mmol) were added, and the resulting mixture was warmed to RT and stirred for a further 16 h. The mixture was quenched with sat. aq. NH_4Cl (15 mL) and extracted by diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified using silica gel chromatography to give compound **2.62** (0.121 g, 63%) as a pale-yellow oil.

R$_f$ 0.29 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2930 (w), 1736 (s), 1704 (s), 1186 (s), 753 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.20 – 7.03 (m, 4H, H1, H2, H3, H6), 4.82 (dd, *J* = 11.0

Hz, 3.5 Hz, 1H, H11), 4.11 (q, *J* = 7.0 Hz, 2H, H16), 3.50 (dd, *J* = 17.0 Hz, 11.0 Hz, 1H, H14a), 3.40 (m, 1H, H8a), 2.70 (ddd, *J* = 17.0 Hz, 7.0 Hz, 3.0 Hz, 2H, H14b, H7a), 1.94 (ddd, *J* = 14.0 Hz, 7.0 Hz, 2.0 Hz, 1H, H7b), 1.63 – 1.52 (m, 1H, H8b), 1.51 (s, 3H, H13), 1.24 (t, *J* = 7.0 Hz, 3H, H17), 1.03 (s, 3H, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 209.1 (C10), 177.1 (C15), 141.4 (C4), 133.9 (C5), 127.9 (C3), 126.2 (C6), 126.1 (C2), 123.8 (C1), 59.6 (C16), 47.7 (C9), 44.2 (C11), 42.1 (C14), 32.2 (C8), 29.6 (C7), 25.4 (C12), 24.0 (C13), 13.2 (C17); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{23}O_3$, 275.1647; found, 275.1647.

7,7-Dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]-annulene-5-carboxylic acid, 2.63

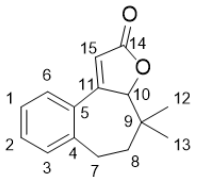


A 6.0M NaOH solution was prepared by dissolving NaOH (0.240 g, 6.00 mmol) in water (0.76 mL), to which was added ester **2.62** (75.6 mg, 0.287 mmol). This mixture was stirred at 50 °C for 5 h; after being cooled to 0 °C, was slowly acidified by 1.0 M HCl until the pH reached 2−3. Afterwards, the mixture was extracted by ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give acid **2.63** (0.265 g, 92%) as an orange oil.

R$_f$ 0.32 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2979 (m), 1716 (s), 1703 (s), 1188 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 – 7.10 (m, 4H, H1, H2, H3, H6), 4.92 (dd, *J* = 11.0 Hz, 3.6 Hz, 1H, H11), 3.65 (dd, *J* = 17.0 Hz, 11.0 Hz, 1H, H14a), 3.55 – 3.35 (m, 1H, H7a), 2.92 – 2.71 (m, 2H, H7b, H14b), 2.05 (ddd, *J* = 14.0 Hz, 7.0 Hz, 1.5 Hz, 1H, H8a), 1.77 – 1.61 (m,

1H, H8b), 1.55 (s, 3H, H12), 1.12 (s, 3H, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 209.1 (C10), 177.3 (C15), 141.4 (C4), 133.5 (C5), 128.0 (C3), 126.4 (C6), 126.2 (C2), 123.8 (C1), 47.7 (C9), 44.2 (C11), 42.1 (C14), 32.2 (C8), 29.6 (C7), 25.4 (C12), 24.0 (C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{19}O_3$, 247.1334; found, 247.1333.

4,4-Dimethyl-3a,4,5,6-tetrahydro-2*H*-benzo[3,4]cyclohepta[1,2-*b*]furan-2-one, 2.64

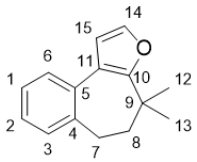


To a mixture of acetic anhydride (3 mL) and phosphorus pentoxide (0.319 g, 1.13 mmol) was added carboxylic acid **2.63** (49.1 mg, 0.225 mmol). The resulting mixture was stirred at 40 °C for 16 h. After being cooled to RT, the mixture was diluted by sat. aq. $NaHCO_3$ (10 mL) and diethyl ether (5 mL), and the two layers were separated. The aqueous layer was extracted by diethyl ether (3 × 5 mL); the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **2.64** (38.7 mg, 75%) as an orange oil.

R_f 0.56 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2939 (w), 1753 (s), 763 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, H6), 7.36 – 7.27 (m, 2H, H1, H2), 7.21 – 7.13 (m, 1H, H3), 6.21 (d, *J* = 2.0 Hz, 1H, H15), 4.88 (d, *J* = 1.5 Hz, 1H, H10), 3.12 – 2.92 (m, 1H, H7a), 2.75 (ddd, *J* = 16.0 Hz, 8.0 Hz, 2.0 Hz, 1H, H7b), 1.97 (ddd, *J* = 14.5 Hz, 11.5 Hz, 2.0 Hz, 1H, H8a), 1.75 (ddd, *J* = 14.5 Hz, 8.0 Hz, 2.0 Hz, 1H, H8b), 1.29 (s, 3H, H12), 0.95 (s, 3H, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.9 (C14), 169.0 (C11), 141.7 (C4), 131.1 (C5), 130.7 (C2), 130.6 (C3), 130.0 (C6), 126.9 (C1), 116.5 (C15), 90.1 (C10), 39.9 (C8), 38.4 (C9),

31.2 (C7), 29.8 (C12), 18.6 (C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{17}O_2$, 229.1229; found, 229.1229.

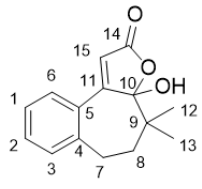
4,4-Dimethyl-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*b*]furan, 2.65



To a 25 mL round-bottom flask containing toluene (1 mL) under argon was added diisobutylaluminium hydride solution (1.0 M in THF, 0.254 mL, 0.254 mmol). This solution was cooled to –75 °C, and a solution of butenolide **2.64** (38.7 mg, 0.170 mmol) in toluene (1 mL) was dropwise added. Stirring was continued for 2 h, and the mixture was warmed to 0 °C and slowly quenched by sat. aq. NH_4Cl (10 mL). The two layers were separated. And the aqueous layer was extracted by ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **2.65** (36.8 mg, 99%) as a pale yellow oil.

R_f 0.93 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2857 (m), 1262 (w), 1154 (m), 752 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.49 (d, *J* = 7.5 Hz, 1H, H6), 7.36 (dd, J = 2.0 Hz, 1.0 Hz, 1H, H14), 7.26 – 7.17 (m, 1H, H1), 7.12 (m, 2H, H2, H3), 6.59 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H15), 2.85 – 2.78 (m, 2H, H7), 1.86 – 1.78 (m, 2H, H8), 1.36 (d, *J* = 1.5 Hz, 6H, H12, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.1 (C10), 140.6 (C4), 139.5 (C14), 130.9 (C5), 127.8 (C3), 125.9 (C2), 125.2 (C1), 124.9 (C6), 116.8 (C11), 109.1 (C15), 52.4 (C9), 39.6 (C8), 30.3 (C7), 28.4 (C12, C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{17}O$, 213.1279; found, 213.1279.

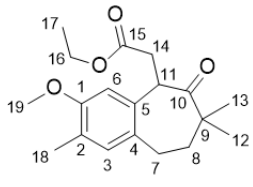
3a-Hydroxy-4,4-dimethyl-3a,4,5,6-tetrahydro-2*H*-benzo[3,4]cyclohepta[1,2-*b*]furan-2-one, 2.52



To a solution of **2.65** (36.8 mg, 0.170 mmol) in chloroform (2 mL) at 0 °C was added sodium bicarbonate (49.4 mg, 0.588 mmol) followed by *m*-CPBA (69.7 mg, 0.404 mmol). This mixture was allowed to warm to RT over 10 min, and the progress of the reaction was tracked by TLC. Upon completion of reaction, the mixture was poured into sat. aq. NH_4Cl (10 mL), and the two layers were separated. The aqueous layer was extracted by ethyl acetate (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give γ-hydroxy butenolide **2.52** (32.0 mg, 77%) as a white solid.

R_f 0.25 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2959 (m), 1734 (w), 1263 (s), 801 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 (m, 2H, H1, H6), 7.30 – 7.27 (m, 1H, H2), 7.19 (m, 1H, H3), 6.12 (m, 1H, H15), 3.04 (m, 1H, H7a), 2.71 (dd, *J* = 15.0 Hz, 7.0 Hz, 1H, H8a), 2.32 – 2.21 (m, 1H, H7b), 1.60 (dd, *J* = 15.0 Hz, 7.0 Hz, 1H, H8b), 1.29 (s, 3H, H12), 1.12 (s, 3H, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.0 (C14), 167 (C11), 140.0 (C2, C3), 129.9 (C3), 129.6 (C2), 129.5 (C1, C6), 125.8 (C15), 116.8 (C10), 40.3 (C9), 37.0 (C8), 30.5 (C7), 23.7 (C12), 20.1 (C13); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{17}O_3$, 245.1178; found, 245.1175.

Ethyl 2-(3-methoxy-2,7,7-trimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)acetate, 2.66

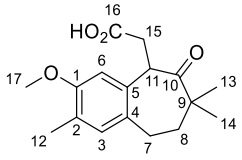


To a stirred solution of DIPA (0.100 mL, 0.700 mmol) in THF (4 mL) at –10 °C was added *n*-butyllithium solution (0.350 mL, 1.60 M solution in hexanes, 0.550 mmol), and this mixture was stirred for 15 minutes before being cooled to –75 °C. A solution of ketone **2.25** (0.116 g, 0.500 mmol) in 1 mL THF was added slowly, then the mixture was slowly warmed to 0 °C over 2 hours with stirring. Afterwards, ethyl bromoacetate (0.0552 mL, 0.500 mmol) and 1,3-dimethyl-2-imidazolidinone (0.0540 mL, 0.500 mmol) were added, and the resulting mixture was warmed to RT and stirred for a further 16 h. The mixture was quenched with sat. aq. NH_4Cl (15 mL) and extracted by diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified using silica gel chromatography (ethyl acetate/pentane, 1:9) to give compound **2.66** (0.102 g, 67%) as a pale-yellow oil.

R_f 0.60 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2979 (m), 1730 (s), 1703 (s), 1180 (s), 1079 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.88 (s, 1H, H6), 6.54 (s, 1H, H3), 4.83 (dd, *J* = 11.0 Hz, 4.0 Hz, 1H, H11), 4.14 (q, *J* = 7.0 Hz, 2H, H16), 3.80 (s, 3H, H19), 3.49 (dd, *J* = 16.5 Hz, 11.0 Hz, 1H, H14a), 3.28 (t, *J* = 14.0 Hz, 1H, H8a), 2.72 (dd, *J* = 16.5 Hz, 4.0 Hz, 1H, H14b), 2.61 (ddd, *J* = 14.0 Hz, 7.0 Hz, 2.0 Hz, 1H, H8b), 2.14 (s, 3H, H18), 1.923 (ddd, *J* = 14.0 Hz, 7.0 Hz, 2.0 Hz, 1H, H7a), 1.61 – 1.52 (m, 1H, H7b), 1.50 (s, 3H, H13), 1.27 (t, *J* = 7.0 Hz, 3H, H17), 1.04 (s, 3H, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.6 (C10), 172.2 (C15), 156.9 (C1), 134.2 (C4), 133.1 (C5), 131.5 (C6), 125.3 (C2), 107.2 (C3), 60.8 (C16), 55.6 (C19), 48.8

(C11), 45.5 (C9), 44.1 (C7), 33.6 (C14), 29.8 (C8), 26.6 (C12), 25.1 (C13), 15.8 (C18), 14.4 (C17); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{27}O_4$, 319.1904; found, 319.1903. Spectroscopic data in agreement with literature.[22]

2-(3-Methoxy-2,7,7-trimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)acetic acid, 2.67

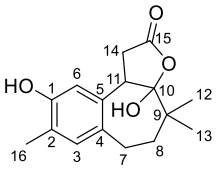


A 6.0M NaOH solution was prepared by dissolving NaOH (0.240 g, 6.00 mmol) in water (0.76 mL), to which was added ester **2.66** (45.7 mg, 0.224 mmol). This mixture was stirred at 50 °C for 15 h; after being cooled to 0 °C, was slowly acidified by 1.0 M HCl until the pH reached 2−3. Afterwards, the mixture was extracted by ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give acid **2.67** (28.9 mg, 45%) as an orange oil.

R_f 0.32 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2979 (w), 1716 (s), 1703 (s), 1188 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.88 (s, 1H, H6), 6.56 (s, 1H, H3), 4.83 (dd, *J* = 11.0 Hz, 3.5 Hz, 1H, H11), 3.78 (s, 3H, H17), 3.51 (dd, *J* = 16.5 Hz, 11.0 Hz, 1H, H15a), 3.38 – 3.25 (m, 1H, H8a), 2.75 (dd, *J* = 16.5 Hz, 3.5 Hz, 1H, H15b), 2.64 (ddd, *J* = 14.0 Hz, 7.0 Hz, 2.0 Hz, 1H, H8b), 2.22 (s, 3H, H12), 1.95 (ddd, *J* = 14.0 Hz, 7.0 Hz, 1.5 Hz, 1H, H7a), 1.63 – 1.55 (m, 1H, H7b), 1.53 (s, 3H, H13), 1.07 (s, 3H, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.3 (C10), 172.1 (C15), 156.7 (C1), 134.1 (C4), 133.0 (C5), 131.4 (C6), 125.1 (C2), 107.0 (C3), 55.4 (C17),

48.7 (C11), 45.4 (C9), 43.9 (C7), 33.5 (C16), 29.7 (C8), 26.5 (C14), 24.9 (C13), 15.6 (C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{23}O_4$, 291.1596; found, 291.1597.

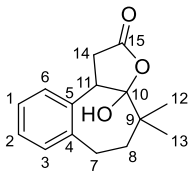
3a,9-Dihydroxy-4,4,8-trimethyl-1,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohepta[1,2-*b*]furan-2-one, 2.69



To a stirred solution of ester **2.66** (31.0 mg, 0.100 mmol) in DCM (2 mL) at −60 °C was dropwise added BBr_3 (0.300 mL, 1.0 M in DCM, 0.300 mmol). The mixture was stirred for 15 h before being diluted by water (5 mL). The layers were separated and the aqueous layer was extracted by DCM (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified using silica gel chromatography (pentane/ethyl acetate, 3:7) to give γ-hydroxy lactone **2.69** (14.2 mg, 49%) as a pale yellow oil.

R_f 0.71 (diethyl ether/pentane, 3:7); **IR** ν_{max}/cm^{-1} 3390 (br w), 2931 (w), 1716 (s), 1731 (w), 1369 (s), 1174 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.00 (s, 1H, H3), 6.67 (s, 1H, H6), 4.01 (dd, *J* = 11.5 Hz, 6.0 Hz, 1H, H11), 3.30 (dd, *J* = 19.0 Hz, 11.5 Hz, 1H, H14a), 2.75 – 2.63 (m, 2H, H7), 2.50 – 2.33 (m, 2H, H8a, H14b), 2.28 (s, 3H, H16), 1.99 (s, 3H, H12), 1.83 (s, 3H, H13), 1.82 – 1.80 (m, 1H, H8b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.2 (C15), 153.0 (C1), 137.4 (C5), 130.6 (C4), 128.8 (C3), 122.7 (C2), 114.3 (C6), 92.8 (C10), 41.4 (C11), 39.7 (C9), 30.7 (C8), 29.4 (C14), 29.2 (C7), 24.8 (C12, C13), 15.5 (C16); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{21}O_4$, 277.1440; found, 277.1440.

