The Development of Natural Products as Phytotoxic Leads for Herbicide Discovery

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Publication List

1. "*Synthetic Approaches to Coronafacic Acid, Coronamic Acid, and Coronatine*" Mairi M. Littleson, Claire J. Russell, Elizabeth C. Frye, Kenneth B. Ling, Craig Jamieson, and Allan J. B. Watson, *Synthesis* **2016**, *48,* A-T

2. "*Comprehensive Phytotoxic SAR Analysis of Coronatine Enabled by Scalable Synthesis"* Mairi M. Littleson, Elizabeth C. Frye, Claire J. Russell, Matthew M. McLachlan, Kenneth B. Ling, Chris M. Baker, Alan R. Kennedy, Craig Jamieson, and Allan J. B. Watson, *manuscript in preparation.*

Abstract

Effective agrochemicals are essential to maintaining sustainable agriculture to support a growing population. Herbicide resistance is an ever increasing problem, and in order to combat this there is a requirement for the introduction of new herbicidal agents with novel modes of action. Natural products serve as an abundant source of structurally diverse phytotoxins, which typically have novel modes of action in comparison with their synthetic counterparts.

The natural product coronatine (COR), isolated from *Pseudomonas syringae*, has been a compound of interest to the agrochemical community since its isolation and elucidation of its phytotoxic properties. Through the industry/academia collaboration described in this thesis, coronatine is now a tractable target for a structure-activity relationship (SAR) campaign.

Through the development of a scalable synthesis of the COR polyketide fragment, coronafacic acid (CFA), a diverse array of *N*-coronafacoyl-amino acid analogues were synthesised. The inherent flexibility of the synthesis, imparted by its convergent nature, has enabled the synthesis of several CFA analogues, featuring single point changes to the parent scaffold. In the complementary study, scalable synthesis of the COR amino acid moiety, coronamic acid (CMA), enabled diverse screening of analogues where the core moiety was varied.

Through the biological evaluation of these compounds, an SAR for herbicidal activity around the COR scaffold has been identified. Initial efforts focused on modification of the amino acid component, however work in this area failed to afford any compounds of significant activity. Retention of the COR amino acid moiety, CMA, with modification of the CFA core has generated several COR analogues with good levels of potency. On analysis of this data set and supporting computational docking, we have concluded that the key convenor of potency in COR is the amino acid fragment, CMA. The CFA moiety appears to be comparatively more amenable to structural modification with the retention of potency, and we suggest that further SAR studies of the COR scaffold focus on analogues of this unit.

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Abbreviations

ABUTH	*Abutilon theophrasti*
Ac	Acyl
ACCs	Aminocyclopropane carboxylic acids
ALB	Aluminium lithium bis(binaphthoxide) complex
AMARE	*Amaranthus retroflexus*
app.	Apparent
aq.	Aqueous
BIDPI	*Bidens pilosa*
BINOL	1,1'-Bi-2-naphthol
BL	Bleaching
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
BTAC	Benzyltriethylammonium chloride
CA	Conjugate addition
CDI	1,1’-Carbonyldiimidazole
CFA	Coronafacic acid
Cfl	Coronafacate ligase
CHEAL	*Chenopodium album*
CMA	Coronamic acid
COI1	COR-insensitive 1
COR	Coronatine
COR-MO	COR methyl oxime
DA	Diels–Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIC	*N,N'*-Diisopropylcarbodiimide
DMF	Dimethylformamide
DMP	Dess-Martin periodinane

DIGSA	*Digitaria sanguinalis*
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
ECHCG	*Echinochloa crus-galli*
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ELEIN	*Eleusine indica*
Equiv	Equivalents
EWG	Electron withdrawing group
GH1	Glasshouse screen one
GH2	Glasshouse screen two
GI	Germination inhibition
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HB	Haller-Bauer
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	High performance liquid chromatography
HPPD	*p*-Hydroxyphenylpyruvate dioxygenase
IC	Intramolecular cyclisation
IMDA	Intramolecular Diels–Alder
JA	Jasmonic acid
JA-Ile	(+)-7-*iso*-Jasmonoyl-*L*-isoleucine
JAZ	Jasmonate ZIM-domain proteins
KCHSC	*Kochia scoparia*
LDA	Lithium diisopropylamide
LOLPE	*Lolium perenne*
MOA	Mode of action
MR	Morphological effects
NC	Necrosis
NMR	Nuclear magnetic resonance
OC	oxy-Cope

PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PFP	Pentafluorophenyl
p-NB	*p*-Nitrobenzene
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
RCM	Ring closing metathesis
RT	Room temperature
SA	Salicylic acid
SAR	Structure-activity relationship
SCF^{COI1}	Skp/Cullin/F-box complex
SETFAL	*Setaria faberi*
SORHA	*Sorghum halepense*
ST	Stunting
STEME	*Stellaria media*
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*t*-Butyldimethylsilyl
TCICA	Trichloroisocyanuric acid
THF	Tetrahydrofuran
THP	Tetrahydropyran

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1 Introduction

1.1 Agrochemicals

Effective agrochemicals are essential to maintaining sustainable agriculture to support a growing population.[1] It has been projected that global food requirements will increase by 70-100% by 2050,[2] and estimated that without crop protection products currently attained crop yields would be reduced by 50%.[3] Therefore the continued development of new, more effective agrochemicals is vital to meet agricultural demands.[1,4,5]

Agrochemicals can be subdivided into three categories depending on their target class; insecticides, fungicides, and herbicides. This thesis will focus on the development of the phytotoxic natural product coronatine and coronatine mimics as herbicidal leads.

Synthetic herbicides are currently used in all major field crops. Herbicides can be defined as crop protection products which act to control undesired vegetation, and are heavily relied upon globally for effective weed control.[6]

Following the success of the herbicide industry in the 1970s and 80s, when a number of vital herbicidal agents with novel modes of action (MOA) were discovered and commercialised, the development of new herbicides has slowed significantly.[4,6] This decline has partly been attributed to increasing regulatory pressures, coupled with rising research and development costs in a competitive market saturated with generic products.[6] The emergence of weed resistance to established phytotoxin classes has also been cited as a key factor.[4,5]

Herbicide resistance is a significant issue facing the agrochemical industry. Resistance has evolved with the widespread use of commercial herbicides,[7] and resistance towards phytotoxins of all currently targeted MOAs have been reported.[8] In order to combat increasing resistance, new phytotoxic agents with novel MOAs are required.[6] Commercial herbicides currently exploit roughly twenty MOAs, and this figure has not increased in the last thirty years.[9] Furthermore, of these twenty MOAs, six currently dominate 80% of the market.[3]

With respect to these findings, continued research into the development of effective, safe, and cost effective herbicides is essential. A variety of sources can be used to identify new starting points for agrochemical discovery, including the screening of compound libraries against an identified target, competitor patents, and natural phytotoxins (Figure 1).[5]

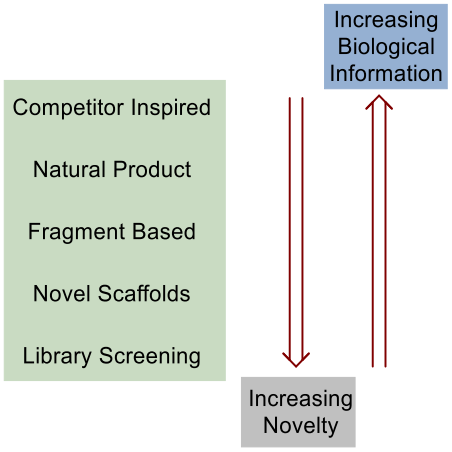


Figure 1: Selected approaches for the identification of leads in agrochemical discovery.[5]

Each approach can be associated with perceived benefits and drawbacks. Competitor inspired and natural product-based leads have established biological activity against a given target, which is highly advantageous in an early stage discovery project, however this often comes with the caveat of reduced novelty. Library screening and fragment-based methods often produce hits accessing novel chemical space, however typically confer low levels of potency and insufficient SAR information to be informative to initial development campaigns.[5]

1.2 Natural Products in Herbicide Development

The identification of phytotoxic natural products has served as an abundant source of novel compounds for agrochemical development. In comparison with insecticidal and fungicidal examples, there are a limited number of natural product-based herbicides which have been commercialised, totalling only 10% of the market.[10]

Natural products typically provide molecular architecture of greater complexity with respect to synthetic compounds. The high degree of structural variance offered, alongside their established biological activity make natural phytotoxins attractive starting points for development (Figure 2).[11]

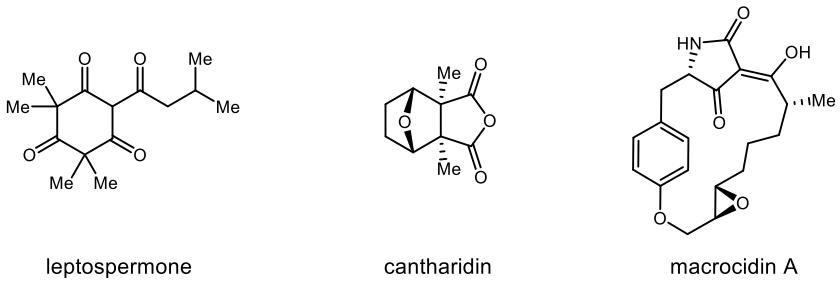


Figure 2: Selected natural products possessing phytotoxic activity, demonstrating their structural variance.

Compound design deriving from a natural product scaffold can be expected to access biologically relevant chemical space,[12] however the structural complexity offered by natural product motifs comes with the caveat of the requirement for extended, and ultimately costly, synthesis campaigns to obtain the active compound synthetically.[13] Furthermore, the biologically optimised natural product structure may have little scope for structural simplification with the retention or enhancement of potency, or for improvement of physicochemical properties.[5,14] There are several examples in the published literature where attempts to simplify a phytotoxic natural product structure have failed to result in a compound possessing sufficient biological activity.[14] Despite this, there are examples where lead optimisation of a natural product has been successful, producing a marketed herbicide (See leptospermone example).

As mentioned above, resistance to traditionally used herbicides is an ever increasing problem, which highlights the need for the development of novel herbicides with new target sites and MOAs.[15] Marketed natural product-derived herbicides have typically acted at target sites which were not utilised by commercial herbicides prior to their introduction.[13] In this regard, the development of natural phytotoxins as herbicidal leads can be viewed favourably,[14] as they often allow the targeting of novel target sites with respect to synthetic phytotoxins.[16]

Furthermore, natural product derived herbicides are generally perceived by thepublic as being more environmentally friendly than their synthetic counterparts, typically possessing shorter half-lives, which may promote greater acceptance and consumer uptake of a new herbicide;[14] however, there is limited evidence to support this viewpoint,[13] and natural products with excessively short half-lives may be challenging to develop into a successful marketable product.[14]

Leptospermone

As a case example, leptospermone can be viewed as a successful development of a phytotoxic natural product lead to marketed herbicide. Isolated from the bottlebrush plant (*Callistemon spp*.) and acting on what was then a novel herbicide target, the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD),[17] leptospermone was viewed as an attractive hit compound for a herbicide discovery programme. Analogue synthesis and SAR mapping around the triketone scaffold has enabled the production of a family of leptospermone derived herbicides.

Mesotrione is a leptospermone derived herbicide developed by Syngenta (Figure 3).

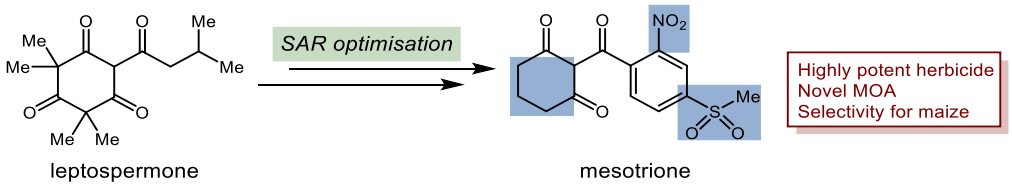


Figure 3: Optimisation of the leptospermone skeleton to mesotrione, highlighting key areas of SAR development.

Following a campaign of SAR development around the natural product scaffold, a number of structural features were identified as conferring herbicidal activity. Introduction of the substituted benzoyl motif was found serendipitously, and an electron-withdrawing group (EWG) at the *ortho*-position of the aromatic ring was shown to be essential for herbicidal activity. A second EWG in the *para*-position was typically beneficial for potency across a series of analogues and the unsubstituted cyclohexanedione moiety gave the desired maize selectivity.[18]

In this example, development of a natural product scaffold allowed the discovery of a herbicidal agent which is more potent than the parent compound, and displays selectivity not observed with leptospermone. The identification of HPPD as a novel and valid herbicide target site represented a new MOA, which enabled the development of a family of phytotoxic agents.[19]

Overall, phytotoxic natural product leads represent an attractive starting point for agrochemical discovery, offering tuned structural scaffolds known to deliver potency, and often enabling the targeting of a novel herbicidal MOA.

1.3 Coronatine

Coronatine (COR) (**1**) is a natural phytotoxin isolated from several strains of *Pseudomonas syringae*.[20] Acting as an agonist of the endogenous bioactive plant hormone (+)-7-*iso*-jasmonoyl-*L*-isoleucine (JA-Ile) (**2**),[21] COR is a non-host specific phytotoxin, displaying a range of bioactivity across a variety of plant species (Figure 4).[20]

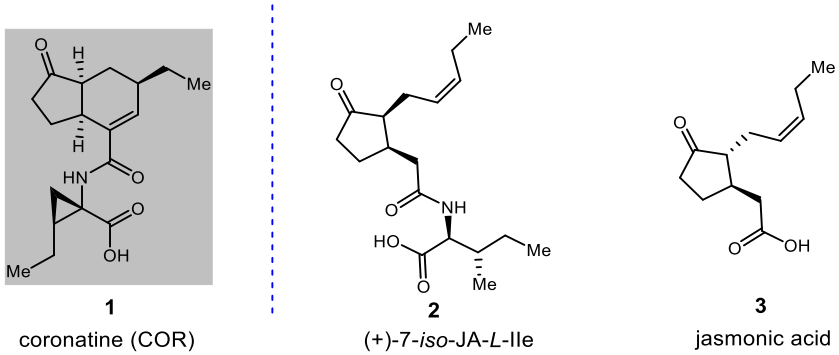


Figure 4: Coronatine (1) acts as a structural and functional mimic of (+)-7-*iso*-jasmonoyl-*L*-isoleucine (2) in the jasmonic acid (3) signalling pathway.

COR interacts with the jasmonate receptor COR-insensitive 1 (COI1),[22] and induces biological effects through activation of the jasmonic acid (JA)-signalling pathway and the resultant suppression of salicyclic acid (SA)-mediated defence mechanisms.[20]

COI1 encodes an F-box protein which is part of an Skp/Cullin/F-box complex (SCF^{COI1}), which functions as a ubiquitin ligase.[23] Jasmonate ZIM-domain proteins (JAZ) function as transcriptional regulators to repress jasmonate signalling, and form the COI1-JAZ complex in response to JA-Ile production.[23] The site of JA-Ile perception has been identified as a three-molecule complex, consisting of COI1, JAZ, and the inositol pentakisphosphate cofactor.[24] Binding of the ligand induces ubiquitination and subsequent degradation of JAZ proteins, which results in the activation of JA regulated gene expression.[22]

SA is a phytohormone involved in plant defence, and JA-mediated suppression of SA-signalling occurs as the result of hormone crosstalk. Through this crosstalk, COR-mediated activation of JA-signalling leads to inhibition of SA-signalling, and subsequent suppression of plant defences.[25]

Through interaction with this biological pathway, COR has been reported to exhibit a range of phytotoxic activity across several plant species. COR induces significant chlorosis in leaf tissue[26] and senescence of leaves,[27] inhibits root growth,[22,28] stimulates the production of ethylene[29] and defence related secondary metabolites,[30] and induces hypertrophy[31] and stomatal opening.[32]

The jasmonate receptor represents a novel MOA not currently exploited by commercial phytotoxins, and as such the development of a COR-based herbicide is highly attractive.[15]

Structurally, COR is composed of two distinct fragments, the bicyclic polyketide coronafacic acid (CFA), and the isoleucine-derived amino acid coronamic acid (CMA) (Figure 5).[33,34]

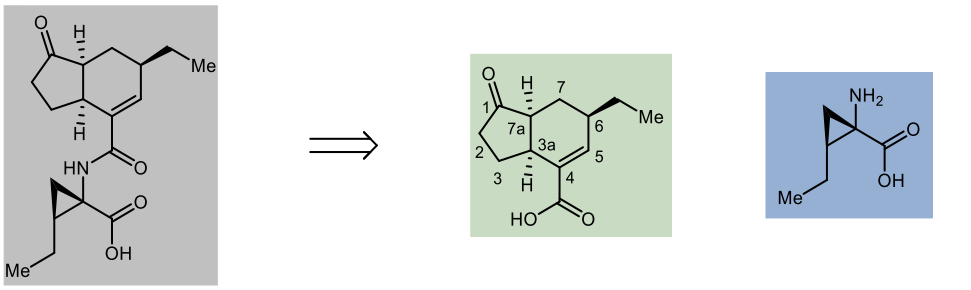


Figure 5: Coronatine structural components, coronafacic acid (4) and coronamic acid (5).

CFA and CMA are synthesised through independent biosynthetic pathways,[35,36] and their final conjugation to form the COR amide linkage is carried out by the enzyme coronafacate ligase (Cfl).[37]

Despite the substantial interest in COR as a potential herbicidal lead, relatively little is known with respect to an SAR around the natural product scaffold. Published SAR to date is summarised in Figure 6.

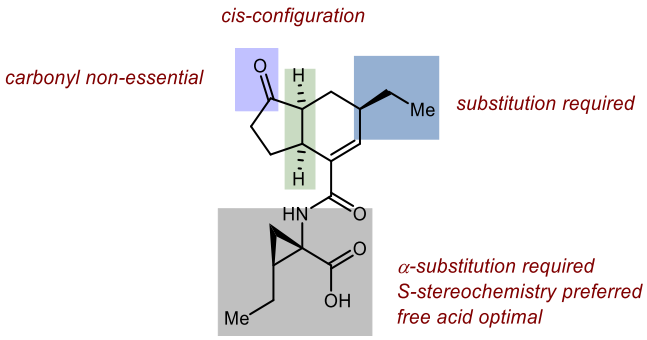


Figure 6: Summary of reported COR SAR.

It has been reported that the natural enantiomer, (+)-COR, confers significantly greater biological activity than other COR stereoisomers.[38,39] COR stereoisomers have also been used to probe the natural product MOA. Through the synthesis and biological evaluation of COR isomers it has been shown that COR induces stomatal opening activity through an alternative function in addition to its COI1-JAZ dependant function (Figure 7).[40]

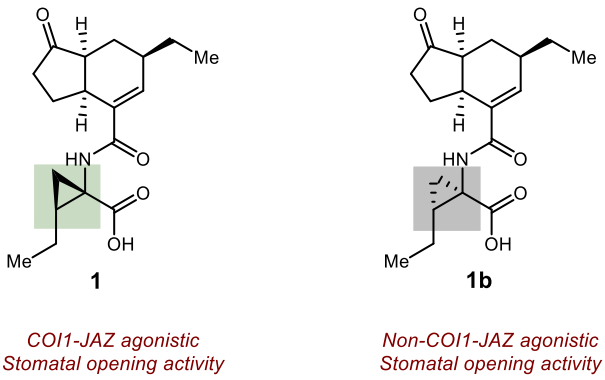


Figure 7: Use of COR stereoisomer 1b to probe MOA.

COR isomer **1b** was found to induce stomatal re-opening through a mechanism distinct from COI1-JAZ agonism. Isomer **1b** did not induce COI1-JAZ coreceptor formation, however was active in a stomatal re-opening assay, suggesting an alternative MOA for stomatal opening and that the stereochemistry of the CMA moiety does not affect stomatal opening activity, and that it is the CFA moiety which is key in this assay.[41]

Both CFA and CMA moieties confer phytotoxic activity separately, however, this is greatly enhanced when the components are coupled to give the parent structure.[39]

With regard to the core moiety (Figure 8), it is known that the *cis*-stereochemistry of the ring junction is important for biological activity, mimicking the side chain configuration of JA-Ile.[21,42,43]

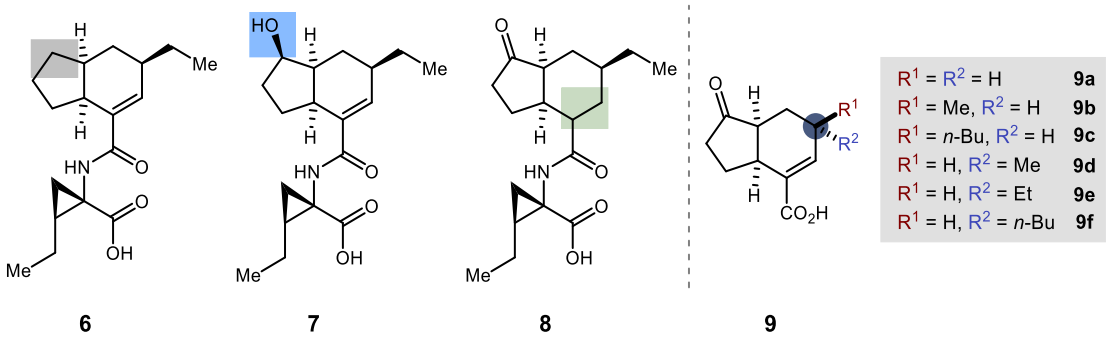


Figure 8: Core modified COR and CFA analogues, highlighting point change from the parent structure.

Substitution at the C^6 position has also been shown to be required for activity in potato tuber inducing assays; deletion analogue **9a** was found to be inactive, whereas methyl substituted analogue **9b** retained potency. Sterically larger, more lipophilic substitution in this position (**9c**) conferred the highest levels of activity when incorporated in CFA analogues.[44] The relative stereochemistry of this substituent has also been found to be significant, with substitution *trans* relative to the *cis*-ring junction found to confer higher levels of tuber inducing activity than the respective C^6 epimers (**4** is more active than **9e**);[44] however, it has also been reported that the ethyl substituent is not crucial for tendril-coiling inducing activity, with deletion analogues conjugated to *L*-Ile retaining potency.[43]

Reduction of the carbonyl moiety (**7**) has been reported to lead to reduced volatile inducing activity in rice leaves with respect to COR,[30,45] however, there have been reports of retained activity of this compound and of the analogous structure were the carbonyl has been completely reduced to afford the unsubstituted cyclopentane ring (**6**).[46]

COR analogue **8**, where the α,β-unsaturated amide has been reduced to afford the fully saturated 6,5-bicycle, has been reported and found to be highly active in volatile emission assays, suggesting that this functionality is not important for interaction with the binding site.[45]

Typically, the amino acid residue of COR has been the main focus of SAR studies. It has been reported that the enzyme responsible for the linkage of CFA and CMA, Cfl, has a degree of tolerance around the amino acid structure,[46] as evidenced through the isolation of several *N*-coronafacoyl compounds alongside COR (Figure 9).[47–50]

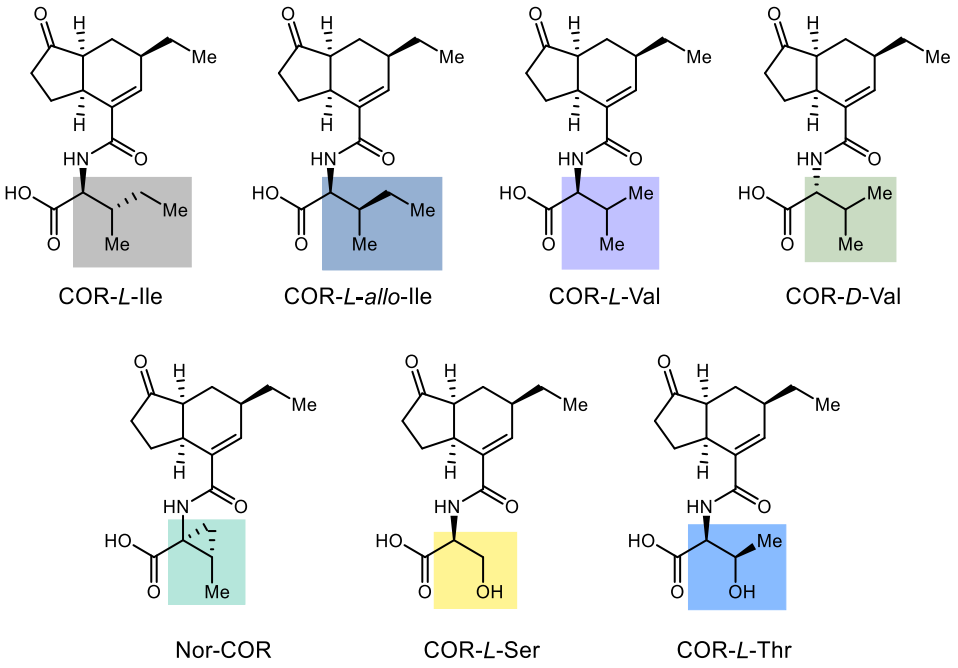


Figure 9: Naturally occurring *N*-coronafacoyl analogues which have been isolated alongside COR, highlighting the varied amino acid residue.

These analogues have been reported to possess COR like bioactivity, however, are less active than the parent compound COR.[48] This perceived tolerance in the amino acid residue suggests that an SAR campaign focusing on amino acid analogues of COR could be fruitful.

SAR studies in this area have reported biological activity arising from analogues with alternative amino acids. *N*-coronafacoyl-*L*-isoleucine (**10b**) has been found to retain COR levels of activity in assays measuring the induction of alkaloid biosynthesis as an indicator of activation of plant defence mechanisms.[51] This analogue has also been shown to retain COR-like activity in tendril-coiling inducing assays, however was less potent than COR itself.[43] This data suggests *L*-Ile acts as a reasonable mimic of CMA, despite conferring weaker bioactivity. Tolerance for further alternative amino acid

substitution with both natural and non-natural amino acids has been demonstrated, however, an SAR for this portion of the molecule remains unclear (Figure 10).[43]

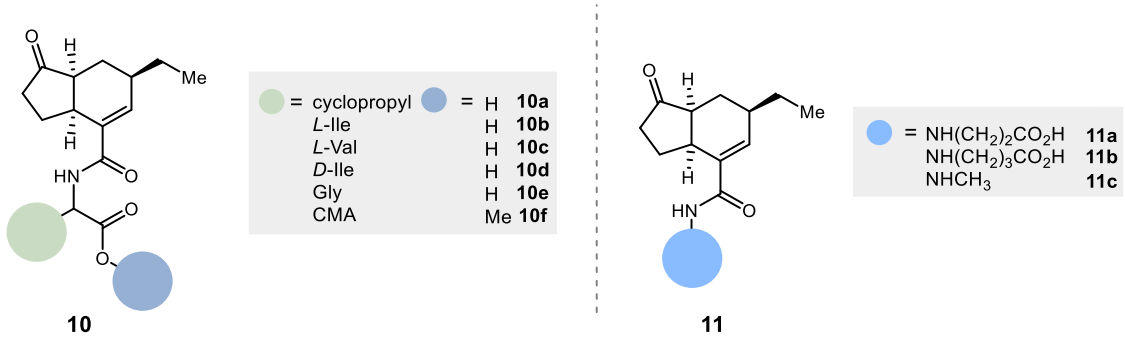


Figure 10: COR analogues with variation in the amino acid residue.

Substitution which retains the *S*-stereochemistry of CMA at the α-carbon is important for activity, as has been demonstrated through the synthesis of other COR stereoisomers (**1** is significantly more active than (-)-COR).[39] Analogues using *L*-valine (**10c**) and the cyclopropyl amino acid **10a** have been found to confer weak activity in potato tuber inducing assays, while glycine analogue **10e** is inactive.[39] It has been widely reported that the free carboxyl terminus of the amino acid is required for maximal activity (**10f** is less active than COR),[30,39] however, in some examples moderate activity has been observed from esterified compounds, which has been attributed to a pro-cide effect where the free acid parent compound is released *in situ* through the action of esterases.[52,53] The relative position of this carboxyl terminus has been assessed through the synthesis of analogues **11a-c**, which gave inactive or very weakly active compounds, indicating the importance of the α-amino acid relationship.[39]

COR-analogues with alternative amino acids have also been used to probe the natural phytotoxin MOA with respect to stomatal opening activity.[41] In this study, it was shown through *in silico* docking that the bulkiness of the amino acid side chain has a significant effect on substrate affinity for the COI1-JAZ co-receptor (Figure 11).

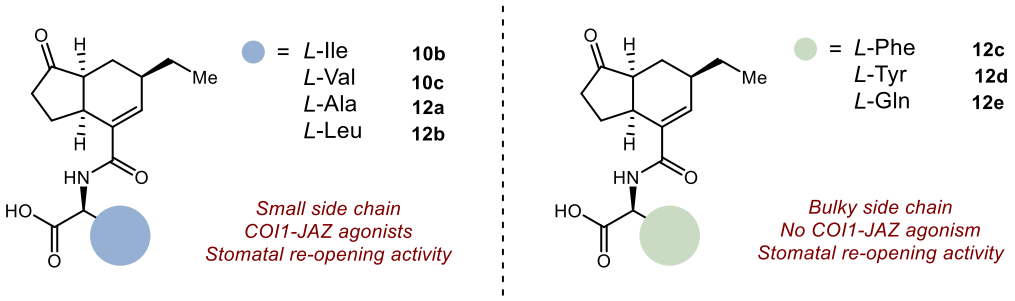


Figure 11: Coronafacoyl-amino acid compounds used to probe MOA for stomatal re-opening.

All analogues synthesised in this study showed stomatal re-opening activity in *Arabidopsis thaliana* guard cells. *In silico* docking studies of these compounds showed that analogues with comparatively small substituents at the α-position, **10b/c** and **12a/b**, had a binding mode very similar to that of natural COR in the COI1-JAZ co-receptor; however, analogues with bulkier substituents, **12c-e**, were not accommodated in the binding pocket. This again suggests an alternative MOA for stomatal opening activity, and is also informative about SAR around the amino acid motif with respect to COI1-JAZ agonism, suggesting smaller amino acid side chains are preferred.

There has also been significant interest in a COR analogue featuring an aromatic CFA-like core, and *L*-Ile amino acid residue, which is known as coronalon (**13**) (Figure 12).[54]

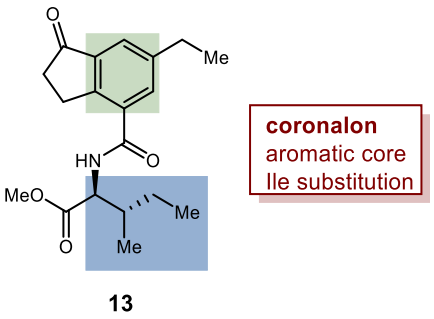


Figure 12: Structurally simplified COR mimic coronalon, highlighting the areas of structural modification from the parent compound.

The aromatic core structure represents a structurally simplified CFA mimic, which is attractive with a view to feasibility of expedient synthesis of COR analogues.[55,56] *L*-Ile-OMe is used as a CMA surrogate, an approach which has been adopted elsewhere to probe SAR around the CFA core motif.[43] The methyl ester is known to hydrolyse

in situ, and has been preferred for analogue synthesis for practicality. The synthetic accessibility of this structure has enabled significant SAR studies to be carried out.

Coronalon and its analogues featuring alternative amino acid motifs have been reported to possess COR like activity, including the induction of volatile biosynthesis and tendril-coiling (Figure 13).[55]

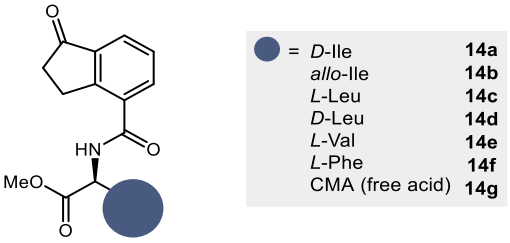


Figure 13: Amino acid variation on coronalon analogues, with deletion of the ethyl unit.

The incorporation of an amino acid is essential, as was observed with COR.[39] *Allo*-Ile analogue **14b** confered weak volatile inducing activity, whilst *L*-leucine (**14c**) and valine (**14e**) incorporation retained volatile inducing activity. Conjugation with the free acid of CMA (**14g**) gave activity comparable to the *L*-leucine conjugate.[55] *L*-phenylalanine analogue **14f** and all conjugates with *D*-configured amino acids were inactive.

Functionalisation at the C^6 position has been shown to be significant in the potency and activity profile of coronalon analogues, and as such the SAR at this position has been probed (Figure 14).

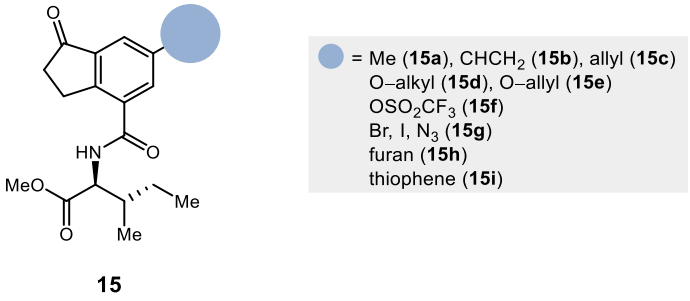


Figure 14: Reported coronalon analogues, featuring variation of the C^6 substituent.

The ethyl substituent on the aromatic ring increases the potency of the compound with respect to the unsubstituted analogue, and also aligns its bioactivity more closely with

a COR-like profile.[54] Methyl (**15a**) and alkoxyl substituted (**15d**) derivatives are inactive or confer weak activity with the exception of the *O*-allyl substituted analogue (**15e**), which gave high levels of activity. Vinyl (**15b**) and allyl (**15c**) substituted derivatives were weakly active, whereas furan (**15h**) and thiophene analogues (**15i**) were inactive, postulated to be due to increased steric effects at the ligand binding site.[56,57]

Further aromatic analogues maintaining the *L*-Ile-OMe substituent have also been reported and tested for phytotoxic activity (Figure 15).

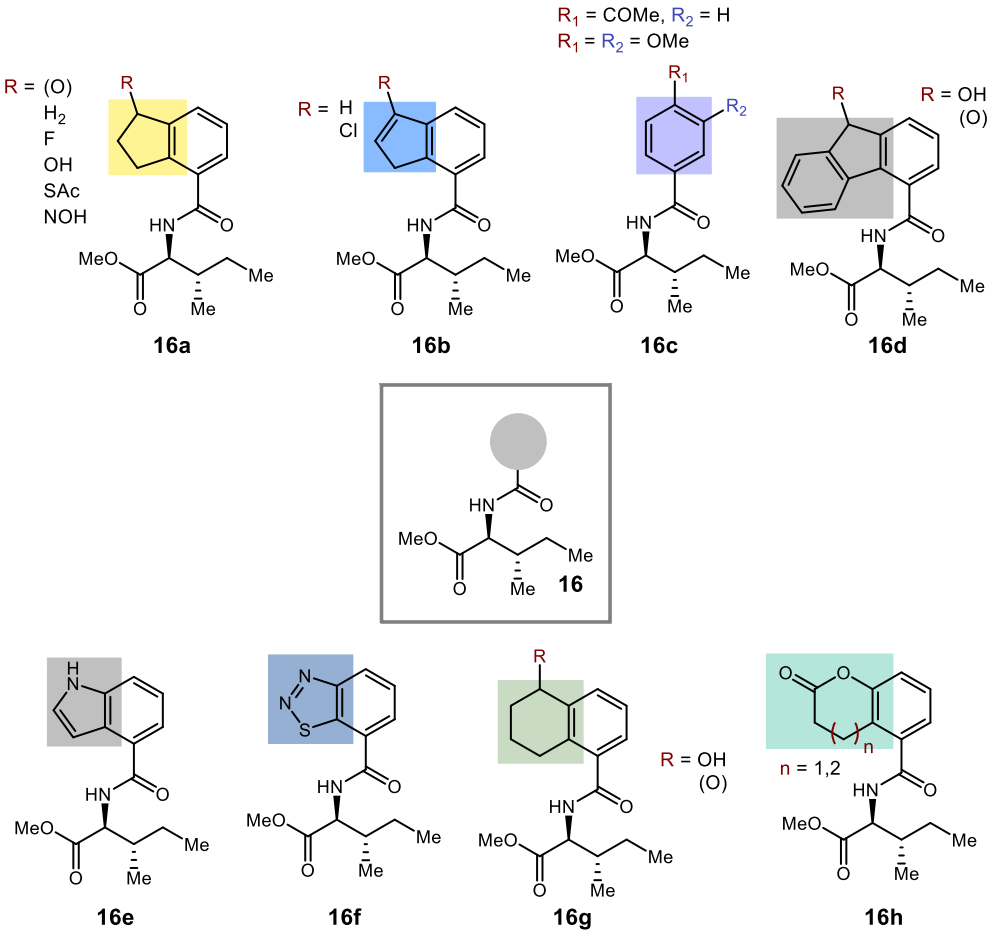


Figure 15: Variation of the aromatic core in coronalon analogues.

Mono-cyclic and tri-cyclic aromatic cores (**16c/d**), as well as heteroatom incorporation (**16e/f**), were not tolerated. Ring-expansion to give 6,6- or 7,6-bicycles (**16g/h**) gave reduced potency, whilst modification of the cyclopentanone ring delivered

biologically active conjugates (**16a**/**b**), however with lower levels of activity than the parent compound coronalon.[56]

The observed activity from coronalon and its analogues is of particular significance as a demonstration of the potential for structural modification and simplification with the retention of a COR-like activity profile.

1.4 Synthetic Approaches Towards Coronafacic Acid

Despite efforts to probe the SAR around the COR scaffold, little conclusive findings around the structural tolerance are known. This has been attributed in part to the complexity of the natural product structure, limiting the practicality of an analogue synthesis campaign.[58,59] In particular, SAR development has been limited by the lack of a scalable synthesis towards the polyketide CFA moiety.[55] Although the synthesis of CFA has been well reported in the chemical literature, syntheses have typically been protracted, challenging to execute on a practical scale for analogue generation, and ultimately low yielding. To effectively assess the structural requirements around the natural product scaffold to achieve phytotoxic activity, a robust, scalable synthetic methodology must be developed, allowing access to CFA and ideally enabling synthetic flexibility to allow modifications to the CFA core.

Numerous total syntheses of racemic CFA have been reported, along with several enantiopure preparations. Table 1 shows the reported syntheses of CFA in chronological order and grouped according to their associated key step; Figure 16 shows these key steps in more detail.

Synthetic strategies towards CFA can generally be grouped into five approaches based on the key transformation in the route: Diels–Alder (DA) reaction, both inter and intramolecular (IMDA), conjugate addition, Haller-Bauer reaction, intramolecular cyclisation, and oxy-Cope methodology.

The presence of the cyclohexene-derived core within CFA has rendered the DA reaction a common key disconnection. DA-based approaches have enabled expedient access to the CFA carbon skeleton with control of the requisite stereochemistry, and therefore have been a particularly effective means of CFA synthesis. Each of these

lynchpin strategies will be reviewed in the following sections, with emphasis given to the DA-based approaches.

Table 1: Literature syntheses of coronafacic acid.

Author (Year)	Key step (No. steps)	Racemic/ enantiopure	Overall Yield (%)	Ref.
Ichihara (1977)	DA (10[a])	Racemic	Unknown	60
Ichihara (1980)	DA (14[b,c])	Racemic	0.4	65
Jung (1981)	DA (8[d])	Racemic	7	67
Llinas-Brunet (1984)	DA (9[a])	Racemic	4	61
Yates (1990)	DA (12[b])	Racemic	24	69
Charette (2007)	DA (6[a])	Racemic	29	68
Ueda (2009)	DA (12[a])	Racemic	5	38
Ueda (2010)	DA (8[a])	Racemic	28	63
Ichihara (1996)	CA (7[a])	Racemic	25	70
Ichihara (1997)	CA (9[b])	Enantiopure	24	71
Shibasaki (1998)	CA (6[e])	Enantiopure	9[f]	72
Mehta (1993)	HB (8[a])	Racemic	11	74
Mehta (1999)	HB (12[a])	Enantiopure	5	77
Tsuji (1981)	IC (15[a])	Racemic	Unknown	79
Nakayama (1981)	IC (12[b])	Racemic	0.9	81
Nakayama (1983)	IC (12[a])	Enantiopure	0.1	82
Blechert (1996)	IC (9[b])	Racemic	16	80
Tori (2000)	IC (18[d])	Racemic	0.9	78
Taber (2009)	IC (12[a])	Enantiopure	4	86
Kobayashi (2011)	IC (12[a,c])	Enantiopure	15	84
Kobayashi (2013)	IC (11[a,c])	Enantiopure	1.6	85
Jung (1980)	OC (14[a])	Racemic	1.7	87

1.6

1.7

[a] From a non-commercial starting material. [b] From commercial starting materials. [c] Based on longest linear sequence. [d] Starting material commercial but not readily accessible. [e] A required catalyst is not commercial. [f] Based on an assumed yield from referenced publication. Diels–Alder (DA), conjugate addition (CA), Haller-Bauer (HB), intramolecular cyclisation (IC), oxy-Cope (OC).

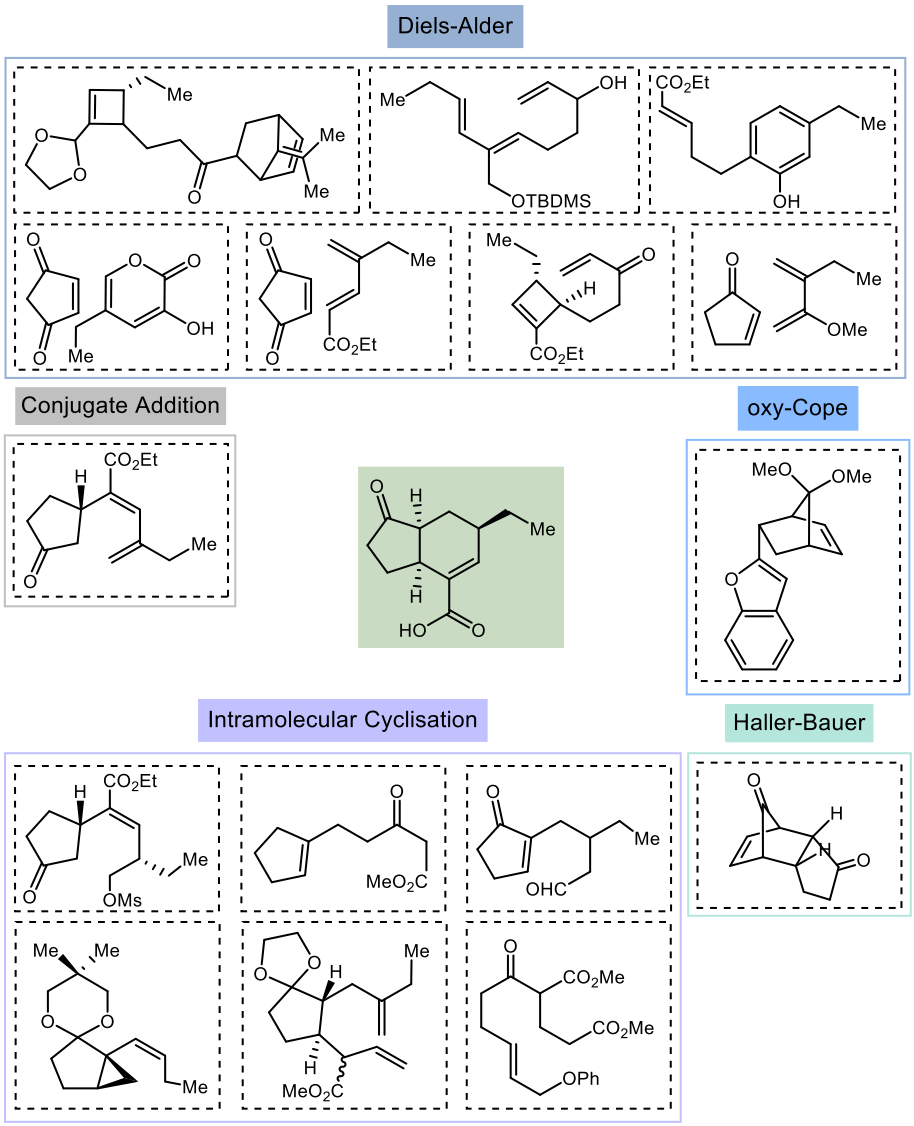
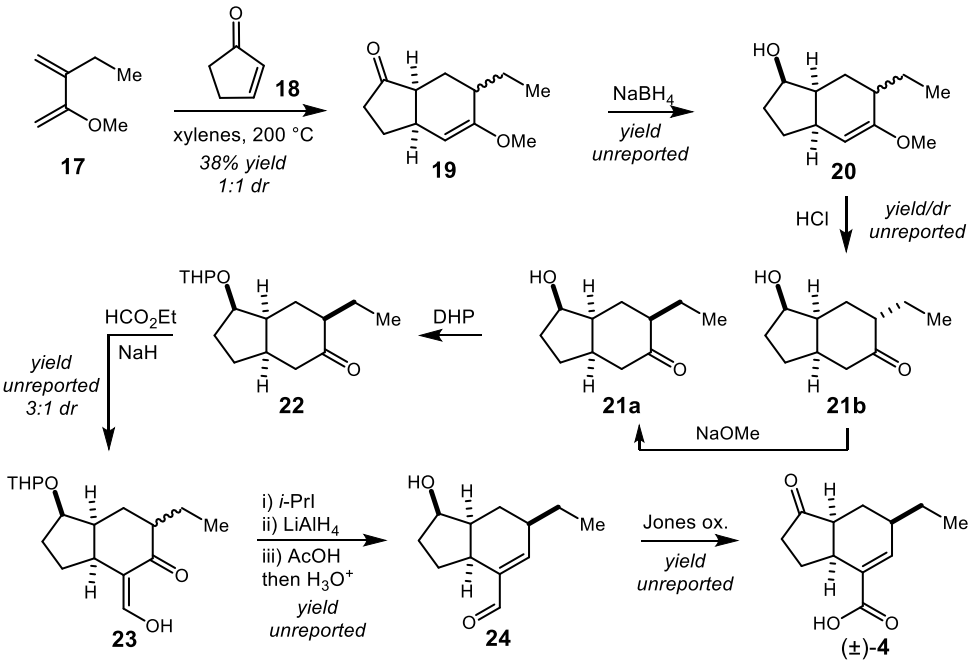


Figure 16: Summary of literature synthetic approaches towards coronafacic acid, detailing the key step in each.

Intermolecular Diels–Alder approaches

In 1977, Ichihara reported the first synthesis of (±)-CFA *via* an intermolecular DA reaction.[60] Despite requiring harsh conditions and proceeding in only moderate yield, the DA reaction provided access to fused bicycle **19**, as a 1:1 mixture of diastereomers, containing the desired *cis*-ring junction (Scheme 1).[60]

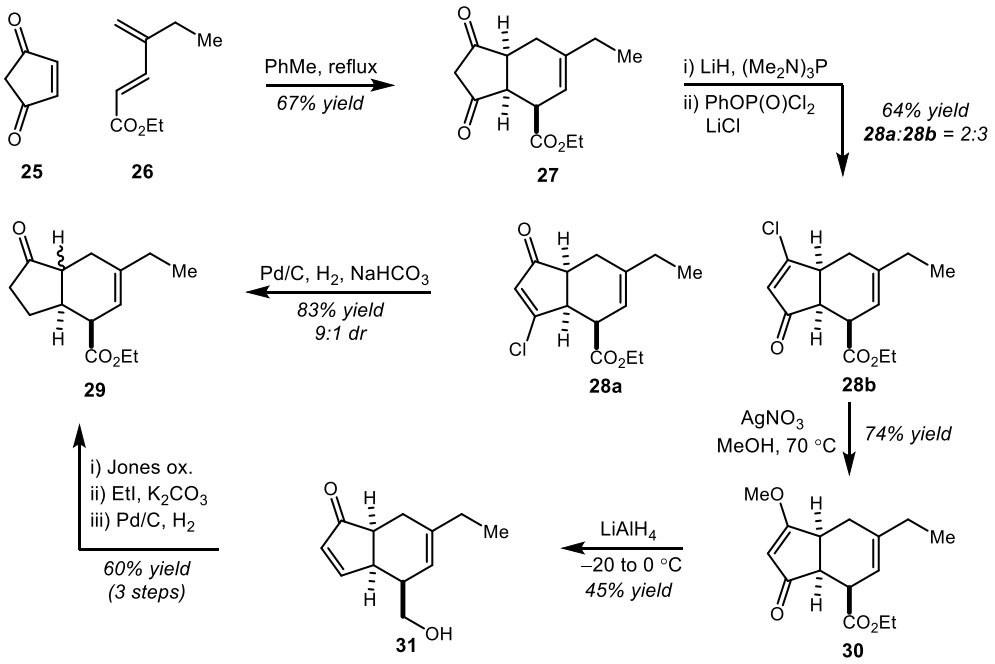


Scheme 1: Ichihara's intermolecular Diels–Alder strategy.

Despite having accessed the complete carbon framework, a further nine transformations, for which yields were not communicated, were required to deliver (±)-CFA.

Reduction of the cyclopentanone **19** from the convex face gave alcohol **20**. Subsequent hydrolysis of the enol ether afforded ketone **21** as a mixture of diastereomers at C^6, for which the ratio was not communicated. **21a**, bearing the desired relative stereochemistry, was found to be the more stable isomer, and the undesired isomer **21b** could be epimerised to **21a** upon treatment with base. Tetrahydropyran (THP) protection was followed by formation of the formylated compound **23**, which was converted to **24** by alcohol protection, ketone reduction, and subsequent acid-mediated dehydration. Deprotection to aldehyde **24** and a final Jones oxidation afforded the first example of synthetic (±)-CFA. Given the lack of yield information, it is difficult to comment further on the utility of this process for rapid analogue generation.

Using an alternative intermolecular Diels–Alder, (±)-CFA was synthesised by Llinas-Brunet *et al.*, again allowing the complete carbon framework to be rapidly assembled (Scheme 2).[61]

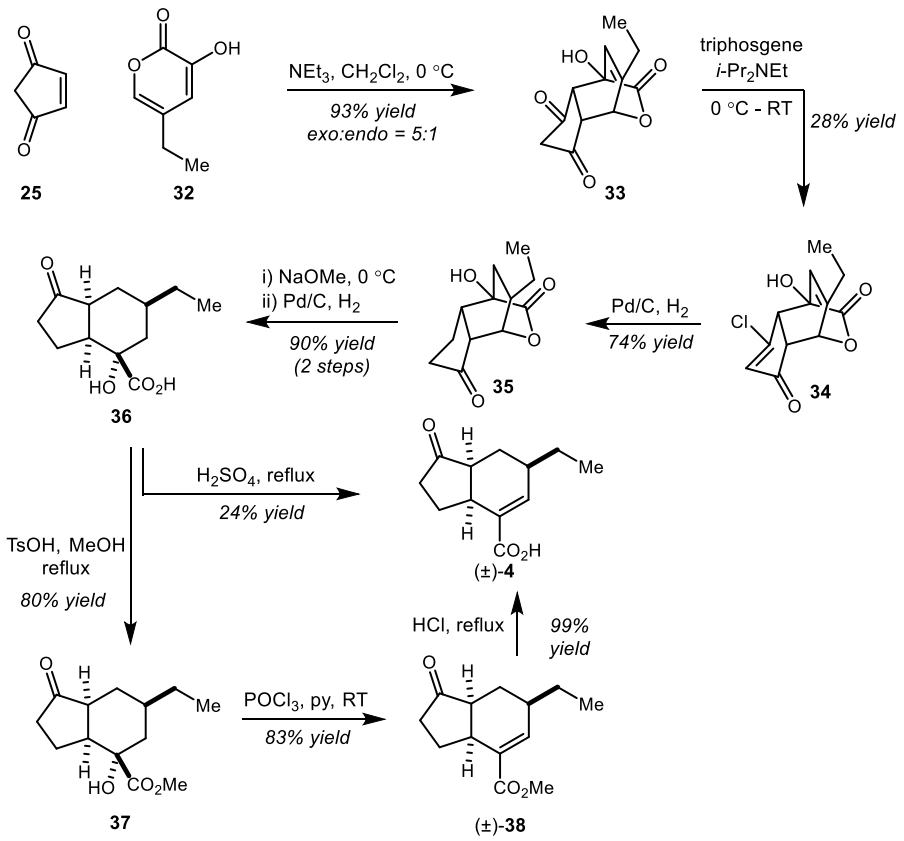


Scheme 2: Llinas-Brunet's Diels–Alder strategy.

Heating cyclopentendione **25** with diene **26** in PhMe smoothly afforded bicycle **27**, which could be advanced to (±)-**4** in four steps. Chlorination using phenyldichlorophosphate gave a mixture of regioisomers **28a** and **28b** in a ratio of 2:3, respectively. With respect to analogue generation, these intermediates are potentially useful for SAR development around the cyclopentane ring of **4** based on the synthetic utility of the chloroenone. **28a** was converted to bicycle **29** in one step *via* chemoselective hydrogenation, as a mixture of diastereomers at C^{7a}. Despite this, conversion of **28b** to **29** required a multi-step procedure: treatment with $AgNO_3$ in MeOH afforded **30**. $LiAlH_4$ reduction delivered enone **31**, which was converted to **29** *via* Jones oxidation, esterification, and chemoselective hydrogenation of the enone alkene. **29** was treated with NaOEt to bring the C^5-C^6 double bond into conjugation with the ester followed by acid-mediated hydrolysis of the ester, which afforded (±)-**4** with the desired relative stereochemistry (52% yield over two steps (not shown)). This synthetic route was used to prepare 11 mg (±)-**4**, which is insufficient for further SAR development; however, the route may be amenable to scale up procedures.

A similar Diels–Alder approach was communicated by Ueda *et al.* (Scheme 3).[38] Functionalised hydroxypyrone **32** was accessed in four steps from commercial materials,[62] which adds to the synthetic complexity of the route. The Diels–Alder

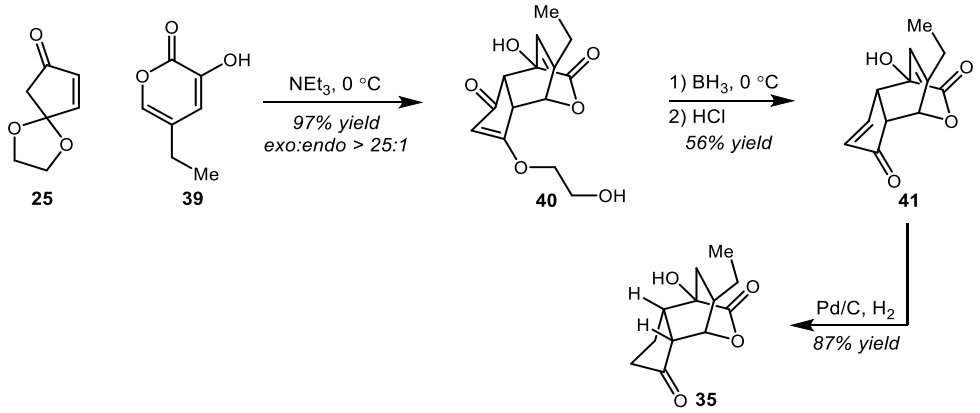
reaction of **25** and **32** gave access to bridged tricycle **33** in high yield and with moderate *exo*-selectivity, rationalised due to a greater stability of the *exo*-transition state, resulting from steric clashes incurred in the *endo*-model.[38]



Scheme 3: Ueda's *exo*-selective DA-based approach.

Intermediate **33** was then converted to (±)-**4** in five steps. Removal of the C^3 carbonyl was achieved using a two-step procedure similar to the Llinas-Brunet approach:[61] chlorination employing triphosgene provided chloroenone **34**, which was hydrogenated to afford ketone **35**. NaOMe-mediated elimination of the carboxylate and subsequent hydrogenation of the resulting enone alkene gave intermediate **36** in 90% yield over two steps. Methyl ester formation (**37**) was followed by dehydration to give **38**, which was then hydrolysed to (±)-**4**. The authors reported that the last three synthetic steps could be shortened to a single step in which bicycle **36** was refluxed in H_2SO_4. While requiring fewer steps, the overall yield from **36** using this approach was found to be significantly lower (24% *vs.* 66%). Ueda utilised this synthetic sequence to prepare 65 mg (±)-**4**, suggesting this route could potentially be used to access useful quantities of CFA for analogue development.

Following this initial success, Ueda reported an improvement of their original synthetic sequence,[63] giving access to tri-cyclic intermediate **35** in an improved step count and associated yield (Scheme 4).[38] Notably, the associated key Diels–Alder using the monoketal derivative of **25** (**39**)[64] was considerably more selective (> 25:1 *exo*:*endo*).



Scheme 4: Ueda's second generation CFA synthesis.

Significantly, the (±)-**4** prepared using this route was then used in the synthesis of fluorescein isothiocyanate labelled COR for use as a molecular probe,[63] illustrating the potential of this route to deliver sufficient quantities of (±)-CFA for further study.

Intramolecular Diels–Alder approaches

Intramolecular DA reactions have been used frequently as a strategy towards (±)-CFA. The majority of these approaches have focused on the generation of the triene intermediate **42** and related derivatives (Figure 17). The Diels–Alder reaction of **42** has been found to be *exo*-selective, resulting in the pharmacologically undesired *trans* ring junction. However, the C^{7a} of **43** is readily epimerised to give the desired *cis* diastereoisomer.[65]

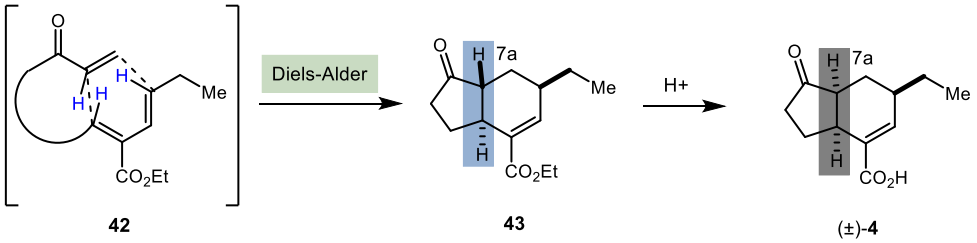
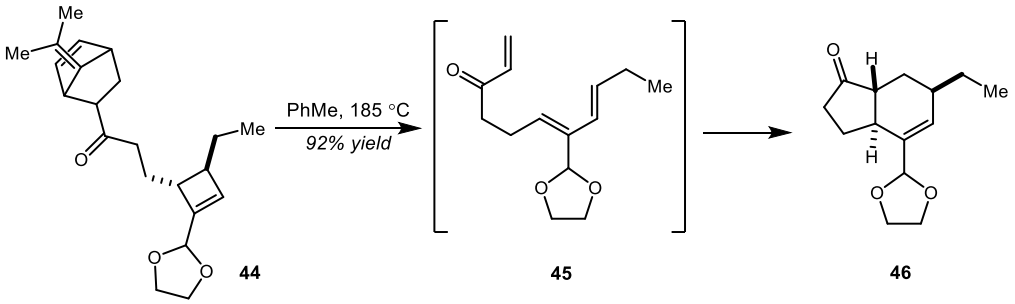


Figure 17: DA reaction of triene intermediate to assemble the CFA core structure.

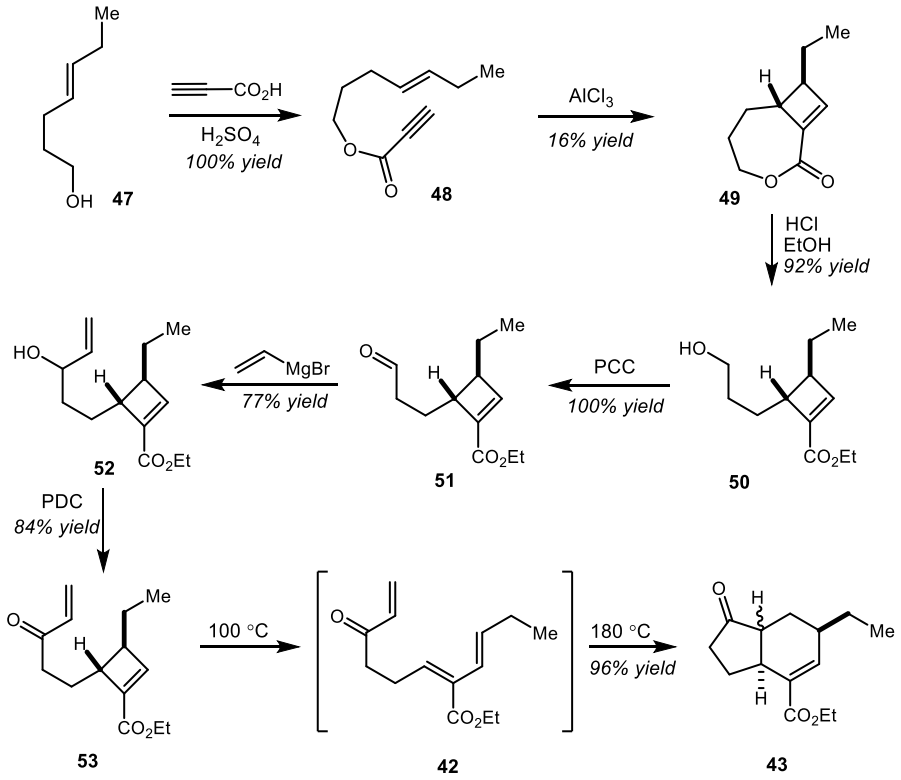
Ichihara reported the first intramolecular Diels–Alder strategy towards (±)-CFA in 1980, utilising a late stage conrotatory ring opening, followed by a retro–Diels Alder to give access to the desired triene, and, finally, an IMDA reaction in one-pot procedure to afford 5,6-fused bicycle **46** in 92% yield (Scheme 5).[65]



Scheme 5: Ichihara's triene generation and IMDA cyclisation.

While providing **46** very rapidly and in high yield, formation of intermediate **44** required twelve steps, albeit from simple starting materials,[65,66] which limits the utility of the route to access sufficient quantities of (±)-CFA for analogue generation. Acetal intermediate **46** was isolated with the expected *trans*-ring junction and was isomerised to the *cis*-isomer using NaOMe. (±)-CFA was then quickly accessed from **46** by one-pot acetal deprotection/Jones oxidation, proceeding in 22% yield (not shown).

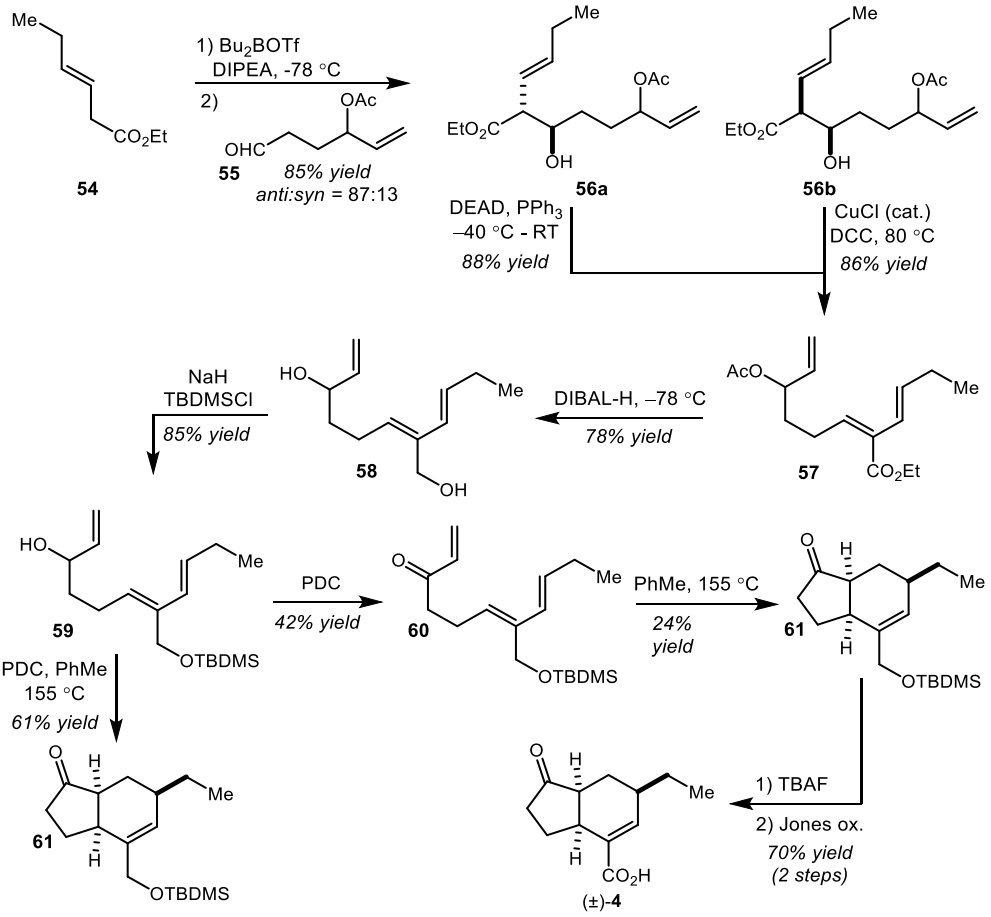
A similar conrotatory ring opening approach to unmask a reactive diene for an intramolecular Diels–Alder reaction has been described by Jung *et al.* (Scheme 6).[67]



Scheme 6: Jung's intramolecular DA approach.

An intramolecular [2+2] cycloaddition of ynoate **48** generated cyclobutene **49** and established the desired relative stereochemistry.[67] Despite optimisation, this transformation was limited to 16% yield but with significant recovered starting material. This low yielding step early in the synthetic route limits the utility of the sequence with respect to the preparation of significant quantities of (±)-CFA. A series of simple, high yielding transformations then gave access to key intermediate **42**: acid-mediated ester hydrolysis was followed by pyridinium chlorochromate (PCC) oxidation, addition of vinyl Grignard, and a second oxidation. Thermolysis of **53** generated triene **42** *in situ*, which, on increasing the temperature, underwent the expected Diels–Alder to deliver **43** in high yield and in approximately 60:40 ratio in favour of the desired *cis*-isomer. This mixture was converted to (±)-**4** in a single step by ester hydrolysis with concomitant epimerisation to the *cis*-ring junction (not shown). The authors also demonstrated that (±)-CFA could be accessed, following the same synthetic route, with an overall yield of 7% when telescoped without purification of the intermediates.

In 2007, the utility of species related to triene **42** as a precursor to (±)-**4** was again demonstrated by Charette *et al.* (Scheme 7).[68] In this example, the triene precursor was formed *via* diastereoselective boron-mediated aldol reaction of ester **54** with aldehyde **55** to deliver aldol products **56a**/**56b** in a 87:13 *anti*:*syn* ratio. Significantly, **56a** and **56b** were readily separated by flash chromatography and, in a convergent strategy, each could be independently and selective dehydrated to afford the desired triene **57**.

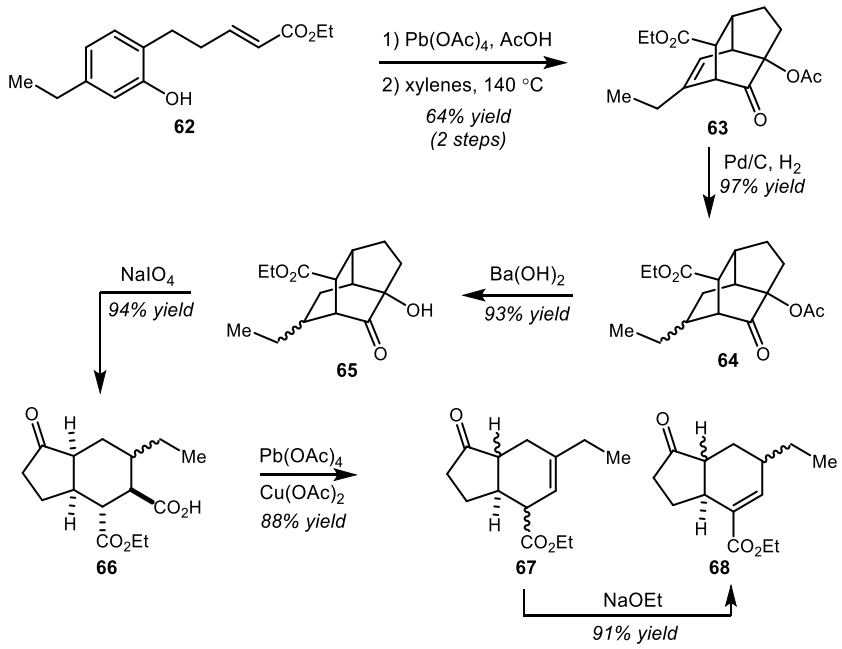


Scheme 7: Charette's approach towards (±)-CFA.

The authors demonstrated that **57** could be advanced to **42**, *via* acetate hydrolysis and oxidation, and ultimately to (±)-**4** through the known Diels–Alder approach (not shown). However, an alternative Diels–Alder reaction was developed in which both esters were reduced to give the corresponding diol **58**, and the primary alcohol was subsequently protected as the *t*-butyldimethyl silyl (TBDMS) ether **59**. Oxidation of **59** to enone **60** enabled a thermal Diels–Alder to give **61** in low yield of 24%, proposed

to be the result of decomposition of triene **60** occurring at a lower temperature than the desired cyclisation. This yield could be improved to 67% by simply heating **59** in the presence of pyridinium dichromate (PDC), allowing for oxidation and DA cyclisation in one pot. While the *trans*-bicycle product would be expected, the authors found that epimerisation of C^{7a} occurred during flash chromatography on silica gel to provide the *cis*-product **61**. Treatment of **61** with tetra-*n*-butylammonium fluoride (TBAF) and a subsequent Jones oxidation completed a concise synthesis of (±)-CFA. It should be noted, however, that aldehyde **55** is not commercial and required six steps to prepare, ultimately adding to the length of the overall synthesis and limiting the prospect for analogue generation *via* this route.

An alternative intramolecular Diels–Alder was favoured by Yates *et al.* who demonstrated the utility of their tandem Wessely oxidation/Diels–Alder methodology towards (±)-CFA.[69] Intermediate phenol **62**, which was synthesised in four high yielding steps from commercially available starting materials, underwent oxidation with $Pb(OAc)_4$ to furnish the quinone derivative, followed by a thermal Diels–Alder to give isotwistanone **63** (Scheme 8).



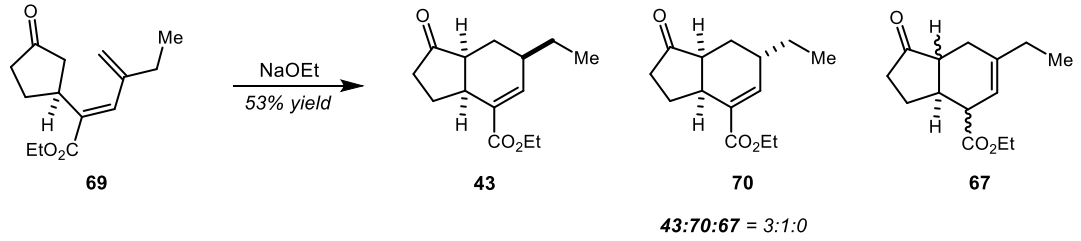
Scheme 8: Yates' DA-based approach to CFA.

Hydrogenation afforded tricycle **64** as a mixture of diastereomers before acetate hydrolysis to give **65**. Oxidative ring opening then gave the key bicyclic structure **66**,

as a mixture of diastereomers at C^6. $Pb(OAc)_4/Cu(OAc)_2$-mediated oxidative decarboxylation gave access to **67** with olefinic isomer **68**. However, **67** could be converted to **68** upon treatment with NaOEt. A final hydrolysis of **68** using aqueous acid afforded (±)-CFA (not shown), with the correct *cis*-ring junction, in 87% yield following several recrystallisations. Despite this synthetic approach being high yielding overall (24%), the use of harsh conditions at several steps throughout the route may limit its attractiveness with regard to scale up procedures.

Conjugate addition approaches

Annulation *via* conjugate addition as a route to both (+)-CFA and (±)-CFA has also been thoroughly explored. Again, the main objective in this approach is the setting of the *cis*-ring junction, relative to the *trans*-ethyl unit. Ichihara *et al.* applied their conjugate addition-based approach towards hydrindane scaffolds to the synthesis of (±)-CFA (Scheme 9).[70]



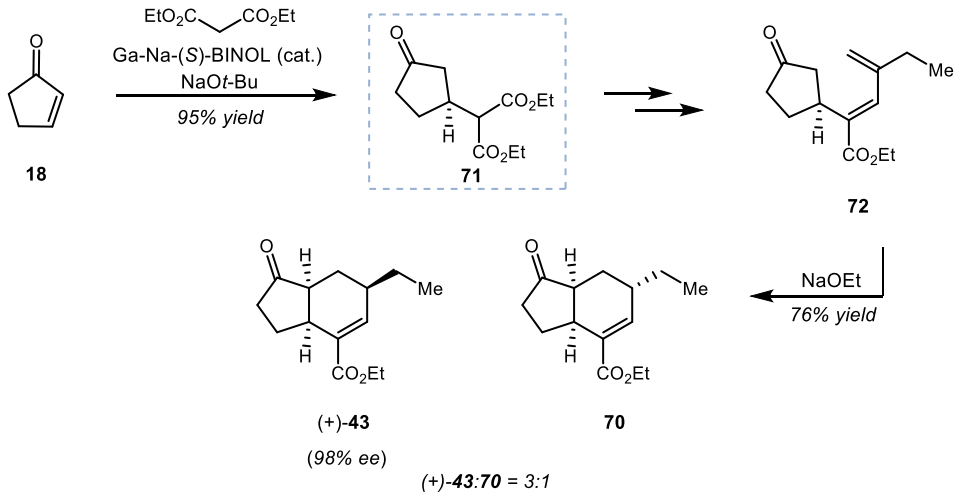
Scheme 9: Ichihara's conjugate addition-based approach to CFA.

