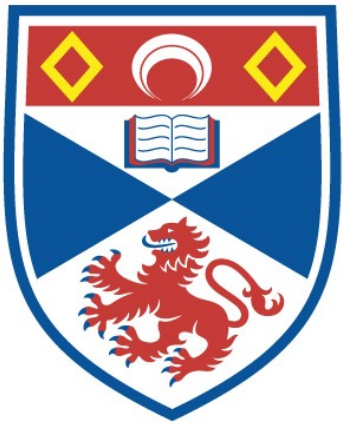
TOTAL SYNTHESIS AND SAR OF ALTERNARIC ACID TOWARDS THE DEVELOPMENT OF A NEW HERBICIDAL LEAD

Eva M. Israel

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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Eva M. Israel

University of
St Andrews

This thesis is submitted in partial fulfilment for the degree of Doctor of Philosophy (PhD) at the University of St Andrews

June 2022

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Abstract

Crop protection is essential in agricultural chemistry to help farmers maintain a healthy and productive cropland. However, agrochemical research faces a constant need for innovation in crop protection to be able to meet the global requirement for food supplies. Over the years, fighting resistance against crop protection products has become one of the biggest challenges in the development of effective agrochemicals. As a result, there is a requirement for new agrochemicals exhibiting novel Modes of Action (MoA). Natural products are privileged scaffolds in agrochemistry, owing to their molecular complexity and rich bioactivity, which can leads to the discovery of novel MoA.

The natural product Alternaric acid, isolated from the phytopathogenic fungus *Alternaria solani*, has been identified as possessing herbicidal activity. As such, it represents an attractive herbicidal lead for the agrochemical industry. However, exploration of the potential of this target has remained undeveloped due to low accessibility and lack of Structure-Activity Relationship (SAR) data.

The research described in this thesis was conducted in collaboration with Syngenta. Herein, we report the development of a scalable and flexible synthetic route, which enabled the synthesis of significant quantities of Alternaric acid as well as a variety of analogues. Through biological evaluation of these compounds, SAR profiling of focused libraries identified a new class of small molecule leads, with enhanced herbicidal activity and developability. Additionally, MoA investigations have been conducted, suggesting that this new class of lead compounds is likely to exhibit a novel MoA, highlighting their potential for herbicidal discovery.

PhD Publications

The work presented in this thesis is partly described in the following publication.

1. E. M. Israel, J. Comas-Barceló, A. M. Z. Slawin, A. J. B. Watson. (in press). Total synthesis and SAR of Alternaric acid delivers a novel herbicide vector. *Nat. Synth.*

Abbreviations

Ac	Acetyl
AMAPA	*Amaranthus palmeri*
AMARE	*Amaranthus retroflexus*
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
BL	Bleaching
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bp	Boiling point
Bu	Butyl
C	Celsius
CAN	Cerium ammonium nitrate
CDI	Carbonyldiimidazole
CL	Chlorosis
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DHQD	Dihydroquinidine
DIGSA	*Digitaria sanguinalis*
DIPA	*N*,*N*-Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide

DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DTBDP	4,4'-Di-*tert*-butyl-1,1'-biphenyl
E	Electrophile
ECHCG	*Echinochloa crus-galli*
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Enz	Enzyme
EPS	Early profiling screen
eq	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
Fm	Fluorenylmethyl
g	Grams
GH	Glasshouse
GI	Germination inhibition
h	Hours
ha	Hectare
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HPPD	*p*-hydroxyphenylpyruvate dioxygenase
HRMS	High resolution mass spectrometry
Hz	Hertz
IC	Inhibitory concentration
IPOHE	*Ipomoea hederacea*
IR	Infrared
L	Litres
LCMS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide

LOLPE	*Lolium perenne*
M	Molar
Me	Methyl
min	Minutes
mol	Moles
MoA	Mode of action
MR	Morphological response
NC	Necrosis
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Pg	Protecting group
Ph	Phenyl
PHAL	Phtalazine
rt	Room temperature
s	Secondary
SAR	Structure-activity relationship
SETFA	*Setaria faberi*
SOLNI	*Solanum nigrum*
ST	Stunting
STEME	*Stellaria media*
t	Tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
Ts	*p*-Toluenesulfonyl
ZEAMX	*Zea mays*

Table of contents

1. Introduction

1.1 Agricultural chemistry

Agricultural chemistry is defined as the study of chemical compositions and changes involved in the production, protection, and use of crops.[1] The agrochemical industry aims to provide a sustainable global agriculture in an environmentally friendly manner. Understanding the biological pathways in plants is essential for the development of safe and effective chemicals for crop production and protection. Being able to manipulate and affect these biochemical reactions can enable crop growth in the desired manner.

Crop protection is essential in agricultural chemistry to help farmers maintain a healthy and productive cropland. The global population is anticipated to expand substantially in the next few decades; it is expected to reach between 9–10 billion people by 2050.[2] As a consequence of increasing global food requirements, agrochemical research faces a constant need for innovation in crop protection to be able to meet the requirement for food supplies.[3]

Agrochemicals designed to protect crops can be divided into three categories according to their function: insecticides, fungicides, and herbicides, which aim to kill, harm, repel or mitigate against insects, fungal, and weed pests, respectively. However, over the last decades, the effectiveness of agrochemicals has been compromised by the resistance developed to existing crop protection products.[4] As a result, there is a requirement for new agrochemicals exhibiting novel Modes of Action (MoA). For example, the MoA of an herbicide is the overall manner by which it affects a plant at the tissue or cellular level. It describes the biological processes that are disrupted by the herbicide, such as photosynthesis inhibition or lipid biosynthesis inhibition.[5] Commercialised herbicides represent

approximately 20 different modes of actions, six of which largely predominate. More than 60% of the herbicide market is represented by products with modes of action that are already associated with serious resistance issues, therefore emphasising the need for novelty in herbicidal discovery.[6]

Different inputs can be used to generate new lead small molecule compounds in crop protection discovery. Designed libraries based on molecular target hypotheses, competitor-inspired chemistry, and natural product-based leads are the most prominent three approaches (Figure 1).[3] Designed libraries based on a molecular target require prior knowledge of the biological target. Whilst competitor-inspired lead generation builds upon a large web of biological knowledge, it suffers from a lack of novelty. In contrast, the molecular complexity and rich bioactivity of natural products allows the study of underexplored biological spaces, which can lead to the discovery of novel MoAs. Once a lead is identified, structure optimisation can start, and a library of structural analogues can be synthesised with a view to improving physicochemical properties and herbicidal activity. This can be achieved with or without prior knowledge of the molecular target site.[3,7]

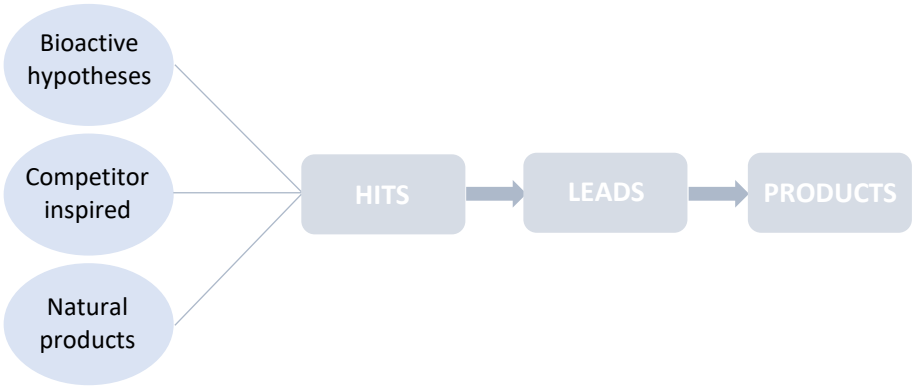


Figure 1: Classical approaches to lead generation

1.2 Natural products for agrochemical development

Historically, natural products have always been used as pest management tools. Some of the earliest pesticides used include natural products such as ground tobacco, essential oils, and lime which were used against aphids and ground pyrethrum flowers.[7,8] Employing natural products as a starting point in agrochemical discovery presents numerous advantages such as a high target specificity and low toxicity towards off-target organisms. As a consequence, there are multiple examples of phytotoxic (toxic to plants) natural products serving as leads for agrochemical discovery.[7,9–11]

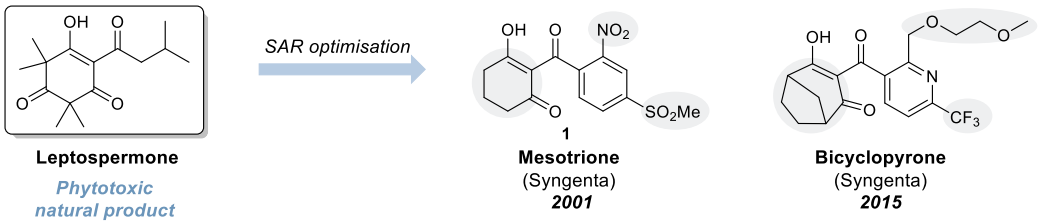
1.2.1 Natural products for herbicide discovery

In comparison to other pesticides or pharmaceuticals, natural product-based discovery has not been as successful for herbicides. Whilst natural product-based herbicide discovery presents various advantages, such as new structural backbones interacting with potentially new molecular target sites, it also has its limitations. Natural products commonly exhibit complex structures that can be expensive to synthesise, and they also usually exhibit high target specificity. The molecular complexity of natural products and the difficulties associated with their synthesis often translate to unsuitability for modification and optimisation. Furthermore, the structure of the compound may already be optimum for activity but unsuitable for physicochemical properties.[12]

Phytotoxic natural products act on a number of unexploited herbicide sites. Some successfully developed natural product-derived herbicides, such as triketones,[9] cinmethylin[10] or bialaphos,[13] target molecular sites which were previously not used by other commercial herbicides.

1.2.1.1 Triketone herbicides

Triketones, a class of *p*-hydroxyphenylpyruvate dioxygenase (HPPD) inhibiting herbicides, originate from the discovery of the phytotoxic properties of the natural product leptospermone.[14] Mesotrione **1** and bicyclopyrone are two examples of successful marketed herbicides derived from the naturally occurring triketone, leptospermone (Scheme 1).[9,15] They are both highly potent and selective corn herbicides that bear the same triketone moiety involved in the inhibition of the enzyme HPPD. Structure-Activity-Relationship (SAR) optimisation on leptospermone first led to the discovery and commercialisation of **1** in 2001 by Syngenta.[9] It was discovered that an electron withdrawing-group at the *ortho*-position of the aromatic ring was essential for herbicidal activity. A second electron withdrawing-group at the *para*-position was demonstrated to be beneficial for potency. Finally, the unsubstituted cyclohexanedione moiety gave the desired selectivity towards maize. More recently, further investigations have led to the discovery of nicotinoyl cyclohexane diones such as bicyclopyrone in 2015.[7,9]

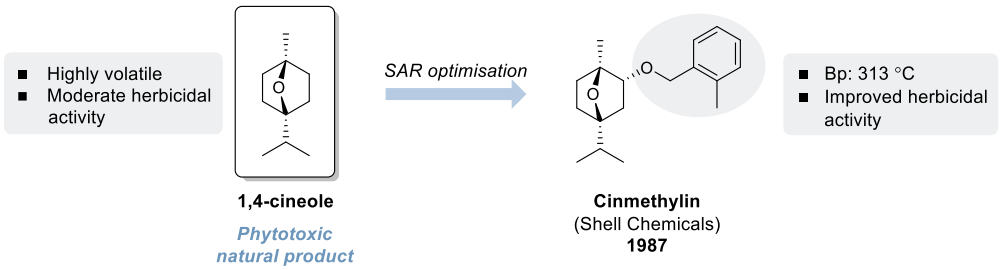


Scheme 1: Natural product-based discovery of novel triketone herbicides

1.2.1.2 Cineole herbicides

Cineoles are a class of phytotoxic monoterpene natural products found in essential oils of a variety of plants. The discovery of naturally occurring 1,4-cineol has led to the development and commercialisation of a new herbicide,

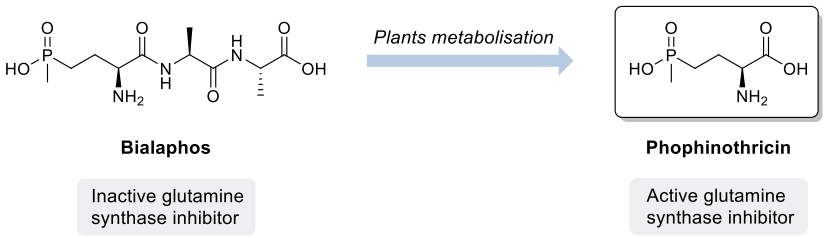
cinmethylin, employed as a weed control agent for monocots.[10] It has been exemplified by Vaughn and Spencer that 1,4-cineol inhibited germination of crabgrass, ryegrass, wheat, and redroot pigweed.[16] However, the volatility of the natural phytotoxin precludes its utilisation as a herbicide. The structure of cinmethylin comprises the entire backbone of 1,4-cineole, with the addition of a benzyl ether moiety which confers cinmethylin a boiling point of 313 °C (Scheme 2). The mode of action of cinmethylin has been the focus of many studies since its discovery.[17,18] Recent reports indicate a new herbicidal site of action, suggesting cinmethylin inhibits plant fatty acid biosynthesis via binding to acyl ACP-thioesterase.[19]



Scheme 2: Natural product-based herbicide discovery of cinmethylin

1.2.1.3 Phosphinothricin and bialaphos

Phosphinothricin is a naturally occurring broad-spectrum post-emergence herbicide, which was discovered in the early 1970s and is produced by chemical synthesis.[20] Unlike leptospermone or 1,4-cineole, no SAR development was required on phosphinothricin as it presents sufficient herbicidal properties in its natural form. The *P*-methylated amino acid phosphinothricin is analogous to glutamine and acts as a glutamine synthetase inhibitor. The tripeptide analogue bialaphos, inactive towards glutamine synthetase, is also commercialised as a pro-herbicide (pro-cide), which is metabolised by plants to release phosphinothricin (Scheme 3). Bialaphos is produced from fermentation cultures of *Streptomyces hygroscopis*.[21]



Scheme 3: Phosphinothricin, a natural herbicide

1.3 Alternaric acid

Alternaric acid is a phytotoxic agent produced by the phytopathogenic fungus *Alternaria solani*, which has been identified as possessing herbicidal and fungicidal activity (Figure 2).[22,23] *Alternaria solani* is the causal fungus of the early blight disease in potato and tomato crops.[24] It is proposed that the natural product Alternaric acid is produced by the fungi as it infects potato and tomato crops, suggesting possible involvement of the phytotoxin in this process.[24] The isolation of Alternaric acid was achieved in 1949 by Brian and co-workers.[25] In 1960, the molecular connectivity of the natural product was determined by Barthel-Keith using classical methods, by analysing UV and IR data of Alternaric acid and several products of reaction with specific functional groups on the natural product.[26,27] However, the absolute stereochemistry of the compound was proposed only a few decades later, in 1994, by Ichihara and co-workers.[28]

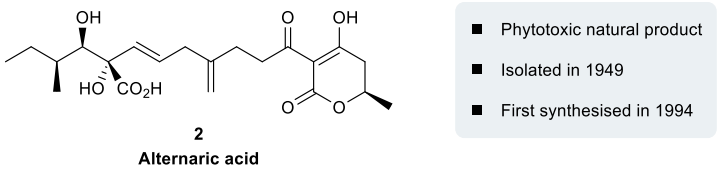
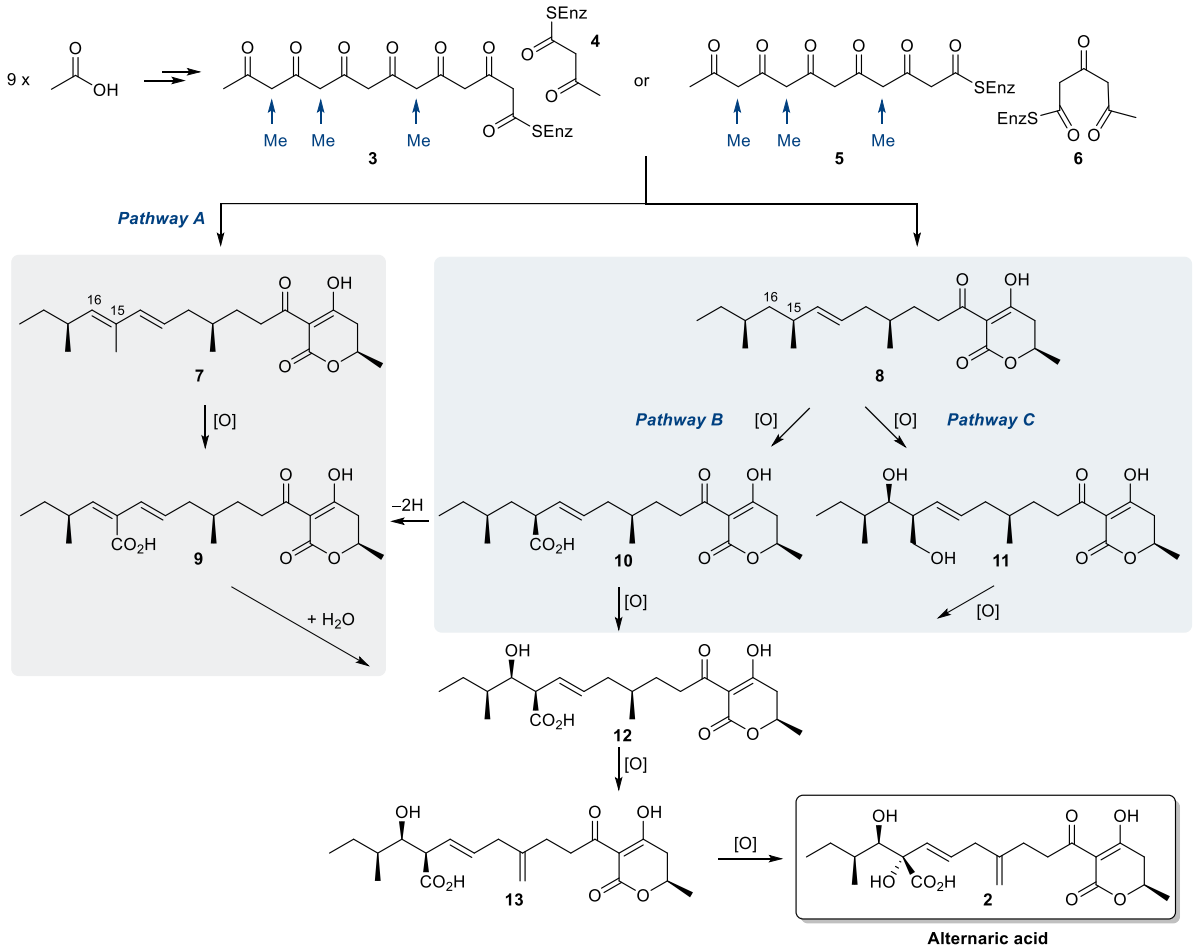


Figure 2: Alternaric acid, background

1.3.1 Biosynthesis of Alternaric acid

Following their work on the total synthesis of Alternaric acid and the determination of its associated stereochemistry,[28] Ichihara and co-workers also investigated potential biosynthetic pathways for the production of the phytotoxic natural compound by *Alternaria solani*. Their biosynthetic studies revealed two potential biosynthetic pathways (Scheme 4).[29] Stothers and co-workers had previously demonstrated that Alternaric acid can be biosynthesised from two polyketide chains **3** and **4** or **5** and **6**, rather than just a single polyketide, through condensation.[30] Chains **3** and **5** can then undergo reaction with β-ketoacylsynthase, methyl transferase, β-ketoreductase, dehydratase, and enoyl reductase to give the putative intermediates **7** and **8**, with the difference being the oxidation state of carbons C_{15} and C_{16}. The introduction of oxygen atoms can occur *via* pathways A, B, and C. In pathway A, **7** can be oxidised to **9** by the action of cytochrome P-450, which upon hydrolysis gives intermediate **12** towards which all the pathways converge. Alternatively, **8** can be oxidised to **10** via pathway B, which can then form either **9** or **12**. Pathway C can also give the common intermediate **12** through oxidation of **8** to **11**. Subsequent conversion of the methyl group to an *exo*-methylene group on **12** by oxidation with cytochrome P-450 generates **13**. Lastly, introduction of a hydroxyl group would produce the natural product Alternaric acid.[29]



Scheme 4: Proposed biosynthetic pathways of Alternaric acid

1.3.2 Alternaric acid, a potential herbicidal lead

Preliminary in-house analysis by Syngenta has demonstrated a good level of activity for Alternaric acid in herbicide screens. Additionally, Ichihara and co-workers have reported that Alternaric acid exhibited phytotoxic activity against tomato seedlings.[31] However, only a limited amount of SAR studies have been carried out: a loss of activity was observed when the C_{10} methylene or C_{15} hydroxyl is removed (Figure 3).[31,32]

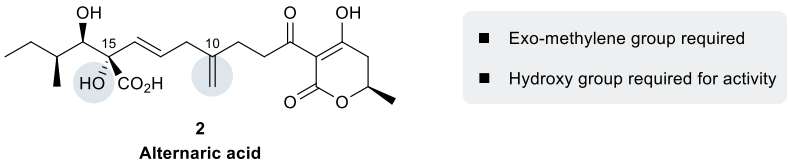
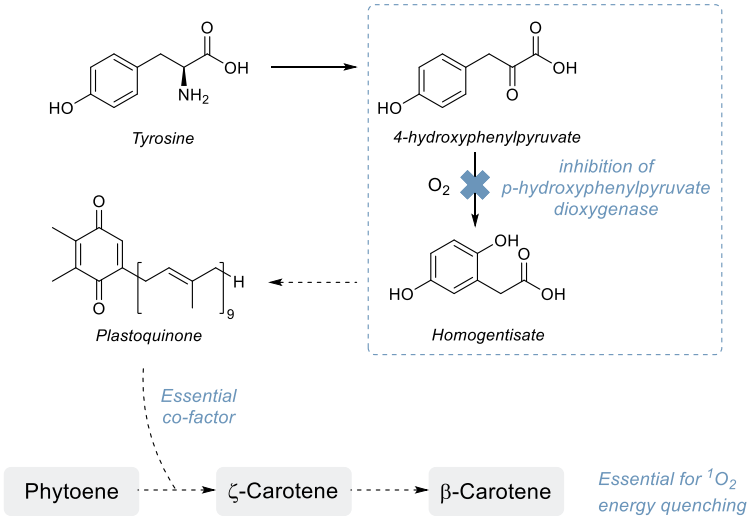


Figure 3: Preliminary SAR assessment of Alternaric acid

The primary mode of action of the phytotoxin is currently uncertain, yet moderate HPPD activity has been observed through in-house analysis at Syngenta. This is perhaps not surprising when looking at the structure of Alternaric acid and its similarities with the triketone class of herbicides, such as Mesotrione (Scheme 1, *vide supra*).

HPPD inhibitors are a class of herbicide, which indirectly interrupt the biosynthesis of β-carotene through inhibition of *p*-hydroxyphenylpyruvate dioxygenase (Scheme 5).[33] β-carotene plays an essential role in quenching the oxidative energy of singlet oxygen. Singlet oxygen can interact with integral membrane components leading to their destruction.[34,35] Inhibition of the synthesis of homogentisate from 4-hydrophenylpyruvate prevents the formation of plastoquinone, which is an essential co-factor for phytoene desaturase required in the biosynthesis of carotenoids. As a consequence, the production of β-carotene is prevented, causing effectively plant destruction. In plants, HPPD inhibition causes a symptom called bleaching, resulting from loss of chlorophyl.[36]



Scheme 5: HPPD inhibition pathway

In-house docking of Alternaric acid into the HPPD pocket of *Arabidopsis thaliana* at Syngenta, based on a crystal structure of *Arabidopsis thaliana* HPPD complexed with Mesotrione, shows that the natural product can fit in the pocket of the protein (Figure 4). However, direct comparison to the commercialised herbicide Mesotrione revealed that the large structure of Alternaric Acid does not fit as well as Mesotrione within the protein binding pocket. This emphasises the idea that HPPD inhibition is unlikely to account for the primary mode of action of Alternaric acid.

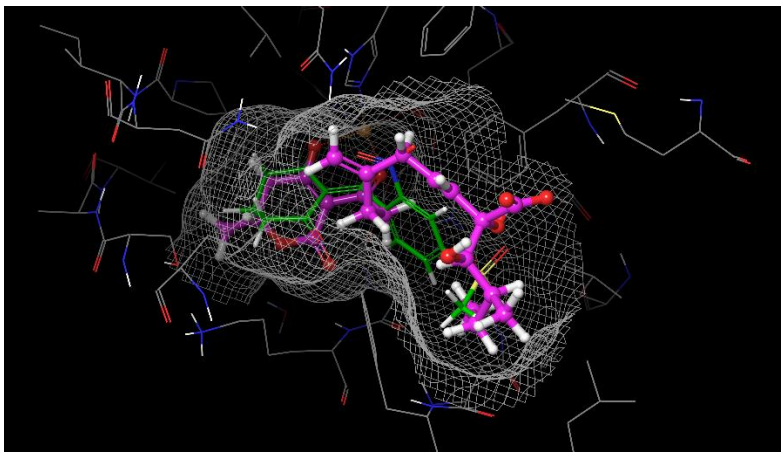


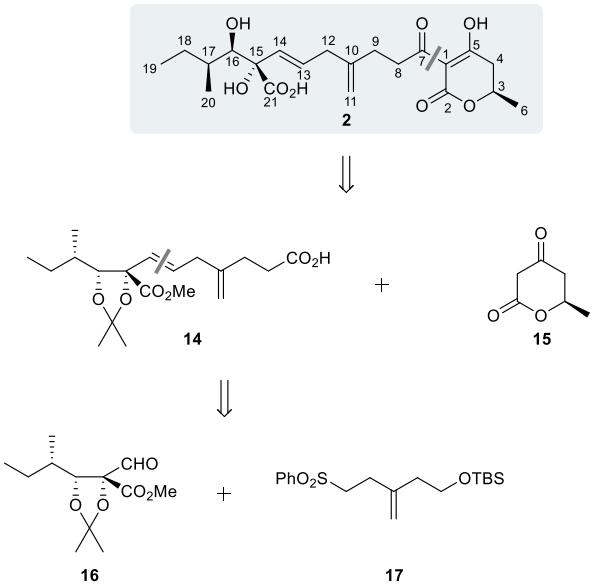
Figure 4: Comparison of Mesotrione (green) and Alternaric acid (purple) docking into *Arabidopsis thaliana* HPPD

The phytotoxic nature of Alternaric acid suggests potential to be used as a starting point for herbicidal discovery,[25] and potential to identify a novel MoA.

1.3.3 Synthetic approaches towards Alternaric acid

1.3.3.1 Ichihara's total synthesis

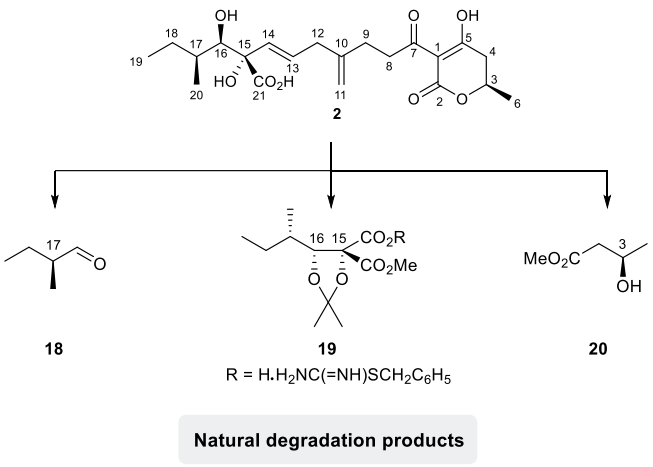
The determination of the stereochemistry and first total synthesis of Alternaric acid were achieved by Ichihara and co-workers in 1994 (Scheme 6).[28] At the time, the stereochemistry at C_{15} and C_{16} was unknown, rendering the synthesis of the natural product even more challenging. Ichihara and co-workers envisioned the following retrosynthetic strategy: breaking of Alternaric acid **2** into two fragments **14** and **15**. Fragment **14** was further disconnected to aldehyde **16** and phenylsulfone **17**. The synthesis of fragment **14** was hypothesised to be achieved *via* Julia olefination[37] of **16** and **17**, whilst esterification coupling of **14** and **15** followed by a subsequent Fries-type rearrangement[38–40] was envisioned to access **2**.



Scheme 6: Retrosynthetic analysis of Alternaric acid by Ichihara and co-workers

➢ *Determination of the absolute stereochemistry of Alternaric acid*

The strategy employed by Ichihara and co-workers to determine the stereochemistry of Alternaric acid relied on the use of natural degradation products. Comparison of the optical rotation values of natural degradation products with synthetically produced material allowed a fair assumption of the complete stereochemistry of the natural product. Using degradation products **18** and **20**, the stereochemistry at C_{17} and C_3 was proposed to be 17-(*S*) and 3-(*R*) (Scheme 7). Determining the stereochemistry at C_{15} and C_{16} proved to be more challenging. The synthesis of all four possible diastereoisomers of degradation product **19** was achieved. Through evaluation and comparison of optical rotation values, Ichihara and co-workers concluded that the stereochemistry at C_{15} and C_{16} was more likely to be 15-(*S*) and 16-(*R*).[28]

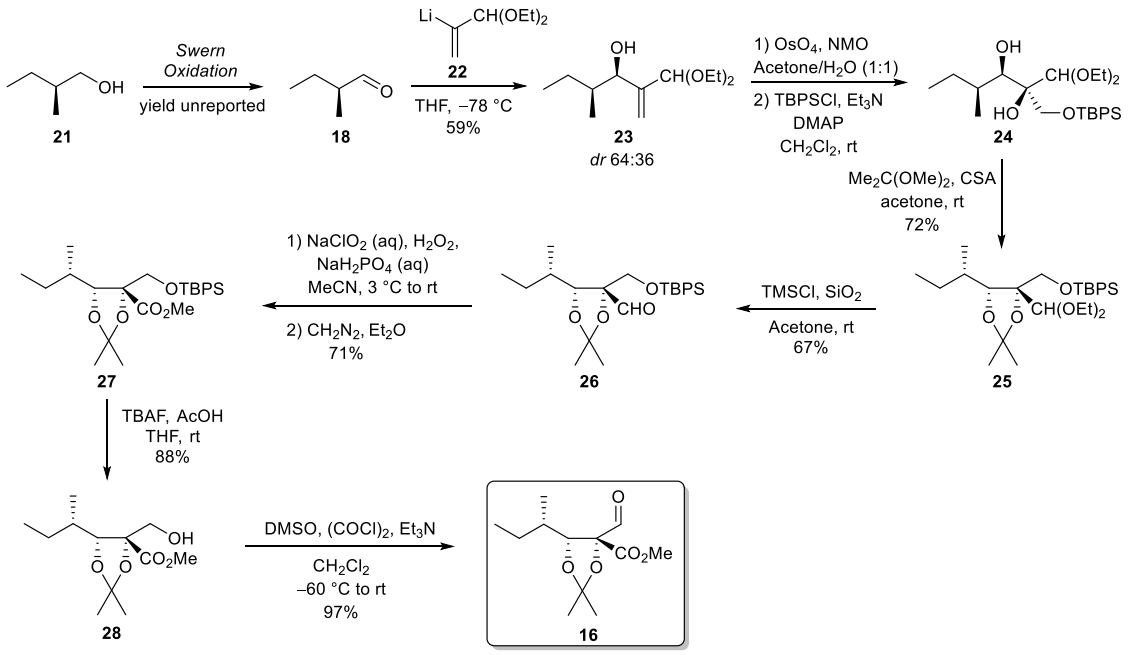


Scheme 7: Stereochemistry determination using degradation products of Alternaric acid

➢ *Synthesis of intermediate **16***

The forward synthesis commenced by Swern oxidation[41–43] of the commercially available (*S*)-(+)-methylbutanol **21** (Scheme 8). Condensation of aldehyde **18** with vinyl lithium reagent **22** yielded a mixture of diastereoisomers **23** in a ratio of

64:36, with the *syn* product observed as the major isomer. Dihydroxylation, followed by selective protection of the primary alcohol as the silyl ether, and subsequent acetonide formation gave access to compound **25** in 72% yield. Hydrolysis of the acetal gave aldehyde **26** in 67% yield, which was followed by Pinnick oxidation and *in situ* methylation of the carboxylic acid using diazomethane to afford methyl ester **27** in 71% yield. Removal of the silyl protecting group and subsequent Swern oxidation gave access to **16** in ten steps.

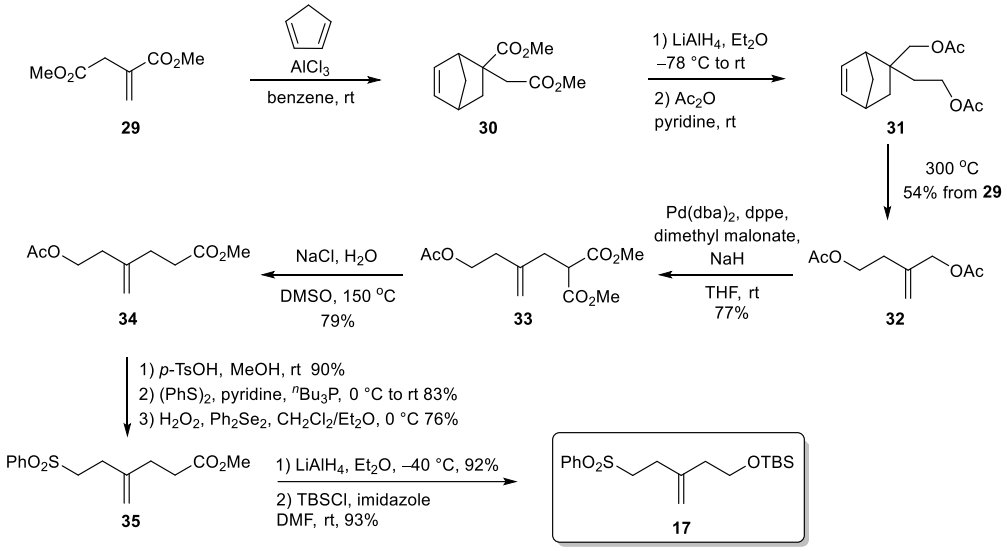


Scheme 8: Synthesis of intermediate 16

➢ *Synthesis of intermediate* ***17***

With aldehyde **16** in hand, the synthesis of the desired phenylsulfone **17** was targeted (Scheme 9). Double reduction of dimethyl itaconate **29** was desired to obtain the corresponding diol. However, in order to prevent undesired 1,4-reduction, the olefin in compound **29** was temporarily protected using a Diels-Alder/retro Diels-Alder strategy.[44] Accordingly, Diels-Alder reaction of **29** with cyclopentadiene yielded intermediate **30** as a diastereomeric mixture. Subsequent

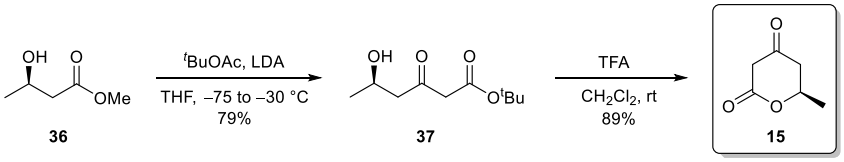
reduction of **30** was followed by acetylation to afford the compound **31**. Heat-promoted retro Diels-Alder reaction of **31** produced olefin **32** in 54% over four steps. The dimethyl ester **33** was obtained in good yield *via* Pd-catalysed allylic alkylation of **32** using sodium dimethyl malonate.[45] Subsequent decarboxylation gave intermediate **34** in 79%. Next, acetate **34** was converted to the corresponding phenylsulfone **35** in three steps. Reduction of the ester group and protection of the corresponding alcohol finally afforded intermediate **17**.



Scheme 9: Synthesis of phenylsulfone intermediate 17

➢ *Synthesis of β-keto-δ-valerolactone **15***

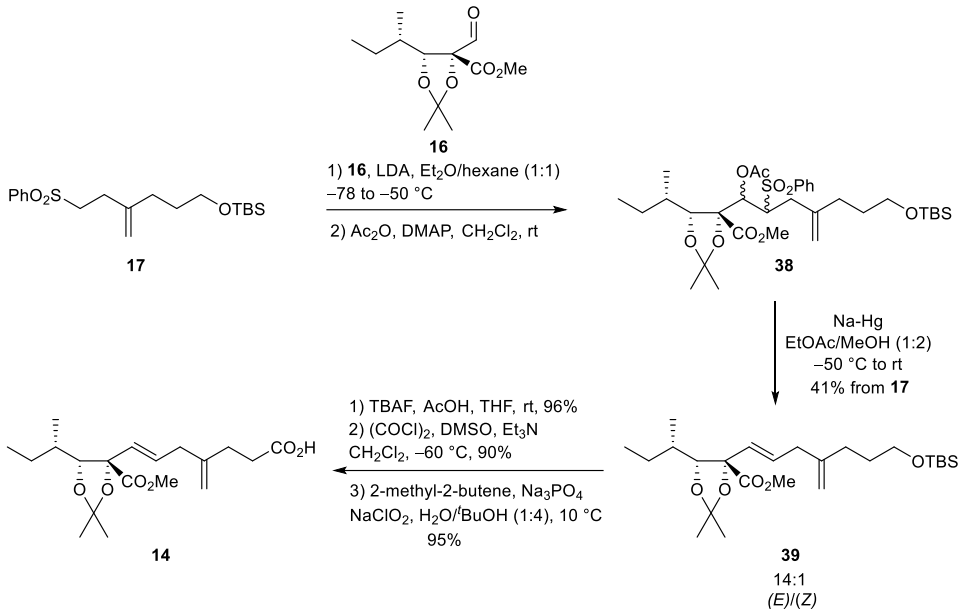
For the construction of the β-keto-δ-valerolactone motif, Ichihara and co-workers opted for a two-step process, involving Claisen condensation of the commercially available starting material **36** and lithium *tert*-butyl acetate (Scheme **10**).[46] The δ-hydroxy-β-keto ester **37** obtained, was treated with trifluoroacetic acid to yield the desired product **15** in 89% yield.



Scheme 10: Synthesis of β-keto-δ-valerolactone 15

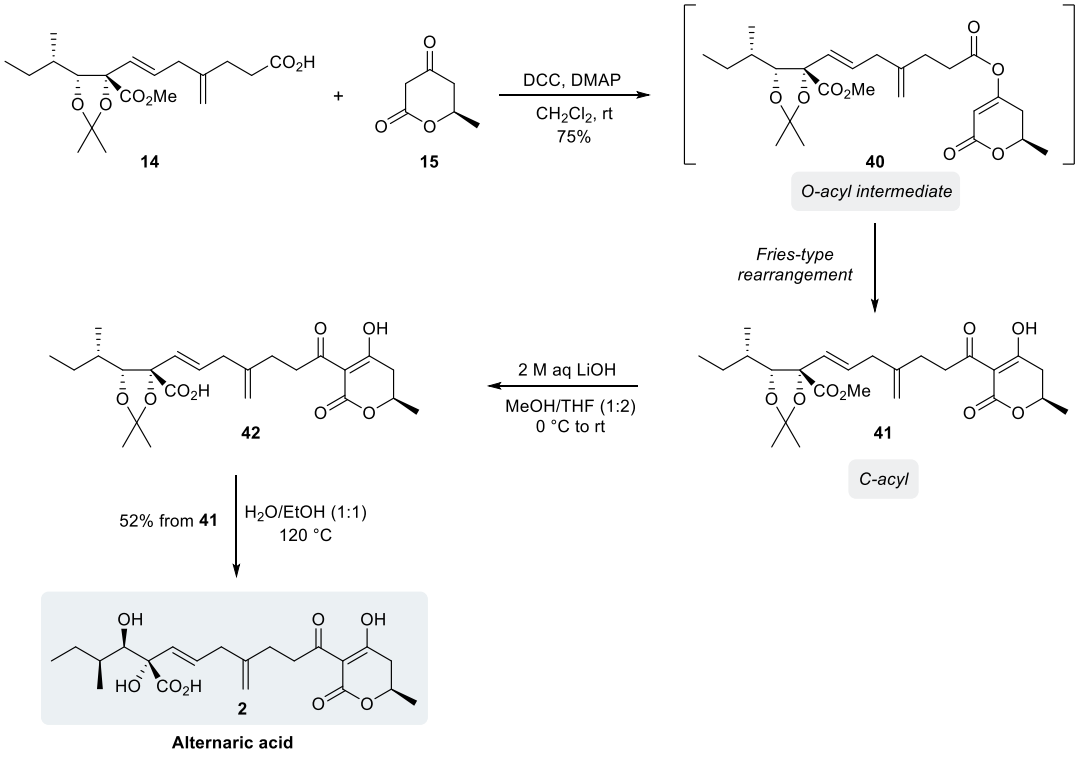
➢ *Coupling of the three fragments*

Condensation of an α-tertiary aldehyde, bearing an electrophilic group (methyl ester), is challenging as it could also easily be attacked by a nucleophile. However, Ichihara and co-workers successfully executed a Julia olefination of aldehyde **16** with phenylsulfone **17** (Scheme 11). During their investigations, the group observed that a lithium dialkylamide base was preferred to an alkyllithium base, and that the reaction proceeded more smoothly in the presence of *n*-hexane as a co-solvent. As such, treatment of **17** with LDA in diethylether/*n*-hexane (1:1) afforded the corresponding sulfone anion, which further reacted with **16**. The resulting *β*-hydroxy sulfones were acetylated to give the corresponding *β*-acetoxy sulfones **38** as a mixture of diastereoisomers. Reduction with sodium amalgam[47] afforded the desired product **39** in 41% yield as a 14:1 mixture of (*E*) and (*Z*)-isomers. The acetyl protected alcohol was then deprotected, oxidised to the aldehyde, and then further oxidised to the corresponding carboxylic acid to obtain intermediate **14**.



Scheme 11: Coupling of intermediate 17 and 16 towards the synthesis of 14

Whilst several methods are available in the literature for the synthesis of 3-acyl-4-hydroxy-5,6-dihydro-2-pyrones, they usually require several steps.[48] In an effort to simplify the synthesis of such a motif, Ichihara and co-workers developed a new methodology for the construction of 3-acyl-4-hydroxy-5,6-dihydro-2-pyrones, from carboxylic acids and β-keto-δ-valerolactones.[49] The method involves esterification coupling of **14** and **15** using DCC and DMAP, followed by a Fries-type rearrangement of the *O*-enol acyl group of the β-keto-δ-valerolactone on **40** towards the α-position of the lactone to give the C-acyl product **41** (Scheme 12). Finally, hydrolysis of the methyl ester and deprotection of the acetonide successfully afforded the natural product **2**.

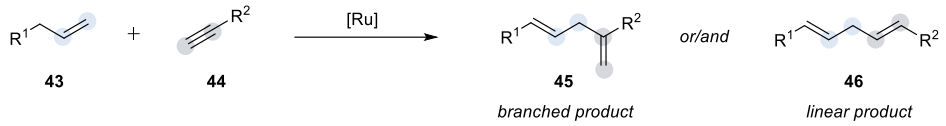


Scheme 12: Coupling of pyrone fragment 15 and final steps towards Alternaric acid

In summary, the determination of the absolute configuration of all stereocentres of Alternaric acid was accomplished, and the total synthesis of the natural product was achieved in 0.001% yield over 29 steps.[28]

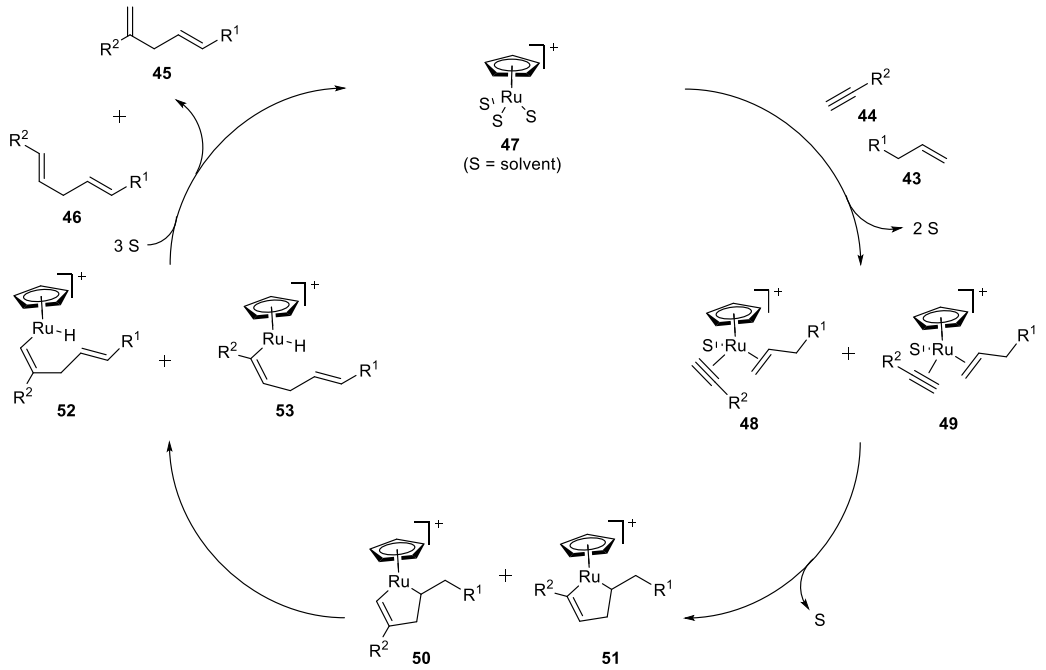
1.3.3.2 Ru-catalysed Alder-Ene-type reaction approach

In 1998, a new strategy was developed by Trost and co-workers for the synthesis of natural products containing a terminal methylene and an (*E*)-1,2-disubstituted alkene. The protocol relied on the utilisation of the Ru-catalysed Alder-Ene-type reaction that the group had previously developed.[50] In this work, the acyclic unit fragment of Alternaric acid was synthesised in 11 steps with 27% overall yield.[51] The Ru-catalysed Alder-Ene reaction is the coupling of a terminal alkene and a terminal alkyne which can either afford a branched or linear 1,4-diene (Scheme **13**).



Scheme 13: General scheme for the ruthenium Alder-Ene reaction

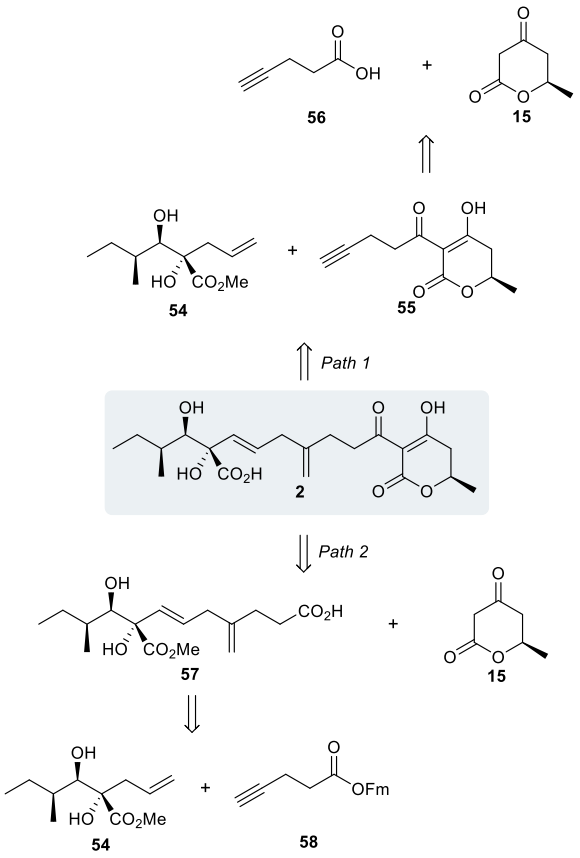
This process is a powerful tool to build the terminal methylene and (*E*)-1,2-disubstituted alkene motifs present in a number of biologically relevant natural products, such as Alternaric acid. The proposed mechanism begins with coordination of alkene **43** and alkyne **44** substrates with catalyst **47**, and cyclisation, which leads to the formation of two possible ruthenacycle intermediates **50** and **51** (Scheme 14). The regioselective outcome arises from the alkyne orientation during this step. The orientation of the terminal alkene is not a factor as only one can generate a productive intermediate. The alkyne orientation results from competition of substituents coordination with the ruthenium. In turn, the regioselectivity of this process is highly substrate dependant. *Syn* β-hydride elimination from **50** and **51**, respectively, yields regioisomeric vinyl ruthenium intermediates **52** and **53**. Finally, reductive elimination produces the branched or linear 1,4-diene compounds **45** and **46**.[50–53]



Scheme 14: Ru-catalysed Alder-Ene type reaction mechanism proposed by Trost and co-workers

With a view to illustrating their methodology and further elucidate the regioselectivity rationale, Trost and co-workers sought to apply it for the construction of the acyclic unit fragment of Alternaric acid.

Two different strategies were envisioned in the retrosynthetic approach of Alternaric acid (Scheme 15). Both pathways make use of alkene partner **54**, a terminal alkyne, and pyrone **15**. Path 1 would aim at coupling pyrone fragment **15** with carboxylic acid **56** and subsequently couple the newly formed terminal alkyne **55** with alkene **54**. Path 2 aimed at coupling alkene **54** with alkyne **58** first, to form the acyclic unit of Alternaric acid **57**, before coupling with pyrone fragment **15**.[51]

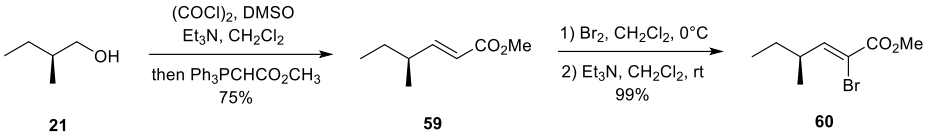


Scheme 15: Retrosynthetic analyses of Alternaric acid by Trost and co-workers

In order to elucidate which strategy would prove best, different model studies were performed.[51] The results of these experiments suggested that while the free hydroxyl group can be tolerated in the Ru-catalysed reaction, acidic substrates, such as carboxylic acid and acyldihydropyrones, may behave as catalyst inhibitors, since they can generate good coordinating anions.[51] For this reason, the synthetic strategy following path 2 was selected.

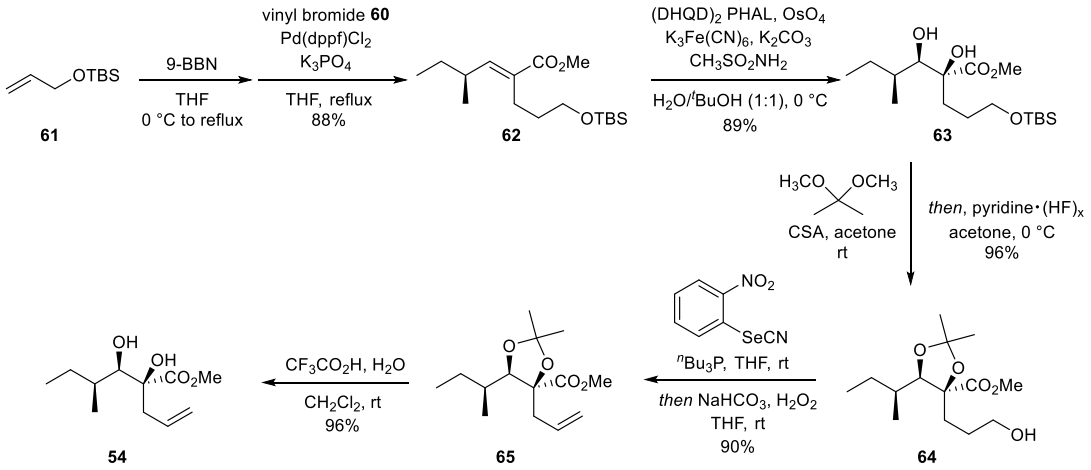
While the synthesis of alkyne coupling partner **58** could be achieved in one step from the commercially available 4-pentynoic acid **56**, the conciseness of the synthesis of the acyclic unit **57** relied heavily on the efficiency of the synthesis of terminal alkene **54**. The synthesis of terminal alkene **54** began with commercially available (*S*)-(+)-methylbutanol **21** (Scheme 16). The alcohol was converted to the α,β-unsaturated ester **59** *via* a one-pot Swern oxidation[41–43]/Wittig

olefination,[54,55] which proceeded without racemisation. Bromination-dehydrobromination of unsaturated ester **59** afforded vinyl bromide **60** in excellent yield.



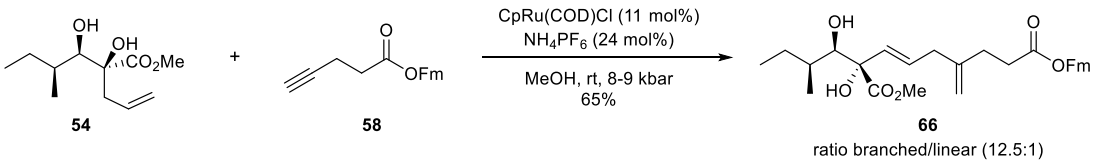
Scheme 16: Synthesis of vinyl bromide 60

Next, a Sharpless dihydroxylation[56] was envisioned for the diastereoselective synthesis of the diol motif. In order to avoid a selective dihydroxylation of the terminal alkene, a primary alcohol was strategically implemented as a surrogate for the monosubstituted alkene. Thus, hydroboration of the *tert*-butyldimethylsilyl ether of allyl alcohol **61** with 9-BBN led to the formation of the corresponding organoborane (Scheme 17). This intermediate was coupled to the vinyl bromide **60** through an sp^2-sp^3 Suzuki-Miyaura cross-coupling.[57] Subsequent asymmetric Sharpless dihydroxylation[56] of **62** afforded diol **63** in 89% yield. One-pot protection of the diol and deprotection of the *tert*-butyldimethylsilyl ether afforded acetonide **64** in 96% yield. Grieco elimination of the primary alcohol afforded the desired terminal alkene.[58] After deprotection of the acetonide moiety, terminal alkene **54** was finally obtained.



Scheme 17: Synthesis of alkene coupling partner 54

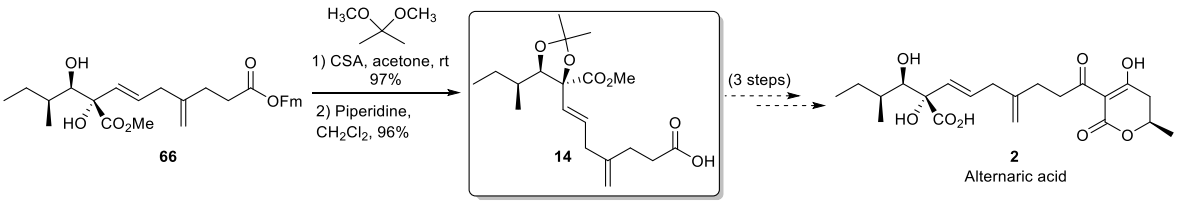
Studies on the Ru-catalysed reaction showed that the free diol was beneficial for the branched regioselectivity of the reaction. Trost and co-workers rationalised this observation by the internal coordination of the diol present on the alkene with the ruthenium. This prevents coordination of the ester functionality present on the alkyne, therefore positively influencing the orientation of the alkyne moiety towards the formation of the branched 1,4-diene.[51] Several ester groups on the alkyne were investigated, with the 9-fluorenylmethanol (Fm) ester ultimately providing the best results in terms of stability and regioselectivity. Thus, the Ru-catalysed Alder-Ene reaction was performed successfully on alkene **54** and alkyne **58,** and yielded the desired terminal methylene and (*E*)-1,2-disubstituted alkene **66** in 65% yield (Scheme 18).



Scheme 18: Ru-catalysed Alder-Ene reaction

As discussed previously, Ichihara and co-workers have shown that the natural product Alternaric acid could be synthesised in three steps from intermediate **14** (Scheme 12, *vide supra*).[28] Trost and co-workers achieved the synthesis of the

targeted intermediate **14** from the skipped diene **66** in two steps, through protection of the diol followed by selective deprotection of the Fm ester (Scheme 19).

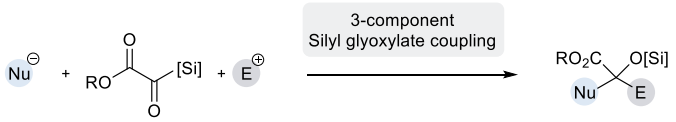


Scheme 19: Synthesis of key intermediate 14

Overall, Trost and co-workers have shown the powerful utility of the Ru-catalysed Alder-Ene reaction and its direct application towards the total synthesis of Alternaric acid. To summarise, the acyclic unit fragment of Alternaric acid was synthesised in 11 steps with 27% yield.[51] This represents a great improvement to Ichihara's synthesis, where the preparation of the same intermediate from the (*S*)-(+)-methylbutanol was accomplished in 26 steps with 0.003% overall yield.[28]

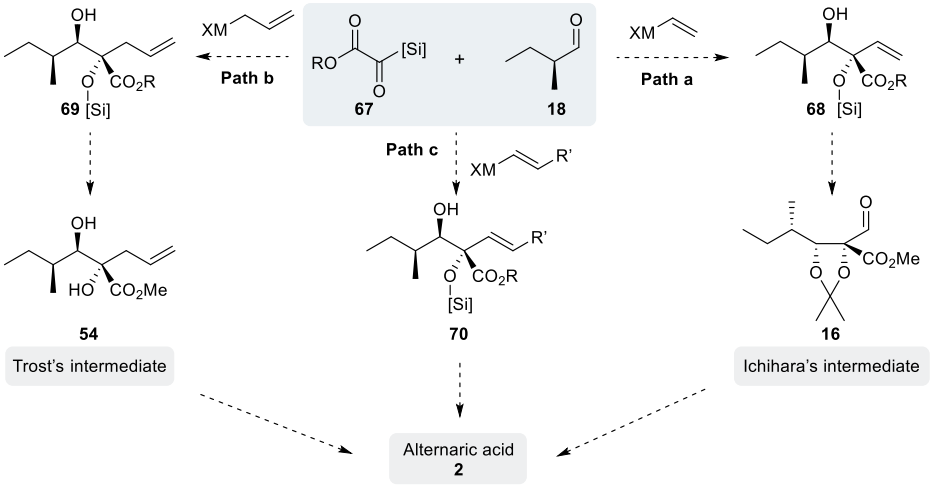
1.3.3.3 Silyl glyoxylate three-component-coupling strategy

In 2013, another approach towards a formal synthesis of Alternaric acid was investigated by Johnson and co-workers,[59] based on their previously developed methodology for the silyl glyoxylate three-component coupling reaction.[60,61] Silyl glyoxylates have the ability to function as linchpin synthons for coupling of a nucleophile and an electrophile at a glycolic acid subunit (Scheme 20). This allows rapid formation of complex molecules.



Scheme 20: Silyl glyoxylate as versatile reagents for three-component coupling reactions

Alternaric acid bears a substituted glycolic acid which makes the natural product an attractive target for the application of silyl glyoxylate chemistries. Thus, Johnson and co-workers exploited their silyl glyoxylate methodology for the formal synthesis of Alternaric acid *via* either the intermediate proposed by Trost and co-workers (**54**)[51] or Ichihara's intermediate (**16**) (Scheme 21).[28] Progress towards a third distinct new route towards Alternaric acid was also achieved, with the synthesis of a novel late-stage intermediate **70**, showcasing the power of this silyl glyoxylate methodology.[59]

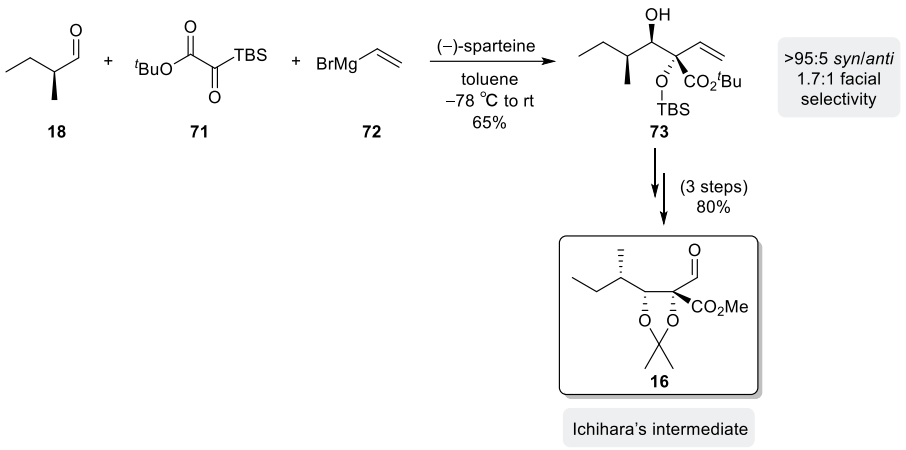


Scheme 21: Potential application of silyl glyoxylate couplings and applications towards the synthesis of Alternaric acid

Investigation of path a and b were first conducted, both involving coupling of (*S*)-(+)-methylbutanal **18** and silyl glyoxylate **67**. In the case of path a, the nucleophile was a vinyl Grignard, and in the case of path b, the nucleophile was an allyl Grignard.