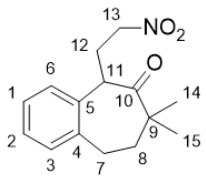
3a-Hydroxy-4,4-dimethyl-1,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohepta[1,2-*b*]furan-2-one, 2.75



To a stirred solution of ester **2.62** (27.4 mg, 0.100 mmol) in DCM (2 mL) at −60 °C was dropwise added BBr_3 (0.300 mL, 1.0 M in DCM, 0.300 mmol). The mixture was stirred for 15 h before being diluted by water (5 mL). The layers were separated and the aqueous layer was extracted by DCM (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified using silica gel chromatography (pentane/ethyl acetate, 3:7) to give γ-hydroxy lactone **2.75** (9.11 mg, 37%) as a pale yellow oil.

R_f 0.64 (diethyl ether/pentane, 3:7); **IR** ν_{max}/cm^{-1} 3417 (br w), 2977 (w), 2944 (w), 1775 (s), 1684 (w), 1273 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 – 7.13 (m, 4H, H1, H2, H3, H6), 4.13 (dd, *J* = 12.0 Hz, 6.5 Hz, 1H, H11), 3.32 (dd, *J* = 19.0 Hz, 12.0 Hz, 1H, H14a), 2.81 (dq, *J* = 8.0 Hz, 4.0 Hz, 2H, H7), 2.46 – 2.30 (m, 2H, H8a, H14b), 2.00 (s, 3H, H12), 7.32 – 7.13 (m, 1H, H8b), 1.84 (s, 3H, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.7 (C15), 138.9 (C5), 137.1 (C4), 128.1 (C3), 128.0 (C2), 127.3 (C1), 127.1 (C6), 92.6 (C10), 41.8 (C11), 39.5 (C14), 30.5 (C8), 29.4 (C13), 29.2 (C12), 25.8 (C7), 24.4 (C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{19}O_3$, 247.1334; found, 247.1334.

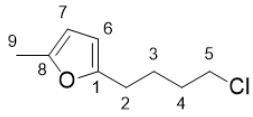
7,7-Dimethyl-5-(2-nitroethyl)-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one, 2.83



To a mixture of nitromethane (0.28 mL, 5.40 mmol) and DCM (1 mL) was added enone **2.61** (54.1 mg, 0.270 mmol), which was followed dropwise by DBU (0.200 mL, 1.35 mmol). The resulting mixture was stirred at RT for 24 h before being poured onto sat. aq. NH_4Cl (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed by brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to afford compound **2.83** (51.6 mg, 73%) as a brown oil.

R_f 0.77 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2930 (w), 1694 (s), 1547 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 – 7.21 (m, 1H, H6), 7.18 (m, 1H, H1), 7.13 (m, 2H, H2, H3), 4.56 – 4.42 (m, 2H, H11, H13a), 4.29 (ddd, *J* = 14.0 Hz, 9.0 Hz, 5.5 Hz, 1H, H13b), 3.30 (ddd, *J* = 15.0 Hz, 13.0 Hz, 2.0 Hz, 1H, H8a), 2.93 (ddt, *J* = 14.0 Hz, 10.5 Hz, 5.5 Hz, 1H, H12a), 2.72 (ddd, *J* = 15.0 Hz, 6.5 Hz, 2.0 Hz, 1H, H8b), 2.54 (m, 1H, H12b), 1.95 (ddd, *J* = 14.0 Hz, 6.5 Hz, 2.0 Hz, 1H, H7a), 1.60 (ddd, *J* = 15.0 Hz, 13.0 Hz, 2.0 Hz, 1H, H7b), 1.36 (s, 3H, H14), 1.04 (s, 3H, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.0 (C10), 142.3 (C5), 134.4 (C4), 129.1 (C6), 127.6 (C1), 127.5 (C2), 124.5 (C3), 73.8 (C13), 46.3 (C11), 42.9 (C7), 30.6 (C8), 26.2 (C15), 25.7 (C12), 24.3 (C14); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{20}NO_3$, 262.1443; found, 262.1443.

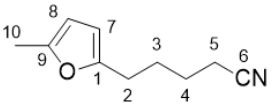
2-(4-Chlorobutyl)-5-methylfuran, 3.04



To a mixture of 2-methylfuran (4.48 mL, 50.0 mmol) and THF (25 mL) at –20 °C was added *n*-butyllithium solution (15.6 mL, 1.6 M in hexanes, 25.0 mmol) dropwise. The mixture was slowly warmed to 0 °C over 10 min and stirred for another 2 h, after which 1-bromo-4-chlorobutane (2.88 mL, 25.0 mmol) was slowly added. Stirring was continued for 15 h and sat. aq. NH_4Cl (15 mL) was added. The layers were separated and the aqueous layer extracted by diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (pentane) to give compound **3.04** (3.43 g, 80%) as a colourless oil.

R_f 0.85 (pentane); **IR** ν_{max}/cm^{-1} 2947 (m), 2866 (w), 1569 (m), 1450 (s), 1217 (s), 1021 (s), 782 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.88 – 5.85 (m, 1H, H6), 5.84 (dt, *J* = 3.0 Hz, 1.0 Hz, 1H, H7), 3.55 (t, *J* = 6.5 Hz, 2H, H5), 2.61 (t, *J* = 6.5 Hz, 2H, H2), 2.26 (s, 3H, H9), 1.88 – 1.74 (m, 4H, H3, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.8 (C1), 150.6 (C8), 106.0 (C6), 105.9 (C7), 45.0 (C5), 32.2 (C4), 27.5 (C2), 25.7 (C3), 13.7 (C9). Spectroscopic data in agreement with literature.[35]

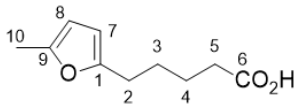
5-(5-Methylfuran-2-yl)pentanenitrile, 3.05



Sodium cyanide (1.47 g, 30.0 mmol), DMSO (6 mL) and compound **3.04** (2.59 g, 15.00 mmol) were added to a sealed glass pressure tube under a nitrogen atmosphere. The mixture was heated to 70 °C for 16 h, after which 0.1 M NaOH solution (20 mL) was added. Diethyl ether (3 × 10 mL) was used to extract the aqueous mixture, which was treated with 10% bleach solution (*ca.* 20 mL) before disposal. The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **3.05** (1.64 g, 67%) as a colourless oil.

R_f 0.32 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2947 (w), 1570 (w), 1020 (s), 739 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.87 (d, *J* = 3.0 Hz, 1H, H7), 5.84 (d, *J* = 3.0 Hz, 1H, H8), 2.64 (t, *J* = 7.0 Hz, 2H, H5), 2.37 (t, *J* = 7.0 Hz, 2H, H2), 2.27 (d, *J* = 1.0 Hz, 3H, H10), 1.85 – 1.68 (m, 4H, H3, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.0 (C1), 150.6 (C9), 119.6 (C6), 105.9 (C7), 105.8 (C8), 27.2 (C5), 27.1 (C4), 24.8 (C2), 17.0 (C3), 13.5 (C10). Spectroscopic data in agreement with literature.[36]

5-(5-Methylfuran-2-yl)pentanoic acid, 3.01

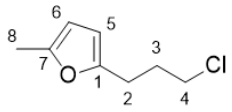


A 40% NaOH solution was prepared by dissolving NaOH (3.20 g, 80.0 mmol) in water (4.8 mL), and it was mixed with a solution of nitrile **3.05** (1.31 g, 8.00 mmol) in isopropyl alcohol (4 mL). This mixture was heated under reflux with stirring in a nitrogen atmosphere for 20 h. It was then cooled to 0 °C and slowly acidified by addition of 50% H_3PO_4 until the pH reached 2~3, during which the temperature was kept below 10 °C. Afterwards, the mixture was extracted by ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4),

filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:3) to give compound **3.01** (1.46 g, 99%) as a colourless oil.

R_f 0.28 (ethyl acetate-pentane, 1:4); **IR** ν_{max}/cm^{-1} 2947 (w), 1691 (s), 751 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.96 – 5.89 (m, 2H, H7, H8), 2.72 – 2.61 (m, 2H, H5), 2.45 (m, 2H, H2), 2.32 (s, 3H, H10), 1.83 – 1.68 (m, 4H, H3, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.5 (C6), 153.8 (C1), 150.3 (C9), 105.8 (C7), 105.5 (C8), 33.7 (C2), 27.7 (C3), 27.6 (C5), 24.2 (C4), 13.5 (C10); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}O_3$, 183.1021; found, 183.1022.

2-(3-Chloropropyl)-5-methylfuran, 3.09

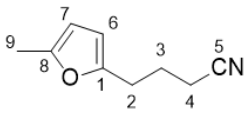


To a mixture of 2-methylfuran (3.00 mL, 33.4 mmol) and THF (25 mL) at –20 °C was added *n*-butyllithium solution (12.5 mL, 1.6 M in hexanes, 20.0 mmol) dropwise. The mixture was slowly warmed to 0 °C over 10 min and stirred for another 2 h, after which 1-bromo-3-chloropropane (1.97 mL, 20.0 mmol) was slowly added. Stirring was continued for 15 h, and sat. aq. NH_4Cl (15 mL) was added. The layers were separated and the aqueous layer extracted by diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (diethyl ether/pentane, 1:9) to give compound **3.09** (2.50 g, 79%) as a colourless oil.

R_f 0.91 (pentane); **IR** ν_{max}/cm^{-1} 2959 (w), 1442 (s), 763 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.88 (s, 1H, H5), 5.83 (s, 1H, H6), 3.54 (t, *J* = 6.5 Hz, 2H, H4), 2.72 (t, *J* = 7.0 Hz, 2H, H2), 2.23 (s, 3H, H8), 2.06 (tt, *J* = 7.0 Hz, 6.5 Hz, 2H, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 152.3

(C1), 150.5 (C7), 106.1 (C5), 105.8 (C6), 44.0 (C4), 30.9 (C3), 25.1 (C2), 13.4 (C8). Spectroscopic data in agreement with literature.[37]

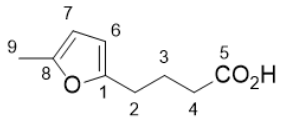
4-(5-Methylfuran-2-yl)butanenitrile, 3.10



Sodium cyanide (0.98 g, 20.0 mmol), DMSO (4 mL) and compound **3.09** (0.952 g, 6.00 mmol) were added to a sealed glass pressure tube under a nitrogen atmosphere. The tube was sealed and its contents were heated to 70 °C for 16 h, after which 0.1 M NaOH solution (20 mL) was added. Diethyl ether (3 × 10 mL) was used to extract the aqueous mixture, which was treated with 10% bleach solution (*ca.* 20 mL) before disposal. The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give nitrile **3.10** (0.883 g, 99%) as a yellow oil.

R_f 0.82 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2922 (m), 2923 (w), 1571 (w), 1443 (s), 1217 (s), 1020 (s), 783 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.93 (d, *J* = 3.0 Hz, 1H, H6), 5.86 (d, *J* = 3.0 Hz, 1H, H7), 2.74 (t, *J* = 7.0 Hz, 2H, H4), 2.36 (t, *J* = 7.0 Hz, 2H, H2), 2.25 (d, *J* = 1.0 Hz, 3H, H9), 1.98 (quin, *J* = 7.0 Hz, 2H, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.3 (C1), 151.1 (C8), 119.3 (C5), 106.8 (C6), 105.9 (C7), 26.7 (C4), 24.1 (C3), 16.3 (C2), 13.4 (C9). Spectroscopic data in agreement with literature.[38]

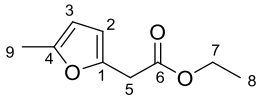
4-(5-Methylfuran-2-yl)butanoic acid, 3.11



A 40% NaOH solution was prepared by dissolving NaOH (2.00 g, 50.0 mmol) in water (3 mL), and it was mixed with a solution of nitrile **3.10** (0.562 g, 3.77 mmol) in isopropyl alcohol (3 mL). This mixture was heated under reflux with stirring in a nitrogen atmosphere for 20 h. It was then cooled to 0 °C and slowly acidified by addition of 50% H_3PO_4 until the pH of the aqueous layer became 2~3, with the temperature being kept below 10 °C at all times. Afterwards, the mixture was extracted by ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give carboxylic acid **3.11** (0.220 g, 54%) as a colourless crystalline solid.

R_f 0.25 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3500 (br w), 2943 (w), 1708 (s), 1410 (s), 1218 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.95 (d, J = 3.0 Hz, 1H, H6), 5.90 (d, J = 3.0 Hz, 1H, H7), 2.71 (t, J = 7.0 Hz, 2H, H4), 2.47 (t, J = 7.0 Hz, 2H, H2), 2.31 (d, J = 1.0 Hz, 3H, H9), 2.02 (quin, J = 7.0 Hz, 2H, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.8 (C5), 152.9 (C1), 150.5 (C8), 106.0 (C6), 105.7 (C7), 33.1 (C2), 27.1 (C4), 23.1 (C3), 13.4 (C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}O_3$, 169.0865; found, 169.0864.

Ethyl 2-(5-methylfuran-2-yl)acetate, 3.15

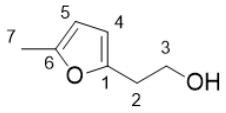


Hydrogen peroxide solution (2.91 mL, 35 wt%, 30.0 mmol) was added dropwise to a stirred mixture of 2-methylfuran (3.28 g, 40.0 mmol), ethyl iodoacetate (2.36 mL, 20.0 mmol) and

$FeSO_4 \cdot 7H_2O$ (139 mg, 0.500 mmol) in DMSO (30 mL), while the mixture was kept at RT with a water bath. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (25 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give ester **3.15** (2.83 g, 84%) as a brown oil, which was used without further purification.

R_f 0.28 (hexane/ethyl acetate, 19:1); **IR** ν_{max}/cm^{-1} 2984 (w), 2925 (w), 1742 (s), 1266 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.07 (d, *J* = 3.0 Hz, 1H, H2), 5.88 (d, *J* = 3.0 Hz, 1H, H3), 4.17 (q, *J* = 7.0 Hz, 2H, H7), 3.60 (s, 2H, H5), 2.24 (s, 3H, H9), 1.26 (t, *J* = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.1 (C6), 152.6 (C1), 145.8 (C4), 108.6 (C2), 106.3 (C3), 61.0 (C7), 34.2 (C5), 14.1 (C9), 13.5 (C8). Spectroscopic data in agreement with literature.[39]

2-(5-Methylfuran-2-yl)ethan-1-ol, 3.16

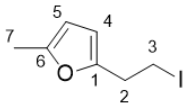


Lithium aluminium hydride (1.04 g, 27.5 mmol) was suspended in 10 mL THF at 0 °C under argon. To this was dropwise added a solution of ester **3.15** (2.31 g, 13.7 mmol) in 2 mL THF. The ice bath was removed, and the resulting mixture was allowed to stir at RT for 2 h. The mixture was cooled again to –10 °C, quenched slowly with water (10 mL), and filtered under reduced pressure. The filtrate was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **3.16** (1.67 g, 97%) as a yellow oil.