The key cyclisation precursor **69** was obtained in five steps in and 67% overall yield (not shown). Following optimisation, it was found that judicious choice of reaction conditions allowed **69** to undergo an intramolecular 1,6-addition to afford **43** as the main product, albeit in moderate overall yield.

The authors reasoned that the desired product was formed from kinetic protonation of the cyclopentanone enolate. Under the reaction conditions, the stereochemical integrity of **43** was found to erode over time to deliver increased quantities of diastereoisomers **70** and **67**. Finally, (±)-**4** was obtained in 70% yield by acidic hydrolysis of **43** (not shown). This approach provided efficient access to (±)-**4**, giving an overall yield of 25% – a significant improvement over previous syntheses. The scalability of this route was not commented on in the text;[70] however, the efficiency

of the route to access (±)-**4** certainly renders it attractive with respect to potential scale-up and subsequent analogue generation for SAR scanning.

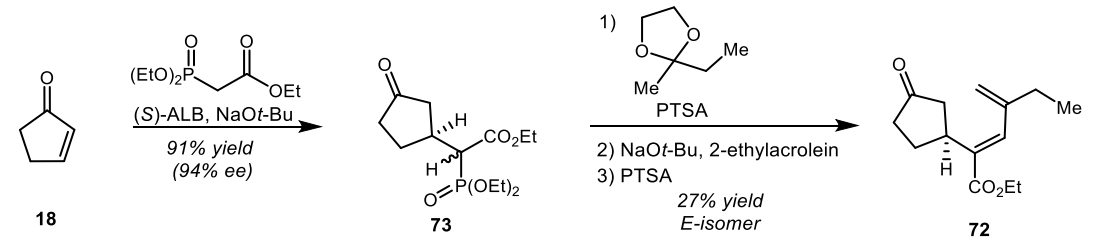
The authors later reported an asymmetric synthesis of (+)-**4** by exploiting the same synthetic route using enantioenriched **71** (Scheme 10).[71]



Scheme 10: Ichihara's modified route to access enantiopure CFA.

A catalytic asymmetric Michael addition of diethylmalonate to cyclopentenone **18** delivered **71**, which was converted to the cyclisation precursor **72** in six steps and in 63% overall yield (not shown). Total synthesis of (+)-**4** followed the previously described strategy,[70] with the key intramolecular conjugate addition proceeding in an improved yield. Optically enriched (+)-**4** was prepared in overall yield of 24% and in only nine steps from **18**. The authors comment that the relatively high overall yield of the synthetic route make it possible to gain access to practical quantities of (+)-**4**, and subsequently (+)-**1**.

In a later communication, Shibasaki *et al.*[72] used Ichihara's approach[70] to demonstrate the utility of their chiral aluminium catalyst in a similar asymmetric conjugate addition of triethylphosphonoacetate using an aluminium lithium bis(binaphthoxide) complex (ALB) to access phosphonate **73** (Scheme 11).[73]

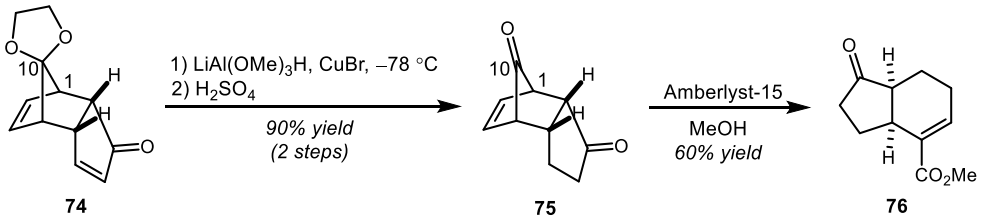


Scheme 11: Shibasaki synthesis of conjugate addition precursor 72.

The 1,4-addition proceeded in high yield and excellent *ee*; however, desired intermediate **72** was the minor product formed in the subsequent Horner-Wadsworth-Emmons reaction, which gave the *Z*-isomer preferentially in 43% yield. Following Ichihara's procedure,[70] diene **72** was then converted to (+)-**4** (not shown).

Haller-Bauer approaches

The Haller-Bauer reaction has also featured in CFA synthesis. Mehta *et al.* applied the Haller-Bauer reaction to access *cis*-hydrindane scaffolds for the synthesis of (±)-**4** (Scheme 12).[74,75]



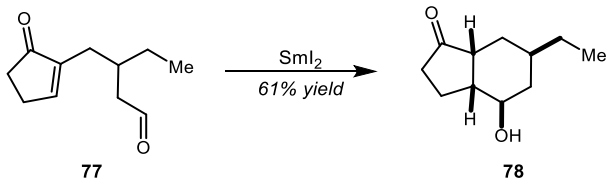
Scheme 12: Haller-Bauer-based approach towards CFA.

Reduction and deprotection of **74**, accessed in three steps and in 43% overall yield from commercial starting materials (not shown),[76] delivered **75**, which underwent Haller-Bauer reaction using Amberlyst resin to give bicycle **76**. The regioselectivity of the Haller-Bauer reaction was found to be predictable, with cleavage occurring between C^1 and C^{10}. The double bond was found to migrate into conjugation with the ester functionality *in situ* and no C^{7a} epimerisation was observed. A further five steps provided (±)-**4** in 20% yield (not shown). The authors comment that this concise approach offers considerable potential for derivatisation, highlighting that **74** can be accessed in multi-gram quantities. Mehta has also reported the enzymatic resolution

of **74** using lipase PS, giving access to enantiopure (+)-**4** following the same synthetic route (not shown).[75,77]

Intramolecular cyclisation approaches

Intramolecular cyclisation has been a popular strategy for assembly of the carbocyclic scaffold of **4**. Tori *et al*. applied a SmI_2-initiated radical cyclisation towards (±)-**4** (Scheme 13).[78]

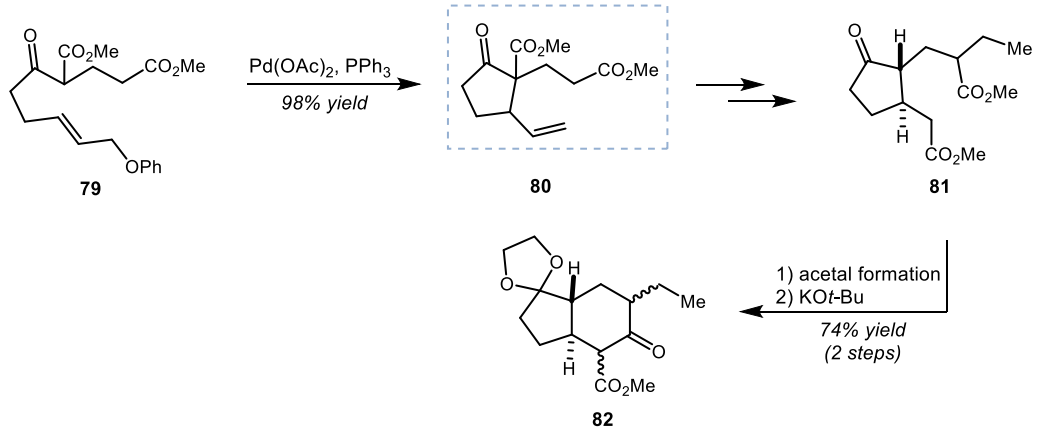


77 78

Scheme 13: Tori's radical mediated intramolecular cyclisation.

Intramolecular cyclisation precursor, aldehyde **77**, was accessed in eleven steps and in 17% yield (not shown). Exposing **77** to SmI_2-initiated a 6-*endo*-trig cyclisation, which delivered a mixture of four stereoisomers, where **78** was the major product. Following six further transformations (±)-**4** was isolated in 9% yield (not shown). The low overall yield obtained from this synthetic sequence (0.9%) reduces the utility of the preparation with respect to generating practically useful quantities of (±)-**4**.

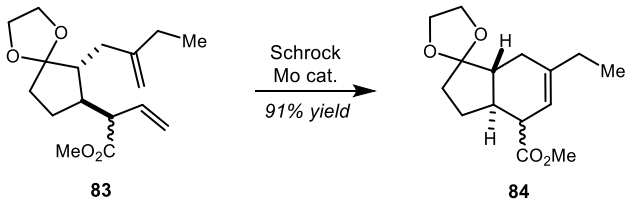
Pd-catalysed allylic alkylation has also been used to good effect for ring construction towards (±)-**4**. Tsuji demonstrated an intramolecular allylic alkylation cyclisation protocol for the construction of the cyclopentanone ring (Scheme 14).[79] It should be noted that precise details for this approach are limited, with many aspects of reaction conditions and outcomes not detailed in the report.



Scheme 14: Tsuji's Pd-catalysed cyclisation-based appraoch to CFA.

The key Pd-catalysed intramolecular allylic alkylation was achieved using $Pd(OAc)_2$ to afford the cyclopentanone product **80** in excellent yield. A further six steps gave the di-ester intermediate **81** (not shown). Protection of the ketone moiety as an acetal preceded a Dieckmann condensation to form the six-membered ring and a further four steps delivered (±)-**4** (not shown). Again, the lack of detail communicated about the synthetic sequence does not allow comment on the synthetic utility of the route regarding yields obtained or scalability of the process.

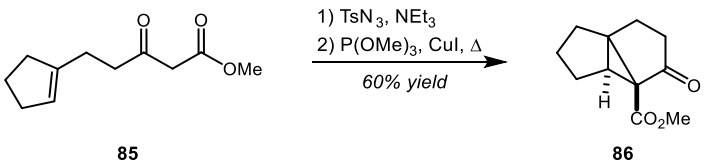
Ring closing metathesis (RCM) was used to construct the cyclohexene ring in Blechert's approach to (±)-**4** (Scheme 15).[80]



Scheme 15: CFA synthesis through RCM.

Ketal **83**, synthesised in five steps and in 32% yield (not shown), underwent efficient RCM using Schrock's Mo catalyst to give access to bicycle **84**. This key step was carried out on a 0.04 mmol scale, and required the use of a glovebox, which reduces the practicality of the route and its applicability to scale up procedures. A further three steps which proceeded in 54% yield afforded (±)-**4** (not shown).

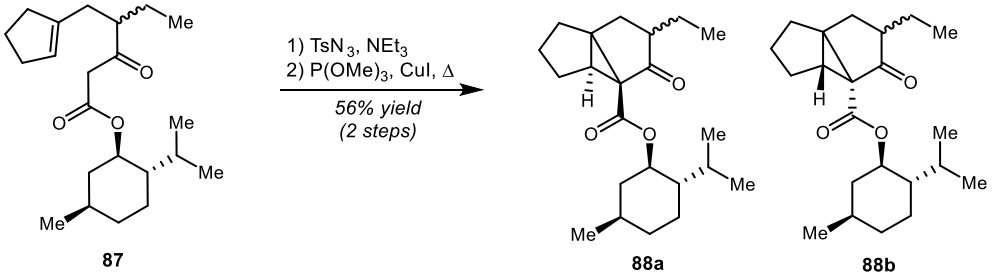
Nakayama *et al.* have reported a synthesis of (±)-**4** featuring an intramolecular [2+1] cycloaddition (Scheme 16).[81]



Scheme 16: Nakayama's [2+1] cycloaddition.

The cyclisation precursor **85** was obtained in three steps and 66% yield (not shown). Treatment of **85** with tosyl azide afforded the corresponding diazo compound, which afforded the tricyclic intermediate **86** through a copper-carbenoid intermediate. Following a further six steps which proceeded in low yield of 5% (±)-**4** was isolated (not shown).

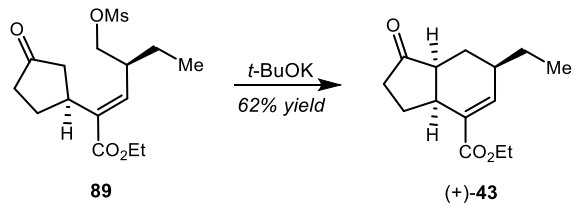
The route was later modified by the Nakayama group to allow access to (+)-**4** (Scheme 17).[82,83] The synthetic strategy focused on the chromatographic separation of the *L*-menthyl ester derivatives. *β*-keto ester **87** was accessed in two steps in 6% yield (not shown), and was cyclised in moderate yield of 56% using the previously communicated conditions,[81] affording **88a** and **88b** as a mixture of C^6-epimers.



Scheme 17: Nakayama's modified synthesis to afford enantiopure CFA.

(+)-**4** was then obtained in a further eight steps which proceeded in 0.8% yield and featured a separation of the menthyl ester derivatives to obtain the enantiomerically pure compound (not shown). The authors also demonstrated that **88b** could be converted to (-)-**4** (not shown). This approach was the first reported synthesis of both isomers of optically active **4**, which is attractive with respect to developing SAR for each enantioseries.[83]

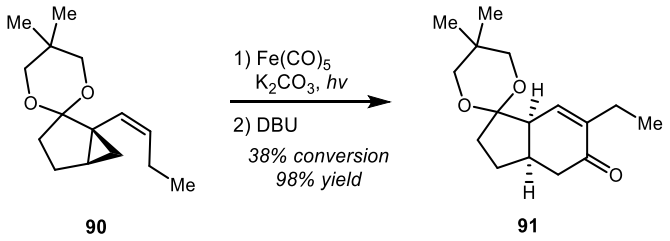
Intramolecular cyclisation has also been used in the synthesis of (+)-**4** by Kobayashi *et al.* (Scheme 18). [84]



Scheme 18: Kobayashi's intramolecular cyclisation-based synthesis of CFA.

Cyclisation precursor **89** was synthesised in ten steps and in an excellent 45% overall yield (not shown). Base-mediated intramolecular S_N2 gave (+)-**43** in moderate yield, allowing late stage formation of the *cis*-ring juncture. Acidic hydrolysis gave access to (+)-**4** in 85% yield (not shown). Furthermore, the authors then demonstrated the coupling of (+)-**4** with CMA isostere *L*-isoleucine, lending strength to the applicability of this strategy for the preparation of COR analogues. In a subsequent publication, Kobayashi *et al.* reported a slightly more efficient synthesis, albeit with a reduced overall yield, featuring the same key cyclisation step.[85]

Intramolecular cyclisation towards **4** has also been reported by Taber *et al.*, who demonstrated the utility of their approach towards enantiopure 5,3- and 6,3-carbocyclic scaffolds by applying the methodology to (+)-**4** (Scheme 19).[86]



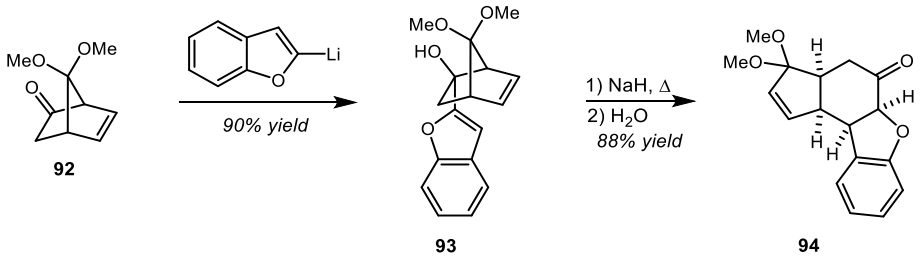
Scheme 19: Taber's cyclocarbonylation-based methodology.

Intermediate **90** was synthesised in five steps and in 51% yield (not shown). Under buffered reaction conditions to prevent acetal deprotection, a novel Fe-mediated cyclocarbonylation then delivered bicycle **91** in 38% conversion. On extending the reaction time, the isolated yield began to decrease and, therefore, the reaction was halted at 38% conversion and the starting material **90** separated and recycled. The authors reported that the kinetic product of the reaction was the *β,γ*-unsaturated ketone,

which was isomerised to the desired enone by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). While the need to separate and recycle the unreacted starting material adds to the synthetic efforts required, the overall high yield of product obtained makes this an attractive key step in the process. Bicycle **91** was then converted to (+)-**4** in five steps and 13% yield (not shown).

Oxy-Cope approaches

An anionic oxy-Cope was used in an early synthesis of (±)-**4**, communicated by Jung and Hudspeth (Scheme 20).[87,88]



Scheme 20: Jung's oxy-Cope-based approach to CFA.

Treatment of ketone **92** with lithiated benzofuran delivered alcohol **93**, which underwent the oxy-Cope rearrangement to afford tetracycle **94** in 88% yield. From **94**, the authors accessed (±)-**4** in ten steps and in 6.3% yield (not shown). The lack of atom economy in this preparation, as well as its overall low yield (1.7%) limits its attractiveness from a scale up perspective; however, it is of synthetic interest as the only example of an oxy-Cope-based methodology towards (±)-**4** synthesis.

Overall, a variety of approaches have been utilised in the synthesis of **4**. Diels–Alder reactions have proven to be a popular key step in several syntheses;[38,60,61,65,67–69] and these often focus on the generation of the same late stage DA precursor.[65,67,68] Conjugate addition approaches and intramolecular cyclisation have also been used several times, providing access to both racemic[70,78,79] and enantiopure[71,72,84–86] **4**. Despite the variety in overall synthetic approaches towards this attractive target, syntheses have typically been long, linear processes, which are ultimately low yielding. As previously intimated, the biological activity of **4** makes it an attractive starting point for analogue synthesis; however, few of the published synthetic routes

offer a practical method for potential diversification, particularly with late stage modifications.

1.5 Synthetic Approaches Towards Coronamic Acid

Natural coronamic acid (**5**) is present in COR (**1**) as the (+)-(2*S*,3*S*)-isomer.[34] Several groups have communicated the synthesis of (+)-**5**, as well as its isomers (Figure 18).

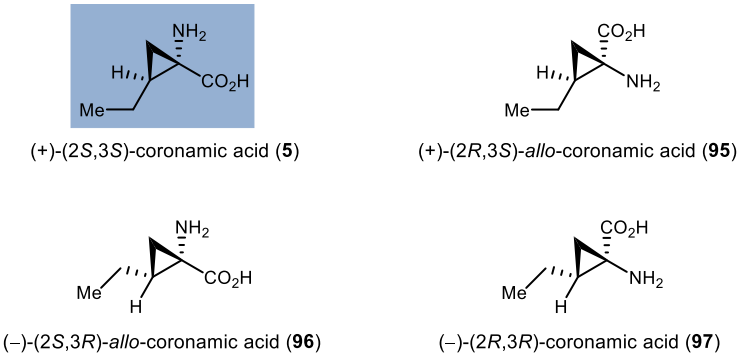


Figure 18: Coronamic acid and its isomers.

Synthetic efforts have also been directed towards (±)-**5**. There exists a multitude of syntheses towards (*E*)-2-alkyl aminocyclopropane carboxylic acids (ACCs) and synthetic pathways can be categorised into seven strategies, grouped according to which ring carbon unit is installed last in the synthesis:[89] final installation of C^1, C^2, or C^3. Table 2 shows the reported syntheses of **5** in chronological order with their associated key step; Figure 19 shows these key steps in more detail.

Table 2: Literature syntheses of coronamic acid.

Author (Year)	Key step (No. steps)	Racemic/ enantiopure	Overall Yield (%)	Ref.
Ichihara (1977)	C^1 (5^a)	Enantiopure	Unknown	90
Stammer (1983)	C^3 (5^a)	Racemic	18	103
Baldwin (1985)	C^1 (8^b)	Racemic	23	97
Williams (1991)	C^2 (7^a)	Enantiopure	51	102
Schöllkopf (1992)	C^1 (5^b)	Enantiopure	14	94
Salaün (1994)	C^1 (9^b)	Enantiopure	21	93
Charette (1995)	C^2 (16^a)	Enantiopure	23	99
Ichihara (1995)	C^1 (10^b)	Enantiopure	30	92
Salaün (1995)	C^1 (3^b)	Racemic	52^c	96
Yamazaki (1995)	C^3 (13^a)	Racemic	9	79
de Meijere (2000)	C^3 (10^b)	Racemic	30	105
Salaün (2000)	C^3 (13^b)	Racemic	32^c	106
Szymoniak (2002)	C^3 (4^b)	Racemic	32	107
Cox and Aggarwal (2003)	C^3 (4^b)	Racemic	17	104
Parsons (2004)	C^1 (7^b)	Racemic	28	98

[a] From a non-commercial starting material. [b] From commercial starting materials. [c] Based on an assumed yield from referenced publication.

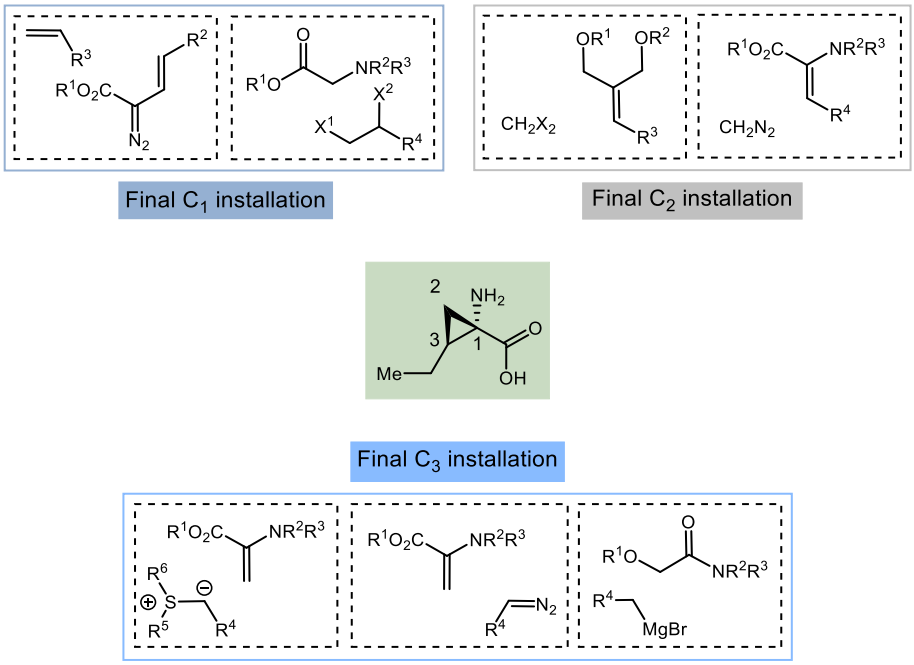
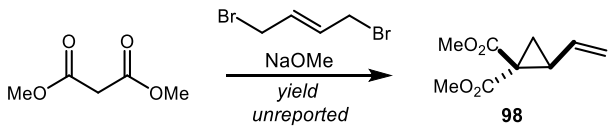


Figure 19: Map of the key steps towards CMA.

Final installation of C^1

Methods for the installation of quaternary C^1 to complete the cyclopropane ring typically focus on the di-alkylation of glycine analogues.[89] The first reported synthesis of (+)-**5** was communicated by Ichihara *et al.* in the partial total synthesis of **3** (Scheme 21).[90]

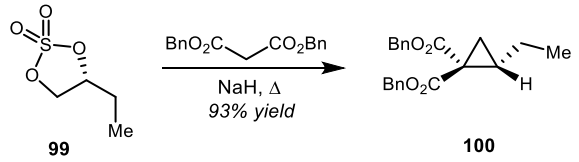


Scheme 21: Ichihara's di-alkylation approach to (±)-CMA.

The cyclopropane **98** was formed in the first step by the known condensation of *trans*-1,4-dibromo-2-butene and methyl malonate.[91] In a subsequent step, selective amidation of the least sterically hindered ester de-symmetrised this intermediate, allowing the synthesis of (±)-**5** as a single diastereoisomer (not shown). From **98**, (±)-**5** was synthesised in four steps (not shown). It was also communicated that the racemate could be resolved by formation of the quinine salt and, following several

fractional recrystallisations, enantiomerically pure (+)-**5** was obtained from this short synthetic sequence.

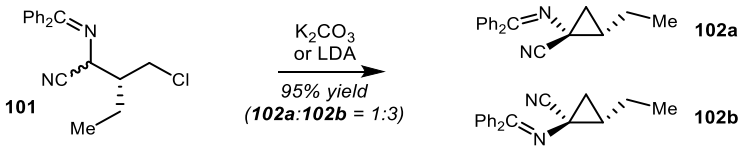
Ichihara *et al.* later reported an asymmetric synthesis of (+)-**5** (Scheme 22).[92]



Scheme 22: Ichihara's approach towards (+)-CMA.

Sulfate ester **99** was synthesised in seven steps from chiral pool starting material (*R*)-malic acid (not shown). Cyclopropanation was achieved through treatment of **99** with dibenzyl malonate, which proceeded with inversion of stereochemistry at C^3. A further three steps in 61% yield gave access to (+)-**5**. Notably, this route allowed synthesis of (+)-**5** on a preparative scale of 11.4 mmol and the authors also demonstrated the utility of the synthetic sequence through the synthesis of all four stereoisomers of **5**, obtained through use of both (*R*)- and (*S*)-malic acid.[92]

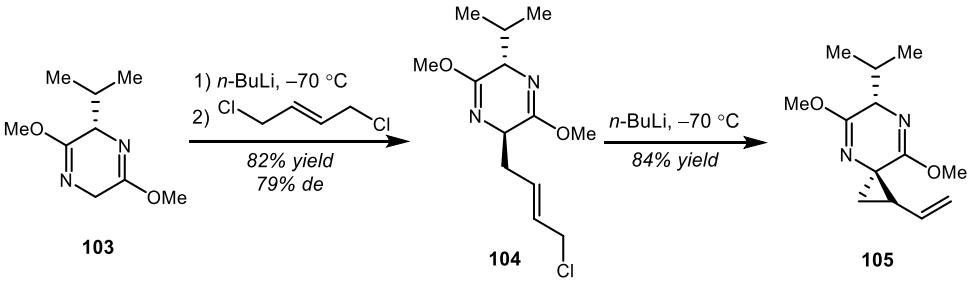
Salaün *et al.* applied their general method towards *E*-2-alkyl ACCs to the synthesis of (+)-**5** (Scheme 23).[93]



Scheme 23: Salaün's synthesis of (+)-CMA.

The key step in this route was the diastereoselective cyclisation to afford **102**, with the desired diastereomer **102b** as the major product. Cyclisation precursor **101** was synthesised in eight steps and in 37% yield. Attempted optimisation of the cyclisation to improve the diastereoselectivity was unsuccessful. (+)-**5** was then obtained from hydrolysis steps in 97% yield.

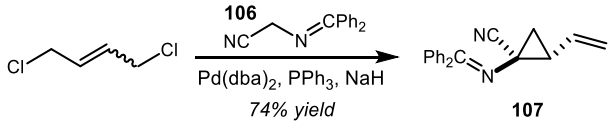
Schöllkopf also reported asymmetric synthetic methodology towards (+)-**5**.[94] Based on previous work by Quinkert,[95] the publication reports a chiral auxiliary-enabled synthesis (Scheme 24).



Scheme 24: Schöllkopf's chiral-auxillary-based methodology towards (+)-CMA.

Alkylation of imine **103** delivered chloride **104** with good diastereocontrol. An intramolecular alkylation *via* S_N2' provided **105** as a mixture of four diastereoisomers, which could be separated by chromatography, thereby allowing access to alternative isomers of **5** from a common intermediate. Further hydrolysis then afforded the free amino acid (+)-**5** in low yield of 20% and in a moderate *ee* of 68% (not shown).

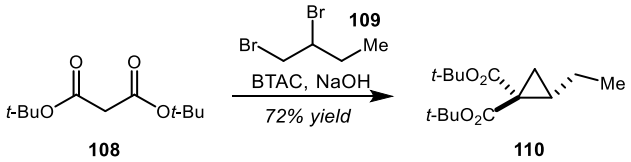
In a follow up to their previous asymmetric synthesis,[93] Salaün *et al.* reported a racemic, Pd-catalysed allylation strategy for the synthesis of (±)-**5** (Scheme 25).[96]



Scheme 25: Salaün's sythesis of CMA featuring a Pd-catalysed alkylation.

Di-alkylation of **106** generated cyclopropane **107** in high yield as a single diastereomer *via* a highly stereoselective cyclisation. **107** was then advanced to (±)-**5** using the methodology employed in their previous synthesis (not shown).[94]

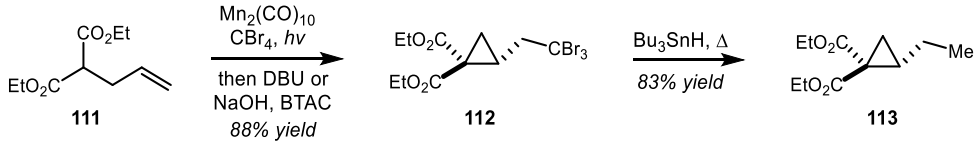
In a report from Baldwin *et al.*,[97] (±)-**5** was prepared following a short synthetic sequence (Scheme 26).



Scheme 26: Baldwin's double alkylation to assemble the cyclopropyl moiety.

Cyclopropanation of di-*tert*-butylmalonate **108** using dibromide **109** delivered cyclopropane **110** in good yield. Following a procedure similar to that employed by Ichihara,[90] (±)-**5** was accessed after six further steps in 32% yield.

Parsons *et al.* reported a short synthetic sequence towards (±)-**5** where the key step was a radical-based 3-*exo*-trig cyclisation of terminal alkene **111** employing Mn-mediated methodology developed within the group (Scheme 27).[98]

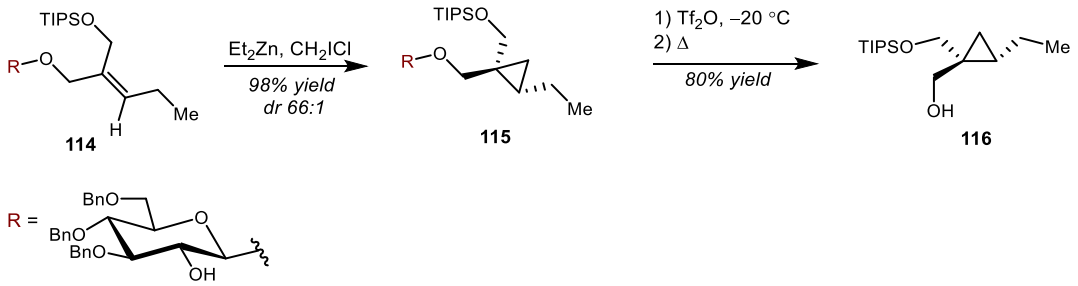


Scheme 27: Parsons' radical-based methodology for the synthesis of CMA.

The use of the phase transfer catalyst benzyltriethylammonium chloride (BTAC) allowed the pentacarbonylmanganese halide to be washed out of the reaction mixture to improve product isolation. Debromination using *n*-Bu_3SnH afforded intermediate **113** which was advanced to (±)-**5** following the route of Baldwin (not shown).[97]

Final installation of C_2

Methods for the final installation of C^2 typically feature Simmons-Smith cyclopropanation or the 1,3-dipolar cycloaddition of diazo-species.[89] Charette *et al.* reported a chiral auxiliary-mediated synthesis of 3-methanoamino acids, focusing on **5** and its isomers, with the key step being a Simmons-Smith cyclopropanation (Scheme 28).[99]

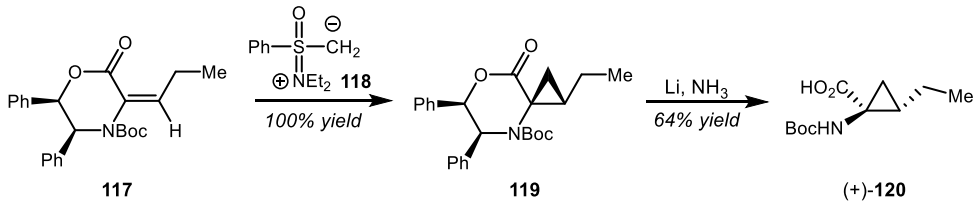


Scheme 28: Charette's chiral-auxillary-based approach to CMA.

Both the *E*- and *Z*-glucosides were prepared from a common starting alcohol by changing the order of the synthetic sequence, using methodology previously

communicated by the Charette group.[100,101] Following optimisation of the Simmons-Smith reaction, intermediate **115** was obtained in high yield and with good diastereocontrol, setting the absolute stereochemistry of the C^3 position. Formation of the triflate facilitated cleavage of the chiral auxillary and gave cyclopropyl **116** in high yield. *t*-Butyloxycarbonyl (Boc)-protected (+)-**5** was then obtained in six steps in 53% yield (not shown). The authors noted that through minor modification the route could also be used to give access to (+)-*allo*-coronamic acid, **95**.

Williams and Fegley have described the asymmetric synthesis of several ACCs through a chiral-auxillary based approach (Scheme 29).[102]

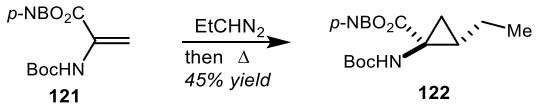


Scheme 29: Williams' chiral-auxillary-based methodology towards CMA.

Alkene **117** was synthesised in three steps in a high yield of 79% (not shown). To achieve a facially selective cyclopropanation, a range of conditions was screened for the formation of intermediate **119**. Diastereoselective cyclopropanation using sulfonium ylide **118** gave **119** as a single diastereomer in excellent yield. Here, the authors hypothesised that this facial selectivity was the result of π-stacking between the aryl ring on the ylide and the phenyl substitution on the lactone. Treatment of intermediate **119** under Birch-like conditions gave the Boc-protected amino acid **120**, which was hydrolysed to afford (+)-**5** (not shown).

Final installation of C^3

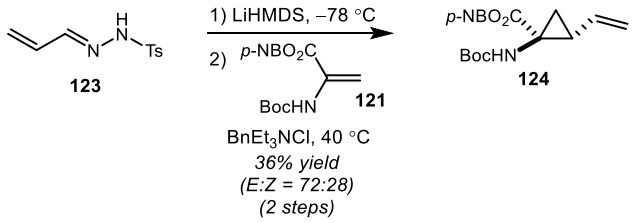
Routes which install C^3 last typically feature cyclopropane formation by a Kulinkovich reaction or the addition of di-polar species to dehydroamino acids.[89] Stammer *et al.* developed a synthesis of (±)-**5**, which featured the addition of a diazonium species to a dehydroalanine derivative (Scheme 30).[103]



Scheme 30: Stammer's amino acid-based synthesis of (±)-CMA.

Dehydration of protected serine gave intermediate **121**, which could then be treated with a diazonium species to give cyclisation product **122** with the desired relative stereochemistry. Hydrolysis of the ester moiety of **122** then afforded Boc protected (±)-**5**.

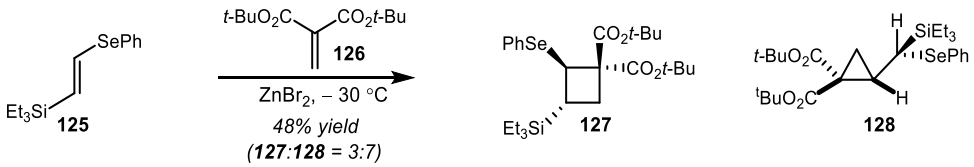
Improved handling of the diazo species was reported by Cox and Aggarwal who applied their methodology for the *in situ* generation of aryl diazomethanes[104] to a one-pot diastereoselective synthesis of cyclopropane amino acids.[89] The reactive diazo species was generated *in situ* from tosylhydrazone derivative **123** (Scheme 31).



Scheme 31: Cox's diazo-based approach towards (±)-CMA.

Under phase transfer conditions, cyclopropanation of alkene **121** with **123** delivered **124** as a 72:28 mixture in favour of the desired diastereomer, which was converted to (±)-**5** in a further two steps (not shown).

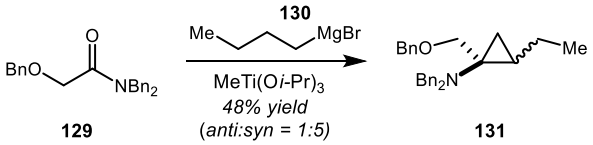
Yamazaki *et al*. utilised a novel [2+1] cycloaddition, featuring a key selenium-enabled [1,2]-silicon migration to afford highly functionalised ACCs, which can then be converted to (±)-**5** (Scheme 32).[105]



Scheme 32: Yamazaki's cycloaddition-based approach to (±)-CMA.

Treatment of alkene **125** with **126** in the presence of $ZnBr_2$ gave [2+2]-adduct **127** and the desired [2+1]-product **128**. A further ten steps which proceeded in 19% yield gave access to (±)-**5** (not shown). While synthetically interesting, this synthesis is lengthier and lower yielding than other preparations of (±)-**5** (see Table 2).

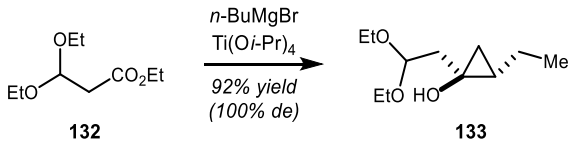
de Meijere and co-workers reported the synthesis of (±)-**5** *via* Ti-mediated ACC formation (Scheme 33).[106]



Scheme 33: de Meijere's Kulinkovich-de Meijere-based approach to (±)-CMA.

Amide **129** was prepared in three high yielding steps and on kilogram scale from inexpensive starting materials. The key cyclopropanation was achieved through a Kulinkovich-de Meijere reaction to deliver **131** in moderate yield and favouring the undesired diastereomer, despite the author's attempts to optimise the reaction. **131** was then advanced to protected (±)-**5**, as a mixture of diastereoisomers, in four steps with an overall yield of 72% (not shown).

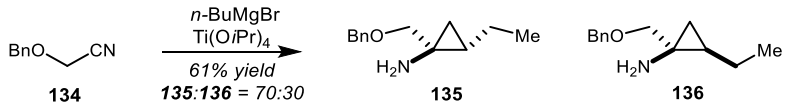
Salaün *et al.* also approached ACCs using a Kulinkovich reaction (Scheme 34).[107]



Scheme 34: Salaün's Kulinkovich-based approach towards (±)-CMA.

In this case, the cyclopropanated product **133** was obtained in high yield of 92% and with complete diastereoselectivity through reaction of ester **132** with *n*-BuMgBr. A further eleven steps which proceeded in 35% yield afforded (±)-**5** (not shown).

Szymoniak *et al.* have demonstrated the synthesis of (±)-CMA using their methodology for Ti-mediated conversion of nitriles to cyclopropylamines (Scheme 35).[108]



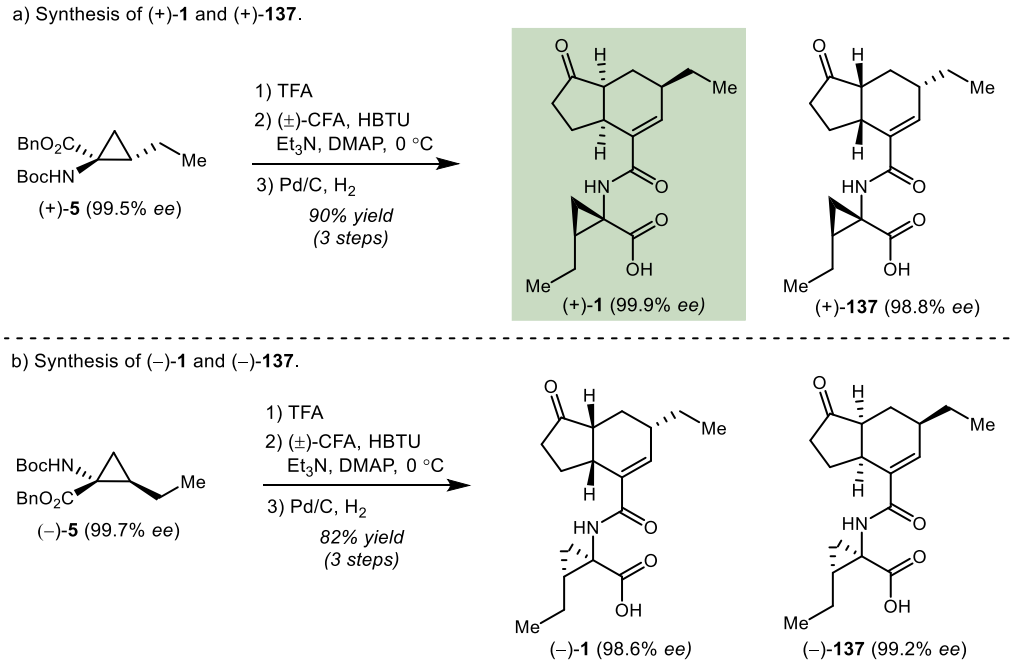
Scheme 35: Szymoniak's approach towards cyclopropyl amines.

Nitrile **134** was treated with *n*-BuMgBr in the presence of Ti(O*i*Pr)$_4$, which generated an intermediate azatitanacycle, and then underwent ring contraction to afford separable **135** and **136** (70:30) in 61% yield. Boc-protected CMA was then obtained in three further steps that proceeded in 74% yield to complete this concise synthesis of CMA (not shown).

Overall, several well-established methodologies have been leveraged to enable the synthesis of ACCs such as **5**. These can generally be grouped with regard to overall synthetic strategy, and typically offer short routes to **5** and analogues thereof. The most synthetically useful of these approaches allow derivative synthesis from a late stage, common intermediate, which is attractive with respect to analogue generation.

1.6 Total Synthesis of Coronatine

Ueda *et al.* communicated the synthesis of four stereoisomers of **1**, accessed through the condensation of enantiopure (+)-**5** and (-)-**5** with (±)-**4** (Scheme 36).[38]



Scheme 36: Total synthesis of coronatine.

Boc deprotection of both enantiomers of **5** was followed by 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)-mediated amidation with (±)-**4**. The free acid was then obtained through chemoselective hydrogenation of the benzyl protecting group. In both cases, the mixture of diastereoisomers was separated by high-performance liquid chromatography (HPLC). This coupling has also been reported using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), again in excellent yield.[59,71]

Overall, it is clear that both components of COR, particularly **4**, pose a synthetic challenge with respect to amenability to agrochemical discovery programmes. In order to use coronatine as a tractable scaffold for herbicide development, a robust, flexible synthetic strategy is required, enabling scalable synthesis of diverse natural product analogues.[4]

Significant efforts have been made to develop efficient syntheses towards **4**, which must take into consideration the stereochemical requirements and ideally be amenable to analogue generation. Varied synthetic routes have been communicated towards the synthesis of **4**, however there exists a need for a less protracted synthetic sequence, ideally from inexpensive and easily accessed starting materials. Cyclopropane amino acids such as **5** have also received considerable attention from a synthetic viewpoint, and several classifications of general methodology amenable to their synthesis are known.[89] Overall, scope exists for the improvement of these approaches, particularly with respect to large scale preparations and the amenability of the route to late stage diversification.

2 Project Aims

Despite the significant interest in COR as a herbicidal lead from both academic research groups and the agrochemical industry, the natural product scaffold remains underdeveloped with respect to the development of a marketable crop protection product. An SAR for herbicidal activity around the bespoke organic framework is currently unclear, which has been largely attributed to the lack of synthetic accessibility of the structurally complex natural product scaffold.[55]

We aimed to adopt a synthetic strategy to enable a thorough SAR investigation around COR. We hoped to carry out SAR scanning of both the core COR moiety, CFA, and the amino acid residue, CMA (Figure 20).

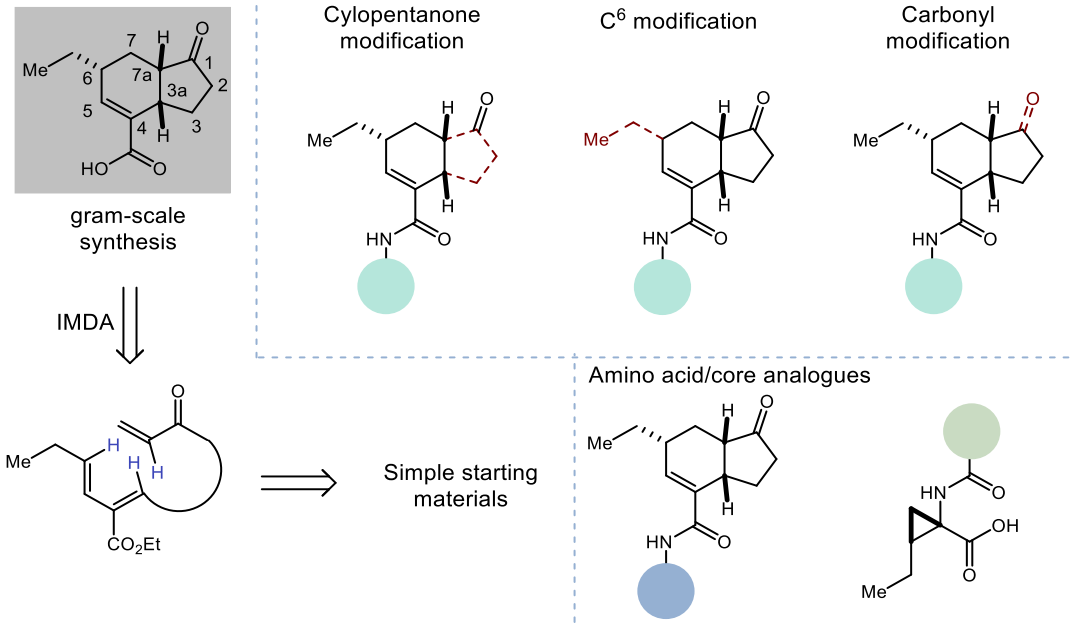


Figure 20: Approach to COR analogues, showing scalable synthesis of CFA, and points of scaffold diversification.

Through the development of a scalable synthetic route towards CFA giving access to synthetically useful quantities of the bicyclic core, we hoped to synthesise a range of coronafacoyl-amino acid analogues. The known biological tolerance for variation of the amino acid residue was encouraging in this regard, and we aimed to incorporate a wide range of both natural and non-natural amino acids for a thorough SAR scanning.

Project Aims

The developed synthetic route was also desired to be flexible in nature, giving access to CFA-derived alternative core motifs through single point changes.

We hoped to achieve this through the utilisation of a convergent synthetic route, focusing on the synthesis of a triene **42**-like intermediate (Figure 18). This would allow expedient access to the bicyclic scaffold through a DA cyclisation, which we had identified as a powerful and efficient means of CFA synthesis through review of the literature.

We aimed to carry out a wide reaching SAR scanning of the core motif, with the retention of CMA as the common amino acid. Again, to enable the synthesis of a significant number of analogues a robust, scalable synthesis of CMA was desired.

Throughout the project, our overall strategy was to use readily accessible CFA and CMA mimics to carry out initial SAR screening, and subsequently direct further synthesis of analogues using our synthetic CFA and CMA (Figure 21).

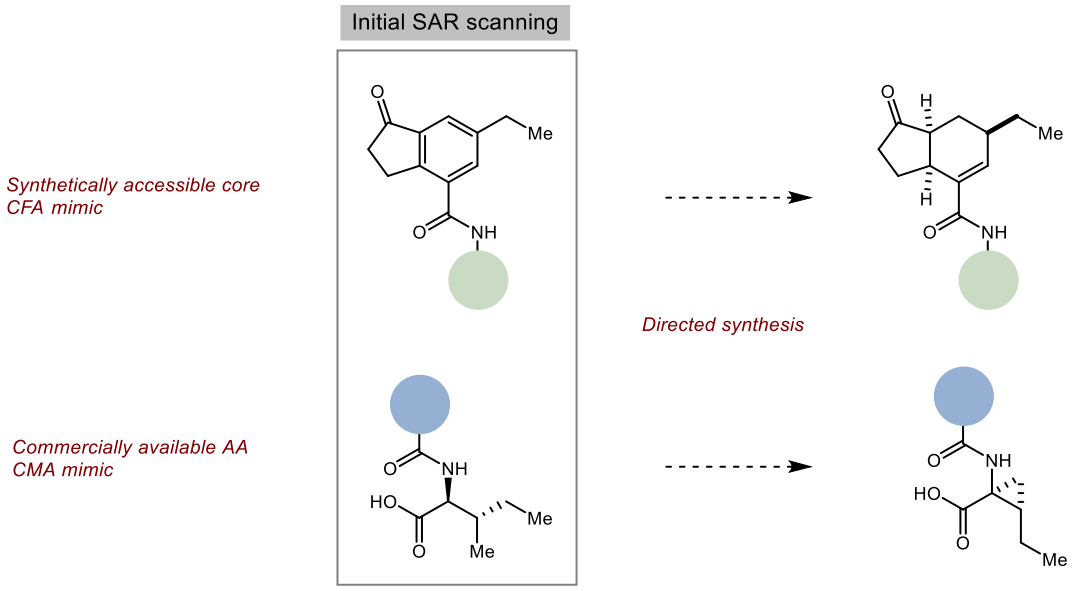


Figure 21: Overall strategy for SAR development: Extensive analogue synthesis using simplified CFA and CMA mimics to enable targeted synthesis of CFA and CMA conjugates.

This was hoped to provide sufficient biological information to allow for a more targeted, informed synthesis of derivatives using our synthetic natural product fragments.

Project Aims

Following biological evaluation of these analogues we hoped to identify an SAR for phytotoxic activity around the COR scaffold. Through the SAR directed synthesis of further analogues we aimed to develop COR into a potent phytotoxic lead, ideally of greater structural simplicity than the parent natural product to deliver a target of increased synthetic accessibility.

3 Results and Discussion

3.1 Biological Testing

All compounds tested in this study were evaluated in herbicide glasshouse screen one (GH1) as an initial assessment, and followed up by further glasshouse screening (GH2) tests if interesting activity was observed.

In GH1, compounds are assessed for pre- and post-emergence activity against four weed species, and scored visually for % phytotoxicity (0-100, where 100 is complete control of the target and 0 is no control). Table 3 shows GH1 screening in more detail.

Table 3: GH1 assessment of phytotoxicity.

Test species	Treatment timing	Rate (g/ha)
Amaranthus retroflexus	Pre/post-emergence	1000
Lolium perenne	Pre/post-emergence	1000
Stellaria media	Pre/post-emergence	1000
Digitarua sanguinalis	Pre/post-emergence	1000

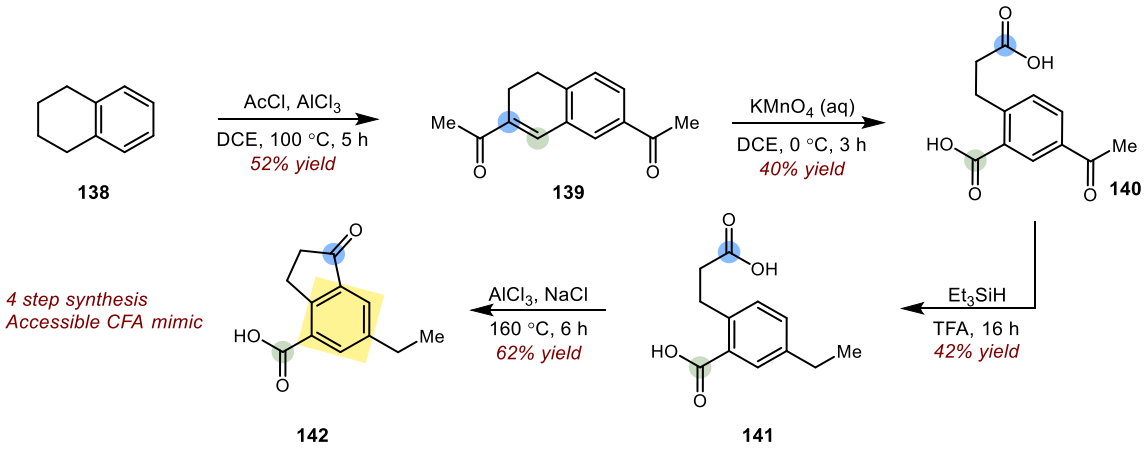
Known herbicides Acetochlor, Atrazine, Mesotrione, Pinoxden, and Glyphosate were used as positive controls in the test.

In this thesis, tested compounds are colour coded according to their activities; no colour: inactive compound, yellow: 40-50% phytotoxicity, pale green: 60-70% phytotoxicity, dark green: 80-100% phytotoxicity.

3.2 Coronalon

Initially, we aimed to carry out an extensive SAR study using the aromatic coronalon core as a surrogate for CFA with variation of the amino acid residue. We viewed this study as serving two purposes; the assessment of the aromatic core as a substitute for CFA, and therefore as a means of structural simplification, and to potentially identify an SAR for the amino acid portion of the natural product motif. As previously mentioned, we aimed to use this study on the more synthetically accessible aromatic core to direct the synthesis of *N*-coronafacoyl analogues.

The coronalon core, **142**, was synthesised by known synthetic methodology in four steps (Scheme 37).[109]



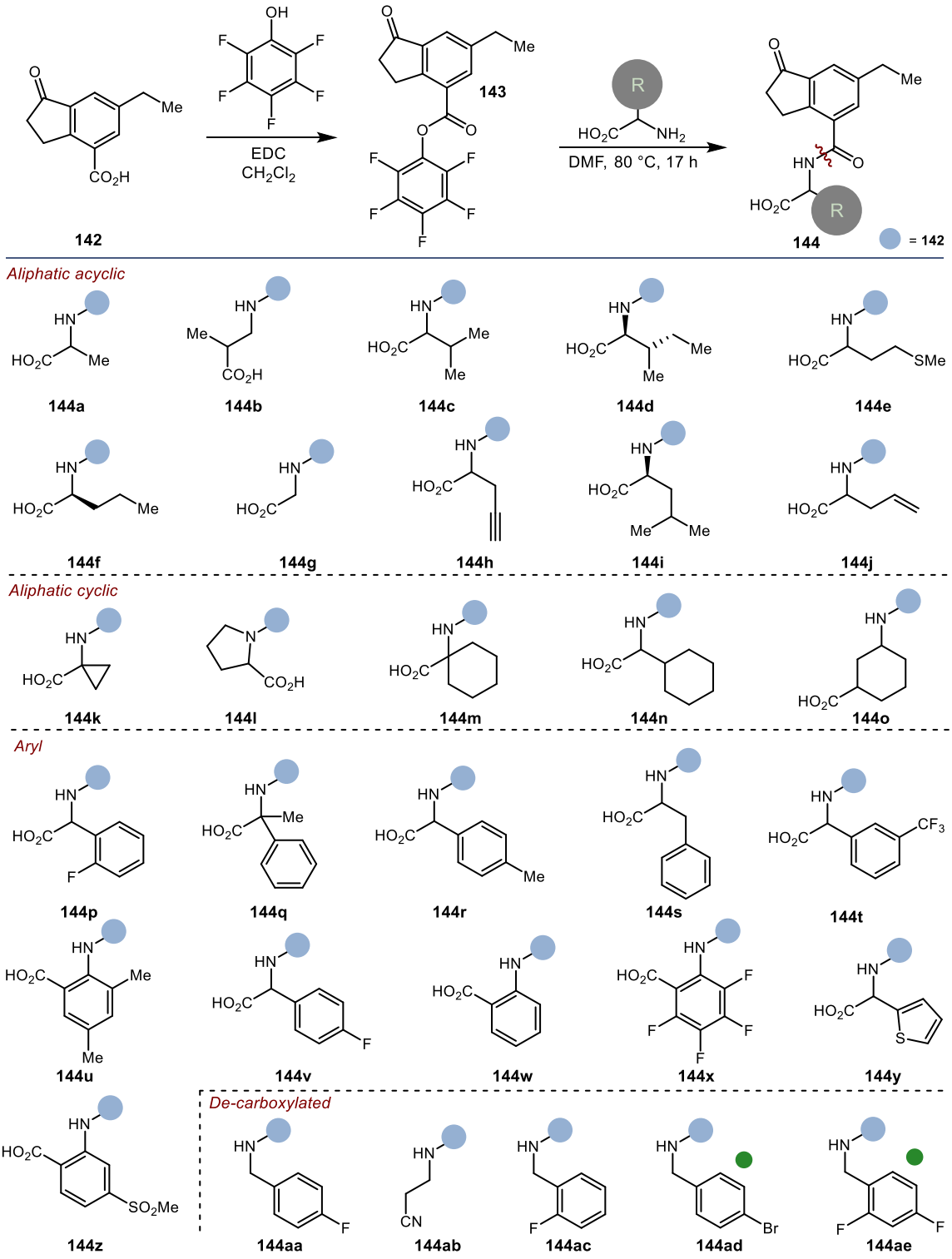
Scheme 37: Synthetic route to aromatic coronalon-core 142, highlighting key elements of the carbon framework.

Regio-selective Friedel-Crafts acylation gave access to bis-ketone intermediate **139**, which then underwent oxidative cleavage of the vinyl unit to afford acid **140**. The pendant ketone moiety was then reduced to give the required ethyl substituent, followed by an intramolecular Friedel-Crafts acylation to form the 5,6-ring system. Despite the low overall yield of this process, 5.4% over four steps, the synthetic sequence was greatly simplified in comparison with approaches towards CFA, and therefore the coronalon core represents an attractive CFA-mimic to enable expedient analogue synthesis on a more easily accessible core moiety.

We then carried out an extensive automated amino acid screen using the aromatic core **142** as our common unit. Significant quantities of the core moiety was available in-house at Syngenta, enabling analogue scanning where amino acids were selected with the intention of covering a broad chemical space.

The analogues were synthesised through coupling with the bench stable pentafluorophenyl (PFP) ester of the core moiety (**143**). Scheme 38 shows the synthesis and initial biological assessment of the compounds made; table 4 shows the biological activity of active hits in more detail. It is worthy of note that several of the substrates with electron deficient amino acids underwent decarboxylation under the

relatively mild coupling conditions, affording products **144aa-144ae**, which were also assessed for phytotoxic activity.



Scheme 38: Coronalon aromatic core amino acid screen, synthesised through coupling of free amino acids with PFP-ester intermediate 177. Activity: ● = 80-100, ● = 60-70, ● = 40-50.

Table 4: Detailed phytotoxic activity of active compounds resulting from coronalon-analogue testing.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
144ad	60	10	80	10	NC/ST	0	0	0	0	NC/ST
144ae	20	0	100	20	NC/MR	0	0	0	0	NC/MR

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). ST = stunting, NC = necrosis, MR = morphological effects.

Disappointingly, limited activity was observed in this screen. All natural amino acids tested and all aliphatic amino acids gave inactive conjugates; however, the two most active compounds, **144ad** and **144ae** featuring decarboxylated aromatic amino acids, showed moderate activity in this initial test (GH1). The observed activity profile, and structural deviation from coronalon/COR of these two hit compounds led to the conclusion that the observed phytotoxicity was unrelated to the project core structure.

These compounds were promoted to further post-emergence testing (GH2) against additional weed species (Table 5).

Table 5: GH2 testing of compounds 144ad and 144ae.

	Post								
Compound	ABUTH	BIDPI	CHEAL	KCHSC	ECHCG	SETFAL	ELEIN	SORHA	Symptom
144ad	20	10	20	10	10	10	10	0	NC/ST
144ae	0	10	10	30	10	10	20	20	NC/ST

Test species: *Abutilon theophrasti* (ABUTH), *Bidens pilosa* (BIDPI), *Chenopodium album* (CHEAL), *Kochia scoparia* (KCHSC), *Echinochloa crus-galli* (ECHCG), *Setaria faberi* (SETFAL), *Eleusine indica* (ELEIN), *Sorghum halepense* (SORHA). ST = stunting, NC = necrosis.

Disappointingly, no interesting biological activity was observed from the second round of testing, and therefore these compounds were no longer considered to be of interest to the herbicide discovery project.

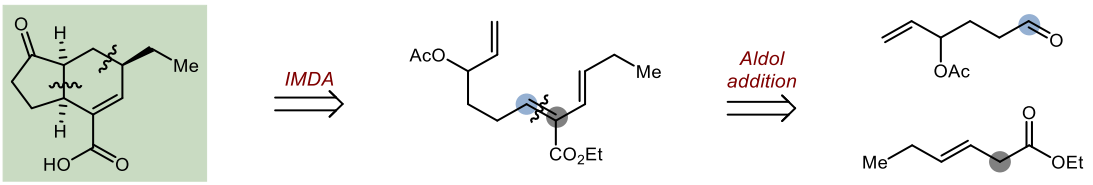
Overall, despite the fact that little activity was observed from these synthesised analogues, learning could still be taken from the results. The wide variety of amino acids chosen and the observed lack of activity across the screen lead us to conclude that the coronalon aromatic core could not generally be considered a substitute for CFA; however, at this point in our investigations, with little information regarding tolerance for modification of the amino acid residue, we could not disregard the possibility that the lack of activity was related to amino acid selection.

3.3 Coronafacic Acid Synthesis

From the outset, and in light of the failure of our coronalon-analogues, we aimed to develop a scalable, robust synthetic strategy to enable the synthesis of gram-scale quantities of (±)-CFA, and ideally to have potential for modification to give synthetic access to CFA analogues. The successful execution of this ideal would then allow a thorough SAR investigation around the amino acid residue and CFA scaffold.

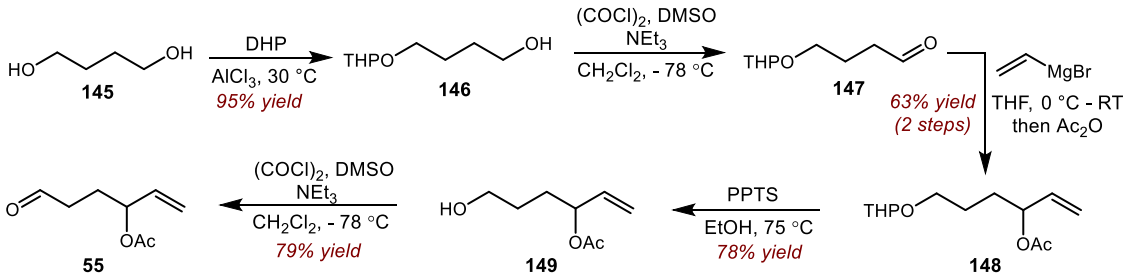
As previously mentioned, it has been reported that the natural enantiomer of COR, (+)-COR, is more potent than its isomers.[38] At this early stage of analogue generation and screening, we chose to focus on the synthesis of racemic analogues to allow expedient access to the desired compounds, with a view to gaining access to the single enantiomers through asymmetric synthesis or chiral separation should a compound of interest be identified.

Following a review of literature syntheses of CFA, particularly the DA-based approaches, we selected the Charette preparation from 2007 (Section 1.4, scheme 7)[68] as a basis for our synthetic strategy to CFA. The Charette strategy featured several key elements which we had identified as being attractive with respect to our aims. We hoped that the convergent nature of the synthesis would give opportunities for expedient CFA analogue generation, and IMDA of the commonly used triene-intermediate to give the bicyclic core is known to be a robust means of assembling the carbon framework with control of the required stereocenters (Scheme 39).[65,67,68]



Scheme 39: Retrosynthetic analysis of CFA.

To begin our synthetic approach, we required a robust, scalable synthesis of the key aldehyde **55** (Scheme 40).

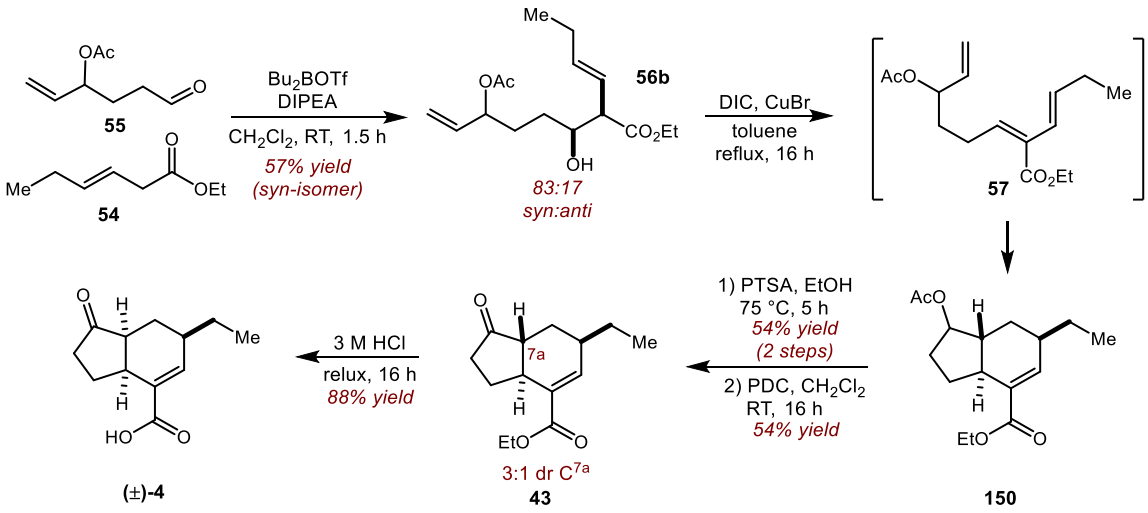


Scheme 40: Synthesis of aldehyde 55.

1,4-Butanediol (**145**) was mono-protected with THP, prior to Swern oxidation of the free alcohol to afford unstable aldehyde **147**, which was used immediately upon isolation. Addition of vinyl Grignard, followed by quenching of the reactive intermediate with acetic anhydride gave intermediate **148** in a single step from **147**, without the need to isolate the intermediate alcohol product. Mild acidic deprotection of the THP group afforded the free alcohol **149**. We found control of the reaction timeframe to be crucial in this step, as prolonged heating resulted in the formation of a by-product through transfer of the acetate group to the primary alcohol. A second Swern oxidation then gave access to the desired aldehyde **55**. This synthetic procedure proved robust for the synthesis of gram-scale quantities of aldehyde **55**, with each step being carried out on >4 g scale.[110]

With robust methodology towards aldehyde **55** in hand, we turned our attention to the diastereoselective aldol addition as described by Charette (Scheme 41). Under the cryogenic conditions reported by Charette, the reaction proceeds with selectivity for the *anti*-aldol isomer (Section 1.4, scheme 7). This is unexpected due to the *syn*-favouring aldol conditions, and Charette attributes this to the Lewis acid-mediated reaction proceeding through an open transition state.

Initially, we found the Charette conditions affording the *anti*-diastereoisomer preferentially to be robust, and then looked to dehydrate this intermediate to deliver the desired triene **57**. Disappointingly, the conditions communicated by Charette to dehydrate the *anti*-isomer (**56a**) (diethyl azodicarboxylate (DEAD), PPh_3) were not reproducible in our hands, affording decomposition products. Attempts to dehydrate this isomer through mesylate formation and subsequent elimination successfully delivered the triene product, however as a mixture of alkene isomers (~ 1:1.3 *Z*:*E*) slightly in favour of the undesired *E*-isomer. To mitigate this, we considered the temperature dependence of the diastereoselectivity of the aldol addition. Isomerisation of the kinetically favoured *E*-enolate to the *Z*-isomer is known to occur at higher temperatures, affording the *syn*-product.[111] Gratifyingly, we found that by carrying out the aldol addition reaction at room temperature, the selectivity of the reaction was reversed with the *syn*-isomer (**56b**) being formed predominantly (83:17 *syn:anti*). These conditions came with the slight caveat that at the elevated temperature some isomerisation (~30%) of the ester alkene occurs affording an inseparable isomer, however this minor impurity does not react in the later IMDA and can be cleanly separated.



Scheme 41: Synthesis of CFA.

CuBr-mediated dehydration of the *syn*-isomer (**56b**) with DIC proceeded cleanly to afford the desired triene intermediate **57**, and we found that when this reaction was carried out at elevated temperature the triene underwent IMDA cyclisation to afford bicycle **150** as a mixture of isomers at C^1. The cyclisation afforded predominantly the

anti-fused product resulting from an *exo*-selective IMDA transition state. Minor quantities of the *cis*-isomer could be observed (~30%) resulting from *endo*-IMDA, however this was inconsequential as the C^{7a} centre was later epimerised to afford the *cis*-fused bicycle. The IMDA cyclisation is worthy of note as it was found to proceed without the need for a sealed vessel or greatly elevated temperatures, which have previously been used in the cyclisation of triene-type intermediates towards CFA.[65,67,68] This enabled the scalability of the reaction, allowing the transformation to be easily carried out on gram-scale.

Hydrolysis of the acetate followed by oxidation to the desired ketone gave **43** in 3:1 *trans*:*cis* dr at C^{7a}. Final acid mediated ester hydrolysis occurred with ring-junction epimerisation to the thermodynamically favoured *cis*-fused ring, giving (±)-CFA in good yield.

Each step of the synthesis was carried out on at least 1 g scale, and the synthetic sequence was used to prepare > 2.5 g CFA for analogue generation.

3.4 Coronafacoyl-Amino Acid Synthesis

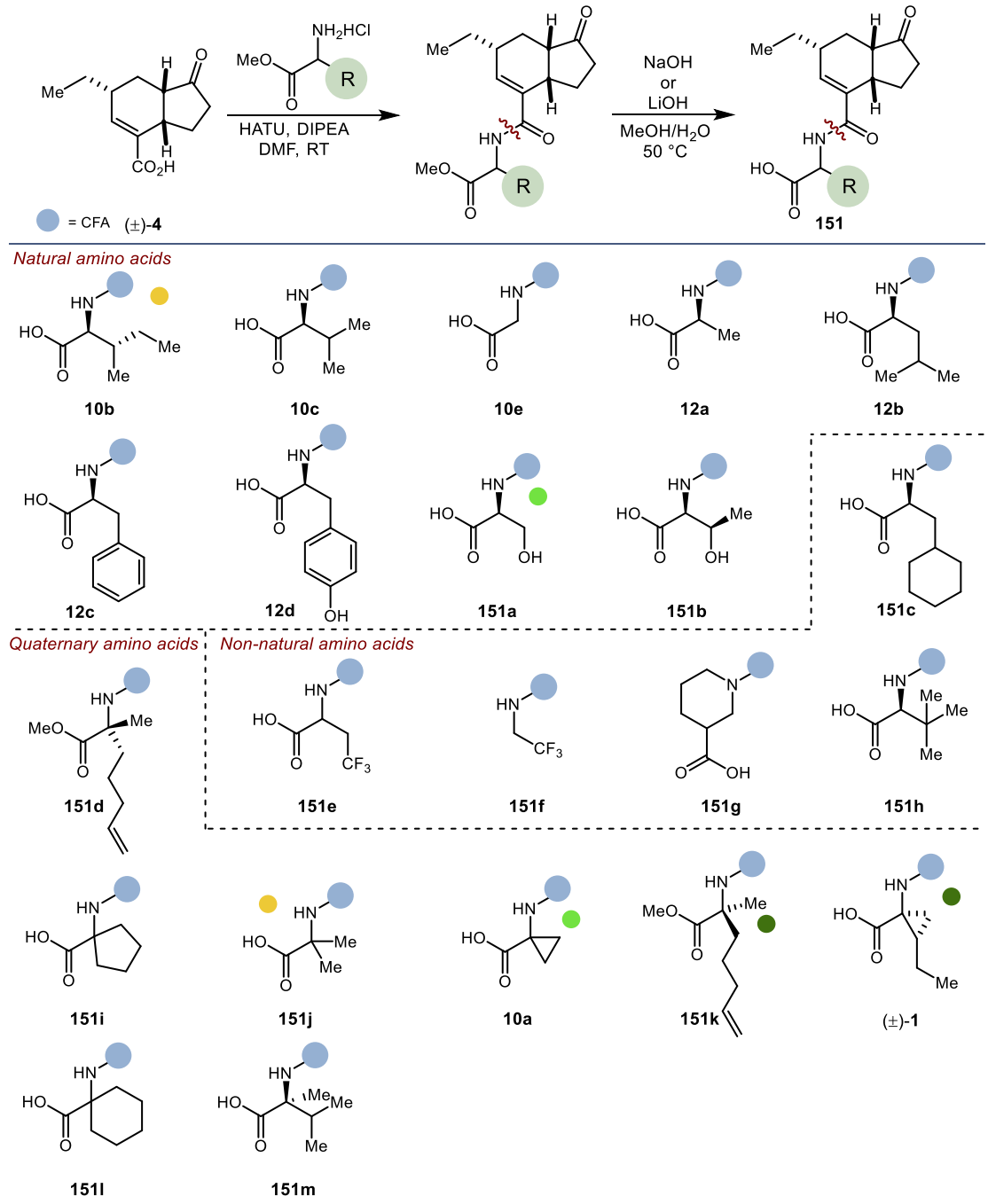
As previously mentioned, we had intended the biological outcome of the coronalon study to direct the design and synthesis of coronafacoyl-analogues. As little direction could be gleaned from these results, we selected the amino acids used for coronafacoyl-analogue synthesis with the intention of covering a wide chemical space.

The compounds were synthesised through 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazole[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) coupling of (±)-CFA with a methyl ester protected amino acid. The intermediate ester compounds formed were of interest as potential pro-cides, thought to release the parent compound *in situ*. The free-acid final compounds were then obtained by basic hydrolysis of the ester moiety (Scheme 42).

Several natural amino acids were selected, including serine, threonine, isoleucine, and valine, the coronafacoyl-conjugates of which have all been isolated alongside COR (Introduction, Figure 9). Non-natural amino acids were also incorporated to ensure breadth to our screening, including **151g** which has a β-amino acid relationship, and **151f**, which was isolated as the decarboxylated product following amide bond

formation, presumably due to the highly electron-withdrawing nature of the substituent. In mimicry of CMA, we synthesised a number of quaternary amino acid conjugates. (*S*)-configured **151k** was used alongside its enantiomer **151d**.

Importantly, racemic COR ((±)-**1**) was synthesised. As the varying levels of activity of COR enantiomers is known, and our analogues were made and tested as racemates, we required a racemic sample of COR to act as a standard for biological evaluation.



