

Studies Towards the Total Synthesis of Heteroclitin F and Taiwanschirin A, B, C, and D



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Declaration

This thesis and the work described herein is entirely my own, except where the help of a named person is acknowledged, or where a reference to a published source is given.

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Trinity Term 2020

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Ross, I would like to dedicate this thesis to you. I know that you won't be able to read it, but I hope that you're with me somewhere, and I know that you would have been proud of what your big brother has achieved.

Abstract

This thesis initially describes model studies developed towards key structural fragments of the taiwanschirin family of natural products. Through the use of these models, an original approach was conceived to enable installation of the (Z)-enone as a single diastereoisomer. This novel alkynylation–cuprate addition sequence has been successfully applied to a wide substrate scope including esters, amides, ketones and thioesters. Furthermore, these studies have led to the assembly of the 8-membered ring in high yield through the development of a Heck cross-coupling reaction. Under palladium-catalysed conditions, we were delighted to observe the formation of the desired alkene as a single (*exo*)-diastereoisomer in 81% yield. Extensive investigations are described into the incorporation of the pyruvate functional group in model compounds. This group proved to be particularly challenging, however a breakthrough was obtained through the use of a Bode salt. This approach enabled the assembly of a model compound that incorporated both the pyruvate group and the (Z)-enone. With a method developed for the incorporation of the three contiguous stereocentres, in addition to the pyruvate functional group, presented herein is a novel approach towards the first total synthesis of the taiwanschirin family. Finally, an approach to the heterocyclic core was developed and the planned synthesis successfully completed up to step 16 inclusive of an anticipated 22 steps. Overall, this sequence was achieved in 2.4% yield from commercially available piperonylic acid. To the best of our knowledge, this is the first work to investigate the total synthesis of this family of highly structurally complex natural products, and represents a significant advancement in this field of research. The taiwanschirins represent an extremely challenging and biologically significant family of targets in total synthesis.

Abbreviations and acronyms

2D	Two-dimensional
[α]	Specific rotation
Å	Ångström
Ac	Acetyl
Ad	Adamantyl
An	Anthracenyl
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Bu	Butyl
c	Concentration
°C	Degrees Celsius
CDI	1,1'-Carbonyldiimidazole
CI	Chemical ionisation
cm ⁻¹	Wavenumber
CMDT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
COSY	Correlated spectroscopy
Cp [*]	Pentamethylcyclopentadienyl
d	Doublet
dba	Dibenzylideneacetone
DBDMH	5,5-Dimethylhydantoin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
dr	Diastereomeric ratio
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIH	1,3-Diiodo-5,5-dimethylhydantoin
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMS	Dimethylsulfide

DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DTBMS	Di- <i>tert</i> -butylmethylsilyl
dtbpf	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene
EDC·HCl	<i>N</i> -(3-Dimethylaminopropyl)- <i>N</i> '-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EI	Electron ionisation
eq.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
FCC	Flash column chromatography
FTIR	Fourier transform infrared
g	Gram(s)
h	Hour(s)
HATU	<i>O</i> -(7-Aza-1 <i>H</i> -benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HBTU	<i>N,N,N',N'</i> -Tetramethyl- <i>O</i> -(1 <i>H</i> -benzotriazol-1-yl)uronium hexafluorophosphate
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazide
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
<i>i</i> –	<i>iso</i> –
IBX	2-Iodoxybenzoic acid
i.e.	That is; in other words (Latin)
<i>in situ</i>	In position (Latin)
<i>in vacuo</i>	In a vacuum (Latin)
<i>in vitro</i>	Within the glass (Latin), i.e. outside a living system
IR	Infrared
<i>J</i>	Coupling constant
LDA	Lithium diisopropylamide
M	Molar
m	Multiplet
m/z	Mass to charge ratio
Me	Methyl
mg	Milligram(s)
min	Minute(s)

mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
mol%	Molar percent
MOM	Methoxymethyl
m.p.	Melting point
Ms	Mesylate (Methanesulfonate)
MTBE	<i>tert</i> -butyl methyl ether
MW	Molecular weight
<i>n</i> –	<i>normal</i> –
N/A	Not applicable
NHK	Nozaki–Hiyama–Kishi
NMR	Nuclear magnetic resonance
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
<i>o</i> –	<i>ortho</i> –
OBO	Oxabicyclo[2.2.2]octyl
<i>p</i> –	<i>para</i> –
PCC	Pyridinium chlorochromate
pH	– log[H ₃ O] ⁺
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PMB	<i>p</i> -Methoxybenzyl
PMBTCA	4-Methoxybenzyl-2,2,2-trichloroacetimidate
ppm	Parts per million
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Pr	Propyl
PTSA	<i>p</i> -Toluenesulfonic acid
Py	Pyridine
PyBOP [®]	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
q	Quartet
R	Generic alkyl group
RSM	Recovered starting material
rt	Room temperature
s	Singlet
sat.	Saturated
sept	Septet
sp.	Species