R_f 0.66 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3618 (br m), 2930 (w), 1047 (s), 752 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.98 (d, *J* = 3.0 Hz, 1H, H4), 5.88 (dq, *J* = 3.0 Hz, 1.0 Hz, 1H,

H5), 3.85 (q, *J* = 6.0 Hz, 2H, H3), 2.85 (t, *J* = 6.0 Hz, 2H, H2), 2.27 (s, 3H, H7), 2.03 (br s, 1H, OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.1 (C1), 150.9 (C6), 107.2 (C4), 106.0 (C5), 61.1 (C3), 31.7 (C2), 13.5 (C7). Spectroscopic data in agreement with literature.[40]

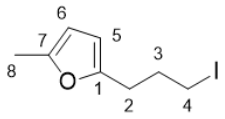
2-(2-Iodoethyl)-5-methylfuran, 3.17



Iodine (0.630 g, 2.48 mmol) was dissolved in DCM (9 mL) under a nitrogen atmosphere, and to the resulting solution was added triphenylphosphine (0.760 g, 2.89 mmol) followed by imidazole (0.197 g, 2.89 mmol). After 10 minutes of stirring, dropwise add a solution of alcohol **3.16** (0.261 g, 2.07 mmol) in DCM (1 mL). The mixture was stirred for a further 2 hours, and sat. aq. $Na_2S_2O_3$ (5 mL) was added. The layers were separated and the aqueous layer extracted by diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (pentane) to give compound **3.17** (0.363 g, 74%) as a colourless oil.

R_f 0.95 (pentane); **IR** ν_{max}/cm^{-1} 2943 (M), 1447 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.09 – 6.04 (m, 1H), 5.95 (dq, *J* = 3.0 Hz, 1.0 Hz, 1H), 3.47 – 3.37 (m, 2H), 3.21 (t, *J* = 7.5 Hz, 2H), 2.31 (dd, *J* = 1.0 Hz, 0.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.0 (C1), 150.5 (C6), 104.5 (C4), 103.5 (C5), 30.2 (C2), 11.0 (C7), 8.6 (C3); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_7H_{10}IO$, 236.9776; found, 236.9775.

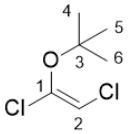
2-(3-Iodopropyl)-5-methylfuran, 3.18



Sodium iodide (3.00 g, 20.0 mmol), acetone (4 mL) and compound **3.17** (1.59 g, 10.0 mmol) were added to a sealed glass pressure tube under a nitrogen atmosphere. The tube was sealed and its contents were heated to 60 °C for 15 h. After being cooled to RT, it was poured into pentane (50 mL) and filtered under reduced pressures. The filtrate was concentrated *in vacuo* to give compound **3.18** (1.75 g, 70%) as a colourless oil, which was used without further purification.

R_f 0.62 (pentane); **IR** ν_{max}/cm^{-1} 2950 (w), 1450 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.90 (d, *J* = 3.0 Hz, 1H, H5), 5.84 (d, *J* = 3.0 Hz, 1H, H6), 3.20 (t, *J* = 7.0 Hz, 2H, H4), 2.70 (t, *J* = 7.0 Hz, 2H, H2), 2.25 (s, 3H, H8), 2.12 (quin, *J* = 7.0 Hz, 2H, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 152.1 (C1), 150.7 (C7), 106.4 (C5), 105.9 (C6), 31.8 (C3), 28.7 (C2), 13.5 (C8), 6.0 (C4). Spectroscopic data in agreement with literature.[41]

(*E*)-2-((1,2-Dichlorovinyl)oxy)-2-methylpropane, 3.21

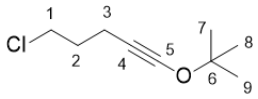


Potassium *tert*-butoxide (6.73 g, 60.0 mmol) was suspended in THF (20 mL) at 0 °C under a nitrogen atmosphere. Trichloroethylene (2.69 mL, 30.0 mmol) was then dropwise added with vigorous stirring, resulting in a brown solution. This was then warmed back to RT with stirring continued for 1 h, before water (40 mL) was added. The layers were separated and the aqueous

layer was extracted with ether (3 × 20 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by vacuum filtration through a pad of silica gel with pentane as eluent to give enol ether **3.21** (3.58 g, 71%) as an orange oil.

R_f 0.66 (pentane); **IR** ν_{max}/cm^{-1} 2984 (m), 1622 (s), 1395 (w), 1162 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.72 (s, 1H, H2), 1.48 (s, 9H, H4, H5, H6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 142.0 (C1), 102.3 (C2), 86.1 (C3), 28.7 (C4, C5, C6). Spectroscopic data in agreement with literature.[42]

1-(*tert*-Butoxy)-5-chloropent-1-yne, 3.23

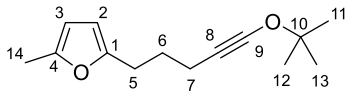


At –75 °C, butyllithium (10.0 mL, 2.50 M solution in hexanes, 25.00 mmol) was added dropwise to a solution of enol ether **3.21** (2.11 g, 12.50 mmol) in THF (10 mL). After 10 min of stirring, HMPA (4.75 mL, 27.5 mmol) was slowly added, followed by 1-bromo-3-chloropropane (1.47 mL, 11.9 mmol). The cooling bath was removed, the mixture was stirred for 24 h and then poured into 25 mL of ice-cold water. The layers were separated, and the aqueous layer extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified with silica gel chromatography (diethyl ether/pentane, 1:19) to give compound **3.23** (0.590 g, 29%) as a colourless oil.

R_f 0.87 (diethyl ether/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2980 (w), 2265 (s), 1370 (s), 1241 (s), 1159 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.66 (t, *J* = 6.5 Hz, 2H, H1), 2.35 (t, *J* = 6.5 Hz, 2H, H3), 1.91 (quin, *J* = 6.5 Hz, 2H, H4), 1.37 (s, 9H, H7, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C

86.3 (C5), 84.5 (C4), 43.9 (C1), 38.1 (C6), 32.4 (C2), 26.9 (C3), 14.9 (C7, C8, C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{16}ClO$, 175.0884; found, 175.0884.

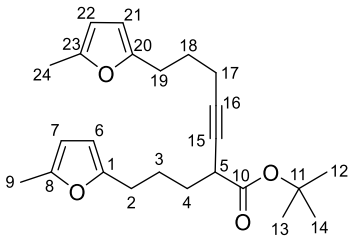
2-(5-(tert-Butoxy)pent-4-yn-1-yl)-5-methylfuran, 3.22



Butyllithium (0.600 mL, 2.5 M, 1.50 mmol) was dropwise added to a solution of 2-methylfuran (0.135 mL, 1.50 mmol) in THF (4 mL) at −50 °C. The mixture was warmed to 0 °C and stirred for 20 minutes. Then HMPA (34.7 µL, 0.200 mmol) and compound **3.23** (0.175 g, 1.00 mmol) were slowly added. The mixture was heated to 40 °C and stirred for 20 hours before being quenched by saturate ammonium chloride solution (15 mL). Diethyl ether (3 × 10 mL) was used to extract the aqueous layer, and the extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give compound **3.22** (0.148 g, 67%) as a pale-yellow oil, which was used directly without further purification.

R_f 0.70 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2980 (s), 2934 (w), 2265 (s), 1370 (s), 1239 (s), 1160 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.02 – 5.81 (m, 2H, H2, H3), 2.74 (t, *J* = 7.0 Hz, 2H, H5), 2.32 (d, *J* = 1.0 Hz, 3H, H14), 2.27 (t, *J* = 7.0 Hz, 2H, H7), 1.94 – 1.78 (m, 2H, H6), 1.45 (s, 9H, H11, H12, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 154.0 (C1, C4), 105.8 (C2), 105.5 (C3), 84.8 (C9), 78.8 (C10), 76.4 (C8), 29.7 (C5), 28.5 (C6), 27.0 (C11, C12, C13), 17.1 (C7), 13.5 (C14); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{21}O_2$, 221.1542; found, 221.1542.

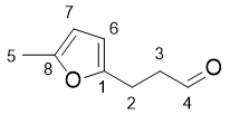
***tert*-Butyl 7-(5-methylfuran-2-yl)-2-(3-(5-methylfuran-2-yl)propyl)hept-3-ynoate, 3.30**



Ynol ether **3.22** (75.0 mg, 0.340 mmol) was added to a glass pressure tube loaded with toluene (3.4 mL) under argon. The tube was then sealed and its contents were heated to 90 °C for 2 hours. Afterwards, the reaction mixture was cooled to RT and transferred to a 25 mL round-bottom flask, where it was concentrated *in vacuo*. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:9) to give ester **3.30** (11.7 mg, 18%) as a colourless oil.

R_f 0.67 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2937 (w), 2256 (w), 1749 (s), 1602 (s), 1370 (s), 1159 (s); **^{1}H NMR** (600 MHz, C_6D_6) δ_H 5.90 (d, *J* = 3.0 Hz, 1H, H22), 5.87 (d, *J* = 3.0 Hz, 1H, H21), 5.78 (tt, *J* = 2.0 Hz, 1.0 Hz, 2H, H6, H7), 3.28 (ddt, *J* = 6.5 Hz, 4.5 Hz, 1.5 Hz, 1H, H5), 2.62 – 2.57 (m, 2H, H19), 2.57 – 2.53 (m, 2H, H2), 2.10 – 2.05 (m, 2H, H17), 2.04 (d, *J* = 1.5 Hz, 6H, H9, H24), 1.95 – 1.79 (m, 2H, H4), 1.79 – 1.66 (m, 2H, H19), 1.66 – 1.52 (m, 2H, H3), 1.03 (s, 9H, H12, H13, H14); **^{13}C NMR** (151 MHz, C_6D_6) δ_C 175.5 (C10), 154.1 (C20), 153.9 (C1), 149.9 (C8, C23), 106.0 (C6, C21), 105.8 (C7, C22), 81.3 (C16), 62.8 (C11), 60.9 (C15), 29.9 (C5), 28.2 (C2, C19), 28.0 (C12, C13, C14), 25.8 (C4), 25.2 (C17, C18), 23.5 (C3), 13.1 (C9, C24); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{33}O_4$, 385.2379; found, 385.2379.

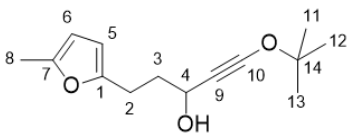
3-(5-Methylfuran-2-yl)propanal, 3.31



To a glass pressure tube were loaded 2-methylfuran (1.79 mL, 20.0 mmol), acrolein (1.47 mL, 22.0 mmol), hydroquinone (0.220 g, 2.00 mmol), acetic acid (0.2 mL) and water (1.4 mL) under an argon atmosphere. The tube was sealed and its contents were heated to 110 °C and stirred for 24 h. After cooling, the mixture in the tube was poured into 30 mL of saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound (2.76 g, 99%) as an orange oil, which was used without further purification.

R_f 0.72 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3461 (br w), 2923 (w), 1725 (s), 1513 (s), 1218 (s), 1021 (s), 753 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.71 (t, *J* = 1.5 Hz, 1H, H4), 5.83 (d, *J* = 3.0 Hz, 1H, H6), 5.82 (d, *J* = 3.0 Hz, 1H, H7), 2.85 (t, *J* = 7.5 Hz, 2H, H2), 2.68 (t, *J* = 7.5 Hz, 2H, H3), 2.18 (s, 3H, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.1 (C4), 152.0 (C1), 150.6 (C8), 106.1 (C6), 106.0 (C7), 41.8 (C3), 20.7 (C2), 13.3 (C5). Spectroscopic data in agreement with literature.[43]

1-(*tert*-Butoxy)-5-(5-methylfuran-2-yl)pent-1-yn-3-ol, 3.32

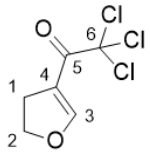


To a stirred solution of (*E*)-2-(1,2-dichlorovinyl)oxy)-2-methylpropane (0.845 g, 5.00 mmol) in THF (10 mL) at –78 °C was dropwise added *n*-butyllithium (1.6 M in hexanes, 5.94 mL,

9.50 mmol). This was stirred for 30 minutes before 3-(5-methylfuran-2-yl)propanal (0.622 g, 4.50 mmol) was slowly added. The mixture was warmed to 0 °C and stirred for a further 2 hours. It was then poured onto 25 mL of water. The layers were separated and the aqueous layer extracted by diethyl ether (3 × 10 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **3.32** (0.892 g, 84%) as a brown oil, which was used without further purification.

IR ν_{max}/cm^{-1} 3458 (br w), 2980 (w), 2924 (w), 2255 (s), 1153 (s), 1020 (s), 751 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.96 – 5.83 (m, 2H, H5, H6), 4.57 (q, *J* = 6.0 Hz, 1H, H4), 2.85 (t, *J* = 9.0 Hz, 2H, H2), 2.35 (s, 3H, H8), 2.18 – 1.99 (m, 2H, H3), 1.50 (d, *J* = 1.5 Hz, 9H, H11, H12, H13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.6 (C1), 150.5 (C7), 105.8 (C5), 105.6 (C6), 90.8 (10), 86.1 (C9), 62.1 (C4), 42.2 (C14), 37.3 (C3), 27.1 (C11, C12, C13), 24.1 (C2), 13.5 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{21}O_3$, 237.1485; found, 237.1483.

2,2,2-Trichloro-1-(4,5-dihydrofuran-3-yl)ethan-1-one, 4.02

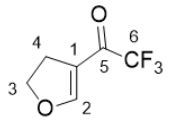


Trichloroacetyl chloride (6.73 mL, 60.0 mmol) was dropwise added to a solution of 2,3-dihydrofuran **4.01** (7.56 mL, 100 mmol) and pyridine (8.86 mL, 120 mmol) in DCM (20 mL). The resulting mixture was stirred for 3 h before being treated with sat. aq. $NaHCO_3$ (20 mL). The organic layer was isolated, washed with sat. aq. $CuSO_4$ (2 × 15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel

chromatography (ethyl acetate/pentane, 1:4) to give compound **4.02** (9.60 g, 74%) as a yellow oil.

R_f 0.91 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2977 (w), 1669 (s), 1594 (s), 1133 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.82 (t, *J* = 1.5 Hz, 1H, H3), 4.65 (t, *J* = 10.0 Hz, 2H, H2), 3.02 (t, *J* = 10.0 Hz, 2H, H1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 177.8 (C5), 162.6 (C3), 109.8 (C4), 96.0 (C6), 73.6 (C2), 28.7 (C1). Spectroscopic data in agreement with literature.[44]

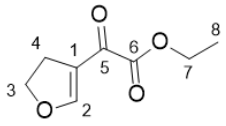
1-(4,5-Dihydrofuran-3-yl)-2,2,2-trifluoroethan-1-one, 4.03



TFAA (1.39 mL, 10.0 mmol) was added dropwise to a solution of 2,3-dihydrofuran **4.01** (3.00 mL, 39.7 mmol) and pyridine (5.00 mL, 62.1 mmol) in DCM (20 mL) at 0 °C. The resulting mixture was stirred for 18 h before being treated with saturated $NaHCO_3$ solution (20 mL). The organic layer was isolated, washed with sat. aq. $CuSO_4$ (2 × 15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **4.03** (1.02 g, 61%) as a yellow oil.