Scheme 42: Coronafacoyl-amino acid compounds. Activity: = 80-100, = 60-70, = 40-50.

151d and **151k**[112] were tested only as the methyl ester pro-cide due to a paucity of available material. Several of these analogues displayed phytotoxic activity; however,

none showed greater activity than COR itself. The activity observed is further detailed in Table 6.

Table 6: Detailed phytotoxic activity of active coronafacoyl-amino acid compounds.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
(±)-1	40	0	50	60	NC/ST	70	40	70	80	NC/ST
10a	50	40	0	60	ST	40	30	50	50	ST
10b	0	0	0	0	ST	0	0	50	0	ST
151a	0	0	70	20	NC/ST	0	0	0	0	NC/ST
151j	0	0	0	0	ST	20	0	50	50	ST
151k	0	0	0	0	ST	50	0	80	0	ST

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). ST = stunting, NC = necrosis.

Figure 22 shows images of weed species treated with three of our tested compounds. Plant species on the left have been treated with inactive coronafacoyl-*L*-alanine (**12a**), plant species in the centre have been treated with (±)-COR and show significant phytotoxic effects, and plant species on the right have been treated with coronafacoyl-*L*-serine (**151a**), and show moderate phytotoxic effects.

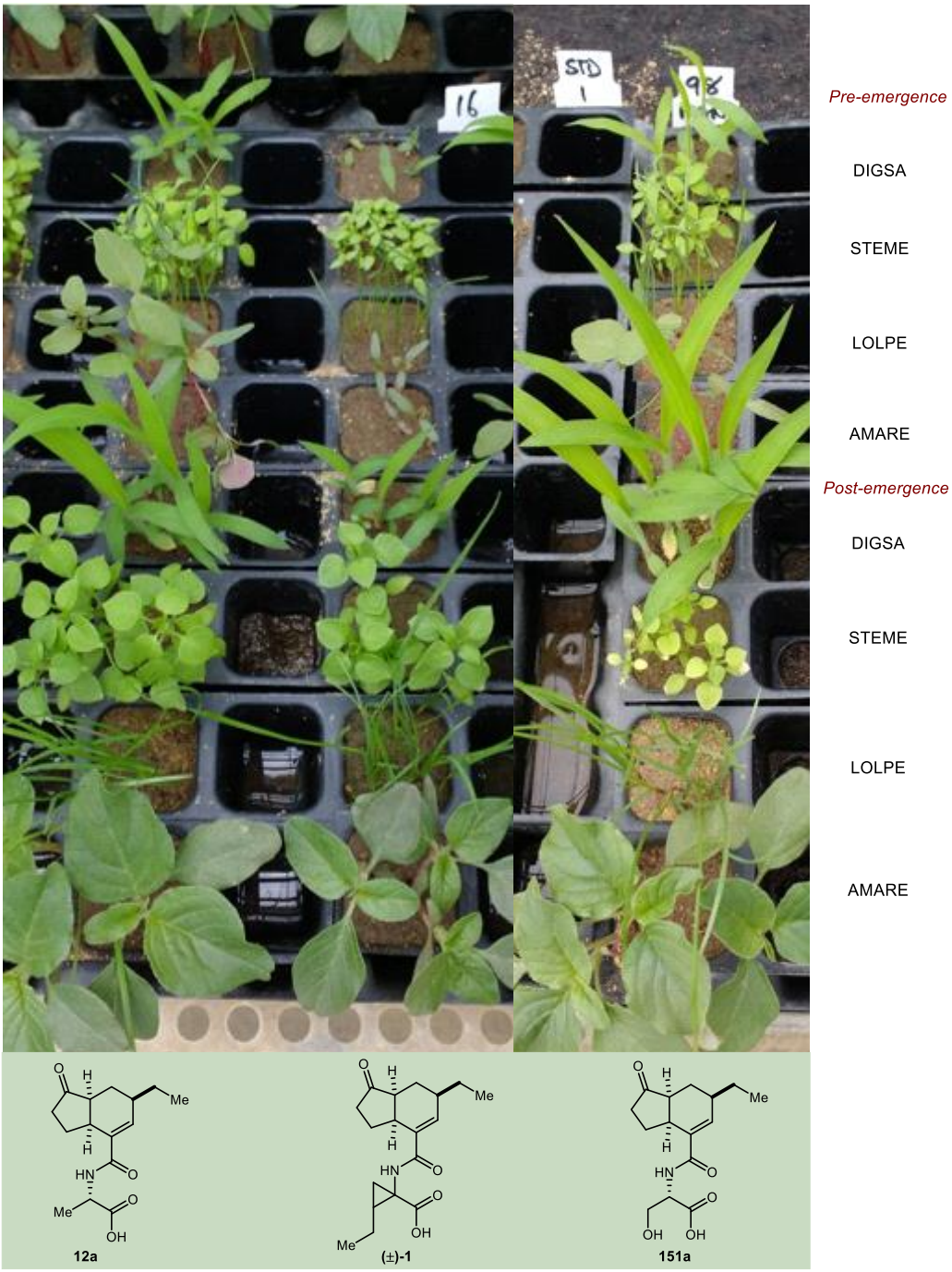
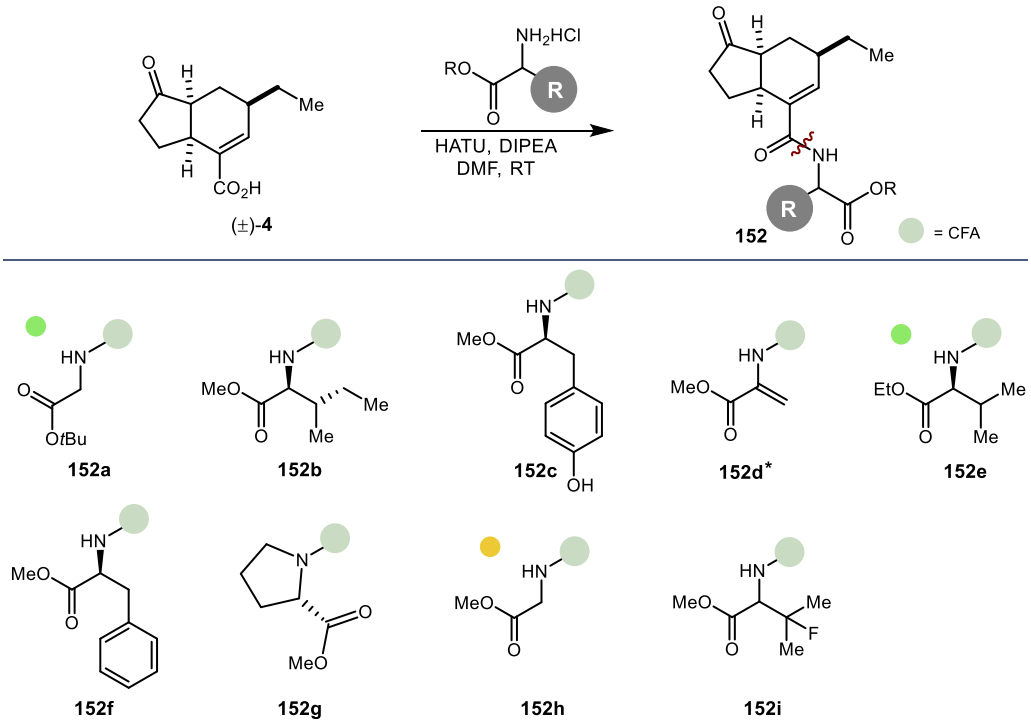


Figure 22: Graphic showing treated plants.

Several pro-cide ester intermediates were also assessed for phytotoxic effects, the results of which are detailed in Scheme 43 and Table 7.



Scheme 43: Biological testing of ester pro-cides. Activity: = 80-100, = 60-70, = 40-50. *Synthesised from *N*-coronafacoyl-*L*-serine (151a), see experimental for details.

Table 7: Detailed phytotoxic activity of weakly active coronafacoyl amino acid pro-cide compounds.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
152a	0	0	0	0	ST	0	0	60	0	ST
152e	10	10	30	60	NC/ST	20	0	20	20	NC/ST
152h	0	0	0	0	ST	0	0	0	50	ST

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). ST = stunting, NC = necrosis.

3.5 Coronafacoyl-Amino Acid SAR

Despite none of our synthetic analogues being as active as COR, the activity profile seen from these conjugates allowed us to tentatively map SAR around the amino acid portion.

Testing of (±)-CFA (**4**) itself (not shown) showed no phytotoxic activity, which is in agreement with literature reports that both CFA and amino acid portions are required for herbicidal action.[39]

The limited activity observed from ester pro-cide compounds **152a** and **152e** suggest that although a pro-cide effect is potentially observed, the highest levels of potency are achieved through application of the free carboxyl compounds.

With regard to amino acid substitution, there appears to be little tolerance for structural modification away from the CMA motif with the retention of phytotoxicity.

The observed activity from *N*-coronafacoyl-*L*-serine (**151a**) and -isoleucine (**10b**) is unsurprising, given previous reports of their isolation and bioactivity.[113]Although the activity seen was weak, the data obtained suggested that *L*-Ile does act as a reasonable mimic of CMA.

Typically, moderate activity was observed from quaternary substituted amino acids, aligning this portion of the molecule closer to the structure of CMA. The phytotoxic effect resulting from cyclopropyl amino acid **10a** suggests that although the CMA ethyl moiety enhances activity, it is not essential to achieve herbicidal action. However, we cannot exclude the possibility that the reduced potency of **10a** relative to COR may result from the loss of stereochemical information at the α-carbon. Through comparison of **151d** and **151k**, we can derive that an *S*-configuration at the α-carbon is important for activity, which, again, agrees with previous literature reports.[39]

Overall, SAR study of the amino acid portion led us to conclude that there is limited tolerance for structural modification away from the CMA scaffold with the retention of significant levels of potency. Our initial SAR hypothesis had focused on the CFA moiety being the key convenor of potency, due to its bespoke polyketide skeleton and the observed tolerance for amino acid substitution by the enzyme Cfl. We had anticipated that the CMA moiety would be amenable to structural modifications, however, considering these results, we concluded that the CMA motif is only moderately tolerant to substitution, and that replacement with alternative amino acids

give COR analogues which are inactive or, where phytotoxic activity is observed, are less potent than COR across the board.

3.6 Coronafacic Acid Analogue Synthesis

As previously mentioned, an attractive feature of the Charette preparation was the convergent nature of the aldol addition, and we viewed our synthetic approach as being amenable to CFA-analogue synthesis through single point changes to both the ester and aldehyde aldol partner (Figure 23).

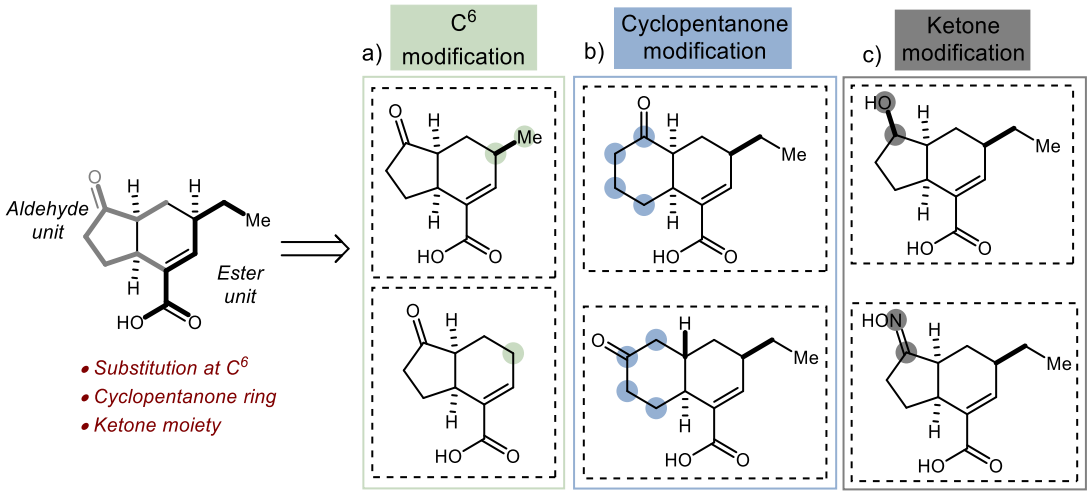
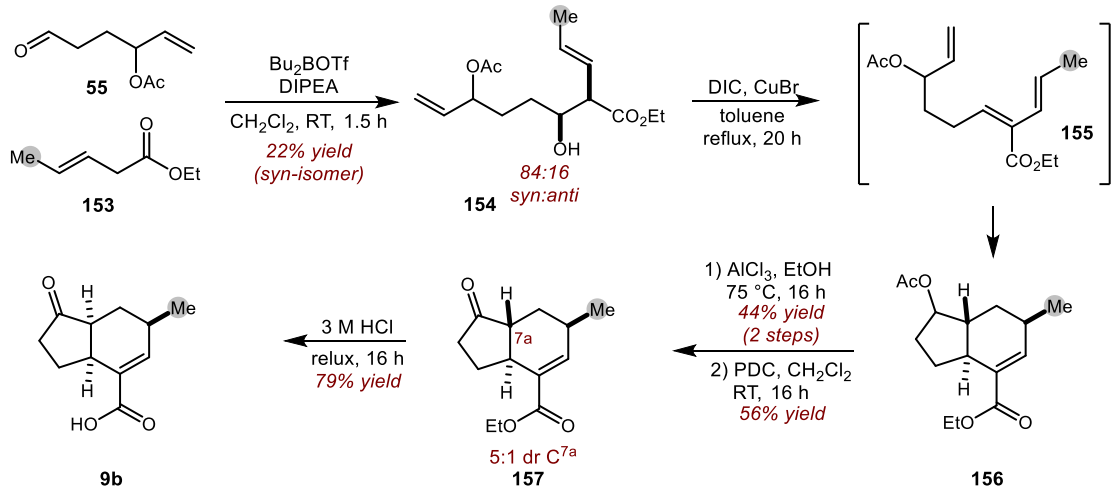


Figure 23: CFA-analogues accessible through single point changes to our developed synthetic route.

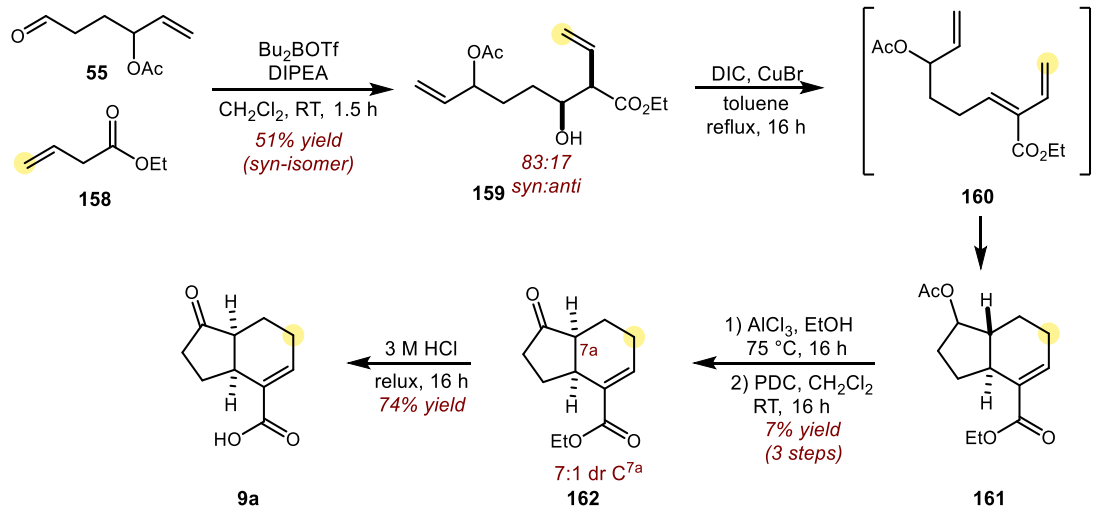
Through minor modifications to the starting materials, we envisioned that our developed synthetic route could be used to access the CFA-analogues shown in Figure 23. Through shortening the carbon chain of the ester used, the C^6 position could be modified to a methyl-substituted, or unsubstituted centre (Figure 23, a). By homologating the aldehyde used, decalin CFA-analogues could be accessed, dependant on which position of the aldehyde chain the additional carbon unit was installed (Figure 23, b). Through late-stage modification of the CFA moiety itself, the reduced carbonyl and oxime analogues could be accessed (Figure 23, c) to further expand the scope of our SAR around the COR motif.

To obtain methyl-substituted analogue **9b**, ester **153** was used in place of the standard ester (**54**) used to synthesise CFA. The synthesis was carried out in accordance with our standard procedure, and allowed efficient access to **9b** (Scheme 44).



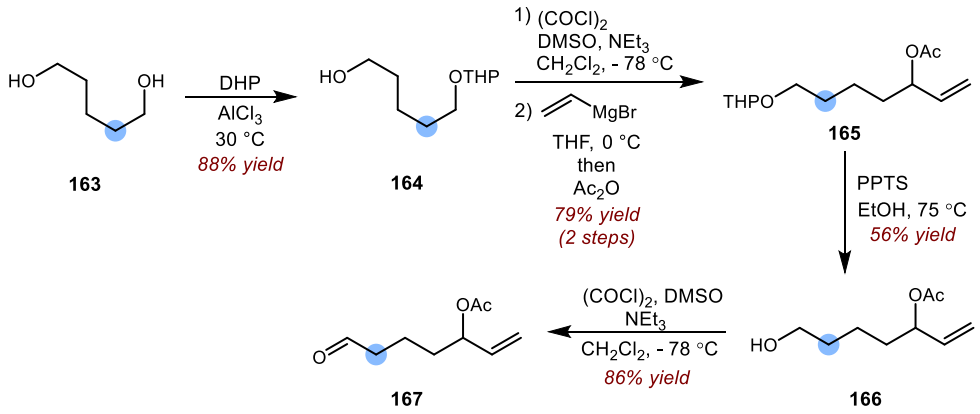
Scheme 44: Synthesis of methyl-substituted CFA analogue 9b.

To access the C^6 deletion analogue **9a**, terminal olefin ester **158** was used in place of **54**. Again, the synthetic sequence was carried out as standard. Ketone **162** was isolated predominantly as the *cis*-ring junction, indicating the greater preference of the C^6-unsubstituted system to exist as the thermodynamically favoured *cis*-fused bicycle in comparison with the equivalent CFA-intermediate **43** (Scheme 45).



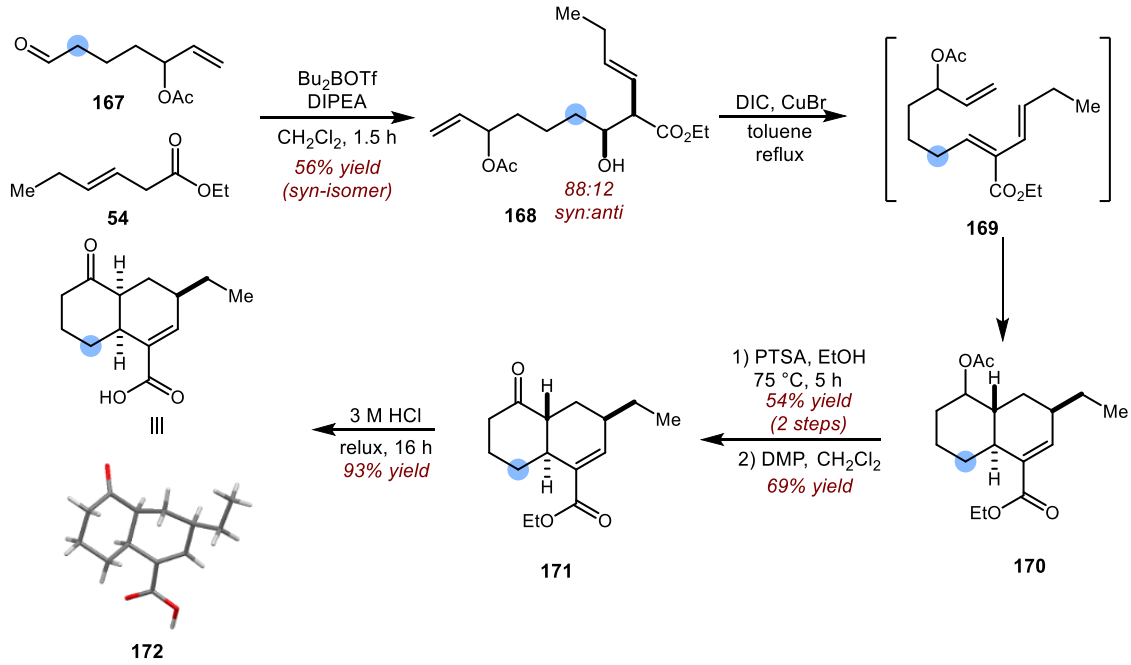
Scheme 45: Synthesis of C^6-deletion analogue 9a.

To access the decalin-CFA analogue **172**, 1,5-diol was used in place of 1,4-diol in our aldehyde synthesis. Our synthetic sequence towards the aldehyde proved robust, and homologated **167** was synthesised in 33% yield over five steps (Scheme 46).



Scheme 46: Synthesis of homologated aldehyde 167.

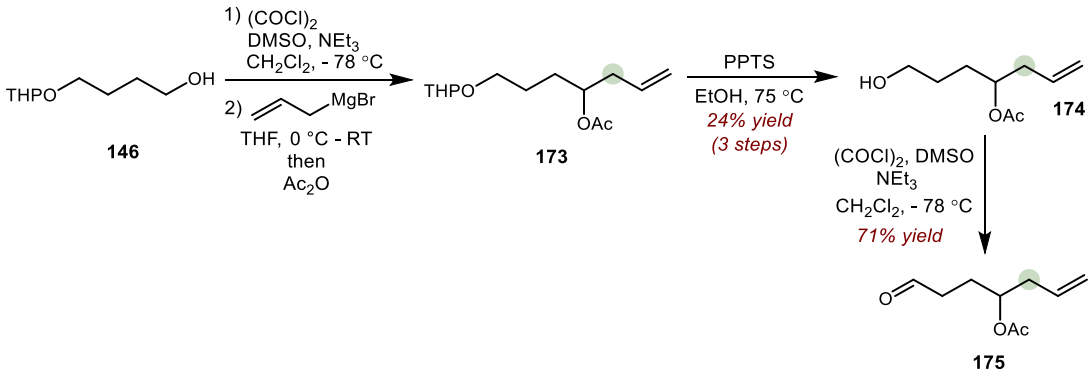
The homologated aldehyde was then carried through the synthetic sequence under our standard conditions (Scheme 47). The IMDA cyclisation proceeded with complete *exo*-selectivity to afford the *trans*-decalin core (**170**). On the final acidic ester hydrolysis step, the ring junction was observed to epirimise to the CFA-like *cis*-configuration (**172**), which was strongly supported through its X-ray crystal structure.



Scheme 47: Synthesis of 6,6-decalin core 172.

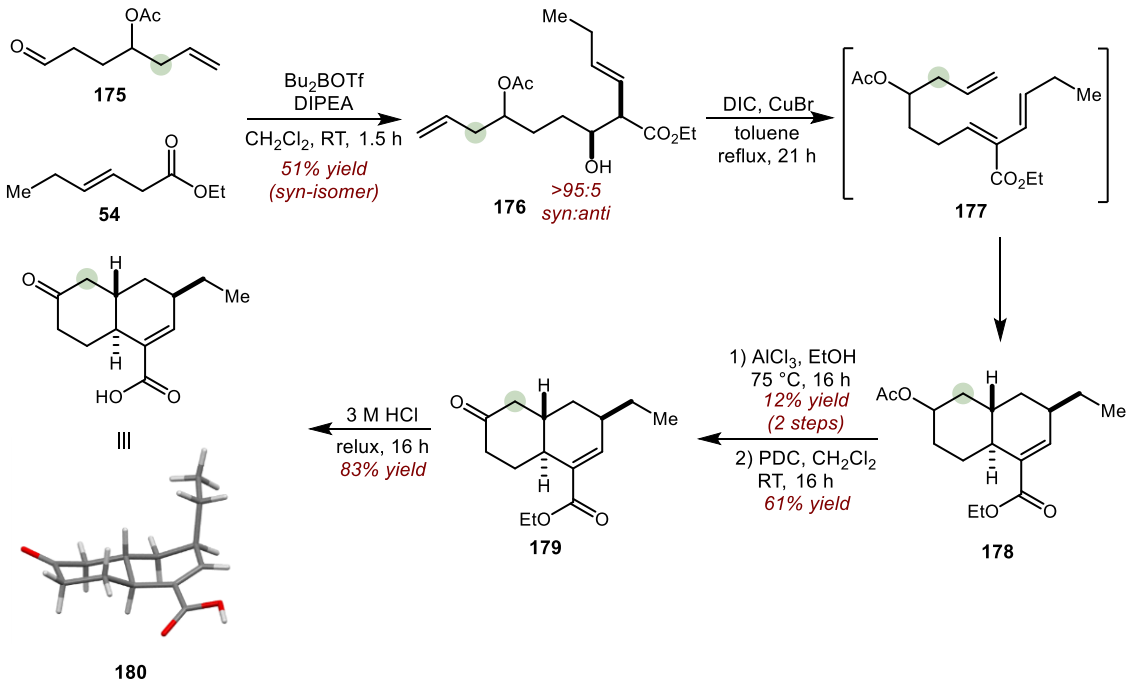
To access the analogous decalin core **180**, the extra methylene unit was installed on the opposite end of the aldehyde carbon backbone with respect to aldehyde **55**, though the use of allyl Grignard in place of the previously used vinyl Grignard (Scheme 48).

Using our established synthetic methodology, aldehyde **175** was accessed in gram-scale quantities for further synthesis.



Scheme 48: Synthesis of aldehyde 175.

The *exo*-IMDA transition state was conserved in the bicycle-forming step, giving **178** as the *trans*-decalin core. In this case, the ring junction was no longer epirimisable due to the homologated position of the carbonyl moiety relative to C^{7a}, and therefore decalin **180** was isolated as the *trans*-ring junction following ester hydrolysis, which was again strongly supported by its X-ray crystal structure (Scheme 49).



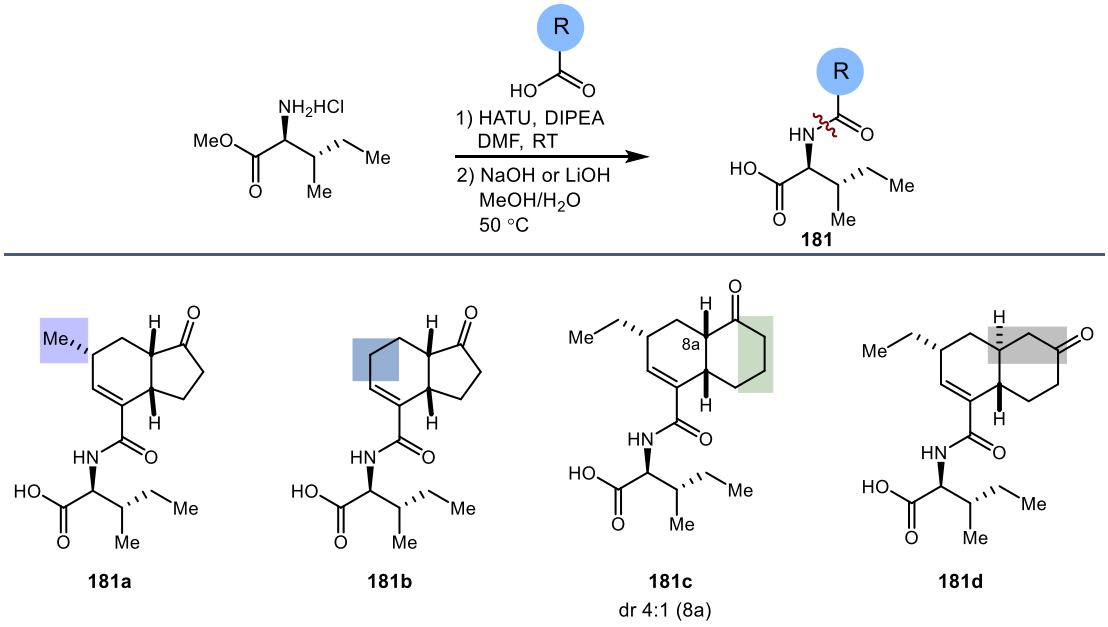
Scheme 49: Synthesis of 6,6-decalin core 180.

Ketone modifications were made through reaction of the final CFA-core structure itself, details of which are described in section 3.7.

Overall, our synthetic strategy proved robust and tolerant to these modifications, allowing access to CFA analogues with variation at several points in the core skeleton.

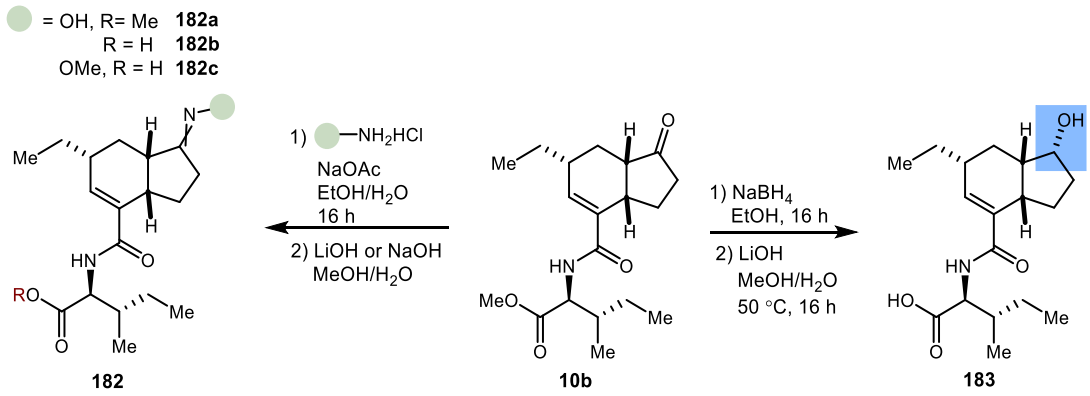
3.7 CFA Analogue *L*-Ile-Conjugation and Biological Evaluation

With regard to the testing of our CFA-analogues, we selected *L*-Ile as the common amino acid as a substitute for CMA in COR analogue synthesis. This strategy has previously been used in the literature to assess structural modifications to the CFA motif,[51] and as *L*-Ile acted as a reasonable CMA mimic in our coronafacoyl-analogue testing we viewed this as an appropriate bioisostere. Conjugates were synthesised using our previous strategy of HATU coupling with *L*-Ile-OMe, and subsequent ester hydrolysis to release the final compound (Scheme 50).



Scheme 50: CFA-analogue-*L*-Ile conjugate synthesis.

Further modifications were also made to the carbonyl unit of *N*-coronafacoyl-*L*-isoleucine (**10b**) to give increased diversity to our analogue synthesis (Scheme 51).



Scheme 51: Synthesis of carbonyl-modified coronafacoyl-*L*-isoleucine compounds.

Reduced compound **183** was synthesised through $NaBH_4$ reduction of the cyclopentanone carbonyl, giving **183**, resulting from hydride addition from the convex face of the bicyclic core.[45] Condensation with hydroxyl amine hydrochloride or methoxy amine hydrochloride gave access to **182b** and **182c** respectively, following final hydrolysis of the methyl ester.

Oxime compounds **182b** and **182c** were of particular interest, as COR methyl oxime (COR-MO) has been reported as the first example of a COR antagonist.[53] It has been proposed that on binding to COI1, the keto-residue of COR remains solvent exposed for interaction with JAZ. The authors hypothesised that the oxime modification could enable the ligand to bind competitively to COI1, whilst preventing complex interaction with JAZ proteins. As such, COR-MO competitively inhibits COR/COI1-JAZ interaction and blocks COI1 function.[53] We were interested to probe this alternative MOA, and the potential herbicidal activity profile resulting from COR antagonism.

These analogues were then submitted for phytotoxic screening, the results of which are detailed in Table 8. Disappointingly, no significant phytotoxic effects were observed from any of these analogues. Reduction of the keto-moiety (**183**) rendered the compound inactive, in line with previous reports.[45] Free acid-methyl oxime **182c** showed no phytotoxic activity, however the unsubstituted oxime **182b** had a moderate phytotoxic effect. In further evidence to the requirement for a free carboxyl unit to deliver potency, the methyl ester of **182b**, **182a**, showed no activity.

Table 8: Phytotoxic screening of core-modified *L*-Ile conjugates.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
181a	0	0	0	0	-	0	0	0	0	-
181b	0	0	0	0	-	0	0	0	0	-
181c	0	0	0	0	-	0	0	0	0	-
181d	NT	NT	NT	NT	-	NT	NT	NT	NT	-
182a	0	0	0	0	-	0	0	0	0	-
182b	20	0	40	0	ST	30	40	70	0	ST
182c	0	0	0	0	-	0	0	0	0	-
183	0	0	0	0	-	0	0	0	0	-

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). NT = not tested, ST = stunting.

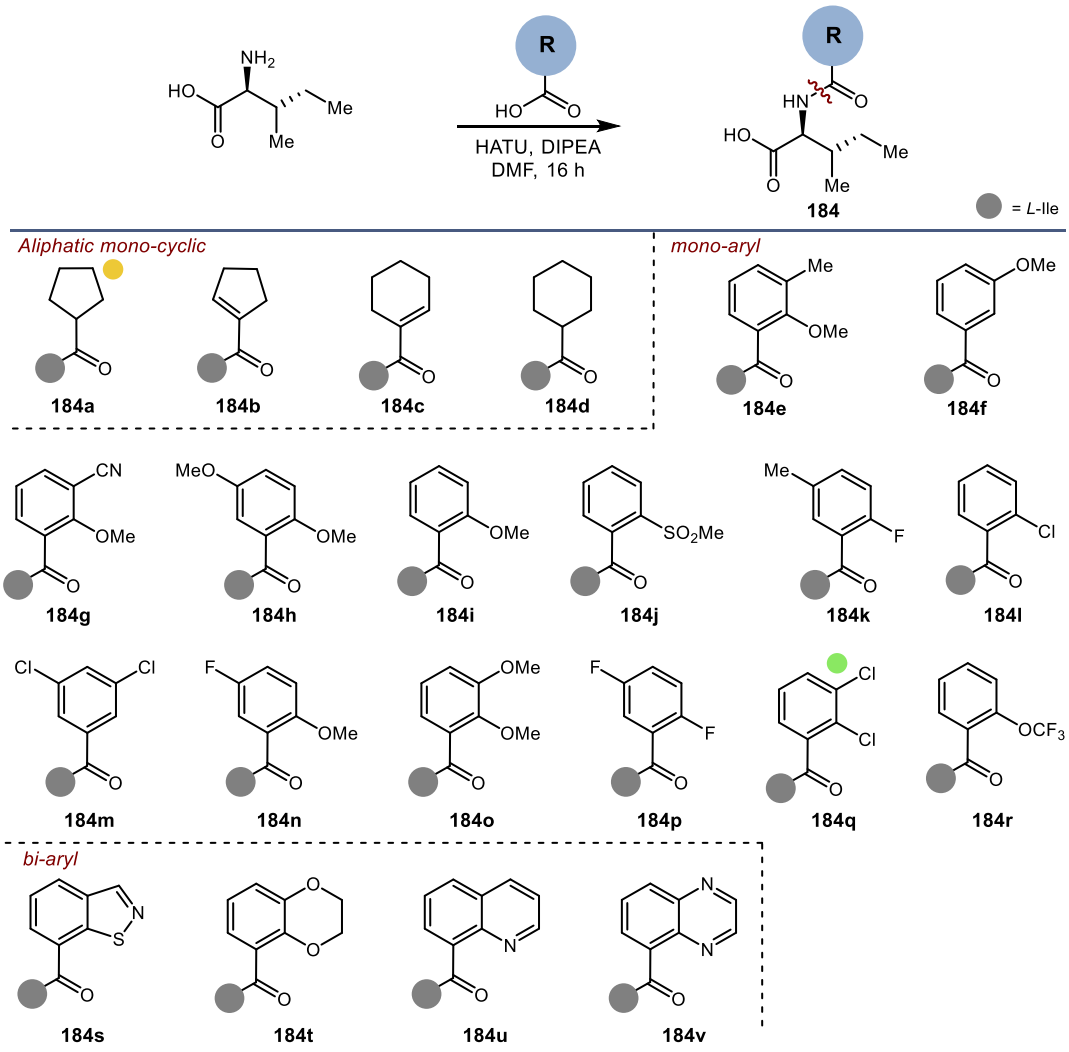
Overall, synthesised *L*-Ile conjugates with CFA analogues delivered inactive or very weakly active compounds. At this stage in our SAR development, we were reluctant to draw firm conclusions from this data. While these results hinted towards a highly constrained SAR around the CFA scaffold, we could not exclude the possibility that this inactivity was a function of the relatively weak bio-mimicry of *L*-Ile as a substitute for CMA, and therefore could not derive reliable SAR information from these compounds.

3.8 Isoleucine-Analogue Synthesis and Biological Evaluation

In keeping with our previously used strategy, we aimed to map SAR around the CFA core moiety through COR analogue synthesis using readily available *L*-Ile as the common amino acid residue. From the biological testing of our coronafacoyl analogues, we had observed that *L*-Ile acts as a moderate mimic of CMA, and the reported activity of analogues deriving from coronalon featuring the *L*-Ile substituent led us to believe this approach could be promising. Like with the coronalon screen, we hoped that active core moieties identified from this study could then be conjugated to CMA, and in this way direct the synthesis of COR analogues.

The conjugates were synthesised through HATU coupling of *L*-Ile to commercially available acids. These acids were selected to cover a broad scope of functionality and

chemical space. Scheme 52 shows the products which were successfully synthesised, isolated, and tested from the automated screen.



Scheme 52: COR analogues with *L*-Ile substitution. Activity: = 80-100, = 60-70, = 40-50.

Following biological evaluation of these compounds, we were disappointed to find that none of our synthesised analogues displayed significant phytotoxic activity. We attributed this to the relatively weak biomimicry of *L*-Ile for CMA; however, these results did suggest that there may be little tolerance for significant modification around the CFA motif. Two analogues (**184a** and **184q**) showed low levels of herbicidal activity, however were not significant enough to be considered active hits. Table 9 shows the biological data of these compounds in greater detail.

Table 9: Detailed phytotoxic activity of weakly active compounds from *L*-Ile screen.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
184a	0	0	0	0	ST	50	0	0	0	ST
184q	30	30	60	0	MR/ST	20	10	50	20	MR/ST

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). MR = morphological effects, ST = stunting.

3.9 Coronamic Acid Synthesis

Having carried out an extensive SAR investigation on variation of the amino acid residue of COR analogues, we then turned our attention to the complementary study, focusing on differentiation of the core CFA unit, with the retention of CMA.

In order to investigate chemical space around the polyketide framework, we required a robust, scalable synthesis of CMA to generate sufficient quantities for analogue preparation. Having reviewed the published literature, we selected the commonly used and synthetically tractable key step of cyclopropyl formation on a readily available malonate, acting as a glycine equivalent (Figure 24).[91]

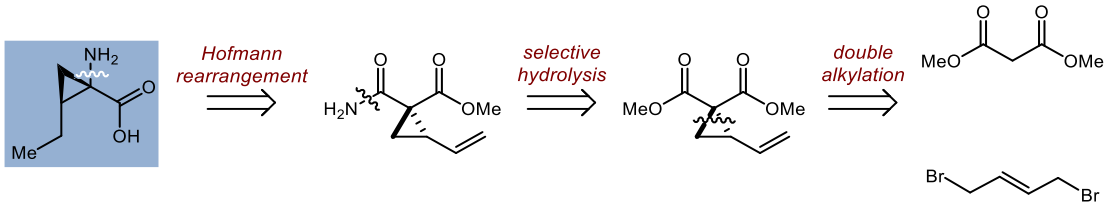
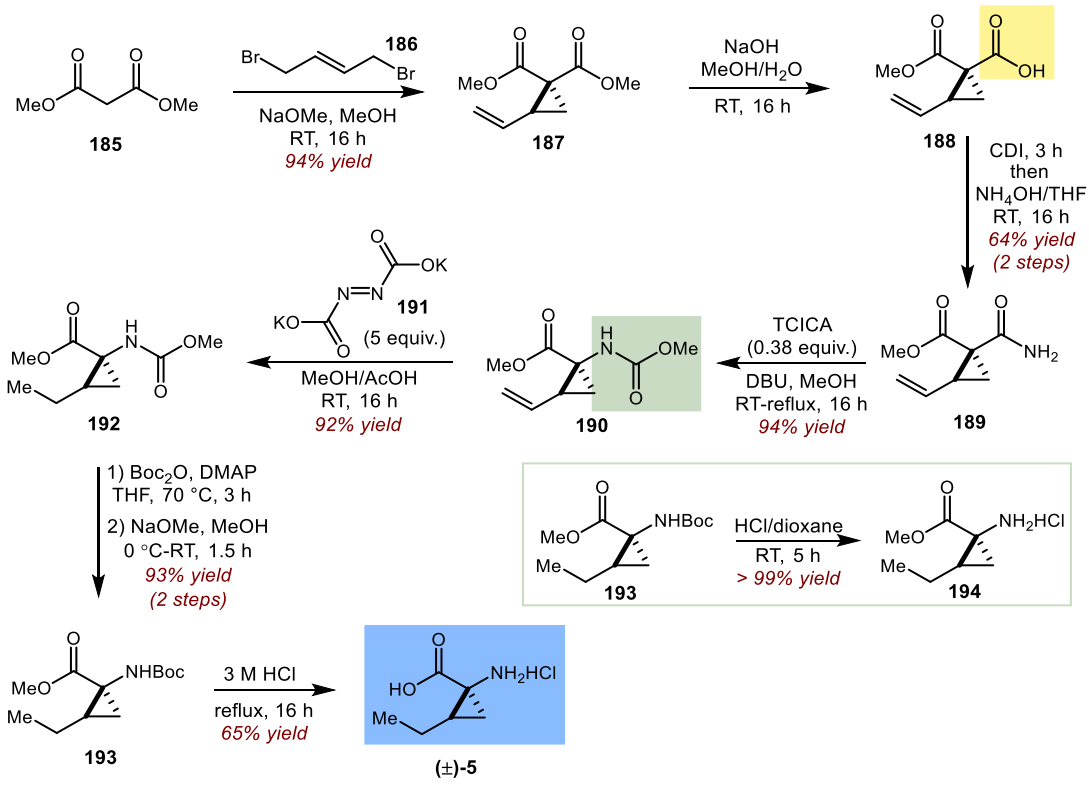


Figure 24: Retrosynthetic analysis of CMA.

Retrosynthetically, we envisioned that the amine functionality could be installed through a Hofmann rearrangement of the parent carboxamide, as has previously been reported in CMA synthesis.[90] The Hofmann precursor could be assembled from selective hydrolysis and carboxamide formation of the least sterically hindered ester of the intermediate substituted malonate. This selective hydrolysis was critical to the stereospecificity of our synthesis, enabling access to CMA as a single diastereosiomer. This strategy to obtain the natural CMA diastereosiomer has also been used several times in the published literature towards **5**, and as such was known to be

robust.[90,92,97,98] Intermediate **187** could be assembled from the double alkylation of dimethyl malonate with dibromide **186**.



Scheme 53: CMA forward synthesis.

Our synthetic route commenced with the known cyclopropanation of dimethyl malonate in excellent yield of 94% (Scheme 53).[114] We then carried out the key hydrolysis step to obtain the required CMA relative stereochemistry (Figure 25).

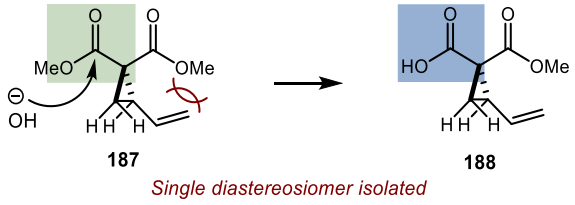


Figure 25: Selective hydrolysis of the least sterically hindered ester, giving access to 188 as a single diastereosiomer.

Selective hydrolysis of the least sterically hindered ester gave access to **188** as a single diastereoisomer, with the remaining ester functionality *cis* to the vinyl unit. Carboxamide formation was then carried out *via* 1,1'-carbonyldiimidazole (CDI) mediated coupling with ammonium hydroxide, affording **189** in 64% yield over two

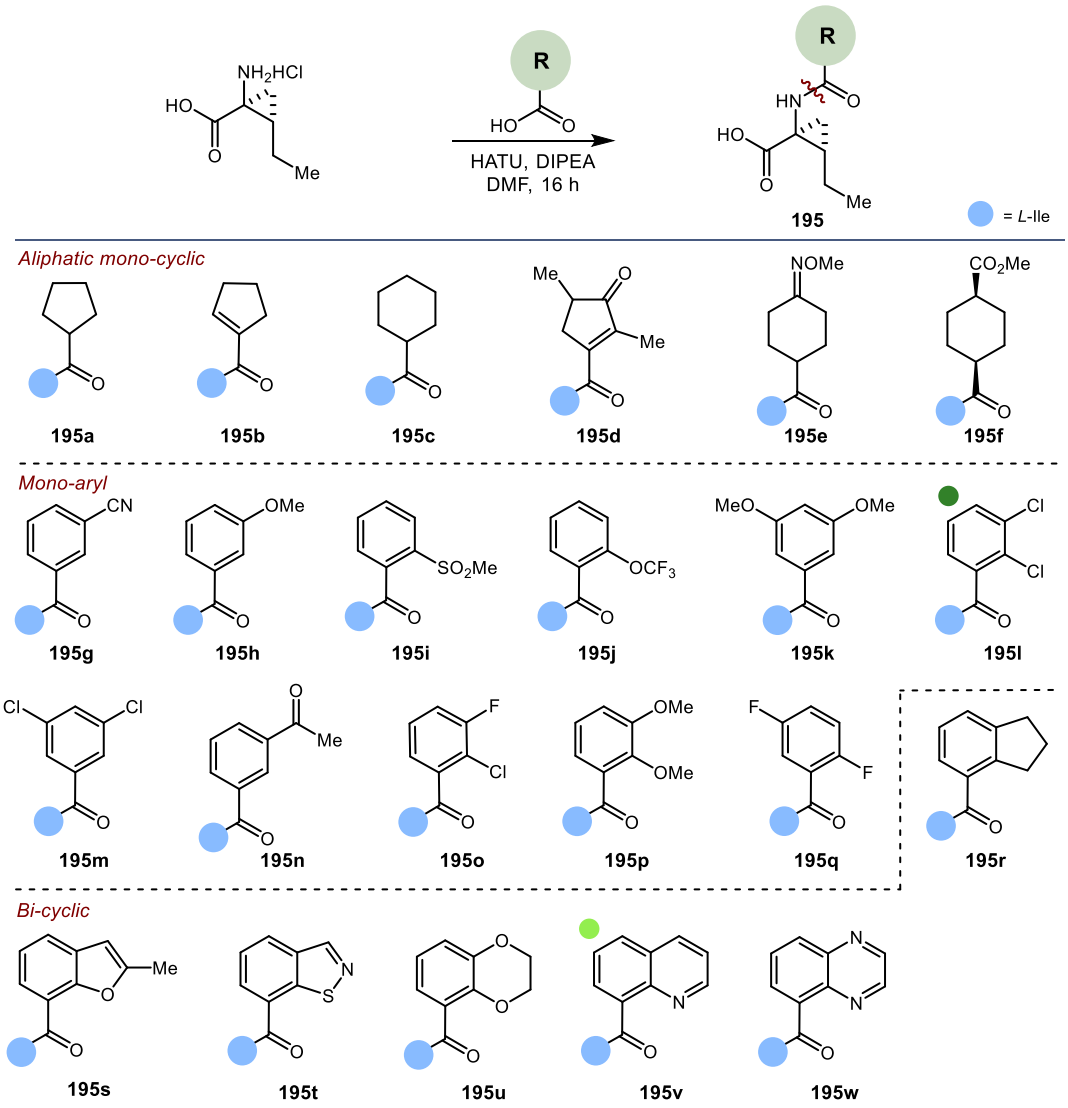
steps. The equivalent reaction where hydrolysis of **187** with methanolic ammonia gave access to **189** directly, however was found to be lower yielding (~20%) than the two-step process.

189 was then transformed to protected CMA equivalent **190** by a trichloroisocyanuric acid (TCICA) mediated Hofmann rearrangement. Treatment of **189** with DBU followed by TCICA at room temperature gave an intermediate *N*-chloroamide. Rearrangement to the isocyanate was then initiated thermally, affording **190** as the methyl carbonate following trapping of the isocyanate with methanol.[113] Carbodiimide-mediated reduction of the vinyl unit was then carried out in high yield.[94] Previous attempts to reduce the terminal alkene by hydrogenation resulted in significant quantities of cyclopropane ring opening, affording **192** in reduced yields of ca. 59%. Through a series of protecting group manipulations, CMA could then be isolated as either the methyl ester **194** or free acid **5**. Boc-protection of the nitrogen followed by selective cleavage of the methyl carbamate afforded protected CMA **193**. (±)-**5** was then obtained through acidic hydrolysis of both the methyl ester and Boc group, or alternatively **194** could be isolated through facile removal of the Boc protecting group.

The synthetic sequence was found to be easily scalable, with each step having been carried out on at least a gram-scale. The route was very high yielding overall (48% over eight steps to **194**, 31% over eight steps to **5**), which enabled the synthesis of over 3.5 g CMA for analogue generation.

3.10 Coronamic Acid Conjugate Synthesis

Following the lack of phytotoxic activity observed from the *L*-Ile-conjugates, the automated screen was repeated using our synthetic CMA. Scheme 54 shows the compounds which were successfully synthesised, isolated, and tested from the automated screen, and Table 10 shows the phytotoxic effect of the active hits in more detail.



Scheme 54: COR analogues with CMA substitution. Activity: ● = 80-100, ● = 60-70, ● = 40-50.

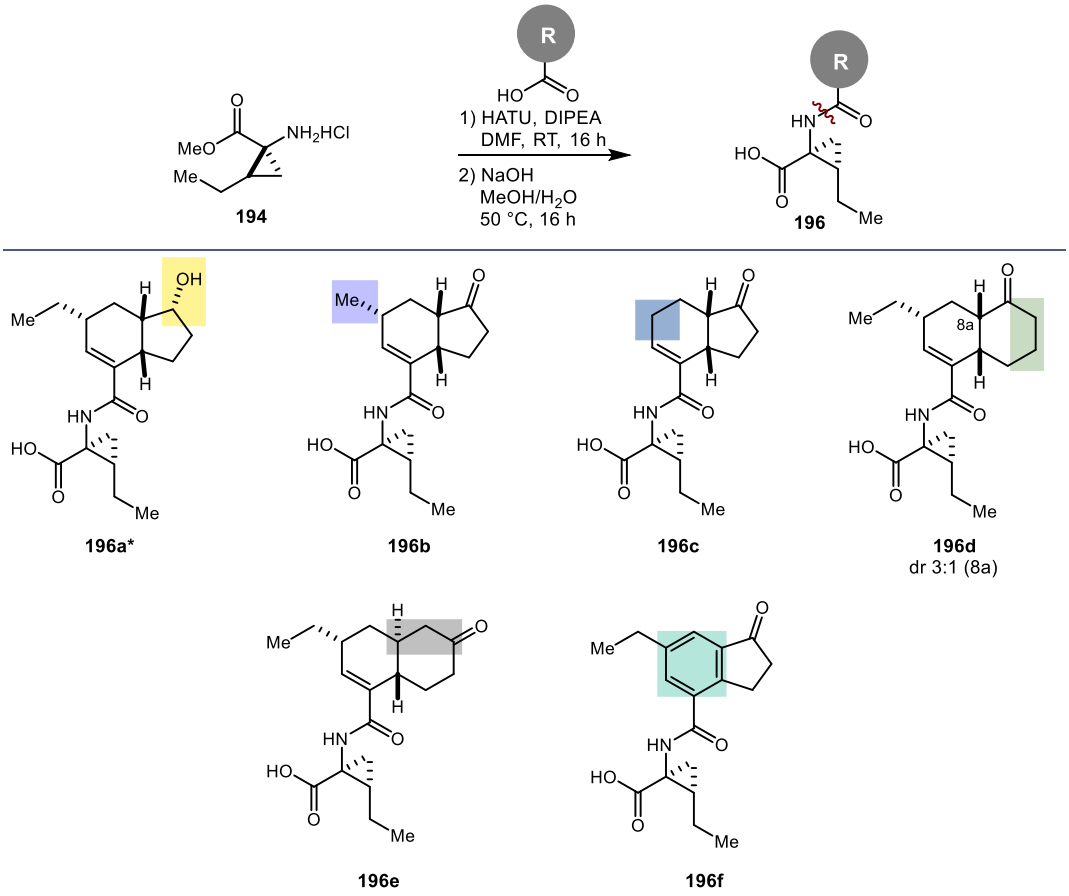
Table 10: Detailed phytotoxic activity of active compounds from CMA screen.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
195l	0	0	80	0	BL/ST	0	0	0	0	BL/ST
195v	0	0	70	0	BL/NC	0	0	-	0	BL/NC

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). BL = Bleach, ST = stunting, NC = necrosis.

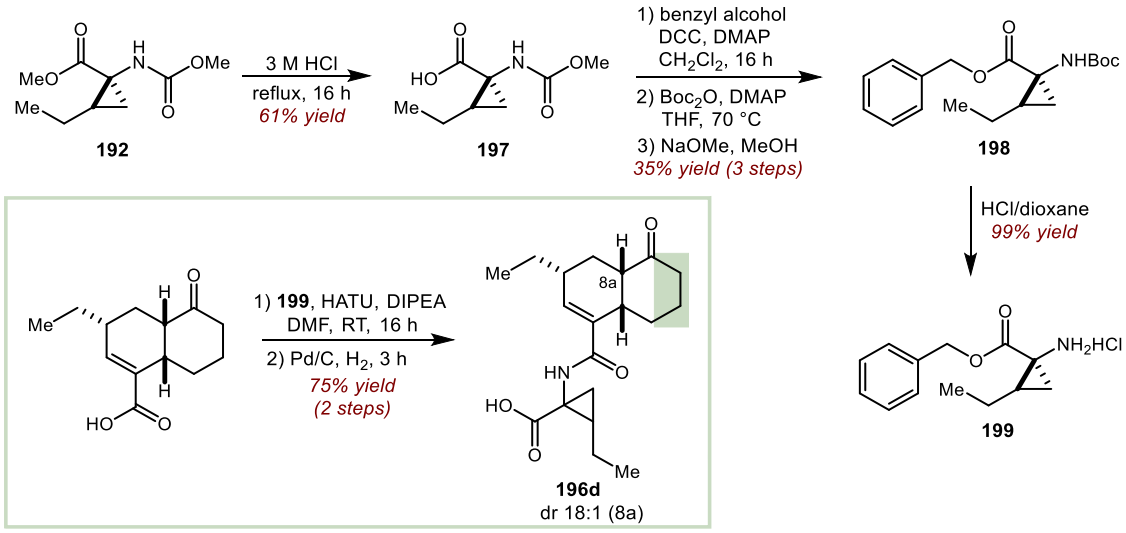
Again, limited activity was observed from these compounds. Where a phytotoxic effect was observed, **195l** and **195v**, it was difficult to rationalise the origins of the potency, and subsequently challenging to disseminate any SAR analysis of this set; however, when taken together with our previous SAR mapping of the COR motif, this data set did encourage us in our emerging belief that retention of the CMA moiety is key to the retention of potency in the final compound, and that substitution of this residue for *L*-Ile is insufficient to achieve maximal phytotoxicity.

CMA was also coupled to our bespoke CFA-like cores, allowing for direct comparison of these analogues with COR to assess tolerance for core modification (Scheme 55).



Scheme 55: Synthesis of CMA-core modified conjugates.*See experimental for synthesis of core unit.

On hydrolysis of the intermediate methyl ester of **196d**, significant epimerisation of the ring-junction was observed, affording the final compound in 3:1 *cis*/*trans* ratio, as had previously been encountered in the synthesis of *L*-Ile analogue **181c**. To circumvent this, benzyl-protected CMA **199** was synthesised (Scheme 56).



Scheme 56: Synthesis of benzyl-protected CMA 199 and coupling to afford COR analogue 196d with reduced ring-junction epimerisation.

The methyl ester of **192** was selectively cleaved by acidic hydrolysis to afford **197**. The free-acid terminus was then benzyl protected through an *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling with benzyl alcohol, and the methyl carbamate substituted for a Boc-protecting group under the conditions used previously in the synthesis of CMA-OMe (**193**) to afford **199**.

Benzyl-protected CMA has been reported previously in the synthesis of COR isomers, and it is known that the benzyl group can be selectively removed by hydrogenation in the presence of the α,β-unsaturated amide.[38] Following HATU coupling with *cis*-decalin core and hydrogenation of the benzyl protecting group, **196d** was isolated in improved dr of 18:1 *cis*/*trans* at C^{8a}. It is worthy of note that the minor epimerisation seen here occurred during amide bond formation, rather than the protecting group removal step.

3.11 Coronamic Acid Conjugates Biological Evaluation

The CMA-conjugates featuring our bespoke CFA-analogue cores were tested for phytotoxic activity, the results of which are detailed in Table 11.

Table 11: Phytotoxic screening of core-modified CMA conjugates.

	Post					Pre				
Compound	AMARE	LOLPE	STEME	DIGSA	Symptom	AMARE	LOLPE	STEME	DIGSA	Symptom
196a	70	70	70	80	NC/ST	80	60	80	80	NC/ST
196b	30	20	30	60	GI/ST	0	20	80	0	GI/ST
196c	0	0	0	0	-	0	0	0	0	-
196d	30	10	0	50	GI/ST	30	60	40	80	GI/ST
196e	0	0	0	0	-	0	0	0	0	-
196f	30	20	10	100	NC/ST	20	20	20	40	NC/ST

Test species: *Amaranthus retroflexus* (AMARE), *Lolium perenne* (LOLPE), *Stellaria media* (STEME), *Digitaria sanguinalis* (DIGSA). ST = stunting, GI = germination inhibition, NC = necrosis.

Gratifyingly, several of these compounds showed significant phytotoxic activity. The observed activity of methyl analogue **196b** in comparison with inactive deletion analogue **196c** implied that substitution at the C^6 position is required for activity, which is in accordance with literature reports.[44] The activity observed from the 6,6-bicyclic analogue **196d** suggests that the cyclopentanone ring is tolerant of modification. The inactivity of the analogous 6,6-bicycle **196e** may be attributed to the *trans*-ring junction, as it is known that the *cis*-configuration of CFA is important for activity; however, this inactivity may also be due to the change in relative positioning of the carbonyl moiety relative to the ring junction. The reduced carbonyl compound, **196a**, showed good levels of activity, suggesting that variation to the ketone moiety is tolerated. To our surprise, the most potent analogue arising from this study was the CMA-substituted aromatic core of coronalon (**196f**). Having previously disregarded the aromatic core as a viable CFA-bioisostere, this result lead us to the conclusion that our previously synthesised, inactive analogues (Scheme 38) failed to achieve significant levels of potency due to the amino acid substitution, and the key contributor of potency is the CMA residue. This hypothesis is further substantiated in that the respective *L*-Ile conjugates of our CFA derivatives failed to induce any phytotoxic action, whereas significant activity was observed from analogues **196a**, **d**, and **f**.

Figure 26 shows images of weed species treated with three of our active compounds **196b**, **196d**, and **196f**. Plant species on the left have been treated with methyl-

substituted **196b**, plant species in the centre have been treated with *cis*-decalin **196d** and show significant phytotoxic effects, and plant species on the right have been treated with coronalon core-containing **196f** and show strong phytotoxic activity, particularly with post-emergence DIGSA.

Figure 26: Graphic showing phytotoxic effects of active compounds from CMA-core modified conjugates.

With respect to reports of differing activities between COR enantiomers, we then obtained the single enantiomers of our compounds of interest **196d** and **196f** through separation by chiral HPLC (Figure 27).

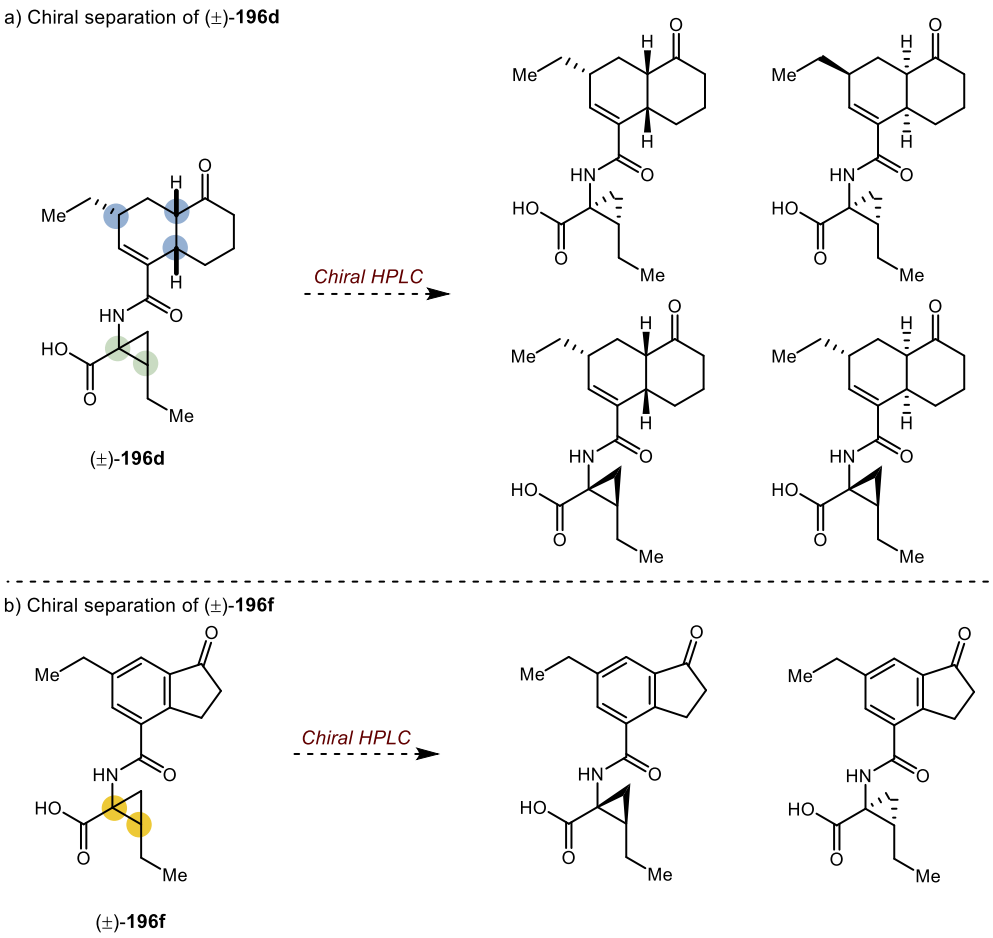


Figure 27: Chiral separation of active racemic compounds 196d and 196f.

Following separation, the single enantiomers were taken for further herbicide testing, the results of which are detailed in Table 12.

Table 12: Biological evaluation of separated enantiomers of (±)-196d and (±)-196f.

	Post							
Compound	ALOMY	AMARE	ECHCG	IPOHE	LOLPE	SETFA	SOLNI	Symptom
196d isomer 1	-	0	0	0	0	-	0	-
196d isomer 2	-	10	0	10	0	-	10	ST/CL
196d isomer 3	-	10	20	50	50	-	70	ST/CL
196d isomer 4	-	10	50	80	50	70	80	ST/NC
196f isomer 1	-	0	0	0	0	-	0	-
196f isomer 2	-	0	40	30	40	-	50	ST

	Pre							
Compound	ALOMY	AMARE	ECHCG	IPOHE	LOLPE	SETFA	SOLNI	Symptom
196d isomer 1	-	0	0	0	0	0	0	-
196d isomer 2	-	0	0	0	0	0	0	-
196d isomer 3	-	20	10	10	60	50	70	ST
196d isomer 4	-	50	0	80	70	60	80	GI
196f isomer 1	-	0	0	0	0	-	0	-
196f isomer 2	-	20	0	0	40	20	60	ST

Test species: *Alopecurus myosuroides* (ALOMY), *Amaranthus retroflexus* (AMARE), *Echinochloa crus-galli* (ECHCG), *Ipomoea hederacea* (IPOHE), *Lolium perenne* (LOLPE), *Setaria faberi* (SETFA), Solanum nigrum (SOLNI). ST = stunting, CL = chlorosis, NC = necrosis, GI = germination inhibition.

The results obtained in this screen clearly demonstrate that the phytotoxic activity observed with compound **196f** is derived from one enantiomer, while the other is inactive. The optical rotation of the separated enantiomers could not be determined at this time due to a paucity of available material; however, this data matched literature precedent for the phytotoxic activity of the natural (+)-enantiomer. Moderate activity levels were observed for two enantiomers of **196d** but in both this case and with the active enantiomer of **196f**, activity was weaker than (+)-COR. Although the complete inactivity of one enantiomer of **196f** may suggest that the aromatic unit is not contributing significantly to the potency of the other enantiomer, we can't exclude the possibility that the assumed (−)-CMA unit precludes substrate binding, and therefore potentially beneficial interactions between the aromatic unit and binding site are not realised.

3.12 Docking Studies

In an attempt to validate our hypothesis of the importance of the CMA moiety, docking studies were conducted to better understand the origins of the potency observed in our study. Figure 28 shows the compounds selected for docking.

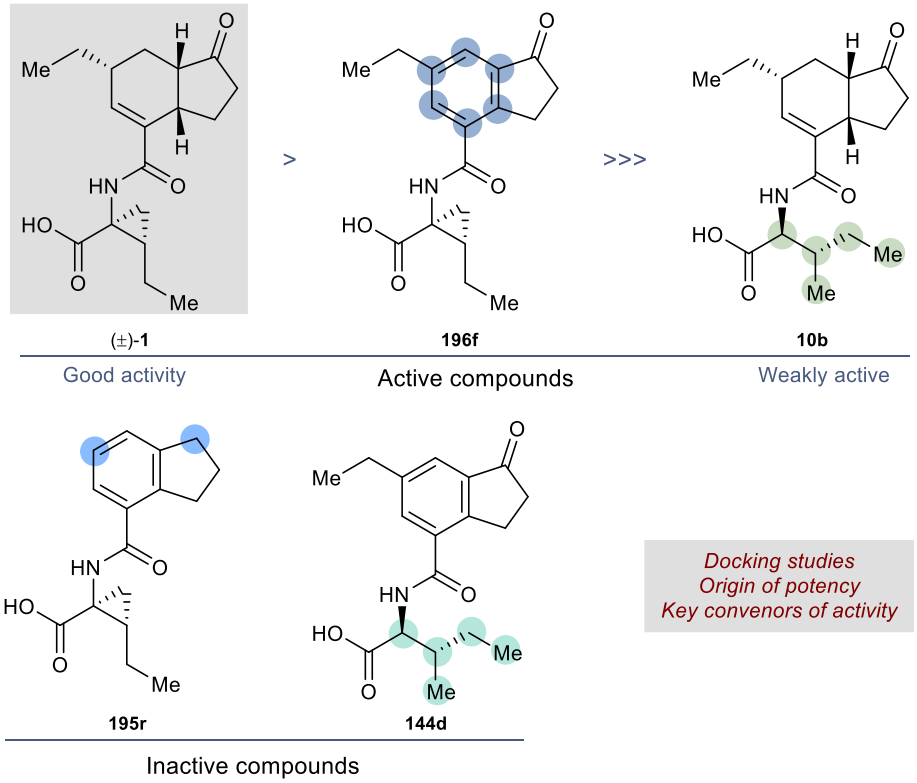


Figure 28: Compounds evaluated in docking studies.

Docking of the native ligand, COR, showed the key ligand/binding site interactions (Figure 29).

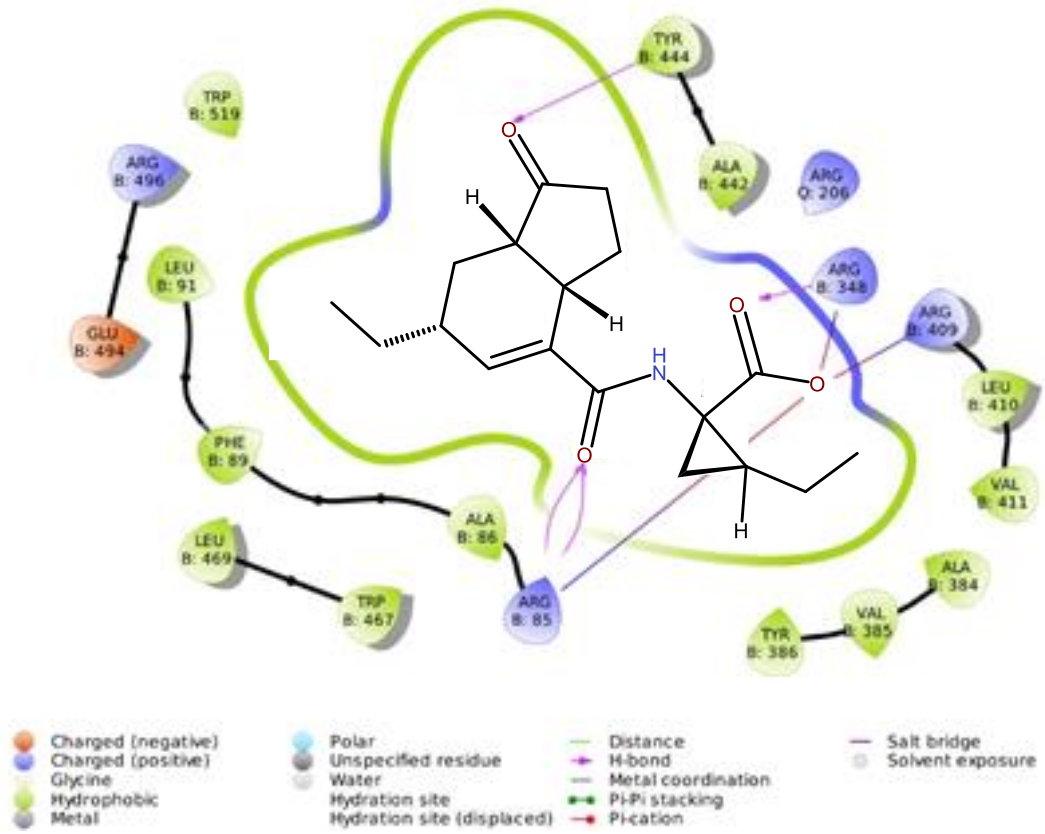


Figure 29: COR binding site, displaying key interactions.

The active site contains three arginine residues which form strong H-bonding interactions. An H-bonding interaction between the ketone of the CFA unit and a tyrosine residue is also favourable. A number of hydrophobic interactions, including the positioning of the CMA ethyl unit into a hydrophobic pocket are also observed.

Comparing the docking of COR and *N*-coronafacoyl-*L*-isoleucine (**10b**), as well as analogue **144d** and analogue **195r**, is informative with respect to the significant drop in phytotoxicity observed when CMA is replaced with *L*-Ile (Figure 30).

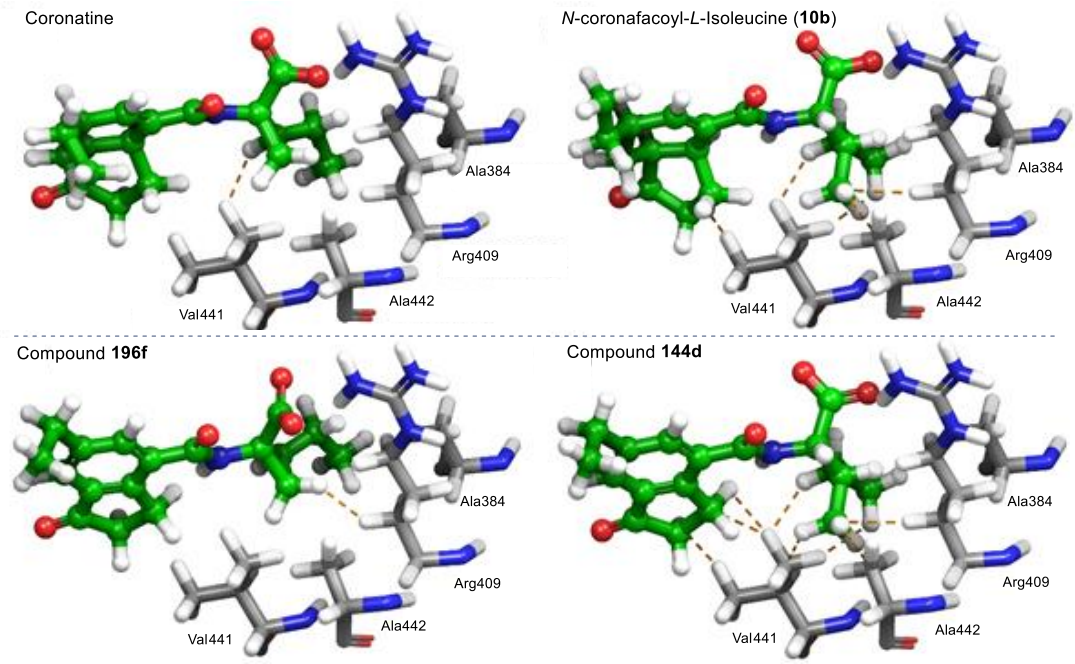


Figure 30: Docking studies to assess the effect of *L*-Ile substitution of the CMA residue. Showing the hydrophobic pocket made up of residues Val411, Ala442, Arg409 and Ala384. Steric clashes are identified by dashed lines.