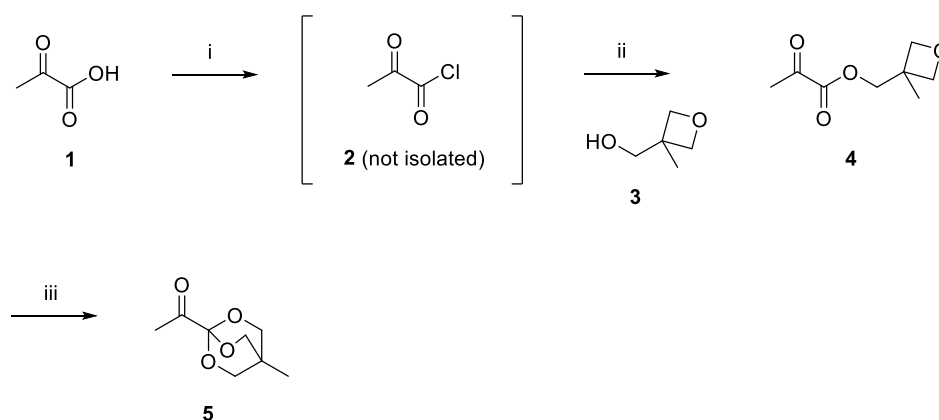
T	Temperature
t	Triplet
<i>t/tert</i> –	<i>tertiary</i> –
T3P®	2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate (triflate)
TFA	Trifluoroacetic acid
TFDO	3-(Trifluoromethyl)dioxirane
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	<i>para</i> -Toluenesulfonyl (tosyl)
UV	Ultraviolet
via	By way of (Latin)
X	Generic heteroatom, halide or leaving group
μL	Microlitre(s)
$\nu_{\max}$	Infrared absorption maximum
$\lambda_{\max}$	Wavelength of maximum absorbance
δ	Chemical shift

Chapter 1: Introduction

1.1 *alpha*-Arylation of OBO ketone 5

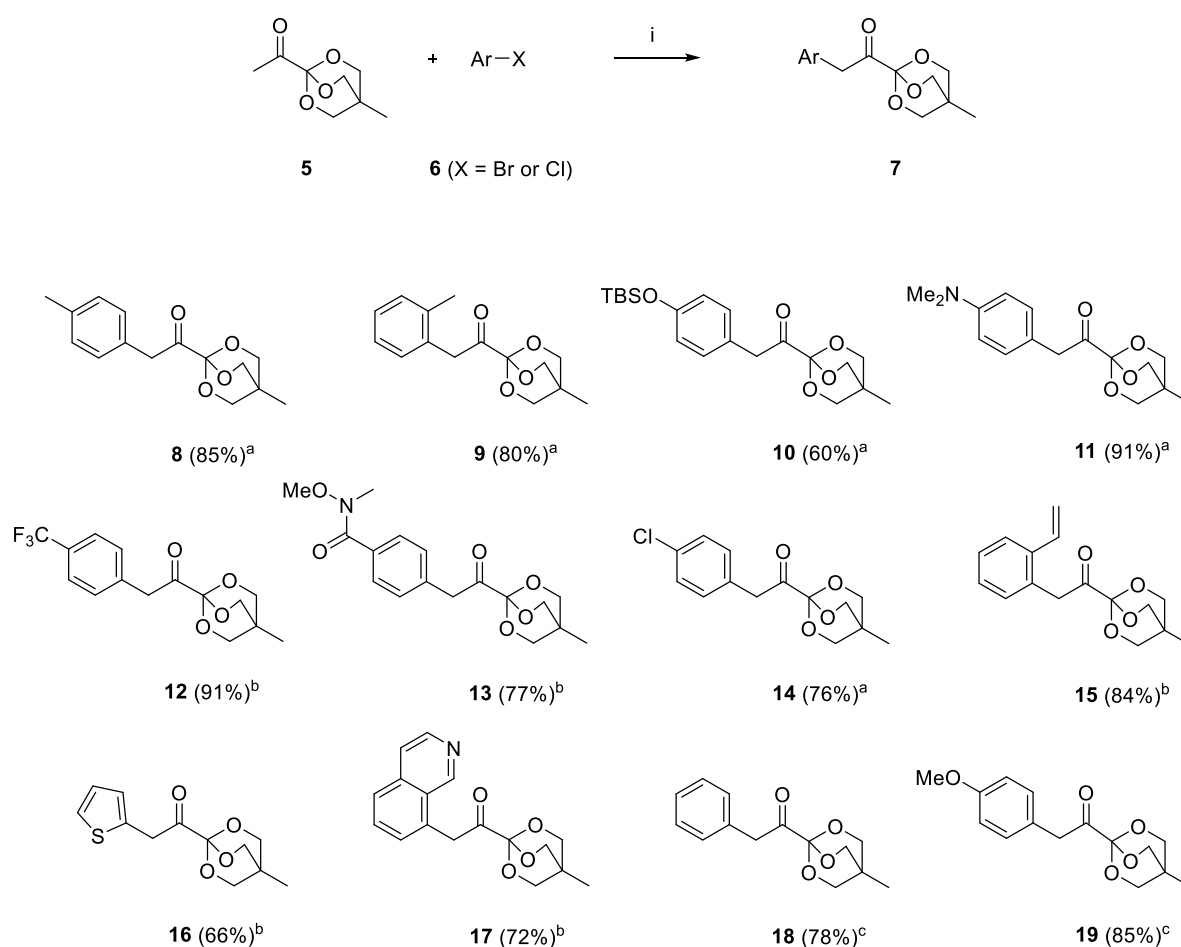
A longstanding program of research in the Donohoe group has focussed on the development of novel methods for the Pd-catalysed *alpha*-arylation of ketones.^{1–5} More recently, we have reported methodologies for the *alpha*-arylation of oxabicyclo[2.2.2]octyl (OBO) *ortho*-ester protected pyruvate equivalents.^{6–8} The OBO group, first developed by Corey, is a highly useful method for the protection of carboxylic acids and can easily be removed under mild acidic conditions.⁹ The stability of the OBO group towards basic conditions makes it an ideal protecting group in the application of *alpha*-arylation reactions. Furthermore, OBO has also found other applications, for example in diastereoselective aldol reactions.¹⁰

OBO ketone **5** is synthesised in 3 steps from commercially available pyruvic acid **1** (Scheme 1). Initially, pyruvic acid is converted to the acyl chloride using oxalyl chloride and DMF. The reaction is then cooled to $-40\text{ }^{\circ}\text{C}$ and the addition of pyridine, followed by alcohol **3**, leads to the formation of ester **4** in 77% yield after purification by column chromatography. The second reaction of the sequence concerns a $\text{BF}_3\cdot\text{OEt}_2$ mediated cyclisation to form OBO ketone **5** in 64% yield.



