Malonyl radical cyclisations in heteroaromatic functionalisation and natural product synthesis

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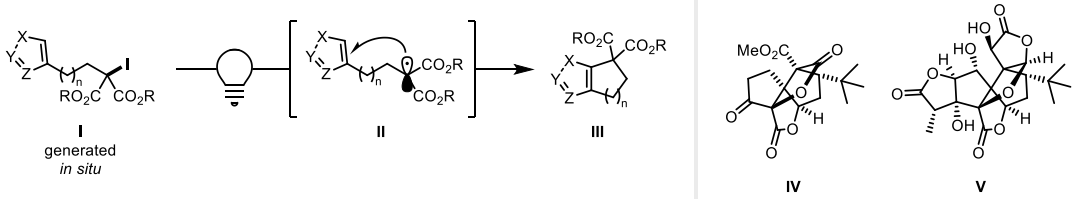
Abstract

This thesis describes the application of malonyl radical cyclisations to the synthesis of annulated heteroaromatics and towards the formal synthesis of ginkgolide B (**V**). It is divided into three chapters:

Chapter 1 provides a general introduction to the generation and reactivity of malonyl radicals as well as a summary of their applications in organic synthesis.

Chapter 2 reviews the available methods for the synthesis of annulated heteroaromatics (**III**) and describes the development and application of a new, malonyl radical-based, photochemical method for their synthesis. This method is based on the photolysis of *in situ* generated iodomalonates (**I**) and builds on previous work in the Burton group. Our investigations into the mechanism of this transformation are also detailed in this chapter.

Chapter 3 covers our efforts towards the formal synthesis of ginkgolide B (**V**) *via* a malonyl radical cascade. It details the investigation of two different routes and the elaboration of a product of the radical cascade into the core of the natural product (**IV**). This chapter also describes the enantioselective synthesis of a key intermediate *via* an organocatalysed Michael addition. Finally, it suggests a synthetic plan to complete the asymmetric formal synthesis of ginkgolide B (**V**).



Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated and does not include any collaborative work. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Pol Hernández Lladó

March 2023

A la memòria del meu avi, Joan Lladó Puig

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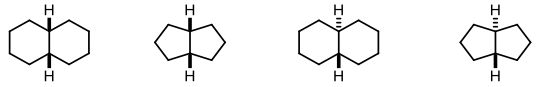
Notes on convention

Throughout this thesis, wedged bonds are used to represent absolute and relative configuration of enantioenriched products, while straight bonds are used to represent relative stereochemical configuration of racemic compounds.[1]

Bicyclo[3.3.0]octane compounds and their oxygen-containing analogues are described as *cis*- and *trans*-5,5-fused systems, following the idiomatic nomenclature of *cis*- and *trans*-decalins.



cis-6,6-fused *cis*-5,5-fused *trans*-6,6-fused *trans*-5,5-fused

Selected abbreviations

ABNO	9-azabicyclo[3.3.1]nonane *N*-oxyl radical
Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
b.p.	boiling point
BBN	9-borabicyclononane
Bn	benzyl
Bz	benzoyl
Bzh	benzhydryl
cat.	catalyst
CFL	compact fluorescent light
COSY	correlation spectroscopy
d	day(s)
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethyl formamide
DMSO	dimethylsulfoxide
DNP	2,4-dinitrophenylhydrazine
E	generic ester group
e.e.	enantiomeric excess
equiv.	equivalent
ESI	electrospray ionisation
GC-MS	gas chromatography–mass spectrometry
h	hour(s)
HAT	hydrogen atom transfer

HG-II	Hoveyda-Grubbs catalyst (2nd generation)
HMBC	heteronuclear multiple bond correlation spectroscopy
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
IBX	2-iodoxybenzoic acid
IPA	isopropyl alcohol
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
lit.	literature
LLS	longest linear sequence
LRMS	low-resolution mass spectrometry
M	molar
m.p.	melting point
m/z	mass/charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
MPO	4-methoxypyridine-*N*-oxide
MS	mass spectroscopy, molecular sieves
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMI	4-methylimidazole
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

NOESY	nuclear Overhauser effect spectroscopy
$PE_{40\text{-}60}$	petroleum ether b.p. 40–60 °C
Ph	phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
PTSC	pre-transition state conformation
R	generic group
R_f	retention factor
RT	room temperature
sat.	saturated
SET	single-electron transfer
TBHP	*tert*-butyl hydroperoxide
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
tert-Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	4-methylbenzenesulfonyl
TS	transition state
UV	ultraviolet

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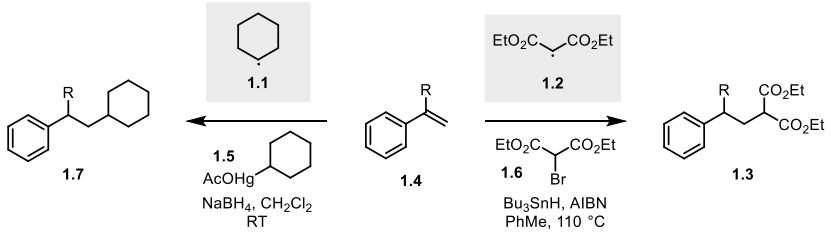
Chapter 1 General introduction

1.1 The malonyl radical

Malonyl radicals are carbon-centred radicals flanked by two esters, which stabilise these open shell species and render them electrophilic. These radicals have been extensively used in organic synthesis since the 1980s for the construction of C–C bonds.[2-4]

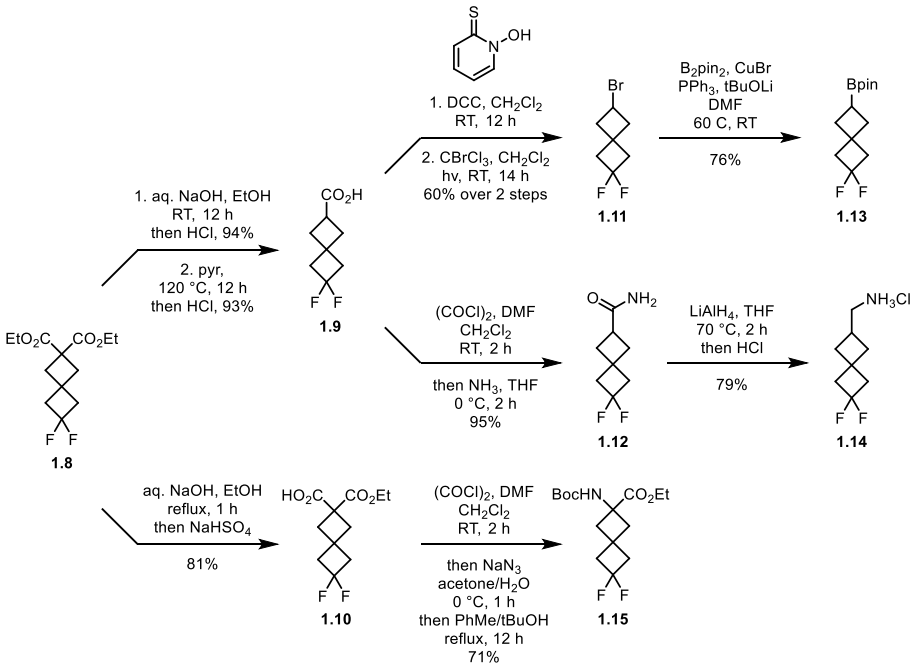
Studies by Giese and co-workers in the 1980s demonstrated that malonyl radicals are electrophilic species.[5] Compared with cyclohexyl radicals (**1.1**), diethyl malonyl radicals (**1.2**) reacted faster with electron rich olefins (Table 1.1). This was an early example of umpolung reactivity, a term coined by Seebach a decade earlier.[6]



Entry	R	Relative rate of addition of 1.1	Relative rate of addition of 1.2	Yield of 1.3/%
1	CO_2Et	42	1.0	26
2	Ph	3.6	3.5	45
3	Me	1.0	3.7	48
4	OMe	–	2.7	45
5	NMe_2	–	23	16

Table 1.1 Relative rates of addition of cyclohexyl (**1.1**) and diethyl malonyl radicals (**1.2**) to styrenes (**1.4**).[5]

Since then, malonyl radicals have been used in both inter- and intramolecular addition reactions to alkenes, alkynes, and aromatic rings.[2-4] The malonate-containing products of these radical transformations have been derivatised to give a wide range of functional groups, for example, through decarboxylation or reduction. The wide array of derivatisation reactions of malonates was exemplified by Radchenko and co-workers, who used cyclic malonates as the starting point for the synthesis of spiro[3.3]heptane derived building blocks (Scheme 1.1).[7]



Scheme 1.1 Examples of derivatisation reactions of malonates by Radchenko et al.[7]

1.2 Generation of malonyl radicals

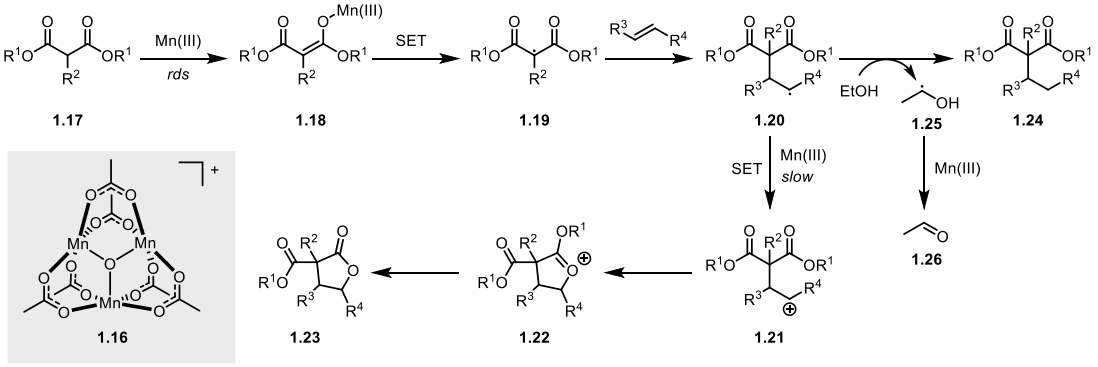
Several methods, both oxidative and reductive, have been developed for the generation of malonyl radicals.

1.2.1 Oxidative malonyl radical generation methods

1.2.1.1 $Mn(OAc)_3$

The most common reagent to generate malonyl radicals from malonates under oxidative conditions is $Mn(OAc)_3$.[8-12] This reagent was first used in the synthesis of *γ*-lactones from alkenes,[13, 14] and has since been widely employed in the generation of radicals from 1,3-dicarbonyl compounds. Excellent reviews have been written on this topic by Snider,[8, 15] Melikyan,[9] and others.[10-12]

$Mn(OAc)_3$ exists in the solid state as an oxygen centred triangle with Mn(III) vertices and bridging acetates (**1.16**, Scheme 1.2).[16] Nonetheless, there is limited understanding of the structure this metal complex takes in solution. The dihydrate salt $Mn(OAc)_3 \cdot 2H_2O$ is the most commonly used in organic synthesis and is commercially available.

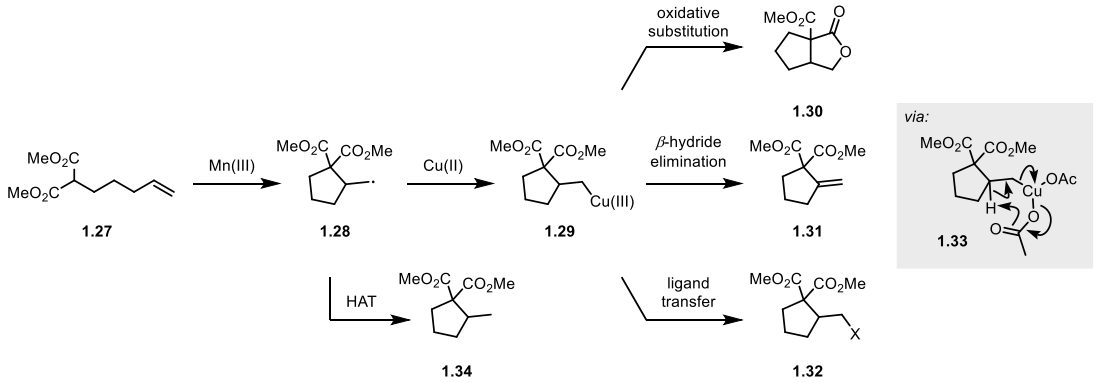


Scheme 1.2 Mechanism of generation of malonyl radicals with $Mn(OAc)_3$ and their reaction with alkenes. Simplified structure of $Mn(OAc)_3$.[15, 17, 18]

The mechanism of the oxidation of malonates with $Mn(OAc)_3$ is summarised in Scheme 1.2.[15, 17, 18] Malonates react with $Mn(OAc)_3$ to give manganese enolates **1.18**, which after a single electron transfer (SET) yield malonyl radicals **1.19**. For substituted malonates ($R^2 \neq H$), the formation of enolates **1.18** is the rate determining step.[17] The carbon-centred radical **1.19** can then add, for example, to an alkene to give secondary

radical **1.20**, which is slowly oxidised by $Mn(OAc)_3$ to give carbocation **1.21** and yield lactone **1.23**. This oxidation is, however, very slow for primary and secondary radicals, and often results in extensive polymerisation due to competing side reactivity.[8] Alternatively, carbon-centred radical **1.20** can abstract a hydrogen atom from the solvent to give malonate **1.24**. This pathway is especially efficient if the reaction is performed in ethanol, which after hydrogen atom transfer gives stabilised radical **1.25**, converted into acetaldehyde after oxidation with $Mn(OAc)_3$.[19]

More efficient termination processes, and thus higher yielding reactions overall, can be achieved in the presence of co-oxidants such as copper(II) salts. This was first described by Kochi, Heiba and Dessau, who showed that $Cu(OAc)_2$ can oxidise secondary radicals 350 times faster than $Mn(OAc)_3$,[20-22] despite being a weaker oxidant ($E_0[Mn(OAc)_3]$ = 1.51 V, $E_0[Cu(OAc)_2]$ = 0.16 V).[23] Snider extensively investigated the effect of the copper salt and reaction solvent on the outcome of malonyl radical cyclisations.[19, 24] Their findings are exemplified below with the cyclisation of malonate **1.27** (Scheme 1.3).



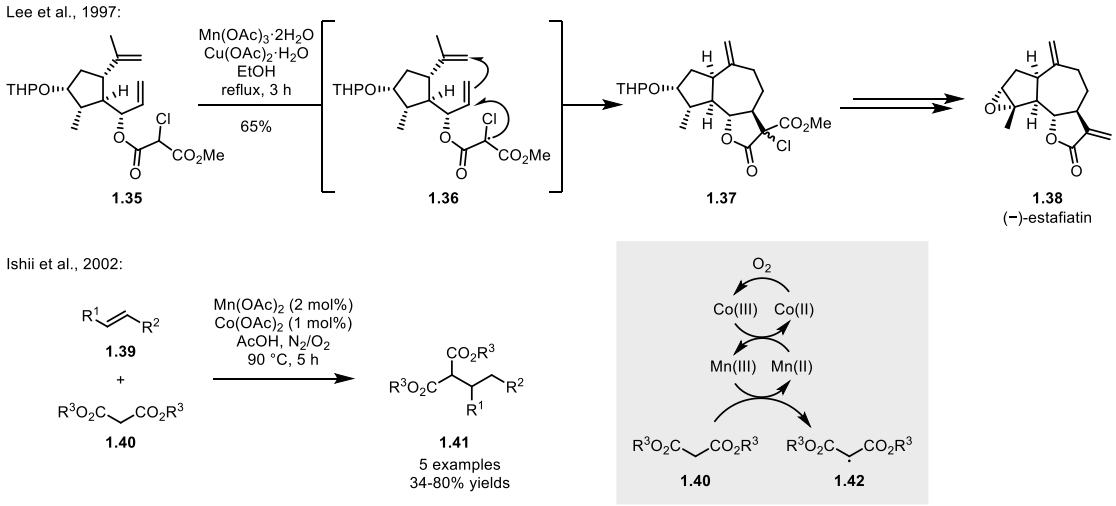
Scheme 1.3 Cyclisation of malonate **1.27** in the presence of $Mn(OAc)_3$ and Cu(II) salts.[19, 24]

The ligand bound to copper has a considerable influence on the reaction outcome of these radical additions.[22, 24-26] $Cu(OAc)_2$, the most common co-oxidant, favours the formation of alkenes **1.31** *via syn* elimination, which was postulated to occur through a

pericyclic reaction involving the acetate ligand (**1.33**).[27] On the other hand, copper salts with weakly coordinating anions ($Cu(OTf)_2$ and $Cu(BF_4)_2$) favour products of oxidative substitution such as fused lactone **1.30**.[25, 26, 28] Ligand transfer to give malonates **1.32** is also possible, albeit uncommon in $Mn(OAc)_3$ and Cu(II) salt systems.[22]

The product distribution of $Mn(OAc)_3$-mediated radical cyclisations also depends on the solvent.[19, 24] In EtOH, as discussed before, the predominant pathway is the hydrogen atom transfer to give formal redox-neutral product **1.34**, while in acetic acid or acetonitrile oxidative substitution products (**1.30**) tend to be favoured. Finally, in DMSO *β*-hydride elimination prevails to give alkene **1.31**.

These reactivity principles were exemplified in Lee and co-workers' total synthesis of (−)-estafiatin (**1.38**),[29] which employed $Mn(OAc)_3$ and $Cu(OAc)_2$ to construct the core of this natural product through a radical cascade (Scheme 1.4). This transformation involved successive 5-*exo-trig* and 7-*endo-trig* cyclisations and a $Cu(OAc)_2$-mediated *β*-hydride elimination.



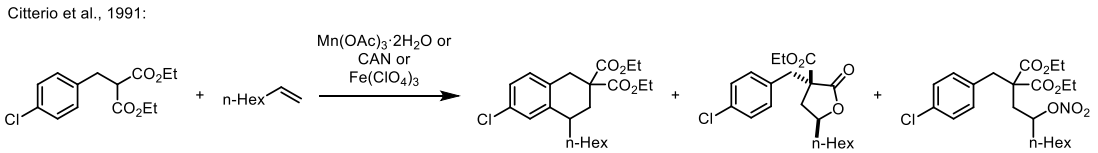
Scheme 1.4 Summary of Lee's total synthesis of (−)-estafiatin,[29] and Ishii's method for the generation of malonyl radicals in the presence of substoichiometric amounts of $Mn(OAc)_2$ and $Co(OAc)_2$.[30, 31]

A limitation of $Mn(OAc)_3$-mediated malonyl radical methods is their need for stoichiometric amounts of Mn and co-oxidant salts. Ishii et al. developed a catalytic methodology to ameliorate this issue based on a Mn/Co system that used oxygen as the terminal oxidant (Scheme 1.4).[30, 31]

1.2.1.2 Ce(IV) and Fe(III) salts

Cerium ammonium nitrate (CAN) and Fe(III) salts can also be used to oxidise malonates to malonyl radicals. This topic was reviewed by Iqbal,[32] Nair,[33] Menéndez,[34] and Burton.[10]

Citterio and co-workers investigated the differences between Mn(III), Ce(IV) and Fe(III) salts in the generation of malonyl radicals (Scheme 1.5).[35] Their results were consistent with a common reaction mechanism, but the product distribution was dependent on the high-valent metal salt. $Fe(ClO_4)_3$ gave similar reaction profiles to $Mn(OAc)_3$, while CAN favoured the formation of ligand-transfer product **1.43**.[35]



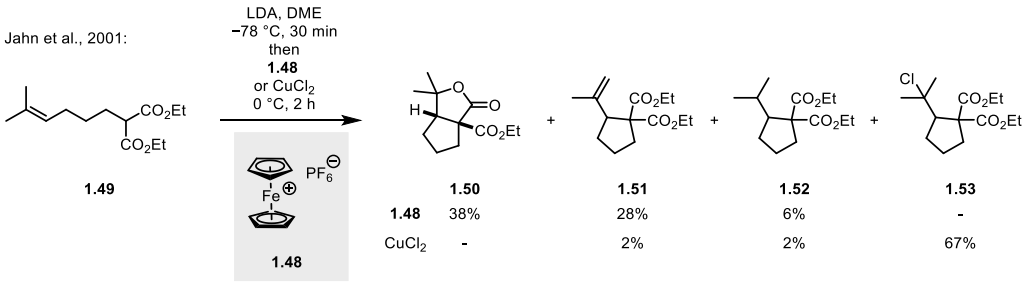
	1.46	1.47	1.43
$Mn(OAc)_3·2H_2O$	86	2	-
CAN	21	10	36
$Fe(ClO_4)_3$	80	10	3

Scheme 1.5 Results of the radical addition of malonate **1.44** to alkene **1.45** in the presence of $Mn(OAc)_3$, CAN, and $Fe(ClO_4)_3$.[35]

1.2.1.3 Oxidation of lithium enolates

Jahn and co-workers showed that malonate enolates can be oxidised to malonyl radicals with the aid of ferrocenium hexafluorophosphate (**1.48**) or $CuCl_2$ (Scheme 1.6).[36-39] The cyclisation of malonate **1.49** was used as a model system to compare the chemistry of both

oxidants.[38] The treatment of the lithium enolate derived from malonate **1.49** with ferrocenium hexafluorophosphate (**1.48**) yielded fused bicyclic lactone **1.50**, and cyclopentanes **1.51** and **1.52**. On the other hand, employing $CuCl_2$ favoured the formation of chloride **1.53**, the product of ligand transfer after the radical cyclisation. This radical generation method was used by Jahn et al. in their synthesis of antiviral cyclopentane derivatives,[40] as well as for the generation of less stabilised radicals from esters, ketones, and amides.[41, 42]



Scheme 1.6 Results of the cyclisation of the lithium enolate of malonate **1.49** in the presence of ferrocenium hexafluorophosphate (**1.48**) and $CuCl_2$.[38]

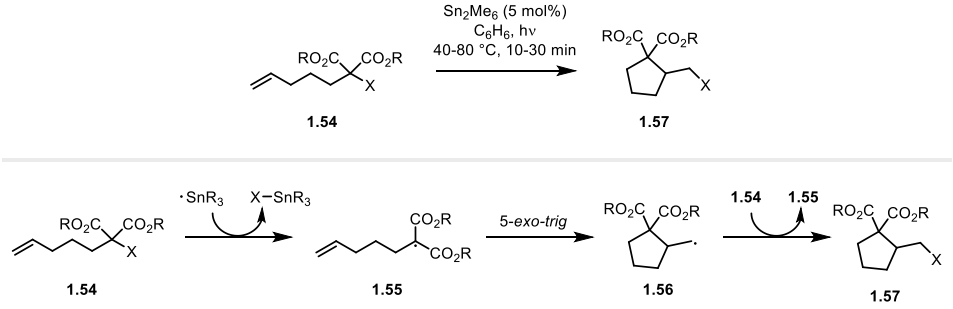
1.2.2 Reductive malonyl radical generation methods

Malonyl radicals can also be generated through the reduction of halomalonates. This transformation was traditionally achieved with organotin hydrides, but more recently photoredox systems have been employed as alternatives.

1.2.2.1 Tin reagents

Bromo- and chloromalonates can be reduced with organotin hydrides to give malonyl radicals.[5] Giese exemplified this radical generation method in 1986 in an early report of umpolung reactivity.[5]

Ditin reagents under photochemical conditions can also be used to generate malonyl radicals from halomalonates to give halogen atom transfer products (Scheme 1.7).[43-46] Under these conditions, ditin reagents are photolysed to give tin-centred radicals, which abstract the halogen atom from the halomalonates (**1.54**) to generate the corresponding malonyl radicals **1.55**. These radicals can then add onto pendant olefins to give adduct radicals **1.56**, which undergo halogen atom transfer to yield halides **1.57** in an overall redox-neutral process. Curran used this method of radical generation in their pivotal studies of radical ring closures.[18, 43, 44, 47]



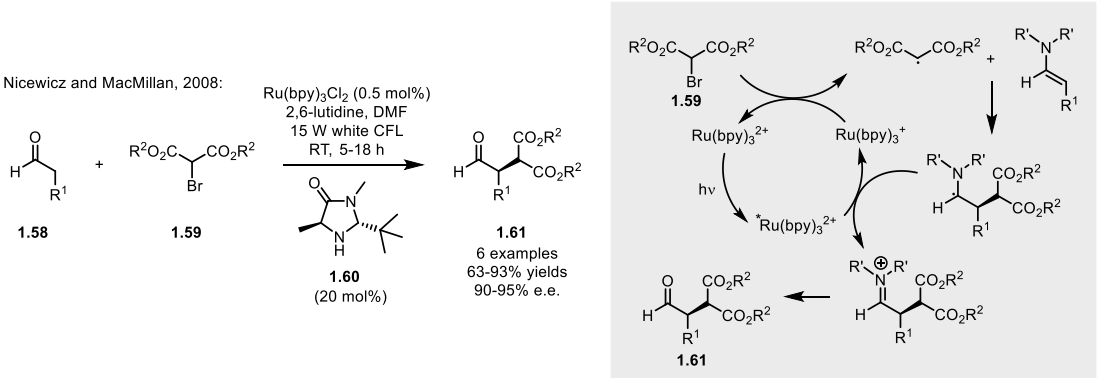
Scheme 1.7 Mechanism of the photochemical tin-mediated cyclisation of halomalonates.[43, 44, 47]

The treatment of bromomalonates with triethyl borane and oxygen is an alternative method for the generation of malonyl radicals that can also give halogen atom transfer products.[48-51] This chemistry was used by Muchowski in their synthesis of ketorolac,[48] and an extensive account of the mechanism of the reaction was described by Curran.[50]

1.2.2.2 Photoredox methods

Iodo-, bromo- and chloromalonates can also be reduced to give malonyl radicals with the aid of photocatalysts, thus circumventing the need for organotin reagents. This field was pioneered by MacMillan in 2008, who reported the ruthenium catalysed asymmetric addition of malonyl radicals onto enamines (Scheme 1.8).[52] Other photochemical malonyl

radical reactions have since been reported, mediated by iridium,[53-55] ruthenium,[54, 56] and iron complexes,[57] organophotoredox catalysts,[58-62] and metal-organic frameworks.[63]

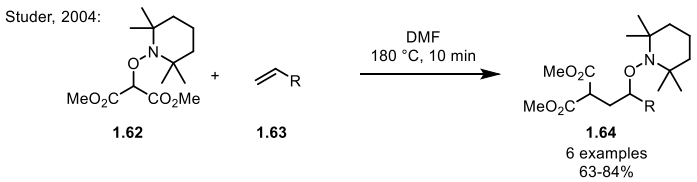


Scheme 1.8 MacMillan's photoredox catalysed α-alkylation of aldehydes with bromomalonates.[52]

1.2.3 Other methods

Finally, malonyl radicals can also be generated through hydrogen atom abstraction and the homolysis of aminoxylmalonates.

Maity described the use of oxyl and peroxyl radicals, generated from TBHP and TBAI, for the generation of malonyl radicals through hydrogen atom abstraction and their addition to styrenes.[64] Studer and co-workers, on the other hand, exploited the persistent radical effect to generate malonyl radicals from aminoxyl malonates.[65-72] This was exemplified in Studer's carboaminoxylation of olefins (Scheme 1.9).



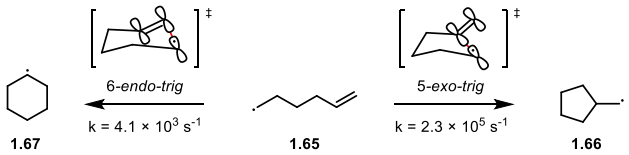
Scheme 1.9 Studer's carboaminoxylation of unactivated olefins *via* malonyl radicals.[72]

1.3 Regio- and stereochemical outcomes of 5-hexenyl radical cyclisations

Chapter 3 outlines our efforts towards ginkgolide B by means of a malonyl radical cascade. This cascade involved the cyclisation of 5-hexenyl radicals, thus the stereochemical models to predict their outcome are summarised below. Specifically, the regio- and stereochemical outcome of these cyclisations can be predicted using the Baldwin rules and the Beckwith-Houk model.

1.3.1 The Baldwin rules

The regioselectivity of intramolecular radical additions can be predicted using the Baldwin rules.[73] These are a set of empirical guidelines for cyclisations under kinetic control that were obtained through the study of experimental selectivity trends and rationalised through orbital overlap. Since Baldwin's influential publication in 1976,[73] numerous experimental and computational studies have been reported, which both complement and challenge the original findings. These were reviewed by Alabugin in 2016.[74]

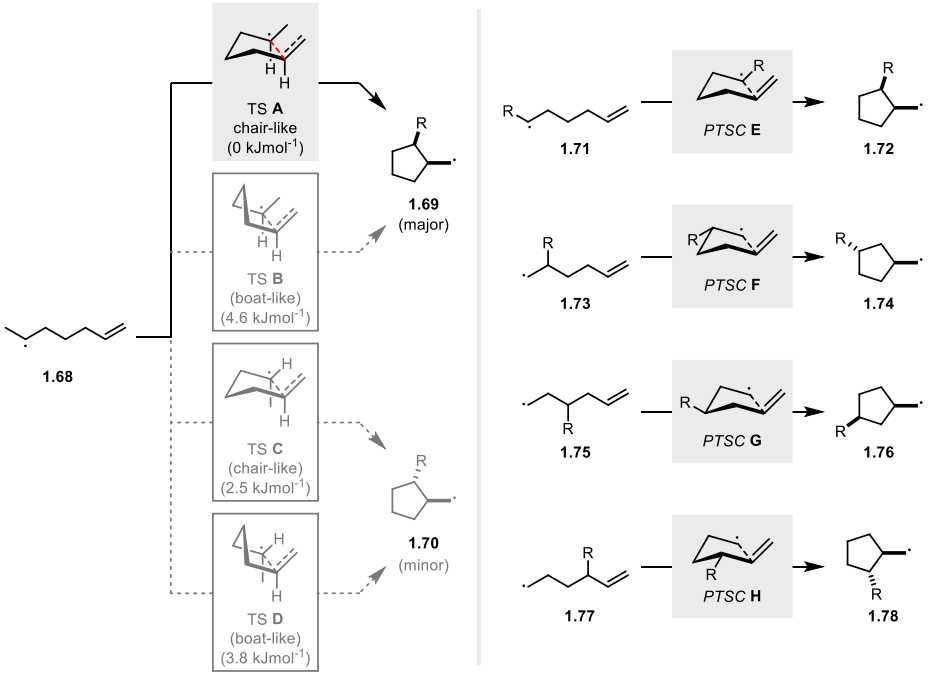


Scheme 1.10 Relative rates of the 5-*exo-trig* and 6-*endo-trig* cyclisation of 5-hexenyl radical **1.65**,[75] and their respective transition states.[73]

The cyclisation of 5-hexenyl radicals (**1.65**) can give two different products *via* 5-*exo-trig* (**1.66**) or 6-*endo-trig* (**1.67**) cyclisations (Scheme 1.10). The Baldwin rules describe both cyclisation categories as favourable, but the 5-*exo-trig* as the typically preferred pathway.[73] Better orbital overlap and lower ring strain in the transition state are responsible for this selectivity, which yields the less-stable primary radical **1.66**.

1.3.2 The Beckwith-Houk model

The Beckwith-Houk model can be used to predict the stereoselectivity of the cyclisation of 5-hexenyl radicals. This stereochemical model was based on calculations of transition states of radical ring closures and showed good correlation with experimental product ratios. [75-77]



Scheme 1.11 Calculated transition states for the cyclisation of radical **1.68** and application of the Beckwith-Houk model to the cyclisation of substituted radicals **1.71**, **1.73**, **1.75** and **1.77**. [77]

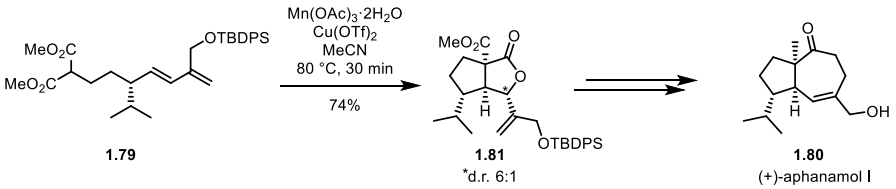
The cyclisation of 5-hexenyl radicals can occur through four transition states (Scheme 1.11). For the archetypical cyclisation of radical **1.68**, these are chair-like TS **A** and **C**, and boat-like TS **B** and **D**, depicted in Scheme 1.11. [27, 75] Houk and co-workers calculated their relative energies and showed that TS **A** was lowest in energy and was followed, in order, by TS **C**, **D**, and **B**. [77] Chair-like transition states were thus lower in energy, and the placement of the methyl group in *pseudo*-equatorial position was preferred. The calculations agreed with the product ratios obtained experimentally. [76]

These findings, along with the calculations of transition states for other radical ring closures, provided the basis for a general stereochemical model, summarised in Scheme 1.11.[77] In short, hexenyl radicals are predicted to cyclise *via* chair-like transition states that place groups with a higher A value in *pseudo*-equatorial positions. As a result, the cyclisations of radicals **1.71**, **1.73**, **1.75** and **1.77** yield cyclopentylmethyl radicals **1.72**, **1.74**, **1.76** and **1.78** as the major adduct radicals. Nonetheless, caution should be taken when applying this model to heavily substituted substrates, which may deviate from these general stereochemical trends.[78]

1.4 Previous work in the Burton group

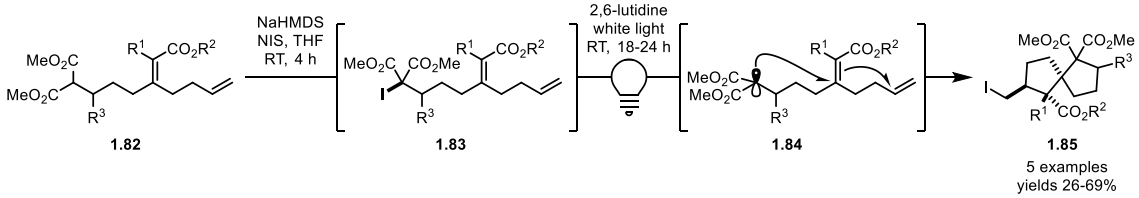
The reactivity of malonyl radicals has been a long-standing subject of interest in the Burton group. This has included the application of oxidative malonate cyclisations to the total synthesis of natural products and, more recently, the development of novel ways to generate malonyl radicals.

Malonyl radicals enabled key steps in the total syntheses of 7,11-cyclobotryococca-5,12,26-triene,[79] (+)-aphanamol I (**1.80**),[80] and salinosporamide A.[28] $Mn(OAc)_3$ was used to trigger radical cyclisations, which yielded fused lactones that were further elaborated into the natural products. This is exemplified by the radical cyclisation of malonate **1.79** in the total synthesis of (+)-aphanamol I (**1.80**).[80]



Scheme 1.12 Summary of Burton's total synthesis of (+)-aphanamol I (**1.80**).[80]

Recently, Kilian Garrec developed a method to generate these malonyl radicals under photochemical conditions and applied it to the synthesis of complex spirocycles (Scheme 1.13).[81] In this reaction, *in situ* generated iodomalonates **1.83** were key intermediates, which underwent homolysis upon white light irradiation in the absence of any photocatalyst.



Scheme 1.13 Summary of Garrec's radical cascade for the synthesis of complex spirocycles.[81]

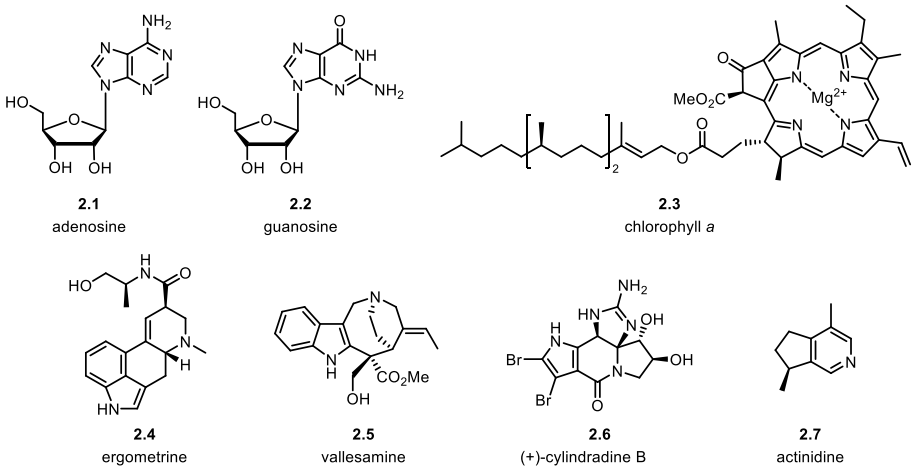
The work described here builds on these results and employs malonyl radicals in the synthesis of fused heteroaromatic rings and towards the formal synthesis of ginkgolide B.

Chapter 2 A light-mediated malonyl radical cyclisation onto heteroaromatics

The results from this chapter have been published in P. Hernández-Lladó, K. Garrec, D. C. Schmitt, J. W. Burton, *Adv. Synth. Catal.* **2022**, *364*, 1724–1731.

2.1 Introduction

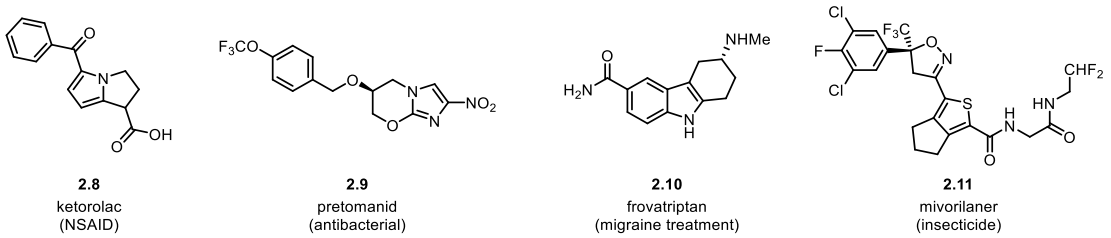
Polycyclic heteroaromatics are abundant in nature, for example, forming part of purine bases (**2.1** and **2.2**), chlorophylls (**2.3**), and numerous alkaloid families (Scheme 2.1). Ring systems with partial saturation (*i.e.* annulated heteroaromatics) are particularly common, as exemplified by the indole alkaloids ergometrine (**2.4**) and vallesamine (**2.5**), pyrrole-containing (+)-cylindradine B (**2.6**), and fused-pyridine actinidine (**2.7**).



Scheme 2.1 Examples of natural products containing polycyclic heteroaromatics.

Annulated heteroaromatics are also widespread in marketed drugs and agrochemicals (Scheme 2.2). These ring systems are often incorporated into such targets because of their

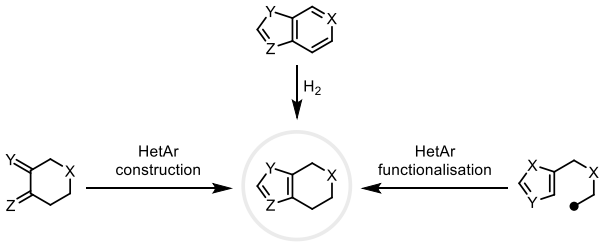
resemblance to naturally-occurring molecules and their high degree of three-dimensionality. Natural products have historically been an important source of new drugs and continue to play a key role in drug discovery, especially in the treatment of cancer and infectious diseases.[82-84] Furthermore, annulated heteroaromatics have a higher fraction of sp^3 centres (Fsp^3) than their fully aromatic counterparts, which correlates with higher selectivity and better physicochemical properties, and ultimately improved clinical success.[85] Consequently, annulated heteroaromatics have been incorporated into drugs and agrochemicals, for example, the anti-inflammatory ketorolac (**2.8**), the antibacterial pretomanid (**2.9**), the treatment for severe migraine frovatriptan (**2.10**), and the insecticide mivorilaner (**2.11**).



Scheme 2.2 Examples of marketed drugs and agrochemicals containing annulated heteroaromatics.

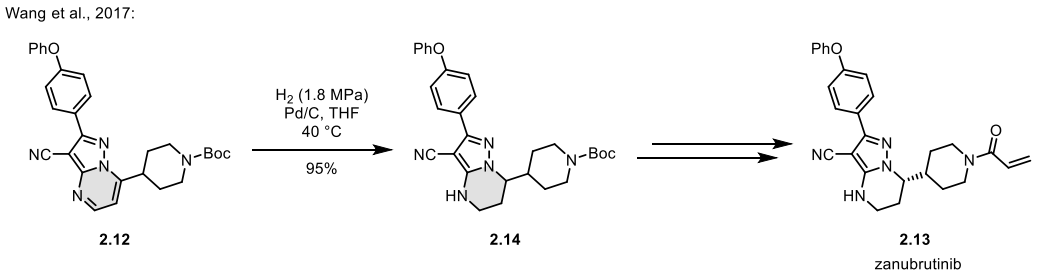
2.1.1 Synthesis of annulated heteroaromatics

Due to the widespread application of compounds containing annulated heteroaromatics, many methodologies have been reported for their synthesis. Some common approaches are summarised below (Scheme 2.3).



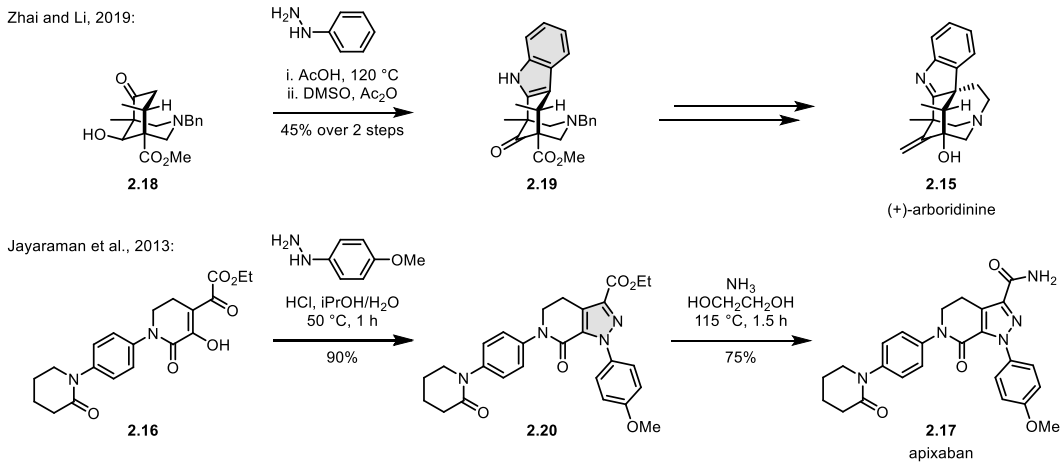
Scheme 2.3 General strategies towards annulated heteroaromatics.

The hydrogenation of fully unsaturated polycyclic heteroaromatics can yield the required partially saturated ring systems. This is often selective for the reduction of 6-membered rings, as exemplified in the hydrogenation of pyrazolo[1,5-*a*]pyrimidine **2.12** in the synthesis of the anticancer agent zanubrutinib (**2.13**) (Scheme 2.4).[86]



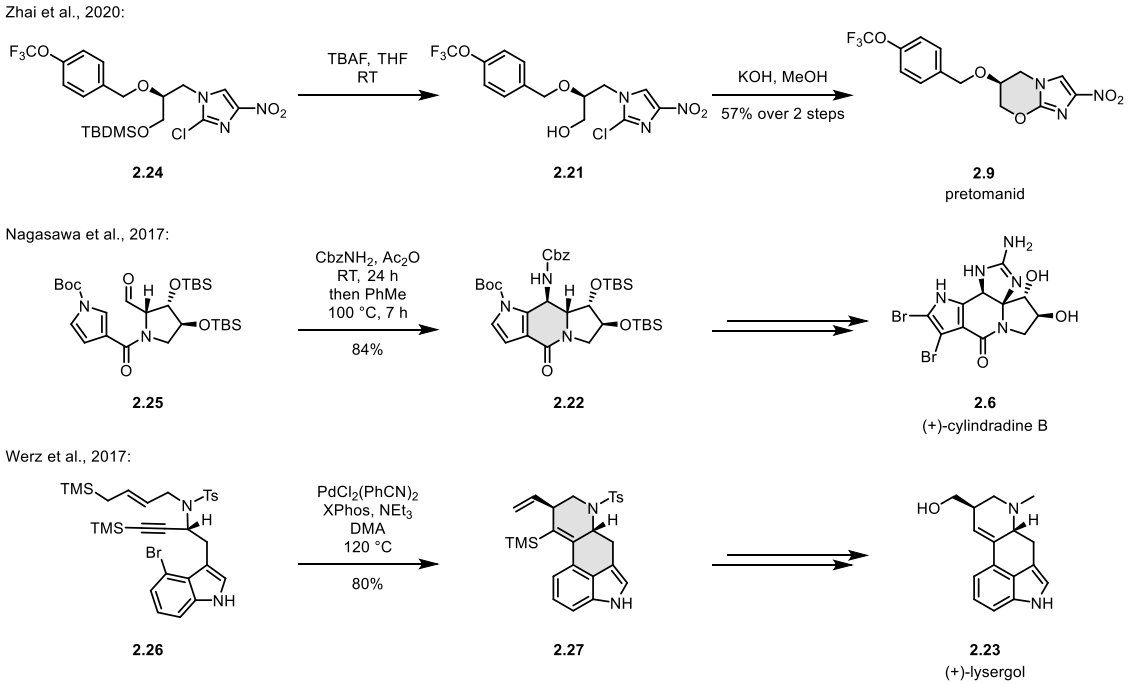
Scheme 2.4 Summary of Wang's synthesis of zanubrutinib (**2.13**).[86]

Annulated heteroaromatics can also be prepared through heteroarene-forming reactions, such as cyclocondensations. These reactions allow the construction of a heteroaromatic fused to a pre-existing saturated ring. The Fischer indole synthesis employed in Zhai and Li's total synthesis of (+)-arboridinine (**2.15**),[87] and the cyclocondensation reaction of 1,3-dicarbonyl compound **2.16** and (4-methoxyphenyl)hydrazine in the synthesis of apixaban (**2.17**),[88] are examples of this approach (Scheme 2.5).



Scheme 2.5 Summary of Zhai and Li's total synthesis of (+)-arboridinine (**2.15**)[87] and Jayaraman's synthesis of apixaban (**2.17**).[88]

Finally, partially saturated ring systems can also be prepared through the functionalisation of a pre-existing aromatic ring *via* a cyclisation reaction. This has previously been achieved through S_NAr, S_EAr, metal-catalysed cross-couplings, and radical additions, among others.



Scheme 2.6 Summary of Zhai's synthesis of pretomanid (**2.9**),[89] Nagasawa's total synthesis of (+)-cylindradine B (**2.6**),[90] and Werz's total synthesis of (+)-lysergol (**2.23**).[91]

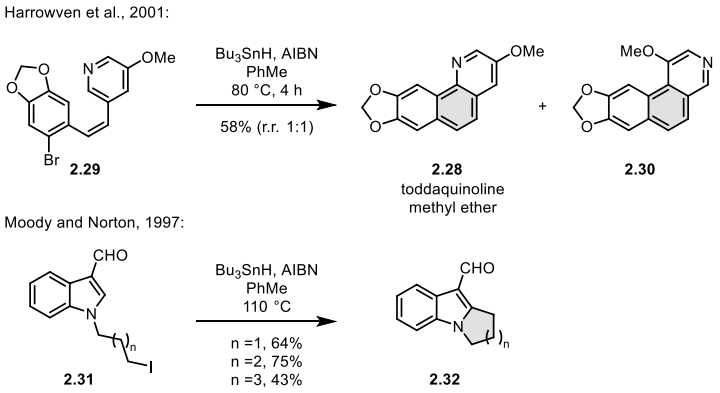
For example, pretomanid (**2.9**) was obtained through an intramolecular S_NAr reaction of alcohol **2.21** (Scheme 2.6).[89] In Nagasawa's total synthesis of (+)-cylindradine B (**2.6**), a Pictet-Spengler-type reaction was used to construct the central *δ*-lactam in pyrrole **2.22**.[90] Finally, in Werz's total synthesis of (+)-lysergol (**2.23**), the core of this natural product was built through a palladium-catalysed cascade reaction.[91]

2.1.2 Radical methods for the synthesis of annulated heteroaromatics

Radical cyclisation reactions can give access to partially saturated polycyclic heteroaromatics. An early example of this approach described the addition of an alkyl radical onto adenosine to yield a modified nucleoside.[92] This work was followed by

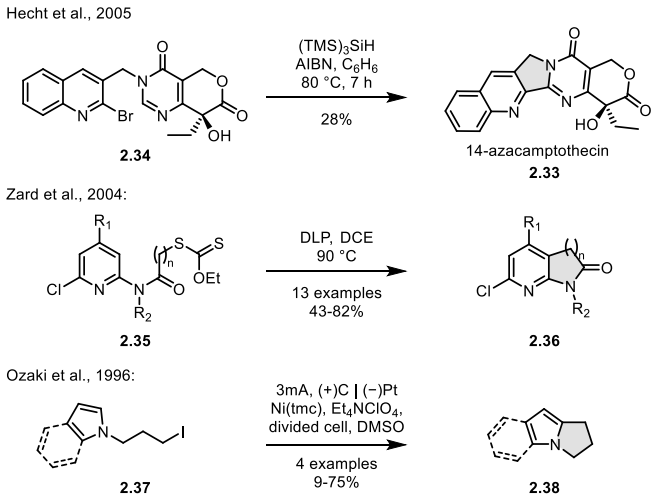
cyclisations of acyl,[93-98] alkoxyl,[99, 100] alkyl,[94, 98, 101-120] aminyl,[121, 122] aryl,[123-133] malonyl,[48, 56, 109, 134-141] selenyl,[142, 143] and vinyl[144] radicals onto (benz)imidazoles, (benzo)furans, indoles, pyrazoles, pyridines/pyridinium ions, pyrroles, (benzo)thiophenes, and triazoles.

Traditionally, radicals were generated from alkyl halides and tin reagents. For example, in Harrowven's synthesis of toddaquinoline methyl ether (**2.28**), an aryl radical was generated from bromide **2.29** with tributyltin hydride and AIBN (Scheme 2.7).[126] Under similar reaction conditions, Moody and Norton reported the cyclisation of alkyl radicals onto indoles to give fused five-, six-, and seven-membered rings.[131] Due to their excellent performance, tin hydrides dominated radical chemistry for decades, a period known as 'the tyranny of tin.'[145] Organotin compounds are extremely toxic and have long lasting effects on aquatic life. This, together with their difficult removal from the reaction products, precluded their application to the synthesis of drugs or other compounds for human or animal use.



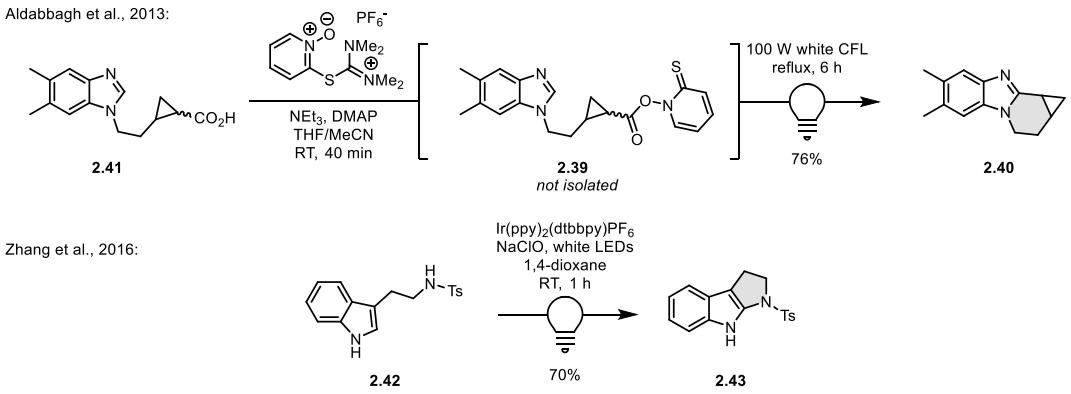
Scheme 2.7 Summary of Harrowven's total synthesis of toddaquinoline methyl ether (**2.28**)[126] and Moody and Norton's method for the synthesis of fused indoles (**2.32**).[131]

The limitations of tin chemistry highlighted above prompted research into alternative radical generation methods.[145, 146] Silanes were used as less-toxic hydrides, for example, in Hecht's synthesis of 14-azacamptothecin (**2.33**) (Scheme 2.8);[132] while peroxides and xanthates found success in Zard and co-workers' synthesis of fused pyridines (**2.36**).[107] Electrochemical reactions are another method for radical generation, as exemplified by Ozaki's electroreductive cyclisation of alkyl iodides onto indoles and pyrroles.[116] Reductive methods using SmI_2[147] or low-valent titanium,[148] and oxidative methods employing Mn(III),[8-12] Ce(IV),[10] or Fe(III)[10] salts were also reported.



Scheme 2.8 Summary of Hecht's synthesis of 14-azacamptothecin (**2.38**),[132] Zard's method for the synthesis of fused pyridines (**2.36**),[107] and Ozaki's electroreductive cyclisation.[116]

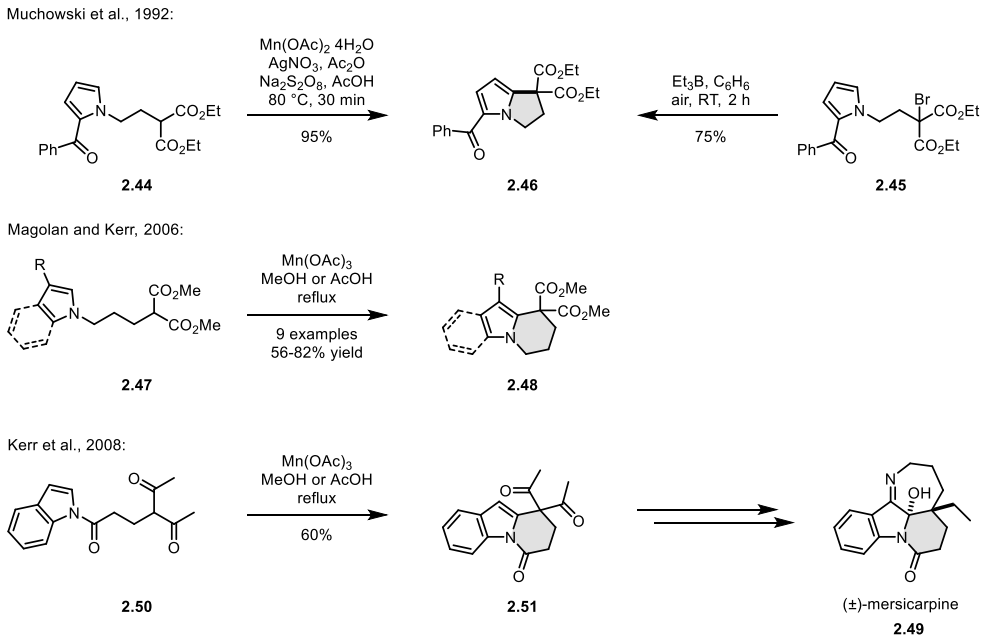
In the last 30 years, radical chemistry has attracted renewed interest due to significant advances in photochemistry. The photolysis of Barton esters was an early development in this field that allowed, for example, the radical cyclisation of benzimidazole **2.39** to build the core of the anti-cancer agent cyclopropamitosene (**2.40**) (Scheme 2.9).[149] More recently, photoredox methods have gained popularity, exemplified by Zhang and Yu's C–H amidation of heteroaromatics.[122]



Scheme 2.9 Summary of Aldabbagh's synthesis of the core of cyclopropamitosene (**2.40**),[149] and Zhang's photoredox-catalysed heteroarene amidation.[122]

2.1.3 Malonyl radical cyclisations onto heteroaromatics

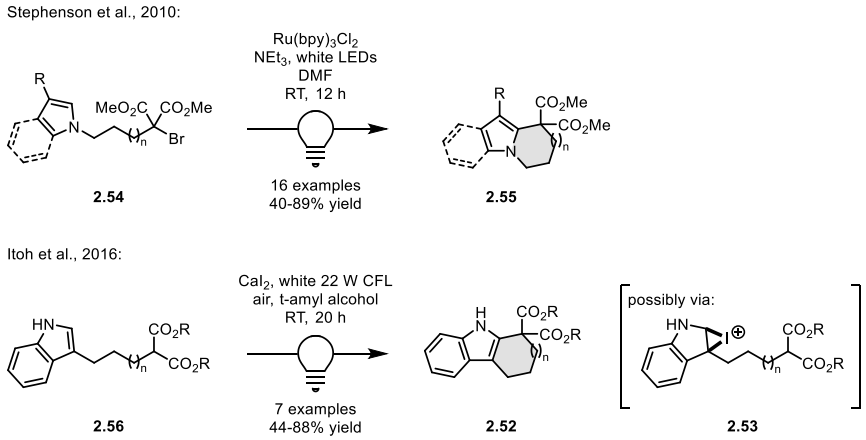
Malonyl radicals are commonly employed in the synthesis of annulated heteroaromatics. In 1988, the first example of their addition onto heteroarenes was reported by Weinstock and Karady.[134] Malonyl radicals generated under oxidative conditions with CAN added onto furans, thiophenes, benzofurans and benzothiophenes. In 1992, Muchowski reported the first cyclisation of malonyl radicals onto heteroaromatics in their synthesis of ketorolac (**2.8**) (Scheme 2.10).[48] Here, a malonyl radical, generated from malonate **2.44** and Mn(III) or bromomalonate **2.45** and Et_3B/O_2, added onto a pyrrole ring to give fused pyrrole **2.46**. $Mn(OAc)_3$, the reagent of choice for the generation of malonyl radicals from malonates, was employed by Kerr and co-workers in their synthesis of fused pyrroles and indoles,[138] as well as in their total synthesis of (±)-mersicarpine (**2.49**)[150] (Scheme 2.10). Recently, Kanai reported a method using substoichiometric amounts of $Mn(acac)_3$ and air in their cyclisation of malonates onto indoles.[151]



Scheme 2.10 Summary of Muchowski's radical cyclisations towards ketorolac (**2.8**),[48] Kerr's oxidative malonate cyclisation onto pyrroles and indoles,[138] and their application to the total synthesis of (±)-mersicarpine (**2.49**).[150]

Cyclisations involving photochemically generated malonyl radicals have also been reported. In 2010, Stephenson described the photoredox-mediated cyclisation of malonyl radicals, generated through the reduction of bromomalonates with a ruthenium photocatalyst, onto indoles and pyrroles (Scheme 2.11).[56] These conditions were also amenable to intermolecular additions to indoles, azaindoles, pyrroles, and furans;[139] and a follow-up methodology using an iridium photocatalyst expanded the scope to thiophenes and 2-pyridones.[140] This work found application in Qin's formal syntheses of actinophyllic acid,[152] and Miranda's construction of the core of tronocarpine.[153] In 2016, Itoh reported a light-mediated method for the cyclisation of malonates onto indoles using substoichiometric amounts of CaI_2 and air as terminal oxidant (Scheme 2.11).[141] The authors proposed a mechanism based on the generation of malonyl radicals through homolysis of iodomalonates formed *in situ*. However, significant amounts of product **2.52** were detected in the dark, in contradiction with a light-mediated mechanism. Itoh and co-

workers invoked iodonium **2.53** as an intermediate to explain product formation under these conditions. Thus, the involvement of malonyl radicals in this transformation remains unclear.



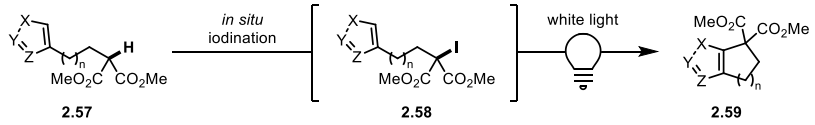
Scheme 2.11 Summary of Stephenson's photoredox-catalysed cyclisation of malonyl radicals,[56] and Itoh's CaI_2-mediated synthesis of fused indoles (**3.52**).[141]

Current malonyl radical cyclisation methods offer a platform for the synthesis of annulated heteroaromatics but suffer from several limitations. The scope of these transformations has only been reported with electron rich aromatics such as indoles, pyrroles, (benzo)thiophenes, and (benzo)furans. Furthermore, the majority of methods are reliant on stoichiometric amounts of transition metal salts (Mn(III), Ce(IV), or Fe(III)) or expensive photoredox catalysts. These drawbacks thus limit their widespread application.

2.2 Project aims

Annulated heteroaromatics are prevalent in nature, medicinal, and agrochemistry, and can be accessed through the radical cyclisation of alkyl radicals onto heteroaromatics. As discussed above (see section 2.1.3), malonyl radicals have often been used in these transformations, though published examples were largely limited to electron rich aromatics such as indole, pyrrole, and thiophene.

Here, we aimed to develop a new malonyl radical cyclisation method for the synthesis of annulated heteroaromatics that would be general and transition metal-free. We envisaged using iodomalonates **2.58** as key radical precursors. Following from Garrec's work (see section 1.4), malonyl radicals would be generated *via* the photolysis of *in situ* prepared iodomalonates **2.58**. These radicals would then add onto pendant heteroaromatics and yield the desired cyclised heteroaromatics **2.59**. Under mild photochemical conditions, we hypothesised that the cyclisation would be compatible with a wide variety of heteroaromatics and would offer a general platform for the synthesis of the ring systems of interest.



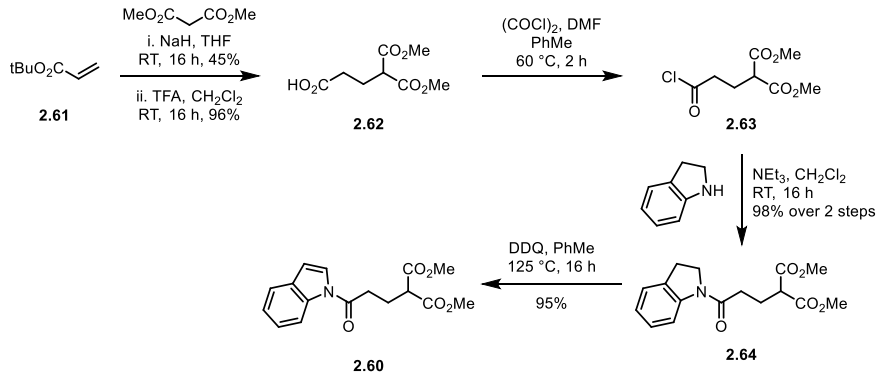
Scheme 2.12 Project proposal: the light-mediated malonyl radical cyclisation of *in situ* generated iodomalonates onto heteroaromatics.

2.3 Results and discussion

2.3.1 Initial reaction optimisation

This project's initial goal was to adapt Garrec's method for the synthesis of complex spirocycles to the synthesis of fused heteroaromatics.[81] We envisaged that heteroaromatic-containing malonates could be iodinated *in situ* in a similar fashion, and then be photolysed to yield malonyl radicals. These radicals could then add onto the vicinal heteroaromatic ring to give a cyclic radical, which after rearomatisation would give the desired cyclised systems.

N-acyl indoles were chosen as the initial substrate, since they often feature in malonyl radical cyclisation methodologies and would be a good benchmark for comparison.[56, 138] *N*-acyl indole **2.60** was chosen as the first substrate for optimisation.

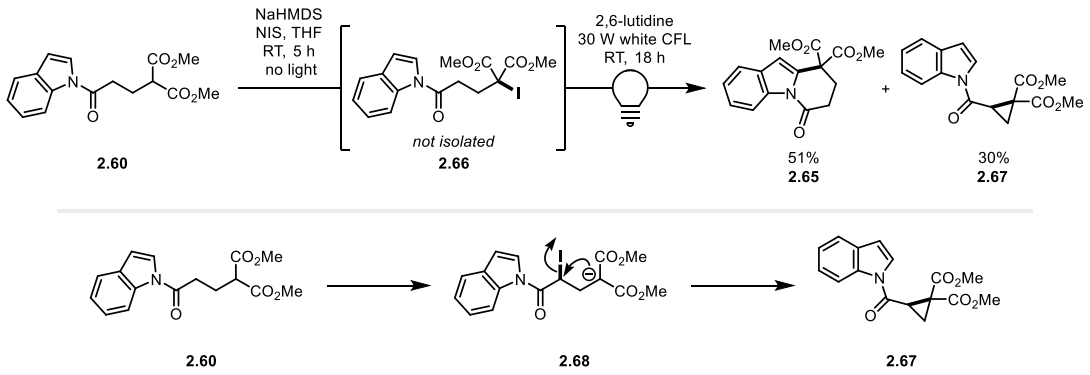


Scheme 2.13 Synthesis of *N*-acyl indole **2.60**.

Previous syntheses of *N*-acyl indole **2.60** involved deprotonation and acylation of indole, but reported yields were low.[56, 138] Instead, following Kerr's precedent, we exploited the higher nucleophilicity and facile oxidation of indoline.[138] Acylation of indoline with acyl chloride **2.63** (derived from acid **2.62**) gave amide **2.64** in 98% yield, which was followed

by DDQ oxidation to yield the desired indole **2.60** in 95% yield. This route, albeit a step longer, gave access to gram-quantities of indole **2.60**.

Our aim was to then develop a one-pot procedure that involved iodination of malonate **2.60** and *in situ* photolysis to give cyclised malonate **2.65**. The initial reaction conditions mirrored Garrec's spirocyclisation conditions and involved deprotonation of malonate **2.60** with NaHMDS and subsequent iodination with NIS in the dark (Scheme 2.14).[81] After 5 h, full conversion to iodomalonate **2.66** was confirmed through TLC and ^{1}H NMR analysis. 2,6-Lutidine was then added and the reaction mixture irradiated with a 30 W white compact fluorescent light (CFL) for 18 h.* Under these conditions, desired product **2.65** was obtained in 51% yield, together with cyclopropane **2.67** in 30% yield. Side product **2.67** could arise from α-iodination of indole **2.60** to give iodide **2.68** and nucleophilic displacement with the malonate enolate (Scheme 2.14). This was in line with a similar cyclopropane-forming reaction described by Chang et al.[154]

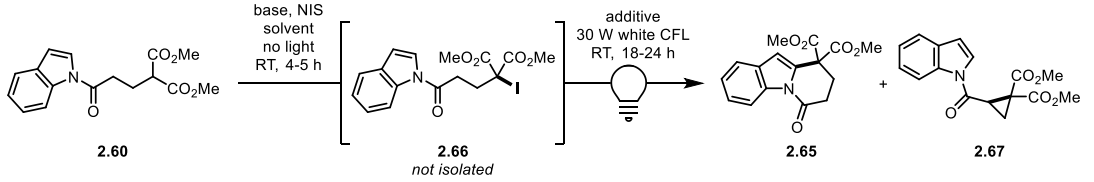


Scheme 2.14 Initial results of the cyclisation of *N*-acyl indole **2.60** and tentative mechanism for the formation of cyclopropane **2.67**.

This first result was followed by a base screen, summarised in Table 2.1. LiHMDS favoured formation of the undesired cyclopropane side product **2.67** (entry 2), while

* The choice of light source was informed by Garrec's spirocyclication, which gave best yields when irradiation was performed with a 30 W white compact fluorescent light (CFL) at 1.0 cm distance. [81]

KHMDS returned mostly starting material **2.60** (entry 3). Both NaH and tBuOK showed high selectivity for the formation of desired product **2.65**, albeit in moderate yields (entries 4, 5). Finally, the addition of 2,6-lutidine, shown to improve product yields in Garrec's closely related iodomalonate cyclisation,[81] had no effect on product yield (entries 1, 6). Thus, it was omitted in subsequent reactions.



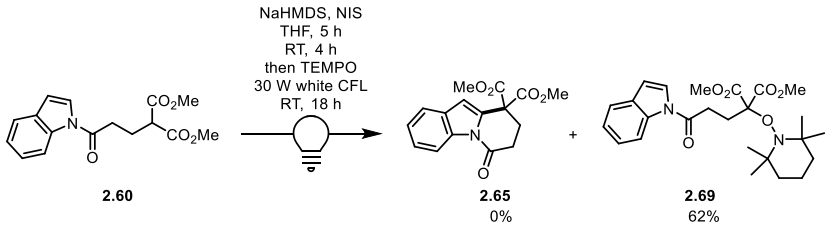
Entry	Base	Additive	Solvent	Yield 2.65/%[a]	Yield 2.67/%[a]
1	NaHMDS	2,6-lutidine	THF	51	30
2	LiHMDS	2,6-lutidine	THF	38	58
3	KHMDS	2,6-lutidine	THF	12	0
4	NaH	2,6-lutidine	THF	39	8
5	tBuOK	2,6-lutidine	THF	37	<5
6	NaHMDS	–	THF	58	28
7[b]	NaHMDS[c]	–	THF	94[d]	<5
8	NaHMDS[c]	–	2-MeTHF	65	8
9	NaHMDS[c]	–	MeCN	52	9
10	NaHMDS[c]	–	1,4-dioxane	76	<5
11	NaHMDS[c]	–	Et_2O	60	5
12	NaHMDS[c]	–	CH_2Cl_2	88	<5
13	NaHMDS[c]	–	PhMe	33	<5
14	NaHMDS[c,e]	–	THF	0	0
15	NaHMDS[c]	TEMPO	THF	0	0

Table 2.1 Summary of the optimisation of the cyclisation of indole **2.60**. *Reagents and conditions:* **2.60** (0.05 mmol), base (1.2 equiv.), NIS (1.2 equiv.), solvent (0.1 M), no light, RT, 4–5 h, then additive (1.2 equiv.), 30 W white CFL, RT, 18–24 h. [a] Calculated yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Reaction performed on a 0.20 mmol scale; [c] Reverse order of addition: NaHMDS added over 30 min to a solution of **2.60** and NIS; [d] Isolated yield; [e] Reaction performed in the dark.

Reversing the order of the addition of reagents (adding NaHMDS to a solution of indole **2.60** and NIS at −78 °C over 30 min) showed the biggest improvement in yield. Under

these conditions, no starting material **2.60** remained, side product **2.67** was not detected, and cyclised indole **2.65** was obtained in 94% isolated yield (entry 7).

This reaction gave best results in THF, but it was compatible with other solvents. For instance, use of the more environmentally-friendly alternative 2-MeTHF[155] gave product **2.60** in lower but synthetically useful yield (entry 8). Similar results were obtained when replacing THF with acetonitrile, 1,4-dioxane, Et_2O, or CH_2Cl_2 (entries 9–12), while toluene gave poor product yield (entry 13).



Scheme 2.15 Results of the malonyl radical cyclisation of indole **2.60** in the presence of TEMPO.

Control experiments were carried out to better understand the mechanism of this transformation. In the dark, no cyclised product **2.65** was detected by ^{1}H NMR and iodomalonate **2.66** was obtained instead (entry 14). In the presence of the radical trapping reagent TEMPO (entry 15), adduct **2.69** was isolated and product **2.65** was not obtained (Scheme 2.15). These results were in keeping with the proposed mechanism involving homolysis of iodomalonate **2.66** to yield a malonyl radical.

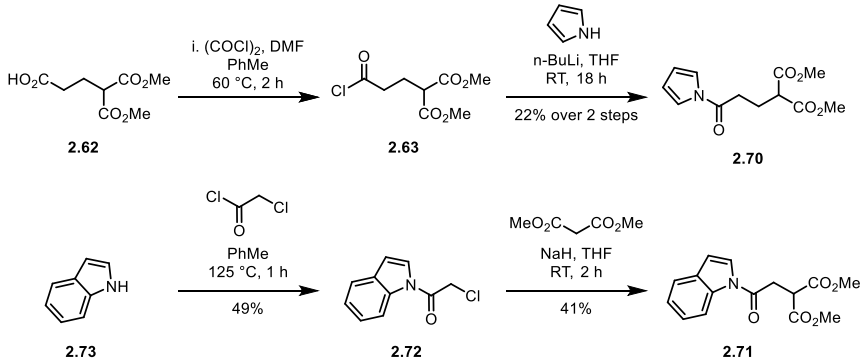
2.3.2 Initial scope of N-tethered malonates

2.3.2.1 Synthesis of *N*-tethered malonates

Having optimised reaction conditions for the cyclisation of *N*-acyl indole **2.60**, the scope of this transformation was investigated. The variables explored were the heteroaromatic ring (indole, pyrrole, imidazole, and 1,2,3-triazole), and the nature (*N*-alkyl and *N*-acyl)

and length of the tether. Consequently, a set of heteroaromatic malonates were synthesised according to the routes outlined in Schemes 2.16 and 2.17.

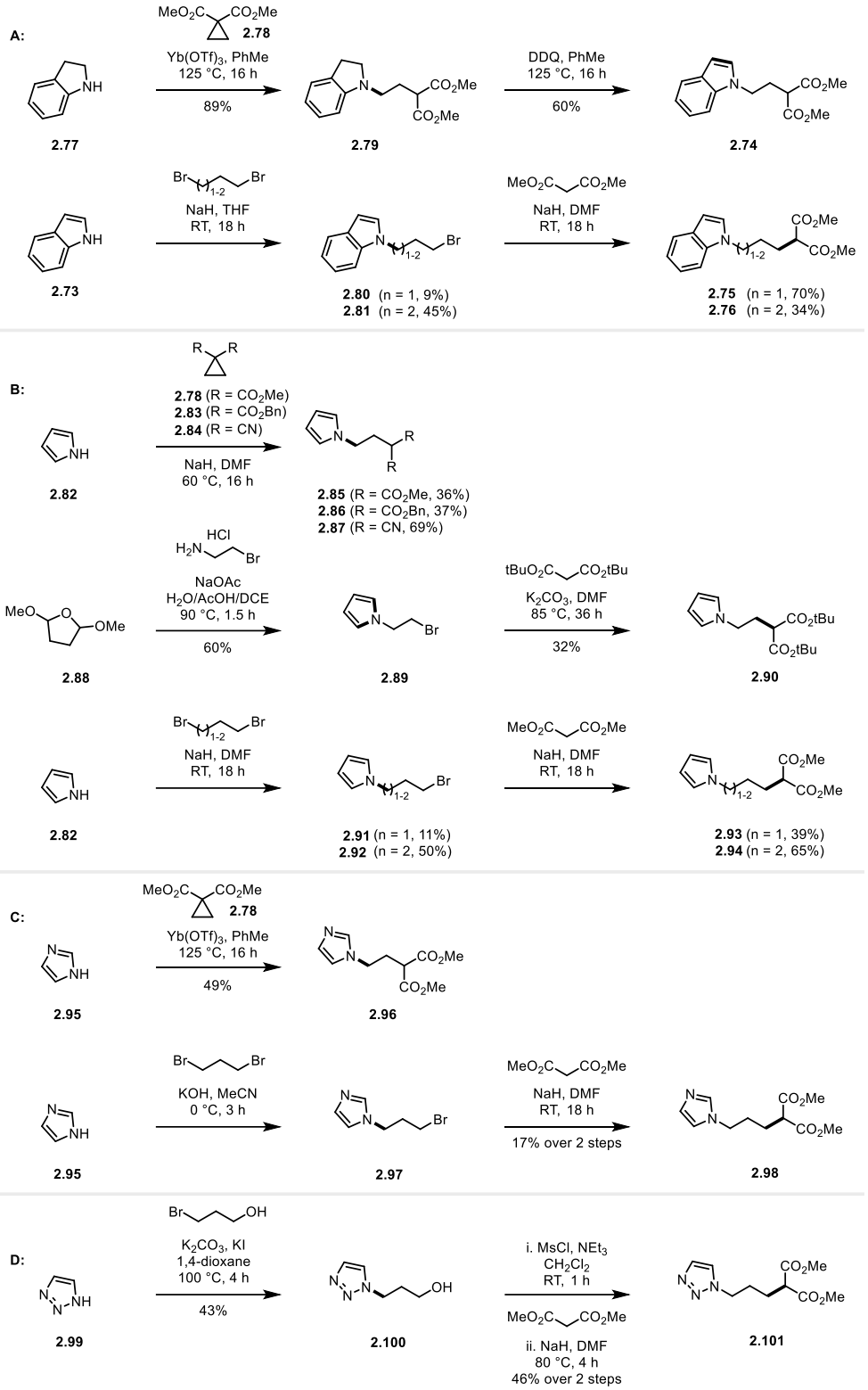
N-Acyl substrates **2.70** and **2.71** were prepared through two different routes. *N*-Acyl pyrrole **2.70** was obtained from acylation of pyrrole with acyl chloride **2.63**, derived from carboxylic acid **2.62**, through a route analogous to that of indole **2.60**. Indole **2.71** was obtained through acylation of indole with chloroacetyl chloride to yield indole **2.72** and halide substitution with dimethyl malonate.



Scheme 2.16 Synthesis of *N*-acyl pyrrole **2.70** and *N*-acyl indole **2.71**.

N-Alkyl indoles, pyrroles and imidazoles with two, three, and four methylene-long linkers were prepared through common routes depicted in Scheme 2.17. Activated cyclopropanes were used to synthesise substrates with two methylene long tethers,[157] while dibromoalkanes were employed as biselectrophiles for the preparation of longer tethered malonates.

Indole cyclisation substrates **2.74**, **2.75**, and **2.76** were prepared according to these general routes (Scheme 2.17, A). Addition of indoline (**2.77**) to cyclopropane **2.78** yielded malonate **2.79** in 89% yield, which upon oxidation with DDQ gave cyclisation substrate **2.74**. Indoles **2.75** and **2.76**, on the other hand, were prepared through double functionalisation of dibromoalkanes.

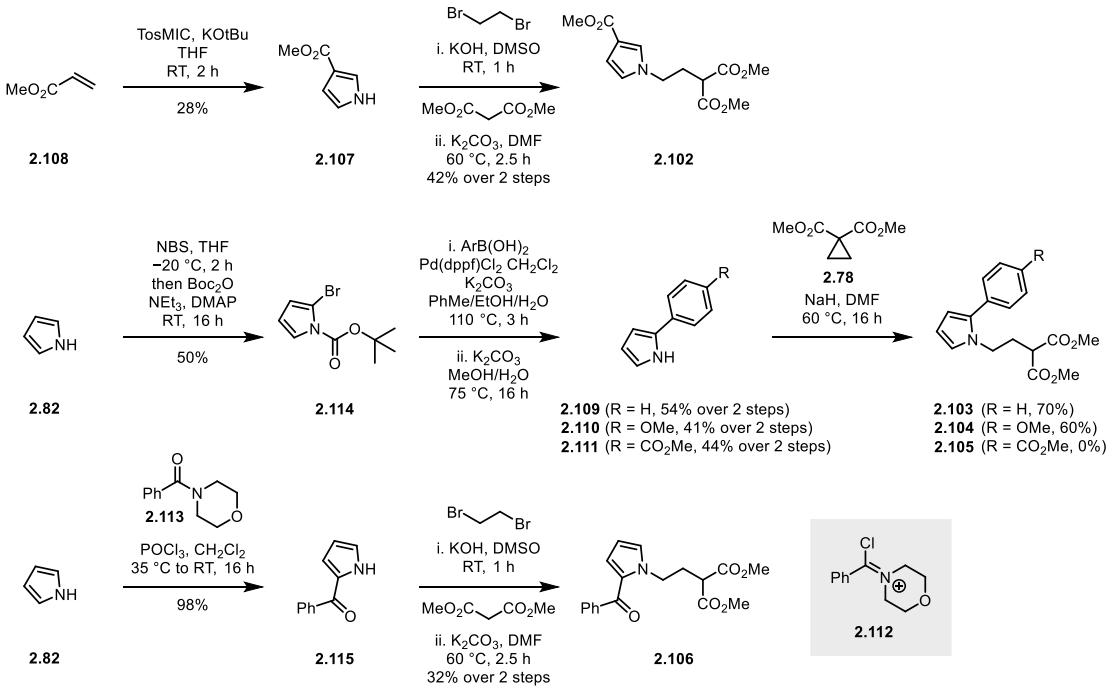


Scheme 2.17 Synthesis of *N*-alkyl indole, pyrrole, imidazole, and 1,2,3-triazole cyclisation substrates.

The same routes, with minor modifications, gave access to pyrroles **2.85**–**2.87**, **2.90**, **2.93**, and **2.94** (Scheme 2.17, B). Cyclopropanes **2.78**, **2.83** and **2.84** were used to prepare methyl malonate **2.85**, benzyl malonate **2.86** and malononitrile **2.87**, respectively. However, due to purification issues this approach could not be used for *tert*-butyl malonate **2.90**. Instead, malonate **2.90** was obtained from dimethoxy tetrahydrofuran **2.88** through pyrrole condensation and nucleophilic substitution of bromide **2.89**. The longer-tethered malonates **2.93** and **2.94** were prepared under analogous conditions to indoles **2.75** and **2.76**.

Imidazole substrates **2.96** and **2.98** were compatible with this approach (Scheme 2.17, C), but 1,2,3-triazole **2.101** required some modifications (Scheme 2.17, D). This entailed alkylation with 1,3-bromopropanol, instead of 1,3-dibromopropane, mesylation of the resulting alcohol **2.100** and nucleophilic displacement to yield triazole **2.101**.

Several substituted pyrroles (**2.102**–**2.106**) were prepared to test the compatibility of aromatic substitution with the cyclisation conditions (Scheme 2.18). 3-Carboxypyrrole **2.107** was constructed *via* a Van Leusen reaction of methyl acrylate (**2.108**).[158] Subsequently, alkylation of pyrrole **2.107** with 1,2-dibromoethane and malonate substitution gave cyclisation substrate **2.102**. For the synthesis of malonates **2.103**–**2.105**, pyrrole was arylated through bromination and Suzuki-Miyaura cross-coupling to give pyrroles **2.109**–**2.111**. These were then treated with cyclopropane **2.78** to yield malonates **2.103** and **2.104**. Unfortunately, starting material **2.111** was recovered when attempting the synthesis of ester-containing pyrrole **2.105**, likely due to the electron withdrawing character of the aryl ring, which reduces its nucleophilicity. Finally, benzoyl pyrrole **2.106** was obtained from pyrrole through a three-step sequence involving acylation with chloroiminium salt **2.112**[159] and sequential substitution of 1,2-dibromoethane.



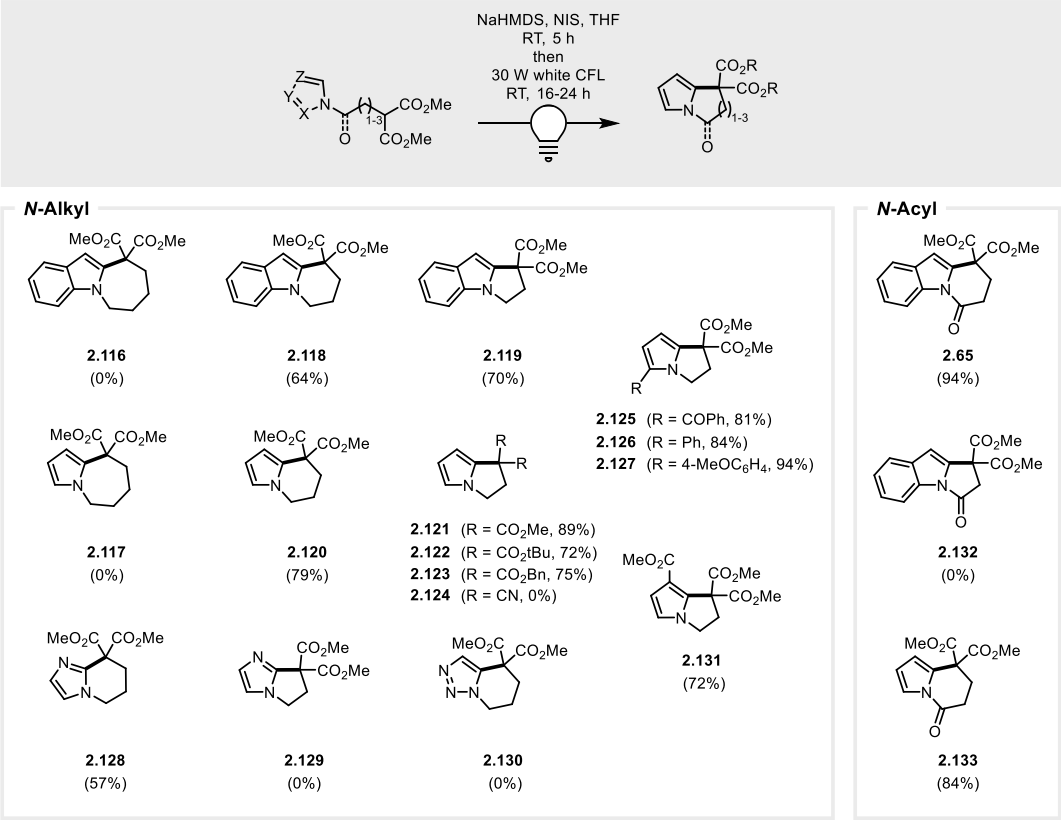
Scheme 2.18 Synthesis of substituted pyrroles **2.102–2.106**.

2.3.2.2 Cyclisation of *N*-tethered malonates

The aforementioned compounds were then subjected to the radical cyclisation conditions. The cyclisation of *N*-acyl substrates was performed using the optimised conditions described in section 2.3.1, which entailed reverse addition of reagents to avoid formation of cyclopropane **2.67**. The cyclisation of *N*-alkyl substrates, on the other hand, did not require reverse addition of reagents, since these substrates did not yield cyclopropyl side products. The results obtained are summarised in Scheme 2.19.

The cyclisation of *N*-alkyl indoles and pyrroles showed dependence on tether length. Seven membered rings **2.116** and **2.117** were not obtained, instead, malonates **2.76** and **2.94** were recovered. On the contrary, cyclisations yielding six- and five-membered rings fused to indoles (**2.118** and **2.119**) and pyrroles (**2.120**–**2.124**) were successful (Scheme 2.19). The lack of cyclisation to form seven-membered rings may be explained by entropic factors; however, it differs from previous reports by Snider and Zard.[156, 157]

Snider described the cyclisation of malonyl radicals onto olefins to give seven- and eight-membered rings,[157] and Zard reported the addition of alkyl radicals onto indoles to form seven-membered rings.[156]



Scheme 2.19 Results of the cyclisation of *N*-acyl and *N*-alkyl substrates.

Imidazoles **2.128** and **2.129** did not follow this trend. Imidazole **2.98** cyclised regioselectively to give six-membered ring **2.128** in 57% yield. Addition to C{2} is preferred for Minisci-type substitutions, hence the observed selectivity agreed with previous reports.[103, 158] On the other hand, the radical addition to form five-membered ring **2.129** was unsuccessful and returned malonate **2.96**; the higher ring strain of the 5,5-ring system compared to the 5,6-ring system may explain these results.

Finally, 1,2,3-triazole **2.101** did not cyclise to give bicycle **2.130**. Polarity mismatch between the electrophilic malonyl radical and the electron poor 1,2,3-triazole may explain

this lack of reactivity. This agrees with observations by Marco-Contelles et al., who described the cyclisation of nucleophilic alkyl radicals onto 1,2,3-triazoles.[111, 112]

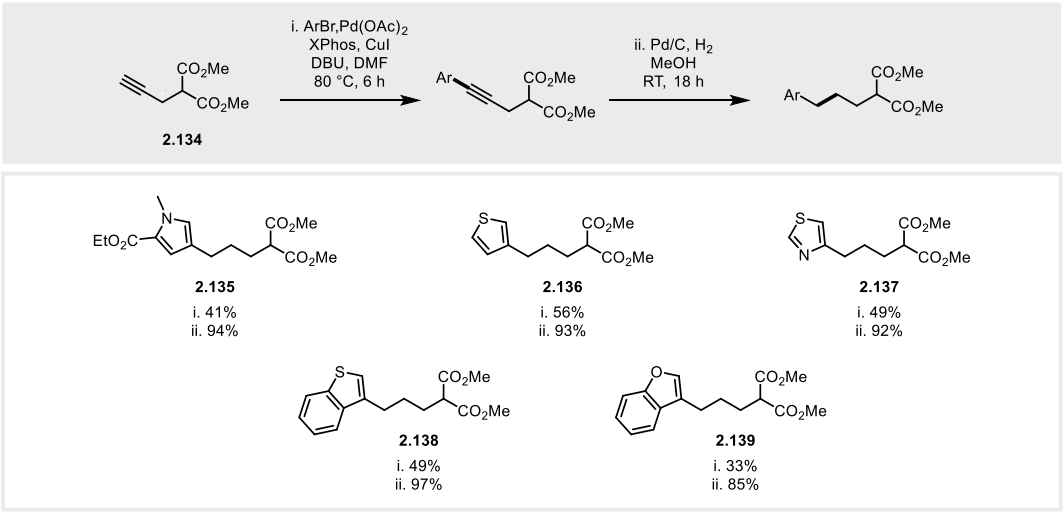
The cyclisation of *N*-acyl substrates was also dependent on tether length. Indole **2.60** and pyrrole **2.70** cyclised in good yields to give six-membered rings **2.65** and **2.133**, while malonate **2.71** was recovered when attempting its cyclisation to give five-membered ring-containing indole **2.132**. This difference may be due to the ring strain in the 5,5-ring system formed, which contains three sp^2 centres.

2.3.3 Expansion to C-substituted heteroaromatics

Encouraged by the results of this initial scope, the cyclisation onto a wider range of heteroaromatics was investigated. This included heteroarenes tethered to the malonate from a carbon atom.

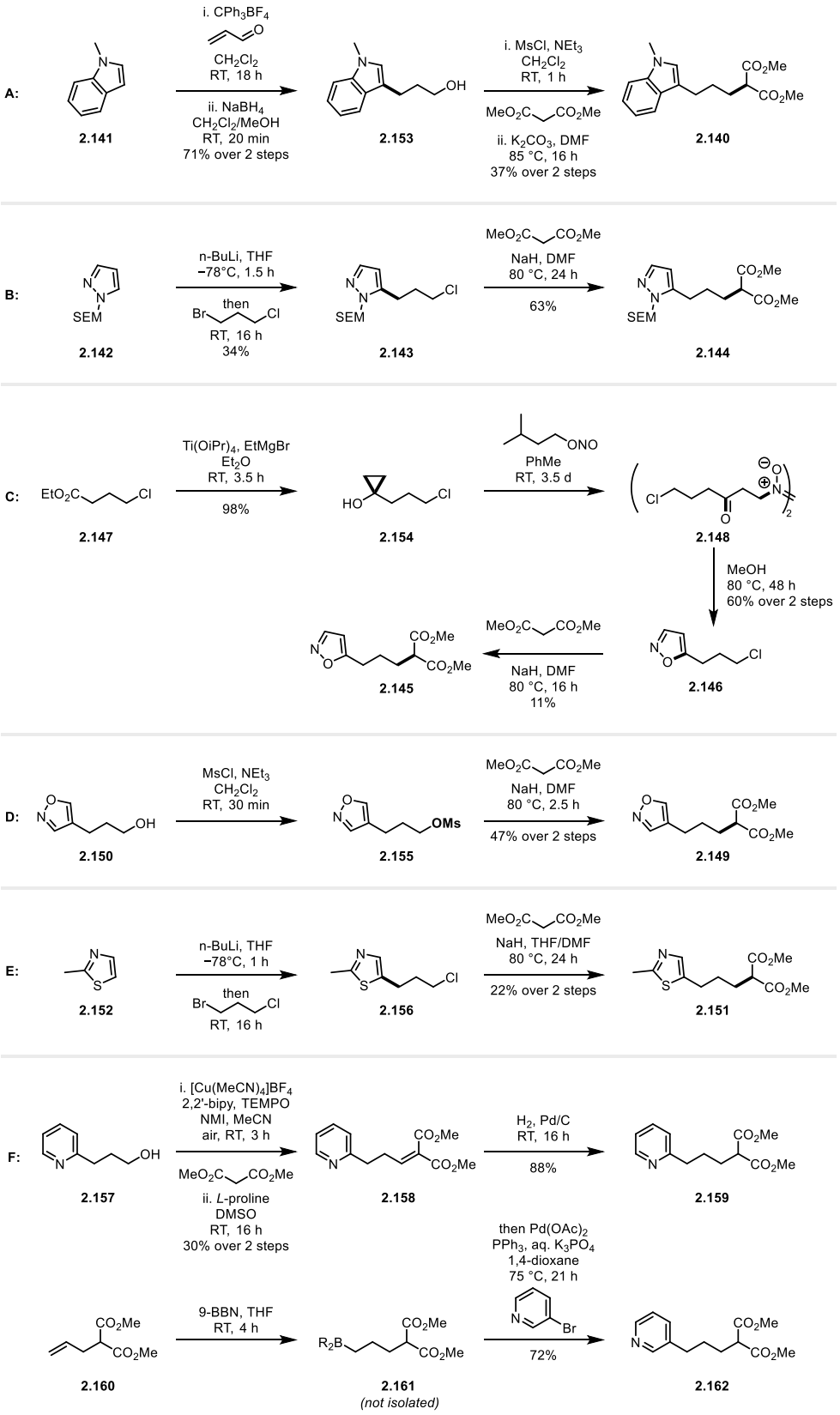
2.3.3.1 Synthesis of *C*-substituted heteroaromatics

A variety of metal-catalysed cross-couplings could give access to the required *C*-tethered substrates after one or two steps from commercially available heteroaryl halides and a common coupling partner (borane, alkene, or alkyne). Among these approaches, the most precedented is a two-step sequence involving Sonogashira coupling of propargyl malonate **2.134** and a heteroaryl bromide, followed by hydrogenation of the triple bond.[159-161] The reaction conditions from the literature were used as the starting point in a high-throughput screen performed by our industrial collaborators at Pfizer. These efforts found the conditions depicted in Scheme 2.20 as most general for the coupling of heteroaryl bromides and propargyl malonate **2.134**. The resulting alkynes were then hydrogenated under standard conditions to give cyclisation substrates **2.135**–**2.139** in moderate but synthetically useful yields over two steps.



Scheme 2.20 Sonogashira route to *C*-tethered cyclisation substrates.

Several heteroaromatics were not compatible under the Sonogashira coupling conditions due to degradation of the heteroaryl bromides. Alternative synthetic sequences, summarised in Scheme 2.21, were used for these cases. Indole **2.140** was obtained through trityl-catalysed conjugate addition of indole **2.141** to acrolein,[162] aldehyde reduction, mesylation, and substitution with dimethyl malonate. Lithiation of pyrazole **2.142** and alkylation with 1-bromo-3-chloropropane led to chloride **2.143**, which was then converted into pyrazole **2.144** after chloride displacement with dimethyl malonate. 5-Substituted isoxazole **2.145** was prepared from chloride **2.146** through substitution with dimethyl malonate. Chloride **2.146**, in turn, was prepared through a sequence described by Kulinkovich and co-workers.[163] This entailed cyclopropanation of ester **2.147** and reaction of the resulting cyclopropanol with isoamyl nitrite to yield dimeric *β*-nitrosoketone **2.148**. This species then underwent condensation in refluxing methanol to give the required chloride **2.146**. Isoxazole **2.149** was obtained from alcohol **2.150** through mesylation/substitution. Similar to the synthesis of pyrazole **2.144**, thiazole **2.151** was obtained from methyl thiazole **2.152** through lithiation, alkylation with 1-bromo-3-chloropropane, and malonate substitution.

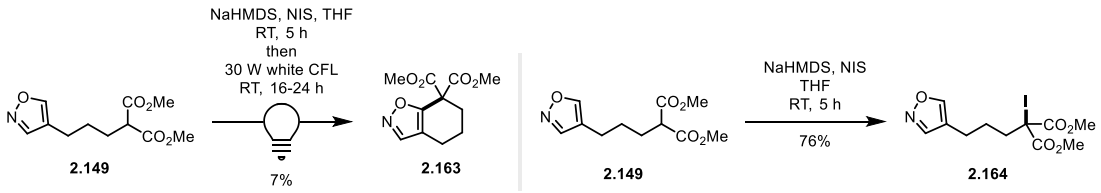


Scheme 2.21 Other routes to *C*-tethered cyclisation substrates.

Finally, pyridines **2.159** and **2.162** were prepared to test the applicability of the radical cyclisation on 6-membered heteroaromatics. 2-Substituted pyridine **2.159** was obtained from alcohol **2.157** through Stahl oxidation,[164] Knoevenagel condensation, and olefin hydrogenation. On the other hand, 3-substituted pyridine **2.162** was synthesised *via* Suzuki-Miyaura cross-coupling of *in situ* generated borane **2.161** and 3-bromopyridine.[81]

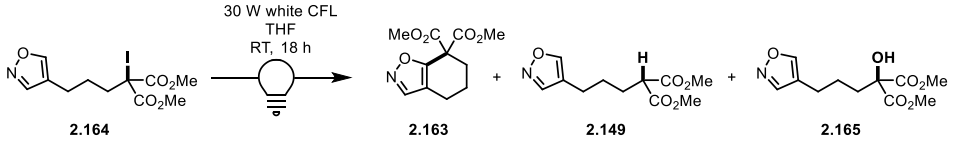
2.3.3.2 Reoptimisation efforts

The *C*-substituted heteroaromatics were subjected to the previously optimised malonyl radical cyclisation conditions (see section 2.3.1); however, products were obtained in poor yields. For instance, isoxazole **2.149** cyclised to give bicycle **2.163** in 7% yield (Scheme 2.22). This highlighted the lack of generality of the conditions optimised for *N*-functionalised aromatics and prompted us to reoptimise this transformation. Isoxazole **2.149** was used as model substrate for the optimisation that followed.



Scheme 2.22 Light-mediated cyclisation of isoxazole **2.149** and preparation of iodomalonate **2.164**.

In this instance, the reaction was optimised in a stepwise manner, separating iodination from malonyl cyclisation. The iodination of isoxazole **2.149** under standard conditions (NaHMDS and NIS) gave iodomalonate **2.164** in 76% isolated yield (Scheme 2.22). However, upon irradiation of iodomalonate **2.164** with white light in the absence of any base, a mixture of desired product **2.163** (11%), malonate **2.149** (7%), and hydroxymalonate **2.165** (7%) were obtained (Table 2.2, entry 1).



Entry	Base (equiv.)	Yield of 2.163/%	Yield of 2.149/%[a]	Yield of 2.165/%[a]
1	–	11	7	8
2[b]	–	0	0	43
3	2,6-lutidine (1.2)	17	11	22
4	DBU (1.2)	0	100	0
5	NEt_3 (1.2)	4	91	0
6	PMP (1.2)	27	25	41
7	quinuclidine (1.2)	17	37	0
8	K_2CO_3 (1.2)	49	12	0
9	TMP (1.2)	66	12	13
10	TMP (2.0)	66	3	29
11	TMP (5.0)	45	0	58
12[c]	TMP (2.0)	48	14	0
13[d]	TMP (2.0)	55	16	0
14[e]	TMP (2.0)	55	16	12
15[f]	TMP (2.0)	0	0	0
16[g]	TMP (2.0)	63[h]	–	–
17[i]	TMP (2.0)	56[h]	–	–

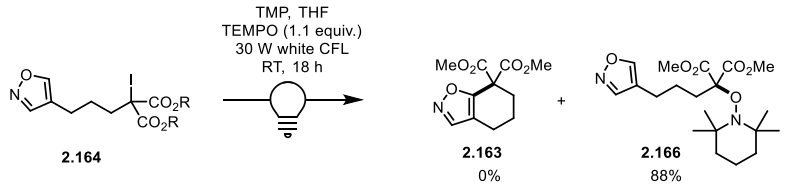
Table 2.2 Summary of the optimisation of the cyclisation of iodomalonate **2.164**. *Reagents and conditions:* **2.164** (0.05 mmol), base, THF (0.1 M), 30 W white CFL, RT, 18–24 h. [a] Calculated yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Reaction carried out under air; [c] Reaction irradiated with 43 W 370 nm Kessil LED light; [d] Reaction irradiated with 45 W 427 nm Kessil LED light; [e] Reaction irradiated with 44 W 525 nm Kessil LED light; [f] Reaction performed in the presence of TEMPO (1.0 equiv.); [g] Reaction carried out on a 0.20 mmol scale; [h] Isolated yield; [i] Reaction performed in a one-pot fashion from malonate **2.149** (0.20 mmol).

Bases and light sources were then screened to improve the outcome of the cyclisation of iodomalonate **2.164** (Table 2.2). Product yields were highly dependent on the choice of base: 2,6-lutidine, used by Garrec in their iodomalonate cyclisation,[81] had no effect on this transformation (entry 3) while DBU caused quantitative deiodination (entry 4). Tertiary amines such as triethylamine, PMP, and quinuclidine increased dehalogenation and did not significantly improve product yield (entries 5–7). Competing C–H abstraction

of the hydrogen α to the nitrogen atom of these bases may explain this behaviour. Based on this hypothesis, an inorganic base (K_2CO_3) and an amine lacking α-hydrogens (TMP) were screened, both improving product formation (entries 8, 9). Among the bases screened, TMP gave the best results (entries 9–11). In the presence of 2.0 equivalents of TMP, product **2.163** was obtained in 66% NMR yield (entry 10).

The light source used for this transformation did not have a significant impact on its outcome. The initial 30 W white compact fluorescent household light gave best results (entry 10), as compared to more powerful lamps with narrower emission spectra (entries 12–14).

Control experiments gave results in line with a malonyl radical mechanism, as observed with the radical cyclisation of acyl indole **2.60** (Table 2.1, section 2.3.1). In the presence of air, hydroxymalonate **2.165** was the main reaction product (entry 2),[165] and the addition of TEMPO inhibited the cyclisation (entry 15). In this instance, TEMPO adduct **2.166** was isolated and characterised, further supporting the role of malonyl radicals in this transformation (Scheme 2.23).

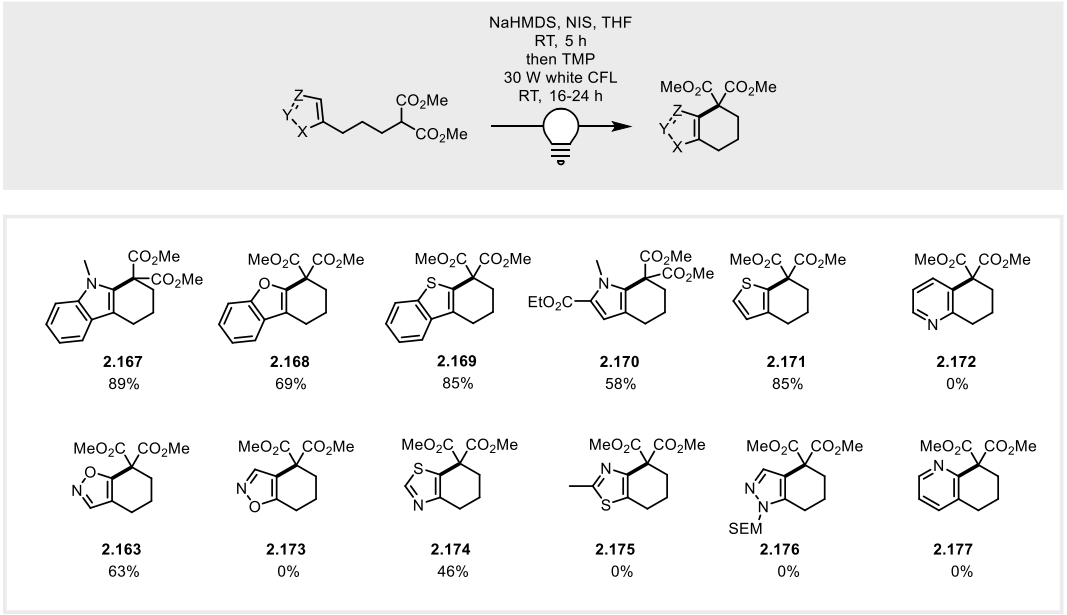


Scheme 2.23 Effect of the addition of TEMPO on the light-mediated cyclisation of iodomalonate **2.164**.

After this extensive reaction screening, the optimised conditions were used in a 0.20 mmol-scale reaction and gave isoxazole **2.163** in 63% yield (entry 16). These conditions were also applicable to the one-pot procedure, providing isoxazole **2.163** from malonate **2.149** in comparable yield (56%) (entry 17).

2.3.3.3 Cyclisation of *C*-substituted heteroaromatics

The conditions reoptimised for the cyclisation of isoxazole **2.149** were then applied to the other *C*-substituted heteroaromatics (Scheme 2.24).



Scheme 2.24 Results of the cyclisation of *C*-tethered substrates.

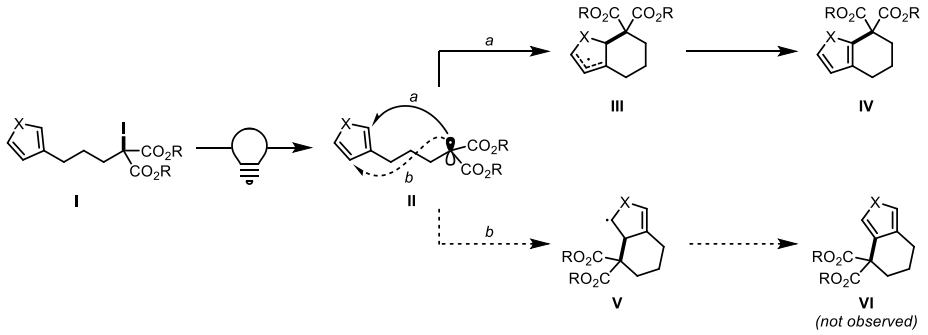
Benzo-fused heteroaromatics indole **2.167**, benzofuran **2.168**, and benzothiophene **2.169** were formed in good yields (69–89%). This agreed with previous malonyl cyclisation methods by Kerr,[138] Stephenson,[56] and Kanai.[151] Pyrrole **2.170** and thiophene **2.171** were obtained as single regioisomers in 58% and 85% yields, respectively. Radical addition to C{3} or C{4} was not observed in either case, in accordance with previous observations of the intermolecular addition of malonyl radicals onto five-ring heteroaromatics by Baciocchi,[166-168] Stephenson,[139] and Yamaguchi.[169]

The cyclisation of malonyl radicals onto azoles showed some clear regiochemical trends. C4-Substituted isoxazole **2.149** cyclised exclusively on C{5} to give isoxazole **2.163**, in line with the observed reactivity of pyrrole **2.135** and thiophene **2.136**. Regioisomeric

isoxazole **2.145** did not cyclise to give isoxazole **2.173**, instead returning starting material **2.145**. Similarly, C4-substituted thiazole **2.137** gave thiazole **2.174** in 46% yield, while the cyclisation of C5-substituted thiazole **2.151** failed to provide thiazole **2.175**. In accordance with these regiochemical results, the cyclisation of pyrazole **2.144** on C{4} was also unsuccessful. Nonetheless, polarity mismatch between the malonyl radical and the electron poor pyrazole ring may also explain this lack of reactivity.

Pyridines were outside the scope of this transformation, with cyclisations to give fused pyridines **2.172** and **2.177** returning starting materials **2.159** and **2.162** instead. This lack of reactivity may again be explained through polarity mismatch of the malonyl radical and the pyridine ring, and is in agreement with Opatz's calculations.[170]

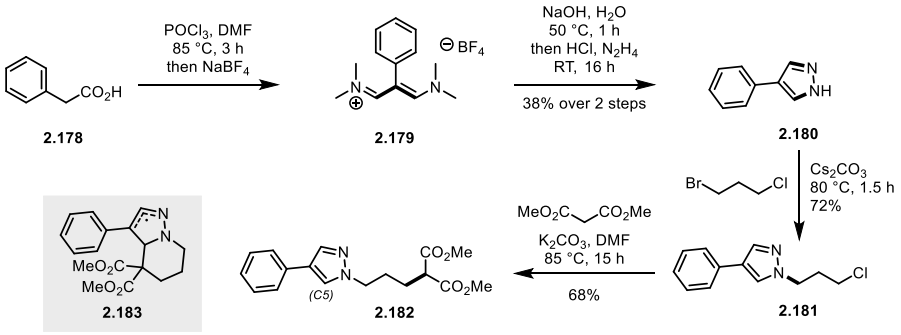
The regioselectivity of this transformation together with the stark difference in reactivity between regioisomeric cyclisation substrates may be explained by differences in stability of intermediary radical species (Scheme 2.25). In systems with two possible radical addition sites (***a*** and ***b***), addition to the C{2} (or C{5}) position yields a radical stabilised through conjugation (**III**). Conversely, the radical obtained from addition to the C{4} (or C{3}) position (**V**) is not conjugated, and thus likely higher in energy. This difference in relative energy between radicals **III** and **V** may explain the regioselective formation of pyrrole **2.170**, thiophene **2.171**, and isoxazole **2.163**, as well as the unsuccessful cyclisations to give isoxazole **2.173**, thiazole **2.175**, and pyrazole **2.176**. This is in agreement with MacMillan, who proposed a similar rationale for the regioselectivity of their radical trifluoromethylation of heteroaromatics.[171]



Scheme 2.25 Proposed explanation for the regioselectivity of the radical cyclisation.

2.3.4 Further expansion of the scope

Encouraged by the scope of this transformation and our better understanding of its reactivity, a final set of cyclisation substrates was prepared to further assess the heteroaromatic scope of this methodology. This was focused on ring systems of particular interest to medicinal chemistry: pyrazoles and nitrogen-rich heteroaromatics.



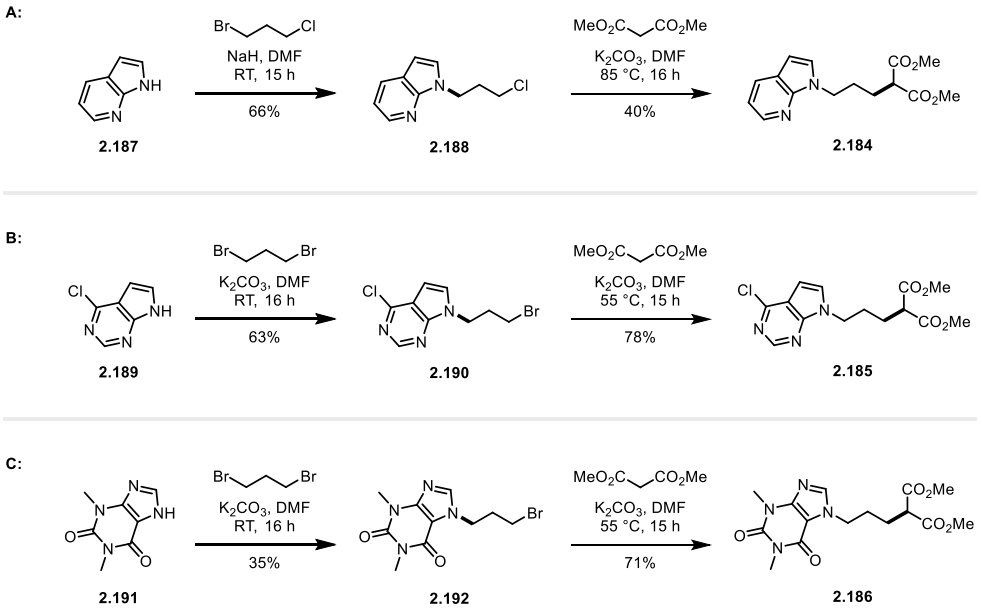
Scheme 2.26 Synthetic route towards pyrazole **2.182**.

So far, the cyclisation of malonyl radicals onto pyrazoles had been unsuccessful (**2.176**, Scheme 2.24). Nonetheless, the lack of cyclisation of pyrazole **2.144** could be explained by the reactivity trends observed for similarly substituted azoles (isoxazole **2.145** and thiazole **2.151**). Pyrazole **2.182** was therefore designed to favour cyclisation (Scheme 2.26). On this substrate, radical addition could only happen at the preferred site (C{5}), and the

resulting radical (**2.183**) would be doubly stabilised through allylic and benzylic conjugation.