IR ν_{max}/cm^{-1} 2988 (w), 1678 (s), 1594 (s), 1193 (s), 1145 (s), 846 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64 (t, *J* = 1.5 Hz, 1H, H2), 4.68 (t, *J* = 10.0 Hz, 2H, H3), 2.98 (tq, *J* = 10.0 Hz, 0.5 Hz, 2H, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.1 (C5), 163.8 (C2), 116.6 (q, *J* = 5.0 Hz, C6), 114.4 (C1), 74.0 (C3), 26.9 (C4). Spectroscopic data in agreement with literature.[45]

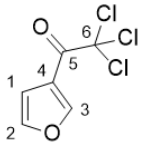
Ethyl 2-(4,5-dihydrofuran-3-yl)-2-oxoacetate, 4.04



To a stirred mixture of 2,3-dihydrofuran **4.01** (0.740 mL, 11.1 mmol) and pyridine (2.00 mL, 24.8 mmol) in 20 mL DCM was dropwise added ethyl chlorooxoacetate (1.12 mL, 10.0 mmol). The mixture was stirred at RT for 19 hours before water (30 mL) was added. The two layers were separated, and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **4.04** (1.65 g, 97%) as a colourless oil.

R_f 0.42 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2983 (w), 1729 (s), 1650 (s), 1590 (m), 1218 (s), 1140 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.96 (t, *J* = 1.5 Hz, 1H, H2), 4.67 (t, *J* = 10.0 Hz, 2H, H3), 4.31 (q, *J* = 7.0 Hz, 2H, H7), 2.88 (td, *J* = 10.0 Hz, 1.5 Hz, 2H, H4), 1.37 (t, *J* = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 178.6 (C5), 165.0 (C6), 161.9 (C2), 117.7 (C1), 73.8 (C3), 62.2 (C7), 27.1 (C4), 14.1 (C8). Spectroscopic data in agreement with literature.[46]

2,2,2-Trichloro-1-(furan-3-yl)ethan-1-one, 4.05

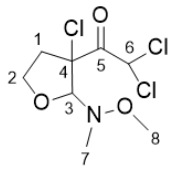


NBS (0.938 g, 5.27 mmol), AIBN (7.90 mg, 4.80 μmol) and compound **4.02** (1.03 g, 4.79 mmol) was added to a 50-mL round-bottom flask containing α,α,α-trifluorotoluene (10 mL). The mixture was heated to 70 °C for 2 h. After being cooled to RT, the mixture was filtered

under reduced pressure, and the filtrate was washed with water (5 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **4.05** (0.631 g, 62%) as an orange oil.

R_f 0.95 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3153 (w), 1706 (s), 1164 (s), 839 (s), 737 (s), 681 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.36 (d, *J* = 1.0 Hz, 1H, H3), 7.50 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H2), 6.96 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.5 (C5), 150.6 (C3), 143.6 (C2), 118.3 (C2), 110.9 (C1), 95.4 (C6). Spectroscopic data in agreement with literature.[47]

2,2-Dichloro-1-(3-chloro-2-(methoxy(methyl)amino)tetrahydrofuran-3-yl)ethan-1-one, 4.07

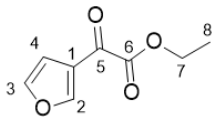


N,*O*-Dimethylhydroxylamine hydrochloride (0.390 g, 4.00 mmol) was suspended in THF (5 mL) at 0 °C. A solution of isopropylmagnesium chloride (2.0 M in THF, 4.00 mL, 8.00 mmol) was added dropwise to this suspension, yielding a clear, light brown solution. Then, a solution of ketone **4.02** (0.431 g, 2.00 mmol) in THF (1 mL) was slowly added. The cooling bath was removed, and the mixture was stirred at RT for 1.5 h before being poured into 15 mL of saturated NH_4Cl solution. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel

chromatography (ethyl acetate/pentane, 1:4) to give compound **4.07** (88.5 mg, 16%) as a colourless oil.

R$_f$ 0.76 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2969 (w), 2901 (w), 1747 (s), 1439 (w), 1035 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.39 (s, 1H, H6), 4.80 (s, 1H, H3), 4.28 (ddd, *J* = 10.0 Hz, 8.0 Hz, 2.0 Hz, 1H, H2a), 4.20 (ddd, *J* = 10.0 Hz, 8.0 Hz, 7.0 Hz, 1H, H2b), 3.25 (s, 3H, H8), 3.23 – 3.16 (m, 1H, H1a), 2.57 (s, 3H, H7), 2.22 (ddd, *J* = 14.0 Hz, 7.0 Hz, 2.0 Hz, 1H, H1b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 188.0 (C5), 171.0 (C4), 102.5 (C3), 67.7 (C2), 66.4 (C6), 58.2 (C8), 39.0 (C1), 36.0 (C7); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_8H_{13}Cl_3NO_3$, 275.9961; found, 275.9958.

Ethyl 2-(furan-3-yl)-2-oxoacetate, 4.11

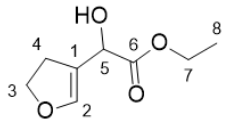


To a 50 mL round-bottom flask fitted with a condenser was loaded NBS (0.712 g, 4.00 mmol) and AIBN (16.4 mg, 0.100 mmol), compound **4.04** (0.340 g, 2.00 mmol) and CCl_4 (8 mL). This mixture was heated to reflux for 2 h; after cooling, it was quenched by saturated aqueous sodium thiosulfate (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **4.11** (0.229 g, 68%) as a yellow oil.

R$_f$ 0.83 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 2988 (w), 1734 (s), 1684 (s), 1249 (s), 1154 (s), 1040 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.56 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H2), 7.49 (t, *J* = 2.0 Hz, 1H, H3), 6.92 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H4), 4.41 (q, *J* = 7.0 Hz, 2H, H7), 1.43 (t,

J = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 178.0 (C5), 161.1 (C6), 152.0 (C2), 144.1 (C3), 123.9 (C1), 109.2 (C4), 62.6 (C7), 14.0 (C8). Spectroscopic data in agreement with literature.[48]

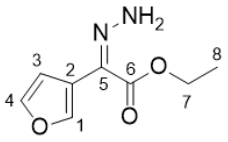
Ethyl 2-(4,5-dihydrofuran-3-yl)-2-hydroxyacetate, 4.12



$CeCl_3 \bullet 7H_2O$ (112 mg, 0.300 mmol) and $NaBH_4$ (39.7 mg, 1.05 mmol) were suspended in THF (2 mL) at 0 °C under argon. To this was added a solution of compound **4.04** (0.170 g, 1.00 mmol) in methanol (0.120 mL, 3.00 mmol). Stirring was continued for 3 h at 0 °C, then saturated aqueous ammonium chloride (5 mL) was added. The two layers were separated, and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give α-hydroxy ketone **4.12** (67.1 mg, 39%) as a colourless oil.

R_f 0.32 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3457 (br w), 2981 (w), 1739 (s), 1659 (w), 1104 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.43 (td, *J* = 2.0 Hz, 1.0 Hz, 1H, H2), 4.83 (d, *J* = 13.0 Hz, 1H, H5), 4.42 (dddd, *J* = 10.5 Hz, 9.0 Hz, 2.5 Hz, 1.5 Hz, 2H, H3), 4.28 (q, *J* = 7.0 Hz, 2H, H7), 2.79 – 2.65 (m, 1H, C4a), 2.61 – 2.43 (m, 1H, C4b), 1.31 (t, *J* = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.2 (C6), 144.9 (C2), 112.0 (C1), 70.7 (C3), 67.0 (C5), 62.0 (C7), 28.6 (C4), 14.1 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_8H_{13}O_4$, 173.0808; found, 173.0807.

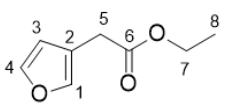
Ethyl 2-(furan-3-yl)-2-hydrazineylideneacetate, 4.13



Glacial acetic acid (0.530 mL, 9.26 mmol) was added to water (0.100 mL) at 5 °C under a nitrogen atmosphere; to this was added hydrazine (1.0 M in THF, 7.00 mL, 7.00 mmol). Then, keto ester **4.12** (0.589 g, 3.50 mmol) was slowly added. Three drops of methanol were introduced to homogenise the mixture, which was stirred at 50 °C for 18 hours. The mixture was poured into saturated aqueous sodium bicarbonate (10 mL), and the aqueous layer was extracted by ethyl acetate (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 2:3) to give hydrazone **4.13** (0.343 g, 54%) as a yellow oil.

R_f 0.37 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 3420 (br w), 2990 (w), 1703 (s), 1058 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.83 – 7.78 (m, 1H, H1), 7.56 (t, *J* = 1.5 Hz, 1H, H4), 6.67 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H3), 6.44 (br s, 2H, NH_2), 4.32 (q, *J* = 7.0 Hz, 2H, H7), 1.36 (t, *J* = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.2 (C6), 143.2 (C4), 143.1 (C1), 130.7 (C5), 113.4 (C2), 110.0 (C3), 61.3 (C7), 14.2 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_8H_{11}N_2O_3$, 183.0770; found, 183.0768.

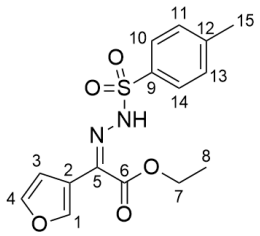
Ethyl 2-(furan-3-yl)acetate, 4.14



Hydrazone **4.13** (0.110 g, 0.604 mmol) was dissolved in chloroform (3 mL) under nitrogen. To this was added DBU (0.460 g, 3.02 mmol) dropwise. The mixture was stirred at RT for 16 hours and then diluted by DCM (15 mL). It was washed by 4% citric acid solution (2 × 5 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (5 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **4.14** (22.0 mg, 24%) as a yellow oil.

R_f 0.62 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2984 (w), 1739 (s), 1167 (s), 1031 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (d, J = 1.5 Hz, 2H, H1, H4), 6.25 (t, J = 1.5 Hz, 1H, H3), 4.20 (q, J = 7.0 Hz, 2H, H7), 3.45 (s, 2H, H5), 1.26 (t, J = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.3 (C6), 143.0 (C1), 140.6 (C4), 117.5 (C2), 111.4 (C3), 60.9 (C7), 31.0 (C5), 14.2 (C8). Spectroscopic data in agreement with literature.[49]

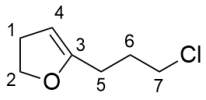
Ethyl 2-(furan-3-yl)-2-(2-tosylhydrazineylidene)acetate, 4.15



p-Toluenesulfonyl hydrazide (0.223 g, 1.20 mmol) and magnesium sulfate (0.181 g, 1.50 mmol) were suspended in a solution of **4.14** (0.168 g, 1.00 mmol) in methanol (2.5 mL). This mixture was placed under nitrogen and heated to 60 °C with stirring for 18 h, after which it was concentrated under reduced pressures. The residue was purified with silica gel chromatography (ethyl acetate/pentane, 2:3) to yield hydrazone **4.15** (0.188 g, 56%) as a white crystalline solid.

R_f 0.73 (ethyl acetate/pentane, 2:3); **IR** ν_{max}/cm^{-1} 3197 (w), 2935 (w), 1744 (w), 1707 (w), 1358 (w), 1170 (s), 1143 (s), 1082 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 11.86 (s, 1H, NH), 7.89 – 7.85 (m, 2H, H10, H14), 7.81 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H1), 7.35 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H, H4), 7.33 – 7.31 (m, 2H, H11, H13), 6.72 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H, H3), 4.37 (q, *J* = 7.0 Hz, 2H, H7), 2.42 (s, 3H, H15), 1.40 (t, *J* = 7.0 Hz, 3H, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 161.5 (C6), 144.3 (C5), 137.0 (C12), 143.3 (C1), 142.7 (C4), 135.4 (C9), 129.6 (C11, C13), 127.8 (C10, C14), 125.3 (C2), 109.0 (C3), 62.4 (C7), 21.5 (C15), 13.9 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{17}N_2O_5S$, 337.0853; found, 337.0847.

5-(3-Chloropropyl)-2,3-dihydrofuran, 4.19

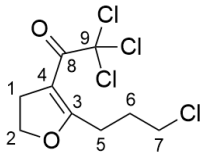


2,3-Dihydrofuran (8.0 mL, 106 mmol) and THF (10.0 mL) were added to a 50 mL round-bottom flask under argon. The solution was cooled to –75 °C, and *tert*-butyllithium solution (5.90 mL, 1.70 M solution in hexanes, 10.0 mmol) was dropwise added. The mixture was slowly warmed to 0 °C and stirred for another hour, then 1-bromo-3-chloropropane (1.08 mL, 11.0 mmol) was slowly added. The mixture was warmed to RT with stirring continued for another 16 h, then it was quenched by sat. aq. NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **4.19** (0.598 g, 41%) as a yellow oil, which was used without further purification.

R_f 0.94 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2958 (w), 2862 (w), 1668 (m), 1003 (s), 724 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.40 (sept, *J* = 1.0 Hz, 1H, H4), 3.99 (t, *J* = 9.0 Hz, 2H,

H2), 3.13 (t, *J* = 6.0 Hz, 2H, H7), 2.24 (tq, *J* = 9.0 Hz, 2.0 Hz, 2H, H5), 2.10 (tq, *J* = 7.0 Hz, 1.0 Hz, 2H, H1), 1.71 (quin, *J* = 7.0 Hz, 2H, H6); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 157.7 (C3), 94.6 (C4), 69.8 (C2), 44.3 (C7), 30.2 (C5), 30.0 (C6), 25.4 (C1). Spectroscopic data in agreement with literature.[50]

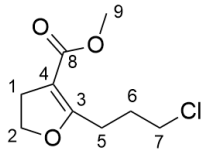
2,2,2-Trichloro-1-(2-(3-chloropropyl)-4,5-dihydrofuran-3-yl)ethan-1-one, 4.20



To a solution of **4.19** (0.325 g, 2.22 mmol) and pyridine (0.54 mL, 6.65 mmol) in DCM (6 mL) was dropwise added trichloroacetyl chloride (0.30 mL, 2.66 mmol). Stirring was continued for 15 h before sat. aq. $NaHCO_3$ (5 mL) was added. The organic layer was isolated, washed with sat. aq. $CuSO_4$ (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **4.20** (0.432 g, 90%) as a yellow oil.

R_f 0.95 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2955 (w), 1732 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.80 (m, 2H, H2), 3.20 (t, *J* = 6.7 Hz, 2H, H7), 2.86 – 2.73 (m, 4H, H1, H5), 1.91 – 1.80 (m, 2H, H6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 180.9 (C8), 176.6 (C3), 103.9 (C4), 98.3 (C9), 71.6 (C2), 43.7 (C7), 30.4 (C5), 29.0 (C1), 26.9 (C6); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{11}Cl_4O_2$, 290.9513; not found.

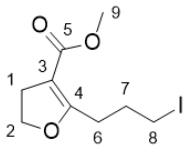
Methyl 2-(3-chloropropyl)-4,5-dihydrofuran-3-carboxylate, 4.21



Methanol (2 mL), compound **4.20** (0.215 g, 1.00 mmol) and sodium methoxide (0.108 g, 2.00 mmol) were added to a glass pressure tube under a nitrogen atmosphere. The tube was sealed and its contents were heated to 80 °C and stirred for 15 h. After being cooled to RT, the mixture was poured into sat. aq. NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **4.21** (0.176 g, 86%) as a yellow oil, which was used without further purification.