Scheme 1. Reagents and conditions: i) Oxalyl chloride, DMF, CH_2Cl_2 , rt, 4 h; ii) **3**, py, CH_2Cl_2 , $-40\text{ }^{\circ}\text{C}$, 1 h, then rt, 77% over 2 steps; iii) $\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 16 h, 64%

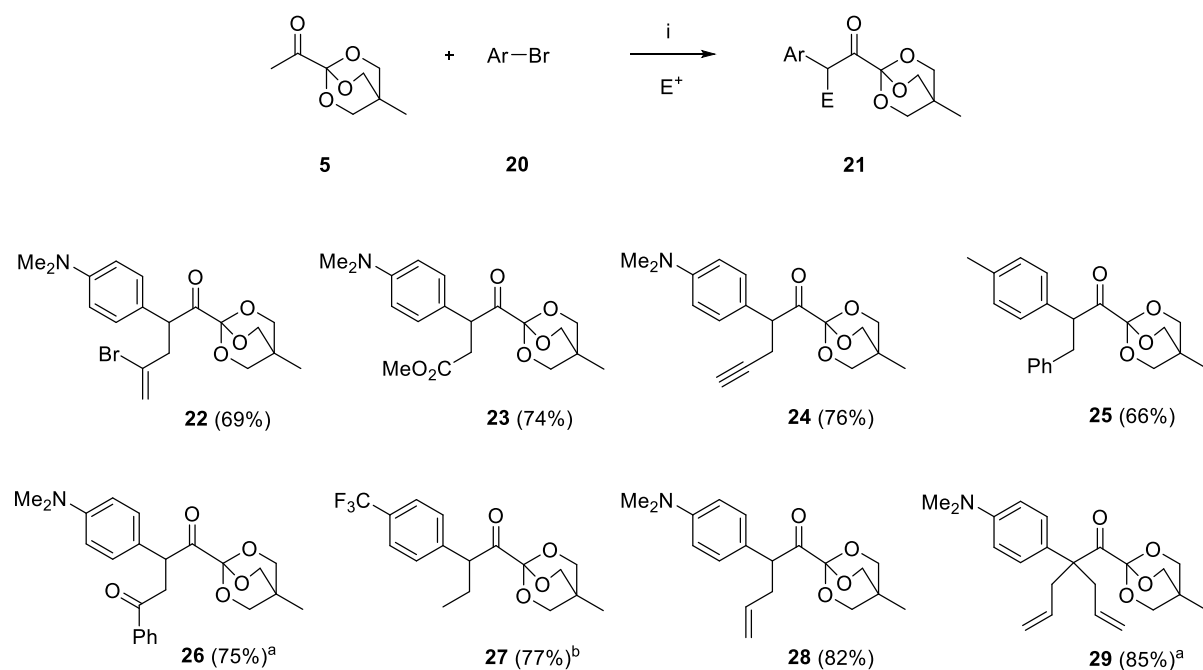
In this methodology, OBO ketone **5** is reacted with an aryl halide **6** in the presence of a palladium catalyst and base (Scheme 2). This reaction was found to be highly general, and demonstrated a large substrate scope including electron donating and withdrawing groups, a TBS-protected phenol, heterocycles and aryl chlorides. It is noteworthy that an excess of two and a half equivalents of base are required for this reaction. The reason for this is that the *alpha*-arylated products are more acidic than the starting material, OBO ketone **5**, due to delocalisation of the negative charge into the aromatic ring.



Scheme 2. Reagents and conditions: i) 5 mol% Pd(dtbpf)Cl₂, 2.5 eq. NaO^tBu, THF, 24 h
^a**5** (1 eq.), aryl bromide (1.1 eq.), 50 °C; ^b**5** (1.5 eq.), aryl bromide (1 eq.), 70 °C; ^c**5** (1.5 eq.), aryl chloride (1 eq.), 70 °C

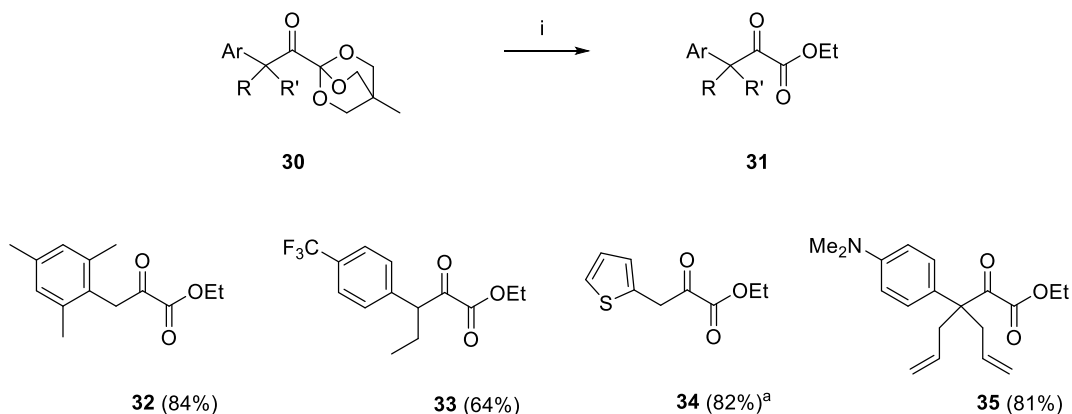
Furthermore, this reaction could be extended to encompass a one-pot arylation alkylation sequence (Scheme 3). A large variety of different alkyl bromides and alkyl iodides were

found to react under the developed conditions, affording a range of *alpha*-substituted protected pyruvate products.