As shown in Figure 30, replacement of CMA with *L*-Ile to afford **10b** and the aromatic analogue **144d** incurs significant steric clashes in the binding pocket. Analysis of docked structure **10b** shows several steric clashes between the *L*-Ile residue and the hydrophobic residues of the binding pocket. *L*-Ile substitution has also caused the CFA moiety to move in closer proximity to the Val441 residue, incurring further unfavourable steric interactions. Similar steric clashes are observed in the docking of compound **144d**, however in this case the positioning of the aromatic core is significantly altered with respect to compound **196f**, incurring several steric clashes with the Val441 residue. It is also expected that binding of the branched alkyl chain of *L*-Ile would have a greater entropic penalty with respect to the structurally constrained cyclopropyl CMA.

The inactivity of compound **195r**, which lacks the C^1 carbonyl and C^6 ethyl unit of active compound **196f**, can also be rationalised through comparison of the docked structures (Figure 31).

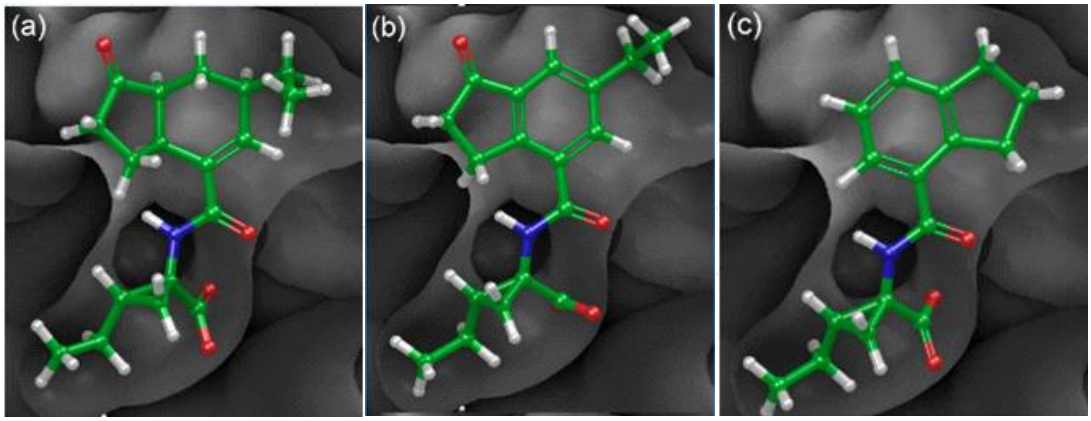


Figure 31: Comparison of binding of COR (a), compound 196f (b), and compound 195r (c).

The binding mode of COR and compound **196f** is well conserved (Figure 31, a and b), however docking of compound **195r** in the active site showed a different binding conformation (Figure 31, c). The bicyclic moiety has rotated to place the cyclopentanone ring in the hydrophobic cavity normally occupied by the COR ethyl unit. This retains the hydrophobic interactions with the Leu91, Phe89, and Ala86 residues, however the H-bonding interaction and hydrophobic interactions with the Tyr444 residue are lost. Figure 32 shows the overlay of the docked compounds in Figure 31.

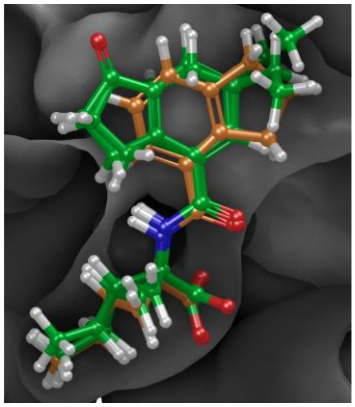


Figure 32: Overlay of COR, compound 196f, and compound 195r (shown in orange).

In each case, the amino acid portion of the structures is positioned almost identically. This suggests that the hydrophobic interactions of the CMA residue are stronger than the interactions surrounding the bicyclic core, and that the inactivity of this compound stems from a loss of interactions around the core unit, rather than an alternative placement of the amino acid residue. This also indicates the importance of the C^6 ethyl

moiety to orient the core unit so as to pick up the favourable interactions with the Tyr444 residue.

3.13 Summary of SAR Analysis

Through review of the SAR derived from our COR-analogue collection, we have drawn several conclusions regarding the tolerance for structural modifications of the COR motif with the retention of phytotoxic activity.

Initial hypotheses focused on the CFA-moiety as being the key contributor of COR phytotoxic activity, and we expected a significantly more constrained SAR around this core motif than with the amino acid residue.

Coronafacoyl-amino acid compounds showed weak phytotoxic activity across the board, with active compounds typically resulting from coronafacoyl-conjugates which are known to occur naturally e.g. *N*-coronafacoyl-*L*-serine **10b**; however, moderate levels of activity were observed from several compounds resulting from the coupling of CFA to more CMA-like non-natural amino acids e.g. *gem*-dimethyl substituted **152j**. These results are indicative of the importance of the CMA moiety. This, combined with the lack of phytotoxic activity observed from other analogues with alternative amino acids; coronalon analogues, CFA analogues with *L*-Ile substitution, and compounds made in the *L*-Ile automated screen, led us to conclude that the CMA moiety is critical for good levels of phytotoxic activity. These results also disproved our original hypothesis that *L*-Ile could act as a viable, simplified CMA bioisostere.

Whilst general screening of potential CFA surrogates with CMA substitution failed to deliver any hits of significant potency, the moderate activity seen from compounds **195l** and **195v** allowed us to conclude that the structural requirements around the CFA unit are less constrained than initially anticipated.

This was exemplified by the synthesis of CMA-substituted analogues where minor modifications to the CFA core had been made (**196a-f**). Good levels of activity were observed from several of these compounds, again suggesting a moderate amount of structural flexibility in the CFA unit.

These hypotheses were further substantiated through docking studies, where the binding mode of COR was compared to the binding of both active and inactive analogues. *L*-Ile substituted analogues were shown to incur significant unfavourable steric clashes in the COR binding site, lending further weight to our conclusion that *L*-Ile does not act as a reasonable CMA surrogate. Comparison of the binding mode of active and inactive CMA containing analogues demonstrated that the positioning of the CMA moiety is highly conserved, indicating strong, favourable interactions in the binding site, again suggesting the importance of this residue. The positioning of the C^6 ethyl unit in a hydrophobic pocket is in line with the observed loss of activity when this position is unsubstituted, which potentially results in an alternative binding mode as observed through modelling of inactive compound **195r**.

Literature reports of the significantly reduced activity of the non-natural, (–)-COR enantiomer were confirmed through the chiral separation and subsequent phytotoxic testing of **196d** and **196f**. The complete inactivity of the presumed non-natural enantiomers clearly displayed the enantiomeric preference of the substrate binding site in order to induce a phytotoxic response.

4 Conclusion

In conclusion, the natural phytotoxin COR has been a compound of interest in agrochemical development since its structural elucidation and evaluation of herbicidal action. Eliciting its effect through interaction with the JAZ signalling pathway, COR can be considered as having a novel MOA, and this, coupled with its biologically privileged structure, has kept COR at the forefront of agrochemical discovery programmes.

Despite its relevance to agrochemical development, relatively little is known around a COR-SAR for phytotoxic activity. This has been largely attributed to the lack of synthetic accessibility of the complex natural product structure, limiting the practicality of COR-derivative synthesis and the generation of a significant number of analogues.

We aimed to carry out a thorough SAR investigation around the COR motif, with the intention of developing an SAR for phytotoxic activity, and ideally achieving structural simplification with the retention or enhancement of potency. To enable this study, we developed the gram-scale synthesis of the COR core unit, CFA. The successful execution of this synthetic sequence has allowed the generation of several coronafacoyl-amino acid conjugates, as well as enabling the incorporation of structural diversity into the CFA motif.

Disappointingly, attempts to use structurally simplified CFA and CMA mimics were largely unsuccessful, with significant deviations away from the parent structure affording inactive compounds. Compounds where the amino acid residue was varied from the CMA moiety were typically inactive or afforded very low levels of phytotoxic activity. Although these were negative results, we took learning from these failures in that the CMA unit is integral to potency, a finding which was enabled by the gram-scale synthesis of CFA and subsequent COR analogue synthesis. Our SAR hypothesis was further substantiated in that COR mimics featuring the CMA moiety typically retain high levels of potency when minor modifications to the CFA unit are made, suggesting that the CFA moiety is more tolerant to modification than CMA.

Conclusion

Modelling studies backed up the conclusions drawn from the experimental data. Analogues featuring *L*-Ile substitution were shown to incur significant steric clashes in the COR binding site, whereas modelling of the CMA residue suggested strong, favourable binding interactions.

Overall, extensive SAR studies around the COR scaffold has led to the conclusion that the bespoke non-natural amino acid residue CMA is essential for high levels of phytotoxicity. The CFA residue appears to tolerate structural modifications, including the simplification of the largely sp3-carbon bicycle to an aromatic mimic (compound **196f**). We suggest that further studies in this area focus on the modification of the CFA residue, with retention of the CMA component.

5 Future Work

Due to the importance of substitution at the C^6 position of CFA, a second-generation synthesis amenable to facile analogue generation at this position is desirable. Retrosynthetic analysis of the IMDA triene precursor (**57**) revealed a chemoselective Suzuki-Miyaura disconnection, which would enable efficient access to CFA derivatives with varied C^6 functionality (Figure 33).

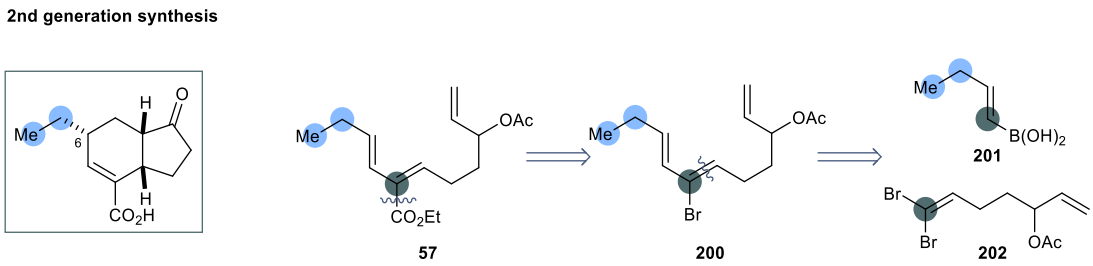


Figure 33: Second generation synthesis of CFA, enabling facile analoging of C^6.

Di-bromo alkene **202** could be generated from aldehyde **55**, and triene **200** assembled through chemoselective cross coupling of the least sterically hindered bromide[115] with vinyl boronic acid **201**. Through variation of the vinyl boronic acid used, CFA analogues at the biologically relevant C^6 position could be readily accessed.

Cinnacidin, **203**, is a non-host specific phytotoxic natural product isolated from the fungus *Nectria* sp. DA060097.[116] Cinnacidin has been identified as a structural and functional mimic of JA and COR, and has been found to display significant phytotoxic activity across a range of weed species (Figure 34).

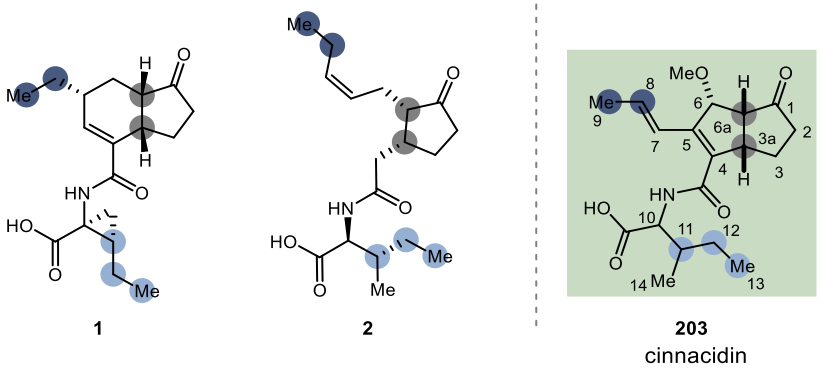


Figure 34: Novel phytotoxin cinnacidin (203), highlighting structural similarities to COR (1), and JA-Ile (2).

Future Work

An SAR campaign, focused around the cinnacidin core motif, may be promising with respect to the identification of a herbicidal lead acting in the JAZ pathway. A scalable, flexible synthesis of the fused 5,5-bicyclic core to enable amino acid and core screening would be desirable.

The cinnacidin scaffold has several structural features which are amenable to analogue generation (Figure 35).

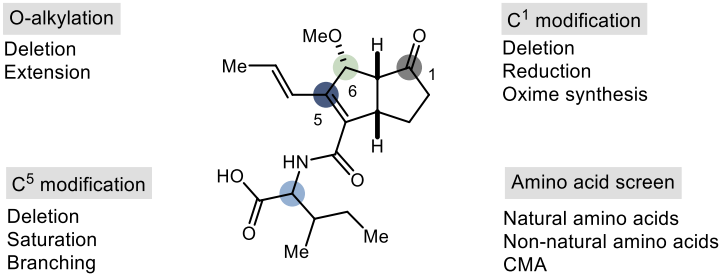


Figure 35: Potential points of diversification for cinnacidin analogue synthesis.

Like with coronatine, an SAR study on the amino acid portion could be carried out. Taking the learning from COR that there is little tolerance for modification in the amino acid residue, the synthesis of a CMA substituted cinnacidin analogue should be prioritised. The carbonyl moiety and C^6 methoxy residue could be modified, as could the C^5 side chain. It is known that the C^5 side chain is not essential for phytotoxic activity,[116] and therefore deletion of this unit may be a feasible means of compound simplification.

6 Experimental

General Techniques

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.[117]

Purification of Solvents

All solvents used for anhydrous reactions (THF, CH_2Cl_2, PhH, MeOH) were ether obtained from a PureSolv SPS-400-5 solvent purification system or dried over previously activated 3 Å molecular sieves. These solvents were transferred to and stored in a septum-sealed oven-dried flask over previously activated 3 Å molecular sieves and purged with and stored under nitrogen. CH_2Cl_2, Et_2O, EtOAc, MeOH, and petroleum ether 40-60 °C for purification purposes were used as obtained from suppliers without further purification.

Experimental Details

Air-sensitive reactions were carried out using conventional glassware. The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Reactions were carried out at −78 °C using dry ice/acetone baths. Reactions were carried out at 0 °C using ice/water baths. Room temperature was generally *ca*. 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer. DIPEA for aldol additions was dried by heating to reflux over CaH_2 and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 3 Å molecular sieves.

Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light and/or

developed using potassium permanganate solution. Flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel.

Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AV 400 spectrometer at 400 MHz and 125 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. ^{19}F NMR spectra were obtained on a Bruker AV 400 or Bruker DRX 500 spectrometer at 376 MHz and 471 MHz respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C), DMSO-d_6 referenced at 2.50 ppm (^{1}H) and 39.52 ppm (^{13}C), acetone-d_6 referenced at 2.05 ppm (^{1}H) and 29.84 ppm (^{13}C), D_2O referenced at 4.79 ppm (^{1}H), and MeOD referenced at 3.31 ppm (^{1}H) and 49.00 ppm (^{13}C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Robot array compounds were purified by mass directed prep HPLC, using a mixed trigger of UV with ES+ on a Waters Fraction Lynx system comprising of a 2767 injector/collector with a 2545 gradient pump, two 515 isocratic pumps, SFO, 2998 photodiode array, 2424 ELSD, and 3100 mass spectrometers. A Waters XBridge dC18 5micron 19x10 mm guard column was used with an ACT ACE C18- AR, 5micron 30 x 100 mm prep column. The preparative HPLC was conducted using a 11.4 minute run time using a gradient method, eluting with MeCN (0.05% TFA)/H_2O (0.05% TFA) at a flow rate of 33 mL/min.

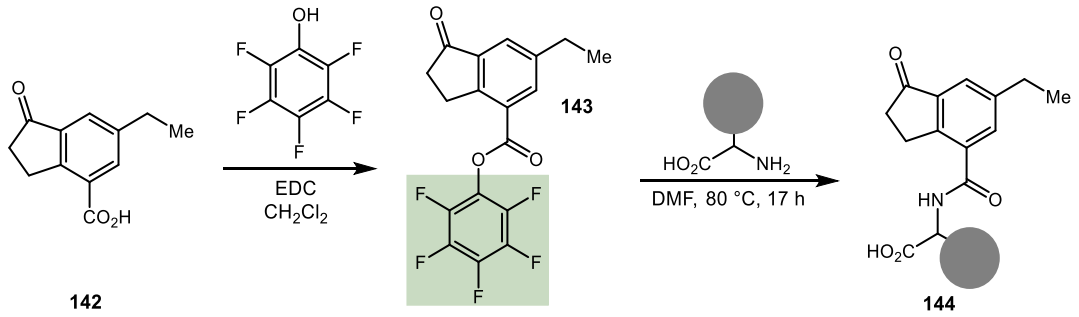
Where compounds were obtained as 1:1 mixtures of two diastereoisomers ((±)-coronafacic acid or coronafacic acid analogue conjugates with enantiopure amino acids or (±)-coronafacic acid or coronafacic acid analogue conjugates with (±)-amino acids eg. (±)-coronamic acid), ^{1}H NMR peaks corresponding to both diastereoisomers were integrated together and integration normalised to one. ^{13}C NMR signals are reported as observed.

Docking Studies

Docking studies were performed using protein data bank[118] (PDB) crystal structure 3OGK,[24] with the binding site occupied by ligand B selected as the target site for docking. The rotameric states of residues TRP519 and TRP467 in this binding site were reassigned to provide a better fit to the bound ligand before H atoms were added and protonation states assigned using the protein preparation wizard[119] from the 2017-01 release of the Schrodinger Suite. With a complete protein model in place, docking calculations were performed using the program Glide,[120,121] accessed via Maestro.[122] A Glide grid file was generated centred on the centroid of the bound coronatine molecule, with a cubic box of length 25 Å. All other options for grid generation were retained at their default values. The five molecules shown in Figure 28 were built in Maestro, and then docked using the standard precision mode of Glide: all options were assigned their default values, with only the highest scoring docking pose retained for each molecule.

6.1 General Experimental Procedures

General Procedure A: General procedure for coronalon core automated screen (Scheme 38).

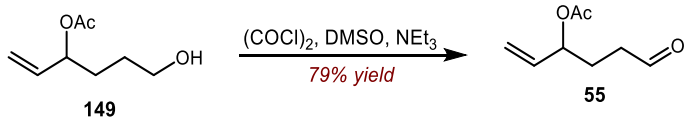


To a solution of amino acid (0.65 mmol, 1.2 equiv.) in DMF (2 mL) in a test tube was added **143** (200 mg, 0.54 mmol, 1 equiv.) in one portion and the reaction agitated at 80 °C for 17 hours. The crude reaction was concentrated *in vacuo*, dissolved in 10% MeOH in DMSO (1 mL) with heating, filtered, and purified by mass-directed HPLC

to give the title compound.

General Procedure B: Swern Oxidation.

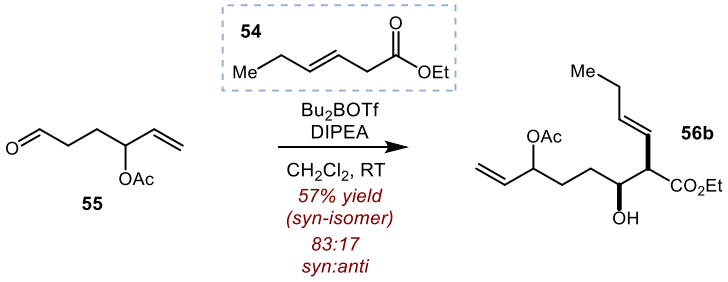
For example, synthesis of aldehyde **55**.



To a three-necked flask under an atmosphere of nitrogen was added oxalyl chloride (3.32 mL, 39.23 mmol, 1.5 equiv.) and anhydrous CH_2Cl_2 (90 mL). The reaction was cooled to −78 °C and DMSO (5.60 mL, 78.84 mmol, 3 equiv.) added dropwise. The reaction was stirred for 15 minutes at −78 °C before a solution of alcohol **149** (4.15 g, 26.24 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was added dropwise. The reaction was stirred at −78 °C for a further 30 minutes before being quenched slowly with triethylamine (22 mL, 157.84 mmol, 5 equiv.). The reaction was allowed to warm to room temperature over 1 h. The pale orange suspension was then diluted with water (40 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale orange liquid. The crude material was loaded directly in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 10-20% EtOAc/petroleum ether to afford the title compound as a pale yellow liquid (3.26 g, 79%).

General Procedure C: Aldol addition.

For example, synthesis of compound **56b**.

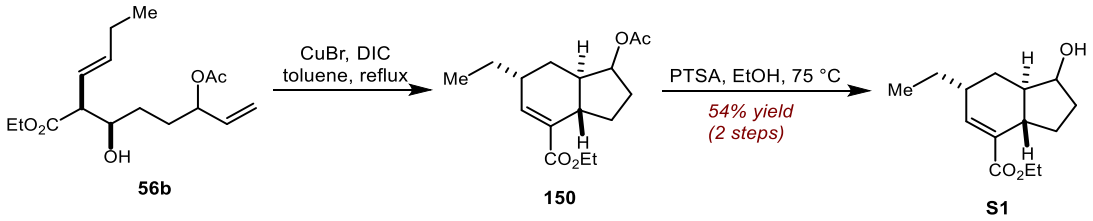


To a three-necked flask at room temperature under an atmosphere of nitrogen was added ester **54** (2.72 mL, 17.12 mmol, 1.3 equiv.) in anhydrous CH_2Cl_2 (50 mL) and DIPEA (3.44 mL, 19.75 mmol, 1.5 equiv.). Dibutylboryltrifluoromethanesulfonate solution (1 M in CH_2Cl_2) (17.1 mL, 17.1 mmol, 1.3 equiv.) was added dropwise and the resulting solution stirred at room temperature for 30 minutes. A solution of aldehyde **55** (2.06 g, 13.16 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was then added dropwise and the reaction stirred at room temperature for 1 h. The reaction was quenched with a potassium buffer solution (pH 7.4, 26 mL), MeOH (40 mL), and H_2O_2 (30% solution, 13 mL) which were added sequentially. A small exotherm was observed on H_2O_2 addition. The reaction was stirred vigorously at room temperature for 16 h, diluted with water (30 mL), and extracted with CH_2Cl_2 (3 x 40 mL). The organics were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material loaded directly in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 20% EtOAc/petroleum ether to afford the title compound as a colourless liquid. (2.81 g, 57% (^{1}H NMR yield)) (83:17 *syn:anti* by ^{1}H NMR).

General Procedure D: Tandem dehydration/Diels–Alder followed by ester hydrolysis.

For example, synthesis of compound **S1**.

Experimental

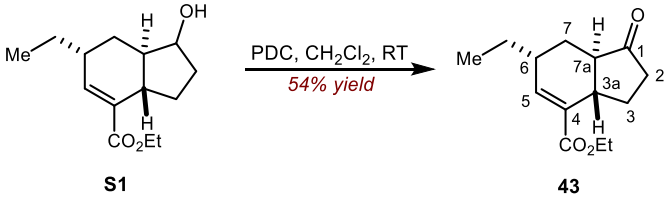


To a round bottom flask under an atmosphere of nitrogen was added compound **56b** (2.00 g, 6.71 mmol, 1 equiv. (79% purity)), CuBr (96 mg, 0.67 mmol, 10 mol%), and anhydrous toluene (1.3 mL). DIC (1.56 mL, 10.07 mmol, 1.5 equiv.) was added in one portion and the resulting solution was brought to 110 °C for 16 h. The reaction was allowed to cool to room temperature and the crude solution was filtered through celite, eluting with EtOAc (30 mL). The organics were washed with water (30 mL), followed by brine (30 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale brown oil. The crude material was directly loaded in a solution of 10% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 10% EtOAc/petroleum ether to afford a pale yellow oil (**150**) (1.49 g, 5.32 mmol) which was not characterised.

To the pale yellow oil was added EtOH (50 mL) and PTSA (mono-hydrate) (1.52 g, 7.99 mmol, 1.5 equiv.) and the resulting solution was brought to 75 °C for 5 h. The reaction was allowed to cool to room temperature and the solvent evaporated to afford an orange oil. The crude material was directly loaded in a solution of 20% EtOAc/petroleum ether and minimal CH_2Cl_2 and purified by flash silica column chromatography, eluent 20% EtOAc/petroleum ether to afford the title compound as a colourless liquid (677 mg, 54% (2 steps)).

General Procedure E: PDC oxidation.

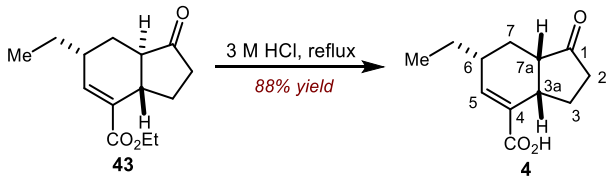
For examples, synthesis of compound **43**.



To a round bottom flask was added compound **S1** (1.79 g, 7.51 mmol, 1 equiv.), anhydrous CH_2Cl_2 (40 mL), and mol. sieves (3 Å, 2.3 g). PDC (4.24 g, 11.26 mmol, 1.5 equiv.) was added in one portion and the reaction was stirred at room temperature for 16 h. The crude reaction mixture was concentrated onto silica gel and purified by flash silica column chromatography, eluent 10-30% EtOAc/petroleum ether to afford the title compound as a colourless oil (957 mg, 54%) (3:1 dr C^{7a}).

General Procedure F: Acidic ester hydrolysis.

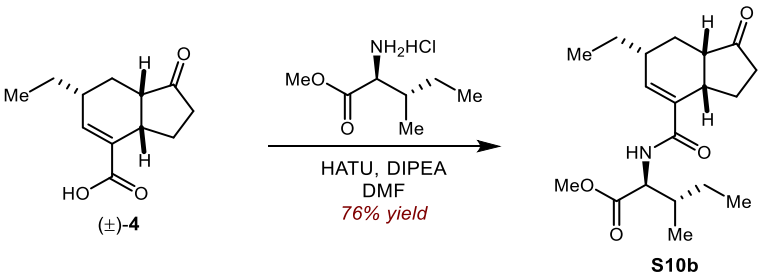
For example, see synthesis of (±)-coronafacic acid, **4**.



To a round bottom flask was added compound **43** (1.10 g, 4.65 mmol) and 3 M HCl (150 mL). The reaction was brought to 100 °C and maintained at this temperature with stirring for 16 h. The reaction was allowed to cool to room temperature and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered, and evaporated to afford an orange oil. The crude material was loaded directly in a solution of 30% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30-60% EtOAc/petroleum ether to afford the title compound as a white solid (850 mg, 88%).

General Procedure G: Synthesis of (±)-CFA-amino acid methyl ester analogues (Scheme 42).

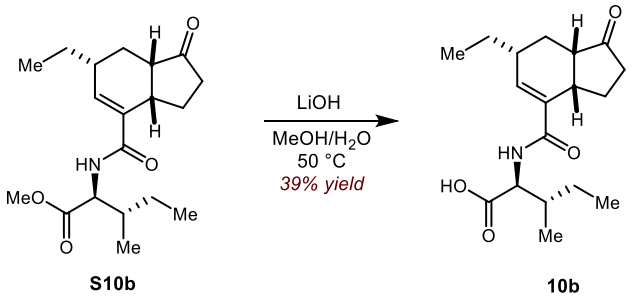
For example, synthesis of compound **S10b**.



To a 2-dram vial was added (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.) and HATU (66 mg, 0.17 mmol, 1.2 equiv.). DMF (0.7 mL) was added, followed by DIPEA (80 µL, 0.46 mmol, 3 equiv.) and the resulting solution stirred at room temperature for 5 minutes. Methyl *L*-isoleucinate hydrochloride (30 mg, 0.21 mmol, 1.5 equiv.) was then added in one portion and the vial capped with a screw top lid. The reaction was stirred for 16 h. The reaction was then diluted with H_2O (10 mL) and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded directly in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 30% EtOAc/CH_2Cl_2 to afford the desired product as a colourless oil which solidified to a white solid on standing (35 mg, 76%).

General Procedure H: Pro-cide ester hydrolysis (Scheme 42).

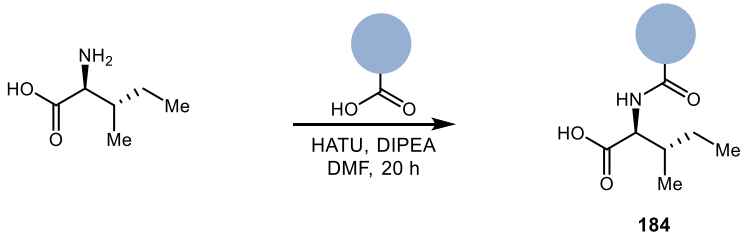
For example, synthesis of compound **10b**.



To a round bottom flask was added compound **S10b** (24 mg, 0.07 mmol, 1 equiv.) and LiOH (5 mg, 0.20 mmol, 3 equiv.). The material was suspended in 1:1 MeOH:H_2O (3 mL) and the resulting suspension brought to 50 °C for 16 h. The reaction was allowed to cool to room temperature, and extracted with EtOAc (1 x 5 mL), and the organics

discarded. The aqueous phase was acidified with HCl (aq.), and extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was taken up in a minimal volume of diethyl ether, and petroleum ether added until a white precipitate formed (where precipitation did not occur spontaneously the solvent was concentrated under a stream of compressed air until precipitation occurred). The solvent was removed using a Pasteur pipette and the precipitate dried under vacuum to afford the desired product as a white solid (9 mg, 39%).

General Procedure I: General procedure for isoleucine automated screen (Scheme 52)



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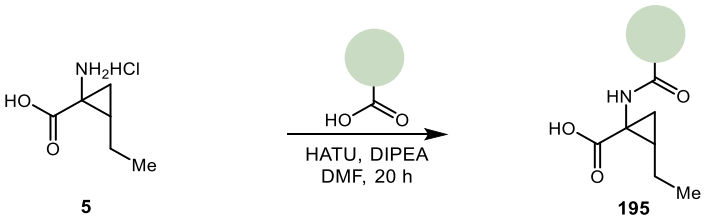
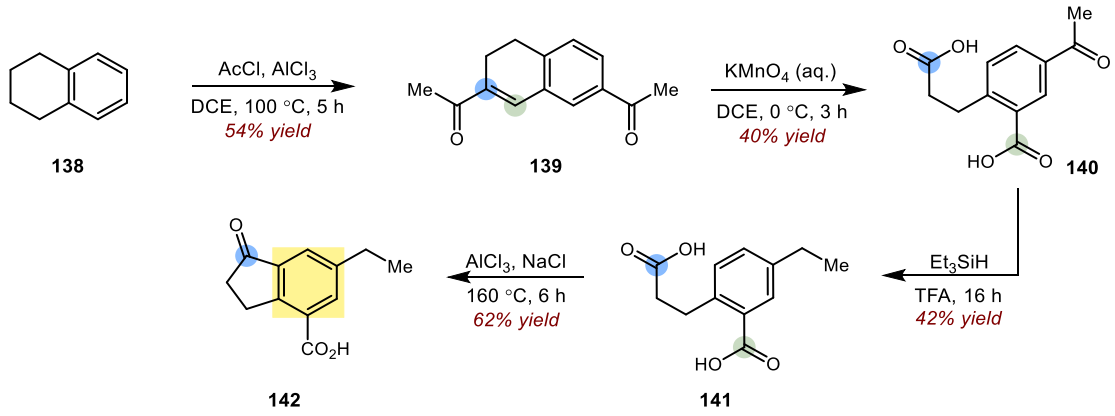
A test tube was charged with carboxylic acid (0.54 mmol, 1 equiv.) and a solution of HATU (251 mg, 0.66 mmol, 1.2 equiv.) in DMF (0.9 mL) added. The reaction mixture was agitated for 1 h before a solution of DIPEA (0.25 mL, 1.42 mmol, 3 equiv.) and isoleucine (108 mg, 0.82 mmol, 1.5 equiv.) in DMF (0.9 mL) was added and the reaction mixture agitated for 20 h. The crude reaction was concentrated *in vacuo*, dissolved in 10% MeOH in DMSO (1 mL) with heating, filtered, and purified by mass-directed HPLC to give the title compound.

General Procedure J: General procedure for CMA automated screen (Scheme 54).



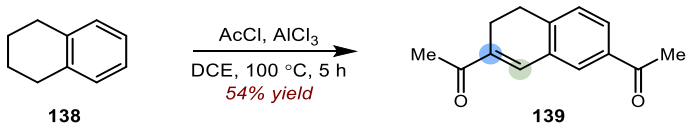
A test tube was charged with carboxylic acid (0.6 mmol, 1 equiv.) and a solution of HATU (266 mg, 0.7 mmol, 1.2 equiv.) in DMF (2 mL) added. The reaction mixture was agitated for 1 h before a solution of DIPEA (0.35 mL, 2 mmol, 3 equiv.) and compound **5** (100 mg, 0.6 mmol, 1 equiv.) in DMF (2 mL) was added and the reaction mixture agitated for 20 h. The crude reaction was concentrated *in vacuo*, dissolved in 10% MeOH in DMSO (1 mL) and purified by mass-directed HPLC to give the title compound.

6.2 Synthesis of compound 142.



6.2.1 Procedures and Characterisation of compound 142.

Compound 139.



To a round bottom flask fitted was added $AlCl_3$ (20 g, 0.15 mol, 4 equiv.) and DCE (12.5 mL). AcCl (8.05 mL, 0.11 mol, 3 equiv.) was added dropwise to the stirring suspension at room temperature. A small exotherm was observed. A solution of 1,2,3,4-tetrahydronapthalene (**138**) (5.15 mL, 0.04 mol, 1 equiv.) in DCE (6 mL) was then added dropwise. A second exotherm was observed. The reaction was stirred for 5 minutes and the solvent removed *in vacuo* to afford a viscous residue. The residue was then heated to 100 °C for 5 h. The reaction was cooled to 0 °C in an ice bath before being quenched slowly with water (100 mL) and $NaHCO_3$ (aq.) (100 mL). On quenching a dark brown precipitate was formed. The precipitate was extracted into EtOAc (3 x 100 mL). The organics were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered, and evaporated to afford a viscous dark red/brown oil. The crude material was loaded in a solution of 30% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30% EtOAc/petroleum ether to afford an orange oil which solidified to an orange solid on standing. The solid was triturated with diethyl ether to afford the title compound as a beige solid (4.41 g, 54 %).

TLC (20% EtOAc/petroleum ether): R_f = 0.32 stained by $KMnO_4$ and visible by UV (short wave).

υ_{max} (neat): 2939, 2893, 1679, 1656, 1623, 1355, 1281, 1271, 1203 cm^{-1}.

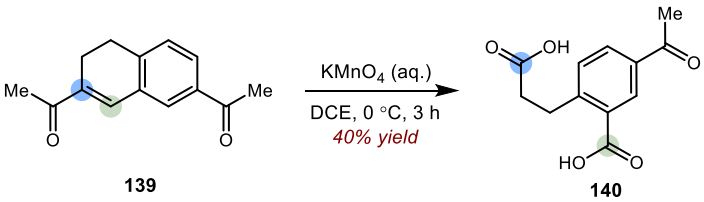
^1H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.83 (m, 2H), 7.44 (s, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 2.89 (t, *J* = 8.3 Hz, 2H), 2.64 – 2.59 (m, 5H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.4, 197.4, 143.1, 139.2, 136.3, 136.2, 133.1, 129.9, 128.3, 128.2, 27.8, 26.7, 25.5, 20.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{15}O_2$) requires *m/z* 215.1067, found *m/z* 215.1067.

The spectral data were consistent with those previously reported in the literature.[122]

Compound 140.



139 140

To a solution of $KMnO_4$ (4.74 g, 29.99 mmol, 1 equiv.) in water (125 mL) in a round bottom flask at 0 °C was added compound **139** (2.57 g, 11.99 mmol, 2.5 equiv.) in a solution of DCE (5 mL) over the course of 5 minutes. The reaction was stirred at ~ 3 °C for 3 h. Powdered NaOH (~ 2.3 g) was added and the solution filtered. The solution was brought to pH 1 with HCl (aq.) and the aqueous was extracted with EtOAc (3 x 50 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a brown solid, which was then triturated with acetone to afford the title compound as an orange solid (1.12 g, 40%).

υ_{max} (neat): 3049 (br.), 2930, 1716, 1693, 1651, 1195 cm^{-1}.

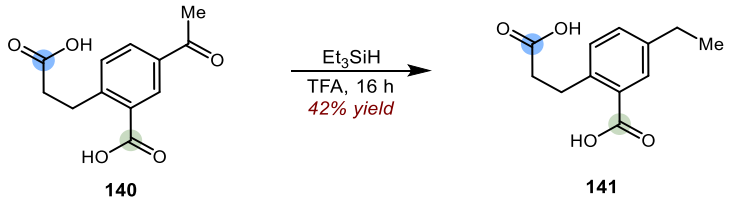
^1H NMR (400 MHz, DMSO-d_6): δ 12.63 (br. s, 2H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 3.20 (t, *J* = 7.7 Hz, 2H), 2.59 (s, 3H), 2.54 (t, *J* = 7.7 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 197.0, 173.5, 147.0, 134.9, 131.3, 131.1, 129.9, 34.9, 29.0, 26.7. Two signals not observed.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{12}H_{11}O_5$) requires *m/z* 235.0612, found *m/z* 235.0612.

The spectral data were consistent with those previously reported in the literature.[122]

Compound 141.



140 **141**

To a round bottom flask charged with compound **140** (444 mg, 1.88 mmol, 1 equiv.) in TFA (6.5 mL) was added triethylsilane (0.85 mL, 5.32 mmol, 2.5 equiv.) dropwise and the resulting orange suspension was stirred at room temperature for 16 h under air. The solvent was removed in *vacuo* to afford a brown oil. The crude material was dry loaded onto silica gel and purified by flash silica column chromatography, eluent 2% AcOH, 30% EtOAc/petroleum ether to afford title compound as a white solid (176 mg, 42%).

TLC (2% AcOH, 30% EtOAc/PE): R_f = 0.22 stained by $KMnO_4$ and visible by UV (short wave).

υ_{max} (neat): 2963 (br.), 2932, 2872, 2634, 1682, 1403, 1277, 1210, 907 cm^{-1}.

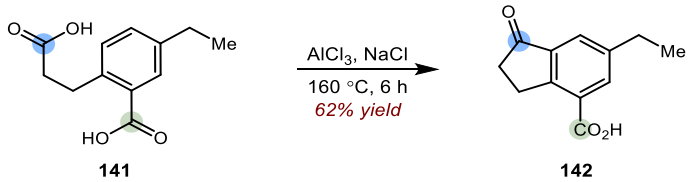
^1H NMR (400 MHz, Acetone-d_6): δ 10.84 (br. s, 1H), 7.80 (d, *J* = 1.7 Hz, 1H), 7.37 – 7.29 (m, 2H), 3.27 – 3.21 (m, 2H), 2.70 – 2.60 (m, 4H), 1.23 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, DMSO-d_6): δ 173.8, 168.8, 141.7, 139.1, 131.2, 130.8, 130.3, 129.5, 35.4, 28.7, 27.5, 15.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{12}H_{13}O_4$) requires *m/z* 221.0819, found *m/z* 221.0819.

The spectral data were consistent with those previously reported in the literature.[122]

Compound 142.



141 **142**

A round bottom flask charged with compound **141** (177 mg, 0.80 mmol, 1 equiv.), $AlCl_3$ (743 mg, 5.57 mmol, 7 equiv.), NaCl (116 mg, 1.98 mmol, 2.5 equiv.) was brought to 160 °C under air and stirred for 6 h. The reaction was allowed to cool to room temperature and water (3 mL) added, followed by HCl (aq.) (0.5 mL), and the resulting suspension stirred at room temperature for 20 h. The reaction was diluted with EtOAc (10 mL) and filtered. Water (10 mL) was added and the layers separated. The organics were dried over Na_2SO_4, filtered, and evaporated to afford a beige solid. The material was dry loaded onto silica gel and purified by flash silica column chromatography, eluent 2% AcOH, 30% EtOAc/petroleum ether to afford the title compound as a white solid (101 mg, 62%).

TLC (2% AcOH, 30% EtOAc/petroleum ether): R_f = 0.35 stained by $KMnO_4$ and visible by UV (short wave).

υ_{max} (neat): 2961, 2924, 2868, 2668, 1708, 1673, 1580, 1435, 1299, 1242 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 1.6 Hz, 1H), 3.54 – 3.47 (m, 2H), 2.83 – 2.72 (m, 4H), 1.30 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 171.5, 155.2, 144.5, 138.9, 137.4, 128.2, 127.3, 36.6, 28.4, 27.2, 15.5.

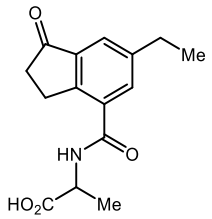
HRMS: exact mass calculated for $[M-H]^-$ ($C_{12}H_{11}O_3$) requires *m/z* 203.0714, found *m/z* 203.0714.

The spectral data were consistent with those previously reported in the literature.[122]

6.3 Coronalon Aromatic Core Amino Acid Analogues (Scheme 38).

Reactions carried out according to General Procedure A.

Compound 144a.



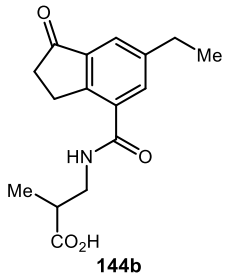
144a

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.5 Hz, 1H), 7.69 (s, 1H), 6.89 (d, *J* = 6.9 Hz, 1H), 4.80 – 4.71 (m, 1H), 3.38 – 3.33 (m, 2H), 2.76 – 2.68 (m, 4H), 1.56 (d, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 175.2, 166.8, 151.7, 144.4, 138.5, 133.4, 132.7, 125.4, 48.7, 36.6, 28.5, 25.9, 18.6, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}NO_4$) requires *m/z* 276.1230, found *m/z* 276.1228.

Compound 144b.



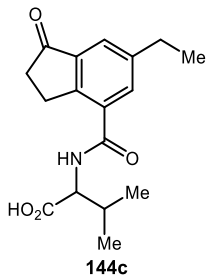
144b

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 2H), 6.87 (t, *J* = 5.5 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.54 – 3.45 (m, 1H), 3.35 – 3.26 (m, 2H), 2.86 – 2.76 (m, 1H), 2.75 – 2.66 (m, 4H), 1.29 – 1.18 (m, 6H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 178.5, 167.5, 151.5, 144.4, 138.5, 133.2, 125.2, 42.0, 39.4, 36.6, 28.4, 25.8, 15.5, 15.1. One signal not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{20}NO_4$) requires *m/z* 290.1387, found *m/z* 290.1384.

Compound 144c.



144c

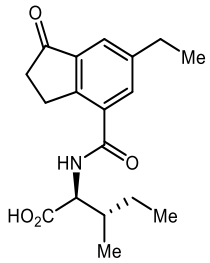
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.68 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.78 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.38 – 3.33 (m, 2H), 2.78 – 2.68 (m, 4H), 2.41 – 2.32 (m, 1H),

1.26 (t, *J* = 7.6 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 174.3, 167.2, 151.4, 144.5, 138.5, 133.4, 133.1, 125.4, 57.5, 36.6, 31.5, 28.5, 25.9, 19.3, 18.0, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}NO_4$) requires *m/z* 304.1543, found *m/z* 304.1541.

Compound 144d.



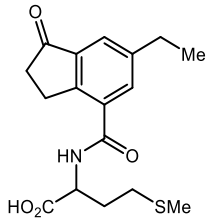
144d

^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.5 Hz, 1H), 7.68 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.79 (dd, *J* = 8.2, 4.4 Hz, 1H), 3.37 – 3.31 (m, 2H), 2.77 – 2.68 (m, 4H), 2.12 – 2.02 (m, 1H), 1.63 – 1.51 (m, 1H), 1.35 – 1.20 (m, 4H), 1.03 – 0.91 (m, 6H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 174.1, 167.0, 151.4, 144.4, 138.5, 133.4, 133.0, 125.3, 57.0, 38.1, 36.6, 28.4, 25.9, 25.4, 15.7, 15.5, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{24}NO_4$) requires *m/z* 318.1700, found *m/z* 318.1696.

Compound 144e.



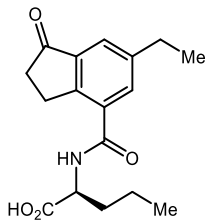
144e

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 1.5 Hz, 1H), 7.72 (s, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 5.44 (br. s, 1H), 4.95 (td, *J* = 7.3, 5.1 Hz, 1H), 3.37 (dd, *J* = 10.8, 4.6 Hz, 2H), 2.80 – 2.63 (m, 6H), 2.41 – 2.29 (m, 1H), 2.26 – 2.15 (m, 1H), 2.13 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.1, 175.4, 167.5, 152.0, 144.6, 138.6, 133.4, 132.2, 125.9, 52.4, 36.6, 31.1, 30.4, 28.5, 26.0, 15.7, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}NO_4S$) requires *m/z* 336.1264, found *m/z* 336.1261.

Compound 144f.



144f

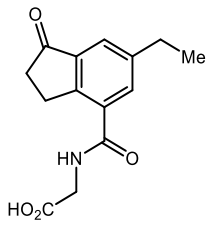
Experimental

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (br. s, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.68 (s, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 4.79 (td, *J* = 7.3, 5.3 Hz, 1H), 3.38 – 3.32 (m, 2H), 2.76 – 2.67 (m, 4H), 2.05 – 1.93 (m, 1H), 1.86 – 1.75 (m, 1H), 1.53 – 1.37 (m, 2H), 1.24 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 175.0, 167.0, 151.6, 144.4, 138.5, 133.4, 132.8, 125.4, 52.6, 36.6, 34.6, 28.4, 25.9, 18.7, 15.5, 13.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}NO_4$) requires *m/z* 304.1543, found *m/z* 304.1540.

Compound 144g.



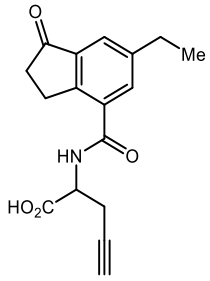
144g

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.5 Hz, 1H), 7.67 (s, 1H), 4.16 (s, 2H), 3.36 – 3.31 (m, 2H), 2.78 – 2.63 (m, 4H), 1.23 (t, *J* = 7.6 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.4, 171.7, 167.6, 152.0, 144.4, 138.4, 133.4, 132.4, 125.4, 41.6, 36.6, 28.4, 25.8, 15.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}NO_4$) requires *m/z* 262.1074, found *m/z* 262.1073.

Compound 144h.



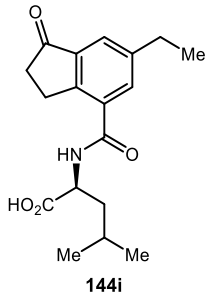
144h

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.6 Hz, 1H), 7.72 (s, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 4.90 (dt, *J* = 7.3, 4.6 Hz, 1H), 3.46 – 3.32 (m, 2H), 3.06 – 2.87 (m, 2H), 2.79 – 2.69 (m, 4H), 2.06 (t, *J* = 2.6 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 172.3, 166.8, 151.5, 144.5, 138.6, 133.7, 132.5, 125.7, 79.0, 71.78, 51.2, 36.6, 28.5, 26.0, 22.5, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}NO_4$) requires *m/z* 300.1230, found *m/z* 300.1228.

Compound 144i.



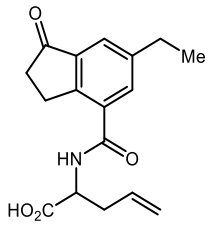
144i

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br. s, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.66 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.79 (td, *J* = 8.4, 4.9 Hz, 1H), 3.41 – 3.25 (m, 2H), 2.75 – 2.65 (m, 4H), 1.86 – 1.63 (m, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.02 – 0.92 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 175.3, 167.2, 151.7, 144.3, 138.4, 133.3, 132.9, 125.3, 51.3, 41.7, 36.6, 28.4, 25.82, 25.15, 22.97, 22.13, 15.47.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{24}NO_4$) requires *m/z* 318.1700, found *m/z* 318.1696.

Compound 144j.



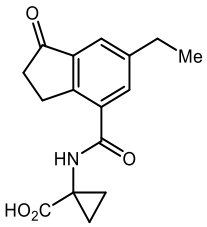
144j

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.68 (m, 2H), 7.18 (br. s, 1H), 6.72 (d, *J* = 7.3 Hz, 1H), 5.80 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.23 – 5.13 (m, 2H), 4.87 (dt, *J* = 7.2, 5.6 Hz, 1H), 3.38 – 3.31 (m, 2H), 2.85 – 2.69 (m, 6H), 1.25 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 174.0, 166.9, 151.5, 144.5, 138.6, 133.4, 132.7, 132.5, 125.5, 119.6, 52.2, 36.6, 36.4, 28.5, 25.9, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}NO_4$) requires *m/z* 302.1387, found *m/z* 302.1383.

Compound 144k.



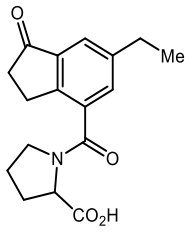
144k

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 2H), 7.05 (s, 1H), 6.71 (br. s, 1H), 3.36 – 3.30 (m, 2H), 2.73 – 2.63 (m, 4H), 1.70 – 1.64 (m, 2H), 1.34 – 1.27 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.1, 176.0, 168.7, 152.3, 144.2, 138.5, 133.0, 132.7, 125.3, 36.6, 33.9, 28.4, 25.8, 17.8, 15.5. One signal not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{18}NO_4$) requires *m/z* 288.1230, found *m/z* 288.1228.

Compound 144l.



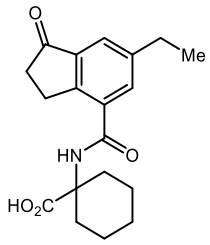
144l

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (br. s, 1H), 7.60 (s, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 4.67 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.49 – 3.40 (m, 1H), 3.40 – 3.31 (m, 1H), 3.22 – 3.05 (m, 2H), 2.74 – 2.65 (m, 4H), 2.36 – 2.23 (m, 1H), 2.20 – 2.08 (m, 1H), 2.06 – 1.94 (m, 1H), 1.93 – 1.82 (m, 1H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 174.0, 168.7, 150.4, 144.2, 138.1, 134.5, 131.9, 123.8, 58.9, 49.5, 36.6, 29.3, 28.4, 25.0, 24.4, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}NO_4$) requires *m/z* 302.1387, found *m/z* 302.1384.

Compound 144m.



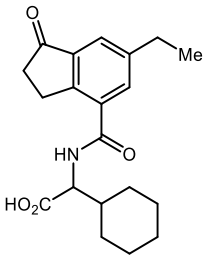
144m

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 2H), 6.30 (s, 1H), 3.36 – 3.28 (m, 2H), 2.78 – 2.66 (m, 4H), 2.27 – 2.16 (m, 2H), 2.01 – 1.92 (m, 2H), 1.81 – 1.64 (m, 3H), 1.57 – 1.44 (m, 2H), 1.43 – 1.34 (m, 1H), 1.26 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.7, 176.8, 167.7, 151.4, 144.4, 138.5, 133.3, 133.2, 125.3, 59.7, 36.6, 32.3, 28.5, 25.9, 25.3, 21.8, 15.5. Two signals equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}NO_4$) requires *m/z* 330.1700, found *m/z* 330.1696.

Compound 144n.



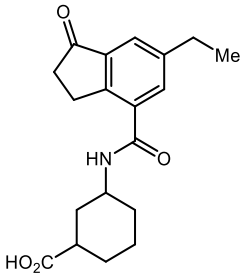
144n

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.68 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.77 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.40 – 3.33 (m, 2H), 2.78 – 2.70 (m, 4H), 2.05 – 1.93 (m, 1H), 1.89 – 1.61 (m, 5H), 1.36 – 1.05 (m, 8H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 174.3, 167.2, 151.5, 144.5, 138.6, 133.5, 132.9, 125.5, 57.3, 41.2, 36.6, 29.8, 28.5, 28.4, 26.2, 26.2, 26.1, 26.0, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}NO_4$) requires *m/z* 344.1856, found *m/z* 344.1853.

Compound 144o.



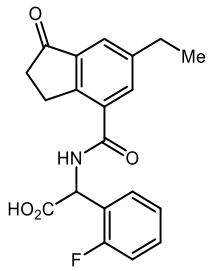
144o

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 6.21 (d, *J* = 7.9 Hz, 1H), 4.12 – 4.00 (m, 1H), 3.38 – 3.31 (m, 2H), 2.78 – 2.67 (m, 4H), 2.59 – 2.50 (m, 1H), 2.41 – 2.31 (m, 1H), 2.14 – 1.99 (m, 2H), 1.95 – 1.87 (m, 1H), 1.56 – 1.36 (m, 3H), 1.31 – 1.19 (m, 4H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 178.7, 166.6, 151.5, 144.2, 138.4, 133.4, 132.7, 124.9, 47.9, 41.7, 36.5, 34.7, 32.4, 28.4, 28.2, 25.7, 23.8, 15.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}NO_4$) requires *m/z* 330.1700, found *m/z* 330.1696.

Compound 144p.



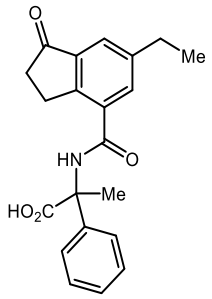
144p

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 1.6 Hz, 1H), 7.71 (s, 1H), 7.51 (td, *J* = 7.5, 1.7 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.17 (td, *J* = 7.5, 1.1 Hz, 1H), 7.12 – 7.06 (m, 1H), 5.93 (d, *J* = 7.0 Hz, 1H), 3.46 – 3.29 (m, 2H), 2.78 – 2.68 (m, 4H), 1.25 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 172.1, 166.4, 160.9 (d, $^{1}J_{C\text{-}F}$ = 247.6 Hz), 151.7, 144.5, 138.6, 133.7, 132.3, 130.6 (d, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 130.5 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 125.7, 124.9 – 124.5 (m), 116.1 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 52.4, 36.6, 28.5, 26.0, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}FNO_4$) requires *m/z* 356.1293, found *m/z* 356.1291.

Compound 144q.



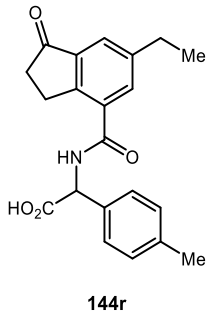
144q

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 1.6 Hz, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.55 – 7.50 (m, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 3.44 – 3.28 (m, 2H), 2.79 – 2.67 (m, 4H), 2.19 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 175.3, 166.2, 151.5, 144.5, 140.0, 138.6, 133.5, 133.1, 128.8, 128.1, 125.9, 125.5, 62.8, 36.6, 28.5, 26.1, 22.7, 15.5. Two peaks equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{22}NO_4$) requires *m/z* 352.1543, found *m/z* 352.1543.

Compound 144r.



144r

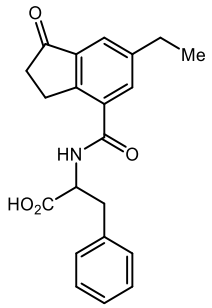
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 1.4 Hz, 1H), 7.71 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 6.5 Hz, 1H), 5.71 (d, *J* = 6.7 Hz, 1H),

3.38 – 3.32 (m, 2H), 2.77 – 2.68 (m, 4H), 2.34 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 166.5, 151.8, 144.5, 138.8, 138.6, 133.5, 132.3, 129.9, 127.4, 125.7, 56.8, 36.6, 28.5, 26.0, 21.3, 15.5. Four signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{22}NO_4$) requires *m/z* 352.1543, found *m/z* 352.1542.

Compound 144s.



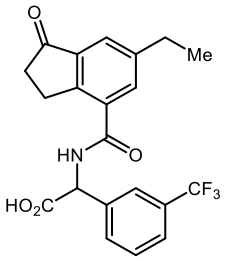
144s

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.32 – 7.19 (m, 5H), 6.60 (d, *J* = 7.2 Hz, 1H), 5.10 – 5.03 (m, 1H), 3.47 – 3.09 (m, 4H), 2.76 – 2.63 (m, 4H), 1.24 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 173.6, 166.8, 151.6, 144.4, 138.5, 136.2, 133.4, 132.6, 129.7, 128.7, 127.3, 125.5, 53.6, 37.4, 36.6, 28.4, 25.7, 15.4. Two signals equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{22}NO_4$) requires *m/z* 352.1543, found *m/z* 352.1542.

Compound 144t.



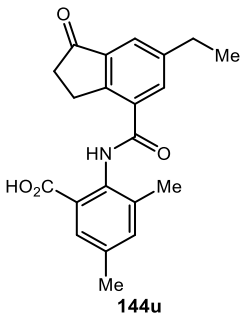
144t

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.67 (m, 4H), 7.61 – 7.56 (m, 1H), 7.54 – 7.40 (m, 2H), 5.77 (d, *J* = 6.3 Hz, 1H), 3.40 – 3.32 (m, 2H), 2.79 – 2.69 (m, 4H), 1.26 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, MeOD): δ 209.0, 172.8, 169.6, 153.5, 145.7, 139.7, 139.2, 135.0, 134.3, 132.9, 132.0 (app. d, $^{2}J_{C\text{-}F}$ = 32.4 Hz), 130.7, 126.1 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 125.8 (app. d, $^{3}J_{C\text{-}F}$ = 4.1 Hz), 125.7, 58.0, 37.3, 29.3, 26.4, 15.8. F bearing carbon not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{19}F_3NO_4$) requires *m/z* 406.1261, found *m/z* 406.1256.

Compound 144u.



144u

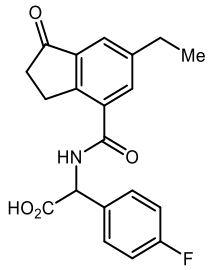
Experimental

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.96 (s, 1H), 7.75 (s, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.33 (s, 1H), 3.48 – 3.41 (m, 2H), 2.83 – 2.69 (m, 4H), 2.35 (s, 3H), 2.33 (s, 3H), 1.30 (t, *J* = 7.6 Hz, 3H). One signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 170.6, 152.7, 144.5, 138.7, 137.2, 135.6, 135.6, 135.1, 133.8, 133.1, 129.7, 125.7, 122.6, 36.7, 28.6, 26.2, 20.9, 19.6, 15.5. One signal not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{22}NO_4$) requires *m/z* 352.1543, found *m/z* 352.1542.

Compound 144v.



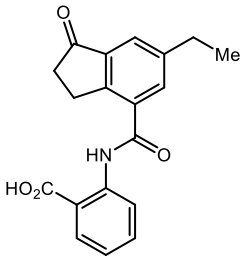
144v

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 1.4 Hz, 1H), 7.73 (s, 1H), 7.50 – 7.44 (m, 2H), 7.19 (d, *J* = 6.4 Hz, 1H), 7.11 – 7.04 (m, 2H), 5.73 (d, *J* = 6.4 Hz, 1H), 3.40 – 3.33 (m, 2H), 2.78 – 2.69 (m, 4H), 1.27 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 151.8, 144.6, 138.7, 133.4, 129.3 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 125.8, 116.2 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 36.6, 28.5, 26.1, 15.6. Two signals equivalent, F bearing carbon not observed. Five signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}FNO_4$) requires *m/z* 356.1293, found *m/z* 356.1290.

Compound 144w.



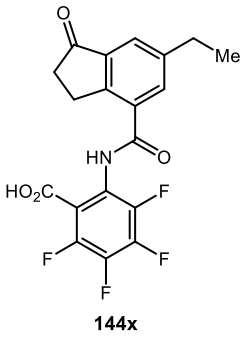
144w

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.86 (d, *J* = 1.5 Hz, 1H), 7.67 (s, 1H), 7.54 (ddd, *J* = 8.7, 7.4, 1.7 Hz, 1H), 7.13 – 7.06 (m, 1H), 3.46 – 3.38 (m, 2H), 2.77 – 2.63 (m, 4H), 1.23 (t, *J* = 7.6 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8, 170.6, 165.8, 152.8, 144.5, 141.3, 138.4, 134.5, 133.6, 133.2, 131.7, 125.5, 123.0, 120.1, 115.9, 36.5, 28.3, 25.8, 15.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}NO_4$) requires *m/z* 324.1230, found *m/z* 324.1228.

Compound 144x.



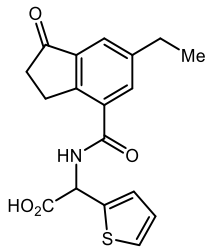
144x

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 7.90 (d, *J* = 1.4 Hz, 1H), 7.78 (s, 1H), 3.47 – 3.39 (m, 2H), 2.81 – 2.71 (m, 4H), 1.28 (t, *J* = 7.6 Hz, 3H). One signal not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 165.3, 164.7, 153.1, 144.7, 138.9, 133.9, 131.3, 126.5, 36.6, 28.5, 26.2, 15.5. Six signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{14}F_4NO_4$) requires *m/z* 396.0853, found *m/z* 396.0853.

Compound 144y.



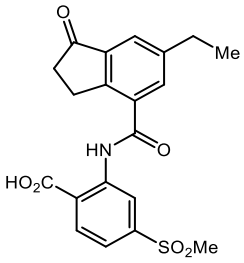
144y

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 1.4 Hz, 1H), 7.72 (s, 1H), 7.27 (d, *J* = 5.1 Hz, 1H), 7.21 – 7.15 (m, 2H), 6.99 (dd, *J* = 4.9, 3.7 Hz, 1H), 6.05 (d, *J* = 7.1 Hz, 1H), 3.40 – 3.35 (m, 2H), 2.78 – 2.68 (m, 4H), 1.26 (t, *J* = 7.6 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9, 171.8, 166.5, 151.8, 144.5, 139.1, 138.7, 133.5, 132.2, 127.3, 126.7, 125.9, 125.8, 52.5, 36.6, 28.5, 26.0, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}SNO_4$) requires *m/z* 344.0951, found *m/z* 344.0949.

Compound 144z.



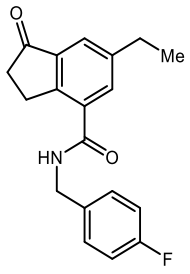
144z

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 9.17 (d, *J* = 1.8 Hz, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 1.4 Hz, 1H), 7.76 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.72 (s, 1H), 3.56 – 3.31 (br. m, 3H), 2.78 (q, *J* = 7.6 Hz, 2H), 2.71 – 2.65 (m, 2H), 2.54 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 205.9, 168.9, 165.1, 152.7, 145.0, 144.1, 140.9, 138.4, 132.7, 132.6, 132.4, 125.2, 121.7, 121.3, 118.3, 43.3, 36.1, 27.7, 25.6, 15.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{20}SNO_6$) requires *m/z* 402.1006, found *m/z* 402.1004.

Compound 144aa.



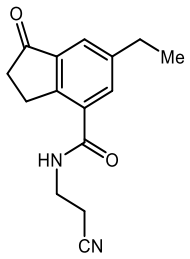
144aa

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.08 – 6.99 (m, 2H), 6.42 (br. s, 1H), 4.62 (d, *J* = 5.8 Hz, 2H), 3.39 – 3.31 (m, 2H), 2.77 – 2.65 (m, 4H), 1.25 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 167.2, 162.4 (d, $^{1}J_{C\text{-}F}$ = 246.3 Hz), 151.9, 144.4, 138.7, 133.9 (d, $J_{C\text{-}F}$ = 3.3 Hz), 133.0, 132.7, 129.8 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 125.3, 115.9 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz), 43.4, 36.6, 28.5, 25.9, 15.6. Two signals equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}FNO_2$) requires *m/z* 312.1394, found *m/z* 312.1391.

Compound 144ab.



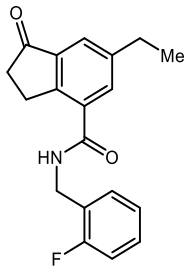
144ab

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 2H), 3.71 – 3.64 (m, 2H), 3.37 – 3.28 (m, 2H), 2.80 – 2.64 (m, 6H), 1.24 (t, *J* = 7.6 Hz, 3H). N*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.1, 168.0, 152.1, 144.4, 138.6, 133.1, 132.3, 125.5, 118.5, 36.6, 36.0, 28.4, 25.8, 18.5, 15.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}N_2O_2$) requires *m/z* 257.1285, found *m/z* 257.1283.

Compound 144ac.



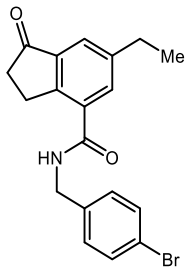
144ac

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.66 (d, *J* = 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.6 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 7.12 – 7.04 (m, 1H), 6.53 (br. s, 1H), 4.70 (d, *J* = 5.9 Hz, 2H), 3.39 – 3.30 (m, 2H), 2.77 – 2.65 (m, 4H), 1.25 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 167.2, 161.3 (d, $^{1}J_{c\text{-}f}$ = 246.0 Hz), 151.8, 144.4, 138.7, 133.0, 132.9, 130.7 (d, $^{3}J_{c\text{-}f}$ = 4.2 Hz), 129.8 (d, $^{3}J_{c\text{-}f}$ = 8.2 Hz), 125.3, 125.1 (d, $^{2}J_{c\text{-}f}$ = 14.7 Hz), 124.6 (d, $J_{c\text{-}f}$ = 3.6 Hz), 115.7 (d, $^{2}J_{c\text{-}f}$ = 21.2 Hz), 38.3 (d, $^{3}J_{c\text{-}f}$ = 3.6 Hz), 36.6, 28.5, 25.9, 15.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}FNO_2$) requires *m/z* 312.1394, found *m/z* 312.1391.

Compound 144ad.



144ad

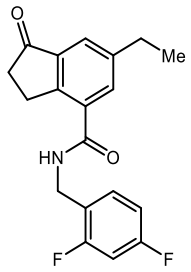
Experimental

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.55 (br. s, 1H), 4.59 (d, *J* = 5.9 Hz, 2H), 3.38 – 3.29 (m, 2H), 2.74 – 2.65 (m, 4H), 1.24 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 167.3, 151.9, 144.4, 138.7, 137.2, 132.9, 132.0, 129.7, 125.3, 121.7, 43.5, 36.6, 28.5, 25.9, 15.5. Three signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}BrNO_2$) requires *m/z* 372.0594, found *m/z* 372.0599.

Compound 144ae.



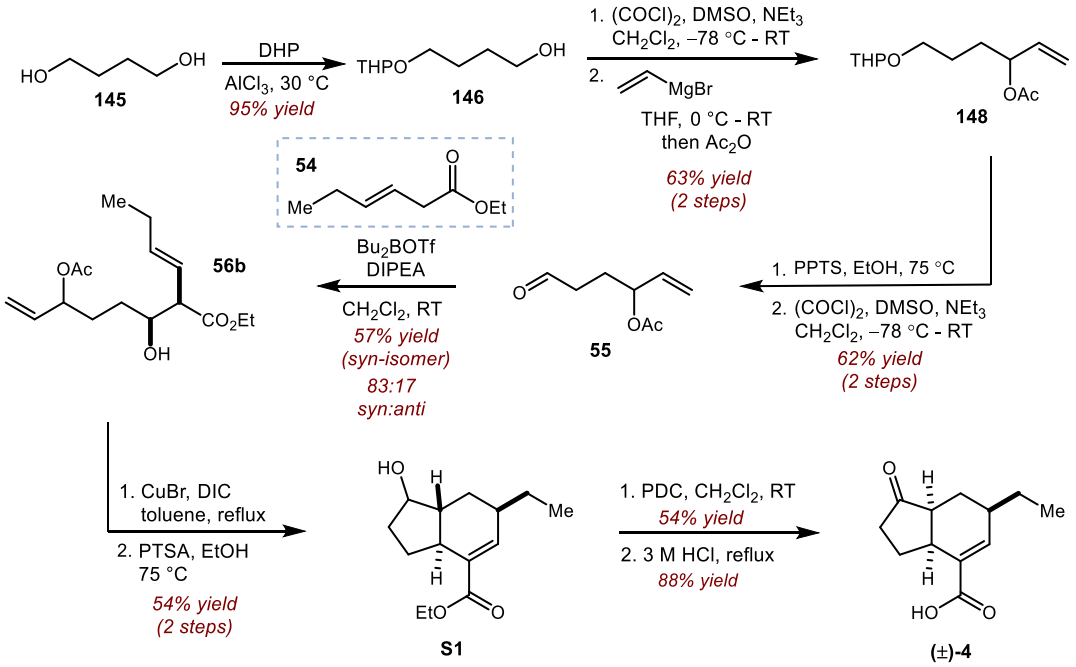
144ae

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.48 – 7.39 (m, 1H), 6.92 – 6.81 (m, 2H), 6.44 (br. s, 1H), 4.66 (d, *J* = 5.9 Hz, 2H), 3.38 – 3.29 (m, 2H), 2.77 – 2.66 (m, 4H), 1.25 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.7, 167.2, 151.8, 144.4, 138.7, 132.8, 132.8, 131.7 – 131.5 (m), 125.4, 121.2 (dd, $^{2}J_{C\text{-}F}$ = 15.0 Hz, $J_{C\text{-}F}$ = 4.0 Hz), 111.7 (dd, $^{2}J_{C\text{-}F}$ = 21.1 Hz, $J_{C\text{-}F}$ = 3.7 Hz), 104.2 (t, $^{2}J_{C\text{-}F}$ = 25.4 Hz), 37.8 (d, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 36.6, 28.5, 25.9, 15.6. F bearing carbons not observed.

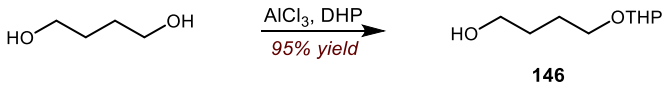
HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}F_2NO_2$) requires *m/z* 330.1300, found *m/z* 330.1296.

6.4 Synthesis of (±)-CFA (3) (Scheme 40/41).



6.4.1 Procedures and Characterisation of CFA synthesis.

Compound 146.



To a round bottom flask was added butane-1,4-diol (27.3 g, 302.93 mmol, 5 equiv.) and anhydrous aluminium trichloride (79 mg, 0.59 mmol, 1 mol%). DHP (5.42 mL, 59.41 mmol, 1 equiv.) was added slowly and the resulting mixture was warmed to 30 °C for 30 minutes, before being allowed to cool to room temperature. The colourless, crude material was loaded directly in a solution of 40% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30−60% EtOAc/petroleum ether to afford the title compound as a colourless liquid (9.86 g, 95%).

TLC (40% EtOAc/PE): R_f = 0.28 stained by $KMnO_4$.

υ_{max} (neat): 3389 (br.), 2937, 2867, 1442, 1353, 1203, 1121, 1022, 907, 870, 812 cm^{-1}.

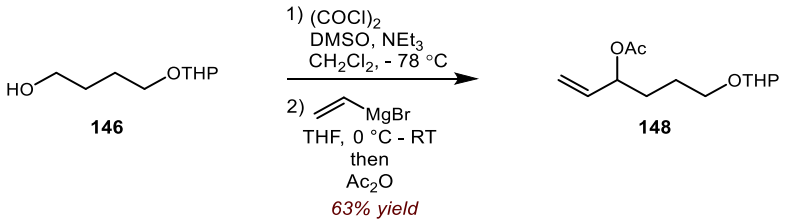
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 – 4.56 (m, 1H), 3.88 – 3.74 (m, 2H), 3.67 – 3.61 (m, 2H), 3.53 – 3.46 (m, 1H), 3.44 – 3.38 (m, 1H), 2.32 (br. s, 1H), 1.86 – 1.73 (m, 1H), 1.73 – 1.61 (m, 5H), 1.61 – 1.43 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 99.1, 98.9, 67.7, 67.5, 62.9, 62.9, 62.5, 62.4, 30.9, 30.8, 30.3, 30.00, 26.7, 25.6, 25.5, 19.7, 19.7. 1:1 mixture of rotamers.

HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_{19}O_4$) requires *m/z* 175.1329, found *m/z* 175.1328.

The spectral data were consistent with those previously reported in the literature.[124]

Compound 148.



Swern oxidation carried out according to General Procedure B using oxalyl chloride (7.91 mL, 93.48 mmol, 1.5 equiv.), DMSO (13.26 mL, 186.69 mmol, 3 equiv.), compound **146** (9.81 g, 56.27 mmol, 1 equiv.), triethylamine (39.6 mL, 284.12 mmol, 5 equiv.), and CH_2Cl_2 (140 mL). The crude material was subjected to purification outlined in General Procedure B (silica gel, 20% EtOAc/PE) to afford the corresponding aldehyde as a pale yellow liquid (7.78 g, 45.00 mmol) which was used immediately.

Vinylmagnesium bromide (1 M in THF, 45 mL, 45.00 mmol, 1 equiv.) was added dropwise to a stirring solution of the isolated material in anhydrous THF (100 mL) at 0 °C in a three-necked flask under an atmosphere of nitrogen. The resulting solution

was allowed to rise to room temperature and stirred for 1.5 h. The reaction was quenched by dropwise addition of acetic anhydride (8.5 mL, 90.09 mmol, 2 equiv.) at room temperature and stirred for a further 1.5 h. The yellow reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated to afford a pale orange oil. The crude material was loaded directly in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 20% EtOAc/petroleum ether to afford the title compound as a colourless liquid (8.65 g, 63%).

TLC (20% EtOAc/petroleum ether): R_f = 0.50 stained by $KMnO_4$ and faintly visible under UV (short wave).

υ_{max} (neat): 2941, 2870, 1736, 1371, 1233, 1200, 1121, 1076, 1020 cm^{-1}.