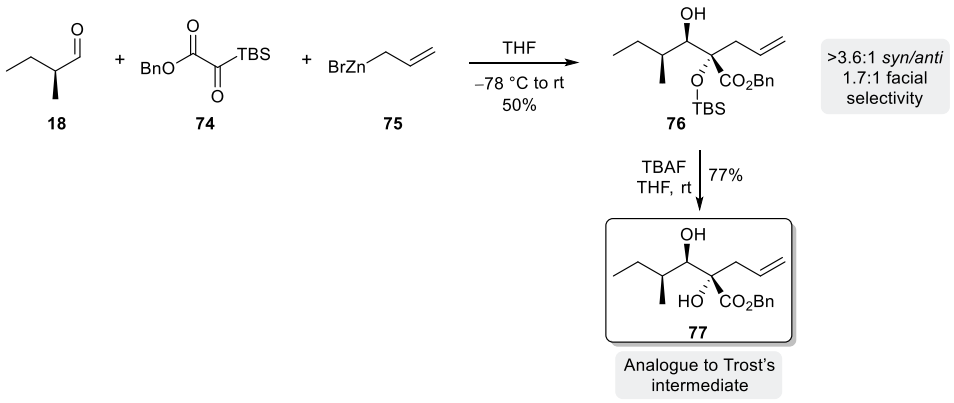
Using vinyl magnesium bromide **72** and sparteine in toluene at low temperature, three-component coupling successfully afforded product **73** in 65% yield with excellent *syn*-/*anti*-aldol diastereoselectivity (>95:5 *syn*/*anti*) but poor facial selectivity (1.7:1) (Scheme 22). Further manipulations on the coupling product

73 (including protecting group manipulations and ozonolysis) led to the formation of aldehyde **16**, a key intermediate in the total synthesis of Alternaric acid originally reported by Ichihara and co-workers.[28]



Scheme 22: Three-component coupling with a vinyl Grignard – towards Ichihara's aldehyde

Exploration of the three-component glyoxylate coupling with an allyl nucleophile then took place (Scheme 23). The optimum conditions were found to make use of allylzinc bromide **75** and silyl glyoxylate **74**, yielding compound **76** in 50%, as a mixture of all four possible diastereoisomers. In this case *syn/anti* selectivity was moderate while facial selectivity was poor again. Deprotection of the silyl ether using TBAF effectively produced intermediate **77**, analogous to Trost's terminal alkene **54**.[51]

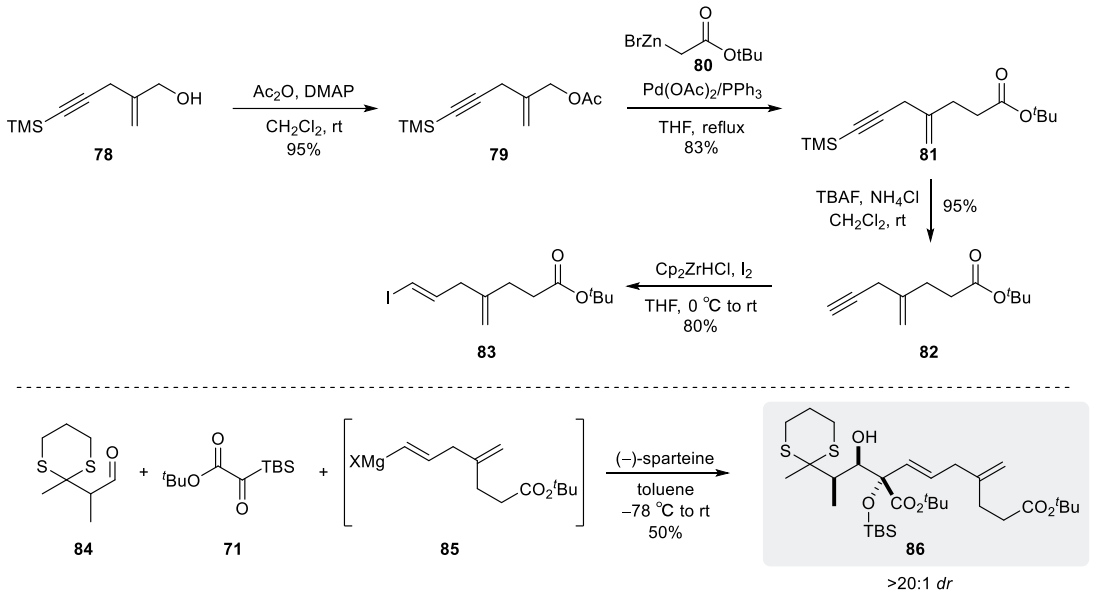


Scheme 23: Three-component coupling with an allyl Grignard – towards Trost's alkene

Both examples of the application of this methodology towards key intermediates in the synthesis of Alternaric acid show the same limitation inherent in the use of (S)-(+)-methylbutanal; the reaction exhibited poor Felkin-Anh facial selectivity,[62] due to minor differences between the ethyl and methyl groups on (S)-(+)-methylbutanal.

With a view to achieve a higher level of stereoselectivity, Johnson and co-workers envisioned two potential strategies. The first involved auxiliary modification of the silyl glyoxylate, and the second consisted of modification of the aldehyde partner using a stereocontrolling element that would easily be converted to the original ethyl group. The auxiliary method did not provide sufficient yields and stereochemical control. Thus, the second approach was considered further. A 1,3-dithiane group was selected due to its large size and ease of single-step desulfurization to alkanes.[63–66] Three-component silyl coupling with an aldehyde partner bearing a 1,3-dithiane group was attempted with vinyl Grignard **72** and silyl glyoxylate **71**. Encouraged by the efficiency of this process, and the excellent stereochemical control (>20:1 (*syn/anti*)), coupling with a more complex nucleophile was then investigated.

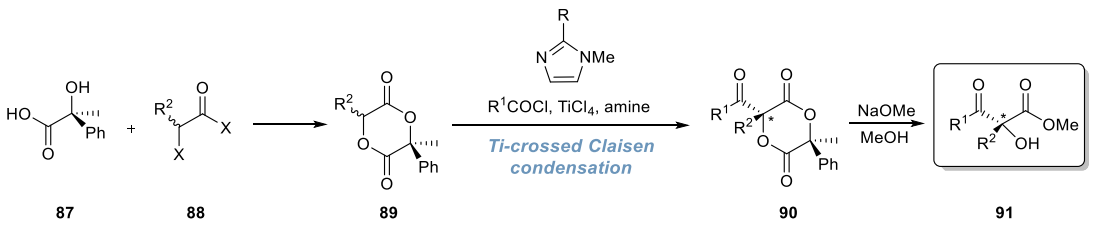
The complex vinyl Grignard **85** was synthesised from allylic alcohol **78** (Scheme 24). Acetylation of allylic alcohol **78** afforded **79**, which was subjected to the Reformatsky reagent[67] **80** to generate **81** in 83% yield. After deprotection of the TMS alkyne, vinyl iodide **83** was generated by hydrozirconation/iodination in 80% yield. The corresponding vinyl Grignard nucleophile **85** was taken into the three-component coupling reaction with silyl glyoxylate **71** and the 1,3-dithiane modified aldehyde **84**. This coupling allowed the construction of **86** which constitutes the majority of the carbon backbone of Alternaric acid in a single step with excellent diastereoselectivity.[59]



Scheme 24: Unique approach for the synthesis of Alternaric acid via three-component coupling reaction using a complex nucleophile and modified aldehyde

1.3.3.4 Asymmetric Ti-crossed Claisen condensation approach

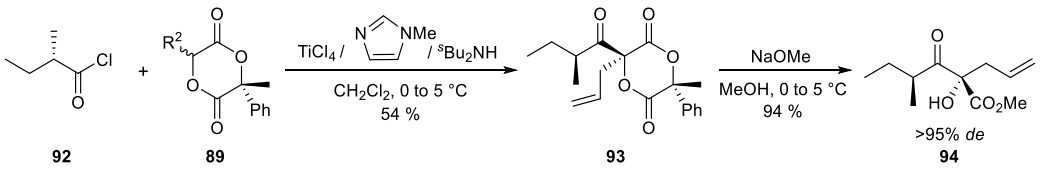
In 2013, Tanabe and co-workers published a total synthesis of Alternaric acid *via* an asymmetric Ti-mediated crossed-Claisen condensation process. They developed a novel and efficient method for the synthesis of chiral α-alkyl-α-hydroxy-β-ketoesters using an asymmetric crossed-Claisen condensation mediated by a Ti-*N*-methylimidazole-amine reagent.[68] The method utilised the chiral templates, 3-methyl-3-phenyl-1,4-dioxane-2,5-diones **89**, which may be readily prepared by cyclocondensation from **87** and **88** (Scheme 25).[69]



Scheme 25: Asymmetric Ti-mediated crossed-Claisen condensation

The developed strategy proved to be successful on a variety of substrates with excellent *anti*-diastereoselectivity between Ph and R^1CO groups. This result can be rationalised by the favoured *Si*-face attack of the Ti-enolate with an activated acyl imidazolium intermediate[70,71] over *Re*-face attack. The targeted products **91** can then easily be accessed *via* methanolysis of **90** in good yields, with recovery of methyl atrolactate (corresponding methyl ester of **87**) in >80% yield.

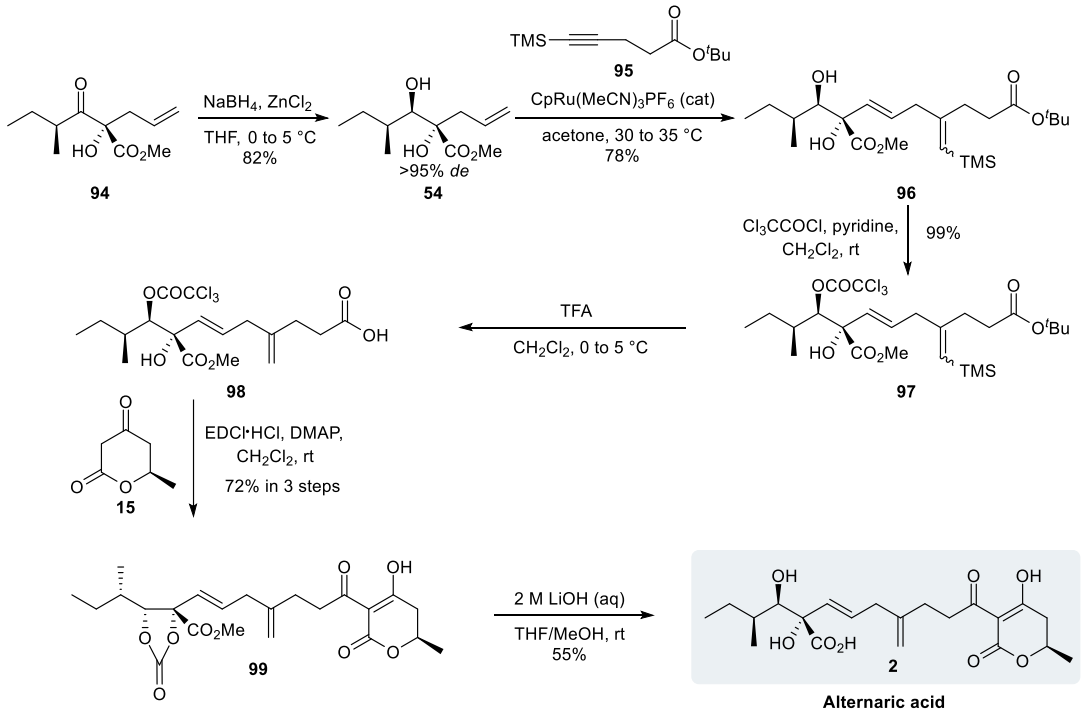
Alternaric acid, with its unique scaffold, bearing three contiguous stereocenters and an α-alkyl-α-hydroxy-β-hydroxyester motif constitutes an ideal target for the application of this methodology. Ti-mediated crossed-Claisen condensation of acid chloride **92** with the chiral template **89** afforded intermediate **93** in 54% yield (Scheme 26). Subsequent methanolysis of **93** gave the desired chiral precursor **94** in 94% yield with over 95% diastereomeric excess.



Scheme 26: Application of the Ti-crossed-Claisen condensation for the preparation of a precursor in the synthesis of Alternaric acid

From **94**, anti-stereoselective reduction using sodium borohydride–zinc chloride led to the formation of Trost's crucial intermediate **54**,[51] with excellent diastereoselectivity (Scheme 27). Trost's methodology[51,70] was then employed to couple **54** to alkyne **95** using the effective $CpRu(MeCN)_3PF_6$ catalyst. The desired vinylsilane **96** was obtained in 78% yield. Selective protection of the secondary alcohol with trichloroacetyl chloride was followed by deprotection of both the *tert*-butyl ester and TMS group to reveal carboxylic acid **98**. With carboxylic acid **98** in hand, C-acylation with pyrone fragment **15** was performed along with the formation of the 1,2-carbonate to yield **99** in 72% yield over three steps.

Hydrolysis of the methyl ester and concomitant deprotection of the 1,2-carbonate afforded Alternaric acid **2** in 55% yield.



Scheme 27: Synthesis of Alternaric acid 2 from the chiral precursor 94

Overall, the Ti-mediated crossed-Claisen condensation is a powerful method that allowed the synthesis of an important chiral precursor in the total synthesis of Alternaric acid in a single step. To summarise, the synthesis of Alternaric acid was achieved in 8 steps following the longest linear sequence with 13% overall yield.[68]

2. Research outline

Despite the phytotoxic nature of Alternaric acid, which makes it an attractive herbicidal lead, very little information has been acquired on the SAR of the natural product.[31,32] Whilst impressive synthetic work has been achieved in the past towards the synthesis of Alternaric acid, restricted synthetic access of the natural product has prohibited a systematic analysis for herbicidal activity.[28,51,59,68] Equally, the mode of action of Alternaric acid has remained elusive.

Consequently, a synthetic strategy that would enable the synthesis of significant quantities of Alternaric acid, as well as a thorough SAR analysis of the natural product towards a new herbicidal lead is desired. For this purpose, a scalable and flexible synthetic route was targeted, with a view to produce a variety of analogues in the most efficient way (Figure 5). It was anticipated that a thorough biological evaluation of Alternaric acid would enable more insight in the MoA of the natural phytotoxin. In addition, SAR investigations were proposed to identify a more active compound with improved herbicidal activity along with other required properties for commercialised herbicides, such as structural simplicity.[72]

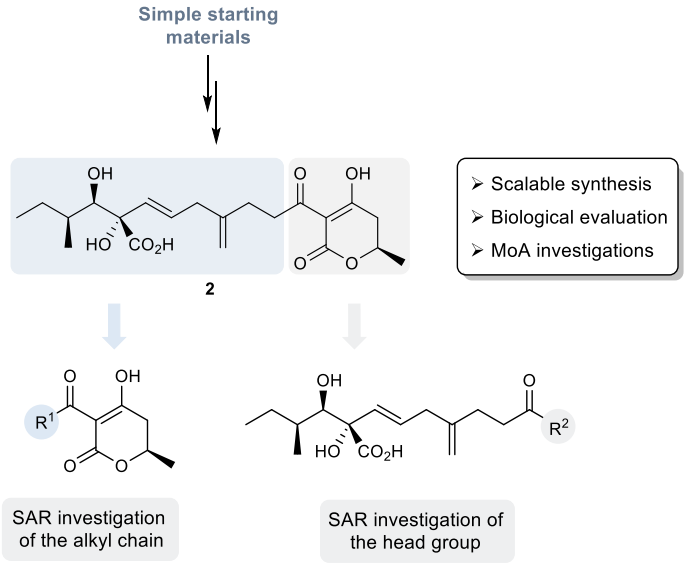


Figure 5: Approach towards a scalable and flexible synthesis of Alternaric acid enabling SAR analysis

Considering the relevance of the triketone motif in agrochemistry,[9,15] its influence in the herbicidal activity of Alternaric acid would be evaluated through the synthesis of natural product derivatives bearing different triketone head group motifs. Finally, to generate highly biologically active compounds but with greater structural simplicity, the synthesis of analogues with modification of the alkyl chain was envisioned.

It was hoped that with this work, a novel compound with improved herbicidal and agrochemical properties could be discovered, with a view to establish a novel and more attractive lead for herbicidal discovery.

In summary, the main aims for this work were:

- Synthesis of sufficient quantities of Alternaric acid
- Biological evaluation of Alternaric acid
- SAR investigations through analogue synthesis
- MoA investigations

3. Results and discussion

3.1 Total synthesis of Alternaric acid

The primary objective of this project was to synthesise significant quantities of Alternaric acid to enable herbicidal evaluation as well as investigations towards elucidation of the MoA of the natural product.

3.1.1 Retrosynthetic strategy

In this context, a cost-effective, scalable, and flexible synthesis was targeted. The esterification/Fries-type rearrangement method, previously established by Ichihara and co-workers was selected as the first disconnection (Figure 6). It was anticipated that using this strategy, a variety of natural product derivatives could also be accessed through the coupling of different 'head groups' with the carboxylic acid intermediate **100** ('tail'). For the construction of the 1,4-diene motif, Trost's efficient Ru-catalysed Alder-Ene reaction[49–51] was chosen.

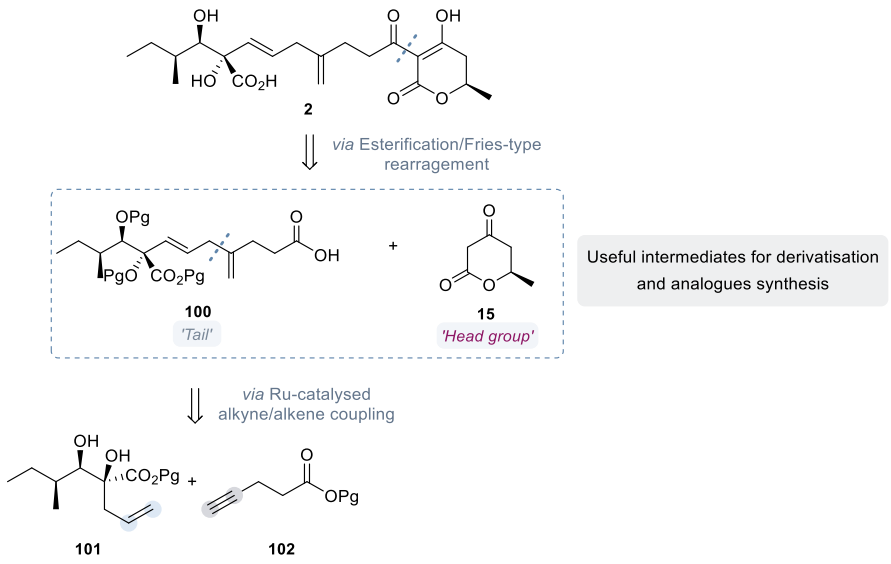


Figure 6: Retrosynthetic strategy for Alternaric acid enable SAR investigations

It was hypothesised that this would allow for flexibility in the synthesis of Alternaric acid, with the possibility to couple different alkene and alkyne partners. This would generate analogues with a view to investigate functional group relevance for biological activity.

While the synthesis of the natural product was a primary objective of this project, the flexibility of the synthesis remained essential to allow rapid and facile derivatisation. It was envisioned that from the targeted late-stage intermediate **103**, derivatisation could be achieved in only two steps, thus efficiently providing complex analogues of the natural product (Figure 7). With this in mind, the synthesis of intermediate **103** was targeted, hypothesising that it could be coupled to a range of head group variants, then subjected to basic hydrolysis conditions to remove all protecting groups at once.

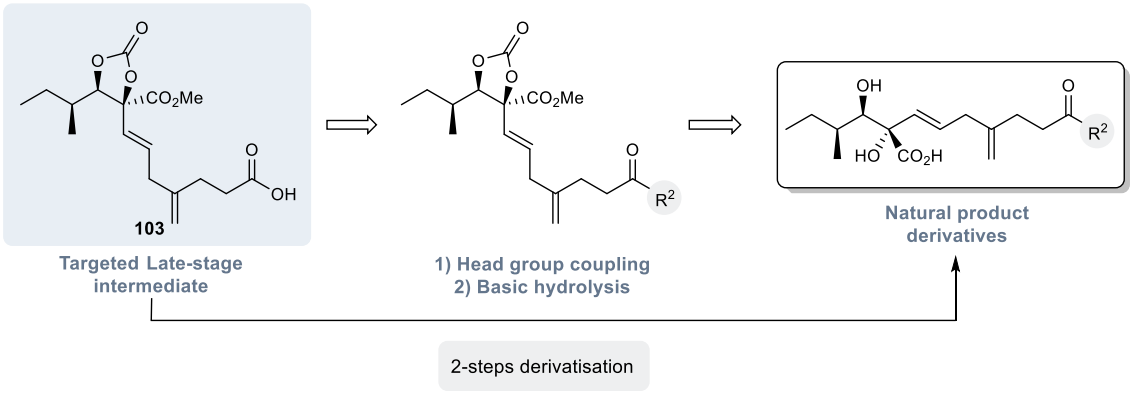
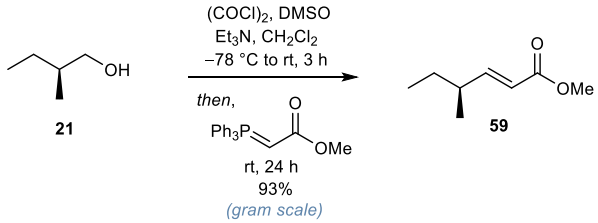


Figure 7: Late-stage derivatisation strategy using the key intermediate 103

3.1.2 Forward synthesis of Alternaric acid

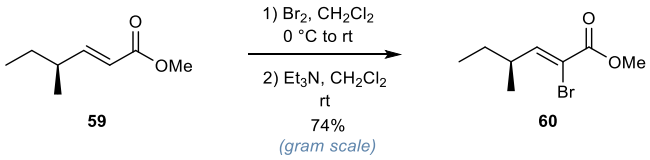
Based on Trost's previous work to prepare the desired terminal alkene **54** for the Ru-catalysed step[50], the synthesis commenced with a one-pot Swern oxidation/Wittig olefination (Scheme 28). The reaction conditions for this process were not reported in Trost's formal synthesis of Alternaric acid.[50] However, employing a telescoped Swern and subsequent Wittig procedure,

several grams of the desired unsaturated ester **59** were obtained in 93% yield, demonstrating the excellent efficiency and scalability of this process.



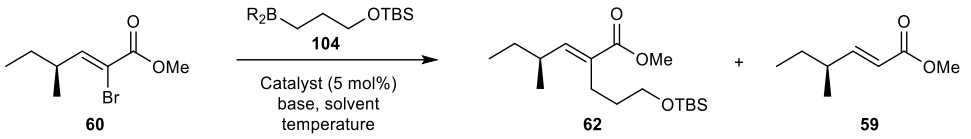
Scheme 28: Telescoped Swern/Wittig synthesis of the unsaturated ester 59

Next, bromination-elimination of the unsaturated ester **59** using bromine and triethylamine afforded the desired vinyl bromide **60** in 74% yield and again on gram scale (Scheme 29). Additionally, the transformation could be achieved in one-pot without variation of the reaction yield (72%, see experimental section).



Scheme 29: Synthesis of the vinyl bromide 60

With the vinyl bromide **60** in hand, a sp^2-sp^3 Suzuki-Miyaura[57] coupling was attempted using the *in situ* generated (using 9-BBN) alkyl organoborane **104** (Table 1). Using the conditions outlined in entry 1 below, no product was obtained; however, full consumption of the starting material was observed and formation of by-product **59** was confirmed, resulting from β-hydride elimination.



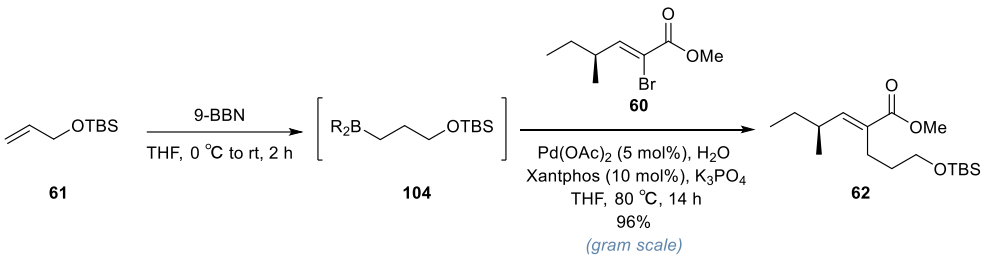
Entry	Catalyst	Base (eq)	Solvent	T (°C)	Time (h)	H_2O (eq)	Ratio 62:59*
1	$Pd(dppf)Cl_2$	K_3PO_4 (3)	THF	80	16 h	/	0 : 100
2	$Pd(dppf)Cl_2$	K_3PO_4 (1)	DMF	50	16 h	/	0 : 100
3	$Pd(OAc)_2$, XPhos	K_3PO_4 (3)	THF	80	16 h	/	33 : 67
4	$Pd(dppf)Cl_2$	K_3PO_4 (3)	THF	80	16 h	5	50 : 50
5	$Pd(dppf)Cl_2$	K_2CO_3 (3)	DMF	50	16 h	5	23 : 77
6	$Pd(dppf)Cl_2$	K_3PO_4 (3)	THF	rt	48 h	5	39 : 61
7	$Pd(OAc)_2$, Xantphos	K_3PO_4 (3)	THF	80	16 h	5	>95 : 5

**Ratio 62:59 was determined by ^1H NMR analysis of the crude reaction mixture*

Table 1: Optimisation of the β-alkyl Suzuki-Miyaura cross-coupling

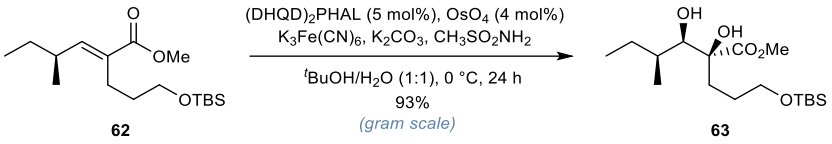
The cross-coupling was then attempted using the conditions originally developed by Miyaura and co-workers (entry 2).[73] Again, the starting material was fully consumed, and only the by-product **59** was observed by ^1H NMR spectroscopy. Using palladium acetate and XPhos as the ligand, the desired product **62** was observed in a 33:67 ratio, with the major product being the undesired side product **59** (entry 3). In order to facilitate the transmetallation step, 5 equivalents of water were added to the reaction mixture which increased the ratio of product formed (entries 4–6). Finally, since competing β-hydride elimination of alkylborane **104** over the reductive elimination was suspected, the use of another hindered bidentate ligand, Xantphos, was investigated.[74,75] Pleasingly, using this particular ligand, the desired product **62** was formed majorly in >95:5 ratio (entry 7).

The optimised Suzuki-Miyaura conditions for this process allowed the synthesis of product **62** in excellent yield on multigram scale (Scheme 30).



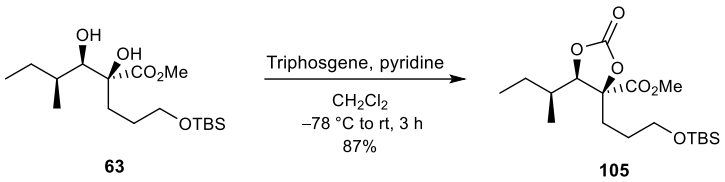
Scheme 30: Successful synthesis of product 62

The trisubstituted alkene **62** is an ideal substrate for Sharpless asymmetric dihydroxylation.[56,76] As such, **62** was treated with AD-mix β to afford the corresponding diol **63** in >95:5 *dr*, which was isolated as a single diastereoisomer in 93% yield (Scheme 31).



Scheme 31: Sharpless asymmetric dihydroxylation of the trisubstituted alkene 62

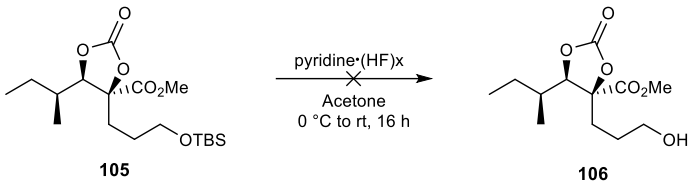
Pursuing the retrosynthetic strategy outlined in Figure 6 and 7 (vide supra), deprotection of the primary alcohol was envisioned, for subsequent elimination towards the formation of the primary alkene target required for Ru-catalysis. As such, protection of the diol **63** to the corresponding carbonate compound **105** was performed at this stage, using triphosgene and pyridine (Scheme 32).



Scheme 32: Synthesis of the carbonate protected intermediate 105

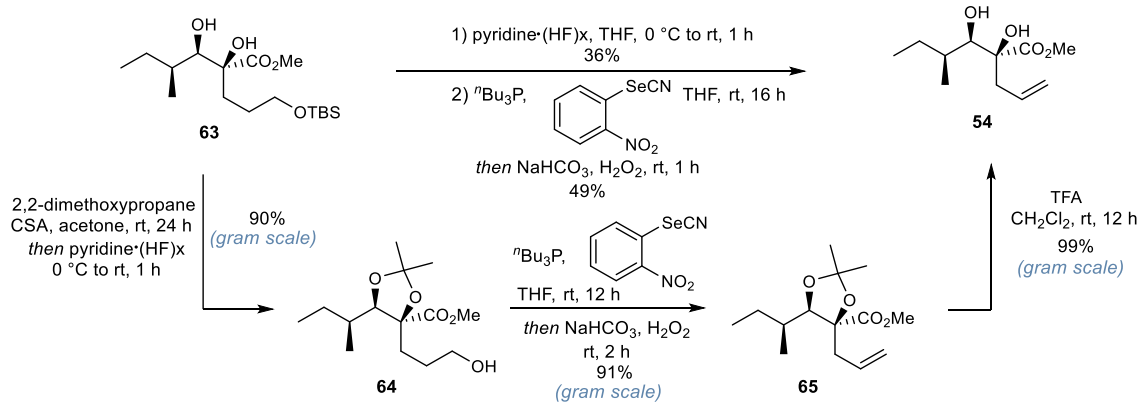
Unfortunately, treatment with pyridine hydrofluoride, to remove the silyl protecting group, failed to give the desired product **106**, and degradation of the starting material was observed (Scheme 33). It was hypothesised that the

instability of the carbonate group was maybe responsible for degradation in this process.



Scheme 33: Attempted synthesis of 106

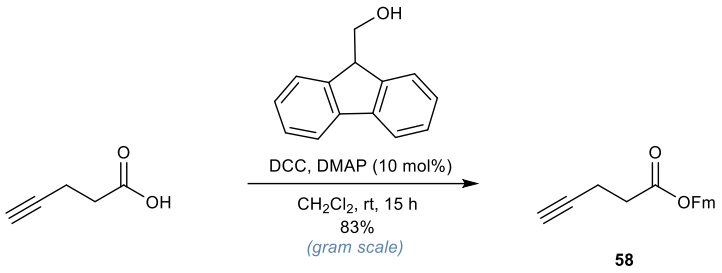
Considering this, deprotection of the silyl ether of diol **63** and subsequent Grieco[58] selective elimination of the primary alcohol on the resulting free diol intermediate was attempted (Scheme 34). The desired alkene **54** could be obtained with a moderate yield (49%). Alternatively, when diol **63** was temporarily protected to the corresponding acetonide **64**, elimination of the primary alcohol and subsequent removal of the acetonide protecting group yielded the desired alkene compound **54** in much higher overall yield (81% over three steps) on gram scale.



Scheme 34: Synthesis of terminal alkene 54

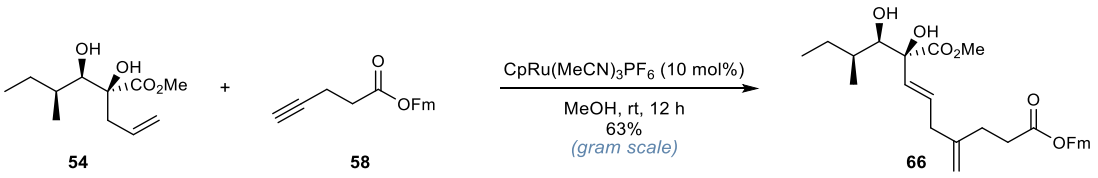
With the synthesis of terminal alkene **54** accomplished, attention was turned to the synthesis of the alkyne coupling partner for the Ru-catalysed coupling. As such, the commercially available 4-pentynoic acid was protected to the

corresponding Fm ester **58** through esterification using DCC and catalytic DMAP (Scheme 35).



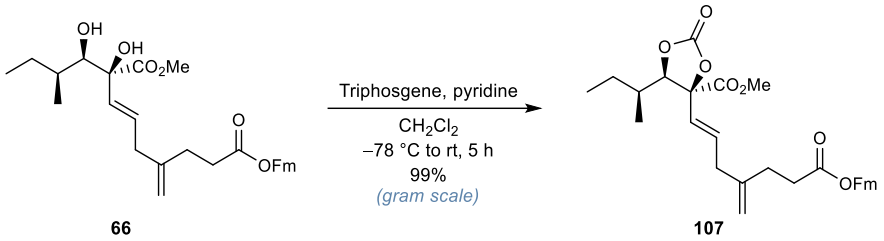
Scheme 35: Synthesis of alkyne coupling partner 58

Thus, Ru-catalysed coupling of alkene **54** and alkyne **58** could be attempted. In the original report,[51] the ruthenium Alder-Ene coupling used to build the acyclic skeleton of Alternaric acid, employed CpRu(COD)Cl as a catalyst and ammonium hexafluorophosphate as an additive (*vide supra*, Scheme 18). The reaction conditions also involved high temperature and elevated pressure. However, a more recent development on the Ru-catalysed Alder-Ene coupling by the Trost group demonstrated the successful use of $CpRu(MeCN)_3PF_6$ as a catalyst which could be used under milder conditions (lower temperature and ambient pressure).[52] Therefore, the $CpRu(MeCN)_3PF_6$ catalyst was employed for coupling of alkene **54** and alkyne **58** (Scheme 36). Pleasingly, the desired branched 1,4-diene **66** was obtained in good yield on gram scale.



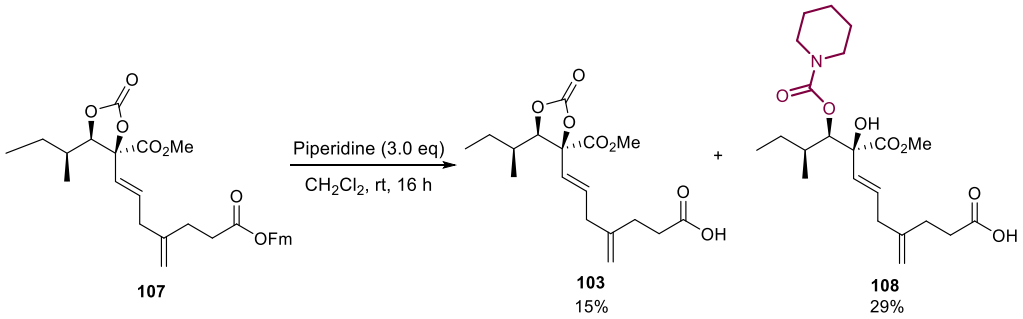
Scheme 36: Ru-catalysed synthesis of 1,4-diene 66

At this stage, protection of the diol was envisioned before selective deprotection of the Fm ester. Thus, using triphosgene and pyridine, diol **66** was converted to the corresponding carbonate **107** in 99% yield on gram scale (Scheme 37).



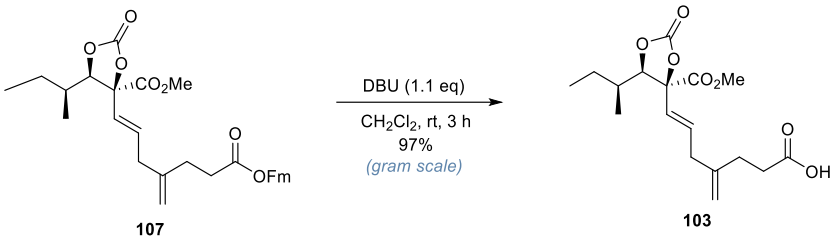
Scheme 37: Protection of diol 66 to carbonate intermediate 107

Next, selective Fm ester hydrolysis of intermediate **107** was attempted using piperidine (Scheme 38). Although ^{1}H NMR analysis of the crude mixture showed presence of the desired product **103**, an undesired by-product was also formed. After separation and isolation of both products, the undesired product was identified and characterised as piperidine carbamate **108**. Purification and separation of these two carboxylic acids (**103** and **108**) was challenging, as a result the desired carboxylic acid **103** was obtained in only 15% yield.



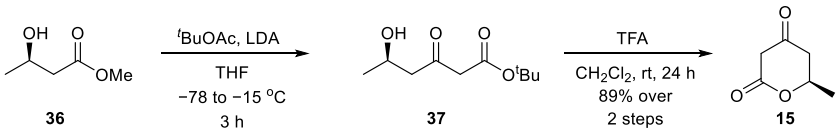
Scheme 38: Attempted selective hydrolysis of Fm ester 107

Whilst this result was unexpected, it can be attributed to the excess use of piperidine in the reaction conditions. To prevent nucleophilic addition of piperidine onto the carbonate, the reaction was attempted again with just one equivalent of piperidine. However, after 3 days complete conversion could not be achieved. Instead, the reaction was performed using DBU, and after 3 h, the desired product **103** was isolated in 97% yield (Scheme 39).



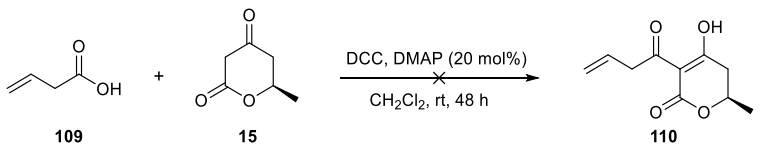
Scheme 39: Selective fluorenyl methyl hydrolysis of 107

At this stage, esterification coupling of head group **15** with carboxylic acid **103** was targeted. To this end, the synthesis of head group **15** was required. Using the commercially available starting material **36**, crossed-Claisen condensation with *tert*-butyl acetate using LDA at low temperature, furnished intermediate **37** which was treated with TFA to yield the cyclised product **15** in 89% over two steps (Scheme 40).



Scheme 40: Synthesis of head group 15

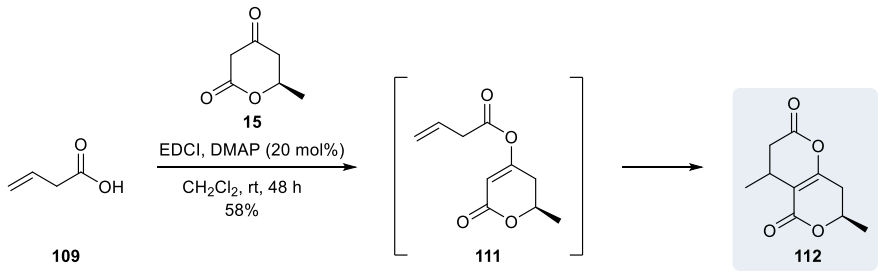
Preliminary attempts for the coupling of carboxylic acid substrate **103** with the head group **15** using Ichihara's conditions[28,49] failed to give the desired C-acyl product. To find optimal reaction conditions, test reactions were carried out on substrate **109**. Once again, employing Ichihara's conditions failed to give the desired product (Scheme 41).



Scheme 41: Failed synthesis of 110

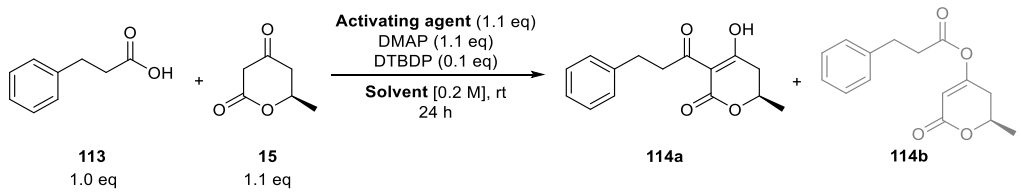
The reaction was next attempted with a different activating agent (EDCI) (Scheme 42). Again, no desired C-acyl product **110** was observed; however an

unexpected product was isolated and characterised as compound **112**. It was proposed that formation of the undesired product **112** occurred *via* esterification to the O-acyl intermediate **111** then subsequent cyclisation.



Scheme 42: Formation of undesired side-product 112

It was hypothesised that Michael acceptors, or substrates capable to rearrange into a Michael acceptor, would be problematic for this reaction. As such, hydrocinnamic acid **(113)** was selected as a model substrate for the optimisation of this process. Consequently, six solvents and four activating agents were first screened, employing a stoichiometric additive (DMAP) (Table 2). The results of these reactions have been quantified by LCMS against a known internal standard 4,4'-di-tert-butyl-1,1'-biphenyl (DTBDP), and the LCMS yields of the C-acyl **(114a)** and O-acyl **(114b)** products are presented below.



113 1.0 eq | **15** 1.1 eq | **114a** | **114b**

	CH_2Cl_2	MeCN	DMF	$CHCl_3$	PhMe	THF
EDCI	84	96	86	82	38	66
DCC	96	96	86	96	72	86
CDI	9	8	7	9	14	5
HATU	4	6	6	3	12	5

C -acyl results

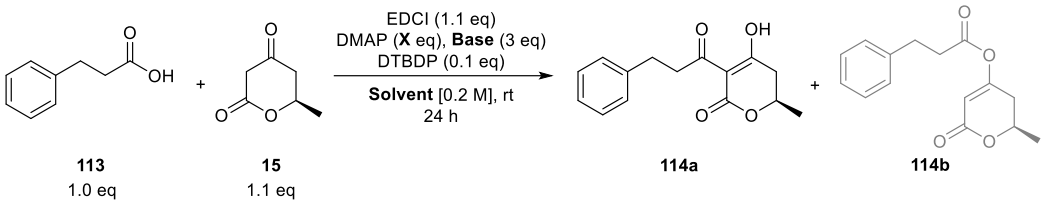
	CH_2Cl_2	MeCN	DMF	$CHCl_3$	PhMe	THF
EDCI	0	0	0	0	0	0
DCC	0	0	0	0	0	0
CDI	0	0	0	0	0	5
HATU	2	1	5	2	7	1

O -acyl results

Table 2: Solvent and Activating agent screen

In terms of activating agents, both EDCI and DCC showed good results for most solvents; however CDI and HATU gave poor results in all solvents (<14% yield). The presence of the O-acyl intermediate **114b** was only detected under HATU-promoted conditions. When conversion to the C-acyl product **114a** was low, the absence of O-acyl product **114b** suggests that esterification reaction was the limiting step, as opposed to the Fries-type rearrangement. Using DCC or EDCI as activating agents, two solvents gave particularly good results, acetonitrile and dichloromethane. Although DCC also furnished excellent results, EDCI was chosen as the optimum activating agent for purification purposes. Indeed, separation of the product from the DCC urea by-product proved to be challenging.

To assess whether DMAP could be used catalytically, the next screen focused on the study of different stoichiometry of DMAP in the presence of different additional bases (Table 3). This screen was performed using both optimum solvents, acetonitrile and dichloromethane.



	CH_2Cl_2			MeCN		
	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP
No base	0	37	80	0	47	96
Et_3N	0	66	72	14	67	80
Pyridine	0	35	79	0	45	70
DIPEA	0	72	78	15	70	83

C-acyl results

	CH_2Cl_2			MeCN		
	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP
No base	89	49	0	63	51	0
Et_3N	46	0	0	8	0	0
Pyridine	79	47	0	84	49	0
DIPEA	65	0	0	10	0	0

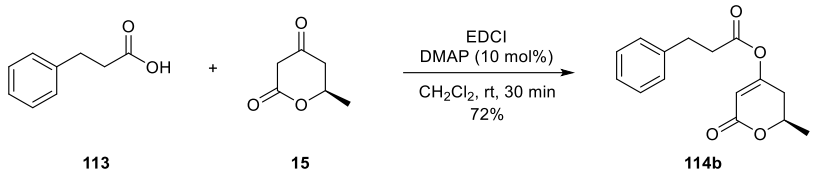
O-acyl results

Table 3: Additive stoichiometry, base, solvent screen

In the absence of base and DMAP, only O-acyl product was obtained. The addition of catalytic DMAP with no additional base or 3 equivalents of pyridine gave a mixture of O-acyl and C-acyl product whereas the use of stoichiometric DMAP gave exclusively C-acyl in excellent yield (96% in acetonitrile). DIPEA and triethylamine, which a have similar pKa_H value, exhibited a similar effect on this reaction giving higher conversion of the O-acyl to C-acyl product when using catalytic DMAP. Overall, when stoichiometric DMAP was employed, the use of any additional base was detrimental to the reaction. Interestingly, these results seem to suggest that the esterification reaction itself performs best in dichloromethane whereas the rearrangement itself proceeds best in acetonitrile.

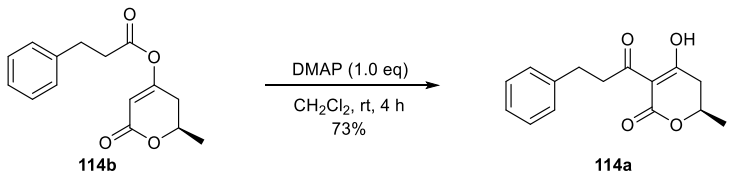
From the optimisation presented above, DMAP appeared to be playing an essential role in promoting the rearrangement for the O-acyl to the C-acyl

position. To probe this, the O-acyl compound **114b** was synthesised using the conditions outlined in Scheme 43.



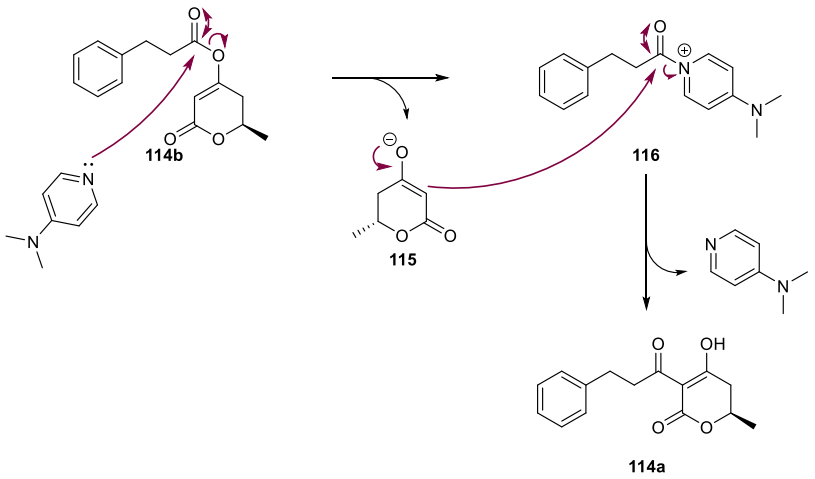
Scheme 43: Synthesis of O-acyl product 114b

The O-acyl product **114b** was then subjected to one equivalent of DMAP in dichloromethane (Scheme 44). As predicted, under these conditions, O-acyl **114b** was converted to C-acyl product **114a** in 73% yield with complete conversion of the starting material **114b**.



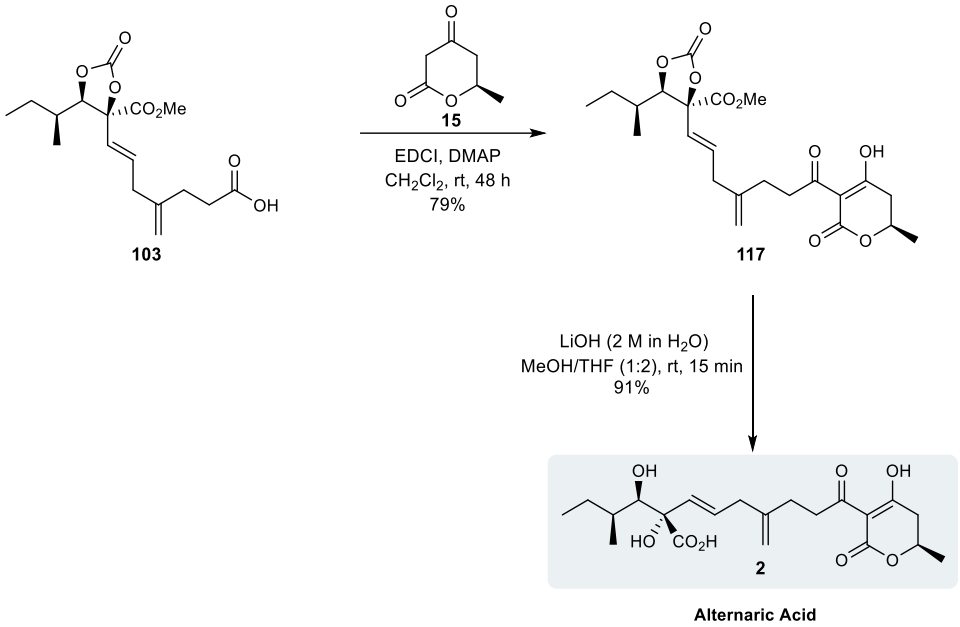
Scheme 44: DMAP-promoted rearrangement of 114b to 114a

Based on this result, the following mechanism was proposed for this rearrangement (Scheme 45). First, reaction of DMAP with O-acyl **114b** would lead to the formation of acyl DMAP intermediate **116**, releasing enolate **115**. Subsequent C-centred attack of **115** onto adduct **116** would regenerate DMAP and afford desired C-acyl product **114a**. Intermediate **116** was observed by LCMS analysis of the reaction profile, further supporting the proposed mechanism. Additionally, after work up, hydrocinnamic acid was observed by ^{1}H NMR spectroscopy, probably resulting from hydrolysis of intermediate **116** and rationalising the non-quantitative yield of the rearrangement after only 4 h.



Scheme 45: Proposed mechanism for the DMAP-promoted rearrangement

With this information in hand regarding the esterification/Fries-type rearrangement step, coupling of the head group **15** with late-stage carboxylic acid intermediate **103** was attempted. Using stoichiometric DMAP and EDCI as the activating agent, the desired product **117** was obtained in 79% (Scheme 46). Subsequent basic hydrolysis using lithium hydroxide ultimately afforded the desired natural product Alternaric acid (**2**).



Scheme 46: Final steps towards the synthesis of Alternaric acid 2

Gratifyingly, crystal growth was successful to provide the first x-ray crystal structure of Alternaric acid, therefore allowing unambiguous confirmation of the structure and stereochemistry of the natural product (Figure 8).

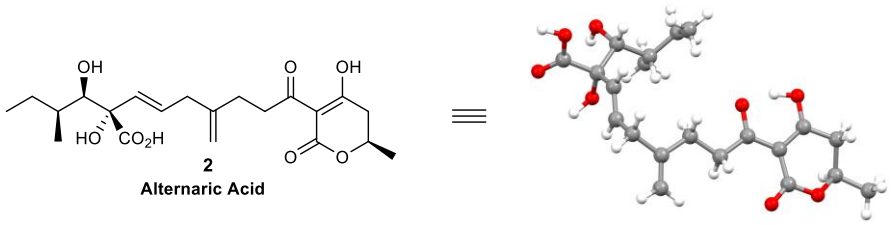
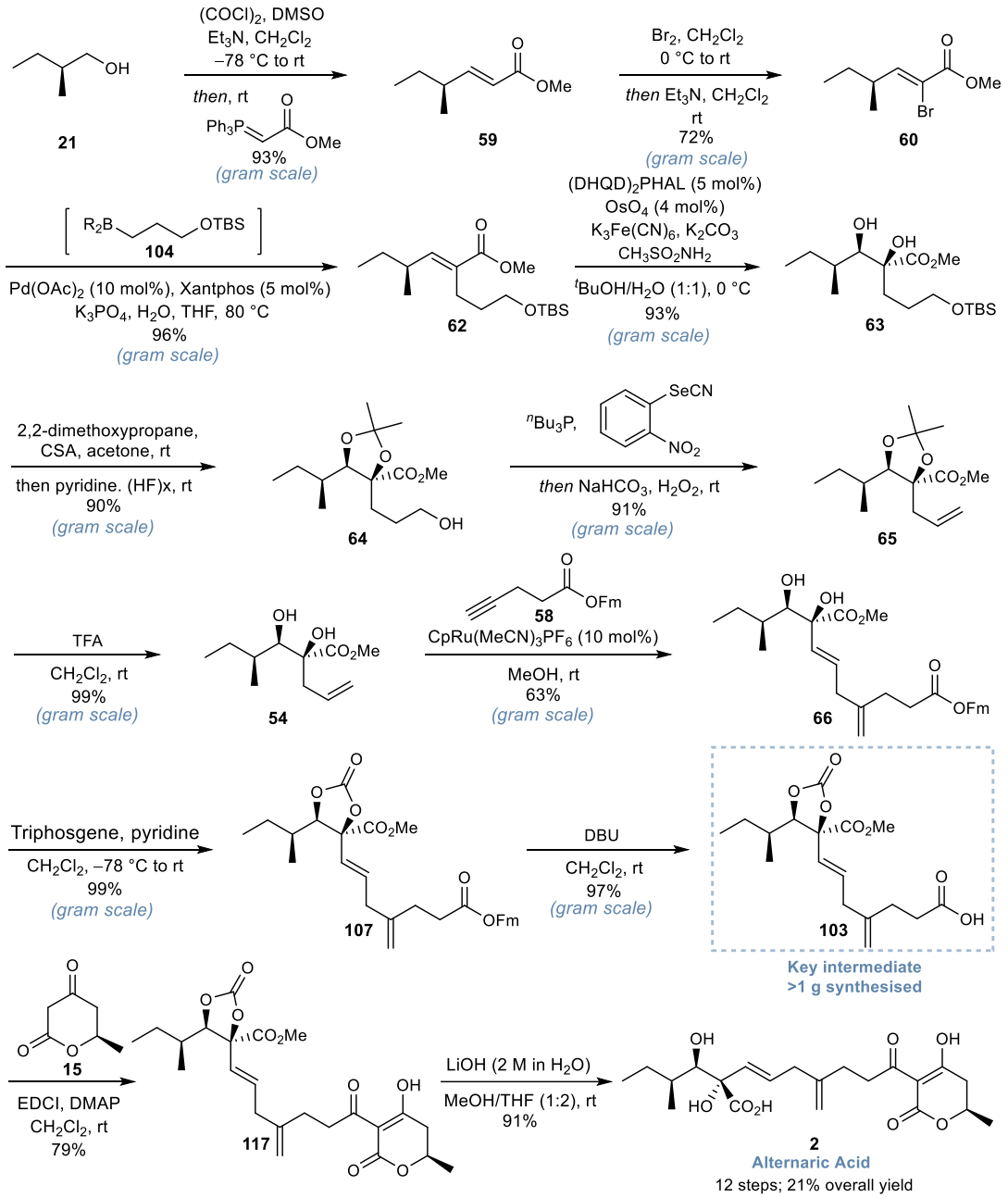


Figure 8: Crystal structure of Alternaric acid 2

Overall, the synthesis of Alternaric acid (**2**) was achieved in 12 steps with a 21% overall yield through a scalable route with potential for late-stage derivatisation from key intermediate **103** (Scheme 47).



Scheme 47: Total synthesis of Alternaric acid

3.2 Biological evaluation of Alternaric acid

Through collaboration with Syngenta, biological assessment of Alternaric acid could be performed by way of probing the herbicidal activity of the natural product over different weed species in different assays.

3.2.1 Glasshouse testing 1 (GH1)

In GH1, compounds are tested for pre- and post-emergence against four weed species with the compound applied at a rate of 1000 g/ha. Phytotoxicity is assessed visually (0–100% where complete control of the target is 100 and 0 is no control). Known commercial herbicides (Acetochlor, Atrazine, Mesotrione, Pinoxaden, and Glyphosate) were used as positive controls for the test. Test species were: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), and *Digitaria sanguinalis* (DIGSA). Symptoms exhibited by the weed species were also visually recorded: NC = necrosis, ST= stunting, BL = bleaching, CL = chlorosis, GI = germination inhibition, and MR = morphological response.

Initial phytotoxic assessment of Alternaric acid in GH1 demonstrated good levels of herbicidal activity with almost complete control of dicot weeds (AMARE and STEME) both post and pre-emergence (Chart 1). High levels of phytotoxicity were also observed against the monocot weed DIGSA when Alternaric acid was applied post-emergence. Interestingly, necrosis and stunting symptoms were observed but no bleaching which is characteristic of HPPD inhibition. For full tabular data see the experimental section.

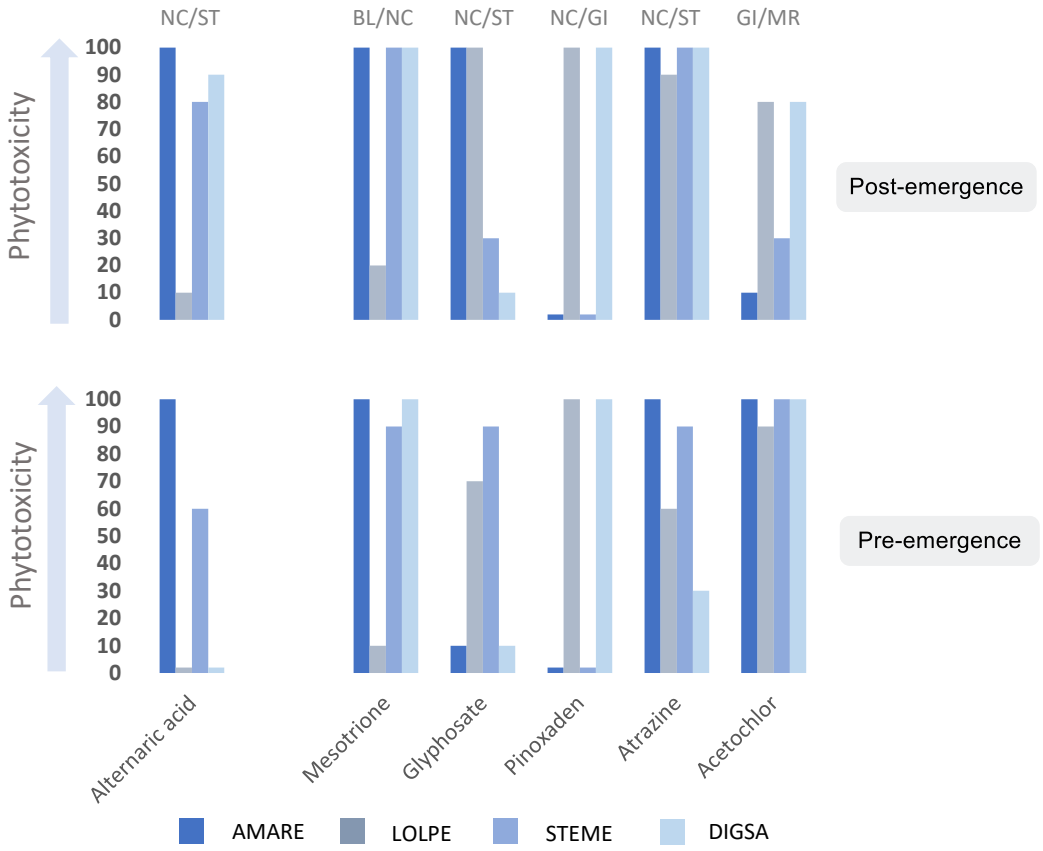


Chart 1: GH1 assessment of Alternaric acid and comparison to known herbicides

3.2.2 Early profiling screen (EPS)

In EPS, compounds are tested for pre- and post-emergence against six weed species with the compound applied at different rates (250–1000 g/ha). Phytotoxicity is assessed visually (0–100% where complete control of the target is 100 and 0 is no control). Known commercial herbicides (Acetochlor, Atrazine, Mesotrione, Pinoxaden, and Glyphosate) were used as positive controls for the test. Test species were: *Amaranthus retroflexus* (AMARE), *Amaranthus palmeri* (AMAPA), *Solanum nigrum* (SOLNI), *Setaria faberi* (SETFA), *Lolium perenne* (LOLPE), *Echinochloa crus-galli* (ECHCG), *Zea mays* (ZEAMX), and *Ipomoea hederacea* (IPOHE).

The phytotoxic profile of Alternaric acid was further evaluated in EPS (Chart 2). In this test, promising compounds are hoped to retain activity at lower rate of

application. Whilst phytotoxicity did not diminish significantly pre-emergence, Alternaric acid showed insufficient herbicidal activity at lower rates (500 and 250 g/ha) both post and pre-emergence.