Scheme 3. Reagents and conditions: i) 5 mol% Pd(dtbpf)Cl₂, 2.5 eq. NaO^tBu, THF, 50 °C, 24 h
^aReaction was heated to 80 °C for 8 h after addition of electrophile; ^bReaction temperature was 70 °C throughout

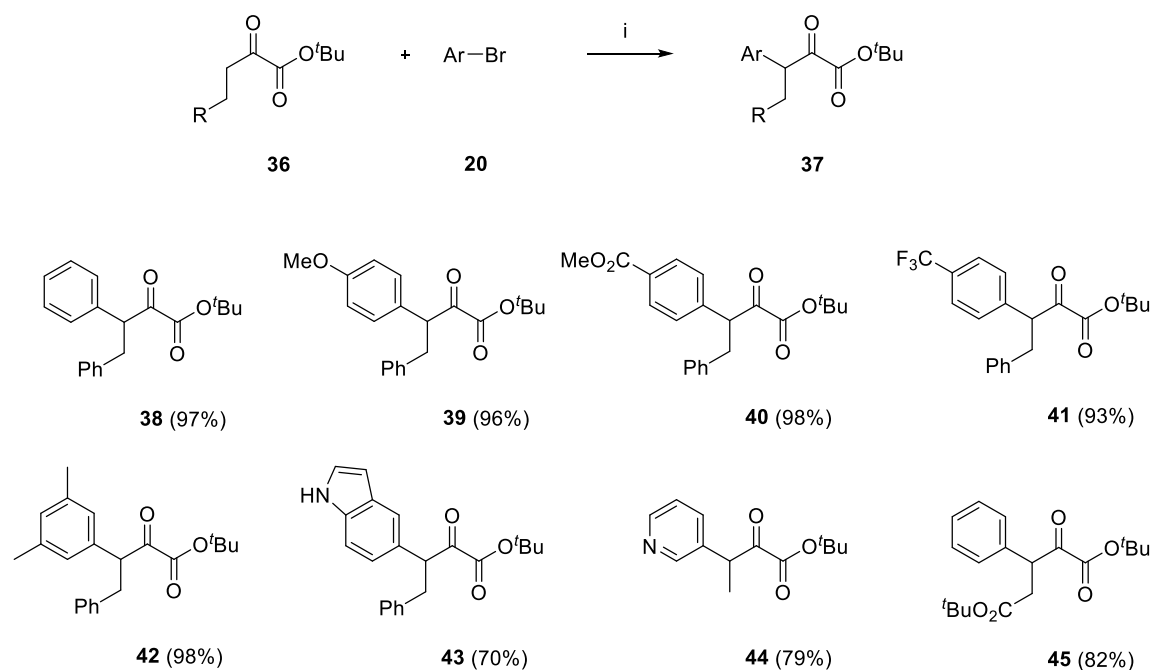
Crucially, conditions for the removal of the OBO group were developed that employed PTSA in EtOH at a temperature of 90 °C for 3–8 h (Scheme 4). In all instances, good yields of the desired ethyl pyruvate were obtained, and a range of functional groups were tolerated including electron rich and poor aromatics, heteroaromatics and alkenes.



Scheme 4. Reagents and conditions: i) PTSA, EtOH, 90 °C, 3 – 8 h
^aReaction was heated to 110 °C for 3 h

1.1.2 α -Arylation of *tert*-butyl pyruvates

The importance of this transformation to the organic chemistry community can be clearly seen, as a complementary method for the α -arylation of *tert*-butyl pyruvates was also reported by Johnson (Scheme 5).¹¹

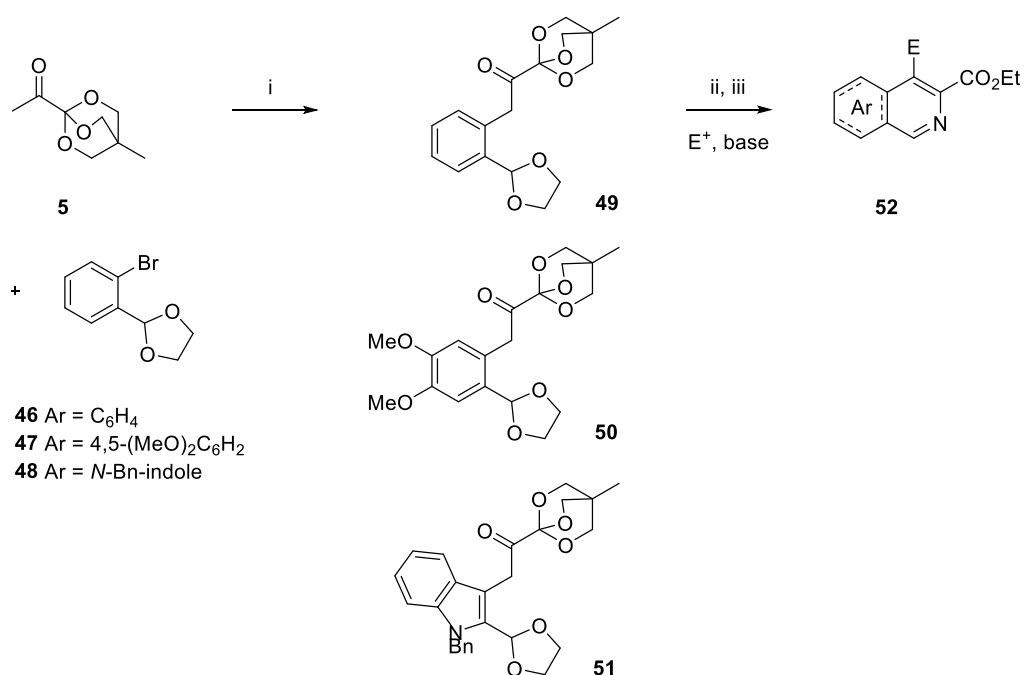


Scheme 5. Reagents and conditions: i) 2 mol% Pd₂(dba)₃, 8 mol% P^{*t*}Bu₃, 3 eq. K₂CO₃, toluene, 110 °C, 12 h

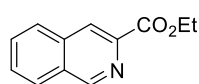
In this system, 1 equivalent of the *tert*-butyl pyruvate was reacted with 2 equivalents of the aryl bromide in the presence of a modified catalytic system employing Pd₂(dba)₃ and ^{*t*}Bu₃P with K₂CO₃ as the base. A reasonable substrate scope was demonstrated, however the potential for double arylation, or quenching with different electrophiles was not discussed. Additionally, the *tert*-butyl pyruvate was not shown to be successfully deprotected to afford the carboxylic acid, or trans-esterified to form other pyruvates.