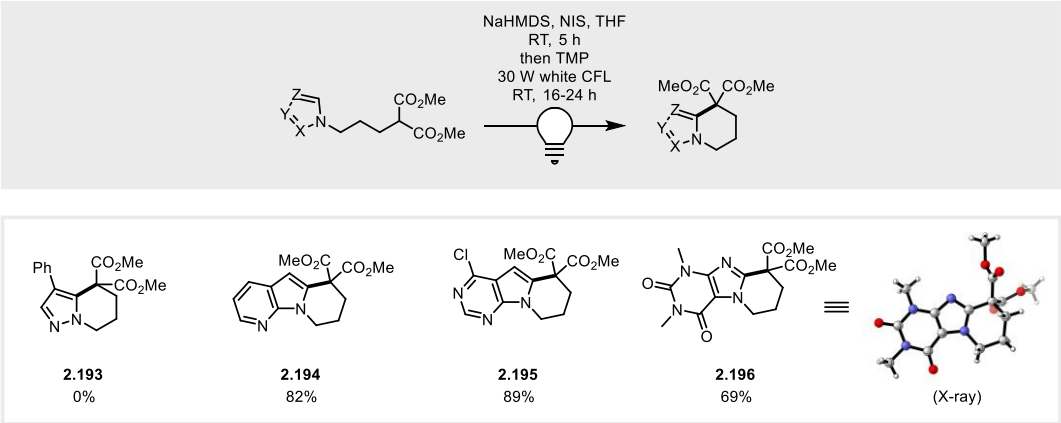
Pyrazole **2.182** was prepared in four steps from acid **2.178** (Scheme 2.26). Decarboxylative functionalisation of phenyl acetic acid (**2.178**) with the Vilsmeier reagent gave iminium ion **2.179**, a 1,3-dialdehyde equivalent.[172] Basic hydrolysis and condensation with hydrazine gave pyrazole **2.180**, which was then alkylated with 1-bromo-3-chloropropane to give chloride **2.181**. Target pyrazole **2.182** was obtained from chloride **2.181** through nucleophilic substitution.

Nitrogen-rich heteroaromatics are also a common motif in medicinal chemistry. To explore the applicability of the malonyl radical cyclisation on these heteroaromatics, malonates **2.184**, **2.185** and **2.186** were prepared. They were all obtained from a common route, based on the sequential nucleophilic substitution of dihaloalkanes (Scheme 2.27).



Scheme 2.27 Synthetic routes towards *N*-rich heteroaromatic substrates **2.184**, **2.185** and **2.186**.

These substrates were then subjected to the optimised cyclisation conditions (Scheme 2.28). Pyrazole **2.182** did not give any cyclised product **2.193** despite its phenyl substitution, envisaged to aid radical addition. Rather, this reaction returned starting material **2.182**. Polarity-mismatch between the electron poor aromatic and the electrophilic radical may explain this lack of reactivity. The nitrogen-rich heteroaromatics **2.184**, **2.185** and **2.186**, on the other hand, cyclised in good yields to give tricycles **2.194**, **2.195** and **2.196**. The connectivity of theophylline **2.196**, which could not be confidently assigned through NMR analysis, was confirmed through X-ray crystallography; this allowed, by extension, the structural confirmation of intermediates **2.186** and **2.192**.



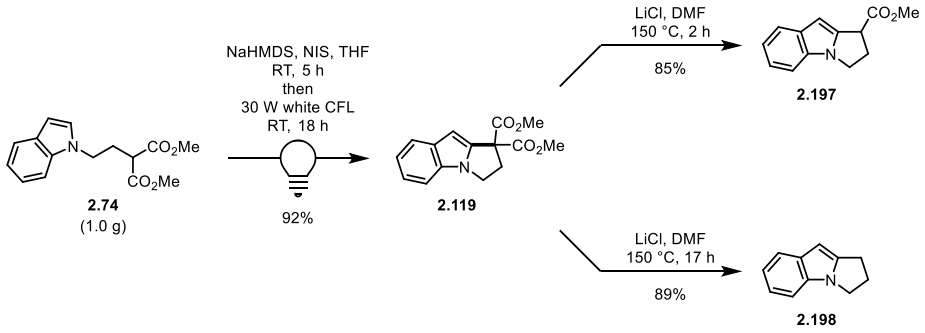
Scheme 2.28 Results of the malonyl radical cyclisation of pyrazole **2.182** and nitrogen-rich heteroaromatic substrates **2.184**, **2.185** and **2.186**. X-ray crystal structure of theophylline **2.196**.

2.3.5 Scale-up and derivatisation of reaction products

To showcase the utility of this transformation, we tested its scalability and derivatised selected cyclisation products.

The cyclisation of indole **2.74** could be performed on a 1.0 g scale (3.6 mmol, Scheme 2.29) with minimal changes to the reaction set up and with the same light source (one 30 W white CFL, placed 1.0 cm away from the vessel). Under these conditions,

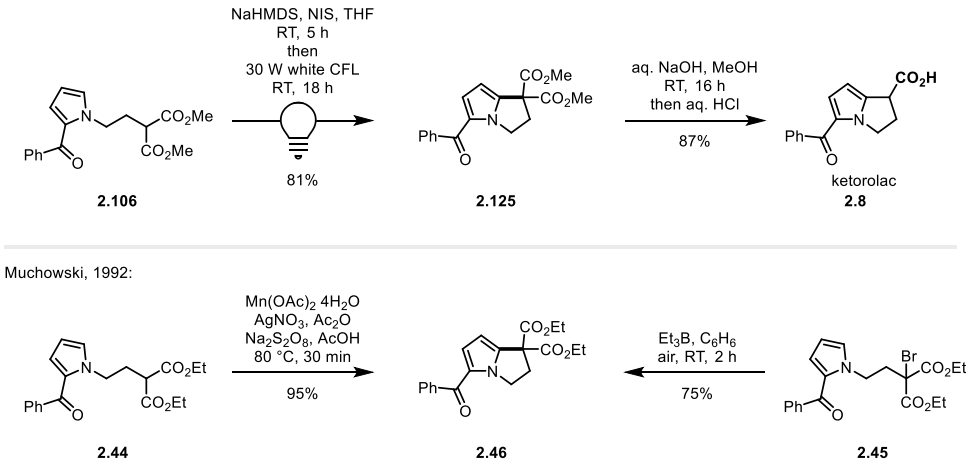
indole **2.119** was isolated in 92% yield, an improvement from the results obtained on 0.20 mmol reaction (70% yield, Scheme 2.19, section 2.3.2.2). This demonstrated the scalability of this transformation, which is often a limiting factor in the widespread application of photochemical reactions. [173-176]



Scheme 2.29 Results of the scaled-up cyclisation of indole **2.74** to yield indole **2.119** and its decarboxylative derivatisation.

Malonate **2.119** was derivatised through Krapcho decarboxylation (Scheme 2.29). Treatment of malonate **2.119** with LiCl in DMF at 150 °C for 2 h gave ester **2.197**, which could be in turn a handle for further functionalisation. Conversely, longer reaction times (17 h) gave fully decarboxylated indole **2.198**, rendering the malonate a traceless linker. Although this full decarboxylation was unexpected, similar double Krapcho reactions of benzylic malonates are known. [177-179]

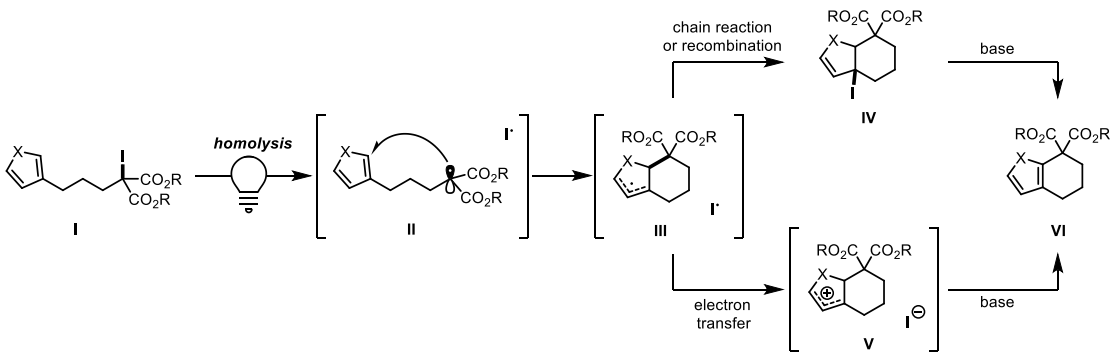
Finally, this light-mediated cyclisation gave access to the non-steroidal anti-inflammatory drug ketorolac (**2.8**) after hydrolysis and decarboxylation of pyrrole **2.125** (Scheme 2.30). This route is complementary to Muchowski's, who reported analogous radical cyclisations using *in situ* generated $Mn(OAc)_3$ on pyrrole **2.44**, and Et_3B/O_2 on bromomalonate **2.45**.[48]



Scheme 2.30 Synthesis of ketorolac (**2.8**) and comparison to previous radical cyclisation routes by Muchowski. [48]

2.3.6 Proposed reaction mechanism

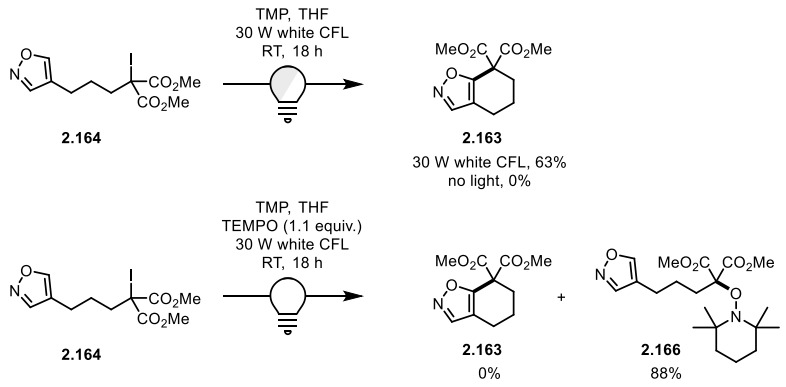
Informed by control experiments and reactivity trends, we postulate a reaction mechanism based on the homolysis of iodomalonates to yield malonyl radicals (Scheme 2.31). Iodomalonate **I** homolyses upon irradiation to give caged radical pair **II**, which after cyclisation yields allylic radical **III**. Radical **III** can then be converted into iodide **IV** through iodine abstraction from iodomalonate **I**, propagating a chain reaction, or recombination with an iodine radical. Cyclised product **VI** is then formed after elimination of HI. Alternatively, a single electron transfer within caged pair **III** could give allylic cation **V**, which upon elimination would yield product **VI**.



Scheme 2.31 Proposed reaction mechanism for the light-mediated radical cyclisation of malonates onto heteroaromatics.

The observations supporting this mechanism are summarised below and include control experiments and UV-Vis spectroscopy.

Control experiments on the cyclisation of iodomalonate **2.164** supported a mechanism involving malonyl radicals that was light-dependent (Scheme 2.32). In the absence of light, isoxazole **2.163** was not detected and iodomalonate **2.164** remained intact, while under irradiation with a 30 W white CFL, isoxazole **2.163** was isolated in 63% yield. In the presence of TEMPO, no cyclisation occurred and adduct **2.166** was obtained instead in 88% yield.



Scheme 2.32 Effect of light and addition of TEMPO on the light-mediated cyclisation of iodomalonate **2.164**.

UV-Vis spectroscopy data were in agreement with a homolysis-based mechanism (Table 2.3). The UV-Vis spectrum of iodomalonate **2.164** (**A**) showed strong absorption bands at 288 nm and 364 nm and a weak but significant absorption tail in the violet-blue region (380–500 nm). Malonate **2.149** (**B**), on the other hand, showed a very weak absorption band at 276 nm and no absorption in the visible light range (*ca.* 380–750 nm). The absorption tail in the visible spectrum of iodomalonate **2.164** (**A**) could therefore be responsible for the reactivity observed.

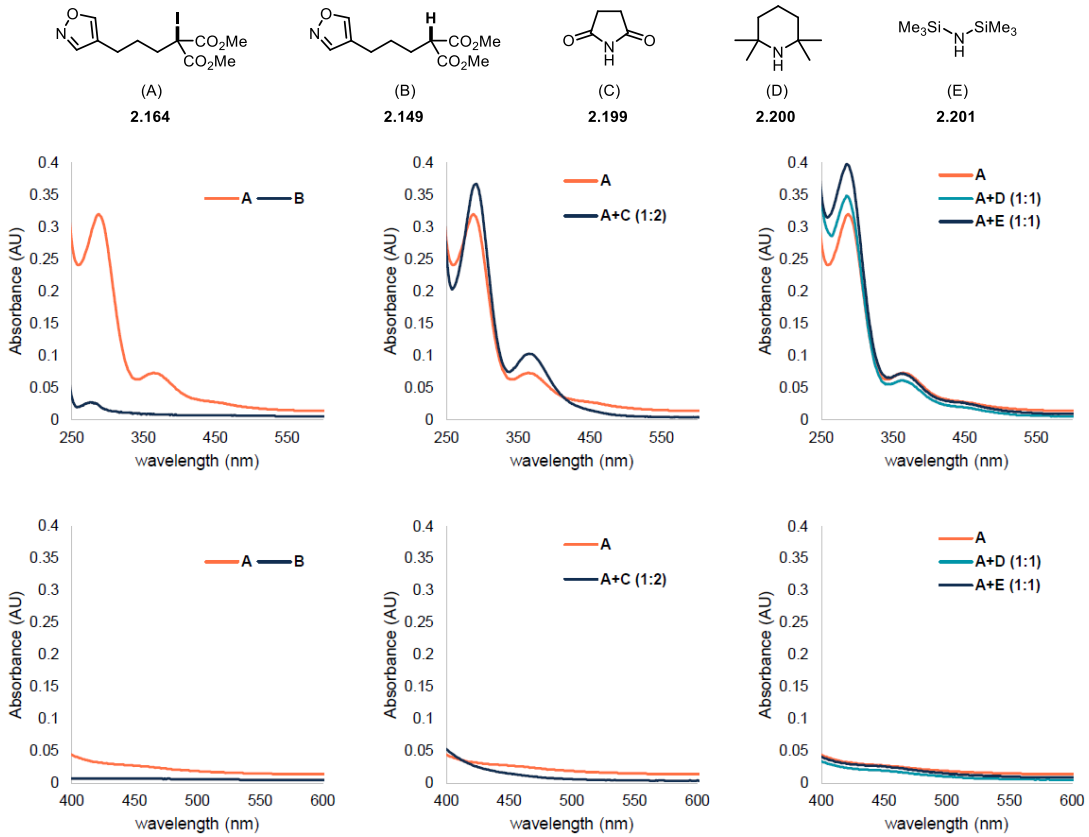


Table 2.3 UV-Vis spectra of iodomalonate **2.164** (**A**), malonate **2.149** (**B**), and mixtures of iodomalonate **2.164** (**A**) with succinimide (**C**), TMP (**D**), and HMDS (**E**).

Alternatively, the homolysis of iodomalonate **2.164** could be dependent on the formation of an electron donor-acceptor (EDA) complex with succinimide, TMP, or HMDS. This would parallel the behaviour of bromomalonates, which Guo et al. proposed homolysed through the formation of an EDA complex with triaryl amines.[180] Similarly, Weaver invoked an EDA complex between a dibromomalonate and *N*,*N*-diisopropylethylamine to explain the light-mediated debromination of *gem*-dibromoalkanes.[181] In this instance, though, the spectrum of iodomalonate **2.164** (**A**) was unchanged after the addition of succinimide (**C**), TMP (**D**), or HMDS (**E**) (Table 2.3). Consequently, no evidence was found to support the formation of an EDA complex.

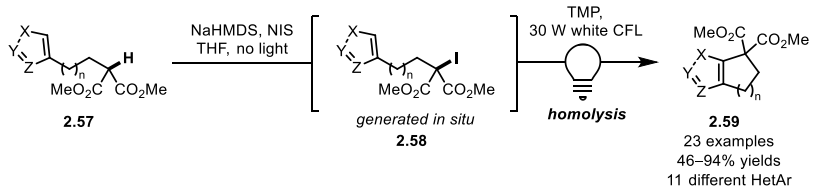
Altogether, this evidence supports a photocatalyst-free light-mediated homolysis mechanism, similar to that reported by Liu in the 1,2-iodoalkylation of alkynes.[182]

2.4 Conclusions

We have developed a new method for the synthesis of annulated heteroaromatics (**2.59**) based on the light-mediated homolysis of *in situ* generated iodomalonates (**2.58**). This method is transition metal-free, requires no photocatalyst for radical generation, and has a wide heteroaromatic scope.

The scope of this transformation included 11 different heteroaromatics, which cyclised to form fused five- and six-membered rings. This included ring systems of particular interest to medicinal and agrochemistry, such as isoxazoles, thiazoles, and nitrogen-rich heteroarenes. Radical additions onto pyridines, 1,2,3-triazoles, and pyrazoles, as well as the construction of seven-membered rings, however, were unsuccessful.

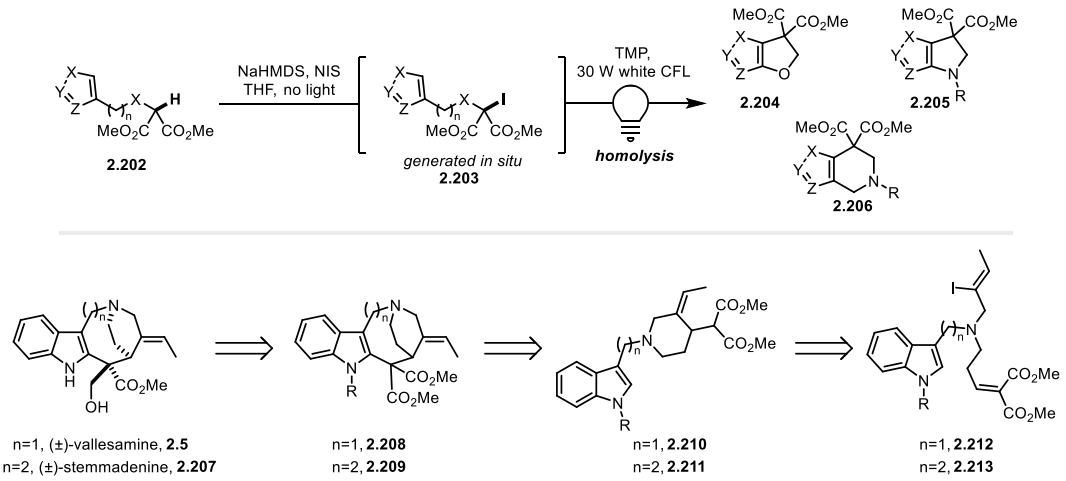
The utility of this transformation was highlighted through its scale-up and the synthesis of a marketed drug (ketorolac, **2.8**). Finally, the study of reactivity trends, control experiments, and UV-Vis spectroscopy gave insight into the reaction mechanism.



Scheme 2.33 Summary of the reaction developed and its scope.

2.5 Future work

We envisage this transformation could give access to more complex ring systems (Scheme 2.34). For instance, the addition of heteroatoms to the tether could provide fused systems containing tetrahydrofurans (**2.204**), pyrrolidines (**2.205**), or piperidines (**2.206**), of potential interest to medicinal and agrochemistry. Alternatively, this light-mediated reaction could be used in the synthesis of heteroaromatic-containing natural products, such as indole alkaloids. Vallesamine (**2.5**) and stemmadenine (**2.207**) would be interesting targets, potentially accessible in racemic form through the common route summarised below (Scheme 2.34). These natural products (**2.5** and **2.207**) could result from the diastereoselective reduction of malonates **2.208** and **2.209**, which would be prepared *via* the radical cyclisation of malonates **2.210** and **2.211**, developed here. In turn, indoles **2.210** and **2.211** could be obtained from vinyl iodides **2.212** and **2.213** through conjugate addition.



Scheme 2.34 Application of the light-mediated malonyl radical cyclisation to the synthesis of fused tetrahydrofurans (**2.204**), pyrrolidines (**2.205**), or piperidines (**2.206**). Potential route towards (±)-vallesamine (**2.5**) and (±)-stemmadenine (**2.207**) *via* a malonyl radical cyclisation.

Chapter 3 Studies towards the asymmetric formal synthesis of ginkgolide B

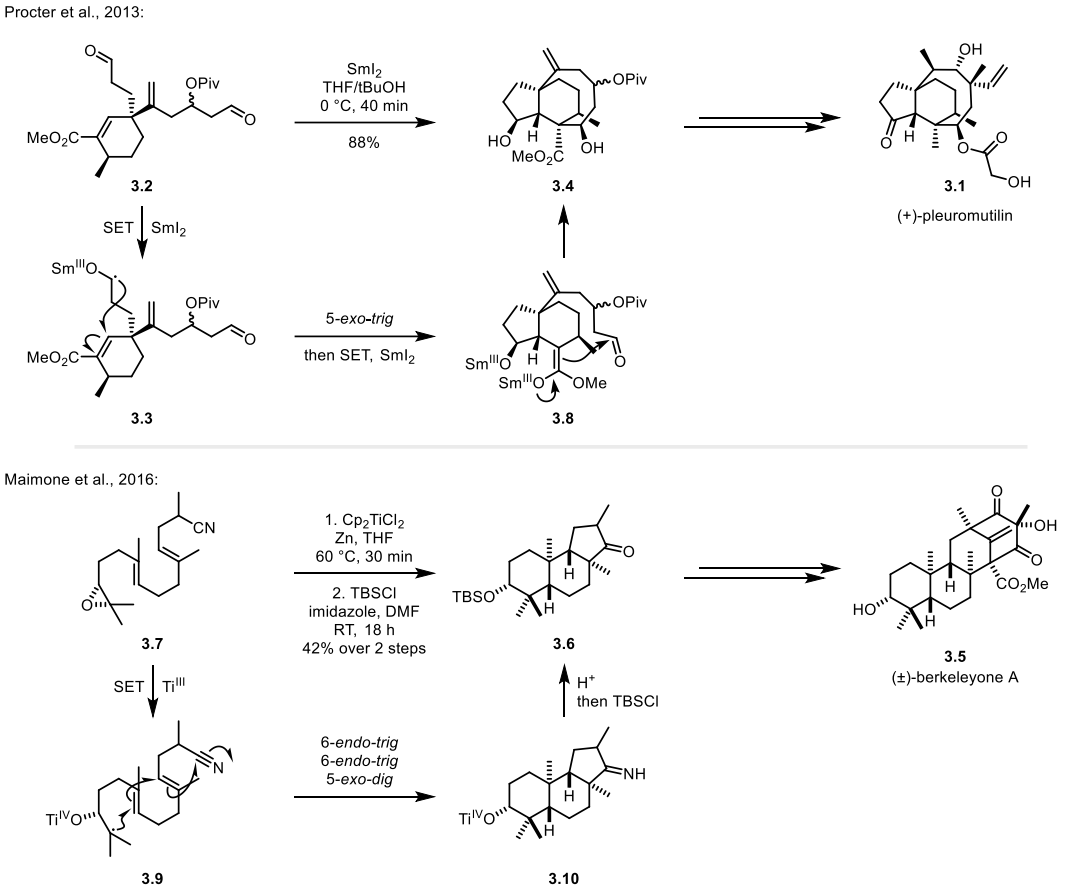
3.1 Introduction

3.1.1 Radical cascades in total synthesis

Radical cascade reactions, both oxidative and reductive, are powerful tools for the rapid generation of complexity. The strength of these methods arises from the high reactivity of radicals, their tolerance of steric hindrance, and the predictable regio- and stereocontrol exhibited by many radical reactions. [183] Consequently, these cascades have been employed in the synthesis of natural products and complex frameworks. This topic has been reviewed by Walton, [184] Nicolaou, [185] Anderson, [186-188] and others. [189-194]

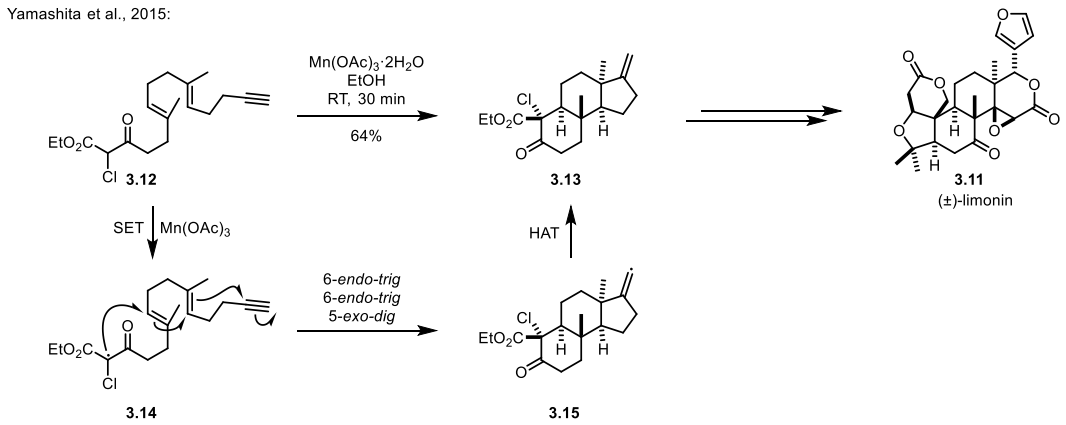
Reductive radical cascades are commonly triggered by a single-electron transfer from low-valent samarium, titanium or copper species. [183] For instance, Procter and co-workers used a SmI_2-mediated cyclisation cascade in their total synthesis of (+)-pleuromutilin (**3.1**, Scheme 3.1). [195] Aldehyde **3.2** was reduced with SmI_2 to give ketyl radical **3.3**, which underwent a 5-*exo-trig* cyclisation. A second SET and aldol addition then gave the tricyclic core of (+)-pleuromutilin (**3.4**). Conversely, low-valent titanium salts are particularly effective for the reductive ring-opening of epoxides. [196, 197] This chemistry was exemplified by Maimone et al. in their total synthesis of (±)-berkeleyone A (**3.5**), which employed

Cp_2TiCl_2 and zinc to trigger a cascade involving three consecutive radical cyclisations to yield tricyclic ketone **3.6** from epoxide **3.7**. [198]



Scheme 3.1 Summary of Procter's SmI_2-mediated cyclisation cascade in their total synthesis of (+)-pleuromutilin (**3.1**) and Maimone's titanium-mediated radical cascade towards (±)-berkeleyone A (**3.5**). [195, 198]

Radical cascades triggered by single-electron oxidations with Mn(III), Ce(IV), and Fe(III) salts have also been used in the synthesis of complex natural products. [10] This was exemplified by Yamashita and co-workers in their total synthesis of (±)-limonin (**3.11**), which employed $Mn(OAc)_3$ to generate radical **3.14** from chloride **3.12**, which underwent three successive cyclisations to give tricycle **3.13** (Scheme 3.2). [199]

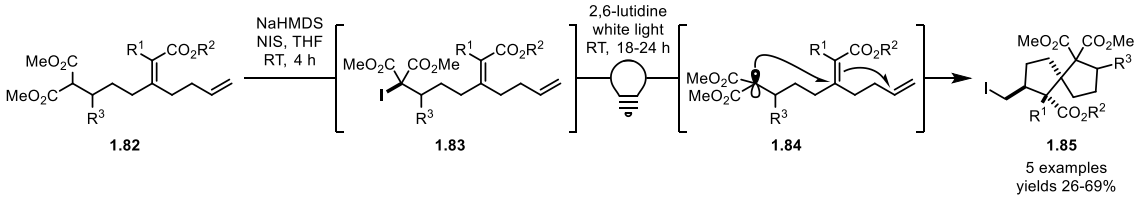


Scheme 3.2 Summary of Yamashita and co-worker's oxidative radical cascade in their total synthesis of (±)-limonin (**3.11**). [199]

3.1.2 Previous synthetic studies in the group

Previous work in the Burton group used $Mn(OAc)_3$-mediated malonyl radical cyclisations in the synthesis of natural products, such as 7,11-cyclobotryococca-5,12,26-triene, [79] aphanamol I, [80] and salinosporamide A. [28] Since then, efforts have focused on the development of radical cascades that could be used towards the synthesis of other complex targets.

As discussed in section 1.4, Garrec developed a transition-metal free method for the synthesis of densely functionalised spirocycles (**1.85**) (Scheme 3.3). [81] Malonates **1.82** were treated with a base and NIS to yield iodomalonates **1.83**, which were then photolysed *in situ*. The malonyl radicals generated (**1.84**) underwent two successive 5-*exo-trig* cyclisations and C–I bond formation (likely through iodine atom transfer from iodomalonate **1.83**) to give spirocycles **1.85**. This transformation was compatible with a range of ester groups (R^2) and blocking groups (R^1). Nonetheless, a blocking group (R^1) was required to avoid competing 6-*endo-trig* cyclisation, and substitution along the chain (R^3) was not well tolerated.



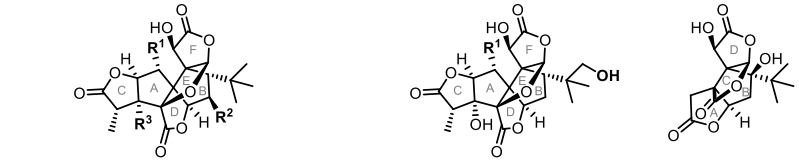
Scheme 3.3 Summary of Garrec's radical cascade for the synthesis of complex spirocycles. [81]

We envisaged that Garrec's method, despite its limitations, could be adapted towards the synthesis of the natural product ginkgolide B (**3.16**).

3.1.3 The ginkgolides

The *Ginkgo biloba* tree is the last surviving member of the *Ginkgoaceae* family. Known as a 'living fossil', this species appeared in the Jurassic period, around 170 million years ago, and has remained largely unchanged for the last 100 million years. [200] Endemic to China and Korea, its leaves, fruit, and bark have been used in traditional medicine for millennia.

The extracts from *G. biloba* contain several complex terpene trilactones (TTLs) exclusive to this species: the ginkgolides and bilobalide (Scheme 3.4). [201] The structures of ginkgolides A (**3.17**), B (**3.16**), C (**3.18**) and M (**3.19**) were elucidated by Nakanishi et al. in 1967, [202-207] and confirmed the same year by X-ray crystallographic analysis by Okabe. [208, 209] The structure of bilobalide (**3.20**), a related terpene also containing three lactones and a *tert*-butyl group, was elucidated in 1971. [210] Later additions to this family of terpenes were ginkgolides J (**3.21**), P (**3.22**) and Q (**3.23**), which are only found in the leaves of *G. biloba*, and were isolated in 1987[211] and 2011. [212] These terpenes all contain a *tert*-butyl group, which is seldom present in natural products.



gingkolide A, **3.17** (R^1 = H, R^2 = H, R^3 = OH)
gingkolide B, **3.16** (R^1 = OH, R^2 = H, R^3 = OH)
gingkolide C, **3.18** (R^1 = OH, R^2 = OH, R^3 = OH)
gingkolide J, **3.21** (R^1 = H, R^2 = OH, R^3 = OH)
gingkolide M, **3.19** (R^1 = OH, R^2 = OH, R^3 = H)

gingkolide P, **3.22** (R^1 = H)
gingkolide Q, **3.23** (R^1 = OH)

bilobalide, **3.20**

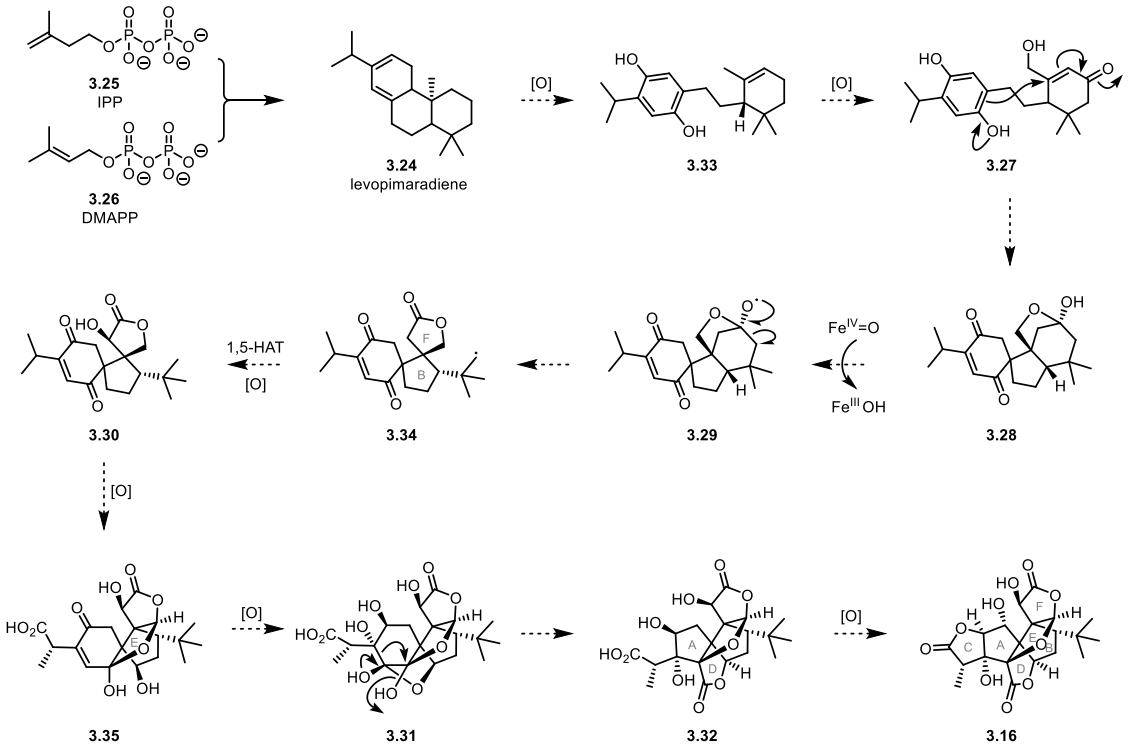
Scheme 3.4 The structure of the ginkgolides and bilobalide.

3.1.4 Biosynthesis of the ginkgolides

The ginkgolides are unique to *G. biloba* and despite numerous studies into their biogenesis the understanding of their biosynthesis remains limited.

In 1999, Arigoni and Schwarz proposed a biosynthetic route to the ginkgolides that was supported by extensive labelling studies in *G. biloba* embryos.[213] This pathway is summarised in Scheme 3.5 for ginkgolide B (**3.16**). Levopimaradiene (**3.24**), a known diterpene obtained from the condensation of two units of isopentenyl diphosphate (IPP, **3.25**) and two units of dimethylallyl pyrophosphate (DMAPP, **3.26**), was proposed as the starting material. A series of oxidations would yield enone **3.27**, which could undergo Michael addition and hemiacetal formation to give strained tetracycle **3.28**. The authors then proposed rings B and F, as well as the *tert*-butyl group characteristic of the ginkgolides, would be obtained after ring opening of oxyl radical **3.29**. Subsequently, a 1,5-hydrogen atom transfer and oxidation would give spirocycle **3.30**, which would in turn be converted into hemiacetal **3.31** after extensive oxidation. The pinacol rearrangement of pentacycle **3.31** would then furnish rings A and D. Finally, ring C would be built through the lactonisation of *γ*-hydroxyacid **3.32** to give, after a final oxidation, ginkgolide B (**3.16**). This biosynthetic proposal agreed with the labelling patterns observed in ginkgolides after ^{13}C-labeled glucose incorporation. Nonetheless, the enzymes responsible

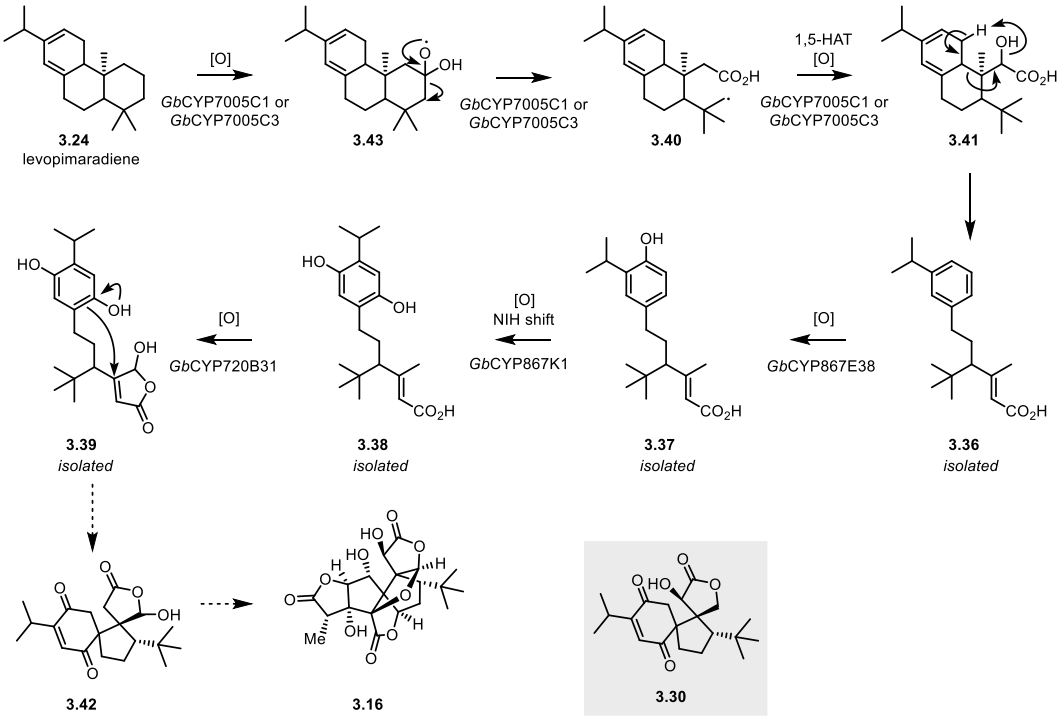
for the conversion of levopimaradiene (**3.24**) into the ginkgolides could not be identified and the intermediates were never isolated. The lack of isolable intermediates pointed towards a highly channelled biosynthetic pathway, which challenged further understanding of this biosynthetic sequence. [214, 215]



Scheme 3.5 Summary of Arigoni and Schwarz's proposal for the biosynthesis of ginkgolide B (**3.16**). [213]

In 2022, Pateraki and co-workers uncovered a gene cluster responsible for the main steps of ginkgolide biosynthesis, aided by gene cluster-guided mining and co-expression analysis. [214] The authors confirmed that levopimaradiene (**3.24**) was the substrate of this biosynthesis and they isolated several *tert*-butyl containing intermediates (**3.36**, **3.37**, **3.38** and **3.39**). Their biosynthetic proposal is summarised in Scheme 3.6. The authors proposed the *tert*-butyl group arose *via* a similar α-cleavage to that described by Arigoni and Schwartz. [213] The resulting primary radical (**3.40**) would then undergo a 1,5-hydrogen atom transfer and oxidation to yield the unstable α-hydroxyester **3.41**. A second ring-

opening reaction with concomitant loss of water would give α,*β*-unsaturated carboxylic acid **3.36**.[214] This acid (**3.36**) was isolated upon treatment of levopimaradiene (**3.24**) with *Gb*CYP7005C1 and *Gb*CYP7005C3, supporting the above hypothesis. Three other enzymes were identified as being capable of converting acid **3.36** into *γ*-hydroxybutenolide **3.39** *via* sequential oxidation and 1,2-alkyl shift.[216] No further enzymes or intermediates could be identified to link *γ*-hydroxybutenolide **3.39** to the ginkgolides.



Scheme 3.6 Summary of Pateraki's proposal for the biosynthesis of ginkgolide B (**3.16**).[214]

Despite the differences between Arigoni and Pateraki's proposals, both routes converge into similar intermediates. A hypothetical intramolecular Michael addition of *γ*-hydroxybutenolide **3.39** would yield tricycle **3.42**, which closely resembles Arigoni's intermediate **3.30**. Nevertheless, further studies are required to understand the biosynthetic sequence connecting tricycle **3.42** and the ginkgolides.

3.1.5 Medicinal relevance of ginkgolide B

For thousands of years, *Ginkgo biloba* extracts have been used in traditional medicine.[201] Today, the standardised extract EGb761 remains one of the most popular food supplements.[201] This preparation is prescribed for the treatment of dementia-related symptoms, but its efficacy and the neurobiological mechanism underlying these effects remain contentious.[201, 217]

The pharmacological effect of EGb761 on the central nervous system (CNS) has been extensively investigated and summarised in several reviews.[217-220] Clinical studies have focused on its application as a treatment for Alzheimer's disease (AD). The administration of EGb761 slowed the progression of dementia symptoms in mild AD patients and improved cognitive performance in healthy individuals. Nonetheless, the magnitude of this neuroprotective effect varied across studies.[201]

The neurobiological mechanism behind this effect is not well understood. Terpene trilactones (TTLs) are the main components of EGb761 that can penetrate the blood brain barrier (BBB) and are widely accepted to be the neurologically active species in these extracts.[201] Among the TTLs, ginkgolide B is the most potent and selective platelet-activating factor (PAF) receptor antagonist. The effect ginkgolide B has on PAF receptors may be responsible for the CNS effects of EGb761 extracts, yet further studies are needed to understand its mode of action.

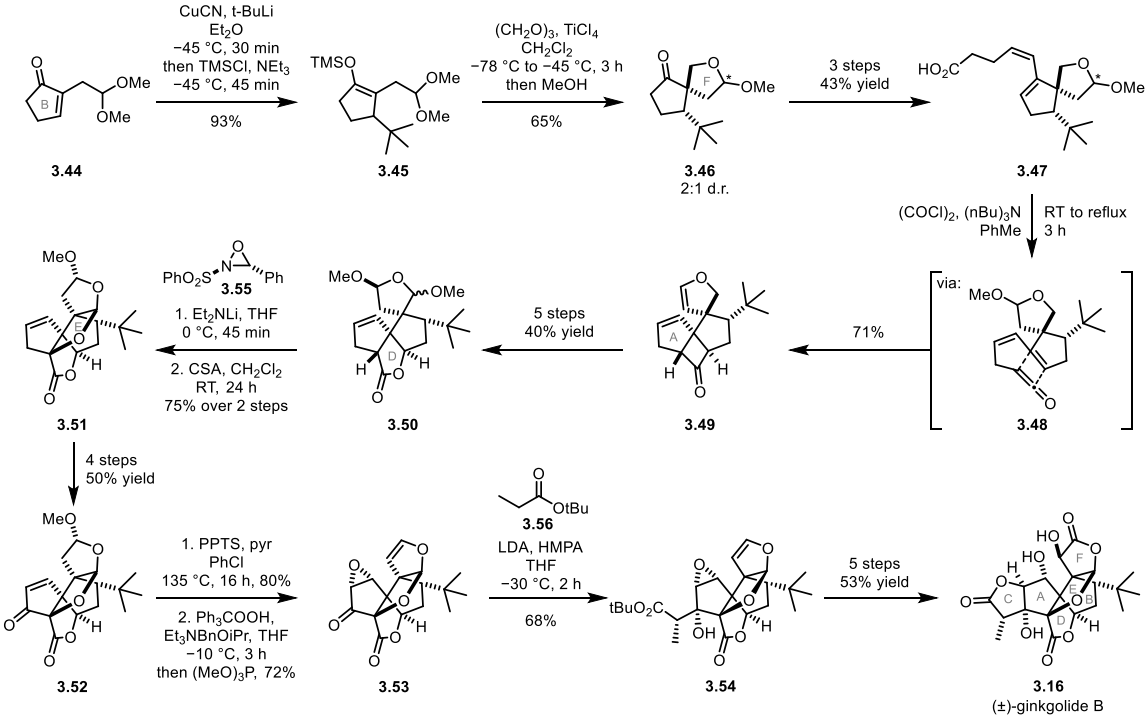
3.1.6 Previous syntheses of ginkgolide B

The complex structure of ginkgolide B and its potential therapeutic effects make it an attractive target for total synthesis. The first total synthesis of ginkgolide B was achieved

by Corey in 1988[221] and was followed by Crimmins in 2000.[222, 223] More recently, Barriault described a formal synthesis that intercepted an intermediate in Corey's route.[224]

3.1.6.1 Corey's total synthesis of (±)-ginkgolide B

Corey and co-workers were the first to report the total synthesis of (±)-ginkgolide B.[221] Their synthetic route featured a [2+2] ketene cycloaddition as the key complexity-building step and is summarised in Scheme 3.7.

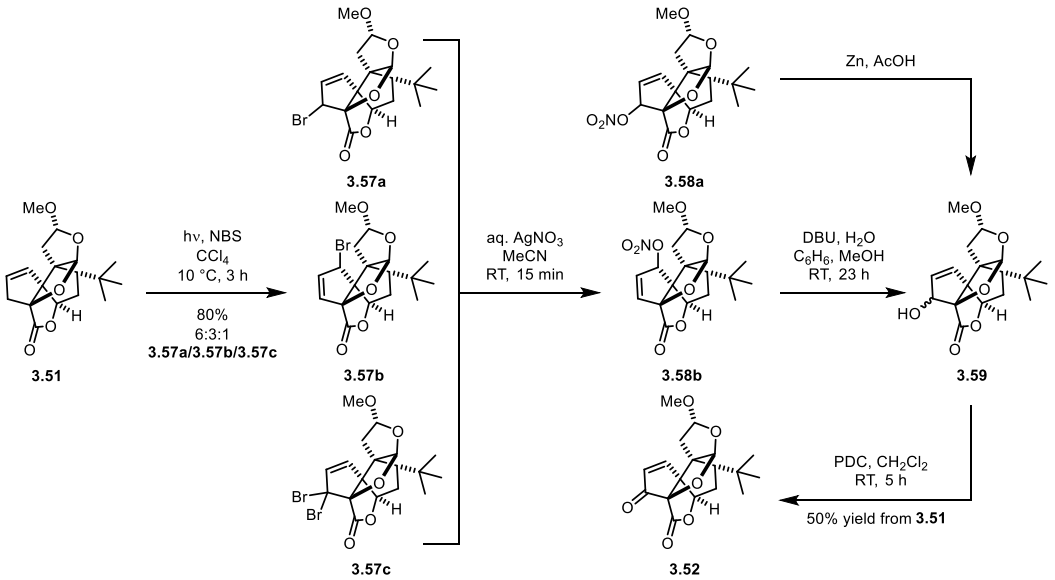


Scheme 3.7 Summary of Corey's total synthesis of (±)-ginkgolide B (**3.16**).[221]

Corey's sequence began with the conjugate addition of [$tBu_2Cu(CN)Li_2$] to cyclopentenone **3.44** and *in situ* formation of silyl enol ether **3.45**. Exposure of enol ether **3.45** to 1,3,5-trioxane under Lewis acid catalysis gave ring F (**3.46**). Then, a three-step sequence involving vinyl triflate formation, Sonogashira coupling, and alkyne reduction gave (*Z*)-alkene **3.47** in 43% overall yield. Carboxylic acid **3.47** was then converted into the corresponding ketene **3.48**, which underwent a [2+2] cycloaddition to give strained

tetracycle **3.49**. Subsequently, the cyclobutanone in tetracycle **3.49** was ring-expanded *via* a Baeyer-Villiger oxidation and the enol ether converted into the bisacetal to give tetracycle **3.50**. The Davis oxidation of tetracycle **3.50** yielded an α-hydroxylactone, which equilibrated to bisacetal **3.51** upon treatment with CSA.

The allylic oxidation to give cyclopentenone **3.52** was the most challenging step in Corey's synthesis, since all attempts to directly obtain cyclopentenone **3.52** from cyclopentene **3.51** failed.[225] Ultimately, the authors resorted to a 'mosaic sequence'[225] involving an unselective allylic bromination, which provided allylic bromides **3.57a**, **3.57b** and **3.57c** in 80% overall yield and 6:3:1 ratio (Scheme 3.8). These bromides were subsequently treated with $AgNO_3$ to give nitrate esters **3.58a** and **3.58b** as well as the desired cyclopentenone **3.52**. Nitrate esters **3.58a** and **3.58b** were converted into alcohol **3.59** through *N–O* bond cleavage and S_N2' displacement, respectively. Alcohol **3.59** was then oxidised with PDC to give the required cyclopentenone **3.52** in 50% overall yield from cyclopentene **3.51**.



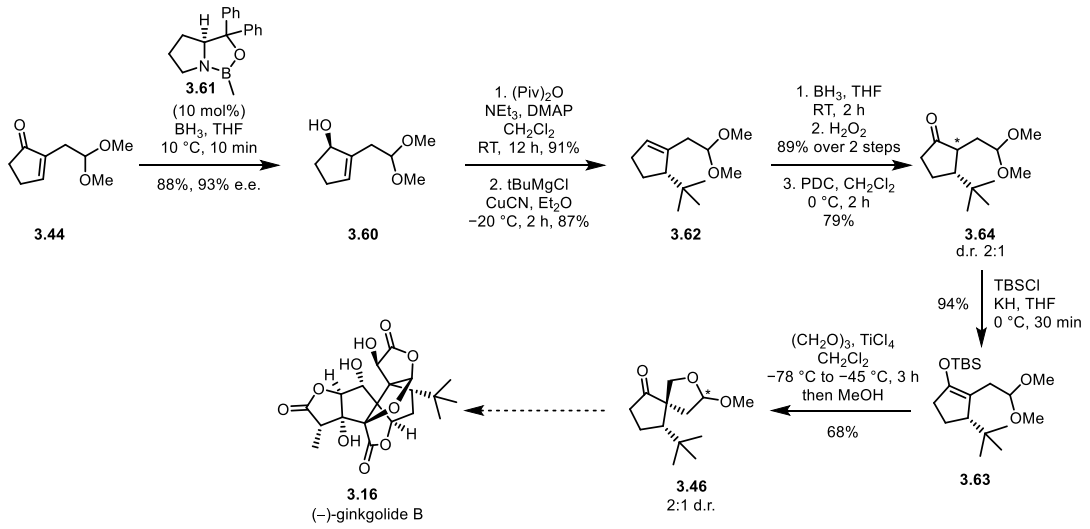
Scheme 3.8 Mosaic sequence for the allylic oxidation of cyclopentene **3.51**.[221, 225]

The last task to complete the synthesis of (±)-ginkgolide B was the construction of ring C. This was achieved by the epoxidation of cyclopentenone **3.52** and ring opening with the enolate derived from ester **3.56** to give *tert*-butyl ester **3.54** (Scheme 3.7). A five-step sequence consisting of *tert*-butyl ester hydrolysis, epoxide ring opening, and enol ether oxidation subsequently yielded (±)-ginkgolide B (**3.16**). Overall, this route gave the natural product in 0.22% yield over 26 steps (LLS) and is considered one of the major achievements in synthetic organic synthesis of the 20th century.

3.1.6.2 Corey's asymmetric formal synthesis of (−)-ginkgolide B

The same year, Corey and co-workers described the asymmetric synthesis of an intermediate in their total synthesis of (±)-ginkgolide B.[226] This was the first, and to this day only, asymmetric route to (−)-ginkgolide B.

The authors envisaged employing a Corey-Bakshi-Shibata reduction to set the absolute configuration of one of the stereocentres of ginkgolide B followed by a series of substrate-controlled chemical reactions to set the remaining 10 stereocentres of the natural product (Scheme 3.9). Cyclopentenone **3.44** was thus reduced to allylic alcohol **3.60** in 88% yield and 93% e.e. in the presence of oxazaborolidine **3.61**. The absolute configuration of alcohol **3.60** was assigned based on analogy to previous systems.[226] Subsequent pivalation and S_N2' substitution with *tert*-BuMgCl in the presence of substoichiometric amounts of CuCN yielded cyclopentene **3.62**. Deuterium labelling experiments were performed to confirm that this substitution predominantly occurred through an S_N2' mechanism.[226] Cyclopentene **3.62** was then converted into spirocycle **3.46**, which is part of Corey's route to (±)-ginkgolide B.[221] Alkene hydroboration, oxidation, and silylation of cyclopentene **3.62** gave silyl enol ether **3.63**, which was converted into spirocycle **3.46** through the sequence used in the author's route to (±)-ginkgolide B.[221]



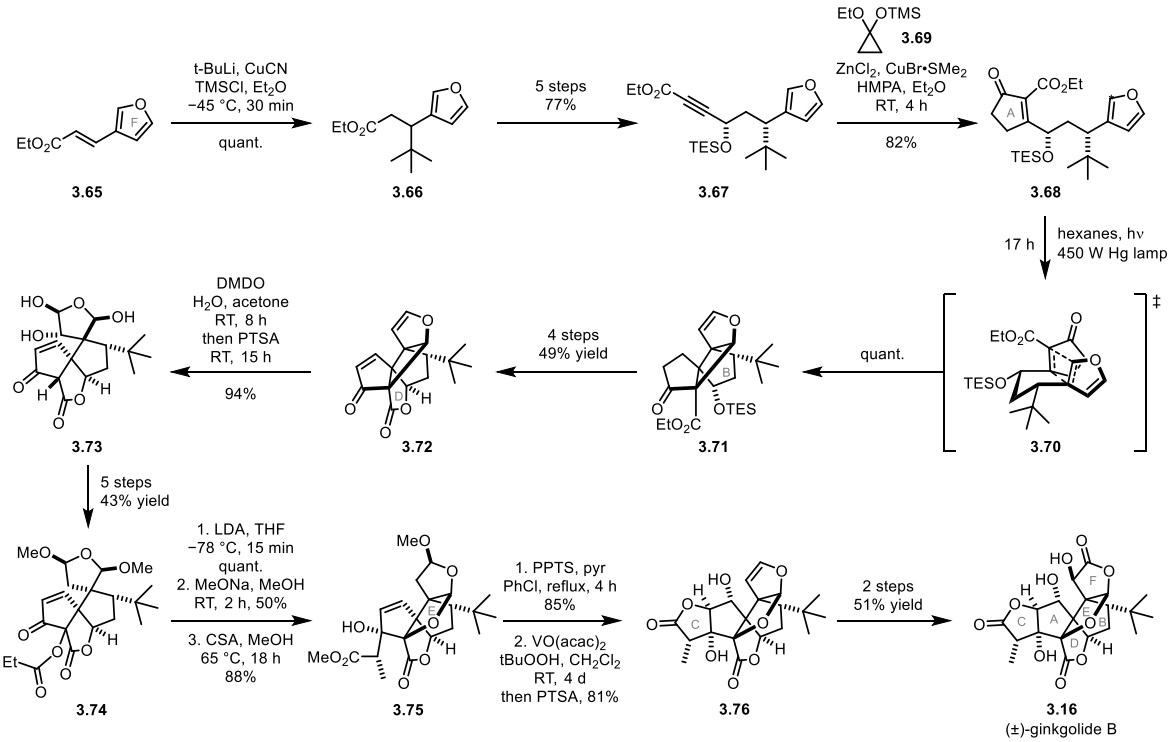
Scheme 3.9 Corey's asymmetric synthesis of spirocycle **3.46**.[226]

This enantioselective route to spirocycle **3.46** was a proof-of-concept that the total synthesis of (−)-ginkgolide B could be rendered asymmetric.

3.1.6.3 Crimmins' total synthesis of (±)-ginkgolide B

In 2000, Crimmins reported the second total synthesis of (±)-ginkgolide B.[222, 223] The key complexity-building reaction of this synthesis was also a [2+2] cycloaddition, in this case between a furan and a cyclopentenone (Scheme 3.10).

The substrate for the [2+2] cycloaddition was obtained from α,*β*-unsaturated ester **3.65**. The *tert*-butyl group was incorporated in a similar manner to Corey through a conjugate addition using *tert*-BuLi and CuCN to give furan **3.66**.[221] A series of functional group manipulations and the addition of an alkynyl Grignard reagent gave alkynyl ester **3.67**. Subsequently, ester **3.67** was converted into cyclopentenone **3.68** through the Michael addition of a copper homoenolate, obtained from the Zn-mediated ring-opening of cyclopropane **3.69** and transmetalation with $CuBr{\cdot}SMe_2$.



Scheme 3.10 Summary of Crimmins' total synthesis of (±)-ginkgolide B (**3.16**). [222, 223]

The [2+2] cycloaddition of cyclopentenone **3.68** gave strained cyclobutane **3.71** in excellent yield and diastereoselectivity. Subsequently, desilylation, alcohol mesylation, nucleophilic substitution, and cyclopentanone dehydrogenation yielded cyclopentenone **3.72** in 49% over four steps. The cyclobutane ring in pentacycle **3.72** was then cleaved *via* the oxidation of enol ether **3.72** with DMDO and acid-mediated retro-aldol reaction.

A five step sequence was employed to convert triol **3.73** into propanoate **3.74**. This entailed conversion of triol **3.73** into a bis-methyl acetal, Barton-McCombie deoxygenation, Davis oxidation, and alcohol acylation.

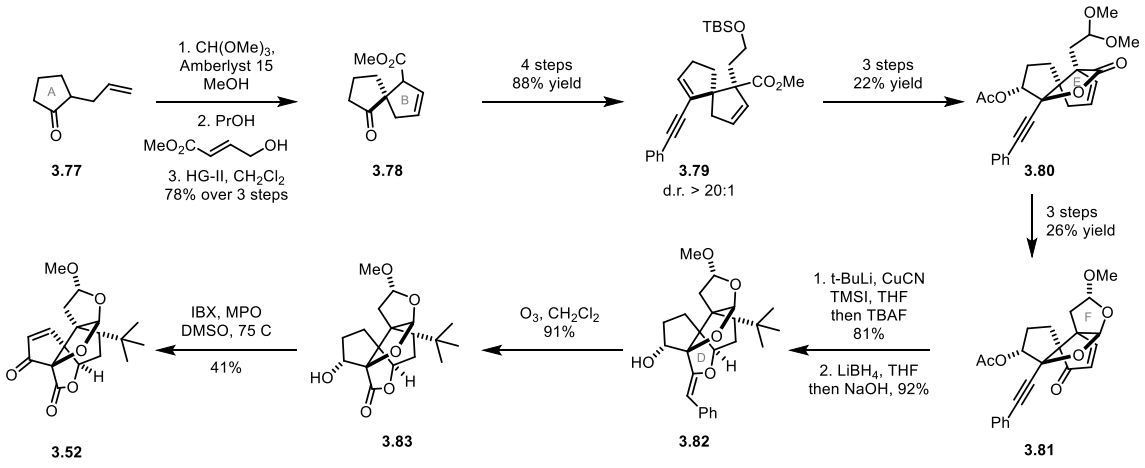
The construction of ring E posed a challenge in Crimmins' work due to unwanted side reactivity. [222, 223] Ultimately, this ring was built *via* a three-step sequence from propanoate **3.74** involving intramolecular aldol addition, lactone hydrolysis and acetal equilibration. The synthesis of (±)-ginkgolide B (**3.16**) was subsequently completed through the

construction of ring C in a sequence analogous to that of Corey.[221] Crimmins' route was 24 steps long (LLS) and had an overall yield of 1.9%.

3.1.6.4 Barriault's formal synthesis of (±)-ginkgolide B

In 2022, Barriault reported the latest synthesis of (±)-ginkgolide B, this time a formal synthesis targeting an intermediate in Corey's route (**3.52**).[221, 224] This work also described the first total synthesis of (±)-ginkgolide C (**3.18**).[224]

Barriault's route used cyclopentanone **3.77** as starting material, which was converted into spirocycle **3.78** after a Claisen rearrangement and ring-closing metathesis (Scheme 3.11). A four-step sequence involving alkylation of the methyl ester, enol triflate formation and Sonogashira coupling then yielded enyne **3.79**. Ring E was built *via* epoxidation of the alkene in enyne **3.79** and intramolecular ring-opening to give tricycle **3.80**. Next, ring F was constructed through the reduction of lactone E in tricycle **3.80** and acetal equilibration. Riley oxidation subsequently allowed the synthesis of cyclopentenone **3.81**.



Scheme 3.11 Summary of Barriault's formal synthesis of (±)-ginkgolide B (**3.16**).[224]

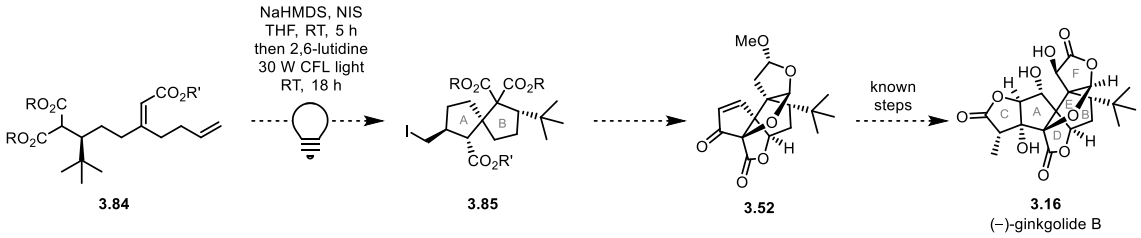
The *tert*-butyl group was then incorporated using a similar approach to Corey and Crimmins,[221-223] *via* the conjugate addition of a *tert*-butyl organocuprate onto enone **3.81**. This was followed by the reduction of the resulting cyclopentanone, which spontaneously underwent a 5-*exo-dig* cyclisation to give ring D (**3.82**). Cyclopentenone **3.52**, the target intermediate in Corey's rote,[227] was then obtained after ozonolysis of enol ether **3.82** and oxidation of alcohol **3.83**. This completed the formal synthesis of (±)-ginkgolide B in 19 steps and 1.6% overall yield. Intermediate **3.52** could be converted into the natural product in 10 further steps.[227]

3.2 Project aims

The aim of this project was to complete the asymmetric formal synthesis of (−)-ginkgolide B. We envisaged using Garrec's malonyl radical cascade as the key complexity-building step in this synthesis (Scheme 3.12).[81] Pentacycle **3.52**, the product of the mosaic allylic oxidation sequence in Corey's route,[221, 225] was chosen as the target for this synthesis. This target was also chosen, independently, by Barriault and co-workers (see section 3.1.6.4).[224]

Garrec's malonyl radical methodology would be adapted to incorporate the key *tert*-butyl group present in the ginkgolides. The cyclisation would then be optimised to maximise yield and diastereoselectivity, and the cascade product elaborated into pentacycle **3.52**.

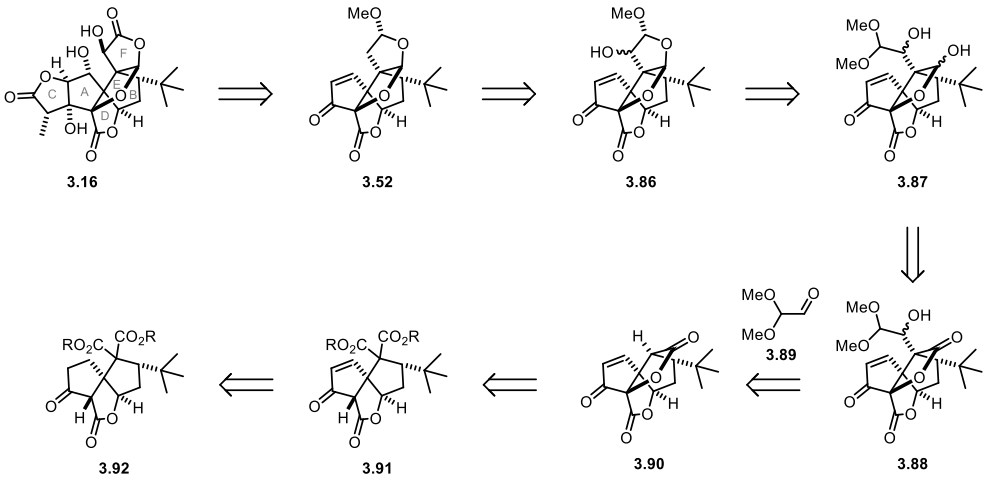
A further aim was to render this sequence enantioselective. We envisaged that the stereocentre in malonate **3.84** could be used to set the absolute configuration of the other six stereogenic carbons in the target of this formal synthesis (**3.52**).



Scheme 3.12 Project proposal: a malonyl radical cascade for the asymmetric formal synthesis of (−)-ginkgolide B.

3.3 Retrosynthetic analysis

The retrosynthetic analysis for the formal synthesis of (±)-ginkgolide B is summarised in Scheme 3.13. The target of this formal synthesis is pentacycle **3.52**, an intermediate in Corey's total synthesis containing rings A, B, D, E, and F of the natural product.[221]



Scheme 3.13 Retrosynthetic analysis for the formal synthesis of (±)-ginkgolide B.

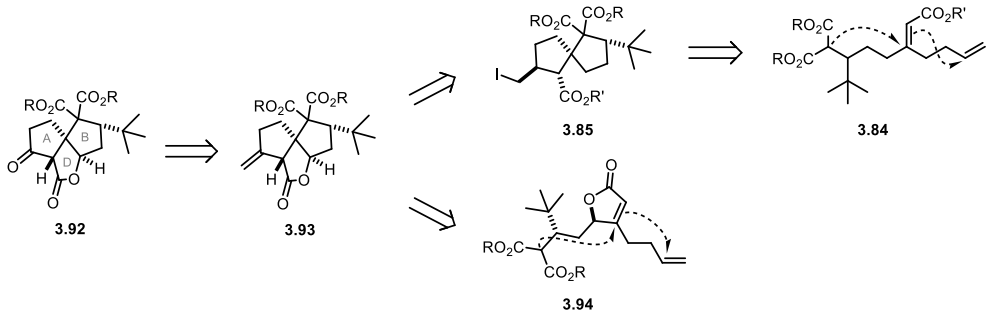
We envisaged that ring F could be built last, in a sequence involving the incorporation of glyoxal dimethyl acetal (**3.89**) followed by several functional group manipulations (Scheme 3.13). Ultimately, Corey's intermediate **3.52** would be obtained from the deoxygenation of alcohol **3.86**. In turn, pentacycle **3.86** would be built through the equilibration of hemiacetal **3.87**; this was inspired by Barriault's construction of ring F in their formal synthesis of (±)-ginkgolide B (see section 3.1.6.4).[224] Hemiacetal **3.87** would arise from the reduction of lactone **3.88**. We envisioned that the *β*-alcohol in tetracycle **3.88** could direct this reduction in the presence of the two other carbonyl groups; for example, *via* an Evans-Saksena reduction with $NMe_4BH(OAc)_3$[228, 229] or an Evans-Tischenko reaction.[230, 231] The stereochemical outcome of this reduction would be inconsequential due to the epimerisation of hemiacetal **3.87** in the following step.[224] In

turn, alcohol **3.88** could be obtained from the aldol addition of lactone **3.90** and glyoxal dimethyl acetal **3.89**.

In a similar approach to Corey's[221] and Crimmins',[222, 223] ring E would be constructed through the hydroxylation of *β*-ketoester **3.91**. The substrate for this hydroxylation would arise from tricycle **3.92** *via* the dehydrogenation of a cyclopentanone ring.

Tricycle **3.92** could be obtained from *exo*-alkene **3.93** by an oxidative cleavage (Scheme 3.14). In turn, tricycle **3.93** could arise from HI elimination and the directed C–H oxidation of spirocycle **3.85**, for example, employing chemistry by White[232, 233] or Costas.[234] Previous work in the Burton group described the synthesis of similarly substituted spirocycles *via* a malonyl radical cascade (see section 1.4);[81] hence an adaptation of this work would be employed to obtain spirocycle **3.85** from acyclic malonate **3.84**. Section 3.4.1 gives an account of these endeavours.

Finally, an analogous malonyl radical cyclisation could give tricycle **3.93** in a single step from *γ*-butenolide **3.94**, circumventing the need for a challenging C–H oxidation methodology. Nonetheless, this route would require the diastereoselective synthesis of *γ*-butenolide **3.94**. This work is described in section 3.4.2.

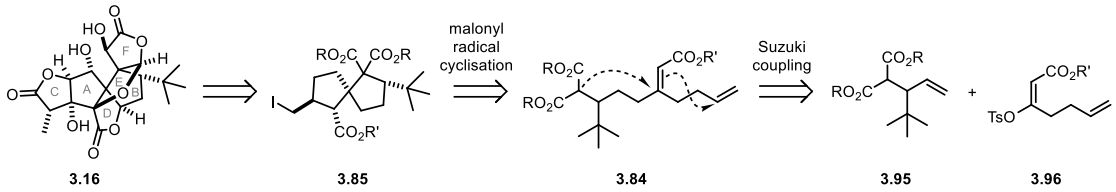


Scheme 3.14 Retrosynthetic analysis for the synthesis of tricycle **3.92**.

3.4 Results and discussion

3.4.1 Route I

We envisaged that the core rings A and B of (±)-ginkgolide B could be accessed through the adaptation of Garrec's malonyl radical cyclisation (Scheme 3.15).[81] *tert*-Butyl containing malonate **3.84** would cyclise to give spirocycle **3.85**. In turn, a Suzuki cross-coupling between the borane derived from alkene **3.95** and vinyl tosylate **3.96** would give access to the cyclisation substrate **3.84**.



Scheme 3.15 Summary of the retrosynthetic approach towards (±)-ginkgolide B, route I.

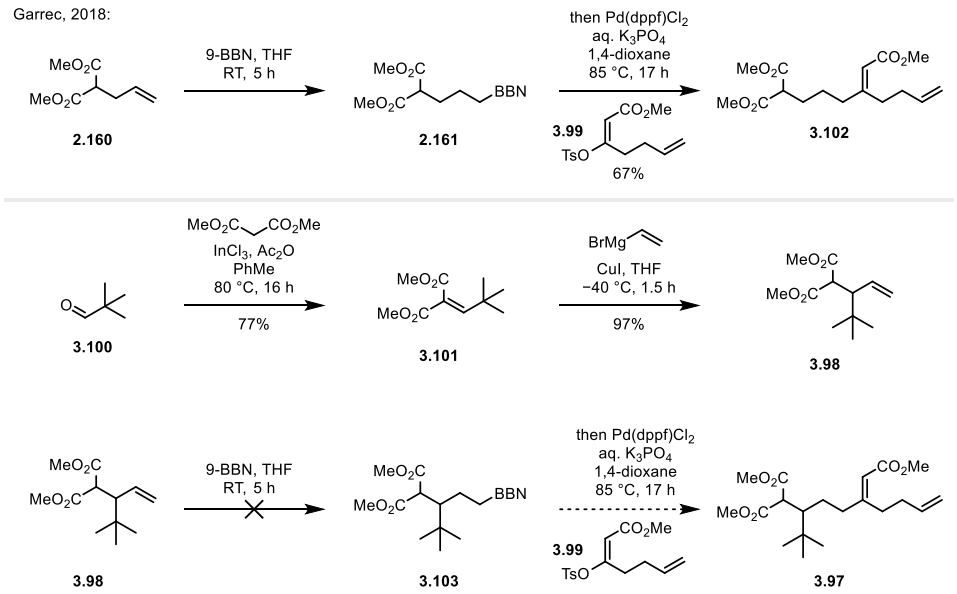
3.4.1.1 Adaptation of Garrec's Suzuki route

Initial efforts focused on the development of a synthetic route to *tert*-butyl containing malonate **3.97**. This entailed preparing alkene **3.98** and investigating its coupling to vinyl tosylate **3.99** (Scheme 3.16).

Alkene **3.98** was synthesised from pivaldehyde (**3.100**) in two steps. First, Knoevenagel condensation of pivaldehyde (**3.100**) and dimethyl malonate yielded alkylidene malonate **3.101**. Conventional Knoevenagel conditions (piperidine, C_6H_6, Dean-Stark)[235] gave poor yields of malonate **3.101**, likely due to the steric hindrance around the aldehyde. Nonetheless, under indium-catalysed conditions developed by Sakai,[236] alkylidene malonate **3.101** was obtained in 77% isolated yield. This reaction could be performed on a multi-gram scale, ultimately delivering over 7 g of malonate **3.101**. Then, treatment of

alkylidene malonate **3.101** with vinylmagnesium bromide and CuI (20 mol%) provided the required alkene **3.98** in excellent yield (97%).

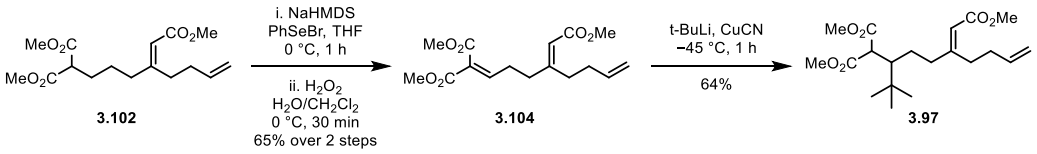
The hydroboration of alkene **3.98** and subsequent Suzuki-coupling with vinyl tosylate **3.99** were then attempted, albeit without success. Treatment of alkene **3.98** with 9-BBN only returned starting material, in contrast with Garrec's precedent, which successfully employed this route to prepare malonate **3.102**.[81] This difference in reactivity was likely caused by the steric hindrance of the *tert*-butyl group. Rhodium and iridium-catalysed hydroboration methods were also unsuccessful.[237, 238]



Scheme 3.16 Garrec's route to malonyl radical cyclisation substrate **3.102** and results of its adaptation to the synthesis of **3.97**.[81]

An alternative route to cyclisation substrate **3.97** involved functionalisation of malonate **3.102**, previously synthesised by Garrec through the sequence depicted in Scheme 3.16. This required the desaturation of malonate **3.102** and conjugate addition of a *tert*-butyl organometallic (Scheme 3.17). Thus, alkylidene malonate **3.104** was synthesised through a desaturation procedure involving α-selenation of malonate **3.102** with PhSeBr and

oxidative elimination. This yielded alkylidene malonate **3.104** in 65% yield over two steps. Then, CuCN-mediated conjugate addition of *tert*-BuLi gave required malonate **3.97** in 64% yield. The *tert*-butyl group was incorporated by conjugate addition, in a manner akin to all previous syntheses of ginkgolide B. [221-224]

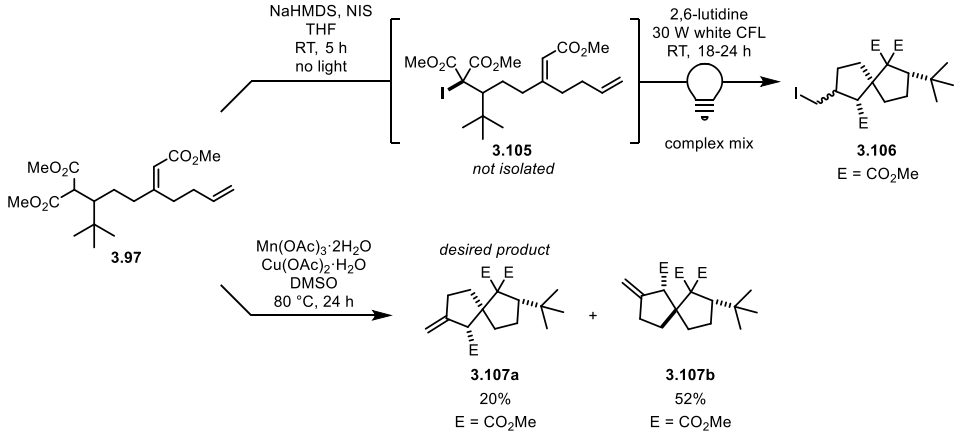


Scheme 3.17 Derivatisation of malonate **3.102** into *tert*-butyl containing malonate **3.97**.

3.4.1.2 Radical cascade of a *tert*-butyl containing malonate

The light-mediated radical cyclisation of malonate **3.97** was then attempted following Garrec's conditions (Scheme 3.18). [81] Malonate **3.97** was treated with NaHMDS and NIS in the dark to form iodomalonate **3.105**, and 2,6-lutidine added before the mixture was irradiated with a 30 W white CFL. The ^{1}H NMR of the crude mixture, however, lacked peaks characteristic of iodide **3.106** and contained starting material and several unidentified species. In an attempt to isolate iodomalonate **3.105**, the reaction was repeated in the dark, although without success.

The stark difference in reactivity between malonate **3.97** and malonate **3.102** may be caused by the steric bulk of the *tert*-butyl group, which hindered malonate deprotonation and iodination, thus allowing side reactivity to become dominant. For example, the terminal olefin of malonate **3.97** could react with NIS, and the resulting iodonium degrade under the reaction conditions.



Scheme 3.18 Results of the light-mediated malonyl radical cyclisation of **3.97** and its $Mn(OAc)_3$-mediated cyclisation.

After the failed cyclisation of malonate **3.97** under light-mediated conditions, alternative radical generation methods were investigated. We envisaged that $Mn(OAc)_3$ could provide the required spirocycle, in this instance through an oxidative cascade to give *exo*-alkene **3.107a** (see section 1.2.1.1). Indeed, treatment of malonate **3.97** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in DMSO gave spirocycles **3.107a** and **3.107b** in 20% and 52% yields, respectively (Scheme 3.18). No starting material or products derived from 6-*endo* cyclisation were detected.

The relative configuration of spirocycles **3.107a** and **3.107b** was assigned using ^{1}H NMR NOESY analysis (Figures 3.1 and 3.2). The nOe interactions between C{8}–H and its surrounding nuclei were key to these assignments. The relative configuration of C{1} and C{8} in spirocycle **3.107b** was assigned based on the nOe interaction between C{8}–H and C{2}–H (Figure 3.2). The configuration of C{5}, however, could not be assigned based on NMR experiments. X-ray crystallography of spirocycle **3.107b** later confirmed the relative configuration of C{1} and C{8} and allowed assignment of the configuration of C{5} (Scheme 3.19). On the other hand, the relative configuration of C{1}, C{5} and C{8} in spirocycle **3.107a** could be assigned based on the key nOe interaction between

C{5}–H and C{8}–H. This could not be confirmed through X-ray crystallography but was in agreement with the ^{1}H NMR NOESY spectra of other spirocyclic products (see sections 3.4.1.3 and 3.4.2.2).

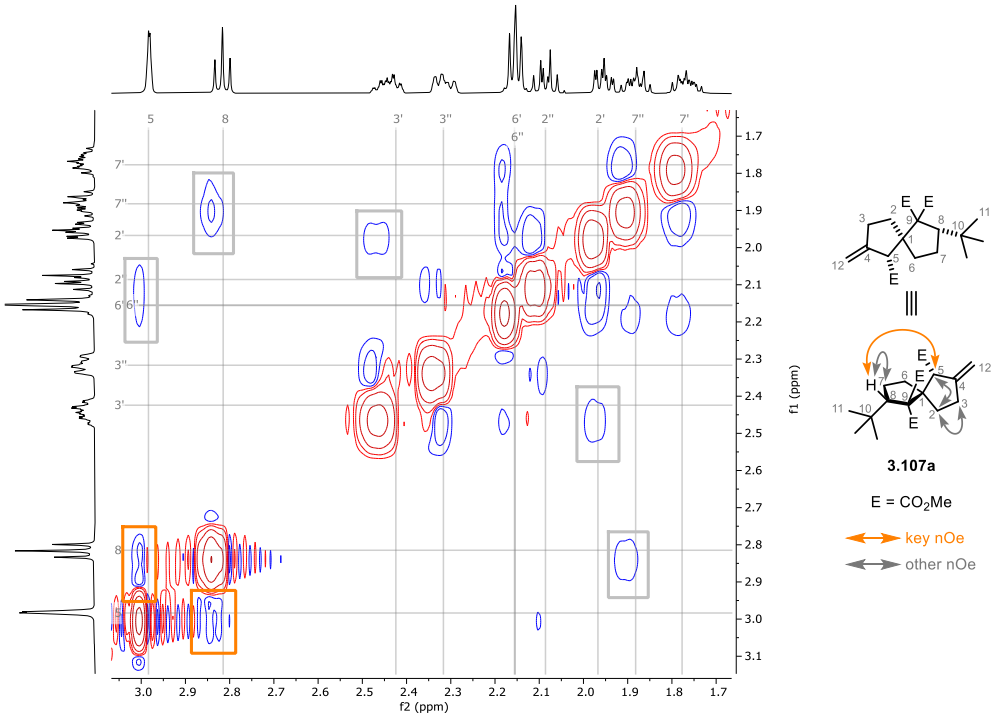


Figure 3.1 Excerpt of the ^{1}H NMR NOESY (600 MHz, $CDCl_3$) spectrum of spirocycle **3.107a**.

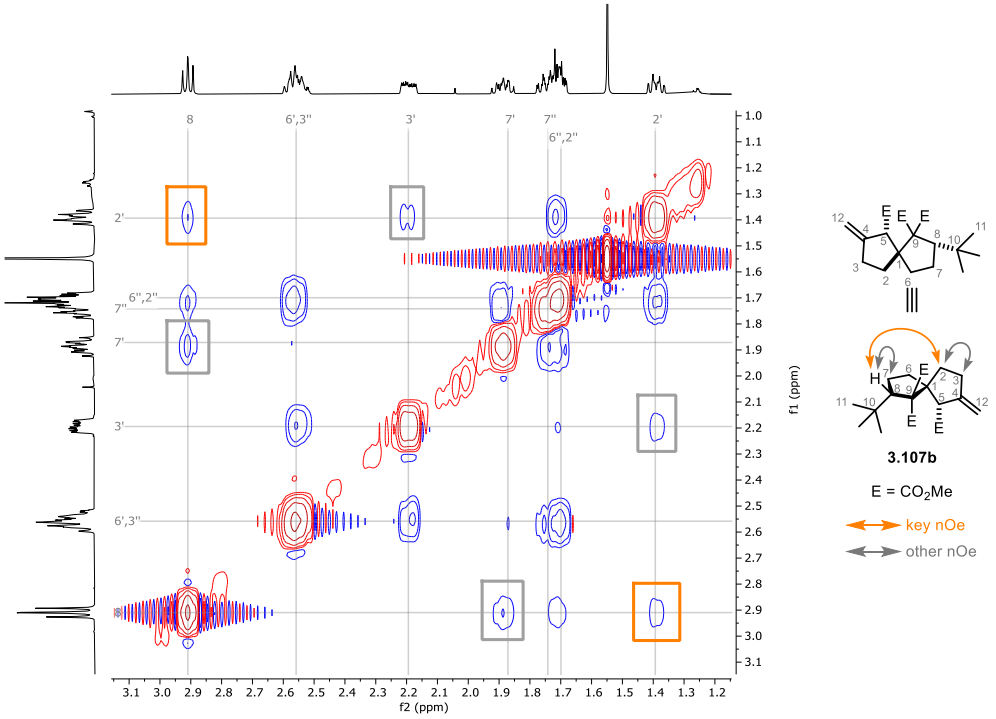
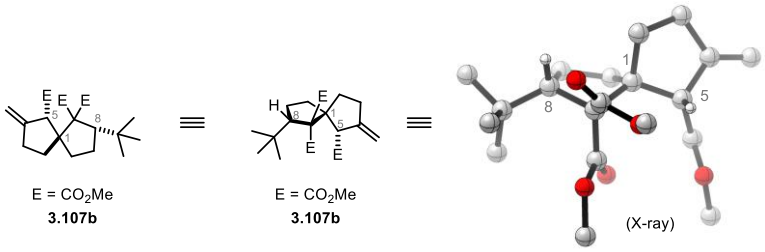


Figure 3.2 Excerpt of the ^{1}H NMR NOESY (600 MHz, $CDCl_3$) spectrum of spirocycle **3.107b**.



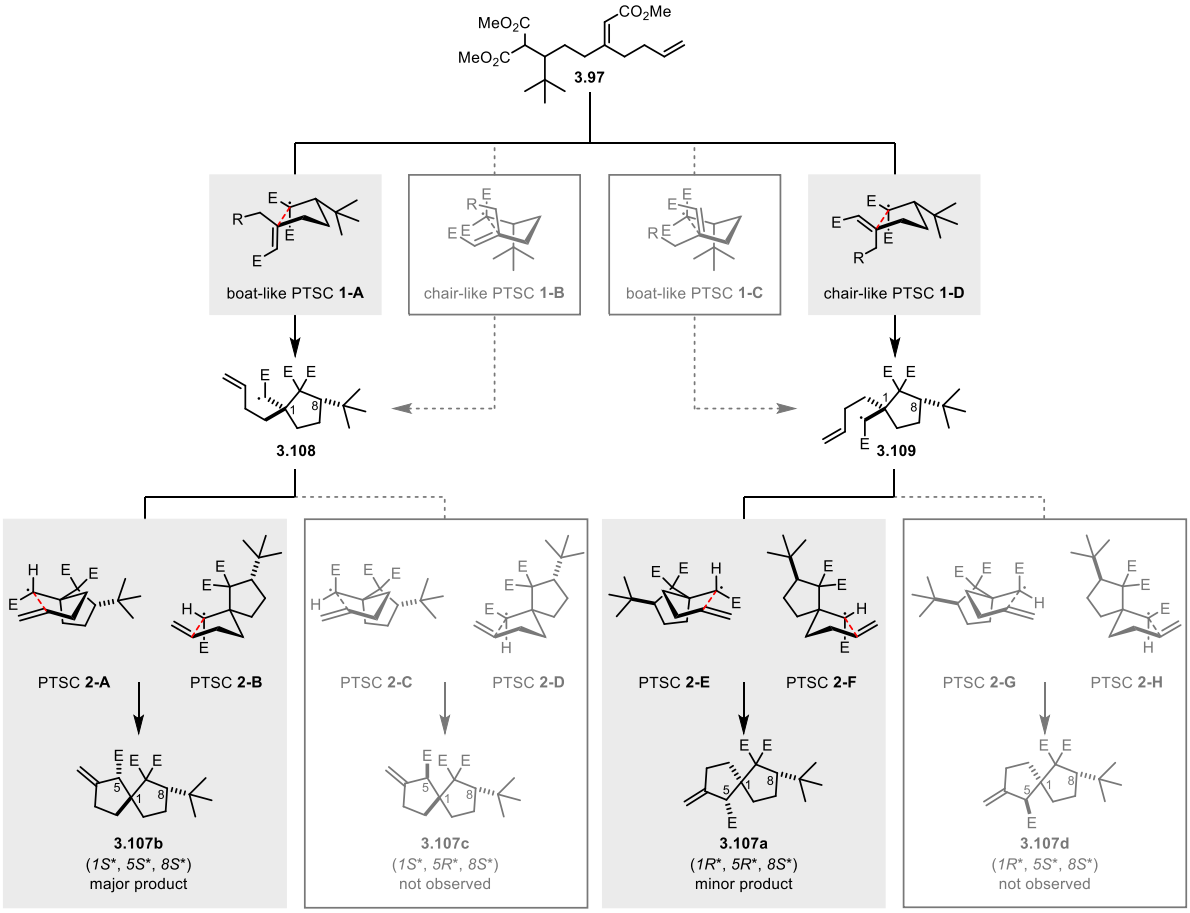
Scheme 3.19 X-ray crystallography of spirocycle **3.107b.** All hydrogen atoms except for C{5}–H and C{8}–H omitted for clarity.

The connectivity and configuration of spirocycles **3.107a** and **3.107b** can be rationalised with the Baldwin rules and the Beckwith-Houk model.[73, 76, 77] Spirocycles **3.107a** and **3.107b** were obtained after two 5-*exo-trig* cyclisations of the malonyl radical derived from malonate **3.97**, while products of 6-*endo-trig* cyclisations were not detected in the reaction mixture, in agreement with the Baldwin rules.[73]

The Beckwith-Houk model can explain the stereochemical outcome of the oxidative radical cascade of malonate **3.97** to give spirocycles **3.107a** and **3.107b**. This model describes the cyclisation of substituted 5-hexenyl radicals and can be used to predict their stereoselectivity (see section 1.3.2).[76, 77] Its application to the radical cyclisation of malonate **3.97** is summarised in Scheme 3.20.

The first 5-*exo-trig* cyclisation of malonate **3.97** determines the relative configuration of C{1} and C{8} and can occur *via* the pre-transition state conformations (PTSC) **1-A**, **1-B**, **1-C**, and **1-D**, depicted in Scheme 3.20. The description of PTSCs as chair- or boat-like is used in the Beckwith-Houk model to predict their relative energies and is suitable for cyclisations onto terminal olefins. Nonetheless, the relative energies of chair- and boat-like transition states of cyclisations onto substituted alkenes, such as the one discussed here, are less straightforward to predict.[78] In this instance, the steric bulk of the *tert*-butyl group is likely the determining factor in the stereochemical outcome of the cyclisation.

PTSCs with the *tert*-butyl in a *pseudo*-equatorial position (PTSCs **1-A** and **1-D**) are likely lower in energy than those with the group in a *pseudo*-axial position (PTSCs **1-B** and **1-C**). Therefore, we shall only consider PTSCs **1-A** and **1-D**. Boat-like PTSC **1-A** results in the major product **3.107b** (1*S**, 5*S**, 8*S**), while the chair-like PTSC **1-D** explains the formation of the minor product **3.107a** (1*R**, 5*R**, 8*S**). Based on the product distribution obtained and assuming no reversibility, PTSC **1-A** is lower in energy than PTSC **1-D**.



Scheme 3.20 Adaptation of the Beckwith-Houk model to the cyclisation of malonate **3.97**.

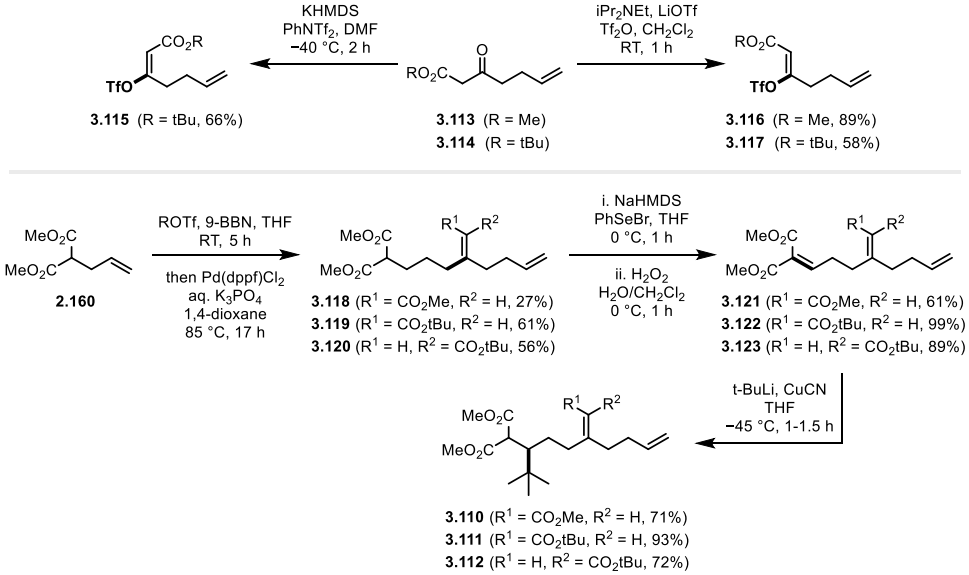
The second cyclisation event, assuming no epimerisation occurs under the reaction conditions, determines the relative configuration at C{5}; for this cyclisation, 16 different PTSCs can be considered (Scheme 3.20). Chair and boat-like PTSCs converge to the same product after *β*-hydride elimination, hence for simplicity only chair-like PTSCs are

illustrated in Scheme 3.20. Radical **3.108** yields major product **3.107b** via PTSCs **2-A** and/or **2-B**. In PTSC **2-A**, the groups with higher A value (CO_2Me *vs* H, and $C(CO_2Me)_2$ *vs* CH_2) [239] are *pseudo*-equatorial, while in PTSC **2-B** these are *pseudo*-axial. Therefore, PTSC **2-A** is likely lower in energy than PTSC **2-B**. The same reasoning can explain the formation of minor product **3.107a** from radical **3.109** *via* PTSC **2-E**, as well as the absence of isomers **3.107c** and **3.107d**. Isomers **3.107c** and **3.107d** would result from PTSCs **2-C**, **2-D**, **2-G**, and **2-H**, all of which contain bulky groups in *pseudo*-axial positions.

3.4.1.3 Optimisation of the stereoselectivity of the radical cascade

Based on this model, the relative energies of PTSC **1-A** and **1-D** determined the diastereoselectivity of the radical cascade (Scheme 3.20). Changing the geometry of the trisubstituted alkene and the steric demands of the α,*β*-unsaturated ester should therefore influence the selectivity of this transformation. To investigate this hypothesis, and with the aim of improving the diastereoselectivity of the radical cascade, malonates **3.110**, **3.111**, and **3.112** were prepared and subjected to cyclisation conditions.

The route to malonate **3.97** was adapted to access malonates **3.110**, **3.111**, and **3.112** (Scheme 3.21). Using *β*-ketoesters **3.113** and **3.114** as starting materials, both (*E*)- and (*Z*)-vinyl triflates **3.115**, **3.116**, and **3.117** could be obtained using conditions by Pale[240] and Gibbs.[241] These triflates were then subjected to Suzuki coupling conditions to give malonates **3.118**, **3.119**, and **3.120**. Malonates **3.110**, **3.111**, and **3.112** were then obtained through selenation, oxidative elimination, and copper-mediated conjugate addition of *tert*-BuLi.

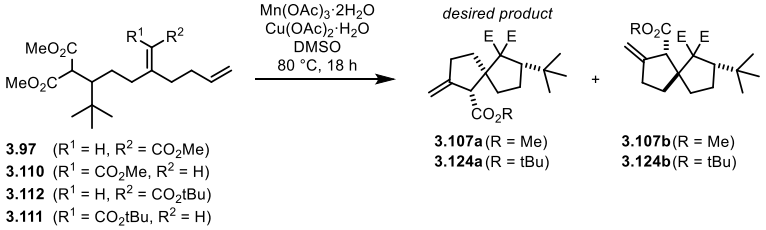


Scheme 3.21 Synthesis of malonates **3.110**, **3.111**, and **3.112**.

Malonates **3.110**, **3.111**, and **3.112** were then subjected to oxidative cyclisation conditions to test our hypothesis regarding the diastereoselectivity of this transformation (Table 3.1). Indeed, changing the geometry of the trisubstituted alkene influenced the diastereoselectivity of the cascade, although only slightly. The cyclisation of (*Z*)-alkenes (**3.110** and **3.111**) favoured the formation of the desired spirocycles (**3.107a** and **3.124a**); an effect that was amplified with the sterically-demanding *tert*-butyl ester **3.111** (entries 2, 4). Nonetheless, the diastereoselectivity of the radical cascade on this preferred substrate (**3.111**) was still low (d.r. 3:2) and thus required further investigation (entry 4).

The oxidative cascade of malonate **3.111** was further investigated to assess the effect temperature and solvent had on the cyclisation diastereocontrol (Table 3.2). Temperature had little impact on the reaction stereoselectivity (entries 1–5). Performing the reaction at lower temperatures, a common strategy to improve selectivity of transformations, had little effect on product yields and did not improve the d.r. of this cascade (entries 3, 4). At room temperature, products **3.124a** and **3.124b** were not formed and starting material

3.111 was recovered (entry 5). Conversely, at higher temperature (100 °C) product was obtained in 44% yield but the d.r. remained unchanged (entry 2).

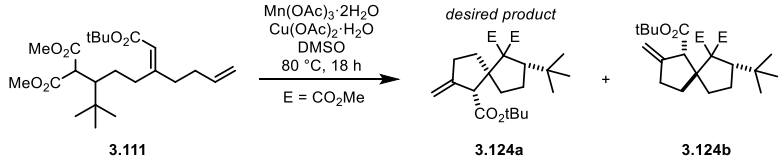


Entry	Substrate	R^1	R^2	Isolated yields/%	d.r. (a:b)[a]
1	**3.97**	H	CO_2Me	20 (**3.107a**), 52 (**3.107b**)	3:7
2	**3.110**	CO_2Me	H	16 (**3.107a**), 21 (**3.107b**)	9:11
3	**3.112**	H	CO_2tBu	54 (**3.124a**+**3.124b**)[b]	3:7
4	**3.111**	CO_2tBu	H	60 (**3.124a**+**3.124b**)[b]	3:2

Table 3.1 Results of the $Mn(OAc)_3$-mediated cyclisation of malonates **3.97**, **3.110**, **3.111**, and **3.112**. *Reagents and conditions*: malonate (0.10 mmol), $Mn(OAc)_3·2H_2O$ (2.2 equiv.), $Cu(OAc)_2·H_2O$ (1.1 equiv.), DMSO (0.20 M), 80 °C, 18 h. [a] Diastereoisomeric ratio measured by ^1H NMR of the reaction crude; [b] Isolated as an inseparable mixture of diastereoisomers.

Changing the reaction solvent from DMSO to AcOH, MeCN, or EtOH lowered both the yield and diastereoselectivity of this transformation (entries 6–8). In these reactions, termination processes other than *β*-hydride elimination became dominant, giving complex mixtures of desired *exo*-alkenes and lactones.

Since changes in alkene geometry and steric demands of the cyclisation substrate had to some extent increased the d.r. of the cascade, further structural modifications were explored. These modifications were designed to improve the diastereoselectivity of the radical cascade while maintaining orthogonality between the malonate and α,*β*-unsaturated ester. For instance, *tert*-butyl, benzyl, phenacyl, and benzhydryl α,*β*-unsaturated esters could be selectively cleaved in the presence of methyl, isopropyl, benzyl, 3,3,3-trichloro, 3,3,3-trifluoro, and adamantanylmethyl malonates.

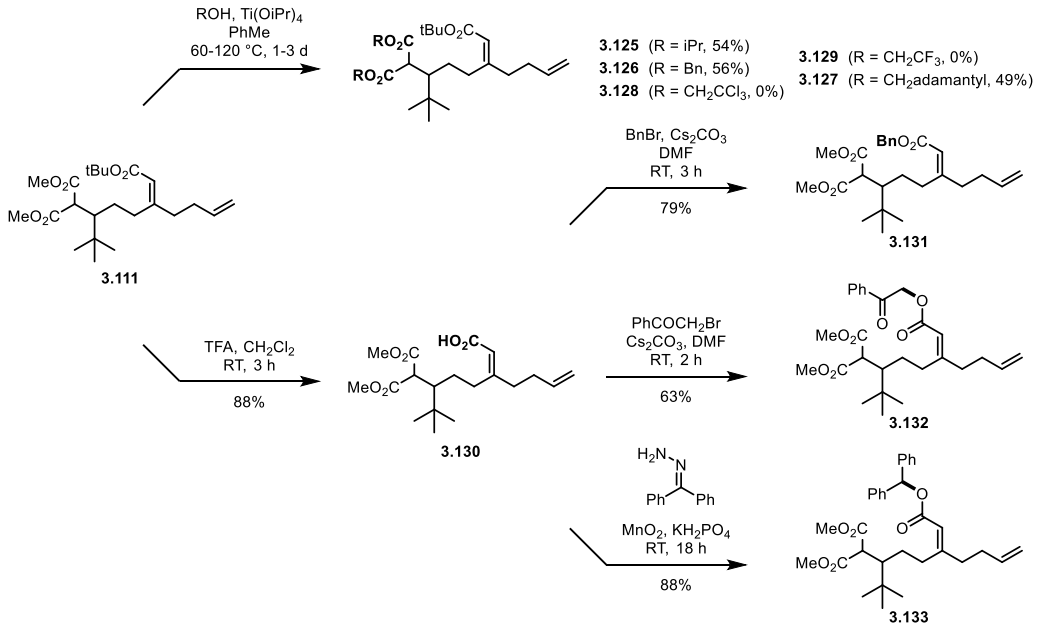


3.111 3.124a 3.124b

Entry	Solvent	T/°C	Yield of 3.124a+3.124b/%[a]	d.r. (a:b)[b]	Remaining 3.111/%[a]
1	DMSO	80	60	3:2	0
2	DMSO	100	44	3:2	0
3	DMSO	60	47	3:2	3
4[c]	DMSO	40	49	11:9	15
5[c]	DMSO	RT	0	–	>90
6	AcOH	80	20	1:1	10
7	MeCN	80	11	1:1	3
8	EtOH	80	14	4:3	15

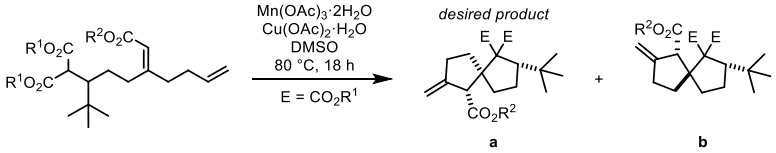
Table 3.2 Summary of the optimisation of the $Mn(OAc)_3$-mediated cyclisation of malonate **3.111**. *Reagents and conditions:* **3.111** (0.10 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (2.2 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.1 equiv.), solvent (0.20 M). [a] Calculated yield by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Diastereoisomeric ratio measured by ^1H NMR of the reaction crude; [c] Reaction allowed to stir for 40 h.

A divergent route using malonate **3.111** as the starting material was devised to prepare a range of cyclisation substrates containing different malonate and α,*β*-unsaturated ester substitution (Scheme 3.22). This route exploited the orthogonality of methyl and *tert*-butyl esters. The titanium-catalysed transesterification of malonate **3.111** yielded isopropyl (**3.125**), benzyl (**3.126**), and adamantanylmethyl malonates (**3.127**), leaving the *tert*-butyl ester intact.[242] Reactions with 2,2,2-trichloroethanol and 2,2,2-trifluoroethanol to give malonates **3.128** and **3.129**, however, were unsuccessful likely due to the lower nucleophilicity of these alcohols. On the other hand, treatment of *tert*-butyl ester **3.111** with TFA gave acid **3.130**. This carboxylic acid (**3.130**) could be selectively alkylated to give benzyl ester **3.131** and phenacyl ester **3.132**. Finally, benzhydryl ester **3.133** was obtained through the trapping of an *in situ* generated diazo compound with carboxylic acid **3.130**, as described by Shaw.[243]



Scheme 3.22 Divergent routes to malonates **3.125**, **3.126**, **3.127**, **3.131**, **3.132** and **3.133** from *tert*-butyl ester **3.111**.

The oxidative cyclisation of these differently substituted malonates showed no improvement in diastereoselectivity (Table 3.3). Increasing the steric bulk of the malonate from methyl (**3.111**) to *iso*-propyl (**3.125**), benzyl (**3.126**), or adamantanylmethyl (**3.127**) did not significantly change the yield or stereoselectivity of this radical cascade (entries 1–3). The cyclisation of adamantanylmethyl malonate **3.127**, nonetheless, was a testament to the steric hindrance tolerated by this transformation. Conversely, substitution of the *tert*-butyl in malonate **3.111** for benzyl (**3.131**) or benzhydryl (**3.133**) groups worsened the selectivity of the cascade, yielding 1:1 mixtures of diastereoisomers (entries 4, 6). Lastly, phenacyl ester **3.132** did not give spirocyclic products, instead yielding a complex mixture of starting material and degradation products (entry 5). Competing oxidation of the phenacyl group may be responsible for this difference in reactivity.



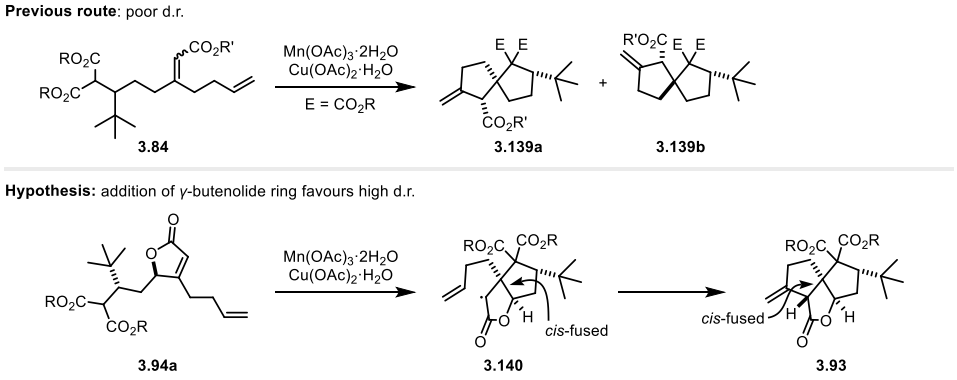
Entry	Substrate	R^1	R^2	Isolated yields/%	d.r. (a:b)[a]
1	**3.125**	iPr	tBu	29 (**3.134a**), 17 (**3.134b**)	11:9
2	**3.126**	Bn	tBu	22 (**3.135a**), 14 (**3.135b**)	3:2
3	**3.127**	CH_2Ad	tBu	21 (**3.136a**), 21 (**3.136b**)	3:2
4	**3.131**	Me	Bn	51 (**3.137a**+**3.137b**)[b]	1:1
5	**3.132**	Me	CH_2COPh	–	–
6	**3.133**	Me	$CHPh_2$	17 (**3.138a**), 21 (**3.138b**)	1:1

Table 3.3 Results of the $Mn(OAc)_3$-mediated cyclisation of malonates **3.125**, **3.126**, **3.127**, **3.131**, **3.132**, and **3.133**. *Reagents and conditions:* malonate (0.10 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (2.2 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.1 equiv.), DMSO (0.20 M), 80 °C, 18 h. [a] Diastereoisomeric ratio measured by ^1H NMR of the reaction crude; [b] Isolated as an inseparable mixture of diastereoisomers.

The current route gave access to the required spirocycle **3.124a** *via* a malonyl radical cascade but with low diastereoselectivity. Despite extensive attempts to ameliorate this, both through structural changes and reaction condition optimisation, the oxidative cascade remained unselective and yielded mixtures of spirocycles with poor diastereoisomeric ratios. Thus, this route was abandoned in favour of alternative approaches.

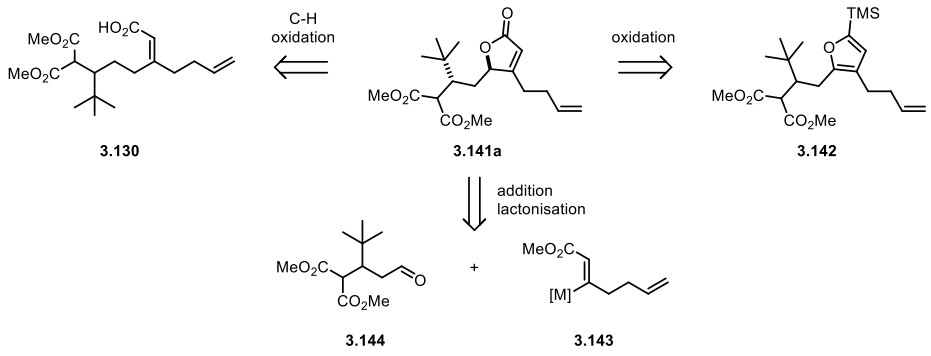
3.4.2 Route II

The previous route was abandoned due to poor diastereoselectivity, despite extensive attempts to optimise reaction conditions and cyclisation substrate structure (see section 3.4.1.3). We hypothesised that a further structural modification, the replacement of the α,*β*-unsaturated ester in malonates **3.84** with a *γ*-butenolide ring (**3.94a**), would solve this issue and provide a diastereoselective route to tricycle **3.93** (Scheme 3.23). This hypothesis was based on the preference for cyclisations to yield *cis*-5,5-fused systems instead of *trans*-5,5 scaffolds, which are higher in energy due to ring strain. [244, 245]



Scheme 3.23 Summary of the previous $Mn(OAc)_3$ oxidative malonyl radical cascade and hypothesis to improve its diastereoselectivity.

Several routes were devised and explored for the synthesis of *γ*-butenolide **3.141a**; they are summarised in Scheme 3.24. The first route was based on the C–H oxidation of carboxylic acid **3.130**, an intermediate in the previous route (see section 3.4.1.3). Alternatively, the *γ*-butenolide ring could result from the oxidation of furan **3.142** or the addition of an organometallic **3.143** to aldehyde **3.144**.



Scheme 3.24 Retrosynthetic disconnections for the synthesis of *γ*-butenolide **3.141a**.

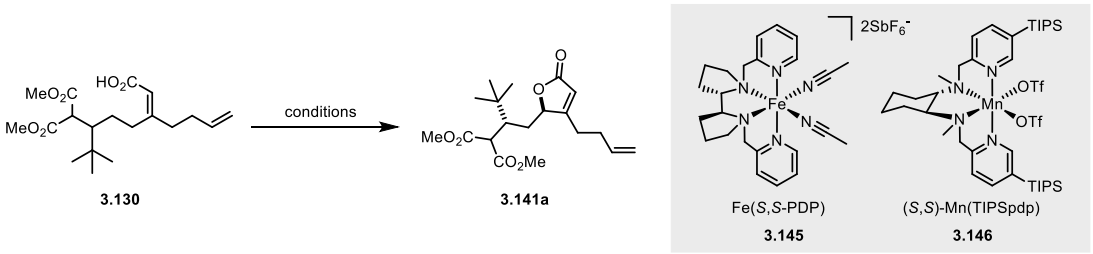
3.4.2.1 Synthesis of the *γ*-butenolide ring by C–H oxidation

The first route explored was the C–H oxidation of carboxylic acid **3.130**. Despite its challenging nature, this approach was chosen because it could give rapid access to *γ*-butenolide **3.141a** from an available intermediate (**3.130**). At this stage, the priority was

to test our hypothesis for the stereoselectivity of the malonyl radical cascade; if successful, the development of a scalable route to *γ*-butenolide **3.141a** would follow.

Several directed C–H oxidation methods were screened for the synthesis of *γ*-butenolide **3.141a** (Table 3.4). White's Fe-catalysed C–H oxidation did not yield any desired product and caused full decomposition of starting material **3.130** (entry 1).[232, 233] Similar results were obtained using Costa's Mn-catalysed C–H oxidation method (entry 2).[234] Unwanted oxidation of the terminal alkene in carboxylic acid **3.130** and subsequent side-reactivity could have been responsible for these results.

Conversely, Ag-mediated methods provided *γ*-butenolide products, although in poor yields (entries 3–5). Employing a method developed by Bertrand and co-workers,[246] *γ*-butenolide **3.141a** was obtained in 10% isolated yield and 4:1 d.r (entry 3). Under these conditions, full conversion of carboxylic acid **3.130** was achieved, but the yield of *γ*-butenolide **3.141a** was low due to extensive decomposition.

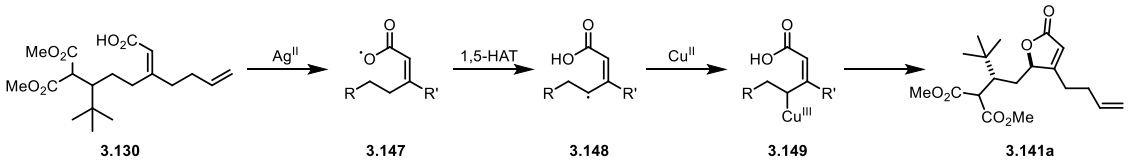


Entry	Reagents (equiv.)	Solvent	T, time	Yield of 3.141a[a] (d.r.)[b]
1	**3.145** (0.20), H_2O_2 (4.0), AcOH (0.50)	MeCN	RT, 1 h	dec.
2	**3.146** (0.01),† H_2O_2 (1.0), TfOH (0.10)	TFE	0 °C, 1 h	dec.
3	$Na_2S_2O_8$ (1.3), $AgNO_3$ (0.20), $CuSO_4$ (0.20)	1:1 MeCN/H_2O	80 °C, 3 h	10% (4:1)
4	$Na_2S_2O_8$ (1.3), $AgNO_3$ (0.20), $CuSO_4$ (1.0)	1:1 MeCN/H_2O	80 °C, 3 h	12% (4:1)
5	$Na_2S_2O_8$ (1.3), $AgNO_3$ (0.20), $CuSO_4$ (1.0)	1:1 MeCN/H_2O	80 °C, 18 h	7% (4:1)

Table 3.4 Summary of the attempts to synthesise *γ*-butenolide **3.141a** *via* C–H oxidation of carboxylic acid **3.130**. [a] Isolated yield; [b] Diastereoisomeric ratio measured by ^{1}H NMR of the reaction crude.

† We are grateful to Prof. Miquel Costas for the generous donation of a sample of catalyst **3.146**

The proposed mechanism of this transformation involves the oxidation of carboxylic acid **3.130** with Ag(II), generated from Ag(I) and $Na_2S_2O_8$, to give acyloxyl radical **3.147** (Scheme 3.25). A 1,5-hydrogen atom transfer (HAT) can then yield radical **3.148**, which after oxidation with Cu(II) gives *γ*-butenolide **3.141a**.[246] Attempts to improve the product yield by increasing the concentration of $CuSO_4$ to limit side-reactivity of radical **3.148** or extending reaction times were unsuccessful (entries 4, 5).



Scheme 3.25 Proposed mechanism for the Ag-mediated synthesis of *γ*-butenolide **3.141a**.[246]

The stereochemical configuration of *γ*-butenolide **3.141a** could not be determined by NMR analysis and was therefore unknown at this stage. It was subsequently assigned based on the relative configuration of the products of its radical cyclisation (see section 3.4.2.2).