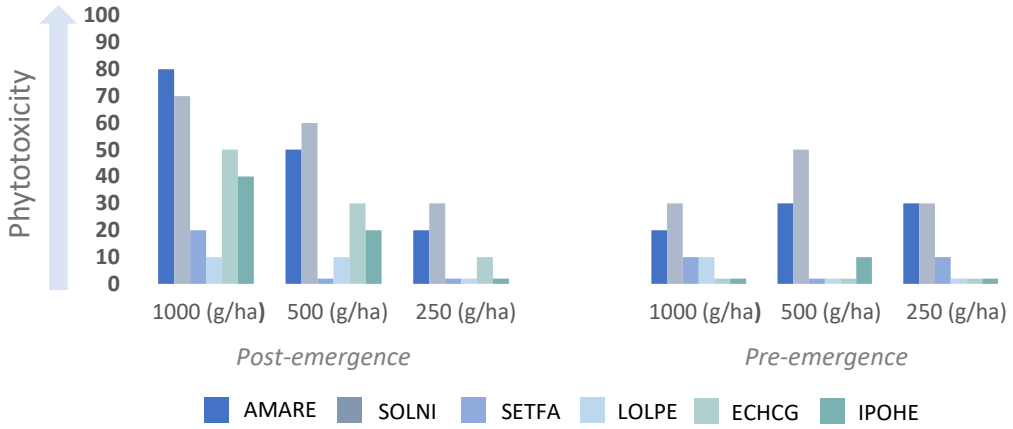


Chart 2: EPS assessment of Alternaric acid

A novel herbicidal solution is only useful if a tractable lead can be identified for development. As such, although EPS testing of Alternaric acid gave moderate results, the ultimate goal is to identify a structurally simpler lead with enhanced herbicidal activity. The structural complexity of Alternaric acid is incompatible with the requirements for production on large scale and at acceptable cost.[72]

3.3 SAR analysis

3.3.1 Preliminary investigations

Initial SAR assessment looked at simplifying the structure of Alternaric acid through deletion of functional groups and motifs towards less complex analogues, with a view to identify key prerequisites for herbicidal activity (Figure 9). Consequently, biological assessment of compounds **118**, **119**, and **120** was first aimed. Compound **118** contains the head group, the 1,4-diene motif, and only one stereocentre. Compound **119** is essentially analogous to **2** with deletion of

the left part of the alkyl chain of the (*E*)-disubstituted alkene. Finally compound **120**, which consists in **2** without the presence of the head group **15** was targeted for herbicidal evaluation.

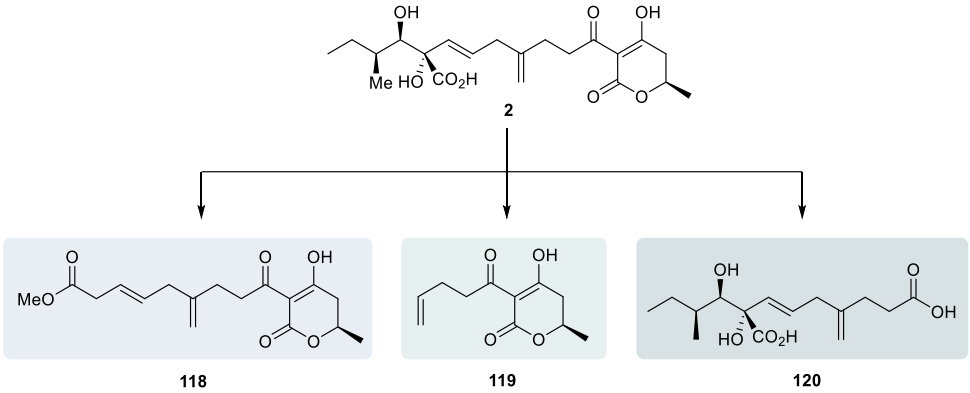
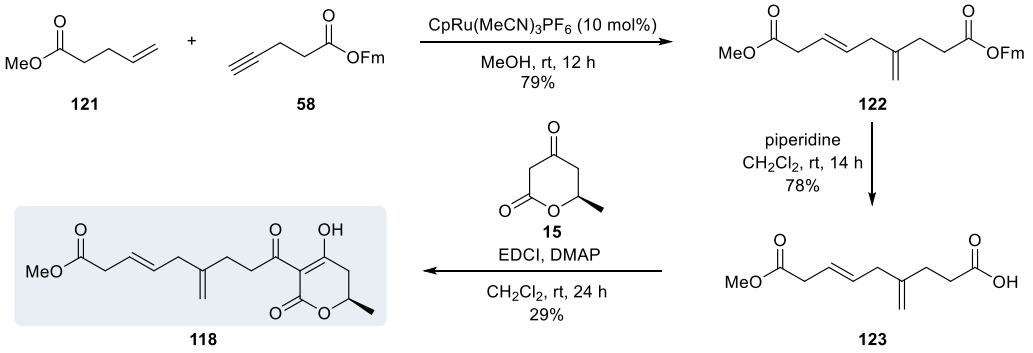


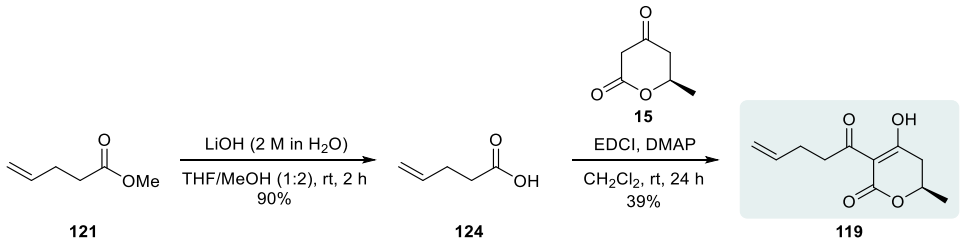
Figure 9: Preliminary analogue design for initial SAR analysis

Owing to the flexibility of the developed total synthesis, compound **118** could be synthesised in just three steps from the commercially available terminal alkene **121** and Fm ester **58** previously employed in the synthesis of Alternaric acid (**2**) (Scheme 48). Using Trost's Ru-catalysed method previously introduced,[52] 1,4-diene **122** was obtained in 79% yield. Selective hydrolysis of Fm ester **122** and subsequent coupling of the head group **15** afforded the desired analogue compound **118**.



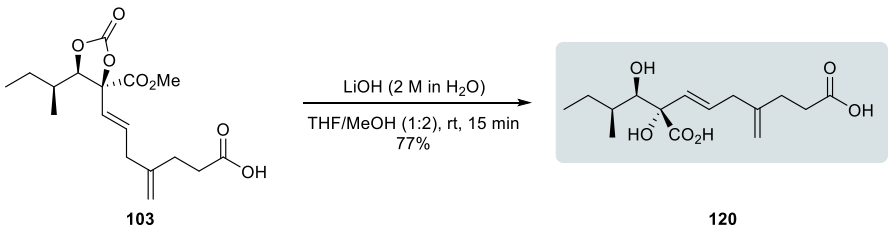
Scheme 48: Synthesis of analogue 118

Compound **119** was produced in two steps from the same homoallylic ester starting material **121** (Scheme 49). Basic hydrolysis was followed by esterification/Fries-type rearrangement using compound **15** to efficiently generate analogue **119**.



Scheme 49: Synthesis of analogue 119

The analogous compound **120** was prepared through basic hydrolysis of key intermediate **103** to reveal the free diol and carboxylic acid motif (Scheme 50).



Scheme 50: Synthesis of analogue 120

These three compounds (**118**, **119,** and **120**) were subjected to GH1 herbicidal assay for evaluation of phytotoxicity (Chart 3). Compound **118** exhibited no phytotoxicity against any of the weeds tested both post- and pre-emergence. Surprisingly analogue **119,** which is an even more simplified version of compound **118,** showed moderate activity against dicot weeds (AMARE and STEME) mostly post-emergence with bleaching and stunting symptoms. However, levels of activity were not satisfactory for further evaluation of this analogue (**119**). More interestingly, herbicidal evaluation of compound **120**, analogous to Alternaric acid without the head group motif, resulted in no activity across the four weed species. This result highlights the crucial involvement of the head group motif in the phytotoxicity of Alternaric acid.

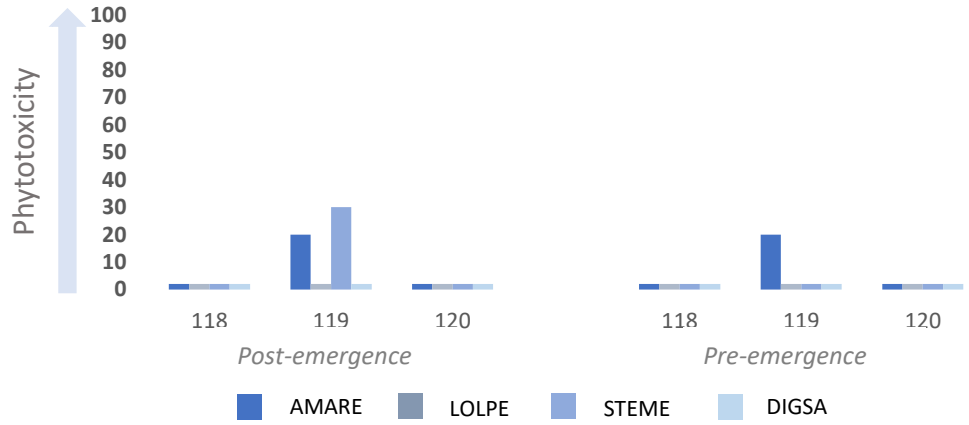


Chart 3: GH1 assessment of simplified analogues of Alternaric acid

3.3.2 SAR investigations of the head group

3.3.2.1 Synthesis of natural product derivatives

Preliminary analysis of the SAR of Alternaric acid confirmed the initial hypothesis that the head group significantly impacts activity. Thus, optimisation of this motif was sought. A range of different head group motifs was investigated for coupling to the key intermediate **103** in order to generate analogues of **2** and identify the most effective head group. The scope of head group motifs examined is presented below in Figure 10. Analogues with modification of the lactone substituent were investigated, such as head group **125a**, the opposite enantiomer of **15**. Ethyl-substituted lactone **125b** and des-methyl **125c** were also selected. The cyclohexanedione motif **125d**, prevalent in commercial herbicides such as Mesotrione,[9] was also chosen. Finally, the synthesis of lactam analogue of Alternaric acid was targeted.

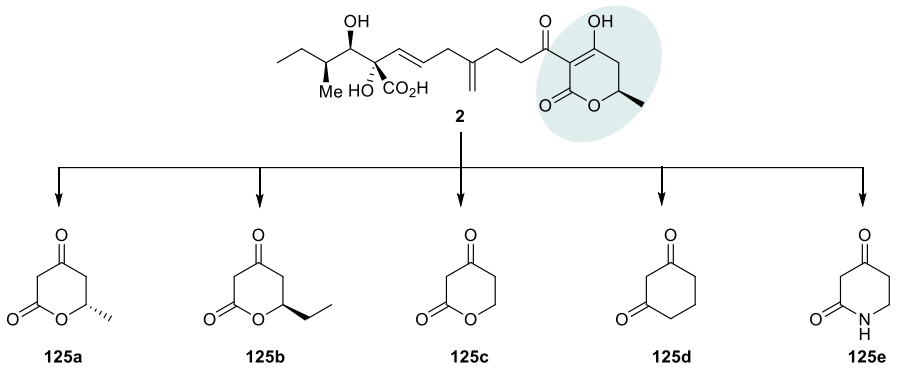
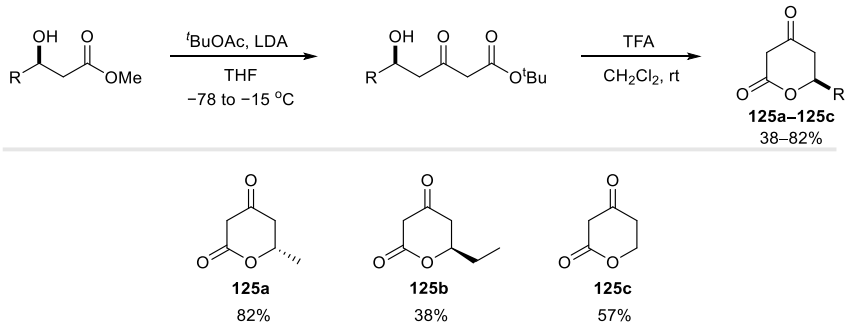


Figure 10: Scope of head groups targeted for SAR evaluation

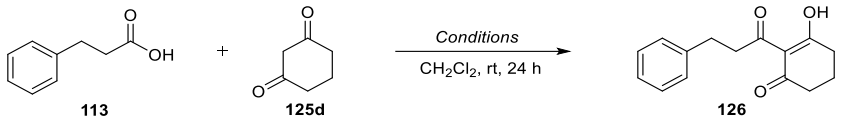
The lactone analogues of head group **15** were synthesised using the conditions previously described for the synthesis of **15** (*vide supra*, Scheme 40). Following this method, compounds **125a**, **125b,** and **125c** were successfully prepared in two steps (Scheme 51). Yields over the two-steps sequence are given below.



Scheme 51: Head groups synthesis

It was anticipated that the cyclohexanedione and piperidine-2,4-dione head groups may require tuning of the coupling conditions due to different acidities. Consequently, prior to attempting coupling of these head groups with late-stage intermediate **103**, the esterification/Fries-type rearrangement process was first investigated using the simpler substrate hydrocinnamic acid (**113**) (Table 4). Using the conditions employed for coupling of lactone head group **15**, the desired product **126** was obtained in 35% yield (Table 4, entry 1). However, when a higher loading of activating agent (EDCI), DMAP, and cyclohexanedione were

employed, the reaction proceeded more efficiently, with 58% isolated product (**126**).



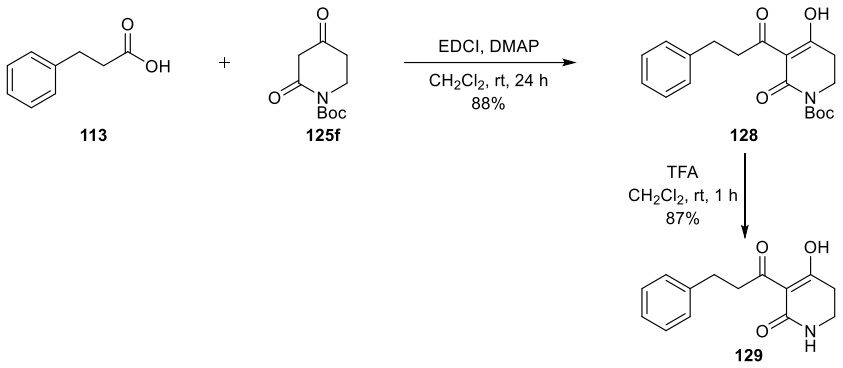
Entry	Conditions	Yield of **126** (%)
1	EDCI (1.2 eq), DMAP (1.2 eq), **125d** (1.2 eq)	35
2	EDCI (1.5 eq), DMAP (3.0 eq), **125d** (1.5 eq)	58

Table 4: Studies of the esterification coupling of cyclohexanedione 125d

Similarly, coupling of **125e** was first attempted using **113** as the acid coupling partner (Scheme 52). Using standard conditions with EDCI and stoichiometric DMAP for this process, no product was obtained.

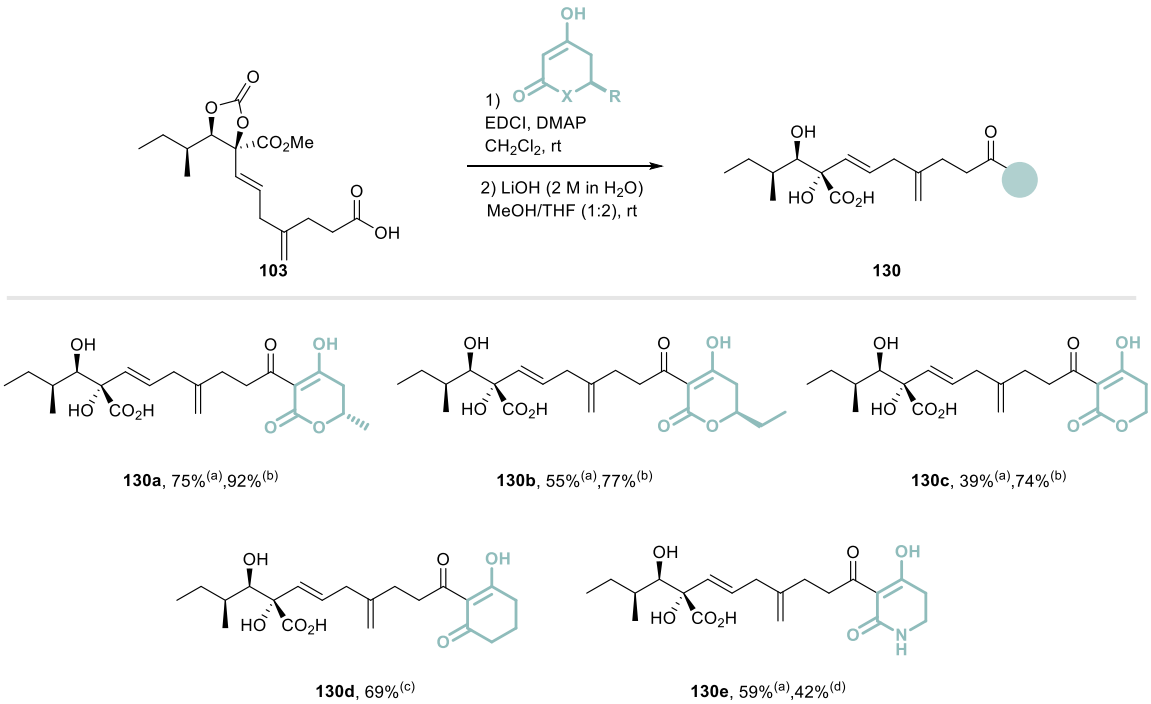
Scheme 52: Attempted coupling of 125e with 113

To achieve the synthesis of the desired product, coupling of the *N*-Boc protected lactam **125f** was first realised (Scheme 53). The corresponding C-acyl product was obtained in 88% yield. Subsequent Boc deprotection using TFA allowed formation of desired product **129** in 87% yield.



Scheme 53: Successful synthesis of lactam 129

Using the key late-stage intermediate **103**, a range of natural product derivatives with head group variation was produced (Scheme 54). Esterification/Fries-type rearrangement sequence performed well for all substrates and was followed by efficient basic hydrolysis to yield the corresponding natural product derivatives in only two steps from key intermediate **103**. Exception is made for lactam derivative **130e** which was prepared from the Boc-protected lactam head group **125f**. Thus, TFA deprotection was required lastly to synthesise compound **130e**.



(a) Yield of esterification step 1); (b) Yield of hydrolysis step 2); (c) Yield over 2 steps esterification and hydrolysis; (d) Yield of hydrolysis followed by TFA N-Boc deprotection using TFA in CH_2Cl_2 at rt.

Scheme 54: Synthesis of Alternaric acid derivatives

3.3.2.2 Biological evaluation of natural product derivatives

These new analogues were submitted for biological evaluation at Syngenta. The data resulting from GH1 evaluation of phytotoxicity were compared to those of Alternaric acid and are presented in Chart 4 below. All compounds showed complete control of AMARE post-emergence, and for most compounds, very good control pre-emergence as well. Good activity was also observed for all compounds post-emergence against STEME and DIGSA. Additionally, all analogues exhibited weak to null activity against LOLPE. Symptoms recorded for all these compounds were stunting and necrosis. Whilst most compounds demonstrated good phytotoxicity in this assay, particularly compound **130c** bearing the unsubstituted lactone head group **125c,** the most promising result obtained was for Alternaric acid, bearing its natural head group motif **15**. Interestingly, weaker activity was observed with the cyclohexanedione motif (compound **130d**), yet present in the herbicide Mesotrione (Scheme 1, *vide supra*).

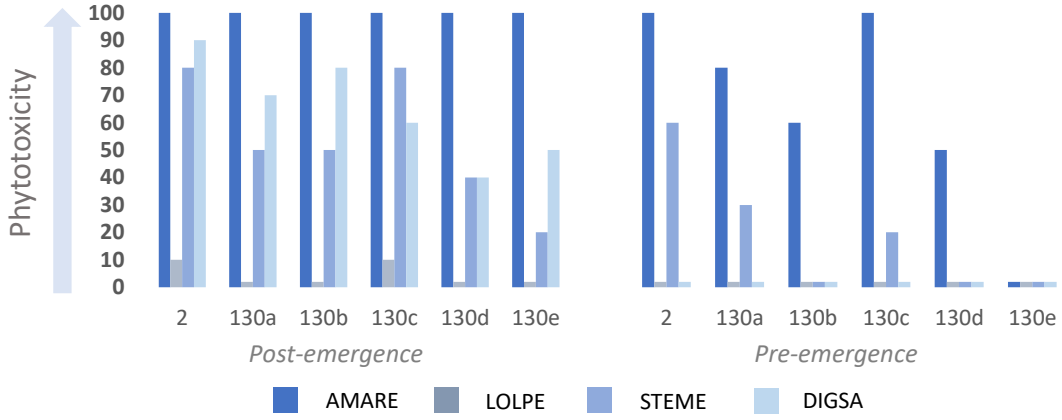


Chart 4: GH1 assessment of Alternaric acid derivatives bearing different head groups

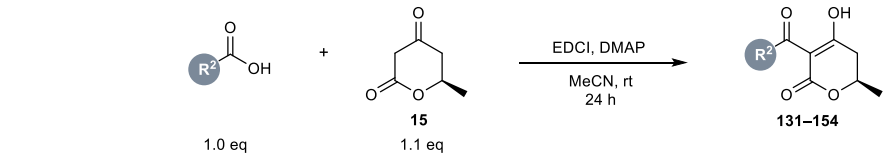
3.3.3 SAR investigations of the alkyl chain ('tail')

The SAR investigations conducted on the head group motif of Alternaric acid allowed to identify the optimum head group for phytotoxicity. With the essential

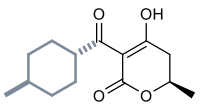
nature of the head group established, the contributions to SAR of the alkyl chain of Alternaric acid were then investigated, with a view to simplify its structure while maintaining good herbicidal activity.

3.3.3.1 Design and synthesis of tail analogues

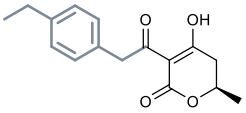
For this purpose, a range of commercially available carboxylic acids with diverse functionalities was selected. Coupling of these acids to head group **15** delivered a small library of simplified analogues of Alternaric acid (Scheme 55). This includes benzylic analogue **132** and cyclopropane containing analogue **134**, which were obtained in good yields using the developed optimised conditions for the esterification/Fries-type rearrangement process (71% and 70% yield, respectively). A selection of fluorinated and trifluoromethylated compounds were also prepared in moderate yields (**135–138**). Ester containing products were obtained in moderate to high yields (**139–142**). In general, substrates substituted at the alpha positions were obtained in moderate to low yields (**131**, **135**, **137** or **151**). Alkyne and sulfide containing molecules afforded the corresponding products, **144** and **145** in excellent yields (73% and 81% yield, respectively). A range of heterocyclic substrates were also evaluated, affording the corresponding products in good yields (**147–151**). Finally, amide, sulfonamide, and amino acid derivatives products were synthesised in good yields (**152–154**).



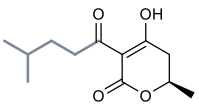
1.0 eq | **15** 1.1 eq | **131–154**



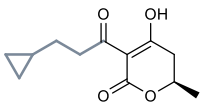
131, 29%



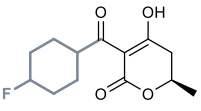
132, 71%



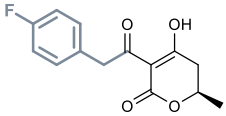
133, 65%



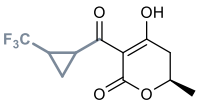
134, 70%



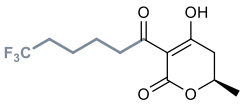
135, 27%; 61:39 *dr*



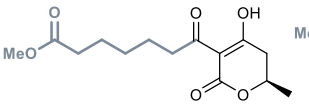
136, 56%



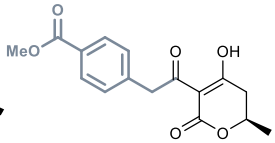
137, 44%; 55:45 *dr*



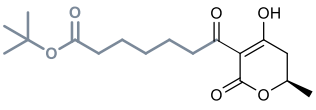
138, 36%



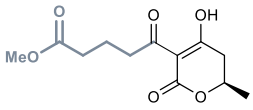
139, 63%



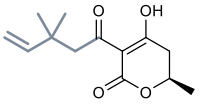
140, 29%



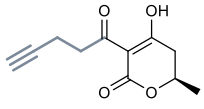
141, 71%



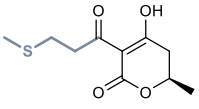
142, 87%



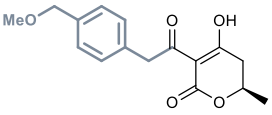
143, 42%



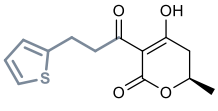
144, 73%



145, 81%



146, 59%



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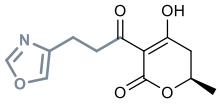
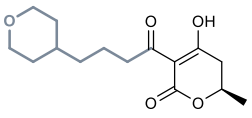
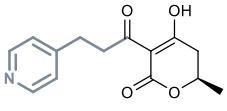


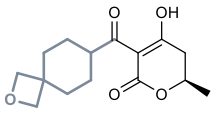
148, 55%



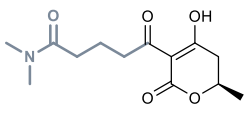
149, 66%



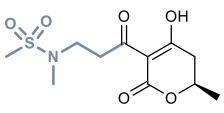
150, 39%



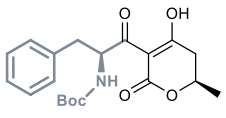
151, 32%



152, 63%



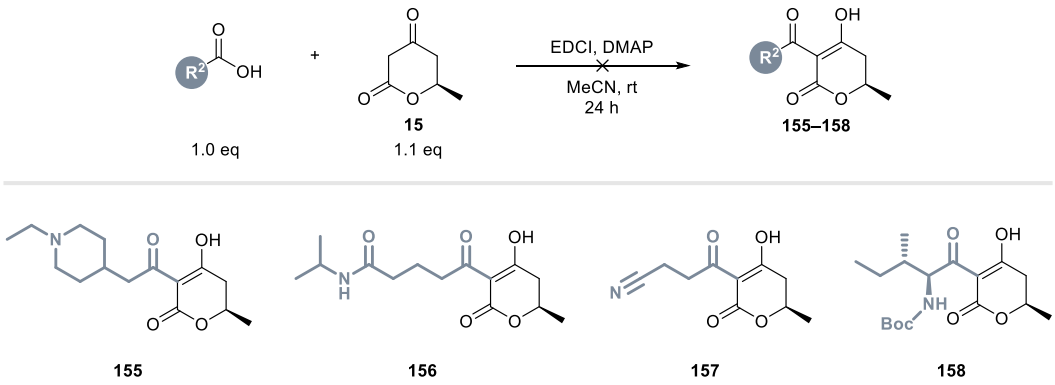
153, 70%



154, 55%

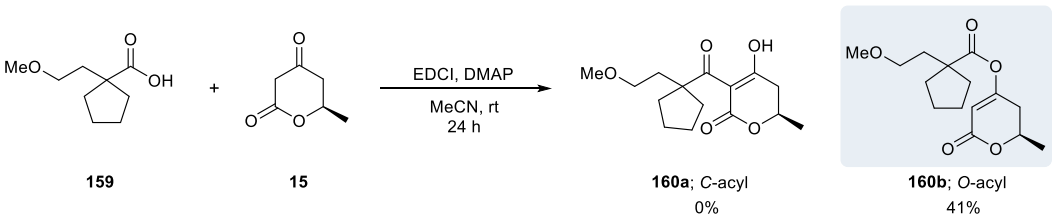
Scheme 55: Small library of 'tail' analogues of Alternaric acid

Amines and other nitrogen containing molecules proved difficult to purify and although products **155–158** were formed and analysed by LCMS and ^{1}H NMR spectroscopy, their isolation failed (Scheme 56).



Scheme 56: Unsuccessful substrates due to purification

The only instance where the desired C-acyl product was not formed is when subjecting **159** to the reaction conditions (Scheme 57). Whilst no C-acyl product **160a** was obtained, *O*-acyl product **160b** was formed and isolated in 41% yield. This result suggests that although esterification proceeded, steric hindrance of the cyclopentyl substituent may have blocked DMAP addition for the rearrangement to proceed successfully.



Scheme 57: Isolation of O-acyl product 160b

3.3.3.2 Biological evaluation of tail analogues

With this small library of tail analogues in hand, herbicidal evaluation through GH1 assay was achieved. The results for compounds **131–142** are shown in

Chart 5. Surprisingly, compounds with extreme structural simplicity exhibited some activity, such as alkyl and benzylic compounds **131–134**. Fluorinated compounds **135–138** showed weak to moderate activity, with phytotoxicity especially post-emergence and mostly against the weed species AMARE. Analogues with longer linker such as ester-containing compounds **139** and **141** demonstrated weak to no phytotoxicity.

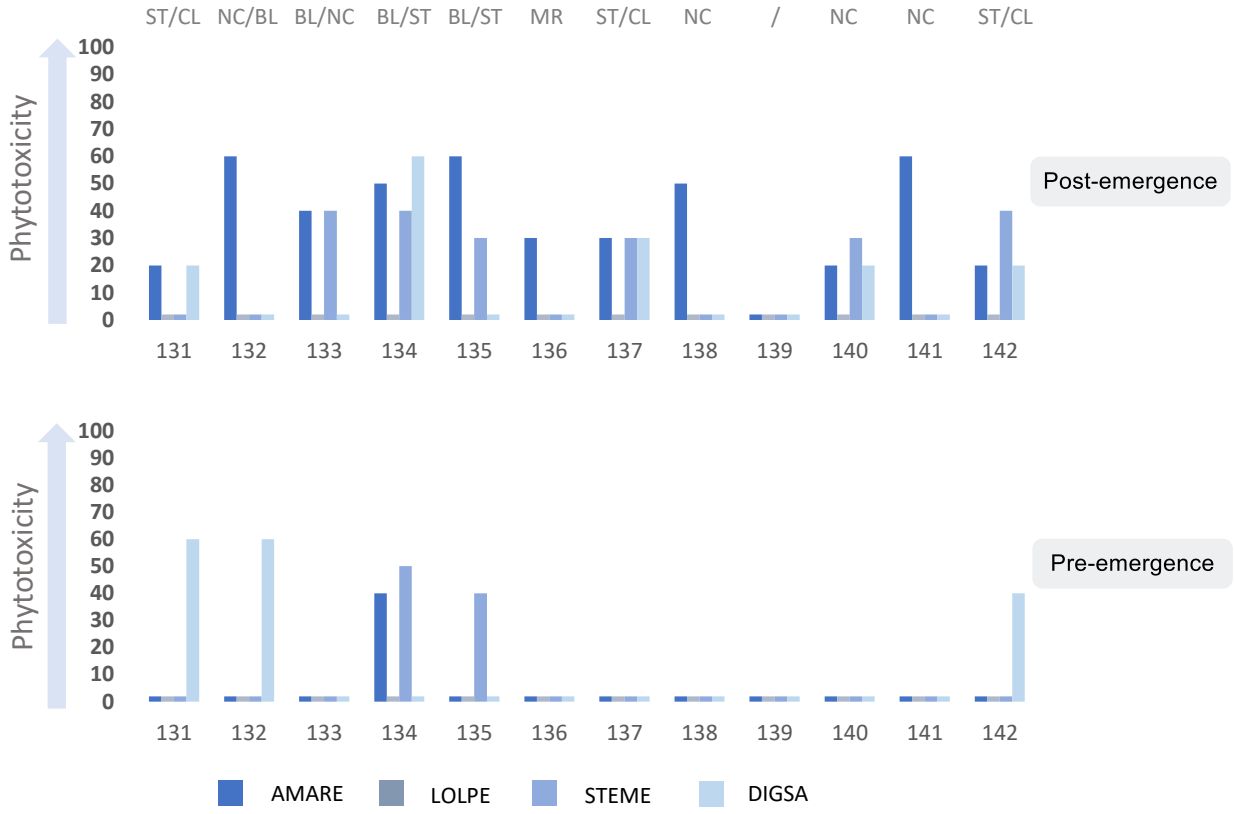


Chart 5: GH1 assessment of compounds 131–142

Evaluation of compounds **143–154** in GH1 assay is shown in Chart 6. Again, moderate activity post-emergence was observed for analogues of unique simplicity such as alkyne **144** and thioether **145**. Most heterocyclic-containing analogues **(148–151)** displayed good activity against at least three weed species post-emergence. Only tetrahydropyran analogue **149** demonstrated pre-emergence activity for this set of heterocyclic molecules. Gratifyingly, dimethylamide compound **152** displayed excellent activity across all weed species, both post- and

pre-emergence, with complete control (100% phytotoxicity) of AMARE, STEME, and DIGSA post-emergence, and complete control of DIGSA pre-emergence. Sulfonamide analogue **153** also exhibited a very satisfactory preliminary phytotoxic profile.

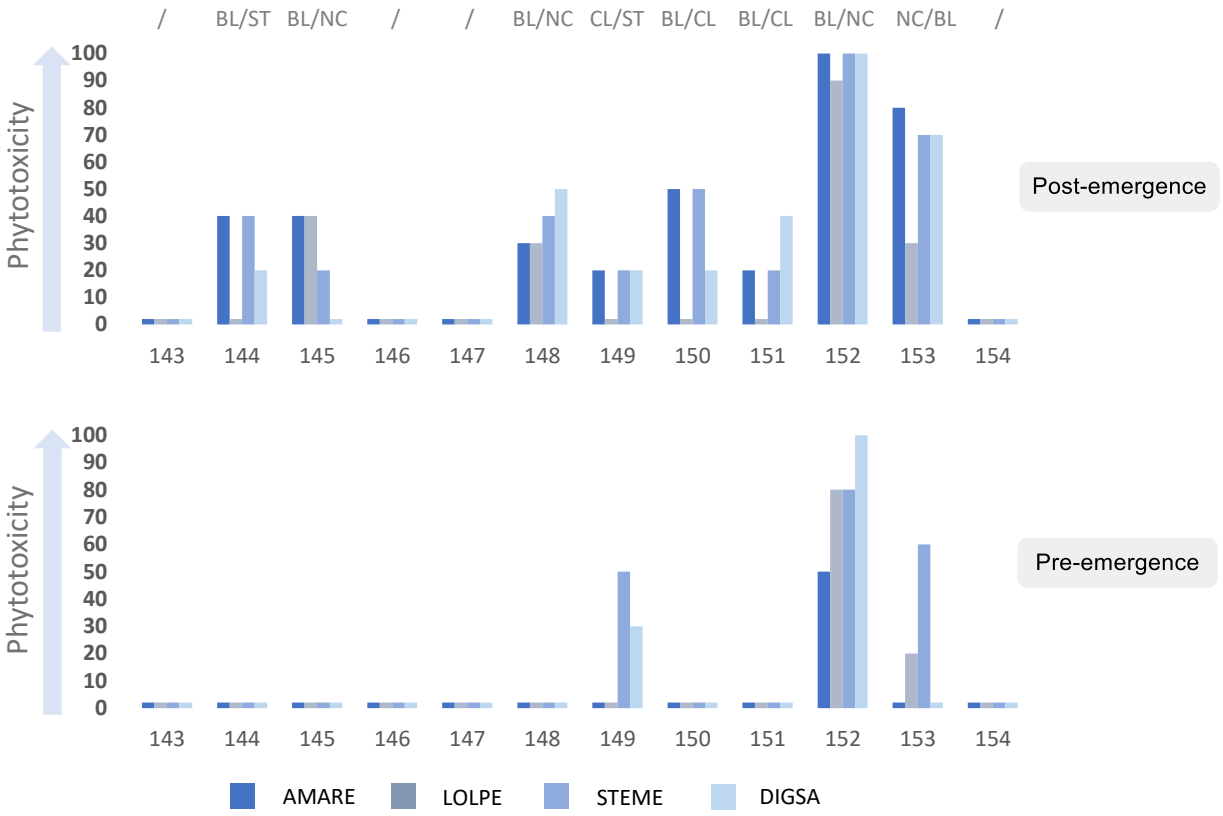


Chart 6: GH1 assessment of compounds 143–154

3.3.4 Discovery of dimethylamide HIT compound

The extreme structural simplicity of dimethylamide **152** renders its biological profile even more attractive. Not only did it demonstrate higher phytotoxicity than the natural product progenitor Alternaric acid but it also displayed similar activity to the commercial standards included in the GH1 assay. Accordingly further evaluation of this dimethylamide hit compound **152** was conducted through EPS testing (Chart 7). While activity at the higher rate (1000 g/ha) against all weed species apart from IPOHE is excellent and remains satisfactory at 500 g/ha, such level of activity is not retained at the lowest rate 250 g/ha.

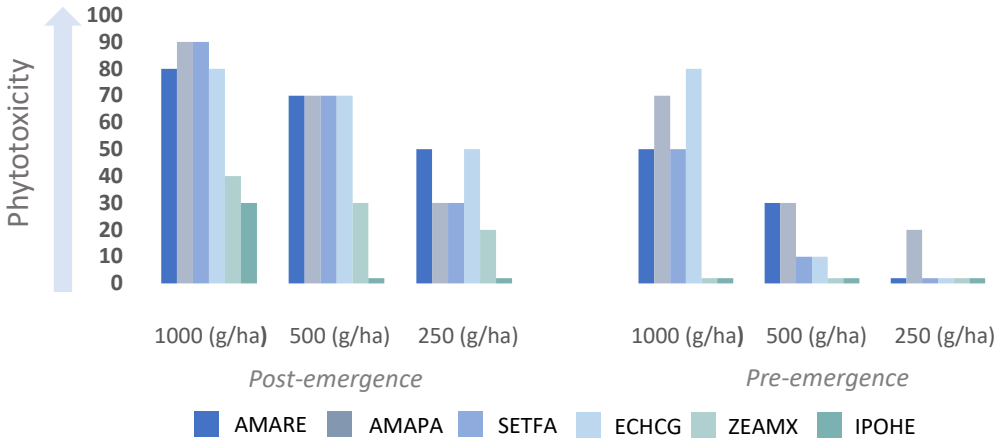


Chart 7: EPS assessment of hit compound 152

Despite its excellent preliminary phytotoxic profile, EPS results for compound **152** were not sufficient to process the compound for further evaluation. Consequently, a second-round amide-based SAR investigations was undertaken. A new library of analogues was designed from hit compound **152**. Considering the knowledge gained about the crucial role of head group **15** for activity during previous SAR evaluation, focus turned towards optimisation of the amide group and the linker (Figure 11).

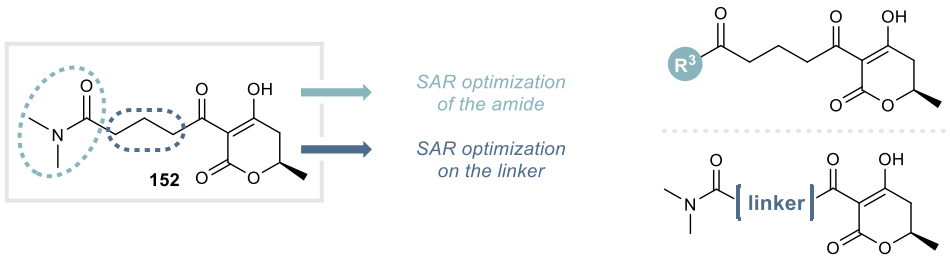


Figure 11: New strategy for SAR optimisation of compound 152

*3.3.4.1 Design and synthesis of amide variants of **152***

The primary focus of this new set of analogues targeted the synthesis of a variety of compounds analogous to **152** but bearing different amide groups. Rapid retrosynthetic analysis immediately suggested carboxylic acid **161** as a precursor

from which amide coupling with a range of amines could afford analogues in just one step (Figure 12).

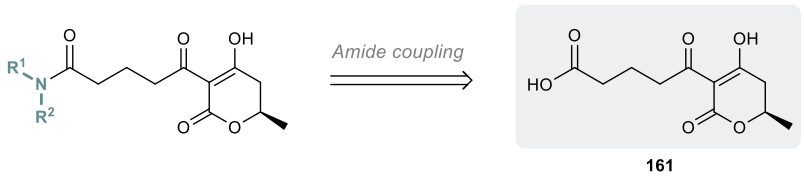
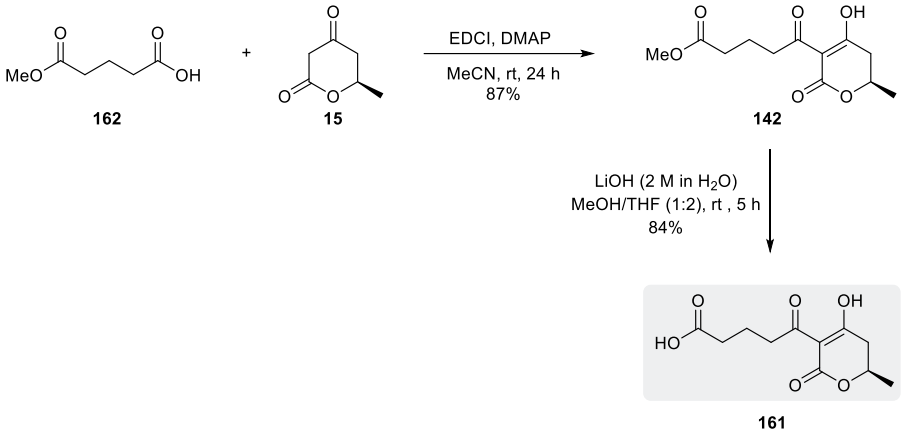


Figure 12: Targeted starting material 161 for the synthesis of amide variants

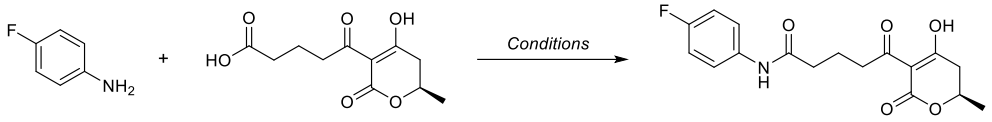
From the commercially available carboxylic acid **162**, coupling with head group **15** generated the corresponding C-acyl product **142** in 87% yield (Scheme 58). Subsequent basic hydrolysis afforded the desired precursor **161** in high yield.



Scheme 58: Synthesis of precursor 161

Initial attempts on amide coupling from **161** were conducted with 4-fluoroaniline (**163**) in order to track the reaction profile through ^{19}F NMR spectroscopy. Using catalytic (20 mol%) DMAP and EDCI in dichloromethane at rt failed to give the desired amide product **164** (Table 5, entry 1). A by-product was observed and was originally thought to be compound **165** resulting from nucleophilic opening of the lactone with **163** and amide coupling (Figure 13, *vide infra*). Consequently, the reaction was then run at 0 °C to try and prevent this side-reaction; however the same by product was observed by ^{1}H NMR

spectroscopy and HRMS (entry 2). Next the reaction was performed with activation of acid **161** with EDCI and DMAP prior to addition of **163** (entry 3). These conditions were again unsuccessful in delivering the desired product **164**. The absence of DMAP or the use of a different activating agent had no effect on the outcome of this reaction (entries 4–6).

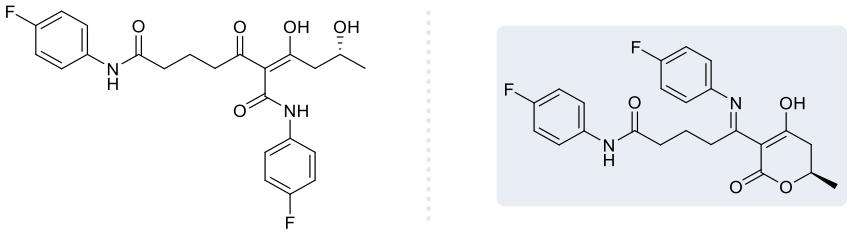


163 **161** **164**

Entry	Conditions	Product
1	EDCI, DMAP (20 mol%), CH_2Cl_2, rt, 17 h	/
2	EDCI, DMAP (20 mol%), CH_2Cl_2, 0 °C, 17 h	/
3	EDCI, DMAP (20 mol%), CH_2Cl_2, rt (with 3 h activation), 17 h	/
4	DCC, DMAP (20 mol%), CH_2Cl_2, rt, 17 h	/
5	EDCI, CH_2Cl_2, rt, 17 h	/
6	CDI, CH_2Cl_2, rt, 17 h	/

Table 5: Attempts to amide coupling of 161 with 4-fluoroaniline

When the conditions outlined in entry **2** (Table **5**) were employed, the by-product formed and observed could be isolated in 31% yield and was then characterised as imine **166** based on all the spectroscopic data, particularly IR spectroscopy which showed a band characteristic of the presence of an imine (Figure 13).



165

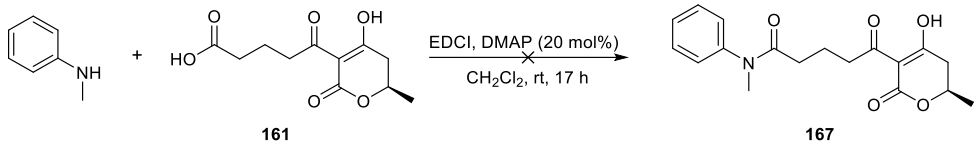
Initial proposed structure of the by-product

166

Structure of the imine by-product characterised

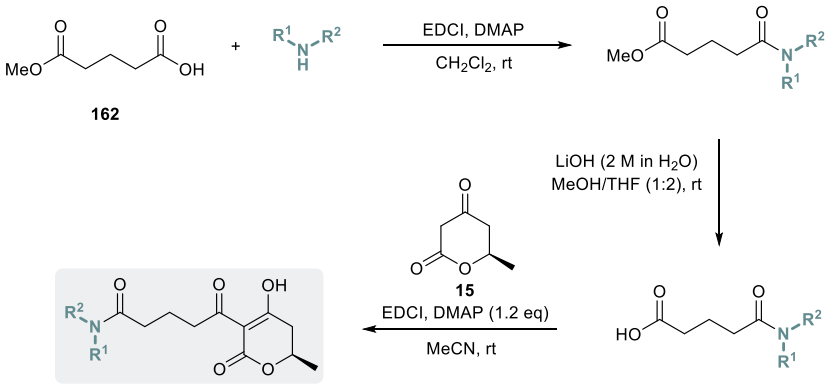
Figure 13: By-product analysis

These results suggest that primary amines are capable of condensing with substrate **161**. Therefore, coupling of acid **161** with a secondary aniline was attempted and using the conditions outlined in Scheme 59, the reaction failed with starting material unreacted. This result was attributed to the weak nucleophilicity of *N*-methylaniline.



Scheme 59: Attempt to the synthesis of 167

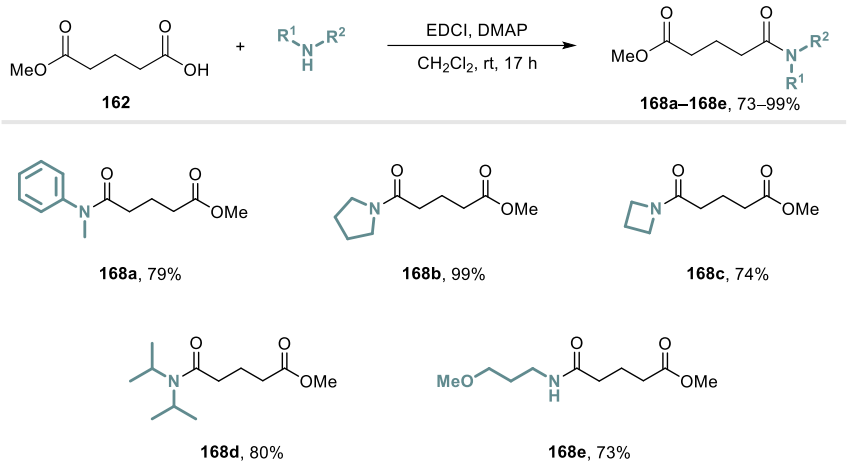
To address these issues, a different synthetic route was envisioned for primary and weakly nucleophilic amines. Amide coupling of amines with carboxylic acid **162** would be performed first, before hydrolysis of the methyl ester and subsequent coupling of head group **15** (Scheme 60).



Scheme 60: Strategy for the coupling of primary and weakly nucleophilic amines

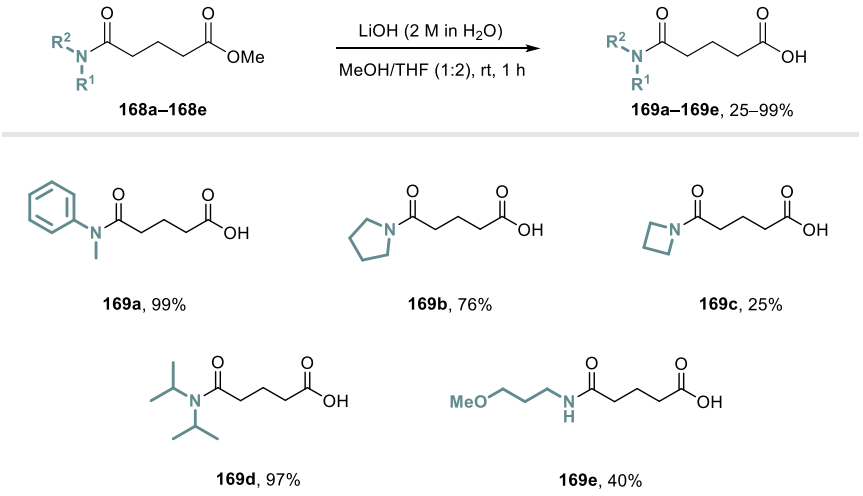
Following this strategy, *N*-methylaniline was successfully coupled to acid **162** and the resulting product **168a** was obtained in high yield (Scheme 61). Similarly, pyrrolidine and DIPA could be directly coupled to acid **161**, although delivering the corresponding products in very low yields. Consequently, these amines as well as azetidine hydrochloride were coupled to acid **162**, generating amides **168b**, **168c,** and **168d** in excellent yields. When direct coupling of 3-methoxypropan-

1-amine with acid **161** was performed, no desired product was obtained and the main by-product formed was analogous to imine by-product **166** (Figure **13**, *vide supra*). Therefore, amide coupling of 3-methoxypropan-1-amine with acid **162** was realised instead, generating the desired intermediate **168e** in 73% yield.



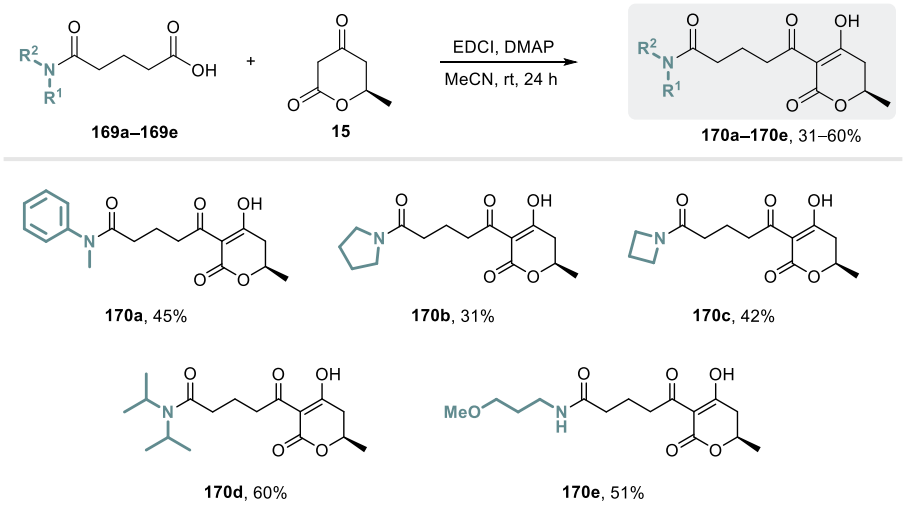
Scheme 61: Amide coupling of acid 162 with challenging amines

Once the desired amide link had been prepared, hydrolysis of the methyl ester motif was required prior to esterification coupling with head group **15**. As such, compounds **168a–168e** were subjected to a basic hydrolysis, using lithium hydroxide to synthesise the corresponding acid products (**169a–169e**) in moderate to excellent yields (Scheme 62).



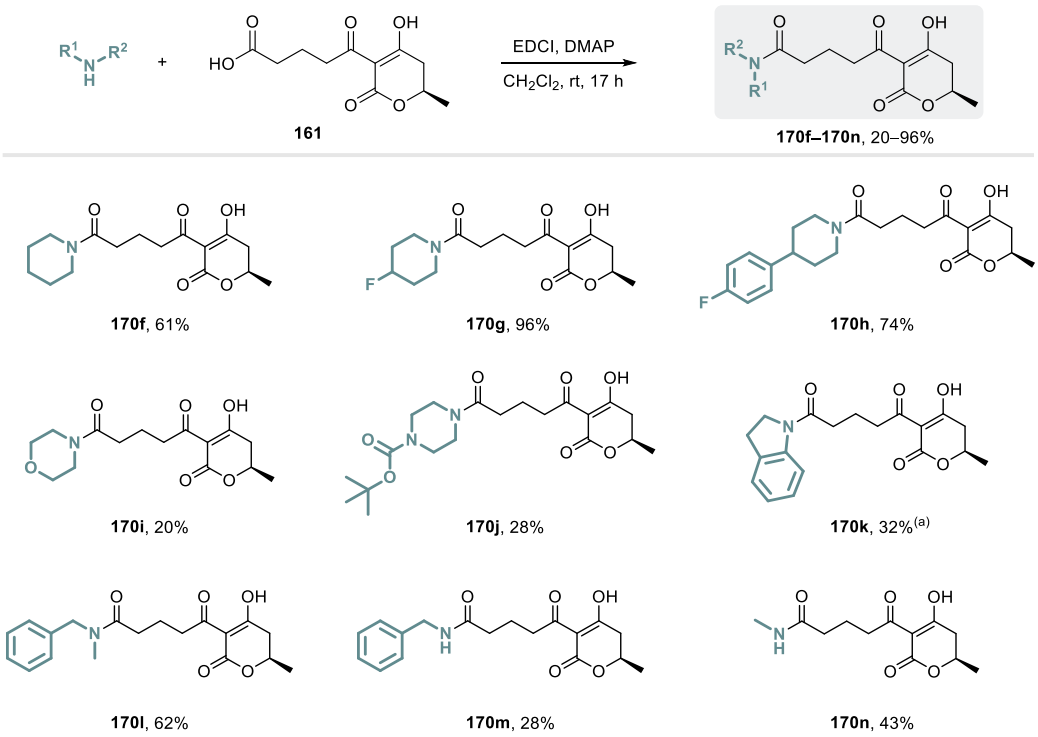
Scheme 62: Methyl ester hydrolysis of compounds 168a–168b

Finally, from acids **169a–169e**, esterification/Fries-type rearrangement sequence with head group **15** produced the desired amide variant analogues **170a–170e** in moderate to good yields (Scheme 63).



Scheme 63: Head group coupling of acids 169a–169e

Pleasingly, a range of amines could directly be coupled to acid intermediate **161** (Scheme 64). Using the conditions outlined in Scheme 64, piperidine-derived amide compounds **170f–170h** were obtained in good to excellent yields (61–96%). Other heterocyclic compounds, such as morpholine- or piperazine-derived amides **170i** and **170j** were also successfully prepared, although challenging purification led to lower yields for these reactions (20–28%). Initial attempt at coupling indoline with acid **161** failed using these conditions. However, when switching the solvent for DMF, indoline-derived amide **170k** was obtained in 32% yield. Additionally, *N*-methylbenzylamine was coupled to acid **161** efficiently, and primary amines such as benzylamine and methylamine hydrochloride were also successful, affording the desired products **170m** and **170n** without generating an imine by-product.



(a) Reaction was ran in DMF instead of CH_2Cl_2.

Scheme 64: Amide coupling of amines with intermediate 161

*3.3.4.2 Biological evaluation of amide variants of **152***

Hoping to identify a more promising herbicidal lead, the amide analogues were first assessed in GH1. Phytotoxic evaluation of compounds **170a–170g** is represented in Chart 8. Overall, all of these analogues demonstrated good levels of phytotoxicity against all four weed species, apart from *N*-methylaniline derived amide **170a** which exhibited weaker activity. This set of compounds showed better phytotoxic activity post- than pre-emergence and symptoms recorded were bleaching and stunting. One compound that stands out of this set is azetidine-derived analogue **170c** which demonstrated complete control of both dicot weed AMARE and monocot weed DIGSA post-emergence.

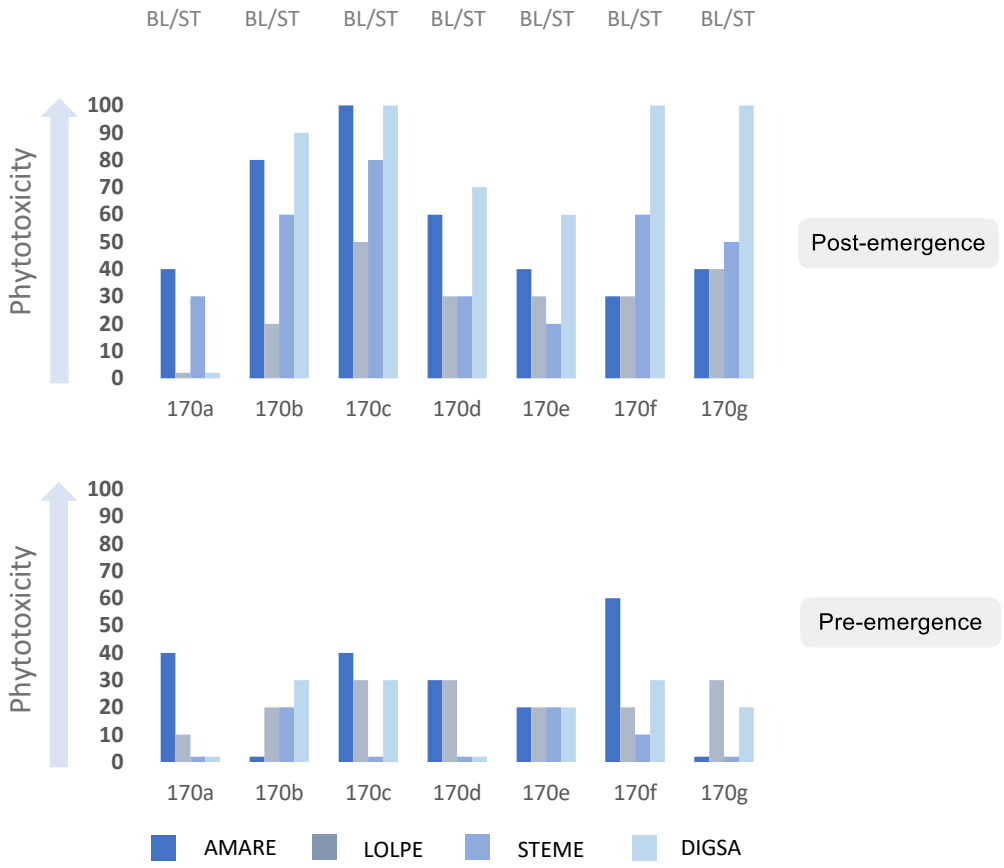


Chart 8: GH1 evaluation of amide variation analogues 170a–170g

Phytotoxic assessment of compounds **170h–170n** in GH1 is represented in Chart 9 below. Here again, the herbicidal activity of most compounds was very high, especially for morpholine-derived analogue **170i** which not only demonstrated excellent phytotoxicity post-emergence, but also showed encouraging data pre-emergence. Similarly, indoline analogue **170k** exhibited high levels of phytotoxicity post- and pre-emergence against both types of weeds (monocot and dicot). As observed for the other amide variant analogues, all these compounds engendered bleaching and stunting symptoms.