1.1.3 Heterocycle synthesis

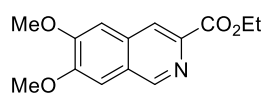
Later work within the Donohoe group disclosed an approach using OBO ketone **5** in the synthesis of heterocycles.¹² Through either pre-functionalisation of the aromatic ring, or alkylation at the *alpha*-position using an appropriate electrophile, a range of heterocyclic compounds were synthesised (Scheme 6).



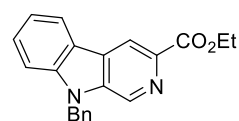
Direct aromative cyclisation



53 (84%)

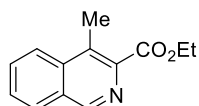


54 (80%)

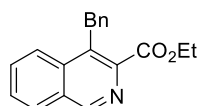


55 (89%)

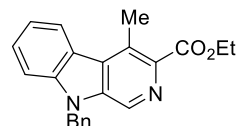
Additional electrophilic functionalisation



56 (47%)^a



57 (53%)^b



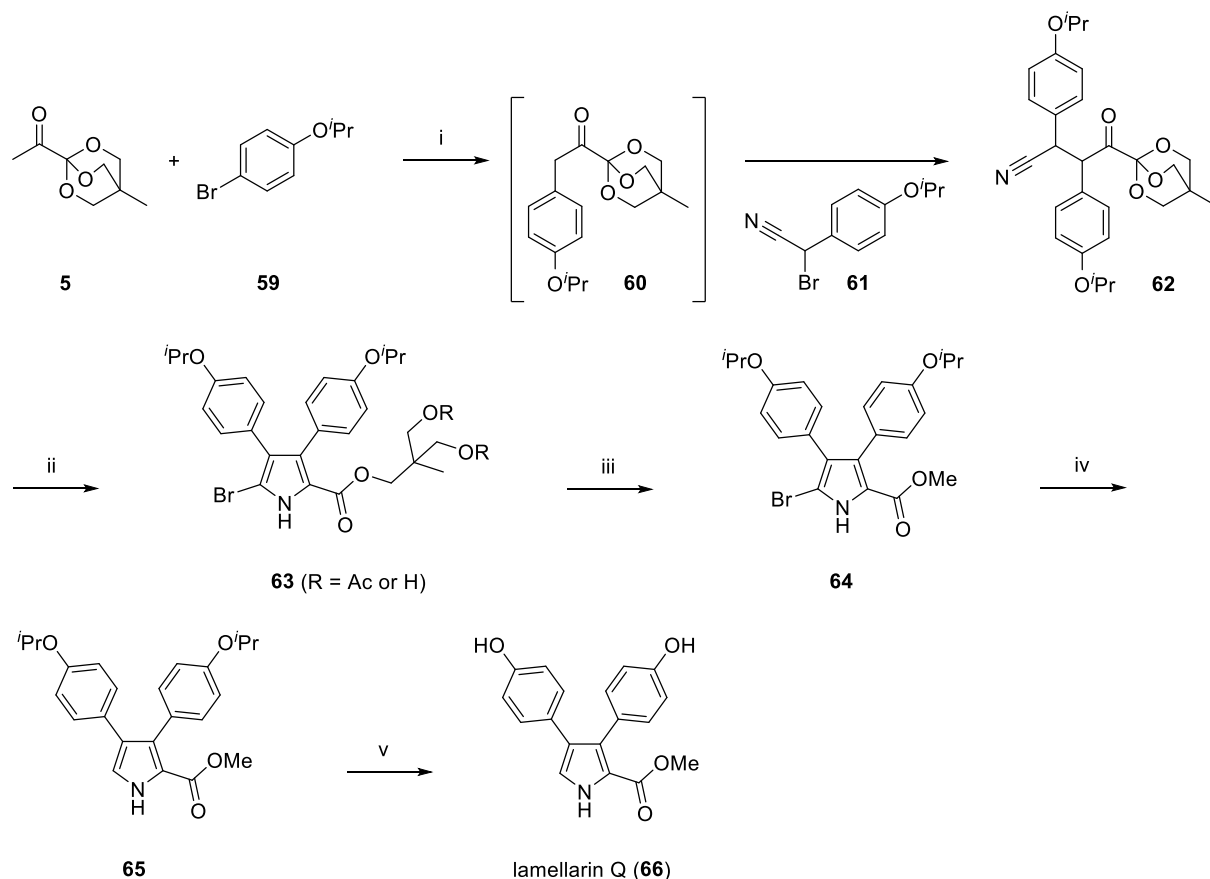
58 (69%)^c

Scheme 6. Reagents and conditions: i) 2.5 – 5 mol% Pd(dtbpf)Cl₂, 2.5 eq. NaO^tBu, THF, 70 °C, 24 h; ii) Electrophile, base; iii) NH₄Cl, EtOH, 115 °C, 12 h, then TsOH, EtOH, 115 °C, 24 – 36 °C
^aMeI/NaO^tBu, THF, 70 °C; ^bBnBr/NaO^tBu, THF, 70 °C; ^cMeI/NaH, DMF, 0 °C – rt

The application of this methodology to aromatic acetals enables the synthesis of a range of isoquinolines and *beta*-carbolines. Both electron rich and electron poor substrates were tolerated and further complexity could be incorporated through an additional electrophilic functionalisation step.