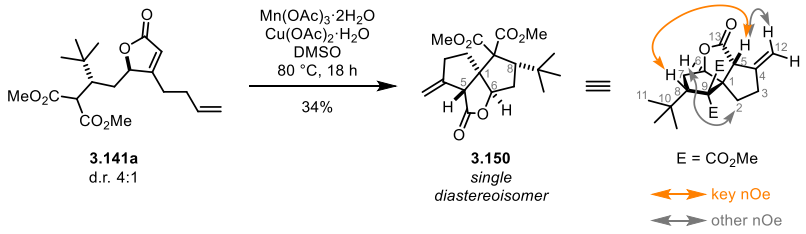
3.4.2.2 Radical cascade of a *γ*-butenolide containing malonate

γ-Butenolide **3.141a**, obtained as a 4:1 mixture of inseparable diastereoisomers, was then subjected to $Mn(OAc)_3$ radical cascade conditions to test our stereoselectivity hypothesis. Pleasingly, the cyclisation of *γ*-butenolide **3.141a** yielded tricycle **3.150** as a single diastereoisomer in 34% isolated yield (Scheme 3.26).

The relative configuration of this cyclisation product (**3.150**) was determined by ^{1}H NMR NOESY analysis, which showed strong correlations between C{5}–H and C{8}–H (Figure 3.3). Together with the absence of a correlation between C{2}–H and C{8}–H, this allowed the assignment of the relative configurations of C{1}, C{5}, C{6} and C{8}

in tricycle **3.150**. By extension, and assuming no butenolide epimerisation took place, this allowed assignment of the relative configuration of the starting material **3.141a** as *anti*.

The cyclisation of *γ*-butenolide **3.141a** confirmed our hypothesis: the addition of a *γ*-butenolide ring to the radical cascade substrate significantly improved the diastereoselectivity of the cascade, yielding the product of two 5-*exo*-*trig* cyclisations to form cis-5,5-fused ring systems (Scheme 3.23). Nonetheless, the synthesis of *γ*-butenolide **3.141a** from carboxylic acid **3.130** was poor yielding; hence, an alternative sequence was required.



Scheme 3.26 $Mn(OAc)_3$-mediated radical cyclisation of *γ*-butenolide **3.141a** and nOe correlations of tricycle **3.150**.

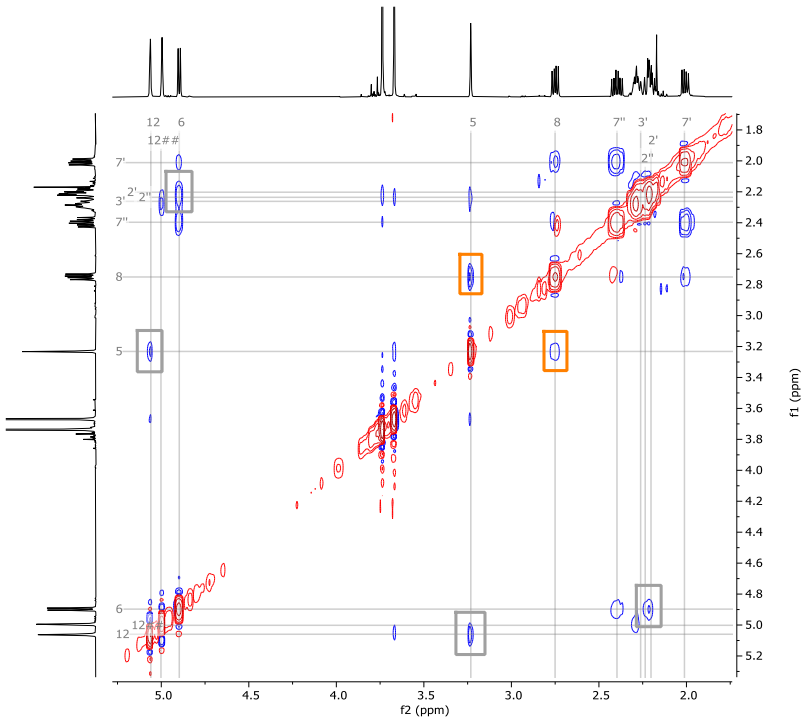
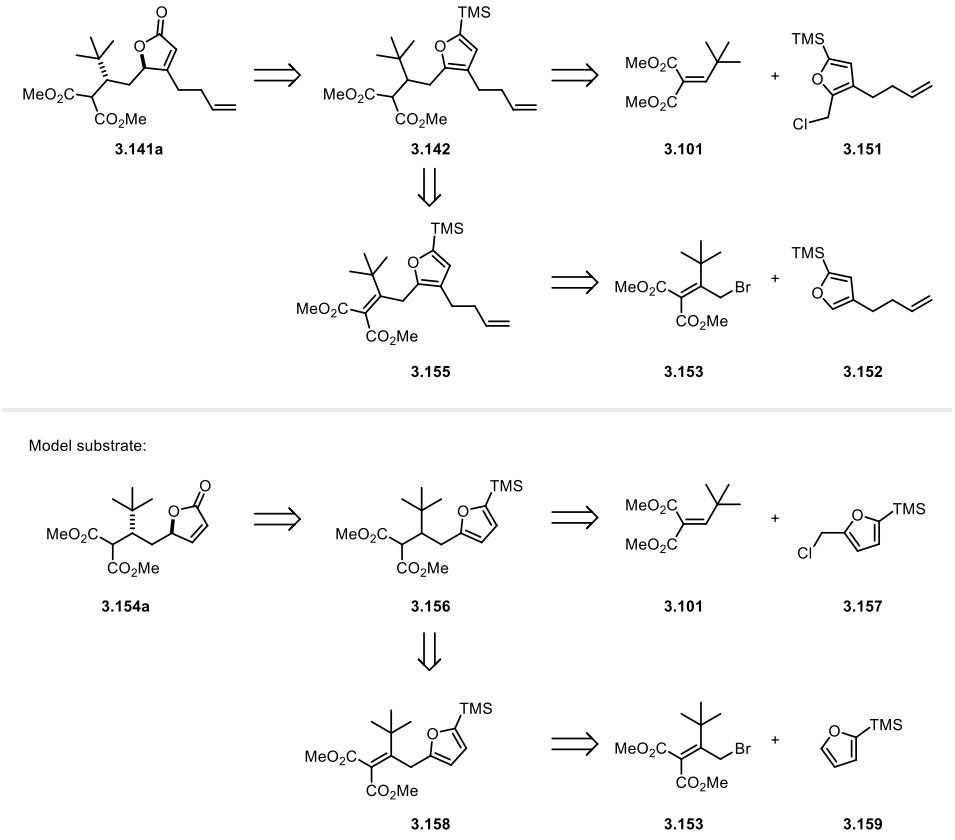


Figure 3.3 Excerpt of the ^{1}H NMR NOESY (600 MHz, $CDCl_3$) spectrum of tricycle **3.150**.

3.4.2.3 Synthesis of the *γ*-butenolide ring by oxidation of a furan

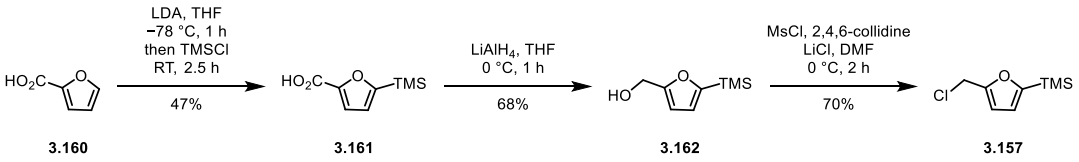
A route based on the use of a 2-silylfuran as a *γ*-butenolide surrogate was investigated next. In this route, *γ*-butenolide **3.141a** would be obtained through oxidation of furan **3.142** with a peracid or singlet oxygen (Scheme 3.27). Careful choice of reagents and reaction conditions could render this reaction diastereoselective. In turn, furan **3.142** could be prepared either from the 1,4-addition of an organometallic reagent derived from chloride **3.151** onto alkylidene malonate **3.101**, or the allylation of furan **3.152** with bromide **3.153** and olefin reduction. The synthesis of a truncated model substrate **3.154a** was studied first to establish the viability of this approach.



Scheme 3.27 Retrosynthetic analysis for the synthesis of *γ*-butenolide **3.141a** *via* the oxidation of furan **3.142** and proposed model substrate **3.154a**.

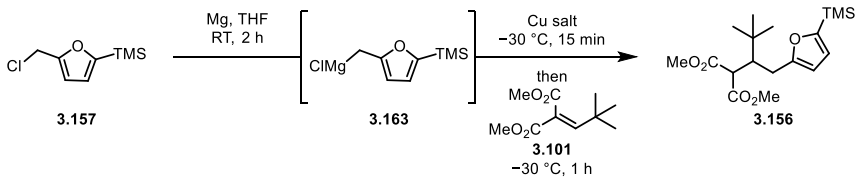
3.4.2.4 Synthesis of a model furan substrate

A route based on the 1,4-addition of an organometallic reagent derived from chloride **3.157** onto alkylidene malonate **3.101** was investigated first. Chloride **3.157** was obtained in three steps from 2-furoic acid (**3.160**), a cheap commercially available starting material (Scheme 3.28). Double deprotonation of acid **3.160** with LDA and treatment with TMSCl yielded 2-silylfuran **3.161** in 47% isolated yield. Reduction of carboxylic acid **3.161** with $LiAlH_4$ and chlorination of the resulting alcohol **3.162** with mesyl chloride and LiCl gave the required chloride **3.157**.



Scheme 3.28 Synthesis of chloride **3.157** from 2-furoic acid.

We then studied the metalation of chloride **3.157** to give Grignard reagent **3.163** and its subsequent conjugate addition onto alkylidene malonate **3.101**. The results of these experiments are summarised in Table 3.5. Grignard reagent **3.163** could be quantitatively formed with magnesium turnings in THF; this was confirmed by TLC and ^{1}H NMR analysis of an aliquot after quenching with benzaldehyde. However, the copper-mediated conjugate addition of organomagnesium **3.163** onto alkylidene malonate **3.101** was unsuccessful (Table 3.5). None of the copper salts screened (CuCN, CuI, CuBr·Me_2S) provided any desired product **3.156**, with malonate **3.101** being recovered in all instances. The steric bulk surrounding the *β*-position of alkylidene malonate **3.101** may explain the lack of conjugate addition.



Entry	Cu salt (equiv.)	Outcome
1	–	n.r.
2	CuCN (0.10)	n.r.
3	CuCN (0.50)	n.r.
4	CuCN (1.0)	n.r.
5	CuI (0.10)	n.r.
6	$CuBr{\cdot}Me_2S$ (0.10)	n.r.

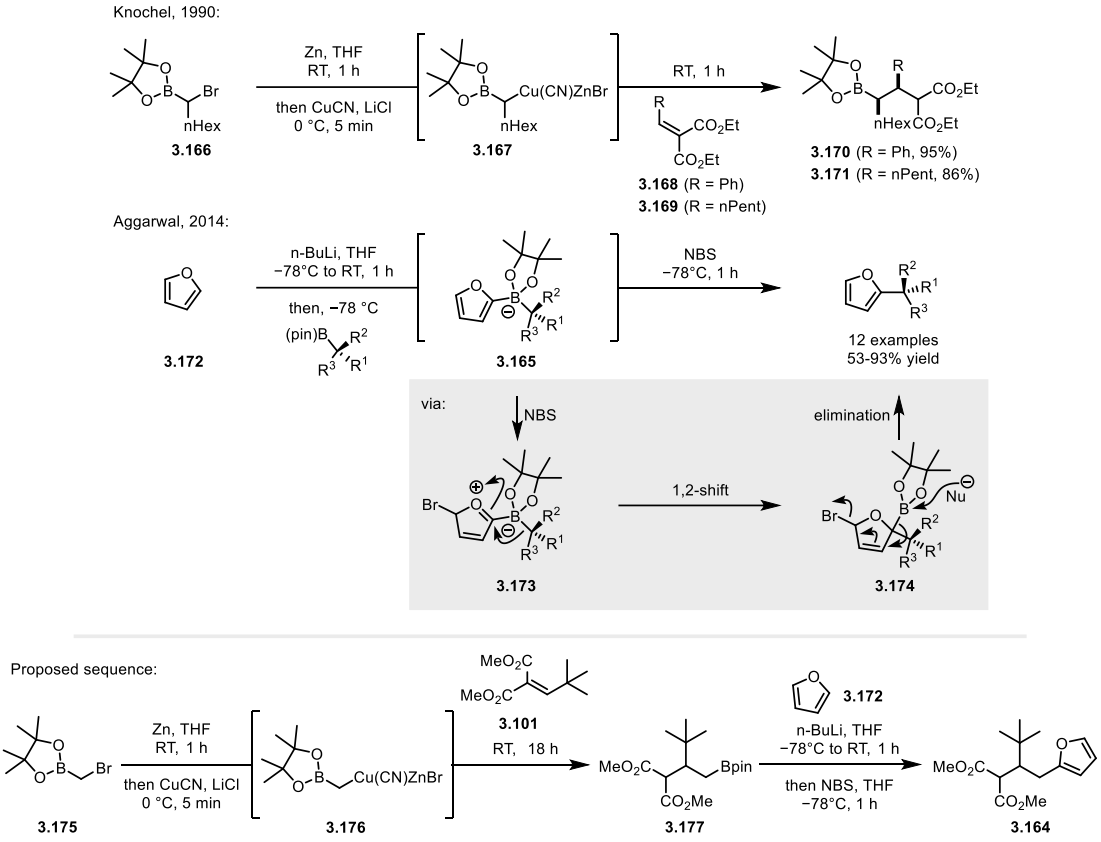
Table 3.5 Results of the copper-mediated 1,4-addition of Grignard reagent **3.163** onto alkylidene malonate **3.101**. n.r. = no reaction.

A different 1,4-addition approach employing chemistry developed by Knochel and Aggarwal could give furan **3.164**,[247, 248] which after oxidation could also yield the model *γ*-butenolide **3.154a** (Scheme 3.29).

Knochel described the conjugate addition of α-stabilised copper organometallics derived from α-halo boronic esters onto alkylidene malonates (Scheme 3.29).[248] This methodology was compatible with hindered secondary boronic esters and *β*-alkyl alkylidene malonates. On the other hand, Aggarwal et al. reported the sp^2-sp^3 coupling of furans and aliphatic boronic esters.[247] This reaction was based on the halogenation of boronate complexes (**3.165**) and subsequent 1,2-migration to yield functionalised furans (Scheme 3.29).

We envisaged a combination of both methodologies could give access to furan **3.164**, which after oxidation would provide the required *γ*-butenolide **3.154a**. Known boronic ester **3.175** would be converted into organocopper reagent **3.176** after metalation with zinc and treatment with CuCN. Alkyl copper **3.176** would then add onto alkylidene malonate **3.101**, as described by Knochel,[248] to give primary boronic ester **3.177**.

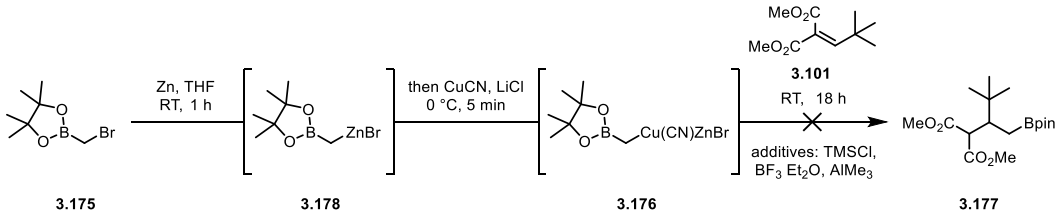
Treatment of boronic ester **3.177** with lithiated furan and subsequent bromination would yield furan **3.164**, a precursor to model *γ*-butenolide **3.154a**.



Scheme 3.29 Summary of Knochel's conjugate addition of α-halo boronic esters to alkylidene malonates and Aggarwal's sp^2–sp^3 coupling.[247, 248] Proposed sequence for their application towards the synthesis of furan **3.164**.

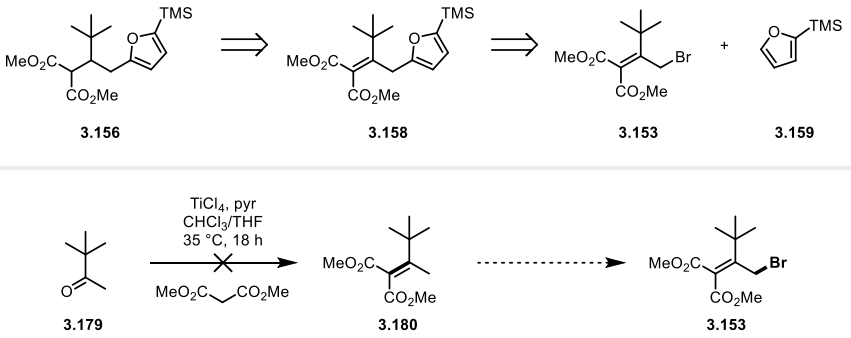
The product of this sequence would be furan **3.164**, instead of the initial target 2-silylfuran **3.156**, since Aggarwal's boronic ester coupling has not been shown to be compatible with 2-substituted furans.[247] Nonetheless, furan **3.164** could be oxidised under the same conditions as 2-silylfuran **3.156** to give model *γ*-butenolide **3.154a**. Therefore, both furan **3.164** and 2-silylfuran **3.156** could give access to the required *γ*-butenolide **3.154a**. If successful, this sequence would be adapted to synthesise required *γ*-butenolide **3.141a**.

This reaction sequence was attempted on alkylidene malonate **3.101** (Scheme 3.30). First, organozinc reagent **3.178** was prepared from α-bromo boronic ester **3.175**; this was confirmed by ^{1}H NMR analysis of a reaction aliquot after quenching with I_2. CuCN was then added to generate alkyl copper **3.176**, followed by alkylidene malonate **3.101**. However, after 18 h at room temperature, no reaction occurred and starting material **3.101** was recovered. All attempts to improve product formation, for example, through the addition of TMSCl, $BF_3{\cdot}Et_2O$, or $AlMe_3$, were unsuccessful. The failed formation of organocopper **3.176** or the steric hindrance of alkylidene malonate **3.101** may explain this lack of reactivity. The latter is most likely, since the transmetalation of organozinc **3.178** with CuCN has literature precedence, while the steric bulk surrounding the *β*-position of alkylidene malonate **3.101** is expected to hinder its reactivity.



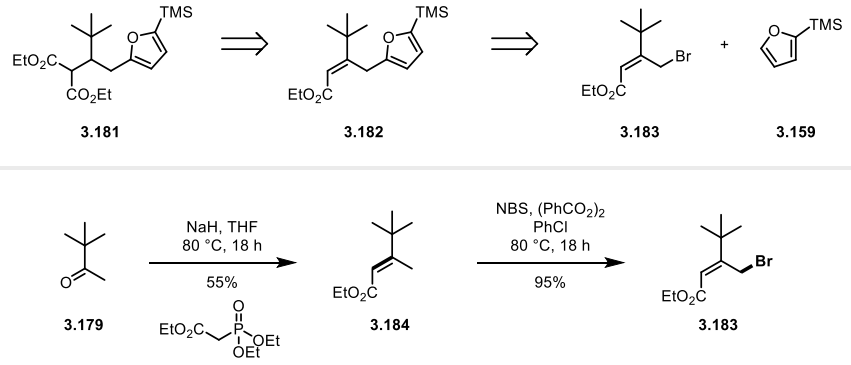
Scheme 3.30 Attempted synthesis of boronic ester **3.177** through the conjugate addition of organocopper **3.176** to alkylidene malonate **3.101**.

After the unsuccessful attempts to prepare furans **3.156** and **3.164** through a conjugate addition onto alkylidene malonate **3.101**, an alternative sequence based on the allylation of furan **3.159** with allyl bromide **3.153** was investigated (Scheme 3.31). This retrosynthetic disconnection placed the bulky *tert*-butyl group, which we hypothesised had prevented reactivity in previous routes, further away from the reacting centre.



Scheme 3.31 Retrosynthetic analysis for the synthesis of malonate **3.156** and attempted synthesis of bromide **3.153**.

First, the synthesis of allyl bromide **3.153** was attempted (Scheme 3.31). We envisaged a Knoevenagel condensation of pinacolone (**3.179**) and dimethyl malonate could provide alkylidene malonate **3.180**. Then, radical allylic bromination would yield the required allylic bromide **3.153**. Nonetheless, all attempts to condense dimethyl malonate with pinacolone (**3.179**) were unsuccessful, likely due to the steric hindrance surrounding the ketone.



Scheme 3.32 Retrosynthetic analysis for the synthesis of malonate **3.181** and synthesis of bromide **3.183**.

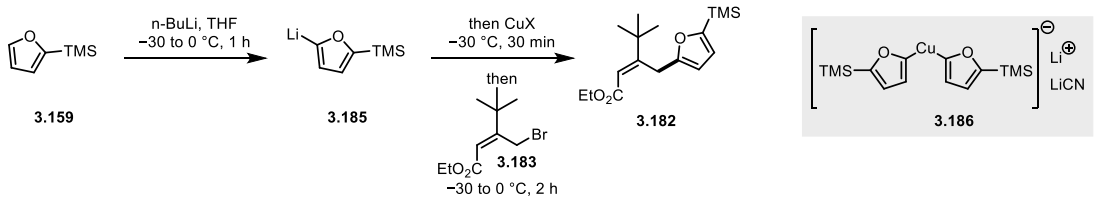
Alternatively, silyl furan **3.181** could be obtained through allylation of furan **3.159** with bromide **3.183**, alkene reduction, and α-ethoxycarbonylation (Scheme 3.32). Ethyl esters, instead of methyl esters, were chosen for this route since bromide **3.183** is a known compound and no reactivity difference was expected from this change. [249, 250]

Unlike the Knoevenagel condensation, the Horner-Wadsworth-Emmons olefination of pinacolone (**3.179**) was successful, giving α,β-unsaturated ester **3.184** in 55% isolated yield (Scheme 3.32).

The bromination of ester **3.184** was then studied. Previously reported syntheses of allyl bromide **3.183** employed a Wohl-Ziegler bromination using NBS, a radical initiator (benzoyl peroxide or AIBN) and CCl_4 as the solvent.[249, 250] However, due to environmental concerns and availability issues, an alternative solvent to CCl_4 had to be found. A short screen showed that chlorobenzene was a good alternative, giving allylic bromide **3.183** in 95% isolated yield (Scheme 3.32).

With bromide **3.183** in hand, efforts were focused on the allylation of 2-silylfuran **3.159**; this reaction required extensive optimisation (Table 3.6). The lithiation of furan **3.159** was achieved with *n*-BuLi at 0 °C following literature precedent,[251] but in the absence of copper salts the organolithium did not react with allyl bromide **3.183** to give furan **3.182** (entry 1). In the presence of substoichiometric amounts of CuCN or CuI, however, furan **3.182** was obtained in low yields (entries 2, 5).

A stoichiometry screen showed that a 2:2:1 ratio of furan/bromide/CuX gave the best results both with CuCN and CuI, with the former giving higher product yields and cleaner reaction profiles (entries 2–7). This reactivity was in line with the formation of a higher-order cyanocuprate (**3.186**), a class of compounds first described by Lipschutz that have enhanced thermal stability and reactivity.[252-254] Organocuprate **3.186** had been previously studied by Lipshutz and co-workers and used in Michael additions, epoxide ring-openings and alkylations.[251]

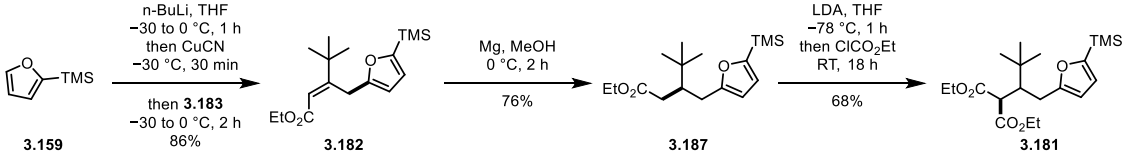


Entry	Equiv. 3.159	Equiv. 3.183	Cu salt (equiv.)	NMR yield of 3.182[a]
1	1.0	2.0	–	0
2	1.0	2.0	CuI (0.10)	13
3	1.0	2.0	CuI (1.0)	24
4	2.0	2.0	CuI (1.0)	36
5	1.0	2.0	CuCN (0.10)	24
6	1.0	2.0	CuCN (1.0)	34
7	2.0	2.0	CuCN (1.0)	>75 (62)[b]
8	2.0	1.5	CuCN (1.0)	52
9	2.0	1.0	CuCN (1.0)	57
10	1.0	2.0	$TMSCH_2Cu{\cdot}LiCN$ (1.0)	18
11	2.0	2.0	CuCN (1.0)	86[b]

Table 3.6 Results of the allylation of furan **3.159** with allyl bromide **3.183** in the presence of Cu(I) salts. *Reagents and conditions*: **3.159** (0.050 mmol), *n*-BuLi (1.0 equiv.), THF (0.30 M), −30 °C to 0 °C, 1 h; then CuX, −30 °C, 30 min; then **3.183**, −30 °C to 0 °C, 2 h. [a] Calculated yield by ^{1}H NMR using dimethyl sulfone as internal standard; [b] Isolated yield.

Only one aryl group can be transferred from these cuprates to an electrophile, resulting in the loss of one equivalent of organolithium.[254] 'Dummy', non-transferable ligands were developed to overcome this limitation; for example, alkynyl, 2-thienyl, and trimethylsilylmethyl groups.[255] Due to the *β*-silicon effect, the incorporation of a trimethylsilylmethyl group is particularly useful, since it enhances the reactivity of the organocuprate species.[256] In this transformation, however, the replacement of CuCN for $TMSCH_2Cu{\cdot}LiCN$ caused a drop in yield (entry 10) and prevented the incorporation of a non-transferable ligand in this reaction. Employing the optimised conditions (entry 7), this reaction was performed on a 4.0 mmol scale, providing 1.06 g of furan **3.182** (entry 11).

Subsequently, α,*β*-unsaturated ester **3.182** was converted into malonate **3.181** (Scheme 3.33). 1,4-Reduction using magnesium in methanol gave furan **3.187** in 76% isolated yield.[257] In turn, furan **3.187** was ethoxycarbonylated after deprotonation with LDA and treatment with ethyl chloroformate to yield the required malonate **3.181** in 68% yield. This route provided 671 mg (1.75 mmol) of furan **3.181**.

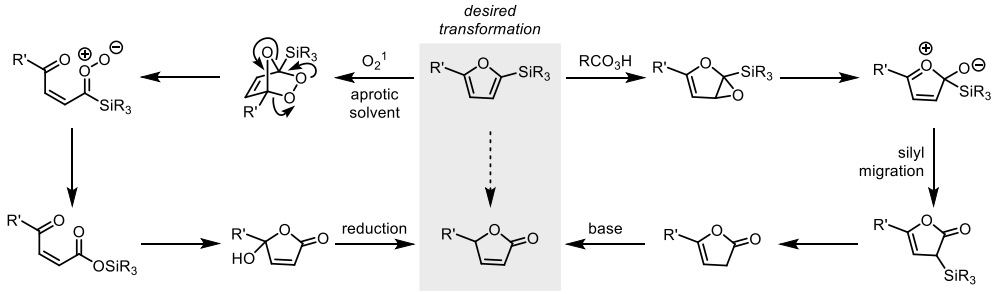


Scheme 3.33 Synthesis of malonate **3.181**.

3.4.2.5 Oxidation of the model furan substrate

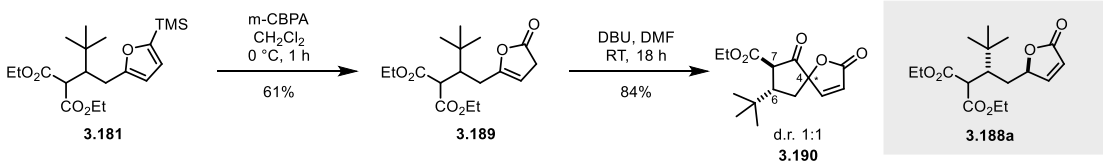
The oxidation of 2-silylfuran **3.181** to yield *γ*-butenolide **3.188a** was then studied. 2-Silylfurans can be converted into *γ*-butenolides through two different routes (Scheme 3.34). On the one hand, treatment of 2-silylfurans with peracids gives α-butenolides *via* the mechanism outlined in Scheme 3.34.[258] Depending on their substitution, α-butenolides can isomerise to yield *γ*-butenolides. This approach was used by Corey et al. in their synthesis of salinosporamide A analogues,[259] and Wong's total synthesis of (±)-pallavicinin and (±)-neopallavicinin.[260] This isomerisation was especially attractive because it could be rendered diastereoselective, for instance, through Deng's method employing cinchona alkaloids as isomerisation catalysts.[261]

Alternatively, the oxidation of 2-silylfurans with singlet oxygen provides *γ*-hydroxy-butenolides, which can be reduced to *γ*-butenolides with $NaBH_4$.[262, 263] Katsumura employed this chemistry in their total synthesis of (*E*)-neomanoalide,[264] as well as Wong and co-workers in their biomimetic synthesis of (±)-pallavicinolide A.[265]



Scheme 3.34 Summary of the oxidation methods to convert silyl furans into *γ*-butenolides.

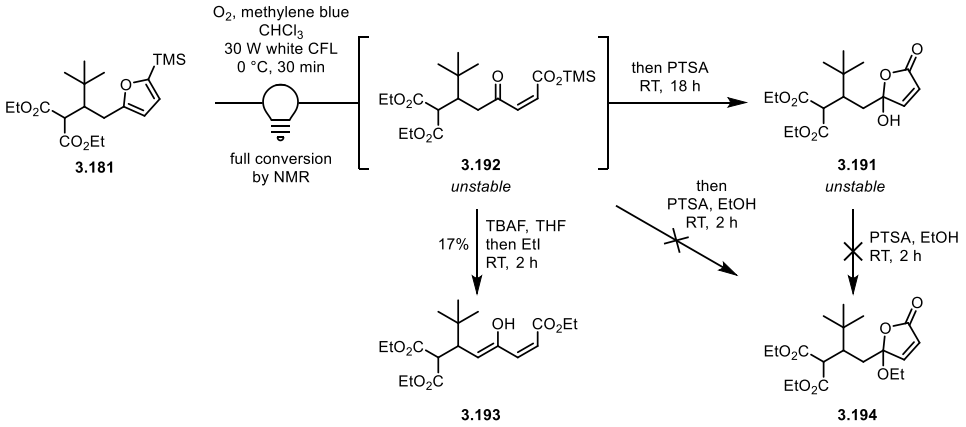
Both approaches were attempted for the synthesis of *γ*-butenolide **3.188a**. Treatment of 2-silylfuran **3.181** with m-CPBA gave the expected α-butenolide **3.189** in 61% isolated yield (Scheme 3.35). Nonetheless, all attempts to isomerise α-butenolide **3.189** into *γ*-butenolide **3.188a** were unsuccessful; instead, Dieckman condensation of the furanolate generated from deprotonation of α-butenolide **3.189** gave spirocycle **3.190**. This spirocycle was obtained as an inseparable 1:1 mixture of C{4}-diastereoisomers, assigned through ^{1}H NMR NOESY analysis. Both isomers of spirocycle **3.190** had an *anti* relative configuration of C{6} and C{7}, likely achieved through equilibration of C{7} under the basic reaction conditions to minimise the steric clash between neighbouring groups.



Scheme 3.35 Oxidation of furan **3.181** with m-CPBA and attempted isomerisation to *γ*-butenolide **3.188a**.

Subsequently, the synthesis of *γ*-butenolide **3.188a** was attempted through the oxidation of 2-silylfuran **3.181** with singlet oxygen, generated through irradiation with methylene blue as the sensitiser (Scheme 3.36). Under these conditions, the oxidation of silyl furan **3.181** did not yield the expected *γ*-hydroxybutenolide **3.191** but instead provided silyl ester **3.192**, a known intermediate in this transformation.[262] *In situ* treatment of the unstable

silyl ester **3.192** with PTSA yielded desired *γ*-hydroxybutenolide **3.191**, but all attempts to isolate and purify it failed due to its rapid decomposition.



Scheme 3.36 Summary of the attempts to convert furan **3.181** into *γ*-butenolide **3.188a** through oxidation with $^1O_2$.

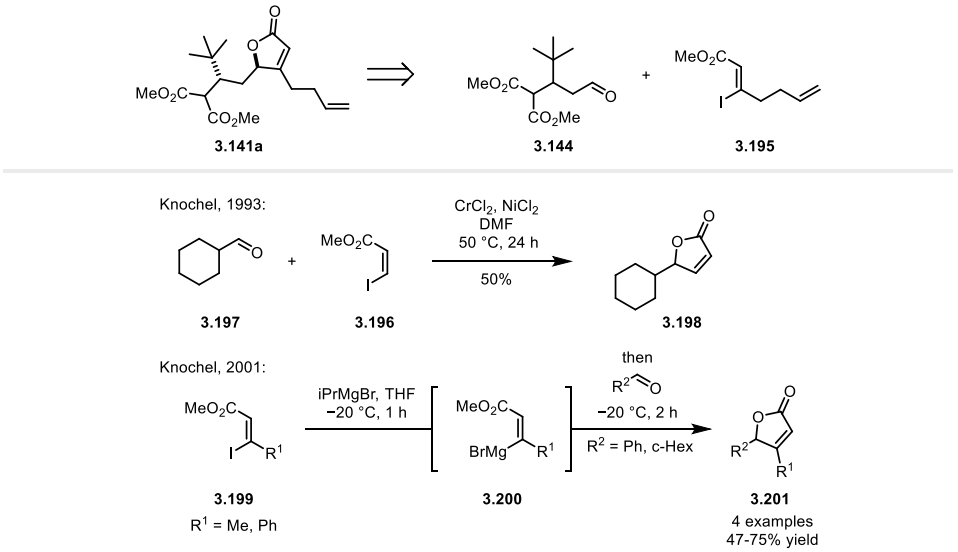
We envisaged that *γ*-ethoxybutenolide **3.194** would be less prone to degradation than *γ*-hydroxybutenolide **3.191**, in line with the relative stability of hemiacetals and acetals. Conversion of silyl ester **3.192** or *γ*-hydroxybutenolide **3.191** into *γ*-ethoxybutenolide **3.194** under acid catalysis, however, was unsuccessful (Scheme 3.36). The *in situ* desilylation of ester **3.192** with TBAF and subsequent alkylation with ethyl iodide did not provide *γ*-ethoxybutenolide **3.194** either, instead yielding ethyl ester **3.193** in 17% yield.

These studies on the synthesis of model cyclisation substrate **3.188a** showed that the oxidation of a furan ring was not a viable strategy to obtain the cyclisation substrate **3.141a**. α-Butenolide **3.189**, obtained through treatment of 2-silylfuran **3.181** with m-CPBA, could not be isomerised to the required *γ*-butenolide **3.188a**; while *γ*-hydroxybutenolide **3.191**, prepared from 2-silylfuran **3.181** with singlet oxygen, was too unstable to progress further. Based on these results, this route was abandoned in favour of alternative strategies for the construction of the *γ*-butenolide ring.

3.4.2.6 Synthesis of the *γ*-butenolide ring by Knochel's method

After the unsuccessful synthesis of *γ*-butenolide **3.141a** through the oxidation of a furan, an alternative sequence was explored. The *γ*-butenolide ring in malonate **3.141a** could be constructed through the addition of a vinyl organometallic derived from iodide **3.195** to aldehyde **3.144** and subsequent lactonisation (Scheme 3.37). This transformation was first reported by Knochel in 1993, who described the Nozaki-Hiyama-Kishi reaction of (*Z*)-iodoacrylate **3.196** and aldehyde **3.197**.[266] Hiemstra and co-workers employed this methodology in their studies towards solanoeclepin A.[267-269] In 2001, Knochel reported a *γ*-butenolide synthesis that circumvented the need for chromium salts, now using Grignard reagents derived from (*Z*)-iodoacrylates.[270] The utility of this methodology was exemplified by Buchwald, who used it in their total synthesis of eupomatilone-3.[271]

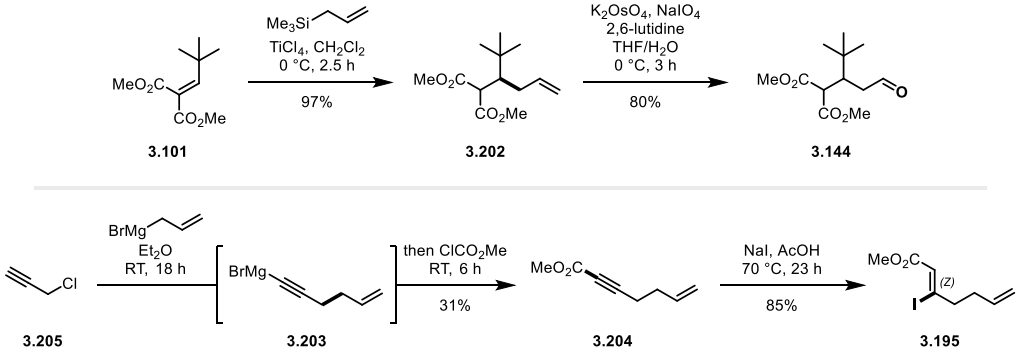
Encouraged by this precedent, aldehyde **3.144** and iodide **3.195** were prepared and their coupling attempted.



Scheme 3.37 Alternative approach for the synthesis of *γ*-butenolide **3.141a** inspired by Knochel's work.[266, 270]

Aldehyde **3.144** was obtained from alkylidene malonate **3.101** after allylation and alkene cleavage (Scheme 3.38). Sakurai reaction of alkylidene malonate **3.101** and allyltrimethylsilane gave homoallyl malonate **3.202** in excellent yield (97%). In turn, Lemieux-Johnson oxidation yielded the required aldehyde **3.144** in 80% isolated yield.

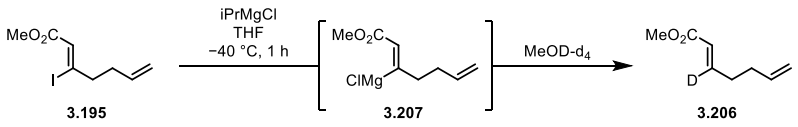
Vinyl iodide **3.195** was prepared in two steps from propargyl chloride (Scheme 3.38). Following a methodology developed by Hopf for the one-pot synthesis of alkenyne derivatives,[272] alkynyl magnesium bromide **3.203** was obtained from propargyl chloride after nucleophilic substitution and alkyne deprotonation. Alkynyl magnesium **3.203** then gave ester **3.204** in 31% yield upon treatment with methyl chloroformate. Hopf reported quantitative formation of alkynyl magnesium **3.203** using this procedure,[272] hence the methoxycarbonylation of magnesiated alkyne **3.203** may be responsible for the poor yield of this sequence. Subsequently, vinyl iodide **3.195** was obtained from alkyne **3.204** through nucleophilic iodination under acidic conditions.[273, 274] This reaction was highly stereoselective, yielding exclusively the (*Z*)-vinyl iodide required. Lu proposed a contact ion pair to explain this stereoselectivity.[273]



Scheme 3.38 Synthetic routes to aldehyde **3.144** and vinyl iodide **3.195**.

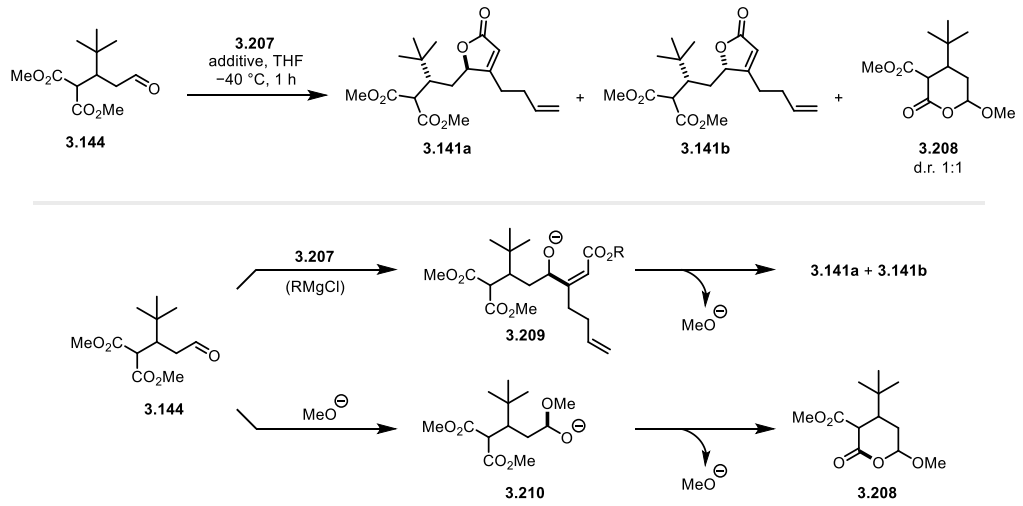
After the development of syntheses for aldehyde **3.144** and vinyl iodide **3.195**, their coupling under Knochel's conditions was attempted.[270] This reaction was investigated in a stepwise fashion, initially decoupling metalation from 1,2-addition.

Iodide **3.195** was treated with iPrMgCl at −40 °C for 1 h and an aliquot of the reaction mixture quenched with MeOD–d_4 (Scheme 3.39). ^{1}H NMR analysis of this sample showed complete disappearance of iodide **3.195** and full conversion to deuterated alkene **3.206**. No alkene isomerisation was observed, hence confirming the clean metalation of iodide **3.195** to give Grignard reagent **3.207**.



Scheme 3.39 Metalation of vinyl iodide **3.195** and quench with MeOD–d_4.

Next, the 1,2-addition of Grignard reagent **3.207** onto aldehyde **3.144** was optimised (Table 3.7). Treatment of aldehyde **3.144** with 1 equivalent of Grignard reagent **3.207** gave inseparable *γ*-butenolide diastereoisomers **3.141a** and **3.141b** in 9% yield and 1:4 d.r. (**a**/**b**) together with lactone **3.208** in *ca.* 40% yield (entry 1). Increasing the amount of organomagnesium **3.207** improved the reaction outcome. In the presence of 2 equivalents, product was obtained in 42% isolated yield and 1:4 d.r. (**a**/**b**) together with lactone **3.208** in *ca.* 20% yield (entry 2), while 3 equivalents of Grignard **3.207** gave products **3.141a** and **3.141b** in 54% yield and <5% conversion to side product **3.208** (entry 3). The diastereoselectivity of this transformation was not influenced by the stoichiometry of reagents, and in all instances it favoured formation of the undesired *syn*-isomer **3.141b** (entries 1–3).



Entry	Equiv. 3.207	Additive (equiv.)	Yield of 3.141a+ 3.141b/%[a]	d.r. (a/b)[b]	Yield of 3.208/%[c]
1	1.0	–	9	1:4	*ca.* 40
2	2.0	–	42	1:4	*ca.* 20
3	3.0	–	54	1:4	*ca.* 10
4	2.0	TMSCl (2.0)	74	1:4	<5
5[d]	2.0	TMSCl (2.0)	85	1:4	<5

Table 3.7 Results of the addition of Grignard reagent **3.207** to aldehyde **3.144**. *Reagents and conditions:* **3.144** (0.10 mmol), **3.207**, additive, THF (0.10 M), −40 °C, 1 h. [a] Isolated yield; [b] Diastereoisomeric ratio measured by ^{1}H NMR of the reaction crude; [c] Approximate yield by ^{1}H NMR based on the relative integration of **3.141a**, **3.141b**, **3.144** and **3.208**; [d] Reaction performed with 11.5 mmol of aldehyde **3.144**.

The different ratios of *γ*-butenolides **3.141a** and **3.141b** and lactone **3.208** obtained in these experiments could be rationalised by examination of the species in solution during the reaction. Organomagnesium **3.207** added to aldehyde **3.144** to yield alkoxide **3.209**, which lactonised *in situ* releasing methoxide (Table 3.7). In the presence of methoxide, the side reaction yielding lactone **3.208** could occur *via* hemiacetal **3.210**, importantly, through a sequence catalytic in methoxide. Thus, at low concentrations of organomagnesium **3.207** (entry 1), the side-reaction to yield lactone **3.208** was prevalent, whereas increasing the concentration of Grignard reagent **3.207** (entries 2, 3) ameliorated the issue.

Based on this hypothesis, the reaction was performed in the presence of TMSCl, which we predicted would react with methoxide and/or alkoxide **3.209** and significantly reduce

the concentration of methoxide in solution. Indeed, under these conditions, lactone **3.208** was not detected and *γ*-butenolides **3.141a** and **3.141b** were isolated in 74% yield and 1:4 d.r (entry 4). This reaction could be scaled up to 11.5 mmol of aldehyde **3.144** without detrimental effects on yield, giving 3.13 g of *γ*-butenolides **3.141a** and **3.141b** (85%, d.r. 1:4, entry 5).

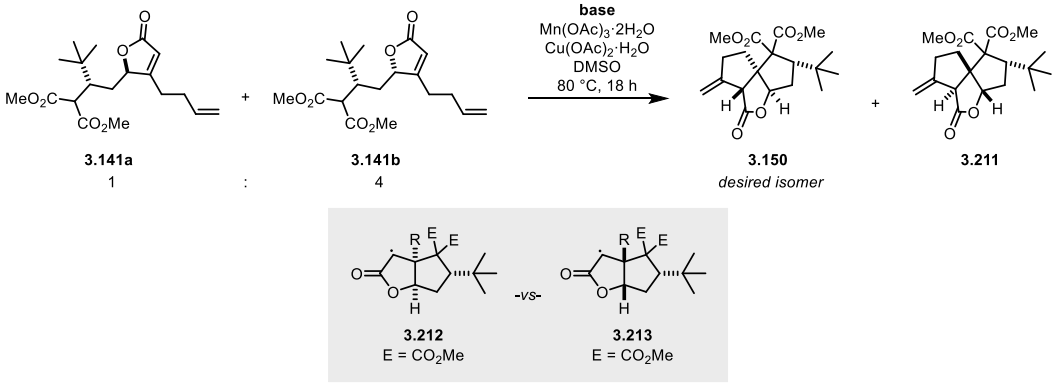
Despite the improvement in *γ*-butenolide yields, the diastereoselectivity of this transformation remained unchanged throughout the optimisation. *γ*-Butenolides **3.141a** and **3.141b** were obtained in 1:4 d.r., favouring the undesired *γ*-butenolide **3.141b**.

3.4.2.7 Potential for a diastereoconvergent radical cascade

The radical cyclisation of *γ*-butenolide **3.141b** (d.r. 4:1) was investigated to test whether epimerisation of *γ*-butenolide **3.141b** would occur *in situ* with the result that a mixture of *γ*-butenolides **3.141a** and **3.141b** could both lead to the desired tricycle **3.150**.

Subjecting a 1:4 mixture of *γ*-butenolides **3.141a** and **3.141b** to the cyclisation conditions for 48 h gave a complex mixture containing desired tricycle **3.150** (11%), undesired tricycle **3.211** (15%), and degradation products (Table 3.8, entry 1). Based on the product distribution of this reaction, the cyclisation of *γ*-butenolide **3.141b** to give tricycle **3.211** was less efficient than that of *γ*-butenolide **3.141a** to give tricycle **3.150**. This could be due to the steric clashes of the *tert*-butyl group in fused lactone radicals **3.212** and **3.213**. The cyclisation of *γ*-butenolide **3.141b** yields fused lactone radical **3.213**, with the *tert*-butyl group in the convex face of the bicycle. On the other hand, this bulky group in fused lactone radical **3.212**, obtained from *γ*-butenolide **3.141a**, is on the less-hindered concave face. This could explain the difference in reactivity of *γ*-butenolides **3.141a** and **3.141b**,

since fused lactone radical **3.213** would likely be higher in energy than lactone radical **3.212** and thus would hinder the radical addition.



Entry	Base	Remaining 3.141a+3.141b/%[a]	Yield of 3.150/%[a]	Yield of 3.211/%[a]
1	–	–	11[b]	15[b]
2	*N*-Me-pyrrolidine	7	3	1
3	DBU	4	5	4
4	NaOAc	0	11	8
5	TMG[c]	0	5	1
6	CsF	10	8	7
7	NaOMe	0	7	6

Table 3.8 Results of the $Mn(OAc)_3$-mediated cyclisation of *γ*-butenolides **3.141a** and **3.141b**. *Reagents and conditions:* **3.141a**+**3.141b** (1:4, 0.05 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (2.2 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (1.1 equiv.), base (2.0 equiv.), DMSO (0.05 M), 80 °C, 18 h. [a] Calculated yield by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Isolated yield; [c] TMG = 1,1,3,3-tetramethylguanidine.

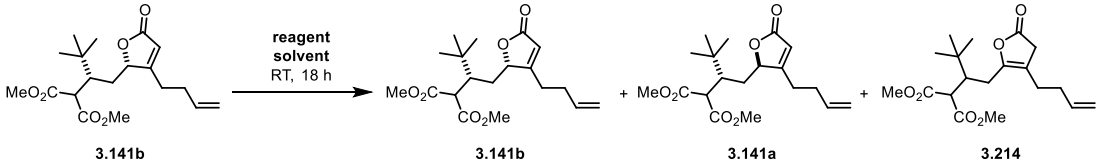
This difference in reactivity could be exploited in a diastereoconvergent radical cascade. If *γ*-butenolides **3.141a** and **3.141b** were quickly equilibrating, and assuming the cyclisation of *anti*-butenolide **3.141a** was faster than that of *syn*-butenolide **3.141b**, a mixture of *γ*-butenolides **3.141a** and **3.141b** could converge into desired tricycle **3.150**. Similar reactions exploiting the facile isomerisation of butenolides are well precedented, for example, by Toste in their palladium-catalysed DKR in the synthesis of (−)-aflatoxin B lactone,[275] and Huang in their rhodium-catalysed enantioselective alkenylation of α-butenolides.[276]

The cyclisation of *γ*-butenolides **3.141a** and **3.141b** (d.r. 1:4) was therefore attempted in the presence of various bases, which we envisaged might promote *γ*-butenolide epimerisation (Table 3.8). Nevertheless, none of the bases screened improved the yields of tricycle **3.150** (entries 2–7), irrespective of their pKa. No *in situ* epimerisation was evident from these experiments, despite the relatively low pKa of the *γ*-butenolide ring (pKa of *γ*-crotonolactone = 17.7).[277] Therefore, this approach was abandoned in favour of a stepwise epimerisation sequence.

3.4.2.8 Studies on the epimerisation of butenolides

The epimerisation of *γ*-butenolide **3.141b** into *γ*-butenolide **3.141a** was then investigated. α- and *γ*-butenolides can isomerise under both acidic and basic conditions *via* furanol and furanolate intermediates. The outcome of such isomerisations is highly dependent on the choice of acid, base, and solvent. For example, Deng described an asymmetric isomerisation of α-butenolides to yield enantioenriched *γ*-butenolides using a cinchona alkaloid as proton transfer catalyst,[261] while Argade described an acid-mediated isomerisation in their synthesis of paenolide.[278] Butenolides can also be isomerised in a two-step sequence through silylation and desilylation, as exemplified by Zhai and co-workers in their formal synthesis of (±)-aplykurodinone-1.[279]

A short screen showed that no isomerisation of *γ*-butenolide **3.141b** occurred under acidic or basic conditions (Table 3.9). This prompted us to investigate a silylation-desilylation approach.

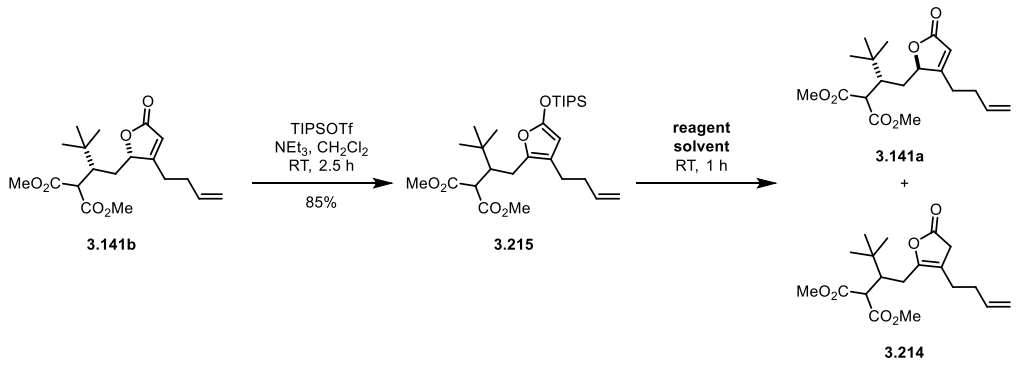


Entry	Reagent (equiv.)	Solvent	Outcome
1	DBU (0.25)	$CDCl_3$	No change
2	NEt_3 (0.25)	$CDCl_3$	No change
3	TFA (0.25)	$CDCl_3$	No change
4	tBuOK (0.25)	tBuOH	No change

Table 3.9 Results of the epimerisation screen of *γ*-butenolide **3.141b**. *Reagents and conditions:* **3.141b** (0.05 mmol, 4:1 d.r.), reagent, solvent, RT, 18 h.

The silylation of *γ*-butenolide **3.141b** using TIPSOTf gave silyloxyfuran **3.215** in 85% yield; this was followed by an extensive study of its desilylation (Table 3.10). Treatment of silyloxyfuran **3.215** with TFA in CH_2Cl_2 gave *γ*-butenolides **3.141a** and **3.141b** in 1:6 d.r. together with significant amounts of undesired α-butenolide **3.214** (32%, entry 1).

On the other hand, acetic acid buffered TBAF gave a complex mixture containing α-butenolide **3.214** in 11% yield and lacking desired *γ*-butenolides **3.141a** and **3.141b** (entry 2). Desilylation of furan **3.215** with aqueous HCl, for the first time, favoured the formation of *γ*-butenolide **3.141a** over its diastereoisomer **3.141b** (d.r. 3:1). The ratio between α- and *γ*-butenolides, however, was dependent on the solvent. In THF, *γ*-butenolides **3.141a** and **3.141b** were obtained in 41% yield and α-butenolide **3.214** in 29% yield (entry 3), while alcoholic solvents favoured formation of α-butenolide **3.214** (entries 4, 5). Finally, the treatment of silyloxyfuran **3.215** with acetic acid gave *γ*-butenolides **3.141a** and **3.141b** in 57% yield and good diastereoselectivity (3:1) with α-butenolide **3.214** being formed in only 6% yield (entry 6). These conditions could be scaled up without detrimental effects on yield or diastereoselectivity and gave access to 2.31 g of *γ*-butenolides **3.141a** and **3.141b** in d.r. 3:1 (87% yield, entry 7).

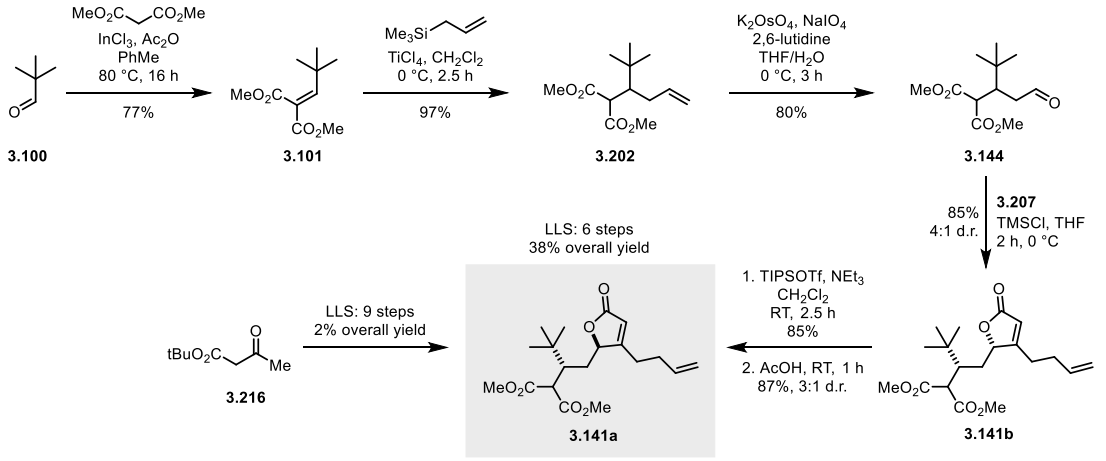


Entry	Reagent (equiv.)	Solvent	Yield of 3.141a+3.141b/%[a]	d.r. (a/b)[b]	Yield of 3.214/%[a]
1	TFA (50)	CH_2Cl_2	54[c]	1:6	32[c]
2[d]	TBAF (5), AcOH (10)	CH_2Cl_2	–	–	11[c,e]
3	2 M aq. HCl (50)	THF	41	3:1	29
4	2 M aq. HCl (50)	MeOH	8	3:1	30
5	2 M aq. HCl (50)	tBuOH	20	3:1	33
6	AcOH	–	57	3:1	6
7[f]	AcOH	–	87[c]	3:1	<5

Table 3.10 Results of the desilylation of silyloxyfuran **3.215**. *Reagents and conditions:* **3.215** (0.05 mmol), reagent, solvent, RT, 1 h. [a] Calculated yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Diastereoisomeric ratio measured by ^{1}H NMR of the reaction crude; [c] Isolated yield; [d] Reaction performed at 0 °C for 10 min; [e] Extensive decomposition observed by ^{1}H NMR; [f] Reaction performed on 7.54 mmol of furan **3.215**.

The silylation-desilylation of *γ*-butenolide **3.141b** allowed its epimerisation into *γ*-butenolide **3.141a**, but the diastereoselectivity of this transformation remained moderate (d.r. 3:1). Due to time constraints, this epimerisation was not optimised further, but variation of the silyl group in silyloxyfuran **3.215** and use of chiral acids could be explored to increase the diastereocontrol of the desilylation.

The 'Knochel' route to *γ*-butenolide **3.141a** was an alternative to the C–H oxidation approach reported in section 3.4.2.1. This sequence was shorter, higher-yielding, and used pivaldehyde as the starting material and source of the *tert*-butyl group (Scheme 3.40). It enabled the gram-scale synthesis of *γ*-butenolide **3.141a** in only six steps from pivaldehyde.

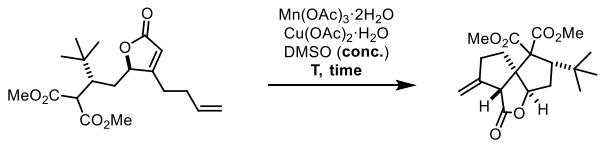


Scheme 3.40 Summary of the synthetic route to *γ*-butenolide **3.141a** and comparison with the previous C–H oxidation sequence.

In contrast, the C–H oxidation route was nine steps-long and incorporated the *tert*-butyl group through the 1,4-addition of an organocopper derived from *tert*-BuLi and CuCN (see sections 3.4.1.3. and 3.4.2.1), in a similar manner to Corey,[221] Crimmins[222, 223] and Barriault.[224] Overall, the newly developed route was superior and was henceforth employed in our studies towards ginkgolide B.

3.4.2.9 Optimisation of the radical cascade

With *γ*-butenolide **3.141a** in hand, the malonyl radical cascade first described in section 3.4.2.2 was optimised. Under the initial reaction conditions, the radical cascade gave tricycle **3.150** in 34% isolated yield (Table 3.11, entry 1). *γ*-Butenolides **3.141a** or **3.141b** could not be detected by ^{1}H NMR analysis of the crude mixture, but significant decomposition was apparent. Degradation of *γ*-butenolide **3.141a** through polymerisation pathways may explain the poor yield of tricycle **3.150** under these initial conditions.



3.141a
d.r. 3:1

3.150

Entry	Scale/mmol	Conc./M	T, time	Yield of 3.150/%[b]
1[a]	0.025	0.06	80 °C, 18 h	34[c]
2	0.020	0.06	60 °C, 18 h	44
3	0.020	0.06	40 °C, 24 h	44
4	0.020	0.12	60 °C, 18 h	47
5	0.020	0.25	60 °C, 18 h	51
6	0.060	0.40	60 °C, 18 h	43
7[d]	0.020	0.25	60 °C, 18 h	46
8	0.28	0.25	60 °C, 18 h	50[c]
9	1.60	0.25	60 °C, 18 h	46[c]
10	6.53	0.25	60 °C, 18 h	50[c]

Table 3.11 Results of the malonyl radical cascade of *γ*-butenolide **3.141a**. *Reagents and conditions:* **3.141a** (3:1 d.r.), $Mn(OAc)_3 \cdot 2H_2O$ (2.2 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.1 equiv.), DMSO, T, time. [a] Reaction performed with **3.141a** (4:1 d.r.), [b] Calculated yield by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [c] Isolated yield; [d] Reaction performed with 2.2 equiv. of $Cu(OAc)_2 \cdot H_2O$.

Concentration and reaction temperature were screened in the optimisation of the oxidative radical cascade, which was performed on γ-butenolide **3.141a** with d.r. 3:1 (Table 3.11).‡ The cascade could be performed at lower temperatures without detrimental effects on the yield of tricycle **3.150** (entries 2, 3); these reactions showed full conversion of *γ*-butenolide **3.141a** and cleaner reaction profiles. However, at 40 °C longer reaction times were required, hence 60 °C was used as the optimal temperature for this transformation. Increasing the reaction concentration improved product yields (entries 2, 4–6), with best results obtained at C = 0.25 M (entry 5). This trend is uncommon in intramolecular cascades, which are often performed at low concentrations to minimise

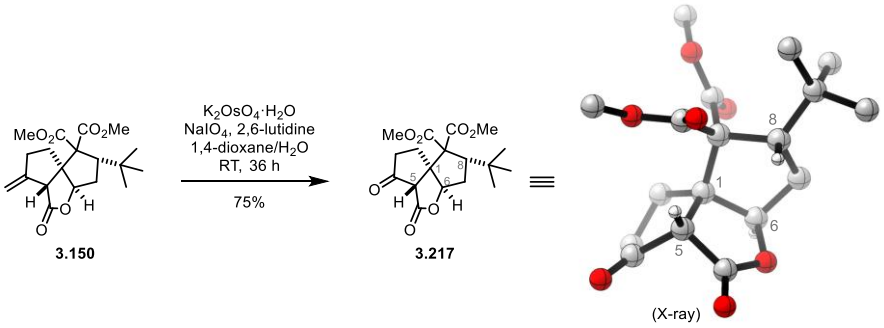
‡ Assuming no epimerisation occurred under the cyclisation conditions, in agreement with experiments described in section 3.4.2.7, yield of tricycle **2.150** could not exceed 75% due to the diastereoisomeric ratio of butenolide **3.141a** (3:1 d.r.).

intermolecular side reactions. The extent of intermolecular reactivity must therefore be limited in this transformation. Finally, increasing the amount of $Cu(OAc)_2$ in the reaction mixture, which we envisaged could improve product yields through more efficient radical termination, did not influence the yield of tricycle **3.150** (entry 7).

The best conditions from this screen (entry 5) could be scaled up and provided tricycle **3.150** in 46–50% yield, (entries 8–10). This radical cascade ultimately gave access to 1.13 g of tricycle **3.150** (entry 10).

3.4.2.10 Lemieux-Johnson oxidation

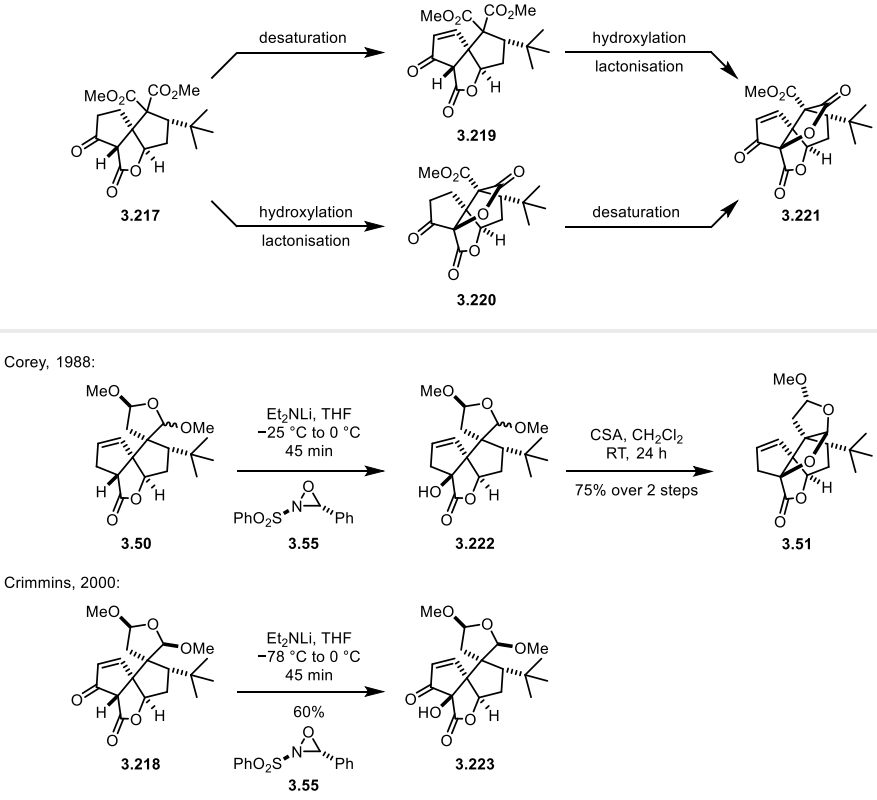
The Lemieux-Johnson oxidation of the *exo*-alkene in tricycle **3.150** gave cyclopentanone **3.217** in 75% yield (Scheme 3.41).[280] Cyclopentanone **3.217** was a solid with a high melting point (**m.p.** 163–164 °C), which was crystallised to give X-ray quality crystals. The X-ray structure of cyclopentanone **3.217** (Scheme 3.41) confirmed the relative configuration of the four stereocentres in cyclopentanone **3.217** (C{1}, C{5}, C{6}, and C{8}) and, by extension, that of tricycle **3.150**. This agreed with the stereochemical assignment of tricycle **3.150** obtained through analysis of ^{1}H NMR NOESY (Figure 3.3, section 3.4.2.2).



Scheme 3.41 Results of the Lemieux-Johnson oxidation of tricycle **3.150** and X-ray crystal structure of cyclopentanone **3.217**. All hydrogen atoms except for C{5}–H, C{6}–H, and C{8}–H omitted for clarity.

3.4.2.11 Construction of ring E

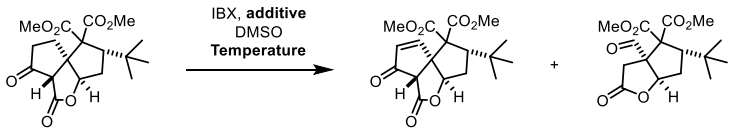
The next two steps in the synthesis required the desaturation of the cyclopentanone ring in tricycle **3.217** and the construction of ring E through hydroxylation and lactonisation. This could be achieved through two equivalent sequences as detailed in Scheme 3.42. Both Corey[221] and Crimmins[222, 223] performed analogous hydroxylations by treating a lithium enolate with Davis oxaziridine (Scheme 3.42). In Crimmins' case,[222, 223] the substrate of this hydroxylation was cyclopentenone **3.218**, a compound with high structural similarity to cyclopentenone **3.219**. Informed by this precedent, the sequence involving the hydroxylation of cyclopentenone **3.219** was investigated first.



Scheme 3.42 Potential routes for the construction of ring E and relevant precedent in Corey and Crimmins' work. [221-223]

Efforts were focused on the desaturation of cyclopentanone **3.217** to yield cyclopentenone **3.219**. This transformation could be achieved, for example, through an

IBX-mediated oxidation. Nicolaou first reported this transformation,[281] which is a one-step alternative to other dehydrogenation procedures, such as the Saegusa-Ito oxidation[282] or selenoxide elimination.[283, 284] The authors described the effect ligands such as PTSA, MPO, and NMO had on the performance of IBX. Specifically, MPO enhanced the reactivity of IBX towards dehydrogenation reactions and allowed this transformation to occur at room temperature.[281]



3.217 3.219 3.224

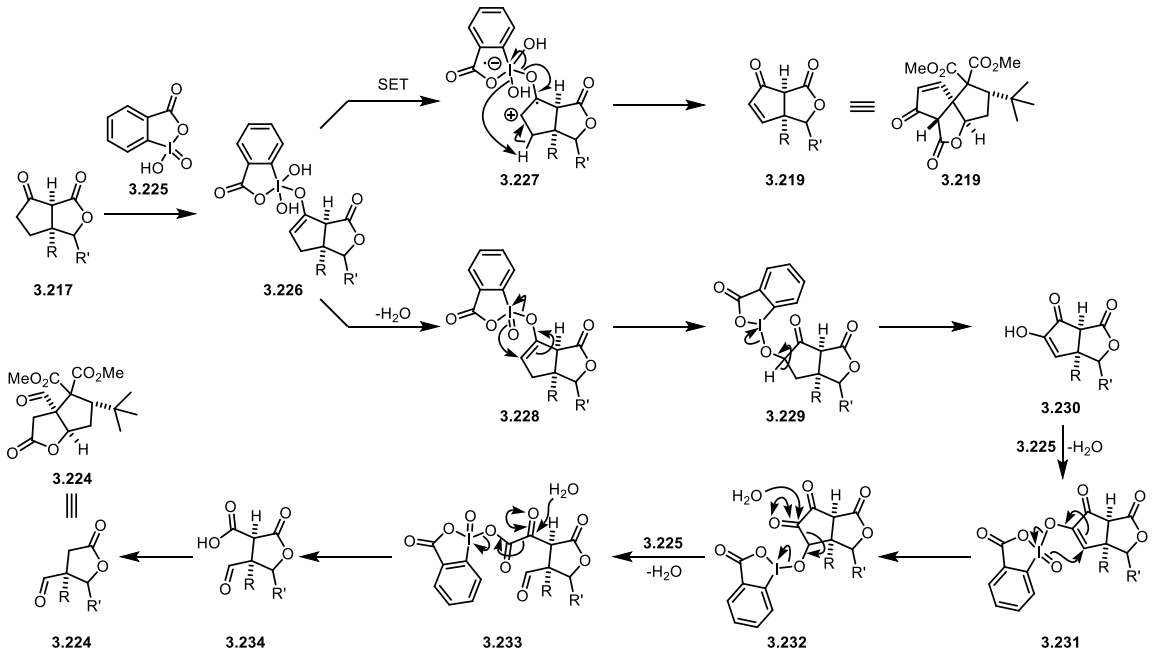
Entry	Equiv. IBX	Ligand (equiv.)	T, time	Yield of 3.219/%[a]	Yield of 3.224/%[a]	Remaining 3.217/%[a]
1	2.0	–	85 °C, 18 h	<5	0	60
2	2.0	PTSA (1.0)	85 °C, 18 h	5	0	45
3	4.0	MPO·H_2O (4.0)	50 °C, 18 h	34	20	4
4	4.0	MPO·H_2O (4.0)	RT, 18 h	12	0	40
5	2.5	MPO·H_2O (2.5)	50 °C, 18 h	31	12	20
6	1.2	MPO·H_2O (1.2)	50 °C, 18 h	16	4	59
7	3.0	NMO (3.0)	80 °C, 18 h	71	7	2
8[b]	3.0	NMO (3.0)	80 °C, 18 h	72[c]	–	–

Table 3.12 Results of the IBX dehydrogenation of **3.217**. *Reagents and conditions:* **3.217** (0.020 mmol), IBX, ligand, DMSO (0.10 M). [a] Calculated yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Reaction performed on 0.20 mmol scale; [c] Isolated yield.

The IBX dehydrogenation of tricycle **3.217** was therefore investigated (Table 3.12). Treatment of tricycle **3.217** with IBX following Nicolaou's method gave trace amounts of enone **3.219** (<5%) together with remaining starting material (entry 1).[281] Next, PTSA, MPO and NMO were screened as ligands. The addition of PTSA did not alter the reaction outcome (entry 2), whereas MPO significantly improved product formation (entries 3–6).

Treatment of tricycle **3.217** with 4 equivalents of IBX and MPO at 50 °C gave product **3.219** in 34% yield with almost complete consumption of starting material **3.217**. However, this was accompanied by the formation of aldehyde **3.224** in 20% yield (entry 3).

The cleavage to yield side product **3.224** was unprecedented in the literature and may have occurred due to the ring strain of tricycle **3.217**. Subjecting enone **3.219** to the reaction conditions did not yield any aldehyde **3.224**, showing that this side product did not derive from the intended reaction product **3.219**. A possible mechanism of its formation is summarised in Scheme 3.43.



Scheme 3.43 Mechanism of the dehydrogenation of cyclopentanone **3.217** with IBX (**3.225**) to give cyclopentenone **3.219**,[281] and possible mechanism for the formation of aldehyde **3.224**.

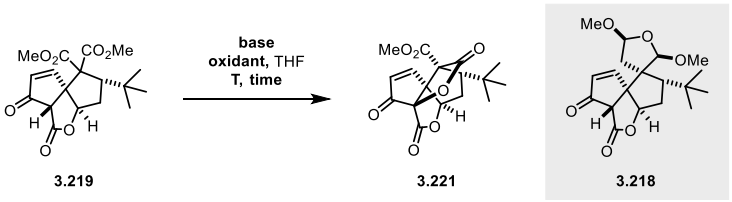
The conversion of cyclopentanone **3.217** into aldehyde **3.224** could begin with an α-hydroxylation and alcohol oxidation to yield hydroxy enone **3.230** (Scheme 3.43). These transformations are known reactions mediated by IBX.[281, 285] Then, a second oxidation

could give λ^3-iodane **3.232**. Addition of water to this electrophilic 1,2-dicarbonyl compound (**3.232**) would result in a C–C bond cleavage to give aldehyde **3.233** and release of 2-iodobenzoic acid. The resulting carboxylic acid could be oxidatively decarboxylated with another equivalent of IBX (**3.225**) to give acid **3.234**. Decarboxylation of acid **3.234** could then give the isolated aldehyde **3.224**.

Reducing the amount of IBX/MPO or lowering the reaction temperature did not improve the reaction outcome, instead resulting in worse yields of cyclopentenone **3.219** and concomitant formation of aldehyde **3.224** (entries 4–6). Replacement of MPO for NMO significantly improved product yield and minimised formation of aldehyde **3.224** (entry 7). This agreed with Nicolaou's reports, which described the modulation of the selectivity of IBX oxidations through ligand selection.[281] The optimised reaction conditions (entry 7), involving treatment of tricycle **3.217** with 3 equivalents of IBX and NMO, gave cyclopentenone **3.219** in 72% isolated yield on a 0.20 mmol scale.

The hydroxylation of cyclopentenone **3.219** was investigated next (Table 3.13). This transformation closely resembled that of Crimmins and co-workers (performed on cyclopentenone **3.218**), hence their conditions were chosen as a starting point for this optimisation.[222, 223] This involved deprotonation of β-ketoester **3.219** with $LiNEt_2$, a smaller lithium amide than LDA, and treatment of the lithium enolate with Davis oxaziridine (**3.55**). Under these conditions, lactone **3.221** did not form and enone **3.219** was recovered (Table 3.13, entry 1). When NaHMDS or KHMDS were used as the base, small amounts of lactone **3.221** were detected by ^{1}H NMR together with residual starting material and several unidentified side products (entries 2, 3). Pure lactone **3.221**, however, could not be isolated from this mixture due to its coelution with species derived from Davis oxaziridine (**3.55**). Alternative oxidants, such as oxygen or DMDO were then

explored. Treatment of enone **3.219** with KOtBu and oxygen did not yield any lactone **3.221**, instead causing extensive decomposition (entry 4). DMDO did not give any desired product **3.221** (entries 5, 6).



Entry	Base (equiv.)	Oxidant (equiv.)	T, time	Yield of 3.221/%[a]	Remaining 3.219/%[a]
1	$LiNEt_2$ (1.5)	**3.55** (3.0)	−78 °C to 0 °C, 4 h	0	>60
2	NaHMDS (1.5)	**3.55** (3.0)	−50 °C to 0 °C, 4 h	<5	25
3	KHMDS (1.5)	**3.55** (3.0)	−50 °C to 0 °C, 4 h	<5	13
4[b]	KOtBu (2.0)	O_2 (balloon)	RT, 2 h	0	34
5	NaHMDS (2.0)	DMDO (3.0)	−50 °C to 0 °C, 2 h	0	46
6	TBAF (2.0)	DMDO (4.0)	RT, 18 h	0	92

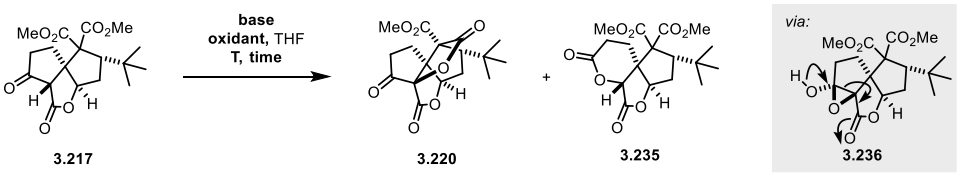
Table 3.13 Results of the attempted hydroxylation of cyclopentenone **3.219**. *Reagents and conditions:* **3.219** (0.05 mmol), base, oxidant, THF (0.05 M), T, time. [a] Calculated yield by ^{1}H NMR using dimethyl sulfone as internal standard; [b] $P(OEt)_3$ was added to the reaction mixture after 2 h and the resulting solution allowed to stir for 1 h at RT before work-up.

Despite the apparent structural similarities between enones **3.219** and **3.218**, the hydroxylation of enone **3.219** to yield lactone **3.221** was unsuccessful.[222, 223] The steric bulk of the malonate in enone **3.219**, which under the hydroxylation conditions would be coordinated to Li^+, Na^+ or K^+ ions, may be responsible for this difference in reactivity.

Consequently, an alternative sequence involving hydroxylation of cyclopentanone **3.217** and subsequent dehydrogenation was explored (Scheme 3.42). Compared to enone **3.219**, cyclopentanone **3.217** had an additional enolisable position on the cyclopentanone ring,

but we hypothesised regioselectivity could be achieved through optimisation of the reaction conditions.

Treatment of cyclopentanone **3.217** with LDA and Davis oxaziridine (**3.55**) did not yield desired lactone **3.220**, instead, it returned starting material **3.217** and several unidentified side products (Table 3.14, entry 1). In the presence of KHMDS, extensive decomposition occurred and no product **3.220** was detected (entry 2). Neither DMDO nor oxygen improved the reaction outcome. Treatment of cyclopentanone **3.217** with DMDO gave the product of formal Baeyer-Villiger oxidation **3.235**, which may have formed *via* ring-opening of epoxide **3.236** (entry 3), while subjection of the potassium enolate of cyclopentanone **3.217** to an oxygen atmosphere yielded starting material **3.217** (entry 4). Ultimately, the oxidation of enolates derived from cyclopentanone **3.217** did not seem a viable approach for the construction of ring E.

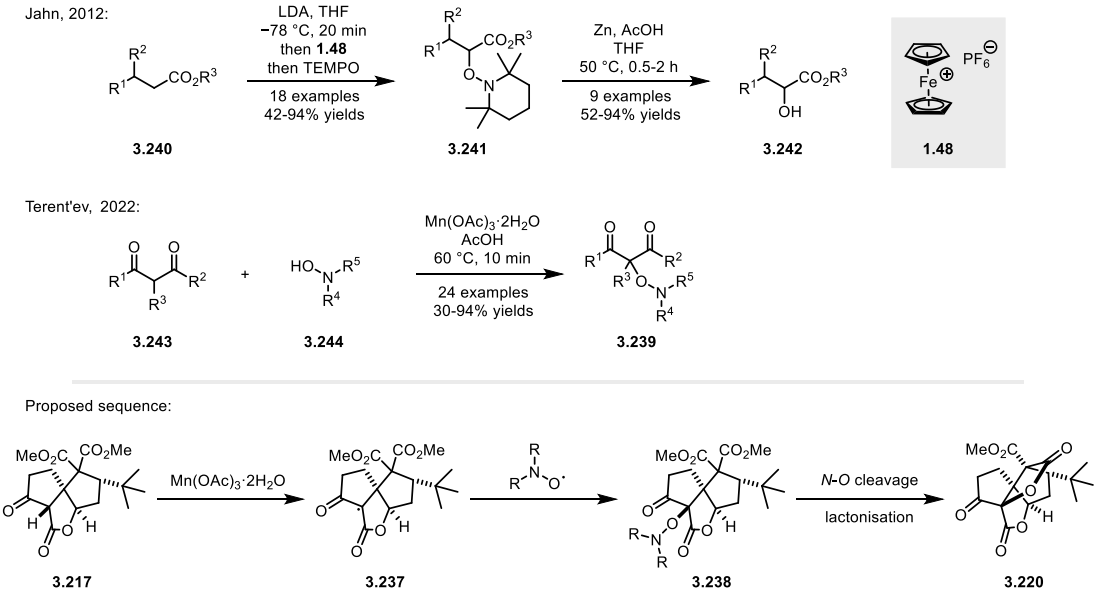


Entry	Base (equiv.)	Oxidant (equiv.)	T, time	Yield of 3.220/%[a]	Yield of 3.235/%[a]	Remaining 3.217/%[a]
1	LDA (1.25)	**3.55** (1.25)	−78 °C to 0 °C, 4 h	0	0	50
2	KHMDS (1.25)	**3.55** (1.25)	−78 °C to 0 °C, 4 h	0	0	<5
3	TBAF (5.0)	DMDO (4.0)	RT, 18 h	0	41[b]	<5
4	KHMDS (1.25)	O_2 (balloon)	0 °C, 4 h	0	0	>80

Table 3.14 Results of the attempted hydroxylation of cyclopentanone **3.217**. *Reagents and conditions:* **3.217** (0.05 mmol), base, oxidant, THF (0.05 M), T, time. [a] Calculated yield by ^{1}H NMR using dimethyl sulfone as internal standard; [b] Isolated yield.

Alternatively, we envisioned a two-step sequence based on the recombination of radical **3.237** and an oxyl radical, such as TEMPO (Scheme 3.44). Oxidation of tricycle **3.217**

with $Mn(OAc)_3$ would generate radical **3.237**, which after recombination with an oxyl radical would yield alkoxyamine **3.238**. *N–O* bond cleavage and lactonisation would then give the desired tetracycle **3.220**. This strategy was inspired by work by Jahn[41] and Terent'ev.[286, 287] Jahn described the two-step α-hydroxylation of carbonyl compounds *via* oxidation of lithium enolates with ferrocenium hexafluorophosphate (**1.48**), recombination with TEMPO and zinc-mediated *N–O* bond cleavage (Scheme 3.44).[41] Terent'ev reported an equivalent method to generate alkoxyamines **3.239** using $Mn(OAc)_3$ as the stoichiometric oxidant.[286, 287]

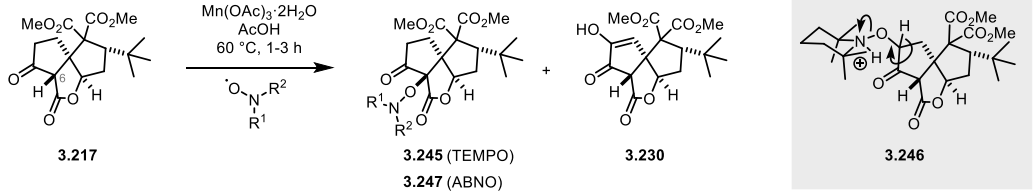


Scheme 3.44 Jahn's method for synthesis of α-hydroxyesters[41] and Terent'ev's $Mn(OAc)_3$-mediated reaction of 1,3-dicarbonyl compounds with hydroxylamines.[286, 287] Proposed sequence for their application to the construction of ring E in ginkgolide B.

Tricycle **3.217** was therefore treated with $Mn(OAc)_3$ and TEMPO (Table 3.15). This did not provide TEMPO adduct **3.245**, but instead yielded hydroxyenone **3.230** (entry 1). We hypothesise this was formed *via* Kornblum-DeLaMare-like rearrangement of TEMPO adduct **3.246**, which was preferentially formed due to the steric hindrance around C{6} in tricycle **3.217**. Replacement of TEMPO with the less sterically-hindered oxyl radical

ABNO gave an entirely different reaction outcome; under these conditions, the desired alkoxyamine **3.247** was obtained in 86% isolated yield (entry 2). This reaction could be scaled up without detrimental effects on yield (entry 3).

In the absence of $Mn(OAc)_3 \cdot 2H_2O$, and contrary to our initial proposed reaction mechanism (Scheme 3.44), alkoxyamine **3.247** was still formed but in lower yield (30%, entry 4). The yield increased to 63% when tricycle **3.217** was treated with 2.4 equivalents of ABNO (entry 5).

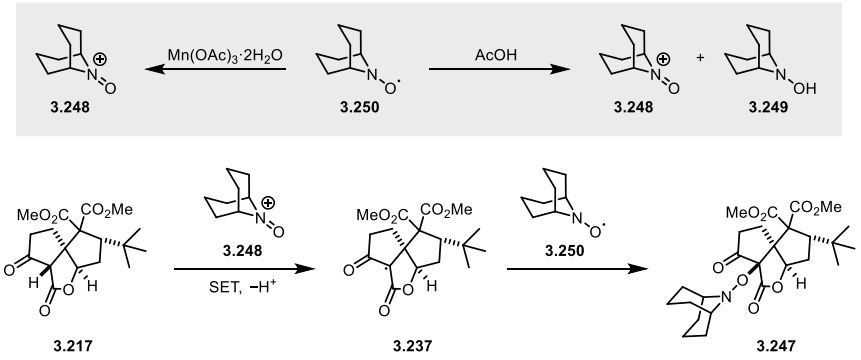


Entry	R^1R^2NO (equiv.)	Yield of 3.245 or 3.247/%[a]	Yield of 3.230/%[a]
1	TEMPO (1.2)	0	46
2	ABNO (1.2)	86	0
3[b]	ABNO (1.2)	84	0
4[c]	ABNO (1.2)	30	0
5[c]	ABNO (2.4)	63	0

Table 3.15 Results of the $Mn(OAc)_3$-mediated alkoxyamination of tricycle **3.217**. *Reagents and conditions:* **3.217** (0.02 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (1.2 equiv.), TEMPO or ABNO, AcOH, 60 °C, 1–3 h. [a] Isolated yield; [b] Reaction performed on 0.10 mmol of tricycle **3.217**; [c] Reaction performed without $Mn(OAc)_3 \cdot 2H_2O$.

The successful formation of alkoxyamine **3.247** in the absence of $Mn(OAc)_3$ (Table 3.15, entries 4, 5) pointed to an oxoammonium-based reaction mechanism, illustrated in Scheme 3.45. We hypothesise that in the presence of $Mn(OAc)_3$, ABNO is oxidised to yield oxoammonium salt **3.248**. Repo et al. described similar oxidations of aminoxyl radicals with Mn(III) for the oxidation of alcohols to aldehydes.[288] Subsequently, a single electron transfer (SET) between oxoammonium **3.248** and tricycle **3.217** could yield radical **3.237**, which after recombination with ABNO would give the desired alkoxyamine

3.247. Alternatively, oxoammonium **3.248** could react with the enol of cyclopentanone **3.217**, giving the same product *via* an ionic mechanism. In the absence of $Mn(OAc)_3$, ABNO could disproportionate into oxoammonium **3.248** and hydroxylamine **3.249** and provide product **3.247** *via* the same mechanism. The disproportionation of aminoxyl radicals such as TEMPO or ABNO under acidic conditions is well precedented.[289-291] The product yields obtained when the reaction was performed without $Mn(OAc)_3$ and with increasing amounts of ABNO (entries 4, 5) were in agreement with this proposed disproportionation event.

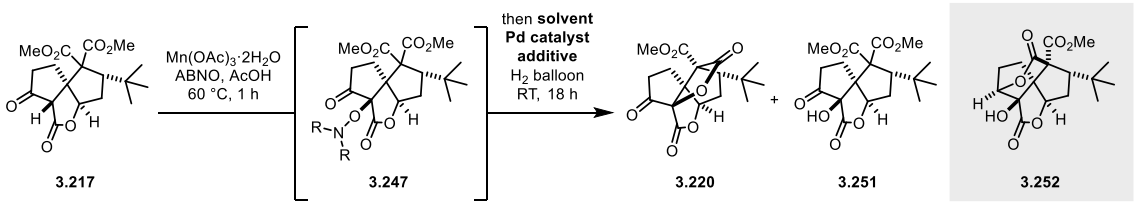


Scheme 3.45 Proposed mechanism for the formation of alkoxyamine **3.247**.

The *N–O* bond cleavage of alkoxyamine **3.247** to yield lactone **3.220** was then investigated. This transformation was optimised as a one-pot procedure from tricycle **3.217** (Table 3.16).

Tricycle **3.217** was thus converted into alkoxyamine **3.247** and the reaction mixture subjected to reductive *N–O* cleavage conditions in the presence of Pd/C and a hydrogen atmosphere. This gave alcohol **3.251** in 34% yield together with several unidentified side products (Table 3.16, entry 1). No lactonisation of alcohol **3.251** to yield lactone **3.220** was observed. The addition of THF or MeOH in the hydrogenation step did not improve the reaction outcome, instead precluding *N–O* cleavage and returning starting material

(entries 2, 3). Replacing Pd/C with Pearlman's catalyst ($Pd(OH)_2$) did not provide alcohol **3.251** or lactone **3.220** but instead gave lactone **3.252**, the product of *N*–*O* cleavage and cyclopentanone reduction (entry 4). The addition of aqueous HCl to the hydrogenation mixture significantly improved the reaction outcome, likely due to protonation of alkoxyamine **3.247**. Under these conditions and in the presence of either Pd/C or Pearlman's catalyst, full conversion was achieved and product **3.251** was obtained in 73% and 69% yield, respectively (entries 6, 7).



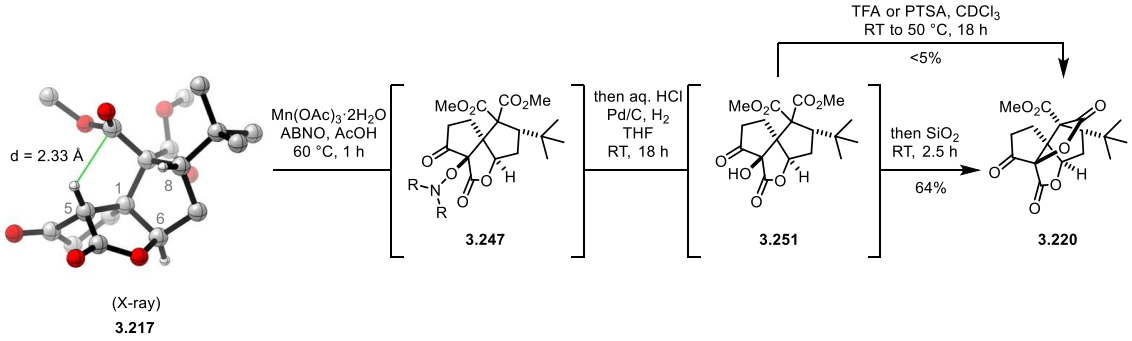
Entry	Added solvent	Pd catalyst	Additive	Yield of 3.220/%[a]	Yield of 3.251/%[a]	Remaining 3.247/%[a]
1	–	Pd/C	–	0	34	<5
2	THF	Pd/C	–	0	0	62
3	MeOH	Pd/C	–	0	0	25
4[b]	MeOH	$Pd(OH)_2/C$	–	0	0	<5
5	MeOH	$Pd(OH)_2/C$	2 M aq. HCl	0	52	<5
6	THF	Pd/C	2 M aq. HCl	0	73	<5
7	THF	$Pd(OH)_2/C$	2 M aq. HCl	0	69	<5

Table 3.16 Results of the one-pot alkoxyamination of tricycle **3.217** and reductive *N*–*O* cleavage to give tetracycle **3.220**. *Reagents and conditions:* **3.217** (0.02 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (1.2 equiv.), ABNO (1.2 equiv.), AcOH, 60 °C, 1 h, then solvent, Pd catalyst (1.2 equiv.), additive, H_2 balloon, RT, 18 h. [a] Calculated yield by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Tetracycle **3.252** isolated in 47% yield.

Despite the improvements in the *N*–*O* cleavage reaction, the product of this transformation was always alcohol **3.251**, not the desired lactone **3.220**. This was unexpected after examination of the X-ray crystal structure of tricycle **3.217**, which showed a 2.33 Å distance between C{5}–H and the malonate carbonyl (Scheme 3.46).

Alcohol **3.251** would likely have a similar conformation and thus C{5}–OH and the malonate carbonyl would be in close proximity.

Experiments on the lactonisation of alcohol **3.251** showed that this reaction was very slow in $CDCl_3$, and acids such as TFA or PTSA did not significantly accelerate it (Scheme 3.46). However, alcohol **3.251** could not be obtained pure after column chromatography due to small amounts of lactone **3.220** being present. 2D TLC showed that alcohol **3.251** was indeed unstable in silica, decomposing into the desired product lactone **3.220**. This finding allowed the one-pot conversion of tricycle **3.217** into tetracycle **3.220** in 64% isolated yield by the addition of silica gel post hydrogenolysis.

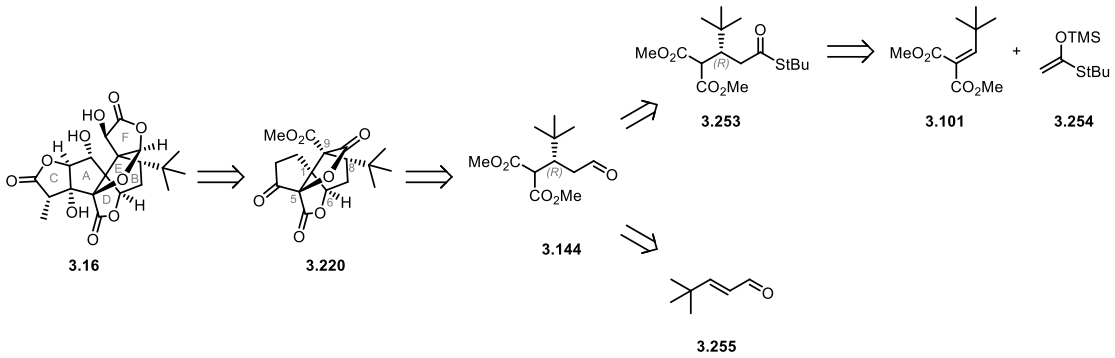


Scheme 3.46 One-pot synthesis of tetracycle **3.220** from tricycle **3.217** *via* alkoxyamination, *in situ* *N*–*O* cleavage and silica-promoted lactonisation. X-ray crystallography of tricycle **3.217**. All hydrogen atoms except for C{5}–H, C{6}–H, and C{8}–H omitted for clarity.

Due to time constraints, further steps towards ginkgolide B were not explored. Nevertheless, the route developed here gave access to the tetracyclic core of ginkgolide B (**3.220**), containing rings A, B, D, and E of the natural product. This route is nine steps long (LLS) from pivaldehyde and builds the spirocyclic framework *via* a novel oxidative malonyl radical cascade.

3.4.3 Asymmetric aldehyde synthesis

The synthetic route to the tetracyclic core of ginkgolide B (**3.220**) could be rendered asymmetric if aldehyde **3.144** was prepared in enantiopure form. The stereochemical configuration of the *tert*-butyl group in aldehyde **3.144** would dictate the absolute configuration of C{1}, C{5}, C{6}, C{8}, and C{9} in tetracycle **3.220**. Therefore, strategies for the asymmetric synthesis of aldehyde **3.144** were investigated and are summarised in Scheme 3.47.



Scheme 3.47 Strategies for the asymmetric synthesis of aldehyde **3.144**.

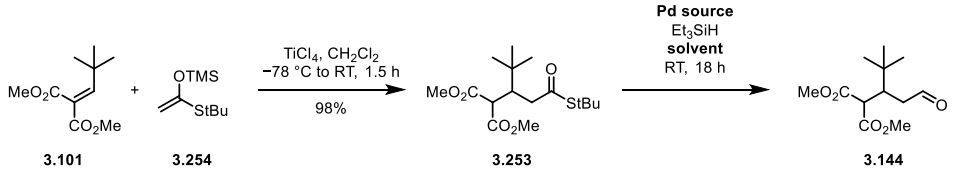
The approach with the best precedent in the literature was the synthesis of aldehyde **3.144** from alkylidene malonate **3.101** through an asymmetric Mukaiyama-Michael addition[292] and subsequent Fukuyama reduction.[293, 294] Evans and co-workers used this route to prepare thioester **3.253** in 89% yield and 90% e.e. through the Cu(II)-catalysed asymmetric addition of silyl enol ether **3.254** to alkylidene malonate **3.101**.[292] However, the Fukuyama reduction of *tert*-butyl thioesters was reported to be challenging and would require extensive optimisation.[293, 294]

Alternatively, the asymmetric Michael addition of dimethyl malonate to α,*β*-unsaturated aldehyde **3.255** could also provide aldehyde **3.144** in enantioenriched form. Hayashi-Jørgensen type catalysts were previously used to enable such transformations, albeit not with α,*β*-unsaturated aldehydes with groups as bulky as *tert*-butyl.[295-302] The steric

hindrance of the *tert*-butyl group was therefore likely to be the main challenge in the development of this transformation.

3.4.3.1 Mukaiyama-Michael route

Employing Evans' conditions, we envisaged that thioester **3.253** could be obtained in good yield and enantioselectivity; however, precedent for the Fukuyama reduction of *tert*-butyl thioesters was scarce.[293, 294] To probe the viability of this sequence, efforts were therefore focused on the reduction of racemic thioester **3.253**.



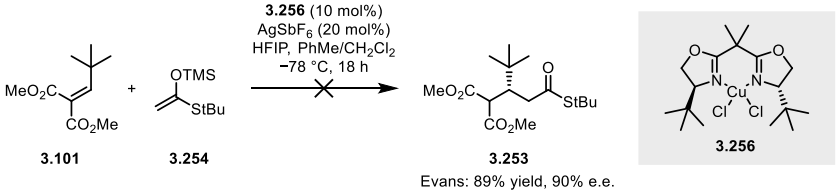
Entry	Pd source (equiv.)	Equiv. Et_3SiH	Solvent	Yield of 3.144/%[a]
1	Pd/C (5)	15	CH_2Cl_2	30
2	Pd/C (5)	15	acetone	10
3	Pd/C (1)	15	CH_2Cl_2	0
4	$Pd(OAc)_2$ (0.2)	5.0	acetone	50
5	$Pd(OAc)_2$ (0.2)	5.0	CH_2Cl_2	15
6	$Pd(OAc)_2$ (0.2)	5.0	acetone	98[b]

Table 3.17 Synthesis of thioester **3.253** and results of its Fukuyama reduction. *Reagents and conditions:* **3.253** (0.05 mmol), Pd source, Et_3SiH, solvent (0.05 M), RT, 18 h. [a] Calculated yield by ^1H NMR using dimethyl sulfone as internal standard; [b] Isolated yield.

Thioester **3.253** was obtained in 98% isolated yield from alkylidene **3.101** through a $TiCl_4$-mediated Mukaiyama-Michael addition.[292] The Fukuyama reduction of thioester **3.253** was then investigated (Table 3.17). In the presence of superstoichiometric amounts of Pd/C and triethylsilane, aldehyde **3.144** was obtained in poor yields, both in CH_2Cl_2 and acetone (entries 1, 2). No conversion was detected when the amount of Pd/C was reduced to 1 equivalent (entry 3). The use of $Pd(OAc)_2$, which upon treatment with Et_3SiH gave a fine suspension of palladium black, significantly improved product formation and gave

aldehyde **3.144** in up to 50% yield (entries 4, 5). Upon scale-up of these conditions, the yield of the reduction further improved, giving desired aldehyde **3.144** in 98% isolated yield (entry 6). The results of this optimisation confirmed thioester **3.253** could be used towards the synthesis of ginkgolide B after its reduction to aldehyde **3.144**.

We then attempted the Mukaiyama-Michael addition developed by Evans and co-workers to give enantioenriched thioester **3.253**,[292] albeit without success (Scheme 3.48). Unreacted alkylidene malonate **3.101** was recovered after the reaction, implying deactivation of the Cu(II) catalyst. This catalyst system is highly sensitive to oxygen and moisture,[292] and without access to a glovebox the reported conditions could not be reproduced. Alternative asymmetric routes to aldehyde **3.144** were thus prioritised.

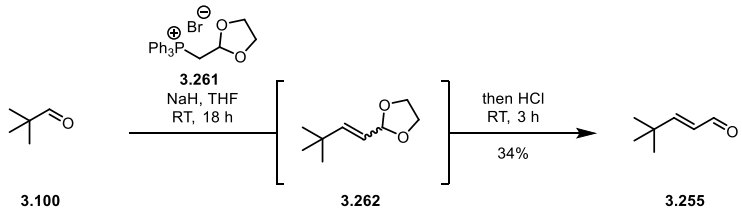


Scheme 3.48 Attempt to reproduce Evans' enantioselective Mukaiyama-Michael addition of silyl enol ether **3.254** to alkylidene malonate **3.101**.[292]

3.4.3.2 Organocatalysed Michael addition route

The organocatalysed Michael addition of dimethyl malonate to aldehyde **3.255** could provide the required aldehyde **3.144** in enantioenriched form. Proline derived catalysts, such as Hayashi-Jørgensen type catalysts **3.257**, **3.258**, **3.259**, and **3.260** were used in similar transformations of α,β-unsaturated aldehydes, for example, by Jørgensen,[296] Ma,[298] and Pfaltz.[299]

Aldehyde **3.255** was prepared from pivaldehyde **3.100** in a single step, using acetonide-containing phosphonium salt **3.261** (Scheme 3.49). The yield of this reaction was moderate but due to time constraints it was not optimised.



Scheme 3.49 Synthesis of α,*β*-unsaturated aldehyde **3.255**.

Before optimising the conjugate addition of dimethyl malonate to α,*β*-unsaturated aldehyde **3.255**, analytical methods were developed for the measurement of product yield and enantiomeric excess. Product yields were calculated *via* ^{1}H NMR analysis with an internal standard (1,3,5-trimethoxybenzene). Nonetheless, the measurement of the enantiomeric excess of aldehyde **3.144** by HPLC was unsuccessful because it decomposed under chromatographic conditions. Consequently, alternative analytical methods to measure the e.e. of aldehyde **3.144** were required. Initially, enantiomeric excesses were measured by ^{1}H NMR analysis after the addition of the chiral shift reagent Eu(hfc)$_3$ (Figure 3.4).[303] More accurate measurements were then obtained through chiral HPLC analysis after derivatisation of aldehyde **3.144** to the DNP hydrazone **3.263**.

With analytical methods for the quick measurement of yield and enantiomeric excess of aldehyde **3.144**, the Michael addition of dimethyl malonate to α,*β*-unsaturated aldehyde **3.255** was optimised (Table 3.18).

A solvent screen employing TES catalyst **3.259** as the organocatalyst showed that H_2O, THF and CH_2Cl_2 gave higher yields of aldehyde **3.144** than toluene, MeCN, and MeOH (entries 1–12). Yields were poor and dependent on the additive present: NaOAc improved

the reaction outcome in H_2O and CH_2Cl_2 (entries 8, 12), while benzoic acid increased yields of aldehyde **3.144** in THF (entry 9). Nonetheless, these reactions were highly enantioselective, giving aldehyde **3.144** in e.e. higher than 95% (entries 8, 9, 12). Further optimisation showed that increasing the amount of dimethyl malonate significantly improved product yields and had no detrimental effect on the enantioselectivity of this transformation (entries 8, 13, 14).

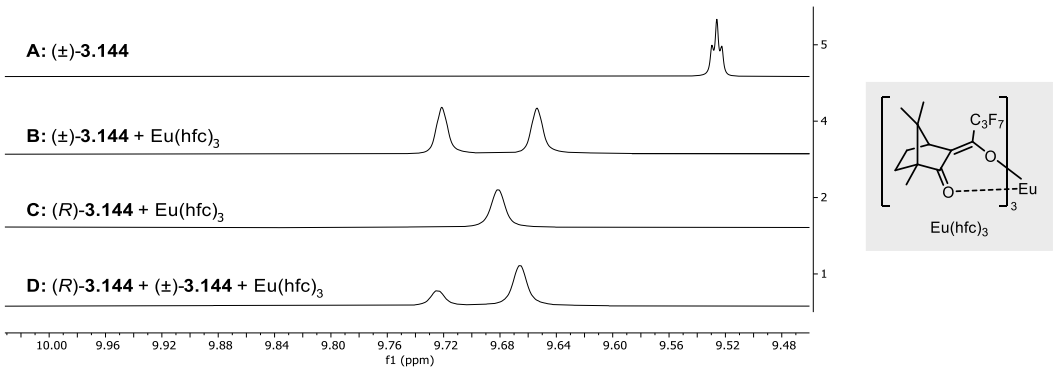
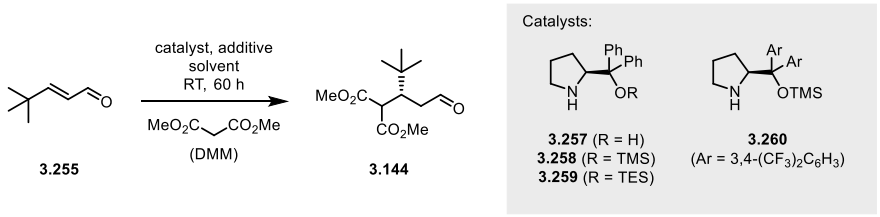


Figure 3.4 Excerpts of the ^{1}H NMR (400 MHz, C_6D_6) spectra of samples of aldehyde **3.144** with and without Eu(hfc)$_3$. **A**: (±)-**3.144**; **B**: (±)-**3.144** + *ca.* 1 equiv. Eu(hfc)$_3$; **C**: (*R*)-**3.144** + *ca.* 1 equiv. Eu(hfc)$_3$; **D**: (*R*)-3.148 + *ca.* 0.10 equiv. (±)-**3.144** + *ca.* 1 equiv. Eu(hfc)$_3$.

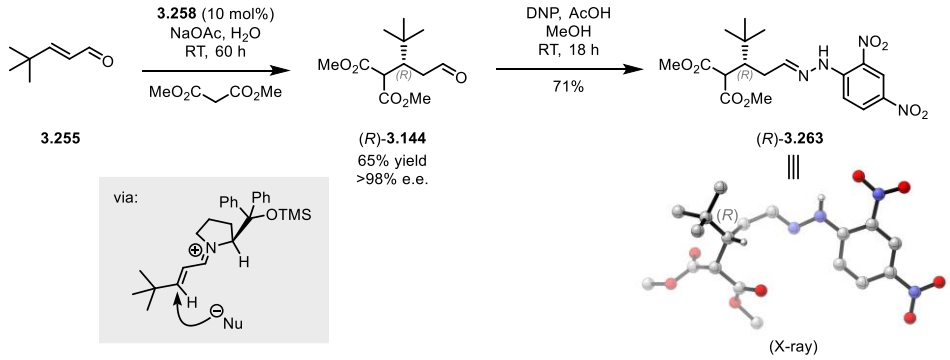
The yield of aldehyde **3.144** and its enantiomeric excess were dependent on the structure of the organocatalyst used (entries 13, 15–17). Prolinol **3.257** gave lower yields and enantioselectivities compared to TES catalyst **3.259** (entries 13, 15), while TMS catalyst **3.258** performed slightly better (entry 16). CF_3-Containing catalyst **3.260** provided aldehyde **3.144** in poor yields and moderate enantioselectivity (entry 17). TMS catalyst **3.258** was thus the optimal catalyst for this transformation, yielding aldehyde **3.144** in 60% yield and 98% e.e. when used in 10 mol% loading and increased reaction concentration (entry 18). Further increasing the catalyst loading did not improve the reaction outcome (entry 19).



Entry	Equiv. DMM	Cat.	Solvent (conc./M)	Additive	Yield of 3.144/%[a]	e.e./%[b]
1	2.0	**3.259**	PhMe (0.50)	$PhCO_2H$	11	–
2	2.0	**3.259**	PhMe (0.50)	NaOAc	12	–
3	2.0	**3.259**	MeCN (0.50)	$PhCO_2H$	10	–
4	2.0	**3.259**	MeCN (0.50)	NaOAc	11	–
5	2.0	**3.259**	MeOH (0.50)	$PhCO_2H$	16	–
6	2.0	**3.259**	MeOH (0.50)	NaOAc	9	–
7	2.0	**3.259**	H_2O (0.50)	$PhCO_2H$	13	–
8	2.0	**3.259**	H_2O (0.50)	NaOAc	22	95[c]
9	2.0	**3.259**	THF (0.50)	$PhCO_2H$	20	>95[c]
10	2.0	**3.259**	THF (0.50)	NaOAc	8	–
11	2.0	**3.259**	CH_2Cl_2 (0.50)	$PhCO_2H$	9	–
12	2.0	**3.259**	CH_2Cl_2 (0.50)	NaOAc	23	>95[c]
13	3.0	**3.259**	H_2O (0.50)	NaOAc	51	>95[c]
14	5.0	**3.259**	H_2O (0.50)	NaOAc	60	>95[c]
15	3.0	**3.257**	H_2O (0.50)	NaOAc	33	52
16	3.0	**3.258**	H_2O (0.50)	NaOAc	59	98
17	3.0	**3.260**	H_2O (0.50)	NaOAc	12	83
18	5.0	**3.258**	H_2O (1.0)	NaOAc	60	98
19	5.0	**3.258**[d]	H_2O (1.0)	NaOAc	61	98
20[e]	5.0	**3.258**	H_2O (1.0)	NaOAc	65[f]	>98

Table 3.18 Results of the optimisation of the organocatalysed Michael addition of dimethyl malonate onto α,*β*-unsaturated aldehyde **3.255**. *Reagents and conditions:* **3.255** (0.05 mmol), dimethyl malonate (DMM), catalyst (10 mol%), additive (30 mol%), solvent, RT, 60 h. [a] Calculated yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] Enantiomeric excess measured by HPLC after derivatisation of aldehyde **3.144** to the DNP hydrazone **3.263**; [c] Enantiomeric excess measured by ^{1}H NMR after the addition of $Eu(hfc)_3$ (*ca.* 1.0 equiv.); [d] Reaction performed with 20 mol% catalyst; [e] Reaction performed on 0.66 mmol scale; [f] Isolated yield.

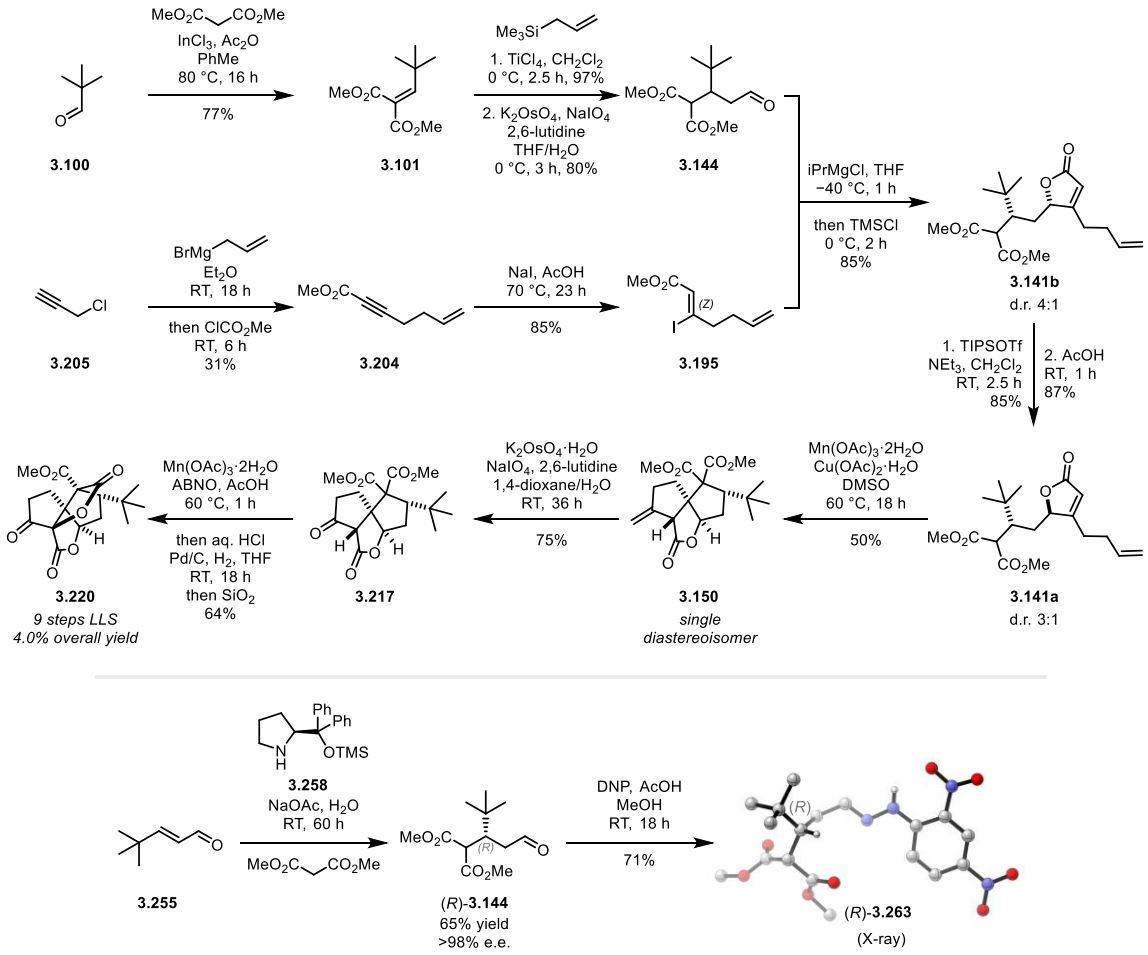
Employing these optimised conditions (entry 18), the Michael addition was performed on a 0.66 mmol scale and provided aldehyde **3.144** in 65% yield and >98% enantiomeric excess (Scheme 3.50). Aldehyde **3.144** was then derivatised to the DNP hydrazone **3.263** and an X-ray crystal structure was obtained, which confirmed the absolute configuration of aldehyde **3.144** as (*R*). This stereochemical configuration agreed with the stereoinduction model depicted in Scheme 3.50[301] and provided the requisite stereochemistry configuration to ultimately synthesise (−)-ginkgolide B.