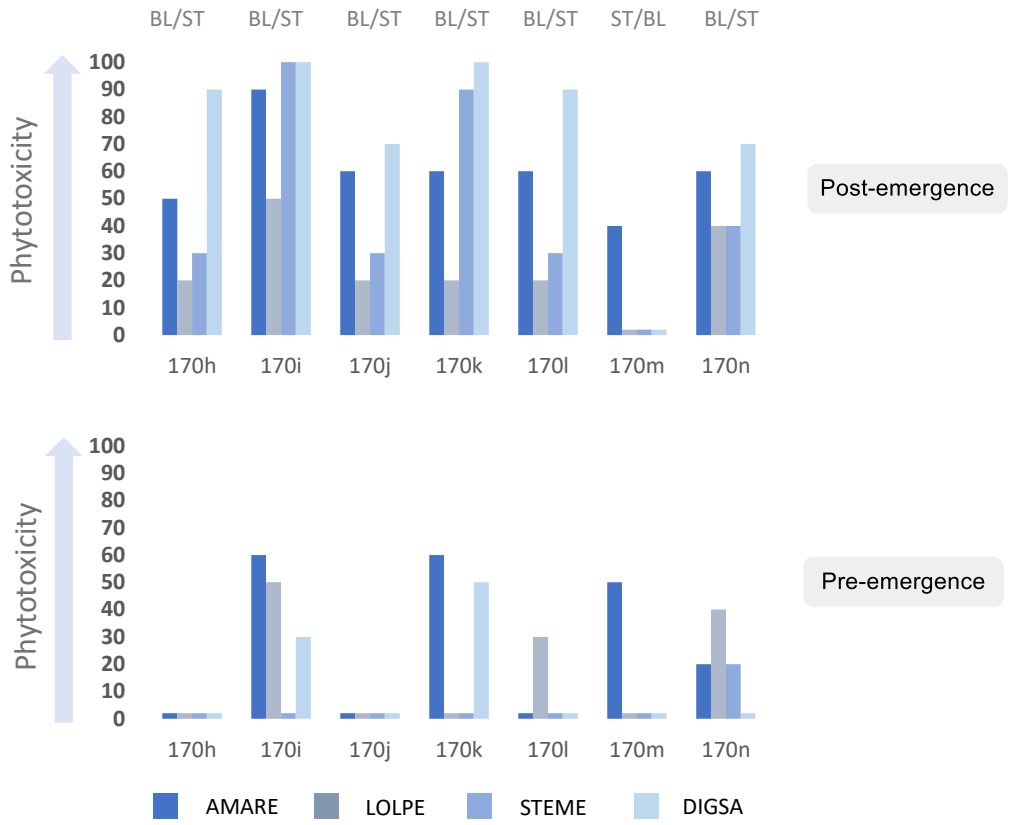


Chart 9: GH1 evaluation of amide variation analogues 170h–170n

*3.3.4.3 Design and synthesis of linker variants of **152***

Next, the synthesis of linker variant analogues of amide hit **152** was envisioned. For this purpose, variation of the linker length was investigated with homologated linker chain **171a** and shorter linker chains with compounds **171b–171e** (Figure 14). Furthermore, more exotic linkers were investigated such as compound **171f** bearing a *gem*-dimethyl or compound **171g** with a cyclic cyclohexyl linker. The synthesis of analogue **171h** with deletion of the ketone alpha to the head group was also desired.

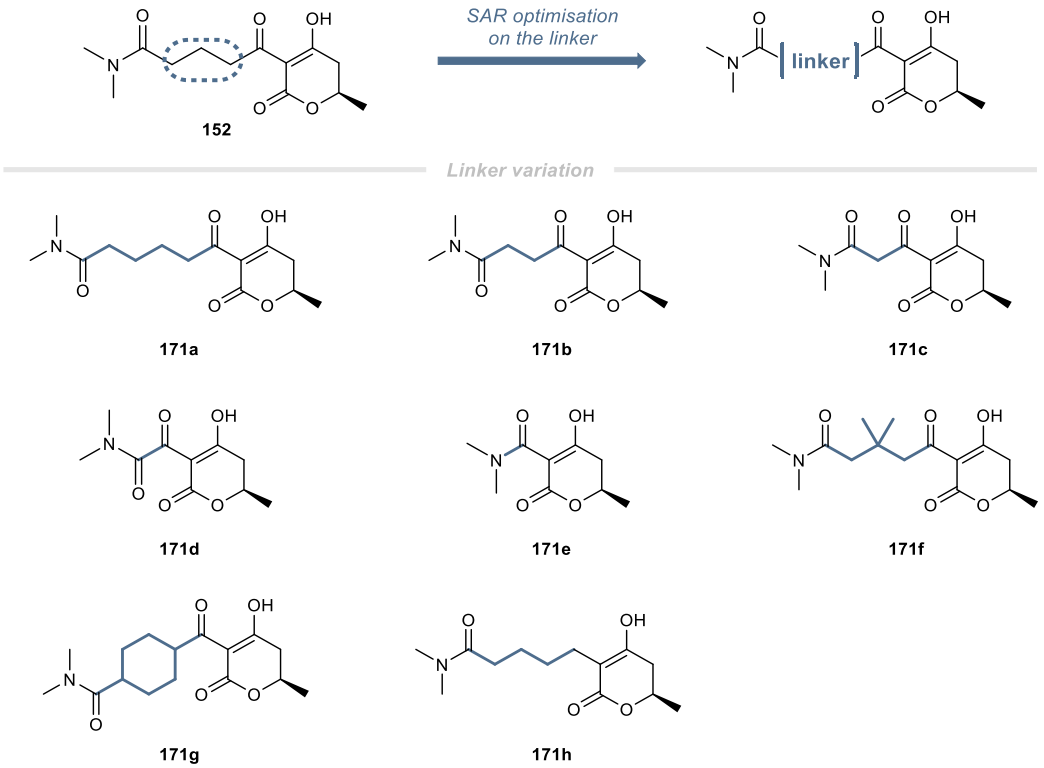
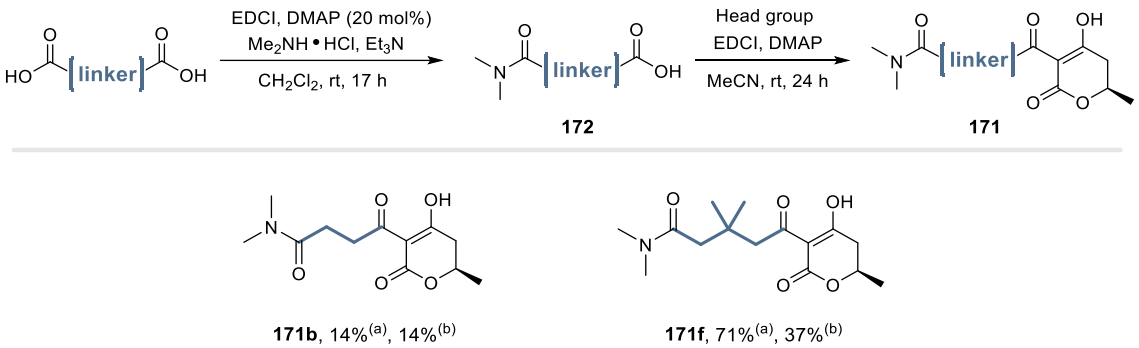


Figure 14: Designed analogues for SAR optimisation of the linker

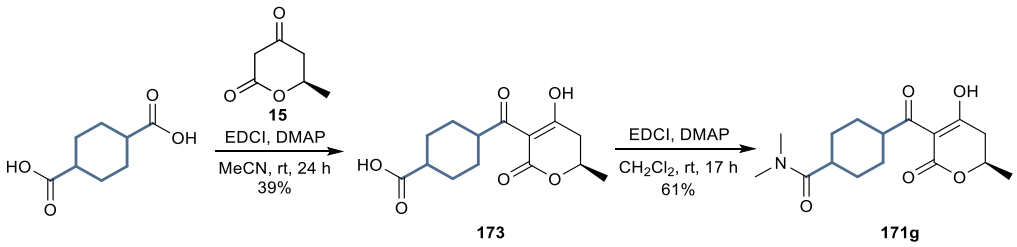
Initially, different symmetrical diacids were selected, hoping they could be monocoupled to dimethylamine hydrochloride and then to head group **15** to obtain the desired linker variant compounds **171b** and **171f** (Scheme 65). In order to selectively obtain the mono-amide coupling products (**172b** and **172f**) from the first step, excess of diacid (3 eq) was usually required. Compounds **171b** and **171f** were successfully synthesised following this synthetic route.



(a) Yield of amide coupling step; (b) Yield of head group coupling step

Scheme 65: Synthesis of linker analogues 171b and 171f

When the synthesis of cyclohexyl linker analogue **171g** was attempted, following the route described in Scheme 65 (*vide supra*), no product could be isolated. However, performing mono-coupling of head group **15** first, prior to amide coupling with dimethylamine hydrochloride, successfully afforded analogue **171g** (Scheme 66).

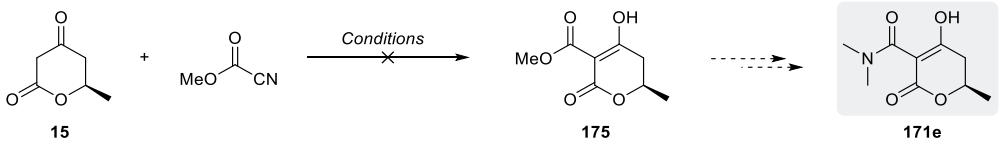


Scheme 66: Synthesis of linker analogue 171g

Next, the synthesis of analogue **171d** was investigated. Using oxamic acid **174**, coupling with the head group was attempted (Scheme 67). Whilst the desired product **171d** was believed to be formed through NMR and mass spectrometry analysis, isolation of the pure compound failed with all the purifications attempted. Consequently, the synthesis of this analogue was abandoned.

Scheme 67: Attempted synthesis of analogue 171d

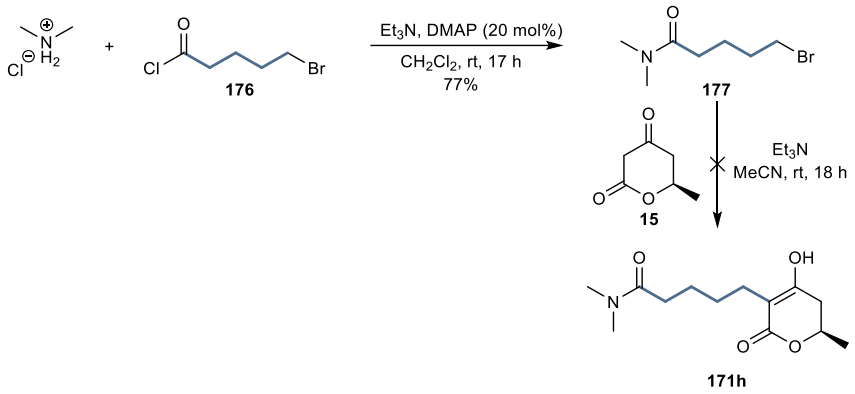
The synthesis of analogue **171e** was envisioned through intermediate **175** which was hypothesised to be accessible *via* alkylation of head group **15** with methyl cyanoformate. Using LDA at low temperature resulted in no reaction with unreacted head group starting material **15** recovered (Table 6, entry 1). Surprisingly when attempting the reaction with a milder base, DBU in acetonitrile, complete degradation of **175** was observed (entry 2). It was anticipated that the target compound **171e** would be unlikely to exhibit significant biological activity. As such its synthesis was abandoned to focus on more promising analogues.



Entry	Conditions	Product
1	LDA, THF −78 to −50 °C, 4 h	/
2	DBU, MeCN 0 °C to rt, 17 h	/

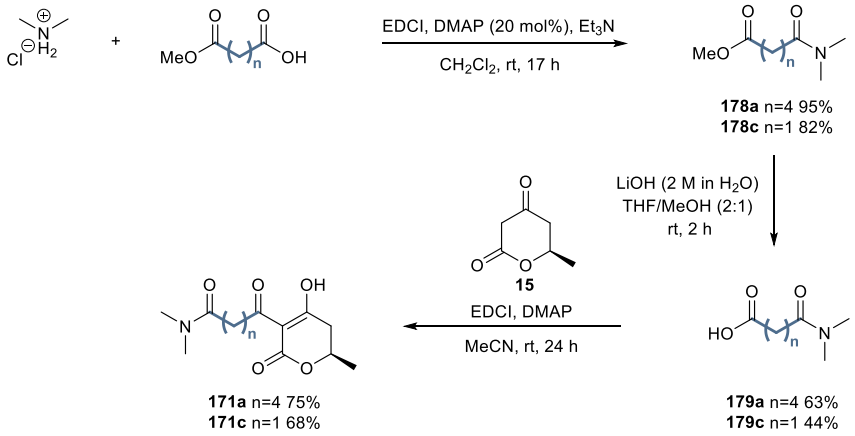
Table 6: Attempts towards the synthesis of precursor 175

Aiming to synthesising the ketone deletion analogue **171h**, dimethylamine hydrochloride was reacted with acid chloride **176** to form the corresponding dimethyl amide **177** in 77% yield (Scheme 68). Subsequent nucleophilic substitution of alkyl bromide **177** with head group **15** was then attempted. Unfortunately, no reactivity was observed and the desired alkylated product **171h** could not be formed. Thus, attention was turned to the synthesis of other analogues.



Scheme 68: Attempted synthesis of linker analogue 171h

Finally, the syntheses of homologated analogue **171a** and shorter linker length analogue **171c** were achieved in three steps from the corresponding monoacid precursors 3-methoxy-3-oxopropanoic acid and 6-methoxy-6-oxohexanoic acid (Scheme 69). From these two starting materials, amide coupling with dimethylamine hydrochloride respectively afforded amides **178a** in 95% yield and **178c** in 82% yield. Subsequent basic hydrolysis furnished acids **179a** and **179c**, which were subjected to coupling with head group **15**. Using our previously optimised conditions for this process, linker length analogues **171a** and **171c** were obtained in 75% and 68% yield, respectively.



Scheme 69: Synthesis of linker length analogues 171a and 171c

*3.3.4.4 Biological evaluation of linker variants of **152***

The linker variants analogues synthesised were evaluated for phytotoxic activity in GH1 (Chart 10). In general, linker analogues were less active in this herbicidal assay than amide variants presented above (Chart 8–9, *vide supra*). Longer linker length had little influence on the herbicidal activity with compound **171a** exhibiting good herbicidal efficacy, although the three-carbon linker (original hit compound **152**) remains optimum for phytotoxicity. Analogues **171f** and **171g** exhibited weak activity against all weed species post-emergence but higher activity pre-emergence against STEME. Overall, shorter linkers (compounds **171b** and **171c**) were detrimental for phytotoxicity compared to hit compound **152**.

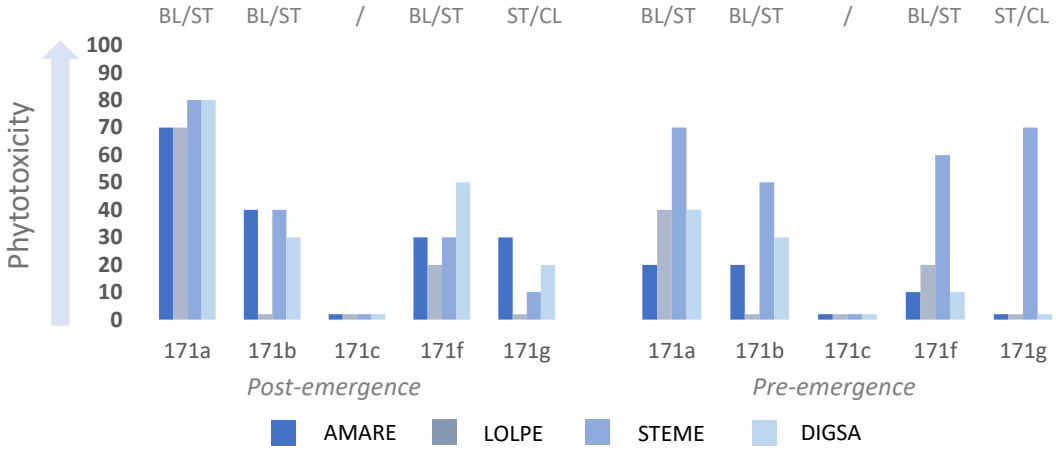


Chart 10: GH1 assessment of linker variant analogues

3.3.4.5 Early profiling screen of promising compounds

Through SAR investigations on the amide group of the dimethylamide hit compound **152**, a series of new analogues demonstrated excellent preliminary herbicidal activity in GH1. As a result, compounds **170c** and **170k** were processed further through the EPS assay and compared to the hit compound **152** (Chart 11). As observed previously, in general, these compounds were more active post- than pre-emergence. In this assay, azetidine-derived analogue **170c** showed very

high phytotoxicity both post- and pre-emergence at 1000 g/ha and activity was mostly retained at 500 g/ha post-emergence. A drop in the phytotoxicity was observed for this compound at 250 g/ha although activity against AMARE and AMAPA remains significant. Indoline-derived analogue **170k** mostly exhibited herbicidal activity post-emergence at all rates with activity retained at 500 g/ha especially against dicot weeds (AMARE, AMAPA, and IPOHE). Overall analogue **170k** did not show sufficiently better data than hit compound **152**; however analogue **170c** exhibited similar levels of activity which is encouraging for future optimisation of either azetidine-amide or dimethylamide lead compounds.

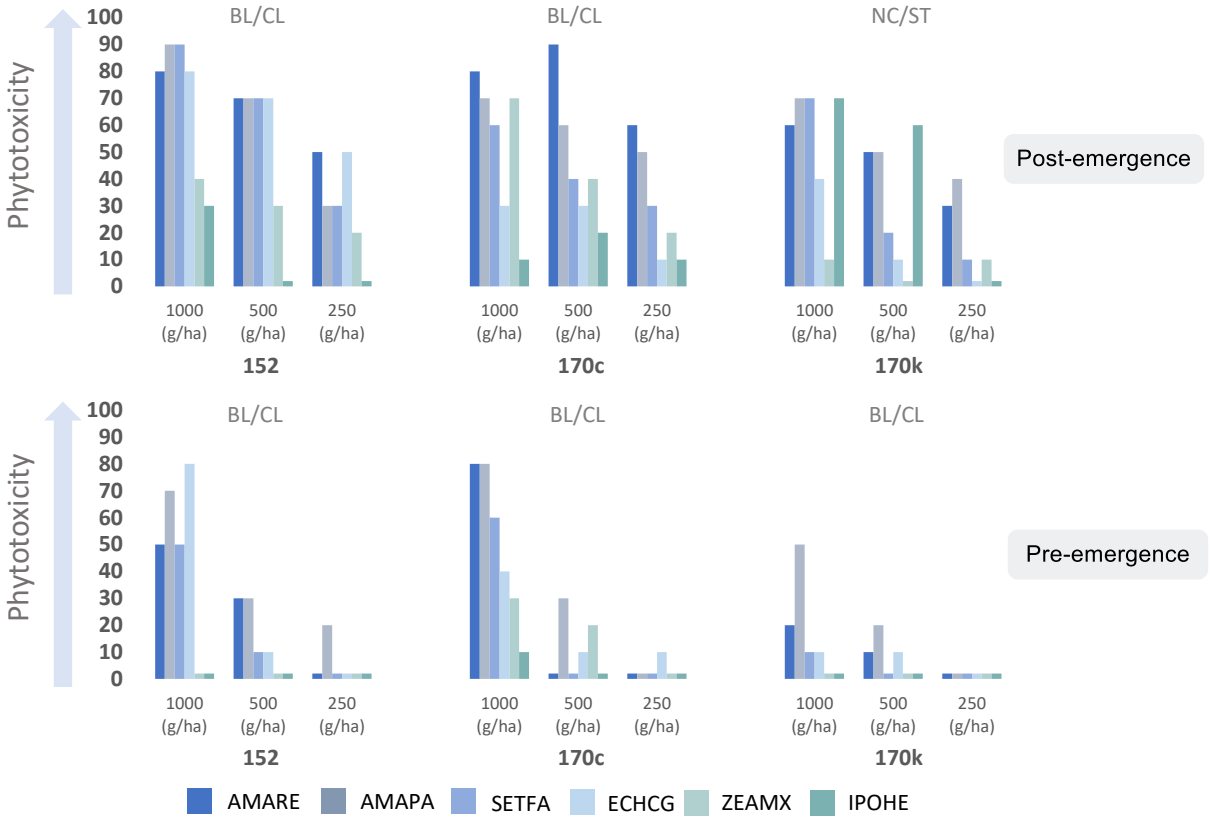


Chart 11: EPS assessment of compound 170c and 170k and comparison with hit 152

Photographic captures of the post-emergence EPS results at the rate of 500 g/ha for these three compounds (**152**, **170c,** and **170k**) were obtained during this assay (Figure 15), which illustrate the data presented above (Chart 11, *vide supra*).

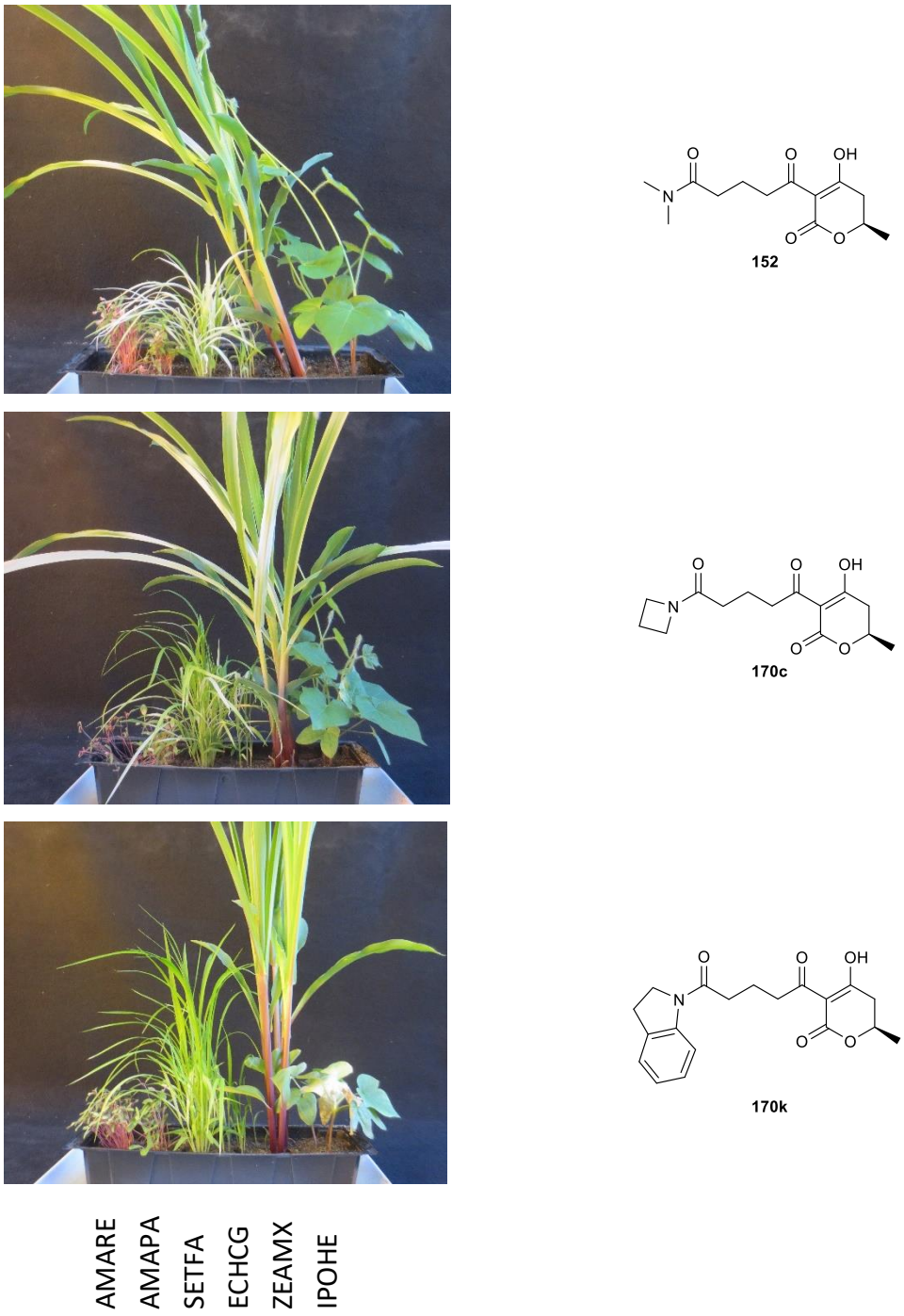


Figure 15: Photographic capture of EPS results of compounds 152, 170c, and 170k (500g/ha)

3.3.5 Mode of action investigations

The similarities of the head group **15** of Alternaric acid **2** with motifs present in commercial herbicidal agents that target the HPPD enzyme (e.g., Mesotrione **1**)

led to an initial assessment of **2** in biochemical assays for HPPD activity; however, **2** gave a low response and a lack of bleaching, suggesting it does not operate via this signalling axis (Figure 16). In addition, broader MoA screening against a series of established assays ruled out activity against other known targets, suggesting **2** operates via a novel MoA.

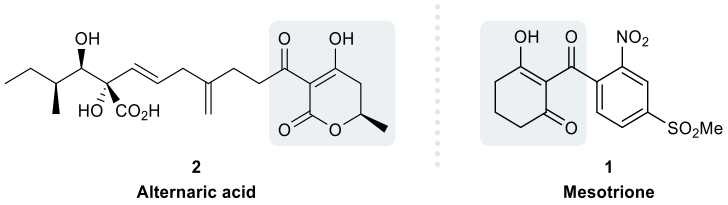


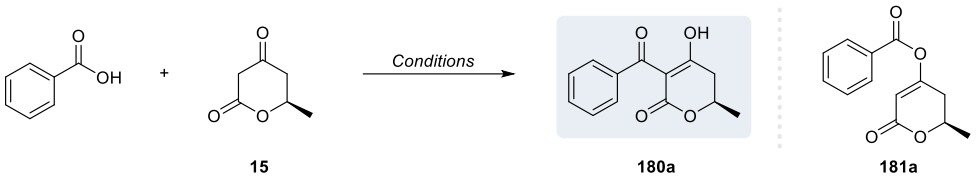
Figure 16: Similarities of head group in Alternaric acid and Mesotrione

However, some active compounds discovered throughout this project, such as amides **152** and **170c** resulted in bleaching symptom responses. Consequently, investigation of the MoA for these compounds was desired with a view to establish whether HPPD was the primary MoA or not. In this optic, the design and synthesis of Mesotrione-Alternaric acid crossover analogues was investigated. Such analogues would bear Alternaric acid's head group motif **15** and an aromatic core characteristic of Mesotrione. The analogues synthesised would be evaluated to see if they follow the same trends as the HPPD inhibitor, Mesotrione, in terms of SAR such as the necessity for electron-withdrawing groups at the *ortho*- and *para*-position (Scheme 1, *vide infra*).[9]

3.3.5.1 Synthesis of Mesotrione-Alternaric acid crossover analogues

Preliminary investigations on the coupling of aryl carboxylic acid were attempted using benzoic acid as a model substrate. Previously optimised conditions for the coupling of alkyl carboxylic acid with head group **15** were unsuccessful (Table 7, entry 1). Increasing the temperature had no effect on the reaction (entry 2). Employing a different activating agent (DCC) and solvent (dichloromethane) also

failed to give the desired product (entry 3). In all cases, both C-acyl **180a** and O-acyl **181a** products were not observed.

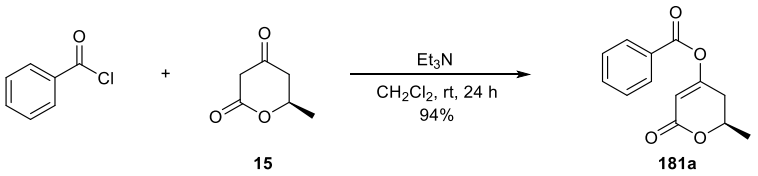


15 **180a** **181a**

Entry	Conditions	C-acyl 180a	O-acyl 181a
1	EDCI, DMAP (1.1 eq), MeCN, rt, 24 h	/	/
2	EDCI, DMAP (1.1 eq), MeCN, 60 °C, 24 h	/	/
3	DCC, DMAP (1.1 eq), CH_2Cl_2, rt, 24 h	/	/

Table 7: Attempted conditions for the synthesis of 180a

Alternatively, the coupling of benzoyl chloride with head group **15** was investigated. Using the conditions outlined below (Scheme 70), O-acyl product **181a** was obtained in 94% yield.

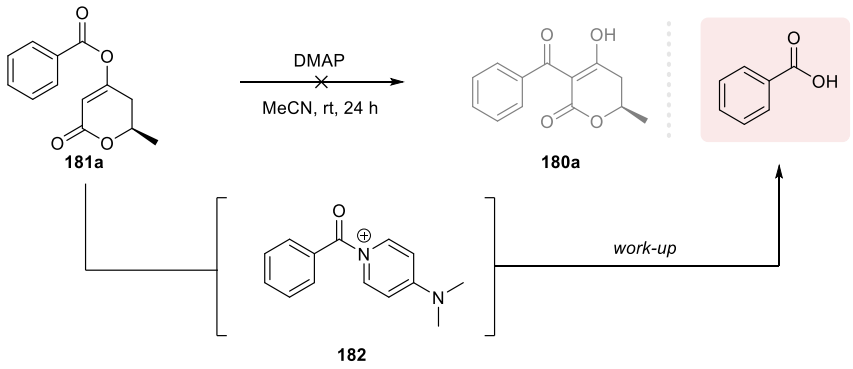


15 **181a**

Scheme 70: Synthesis of O-acyl 181a from benzoyl chloride

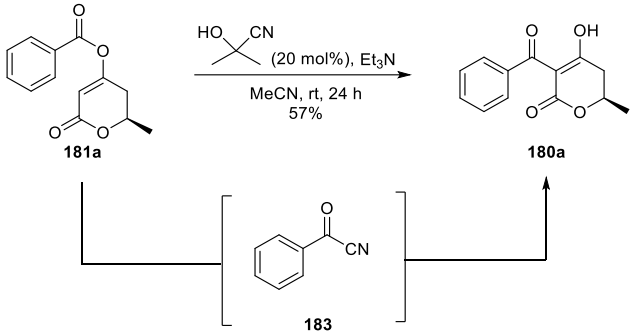
Previous results have shown that the rearrangement of the O-acyl to the C-acyl product for alkyl substrates, could be achieved using stoichiometric DMAP in acetonitrile (Scheme 45, *vide supra*). Interestingly, when aromatic O-acyl compound **181a** was subjected to these conditions, no C-acyl product **180a** was obtained, instead benzoic acid was recovered after work-up (Scheme 71). From this result, it was hypothesised that for an aromatic substrate, DMAP can react with O-acyl **181a** to form adduct **182** which may then be too bulky to be nucleophilically attacked. Aqueous work-up of adduct **182** would then lead to

the formation of benzoic acid. Altogether, these results rationalise the detrimental effect of DMAP for the coupling of aromatic acids with head group **15**.



Scheme 71: Unsuccessful DMAP-promoted rearrangement and proposed rational

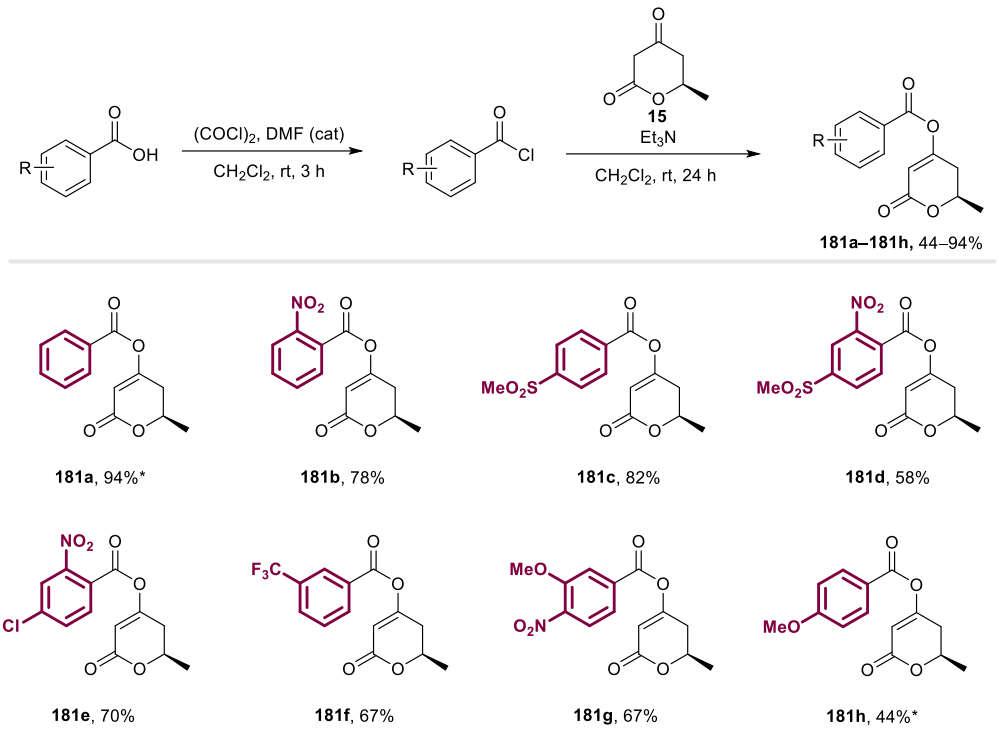
In order to overcome the difficulties encountered when trying to promote the O-acyl to C-acyl rearrangement, acetone cyanohydrin was selected as an acyl transfer reagent for this reaction (Scheme 72). Using catalytic amount of this reagent, C-acyl **180a** was successfully synthesised from O-acyl **181a** in 57% yield. This result can be rationalised from the hypothesis that proposed intermediate **183** is more accessible than DMAP adduct **182** (Scheme 71, *vide supra*) and thus can be attacked by head group **15** to produce the desired product **180a**.



Scheme 72: Acetone cyanohydrin-promoted rearrangement

Since the SAR for Mesotrione is well known[7,9] with *ortho* and *para*-electron-withdrawing groups essential for potency, a range of cross-over analogues were

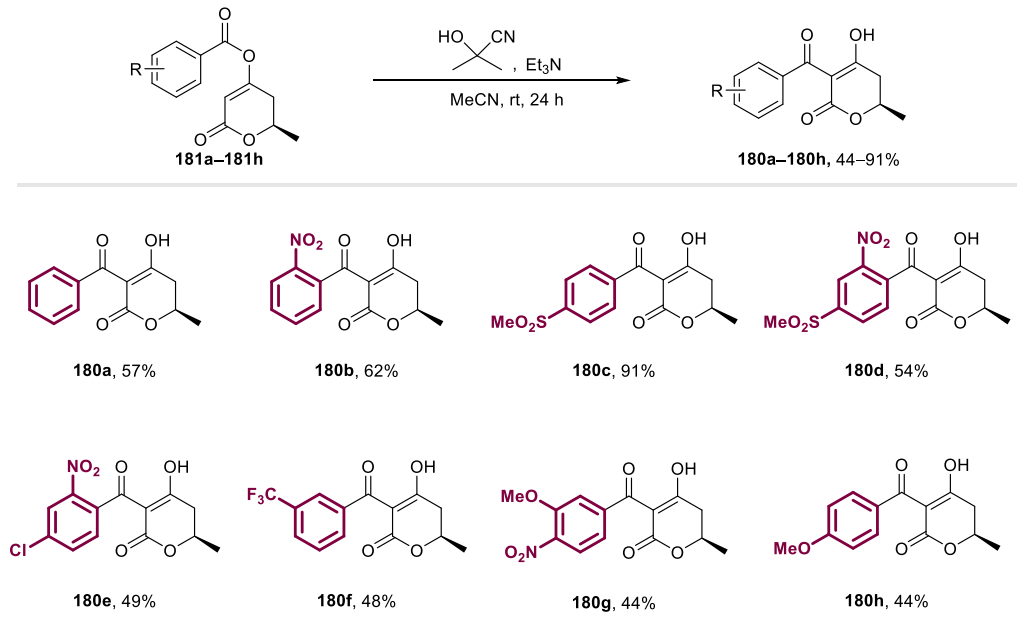
designed specifically to see if they would follow the same trends. Consequently, the synthesis of analogues with different electronic characteristics was pursued. Unsubstituted aromatic *O*-acyl **181a** was first synthesised in one step and with a 94% yield from the commercially available acid chloride precursor (Scheme 73). SAR investigations during the development of Mesotrione highlighted the essential necessity of the *ortho*-nitro group for herbicidal activity as well as the benefit of adding the *para*-methylsulfone group for potency.[9] As such, *O*-acyl analogues **181b–181d** were prepared in two steps from the carboxylic acid precursor, through formation of the acid chlorides and subsequent esterification to obtain compounds **181b–181d** in good to excellent yields. The analogous compound **181e** of **181d** with a chloride instead of the methylsulfone at the *para*-position was also generated in high yield following the conditions outlined in Scheme 73. Less electron-deficient substrates such as *meta*-trifluoromethylated analogue **181f** and *O*-acyl **181g** were synthesised in good yields (67% for both). Finally, esterification of the more electron-rich *p*-methoxybenzoyl chloride proved to be less efficient as expected, giving the corresponding *O*-acyl product **181h** in 44% yield.



* Obtained in one step from the commercially available corresponding acid chloride.

Scheme 73: Synthesis of O-acyl analogues

Once synthesis of O-acyl analogues was complete, acetone cyanohydrin-promoted rearrangement could be performed in order to generate the desired C-acyl cross-over analogues (Scheme 74). In general, electron-deficient and less hindered substrates proceeded best for this reaction (for example, compound **180c**, 91%). More electron-rich systems and *ortho*-substituted substrates afforded the desired corresponding products in moderate yields, with remaining O-acyl starting material in these cases (for example compounds **180e**, 49% and **180h**, 44%).



Scheme 74: Acyl rearrangement for the synthesis of analogues 180a–180h

3.3.5.2 Biological evaluation of Mesotrione-Alternaric acid crossover analogues

Next, these cross-over analogues were first assessed for phytotoxicity in GH1 and the results were compared to those of Mesotrione (**1**) (Chart 12). As anticipated *ortho*- and *para*-substituted electron-deficient analogues performed very well in this assay such as compound **180d**, direct analogue of Mesotrione with Alternaric acid head group, which showed high phytotoxicity against AMARE, STEME, and DIGSA but no activity against LOLPE, similarly to Mesotrione. Compound **180e** also demonstrated an excellent phytotoxic profile with strong activity against all four weed species both post- and pre-emergence. The essential role of the *ortho*-nitro group in Mesotrione for activity, translates to this cross-over system where compound **180a** and **180c** exhibited weaker phytotoxicity. Having an electron-rich aryl system completely removed the activity (compound **180h**). Additionally, all the most active compounds in this assay resulted in bleaching symptoms similarly to the commercial herbicide Mesotrione.

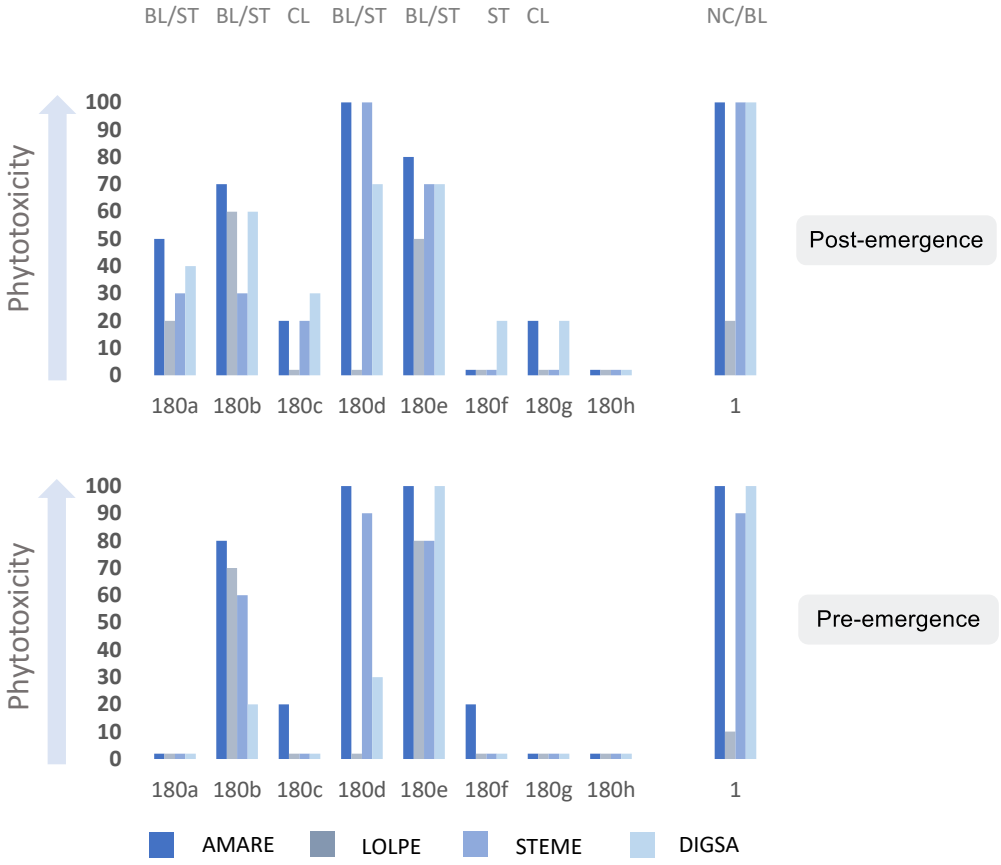


Chart 12: GH1 evaluation of Mesotrione cross-over analogues 180a–180h

3.3.5.3 HPPD assay

Following this, the cross-over analogues were next evaluated through an enzymatic HPPD assay. In this assay the half maximal inhibitory concentration (IC_{50}) is recorded. This value is a measure of the potency of the tested compounds in inhibiting the HPPD protein *in vitro*. The IC_{50} is the concentration of compound required for 50% inhibition of the target.[77] The commercial HPPD inhibitor herbicide Sulcotrione was used as a control in this assay. The IC_{50} values can be converted to pIC_{50} according to equation 1 for ease of data comparison.

$$pIC_{50} = -\log_{10}(IC_{50}) \qquad \text{(equation 1)}$$

Consequently, the potency of each cross-over analogue was compared to that of the known HPPD inhibitor Sulcotrione (Chart 13). As anticipated the close analogues of Mesotrione, compounds **180d** and **180e,** which were highly active in GH1 (Chart 12, *vide supra*), demonstrated high potency against HPPD (pIC_{50}>7) and in fact even higher than Sulcotrione itself. Other analogues were substantially less potent (with pIC_{50}<6). Altogether, these results suggest that when the head group **(15)** of Alternaric acid is connected to Mesotrione-like cores, the same trends in SAR and activity can be observed. It is likely that for these compounds HPPD is also the primary MoA. However, when Alternaric acid **(2)** and dimethylamide hit compound **152** were evaluated in the HPPD assay (Chart 13), both compounds showed much weaker *in vitro* potency, suggesting that HPPD inhibition is unlikely to be the primary MoA of these compounds (with pIC_{50}<6).

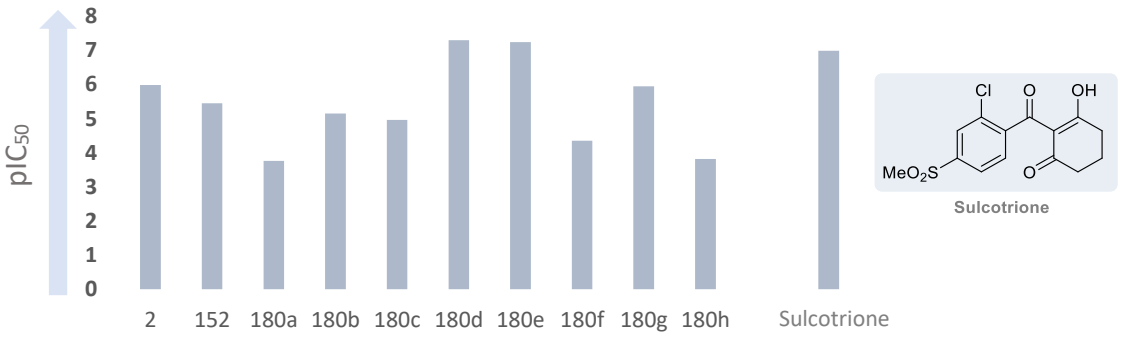


Chart 13: Representation of potency of relevant compounds in HPPD assays

Additionally, the lack of bleaching induced by Alternaric acid and compound **170k** (Chart 11, *vide supra*) suggests the natural product **2** and these amide compounds are likely to operate *via* a different MoA or a combination of HPPD activity with a potential novel MoA.

4. Conclusions and outlook

The natural phytotoxin Alternaric acid has been identified as a compound of interest for agrochemical development and in particular herbicidal discovery. However, very limited information had been gathered on the SAR of the natural product. The lack of SAR and MoA investigations is likely linked to low accessibility to sufficient quantities of Alternaric acid due to structural complexity of this natural product and long and low-yielding synthetic sequences available to date.

The primary goal of this project was to produce Alternaric acid on significant scale to enable herbicidal evaluation. Through a scalable and practical synthesis, Alternaric acid was synthesised in only 12 steps with 21% overall yield (Figure 17).

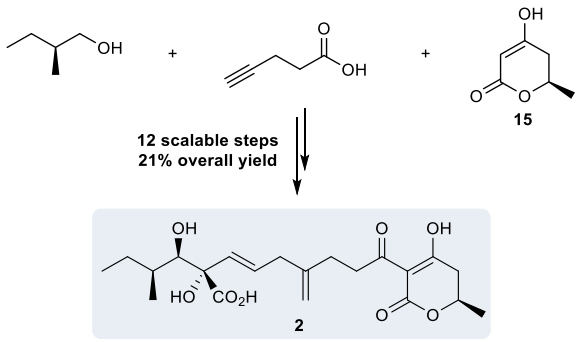


Figure 17: Summary of the total synthesis of Alternaric acid

Additionally, the flexibility associated with the developed synthetic route allowed the synthesis of a variety of analogues which helped probing the SAR of the natural product through biological evaluation. Following identification of the key contributor of herbicidal activity (head group **15**) and optimisation of this motif, further investigations aimed at discovering a more tractable herbicidal lead with greater structural simplicity and retained herbicidal activity. Gratifyingly,

dimethyl amide **152** was identified as a new herbicidal lead with enhanced phytotoxic properties compared to Alternaric acid (Figure 18). This new lead exhibits exquisite structural simplicity and can be accessed in only 3 steps with 56% overall yield.

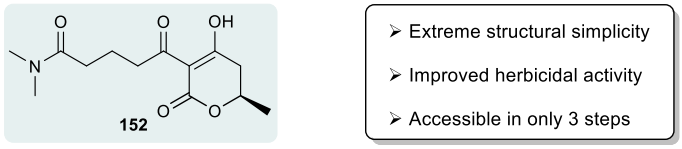


Figure 18: Discovery of the more active dimethylamide hit compound 152

Further SAR optimisation of this target helped identifying a new class of structurally simple and more developable lead compounds that display superior herbicidal activity and with a broader spectrum profile (Figure 19).

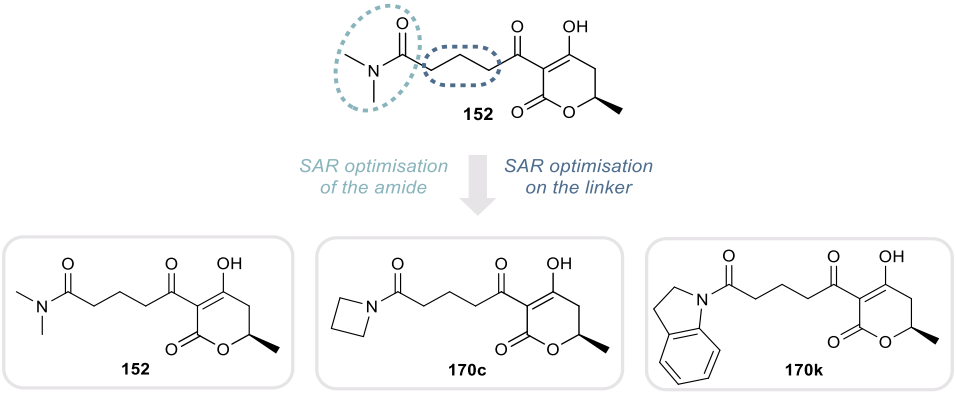


Figure 19: Discovery of new class of herbicidal leads

Additionally, investigations have allowed us to conclude that Alternaric acid as well as the new herbicidal leads identified are unlikely to operate *via* HPPD inhibition exclusively. A novel MoA is possible, highlighting the potential attractiveness of these compounds as herbicidal leads for agrochemical discovery.

Future work could focus on the elucidation of the MoA of this new class of herbicidal lead compounds. Further optimisation of the leads identified throughout this project could be conducted, with a view to identify suitable

candidates for the development of a new herbicide. Additional studies on the development of such candidates could facilitate MoA investigations towards the discovery of a novel MoA which is a long-standing goal of the agrochemical industry.

5. Experimental

5.1 General experimental

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[78]

5.1.1 Purification of solvents and reagents

Anhydrous solvents (THF and CH_2Cl_2) were obtained after passing through an alumina column (MBraun SPS-800) and stored over activated 4 Å molecular sieves under inert gas. MeCN was dried by heating to reflux over CaH_2 and distilled under N_2 and stored under N_2 in an oven-dried flask over previously activated 4 Å molecular sieves. All other solvents and commercial reagents were used as received without further purification unless otherwise stated. CH_2Cl_2, Et_2O, EtOAc, MeOH, hexane, cyclohexane, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification. DIPA for LDA was distilled under N_2 over KOH before being purged with and stored under N_2 in an oven-dried flask over previously activated 4 Å molecular sieves.

5.1.2 Experimental details

Water-sensitive reactions were carried out in oven-dried glassware (150 °C) under an inert atmosphere (N_2 or Ar) using standard Schlenk line techniques. Room temperature refers to 20–25 °C. Reactions were carried out at −78 °C using dry ice/acetone baths. Reactions were carried out at 0 °C using ice/water baths. Reactions at −50 °C and −15 °C were carried out using a Dewar containing

isopropanol and cooled with a cryocooler. Reactions were carried out at elevated temperature using a temperature-regulated hotplate/stirrer.

5.1.3 Purification of products

Analytical thin layer chromatography was performed on pre-coated aluminum plates (Kieselgel 60 F_{254} silica) and visualisation was achieved using UV light (254 nm) and/or staining with either aqueous $KMnO_4$ solution or ethanolic vanillin solution, followed by heating. Flash chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated.

5.1.4 Analysis of products

Infrared spectra (ν_{max}) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (ν_{max}) reported in cm^{-1}.

Optical rotations $[\alpha]_D^{20}$ were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$ NMR spectra were acquired on either a Bruker AV 300 with a BBFO probe (^1H 300 MHz; $^{13}C\{^1H\}$ 101 MHz), a Bruker AV-II 400 with a BBFO probe (^1H 400 MHz; $^{13}C\{^1H\}$ 101 MHz, $^{19}F\{^1H\}$ 376 MHz), a Bruker AV-III HD 400 with a BBFO probe (^1H 400 MHz; $^{13}C\{^1H\}$ 101 MHz), a Bruker AV-III HD 500 with a SmartProbe BBFO+ probe (^1H 500 MHz; $^{13}C\{^1H\}$ 126 MHz, $^{19}F\{^1H\}$ 470 MHz), or a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^1H 500 MHz; ^{13}C 126 MHz, $^{19}F\{^1H\}$ 470 MHz). All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak, with $CDCl_3$ referenced at 7.26 ppm (^1H) and 77.16 ppm (^{13}C), and MeOD referenced at 3.31

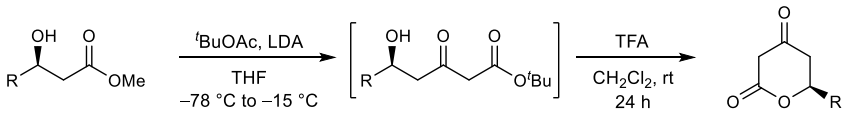
ppm (^{1}H) and 49.00 (^{13}C). All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), hept (heptet), and m (multiplet). The abbreviation br denotes broad, and app denotes apparent.

High resolution mass spectrometry (HRMS) data were acquired by electrospray ionisation (ESI) at the University of St Andrews Mass Spectrometry Facility.

Reactions monitored by LCMS employed a Waters Aquity UPLC-MS using a Sample Organiser with Sample Manager FTN, H-class QSM, Column Manager, 2 x Column Manager Aux, photodiode array, ELSD, and a QDA or SQD 2 equipped with a Waters CORTECS T3 C18 column (column length 30 mm, internal diameter of column 2.1 mm, particle size 1.6 μM). The analysis was conducted using a four minute run time, eluting with 5% to 95% MeCN : water gradient containing 0.1% formic acid at a flow rate of 1.1 mL/min.

5.2 General procedures

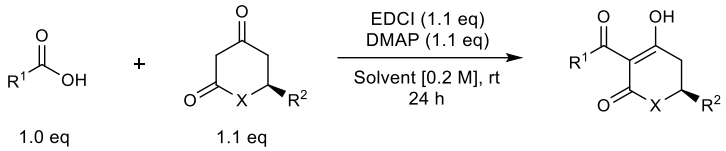
5.2.1 General procedure A: synthesis of head groups



To a solution of freshly distilled DIPA (3.5 eq) in anhydrous THF at 0 °C was added dropwise ^{n}BuLi (3.5 eq). The resulting LDA was stirred at 0 °C for 20 min. The mixture was cooled to −78 °C, ^{t}BuOAc (3.0 eq) was added dropwise, and the resulting mixture was stirred for 40 min at −78 °C. A solution of the appropriate ester (1.0 eq) in anhydrous THF was added dropwise to the mixture at −78 °C. The reaction was warmed to −50 °C and stirred for 2 h then warmed to −15 °C and allowed to stir for 1 h. The reaction mixture was slowly quenched with H_2O, acidified with 1 M aqueous HCl, and extracted with Et_2O (3 ×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. The residue was diluted with anhydrous CH_2Cl_2, and the solution cooled to 0 °C. TFA (1.1 eq) was added dropwise, the mixture was allowed to warm up to rt, and stirred for 24 h unless otherwise stated. The mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography (silica gel) to afford the desired product.

5.2.2 General procedure B1: esterification/Fries-type rearrangement



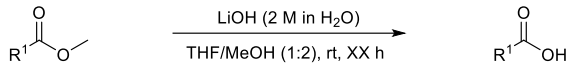
A mixture of EDCI (1.1 eq), the appropriate head group (1.1 eq), DMAP (1.1 eq), and the appropriate carboxylic acid (1.0 eq), was dissolved in anhydrous MeCN or CH_2Cl_2 (0.20 M), and the resulting mixture was stirred at rt for 24 h unless otherwise stated. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl, and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired product.

5.2.3 General procedure B2: esterification/Fries-type rearrangement with additional basic work-up

A mixture of EDCI (1.1 eq), the appropriate head group (1.1 eq), DMAP (1.1 eq), and the appropriate carboxylic acid (1.0 eq), was dissolved in anhydrous MeCN or CH_2Cl_2 (0.20 M), and the resulting mixture was stirred at rt for 24 h unless otherwise stated. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl, and extracted with CH_2Cl_2 (3 ×). The combined organic layers

were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired product.

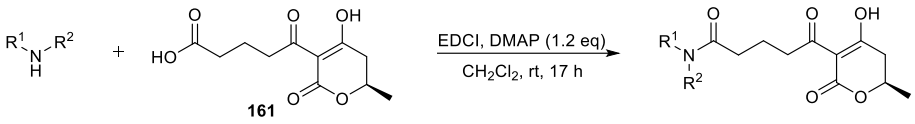
5.2.4 General procedure C: basic hydrolysis of methyl esters



The appropriate methyl ester (1.0 eq) was dissolved in (2 M aqueous solution LiOH)/MeOH/THF (1:1:2) and the mixture was stirred at rt for the specified time. The mixture was neutralised with 1 M aqueous HCl and the organic solvents were removed under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (5 ×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Unless otherwise specified, the crude residue was purified by column chromatography (silica gel) to afford the desired product.

5.2.5 General procedure D: amide coupling

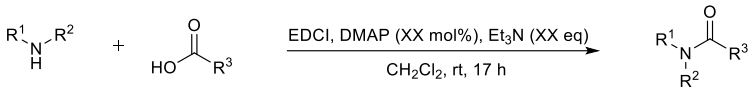
D1: Amide coupling of compound **161**



A mixture of EDCI (1.1 eq), compound **161** (1.1 eq), and DMAP (1.2 eq) was dissolved in anhydrous CH_2Cl_2 (0.20 M) and the resulting mixture was stirred at rt for 1 h. The appropriate amine (1.0 eq) was added, and the resulting mixture stirred at rt for 16 h. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl, and extracted with CH_2Cl_2 (3 ×). The combined organic layers

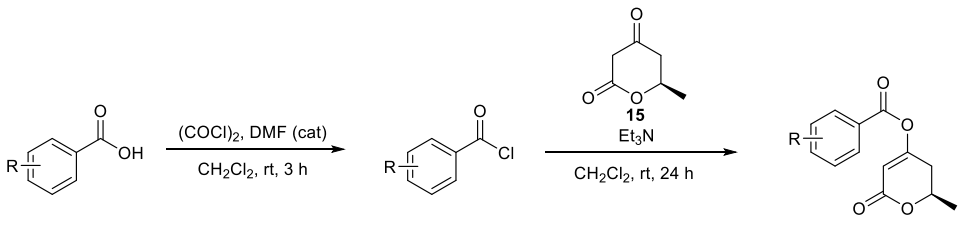
were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired amide product.

D2: General amide coupling



A mixture of EDCI (1.1 eq), the appropriate amine (1.0 eq), the appropriate carboxylic acid (1.1 eq), and DMAP (1.2 eq) was dissolved in anhydrous CH_2Cl_2 (0.20 M), and the resulting mixture was stirred at rt for 17 h unless otherwise specified. In some cases, in place of stoichiometric DMAP (1.2 eq), catalytic DMAP (20 mol%) and Et_3N (1.0 eq) were used. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl, and extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Unless otherwise specified, the crude residue was purified by column chromatography (silica gel) to afford the desired amide product.

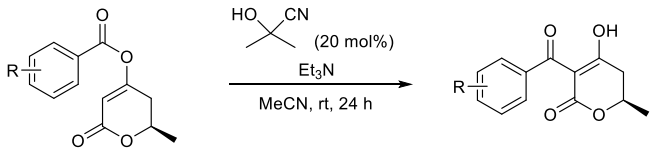
5.2.6 General procedure E: coupling of 15 with aromatic acids



To a solution of aromatic acid (1.0 eq) in CH_2Cl_2, was added dropwise $(COCl)_2$ (1.2 eq) at rt under stirring. Afterwards DMF (2 drops) was added and the resulting mixture was stirred at rt for 3 h. The mixture was then concentrated under reduced pressure and the obtained acid chloride was subsequently used

without further purification. To a solution of compound **15** (1.1 eq) in CH_2Cl_2 (2.0 mL, 0.2 M), was added Et_3N (1.5 eq) and the resulting mixture was stirred at rt for 30 min. Acid chloride (1.0 eq) was then added and the resulting mixture stirred at rt for 24 h. The reaction mixture was acidified with 1 M aqueous HCl and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired ester product.

5.2.7 General procedure F: *O*-acyl to *C*-acyl rearrangement of aryl substrates



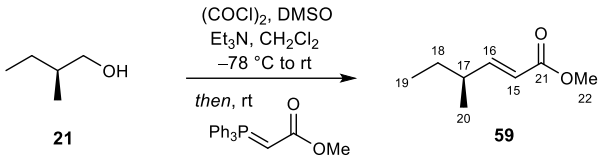
To a solution of *O*-acyl compound (1.0 eq) and Et_3N (1.5 eq) in MeCN (0.1 M), was added acetone cyanohydrin (20 mol%) and the resulting mixture was stirred at rt for 24 h. The reaction mixture was acidified with 1 M aqueous HCl and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired C-acyl product.

5.3 Compound characterisation

In this section, spectral data for novel compounds have been fully assigned (^1H and ^{13}C NMR signals). For compounds known in the literature, ^1H NMR signals have been assigned. Atoms number for all intermediates in the total synthesis of

Alternaric acid, and derivatives of the natural product, are consistent with the corresponding atom numbers found in Alternaric acid.

Compound 59.



DMSO (9.70 mL, 136 mmol, 3.0 eq) was added dropwise to a solution of $(COCl)_2$ (5.80 mL, 68.1 mmol, 1.5 eq) in anhydrous CH_2Cl_2 (100 mL, 0.45 M) at −78 °C and the resulting mixture was stirred for 30 min. A solution of (*S*)-2-methylbutan-1-ol (**21**) (4.90 mL, 45.4 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added dropwise and the mixture stirred at −78 °C for 1 h. Et_3N (31.6 mL, 227 mmol, 5.0 eq) was added and the reaction mixture allowed to warm up to room temperature and stirred at rt for 1.5 h. A solution of methyl(triphenylphosphoranylidene)acetate (15.2 g, 45.4 mmol, 1.0 eq) in CH_2Cl_2 (40 mL, 0.30 M) was added and the resulting mixture stirred at rt for 24 h. The reaction mixture was acidified with 10% aqueous HCl (50 mL). Organics were extracted with CH_2Cl_2 (3 × 100 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5% Et_2O in petroleum ether) to afford the desired product as a colourless oil (5.99 g, 93%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +25.4 (c 11.5, $CHCl_3$).