This work disclosed further methods for the synthesis of other heterocycles, including indoles, pyrroles, furans, and pyridines. Given the importance of heterocyclic compounds in the context of the pharmaceutical industry, this methodology will surely prove highly useful to the scientific community.

Recently, this OBO ketone *alpha*-arylation methodology was applied to the synthesis of two bioactive members of the lamellarin family of natural products.⁸ Lamellarin D and Q (**66**) were synthesised in 7 steps from pyruvic acid in 22% and 20% yields, respectively. The scheme below outlines the synthesis of lamellarin Q (**66**) from the OBO ketone **5** intermediate (Scheme 7).



Scheme 7. Reagents and conditions: i) 5 mol% $\text{Pd}(\text{dtbpf})\text{Cl}_2$, 2.5 eq. NaO^iBu , THF, 55 °C, 20 h, then 61, 3 h, 75%; ii) 3% HBr in AcOH, $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (1:1), 0 °C – rt, 3.5 h; iii) K_2CO_3 , MeOH, 65 °C, 62% over 2 steps; iv) H_2 , 10% Pd/C, NaOAc, MeOH, rt, 1 h, 99%; v) BBr_3 , CH_2Cl_2 , –78 °C to rt, 99%

An α -arylation reaction between OBO ketone 5 and aryl bromide 59 provided access to the intermediate ketone 60. As an excess of base was used in the reaction, benzyl bromide 61 was then added and the reaction mixture was heated for a further 3 h to afford ketone 62 in 75% yield over 2 steps. An acid-mediated cyclisation reaction to afford a mixture of OBO ring-opened esters 63, followed by transesterification, led to the isolation of pyrrole 64 in 62% yield over 2 steps. The hydrogenation of pyrrole 64 using Pd/C resulted in the removal of bromine from the aromatic ring to form pyrrole 65 in near quantitative yield. Finally, treatment with BBr_3 resulted in a double ArO^iPr deprotection to afford lamellarin Q (66) in 99% yield. Overall, this sequence represents an extremely convergent approach towards this natural product and demonstrates the power of this methodology in the context of natural product synthesis.

Given the successful total synthesis of the lamellarin natural products, and the interest of our group in the use of OBO ketone in total synthesis, we decided to investigate the development of this methodology in a more complex setting. Our search for potential targets in natural product synthesis led us to the taiwanschirin family (Figure 1). These highly structurally complex natural products feature a pyruvate group, (*Z*)-enone, and three contiguous stereocentres on an 8-membered ring, thereby representing highly challenging targets in total synthesis.

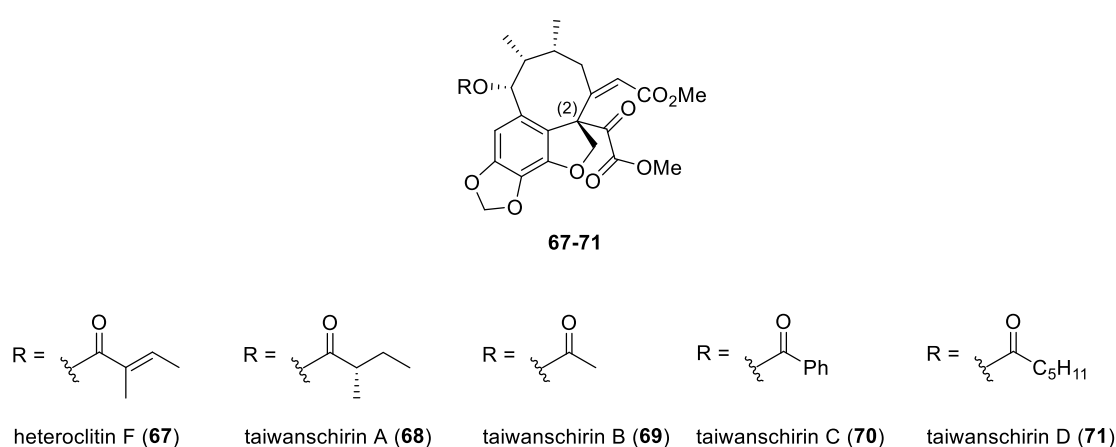


Figure 1. heteroclitin F (**67**) and taiwanschirin A (**68**), B (**69**), C (**70**), and D (**71**)

We postulated that the OBO ketone *alpha*-arylation methodology developed previously within the group could be extended to enable an *alpha*-vinylation reaction. This would enable us to install the key (*Z*)-enone fragment found within the taiwanschirin family, and deprotect at a later stage to reveal the methyl pyruvate.