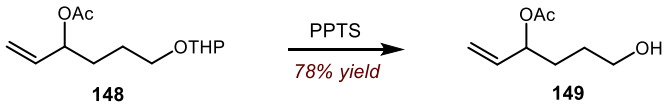
^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 5.31 – 5.14 (m, 3H), 4.57 (t, *J* = 3.5 Hz, 1H), 3.89 – 3.82 (m, 1H), 3.78 – 3.70 (m, 1H), 3.53 – 3.46 (m, 1H), 3.43 – 3.36 (m, 1H), 2.06 (s, 3H), 1.86 – 1.77 (m, 1H), 1.77 – 1.46 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 136.6, 116.9, 99.0, 74.7, 74.7, 67.2, 62.5, 31.1, 30.9, 25.6, 25.6, 25.5, 21.4, 19.8.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{13}H_{22}O_4Na$) requires *m/z* 265.1410, found *m/z* 265.1410.

The spectral data were consistent with those previously reported in the literature.[110]

Compound 149.



148 **149**

Experimental

To a round bottom flask was added compound **148** (11.51 g, 47.51 mmol, 1 equiv.) and EtOH (170 mL). PPTS (1.15 g, 4.58 mmol, 0.1 equiv.) was added portionwise and the resulting solution heated to 65 °C and maintained at this temperature for 3 h. The reaction was allowed to cool to room temperature and was then evaporated onto silica gel and purified by flash silica column chromatography, eluent 40% EtOAc/petroleum ether to afford the title compound as a colourless liquid (5.87 g, 78%).

TLC (40% EtOAc/petroleum ether): R_f = 0.40 stained by $KMnO_4$.

υ_{max} (neat): 3402 (br.), 2943, 2870, 1732, 1374, 1236, 1020, 968, 927 cm^{-1}.

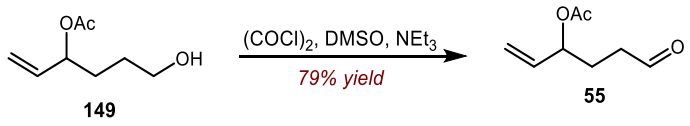
^1H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.29 – 5.14 (m, 3H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.06 (s, 3H), 1.73 – 1.67 (m, 2H), 1.63 – 1.55 (m, 2H). O*H* not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.6, 136.4, 117.0, 74.6, 62.5, 30.6, 28.3, 21.3.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_8H_{18}O_3N$) requires *m/z* 176.1281, found *m/z* 176.1281.

The spectral data were consistent with those previously reported in the literature.[110]

Compound 55.



Prepared according to General Procedure B using oxalyl chloride (3.32 mL, 39.23 mmol, 1.5 equiv.), DMSO (5.60 mL, 78.84 mmol, 3 equiv.), compound **149** (4.15 g, 26.24 mmol, 1 equiv.), triethylamine (22 mL, 157.84 mmol, 5 equiv.), and CH_2Cl_2 (100 mL). The crude material was subjected to purification outlined in General

Experimental

Procedure B (silica gel, 10-20% EtOAc/petroleum ether) to afford the corresponding aldehyde as a pale yellow liquid (3.26 g, 79%).

TLC (20% EtOAc/petroleum ether): R_f = 0.37 stained by $KMnO_4$.

υ_{max} (neat): 2931, 2830, 1722, 1372, 1231, 1021, 930 cm^{-1}.

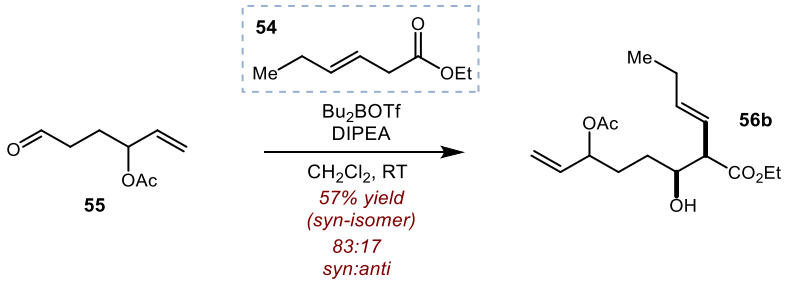
^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (t, *J* = 1.3 Hz, 1H), 5.80 – 5.70 (m, 1H), 5.30 – 5.18 (m, 3H), 2.53 – 2.47 (m, 2H), 2.06 (s, 3H), 2.01 – 1.94 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.2, 170.3, 135.7, 117.5, 73.7, 39.6, 26.5, 21.2.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_8H_{16}O_3N$) requires *m/z* 174.1125, found *m/z* 174.1125.

The spectral data were consistent with those previously reported in the literature.[68]

Compound 56b.



Prepared according to General Procedure C using ethyl (*E*)-hex-3-enoate (**54**) (2.72 mL, 17.12 mmol, 1.3 equiv.), DIPEA (3.44 mL, 19.75 mmol, 1.5 equiv.), dibutylboryltrifilate solution (1 M in CH_2Cl_2) (17.10 mL, 17.10 mmol, 1.3 equiv.), compound **55** (2.06 g, 13.16 mmol, 1 equiv.), CH_2Cl_2 (60 mL), potassium buffer solution (pH 7.4, 26 mL), MeOH (40 mL) and H_2O_2 (30 % solution, 13 mL). After 16 h the reaction was subjected to purification outlined in General Procedure C (silica gel,

20% EtOAc/petroleum ether) to afford the title compound as a colourless liquid (2.81 g, 57% (^{1}H NMR yield)). (83:17 *syn:anti* by ^{1}H NMR).

Product contains 21% alkene isomerisation impurity. Data reported of products resulting from reaction carried out at – 78 °C to where isomerisation does not take place.[68]

TLC (20% EtOAc/petroleum ether): R_f = 0.31 stained by $KMnO_4$.

υ_{max} (neat): 3496 (br.), 2963, 2934, 2874, 1733, 1374, 1240, 1178, 1024, 975 cm^{-1}.

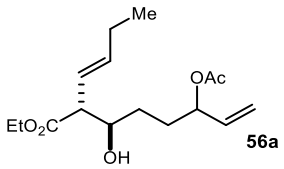
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 – 5.66 (m, 2H), 5.51 (ddt, *J* = 15.4, 9.2, 1.5 Hz, 1H), 5.29 – 5.14 (m, 3H), 4.20 – 4.12 (m, 2H), 3.88 – 3.81 (m, 1H), 2.96 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.67 (br. s, 1H), 2.13 – 2.02 (m, 5H), 1.89 – 1.78 (m, 1H), 1.72 – 1.60 (m, 1H), 1.55 – 1.35 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.00 (td, *J* = 7.4, 0.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 173.9, 170.5, 139.0, 136.5, 136.4, 122.1, 117.0, 116.9, 74.9, 74.5, 71.3, 71.1, 61.0, 55.0, 54.9, 30.4, 30.3, 29.7, 29.5, 25.8, 21.3, 21.3, 14.3, 13.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{27}O_5$) requires *m/z* 299.1853, found *m/z* 299.1856. Calculated for a mixture of the *syn*- and *anti*-diastereoisomers.

The spectral data were consistent with those previously reported in the literature.[68]

Compound **56a**.



TLC (20% EtOAc/petroleum ether): R_f = 0.22 stained by $KMnO_4$.

υ_{max} (neat): 3478 (br.), 2963, 2934, 1732, 1371, 1236, 1020, 970, 930 cm^{-1}.

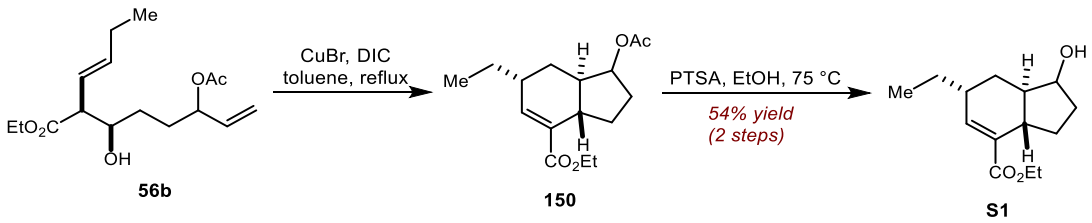
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 – 5.64 (m, 2H), 5.44 – 5.35 (m, 1H), 5.29 – 5.14 (m, 3H), 4.21 – 4.13 (m, 2H), 3.83 – 3.76 (m, 1H), 3.04 – 2.97 (m, 1H), 2.55 (br. s, 1H), 2.10 – 2.01 (m, 5H), 1.91 – 1.80 (m, 1H), 1.74 – 1.52 (m, 2H), 1.43 – 1.30 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.98 (td, *J* = 7.4, 0.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 170.5, 170.4, 137.7, 136.5, 136.4, 123.4, 117.0, 116.8, 74.9, 74.5, 72.4, 72.2, 60.9, 56.0, 55.9, 30.3, 30.2, 30.1, 29.9, 25.7, 21.3, 21.3, 14.3, 13.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{27}O_5$) requires *m/z* 299.1853, found *m/z* 299.1856. Calculated for a mixture of the *syn*- and *anti*-diastereoisomers.

The spectral data were consistent with those previously reported in the literature.[68]

Compound S1.



Compound **150** was prepared according to General Procedure D using compound **56b** (2.00 g, 6.71 mmol, 1 equiv. (79% purity)), CuBr (96 mg, 0.67 mmol, 10 mol%), DIC (1.56 mL, 10.07 mmol, 1.5 equiv.) and toluene (1.3 mL). After 16 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 10% EtOAc/petroleum ether) to afford a pale yellow oil (**150**) (1.49 g, 5.32 mmol).
Compound **S1** was prepared according to General Procedure D using compound **150** (1.49 g, 5.32 mmol, 1 equiv.), PTSA (mono-hydrate) (1.52 g, 7.99 mmol, 1.5 equiv.), and EtOH (50 mL). After 5 h the reaction was subjected to purification outlined in

Experimental

General Procedure D (silica gel, 20% EtOAc/petroleum ether) to afford the title compound as a colourless liquid (677 mg, 54% (2 steps, based on 79% purity of starting material)).

TLC (20% EtOAc/petroleum ether): R_f = 0.16 stained by $KMnO_4$.

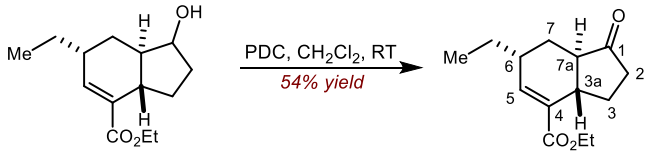
υ_{max} (neat): 3434 (br.), 2958, 2928, 2870, 1708, 1693, 1266, 1230, 1098, 1024 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.85 – 6.79 (m, 1H), 4.28 – 4.07 (m, 2.5H), 3.92 – 3.84 (m, 0.5H), 2.56 – 1.98 (m, 4.5H), 1.92 (d, *J* = 10.0 Hz, 0.5H), 1.74 – 1.32 (m, 6H), 1.32 – 1.25 (m, 3H), 1.23 – 1.12 (m, 1H), 1.02 – 0.95 (m, 3H). Mixture of isomers.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 167.4, 144.0, 143.6, 143.0, 134.2, 133.4, 79.4, 76.1, 73.5, 60.4, 60.3, 48.0, 47.6, 46.0, 42.5, 40.8, 39.4, 38.8, 38.6, 38.2, 36.7, 35.1, 33.5, 33.3, 30.4, 29.3, 28.7, 28.5, 28.4, 28.3, 27.3, 26.0, 24.0, 14.5, 12.7, 11.4. Mixture of isomers, peaks reported as observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}O_3$) requires *m/z* 239.1642, found *m/z* 239.1641.

Compound 43.



S1 **43**

Compound **43** was prepared according to General Procedure E using compound **S1** (1.79 g, 7.51 mmol, 1 equiv.), PDC (4.24 g, 11.26 mmol, 1.5 equiv.) and CH_2Cl_2 (40 mL). After 16 h the reaction was subjected to purification outlined in General Procedure E (silica gel, 10-30% EtOAc/petroleum ether) to afford the title compound as a colourless oil (957 mg, 54% (3:1 dr C^{7a})).

TLC (30% EtOAc/petroleum ether): R_f = 0.72 stained by $KMnO_4$.

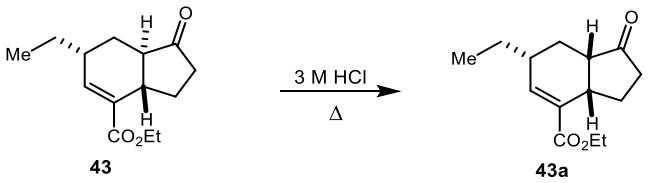
υ_{max} (neat): 2960, 2928, 2872, 1742, 1705, 1258, 1232, 1216, 1095 cm^{-1}.

Major *anti*-isomer:
^1H NMR (400 MHz, $CDCl_3$): δ 6.92 – 6.87 (m, 1H), 4.30 – 4.14 (m, 2H), 2.75 – 2.66 (m, 1H), 2.51 – 2.33 (m, 3H), 2.29 – 2.17 (m, 1H), 2.05 – 1.86 (m, 2H), 1.64 – 1.44 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H).

Major *anti*-isomer:
^{13}C NMR (101 MHz, $CDCl_3$): δ 216.9, 166.7, 145.4, 133.0, 60.5, 51.1, 41.1, 38.5, 38.4, 28.3, 26.2, 24.8, 14.5, 12.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}O_3$) requires *m/z* 237.1485, found *m/z* 237.1487.

Compound 43a.



43 **43a**

To a round bottom flask was added compound **43** (245 mg, 1.04 mmol) and 3 M HCl (36 mL) and the resulting suspension brought to 60 °C for 16 h. The reaction was allowed to cool to room temperature and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded directly in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 10% EtOAc/petroleum ether to afford the title compound as a colourless oil (186 mg, 76%).

TLC (30% EtOAc/petroleum ether): R_f = 0.72 stained by $KMnO_4$.

υ_{max} (film): 2961, 2932, 2876, 2859, 1742, 1706, 1244, 1097, 920, 753 cm^{-1}.

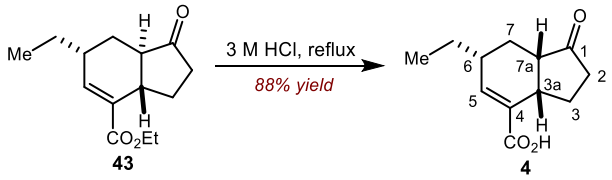
^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 1H), 4.29 – 4.14 (m, 2H), 3.11 – 3.02 (m, 1H), 2.59 – 2.51 (m, 1H), 2.43 – 2.22 (m, 3H), 2.22 – 2.12 (m, 1H), 1.84 (dt, *J* = 12.9, 4.8 Hz, 1H), 1.62 – 1.45 (m, 2H), 1.43 – 1.36 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.01 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 144.0, 131.7, 60.6, 46.8, 38.3, 37.8, 36.4, 28.3, 28.0, 26.0, 14.4, 11.3. Carbonyl *C*O not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}O_3$) requires *m/z* 237.1485, found *m/z* 237.1487.

The spectral data were consistent with those previously reported in the literature.[68]

(±)-coronafacic acid, 4.



Prepared according to General Procedure F using compound **43** (1.10 g, 4.65 mmol) and 3 M HCl (150 mL). After 16 h the reaction was subjected to purification outlined in General Procedure F (silica gel, 30-60% EtOAc/petroleum ether) to afford a white solid, which was washed with minimal petroleum ether to afford the title compound as a white solid (850 mg, 88%).

TLC (30% EtOAc/petroleum ether): R_f = 0.21 stained by $KMnO_4$.

υ_{max} (neat): 2954 (br.), 2930 (br.), 2855, 2629, 2525, 1732, 1673, 1625, 1428, 1270, 1139, 1069, 926, 727 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H, H^5), 3.13 – 3.04 (m, 1H, H^{3a}), 2.66 – 2.56 (m, 1H, H^3), 2.47 – 2.28 (m, 3H, H^{7a}, H^2), 2.28 – 2.19 (m, 1H, H^6), 1.89 (dt, *J* = 12.9, 4.8 Hz, 1H, H^7), 1.67 – 1.39 (m, 3H, $H^{3'}$, CH_3CH_2), 1.14 – 1.04 (m, 1H, $H^{7'}$), 0.99 (t, *J* = 7.4 Hz, 3H, CH_2CH_3).

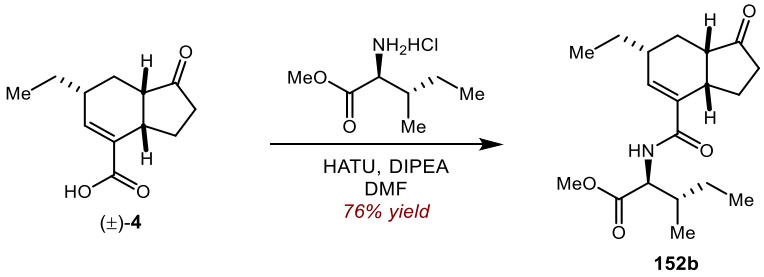
^{13}C NMR (101 MHz, $CDCl_3$) δ 220.3 (C^1), 171.3 (CO_2H), 147.0 (C^5), 130.9 (C^4), 46.7 (C^{7a}), 38.3 ($C^{2/6}$), 38.0 ($C^{2/6}$), 36.2 (C^{3a}), 28.2 (CH_3CH_2), 27.9 (C^3), 25.9 (C^7), 11.3 (CH_2CH_3).

HRMS: exact mass calculated for $[M-H]^-$ ($C_{12}H_{15}O_3$) requires *m/z* 207.1027, found *m/z* 207.1030.

The spectral data were consistent with those previously reported in the literature.[68]

6.5 *N*-coronafacoyl Analogue Procedures and Characterisation (Scheme 42/43).

Compound 152b.



Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), methyl *L*-isoleucinate hydrochloride (30 mg, 0.21 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.), and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General

Experimental

Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil which solidified to a white solid on standing (35 mg, 76%).

TLC (30% EtOAc/petroleum ether): R_f = 0.19 stained by $KMnO_4$.

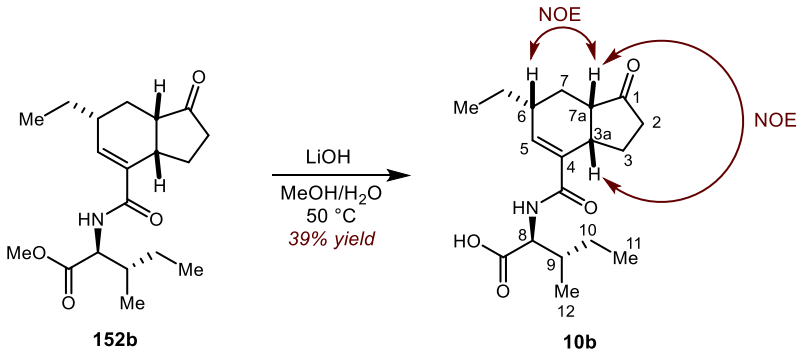
υ_{max} (film): 3323 (br.), 2963, 2938, 2877, 1735, 1658, 1621, 1518, 1203, 1147 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.42 – 6.34 (m, 1H), 6.31 – 6.23 (m, 1H), 4.73 – 4.65 (m, 1H), 3.76 (s, 3H), 3.23 – 3.09 (m, 1H), 2.54 – 2.23 (m, 4H), 2.21 – 2.11 (m, 1H), 1.98 – 1.86 (m, 2H), 1.68 – 1.35 (m, 4H), 1.28 – 1.16 (m, 1H), 1.13 – 1.01 (m, 1H), 1.01 – 0.91 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 220.3, 173.0, 167.9, 167.8, 137.1, 135.8, 135.6, 56.5, 56.5, 52.3, 46.6, 46.6, 38.3, 38.3, 38.2, 37.5, 37.4, 36.4, 36.4, 28.3, 28.2, 28.0, 28.0, 26.2, 26.2, 25.5, 25.4, 15.7, 15.6, 11.7, 11.7, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}NO_4$) requires *m/z* 336.2169, found *m/z* 336.2173.

Compound 10b.



Prepared according to General Procedure H using compound **152b** (24 mg, 0.07 mmol, 1 equiv.), LiOH (5 mg, 0.20 mmol, 3 equiv.), and 1:1 MeOH:H_2O (3 mL). After 16 h at 50 °C the reaction mixture was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (9 mg, 39%).

υ_{max} (film): 2967, 2926, 2862, 1728, 1655, 1610, 1516, 1457, 1142 cm^{-1}.

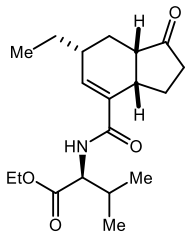
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 – 6.38 (m, 1H, H^5), 6.29 – 6.25 (m, 1H, N*H*), 4.73 – 4.66 (m, 1H, H^8), 3.22 – 3.10 (m, 1H, H^{3a}), 2.53 – 2.25 (m, 4H, H^3, H^{7a}, H^2), 2.21 – 2.12 (m, 1H, H^6), 2.07 – 1.97 (m, 1H, H^9), 1.94 – 1.86 (m, 1H, H^7), 1.67 – 1.48 (m, 3H, $H^{3'}$, H^{10}, CH_3CH_2), 1.44 – 1.35 (m, 1H, CH_3CH_2'), 1.31 – 1.19 (m, 1H, $H^{10'}$), 1.13 – 1.02 (m, 1H, $H^{7'}$), 1.02 – 0.92 (m, 9H, H^{12}, H^{11}, CH_3CH_2). CO_2H not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 175.5, 168.5, 168.4, 137.8, 137.7, 135.5, 135.4, 56.8, 56.6, 46.6, 46.6, 38.3, 37.9, 37.8, 37.5, 37.4, 36.4, 36.4, 28.2, 28.2, 28.0, 27.9, 26.1, 26.1, 25.4, 25.3, 15.8, 15.7, 11.7, 11.7, 11.5, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1867, found *m/z* 320.1865.

The spectral data were consistent with those previously reported in the literature.[84]

Compound 152e.



152e

Prepared according to General Procedure G using (±)-CFA (**4**) (27 mg, 0.13 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), *L*-valine ethyl ester hydrochloride (39 mg, 0.21 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.), and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/petroleum ether) to afford the title compound as a colourless oil (35 mg, 85%).

Experimental

TLC (30% EtOAc/petroleum ether): R_f = 0.26 stained by $KMnO_4$.

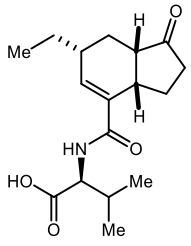
υ_{max} (film): 3341 (br.), 2962, 2930, 2875, 1735, 1659, 1624, 1513, 1192, 1148, 1025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.43 – 6.35 (m, 1H), 6.30 – 6.22 (m, 1H), 4.66 – 4.59 (m, 1H), 4.28 – 4.15 (m, 2H), 3.22 – 3.11 (m, 1H), 2.53 – 2.11 (m, 6H), 1.92 – 1.85 (m, 1H), 1.66 – 1.57 (m, 1H), 1.57 – 1.46 (m, 1H), 1.42 – 1.35 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.01 (m, 1H), 1.00 – 0.91 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.5, 168.1, 168.0, 137.0, 137.0, 135.9, 135.8, 61.5, 57.2, 57.1, 46.7, 46.6, 38.3, 37.5, 37.4, 36.4, 31.7, 31.7, 28.3, 28.3, 28.0, 28.0, 26.2, 26.2, 19.2, 19.2, 18.1, 18.0, 14.4, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}NO_4$) requires *m/z* 336.2169, found *m/z* 336.2171.

Compound 10c.



10c

Prepared according to General Procedure H using compound **152e** (23 mg, 0.07 mmol, 1 equiv.), NaOH (8 mg, 0.20 mmol, 3 equiv.), and 1:1 MeOH:H_2O (1 mL). After 16 h a further portion of NaOH (4 mg, 0.10 mmol, 1.5 equiv.) was added and the reaction stirred at 50 °C for a further 1.5 h. The reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (16 mg, 76%).

υ_{max} (film): 3323 (br.), 2961, 2924, 2874, 1730, 1651, 1607, 1518, 1204, 1146 cm^{-1}.

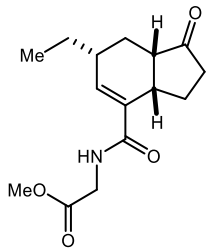
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44 – 6.39 (m, 1H), 6.29 – 6.23 (m, 1H), 4.69 – 4.62 (m, 1H), 3.22 – 3.11 (m, 1H), 2.53 – 2.36 (m, 3H), 2.36 – 2.25 (m, 2H), 2.21 – 2.13 (m, 1H), 1.93 – 1.86 (m, 1H), 1.67 –1.58 (m, 1H), 1.58 – 1.49 (m, 1H), 1.45 – 1.35 (m, 1H), 1.12 – 1.04 (m, 1H), 1.04 – 0.96 (m, 9H). CO_2H not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.6, 168.6, 168.5, 137.7, 137.6, 135.6, 135.5, 57.4, 57.3, 46.6, 46.6, 38.3, 37.5, 37.4, 36.4, 31.3, 31.2, 28.3, 28.2, 28.0, 27.9, 26.2, 26.1, 19.3, 19.2, 18.0, 18.0, 11.5, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{17}H_{24}NO_4$) requires *m/z* 306.1711, found *m/z* 306.1709.

The spectral data were consistent with those previously reported in the literature.[41]

Compound S10e.



S10e

Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.12 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), glycine methyl ester hydrochloride (36 mg, 0.21 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.) and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 70% EtOAc/petroleum ether) to afford the title compound as a colourless oil (18 mg, 45%).

TLC (50% EtOAc/petroleum ether): R_f = 0.15 stained by $KMnO_4$.

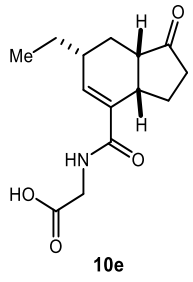
υ_{max} (film): 3344 (br.), 2956, 2937, 2875, 2858, 1735, 1655, 1624, 1204, 1181, 1151 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (s, 1H), 6.30 (br. s, 1H), 4.12 (d, *J* = 5.2 Hz, 2H), 3.78 (s, 3H), 3.21 – 3.13 (m, 1H), 2.51 – 2.43 (m, 1H), 2.43 – 2.23 (m, 3H), 2.21 – 2.12 (m, 1H), 1.91 – 1.85 (m, 1H), 1.65 – 1.55 (m, 1H), 1.54 – 1.46 (m, 1H), 1.43 – 1.35 (m, 1H), 1.11 – 1.02 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.5, 170.8, 168.2, 137.4, 135.4, 52.6, 46.5, 41.5, 38.3, 37.4, 36.3, 28.2, 28.0, 26.1, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}NO_4$) requires *m/z* 280.1543, found *m/z* 280.1543.

Compound 10e.



10e

Prepared according to General Procedure H using compound **S10e** (20 mg, 0.05 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.), and 1:1 MeOH:H_2O (4 mL). After 16 h the reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 1% AcOH, 30-70% EtOAc/CH_2Cl_2 to afford a colourless oil. The solid material was washed with petroleum ether to afford the title compound as a colourless oil (13 mg, 68%).

Experimental

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.09 stained by $KMnO_4$.

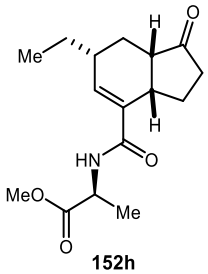
υ_{max} (film): 3351 (br.), 2962, 2925, 2856, 1735, 1654, 1613, 1523, 1214 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.51 (s, 1H), 3.88 (br. s, 2H), 3.13 – 3.04 (br. s, 1H), 2.47 – 2.18 (m, 4H), 2.12 (br. s, 1H), 1.87 – 1.79 (m, 1H), 1.61 – 1.43 (m, 2H), 1.38 – 1.30 (m, 1H), 1.09 – 0.99 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H). CO_2H and N*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.0, 169.1, 156.2, 138.7, 134.6, 46.8, 43.0, 38.1, 37.5, 36.1, 28.2, 28.2, 25.9, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_4$) requires *m/z* 266.1392, found *m/z* 266.1396.

Compound 152h.



152h

Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), *L*-alanine methyl ester hydrochloride (30 mg, 0.21 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.), and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 20-35% EtOAc/petroleum ether) to afford the desired product as a colourless oil (35 mg, 83%).

TLC (40% EtOAc/petroleum ether): R_f = 0.17 stained by $KMnO_4$.

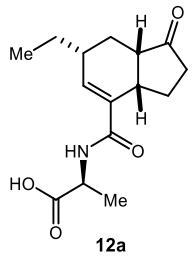
υ_{max} (film): 3312 (br.), 2934, 2958, 2878, 2857, 1738, 1658, 1621, 1521, 1455, 1210, 1158, 1072 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 – 6.30 (m, 2H), 4.71 – 4.62 (m, 1H), 3.77 (s, 3H), 3.21 – 3.11 (m, 1H), 2.53 – 2.24 (m, 4H), 2.19 – 2.12 (m, 1H), 1.92 – 1.84 (m, 1H), 1.64 – 1.55 (m, 1H), 1.55 – 1.47 (m, 1H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.42 – 1.35 (m, 1H), 1.11 – 1.01 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 167.8, 167.5, 137.4, 136.9, 135.7, 135.3, 52.7, 48.2, 48.2, 46.6, 46.5, 38.2, 37.4, 36.3, 36.3, 28.2, 28.2, 28.0, 27.9, 26.2, 26.1, 18.6, 18.6, 11.4, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO_4$) requires *m/z* 294.1700, found *m/z* 294.1703.

Compound 12a.



12a

Prepared according to General Procedure H using compound **152h** (18 mg, 0.06 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.), and 1:1 MeOH:H_2O (2 mL). After 6 h the reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and was purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil which solidified to a white solid on standing (16 mg, 94%).

Experimental

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.14 stained by $KMnO_4$.

υ_{max} (film): 3323 (br.), 2954, 2924, 2855, 1735, 1654, 1617, 1526, 1453, 1147 cm^{-1}.

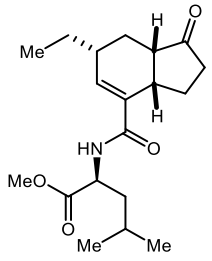
^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (br. s, 1H), 6.55 (s, 1H), 6.45 – 6.39 (m, 1H), 4.60 – 4.49 (m, 1H), 3.19 – 3.07 (m, 1H), 2.51 – 2.23 (m, 4H), 2.19 – 2.10 (m, 1H), 1.91 – 1.83 (m, 1H), 1.63 – 1.42 (m, 5H), 1.41 – 1.33 (m, 1H), 1.11 – 1.01 (m, 1H), 1.00 – 0.94 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3, 168.6, 168.4, 138.1, 138.0, 135.1, 135.0, 49.2, 49.1, 46.6, 46.6, 38.2, 37.5, 37.5, 36.2, 36.2, 28.2, 28.0, 27.9, 26.1, 26.0, 18.1, 18.0, 11.5, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{15}H_{20}NO_4$) requires *m/z* 278.1398, found *m/z* 278.1400.

The spectral data were consistent with those previously reported in the literature.[41]

Compound S12b.



S12b

Prepared according to General Procedure G using (±)-CFA (**4**) (50 mg, 0.24 mmol, 1 equiv.), HATU (110 mg, 0.30 mmol, 1.2 equiv.), DIPEA (0.13 mL, 0.72 mmol, 3 equiv.), *L*-leucine methyl ester hydrochloride (48 mg, 0.26 mmol, 1.1 equiv.), and DMF (1.2 mL). After 16 h the reaction was subjected to purification outlined in

Experimental

General Procedure G (silica gel, 30% EtOAC/petroleum ether) to afford the title compound colourless oil (74 mg, 91%).

TLC (30% EtOAc/petroleum ether): R_f = 0.31 stained by $KMnO_4$ and visible under UV (short wave).

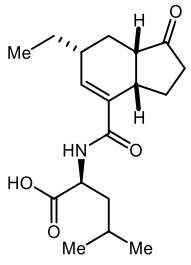
υ_{max} (film): 3315 (br.), 2958, 2874, 1744, 1657, 1627, 1524, 1206, 1156 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.39 – 6.31 (m, 1H), 6.22 – 6.16 (m, 1H), 4.74 – 4.64 (m, 1H), 3.72 (s, 3H), 3.19 – 3.09 (m, 1H), 2.50 – 2.20 (m, 4H), 2.16 – 2.08 (m, 1H), 1.88 – 1.82 (m, 1H), 1.71 – 1.61 (m, 2H), 1.61 – 1.53 (m, 2H), 1.53 – 1.44 (m, 1H), 1.41 – 1.32 (m, 1H), 1.08 – 0.99 (m, 1H), 0.98 – 0.90 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 168.0, 167.8, 137.1, 137.0, 135.7, 135.5, 52.4, 50.9, 50.8, 46.5, 46.5, 41.8, 38.2, 37.4, 37.3, 36.3, 36.3, 28.2, 28.2, 27.9, 27.9, 26.1, 26.1, 25.1, 25.1, 22.9, 22.9, 22.1, 11.4, 11.4.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{29}NO_4Na$) requires *m/z* 358.1989, found *m/z* 358.1989.

Compound 12b.



12b

To a round bottom flask was added compound **S12b (**63 mg, 0.19 mmol). The material was suspended in 3 M HCl (1.5 mL) and the resulting suspension brought to 80 °C for 3 h. The reaction was then allowed to cool to room temperature and diluted with EtOAc

(5 mL). The layers were separated and the aqueous phase washed twice more with EtOAc (2 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered and evaporated to afford a white gum. The crude material was loaded in a solution of EtOAc and purified by flash silica column chromatography, eluent 1% AcOH/EtOAc to afford the title compound as a colourless oil (32 mg, 53%).

TLC (1% AcOH/EtOAc): R_f = 0.48 stained by $KMnO_4$.

υ_{max} (film): 3319 (br.), 2958, 2926, 2874, 1733, 1653, 1615, 1526, 1195, 1150 cm^{-1}.

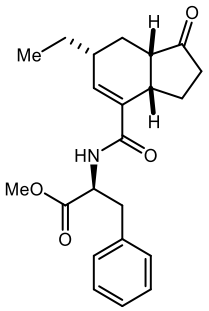
^1H NMR (500 MHz, $CDCl_3$): δ 9.22 (br. s, 1H), 6.42 – 6.35 (m, 1H), 6.30 – 6.22 (m, 1H), 4.74 – 4.64 (m, 1H), 3.21 – 3.11 (m, 1H), 2.51 – 2.24 (m, 4H), 2.19 – 2.11 (m, 1H), 1.91 – 1.84 (m, 1H), 1.80 – 1.68 (m, 2H), 1.68 – 1.55 (m, 2H), 1.55 – 1.47 (m, 1H), 1.43 – 1.34 (m, 1H), 1.11 – 1.01 (m, 1H), 1.01 – 0.94 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 176.8, 168.7, 168.5, 137.8, 137.7, 135.4, 135.3, 51.2, 51.1, 46.6, 46.5, 41.4, 41.3, 38.2, 37.5, 37.4, 36.3, 28.2, 28.2, 27.9, 27.8, 26.1, 26.1, 25.2, 25.2, 23.0, 23.0, 22.1, 22.0, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}NO_4$) requires *m/z* 322.2013, found *m/z* 322.2016.

The spectral data were consistent with those previously reported in the literature.[41]

Compound 152f.



152f

Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), *L*-phenylalanine methyl ester hydrochloride (47 mg, 0.22 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.) and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 40% EtOAc/petroleum ether to afford the title compound as a white gum (42 mg, 79%).

TLC (60% EtOAc/petroleum ether): R_f = 0.48 stained by $KMnO_4$.

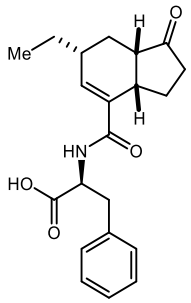
υ_{max} (film): 3317 (br.), 2960, 2932, 2876, 2859, 1740, 1658, 1625, 1526, 1215, 705 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 3H), 7.14 – 7.08 (m, 2H), 6.33 – 6.23 (m, 1H), 6.19 – 6.11 (m, 1H), 4.98 – 4.92 (m, 1H), 3.79 – 3.75 (m, 3H), 3.26 – 3.02 (m, 3H), 2.44 – 2.20 (m, 4H), 2.16 – 2.07 (m, 1H), 1.90 – 1.83 (m, 1H), 1.64 – 1.31 (m, 3H), 1.10 – 0.98 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 167.6, 167.5, 137.3, 137.2, 136.0, 135.6, 135.3, 129.4, 129.4, 128.7, 128.7, 127.4, 127.3, 53.2, 52.5, 52.5, 46.6, 46.5, 38.2, 37.9, 37.8, 37.4, 37.3, 36.3, 36.2, 28.1, 28.0, 27.7, 26.2, 26.1, 11.4, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{28}NO_4$) requires *m/z* 370.2013, found *m/z* 370.2013.

Compound 12c.



Prepared according to General Procedure H using compound **152f** (36 mg, 0.10 mmol, 1 equiv.), LiOH (8 mg, 0.33 mmol, 3 equiv.), and 1:1 MeOH:H_2O (5 mL) and the resulting suspension brought to 40 °C for 16 h. The reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and was purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil which solidified to a white solid on standing (11 mg, 32%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.15 stained by $KMnO_4$.

υ_{max} (film): 3312 (br.), 2957, 2924, 2855, 1726, 1719, 1653, 1611, 1522, 1211 cm^{-1}.

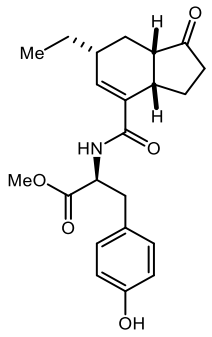
^1H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 3H), 7.22 – 7.14 (m, 2H), 6.34 – 6.20 (m, 2H), 5.31 – 4.45 (m, 2H), 3.36 – 3.24 (m, 1H), 3.22 – 3.09 (m, 1H), 3.09 – 2.95 (m, 1H), 2.39 – 2.02 (m, 5H), 1.88 – 1.77 (m, 1H), 1.55 – 1.20 (m, 3H), 1.07 – 0.95 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3, 220.2, 170.7, 168.4, 138.5, 138.0, 136.2, 135.0, 135.0, 129.5, 128.9, 128.8, 127.5, 127.4, 46.6, 46.5, 38.2, 37.5, 37.3, 36.3, 36.1, 28.1, 28.0, 27.6, 26.1, 26.0, 11.4, 11.3.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{21}H_{24}NO_4$) requires *m/z* 354.1711, found *m/z* 354.1706.

The spectral data were consistent with those previously reported in the literature.[41]

Compound 152c.



152c

Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), *L*-tyrosine methyl ester (42 mg, 0.22 mmol, 1.5 equiv.), DIPEA (50 µL, 0.29 mmol, 2 equiv.), and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 60-70% EtOAc/petroleum ether) to afford the title compound as a pale yellow gum (47 mg, 85%).

TLC (70% EtOAc/petroleum ether): R_f = 0.43 stained by $KMnO_4$.

υ_{max} (film): 3312 (br.), 2959, 2923, 2857, 1732, 1654, 1614, 1515, 1213 cm^{-1}.

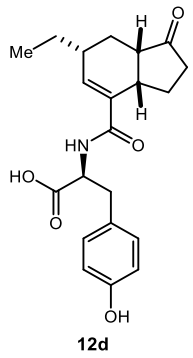
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 – 6.91 (m, 2H), 6.76 – 6.71 (m, 2H), 6.46 (br. s, 1H), 6.38 – 6.27 (m, 1H), 6.27 – 6.20 (m, 1H), 4.93 – 4.87 (m, 1H), 3.78 – 3.74 (m,

3H), 3.17 – 3.02 (m, 3H), 2.41 – 2.19 (m, 4H), 2.16 – 2.07 (m, 1H), 1.88 – 1.82 (m, 1H), 1.59 – 1.40 (m, 2H), 1.40 – 1.32 (m, 1H), 1.09 – 0.98 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.6, 168.0, 167.8, 155.6, 155.6, 137.9, 137.7, 135.4, 135.1, 130.5, 127.3, 115.7, 115.7, 53.5, 52.7, 52.6, 46.7, 46.5, 38.2, 37.4, 37.4, 37.2, 37.2, 36.3, 36.2, 28.1, 28.0, 27.7, 26.2, 26.0, 11.4, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{28}NO_5$) requires *m/z* 386.1962, found *m/z* 386.1961.

Compound 12d.



12d

Prepared according to General Procedure H using compound **152c** (30 mg, 0.07 mmol, 1 equiv.), LiOH (10 mg, 0.42 mmol, 3 equiv.), and 1:1 MeOH:H_2O (5 mL). After 16 h the reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 1% AcOH, 30-50% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil which solidified to a white solid on standing (15 mg, 52%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.13 stained by $KMnO_4$.

υ_{max} (film): 3289 (br.), 2961, 2924, 2855, 1719, 1653, 1611, 1514 cm^{-1}.

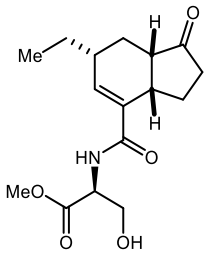
^{1}H NMR (500 MHz, MeOD): δ 7.10 – 6.99 (m, 2H), 6.72 – 6.64 (m, 2H), 6.41 – 6.28 (m, 1H), 4.74 – 4.57 (m, 1H), 3.24 – 3.14 (m, 1H), 3.13 – 3.02 (m, 1H), 3.02 – 2.92 (m, 1H), 2.38 – 2.07 (m, 5H), 1.80 – 1.72 (m, 1H), 1.54 – 1.35 (m, 3H), 1.15 – 1.04 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H). CO_2H, O*H*, and N*H* not observed.

^{13}C NMR (101 MHz, MeOD): δ 222.9, 222.9, 157.3, 157.2, 138.3, 137.9, 136.6, 131.4, 129.6, 116.1, 116.1, 47.8, 38.7, 38.6, 38.5, 37.7, 37.6, 37.3, 37.3, 29.1, 28.7, 28.5, 27.2, 27.0, 11.6, 11.6.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{21}H_{24}NO_5$) requires *m/z* 370.1660, found *m/z* 370.1655.

The spectral data were consistent with those previously reported in the literature.[41]

Compound S151a.



S151a

To a 2-dram vial was added (±)-CFA (**4**) (30 mg, 0.13 mmol, 1 equiv.) and COMU (123 mg, 0.17 mmol, 1.2 equiv.). DMF (0.7 mL) was added, followed by DIPEA (80 µL, 0.46 mmol, 3 equiv.) and the resulting solution stirred at room temperature under air for 5 minutes. *L*-serine methyl ester hydrochloride (34 mg, 0.21 mmol, 1.5 equiv.) was then added portionwise and the reaction stirred for 16 h. The yellow solution was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to

afford a red oil. The crude material was loaded in a solution of EtOAc and purified by flash silica column chromatography, eluent 1% MeOH/EtOAc to afford a red oil. The material was taken up in Et_2O, and petroleum ether added until a solid precipitated. The solvent was removed by Pasteur pipette and the solid dried under vacuum to afford the title compound as a pale red solid (22 mg, 49%).

TLC (1% MeOH/EtOAc): R_f = 0.45 stained by $KMnO_4$ and faintly visible by UV (short wave).

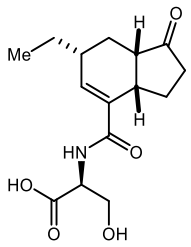
υ_{max} (film): 3387 (br.), 2955, 1736, 1655, 1618, 1522, 1209 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.77 – 6.69 (m, 1H), 6.52 – 6.42 (m, 1H), 4.78 – 4.71 (m, 1H), 4.06 – 3.94 (m, 2H), 3.81 (s, 3H), 3.21 – 3.12 (m, 1H), 2.78 – 2.54 (m, 1H), 2.54 – 2.24 (m, 4H), 2.21 – 2.12 (m, 1H), 1.92 – 1.85 (m, 1H), 1.66 – 1.57 (m, 1H), 1.56 – 1.47 (m, 1H), 1.44 – 1.34 (m, 1H), 1.11 – 1.02 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3, 220.2, 171.3, 168.5, 168.3, 138.4, 137.8, 135.3, 134.9, 63.8, 63.6, 55.0, 55.0, 53.0, 46.7, 46.6, 38.2, 37.5, 36.3, 28.2, 28.0, 26.1, 26.1, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO_5$) requires *m/z* 310.1649, found *m/z* 310.1651.

Compound 151a.



151a

Experimental

Prepared according to General Procedure H using compound **S151a** (26 mg, 0.08 mmol, 1 equiv.), LiOH (4 mg, 0.17 mmol, 2 equiv.), and 1:1 MeOH:H_2O (2 mL). After 16 h at 50 °C the reaction mixture was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (4 mg, 18%).

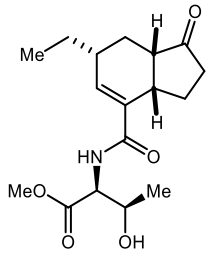
υ_{max} (film): 3356 (br.), 2953, 2924, 2855, 1734, 1709, 1228, 1057 cm^{-1}.

^1H NMR (500 MHz, MeOD): δ 6.61 – 6.54 (m, 1H), 4.60 – 4.52 (m, 1H), 4.00 – 3.94 (m, 1H), 3.92 – 3.86 (m, 1H), 3.25 – 3.17 (m, 1H), 2.49 – 2.30 (m, 4H), 2.24 – 2.15 (m, 1H), 1.85 – 1.78 (m, 1H), 1.69 – 1.59 (m, 1H), 1.59 – 1.50 (m, 1H), 1.48 – 1.40 (m, 1H), 1.20 – 1.10 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H). CO_2H, O*H*, and N*H* not observed.

^{13}C NMR (101 MHz, MeOD): δ 222.9, 222.8, 170.9, 170.5, 139.0, 138.6, 136.5, 136.2, 63.0, 63.0, 47.9, 47.9, 38.8, 38.7, 37.4, 37.3, 29.1, 28.8, 28.8, 27.1, 11.6, 11.6.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{15}H_{20}NO_5$) requires *m/z* 294.1347, found *m/z* 294.1343.

Compound S151b.



S151b

To a round bottom flask was added (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.) and COMU (80 mg, 0.19 mmol, 1.2 equiv.). DMF (0.7 mL) was added, followed by DIPEA (80 µL, 0.46 mmol, 3 equiv.) and the resulting solution stirred at room temperature under air for 5 minutes. *L*-threonine methyl ester hydrochloride (37 mg,

0.22 mmol, 1.5 equiv.) was then added and the reaction stirred for 16 h. The red solution was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a red oil. The crude material was loaded in a solution of 40% EtOAc/CH_2Cl_2 and purified by flash silica column chromatography, eluent 40-50% EtOAc/CH_2Cl_2 to afford a pale yellow oil which was taken up in Et_2O and petroleum ether added until a precipitate formed. The solvent was removed by Pasteur pipette and the residue dried under vacuum to afford the title compound as a white solid (21 mg, 64%).

TLC (40% EtOAc/CH_2Cl_2): R_f = 0.17 stained by $KMnO_4$.

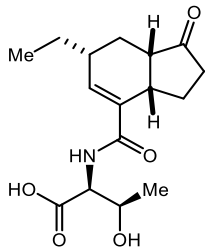
υ_{max} (film): 3376 (br.), 2956, 2930, 2872, 2855, 1736, 1654, 1619, 1513, 1210, 1151 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56 – 6.51 (m, 1H), 6.48 – 6.44 (m, 1H), 4.72 – 4.65 (m, 1H), 4.44 – 4.37 (m, 1H), 3.80 – 3.76 (m, 3H), 3.23 – 3.14 (m, 1H), 2.53 – 2.25 (m, 5H), 2.20 – 2.13 (m, 1H), 1.92 – 1.86 (m, 1H), 1.68 – 1.57 (m, 1H), 1.57 – 1.47 (m, 1H), 1.43 – 1.34 (m, 1H), 1.27 – 1.22 (m, 3H), 1.12 – 1.02 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 220.3, 171.8, 171.8, 168.7, 168.5, 137.8, 137.7, 135.4, 135.3, 68.2, 57.3, 52.8, 46.6, 38.2, 37.5, 37.5, 36.4, 36.3, 28.2, 28.0, 27.9, 26.1, 20.3, 20.2, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}NO_5$) requires *m/z* 324.1805, found *m/z* 324.1807.

Compound 151b.



151b

Prepared according to General Procedure H using compound **S151b** (20 mg, 0.06 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.) and 1:1 MeOH:H_2O (4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (12 mg, 63%).

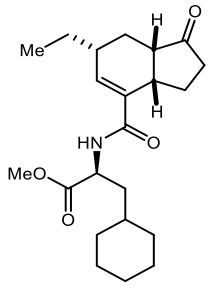
υ_{max} (film): 3374 (br.), 2959, 2920, 2853, 1730, 1651, 1607, 1524 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 1H), 6.53 (s, 1H), 5.39 – 4.32 (m, 3H), 3.23 – 3.08 (m, 1H), 2.54 – 2.25 (m, 4H), 2.17 (br. s, 1H), 1.95 – 1.84 (m, 1H), 1.67 – 1.47 (m, 2H), 1.44 – 1.34 (m, 1H), 1.26 (br. s, 3H), 1.13 – 1.02 (m, 1H), 0.98 (t, *J* = 6.9 Hz, 3H). O*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 220.1, 169.7, 169.4, 139.4, 139.0, 134.7, 67.5, 67.2, 46.7, 46.6, 38.2, 37.6, 37.5, 36.3, 36.2, 28.2, 28.1, 27.9, 26.0, 19.5, 11.5, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{16}H_{22}NO_5$) requires *m/z* 308.1503, found *m/z* 308.1496.

Compound S151c.



S151c

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl (*S*)-2-amino-3-cyclohexylpropanoate hydrochloride (32 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 20% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (33 mg, 91%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.49 stained by $KMnO_4$.

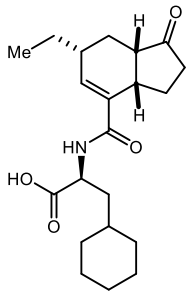
υ_{max} (film): 3322 (br.), 2919, 2850, 1738, 1656, 1619, 1524, 1203, 1152 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.41 – 6.30 (m, 1H), 6.16 – 6.07 (m, 1H), 4.80 – 4.68 (m, 1H), 3.75 (s, 3H), 3.21 – 3.12 (m, 1H), 2.51 – 2.23 (m, 4H), 2.19 – 2.11 (m, 1H), 1.92 – 1.85 (m, 1H), 1.85 – 1.76 (m, 1H), 1.76 – 1.47 (m, 8H), 1.41 – 1.28 (m, 2H), 1.23 – 1.11 (m, 3H), 1.11 – 1.01 (m, 1H), 1.01 – 0.89 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 220.3, 174.1, 168.0, 167.8, 137.0, 136.9, 135.8, 135.7, 52.5, 50.3, 50.2, 46.6, 40.4, 40.4, 38.3, 37.5, 37.4, 36.4, 36.3, 34.5, 34.4, 33.6, 32.8, 32.7, 28.3, 28.2, 27.9, 27.9, 26.5, 26.3, 26.3, 26.2, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{34}NO_4$) requires *m/z* 376.2482, found *m/z* 376.2476.

Compound 151c.



151c

Prepared according to General Procedure H using compound **S151c** (27 mg, 0.07 mmol, 1 equiv.), NaOH (9 mg, 0.23 mmol, 3 equiv.), and 1:1 MeOH:H_2O (4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (18 mg, 69%).

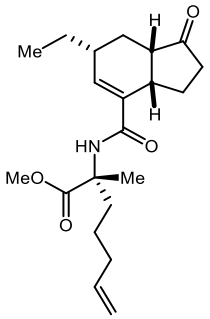
υ_{max} (film): 3325 (br.), 2922, 2854, 1733, 1653, 1616, 1526, 1195, 1150 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.97 (br. s, 1H), 6.43 – 6.33 (m, 1H), 6.25 – 6.14 (m, 1H), 4.78 – 4.63 (m, 1H), 3.22 – 3.12 (m, 1H), 2.51 – 2.24 (m, 4H), 2.16 (br. s, 1H), 1.93 – 1.86 (m, 1H), 1.86 – 1.77 (m, 2H), 1.77 – 1.46 (m, 7H), 1.44 – 1.34 (m, 2H), 1.26 – 1.12 (m, 3H), 1.12 – 1.02 (m, 1H), 1.01 – 0.88 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 176.8, 168.7, 168.4, 137.7, 137.6, 135.4, 135.4, 50.6, 50.5, 46.5, 39.9, 39.8, 38.3, 37.5, 37.4, 36.3, 36.3, 34.5, 34.4, 33.6, 32.7, 32.6, 26.4, 26.3, 26.3, 26.2, 26.1, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{32}NO_4$) requires *m/z* 362.2326, found *m/z* 362.2327.

Compound 151d.



151d

Prepared according to General Procedure G using (±)-CFA (**4**) (15 mg, 0.07 mmol, 1 equiv.), HATU (33 mg, 0.09 mmol, 1.2 equiv.), methyl (*R*)-2-amino-2-methylhept-6-enoate hydrochloride (25 mg, 0.12 mmol, 1.7 equiv.), DIPEA (40 µL, 0.23 mmol, 3 equiv.), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a white solid (5 mg, 20%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.66 stained by $KMnO_4$.

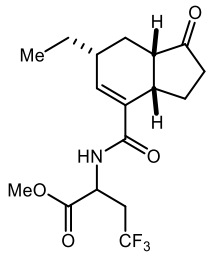
υ_{max} (film): 3304, 3057, 2922, 2857, 1736, 1659, 1624, 1516, 1462, 1202, 1076 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.37 – 6.32 (m, 1H), 5.80 – 5.70 (m, 1H), 5.02 – 4.93 (m, 2H), 3.78 (s, 3H), 3.19 – 3.10 (m, 1H), 2.49 – 2.24 (m, 5H), 2.19 – 2.11 (m, 1H), 2.08 – 1.99 (m, 2H), 1.91 – 1.79 (m, 2H), 1.64 (s, 3H), 1.63 – 1.60 (m, 1H), 1.54 – 1.47 (m, 1H), 1.41 – 1.31 (m, 2H), 1.20 – 1.11 (m, 1H), 1.10 – 1.01(m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5, 167.3, 167.2, 138.3, 138.2, 136.6, 136.4, 136.4, 136.3, 115.1, 60.7, 53.0, 46.7, 46.6, 38.3, 37.4, 36.4, 36.3, 36.0, 35.8, 33.5, 28.3, 27.9, 26.2, 23.9, 23.3, 23.3, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{32}NO_4$) requires *m/z* 362.2326, found *m/z* 362.2328.

Compound S151e.



S151e

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl 2-amino-4,4,4-trifluorobutanoate hydrochloride (30 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 20% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (24 mg, 69%).

TLC (20% EtOAc/CH_2Cl_2): R_f = 0.61 stained by $KMnO_4$.

υ_{max} (film): 3802 (br.), 2963, 2870, 1705, 1532, 1364, 1165 cm^{-1}.

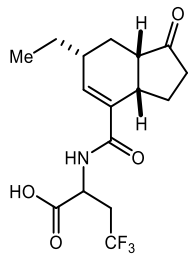
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 – 6.47 (m, 1H), 6.44 – 6.37 (m, 1H), 4.93 – 4.83 (m, 1H), 3.82 (s, 3H), 3.23 – 3.08 (m, 1H), 2.96 – 2.84 (m, 1H), 2.81 – 2.67 (m, 1H), 2.52 – 2.22 (m, 4H), 2.22 – 2.11 (m, 1H), 1.94 – 1.85 (m, 1H), 1.64 – 1.46 (m, 2H), 1.46 – 1.33 (m, 1H), 1.13 – 1.01 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.1, 220.1, 170.6, 167.8, 167.8, 138.1, 138.0, 135.2, 125.8 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 53.3, 47.6, 46.6, 46.5, 38.2, 37.5, 37.4, 36.3, 36.2, 35.2 (q, $^2J_{C\text{-}F}$ = 28.2 Hz), 28.2, 27.9, 27.8, 26.1, 26.1, 11.4, 11.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ −62.85 (t, *J* = 10.4 Hz), −62.96 (t, *J* = 10.4 Hz) (1:1 diastereosiomers).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}F_3NO_4$) requires *m/z* 362.1574, found *m/z* 362.1574.

Compound 151e.



151e

Prepared according to General Procedure H using compound **S151e** (24 mg, 0.07 mmol, 1 equiv.), NaOH (10 mg, 0.25 mmol, 3 equiv.), and 1:1 MeOH:H_2O (3 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a pale orange solid (18 mg, 74%).

υ_{max} (film): 3339 (br.), 2967, 2930, 2880, 1740, 1718, 1653, 1617, 1523, 1247, 1133 cm^{-1}.

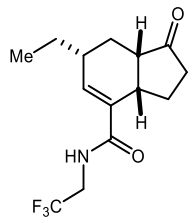
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (br. s, 1H), 6.67 (s, 1H), 6.45 (s, 1H), 4.83 (br. s, 1H), 3.20 – 3.08 (m, 1H), 3.00 – 2.84 (m, 1H), 2.78 (br. s, 1H), 2.49 – 2.24 (m, 4H), 2.17 (br. s, 1H), 1.93 – 1.84 (m, 1H), 1.66 – 1.47 (m, 2H), 1.43 – 1.34 (m, 1H), 1.13 – 1.01 (m, 1H), 0.98 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.6, 173.2 – 172.6 (m), 168.7, 168.6, 139.2, 138.7, 134.8, 134.8, 125.9 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 48.3 – 47.7 (m), 46.6, 46.5, 38.2, 37.5, 37.5, 36.2, 36.1, 35.4 – 34.3 (m), 28.4, 28.1, 27.9, 27.7, 26.0, 26.0, 11.4, 11.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ −62.90 (t, *J* = 10.0 Hz), −63.00 (t, *J* = 10.1 Hz). (1:1 mixture of diastereoisomers).

HRMS: exact mass calculated for $[M-H]^-$ ($C_{16}H_{19}F_3NO_4$) requires *m/z* 346.1272, found *m/z* 346.1264.

Compound 151f.



151f

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.1 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl 2-amino-3,3,3-trifluoropropanoate hydrochloride (50 mg, 0.26 mmol, 2.6 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 20% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (7 mg, 25%).

TLC (20% EtOAc/CH_2Cl_2): R_f = 0.54 stained by $KMnO_4$.

υ_{max} (film): 3330 (br.), 2963, 2926, 2880, 2861, 1740, 1662, 1632, 1532, 1256 cm^{-1}.

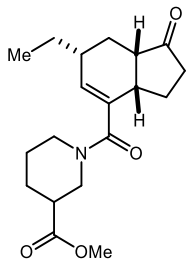
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 6.00 (br. s, 1H), 4.12 – 3.88 (m, 2H), 3.24 – 3.14 (m, 1H), 2.51 – 2.24 (m, 4H), 2.23 – 2.13 (m, 1H), 1.91 (dt, *J* = 13.0, 4.8 Hz, 1H), 1.64 – 1.46 (m, 2H), 1.45 – 1.34 (m, 1H), 1.13 – 1.02 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.0, 168.1, 137.8, 135.6, 124.3 (q, $^1J_{C-F}$ = 278.6 Hz), 46.44, 40.9 (q, $^2J_{C-F}$ = 34.5 Hz), 38.3, 37.5, 36.4, 28.2, 27.9, 26.1, 11.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -72.45 (t, *J* = 9.1 Hz).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}F_3NO_2$) requires *m/z* 290.1362, found *m/z* 290.1365.

Compound S151g.



S151g

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl piperidine-3-carboxylate hydrochloride (26 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30-50% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (17 mg, 53%).

TLC (20% EtOAc/CH_2Cl_2): R_f = 0.12 stained by $KMnO_4$.

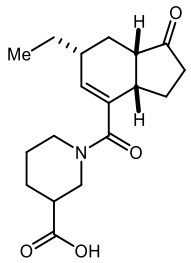
υ_{max} (film): 3445 (br.), 2956, 2939, 2922, 2902, 2872, 2855, 1738, 1619, 1435, 1245 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 – 5.67 (m, 1H), 4.36 (br. s, 2H), 3.71 – 3.66 (m, 3H), 3.24 – 2.77 (m, 3H), 2.53 – 2.31 (m, 3H), 2.31 – 2.19 (m, 2H), 2.17 – 2.07 (m, 2H), 1.91 – 1.84 (m, 1H), 1.83 – 1.62 (m, 3H), 1.53 – 1.34 (m, 3H), 1.19 – 1.09 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 173.5, 170.8, 170.7, 134.6, 133.0, 52.0, 52.0, 46.3, 46.3, 42.0 (br.), 38.4, 38.3, 37.6, 37.4, 36.7, 36.6, 28.3, 27.6, 27.3, 27.2, 26.2, 26.1, 25.0 (br.), 11.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{28}NO_4$) requires *m/z* 334.2013, found *m/z* 334.2014.

Compound 151g.



Prepared according to General Procedure H using compound **S151g** (15 mg, 0.04 mmol, 1 equiv.), NaOH (5 mg, 0.13 mmol, 3 equiv.), and 1:1 MeOH:H_2O (2 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (9 mg, 63%).

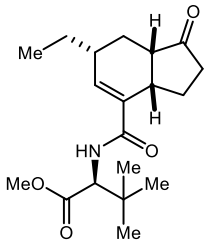
υ_{max} (film): 2934 (br.), 2861 (br.), 1733, 1584, 1444, 1266, 1186, 917 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 – 5.68 (m, 1H), 4.51 – 3.71 (m, 2H), 3.41 – 3.01 (m, 3H), 2.59 – 2.31 (m, 3H), 2.30 – 2.18 (m, 2H), 2.12 (br. s, 2H), 1.92 – 1.84 (m, 1H), 1.84 – 1.61 (m, 3H), 1.58 – 1.33 (m, 3H), 1.20 – 1.07 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3, 177.3, 171.2, 171.0, 134.4, 133.3, 133.0, 46.3, 46.3, 38.4, 37.6, 37.4, 36.7, 36.7, 28.3, 27.4, 27.3, 27.2, 26.2, 26.1, 11.3.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{24}NO_4$) requires *m/z* 318.1711, found *m/z* 318.1706.

Compound S151h.



S151h

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl (*S*)-2-amino-3,3-dimethylbutanoate hydrochloride (26 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 10% EtOAc/CH_2Cl_2) to afford the title compound as a pale orange oil (29 mg, 90%).

TLC (10% EtOAc/CH_2Cl_2): R_f = 0.14 stained by $KMnO_4$.

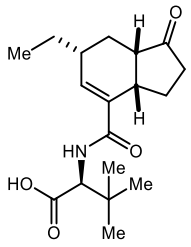
υ_{max} (film): 3359 (br.), 2960, 2874, 1738, 1662, 1627, 1509, 1216, 1165 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 6.32 – 6.22 (m, 1H), 4.59 – 4.52 (m, 1H), 3.74 (s, 3H), 3.22 – 3.09 (m, 1H), 2.52 – 2.22 (m, 4H), 2.20 – 2.09 (m, 1H), 1.92 – 1.84 (m, 1H), 1.66 – 1.47 (m, 2H), 1.43 – 1.34 (m, 1H), 1.12 – 1.01 (m, 1H), 1.01 – 0.93 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 172.6, 172.5, 167.9, 167.8, 137.1, 136.9, 135.9, 135.8, 60.0, 59.9, 52.0, 46.6, 38.2, 37.5, 37.4, 36.4, 35.3, 35.1, 28.3, 28.2, 28.0, 27.9, 26.8, 26.8, 26.2, 26.1, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}NO_4$) requires *m/z* 336.2169, found *m/z* 336.2169.

Compound 151h.



151h

Prepared according to General Procedure H using compound **S151h** (24 mg, 0.07 mmol, 1 equiv.), NaOH (9 mg, 0.23 mmol, 3 equiv.), and 1:1 MeOH:H_2O (3 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a pale orange solid (18 mg, 78%).

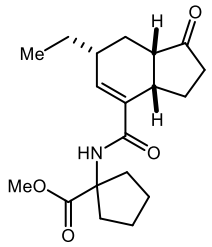
υ_{max} (film): 3343 (br.), 2963, 2876, 1733, 1658, 1616, 1515, 1213 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.43 – 6.37 (m, 1H), 6.37 – 6.29 (m, 1H), 4.59 – 4.50 (m, 1H), 3.22 – 3.10 (m, 1H), 2.51 – 2.24 (m, 4H), 2.15 (br. s, 1H), 1.93 – 1.85 (m, 1H), 1.67 – 1.48 (m, 2H), 1.44 – 1.34 (m, 1H), 1.11 – 1.02 (m, 10H), 1.01 – 0.94 (m, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.5, 175.3, 168.4, 168.3, 137.7, 137.4, 135.6, 60.4, 46.6, 38.2, 37.5, 37.4, 36.4, 35.0, 34.9, 28.2, 28.2, 28.0, 27.9, 26.9, 26.8, 26.1, 26.1, 11.5, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1867, found *m/z* 320.1860.

Compound S151i.



S151i

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.1 mmol, 1 equiv.), HATU (44 mg, 0.15 mmol, 1.2 equiv.), methyl 1-aminocyclopropane-1-carboxylate (26 mg, 0.15 mmol, 1.5 equiv.), DIPEA (50 µL, 0.29 mmol, 3 equiv.), and DMF (0.2 mL). After 16 h the reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a white solid (26 mg, 81%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.62 stained by $KMnO_4$.

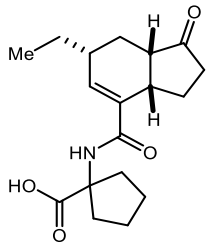
υ_{max} (film): 3329 (br.), 2957, 2874, 1736, 1655, 1618, 1516, 1449, 1267, 1194 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.29 (s, 1H), 6.18 (s, 1H), 3.73 (s, 3H), 3.19 – 3.12 (m, 1H), 2.47 – 2.20 (m, 6H), 2.17 – 2.09 (m, 1H), 2.06 – 1.93 (m, 2H), 1.87 (dt, *J* = 12.9, 4.8 Hz, 1H), 1.84 – 1.77 (m, 4H), 1.64 – 1.45 (m, 2H), 1.42 – 1.33 (m, 1H), 1.10 – 1.00 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 175.1, 168.2, 136.4, 136.2, 66.1, 52.7, 46.5, 38.3, 37.8, 37.4, 37.3, 36.4, 28.3, 27.9, 26.2, 25.1, 11.5. One signal equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{28}NO_4$) requires *m/z* 334.2013, found *m/z* 334.2015.

Compound 151i.



151i

Prepared according to General Procedure H using compound **S151i** (26 mg, 0.08 mmol, 1 equiv.), LiOH (6 mg, 0.25 mmol, 3 equiv.), and 1:1 MeOH:H_2O (3 mL). After 16 h the reaction was allowed to cool to room temperature, acidified with AcOH, and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil (18 mg, 72%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.59 stained by $KMnO_4$.

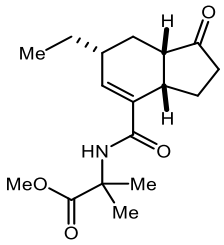
υ_{max} (film): 3281, 2959, 2934, 2862, 1734, 1719, 1695, 1612, 1528 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (br. s, 1H), 6.34 (s, 1H), 6.29 (s, 1H), 3.18 – 3.11 (m, 1H), 2.47 – 2.23 (m, 6H), 2.18 – 2.10 (m, 1H), 2.07 – 1.92 (m, 2H), 1.88 (dt, *J* = 12.9, 4.8 Hz, 1H), 1.85 – 1.73 (m, 4H), 1.63 – 1.45 (m, 2H), 1.41 – 1.34 (m, 1H), 1.10 – 1.00 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 178.0, 169.4, 137.6, 135.7, 66.7, 46.5, 38.3, 37.6, 37.5, 37.1, 36.3, 28.2, 27.9, 26.1, 24.8, 24.8, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1862, found *m/z* 320.1864.

Compound S151j.



S151j

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl 2-amino-2-methylpropanoate hydrochloride (17 mg, 0.15 mmol, 1.5 equiv.), DIPEA (50 µL, 0.29 mmol, 3 equiv.), and DMF (0.2 mL). After 16 h the reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (24 mg, 81%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.32 stained by $KMnO_4$.

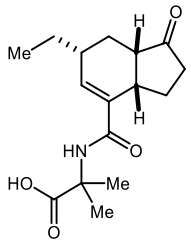
υ_{max} (film): 3304, 2938, 1734, 1649, 1607, 1522, 1267, 1148 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (br. s, 1H), 6.31 (s, 1H), 3.75 (s, 3H), 3.18 – 3.11 (m, 1H), 2.47 – 2.22 (m, 4H), 2.17 – 2.09 (m, 1H), 1.87 (dt, *J* = 12.8, 4.8 Hz, 1H), 1.64 – 1.55 (m, 7H), 1.53 – 1.45 (m, 1H), 1.43 – 1.33 (m, 1H), 1.09 – 1.00 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4, 167.7, 136.4, 136.2, 56.7, 52.8, 46.6, 38.3, 37.4, 36.4, 28.3, 27.9, 26.2, 25.0, 24.8, 11.5. Carbonyl *C*O not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}NO_4$) requires *m/z* 308.1856, found *m/z* 308.1858.

Compound 151j.



Prepared according to General Procedure H using compound **S151j** (24 mg, 0.08 mmol, 1 equiv.), LiOH (6 mg, 0.25 mmol, 3 equiv.), and 1:1 MeOH:H_2O (2 mL). After 16 h the reaction was purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil (9 mg, 39%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.40 stained by $KMnO_4$ and visible under UV (short wave).

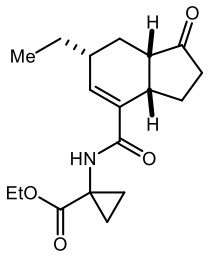
υ_{max} (film): 3271, 2922, 2862, 1734, 1719, 1701, 1616, 1528 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.34 (s, 1H), 6.31 (s, 1H), 3.18 – 3.11 (m, 1H), 2.48 – 2.24 (m, 4H), 2.19 – 2.11 (m, 1H), 1.88 (dt, *J* = 12.7, 4.7 Hz, 1H), 1.66 – 1.54 (m, 7H), 1.54 – 1.47 (m, 1H), 1.42 – 1.32 (m, 1H), 1.10 – 1.01 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 178.3, 168.6, 137.4, 135.8, 57.0, 46.5, 38.3, 37.5, 36.3, 28.2, 27.9, 26.1, 25.1, 24.9, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO_4$) requires *m/z* 294.1705, found *m/z* 294.1704.

Compound S10a.



S10a

Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.), HATU (66 mg, 0.18 mmol, 1.2 equiv.), ethyl 1-aminocyclopropane-1-carboxylate hydrochloride (36 mg, 0.22 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.), and DMF (0.8 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a pale orange oil (30 mg, 65%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.24 stained by $KMnO_4$ and faintly visible by UV (short wave).

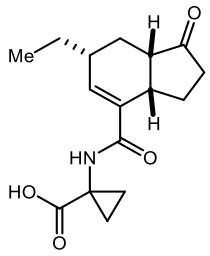
υ_{max} (film): 3320 (br.), 2958, 2930, 2872, 2854, 1729, 1658, 1625, 1513, 1333, 1180, 1156 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.31 (s, 1H), 6.29 (s, 1H), 4.20 – 4.08 (m, 2H), 3.23 – 3.15 (m, 1H), 2.52 – 2.43 (m, 1H), 2.41 – 2.22 (m, 3H), 2.18 – 2.09 (m, 1H), 1.87 (dt, *J* = 11.7, 4.5 Hz, 1H), 1.65 – 1.53 (m, 3H), 1.52 – 1.43 (m, 1H), 1.42 – 1.31 (m, 1H), 1.29 – 1.16 (m, 5H), 1.11 – 1.01 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 172.4, 169.5, 136.5, 136.2, 61.6, 46.5, 38.3, 37.3, 36.4, 34.0, 28.3, 27.9, 26.2, 17.5, 14.3, 11.4. One signal equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1856, found *m/z* 320.1855.

Compound 10a.



10a

Prepared according to General Procedure H using compound **S10a** (30 mg, 0.09 mmol, 1 equiv.), LiOH (8 mg, 0.33 mmol, 3 equiv.), and 1:1 MeOH:H_2O (4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (4 mg, 15%).

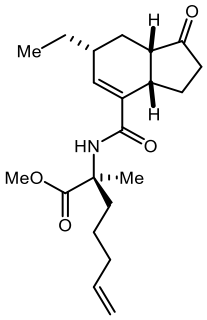
υ_{max} (film): 3327 (br.), 2965, 2934, 2874, 1736, 1655, 1624, 1508, 1273, 1196, 1146 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.36 (s, 1H), 5.43 (br. s, 1H), 3.20 – 3.09 (m, 1H), 2.51 – 2.21 (m, 4H), 2.18 – 2.07 (m, 1H), 1.91 – 1.82 (m, 1H), 1.57 (br. s, 3H), 1.52 – 1.44 (m, 1H), 1.39 – 1.33 (m, 1H), 1.16 (br. s, 2H), 1.10 – 1.00 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.5, 170.0, 137.5, 135.6, 46.6, 38.3, 37.4, 36.3, 28.3, 28.0, 26.1, 17.9, 17.8, 11.5. One signal not observed, one signal equivalent.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{16}H_{20}NO_4$) requires *m/z* 290.1398, found *m/z* 290.1393.

Compound 151k.