Scheme 3.50 Enantioselective synthesis of aldehyde **3.144** and X-ray crystal structure of DNP hydrazone **3.263**. Hydrogen atoms omitted for clarity.

3.5 Conclusions

A nine-step route to the core of ginkgolide B (**3.220**), containing rings A, B, D and E of the natural product, has been developed (Scheme 3.51). This sequence used pivaldehyde as the starting material and employed a malonyl radical cascade as the key complexity-building reaction. Aldehyde **3.144**, an intermediate in this synthesis, was prepared in enantiopure form *via* an asymmetric organocatalysed Michael addition.



Scheme 3.51 Summary of the synthetic route to the core of ginkgolide B (**3.220**) and the organocatalysed enantioselective synthesis of aldehyde **3.144**.

The substrate of the key malonyl radical cascade, *γ*-butenolide **3.141a**, was prepared following chemistry developed by Knochel (Scheme 3.51).[270] This entailed the addition

of the Grignard reagent derived from vinyl iodide **3.195** to aldehyde **3.144**. Aldehyde **3.144**, in turn, was obtained from pivaldehyde after Knoevenagel condensation, Sakurai allylation and Lemieux-Johnson oxidation. Vinyl iodide **3.195** was synthesised in two steps from propargyl chloride after substitution with allylmagnesium bromide, acylation, and nucleophilic iodination.

The addition of the Grignard reagent derived from iodide **3.195** to aldehyde **3.144**, however, gave *γ*-butenolide **3.141b** with the wrong relative stereochemical configuration. Extensive experimentation was required to selectively epimerise *γ*-butenolide **3.141b** into *γ*-butenolide **3.141a**, which was ultimately achieved through a silylation-desilylation sequence.

A $Mn(OAc)_3$-mediated malonyl radical cascade gave tricycle **3.150** as a single diastereoisomer from *γ*-butenolide **3.141a**. This reaction built rings A and D of the natural product in a single step and set the relative configuration of four stereocentres. This was confirmed by X-ray crystallographic analysis of cyclopentanone **3.217**, obtained from the alkene cleavage of tricycle **3.150** (Scheme 3.41, section 3.4.2.10).

The tetracyclic core of ginkgolide B was obtained after construction of ring E through hydroxylation and lactonisation of cyclopentanone **3.217**. Conventional α-hydroxylation approaches were unsuccessful for this transformation, which required the development of a radical hydroxylation using ABNO and $Mn(OAc)_3$, inspired by work by Terent'ev[286, 287] and Jahn. [41]

Several strategies were explored to prepare aldehyde **3.144** in enantioenriched form, which would render this route towards ginkgolide B enantioselective. An organocatalysed enantioselective Michael addition was ultimately developed, giving aldehyde (*R*)-**3.144** in

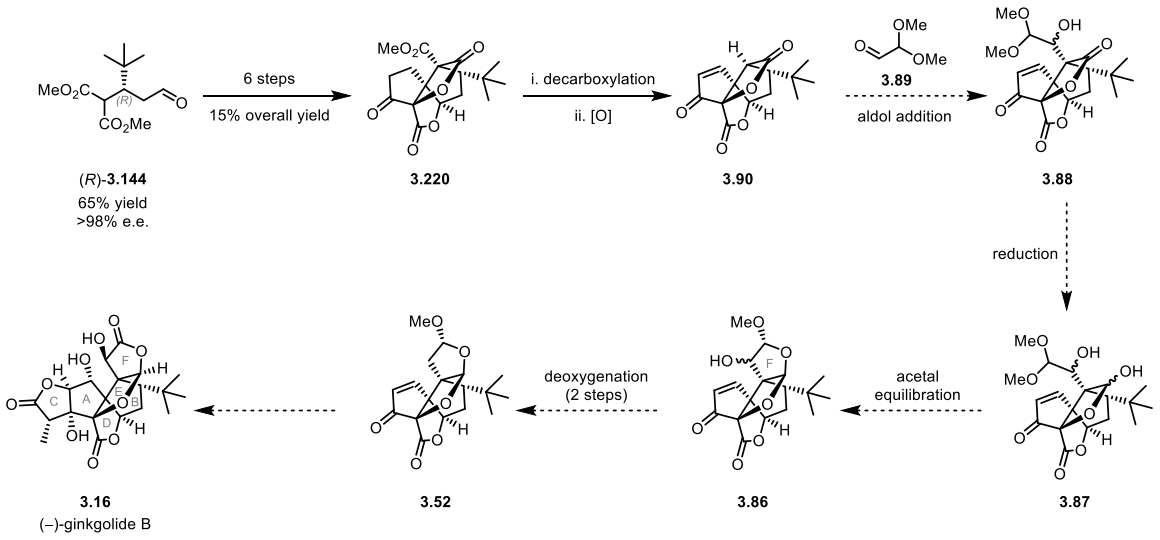
65% yield and >98% enantiomeric excess. This provided a proof-of-concept that the route developed here could be rendered enantioselective (Scheme 3.51). The absolute configuration of aldehyde **3.144** was confirmed through X-ray crystallographic analysis of DNP hydrazone (*R*)-**3.263**.

In conclusion, these studies build on previous work in the Burton group and offer a platform for the enantioselective synthesis of the tetracyclic core of ginkgolide B (**3.220**). This compound will, in the future, be used towards the formal synthesis of ginkgolide B.

3.6 Future work

These studies offered a scalable enantioselective route to the tetracyclic core of ginkgolide B (**3.220**). Future work towards the synthesis of the natural product will focus on the elaboration of tetracycle **3.220** into pentacycle **3.52**, an intermediate in Corey's total synthesis of ginkgolide B.[221] This would complete its asymmetric formal synthesis.

A seven-step sequence to construct ring F could deliver intermediate **3.52** from tetracycle **3.220** (Scheme 3.52). First, decarboxylation of methyl ester **3.220** and dehydrogenation would give cyclopentanone **3.90**. Alcohol **3.88**, in turn, could be obtained *via* aldol addition of lactone **3.90** to glyoxal dimethyl acetal **3.89**. We envisage a directed reduction such as an Evans-Saksena[228, 229] or Evans-Tischenko[230, 231] reaction would then allow for the selective formation of hemiacetal **3.87** from lactone **3.88**. Like Barriault,[224] this hemiacetal would then be equilibrated to build ring F, and alcohol **3.86** deoxygenated to give pentacycle **3.52**, the target of this formal synthesis.



Scheme 3.52 Future work towards the asymmetric formal synthesis of (−)-ginkgolide B.

Chapter 4 Experimental details

4.1 General experimental details

Solvents and reagents

All reactions were performed using flame-dried reaction vessels under an atmosphere of argon unless stated otherwise. Anhydrous diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), acetonitrile (MeCN), tetrahydrofuran (THF), and toluene (PhMe) were obtained from solvent dispenser units having been passed through an activated alumina column under argon. Methanol was dried over 4 Å molecular sieves under argon. Oxalyl chloride and pyrrole were distilled in an S-bend immediately before use. *N*-Bromosuccinimide was recrystallised from water before use. All other chemical reagents used were commercially available from Alfa Aesar, Fluorochem and Sigma-Aldrich and used as supplied.

Chromatography

Thin layer chromatography (TLC) was carried out using Merck aluminium-backed TLC Silica Gel 60 F254 pre-coated plates (particle size 0.2 mm). Plates were visualised by the quenching of fluorescence under ultraviolet light (λ_{max} = 254 nm) and by staining and heating with $KMnO_4$ or vanillin. Flash column chromatography was performed using Merck Geduran 60 silica gel (particle size 40–63 μm) with the solvent system given. HPLC analysis was performed on an Agilent 1200 series using a Daicel Chiralpak IA column

(4.6 mm × 250 mm, 5 μm). All solvents used for chromatography purification were HPLC grade or equivalent and supplied by Sigma Aldrich.

NMR spectroscopy

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on Bruker AVIII HD 400 nanobay (400/101/377 MHz), Bruker AVII 500 (500/126/471 MHz), and Bruker NEO 600 (600/151/565 MHz) spectrometers in deuterated solvents. ^{13}C and ^{19}F spectra were recorded with broadband decoupling. Chemical shifts (δ_H, δ_C, δ_F) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR and ^{19}F NMR and 0.1 ppm for ^{13}C NMR. ^{1}H and ^{13}C NMR spectra were referenced relative to the solvent residual peak. Peak assignments were made on the basis of chemical shifts, integrations, coupling constants, and comparison to known compounds, using COSY, HSQC, and HMBC experiments where appropriate. Multiplets are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or combinations thereof. Unassigned quaternary carbons are labelled as C{Q}. Coupling constants (*J*) are reported to the nearest 0.5 Hz.

Mass spectrometry

High resolution mass spectrometry (HRMS) was recorded by the staff of the Chemistry Research Laboratory Mass Spectrometry facilities using a Bruker MicroTOF spectrometer. The mass reported is that containing the most abundant isotopes, with each value to 4 or 5 decimal places and within 5 ppm of the calculated mass.

Infrared spectra

Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer as neat samples on the ATR diamond module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w), and broad (br).

Melting points

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

Optical rotations

Optical rotations were measured using a Perkin-Elmer 241 polarimeter in a 10 cm long path cell (l). Specific rotations are denoted as $[\alpha]^{25}_{D}$ and are calculated according to the formula: $[\alpha]^{25}_{D} = (100\alpha)/(lc)$, where α = observed rotation (°), l = path length (dm), c = concentration (g/100 mL).

Reporting of compounds

Systematic names were generated by the computer programme ChemDraw according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). However, the numbering on the structures may not correspond to the systematic name. The NMR assignments follow the numbering system shown on the structures for straightforward comparison of data.

Handling of light-sensitive compounds

Light-sensitive iodomalonates were prepared and handled with the fume hood light turned off. Reaction vessels and flash column chromatography apparatus were covered in aluminium foil during use. Where possible a tinted NMR tube was used to record NMR spectra.

4.2 General experimental procedures

General Procedure A: Synthesis of iodomalonates

To a solution of the malonate (1.0 equiv.) in dry degassed (3 × freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) cooled to −78 °C was added dropwise NaHMDS (1.0 M in THF, 1.2 equiv.) in the dark. The resulting solution was allowed to stir for 15 min at this temperature before the dropwise addition of *N*-iodosuccinimide (1.2 equiv.) in dry degassed (3 × freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) over 5 min. The mixture was then allowed to stir at room temperature for 5 h in the dark. After this time, the reaction mixture was diluted with water (20 mL/mmol of substrate) and extracted with EtOAc (3 × 30 mL/mmol of substrate). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

General Procedure B: One-pot cyclisation of malonates

To a solution of the malonate (1.0 equiv.) in dry degassed (3 × freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) cooled to −78 °C was added dropwise NaHMDS (1.0 M in THF, 1.2 equiv.) in the dark. The resulting solution was allowed to stir for 15 min at this temperature before the dropwise addition of *N*-iodosuccinimide (1.2 equiv.) in dry degassed (3 × freeze/pump/thaw cycles) THF (5 mL/mmol of substrate) over 5 min. The mixture was then allowed to stir at room temperature for 5 h in the dark. After this time, TMP (2.0 equiv.) was added and the reaction mixture irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16–24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography.

General Procedure C: One-pot cyclisation of malonates for enolisable substrates

To a solution of the malonate (1.0 equiv.) and *N*-iodosuccinimide (1.2 equiv.) in dry degassed (3 × freeze/pump/thaw cycles) THF (10 mL/mmol of substrate) cooled to −78 °C was added dropwise NaHMDS (1.0 M in THF, 1.1 equiv.) over 30 min in the dark. The resulting solution was allowed to warm up to room temperature and irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16–24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography.

General Procedure D: Sonogashira coupling

$Pd(OAc)_2$ (10 mol%) and XPhos (20 mol%) were dissolved in DMF (2.5 mL/mmol of substrate) and allowed to stir at room temperature under Ar for 30 min. To the resulting dark brown solution were added heterocyclic bromide (1.0 equiv.), dimethyl 2-(prop-2-yn-1-yl)malonate **2.134** (1.2 equiv.), CuI (5 mol%), and DMF (7.5 mL/mmol of substrate). The reaction mixture was degassed (Ar bubbling for 10 min) and DBU (3.0 equiv.) added. The resulting solution was allowed to stir at 80 °C for 6 h. After this time, all volatiles were removed under a flow of N_2 and the crude mixture purified by flash-chromatography.

General Procedure E: Hydrogenation of Sonogashira coupling products

Pd (10% w/w on activated carbon, 5 mol%) was added to an Ar purged solution of Sonogashira coupling product (1.0 equiv.) in dry MeOH (10 mL/mmol of substrate). The atmosphere was then replaced with hydrogen and the resulting mixture allowed to stir for 5 h at room temperature. After this time, the reaction was filtered through a Celite pad,

which was eluted with EtOAc. All volatiles were then removed *in vacuo* to give the desired product with no need for further purification.

General Procedure F: Synthesis of *cis*-vinyl triflates

According to the modified procedure of Specklin,[240] *N*,*N*-diisopropylethylamine (1.1 equiv.) was added to a mixture of acetoacetate (1.0 equiv.) and lithium triflate (2.0 equiv.) in anhydrous CH_2Cl_2 (30 mL/mmol of substrate) at 0 °C. The resulting mixture was allowed to stir for 30 min at this temperature before the dropwise addition of triflic anhydride (1.1 equiv.). The reaction was then allowed to stir at this temperature for 1 h, and quenched with sat. aq. NH_4Cl (30 mL/mmol of substrate). The phases were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL/mmol of substrate). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

General Procedure G: Synthesis of *trans*-vinyl triflates

According to the modified procedure of Gibbs,[241] anhydrous DMF (3.4 mL/mmol of substrate) was added to a multi-neck flask equipped with a thermometer and containing acetoacetate (1.0 equiv.). The resulting solution was cooled to −50 °C before the slow addition of KHMDS (0.5 M in toluene, 1.2 equiv.) (internal temperature should remain between −40 °C and −55 °C). The reaction was then allowed to stir for 1 h at this temperature. Then, bis(trifluoromethanesulfonyl)aniline (1.1 equiv.) in DMF (1.2 mL/mmol of substrate) was added over 15 min while maintaining the internal temperature between −40 °C and −55 °C. The resulting pale brown solution was allowed to stir at this temperature for 2 h. The reaction was then diluted with Et_2O (20 mL/mmol of substrate), washed with aq. citric acid (10% w/w, 3 × 20 mL/mmol of substrate), and

water (20 mL/mmol of substrate). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

General Procedure H: Suzuki coupling of vinyl triflates and allyl malonates

According to the modified procedure of Swidorski,[304] 9-BBN (0.5 M in THF, 1.5 equiv.) was added to a solution of dimethyl 2-allylmalonate **2.160** (1.5 equiv.) at 0 °C in dry degassed (3 × freeze/pump/thaw cycles) THF (5.5 mL/mmol of malonate). The solution was allowed to stir at room temperature for 4 h. Subsequently, a degassed (Ar bubbling, 2 h) 1 M aq. solution of K_3PO_4 (2.5 equiv.) was added, followed by a degassed (Ar bubbling, 30 min) solution of vinyl triflate (1.0 equiv.) in 1,4-dioxane (9 mL/mmol of triflate) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol%). The resulting brown solution was allowed to stir at 85 °C for 17–20 h. After this time, the reaction mixture was allowed to cool down and was diluted with H_2O (10 mL/mmol triflate) and EtOAc (10 mL/mmol triflate). The layers were separated and the aqueous extracted with EtOAc (4 × 10 mL/mmol of triflate). The combined organic layers were washed with brine (20 mL/mmol triflate), dried (Na_2SO_4), and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

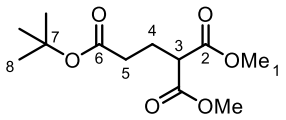
General Procedure I: $Mn(OAc)_3$-mediated radical cascade

$Mn(OAc)_3 \cdot 2H_2O$ (2.2 equiv.) and $Cu(OAc)_2 \cdot H_2O$ (1.1 equiv.) were added to a solution of malonate (1.0 equiv.) in dry degassed (Ar bubbling, 2 h) DMSO (4–7 mL/mmol of malonate) at room temperature. The resulting brown solution was allowed to stir at 60–80 °C for 16–24 h, when it had turned deep green. This solution was allowed to cool to room temperature and was quenched with sat. aq. $Na_2S_2O_3$ (10 mL/mmol of malonate). The resulting mixture was extracted with EtOAc (3 × 10 mL/mmol of malonate). The

combined organic layers were washed with water (3 × 10 mL/mmol of malonate), brine (20 mL/mmol of malonate), dried (Na_2SO_4), and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

4.3 Compound synthesis and characterisation

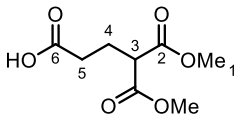
3-(*tert*-Butyl) 1,1-dimethyl propane-1,1,3-tricarboxylate, 4.1



According to the modified procedure of Katti,[305] sodium hydride (60% w/w dispersion in mineral oil, 3.2 g, 80 mmol) was dissolved in THF (100 mL) and cooled to 0 °C before dimethyl malonate (9.1 mL, 80 mmol) was added dropwise over 10 min. The resulting mixture was allowed to stir for 20 min at 0 °C, *tert*-butyl acrylate (5.9 mL, 40 mmol) was added dropwise and the mixture allowed to stir for 16 h at room temperature. After this time, the reaction was cooled down to 0 °C, quenched with sat. aq. NH_4Cl (40 mL) and allowed to stir for 1 h. The resulting mixture was diluted with water (40 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by vacuum distillation (30 °C to 150 °C, 1.32 mbar) and the fractions collected at 115 °C were re-purified by flash-chromatography (10% to 20% Et_2O in $PE_{40\text{-}60}$) to give the *title compound* as a colourless oil (4.69 g, 18.0 mmol, 45%).

R_f 0.50 (40% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); **b.p.** 115 °C (1.32 mbar); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.74 (s, 6H, C{1}–H), 3.47 (t, 1H, J = 7.5 Hz, C{3}–H), 2.33–2.25 (m, 2H, C{5}–H), 2.21–2.13 (m, 2H, C{4}–H), 1.43 (s, 9H, C{8}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 171.8 (C{6}), 169.6 (C{2}), 80.8 (C{7}), 52.7 (C{1}), 50.7 (C{3}), 32.8 (C{5}), 28.2 (C{8}), 24.1 (C{4}); **LRMS** (m/z +ESI): Found: $[M+Na]^+$, 283.1. $C_{12}H_{20}NaO_6^+$ requires 283.1. All data in accordance with the literature.[305]

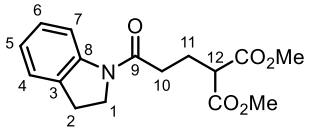
5-Methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid, 2.62



According to the modified procedure of Wu,[306] trifluoroacetic acid (5.0 mL, 65 mmol) was added to a solution of 3-(*tert*-butyl)-1,1-dimethyl propane-1,1,3-tricarboxylate **4.1** (4.0 g, 15.3 mmol) in CH_2Cl_2 (30 mL). The resulting solution was allowed to stir for 16 h at room temperature. After this time, all volatiles were removed *in vacuo* to give the *title compound* as a yellow oil (3.00 g, 14.7 mmol, 96%).

R$_f$ 0.05 (40% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 6H, C{1}–H), 3.49 (t, 1H, J = 7.5 Hz, C{3}–H), 2.45 (t, 2H, J = 7.5 Hz, C{5}–H), 2.20 (dt, 2H, J = 8.0, 7.5 Hz, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 178.6 (C{6}), 169.4 (C{2}), 52.8 (C{1}), 50.4 (C{3}), 31.2 (C{5}), 23.5 (C{4}); **LRMS** (m/z +ESI): Found: $[M+H]^+$, 203.0. $C_8H_{11}O_6^+$ requires 203.2. All data in accordance with the literature.[306]

Dimethyl 2-(3-(indolin-1-yl)-3-oxopropyl)malonate, 2.64

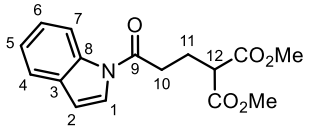


According to the modified procedure of Kerr,[138] DMF (3 drops) and oxalyl chloride (0.65 mL, 7.16 mmol) were added to a solution of 5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid **2.62** (1.17 g, 5.73 mmol) in dry toluene (50 mL). The resulting solution was allowed to stir at room temperature for 30 min and was heated to 60 °C for 2 h. After this time, the mixture was allowed to cool down to room temperature and all volatiles were evaporated *in vacuo* to give a yellow oil (dimethyl 2-(3-chloro-3-oxopropyl)malonate, **2.63**) which was dissolved in CH_2Cl_2 (10 mL). This solution was added dropwise to a

solution of indoline (0.54 mL, 4.8 mmol) and triethylamine (1.0 mL, 7.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was allowed to stir at room temperature for 16 h. After this time, the mixture was poured into sat. aq. NH_4Cl (100 mL), and was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (50% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a white solid (1.44 g, 4.72 mmol, 98%).

R$_f$ 0.38 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 94–95 °C (from EtOAc) (lit.[138] 95–96 °C); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, 1H, J = 8.0 Hz, C{7}–H), 7.20–7.12 (m, 2H, C{4,6}–H), 6.98 (dd, 1H, J = 7.5, 7.5 Hz, C{5}–H), 3.98 (t, 2H, J = 8.5 Hz, C{1}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.63 (t, 1H, J = 7.0 Hz, C{12}–H), 3.16 (t, 2H, J = 8.5 Hz, C{2}–H), 2.49 (t, 2H, J = 7.0 Hz, C{10}–H), 2.31 (dt, 2H, J = 7.0, 7.0 Hz, C{11}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.7 (9, **C**O_2Me), 143.0 (C{8}), 131.1 (C{3}), 127.6 (C{6}), 124.6 (C{4}), 123.7 (C{5}), 117.0 (C{7}), 52.6 (CO_2**Me**), 50.5 (C{12}), 47.9 (C{1}), 32.8 (C{10}), 28.0 (C{2}), 23.6 (C{11}); **LRMS** (m/z +ESI): Found: $[M+Na]^+$, 328.0. $C_{16}H_{19}NNaO_5^+$ requires 328.3. All data in accordance with the literature.[138]

Dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate, 2.60

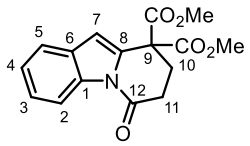


According to the modified procedure of Kerr,[138] DDQ (1.29 g, 5.68 mmol) was added to a solution of dimethyl 2-(3-(indolin-1-yl)-3-oxopropyl)malonate **2.64** (1.44 g, 4.72 mmol) in dry toluene (23 mL) at room temperature. The reaction mixture was refluxed for 16 h. After this time, the reaction was allowed to cool to room temperature, diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were

washed with brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (30% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as an off-white solid (1.36 g, 4.48 mmol, 95%).

R$_f$ 0.19 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 86–88 °C (from EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, 1H, J = 8.0 Hz, C{7}–H), 7.56 (ddd, 1H, J = 7.5, 1.5, 1.0 Hz, C{4}–H), 7.47 (d, 1H, J = 4.0 Hz, C{1}–H), 7.35 (ddd, 1H, J = 8.5, 7.0, 1.5 Hz, C{6}–H), 7.27 (td, 1H, J = 7.5, 1.0 Hz, C{5}–H), 6.65 (dd, 1H, J = 4.0, 1.0 Hz, C{2}–H), 3.77 (s, 6H, 2 × CO_2**Me**), 3.66 (t, 1H, J = 7.0 Hz, C{12}–H), 3.05 (t, 2H, J = 7.0 Hz, C{10}–H), 2.44 (dt, 2H, J = 7.0, 7.0 Hz, C{11}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.3 (C{9}), 169.6 (**C**O_2Me), 135.8 (C{8}), 130.5 (C{3}), 125.4 (C{6}), 124.6 (C{1}), 123.9 (C{5}), 121.0 (C{4}), 116.7 (C{7}), 109.6 (C{2}), 52.8 (CO_2**Me**), 50.4 (C{12}), 33.0 (C{10}), 23.7 (C{11}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 326.0. $C_{16}H_{17}NNaO_5^+$ requires 326.1. All data in accordance with the literature.[138]

Dimethyl 6-oxo-7,8-dihydropyrido[1,2-*a*]indole-9,9(6*H*)-dicarboxylate, 2.65

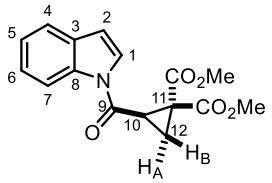


The *title compound* was prepared from dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate **2.60** (303 mg, 1.00 mmol) in accordance with **General Procedure C**. Purification by flash-chromatography (5% to 15% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (284 mg, 0.94 mmol, 94%).

R$_f$ 0.18 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.48 (ddd, 1H, J = 8.0, 1.5, 1.0 Hz, C{2}–H), 7.53 (ddd, 1H, J = 7.5, 1.5, 1.0 Hz, C{5}–H), 7.36 (ddd, 1H, J = 8.0, 7.5, 1.5 Hz, C{3}–H), 7.29 (ddd, 1H, J = 7.5, 7.5, 1.5 Hz, C{4}–H), 6.70 (d,

1H, *J* = 1.0 Hz, C{7}–H), 3.85 (s, 6H, 2 × CO_2**Me**), 2.85–2.79 (m, 2H, C{11}–H), 2.73–2.67 (m, 2H, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.0 (**C**O_2Me), 167.6 (C{12}), 135.3 (C{8}), 132.8 (C{1}), 129.1 (C{6}), 125.6 (C{3}), 124.5 (C{4}), 120.8 (C{5}), 116.8 (C{2}), 109.5 (C{7}), 55.5 (C{9}), 53.7 (CO_2**Me**), 30.9 (C{11}), 28.5 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 302.0. $C_{16}H_{16}NO_5^+$ requires 302.1. All data in accordance with the literature.[138]

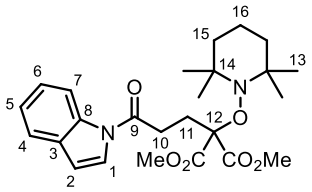
Dimethyl 2-(1*H*-indole-1-carbonyl)cyclopropane-1,1-dicarboxylate, 2.67



Isolated from the cyclisation of dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate **2.60** in variable yields.

R$_f$ 0.32 (30% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.38 (d, 1H, *J* = 8.0 Hz, C{7}–H), 7.64 (d, 1H, *J* = 4.0 Hz, C{1}–H), 7.57 (d, 1H, *J* = 7.5 Hz, C{4}–H), 7.34 (dd, 1H, *J* = 8.0, 7.0 Hz, C{6}–H), 7.29 (dd, 1H, *J* = 7.5, 7.0 Hz, C{5}–H), 6.70 (d, 1H, *J* = 4.0 Hz, C{2}–H), 3.84 (s, 3H, CO_2**Me**), 3.67 (s, 3H, CO_2**Me'**), 3.25 (dd, 1H, *J* = 8.5, 7.0 Hz, C{10}–H), 2.34 (dd, 1H, *J* = 7.0, 5.0 Hz, H_B), 1.83 (dd, 1H, *J* = 8.5, 5.0 Hz, H_A); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.2 (C{9}), 166.4 (**C**O_2Me), 166.2 (**C**O_2Me'), 135.8 (C{3}), 130.6 (C{8}), 125.4 (C{6}), 124.9 (C{1}), 124.2 (C{5}), 121.1 (C{4}), 116.7 (C{7}), 110.1 (C{2}), 53.7 (CO_2**Me**), 53.3 (CO_2**Me'**), 37.7 (C{11}), 29.1 (C{10}), 20.1 (C{12}); ν/**cm**$^{-1}$ (film) 2954w, 1735s, 1670m, 1319s, 1208m; **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 324.0. $C_{16}H_{15}NNaO_5^+$ requires 324.1.

Dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)-2-((2,2,6,6-tetramethylpiperidin1-yl) oxy)malonate, 2.69

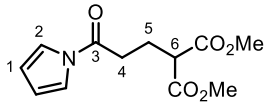


The *title compound* was prepared from dimethyl 2-(3-(1*H*-indol-1-yl)-3-oxopropyl)malonate **2.60** (45 mg, 0.15 mmol) in accordance with **General Procedure C** with the addition of TEMPO (26 mg, 0.17 mmol) immediately before irradiation. Purification by flash-chromatography (5% to 20% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a yellow oil (42.6 mg, 0.093 mmol, 62%).

R$_f$ 0.52 (30% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, 1H, J = 8.0 Hz, C{7}–H), 7.60 (d, 1H, J = 4.0 Hz, C{1}–H), 7.57 (ddd, 1H, J = 7.5, 1.0, 1.0 Hz, C{4}–H), 7.34 (ddd, 1H, J = 8.5, 7.5, 1.5 Hz, C{6}–H), 7.27 (ddd, 1H, J = 7.5, 1.0, 1.0 Hz, C{5}–H), 6.65 (dd, 1H, J = 4.0, 1.0 Hz, C{2}–H), 3.76 (s, 6H, 2 × CO_2**Me**), 3.22–3.13 (m, 2H, C{10}–H), 2.83–2.74 (m, 2H, C{11}–H), 1.66–1.38 (m, 6H, C{15, 16}–H), 1.23 (s, 6H, C{13}–H), 1.15 (s, 6H, C{13'}–H); ν/**cm**$^{-1}$ (film) 2935m, 1742s, 1708m, 1453m, 1208m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 459.2488. $C_{25}H_{35}N_2O_6^+$ requires 459.2490.

Note: This compound quickly decomposed. ^{13}*C NMR could not be obtained.*

Dimethyl 2-(3-oxo-3-(1*H*-pyrrol-1-yl)propyl)malonate, 2.70



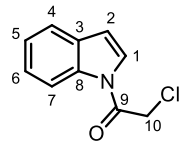
According to the modified procedure of Kerr,[138] DMF (3 drops) and oxalyl chloride (0.30 mL, 3.7 mmol) were added to a solution of 5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid **2.62** (600 mg, 2.94 mmol) in dry toluene (30 mL). The resulting

solution was allowed to stir at room temperature for 30 min and was heated to 60 °C for 2 h. After this time, the mixture was allowed to cool down to room temperature and all volatiles were evaporated *in vacuo* to give a yellow oil (dimethyl 2-(3-chloro-3-oxopropyl)malonate, **2.63**) which was dissolved in THF (4.0 mL).

n-BuLi (2.5 M in hexanes, 0.98 mL, 2.4 mmol) was added dropwise to a solution of freshly distilled pyrrole (0.17 mL, 2.4 mmol) in THF (4.0 mL) at 0 °C. The reaction mixture was allowed to stir at this temperature for 20 min before being cooled down to −78 °C. The solution of dimethyl 2-(3-chloro-3-oxopropyl)malonate **2.63** in THF was then added dropwise and the resulting mixture allowed to stir at room temperature for 16 h. After this time, the mixture was poured into sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (5% to 15% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a yellow oil (168 mg, 0.663 mmol, 22%).

R_f 0.17 (15% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.30 (br, 2H, C{2}–H), 6.29 (br, 2H, C{1}–H), 3.76 (s, 6H, 2 × CO_2**Me**), 3.60 (t, 1H, J = 7.0 Hz, C{6}–H), 2.96 (t, 2H, J = 7.0 Hz, C{4}–H), 2.38 (dt, 2H, J = 7.0, 7.0 Hz, C{5}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.5 (C{3}, **C**O_2Me), 119.1 (C{2}), 113.4 (C{1}), 52.8 (CO_2**Me**), 50.3 (C{6}), 31.8 (C{4}), 23.5 (C{5}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 276.0. $C_{12}H_{15}NNaO_5^+$ requires 276.2. All data in accordance with the literature.[138]

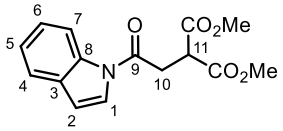
2-Chloro-1-(1*H*-indol-1-yl)ethan-1-one, 2.72



According to the modified procedure of Winkler,[307] chloroacetyl chloride (1.3 mL, 16 mmol) was added dropwise to a solution of indole (1.17 g, 10.0 mmol) in dry toluene (20 mL). The resulting solution was allowed to stir at 125 °C for 1 h. After this time, all volatiles were removed *in vacuo* and the resulting residue recrystallized in ethanol to give the *title compound* as a tan solid (939 mg, 4.85 mmol, 49%).

R$_f$ 0.52 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 104–108 °C (from EtOH) (lit.[307] 115 °C); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 8.0 Hz, C{7}–H), 7.58 (d, 1H, J = 7.5 Hz, C{4}–H), 7.43 (d, 1H, J = 4.0 Hz, C{1}–H), 7.39 (ddd, 1H, J = 8.0, 7.5, 1.5 Hz, C{6}–H), 7.32 (ddd, 1H, J = 7.5, 7.5, 1.0 Hz, C{5}–H), 6.71 (dd, 1H, J = 4.0, 1.0 Hz, C{2}–H), 4.58 (s, 2H, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 164.1 (C{9}), 135.7 (C{8}), 130.3 (C{3}), 125.70 (C{5}), 124.4 (C{6}), 124.2 (C{1}), 121.1 (C{4}), 116.7 (C{7}), 110.6 (C{2}), 42.4 (C{10}); **LRMS** (m/z +ESI): Found: $[M+Na]^+$, 216.9. $C_{10}H_8{}^{35}ClNNaO^+$ requires 216.6. All data in accordance with the literature.[307]

Dimethyl 2-(2-(1*H*-indol-1-yl)-2-oxoethyl)malonate, 2.71

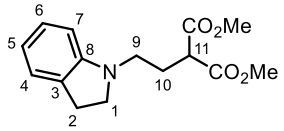


According to the modified procedure of Kerr,[138] dimethyl malonate (0.12 mL, 1.0 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 42 mg, 1.0 mmol) in THF (4.0 mL) which was then allowed to stir for 30 min at room temperature. After this time, a solution of 2-chloro-1-(1*H*-indol-1yl)ethan-1-one **2.72**

(100 mg, 0.52 mmol) in THF (1.0 mL) was added dropwise and the resulting solution allowed to stir at room temperature for 2 h. The reaction mixture was then quenched with water (10 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (30% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (62 mg, 0.21 mmol, 41%).

R_f 0.28 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, 1H, J = 8.5 Hz, C{7}–H), 7.56 (ddd, 1H, J = 7.5, 1.5, 1.0 Hz, C{4}–H), 7.50 (d, 1H, J = 4.0 Hz, C{1}–H), 7.34 (ddd, 1H, J = 8.5, 7.0, 1.5 Hz, C{6}–H), 7.31–7.27 (m, 1H, C{5}–H), 6.68 (d, 1H, J = 4.0 Hz, C{2}–H), 4.16 (t, 1H, J = 7.0 Hz, C{11}–H), 3.82 (s, 6H, 2 × CO_2**Me**), 3.60 (d, 2H, J = 7.0 Hz, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.1 (C{9}, **C**O_2Me), 130.5 (C{3}), 125.5 (C{5}), 124.4 (C{6}), 124.1(C{1}), 121.1 (C{4}), 116.7 (C{7}), 110.1 (C{2}), 53.2 (CO_2**Me**), 47.3 (C{11}), 35.2 (C{10}), C{*8*} *not observed*; ν**/cm**$^{-1}$ (film) 2955w, 1736s, 1704s, 1454m, 1317m, 753w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 290.10245. $C_{15}H_{16}NO_5^+$ requires 290.10230.

Dimethyl 2-(2-(indolin-1-yl)ethyl)malonate, 2.79

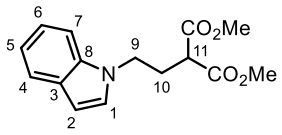


According to the modified procedure of Kerr,[138] indoline (0.21 mL, 1.9 mmol) and dimethyl cyclopropane-1,1-dicarboxylate **2.78** (0.30 g, 1.9 mmol) were dissolved in toluene (4.0 mL) before the addition of ytterbium(III) trifluoromethanesulfonate hydrate (Yb 25-28% w/w, 59 mg, 0.10 mmol). The resulting solution was heated to reflux for 16 h. After this time, the yellow solution was allowed to cool down to room temperature and was partitioned between water (20 mL) and CH_2Cl_2 (30 mL). The phases were

separated and the aqueous extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow oil (469 mg, 1.69 mmol, 89%).

R$_f$ 0.45 (30% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.09–7.02 (m, 2H, C{4,6}–H), 6.66 (ddd, 1H, J = 7.5, 7.5, 1.0 Hz, C{5}–H), 6.46 (d, 1H, J = 8.0 Hz, C{7}–H), 3.72 (s, 6H, 2 × CO_2**Me**), 3.57 (t, 1H, J = 7.5 Hz, C{11}–H), 3.33 (t, 2H, J = 8.5 Hz, C{1}–H), 3.13 (t, 2H, J = 7.0 Hz, C{9}–H), 2.95 (t, 2H, J = 8.5 Hz, C{2}–H), 2.23 (dt, 2H, J = 7.5, 7.0 Hz, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 152.3 (C{8}), 130.1 (C{3}), 127.5 (C{6}), 124.6 (C{4}), 118.1 (C{5}), 107.3 (C{7}), 53.5 (C{1}), 52.7 (CO_2**Me**), 49.4 (C{11}), 47.5 (C{9}), 28.7 (C{2}), 27.1 (C{10}); **LRMS** (m/z +ESI): Found: $[M+H]^+$, 278.1. $C_{15}H_{20}NO_4^+$ requires 278.1. All data in accordance with the literature.[138]

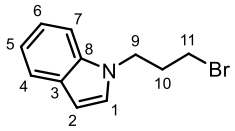
Dimethyl 2-(2-(1*H*-indol-1-yl)ethyl)malonate, 2.74



According to the modified procedure of Kerr,[138] DDQ (393 mg, 1.73 mmol) was added to a solution of dimethyl 2-(2-(indolin-1-yl)ethyl)malonate **2.79** (400 mg, 1.44 mmol) in dry toluene (7.0 mL) at room temperature. The reaction mixture was refluxed for 16 h. After this time, the reaction was allowed to cool to room temperature, diluted with water (50 mL) and extracted with EtOAc (3 × 50mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacu*o to give a dark brown oil. Purification of the crude mixture by flash-chromatography (30% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (237 mg, 0.861 mmol, 60%).

R$_f$ 0.24 (30% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.63 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.35 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.22 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.11 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{5}–H), 7.07 (d, 1H, J = 3.0 Hz, C{1}–H), 6.51 (dd, 1H, J = 3.0, 1.0 Hz, C{2}–H), 4.24 (t, 2H, J = 7.0 Hz, C{9}–H), 3.72 (s, 6H, 2 × CO_2**Me**), 3.32 (t, 1H, J = 7.5 Hz, C{11}–H), 2.45 (dt, 2H, J = 7.5, 7.0 Hz, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.3 (**C**O_2Me), 136.1 (C{8}), 128.8 (C{3}), 127.8 (C{1}), 121.8 (C{6}), 121.2 (C{4}), 119.7 (C{5}), 109.4 (C{7}), 101.9 (C{2}), 52.8 (CO_2**Me**), 48.9 (C{11}), 43.9 (C{9}), 29.4 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 276.0. $C_{15}H_{18}NO_4^+$ requires 276.1. All data in accordance with the literature.[151]

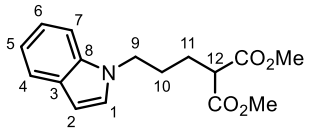
1-(3-Bromopropyl)-1*H*-indole, 2.80



According to the modified procedure of Barriault,[308] a solution of indole (1.0 g, 8.5 mmol) in THF (5.0 mL) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 408 mg, 10.2 mmol) in THF (15 mL). The resulting solution was allowed to stir for 30 min at room temperature. After this time, 1,3-dibromopropane (1.7 mL, 17 mmol) was added and the solution stirred at room temperature for 16 h. The reaction mixture was then quenched by the addition of sat. aq. NH_4Cl (30 mL), the layers separated, and the aqueous phase extracted with Et_2O (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (5% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (172 mg, 0.722 mmol, 9%).

R$_f$ 0.64 (30% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.64 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.38 (ddd, 1H, J = 8.5, 1.0, 1.0 Hz, C{7}–H), 7.22 (ddd, 1H, J = 8.5, 7.0, 1.0 Hz, C{6}–H), 7.15 (d, 1H, J = 3.0 Hz, C{1}–H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.51 (d, 1H, J = 3.0 Hz, C{2}–H), 4.34 (t, 2H, J = 6.5 Hz, C{9}–H), 3.31 (t, 2H, J = 6.0 Hz, C{11}–H), 2.36 (tt, 2H, J = 6,5 6.0 Hz, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 136.0 (C{8}), 128.9 (C{3}), 128.2 (C{1}), 121.8 (C{6}), 121.3 (C{4}), 119.7 (C{5}), 109.4 (C{7}), 101.7 (C{2}), 44.1 (C{9}), 32.9 (C{11}), 30.7 (C{10}); **LRMS** (m/z +ESI): Found: $[M]^+$, 237.0. $C_{11}H_{12}{}^{79}BrN^+$ requires 237.0. All data in accordance with the literature.[309]

Dimethyl 2-(3-(1*H*-indol-1-yl)propyl)malonate, 2.75

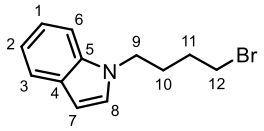


According to the modified procedure of Kerr,[138] dimethyl malonate (0.36 mL, 3.2 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 101 mg, 2.52 mmol) in DMF (5.0 mL) which was then allowed to stir for 30 min at room temperature. After this time, a solution of 1-(3-bromopropyl)-1*H*-indole **2.80** (150 mg, 0.63 mmol) in DMF (5.0 mL) was added dropwise and the resulting solution allowed to stir at room temperature for 16 h. The reaction mixture was then cooled to 0 °C before the dropwise addition of water (10 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL) and the organic layers dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (127 mg, 0.439 mmol, 70%).

R$_f$ 0.42 (30% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 8.0 Hz, C{4}–H), 7.32 (d, 1H, J = 8.5 Hz, C{7}–H), 7.21 (ddd, 1H, J = 8.5, 7.0, 1.0 Hz,

C{6}–H), 7.13–7.06 (m, 2H, C{1, 5}–H), 6.49 (d, 1H, J = 3.0 Hz, C{2}–H), 4.15 (t, 2H, J = 6.5 Hz, C{9}–H), 3.70 (s, 6H, 2 × CO_2**Me**), 3.34 (t, 1H, J = 7.0 Hz, C{12}–H), 2.00–1.84 (m, 4H, C{10, 11}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.6 (**C**O_2Me), 136.0 (C{8}), 128.8 (C{3}), 127.8 (C{1}), 121.7 (C{6}), 121.2 (C{4}), 119.5 (C{5}), 109.4 (C{7}), 101.5 (C{2}), 52.7 (CO_2**Me**), 51.3 (C{12}), 46.0 (C{9}), 28.0 (C{10}), 26.3 (C{11}); **LRMS** (m/z +ESI): Found: $[M+H]^+$, 290.1. $C_{16}H_{20}NO_4^+$ requires 290.2. All data in accordance with the literature.[138]

1-(4-Bromobutyl)-1*H*-indole, 2.81

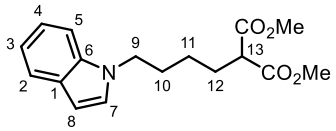


According to the modified procedure of Barriault,[308] to a stirred suspension of NaH (60% in oil, 58 mg, 2.4 mmol) in THF (12 mL) was added a solution of indole (234 mg, 2.0 mmol) in THF (10 mL) at room temperature. The resulting mixture was allowed to stir for 30 min at room temperature. This solution was then transferred into a dropping funnel and added dropwise to a solution of 1,4-dibromobutane (0.48 mL, 4.0 mmol) in THF (20 mL) over 30 min. The resulting mixture was then stirred at room temperature overnight. After this time, the reaction mixture was quenched with sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (3 × 40 mL). The resulting organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 7% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 4 cm, L = 8 cm) afforded the *title compound* as a colourless oil (223.2 mg, 0.89 mmol, 45%).

R$_f$ 0.52 (33% Et_2O in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.64 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{3}–H), 7.35 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{6}–H), 7.22 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{1}–H), 7.14–7.08 (m, 2H, C{2, 8}–H), 6.51 (dd, 1H, J

= 3.0, 1.0 Hz, C{7}–H), 4.18 (t, 2H, *J* = 7.0 Hz, C{9}–H), 3.38 (t, 2H, *J* = 6.5 Hz, C{12}–H), 2.07–1.98 (m, 2H, C{10}–H), 1.90–1.82 (m, 2H, C{11}–H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.0 (C{5}), 128.8 (C{4}), 127.7 (C{8}), 121.7 (C{1}), 121.2 (C{3}), 119.5 (C{2}), 109.4 (C{6}), 101.5 (C{7}), 45.6 (C{9}), 33.1 (C{12}), 30.1 (C{11}), 29.0 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 251.9. $C_{12}H_{15}{}^{79}BrN^+$ requires 252.0. All data in accordance with the literature.[308]

Dimethyl 2-(4-(1*H*-indol-1-yl)butyl)malonate, 2.76

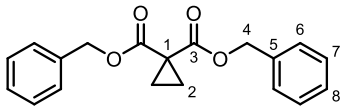


According to the modified procedure of Kerr,[138] dimethyl malonate (0.45 mL, 3.95 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in oil, 126 mg, 3.16 mmol) in DMF (8 mL). The resulting suspension was allowed to stir at room temperature for 30 min before the addition of 1-(4-bromobutyl)-1*H*-indole **2.81** (200 mg, 0.79 mmol) in DMF (4 mL). The resulting solution was allowed to stir for 16 h at room temperature. After this time, the reaction was quenched with water (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (33% Et_2O in $PE_{40\text{-}60}$) afforded the *title compound* as a colourless oil (83 mg, 0.27 mmol, 34%).

R$_f$ 0.17 (33 % Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{2}–H), 7.32 (dd, 1H, *J* = 8.0, 1.0 Hz, C{5}–H), 7.20 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{4}–H), 7.09 (m, 2H, C{3, 7}–H), 6.48 (dd, 1H, *J* = 3.0, 1.0 Hz, C{8}–H), 4.12 (t, 2H, *J* = 7.0 Hz, C{9}–H), 3.70 (s, 6H, 2 × CO_2**Me**), 3.32 (t, 1H, *J* = 7.5 Hz, C{13}–H), 1.97–1.90 (m, 2H, C{12}–H), 1.90–1.82 (m, 2H, C{10}–H), 1.38–

1.28 (m, 2H, C{11}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.8 (**C**O_2Me), 136.0 (C{6}), 128.7 (C{1}), 127.9 (C{7}), 121.5 (C{4}), 121.1 (C{2}), 119.4 (C{3}), 109.4 (C{5}), 101.2 (C{8}), 52.7 (CO_2**Me**), 51.6 (C{13}), 46.1 (C{9}), 29.9 (C{10}), 28.5 (C{12}), 24.8 (C{11}); ν/**cm**$^{-1}$ (film) 2953w, 1734s, 1512m, 1155m, 743s; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 304.1544. $C_{17}H_{22}O_4N^+$ requires 304.1543.

Dibenzyl cyclopropane-1,1-dicarboxylate, 2.83



According to the modified procedure of Saruta,[310] K_2CO_3 (6.9 g, 50 mmol) and 1,2-dibromoethane (1.20 mL, 15.0 mmol) were added to a solution of dibenzyl malonate (1.25 mL, 5.0 mmol) in DMF (14 mL). The resulting mixture was allowed to stir at room temperature for 16 h. After this time, the reaction was diluted with water (40 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give the *title compound* as a colourless oil (968.4 mg, 3.12 mmol, 62%).

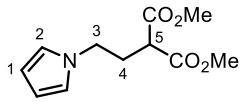
R$_f$ 0.41 (30% Et_2O in $PE_{40\text{-}60}$, yellow in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 10H, C{6, 7, 8}–H), 5.16 (s, 4H, C{4}–H), 1.50 (s, 4H, C{2}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.7 (C{3}), 135.7 (C{5}), 128.7 (C{6/7/8}), 128.4 (C{6/7/8}), 128.2 (C{6/7/8}), 67.4 (C{4}), 28.4 (C{1}), 17.1 (C{2}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 333.0. $C_{19}H_{18}NaO_4^+$ requires 333.1.All data in accordance with the literature.[310]

Cyclopropane-1,1-dicarbonitrile, 2.84

According to the modified procedure of Rodriguez,[311] 1,2-dibromoethane (2.4 mL, 28 mmol) was added dropwise to a mixture of malononitrile (1.32 g, 20.0 mmol) and K_2CO_3 (8.29 g, 60 mmol) in THF (25 mL). The resulting mixture was allowed to stir at 80 °C for 2 h. After this time, the resulting orange mixture was passed through a short silica plug (eluted with EtOAc) and evaporated *in vacuo*. Kugelrohr distillation (85 °C, 3.0 mbar) provided the *title compound* as a colourless oil (182.2 mg, 1.98 mmol, 10%).

R_f 0.32 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **b.p.** 73 °C, 3.0 mbar; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 1.82 (s, 4H, C{2}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 115.3 (**C**N), 18.8 (C{2}), −1.1 (C{1}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[311]

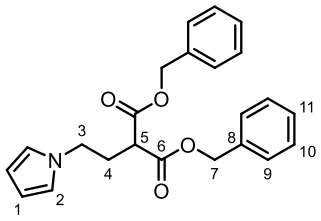
Dimethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 2.85



According to the modified procedure of Greenhouse,[312] pyrrole (0.10 mL, 1.5 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 60 mg, 24 mmol) in dry DMF (3.0 mL) and stirred for 30 min at room temperature. After this time, dimethyl cyclopropane-1,1-dicarboxylate **2.78** (158 mg, 1.0 mmol) was added dropwise in DMF (1.0 mL). The resulting mixture was allowed to stir for 16 h at 60 °C. It was then quenched with sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (20% Et_2O in $PE_{40\text{-}60}$) afforded the *title compound* as a colourless oil (80 mg, 0.36 mmol, 36%).

R_f 0.17 (20% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.62 (t, 2H, J = 2.0 Hz, C{2}–H), 6.14 (t, 2H, J = 2.0 Hz, C{1}–H), 3.97 (t, 2H, J = 7.0 Hz, C{3}–H), 3.74 (s, 6H, 2 × CO_2**Me**), 3.28 (t, 1H, J = 7.5 Hz, C{5}–H), 2.35 (dt, 2H, J = 7.5, 7.0 Hz, C{4}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.4 (**C**O_2Me), 120.7 (C{2}), 108.7 (C{1}), 52.8 (CO_2**Me**), 48.7 (C{5}), 47.0 (C{3}); 30.8 (C{4}); ν**/cm**$^{-1}$ (film) 2955w, 1731s, 1436m, 1154m, 727s; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 226.10759. $C_{11}H_{16}NO_4^+$ requires 226.10848.

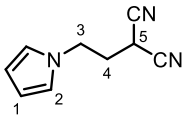
Dibenzyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 2.86



According to the modified procedure of Inaba,[313] sodium hydride (60% w/w dispersion in mineral oil, 96 mg, 2.4 mmol) was added to a solution of freshly distilled pyrrole (0.14 mL, 2.0 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) and allowed to stir at room temperature for 15 min. After this time, a solution of dibenzyl cyclopropane-1,1-dicarboxylate **2.83** (310 mg, 1.0 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) was added to the mixture, which was allowed to stir at 120 °C for 16 h. After this time, the reaction was quenched with water (1 mL) and filtered through a silica plug (eluted with EtOAc). All volatiles were evaporated *in vacuo*. The remaining oil was diluted with water (20 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (10% to 15% Et_2O in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (138.5 mg, 0.37 mmol, 37%).

R$_f$ 0.33 (30% Et_2O in $PE_{40\text{-}60}$, orange in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.36–7.31 (m, 6H, C{10, 11}–H), 7.31–7.27 (m, 4H, C{9}–H), 6.54 (t, 2H, J = 2.0 Hz, C{2}–H), 6.11 (t, 2H, J = 2.0 Hz, C{1}–H), 5.14 (s, 4H, C{7}–H), 3.91 (t, 2H, J = 7.0 Hz, C{3}–H), 3.35 (t, 1H, J = 7.5 Hz, C{5}–H), 2.37 (dt, 2H, J = 7.5, 7.0 Hz, C{4}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.6 (C{6}), 135.3 (C{8}), 128.8 (C{10}), 128.6 (C{11}), 128.4 (C{9}), 120.7 (C{2}), 108.6 (C{1}), 67.5 (C{7}), 49.1 (C{5}), 46.8 (C{3}), 30.7 (C{4}); ν**/cm**$^{-1}$ (film) 2956w, 1731s, 1499w, 1150m, 729m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 378.1698. $C_{23}H_{23}NO_4^+$ requires 378.1700.

2-(2-(1*H*-Pyrrol-1-yl)ethyl)malononitrile, 2.87

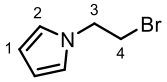


According to the modified procedure of Greenhouse,[312] sodium hydride (60% w/w dispersion in mineral oil, 100 mg, 2.5 mmol) was added to a solution of freshly distilled pyrrole (0.14 mL, 2.0 mmol) in DMF (4.0 mL) and allowed to stir for 30 min at room temperature. After this time, cyclopropane-1,1-dicarbonitrile **2.84** (92 mg, 1.0 mmol) was added, and the resulting solution allowed to stir at 60 °C for 2 h. It was then quenched with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (10% to 20% EtOAc in pentane) provided the *title compound* as a colourless oil (109.1 mg, 0.69 mmol, 69%).

R$_f$ 0.23 (20% EtOAc in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.66 (t, 2H, J = 2.0 Hz, C{2}–H), 6.23 (t, 2H, J = 2.0 Hz, C{1}–H), 4.20 (t, 2H, J = 6.0 Hz, C{3}–H), 3.33 (t, 1H, J = 7.5 Hz, C{5}–H), 2.47 (dt, 2H, J = 7.5, 6.0 Hz, C{4}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 120.6 (C{2}), 111.9 (**C**N), 110.2 (C{1}), 45.4 (C{3}), 33.2

(C{4}), 19.9 (C{5}); ν/**cm**$^{-1}$ (film) 2980w, 1499m, 1284m, 1091m, 729s; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 160.0870. $C_9H_{10}N_3^+$ requires 160.0869.

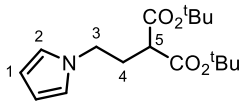
1-(2-Bromoethyl)-1*H*-pyrrole, 2.89



According to the modified procedure of Kandula,[314] a mixture of 2-bromoethylamine hydrochloride (2.05 g, 10.0 mmol), NaOAc (820 mg, 10.0 mmol), H_2O (12 mL), acetic acid (4.0 mL), and 1,2-dichloroethane (12 mL) was heated to 80 °C before the addition of 2,5-dimethoxytetrahydrofuran (mixture of *cis* and *trans*, 1.3 mL, 10.0 mL). The resulting mixture was then allowed to stir at 90 °C for 1.5 h. After this time, the reaction was allowed to cool down and was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (10% Et_2O in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (1.05 g, 6.03 mmol, 60%).

R$_f$ 0.59 (25% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.70 (t, 2H, J = 2.0 Hz, C{2}–H), 6.19 (t, 2H, J = 2.0 Hz, C{1}–H), 4.28 (t, 2H, J = 7.0 Hz, C{3}–H), 3.59 (t, 2H, J = 7.0 Hz, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 120.6 (C{2}), 108.8 (C{1}), 51.0 (C{3}), 31.0 (C{4}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[314]

Di-*tert*-butyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 2.90

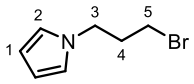


According to the modified procedure of Browne,[315] a mixture of 1-(2-bromoethyl)-1*H*-pyrrole **2.89** (174 mg, 1.0 mmol), di-*tert*-butyl malonate (0.17 mL, 0.75 mmol), and K_2CO_3

(138 mg, 1.0 mmol) in DMF (5.0 mL) was allowed to stir at 85 °C for 36 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (0% to 10% Et_2O in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (75.1 mg, 0.24 mmol, 32%).

R_f 0.35 (10% acetone in $PE_{40\text{-}60}$, red in vanillin); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.65 (t, 2H, J = 2.0 Hz, C{2}–H), 6.15 (t, 2H, J = 2.0 Hz, C{1}–H), 3.95 (t, 2H, J = 7.0 Hz, C{3}–H), 3.06 (t, 1H, J = 7.5 Hz, C{5}–H), 2.24 (dt, 2H, J = 7.5, 7.0 Hz, C{4}–H), 1.46 (s, 18H, C**Me**$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.3 (**C**O_2R), 120.6 (C{2}), 108.3 (C{1}), 81.8 (**C**Me_3), 50.9 (C{5}), 46.9 (C{3}), 30.6 (C{4}), 27.9 (C**Me**$_3$); **ν/cm^{-1}** (film) 2979m, 1725s, 1369m, 1140s, 724m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 332.3314. $C_{17}H_{27}NNaO_4^+$ requires 332.1832.

1-(3-Bromopropyl)-1*H*-pyrrole, 2.91

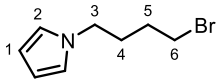


According to the modified procedure of Zhang,[316] pyrrole (0.70 mL, 10 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 0.48 g, 12 mmol) in DMF (20 mL). The resulting solution was allowed to stir for 30 min at room temperature. After this time, 1,3-dibromopropane (2.0 mL, 20 mmol) was added and the solution stirred at room temperature for 16 h. The reaction mixture was then quenched with water (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude

mixture by flash-chromatography (0% to 20% CH_2Cl_2 in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (205 mg, 1.09 mmol, 11%).

R_f 0.44 (25% CH_2Cl_2 in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.68 (t, 2H, J = 2.0 Hz, C{2}–H), 6.16 (t, 2H, J = 2.0 Hz, C{1}–H), 4.08 (t, 2H, J = 6.5 Hz, C{3}–H), 3.31 (t, 2H, J = 6.0 Hz, C{5}–H), 2.26 (tt, 2H, J = 6.5, 6.0 Hz, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 120.8 (C{2}), 108.6 (C{1}), 47.2 (C{3}), 34.3 (C{4}), 30.4 (C{5}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[317]

1-(4-Bromobutyl)-1*H*-pyrrole, 2.92

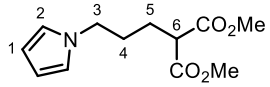


According to the modified procedure of Hassner,[318] ground KOH (224 mg, 4.00 mmol) was added to a solution of pyrrole (0.28 mL, 4.0 mmol) and 1,4-dibromobutane (1.4 mL, 12 mmol) in DMF (20 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 15 h. After this time, the reaction was quenched with water (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (4% Et_2O in $PE_{40\text{-}60}$) afforded the *title compound* as a colourless oil (405 mg, 2.0 mmol, 50%).

R_f 0.27 (5% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.65 (t, 2H, J = 2.0 Hz, C{2}–H), 6.15 (t, 2H, J = 2.0 Hz, C{1}–H), 3.92 (t, 2H, J = 7.0 Hz, C{3}–H), 3.38 (t, 2H, J = 6.5 Hz, C{6}–H), 1.97–1.88 (m, 2H, C{4}–H), 1.88–1.77 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 120.6 (C{2}), 108.3 (C{1}), 48.8 (C{3}), 33.1 (C{6}),

30.2 (C{4}), 29.9 (C{5}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 226.2. $C_8H_{12}{}^{81}BrNNa^+$ requires 226.0. All data in accordance with the literature.[318]

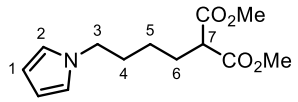
Dimethyl 2-(3-(1*H*-pyrrol-1-yl)propyl)malonate, 2.93



According to the modified procedure of Kerr,[138] dimethyl malonate (0.61 mL, 5.3 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 170 mg, 4.24 mmol) in DMF (8.0 mL) which was then allowed to stir for 30 min at room temperature. After this time, a solution of 1-(3-bromopropyl)-1*H*-pyrrole **2.91** (200 mg, 1.06 mmol) in DMF (8.0 mL) was added dropwise and the resulting solution allowed to stir at room temperature for 16 h. The reaction mixture was then cooled to 0 °C before the dropwise addition of water (10 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL), the organic layers dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (20% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (96.9 mg, 0.405 mmol, 39%).

R$_f$ 0.27 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.63 (t, 2H, J = 2.0 Hz, C{2}–H), 6.14 (t, 2H, J = 2.0 Hz, C{1}–H), 3.90 (t, 2H, J = 7.0 Hz, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.33 (t, 1H, J = 7.5 Hz, C{6}–H), 1.95–1.85 (m, 2H, C{5}–H), 1.85–1.74 (m, 2H, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.6 (**C**O_2Me), 120.6 (C{2}), 108.3 (C{1}), 52.7 (CO_2**Me**), 51.3 (C{6}), 49.2 (C{3}), 29.4 (C{4}), 26.2 (C{5}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 262.1. $C_{12}H_{17}NNaO_4^+$ requires 262.1. All data in accordance with the literature.[138]

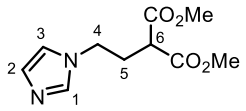
Dimethyl 2-(4-(1*H*-pyrrol-1-yl)butyl)malonate, 2.94



According to the modified procedure of Kerr,[138] dimethyl malonate (0.86 mL, 7.5 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in oil, 240 mg, 6.00 mmol) in DMF (14 mL). The resulting suspension was allowed to stir at room temperature for 30 min before the addition of 1-(4-bromobutyl)-1*H*-pyrrole **2.92** (303 mg, 1.50 mmol) in DMF (7 mL). The resulting solution was allowed to stir for 16 h at room temperature. After this time, the reaction was quenched with water (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (30% to 40% Et_2O in $PE_{40\text{-}60}$) afforded the *title compound* as a yellow oil (248 mg, 0.98 mmol, 65%).

R$_f$ 0.20 (30 % Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.63 (t, 2H, J = 2.0 Hz, C{2}–H), 6.13 (t, 2H, J = 2.0 Hz, C{1}–H), 3.87 (t, 2H, J = 7.0 Hz, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.34 (t, 1H, J = 7.5 Hz, C{7}–H), 1.97–1.88 (m, 2H, C{6}–H), 1.84–1.74 (m, 2H, C{4}–H), 1.37–1.25 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.8 (**C**O_2Me), 120.6 (C{2}), 108.1 (C{1}), 52.7 (CO_2**Me**), 51.6 (C{7}), 49.2 (C{3}), 31.3 (C{4}), 28.5 (C{6}), 24.6 (C{5}); ν**/cm**$^{-1}$ (film) 2953w, 1733s, 1435m, 1150m, 726s; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 304.1544. $C_{17}H_{22}O_4N^+$ requires 304.1543.

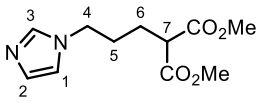
Dimethyl 2-(2-(1*H*-imidazol-1-yl)ethyl)malonate, 2.96



According to the modified procedure of Kerr,[138] imidazole (100 mg, 1.43 mmol) and ytterbium(III) trifluoromethanesulfonate hydrate (Yb 25-28% w/w, 30 mg, 0.05 mmol) were added to a solution of dimethyl cyclopropane-1,1-dicarboxylate **2.78** (150 mg, 0.95 mmol) in toluene (4.0 mL). The resulting solution was allowed to stir at 125 °C for 16 h. After this time, the reaction mixture was allowed to cool down to room temperature, it was diluted with sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (5% MeOH in CH_2Cl_2) gave the *title compound* as a colourless oil (105 mg, 0.437 mmol, 49%).

R$_f$ 0.30 (5% MeOH in CH_2Cl_2, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.47 (br, 1H, C{1}–H), 7.07 (br, 1H, C{2}–H), 6.91 (br, 1H, C{3}–H), 4.04 (t, 2H, J = 7.0 Hz, C{4}–H), 3.74 (s, 6H, 2 × CO_2**Me**), 3.29 (t, 1H, J = 7.5 Hz, C{6}–H), 2.36 (dt, 2H, J = 7.5, 7.0 Hz, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.0 (**C**O_2Me), 137.4 (C{1}), 130.0 (C{2}), 118.9 (C{3}), 53.0 (CO_2**Me**), 48.5 (C{6}), 44.5 (C{4}), 30.2 (C{5}); ν**/cm**$^{-1}$ (film) 2956w, 1730s, 1437m, 1229m, 665w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 227.10280. $C_{10}H_{15}N_2O_4^+$ requires 227.10263.

Dimethyl 2-(3-(1*H*-imidazol-1-yl)propyl)malonate, 2.98



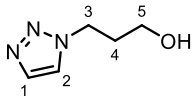
Step 1: According to the modified procedure of Zhang,[316] 1,3-dibromopropane (1.0 mL, 10 mmol) and imidazole (0.34 g, 5.0 mmol) were added to a suspension of KOH (0.34 g,

6.0 mmol) in acetonitrile (2.5 mL) at 0 °C. The resulting mixture was allowed to stir for 3 h at 0 °C. After this time, the reaction was diluted with sat. aq. $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), then diluted with DMF (10 mL) and evaporated *in vacuo* to give a colourless clear solution of 1-(3-bromopropyl)-1*H*-imidazole **2.97** in DMF, which was used with no further purification in the following step.

Step 2: Dimethyl malonate (2.9 mL, 25 mmol) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 1.0 g, 25 mmol) in dry DMF (40 mL) and stirred for 30 min at room temperature. After this time, the solution of 1-(3-bromopropyl)-1*H*-imidazole **2.97** in DMF (10 mL) was added to the mixture, which was allowed to stir for 16 h at room temperature. The reaction mixture was then cooled down to 0 °C, quenched with water (20 mL) and extracted with EtOAc (3 × 30mL) – these extracts were discarded. The aqueous layer was then extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers dried ($MgSO_4$) and evaporated *in vacuo* to give a clear oil. Purification of the crude mixture by flash-chromatography (3% MeOH in CH_2Cl_2) gave the *title compound* as a colourless oil (204 mg, 0.850 mmol, 17% over 2 steps).

R_f 0.14 (3% MeOH in CH_2Cl_2, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.46 (br, 1H, C{3}–H), 7.04 (br, 1H, C{2}–H), 6.89 (br, 1H, C{1}–H), 3.94 (t, 2H, J = 7.0 Hz, C{4}–H), 3.71 (s, 6H, 2 × CO_2**Me**), 3.33 (t, 1H, J = 7.0 Hz, C{7}–H), 1.95–1.75 (m, 4H, C{5, 6}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.4 (**C**O_2Me), 137.1 (C{3}), 129.7 (C{2}), 118.8 (C{1}), 52.8 (CO_2**Me**), 51.0 (C{7}), 46.6 (C{4}), 28.8 (C{5}), 25.8 (C{6}); **ν/cm^{-1}** (film) 2955w, 1729s, 1230m, 1154m, 665m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 241.11819. $C_{11}H_{17}N_2O_4^+$ requires 241.11828.

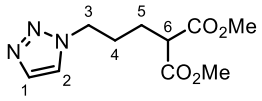
3-(1*H*-1,2,3-Triazol-1-yl)propan-1-ol , 2.100



According to the modified procedure of Sohn,[319] K_2CO_3 (2.00 g, 14.5 mmol), KI (240 mg, 1.45 mmol) and 1,3-bromopropanol (1.0 mL, 10.8 mmol) were added to a solution of 1,2,3-triazole (500 mg, 7.25 mmol) in 1,4-dioxane (10 mL). The resulting mixture was allowed to stir at 100 °C for 4 h. After this time, the reaction mixture was allowed to cool down to room temperature, filtered and all volatiles evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (eluent: 5% MeOH in CH_2Cl_2; column size: Ø = 5 cm, L = 9 cm) gave the *title compound* as a colourless oil (401 mg, 3.15 mmol, 43%).

R$_f$ 0.21 (10% MeOH in CH_2Cl_2, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 1.0 Hz, C{1}–H), 7.63 (d, 1H, J = 1.0 Hz, C{2}–H), 4.55 (t, 2H, J = 7.0 Hz, C{3}–H), 3.64 (t, 2H, J = 6.0 Hz, C{5}–H), 2.98 (s, 1H, O–H), 2.13 (tt, 2H, J = 7.0, 6.0 Hz, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 133.7 (C{1}), 124.1 (C{2}), 58.7 (C{5}), 47.1 (C{3}), 32.8 (C{4}). All data in accordance with the literature.[320]

Dimethyl 2-(3-(1*H*-1,2,3-triazol-1-yl)propyl)malonate, 2.101



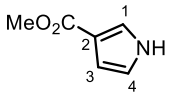
Step 1: According to the modified procedure of Itoh,[321] triethylamine (0.37 mL, 2.7 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) were added dropwise to a solution of 3-(1*H*-1,2,3-triazol-1-yl)propan-1-ol **2.100** (225 mg, 1.77 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The resulting mixture was allowed to stir for 1 h at room temperature. After this time, the reaction was quenched with 0.5 M aq. HCl (8 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in*

vacuo to give a colourless oil (3-(1*H*-1,2,3-triazol-1yl)propyl methanesulfonate), used in the next step without further purification.

Step 2: Dimethyl malonate (0.51 mL, 4.43 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 177 mg, 4.43 mmol) in DMF (8 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 3-(1*H*-1,2,3-triazol-1-yl)propyl methanesulfonate in THF (8 mL) was added dropwise to the mixture, which was allowed to stir at 80 °C for 4 h. The reaction was then quenched with sat. aq. NH_4Cl (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 80% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 12 cm) gave the *title compound* as a colourless oil (196 mg, 0.81 mmol, 46% over 2 steps).

R$_f$ 0.46 (EtOAc, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.70 (br, 1H, C{1}–H), 7.56 (br, 1H, C{2}–H), 4.41 (t, 2H, J = 7.0 Hz, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.38 (t, 1H, J = 7.0 Hz, C{6}–H), 2.05–1.82 (m, 4H, C{4,5}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.4 (**C**O_2Me), 134.0 (C{1}), 123.5 (C{2}), 52.8 (CO_2**Me**), 51.0 (C{6}), 49.7 (C{3}), 28.0 (C{4}), 25.8 (C{5}); **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 242.11364. $C_{10}H_{16}O_4N_3^+$ requires 242.11353.

Methyl 1*H*-pyrrole-3-carboxylate, 2.107

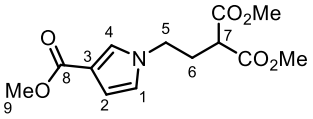


According to the modified procedure of Masahiro,[322] a solution of *p*-toluenesulfonylmethyl isocyanide (976 mg, 5.0 mmol) and methyl acrylate (0.45 mL,

5.0 mmol) in THF (8.0 mL) was added to a mixture of potassium *tert*-butoxide (785 mg, 7.0 mmol) in THF (8.0 mL) at room temperature over 30 min. The resulting orange solution was allowed to stir at the same temperature for 2 h. After this time, the reaction was diluted with water (30 mL), and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (20% to 40% Et_2O in $PE_{40\text{-}60}$) provided the *title compound* as a white solid (175.1 mg, 1.40 mmol, 28%).

R$_f$ 0.36 (66% Et_2O in $PE_{40\text{-}60}$, purple in vanillin); **m.p.** 81–85 °C (from hexane) (lit.[323] 87–88 °C); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.65 (br, 1H, N–H), 7.43 (ddd, 1H, J = 3.5, 2.0, 1.5 Hz, C{1}–H), 6.76 (ddd, 1H, J = 3.0, 2.0, 2.0 Hz, C{3}–H), 6.65 (ddd, 1H, J = 3.0, 3.0, 1.5 Hz, C{4}–H), 3.82 (s, 3H, CO_2**Me**); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 165.5 (**C**O_2Me), 123.5 (C{1}), 118.8 (C{3}), 116.3 (C{2}), 109.8 (C{4}), 51.1 (CO_2**Me**); **LRMS** (m/z +ESI): Found: $[M+H]^+$, 126.0. $C_6H_8NO_2^+$ requires 126.1. All data in accordance with the literature.[323]

Dimethyl 2-(2-(3-(methoxycarbonyl)-1*H*-pyrrol-1-yl)ethyl)malonate, 2.102



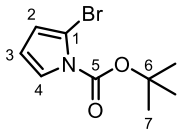
Step 1: According to the modified procedure of Lautens,[317] KOH (673 mg, 12.0 mmol) was added to a solution of methyl 1*H*-pyrrole-3-carboxylate **2.107** (150 mg, 1.20 mmol) in DMSO (3.0 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 1 h, before the addition of 1,2-dibromoethane (2.1 mL, 24 mmol). The reaction was then allowed to stir for 1 h. After this time, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers

were washed with brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in DMF (8.0 mL) before the addition of dimethyl malonate (0.55 mL, 4.8 mmol) and K_2CO_3 (663 mg, 4.80 mmol). The resulting mixture was allowed to stir at 60 °C for 2 h and 20 min. After this time, the mixture was diluted with water (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (25% to 30% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (144.0 mg, 0.51 mmol, 42% over 2 steps).

$\mathbf{R}_f$ 0.19 (30% EtOAc in $PE_{40\text{-}60}$, purple in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, 1H, J = 2.0 Hz, C{4}–H), 6.60–6.55 (m, 2H, C{1, 2}–H), 3.97 (t, 2H, J = 7.0 Hz, C{5}–H), 3.79 (s, 3H, C{9}–H), 3.74 (s, 6H, 2 × CO_2**Me**), 3.27 (t, 1H, J = 7.5 Hz, C{7}–H), 2.36 (dt, 2H, J = 7.5, 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.1 (**C**O_2Me), 165.3 (C{8}), 126.0 (C{4}), 121.8 (C{1}), 116.4 (C{3}), 110.6 (C{2}), 53.0 (CO_2**Me**), 51.2 (C{9}), 48.5 (C{7}), 47.5 (C{5}), 30.4 (C{6}); ν**/cm**$^{-1}$ (film) 2954w, 1732s, 1705s, 1438m, 1200s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 306.0948. $C_{13}H_{17}NNaO_6^+$ requires 306.0948.

***tert*-Butyl 2-bromo-1*H*-pyrrole-1-carboxylate, 2.114**

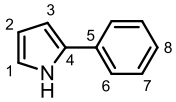


According to the modified procedure of Blagg,[324] *N*-bromosuccinimide (1.78 g, 10.0 mmol) was added in 4 portions to a solution of freshly distilled pyrrole (0.70 mL,

10.0 mmol) in THF (27 mL) at −78 °C. The resulting green solution was kept at −20 °C for 2 h. The reaction mixture was then filtered through a cannula into a flask cooled to −78 °C. Triethylamine (1.40 mL, 10.0 mmol) and DMAP (61 mg, 0.50 mmol) were added, followed by a solution of di-*tert*-butyl dicarbonate (3.06 g, 14.0 mmol) in THF (5 mL). The resulting mixture was allowed to stir at room temperature for 16 h. After this time, all volatiles were evaporated *in vacuo*, and the residue obtained dissolved in EtOAc (40 mL), washed with water (3 × 30 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (0% to 6% Et_2O in $PE_{40\text{-}60}$:NEt_3 50:1) provided the *title compound* as a colourless oil (1.239 g, 5.03 mmol, 50%).

R$_f$ 0.38 (5% EtOAc in $PE_{40\text{-}60}$, brown in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.31 (dd, 1H, J = 3.5, 2.0 Hz, C{4}–H), 6.29 (dd, 1H, J = 3.5, 2.0 Hz, C{2}–H), 6.15 (t, 1H, J = 3.5 Hz, C{3}–H), 1.61 (s, 9H, C{7}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 148.1 (C{5}), 123.0 (C{4}), 117.2 (C{2}), 111.6 (C{3}), 100.3 (C{1}), 84.8 (C{6}), 27.8 (C{7}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[324]

2-Phenyl-1*H*-pyrrole, 2.109



According to the modified procedure of Blagg:[324]

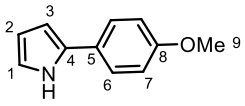
Step 1: K_2CO_3 (415 mg, 3.0 mmol) and phenylboronic acid (134 mg, 1.1 mmol) were added to a solution of *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **2.114** (246 mg, 1.0 mmol) in toluene (3.0 mL) in a microwave vial. EtOH (0.5 mL) and H_2O (0.5 mL) were then added to the mixture, which was degassed (Ar bubbling for 20 min). $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (41 mg, 0.05 mmol) was then added, the vial sealed, and the reaction

allowed to stir at 110 °C for 3 h. After this time, all volatiles were removed *in vacuo* and the resulting residue partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was re-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered through a short silica plug (eluted with EtOAc), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in MeOH/H_2O (3:1, 4.0 mL), and K_2CO_3 (415 mg, 3.0 mmol) added. The resulting dark brown mixture was allowed to stir at 75 °C for 16 h. After this time, volatiles were removed *in vacuo*, and the resulting residue was dissolved in water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), and evaporated *in vacuo* to give a dark brown oil. Purification of the crude mixture by flash-chromatography (5% to 10% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as an off-white solid (77.2 mg, 0.54 mmol, 54% over 2 steps).

R$_f$ 0.39 (20% EtOAc in $PE_{40\text{-}60}$, pink in vanillin); **m.p.** 125 °C (dec., from EtOAc) (lit.[325] 130–132 °C); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.43 (br, 1H, N–H), 7.54–7.43 (m, 2H, C{6}–H), 7.42–7.32 (m, 2H, C{7}–H), 7.25–7.17 (m, 1H, C{8}–H), 6.87 (ddd, 1H, J = 2.5, 2.5, 1.5 Hz, C{1}–H), 6.54 (ddd, 1H, J = 3.5, 2.5, 1.5 Hz, C{3}–H), 6.32 (ddd, 1H, J = 3.5, 2.5, 2.5 Hz, C{2}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 132.9 (C{4/5}), 132.3 (C{4/5}), 129.0 (C{7}), 126.3 (C{8}), 124.0 (C{6}), 119.0 (C{1}), 110.3 (C{2}), 106.1 (C{5}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 144.0. $C_{10}H_{10}N^+$ requires 144.1. All data in accordance with the literature.[325]

2-(4-Methoxyphenyl)-1*H*-pyrrole, 2.110



According to the modified procedure of Blagg:[324]

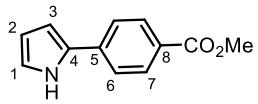
Step 1: K_2CO_3 (622 mg, 4.5 mmol) and 4-methoxyphenylboronic acid (251 mg, 1.65 mmol) were added to a solution of *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **2.114** (369 mg, 1.5 mmol) in toluene (4.5 mL) in a microwave vial. EtOH (0.75 mL) and H_2O (0.75 mL) were then added to the mixture, which was degassed (Ar bubbling for 20 min). $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (61 mg, 0.075 mmol) was then added, the vial sealed, and the reaction allowed to stir at 110 °C for 6 h. After this time, all volatiles were removed *in vacuo* and the resulting residue partitioned between water (15 mL) and EtOAc (15 mL). The aqueous layer was re-extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered through a short silica plug (eluted with EtOAc), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in MeOH/H_2O (3:1, 6.0 mL), and K_2CO_3 (622 mg, 4.5 mmol) added. The resulting dark brown mixture was allowed to stir at 75 °C for 16 h. After this time, volatiles were removed *in vacuo*, and the resulting residue was dissolved in water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a dark brown oil. Purification of the crude mixture by flash-chromatography (5% to 10% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a grey solid (105.8 mg, 0.61 mmol, 41% over 2 steps).

R_f 0.17 (10% EtOAc in $PE_{40\text{-}60}$, red in vanillin); **m.p.** 138–142 °C (from EtOAc) (lit.[326] 147–148 °C) ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.34 (br, 1H, N–H), 7.44–7.37 (m, 2H, C{6}–H), 6.95–6.89 (m, 2H, C{7}–H), 6.83 (ddd, 1H, J = 2.5, 2.5, 1.5 Hz, C{1}–H), 6.41 (ddd, 1H, J = 3.5, 2.5, 1.5 Hz, C{3}–H), 6.28 (ddd, 1H, J = 3.5, 2.5, 2.5 Hz, C{2}–H), 3.83 (s, 3H, C{9}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 158.4 (C{8}), 132.3 (C{4}), 126.1 (C{5}), 125.4 (C{6}), 118.3 (C{1}), 114.5 (C{7}), 110.1 (C{2}), 105.0 (C{3}), 55.5

(C{9}); **LRMS** (*m/z* +ESI): Found: $[M+H]^+$, 174.0. $C_{11}H_{12}NO^+$ requires 174.1. All data in accordance with the literature.[326]

Methyl 4-(1*H*-pyrrol-2-yl)benzoate, 2.111



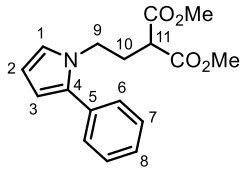
Step 1: According to the modified procedure of Blagg,[324] K_2CO_3 (1.66 g, 12.0 mmol) and (4-(methoxycarbonyl)phenyl)boronic acid (792 mg, 4.4 mmol) were added to a solution of *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **2.114** (738 mg, 4.0 mmol) in toluene (12.0 mL) in a sealed vessel. EtOH (2.0 mL) and H_2O (2.0 mL) were then added to the mixture, which was degassed (Ar bubbling for 20 min). $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (162 mg, 0.20 mmol) was then added, the vessel sealed, and the reaction allowed to stir at 110 °C for 4.5 h. After this time, all volatiles were removed *in vacuo* and the resulting residue partitioned between water (40 mL) and EtOAc (40 mL). The aqueous layer was re-extracted with EtOAc (2 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a brown oil.

Step 2: According to the modified procedure of Maeda,[327] the aforementioned oil was dissolved in anhydrous ethylene glycol (16 mL) and the resulting dark brown mixture was allowed to stir at 170 °C for 30 min. After this time, the reaction mixture was diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a black oil. Purification of the crude mixture by flash-chromatography (10% to 14% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a grey solid (353.4 mg, 1.76 mmol, 44% over 2 steps).

R_f 0.29 (20% EtOAc in $PE_{40\text{-}60}$, pink in vanillin); **m.p.** 174.8 (dec.) (from EtOAc) (lit.[328] 173–176 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (br, 1H, N–H), 8.10–7.96 (m, 2H,

C{7}–H), 7.60–7.47 (m, 2H, C{6}–H), 6.92 (ddd, 1H, J = 2.5, 2.5, 1.5 Hz, C{1}–H), 6.66 (ddd, 1H, J = 4.0, 2.5, 1.5 Hz, C{3}–H), 6.33 (ddd, 1H, J = 4.0, 2.5, 2.5 Hz, C{2}–H), 3.92 (s, 3H, CO_2**Me**); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 167.1 (**C**O_2Me), 137.0 (C{Q}), 131.1 (C{Q}), 130.5 (C{7}), 127.5 (C{Q}), 123.3 (C{6}), 120.4 (C{1}), 110.8 (C{2}), 108.1 (C{3}), 52.2 (CO_2**Me**); **LRMS** (m/z +ESI): Found: $[M+H]^+$, 202.0. $C_{12}H_{12}NO_2^+$ requires 202.1. All data in accordance with the literature.[328]

Dimethyl 2-(2-(2-phenyl-1*H*-pyrrol-1-yl)ethyl)malonate, 2.103



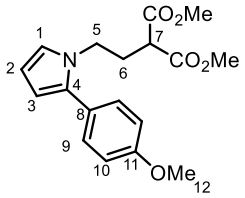
According to the modified procedure of Greenhouse,[312] sodium hydride (60% w/w dispersion in mineral oil, 22 mg, 0.55 mmol) was added to a solution of 2-phenyl-1*H*-pyrrole **2.109** (61 mg, 0.43 mmol) in DMF (2.5 mL) and allowed to stir for 30 min at room temperature. After this time, dimethyl cyclopropane-1,1-dicarboxylate **2.78** (0.14 mL, 1.0 mmol) was added, and the resulting solution allowed to stir at 60 °C for 16 h. The reaction was then quenched with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (5% to 10% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (91.7 mg, 0.30 mmol, 70%).

R$_f$ 0.15 (10% EtOAc in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 4H, C{6,7}–H), 7.33–7.28 (m, 1H, C{8}–H), 6.74 (dd, 1H, J = 3.0, 1.5 Hz, C{1}–H), 6.22 (dd, 1H, J = 3.5, 3.0 Hz, C{2}–H), 6.18 (dd, 1H, J = 3.5, 1.5 Hz, C{3}–H), 4.04 (t, 2H, J = 7.0 Hz, C{9}–H), 3.63 (s, 6H, 2 × CO_2**Me**), 3.14 (t, 1H, J = 7.5 Hz, C{11}–H), 2.20 (dt, 2H, J = 7.5, 7.0 Hz, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.2 (**C**O_2Me),

134.6 (C{4}), 133.4 (C{5}), 129.1 (C{6/7}), 128.6 (C{6/7}), 127.2 (C{8}), 122.2 (C{1}), 109.4 (C{3}), 108.6 (C{2}), 52.7 (CO_2**Me**), 48.6 (C{11}), 44.6 (C{9}), 30.6 (C{10}); ν**/cm**$^{-1}$ (film) 2954w, 1734s, 1436m, 1235s, 762w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 302.1388. $C_{17}H_{20}O_4N^+$ requires 302.1387.

Note: This compound was unstable in $CDCl_3$, even when treated with basic alumina.

Dimethyl 2-(2-(2-(4-methoxyphenyl)-1*H*-pyrrol-1-yl)ethyl)malonate, 2.104

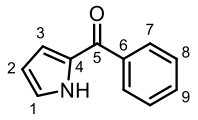


According to the modified procedure of Greenhouse,[312] sodium hydride (60% w/w dispersion in mineral oil, 48 mg, 1.2 mmol) was added to a solution of 2-(4-methoxyphenyl)-1*H*-pyrrole **2.110** (173 mg, 1.0 mmol) in DMF (5.0 mL) and allowed to stir for 30 min at room temperature. After this time, dimethyl cyclopropane-1,1-dicarboxylate **2.78** (0.28 mL, 2.0 mmol) was added, and the resulting solution allowed to stir at 60 °C for 16 h. It was then quenched with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (10% to 20% EtOAc in pentane) provided the *title compound* as a colourless oil (200.4 mg, 0.60 mmol, 60%).

R$_f$ 0.40 (33% EtOAc in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H, C{9}–H), 6.96–6.90 (m, 2H, C{10}–H), 6.71 (dd, 1H, J = 3.0, 2.0 Hz, C{1}–H), 6.20 (dd, 1H, J = 3.5, 3.0 Hz, C{2}–H), 6.11 (dd, 1H, J = 3.5, 2.0 Hz, C{3}–H), 3.99 (t, 2H, J = 7.0 Hz, C{5}–H), 3.84 (s, 3H, C{12}–H), 3.65 (s, 6H, 2 × CO_2**Me**), 3.15 (t, 1H,

J = 7.5 Hz, C{7}–H), 2.19 (dt, 2H, J = 7.5, 7.5 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.3 (**C**O_2Me), 159.0 (C{11}), 134.2 (C{4}), 130.5 (C{9}), 125.9 (C{8}), 121.6 (C{1}), 114.0 (C{10}), 108.9 (C{3}), 108.4 (C{2}), 55.4 (C{12}), 52.8 (CO_2**Me**), 48.7 (C{7}), 44.6 (C{5}), 44.6 (C{6}); ν**/cm**$^{-1}$ (film) 2954w, 1733s, 1506m, 1249s, 837w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 332.1493. $C_{18}H_{22}NO_5^+$ requires 332.1492.

Phenyl(1*H*-pyrrol-2-yl)methanone, 2.115

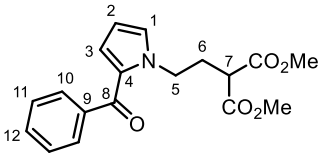


According to the modified procedure of Booker-Milburn,[329] morpholino(phenyl) methanone (574 mg, 3.0 mmol) was added to freshly distilled $POCl_3$ (0.60 mL, 6.5 mmol) and the resulting mixture was allowed to stir at 35 °C until full dissolution. The resulting colourless solution was then allowed to stir at room temperature for 5 h, before a solution of freshly distilled pyrrole (0.14 mL, 2.0 mmol) in CH_2Cl_2 (8 mL) was added rapidly. The reaction was allowed to stir at the same temperature for 16 h. After this time, the reaction was carefully quenched with sat. aq. $NaHCO_3$ (20 mL), and allowed to stir for 15 min at room temperature, then for 3 h at 55 °C. The mixture was then allowed to cool down, the layers separated, and the aqueous extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a white solid (338.7 mg, 1.98 mmol, 98%).

R$_f$ 0.56 (50% EtOAc in $PE_{40\text{-}60}$, brown in vanillin); **m.p.** 78–80 °C (from EtOAc) (lit.[329] 78–81 °C) ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 9.89 (br, 1H, N–H), 7.98–7.84 (m, 2H, C{7}–H), 7.62–7.53 (m, 1H, C{9}–H), 7.53–7.45 (m, 2H, C{8}–H), 7.16 (ddd, 1H, J = 2.5, 2.5, 1.5 Hz, C{1}–H), 6.90 (ddd, 1H, J = 4.0, 2.5, 1.5 Hz, C{3}–H), 6.35 (ddd, 1H, J

= 4.0, 2.5, 2.5 Hz, C{2}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 184.8 (C{5}), 138.3 (C{6}), 131.8 (C{9}), 131.1 (C{4}), 129.0 (C{7}), 128.3 (C{8}), 125.3 (C{1}), 119.5 (C{3}), 111.0 (C{2}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 172.0. $C_{11}H_{10}NO^+$ requires 172.1. All data in accordance with the literature.[329]

Dimethyl 2-(2-(2-benzoyl-1*H*-pyrrol-1-yl)ethyl)malonate, 2.106

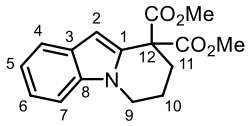


Step 1: According to the modified procedure of Lautens,[317] KOH (1.41 g, 25.0 mmol) was added to a solution of phenyl(1*H*-pyrrol-2-yl)methanone **2.115** (430 mg, 2.50 mmol) in DMSO (6.25 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 1 h, before the addition of 1,2-dibromoethane (4.3 mL, 50 mmol). The reaction was then allowed to stir for 1 h. After this time, the reaction mixture was diluted with water (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil.

Step 2: The aforementioned oil was dissolved in DMF (14 mL) before the addition of dimethyl malonate (0.95 mL, 8.3 mmol) and K_2CO_3 (1.15 g, 8.3 mmol). The resulting mixture was allowed to stir at 60 °C for 2 h and 20 min. After this time, the mixture was diluted with water (50 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (15% to 25% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (219.2 mg, 0.67 mmol, 32% over 2 steps).

R$_f$ 0.28 (30% EtOAc in PE$_{40\text{-}60}$, orange in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.80–7.74 (m, 2H, C{10}–H), 7.56–7.51 (m, 1H, C{12}–H), 7.47–7.42 (m, 2H, C{11}–H), 6.97 (dd, 1H, J = 2.5, 1.5 Hz, C{1}–H), 6.74 (dd, 1H, J = 4.0, 1.5 Hz, C{3}–H), 6.18 (dd, 1H, J = 4.0, 2.5 Hz, C{2}–H), 4.50 (t, 2H, J = 7.0 Hz, C{5}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.40 (t, 1H, J = 7.0 Hz, C{7}–H), 2.45 (dt, 2H, J = 7.0, 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 186.2 (C{8}), 169.5 (**C**O_2Me), 140.1 (C{9}), 131.5 (C{12}), 131.0 (C{1}), 130.0 (C{4}), 129.3 (C{10}), 128.2 (C{11}), 123.8 (C{3}), 108.8 (C{2}), 52.8 (CO_2**Me**), 48.9 (C{7}), 47.0 (C{5}), 30.7 (C{6}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 352.0. $C_{18}H_{19}NNaO_5^+$ requires 352.1. All data in accordance with the literature.[330]

Dimethyl 7,8-dihydropyrido[1,2-*a*]indole-9,9(6*H*)-dicarboxylate, 2.118

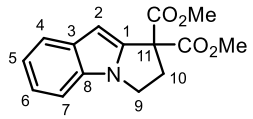


The *title compound* was prepared from dimethyl 2-(3-(1*H*-indol-1-yl)propyl)malonate **2.75** (48 mg, 0.17 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (20% EtOAc in PE$_{40\text{-}60}$) gave the *title compound* as a colourless oil (31 mg, 0.11 mmol, 64%).

R$_f$ 0.40 (30% EtOAc in PE$_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.59 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.29 (ddd, 1H, J = 8.5, 1.0, 1.0 Hz, C{4}–H), 7.20 (ddd, 1H, J = 8.5, 7.0, 1.0 Hz, C{5}–H), 7.11 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{6}–H), 6.60 (d, 1H, J = 1.0 Hz, C{2}–H), 4.08 (t, 2H, J = 6.0 Hz, C{9}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 2.58–2.50 (m, 2H, C{11}–H), 2.18–2.07 (m, 2H, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.5 (**C**O_2Me), 136. (C{1}), 131. (C{8}), 127. (C{3}), 121.8 (C{5}), 120.9 (C{7}), 120.2 (C{6}), 109.2 (C{4}), 102.3 (C{2}), 56.3 (C{12}), 53.3 (CO_2**Me**), 42.0

(C{9}), 28.9 (C{11}), 20.0 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 288.0. $C_{16}H_{18}NO_4^+$ requires 288.1. All data in accordance with the literature.[138]

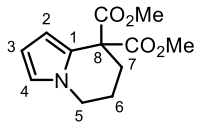
Dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate, 2.119



The *title compound* was prepared from dimethyl 2-(2-(1*H*-indol-1-yl)ethyl)malonate **2.74** (1.00 g, 3.63 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (20% to 30% EtOAc in pentane) gave the *title compound* as a colourless oil (911 mg, 3.33 mmol, 92%).

R$_f$ 0.37 (30% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.61 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.27 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.19 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.10 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.55 (d, 1H, J = 1.0 Hz, C{2}–H), 4.21 (t, 2H, J = 7.0 Hz, C{9}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 3.19 (t, 2H, J = 7.0 Hz, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.6 (**C**O_2Me), 139.0 (C{1}), 132.9 (C{8}), 132.6 (C{3}), 121.8 (C{6}), 121.5 (C{4}), 119.9 (C{5}), 109.9 (C{7}), 96.7 (C{2}), 58.9 (C{11}), 53.5 (CO_2**Me**), 42.7 (C{9}), 37.1 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 274.1. $C_{15}H_{16}NO_4^+$ requires 274.1. All data in accordance with the literature.[138]

Dimethyl 6,7-dihydroindolizine-8,8(5*H*)-dicarboxylate, 2.120

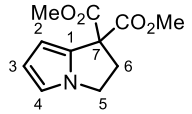


The *title compound* was prepared from dimethyl 2-(3-(1*H*-pyrrol-1-yl)propyl)malonate **2.93** (45 mg, 0.19 mmol) in accordance with **General Procedure B**. Purification by flash-

chromatography (15% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (35 mg, 0.15 mmol, 79%).

R_f 0.28 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.60 (dd, 1H, J = 2.5, 1.5 Hz, C{4}–H), 6.23 (dd, 1H, J = 3.5, 1.5 Hz, C{2}–H), 6.17 (dd, 1H, J = 3.5, 2.5 Hz, C{3}–H), 3.95 (t, 2H, J = 6.0 Hz, C{5}–H), 3.76 (s, 6H, 2 × CO_2**Me**), 2.47–2.38 (m, 2H, C{7}–H), 2.06–1.96 (m, 2H, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.1 (**C**O_2Me), 123.3 (C{1}), 120.6 (C{4}), 109.1 (C{2}), 108.3 (C{3}), 55.4 (C{8}), 53.1 (CO_2**Me**), 45.2 (C{5}), 29.2 (C{7}), 20.7 (C{6}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 238.0. $C_{12}H_{16}NO_4^+$ requires 238.1. All data in accordance with the literature.[138]

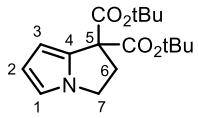
Dimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.121



The *title compound* was prepared from dimethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate **2.85** (437 mg, 1.94 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (20% Et_2O in pentane) afforded the *title compound* as a colourless oil (386 mg, 1.73 mmol, 89%).

R_f 0.41 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.64 (dd, 1H, J = 2.5, 1.5 Hz, C{4}–H), 6.26 (dd, 1H, J = 3.5, 2.5 Hz, C{3}–H), 6.15 (dd, 1H, J = 3.5, 1.5 Hz, C{2}–H), 4.08 (t, 2H, J = 7.0 Hz, C{5}–H), 3.77 (s, H, CO_2**Me**), 3.06 (t, 2H, J = 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.1 (**C**O_2Me), 132.2 (C{1}), 115.3 (C{4}), 113.2 (C{3}), 103.1 (C{2}), 58.6 (C{7}), 53.3 (CO_2**Me**), 45.0 (C{5}), 37.1 (C{6}); **ν/cm^{-1}** (film) 2955w, 1732s, 1267m, 1226m, 1098m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 224.09195. $C_{11}H_{14}NO_4^+$ requires 224.09173.

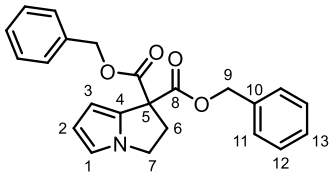
Di-*tert*-butyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.122



The *title compound* was prepared from di-*tert*-butyl 2-(2-(1*H*-pyrrol-1-yl)ethyl) malonate **2.90** (61 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (5% to 7.5% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a white powder (44.0 mg, 0.14 mmol, 72%).

R$_f$ 0.40 (20% EtOAc in $PE_{40\text{-}60}$, purple in vanillin); **m.p.** 110–112 °C (from EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.60 (dd, 1H, J = 2.5, 1.5 Hz, C{1}–H), 6.24 (dd, 1H, J = 3.5, 2.5 Hz, C{2}–H), 6.10 (dd, 1H, J = 3.5, 1.5 Hz, C{3}–H), 4.03 (t, 2H, J = 7.0 Hz, C{7}–H), 2.95 (t, 2H, J = 7.0 Hz, C{6}–H), 1.47 (s, 18H, C**Me**$_3$); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.8 (**C**O_2R), 133.3 (C{4}), 114.9 (C{1}), 113.0 (C{2}), 102.7 (C{3}), 82.0 (**C**Me_3), 60.4 (C{5}), 44.9 (C{7}), 36.4 (C{6}), 28.0 (C**Me**$_3$); ν**/cm**$^{-1}$ (film) 2976w, 1726s, 1160m, 1100m, 715m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 308.1857. $C_{17}H_{26}NO_4^+$ requires 308.1856.

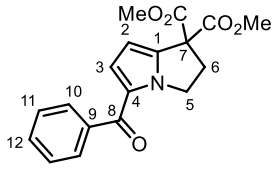
Dibenzyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.123



The *title compound* was prepared from dibenzyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate **2.86** (75 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (10% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (55.3 mg, 0.15 mmol, 75%).

R$_f$ 0.28 (20% EtOAc in PE$_{40\text{-}60}$, orange in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 6H, C{12, 13}–H), 7.26–7.23 (m, 4H, C{11}–H), 6.63 (dd, 1H, J = 2.5, 1.5 Hz, C{1}–H), 6.25 (dd, 1H, J = 3.5, 2.5 Hz, C{2}–H), 6.14 (dd, 1H, J = 3.5, 1.5 Hz, C{3}–H), 5.19–5.11 (m, 4H, C{9}–H), 4.06 (t, 2H, J = 7.0 Hz, C{7}–H), 3.07 (t, 2H, J = 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.3 (**C**O_2R), 135.4 (C{10}), 132.0 (C{4}), 128.7 (C{12}), 128.4 (C{13}), 128.1 (C{11}), 115.3 (C{1}), 113.3 (C{2}), 103.4 (C{3}), 67.7 (C{9}), 58.9 (C{5}), 45.0 (C{7}), 36.9 (C{6}); ν**/cm**$^{-1}$ (film) 2980w, 1734s, 1263m, 1097m, 697w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 376.1543. $C_{23}H_{22}NO_4^+$ requires 376.1543.

Dimethyl 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.125

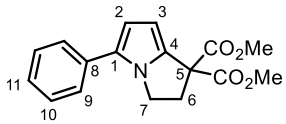


The *title compound* was prepared from dimethyl 2-(2-(2-benzoyl-1*H*-pyrrol-1yl)ethyl) malonate **2.106** (66 mg, 0.20 mmol) in accordance with **General Procedure B** (irradiation time = 48 h). Purification by flash-chromatography (10% to 25% EtOAc in PE$_{40\text{-}60}$) provided the *title compound* as a colourless oil (52.8 mg, 0.16 mmol, 81% yield).

R$_f$ 0.41 (40% EtOAc in PE$_{40\text{-}60}$, orange in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H, C{10}–H), 7.57–7.50 (m, 1H, C{12}–H), 7.48–7.42 (m, 2H, C{11}–H), 6.84 (d, 1H, J = 4.0 Hz, C{3}–H), 6.27 (d, 1H, J = 4.0 Hz, C{2}–H), 4.55 (t, 2H, J = 7.0 Hz, C{5}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 3.14 (t, 2H, J = 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 185.4 (C{8}), 169.2 (**C**O_2Me), 140.4 (C{1}), 139.1 (C{9}), 131.7 (C{12}), 129.1 (C{10}), 128.3 (C{11}), 127.6 (C{4}), 124.7 (C{3}), 105.0 (C{2}), 58.9 (C{7}), 53.6 (CO_2**Me**), 47.1 (C{5}), 36.6 (C{6}); ν**/cm**$^{-1}$ (film) 2955w, 1737s, 1625m,

1262s, 1099m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 328.1178. $C_{18}H_{18}NO_5^+$ requires 328.1179.

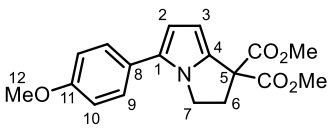
Dimethyl 5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.126



The *title compound* was prepared from dimethyl 2-(2-(2-phenyl-1*H*-pyrrol-1-yl)ethyl) malonate **2.103** (60 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (15% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (50.1 mg, 0.17 mmol, 84%).

R$_f$ 0.23 (20% EtOAc in $PE_{40\text{-}60}$, orange in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H, C{9}–H), 7.39–7.33 (m, 2H, C{10}–H), 7.25–7.19 (m, 1H, C{11}–H), 6.45 (d, 1H, J = 3.5 Hz, C{2}–H), 6.25 (d, 1H, J = 3.5 Hz, C{3}–H), 4.26 (t, 2H, J = 7.0 Hz, C{7}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 3.10 (t, 2H, J = 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.0 (**C**O_2Me), 133.5 (C{4}), 133.1 (C{8}), 130.1 (C{1}), 128.8 (C{10}), 126.4 (C{11}), 126.0 (C{9}), 111.7 (C{2}), 104.2 (C{3}), 58.6 (C{5}), 53.4 (CO_2**Me**), 45.5 (C{7}), 37.0 (C{6}); ν**/cm**$^{-1}$ (film) 2954w, 1735s, 1435m, 1247m, 755m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 300.1231. $C_{17}H_{18}NO_4^+$ requires 300.1230.

Dimethyl 5-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.127

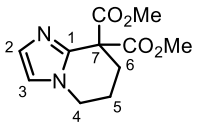


The *title compound* was prepared from dimethyl 2-(2-(2-(4-methoxyphenyl)-1*H*-pyrrol-1-yl)ethyl)malonate **2.104** (66 mg, 0.20 mmol) in accordance with **General Procedure B**.

Purification by flash-chromatography (20% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (61.9 mg, 0.19 mmol, 94%).

R_f 0.16 (20% EtOAc in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.34 (m, 2H, C{9}–H), 6.96–6.87 (m, 2H, C{10}–H), 6.34 (d, 1H, J = 3.5 Hz, C{2}–H), 6.22 (d, 1H, J = 3.5 Hz, C{3}–H), 4.20 (t, 2H, J = 7.0 Hz, C{7}–H), 3.83 (s, 3H, C{12}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 3.09 (t, 2H, J = 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.1 (**C**O_2Me), 158.4 (C{11}), 132.7 (C{4}), 129.9 (C{1}), 127.5 (C{9}), 125.9 (C{8}), 114.3 (C{10}), 110.8 (C{2}), 104.0 (C{3}), 58.7 (C{5}), 55.4 (C{12}), 53.3 (CO_2**Me**), 45.2 (C{7}), 37.1 (C{6}); **ν/cm^{-1}** (film) 2955w, 1735s, 1556m, 1250s, 832w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 330.1335. $C_{18}H_{20}NO_5^+$ requires 330.1336.

Dimethyl 6,7-dihydroimidazo[1,2-*a*]pyridine-8,8(5*H*)-dicarboxylate, 2.128

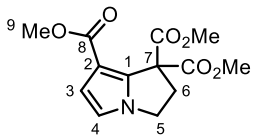


The *title compound* was prepared from dimethyl 2-(3-(1*H*-imidazol-1-yl)propyl) malonate **2.98** (48 mg, 0.20 mmol) in accordance with **General Procedure B** (NIS added over 3 h at −78 °C). Purification by flash-chromatography (2.5% MeOH in CH_2Cl_2) gave the *title compound* as a colourless oil (27.3 mg, 0.11 mmol, 57%).

R_f 0.14 (EtOAc, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.11 (d, 1H, J = 1.5 Hz, C{2}–H), 6.86 (d, 1H, J = 1.5 Hz, C{3}–H), 4.01 (t, 2H, J = 6.0 Hz, C{4}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 2.59–2.52 (m, 2H, C{6}–H), 2.06–1.97 (m, 2H, C{5}–H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.5 (**C**O_2Me), 139.7 (C{1}), 128.8 (C{2}), 119.2 (C{3}), 56.7 (C{7}), 53.6 (CO_2**Me**), 44.7 (C{4}), 29.5 (C{6}), 20.0 (C{5}); **ν/cm^{-1}** (film) 2956w,

1731s, 1436m, 1260m, 1114w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 239.10271. $C_{11}H_{15}N_2O_4^+$ requires 239.10263.

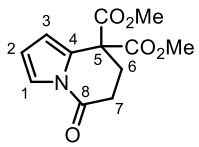
Trimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1,7-tricarboxylate, 2.131



The *title compound* was prepared from dimethyl 2-(2-(3-(methoxycarbonyl)-1*H*-pyrrol-1-yl)ethyl)malonate **2.102** (57 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (35% EtOAc in pentane) provided the *title compound* as a pale-yellow powder (40.4 mg, 0.14 mmol, 72% yield).

R$_f$ 0.23 (40% EtOAc in $PE_{40\text{-}60}$, orange in vanillin); **m.p.** 94–97 °C (from EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.67 (d, 1H, J = 3.0 Hz, C{3}–H), 6.59 (d, 1H, J = 3.0 Hz, C{4}–H), 4.05 (t, 2H, J = 7.0 Hz, C{5}–H), 3.76 (s, 6H, 2 × CO_2**Me**), 3.75 (s, 3H, C{9}–H), 3.20 (t, 2H, J = 7.0 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.6 (**C**O_2Me), 164.5 (C{8}), 137.6 (C{1}), 115.6 (C{4}), 115.0 (C{3}), 110.0 (C{2}), 60.1 (C{7}), 53.4 (CO_2**Me**), 51.0 (C{9}), 45.8 (C{5}), 39.1 (C{6}); ν**/cm**$^{-1}$ (film) 2952w, 1750s, 1733m, 1436m, 1228m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 304.0789. $C_{13}H_{15}NNaO_6^+$ requires 304.0792.

Dimethyl 5-oxo-6,7-dihydroindolizine-8,8(5*H*)-dicarboxylate, 2.133

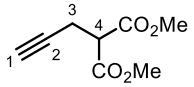


The *title compound* was prepared from dimethyl 2-(3-oxo-3-(1*H*-pyrrol-1-yl)propyl) malonate **2.70** (52 mg, 0.20 mmol) in accordance with **General Procedure C**.

Purification by flash-chromatography (20% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (42 mg, 0.17 mmol, 84%).

R_f 0.38 (30% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.44 (dd, 1H, J = 3.5, 1.5 Hz, C{1}–H), 6.35 (dd, 1H, J = 3.5, 1.5 Hz, C{3}–H), 6.29 (dd, 1H, J = 3.5, 3.5 Hz, C{2}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 2.80–2.71 (m, 2H, C{7}–H), 2.66–2.58 (m, 2H, C{6}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.3 (**C**O_2Me), 166.6 (C{8}), 127.7 (C{4}), 118.0 (C{1}), 113.6 (C{3}), 113.0 (C{2}), 54.5 (C{5}), 53.6 (CO_2**Me**), 30.0 (C{7}), 28.8 (C{6}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 252.0. $C_{12}H_{14}NO_5^+$ requires 252.1. All data in accordance with the literature.[138]

Dimethyl 2-(prop-2-yn-1-yl)malonate, 2.134

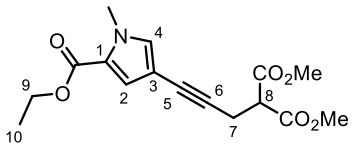


According to the modified procedure of Tang,[331] dimethyl malonate (1.7 mL, 15 mmol) and propargyl bromide (1.1 mL, 10 mmol) were added to a suspension of K_2CO_3 in acetone (40 mL). The resulting mixture was allowed to stir at room temperature for 24 h. After this time, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (eluent: 5% MeOH in CH_2Cl_2; column size: Ø = 7 cm, L = 8 cm) gave the *title compound* as a colourless oil (1.06 g, 6.25 mmol, 63% yield).

R_f 0.52 (30% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.77 (s, 6H, 2 × CO_2**Me**), 3.61 (t, 1H, J = 8.0 Hz, C{4}–H), 2.79 (dd, 2H, J = 8.0, 3.0 Hz, C{3}–H), 2.02 (t, 1H, J = 3.0 Hz, C{1}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 168.3 (**C**O_2Me), 79.8 (C{2}),

70.5 (C{1}), 52.8 (C{4}), 50.9 (CO_2**Me**), 18.5 (C{3}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 171.0. $C_8H_{11}O_4^+$ requires 171.0. All data in accordance with the literature.[331]

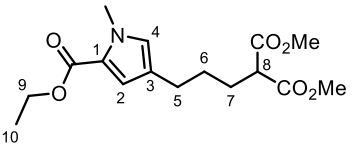
Dimethyl 2-(3-(5-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)prop-2-yn-1-yl)malonate, 4.2



The *title compound* was prepared from ethyl 4-bromo-1-methyl-1*H*-pyrrole-2-carboxylate (116 mg, 0.50 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **2.134** (100 mg, 0.60 mmol) in accordance with **General Procedure D**. Purification of the crude mixture by flash-chromatography (eluent: 20% to 30% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 4 cm, L = 8 cm) gave the *title compound* as a colourless oil (66 mg, 0.21 mmol, 41% yield).