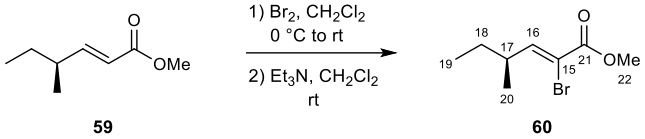
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 6.87 (dd, *J* = 15.7, 7.9 Hz, 1H, H_{16}), 5.78 (dd, *J* = 15.7, 1.2 Hz, 1H, H_{15}), 3.73 (s, 3H, H_{22}), 2.25 – 2.18 (m, 1H, H_{17}), 1.44 – 1.36 (m, 2H, H_{18}), 1.04 (d, *J* = 6.8 Hz, 3H, H_{20}), 0.87 (t, *J* = 7.4 Hz, 3H, H_{19}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 155.0, 119.5, 51.5, 38.3, 28.9, 19.0, 11.7.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 60.

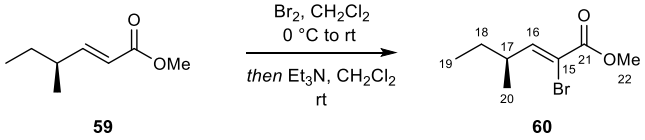
Method 1:



59 **60**

Bromine (2.50 mL, 48.7 mmol, 1.4 eq) was added dropwise to a solution of **59** (4.95 g, 31.8 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (100 mL, 0.35 M) at 0 °C. After 2 h of stirring, the solution was diluted with aqueous saturated $Na_2S_2O_3$ (100 mL). Organics were extracted with CH_2Cl_2 (3 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 (100 mL, 0.35 M) and Et_3N (24.3 mL, 174 mmol, 5.0 eq) was added. The resulting mixture was stirred at rt for 14 h. The heterogeneous mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5% Et_2O in petroleum ether) to afford the desired product as a colourless oil (5.72 g, 74%).

Method 2:



59 **60**

Bromine (86 µL, 0.70 mmol, 1.0 eq) was added dropwise to a solution of **59** (100 mg, 0.70 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (4.7 mL, 0.15 M) at 0 °C. After 2

h of stirring, the mixture was cooled to 0 °C and Et_3N (0.49 mL, 3.52 mmol, 5.0 eq) was added. The resulting mixture was stirred at rt for 14 h. The heterogeneous mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5% Et_2O in petroleum ether) to afford the desired product as a colourless oil (112 mg, 72%).

$[\alpha]_D^{20}$ = +16.1 (c 2.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 9.6 Hz, 1H, H_{16}), 3.82 (s, 3H, H_{22}), 2.71 – 2.63 (m, 1H, H_{17}), 1.49 – 1.40 (m, 2H, H_{18}), 1.05 (d, *J* = 6.7 Hz, 3H, H_{20}), 0.90 (t, *J* = 7.5 Hz, 3H, H_{19}).

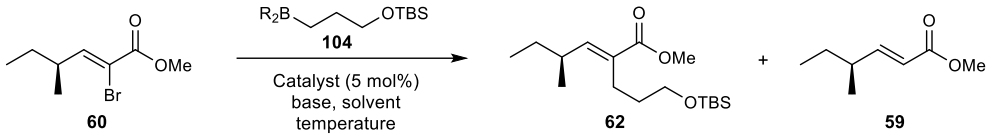
^{13}C NMR (126 MHz, $CDCl_3$): δ 163.4, 151.8, 114.7, 53.4, 38.7, 28.9, 18.6, 11.9.

The spectral data were consistent with those previously reported in the literature.[51]

Optimization of the β-alkyl Suzuki-Miyaura cross-coupling

To a solution of 9-BBN (0.5 M in THF, 0.90 mL, 0.45 mmol, 2.0 eq), (allyloxy)(*tert*-butyl)dimethylsilane (90 µL, 0.45 mmol, 2.0 eq) was added dropwise at 0 °C and the reaction mixture was allowed to stir at rt. After 2 h of stirring, H_2O (0–5.0 eq) was added and the subsequent mixture transferred to a flask containing a solution of vinyl bromide **60** (50 mg, 0.225 mmol, 1.0 eq), catalyst (X mol%), ligand (X mol%), and base (1.0–3.0 eq) in solvent (2.0 mL, 0.12 M). The resulting mixture was heated to reflux for 14 h. The mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude residue was analysed by ^{1}H NMR (Table 8).

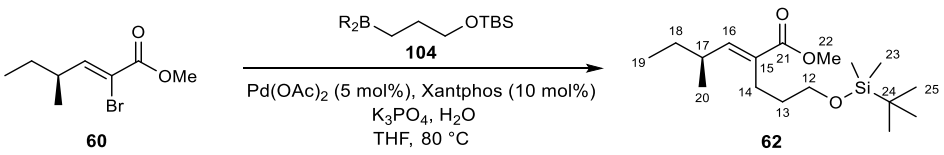


Entry	Catalyst	Base (eq)	Solvent	T (°C)	Time (h)	H_2O (eq)	Ratio 62:59*
1	$Pd(dppf)Cl_2$	K_3PO_4 (3)	THF	80	15 h	/	0 : 100
2	$Pd(dppf)Cl_2$	K_3PO_4 (1)	DMF	50	15 h	/	0 : 100
3	$Pd(OAc)_2$, XPhos	K_3PO_4 (3)	THF	80	15 h	/	33 : 67
4	$Pd(dppf)Cl_2$	K_3PO_4 (3)	THF	80	15 h	5	50 : 50
5	$Pd(dppf)Cl_2$	K_2CO_3 (3)	DMF	50	15 h	5	23 : 77
6	$Pd(dppf)Cl_2$	K_3PO_4 (3)	THF	rt	48 h	5	39 : 61
7	$Pd(OAc)_2$, Xantphos	K_3PO_4 (3)	THF	80	15 h	5	>95 : 5

Ratio **62:**59** was determined by ^{1}H NMR of the crude mixture*

Table 8: Optimization of the β-alkyl Suzuki-Miyaura cross-coupling

Compound 62.



To a solution of 9-BBN (0.5 M in THF, 88.4 mL, 44.2 mmol, 2.0 eq), (allyloxy)(*tert*-butyl)dimethylsilane (9.66 mL, 44.2 mmol, 2.0 eq) was added dropwise at 0 °C and the reaction mixture was allowed to stir at rt. After 2 h of stirring, H_2O (2.0 mL, 111 mmol, 5.0 eq) was added and the subsequent mixture transferred to a flask containing a solution of vinyl bromide **60** (4.89 g, 22.1 mmol, 1.0 eq), $Pd(OAc)_2$ (247 mg, 1.10 mmol, 5 mol%), Xantphos (1.27 g, 2.20 mmol, 10 mol%), and K_3PO_4 (14.1 g, 66.3 mmol, 3.0 eq) in THF (100 mL, 0.12 M). The resulting mixture was heated to reflux for 14 h. The mixture was diluted with H_2O (150 mL) and extracted with Et_2O (3 × 150 mL). The combined organic

layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–5% Et_2O in petroleum ether) to afford the desired product as a colourless oil (6.67 g, 96%).

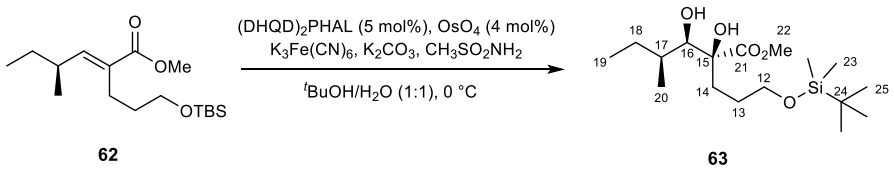
$[\alpha]_D^{20}$ = +17.1 (c 8.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (d, *J* = 10.3 Hz, 1H, H_{16}), 3.72 (s, 3H, H_{22}), 3.61 (t, *J* = 6.3 Hz, 2H, H_{12}), 2.53 – 2.40 (m, 1H, H_{17}), 2.40 – 2.30 (m, 2H, H_{14}), 1.65 – 1.55 (m, 2H, H_{13}), 1.45 – 1.28 (m, 2H, H_{18}), 0.99 (d, *J* = 6.6 Hz, 3H, H_{20}), 0.90 (s, 9H, H_{25}), 0.85 (t, *J* = 7.5, 3H, H_{19}), 0.05 (s, 6H, H_{23}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 148.9, 130.7, 62.8, 51.7, 34.8, 32.9, 29.8, 26.0, 23.5, 20.2, 18.4, 12.1, −5.2.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 63.



62 **63**

A heterogeneous mixture of potassium carbonate (8.76 g, 63.4 mmol, 3.0 eq), potassium ferricyanide (20.9 g, 63.4 mmol, 3.0 eq), $(DHQD)_2PHAL$ (823 mg, 1.06 mmol, 5 mol%), osmium tetroxide (5.60 mL, 0.85 mmol, 4 mol%) in H_2O, methanesulfonamide (2.11 g, 21.1 mmol, 1.0 eq), and compound **62** (6.65 g, 21.1 mmol, 1.0 eq) in ^{t}BuOH/H_2O (1:1, 200 mL, 0.11 M) was stirred for 24 h at 0 °C. The heterogeneous mixture was diluted with saturated aqueous sodium

dithionite (80 mL), stirred until the solution became homogeneous, and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 40% Et_2O in petroleum ether) to afford the desired product as a colourless oil (6.69 g, 93%).

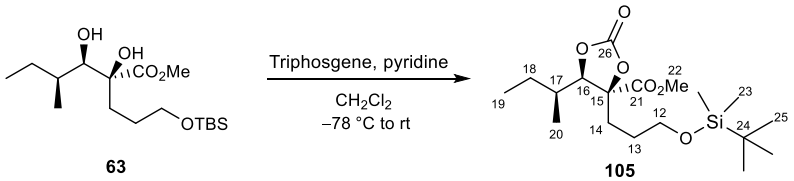
$[\alpha]_D^{20}$ = +12.0 (c 8.3, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 3H, H_{22}), 3.75 (s, 1H, H_{16}), 3.65 – 3.57 (m, 2H, H_{12}), 2.16 (d, *J* = 10.7 Hz, 1H, O*H*), 1.84 – 1.78 (m, 1H, H_{13}), 1.77 – 1.69 (m, 1H, H_{17}), 1.68 – 1.60 (m, 2H, $H_{14,13}$), 1.49 – 1.42 (m, 1H, H_{18}), 1.37 – 1.22 (m, 2H, $H_{14,18}$), 0.95 – 0.85 (m, 15H, $H_{19,20,25}$), 0.05 (s, 3H, H_{23}), 0.04 (s, 3H, H_{23}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 80.9, 76.6, 63.1, 53.2, 35.3, 32.5, 28.5, 27.3, 26.0, 18.4, 12.9, 12.1, −5.2.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 105.



A solution of triphosgene (256 mg, 0.86 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (2.0 mL) was added to a solution of compound **63** (300 mg, 0.86 mmol, 1.0 eq) and pyridine (0.42 mL, 5.17 mmol, 6.0 eq) in anhydrous CH_2Cl_2 (5.0 mL, 0.12 M) at −78 °C. The resulting mixture was stirred for 1 h at −78 °C then 2 h at 0 °C. The

mixture was quenched with aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 30% Et_2O in petroleum ether) to afford the desired product as a colourless oil (281 mg, 87%).

$[\alpha]_D^{20}$ = +42.9 (c 3.5, $CHCl_3$).

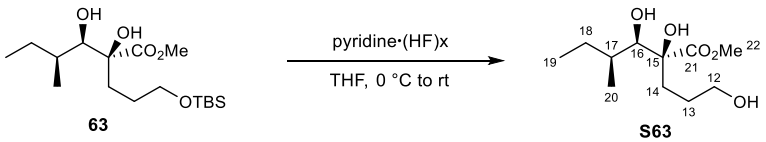
υ_{max} (film): 2967, 1809, 1744, 1186, 1117, 1038, 735.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.51 (d, *J* = 4.6 Hz, 1H, H_{16}), 3.84 (s, 3H, H_{22}), 3.67 – 3.59 (m, 2H, H_{12}), 2.13 (ddd, *J* = 14.0, 11.7, 4.5 Hz, 1H, H_{14}), 1.99 (ddd, *J* = 14.0, 11.6, 4.5 Hz, 1H, H_{12}), 1.86 – 1.78 (m, 1H, H_{17}), 1.76 – 1.68 (m, 1H, H_{13}), 1.55 – 1.50 (m, 1H, H_{18}), 1.48 – 1.40 (m, 1H, H_{13}), 1.33 – 1.27 (m, 1H, H_{18}), 1.03 (d, *J* = 6.6 Hz, 3H, H_{20}), 0.94 (t, *J* = 7.4 Hz, 3H, H_{19}), 0.88 (s, 9H, H_{25}), 0.04 (s, 6H, H_{23}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9 (C_{21}), 153.5 (C_{26}), 86.9 (C_{15}), 85.6 (C_{16}), 62.2 (C_{12}), 53.6 (C_{22}), 34.9 (C_{17}), 27.7 (C_{14}), 27.3 (C_{13}), 26.8 (C_{18}), 26.0 (C_{25}), 18.4 (C_{24}), 13.9 (C_{20}), 11.3 (C_{19}), −5.2 (C_{23}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{34}O_6NaSi$) requires *m/z* 397.2017, found *m/z* 397.2010.

Compound S63.



Pyridine hydrofluoride (2.24 mL, 25.9 mmol, 6.0 eq) was added to a solution of compound **63** (1.50 g, 4.30 mmol, 1.0 eq) in anhydrous THF (20 mL, 0.22 M) at 0 °C, and the resulting mixture was stirred at rt for 2 h. The mixture was neutralised with 1 M aqueous NaOH, diluted with H_2O (20 mL), and extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 50–100% Et_2O in petroleum ether) to afford the desired product as a colourless oil (345 mg, 36%).

$[\alpha]_D^{20}$ = +25.3 (c 3.2, $CHCl_3$).

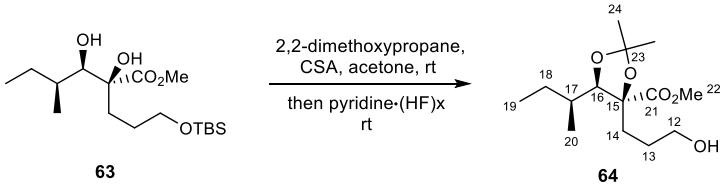
υ_{max} **(film)**: 3724, 3447, 2922, 1732, 1456, 1261.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 3.82 (s, 3H, H_{22}), 3.79 (d, *J* = 9.8 Hz, 1H, H_{16}), 3.74 (s, 1H, OH), 3.68 – 3.63 (m, 2H, H_{12}), 2.09 (d, *J* = 10.7 Hz, 1H, O*H*), 1.87 – 1.82 (m, 1H, H_{13}), 1.76 – 1.60 (m, 3H, $H_{14,13,17}$), 1.48 – 1.43 (m, 1H, H_{18}), 1.39 – 1.31 (m, 2H, $H_{14,18}$), 0.94 – 0.90 (m, 6H, $H_{19,20}$).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 176.7 (C_{21}), 81.0 (C_{15}), 76.6 (C_{16}), 62.8 (C_{12}), 53.3 (C_{22}), 35.3 (C_{17}), 32.2 (C_{13}), 28.5 (C_{18}), 27.1 (C_{14}), 12.9 (C_{20}), 12.1 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{22}O_5Na$) requires *m/z* 257.1359, found *m/z* 257.1354.

Compound 64.



CSA (173 mg, 0.75 mmol, 0.2 eq) was added to a solution of compound **63** (1.30 g, 3.73 mmol, 1.0 eq) and 2,2-dimethoxypropane (4.6 mL, 37.3 mmol, 10 eq) in acetone (20 mL, 0.19 M) at rt. After 24 h of stirring, pyridine hydrofluoride (1.9 mL, 22.4 mmol, 6.0 eq) was added at 0 °C, and the reaction was stirred for 1 h. The reaction mixture was diluted with H_2O (20 mL), extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20–50% Et_2O in petroleum ether) to afford the desired product as a colourless oil (919 mg, 90%).

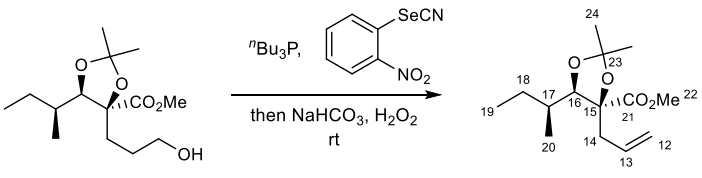
$[\alpha]_D^{20}$ = −32.5 (c 3.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (d, *J* = 9.0 Hz, 1H, H_{16}), 3.76 (s, 3H, H_{22}), 3.66 – 3.64 (m, 2H, H_{12}), 2.03 – 1.96 (m, 1H, H_{17}), 1.78 – 1.72 (m, 2H, H_{14}), 1.68 – 1.59 (m, 4H, $H_{13,18}$, O*H*), 1.54 – 1.49 (m, 1H, H_{18}), 1.46 (s, 6H, H_{24}), 1.02 (d, *J* = 6.6 Hz, 3H, H_{20}), 0.87 (t, *J* = 7.4 Hz, 3H, H_{19}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 108.9, 85.6, 85.2, 63.1, 52.8, 34.0, 28.7, 28.1, 27.4, 25.4, 25.1, 16.4, 10.9.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 65.



Tri-*n*-butylphosphine (2.84 mL, 11.4 mmol, 2.0 eq) was added to a solution of compound **64** (1.56 g, 5.69 mmol, 1.0 eq) and *o*-nitrophenylselenocyante (2.58 g, 11.4 mmol, 2.0 eq) in anhydrous THF (30 mL, 0.19 M), on addition the solution immediately turned dark brown. After 12 h of stirring at rt, $NaHCO_3$ (955 mg, 11.4 mmol, 2.0 eq) was added, followed by the addition of 30% (w/w) H_2O_2 in H_2O (5.91 mL, 56.9 mmol, 10 eq). After 2 h of stirring, the heterogeneous mixture was diluted with 10% aqueous HCl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% Et_2O in petroleum ether) to afford the desired product as a colourless oil (1.32 g, 91%).

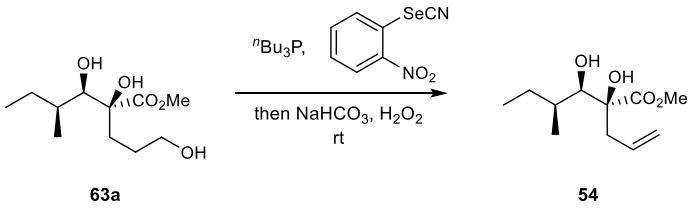
$[\alpha]_D^{20}$ = +51.2 (c 6.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 – 5.80 (m, 1H, H_{13}), 5.15 – 5.12 (m, 1H, H_{12}), 5.10 (app t, 1H, H_{12}), 3.92 (d, *J* = 8.9 Hz, 1H, H_{16}), 3.74 (s, 3H, H_{22}), 2.65 (dd, *J* = 13.7, 7.1 Hz, 1H, H_{14}), 2.36 (dd, *J* = 13.7, 6.9 Hz, 1H, H_{14}), 1.77 – 1.74 (m, 1H, H_{17}), 1.57 – 1.51 (m, 1H, H_{18}), 1.47 (s, 3H, H_{24}), 1.44 (s, 3H, H_{24}), 1.14 – 1.04 (m, 1H, H_{18}), 1.03 (d, *J* = 6.6 Hz, 3H, H_{20}), 0.88 (t, *J* = 7.4 Hz, 3H, H_{19}).

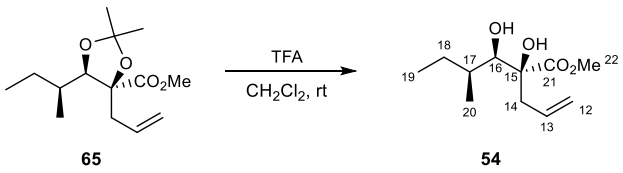
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 133.0, 118.8, 108.9, 85.2, 85.0, 52.6, 37.2, 34.1, 28.0, 25.4, 25.3, 16.4, 11.0.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 54.



Tri-*n*-butylphosphine (0.65 mL, 2.64 mmol, 2.0 eq) was added to a solution of compound **63a** (310 mg, 1.32 mmol, 1.0 eq) and *o*-nitrophenylselenocyante (599 mg, 2.64 mmol, 2.0 eq) in anhydrous THF (10 mL, 0.13 M), on addition the solution immediately turned dark brown. After 16 h of stirring at rt, $NaHCO_3$ (222 mg, 2.64 mmol, 2.0 eq) was added, followed by the addition of 30% (w/w) H_2O_2 in H_2O (1.35 mL, 13.2 mmol, 10 eq). After 1 h of stirring, the heterogeneous mixture was diluted with 10% aqueous HCl (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 25% Et_2O in petroleum ether) to afford the desired product as a red oil (141 mg, 49%).



Compound **65** (1.32 g, 5.15 mmol, 1.0 eq) was dissolved in anhydrous CH_2Cl_2 (15 mL), trifluoroacetic acid (8.0 mL) and H_2O (0.6 mL) at rt. After 12 h of stirring, the solution was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 25% Et_2O in petroleum ether) to afford the desired product as a colourless oil (1.09 g, 99%).

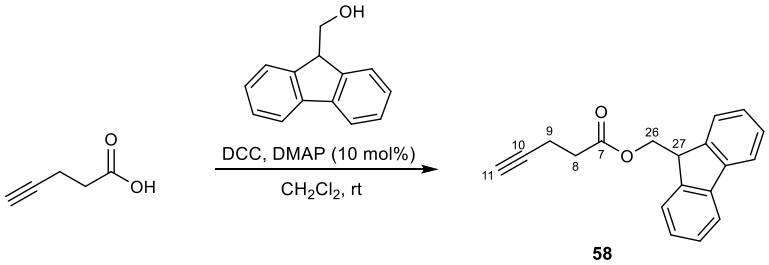
$[\alpha]_D^{20}$ = −13.4 (c 4.4, $CHCl_3$).

^{1}H NMR (500 MHz $CDCl_3$): δ 5.75 – 5.67 (m, 1H, H_{13}), 5.15 – 5.08 (m, 2H, H_{12}), 3.81 – 3.79 (m, 4H, $H_{16,22}$, O*H*), 2.42 (dd, *J* = 7.3, 1.2 Hz, 2H, H_{14}), 1.75 – 1.68 (m, 1H, H_{17}), 1.51 – 1.43 (m, 1H, H_{18}), 1.39 – 1.30 (m, 1H, H_{18}), 0.95 – 0.90 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.2, 131.9, 119.5, 81.0, 76.2, 53.2, 40.5, 35.3, 28.5, 12.9, 12.1.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 58.



58

A solution of 4-pentynoic acid (1.13 g, 11.5 mmol, 1.0 eq), 9-fluorenylmethanol (2.48 g, 12.7 mmol, 1.1 eq), DCC (3.56 g, 17.3 mmol, 1.5 eq), and DMAP (141 mg, 1.15 mmol, 10 mol%) in anhydrous CH_2Cl_2 (50 mL, 0.23 M) was stirred at rt for 15 h. The mixture was filtered then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 10% Et_2O in petroleum ether) to afford the desired product as a beige solid (2.64 g, 83%).

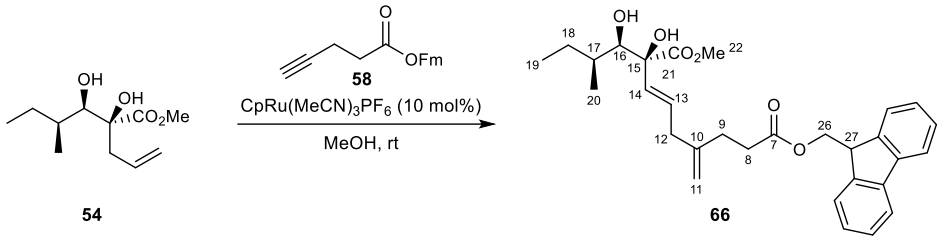
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H, ArC*H*), 7.62 – 7.59 (m, 2H, ArC*H*), 7.43 – 7.39 (m, 2H, ArC*H*), 7.32 (td, *J* = 7.4, 1.2 Hz, 2H, ArC*H*),

4.43 (d, *J* = 7.1 Hz, 2H, H_{26}), 4.23 (t, *J* = 7.1 Hz, 1H, H_{27}), 2.67 – 2.63 (m, 2H, H_8), 2.55 – 2.50 (m, 2H, H_9), 1.99 (t, *J* = 2.6 Hz, 1H, H_{11}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 143.8, 141.4, 128.0, 127.3, 125.2, 120.2, 82.5, 69.4, 66.8, 46.9, 33.5, 14.5.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 66.



Compounds **54** (500 mg, 2.33 mmol, 1.0 eq), **58** (773 mg, 2.80 mmol, 1.2 eq), and $CpRu(MeCN)_3PF_6$ (101 mg, 0.23 mmol, 10 mol%), were dissolved in anhydrous MeOH (8.0 mL, 0.29 M) and the mixture was stirred at rt for 12 h. The mixture was filtered through celite then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 30–50% Et_2O in petroleum ether) to afford the desired product as a colourless oil (724 mg, 63%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.0 (c 0.5, $CHCl_3$).

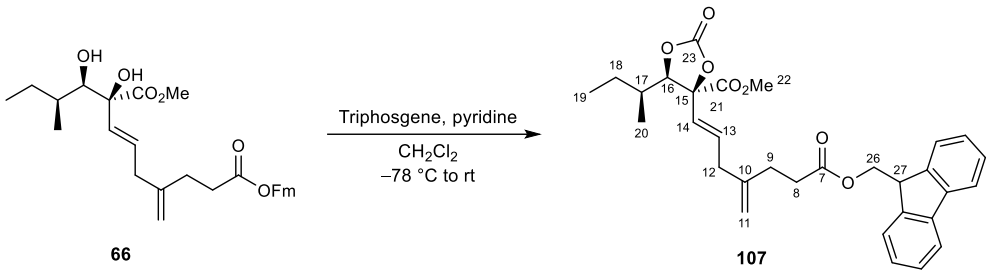
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 2H, ArC*H*), 7.60 – 7.58 (m, 2H, ArC*H*), 7.43 – 7.39 (m, 2H, ArC*H*), 7.32 (td, *J* = 7.5, 1.2 Hz, 2H, ArC*H*), 6.00 (dt, *J* = 15.3, 7.1 Hz, 1H, H_{13}), 5.56 (dt, *J* = 15.3, 1.4 Hz, 1H, H_{14}), 4.77 – 4.75 (m, 2H, H_{11}), 4.40 (d, *J* = 7.1 Hz, 2H, H_{26}), 4.21 (t, *J* = 7.0 Hz, 1H, H_{27}), 3.95

– 3.90 (m, 1H, H_{16}), 3.82 (s, 3H, H_{22}), 3.59 (br s, 1H, O*H*), 2.78 (d, *J* = 7.1 Hz, 2H, H_{12}), 2.57 – 2.47 (m, 2H, H_8), 2.32 (t, *J* = 7.7 Hz, 2H, H_9), 2.17 (s, 1H, O*H*), 1.69 – 1.62 (m, 1H, H_{17}), 1.47 – 1.38 (m, 1H, H_{18}), 1.31 – 1.25 (m, 1H, H_{18}), 0.90 – 0.85 (m, 6H, $H_{19,20}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 173.1, 146.1, 143.9, 141.5, 129.5, 129.3, 127.9, 127.2, 125.1, 120.2, 111.0, 81.4, 76.1, 66.5, 53.7, 47.0, 39.2, 35.5, 32.6, 30.9, 28.4, 13.0, 12.0.

The spectral data were consistent with those previously reported in the literature.[51]

Compound 107.



A solution of triphosgene (795 mg, 2.68 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (3.0 mL), was added to a solution of compound **66** (1.32 g, 2.68 mmol, 1.0 eq) and pyridine (1.3 mL, 16.1 mmol, 6.0 eq) in anhydrous CH_2Cl_2 (10 mL, 0.21 M) at −78 °C. The resulting mixture was stirred for 3 h at 0 °C then 2 h at rt. The mixture was quenched with aqueous NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 25% Et_2O in petroleum ether) to afford the desired product as a yellow oil (1.38 g, 99%).

$[\alpha]_D^{20}$ = +62.3 (c 6.0, $CHCl_3$).

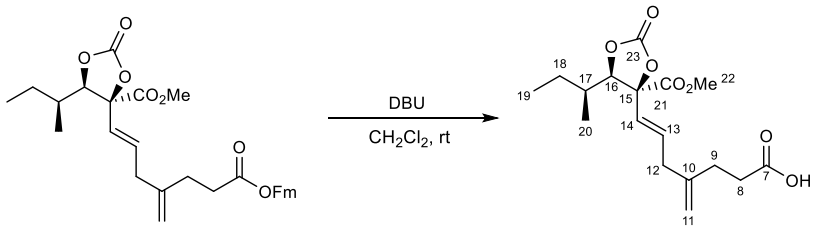
υ_{max} (film): 1811, 1736, 2924, 1450, 1250, 1155, 741.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.6 Hz, 2H, ArC*H*), 7.60 – 7.58 (m, 2H, ArC*H*), 7.43 – 7.40 (m, 2H, ArC*H*), 7.32 (td, *J* = 7.5, 1.2 Hz, 2H, ArC*H*), 6.08 (dt, *J* = 15.7, 7.0 Hz, 1H, H_{13}), 5.69 (dt, *J* = 15.6, 1.5 Hz, 1H, H_{14}), 4.80 – 4.77 (m, 2H, H_{11}), 4.66 (d, *J* = 4.8 Hz, 1H, H_{16}), 4.41 (d, *J* = 7.0 Hz, 2H, H_{26}), 4.21 (t, *J* = 7.0 Hz, 1H, H_{27}), 3.83 (s, 3H, H_{22}), 2.84 (d, *J* = 7.0 Hz, 2H, H_{12}), 2.53 (dd, *J* = 8.6, 6.7 Hz, 2H, H_8), 2.31 (t, *J* = 7.6 Hz, 2H, H_9), 1.76 – 1.70 (m, 1H, H_{17}), 1.52 – 1.45 (m, 1H, H_{18}), 1.32 – 1.27 (m, 1H, H_{18}), 0.96 – 0.90 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1 (C_7), 169.9 (C_{21}), 153.2 (C_{23}), 145.1 (C_{10}), 144.0 (ArC), 141.6 (ArC), 133.4 (C_{13}), 128.0 (ArCH), 127.3 (ArCH), 125.2 (ArCH), 121.8 (C_{14}), 120.3 (ArCH), 111.9 (C_{11}), 85.8 (C_{16}), 85.3 (C_{15}), 66.5 (C_{26}), 53.9 (C_{22}), 47.0 (C_{27}), 39.4 (C_{12}), 35.7 (C_{17}), 32.6 (C_8), 30.9 (C_9), 26.5 (C_{18}), 13.1 (C_{20}), 11.4 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{31}H_{34}O_7Na$) requires *m/z* 541.2197, found *m/z* 541.2179.

Compound 103.



107 **103**

DBU (0.14 mL, 0.94 mmol, 1.1 eq) was added to a solution of compound **107** (443 mg, 0.85 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (13 mL, 0.07 M), and the mixture was stirred at rt for 3 h. The mixture was diluted with H_2O (10 mL), acidified with 1 M aqueous HCl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20% EtOAc in CH_2Cl_2) to afford the desired product as a yellow oil (282 mg, 97%).

$[\alpha]_D^{20}$ = +12.1 (c 8.3, $CHCl_3$).

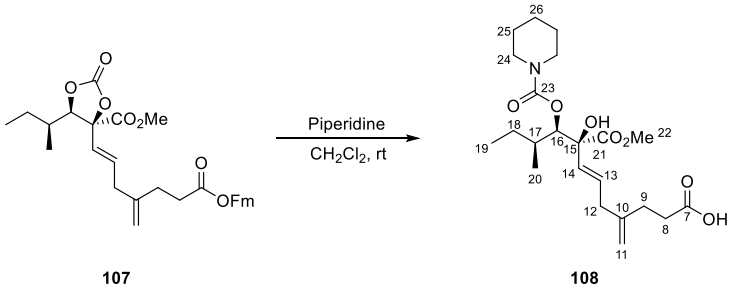
υ_{max} (film): 2965, 2359, 1809, 1742, 1184, 1045, 770.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (dt, *J* = 15.6, 7.0 Hz, 1H, H_{13}), 5.69 (dt, *J* = 15.6, 1.5 Hz, 1H, H_{14}), 4.84 (s, 1H, H_{11}), 4.81 (s, 1H, H_{11}), 4.66 (d, *J* = 4.8 Hz, 1H, H_{16}), 3.84 (s, 3H, H_{22}), 2.86 (d, *J* = 6.9 Hz, 2H, H_{12}), 2.59 – 2.44 (m, 2H, H_8), 2.33 (t, *J* = 7.6 Hz, 2H, H_9), 1.77 – 1.70 (m, 1H, H_{17}), 1.53 – 1.45 (m, 1H, H_{18}), 1.32 – 1.23 (m, 1H, H_{18}), 1.01 – 0.85 (m, 6H, $H_{19,20}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4 (C_7), 169.8 (C_{21}), 153.1 (C_{23}), 144.7 (C_{10}), 133.3 (C_{13}), 121.8 (C_{14}), 112.0 (C_{11}), 85.8 (C_{16}), 85.3 (C_{15}), 53.9 (C_{22}), 39.4 (C_{12}), 35.7 (C_{17}), 32.2 (C_8), 30.5 (C_9), 26.4 (C_{18}), 13.0 (C_{20}), 11.2 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}O_7Na$) requires *m/z* 363.1414, found *m/z* 363.1410.

Compound 108.



107 **108**

Piperidine (0.79 mL, 8.09 mmol, 3.0 eq) was added to a solution of compound **107** (1.39 g, 2.68 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (13 mL, 0.21 M), and the mixture was stirred at rt for 14 h. The mixture was diluted with H_2O, acidified with 1 M aqueous HCl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 5–20% EtOAc in CH_2Cl_2) to afford the desired product as a yellow oil (333 mg, 29%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +21.7 (c 3.0, $CHCl_3$).

$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2936, 1732, 1699, 1435, 1265, 1151, 1024.

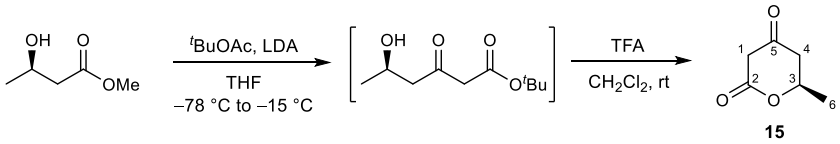
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 6.03 (dt, *J* = 15.3, 7.1 Hz, 1H, H_{13}), 5.63 (dt, *J* = 15.2, 1.4 Hz, 1H, H_{14}), 5.07 (d, *J* = 2.8 Hz, 1H, H_{16}), 4.79 (s, 2H, H_{11}), 3.74 (s, 3H, H_{22}), 3.39 (br s, 4H, H_{24}), 2.80 (d, *J* = 7.0 Hz, 2H, H_{12}), 2.49 (dd, *J* = 8.8, 6.5 Hz, 2H, H_8), 2.32 (t, *J* = 7.7 Hz, 2H, H_9), 1.86 – 1.78 (m, 1H, H_{17}), 1.62 – 1.56 (m, 2H, H_{26}), 1.54 – 1.48 (m, 4H, H_{25}), 1.43 – 1.37 (m, 1H, H_{18}), 1.23 – 1.17 (m, 1H, H_{18}), 0.93 (d, *J* = 6.8 Hz, 3H, H_{20}), 0.87 (t, *J* = 7.4 Hz, 3H, H_{19}).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 178.3 (C_7), 174.7 (C_{21}), 154.7 (C_{23}), 145.9 (C_{10}), 130.0 (C_{13}), 128.7 (C_{14}), 111.1 (C_{11}), 80.3 (C_{15}), 78.7 (C_{16}), 53.3 (C_{22}), 45.2 (C_{24}),

39.3 (C_{12}), 35.0 (C_{17}), 32.3 (C_8), 30.6 (C_9), 28.4 (C_{18}), 25.9 (C_{25}), 24.6 (C_{26}), 14.6 (C_{20}), 11.9 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{35}NO_7Na$) requires *m/z* 448.2306, found *m/z* 448.2299.

Compound 15.



15

Prepared according to general procedure A using DIPA (2.08 mL, 14.8 mmol, 3.5 eq), ^{n}BuLi (2.5 M in hexane, 5.92 mL, 14.8 mmol, 3.5 eq), ^{t}BuOAc (1.70 mL, 12.7 mmol, 3.0 eq), methyl (*R*)-3-hydroxybutanoate (500 mg, 4.23 mmol, 1.0 eq), anhydrous THF (20 mL, 0.21 M), then TFA (0.33 mL, 4.23 mmol, 1.0 eq) and anhydrous CH_2Cl_2 (20 mL, 0.21 M). After 24 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a beige solid (472 mg, 89%).

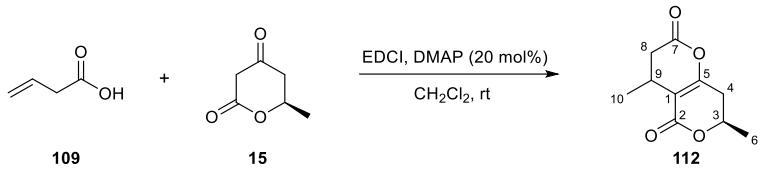
$[\alpha]_D^{20}$ = −141.2 (c 6.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 – 4.78 (m, 1H, H_3), 3.56 (d, *J* = 18.9 Hz, 1H, H_1), 3.43 (d, *J* = 18.9 Hz, 1H, H_1), 2.72 (dd, *J* = 18.3, 2.7 Hz, 1H, H_4), 2.46 (dd, *J* = 18.3, 11.4 Hz, 1H, H_4), 1.52 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.1, 167.4, 72.1, 46.9, 45.1, 20.6.

The spectral data were consistent with those previously reported in the literature.[28]

Compound 112.



109 **15** **112**

A mixture of **109** (20 µL, 0.23 mmol, 1.0 eq), compound **15** (31.5 mg, 0.25 mmol, 1.1 eq), EDCI (66.1 mg, 0.35 mmol, 1.2 eq), and DMAP (5.6 mg, 0.05 mmol, 20 mol%) was dissolved in anhydrous CH_2Cl_2 (1.5 mL, 0.15 M). The resulting mixture was stirred at rt for 48 h. The mixture was acidified with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (26.3 mg, 58%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –71.0 (c 1.0, $CHCl_3$).

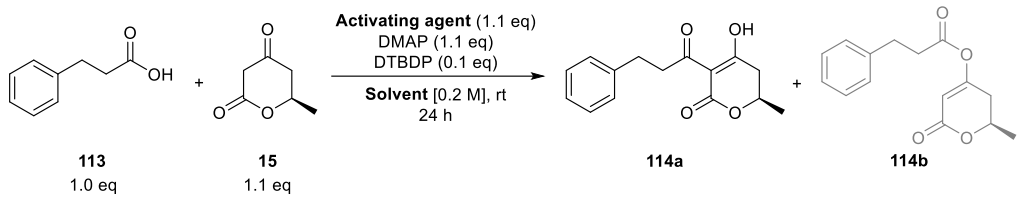
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2920, 2359, 1775, 1713, 1676, 1130.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.69 – 4.60 (m, 1H, H_3), 3.05 – 2.98 (m, 1H, H_9), 2.79 (dd, *J* = 15.7, 6.7 Hz, 1H, H_8), 2.69 – 2.58 (m, 2H, $H_{8,4}$), 2.47 (ddd, *J* = 17.6, 4.3, 1.4 Hz, 1H, H_4), 1.48 (d, *J* = 6.3 Hz, 3H, H_6), 1.18 (d, *J* = 7.0 Hz, 3H, H_{10}).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 165.7 (C_7), 165.2 (C_2), 160.8 (C_5), 109.9 (C_1), 72.8 (C_3), 36.4 (C_8), 32.8 (C_4), 25.8 (C_9), 20.8 (C_6), 19.5 (C_{10}).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{10}H_{13}O_4$) requires *m/z* 197.0808, found *m/z* 197.0807.

Optimisation of the head group coupling



A mixture of **activating agent** (0.22 mmol, 1.1 eq), compound **15** (28.3 mg, 0.22 mmol, 1.1 eq), DMAP (27.5 mg, 0.22 mmol, 1.1 eq), compound **113** (30.1 mg, 0.20 mmol, 1.0 eq), and 4,4'-di-*tert*-butyl-1,1'-biphenyl (5.34 mg, 0.02 mmol, 0.1 eq) was dissolved in anhydrous **solvent** (1.0 mL, 0.20 M). The resulting mixture was stirred at rt for 24 h. Aliquots (15 µL) were taken from each vial and diluted with MeCN (1.0 mL) for LCMS analysis. By comparing product peaks with internal standard 4,4'-di-*tert*-butyl-1,1'-biphenyl and calibrated from authentic samples, the conversion of each reaction to the desired product could be quantified. Results (LCMS yield of **114a** (C-acyl product) and **114b** (O-acyl product)) are shown below (Table 9).

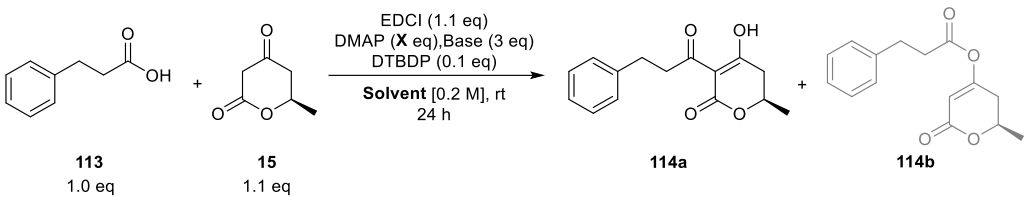
	CH_2Cl_2	MeCN	DMF	$CHCl_3$	PhMe	THF
EDCI	84	96	86	82	38	66
DCC	96	96	86	96	72	86
CDI	9	8	7	9	14	5
HATU	4	6	6	3	12	5

C-acyl results

	CH_2Cl_2	MeCN	DMF	$CHCl_3$	PhMe	THF
EDCI	0	0	0	0	0	0
DCC	0	0	0	0	0	0
CDI	0	0	0	0	0	5
HATU	2	1	5	2	7	1

O-acyl results

Table 9: Solvent and activating agent screen



A mixture of EDCI (43.1 mg, 0.22 mmol, 1.1 eq), compound **15** (28.3 mg, 0.22 mmol, 1.1 eq), **DMAP (X mmol, X eq)**, compound **113** (30.1 mg, 0.20 mmol, 1.0 eq), **base** (0.60 mmol, 3 eq), and 4,4'-di-*tert*-butyl-1,1'-biphenyl (5.34 mg, 0.02 mmol, 0.1 eq) was dissolved in anhydrous **solvent** (1.0 mL, 0.20 M). The resulting mixture was stirred at rt for 24 h. Aliquots (15 µL) were taken from each vial and diluted with MeCN (1.0 mL) for LCMS analysis. By comparing product peaks with internal standard 4,4'-di-*tert*-butyl-1,1'-biphenyl and calibrated from authentic samples, the conversion of each reaction to the desired product could be quantified. Results (LCMS yield of **114a** (C-acyl product) and **114b** (O-acyl product)) are shown below (Table 10).

	CH_2Cl_2			MeCN		
	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP
No base	0	37	80	0	47	96
Et_3N	0	66	72	14	67	80
Pyridine	0	35	79	0	45	70
DIPEA	0	72	78	15	70	83

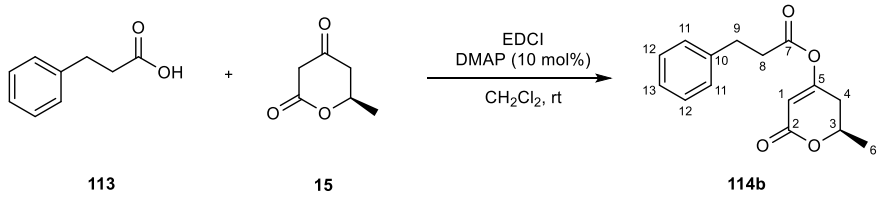
C-acyl results

	CH_2Cl_2			MeCN		
	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP	No DMAP	0.1 eq. DMAP	1.1 eq. DMAP
No base	89	49	0	63	51	0
Et_3N	46	0	0	8	0	0
Pyridine	79	47	0	84	49	0
DIPEA	65	0	0	10	0	0

O-acyl results

Table 10: Additive stoichiometry, base, and solvent screen

Compound 114b.



113 **15** **114b**

A mixture of EDCI (156 mg, 0.80 mmol, 1.2 eq), compound **15** (102 mg, 0.80 mmol, 1.2 eq), DMAP (8.30 mg, 0.07 mmol, 10 mol%), and **113** (100 mg, 0.66 mmol, 1.0 eq) was dissolved in anhydrous CH_2Cl_2 (3.3 mL, 0.20 M). The resulting mixture was stirred at rt for 30 min. The mixture was diluted with H_2O, acidified with 2 M aqueous HCl (2 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a colourless oil (124 mg, 72%).

$[\alpha]_D^{20}$ = –94.5 (c 7.5, $CHCl_3$).

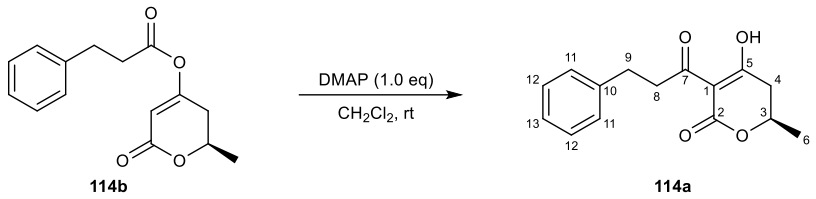
υ_{max} (film): 2970, 2937, 1716, 1372, 1282, 1095, 699.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 2H, H_{12}), 7.26 – 7.19 (m, 3H, $H_{11,13}$), 5.86 (d, *J* = 2.1 Hz, 1H, H_1), 4.62 – 4.56 (m, 1H, H_3), 3.00 (t, *J* = 7.5 Hz, 2H, H_9), 2.81 (td, *J* = 7.5, 0.7 Hz, 2H, H_8), 2.57 (ddd, *J* = 17.6, 11.5, 2.2 Hz, 1H, H_4), 2.35 (dd, *J* = 17.6, 3.9 Hz, 1H, H_4), 1.44 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3 (C_7), 165.6 (C_2), 163.9 (C_5), 139.5 (C_{10}), 128.8 (C_{12}), 128.4 (C_{11}), 126.8 (C_{13}), 106.9 (C_1), 73.0 (C_3), 36.1 (C_8), 34.1 (C_4), 30.7 (C_9), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}O_4Na$) requires *m/z* 283.0941, found *m/z* 283.0940.

Compound 114a.



114b **114a**

A mixture of **114b** (22.0 mg, 0.08 mmol, 1.0 eq) and DMAP (10.3 mg, 0.08 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (1.0 mL, 0.08 M), was stirred at rt for 4 h. The mixture was diluted with H_2O, acidified with 2 M aqueous HCl (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a colourless oil (16.0 mg, 73%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –33.7 (c 4.5, $CHCl_3$).

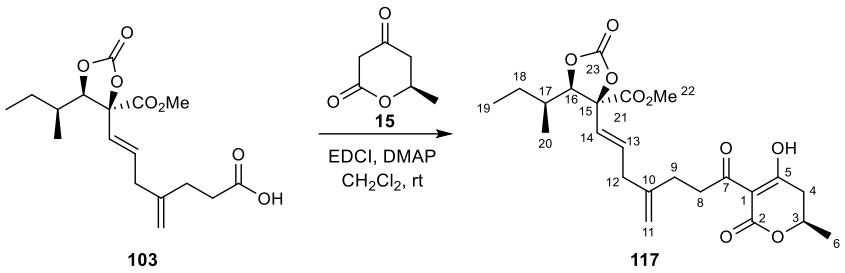
υ_{max} **(film)**: 3460, 3016, 2970, 1739, 1441, 1365, 1229, 1217.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 3H, $H_{12,13}$), 7.21 (m, 2H, H_{11}), 4.53 – 4.46 (m, 1H, H_3), 3.48 – 3.26 (m, 2H, H_8), 3.02 – 2.92 (m, 2H, H_9), 2.68 – 2.58 (m, 2H, H_4), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 203.6 (C_7), 194.6 (C_5), 164.4 (C_2), 140.6 (C_{10}), 128.7 ($C_{12\text{ or }13}$), 128.6 ($C_{12\text{ or }13}$), 126.5 (C_{11}), 103.4 (C_1), 70.5 (C_3), 40.6 (C_8), 39.2 (C_4), 30.8 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}O_4$) requires *m/z* 261.1121, found *m/z* 261.1122.

Compound 117.



Prepared according to general procedure B1 using EDCI (135 mg, 0.71 mmol, 1.2 eq), compound **15** (88.9 mg, 0.71 mmol, 1.2 eq), compound **103** (200 mg, 0.59 mmol, 1.0 eq), DMAP (86.2 mg, 0.71 mmol, 1.2 eq), and anhydrous CH_2Cl_2 (4.0 mL, 0.15 M) for 48 h. The crude residue was purified by column chromatography (silica gel, 10–20% EtOAc in CH_2Cl_2) to afford the desired product as a yellow oil (210 mg, 79%).

$[\alpha]_D^{20}$ = +39.4 (c 9.0, $CHCl_3$).

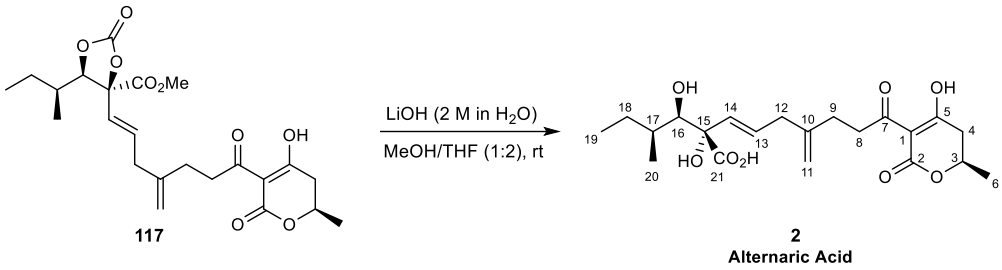
υ_{max} **(film)**: 3734, 2962, 2361, 1809, 1707, 1043, 769.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 6.07 (dt, *J* = 15.6, 7.0 Hz, 1H, H_{13}), 5.70 (dt, *J* = 15.7, 1.4 Hz, 1H, H_{14}), 4.85 (br s, 1H, H_{11}), 4.77 (br s, 1H, H_{11}), 4.66 (d, *J* = 4.7 Hz, 1H, H_{16}), 4.61 – 4.45 (m, 1H, H_3), 3.84 (s, 3H, H_{22}), 3.29 – 3.07 (m, 2H, H_8), 2.88 (d, *J* = 6.9 Hz, 2H, H_{12}), 2.73 – 2.57 (m, 2H, H_4), 2.38 – 2.32 (m, 2H, H_9), 1.76 – 1.72 (m, 1H, H_{17}), 1.48 (m, 1H, H_{18}), 1.46 (d, *J* = 6.3 Hz, 3H, H_6), 1.32 – 1.24 (m, 1H, H_{18}), 0.96 – 0.89 (m, 6H, $H_{19,20}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7 (C_7), 194.5 (C_5), 169.8 (C_{21}), 164.4 (C_2), 153.1 (C_{23}), 145.0 (C_{10}), 133.4 (C_{13}), 121.6 (C_{14}), 112.3 (C_{11}), 103.3 (C_1), 85.8 (C_{16}), 85.4 (C_{15}), 70.5 (C_3), 53.8 (C_{22}), 39.2 (C_4), 39.1 (C_{12}), 37.1 (C_8), 35.6 (C_{17}), 30.7 (C_9), 26.4 (C_{18}), 20.7 (C_6), 13.0 (C_{20}), 11.2 (C_{19}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{23}H_{29}O_9$) requires *m/z* 449.1817, found *m/z* 449.1822.

Alternaric acid 2.



117 **2**
Alternaric Acid

Prepared according to general procedure C using compound **117** (30 mg, 0.067 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.0 mL) for 15 min. The desired product was obtained without further purification as a white solid (25.0 mg, 91%).

$[\alpha]_D^{20}$ = −0.5 (c 10.0, $CHCl_3$).

υ_{max} (solid): 3462, 2932, 2361, 1705, 1558, 1456, 1265, 1144, 1055, 905.

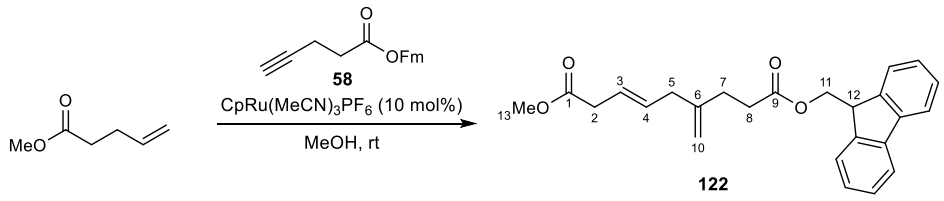
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (dt, *J* = 14.3, 6.8 Hz, 1H, H_{13}), 5.69 (d, *J* = 15.3 Hz, 1H, H_{14}), 4.82 – 4.79 (m, 2H, H_{11}), 4.57 – 4.52 (m, 1H, H_3), 3.98 (br s, 1H, H_{16}), 3.23 (ddd, *J* = 15.3, 10.0, 5.5 Hz, 1H, H_8), 3.01 (ddd, *J* = 15.3, 10.0, 5.8 Hz, 1H, H_8), 2.82 (d, *J* = 7.1 Hz, 2H, H_{12}), 2.70 – 2.60 (m, 2H, H_4), 2.40 (ddd, *J* = 15.3, 9.9, 5.5 Hz, 1H, H_9), 2.29 (ddd, *J* = 15.3, 10.0, 5.8 Hz, 1H, H_9), 1.78 –

1.74 (m, 1H, H_{17}), 1.46 (d, *J* = 6.3 Hz, 3H, H_6), 1.43 – 1.38 (m, 1H, H_{18}), 1.32 – 1.25 (m, 1H, H_{18}), 0.91 – 0.85 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.0 (C_7), 195.2 (C_5), 177.0 (C_{21}), 165.1 (C_2), 145.8 (C_{10}), 129.8 (C_{14}), 129.7 (C_{13}), 112.0 (C_{11}), 103.0 (C_1), 79.8 (C_{15}), 76.8 (C_{16}), 70.8 (C_3), 39.3 (C_4), 39.1 (C_{12}), 37.3 (C_8), 35.2 (C_{17}), 31.0 (C_9), 28.1 (C_{18}), 20.7 (C_6), 12.8 (C_{20}), 11.9 (C_{19}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{21}H_{29}O_8$) requires *m/z* 409.1868, found *m/z* 409.1871.

Compound 122.



Methyl pent-4-enoate (300 mg, 2.63 mmol, 1.0 eq), compound **58** (727 mg, 2.63 mmol, 1.0 eq), and $CpRu(MeCN)_3PF_6$ (114 mg, 0.26 mmol, 10 mol%) were dissolved in anhydrous MeOH (12 mL, 0.22 M) and the mixture was stirred for 12 h. The mixture was filtered through celite then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 10–50% Et_2O in petroleum ether) to afford the desired product as a pink/brown oil (810 mg, 79%).

υ_{max} (film): 2951, 1732, 1450, 1194, 1159.

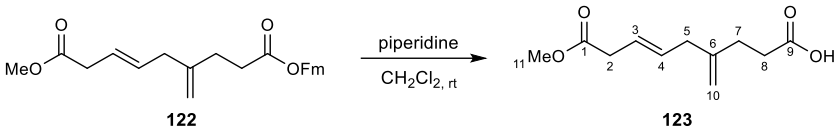
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H, ArC*H*), 7.61 – 7.59 (m, 2H, ArC*H*), 7.43 – 7.39 (m, 2H, ArC*H*), 7.34 – 7.30 (m, 2H, ArC*H*), 5.67 – 5.47 (m, 2H, $H_{3,4}$), 4.87 (s, 1H, H_{10}), 4.67 (s, 1H, H_{10}), 4.40 (d, *J* = 7.0 Hz, 2H, H_{11}),

4.21 (t, *J* = 7.0 Hz, 1H, H_{12}), 3.68 (s, 3H, H_{13}), 3.12 – 3.01 (m, 2H, H_2), 2.76 (d, *J* = 5.3 Hz, 2H, H_5), 2.58 – 2.51 (m, 2H, H_8), 2.39 – 2.27 (t, *J* = 7.7 Hz, 2H, H_7).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3 (C_9), 172.5 (C_1), 146.4 (C_6), 143.9 (ArC), 141.4 (ArC), 131.9 (C_4), 127.9 (ArCH), 127.2 (ArCH), 125.1 (ArCH), 123.9 (C_3), 120.2 (ArCH), 110.7 (C_{10}), 66.4 (C_{11}), 52.0 (C_{13}), 47.0 (C_{12}), 39.7 (C_5), 37.9 (C_2), 32.7 (C_8), 30.8 (C_7).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{25}H_{26}O_4Na$) requires *m/z* 413.1723, found *m/z* 413.1721.

Compound 123.



122 123

Piperidine (85 µL, 0.86 mmol, 3.0 eq) was added to a solution of compound **122** (100 mg, 0.29 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (3.0 mL, 0.10 M), and the mixture was stirred at rt for 14 h. The mixture was diluted with H_2O, acidified with 1 M aqueous HCl (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was diluted with H_2O, basified with saturated $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The resulting organic layer was discarded, the aqueous layer was re-acidified with 1 M aqueous HCl (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product as a yellow oil (46.2 mg, 78%).

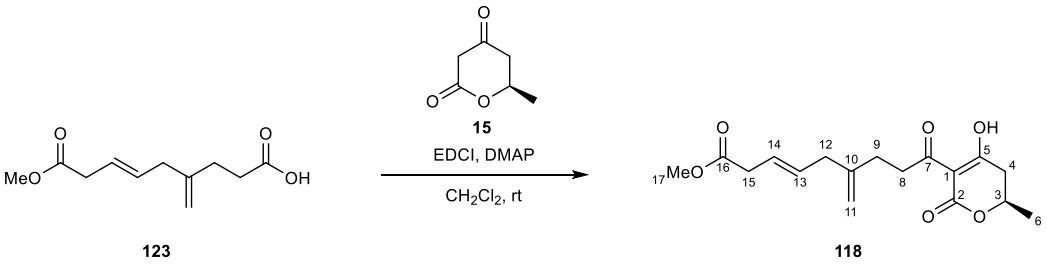
υ_{max} (film): 2954, 2361, 1732, 1200, 1169.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 – 5.52 (m, 2H, $H_{3,4}$), 4.85 (s, 1H, H_{10}), 4.73 (s, 1H, H_{10}), 3.68 (s, 3H, H_{11}), 3.09 – 3.04 (m, 2H, H_2), 2.77 (d, *J* = 5.9 Hz, 2H, H_5), 2.51 (dd, *J* = 8.8, 6.5 Hz, 2H, H_8), 2.34 (t, *J* = 7.6 Hz, 2H, H_7).

^{13}C NMR (126 MHz, $CDCl_3$): δ 179.1 (C_9), 172.6 (C_1), 146.2 (C_6), 131.9 (C_4), 123.9 (C_3), 110.9 (C_{10}), 52.0 (C_{11}), 39.7 (C_5), 37.9 (C_2), 32.4 (C_8), 30.5 (C_7).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{16}O_4Na$) requires *m/z* 235.0941, found *m/z* 235.0946.

Compound 118.



Prepared according to general procedure B1 using EDCI (163 mg, 0.85 mmol, 1.2 eq), compound **15** (107 mg, 0.85 mmol, 1.2 eq), compound **123** (150 mg, 0.71 mmol, 1.0 eq), DMAP (104 mg, 0.85 mmol, 1.2 eq), and anhydrous CH_2Cl_2 (4.0 mL, 0.18 M). The crude residue was purified by column chromatography (silica gel, 2% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (66.2 mg, 29%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −38.9 (c 5.3, $CHCl_3$).

υ_{max} (film): 3620, 2951, 1734, 1715, 1437, 1163.