151k

Prepared according to General Procedure G using (±)-CFA (**4**) (7 mg, 0.03 mmol, 1 equiv.), HATU (15 mg, 0.04 mmol, 1.2 equiv.), methyl (*S*)-2-amino-2-methylhept-6-enoate hydrochloride (10 mg, 0.05 mmol, 1.5 equiv.), DIPEA (20 µL, 0.10 mmol, 3 equiv.), and DMF (0.15 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 10% EtOAc/CH_2Cl_2) to afford the title compound as a white solid (4 mg, 29%). Compound tested as the methyl ester due to paucity of available material.

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.68 stained by $KMnO_4$ and visible under UV (short wave).

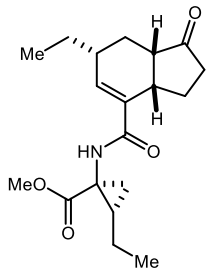
υ_{max} (film): 3341 (br.), 2926, 2857, 1736, 1659, 1624, 1514, 1204, 1146, 1123 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.38 – 6.32 (m, 1H), 5.81 – 5.70 (m, 1H), 5.02 – 4.93 (m, 2H), 3.79 (s, 3H), 3.19 – 3.11 (m, 1H), 2.48 – 2.25 (m, 5H), 2.20 – 2.11 (m, 1H), 2.08 – 2.00 (m, 2H), 1.91 – 1.79 (m, 2H), 1.64 (s, 3H), 1.63 – 1.60 (m, 1H), 1.54 – 1.49 (m, 1H), 1.42 – 1.31 (m, 2H), 1.19 – 1.12 (m, 1H), 1.10 – 1.02 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5, 138.3, 138.2, 136.6, 136.5, 136.4, 136.3, 115.1, 115.1, 60.7, 53.0, 46.7, 46.6, 38.3, 37.4, 36.4, 36.4, 36.0, 35.8, 33.5, 28.3, 27.9, 26.2, 23.9, 23.3, 23.3, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{32}NO_4$) requires *m/z* 362.2326, found *m/z* 362.2328.

Compound 10f.



10f

Prepared according to General Procedure G using (±)-CFA (**4**) (22 mg, 0.1 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), compound **194** (38 mg, 0.2 mmol, 2 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (7 mg, 20%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.33 stained by $KMnO_4$.

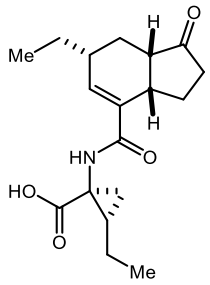
υ_{max} (film): 3312 (br.), 2961, 2928, 2874, 1734, 1655, 1624, 1510, 1337 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.30 – 6.25 (m, 2H), 3.73 – 3.69 (m, 3H), 3.23 – 3.14 (m, 1H), 2.52 – 2.23 (m, 4H), 2.19 – 2.10 (m, 1H), 1.92 – 1.85 (m, 1H), 1.67 – 1.55 (m, 4H), 1.53 – 1.45 (m, 2H), 1.41 – 1.34 (m, 1H), 1.34 – 1.26 (m, 1H), 1.11 – 1.02 (m, 1H), 1.02 – 0.95 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 171.8, 169.4, 169.2, 136.6, 136.6, 136.2, 136.1, 52.5, 52.5, 46.5, 46.5, 38.4, 38.4, 38.3, 37.4, 36.4, 36.4, 33.3, 33.1, 28.3, 27.9, 27.8, 26.2, 26.2, 23.3, 23.1, 20.6, 13.6, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{28}NO_4$) requires *m/z* 334.2013, found *m/z* 334.2016.

(±)-coronatine (1).



Prepared according to General Procedure H compound **10f** (20 mg, 0.10 mmol, 1 equiv.), LiOH (8 mg, 0.33 mmol, 3 equiv.), and 1:1 MeOH:H_2O (5 mL). After 16 h the reaction was allowed to cool to room temperature, acidified with AcOH, and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford a colourless oil. The crude material was dissolved in a minimal volume of diethyl ether and petroleum ether added until a white precipitate formed. The solvent was removed by Pasteur pipette and the residue dried under vacuum to afford the desired product as a white solid (9 mg, 47%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.38 stained by $KMnO_4$.

υ_{max} (film): 3314 (br.), 2961, 2928, 2872, 1719, 1655, 1618, 1508, 1167 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.52 – 6.40 (m, 1H), 6.39 – 6.32 (m, 1H), 3.21 – 3.12 (m, 1H), 2.51 – 2.23 (m, 4H), 2.21 – 2.10 (m, 1H), 1.92 – 1.85 (m, 1H), 1.68 – 1.53 (m, 4H), 1.53 – 1.44 (m, 2H), 1.44 – 1.34 (m, 1H), 1.31 – 1.26 (m, 1H), 1.11 – 1.00 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H). CO_2H not observed.

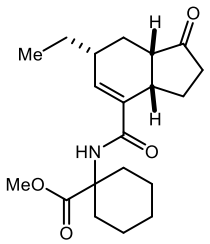
Experimental

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 220.1, 174.9, 174.2, 170.9, 170.5, 138.7, 137.9, 135.4, 135.3, 46.5, 46.4, 39.3, 38.9, 38.3, 37.6, 37.5, 36.4, 36.3, 33.9, 33.8, 28.2, 28.2, 28.0, 27.9, 26.1, 26.0, 22.6, 22.1, 21.0, 20.9, 13.6, 13.5, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1862, found *m/z* 320.1865.

The spectral data were consistent with those previously reported in the literature.[38]

Compound S151l.



S151l

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl 1-aminocyclohexane-1-carboxylate hydrochloride (28 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv.), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 20% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (26 mg, 78%).

TLC (20% EtOAc/CH_2Cl_2): R_f = 0.34 stained by $KMnO_4$.

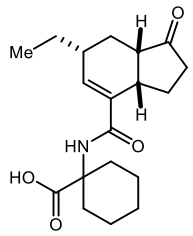
υ_{max} (film): 3357 (br.), 2932, 2855, 1738, 1660, 1625, 1517, 1277, 1238 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31 (s, 1H), 5.86 (s, 1H), 3.71 (s, 3H), 3.15 (br. s, 1H), 2.46 – 2.22 (m, 4H), 2.19 – 2.10 (m, 2H), 2.06 – 1.97 (m, 1H), 1.95 – 1.82 (m, 3H), 1.75 – 1.48 (m, 5H), 1.47 – 1.29 (m, 4H), 1.12 – 1.01 (m, 1H), 0.98 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3, 174.7, 168.0, 136.4, 136.3, 58.9, 52.4, 46.5, 38.3, 37.3, 36.4, 33.1, 32.0, 28.3, 27.8, 26.2, 25.3, 21.8, 21.8, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{30}NO_4$) requires *m/z* 348.2169, found *m/z* 348.2167.

Compound 151l.



151l

Prepared according to General Procedure H using compound **S151l** (24 mg, 0.07 mmol, 1 equiv.), NaOH (8 mg, 0.20 mmol, 3 equiv.), and 1:1 MeOH:H_2O (4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (22 mg, 96%).

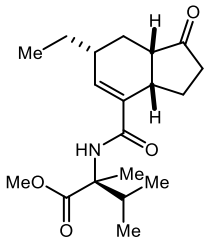
υ_{max} (film): 3323 (br.), 2928, 2859, 1733, 1617, 1526, 1146 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (s, 1H), 5.96 (s, 1H), 3.19 – 3.12 (m, 1H), 2.48 – 2.24 (m, 4H), 2.24 – 2.12 (m, 2H), 2.10 – 2.02 (m, 1H), 1.97 – 1.84 (m, 3H), 1.78 – 1.48 (m, 5H), 1.47 – 1.29 (m, 4H), 1.11 – 1.01 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). CO_2H not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 177.1, 169.4, 137.8, 135.9, 59.6, 46.5, 38.3, 37.5, 36.3, 32.7, 31.7, 28.2, 27.9, 26.1, 25.2, 21.7, 21.6, 11.5. Carbonyl *C*O not observed.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{19}H_{26}NO_4$) requires *m/z* 332.1867, found *m/z* 332.1860.

Compound S151m.



S151m

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl (*S*)-2-amino-2,3-dimethylbutanoate hydrochloride (26 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv.), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 10% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (26 mg, 81%).

TLC (10% EtOAc/CH_2Cl_2): R_f = 0.15 stained by $KMnO_4$.

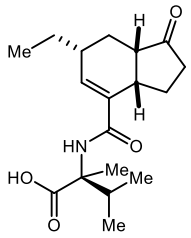
υ_{max} (film): 3460 (br.), 2960, 2874, 2855, 1736, 1660, 1513, 1463, 1260, 1147 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 – 6.29 (m, 2H), 3.78 – 3.74 (m, 3H), 3.20 – 3.10 (m, 1H), 2.52 – 2.23 (m, 5H), 2.20 – 2.10 (m, 1H), 1.92 – 1.84 (m, 1H), 1.67 – 1.56 (m, 4H), 1.56 – 1.45 (m, 1H), 1.43 – 1.33 (m, 1H), 1.12 – 0.95 (m, 7H), 0.94 – 0.90 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 174.5, 174.4, 167.7, 167.6, 136.5, 136.5, 136.3, 136.3, 63.5, 63.4, 52.5, 52.5, 46.6, 46.6, 38.3, 37.4, 36.5, 36.4, 34.9, 28.3, 28.0, 27.9, 26.2, 18.9, 18.4, 17.8, 17.7, 17.7, 17.6, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}NO_4$) requires *m/z* 336.2169, found *m/z* 336.2170.

Compound 151m.



151m

Prepared according to General Procedure H using compound **S151m** (26 mg, 0.08 mmol, 1 equiv.), NaOH (9 mg, 0.23 mmol, 3 equiv.), and 1:1 MeOH:H_2O (4 mL). After 20 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (17 mg, 68%).

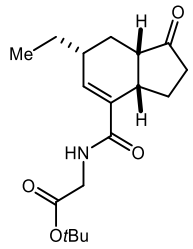
υ_{max} (film): 3414 (br.), 2965, 2939, 2878, 1733, 1662, 1623, 1513, 1448, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.38 – 6.33 (m, 1H), 6.22 – 6.16 (m, 1H), 3.20 – 3.09 (m, 1H), 2.65 – 2.24 (m, 5H), 2.22 – 2.12 (m, 1H), 1.94 – 1.85 (m, 1H), 1.66 – 1.47 (m, 5H), 1.44 – 1.35 (m, 1H), 1.12 – 0.92 (m, 10H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 220.1, 176.4, 175.9, 169.4, 169.1, 138.1, 137.5, 136.0, 135.9, 64.7, 64.2, 46.6, 46.5, 38.2, 37.5, 37.4, 36.4, 36.3, 33.3, 32.6, 28.2, 28.0, 27.9, 26.1, 26.1, 18.5, 18.3, 17.5, 17.2, 17.1, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1867, found *m/z* 320.1858.

Compound 152a.



152a

Prepared according to General Procedure G using (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.), HATU (66 mg, 0.17 mmol, 1.2 equiv.), glycine *t*-butyl ester hydrochloride (36 mg, 0.21 mmol, 1.5 equiv.), DIPEA (80 µL, 0.46 mmol, 3 equiv.), and DMF (0.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30-40% EtOAc/petroleum ether) to afford the title compound as a colourless oil (45 mg, 98%).

TLC (30% EtOAc/petroleum ether): R_f = 0.18 stained by $KMnO_4$.

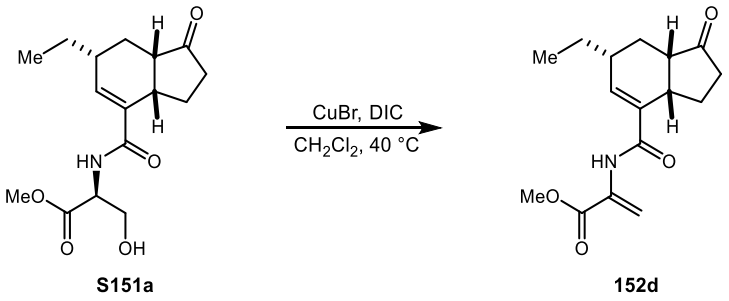
υ_{max} (film): 3337 (br.), 2930, 2857, 1738, 1655, 1611, 1528, 1368, 1225, 1152 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.40 (s, 1H), 6.29 (br. s, 1H), 4.00 (d, *J* = 4.9 Hz, 2H), 3.22 – 3.12 (m, 1H), 2.51 – 2.43 (m, 1H), 2.42 – 2.22 (m, 3H), 2.19 – 2.10 (m, 1H), 1.86 (dt, *J* = 12.4, 4.7 Hz, 1H), 1.65 – 1.53 (m, 1H), 1.53 – 1.42 (m, 10H), 1.43 – 1.32 (m, 1H), 1.05 (dd, *J* = 24.2, 13.0 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 169.5, 168.0, 137.2, 135.5, 82.6, 46.6, 42.3, 38.3, 37.4, 36.3, 28.2, 28.2, 28.0, 26.1, 11.4. Two signals equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}NO_4$) requires *m/z* 322.2013, found *m/z* 322.2014.

Compound 152d.



S151a **152d**

To a round bottom flask charged with compound **S151a** (73 mg, 0.24 mmol, 1 equiv.) was added CuBr (3 mg, 0.02 mmol, 10 mol%), CH_2Cl_2 (2.5 mL), and DIC (70 µl, 0.45 mmol, 2 equiv.) sequentially. The reaction was brought to 40 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, eluting with CH_2Cl_2, and concentrated *in vacuo* to afford a pale orange oil. The crude material was loaded in a solution of 10% EtOAc/CH_2Cl_2 and purified by flash silica column chromatography, eluent 10% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil which solidified to a white solid on standing (30 mg, 44%).

TLC (10% EtOAc/CH_2Cl_2): R_f = 0.52 stained by $KMnO_4$.

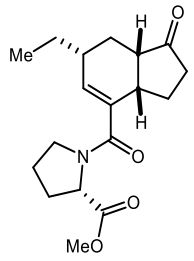
υ_{max} (film): 3414, 2958, 2941, 2876, 1733, 1711, 1670, 1515, 1318, 1202 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (br. s, 1H), 6.64 (s, 1H), 6.45 (s, 1H), 5.91 (s, 1H), 3.86 (s, 3H), 3.24 – 3.15 (m, 1H), 2.55 – 2.46 (m, 1H), 2.44 – 2.25 (m, 3H), 2.24 – 2.15 (m, 1H), 1.89 (dt, *J* = 12.8, 4.7 Hz, 1H), 1.66 – 1.48 (m, 2H), 1.45 – 1.37 (m, 1H), 1.12 – 1.03 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.0, 166.4, 165.1, 138.1, 136.1, 131.0, 108.8, 53.2, 46.6, 38.2, 37.5, 36.2, 28.1, 28.0, 26.0, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}NO_4$) requires *m/z* 292.1543, found *m/z* 292.1543.

Compound 152g.



152g

To a round bottom flask was added (±)-CFA (**4**) (30 mg, 0.14 mmol, 1 equiv.) and COMU (123 mg, 0.29 mmol, 2 equiv.). DMF (0.7 mL) was added, followed by DIPEA (80 µL, 0.46 mmol, 3 equiv.) and the resulting solution stirred at room temperature under air for 5 minutes. *L*-proline methyl ester hydrochloride (36 mg, 0.22 mmol, 1.5 equiv.) was then added and the reaction stirred for 22 h. The red solution was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a red oil. The crude material was loaded in a solution of 60% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 60% EtOAc/petroleum ether to afford the title compound as a pale yellow solid (34 mg, 74%).

TLC (60% EtOAc/petroleum ether): R_f = 0.18 stained by $KMnO_4$.

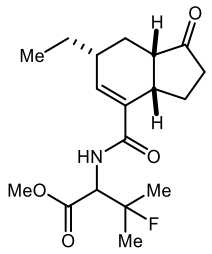
υ_{max} (film): 3350 (br.), 2959, 1738, 1609, 1433, 1196, 1175, 843 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.09 – 5.82 (m, 1H), 4.60 – 4.44 (m, 1H), 3.81 – 3.52 (m, 5H), 3.29 – 3.09 (m, 1H), 2.46 – 2.18 (m, 4H), 2.18 – 2.08 (m, 1H), 2.06 – 1.78 (m, 5H), 1.77 – 1.51 (m, 1H), 1.51 – 1.32 (m, 2H), 1.17 – 1.07 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.6, 173.0, 172.8, 170.1, 169.8, 135.6, 135.6, 134.1, 59.0, 58.8, 52.4, 52.3, 49.7, 49.6, 46.2, 38.5, 38.3, 37.3, 36.9, 36.7, 36.6, 29.4, 29.3, 28.3, 28.3, 27.4, 27.3, 26.1, 25.7, 24.8, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1856, found *m/z* 320.1860.

Compound 152i.



152i

Prepared according to General Procedure G using (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.), HATU (44 mg, 0.12 mmol, 1.2 equiv.), methyl 2-amino-3-fluoro-3-methylbutanoate hydrochloride (27 mg, 0.15 mmol, 1.5 equiv.), DIPEA (50 µL, 0.29 mmol, 3 equiv.), and DMF (0.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 10% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (18 mg, 55%).

TLC (10% EtOAc/CH_2Cl_2): R_f = 0.34 stained by $KMnO_4$.

υ_{max} (film): 3332 (br.), 2960, 2878, 2861, 1740, 1662, 1630, 1508, 1223, 1146 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 – 6.48 (m, 1H), 6.44 (s, 1H), 4.86 – 4.71 (m, 1H), 3.80 (s, 3H), 3.22 – 3.11 (m, 1H), 2.52 – 2.23 (m, 4H), 2.22 – 2.11 (m, 1H), 1.95 – 1.83 (m, 1H), 1.67 – 1.33 (m, 9H), 1.13 – 1.00 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H).

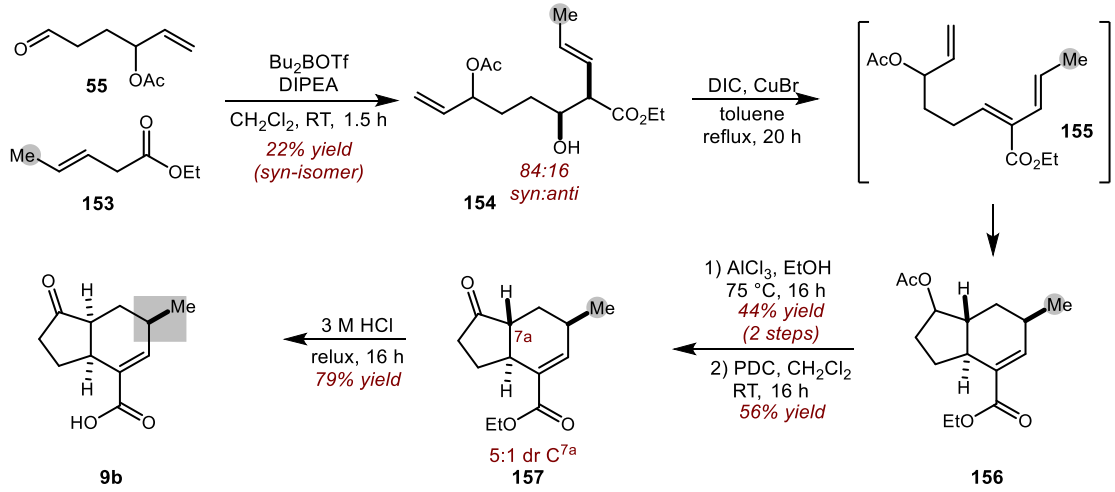
Experimental

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 220.1, 170.1, 170.0, 168.0, 167.9, 138.0, 137.9, 135.4, 135.3, 96.6 – 94.6 (m), 58.9 – 58.6 (m), 52.67, 46.58, 38.25, 37.57, 37.49, 36.35, 28.23, 27.98, 27.96, 26.15, 25.2 – 24.7 (m), 11.48.

^{19}F NMR (471 MHz, $CDCl_3$): δ −148.82 – −149.18 (m).

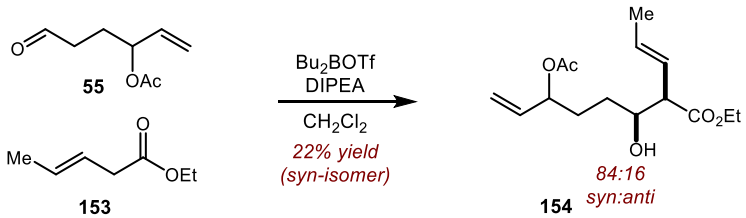
HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}FNO_4$) requires *m/z* 340.1919, found *m/z* 340.1921.

6.6 Synthesis of Compound 9b (Scheme 44).



6.6.1 Procedures and Characterisation of Compound 9b Synthesis.

Compound 154.



Experimental

Prepared according to General Procedure C using ethyl (*E*)-pent-3-enoate (**153**) (265 mg, 2.07 mmol, 1.3 equiv.), DIPEA (0.4 mL, 2.30 mmol, 1.5 equiv.), dibutylboryltrifilate solution (1 M in CH_2Cl_2) (2.10 mL, 2.10 mmol, 1.3 equiv.), compound **55** (250 mg, 1.60 mmol, 1 equiv.), CH_2Cl_2 (7 mL), potassium buffer solution (pH 7.4, 3 mL), MeOH (5 mL) and H_2O_2 (30 % solution, 1.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure C (silica gel, 15-20% EtOAc/petroleum ether) to afford the title compound as a colourless oil (101 mg, 22% (^{1}H NMR yield)). (*syn*:*anti* = 84:16, isolated).

Product contains 35% alkene isomerisation impurity. Data reported of products resulting from reaction carried out at – 78 °C to where isomerisation does not take place.[68]

TLC (30% EtOAc/petroleum ether): R_f = 0.64 stained by $KMnO_4$.

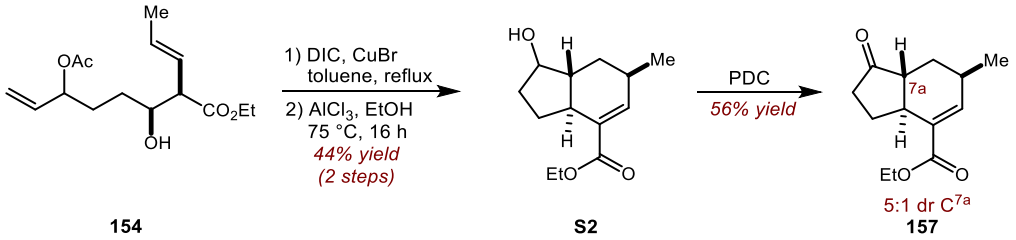
υ_{max} (neat): 3522 (br.), 2954, 1730, 1370, 1235, 1176, 1021, 969 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 – 5.72 (m, 1H), 5.72 – 5.62 (m, 1H), 5.58 – 5.50 (m, 1H), 5.29 – 5.14 (m, 3H), 4.21 – 4.10 (m, 2H), 3.87 – 3.81 (m, 1H), 2.97 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.67 (br. s, 1H), 2.05 (s, 3H), 1.89 – 1.79 (m, 1H), 1.74 (d, *J* = 6.4 Hz, 3H), 1.71 – 1.61 (m, 1H), 1.54 – 1.37 (m, 2H), 1.30 – 1.22 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 170.5, 136.5, 136.4, 132.0, 124.3, 117.0, 116.9, 74.9, 74.5, 71.4, 71.1, 61.0, 55.0, 55.0, 30.5, 30.3, 29.7, 29.5, 21.4, 21.3, 18.3, 14.3.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{15}H_{24}O_5Na$) requires *m/z* 307.1516, found *m/z* 307.1513.

Compound 157.



154 **S2** **157**

Intermediate **S2** prepared according to General Procedure D using compound **154** (880 mg, 3.09 mmol, 1 equiv. (65% purity)), CuBr (44 mg, 0.31 mmol, 0.1 equiv.), DIC (0.73 mL, 4.66 mmol, 1.5 equiv.), and toluene (25 mL). After 20 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 10% EtOAc/petroleum ether) to afford a colourless oil (**156**) (838 mg, 3.15 mmol) which was further reacted according to General Procedure D using $AlCl_3$ (420 mg, 3.15 mmol, 1 equiv.) and EtOH (60 ml). After 16 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 20% EtOAc/petroleum ether) to afford compound **S2** as a colourless oil and a mixture of diastereoisomers which was not characterised. (199 mg, 44% based on 65% purity of starting material).
Compound **157** was prepared according to General Procedure E using compound **S2** (171 mg, 0.76 mmol, 1 equiv.), PDC (430 mg, 1.14 mmol, 1.5 equiv.) and CH_2Cl_2 (5 ml). After 16 h the reaction was subjected to purification outlined in General Procedure E (silica gel, 10% EtOAc/petroleum ether) to afford the title compound as a colourless oil (95 mg, 56% (5:1 dr C^{7a})).

TLC (10% EtOAc/petroleum ether): R_f = 0.26 stained by $KMnO_4$.

υ_{max} (neat): 3375, 2957, 2874, 1736, 1707, 1240, 1211, 1091, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.84 – 6.80 (m, 1H), 4.31 – 4.13 (m, 2H), 2.76 – 2.63 (m, 2H), 2.51 – 2.30 (m, 2H), 2.29 – 2.17 (m, 1H), 2.01 – 1.85 (m, 2H), 1.64 – 1.51 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 7.3 Hz, 3H).

Experimental

Major *trans*-isomer:

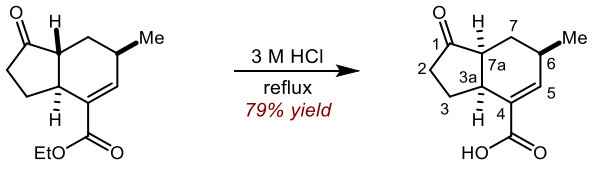
^{13}C NMR (101 MHz, $CDCl_3$): δ 217.0, 166.7, 146.3, 132.6, 60.5, 50.6, 40.9, 38.4, 31.5, 27.5, 26.2, 21.0, 14.5.

Minor *cis*-isomer:

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.2, 60.6, 47.0, 38.3, 36.1, 31.3, 28.6, 28.3, 20.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}O_3$) requires *m/z* 223.1334 found *m/z* 223.1345.

Compound 9b.



157 **9b**

Prepared according to General Procedure F using compound **157** (83 mg, 0.37 mmol, 1 equiv.) and 3 M HCl (12 mL). After 16 h the reaction was subjected to purification outlined in General Procedure F (silica gel, 40-70% EtOAc/petroleum ether) to afford the tile compound as a white solid (57 mg, 79%).

TLC (30% EtOAc/petroleum ether): R_f = 0.15 stained by $KMnO_4$.

υ_{max} (neat): 2947 (br.), 2641 (br.), 2521 (br.), 1730, 1674, 1626, 1269, 1136, 1057 cm^{-1}.

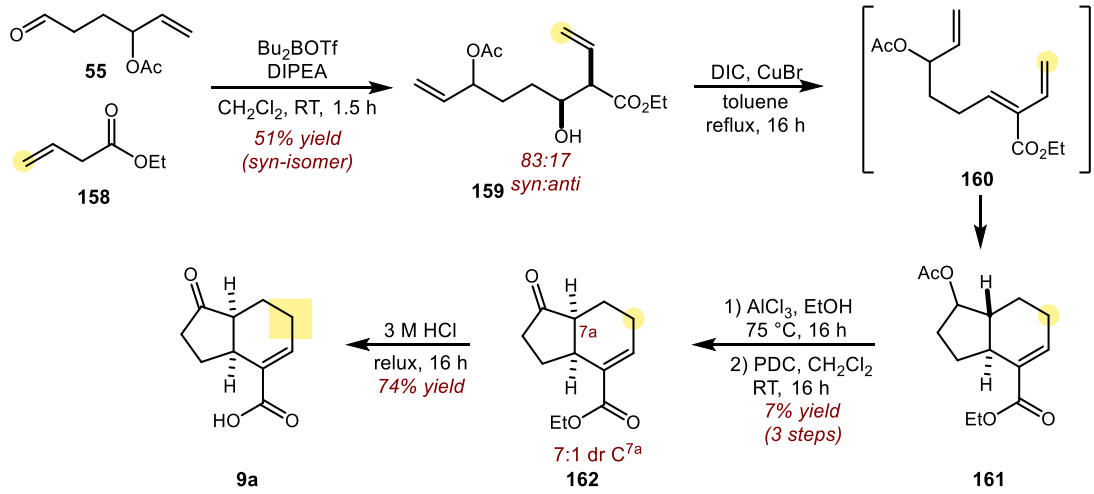
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, H^5), 3.12 – 3.03 (m, 1H, H^{3a}), 2.61 (dt, *J* = 12.9, 7.7 Hz, 1H, H^3), 2.47 – 2.24 (m, 4H, H^2, H^6, H^{7a}), 1.87 (dt, *J* = 12.9, 4.8 Hz, 1H, H^7), 1.68 – 1.54 (m, 1H, $H^{3'}$), 1.14 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.12 – 1.02 (m, 1H, $H^{7'}$). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2 (C^1), 172.0 (CO_2H), 148.2 (C^5), 130.7 (C^4), 46.9 (*C*H), 38.3 (C^2), 35.8 (*C*H), 31.5 (C^6), 28.4 ($C^{3/7}$), 28.2 ($C^{3/7}$), 20.5 (CH_3).

HRMS: exact mass calculated for $[M-H]^-$ ($C_{11}H_{13}O_3$) requires *m/z* 193.0870 found *m/z* 193.0872.

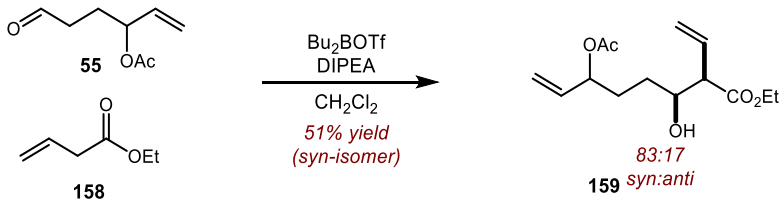
The spectral data were consistent with those previously reported in the literature.[44]

6.7 Synthesis of Compound 9a (Scheme 45).



6.7.1 Procedures and Characterisation of Compound 9a Synthesis.

Compound 159.



Prepared according to General Procedure C using ethyl but-3-enoate (1.50 g, 13.14 mmol, 1.3 equiv.), DIPEA (2.3 mL, 13.20 mmol, 1.5 equiv.), dibutylboryltrifilate solution (1 M in CH_2Cl_2) (13.14 mL, 13.14 mmol, 1.3 equiv.), compound **55** (1.37 g,

8.77 mmol, 1 equiv.), CH_2Cl_2 (50 mL), potassium buffer solution (pH 7.4, 17 mL), MeOH (25 mL) and H_2O_2 (30 % solution, 9 mL). After 16 h the reaction was subjected to purification outlined in General Procedure C (silica gel, 15-40% EtOAc/petroleum ether) to afford the title compound as a colourless oil (1.46 g, 51% (^{1}H NMR yield), 83:17 *syn/anti* as inseparable *syn/anti* diastereoisomers).

TLC (30% EtOAc/petroleum ether): R_f = 0.44 stained by $KMnO_4$.

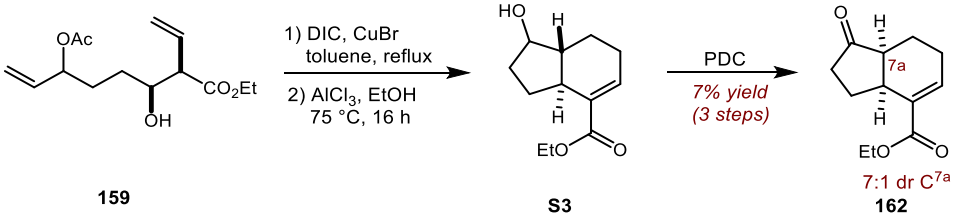
υ_{max} (neat): 3525 (br.), 2978, 2935, 2867, 1729, 1238 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 – 5.86 (m, 1H), 5.81 – 5.71 (m, 1H), 5.34 – 5.14 (m, 5H), 4.22 – 4.13 (m, 2H), 3.94 – 3.88 (m, 1H), 3.03 (dd, *J* = 9.2, 4.5 Hz, 1H), 2.05 (s, 3H), 1.90 – 1.80 (m, 1H), 1.73 – 1.60 (m, 1H), 1.59 – 1.35 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 173.3, 170.5, 136.4, 136.4, 131.7, 120.8, 117.1, 117.0, 74.8, 74.4, 71.2, 70.9, 61.2, 56.0, 55.9, 30.5, 30.3, 29.7, 29.5, 21.3, 14.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}O_5$) requires *m/z* 271.1540, found *m/z* 271.1541.

Compound 162.



159 **S3** **162**

Intermediate **S3** prepared according to General Procedure D using compound **159** (1.45 g, 5.42 mmol, 1 equiv.), CuBr (78 mg, 0.54 mmol, 0.1 equiv.), DIC (1.27 mL, 8.11 mmol, 1.5 equiv.) and toluene (40 mL). After 16 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 10% EtOAc/petroleum ether)

to afford a colourless oil (**161**) (1.11 g, 4.16 mmol) which was further reacted according to General Procedure D using $AlCl_3$ (555 mg, 4.16 mmol, 1 equiv.) and EtOH (65 ml). After 16 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 30% EtOAc/petroleum ether) to afford a colourless oil (**S3**) as two separable diastereoisomers (163 g, 0.78 mmol) which were not characterised.
Compound **162** was prepared according to General Procedure E using **S3** (163 mg, 0.78 mmol, 1 equiv.), PDC (437 mg, 1.16 mmol, 1.5 equiv.) and CH_2Cl_2 (5 ml). After 16 h the reaction was subjected to purification outlined in General Procedure E (silica gel, 10% EtOAc/petroleum ether) to afford the title compound as a colourless oil (83 mg, 7% (3 steps) 7:1 dr C^{7a})

TLC (10% EtOAc/petroleum ether): R_f = 0.16 stained by $KMnO_4$.

υ_{max} (neat): 3362 (br.), 2978, 2938, 1736, 1705, 1248, 1092, 1057 cm^{-1}.

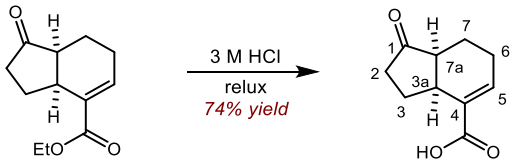
^1H NMR (500 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 3.9, 3.3 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.20 – 3.13 (m, 1H), 2.45 – 2.29 (m, 2H), 2.25 – 2.05 (m, 4H), 1.83 – 1.74 (m, 1H), 1.70 – 1.61 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

Major *cis*-isomer:
^{13}C NMR (101 MHz, $CDCl_3$): δ 216.0, 166.8, 140.23, 131.9, 60.4, 46.7, 37.2, 35.8, 27.5, 24.0, 19.6, 14.3.

Minor *trans*-isomer:
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 141.2, 133.4, 60.4, 53.9, 40.3, 37.9, 27.1, 26.2, 20.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_3$) requires *m/z* 209.1178, found *m/z* 209.1176.

Compound 9a.



162 **9a**

Prepared according to General Procedure F using compound **162** (159 mg, 0.88 mmol) and 3 M HCl (20 mL). After 16 h the reaction was subjected to purification outlined in General Procedure F (silica gel, 30-70% EtOAc/petroleum ether) to afford a white solid, which was washed with minimal petroleum ether to afford the title compound as a white solid (102 mg, 74%).

TLC (30% EtOAc/petroleum ether): R_f = 0.20 stained by $KMnO_4$.

υ_{max} (neat): 2938, 2895, 2627, 2532, 1736, 1661, 1632, 1427, 1283, 930 cm^{-1}.

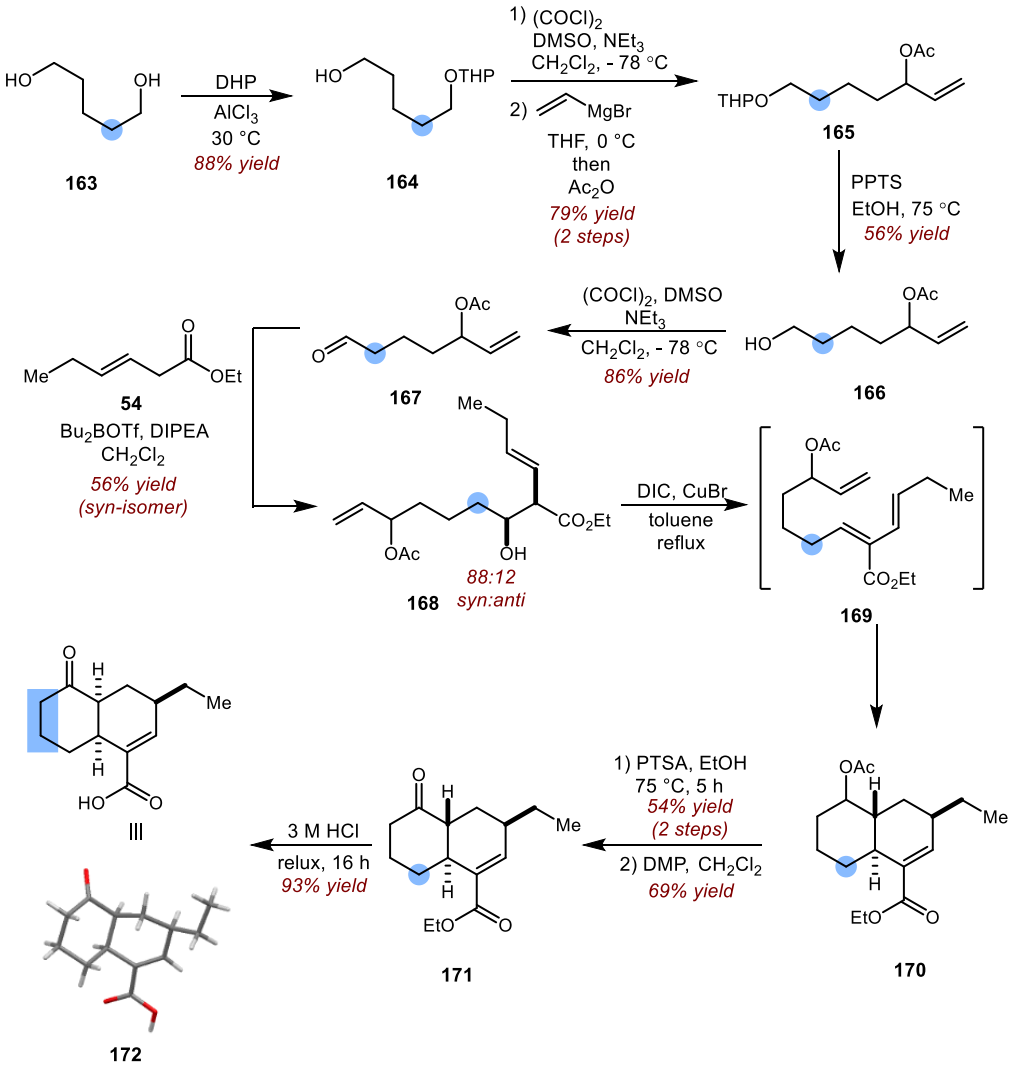
^1H NMR (400 MHz, $CDCl_3$): δ 11.75 (br. s, 1H, CO_2H), 7.24 (td, *J* = 4.1, 1.1 Hz, 1H, H^5), 3.25 – 3.15 (m, 1H, H^{3a}), 2.50 – 2.36 (m, 2H, H^3, H^{7a}), 2.34 – 2.19 (m, 4H, H^2, H^6), 1.92 – 1.82 (m, 1H, $H^{3'}$), 1.78 – 1.66 (m, 2H, H^7).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.6 (C^1), 172.3 (CO_2H), 143.6 (C^5), 131.3 (C^4), 46.7 (C^{7a}), 37.3 (CH_2), 35.7 (C^{3a}), 27.5 (C^3), 24.4 (CH_2), 19.6 (C^7).

HRMS: exact mass calculated for $[M-H]^-$ ($C_{10}H_{11}O_3$) requires *m/z* 179.0714, found *m/z* 179.0716.

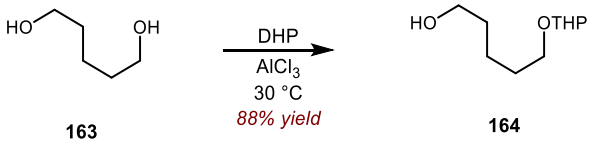
The spectral data were consistent with those previously reported in the literature.[44]

6.8 Synthesis of Compound 172 (Scheme 47).



6.8.1 Procedures and Characterisation of Compound 172 Synthesis.

Compound 164.



Experimental

To a round bottom flask charged with 1,5-pentane diol (31 g, 295.86 mmol, 5 equiv.) was added anhydrous aluminium trichloride (79 mg, 0.59 mmol, 1 mol%) followed by dropwise addition of DHP (5.42 mL, 59.41 mmol, 1 equiv.). The resulting mixture was warmed to 30 °C and maintained at this temperature for 1 h, before being allowed to cool to room temperature. The colourless, crude material was loaded directly in a solution of 30% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30-60% EtOAc/petroleum ether to afford the title compound as a colourless liquid (9.90 g, 88%).

TLC (40% EtOAc/petroleum ether): R_f = 0.57 stained by $KMnO_4$

υ_{max} (neat): 3404 (br.), 2936, 2865, 1137, 1120, 1076, 1021 cm^{-1}.

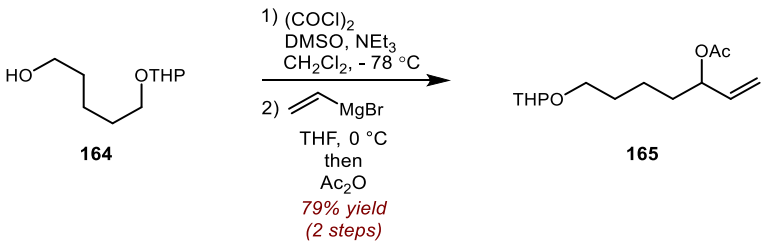
^1H NMR (500 MHz, $CDCl_3$): δ 4.55 – 4.52 (m, 1H), 3.86 – 3.79 (m, 1H), 3.71 (dt, *J* = 9.6, 6.7 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.49 – 3.43 (m, 1H), 3.36 (dt, *J* = 9.6, 6.5 Hz, 1H), 2.05 (br. s, 1H), 1.83 – 1.74 (m, 1H), 1.71 – 1.63 (m, 1H), 1.63 – 1.45 (m, 8H), 1.44 – 1.37 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 99.0, 67.6, 62.7, 62.4, 32.6, 30.8, 29.5, 25.5, 22.5, 19.7.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{10}H_{20}O_3Na$) requires *m/z* 211.1305, found *m/z* 211.1302.

The spectral data were consistent with those previously reported in the literature.[125]

Compound 165.



Compound **165** was prepared according to General Procedure B using oxalyl chloride (6.68 mL, 78.95 mmol, 1.5 equiv.), DMSO (11.21 mL, 157.83 mmol, 3 equiv.), compound **164** (9.90 g, 52.58 mmol, 1 equiv.), triethylamine (29 mL, 208.06 mmol, 4 equiv.), and CH_2Cl_2 (140 mL). After 2 h the reaction was subjected to purification outlined in General Procedure B (silica gel, 20% EtOAc/petroleum ether) to afford the corresponding aldehyde as a pale yellow liquid (9.55 g, 51.28 mmol) which was used immediately.

Vinylmagnesium bromide (1 M in THF, 56.4 mL, 56.40 mmol, 1.1 equiv.) was added dropwise to a stirring solution of the aldehyde (9.55 g, 51.28 mmol) in THF (100 mL) at 0 °C in a three-necked flask under an atmosphere of nitrogen. The resulting solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by dropwise addition of acetic anhydride (9.7 mL, 102.62 mmol, 2 equiv.) at room temperature and stirred for a further 16 h. The yellow reaction was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale orange oil. The crude material was loaded in a solution of CH_2Cl_2, and purified by flash silica column chromatography, eluent 10% EtOAc/petroleum ether to afford the title compound (10.66 g, 79% (2 steps)) as a colourless liquid.

TLC (20% EtOAc/petroleum ether): R_f = 0.74 stained by $KMnO_4$.

υ_{max} (neat): 2940, 2870, 1736, 1370, 1236, 1120 cm^{-1}.

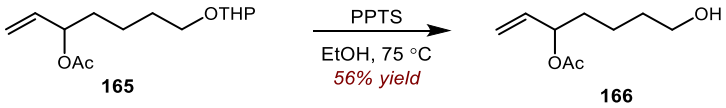
Experimental

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddd, *J* = 17.1, 10.5, 6.3 Hz, 1H), 5.26 – 5.14 (m, 3H), 4.58 – 4.54 (m, 1H), 3.89 – 3.82 (m, 1H), 3.73 (dtd, *J* = 9.4, 6.7, 1.0 Hz, 1H), 3.53 – 3.46 (m, 1H), 3.38 (dt, *J* = 9.5, 6.7 Hz, 1H), 2.06 (s, 3H), 1.86 – 1.76 (m, 1H), 1.74 – 1.48 (m, 9H), 1.46 – 1.35 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 136.6, 116.8, 99.0, 74.9, 67.4, 62.5, 34.1, 30.9, 29.6, 25.6, 22.0, 21.4, 19.8.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{14}H_{24}O_4Na$) requires *m/z* 279.1567, found *m/z* 279.1563.

Compound 166.



To a round bottom flask was added compound **165** (10.66 g, 41.59 mmol, 1 equiv.) and EtOH (160 mL). PPTS (1.05 g, 4.18 mmol, 0.1 equiv.) was added portionwise and the resulting solution was brought to 60 °C for 4 h. The reaction was allowed to cool to room temperature and was then evaporated to afford a pale orange oil. The crude material was loaded directly in a solution of 30% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30-50% EtOAc/petroleum ether to afford the title compound (4.02 g, 56%) as a colourless liquid.

TLC (30% EtOAc/petroleum ether): R_f = 0.18 stained by $KMnO_4$.

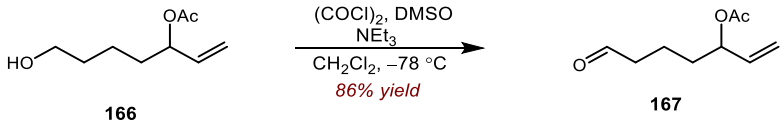
υ_{max} (neat): 3407 (br.), 2936, 2865, 1735, 1371, 1236, 1019 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddd, *J* = 17.2, 10.5, 6.4 Hz, 1H), 5.26 – 5.15 (m, 3H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.06 (s, 3H), 1.72 – 1.55 (m, 5H), 1.47 – 1.34 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.6, 136.5, 116.9, 74.8, 62.9, 34.1, 32.5, 21.5, 21.4.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_9H_{16}O_3Na$) requires *m/z* 195.0992, found *m/z* 195.0989.

Compound 167.



166 **167**

Prepared according to General Procedure B using oxalyl chloride (2.96 mL, 34.98 mmol, 1.5 equiv.), DMSO (4.97 mL, 69.97 mol, 3 equiv.), compound **166** (4.02 g, 23.34 mmol, 1 equiv.), triethylamine (13 mL, 93.27 mmol, 4 equiv.) and CH_2Cl_2 (55 mL). After 2 h the reaction was subjected to purification outlined in General Procedure B (silica gel, 20% EtOAc/petroleum ether) to afford the title compound as a pale yellow liquid (3.40 g, 86%).

TLC (20% EtOAc/petroleum ether): R_f = 0.41 stained by $KMnO_4$.

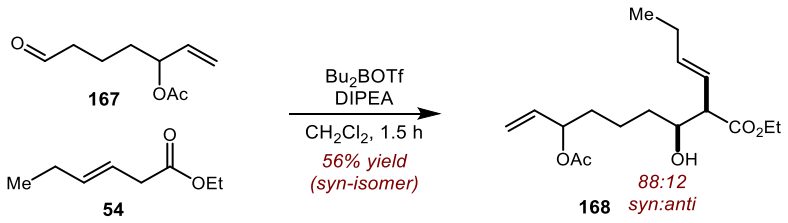
υ_{max} (neat): 2935 (br.), 1734, 1372, 1238, 1022 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.76 (t, *J* = 1.5 Hz, 1H), 5.80 – 5.72 (m, 1H), 5.27 – 5.16 (m, 3H), 2.50 – 2.43 (m, 2H), 2.06 (s, 3H), 1.72 – 1.59 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 202.0, 170.4, 136.2, 117.2, 74.3, 43.6, 33.6, 21.3, 17.7.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_9H_{18}O_3N$) requires *m/z* 188.1281, found *m/z* 188.1277.

Compound 168.



Prepared according to General Procedure C using ethyl (*E*)-hex-3-enoate (1.38 ml, 8.70 mmol, 1.3 equiv.), DIPEA (1.73 mL, 9.93 mmol, 1.5 equiv.), Dibutylboryltrifluoromethanesulfonate solution (1 M in CH_2Cl_2) (8.74 mL, 8.74 mmol, 1.3 equiv.), compound **167** (1.15 g, 6.76 mmol, 1 equiv.), CH_2Cl_2 (35 mL), potassium buffer solution (pH 7.4, 15 mL), MeOH (25 mL), and H_2O_2 (30% solution, 8 mL). After 16 h the reaction was subjected to purification outlined in General Procedure C (silica gel, 20% EtOAc/petroleum ether) to afford the title compound as a colourless oil (1.49 g, 56% (yield by ^{1}H NMR analysis)). (*syn*:*anti* = 88:12 isolated).

TLC (30% EtOAc/petroleum ether): R_f = 0.65 stained by $KMnO_4$.

υ_{max} (neat): 3517 (br.), 2937, 2873, 1730, 1370, 1237, 1174, 1020 cm^{-1}.

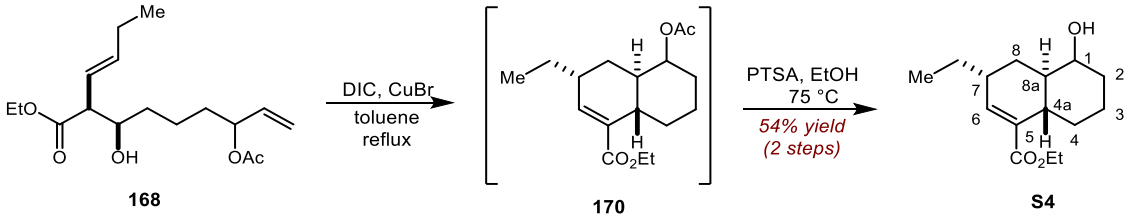
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 – 5.65 (m, 2H), 5.55 – 5.45 (m, 1H), 5.26 – 5.13 (m, 3H), 4.20 – 4.11 (m, 2H), 3.92 – 3.80 (m, 1H), 3.35 (dd, *J* = 10.3, 4.3 Hz, 0.2H (minor)), 2.96 (dd, *J* = 9.2, 4.8 Hz, 0.8H (major)), 2.77 – 2.71 (m, 0.2H (minor)), 2.67 – 2.60 (m, 0.8H (major)), 2.15 – 2.02 (m, 5H), 1.71 – 1.31 (m, 6H), 1.29 – 1.23 (m, 3H), 1.02 – 0.97 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 174.0, 170.5, 138.9, 136.6, 122.2, 116.9, 116.8, 74.8, 71.4, 61.0, 55.1, 55.0, 34.2, 33.9, 25.8, 21.4, 14.3, 13.6. Major signals reported. One signal coincident.

Experimental

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{17}H_{28}O_5Na$) requires *m/z* 335.1829, found *m/z* 335.1827.

Compound S4.



Compound **170** was prepared according to General Procedure D using compound **168** (1.49 g, 4.76 mmol, 1 equiv. (79% purity)), CuBr (74 mg, 0.52 mmol, 10 mol%), DIC (1.19 mL, 7.60 mmol, 1.5 equiv.) and toluene (0.9 mL). After 16 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 5% EtOAc/petroleum ether) to afford a pale yellow oil (**170**) (1.11 g, 3.77 mmol).

Compound **S4** was prepared according to General Procedure D using compound **170** (1.11 g, 3.77 mmol, 1 equiv.), PTSA (mono-hydrate) (1.07 g, 5.63 mmol, 1.5 equiv.), and EtOH (35 mL). After 6 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 20% EtOAc/petroleum ether) to afford the title compound as a colourless liquid (511 mg, 54% based on 79% purity of starting material (2 steps)). Isolated as a single diastereoisomer at C^1, the stereochemistry of which was not determined.

TLC (20% EtOAc/petroleum ether): R_f = 0.19 stained by $KMnO_4$.

υ_{max} (neat): 3377 (br.), 2972, 2932, 2662, 1711, 1447, 1245, 1045 cm^{-1}.

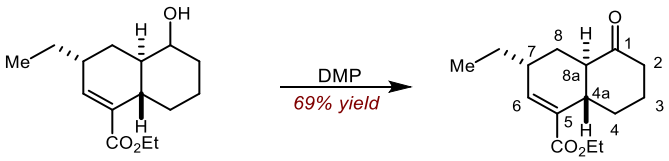
^1H NMR (400 MHz, $CDCl_3$): δ 6.72 – 6.67 (m, 1H), 4.22 – 4.08 (m, 2H), 3.36 – 3.28 (m, 1H), 2.25 – 2.12 (m, 2H), 2.11 – 1.95 (m, 3H), 1.85 – 1.70 (m, 1H), 1.59 – 1.11 (m, 10H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.88 – 0.76 (m, 1H).

Experimental

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3, 142.0, 134.3, 73.6, 60.3, 43.7, 40.2, 36.7, 36.2, 29.6, 27.5, 27.4, 24.3, 14.4, 12.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{25}O_3$) requires *m/z* 253.1798, found *m/z* 253.1799.

Compound 171.



170 **171**

To a round bottom flask charged with compound **170** (511 mg, 2.02 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (20 mL) was added DMP (1.29 g, 3.04 mmol, 1.5 equiv.) in one portion under an atmosphere of nitrogen. The reaction was stirred at room temperature for 16 h before 2 M NaOH (10 mL) was added and the layers stirred vigorously for 10 minutes. The layers were separated and the aqueous further extracted with CH_2Cl_2 (2 x 20 ml). The organics were combined, washed with brine (20 ml), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of 10% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 10% EtOAc/petroleum ether to afford the title compound as a colourless oil (350 mg, 69%).

TLC (10% EtOAc/petroleum ether): R_f = 0.36 stained by $KMnO_4$.

υ_{max} (neat): 2958, 2928, 2863, 1706, 1260, 1234, 1082 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (d, *J* = 5.2 Hz, 1H, H^6), 4.26 – 4.14 (m, 2H, $CO_2CH_2CH_3$), 2.53 (dd, *J* = 13.0, 3.0 Hz, 1H, H^4), 2.48 – 2.32 (m, 3H, H^2, H^{4a}), 2.30 – 2.20 (m, 2H, H^7, H^{8a}), 2.16 – 2.07 (m, 1H, H^3), 1.95 (d, *J* = 13.9 Hz, 1H, H^8), 1.84 –

1.72 (m, 1H, $H^{3'}$), 1.55 – 1.43 (m, 2H, $H^{8'}$, CH_3CH_2), 1.37 – 1.25 (m, 5H, H4', CH_3CH_2', $CO_2CH_2CH_3$), 0.99 (t, *J* = 7.4 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.9 (C^1), 167.5 (CO_2Et), 142.9 (C^6), 133.7 (C^5), 60.5 ($CO_2CH_2CH_3$), 48.4 ($C^{7/8a}$), 42.8 (C^{4a}), 41.6 (C^2), 36.4 ($C^{7/8a}$), 29.7 (C^4), 27.6 (CH_2CH_3), 26.1 (C^3), 24.3 (C^8), 14.4 ($CO_2CH_2CH_3$), 12.5 (CH_2CH_3).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}O_3$) requires *m/z* 251.1642, found *m/z* 251.1647.

Compound 172.

171 **172**

Prepared according to General Procedure F using compound **171** (350 mg, 1.57 mmol) and 3 M HCl (44 mL). After 20 h the reaction was subjected to purification outlined in General Procedure F (silica gel, 30-50% EtOAc/petroleum ether) to afford the title compound as a pale orange solid (288 mg, 93%).

TLC (30% EtOAc/petroleum ether): R_f = 0.08 stained by $KMnO_4$.

m.p.: 114-116 °C. Crystallised by vapour diffusion (EtOAc/petroleum ether).

υ_{max} (neat): 2936, 2872, 2635, 2524, 1701, 1676, 1634, 1281cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 11.51 (br. s, 1H), 7.05 (s, 1H), 2.91 – 2.80 (m, 1H), 2.57 – 2.46 (m, 1H), 2.45 – 2.24 (m, 3H), 2.20 – 2.08 (m, 1H), 2.06 – 1.94 (m, 1H), 1.81 – 1.61 (m, 2H), 1.61 – 1.36 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 214.4, 172.2, 146.6, 132.2, 50.1, 38.6, 38.5, 36.6, 27.9, 27.6, 27.5, 24.9, 11.3.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{13}H_{17}O_3$) requires *m/z* 221.1183, found *m/z* 211.1185.

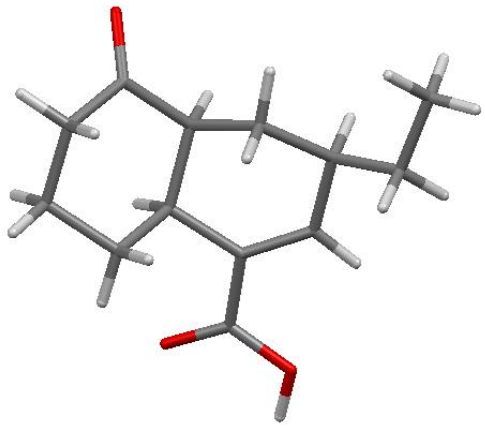
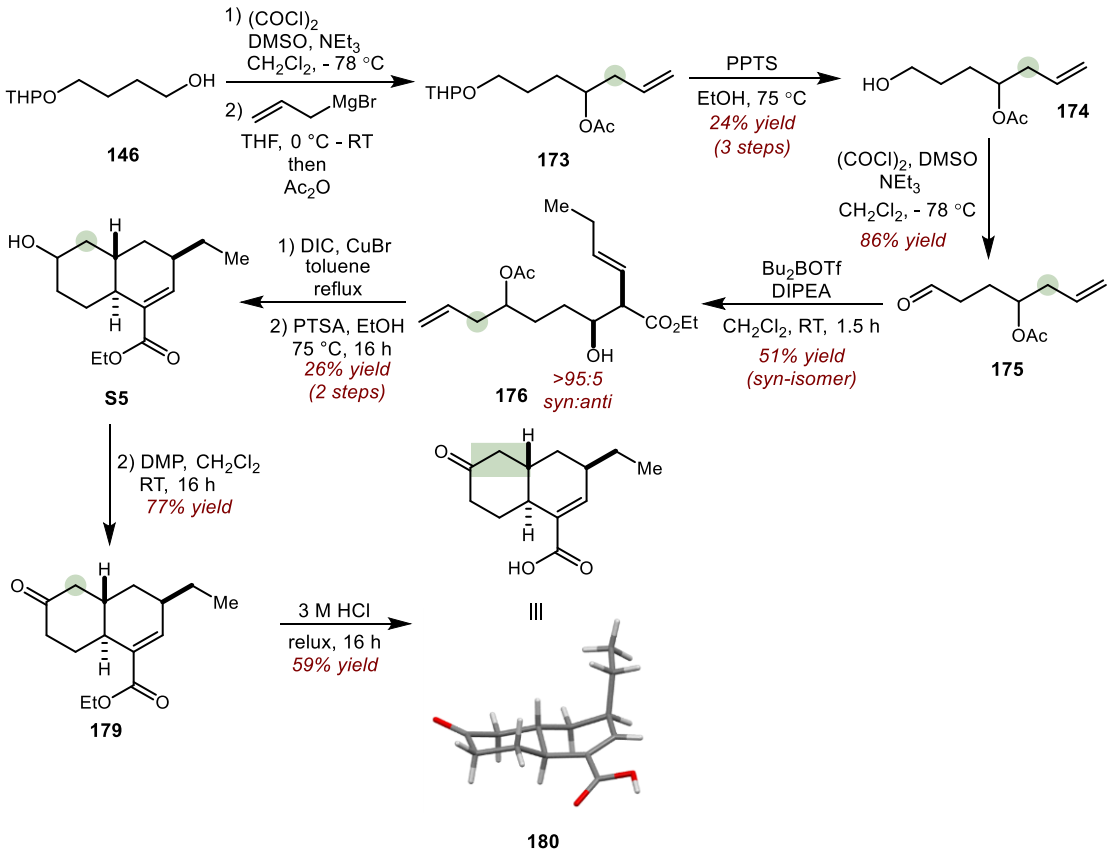


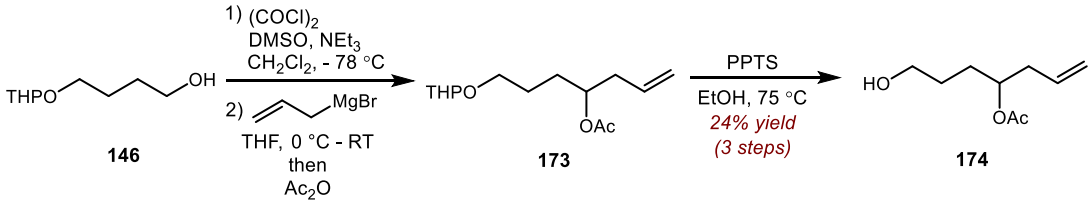
Table 1. Crystal data and structure refinement for watson_ml66.

6.9 Synthesis of Compound 180 (Scheme 48/49).



6.9.1 Synthesis and Characterisation of compound 180 Synthesis.

Compound 174.



Experimental

Compound **174** was prepared according to General Procedure B using DMSO (5.82 mL, 81.94 mmol, 3 equiv.), oxalyl chloride (3.51 mL, 40.93 mmol, 1.5 equiv.), compound **146** (4.76 g, 27.32 mmol, 1 equiv.), triethylamine (15.24 mL, 109.34 mmol, 4 equiv.), and CH_2Cl_2 (55 mL). After 2 h the reaction was subjected to purification outlined in General Procedure B (silica gel, 10-30% EtOAc/petroleum ether) to afford a pale yellow oil which was dissolved in THF (50 mL) under an atmosphere of nitrogen and allylmagnesium bromide (1 M in Et_2O) (30.0 mL, 30.00 mmol, 1.1 equiv.) added dropwise at 0 °C over 5 minutes. The resulting solution was allowed to rise to room temperature and stirred for 16 h. The reaction was slowly quenched with water (70 mL) and stirred vigorously for 10 minutes. The organics were extracted with EtOAc (3 x 30 mL), washed with brine (30 mL) and dried over Na_2SO_4, filtered, and evaporated to afford a yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 40% EtOAc/petroleum ether to afford compound **173** as a colourless oil (3.86 g, 15.06 mmol) which was used without further purification.

To a round bottom flask was added compound **173** (3.86 g, 15.06 mmol, 1 equiv.) and EtOH (30 mL). PPTS (379 mg, 1.51 mmol, 0.1 equiv.) was added portionwise and the resulting solution was brought to 60 °C for 4 h. The reaction was allowed to cool to room temperature and was then evaporated to afford a pale orange oil. The crude material was loaded directly in a solution of 30% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30-50% EtOAc/petroleum ether to afford the title compound (1.13 g, 24% (3 steps)) as a colourless liquid.

TLC (60% EtOAc/petroleum ether): R_f = 0.12 stained by $KMnO_4$.

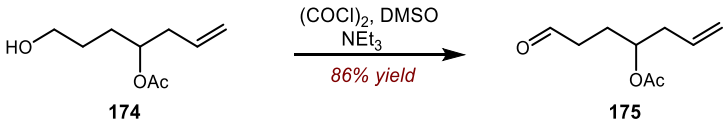
υ_{max} (neat): 3434 (br.), 2945, 2870, 1732, 1716, 1376, 1238, 1024 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.11 – 5.03 (m, 2H), 4.98 – 4.90 (m, 1H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.37 – 2.26 (m, 2H), 2.03 (s, 3H), 1.71 – 1.53 (m, 4H). O*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 133.7, 117.9, 73.2, 62.7, 38.8, 30.1, 28.6, 21.3.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_9H_{16}O_3Na$) requires *m/z* 195.0992, found *m/z* 195.0991.

Compound 175.



174 **175**

Prepared according to General Procedure B using oxalyl chloride (0.24 mL, 2.84 mmol, 1.5 equiv.), DMSO (0.40 mL, 5.63 mmol, 3 equiv.), compound **174** (324 mg, 1.88 mmol, 1 equiv.), triethylamine (1.05 mL, 7.53 mmol, 4 equiv.) and CH_2Cl_2 (5 mL). After 2 h the reaction was subjected to purification outlined in General Procedure B (silica gel, 40% EtOAc/petroleum ether) to afford the title compound as a pale yellow oil (275 mg, 86%).

TLC (40% Et_2O/petroleum ether): R_f = 0.50 stained by $KMnO_4$.

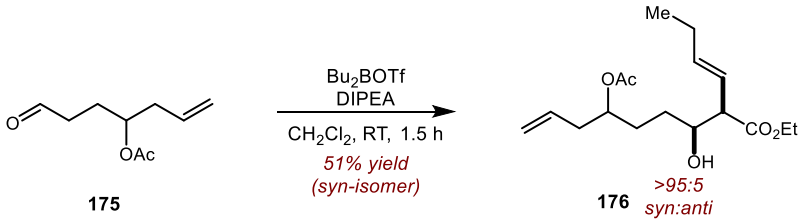
υ_{max} (neat): 3366, 2963, 1727, 1374, 1234, 1020, 916 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.3 Hz, 1H), 5.73 (ddt, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.13 – 5.05 (m, 2H), 4.96 – 4.88 (m, 1H), 2.48 (td, *J* = 7.4, 1.3 Hz, 2H), 2.35 – 2.29 (m, 2H), 2.03 (s, 3H), 2.00 – 1.90 (m, 1H), 1.90 – 1.79 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5, 170.8, 133.2, 118.4, 72.5, 40.1, 38.8, 26.0, 21.2.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_9H_{18}O_3N$) requires *m/z* 188.1281, found *m/z* 188.1281.

Compound 176.



Prepared according to General Procedure B using ethyl (*E*)-hex-3-enoate (1.21 mL, 7.62 mmol, 1.3 equiv.), DIPEA (1.53 mL, 8.78 mmol, 1.5 equiv.), dibutylboryltrifilate solution (1 M in CH_2Cl_2) (7.64 mL, 7.64 mmol, 1.3 equiv.), and compound **175** (1.00 g, 5.88 mmol, 1 equiv.), CH_2Cl_2 (30 mL), potassium buffer solution (pH 7.4, 13 mL), MeOH (20 mL), and H_2O_2 (30 % solution, 6.9 mL). After 16 h the reaction was subjected to purification outlined in General Procedure B (silica gel, 15-20% EtOAc/petroleum ether) to afford the title compound as a colourless oil (1.21 g, 51% (^{1}H NMR yield). > 95:5 *syn:anti* ^{1}H NMR.

TLC (20% EtOAc/petroleum ether): R_f = 0.42 stained by $KMnO_4$.

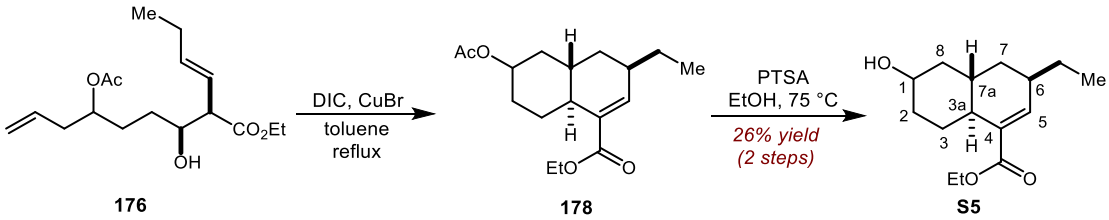
υ_{max} (neat): 3502, 2958, 2930, 2870, 1727, 1372, 1236, 1022 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 – 5.64 (m, 2H), 5.53 – 5.44 (m, 1H), 5.09 – 5.02 (m, 2H), 4.95 – 4.86 (m, 1H), 4.19 – 4.10 (m, 2H), 3.91 – 3.78 (m, 1H), 3.37 – 3.31 (m, 0.2H (minor)), 2.98 – 2.91 (m, 0.8H (major)), 2.83 (br. s, 0.2H (minor)), 2.74 (br. s, 0.8H (major)), 2.34 – 2.24 (m, 2H), 2.12 – 2.04 (m, 2H), 2.04 – 1.98 (m, 3H), 1.83 – 1.67 (m, 1H), 1.65 – 1.31 (m, 3H), 1.30 – 1.20 (m, 3H), 1.01 – 0.95 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.91, 170.88, 138.93, 137.66 (minor), 133.70, 133.66, 122.03, 122.00, 121.63 (minor), 117.88, 73.46, 72.95, 71.64 (minor), 71.52, 71.15 (minor), 71.03, 61.03 (minor), 60.99, 54.89, 54.86, 49.5 (minor), 49.39 (minor), 38.83 (minor), 38.78, 38.74, 30.06 (minor), 30.02 (minor), 29.93, 29.76 (minor), 29.70 (minor), 29.66, 29.62, 25.79, 21.29, 14.25, 14.12 (minor), 13.61.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{29}O_5$) requires *m/z* 313.2010, found *m/z* 313.2009.

Compound S5.



S5 was prepared according to General Procedure D using compound **176** (103 mg, 0.33 mmol, 1 equiv. 78% purity), CuBr (5 mg, 0.03 mmol, 10 mol%), DIC (80 µL, 0.51 mmol, 1.5 equiv.) and toluene (0.1 mL). After 16 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 10% EtOAc/petroleum ether) to afford compound **178** as a colourless oil which was not characterised.

S5 was prepared according to General Procedure D using PTSA (mono-hydrate) (43 mg, 0.23 mmol, 1.2 equiv.), and EtOH (2 mL). After 5 h the reaction was subjected to purification outlined in General Procedure D (silica gel, 30% EtOAc/petroleum ether) to afford the title compound as a colourless oil and as two separable diastereoisomers at C^1 (17 mg, 26% (combined yield)), the relative stereochemistry of which were not confirmed.

Isomer 1:

TLC (30% EtOAc/petroleum ether): R_f = 0.28 stained by $KMnO_4$.

υ_{max} (neat): 3456 (br.), 2960, 2922, 2871, 1708, 1447, 1371, 1262, 1234, 1079, 1026 cm^{-1}.

Experimental

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 – 6.68 (m, 1H), 4.25 – 4.12 (m, 3H), 2.17 – 2.09 (m, 2H), 2.00 – 1.92 (m, 1H), 1.87 – 1.80 (m, 1H), 1.78 – 1.62 (m, 3H), 1.59 – 1.49 (m, 1H), 1.45 – 1.32 (m, 5H), 1.32 – 1.25 (m, *J* = 7.1 Hz, 4H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 142.2, 134.4, 66.8, 60.2, 42.5, 40.3, 37.1, 33.7, 32.8, 29.6, 27.8, 24.1, 14.5, 12.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{25}O_3$) requires *m/z* 253.1798, found *m/z* 253.1801.
Calculated for a mixture of isomer 1 and 2.

Isomer 2:

TLC (30% EtOAc/petroleum ether): R_f = 0.17 stained by $KMnO_4$.

υ_{max} (neat): 3359 (br.), 2968, 2929, 2865, 1708, 1449, 1370, 1247, 1075, 1024 cm^{-1}.

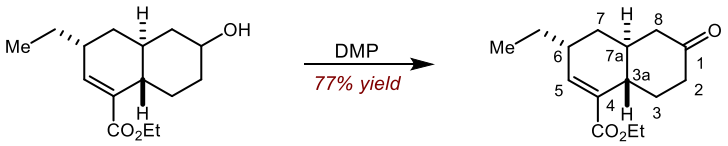
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (dd, *J* = 4.8, 1.8 Hz, 1H), 4.26 – 4.09 (m, 2H), 3.73 – 3.64 (m, 1H), 2.39 –2.32 (m, 1H), 2.19 – 2.12 (m, 1H), 2.09 – 2.02 (m, 1H), 1.97 – 1.89 (m, 2H), 1.58 – 1.43 (m, 5H), 1.43 – 1.32 (m, 2H), 1.32 – 1.24 (m, 3H), 1.23 – 1.11 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.96 – 0.85 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 142.3, 134.1, 70.9, 60.3, 42.6, 41.7, 37.1, 36.1, 34.5, 33.0, 28.1, 27.8, 14.5, 12.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{25}O_3$) requires *m/z* 253.1798, found *m/z* 253.1801.
Calculated for a mixture of isomer 1 and 2.

Compound 179.

Experimental



S5 **179**

To a round bottom flask charged with compound **S5** (17 mg, 0.07 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (0.7 mL) was added DMP (43 mg, 0.10 mmol, 1.5 equiv.) in one portion under an atmosphere of nitrogen. The reaction was stirred at room temperature for 16 h before being diluted with CH_2Cl_2 (5 mL), 2 M NaOH (2 mL) added and the layers stirred vigorously for 10 minutes. The layers were separated and the aqueous further extracted with CH_2Cl_2 (2 x 10 ml). The organics were combined, washed with brine (10 ml), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of 10% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 10% EtOAc/petroleum ether to afford the title compound as a colourless oil (13 mg, 77%).

TLC (10% EtOAc/petroleum ether): R_f = 0.20 stained by $KMnO_4$.