1.2 Isolation and biological activity

1.2.1 Heteroclitin F (**67**)

The therapeutic properties of the *Schisandraceae* family have long been known and applied in traditional Chinese medicine.^{13,14} Together this family comprises around 60 species, 29

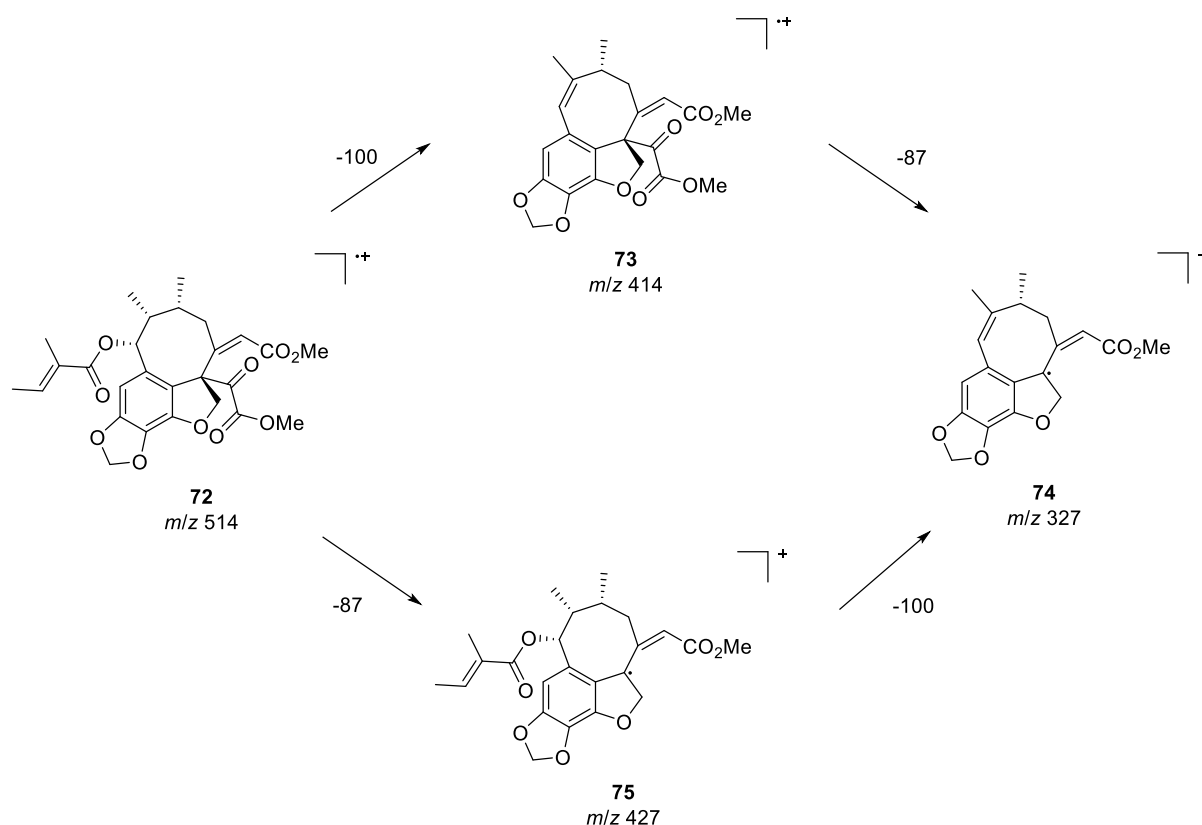
of which are native to China including 19 of the *Schisandra* and 10 of the *Kadsura* genus.¹⁵ The stems of *Kadsura heteroclita* have been reportedly used for the treatment of gastric ulcers, gastroenteritis, dysmenorrhea, and other abdominal pain. As a result of this, there has been a surge of interest in recent years in the isolation and characterisation of natural products responsible for these therapeutic effects. Isolated by Hattori in 1992 from the stems of *Kadsura heteroclita*, heteroclitin F (**67**) was the first member of the taiwanschirin family to be discovered (Figure 1).¹⁶

In order to isolate heteroclitin F (**67**), 4 kg of dried and pulverised *Kadsura heteroclita* stems was extracted 5 times with EtOH under reflux for a period of 8 h. Upon concentration, 114 g of crude material was obtained and was suspended in MeOH before being extracted with hexane, to afford a hexane-soluble fraction (37 g). This fraction was then purified by column chromatography and preparative TLC (SiO₂, hexane:CHCl₃, 2:1) to afford heteroclitin F (**67**) (19 mg).

The infrared spectrum showed two key carbonyl absorptions at ν_{max} 1718 and 1740 cm⁻¹. The authors assigned the lower absorption to a conjugated carbonyl i.e. the (Z)-enone, and the higher absorbance to a carbonyl of the pyruvate functional group.

The molecular formula of heteroclitin F (**67**) was proven by high resolution mass spectrometry (Scheme 8). Fragmentation patterns showed the loss of angeloyl group from radical cation **72** to form radical cation **73** m/z 414 which underwent a further fragmentation to afford radical cation **74** m/z 327. The reverse pathway for this transformation was also proposed, with the initial loss of the pyruvate group to afford radical cation **75** m/z 427.

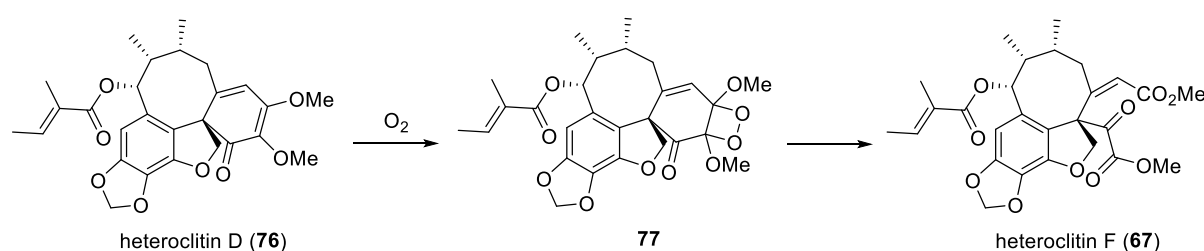
Further evidence for the angeloyl group was found in the ^1H NMR spectrum.