R_f 0.95 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2950 (w), 1697 (s), 1642 (s), 1122 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.30 – 4.21 (m, 2H, H7), 3.70 (s, 3H, H9), 3.52 (m, 2H, H2), 3.15 – 3.05 (m, 2H, H5), 2.82 – 2.74 (m, 2H, H1), 2.16 – 2.05 (m, 2H, H6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.3 (C8), 168.7 (C3), 98.4 (C4), 71.8 (C7), 50.9 (C9), 43.0 (C2), 31.2 (C5), 29.7 (C1), 24.1 (C6); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{14}ClO_3$, 205.0631; found, 205.0631.

Methyl 2-(3-iodopropyl)-4,5-dihydrofuran-3-carboxylate, 4.22

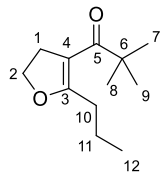


Compound **4.21** (0.106 g, 0.518 mmol), acetone (2 mL) and sodium iodide (0.250 g, 1.668 mmol) were added to a glass pressure tube under N_2. The tube was sealed and its contents were

heated to 65 °C and stirred for 24 h. After being cooled to RT, the mixture was poured into 50 mL of pentane and filtered under reduced pressures. The filtrate was concentrated *in vacuo* to give compound **4.22** (0.143 g, 93%) as a yellow oil, which was used without further purification.

R_f 0.96 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2952 (w), 1688 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.45 – 4.36 (m, 2H, H2), 3.72 (d, *J* = 0.7 Hz, 3H, H9), 3.20 (t, *J* = 7.0 Hz, 2H, H8), 2.88 (m, 2H, H1), 2.75 (tt, *J* = 7.5 Hz, 2H, H6), 2.16 – 2.04 (m, 2H, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.2 (C5), 166.2 (C4), 102.4 (C3), 70.4 (C2), 50.9 (C9), 30.7 (C7), 29.6 (C1), 28.6 (C6), 5.2 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{14}IO_3$, 296.9988, not found.

2,2-Dimethyl-1-(2-propyl-4,5-dihydrofuran-3-yl)propan-1-one, 4.24

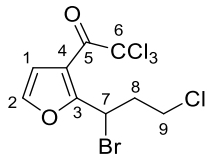


tert-Butyllithium solution (0.710 mL, 1.7 M in hexanes, 1.21 mmol) was dropwise added to a solution of **4.22** (0.143 g, 0.484 mmol) in THF (10 mL) at −78 °C. Stirring was continued for another 30 min, then the mixture was quenched with sat. aq. NH_4Cl (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (diethyl ether/pentane, 1:4) to give compound **4.24** (7.30 mg, 8%) as a yellow oil.

R_f 0.96 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2944 (w), 1720 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.37 (t, *J* = 9.0 Hz, 2H, H2), 3.21 – 3.04 (m, 2H, H1), 2.61 – 2.48 (m, 2H, H10), 1.64 – 1.49 (m, 2H, H11), 1.17 (s, 9H, H7, H8, H9), 1.01 – 0.90 (m, 3H, H12); **^{13}C NMR** (101

MHz, $CDCl_3$) δ_C 203.3 (C3), 174.4 (C4), 109.4 (C6), 70.4 (C2), 31.8 (C1), 30.7 (C10), 26.5 (C7, C8, C9), 20.2 (C11), 14.0 (C12); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{21}O_2$, 197.1542; found, 197.1542.

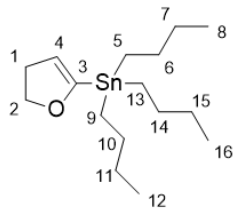
1-(2-(1-Bromo-3-chloropropyl)furan-3-yl)-2,2,2-trichloroethan-1-one, 4.25



NBS (0.395 g, 2.22 mmol), AIBN (4.85 mg, 0.296 mmol) and compound **4.20** (0.431 g, 1.48 mmol) was added to a 50-mL round-bottom flask containing α,α,α-trifluorotoluene (10 mL). The mixture was heated to 70 °C for 2 h. After being cooled to RT, the mixture was filtered under reduced pressure, and the filtrate was washed with sat. aq. $Na_2S_2O_3$ (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **4.25** (0.219 g, 40%) as an orange oil.

R_f 0.75 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2939 (w), 1672 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 (t, *J* = 1.5 Hz, 1H, H2), 7.04 (t, *J* = 1.5 Hz, 1H, H1), 6.02 (dd, *J* = 9.0 Hz, 5.5 Hz, 1H, H7), 3.79 – 3.61 (m, 2H, H9), 2.79 (m, 1H, H8a), 2.72 – 2.52 (m, 1H, H8b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 178.7 (C5), 162.8 (C3), 142.1 (C2), 119.2 (C4), 111.4 (C1), 93.1 (C6), 41.2 (C7), 38.2 (C9), 23.1 (C8); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_8BrCl_4O_2$, 366.8462; not found.

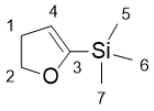
Tributyl(4,5-dihydrofuran-2-yl)stannane, 4.26



2,3-Dihydrofuran (0.380 mL, 5.00 mmol) and THF (6 mL) were added to a 50 mL round-bottom flask under argon. The solution was cooled to –75 °C, and *tert*-butyllithium solution (4.41 mL, 1.70 M solution in hexanes, 7.50 mmol) was dropwise added. The mixture was slowly warmed to 0 °C over 1 h before cooled to –30 °C; tributyltin chloride (1.22 mL, 4.50 mmol) was slowly added, and the mixture was warmed to RT over 1 h. The mixture was quenched with sat. aq. NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **4.26** (1.76 g, 98%) as a colourless volatile liquid, which was used without further purification.

IR ν_{max}/cm^{-1} 2953 (w), 1464 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.06 (t, J = 2.5 Hz, 1H, H4), 4.22 (t, J = 9.5 Hz, 2H, H2), 2.56 (td, J = 9.5 Hz, 2.5 Hz, 2H, H1), 1.64 – 1.46 (m, 6H, H5, H9, H13), 1.42 – 1.26 (m, 6H, H6, H10, H14), 1.05 – 0.96 (m, 6H, H7, H11, H15), 0.92 (t, J = 7.5 Hz, 12H, H8, H12, H16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.4 (C3), 111.5 (C4), 69.8 (C2), 29.9 (C1), 28.9 (C5, C9, C13), 27.2 (C6, C10, C14), 13.6 (C7, C11, C15), 9.5 (C8, C12, C16). Spectroscopic data in agreement with literature.[51]

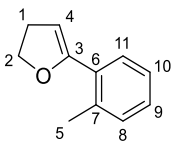
(4,5-Dihydrofuran-2-yl)trimethylsilane, 4.27



2,3-Dihydrofuran (0.380 mL, 5.00 mmol) and THF (6 mL) were added to a 50 mL round-bottom flask under argon. The solution was cooled to –75 °C, and *tert*-butyllithium solution (3.53 mL, 1.70 M solution in hexanes, 6.00 mmol) was dropwise added. The mixture was slowly warmed to 0 °C over 1 h before cooled to –30 °C; trimethylsilyl chloride (0.57 mL, 4.50 mmol) was slowly added, and the mixture was warmed to RT over 1 h. The mixture was quenched with sat. aq. NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give silane **4.27** (0.354 g, 55%) as a colourless volatile liquid, which was used without further purification.

IR ν_{max}/cm^{-1} 2960 (m), 1580 (w), 1249 (s), 1050 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.19 (t, J = 2.5 Hz, 1H, H4), 4.27 (tt, J = 10.0 Hz, 1.0 Hz, 1H, H2), 2.58 (dt, J = 10.0 Hz, 2.5 Hz, 1H, H1), 0.15 (s, 9H, H5, H6, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.4 (C3), 111.2 (C4), 70.5 (C2), 30.7 (C1), −2.20 (C5, C6, C7). Spectroscopic data in agreement with literature.[52]

5-(*o*-Tolyl)-2,3-dihydrofuran, 4.31

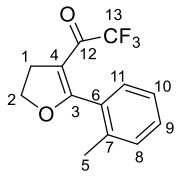


Stannane **4.26** (0.359 g, 1.00 mmol), 2-iodotoluene (0.196 g, 0.90 mmol), palladium(II) acetate (11.2 mg, 0.0500 mmol) and acetonitrile (3 mL) were added to a glass pressure tube under a

nitrogen atmosphere. The tube was sealed, and its contents were stirred at RT for 18 h. Afterwards, it was concentrated under reduced pressures to give compound **4.31** (68.9 mg, 43%) as a yellow oil, which was used without further purification.

IR ν_{max}/cm^{-1} 2961 (w), 1573 (s), 1224 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (d, *J* = 8.0 Hz, 1H, H11), 7.72 – 7.37 (m, 3H, H8, H9, H10), 5.20 (t, *J* = 3.0 Hz, 1H, H4), 4.68 – 4.37 (m, 2H, H2), 2.92 (td, *J* = 9.5 Hz, 3.0 Hz, 2H, H1), 2.50 (d, *J* = 3.0 Hz, 3H, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 155.8 (C3), 137.4 (C7), 131.1 (C6), 129.5 (C8), 129.3 (C9), 126.3 (C11), 125.6 (C10), 100.5 (C4), 70.7 (C2), 28.8 (C1), 20.8 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{13}O$, 161.0966; found, 161.0966.

2,2,2-Triluoro-1-(2-(*o*-tolyl)-4,5-dihydrofuran-3-yl)ethan-1-one, 4.32

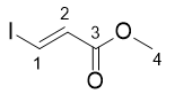


Compound **4.31** (0.385 g, 2.40 mmol) and pyridine (0.290 mL, 3.60 mmol) were dissolved in DCM (3 mL) under nitrogen. To this was added TFAA (0.350 mL, 2.52 mmol), and the mixture was stirred at RT for 22 h. Afterwards, it was diluted by water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:9) to give ketone **4.32** (20.8 mg, 34%) as an orange oil.

R_f 0.77 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2929 (w), 1693 (s), 1613 (s), 1137 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45 (td, *J* = 7.5 Hz, 2.0 Hz, 1H, H11), 7.39 – 7.27 (m, 3H, H8,

H9, H10), 4.83 (t, *J* = 9.5 Hz, 2H, H2), 3.46 – 3.25 (m, 2H, H1), 2.38 (s, 3H, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.0 (C12), 136.9 (C3), 130.5 (C8, C9), 128.9 (C6, C7), 125.2 (C10, C11), 115.4 (q, *J* = 5.0 Hz, C13), 108.0 (C4), 72.4 (C9), 29.2 (C10), 19.2 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{12}F_3O_2$, 257.0789; found, 257.0788.

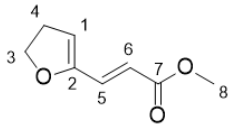
Methyl (*E*)-3-iodoacrylate, 4.36



Sodium iodide (2.70 g, 18.0 mmol), methyl propiolate (1.34 mL, 15.0 mmol) and acetic acid (3 mL) was added to a glass pressure tube under a nitrogen atmosphere. The tube was sealed and its content heated to 70 °C and stirred for 15 h. After cooling the content was poured onto 40 mL of saturated $NaHCO_3$ solution and diluted with 10 mL water. The two layers were separated, and the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified with silica gel chromatography (diethyl ether/pentane, 1:19) to give compound **4.36** (2.41 g, 76%) as a colourless oil.

R_f 0.68 (ethyl acetate/pentane, 1:19); **IR** ν_{max}/cm^{-1} 2950 (w), 1730 (s), 1598 (s), 1327 (s), 1204 (s), 1166 (s), 809 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.89 (d, *J* = 15.0 Hz, 1H, H1), 6.88 (d, *J* = 15.0 Hz, 1H, H2), 3.75 (m, 3H, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.8 (C3), 136.2 (C1), 99.7 (C2), 52.1 (C4). Spectroscopic data in agreement with literature.[53]

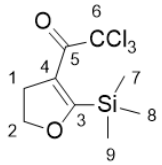
Methyl (*E*)-3-(4,5-dihydrofuran-2-yl)acrylate, 4.37



Stannane **4.26** (0.359 g, 1.00 mmol), methyl 3-iodoacrylate **4.36** (0.212 g, 1.00 mmol), bis(triphenylphosphine)palladium(II) dichloride (7.02 mg, 0.0100 mmol) and benzene (3 mL) were added to a glass pressure tube under a nitrogen atmosphere. The tube was sealed, and its contents were heated to 80 °C and stirred for 4 h. After cooling to RT, the reaction mixture was transferred into a 50 mL round-bottom flask and concentrated under reduced pressures to give compound **4.37** (0.129 g, 84%) as a yellow oil, which was used without further purification.

R_f 0.66 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2958 (s), 2931 (s), 1723 (s), 1463 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.12 (d, J = 15.5 Hz, 1H, H5), 6.09 (d, J = 15.5 Hz, 1H, H6), 5.41 – 5.35 (m, 1H, H1), 4.43 (t, J = 9.5 Hz, 2H, H3), 3.76 (s, 3H, H8), 2.84 – 2.73 (m, 2H, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.4 (C7), 154.5 (C2), 132.2 (C5), 118.5 (C6), 109.2 (C1), 70.0 (C3), 51.6 (C8), 30.8 (C4); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_8H_{11}O_3$, 155.0703; found, 155.0702.

2,2,2-Trichloro-1-(2-(trimethylsilyl)-4,5-dihydrofuran-3-yl)ethan-1-one, 4.40

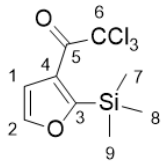


To a solution of silane **4.27** (0.142 g, 1.00 mmol) and pyridine (2.00 mL, 24.8 mmol) in DCM (3 mL) was dropwise added trichloroacetyl chloride (0.10 mL, 0.90 mmol). Stirring was

continued for 15 h before sat. aq. $NaHCO_3$ (5 mL) was added. The organic layer was isolated, washed with sat. aq. $CuSO_4$ (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **4.40** (0.194 g, 67%) as a yellow oil, which was used without further purification.

R_f 0.90 (diethyl ether/pentane, 1:4); **IR** ν_{max}/cm^{-1} 2972 (w), 2901 (w), 1670 (s), 1514 (s), 1153 (s), 842 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.63 (t, *J* = 10.0 Hz, 2H, H2), 3.25 (t, *J* = 10.0 Hz, 2H, H1), 0.28 (s, 9H, H7, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.3 (C5), 130.4 (C3), 114.5 (C4), 104.3 (C6), 75.3 (C2), 30.7 (C1), −2.8 (C7, C8, C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{14}Cl_3O_2Si$, 286.9829; found, 286.9823.

2,2,2-Trichloro-1-(2-(trimethylsilyl)furan-3-yl)ethan-1-one, 4.41

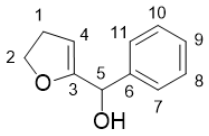


Compound **4.40** (0.133 g, 0.463 mmol), NBS (0.0905 g, 0.509 mmol) and AIBN (1.50 mg, 9.30 µmol) was added to a 50 mL round-bottom flask containing α,α,α-trifluorotoluene (6 mL). The mixture was heated to 80 °C with stirring for 1 hour. After being cooled to RT, the mixture was filtered *in vacuo*. The filtrate was washed by brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressures to give furan **4.41** (0.0972 g, 74%) as a yellow oil, which was used without further purification.