$\mathbf{R}_f$ 0.17 (30% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.92 (d, 1H, J = 2.0 Hz, C{2}–H), 6.85 (d, 1H, J = 2.0 Hz, C{4}–H), 4.26 (q, 2H, J = 7.0 Hz, C{9}–H), 3.87 (s, 3H, N-**Me**), 3.77 (s, 6H, 2 × CO_2**Me**), 3.65 (t, 1H, J = 8.0 Hz, C{8}–H), 2.96 (d, 2H, J = 8.0 Hz, C{7}–H), 1.33 (t, 3H, J = 7.0 Hz, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.7 (**C**O_2Me), 161.0 (**C**O_2Et), 132.3 (C{4}), 122.6 (C{1}), 120.6 (C{2}), 103.9 (C{3}), 83.8 (C{6}), 76.4 (C{5}), 60.2 (C{9}), 52.9 (CO_2**Me**), 51.5 (C{8}), 37.1 (N-**Me**), 19.7 (C{7}), 14.5 (C{10}); ν**/cm**$^{-1}$ (film) 2956w, 1737s, 1702s, 1437m, 1101m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 344.1104. $C_{16}H_{19}NNaO_6^+$ requires 344.1105.

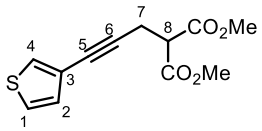
Dimethyl 2-(3-(5-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)propyl) malonate, 2.135



The *title compound* was prepared from dimethyl 2-(3-(5-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)prop-2-yn-1-yl)malonate **4.2** (58 mg, 0.18 mmol) in accordance with **General Procedure E** to give the *title compound* as a brown oil (56 mg, 0.17 mmol, 94% yield).

R$_f$ 0.35 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.75 (d, 1H, J = 2.0 Hz, C{2}–H), 6.57 (d, 1H, J = 2.0 Hz, C{4}–H), 4.25 (q, 2H, J = 7.0 Hz, C{9}–H), 3.86 (s, 3H, N-**Me**), 3.73 (s, 6H, 2 × CO_2**Me**), 3.37 (t, 1H, J = 7.5 Hz, C{8}–H), 2.44 (t, 2H, J = 7.5 Hz, C{5}–H), 1.97–1.89 (m, 2H, C{7}–H), 1.61–1.52 (m, 2H, C{6}–H), 1.33 (t, 3H, J = 7.0 Hz, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.0 (**C**O_2Me), 161.5 (**C**O_2Et), 127.7 (C{4}), 122.9 (C{3}), 122.4 (C{1}), 117.1 (C{2}), 59.8 (C{9}), 52.6 (CO_2**Me**), 51.7 (C{8}), 36.7 (N-**Me**), 28.8 (C{6}), 28.6 (C{7}),26.3 (C{5}),14.6 (C{10}); ν**/cm**$^{-1}$ (film) 2954w, 1734s, 1697s, 1435m, 1097m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 348.1418. $C_{16}H_{23}NNaO_6^+$ requires 348.1418.

Dimethyl 2-(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate), 4.3

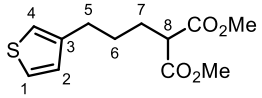


The *title compound* was prepared from 3-bromothiophene (163 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **2.134** (204 mg, 1.20 mmol) in accordance with **General Procedure D**. Purification of the crude mixture by flash-chromatography

(eluent: 20% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 4 cm, L = 10 cm) gave the *title compound* as a yellow oil (140 mg, 0.56 mmol, 56%).

R_f 0.35 (33 % Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.36 (dd, 1H, J = 3.0, 1.0 Hz, C{4}–H), 7.22 (dd, 1H, J = 5.0, 3.0 Hz, C{1}–H), 7.04 (dd, 1H, J = 5.0, 1.0 Hz, C{2}–H), 3.78 (s, 6H, 2 × CO_2**Me**), 3.68 (t, 1H, J = 7.5 Hz, C{8}–H), 2.99 (d, 2H, J = 7.5 Hz, C{7}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.6 (**C**O_2Me), 130.1 (C{2}), 128.6 (C{4}), 125.3 (C{1}), 122.2 (C{3}), 84.9 (C{6}), 77.7 (C{5}), 53.0 (CO_2**Me**), 51.3 (C{8}), 19.6 (C{7}); ν**/cm**$^{-1}$ (film) 2954w, 1736s, 1436m, 1341m, 785m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 275.0349. $C_{12}H_{12}O_4NaS^+$ requires 275.0349.

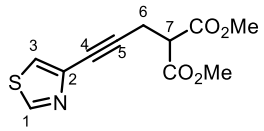
Dimethyl 2-(3-(thiophen-3-yl)propyl)malonate, 2.136



The *title compound* was prepared from dimethyl 2-(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate **4.3** (118 mg, 0.47 mmol) in accordance with **General Procedure E** to give the *title compound* as a yellow oil (112 mg, 0.44 mmol, 93%).

R_f 0.16 (20 % Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.24 (dd, 1H, J = 5.0, 3.0 Hz, C{1}–H), 6.95–6.93 (m, 1H, C{4}–H), 6.92 (dd, 1H, J = 5.0, 1.5 Hz, C{2}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.38 (t, 1H, J = 7.5 Hz, C{8}–H), 2.66 (t, 2H, J = 7.5 Hz, C{5}–H), 1.99–1.91 (m, 2H, C{7}–H), 1.70–1.61 (m, 2H, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 142.0 (C{3}), 128.2 (C{2}), 125.5 (C{1}), 120.4 (C{4}), 52.7 (CO_2**Me**), 51.7 (C{8}), 29.9 (C{5}), 28.6 (C{7}), 28.3 (C{6}); ν**/cm**$^{-1}$ (film) 2953w, 1734s, 1435m, 1154m, 776w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 279.0663. $C_{12}H_{16}O_4NaS^+$ requires 279.0662.

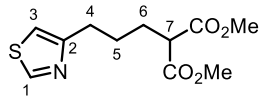
Dimethyl 2-(3-(thiazol-4-yl)prop-2-yn-1-yl)malonate, 4.4



The *title compound* was prepared from 4-bromothiazole (164 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **2.134** (204 mg, 1.20 mmol) in accordance with **General Procedure D**. Purification of the crude mixture by flash-chromatography (5% to 25% acetone in $PE_{40\text{-}60}$) gave the *title compound* as a yellow oil (124 mg, 0.49 mmol, 49%).

R$_f$ 0.39 (40% acetone in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.73 (d, 1H, J = 2.0 Hz, C{1}–H), 7.42 (d, 1H, J = 2.0 Hz, C{3}–H), 3.79 (s, 6H, 2 × CO_2**Me**), 3.72 (t, 1H, J = 7.5 Hz, C{7}–H), 3.04 (d, 2H, J = 7.5 Hz, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.4 (**C**O_2Me), 152.4 (C{1}), 138.4 (C{2}), 122.1 (C{3}), 86.1 (C{5}), 76.5 (C{4}), 53.1 (CO_2**Me**), 50.9 (C{6}), 19.5 (C{7}); ν**/cm**$^{-1}$ (film) 2955w, 1736s, 1436m, 1240m, 1158w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 254.0483. $C_{11}H_{12}O_4NS^+$ requires 254.0482.

Dimethyl 2-(3-(thiazol-4-yl)propyl)malonate, 2.137

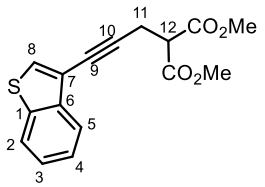


The *title compound* was prepared from dimethyl 2-(3-(thiazol-4-yl)prop-2-yn-1-yl)malonate **4.4** (92.8 mg, 0.37 mmol) in accordance with **General Procedure E** (reaction time = 24 h) to give the *title compound* as a yellow oil (87.7 mg, 0.34 mmol, 92%).

R$_f$ 0.14 (20% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.79 (d, 1H, J = 2.0 Hz, C{1}–H), 7.00 (br, 1H, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.40 (t, 1H, J = 7.5 Hz, C{7}–H), 2.88 (t, 2H, J = 7.5 Hz, C{4}–H), 2.00–1.93 (m, 2H, C{6}–H), 1.83–

1.74 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 157.0 (C{2}), 152.7 (C{1}), 113.5 (C{3}), 52.7 (CO_2**Me**), 51.6 (C{7}), 30.8 (C{4}), 28.4 (C{6}), 27.0 (C{5}); ν**/cm**$^{-1}$ (film) 2954w, 1733s, 1436m, 1150m, 731w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 258.0796. $C_{11}H_{16}O_4NS^+$ requires 258.0795.

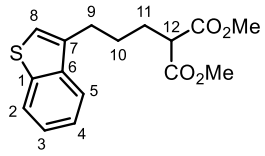
Dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)prop-2-yn-1-yl)malonate, 4.5



The *title compound* was prepared from 3-bromobenzothiophene (213 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **2.134** (204 mg, 1.20 mmol) in accordance with **General Procedure D**. Purification of the crude mixture by flash-chromatography (eluent: 16% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 4 cm, L = 10 cm) gave the *title compound* as a yellow oil (147 mg, 0.49 mmol, 49%).

R$_f$ 0.33 (33 % Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.88 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{5}–H), 7.83 (ddd, 1H, *J* = 8.0, 1.0, 1.0 Hz, C{2}–H), 7.53 (s, 1H, C{8}–H), 7.43 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{4}–H), 7.38 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz, C{3}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 3.77 (t, 1H, *J* = 7.5 Hz, C{12}–H), 3.12 (d, 2H, *J* = 7.5 Hz, C{11}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.6 (**C**O_2Me), 139.5 (C{1}), 138.9 (C{6}), 129.7 (C{8}), 125.1 (C{3}), 124.8 (C{4}), 123.0 (C{5}), 122.7 (C{2}), 118.3 (C{7}), 87.9 (C{10}), 76.4 (C{9}), 53.0 (CO_2**Me**), 51.4 (C{12}), 19.8 (C{11}); ν**/cm**$^{-1}$ (film) 2954w, 1737s, 1435m, 1159m, 760w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 325.0505. $C_{16}H_{14}O_4NaS^+$ requires 325.0505.

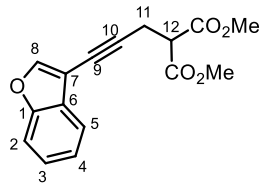
Dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)propyl)malonate, 2.138



The *title compound* was prepared from dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)prop-2-yn-1-yl)malonate **4.5** (124 mg, 0.41 mmol) in accordance with **General Procedure E** to give the *title compound* as a yellow oil (122 mg, 0.40 mmol, 97%).

R$_f$ 0.14 (20 % Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 8.0 Hz, C{2}–H), 7.72 (d, 1H, J = 8.0 Hz, C{5}–H), 7.38 (ddd, 1H, J = 8.0, 7.5, 1.5 Hz, C{4}–H), 7.34 (ddd, 1H, J = 7.5, 7.0, 1.5 Hz, C{3}–H), 7.11 (s, 1H, C{8}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.42 (t, 1H, J = 7.5 Hz, C{12}–H), 2.88 (t, 2H, J = 7.5 Hz, C{9}–H), 2.08–1.99 (m, 2H, C{11}–H), 1.84–1.73 (m, 2H, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 140.6 (C{1}), 139.0 (C{6}), 136.0 (C{7}), 124.3 (C{3}), 124.0 (C{4}), 123.0 (C{2}), 121.7 (C{5}), 121.5 (C{8}), 52.7 (CO_2**Me**), 51.7 (C{12}), 28.8 (C{11}), 28.3 (C{9}), 26.9 (C{10}); ν**/cm**$^{-1}$ (film) 2952w, 1732s, 1434m, 1149m, 762w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 329.0818. $C_{16}H_{18}O_4NaS^+$ requires 329.0818.

Dimethyl 2-(3-(benzofuran-3-yl)prop-2-yn-1-yl)malonate, 4.6

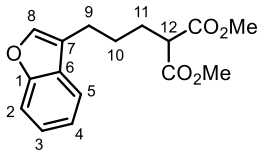


The *title compound* was prepared from 3-bromobenzofuran (197 mg, 1.00 mmol) and dimethyl 2-(prop-2-yn-1-yl)malonate **2.134** (204 mg, 1.20 mmol) in accordance with **General Procedure D**. Purification of the crude mixture by flash-chromatography

(eluent: 10% to 25% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 4 cm, L = 10 cm) gave the *title compound* as a yellow oil (94 mg, 0.33 mmol, 33%).

$\mathbf{R}_f$ 0.19 (20% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.73 (s, 1H, C{8}–H), 7.62 (d, 1H, J = 7.0 Hz, C{5}–H), 7.47 (d, 1H, J = 8.5 Hz, C{2}–H), 7.36–7.25 (m, 2H, C{3, 4}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 3.74 (t, 1H, J = 7.5 Hz, C{12}–H), 3.09 (d, 2H, J = 7.5 Hz, C{11}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.5 (**C**O_2Me), 154.6 (C{1}), 147.5 (C{8}), 127.9 (C{6}), 125.2 (C{3}), 123.4 (C{4}), 120.5 (C{5}), 111.7 (C{2}), 104.4 (C{7}), 90.1 (C{10}), 72.1 (C{9}), 53.0 (CO_2**Me**), 51.4 (C{12}), 19.9 (C{11}); ν/**cm**$^{-1}$ (film) 2955w, 1737s, 1435m, 1089w, 749m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 287.0916. $C_{16}H_{15}O_5^+$ requires 287.0914.

Dimethyl 2-(3-(benzofuran-3-yl)propyl)malonate, 2.139

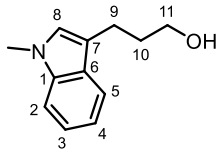


The *title compound* was prepared from dimethyl 2-(3-(benzofuran-3-yl)prop-2-yn-1-yl)malonate **4.6** (94 mg, 0.33 mmol) in accordance with **General Procedure E** to give the *title compound* as a colourless oil (81 mg, 0.28 mmol, 85%).

$\mathbf{R}_f$ 0.40 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, 1H, J = 8.0 Hz, C{2}–H), 7.46 (d, 1H, J = 8.0 Hz, C{5}–H), 7.42 (s, 1H, C{8}–H), 7.28 (dd, 1H, J = 8.0, 7.5 Hz, C{4}–H), 7.23 (dd, 1H, J = 8.0, 7.5 Hz, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.41 (t, 1H, J = 7.5 Hz, C{12}–H), 2.71 (t, 2H, J = 7.5 Hz, C{9}–H), 2.06–1.97 (m, 2H, C{11}–H), 1.80–1.71 (m, 2H, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 155.5 (C{1}), 141.3 (C{8}), 128.2 (C{6}), 124.3 (C{4}), 122.4 (C{3}), 119.7 (C{7}), 119.7 (C{2}), 111.6 (C{5}), 52.6 (CO_2**Me**), 51.6 (C{12}), 28.7 (C{11}), 26.8

(C{10}), 23.4 (C{9}); ν/**cm**$^{-1}$ (film) 2953w, 1733s, 1453m, 1153s, 748m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 291.1227. $C_{16}H_{19}O_5^+$ requires 291.1227.

3-(1-Methyl-1*H*-indol-3-yl)propan-1-ol, 2.153



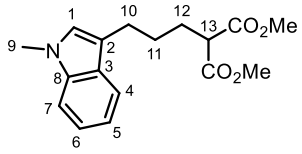
Step 1: According to the modified procedure of Franzén,[162] acrolein (0.20 mL, 3.0 mmol) and *N*-methyl indole (0.56 mL, 4.50 mL) were added to a solution of tritylium tetrafluoroborate (10 mg, 0.030 mmol) in CH_2Cl_2 (10 mL). The resulting pale-yellow solution was allowed to stir at room temperature for 16 h, by which time it had turned pink. This solution was then passed through a short silica plug, which was eluted with CH_2Cl_2. All volatiles were evaporated *in vacuo* to give 3-(1-methyl-1*H*-indol-3-yl)propanal as a colourless oil, which was used in the next step without further purification.

Step 2: According to the modified procedure of Oestreich,[332] the crude 3-(1-methyl-1*H*-indol-3-yl)propanal was dissolved in CH_2Cl_2/MeOH (1:1, 5.2 mL) and cooled to 0 °C. $NaBH_4$ (136 mg, 3.60 mmol) was added in 2 portions over 10 min. The resulting mixture was allowed to stir for 10 min at the same temperature before being quenched with 1.0 M aq. HCl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (33% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (401.9 mg, 2.12 mmol, 71% over 2 steps).

R$_f$ 0.17 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.61 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{5}–H), 7.30 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{2}–H), 7.23 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{3}–H), 7.11 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{4}–H), 6.86 (s,

1H, C{8}–H), 3.75 (s, 3H, N–**Me**), 3.73 (t, 2H, *J* = 6.5 Hz, C{11}–H), 2.86 (t, 2H, *J* = 7.5 Hz, C{9}–H), 1.99 (tt, 2H, *J* = 7.5, 6.5 Hz, C{10}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 137.1 (C{1}), 127.9 (C{6}), 126.1 (C{8}), 121.5 (C{3}), 119.0 (C{5}), 118.6 (C{4}), 114.4 (C{7}), 109.1 (C{2}), 62.7 (C{11}), 33.2 (C{10}), 32.5 (N–**Me**), 21.3 (C{9}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 190.0. $C_{15}H_{17}O_4N_2^+$ requires 190.1. All data in accordance with the literature.[332]

Dimethyl 2-(3-(1-methyl-1*H*-indol-3-yl)propyl)malonate, 2.140



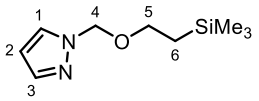
Step 1: Triethylamine (0.21 mL, 1.5 mmol) and methanesulfonyl chloride (0.10 mL, 1.2 mmol) were added dropwise to a solution of 3-(1-methyl-1*H*-indol-3-yl)propan-1-ol **2.153** (189 mg, 1.0 mmol) at 0 °C. The resulting solution was allowed to stir at room temperature for 1 h. After this time, it was quenched with sat. aq. $NaHCO_3$ (30 mL), and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give 3-(1-methyl-1*H*-indol-3-yl)propyl methanesulfonate as a yellow oil.

Step 2: The crude 3-(1-methyl-1*H*-indol-3-yl)propyl methanesulfonate was dissolved in DMF (6.5 mL), before the addition of K_2CO_3 (553 mg, 4.0 mmol) and dimethyl malonate (0.46 mL, 4.0 mmol). The resulting mixture was allowed to stir at 85 °C for 16 h. After this time, the reaction was diluted with water (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-

chromatography (20% to 50% Et_2O in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (111.2 mg, 0.37 mmol, 37% over 2 steps).

R_f 0.33 (50% Et_2O in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.56 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.28 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.21 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.09 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.84 (s, 1H, C{1}–H), 3.74 (s, 3H, C{9}–H), 3.72 (s, 6H, 2 × CO_2**Me**), 3.41 (t, 1H, J = 7.5 Hz, C{13}–H), 2.78 (t, 2H, J = 7.5 Hz, C{10}–H), 2.06–1.97 (m, 2H, C{12}–H), 1.78–1.69 (m, 2H, C{11}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 137.0 (C{8}), 127.7 (C{3}), 126.2 (C{1}), 121.5 (C{6}), 118.9 (C{4}), 118.6 (C{5}), 114.3 (C{2}), 109.1 (C{7}), 52.5 (**C**O_2Me), 51.6 (C{13}), 32.6 (C{9}), 28.7 (C{12}), 28.0 (C{11}), 24.7 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 304.2. $C_{17}H_{22}NO_4^+$ requires 304.2. All data in accordance with the literature.[151]

1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole, 2.142

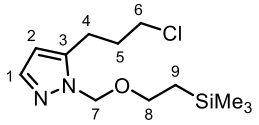


According to the modified procedure of Cossy,[333] a solution of 1*H*-pyrazole (250 mg, 3.67 mmol) in THF (2.5 mL) was added to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 220 mg, 5.5 mmol) in THF (2.5 mL) at 0 °C. The resulting mixture was allowed to stir at room temperature for 2 h before the dropwise addition of 2-(trimethylsilyl)ethoxymethyl chloride (0.72 mL, 4.04 mmol) at 0 °C over 5 min. The reaction was allowed to stir at room temperature for 16 h. After this time, the mixture was cooled to 0 °C, quenched with water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 15% EtOAc in

$PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 11 cm) gave the *title compound* as a colourless oil (385 mg, 1.94 mmol, 53%).

R_f 0.50 (15 % EtOAc in $PE_{40\text{-}60}$, red in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.56 (dd, 1H, J = 2.5, 0.5 Hz, C{1}–H), 7.55 (dd, 1H, J = 2.0, 0.5 Hz, C{3}–H), 6.33 (dd, 1H, J = 2.5, 2.0 Hz, C{2}–H), 5.44 (s, 2H, C{4}–H), 3.61–3.46 (m, 2H, C{5}–H), 0.96–0.78 (m, 2H, C{6}–H), −0.03 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 140.0 (C{3}), 129.5 (C{1}), 106.9 (C{2}), 80.2 (C{4}), 66.8 (C{5}), 17.9 (C{6}), −1.3 (Si(**Me**)$_3$); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 221.0. $C_9H_{18}N_2NaOSi^+$ requires 221.1. All data in accordance with the literature.[333]

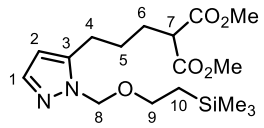
5-(3-Chloropropyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole, 2.143



According to the modified procedure of Zhang,[334] *n*-BuLi (2.5 M in hexanes, 0.65 mL, 1.62 mmol) was added dropwise over 5 min to a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole **2.142** (230 mg, 1.16 mmol) in THF (9.0 mL) at −78 °C. The resulting solution was allowed to stir at this temperature for 1.5 h, before the dropwise addition of 1-bromo-3-chloropropane (0.23 mL, 2.33 mmol). The mixture was then allowed to stir at room temperature for 16 h. After this time, the mixture was cooled to 0 °C, quenched with water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 20% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 12 cm) gave the *title compound* as a colourless oil (110 mg, 0.40 mmol, 34%).

R$_f$ 0.26 (15% EtOAc in $PE_{40\text{-}60}$, vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.43 (d, 1H, J = 2.0 Hz, C{1}–H), 6.12 (d, 1H, J = 2.0 Hz, C{2}–H), 5.43 (s, 2H, C{7}–H), 3.58 (t, 2H, J = 6.5 Hz, C{6}–H), 3.56–3.51 (m, 2H, C{8}–H), 2.89 (t, 2H, J = 7.5 Hz, C{4}–H), 2.20–2.08 (m, 2H, C{5}–H), 0.95–0.81 (m, 2H, C{9}–H), −0.03 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 142.1 (C{3}), 139.1 (C{1}), 105.9 (C{2}), 77.9 (C{7}), 66.4 (C{8}), 44.1 (C{6}), 31.5 (C{5}), 22.5 (C{4}), 18.0 (C{9}), −1.3 (Si(**Me**)$_3$); ν**/cm**$^{-1}$ (film) 2955s, 1733m, 1248s, 1081s, 836s; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 275.13410. $C_{12}H_{24}ON_2{}^{35}Cl^{28}Si^+$ requires 275.13409.

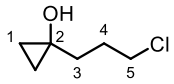
Dimethyl 2-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)propyl) malonate, 2.144



According to the modified procedure of Kerr,[138] dimethyl malonate (0.10 mL, 0.88 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 36 mg, 0.88 mmol) in DMF (1.7 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 5-(3-chloropropyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole **2.143** (95 mg, 0.35 mmol) in THF (1.7 mL) was added dropwise to the mixture, which was allowed to stir at 80 °C for 24 h. The reaction was then quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 12 cm) gave the *title compound* as a colourless oil (81 mg, 0.22 mmol, 63%).

R$_f$ 0.35 (67% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.40 (d, 1H, J = 2.0 Hz, C{1}–H), 6.09 (d, 1H, J = 2.0 Hz, C{2}–H), 5.40 (s, 2H, C{8}–H), 3.74 (s, 6H, 2 × CO_2**Me**), 3.55–3.47 (m, 2H, C{9}–H), 3.40 (t, 1H, J = 7.5 Hz, C{7}–H, 2.73 (t, 2H, J = 7.5 Hz, C{4}–H), 2.03–1.93 (m, 2H, C{6}–H), 1.78–1.66 (m, 2H, C{5}–H), 0.92–0.82 (m, 2H, C{10}–H), −0.04 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.8 (**C**O_2Me), 142.9 (C{3}), 139.0 (C{1}), 105.6 (C{2}), 77.9 (C{8}), 66.3 (C{9}), 52.7 (CO_2**Me**), 51.5 (C{7}), 28.5 (C{6}), 26.4 (C{5}), 24.9 (C{4}), 17.9 (C{10}), −1.3 (Si(**Me**)$_3$); ν**/cm**$^{-1}$ (film) 2953w, 1736s, 1436m, 1248m, 836w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 371.20005. $C_{17}H_{31}O_5N_2{}^{28}Si^+$ requires 371.19968.

1-(3-Chloropropyl)cyclopropan-1-ol, 2.154

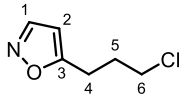


According to the modified procedure of Kulinkovich,[335] titanium(IV) isopropoxide (0.20 mL, 0.66 mmol) was added to a solution of ethyl 4-chlorobutanoate (1.00 g, 6.64 mmol) in Et_2O (13 mL). Ethyl magnesium bromide (1 M in Et_2O, 16.3 mL, 16.3 mmol) was added dropwise over 2.5 h at room temperature; the reaction was then allowed to stir for 1 h at the same temperature. After this time, the mixture was cooled down to 0 °C, quenched with 10% w/w aq. H_2SO_4 (13 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (25 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 5 cm, L = 5.5 cm) gave the *title compound* as a colourless oil (878.3 mg, 6.53 mmol, 98%).

R$_f$ 0.33 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.64 (t, 2H, J = 6.5 Hz, C{5}–H), 2.09–1.96 (m, 2H, C{4}–H), 1.85 (br, 1H, O–H), 1.74–1.61 (m, 2H,

C{3}–H), 0.80–0.73 (m, 2H, C{1}–H), 0.52–0.44 (m, 2H, C{1'}–H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 55.2 (C{2}), 45.2 (C{5}), 35.6 (C{3}), 29.4 (C{4}), 13.8 (C{1}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature. [335]

5-(3-Chloropropyl)isoxazole, 2.146

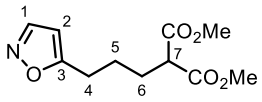


Step 1: According to the modified procedure of Kulinkovich, [163] isoamyl nitrite (0.80 mL, 5.96 mmol) was added to a solution of 1-(3-chloropropyl)cyclopropan-1-ol **2.154** (200 mg, 1.49 mmol) in toluene (0.25 mL) at 0 °C. The reaction was allowed to stir at 0 °C for 2 h and then at room temperature for 87 h. After this time, all volatiles were evaporated *in vacuo* and the resulting oil used in the next step with no further purification.

Step 2: The aforementioned oil was dissolved in methanol (2.5 mL) and allowed to stir at 80 °C for 48 h. After this time, all volatiles were evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (eluent: 50% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 3.5 cm, L = 10 cm) gave the *title compound* as a colourless oil (129.3 mg, 0.89 mmol, 60% over 2 steps).

R_f 0.69 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (br, 1H, C{1}–H), 6.04 (br, 1H, C{2}–H), 3.57 (t, 2H, J = 6.5 Hz, C{6}–H), 2.98 (t, 2H, J = 7.5 Hz, C{4}–H), 2.22–2.13 (m, 2H, C{5}–H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0 (C{3}), 150.3 (C{1}), 100.7 (C{2}), 43.6 (C{6}), 30.2 (C{5}), 23.8 (C{4}); **LRMS** (*m/z* +ESI): Found: $[M+H]^+$, 146.0. $C_6H_9{}^{35}ClNO^+$ requires 146.0. All data in accordance with the literature. [163]

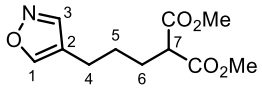
Dimethyl 2-(3-(isoxazol-5-yl)propyl)malonate, 2.145



According to the modified procedure of Kerr,[138] dimethyl malonate (0.20 mL, 1.70 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 68 mg, 1.70 mmol) in DMF (3.5 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 5-(3-chloropropyl)isoxazole **2.146** (100 mg, 0.68 mmol) in THF (3.5 mL) was added dropwise to the mixture, which was then allowed to stir at 80 °C for 16 h. The reaction was then quenched with sat. aq. NH_4Cl (40 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 50 mL) dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 20% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 9 cm) gave the *title compound* as a colourless oil (18.5 mg, 0.077 mmol, 11%).

R$_f$ 0.56 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.14 (d, 1H, J = 2.0 Hz, C{1}–H), 6.01 (dd, 1H, J = 2.0, 1.0 Hz, C{2}–H), 3.74 (s, 6H, 2 × CO_2**Me**), 3.39 (t, 1H, J = 7.5 Hz, C{7}–H), 2.81 (t, 2H, J = 7.5 Hz, C{4}–H), 2.01–1.93 (m, 2H, C{6}–H), 1.80–1.69 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.9 (C{3}), 169.6 (**C**O_2Me), 150.4 (C{1}), 100.4 (C{2}), 52.8 (CO_2**Me**), 51.4 (C{7}), 28.3 (C{6}), 26.3 (C{4}), 25.4 (C{5}); ν**/cm**$^{-1}$ (film) 2958w, 1731s, 1594w, 1435m, 1154s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 264.08416. $C_{11}H_{15}O_5NNa^+$ requires 264.08424.

Dimethyl 2-(3-(isoxazol-4-yl)propyl)malonate, 2.149



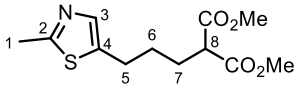
Step 1: According to the modified procedure of Itoh,[321] triethylamine (0.37 mL, 2.7 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) were added dropwise to a solution of 3-(isoxazol-4-yl)propan-1-ol **2.150** (250 mg, 1.97 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C. The resulting mixture was allowed to stir for 25 min at room temperature. After this time, the reaction was quenched with 0.5 M aq. HCl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil, 3-(isoxazol-4-yl)propyl methanesulfonate **2.155**, used in the next step without further purification.

Step 2: Dimethyl malonate (0.56 mL, 4.93 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 197 mg, 4.93 mmol) in DMF (8.0 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of 3-(isoxazol-4-yl)propyl methanesulfonate **2.155** in THF (8.0 mL) was added dropwise to the mixture, which was then allowed to stir at 80 °C for 2.5 h. The reaction was then quenched with sat. aq. NH_4Cl (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 3.5 cm, L = 10 cm) gave the *title compound* as a colourless oil (224.2 mg, 0.93 mmol, 47% over 2 steps).

R_f 0.23 (40% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (t, 1H, C{1}–H), 8.14 (s, 1H, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.37 (t, 1H, J = 7.5 Hz, C{7}–H), 2.50 (t, 2H, J = 7.5 Hz, C{4}–H), 1.99–1.87 (m, 2H, C{6}–H), 1.68–1.54 (m, 2H, C{5}–H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7 (**C**O_2Me), 154.5 (C{1}), 150.2 (C{3}), 118.5 (C{2}), 52.7 (CO_2**Me**), 51.4 (C{7}), 28.3 (C{6}), 27.7 (C{5}), 21.9 (C{4});

ν/**cm**$^{-1}$ (film) 2955w, 1731s, 1435m, 1148m, 851w; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 264.08419. $C_{11}H_{15}O_5NNa^+$ requires 264.08424.

Dimethyl 2-(3-(2-methylthiazol-5-yl)propyl)malonate, 2.151



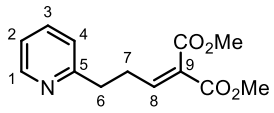
Step 1: According to the modified procedure of Kaufman,[336] *n*-BuLi (2.5 M in hexanes, 2.7 mL, 6.8 mmol) was added dropwise to a solution of 2-methylthiazole (520 mg, 5.24 mmol) in THF (50 mL) at −78 °C. The resulting solution was allowed to stir at this temperature for 1 h before the addition of 1-bromo-3-chloropropane (1.0 mL, 11 mmol). The reaction was then allowed to warm up to room temperature and stirred for 16 h. After this time, the reaction mixture was quenched with water (6 mL) and all volatiles were evaporated *in vacuo*. The resulting oil was partitioned between water (30 mL) and EtOAc (50 mL), the layers separated and the aqueous re-extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 40% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 3.5 cm, L = 14 cm) gave a mixture of regioisomers of the desired 5-(3-chloropropyl)-2-methylthiazole **2.156**, which was used in the next step without further purification (477.4 mg).

Step 2: According to the modified procedure of Kerr,[138] dimethyl malonate (0.24 mL, 2.13 mmol) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 85 mg, 2.13 mmol) in DMF (4.0 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 30 min. After this time, a solution of crude 5-(3-chloropropyl)-2-methylthiazole **2.156** (150 mg) in THF (4.0 mL) was added dropwise to the mixture, which was then allowed to stir at 80 °C for 24 h. The reaction

was then quenched with sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 50% to 60% Et_2O in $PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 12 cm) gave the *title compound* as a colourless oil (101.4 mg, 0.37 mmol, 22% over 2 steps).

R_f 0.24 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, 1H, J = 1.0 Hz, C{3}–H), 3.74 (s, 6H, 2 × CO_2**Me**), 3.37 (t, 1H, J = 7.5 Hz, C{8}–H), 2.80 (t, 2H, J = 7.5 Hz, C{5}–H), 2.64 (s, 3H, C{1}–H), 2.00–1.90 (m, 2H, C{7}–H), 1.71–1.61 (m, 2H, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.7 (**C**O_2Me), 164.7 (C{2}), 139.3 (C{3}), 138.1 (C{4}), 52.7 (CO_2**Me**), 51.5 (C{8}), 29.3 (C{6}), 28.2 (C{7}), 26.8 (C{5}), 19.4 (C{1}); **ν/cm^{-1}** (film) 2955w, 1732s, 1436m, 1157s, 638w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 272.09506. $C_{12}H_{18}O_4N^{32}S^+$ requires 272.09511.

Dimethyl 2-(3-(pyridin-2-yl)propylidene)malonate, 2.158

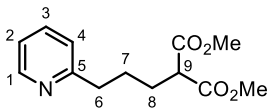


Step 1: According to the modified procedure of Stahl,[164] to a solution of 3-(pyridin-2-yl)propan-1-ol **2.157** (484 mg, 3.53 mmol) in dry MeCN (3.5 mL) were added the following solutions: $[Cu(MeCN)_4)]BF_4$ (56 mg, 0.18 mmol in 3.5 mL MeCN), 2,2-dipyridyl (28 mg, 0.18 mmol in 3.5 mL MeCN), TEMPO (28 mg, 0.18 mmol in 3.5 mL MeCN), *N*-methyl imidazole (29 mg, 0.35 mmol in 3.5 mL MeCN). The resulting dark red solution was allowed to stir vigorously under air for 3 h (accompanied by a change in colour to dark green). The reaction mixture was then diluted with EtOAc (60 mL), filtered through Celite, and evaporated *in vacuo* to give 3-(pyridin-2-yl)propanal as a brown oil, used in the next step without further purification.

Step 2: According to the modified procedure of Wang,[337] *L*-proline (81 mg, 0.71 mmol) was added to a solution of 3-(pyridin-2-yl)propanal in DMSO (17 mL) and stirred for 5 min. After this time, dimethyl malonate (0.81 mL, 7.1 mmol) was added to the solution, which was then allowed to stir at room temperature for 16 h. The reaction mixture was then diluted with EtOAc (20 mL) and washed with brine (30 mL). The organic layer was dried ($MgSO_4$), and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (eluent: 30% to 100% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 5.5 cm, L = 8 cm) afforded the *title compound* as a yellow oil (246 mg, 1.0 mmol, 30% over 2 steps).

$\mathbf{R}_f$ 0.15 (EtOAc, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.52 (d, 1H, J = 5.0 Hz, C{1}–H), 7.59 (ddd, 1H, J = 8.0, 7.5, 2.0 Hz, C{3}–H), 7.15–7.10 (m, 2H, C{4,8}–H), 7.08 (dd, 1H, J = 8.0, 8.0 Hz, C{2}–H), 3.79 (s, 3H, CO_2**Me**), 3.75 (s, 3H, CO_2**Me**), 2.98–2.93 (m, 2H, C{6}–H), 2.80–2.73 (m, 2H, C{7}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 165.8 (**C**O_2Me), 164.4 (**C**O_2Me), 159.9 (C{5}), 149.5 (C{1}), 149.3 (C{2}), 136.7 (C{3}), 128.5 (C{9}), 123.0 (C{8}), 121.6 (C{4}), 52.5 (CO_2**Me**), 52.4 (CO_2**Me**), 36.6 (C{6}), 29.7 (C{7}); ν**/cm**$^{-1}$ (film) 2981m, 1723s, 1435m, 1229s, 7566m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 250.10747. $C_{13}H_{16}O_4N^+$ requires 250.10738.

Dimethyl 2-(3-(pyridin-2-yl)propyl)malonate, 2.159

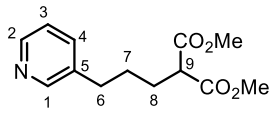


To a solution of dimethyl 2-(3-(pyridin-2-yl)propylidene)malonate **2.158** (100 mg, 0.40 mmol) in EtOAc (5 mL) in a 25 mL round-bottom flask was added palladium on carbon (10% w/w, 21 mg, 0.020 mmol). The flask was sealed and filled with hydrogen (balloon) and allowed to stir for 16 h. After this time, the reaction mixture was filtered

through Celite under a nitrogen blanket and the filtrate evaporated *in vacuo* to give the *title compound* as a yellow oil (87.6 mg, 0.35 mmol, 88%) with no need for further purification.

R$_f$ 0.24 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.51 (ddd, 1H, J = 5.0, 2.0, 1.0 Hz, C{1}–H), 7.58 (ddd, 1H, J = 8.0, 8.0, 2.0 Hz, C{3}–H), 7.13 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.10 (ddd, 1H, J = 8.0, 5.0, 1.0 Hz, C{2}–H), 3.72 (s, 6H, 2 × CO_2**Me**), 3.40 (t, 1H, J = 7.5 Hz, C{9}–H), 2.81 (t, 2H, J = 7.5 Hz, C{6}–H), 2.02–1.91 (m, 2H, C{8}–H), 1.84–1.70 (m, 2H, C{7}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 161.4 (C{5}), 149.4 (C{1}), 136.5 (C{3}), 122.9 (C{4}), 121.3 (C{2}), 52.6 (CO_2**Me**), 51.7 (C{9}), 37.9 (C{6}), 28.6 (C{8}), 27.5 (C{7}); ν**/cm**$^{-1}$ (film) 2955w, 1732s, 1435m, 1152m, 769w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 252.12314. $C_{13}H_{18}O_4N^+$ requires 252.12303.

Dimethyl 2-(3-(pyridin-3-yl)propyl)malonate, 2.162

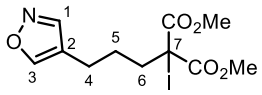


According to the modified procedure of Garrec,[81] 9-BBN (0.5 M in THF, 3.4 mL, 1.7 mmol) was added dropwise to a solution of allyl dimethyl malonate **2.160** (0.24 mL, 1.50 mmol) in dry, degassed THF (8.0 mL) at 0 °C. The resulting solution was allowed to stir at this temperature for 5 min and then at room temperature for 4 h. After this time, K_3PO_4 (1 M in degassed H_2O, 2.7 mL, 2.7 mmol), 3-bromopyridine (0.10 mL, 1.0 mmol) and a solution of $Pd(OAc)_2$ (11 mg, 0.05 mmol) and triphenylphosphine (39 mg, 0.15 mmol) in degassed 1,4-dioxane (9.0 mL) were added to the reaction mixture. The reaction was then allowed to stir at 75 °C for 21 h. After this time, the reaction was diluted with brine (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown

oil. Purification of the crude mixture by flash-chromatography (eluent: 6% to 70% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 3 cm, L = 11 cm) afforded the *title compound* as a colourless oil (181 mg, 0.72 mmol, 72%).

$\mathbf{R}_f$ 0.46 (EtOAc, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.48–8.38 (m, 2H, C{1,2}–H), 7.48 (ddd, 1H, J = 7.5, 2.0, 2.0 Hz, C{4}–H), 7.21 (dd, 1H, J = 7.5, 5.0 Hz, C{3}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.38 (t, 1H, J = 7.5 Hz, C{9}–H), 2.64 (t, 2H, J = 7.5 Hz, C{6}–H), 1.99–1.88 (m, 2H, C{8}–H), 1.75–1.58 (m, 2H, C{7}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.8 (**C**O_2Me), 150.0 (C{1}), 147.7 (C{2}), 136.9 (C{5}), 135.9 (C{4}), 123.5 (C{3}), 52.7 (CO_2**Me**), 51.6 (C{9}), 32.7 (C{6}), 28.9 (C{7}), 28.4 (C{8}); ν**/cm**$^{-1}$ (film) 2954w, 1733s, 1435m, 1151m, 716w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 252.12299. $C_{13}H_{18}O_4N^+$ requires 252.12303.

Dimethyl 2-iodo-2-(3-(isoxazol-4-yl)propyl)malonate, 2.164

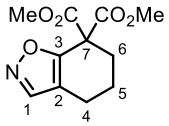


The *title compound* was prepared from dimethyl 2-(3-(isoxazol-4-yl)propyl)malonate **2.149** (300 mg, 1.24 mmol) in accordance with **General Procedure A**. The crude residue was purified by flash-chromatography (eluent: 50% Et_2O in $PE_{40\text{-}60}$) to give the *title compound* as a yellow oil (344 mg, 0.94 mmol, 76% yield).

$\mathbf{R}_f$ 0.29 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.25 (s, 1H, C{3}–H), 8.16 (s, 1H, C{1}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 2.55 (t, 2H, J = 7.5 Hz, C{4}–H), 2.24–2.17 (m, 2H, C{6}–H), 1.73–1.63 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.7 (**C**O_2Me), 154.6 (C{3}), 150.2 (C{1}), 118.3 (C{2}), 54.2 (CO_2**Me**), 42.6 (C{7}), 39.6 (C{6}), 28.2 (C{5}), 21.7 (C{4}); ν**/cm**$^{-1}$ (film) 2954w,

1732s, 1435m, 1249s, 1104m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 367.9989. $C_{11}H_{15}INO_5^+$ requires 367.9989.

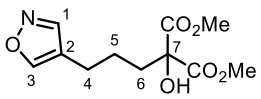
Dimethyl 5,6-dihydrobenzo[*d*]isoxazole-7,7(4*H*)-dicarboxylate, 2.163



TMP (68 μL, 0.40 mmol) was added to a solution of dimethyl 2-iodo-2-(3-(isoxazol-4-yl)propyl)malonate **2.164** (48 mg, 0.20 mmol) in THF (2.0 mL). The reaction mixture was then irradiated using a white 30 W CFL light (at 1.0 cm distance) for 24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography (30% to 33% Et_2O in $PE_{40\text{-}60}$) to give the *title compound* as a colourless oil (30 mg, 0.13 mmol, 63% yield).

R$_f$ 0.33 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.13 (s, 1H, C{1}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 2.52 (t, 2H, J = 6.0 Hz, C{4}–H), 2.48–2.41 (m, 2H, C{6}–H), 1.88–1.80 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.6 (**C**O_2Me), 161.1 (C{3}), 149.5 (C{1}), 115.4 (C{2}), 55.5 (C{7}), 53.6 (CO_2**Me**), 31.6 (C{6}), 20.3 (C{5}), 19.6 (C{4}); ν**/cm**$^{-1}$ (film) 2980m, 1733s, 1436w, 1252m, 1158m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 240.08680. $C_{11}H_{14}NO_5^+$ requires 240.08665.

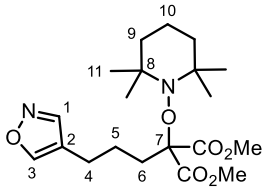
Dimethyl 2-hydroxy-2-(3-(isoxazol-4-yl)propyl)malonate, 2.165



Isolated as a side product of the cyclisation reaction of dimethyl 2-(3-(isoxazol-4yl)propyl) malonate **2.149** in variable yields.

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.22 (s, 1H, C{3}–H), 8.14 (s, 1H, C{1}–H), 3.80 (s, 6H, 2 × CO_2**Me**), 2.50 (t, 2H, J = 7.5 Hz, C{4}–H), 2.10–2.03 (m, 2H, C{6}–H), 1.68–1.58 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.9 (**C**O_2Me), 154.6 (C{3}), 150.3 (C{1}), 118.6 (C{2}), 78.9 (C{7}), 53.7 (CO_2**Me**), 34.2 (C{6}), 23.6 (C{5}), 22.0 (C{4}); **LRMS** (m/z +ESI): Found: $[M+Na]^+$, 280.0. $C_{11}H_{15}NNaO_6^+$ requires 280.1.

Dimethyl 2-(3-(isoxazol-4-yl)propyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-malonate, 2.166

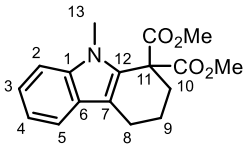


To a solution of dimethyl 2-iodo-2-(3-(isoxazol-4-yl)propyl)malonate **2.164** (50 mg, 0.14 mmol) in dry degassed THF (1.0 mL) were added TMP (51 μL) and TEMPO (26 mg, 0.15 mmol). The reaction mixture was irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography (0% to 30% Et_2O in $PE_{40\text{-}60}$) to give the *title compound* as a yellow oil (47.4 mg, 0.12 mmol, 88%).

R$_f$ 0.32 (40% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.24 (t, 1H, J = 1.0 Hz, C{1}–H), 8.15 (s, 1H, C{3}–H), 3.75 (s, 6H, 2 × CO_2**Me**), 2.50 (t, 2H, J = 7.5 Hz, C{4}–H), 2.32–2.13 (m, 2H, C{6}–H), 1.71–1.59 (m, 2H, C{5}–H), 1.58–1.52 (m, 1H, C{10}–H), 1.52–1.31 (m, 4H, C{9}–H), 1.30–1.22 (m, 1H, C{10'}–H), 1.18 (s, 6H, C{11}–H), 1.06 (s, 6H, C{11'}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.4 (**C**O_2Me), 154.1 (C{1}), 149.9 (C{3}), 118.3 (C{2}), 88.4 (C{7}), 60.6 (C{8}), 51.8 (CO_2**Me**), 40.8 (C{9}), 33.5 (C{6}), 33.0 (C{11}), 24.3 (C{5}), 22.0 (C{4}), 20.5 (C{11'}), 16.6 (C{10}); ν**/cm**$^{-1}$

(film) 2936m, 1743s, 1364w, 1009w, 699w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 397.2338. $C_{20}H_{33}N_2O_6^+$ requires 397.2333.

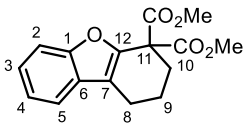
Dimethyl 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-1,1-dicarboxylate, 2.167



The *title compound* was prepared from dimethyl 2-(3-(1-methyl-1*H*-indol-3-yl)propyl) malonate **2.140** (61 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (0% to 30% Et_2O in $PE_{40\text{-}60}$) provided the *title compound* as a colourless oil (53.1 mg, 0.18 mmol, 89%).

R$_f$ 0.47 (50% Et_2O in $PE_{40\text{-}60}$, brown in vanillin); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.52 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{5}–H), 7.30 (ddd, 1H, J = 8.5, 1.0, 1.0 Hz, C{2}–H), 7.27–7.23 (m, 1H, C{3}–H), 7.10 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{4}–H), 3.78 (s, 6H, 2 × CO_2**Me**), 3.65 (s, 3H, C{13}–H), 2.82 (t, 2H, J = 6.5 Hz, C{8}–H), 2.53–2.47 (m, 2H, C{10}–H), 1.99–1.88 (m, 2H, C{9}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.2 (**C**O_2Me), 137.9 (C{1}), 129.9 (C{12}), 126.1 (C{6}), 122.4 (C{3}), 119.1 (C{4}), 118.8 (C{5}), 112.7 (C{7}), 109.2 (C{2}), 56.2 (C{11}), 53.2 (CO_2**Me**), 33.9 (C{10}), 31.0 (C{13}), 21.0 (C{8}), 20.6 (C{9}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 324.0. $C_{17}H_{19}NNaO_4^+$ requires 324.1. All data in accordance with the literature.[56]

Dimethyl 2,3-dihydrodibenzo[*b*,*d*]furan-4,4(1*H*)-dicarboxylate, 2.168

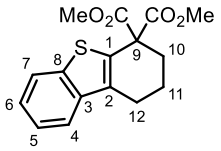


The *title compound* was prepared from dimethyl 2-(3-(benzofuran-3-yl)propyl)malonate **2.139** (58 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by

flash-chromatography (20% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a yellow oil (40.0 mg, 0.14 mmol, 69%).

R_f 0.40 (50% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.50 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{2}–H), 7.47 (ddd, 1H, J = 7.5, 1.0, 1.0 Hz, C{5}–H), 7.29 (ddd, 1H, J = 8.0, 7.5, 1.0 Hz, C{3}–H), 7.23 (ddd, 1H, J = 7.5, 7.5, 1.0 Hz, C{4}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 2.71 (t, 2H, J = 6.0 Hz, C{8}–H), 2.55–2.48 (m, 2H, C{10}–H), 1.97–1.90 (m, 2H, C{9}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.0 (**C**O_2Me), 154.9 (C{1}), 146.8 (C{12}), 127.6 (C{6}), 124.6 (C{3}), 122.5 (C{4}), 119.3 (C{5}), 117.0 (C{7}), 111.6 (C{2}), 56.1 (C{11}), 53.2 (CO_2**Me**), 31.9 (C{10}), 20.3 (C{8}), 20.0 (C{9}); ν**/cm**$^{-1}$ (film) 2953w, 1734s, 1452m, 1253s, 748m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 289.1071. $C_{16}H_{17}O_5^+$ requires 289.1071.

Dimethyl 2,3-dihydrodibenzo[*b,d*]thiophene-4,4(1*H*)-dicarboxylate, 2.169

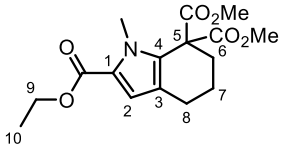


The *title compound* was prepared from dimethyl 2-(3-(benzo[*b*]thiophen-3-yl)propyl)malonate **2.138** (61 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (20% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as an off-white solid (51.8 mg, 0.17 mmol, 85%).

R_f 0.19 (20% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 138–140 °C (from hexane); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.75 (m, 1H, C{7}–H), 7.66–7.60 (m, 1H, C{4}–H), 7.38–7.30 (m, 2H, C{5, 6}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 2.83 (t, 2H, J = 6.5 Hz, C{12}–H), 2.58–2.50 (m, 2H, C{10}–H), 2.02–1.94 (m, 2H, C{11}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.8 (**C**O_2Me), 139.8 (C{8}), 138.5 (C{3}), 133.6 (C{2}), 131.7 (C{1}), 125.0 (C{5}),

124.1 (C{6}), 122.3 (C{7}), 121.6 (C{4}), 57.5 (C{9}), 53.2 (CO_2**Me**), 31.7 (C{10}), 23.9 (C{12}), 19.4 (C{11}); ν/**cm**$^{-1}$ (film) 2952w, 1735s, 1435m, 1247m, 754w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 305.0843. $C_{16}H_{17}O_4S^+$ requires 305.0842.

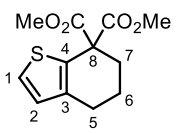
2-Ethyl 7,7-dimethyl 1-methyl-1,4,5,6-tetrahydro-7*H*-indole-2,7,7-tricarboxylate, 2.170



The *title compound* was prepared from dimethyl 2-(3-(5-(ethoxycarbonyl)-1-methyl-1*H*-pyrrol-3-yl)propyl) malonate **2.135** (50 mg, 0.15 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (40% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (28 mg, 0.087 mmol, 58% yield).

R$_f$ 0.16 (33% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.76 (s, 1H, C{2}–H), 4.26 (q, 2H, J = 7.0 Hz, C{9}–H), 3.78 (s, 6H, 2 × CO_2**Me**), 3.76 (s, 3H, N-**Me**), 2.55 (t, 2H, J = 6.5 Hz, C{8}–H), 2.43–2.35 (m, 2H, C{6}–H), 1.82–1.71 (m, 2H, C{7}–H), 1.32 (t, 3H, J = 7.0 Hz, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.9 (**C**O_2Me), 161.6 (**C**O_2Et), 130.4 (C{4}), 123.6 (C{1}), 120.2 (C{3}), 115.6 (C{2}), 59.9 (C{9}), 56.3 (C{5}), 53.3 (CO_2**Me**), 34.1 (N-**Me**), 33.9 (C{6}), 22.8 (C{8}), 20.9 (C{7}), 14.6 (C{10}); ν/**cm**$^{-1}$ (film) 2980w, 1734s, 1700s, 1248s, 1086m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 346.1260. $C_{16}H_{21}NNaO_6^+$ requires 346.1261.

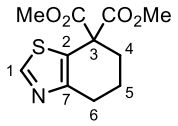
Dimethyl 5,6-dihydrobenzo[*b*]thiophene-7,7(4*H*)-dicarboxylate, 2.171



The *title compound* was prepared from dimethyl 2-(3-(thiophen-3-yl)propyl) malonate **2.136** (51 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (20% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (42.6 mg, 0.17 mmol, 85%).

R_f 0.22 (20% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, 1H, J = 5.0 Hz, C{1}–H), 6.77 (d, 2H, J = 5.0 Hz, C{2}–H), 3.78 (s, 6H, 2 × CO_2**Me**), 2.67 (t, 2H, J = 6.5 Hz, C{5}–H), 2.45–2.39 (m, 2H, C{7}–H), 1.89–1.82 (m, 2H, C{6}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 171.2 (**C**O_2Me), 138.9 (C{3}), 130.3 (C{4}), 127.1 (C{2}), 125.8 (C{1}), 56.9 (C{8}), 53.1 (CO_2**Me**), 31.5 (C{7}), 25.7 (C{5}), 20.0 (C{6}); **ν/cm^{-1}** (film) 2952w, 1736s, 1434m, 1240m, 1177m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 255.0687. $C_{12}H_{15}O_5S^+$ requires 255.0686.

Dimethyl 5,6-dihydrobenzo[*d*]thiazole-7,7(4*H*)-dicarboxylate, 2.174

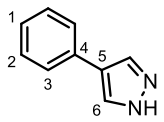


The *title compound* was prepared from dimethyl 2-(3-(thiazol-4-yl)propyl)malonate **2.137** (51 mg, 0.20 mmol) in accordance with **General Procedure B** (irradiation time = 48 h). Purification by flash-chromatography (20% to 30% EtOAc in pentane) provided the *title compound* as a yellow oil (23.0 mg, 0.090 mmol, 46% yield).

R_f 0.31 (60% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.76 (s, 1H, C{1}–H), 3.77 (s, 6H, 2 × CO_2**Me**), 2.87 (t, 2H, J = 6.5 Hz, C{6}–H), 2.45–2.39 (m, 2H, C{4}–H), 2.01–1.90 (m, 2H, C{5}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.4 (**C**O_2Me), 154.1 (C{7}), 153.5 (C{1}), 124.9 (C{2}), 56.1 (C{3}), 53.4 (CO_2**Me**), 31.2 (C{4}), 26.9

(C{6}), 20.1 (C{5}); ν/**cm**$^{-1}$ (film) 2954w, 1736s, 1244m, 1103w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 256.0640. $C_{11}H_{14}NO_4S^+$ requires 256.0638.

4-Phenyl-1*H*-pyrazole, 2.180



According to the modified procedure of Brooke:[172]

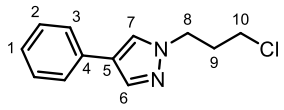
Step 1: $POCl_3$ (2.0 mL, 21.4 mmol) was added to dry DMF (4.5 mL) over 30 min. The resulting mixture was then allowed to stir at room temperature for 1 h before the addition of phenyl acetic acid (1.0 g, 7.3 mmol). The reaction was then allowed to stir at 85 °C for 3 h. After this time, the reaction mixture was allowed to cool down and was poured onto ice (10 mL). Once stirred at room temperature for 30 min, $NaBF_4$ (1.5 g in 1.5 mL H_2O) was added, and the resulting yellow solid filtered. It was then washed with cold water (2 mL) and dried *in vacuo*.

Step 2: The aforementioned solid was added to aq. NaOH (0.60 g in 10 mL H_2O) at 50 °C and the resulting mixture stirred until no solid remained. The solution was then neutralised with 10% w/w HCl to pH *ca.* 5 before the dropwise addition of hydrazine hydrate (50-60% w/w, 1.6 mL, 25.5 mmol). The resulting mixture was allowed to stir for 16 h. After this time, a white solid had formed, which was filtered off and dried *in vacuo* to give the *title compound* as a white crystalline solid (399 mg, 2.78 mmol, 38% over 2 steps).

R$_f$ 0.22 (50 % EtOAc in $PE_{40\text{-}60}$, UV); ^{1}**H NMR** (400 MHz, DMSO–d_6) δ 8.05 (br, 2H, C{6}–H), 7.63–7.56 (m, 2H, C{3}–H), 7.38–7.29 (m, 2H, C{2}–H), 7.22–7.13 (m, 1H, C{1}–H); ^{13}**C NMR** (101 MHz, DMSO–d_6) δ 132.8 (C{4}), 128.7 (C{2}), 125.8 (C{1}),

125.0 (C{3, 6}), 121.1 (C{5}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 145.0. $C_9H_9N_2^+$ requires 145.1. All data in accordance with the literature.[172]

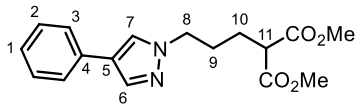
1-(3-chloropropyl)-4-phenyl-1*H*-pyrazole, 2.181



According to the modified procedure of Chen,[338] a mixture of 4-phenyl-1*H*-pyrazole **2.180** (144 mg, 1.00 mmol), 1-bromo-3-chloropropane (0.20 mL, 2.0 mmol) and Cs_2CO_3 (391 mg, 1.20 mmol) was allowed to stir at 80 °C for 1.5 h. After this time, the reaction was allowed to cool to room temperature and poured into water (30 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL), washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (40% to 60% Et_2O in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (160 mg, 0.72 mmol, 72%).

R$_f$ 0.50 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, 1H, J = 1.0 Hz, C{6}–H), 7.68 (d, 1H, J = 1.0 Hz, C{7}–H), 7.51–7.45 (m, 2H, C{3}–H), 7.41–7.32 (m, 2H, C{2}–H), 7.26–7.19 (m, 1H, C{1}–H), 4.35 (t, 2H, J = 6.5 Hz, C{8}–H), 3.51 (t, 2H, J = 6.0 Hz, C{10}–H), 2.36 (tt, 2H, J = 6.5, 6.0 Hz, C{9}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 137.4 (C{6}), 132.6 (C{4}), 129.0 (C{2}), 126.9 (C{7}), 126.6 (C{1}), 125.6 (C{3}), 123.1 (C{5}), 48.9 (C{8}), 41.8 (C{10}), 32.8 (C{9}); ν/**cm**$^{-1}$ (film) 2956w, 1607m, 954m, 760s, 695s; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 221.0842. $C_{12}H_{14}N_2{}^{35}Cl^+$ requires 221.0840.

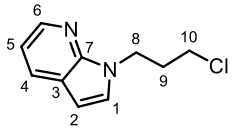
Dimethyl 2-(3-(4-phenyl-1*H*-pyrazol-1-yl)propyl)malonate, 2.182



According to the modified procedure of Browne,[315] a mixture of 1-(3-chloropropyl)-4-phenyl-1*H*-pyrazole **2.181** (132 mg, 0.60 mmol), dimethyl malonate (0.27 mL, 2.4 mmol), and K_2CO_3 (332 mg, 2.4 mmol) in DMF (5.0 mL) was allowed to stir at 85 °C for 15 h. After this time, the solvent was evaporated under a flow of N_2 and the resulting residue partitioned between water (20 mL) and EtOAc (40 mL). The layers were separated and the aqueous re-extracted with EtOAc (2 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (30% to 40% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a white solid (130 mg, 0.41 mmol, 68%).

R$_f$ 0.31 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 66–67 °C (from EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, 1H, J = 1.0 Hz, C{6}–H), 7.63 (d, 1H, J = 1.0 Hz, C{7}–H), 7.50–7.44 (m, 2H, C{3}–H), 7.39–7.32 (m, 2H, C{2}–H), 7.25–7.18 (m, 1H, C{1}–H), 4.21–4.13 (m, 2H, C{8}–H), 3.73 (s, 6H, 2 × CO_2**Me**), 3.43–3.36 (m, 1H, C{11}–H), 2.01–1.89 (m, 4H, C{9, 10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.4 (**C**O_2Me), 136.9 (C{6}), 132.6 (C{4}), 128.8 (C{2}), 126.4 (C{1}), 126.0 (C{7}), 125.5 (C{3}), 123.0 (C{5}), 52.6 (CO_2**Me**), 51.8 (C{8}), 51.1 (C{11}), 28.0 (C{9}), 25.9 (C{10}); ν**/cm**$^{-1}$ (film) 2954w, 1733s, 1608m, 1436m, 762m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 317.1497. $C_{17}H_{21}O_4N_2^+$ requires 317.1496.

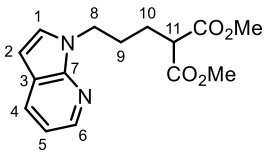
1-(3-Chloropropyl)-1*H*-pyrrolo[2,3-*b*]pyridine, 2.188



According to the modified procedure of Aoki,[339] sodium hydride (60% w/w dispersion in mineral oil, 800 mg, 20.0 mmol) was added to a solution of 7-azaindole (473 mg, 4.00 mmol) in DMF (6 mL) at 0 °C under argon. The resulting mixture was allowed to stir at room temperature for 30 min before the addition of 1-bromo-3-chloropropane (1.2 mL, 12 mmol). The reaction mixture was allowed to stir at room temperature for 15 h. After this time, it was quenched with water (20 mL) and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (20% to 40% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (514 mg, 2.64 mmol, 66%).

R$_f$ 0.37 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.31 (dd, 1H, J = 4.5, 1.5 Hz, C{6}–H), 7.91 (dd, 1H, J = 8.0, 1.5 Hz, C{4}–H), 7.26 (d, 1H, J = 3.5 Hz, C{1}–H), 7.07 (dd, 1H, J = 8.0, 4.5 Hz, C{5}–H), 6.46 (d, 1H, J = 3.5 Hz, C{2}–H), 4.49 (t, 2H, J = 6.5 Hz, C{8}–H), 3.49 (t, 2H, J = 6.5 Hz, C{10}–H), 2.36 (tt, 2H, J = 6.5, 6.5 Hz, C{9}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 147.5 (C{7}), 143.0 (C{6}), 129.0 (C{4}), 128.6 (C{1}), 120.9 (C{3}), 115.9 (C{5}), 99.7 (C{2}), 42.2 (C{10}), 41.9 (C{8}), 32.8 (C{9}); **LRMS** (m/z +ESI): Found: $[M+H]^+$, 195.0. $C_{10}H_{12}{}^{35}ClN_2^+$ requires 195.1. All data in accordance with the literature.[339]

Dimethyl 2-(3-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propyl)malonate, 2.184

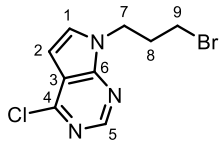


According to the modified procedure of Browne,[315] a mixture of 1-(3-chloropropyl)-1*H*-pyrrolo[2,3-*b*]pyridine **2.188** (195 mg, 1.0 mmol), dimethyl malonate (0.46 mL, 4.0 mmol), and K_2CO_3 (553 mg, 4.0 mmol) in DMF (8.0 mL) was allowed to stir at 85 °C for 16 h.

After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 2 M aq. HCl (3 × 10 mL). These extracts were then basified with 2 M aq. NaOH to pH *ca.* 10, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and evaporated *in vacuo* to give the *title compound* as a red oil (116.9 mg, 0.40 mmol, 40%).

R$_f$ 0.19 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.30 (dd, 1H, J = 4.5, 1.5 Hz, C{6}–H), 7.91 (dd, 1H, J = 8.0, 1.5 Hz, C{4}–H), 7.21 (d, 1H, J = 3.5 Hz, C{1}–H), 7.05 (dd, 1H, J = 8.0, 4.5 Hz, C{5}–H), 6.46 (d, 1H, J = 3.5 Hz, C{2}–H), 4.38–4.28 (m, 2H, C{8}–H), 3.70 (s, 6H, 2 × CO_2**Me**), 3.46–3.35 (m, 1H, C{11}–H), 1.99–1.88 (m, 4H, C{9, 10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.6 (**C**O_2Me), 147.3 (C{7}), 142.6 (C{6}), 129.0 (C{4}), 127.9 (C{1}), 120.7 (C{3}), 115.7 (C{5}), 99.7 (C{2}), 52.6 (CO_2**Me**), 51.1 (C{11}), 44.1 (C{8}), 28.0 (C{9/10}), 26.0 (C{9/10}); ν/**cm**$^{-1}$ (film) 2955w, 1734s, 1428m, 1234m, 776w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 291.1341. $C_{15}H_{19}N_2O_4^+$ requires 291.1339.

7-(3-Bromopropyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine, 2.190

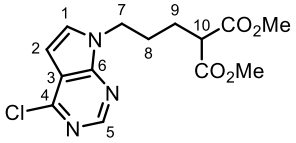


According to the modified procedure of Raić-Malić,[340] K_2CO_3 (829 mg, 6.0 mmol) was added to a solution of 6-chloro-7-deazapurine (768 mg, 5.0 mmol) in DMF (16 mL). The resulting mixture was allowed to stir at room temperature for 1 h before the addition of 1,3-dibromopropane (1.0 mL, 10.0 mmol). It was then allowed to stir for 16 h at the same temperature. After this time, all volatiles were evaporated under a flow of N_2. Purification

of the crude mixture by flash-chromatography (10% EtOAc in $PE_{40\text{-}60}$) gave the *title compound* as a colourless oil (858.4 mg, 3.13 mmol, 63%).

R_f 0.42 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.60 (s, 1H, C{5}–H), 7.29 (d, 1H, J = 3.5 Hz, C{1}–H), 6.58 (d, 1H, J = 3.5 Hz, C{2}–H), 4.44 (t, 2H, J = 6.5 Hz, C{7}–H), 3.31 (t, 2H, J = 6.5 Hz, C{9}–H), 2.40 (tt, 2H, J = 6.5, 6.5 Hz, C{8}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 152.2 (C{4}), 150.9 (C{6}), 150.7 (C{5}), 129.6 (C{1}), 117.7 (C{3}), 99.6 (C{2}), 43.5 (C{7}), 32.4 (C{8}), 29.8 (C{9}); ν**/cm**$^{-1}$ (film) 2947w, 1587s, 1351s, 923s, 726s; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 273.9742. $C_9H_{10}N_3{}^{79}Br^{35}Cl^+$ requires 273.9741.

Dimethyl 2-(3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propyl)malonate, 2.185

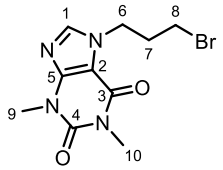


According to the modified procedure of Browne,[315] a mixture of 7-(3-bromopropyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **2.190** (275 mg, 1.0 mmol), dimethyl malonate (0.46 mL, 4.0 mmol), and K_2CO_3 (553 mg, 4.0 mmol) in DMF (5.0 mL) was allowed to stir at 55 °C for 15 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (30% to 40% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as a pink oil (254.6 mg, 0.78 mmol, 78%).

R_f 0.29 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.63 (s, 1H, C{5}–H), 7.25 (d, 1H, J = 3.5 Hz, C{1}–H), 6.62 (d, 1H, J = 3.5 Hz, C{2}–H), 4.30 (t, 2H, J = 6.5 Hz, C{7}–H), 3.71 (s, 6H, 2 × CO_2**Me**), 3.41 (t, 1H, J = 7.0 Hz, C{10}–H),

1.97–1.84 (m, 4H, C{8, 9}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.3 (**C**O_2Me), 152.0 (C{4}), 150.9 (C{6}), 150.4 (C{5}), 129.1 (C{1}), 117.5 (C{3}), 99.8 (C{2}), 52.6 (CO_2**Me**), 50.8 (C{10}), 44.6 (C{7}), 27.8 (C{8}), 25.8 (C{9}); ν**/cm**$^{-1}$ (film) 2954w, 1733s, 1352m, 1234m, 927w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 326.0904. $C_{14}H_{17}{}^{35}ClN_3O_4^+$ requires 326.0902.

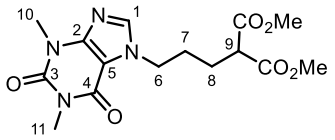
7-(3-Bromopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione, 2.192



According to the modified procedure of Firouzabadi,[341] K_2CO_3 (1.38 g, 10.0 mmol) and 1,3-dibromopropane (1.0 mL, 10.0 mmol) were added to a solution of theophylline (900 mg, 5.0 mmol) in DMF (25 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 16 h. After this time, the reaction was diluted with water (40 mL) and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a white solid. Recrystallisation from hot ethanol provided the *title compound* as a white powder (530.9 mg, 1.77 mmol, 35%).

R$_f$ 0.31 (EtOAc, $KMnO_4$); **m.p.** 132–134 °C (from EtOH) (lit.[342] 132 °C); ^{1}**H NMR** (400 MHz, DMSO–d_6) δ 8.07 (s, 1H, C{1}–H), 4.35 (t, 2H, J = 7.0 Hz, C{6}–H), 3.46 (t, 2H, J = 6.5 Hz, C{8}–H), 3.42 (s, 3H, C{9}–H), 3.22 (s, 3H, C{10}–H), 2.35 (tt, 2H, J = 7.0, 6.5 Hz, C{7}–H); ^{13}**C NMR** (101 MHz, DMSO–d_6) δ 154.3 (C{3}), 150.9 (C{4}), 148.5 (C{5}), 142.5 (C{1}), 106.0 (C{2}), 44.9 (C{6}), 32.7 (C{7}), 30.7 (C{8}), 29.4 (C{9}), 27.5 (C{10}); **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 303.0. $C_{10}H_{14}{}^{81}BrN_4O_2^+$ requires 303.0. All data in accordance with the literature.[341]

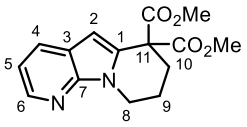
Dimethyl 2-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propyl)-malonate, 2.186



According to the modified procedure of Browne, [315] a mixture of 7-(3-bromopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **2.192** (301 mg, 1.0 mmol), dimethyl malonate (0.46 mL, 4.0 mmol), and K_2CO_3 (553 mg, 4.0 mmol) in DMF (5.0 mL) was allowed to stir at 55 °C for 15 h. After this time, the reaction was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (33% to 60% acetone in $PE_{40\text{-}60}$) gave the *title compound* as a white powder (251.6 mg, 0.71 mmol, 71%).

R_f 0.27 (EtOAc, $KMnO_4$); **m.p.** 108–110 °C (from acetone); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.55 (s, 1H, C{1}–H), 4.30 (t, 2H, J = 6.5 Hz, C{6}–H), 3.72 (s, 6H, 2 × CO_2**Me**), 3.58 (s, 3H, C{10}–H), 3.40 (s, 3H, C{11}–H), 3.39 (t, 1H, J = 7.0 Hz, C{9}–H), 1.99–1.85 (m, 4H, C{7, 8}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.3 (**C**O_2Me), 155.1 (C{4}), 151.7 (C{3}), 149.0 (C{2}), 140.9 (C{1}), 106.9 (C{5}), 52.7 (CO_2**Me**), 50.8 (C{9}), 46.7 (C{6}), 29.8 (C{10}), 28.5 (C{7}), 28.0 (C{11}), 25.4 (C{8}); **ν/cm^{-1}** (film) 2955w, 1733m, 1702s, 1657s, 1234m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 353.1458. $C_{15}H_{21}N_4O_6^+$ requires 353.1456.

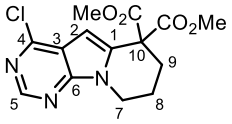
Dimethyl 8,9-dihydropyrido[3,2-*b*]indolizine-6,6(7*H*)-dicarboxylate, 2.194



The *title compound* was prepared from dimethyl 2-(3-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)propyl)malonate **2.184** (130 mg, 0.45 mmol) in accordance with **General Procedure B**. After 48 h of irradiation, the solvent was evaporated *in vacuo*. The resulting residue was diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 2 M aq. HCl (3 × 10 mL). These aqueous layers were combined, neutralised with 2 M NaOH to pH *ca.* 12, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a white solid (106.9 mg, 0.37 mmol, 82%).

R$_f$ 0.15 (33% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 140–142 °C (from EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.30 (dd, 1H, J = 4.5, 1.5 Hz, C{6}–H), 7.87 (dd, 1H, J = 8.0, 1.5 Hz, C{4}–H), 7.06 (dd, 1H, J = 8.0, 4.5 Hz, C{5}–H), 6.56 (s, 1H, C{2}–H), 4.26 (t, 2H, J = 6.0 Hz, C{8}–H), 3.81 (s, 6H, 2 × CO_2**Me**), 2.58–2.52 (m, 2H, C{10}–H), 2.15–2.07 (m, 2H, C{9}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 170.2 (**C**O_2Me), 147.6 (C{7}), 143.1 (C{6}), 131.8 (C{1}), 128.7 (C{4}), 120.3 (C{3}), 116.5 (C{5}), 100.4 (C{2}), 56.3 (C{11}), 53.5 (CO_2**Me**), 41.0 (C{8}), 28.9 (C{10}), 19.8 (C{9}); ν**/cm**$^{-1}$ (film) 2954w, 1734s, 1434m, 1257m, 1064w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 289.1182. $C_{15}H_{17}O_4N_2^+$ requires 289.1183.

Dimethyl 4-chloro-8,9-dihydropyrimido[5,4-*b*]indolizine-6,6(7*H*)-dicarboxylate, 2.195

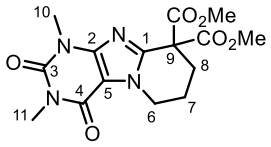


The *title compound* was prepared from dimethyl 2-(3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propyl)malonate **2.185** (65 mg, 0.20 mmol) in accordance with **General Procedure**

B. Purification by flash-chromatography (33% to 50% EtOAc in $PE_{40\text{-}60}$) provided the *title compound* as an off-white powder (57.7 mg, 0.18 mmol, 89%).

R_f 0.32 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 171–172 °C (from EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.62 (s, 1H, C{5}–H), 6.71 (s, 1H, C{2}–H), 4.25 (t, 2H, J = 6.5 Hz, C{7}–H), 3.84 (s, 6H, 2 × CO_2**Me**), 2.59–2.53 (m, 2H, C{9}–H), 2.16–2.08 (m, 2H, C{8}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.3 (**C**O_2Me), 151.9 (C{4/6}), 150.7 (C{4/6}), 150.6 (C{5}), 133.4 (C{1}), 117.2 (C{3}), 100.0 (C{2}), 55.9 (C{10}), 53.6 (CO_2**Me**), 41.5 (C{7}), 28.5 (C{9}), 19.3 (C{8}); ν**/cm**$^{-1}$ (film) 2957w, 1733s, 1432m, 1259s, 1180s; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 324.0747. $C_{14}H_{15}{}^{35}ClN_3O_4^+$ requires 324.0746.

Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4,7,8-hexahydropyrido[2,1-*f*]purine-9,9-(6*H*)-dicarboxylate, 2.196

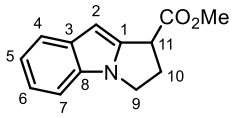


The *title compound* was prepared from dimethyl 2-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propyl) malonate **2.186** (70 mg, 0.20 mmol) in accordance with **General Procedure B**. Purification by flash-chromatography (30% to 70% EtOAc in $PE_{40\text{-}60}$) provided the *title compound*, together with some residual succinimide. It was then dissolved in EtOAc (10 mL) and washed with water (2 × 5 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* in pure form, as a white powder (48.0 mg, 0.14 mmol, 69%).

R_f 0.25 (80% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 201–204 °C (from EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 4.38 (t, 2H, J = 6.5 Hz, C{6}–H), 3.84 (s, 6H, 2 × CO_2**Me**), 3.57 (s,

3H, C{10}–H), 3.39 (s, 3H, C{11}–H), 2.62–2.56 (m, 2H, C{8}–H), 2.10–2.01 (m, 2H, C{7}–H), ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 168.4 (**C**O_2Me), 155.3 (C{4}), 151.7 (C{3}), 148.2 (C{2}), 144.7 (C{1}), 107.4 (C{5}), 57.1 (C{9}), 53.7 (CO_2**Me**), 44.8 (C{6}), 30.1 (C{10}), 28.5 (C{8}), 27.9 (C{11}), 19.1 (C{7}); ν**/cm**$^{-1}$ (film) 2956m, 1737m, 1704s, 1663s, 1262m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 351.1299. $C_{15}H_{18}N_4O_6^+$ requires 351.1299.

Methyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1-carboxylate, 2.197

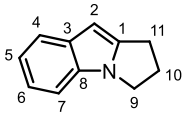


LiCl (84 mg, 2.0 mmol) was added to a solution of dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate **2.119** (110 mg, 0.40 mmol) in DMF/H_2O (100:1, 2.0 mL) at room temperature. The resulting solution was allowed to stir at 150 °C for 2 h. After this time, the reaction mixture was partitioned between Et_2O (15 mL) and water (10 mL). The layers were separated and the aqueous re-extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with water (4 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (5% to 25% EtOAc in pentane) provided the *title compound* as a colourless oil (73.2 mg, 0.34 mmol, 85%).

R$_f$ 0.40 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.57 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.25 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.15 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.08 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.35 (dd, 1H, J = 1.0, 1.0 Hz, C{2}–H), 4.29–4.18 (m, 2H, C{9, 11}–H), 4.10 (ddd, 1H, J = 9.5, 8.5, 5.0 Hz, C{9'}–H), 3.76 (s, 3H, CO_2**Me**), 3.00 (dddd, 1H, J = 13.0, 8.5, 5.0, 5.0 Hz, C{10}–H), 2.83 (dddd, 1H, J = 13.0, 8.5, 8.5, 6.0 Hz, C{10'}–H); ^{13}**C NMR** (126 MHz,

$CDCl_3$) δ 172.3 (**C**O_2Me), 140.9 (C{1}), 132.9 (C{3}), 132.9 (C{8}), 121.2 (C{6}), 121.0 (C{4}), 119.6 (C{5}), 109.8 (C{7}), 94.4 (C{2}), 52.7 (CO_2**Me**), 43.2 (C{9}), 42.5 (C{11}), 31.5 (C{10}); ν/**cm**$^{-1}$ (film) 2951w, 1738s, 1457w, 1207m, 745m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 216.1021. $C_{13}H_{14}O_2N^+$ requires 216.1019.

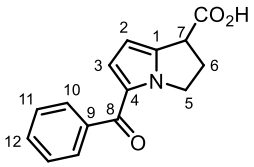
2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole, 2.198



LiCl (64 mg, 1.5 mmol) was added to a solution of dimethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,1-dicarboxylate **2.119** (41 mg, 0.15 mmol) in DMF/H_2O (100:1, 1.5 mL) at room temperature. The resulting solution was allowed to stir at 150 °C for 18 h. After this time, the reaction mixture was partitioned between Et_2O (10 mL) and water (10 mL). The layers were separated and the aqueous re-extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with water (4 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a colourless oil (21.2 mg, 0.13 mmol, 89%).

R$_f$ 0.58 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.57 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{4}–H), 7.26 (ddd, 1H, J = 8.0, 1.0, 1.0 Hz, C{7}–H), 7.14 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{6}–H), 7.08 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C{5}–H), 6.19 (dt, 1H, J = 1.0, 1.0 Hz, C{2}–H), 4.08 (t, 2H, J = 7.0 Hz, C{9}–H), 3.04 (t, 2H, J = 7.5 Hz, C{11}–H), 2.63 (tt, 2H, J = 7.5, 7.0 Hz, C{10}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 144.7 (C{1}), 133.4 (C{3/8}), 132.8 (C{3/8}), 120.4 (C{4}), 120.2 (C{6}), 119.2 (C{5}), 109.5 (C{7}), 92.4 (C{2}), 43.7 (C{9}), 28.0 (C{10}), 24.4 (C{11}); ν/**cm**$^{-1}$ (film) 2951w, 1738s, 1479m, 1207m, 771m. All data in accordance with the literature.[343]

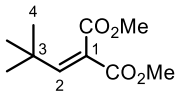
5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid (ketorolac), 2.8



According to the modified procedure of Muchowski,[344] 1 M aq. NaOH (0.12 mL, 0.12 mmol) was added to a solution of dimethyl 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate **2.125** (20 mg, 0.061 mmol) in MeOH (2.0 mL). The resulting solution was allowed to stir at room temperature for 16 h. After this time, all volatiles were removed *in vacuo* and the resulting residue was dissolved in water (5 mL). This solution was washed with EtOAc (2 × 5 mL), and then acidified with 2 M aq. HCl to pH *ca.* 2. The acidic aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a white solid (13.5 mg, 0.053 mmol, 87%).

R$_f$ 0.05 (40% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); **m.p.** 159–160 °C (from EtOAc) (lit.[345] 160–161 °C); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.87–7.75 (m, 2H, C{10}–H), 7.58–7.49 (m, 1H, C{12}–H), 7.49–7.39 (m, 2H, C{11}–H), 6.84 (d, 1H, J = 4.0 Hz, C{3}–H), 6.15 (d, 1H, J = 4.0 Hz, C{2}–H), 4.58 (ddd, 1H, J = 12.0, 8.5, 6.0 Hz, C{5}–H), 4.47 (ddd, 1H, J = 12.0, 8.5, 6.0 Hz, C{5'}–H), 4.11 (dd, 1H, J = 9.0, 5.5 Hz, C{7}–H), 3.02–2.74 (m, 2H, C{6}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 185.3 (C{8}), 176.8 (**C**O_2H), 141.9 (C{1}), 139.2 (C{9}), 131.6 (C{12}), 129.1 (C{10}), 128.3 (C{11}), 127.4 (C{4}), 125.3 (C{3}), 103.6 (C{2}), 47.7 (C{5}), 42.5 (C{7}), 31.1 (C{6}); ν**/cm**$^{-1}$ (film) 3000br (CO_2H), 1739s, 1712s, 1270s, 723s; **HRMS** (*m*/*z* −ESI): Found: $[M–H]^-$, 254.0832. $C_{15}H_{12}NO_3^-$ requires 254.0823. All data in accordance with the literature.[346]

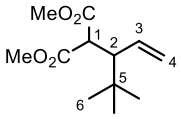
Dimethyl 2-(2,2-dimethylpropylidene)malonate, 3.101



According to the modified procedure of Sakai,[236] pivaldehyde (4.4 mL, 40 mmol), dimethyl malonate (9.2 mL, 80 mmol), and acetic anhydride (3.8 mmol, 40 mmol) were added to a suspension of $InCl_3$ (1.76 g, 8.00 mmol) in dry toluene (20.0 mL). The resulting white suspension was allowed to stir at 80 °C for 16 h. After this time, the reaction mixture was allowed to cool down and was quenched with a mixture of sat. aq. $NaHCO_3$ (150 mL) and brine (40 mL). It was then extracted with EtOAc (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 10% to 15% EtOAc in pentane; 300 g SiO_2) provided the *title compound* as a colourless oil (6.16 g, 30.8 mmol, 77%).

R$_f$ 0.50 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.91 (s, 1H, C{2}–H), 3.80 (s, 3H, CO_2**Me**), 3.76 (s, 3H, CO_2**Me'**), 1.12 (s, 9H, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 167.5 (**C**O_2Me), 165.0 (**C**O_2Me'), 156.0 (C{2}), 124.7 (C{1}), 52.6 (CO_2**Me**), 52.4 (CO_2**Me'**), 34.3 (C{3}), 28.9 (C{4}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 223.0. $C_{10}H_{16}NaO_4^+$ requires 223.1. All data in accordance with the literature.[236]

Dimethyl 2-(4,4-dimethylpent-1-en-3-yl)malonate, 3.98

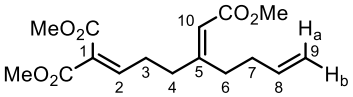


A mixture of dimethyl 2-(2,2-dimethylpropylidene)malonate **3.101** (1.00 g, 5.00 mmol) and CuI (200 mg, 1.05 mmol) in THF (50 mL) was cooled to −78 °C before the dropwise addition of vinylmagnesium bromide (1.0 M in THF, 10 mL, 10 mmol). The resulting

solution was allowed to stir at −40 °C for 1.5 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (125 mL) and extracted with Et_2O (4 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a pale yellow oil (1.11 g, 4.86 mmol, 97%) with no need for further purification.

R$_f$ 0.22 (10% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.84 (ddd, 1H, J = 17.0, 10.0, 10.0 Hz, C{3}–H), 5.12–5.03 (m, 2H, C{4}–H), 3.71 (s, 3H, CO_2**Me**), 3.66 (s, 3H, CO_2**Me'**), 3.61 (d, 1H, J = 7.0 Hz, C{1}–H), 2.72 (dd, 1H, J = 10.0, 7.0 Hz, C{2}–H), 0.88 (s, 9H, C{6}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.0 (**C**O_2Me), 169.3 (**C**O_2Me'), 135.6 (C{3}), 118.7 (C{4}), 54.2 (C{2}), 53.4 (C{1}), 52.7 (CO_2**Me**), 52.3 (CO_2**Me'**), 33.4 (C{5}), 27.8 (C{6}); ν**/cm**$^{-1}$ (film) 2955w, 1737s, 1435w, 1153m, 921w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 251.1253. $C_{12}H_{20}O_4Na^+$ requires 251.1254.

Trimethyl (*E*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate, 3.104



Step 1: NaHMDS (1.0 M in THF, 1.2 mL, 1.2 mmol) was added to a solution of trimethyl (*Z*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.102** (288 mg, 0.92 mmol) in THF (8 mL) at −78 °C. The resulting solution was allowed to stir at this temperature for 20 min. After this time, freshly prepared phenylselenyl bromide[§] (2.0 M in THF, 0.65 mL, 1.3 mmol) was added dropwise. The resulting solution was allowed to stir at −78 °C for 15 min and then at 0 °C for 1 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers

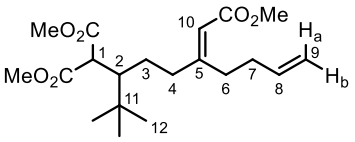
§ **Preparation of phenylselenyl bromide in THF**: Bromine (0.050 mL, 1.95 mmol) was added to a solution of diphenyl diselenide (338 mg, 1.08 mmol) in THF (1.0 mL) at room temperature. The resulting brown solution was allowed to stir at room temperature for 15 min to give a *ca.* 2.0 M solution of phenylselenyl bromide in THF.

were dried (Na_2SO_4) and evaporated *in vacuo* to give trimethyl (*Z*)-5-(but-3-en-1-yl)-1-(phenylselanyl)hex-5-ene-1,1,6-tricarboxylate as a yellow oil, which was used in the next step without further purification.

Step 2: The aforementioned oil was dissolved in CH_2Cl_2 (4.0 mL) and cooled to 0 °C before the dropwise addition of H_2O_2 (30% w/w aq., 1.0 mL, 9.7 mmol). The resulting mixture was allowed to stir at this temperature for 35 min. After this time, the reaction was carefully quenched with sat. aq. $Na_2S_2O_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 30% Et_2O in pentane; 35 g SiO_2) provided the *title compound* as a colourless oil (187 mg, 0.60 mmol, 65% over 2 steps).

R_f 0.33 (20% EtOAc in pentane, brown in vanillin); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.98 (t, 1H, J = 8.0 Hz, C{2}–H), 5.83 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{8}–H), 5.67 (s, 1H, C{10}–H), 5.04 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H_a), 4.97 (ddt, 1H, J = 10.0, 1.5, 1.5 Hz, C{9}–H_b), 3.83 (s, 3H, CO_2**Me**), 3.78 (s, 3H, CO_2**Me'**), 3.69 (s, 3H, CO_2**Me"**), 2.73–2.67 (m, 2H, C{6}–H), 2.52–2.45 (m, 2H, C{3}–H), 2.36–2.30 (m, 2H, C{4}–H), 2.25–2.18 (m, 2H, C{7}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.6 (**C**O_2Me), 165.7 (**C**O_2Me'), 164.3 (**C**O_2Me"), 161.2 (C{5}), 148.5 (C{2}), 137.8 (C{8}), 128.9 (C{1}), 116.4 (C{10}), 115.3 (C{9}), 52.6 (CO_2**Me**), 52.5 (CO_2**Me'**), 51.1 (CO_2**Me"**), 36.6 (C{4}), 32.7 (C{7}), 31.5 (C{6}), 27.8 (C{3}); **ν/cm^{-1}** (film) 2981w, 1719s, 1436m, 1130m, 999w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 333.1307. $C_{16}H_{22}O_6Na^+$ requires 333.1309.

Trimethyl (*E*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.97

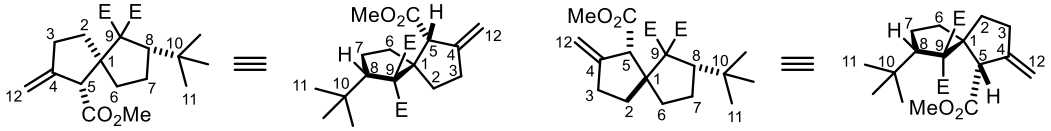


tert-BuLi (1.7 M in hexanes, 0.10 mL, 0.17 mmol) was added dropwise to a suspension of CuCN (8 mg, 0.09 mmol) in dry, degassed THF (3 × freeze/pump/thaw cycles, 0.40 mL) at −78 °C. The resulting yellow mixture was allowed to stir at this temperature for 15 min, and then at −45 °C until all CuCN had dissolved (5–10 min). The resulting pale yellow solution was cooled to −78 °C before the dropwise addition of trimethyl (*E*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate **3.104** (17.5 mg, 0.057 mmol) in THF (0.30 mL). The reaction was then allowed to stir at −45 °C for 1 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (2 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 10% EtOAc in pentane; 2 g SiO_2) provided the *title compound* as a colourless oil (13.5 mg, 0.037 mmol, 64%).

R$_f$ 0.49 (20% EtOAc in pentane, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{8}–H), 5.66 (s, 1H, C{10}–H), 5.04 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H$_a$), 4.95 (ddt, 1H, J = 10.0, 1.5, 1.5 Hz, C{9}–H$_b$), 3.73 (s, 3H, CO_2**Me**), 3.71 (s, 3H, CO_2**Me**'), 3.68 (s, 3H, CO_2**Me**''), 3.66 (d, 1H, J = 4.0 Hz, C{1}–H), 2.72 (dt, 1H, J = 12.5, 8.0 Hz, C{6}–H), 2.64 (dt, 1H, J = 12.5, 8.0 Hz, C{6'}–H), 2.27 (dddd, 1H, J = 14.5, 12.0, 5.0, 1.0 Hz, C{4}–H), 2.24–2.18 (m, 2H, C{7}–H), 2.10–2.03 (m, 2H, C{2, 4'}–H), 1.73 (dddd, 1H, J = 14.5, 12.0, 7.5, 5.0 Hz, C{3}–H), 1.61 (dddd, 1H, J = 14.5, 12.0, 5.0, 4.0 Hz, C{3'}–H), 0.91 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.9 (**C**O_2Me), 169.9 (**C**O_2Me'), 167.0 (**C**O_2Me''), 164.3 (C{5}), 138.2 (C{8}),

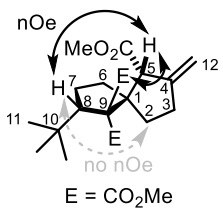
115.4 (C{10}), 114.9 (C{9}), 52.8 (CO_2**Me**), 52.3 (CO_2**Me'**), 51.9 (C{1}), 51.0 (CO_2**Me"**), 48.9 (C{2}), 39.0 (C{4}), 34.6 (C{11}), 32.9 (C{7}), 31.7 (C{6}), 28.0 (C{12}), 26.3 (C{3}); ν**/cm**$^{-1}$ (film) 2953w, 1735s, 1719s, 1435m, 1148s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 391.2087. $C_{20}H_{32}O_6Na^+$ requires 391.2091.

Trimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.107a and trimethyl (2*S**,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]-nonane-1,1,6-tricarboxylate, 3.107b**



The *title compounds* were prepared from trimethyl (*E*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.97** (100 mg, 0.27 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (161 mg, 0.59 mmol), $Cu(OAc)_2 \cdot H_2O$ (59 mg, 0.30 mmol, and DMSO (1.4 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 24 h. Purification of the crude mixture by flash-chromatography (eluent: 0% to 12% EtOAc in pentane; 20 g SiO_2) provided spirocycle **3.107a** as an off-white solid (19.2 mg, 0.052 mmol, 20%) and spirocycle **3.107b** as an off-white solid (52.6 mg, 0.14 mmol, 52%).

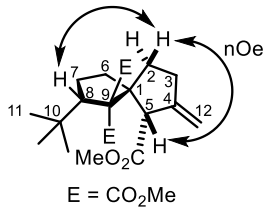
Trimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.107a**



R$_f$ 0.55 (20% EtOAc in pentane, brown in vanillin); **m.p.** 57.2–60.1 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.91 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.76 (ddd, 1H, J = 2.5, 2.5, 2.0 Hz, C{12'}–H), 3.72 (s, 3H, CO_2**Me**), 3.69 (s, 3H, CO_2**Me'**), 3.68 (s, 3H, CO_2**Me"**), 2.98 (ddd, 1H, J = 2.5, 2.0, 2.0 Hz, C{5}–H), 2.82 (dd, 1H, J = 10.5, 10.5 Hz, C{8}–H), 2.44

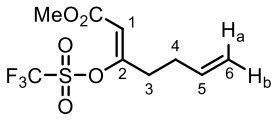
(dddddd, 1H, J = 17.0, 9.5, 9.5, 2.5, 2.5, 2.5 Hz, C{3}–H), 2.32 (ddddd, 1H, J = 17.0, 9.0, 2.5, 2.5, 2.0 Hz, C{3'}–H), 2.18–2.12 (m, 2H, C{6}–H), 2.09 (ddd, 1H, J = 13.0, 9.5, 9.5 Hz, C{2}–H), 1.95 (ddd, 1H, J = 13.0, 9.5, 3.0 Hz, C{2'}–H), 1.92–1.84 (m, 1H, C{7}–H), 1.82–1.72 (m, 1H, C{7'}–H), 0.87 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 173.5 (**C**O_2Me), 170.9 (**C**O_2Me'), 170.8 (**C**O_2Me''), 150.1 (C{4}), 108.2 (C{12}), 68.4 (C{9}), 63.5 (C{1}), 58.3 (C{5}), 54.7 (C{8}), 51.7 (CO_2**Me**), 51.6 (CO_2**Me'**), 51.6 (CO_2**Me''**), 34.7 (C{2}), 33.5 (C{10}), 32.4 (C{6}), 30.0 (C{3}), 28.7 (C{11}), 24.8 (C{7}); ν**/cm**$^{-1}$ (film) 2952w, 1728s, 1434w, 1230m, 1199m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 389.1936. $C_{20}H_{30}O_6Na^+$ requires 389.1935.

Trimethyl (2*S,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.107b**



R$_f$ 0.46 (20% EtOAc in pentane, brown in vanillin); **m.p.** 84.2–86.1 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.90 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.81 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12'}–H), 3.82 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{5}–H), 3.69 (s, 3H, CO_2**Me**), 3.68 (s, 3H, CO_2**Me'**), 3.67 (s, 3H, CO_2**Me''**), 2.91 (dd, 1H, J = 11.0, 9.5 Hz, C{8}–H), 2.61–2.51 (m, 2H, C{3, 6}–H), 2.19 (ddddd, 1H, J = 16.0, 8.0, 3.5, 1.5, 1.5 Hz, C{3'}–H), 1.93–1.84 (m, 1H, C{7}–H), 1.79–1.73 (m, 1H, C{7'}–H), 1.73–1.67 (m, 2H, C{2, 6'}–H), 1.39 (dddd, 1H, J = 13.0, 9.5, 8.0, 1.5 Hz, C{2'}–H), 0.88 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 174.0 (**C**O_2Me), 171.3 (**C**O_2Me'), 171.3 (**C**O_2Me''), 151.3 (C{4}), 107.4 (C{12}), 68.8 (C{9}), 62.1 (C{1}), 55.4 (C{5}), 53.8 (C{8}), 52.0 (CO_2**Me**), 51.7 (CO_2**Me'**), 51.6 (CO_2**Me''**), 36.9 (C{2}), 33.7 (C{10}), 33.4 (C{6}), 31.4 (C{3}), 28.5 (C{11}), 23.9 (C{7}); ν**/cm**$^{-1}$ (film) 2991w, 1728s, 1434w, 1242m, 1073w; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 389.1939. $C_{20}H_{30}O_6Na^+$ requires 389.1935.

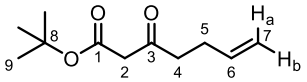
Methyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate, 3.116



The *title compound* was prepared from methyl 3-oxohept-6-enoate **3.113** (780 mg, 5.0 mmol) in accordance with **General Procedure F**. Purification of the crude mixture by flash-chromatography (eluent: 5% to 15% Et_2O in pentane; 200 g SiO_2) provided the *title compound* as a colourless oil (1.28 g, 4.44 mmol, 89%).

R$_f$ 0.53 (30% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.82–5.69 (m, 2H, C{1, 5}–H), 5.12 (dddd, 1H, J = 10.0, 1.5, 1.5, 1.5 Hz, C{6}–H_b), 5.10–5.06 (m, 1H, C{6}–H_a), 3.78 (s, 3H, CO_2**Me**), 2.53–2.46 (m, 2H, C{3}–H), 2.38–2.29 (m, 2H, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 162.9 (**C**O_2Me), 158.3 (C{2}), 134.9 (C{5}), 118.5 (q, J = 321 Hz, **C**F_3), 117.3 (C{6}), 112.1 (C{1}), 52.1 (CO_2**Me**), 34.0 (C{3}), 29.9 (C{4}); ^{19}**F NMR** (376 MHz, $CDCl_3$) δ −74.62; ν**/cm**$^{-1}$ (film) 2957w, 1736m, 1427m, 1206s, 926m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 311.0169. $C_9H_{11}O_5F_3NaS^+$ requires 311.0171.

***tert*-Butyl 3-oxohept-6-enoate, 3.114**

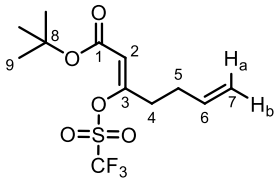


According to the modified procedure of Mattay,[347] *tert*-butyl 3-oxobutanoate (6.6 mL, 40 mmol) in THF (24 mL) was added over 10 min to a mixture of sodium hydride (60% w/w dispersion in mineral oil, 2.0 g, 50 mmol) in THF (120 mL) at 0 °C. The resulting suspension was allowed to stir at this temperature for 1 h. Then, *n*-BuLi (1.6 M in hexanes, 28 mL, 44 mmol) was added over 10 min, and the resulting yellow solution allowed to stir for 20 min at 0 °C. Allyl bromide (3.4 mL, 40 mmol) was then added dropwise and the

reaction allowed to stir for 3 h at 0 °C. After this time, the resulting thick pale-yellow suspension was quenched with sat. aq. NH_4Cl (100 mL) and extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 10% Et_2O in pentane; 250 g SiO_2) provided the *title compound* as a yellow oil (6.11 g, 30.8 mmol, 77%).

R$_f$ 0.45 (20% Et_2O in pentane, purple in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.79 (m, 1H, C{6}–H), 5.09–5.00 (m, 1H, C{7}–H_a), 5.00–4.93 (m, 1H, C{7}–H_a), 3.34 (s, 2H, C{2}–H), 2.67–2.58 (m, 2H, C{4}–H), 2.39–2.28 (m, 2H, C{5}–H), 1.46 (s, 9H, C{9}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 202.6 (C{3}), 166.5 (C{1}), 136.8 (C{6}), 115.6 (C{7}), 82.1 (C{8}), 50.8 (C{2}), 42.1 (C{4}), 28.1 (C{9}), 27.6 (C{5}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 221.0. $C_{11}H_{18}NaO_3^+$ requires 221.1. All data in accordance with the literature.[347]

***tert*-Butyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate, 3.117**

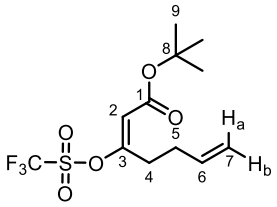


The *title compound* was prepared from *tert*-butyl 3-oxohept-6-enoate **3.114** (6.11 g, 30.8 mmol) in accordance with **General Procedure F**. Purification of the crude mixture by flash-chromatography (eluent: 0% to 6% Et_2O in pentane; 250 g SiO_2) provided the *title compound* as a colourless oil (5.86 g, 17.7 mmol, 58%).

R$_f$ 0.58 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.76 (dddd, 1H, *J* = 17.0, 10.5, 6.5, 6.5 Hz, C{6}–H), 5.68 (t, 1H, *J* = 1.0 Hz, C{2}–H), 5.10 (dddd, 1H, *J*

= 17.0, 1.5, 1.5, 1.5 Hz, C{7}–H_a), 5.08 (dddd, 1H, J = 10.5, 1.5, 1.5, 1.5 Hz, C{7}–H_b), 2.48–2.41 (m, 2H, C{4}–H), 2.36–2.27 (m, 2H, C{5}–H), 1.50 (s, 9H, C{9}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 161.8 (C{1}), 156.6 (C{3}), 135.2 (C{6}), 118.5 (q, J = 320 Hz, **C**F_3), 117.1 (C{7}), 114.1 (C{2}), 82.6 (C{8}), 33.8 (C{4}), 29.9 (C{5}), 28.1 (C{9}); ^{19}**F NMR** (376 MHz, $CDCl_3$) δ −74.62; ν**/cm**$^{-1}$ (film) 2983w, 1725m, 1427m, 1208s, 921s; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 353.0639. $C_{12}H_{17}O_5F_3NaS^+$ requires 353.0641.

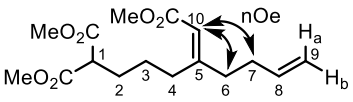
***tert*-Butyl (*E*)-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate, 3.115**



The *title compound* was prepared from *tert*-butyl 3-oxohept-6-enoate **3.114** (991 mg, 5.0 mmol) in accordance with **General Procedure G**. Purification of the crude mixture by flash-chromatography (eluent: 0% to 7% Et_2O in pentane; 150 g SiO_2) provided the *title compound* as a colourless oil (1.09 g, 3.31 mmol, 66%).

R$_f$ 0.58 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.88 (s, 1H, C{2}–H), 5.79 (dddd, 1H, J = 17.0, 10.0, 6.5, 6.5 Hz, C{6}–H), 5.10 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz, C{7}–H_a), 5.05 (dddd, 1H, J = 10.0, 1.5, 1.5, 1.5 Hz, C{7}–H_b), 3.03–2.95 (m, 2H, C{4}–H), 2.40–2.31 (m, 2H, C{5}–H), 1.49 (s, 9H, C{9}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 163.8 (C{1}), 163.2 (C{3}), 135.7 (C{6}), 118.5 (q, J = 320 Hz, **C**F_3), 116.6 (C{7}), 115.0 (C{2}), 82.4 (C{8}), 30.9 (C{4}), 30.4 (C{5}), 28.2 (C{9}); ^{19}**F NMR** (376 MHz, $CDCl_3$) δ −74.02; ν**/cm**$^{-1}$ (film) 2985w, 1723m, 1424m, 1215s, 1143s; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 353.0639. $C_{12}H_{17}O_5F_3NaS^+$ requires 353.0641.

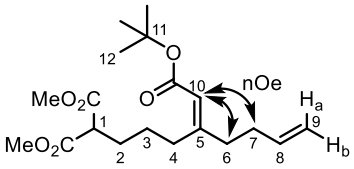
Trimethyl (*E*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate, 3.118



The *title compound* was prepared from methyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.116** (288 mg, 1.0 mmol), dimethyl 2-allylmalonate **2.160** (0.24 mL, 1.5 mmol), 9-BBN (0.5 M in THF, 3.0 mL, 1.5 mmol), aq. K_3PO_4 (1 M, 2.5 mL, 2.5 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (41 mg, 0.050 mmol) in accordance with **General Procedure H**. Purification of the crude mixture by flash-chromatography (eluent: 0% to 12% EtOAc in CH_2Cl_2; 15 g SiO_2) provided the *title compound* as a colourless oil (85.2 mg, 0.27 mmol, 27%).

R$_f$ 0.41 (10% EtOAc in toluene, $KMnO_4$, purple in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84–5.71 (m, 1H, C{8}–H), 5.65 (s, 1H, C{10}–H), 5.03 (dddd, 1H, J = 17.5, 1.5, 1.5, 1.5 Hz, C{9}–H_a), 4.98 (dddd, 1H, J = 10.5, 2.0, 1.0, 1.0 Hz, C{9}–H_b), 3.73 (s, 6H, 2 × CO_2**Me**), 3.67 (s, 3H, CO_2**Me'**), 3.42 (t, 1H, J = 7.5 Hz, C{1}–H), 2.66–2.58 (m, 2H, C{4}–H), 2.24–2.18 (m, 4H, C{6, 7}–H), 1.98–1.91 (m, 2H, C{2}–H), 1.54–1.44 (m, 2H, C{3}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 169.9 (**C**O_2Me), 166.8 (**C**O_2Me'), 162.6 (C{5}), 137.3 (C{8}), 116.0 (C{10}), 115.6 (C{9}), 52.6 (CO_2**Me**), 51.5 (C{1}), 51.0 (CO_2**Me'**), 37.5 (C{6}), 31.7 (C{7}), 31.5 (C{4}), 28.8 (C{2}), 26.2 (C{3}); ν**/cm**$^{-1}$ (film) 2952w, 1736s, 1717s, 1435m, 1158s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 335.1463. $C_{16}H_{24}O_6Na^+$ requires 335.1465.

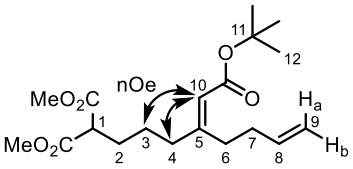
6-(*tert*-Butyl) 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate, 3.119



The *title compound* was prepared from *tert*-butyl (*Z*)-3-(((trifluoromethyl)-sulfonyl) oxy)hepta-2,6-dienoate **3.117** (2.64 g, 8.00 mmol), dimethyl 2-allylmalonate **2.160** (2.1 mL, 13.1 mmol), 9-BBN (0.5 M in THF, 24 mL, 12 mmol), aq. K_3PO_4 (1 M, 20 mL, 20 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (325 mg, 0.40 mmol) in accordance with **General Procedure H**. Purification of the crude mixture by flash-chromatography (eluent: 2.5% to 20% Et_2O in pentane; 350 g SiO_2) provided the *title compound* as a colourless oil (1.74 g, 4.90 mmol, 61%).

R$_f$ 0.38 (30% Et_2O in pentane, $KMnO_4$, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84–5.74 (m, 1H, C{8}–H), 5.57 (s, 1H, C{10}–H), 5.03 (d, 1H, J = 17.0 Hz, C{9}–H_a), 4.98 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.73 (s, 6H, 2 × CO_2**Me**), 3.42 (t, 1H, J = 7.5 Hz, C{1}–H), 2.63–2.56 (m, 2H, C{4}–H), 2.25–2.13 (m, 4H, C{6, 7}–H), 1.99–1.88 (m, 2H, C{2}–H), 1.53–1.44 (m, 2H, C{3}–H), 1.46 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.0 (**C**O_2Me), 166.0 (**C**O_2tBu), 160.2 (C{5}), 137.6 (C{8}), 118.3 (C{10}), 115.4 (C{9}), 79.8 (C{11}), 52.6 (CO_2**Me**), 51.6 (C{1}), 37.5 (C{6}), 31.9 (C{7}), 31.2 (C{4}), 28.8 (C{2}), 28.4 (C{12}), 26.2 (C{3}); ν**/cm**$^{-1}$ (film) 2954w, 1737m, 1708m, 1641w, 1147s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 377.1931. $C_{19}H_{30}O_6Na^+$ requires 377.1935.

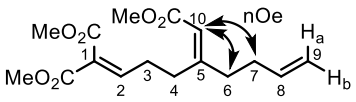
6-(*tert*-Butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate, 3.120



The *title compound* was prepared from *tert*-butyl (*E*)-3-(((trifluoromethyl)-sulfonyl) oxy)hepta-2,6-dienoate **3.115** (495 mg, 1.50 mmol), dimethyl 2-allylmalonate **2.160** (0.39 mL, 2.4 mmol), 9-BBN (0.5 M in THF, 4.5 mL, 2.3 mmol), aq. K_3PO_4 (1 M, 3.8 mL, 3.8 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (61 mg, 0.075 mmol) in accordance with **General Procedure H**. Purification of the crude mixture by flash-chromatography (eluent: 0% to 20% Et_2O in pentane; 125 g SiO_2) provided the *title compound* as a colourless oil (299 mg, 0.84 mmol, 56%).

R$_f$ 0.35 (30% Et_2O in pentane, $KMnO_4$, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.83 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{8}–H), 5.54 (s, 1H, C{10}–H), 5.03 (ddt, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz, C{9}–H$_a$), 4.95 (ddt, 1H, J = 10.0, 1.5, 1.0, 1.0 Hz, C{9}–H$_b$), 3.74 (s, 6H, 2 × CO_2**Me**), 3.37 (t, 1H, J = 7.5 Hz, C{1}–H), 2.67–2.59 (m, 2H, C{6}–H), 2.23–2.16 (m, 2H, C{7}–H), 2.16–2.10 (m, 2H, C{4}–H), 1.95–1.87 (m, 2H, C{2}–H), 1.53–1.47 (m, 2H, C{3}–H), 1.47 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 169.8 (**C**O_2Me), 166.0 (**C**O_2tBu), 160.0 (C{5}), 138.2 (C{8}), 118.3 (C{10}), 114.9 (C{9}), 79.8 (C{11}), 52.7 (CO_2**Me**), 51.6 (C{1}), 37.9 (C{4}), 32.8 (C{7}), 31.1 (C{6}), 28.6 (C{2}), 28.4 (C{12}), 25.4 (C{3}); ν**/cm**$^{-1}$ (film) 2931w, 1754m, 1737m, 1708m, 1141s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 377.1935. $C_{19}H_{30}O_6Na^+$ requires 377.1935.

Trimethyl (*Z*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate, 3.121



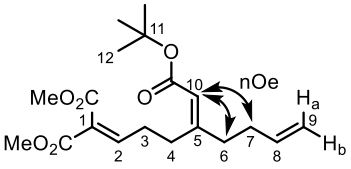
Step 1: NaHMDS (1.0 M in THF, 0.32 mL, 0.32 mmol) was added to a solution of trimethyl (*E*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.118** (85 mg, 0.27 mmol) in THF (2.7 mL) at −78 °C. The resulting solution was allowed to stir at this temperature for 15 min. After this time, freshly prepared phenylselenyl bromide (2.0 M in THF, 0.18 mL, 0.36 mmol) was added dropwise. The resulting solution was allowed to stir at −78 °C for 15 min and then at 0 °C for 1 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give trimethyl (*E*)-5-(but-3-en-1-yl)-1-(phenylselanyl)hex-5-ene-1,1,6-tricarboxylate as a yellow oil, which was used in the next step without further purification.

Step 2: The aforementioned oil was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C before the dropwise addition of H_2O_2 (30% w/w aq., 0.28 mL, 2.7 mmol). The resulting mixture was allowed to stir at this temperature for 35 min. After this time, the reaction was carefully quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 30% Et_2O in pentane; 10 g SiO_2) provided the *title compound* as a colourless oil (51.5 mg, 0.17 mmol, 61% over 2 steps).