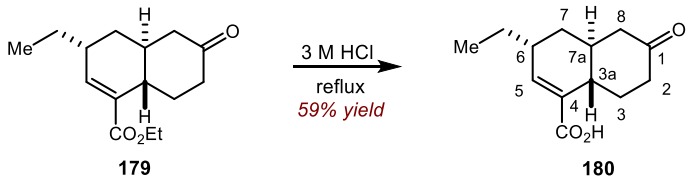
υ_{max} (neat): 3385 (br.), 2972, 2931, 2874, 1707, 1460, 1446, 1265 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 5.2, 2.2 Hz, 1H, H^5), 4.26 – 4.14 (m, 2H, $CO_2CH_2CH_3$), 2.69 – 2.63 (m, 1H, H^3), 2.50 – 2.33 (m, 4H, H^2, H^{3a}, H^7), 2.27 – 2.18 (m, 2H, H^6, $H^{7'}$), 1.75 – 2.18 (m, 1H, H^{7a}), 1.57 – 1.48 (m, 3H, H^8, CH_3CH_2), 1.38 – 1.21 (m, 5H, $H^{3'}$, CH_3CH_2', $CO_2CH_2CH_3$), 0.98 (t, *J* = 7.4 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.8 (*C*O), 167.5 (CO_2Et), 143.0 (C^5), 132.8 (C^4), 60.4 ($CO_2CH_2CH_3$), 48.2 (C^7), 41.5 (C^2), 40.9 (C^{3a}), 36.9 ($C^{6/7a}$), 36.6 ($C^{6/7a}$), 32.9 (C^8), 29.5 (C^3), 27.5 (CH_2CH_3), 14.3 ($CO_2CH_2CH_3$), 12.4 (CH_2CH_3).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}O_3$) requires *m/z* 251.1642, found *m/z* 251.1645.

Compound 180.



179 **180**

Prepared according to General Procedure F using compound **179** (103 mg, 0.41 mmol) and 3 M HCl (12 mL). After 16 h the reaction was subjected to purification outlined in General Procedure F (silica gel, 30% EtOAc/petroleum ether) to afford the desired product as a colourless oil which solidified to a white solid on standing (54 mg, 59%).

TLC (30% EtOAc/petroleum ether): R_f = 0.19 stained by $KMnO_4$.

υ_{max} (neat): 2916 (br.), 2871, 1706, 1676, 1429, 1278 cm^{-1}.

m.p.: 114-116 °C. Crystallised by vapour diffusion (EtOAc/petroleum ether).

^1H NMR (500 MHz, $CDCl_3$): δ 11.44 (br. s, 1H, CO_2H), 7.07 (dd, *J* = 5.2, 2.0 Hz, 1H, H^5), 2.81 – 2.74 (m, 1H, H^3), 2.52 – 2.35 (m, 4H, H^2, H^{3a}, H^7), 2.31 – 2.20 (m, 2H, H^6, $H^{7'}$), 1.78 – 1.66 (m, 1H, H^{7a}), 1.59 – 1.49 (m, 3H, H^8, CH_3CH_2), 1.41 – 1.24 (m, 2H, $H^{3'}$, CH_3CH_2'), 0.99 (t, *J* = 7.4 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.8 (C^1), 172.5 (CO_2H), 146.6 (C^5), 131.8 (C^4), 48.3 (C^7), 41.6 (C^2), 40.7 (C^{3a}), 37.2 (C^6), 36.7 (C^{7a}), 32.9 (C^8), 29.6 (C^3), 27.5 (CH_2CH_3), 12.5 (CH_2CH_3).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}O_3$) requires *m/z* 223.1334, found *m/z* 223.1336.

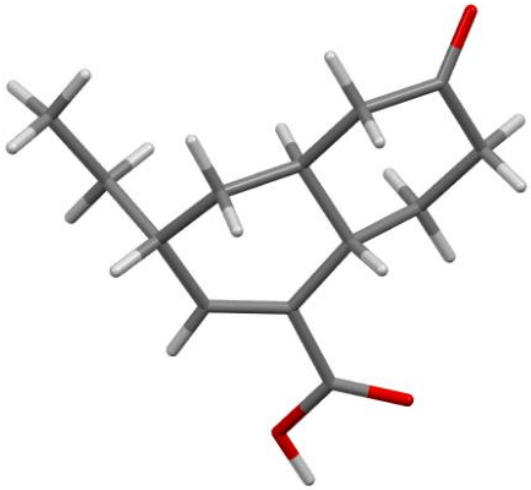
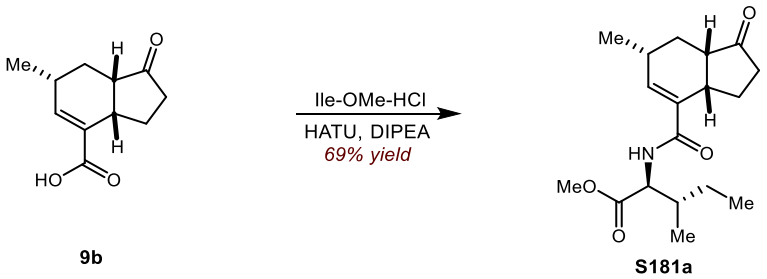


Table 1. Crystal data and structure refinement for watson_mllb04s401monop.

6.10 Core Analogue *L*-Ile-Conjugation (Scheme 50).

Compound S181a.



Prepared according to General Procedure G using compound **9b** (20 mg, 0.10 mmol, 1 equiv.), HATU (51 mg, 0.12 mmol, 1.2 equiv.), *L*-isoleucine methyl ester hydrochloride (28 mg, 0.15 mmol, 1.5 equiv.), DIPEA (60 µL, 0.34 mmol, 3 equiv.), and DMF (0.5 mL). After 16 h the reaction was subjected to the purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a pale yellow oil (23 mg, 69%).

Experimental

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.56 stained by $KMnO_4$ and faintly visible by UV (short wave).

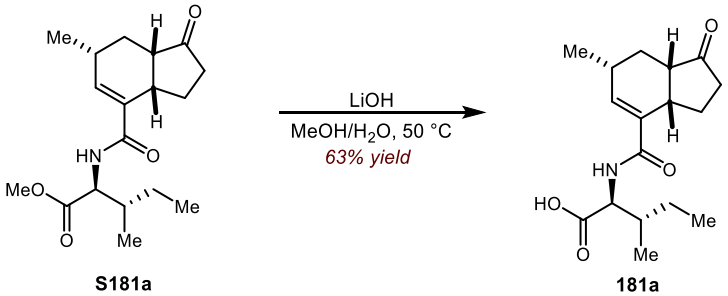
υ_{max} (film): 3346 (br.), 2961, 2933, 2874, 1735, 1659, 1622, 1513, 1199, 1147 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.34 – 6.23 (m, 2H), 4.71 – 4.66 (m, 1H), 3.77 – 3.73 (m, 3H), 3.22 – 3.09 (m, 1H), 2.53 – 2.22 (m, 5H), 1.98 – 1.89(m, 1H), 1.88 – 1.81 (m, 1H), 1.65 – 1.52 (m, 1H), 1.52 – 1.39 (m, 1H), 1.28 – 1.14 (m, 1H), 1.13 – 1.00 (m, 4H), 0.97 – 0.89 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.1, 220.1, 172.9, 167.9, 167.8, 138.1, 138.0, 135.7, 135.6, 56.5, 56.5, 52.3, 46.7, 38.3, 38.3, 38.2, 36.0, 36.0, 30.9, 30.8, 28.7, 28.0, 27.9, 25.5, 25.4, 20.9, 15.7, 15.6, 11.7, 11.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}NO_4$) requires *m/z* 322.2013, found *m/z* 322.2012.

Compound 181a.



S181a **181a**

Prepared according to General Procedure H using compound **S181a** (20 mg, 0.06 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.), and 1:1 MeOH:H_2O (5 mL) and the resulting suspension brought to 50 °C for 16 h. The reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of CH_2Cl_2 and was

purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford a colourless oil. The material was washed with petroleum ether to afford the title compound as a colourless oil (12 mg, 63%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.27 stained by $KMnO_4$ and faintly visible by UV (short wave).

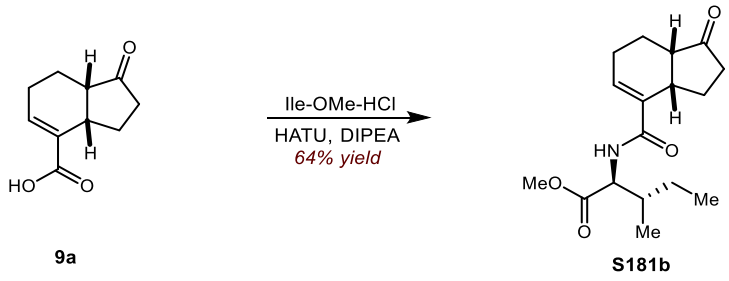
υ_{max} (film): 3337 (br.), 2958, 2921, 2870, 2850, 1731, 1654, 1613, 1519, 1195, 1149 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.35 – 6.30 (m, 1H), 6.29 – 6.23 (m, 1H), 4.72 – 4.67 (m, 1H), 3.22 – 3.10 (m, 1H), 2.53 – 2.25 (m, 5H), 2.07 – 1.98 (m, 1H), 1.89 – 1.83 (m, 1H), 1.67 – 1.49 (m, 2H), 1.30 – 1.19 (m, 1H), 1.15 – 1.03 (m, 4H), 1.02 – 0.94 (m, 6H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 220.1, 175.3, 175.3, 168.4, 168.3, 138.6, 138.5, 135.5, 135.4, 56.6, 46.7, 38.3, 37.9, 37.8, 36.0, 30.9, 30.9, 28.7, 28.0, 27.9, 25.4, 25.3, 20.9, 15.8, 15.7, 11.7, 11.7.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{17}H_{24}NO_4$) requires *m/z* 306.1711, found *m/z* 306.1706.

Compound S181b.



Prepared according to General Procedure G using compound **9a** (20 mg, 0.09 mmol, 1 equiv.), HATU (51 mg, 0.12 mmol, 1.2 equiv.), *L*-isoleucine methyl ester

hydrochloride (30 mg, 0.17 mmol, 1.5 equiv.), DIPEA (60 µL, 0.34 mmol, 3 equiv.), and DMF (0.5 mL). After 16 h the reaction was subjected to the purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a pale yellow oil (22 mg, 64%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.50 stained by $KMnO_4$ and faintly visible by UV (short wave).

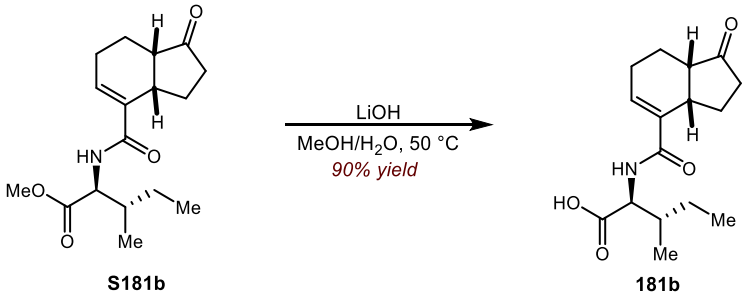
υ_{max} (film): 3319 (br.), 2963, 2933, 2877, 1735, 1660, 1624, 1513, 1202, 1148 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.57 – 6.50 (m, 1H), 6.26 – 6.17 (m, 1H), 4.71 – 4.63 (m, 1H), 3.75 (s, 3H), 3.36 – 3.24 (m, 1H), 2.45 – 2.37 (m, 1H), 2.36 – 2.19 (m, 3H), 2.17 – 2.10 (m, 2H), 1.99 – 1.89 (m, 1H), 1.88 – 1.65 (m, 3H), 1.51 – 1.39 (m, 1H), 1.29 – 1.12 (m, 1H), 0.97 – 0.90 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 220.3, 172.9, 172.8, 168.3, 168.1, 136.4, 136.1, 133.2, 133.1, 56.5, 56.4, 52.3, 46.8, 38.2, 38.2, 37.0, 35.9, 27.0, 27.0, 25.5, 25.4, 23.3, 23.3, 19.8, 19.7, 15.7, 15.7, 11.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}NO_4$) requires *m/z* 308.1856, found *m/z* 308.1857.

Compound 181b.



S181b **181b**

Experimental

Prepared according to General Procedure H using compound **S181b** (21 mg, 0.07 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.), and 1:1 MeOH:H_2O (5 mL). The reaction was brought to 50 °C for 16 h. The reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford a colourless oil. The material was washed with petroleum ether to afford the title compound as a colourless oil (18 mg, 90%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.51 stained by $KMnO_4$ and faintly visible by UV (short wave).

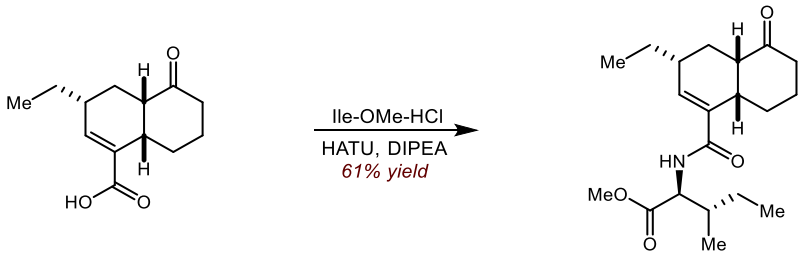
υ_{max} (film): 3327 (br.), 2961, 2924, 2876, 1730, 1655, 1618, 1518, 1202, 1144 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 1H), 6.38 – 6.30 (m, 1H), 4.68 – 4.56 (m, 1H), 3.36 – 3.25 (m, 1H), 2.46 – 2.39 (m, 1H), 2.34 – 2.20 (m, 3H), 2.13 (br. s, 2H), 1.99 (br. s, 1H), 1.87 – 1.67 (m, 3H), 1.58 – 1.46 (m, 1H), 1.31 – 1.16 (m, 1H), 1.02 – 0.90 (m, 6H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.6, 220.5, 175.9, 168.9, 168.7, 136.1, 136.0, 133.9, 133.6, 57.1, 46.8, 37.7, 37.7, 37.0, 35.9, 27.0, 26.9, 25.4, 25.3, 23.3, 23.3, 19.7, 15.8, 15.7, 11.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO_4$) requires *m/z* 294.1705, found *m/z* 294.1707.

Compound S181c.



172 **S181c**

Prepared according to General Procedure G using compound **172** (20 mg, 0.09 mmol, 1 equiv.), HATU (41 mg, 0.12 mmol, 1.2 equiv.), *L*-isoleucine methyl ester hydrochloride (25 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv.) and DMF (0.4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a pale yellow oil (19 mg, 61%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.63 stained by $KMnO_4$ and faintly visible by UV (short wave).

υ_{max} (film): 3321 (br.), 2959, 2930, 2874, 1740, 1703, 1657, 1624, 1518, 1200, 1150 cm^{-1}.

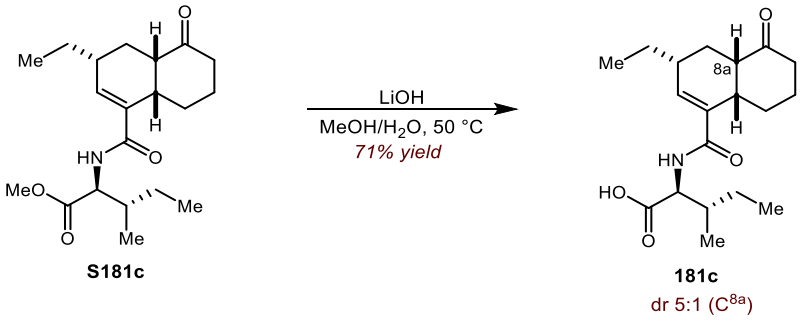
^1H NMR (400 MHz, $CDCl_3$): δ 6.34 – 6.25 (m, 1H), 6.25 – 6.20 (m, 1H), 4.70 – 4.61 (m, 1H), 3.78 – 3.73 (m, 3H), 3.01 – 2.90 (m, 1H), 2.56 – 2.49 (m, 1H), 2.43 – 2.31 (m, 2H), 2.27 – 2.15 (m, 1H), 2.06 – 1.87 (m, 3H), 1.81 – 1.62 (m, 2H), 1.57 – 1.35 (m, 5H), 1.27 – 1.13 (m, 1H), 1.01 – 0.89 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.7, 213.6, 172.3, 172.3, 167.6, 167.3, 136.9, 136.7, 135.5, 135.4, 56.0, 55.9, 51.7, 49.3, 49.3, 38.0, 37.6, 37.5, 37.4, 36.3, 27.8, 27.8, 27.5, 27.4, 26.9, 26.8, 24.9, 24.8, 24.2, 24.2, 15.1, 15.0, 11.1, 10.8, 10.8.

Experimental

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{32}NO_4$) requires *m/z* 350.2326, found *m/z* 350.2326.

Compound S181c.



Prepared according to General Procedure H using compound **S181c** (19 mg, 0.06 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.), and 1:1 MeOH:H_2O (5 mL) and the resulting suspension brought to 50 °C for 16 h. The reaction was allowed to cool to room temperature, acidified with AcOH and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of CH_2Cl_2 and was purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford a colourless oil. The material was washed with petroleum ether to afford the title compound as a colourless oil (13 mg, 71%). dr 5:1 C^{8a}.

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.63 stained by $KMnO_4$ and faintly visible by UV (short wave).

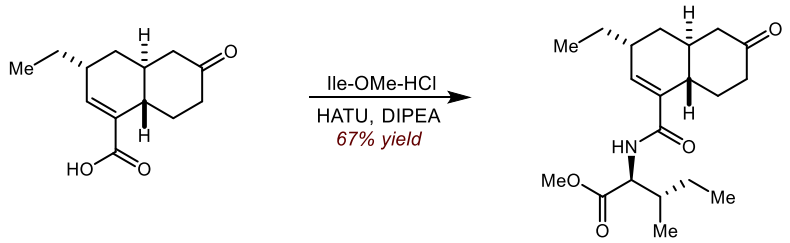
υ_{max} (film): 3325 (br.), 2959, 2924, 2872, 1701, 1655, 1616, 1522, 1231, 1152 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.35 – 6.28 (m, 1H), 6.26 – 6.20 (m, 1H), 4.69 – 4.63 (m, 1H), 3.01 – 2.90 (m, 1H), 2.57 – 2.51 (m, 1H), 2.41 – 2.33 (m, 2H), 2.27 – 2.19 (m, 1H), 2.06 – 1.93 (m, 3H), 1.81 – 1.76 (m, 1H), 1.75 – 1.64 (m, 1H), 1.59 – 1.36 (m, 4H), 1.35 – 1.27 (m, 2H), 1.02 – 0.94 (m, 9H). CO_2H not observed. Minor isomerisation to *trans*-ring junction observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 214.4, 214.4, 175.4, 168.6, 168.4, 137.3, 137.1, 136.6, 56.8, 56.7, 49.9, 38.6, 38.2, 38.1, 37.8, 37.7, 36.9, 28.4, 28.4, 28.1, 28.0, 27.5, 27.4, 25.4, 25.3, 24.8, 24.8, 15.8, 15.7, 11.7, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}NO_4$) requires *m/z* 336.2175, found *m/z* 336.2177.

Compound S181d.



180 **S181d**

Prepared according to General Procedure G using compound **180** (20 mg, 0.09 mmol, 1 equiv.), HATU (41 mg, 0.12 mmol, 1.2 equiv.), *L*-isoleucine methyl ester hydrochloride (25 mg, 0.14 mmol, 1.5 equiv.), DIPEA (50 µL, 0.30 mmol, 3 equiv.), and DMF (0.4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a pale yellow oil (21 mg, 67%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.42 stained by $KMnO_4$ and faintly visible by UV (short wave).

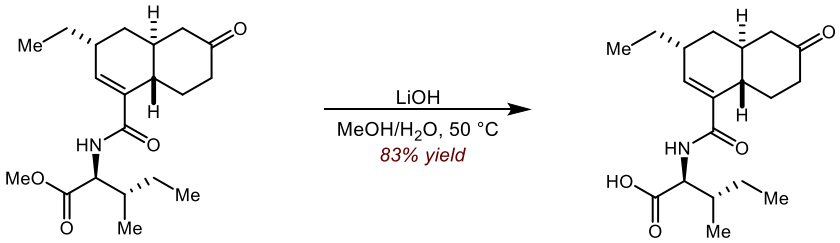
υ_{max} (film): 3314 (br.), 2959, 2924, 2874, 1742, 1713, 1657, 1624, 1518 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.25 – 6.19 (m, 1H), 6.13 – 6.08 (m, 1H), 4.68 – 4.61 (m, 1H), 3.76 – 3.73 (m, 3H), 2.55 – 2.46 (m, 1H), 2.47 – 2.33 (m, 4H), 2.25 – 2.15 (m, 2H), 1.97 – 1.89 (m, 1H), 1.71 – 1.62 (m, 1H), 1.57 – 1.52 (m, 2H), 1.52 – 1.39 (m, 2H), 1.37 – 1.12 (m, 3H), 1.00 – 0.89 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.8, 172.8, 172.8, 169.7, 169.4, 138.1, 138.1, 135.2, 134.9, 56.4, 56.2, 52.3, 48.3, 41.6, 40.9, 40.8, 38.2, 38.0, 36.4, 36.3, 36.3, 33.0, 33.0, 29.2, 29.1, 28.0, 25.4, 25.2, 15.8, 15.7, 12.5, 11.7, 11.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{32}NO_4$) requires *m/z* 350.2326, found *m/z* 350.2326.

Compound 181d.



S181d **181d**

Prepared according to General Procedure H using compound **S181d** (20 mg, 0.06 mmol, 1 equiv.), LiOH (5 mg, 0.21 mmol, 3 equiv.), and 1:1 MeOH:H_2O (3 mL). After 16 h the reaction was allowed to cool to room temperature, acidified with AcOH, and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered and evaporated to afford a colourless oil. The crude material was loaded in a solution of CH_2Cl_2 and was purified by flash silica column chromatography, eluent 1% AcOH, 30% EtOAc/CH_2Cl_2 to afford a colourless oil. The material was washed with petroleum ether to afford the title compound as a colourless oil (16 mg, 83%).

TLC (1% AcOH, 30% EtOAc/CH_2Cl_2): R_f = 0.76 and 0.66 stained by $KMnO_4$ and faintly visible by UV (short wave). Separation of isomers observed.

υ_{max} (film): 3310 (br.), 2961, 2922, 2872, 1711, 1655, 1611, 1522, 1202 cm^{-1}.

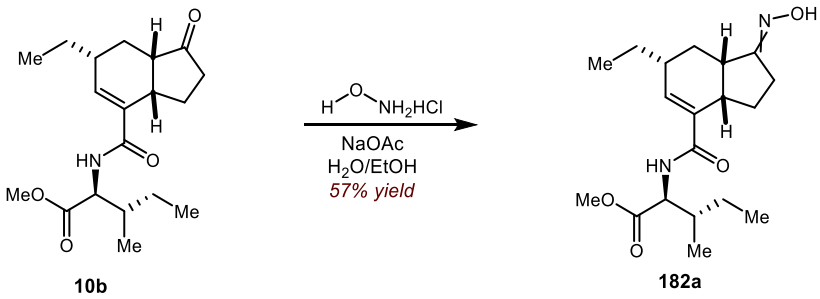
Experimental

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 – 6.17 (m, 2H), 4.68 – 4.55 (m, 1H), 2.54 – 2.46 (m, 1H), 2.47 – 2.32 (m, 4H), 2.26 – 2.15 (m, 2H), 1.99 (br. s, 1H), 1.72 – 1.61 (m, 1H), 1.60 – 1.43 (m, 4H), 1.38 – 1.15 (m, 3H), 1.02 – 0.90 (m, 9H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.3, 211.1, 175.6, 170.5, 170.0, 137.8, 135.7, 135.4, 56.8, 56.7, 48.2, 41.5, 40.8, 40.7, 37.7, 37.6, 36.4, 36.4, 36.3, 32.9, 29.1, 28.0, 25.4, 25.2, 15.8, 15.7, 12.5, 11.7, 11.7.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{19}H_{28}NO_4$) requires *m/z* 334.2024, found *m/z* 334.2018.

Compound 182a.



To a round bottom flask charged with hydroxylamine hydrochloride (10 mg, 0.14 mmol, 1.5 equiv.) and NaOAc (10 mg, 0.12 mmol, 1.2 equiv.) in a solution of H_2O (0.5 mL) was added compound **10b** (32 mg, 0.10 mmol, 1 equiv.) in EtOH (0.2 mL) at room temperature. The reaction was stirred for 16 h before being diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was taken up in diethyl ether and petroleum ether added until a precipitate formed. The solvent was removed with a Pasteur pipette and the residue dried under vacuum to afford the title compound as a colourless oil (19 mg, 57%). 7:3 oxime isomers.

Experimental

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.29 stained by $KMnO_4$ and faintly visible by UV (short wave).

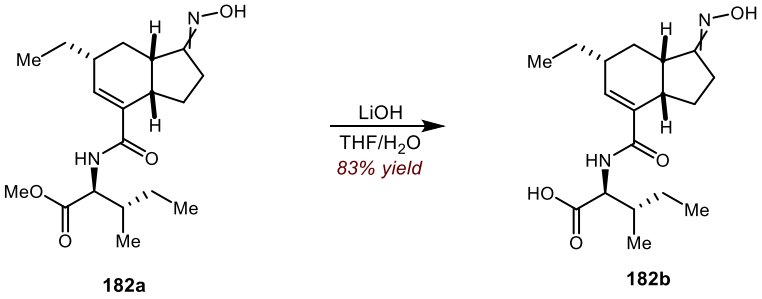
υ_{max} (film): 3316 (br.), 2957, 2922, 2876, 2855, 1744, 1649, 1612, 1518 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (br. s, 1H), 6.46 – 6.38 (m, 1H), 6.31 – 6.25 (m, 1H), 4.72 – 4.65 (m, 1H), 3.75 (s, 3H), 3.22 – 3.14 (m, 0.3H (minor)), 3.00 – 2.68 (m, 2.7H), 2.59 – 2.14 (m, 4H), 1.99 – 1.89 (m, 1.3H), 1.86 – 1.80 (m, 0.7H (major)), 1.56 – 1.33 (m, 3H), 1.27 – 1.09 (m, 2H), 1.02 – 0.89 (m, 9H). Major/minor isomers reported where separation of signals observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1, 173.0, 168.0, 167.9, 137.7, 137.7, 137.5, 135.6, 135.4, 56.5, 56.5, 52.3, 41.3, 41.2, 38.3, 38.3, 38.1, 37.7, 37.6, 37.5, 29.9, 29.9, 29.6, 29.5, 29.4, 29.3, 28.3, 26.4, 25.5, 25.4, 15.7, 15.6, 11.7, 11.7, 11.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{31}N_2O_4$) requires *m/z* 351.2278, found *m/z* 351.2281.

Compound 182b.



To a round bottom flask was added compound **182a** (10 mg, 0.03 mmol, 1 equiv.) and LiOH (3 mg, 0.13 mmol, 4 equiv.). The material was suspended in 1:1 THF:H_2O (1 mL) and the resulting suspension brought to 40 °C for 16 h. The reaction was allowed to cool to room temperature, extracted once with EtOAc (10 mL), the aqueous acidified with AcOH and the organics extracted with EtOAc (3 x 5 mL). The organics

were combined, washed with brine (5 mL) dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was dissolved in a minimal volume of diethyl ether and petroleum ether added until a white precipitate formed. The solvent was removed by Pasteur pipette and the residue dried under vacuum to afford the title compound as a white solid (8 mg, 83%). 7:3 oxime isomers.

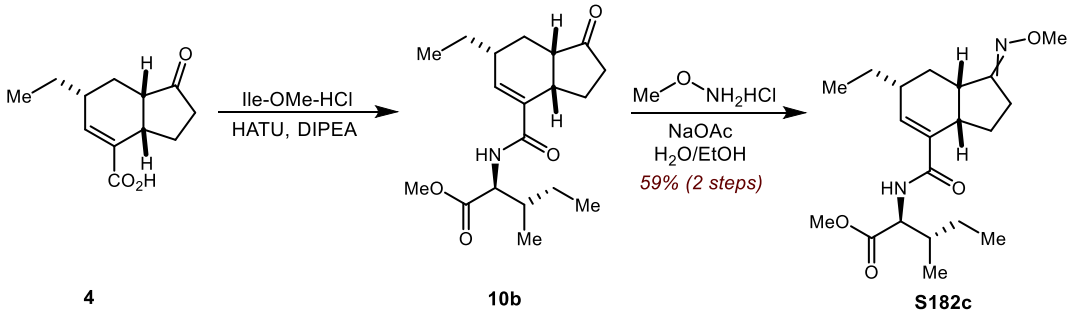
υ_{max} (film): 3323 (br.), 2963, 2928, 2874, 1719, 1655, 1612, 1508, 1202 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.47 – 6.41 (m, 1H), 6.34 – 6.28 (m, 1H), 5.81 (br. s, 1H), 4.72 – 4.67 (m, 1H), 3.24 – 3.15 (m, 0.3H (minor)), 3.03 – 2.71 (m, 2.7 H), 2.62 – 2.27 (m, 3H), 2.21 (br. s, 1H), 2.06 – 1.95 (m, 1H), 1.84 – 1.75 (m, 0.7H (major)), 1.61 – 1.35 (m, 4.3H), 1.33 – 1.09 (m, 1H), 1.03 – 0.90 (m, 9H). One signal not observed. Major/minor isomers reported where separation of signals observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.0, 168.2, 168.1, 137.7, 137.5, 135.3, 56.8, 56.7, 56.7, 41.2, 41.2, 38.2, 38.2, 38.2, 38.0, 38.0, 37.6, 37.5, 29.8, 29.8, 29.6, 29.5, 29.3, 29.2, 28.2, 28.2, 26.8, 25.4, 25.4, 15.7, 15.7, 11.8, 11.8, 11.5, 11.4, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{27}N_2O_4$) requires *m/z* 335.1976, found *m/z* 335.1973.

Compound S182c.



To a 2-dram vial was added (±)-CFA (**4**) (20 mg, 0.10 mmol, 1 equiv.) and HATU (44 mg, 0.12 mmol, 1.2 equiv.). DMF (0.5 mL) was added, followed by DIPEA (50 µL,

0.29 mmol, 3 equiv.) and the resulting solution stirred at room temperature for 5 minutes. Methyl *L*-isoleucinate hydrochloride (26 mg, 0.14 mmol, 1.5 equiv.) was then added in one portion and the vial capped with a screw top lid. The reaction was stirred for 16 h under air. The reaction was then diluted with H_2O (10 mL) and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 30% EtOAc/CH_2Cl_2 to afford compound **10b** as a colourless oil. The residue which was taken up in EtOH (0.18 mL) and added to a stirring solution of *O*-methylhydroxylamine hydrochloride (13 mg, 0.16 mmol, 1.5 equiv.) and NaOAc (11 mg, 0.13 mmol, 1.25 equiv.) in H_2O (0.55 mL). The reaction was stirred for 16 h before being diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 10-20% EtOAc/CH_2Cl_2 to afford the title compound as a colourless oil (23 mg, 59% (2 steps)). 7:3 oxime isomers.

TLC (10% EtOAc/CH_2Cl_2): R_f = 0.14 and 0.08 stained by $KMnO_4$ and faintly visible by UV (short wave). Separation of isomers visible.

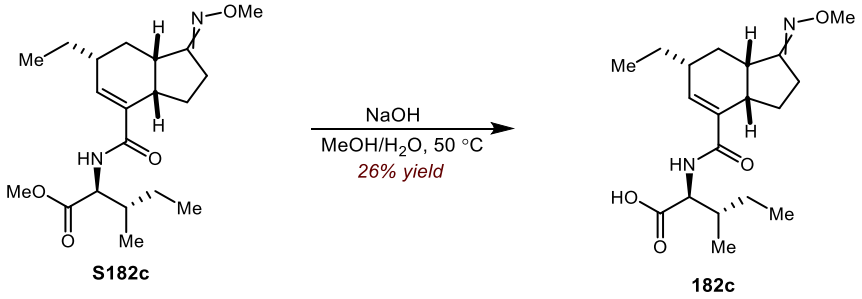
υ_{max} (film): 3315 (br.), 2958, 2934, 2874, 2857, 1742, 1656, 1619, 1519, 1050 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 – 6.35 (m, 1H), 6.27 – 6.20 (m, 1H), 4.70 – 4.63 (m, 1H), 3.87 – 3.80 (m, 3H), 3.74 (s, 3H), 3.12 – 3.02 (m, 0.3H (minor)), 2.98 – 2.79 (m, 1H), 2.76 – 2.60 (m, 1.3H (minor)), 2.59 – 2.10 (m, 3.7H (major)), 1.97 – 1.87 (m, 1H), 1.87 – 1.80 (m, 0.7H (major)), 1.56 – 1.30 (m, 4H), 1.22 – 1.07 (m, 2H), 1.01 – 0.88 (m, 9H). Major/minor isomers reported where separation of signals observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 172.9, 168.0, 168.0, 168.0, 167.9, 167.5, 167.5, 167.0, 137.6, 137.5, 135.6, 135.6, 135.5, 135.4, 61.6, 56.5, 56.4, 52.3, 41.4, 41.3, 39.4, 39.4, 38.3, 38.2, 38.1, 37.7, 37.6, 37.5, 37.4, 30.1, 30.1, 29.8, 29.7, 29.5, 29.4, 28.3, 28.2, 26.8, 25.8, 25.7, 25.5, 25.4, 15.7, 15.6, 11.7, 11.7, 11.5, 11.4, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{33}N_2O_4$) requires *m/z* 365.2435, found *m/z* 365.2431.

Compound 182c.



Prepared according to General Procedure H using compound **S182c** (20 mg, 0.05 mmol, 1 equiv.) NaOH (5 mg, 0.13 mmol, 2 equiv.), and 1:1 MeOH:H_2O (4 mL). After 5 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (5 mg, 26%). 7:3 oxime isomers.

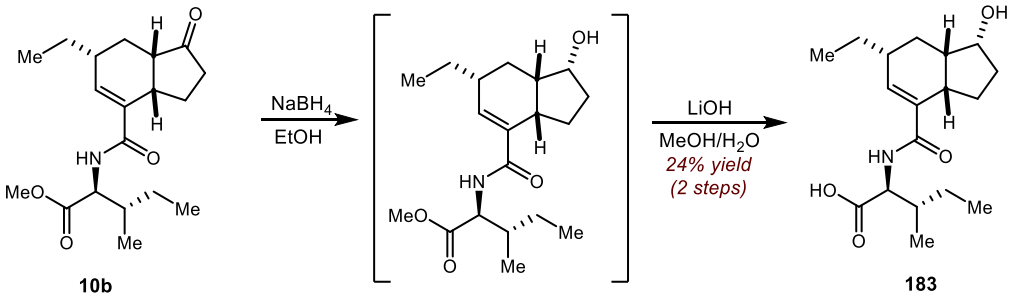
υ_{max} (film): 3323 (br.), 2963, 2937, 2878, 1727, 1659, 1616, 1521, 1052 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.49 – 6.38 (m, 1H), 6.31 – 6.25 (m, 1H), 4.69 – 4.63 (m, 1H), 3.93 – 3.76 (m, 3H), 3.15 – 3.03 (m, 0.3H (minor)), 2.97 – 2.79 (m, 1H), 2.77 – 2.62 (m, 1.3H), 2.59 – 2.13 (m, 3.7H), 2.00 (br. s, 1H), 1.89 – 1.81 (m, 0.7H (major)), 1.58 – 1.32 (m, 4H), 1.32 – 1.05 (m, 2H), 1.01 – 0.91 (m, 9H). CO_2H not observed. Major/minor isomers reported where separation of signals observed.

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 168.5, 168.5, 168.4, 167.7, 167.7, 167.6, 167.1, 138.2, 138.1, 138.1, 138.0, 135.4, 135.3, 135.2, 61.6, 56.8, 56.8, 45.7, 41.4, 41.3, 39.5, 39.4, 38.3, 38.1, 37.9, 37.8, 37.8, 37.7, 37.6, 37.5, 30.1, 30.0, 29.6, 29.5, 29.4, 28.3, 26.9, 25.7, 25.7, 25.4, 25.4, 15.8, 15.7, 11.7, 11.7, 11.5, 11.4, 11.4.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{19}H_{29}N_2O_4$) requires *m/z* 349.2133, found *m/z* 349.2123.

Compound 183.



To a round bottom flask charged with compound **10b** (34 mg, 0.10 mmol, 1 equiv.) in a solution of EtOH (3 mL) was added $NaBH_4$ (6 mg, 0.16 mmol, 1.5 equiv.) in one portion under an atmosphere of nitrogen. The reaction was stirred at room temperature for 16 h, before being quenched with water (5 mL). The organics were extracted with EtOAc (3 x 10 mL) and the layers combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The residue was suspended in 1:1 MeOH:H_2O (5 mL) and LiOH (7 mg, 0.29 mmol, 3 equiv.) added. The resulting suspension was brought to 50 °C and maintained at this temperature for 16 h. The reaction was allowed to cool to room temperature, acidified with AcOH, and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was taken up in diethyl ether and petroleum ether added until a white precipitate formed. The solvent was removed with a Pasteur pipette, and the residue dried under vacuum to afford the title compound as a white solid (8 mg, 24%).

υ_{max} (film): 3412 (br.), 3174, (br.) 1709, 1679, 1400, 1331, 1136, 1108 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.54 – 6.46 (m, 1H), 6.39 – 6.26 (m, 1H), 4.52 (br. s, 1H), 4.42 – 4.34 (m, 1H), 4.19 (br. s, 1H), 2.77 – 2.66 (m, 1H), 2.21 – 2.12 (m, 1H),

2.11 – 1.91 (m, 4H), 1.92 – 1.83 (m, 1H), 1.72 – 1.61 (m, 1H), 1.59 – 1.36 (m, 4H), 1.23 – 1.12 (m, 1H), 1.02 – 0.81 (m, 10H). One signal not observed.

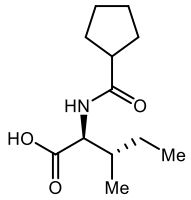
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 168.5, 139.2, 138.5, 136.1, 135.8, 75.0, 75.0, 42.6, 42.5, 37.7, 37.6, 37.6, 36.3, 36.1, 31.1, 31.0, 28.6, 28.2, 28.2, 25.4, 25.3, 24.1, 15.8, 15.7, 11.7, 11.6, 11.5.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{28}NO_4$) requires *m/z* 322.2024, found *m/z* 322.2024.

6.11 *L*-Ile Automated Screen (Scheme 52).

Reactions carried out according to General Procedure I.

Compound 184a.



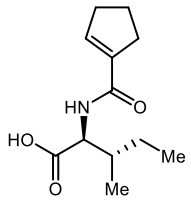
184a

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (d, *J* = 8.4 Hz, 1H), 5.14 (br. s, 1H), 4.46 (app. dd, *J* = 8.5, 4.7 Hz, 1H), 2.54 – 2.48 (m, 1H), 1.87 – 1.59 (m, 7H), 1.53 – 1.35 (m, 3H), 1.15 – 1.04 (m, 1H), 0.86 – 0.81 (m, 6H). Rotameric peaks observed but not reported.

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.2, 173.9, 56.2, 45.6, 37.7, 30.6, 30.0, 25.9, 25.8, 25.0, 15.4, 11.6. Rotameric peaks observed but not reported.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{22}NO_3$) requires *m/z* 228.1600, found *m/z* 228.1588.

Compound 184b.



184b

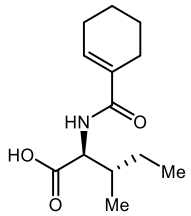
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 – 6.55 (m, 1H), 6.26 (d, *J* = 8.3 Hz, 0.6H) major rotamer, 6.16 (d, *J* = 8.7 Hz, 0.4H) minor rotamer, 5.97 (br. s, 1H), 4.75 (dd, *J* = 8.8, 3.8 Hz, 0.4H) minor rotamer, 4.63 (dd, *J* = 8.4, 4.7 Hz, 0.6H) major rotamer, 2.61 – 2.52 (m, 2H), 2.51 – 2.45 (m, 2H), 2.06 – 1.92 (m, 3H), 1.56 – 1.40 (m, 1H), 1.26 – 1.13 (m, 1H), 0.97 – 0.87 (m, 6H).

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 165.6, 139.3, 138.9, 56.5, 38.0, 33.3, 31.5, 25.3, 23.4, 15.5, 11.8.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.8, 165.8, 139.3, 138.9, 55.3, 38.0, 31.5, 26.4, 14.7, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{20}NO_3$) requires *m/z* 226.1443, found *m/z* 226.1431.

Compound 184c.



184c

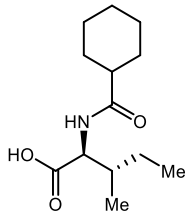
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (br. s, 1H), 6.64 – 6.59 (m, 1H), 6.33 (d, *J* = 8.3 Hz, 0.7H) major rotamer, 6.23 (d, *J* = 8.7 Hz, 0.3H) minor rotamer, 4.68 (dd, *J* = 8.8, 3.8 Hz, 0.3H) minor rotamer, 4.56 (dd, *J* = 8.3, 4.6 Hz, 0.7H) major rotamer, 2.28 – 2.13 (m, 2H), 2.13 – 2.07 (m, 2H), 1.99 – 1.86 (m, 1H), 1.65 – 1.59 (m, 2H), 1.59 – 1.50 (m, 2H), 1.50 – 1.34 (m, 1H), 1.20 – 1.09 (m, 1H), 0.91 – 0.82 (m, 6H).

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 168.6, 134.5, 132.8, 56.4, 37.9, 26.3, 25.4, 24.1, 22.0, 21.5, 15.4, 11.7.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 168.8, 134.4, 132.9, 55.2, 25.2, 24.2, 14.6, 11.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{22}NO_3$) requires *m/z* 240.1600, found *m/z* 240.1589.

Compound 184d.



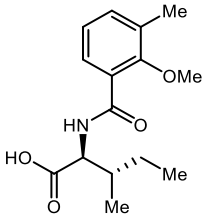
184d

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (app. d, *J* = 8.3 Hz, 0.2H) minor rotamer, 5.93 (app. d, *J* = 8.7 Hz, 0.8H) major rotamer, 4.70 (app. dd, *J* = 8.8, 4.0 Hz, 0.8H) major rotamer, 4.59 (app. dd, *J* = 8.4, 4.8 Hz, 0.2H) minor rotamer, 2.21 – 2.12 (m, 1H), 2.05 – 1.92 (m, 1H), 1.92 – 1.84 (m, 2H), 1.83 – 1.76 (m, 2H), 1.70 – 1.64 (m, 1H), 1.53 – 1.37 (m, 3H), 1.35 – 1.14 (m, 4H), 0.98 – 0.88 (m, 6H). One signal not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.8, 175.4, 55.1, 45.6, 37.6, 30.0, 29.5, 26.5, 25.8, 25.7, 14.7, 11.9. Rotameric peaks observed but not reported.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{24}NO_3$) requires *m/z* 242.1756, found *m/z* 242.1745.

Compound 184e.



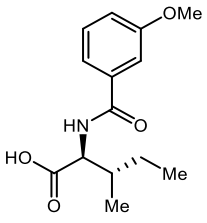
184e

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.45 (br. s, 1H), 8.56 (d, *J* = 8.3 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.30 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.82 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.80 (s, 3H), 2.32 (s, 3H), 2.10 – 1.99 (m, 1H), 1.63 – 1.54 (m, 1H), 1.32 – 1.20 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.2, 165.9, 157.0, 135.0, 131.7, 129.6, 125.7, 124.6, 61.8, 57.1, 37.9, 25.3, 16.0, 15.8, 11.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}NO_4$) requires *m/z* 280.1549, found *m/z* 280.1537.

Compound 184f.



184f

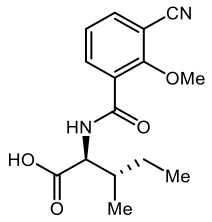
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (br. s, 1H), 7.39 – 7.36 (m, 1H), 7.36 – 7.30 (m, 2H), 7.04 (app. dt, *J* = 6.8, 2.5 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 0.7H) major rotamer, 6.66 (d, *J* = 8.7 Hz, 0.3H) minor rotamer, 4.92 (dd, *J* = 8.8, 3.8 Hz, 0.3H) minor rotamer, 4.81 (dd, *J* = 8.3, 4.7 Hz, 0.7H) major rotamer, 3.84 (s, 3H), 2.15 – 2.02 (m, 1H), 1.62 – 1.46 (m, 1H), 1.34 – 1.21 (m, 1H), 1.03 – 0.92 (m, 6H).

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4, 167.6, 160.0, 135.6, 129.8, 119.0, 118.1, 112.7, 57.1, 55.6, 38.1, 25.4, 15.6, 11.8.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9, 167.8, 135.6, 112.7, 55.9, 38.1, 26.5, 14.8, 12.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_4$) requires *m/z* 266.1392, found *m/z* 266.1383.

Compound 184g.



184g

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (brs, 1H), 8.35 – 8.29 (m, 1H), 7.74 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 4.91 (dd, *J* = 8.6, 3.4 Hz, 0.3H) minor rotamer, 4.81 (dd, *J* = 8.2, 4.3 Hz, 0.7H) major rotamer, 4.15 (app. d, *J* = 3.3 Hz, 3H), 2.17 – 2.02 (m, 1H), 1.63 – 1.53 (m, 0.7H) major rotamer, 1.52 – 1.41 (m, 0.3H) minor rotamer, 1.33 – 1.21 (m, 1H), 1.04 – 0.93 (m, 6H).

Experimental

Major rotamer:

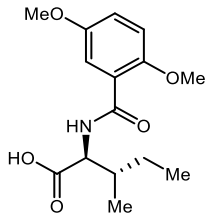
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 163.4, 160.7, 137.3, 136.8, 126.9, 125.1, 115.9, 107.4, 63.8, 57.2, 37.8, 25.3, 15.8, 11.8.

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 163.7, 136.9, 107.4, 63.9, 56.0, 37.6, 26.7, 14.8, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}N_2O_4$) requires *m/z* 291.1345, found *m/z* 291.1334.

Compound 184h.



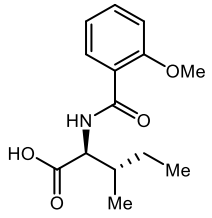
184h

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (br. s, 1H), 8.69 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 3.2 Hz, 1H), 6.98 (dd, *J* = 9.0, 3.3 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 4.78 (dd, *J* = 8.0, 4.5 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 2.12 – 2.01 (m, 1H), 1.64 – 1.54 (m, 1H), 1.32 – 1.20 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.1, 165.2, 153.9, 152.2, 121.5, 119.9, 115.5, 113.4, 57.3, 56.9, 55.9, 37.7, 25.3, 15.7, 11.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}NO_5$) requires *m/z* 296.1498, found *m/z* 296.1482.

Compound 184i.



184i

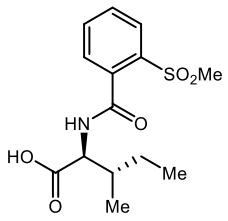
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (br. s, 1H), 8.51 (d, *J* = 7.8 Hz, 0.6H) major rotamer, 8.45 (d, *J* = 8.1 Hz, 0.4H) minor rotamer, 8.20 – 8.16 (m, 1H), 7.49 – 7.40 (m, 1H), 7.07 (appt. t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.90 (dd, *J* = 8.2, 3.8 Hz, 0.4H) minor rotamer, 4.79 (dd, *J* = 7.9, 4.8 Hz, 0.6H) major rotamer, 3.98 (app. d, *J* = 1.9 Hz, 3H), 2.17 – 2.04 (m, 1H), 1.67 – 1.57 (m, 0.6H), 1.57 – 1.47 (m, 0.4H), 1.34 – 1.23 (m, 1H), 1.05 – 0.93 (m, 6H).

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.7, 165.6, 157.9, 133.3, 132.4, 121.5, 121.0, 111.6, 57.4, 56.3, 37.6, 25.4, 15.8, 11.8.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 176.2, 165.8, 133.3, 132.5, 121.5, 111.6, 56.3, 56.1, 37.4, 26.7, 14.9, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_4$) requires *m/z* 266.1392 found *m/z* 266.1383.

Compound 184j.



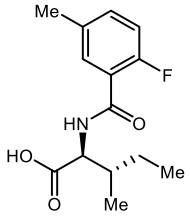
184j

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.65 – 7.58 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 4.76 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.34 (s, 3H), 2.14 – 2.06 (m, 1H), 1.61 – 1.51 (m, 1H), 1.35 – 1.24 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). One signal not observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 168.0, 138.5, 137.0, 133.9, 130.6, 129.8, 128.8, 57.4, 45.4, 37.8, 25.3, 15.6, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_5S$) requires *m/z* 314.1062, found *m/z* 314.1049.

Compound 184k.



184k

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (app. dd, *J* = 7.5, 1.9 Hz, 1H), 7.32 – 7.15 (m, 2H), 7.02 –6.95 (m, 1H), 6.79 (br. s, 1H), 4.90 (ddd, *J* = 8.5, 3.5, 2.4 Hz, 0.2H) minor rotamer, 4.79 (ddd, *J* = 8.0, 4.5, 2.2 Hz, 0.8H) major rotamer, 2.32 (s, 3H), 2.11 – 1.99 (m, 1H), 1.62 – 1.45 (m, 1H), 1.31 – 1.19 (m, 1H), 1.01 – 0.90 (m, 6H).

Experimental

Major rotamer:

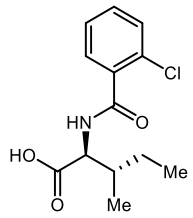
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 163.5 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 159.1 (d, $^1J_{C\text{-}F}$ = 245.4 Hz), 134.5 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 134.0 (d, $^3J_{C\text{-}F}$ = 9.1 Hz), 132.1 (d, $J_{C\text{-}F}$ = 1.8 Hz), 120.3 (d, $^2J_{C\text{-}F}$ = 11.4 Hz), 115.9 (d, $^2J_{C\text{-}F}$ = 24.8 Hz), 57.1, 37.9, 25.3, 20.6, 15.6, 11.8.

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 163.7 (d, $^3J_{C\text{-}F}$ = 3.3Hz), 132.1 (d, $J_{C\text{-}F}$ = 1.9 Hz), 55.9, 37.8, 26.5, 14.7, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}FNO_3$) requires *m/z* 268.1349, found *m/z* 268.1341.

Compound 184l.



184l

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (br. s, 1H), 7.69 – 7.65 (m, 1H), 7.42 – 7.29 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 0.7H) major rotamer, 6.76 (d, *J* = 8.8 Hz, 0.3H) minor rotamer, 4.94 (dd, *J* = 8.8, 3.7 Hz, 0.3H) minor rotamer, 4.83 (dd, *J* = 8.4, 4.5 Hz, 0.7H) major rotamer, 2.15 – 2.03 (m, 1H), 1.62 – 1.50 (m, 1H), 1.35 – 1.22 (m, 1H), 1.07 – 0.92 (m, 6H).

Major rotamer:

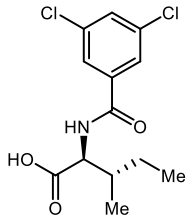
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 166.5, 134.6, 131.7, 130.9, 130.4, 130.4, 127.2, 57.2, 38.0, 25.3, 15.7, 11.8.

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 166.7, 134.6, 130.9, 130.5, 56.0, 38.0, 26.5, 14.9, 12.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}ClNO_3$) requires *m/z* 270.0897, found *m/z* 270.0887.

Compound 184m.



184m

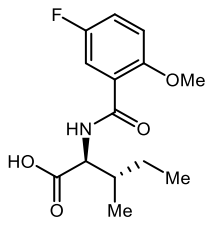
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (br. s, 1H), 7.66 (app. d, *J* = 1.8 Hz, 2H), 7.48 (app. t, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 0.7H) major rotamer, 6.75 (d, *J* = 8.7 Hz, 0.3H) minor rotamer, 4.88 (dd, *J* = 8.7, 3.8 Hz, 0.3H) minor rotamer, 4.76 (dd, *J* = 8.3, 4.7 Hz, 0.7H) major rotamer, 2.13 – 1.99 (m, 1H), 1.60 – 1.44 (m, 1H), 1.33 – 1.17 (m, 1H), 1.01 – 0.91 (m, 6H).

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 165.0, 137.1, 135.6, 131.7, 125.9, 57.2, 38.1, 25.4, 15.6, 11.8. Two signals equivalent.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.2, 165.3, 137.2, 125.9, 56.1, 26.5, 14.8, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}Cl_2NO_3$) requires *m/z* 304.1507, found *m/z* 304.0498.

Compound 184n.



184n

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.33 (br. s, 1H), 8.59 (d, *J* = 8.0 Hz, 0.9H) major rotamer, 8.52 (d, *J* = 8.3 Hz, 0.1H) minor rotamer, 7.86 (app. dd, *J* = 9.4, 3.3 Hz, 1H), 7.15 – 7.09 (m, 1H), 6.95 – 6.90 (m, 1H), 4.88 (dd, *J* = 8.4, 3.6 Hz, 0.1H) minor rotamer, 4.78 (dd, *J* = 8.0, 4.5 Hz, 0.9H) major rotamer, 3.96 (app. d, *J* = 4.7 Hz, 3H), 2.15 – 2.01 (m, 1H), 1.64 – 1.54 (m, 0.9H) major rotamer, 1.53 – 1.43 (m, 0.1H) minor rotamer, 1.32 – 1.20 (m, 1H), 1.03 – 0.92 (m, 6H).

Major rotamer:

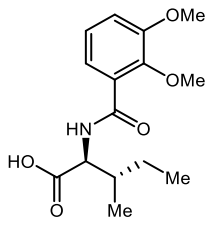
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3, 164.2 (d, $J_{C\text{-}F}$ = 1.7 Hz), 157.2 (d, $^{1}J_{C\text{-}F}$ = 240.0 Hz), 154.0 (d, $J_{C\text{-}F}$ = 2.1 Hz), 122.5 (d, $^{3}J_{C\text{-}F}$ = 6.8 Hz), 119.5 (d, $^{2}J_{C\text{-}F}$ = 23.5 Hz), 118.6 (d, $^{2}J_{C\text{-}F}$ = 25.1 Hz), 113.1 (d, $^{3}J_{C\text{-}F}$ = 7.6 Hz), 57.3, 56.9, 37.8, 25.4, 15.7, 11.8.

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9, 164.4 (d, $J_{C\text{-}F}$ = 1.8 Hz), 57.0, 56.1, 37.6, 26.6, 14.9, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}FNO_4$) requires *m/z* 284.1298, found *m/z* 284.1288.

Compound 184o.



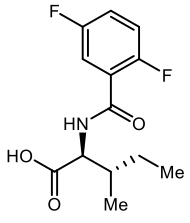
184o

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (br. s, 1H), 8.72 (d, *J* = 8.3 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.5 Hz, 1H), 4.79 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 2.11 – 1.98 (m, 1H), 1.62 – 1.51 (m, 1H), 1.30 – 1.19 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.2, 165.3, 152.7, 147.9, 126.0, 124.5, 122.9, 115.7, 61.8, 57.1, 56.1, 37.7, 25.2, 15.8, 11.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}NO_5$) requires *m/z* 296.1498, found *m/z* 296.1486.

Compound 184p.



184p

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (br. s, 1H), 7.79 – 7.72 (m, 1H), 7.33 – 7.26 (m, 1H), 7.22 – 7.07 (m, 2H), 4.95 – 4.89 (m, 0.3H) minor rotamer, 4.84 – 4.78 (m, 0.7H) major rotamer, 2.16 – 2.02 (m, 1H), 1.62 – 1.53 (m, 0.7H) major rotamer, 1.53 – 1.45 (m, 0.3H) minor rotamer, 1.34 – 1.22 (m, 1H), 1.05 – 0.91 (m, 6H).

Experimental

Major rotamer:

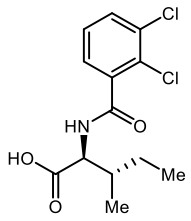
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.4, 162.1 (dd, $^3J_{C\text{-}F}$ = 3.4 Hz, $J_{C\text{-}F}$ = 1.4 Hz), 159.0 (dd, $^1J_{C\text{-}F}$ = 244.5 Hz, $J_{C\text{-}F}$ = 1.8 Hz), 156.8 (dd, $^1J_{C\text{-}F}$ = 243.7 Hz, $J_{C\text{-}F}$ = 2.3 Hz), 122.2 (dd, $^2J_{C\text{-}F}$ = 14.0 Hz, $^3J_{C\text{-}F}$ = 7.4 Hz), 120.4 (dd, $^2J_{C\text{-}F}$ = 24.5 Hz, $^3J_{C\text{-}F}$ = 9.8 Hz), 118.3 (dd, $^2J_{C\text{-}F}$ = 25.9 Hz, $^3J_{C\text{-}F}$ = 2.6 Hz), 117.7 (dd, $^2J_{C\text{-}F}$ = 28.1 Hz, $^3J_{C\text{-}F}$ = 8.1 Hz), 57.3, 37.8, 25.3, 15.7, 11.8.

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9, 162.4 (dd, $^3J_{C\text{-}F}$ = 3.6 Hz, $J_{C\text{-}F}$ = 1.6 Hz), 56.1, 37.7, 26.5, 14.8, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}F_2NO_3$) requires *m/z* 272.1098, found *m/z* 272.1084.

Compound 184q.



184q

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (br. s, 1H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 0.7H) major rotamer, 6.59 (d, *J* = 8.8 Hz, 0.3H) minor rotamer, 4.92 (dd, *J* = 8.9, 3.6 Hz, 0.3H) minor rotamer, 4.81 (dd, *J* = 8.5, 4.4 Hz, 0.7H) major rotamer, 2.15 – 2.04 (m, 1H), 1.60 – 1.51 (m, 1H), 1.35 – 1.23 (m, 1H), 1.06 – 0.93 (m, 6H).

Major rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.8, 166.2, 137.4, 134.1, 132.1, 129.5, 127.8, 57.2, 38.0, 25.3, 15.7, 11.8. One signal not observed.

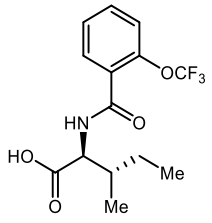
Experimental

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.3, 166.4, 137.5, 133.6, 129.5, 56.0, 38.0, 26.5, 14.8, 12.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}Cl_2NO_3$) requires *m/z* 304.0507, found *m/z* 304.0498.

Compound 184r.



184r

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (br. s, 1H), 8.01 – 7.97 (m, 1H), 7.54 – 7.48 (m, 1H), 7.41 – 7.36 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 0.8H) major rotamer, 7.03 (d, *J* = 8.5 Hz, 0.2H) minor rotamer, 4.94 (dd, *J* = 8.6, 3.6 Hz, 0.2H) minor rotamer, 4.83 (dd, *J* = 8.2, 4.5 Hz, 0.8H) major rotamer, 2.16 – 2.01 (m, 1H), 1.61 – 1.47 (m, 1H), 1.33 – 1.21 (m, 1H), 1.05 – 0.93 (m, 6H).

Major rotamer:

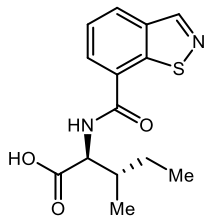
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.8, 164.4, 146.3 (d, $J_{C\text{-}F}$ = 1.4 Hz), 132.7, 132.0, 127.5, 127.4, 121.0 (d, $J_{C\text{-}F}$ = 1.3 Hz), 120.4 (q, $^1J_{C\text{-}F}$ = 260.0 Hz), 57.3, 38.0, 25.2, 15.5, 11.8.

Peaks observed for minor rotamer:

^{13}C NMR (126 MHz, $CDCl_3$): δ 176.4, 164.6, 56.1, 37.7, 26.4, 14.6, 11.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}F_3NO_4$) requires *m/z* 320.1110, found *m/z* 320.1097.

Compound 184s.



184s

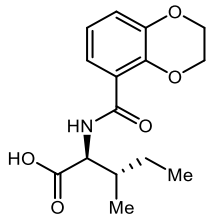
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.21 (dd, *J* = 7.9, 2.2 Hz, 1H), 7.87 (dd, *J* = 7.3, 3.7 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 0.7H) major rotamer, 7.02 (d, *J* = 8.4 Hz, 0.3H) minor rotamer, 5.00 (dd, *J* = 8.5, 3.8 Hz, 0.3H) minor rotamer, 4.90 (dd, *J* = 8.0, 4.6 Hz, 0.7H) major rotamer, 2.21 – 2.08 (m, 1H), 1.70 – 1.54 (m, 1H), 1.41 – 1.22 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). One signal not observed.

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 165.2, 153.6, 151.1, 137.1, 127.9, 125.8, 125.0, 124.8, 57.3, 38.2, 25.5, 15.6, 11.9.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 165.5, 151.1, 127.9, 125.9, 124.9, 56.3, 38.1, 26.4, 14.9, 12.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}N_2O_3S$) requires *m/z* 293.0960, found *m/z* 293.0946.

Compound 184t.



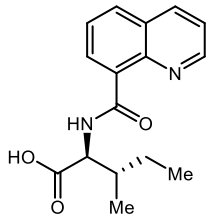
184t

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.00 (br. s, 1H), 7.66 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 1H), 4.76 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.44 – 4.37 (m, 2H), 4.31 – 4.24 (m, 2H), 2.09 – 2.00 (m, 1H), 1.62 – 1.52 (m, 1H), 1.30 – 1.19 (m, 1H), 1.00 – 0.92 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 164.9, 143.7, 142.4, 124.1, 121.6, 121.3, 121.0, 65.1, 63.6, 57.2, 37.7, 25.4, 15.7, 11.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}NO_5$) requires *m/z* 294.1341, found *m/z* 294.1328.

Compound 184u.



184u

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.99 (d, *J* = 6.9 Hz, 1H), 8.94 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.84 – 8.78 (m, 1H), 8.45 (br. s, 1H), 8.30 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.00 – 7.94 (m, 1H), 7.70 – 7.63 (m, 1H), 7.51 (dd, *J* = 8.3, 4.3 Hz, 1H), 4.95 (dd, *J* = 7.7, 3.8 Hz, 0.2H) minor rotamer, 4.82 (dd, *J* = 7.5, 5.0 Hz, 0.8H) major rotamer, 2.29 – 2.18 (m,

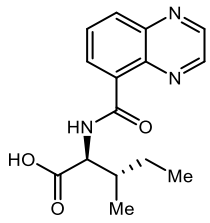
1H), 1.78 – 1.68 (m, 0.8H) major rotamer, 1.63 – 1.51 (td, *J* = 14.1, 7.2 Hz, 0.2H) minor rotamer, 1.47 – 1.33 (m, 1H), 1.18 – 1.05 (m, 3H), 1.04 – 0.93 (m, 3H).

Major rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.2, 166.9, 149.5, 145.4, 138.3, 134.3, 132.6, 128.6, 127.6, 126.8, 121.3, 58.4, 37.1, 25.5, 16.2, 11.8.

Peaks observed for minor rotamer:
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.8, 167.0, 149.5, 145.5, 138.3, 128.7, 127.7, 57.0, 37.0, 27.0, 15.3, 12.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2O_3$) requires *m/z* 287.1396, found *m/z* 287.1396.

Compound 184v.



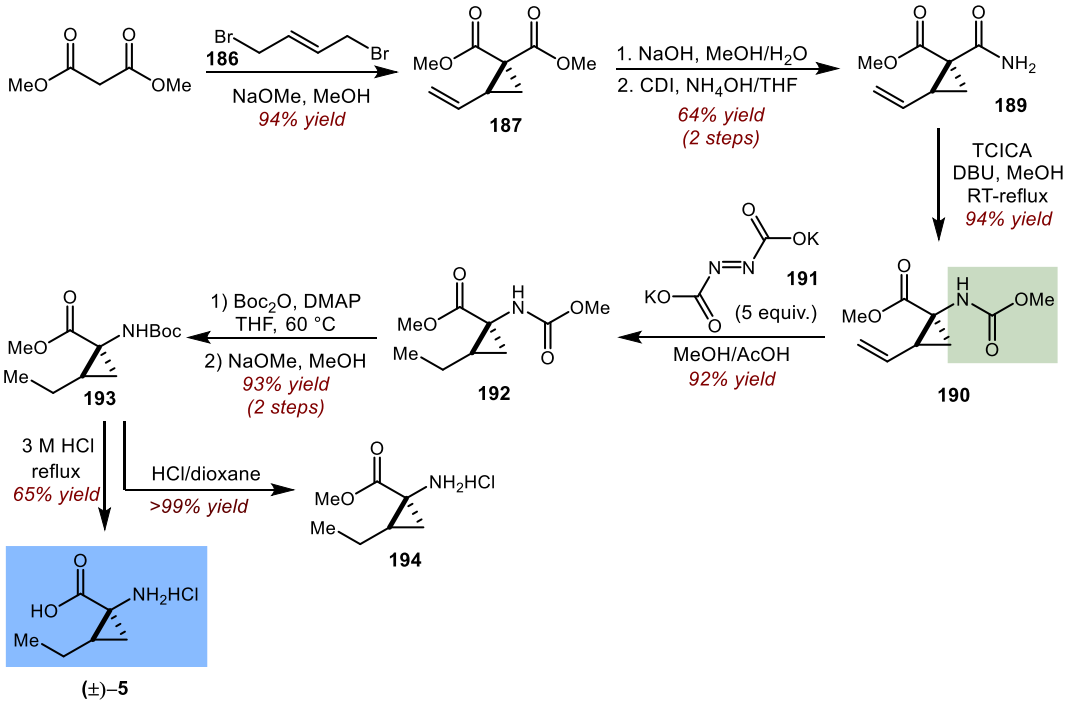
184v

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.06 – 10.97 (m, 1H), 8.94 (d, *J* = 1.7 Hz, 1H), 8.89 (d, *J* = 1.8 Hz, 1H), 8.84 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.23 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.17 (brs, 1H), 7.90 – 7.84 (m, 1H), 5.00 (dd, *J* = 8.3, 3.6 Hz, 0.1H) minor rotamer, 4.89 (dd, *J* = 8.1, 4.6 Hz, 0.9H) major rotamer, 2.23 – 2.10 (m, 1H), 1.73 – 1.60 (m, 0.9H) major rotamer, 1.57 – 1.48 (m, 0.1H) minor rotamer, 1.41 – 1.28 (m, 1H), 1.11 – 1.02 (m, 3H), 1.00 – 0.93 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6, 164.8, 144.7, 143.7, 142.9, 140.5, 134.6, 133.6, 130.2, 128.9, 57.7, 37.7, 25.5, 16.0, 11.8.

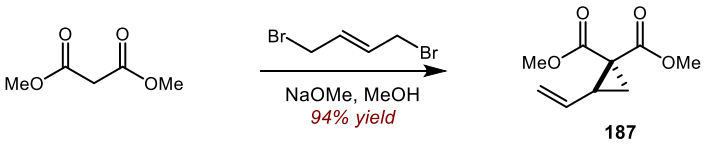
HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3O_3$) requires *m/z* 288.1348, found *m/z* 288.1336.

6.12 Synthesis of (±)-CMA (4) (Scheme 53).



6.12.1 Procedures and Characterisation of (±)-CMA (4) Synthesis.

Compound 187.



To a round bottom flask was added anhydrous MeOH (15 mL) followed by portionwise addition of Na metal (1.18 g, 51.30 mmol, 2.2 equiv.) at room temperature. The resulting solution was then added dropwise under nitrogen to a stirring solution of (*E*)-1,4-dibromobut-2-ene (5.00 g, 23.38 mmol, 1 equiv.) and dimethyl malonate (2.94 mL, 25.73 mmol, 1.1 equiv.) in anhydrous MeOH (10 mL) at room temperature.

The resulting beige suspension was stirred at room temperature for 16 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of 10% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 10% EtOAc/petroleum ether to afford the title compound as a colourless oil (4.07 g, 94%).

TLC (10% EtOAc/petroleum ether): R_f = 0.18 stained by $KMnO_4$.

υ_{max} (neat): 2951, 1722, 1437, 1329, 1272, 1209, 1127 cm^{-1}.

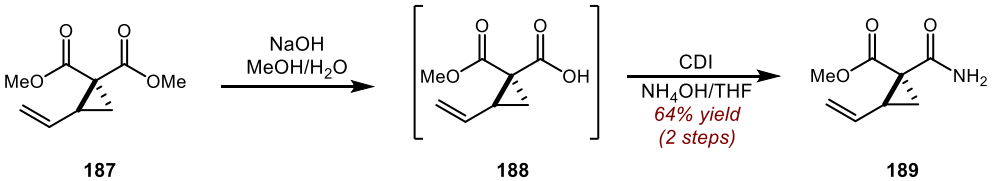
^1H NMR (500 MHz, $CDCl_3$): δ 5.47 – 5.38 (m, 1H), 5.32 – 5.27 (m, 1H), 5.16 – 5.12 (m, 1H), 3.74 (s, 6H), 2.61 – 2.55 (m, 1H), 1.72 (dd, *J* = 7.6, 4.9 Hz, 1H), 1.61 – 1.55 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 167.9, 133.1, 118.8, 52.9, 52.7, 35.9, 31.6, 20.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_{13}O_4$) requires *m/z* 185.0814, found *m/z* 185.0450.

The spectral data were consistent with those previously reported in the literature.[114]

Compound 189.



187 188 189

To a round bottom flask was added compound **187** (11.36 g, 61.68 mmol, 1 equiv.) and MeOH/H_2O (1:1, 90 mL). NaOH (2.71 g, 67.75 mmol, 1.1 equiv.) was added in

one portion and the resulting solution stirred at room temperature for 16 h. The reaction brought to pH 1 with HCl and extracted with EtOAc (3 x 50 ml). The organics were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil (**188**) (10.04 g, 59.00 mmol).

To the colourless oil in a round bottom flask was added THF (240 mL), followed by CDI (10.53 g, 64.92 mmol, 1.1 equiv.) at room temperature. The reaction was stirred for 3 h, and NH_4OH (aq.) (200 mL) added slowly. The reaction was stirred for a further 16 h. The reaction was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The organics were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil which solidified to a white solid on standing. The crude material was dry loaded onto silica gel and purified by flash silica column chromatography, eluent 30-50% EtOAc/petroleum ether to afford the title compound as a white solid (6.67 g, 64%).

TLC (40% EtOAc/petroleum ether): R_f = 0.26 stained by $KMnO_4$.

υ_{max} (neat): 3411, 3169 (br.), 1709, 1679, 1400, 1329, 1134, 1108 cm^{-1}.

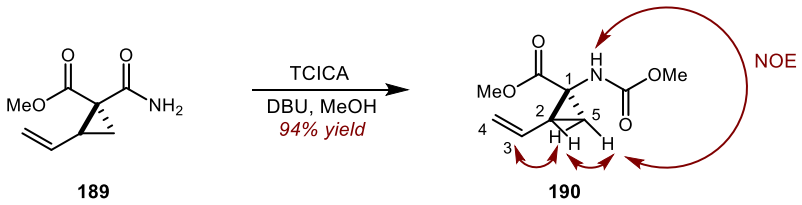
^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (br. s, 1H), 5.68 – 5.57 (m, 2H), 5.35 (dd, *J* = 17.0, 0.6 Hz, 1H), 5.18 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.73 (s, 3H), 2.58 (q, *J* = 8.7 Hz, 1H), 2.07 (dd, *J* = 9.2, 4.4 Hz, 1H), 1.90 (dd, *J* = 8.0, 4.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 170.4, 133.2, 120.0, 52.3, 37.6, 34.6, 21.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_8H_{12}NO_3$) requires *m/z* 170.0812, found *m/z* 170.0812.

The spectral data were consistent with those previously reported in the literature.[114]

Compound 190.



To a round bottom flask was added compound **189** (1.49 g, 8.81 mmol, 1 equiv.) and MeOH (15 mL) under an atmosphere of nitrogen. DBU (2.96 mL, 19.79 mmol, 2.25 equiv.) was added, followed by portionwise addition of TCICA (778 mg, 3.35 mmol, 0.38 equiv.) and the resulting solution brought to 65 °C for 16 h. The solvent was removed *in vacuo* to afford an orange oil which solidified to an orange solid on standing. The material was dry loaded and purified by flash silica column chromatography, eluent 30% EtOAc/petroleum ether to afford the title compound colourless oil (1.65 g, 94%).

TLC (30% EtOAc/petroleum ether): R_f = 0.37 stained by $KMnO_4$.

υ_{max} (neat): 3321 (br.), 2951, 1705, 1514, 1324, 1248, 1164 cm^{-1}.

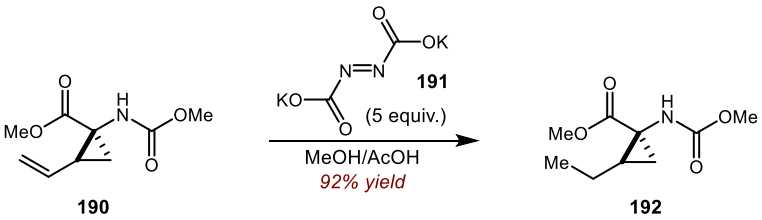
^1H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddd, *J* = 17.2, 10.2, 8.9 Hz, 1H, H^3), 5.41 (br. s, 1H, N*H*), 5.28 (d, *J* = 17.0 Hz, 1H, H^4), 5.11 (dd, *J* = 10.3, 1.4 Hz, 1H, $H^{4'}$), 3.70 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 2.16 (q, *J* = 8.8 Hz, 1H, H^2), 1.85 – 1.78 (m, 1H, H^5), 1.53 (br. s, 1H, $H^{5'}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2 (*C*O), 133.6 (C^3), 118.1 (C^4), 52.6 (*C*H_3 x 2), 41.0 (C^1), 34.7 (C^2), 23.5 (C^5). One carbonyl *C*O not observed, one peak equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_{14}NO_4$) requires *m/z* 200.0917, found *m/z* 200.0915.