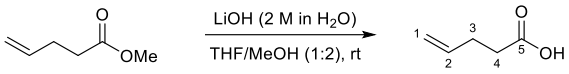
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 – 5.51 (m, 2H, $H_{13,14}$), 4.79 (br s, 2H, H_{11}), 4.58 – 4.46 (m, 1H, H_3), 3.68 (s, 3H, H_{17}), 3.28 – 3.09 (m, 2H, H_8), 3.09 – 3.03

(m, 2H, H_{15}), 2.79 (d, *J* = 5.2 Hz, 2H, H_{12}), 2.69 – 2.57 (m, 2H, H_4), 2.44 – 2.27 (m, 2H, H_9), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.1 (C_7), 194.6 (C_5), 172.5 (C_{16}), 164.4 (C_2), 146.5 (C_{10}), 132.0 (C_{13}), 123.9 (C_{14}), 111.1 (C_{11}), 103.3 (C_1), 70.5 (C_3), 51.9 (C_{17}), 39.5 (C_{12}), 39.3 (C_4), 37.9 (C_{15}), 37.1 (C_8), 30.6 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}O_6Na$) requires *m/z* 345.1309, found *m/z* 345.1304.

Compound 124.



121 **124**

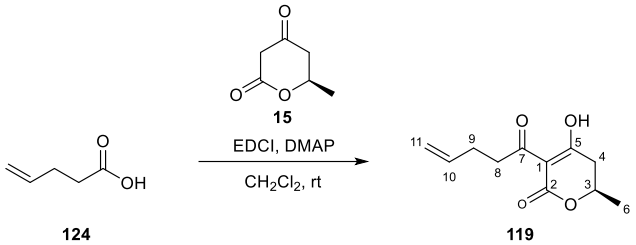
Compound **121** (367 mg, 3.22 mmol, 1.0 eq) was dissolved in 2 M solution of LiOH/MeOH/THF (1:1:2, 19.3 mL), and the mixture was stirred at rt for 14 h. The mixture was neutralised with 1 M aqueous HCl (5 mL) and the organic solvents were removed under reduced pressure. The resulting mixture was extracted with Et_2O (5 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product as a yellow oil (290 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 – 5.79 (m, 1H, H_2), 5.16 – 4.92 (m, 2H, H_1), 2.54 – 2.27 (m, 4H, $H_{3,4}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 179.4, 136.4, 115.9, 33.4, 28.6.

The spectral data were consistent with those previously reported in the literature.[79]

Compound 119.



Prepared according to general procedure B1 using EDCI (230 mg, 1.20 mmol, 1.2 eq), compound **15** (151 mg, 1.20 mmol, 1.2 eq), compound **124** (100 mg, 1.00 mmol, 1.0 eq), DMAP (147 mg, 1.20 mmol, 1.2 eq), and anhydrous CH_2Cl_2 (5.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 2% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (81.1 mg, 39%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –63.5 (c 2.0, $CHCl_3$).

$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 3620, 2980, 1713, 1562, 1065.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 5.90 – 5.80 (m, 1H, H_{10}), 5.10 – 4.97 (m, 2H, H_{11}), 4.57 – 4.48 (m, 1H, H_3), 3.25 – 3.06 (m, 2H, H_8), 2.69 – 2.58 (m, 2H, H_4), 2.46 – 2.38 (m, 2H, H_9), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 204.0 (C_7), 194.5 (C_5), 164.4 (C_2), 136.9 (C_{10}), 115.8 (C_{11}), 103.3 (C_1), 70.5 (C_3), 39.3 (C_4), 38.2 (C_8), 28.7 (C_9), 20.8 (C_6).

HRMS (ESI): exact mass calculated for $[M–H]^-$ ($C_{11}H_{13}O_4$) requires *m/z* 209.0819, found *m/z* 209.0814.

Compound 120.

Prepared according to general procedure C using compound **103** (50.0 mg, 0.147 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.0 mL) for 15 min. The crude product was triturated with $CHCl_3$. The $CHCl_3$ solution was pipetted off and the resulting solid was dried under reduced pressure to afford the desired product as white solid (34.0 mg, 77%).

$[\alpha]_D^{20}$ = +39.5 (c 2.1, MeOH).

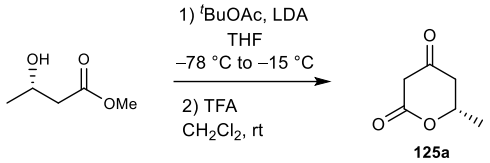
υ_{max} **(film)**: 3449, 2963, 2361, 1713, 1647, 1248, 1148, 982.

^{1}**H NMR** (500 MHz, MeOD): δ 5.95 (dt, *J* = 15.4, 7.1 Hz, 1H, H_{13}), 5.67 (dt, *J* = 15.3, 1.4 Hz, 1H, H_{14}), 4.79 (br s, 2H, H_{11}), 3.92 (d, *J* = 2.5 Hz, 1H, H_{16}), 2.82 (dd, *J* = 7.1, 1.4 Hz, 2H, H_{12}), 2.51 – 2.37 (m, 2H, H_8), 2.36 – 2.24 (m, 2H, H_9), 1.73 – 1.66 (m, 1H, H_{17}), 1.47 – 1.38 (m, 1H, H_{18}), 1.30 – 1.20 (m, 1H, H_{18}), 1.00 – 0.80 (m, 6H, $H_{19,20}$).

^{13}**C NMR** (126 MHz, MeOD): δ 177.5 (C_{21}), 176.9 (C_7), 148.2 (C_{10}), 132.0 (C_{14}), 129.7 (C_{13}), 111.1 (C_{11}), 82.5 (C_{15}), 77.3 (C_{16}), 40.1 (C_{12}), 36.8 (C_{17}), 33.4 (C_8), 31.9 (C_9), 29.6 (C_{18}), 14.0 (C_{20}), 12.2 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{24}O_6Na$) requires *m/z* 323.1465, found *m/z* 323.1466.

Compound 125a.

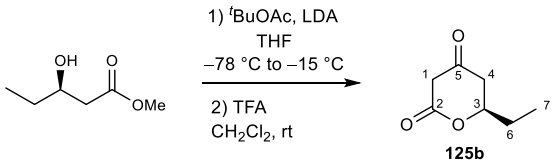


Prepared according to general procedure A using DIPA (3.74 mL, 26.7 mmol, 3.5 eq), ^{n}BuLi (2.5 M in hexane, 10.7 mL, 26.7 mmol, 3.5 eq), ^{t}BuOAc (3.07 mL, 22.9 mmol, 3.0 eq), methyl (*S*)-3-hydroxypentanoate (900 mg, 7.62 mmol, 1.0 eq), anhydrous THF (35 mL, 0.22 M), then TFA (0.59 mL, 7.62 mmol, 1.0 eq) and anhydrous CH_2Cl_2 (35 mL, 0.22 M). After 2 days, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography (silica gel, 50–100% EtOAc in petroleum ether) to afford the desired product as a white solid (802 mg, 82%).

Data consistent with that of compound **15** above.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +146.6 (c 7.3, $CHCl_3$).

Compound 125b.



Prepared according to general procedure A using DIPA (4.08 mL, 29.1 mmol, 3.5 eq), ^{n}BuLi (2.5 M in hexane, 11.7 mL, 29.1 mmol, 3.5 eq), ^{t}BuOAc (3.35 mL, 25.0 mmol, 3.0 eq), methyl (*R*)-3-hydroxypentanoate (1.10 g, 8.32 mmol, 1.0 eq), anhydrous THF (50 mL, 0.17 M), then TFA (0.64 mL, 8.32 mmol, 1.0 eq) and anhydrous CH_2Cl_2 (40 mL, 0.21 M). After 2 days, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by

column chromatography (silica gel, 50–100% Et_2O in petroleum ether) to afford the desired product as a beige solid (455 mg, 38%).

$[\alpha]_D^{20}$ = −91.8 (c 9.0, $CHCl_3$).

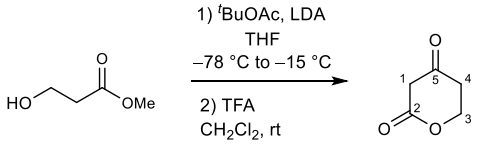
υ_{max} (film): 2970, 1653, 1610, 1395, 1369, 1271, 1231, 1036.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.62 – 4.53 (m, 1H, H_3), 3.58 (d, *J* = 18.9 Hz, 1H, H_1), 3.43 (dd, *J* = 18.8, 0.7 Hz, 1H, H_1), 2.71 (dd, *J* = 18.3, 2.8 Hz, 1H, H_4), 2.47 (ddd, *J* = 18.3, 11.5, 0.7 Hz, 1H, H_4), 1.90 – 1.73 (m, 2H, H_6), 1.07 (t, *J* = 7.4 Hz, 3H, H_7).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3 (C_5), 167.5 (C_2), 76.8 (C_3), 47.1 (C_1), 43.3 (C_4), 27.8 (C_6), 9.3 (C_7).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_7H_9O_3$) requires *m/z* 141.0557, found *m/z* 141.0552.

Compound 125c.



125c

Prepared according to general procedure A using DIPA (1.42 mL, 10.1 mmol, 3.5 eq), ^{n}BuLi (2.1 M in hexane, 4.80 mL, 10.1 mmol, 3.5 eq), ^{t}BuOAc (1.16 mL, 8.64 mmol, 3.0 eq), methyl 3-hydroxypropanoate (300 mg, 2.88 mmol, 1.0 eq), anhydrous THF (12 mL, 0.24 M), then TFA (0.22 mL, 2.88 mmol, 1.0 eq) and anhydrous CH_2Cl_2 (12 mL, 0.24 M). After 24 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by

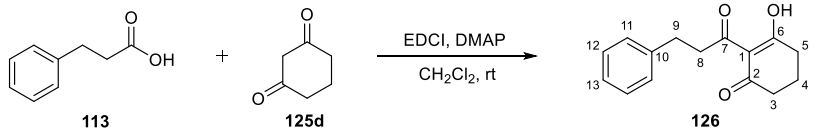
column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford the desired product as a beige gum (187.3 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (t, *J* = 5.9 Hz, 2H, H_4), 3.56 (s, 2H, H_1), 2.73 (t, *J* = 5.9 Hz, 2H, H_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_5H_6O_3Na$) requires *m/z* 137.0209, found *m/z* 137.0207.

The spectral data were consistent with those previously reported in the literature.[80]

Compound 126.



A mixture of EDCI (97.7 mg, 0.50 mmol, 1.5 eq), compound **125d** (56.0 mg, 0.50 mmol, 1.5 eq), DMAP (124.5 mg, 1.00 mmol, 3.0 eq), and compound **113** (50.0 mg, 0.33 mmol, 1.0 eq) was dissolved in anhydrous CH_2Cl_2 (1.66 mL, 0.20 M). The resulting mixture was stirred at rt for 48 h. The mixture was diluted with H_2O, acidified with 2 M aqueous HCl (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a colourless oil (47 mg, 58%).

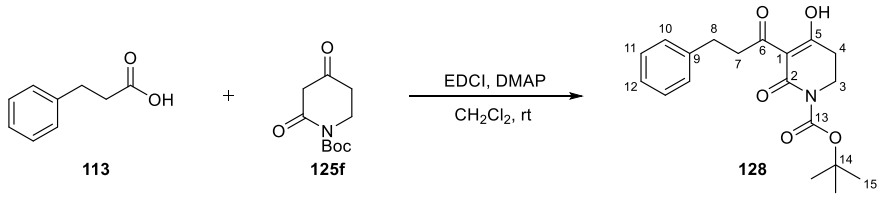
υ_{max} (film): 2927, 2360, 1663, 1562, 1411, 1190, 1008, 700.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 4H, $H_{11,12}$), 7.23 – 7.16 (m, 1H, H_{13}), 3.40 – 3.32 (m, 2H, H_8), 2.99 – 2.90 (m, 2H, H_9), 2.67 (t, *J* = 6.4 Hz, 2H, H_3), 2.51 – 2.45 (m, 2H, H_5), 1.97 (p, *J* = 6.6 Hz, 2H, H_4).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}O_3$) requires *m/z* 245.1172, found *m/z* 245.1172.

The spectral data were consistent with those previously reported in the literature.[81]

Compound 128.



A mixture of EDCI (156 mg, 0.80 mmol, 1.2 eq), compound **125f** (170 mg, 0.80 mmol, 1.2 eq), DMAP (99.6 mg, 0.80 mmol, 1.2 eq), and compound **113** (100 mg, 0.67 mmol, 1.0 eq) was dissolved in anhydrous CH_2Cl_2 (3.35 mL, 0.20 M). The resulting mixture was stirred at rt for 18 h. The mixture was diluted with H_2O, acidified with 2 M aqueous HCl (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a white solid (202 mg, 88%).

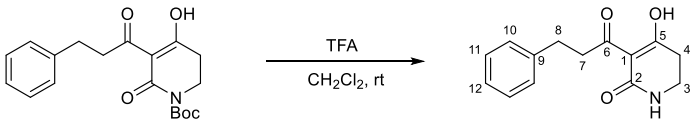
υ_{max} (film): 2980, 1710, 1552, 1454, 1307, 1249, 700.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 4H, $H_{10,11}$), 7.23 – 7.16 (m, 1H, H_{12}), 3.84 (m, 2H, H_3), 3.43 – 3.30 (m, 2H, H_7), 3.01 – 2.92 (m, 2H, H_8), 2.71 – 2.59 (m, 2H, H_4), 1.55 (s, 9H, H_{15}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.8 (C_6), 195.1 (C_5), 163.4 (C_2), 152.4 (C_{13}), 140.9 (C_9), 128.7 (C_{10}), 128.5 (C_{11}), 126.2 (C_{12}), 107.4 (C_1), 83.4 (C_{14}), 41.2 (C_7), 40.6 (C_3), 33.0 (C_4), 30.8 (C_8), 28.2 (C_{15}).

HRMS (ESI): exact mass calculated for $[M–H]^-$ ($C_{19}H_{22}O_5N$) requires *m/z* 344.1493, found *m/z* 344.1503.

Compound 129.



128 129

To a solution of compound **128** (21.0 mg, 0.06 mmol, 1.0 eq) in CH_2Cl_2 (2.0 mL, 0.03 M), trifluoroacetic acid (24 µL, 0.30 mmol, 5.0 eq) was added dropwise. The resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated and the crude residue purified by column chromatography (silica gel, 0–80% EtOAc in cyclohexane) to afford the desired product as a white solid (13 mg, 87%).

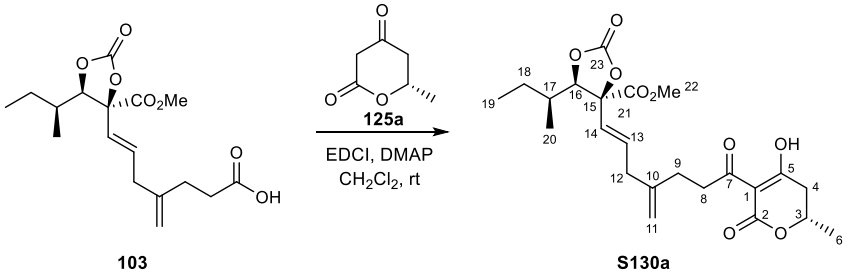
υ_{max} (film): 3271, 1603, 1528, 1444, 1349, 1229, 1036, 700.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 4H, $H_{10,11}$), 7.16 (m, 1H, H_{12}), 6.10 (s, 1H, N*H*), 3.44 (td, *J* = 6.8, 2.7 Hz, 2H, H_3), 3.28 – 3.21 (m, 2H, H_7), 2.93 – 2.87 (m, 2H, H_8), 2.57 (t, *J* = 6.8 Hz, 2H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.4 (C_6), 191.2 (C_5), 174.8 (C_2), 141.1 (C_9), 128.7 (C_{10}), 128.5 (C_{11}), 126.2 (C_{12}), 101.9 (C_1), 39.0 (C_7), 37.8 (C_4), 37.3 (C_3), 31.9 (C_8).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}O_3N$) requires *m/z* 246.1125, found *m/z* 246.1126.

Compound S130a.



103 **S130a**

Prepared according to general procedure B1 using EDCI (20.3 mg, 0.11 mmol, 1.2 eq), compound **125a** (13.6 mg, 0.11 mmol, 1.2 eq), compound **103** (30.0 mg, 0.088 mmol, 1.0 eq), DMAP (12.9 mg, 0.11 mmol, 1.2 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.09 M) for 48 h. The crude residue was purified by column chromatography (silica gel, 10% EtOAc in CH_2Cl_2) to afford the desired product as a yellow oil (29.8 mg, 75%).

$[\alpha]_D^{20}$ = +85.7 (c 7.7, $CHCl_3$).

υ_{max} **(film)**: 2963, 2349, 1812, 1713, 1562, 1265, 1186, 1047, 770.

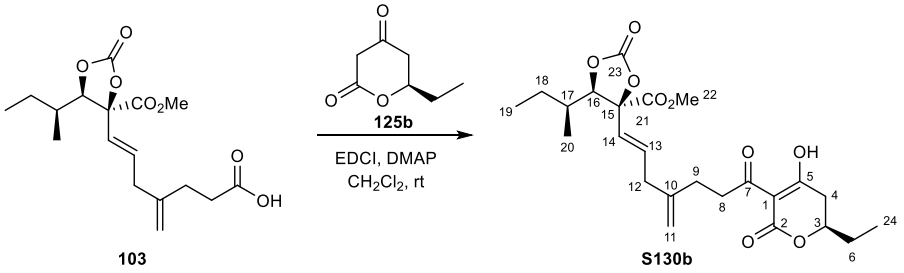
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (dt, *J* = 15.6, 6.9 Hz, 1H, H_{13}), 5.70 (dt, *J* = 15.6, 1.5 Hz, 1H, H_{14}), 4.90 (s, 1H, H_{11}), 4.74 (s, 1H, H_{11}), 4.67 (d, *J* = 4.7 Hz, 1H, H_{16}), 4.57 – 4.49 (m, 1H, H_3), 3.84 (s, 3H, H_{22}), 3.30 – 3.09 (m, 2H, H_8),

2.89 (d, *J* = 7.0 Hz, 2H, H_{12}), 2.73 – 2.60 (m, 2H, H_4), 2.43 – 2.28 (m, 2H, H_9), 1.77 – 1.71 (m, 1H, H_{17}), 1.52 – 1.45 (m, 4H, $H_{6,18}$) 1.34 – 1.27 (m, 1H, H_{18}), 0.96 – 0.91 (m, 6H, $H_{19,20}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7 (C_7), 194.5 (C_5), 169.8 (C_{21}), 164.4 (C_2), 153.1 (C_{23}), 145.0 (C_{10}), 133.4 (C_{13}), 121.6 (C_{14}), 112.2 (C_{11}), 103.3 (C_1), 85.8 (C_{16}), 85.4 (C_{15}), 70.5 (C_3), 53.8 (C_{22}), 39.2 (C_4), 39.1 (C_{12}), 37.1 (C_8), 35.6 (C_{17}), 30.7 (C_9), 26.4 (C_{18}), 20.7 (C_6), 13.0 (C_{20}), 11.2 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{23}H_{30}O_9Na$) requires *m/z* 473.1782, found *m/z* 473.1772.

Compound S130b.



Prepared according to general procedure B1 using EDCI (33.7 mg, 0.18 mmol, 1.2 eq), compound **125b** (25.0 mg, 0.18 mmol, 1.2 eq), compound **103** (50.0 mg, 0.15 mmol, 1.0 eq), DMAP (21.5 mg, 0.18 mmol, 1.2 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.15 M) for 48 h. The crude residue was purified by column chromatography (silica gel, 10–20% EtOAc in CH_2Cl_2) to afford the desired product as a yellow oil (37.8 mg, 55%).

$[\alpha]_D^{20}$ = +45.5 (*c* 2.2, $CHCl_3$).

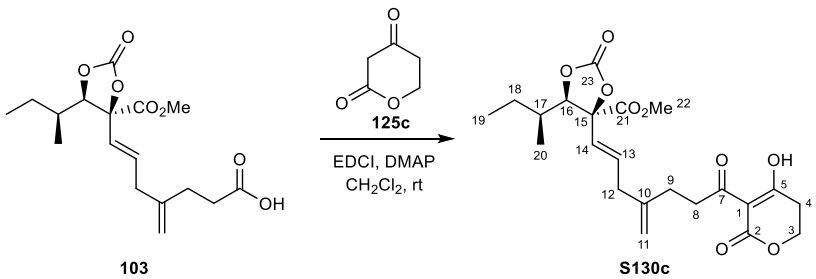
υ_{max} (film): 2968, 2926, 2344, 1813, 1744, 1713, 1566, 1460, 1252, 1186, 1063, 912.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.07 (dt, *J* = 15.7, 6.9 Hz, 1H, H_{13}), 5.70 (dt, *J* = 15.6, 1.6 Hz, 1H, H_{14}), 4.85 (s, 1H, H_{11}), 4.77 (s, 1H, H_{11}), 4.66 (d, *J* = 4.6 Hz, 1H, H_{16}), 4.40 – 4.22 (m, 1H, H_3), 3.84 (s, 3H, H_{22}), 3.28 – 3.21 (m, 1H, H_8), 3.14 – 3.08 (m, 1H, H_8), 2.88 (d, *J* = 7.0 Hz, 2H, H_{12}), 2.71 – 2.58 (m, 2H, H_4), 2.40 – 2.29 (m, 2H, H_9), 1.85 – 1.76 (m, 1H, H_6), 1.77 – 1.69 (m, 2H, $H_{6,17}$), 1.51 – 1.45 (m, 1H, H_{18}), 1.32 – 1.25 (m, 1H, H_{18}), 1.04 (t, *J* = 7.5 Hz, 3H, H_{24}), 0.96 – 0.89 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.6 (C_7), 194.8 (C_5), 169.8 (C_{21}), 164.5 (C_2), 153.1 (C_{23}), 145.0 (C_{10}), 133.4 (C_{13}), 121.6 (C_{14}), 112.3 (C_{11}), 103.4 (C_1), 85.8 (C_{16}), 85.4 (C_{15}), 75.2 (C_3), 53.8 (C_{22}), 39.1 (C_{12}), 37.2 (C_4), 37.0 (C_8), 35.6 (C_{17}), 30.7 (C_9), 27.8 (C_6), 26.4 (C_{18}), 13.0 (C_{20}), 11.2 (C_{19}), 9.2 (C_{24}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{24}H_{31}O_9$) requires *m/z* 463.1974, found *m/z* 463.1967.

Compound S130c.



103 **S130c**

Prepared according to general procedure B1 using EDCI (33.7 mg, 0.18 mmol, 1.2 eq), compound **125c** (20.1 mg, 0.18 mmol, 1.2 eq), compound **103** (50.0 mg, 0.15 mmol, 1.0 eq), DMAP (21.5 mg, 0.18 mmol, 1.2 eq), and anhydrous CH_2Cl_2

(1.0 mL, 0.15 M) for 48 h. The crude residue was purified by column chromatography (silica gel, 10–20% EtOAc in CH_2Cl_2) to afford the desired product as a colourless oil (25.1 mg, 39%).

$[\alpha]_D^{20}$ = +82.5 (c 4.0, $CHCl_3$).

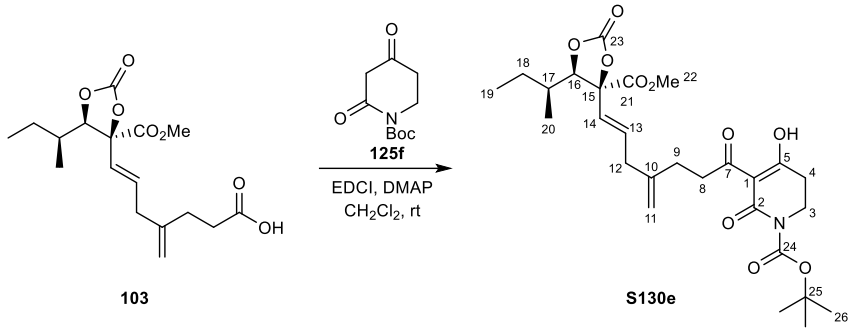
υ_{max} **(film)**: 2963, 2926, 2361, 1811, 1742, 1715, 1558, 1456, 1396, 1263, 1188, 1043.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 6.08 (dt, *J* = 15.6, 7.0 Hz, 1H, H_{13}), 5.70 (dt, *J* = 15.6, 1.5 Hz, 1H, H_{14}), 4.86 (d, *J* = 1.3 Hz, 1H, H_{11}), 4.79 (d, *J* = 1.3 Hz, 1H, H_{11}) 4.67 (d, *J* = 4.7 Hz, 1H, H_{16}), 4.37 (dd, *J* = 6.5, 6.0 Hz, 2H, H_3), 3.84 (s, 3H, H_{22}), 3.27 – 3.09 (m, 2H, H_8), 2.89 (d, *J* = 7.1 Hz, 2H, H_{12}), 2.79 (dd, *J* = 6.5, 5.9 Hz, 2H, H_4), 2.36 (t, *J* = 7.6 Hz, 2H, H_9), 1.78 – 1.70 (m, 1H, H_{17}), 1.53 – 1.45 (m, 1H, H_{18}), 1.34 – 1.27 (m, 1H, H_{18}), 0.96 – 0.90 (m, 6H, $H_{19,20}$).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 203.9 (C_7), 194.8 (C_5), 169.8 (C_{21}), 164.1 (C_2), 153.1 (C_{23}), 145.0 (C_{10}), 133.4 (C_{13}), 121.6 (C_{14}), 112.3 (C_{11}), 103.8 (C_1), 85.8 (C_{16}), 85.4 (C_{15}), 62.7 (C_3), 53.8 (C_{22}), 39.1 (C_{12}), 37.2 (C_8), 35.6 (C_{17}), 32.4 (C_4), 30.7 (C_9), 26.5 (C_{18}), 13.0 (C_{20}), 11.3 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{28}O_9Na$) requires *m/z* 459.1626, found *m/z* 459.1614.

Compound S130e.



103 **S130e**

Prepared according to general procedure B1 using EDCI (48.3 mg, 0.25 mmol, 1.2 eq), compound **125f** (52.6 mg, 0.25 mmol, 1.2 eq), compound **103** (70.0 mg, 0.21 mmol, 1.0 eq), DMAP (30.8 mg, 0.25 mmol, 1.2 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.21 M). The crude residue was purified by column chromatography (silica gel, 0–80% EtOAc in cyclohexane) to afford the desired product as a colourless oil (65.0 mg, 59%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +19.7 (c 6.1, $CHCl_3$).

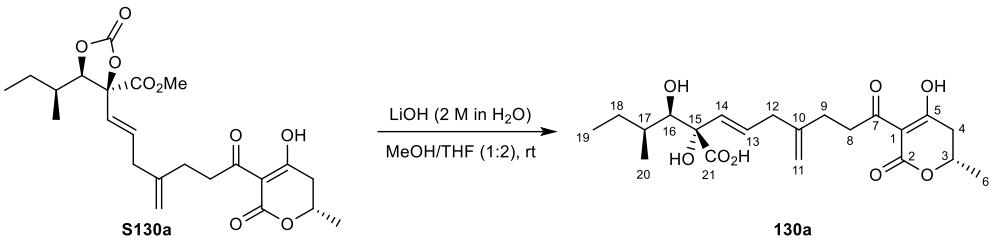
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2976, 1812, 1756, 1712, 1553, 1437, 1306, 1145, 1042, 912.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 6.08 (dt, *J* = 15.7, 7.0 Hz, 1H, H_{13}), 5.75 – 5.62 (m, 1H, H_{14}), 4.87 – 4.85 (m, 1H, H_{11}), 4.78 – 4.76 (m, 1H, H_{11}), 4.67 (d, *J* = 4.7 Hz, 1H, H_{16}), 3.94 – 3.76 (m, 5H, $H_{3,22}$), 3.28 – 3.08 (m, 2H, H_8), 2.91 – 2.87 (m, 2H, H_{12}), 2.69 – 2.60 (m, 2H, H_4), 2.37 – 2.32 (m, 2H, H_9), 1.78 – 1.70 (m, 1H, H_{17}), 1.55 (s, 9H, H_{26}), 1.52 – 1.45 (m, 1H, H_{18}), 1.33 – 1.24 (m, 1H, H_{18}), 1.01 – 0.85 (m, 6H, $H_{19,20}$).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 204.1 (C_7), 195.0 (C_5), 169.8 (C_{21}), 163.5 (C_2), 153.1 (C_{23}), 152.2 (C_{24}), 145.3 (C_{10}), 133.5 (C_{13}), 121.5 (C_{14}), 112.0 (C_{11}), 107.3 (C_1), 85.8 (C_{16}), 85.4 (C_{15}) 83.5 (C_{25}), 53.8 (C_{22}), 40.7 (C_3), 39.2 (C_{12}), 37.8 (C_8), 35.6 (C_{17}), 32.9 (C_4), 30.6 (C_9), 28.2 (C_{26}), 26.5 (C_{18}), 13.0 (C_{20}), 11.3 (C_{19}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{27}H_{36}O_{10}N$) requires *m/z* 534.2345, found *m/z* 534.2338.

Compound 130a.



Prepared according to general procedure C using compound **S130a** (36 mg, 0.08 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.0 mL) for 15 min. The desired product was obtained without further purification as a white solid (30.2 mg, 92%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +46.5 (c 6.6, $CHCl_3$).

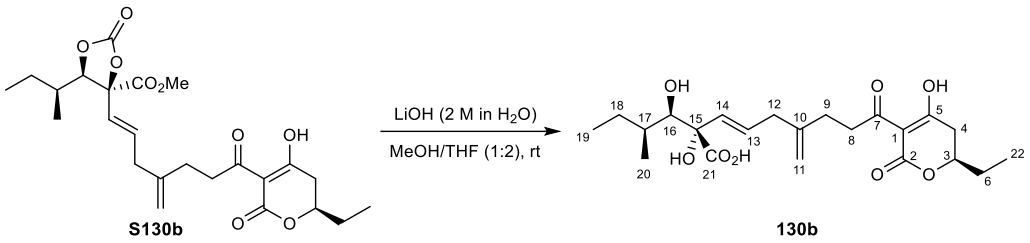
$\boldsymbol{\upsilon}_{max}$ **(film)**: 3470, 2961, 2359, 1707, 1558, 1456, 1263, 1144, 1053, 980, 905.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 5.98 (dt, *J* = 15.4, 6.8 Hz, 1H, H_{13}), 5.74 – 5.69 (m, 1H, H_{14}), 4.83 – 4.80 (m, 2H, H_{11}), 4.57 – 4.49 (m, 1H, H_3), 3.97 (d, *J* = 2.3 Hz, 1H, H_{16}), 3.21 (ddd, *J* = 14.9, 8.7, 7.1 Hz, 1H, H_8), 3.07 (ddd, *J* = 15.1, 9.0, 6.9 Hz, 1H, H_8), 2.89 – 2.75 (m, 2H, H_{12}), 2.68 – 2.65 (m, 2H, H_4), 2.37 – 2.29 (m, 2H, H_9), 1.82 – 1.74 (m, 1H, H_{17}), 1.49 – 1.40 (m, 4H, $H_{6,18}$), 1.34 – 1.27 (m, 1H, H_{18}), 0.91 – 0.87 (m, 6H, $H_{19,20}$).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.1 (C_7), 195.2 (C_5), 176.9 (C_{21}), 165.2 (C_2), 145.7 (C_{10}), 129.9 (C_{14}), 129.8 (C_{13}), 112.2 (C_{11}), 102.9 (C_1), 79.5 (C_{15}), 76.8 (C_{16}), 70.8 (C_3), 39.3 (C_4), 39.1 (C_{12}), 37.4 (C_8), 35.2 (C_{17}), 31.1 (C_9), 28.1 (C_{18}), 20.7 (C_6), 12.7 (C_{20}), 11.9 (C_{19}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{21}H_{29}O_8$) requires *m/z* 409.1868, found *m/z* 409.1868.

Compound 130b.



Prepared according to general procedure C using compound **S130b** (30 mg, 0.06 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.0 mL) for 15 min. The crude residue was purified by column chromatography (silica gel, 5–10% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (21.0 mg, 77%).

$[\alpha]_D^{20}$ = +70 (c 5.0, $CHCl_3$).

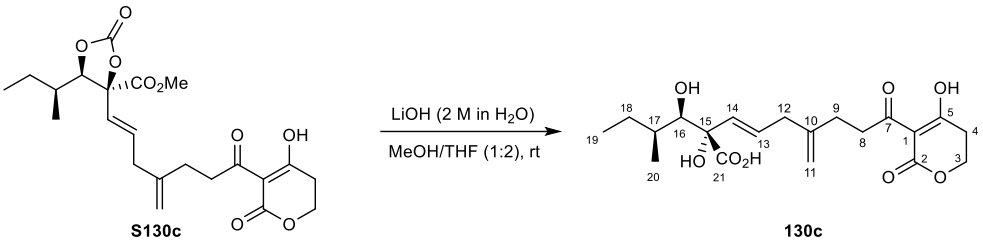
υ_{max} **(film)**: 3468, 2965, 2359, 1705, 1645, 1559, 1458, 1273, 1248, 1067, 980, 907.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 5.98 (dt, *J* = 15.3, 6.9 Hz, 1H, H_{13}), 5.69 (d, *J* = 15.4 Hz, 1H, H_{14}), 4.82 – 4.79 (m, 2H, H_{11}), 4.37 – 4.26 (m, 1H, H_3), 3.98 (d, *J* = 2.3 Hz, 1H, H_{16}), 3.23 (ddd, *J* = 15.2, 10.0, 5.5 Hz, 1H, H_8), 3.01 (ddd, *J* = 15.3, 10.1, 5.8 Hz, 1H, H_8), 2.90 – 2.73 (m, 2H, H_{12}), 2.71 – 2.59 (m, 2H, H_4), 2.40 (ddd, *J* = 15.4, 10.0, 5.5 Hz, 1H, H_9), 2.28 (ddd, *J* = 15.3, 10.0, 5.8 Hz, 1H, H_9), 1.85 – 1.68 (m, 3H, $H_{6,17}$), 1.47 – 1.38 (m, 1H, H_{18}), 1.34 – 1.26 (m, 1H, H_{18}), 1.04 (t, *J* = 7.4 Hz, 3H, H_{22}), 0.91 – 0.84 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.9 (C_7), 195.4 (C_5), 177.0 (C_{21}), 165.2(C_2), 145.8 (C_{10}), 129.8 (C_{14}), 129.7 (C_{13}), 112.0 (C_{11}), 103.2 (C_1), 79.7 (C_{15}), 76.8 (C_{16}), 75.4 (C_3), 39.0 (C_{12}), 37.4 (C_4), 37.3 (C_8), 35.2 (C_{17}), 31.0 (C_9), 28.1 (C_{18}), 27.8 (C_6), 12.8 (C_{20}), 11.9 (C_{19}), 9.2 (C_{22}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{22}H_{31}O_8$) requires *m/z* 423.2024, found *m/z* 423.2027.

Compound 130c.



Prepared according to general procedure C using compound **S130c** (22 mg, 0.05 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.0 mL) for 15 min. The desired product was obtained without further purification as a colourless oil (14.6 mg, 74%).

$[\alpha]_D^{20}$ = +36 (c 3.0, $CHCl_3$).

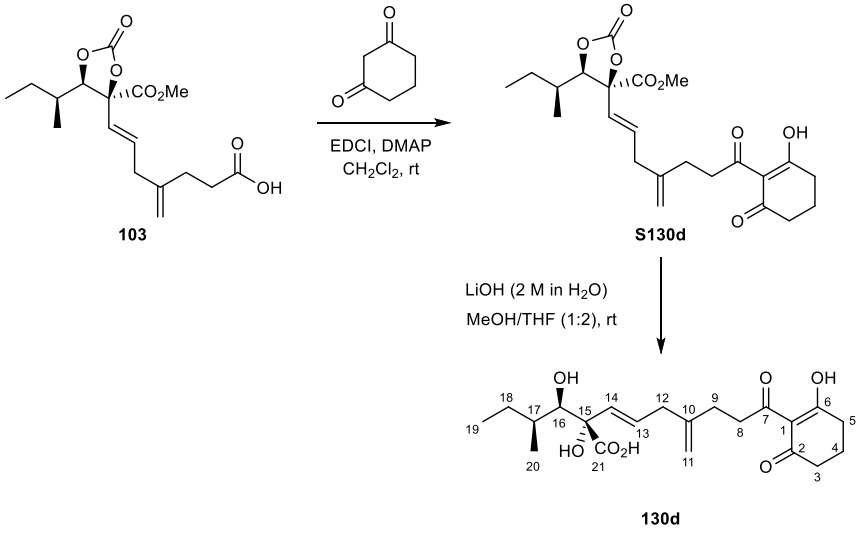
υ_{max} (film): 3474, 2926, 2361, 1717, 1695, 1560, 1398, 1265, 1146, 1094, 909.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (dt, *J* = 15.4, 6.9 Hz, 1H, H_{13}), 5.74 – 5.64 (m, 1H, H_{14}), 4.83 – 4.80 (m, 2H, H_{11}), 4.37 (t, *J* = 6.2 Hz, 2H, H_3), 3.98 (d, *J* = 2.3 Hz, 1H, H_{16}), 3.20 (ddd, *J* = 15.4, 9.7, 5.9 Hz, 1H, H_8), 3.05 (ddd, *J* = 15.3, 9.7, 6.0 Hz, 1H, H_8), 2.89 – 2.70 (m, 4H, $H_{4,12}$), 2.40 – 2.29 (m, 2H, H_9), 1.82 – 1.72 (m, 1H, H_{17}), 1.47 – 1.39 (m, 1H, H_{18}), 1.34 – 1.25 (m, 1H, H_{18}), 0.90 – 0.87 (m, 6H, $H_{19,20}$).

^{13}C NMR (176 MHz, $CDCl_3$): δ 204.2 (C_7), 195.4 (C_5), 176.9 (C_{21}), 165.0 (C_2), 145.7 (C_{10}), 129.9 (C_{14}), 129.7 (C_{13}), 112.1 (C_{11}), 103.5 (C_1), 79.7 (C_{15}), 76.8 (C_{16}), 62.8 (C_3), 39.1 (C_{12}), 37.4 (C_8), 35.2 (C_{17}), 32.6 (C_4), 31.1 (C_9), 28.1 (C_{18}), 12.8 (C_{20}), 11.9 (C_{19}).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{20}H_{28}O_8Na$) requires *m/z* 419.1676, found *m/z* 419.1667.

Compound 130d.



A mixture of EDCI (42.1 mg, 0.215 mmol, 1.5 eq), cyclohexane-1,3-dione (1.1 eq), DMAP (53.6 mg, 0.43 mmol, 3.0 eq), and compound **103** (48.8 mg, 0.14 mmol, 1.0 eq) was dissolved in anhydrous CH_2Cl_2 (1.0 mL, 0.14 M), and the resulting mixture was stirred at rt for 24 h. The reaction mixture was diluted with H_2O (3 mL), acidified with 2 M aqueous HCl (2 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford intermediate **S130d** which was directly used into the next step without further purification. Intermediate **S130d** was dissolved in (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.0 mL), and the mixture stirred at rt for 15 min. The mixture was neutralized with 1 M

aqueous HCl (2 mL) and the organic solvents were removed under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–10% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (57.9 mg, 69%).

$[\alpha]_D^{20}$ = +31.9 (c 4.7, $CHCl_3$).

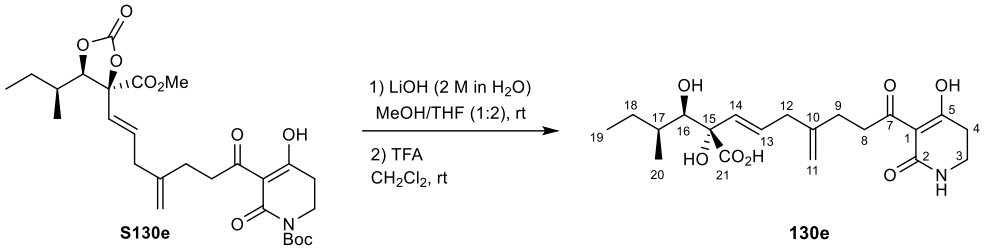
υ_{max} (film): 3443, 2961, 2932, 2361, 1717, 1645, 1558, 1190, 1140, 980.

^{1}H NMR (500 MHz, MeOD): δ 5.99 – 5.90 (m, 1H, H_{13}), 5.67 (dt, *J* = 15.4, 1.4 Hz, 1H, H_{14}), 4.78 (br s, 2H, H_{11}), 3.92 – 3.91 (m, 1H, H_{16}), 3.24 – 3.03 (m, 2H, H_8), 2.85 – 2.81 (m, 2H, H_{12}), 2.60 (br s, 3H, $H_{3,5}$), 2.44 – 2.42 (m, 1H, H_5), 2.34 – 2.29 (m, 2H, H_9), 2.05 – 1.89 (m, 2H, H_4), 1.72 – 1.65 (m, 1H, H_{17}), 1.45 – 1.38 (m, 1H, H_{18}), 1.28 – 1.21 (m, 1H, H_{18}), 0.93 – 0.85 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, MeOD): δ 206.6 (C_7), 199.0 (C_2), 198.7 (C_6), 177.6 (C_{21}), 148.5 (C_{10}), 132.0 (C_{14}), 129.7 (C_{13}), 114.0 (C_1), 111.2 (C_{11}), 82.4 (C_{15}), 77.3 (C_{16}), 40.4 (C_8), 40.2 (C_{12}), 36.8 (C_{17}), 33.4 (C_5), 31.9 (C_3), 31.4 (C_9), 29.6 (C_{18}), 20.1 (C_4), 14.0 (C_{20}), 12.2 (C_{19}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{21}H_{29}O_7$) requires *m/z* 393.1919, found *m/z* 393.1920.

Compound 130e.



Compound **S130e** (55.0 mg, 0.10 mmol, 1.0 eq) was dissolved in 2 M solution LiOH/MeOH/THF (1:1:2, 2.0 mL) and the mixture stirred at rt for 30 min. The mixture was neutralised with 1 M aqueous HCl (5 mL) and the organic solvents were removed under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was then dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.05 M), and trifluoroacetic acid (39 µL, 0.51 mmol, 5.0 eq) was added dropwise. The resulting mixture was stirred at rt for 1 h then concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (5 mL), acidified with 1 M aqueous HCl (5 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–20% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (17.0 mg, 42%).

$[\alpha]_D^{20}$ = +45.0 (c 2.2, $CHCl_3$).

υ_{max} **(film)**: 3319, 2961, 2930, 2342, 1717, 1558, 1236, 1036, 982.

^{1}**H NMR** (500 MHz, MeOD): δ 5.95 (dt, *J* = 15.4, 7.1 Hz, 1H, H_{13}), 5.67 (dt, *J* = 15.4, 1.4 Hz, 1H, H_{14}), 4.81 – 4.78 (m, 2H, H_{11}), 3.92 – 3.91 (m, 1H, H_{16}), 3.43 (t, *J* = 6.9 Hz, 2H, H_3), 3.08 (t, *J* = 7.9 Hz, 2H, H_8), 2.86 (d, *J* = 7.1 Hz, 2H, H_{12}),

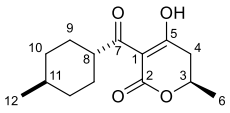
2.64 – 2.47 (m, 2H, H_4), 2.31 (t, J = 7.9 Hz, 2H, H_9), 1.73 – 1.65 (m, 1H, H_{17}), 1.46 – 1.37 (m, 1H, H_{18}), 1.28 – 1.20 (m, 1H, H_{18}), 0.93 – 0.85 (m, 6H, $H_{19,20}$).

^{13}C NMR (126 MHz, MeOD): δ 198.2 (C_7), 193.9 (C_5), 177.6 (C_{21}), 175.7 (C_2), 148.6 (C_{10}), 131.9 (C_{14}), 129.8 (C_{13}), 111.3 (C_{11}), 101.7 (C_1), 82.5(C_{15}), 77.3 (C_{16}), 40.0 (C_{12}), 38.2 (C_4), 37.7 (C_3), 37.4 (C_8), 36.7 (C_{17}), 32.7 (C_9), 29.6 (C_{18}), 14.0 (C_{20}), 12.2 (C_{19}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{20}H_{28}O_7$) requires *m/z* 394.1871, found *m/z* 394.1865.

Synthesis of tail analogues

Compound 131.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), *trans*-4-methylcyclohexanecarboxylic acid (56.9 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–50% EtOAc in cyclohexane) to afford the desired product as a white solid (29 mg, 29%).

$[\alpha]_D^{20}$ = −66.4 (c 3.6, $CHCl_3$).

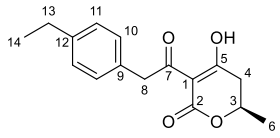
υ_{max} (film): 2916, 2361, 1707, 1545, 1065, 943, 908.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51 (br s, 1H, H_3), 3.60 (t, *J* = 11.9 Hz, 1H, H_8), 2.69 – 2.56 (m, 2H, H_4), 1.99 – 1.89 (m, 1H, H_9), 1.80 – 1.73 (m, 3H, $H_{9,10}$), 1.55 – 1.32 (m, 6H, $H_{6,9,11}$), 1.13 – 1.02 (m, 2H, H_{10}), 0.90 (d, *J* = 6.5 Hz, 3H, H_{12}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8 (C_7), 195.8 (C_5), 164.3 (C_2), 102.4 (C_1), 70.3 (C_3), 44.6 (C_8), 39.9 (C_4), 34.4 (C_{10}), 34.3 (C_{10}), 32.2 (C_{11}), 29.0 (C_9), 22.6 (C_{12}), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}O_4$) requires *m/z* 253.1434, found *m/z* 253.1434.

Compound 132.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 2-(4-ethylphenyl)acetic acid (65.7 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a white solid (78 mg, 71%).

$[\alpha]_D^{20}$ = −40.0 (c 5.6, $CHCl_3$).

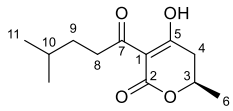
υ_{max} (film): 2965, 1709, 1557, 1456, 1067.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.19 (m, 2H, H_{10}), 7.19 – 7.13 (m, 2H, H_{11}), 4.60 – 4.46 (m, 1H, H_3), 4.44 – 4.27 (m, 2H, H_8), 2.73 – 2.55 (m, 4H, $H_{4,13}$), 1.46 (d, *J* = 6.3 Hz, 3H, H_6), 1.23 (t, *J* = 7.6 Hz, 3H, H_{14}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.2 (C_7), 194.8 (C_5), 164.4 (C_2), 143.3 (C_{12}), 131.4 (C_9), 130.0 (C_{10}), 128.2 (C_{11}), 103.0 (C_1), 70.5 (C_3), 44.2 (C_8), 39.3 (C_4), 28.6 (C_{13}), 20.8 (C_6), 15.6 (C_{14}).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}O_4$) requires *m/z* 275.1278, found *m/z* 275.1280.

Compound 133.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 4-methylpentanoic acid (46.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–50% EtOAc in cyclohexane) to afford the desired product as a white solid (59 mg, 62%).

$[\alpha]_D^{20}$ = −73.8 (c 2.6, $CHCl_3$).

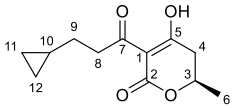
υ_{max} (film): 3671, 2959, 2359, 1713, 1456, 1065, 905.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 – 4.47 (m, 1H, H_3), 3.08 – 2.94 (m, 2H, H_8), 2.72 – 2.53 (m, 2H, H_4), 1.67 – 1.42 (m, 6H, $H_{6,9,10}$), 0.91 (d, *J* = 6.4 Hz, 6H, H_{11}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.1 (C_7), 195.1 (C_5), 164.4 (C_2), 103.0 (C_1), 70.4 (C_3), 39.6 (C_4), 36.8 (C_8), 34.0 (C_9), 28.0 (C_{10}), 22.4 (C_{11}), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{18}O_4Na$) requires *m/z* 249.1097, found *m/z* 249.1089.

Compound 134.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 3-cyclopropylpropanoic acid (45.7 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a colourless oil (63 mg, 70%).

$[\alpha]_D^{20}$ = −66.6 (c 4.1, $CHCl_3$).

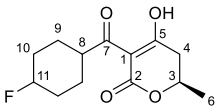
υ_{max} (film): 3078, 2999, 2934, 1554, 1447, 1407, 1291, 1062, 905.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67 – 4.40 (m, 1H, H_3), 3.26 – 3.04 (m, 2H, H_8), 2.74 – 2.54 (m, 2H, H_4), 1.59 – 1.52 (m, 2H, H_9), 1.47 (d, *J* = 6.3 Hz, 3H, H_6), 0.77 (m, 1H, H_{10}), 0.47 – 0.41 (m, 2H, $H_{11\text{ or }12}$), 0.09 – 0.05 (m, 2H, $H_{11\text{ or }12}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.6 (C_7), 195.1 (C_5), 164.4 (C_2), 103.2 (C_1), 70.4 (C_3), 39.5 (C_4), 38.9 (C_8), 30.3 (C_9), 20.7 (C_6), 10.8 (C_{10}), 4.8 ($C_{11\text{ or }12}$), 4.8 ($C_{11\text{ or }12}$).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_4$) requires *m/z* 225.1121, found *m/z* 225.1122.

Compound 135.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 4-fluorocyclohexanecarboxylic acid (58.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a white solid (mixture of diastereoisomers, 61:39 *dr*) (28 mg, 27%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −57.8 (c 9.0, $CHCl_3$).

$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2939, 1708, 1552, 443, 1288, 1065, 1032, 930, 905.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86 (d, J_{H-F} = 47.8 Hz, 0.7H, H_{11}, *trans*), 4.64 – 4.43 (m, 1.3H, H_3 and H_{11}, *cis*), 3.81 – 3.57 (m, 1H, H_8), 2.73 – 2.57 (m, 2H, H_4), 2.22 – 2.05 (m, 2H, H_{10}), 1.94 – 1.78 (m, 2H, H_9), 1.76 – 1.50 (m, 4H, $H_{9,10}$), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

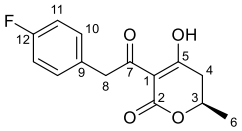
^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8 (C_7), 195.7 (C_5, *trans*), 195.4 (C_5, *cis*), 164.3 (C_2, *trans*), 164.2 (C_2, *cis*), 102.6 (C_1, *cis*), 102.3 (C_1, *trans*), 91.5 (d, $^1J_{C-F}$ = 172.6 Hz, C_{11}, *trans*), 88.02 (d, $^1J_{C-F}$ = 167.9 Hz, C_{11}, *cis*), 70.4 (C_3), 43.8 (C_8, *trans*), 43.5 (C_8, *cis*), 39.6 (C_4, *trans*), 39.5 (C_4, *cis*), 31.9 (m, C_{10}, *cis* or *trans*), 31.7 (m, C_{10}, *cis* or *tans*), 30.2 (d, $^2J_{C-F}$ = 21.3 Hz, C_{10}, *trans*), 30.1 (d, $^2J_{C-F}$ = 21.2 Hz, C_{10}, *trans*),

26.7 (d, $^{3}J_{C–F}$ = 11.7 Hz, C_9, *cis*), 26.6 (d, $^{3}J_{C–F}$ = 11.7 Hz, C_9, *cis*), 23.3 (d, $^{3}J_{C–F}$ = 1.2 Hz, C_9, *trans*), 22.9 (d, $^{3}J_{C–F}$ = 1.2 Hz, C_9, *trans*), 20.7 (C_6).

^{19}F NMR (376 MHz, $CDCl_3$): δ −185.06 (*trans*), −170.43 (*cis*).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}FO_4$) requires *m/z* 257.1184, found *m/z* 257.1185.

Compound 136.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 2-(4-fluorophenyl)acetic acid (61.7 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–60% EtOAc in cyclohexane) to afford the desired product as a white solid (59 mg, 56%).

$[\alpha]_D^{20}$ = −43.7 (c 4.5, $CHCl_3$).

υ_{max} (film): 2986, 1707, 1512, 1217, 1062, 795.

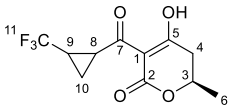
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.4, 5.4 Hz, 2H, H_{10}), 7.03 – 6.98 (m, 2H, H_{11}), 4.59 – 4.47 (m, 1H, H_3), 4.35 (s, 2H, H_8), 2.72 – 2.60 (m, 2H, H_4), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.8 (C_7), 194.6 (C_5), 164.4 (C_2), 162.1 (d, $^1J_{C-F}$ = 245.7 Hz, C_{12}), 131.5 (d, $^3J_{C-F}$ = 8.0 Hz, C_{10}), 129.7 (d, $^4J_{C-F}$ = 3.2 Hz, C_9) 115.4 (d, $^2J_{C-F}$ = 21.3 Hz, C_{11}), 103.0 (C_1), 70.5 (C_3), 43.9 (C_8), 39.1 (C_4), 20.7 (C_6).

^{19}F NMR (376 MHz, $CDCl_3$): δ −115.51.

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{12}FO_4$) requires *m/z* 263.0725, found *m/z* 263.0728.

Compound 137.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 2-(trifluoromethyl)cyclopropanecarboxylic acid (61.6 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–70% EtOAc in cyclohexane) to afford the desired product as a white solid (mixture of diastereoisomers, 55:45 *dr*) (46 mg, 44%).

υ_{max} (film): 2986, 2359, 1709, 1449, 1261, 1138, 1065, 935.

Data for major diasteroisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 – 4.44 (m, 1H, H_3), 3.74 (dt, *J* = 9.5, 4.9 Hz, 1H, H_8), 2.75 – 2.60 (m, 2H, H_4), 2.45 – 2.38 (m, 1H, H_9), 1.61 – 1.41 (m, 5H, $H_{6, 10}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2 (C_7), 193.2 (C_5), 164.5 (C_2), 124.9 (q, $^1J_{C-F}$ = 271.3 Hz, C_{11}), 104.0 (C_1), 70.8 (C_3), 38.6 (C_4), 25.0 (q, $^2J_{C-F}$ = 38.1 Hz, C_9), 20.7 (C_6), 20.2 (m, C_8), 14.4 (m, C_{10}).

^{19}F NMR (470 MHz, $CDCl_3$): δ −66.87.

Data for minor diastereoisomer:

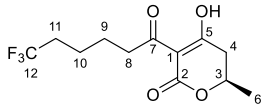
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 – 4.44 (m, 1H, H_3), 3.88 (dt, *J* = 9.5, 5.0 Hz, 1H, H_8), 2.75 – 2.60 (m, 2H, H_4), 2.45 – 2.38 (m, 1H, H_9), 1.61 – 1.41 (m, 5H, $H_{6,10}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2 (C_7), 193.3 (C_5), 164.3 (C_2), 124.9 (q, $^1J_{C-F}$ = 271.3 Hz, C_{11}), 103.9 (C_1), 70.6 (C_3), 38.5 (C_4), 25.0 (q, $^2J_{C-F}$ = 38.3 Hz, C_9), 20.7 (C_6), 20.2 (m, C_8), 14.4 (m, C_{10}).

^{19}F NMR (470 MHz, $CDCl_3$): δ −66.96.

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{11}H_{10}F_3O_4$) requires *m/z* 263.0537, found *m/z* 263.0534.

Compound 138.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 6,6,6-trifluorohexanoic acid (68.1 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column

chromatography (silica gel, 0–50% EtOAc in cyclohexane) to afford the desired product as a white solid (40 mg, 36%).

$[\alpha]_D^{20}$ = −62.6 (c 4.2, $CHCl_3$).

υ_{max} (film): 2926, 2363, 1697, 1551, 1271, 1069, 1026, 907.

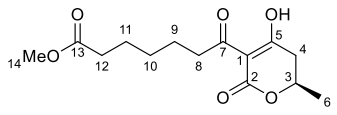
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 – 4.49 (m, 1H, H_3), 3.14 (ddd, *J* = 16.2, 8.2, 6.2 Hz, 1H, H_8), 3.00 (ddd, *J* = 16.2, 8.3, 6.3 Hz, 1H, H_8), 2.73 – 2.59 (m, 2H, H_4), 2.19 – 2.06 (m, 2H, H_{11}), 1.78 – 1.73 (m, 2H, H_9), 1.70 – 1.61 (m, 2H, H_{10}), 1.47 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9 (C_7), 194.7 (C_5), 164.4 (C_2), 127.2 (q, $^1J_{C–F}$ = 276.4 Hz, C_{12}), 103.2 (C_1), 70.5 (C_3), 39.2 (C_4), 38.4 (C_8), 33.6 (q, $^2J_{C–F}$ = 28.5 Hz, C_{11}), 23.9 (C_9), 21.7 (q, $^3J_{C–F}$ = 3.7 Hz, C_{10}), 20.8 (C_6).

^{19}F NMR (376 MHz, $CDCl_3$): δ −66.33.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}F_3O_4$) requires *m/z* 281.0995, found *m/z* 281.0998.

Compound 139.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 7-methoxy-7-oxo-heptanoic acid (69.7 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by

column chromatography (silica gel, 0–60% EtOAc in cyclohexane) to afford the desired product as a colourless oil (72 mg, 63%).

$[\alpha]_D^{20}$ = −53.0 (c 4.4, $CHCl_3$).

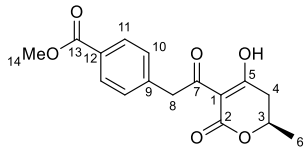
υ_{max} (film): 2938, 2361, 1713, 1558, 1437, 1202, 1065.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 – 4.40 (m, 1H, H_3), 3.64 (s, 3H, H_{14}), 3.12 – 2.90 (m, 2H, H_8), 2.72 – 2.52 (m, 2H, H_4), 2.30 (t, *J* = 7.5 Hz, 2H, H_{12}), 1.72 – 1.58 (m, 4H, $H_{9,11}$), 1.47 – 1.35 (m, 5H, $H_{6,10}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4 (C_7), 194.9 (C_5), 174.1 (C_{13}), 164.3 (C_2), 103.1 (C_1), 70.4 (C_3), 51.6 (C_{14}), 39.4 (C_4), 38.5 (C_8), 33.9 (C_{12}), 28.8 (C_{10}), 24.7 (C_{11}), 24.5 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{19}O_6$) requires *m/z* 283.1187, found *m/z* 283.1187.

Compound 140.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 2-(4-methoxycarbonylphenyl)acetic acid (77.7 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a white solid (35 mg, 29%).

$[\alpha]_D^{20}$ = −55.0 (c 16.0, $CHCl_3$).

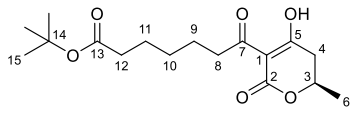
υ_{max} **(film)**: 2980, 2918, 1702, 1561, 1443, 1066, 905.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.04 – 7.92 (m, 2H, H_{11}), 7.38 (d, *J* = 8.3 Hz, 2H, H_{10}), 4.55 – 4.50 (m, 1H, H_3), 4.43 (s, 2H, H_8), 3.90 (s, 3H, H_{14}), 2.75 – 2.57 (m, 2H, H_4), 1.46 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 201.2 (C_7), 194.4 (C_5), 167.0 (C_{13}), 164.3 (C_2), 139.5 (C_9), 130.1 (C_{10}), 129.9 (C_{11}), 129.2 (C_{12}), 103.1 (C_1), 70.5 (C_3), 52.2 (C_{14}), 44.9 (C_8), 39.0 (C_4), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}O_5$) requires *m/z* 305.1020, found *m/z* 305.1020.

Compound 141.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 7-*tert*-butoxy-7-oxo-heptanoic acid (86.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–60% EtOAc in cyclohexane) to afford the desired product as a colourless oil (92 mg, 71%).

$[\alpha]_D^{20}$ = −6.9 (c 5.2, $CHCl_3$).

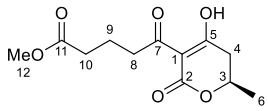
υ_{max} **(film)**: 2978, 2934, 1715, 1558, 1456, 1368, 1155, 1065.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 – 4.36 (m, 1H, H_3), 3.11 – 2.91 (m, 2H, H_8), 2.72 – 2.52 (m, 2H, H_4), 2.20 (t, *J* = 7.5 Hz, 2H, H_{12}), 1.72 – 1.56 (m, 4H, $H_{9,11}$), 1.48 – 1.33 (m, 14H, $H_{6,10,15}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.5 (C_7), 194.9 (C_5), 173.1 (C_{13}), 164.4 (C_2), 103.1 (C_1), 80.1 (C_{14}), 70.4 (C_3), 39.4 (C_4), 38.6 (C_8), 35.4 (C_{12}), 28.8 (C_{10}), 28.2 (C_{15}), 24.9 (C_{11}), 24.6 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{26}O_6Na$) requires *m/z* 349.1622, found *m/z* 349.1614.

Compound 142.