R$_f$ 0.42 (10% EtOAc in pentane, $KMnO_4$, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.08 (t, 1H, J = 8.0 Hz, C{2}–H), 5.82–5.72 (m, 1H, C{8}–H), 5.70 (s, 1H, C{10}–H), 5.07–5.02 (m, 1H, C{9}–H_a), 5.02–4.99 (m, 1H, C{9}–H_b), 3.82 (s, 3H,

CO_2**Me**), 3.77 (s, 3H, CO_2**Me'**), 3.69 (s, 3H, CO_2**Me'**), 2.79–2.74 (m, 2H, C{4}–H), 2.54–2.47 (m, 2H, C{3}–H), 2.24–2.20 (m, 4H, C{6, 7}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 166.7 (**C**O_2Me), 165.8 (**C**O_2Me'), 164.4 (**C**O_2Me"), 161.1 (C{5}), 149.4 (C{2}), 137.2 (C{8}), 128.4 (C{1}), 116.7 (C{10}), 115.8 (C{9}), 52.5 (CO_2**Me**), 52.4 (CO_2**Me'**), 51.1 (CO_2**Me"**), 37.7 (C{6}), 31.6 (C{7}), 30.7 (C{4}), 28.8 (C{3}); ν**/cm**$^{-1}$ (film) 2954w, 1718s, 1644m, 1223s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 333.1303. $C_{16}H_{22}O_6Na^+$ requires 333.1309.

6-(*tert*-Butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate, 3.122



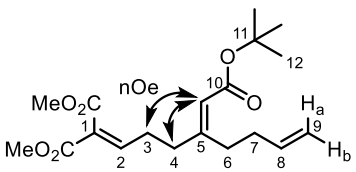
Step 1: NaHMDS (1.0 M in THF, 5.8 mL, 5.8 mmol) was added to a solution of 6-(*tert*-butyl) 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.119** (1.73 g, 4.88 mmol) in THF (50 mL) at −78 °C. The resulting solution was allowed to stir at this temperature for 15 min. After this time, freshly prepared phenylselenyl bromide (2.0 M in THF, 3.7 mL, 7.4 mmol) was added dropwise. The resulting solution was allowed to stir at −78 °C for 15 min and then at 0 °C for 1 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (40 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give 6-(*tert*-butyl) 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)-1-(phenylselanyl)hex-5-ene1,1,6-tricarboxylate as a yellow oil, which was used in the next step without further purification.

Step 2: The aforementioned oil was dissolved in CH_2Cl_2 (18 mL) and cooled to 0 °C before the dropwise addition of H_2O_2 (30% w/w aq., 5.1 mL, 50 mmol). The resulting

mixture was allowed to stir at this temperature for 1 h. After this time, the reaction was filtered through a glass frit and the filtrate washed with sat. aq. $NaHCO_3$ (2 × 20 mL) and sat. aq. $Na_2S_2O_3$ (20 mL). The resulting solution was dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a colourless oil (1.71 g, 0.47 mmol, 99% over 2 steps) with no need for further purification.

R$_f$ 0.48 (10% EtOAc in pentane, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.09 (t, 1H, J = 8.0 Hz, C{2}–H), 5.84–5.73 (m, 1H, C{8}–H), 5.61 (s, 1H, C{10}–H), 5.04 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H$_a$), 4.99 (ddt, 1H, J = 10.0, 2.0, 1.0 Hz, C{9}–H$_b$), 3.82 (s, 3H, CO_2**Me**), 3.77 (s, 3H, CO_2**Me'**), 2.78–2.72 (m, 2H, C{4}–H), 2.53–2.46 (m, 2H, C{3}–H), 2.24–2.14 (m, 4H, C{6, 7}–H), 1.47 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 165.8 (**C**O_2Me), 165.8 (**C**O_2tBu), 164.4 (**C**O_2Me'), 158.9 (C{5}), 149.6 (C{2}), 137.4 (C{8}), 128.3 (C{1}), 118.9 (C{10}), 115.6 (C{9}), 80.0 (C{11}), 52.4 (CO_2**Me**), 52.4 (CO_2**Me'**), 37.6 (C{6}), 31.8 (C{7}), 30.3 (C{4}), 28.9 (C{3}), 28.4 (C{12}); ν/**cm**$^{-1}$ (film) 2924w, 1730s, 1708s, 1643w, 1139s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 375.1774. $C_{19}H_{28}O_6Na^+$ requires 375.1778.

6-(*tert*-Butyl) 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate, 3.123



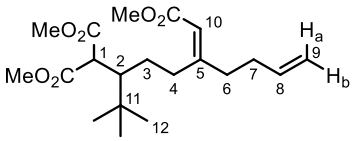
Step 1: NaHMDS (1.0 M in THF, 0.95 mL, 0.95 mmol) was added to a solution of 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.120** (284 mg, 0.80 mmol) in THF (8 mL) at −78 °C. The resulting solution was allowed to stir at this temperature for 15 min. After this time, freshly prepared phenylselenyl bromide (2.0 M

in THF, 1.0 mL, 1.0 mmol) was added dropwise. The resulting solution was allowed to stir at −78 °C for 15 min and then at 0 °C for 1.5 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-(phenylselanyl)hex5-ene-1,1,6-tricarboxylate as a yellow oil, which was used in the next step without further purification.

Step 2: The aforementioned oil was dissolved in CH_2Cl_2 (3.0 mL) and cooled to 0 °C before the dropwise addition of H_2O_2 (30% w/w aq., 0.83 mL, 8.1 mmol). The resulting mixture was allowed to stir at this temperature for 1 h. After this time, the reaction was carefully quenched with sat. aq. $Na_2S_2O_3$ (10 mL), and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a colourless oil (250.6 mg, 0.71 mmol, 89% over 2 steps) with no need for further purification.

R_f 0.47 (10% EtOAc in pentane, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.99 (t, 1H, J = 8.0 Hz, C{2}–H), 5.83 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{8}–H), 5.58 (s, 1H, C{10}–H), 5.03 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H_a), 4.97 (ddt, 1H, J = 10.0, 1.5, 1.5 Hz, C{9}–H_b), 3.83 (s, 3H, CO_2**Me**), 3.79 (s, 3H, CO_2**Me'**), 2.68–2.63 (m, 2H, C{6}–H), 2.51–2.44 (m, 2H, C{3}–H), 2.31–2.25 (m, 2H, C{4}–H), 2.24–2.17 (m, 2H, C{7}–H), 1.47 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 165.8 (**C**O_2Me), 165.7 (**C**O_2tBu), 164.4 (**C**O_2Me'), 158.5 (C{5}), 148.8 (C{2}), 138.0 (C{8}), 128.8 (C{1}), 118.8 (C{10}), 115.1 (C{9}), 80.1 (C{11}), 52.6 (CO_2**Me**), 52.5 (CO_2**Me'**), 36.6 (C{4}), 32.7 (C{7}), 31.2 (C{6}), 28.4 (C{12}), 28.0 (C{3}); ν**/cm**$^{-1}$ (film) 3078w, 1729s, 1718s, 1643w, 1141m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 375.1776. $C_{19}H_{28}O_6Na^+$ requires 375.1778.

Trimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.110

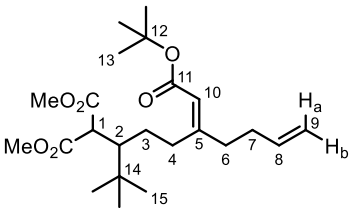


tert-BuLi (1.7 M in hexanes, 0.25 mL, 0.43 mmol) was added dropwise to a suspension of CuCN (20 mg, 0.22 mmol) in dry, degassed THF (3 × freeze/pump/thaw cycles, 0.50 mL) at −78 °C. The resulting yellow mixture was allowed to stir at this temperature for 15 min, and then at −45 °C until all CuCN had dissolved (5–10 min). The resulting pale yellow solution was cooled to −78 °C before the dropwise addition of trimethyl (*Z*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate **3.121** (44 mg, 0.14 mmol) in THF (1.0 mL). The reaction was then allowed to stir at −45 °C for 45 min. After this time, the reaction was quenched with sat. aq. NH_4Cl (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% EtOAc in pentane; 5 g SiO_2) provided the *title compound* as a colourless oil (36.7 mg, 0.10 mmol, 71%).

R$_f$ 0.40 (30% Et_2O in pentane, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84–5.74 (m, 1H, C{8}–H), 5.60 (s, 1H, C{10}–H), 5.04 (ddt, 1H, J = 16.5, 1.5, 1.5 Hz, C{9}–H_a), 4.98 (ddt, 1H, J = 10.0, 1.0, 1.0 Hz, C{9}–H_b), 3.74 (s, 3H, CO_2**Me**), 3.72 (s, 3H, CO_2**Me**'), 3.68 (d, 1H, J = 4.0 Hz, C{1}–H), 3.67 (s, 3H, CO_2**Me**''), 2.92 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.31–2.24 (m, 1H, C{4'}–H), 2.26–2.16 (m, 4H, C{6, 7}–H), 2.11 (ddd, 1H, J = 7.0, 4.0, 4.0 Hz, C{2}–H), 1.76 (dddd, 1H, J = 14.0, 12.0, 7.0, 5.0 Hz, C{3}–H), 1.65 (dddd, 1H, J = 16.5, 14.0, 7.5, 3.5 Hz, C{3'}–H), 0.94 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.0 (**C**O_2Me), 170.1 (**C**O_2Me'), 166.7 (**C**O_2Me''), 163.5 (C{5}), 137.6 (C{8}), 115.4 (C{9}), 115.3 (C{10}), 52.7 (CO_2**Me**), 52.2

(CO_2**Me**'), 52.0 (C{1}), 51.0 (CO_2**Me**"), 49.8 (C{2}), 37.6 (C{6}), 34.7 (C{11}), 33.2 (C{4}), 31.9 (C{7}), 28.1 (C{12}), 26.7 (C{3}); ν**/cm**$^{-1}$ (film) 2953w, 1757s, 1734s, 1719s, 1164s; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 369.2269. $C_{20}H_{33}O_6^+$ requires 369.2272.

6-(*tert*-Butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.111

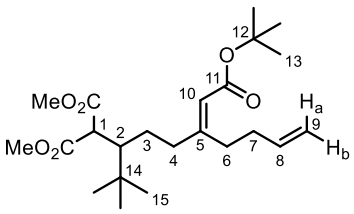


tert-BuLi (1.7 M in hexanes, 8.6 mL, 15 mmol) was added dropwise to a suspension of CuCN (652 mg, 7.28 mmol) in dry, degassed THF (3 × freeze/pump/thaw cycles, 18 mL) at −78 °C. The resulting yellow mixture was allowed to stir at this temperature for 15 min, and then at −45 °C until all CuCN had dissolved (5–10 min). The resulting pale yellow solution was cooled to −78 °C before the dropwise addition of 6-(*tert*-butyl)-1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate **3.122** (1.71 g, 4.85 mmol) in THF (35 mL) over 10 min. The reaction was then allowed to stir at −45 °C for 1 h. After this time, the reaction was quenched with sat. aq. NH_4Cl (100 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a colourless oil (1.86 g, 4.53 mmol, 93%) with no need for further purification.

R$_f$ 0.47 (30% Et_2O in pentane, $KMnO_4$, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.86–5.74 (m, 1H, C{8}–H), 5.52 (s, 1H, C{10}–H), 5.04 (d, 1H, J = 17.0 Hz, C{9}–H_a), 4.97 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.74 (s, 3H, CO_2**Me**), 3.72 (s, 3H, CO_2**Me**'), 3.67 (d, 1H, J = 4.0 Hz, C{1}–H), 2.89 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.26 (ddd, 1H,

J = 12.0, 12.0, 5.0 Hz, C{4'}–H), 2.25–2.14 (m, 4H, C{6, 7}–H), 2.12 (ddd, 1H, *J* = 7.5, 4.0, 4.0 Hz, C{2}–H), 1.76 (dddd, 1H, *J* = 14.0, 12.0, 7.5, 5.0 Hz, C{3}–H), 1.65–1.57 (m, 1H, C{3'}–H), 1.46 (s, 9H, C{13}–H), 0.93 (s, 9H, C{15}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.0 (**C**O_2Me), 170.1 (**C**O_2Me'), 165.9 (C{11}), 161.5 (C{5}), 137.9 (C{8}), 117.4 (C{10}), 115.2 (C{9}), 79.5 (C{12}), 52.7 (CO_2**Me**), 52.2 (CO_2**Me'**), 52.0 (C{1}), 49.6 (C{2}), 37.6 (C{6}), 34.7 (C{14}), 32.4 (C{4}), 32.0 (C{7}), 28.4 (C{13}), 28.1 (C{15}), 26.8 (C{3}); ν**/cm**$^{-1}$ (film) 2954w, 1758m, 1736m, 1709m, 1143s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 433.2542. $C_{23}H_{38}O_6Na^+$ requires 433.2551.

6-(*tert*-Butyl) 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tri-carboxylate, 3.112

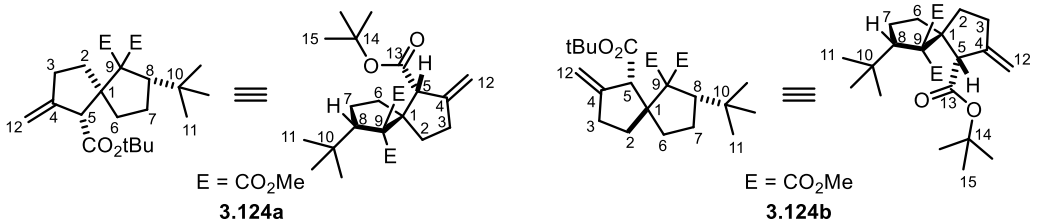


tert-BuLi (1.7 M in hexanes, 1.2 mL, 2.1 mmol) was added dropwise to a suspension of CuCN (93 mg, 1.0 mmol) in dry, degassed THF (3 × freeze/pump/thaw cycles, 2.5 mL) at −78 °C. The resulting yellow mixture was allowed to stir at this temperature for 15 min, and then at −45 °C until all CuCN had dissolved (5–10 min). The resulting pale yellow solution was cooled to −78 °C before the dropwise addition of 6-(*tert*-butyl)-1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hexa-1,5-diene-1,1,6-tricarboxylate **3.123** (243 mg, 0.69 mmol) in THF (5.0 mL). The reaction was then allowed to stir at −45 °C for 1 h 20 min. After this time, the reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 10%

Et_2O in pentane; 20 g SiO_2) provided the *title compound* as a colourless oil (203.3 mg, 0.50 mmol, 72%).

R$_f$ 0.50 (30% Et_2O in pentane, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{8}–H), 5.55 (s, 1H, C{10}–H), 5.03 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H_a), 4.95 (ddt, 1H, J = 10.0, 2.5, 1.5 Hz, C{9}–H_b), 3.73 (s, 3H, CO_2**Me**), 3.71 (s, 3H, CO_2**Me'**), 3.66 (d, 1H, J = 4.0 Hz, C{1}–H), 2.68 (ddd, 1H, J = 12.0, 8.0, 8.0 Hz, C{6}–H), 2.59 (ddd, 1H, J = 12.0, 7.5, 7.5 Hz, C{6'}–H), 2.27–2.16 (m, 3H, C{4, 7, 7'}–H), 2.08–1.98 (m, 2H, C{2, 4'}–H), 1.73 (dddd, 1H, J = 14.5, 12.0, 7.5, 5.0 Hz, C{3}–H), 1.64–1.57 (m, 1H, C{3'}–H), 1.47 (s, 9H, C{13}–H), 0.91 (s, 9H, C{15}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.9 (**C**O_2Me), 169.9 (**C**O_2Me'), 166.3 (C{11}), 161.5 (C{5}), 138.3 (C{8}), 117.8 (C{10}), 114.8 (C{9}), 79.7 (C{12}), 52.8 (CO_2**Me**), 52.3 (CO_2**Me'**), 52.0 (C{1}), 49.1 (C{2}), 39.1 (C{4}), 34.7 (C{14}), 32.9 (C{7}), 31.4 (C{6}), 28.4 (C{13}), 28.0 (C{15}), 26.4 (C{3}); ν**/cm**$^{-1}$ (film) 2955w, 1736m, 1708m, 1640w, 1140s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 433.2544. $C_{23}H_{38}O_6Na^+$ requires 433.2551.

6-(*tert*-Butyl) 1,1-dimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylene-spiro[4.4]nonane-1,1,6-tricarboxylate, 3.124a and 6-(*tert*-butyl) 1,1-dimethyl (2*S**, 5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.124b**



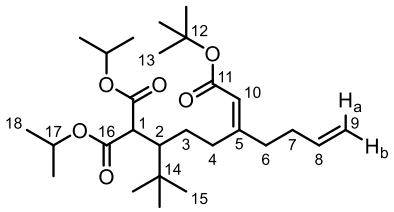
The *title compounds* were prepared from 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.111** (41 mg, 0.10 mmol), $Mn(OAc)_3 \cdot 2H_2O$

(59 mg, 0.22 mmol), $Cu(OAc)_2 \cdot H_2O$ (22 mg, 0.11 mmol), and DMSO (0.50 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 18 h. Purification of the crude mixture by flash-chromatography (eluent: 0% to 20% Et_2O in pentane; 5 g SiO_2) provided the *title compounds* as a colourless oil (24.6 mg, 60 μmol, 3:2 mixture of inseparable diastereoisomers (major: **3.124a**), 60%).

Characterised as a 3:2 mixture of diastereoisomers (major: **3.124a**): $\mathbf{R}_f$ 0.44 (30% Et_2O in pentane, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.90 (ddd, 1H, J = 2.5, 2.5, 2.0 Hz, C{12^{maj}}–H), 4.85 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12^{min}}–H), 4.82 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12'^{min}}–H), 4.81 (ddd, 1H, J = 2.5, 2.5, 2.5 Hz, C{12'^{maj}}–H), 3.70 (s, 3H, CO_2**Me**), 3.70 (s, 3H, CO_2**Me'**), 3.69 (s, 3H, CO_2**Me"**), 3.63 (s, 3H, CO_2**Me"'**), 3.62 (br, 1H, C{5^{min}}–H), 2.90 (dd, 1H, J = 11.0, 9.0 Hz, C{8^{min}}–H), 2.88 (dd, 1H, J = 11.0, 11.0 Hz, C{8^{maj}}–H), 2.79 (ddd, 1H, J = 2.5, 2.5, 2.5 Hz, C{5^{maj}}–H), 2.60 (ddd, 1H, J = 13.0, 12.5, 8.5 Hz, C{6^{min}}–H), 2.54 (dddddd, 1H, J = 16.0, 9.0, 9.0, 2.0, 2.0, 2.0 Hz, C{3^{min}}–H), 2.39 (dddddd, 1H, J = 17.0, 9.5, 9.5, 2.0, 2.0, 2.0 Hz, C{3^{maj}}–H), 2.33–2.25 (m, 2H, C{3'^{maj}, 6^{maj}}–H), 2.13–2.00 (m, 3H, C{2^{maj}, 3'^{min}, 6'^{maj}}–H), 1.98–1.83 (m, 3H, C{2'^{maj}, 7^{maj}, 7^{min}}–H), 1.82–1.73 (m, 3H, C{6'^{min}, 7'^{maj}, 7'^{min}}–H), 1.73–1.67 (m, 1H, C{2^{min}}–H), 1.55–1.48 (m, 1H, C{2'^{min}}–H), 1.50 (s, 9H, C{15^{maj}}–H), 1.46 (s, 9H, C{15^{min}}–H), 0.88 (s, 9H, C{11^{min}}–H), 0.87 (s, 9H, C{11^{maj}}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 172.7 (C{13^{min}}), 172.2 (C{13^{maj}}), 171.5 (**C**O_2Me^{min}), 171.3 (**C**O_2Me'^{min}), 170.9 (**C**O_2Me^{maj}), 170.8 (**C**O_2Me'^{maj}), 152.5 (C{4^{min}}), 150.8 (C{4^{maj}}), 107.7 (C{12^{maj}}), 106.4 (C{12^{min}}), 80.8 (C{14^{maj}}), 80.2 (C{14^{min}}), 69.3 (C{9^{min}}), 68.4 (C{9^{maj}}), 63.4 (C{1^{maj}}), 62.2 (C{1^{min}}), 58.9 (C{5^{maj}}), 57.4 (C{5^{min}}), 54.5 (C{8^{maj}}), 53.6 (C{8^{min}}), 51.8 (CO_2**Me**^{min}), 51.7 (CO_2**Me'**^{min}), 51.6 (CO_2**Me**^{maj}), 51.5 (CO_2**Me'**^{maj}), 37.5 (C{2^{min}}), 35.2 (C{6^{min}}), 34.6 (C{2^{maj}}), 33.7 (C{10^{min}}), 33.5 (C{10^{maj}}), 32.0 (C{3^{min}}), 31.7 (C{6^{maj}}),

29.8 (C{3^{maj}}), 28.7 (C{11^{maj}}), 28.4 (C{11^{min}}), 28.2 (C{15^{min}}), 28.1 (C{15^{maj}}), 25.0 (C{7^{maj}}), 24.0 (C{7^{min}}); ν/**cm**$^{-1}$ (film) 2953w, 1728s, 1367w, 1241m, 1140m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 431.2401. $C_{23}H_{36}O_6Na^+$ requires 431.2404.

6-(*tert*-Butyl) 1,1-diisopropyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)-hex-5-ene-1,1,6-tri-carboxylate, 3.125

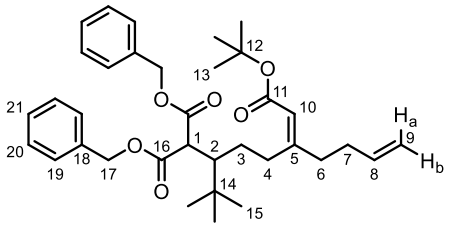


According to the modified procedure of Mahboobi,[348] $Ti(OiPr)_4$ (0.20 M in iPrOH, 0.76 mL, 0.15 mmol) was added to a solution of 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.111** (41 mg, 0.10 mmol) in iPrOH (0.24 mL) at room temperature. The resulting solution was allowed to stir at 85 °C for 3 days. After this time, volatiles were evaporated *in vacuo* and the resulting oil diluted with Et_2O (10 mL) and water (0.50 mL). The mixture was then allowed to stir vigorously for 15 min, dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 6% EtOAc in pentane; 7 g SiO_2) provided the *title compound* as a colourless oil (25.1 mg, 0.054 mmol, 54%).

R$_f$ 0.58 (20% Et_2O in pentane, $KMnO_4$, pale brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.80 (ddt, 1H, J = 17.0, 10.5, 6.5 Hz, C{8}–H), 5.51 (s, 1H, C{10}–H), 5.10–5.00 (m, 3H, C{9}–H$_a$, C{17}–H), 4.96 (d, 1H, J = 10.0 Hz, C{9}–H$_b$), 3.56 (d, 1H, J = 3.5 Hz, C{1}–H), 3.01 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.28–2.15 (m, 5H, C{4', 6, 7}–H), 2.11 (ddd, 1H, J = 7.5, 4.0, 3.5 Hz, C{2}–H), 1.86–1.76 (m, 1H, C{3}–H), 1.64–1.57 (m, 1H, C{3'}–H), 1.46 (s, 9H, C{13}–H), 1.27–1.21 (m, 12H, C{18}–H), 0.94 (s, 9H, C{15}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.2 (C{16}), 169.2 (C{16'}), 166.0

(C{11}), 161.7 (C{5}), 137.9 (C{8}), 117.3 (C{10}), 115.1 (C{9}), 79.4 (C{12}), 69.0 (C{17}), 68.3 (C{17'}), 52.7 (C{1}), 49.2 (C{2}), 37.6 (C{6}), 34.7 (C{14}), 32.6 (C{4}), 32.0 (C{7}), 28.4 (C{13}), 28.3 (C{15}), 26.9 (C{3}), 21.8 (C{18}), 21.8 (C{18'}), 21.7 (C{18"}); ν/**cm**$^{-1}$ (film) 2977w, 1747s, 1728s, 1711s, 1149s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 489.3184. $C_{27}H_{46}O_6Na^+$ requires 489.3187.

1,1-Dibenzyl 6-(*tert*-butyl) (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.126

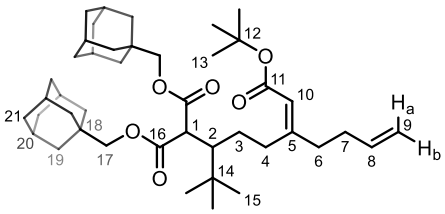


According to the modified procedure of Mahboobi,[348] $Ti(OEt)_4$ (0.20 M in BnOH, 0.10 mL, 0.020 mmol) was added to a solution of 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.111** (41 mg, 0.10 mmol) in BnOH (0.50 mL) at room temperature. The resulting solution was allowed to stir at 85 °C for 24 h. After this time, a second portion of $Ti(OEt)_4$ (30 μL, 0.10 mmol) and 120 mg 4 Å molecular sieves were added to the reaction, which was then allowed to stir at 105 °C for 3 days. After this time, the reaction was filtered and diluted with Et_2O (10 mL) and water (0.50 mL). The mixture was then allowed to stir vigorously for 15 min, dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 10% EtOAc in pentane; 12 g SiO_2) provided the *title compound* as a colourless oil (31.3 mg, 0.056 mmol, 56%).

R$_f$ 0.53 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.33–7.28 (m, 10H, C{19, 20, 21}–H), 5.82–2.71 (m, 1H, C{8}–H), 5.49 (s, 1H, C{10}–H), 5.19–5.09

(m, 4H, C{17}–H), 5.02 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H_a), 4.96 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.75 (d, 1H, J = 4.0 Hz, C{1}–H), 2.89 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.24 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4'}–H), 2.20–2.09 (m, 5H, C{2, 6, 7}–H), 1.87–1.76 (m, 1H, C{3}–H), 1.68–1.57 (m, 1H, C{3'}–H), 1.45 (s, 9H, C{13}–H), 0.91 (s, 9H, C{15}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.3 (C{16}), 169.3 (C{16'}), 165.9 (C{11}), 161.6 (C{5}), 137.9 (C{8}), 135.6 (C{18}), 128.7 (C{19/20}), 128.6 (C{19/20}), 128.5 (C{19/20}), 128.4 (C{19/20}), 128.4 (C{21}), 128.4 (C{21'}), 117.3 (C{10}), 115.2 (C{9}), 79.4 (C{12}), 67.4 (C{17}), 67.0 (C{17'}), 52.3 (C{1}), 49.6 (C{2}), 37.5 (C{6}), 34.7 (C{14}), 32.5 (C{4}), 31.9 (C{7}), 28.4 (C{13}), 28.2 (C{15}), 26.8 (C{3}); ν**/cm**$^{-1}$ (film) 2941w, 1733m, 1709m, 1641w, 1139s; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 585.3177. $C_{35}H_{46}O_6Na^+$ requires 585.3187.

1,1-Bis(adamantan-1-ylmethyl) 6-(*tert*-butyl) (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)-hex-5-ene-1,1,6-tricarboxylate, 3.127

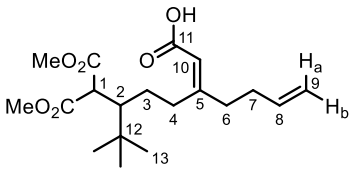


According to the modified procedure of Mahboobi,[348] adamantan-1-ylmethanol (333 mg, 2.0 mmol), $Ti(OiPr)_4$ (0.50 M in PhMe, 0.20 mL, 0.10 mmol), and 4 Å molecular sieves (300 mg) were added to a solution of 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.111** (41 mg, 0.10 mmol) in PhMe (0.50 mL) at room temperature. The resulting solution was allowed to stir at 100 °C for 3 days. After this time, the reaction was filtered and diluted with Et_2O (5 mL) and water (0.25 mL). The mixture was then allowed to stir vigorously for 15 min, dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography

(eluent: 0% to 6% Et_2O in pentane; 25 g SiO_2) provided the *title compound* as a colourless oil (33.2 mg, 0.049 mmol, 49%).

R$_f$ 0.38 (10% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84–5.75 (m, 1H, C{8}–H), 5.51 (s, 1H, C{10}–H), 5.03 (d, 1H, J = 17.0 Hz, C{9}–H_a), 4.97 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.73–3.65 (m, 5H, C{1, 17}–H), 3.02 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.26–2.14 (m, 5H, C{4', 6, 7}–H), 2.12 (ddd, 1H, J = 7.5, 4.0, 4.0 Hz, C{2}–H), 1.98 (br, 6H, C{20}–H), 1.82–1.73 (m, 1H, C{3}–H), 1.75–1.70 (m, 6H, C{21}–H), 1.67–1.61 (m, 7H, C{3', 21'}–H), 1.56–1.51 (m, 12H, C{19}–H), 1.46 (s, 9H, C{13}–H), 0.95 (s, 9H, C{15}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.7 (C{16}), 170.0 (C{16'}), 165.9 (C{11}), 161.6 (C{5}), 137.9 (C{8}), 117.2 (C{10}), 115.2 (C{9}), 79.4 (C{12}), 75.2 (C{17}), 75.1 (C{17'}), 52.5 (C{1}), 49.5 (C{2}), 39.5 (C{19}), 39.4 (C{19'}), 37.6 (C{6}), 37.1 (C{21}), 37.0 (C{21'}), 34.7 (C{14}), 33.3 (C{18}), 33.1 (C{18'}), 32.8 (C{4}), 32.0 (C{7}), 28.4 (C{13}), 28.3 (C{15}), 28.2 (C{20}), 28.2 (C{20'}), 27.1 (C{3}); ν**/cm**$^{-1}$ (film) 2904s, 1734m, 1711m, 1145s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 701.4742. $C_{43}H_{66}O_6Na^+$ requires 701.4752.

(*Z*)-3-(But-3-en-1-yl)-6-(*tert*-butyl)-8-methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid, 3.130

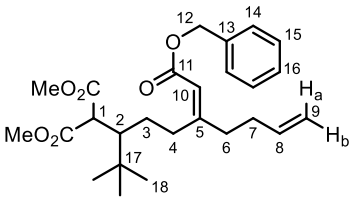


TFA (0.30 mL, 4.0 mmol) was added to a solution of 6-(*tert*-butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.111** (164 mg, 0.40 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. The resulting solution was allowed to stir at room temperature

for 3 h. After this time, all volatiles were evaporated *in vacuo* to give the *title compound* as a colourless oil (124.3 mg, 0.35 mmol, 88%) with no need for further purification.

R$_f$ 0.08 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.86–5.74 (m, 1H, C{8}–H), 5.64 (s, 1H, C{10}–H), 5.05 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{9}–H_a), 4.99 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.73 (s, 3H, CO_2**Me**), 3.72 (s, 3H, CO_2**Me'**), 3.68 (d, 1H, J = 4.0 Hz, C{1}–H), 2.92 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.33–2.17 (m, 5H, C{4', 6, 7}–H), 2.09 (ddd, 1H, J = 7.0, 4.0, 3.5 Hz, C{2}–H), 1.81–1.72 (m, 1H, C{3}–H), 1.71–1.61 (m, 1H, C{3'}–H), 0.93 (s, 9H, C{13}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.0 (**C**O_2Me), 170.7 (C{11}), 170.1 (**C**O_2Me'), 166.7 (C{5}), 137.4 (C{8}), 115.5 (C{9}), 114.9 (C{10}), 52.7 (CO_2**Me**), 52.3 (CO_2**Me'**), 52.0 (C{1}), 49.8 (C{2}), 37.9 (C{6}), 34.7 (C{12}), 33.4 (C{4}), 31.8 (C{7}), 28.1 (C{13}), 26.6 (C{3}); ν**/cm**$^{-1}$ (film) 2956br, 1754s, 1735s, 1689s, 1150s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 377.1935. $C_{19}H_{30}O_6Na^+$ requires 377.1935.

6-Benzyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.131

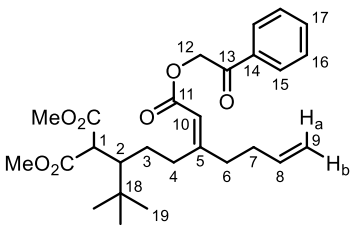


To a solution of (*Z*)-3-(but-3-en-1-yl)-6-(*tert*-butyl)-8-methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid **3.130** (33 mg, 0.093 mmol) in DMF (1.0 mL) were added Cs_2CO_3 (36 mg, 0.11 mmol) and benzyl bromide (13 μL, 0.11 mmol) at room temperature. The resulting solution was allowed to stir at room temperature for 3 h. After this time, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and

evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 15% EtOAc in pentane; 10 g SiO_2) provided the *title compound* as a colourless oil (32.8 mg, 0.074 mmol, 79%).

R_f 0.44 (30% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H, C{14, 15}–H), 7.33–7.28 (m, 1H, C{16}–H), 5.83–5.75 (m, 1H, C{8}–H), 5.66 (s, 1H, C{10}–H), 5.17–5.08 (m, 2H, C{12}–H), 5.04 (d, 1H, J = 17.0 Hz, C{9}–H_a), 4.98 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.73 (s, 3H, CO_2**Me**), 3.72 (s, 3H, CO_2**Me'**), 3.68 (d, 1H, J = 4.0 Hz, C{1}–H), 2.96 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.33–2.26 (m, 1H, C{4'}–H), 2.26–2.16 (m, 4H, C{6, 7}–H), 2.11 (ddd, 1H, J = 7.5, 4.0, 4.0 Hz, C{2}–H), 1.82–1.72 (m, 1H, C{3}–H), 1.69–1.60 (m, 1H, C{3'}–H), 0.92 (s, 9H, C{18}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.0 (**C**O_2Me), 170.1 (**C**O_2Me'), 166.0 (C{11}), 164.2 (C{5}), 137.6 (C{8}), 136.6 (C{13}), 128.6 (C{14/15}), 128.3 (C{14/15}), 128.2 (C{16}), 115.4 (C{10}), 115.3 (C{9}), 65.6 (C{12}), 52.7 (CO_2**Me**), 52.2 (CO_2**Me'**), 52.0 (C{1}), 49.7 (C{2}), 37.7 (C{6}), 34.7 (C{17}), 33.1 (C{4}), 31.8 (C{7}), 28.1 (C{18}), 26.7 (C{3}); ν**/cm**$^{-1}$ (film) 2955m, 1756s, 1734s, 1641m, 1147s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 467.2398. $C_{26}H_{36}O_6Na^+$ requires 467.2404.

1,1-Dimethyl 6-(2-oxo-2-phenylethyl) (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.132

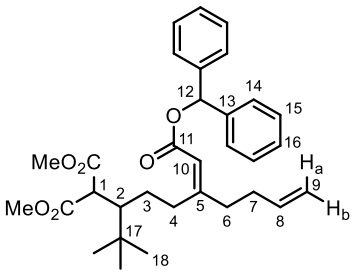


To a solution of (*Z*)-3-(but-3-en-1-yl)-6-(*tert*-butyl)-8-methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid **3.130** (46 mg, 0.13 mmol) in DMF (1.4 mL) were added Cs_2CO_3

(50 mg, 0.15 mmol) and phenacyl bromide (31 mg, 0.15 mmol) at room temperature. The resulting solution was allowed to stir at room temperature for 2 h. After this time, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 17% EtOAc in pentane; 15 g SiO_2) provided the *title compound* as a colourless oil (38.9 mg, 0.082 mmol, 63%).

R_f 0.24 (20% EtOAc in pentane, $KMnO_4$, brown in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.93 (d, 2H, J = 8.0 Hz, C{15}–H), 7.63–7.57 (m, 1H, C{17}–H), 7.51–7.45 (m, 2H, C{16}–H), 5.87–5.77 (m, 2H, C{8, 10}–H), 5.40–5.31 (m, 2H, C{12}–H), 5.07 (d, 1H, J = 17.0 Hz, C{9}–H_a), 5.00 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.71 (s, 6H, 2 × CO_2**Me**), 3.67 (d, 1H, J = 4.0 Hz, C{1}–H), 2.94 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.35–2.21 (m, 5H, C{4', 6, 7}–H), 2.10 (ddd, 1H, J = 7.5, 4.0, 4.0 Hz, C{2}–H), 1.83–1.73 (m, 1H, C{3}–H), 1.71–1.61 (m, 1H, C{3'}–H), 0.92 (s, 9H, C{19}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 192.8 (C{13}), 171.0 (**C**O_2Me), 170.1 (**C**O_2Me'), 165.6 (C{5}), 165.3 (C{11}), 137.6 (C{8}), 134.7 (C{14}), 133.9 (C{17}), 129.0 (C{16}), 128.0 (C{15}), 115.5 (C{9}), 114.6 (C{10}), 65.5 (C{12}), 52.7 (CO_2**Me**), 52.2 (CO_2**Me'**), 52.0 (C{1}), 49.7 (C{2}), 37.8 (C{6}), 34.7 (C{18}), 33.3 (C{4}), 31.8 (C{7}), 28.1 (C{19}), 26.6 (C{3}); ν**/cm**$^{-1}$ (film) 2954w, 1730s, 1705s, 1152s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 495.2348. $C_{27}H_{36}O_7Na^+$ requires 495.2353.

6-Benzhydryl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.133

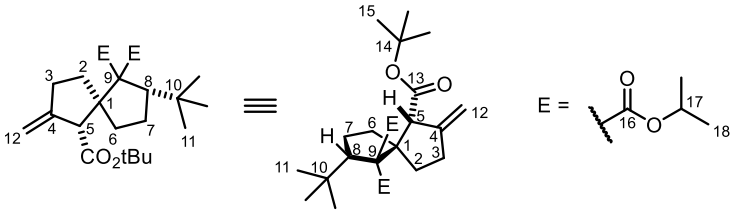


According to the modified procedure of Squitieri,[243] MnO_2 (65 mg, 0.74 mmol) and KH_2PO_4 (101 mg, 0.74 mmol) were added to a solution of benzophenone hydrazone (24 mg, 0.12 mmol) in CH_2Cl_2 (0.50 mL) at room temperature. The resulting deep purple solution was allowed to stir for 5 min at this temperature before the addition of (*Z*)-3-(but-3-en-1-yl)-6-(*tert*-butyl)-8-methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid **3.130** (33 mg, 0.093 mmol) in CH_2Cl_2 (1.0 mL). The resulting solution was allowed to stir at room temperature for 18 h. After this time, the reaction mixture was filtered, the solids rinsed with EtOAc (5 mL), and the resulting solution evaporated *in vacuo* to give a pink oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 15% EtOAc in pentane; 10 g SiO_2) provided the *title compound* as a colourless oil (42.8 mg, 0.082 mmol, 88%).

R$_f$ 0.17 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.40–7.29 (m, 8H, C{14, 15}–H), 7.29–7.24 (m, 2H, C{16}–H), 6.91 (s, 1H, C{12}–H), 5.84–5.77 (m, 1H, C{8}–H), 5.77 (s, 1H, C{10}–H), 5.05 (d, 1H, J = 17.0 Hz, C{9}–H$_a$), 4.99 (d, 1H, J = 10.0 Hz, C{9}–H$_b$), 3.69 (s, 3H, CO_2**Me**), 3.68 (s, 3H, CO_2**Me**'), 3.65 (d, 1H, J = 4.0 Hz, C{1}–H), 2.95 (ddd, 1H, J = 12.0, 12.0, 5.0 Hz, C{4}–H), 2.33–2.17 (m, 5H, C{4', 6, 7}–H), 2.08 (ddd, 1H, J = 7.5, 4.0, 4.0 Hz, C{2}–H), 1.80–1.68 (m, 1H, C{3}–H), 1.65–1.56 (m, 1H, C{3'}–H), 0.87 (s, 9H, C{18}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.0

(**C**O_2Me), 170.0 (**C**O_2Me'), 165.1 (C{5/11}), 164.8 (C{5/11}), 140.9 (C{13}), 140.8 (C{13'}), 137.6 (C{8}), 128.6 (C{14/15}), 128.6 (C{14/15}), 127.8 (C{16}), 127.8 (C{16'}), 127.3 (C{14/15}), 127.3 (C{14/15}), 115.4 (C{9}), 115.3 (C{10}), 75.9 (C{12}), 52.6 (CO_2**Me**), 52.2 (CO_2**Me**'), 51.9 (C{1}), 49.6 (C{2}), 37.7 (C{6}), 34.7 (C{17}), 32.9 (C{4}), 31.9 (C{7}), 28.1 (C{18}), 26.7 (C{3}); ν**/cm**$^{-1}$ (film) 2980w, 1732s, 1454w, 1145s, 700m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 543.2716. $C_{32}H_{40}O_6Na^+$ requires 543.2717.

6-(*tert*-Butyl) 1,1-diisopropyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro[4.4]-nonane-1,1,6-tricarboxylate, 3.134a**

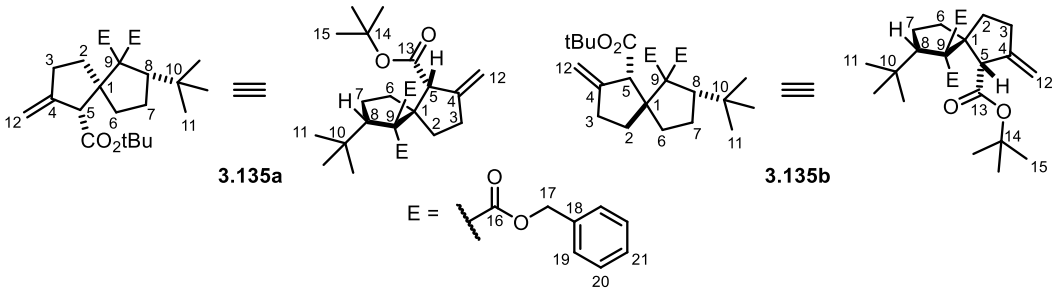


The *title compound* was prepared from 6-(*tert*-butyl) 1,1-diisopropyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.125** (16 mg, 0.034 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (21 mg, 0.078 mmol), $Cu(OAc)_2 \cdot H_2O$ (8 mg, 0.04 mmol), and DMSO (0.25 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 18 h. Purification of the crude mixture by flash-chromatography (eluent: 0% to 8% Et_2O in pentane; 4 g SiO_2) provided the *title compound* as a colourless oil (4.6 mg, 9.9 μmol, 29%).

R$_f$ 0.56 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.99 (hept, 2H, J = 6.5 Hz, C{17}–H), 4.89 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.79 (ddd, 1H, J = 2.5, 2.5, 2.5 Hz, C{12'}–H), 2.90 (ddd, 1H, J = 2.5, 2.5, 2.5 Hz, C{5}–H), 2.80 (dd, 1H, J = 11.0, 10.5 Hz, C{8}–H), 2.41 (dddddd, 1H, J = 16.5, 11.0, 9.0, 2.5, 2.5, 2.5 Hz, C{3}–H), 2.34–2.27 (m, 2H, C{3', 6}–H), 2.12 (dd, 1H, J = 10.5, 9.5 Hz, C{2}–H), 2.10–

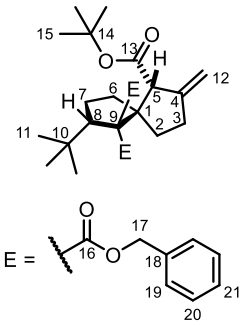
2.03 (m, 1H, C{6'}–H), 1.95 (ddd, 1H, *J* = 12.5, 9.0, 2.5 Hz, C{2'}–H), 1.93–1.86 (m, 1H, C{7}–H), 1.77 (dddd, 1H, *J* = 12.5, 12.5, 11.0, 4.0 Hz, C{7'}–H), 1.50 (s, 9H, C{15}–H), 1.30 (d, 3H, *J* = 6.0 Hz, C{18}–H), 1.28 (d, 3H, *J* = 6.0 Hz, C{18'}–H), 1.26 (d, 3H, *J* = 6.0 Hz, C{18"}–H), 1.25 (d, 3H, *J* = 6.0 Hz, C{18'"}–H), 0.90 (s, 9H, C{11}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.4 (C{13}), 170.2 (C{16}), 169.8 (C{16'}), 151.0 (C{4}), 107.5 (C{12}), 80.7 (C{14}), 68.6 (C{17}), 68.5 (C{17'}), 68.1 (C{9}), 63.2 (C{1}), 58.3 (C{5}), 54.3 (C{8}), 34.9 (C{2}), 33.8 (C{10}), 32.0 (C{6}), 30.2 (C{3}), 29.0 (C{11}), 28.1 (C{15}), 24.9 (C{7}), 21.8 (C{18}), 21.8 (C{18'}), 21.7 (C{18"}), 21.5 (C{18'"}); **ν/cm^{-1}** (film) 2977w, 1720s, 1369w, 1141m, 1109m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 487.3027. $C_{27}H_{44}O_6Na^+$ requires 487.3030.

1,1-Dibenzyl 6-(*tert*-butyl) (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylene spiro[4.4]nonane-1,1,6-tricarboxylate, 3.135a and 1,1-dibenzyl 6-(*tert*-butyl) (2*S**, 5*S**, 6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tri-carboxylate, 3.135b**



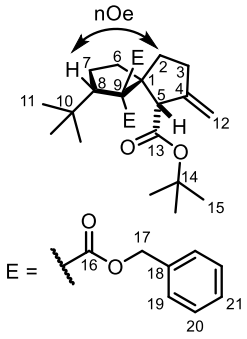
The *title compounds* were prepared from 1,1-dibenzyl 6-(*tert*-butyl) (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.126** (21 mg, 0.037 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (28 mg, 0.10 mmol), $Cu(OAc)_2 \cdot H_2O$ (11 mg, 0.055 mmol), and DMSO (0.30 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 18 h. Purification of the crude mixture by flash-chromatography (eluent: 0% to 8% Et_2O in pentane; 7 g SiO_2) provided spirocycle **3.135a** as a colourless oil (4.6 mg, 8.2 μmol, 22%) and spirocycle **3.135b** as a colourless oil (2.8 mg, 5.0 μmol, 14%).

1,1-Dibenzyl 6-(*tert*-butyl) (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylene-spiro[4.4]nonane-1,1,6-tricarboxylate, 3.135a**



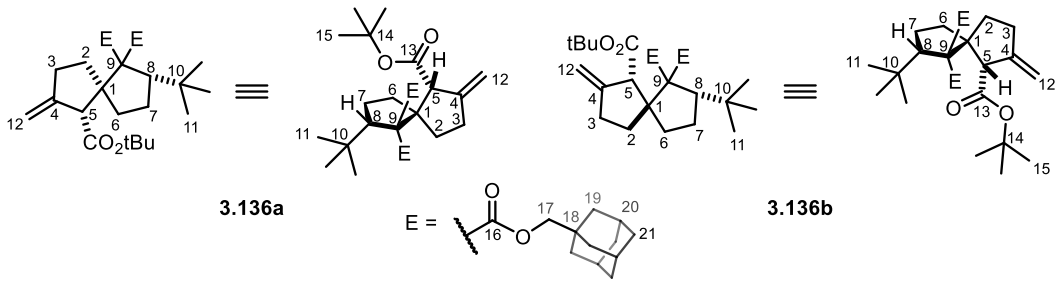
R$_f$ 0.55 (30% Et_2O in pentane, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.33–7.21 (m, 10H, C{19, 20, 21}–H), 5.16 (d, 1H, J = 12.5 Hz, C{17}–H), 5.12–5.03 (m, 2H, C{17'}–H), 5.01 (d, 1H, J = 12.5 Hz, C{17''}–H), 4.85 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.78 (ddd, 1H, J = 2.5, 2.5, 2.0 Hz, C{12'}–H), 2.90 (dd, 1H, J = 10.5, 10.5 Hz, C{8}–H), 2.86 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{5}–H), 2.35 (dddddd, 1H, J = 16.5, 9.5, 9.5, 2.5, 2.5, 2.5 Hz, C{3}–H), 2.22 (ddd, 1H, J = 13.5, 10.0, 3.5 Hz, C{6}–H), 2.19–2.02 (m, 3H, C{2, 3', 6'}–H), 1.98–1.90 (m, 1H, C{7}–H), 1.95 (ddd, 1H, J = 13.0, 9.5, 3.0 Hz, C{2'}–H), 1.78 (dddd, 1H, J = 12.0, 10.5, 10.0, 3.5 Hz, C{7'}–H), 1.49 (s, 9H, C{15}–H), 0.90 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 172.2 (C{13}), 170.4 (C{16}), 170.1 (C{16'}), 150.9 (C{4}), 135.7 (C{18}), 135.2 (C{18'}), 128.7 (C{19/20}), 128.6 (C{19/20}), 128.6 (C{19/20}), 128.4 (C{19/20}), 128.4 (C{21}), 128.2 (C{21'}), 107.6 (C{12}), 80.8 (C{14}), 68.6 (C{9}), 67.0 (C{17}), 67.0 (C{17'}), 63.6 (C{1}), 58.9 (C{5}), 54.8 (C{8}), 34.8 (C{2}), 33.7 (C{10}), 32.3 (C{6}), 30.2 (C{3}), 28.9 (C{11}), 28.1 (C{15}), 25.0 (C{7}); ν**/cm**$^{-1}$ (film) 3033w, 1726s, 1141m, 1074m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 583.3027. $C_{35}H_{44}O_6Na^+$ requires 583.3030.

1,1-Dibenzyl 6-(*tert*-butyl) (2*S,5*S**,6*S**)-2-(*tert*-butyl)-7-methylene-spiro[4.4]nonane-1,1,6-tricarboxylate, 3.135b**



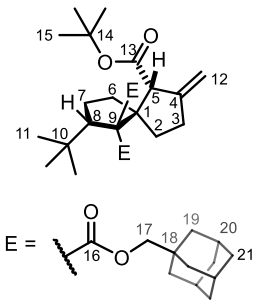
R$_f$ 0.53 (30% Et_2O in pentane, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.32–7.19 (m, 10H, C{19, 20, 21}–H), 5.25 (d, 1H, J = 12.5 Hz, C{17}–H), 5.13 (d, 1H, J = 12.5 Hz, C{17'}–H), 4.93 (d, 1H, J = 12.5 Hz, C{17"}–H), 4.89 (d, 1H, J = 12.5 Hz, C{17"'}–H), 4.80 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.73 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12'}–H), 3.72 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{5}–H), 2.93 (dd, 1H, J = 11.0, 9.5 Hz, C{8}–H), 2.72 (ddd, 1H, J = 12.5, 12.5, 8.0 Hz, C{6}–H), 2.54–2.45 (m, 1H, C{3}–H), 2.11–2.04 (m, 1H, C{3'}–H), 1.93–1.84 (m, 1H, C{7}–H), 1.79–1.72 (m, 2H, C{6', 7'}–H), 1.69 (ddd, 1H, J = 13.5, 8.5, 4.8 Hz, C{2}–H), 1.52–1.43 (m, 1H, C{2'}–H), 1.41 (s, 9H, C{15}–H), 0.89 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 172.7 (C{13}), 170.8 (C{16}), 170.4 (C{16'}), 152.1 (C{4}), 135.5 (C{18}), 135.2 (C{18'}), 128.6 (C{19/20}), 128.6 (C{19/20}), 128.5 (C{19/20}), 128.5 (C{19/20}), 128.3 (C{21}), 128.2 (C{21'}), 106.8 (C{12}), 80.2 (C{14}), 68.9 (C{9}), 67.2 (C{17}), 67.1 (C{17'}), 62.7 (C{1}), 56.9 (C{5}), 54.0 (C{8}), 37.0 (C{2}), 34.3 (C{6}), 33.8 (C{10}), 31.7 (C{3}), 28.7 (C{11}), 28.2 (C{15}), 23.9 (C{7}); ν**/cm**$^{-1}$ (film) 2970w, 1725s, 1139m, 1044m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 583.3029. $C_{35}H_{44}O_6Na^+$ requires 583.3030.

1,1-Bis(adamantan-1-ylmethyl) 6-(*tert*-butyl) (2*S,5*R**,6*R**)-2-(*tert*-butyl)7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.136a and 1,1-bis(adamantan-1-ylmethyl) 6-(*tert*-butyl) (2*S**,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4] nonane-1,1,6-tricarboxylate, 3.136b**



The *title compounds* were prepared from 1,1-bis(adamantan-1-ylmethyl) 6-(*tert*-butyl) (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.127** (29 mg, 0.043 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (25 mg, 0.095 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.047 mmol), and DMSO (0.20 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 40 h. Purification of the crude mixture by flash-chromatography (eluent: 0% to 8% Et_2O in pentane; 5 g SiO_2) provided spirocycle **3.136a** as a colourless oil (6.2 mg, 9.2 μmol, 21%) and spirocycle **3.136b** as a colourless oil (6.1 mg, 9.0 μmol, 21%).

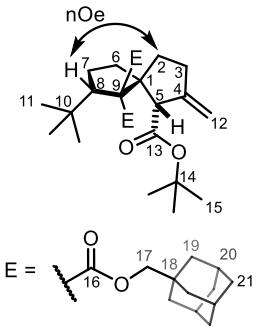
1,1-Bis(adamantan-1-ylmethyl) 6-(*tert*-butyl) (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.136a**



R$_f$ 0.51 (10% Et_2O in pentane, $KMnO_4$, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.90 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.79 (ddd, 1H, J = 2.5, 2.5, 2.0 Hz, C{12'}–H), 3.77 (d, 1H, J = 11.0 Hz, C{17}–H), 3.68 (d, 1H, J = 11.0 Hz, C{17'}–H), 3.67 (d, 1H, J = 11.0 Hz, C{17"}–H), 3.63 (d, 1H, J = 11.0 Hz, C{17"'}–H), 2.89 (ddd, 1H, J = 2.0, 2.0, 2.0 Hz, C{5}–H), 2.86 (dd, 1H, J = 10.5, 10.5 Hz,

C{8}–H), 2.44 (dddddd, 1H, *J* = 17.0, 9.5, 9.5, 2.0, 2.0, 2.0 Hz, C{3}–H), 2.37–2.27 (m, 2H, C{3', 6}–H), 2.20 (ddd, 1H, *J* = 12.5, 10.0, 10.0 Hz, C{2}–H), 2.08 (ddd, 1H, *J* = 12.5, 12.5, 6.5 Hz, C{6'}–H), 2.02–1.95 (m, 7H, C{2', 20}–H), 1.96–1.90 (m, 1H, C{7}–H), 1.81 (dddd, 1H, *J* = 12.5, 12.5, 12.5, 4.0 Hz, C{7'}–H), 1.77–1.69 (m, 6H, C{21}–H), 1.67–1.61 (m, 6H, C{21'}–H), 1.60–1.57 (m, 6H, C{19}–H), 1.57–1.53 (m, 6H, C{19'}–H), 1.50 (s, 9H, C{15}–H), 0.89 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 172.4 (C{13}), 171.1 (C{16}), 170.7 (C{16'}), 150.6 (C{4}), 107.7 (C{12}), 80.8 (C{14}), 75.8 (C{17}), 75.2 (C{17'}), 69.3 (C{9}), 63.1 (C{1}), 58.8 (C{5}), 54.6 (C{8}), 39.9 (C{19}), 39.7 (C{19'}), 37.1 (C{21}), 37.1 (C{21'}), 35.1 (C{2}), 33.7 (C{10}), 33.3 (C{18}), 32.9 (C{18'}), 32.3 (C{6}), 30.1 (C{3}), 29.0 (C{11}), 28.2 (C{15}), 28.2 (C{20}), 28.1 (C{20'}), 25.3 (C{7}); ν**/cm**$^{-1}$ (film) 2904s, 1726s, 1141m, 735w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 699.4590. $C_{43}H_{64}O_6Na^+$ requires 699.4595.

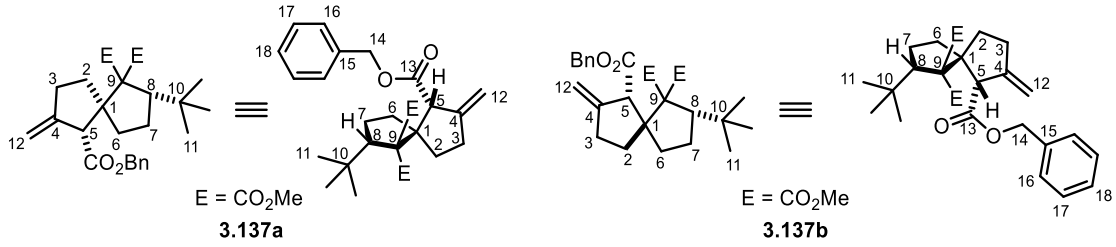
1,1-Bis(adamantan-1-ylmethyl) 6-(*tert*-butyl) (2*S,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.136b**



R$_f$ 0.36 (10% Et_2O in pentane, $KMnO_4$, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.91 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.87 (ddd, 1H, *J* = 2.5, 2.5, 2.0 Hz, C{12'}–H), 3.90 (ddd, 1H, *J* = 2.5, 2.5, 2.5 Hz, C{5}–H), 3.86 (d, 1H, *J* = 11.0 Hz, C{17}–H), 3.78 (d, 1H, *J* = 11.0 Hz, C{17'}–H), 3.65 (d, 1H, *J* = 11.0 Hz, C{17''}–H), 3.56 (d, 1H, *J* = 11.0 Hz, C{17'''}–H), 2.91 (dd, 1H, *J* = 10.5, 10.0 Hz, C{8}–H), 2.90–2.83 (m, 1H, C{6}–H), 2.49 (dddddd, 1H, *J* = 17.0, 10.5, 10.5, 2.0, 2.0, 2.0 Hz, C{3}–H), 2.20 (dddd, 1H, *J* = 16.5, 8.0, 2.0, 2.0 Hz, C{3'}–H), 2.03–1.94 (m, 6H, C{20}–H), 1.93–1.85 (m, 1H, C{7}–H), 1.81–1.74 (m, 1H, C{7'}–H), 1.76–1.68 (m, 8H, C{2, 6', 21}–H), 1.67–1.61 (m, 6H, C{21'}–H), 1.58–1.55

(m, 6H, C{19}–H), 1.56–1.50 (m, 6H, C{19'}–H), 1.47 (s, 9H, C{15}–H), 1.42–1.36 (m, 1H, C{2'}–H), 0.90 (s, 9H, C{11}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.6 (C{13}), 171.2 (C{16}), 170.8 (C{16'}), 152.0 (C{4}), 107.0 (C{12}), 79.9 (C{14}), 75.6 (C{17}), 75.1 (C{17'}), 68.8 (C{9}), 62.5 (C{1}), 55.5 (C{5}), 54.0 (C{8}), 39.9 (C{19}), 39.6 (C{19'}), 37.1 (C{21}), 37.0 (C{21'}), 36.3 (C{2}), 33.8 (C{10}), 33.2 (C{18}), 32.9 (C{18'}), 31.8 (C{6}), 31.0 (C{3}), 28.8 (C{11}), 28.3 (C{15}), 28.2 (C{20}), 28.2 (C{20'}), 24.0 (C{7}); **ν/cm^{-1}** (film) 2904s, 1724s, 1259w, 1136w, 735w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 699.4590. $C_{43}H_{64}O_6Na^+$ requires 699.4595.

6-Benzyl 1,1-dimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro-[4.4] nonane-1,1,6-tricarboxylate, 3.137a and 6-benzyl 1,1-dimethyl (2*S**,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.137b**

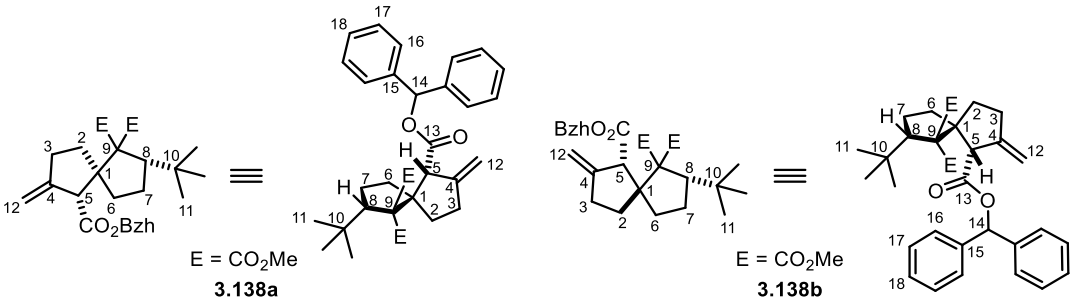


The *title compounds* were prepared from 6-benzyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.131** (27.5 mg, 0.062 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (38 mg, 0.14 mmol), $Cu(OAc)_2{\cdot}H_2O$ (14 mg, 0.068 mmol), and DMSO (0.30 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 18 h. Purification of the crude mixture by flash-chromatography (eluent: 5% EtOAc in pentane; 4 g SiO_2) provided the *title compounds* as a colourless oil (13.9 mg, 31 μmol, 6:5 mixture of inseparable diastereoisomers (major: **3.137b**), 51%).

Characterised as a 6:5 mixture of diastereoisomers (major: **3.137b**): **R**$_f$ 0.26 (20% Et_2O in pentane, brown in vanillin); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43–7.28 (m, 10H,

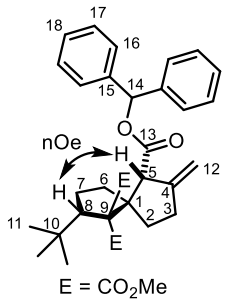
C{Ar}–H), 5.24–5.17 (m, 2H, C{14}–H), 5.11 (d, 1H, *J* = 12.5 Hz, C{14'}–H), 5.08 d, 1H, *J* = 12.5 Hz, C{14''}–H), 4.90 (ddd, 1H, *J* = 2.5, 2.5, 2.0 Hz, C{12^{min}}–H), 4.88 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{12^{maj}}–H), 4.78 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{12'^{maj}}–H), 4.75 (ddd, 1H, *J* = 2.5, 2.5, 2.5 Hz, C{12'^{min}}–H), 3.85 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{5^{maj}}–H), 3.68 (s, 3H, CO$_2$**Me**^{min}), 3.67 (s, 3H, CO$_2$**Me**^{maj}), 3.58 (s, 3H, CO$_2$**Me'**^{maj}), 3.56 (s, 3H, CO$_2$**Me'**^{min}), 3.00 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{5^{min}}–H), 2.90 (dd, 1H, *J* = 11.0, 9.0 Hz, C{8^{maj}}–H), 2.80 (dd, 1H, *J* = 10.5, 10.5 Hz, C{8^{min}}–H), 2.65–2.57 (m, 1H, C{6^{maj}}–H), 2.58–2.51 (m, 1H, C{3^{maj}}–H), 2.43 (dddddd, 1H, *J* = 17.0, 9.5, 9.5, 2.5, 2.5, 2.5 Hz, C{3^{min}}–H), 2.31 (ddddd, 1H, *J* = 16.5, 9.5, 2.0, 2.0, 2.0 Hz, C{3'^{min}}–H), 2.22–2.15 (m, 2H, C{3'^{maj}, 6^{min}}–H), 2.15–2.09 (m, 1H, C{6'^{min}}–H), 2.09–2.03 (m, 1H, C{2^{min}}–H), 1.94 (ddd, 1H, *J* = 12.5, 9.5, 3.0 Hz, C{2'^{min}}–H), 1.91–1.79 (m, 2H, C{7^{maj}, 7^{min}}–H), 1.78–1.68 (m, 4H, C{2^{maj}, 6'^{maj}, 7'^{maj}, 7'^{min}}–H), 1.40 (dddd, 1H, *J* = 13.0, 9.5, 8.0, 1.5 Hz, C{2'^{maj}}–H), 0.88 (s, 9H, C{11^{maj}}–H), 0.83 (s, 9H, C{11^{min}}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) *δ* 173.3 (C{13}), 172.8 (C{13'}), 171.4 (**C**O$_2$Me), 171.3 (**C**O$_2$Me'), 170.8 (**C**O$_2$Me''), 170.8 (**C**O$_2$Me'''), 151.3 (C{4^{maj}}), 150.2 (C{4^{min}}), 136.4 (C{15^{maj}}), 136.0 (C{15^{min}}), 128.7 (C{Ar}), 128.7 (C{Ar}), 128.6 (C{Ar}), 128.4 (C{Ar}), 128.3 (C{Ar}), 128.2 (C{Ar}), 108.3 (C{12^{min}}), 107.5 (C{12^{maj}}), 69.0 (C{9^{maj}}), 68.4 (C{9^{min}}), 66.5 (C{14^{min}}), 66.3 (C{14^{maj}}), 63.6 (C{1^{min}}), 62.1 (C{1^{maj}}), 58.2 (C{5^{min}}), 55.5 (C{5^{maj}}), 54.6 (C{8^{min}}), 53.7 (C{8^{maj}}), 52.0 (CO$_2$**Me**), 51.6 (CO$_2$**Me'**), 51.6 (CO$_2$**Me''**), 51.5 (CO$_2$**Me'''**), 37.0 (C{2^{maj}}), 34.6 (C{2^{min}}), 33.7 (C{10^{maj}}), 33.7 (C{6^{maj}}), 33.5 (C{10^{min}}), 32.2 (C{6^{min}}), 31.6 (C{3^{maj}}), 30.0 (C{3^{min}}), 28.6 (C{11^{min}}), 28.4 (C{11^{maj}}), 24.8 (C{7^{min}}), 24.0 (C{7^{maj}}); ***ν*/cm**$^{-1}$ (film) 2954w, 1727s, 1198w, 1138w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 465.2250. $C_{26}H_{34}O_6Na^+$ requires 465.2248.

6-Benzhydryl 1,1-dimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.138a and 6-benzhydryl 1,1-dimethyl (2*S**, 5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.138b**



The *title compounds* were prepared from 6-benzhydryl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate **3.133** (37 mg, 0.071 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (43 mg, 0.16 mmol), $Cu(OAc)_2 \cdot H_2O$ (16 mg, 0.078 mmol), and DMSO (0.50 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 80 °C for 18 h. Purification of the crude mixture by flash-chromatography (eluent: 1% to 14% Et_2O in pentane; 10 g SiO_2) provided spirocycle **3.138a** as a colourless oil (6.7 mg, 13 μmol, 17%) and spirocycle **3.138b** as a colourless oil (7.8 mg, 15 μmol, 21%).

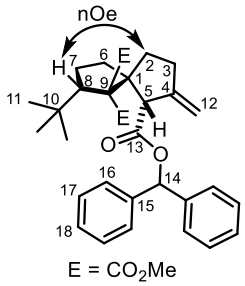
6-Benzhydryl 1,1-dimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro-[4.4]nonane-1,1,6-tricarboxylate, 3.138a**



R$_f$ 0.21 (5%Et_2O in pentane, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.43–7.39 (m, 2H, C{Ar}–H), 7.38–7.31 (m, 6H, C{Ar}–H), 7.31–7.26 (m, 2H, C{Ar}–H), 6.95 (s, 1H, C{14}–H), 4.86 (ddd, 1H, *J* = 2.5, 2.0, 2.0 Hz, C{12}–H), 4.66 (ddd, 1H, *J* = 2.5, 2.5, 2.5 Hz, C{12'}–H), 3.67 (s, 3H, CO_2**Me**), 3.55 (s, 3H, CO_2**Me'**), 3.09 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{5}–H), 2.74 (dd, 1H, *J* = 10.5, 10.5 Hz, C{8}–H), 2.46 (dddddd, 1H, *J* = 17.0, 10.0, 10.0, 2.5, 2.0, 2.0 Hz, C{3}–H), 2.36–2.26 (m, 1H, C{3'}–H), 2.19–2.05 (m, 3H, C{2, 6, 6'}–H), 1.95 (ddd, 1H, *J* = 13.0, 9.5, 3.0 Hz, C{2'}–H),

1.79–1.70 (m, 1H, C{7}–H), 1.69–1.60 (m, 1H, C{7'}–H), 0.78 (s, 9H, C{11}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.1 (C{13}), 170.9 (**C**O_2Me), 170.9 (**C**O_2Me'), 150.4 (C{4}), 140.2 (C{15}), 128.6 (C{16/17}), 128.6 (C{16/17}), 128.1 (C{18}), 128.0 (C{18'}), 127.6 (C{16/17}), 127.5 (C{16/17}), 108.6 (C{12}), 77.3 (C{14}), 68.5 (C{9}), 63.8 (C{1}), 58.1 (C{5}), 54.5 (C{8}), 51.6 (CO_2**Me**), 51.5 (CO_2**Me'**), 34.6 (C{2}), 33.5 (C{10}), 32.2 (C{6}), 30.3 (C{3}), 28.5 (C{11}), 24.6 (C{7}); **ν/cm^{-1}** (film) 2953w, 1727s, 1230m, 1197m, 700w; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 541.2559. $C_{32}H_{38}O_6Na^+$ requires 541.2561.

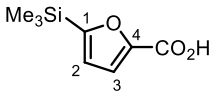
6-Benzhydryl 1,1-dimethyl (2*S,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro-[4.4]nonane-1,1,6-tricarboxylate, 3.138b**



R$_f$ 0.18 (5% Et_2O in pentane, blue in vanillin); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 7.40–7.36 (m, 4H, C{Ar}–H), 7.35–7.29 (m, 4H, C{Ar}–H), 7.30–7.23 (m, 2H, C{Ar}–H), 6.87 (s, 1H, C{14}–H), 4.83 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{12}–H), 4.65 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{12'}–H), 3.90 (ddd, 1H, *J* = 2.0, 2.0, 2.0 Hz, C{5}–H), 3.68 (s, 3H, CO_2**Me**), 3.42 (s, 3H, CO_2**Me'**), 2.88 (dd, 1H, *J* = 10.5, 9.0 Hz, C{8}–H), 2.61–2.52 (m, 2H, C{3, 6}–H), 2.21–2.13 (m, 1H, C{3'}–H), 1.88–1.78 (m, 1H, C{7}–H), 1.74–1.61 (m, 3H, C{2, 6', 7'}–H), 1.48–1.40 (m, 1H, C{2'}–H), 0.86 (s, 9H, C{11}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 172.3 (C{13}), 171.4 (**C**O_2Me), 171.2 (**C**O_2Me'), 151.2 (C{4}), 140.7 (C{15}), 140.5 (C{15'}), 128.7 (C{Ar}), 128.5 (C{Ar}), 128.4 (C{Ar}), 128.0 (C{Ar}), 127.8 (C{Ar}), 127.7 (C{Ar}), 127.7 (C{Ar}), 127.2 (C{Ar}), 126.7 (C{Ar}), 107.6 (C{12}), 77.1 (C{14}), 69.1 (C{9}), 62.2 (C{1}), 55.8 (C{5}), 53.7 (C{8}), 52.0 (CO_2**Me**), 51.5 (CO_2**Me'**), 37.2 (C{2}), 33.9 (C{10}), 33.6

(C{6}), 31.7 (C{3}), 28.4 (C{11}), 23.9 (C{7}); **ν/cm**$^{-1}$ (film) 2953w, 1727s, 1240w, 700m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 541.2558. $C_{32}H_{38}O_6Na^+$ requires 541.2561.

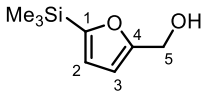
5-(Trimethylsilyl)furan-2-carboxylic acid, 3.161



According to the modified procedure of Abe,[349] *n*-BuLi (2.5 M in hexanes, 39 mL, 19 mmol) was added dropwise to a solution of diisopropylamine (10.5 mL, 20.3 mmol) in THF (200 mL) at −78 °C over 5 min. A solution of furan-2-carboxylic acid (5.1 g, 9.0 mmol) in THF (100 mL) was then added *via* cannula over 15 min. The resulting yellow solution was allowed to stir for 1 h at −78 °C before the dropwise addition of freshly distilled trimethylsilyl chloride (6.9 mL, 11 mmol). The solution was then allowed to stir for 2.5 h at room temperature. After this time, the reaction was cooled to 0 °C and 2 M HCl (60 mL) added over 10 min. The mixture was then diluted with H_2O (250 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow residue. Recrystallisation of the crude mixture from hot hexane provided the *title compound* as a pale yellow powder (3.90 g, 21.1 mmol, 47%).

R$_f$ 0.09 (50% EtOAc in $PE_{40\text{-}60}$, UV); **m.p.** 107–110 °C (from hexane) (lit.[350] 109–111 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.80 (br, 1H, CO_2H), 7.29 (d, 1H, J = 3.5 Hz, C{3}–H), 6.71 (d, 1H, J = 3.5 Hz, C{2}–H), 0.33 (s, 9H, Si(**Me**)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1 (C{1}), 163.8 (**C**O_2H), 147.6 (C{4}), 121.4 (C{2}), 120.0 (C{3}), −1.7 (Si(**Me**)$_3$); **LRMS** (*m*/*z* −ESI): Found: $[M-H]^-$, 183.1. $C_8H_{11}O_3Si^-$ requires 183.1. All data in accordance with the literature.[350]

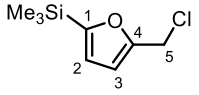
(5-(Trimethylsilyl)furan-2-yl)methanol, 3.162



$LiAlH_4$ (4 M in Et_2O, 8.1 mL, 32 mmol) was added to a solution of 5-(trimethylsilyl) furan-2-carboxylic acid **3.161** (3.0 g, 16 mmol) in THF (80 mL) at 0 °C at a rate that ensured the internal temperature of the solution remained under 5 °C. The resulting mixture was allowed to stir for 1 h at 0 °C. After this time, EtOAc (10 mL) was added over 5 min, followed by aq. sat. Rochelle's salt (75 mL), H_2O (75 mL), and EtOAc (200 mL). The resulting biphasic mixture was vigorously stirred for 30 min. It was then diluted with H_2O (100 mL), the layers separated, and the organic phase extracted with EtOAc (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 15% to 20% EtOAc in pentane; 200 g SiO_2) provided the *title compound* as a colourless oil (1.88 g, 11.1 mmol, 68%).

R$_f$ 0.44 (30% EtOAc in $PE_{40\text{-}60}$, blue in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, J = 3.0 Hz, C{2}–H), 6.27 (d, 1H, J = 3.0 Hz, C{3}–H), 4.64 (s, 2H, C{5}–H), 0.26 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 160.8 (C{1/4}), 158.2 (C{1/4}), 120.5 (C{2}), 107.8 (C{3}), 57.9 (C{5}), −1.5 (Si(**Me**)$_3$); ν**/cm**$^{-1}$ (film) 3324br, 1250m, 1013m, 841s. *Note: MS data not available due to lack of ionisation under ESI.*

(5-(Chloromethyl)furan-2-yl)trimethylsilane, 3.157

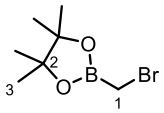


According to the modified procedure of Klein,[351] LiCl (708 mg, 16.7 mmol) and 2,4,6-collidine (2.9 mL, 22 mmol) were added to a solution of (5-(trimethylsilyl)furan-2-

yl)methanol **3.162** (1.88 g, 11.1 mmol) in DMF (40 mL) at 0 °C. Methanesulfonyl chloride (1.7 mL, 22 mmol) was then added dropwise over 5 min and the resulting solution allowed to stir at 0 °C for 2 h. After this time, the resulting white suspension was quenched with 1 M HCl (150 mL) and was extracted with pentane (3 × 200 mL). Each organic layer was washed with aq. sat. $NaHCO_3$ (150 mL), H_2O (2 × 150 mL), and brine (150 mL). The combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo* at 20 °C to give the *title compound* as an orange oil (1.46 g, 7.74 mmol, 70%) which was used in the next step without further purification and was stored under argon at −20 °C.

R$_f$ 0.78 (30% EtOAc in $PE_{40\text{-}60}$, blue in vanillin); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.55 (d, 1H, J = 3.0 Hz, C{2}–H), 6.34 (d, 1H, J = 3.0 Hz, C{3}–H), 4.62 (s, 2H, C{5}–H), 0.27 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 162.2 (C{1/4}), 154.2 (C{1/4}), 120.7 (C{2}), 109.8 (C{3}), 37.8 (C{5}), −1.5 (Si(**Me**)$_3$); ν**/cm**$^{-1}$ (film) 2958w, 1251m, 843s, 758w. *Note: MS data not available due to lack of ionisation under ESI.*

2-(Bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 3.175

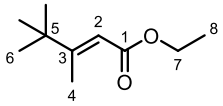


According to the modified procedure of Aggarwal,[352] *n*-BuLi (2.5 M in hexanes, 8.0 mL, 20 mmol) was added over 1 h to a solution of triisopropyl borate (5.1 mL, 22 mmol), and dibromomethane (1.7 mL, 24 mmol) in THF (35 mmol) at −78 °C. The resulting solution was allowed to stir for 1.5 h at this temperature, and 2 h at room temperature before being cooled down to 0 °C. Methanesulfonic acid (1.3 mL, 20 mmol) was added over 5 min, and the resulting solution allowed to stir at room temperature for 1 h. Pinacol (2.36 g, 20.0 mmol) was then added in one portion at 0 °C, and the reaction allowed to stir for a further 1 h at room temperature. Volatiles were then evaporated *in vacuo* to give a yellow

paste. Purification of the crude mixture by distillation (59 °C, 2.8 mbar) provided the *title compound* as a colourless oil (1.74 g, 7.88 mmol, 40%).

R$_f$ 0.13 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.58 (s, 2H, C{1}–H), 1.28 (s, 12H, C{3}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 84.7 (C{2}), 24.7 (C{3}), *Note:* C{1} *not observed*; **LRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 223.0. $C_7H_{15}B^{81}BrO_2^+$ requires 223.0. All data in accordance with the literature.[352]

Ethyl (*E*)-3,4,4-trimethylpent-2-enoate, 3.184

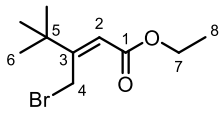


According to the modified procedure of Andersson,[353] triethyl phosphonoacetate (14.4 mL, 72 mmol) was added over 5 min to a suspension of sodium hydride (60% w/w dispersion in mineral oil, 2.40 g, 60.0 mmol) in THF (250 mmol) at 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C before the dropwise addition of pinacolone (5.0 mL, 40 mmol). The reaction was then allowed to stir for 18 h at 80 °C. After this time, it was diluted with sat. aq. NH_4Cl (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the crude mixture by flash-chromatography (eluent: 2.4% Et_2O in pentane; 350 g SiO_2) provided the *title compound* as a colourless oil (3.72 g, 21.8 mmol, 55%).

R$_f$ 0.39 (10% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.73 (s, 1H, C{2}–H), 4.14 (q, 2H, J = 7.0 Hz, C{7}–H), 2.16 (s, 3H, C{4}–H), 1.28 (t, 3H, J = 7.0 Hz, C{8}–H), 1.10 (s, 9H, C{6}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 167.7 (C{1/3}), 167.4 (C{1/3}), 113.1 (C{2}), 59.6 (C{7}), 38.1 (C{5}), 28.7 (C{6}), 15.3 (C{4}), 14.5 (C{8});

LRMS (*m*/*z* +ESI): Found: $[M+H]^+$, 171.2. $C_{10}H_{19}O_2^+$ requires 171.1. All data in accordance with the literature.[354]

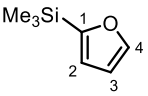
Ethyl (*Z*)-3-(bromomethyl)-4,4-dimethylpent-2-enoate, 3.183



According to the modified procedure of DeBoer,[249] *N*-bromosuccinimide (4.27 g, 24.0 mmol) and benzoyl peroxide (264 mg, 1.1 mmol) were added to a solution of ethyl (*E*)-3,4,4-trimethylpent-2-enoate **3.184** (3.71 g, 21.8 mmol) in chlorobenzene (100 mL). The resulting colourless solution was allowed to stir at 80 °C for 18 h. After this time, the reaction mixture was allowed to cool down and was filtered. Water (100 mL) was added to the resulting solution, which was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with 1 M NaOH (2 × 100 mL), brine (100 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give the *title compound* as a yellow oil (5.16 g, 20.7 mmol, 95%) with no need for further purification.

R$_f$ 0.53 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.90 (s, 1H, C{2}–H), 4.55 (s, 2H, C{4}–H), 4.21 (q, 2H, J = 7.0 Hz, C{7}–H), 1.31 (t, 3H, J = 7.0 Hz, C{8}–H), 1.21 (s, 9H, C{6}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 166.1 (C{1/3}), 164.0 (C{1/3}), 118.2 (C{2}), 60.4 (C{7}), 38.1 (C{5}), 29.4 (C{6}), 24.7 (C{4}), 14.4 (C{8}); **LRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 271.0. $C_{10}H_{17}{}^{79}BrNaO_2^+$ requires 271.0. All data in accordance with the literature.[249]

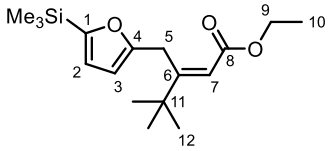
Furan-2-yltrimethylsilane, 3.159



According to the modified procedure of Ando,[355] *n*-BuLi (2.43 M in hexanes, 12 mL, 29.4 mmol) was added over 5 min to a solution of furan (2.2 mL, 29 mmol) in Et_2O (50 mL) at room temperature. The resulting solution was allowed to stir at 40 °C for 2.5 h. After this time, the mixture was cooled to 0 °C and trimethylsilyl chloride (3.6 mL, 28 mmol) added dropwise. The reaction was then allowed to stir for 1 h at room temperature. After this time, the reaction was quenched with water (40 mL) and the layers separated. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by distillation (160 °C, 1 atm) provided the *title compound* as a colourless oil (1.95 g, 13.9 mmol, 50%).

R_f 0.15 (2% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.65 (d, 1H, J = 1.5 Hz, C{4}–H), 6.63 (d, 1H, J = 3.0 Hz, C{2}–H), 6.38 (dd, 1H, J = 3.0, 1.5 Hz, C{3}–H), 0.27 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 160.4 (C{1}), 146.7 (C{4}), 119.6 (C{2}), 109.4 (C{3}), −1.5 (Si(**Me**)$_3$). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[355]

Ethyl (*E*)-4,4-dimethyl-3-((5-(trimethylsilyl)furan-2-yl)methyl)pent-2-enoate, 3.182

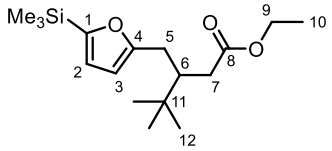


n-BuLi (2.43 M in hexanes, 1.65 mL, 4.01 mmol) was added dropwise to a solution of furan-2-yltrimethylsilane **3.159** (561 mg, 4.00 mmol) in dry, degassed THF (3 × freeze/pump/thaw cycles, 11 mL) at −30 °C. The resulting solution was allowed to stir at 0 °C for 1 h before it was transferred *via* cannula onto a suspension of CuCN (179 mg, 2.00 mmol) in dry, degassed THF (3 × freeze/pump/thaw cycles, 2.0 mL) at −30 °C. The

mixture was allowed to stir at 0 °C for 5 min, and the resulting pale yellow solution cooled back to −30 °C. Ethyl (*Z*)-3-(bromomethyl)-4,4-dimethylpent-2-enoate **3.183** (1.00 g, 4.01 mmol) was then added dropwise, and the reaction allowed to stir for 2 h at 0 °C. The resulting brown solution was quenched with 9:1 sat. aq. NH_4Cl/aq. 30% w/w NH_4OH (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as an orange oil (1.06 g, 3.44 mmol, 86%) with no need for further purification.

R$_f$ 0.41 (10% Et_2O in pentane, purple in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.47 (d, 1H, J = 3.0 Hz, C{2}–H), 5.92 (dt, 1H, J = 3.0, 1.0 Hz, C{3}–H), 5.90 (s, 1H, C{7}–H), 4.12 (q, 2H, J = 7.0 Hz, C{9}–H), 4.06 (s, 2H, C{5}–H), 1.23 (t, 3H, J = 7.0 Hz, C{10}–H), 1.10 (s, 9H, C{12}–H), 0.21 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 167.1 (C{8}), 165.1 (C{6}), 158.1 (C{4}), 158.0 (C{1}), 120.6 (C{2}), 116.0 (C{7}), 105.8 (C{3}), 59.9 (C{9}), 38.3 (C{11}), 29.0 (C{12}), 28.0 (C{5}), 14.4 (C{10}), −1.4 (Si(**Me**)$_3$); ν/**cm**$^{-1}$ (film) 2960w, 1719s, 1182m, 1154m, 841s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 331.1700. $C_{17}H_{28}O_3NaSi^+$ requires 331.1700.

Ethyl 4,4-dimethyl-3-((5-(trimethylsilyl)furan-2-yl)methyl)pentanoate, 3.187

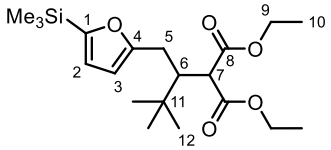


According to the modified procedure of Kwon,[257] iodine (27 mg, 0.11 mmol) was added to a mixture of magnesium turnings (832 mg, 34.2 mmol) in MeOH (5 mL). The mixture was briefly refluxed before the solvent was removed *via* cannula. MeOH (20 mL) was then added to the activated magnesium, and the mixture cooled to 0 °C. Ethyl (*E*)-4,4-dimethyl-3-((5-(trimethylsilyl)furan-2-yl)methyl)pent-2-enoate **3.182** (1.06 g, 3.42 mmol)

in MeOH (9 mL) was then added dropwise, and the resulting suspension stirred at 0 °C for 2 h. After this time, the reaction was quenched with aq. sat. NH_4Cl (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 4% Et_2O in pentane; 100 g SiO_2) provided the *title compound* as a colourless oil (809 mg, 2.60 mmol, 76%).

R_f 0.50 (10% Et_2O in pentane, purple in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.49 (d, 1H, J = 3.0 Hz, C{2}–H), 6.03 (dt, 1H, J = 3.0, 1.0 Hz, C{3}–H), 4.07–3.94 (m, 2H, C{9}–H), 2.86 (dd, 1H, J = 15.0, 3.0 Hz, C{5}–H), 2.55–2.44 (m, 1H, C{5'}–H), 2.44–2.33 (m, 1H, C{7}–H), 2.30–2.15 (m, 2H, C{6, 7'}–H), 1.19 (t, 3H, J = 7.0 Hz, C{10}–H), 0.91 (s, 9H, C{12}–H), 0.23 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 173.9 (C{8}), 159.5 (C{4}), 158.6 (C{1}), 120.5 (C{2}), 106.4 (C{3}), 60.3 (C{9}), 43.9 (C{6}), 35.7 (C{7}), 33.5 (C{11}), 29.5 (C{5}), 27.5 (C{12}), 14.3 (C{10}), −1.4 (Si(**Me**)$_3$); **ν/cm^{-1}** (film) 2969m, 1735s, 1249m, 1148w, 840s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 333.1857. $C_{17}H_{30}O_3NaSi^+$ requires 333.1856.

Diethyl 2-(3,3-dimethyl-1-(5-(trimethylsilyl)furan-2-yl)butan-2-yl)malonate, 3.181

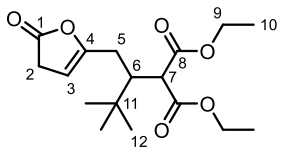


n-BuLi (2.43 M in hexanes, 2.3 mL, 5.6 mmol) was added to a solution of di-isopropylamine (0.80 mL, 5.7 mmol) in THF (6.0 mL) at −78 °C. After 2 minutes stirring at this temperature it was transferred *via* cannula to a vessel containing ethyl 4,4-dimethyl-3-((5-(trimethylsilyl)furan-2-yl)methyl)pentanoate **3.187** (805 mg, 2.59 mmol) in THF (16 mL) at −78 °C. The resulting yellow solution was allowed to stir for 1 h at this

temperature before the dropwise addition of ethyl chloroformate (0.50 mL, 5.2 mmol). The reaction was then allowed to stir at room temperature for 18 h. After this time, the mixture was quenched with aq. sat. NH_4Cl (40 mL) and was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 2.5% EtOAc in pentane; 130 g SiO_2) provided the *title compound* as a colourless oil (671 mg, 1.75 mmol, 68%).

R$_f$ 0.26 (10% Et_2O in pentane, blue in vanillin); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.46 (d, 1H, J = 3.0 Hz, C{2}–H), 6.05 (dt, 1H, J = 3.0, 1.0 Hz, C{3}–H), 4.18–3.92 (m, 4H, C{9}–H), 3.60 (d, 1H, J = 4.5 Hz, C{7}–H), 3.13 (dd, 1H, J = 16.0, 7.5 Hz, C{5}–H), 2.89 (dd, 1H, J = 16.0, 5.0 Hz, C{5'}–H), 2.64 (ddd, 1H, J = 7.5, 5.0, 4.5 Hz, C{6}–H), 1.23 (t, 3H, J = 7.0 Hz, C{10}–H), 1.18 (t, 3H, J = 7.0 Hz, C{10'}–H), 0.93 (s, 9H, C{12}–H), 0.23 (s, 9H, Si(**Me**)$_3$); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.0 (C{8}), 169.5 (C{8'}), 159.8 (C{4}), 158.1 (C{1}), 120.5 (C{2}), 106.5 (C{3}), 61.4 (C{9}), 61.1 (C{9'}), 52.2 (C{7}), 47.4 (C{6}), 34.3 (C{11}), 28.1 (C{12}), 26.3 (C{5}), 14.1 (C{10}), 14.1 (C{10'}), −1.4 (Si(**Me**)$_3$); **ν/cm**$^{-1}$ (film) 2961m, 1753m, 1732s, 1249m, 842s; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 405.2067. $C_{20}H_{34}O_5NaSi^+$ requires 405.2068.

Diethyl 2-(3,3-dimethyl-1-(5-oxo-4,5-dihydrofuran-2-yl)butan-2-yl)malonate, 3.189

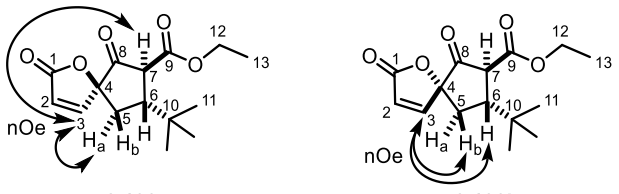


NaOAc (38 mg, 0.46 mmol) was added to a solution of diethyl 2-(3,3-dimethyl-1-(5-(trimethylsilyl)furan-2-yl)butan-2-yl)malonate **3.181** (326 mg, 0.85 mmol) in CH_2Cl_2 (25 mL) at 0 °C. m-CPBA (50% w/w, 353 mg, 1.02 mmol) was then added over 10 min

in four equal portions, and the resulting mixture allowed to stir for 1 h at 0 °C. After this time, the reaction was quenched with aq. sat. $Na_2S_2O_3$ (6 mL) and aq. sat. $NaHCO_3$ (30 mL). The layers were separated, and the aqueous extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 17.5% EtOAc in pentane; 35 g SiO_2) provided the *title compound* as a colourless oil (169 mg, 0.52 mmol, 61%).

R$_f$ 0.31 (20% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.26 (dddd, 1H, J = 2.5, 2.5, 1.5, 1.5 Hz, C{3}–H), 4.21–4.06 (m, 4H, C{9}–H), 3.64 (d, 1H, J = 3.5 Hz, C{7}–H), 3.20–3.03 (m, 2H, C{2}–H), 2.99–2.89 (m, 1H, C{5}–H), 2.53–2.43 (m, 2H, C{5',6}–H), 1.28 (t, 3H, J = 7.0 Hz, C{10}–H), 1.25 (t, 3H, J = 7.0 Hz, C{10'}–H), 0.95 (s, 9H, C{12}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 176.9 (C{1}), 170.0 (C{8}), 169.4 (C{8'}), 156.5 (C{4}), 100.4 (C{3}), 61.7 (C{9}), 61.2 (C{9'}), 51.3 (C{7}), 45.2 (C{6}), 34.3 (C{11}), 34.2 (C{2}), 28.0 (C{12}), 26.0 (C{5}), 14.1 (C{10}); ν**/cm**$^{-1}$ (film) 2965w, 1799s, 1730s, 1146m, 1108m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 349.1622. $C_{17}H_{26}O_6Na^+$ requires 349.1622.

Ethyl (5*S,7*S**,8*R**)-8-(*tert*-butyl)-2,6-dioxo-1-oxaspiro[4.4]non-3-ene-7-carboxylate, 3.190a and ethyl (5*R**,7*S**,8*R**)-8-(*tert*-butyl)-2,6-dioxo-1-oxaspiro[4.4]non-3-ene-7-carboxylate, 3.190b**

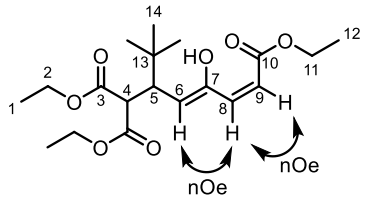


3.190a (A) **3.190b** (B)

DBU (8 μL, 0.05 mmol) was added to a solution of diethyl 2-(3,3-dimethyl-1-(5-oxo-4,5-dihydrofuran-2-yl)butan-2-yl)malonate **3.189** (7.5 mg, 0.023 mmol) in DMF (1.1 mL). The resulting solution was allowed to stir at room temperature for 18 h. After this time, the reaction was quenched with 1.0 M HCl (1.0 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with water (3 × 3 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compounds* as a colourless oil (5.4 mg, 0.019 mmol, 1:1 mixture of inseparable diastereoisomers, 84%).

Characterised as a 1:1 mixture of diastereoisomers: $\mathbf{R}_f$ 0.29 (33% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 5.5 Hz, C{3^B}–H), 7.20 (d, 1H, J = 5.5 Hz, C{3^A}–H), 6.27 (d, 1H, J = 5.5 Hz, C{2^A}–H), 6.17 (d, 1H, J = 5.5 Hz, C{2^B}–H), 4.33–4.13 (m, 4H, C{12}–H), 3.28 (d, 1H, J = 10.5 Hz, C{7^B}–H), 3.22 (d, 1H, J = 12.0 Hz, C{7^A}–H), 2.96 (ddd, 1H, J = 13.0, 13.0, 6.5 Hz, C{6^A}–H), 2.68 (ddd, 1H, J = 13.0, 10.5, 6.5 Hz, C{6^B}–H), 2.34 (dd, 1H, J = 13.0, 6.5 Hz, C{5^B}–H_b), 2.29 (dd, 1H, J = 14.5, 6.5 Hz, C{5^A}–H_b), 2.23 (dd, 1H, J = 13.0, 13.0 Hz, C{5^B}–H_a), 2.04 (dd, 1H, J = 14.5, 14.0 Hz, C{5^A}–H_a), 1.29 (t, 3H, J = 7.0 Hz, C{13}–H), 1.28 (t, 3H, J = 7.0 Hz, C{13'}–H), 0.96 (s, 18H, C{11}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 203.2 (C{8^A}), 202.1 (C{8^B}), 171.6 (C{1^B}), 171.0 (C{1^A}), 169.5 (C{9^B}), 168.4 (C{9^A}), 152.6 (C{3^A}), 151.5 (C{3^B}), 124.0 (C{2^A}), 121.4 (C{2^B}), 93.3 (C{4^B}), 91.2 (C{4^A}), 62.4 (C{12}), 62.1 (C{12}), 57.6 (C{7^A}), 55.3 (C{7^B}), 47.7 (C{6^A}), 45.3 (C{6^B}), 34.2 (C{5^A}), 32.6 (C{10^A}), 32.3 (C{10^B}), 31.9 (C{5^B}), 27.2 (C{11}), 27.1 (C{11'}), 14.2 (C{13}), 14.2 (C{13'}); ν**/cm**$^{-1}$ (film) 2965w, 1774s, 1730s 1293w, 1090m; **HRMS** (m/z −ESI): Found: $[M\text{-}H]^-$, 279.1232. $C_{15}H_{19}O_5^-$ requires 279.1238.

Triethyl (3*Z*,5*Z*)-2-(*tert*-butyl)-4-hydroxyhexa-3,5-diene-1,1,6-tricarboxylate, 3.193

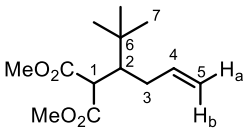


According to the modified procedure of Vanderwal,[356] methylene blue (1 mg, 3 μmol) was added to a solution of diethyl 2-(3,3-dimethyl-1-(5-(trimethylsilyl)furan-2-yl)butan-2-yl)malonate **3.181** (20 mg, 0.052 mmol) in $CHCl_3$ (3.0 mL). The resulting solution was cooled to 0 °C and irradiated for 30 min with a 30 W white compact fluorescent light while oxygen was bubbled through. After this time, all volatiles were evaporated *in vacuo*, the resulting blue residue dissolved in THF (3.0 mL), and cooled to −20 °C. TBAF (1.0 M in THF, 80 μL, 0.080 mmol) was added and the solution allowed to stir for 10 min at −20 °C. After this time, ethyl iodide (6 μL, 0.068 mmol) was added and the solution allowed to stir for 2 h at room temperature. The reaction was then quenched with aq. sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 25% EtOAc in pentane; 5 g SiO_2) provided the *title compound* as a colourless oil (3.3 mg, 8.9 μmol, 17%).

R_f 0.50 (20% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 10.46 (dd, 1H, J = 1.5, 0.5 Hz, O–H), 6.36 (d, 1H, J = 13.0 Hz, C{8}–H), 5.56 (d, 1H, J = 13.0 Hz, C{9}–H), 5.13 (d, 1H, J = 11.0 Hz, C{6}–H), 4.26–4.03 (m, 6H, C{2, 11}–H), 3.61 (d, 1H, J = 6.0 Hz, C{4}–H), 3.48 (dd, 1H, J = 11.0, 6.0 Hz, C{5}–H), 1.30 (t, 3H, J = 7.0 Hz, C{12}–H), 1.27–1.21 (m, 6H, C{1}–H), 0.93 (s, 9H, C{14}–H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 169.8 (**C**O_2Et), 169.5 (**C**O_2Et'), 169.2 (**C**O_2Et"), 151.2 (C{7}), 145.1 (C{8}), 118.8 (C{6}), 114.2 (C{9}), 61.8 (C{11}), 61.6 (C{2}), 61.2 (C{2'}), 53.2 (C{4}),

45.1 (C{5}), 35.1 (C{13}), 28.0 (C{14}), 14.2 (C{12}), 14.1 (C{1}); ν/**cm**$^{-1}$ (film) 3127w, 2962w, 1732m, 1595w, 1207s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 393.1883. $C_{19}H_{30}O_7Na^+$ requires 393.1884.

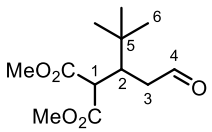
Dimethyl 2-(2,2-dimethylhex-5-en-3-yl)malonate, 3.202



According to the modified procedure of Sakurai,[357] $TiCl_4$ (3.8 mL, 35 mmol) was added dropwise to a solution of dimethyl 2-(2,2-dimethylpropylidene)malonate **3.101** (6.15 g, 30.7 mmol) in CH_2Cl_2 (190 mL) at −78 °C. The resulting yellow solution was allowed to stir for 5 min before the dropwise addition of allyltrimethylsilane (5.9 mL, 37 mmol). The deep purple solution was then allowed to stir at 0 °C for 2.5 h before being quenched with water (250 mL). The layers were separated, and the aqueous phase extracted with Et_2O (2 × 250 mL). The combined organic layers were washed with water (3 × 200 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a yellow oil (7.19 g, 29.7 mmol, 97%) with no need for further purification.

R$_f$ 0.46 (25% Et_2O in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.75 (dddd, 1H, *J* = 17.0, 10.0, 7.5, 6.0 Hz, C{4}–H), 5.02 (dddd, 1H, *J* = 17.0, 1.5, 1.5, 1.5 Hz, C{5}–H_b), 4.92 (dddd, 1H, *J* = 10.0, 1.5, 1.5, 1.5 Hz, C{5}–H_a), 3.68 (s, 6H, 2 × CO_2**Me**), 3.61 (d, 1H, *J* = 4.5 Hz, C{1}–H), 2.55–2.42 (m, 1H, C{3}–H), 2.36–2.26 (m, 1H, C{3'}–H), 2.22 (ddd, 1H, *J* = 8.5, 4.5, 4.0 Hz, C{2}–H), 0.91 (s, 9H, C{7}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.9 (**C**O_2Me), 169.9 (**C**O_2Me'), 139.0 (C{4}), 115.5 (C{5}), 52.5 (CO_2**Me**), 52.1 (CO_2**Me'**), 51.6 (C{1}), 48.9 (C{2}), 34.4 (C{6}), 31.9 (C{3}), 28.1 (C{7}); ν/**cm**$^{-1}$ (film) 2954w, 1734s, 1435m, 1147s, 913w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 243.1592. $C_{13}H_{23}O_4^+$ requires 243.1591.

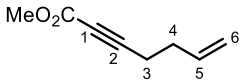
Dimethyl 2-(4,4-dimethyl-1-oxopentan-3-yl)malonate, 3.144



According to the modified procedure of Jin,[358] 2,6-lutidine (5.3 mL, 46 mmol), $K_2OsO_4 \cdot 2H_2O$ (39 mg, 0.11 mmol), and $NaIO_4$ (18.8 g, 87.9 mmol) were added to a solution of dimethyl 2-(2,2-dimethylhex-5-en-3-yl)malonate **3.202** (5.29 g, 21.8 mmol) in THF/H_2O (4:1, 87 mL) at 0 °C. The resulting mixture was allowed to stir at this temperature for 15 min and at room temperature for 3 h. After this time, the reaction was partitioned between water (300 mL) and CH_2Cl_2 (300 mL). The layers were separated, and the aqueous extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were washed with aq. sat. $CuSO_4$ (300 mL), water (300 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a grey oil. Purification of the crude mixture by flash-chromatography (eluent: 10% to 20% EtOAc in pentane; 250 g SiO_2) provided the *title compound* as a grey oil (4.27 g, 17.5 mmol, 80%).

R_f 0.33 (20% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, C_6D_6) δ 9.53 (t, 1H, J = 1.5 Hz, C{4}–H), 3.70 (d, 1H, J = 3.5 Hz, C{1}–H), 3.29 (s, 3H, CO_2**Me**), 3.28 (s, 3H, CO_2**Me'**), 3.01 (ddd, 1H, J = 18.5, 5.5, 1.5 Hz, C{3}–H), 2.85 (ddd, 1H, J = 5.5, 5.5, 3.5 Hz, C{2}–H), 2.30 (ddd, 1H, J = 18.5, 5.5, 1.5 Hz, C{3'}–H), 0.69 (s, 9H, C{6}–H); ^{13}**C NMR** (101 MHz, C_6D_6) δ 200.3 (C{4}), 169.9 (**C**O_2Me), 169.5 (**C**O_2Me'), 52.3 (CO_2**Me**), 51.8 (CO_2**Me'**), 51.4 (C{1}), 42.5 (C{3}), 42.1 (C{2}), 33.8 (C{5}), 27.7 (C{6}); ν**/cm**$^{-1}$ (film) 2957w, 1730s, 1203m, 1150s; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 267.1201. $C_{12}H_{20}O_5Na^+$ requires 267.1203.

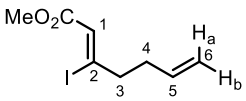
Methyl hept-6-en-2-ynoate, 3.204



According to the modified procedure of Hopf,[272] propargyl chloride (6.6 mL, 90 mmol) was added over 10 min to a solution of allylmagnesium bromide (1 M in Et_2O, 180 mL, 180 mmol) at −10 °C. The resulting mixture was allowed to stir at room temperature for 18 h. After this time, the reaction was cooled to 0 °C and methyl chloroformate (21 mL, 272 mmol) was added. The resulting off-white suspension was allowed to stir at room temperature for 6 h. It was then cooled to 0 °C and carefully quenched with sat. aq. NH_4Cl (150 mL). The resulting mixture was diluted with water (100 mL) and extracted with Et_2O (2 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 10% to 60% CH_2Cl_2 in pentane; 200 g SiO_2) provided the *title compound* as a colourless oil (3.83 g, 27.7 mmol, 31%).

$\mathbf{R}_f$ 0.30 (30% CH_2Cl_2 in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.83 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{5}–H), 5.15–5.04 (m, 2H, C{6}–H), 3.75 (s, 3H, CO_2**Me**), 2.45–2.39 (m, 2H, C{3}–H), 2.36–2.28 (m, 2H, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 154.3 (**C**O_2Me), 135.9 (C{5}), 116.6 (C{6}), 89.0 (C{2}), 73.3 (C{1}), 52.7 (CO_2**Me**), 31.7 (C{4}), 18.6 (C{3}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[274]

Methyl (*Z*)-3-iodohepta-2,6-dienoate, 3.195

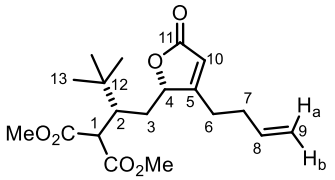


According to the modified procedure of Yun,[359] sodium iodide (10.5 g, 70 mmol) was added to a solution of methyl hept-6-en-2-ynoate **3.204** (3.83 g, 27.7 mmol) in acetic acid

(25 mL). The resulting solution was allowed to stir at 70 °C for 23 h. After this time, the reaction was allowed to cool down to room temperature and was diluted with Et_2O (300 mL) and water (150 mL). The layers were separated, and the organic phase washed with water (3 × 100 mL), sat. aq. $NaHCO_3$ (100 mL), and sat. aq. $Na_2S_2O_3$ (70 mL). This solution was then dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a brown oil (6.25 g, 23.5 mmol, 85%) with no need for further purification.

R$_f$ 0.48 (10% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.35 (t, 1H, J = 1.0 Hz, C{1}–H), 5.75 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz, C{5}–H), 5.08 (ddt, 1H, J = 17.0, 1.5, 1.5 Hz, C{6}–H$_a$), 5.03 (ddt, 1H, J = 10.0, 1.5, 1.5 Hz, C{6}–H$_b$), 3.75 (s, 3H, CO_2**Me**), 2.82–2.75 (m, 2H, C{3}–H), 2.40–2.31 (m, 2H, C{4}–H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 165.0 (**C**O_2Me), 135.5 (C{5}), 125.0 (C{1}), 120.8 (C{2}), 116.5 (C{6}), 51.7 (CO_2**Me**), 47.3 (C{3}), 33.4 (C{4}); ν**/cm**$^{-1}$ (film) 2950w, 1732s, 1623m, 1170s, 852w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 266.9875. $C_8H_{12}IO_2^+$ requires 266.9876.

Dimethyl 2-((*R)-1-((*S**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate, 3.141b**

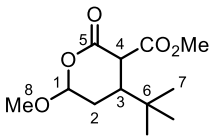


iPrMgCl (2.0 M in THF, 12 mL, 24 mmol) was added over 5 min to a solution of methyl (*Z*)-3-iodohepta-2,6-dienoate **3.195** (6.25 g, 23.5 mmol) in dry THF (100 mL) at −40 °C. The resulting solution was allowed to stir at this temperature for 1 h. After this time, and in a separate flask, freshly distilled trimethylsilyl chloride (3.0 mL, 24 mmol) was added to a solution of dimethyl 2-(4,4-dimethyl-1-oxopentan-3-yl)malonate **3.144** (2.80 g, 11.5 mmol) in THF (60 mL) at −40 °C and was allowed to stir at this temperature for

5 min. After this time, the Grignard reagent solution was transferred to the flask containing aldehyde **3.144** with the aid of a cannula, while maintaining both solutions at −40 °C. The resulting orange solution was then allowed to stir for 50 min at this temperature. Subsequently, the reaction was quenched through the addition of a solution of acetic acid (15 mL) in THF (20 mL) at −40 °C over 5 min, before it was allowed to warm up to room temperature and was diluted with water (200 mL). This mixture was extracted with EtOAc (3 × 200 mL) and the combined organic layers washed with brine (150 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a brown oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 30% EtOAc in pentane; 300 g SiO_2) provided the *title compound* as a colourless oil (3.13 g, 8.89 mmol, 4:1 mixture of inseparable diastereoisomers (major: **3.141b**), 85%).

Characterised as a 4:1 mixture of diastereoisomers, data for the major diastereoisomer (**3.141b**): $\mathbf{R}_f$ 0.40 (30% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.86–5.78 (m, 1H, C{8}–H), 5.76 (ddd, 1H, J = 1.5, 1.5, 1.5 Hz, C{10}–H), 5.11 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz, C{9}–H_a), 5.07–5.01 (m, 2H, C{4}–H, C{9}–H_b), 3.83 (d, 1H, J = 2.0 Hz, C{1}–H), 3.77 (s, 3H, CO_2**Me**), 3.74 (s, 3H, CO_2**Me'**), 2.55–2.43 (m, 4H, C{2, 3, 3', 6/7}–H), 2.43–2.31 (m, 3H, C{6, 7}–H), 0.92 (s, 9H, C{13}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 173.7 (C{11}), 173.4 (C{5}), 171.3 (**C**O_2Me), 170.0 (**C**O_2Me'), 136.5 (C{8}), 116.4 (C{9}), 115.3 (C{10}), 83.1 (C{4}), 53.1 (CO_2**Me**), 52.4 (CO_2**Me'**), 50.2 (C{1}), 46.0 (C{2}), 34.3 (C{12}), 31.1 (C{6/7}), 30.9 (C{6/7}), 28.0 (C{13}), 27.5 (C{3}); ν**/cm**$^{-1}$ (film) 2955w, 1754s, 1436w, 1148m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 375.1780. $C_{19}H_{28}O_6Na^+$ requires 375.1778.

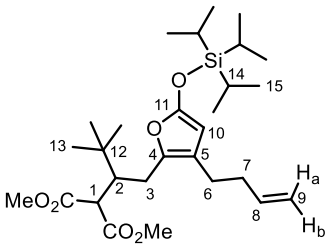
Methyl 4-(*tert*-butyl)-6-methoxy-2-oxotetrahydro-2*H*-pyran-3-carboxylate, 3.208



Isolated in variable amounts as a single diastereoisomer during the optimisation of the synthesis of dimethyl 2-((*R**)-1-((*S**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl) malonate **3.141b** from iodide **3.195** and aldehyde **3.144**.

R$_f$ 0.40 (30% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.24 (dd, 1H, J = 2.5, 2.5 Hz, C{1}–H), 3.77 (s, 3H, CO_2**Me**), 3.43 (d, 1H, J = 4.0 Hz, C{4}–H), 3.42 (s, 3H, C{8}–H), 2.69 (ddd, 1H, J = 11.5, 7.5, 4.0 Hz, C{3}–H), 2.06 (ddd, 1H, J = 14.0, 7.5, 2.5 Hz, C{2}–H), 1.66 (ddd, 1H, J = 14.0, 11.5, 2.5 Hz, C{2'}–H), 0.90 (s, 9H, C{7}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.0 (**C**O_2Me), 168.1 (C{5}), 102.6 (C{1}), 56.4 (C{8}), 53.0 (CO_2**Me**), 49.9 (C{4}), 40.4 (C{3}), 33.5 (C{6}), 29.0 (C{2}), 26.6 (C{7}); ν**/cm**$^{-1}$ (film) 2961w, 1740s, 1035w, 992m; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 267.1202. $C_{12}H_{20}O_5Na^+$ requires 267.1203.

Dimethyl 2-(1-(3-(but-3-en-1-yl)-5-((triisopropylsilyl)oxy)furan-2-yl)-3,3-dimethylbutan-2-yl)malonate, 3.215

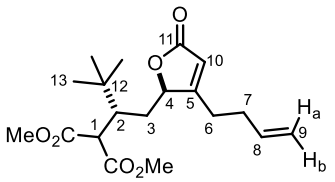


Triethylamine (3.1 mL, 22 mmol) was added to a solution of dimethyl 2-((*R**)-1-((*S**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate **3.141b** (3.13 g, 8.89 mmol, 4:1 d.r.) in CH_2Cl_2 (100 mL) at 0 °C. The resulting solution was allowed to stir at this temperature for 15 min before the addition of triisopropylsilyl

trifluoromethanesulfonate (2.7 mL, 10 mmol). The reaction was then allowed to stir at room temperature for 2.5 h before being quenched with water (100 mL) and the resulting layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 1:5:94 NEt_3/EtOAc/pentane; 125 g SiO_2) provided the *title compound* as a colourless oil (3.84 g, 7.54 mmol, 85%).