The spectral data were consistent with those previously reported in the literature.[114]

Compound 192.



To a round bottom flask was added compound **190** (6.28 g, 34.24 mmol, 1 equiv.), dipotassium azo-1,2-dicarboxylate[126] (**191**) (33.00 g, 169.90 mmol, 5 equiv.), and MeOH (55 mL). AcOH was added dropwise at 0 °C and the resulting suspension allowed to rise to room temperature and stir for 16 h. The reaction concentrated *in vacuo*, diluted with water (30 mL) and extracted with EtOAc (3 x 40 mL). The organics were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was loaded in a solution of 30% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 30% EtOAc/petroleum ether to afford the title compound as a colourless oil (6.36 g, 92%).

TLC (30% EtOAc/petroleum ether): R_f = 0.37 stained by $KMnO_4$.

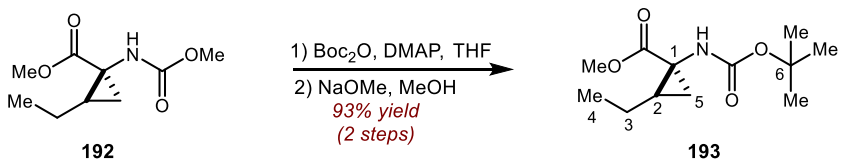
υ_{max} (neat): 2921 (br.), 2572 (br.), 1666, 1588, 1311, 1283, 1216 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 5.33 (br. s, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 1.65 – 1.42 (m, 4H), 1.33 – 1.22 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 52.5, 38.9, 33.9, 23.4, 20.5, 13.5. One carbonyl *C*O not observed, one peak coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_{16}NO_4$) requires *m/z* 202.1074, found *m/z* 202.1070.

Compound 193.



To a round bottom flask charged with compound **192** (6.36 g, 31.61 mmol, 1 equiv.) and Boc_2O (8.97 g, 41.10 mmol, 1.3 equiv.) in a solution of THF (50 mL) was added DMAP (777 mg, 6.33 mmol, 0.2 equiv.) at room temperature under an atmosphere of nitrogen. The reaction was brought to 70 °C for 3 h. The reaction was then allowed to cool to room temperature and diluted with anhydrous MeOH (30 mL). To a separate round bottom flask charged with anhydrous MeOH (35 mL) was added Na metal (223 mg, 9.70 mmol, 0.3 equiv.) portionwise under an atmosphere of nitrogen. The resulting solution was then added dropwise to the reaction flask at 0 °C in an ice bath. The reaction was allowed to rise to room temperature and stirred for 1.5 h. The reaction was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The organics were combined, washed with brine (150 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale orange oil. The crude material was loaded in a solution of 20% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 20% EtOAc/petroleum ether to afford the title compound as a pale yellow oil (7.18 g, 93%).

TLC (30% EtOAc/petroleum ether): R_f = 0.60 stained by $KMnO_4$.

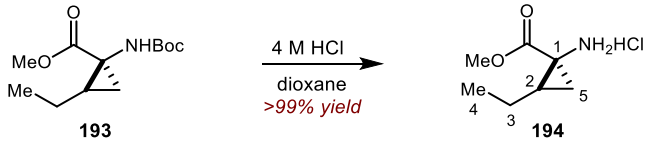
υ_{max} (neat): 3261 (br.), 3131, 2961, 2926, 2868, 1705, 1377, 1364, 1335, 1165, 1022 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 5.13 (br. s, 1H, N*H*), 3.74 (s, 3H, OCH_3), 1.63 – 1.54 (m, 2H, H^3), 1.49 – 1.43 (m, 11H, H^2, H^5, 3CH_3), 1.29 (br. s, 1H, $H^{5'}$), 0.97 (t, *J* = 7.4 Hz, 3H, H^4).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.5 (*C*O), 156.1 (*C*O), 80.0 (br., C^6), 52.3 (*C*H_3), 39.0 (br., C^1), 33.5 (br., C^2), 28.5 (*C*H_3), 28.5 (*C*H_3), 28.4 (*C*H_3), 23.3 (br., C^5), 20.5 (C^3), 13.6 (C^4).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{22}NO_4$) requires *m/z* 244.1543, found *m/z* 244.1544.

Compound 194.



To a round bottomed flask charged with compound **193** (150 mg, 0.62 mmol, 1 equiv.) and dioxane (1.2 mL) was added 6 M HCl (1.5 mL) dropwise at room temperature and the resulting solution stirred for 5 h. The solvent was removed *in vacuo* to afford a colourless oil, which was dissolved in acetone (2 mL) and the solvent removed *in vacuo* to afford the title compound as a colourless oil which solidified to a white solid on standing (113 mg, > 99%).

υ_{max} (neat): 2872 (br.), 1745, 1526, 1444, 1370, 1201, 1167 cm^{-1}.

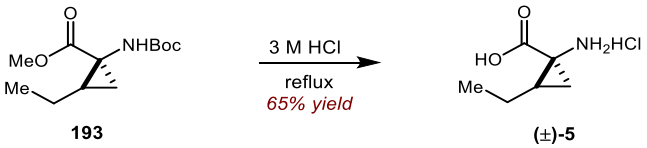
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (br. s, 2H, N*H*$_2$), 3.84 (s, 3H, OC*H*$_3$), 2.05 – 1.94 (m, 1H, H^2), 1.90 – 1.82 (m, 1H, H^5), 1.72 – 1.54 (m, 2H, H^3), 1.51 – 1.44 (m, 1H, $H^{5'}$), 0.99 (t, *J* = 7.4 Hz, 3H, H^4).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6 (*C*O), 53.3 (O*C*H_3), 38.5 (C^1), 30.5 (C^2), 20.1 ($C^{3/5}$), 20.0 ($C^{3/5}$), 13.5 (C^4).

HRMS: exact mass calculated for $[M+H]^+$ ($C_7H_{14}NO_2$) requires *m/z* 144.1019, found *m/z* 144.1016.

The spectral data were consistent with those previously reported in the literature.[127]

(±)-CMA (4).



To a round bottomed flask was added compound **193** (1.35 g, 4.11 mmol) and 3 M HCl (60 mL). The reaction was brought to 100 °C for 16 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo* to afford a pale orange solid. The solid material was washed sparingly with acetone to afford the title compound as a beige solid (596 mg, 65%).

υ_{max} (neat): 2956 (br.), 1714, 1500, 1253, 1165 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ 1.80 – 1.68 (m, 2H), 1.61 – 1.51 (m, 3H), 0.98 (t, *J* = 7.0 Hz, 3H). N*H*$_2$ and CO_2*H* not observed.

^{13}C NMR (101 MHz, DMSO-d_6): δ 170.1, 37.2, 28.2, 19.4, 18.2, 13.3.

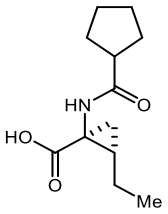
HRMS: exact mass calculated for $[M-H]^-$ ($C_6H_{10}NO_2$) requires *m/z* 128.0717, found *m/z* 128.0721.

The spectral data were consistent with those previously reported in the literature.[92]

6.13 Coronamic Acid Automated Screen (Scheme 54).

Reactions carried out according to General Procedure J.

Compound 195a.



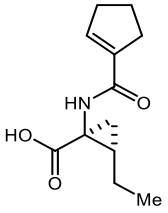
195a

^{1}H NMR (500 MHz, MeOD): δ 2.64 – 2.56 (m, 1H), 1.90 – 1.67 (m, 6H), 1.67 – 1.53 (m, 4H), 1.47 – 1.39 (m, 2H), 1.14 – 1.06 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 180.2, 174.9, 46.0, 39.0, 33.2, 31.2, 31.1, 27.1, 27.0, 23.3, 21.6, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{20}NO_3$) requires *m/z* 226.1443, found *m/z* 226.1441.

Compound 195b.



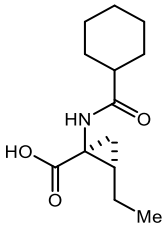
195b

^{1}H NMR (500 MHz, MeOD): δ 6.58 – 6.56 (m, 1H), 2.58 – 2.52 (m, 2H), 2.52 – 2.46 (m, 2H), 2.00 – 1.92 (m, 2H), 1.67 – 1.59 (m, 2H), 1.55 – 1.43 (m, 2H), 1.17 – 1.12 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 175.0, 169.2, 140.5, 139.8, 39.1, 34.1, 33.2, 32.4, 24.3, 23.3, 21.7, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{18}NO_3$) requires *m/z* 224.1282, found *m/z* 224.1287.

Compound 195c.



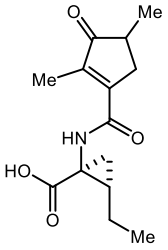
195c

^{1}H NMR (500 MHz, MeOD): δ 2.18 – 2.10 (m, 1H), 1.94 – 1.53 (m, 8H), 1.48 – 1.36 (m, 2H), 1.35 – 1.18 (m, 4H), 1.12 – 1.05 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 180.2, 174.9, 46.0, 44.3, 38.8, 33.2, 30.4, 26.9, 26.8, 26.8, 23.3, 21.6, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{22}NO_3$) requires *m/z* 240.1600, found *m/z* 240.1595.

Compound 195d.



195d

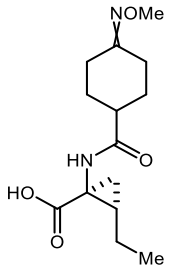
Experimental

^{1}H NMR (500 MHz, MeOD): δ 3.05 – 2.97 (m, 1H), 2.51 – 2.44 (m, 1H), 2.39 – 2.31 (m, 1H), 1.87 (t, *J* = 2.2 Hz, 3H), 1.72 – 1.61 (m, 2H), 1.60 – 1.49 (m, 2H), 1.26 – 1.22 (m, 1H), 1.17 (d, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 214.3, 174.2, 169.9, 160.9, 141.0, 40.7, 38.8, 36.8, 33.4, 23.4, 21.6, 16.3, 13.7, 9.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_4$) requires *m/z* 266.1392, found *m/z* 266.1389.

Compound 195e.



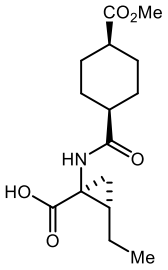
195e

^{1}H NMR (500 MHz, MeOD): δ 3.77 (s, 3H), 3.22 – 3.14 (m, 1H), 2.46 – 2.36 (m, 2H), 2.19 – 2.09 (m, 1H), 2.06 – 1.84 (m, 3H), 1.69 – 1.51 (m, 4H), 1.47 – 1.39 (m, 2H), 1.14 – 1.07 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H). 1:1 mixture of oxime isomers. N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 178.6, 174.8, 160.2, 61.3, 44.4, 38.9, 33.2, 31.4, 31.3, 30.5, 30.4, 29.2, 29.1, 24.5, 24.4, 23.3, 21.6, 13.8. Oxime isomer peaks observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}N_4O_2$) requires *m/z* 283.1658, found *m/z* 283.1653.

Compound 195f.



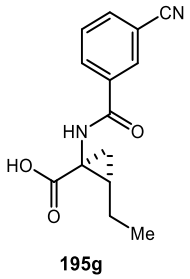
195f

^{1}H NMR (500 MHz, MeOD): δ 4.58 (br. s, 1H), 3.65 (s, 3H), 2.35 – 2.27 (m, 1H), 2.18 – 2.10 (m, 1H), 2.05 – 1.97 (m, 2H), 1.96 – 1.89 (m, 1H), 1.87 – 1.81 (m, 1H), 1.66 – 1.54 (m, 2H), 1.53 – 1.36 (m, 5H), 1.10 – 1.05 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 179.4, 177.8, 52.1, 45.2, 43.8, 33.0, 29.4, 29.3, 29.3, 23.2, 21.6, 13.8. Three signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{24}NO_5$) requires *m/z* 298.1654, found *m/z* 298.1649.

Compound 195g.



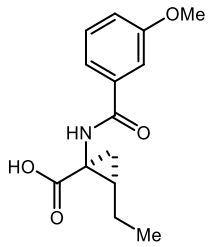
195g

^{1}H NMR (500 MHz, MeOD): δ 8.18 (t, *J* = 1.4 Hz, 1H), 8.14 – 8.10 (m, 1H), 7.91 – 7.88 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 1.73 – 1.59 (m, 3H), 1.57 – 1.53 (m, 1H), 1.31 – 1.25 (m, 1H), 1.06 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.6, 168.8, 136.8, 136.0, 133.0, 132.2, 130.8, 119.1, 113.8, 39.4, 33.4, 23.4, 21.6, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{15}N_2O_3$) requires *m/z* 259.1083, found *m/z* 259.1077.

Compound 195h.



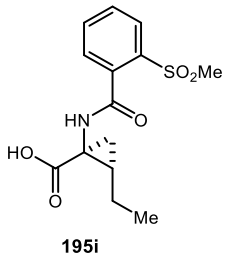
195h

^{1}H NMR (500 MHz, MeOD): δ 7.42 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.11 – 7.06 (m, 1H), 3.84 (s, 3H), 1.74 – 1.64 (m, 2H), 1.64 – 1.57 (m, 1H), 1.55 – 1.51 (m, 1H), 1.26 – 1.22 (m, 1H), 1.06 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2H not observed.

^{13}C NMR (126 MHz, MeOD): δ 175.0, 171.0, 161.2, 136.9, 130.5, 120.6, 118.7, 113.6, 55.9, 39.6, 33.2, 23.3, 21.7, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}NO_4$) requires *m/z* 264.1236, found *m/z* 264.1232.

Compound 195i.



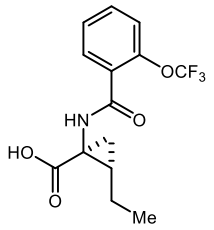
195i

^{1}H NMR (500 MHz, MeOD): δ 8.05 – 8.01 (m, 1H), 7.80 – 7.75 (m, 1H), 7.71 – 7.66 (m, 2H), 3.29 (s, 3H), 1.72 – 1.59 (m, 3H), 1.54 – 1.42 (m, 2H), 1.03 (t, *J* = 7.1 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.7, 171.1, 139.1, 138.6, 135.0, 131.3, 130.5, 129.9, 45.6, 39.0, 33.5, 23.1, 21.6, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}NO_5S$) requires *m/z* 312.0906, found *m/z* 312.0901.

Compound 195j.



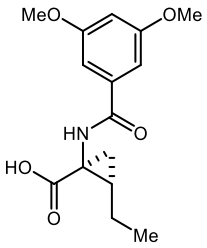
195j

^{1}H NMR (500 MHz, MeOD): δ 7.65 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.56 (td, *J* = 7.9, 1.8 Hz, 1H), 7.44 (td, *J* = 7.6, 0.9 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.57 – 1.49 (m, 2H), 1.27 – 1.21 (m, 1H), 1.03 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.8, 168.8, 146.9, 132.9, 131.9, 130.9, 128.6, 122.9, 39.4, 33.3, 23.1, 21.6, 13.8. One signal not observed, F splitting not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{15}NF_3O_4$) requires *m/z* 318.0953, found *m/z* 318.0944.

Compound 195k.



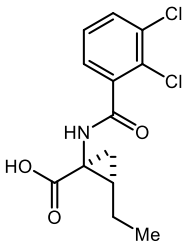
195k

^{1}H NMR (500 MHz, MeOD): δ 7.00 (d, *J* = 2.3 Hz, 2H), 6.63 (t, *J* = 2.3 Hz, 1H), 3.81 (s, 6H), 1.71 – 1.58 (m, 3H), 1.55 – 1.51 (m, 1H), 1.26 – 1.22 (m, 1H), 1.06 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.9, 170.9, 162.3, 137.4, 106.3, 104.8, 56.0, 39.5, 33.3, 23.4, 21.7, 13.8. Three signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}NO_5$) requires *m/z* 294.1341, found *m/z* 294.1337.

Compound 195l.



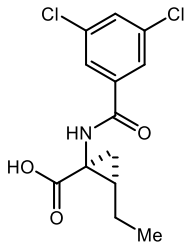
195l

^{1}H NMR (500 MHz, MeOD): δ 7.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 1.72 – 1.52 (m, 4H), 1.35 – 1.28 (m, 1H), 1.03 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.5, 170.0, 139.8, 134.4, 132.6, 130.4, 129.1, 128.2, 39.1, 33.4, 23.3, 21.6, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}NO_3Cl_2$) requires *m/z* 302.0351, found *m/z* 302.0347.

Compound 195m.



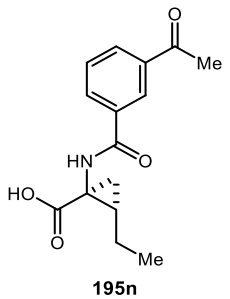
195m

^{1}H NMR (500 MHz, MeOD): δ 7.79 (t, *J* = 1.9 Hz, 2H), 7.62 (t, *J* = 1.9 Hz, 1H), 1.71 – 1.63 (m, 2H), 1.62 – 1.54 (m, 1H), 1.54 – 1.50 (m, 1H), 1.26 – 1.22 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2H not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.8, 168.0, 138.8, 136.4, 132.3, 127.3, 39.6, 33.2, 23.2, 21.7, 13.8. Two signals equivalent.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}NO_3Cl_2$) requires *m/z* 302.0351, found *m/z* 302.0344.

Compound 195n.



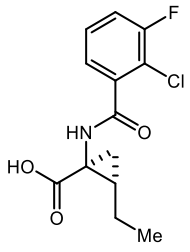
195n

^{1}H NMR (500 MHz, MeOD): δ 8.46 (t, *J* = 1.6 Hz, 1H), 8.16 – 8.13 (m, 1H), 8.08 – 8.05 (m, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 2.65 (s, 3H), 1.73 – 1.66 (m, 2H), 1.66 – 1.58 (m, 1H), 1.58 – 1.53 (m, 1H), 1.29 – 1.24 (m, 1H), 1.07 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 199.6, 175.1, 170.1, 138.5, 136.2, 133.1, 132.2, 130.0, 128.5, 39.8, 33.1, 26.8, 23.2, 21.7, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}NO_4$) requires *m/z* 276.1236, found *m/z* 276.1234.

Compound 195o.



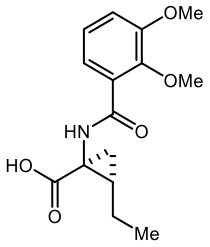
195o

^{1}H NMR (500 MHz, MeOD): δ 7.42 – 7.37 (m, 1H), 7.37 – 7.29 (m, 2H), 1.74 – 1.52 (m, 4H), 1.34 – 1.29 (m, 1H), 1.03 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.4, 169.5 (d, $J_{C\text{-}F}$ = 2.7 Hz), 159.5 (d, $^{1}J_{C\text{-}F}$ = 248.5 Hz), 139.6, 129.6 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 125.3 (d, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 119.5 (d, $^{2}J_{C\text{-}F}$ = 19.1 Hz), 118.7 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 39.1, 33.5, 23.3, 21.6, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}NO_3ClF$) requires *m/z* 286.0646, found *m/z* 286.0645.

Compound 195p.



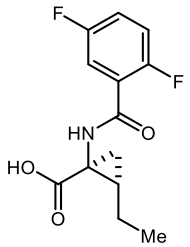
195p

^{1}H NMR (500 MHz, MeOD): δ 7.30 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.19 – 7.11 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 1.71 – 1.63 (m, 2H), 1.62 – 1.52 (m, 2H), 1.32 – 1.28 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.6, 169.6, 154.3, 148.8, 129.4, 125.5, 122.3, 116.6, 62.0, 56.6, 39.3, 33.7, 23.5, 21.6, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}NO_5$) requires *m/z* 294.1341, found *m/z* 294.1339.

Compound 195q.



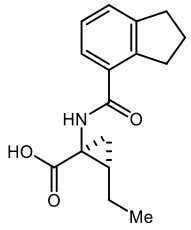
195q

^{1}H NMR (500 MHz, MeOD): δ 7.43 – 7.38 (m, 1H), 7.30 – 7.19 (m, 2H), 1.71 – 1.56 (m, 3H), 1.55 – 1.51 (m, 1H), 1.31 – 1.26 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.4, 166.6, 159.9 (dd, $^{1}J_{C\text{-}F}$ = 242.6 Hz, $J_{C\text{-}F}$ = 2.0 Hz), 157.4 (dd, $^{1}J_{C\text{-}F}$ = 246.3 Hz, $J_{C\text{-}F}$ = 2.2 Hz), 125.8 (dd, $^{2}J_{C\text{-}F}$ = 16.9 Hz, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 120.4 (dd, $^{2}J_{C\text{-}F}$ = 24.5 Hz, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 119.0 (dd, $^{2}J_{C\text{-}F}$ = 26.1 Hz, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 117.5 (dd, $^{2}J_{C\text{-}F}$ = 25.9 Hz, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 39.4, 33.6, 23.5, 21.6, 13.7.

HRMS: exact mass calculated for $[M+H]^{+}$ ($C_{13}H_{14}NO_3F_2$) requires *m/z* 270.0942, found *m/z* 270.0938.

Compound 195r.



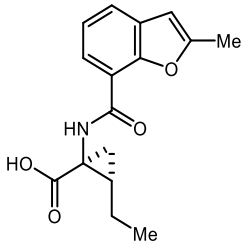
195r

^{1}H NMR (500 MHz, MeOD): δ 7.35 – 7.30 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.10 (t, *J* = 7.4 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.06 (p, *J* = 7.4 Hz, 2H), 1.71 – 1.63 (m, 2H), 1.63 – 1.55 (m, 1H), 1.55 – 1.51 (m, 1H), 1.28 – 1.24 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.8, 173.1, 146.7, 144.3, 133.1, 127.7, 127.3, 125.9, 39.3, 33.6, 33.3, 33.3, 26.4, 23.5, 21.6, 13.8.

HRMS: exact mass calculated for $[M+H]^{+}$ ($C_{16}H_{20}NO_3$) requires *m/z* 274.1443, found *m/z* 274.1437.

Compound 195s.



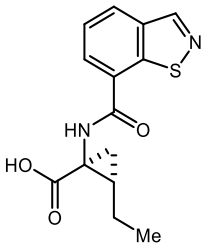
195s

^{1}H NMR (500 MHz, MeOD): δ 7.72 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 1.0 Hz, 1H), 2.52 (app. d, *J* = 0.8 Hz, 3H), 1.77 – 1.65 (m, 3H), 1.61 – 1.57 (m, 1H), 1.39 – 1.35 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.7, 168.1, 157.8, 153.1, 131.7, 125.1, 125.0, 123.7, 118.6, 103.9, 39.5, 33.9, 23.7, 21.7, 13.8, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{18}NO_4$) requires *m/z* 288.1236, found *m/z* 288.1233.

Compound 195t.



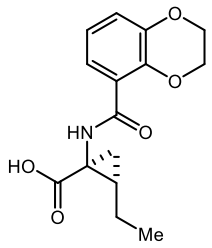
195t

^{1}H NMR (500 MHz, MeOD): δ 9.01 (s, 1H), 8.36 (d, *J* = 7.3 Hz, 1H), 8.21 (d, *J* = 7.3 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 1.76 – 1.65 (m, 3H), 1.63 – 1.58 (m, 1H), 1.34 – 1.28 (m, 1H), 1.09 (t, *J* = 7.2 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.7, 168.6, 155.2, 151.8, 138.2, 129.2, 127.3, 127.2, 126.4, 39.5, 33.4, 23.5, 21.7, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{15}N_2O_3S$) requires *m/z* 291.0803, found *m/z* 291.0797.

Compound 195u.



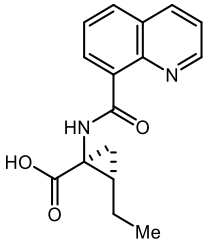
195u

^{1}H NMR (500 MHz, MeOD): δ 7.38 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.89 (t, *J* = 7.9 Hz, 1H), 4.41 – 4.37 (m, 2H), 4.31 – 4.27 (m, 2H), 1.72 – 1.63 (m, 2H), 1.63 – 1.55 (m, 1H), 1.56 – 1.51 (m, 1H), 1.29 – 1.24 (m, 1H), 1.05 (t, *J* = 7.3 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.7, 168.9, 145.4, 143.7, 123.8, 123.7, 121.9, 121.6, 66.2, 65.1, 39.4, 33.7, 23.6, 21.6, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}NO_5$) requires *m/z* 292.1185, found *m/z* 292.1183.

Compound 195v.



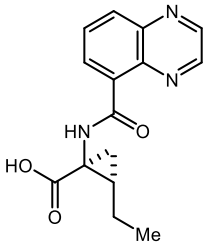
195v

^{1}H NMR (500 MHz, MeOD): δ 9.11 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.77 (d, *J* = 8.2 Hz, 1H), 8.65 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.81 (m, 2H), 1.78 – 1.68 (m, 3H), 1.65 – 1.60 (m, 1H), 1.43 – 1.37 (m, 1H), 1.10 (t, *J* = 7.2 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.7, 169.1, 149.7, 143.1 (br), 134.8, 134.3, 130.5, 128.6, 123.1, 39.5, 33.6, 23.5, 21.7, 13.8. Two signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}N_2O_3$) requires *m/z* 285.1239, found *m/z* 285.1235.

Compound 195w.



195w

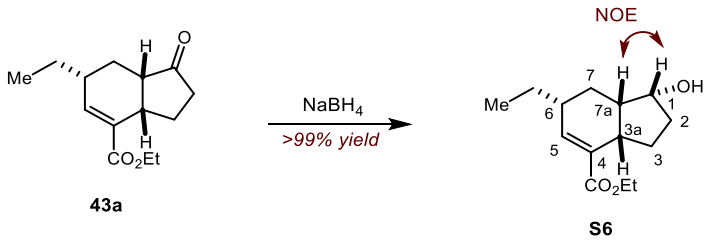
^{1}H NMR (500 MHz, MeOD): δ 9.02 – 8.98 (m, 2H), 8.64 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.28 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.99 – 7.94 (m, 1H), 1.77 – 1.67 (m, 3H), 1.64 – 1.60 (m, 1H), 1.43 – 1.37 (m, 1H), 1.09 (t, *J* = 7.2 Hz, 3H). N*H* and CO_2*H* not observed.

^{13}C NMR (126 MHz, MeOD): δ 174.6, 168.1, 146.8, 145.9, 144.0, 141.5, 134.6, 134.3, 131.1, 131.0, 39.5, 33.8, 23.6, 21.7, 13.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}N_3O_3$) requires *m/z* 286.1192, found *m/z* 286.1187.

6.14 CMA Conjugate Synthesis (Scheme 55).

Compound S6.



To a round bottom flask charged with compound **43a** (50 mg, 0.21 mmol, 1 equiv.) in a solution was EtOH (1 mL) was added $NaBH_4$ (9 mg, 0.24 mmol, 1.2 equiv.) in one portion at room temperature under an atmosphere of nitrogen. The reaction was stirred for 30 minutes, quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford the title compound as a colourless oil (50 mg, >99%). >20:1 dr C[1].

TLC (20% EtOAc/petroleum ether): R_f = 0.21 stained by $KMnO_4$.

υ_{max} (neat): 3406 (br.), 2956, 2919, 2870, 2855, 1708, 1640, 1463, 1242, 1100 cm^{-1}.

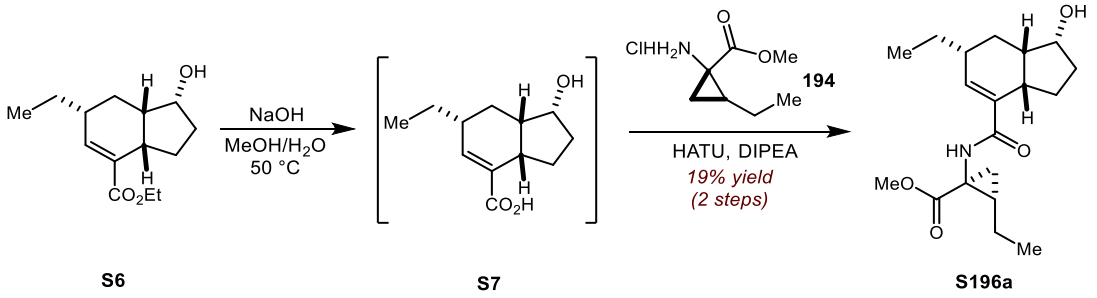
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 1H, H^5), 4.37 (td, *J* = 8.4, 6.5 Hz, 1H, H^1), 4.24 – 4.09 (m, 2H, $CO_2CH_2CH_3$), 2.76 – 2.67 (m, 1H, H^{3a}), 2.16 – 1.97 (m, 4H, H^2, H^3, H^{7a}, H^6), 1.87 – 1.79 (m, 1H, H^7), 1.68 – 1.32 (m, 4H, $H^{2'}$, $H^{3'}$, CH_2CH_3), 1.27 (t,

J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.98 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.95 – 0.85 (m, 1H, $H^{7'}$). O*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (CO_2Et), 143.5 (C^5), 133.5 (C^4), 75.2 (C^1), 60.3 ($CO_2CH_2CH_3$), 42.5 (CH), 38.0 (CH), 36.4 (C^{3a}), 31.1 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 23.9 (C^7), 14.4 ($CO_2CH_2CH_3$), 11.5 (CH_2CH_3).

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{14}H_{26}NO_3$) requires *m/z* 256.1909, found *m/z* 256.1884.

Compound S6.



To a round bottom flask charged with compound **S6** (31 mg, 0.13 mmol, 1 equiv.) in a solution of 1:1 MeOH/H_2O (9 mL) was added NaOH (22 mg, 0.55 mmol, 4.4 equiv.) in one portion. The resulting solution was brought to 50 °C for 21 h. The reaction was allowed to cool to room temperature, extracted with EtOAc (5 mL) and the aqueous brought to pH 1 with HCl (aq.). The aqueous was extracted with EtOAc (3 x 10 mL), and the organics combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated to afford compound **S7** as a colourless oil (11 mg, 0.05 mmol).

The oil was transferred to a 2-dram vial and HATU (26 mg, 0.07 mmol, 1.2 equiv.) added, followed by DMF (0.3 mL) and DIPEA (30 µL, 0.17 mmol, 3 equiv.). The reaction was stirred at room temperature for 5 minutes before compound **194** (14 mg, 0.08 mmol, 1.5 equiv.) was added. The resulting solution was stirred at room temperature for 6 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine (10 mL), dried

over Na_2SO_4, filtered, and evaporated to afford a pale orange oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 40-50% EtOAc/CH_2Cl_2 to afford the title compound as a white solid (6 mg, 19% (2 steps)).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.16 stained by $KMnO_4$ and faintly visible by UV (short wave).

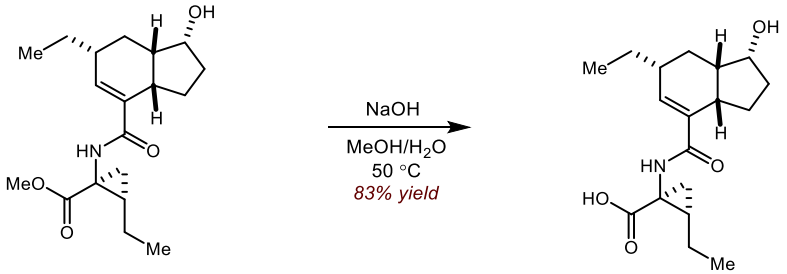
υ_{max} (film): 3359 (br.), 2956, 2926, 2894, 1734, 1508, 1459, 1253, 1193 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.37 – 6.32 (m, 1H), 6.19 (s, 1H), 4.42 – 4.36 (m, 1H), 3.69 (s, 3H), 2.80 – 2.72 (m, 1H), 2.21 – 2.12 (m, 1H), 2.09 – 1.97 (m, 3H), 1.89 – 1.83 (m, 1H), 1.68 – 1.36 (m, 8H), 1.29 – 1.23 (m, 1H), 1.02 – 0.95 (m, 6H), 0.94 – 0.84 (m, 1H). O*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 169.5, 169.4, 137.3, 137.2, 137.0, 75.1, 52.5, 52.4, 42.4, 38.4, 38.3, 37.6, 37.6, 36.4, 33.3, 33.2, 31.4, 28.7, 28.1, 28.0, 24.3, 24.2, 23.3, 23.2, 20.6, 13.6, 11.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{30}NO_4$) requires *m/z* 336.2169, found *m/z* 336.2173.

Compound 196a.



S196a **196a**

Experimental

Prepared according to General Procedure H using compound **S196a** (5 mg, 0.01 mmol, 1 equiv.), NaOH (2 mg, 0.05 mmol, 5 equiv.), and 1:1 MeOH/H_2O (1 mL). After 7 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (4 mg, 83 %).

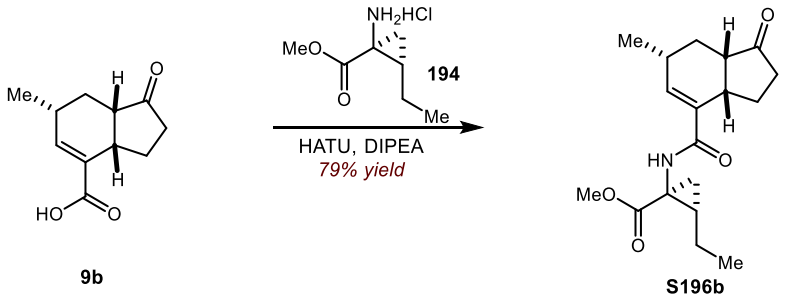
υ_{max} (film): 3317 (br.), 2956, 2921, 2870, 1697, 1654, 1619, 1509, 1275, 1182 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.38 – 6.28 (m, 1H), 4.44 – 4.35 (m, 1H), 2.77 – 2.63 (m, 1H), 2.23 – 2.13 (m, 1H), 2.12 – 1.92 (m, 3H), 1.92 – 1.83 (m, 1H), 1.73 – 1.32 (m, 8H), 1.22 – 1.12 (m, 1H), 1.06 – 0.97 (m, 6H), 0.94 – 0.86 (m, 1H). CO_2H and O*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 172.3, 172.0, 171.6, 140.5, 139.9, 135.6, 74.9, 42.5, 42.4, 40.1, 39.8, 37.8, 37.8, 36.3, 36.2, 33.6, 33.5, 31.3, 28.5, 28.5, 28.3, 28.0, 24.0, 21.3, 21.3, 21.2, 20.8, 13.5, 13.4, 11.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}NO_4$) requires *m/z* 322.2013, found *m/z* 322.2015.

Compound S196b.



Prepared according to General Procedure G using compound **9b** (10 mg, 0.05 mmol, 1 equiv.), HATU (23 mg, 0.06 mmol, 1.2 equiv.), compound **194** (14 mg, 0.08 mmol, 1.5 equiv.), DIPEA (30 µL, 0.17 mmol, 3 equiv.), and DMF (0.3 mL). After 16 h the

reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) afford the title compound as a colourless oil (13 mg, 79%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.34 stained by $KMnO_4$ and faintly visible by UV (short wave).

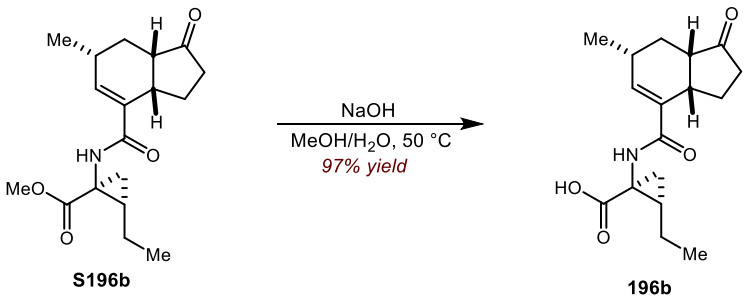
υ_{max} (film): 3320 (br.), 2956, 2922, 2870, 2852, 1732, 1658, 1625, 1515, 1162 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.30 (s, 1H), 6.24 – 6.18 (m, 1H), 3.72 – 3.68 (m, 3H), 3.23 – 3.13 (m, 1H), 2.52 – 2.21 (m, 5H), 1.88 – 1.80 (m, 1H), 1.67 – 1.55 (m, 4H), 1.53 – 1.44 (m, 1H), 1.32 – 1.26 (m, 1H), 1.12 – 0.96 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 220.2, 171.7, 169.3, 169.2, 137.7, 137.7, 136.0, 135.9, 52.5, 52.5, 46.6, 46.6, 38.4, 38.3, 36.0, 36.0, 33.3, 33.1, 30.8, 30.8, 28.7, 27.9, 27.8, 23.3, 23.1, 20.9, 20.6, 13.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1856, found *m/z* 320.1857.

Compound 196b.



Prepared according to General Procedure H using compound **S196b** (13 mg, 0.04 mmol, 1 equiv.), NaOH (5 mg, 0.13 mmol, 3 equiv.), and 1:1 MeOH/H_2O (2 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (12 mg, 97%).

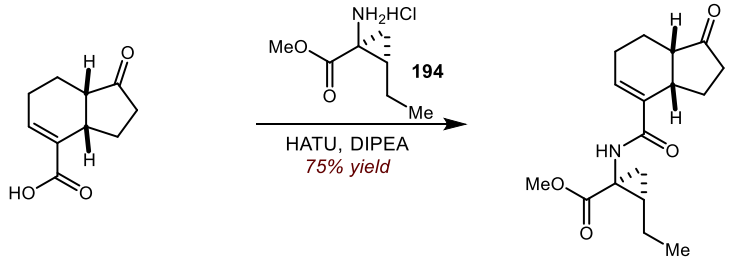
υ_{max} (film): 3339 (br.), 2950, 2935, 2870, 1731, 1656, 1625, 1519, 1178 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 – 6.48 (m, 1H), 6.33 – 6.24 (m, 1H), 4.68 (br. s, 1H), 3.22 – 3.09 (m, 1H), 2.51 – 2.42 (m, 1H), 2.42 – 2.23 (m, 4H), 1.92 – 1.80 (m, 1H), 1.69 – 1.53 (m, 4H), 1.53 – 1.40 (m, 1H), 1.32 – 1.26 (m, 1H), 1.13 – 0.96 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3, 220.1, 175.1, 174.5, 170.7, 170.3, 139.6, 138.9, 135.3, 135.1, 46.6, 46.6, 39.0, 38.7, 38.3, 36.0, 35.9, 33.9, 33.8, 30.9, 30.9, 28.6, 28.6, 27.9, 27.8, 22.7, 22.3, 20.9, 20.8, 20.8, 13.6, 13.5.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{17}H_{22}NO_4$) requires *m/z* 304.1554, found *m/z* 304.1551.

Compound S196c.



Prepared according to General Procedure G using compound **9a** (15 mg, 0.08 mmol, 1 equiv.), HATU (38 mg, 0.10 mmol, 1.2 equiv.), compound **194** (22 mg, 0.12 mmol, 1.5 equiv.), DIPEA (40 µL, 0.23 mmol, 3 equiv.), and DMF (0.4 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (19 mg, 75%).

(TLC (30% EtOAc/CH_2Cl_2): R_f = 0.32 stained by $KMnO_4$ and faintly visible by UV (short wave).

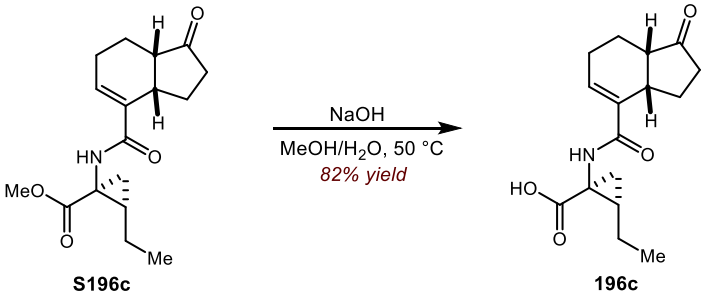
υ_{max} (film): 3318 (br.), 2956, 2928, 2874, 1731, 1660, 1628, 1515, 1164 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 – 6.40 (m, 1H), 6.29 (s, 1H), 3.70 (s, 3H), 3.35 – 3.28 (m, 1H), 2.44 – 2.38 (m, 1H), 2.31 – 2.15 (m, 3H), 2.13 – 2.06 (m, 2H), 1.89 – 1.81 (m, 1H), 1.81 – 1.65 (m, 2H), 1.65 – 1.53 (m, 3H), 1.49 – 1.42 (m, 1H), 1.30 – 1.25 (m, 1H), 1.01 – 0.94 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.7, 171.7, 169.7, 169.5, 136.6, 136.5, 132.9, 132.8, 52.5, 52.4, 46.8, 38.3, 38.2, 37.0, 36.9, 36.0, 36.0, 33.4, 33.0, 26.8, 26.8, 23.3, 23.1, 23.1, 20.6, 20.6, 19.7, 13.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}NO_4$) requires *m/z* 306.1700, found *m/z* 306.1698.

Compound 196c.



Prepared according to General Procedure H using compound **S196c** (18 mg, 0.05 mmol, 1 equiv.), NaOH (7 mg, 0.18 mmol, 3 equiv.), and 1:1 MeOH/H_2O (2.5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (14 mg, 82%).

υ_{max} (film): 3305 (br.), 2960, 2928, 2872, 1725, 1656, 1621, 1513, 1169 cm^{-1}.

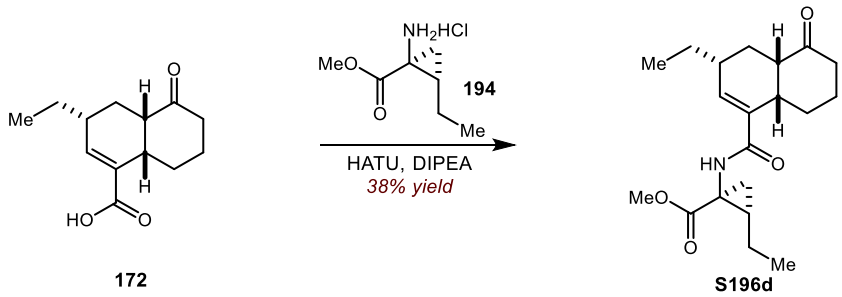
Experimental

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56 – 6.52 (m, 1H), 6.51 – 6.46 (m, 1H), 3.34 – 3.26 (m, 1H), 2.46 – 2.38 (m, 1H), 2.33 – 2.16 (m, 3H), 2.15 – 2.07 (m, 2H), 1.88 – 1.66 (m, 3H), 1.66 – 1.52 (m, 3H), 1.51 – 1.41 (m, 1H), 1.31 – 1.23 (m, 1H), 1.05 – 0.99 (m, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.5, 220.4, 175.4, 174.6, 171.1, 170.6, 135.9, 135.7, 134.9, 134.0, 46.8, 39.1, 38.6, 37.0, 36.9, 35.9, 35.9, 33.9, 26.9, 26.8, 23.3, 23.2, 22.8, 22.2, 20.9, 20.7, 19.6, 19.6, 13.6, 13.5.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{16}H_{20}NO_4$) requires *m/z* 290.1398, found *m/z* 290.1395.

Compound S196d.



Prepared according to General Procedure G using compound **172** (10 mg, 0.04 mmol, 1 equiv.), HATU (21 mg, 0.06 mmol, 1.2 equiv.), compound **194** (12 mg, 0.07 mmol, 1.5 equiv.), DIPEA (20 µL, 0.11 mmol, 3 equiv.), and DMF (0.2 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (6 mg, 38%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.36 stained by $KMnO_4$.

υ_{max} (film): 3313 (br.), 2956, 2924, 2870, 2854, 1731, 1708, 1660, 1627, 1515, 1165 cm^{-1}.

Experimental

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 – 6.18 (m, 2H), 3.73 – 3.69 (m, 3H), 3.01 – 2.93 (m, 1H), 2.55 – 2.47 (m, 1H), 2.40 – 2.33 (m, 2H), 2.26 – 2.15 (m, 1H), 2.06 – 1.94 (m, 2H), 1.81 – 1.33 (m, 10H), 1.31 – 1.26 (m, 1H), 1.03 – 0.93 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 214.4, 214.3, 171.8, 169.5, 169.4, 137.7, 137.7, 135.8, 52.5, 52.5, 49.9, 38.7, 38.5, 38.4, 38.1, 36.9, 33.4, 33.1, 28.4, 28.1, 28.1, 27.4, 27.3, 24.8, 23.3, 23.1, 20.6, 13.6, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{30}NO_4$) requires *m/z* 348.2169, found *m/z* 348.2172.

Compound 196d.

Prepared according to General Procedure H using compound **27c** (26 mg, 0.07 mmol, 1 equiv.), NaOH (9 mg, 0.23 mmol, 3 equiv.), and 1:1 MeOH/H_2O (5 mL). After 16 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (23 mg, 92%). Isomerisation to the *trans*-isomer observed (dr 3:1 C^{8a}).

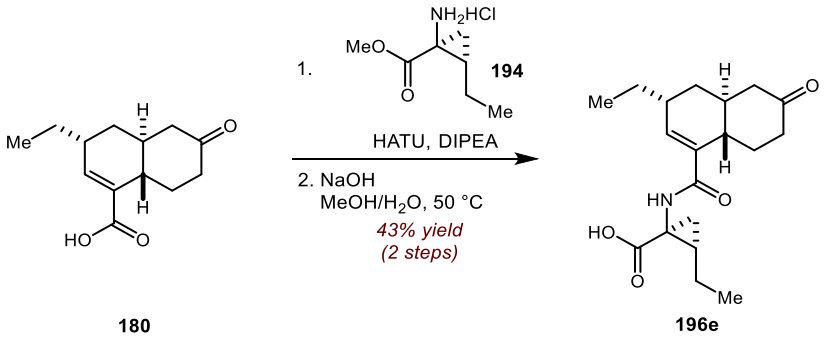
υ_{max} (film): 3296 (br.), 2958, 2924, 2870, 1693, 1656, 1625, 1513, 1169 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 – 6.49 (m, 1H), 6.32 – 6.25 (m, 1H), 3.00 – 2.90 (m, 1H), 2.53 –2.47 (m, 1H), 2.39 – 2.27 (m, 2H), 2.24 – 2.15 (m, 1H), 2.03 – 1.93 (m, 2H), 1.80 – 1.31 (m, 10H), 1.29 – 1.22 (m, 1H), 1.05 – 0.98 (m, 3H), 0.98 – 0.91 (m, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 214.5, 214.4, 175.4, 174.8, 170.8, 170.4, 137.7, 137.0, 136.8, 49.9, 49.8, 39.1, 38.7, 38.6, 38.2, 38.2, 36.8, 36.7, 33.9, 33.8, 28.3, 28.3, 28.0, 27.9, 27.4, 27.4, 24.8, 24.8, 22.7, 22.2, 20.9, 20.8, 13.6, 13.5, 11.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{28}NO_4$) requires *m/z* 334.2013, found *m/z* 334.2013.

Compound 196e.



To a 2-dram vial was added compound **180** (10 mg, 0.04 mmol, 1 equiv.) and HATU (21 mg, 0.06 mmol, 1.2 equiv.). DMF (0.2 mL) was added, followed by DIPEA (20 µL, 0.11 mmol, 3 equiv.) and the resulting solution stirred at room temperature for 5 minutes. Compound **194** (12 mg, 0.07 mmol, 1.5 equiv.) was then added in one portion and the vial capped with a screw top lid. The reaction was stirred for 16 h under air. The reaction was then diluted with H_2O (10 mL) and the organics extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of CH_2Cl_2 and purified by flash silica column chromatography, eluent 30% EtOAc/CH_2Cl_2 to afford a pale yellow oil which was taken up in 1:1 MeOH/H_2O (1.5 mL) and NaOH (5 mg, 0.13 mmol, 3 equiv.) added. The reaction was brought to 50 °C for 16 h. The reaction was then subjected to purification outlined in General Procedure H to afford the title compound as an orange solid (7 mg, 43% (2 steps)).

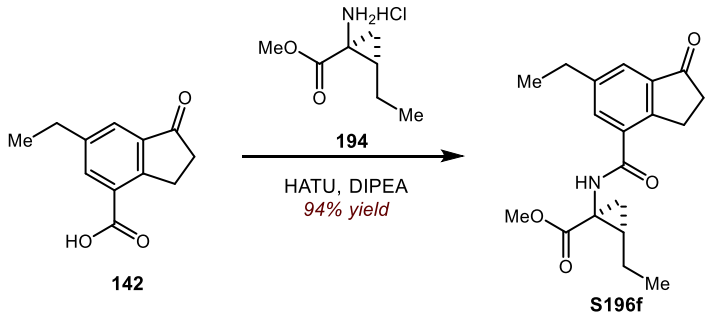
υ_{max} (film): 3289 (br.), 2958, 2930, 1697, 1625, 1509, 1400, 1307 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 – 6.31 (m, 1H), 6.27 – 6.17 (m, 1H), 2.55 – 2.47 (m, 1H), 2.47 – 2.38 (m, 3H), 2.38 – 2.31 (m, 1H), 2.26 – 2.14 (m, 2H), 1.70 – 1.51 (m, 6H), 1.51 – 1.40 (m, 2H), 1.36 – 1.20 (m, 3H), 1.06 – 1.00 (m, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.1, 210.8, 174.8, 173.8, 172.6, 172.0, 137.5, 137.2, 137.2, 135.9, 48.2, 48.2, 41.6, 41.5, 40.9, 40.9, 39.1, 38.5, 36.5, 36.4, 36.3, 34.0, 33.9, 33.0, 32.9, 29.1, 28.1, 28.0, 22.7, 22.1, 21.0, 20.8, 13.6, 13.5, 12.5.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{19}H_{26}NO_4$) requires *m/z* 332.1867, found *m/z* 332.1863.

Compound S196f.



Prepared according to General Procedure G using compound **142** (10 mg, 0.05 mmol, 1 equiv.), HATU (22 mg, 0.06 mmol, 1.2 equiv.), compound **194** (10 mg, 0.06 mmol, 1.1 equiv.), DIPEA (30 µL, 0.17 mmol, 3 equiv.), and DMF (0.3 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 30% EtOAc/CH_2Cl_2) to afford the title compound as a colourless oil (15 mg, 94%).

TLC (30% EtOAc/CH_2Cl_2): R_f = 0.55 stained by $KMnO_4$ and faintly visible by UV (short wave).

Experimental

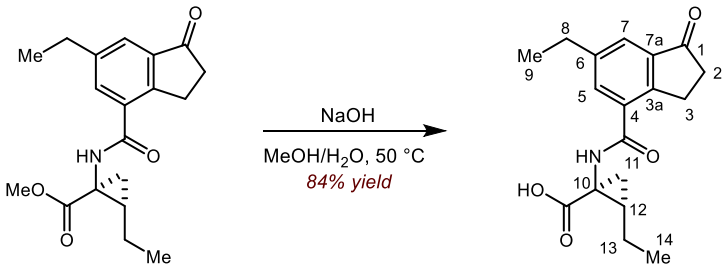
υ_{max} (film): 3305 (br.), 2960, 2922, 2872, 2852, 1714, 1651, 1519, 1336, 1162 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.62 (s, 1H), 6.66 (s, 1H), 3.74 (s, 3H), 3.37 – 3.32 (m, 2H), 2.75 – 2.65 (m, 4H), 1.71 – 1.54 (m, 4H), 1.42 – 1.38 (m, 1H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.01 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 171.5, 168.2, 152.1, 144.4, 138.7, 132.8, 132.8, 125.4, 52.6, 38.7, 36.6, 33.3, 28.5, 25.9, 23.3, 20.6, 15.6, 13.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}NO_4$) requires *m/z* 330.1700, found *m/z* 330.1702.

Compound 196f.



S196f **196f**

Prepared according to General Procedure H using compound **S196f** (15 mg, 0.05 mmol, 1 equiv.), NaOH (7 mg, 0.18 mmol, 3 equiv.), and 1:1 MeOH/H_2O (2.5 mL). After 6 h the reaction was subjected to purification outlined in General Procedure H to afford the title compound as a white solid (12 mg, 84 %).

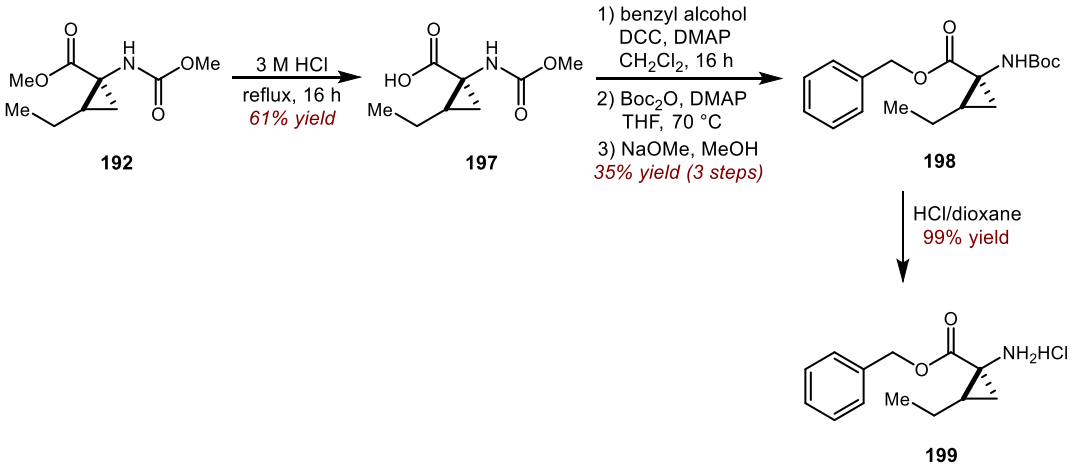
υ_{max} (film): 3272 (br.), 2963, 2934, 2872, 1654, 1586, 1396, 1305 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H, $H^{5/7}$), 7.63 (s, 1H, $H^{5/7}$), 6.83 (s, 1H, N*H*), 3.40 – 3.30 (m, 2H, CH_2), 2.76 – 2.63 (m, 4H, H^{8},CH_2), 1.74 – 1.55 (m, 4H, H^{13}, H^{12}, H^{11}), 1.46 – 1.38 (m, 1H, $H^{11'}$), 1.25 (t, *J* = 7.6 Hz, 3H, H^{9}), 1.04 (t, *J* = 7.0 Hz, 3H, H^{14}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8 (*C*O), 175.6 (*C*O), 169.1 (*C*O), 152.2 (Ar), 144.4 (Ar), 138.7 (Ar), 133.0 ($C^{5/7}$), 132.2 (Ar), 125.7 ($C^{5/7}$), 38.8 (C^{10}), 36.6 (*C*H_2), 34.1 (C^{12}), 28.5 (*C*H_2), 25.9 (*C*H_2), 23.2 (C^{11}), 20.7 (C^{13}), 15.5 (C^9), 13.6 (C^{14}).

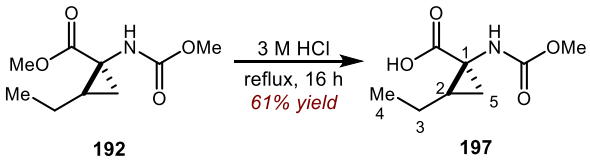
HRMS: exact mass calculated for $[M-H]^-$ ($C_{18}H_{20}NO_4$) requires *m/z* 314.1398, found *m/z* 314.1394.

6.15 Synthesis of Compound 199 (Scheme 56).



6.15.1 Procedures and Characterisation of Compound 199.

Compound 197.



To a round bottomed flask was added compound **192** (894 mg, 4.44 mmol) and 3 M HCl (16 mL). The reaction was brought to 100 °C for 16 h. The reaction was allowed to cool to room temperature and extracted with EtOAc (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow oil. The crude material was loaded in a solution of 50%

Experimental

EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 50-60% EtOAc/petroleum ether to afford the title compound as a colourless oil which solidified to a white solid on standing (508 mg, 61%).

TLC (50% EtOAc/petroleum ether): R_f = 0.14 stained by $KMnO_4$.

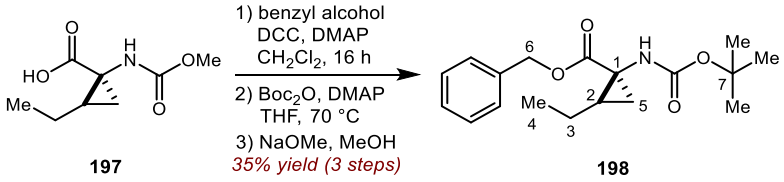
υ_{max} (neat): 3331, 2958 (br.), 2874, 1703, 1686, 1526, 1268, 1191 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 12.33 (s, 1H, N*H*/O*H*), 7.73 (s, 1H, N*H*/O*H*), 3.50 (s, 3H, OCH_3), 1.59 – 1.40 (m, 2H, H^3), 1.40 – 1.30 (m, 1H, H^2), 1.26 – 1.18 (m, 1H, H^5), 1.08 – 0.98 (m, 1H, $H^{5'}$), 0.91 (t, *J* = 7.3 Hz, 3H, H^4).

^{13}C NMR (101 MHz, DMSO-d_6): δ 173.2 (*C*O), 156.7 (*C*O), 51.1 (O*C*H_3), 37.9 (C^1), 31.4 (C^2), 22.1 (C^5), 20.0 (C^3), 13.4 (C^4).

HRMS: exact mass calculated for $[M-H]^-$ ($C_8H_{12}NO_4$) requires *m/z* 186.0772, found *m/z* 186.0776.

Compound 198.



197 **198**

To a round bottom flask charged with **197** (300 mg, 1.60 mmol, 1 equiv.) and CH_2Cl_2/DMF (3:1, 8 mL) was added DMAP (20 mg, 0.16 mmol, 0.1 equiv.), DCC (364 mg, 1.76 mmol, 1.1 equiv.), and benzyl alcohol (0.18 mL, 1.76 mmol, 1.1 equiv.). The reaction was stirred at room temperature for 16 h before being diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a colourless residue. The crude material was loaded in a solution of 20% EtOAc/petroleum ether

and purified by flash silica column chromatography, eluent 20% EtOAc/petroleum ether to afford a colourless oil which was not characterised. The colourless oil was dissolved in THF (3 mL) in a round bottom flask. Boc_2O (454 mg, 2.08 mmol, 1.3 equiv.) and DMAP (39 mg, 0.32 mmol, 0.2 equiv.) were added and the reaction was brought to 70 °C for 16 h under an atmosphere of nitrogen. The reaction was then allowed to cool to room temperature and diluted with anhydrous MeOH (2 mL). To a separate round bottom flask charged with anhydrous MeOH (2 mL) was added Na metal (11 mg, 0.48 mmol, 0.3 equiv.) under an atmosphere of nitrogen. The resulting solution was then added dropwise to the reaction flask at 0 °C. The reaction was allowed to rise to room temperature and stirred for 1.5 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a pale orange oil. The crude material was loaded in a solution of 15% EtOAc/petroleum ether and purified by flash silica column chromatography, eluent 15-20% EtOAc/petroleum ether to afford the title compound as a pale yellow oil (177 mg, 35% over three steps).

TLC (20% EtOAc/petroleum ether): R_f = 0.46 stained by $KMnO_4$.

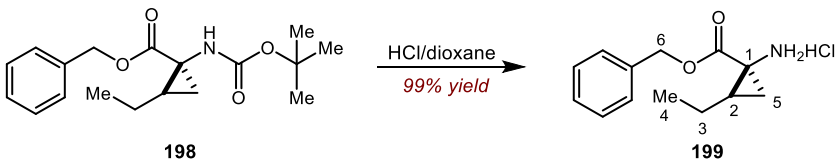
υ_{max} (neat): 3398 (br.), 3363 (br.), 2974, 1734, 1560, 1498, 1389, 1366, 1164 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 5H, Ar*H*), 5.22 – 5.08 (m, 2H, H^6), 1.62 – 1.49 (m, 3H, H^3, H^5), 1.48 – 1.42 (m, 1H, H^2), 1.39 (s, 9H, *t*Bu), 1.32 – 1.24 (m, 1H, $H^{5'}$), 0.91 (t, *J* = 7.4 Hz, 3H, H^4). N*H* not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (*C*O), 155.9 (*C*O), 136.0 (Ar), 128.5 (Ar), 128.1 (Ar), 79.8 (br., C^7), 66.9 (C^6), 38.8 (br., C^1), 33.6 (br., C^2), 28.3 (*C*H_3), 23.4 (br., C^5), 20.4 (C^3), 13.6 (C^4). Five signals not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}NO_4$) requires *m/z* 320.1856, found *m/z* 320.1859.

Compound 199.



198 199

To a round bottom flask charged with compound **198** (167 mg, 0.52 mmol) was added dioxane (1 mL), followed by dropwise addition of 6 M HCl (1 mL). The reaction was stirred at room temperature for 3 h, before the addition of further 6 M HCl (1 mL). The reaction was stirred at room temperature for a further 1 h, before being concentrated *in vacuo* to afford the title compound as a pale brown solid (132 mg, 99%).

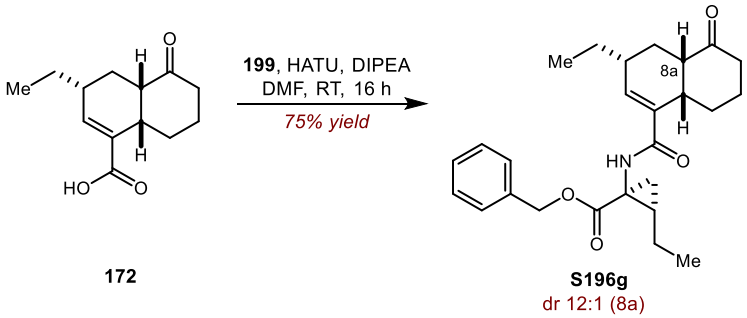
υ_{max} (neat): 3411 (br.), 2961 (br.), 2874 (br.), 2683 (br.), 1727, 1455, 1355, 1262, 1190, 1169 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (br. s, 2H), 7.41 – 7.36 (m, 2H, Ar*H*), 7.36 – 7.27 (m, 3H, Ar*H*), 5.22 (s, 2H, H^6), 2.02 – 1.92 (m, 1H, H^2), 1.85 – 1.76 (m, 1H, H^5), 1.64 – 1.44 (m, 2H, H^3), 1.44 – 1.36 (m, 1H, $H^{5'}$), 0.87 (t, *J* = 7.4 Hz, 3H, H^4).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2 (*C*O), 134.8 (Ar), 128.7 (Ar), 128.7 (Ar), 128.6 (Ar), 68.2 (C^6), 38.5 (C^1), 30.5 (C^2), 20.0 (C^5, C^3), 13.3 (C^4). Two signals equivalent, one signal coincident.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{18}NO_2$) requires *m/z* 220.1332, found *m/z* 220.1331.

Compound S196g.



Prepared according to General Procedure G using compound **172** (50 mg, 0.22 mmol, 1 equiv.), HATU (111 mg, 0.29 mmol, 1.3 equiv.), compound **199** (86 mg, 0.34 mmol, 1.5 equiv.), DIPEA (0.12 mL, 0.69 mmol, 3 equiv.), and DMF (1.7 mL). After 16 h the reaction was subjected to purification outlined in General Procedure G (silica gel, 10% EtOAc/CH_2Cl_2) to afford the title compound as an orange oil (71 mg, 75%), (dr 12:1 C^{8a}).

TLC (10% EtOAc/CH_2Cl_2): R_f = 0.28 stained by $KMnO_4$ and faintly visible by UV (short wave).

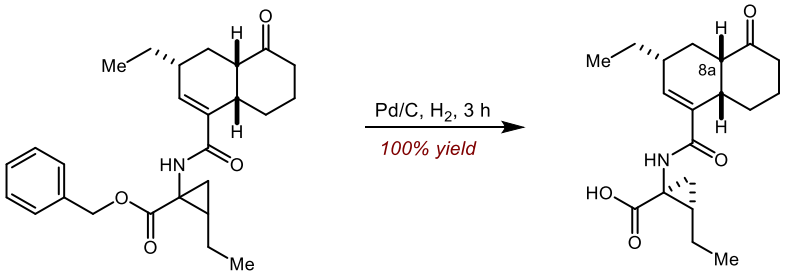
υ_{max} (film): 3307 (br.), 2958, 2928, 2870, 1723, 1703, 1658, 1627, 1500, 1455, 1327, 1264, 1158 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 5H), 6.36 – 6.31 (m, 1H), 6.17 – 6.10 (m, 1H), 5.22 – 5.03 (m, 2H), 2.96 – 2.85 (m, 1H), 2.51 – 2.41 (m, 1H), 2.35 – 2.24 (m, 2H), 2.18 – 2.06 (m, 1H), 1.93 – 1.77 (m, 2H), 1.76 – 1.66 (m, 1H), 1.66 – 1.53 (m, 4H), 1.53 – 1.19 (m, 6H), 1.00 – 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 214.3, 214.3, 171.1, 171.1, 169.5, 169.4, 137.7, 137.6, 135.8, 135.7, 128.5, 128.4, 128.4, 128.3, 67.3, 67.2, 49.9, 49.8, 38.6, 38.4, 38.3, 38.0, 36.8, 36.7, 33.5, 33.2, 28.3, 28.0, 28.0, 27.2, 27.2, 24.8, 23.4, 23.2, 20.6, 20.5, 13.6, 11.4, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{26}H_{34}NO_4$) requires *m/z* 424.2482, found *m/z* 424.2481.

Compound 196d.



S196g **196d**
dr 18:1 (8a)

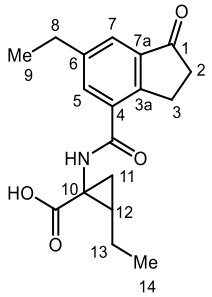
To a round bottom flask charged with compound **S196g** (66 mg, 0.16 mmol, 1 equiv.) was added 10% Pd/C (30 mg, 0.03 mmol, 20 mol%) and EtOAc (3 mL). The reaction was sparged with H_2 (balloon) for 1 minute, and stirred under an atmosphere of H_2 (balloon) for 3 h. The reaction was filtered through celite, eluting with EtOAc. The organics were concentrated *in vacuo* to afford a colourless oil, which was taken up in a minimal volume of diethyl ether, and petroleum ether added until a white precipitate formed. The solvent was removed using a Pasteur pipette and the precipitate dried under vacuum to afford the desired product as a white solid (52 mg, 100%), (dr 18:1 C^{8a}).

^{1}H NMR (400 MHz, Acetone-d_6): δ 8.04 – 7.90 (m, 1H), 6.47 – 6.34 (m, 1H), 3.00 – 2.91 (m, 1H), 2.54 – 2.29 (m, 2H), 2.25 – 2.13 (m, 2H), 2.00 – 1.90 (m, 2H), 1.69 – 1.24 (m, 10H), 1.21 – 1.06 (m, 1H), 1.01 – 0.91 (m, 6H). One signal not observed.

^{13}C NMR (101 MHz, Acetone-d_6): δ 213.1, 213.0, 172.9, 172.7, 170.2, 169.9, 138.1, 137.9, 136.6, 136.1, 50.9, 38.9, 38.9, 38.8, 37.5, 37.5, 32.7, 32.5, 28.9, 28.9, 28.6, 28.5, 28.0, 25.6, 22.6, 22.4, 21.4, 21.3, 13.7, 11.4.

6.16 Single enantiomer data.

Compound 196f



Isomer 1.

υ_{max} (film): 3348 (br.), 2969, 2928, 2874, 1701, 1654, 1522, 1273 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H, $H^{5/7}$), 7.63 (s, 1H, $H^{5/7}$), 6.66 (s, 1H, N*H*), 3.40 – 3.34 (m, 2H, CH_2), 2.79 – 2.67 (m, 4H, H^{8}, CH_2), 1.74 – 1.51 (m, 4H, H^{11}, H^{12}, H^{13}), 1.45 – 1.38 (m, 1H, $H^{11'}$), 1.27 (t, *J* = 7.6 Hz, 3H, H^{9}), 1.07 (t, *J* = 7.2 Hz, 3H, H^{14}). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.7 (C^{1}), 152.3 (Ar), 144.5 (Ar), 138.8 (Ar), 132.9 ($C^{5/7}$), 125.9 ($C^{5/7}$), 39.0 (C^{10}), 36.6 (CH_2), 34.2 (C^{12}), 28.5 (CH_2), 26.0 (CH_2), 22.9 (C^{11}), 20.8 (C^{13}), 15.6 (C^{9}), 13.6 (C^{14}). Three signals not observed.

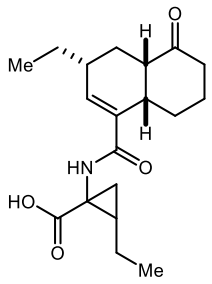
Isomer 2.

υ_{max} (film): 3279 (br.), 2963, 2928, 2872, 1697, 1651, 1524, 1270, 1184 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H, $H^{5/7}$), 7.63 (s, 1H, $H^{5/7}$), 6.79 (s, 1H, N*H*), 3.42 – 3.29 (m, 2H, CH_2), 2.78 – 2.64 (m, 4H, H^{8}, CH_2), 1.77 – 1.48 (m, 4H, H^{11}, H^{12}, H^{13}), 1.46 – 1.38 (m, 1H, $H^{11'}$), 1.25 (t, *J* = 7.6 Hz, 3H, H^{9}), 1.05 (t, *J* = 7.2 Hz, 3H, H^{14}). CO_2H not observed.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.9 (C^1), 175.4 (*C*O), 169.1 (*C*O), 152.3 (Ar), 144.4 (Ar), 138.7 (Ar), 133.0 ($C^{5/7}$), 132.2 (Ar), 125.8 ($C^{5/7}$), 38.8 (C^{10}), 36.6 (CH_2), 34.1 (C^{12}), 28.5 (CH_2), 25.9 (CH_2), 23.2 (C^{11}), 20.7 (C^{13}), 15.5 (C^9), 13.6 (C^{14}).

Compound 196d



Isomer 1.

υ_{max} (film): 3302 (br.), 2963, 2924, 2867, 1703, 1654, 1625, 1509, 1459 cm^{-1}.
^{1}H NMR (400 MHz, Acetone-d_6): δ 7.97 (s, 1H), 6.43 (s, 1H), 2.99 – 2.90 (m, 1H), 2.52 – 2.35 (m, 2H), 2.24 – 2.13 (m, 2H), 2.00 – 1.91 (m, 2H), 1.69 – 1.32 (m, 10H), 1.20 – 1.14 (m, 1H), 1.01 – 0.92 (m, 6H). CO_2H not observed.

^{13}C NMR (101 MHz, Acetone-d_6): δ 211.5, 136.6, 135.1, 49.5, 37.5, 36.1, 31.2, 27.5, 27.1, 26.6, 24.2, 20.8, 20.0, 12.3, 10.0. Four signals not observed.

Isomer 2.

υ_{max} (film): 3320 (br), 2961, 2934, 2876, 1703, 1656, 1630, 1519, 1459, 1190 cm^{-1}.

^{1}H NMR (500 MHz, Acetone-d_6): δ 7.92 (s, 1H), 6.38 (s, 1H), 3.00 – 2.92 (m, 1H), 2.51 – 2.34 (m, 2H), 2.24 – 2.10 (m, 2H), 1.99 – 1.91 (m, 2H), 1.67 – 1.35 (m, 10H), 1.13 – 1.07 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 6H). CO_2H not observed.

^{13}C NMR (101 MHz, Acetone-d_6): δ 213.0, 172.8, 138.1, 136.0, 51.0, 38.9, 38.9, 37.6, 32.5, 29.0, 28.6, 28.0, 25.6, 22.6, 21.3, 13.7, 11.4. Two signals not observed.

Isomer 3.

υ_{max} (film): 3302 (br), 2960, 2934, 2870, 1697, 1656, 1625, 1519, 1191 cm^{-1}.

^{1}H NMR (600 MHz, Acetone-d_6): δ 7.96 (s, 1H), 6.43 (s, 1H), 2.98 – 2.93 (m, 1H), 2.46 (td, *J* = 14.3, 6.0 Hz, 1H), 2.41 – 2.35 (m, 1H), 2.24 – 2.13 (m, 2H), 2.01 – 1.92 (m, 2H), 1.67 – 1.34 (m, 10H), 1.17 (dd, *J* = 9.2, 4.8 Hz, 1H), 1.01 – 0.93 (m, 6H). CO_2*H* not observed.

^{13}C NMR (101 MHz, Acetone-d_6): δ 213.0, 138.0, 136.5, 51.0, 38.9, 37.5, 32.6, 28.9, 28.5, 28.0, 25.6, 22.3, 21.4, 13.7, 11.4. Four signals not observed.

Isomer 4.

υ_{max} (film): 3307 (br), 2961, 2935, 2870, 1701, 1654, 1638, 1522, 1459, 1186 cm^{-1}.

^{1}H NMR (400 MHz, Acetone-d_6): δ 7.94 (s, 1H), 6.38 (s, 1H), 3.00 – 2.90 (m, 1H), 2.51 – 2.33 (m, 2H), 2.23 – 2.13 (m, 2H), 2.00 – 1.90 (m, 2H), 1.69 – 1.34 (m, 10H), 1.11 – 1.06 (m, 1H), 0.99 – 0.91 (m, 6H). CO_2*H* not observed.

^{13}C NMR (101 MHz, Acetone-d_6): δ 213.0, 169.8, 138.2, 135.9, 51.0, 38.9, 38.9, 37.6, 32.3, 29.0, 28.6, 28.0, 25.6, 22.3, 21.3, 13.8, 11.5. Two signals not observed.

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