Prepared according to general procedure B2 using EDCI (923 mg, 4.82 mmol, 1.1 eq), compound **15** (617 mg, 4.82 mmol, 1.1 eq), DMAP (589 mg, 4.82 mmol, 1.1 eq), 5-methoxy-5-oxopentanoic acid (640 mg, 4.38 mmol, 1.0 eq), and anhydrous MeCN (21.9 mL, 0.20 M). The desired product was obtained without further purification as a yellow oil (972 mg, 87%).

$[\alpha]_D^{20}$ = –58.0 (c 6.0, $CHCl_3$).

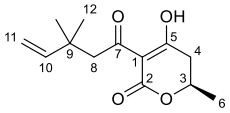
υ_{max} (film): 3397, 2955, 2361, 1711, 1564, 1261, 1065, 907.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 – 4.49 (m, 1H, H_3), 3.67 (s, 3H, H_{12}), 3.17 (ddd, *J* = 16.9, 8.1, 6.4 Hz, 1H, H_8), 3.03 (ddd, *J* = 16.9, 8.2, 6.6 Hz, 1H, H_8), 2.70 – 2.59 (m, 2H, H_4), 2.40 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.04 – 1.96 (m, 2H, H_9), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.9 (C_7), 194.3 (C_5), 173.6 (C_{11}), 164.4 (C_2), 103.3 (C_1), 70.5 (C_3), 51.8 (C_{12}), 39.1 (C_4), 38.2 (C_8), 33.3 (C_{10}), 20.7 (C_6), 19.8 (C_9).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{12}H_{15}O_6$) requires *m/z* 255.0874, found *m/z* 255.0874.

Compound 143.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 3,3-dimethylpent-4-enoic acid (51.3 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–50% EtOAc in cyclohexane) to afford the desired product as a yellow oil (40 mg, 42%).

$[\alpha]_D^{20}$ = −52.7 (c 3.7, $CHCl_3$).

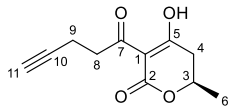
υ_{max} (film): 2965, 2361, 1713, 1557, 1410, 1067, 910.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (dd, *J* = 17.6, 10.5 Hz, 1H, H_{10}), 4.93 – 4.88 (m, 2H, H_{11}), 4.53 – 4.44 (m, 1H, H_3), 3.33 (d, *J* = 13.3 Hz, 1H, H_8), 2.94 (d, *J* = 13.3 Hz, 1H, H_8), 2.66 – 2.57 (m, 2H, H_4), 1.44 (d, *J* = 6.3 Hz, 3H, H_6), 1.14 (app d, 6H, H_{12}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.2 (C_7), 195.4 (C_5), 164.7 (C_2), 146.9 (C_{10}), 111.0 (C_{11}), 104.6 (C_1), 70.2 (C_3), 48.2 (C_8), 40.0 (C_4), 38.4 (C_9), 27.8 (C_{12}), 27.0 (C_{12}), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}O_4$) requires *m/z* 239.1278, found *m/z* 239.1281.

Compound 144.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), pent-4-ynoic acid (39.2 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–50% EtOAc in cyclohexane) to afford the desired product as a white solid (61 mg, 73%).

$[\alpha]_D^{20}$ = −80.0 (c 2.0, $CHCl_3$).

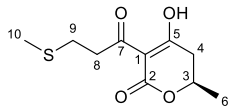
υ_{max} (film): 3262, 2983, 1706, 1562, 1441, 1305, 1055, 696.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 – 4.50 (m, 1H, H_3), 3.44 – 3.21 (m, 2H, H_8), 2.74 – 2.61 (m, 2H, H_4), 2.57 (td, *J* = 7.0, 2.7 Hz, 2H, H_9), 1.97 (t, *J* = 2.7 Hz, 1H, H_{11}), 1.47 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.8 (C_7), 193.2 (C_5), 164.3 (C_2), 103.4 (C_1), 82.9 (C_{10}), 70.6 (C_3), 69.1 (C_{11}), 38.6 (C_4), 38.5 (C_8), 20.8 (C_6), 13.5 (C_9).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_{13}O_4$) requires *m/z* 209.0808, found *m/z* 209.0811.

Compound 145.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 3-methylsulfanylpropanoic acid (48.1 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–40% EtOAc in cyclohexane) to afford the desired product as a colourless oil (75 mg, 81%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −56.7 (c 8.3, $CHCl_3$).

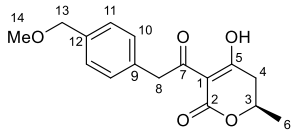
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2980, 2917, 1702, 1558, 1442, 1296, 1065, 905.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.58 – 4.50 (m, 1H, H_3), 3.47 – 3.26 (m, 2H, H_8), 2.82 (t, *J* = 7.3 Hz, 2H, H_9), 2.70 – 2.61 (m, 2H, H_4), 2.15 (s, 3H, H_{10}), 1.47 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 202.7 (C_7), 194.1 (C_5), 164.4 (C_2), 103.6 (C_1), 70.6 (C_3), 39.0 (C_4), 38.9 (C_8), 28.9 (C_9), 20.7 (C_6), 15.8 (C_{10}).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{10}H_{15}O_4S$) requires *m/z* 231.0691, found *m/z* 231.0688.

Compound 146.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 2-[4-(methoxymethyl)phenyl]acetic acid (72.1 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–80% EtOAc in cyclohexane) to afford the desired product as a white solid (69 mg, 59%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −44.6 (c 3.5, $CHCl_3$).

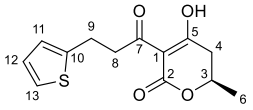
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2926, 2359, 1705, 1568, 1439, 1099, 1053, 783.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 4H, $H_{10,11}$), 4.52 (br s, 1H, H_3), 4.45 – 4.31 (m, 4H, $H_{8,13}$), 3.38 (s, 3H, H_{14}), 2.73 – 2.57 (m, 2H, H_4), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 201.9 (C_7), 194.7 (C_5), 164.4 (C_2), 137.3 (C_{12}), 133.6 (C_9) , 130.0 (C_{10}), 128.0 (C_{11}), 103.0 (C_1), 74.5 (C_{13}), 70.5 (C_3), 58.3 (C_{14}), 44.3 (C_8), 39.1 (C_4), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}O_5Na$) requires *m/z* 313.1046, found *m/z* 313.1044.

Compound 147.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), (3-(2-thienyl)propanoic acid (62.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–30% EtOAc in cyclohexane) to afford the desired product as a colourless oil (63 mg, 59%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −46.9 (c 4.8, $CHCl_3$).

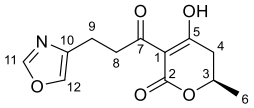
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2916, 2361, 1711, 1558, 1065, 700.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 5.1, 1.2 Hz, 1H, H_{12}), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1H, H_{13}), 6.86 – 6.84 (m, 1H, H_{11}), 4.49 – 4.54 (m, 1H, H_3), 3.53 – 3.45 (m, 1H, H_8), 3.43 – 3.35 (m, 1H, H_8), 3.27 – 3.15 (m, 2H, H_9), 2.73 – 2.57 (m, 2H, H_4), 1.46 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 203.2 (C_7), 193.9 (C_5), 164.3 (C_2), 143.2 (C_{10}), 126.9 (C_{13}), 125.0 (C_{11}), 123.6 (C_{12}), 103.4 (C_1), 70.5 (C_3), 40.9 (C_8), 38.9 (C_4), 24.6 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_4S$) requires *m/z* 267.0686, found *m/z* 267.0690.

Compound 148.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 3-oxazol-4-ylpropanoic acid (56.4 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–70% EtOAc in cyclohexane) to afford the desired product as a white solid (55 mg, 55%).

$[\alpha]_D^{20}$ = −120 (c 4.0, $CHCl_3$).

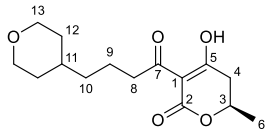
υ_{max} **(film)**: 2917, 2160, 1705, 1561, 1446, 1105, 1055, 904.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.27 (s, 1H, H_{11}), 8.20 (s, 1H, H_{12}), 4.56 – 4.47 (m, 1H, H_3), 3.44 (dt, *J* = 17.4, 7.0 Hz, 1H, H_8), 3.23 (dt, *J* = 17.4, 7.2 Hz, 1H, H_8), 2.85 (td, *J* = 6.9, 0.9 Hz, 2H, H_9), 2.70 – 2.58 (m, 2H, H_4), 1.46 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 203.1 (C_7), 193.7 (C_5), 164.3 (C_2), 155.1 (C_{11}), 150.5 (C_{12}), 117.9 (C_{10}), 103.5 (C_1), 70.6 (C_3), 39.6 (C_8), 38.7 (C_4), 20.7 (C_6), 16.9 (C_9).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{14}O_5N$) requires *m/z* 252.0867, found *m/z* 252.0870.

Compound 149.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 4-tetrahydropyran-4-ylbutanoic acid (68.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–70% EtOAc in cyclohexane) to afford the desired product as a white solid (75 mg, 66%).

$[\alpha]_D^{20}$ = −113 (*c* 3.2, $CHCl_3$).

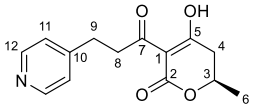
υ_{max} (film): 2925, 2843, 1710, 1557, 1456, 1064, 905.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55 – 4.50 (m, 1H, H_3), 3.94 (dd, *J* = 11.2, 5.1, 2H, H_{13}), 3.39 – 3.34 (m, 2H, H_{13}), 3.08 (ddd, *J* = 15.2, 9.0, 6.0 Hz, 1H, H_8), 2.97 (ddd, *J* = 15.6, 8.9, 6.2 Hz, 1H, H_8), 2.72 – 2.56 (m, 2H, H_4), 1.77 – 1.64 (m, 2H, H_9), 1.63 – 1.58 (m, 2H, H_{12}), 1.56 – 1.42 (m, 4H, $H_{6,11}$), 1.36 – 1.30 (m, 2H, H_{10}), 1.29 – 1.22 (m, 2H, H_{12}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.6 (C_7), 195.0 (C_5), 164.4 (C_2), 103.2 (C_1), 70.4 (C_3), 68.2 (C_{13}), 39.5 (C_4), 38.8 (C_8), 36.6 (C_{10}), 34.8 (C_{11}), 33.2 (C_{12}), 21.9 (C_9), 20.8 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}O_5$) requires *m/z* 283.1540, found *m/z* 283.1544.

Compound 150.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 3-(4-pyridyl)propanoic acid (60.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–100% EtOAc in cyclohexane) to afford the desired product as a yellow oil (41 mg, 39%).

$[\alpha]_D^{20}$ = −48.8 (c 3.2, $CHCl_3$).

υ_{max} **(film)**: 3676, 2988, 2359, 1709, 1605, 1395, 1067.

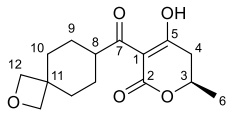
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.49 (d, *J* = 6.1 Hz, 2H, H_{12}), 7.19 (d, *J* = 6.1 Hz, 2H, H_{11}), 4.56 – 4.50 (m, 1H, H_3), 3.52 – 3.42 (m, 1H, H_8), 3.36 – 3.28 (m, 1H, H_8), 3.05 – 2.92 (m, 2H, H_9), 2.71 – 2.60 (m, 2H, H_4), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR*** (101 MHz, $CDCl_3$): δ 202.9 (C_7), 194.0 (C_5), 163.5 (C_2), 149.7 (C_{10}), 149.7 (C_{12}), 124.0 (C_{11}), 103.2 (C_1), 70.4 (C_3), 39.3 (C_8), 38.7 (C_4), 29.6 (C_9), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}O_4N$) requires *m/z* 262.1074, found *m/z* 262.1068.

**Quaternary carbon signals were quite weak compared to aromatic signals and others. The shifts were further confirmed with 2D NMR.*

Compound 151.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 2-oxaspiro[3.5]nonane-7-carboxylic acid (68.1 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–70% EtOAc in cyclohexane) to afford the desired product as a white solid (36 mg, 32%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −21.2 (c 3.3, $CHCl_3$).

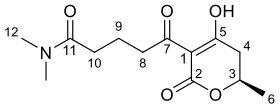
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2930, 2857, 1709, 1558, 1449, 1067, 976.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.56 – 4.47 (m, 1H, H_3), 4.44 (s, 2H, H_{12}), 4.35 (s, 2H, H_{12}), 3.59 (tt, *J* = 11.2, 3.1 Hz, 1H, H_8), 2.70 – 2.58 (m, 2H, H_4), 2.25 – 2.19 (m, 2H, H_{10}), 1.94 – 1.89 (m, 1H, H_9), 1.77 – 1.71 (m, 1H, H_9), 1.60 – 1.33 (m, 7H, $H_{6,9,10}$).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 206.9 (C_7), 195.5 (C_5), 164.2 (C_2), 102.4 (C_1), 82.5 (C_{12}), 81.9 (C_{12}), 70.4 (C_3), 43.8 (C_8), 39.8 (C_{11}), 39.6 (C_4), 34.4 (C_{10}), 34.3 (C_{10}), 25.7 (C_9), 25.5 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{15}H_{19}O_5$) requires *m/z* 279.1238, found *m/z* 279.1236.

Compound 152.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 5-(dimethylamino)-5-oxo-pentanoic acid (63.7 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–100% EtOAc in cyclohexane) to afford the desired product as a white solid (68 mg, 63%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −56.3 (c 4.0, $CHCl_3$).

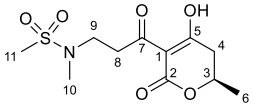
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2938, 1709, 1631, 1456, 1065, 912.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.55 – 4.50 (m, 1H, H_3), 3.24 – 3.03 (m, 2H, H_8), 3.00 (s, 3H, H_{12}), 2.94 (s, 3H, H_{12}), 2.73 – 2.56 (m, 2H, H_4), 2.40 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.07 – 1.95 (m, 2H, H_9), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 204.3 (C_7), 194.4 (C_5), 172.2 (C_{11}), 164.4 (C_2), 103.2 (C_1), 70.5 (C_3), 39.2 (C_4), 38.5 (C_8), 37.3 (C_{12}), 35.5 (C_{12}), 32.7 (C_{10}), 20.7 (C_6), 20.2 (C_9).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{13}H_{20}O_5N$) requires *m/z* 270.1336, found *m/z* 270.1336.

Compound 153.



Prepared according to general procedure B1 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 3-[methyl(methylsulfonyl)amino]propanoic acid (72.5 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–80% EtOAc in cyclohexane) to afford the desired product as a white solid (82 mg, 70%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −77.8 (c 3.6, $CHCl_3$).

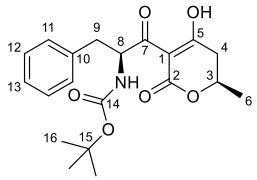
$\boldsymbol{\upsilon}_{max}$ **(film)**: 2934, 1705, 1564, 1456, 1329, 1148, 963, 776.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.61 – 4.53 (m, 1H, H_3), 3.55 – 3.49 (m, 2H, H_9), 3.42 – 3.26 (m, 2H, H_8), 2.91 (s, 3H, H_{10}), 2.81 (s, 3H, H_{11}), 2.73 – 2.59 (m, 2H, H_4), 1.47 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 201.6 (C_7), 194.0 (C_5), 164.5 (C_2), 103.8 (C_1), 70.6 (C_3), 46.1 (C_9), 38.9 (C_4), 38.1 (C_8), 36.1 (C_{11}), 35.0 (C_{10}), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_{18}NO_6S$) requires *m/z* 292.0849, found *m/z* 292.0852.

Compound 154.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), (2*S*)-2-(*tert*-butoxycarbonylamino)-3-phenyl-propanoic acid (106

mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–80% EtOAc in cyclohexane) to afford the desired product as a white solid (82 mg, 55%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.6 (c 4.6, $CHCl_3$).

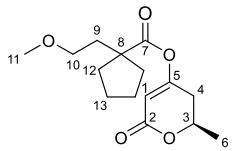
$\boldsymbol{\upsilon}_{max}$ **(film)**: 3350, 2978, 1707, 1694, 1250, 1169, 702.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (m, 2H, H_{12}), 7.26 – 7.17 (m, 3H, $H_{11,13}$), 6.01 – 5.85 (m, 1H, H_8), 5.16 – 4.97 (m, 1H, N*H*), 4.58 – 4.34 (m, 1H, H_3), 3.16 – 3.13 (m, 1H, H_9), 2.80 – 2.74 (m, 1H, H_9), 2.71 – 2.57 (m, 2H, H_4), 1.47 (d, *J* = 6.3 Hz, 3H, H_6), 1.37 (s, 9H, H_{16}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7 (C_7), 192.9 (C_5), 163.7 (C_2), 155.2 (C_{14}), 136.3 (C_{10}), 129.6 (C_{11}), 128.6 (C_{12}), 127.0 (C_{13}), 102.3 (C_1), 79.9 (C_{15}) 70.5 (C_3), 57.1 (C_8), 39.0 (C_9), 38.1 (C_4), 28.4 (C_{16}), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{20}H_{24}O_6N$) requires *m/z* 374.1609, found *m/z* 374.1602.

Compound 160b.



Prepared according to general procedure B2 using EDCI (86.1 mg, 0.44 mmol, 1.1 eq), compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), DMAP (54.9 mg, 0.44 mmol, 1.1 eq), 7-*tert*-butoxy-7-oxo-heptanoic acid (68.9 mg, 0.40 mmol, 1.0 eq), and anhydrous MeCN (2.0 mL, 0.20 M). The crude residue was purified by

column chromatography (silica gel, 0–100% EtOAc in cyclohexane) to afford the O-acyl product as a colourless oil (46 mg, 41%).

$[\alpha]_D^{20}$ = –88.6 (c 3.5, $CHCl_3$).

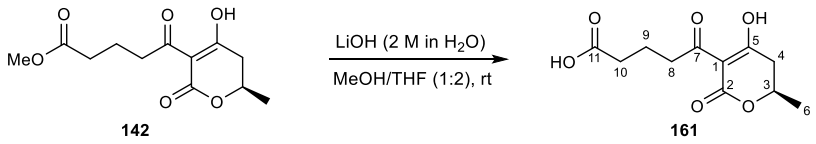
υ_{max} (film): 2874, 2361, 1755, 1717, 1391, 1332, 1283, 1238, 1136, 1092, 743.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (d, *J* = 2.1 Hz, 1H, H_1), 4.66 – 4.58 (m, 1H, H_3), 3.40 (t, *J* = 6.0 Hz, 2H, H_{10}), 3.24 (s, 3H, H_{11}), 2.62 (ddd, *J* = 17.6, 11.5, 2.2 Hz, 1H, H_4), 2.47 (dd, *J* = 17.6, 3.9 Hz, 1H, H_4), 2.21 – 2.11 (m, 2H, H_{12}), 2.02 – 1.91 (m, 2H, H_9), 1.70 – 1.64 (m, 4H, H_{13}), 1.61 – 1.52 (m, 2H, H_{12}), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C_7), 166.0 (C_5), 165.1 (C_2), 106.4 (C_1), 73.1 (C_3), 69.9 (C_{10}), 58.9 (C_{11}), 52.7 (C_8), 38.6 (C_9), 36.1 (C_{12}), 35.8 (C_{12}), 33.9 (C_4), 24.7 (C_{13}), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{22}O_5Na$) requires *m/z* 305.1359, found *m/z* 305.1357.

Compound 161.



Prepared according to general procedure C using compound **142** (600 mg, 2.34 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 8.0 mL) for 5 h. The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a beige solid (479 mg, 84%).

$[\alpha]_D^{20}$ = –49.2 (c 6.5, $CHCl_3$).

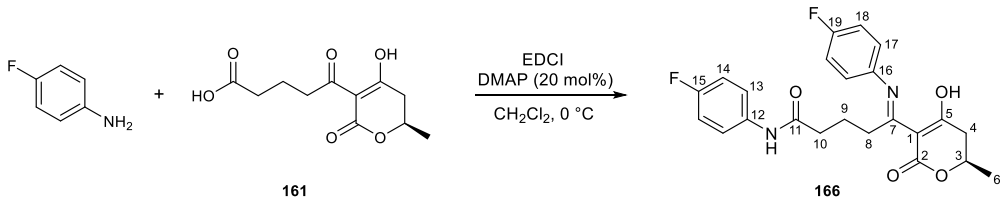
υ_{max} (film): 3464, 2980, 2938, 2361, 1701, 1558, 1406, 1263, 1069, 907.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.53 – 4.46 (m, 1H, H_3), 3.15 (ddd, *J* = 17.0, 8.0, 6.5 Hz, 1H, H_8), 3.00 (ddd, *J* = 17.1, 8.0, 6.7 Hz, 1H, H_8), 2.67 – 2.57 (m, 2H, H_4), 2.41 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.00 – 1.92 (m, 2H, H_9), 1.42 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.8 (C_7), 194.2 (C_5), 179.0 (C_{11}), 164.4 (C_2), 103.2 (C_1), 70.5 (C_3), 38.8 (C_4), 37.9 (C_8), 33.1 (C_{10}), 20.6 (C_6), 19.3 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{14}O_6Na$) requires *m/z* 265.0683, found *m/z* 265.0682.

Compound 166.



A solution of compound **161** (66.6 mg, 0.28 mmol, 1.1 eq), DMAP (6.1 mg, 0.05 mmol, 20 mol%), and EDCI (52.7 mg, 0.28 mmol, 1.1 eq) was stirred in anhydrous CH_2Cl_2 (1.3 mL, 0.2 M) at 0 °C for 15 min. 4-Fluoroaniline (23.7 µL, 0.25 mmol, 1.0 eq) was then added to the reaction mixture, and the resulting mixture stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl (2 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), dried over Na_2SO_4, then concentrated under reduced pressure. The crude

residue was purified by column chromatography (silica gel, 25–100% EtOAc in petroleum ether) to afford the unexpected imine by-product as a white solid (34.3 mg, 31%).

$[\alpha]_D^{20}$ = +46.0 (c 1.0, $CHCl_3$).

υ_{max} **(film)**: 3306, 2924, 2357, 1668, 1603, 1508, 1211, 1063, 833.

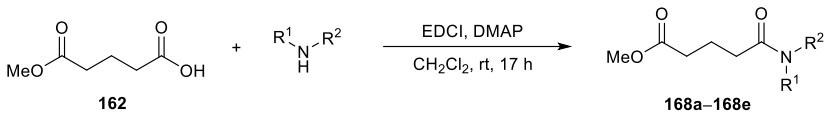
^{1}**H NMR** (500 MHz, MeOD): δ 7.43 (dd, *J* = 9.2, 4.9 Hz, 2H, H_{13} or H_{17}), 7.32 (dd, *J* = 8.9, 4.7 Hz, 2H, H_{13} or H_{17}), 7.18 – 7.15 (m, 2H, H_{14} or H_{18}), 7.01 (dd, *J* = 9.2, 8.5 Hz, 2H, H_{14} or H_{18}), 4.61 – 4.53 (m, 1H, H_3), 3.10 – 2.99 (m, 1H, H_8), 2.92 – 2.82 (m, 1H, H_8), 2.65 – 2.52 (m, 2H, H_4), 2.35 – 2.25 (m, 2H, H_9), 2.01 – 1.93 (m, 1H, H_{10}), 1.90 – 1.80 (m, 1H, H_{10}), 1.41 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, MeOD): δ 195.3 (C_5), 178.1 (C_7), 173.0 (C_{11}), 169.3 (C_2) 163.6 (d, $^1J_{C–F}$ = 247.3 Hz, C_{15} or C_{19}), 160.6 (d, $^1J_{C–F}$ = 241.5 Hz, C_{15} or C_{19}), 136.0 (m, C_{12} or C_{16}), 133.4 (d, $^4J_{C–F}$ = 3.2 Hz, C_{12} or C_{16}), 129.7 (d, $^3J_{C–F}$ = 8.9 Hz, C_{13} or C_{17}), 122.9 (d, $^3J_{C–F}$ = 7.8 Hz, C_{13} or C_{17}), 117.6 (d, $^2J_{C–F}$ = 23.2 Hz, C_{14} or C_{18}), 116.2 (d, $^2J_{C–F}$ = 22.5 Hz, C_{14} or C_{18}), 97.7 (C_1), 71.9 (C_3), 44.8 (C_4), 37.6 (C_9), 30.8 (C_8), 25.8 (C_{10}), 20.8 (C_6).

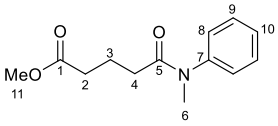
^{19}**F NMR** (376 MHz, $CDCl_3$): δ −112.00, −118.44.

HRMS (ESI): exact mass calculated for $[M–H]^-$ ($C_{23}H_{21}F_2N_2O_4$) requires m/z 427.1475, found m/z 427.1468.

Amide coupling of acid 162 for the synthesis of amides 168a–168e



Compound 168a.



Prepared according to general procedure D2 using EDCI (211 mg, 1.10 mmol, 1.1 eq), 5-methoxy-5-oxopentanoic acid (161 mg, 1.10 mmol, 1.1 eq), DMAP (24.4 mg, 0.20 mmol, 20 mol%), *N*-methylaniline (107 mg, 1.00 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (5.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 50–100% EtOAc in hexane) to afford the desired product as a pale yellow oil (185 mg, 79%).

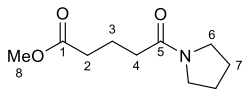
υ_{max} (film): 2951, 2359, 1732, 1651, 1595, 1497, 1389, 1123.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.37 (m, 2H, H_8), 7.35 – 7.31 (m, 1H, H_{10}), 7.19 – 7.12 (m, 2H, H_9), 3.59 (s, 3H, H_{11}), 3.25 (s, 3H, H_6), 2.28 (t, *J* = 7.3 Hz, 2H, H_2), 2.10 (t, *J* = 7.3 Hz, 2H, H_4), 1.89 (p, *J* = 7.3 Hz, 2H, H_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7 (C_1), 172.3 (C_5), 144.1 (C_7), 129.9 (C_8), 127.9 (C_{10}), 127.4 (C_9), 51.6 (C_{11}), 37.4 (C_6), 33.4 (C_2), 33.2 (C_4), 20.8 (C_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{17}NO_3Na$) requires *m/z* 258.1100, found *m/z* 258.1101.

Compound 168b.



Prepared according to general procedure D2 using EDCI (295 mg, 1.54 mmol, 1.1 eq), 5-methoxy-5-oxopentanoic acid (225 mg, 1.54 mmol, 1.1 eq), DMAP (205 mg, 1.68 mmol, 1.2 eq), pyrrolidine (117 µL, 1.40 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (7.0 mL, 0.20 M). The desired product was obtained without further purification as a colourless oil (275 mg, 99%).

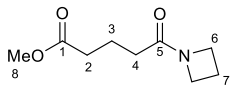
υ_{max} (film): 3472, 2953, 2361, 1732, 1632, 1437, 1169.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.66 (s, 3H, H_8), 3.47 – 3.40 (m, 4H, H_6), 2.42 (t, *J* = 7.1 Hz, 2H, H_2), 2.32 (t, *J* = 7.4 Hz, 2H, H_4), 2.01 – 1.90 (m, 4H, H_7), 1.86 – 1.84 (m, 2H, H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0 (C_1), 170.9 (C_5), 51.7 (C_8), 46.7 (C_6), 45.8 (C_6), 33.7 (C_4), 33.4 (C_2), 26.2 (C_7), 24.5 (C_7), 20.2 (C_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{17}NO_3Na$) requires *m/z* 222.1101, found *m/z* 222.1094.

Compound 168c.



Prepared according to general procedure D2 using EDCI (295 mg, 1.54 mmol, 1.1 eq), 5-methoxy-5-oxopentanoic acid (225 mg, 1.54 mmol, 1.1 eq), DMAP (205 mg, 1.68 mmol, 1.2 eq), azetidine hydrochloride (131 mg, 1.40 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (7.0 mL, 0.20 M). The desired product was obtained without further purification as a colourless oil (193 mg, 74%).

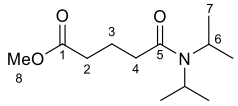
υ_{max} (film): 3449, 2953, 2357, 1732, 1628, 1437, 1244, 1157.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 (t, *J* = 7.6 Hz, 2H, H_6), 4.01 (t, *J* = 7.7 Hz, 2H, H_6), 3.66 (s, 3H, H_8), 2.38 (t, *J* = 7.1 Hz, 2H, H_2), 2.29 – 2.22 (m, 2H, H_7), 2.11 (t, *J* = 7.4 Hz, 2H, H_4), 1.96 – 1.90 (m, 2H, H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9 (C_1), 172.3 (C_5), 51.7 (C_8), 50.2 (C_6), 47.9 (C_6), 33.3 (C_2), 30.1 (C_4), 20.1 (C_3), 15.2 (C_7).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_9H_{15}NO_3Na$) requires *m/z* 208.0944, found *m/z* 208.0941.

Compound 168d.



Prepared according to general procedure D2 using EDCI (211 mg, 1.10 mmol, 1.1 eq), 5-methoxy-5-oxopentanoic acid (161 mg, 1.10 mmol, 1.1 eq), DMAP (147 mg, 1.20 mmol, 1.2 eq), DIPA (101 mg, 1.00 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (5.0 mL, 0.20 M). The desired product was obtained without further purification as a pale yellow oil (184 mg, 80%).

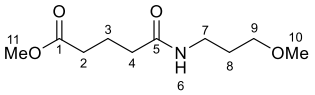
υ_{max} (film): 2967, 2357, 1736, 1636, 1441, 1369, 1215, 1045.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (hept, *J* = 6.3 Hz, 1H, H_6), 3.66 (s, 3H, H_8), 3.48 (br s, 1H, H_6), 2.40 (t, *J* = 7.1 Hz, 2H, H_2), 2.37 – 2.29 (m, 2H, H_4), 1.94 (p, *J* = 7.2 Hz, 2H, H_3), 1.36 (d, *J* = 6.8 Hz, 6H, H_7), 1.19 (d, *J* = 6.7 Hz, 6H, H_7).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1 (C_1), 171.1 (C_5), 51.7 (C_8), 48.4 (C_6), 45.8 (C_6), 34.2 (C_4), 33.5 (C_2), 21.1 (C_7), 20.8 (C_7), 20.7 (C_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{23}NO_3Na$) requires *m/z* 252.1576, found *m/z* 252.1562.

Compound 168e.



Prepared according to general procedure D2 using EDCI (295 mg, 1.54 mmol, 1.1 eq), 5-methoxy-5-oxopentanoic acid (225 mg, 1.54 mmol, 1.1 eq), DMAP (205 mg, 1.68 mmol, 1.2 eq), 3-methoxypropylamine (125 mg, 1.40 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (7.0 mL, 0.20 M). The desired product was obtained without further purification as a colourless oil (222 mg, 73%).

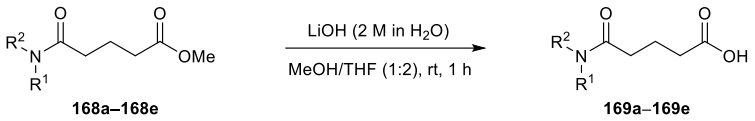
υ_{max} (film): 3294, 2951, 2361, 1732, 1643, 1551, 1439, 1223, 1115, 891.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.10 (br s, 1H, H_6), 3.66 (s, 3H, H_{11}), 3.46 (t, *J* = 5.8 Hz, 2H, H_9), 3.37 – 3.33 (m, 5H, $H_{7,10}$), 2.37 (t, *J* = 7.2 Hz, 2H, H_2), 2.22 (t, *J* = 7.4 Hz, 2H, H_4), 1.95 (p, *J* = 7.3 Hz, 2H, H_3), 1.83 – 1.69 (m, 2H, H_8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8 (C_1), 172.1 (C_5), 72.0 (C_9), 58.9 (C_{10}), 51.7 (C_{11}), 38.3 (C_7), 35.7 (C_4), 33.2 (C_2), 29.2 (C_8), 21.0 (C_3).

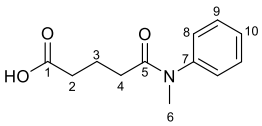
HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{19}NO_4Na$) requires *m/z* 240.1206, found *m/z* 240.1200.

Methyl ester hydrolysis of compounds 168a–168b



168a–168e 169a–169e

Compound 169a.



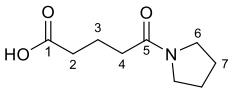
Prepared according to general procedure C using compound **168a** (180 mg, 0.77 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 4.0 mL) for 1 h. The desired product was obtained without further purification as a white solid (167 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.38 (m, 2H, H_8), 7.36 – 7.30 (m, 1H, H_{10}), 7.19 – 7.14 (m, 2H, H_9), 3.25 (s, 3H, H_6), 2.32 (t, *J* = 7.2 Hz, 2H, H_2), 2.15 (t, *J* = 7.2 Hz, 2H, H_4), 1.88 (p, *J* = 7.2 Hz, 2H, H_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2 (C_1), 172.7 (C_5), 143.9 (C_7), 130.0 (C_8), 128.1 (C_{10}), 127.4 (C_9), 37.6 (C_6), 33.3 (C_2), 33.0 (C_4), 20.6 (C_3).

The spectral data were consistent with those previously reported in the literature.[82]

Compound 169b.



Prepared according to general procedure C using compound **168b** (115 mg, 0.58 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 3.0 mL) for 1 h. The desired product was obtained without further purification as a white solid (81.0 mg, 76%).

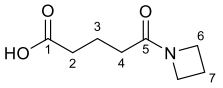
υ_{max} (film): 3503, 2924, 2363, 1721, 1593, 1454, 1227, 1192, 532.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.46 (t, *J* = 6.9 Hz, 2H, H_6), 3.41 (t, *J* = 6.9 Hz, 2H, H_6), 2.45 (t, *J* = 7.0 Hz, 2H, H_2), 2.38 (t, *J* = 7.3 Hz, 2H, H_4), 2.00 – 1.92 (m, 4H, H_7), 1.85 (p, *J* = 6.8 Hz, 2H, H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 177.4 (C_1), 171.5 (C_5), 46.9 (C_6), 46.0 (C_6), 33.6 (C_2), 33.6 (C_4), 26.1 (C_7), 24.5 (C_7), 20.1 (C_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_9H_{15}NO_3Na$) requires *m/z* 208.0944, found *m/z* 208.0943.

Compound 169c.



Prepared according to general procedure C using compound **168c** (180 mg, 0.97 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 3.9 mL) for 1 h. The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (166 mg, 25%).

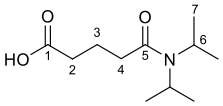
υ_{max} (film): 2955, 1717, 1597, 1474, 1447, 1157, 556.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.08 (br s, 4H, H_6), 2.41 (t, *J* = 7.1 Hz, 2H, H_2), 2.30 – 2.23 (m, 2H, H_7), 2.17 (t, *J* = 7.3 Hz, 2H, H_4), 1.92 (p, *J* = 7.1 Hz, 2H, H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ 177.4 (C_1), 172.9 (C_5), 50.4 (C_6), 48.2 (C_6), 33.4 (C_2), 30.0 (C_4), 20.0 (C_3), 15.1 (C_7).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_8H_{13}NO_3Na$) requires *m/z* 194.0788, found *m/z* 194.0783.

Compound 169d.



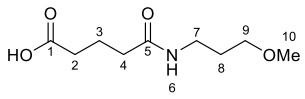
Prepared according to general procedure C using compound **168d** (152 mg, 0.66 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 2.5 mL) for 1 h. The desired product was obtained without further purification as a white solid (138 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97 (hept, *J* = 6.6 Hz, 1H, H_6), 3.50 (br s, 1H, H_6), 2.45 – 2.42 (m, 4H, $H_{2,4}$), 1.95 (p, *J* = 7.0 Hz, 2H, H_3), 1.38 (d, *J* = 6.8 Hz, 6H, H_7), 1.21 (d, *J* = 6.7 Hz, 6H, H_7).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 172.0, 48.9, 46.2, 33.8, 33.8, 21.0, 20.7, 20.7.

The spectral data were consistent with those previously reported in the literature.[83]

Compound 169e.



Prepared according to general procedure C using compound **168e** (210 mg, 0.97 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 3.9 mL) for 1 h. The desired product was obtained without further purification as a colourless oil (78.6 mg, 40%).

υ_{max} (film): 3310, 2932, 2361, 1713, 1628, 1555, 1223, 1111, 914, 745.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (br s, 1H, H_6), 3.49 (t, *J* = 5.7 Hz, 2H, H_9), 3.37 – 3.34 (m, 5H, $H_{7,10}$), 2.41 (t, *J* = 7.0 Hz, 2H, H_2), 2.29 (t, *J* = 7.4 Hz, 2H, H_4), 1.96 (p, *J* = 7.2 Hz, 2H, H_3), 1.80 – 1.75 (m, 2H, H_8).

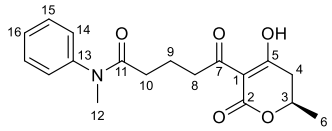
^{13}C NMR (126 MHz, $CDCl_3$): δ 177.1 (C_1), 172.9 (C_5), 71.8 (C_9), 58.8 (C_{10}), 38.4 (C_7), 35.4 (C_4), 33.2 (C_2), 28.9 (C_8), 21.0 (C_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_9H_{17}NO_4Na$) requires *m/z* 226.1050, found *m/z* 226.1043.

Head group coupling of acids 169a–169e

169a–169e **15** **170a–170e**

Compound 170a.



Prepared according to general procedure B2 using EDCI (124 mg, 0.65 mmol, 1.1 eq), compound **15** (82.8 mg, 0.65 mmol, 1.1 eq), DMAP (79.0 mg, 0.65 mmol, 1.1 eq), compound **169a** (130 mg, 0.59 mmol, 1.0 eq), and anhydrous MeCN (2.9 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 75–100% EtOAc in hexane) to afford the desired product as a yellow gum (87.2 mg, 45%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −36.7 (c 8.3, $CHCl_3$).

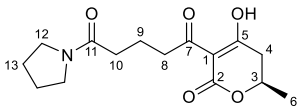
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2976, 1707, 1649, 1595, 1497, 1387, 1263, 1065.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 2H, H_{14}), 7.31 (t, *J* = 7.4 Hz, 1H, H_{16}), 7.19 – 7.13 (m, 2H, H_{15}), 4.55 – 4.38 (m, 1H, H_3), 3.23 (s, 3H, H_{12}), 3.04 – 2.83 (m, 2H, H_8), 2.66 – 2.52 (m, 2H, H_4), 2.11 (t, *J* = 7.4 Hz, 2H, H_{10}), 1.97 – 1.85 (m, 2H, H_9), 1.41 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.1 (C_7), 194.2 (C_5), 172.2 (C_{11}), 164.3 (C_2), 144.0 (C_{13}), 129.9 (C_{14}), 127.9 (C_{16}), 127.4 (C_{15}), 103.1 (C_1), 70.3 (C_3), 39.0 (C_4), 38.2 (C_8), 37.3 (C_{12}), 33.3 (C_{10}), 20.6 (C_6), 20.3 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{21}NO_5Na$) requires *m/z* 354.1312, found *m/z* 354.1307.

Compound 170b.



Prepared according to general procedure B2 using EDCI (188 mg, 0.98 mmol, 1.1 eq), compound **15** (126 mg, 0.98 mmol, 1.1 eq), DMAP (120 mg, 0.98 mmol, 1.1 eq), compound **169b** (165 mg, 0.89 mmol, 1.0 eq), and anhydrous MeCN (4.5 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (82.0 mg, 31%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −49.1 (c 3.4, $CHCl_3$).

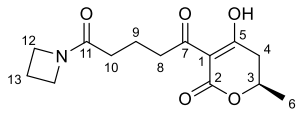
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2974, 2361, 1707, 1630, 1558, 1437, 1063, 907.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.61 – 4.39 (m, 1H, H_3), 3.44 – 3.37 (m, 4H, H_{12}), 3.19 – 3.00 (m, 2H, H_8), 2.70 – 2.55 (m, 2H, H_4), 2.33 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.04 – 1.97 (m, 2H, H_{13}), 1.95 – 1.90 (m, 2H, H_9), 1.86 – 1.81 (m, 2H, H_{13}), 1.43 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 204.3 (C_7), 194.4 (C_5), 170.8 (C_{11}), 164.4 (C_2), 103.2 (C_1), 70.4 (C_3), 46.6 (C_{12}), 45.7 (C_{12}), 39.1 (C_4), 38.4 (C_8), 33.9 (C_{10}), 26.2 (C_{13}), 24.5 (C_{13}), 20.7 (C_6), 19.9 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{21}NO_5Na$) requires *m/z* 318.1312, found *m/z* 318.1300.

Compound 170c.



Prepared according to general procedure B2 using EDCI (57.9 mg, 0.30 mmol, 1.1 eq), compound **15** (38.7 mg, 0.30 mmol, 1.1 eq), DMAP (36.9 mg, 0.30 mmol, 1.1 eq), compound **169c** (47.0 mg, 0.28 mmol, 1.0 eq), and anhydrous MeCN (1.4 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (32.1 mg, 42%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −49.8 (c 8.2, $CHCl_3$).

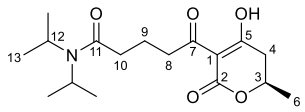
$\boldsymbol{\upsilon}_{\boldsymbol{max}}$ **(film)**: 3628, 2974, 2361, 1709, 1636, 1560, 1458, 1443, 1067, 750.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.55 – 4.48 (m, 1H, H_3), 4.10 – 4.02 (m, 4H, H_{12}), 3.17 – 2.98 (m, 2H, H_8), 2.71 – 2.53 (m, 2H, H_4), 2.29 – 2.21 (m, 2H, H_{13}), 2.14 (t, *J* = 7.2 Hz, 2H, H_{10}), 2.02 – 1.92 (m, 2H, H_9), 1.45 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.1 (C_7), 194.3 (C_5), 172.3 (C_{11}), 164.4 (C_2), 103.2 (C_1), 70.5 (C_3), 50.0 (C_{12}), 48.2 (C_{12}), 39.1 (C_4), 38.4 (C_8), 30.5 (C_{10}), 20.7 (C_6), 19.8 (C_9), 15.2 (C_{13}).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{18}NO_5$) requires *m/z* 280.1189, found *m/z* 280.1190.

Compound 170d.



Prepared according to general procedure B2 using EDCI (78.4 mg, 0.41 mmol, 1.1 eq), compound **15** (52.4 mg, 0.41 mmol, 1.1 eq), DMAP (49.9 mg, 0.41 mmol, 1.1 eq), compound **169d** (80.0 mg, 0.37 mmol, 1.0 eq), and anhydrous MeCN (1.9 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a pale yellow gum (72.4 mg, 60%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −41.8 (c 3.4, $CHCl_3$).

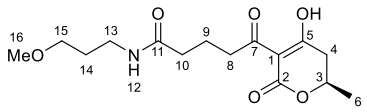
υ_{max} (film): 2967, 2361, 1711, 1630, 1558, 1441, 1369, 1061, 1043, 907.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.54 – 4.47 (m, 1H, H_3), 3.94 (hept, *J* = 6.8 Hz, 1H, H_{12}), 3.44 (br s, 1H, H_{12}), 3.16 – 2.97 (m, 2H, H_8), 2.69 – 2.53 (m, 2H, H_4), 2.37 – 2.31 (m, 2H, H_{10}), 2.01 – 1.90 (m, 2H, H_9), 1.43 (d, *J* = 6.4 Hz, 3H, H_6), 1.34 (d, *J* = 6.8 Hz, 6H, H_{13}), 1.17 (d, *J* = 6.7 Hz, 6H, H_{13}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.3 (C_7), 194.5 (C_5), 170.9 (C_{11}), 164.4 (C_2), 103.2 (C_1), 70.4 (C_3), 48.3 (C_{12}), 45.7 (C_{12}), 39.2 (C_4), 38.4 (C_8), 34.4 (C_{10}), 21.1 (C_{13}), 20.8 (C_{13}), 20.7 (C_6), 20.5 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{27}NO_5Na$) requires *m/z* 348.1781, found *m/z* 348.1784.

Compound 170e.



Prepared according to general procedure B2 using EDCI (41.5 mg, 0.22 mmol, 1.1 eq), compound **15** (27.7 mg, 0.22 mmol, 1.1 eq), DMAP (26.4 mg, 0.22 mmol, 1.1 eq), compound **169e** (40.0 mg, 0.20 mmol, 1.0 eq), and anhydrous MeCN (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a white solid (31.5 mg, 51%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −37.9 (c 4.7, $CHCl_3$).

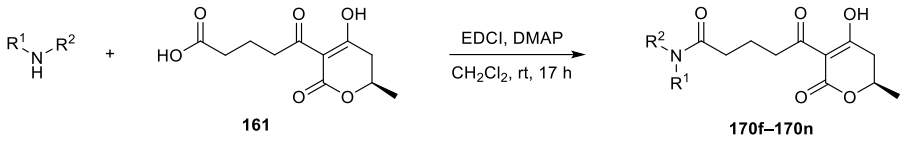
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 3291, 2932, 1709, 1639, 1555, 1454, 1115, 1069, 949.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (br s, 1H, H_{12}), 4.54 – 4.47 (m, 1H, H_3), 3.45 (t, *J* = 5.8 Hz, 2H, H_{15}), 3.36 – 3.30 (m, 5H, $H_{13,16}$), 3.14 – 2.94 (m, 2H, H_8), 2.70 – 2.55 (m, 2H, H_4), 2.23 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.03 – 1.92 (m, 2H, H_9), 1.78 – 1.72 (m, 2H, H_{14}), 1.44 (d, *J* = 6.3 Hz, 3H, H_6).

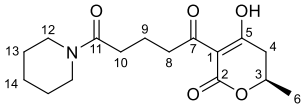
^{13}C NMR (126 MHz, $CDCl_3$): δ 203.9 (C_7), 194.5 (C_5), 172.1 (C_{11}), 164.4 (C_2), 103.2 (C_1), 71.8 (C_{15}), 70.5 (C_3), 58.9 (C_{16}), 39.2 (C_4), 38.2 (C_8), 38.1 (C_{13}), 35.9 (C_{10}), 29.2 (C_{14}), 20.8 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{15}H_{22}NO_6$) requires *m/z* 312.1453, found *m/z* 312.1452.

Amide coupling of amines with intermediate 161



Compound 170f.



Prepared according to general procedure D1 using EDCI (42.2 mg, 0.22 mmol, 1.1 eq), compound **161** (53.3 mg, 0.22 mmol, 1.1 eq), DMAP (29.3 mg, 0.24 mmol, 1.2 eq), piperidine (17.0 mg, 0.20 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–1% MeOH in CH_2Cl_2) to afford the desired product as a white solid (37.5 mg, 61%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −37.5 (c 3.6, $CHCl_3$).

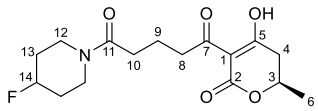
$\boldsymbol{\upsilon}_{max}$ **(film)**: 2936, 2361, 1709, 1632, 1558, 1441, 1254, 1065, 907.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.55 – 4.49 (m, 1H, H_3), 3.53 (br s, 2H, H_{12}) 3.40 (br s, 2H, H_{12}), 3.20 – 3.00 (m, 2H, H_8), 2.72 – 2.53 (m, 2H, H_4), 2.40 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.04 – 1.95 (m, 2H, H_9), 1.64 – 1.61 (m, 2H, H_{14}), 1.57 – 1.51 (m, 4H, H_{13}), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.3 (C_7), 194.4 (C_5), 170.5 (C_{11}), 164.4 (C_2), 103.2 (C_1), 70.5 (C_3), 46.7 (C_{12}), 42.8 (C_{12}), 39.2 (C_4), 38.5 (C_8), 32.7 (C_{10}), 26.5 (C_{13}), 25.7 (C_{13}), 24.7 (C_{14}), 20.8 (C_6), 20.4 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{23}NO_5Na$) requires *m/z* 332.1468, found *m/z* 332.1462.

Compound 170g.



Prepared according to general procedure D1 using EDCI (42.2 mg, 0.22 mmol, 1.1 eq), compound **161** (53.3 mg, 0.22 mmol, 1.1 eq), DMAP (29.3 mg, 0.24 mmol, 1.2 eq), 4-fluoropiperidine hydrochloride (27.9 mg, 0.20 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 70–100% EtOAc in cyclohexane) to afford the desired product as a white solid (mixture of diastereoisomers) (62.8 mg, 96%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −50.2 (c 4.5, $CHCl_3$).

$\boldsymbol{\upsilon}_{\textbf{max}}$ **(film)**: 2936, 2361, 1707, 1636, 1558, 1443, 1263, 1040, 906.

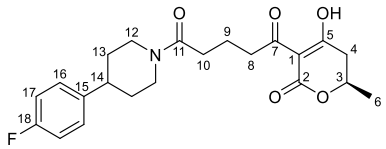
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.95 – 4.75 (m, 1H, H_{14}), 4.55 – 4.49 (m, 1H, H_3), 3.87 – 3.84 (m, 1H, H_{12}), 3.58 – 3.54 (m, 1H, H_{12}), 3.50 – 3.46 (m, 2H, H_{12}), 3.19 – 3.11 (m, 1H, H_8), 3.07 – 3.00 (m, 1H, H_8), 2.68 – 2.59 (m, 2H, H_4), 2.44 – 2.40 (m, 2H, H_{10}), 2.03 – 1.97 (m, 2H, H_9), 1.89 – 1.84 (m, 4H, H_{13}), 1.45 (d, J = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 204.2 (C_7), 194.4 (C_5), 170.7 (C_{11}), 164.4 (C_2), 103.3 (C_1), 87.8 (d, $^1J_{C–F}$ = 171.4 Hz, C_{14}), 70.5 (C_3), 41.5 (d, $^3J_{C–F}$ = 5.2 Hz, C_{12}), 39.2 (C_4), 38.5 (C_8), 37.7 (d, $^3J_{C–F}$ = 4.9 Hz, C_{12}), 32.6 (C_{10}), 31.9 (d, $^2J_{C–F}$ = 20.4 Hz, C_{13}), 31.0 (d, $^2J_{C–F}$ = 20.0 Hz, C_{13}), 20.8 (C_6), 20.4 (C_9).

^{19}**F NMR** (470 MHz, $CDCl_3$): δ −183.37, −183.35.

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}FNO_5Na$) requires *m/z* 350.1374, found *m/z* 350.1371.

Compound 170h.



Prepared according to general procedure D1 using EDCI (31.6 mg, 0.17 mmol, 1.1 eq), compound **161** (40.0 mg, 0.17 mmol, 1.1 eq), DMAP (22.0 mg, 0.18 mmol, 1.2 eq), 4-(4-fluorophenyl)piperidine (26.9 mg, 0.15 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (0.75 mL, 0.20 M). The desired product was obtained without further purification as a yellow oil (44.9 mg, 74%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −26.9 (c 7.1, $CHCl_3$).

$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2934, 1709, 1607, 1510, 1445, 1406, 1219, 1059.

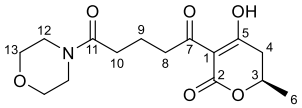
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.16 – 7.11 (m, 2H, H_{16}), 7.01 – 6.96 (m, 2H, H_{17}), 4.79 – 4.76 (m, 1H, H_{12}), 4.57 – 4.48 (m, 1H, H_3), 3.99 – 3.96 (m, 1H, H_{12}), 3.21 – 3.06 (m, 3H, $H_{8,12}$), 2.75 – 2.56 (m, 4H, $H_{4,12,14}$), 2.45 (t, *J* = 7.3 Hz, 2H, H_{10}), 2.09 – 1.94 (m, 2H, H_9), 1.91 – 1.82 (m, 2H, H_{13}), 1.63 – 1.52 (m, 2H, H_{13}), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.2 (C_7), 194.4 (C_5), 170.5 (C_{11}), 164.4 (C_2), 161.6 (d, $^1J_{C–F}$ = 244.3 Hz, C_{18}), 141.0 (d, $^4J_{C–F}$ = 3.2 Hz, C_{15}), 128.2 (d, $^3J_{C–F}$ = 7.7 Hz, C_{16}), 115.4 (d, $^2J_{C–F}$ = 21.2 Hz, C_{17}) , 103.2 (C_1), 70.5 (C_3), 46.2 (C_{12}), 42.4 (C_{12}), 42.2 (C_{14}), 39.1 (C_4), 38.5 (C_8), 34.1 (C_{13}), 33.1 (C_{13}), 32.7 (C_{10}), 20.7 (C_6), 20.4 (C_9).

^{19}F NMR (470 MHz, $CDCl_3$): δ −116.71.

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}FNO_5Na$) requires *m/z* 426.1687, found *m/z* 426.1683.

Compound 170i.



Prepared according to general procedure D1 using EDCI (42.2 mg, 0.22 mmol, 1.1 eq), compound **161** (53.3 mg, 0.22 mmol, 1.1 eq), DMAP (29.3 mg, 0.24 mmol, 1.2 eq), morpholine (17.4 mg, 0.20 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (12.7 mg, 20%).

$[\alpha]_D^{20}$ = −35.0 (c 3.0, $CHCl_3$).

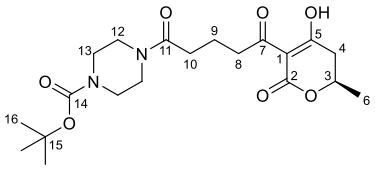
υ_{max} (film): 2970, 2922, 2361, 1711, 1641, 1566, 1447, 1277, 1115, 1067, 766.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 – 4.49 (m, 1H, H_3), 3.67 (t, *J* = 4.7 Hz, 4H, H_{13}), 3.61 (br s, 2H, H_{12}), 3.47 (br s, 2H, H_{12}), 3.21 – 3.01 (m, 2H, H_8), 2.73 – 2.55 (m, 2H, H_4), 2.41 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.05 – 1.97 (m, 2H, H_9), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.2 (C_7), 194.3 (C_5), 171.0 (C_{11}), 164.4 (C_2), 103.3 (C_1), 70.5 (C_3), 67.0 (C_{13}), 66.8 (C_{13}), 46.0 (C_{12}), 42.0 (C_{12}), 39.1 (C_4), 38.5 (C_8), 32.5 (C_{10}), 20.8 (C_6), 20.2 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{21}NO_6Na$) requires *m/z* 334.1261, found *m/z* 334.1264.

Compound 170j.



Prepared according to general procedure D1 using EDCI (42.2 mg, 0.22 mmol, 1.1 eq), compound **161** (53.3 mg, 0.22 mmol, 1.1 eq), DMAP (29.3 mg, 0.24 mmol, 1.2 eq), 1-*tert*-butoxycarbonylamino-piperazine (37.3 mg, 0.20 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (23.1 mg, 28%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −27.7 (c 8.1, $CHCl_3$).

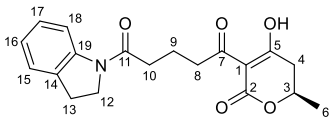
$\boldsymbol{\upsilon}_{max}$ **(film)**: 2976, 2930, 1692, 1641, 1562, 1416, 1236, 1167, 731.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.54 – 4.48 (m, 1H, H_3), 3.56 (br t, *J* = 6.6, 2H, H_{12}), 3.43 – 3.37 (m, 6H, $H_{12,13}$), 3.19 – 2.99 (m, 2H, H_8), 2.75 – 2.51 (m, 2H, H_4), 2.41 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.07 – 1.92 (m, 2H, H_9), 1.45 – 1.44 (m, 12H, $H_{6,16}$).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.1 (C_7), 194.3 (C_5), 170.9 (C_{11}), 164.4 (C_2), 154.7 (C_{14}), 103.2 (C_1), 80.4 (C_{15}), 70.5 (C_3), 45.4 (C_{13}), 41.4 (C_{12}), 39.1 (C_4), 38.4 (C_8), 32.6 (C_{10}), 28.5 (C_{15}), 20.7 (C_6), 20.2 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{20}H_{30}N_2O_7Na$) requires *m/z* 433.1945, found *m/z* 433.1935.

Compound 170k.



A mixture of EDCI (73.8 mg, 0.39 mmol, 1.1 eq), compound **161** (93.3 mg, 0.39 mmol, 1.1 eq), and DMAP (51.3 mg, 0.42 mmol, 1.2 eq) was dissolved in anhydrous DMF (1.75 mL, 0.20 M), and the resulting mixture was stirred at rt for 1 h. Indoline (41.7 mg, 0.35 mmol, 1.0 eq) was added and the resulting mixture stirred at rt for 16 h. The reaction mixture was diluted with H_2O (1 mL), acidified with 2 M aqueous HCl (1 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 10% aqueous LiCl (3 × 10 mL), washed with saturated aqueous $NaHCO_3$ (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 0–1% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (38.8 mg, 32%).

$[\alpha]_D^{20}$ = −28.2 (c 1.1, $CHCl_3$).

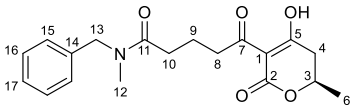
υ_{max} **(film)**: 2932, 2365, 1711, 1655, 1481, 1412, 1261, 1069.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 8.26 – 8.16 (m, 1H, H_{16}), 7.19 – 7.15 (m, 2H, $H_{15,17}$), 7.00 (dd, *J* = 7.4, 1.1 Hz, 1H, H_{18}), 4.54 – 4.48 (m, 1H, H_3), 4.04 (t, *J* = 8.5 Hz, 2H, H_{12}), 3.26 – 3.17 (m, 3H, $H_{8,13}$), 3.16 – 3.08 (m, 1H, H_8), 2.70 – 2.58 (m, 2H, H_4), 2.52 (t, *J* = 7.2 Hz, 2H, H_{10}), 2.15 – 2.08 (m, 2H, H_9), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.2 (C_7), 194.4 (C_5), 170.5 (C_{11}), 164.4 (C_2), 143.1 (C_{19}), 131.2 (C_{14}), 127.6 (C_{17}), 124.6 (C_{15}), 123.7 (C_{18}), 117.1 (C_{16}), 103.3 (C_1), 70.5 (C_3), 48.0 (C_{12}), 39.2 (C_4), 38.3 (C_8), 35.1 (C_{10}), 28.2 (C_{13}), 20.7 (C_6), 19.6 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{21}NO_5Na$) requires *m/z* 366.1312, found *m/z* 366.1305.

Compound 170l.



Prepared according to general procedure D1 using EDCI (42.2 mg, 0.22 mmol, 1.1 eq), compound **161** (53.3 mg, 0.22 mmol, 1.1 eq), DMAP (29.3 mg, 0.24 mmol, 1.2 eq), *N*-benzylmethylamine (24.2 mg, 0.20 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 2% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (42.7 mg, 62%).

$[\alpha]_D^{20}$ = −41.8 (c 3.8, $CHCl_3$).

υ_{max} (film): 2980, 2361, 1707, 1638, 1558, 1452, 1406, 1263, 1067, 735, 700.

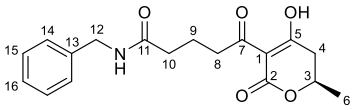
^{1}H NMR* (500 MHz, $CDCl_3$): δ 7.38 – 7.35 (m, 1H, H_{16}), 7.34 – 7.27 (m, 2H, H_{15}), 7.25 – 7.21 (m, 1H, H_{16}), 7.20 – 7.08 (m, 1H, H_{17}), 4.66 – 4.45 (m, 3H, $H_{3,13}$), 3.23 – 3.00 (m, 2H, H_8), 2.91 (s, 3H, H_{12}), 2.70 – 2.55 (m, 2H, H_4), 2.49 – 2.44 (m, 2H, H_{10}), 2.11 – 2.00 (m, 2H, H_9), 1.45 (d, *J* = 6.2 Hz, 3H, H_6).

^{13}C NMR* (126 MHz, $CDCl_3$): δ 204.3 (C_7), 194.4 (C_5), 172.4 (C_{11}), 164.4 (C_2), 137.5 (C_{14}), 129.1 (C_{15}), 128.7 (C_{16}), 128.2 (C_{16}), 127.5 (C_{15}), 126.4 (C_{17}), 103.2 (C_1), 70.5 (C_3), 50.9 (C_{13}), 39.2 (C_4), 38.5 (C_8), 34.8 (C_{12}), 32.8 (C_{10}), 20.7 (C_6), 20.2 (C_9).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{23}NO_5Na$) requires *m/z* 368.1468, found *m/z* 368.1464.

**Data of major rotamer reported (restricted rotation around amide bond).*

Compound 170m.



Prepared according to general procedure D1 using EDCI (42.2 mg, 0.22 mmol, 1.1 eq), compound **161** (53.3 mg, 0.22 mmol, 1.1 eq), DMAP (29.3 mg, 0.24 mmol, 1.2 eq), benzylamine (21.4 mg, 0.20 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 1% MeOH in CH_2Cl_2) to afford the desired product as a white solid (18.5 mg, 28%).

$[\alpha]_D^{20}$ = −34.4 (c 1.6, $CHCl_3$).