R_f 0.94 (diethyl ether/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2960 (w), 1704 (w), 1251 (w), 845 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62 (d, *J* = 2.0 Hz, 1H, H2), 7.03 (d, *J* = 2.0 Hz, 1H, H1), 0.37 (s, 9H, H7, H8, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.8 (C5), 146.0 (C2), 126.7 (C3),

111.1 (C1), 75.3 (C4), 30.6 (C6), −2.7 (C7, C8, C9); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_9H_{11}Cl_3O_2Si$, 284.9667; found, 284.9662.

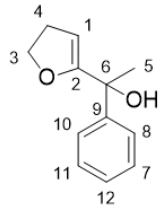
(4,5-Dihydrofuran-2-yl)(phenyl)methanol, 4.42



2,3-Dihydrofuran (0.460 mL, 6.00 mmol) and THF (20 mL) were added to a 50 mL round-bottom flask under argon. The solution was cooled to –75 °C, and *tert*-butyllithium solution (4.24 mL, 1.70 M solution in hexanes, 7.20 mmol) was dropwise added. The mixture was slowly warmed to 0 °C over 1 h before cooled to –30 °C; benzaldehyde (0.550 mL, 5.40 mmol) was slowly added, and the mixture was warmed to RT over 1 h. The mixture was quenched by slow addition of sat. aq. NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield compound **4.42** (0.880 g, 92%) as a colourless oil, which was used without further purification.

R_f 0.31 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3424 (br), 2863 (w), 1667 (w), 938 (s), 700 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 (dd, *J* = 8.0 Hz, 1.5 Hz, 2H, H7, H11), 7.38 – 7.27 (m, 3H, H8, H9, H10), 5.25 (s, 1H, H4), 4.78 (td, *J* = 2.5 Hz, 1.0 Hz, 1H, H5), 4.37 (t, *J* = 9.5 Hz, 2H, H2), 2.65 (d, *J* = 4.5 Hz, 1H, OH), 2.64 (tdd, *J* = 9.5 Hz, 2.5 Hz, 1.5 Hz, 2H, H1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 158.9 (C3), 140.6 (C6), 128.2 (C8, C10), 127.9 (C9), 126.6 (C7, C11), 96.9 (C4), 70.5 (C5), 70.2 (C2), 29.8 (C1); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0833. Spectroscopic data in agreement with literature.[54]

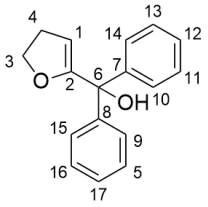
1-(4,5-Dihydrofuran-2-yl)-1-phenylethan-1-ol, 4.43



2,3-Dihydrofuran (0.460 mL, 6.00 mmol) and THF (20 mL) were added to a 50 mL round-bottom flask under argon. The solution was cooled to –75 °C, and *tert*-butyllithium solution (4.24 mL, 1.70 M solution in hexanes, 7.20 mmol) was dropwise added. This mixture was then slowly warmed to 0 °C and stirred for 2 h before acetophenone (0.630 mL, 5.40 mmol) was added. The cooling bath was removed and the mixture stirred for a further 15 h. Then the mixture was poured onto 20 mL of water. The two layers were separated, and the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified with silica gel chromatography (diethyl ether/pentane, 1:19) to give alcohol **4.43** (0.662 g, 73%) as a colourless oil.

R_f 0.68 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3581 (w), 2983 (w), 1659 (w), 1030 (s), 701 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56 – 7.46 (m, 2H, H8, H10), 7.40 – 7.28 (m, 2H, H7, H11), 7.27 – 7.24 (m, 1H, H12), 5.10 – 4.83 (m, 1H, H1), 4.37 (t, *J* = 9.0 Hz, 2H, H3), 2.70 (td, *J* = 9.0 Hz, 2.5 Hz, 2H, H4), 1.67 (s, 3H, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.1 (C2), 143.5 (C9), 128.1 (C7, C11), 127.8 (C10), 126.3 (C8, C12), 97.3 (C1), 74.8 (C6), 70.7 (C3), 29.7 (C4), 28.3 (C5); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{15}O_2$, 191.1067; found, 191.1068.

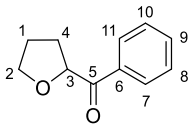
(4,5-Dihydrofuran-2-yl)diphenylmethanol, 4.44



2,3-Dihydrofuran (0.230 mL, 3.00 mmol) and THF (5 mL) were added to a 50 mL round-bottom flask under argon. The solution was cooled to –75 °C, and *tert*-butyllithium solution (2.12 mL, 1.70 M solution in hexanes, 3.60 mmol) was dropwise added. This mixture was then slowly warmed to 0 °C and stirred for 2 h before benzophenone (0.492 g, 2.70 mmol) was added. The cooling bath was removed and the mixture stirred for a further 15 h. Then the mixture was poured onto 20 mL of water. The two layers were separated, and the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified with silica gel chromatography (diethyl ether/pentane, 1:4) to give alcohol **4.44** (0.237 g, 35%) as a colourless oil.

R_f 0.77 (ethyl acetate/pentane, 1:4); **IR** ν_{max}/cm^{-1} 3490 (br w), 2922 (w), 1450 (s), 1279 (s); 1H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.37 (m, 4H, H9, H10, H14, H15), 7.27 – 7.18 (m, 6H, H5, H11, H12, H13, H16, H17), 4.50 (t, *J* = 2.5 Hz, 1H, H1), 4.35 (t, *J* = 9.5 Hz, 2H, H3), 3.32 (s, 1H, OH), 2.58 (dt, *J* = 9.5 Hz, 2.5 Hz, 2H, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 160.1 (C2), 143.9 (C7, C8), 127.6 (C5, C11, C13, C16), 127.2 (C12, C17), 127.0 (C9, C10, C14, C15), 100.1 (C1), 77.3 (C6), 70.6 (C3), 30.0 (C4). Spectroscopic data in agreement with literature.[55]

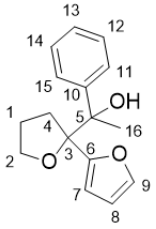
Phenyl(tetrahydrofuran-2-yl)methanone, 4.45



Alcohol **4.42** (52.9 mg, 0.300 mmol) was added to a solution of CSA (6.97 mg, 30.0 µmol) in HFIP/chloroform (1:4 v/v, 2.5 mL) under nitrogen. The mixture was stirred at RT for 40 hours before being quenched by sat. aq. $NaHCO_3$ (5 mL). The two layers were separated, and the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified with silica gel chromatography (ethyl acetate/pentane, 1:9) to give compound **4.45** (0.345 g, 65%) as a yellow oil.

R_f 0.39 (ethyl acetate/pentane, 1:9); **IR** ν_{max}/cm^{-1} 2977 (w), 2873 (w), 1687 (s), 1224 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.04 – 7.98 (m, 2H, H7, H11), 7.61 – 7.55 (m, 1H, H9), 7.48 (dd, *J* = 8.5 Hz, 7.0 Hz, 2H, H8, H10), 5.27 (dd, 1H, *J* = 8.5 Hz, 6.0 Hz, H3), 4.05 (dt, *J* = 8.6, 7.0 Hz, 1H, H2a), 3.99 (dt, *J* = 8.5 Hz, 7.0 Hz, 1H, H2b), 2.36 – 2.25 (m, 1H, H4a), 2.15 (ddt, *J* = 12.5 Hz, 8.0 Hz, 6.0 Hz, 1H, H4b), 2.03 – 1.94 (m, 2H, H1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 198.8 (C5), 135.1 (C6), 133.3 (C9), 128.7 (C8, C10), 128.6 (C7, C11), 79.9 (C3), 69.4 (C2), 29.3 (C4), 25.6 (C1). Spectral information in agreement with literature.[56]

1-(2-(Furan-2-yl)tetrahydrofuran-2-yl)-1-phenylethan-1-ol, 4.48



To a stirred mixture containing chloroform (2.0 mL) and HFIP (0.5 mL) at RT was added CSA (5.80 mg, 25.0 μmol). This was followed by dropwise addition of a solution of **4.43** (95.1 mg, 0.500 mmol) in furan (0.180 mL, 2.50 mmol). After 17 h of stirring at RT, the mixture was poured into saturated $NaHCO_3$ solution (5 mL). Diethyl ether (3 × 5 mL) was used to extract the aqueous layer. The extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (ethyl acetate/pentane, 1:4) to give compound **4.48** (59.4 mg, 46%) as a yellow oil.

R_f 0.56 (ethyl acetate/pentane, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 (ddd, *J* = 9.0 Hz, 2.0 Hz, 1.0 Hz, 1H, H9), 7.35 – 7.23 (m, 5H, H11, H12, H13, H14, H15), 6.33 (ddd, *J* = 9.0 Hz, 3.0 Hz, 2.0 Hz, 1H, H8), 6.13 (ddd, *J* = 8.0 Hz, 3.0 Hz, 1.0 Hz, 1H, H7), 4.00 − 3.78 (m, 2H, H2), 3.06 (s, 1H, OH), 2.44 – 2.18 (m, 2H, H4), 1.96 – 1.81 (m, 2H, H1), 1.63 (s, 3H, H16); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.3 (C10), 143.4 (C6), 141.7 (C9), 127.4 (C13), 127.2 (C12), 126.8 (C14), 126.6 (C11), 125.1 (C15), 110.2 (C8), 108.7 (C7), 89.2 (C3), 77.2 (C5), 69.2 (C2), 32.2 (C4), 25.8 (C1), 25.6 (C16); **HRMS** (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_3$, 259.1329; found, 259.1329.

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Appendices

Appendix 1: P450 enzyme screening data

List of all $P450_{BM3}$ variants used

Abbreviation	Mutations
-	A330P
GLQ	GLQ/IG/A328G
GV	GV/A184I
	GV/A184I/I263G/A328G
GVQ	GVQ
	GVQ/A328G
	GVQ/A330W
	GVQ/I263G/V78L
K19	K19/F87V
	K19/F87V/A328V
	K19/F87V/E267V
	K19/F87V/E267V/V78I
	K19/F87V/Q403P
KSK19	KSK19/A82M
	KSK19/A82M/I263G
	KSK19/F81W
	KSK19/I263A
	KSK19/I264G
	KSK19IG
KU3	KU3/A330P/I263G
	KU3/AP/IA
	KU3/AP/S72W
R19	R19/A328L/A184I

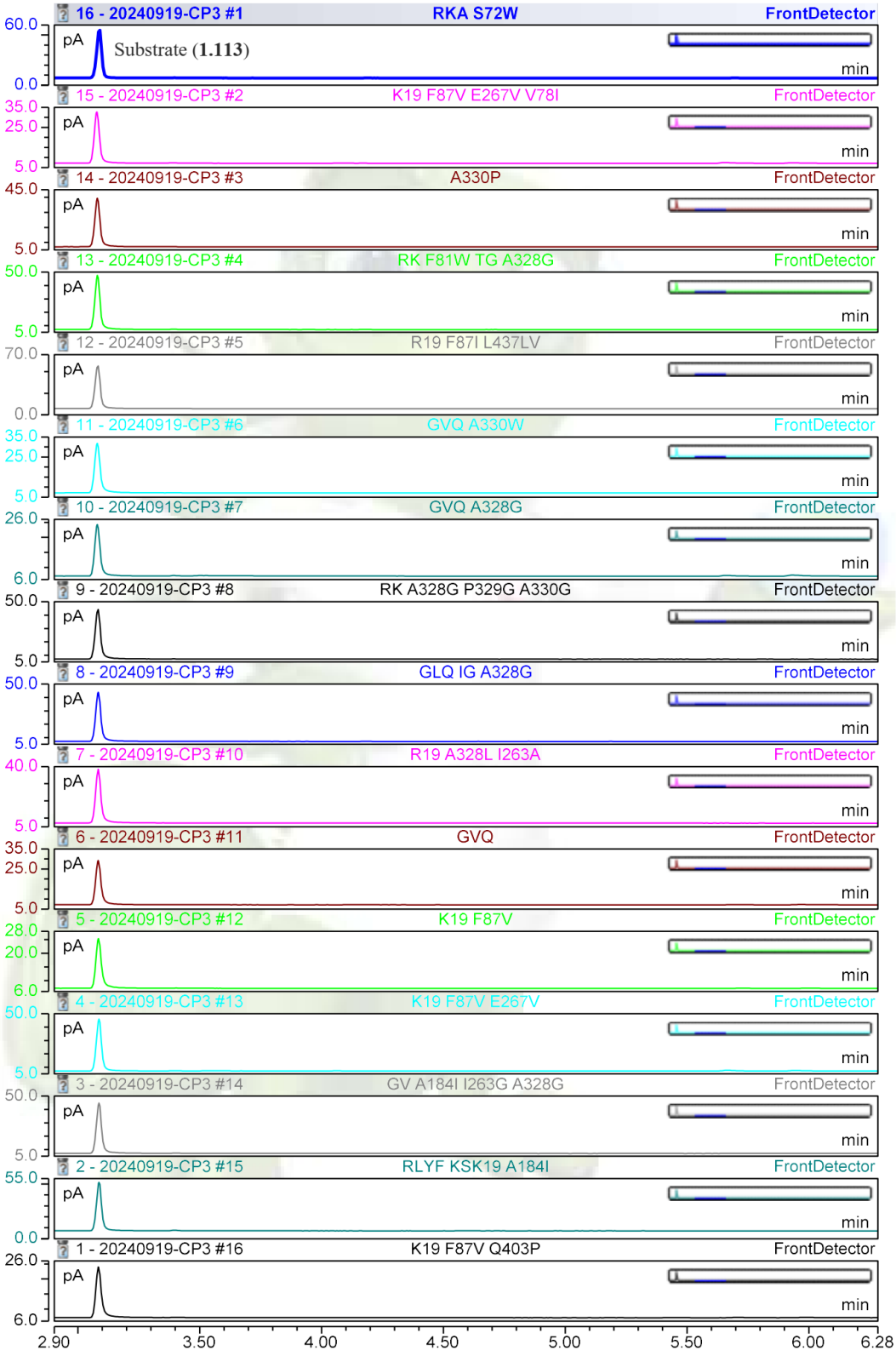
R19	R19/A328L/I263A
	R19/A330W
	R19/F87I
	R19/F87I/L437LV
	R19FI
RK	RK
	RK/A184I/T260G/A328G
	RK/A328G
	RK/A328G/P329G/A330G
	RK/A328L
	RK/F81W/TG/A328G
	RK/I263G
	RKA/S72W
	RK/A184I/T260G/A328G
RLYF	RLYF/K19
	RLYF/KSK19
	RLYF/KSK19/A184I
RP	RP/H171L/I263G
RT2	RT2/A330P/V78I/A184I
	RT2/S72G/A330W

Full screening data for substrate 1.113 (see *Scheme 39* and *Table 1* in Chapter 1)