R_f 0.75 (20% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.84 (dddd, 1H, J = 17.0, 10.0, 6.5, 6.5 Hz, C{8}–H), 5.01 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz, C{9}–H_a), 4.94 (dddd, 1H, J = 10.0, 2.0, 1.0, 1.0 Hz, C{9}–H_b), 4.89 (s, 1H, C{10}–H), 3.69 (s, 3H, CO_2**Me**), 3.64 (d, 1H, J = 3.5 Hz, C{1}–H), 3.57 (s, 3H, CO_2**Me'**), 3.02 (dd, 1H, J = 15.5, 8.5 Hz, C{3}–H), 2.65 (dd, 1H, J = 15.5, 4.5 Hz, C{3'}–H), 2.56 (ddd, 1H, J = 8.5, 4.5, 3.5 Hz, C{2}–H), 2.46–2.36 (m, 1H, C{6}–H), 2.36–2.26 (m, 1H, C{6'}–H), 2.24–2.14 (m, 2H, C{7}–H), 1.31–1.18 (m, 3H, C{14}–H), 1.13–1.06 (m, 18H, C{15}–H), 0.93 (s, 9H, C{13}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.2 (**C**O_2Me), 170.1 (**C**O_2Me'), 155.0 (C{11}), 138.8 (C{8}), 138.4 (C{4}), 120.8 (C{5}), 114.8 (C{9}), 85.0 (C{10}), 52.5 (CO_2**Me**), 52.1 (CO_2**Me'**), 51.3 (C{1}), 48.0 (C{2}), 34.4 (C{7}), 34.0 (C{12}), 28.3 (C{13}), 24.8 (C{6}), 23.4 (C{3}), 17.8 (C{15}), 12.4 (C{14}); ν**/cm**$^{-1}$ (film) 2949m, 1759s, 1737s, 1148s, 860m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 509.3290. $C_{28}H_{49}O_6Si^+$ requires 509.3293.

Dimethyl 2-((*R)-1-((*R**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate, 3.141a**

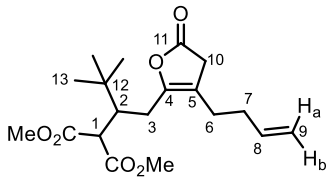


Dimethyl 2-(1-(3-(but-3-en-1-yl)-5-((triisopropylsilyl)oxy)furan-2-yl)-3,3-dimethylbutan-2-yl)malonate **3.215** (3.84 g, 7.54 mmol) was dissolved in acetic acid (70 mL) and allowed to stir at room temperature for 1 h. After this time, all volatiles were evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 30% EtOAc in pentane; 250 g SiO_2) provided the *title compound* as a colourless oil (2.31 g, 6.55 mmol, 3:1 mixture of inseparable diastereoisomers (major: **3.141a**), 87%).

Characterised as a 3:1 mixture of diastereoisomers, data for the major diastereoisomer (**3.141a**): $\mathbf{R}_f$ 0.40 (30% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.85–5.77 (m, 1H, C{8}–H), 5.77 (ddd, 1H, J = 1.5, 1.5, 1.5 Hz, C{10}–H), 5.11 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz, C{9}–H_a), 5.07 (dddd, 1H, J = 10.0, 1.5, 1.5, 1.5 Hz, C{9}–H_b), 4.77 (ddd, 1H, J = 11.0, 3.0, 1.5 Hz, C{4}–H), 3.81 (s, 3H, CO_2**Me**), 3.75 (d, 1H, J = 3.0 Hz, C{1}–H), 3.70 (s, 3H, CO_2**Me**'), 2.58–2.51 (m, 1H, C{6}–H), 2.41–2.33 (m, 4H, C{2, 6', 7}–H), 2.11 (ddd, 1H, J = 16.0, 6.5, 3.0 Hz, C{3}–H), 2.01 (ddd, 1H, J = 16.0, 11.0, 3.0 Hz, C{3'}–H), 0.98 (s, 9H, C{13}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 172.7 (C{11}), 172.4 (C{5}), 170.3 (**C**O_2Me), 169.7 (**C**O_2Me'), 136.2 (C{8}), 116.7 (C{9}), 115.9 (C{10}), 84.8 (C{4}), 53.2 (CO_2**Me**), 52.3 (CO_2**Me**), 51.5 (C{1}), 46.3 (C{2}), 35.0 (C{12}), 31.1 (C{7}), 30.8 (C{3}), 28.3 (C{13}), 27.7 (C{6}); ν**/cm**$^{-1}$ (film) 2954w, 1756s, 1147w, 857w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 353.1959. $C_{19}H_{29}O_6^+$ requires 353.1959.

γ-Butenolide **3.141a** was also prepared from (*Z*)-3-(but-3-en-1-yl)-6-(*tert*-butyl)-8-methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid **3.130** following Bertrand's conditions.[246] A solution of $Na_2S_2O_8$ (20 mg, 0.084 mmol) in H_2O (0.20 mL) was added over 1 h to a mixture of acid **3.130** (20 mg, 0.056 mmol), $CuSO_4 \cdot 5H_2O$ (17 mg, 0.068 mmol), and $AgNO_3$ (3.2 mg, 0.019 mmol) in 2:1 MeCN/H_2O (0.30 mL) at 80 °C. The resulting mixture was then allowed to stir at this temperature for 3 h. After this time, the reaction was diluted with sat. aq. Na_2CO_3 (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 25% EtOAc in pentane; 3 g SiO_2) provided the *title compound* as a colourless oil (2 mg, 6 μmol, 4:1 mixture of inseparable diastereoisomers (major: **3.141a**), 12%).

Dimethyl 2-(1-(3-(but-3-en-1-yl)-5-oxo-4,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate, 3.214

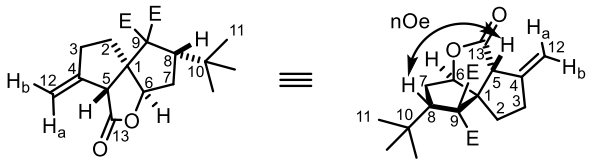


Isolated in variable amounts during the optimisation of the epimerisation of dimethyl 2-((*R**)-1-((*S**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate **3.141b**.

R$_f$ 0.47 (30% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.79 (dddd, 1H, J = 16.5, 10.0, 6.5, 6.5 Hz, C{8}–H), 5.05 (d, 1H, J = 16.5 Hz, C{9}–H_a), 5.00 (d, 1H, J = 10.0 Hz, C{9}–H_b), 3.73 (s, 3H, CO_2**Me**), 3.72 (d, 1H, J = 3.0 Hz, C{1}–H), 3.65 (s, 3H, CO_2**Me**'), 3.14 (dd, 1H, J = 15.0, 8.5 Hz, C{3}–H), 3.12–3.00 (m, 2H, C{10}–H), 2.49 (ddd, 1H, J = 9.0, 3.5, 3.0 Hz, C{2}–H), 2.44 (ddd, 1H, J = 15.0, 2.5, 2.5 Hz,

C{3'}–H), 2.41–2.25 (m, 1H, C{6}–H), 2.26–2.15 (m, 2H, C{6', 7}–H), 2.15–2.08 (m, 1H, C{7'}–H), 0.96 (s, 9H, C{13}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 176.3 (C{11}), 170.2 (**C**O_2Me), 169.7 (**C**O_2Me'), 149.1 (C{4}), 137.8 (C{8}), 115.7 (C{9}), 113.4 (C{5}), 52.6 (CO_2**Me**), 52.3 (CO_2**Me'**), 50.5 (C{1}), 45.7 (C{2}), 36.3 (C{10}), 34.2 (C{12}), 32.4 (C{7}), 28.2 (C{13}), 25.1 (C{6}), 22.8 (C{3}); ν**/cm**$^{-1}$ (film) 2955w, 1797s, 1756s, 1734s, 1148m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 375.1780. $C_{19}H_{28}O_6Na^+$ requires 375.1778.

Dimethyl (2*S,3a*R**,5a*R**,8a*S**)-2-(*tert*-butyl)-6-methylene-5-oxohexa-hydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.150**

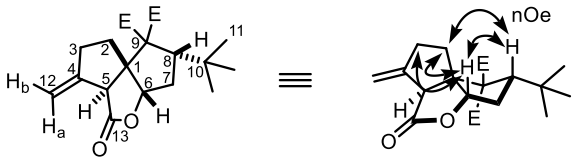


The *title compound* was prepared from dimethyl 2-((*R**)-1-((*R**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate **3.141a** (2.30 g, 6.53 mmol, 3:1 d.r.), $Mn(OAc)_3{\cdot}2H_2O$ (4.01 g, 15.0 mmol), $Cu(OAc)_2{\cdot}H_2O$ (1.48 g, 7.41 mmol), and DMSO (26 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 60 °C for 18 h. Purification of the crude mixture by flash-chromatography (eluent: 20% EtOAc in pentane; 150 g SiO_2) provided the *title compound* as a white solid (1.13 g, 3.23 mmol, 50%).

R$_f$ 0.50 (30% EtOAc in pentane, $KMnO_4$); **m.p.** 90.7–95.8 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.06 (br, 1H, C{12}–H_a), 5.00 (br, 1H, C{12}–H_b), 4.90 (d, 1H, J = 8.0 Hz, C{6}–H), 3.75 (s, 3H, CO_2**Me**), 3.67 (s, 3H, CO_2**Me'**), 3.23 (s, 1H, C{5}–H), 2.75 (dd, 1H, J = 14.0, 7.5 Hz, C{8}–H), 2.40 (ddd, 1H, J = 14.5, 13.5, 8.0 Hz, C{7}–H), 2.33–

2.17 (m, 4H, C{2, 3}–H), 2.01 (ddd, 1H, J = 14.5, 7.5, 1.0 Hz, C{7'}–H), 0.90 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 176.0 (C{13}), 170.1 (**C**O_2Me), 169.9 (**C**O_2Me'), 146.8 (C{4}), 110.2 (C{12}), 89.7 (C{6}), 68.8 (C{1/9}), 65.2 (C{1/9}), 55.9 (C{5}), 52.7 (C{8}), 52.2 (CO_2**Me**), 52.1 (CO_2**Me'**), 36.0 (C{2}), 33.8 (C{7}), 32.9 (C{10}), 31.9 (C{3}), 28.7 (C{11}); ν**/cm**$^{-1}$ (film) 2955w, 1773s, 1734s, 1266m, 1201m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 351.1801. $C_{19}H_{27}O_6^+$ requires 351.1802.

Dimethyl (2*S,3a*S**,5a*S**,8a*R**)-2-(*tert*-butyl)-6-methylene-5-oxohexa-hydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.211**



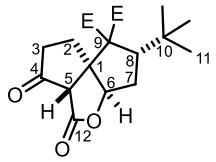
E = CO_2Me E = CO_2Me

The *title compound* was prepared from dimethyl 2-((*R**)-1-((*S**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate **3.141b** (40 mg, 0.11 mmol, 4:1 d.r.), $Mn(OAc)_3 \cdot 2H_2O$ (70 mg, 0.25 mmol), $Cu(OAc)_2 \cdot H_2O$ (26 mg, 0.13 mmol), and DMSO (0.40 mL) in accordance with **General Procedure I**. The reaction was allowed to stir at 60 °C for 36 h. Purification of the crude mixture by flash-chromatography (eluent: 0% to 30% EtOAc in pentane; 7 g SiO_2) provided the *title compound* as a colourless oil (5 mg, 0.014 mmol, 13%).

R$_f$ 0.40 (30% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.25 (br, 1H, C{12}–H_a), 5.07 (br, 1H, C{12}–H_b), 4.42 (dd, 1H, J = 8.0, 5.5 Hz, C{6}–H), 3.73 (s, 3H, CO_2**Me**), 3.73 (s, 3H, CO_2**Me'**), 3.32 (ddd, 1H, J = 2.0, 2.0, 1.5 Hz, C{5}–H), 2.70 (dd, 1H, J = 14.5, 7.0 Hz, C{8}–H), 2.51 (ddd, 1H, J = 14.0, 8.5, 7.0 Hz, C{7}–H), 2.46–2.33 (m, 2H, C{3}–H), 2.16 (ddd, 1H, J = 14.5, 14.0, 5.5 Hz, C{7'}–H), 1.72 (dd, 1H, J

= 12.5, 6.5 Hz, C{2}–H), 1.31 (ddd, 1H, *J* = 12.5, 12.5, 7.5 Hz, C{2'}–H), 0.94 (s, 9H, C{11}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.8 (C{13}), 170.3 (**C**O_2Me), 170.1 (**C**O_2Me'), 146.0 (C{4}), 111.2 (C{12}), 86.1 (C{6}), 67.7 (C{9}), 64.9 (C{1}), 55.0 (C{5}), 53.5 (C{8}), 52.5 (CO_2**Me**), 52.2 (CO_2**Me'**), 35.9 (C{2}), 33.4 (C{7}), 33.0 (C{10}), 31.6 (C{3}), 28.8 (C{11}); ν**/cm^{-1}** (film) 2958w, 1771s, 1731s, 1241m, 784w; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 351.1799. $C_{19}H_{27}O_6^+$ requires 351.1802.

Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclo-penta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.217**

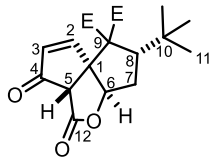


E = CO_2Me

According to the modified procedure of Jin,[358] 2,6-lutidine (0.80 mL, 7.1 mmol), $K_2OsO_4 \cdot 2H_2O$ (115 mg, 0.31 mmol), and $NaIO_4$ (3.53 g, 16.5 mmol) were added to a solution of dimethyl (2*S**,3a*R**,5a*R**,8a*S**)-2-(*tert*-butyl)-6-methylene-5-oxohexahydro-5*H*-dicyclo-penta[*b,c*]furan-1,1(2*H*)-dicarboxylate **3.150** (1.13 g, 3.22 mmol) in 1,4-dioxane/H_2O (3:1, 60 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 36 h. After this time, the reaction was quenched with aq. sat. $Na_2S_2O_3$ (40 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 0.5 M aq. HCl (100 mL), brine (100 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 30% to 40% EtOAc in pentane; 100 g SiO_2) provided the *title compound* as a white solid (856 mg, 2.43 mmol, 75%).

R$_f$ 0.51 (50% EtOAc in pentane, $KMnO_4$); **m.p.** 163–164 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.03 (d, 1H, J = 7.5 Hz, C{6}–H), 3.78 (s, 3H, CO_2**Me**), 3.69 (s, 3H, CO_2**Me'**), 3.17 (s, 1H, C{5}–H), 2.70 (dd, 1H, J = 13.5, 7.5 Hz, C{8}–H), 2.51–2.36 (m, 5H, C{2, 2', 3, 3', 7}–H), 2.05 (dd, 1H, J = 15.0, 7.5 Hz, C{7'}–H), 0.92 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 204.7 (C{4}), 169.7 (**C**O_2Me), 169.5 (**C**O_2Me'), 168.9 (C{12}), 90.3 (C{6}), 68.9 (C{9}), 62.7 (C{1}), 59.6 (C{5}), 52.7 (C{8}), 52.7 (CO_2**Me**), 52.5 (CO_2**Me'**), 36.8 (C{3}), 33.7 (C{7}), 33.0 (C{10}), 30.7 (C{2}), 28.8 (C{11}); ν/**cm**$^{-1}$ (film) 2957w, 1787s, 1734s, 1208m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 353.1595. $C_{18}H_{25}O_7^+$ requires 353.1595.

Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxo-3,3a,5a,6-tetrahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.219**

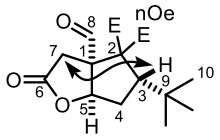


E = CO_2Me

According to the modified procedure of Nicolaou,[281] 2-iodoxybenzoic acid (200 mg, 0.71 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (100 mg, 0.74 mmol) were added to a solution of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate **3.217** (72 mg, 0.20 mmol) in dry DMSO (2 mL). The resulting solution was allowed to stir at 80 °C for 18 h. After this time, the reaction was diluted with EtOAc (30 mL) and washed with sat. aq. $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 0% to 50% EtOAc in pentane; 15 g SiO_2) provided the *title compound* as an off-white solid (50.6 mg, 0.14 mmol, 72%).

R$_f$ 0.20 (30% EtOAc in pentane, $KMnO_4$); **m.p.** 167–170 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.83 (d, 1H, J = 5.5 Hz, C{2}–H), 6.25 (d, 1H, J = 5.5 Hz, C{3}–H), 5.09 (d, 1H, J = 8.0 Hz, C{6}–H), 3.80 (s, 3H, CO_2**Me**), 3.62 (s, 3H, CO_2**Me'**), 3.30 (s, 1H, C{5}–H), 2.82 (dd, 1H, J = 14.0, 7.5 Hz, C{8}–H), 2.47 (ddd, 1H, J = 14.5, 14.0, 8.0 Hz, C{7}–H), 2.15 (dd, 1H, J = 14.5, 7.5 Hz, C{7'}–H), 0.94 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 196.0 (C{4}), 169.5 (**C**O_2Me), 168.7 (**C**O_2Me'), 168.0 (C{12}), 162.8 (C{2}), 134.2 (C{3}), 84.7 (C{6}), 68.4 (C{9}), 67.1 (C{1}), 55.8 (C{5}), 53.0 (C{8}), 52.8 (2 × CO_2**Me**), 34.0 (C{7}), 33.2 (C{10}), 28.8 (C{11}); ν**/cm**$^{-1}$ (film) 2959w, 1786s, 1722s, 1205w; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 351.1440. $C_{18}H_{23}O_7^+$ requires 351.1438.

Dimethyl (3a*R,5*S**,6a*R**)-5-(*tert*-butyl)-3a-formyl-2-oxohexahydro-4*H*-cyclopenta[*b*]furan-4,4-dicarboxylate, 3.224**



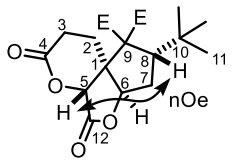
E = CO_2Me

Isolated in variable amounts during the optimisation of the oxidation of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b*,*d*]furan-1,1-(2*H*)-dicarboxylate **3.217** with IBX to give dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxo-3,3a,5a,6-tetrahydro-5*H*-dicyclopenta[*b*,*d*]furan-1,1(2*H*)-dicarboxylate **3.219**.

R$_f$ 0.36 (30% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 9.75 (s, 1H, C{8}–H), 5.34 (dd, 1H, J = 8.0, 1.5 Hz, C{5}–H), 3.79 (s, 3H, CO_2**Me**), 3.78 (s, 3H, CO_2**Me'**), 2.84 (dd, 1H, J = 13.5, 8.0 Hz, C{3}–H), 2.61–2.49 (m, 2H, C{7}–H), 2.31 (ddd, 1H, J = 15.0, 13.5, 8.0 Hz, C{4}–H), 2.12 (ddd, 1H, J = 15.0, 8.0, 1.5 Hz, C{4'}–H), 0.95 (s, 9H, C{10}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 197.2 (C{8}), 173.1 (C{6}), 169.8

(**C**O_2Me), 169.4 (**C**O_2Me'), 83.0 (C{5}), 66.5 (C{2}), 66.0 (C{1}), 53.3 (CO_2**Me**), 53.1 (CO_2**Me'**), 52.1 (C{3}), 34.5 (C{7}), 33.5 (C{4}), 33.1 (C{9}), 28.8 (C{10}); ν**/cm**$^{-1}$ (film) 2961w, 1788s, 1751m, 1723s, 1182m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 327.1439. $C_{16}H_{23}O_7^+$ requires 327.1438.

Dimethyl (2*S,3a*R**,5a*R**,9a*S**)-2-(*tert*-butyl)-5,7-dioxohexahydro-7*H*-cyclopenta[4,5]furo[3,4-*b*]pyran-1,1 (2*H*)-dicarboxylate, 3.235**

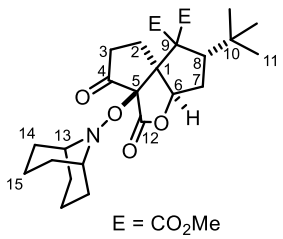


E = CO_2Me

Isolated in variable amounts during the optimisation of the hydroxylation of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b*,*d*]furan-1,1 (2*H*)-dicarboxylate **3.217** with DMDO.

R$_f$ 0.31 (40% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.09 (s, 1H, C{5}–H), 5.06 (dd, 1H, *J* = 9.0, 1.5 Hz, C{6}–H), 3.80 (s, 3H, CO_2**Me**), 3.77 (s, 3H, CO_2**Me'**), 2.90 (dd, 1H, *J* = 13.5, 8.5 Hz, C{8}–H), 2.62–2.55 (m, 1H, C{3}–H), 2.54–2.41 (m, 2H, C{2, 7}–H), 2.34–2.17 (m, 2H, C{2', 3'}–H), 2.03 (ddd, 1H, *J* = 15.0, 8.5, 1.5 Hz, C{7'}–H), 0.92 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.1 (C{12}), 169.2 (C{4}/**C**O_2Me), 169.2 (C{4}/**C**O_2Me), 168.9 (C{4}/**C**O_2Me), 88.6 (C{6}), 75.4 (C{5}), 67.4 (C{9}), 55.5 (C{1}), 53.4 (CO_2**Me**), 52.6 (CO_2**Me'**), 52.5 (C{8}), 33.2 (C{10}), 32.9 (C{7}), 28.5 (C{3}), 28.5 (C{11}), 27.2 (C{2}); ν**/cm**$^{-1}$ (film) 2959w, 1791s, 1737m, 1213s, 1125s; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 391.1347. $C_{18}H_{24}O_8Na^+$ requires 391.1363.

Dimethyl (2*S,3a*R**,5a*R**,8a*S**)-5a-(((1*S*,5*S*)-9-azabicyclo[3.3.1]nonan-9-yl)oxy)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)dicarboxylate, 3.247**

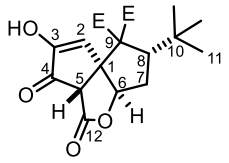


According to the modified procedure of Terent'ev,[360] $Mn(OAc)_3 \cdot 2H_2O$ (32 mg, 0.12 mmol) was added to a solution of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b*,*c*]furan-1,1(2*H*)-dicarboxylate **3.217** (35 mg, 0.10 mmol) and ABNO (17 mg, 0.12 mmol) in anhydrous acetic acid (1.0 mL). The resulting yellow solution was allowed to stir at 60 °C for 2 h. After this time, the reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aq. sat. $Na_2S_2O_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 10% to 40% EtOAc in pentane; 7 g SiO_2) provided the *title compound* as a colourless oil (41 mg, 0.084 mmol, 84%).

R$_f$ 0.60 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.07 (dd, 1H, J = 9.5, 4.5 Hz, C{6}–H), 3.76 (s, 3H, CO_2**Me**), 3.75 (br, 1H, C{13}–H), 3.58 (s, 3H, CO_2**Me**'), 3.43 (dd, 1H, J = 11.5, 9.5 Hz, C{8}–H), 3.22 (br, 1H, C{13'}–H), 2.46 (ddd, 1H, J = 15.0, 9.5, 9.5 Hz, C{7}–H), 2.40–2.25 (m, 4H, C{2, 3, 3', 14}–H), 2.25–2.12 (m, 2H, C{2', 14'}–H), 2.10–2.00 (m, 3H, C{7', 14'', 14'''}–H), 1.99–1.88 (m, 1H, C{15}–H), 1.85–1.68 (m, 3H, C{14'''', 14''''', 15'}–H), 1.61 (ddd, 1H, J = 14.0, 7.0, 7.0 Hz, C{15''}–H), 1.46–1.36 (m, 3H, C{14''''', 14''''''', 15'''}–H), 0.93 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 205.9 (C{4}), 169.9 (**C**O_2Me), 169.1 (C{12}), 168.6

(**C**O_2Me'), 91.7 (C{5}), 89.9 (C{6}), 67.4 (C{9}), 64.7 (C{1}), 56.0 (C{13}), 55.9 (C{13'}), 53.4 (C{8}), 52.4 (CO_2**Me**), 51.6 (CO_2**Me'**), 34.0 (C{10}), 33.6 (C{7}), 32.6 (C{14}), 32.0 (C{14'}), 32.0 (C{3}), 29.2 (C{11}), 28.5 (C{2}), 24.0 (C{14"}), 23.4 (C{14"'}), 19.9 (C{15}), 19.6 (C{15'}); ν**/cm**$^{-1}$ (film) 2951m, 1784s, 1766s, 1734s, 1145m; **HRMS** (*m*/*z* +ESI): Found: $[M+H]^+$, 492.2570. $C_{26}H_{38}NO_8^+$ requires 492.2592.

Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-7-hydroxy-5,6-dioxo-3,3a,5a,6-tetrahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.230**



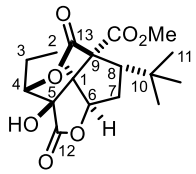
E = CO_2Me

According to the modified procedure of Terent'ev,[360] $Mn(OAc)_3 \cdot 2H_2O$ (5.0 mg, 20 μmol) was added to a solution of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate **3.217** (3.5 mg, 10 μmol) and TEMPO (3.0 mg, 20 μmol) in anhydrous acetic acid (0.10 mL). The resulting yellow solution was allowed to stir at 60 °C for 3 h. After this time, the reaction was diluted with water (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with aq. sat. $Na_2S_2O_3$ (4 mL), brine (4 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 30% to 40% EtOAc in pentane; 1 g SiO_2) provided the *title compound* as a colourless oil (1.7 mg, 4.6 μmol, 46%).

R$_f$ 0.24 (40% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.71 (s, 1H, C{2}–H), 5.08 (d, 1H, J = 8.0 Hz, C{6}–H), 3.79 (s, 3H, CO_2**Me**), 3.62 (s, 3H, CO_2**Me'**), 3.42 (s, 1H, C{5}–H), 2.83 (dd, 1H, J = 14.0, 7.5 Hz, C{8}–H), 2.46 (ddd, 1H, J = 15.0,

14.0, 8.0 Hz, C{7}–H), 2.13 (dd, 1H, J = 15.0, 7.5 Hz, C{7'}–H), 0.94 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 191.2 (C{4}), 169.5 (**C**O_2Me), 169.0 (**C**O_2Me'), 167.5 (C{12}), 152.6 (C{3}), 128.8 (C{2}), 85.9 (C{6}), 68.5 (C{9}), 61.9 (C{1}), 54.2 (C{5}), 52.9 (CO_2**Me**), 52.7 (CO_2**Me'**), 52.6 (C{8}), 33.8 (C{7}), 33.2 (C{10}), 28.7 (C{11}); ν/**cm**$^{-1}$ (film) 3421br, 2969m, 1783s, 722s, 1373s; **HRMS** (m/z +ESI): Found: $[M+Na]^+$, 389.1201. $C_{18}H_{22}O_8Na^+$ requires 389.1207.

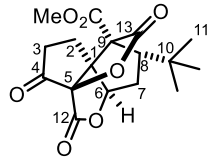
Methyl (1*S,2*S**,3a*R**,5a*R**,6*S**,8a*S**)-2-(*tert*-butyl)-5a-hydroxy-5,10-dioxohexahydro-5*H*-6,1-(epoxymethano)dicyclopenta[*b,c*]furan-1(2*H*)-carboxylate, 3.252**



According to the modified procedure of Terent'ev,[360] $Mn(OAc)_3 \cdot 2H_2O$ (3.0 mg, 12 μmol) was added to a solution of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate **3.217** (3.4 mg, 10 μmol) and ABNO (1.8 mg, 12 μmol) in anhydrous acetic acid (0.10 mL). The resulting yellow solution was allowed to stir at 60 °C for 1 h. After this time, the reaction mixture was transferred into a separate vial containing $Pd(OH)_2$ (5% w/w on activated carbon, 28 mg, 10 μmol) in MeOH (0.90 mL). The atmosphere was then replaced with hydrogen and the resulting mixture allowed to stir for 18 h at room temperature. After this time, the reaction was filtered through a Celite pad, which was eluted with EtOAc. All volatiles were then removed *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 40% to 60% EtOAc in pentane; 1 g SiO_2) provided the *title compound* as a colourless oil (1.6 mg, 4.7 μmol, 47%).

R$_f$ 0.31 (50% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.69 (d, 1H, J = 5.0 Hz, C{6}–H), 4.45 (d, 1H, J = 4.0 Hz, C{4}–H), 3.79 (s, 3H, CO_2**Me**), 2.55 (ddd, 1H, J = 14.0, 14.0, 5.0 Hz, C{7}–H), 2.35 (dd, 1H, J = 14.0, 5.0 Hz, C{8}–H), 2.25 (dd, 1H, J = 14.0, 5.0 Hz, C{7'}–H), 2.14 (dd, 1H, J = 14.5, 5.5 Hz, C{3}–H), 2.10–2.00 (m, 2H, C{2}–H), 1.65 (dddd, 1H, J = 14.0, 12.5, 6.5, 4.0 Hz, C{3'}–H), 1.01 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 171.8 (C{12}), 170.5 (**C**O_2Me/C{13}), 167.2 (**C**O_2Me/C{13}), 89.0 (C{5}), 88.6 (C{6}), 73.6 (C{4}), 67.0 (C{1}), 64.8 (C{9}), 59.8 (C{8}), 52.5 (CO_2**Me**), 36.3 (C{7}), 33.6 (C{10}), 33.6 (C{2}), 32.0 (C{3}), 29.3 (C{11}); ν**/cm**$^{-1}$ (film) 3504br, 2965w, 1806s, 1779s, 1734m, 1015m; **HRMS** (*m*/*z* +ESI): Found: $[M+Na]^+$, 361.1252. $C_{17}H_{22}O_7Na^+$ requires 361.1258.

Methyl (1*S,2*S**,3a*R**,5a*R**,8a*S**)-2-(*tert*-butyl)-5,6,10-trioxotetrahydro-5*H*,6*H*-5a,1-(epoxymethano)dicyclopenta[*b,c*]furan-1(2*H*)-carboxylate, 3.220**

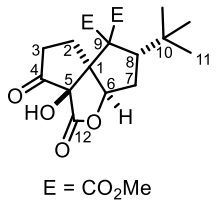


According to the modified procedure of Terent'ev,[360] $Mn(OAc)_3 \cdot 2H_2O$ (32 mg, 0.12 mmol) was added to a solution of dimethyl (2*S**,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b*,*c*]furan-1,1(2*H*)-dicarboxylate **3.217** (35 mg, 0.10 mmol) and ABNO (17 mg, 0.12 mmol) in anhydrous acetic acid (1.0 mL). The resulting yellow solution was allowed to stir at 60 °C for 1.5 h. After this time, the reaction mixture was transferred into a separate flask containing Pd (10% w/w on activated carbon, 53 mg, 0.050 mmol) and aq. HCl (2 M, 0.35 mL) in THF (6.5 mL). The atmosphere was then replaced with hydrogen and the resulting mixture allowed to stir for 18 h at room temperature. After this time, the reaction was filtered through a Celite pad, which was eluted with EtOAc (20 mL). This solution was then washed with water

(10 mL), sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL). It was then dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. This oil was dissolved in 40% EtOAc in pentane (6 mL), SiO_2 (1 g) added, and the resulting mixture allowed to stand at room temperature for 2.5 h. After this time, all volatiles were evaporated *in vacuo* and the crude mixture purified by flash-chromatography (50% to 100% EtOAc in pentane) to give the *title compound* as an off-white solid (21.5 mg, 0.064 mmol, 64%).

R_f 0.29 (60% EtOAc in pentane, $KMnO_4$); **m.p.** 226–232 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.99 (d, 1H, J = 5.0 Hz, C{6}–H), 3.83 (s, 3H, CO_2**Me**), 2.75–2.66 (m, 2H, C{3, 7}–H), 2.59 (ddd, 1H, J = 18.0, 13.5, 8.5 Hz, C{3'}–H), 2.49 (dd, 1H, J = 14.0, 8.5 Hz, C{2}–H), 2.36–2.30 (m, 2H, C{7', 8}–H), 1.84 (ddd, 1H, J = 14.0, 13.5, 8.0 Hz, C{2'}–H), 1.01 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 199.5 (C{4}), 168.8 (C{13}), 166.6 (**C**O_2Me/C{12}), 166.5 (**C**O_2Me/C{12}), 87.4 (C{6}), 83.1 (C{5}), 65.9 (C{9}), 64.8 (C{1}), 58.9 (C{8}), 52.9 (CO_2**Me**), 37.4 (C{7}), 37.1 (C{3}), 33.6 (C{10}), 29.2 (C{11}), 27.9 (C{2}); ν**/cm**$^{-1}$ (film) 2928w, 1821s, 1793s, 1745s, 1012m; **HRMS** (*m/z* +ESI): Found: $[M+H]^+$, 337.1270. $C_{17}H_{21}O_7^+$ requires 337.1282.

Dimethyl (2*S,3*aR**,5*aR**,8*aS**)-2-(*tert*-butyl)-5a-hydroxy-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.251**

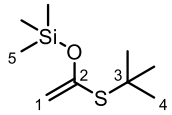


E = CO_2Me

Isolated in variable amounts during the reduction of dimethyl (2*S**,3a*R**,5a*R**,8a*S**)-5a-(((1*S*,5*S*)-9-azabicyclo[3.3.1]nonan-9-yl)oxy)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate **3.247**. *Note: This compound was unstable on silica so was it characterised as the crude.*

R$_f$ 0.57 (60% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.20 (dd, 1H, J = 9.5, 3.5 Hz, C{6}–H), 3.76 (s, 3H, CO_2**Me**), 3.54 (s, 3H, CO_2**Me'**), 3.15 (dd, 1H, J = 11.0, 11.0 Hz, C{8}–H), 2.61–2.45 (m, 4H, C{2, 3, 3', 7}–H), 2.31–2.24 (m, 1H, C{2'}–H), 2.09 (ddd, 1H, J = 15.0, 11.0, 3.5 Hz, C{7'}–H), 0.95 (s, 9H, C{11}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 206.9 (C{4}), 171.7 (C{12}), 169.8 (**C**O_2Me), 169.0 (**C**O_2Me'), 91.7 (C{6}), 83.7 (C{5}), 68.0 (C{9}), 62.2 (C{1}), 52.7 (C{8}), 52.7 (CO_2**Me**), 51.7 (CO_2**Me'**), 34.2 (C{7}), 34.0 (C{10}), 32.2 (C{3}), 29.7 (C{2}), 29.3 (C{11}); ν/**cm**$^{-1}$ (film) 3422br, 2959m, 1786s, 1734s, 1261m; **HRMS** (m/z +ESI): Found: $[M+H]^+$, 369.1542. $C_{18}H_{25}O_8^+$ requires 369.1544.

((1-(*tert*-Butylthio)vinyl)oxy)trimethylsilane, 3.254

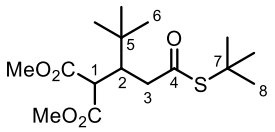


According to the modified procedure of Angell,[361] *n*-BuLi (1.6 M in hexanes, 4.5 mL, 7.2 mmol) was added to a solution of diisopropylamine (1.1 mL, 7.8 mmol) in THF (4.0 mL) at −78 °C and the mixture allowed to stir at this temperature for 5 min. Then, *S*-(*tert*-butyl) ethanethioate (790 mg, 5.98 mmol) was added over 5 min. The resulting solution was allowed to stir at this temperature for 30 min before the addition of trimethylsilyl chloride (0.91 mL, 7.2 mmol). The reaction was then allowed to stir at room temperature for 1 h. After this time, the mixture was quenched with water (30 mL) and extracted with hexane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a pale yellow oil (1.21 g, 5.94 mmol, 99%) with no need for further purification.

R$_f$ 0.32 (20% EtOAc in pentane, $KMnO_4$); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.67 (s, 1H, C{1}–H), 4.58 (s, 1H, C{1'}–H), 1.37 (s, 9H, C{4}–H), 0.25 (s, 9H, C{5}–H); ^{13}**C NMR**

(101 MHz, $CDCl_3$) δ 153.0 (C{2}), 102.7 (C{1}), 45.6 (C{3}), 31.5 (C{4}), 0.2 (C{5}). *Note: MS data not available due to lack of ionisation under ESI.* All data in accordance with the literature.[292]

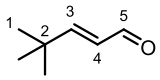
Dimethyl 2-(1-(*tert*-butylthio)-4,4-dimethyl-1-oxopentan-3-yl)malonate, 3.253



According to the modified procedure of Evans,[292] $TiCl_4$ (60 μL, 0.55 mmol) was added dropwise to a solution of dimethyl 2-(2,2-dimethylpropylidene)malonate **3.101** (80 mg, 0.40 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The mixture was allowed to stir at this temperature for 5 min before the addition of ((1-(*tert*-butylthio)vinyl)oxy)trimethylsilane **3.254** (180 mg, 0.88 mmol). The resulting purple solution was allowed to stir at room temperature for 1.5 h. After this time, the reaction was quenched with water (10 mL), and the resulting mixture extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a colourless oil (130 mg, 0.39 mmol, 98%) with no need for further purification.

R_f 0.31 (25% Et_2O in pentane, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.71 (s, 3H, CO_2**Me**), 3.70 (s, 3H, CO_2**Me'**), 3.68 (d, 1H, J = 3.0 Hz, C{1}–H), 3.04–2.94 (m, 1H, C{3}–H), 2.80–2.68 (m, 2H, C{2, 3'}–H), 1.43 (s, 9H, C{8}–H), 0.88 (s, 9H, C{6}–H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 199.8 (C{4}), 170.1 (**C**O_2Me), 169.8 (**C**O_2Me'), 52.8 (CO_2**Me**), 52.4 (CO_2**Me'**), 51.3 (C{1}), 47.9 (C{7}), 44.2 (C{2}), 42.6 (C{3}), 34.4 (C{5}), 29.9 (C{8}), 27.9 (C{6}); **LRMS** (m/z +ESI): Found: $[M+Na]^+$, 355.2. $C_{16}H_{28}NaO_5S^+$ requires 355.2. All data in accordance with the literature.[292]

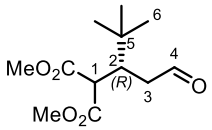
(*E*)-4,4-Dimethylpent-2-enal, 3.255



According to the modified procedure of Vicha,[362] sodium hydride (60% w/w dispersion in mineral oil, 960 mg, 24.0 mmol) was added in three equal portions over 10 min to a suspension of ((1,3-dioxolan-2-yl)methyl)triphenyl phosphonium bromide **3.261** (5.2 g, 12 mmol) in THF (45 mL) at 0 °C. The resulting solution was allowed to stir at room temperature for 30 min before the dropwise addition of pivaldehyde (1.0 mL, 9.2 mmol) in THF (15 mL) over 5 min. The reaction was then allowed to stir at room temperature for 18 h. After this time, aq. HCl (2 M, 60 mL, 120 mmol) was added and the biphasic mixture allowed to stir for 3 h. This mixture was then extracted with Et_2O (3 × 50 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow oil. Purification of the crude mixture by flash-chromatography (eluent: 5% to 10% Et_2O in pentane; 75 g SiO_2) provided the *title compound* as a volatile colourless oil (349 mg, 3.11 mmol, 34%).

R$_f$ 0.45 (20% Et_2O in pentane, $KMnO_4$); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 9.52 (d, 1H, J = 7.5 Hz, C{5}–H), 6.80 (d, 1H, J = 16.0 Hz, C{3}–H), 6.05 (dd, 1H, J = 16.0, 7.5 Hz, C{4}–H), 1.13 (s, 9H, C{1}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 194.8 (C{5}), 168.8 (C{3}), 128.5 (C{4}), 34.6 (C{2}), 28.7 (C{1}); **LRMS** (m/z +ESI): Found: $[M+Na]^+$, 135.0. $C_7H_{12}NaO^+$ requires 135.1. All data in accordance with the literature.[363]

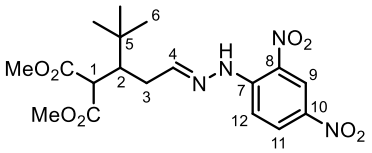
Dimethyl (*R*)-2-(4,4-dimethyl-1-oxopentan-3-yl)malonate, (*R*)-3.144



(*E*)-4,4-Dimethylpent-2-enal **3.255** (74 mg, 0.66 mmol), NaOAc (16 mg, 0.20 mmol), and dimethyl malonate (0.38 mL, 3.3 mmol) were added to a flask containing (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine **3.258** (23 mg, 0.070 mmol) and H_2O (0.70 mL) at room temperature. The resulting mixture was allowed to stir at this temperature for 3 days. After this time, the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil. Purification of the crude mixture by flash-chromatography (eluent: 10% to 20% EtOAc in pentane; 25 g SiO_2) provided the *title compound* as a colourless oil (104 mg, 0.43 mmol, 65%, >98% e.e.[**])

Physical data matched the racemic aldehyde (±)-**3.144**; $[\alpha]^{25}_D$ −11.5 (c = 0.49 in $CHCl_3$).

Dimethyl (*E*)-2-(1-(2-(2,4-dinitrophenyl)hydrazineylidene)-4,4-dimethylpentan-3-yl)malonate, 3.263



(2,4-Dinitrophenyl)hydrazine (75% w/w, 36 mg, 0.11 mmol) and AcOH (1 drop) were added to a solution of dimethyl 2-(4,4-dimethyl-1-oxopentan-3-yl)malonate **3.144** (24 mg, 0.10 mmol) in MeOH (1.0 mL). The resulting yellow solution was allowed to stir at room

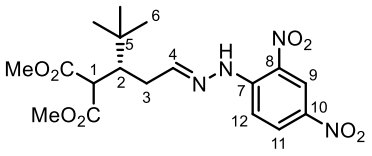
[**] Enantiomeric excess determined by chiral HPLC after derivatisation of aldehyde **3.144** to the 2,4-dinitrophenylhydrazone **3.263**. Daicel Chiralpak IA column (4.6 mm × 250 mm, 5 μm), flow rate: 1 mL/min, solvent: 15% iPrOH in hexane.

temperature for 18 h. After this time, water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (eluent: 30% to 50% EtOAc in pentane; 10 g SiO_2) provided the *title compound* as an orange crystalline solid (32.4 mg, 0.076 mmol, 4:1 mixture of inseparable (*E*)- and (*Z*)-isomers (major: (*E*)-**3.263**), 76%).

Characterised as a 4:1 mixture of (*E*)- and (*Z*)-isomers: $\mathbf{R}_f$ 0.74 (50% EtOAc in pentane, $KMnO_4$); **m.p.** 147–149 °C (from EtOAc); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 11.25 (s, 1H, N–H^Z), 10.97 (s, 1H, N–H^E), 9.14 (d, 1H, J = 2.5 Hz, C{9^Z}–H), 9.11 (d, 1H, J = 2.5 Hz, C{9^E}–H), 8.32 (dd, 1H, J = 10.0, 2.5 Hz, C{11^Z}–H), 8.30 (dd, 1H, J = 9.5, 3.0 Hz, C{11^E}–H), 7.94 (d, 1H, J = 10.0 Hz, C{12^Z}–H), 7.93 (d, 1H, J = 9.5 Hz, C{12^E}–H), 7.57 (dd, 1H, J = 5.5, 5.0 Hz, C{4^E}–H), 7.00 (dd, 1H, J = 6.0, 4.5 Hz, C{4^Z}–H), 3.76 (d, 1H, J = 3.0 Hz, C{1^Z}–H), 3.74 (s, 3H, CO$_2$**Me**^{Z}), 3.74 (d, 1H, J = 3.5 Hz, C{1^E}–H), 3.72 (s, 3H, CO$_2$**Me**^{E}), 3.70 (s, 3H, CO$_2$**Me'**^{Z}), 3.69 (s, 3H, CO$_2$**Me'**^{E}), 2.91 (ddd, 1H, J = 18.0, 8.5, 5.5 Hz, C{3^Z}–H), 2.86 (ddd, 1H, J = 16.0, 7.5, 5.0 Hz, C{3^E}–H), 2.66 (ddd, 1H, J = 16.0, 5.0, 5.0 Hz, C{3'^{E}}–H), 2.57–2.48 (m, 3H, C{2^E, 2^Z, 3'^{Z}}–H), 1.00 (s, 9H, C{6^Z}–H), 0.98 (s, 9H, C{6^E}–H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 170.5 (**C**O$_2$Me^E), 170.2 (**C**O$_2$Me^Z), 169.8 (**C**O$_2$Me'^{E}), 169.6 (**C**O$_2$Me'^{Z}), 153.4 (C{4^E}), 151.6 (C{4^Z}), 145.5 (C{7^Z}), 145.3 (C{7^E}), 138.4 (C{10^Z}), 138.0 (C{10^E}), 130.2 (C{11^Z}), 130.1 (C{11^E}), 129.8 (C{8^Z}), 129.0 (C{8^E}), 123.7 (C{9^E}), 123.6 (C{9^Z}), 116.7 (C{12^E}), 116.6 (C{12^Z}), 53.1 (CO$_2$**Me**^{Z}), 53.0 (CO$_2$**Me**^{E}), 52.7 (CO$_2$**Me'**^{Z}), 52.5 (CO$_2$**Me'**^{E}), 51.3 (C{1^E}), 51.1 (C{1^Z}), 46.7 (C{2^Z}), 46.7 (C{2^E}), 34.5 (C{5^E}), 34.4 (C{5^Z}), 31.0 (C{3^E}), 28.1 (C{6^E}), 27.9 (C{6^Z}), 26.3 (C{3^Z}); ν/**cm**$^{-1}$ (film) 2959w, 1734m, 1620s, 1336s, 1079w; **HRMS** (*m*/*z* +ESI): Found: [M+Na]$^+$, 447.1484. $C_{18}H_{24}N_4O_8Na^+$ requires

447.1486; **HPLC** (Daicel Chiralpak IA column (4.6 mm × 250 mm, 5 μm), flow rate: 1 mL/min, solvent: 15% iPrOH in hexane): retention time for (*S*, *E*)-**3.263**, 12.47 min, (*R*, *E*)-**3.263**, 18.42 min.

Dimethyl (*R*,*E*)-2-(1-(2-(2,4-dinitrophenyl)hydrazineylidene)-4,4-dimethylpentan-3-yl)malonate, (*R*)-3.263

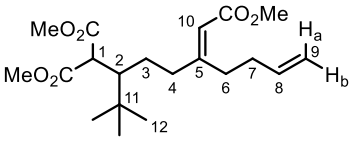


(2,4-Dinitrophenyl)hydrazine (75% w/w, 16 mg, 0.062 mmol) and AcOH (1 drop) were added to a solution of dimethyl (*R*)-2-(4,4-dimethyl-1-oxopentan-3-yl)malonate (*R*)-**3.144** (10 mg, 0.041 mmol) in MeOH (1.0 mL). The resulting yellow solution was allowed to stir at room temperature for 18 h. After this time, water (5 mL) was added, and the mixture extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Purification of the crude mixture by flash-chromatography (eluent: 10% to 15% EtOAc in pentane; 10 g SiO_2) provided the *title compound* as an orange crystalline solid (12.2 mg, 0.029 mmol, 4:1 mixture of inseparable (*R*, *E*)- and (*R*, *Z*)-isomers (major: (*R*, *E*)-**3.263**), 71%, >98% e.e.).

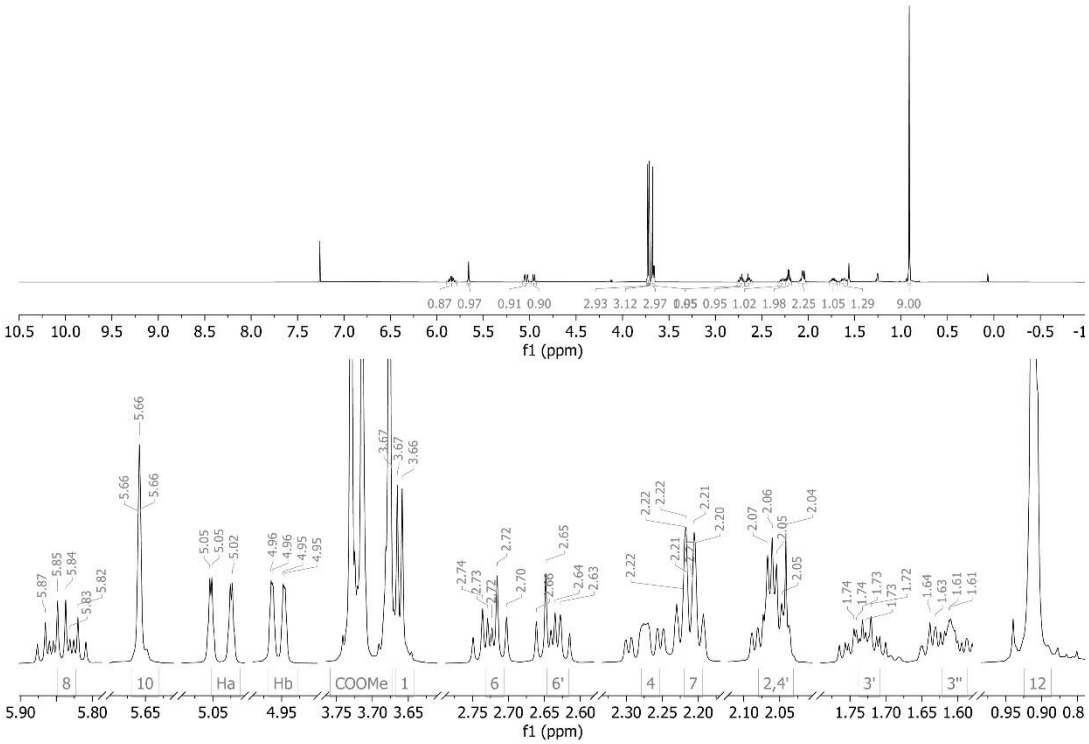
Physical data matched the racemic hydrazone (±)-**3.263**; $[\alpha]^{25}_{D}$ −39.8 (c = 0.51 in $CHCl_3$); **m.p.** 153–156 °C (from EtOAc).

4.4 Selected spectra

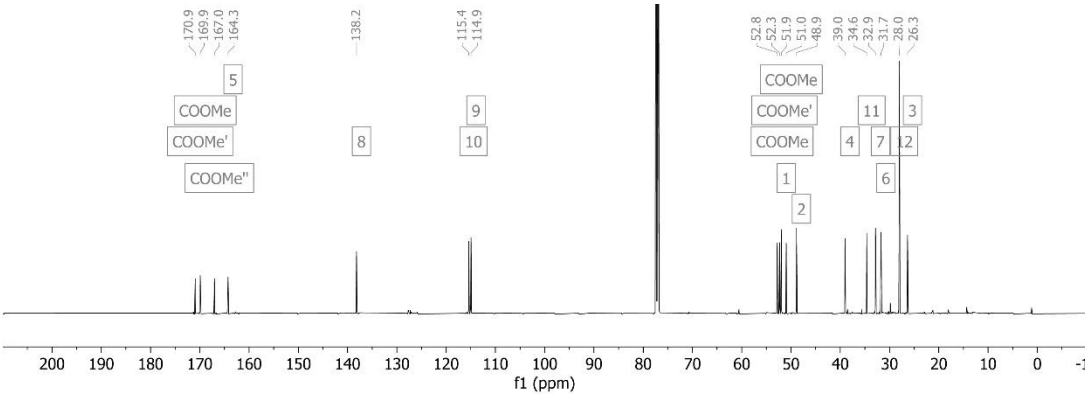
Trimethyl (*E*)-5-(but-3-en-1-yl)-2-(*tert*-butyl)hex-5-ene-1,1,6-tricarboxylate, 3.97



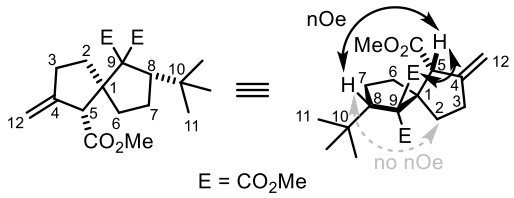
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



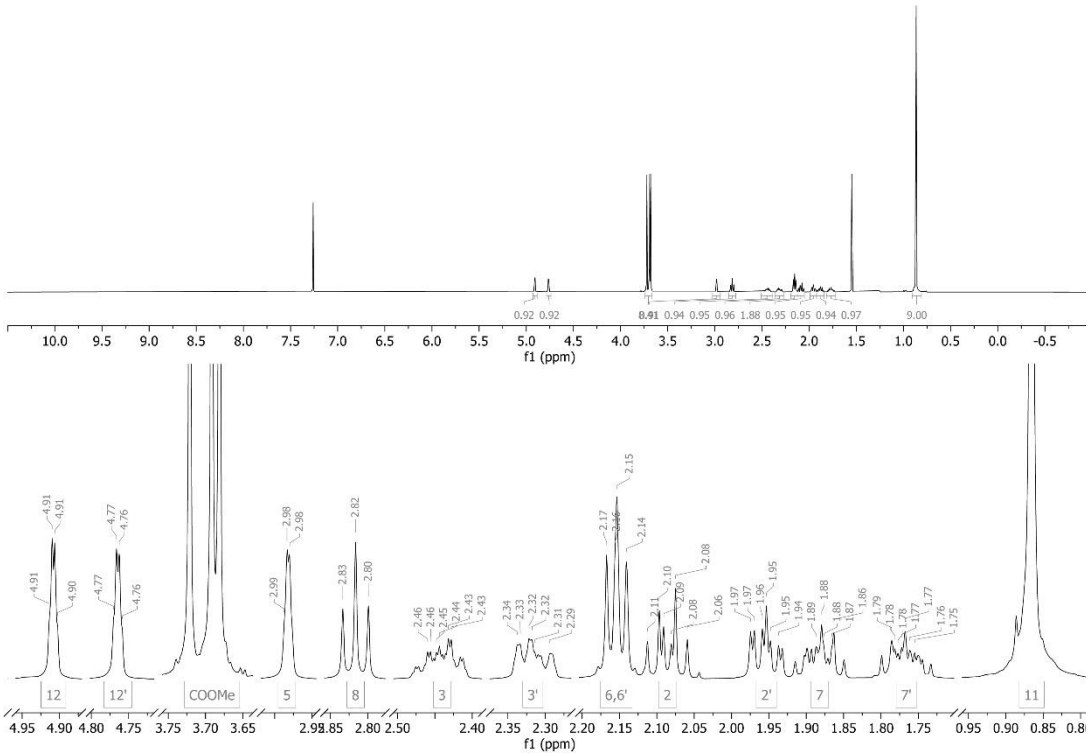
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



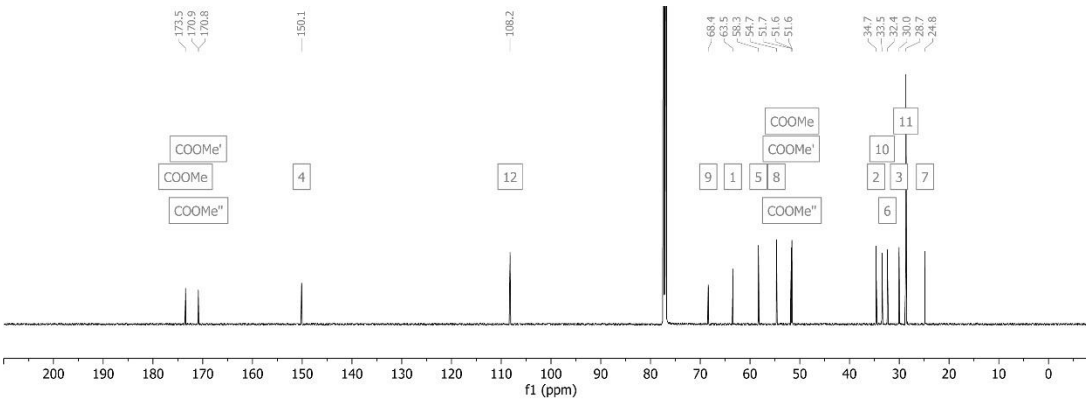
Trimethyl (2*S,5*R**,6*R**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.107a**



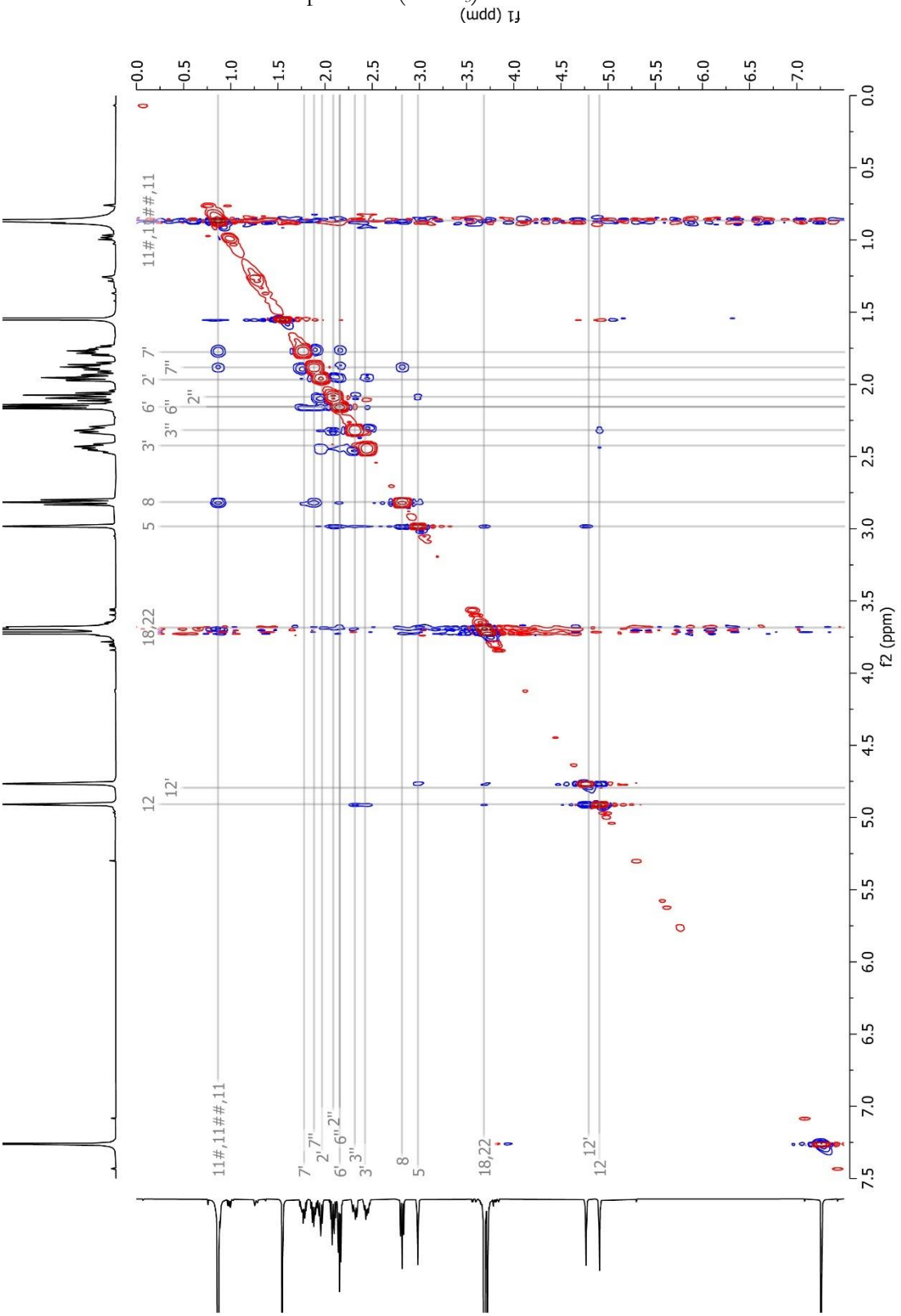
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



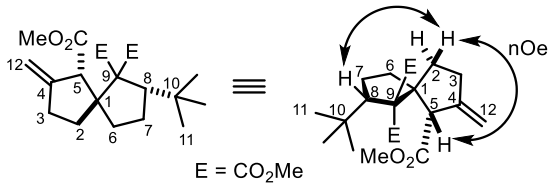
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



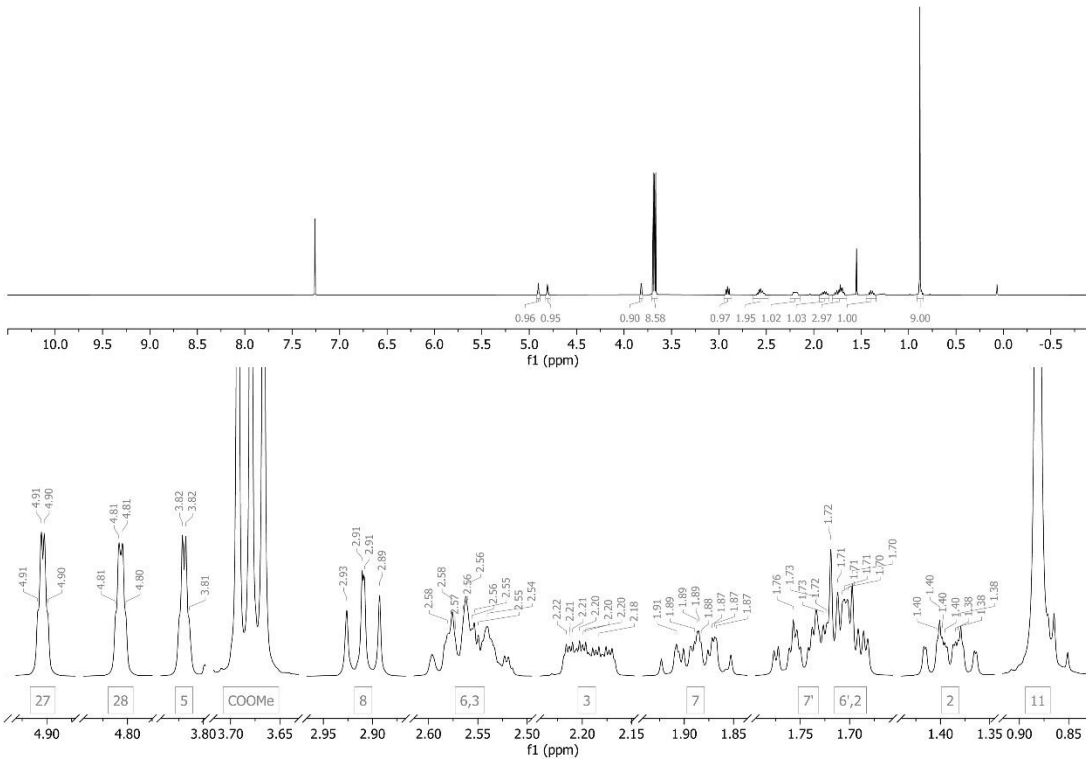
600 MHz ^{1}H NMR NOESY spectrum ($CDCl_3$)



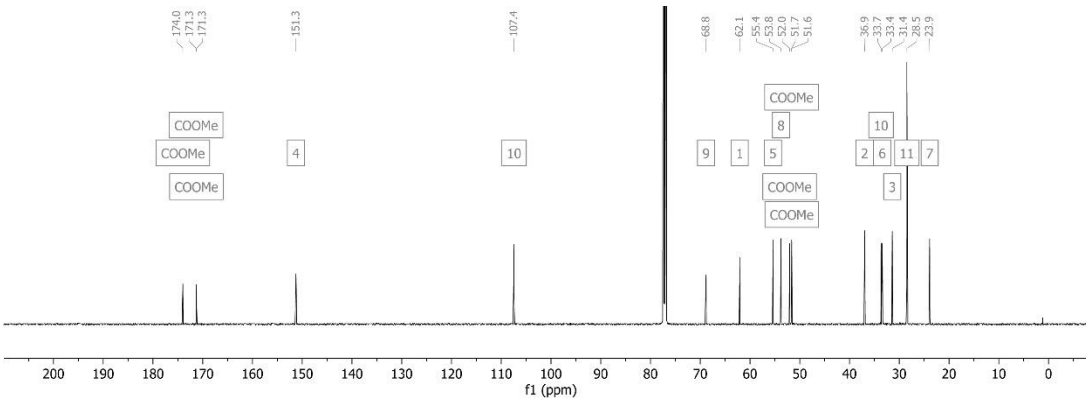
Trimethyl (2*S,5S*,6S*)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.107b**



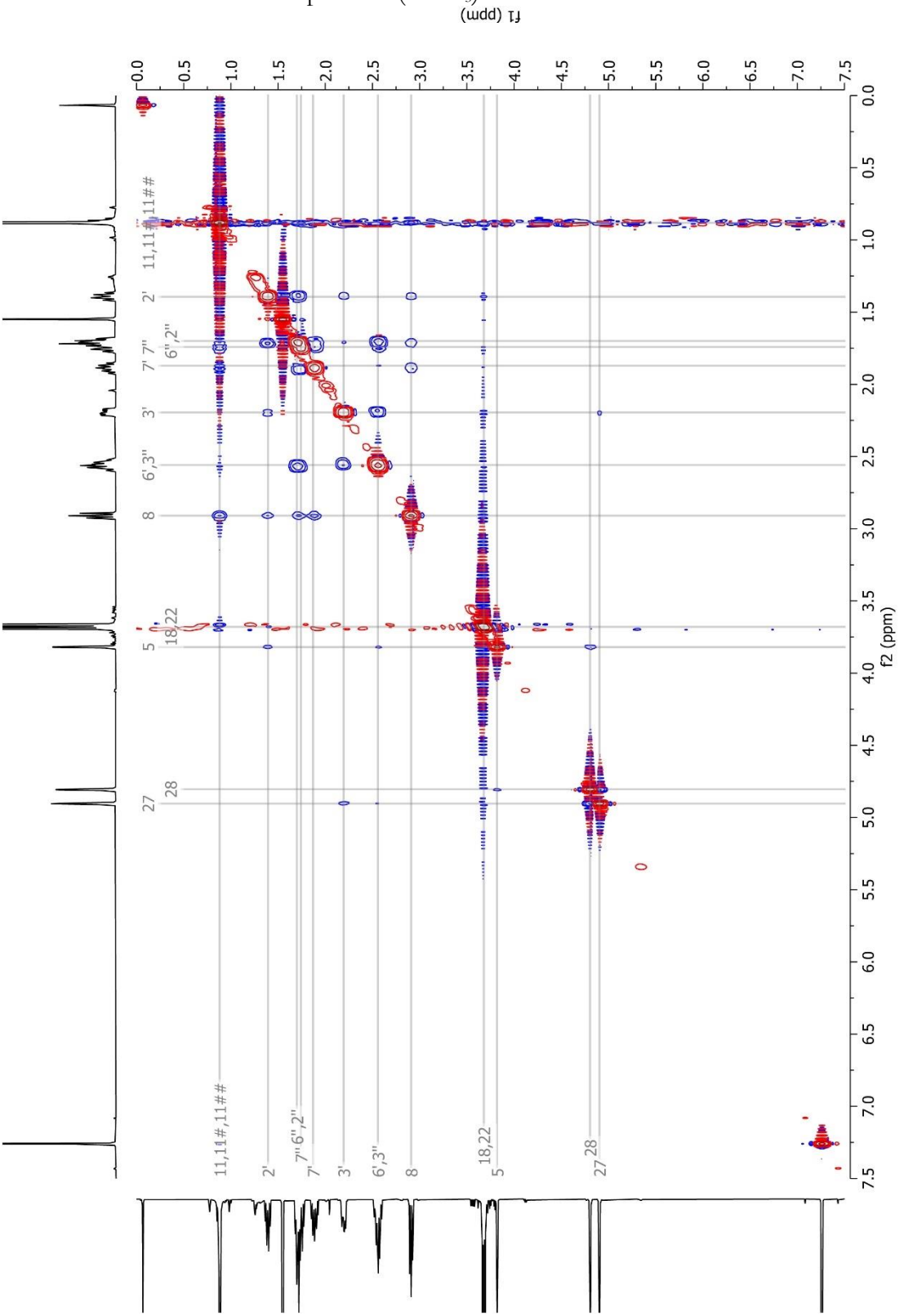
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



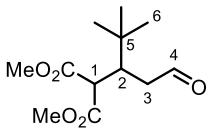
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



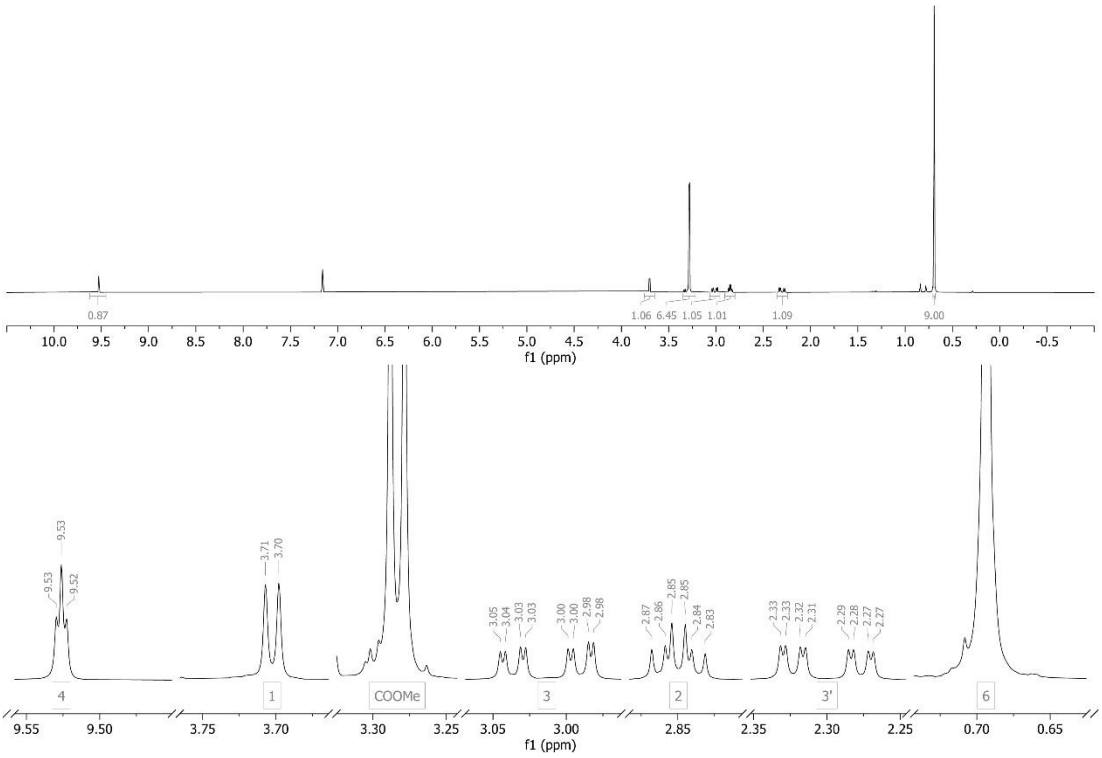
600 MHz ^{1}H NMR NOESY spectrum ($CDCl_3$)



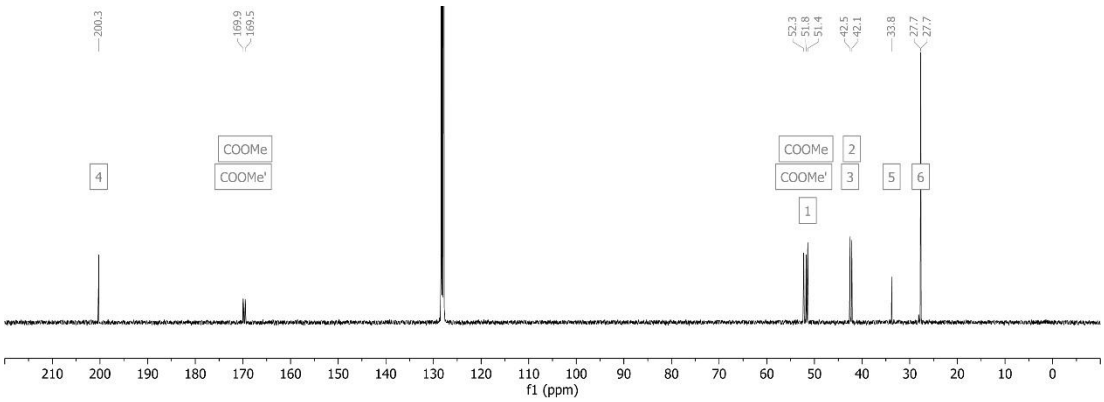
Dimethyl 2-(4,4-dimethyl-1-oxopentan-3-yl)malonate, 3.144



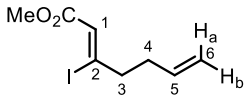
400 MHz ^{1}H NMR spectrum (C_6D_6)



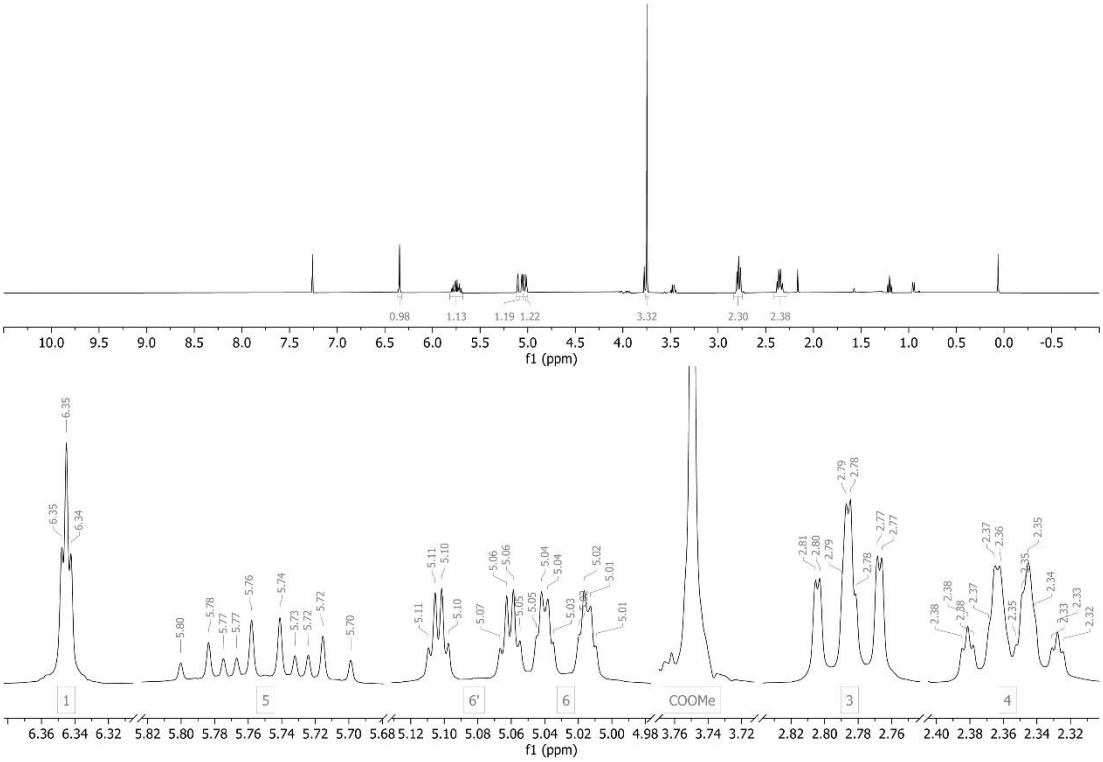
101 MHz ^{13}C NMR spectrum (C_6D_6)



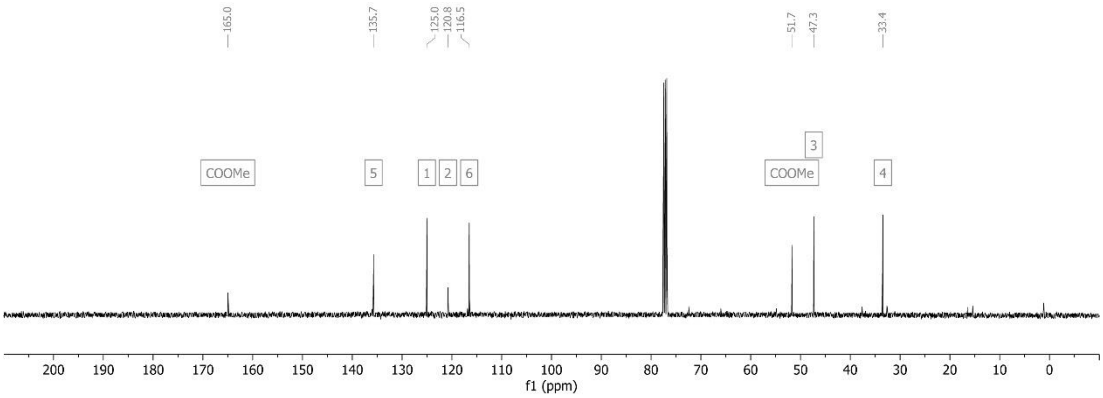
Methyl (*Z*)-3-iodohepta-2,6-dienoate, 3.195



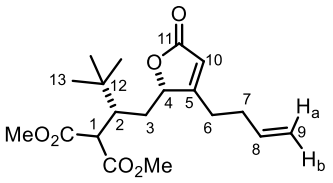
400 MHz ^{1}H NMR spectrum ($CDCl_3$)



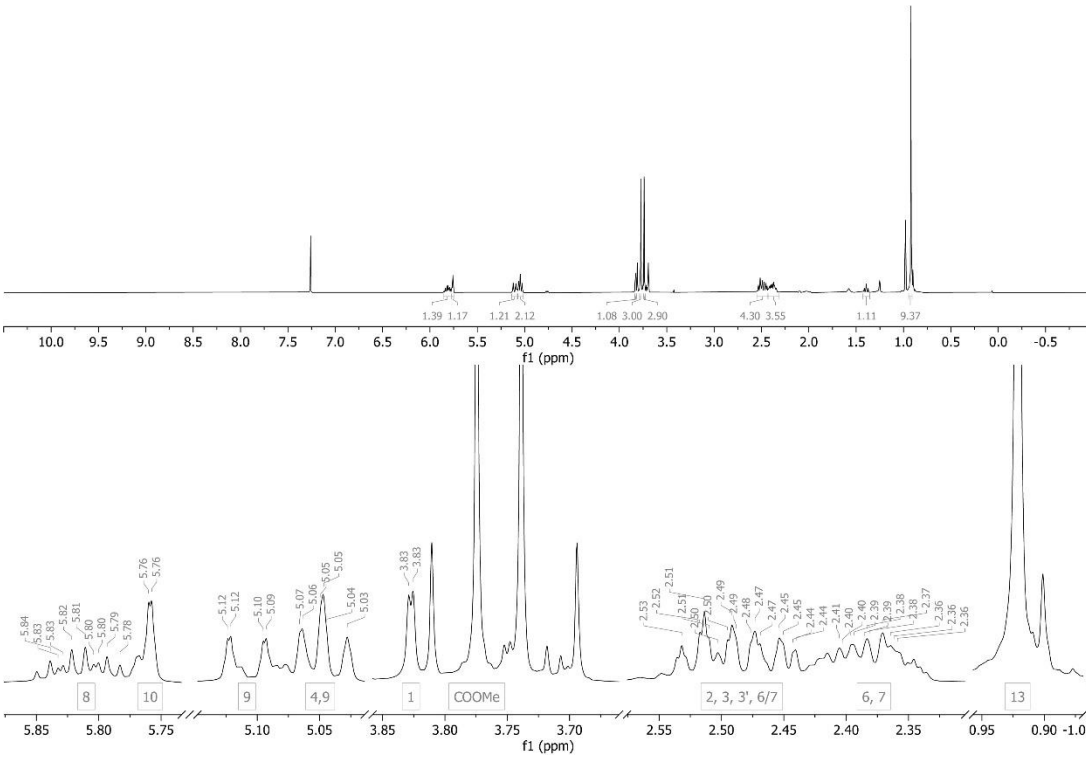
101 MHz ^{13}C NMR spectrum ($CDCl_3$)



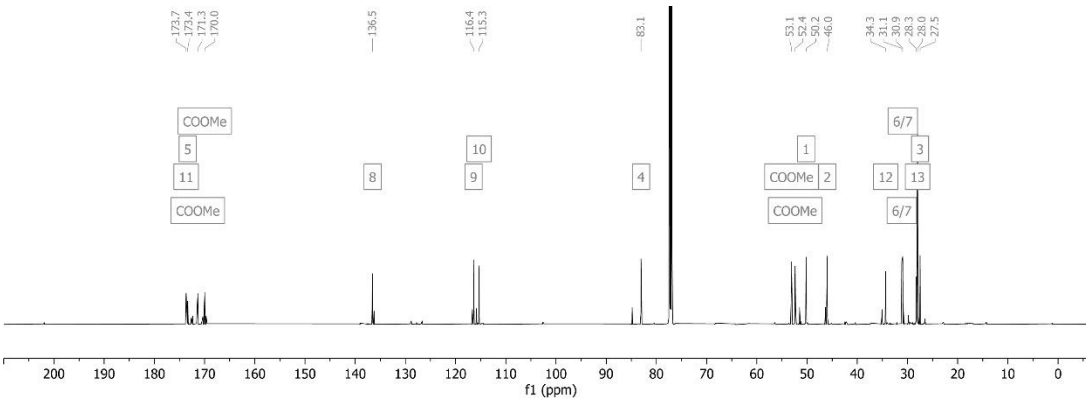
Dimethyl 2-((*R)-1-((*S**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate, 3.141b, 4:1 d.r.**



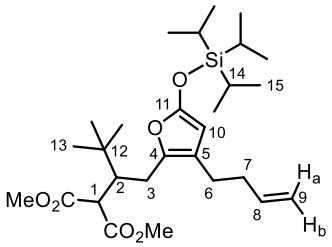
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



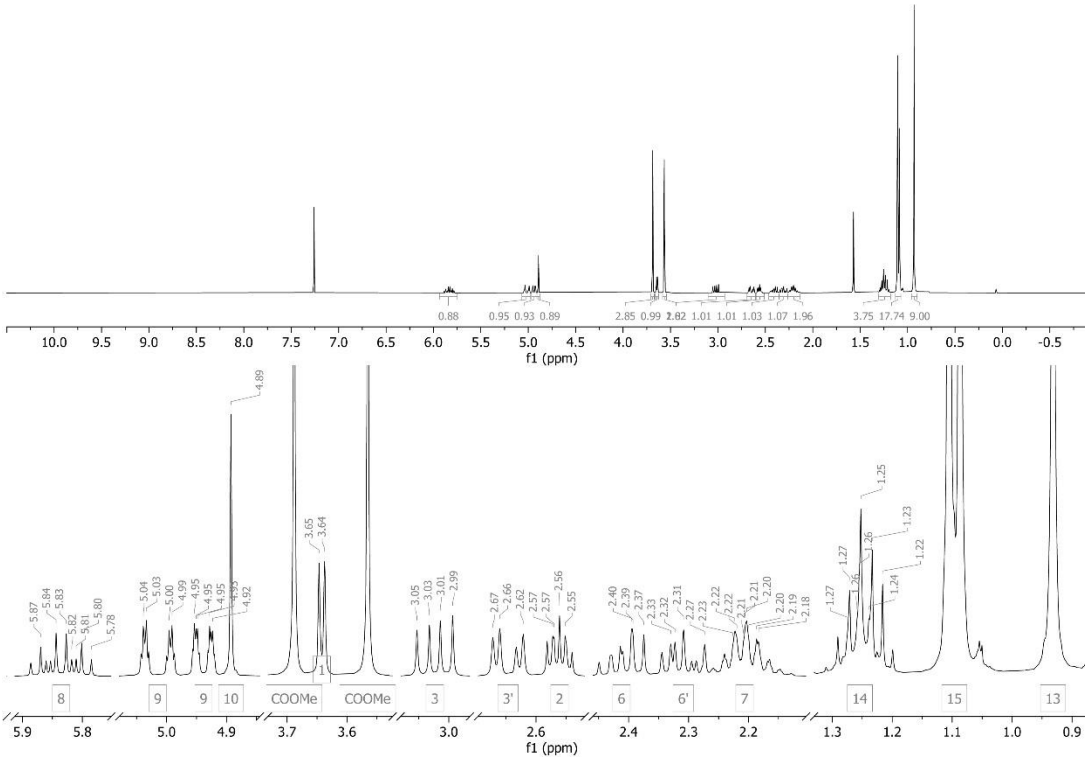
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



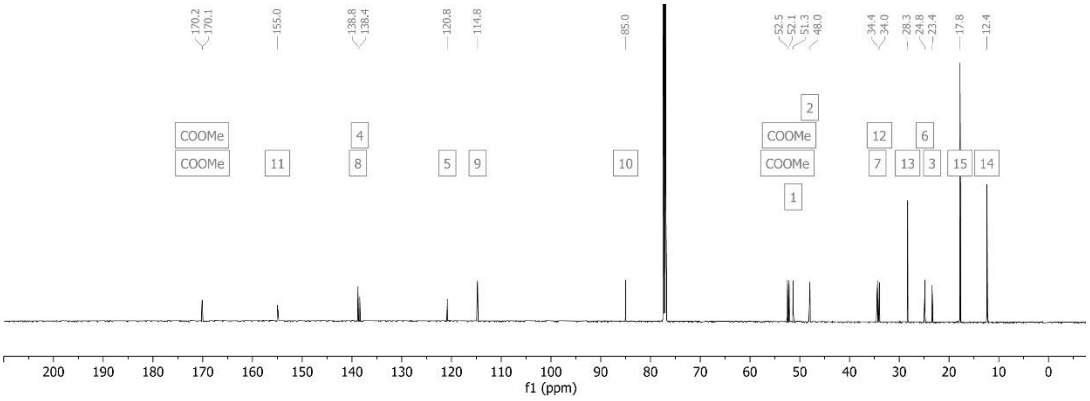
Dimethyl 2-(1-(3-(but-3-en-1-yl)-5-((triisopropylsilyl)oxy)furan-2-yl)-3,3-dimethyl-butan-2-yl)malonate, 3.215



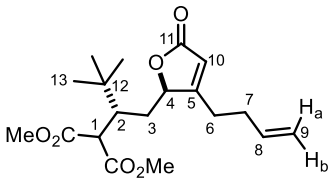
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



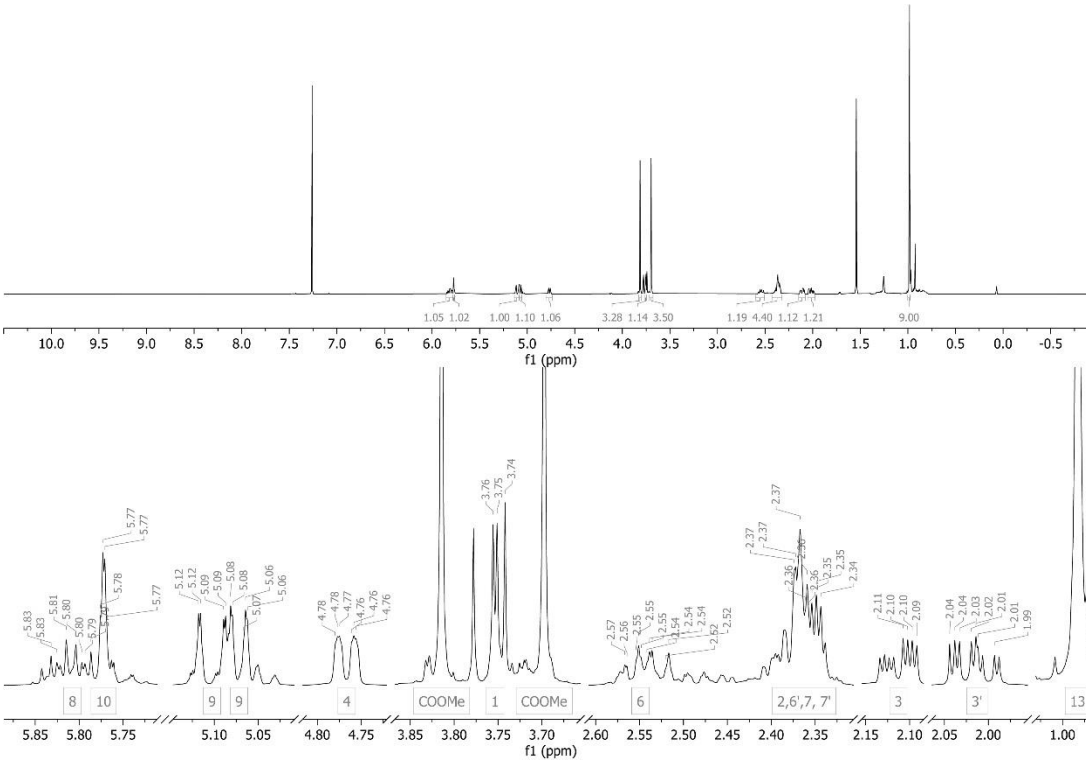
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



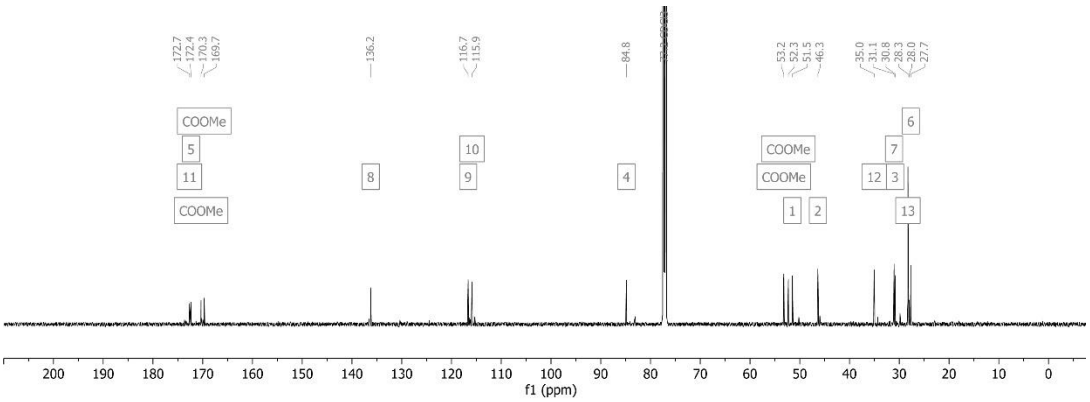
Dimethyl 2-((*R)-1-((*R**)-3-(but-3-en-1-yl)-5-oxo-2,5-dihydrofuran-2-yl)-3,3-dimethylbutan-2-yl)malonate, 3.141a, 4:1 d.r.**



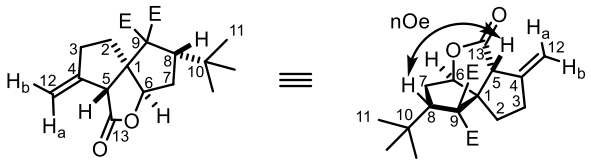
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



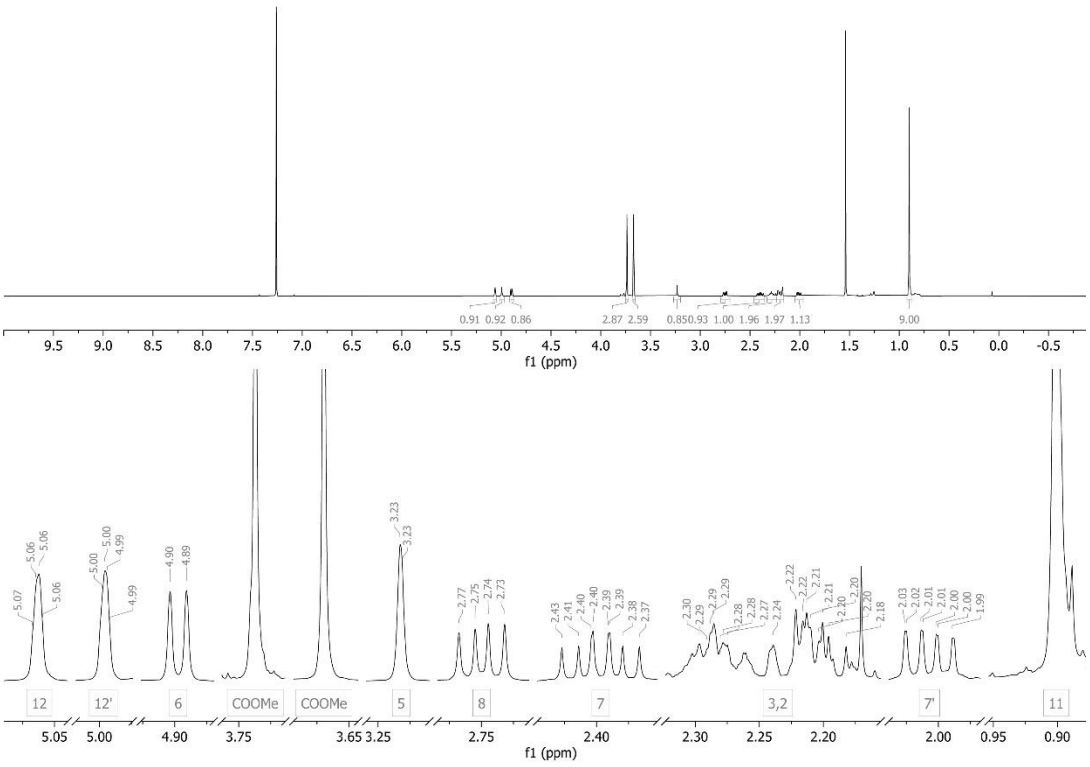
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



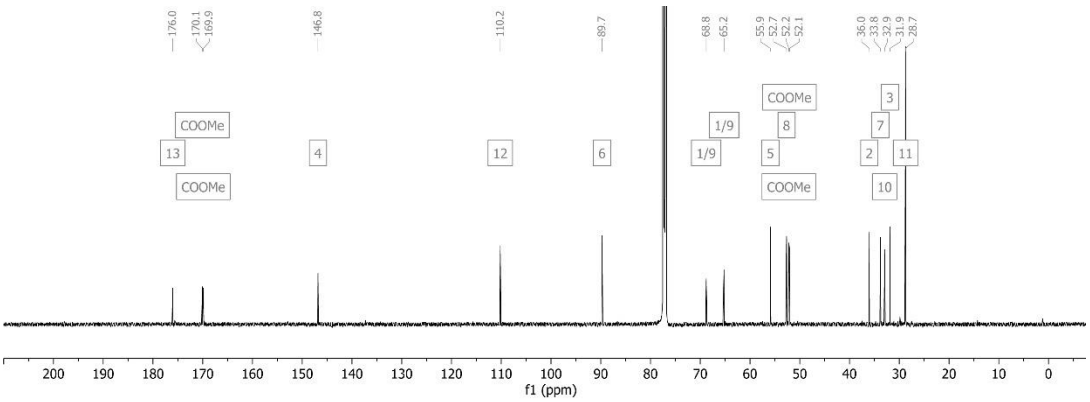
Dimethyl (2*S,3a*R**,5a*R**,8a*S**)-2-(*tert*-butyl)-6-methylene-5-oxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.150**



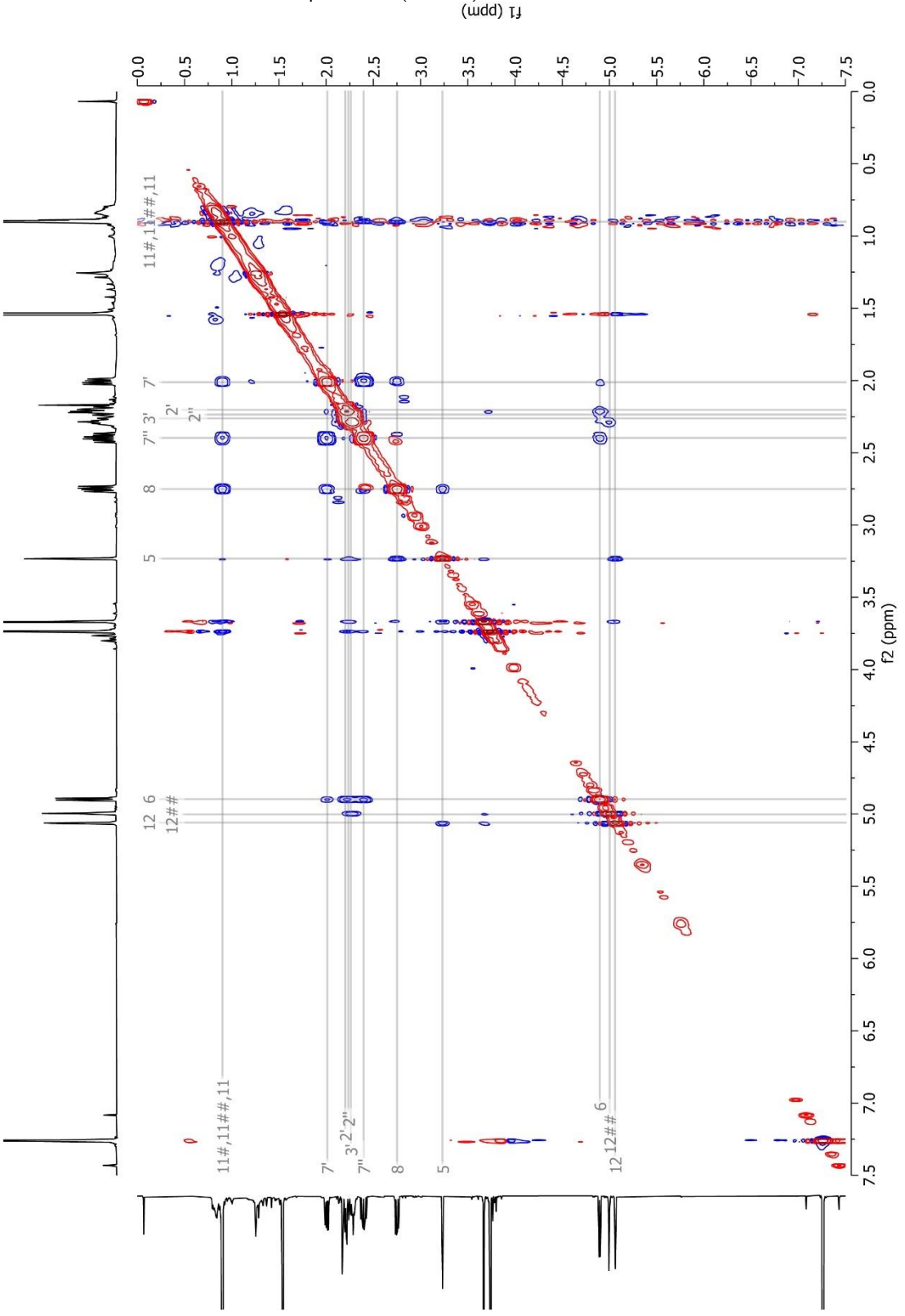
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



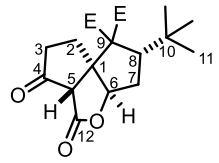
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



600 MHz ^{1}H NMR NOESY spectrum ($CDCl_3$)

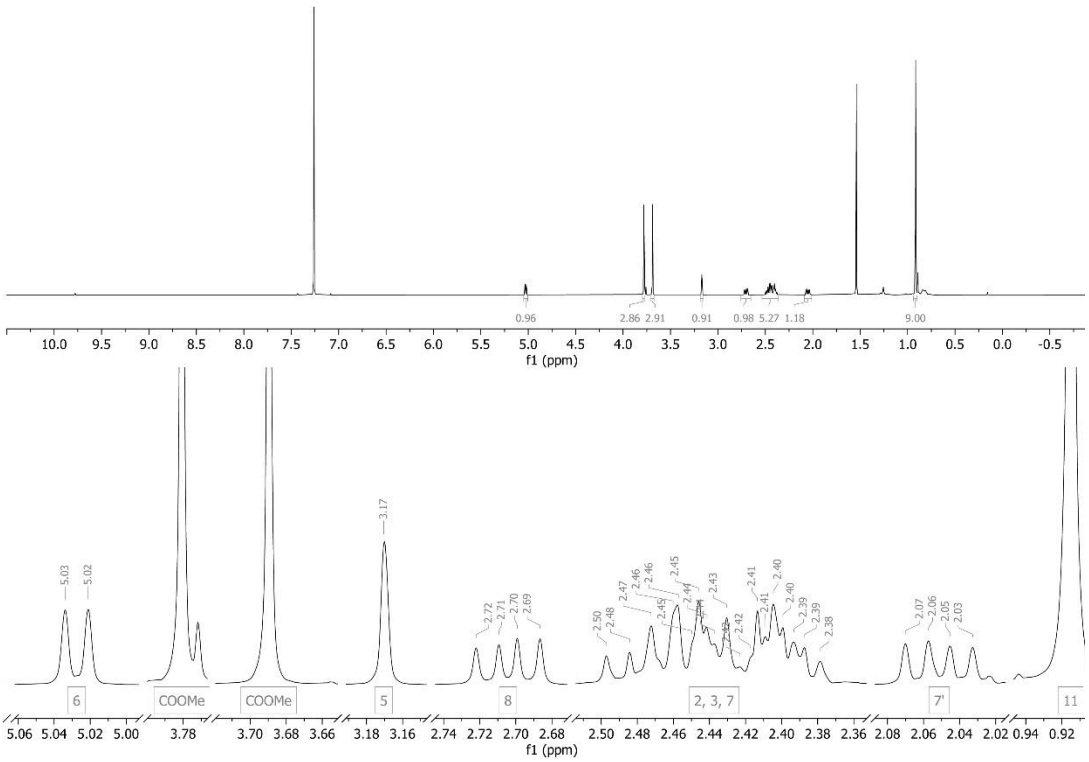


Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.217**

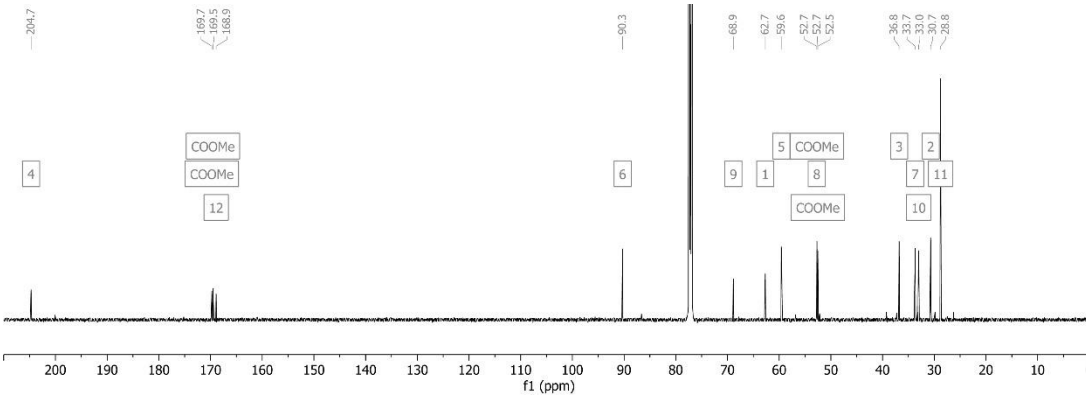


E = CO_2Me

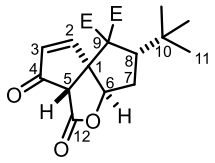
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



151 MHz ^{13}C NMR spectrum ($CDCl_3$)

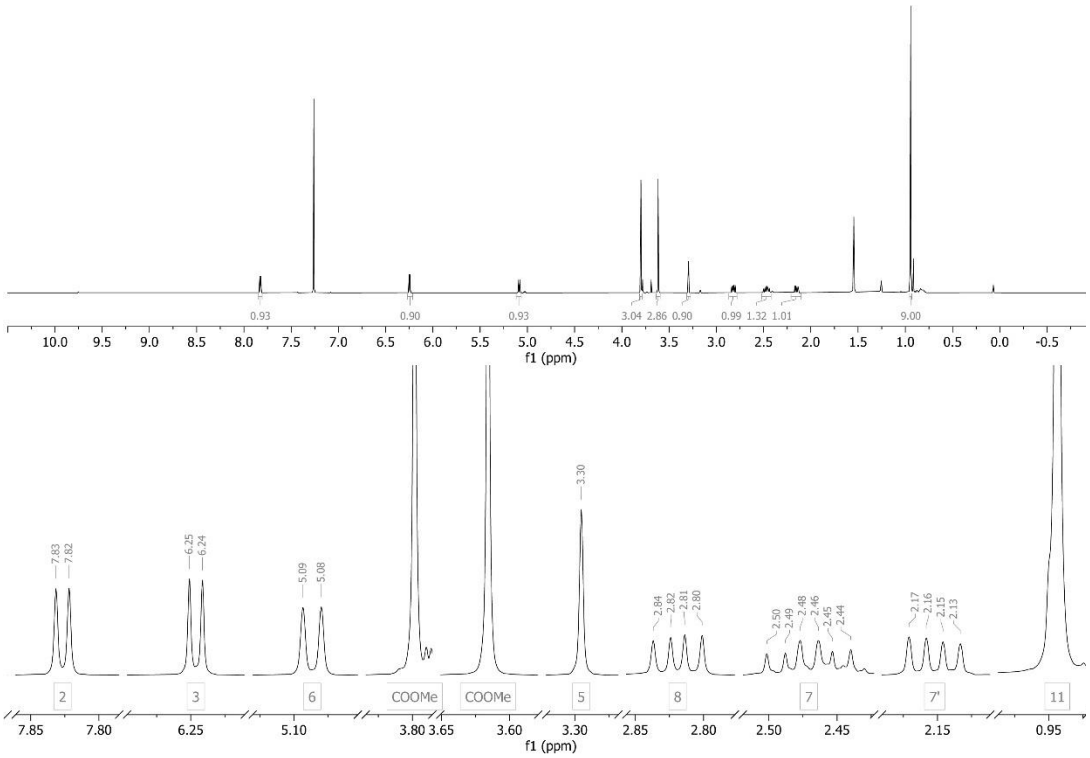


Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxo-3,3a,5a,6-tetrahydro-5*H*-dicyclopenta[*b*,*c*]furan-1,1(2*H*)-dicarboxylate, 3.219**

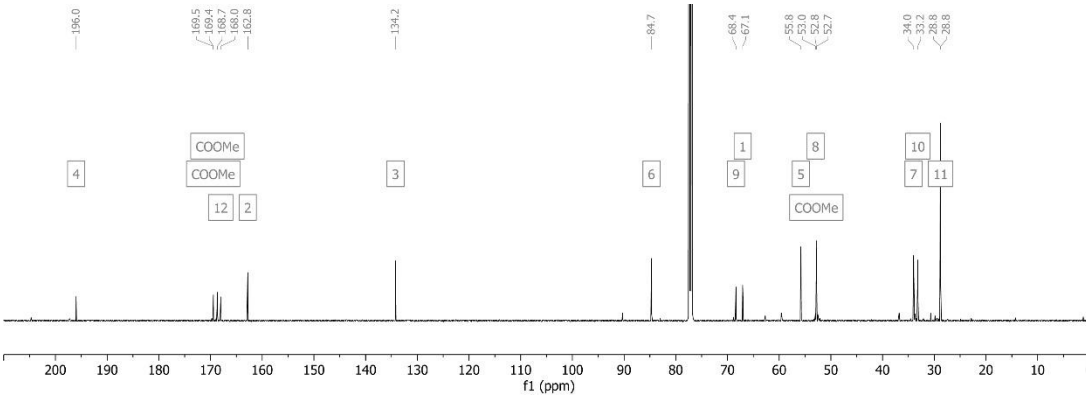


E = CO_2Me

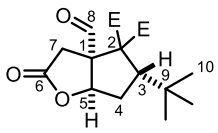
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



151 MHz ^{13}C NMR spectrum ($CDCl_3$)

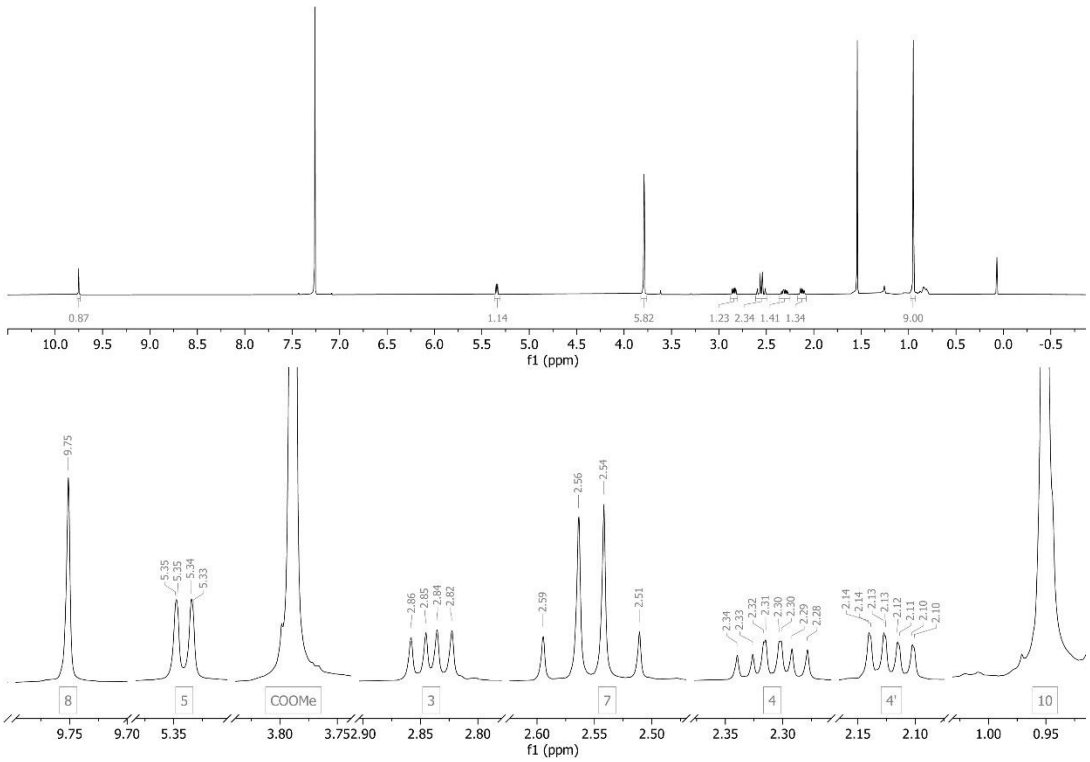


Dimethyl (3a*R,5*S**,6a*R**)-5-(*tert*-butyl)-3a-formyl-2-oxohexahydro-4*H*-cyclopenta[*b*]furan-4,4-dicarboxylate, 3.224**

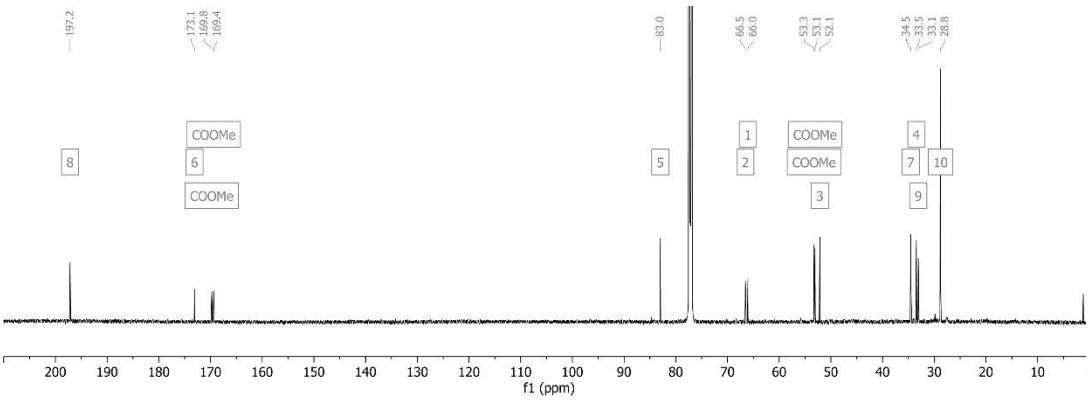


E = CO_2Me

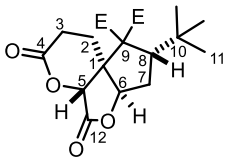
600 MHz ^1H NMR spectrum ($CDCl_3$)