υ_{max} (film): 3306, 2928, 2359, 1707, 1645, 1545, 1454, 1261, 1065, 700.

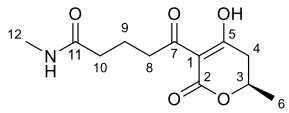
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 2H, H_{15}), 7.31 – 7.26 (m, 3H, $H_{14,16}$), 5.92 (br s, 1H, N*H*), 4.57 – 4.47 (m, 1H, H_3), 4.45 (dd, *J* = 5.7, 1.7 Hz, 2H, H_{12}), 3.20 – 3.12 (m, 1H, H_8), 3.06 – 2.96 (m, 1H, H_8), 2.69 – 2.58 (m, 2H,

H_4), 2.32 (t, *J* = 7.4 Hz, 2H, H_{10}), 2.09 – 2.00 (m, 2H, H_9), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.9 (C_7), 194.6 (C_5), 172.1 (C_{11}), 164.5 (C_2), 138.3 (C_{13}), 128.9 (C_{15}), 128.0 (C_{14}), 127.7 (C_{16}), 103.3 (C_1), 70.6 (C_3), 43.8 (C_{12}), 39.2 (C_4), 38.2 (C_8), 35.8 (C_{10}), 20.9 (C_9), 20.8 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{21}NO_5Na$) requires *m/z* 354.1312, found *m/z* 354.1312.

Compound 170n.



Prepared according to general procedure D1 using EDCI (95.9 mg, 0.50 mmol, 2.0 eq), compound **161** (66.6 mg, 0.28 mmol, 1.1 eq), DMAP (61.1 mg, 0.50 mmol, 2.0 eq), methylamine hydrochloride (16.9 mg, 0.25 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.3 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–10% MeOH in CH_2Cl_2) to afford the desired product as a white solid (27.2 mg, 43%).

$[\alpha]_D^{20}$ = −38.6 (c 3.0, $CHCl_3$).

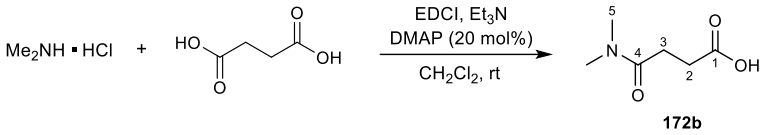
υ_{max} (film): 3287, 2936, 1703, 1641, 1550, 1412, 1265, 1070, 905.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (br s, 1H, *NH*), 4.59 – 4.45 (m, 1H, H_3), 3.16 – 3.07 (m, 1H, H_8), 3.00 – 2.92 (m, 1H, H_8), 2.79 (d, *J* = 4.8, 3H, H_{12}), 2.68 – 2.57 (m, 2H, H_4), 2.27 (t, *J* = 8.3 Hz, 2H, H_{10}), 2.04 – 1.95 (m, 2H, H_9), 1.45 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.8 (C_7), 194.7 (C_5), 172.8 (C_{11}), 164.5 (C_2), 103.2 (C_1), 70.6 (C_3), 39.2 (C_4), 38.2 (C_8), 35.7 (C_{10}), 26.4 (C_{12}), 20.9 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{18}NO_5$) requires *m/z* 256.1179, found *m/z* 256.1172.

Compound 172b.



172b

Prepared according to general procedure D2 using EDCI (388 mg, 1.84 mmol, 1.0 eq), succinic acid (652 mg, 5.52 mmol, 3.0 eq), DMAP (44.9 mg, 0.37 mmol, 20 mol%), dimethylamine hydrochloride (150 mg, 1.84 mmol, 1.0 eq), Et_3N (256 µL, 1.84 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (18.4 mL, 0.10 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (37.5 mg, 14%).

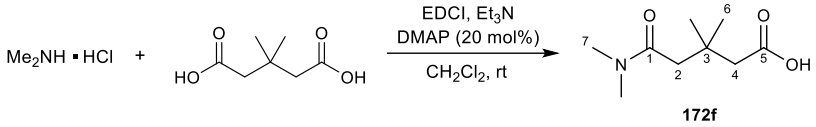
υ_{max} (film): 2932, 1728, 1616, 1402, 1261, 1151, 764.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.04 (s, 3H, H_5), 2.98 (s, 3H, H_5), 2.74 – 2.62 (m, 4H, $H_{2,3}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9 (C_1), 172.4 (C_4), 37.4 (C_5), 35.9 (C_5), 30.0 (C_2), 28.4 (C_3).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_6H_{11}NO_3Na$) requires *m/z* 168.0631, found *m/z* 168.0628.

Compound 172f.



Prepared according to general procedure D2 using EDCI (353 mg, 1.84 mmol, 1.0 eq), 3,3-dimethylglutaric acid (884 mg, 5.52 mmol, 3.0 eq), DMAP (44.9 mg, 0.37 mmol, 20 mol%), dimethylamine hydrochloride (150 mg, 1.84 mmol, 1.0 eq), Et_3N (256 µL, 1.84 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (18.4 mL, 0.10 M). The crude residue was purified by column chromatography (silica gel, 0.5–2% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (245 mg, 71%).

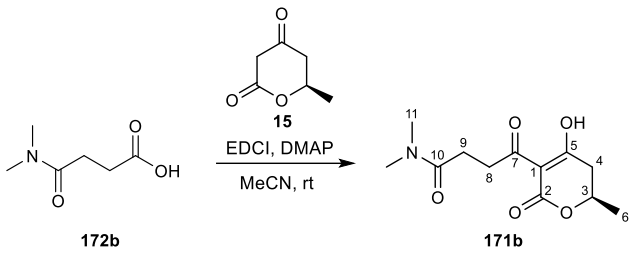
υ_{max} (film): 2963, 2361, 1720, 1582, 1404, 1234, 1107, 683.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.13 (s, 3H, H_7), 3.02 (s, 3H, H_7), 2.49 (s, 2H, H_2), 2.38 (s, 2H, H_4), 1.08 (s, 6H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8 (C_1), 172.8 (C_5), 47.5 (C_4), 41.1 (C_2), 38.8 (C_7), 36.2 (C_7), 34.7 (C_3), 29.3 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_9H_{17}NO_3Na$) requires *m/z* 210.1094, found *m/z* 210.1101.

Compound 171b.



Prepared according to general procedure B1 using EDCI (52.7 mg, 0.28 mmol, 1.1 eq), compound **15** (35.2 mg, 0.28 mmol, 1.1 eq), DMAP (33.6 mg, 0.28 mmol, 1.1 eq), compound **172b** (36.3 mg, 0.25 mmol, 1.0 eq), and anhydrous MeCN (1.3 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a pale yellow oil (9.2 mg, 14%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −115.9 (c 6.3, $CHCl_3$).

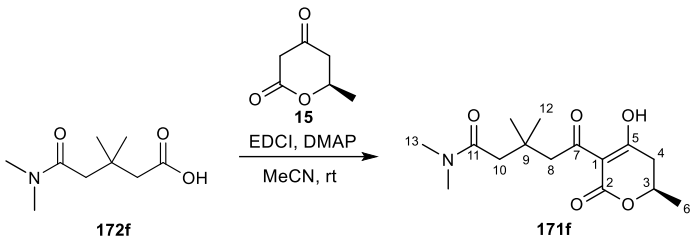
$\boldsymbol{\upsilon}_{\mathbf{max}}$ **(film)**: 2932, 2359, 1705, 1638, 1558, 1449, 1398, 1263, 1144, 1059, 905.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.58 – 4.51 (m, 1H, H_3), 3.43 – 3.31 (m, 2H, H_8), 3.05 (s, 3H, H_{11}), 2.93 (s, 3H, H_{11}), 2.78 (ddd, *J* = 16.4, 8.4, 5.0 Hz, 1H, H_9), 2.69 – 2.56 (m, 3H, $H_{4,9}$), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 204.5 (C_7), 192.5 (C_5), 171.3 (C_{10}), 164.5 (C_2), 103.5 (C_1), 70.5 (C_3), 38.4 (C_4), 37.2 (C_{11}), 35.6 (C_{11}), 34.9 (C_8), 27.3 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{18}NO_5$) requires *m/z* 256.1179, found *m/z* 256.1175.

Compound 171f.



Prepared according to general procedure B2 using EDCI (113 mg, 0.59 mmol, 1.1 eq), compound **15** (75.3 mg, 0.59 mmol, 1.1 eq), DMAP (71.8 mg, 0.59 mmol, 1.1 eq), compound **172f** (100 mg, 0.53 mmol, 1.0 eq), and anhydrous MeCN (2.7 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a yellow gum (58.4 mg, 37%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −26.0 (c 4.9, $CHCl_3$).

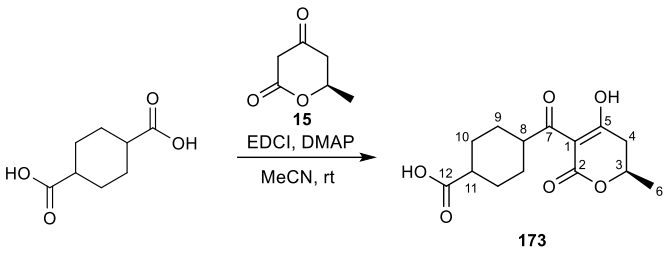
υ_{max} **(film)**: 3659, 2970, 1711, 1636, 1611, 1454, 1374, 1260, 1067, 907.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.55 – 4.48 (m, 1H, H_3), 3.37 – 3.28 (m, 2H, H_8), 3.02 (s, 3H, H_{13}), 2.92 (s, 3H, H_{13}), 2.67 – 2.58 (m, 2H, H_4), 2.52 – 2.45 (m, 2H, H_{10}), 1.45 (d, *J* = 6.4 Hz, 3H, H_6), 1.18 (s, 3H, H_{12}), 1.16 (s, 3H, H_{12}).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 203.9 (C_7), 195.0 (C_5), 171.7 (C_{11}), 164.6 (C_2), 104.6 (C_1), 70.3 (C_3), 47.0 (C_8), 42.8 (C_{10}), 39.8 (C_4), 38.1 (C_{13}), 35.5 (C_{13}), 35.1 (C_9), 28.5 (C_{12}), 28.4 (C_{12}), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{24}NO_5$) requires *m/z* 298.1649, found *m/z* 298.1645.

Compound 173.



Prepared according to general procedure B1 using EDCI (158 mg, 0.83 mmol, 1.1 eq), cyclohexane-1,4-dicarboxylic acid (150 mg, 0.75 mmol, 1.0 eq), DMAP (101 mg, 0.83 mmol, 1.1 eq), compound **15** (106 mg, 0.83 mmol, 1.1 eq), and anhydrous MeCN (3.8 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–10% MeOH in CH_2Cl_2) to afford the desired product as a yellow solid (115 mg, 54%).

$[\alpha]_D^{20}$ = −45.0 (c 4.6, $CHCl_3$).

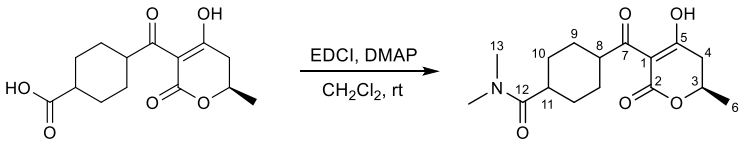
υ_{max} (film): 2934, 1701, 1560, 1452, 1408, 1067, 955, 907.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55 – 4.49 (m, 1H, H_3), 3.76 – 3.70 (m, 1H, H_8), 2.74 – 2.69 (m, 1H, H_{11}), 2.68 – 2.57 (m, 2H, H_4), 2.24 – 2.16 (m, 2H, H_{10}), 1.88 – 1.81 (m, 1H, H_9), 1.76 – 1.64 (m, 5H, $H_{9,10}$), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.3 (C_7), 195.5 (C_5), 180.6 (C_{12}), 164.3 (C_2), 102.3 (C_1), 70.4 (C_3), 43.6 (C_8), 39.5 (C_4), 39.0 (C_{11}), 26.3 (C_{10}), 26.1 (C_9 or C_{10}), 26.0 (C_{10} or C_9), 25.5 (C_9), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}O_6Na$) requires *m/z* 305.0996, found *m/z* 305.0994.

Compound 171g.



173 171g

Prepared according to general procedure D2 using EDCI (43.3 mg, 0.23 mmol, 1.1 eq), compound **173** (58.0 mg, 0.21 mmol, 1.0 eq), DMAP (30.1 mg, 0.25 mmol, 1.2 eq), dimethylamine hydrochloride (16.8 mg, 0.21 mmol, 1.0 eq), and anhydrous CH_2Cl_2 (1.0 mL, 0.20 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (38.8 mg, 61%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −40.9 (c 8.6, $CHCl_3$).

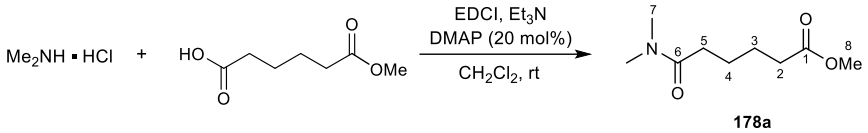
$\boldsymbol{\upsilon}_{max}$ **(film)**: 2932, 1707, 1634, 1553, 1449, 1065, 907.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.55 – 4.47 (m, 1H, H_3), 3.82 – 3.77 (m, 1H, H_8), 3.02 (s, 3H, H_{13}), 2.92 (s, 3H, H_{13}), 2.73 – 2.66 (m, 1H, H_{11}), 2.65 – 2.57 (m, 2H, H_4), 2.10 – 2.01 (m, 2H, H_9), 1.99 – 1.76 (m, 2H, H_{10}), 1.73 – 1.59 (m, 4H, $H_{9,10}$), 1.44 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 207.9 (C_7), 194.9 (C_5), 175.6 (C_{12}), 164.3 (C_2), 102.1 (C_1), 70.3 (C_3), 42.0 (C_8), 39.3 (C_4), 37.3 (C_{13}), 36.8 (C_{11}), 35.6 (C_{13}), 26.4 (C_{10} or C_9), 26.3 (C_9 or C_{10}), 26.1 (C_9), 25.4 (C_9), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{23}NO_5Na$) requires *m/z* 332.1468, found *m/z* 332.1462.

Compound 178a.



178a

Prepared according to general procedure D2 using EDCI (295 mg, 1.54 mmol, 1.1 eq), mono-methyl adipate (247 mg, 1.54 mmol, 1.1 eq), DMAP (34.2 mg, 0.28 mmol, 20 mol%), dimethylamine hydrochloride (114 mg, 1.40 mmol, 1.0 eq), Et_3N (195 µL, 1.40 mmol, 1.0 eq), anhydrous CH_2Cl_2 (7.0 mL, 0.20 M). The desired product was obtained without further purification as a colourless oil (248 mg, 95%).

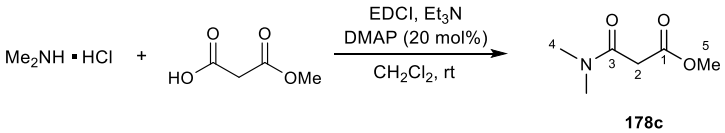
υ_{max} (film): 2949, 2363, 1732, 1639, 1437, 1196, 1171, 1136, 914, 743.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68 (s, 3H, H_8), 3.02 (s, 3H, H_7), 2.96 (s, 3H, H_7), 2.39 – 2.33 (m, 4H, $H_{2,5}$), 1.71 – 1.68 (m, 4H, $H_{3,4}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1 (C_1), 172.8 (C_6), 51.7 (C_8), 37.4 (C_7), 35.5 (C_7), 34.0 (C_2 or C_5), 33.0 (C_2 or C_5), 24.8 (C_3 or C_4), 24.7 (C_3 or C_4).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_9H_{18}NO_3$) requires *m/z* 188.1281, found *m/z* 188.1275.

Compound 178c.



178c

Prepared according to general procedure D2 using EDCI (295 mg, 1.54 mmol, 1.1 eq), 3-methoxy-3-oxopropanoic acid (182 mg, 1.54 mmol, 1.1 eq), DMAP (34.2 mg, 0.28 mmol, 20 mol%), dimethylamine hydrochloride (114 mg, 1.40

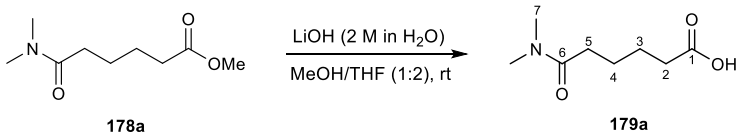
mmol, 1.0 eq), Et_3N (195 µL, 1.40 mmol, 1.0 eq), anhydrous CH_2Cl_2 (7.0 mL, 0.20 M), and stirred at rt for 3 days. The desired product was obtained without further purification as a yellow oil (167 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H, H_5), 3.46 (s, 2H, H_2), 3.02 (s, 3H, H_4), 2.98 (s, 3H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 166.0, 52.6, 41.3, 38.0, 35.7.

The spectral data were consistent with those previously reported in the literature.[84]

Compound 179a.



178a **179a**

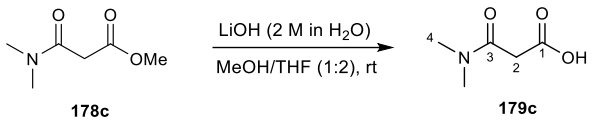
Prepared according to general procedure C using compound **178a** (238 mg, 1.27 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 5.1 mL) for 2 h. The desired product was obtained without further purification as a colourless oil (139 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (s, 3H, H_7) 2.97 (s, 3H, H_7), 2.47 – 2.25 (m, 4H, $H_{2,5}$), 1.79 – 1.57 (m, 4H, $H_{3,4}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 178.1, 173.2, 37.5, 35.7, 33.9, 33.0, 24.6, 24.5.

The spectral data were consistent with those previously reported in the literature.[85]

Compound 179c.



Prepared according to general procedure C using compound **178c** (155 mg, 1.07 mmol, 1.0 eq) and (2 M aqueous solution LiOH)/MeOH/THF (1:1:2, 4.3 mL) for 2 h. The desired product was obtained without further purification as a beige solid (62.2 mg, 44%).

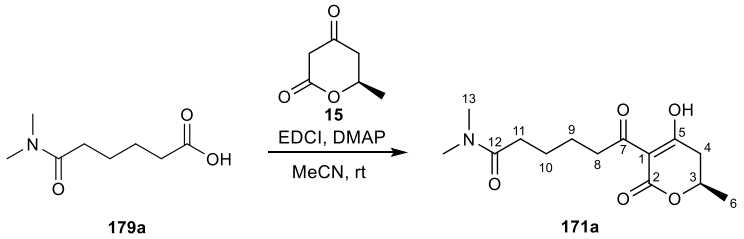
υ_{max} (film): 2920, 1702, 1603, 1506, 1398, 1246, 1144, 949, 883, 716, 637.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (s, 2H, H_2), 3.05 (s, 3H, H_4), 3.05 (s, 3H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1 (C_3), 167.9 (C_1), 37.1 (C_4), 36.0 (C_4), 34.9 (C_2).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_5H_9NO_3Na$) requires *m/z* 154.0475, found *m/z* 154.0469.

Compound 171a.



Prepared according to general procedure B1 using EDCI (122 mg, 0.64 mmol, 1.1 eq), compound **15** (81.4 mg, 0.64 mmol, 1.1 eq), DMAP (77.6 mg, 0.64 mmol, 1.1 eq), compound **179a** (100 mg, 0.58 mmol, 1.0 eq), and anhydrous MeCN (2.9 mL, 0.20 M). The crude residue was purified by column

chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (123 mg, 75%).

$[\alpha]_D^{20}$ = −60.0 (c 3.6, $CHCl_3$).

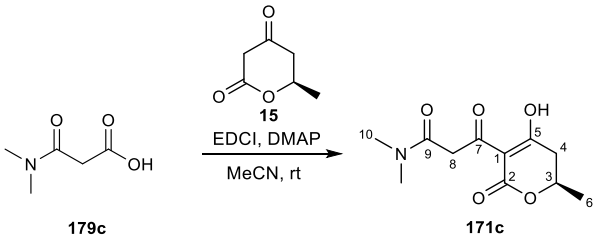
υ_{max} (film): 2934, 1711, 1641, 1458, 1265, 951, 772.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68 – 4.38 (m, 1H, H_3), 3.22 – 2.74 (m, 8H, $H_{8,13}$), 2.71 – 2.55 (m, 2H, H_4), 2.39 – 2.35 (m, 2H, H_{11}), 1.83 – 1.59 (m, 4H, $H_{9,10}$), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.3 (C_7), 194.9 (C_5), 172.9 (C_{12}), 164.4 (C_2), 103.2 (C_1), 70.5 (C_3), 39.4 (C_4), 38.4 (C_8), 37.2 (C_{13}), 35.3 (C_{13}), 33.0 (C_{11}), 24.7 ($C_{9,10}$), 20.8 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{22}NO_5Na$) requires *m/z* 306.1312, found *m/z* 306.1306.

Compound 171c.



Prepared according to general procedure B1 using EDCI (77.2 mg, 0.40 mmol, 1.1 eq), compound **15** (51.6 mg, 0.40 mmol, 1.1 eq), DMAP (49.2 mg, 0.40 mmol, 1.1 eq), compound **179c** (48.0 mg, 0.37 mmol, 1.0 eq), and anhydrous MeCN (1.8 mL, 0.20 M). The crude residue was purified by column

chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a yellow oil (60.0 mg, 68%).

$[\alpha]_D^{20}$ = −38.6 (c 5.0, $CHCl_3$).

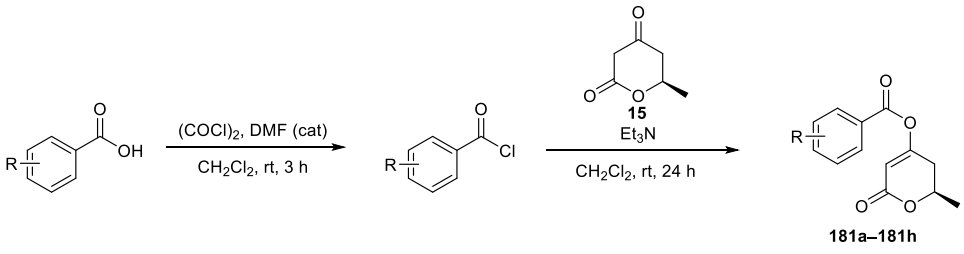
υ_{max} (film): 2936, 1709, 1645, 1612, 1396, 1263, 1067, 905, 770.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61 – 4.53 (m, 1H, H_3), 4.18 (d, *J* = 15.3 Hz, 1H, H_8), 3.93 (d, *J* = 15.3 Hz, 1H, H_8), 3.05 (s, 3H, H_{10}), 2.96 (s, 3H, H_{10}), 2.74 – 2.60 (m, 2H, H_4), 1.45 (d, *J* = 6.3 Hz, 3H, H_6).

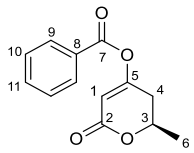
^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6 (C_7), 192.8 (C_5), 167.1 (C_9), 164.7 (C_2), 104.0 (C_1), 70.7 (C_3), 45.5 (C_8), 38.4 (C_4), 37.8 (C_{10}), 35.5 (C_{10}), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_{16}NO_5$) requires *m/z* 242.1023, found *m/z* 242.1016.

Synthesis of aromatic *O*-acyl compounds



Compound 181a.



To a solution of compound **15** (56.4 mg, 0.44 mmol, 1.1 eq) in CH_2Cl_2 (2.0 mL, 0.2 M), was added Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and the resulting mixture

was stirred at rt for 30 min. Benzoyl chloride (46.4 µL, 0.40 mmol, 1.0 eq) was then added and the resulting mixture was stirred at rt for 24 h. The reaction mixture was acidified with 1 M aqueous HCl (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford the desired product as a white solid (87.4 mg, 94%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –99.6 (c 11.0, $CHCl_3$).

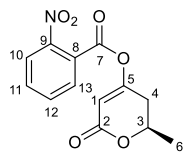
υ_{max} **(film)**: 2982, 1744, 1717, 1452, 1391, 1232, 1155, 1057, 1020, 991, 706.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.10 – 8.03 (m, 2H, H_9), 7.67 – 7.64 (m, 1H, H_{11}), 7.54 – 7.47 (m, 2H, H_{10}), 6.06 (d, *J* = 2.1 Hz, 1H, H_1), 4.76 – 4.67 (m, 1H, H_3), 2.79 (ddd, *J* = 17.6, 11.4, 2.2 Hz, 1H, H_4), 2.63 (dd, *J* = 17.6, 3.9 Hz, 1H, H_4), 1.51 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (101 MHz, $CDCl_3$): δ 165.7 (C_2), 164.4 (C_5), 163.1 (C_7), 134.6 (C_{11}), 130.4 (C_9), 129.0 (C_{10}), 128.1 (C_8) 107.3 (C_1), 73.2 (C_3), 34.3 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}O_4$) requires *m/z* 233.0808, found *m/z* 233.0801.

Compound 181b.



Prepared according to general procedure E using 2-nitrobenzoic acid (0.31 µL, 0.40 mmol, 1.0 eq), $(COCl)_2$ (40.6 µL, 0.48 mmol, 1.2 eq), DMF (2 drops), and

anhydrous CH_2Cl_2 (2.0 mL, 0.2 M), then compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M). The crude residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to afford the desired product as a white solid (87.0 mg, 78%).

$[\alpha]_D^{20}$ = –83.1 (c 9.8, $CHCl_3$).

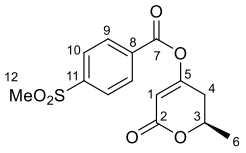
υ_{max} (film): 3009, 1761, 1721, 1533, 1350, 1279, 1234, 1132, 1155, 1057, 933, 772.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 – 7.97 (m, 1H, H_{10}), 7.85 – 7.69 (m, 3H, $H_{11,12,13}$), 6.03 (d, *J* = 2.1 Hz, 1H, H_1), 4.77 – 4.63 (m, 1H, H_3), 2.78 (ddd, *J* = 17.8, 11.3, 2.2 Hz, 1H, H_4), 2.67 (dd, *J* = 17.8, 4.2 Hz, 1H, H_4), 1.51 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4 (C_2), 163.8 (C_5), 162.1 (C_7), 147.7 (C_9), 133.9 (C_{12}), 132.9 (C_{11}), 130.3 (C_{13}), 126.3 (C_8), 124.6 (C_{10}), 107.8 (C_1), 73.4 (C_3), 33.2 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{11}O_6NNa$) requires *m/z* 300.0479, found *m/z* 300.0474.

Compound 181c.



Prepared according to general procedure E using 4-(methylsulfonyl)benzoic acid (80.1 mg, 0.40 mmol, 1.0 eq), $(COCl)_2$ (40.6 µL, 0.48 mmol, 1.2 eq), DMF (2

drops), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M), then compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (102 mg, 82%).

$[\alpha]_D^{20}$ = –62.6 (c 3.1, $CHCl_3$).

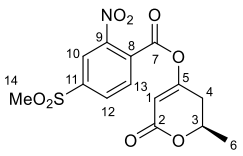
υ_{max} (film): 2982, 1749, 1717, 1398, 1300, 1258, 1234, 1151, 1059, 750.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 – 8.24 (m, 2H, H_9), 8.13 – 8.06 (m, 2H, H_{10}), 6.10 (d, *J* = 2.2 Hz, 1H, H_1), 4.77 – 4.69 (m, 1H, H_3), 3.10 (s, 3H, H_{12}), 2.81 (ddd, *J* = 17.6, 11.4, 2.2 Hz, 1H, H_4), 2.64 (dd, *J* = 17.6, 4.0 Hz, 1H, H_4), 1.52 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2 (C_2), 163.7 (C_5), 161.5 (C_7), 145.7 (C_{11}), 132.9 (C_8), 131.4 (C_9), 128.1 (C_{10}), 108.0 (C_1), 73.2 (C_3), 44.4 (C_{12}), 34.1 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{14}NaO_6S$) requires *m/z* 333.0403, found *m/z* 333.0397.

Compound 181d.



Prepared according to general procedure E using 4-(methylsulfonyl)-2-nitrobenzoic acid (98.1 mg, 0.40 mmol, 1.0 eq), $(COCl)_2$ (40.6 µL, 0.48 mmol,

1.2 eq), DMF (2 drops), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M), then compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M). The crude residue was purified by column chromatography (silica gel, 50–100% EtOAc in hexane) to afford the desired product as a yellow gum (82.0 mg, 58%).

$[\alpha]_D^{20}$ = –66.6 (c 5.7, $CHCl_3$).

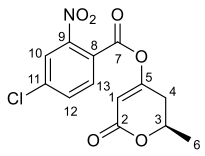
υ_{max} (film): 2926, 1763, 1717, 1541, 1233, 1148, 1038, 783.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 1.7 Hz, 1H, H_{10}), 8.36 (dd, *J* = 7.9, 1.7 Hz, 1H, H_{13}), 8.01 (d, *J* = 7.9 Hz, 1H, H_{12}), 6.05 (d, *J* = 2.2 Hz, 1H, H_1), 4.75 – 4.68 (m, 1H, H_3), 3.17 (s, 3H, H_{14}), 2.79 (ddd, *J* = 17.8, 11.4, 2.2 Hz, 1H, H_4), 2.67 (dd, *J* = 17.8, 4.0 Hz, 1H, H_4), 1.52 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.9 (C_2), 163.3 (C_5), 160.8 (C_7), 147.6 (C_9), 145.2 (C_{11}), 132.7 (C_{13}), 131.5 (C_{12}), 130.9 (C_8), 124.0 (C_{10}), 108.3 (C_1), 73.4 (C_3), 44.4 (C_{14}), 33.2 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{13}NNaO_8S$) requires *m/z* 378.0254, found *m/z* 378.0245.

Compound 181e.



Prepared according to general procedure E using 4-chloro-2-nitrobenzoic acid (94.9 µL, 0.50 mmol, 1.0 eq), $(COCl)_2$ (50.8 µL, 0.60 mmol, 1.2 eq), DMF (2

drops), and anhydrous CH_2Cl_2 (2.5 mL, 0.2 M), then compound **15** (70.5 mg, 0.55 mmol, 1.1 eq), Et_3N (105 µL, 0.75 mmol, 1.5 eq), and anhydrous CH_2Cl_2 (2.5 mL, 0.2 M). The crude residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford the desired product as a colourless oil (109 mg, 70%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –80.5 (c 7.3, $CHCl_3$).

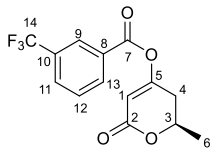
υ_{max} (film): 3092, 2984, 1757, 1715, 1539, 1350, 1231, 1134, 1036, 766.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 1.9 Hz, 1H, H_{10}), 7.78 (d, *J* = 8.2 Hz, 1H, H_{13}), 7.75 (dd, *J* = 8.3, 1.9 Hz, 1H, H_{12}), 6.03 (d, *J* = 2.2 Hz, 1H, H_1), 4.73 – 4.66 (m, 1H, H_3), 2.76 (ddd, *J* = 17.8, 11.4, 2.2 Hz, 1H, H_4), 2.63 (dd, *J* = 17.8, 4.0 Hz, 1H, H_4), 1.51 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1 (C_2), 163.5 (C_5), 161.0 (C_7), 148.6 (C_9), 139.5 (C_{11}), 133.7 (C_{12}), 131.6 (C_{13}), 124.9 (C_{10}), 124.1 (C_8), 108.0 (C_1), 73.3 (C_3), 33.2 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{10}ClNO_6Na$) requires *m/z* 334.0089, found *m/z* 334.0084.

Compound 181f.



Prepared according to general procedure E using 2-nitro-3-(trifluoromethyl)benzoic acid (76.0, 0.40 mmol, 1.0 eq), $(COCl)_2$ (40.6 µL, 0.48

mmol, 1.2 eq), DMF (2 drops), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M), then compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M). The crude residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford the desired product as a white solid (80.6 mg, 67%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –82.2 (c 7.8, $CHCl_3$).

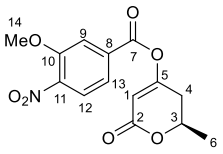
υ_{max} (film): 2924, 1749, 1719, 1333, 1223, 1157, 1134, 748.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 – 8.31 (m, 1H, H_9), 8.29 – 8.26 (m, 1H, H_{13}), 7.94 – 7.91 (m, 1H, H_{11}), 7.70 – 7.66 (m, 1H, H_{12}), 6.10 (d, *J* = 2.2 Hz, 1H, H_1), 4.78 – 4.69 (m, 1H, H_3), 2.81 (ddd, *J* = 17.6, 11.4, 2.2 Hz, 1H, H_4), 2.64 (dd, *J* = 17.6, 3.9 Hz, 1H, H_4), 1.52 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4 (C_2), 163.9 (C_5), 161.8 (C_7), 133.6 (C_{13}), 131.8 (q, $^2J_{C–F}$ = 33.2 Hz, C_{10}) 131.1 (q, $^3J_{C–F}$ = 3.1 Hz, C_{11}), 129.8 (C_{12}), 129.2 (C_8), 127.3 (q, $^3J_{C–F}$ = 3.5 Hz, C_9), 123.5 (q, $^1J_{C–F}$ = 272.7 Hz, C_{14}). 107.8 (C_1), 73.2 (C_3), 34.2 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{11}F_3O_4Na$) requires *m/z* 323.0502, found *m/z* 323.0495.

Compound 181g.



Prepared according to general procedure E using 3-methoxy-4-nitrobenzoic acid (78.9 mg, 0.40 mmol, 1.0 eq), $(COCl)_2$ (40.6 µL, 0.48 mmol, 1.2 eq), DMF (2

drops), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M), then compound **15** (56.4 mg, 0.44 mmol, 1.1 eq), Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and anhydrous CH_2Cl_2 (2.0 mL, 0.2 M). The crude residue was purified by column chromatography (silica gel, 20–50% EtOAc in hexane) to afford the desired product as a white solid (82.6 mg, 67%).

$[\alpha]_D^{20}$ = –90.0 (c 7.0, $CHCl_3$).

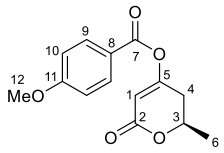
υ_{max} (film): 2920, 1751, 1711, 1528, 1281, 1207, 1155, 1016, 741.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 1H, H_9), 7.80 – 7.74 (m, 2H, $H_{12,13}$), 6.12 – 6.11 (m, 1H, H_1), 4.79 – 4.71 (m, 1H, H_3), 4.06 (s, 3H, H_{14}), 2.83 (dd, *J* = 17.6, 11.4 Hz, 1H, H_4), 2.65 (dd, *J* = 17.6, 3.9 Hz, 1H, H_4), 1.54 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2 (C_2), 163.7 (C_5), 161.4 (C_7), 152.7 (C_{10}), 143.4 (C_{11}), 132.8 (C_8), 125.7 (C_9), 122.2 (C_{12}), 115.2 (C_{13}), 108.0 (C_1), 73.2 (C_3), 57.0 (C_{14}), 34.1 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{13}NO_7Na$) requires *m/z* 330.0584, found *m/z* 330.0579.

Compound 181h.



To a solution of compound **15** (56.4 mg, 0.44 mmol, 1.1 eq) in CH_2Cl_2 (2.0 mL, 0.2 M), was added Et_3N (83.6 µL, 0.60 mmol, 1.5 eq), and the resulting mixture

was stirred at rt for 30 min. 4-Methoxybenzoyl chloride (46.4 µL, 0.40 mmol, 1.0 eq) was then added, and the resulting mixture was stirred at rt for 24 h. The reaction mixture was acidified with 1 M aqueous HCl (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford the desired product as a white solid (46.5 mg, 44%).

$[\alpha]_D^{20}$ = –75.9 (c 6.7, $CHCl_3$).

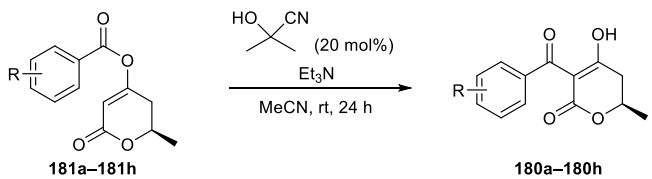
υ_{max} (film): 2980, 1713, 1603, 1252, 1150, 1022, 847, 762.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.9 Hz, 2H, H_9), 6.96 (d, *J* = 9.0 Hz, 2H, H_{10}), 6.03 (d, *J* = 2.1 Hz, 1H, H_1), 4.73 – 4.66 (m, 1H, H_3), 3.89 (s, 3H, H_{12}), 2.77 (ddd, *J* = 17.6, 11.5, 2.2 Hz, 1H, H_4), 2.62 (dd, *J* = 17.5, 3.9 Hz, 1H, H_4), 1.50 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.8 (C_2), 164.7 (C_5), 164.7 (C_{11}) 162.7 (C_7), 132.7 (C_9), 120.3 (C_8), 114.2 (C_{10}), 106.9 (C_1), 73.2 (C_3), 55.7 (C_{12}), 34.3 (C_4), 20.6 (C_6).

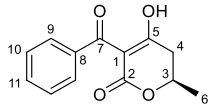
HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{14}O_5Na$) requires *m/z* 285.0733, found *m/z* 285.0726.

Synthesis of aromatic *C*-acyl compounds



181a–181h **180a–180h**

Compound 180a.



Prepared according to general procedure F using compound **181a** (46.0 mg, 0.20 mmol, 1.0 eq), Et_3N (55.2 µL, 0.40 mmol, 2.0 eq), acetone cyanohydrin (3.6 µL, 0.04 mmol, 20 mol%), and MeCN (2.0 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 30–100% EtOAc in hexane) to afford the desired product as a white solid (26.1 mg, 57%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −190.0 (c 7.6, $CHCl_3$).

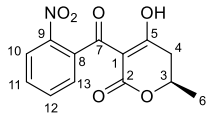
υ_{max} (film): 2980, 1713, 1599, 1570, 1447, 1404, 1260, 1125, 1045, 883, 698.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 8.4, 1.4 Hz, 2H, H_9), 7.57 – 7.53 (m, 1H, H_{11}), 7.45 – 7.40 (m, 2H, H_{10}), 4.75 – 4.68 (m, 1H, H_3), 2.79 – 2.67 (m, 2H, H_4), 1.52 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 196.8 (C_7), 193.5 (C_5), 164.3 (C_2), 135.9 (C_8), 133.0 (C_{11}), 129.0 (C_9), 128.1 (C_{10}), 103.0 (C_1), 70.8 (C_3), 39.1 (C_4), 20.5 (C_6).

HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{12}O_4Na$) requires *m/z* 255.0628, found *m/z* 255.0627.

Compound 180b.



Prepared according to general procedure F using compound **181b** (42.0 mg, 0.15 mmol, 1.0 eq), Et_3N (42.2 µL, 0.30 mmol, 2.0 eq), acetone cyanohydrin (2.8 µL, 0.03 mmol, 20 mol%), and MeCN (1.5 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 1% MeOH in CH_2Cl_2) to afford the desired product as a white solid (26.0 mg, 62%).

$[\alpha]_D^{20}$ = –61.1 (c 4.7, $CHCl_3$).

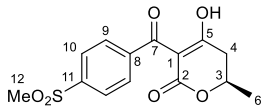
υ_{max} (film): 2982, 1713, 1599, 1574, 1526, 1348, 1310, 1260, 905, 712.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (dd, *J* = 8.3, 1.1 Hz, 1H, H_{10}), 7.74 – 7.71 (m, 1H, H_{12}), 7.63 – 7.59 (m, 1H, H_{11}), 7.32 (dd, *J* = 7.6, 1.4 Hz, 1H, H_{13}), 4.63 – 4.56 (m, 1H, H_3), 2.84 – 2.71 (m, 2H, H_4), 1.46 (d, *J* = 6.4 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 197.4 (C_7), 190.7 (C_5), 163.3 (C_2), 145.7 (C_9), 135.0 (C_8), 134.2 (C_{12}), 130.5 (C_{11}), 127.4 (C_{13}), 124.1 (C_{10}), 103.6 (C_1), 70.9 (C_3), 37.4 (C_4), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{13}H_{10}NO_6$) requires *m/z* 276.0514, found *m/z* 276.0515.

Compound 180c.



Prepared according to general procedure F using compound **181c** (50.0 mg, 0.16 mmol, 1.0 eq), Et_3N (44.9 µL, 0.32 mmol, 2.0 eq), acetone cyanohydrin (2.9 µL, 0.03 mmol, 20 mol%), and MeCN (1.6 mL, 0.1 M). The crude residue was

purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a white solid (45.7 mg, 91%).

$[\alpha]_D^{20}$ = –52.8 (c 6.0, DMSO).

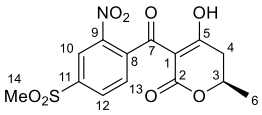
υ_{max} **(film)**: 2926, 2361, 1709, 1603, 1558, 1302, 1150, 772.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 2H, H_{10}), 7.77 (d, *J* = 8.3 Hz, 2H, H_9), 4.77 – 4.68 (m, 1H, H_3), 3.08 (s, 3H, H_{12}), 2.78 (d, *J* = 7.4 Hz, 2H, H_4), 1.53 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}**C NMR** (126 MHz, $CDCl_3$): δ 196.0 (C_7), 193.6 (C_5), 164.0 (C_2), 143.5 (C_{11}), 141.4 (C_8), 129.5 (C_9), 127.3 (C_{10}), 103.4 (C_1), 71.1 (C_3), 44.7 (C_{12}), 38.6 (C_4), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M–H]^-$ ($C_{14}H_{13}O_6$) requires *m/z* 309.0438, found *m/z* 309.0442.

Compound 180d.



Prepared according to general procedure F using compound **181d** (40.0 mg, 0.11 mmol, 1.0 eq), Et_3N (31.4 µL, 0.23 mmol, 2.0 eq), acetone cyanohydrin (2.1 µL, 0.02 mmol, 20 mol%), and MeCN (1.1 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (21.6 mg, 54%).

$[\alpha]_D^{20}$ = –28.4 (c 5.7, $CHCl_3$).

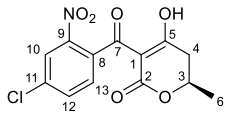
υ_{max} (film): 2924, 2853, 1711, 1568, 1535, 1354, 1317, 1163, 1145, 770.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 1.7 Hz, 1H, H_{10}), 8.28 (dd, *J* = 8.0, 1.7 Hz, 1H, H_{13}), 7.54 (d, *J* = 8.0 Hz, 1H, H_{12}), 4.67 – 4.57 (m, 1H, H_3), 3.15 (s, 3H, H_{14}), 2.89 – 2.75 (m, 2H, H_4), 1.48 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.7 (C_7), 190.5 (C_5), 163.4 (C_2), 146.0 (C_9), 142.8 (C_{11}), 139.7 (C_8), 132.9 (C_{13}), 128.8 (C_{12}), 123.6 (C_{10}), 103.5 (C_1), 71.2 (C_3), 44.6 (C_{14}), 37.1 (C_4), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{12}NO_8S$) requires *m/z* 354.0289, found *m/z* 354.0293.

Compound 180e.



Prepared according to general procedure F using compound **181e** (65.0 mg, 0.21 mmol, 1.0 eq), Et_3N (58.1 µL, 0.42 mmol, 2.0 eq), acetone cyanohydrin (3.81 µL, 0.04 mmol, 20 mol%), and MeCN (2.1 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a colourless oil (31.7 mg, 49%).

$[\alpha]_D^{20}$ = –41.4 (c 5.9, $CHCl_3$).

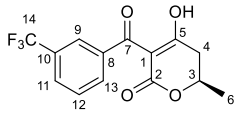
υ_{max} (film): 2924, 1709, 1562, 1531, 1348, 1310, 897.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 2.0 Hz, 1H, H_{10}), 7.68 (dd, *J* = 8.2, 2.0 Hz, 1H, H_{12}), 7.27 (d, *J* = 8.1 Hz, 1H, H_{13}), 4.62 – 4.56 (m, 1H, H_3), 2.86 – 2.71 (m, 2H, H_4), 1.46 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 196.3 (C_7), 190.7 (C_5), 163.3 (C_2), 146.4 (C_9), 136.5 (C_8), 134.2 (C_{12}), 133.3 (C_{11}), 128.6 (C_{13}), 124.3 (C_{10}), 103.5 (C_1), 71.0 (C_3), 37.3 (C_4), 20.7 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{13}H_9ClNO_6$) requires *m/z* 310.0124, found *m/z* 310.0126.

Compound 180f.



Prepared according to general procedure F using compound **181f** (65.0 mg, 0.22 mmol, 1.0 eq), Et_3N (60.4 µL, 0.44 mmol, 2.0 eq), acetone cyanohydrin (4.0 µL, 0.04 mmol, 20 mol%), and MeCN (2.2 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (31.3 mg, 48%).

$[\alpha]_D^{20}$ = −133.0 (c 3.7, $CHCl_3$).

υ_{max} (film): 2922, 2853, 1717, 1616, 1558, 1333, 1126, 1072.

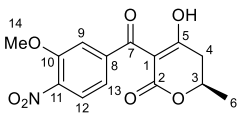
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (br s, 1H, H_9), 7.81 – 7.77 (m, 2H, $H_{11,13}$), 7.57 – 7.53 (m, 1H, H_{12}), 4.76 – 4.70 (m, 1H, H_3), 2.79 – 2.74 (m, 2H, H_4), 1.54 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 195.9 (C_7), 193.5 (C_5), 163.9 (C_2), 137.0 (C_8), 132.2 (C_{13}), 130.7 (q, $^2J_{C–F}$ = 33.0 Hz, C_{10}) 129.2 (q, $^3J_{C–F}$ = 3.7 Hz, C_{11}), 128.5 (C_{12}), 125.7 (q, $^3J_{C–F}$ = 3.9 Hz, C_9), 123.8 (d, $^1J_{C–F}$ = 272.5 Hz, C_{14}), 103.0 (C_1), 70.8 (C_3), 38.7 (C_4), 20.6 (C_6).

^{19}F NMR (376 MHz, $CDCl_3$) δ −62.74.

HRMS (ESI): exact mass calculated for $[M–H]^-$ ($C_{14}H_{10}F_3O_4$) requires *m/z* 299.0537, found *m/z* 299.0534.

Compound 180g.



Prepared according to general procedure F using compound **181g** (70.0 mg, 0.23 mmol, 1.0 eq), Et_3N (63.5 µL, 0.46 mmol, 2.0 eq), acetone cyanohydrin (4.2 µL, 0.05 mmol, 20 mol%), and MeCN (2.3 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 0–2% MeOH in CH_2Cl_2) to afford the desired product as a white solid (30.1 mg, 44%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −136.8 (c 5.0, $CHCl_3$).

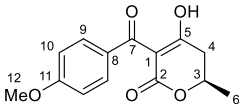
υ_{max} (film): 2976, 1713, 1584, 1522, 1354, 1263, 1024, 851.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 1H, H_{12}), 7.31 (d, *J* = 1.7 Hz, 1H, H_9), 7.21 (dd, *J* = 8.3, 1.7 Hz, 1H, H_{13}), 4.76 – 4.68 (m, 1H, H_3), 3.99 (s, 3H, H_{14}), 2.82 – 2.76 (m, 2H, H_4), 1.54 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 195.6 (C_7), 193.3 (C_5), 163.6 (C_2), 152.6 (C_{10}), 141.6 (C_{11}), 141.6 (C_8) 125.2 (C_{12}), 120.6 (C_{13}), 113.7 (C_9), 103.3 (C_1), 70.9 (C_3), 56.9 (C_{14}), 38.5 (C_4), 20.6 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{12}NO_7$) requires *m/z* 306.0619, found *m/z* 306.0616.

Compound 180h.



Prepared according to general procedure F using compound **181h** (40.0 mg, 0.15 mmol, 1.0 eq), Et_3N (42.5 µL, 0.31 mmol, 2.0 eq), acetone cyanohydrin (2.8 µL, 0.03 mmol, 20 mol%), and MeCN (1.5 mL, 0.1 M). The crude residue was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2) to afford the desired product as a white solid (17.6 mg, 44%).

$[\alpha]_D^{20}$ = −127.5 (c 7.1, $CHCl_3$).

υ_{max} **(film)**: 2936, 1707, 1601, 1254, 1175, 1024, 843.

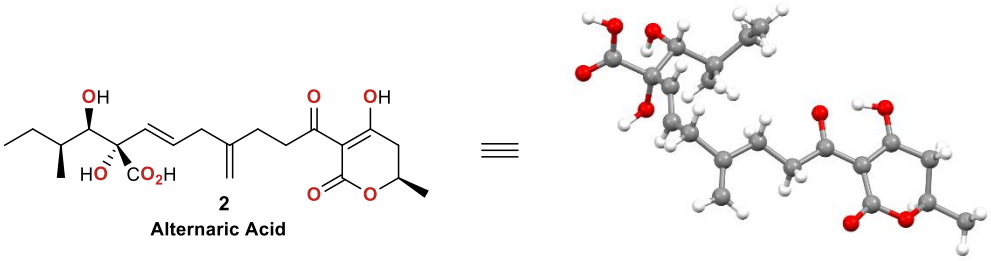
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H, H_9), 6.94 – 6.88 (m, 2H, H_{10}), 4.76 – 4.66 (m, 1H, H_3), 3.87 (s, 3H, H_{12}), 2.75 – 2.66 (m, 2H, H_4), 1.52 (d, *J* = 6.3 Hz, 3H, H_6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 194.9 (C_7), 193.5 (C_5), 164.8 (C_2), 164.0 (C_{11}), 132.0 (C_9), 127.7 (C_8), 113.5 (C_{10}), 102.3 (C_1), 70.7 (C_3), 55.6 (C_{12}), 39.3 (C_4), 20.5 (C_6).

HRMS (ESI): exact mass calculated for $[M-H]^-$ ($C_{14}H_{13}O_5$) requires *m/z* 261.0768, found *m/z* 261.0771.

5.4 X-Ray data

The data for Alternaric acid **2** were collected using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer. CCDC 2169366 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/structures.



Crystal data

Identification code	1
Empirical formula	$C_{21}H_{30}O_8$
Formula weight	410.46
Temperature/K	125
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.8310(3)
b/Å	5.4679(2)
c/Å	24.6153(17)
α/°	90.0000
β/°	97.383(5)
γ/°	90.0000
Volume/Å^3	1045.27(9)
Z	2
ρ_{calc}g/cm^3	1.304
μ/mm^{-1}	0.833
F(000)	440.0
Crystal size/mm^3	0.150 × 0.100 × 0.010
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	3.62 to 151
Index ranges	−9 ≤ h ≤ 9, −6 ≤ k ≤ 6, −30 ≤ l ≤ 30
Reflections collected	11153
Independent reflections	3819 [R_{int} = 0.0607, R_{sigma} = 0.0341]
Data/restraints/parameters	3819/5/282
Goodness of fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0553, wR_2 = 0.1590
Final R indexes [all data]	R_1 = 0.0661, wR_2 = 0.1729
Largest diff. peak/hole / e Å^{-3}	0.27/−0.25
Flack parameter	−0.1(3)

5.5 Biological data

In this section, full tabular data for the biological data presented in charts 1–13 in section **3.** can be found below.

5.5.1 Glasshouse testing 1 (GH1)

In GH1, compounds are tested for pre- and post-emergence against four weed species with the compound applied at a rate of 1000 g/ha. Phytotoxicity is assessed visually (0–100% where complete control of the target is 100 and 0 is no control). Known commercial herbicides (Acetochlor, Atrazine, Mesotrione, Pinoxaden, and Glyphosate) were used as positive controls for the test. Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), and *Digitaria sanguinalis* (DIGSA). Symptoms: NC = necrosis, ST= stunting, BL = bleaching, CL = chlorosis, and MR = morphological response.

		Post-emergence				Pre-emergence				
Compound	Rate(g/ha)	AMARE	LOLPE	STEME	DIGSA	AMARE	LOLPE	STEME	DIGSA	Symptom
2	1000	100	10	80	90	100	0	60	0	NC/ST
118	1000	0	0	0	0	0	0	0	0	–
119	1000	20	0	30	0	20	0	0	0	BL/ST
120	1000	0	0	0	0	0	0	0	0	–

Table 11: GH1 evaluation of Alternaric acid and preliminary analogues

		Post-emergence				Pre-emergence				
Compound	Rate(g/ha)	AMARE	LOLPE	STEME	DIGSA	AMARE	LOLPE	STEME	DIGSA	Symptom
2	1000	100	10	80	90	100	0	60	0	NC/ST
130a	1000	100	0	50	70	60	0	0	0	NC/ST
130b	1000	100	0	50	80	100	0	20	0	NC/ST
130c	1000	100	10	80	60	80	0	30	0	NC/ST
130d	1000	100	0	40	40	50	0	0	0	NC/ST
130e	1000	100	0	20	50	0	0	0	0	NC/ST

Table 12: GH1 evaluation Alternaric acid derivatives

		Post-emergence				Pre-emergence				
Compound	Rate(g/ha)	AMARE	LOLPE	STEME	DIGSA	AMARE	LOLPE	STEME	DIGSA	Symptom
2	1000	100	10	80	90	100	0	60	0	NC/ST
131	1000	20	0	0	20	0	0	0	60	ST/CL
132	1000	60	0	0	0	0	0	0	60	NC/BL
133	1000	40	0	40	0	0	0	0	0	BL/NC
134	1000	50	0	40	60	40	0	50	0	BL/ST
135	1000	60	0	30	0	0	0	40	0	BL/ST
136	1000	30	0	0	0	0	0	0	0	MR
137	1000	30	0	30	30	0	0	0	0	ST/CL
138	1000	50	0	0	0	0	0	0	0	NC
139	1000	0	0	0	0	0	0	0	0	–
140	1000	20	0	30	20	0	0	0	0	NC
141	1000	60	0	0	0	0	0	0	0	NC
143	1000	0	0	0	0	0	0	0	0	–
144	1000	40	0	40	20	0	0	0	0	BL/ST
145	1000	40	40	20	0	0	0	0	0	BL/NC
146	1000	0	0	0	0	0	0	0	0	–
147	1000	0	0	0	0	0	0	0	0	–
148	1000	30	30	40	50	0	0	0	0	BL/NC
149	1000	20	0	20	20	0	0	50	30	CL/ST
150	1000	50	0	50	20	0	0	0	0	BL/CL
151	1000	20	0	20	40	0	0	0	0	BL/CL
152	1000	100	90	100	100	50	80	80	100	BL/NC
153	1000	80	30	70	70	0	20	60	0	NC/BL
154	1000	0	0	0	0	0	0	0	0	–

Table 13: GH1 evaluation of Alternaric acid tail analogues

		Post-emergence				Pre-emergence				
Compound	Rate(g/ha)	AMARE	LOLPE	STEME	DIGSA	AMARE	LOLPE	STEME	DIGSA	Symptom
152	1000	100	90	100	100	50	80	80	100	BL/NC
170a	1000	40	0	30	0	40	10	0	0	BL/ST
170b	1000	80	20	60	90	0	20	20	30	BL/ST
170c	1000	100	50	80	100	40	30	0	30	BL/ST
170d	1000	40	30	20	60	20	20	20	20	BL/ST
170e	1000	60	30	30	70	30	30	0	0	BL/ST
170f	1000	30	30	60	100	60	20	10	30	BL/ST
170g	1000	40	40	50	100	0	30	0	20	BL/ST
170h	1000	50	20	30	90	0	0	0	0	BL/ST
170i	1000	90	50	100	100	60	50	0	30	BL/ST
170j	1000	60	20	30	70	0	0	0	0	BL/ST
170k	1000	60	20	90	100	60	0	0	50	BL/ST
170l	1000	60	20	30	90	0	30	0	0	BL/ST
170m	1000	40	0	0	0	50	0	0	0	ST/BL
170n	1000	60	40	40	70	20	40	20	0	BL/ST
171a	1000	70	70	80	80	20	40	70	40	BL/ST
171b	1000	40	0	40	30	20	0	50	30	BL/ST
171c	1000	0	0	0	0	0	0	0	0	–
171f	1000	30	20	30	50	10	20	60	10	BL/ST
171g	1000	30	0	10	20	0	0	70	0	ST/CL

Table 14: GH1 evaluation of amide and linker variants of 152

		Post-emergence				Pre-emergence				
Compound	Rate(g/ha)	AMARE	LOLPE	STEME	DIGSA	AMARE	LOLPE	STEME	DIGSA	Symptom
Mesotrione	1000	100	20	100	100	100	10	90	100	NC/BL
180a	1000	50	20	30	40	0	0	0	0	BL/ST
180b	1000	70	60	30	60	80	70	60	20	BL/ST
180c	1000	20	0	20	30	20	0	0	0	CL
180d	1000	100	0	100	70	100	0	90	30	BL/ST
180e	1000	80	50	70	70	100	80	80	100	BL/ST
180f	1000	0	0	0	20	20	0	0	0	ST
180g	1000	20	0	0	20	0	0	0	0	CL
180h	1000	0	0	0	0	0	0	0	0	/

Table 15: GH1 evaluation of Mesotrione-Alternaric acid crossover analogues

5.5.2 Early profiling screen (EPS)

In EPS, compounds are tested for pre- and post-emergence against six weed species with the compound applied at different rates (250–1000 g/ha). Phytotoxicity is assessed visually (0–100% where complete control of the target is 100 and 0 is no control). Known commercial herbicides (Acetochlor, Atrazine, Mesotrione, Pinoxaden, and Glyphosate) were used as positive controls for the test. Test species: *Amaranthus retroflexus* (AMARE), *Amaranthus palmeri* (AMAPA), *Solanum nigrum* (SOLNI), *Setaria faberi* (SETFA), *Lolium perenne* (LOLPE), *Echinochloa crus-galli* (ECHCG), *Zea mays* (ZEAMX), and *Ipomoea hederacea* (IPOHE). Symptoms: NC = necrosis, ST= stunting, BL = bleaching, and CL = chlorosis, GI = germination inhibition.

	Rate(g/ha)	AMARE	SOLNI	SETFA	LOLPE	ECHCG	IPOHE	Symptom
Post-emergence	1000	80	70	20	10	50	40	ST/NC
	500	50	60	0	10	30	20	
	250	20	30	0	0	10	0	
Pre-emergence	1000	20	30	10	10	0	0	GI
	500	30	50	0	0	0	10	
	250	30	30	10	0	0	0	

Table 16: EPS evaluation of Alternaric acid

Post-emergence

Compound	Rate(g/ha)	AMARE	AMAPA	SETFA	ECHCG	ZEAMX	IPOHE	Symptom
152	1000	80	90	90	80	40	30	BL/CL
	500	60	40	30	30	50	0	
	250	50	30	30	50	20	0	
170c	1000	80	70	60	30	70	10	BL/CL
	500	90	60	40	30	40	20	
	250	60	50	30	10	20	10	
170k	1000	60	70	70	40	10	70	NC/ST
	500	50	50	20	10	0	60	
	250	30	40	10	0	10	0	

Table 17: EPS post-emergence evaluation of most promising compounds

Pre-emergence

Compound	Rate(g/ha)	AMARE	AMAPA	SETFA	ECHCG	ZEAMX	IPOHE	Symptom
152	1000	50	70	50	80	0	0	BL/CL
	500	30	30	10	10	0	0	
	250	0	20	0	0	0	0	
170c	1000	80	80	60	40	30	10	BL/CL
	500	0	30	0	10	20	0	
	250	0	0	0	10	0	0	
170k	1000	20	50	10	10	0	0	BL/CL
	500	10	20	0	10	0	0	
	250	0	0	0	0	0	0	

Table 18: EPS pre-emergence evaluation of most promising compounds

5.5.3 HPPD assay

The HPPD coupled assay involves two enzymes, 4-hydroxyphenylpyruvate dioxygenase and homogentisic acid oxidase, which are both from *Arabidopsis thaliana* and are recombinantly expressed in *E. coli*. HPPD. The compounds are incubated for 10 minutes, and 4-hydroxyphenylpyruvate is used to start the reaction. The end product of the coupled assay is maleylacetoacetate, which can be detected at 330 nm on a plate reader. The plate is read at 0 and 30 minutes. In this assay the half maximal inhibitory concentration (IC_{50}) is recorded. This value is a measure of the potency of the tested compounds in inhibiting the HPPD protein. The IC_{50} is the concentration of compound required for 50% inhibition of the target.[77] The commercial HPPD inhibitor herbicide Sulcotrione is used as a control in this assay.

Compound	IC_{50} (ppm)	Sulcotrione ref IC_{50} (ppm)
2	0.422	0.034
152	0.950	0.034
180a	2.91	0.034
180b	8.82	0.034
180c	0.17	0.034
180d	0.02	0.034
180e	0.9	0.034
180f	0.71	0.034
180g	0.18	0.034
180h	0.14	0.034

Table 19: Evaluation of HPPD inhibition of relevant compounds

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