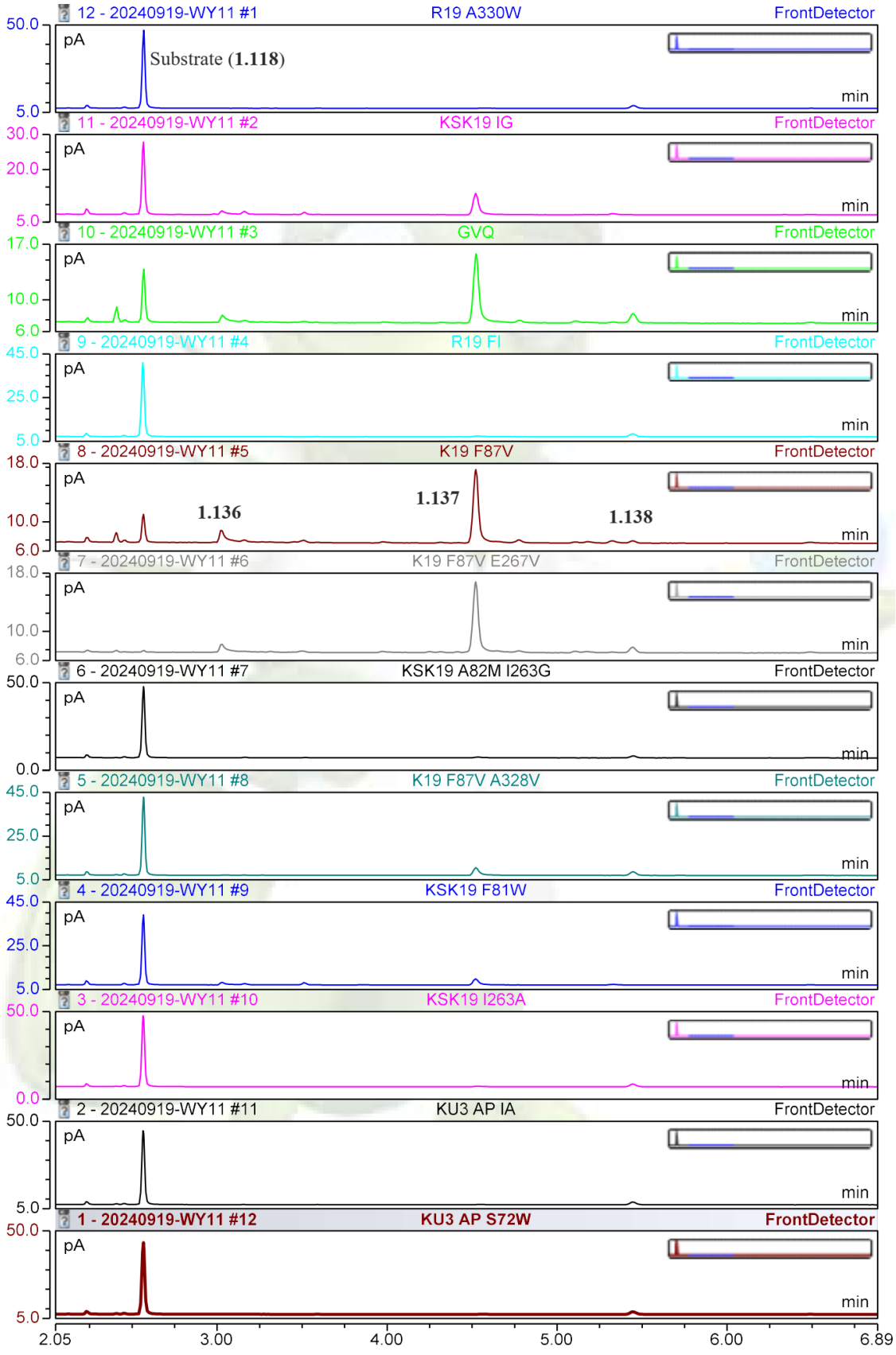
Entry	Enzyme variant	Substrate Conversion	1.134	1.135	Others
1	GVQ/A328G	12%	9%	71%	20%
2	K19/F87V/E267V/V78I	8%	13%	87%	0%
3	K19/F87V/E267V	6%	9%	91%	0%
4	GVQ	4%	0%	100%	0%
5	RKA/S72W	1%	100%	0%	0%
6	RK/F81W/TG/A328G	1%	100%	0%	0%
7	RLYF/KSK19/A184I	1%	100%	0%	0%
8	A330P	0%			
9	GLQ/IG/A328G	0%			
10	GV/A184I/I263G/A328G	0%			
11	GVQ/A330W	0%			
12	K19/F87V	0%			
13	K19/F87V/Q403P	0%			
14	R19/A328L/I263A	0%			
15	R19/F87I/L437LV	0%			
16	RK/A328G/P329G/A330G	0%			

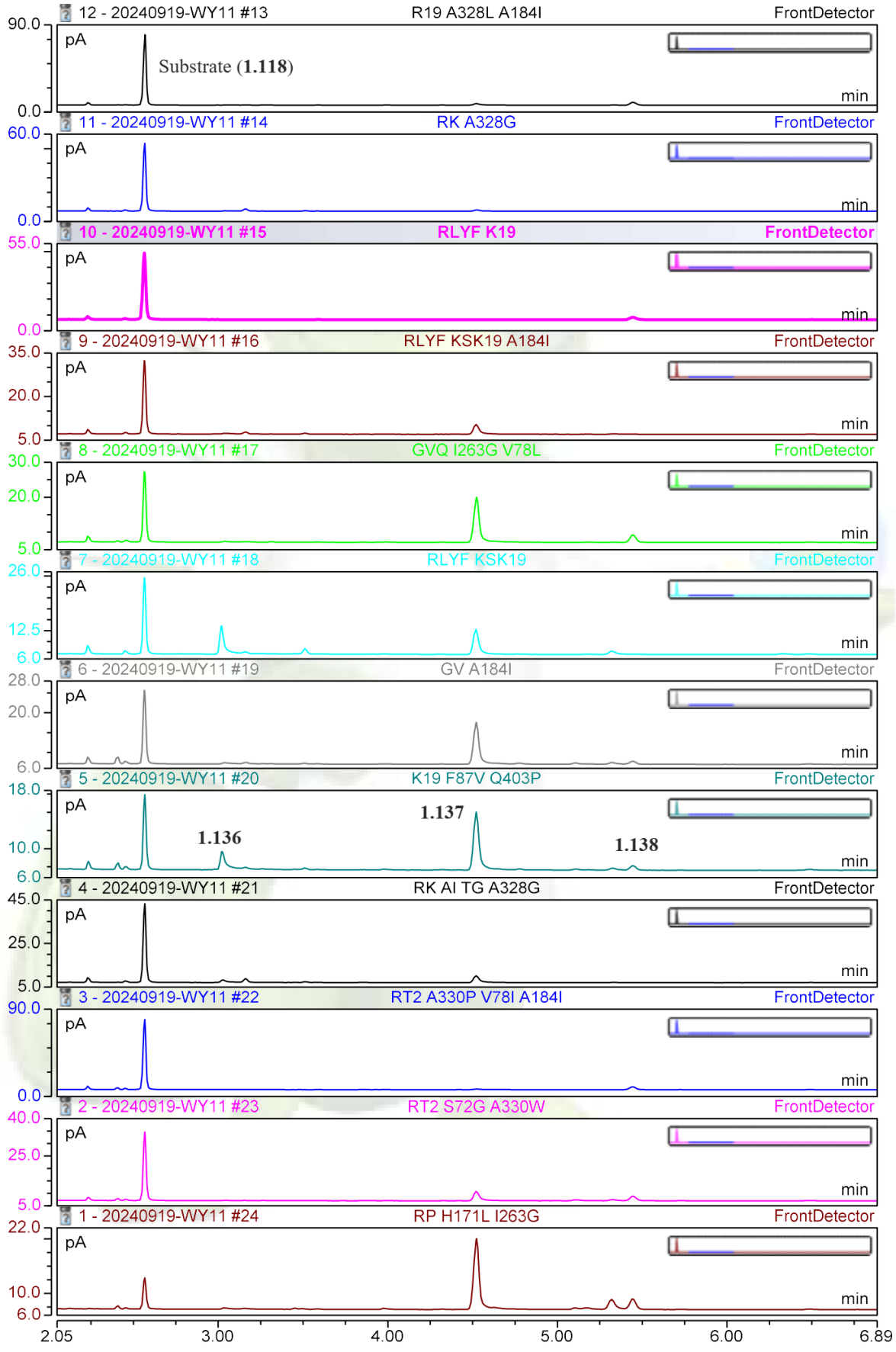
GC chromatograms of P450 enzyme screens

Substrate 1.113

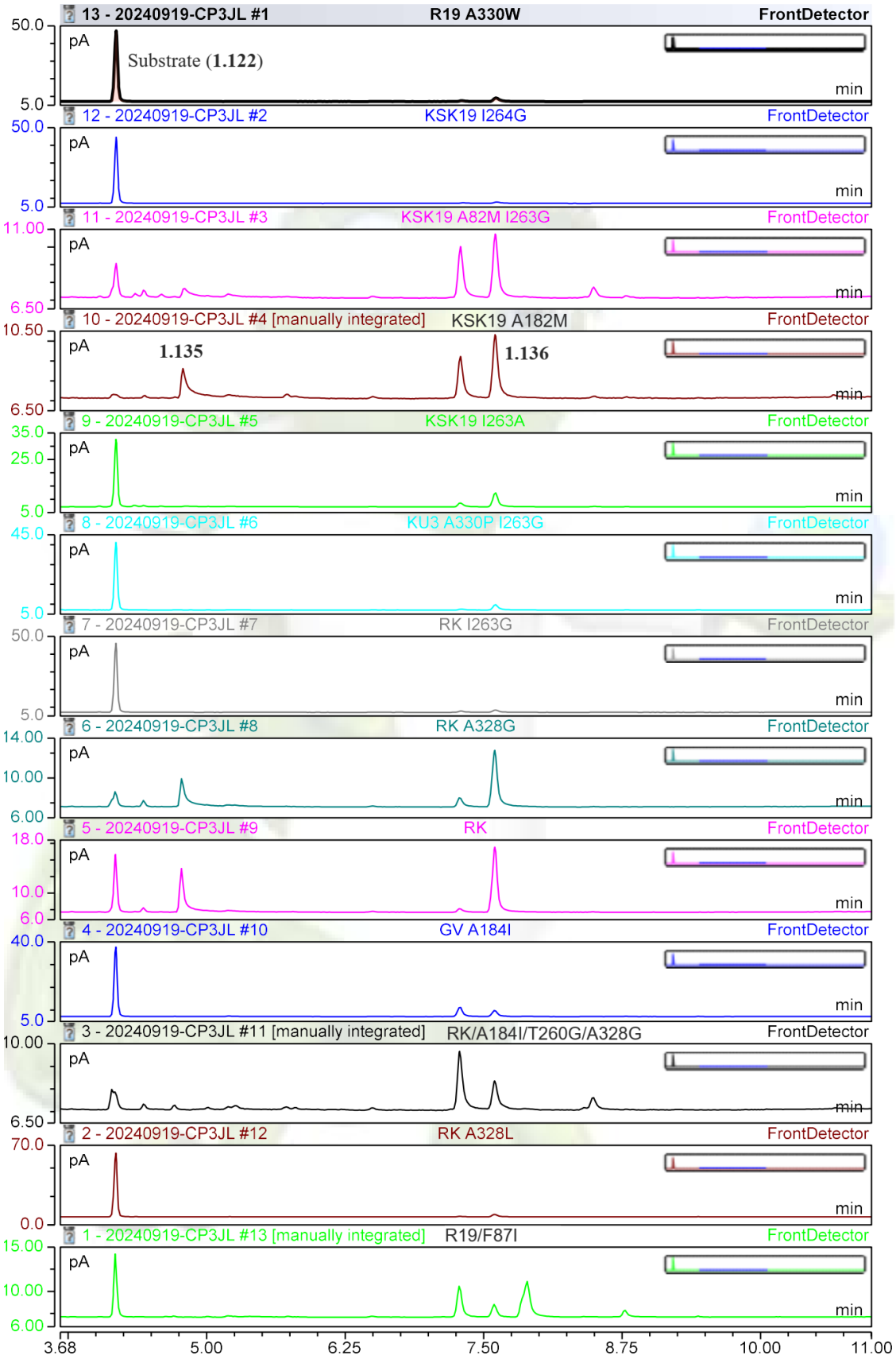


Substrate 1.118



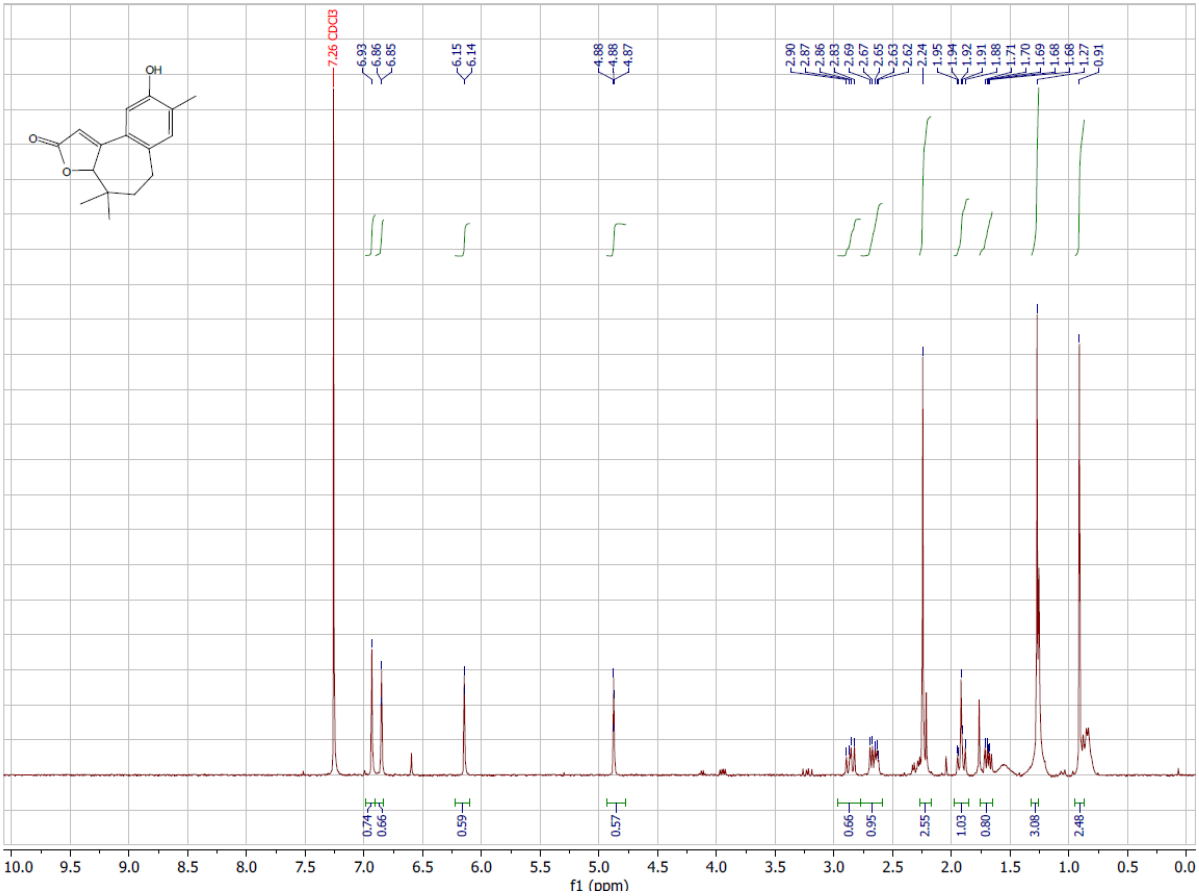

12 - 20240919-WY11 #13
R19 A328L A184I
FrontDetector
pA
Substrate (1.118)
min
11 - 20240919-WY11 #14
RK A328G
10 - 20240919-WY11 #15
RLYF K19
9 - 20240919-WY11 #16
RLYF KSK19 A184I
8 - 20240919-WY11 #17
GVQ I263G V78L
7 - 20240919-WY11 #18
RLYF KSK19
6 - 20240919-WY11 #19
GV A184I
5 - 20240919-WY11 #20
K19 F87V Q403P
1.136
1.137
1.138
4 - 20240919-WY11 #21
RK AI TG A328G
3 - 20240919-WY11 #22
RT2 A330P V78I A184I
2 - 20240919-WY11 #23
RT2 S72G A330W
1 - 20240919-WY11 #24
RP H171L I263G
2.05
3.00
4.00
5.00
6.00
6.89