151 MHz ^{13}C NMR spectrum ($CDCl_3$)

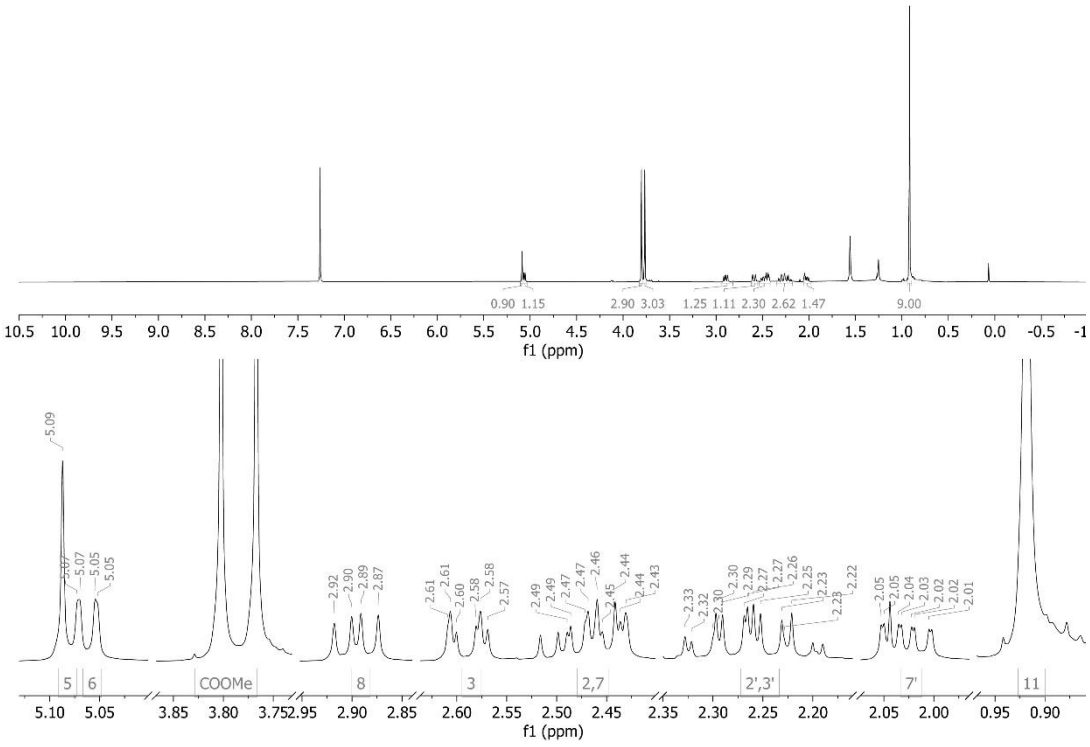


Dimethyl (2*S,3a*R**,5a*R**,9a*S**)-2-(*tert*-butyl)-5,7-dioxohexahydro-7*H*-cyclopenta[4,5]furo[3,4-*b*]pyran-1,1 (2*H*)-dicarboxylate, 3.235**

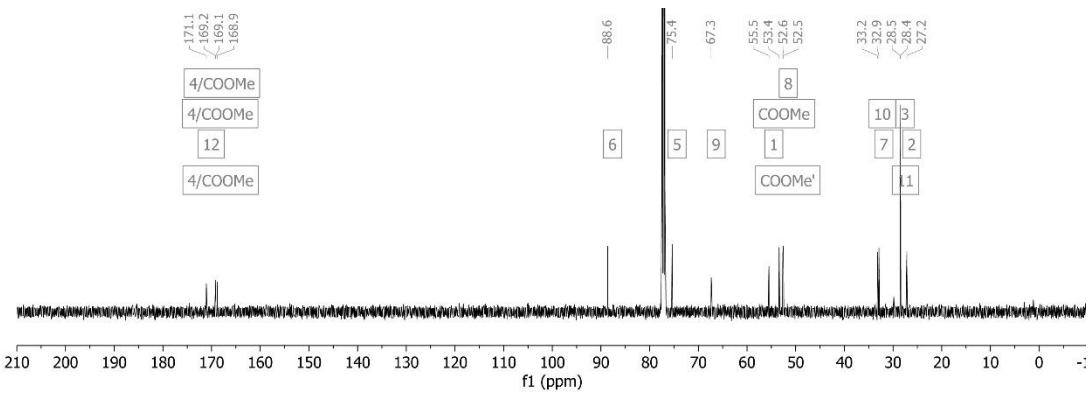


E = CO_2Me

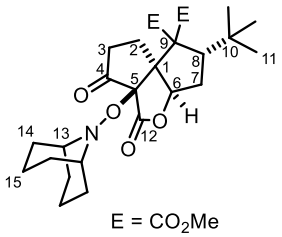
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



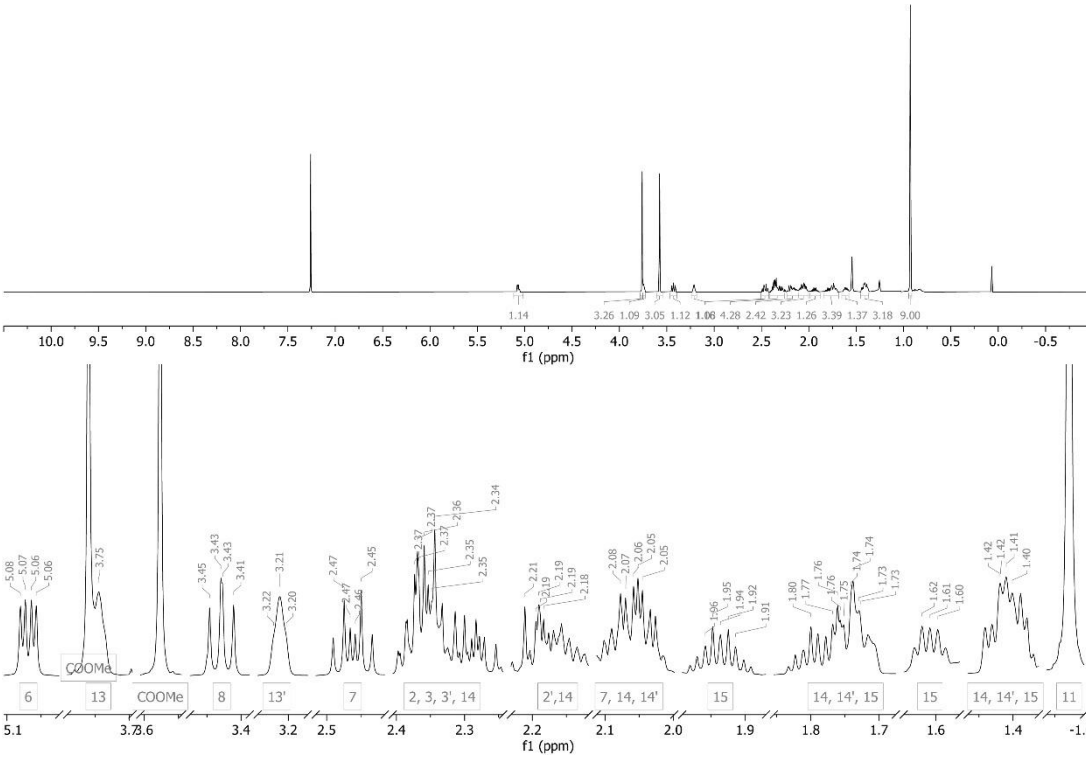
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



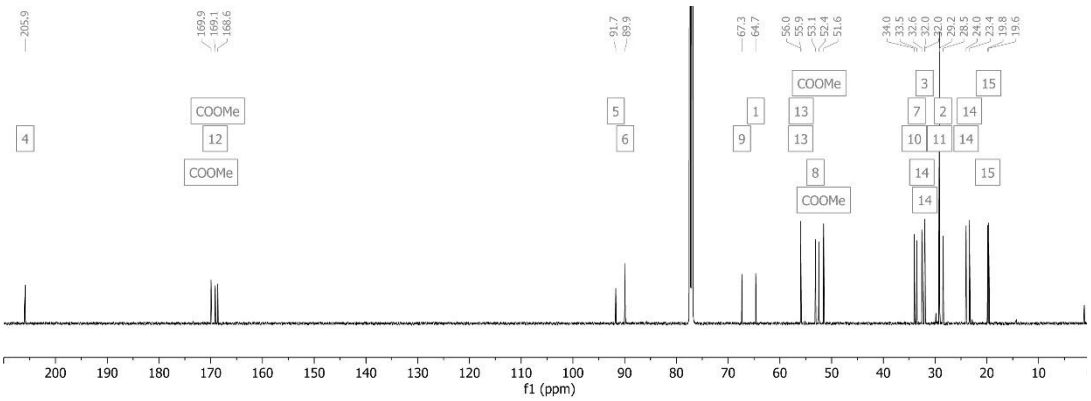
Dimethyl (2*S,3a*R**,5a*R**,8a*S**)-5a-(((1*S*,5*S*)-9-azabicyclo[3.3.1]nonan-9-yl) oxy)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1-(2*H*)-dicarboxylate, 3.247**



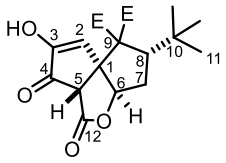
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



151 MHz ^{13}C NMR spectrum ($CDCl_3$)

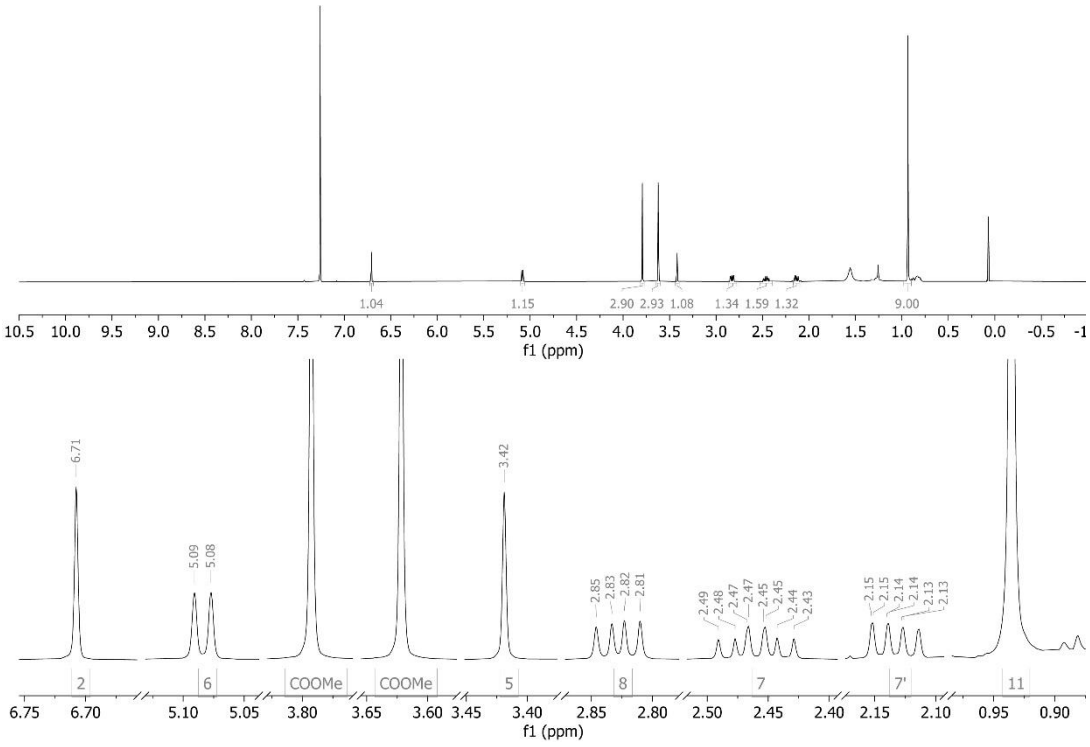


Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-7-hydroxy-5,6-dioxo-3,3a,5a,6-tetrahydro-5*H*-dicyclopenta[*b*,*c*]furan-1,1(2*H*)-dicarboxylate, 3.230**

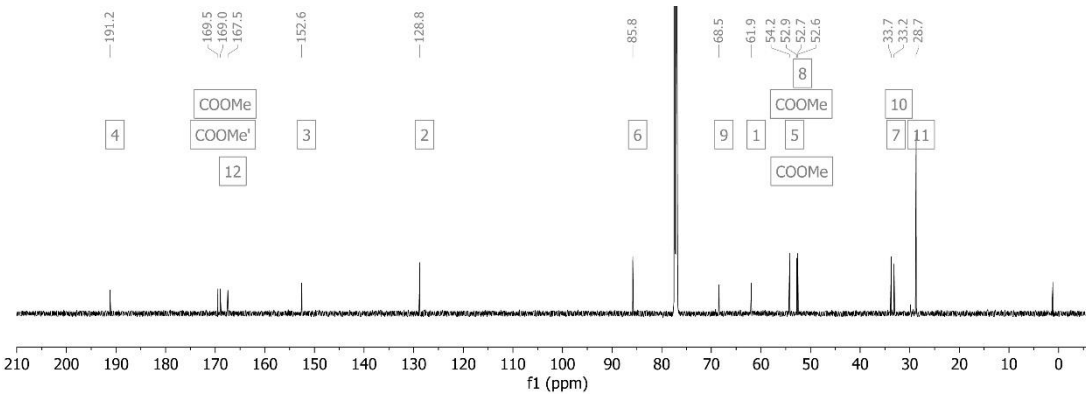


E = CO_2Me

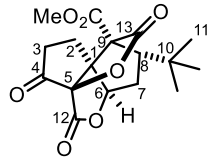
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



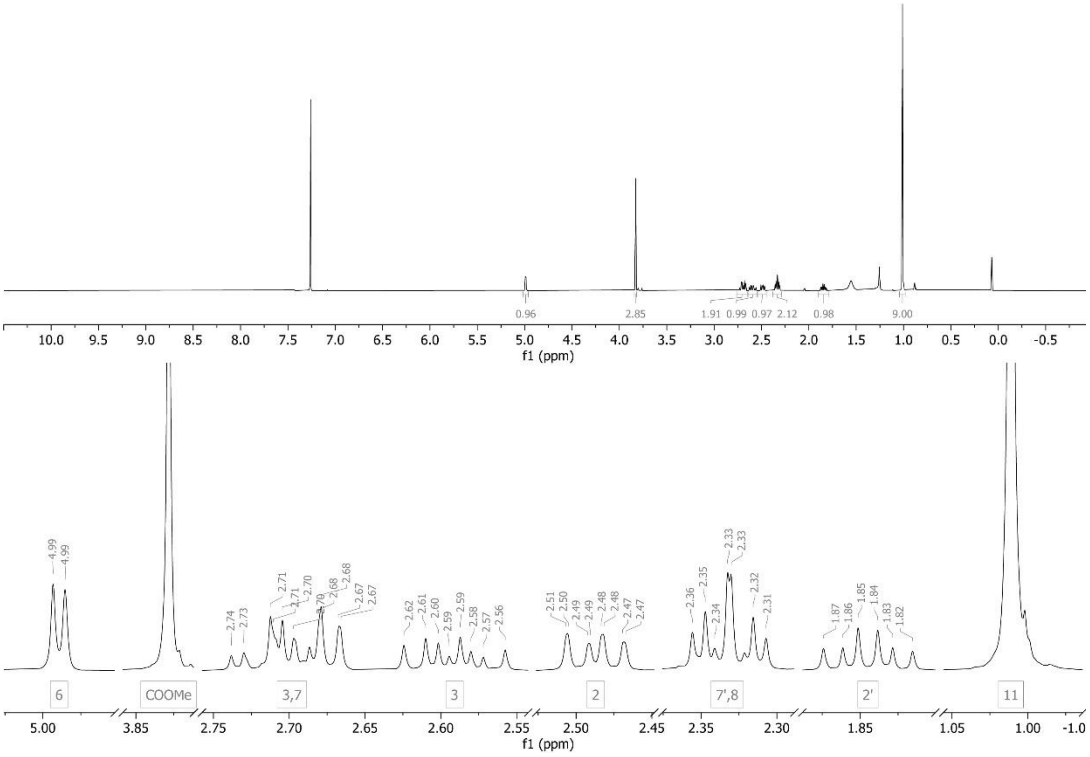
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



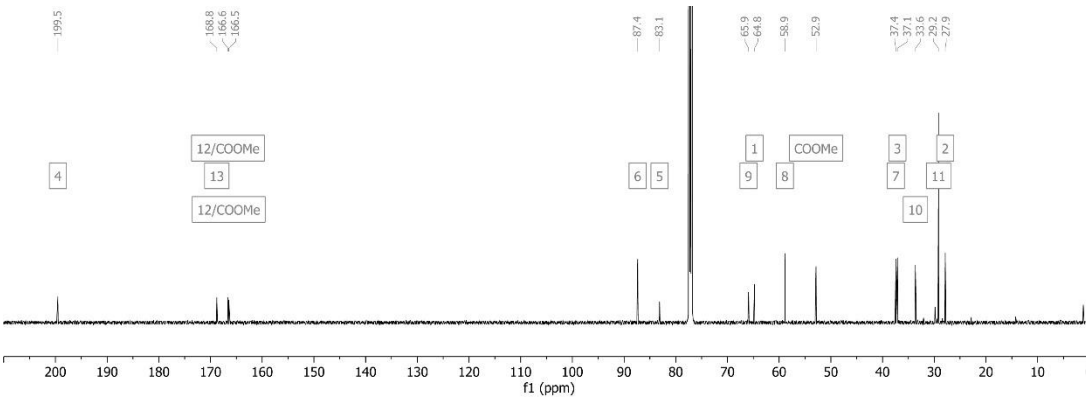
Methyl (1*S,2*S**,3a*R**,5a*R**,8a*S**)-2-(*tert*-butyl)-5,6,10-trioxotetrahydro-5*H*,6*H*-5a,1-(epoxymethano)dicyclopenta[*b,c*]furan-1(2*H*)-carboxylate, 3.220**



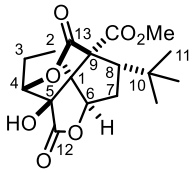
600 MHz ^{1}H NMR spectrum ($CDCl_3$)



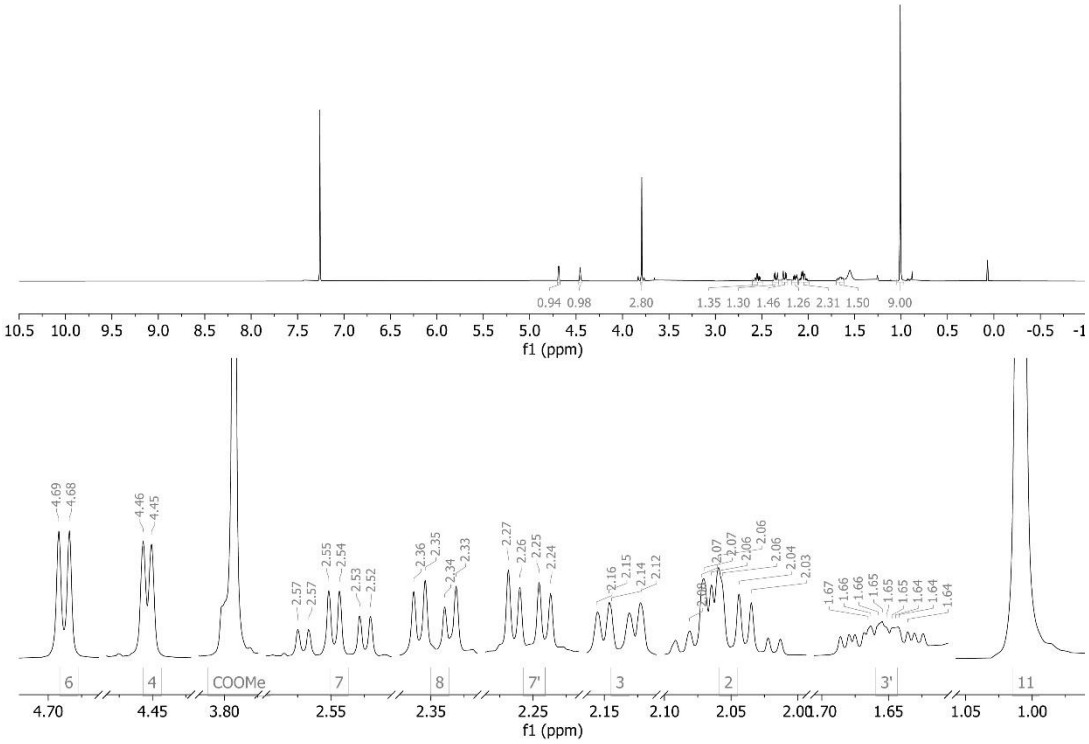
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



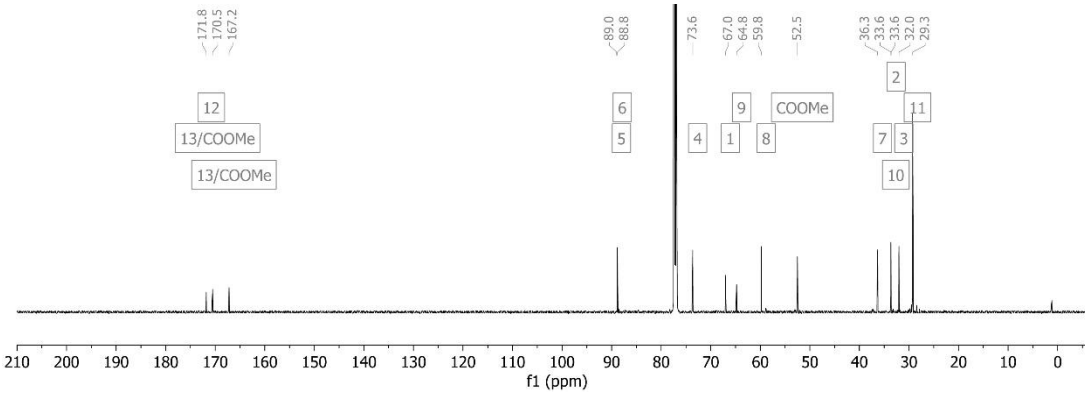
Methyl (1*S,2*S**,3a*R**,5a*R**,6*S**,8a*S**)-2-(*tert*-butyl)-5a-hydroxy-5,10-dioxohexahydro-5*H*-6,1-(epoxymethano)dicyclopenta[*b*,*c*]furan-1(2*H*)-carboxylate, 3.252**



600 MHz ^{1}H NMR spectrum ($CDCl_3$)



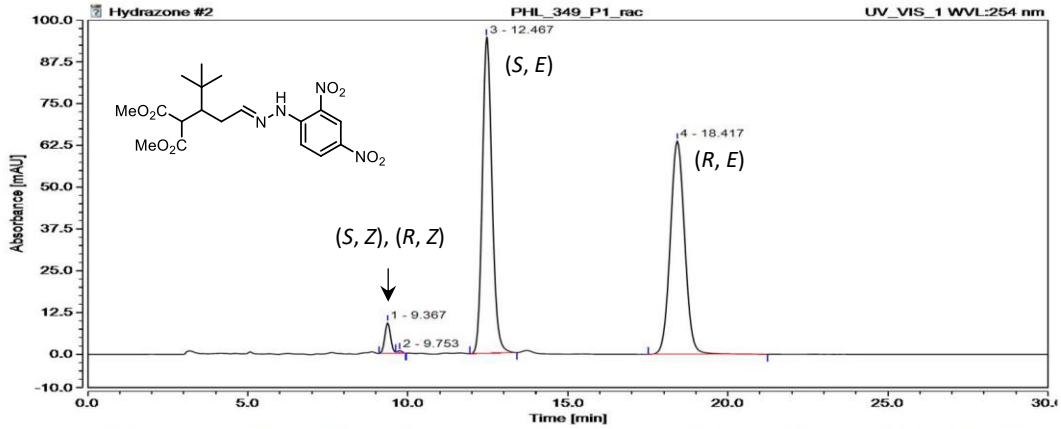
151 MHz ^{13}C NMR spectrum ($CDCl_3$)



4.5 Selected HPLC traces

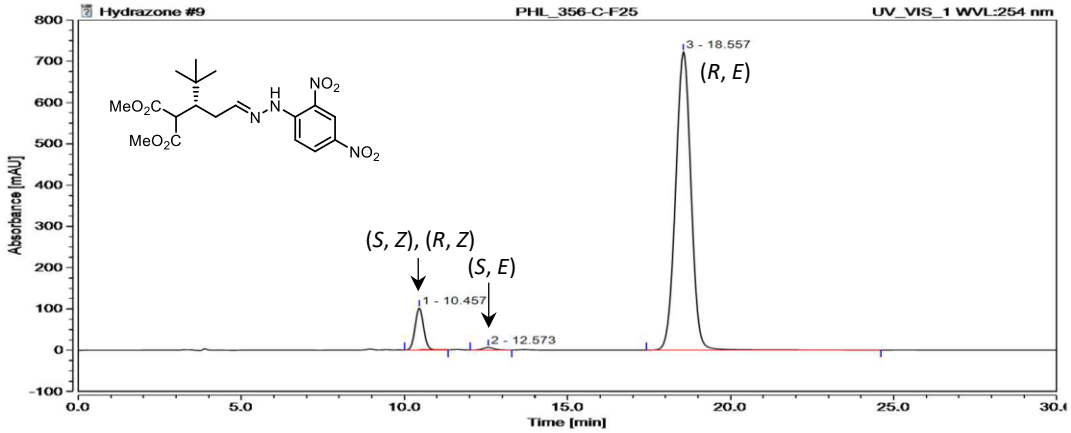
Daicel Chiralpak IA column (4.6 mm × 250 mm, 5 μm), flow rate: 1 mL/min, solvent: 15% iPrOH in hexane.

Dimethyl (*E*)-2-(1-(2-(2,4-dinitrophenyl)hydrazineylidene)-4,4-dimethylpentan-3-yl)malonate, (±)-3.263



Peak #	Retention Time/min	Area/mAU*min	Height/mAU	Relative Area/%
3	12.467	33.145	94.719	59.72
4	18.417	33.321	63.892	40.28
Total:		**66.465**	**158.611**	**100.00**

Dimethyl (*R*, *E*)-2-(1-(2-(2,4-dinitrophenyl)hydrazineylidene)-4,4-dimethylpentan-3-yl)malonate, (*R*)-3.263



Peak #	Retention Time/min	Area/mAU*min	Height/mAU	Relative Area/%
2	12.573	2.426	6.172	0.85
3	18.557	394.633	722.930	99.15
Total:		**397.060**	**729.102**	**100.00**

4.6 X-ray crystallographic data

Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4,7,8-hexahydropyrido[2,1-*f*]purine-9,9-(6*H*)-dicarboxylate, 2.196

Crystal data

$C_{15}H_{18}N_4O_6$	
$M_r = 350.33$	
Monoclinic, *I*2/*a*	
Hall symbol: -I 2ya	
$a = 12.7979$ (3) Å	
$b = 19.0627$ (4) Å	
$c = 14.1683$ (3) Å	
$\beta = 114.602$ (3)°	
$V = 3142.76$ (14) Å^3	
$Z = 8$	

Data collection

Oxford Diffraction SuperNova diffractometer	
Focussing mirrors monochromator	
ω scans	
Absorption correction: multi-scan *CrysAlis PRO* (Rigaku Oxford Diffraction, 2017)	
$T_{min} = 0.78$, $T_{max} = 0.83$	
7490 measured reflections	
3264 independent reflections	

Refinement

Refinement on F^2	
Least-squares matrix: full	
$R[F^2 > 2\sigma(F^2)] = 0.038$	
$wR(F^2) = 0.105$	
$S = 1.02$	
3264 reflections	
226 parameters	
0 restraints	

$F(000) = 1472$	
$D_x = 1.481$ Mg m^{-3}	
Melting point: not measured K	
Cu *K*α radiation, λ = 1.54180 Å	
Cell parameters from 5642 reflections	
θ = 4.1–76.4°	
μ = 0.99 mm^{-1}	
T = 150 K	
Block, colourless	
0.29 × 0.25 × 0.19 mm	

3064 reflections with $I > 2.0\sigma(I)$	
$R_{int} = 0.018$	
$\theta_{max} = 76.9°$, $\theta_{min} = 4.1°$	
$h = -15 \rightarrow 15$	
$k = -23 \rightarrow 22$	
$l = -14 \rightarrow 17$	

Primary atom site location: other	
Hydrogen site location: difference Fourier map	
H-atom parameters constrained	
Method = Modified Sheldrick $w = 1/[\sigma^2(F_o^2) + (0.06P)^2 + 2.02P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$	
$(\Delta/\sigma)_{max} = 0.0003$	
$\Delta\rho_{max} = 0.31$ e Å^{-3}	
$\Delta\rho_{min} = -0.27$ e Å^{-3}	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for (global)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.25631 (8)	0.44739 (6)	0.19559 (7)	0.0311
C2	0.34905 (10)	0.41085 (6)	0.20562 (9)	0.0229
O3	0.36707 (9)	0.38784 (6)	0.13549 (7)	0.0379
C4	0.43032 (10)	0.40414 (6)	0.32135 (9)	0.0208
C5	0.52709 (10)	0.35431 (6)	0.33517 (8)	0.0193
N6	0.63121 (9)	0.37891 (5)	0.34754 (8)	0.0200
C7	0.70014 (10)	0.32069 (6)	0.36114 (9)	0.0203
C8	0.63102 (10)	0.26448 (6)	0.35489 (8)	0.0200
N9	0.52318 (9)	0.28434 (5)	0.33912 (8)	0.0212
N10	0.67129 (9)	0.19674 (6)	0.36408 (8)	0.0246
C11	0.78467 (12)	0.18484 (7)	0.38263 (10)	0.0255
O12	0.82315 (9)	0.12558 (5)	0.39022 (9)	0.0376
N13	0.85373 (9)	0.24379 (6)	0.39305 (8)	0.0233
C14	0.81890 (10)	0.31459 (6)	0.38243 (9)	0.0226
O15	0.88605 (8)	0.36240 (5)	0.39210 (9)	0.0352
C16	0.97567 (11)	0.22986 (8)	0.41947 (11)	0.0300
C17	0.59481 (13)	0.13647 (7)	0.34608 (12)	0.0330
C18	0.66615 (11)	0.45223 (6)	0.34542 (11)	0.0259
C19	0.56262 (11)	0.50035 (7)	0.31619 (10)	0.0269
C20	0.48270 (11)	0.47628 (7)	0.36516 (10)	0.0253
C21	0.35820 (10)	0.37621 (7)	0.37728 (9)	0.0223
O22	0.29370 (8)	0.32270 (5)	0.32375 (7)	0.0294
C23	0.21912 (12)	0.29075 (8)	0.36481 (11)	0.0301
O24	0.35862 (9)	0.40028 (6)	0.45522 (7)	0.0330
C25	0.16764 (12)	0.45537 (8)	0.09132 (10)	0.0347
H161	1.0067	0.2689	0.4024	0.0487*
H162	1.0152	0.2188	0.4905	0.0465*
H163	0.9781	0.1914	0.3786	0.0471*
H171	0.6199	0.1074	0.4080	0.0515*
H172	0.5192	0.1521	0.3331	0.0506*
H173	0.5932	0.1094	0.2892	0.0518*
H181	0.7246	0.4626	0.4156	0.0308*
H182	0.7010	0.4549	0.2953	0.0303*
H191	0.5877	0.5462	0.3380	0.0329*
H192	0.5202	0.5016	0.2403	0.0315*

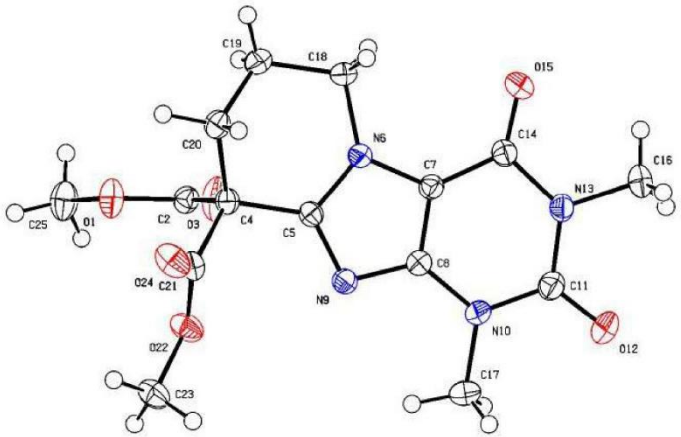
H201	0.5249	0.4705	0.4394	0.0305*
H202	0.4194	0.5096	0.3509	0.0309*
H231	0.1591	0.2689	0.3063	0.0440*
H232	0.1885	0.3257	0.3960	0.0443*
H233	0.2622	0.2568	0.4165	0.0441*
H251	0.1014	0.4705	0.0982	0.0552*
H252	0.1940	0.4887	0.0582	0.0538*
H253	0.1534	0.4119	0.0544	0.0534*

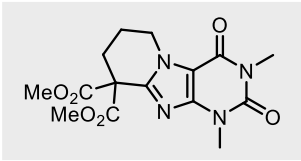
Atomic displacement parameters (Å²) for (global)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0262 (5)	0.0407 (5)	0.0235 (4)	0.0123 (4)	0.0075 (4)	-0.0031 (4)
C2	0.0238 (6)	0.0226 (6)	0.0239 (6)	0.0027 (4)	0.0116 (5)	0.0003 (4)
O3	0.0397 (6)	0.0524 (7)	0.0237 (5)	0.0194 (5)	0.0153 (4)	0.0024 (4)
C4	0.0209 (5)	0.0216 (6)	0.0223 (5)	0.0018 (4)	0.0114 (4)	-0.0013 (4)
C5	0.0191 (5)	0.0212 (6)	0.0187 (5)	-0.0003 (4)	0.0091 (4)	-0.0009 (4)
N6	0.0196 (5)	0.0185 (5)	0.0234 (5)	-0.0002 (4)	0.0106 (4)	0.0003 (4)
C7	0.0209 (6)	0.0193 (6)	0.0211 (5)	0.0007 (4)	0.0091 (4)	-0.0001 (4)
C8	0.0209 (5)	0.0199 (6)	0.0191 (5)	0.0001 (4)	0.0082 (4)	-0.0004 (4)
N9	0.0208 (5)	0.0208 (5)	0.0226 (5)	-0.0007 (4)	0.0097 (4)	-0.0011 (4)
N10	0.0236 (5)	0.0176 (5)	0.0315 (5)	-0.0004 (4)	0.0105 (4)	-0.0009 (4)
C11	0.0260 (6)	0.0226 (6)	0.0273 (6)	0.0028 (5)	0.0105 (5)	-0.0004 (5)
O12	0.0355 (5)	0.0240 (5)	0.0531 (6)	0.0082 (4)	0.0183 (5)	0.0017 (4)
N13	0.0204 (5)	0.0238 (5)	0.0260 (5)	0.0030 (4)	0.0098 (4)	-0.0002 (4)
C14	0.0208 (6)	0.0238 (6)	0.0237 (5)	0.0005 (4)	0.0096 (5)	-0.0006 (4)
O15	0.0233 (5)	0.0281 (5)	0.0554 (6)	-0.0037 (4)	0.0177 (4)	0.0009 (4)
C16	0.0220 (6)	0.0339 (7)	0.0355 (7)	0.0060 (5)	0.0133 (5)	0.0004 (5)
C17	0.0314 (7)	0.0198 (6)	0.0469 (8)	-0.0048 (5)	0.0155 (6)	-0.0019 (5)
C18	0.0249 (6)	0.0181 (6)	0.0367 (7)	-0.0022 (5)	0.0148 (5)	0.0012 (5)
C19	0.0287 (6)	0.0184 (6)	0.0362 (6)	0.0004 (5)	0.0159 (5)	0.0001 (5)
C20	0.0264 (6)	0.0218 (6)	0.0303 (6)	0.0012 (5)	0.0143 (5)	-0.0047 (5)
C21	0.0184 (5)	0.0268 (6)	0.0220 (5)	0.0029 (4)	0.0088 (4)	0.0005 (4)
O22	0.0298 (5)	0.0338 (5)	0.0316 (5)	-0.0080 (4)	0.0196 (4)	-0.0076 (4)
C23	0.0268 (6)	0.0352 (7)	0.0331 (6)	-0.0059 (5)	0.0174 (5)	-0.0030 (5)
O24	0.0322 (5)	0.0456 (6)	0.0265 (5)	-0.0076 (4)	0.0175 (4)	-0.0093 (4)
C25	0.0297 (7)	0.0426 (8)	0.0256 (6)	0.0108 (6)	0.0054 (5)	-0.0007 (5)

Geometric parameters (Å, º) for (global)

O1—C2	1.3317 (15)	C16—H162	0.943
O1—C25	1.4482 (15)	C16—H163	0.943
C2—O3	1.1931 (16)	C17—H171	0.973
C2—C4	1.5385 (16)	C17—H172	0.954
C4—C5	1.5074 (16)	C17—H173	0.950
C4—C20	1.5426 (16)	C18—C19	1.5203 (17)
C4—C21	1.5402 (16)	C18—H181	0.984
C5—N6	1.3534 (15)	C18—H182	0.984
C5—N9	1.3369 (16)	C19—C20	1.5261 (17)
N6—C7	1.3805 (15)	C19—H191	0.938
N6—C18	1.4715 (15)	C19—H192	0.983
C7—C8	1.3686 (16)	C20—H201	0.969
C7—C14	1.4257 (17)	C20—H202	0.982
C8—N9	1.3569 (15)	C21—O22	1.3326 (15)
C8—N10	1.3762 (15)	C21—O24	1.1937 (15)
N10—C11	1.3814 (16)	O22—C23	1.4431 (15)
N10—C17	1.4614 (16)	C23—H231	0.959
C11—O12	1.2191 (16)	C23—H232	0.968
C11—N13	1.3989 (17)	C23—H233	0.961
N13—C14	1.4097 (16)	C25—H251	0.937
N13—C16	1.4695 (15)	C25—H252	0.933
C14—O15	1.2207 (16)	C25—H253	0.956
C16—H161	0.923		
C2—O1—C25	116.67 (10)	N10—C17—H171	110.2
O1—C2—O3	125.18 (12)	N10—C17—H172	109.9
O1—C2—C4	109.53 (10)	H171—C17—H172	106.2
O3—C2—C4	125.28 (11)	N10—C17—H173	110.5
C2—C4—C5	110.20 (9)	H171—C17—H173	109.8
C2—C4—C20	110.02 (10)	H172—C17—H173	110.2
C5—C4—C20	108.27 (10)	N6—C18—C19	109.93 (10)
C2—C4—C21	107.05 (9)	N6—C18—H181	106.3
C5—C4—C21	110.57 (10)	C19—C18—H181	111.3
C20—C4—C21	110.75 (10)	N6—C18—H182	107.2
C4—C5—N6	120.66 (10)	C19—C18—H182	112.2
C4—C5—N9	126.23 (10)	H181—C18—H182	109.7
N6—C5—N9	113.10 (10)	C18—C19—C20	111.58 (10)
C5—N6—C7	106.08 (10)	C18—C19—H191	109.4





C5—N6—C18	128.14 (10)	C20—C19—H191	109.4
C7—N6—C18	125.77 (10)	C18—C19—H192	109.5
N6—C7—C8	105.20 (10)	C20—C19—H192	109.6
N6—C7—C14	131.15 (11)	H191—C19—H192	107.2
C8—C7—C14	123.59 (11)	C4—C20—C19	110.26 (10)
C7—C8—N9	112.20 (11)	C4—C20—H201	106.8
C7—C8—N10	121.46 (11)	C19—C20—H201	110.6
N9—C8—N10	126.33 (11)	C4—C20—H202	108.1
C8—N9—C5	103.42 (10)	C19—C20—H202	111.4
C8—N10—C11	119.63 (10)	H201—C20—H202	109.6
C8—N10—C17	121.60 (11)	C4—C21—O22	109.49 (10)
C11—N10—C17	118.57 (11)	C4—C21—O24	124.77 (12)
N10—C11—O12	121.51 (12)	O22—C21—O24	125.72 (12)
N10—C11—N13	117.11 (11)	C21—O22—C23	116.78 (10)
O12—C11—N13	121.38 (12)	O22—C23—H231	105.1
C11—N13—C14	126.86 (11)	O22—C23—H232	110.7
C11—N13—C16	116.05 (11)	H231—C23—H232	111.3
C14—N13—C16	117.08 (11)	O22—C23—H233	109.0
C7—C14—N13	111.26 (10)	H231—C23—H233	111.4
C7—C14—O15	126.98 (12)	H232—C23—H233	109.2
N13—C14—O15	121.75 (11)	O1—C25—H251	106.6
N13—C16—H161	108.4	O1—C25—H252	106.9
N13—C16—H162	110.7	H251—C25—H252	112.0
H161—C16—H162	111.2	O1—C25—H253	110.9
N13—C16—H163	106.7	H251—C25—H253	110.4
H161—C16—H163	109.8	H252—C25—H253	110.0
H162—C16—H163	110.0		

Hydrogen-bond geometry (Å, º) for (global)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C16—H163···O3^{i}	0.94	2.56	3.3161 (19)	137
C20—H202···O15^{ii}	0.98	2.59	3.3949 (19)	140
C23—H231···N9^{i}	0.96	2.59	3.5430 (19)	171

Symmetry codes: (i) -*x*+3/2, -*y*+1/2, -*z*+1/2; (ii) *x*-1/2, -*y*+1, *z*; (iii) -*x*+1/2, -*y*+1/2, -*z*+1/2.

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Trimethyl (2*S**,5*S**,6*S**)-2-(*tert*-butyl)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate, 3.107b

Table 1. Crystal data and structure refinement for 7544.

Identification code	7544
Empirical formula	C20 H30 O6
Formula weight	366.45
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.0733(4) Å α= 77.990(3)°. b = 13.3622(6) Å β= 89.523(3)°. c = 16.4582(4) Å γ = 77.875(4)°.
Volume	1906.86(13) Å^3
Z	4
Density (calculated)	1.276 Mg/m^3
Absorption coefficient	0.764 mm^{-1}
F(000)	792
Crystal size	0.20 x 0.19 x 0.04 mm^3
Theta range for data collection	3.461 to 76.411°.
Index ranges	-11<=h<=11, -16<=k<=16, -20<=l<=20
Reflections collected	39938
Independent reflections	7872 [R(int) = 0.064]
Completeness to theta = 73.355°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.74
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7872 / 0 / 469
Goodness-of-fit on F^2	1.0175
Final R indices [I>2sigma(I)]	R1 = 0.0615, wR2 = 0.1629
R indices (all data)	R1 = 0.0758, wR2 = 0.1817
Largest diff. peak and hole	0.59 and -0.39 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 7544. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	10661(3)	6920(2)	1802(2)	43
C(2)	9420(2)	7395(2)	2102(1)	32
C(3)	8721(2)	6978(2)	2922(1)	28
C(4)	7055(2)	7618(2)	2818(1)	28
C(5)	7295(3)	8706(2)	2351(1)	33
C(6)	8463(3)	8450(2)	1702(1)	36
C(7)	6016(2)	7221(2)	2284(1)	31
C(8)	4417(2)	7781(2)	2434(1)	36
C(9)	4479(2)	8199(2)	3242(1)	29
C(10)	6129(2)	7711(2)	3629(1)	27
C(11)	3053(2)	8144(2)	3772(1)	31
C(12)	1709(3)	8818(2)	3205(2)	39
C(13)	2745(3)	7042(2)	4061(2)	37
C(14)	3108(3)	8629(2)	4534(1)	39
C(15)	8958(2)	5800(2)	3118(1)	29
O(16)	8672(2)	5267(1)	2655(1)	35
O(17)	9586(2)	5393(1)	3888(1)	32
C(18)	9743(3)	4275(2)	4154(1)	36
C(21)	6690(2)	8453(2)	4091(1)	28
O(22)	6039(2)	9317(1)	4124(1)	38
O(23)	8080(2)	8018(1)	4442(1)	31
C(24)	8613(3)	8628(2)	4958(2)	39
C(25)	6227(2)	6640(2)	4206(1)	26
O(26)	6306(2)	5831(1)	3978(1)	32
C(28)	6267(3)	5730(2)	5606(1)	35
O(27)	6176(2)	6712(1)	5007(1)	30
C(51)	3245(3)	6743(2)	6891(2)	41
C(52)	4172(2)	7259(2)	7159(1)	31
C(53)	5144(2)	6884(2)	7964(1)	27
C(54)	6380(2)	7558(2)	7825(1)	27
C(55)	5438(2)	8617(2)	7336(1)	32

C(56)	4440(3)	8311(2)	6724(1)	37
C(57)	7681(2)	7149(2)	7293(1)	31
C(58)	8941(3)	7704(2)	7433(1)	37
C(59)	8579(2)	8185(2)	8206(1)	28
C(60)	7223(2)	7711(2)	8614(1)	26
C(61)	10015(2)	8177(2)	8728(1)	31
C(62)	10973(3)	7083(2)	9081(2)	40
C(63)	9610(3)	8756(2)	9440(2)	41
C(64)	10995(2)	8788(2)	8127(1)	36
C(65)	5661(2)	5706(2)	8165(1)	28
O(66)	6311(2)	5178(1)	7708(1)	35
O(67)	5241(2)	5295(1)	8931(1)	32
C(68)	5763(3)	4181(2)	9197(1)	38
C(71)	6176(2)	8494(2)	9037(1)	28
O(72)	6240(2)	9393(1)	8986(1)	37
O(73)	5087(2)	8069(1)	9441(1)	31
C(74)	4107(3)	8734(2)	9902(2)	38
C(75)	7774(2)	6662(2)	9218(1)	27
O(76)	8195(2)	5841(1)	9007(1)	33
O(77)	7769(2)	6756(1)	10012(1)	32
C(78)	8276(3)	5784(2)	10620(1)	36

Table 3. Bond lengths [Å] and angles [°] for 7544.

C(1)-C(2)	1.317(3)	C(13)-H(133)	0.968
C(1)-H(11)	0.920	C(13)-H(132)	0.966
C(1)-H(12)	0.937	C(14)-H(141)	0.974
C(2)-C(3)	1.535(3)	C(14)-H(143)	0.970
C(2)-C(6)	1.512(3)	C(14)-H(142)	0.961
C(3)-C(4)	1.564(3)	C(15)-O(16)	1.208(3)
C(3)-C(15)	1.508(3)	C(15)-O(17)	1.350(2)
C(3)-H(31)	0.961	O(17)-C(18)	1.443(3)
C(4)-C(5)	1.555(3)	C(18)-H(181)	0.952
C(4)-C(7)	1.536(3)	C(18)-H(182)	0.950
C(4)-C(10)	1.583(3)	C(18)-H(183)	0.956
C(5)-C(6)	1.536(3)	C(21)-O(22)	1.194(3)
C(5)-H(51)	0.984	C(21)-O(23)	1.351(3)
C(5)-H(52)	0.969	O(23)-C(24)	1.442(2)
C(6)-H(62)	0.971	C(24)-H(242)	0.963
C(6)-H(61)	0.968	C(24)-H(241)	0.952
C(7)-C(8)	1.529(3)	C(24)-H(243)	0.954
C(7)-H(71)	0.970	C(25)-O(26)	1.204(3)
C(7)-H(72)	0.972	C(25)-O(27)	1.340(2)
C(8)-C(9)	1.552(3)	C(28)-O(27)	1.455(3)
C(8)-H(82)	0.973	C(28)-H(282)	0.955
C(8)-H(81)	0.965	C(28)-H(281)	0.943
C(9)-C(10)	1.583(3)	C(28)-H(283)	0.964
C(9)-C(11)	1.560(3)	C(51)-C(52)	1.324(3)
C(9)-H(91)	0.973	C(51)-H(511)	0.942
C(10)-C(21)	1.533(3)	C(51)-H(512)	0.941
C(10)-C(25)	1.530(3)	C(52)-C(53)	1.531(3)
C(11)-C(12)	1.542(3)	C(52)-C(56)	1.507(3)
C(11)-C(13)	1.534(3)	C(53)-C(54)	1.566(3)
C(11)-C(14)	1.531(3)	C(53)-C(65)	1.511(3)
C(12)-H(122)	0.979	C(53)-H(531)	0.974
C(12)-H(121)	0.975	C(54)-C(55)	1.552(3)
C(12)-H(123)	0.981	C(54)-C(57)	1.539(3)
C(13)-H(131)	0.955	C(54)-C(60)	1.584(3)

C(55)-C(56)	1.531(3)	O(73)-C(74)	1.448(3)	C(5)-C(6)-H(62)	111.0	C(11)-C(12)-H(121)	110.2	
C(55)-H(551)	0.977	C(74)-H(742)	0.971	C(2)-C(6)-H(62)	112.0	H(122)-C(12)-H(121)	108.3	
C(55)-H(552)	0.987	C(74)-H(741)	0.965	C(5)-C(6)-H(61)	110.8	C(11)-C(12)-H(123)	111.5	
C(56)-H(562)	0.958	C(74)-H(743)	0.955	C(2)-C(6)-H(61)	111.1	H(122)-C(12)-H(123)	109.1	
C(56)-H(561)	0.983	C(75)-O(76)	1.205(3)	H(62)-C(6)-H(61)	107.3	H(121)-C(12)-H(123)	108.3	
C(57)-C(58)	1.530(3)	C(75)-O(77)	1.339(2)	C(4)-C(7)-C(8)	105.11(17)	C(11)-C(13)-H(131)	110.0	
C(57)-H(571)	0.974	O(77)-C(78)	1.454(3)	C(4)-C(7)-H(71)	110.2	C(11)-C(13)-H(133)	110.8	
C(57)-H(572)	0.981	C(78)-H(782)	0.966	C(8)-C(7)-H(71)	111.4	H(131)-C(13)-H(133)	108.5	
C(58)-C(59)	1.544(3)	C(78)-H(781)	0.950	C(4)-C(7)-H(72)	109.7	C(11)-C(13)-H(132)	111.8	
C(58)-H(582)	0.978	C(78)-H(783)	0.958	C(8)-C(7)-H(72)	110.9	H(131)-C(13)-H(132)	107.2	
C(58)-H(581)	0.971			H(71)-C(7)-H(72)	109.4	H(133)-C(13)-H(132)	108.4	
C(59)-C(60)	1.582(3)	C(2)-C(1)-H(11)	118.7	C(7)-C(8)-C(9)	107.74(17)	C(11)-C(14)-H(141)	110.8	
C(59)-C(61)	1.564(3)	C(2)-C(1)-H(12)	121.6	C(7)-C(8)-H(82)	111.4	C(11)-C(14)-H(143)	109.9	
C(59)-H(591)	0.980	H(11)-C(1)-H(12)	119.6	C(9)-C(8)-H(82)	108.0	H(141)-C(14)-H(143)	108.4	
C(60)-C(71)	1.535(3)	C(1)-C(2)-C(3)	125.7(2)	C(7)-C(8)-H(81)	109.2	C(11)-C(14)-H(142)	110.5	
C(60)-C(75)	1.529(3)	C(1)-C(2)-C(6)	125.6(2)	C(9)-C(8)-H(81)	111.0	H(141)-C(14)-H(142)	109.8	
C(61)-C(62)	1.533(3)	C(3)-C(2)-C(6)	108.66(18)	H(82)-C(8)-H(81)	109.5	H(143)-C(14)-H(142)	107.3	
C(61)-C(63)	1.535(3)	C(2)-C(3)-C(4)	103.48(16)	C(8)-C(9)-C(10)	105.20(16)	C(3)-C(15)-O(16)	126.08(18)	
C(61)-C(64)	1.548(3)	C(2)-C(3)-C(15)	112.35(17)	C(8)-C(9)-C(11)	113.46(17)	C(3)-C(15)-O(17)	110.89(17)	
C(62)-H(622)	0.972	C(4)-C(3)-C(15)	117.22(17)	C(10)-C(9)-C(11)	121.86(16)	O(16)-C(15)-O(17)	123.0(2)	
C(62)-H(621)	0.977	C(2)-C(3)-H(31)	108.4	C(8)-C(9)-H(91)	108.0	C(15)-O(17)-C(18)	114.72(17)	
C(62)-H(623)	0.973	C(4)-C(3)-H(31)	108.4	C(10)-C(9)-H(91)	104.8	O(17)-C(18)-H(181)	107.5	
C(63)-H(631)	0.965	C(15)-C(3)-H(31)	106.7	C(11)-C(9)-H(91)	102.5	O(17)-C(18)-H(182)	110.3	
C(63)-H(633)	0.979	C(3)-C(4)-C(5)	100.52(16)	C(9)-C(10)-C(4)	101.25(15)	H(181)-C(18)-H(182)	111.3	
C(63)-H(632)	0.981	C(3)-C(4)-C(7)	114.48(17)	C(9)-C(10)-C(21)	111.32(17)	O(17)-C(18)-H(183)	108.9	
C(64)-H(641)	0.971	C(5)-C(4)-C(7)	109.26(17)	C(4)-C(10)-C(21)	110.32(16)	H(181)-C(18)-H(183)	109.0	
C(64)-H(643)	0.974	C(3)-C(4)-C(10)	118.35(16)	C(9)-C(10)-C(25)	111.88(16)	H(182)-C(18)-H(183)	109.8	
C(64)-H(642)	0.975	C(5)-C(4)-C(10)	111.13(17)	C(4)-C(10)-C(25)	111.59(17)	C(10)-C(21)-O(22)	126.01(19)	
C(65)-O(66)	1.205(3)	C(7)-C(4)-C(10)	103.10(16)	C(21)-C(10)-C(25)	110.21(16)	C(10)-C(21)-O(23)	111.07(17)	
C(65)-O(67)	1.352(2)	C(4)-C(5)-C(6)	104.20(18)	C(9)-C(11)-C(12)	105.64(17)	O(22)-C(21)-O(23)	122.87(19)	
O(67)-C(68)	1.438(3)	C(4)-C(5)-H(51)	109.4	C(9)-C(11)-C(13)	114.86(18)	C(21)-O(23)-C(24)	113.97(17)	
C(68)-H(681)	0.958	C(6)-C(5)-H(51)	109.7	C(12)-C(11)-C(13)	107.99(18)	O(23)-C(24)-H(242)	107.3	
C(68)-H(682)	0.970	C(4)-C(5)-H(52)	112.4	C(9)-C(11)-C(14)	111.92(18)	O(23)-C(24)-H(241)	109.2	
C(68)-H(683)	0.958	C(6)-C(5)-H(52)	113.2	C(12)-C(11)-C(14)	107.50(19)	H(242)-C(24)-H(241)	110.6	
C(71)-O(72)	1.200(3)	H(51)-C(5)-H(52)	107.9	C(13)-C(11)-C(14)	108.58(18)	O(23)-C(24)-H(243)	110.8	
C(71)-O(73)	1.345(3)	C(5)-C(6)-C(2)	104.69(17)	C(11)-C(12)-H(122)	109.3	H(242)-C(24)-H(243)	110.3	

H(241)-C(24)-H(243)	108.5	C(55)-C(56)-H(562)	111.1	C(61)-C(62)-H(621)	112.4	O(67)-C(68)-H(683)	109.1
C(10)-C(25)-O(26)	124.88(18)	C(52)-C(56)-H(562)	110.4	H(622)-C(62)-H(621)	108.7	H(681)-C(68)-H(683)	110.8
C(10)-C(25)-O(27)	111.57(17)	C(55)-C(56)-H(561)	109.3	C(61)-C(62)-H(623)	110.7	H(682)-C(68)-H(683)	109.7
O(26)-C(25)-O(27)	123.54(19)	C(52)-C(56)-H(561)	111.3	H(622)-C(62)-H(623)	106.7	C(60)-C(71)-O(72)	125.62(19)
O(27)-C(28)-H(282)	108.9	H(562)-C(56)-H(561)	109.9	H(621)-C(62)-H(623)	109.2	C(60)-C(71)-O(73)	111.42(18)
O(27)-C(28)-H(281)	110.4	C(54)-C(57)-C(58)	105.47(17)	C(61)-C(63)-H(631)	109.7	O(72)-C(71)-O(73)	122.83(19)
H(282)-C(28)-H(281)	109.3	C(54)-C(57)-H(571)	109.0	C(61)-C(63)-H(633)	108.8	C(71)-O(73)-C(74)	114.94(17)
O(27)-C(28)-H(283)	110.2	C(58)-C(57)-H(571)	111.6	H(631)-C(63)-H(633)	108.2	O(73)-C(74)-H(742)	107.2
H(282)-C(28)-H(283)	109.3	C(54)-C(57)-H(572)	110.1	C(61)-C(63)-H(632)	111.3	O(73)-C(74)-H(741)	109.9
H(281)-C(28)-H(283)	108.7	C(58)-C(57)-H(572)	112.4	H(631)-C(63)-H(632)	108.6	H(742)-C(74)-H(741)	109.3
C(28)-O(27)-C(25)	115.65(16)	H(571)-C(57)-H(572)	108.2	H(633)-C(63)-H(632)	110.2	O(73)-C(74)-H(743)	110.3
C(52)-C(51)-H(511)	121.2	C(57)-C(58)-C(59)	108.15(17)	C(61)-C(64)-H(641)	109.3	H(742)-C(74)-H(743)	110.6
C(52)-C(51)-H(512)	118.6	C(57)-C(58)-H(582)	109.2	C(61)-C(64)-H(643)	111.6	H(741)-C(74)-H(743)	109.5
H(511)-C(51)-H(512)	120.2	C(59)-C(58)-H(582)	111.0	H(641)-C(64)-H(643)	107.7	C(60)-C(75)-O(76)	124.04(18)
C(51)-C(52)-C(53)	125.5(2)	C(57)-C(58)-H(581)	110.9	C(61)-C(64)-H(642)	111.6	C(60)-C(75)-O(77)	112.55(17)
C(51)-C(52)-C(56)	123.7(2)	C(59)-C(58)-H(581)	110.2	H(641)-C(64)-H(642)	107.4	O(76)-C(75)-O(77)	123.40(19)
C(53)-C(52)-C(56)	108.83(17)	H(582)-C(58)-H(581)	107.3	H(643)-C(64)-H(642)	109.0	C(75)-O(77)-C(78)	115.30(17)
C(52)-C(53)-C(54)	103.62(16)	C(58)-C(59)-C(60)	105.11(16)	C(53)-C(65)-O(66)	126.00(19)	O(77)-C(78)-H(782)	108.9
C(52)-C(53)-C(65)	111.27(17)	C(58)-C(59)-C(61)	113.40(17)	C(53)-C(65)-O(67)	110.86(17)	O(77)-C(78)-H(781)	109.4
C(54)-C(53)-C(65)	117.97(17)	C(60)-C(59)-C(61)	121.82(16)	O(66)-C(65)-O(67)	123.1(2)	H(782)-C(78)-H(781)	109.4
C(52)-C(53)-H(531)	108.5	C(58)-C(59)-H(591)	107.5	C(65)-O(67)-C(68)	114.77(17)	O(77)-C(78)-H(783)	111.5
C(54)-C(53)-H(531)	107.2	C(60)-C(59)-H(591)	105.1	O(67)-C(68)-H(681)	108.1	H(782)-C(78)-H(783)	108.4
C(65)-C(53)-H(531)	107.9	C(61)-C(59)-H(591)	102.9	O(67)-C(68)-H(682)	109.2	H(781)-C(78)-H(783)	109.2
C(53)-C(54)-C(55)	100.63(16)	C(59)-C(60)-C(54)	101.62(15)	H(681)-C(68)-H(682)	109.9		
C(53)-C(54)-C(57)	113.96(17)	C(59)-C(60)-C(71)	111.04(17)				
C(55)-C(54)-C(57)	109.47(17)	C(54)-C(60)-C(71)	109.84(16)				
C(53)-C(54)-C(60)	118.43(16)	C(59)-C(60)-C(75)	111.92(16)				
C(55)-C(54)-C(60)	111.07(17)	C(54)-C(60)-C(75)	110.75(16)				
C(57)-C(54)-C(60)	103.30(15)	C(71)-C(60)-C(75)	111.28(16)				
C(54)-C(55)-C(56)	104.49(17)	C(59)-C(61)-C(62)	114.54(19)				
C(54)-C(55)-H(551)	108.8	C(59)-C(61)-C(63)	111.48(18)				
C(56)-C(55)-H(551)	109.4	C(62)-C(61)-C(63)	109.19(19)				
C(54)-C(55)-H(552)	112.9	C(59)-C(61)-C(64)	105.92(16)				
C(56)-C(55)-H(552)	111.2	C(62)-C(61)-C(64)	107.71(18)				
H(551)-C(55)-H(552)	109.9	C(63)-C(61)-C(64)	107.67(19)				
C(55)-C(56)-C(52)	104.86(17)	C(61)-C(62)-H(622)	109.0				

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7544. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	38(1)	49(1)	39(1)	-6(1)	14(1)	-9(1)
C(2)	32(1)	41(1)	25(1)	-8(1)	4(1)	-14(1)
C(3)	25(1)	40(1)	21(1)	-9(1)	2(1)	-9(1)
C(4)	27(1)	36(1)	21(1)	-6(1)	0(1)	-8(1)
C(5)	34(1)	38(1)	26(1)	-4(1)	5(1)	-9(1)
C(6)	38(1)	43(1)	27(1)	-4(1)	7(1)	-11(1)
C(7)	31(1)	42(1)	21(1)	-7(1)	0(1)	-10(1)
C(8)	29(1)	54(1)	25(1)	-10(1)	-2(1)	-8(1)
C(9)	27(1)	38(1)	23(1)	-4(1)	0(1)	-8(1)
C(10)	27(1)	35(1)	21(1)	-5(1)	0(1)	-11(1)
C(11)	25(1)	41(1)	26(1)	-6(1)	1(1)	-7(1)
C(12)	28(1)	48(1)	36(1)	-3(1)	-1(1)	-7(1)
C(13)	30(1)	47(1)	35(1)	-4(1)	2(1)	-12(1)
C(14)	32(1)	55(1)	33(1)	-15(1)	7(1)	-8(1)
C(15)	25(1)	41(1)	21(1)	-7(1)	2(1)	-8(1)
O(16)	43(1)	40(1)	24(1)	-10(1)	1(1)	-12(1)
O(17)	33(1)	40(1)	22(1)	-5(1)	-4(1)	-9(1)
C(18)	39(1)	40(1)	28(1)	-5(1)	-3(1)	-7(1)
C(21)	28(1)	36(1)	20(1)	-5(1)	2(1)	-11(1)
O(22)	39(1)	35(1)	39(1)	-10(1)	-2(1)	-8(1)
O(23)	28(1)	43(1)	27(1)	-12(1)	-1(1)	-11(1)
C(24)	37(1)	53(1)	34(1)	-19(1)	0(1)	-18(1)
C(25)	21(1)	36(1)	24(1)	-6(1)	1(1)	-9(1)
O(26)	35(1)	34(1)	28(1)	-7(1)	6(1)	-11(1)
C(28)	40(1)	40(1)	24(1)	0(1)	-1(1)	-15(1)
O(27)	35(1)	36(1)	21(1)	-4(1)	2(1)	-12(1)
C(51)	40(1)	46(1)	39(1)	-7(1)	-10(1)	-16(1)
C(52)	29(1)	40(1)	26(1)	-9(1)	-3(1)	-8(1)
C(53)	26(1)	37(1)	21(1)	-8(1)	2(1)	-9(1)
C(54)	28(1)	35(1)	19(1)	-5(1)	0(1)	-11(1)
C(55)	32(1)	38(1)	26(1)	-4(1)	-5(1)	-12(1)
C(56)	37(1)	46(1)	29(1)	-4(1)	-9(1)	-14(1)
C(57)	32(1)	41(1)	21(1)	-9(1)	3(1)	-12(1)
C(58)	33(1)	57(1)	26(1)	-14(1)	6(1)	-17(1)
C(59)	27(1)	38(1)	21(1)	-4(1)	1(1)	-10(1)
C(60)	25(1)	36(1)	20(1)	-8(1)	0(1)	-8(1)
C(61)	27(1)	43(1)	25(1)	-6(1)	-1(1)	-12(1)
C(62)	30(1)	50(1)	38(1)	-1(1)	-1(1)	-11(1)
C(63)	37(1)	61(2)	31(1)	-17(1)	-1(1)	-18(1)
C(64)	28(1)	47(1)	35(1)	-7(1)	1(1)	-14(1)
C(65)	28(1)	39(1)	21(1)	-7(1)	1(1)	-12(1)
O(66)	42(1)	39(1)	25(1)	-10(1)	2(1)	-8(1)
O(67)	34(1)	39(1)	24(1)	-4(1)	5(1)	-10(1)
C(68)	45(1)	38(1)	29(1)	-2(1)	5(1)	-12(1)
C(71)	26(1)	38(1)	23(1)	-7(1)	-2(1)	-7(1)
O(72)	38(1)	36(1)	41(1)	-12(1)	5(1)	-10(1)
O(73)	28(1)	41(1)	27(1)	-11(1)	5(1)	-8(1)
C(74)	33(1)	49(1)	35(1)	-18(1)	9(1)	-8(1)
C(75)	23(1)	36(1)	23(1)	-6(1)	1(1)	-9(1)
O(76)	33(1)	37(1)	28(1)	-8(1)	-3(1)	-5(1)
O(77)	35(1)	39(1)	19(1)	-5(1)	-1(1)	-5(1)
C(78)	38(1)	43(1)	24(1)	-2(1)	0(1)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7544.

	x	y	z	U(eq)
H(11)	11054	7276	1340	52
H(12)	11137	6229	2040	51
H(31)	9213	7164	3366	34
H(51)	7715	9047	2742	38
H(52)	6363	9168	2107	38
H(62)	9056	8985	1568	43
H(61)	7972	8421	1191	43
H(71)	6255	7392	1703	38
H(72)	6142	6467	2463	36
H(82)	4043	8377	1981	44
H(81)	3756	7294	2486	43
H(91)	4434	8949	3085	32
H(122)	780	8831	3513	57
H(121)	1846	9535	3030	57
H(123)	1605	8541	2706	58
H(131)	1749	7085	4265	55
H(133)	3456	6632	4502	56
H(132)	2809	6672	3612	55
H(141)	2173	8643	4831	58
H(143)	3247	9341	4362	59
H(142)	3946	8243	4902	59
H(181)	10220	4074	4694	55
H(182)	10317	3924	3772	55
H(183)	8762	4117	4189	54
H(242)	9585	8240	5193	58
H(241)	8692	9287	4626	58
H(243)	7929	8747	5389	58
H(282)	6315	5857	6154	52
H(281)	7135	5236	5525	51
H(283)	5390	5448	5543	52
H(511)	3152	6078	7189	48
H(512)	2680	7053	6392	49
H(531)	4538	7086	8418	32
H(551)	4802	8961	7723	38
H(552)	6068	9086	7042	38
H(562)	3502	8811	6604	45
H(561)	4980	8265	6208	45
H(571)	7995	6392	7478	36
H(572)	7340	7302	6707	37
H(582)	9904	7197	7514	45
H(581)	9024	8247	6951	44
H(591)	8156	8934	8009	32
H(622)	11948	7152	9275	59
H(621)	10500	6696	9543	60
H(623)	11169	6677	8649	60
H(631)	10520	8777	9730	60
H(633)	9088	9476	9205	61
H(632)	8973	8406	9839	60
H(641)	11874	8847	8431	53
H(643)	10446	9494	7882	53
H(642)	11357	8428	7682	53
H(681)	5350	3964	9725	57
H(682)	6856	4018	9248	56
H(683)	5439	3843	8793	57
H(742)	3389	8339	10172	56
H(741)	4691	8909	10319	56
H(743)	3596	9362	9536	56
H(782)	8120	5922	11171	55
H(781)	9320	5523	10558	55
H(783)	7725	5266	10554	55

Table 6. Hydrogen bonds for 7544 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(31)...O(23)	0.96	2.41	3.101(3)	128
C(7)-H(72)...O(16)	0.97	2.49	3.117(3)	122
C(14)-H(142)...O(27)	0.96	2.54	3.336(3)	141
C(18)-H(181)...O(17)#1	0.95	2.60	3.419(3)	145
C(28)-H(282)...O(66)	0.95	2.53	3.382(3)	149
C(28)-H(283)...O(26)#2	0.96	2.54	3.419(3)	152
C(53)-H(531)...O(73)	0.97	2.45	3.159(3)	129
C(57)-H(571)...O(66)	0.97	2.43	3.092(3)	125
C(62)-H(621)...O(77)	0.98	2.58	3.343(3)	135
C(78)-H(782)...O(16)#3	0.97	2.44	3.284(3)	146
C(78)-H(781)...O(76)#4	0.95	2.58	3.450(3)	152

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+1,-z+1 #2 -x+1,-y+1,-z+1 #3 x,y,z+1

#4 -x+2,-y+1,-z+2

Dimethyl (2*S,3a*R**,5a*S**,8a*S**)-2-(*tert*-butyl)-5,6-dioxohexahydro-5*H*-dicyclopenta[*b,c*]furan-1,1(2*H*)-dicarboxylate, 3.217**

Table 1. Crystal data and structure refinement for 7633.

Identification code	7633
Empirical formula	C18 H24 O7
Formula weight	352.38
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 11.44610(10) Å α= 90°. b = 10.29590(10) Å β= 92.0781(12)°. c = 15.0471(2) Å γ = 90°.
Volume	1772.10(3) Å^3
Z	4
Density (calculated)	1.321 Mg/m^3
Absorption coefficient	0.849 mm^{-1}
F(000)	752
Crystal size	0.26 x 0.23 x 0.15 mm^3
Theta range for data collection	3.864 to 76.425°.
Index ranges	-14<=h<=12, -12<=k<=12, -18<=l<=18
Reflections collected	21497
Independent reflections	3701 [R(int) = 0.025]
Completeness to theta = 74.897°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.88 and 0.78
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3701 / 0 / 227
Goodness-of-fit on F^2	1.0024
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0875
R indices (all data)	R1 = 0.0353, wR2 = 0.0892
Extinction coefficient	20(4)
Largest diff. peak and hole	0.35 and -0.25 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 7633. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1922(1)	870(1)	7433(1)	34
C(2)	1710(1)	2010(1)	7380(1)	24
O(3)	1474(1)	2732(1)	8089(1)	25
C(4)	1189(1)	4071(1)	7857(1)	21
C(5)	2058(1)	4957(1)	8336(1)	23
C(6)	3072(1)	5118(1)	7701(1)	20
C(7)	2411(1)	5231(1)	6771(1)	18
C(8)	1370(1)	4224(1)	6839(1)	19
C(9)	246(1)	4597(1)	6286(1)	23
C(10)	-349(1)	3315(1)	6037(1)	31
C(11)	638(1)	2377(1)	5931(1)	34
C(12)	1665(1)	2830(1)	6545(1)	22
O(13)	674(1)	1437(1)	5463(1)	66
C(15)	4010(1)	6137(1)	8017(1)	26
C(16)	4919(1)	6399(1)	7315(1)	35
C(17)	3494(1)	7441(1)	8302(1)	34
C(18)	4662(1)	5546(1)	8832(1)	39
C(21)	1914(1)	6599(1)	6636(1)	20
O(22)	1097(1)	7009(1)	7036(1)	26
O(23)	2499(1)	7290(1)	6052(1)	26
C(24)	2076(1)	8610(1)	5900(1)	35
C(26)	3144(1)	4787(1)	6000(1)	19
O(27)	4084(1)	4270(1)	6079(1)	28
O(28)	2555(1)	4913(1)	5223(1)	23
C(29)	3149(1)	4416(1)	4457(1)	32

Table 3. Bond lengths [Å] and angles [°] for 7633.

O(1)-C(2)	1.2003(14)	C(17)-H(172)	0.994		C(5)-C(6)-C(7)	102.24(7)	C(11)-C(12)-H(121)	110.4	
C(2)-O(3)	1.3355(13)	C(17)-H(171)	0.993		C(5)-C(6)-C(15)	114.08(8)	C(8)-C(12)-H(121)	116.5	
C(2)-C(12)	1.5136(14)	C(18)-H(183)	0.986		C(7)-C(6)-C(15)	121.67(8)	C(2)-C(12)-H(121)	107.5	
O(3)-C(4)	1.4569(12)	C(18)-H(182)	0.986		C(5)-C(6)-H(61)	108.0	C(6)-C(15)-C(16)	112.56(8)	
C(4)-C(5)	1.5133(14)	C(18)-H(181)	0.977		C(7)-C(6)-H(61)	103.2	C(6)-C(15)-C(17)	113.89(8)	
C(4)-C(8)	1.5605(13)	C(21)-O(22)	1.2063(12)		C(15)-C(6)-H(61)	106.6	C(16)-C(15)-C(17)	108.45(10)	
C(4)-H(41)	0.984	C(21)-O(23)	1.3306(12)		C(6)-C(7)-C(8)	103.49(7)	C(6)-C(15)-C(18)	106.58(9)	
C(5)-C(6)	1.5390(13)	O(23)-C(24)	1.4577(13)		C(6)-C(7)-C(21)	110.59(7)	C(16)-C(15)-C(18)	107.32(9)	
C(5)-H(52)	0.978	C(24)-H(243)	0.966		C(8)-C(7)-C(21)	109.46(7)	C(17)-C(15)-C(18)	107.7(1)	
C(5)-H(51)	0.978	C(24)-H(242)	0.948		C(6)-C(7)-C(26)	113.26(7)	C(15)-C(16)-H(163)	107.1	
C(6)-C(7)	1.5701(12)	C(24)-H(241)	0.971		C(21)-C(7)-C(26)	106.73(7)	C(15)-C(16)-H(162)	110.8	
C(6)-C(15)	1.5636(13)	C(26)-O(27)	1.2027(12)		C(7)-C(8)-C(4)	112.77(8)	H(163)-C(16)-H(162)	108.3	
C(6)-H(61)	0.979	C(26)-O(28)	1.3345(12)		C(7)-C(8)-C(9)	104.82(7)	C(15)-C(16)-H(161)	112.0	
C(7)-C(8)	1.5855(12)	O(28)-C(29)	1.4521(12)		C(4)-C(8)-C(9)	114.40(8)	H(163)-C(16)-H(161)	109.7	
C(7)-C(21)	1.5302(13)	C(29)-H(293)	0.957		C(4)-C(8)-C(12)	114.45(8)	H(162)-C(16)-H(161)	108.8	
C(7)-C(26)	1.5258(12)	C(29)-H(292)	0.969		C(7)-C(8)-C(12)	103.02(7)	C(15)-C(17)-H(173)	109.1	
C(8)-C(9)	1.5545(13)	C(29)-H(291)	0.957		C(9)-C(8)-C(12)	114.63(7)	C(15)-C(17)-H(172)	111.7	
C(8)-C(12)	1.5427(13)				C(8)-C(9)-C(10)	105.19(8)	H(173)-C(17)-H(172)	108.1	
C(9)-C(10)	1.5257(15)	O(1)-C(2)-O(3)	122.54(10)		C(8)-C(9)-H(92)	105.76(8)	C(15)-C(17)-H(171)	110.4	
C(9)-H(92)	0.973	O(1)-C(2)-C(12)	126.94(10)		C(10)-C(9)-H(92)	110.7	H(173)-C(17)-H(171)	107.8	
C(9)-H(91)	0.973	O(3)-C(2)-C(12)	110.52(8)		C(8)-C(9)-H(91)	112.8	H(172)-C(17)-H(171)	109.7	
C(10)-C(11)	1.4997(18)	C(2)-O(3)-C(4)	112.65(7)		C(10)-C(9)-H(91)	109.3	C(15)-C(18)-H(183)	110.3	
C(10)-H(102)	0.972	O(3)-C(4)-C(5)	108.56(8)		H(92)-C(9)-H(91)	109.6	C(15)-C(18)-H(182)	112.1	
C(10)-H(101)	0.969	O(3)-C(4)-C(8)	107.15(8)		C(9)-C(10)-C(11)	108.7	H(183)-C(18)-H(182)	108.1	
C(11)-C(12)	1.5414(15)	C(5)-C(4)-C(8)	107.40(8)		C(9)-C(10)-H(102)	104.59(9)	C(15)-C(18)-H(181)	111.0	
C(11)-O(13)	1.1987(16)	O(3)-C(4)-H(41)	107.3		C(9)-C(10)-H(101)	110.5	H(183)-C(18)-H(181)	108.7	
C(12)-H(121)	0.981	C(5)-C(4)-H(41)	113.6		C(11)-C(10)-H(102)	105.7	H(182)-C(18)-H(181)	106.4	
C(15)-C(16)	1.5332(15)	C(8)-C(4)-H(41)	112.6		C(11)-C(10)-H(101)	114.1	C(7)-C(21)-O(22)	123.17(9)	
C(15)-C(17)	1.5338(16)	C(4)-C(5)-C(6)	105.41(8)		H(102)-C(10)-H(101)	111.1	C(7)-C(21)-O(23)	112.71(8)	
C(15)-C(18)	1.5371(16)	C(4)-C(5)-H(52)	109.8		C(10)-C(11)-C(12)	110.4	O(22)-C(21)-O(23)	124.09(9)	
C(16)-H(163)	0.973	C(6)-C(5)-H(52)	113.4		C(10)-C(11)-O(13)	107.60(9)	C(21)-O(23)-C(24)	115.46(8)	
C(16)-H(162)	0.974	C(4)-C(5)-H(51)	109.2		C(12)-C(11)-O(13)	128.69(12)	O(23)-C(24)-H(243)	105.8	
C(16)-H(161)	0.987	C(6)-C(5)-H(51)	110.6		C(11)-C(12)-C(8)	123.71(12)	O(23)-C(24)-H(242)	109.6	
C(17)-H(173)	0.969	H(52)-C(5)-H(51)	108.4		C(11)-C(12)-C(2)	106.46(8)	H(243)-C(24)-H(242)	110.3	
					C(8)-C(12)-C(2)	109.33(8)	O(23)-C(24)-H(241)	109.7	
						106.42(8)	H(243)-C(24)-H(241)	110.0	

H(242)-C(24)-H(241)	111.3	O(28)-C(29)-H(292)	109.6
C(7)-C(26)-O(27)	124.89(9)	H(293)-C(29)-H(292)	111.7
C(7)-C(26)-O(28)	111.31(8)	O(28)-C(29)-H(291)	109.3
O(27)-C(26)-O(28)	123.42(9)	H(293)-C(29)-H(291)	110.4
C(26)-O(28)-C(29)	115.20(8)	H(292)-C(29)-H(291)	109.1
O(28)-C(29)-H(293)	106.7		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7633. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	45(1)	23(1)	33(1)	3(1)	-5(1)	3(1)
C(2)	22(1)	23(1)	25(1)	1(1)	-3(1)	-3(1)
O(3)	31(1)	25(1)	21(1)	3(1)	1(1)	-2(1)
C(4)	21(1)	24(1)	20(1)	1(1)	3(1)	-1(1)
C(5)	25(1)	27(1)	18(1)	-2(1)	2(1)	-1(1)
C(6)	19(1)	23(1)	18(1)	-2(1)	-1(1)	1(1)
C(7)	15(1)	20(1)	18(1)	-1(1)	1(1)	0(1)
C(8)	17(1)	20(1)	19(1)	-1(1)	1(1)	-2(1)
C(9)	17(1)	28(1)	24(1)	1(1)	-2(1)	-2(1)
C(10)	30(1)	35(1)	28(1)	7(1)	-9(1)	-13(1)
C(11)	50(1)	24(1)	27(1)	2(1)	-12(1)	-8(1)
C(12)	26(1)	20(1)	21(1)	-1(1)	2(1)	-2(1)
O(13)	99(1)	35(1)	61(1)	-20(1)	-42(1)	8(1)
C(15)	19(1)	32(1)	26(1)	-6(1)	-3(1)	-2(1)
C(16)	22(1)	45(1)	38(1)	-8(1)	2(1)	-10(1)
C(17)	27(1)	32(1)	44(1)	-15(1)	-4(1)	-5(1)
C(18)	30(1)	52(1)	33(1)	-4(1)	-12(1)	-1(1)
C(21)	19(1)	21(1)	20(1)	-3(1)	-2(1)	-1(1)
O(22)	22(1)	26(1)	30(1)	-4(1)	3(1)	4(1)
O(23)	31(1)	19(1)	28(1)	1(1)	6(1)	-1(1)
C(24)	50(1)	19(1)	35(1)	2(1)	3(1)	1(1)
C(26)	18(1)	19(1)	21(1)	-1(1)	2(1)	-2(1)
O(27)	21(1)	38(1)	27(1)	-3(1)	2(1)	8(1)
O(28)	23(1)	30(1)	17(1)	-3(1)	1(1)	2(1)
C(29)	37(1)	39(1)	20(1)	-6(1)	6(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7633.

	x	y	z	U(eq)
H(41)	374	4222	8016	24
H(52)	2299	4576	8910	29
H(51)	1686	5794	8445	27
H(61)	3476	4283	7664	23
H(92)	-248	5166	6627	29
H(91)	464	5049	5749	26
H(102)	-788	2989	6531	38
H(101)	-844	3357	5502	38
H(121)	2409	2713	6251	29
H(163)	5481	7013	7574	51
H(162)	5333	5605	7170	52
H(161)	4561	6765	6763	51
H(173)	4122	8001	8518	51
H(172)	2936	7331	8788	52
H(171)	3096	7878	7787	50
H(183)	5290	6135	9049	57
H(182)	4137	5385	9326	57
H(181)	5008	4709	8686	57
H(243)	2589	8987	5474	53
H(242)	2123	9082	6441	50
H(241)	1280	8586	5654	51
H(293)	2664	4620	3944	45
H(292)	3913	4816	4428	46
H(291)	3242	3496	4515	46

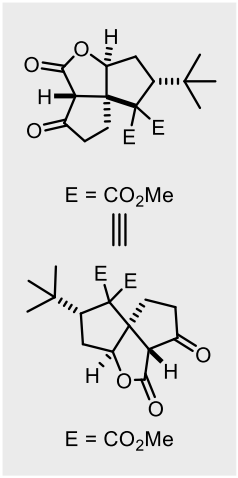
Table 6. Hydrogen bonds for 7633 [Å and °].

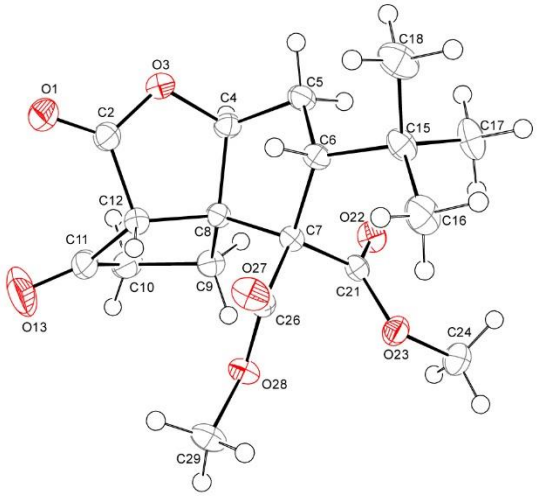
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(9)-H(92)...O(1)#1	0.97	2.53	3.4547(15)	159
C(9)-H(91)...O(28)	0.97	2.55	3.1558(15)	120
C(10)-H(102)...O(22)#2	0.97	2.42	3.3357(15)	157
C(12)-H(121)...O(27)	0.98	2.52	3.2395(15)	130
C(17)-H(173)...O(27)#3	0.97	2.49	3.4512(15)	172
C(17)-H(171)...C(21)	0.99	2.53	3.1592(15)	121
C(24)-H(242)...O(1)#4	0.95	2.39	3.2855(15)	158
C(29)-H(293)...O(1)#5	0.96	2.45	3.3207(15)	151

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+3/2 #2 -x,y-1/2,-z+3/2 #3 -x+1,y+1/2,-z+3/2

#4 x,y+1,z #5 x,-y+1/2,z-1/2





Dimethyl (*R*, *E*)-2-(1-(2-(2,4-dinitrophenyl)hydrazineylidene)-4,4-dimethylpentan-3-yl)malonate, (*R*)-3.263

Crystal Data

a = 6.75530(10) Å	α = 99.6009(17)°		
b = 8.4912(2) Å	β = 96.3344(17)°		
c = 17.9851(3) Å	γ = 90.4040(17)°		
Volume	1010.64(3) Å^3	Crystal Class	triclinic
Space group	P 1	Z =	2
Formula	$C_{18}H_{24}N_4O_8$	M_r	424.41
Cell determined from	29624 reflections	Cell θ range =	5 - 76°
Temperature	150K		
Shape	plate		
Colour	yellow	Size	0.05 × 0.20 × 0.30 mm
D_x	1.39 Mg m^{-3}	F000	448.000
μ	0.942 mm^{-1}		
Absorption correction	multi-scan		
T_{min}	0.76	T_{max}	0.95

Data Collection

Diffractometer	multi-scan		
Scan type	ω scans		
Reflections measured	42041		
Independent reflections	7959		
Rint	0.0236		
θ_{max}	76.3935		
h =	-8 → 7		
k =	-10 → 10		
l =	-22 → 22		

Refinement

$\Delta\rho_{min}$ =	-0.26 e Å^{-3}		
$\Delta\rho_{max}$ =	0.29 e Å^{-3}		
Reflections used	7958		
Cutoff: I >	-3.00σ(I)		
Parameters refined	550		
S =	0.98		
R-factor	0.043		
weighted R-factor	0.107		
Δ/σ_{max}	0.0006		

Flack parameter -0.06(4) — Parsons, Flack & Wagner (2013)

Refinement on F^2

$w = 1/[\sigma^2(F_{obs}^2) + (0.061 \times P)^2 + 0.505 \times P + 0.000 + 0.000 \times \sin\theta]$,
$P = 0.333 \times \max(F_{obs}^2, 0) + 0.667 \times F_{calc}^2$

Completeness to theta = 74.102° 99.5 %

Data / restraints / parameters 7958 / 11/ 550

Goodness-of-fit on F^2 0.9818

Parameters

Label	*x*	*y*	*z*	$U_{iso/equiv}$	Occupancy
O1	1.1927(2)	0.67943(19)	0.82838(9)	0.0274	1.0000
N2	1.3329(3)	0.6389(2)	0.79090(10)	0.0228	1.0000
O3	1.3436(3)	0.6736(2)	0.72797(10)	0.0383	1.0000
C4	1.4912(3)	0.5485(2)	0.82345(11)	0.0197	1.0000
C5	1.4884(3)	0.5030(2)	0.89597(11)	0.0197	1.0000
N6	1.3411(3)	0.5369(2)	0.94051(10)	0.0227	1.0000
N7	1.3538(3)	0.4797(2)	1.00886(10)	0.0234	1.0000
C8	1.2258(3)	0.5273(3)	1.05288(12)	0.0255	1.0000
C9	1.2383(3)	0.4738(3)	1.12856(12)	0.0224	1.0000
C10	1.3782(3)	0.5855(2)	1.18985(11)	0.0247	1.0000
C11	1.5203(3)	0.4875(2)	1.23734(11)	0.0225	1.0000
C12	1.4186(3)	0.3789(2)	1.28158(11)	0.0201	1.0000
O13	1.2739(2)	0.2956(2)	1.25894(9)	0.0292	1.0000
O14	1.5148(2)	0.39156(17)	1.35200(8)	0.0245	1.0000
C15	1.6580(3)	0.3947(3)	1.18584(12)	0.0288	1.0000
O16	1.7427(3)	0.4534(3)	1.14094(13)	0.0585	1.0000
O17	1.6771(3)	0.2445(2)	1.19598(9)	0.0321	1.0000
C18	1.6583(3)	0.4186(3)	0.92190(12)	0.0239	1.0000
C19	1.8082(3)	0.3785(3)	0.87833(12)	0.0252	1.0000
C20	1.8005(3)	0.4215(3)	0.80607(12)	0.0215	1.0000
C21	1.6456(3)	0.5073(2)	0.77916(12)	0.0197	1.0000
N22	1.9569(3)	0.3750(2)	0.75867(10)	0.0255	1.0000
O23	1.9386(3)	0.4023(3)	0.69378(10)	0.0415	1.0000
O24	2.1031(3)	0.3093(2)	0.78559(10)	0.0325	1.0000
O25	0.9434(2)	0.77422(19)	0.93120(9)	0.0258	1.0000

N26	0.8024(3)	0.8125(2)	0.96875(10)	0.0206	1.0000	H181	1.6651(3)	0.3917(3)	0.97025(12)	0.0293	1.0000	
O27	0.7913(3)	0.7733(2)	1.03064(9)	0.0328	1.0000	H191	1.9163(3)	0.3211(3)	0.89598(12)	0.0332	1.0000	
C28	0.6447(3)	0.9040(2)	0.93737(11)	0.0184	1.0000	H211	1.6395(3)	0.5395(2)	0.73060(12)	0.0253	1.0000	
C29	0.6430(3)	0.9492(2)	0.86429(11)	0.0182	1.0000	H321	1.0191(3)	0.8764(3)	0.72650(11)	0.0281	1.0000	
N30	0.7901(3)	0.9157(2)	0.81949(9)	0.0211	1.0000	H401	0.4626(3)	1.0619(3)	0.78984(12)	0.0287	1.0000	
N31	0.7695(3)	0.9658(2)	0.74951(10)	0.0222	1.0000	H411	0.2181(3)	1.1314(3)	0.86713(12)	0.0279	1.0000	
C32	0.9113(3)	0.9328(3)	0.70928(11)	0.0214	1.0000	H431	0.4998(3)	0.9132(2)	1.03030(11)	0.0240	1.0000	
C40	0.4741(3)	1.0337(3)	0.83922(12)	0.0225	1.0000	H241	1.1710(4)	0.8848(3)	0.48706(13)	0.0449	1.0000	
C41	0.3257(3)	1.0735(3)	0.88383(12)	0.0233	1.0000	H251	1.1090(4)	0.8209(3)	0.60407(12)	0.0365	1.0000	
C42	0.3377(3)	1.0312(2)	0.95586(12)	0.0211	1.0000	H31	1.7895(4)	0.0389(4)	1.15274(14)	0.0696	1.0000	
C43	0.4930(3)	0.9454(2)	0.98241(11)	0.0208	1.0000	H32	1.9475(4)	0.1847(4)	1.17164(14)	0.0680	1.0000	
N44	0.1807(3)	1.0759(2)	1.00391(10)	0.0249	1.0000	H33	1.7837(4)	0.1702(4)	1.09892(14)	0.0692	1.0000	
O45	0.0318(3)	1.1402(2)	0.97700(10)	0.0321	1.0000	H21	1.5281(4)	0.2904(3)	1.44372(12)	0.0467	1.0000	
O46	0.2019(3)	1.0476(3)	1.06872(11)	0.0440	1.0000	H22	1.3155(4)	0.3566(3)	1.41893(12)	0.0470	1.0000	
C23	0.9739(3)	1.0644(2)	0.47682(11)	0.0209	1.0000	H23	1.3874(4)	0.1991(3)	1.37444(12)	0.0469	1.0000	
C24	1.1063(4)	0.9614(3)	0.52190(13)	0.0339	1.0000	H221	0.9843(4)	1.1519(3)	0.31497(12)	0.0459	1.0000	
C25	1.0001(4)	0.8689(3)	0.57427(12)	0.0309	1.0000	H222	0.8914(4)	1.2520(3)	0.38267(12)	0.0459	1.0000	
O5	0.8398(3)	1.1439(2)	0.49909(9)	0.0297	1.0000	H223	0.7845(4)	1.0961(3)	0.33980(12)	0.0463	1.0000	
O6	1.0292(2)	1.05508(18)	0.40680(8)	0.0264	1.0000	H271	1.0799(6)	0.8965(4)	1.21601(19)	0.1012	1.0000	
C3	1.8140(4)	0.1509(4)	1.15042(14)	0.0447	1.0000	H272	1.1994(6)	0.8349(4)	1.14770(19)	0.1012	1.0000	
C2	1.4289(4)	0.3008(3)	1.40203(12)	0.0305	1.0000	H273	1.0152(6)	0.7344(4)	1.16232(19)	0.1009	1.0000	
C22	0.9138(4)	1.1467(3)	0.35746(12)	0.0316	1.0000	H11	0.9731(3)	1.0899(2)	0.64323(11)	0.0240	1.0000	
C27	1.1271(6)	0.8026(4)	1.18597(19)	0.0670	1.0000	H12	0.7646(3)	1.0030(2)	0.61599(11)	0.0254	1.0000	
C36	1.2722(5)	0.7197(3)	1.23900(15)	0.0465	1.0000	H172	0.6655(10)	0.5716(4)	0.56203(18)	0.1677	1.0000	
O2	1.2798(3)	1.2087(3)	0.55894(10)	0.0516	1.0000	H171	0.8435(10)	0.6196(4)	0.62547(18)	0.1680	1.0000	
C1	0.9031(3)	0.9851(2)	0.63370(11)	0.0198	1.0000	H173	0.6691(10)	0.7404(4)	0.61264(18)	0.1678	1.0000	
C17	0.7500(10)	0.6585(4)	0.58814(18)	0.1068	1.0000	H492	0.9185(14)	0.5004(5)	0.4750(3)	0.2379	1.0000	
C33	0.8651(7)	0.7281(3)	0.53122(15)	0.0689	1.0000	H491	1.0976(14)	0.5730(5)	0.5340(3)	0.2379	1.0000	
C13	1.2755(4)	1.0596(5)	0.56978(19)	0.0629	1.0000	H493	1.0582(14)	0.6331(5)	0.4546(3)	0.2380	1.0000	
C49	0.9968(14)	0.5969(5)	0.4950(3)	0.1563	1.0000	H162	0.6079(8)	0.6964(5)	0.45480(17)	0.1360	1.0000	
C16	0.7119(8)	0.7752(5)	0.46988(17)	0.0895	1.0000	H161	0.6536(8)	0.8752(5)	0.49072(17)	0.1361	1.0000	
C14	1.1498(6)	0.6598(4)	1.29582(15)	0.0640	1.0000	H163	0.7775(8)	0.7873(5)	0.42629(17)	0.1356	1.0000	
O9	1.3895(4)	1.0099(7)	0.6134(3)	0.1707	1.0000	H142	1.0647(6)	0.7415(4)	1.31751(15)	0.0968	1.0000	
C26	1.4294(6)	1.3124(8)	0.60794(19)	0.1095	1.0000	H141	1.2384(6)	0.6238(4)	1.33457(15)	0.0968	1.0000	
C34	1.4277(8)	0.8437(4)	1.2807(3)	0.1000	1.0000	H143	1.0670(6)	0.5682(4)	1.26819(15)	0.0977	1.0000	
H81	1.1246(3)	0.5960(3)	1.03890(12)	0.0338	1.0000	H262	1.4000(6)	1.4222(8)	0.60621(19)	0.1783	1.0000	
H92	1.1074(3)	0.4765(3)	1.14570(12)	0.0292	1.0000	H261	1.4272(6)	1.2937(8)	0.65799(19)	0.1778	1.0000	
H91	1.2884(3)	0.3647(3)	1.12298(12)	0.0279	1.0000	H263	1.5583(6)	1.2885(8)	0.59231(19)	0.1776	1.0000	
H101	1.4658(3)	0.6382(2)	1.16015(11)	0.0297	1.0000	H342	1.3647(8)	0.9302(4)	1.3104(3)	0.1528	1.0000	
H111	1.6094(3)	0.5608(2)	1.27268(11)	0.0284	1.0000	H341	1.5238(8)	0.7943(4)	1.3135(3)	0.1530	1.0000	

H343	1.4979(8)	0.8894(4)	1.2446(3)	0.1534	1.0000
H61	1.241(3)	0.595(3)	0.9279(11)	0.0278(19)	1.0000
H301	0.896(3)	0.871(3)	0.8358(11)	0.0266(19)	1.0000

Thermal Parameters

Label	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0262(9)	0.0335(9)	0.0255(7)	0.0096(6)	0.0082(6)	0.0098(7)
N2	0.0253(10)	0.0236(9)	0.0211(8)	0.0059(7)	0.0061(7)	0.0062(7)
O3	0.0430(11)	0.0528(11)	0.0273(8)	0.0237(8)	0.0125(7)	0.0220(8)
C4	0.0224(11)	0.0185(9)	0.0182(9)	0.0040(7)	0.0006(8)	0.0006(8)
C5	0.0208(10)	0.0195(9)	0.0187(9)	0.0029(7)	0.0024(8)	-0.0000(8)
N6	0.0239(10)	0.0273(9)	0.0187(8)	0.0078(7)	0.0034(7)	0.0051(7)
N7	0.0248(10)	0.0270(9)	0.0194(8)	0.0065(7)	0.0031(7)	0.0027(7)
C8	0.0232(11)	0.0348(12)	0.0203(10)	0.0088(8)	0.0031(8)	0.0073(9)
C9	0.0189(10)	0.0297(10)	0.0202(9)	0.0079(8)	0.0039(8)	0.0023(8)
C10	0.0282(11)	0.0247(9)	0.0219(9)	0.0100(7)	-0.0032(8)	-0.0003(8)
C11	0.0201(10)	0.0267(9)	0.0217(9)	0.0092(7)	-0.0013(7)	-0.0018(7)
C12	0.0210(10)	0.0205(9)	0.0201(9)	0.0052(7)	0.0048(7)	0.0062(7)
O13	0.0270(9)	0.0357(8)	0.0259(7)	0.0096(6)	0.0009(6)	-0.0090(7)
O14	0.0263(8)	0.0278(7)	0.0207(6)	0.0094(5)	0.0006(5)	-0.0007(6)
C15	0.0163(10)	0.0462(12)	0.0270(10)	0.0164(9)	0.0009(8)	0.0020(9)
O16	0.0338(11)	0.0945(17)	0.0640(13)	0.0492(12)	0.0247(10)	0.0102(10)
O17	0.0293(9)	0.0398(8)	0.0284(8)	0.0046(6)	0.0092(6)	0.0101(7)
C18	0.0254(11)	0.0277(11)	0.0191(9)	0.0074(8)	-0.0006(8)	0.0003(8)
C19	0.0218(11)	0.0268(11)	0.0264(11)	0.0052(9)	-0.0010(9)	0.0048(8)
C20	0.0196(11)	0.0228(10)	0.0208(9)	0.0001(8)	0.0022(8)	-0.0002(8)
C21	0.0204(11)	0.0191(9)	0.0193(9)	0.0023(7)	0.0024(8)	-0.0009(7)
N22	0.0236(10)	0.0284(9)	0.0242(9)	0.0021(7)	0.0038(7)	0.0040(7)
O23	0.0397(11)	0.0617(12)	0.0273(9)	0.0134(8)	0.0125(7)	0.0221(9)
O24	0.0226(9)	0.0372(9)	0.0382(9)	0.0073(7)	0.0032(7)	0.0094(7)
O25	0.0233(8)	0.0327(8)	0.0236(7)	0.0079(6)	0.0075(6)	0.0116(6)
N26	0.0217(9)	0.0242(8)	0.0155(7)	0.0030(6)	0.0007(6)	0.0034(7)
O27	0.0328(9)	0.0503(10)	0.0196(7)	0.0158(7)	0.0060(6)	0.0158(8)
C28	0.0177(10)	0.0186(9)	0.0180(9)	0.0021(7)	0.0003(8)	0.0023(8)
C29	0.0184(10)	0.0185(9)	0.0172(9)	0.0019(7)	0.0019(7)	-0.0012(7)
N30	0.0201(9)	0.0290(9)	0.0160(8)	0.0073(7)	0.0038(7)	0.0070(7)
N31	0.0238(10)	0.0299(9)	0.0143(8)	0.0066(7)	0.0039(7)	0.0017(7)
C32	0.0202(10)	0.0255(10)	0.0196(9)	0.0073(8)	0.0016(8)	0.0052(8)
C40	0.0225(11)	0.0253(10)	0.0216(10)	0.0087(8)	0.0033(8)	0.0038(8)
C41	0.0213(11)	0.0230(10)	0.0269(10)	0.0072(8)	0.0040(8)	0.0039(8)
C42	0.0207(11)	0.0192(9)	0.0236(10)	0.0012(8)	0.0067(8)	0.0017(8)
C43	0.0243(11)	0.0216(10)	0.0158(9)	0.0019(7)	0.0019(8)	-0.0016(8)
N44	0.0244(10)	0.0235(9)	0.0276(9)	0.0030(7)	0.0082(8)	0.0036(7)
O45	0.0242(9)	0.0355(9)	0.0388(9)	0.0087(7)	0.0100(7)	0.0102(7)
O46	0.0476(12)	0.0607(12)	0.0308(9)	0.0164(8)	0.0212(8)	0.0238(9)
C23	0.0247(10)	0.0194(8)	0.0193(9)	0.0044(7)	0.0040(7)	-0.0014(7)
C24	0.0378(13)	0.0434(13)	0.0299(11)	0.0210(9)	0.0207(10)	0.0233(10)
C25	0.0514(15)	0.0253(10)	0.0216(10)	0.0114(8)	0.0162(9)	0.0152(9)
O5	0.0293(9)	0.0391(9)	0.0246(7)	0.0135(6)	0.0068(6)	0.0117(7)
O6	0.0331(8)	0.0297(7)	0.0189(6)	0.0088(5)	0.0065(6)	0.0041(6)
C3	0.0334(14)	0.0662(18)	0.0305(12)	-0.0059(11)	0.0068(10)	0.0188(12)
C2	0.0345(12)	0.0381(12)	0.0218(10)	0.0127(8)	0.0043(8)	-0.0002(9)
C22	0.0344(13)	0.0415(12)	0.0210(9)	0.0127(9)	0.0012(8)	0.0022(10)
C27	0.102(3)	0.0452(16)	0.0520(17)	0.0104(13)	-0.0054(17)	0.0457(18)
C36	0.071(2)	0.0260(12)	0.0350(13)	-0.0016(10)	-0.0156(13)	0.0199(12)
O2	0.0312(10)	0.0911(16)	0.0258(8)	-0.0045(9)	-0.0029(7)	-0.0132(9)
C1	0.0211(10)	0.0236(10)	0.0160(9)	0.0057(7)	0.0037(7)	0.0019(8)
C17	0.227(6)	0.056(2)	0.0365(15)	0.0065(14)	0.020(2)	-0.082(3)
C33	0.163(4)	0.0203(12)	0.0244(12)	0.0009(10)	0.0218(17)	-0.0179(17)
C13	0.0129(12)	0.131(3)	0.0637(19)	0.069(2)	0.0052(11)	-0.0010(14)
C49	0.381(12)	0.0361(19)	0.067(3)	0.0061(17)	0.091(5)	0.060(4)
C16	0.156(4)	0.074(2)	0.0326(14)	0.0119(15)	-0.0131(19)	-0.080(3)
C14	0.092(3)	0.070(2)	0.0287(13)	0.0006(12)	0.0102(14)	0.0576(19)
O9	0.0308(14)	0.303(6)	0.228(4)	0.230(5)	-0.046(2)	-0.039(2)
C26	0.059(2)	0.217(6)	0.0364(17)	-0.017(2)	0.0011(16)	-0.077(3)
C34	0.135(4)	0.0324(16)	0.104(3)	-0.0259(18)	-0.056(3)	0.011(2)

Distances

O1	N2	1.240(2)Å	N2	O3	1.225(2)Å
N2	C4	1.449(3)Å	C4	C5	1.423(3)Å
C4	C21	1.393(3)Å	C5	N6	1.348(3)Å
C5	C18	1.433(3)Å	N6	N7	1.390(2)Å
N6	H61	0.870(17)Å	N7	C8	1.260(3)Å
C8	C9	1.499(3)Å	C8	H81	0.942Å
C9	C10	1.554(3)Å	C9	H92	0.968Å
C9	H91	0.982Å	C10	C11	1.552(3)Å
C10	C36	1.552(3)Å	C10	H101	0.991Å
C11	C12	1.520(3)Å	C11	C15	1.517(3)Å

C11	H111	0.966Å	C12	O13	1.195(3)Å
C12	O14	1.345(2)Å	O14	C2	1.442(2)Å
C15	O16	1.208(3)Å	C15	O17	1.324(3)Å
O17	C3	1.455(3)Å	C18	C19	1.359(3)Å
C18	H181	0.932Å	C19	C20	1.403(3)Å
C19	H191	0.936Å	C20	C21	1.370(3)Å
C20	N22	1.446(3)Å	C21	H211	0.954Å
N22	O23	1.221(3)Å	N22	O24	1.230(2)Å
O25	N26	1.242(2)Å	N26	O27	1.224(2)Å
N26	C28	1.443(3)Å	C28	C29	1.428(3)Å
C28	C43	1.386(3)Å	C29	N30	1.350(3)Å
C29	C40	1.423(3)Å	N30	N31	1.387(2)Å
N30	H301	0.860(16)Å	N31	C32	1.268(3)Å
C32	C1	1.495(3)Å	C32	H321	0.927Å
C40	C41	1.362(3)Å	C40	H401	0.953Å
C41	C42	1.395(3)Å	C41	H411	0.931Å
C42	C43	1.370(3)Å	C42	N44	1.454(3)Å
C43	H431	0.943Å	N44	O45	1.238(3)Å
N44	O46	1.222(3)Å	C23	C24	1.520(3)Å
C23	O5	1.198(3)Å	C23	O6	1.343(2)Å
C24	C25	1.551(3)Å	C24	C13	1.508(4)Å
C24	H241	0.967Å	C25	C1	1.535(3)Å
C25	C33	1.543(4)Å	C25	H251	0.992Å
O6	C22	1.444(2)Å	C3	H31	0.973Å
C3	H32	0.962Å	C3	H33	0.967Å
C2	H21	0.965Å	C2	H22	0.955Å
C2	H23	0.946Å	C22	H221	0.951Å
C22	H222	0.954Å	C22	H223	0.968Å
C27	C36	1.547(4)Å	C27	H271	0.963Å
C27	H272	0.961Å	C27	H273	0.963Å
C36	C14	1.530(5)Å	C36	C34	1.523(5)Å
O2	C13	1.313(4)Å	O2	C26	1.451(4)Å
C1	H11	0.985Å	C1	H12	0.976Å
C17	C33	1.540(5)Å	C17	H172	0.954Å
C17	H171	0.970Å	C17	H173	0.966Å
C33	C49	1.535(6)Å	C33	C16	1.533(6)Å
C13	O9	1.170(4)Å	C49	H492	0.967Å
C49	H491	0.970Å	C49	H493	0.967Å
C16	H162	0.951Å	C16	H161	0.974Å
C16	H163	0.961Å	C14	H142	0.964Å
C14	H141	0.958Å	C14	H143	0.984Å
C26	H262	0.960Å	C26	H261	0.941Å
C26	H263	0.957Å	C34	H342	0.964Å
C34	H341	0.972Å	C34	H343	0.973Å

Angles

O1	N2	O3	122.64(18)°	O1	N2	C4	118.44(16)°
O3	N2	C4	118.92(18)°	N2	C4	C5	122.07(18)°
N2	C4	C21	115.99(17)°	C5	C4	C21	121.94(19)°
C4	C5	N6	124.42(19)°	C4	C5	C18	115.81(19)°
N6	C5	C18	119.76(18)°	C5	N6	N7	118.35(17)°
C5	N6	H61	121.8(11)°	N7	N6	H61	119.8(11)°
N6	N7	C8	116.85(18)°	N7	C8	C9	118.75(19)°
N7	C8	H81	120.878°	C9	C8	H81	120.364°
C8	C9	C10	111.91(18)°	C8	C9	H92	109.296°
C10	C9	H92	107.259°	C8	C9	H91	108.514°
C10	C9	H91	109.528°	H92	C9	H91	110.330°
C9	C10	C11	111.17(16)°	C9	C10	C36	115.06(19)°
C11	C10	C36	113.43(17)°	C9	C10	H101	104.043°
C11	C10	H101	104.981°	C36	C10	H101	107.090°
C10	C11	C12	115.39(17)°	C10	C11	C15	108.86(16)°
C12	C11	C15	111.29(16)°	C10	C11	H111	108.554°
C12	C11	H111	108.466°	C15	C11	H111	103.576°
C11	C12	O13	126.33(17)°	C11	C12	O14	109.61(16)°
O13	C12	O14	124.06(18)°	C12	O14	C2	115.89(16)°
C11	C15	O16	123.1(2)°	C11	C15	O17	113.06(17)°
O16	C15	O17	123.9(2)°	C15	O17	C3	115.7(2)°
C5	C18	C19	121.91(19)°	C5	C18	H181	118.304°
C19	C18	H181	119.788°	C18	C19	C20	120.0(2)°
C18	C19	H191	120.410°	C20	C19	H191	119.603°
C19	C20	C21	120.9(2)°	C19	C20	N22	120.13(19)°
C21	C20	N22	118.97(19)°	C4	C21	C20	119.38(19)°
C4	C21	H211	118.643°	C20	C21	H211	121.980°
C20	N22	O23	118.82(18)°	C20	N22	O24	118.44(18)°
O23	N22	O24	122.74(19)°	O25	N26	O27	122.34(17)°
O25	N26	C28	118.57(16)°	O27	N26	C28	119.08(17)°
N26	C28	C29	122.45(18)°	N26	C28	C43	115.95(17)°
C29	C28	C43	121.60(18)°	C28	C29	N30	123.65(18)°
C28	C29	C40	116.40(18)°	N30	C29	C40	119.95(17)°

C29	N30	N31	117.85(17)°	C29	N30	H301	120.1(11)°
N31	N30	H301	121.9(11)°	N30	N31	C32	115.93(17)°
N31	C32	C1	119.45(18)°	N31	C32	H321	120.338°
C1	C32	H321	120.208°	C29	C40	C41	121.51(19)°
C29	C40	H401	119.689°	C41	C40	H401	118.795°
C40	C41	C42	119.8(2)°	C40	C41	H411	120.372°
C42	C41	H411	119.782°	C41	C42	C43	121.6(2)°
C41	C42	N44	119.79(19)°	C43	C42	N44	118.62(18)°
C28	C43	C42	119.02(18)°	C28	C43	H431	118.908°
C42	C43	H431	122.069°	C42	N44	O45	118.31(18)°
C42	N44	O46	118.43(18)°	O45	N44	O46	123.27(19)°
C24	C23	O5	126.27(18)°	C24	C23	O6	109.97(17)°
O5	C23	O6	123.76(18)°	C23	C24	C25	115.75(19)°
C23	C24	C13	110.9(2)°	C25	C24	C13	107.99(19)°
C23	C24	H241	108.967°	C25	C24	H241	108.233°
C13	C24	H241	104.365°	C24	C25	C1	110.69(17)°
C24	C25	C33	113.97(19)°	C1	C25	C33	115.4(2)°
C24	C25	H251	105.037°	C1	C25	H251	104.512°
C33	C25	H251	106.067°	C23	O6	C22	115.73(17)°
O17	C3	H31	107.646°	O17	C3	H32	107.839°
H31	C3	H32	111.244°	O17	C3	H33	107.054°
H31	C3	H33	110.225°	H32	C3	H33	112.591°
O14	C2	H21	108.814°	O14	C2	H22	107.485°
H21	C2	H22	111.907°	O14	C2	H23	108.759°
H21	C2	H23	110.500°	H22	C2	H23	109.279°
O6	C22	H221	108.063°	O6	C22	H222	111.930°
H221	C22	H222	109.812°	O6	C22	H223	110.790°
H221	C22	H223	109.033°	H222	C22	H223	107.185°
C36	C27	H271	107.735°	C36	C27	H272	108.505°
H271	C27	H272	108.722°	C36	C27	H273	112.550°
H271	C27	H273	109.449°	H272	C27	H273	109.790°
C10	C36	C27	108.7(2)°	C10	C36	C14	113.9(2)°
C27	C36	C14	107.2(3)°	C10	C36	C34	108.9(3)°
C27	C36	C34	108.1(3)°	C14	C36	C34	109.9(3)°
C13	O2	C26	115.6(3)°	C32	C1	C25	113.71(17)°
C32	C1	H11	105.612°	C25	C1	H11	110.194°
C32	C1	H12	108.834°	C25	C1	H12	111.210°
H11	C1	H12	106.917°	C33	C17	H172	109.755°
C33	C17	H171	109.568°	H172	C17	H171	108.848°
C33	C17	H173	109.234°	H172	C17	H173	109.014°

H171	C17	H173	110.409°	C25	C33	C17	109.1(2)°
C25	C33	C49	108.8(4)°	C17	C33	C49	108.0(3)°
C25	C33	C16	113.6(2)°	C17	C33	C16	107.7(4)°
C49	C33	C16	109.5(4)°	C24	C13	O2	113.1(2)°
C24	C13	O9	123.8(4)°	O2	C13	O9	123.0(4)°
C33	C49	H492	110.502°	C33	C49	H491	108.446°
H492	C49	H491	108.140°	C33	C49	H493	109.714°
H492	C49	H493	109.479°	H491	C49	H493	110.540°
C33	C16	H162	111.526°	C33	C16	H161	108.231°
H162	C16	H161	108.442°	C33	C16	H163	109.130°
H162	C16	H163	108.838°	H161	C16	H163	110.677°
C36	C14	H142	111.419°	C36	C14	H141	109.135°
H142	C14	H141	110.992°	C36	C14	H143	107.476°
H142	C14	H143	109.149°	H141	C14	H143	108.564°
O2	C26	H262	110.063°	O2	C26	H261	108.445°
H262	C26	H261	108.998°	O2	C26	H263	109.669°
H262	C26	H263	110.387°	H261	C26	H263	109.244°
C36	C34	H342	110.431°	C36	C34	H341	110.048°
H342	C34	H341	109.961°	C36	C34	H343	110.302°
H342	C34	H343	107.188°	H341	C34	H343	108.854°

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