Substrate 1.122

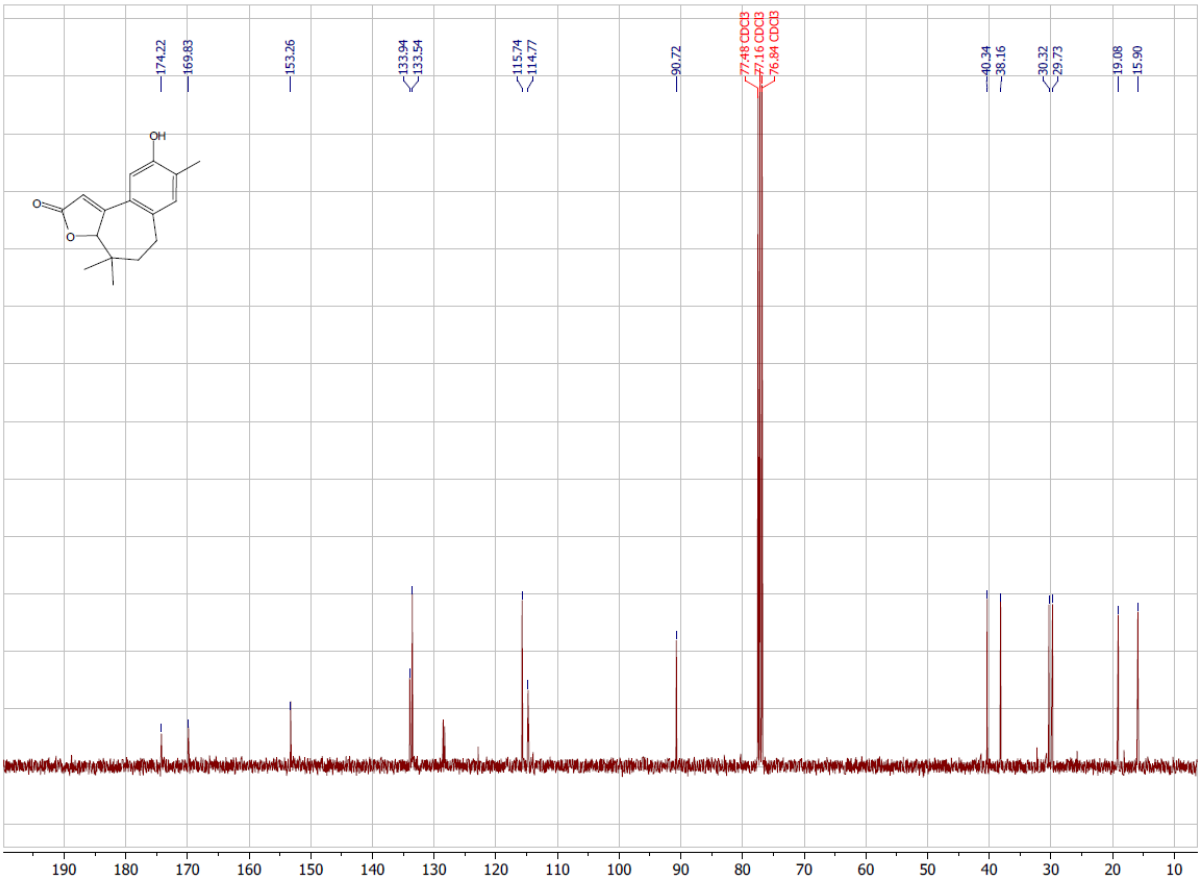


Appendix 2: NMR spectra of trigoxyphins K and L

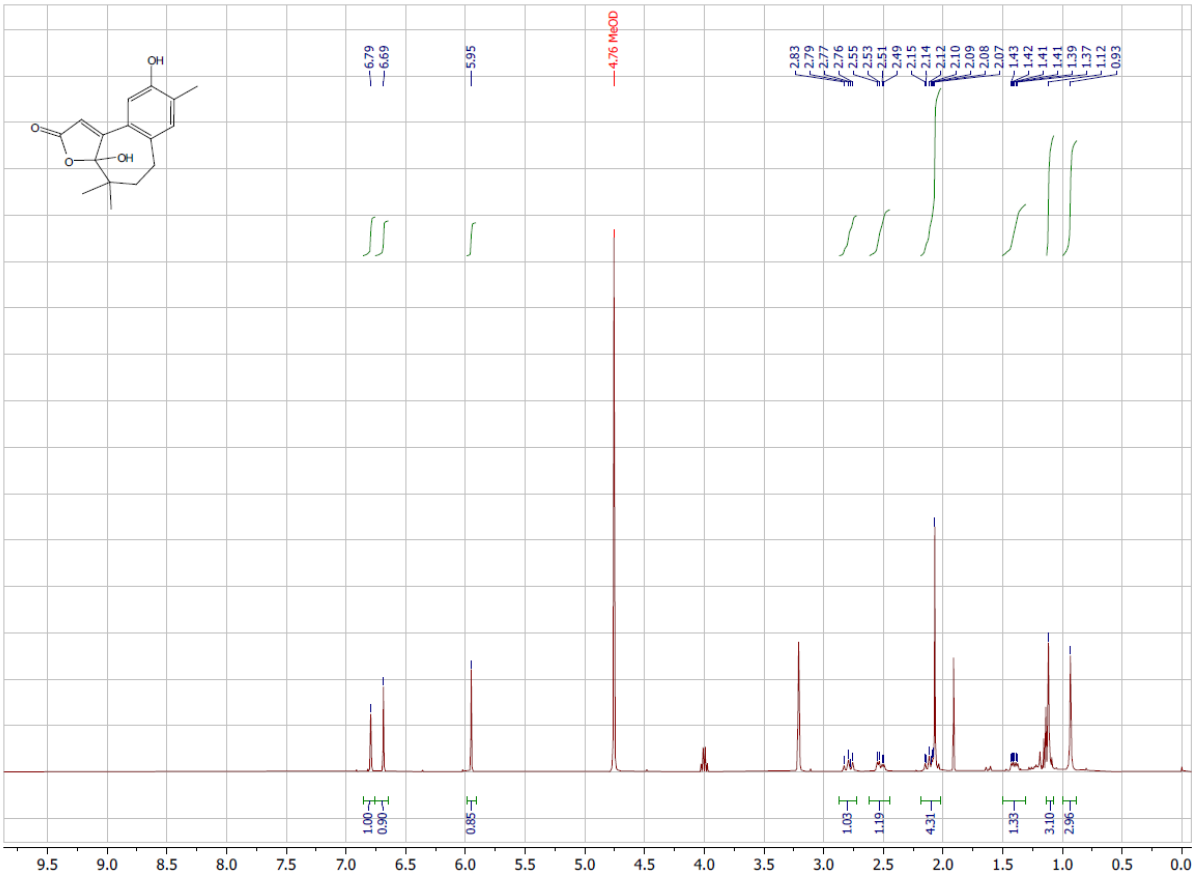
Trigoxyphin K, in chloroform-*d*, ^{1}H NMR (400 MHz)



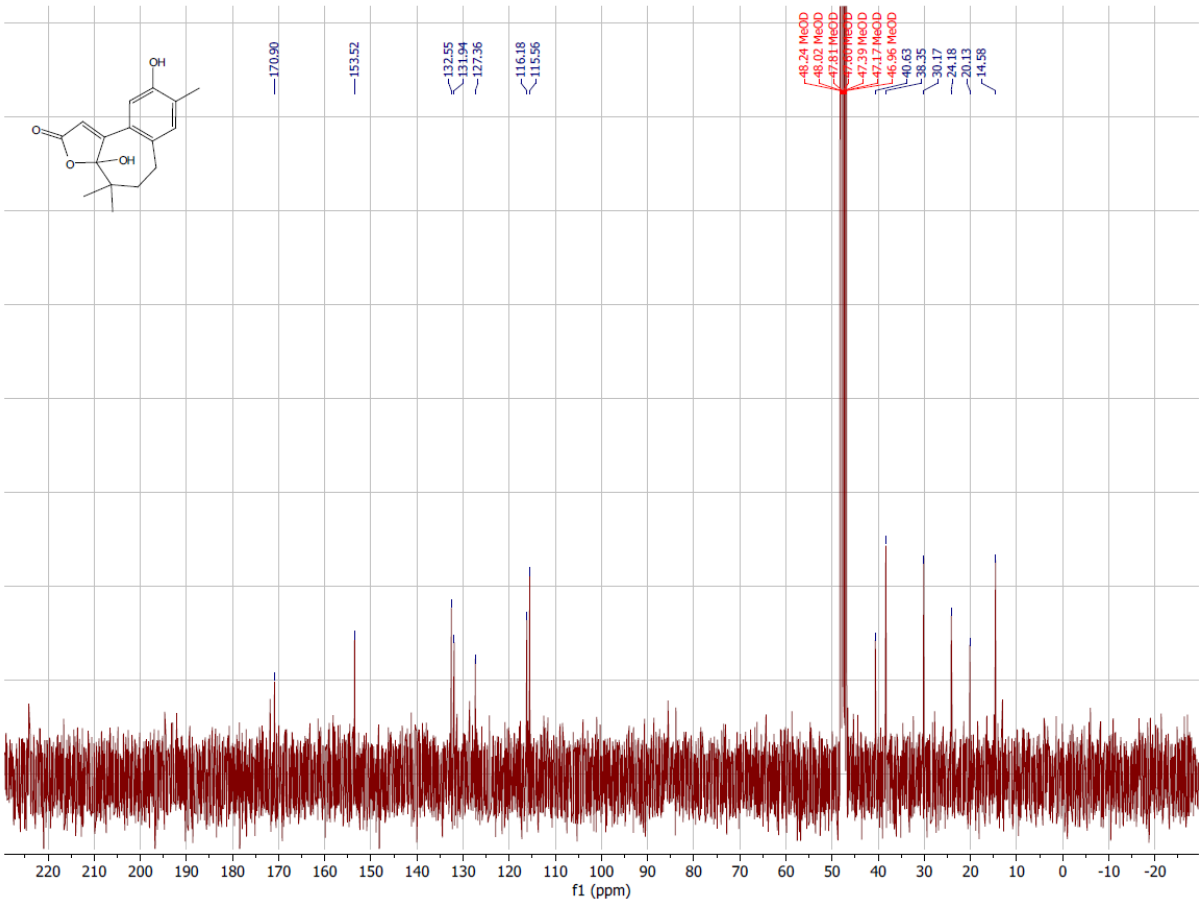
Trigoxyphin K, in chloroform-*d*, ^{13}C NMR (101 MHz)



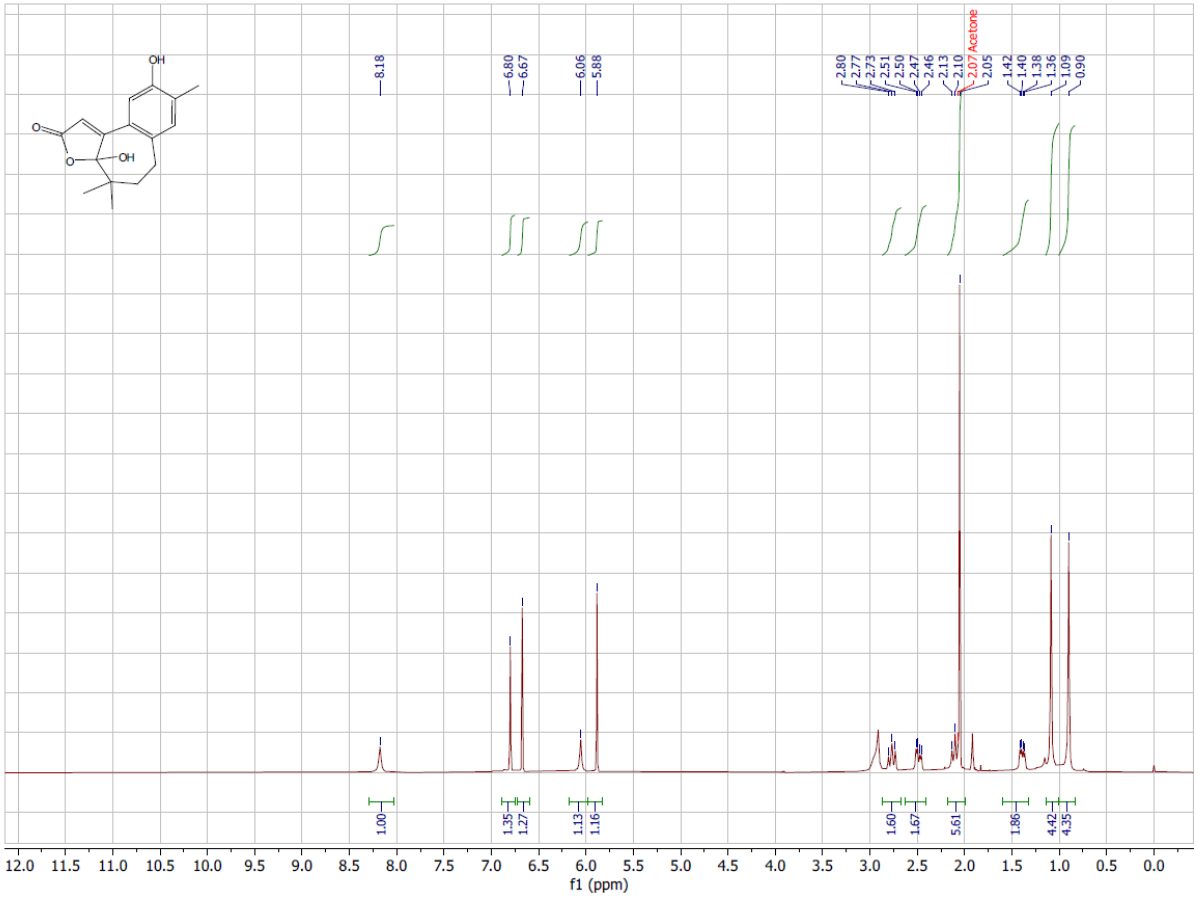
Trigoxyphin L, weak sample in methanol-d_4, ^{1}H NMR (400 MHz, same solvent as used in isolation paper, see reference 1 of Chapter 2)



Trigoxyphin L, weak sample in methanol-*d*$_4$, ^{13}C NMR (101 MHz)



Trigoxyphin L, strong sample in acetone-d_6, ^{1}H NMR (400 MHz)



Trigoxyphin L, strong sample in acetone-d_6, ^{13}C NMR (101 MHz)