Scheme 8. Mass fragmentation pattern for heteroclitin F (**67**)

^1H NMR confirmed the presence of the methylenedioxy group due to the presence of two doublets in the spectrum $\delta = 6.01$ (1H, d, $J = 1.2$ Hz, $\text{OCH}_\text{A}\text{H}_\text{B}\text{O}$) and 5.99 (1H, d, $J = 1.2$ Hz, $\text{OCH}_\text{A}\text{H}_\text{B}\text{O}$). Long range HMBC experiments revealed the spirobenzofuranoid structure, and relative stereochemistry was confirmed by detailed nOe experiments. The absolute stereochemistry of the C(2) carbon was assigned by analogy with other members of the heteroclitin family. X-ray crystallography was used to unequivocally assign the C(2) stereochemistry of closely related heteroclitin G as (*S*). Circular dichroism spectra obtained for heteroclitin G and heteroclitin D (**76**) showed close agreement, suggesting that they both featured the same C(2) stereochemistry. Biosynthetically, it was proposed that heteroclitin F (**67**) is derived from an oxidative cleavage of heteroclitin D (**67**). The reaction with oxygen would generate peroxide intermediate **77** that may then undergo a

cycloreversion reaction to afford heteroclitin F (**67**). Although an unusual biosynthetic proposal, this pathway would explain the presence of the thermodynamically less stable (*Z*)-enone in the structure of heteroclitin F (**67**), in addition to the pyruvate, both of which are highly unusual motifs found in natural products. Assuming that this pathway is correct, and that heteroclitin F (**67**) is indeed derived from heteroclitin D (**76**), then the absolute configuration at C(2) in both cases would be (*S*). Later work reported the re-isolation of heteroclitin F (**67**) from *Kadsura japonica*¹⁷ and *Kadsura interior*.¹⁸



Scheme 9. Proposed biosynthesis pathway of heteroclitin F (**67**) from heteroclitin D (**76**)

1.2.2 Taiwanschirin A (**68**), B (**69**), and C (**70**)

In 1999, Kuo reported the isolation of taiwanschirins A (**68**), B (**69**) and C (**70**) from *Schisandra arisanensis*.¹⁹ Structurally the taiwanschirin natural products are identical to heteroclitin F (**67**), with the notable exception of the exocyclic ester group. The assignment of these natural products was made using 2D NMR techniques similarly to before for heteroclitin F (**67**). Furthermore, the structure of taiwanschirin A (**68**) was confirmed unequivocally by X-ray crystallography. Biological studies showed that taiwanschirin C (**70**) demonstrated a notable *in vitro* cytotoxicity against hepatoma (Hepa-3B, ED₅₀ = 2.2 μg mL⁻¹). In later work, taiwanschirins A (**68**), B (**69**) and C (**70**) were re-isolated from *Kadsura matsudai*²⁰ and *Kadsura japonica*.¹⁷

1.2.3 Taiwanschirin D (71)

The final member of the taiwanschirin family to be discovered was taiwanschirin D (**71**), isolated from *Kadsura matsudai* in 2000.²¹ This natural product is again very similar to the other members of the family, and features an hexanoate ester within its structure. The two natural products were investigated for anti-cancer activity in several human cell lines, including: epidermoid carcinoma of nasopharynx (KB); colon carcinoma (COLO-205); hepatoma (Hepa-3B) and cervic (Hela). The authors confirmed that taiwanschirin C (**70**) showed cytotoxicity against hepatoma ($ED_{50} = 2.3 \mu\text{g mL}^{-1}$) as reported previously, whereas taiwanschirin D (**71**) was greater than $10 \mu\text{g mL}^{-1}$. Taiwanschirin D (**71**) also demonstrated a moderate activity against hepatitis B at a concentration of $50 \mu\text{g mL}^{-1}$, however no effect was observed in the case of taiwanschirin C (**70**). A study by Hikino in 1984 examined the antihepatotoxic activities of twenty lignan natural products isolated from *Schisandra chinensis* fruits. The study concluded that the methylenedioxy group may play an important role in determining activity against hepatitis B. However, since both taiwanschirin C (**70**) and D (**71**) feature a methylenedioxy group within their structure, the explanation for this differing activity is clearly more complex.²²

Given the high level of structural complexity present in the taiwanschirin family, and their interesting biological activities, we felt that these natural products represented highly suitable targets in total synthesis. Furthermore, the opportunity to develop the highly successful OBO ketone methodology developed previously within the Donohoe group provided an additional motivation for this project.

1.3 Project aims

This project aimed to develop a route towards the total synthesis of the taiwanschirin family, none of which have been previously synthesised. We envisaged that a vinylation approach using OBO ketone could enable the rapid assembly of the taiwanschirin core, and a late-stage deprotection of the OBO cage would reveal the pyruvate group.

This work also aimed to investigate the biological activities of the taiwanschirin family of natural products and build further on the limited reports present in the literature. We were fortunate to have GlaxoSmithKline as industrial sponsors for this work, and together we hoped to learn more about this intriguing family of natural products. Time-permitting, analogues could be prepared, and structural–activity relationships investigated against various targets. This would hopefully allow us to build further on literature reports and gain a greater understanding of which fragments within these natural products are responsible for their biological activity.

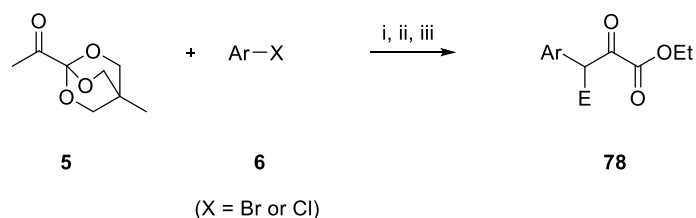
Chapter 2: Results and discussion

2.1 (Z)–Enone formation

2.1.1 Enolate vinylation

Setting the quaternary C–2 stereocentre and enone geometry control were identified as key challenges in the synthesis of this family of natural products. As described previously, our group has developed several methodologies for the palladium–catalysed *alpha*–arylation of ketones,^{1–5} and of particular note the *alpha*–arylation of OBO *ortho*–ester protected pyruvate equivalents.^{6,7}

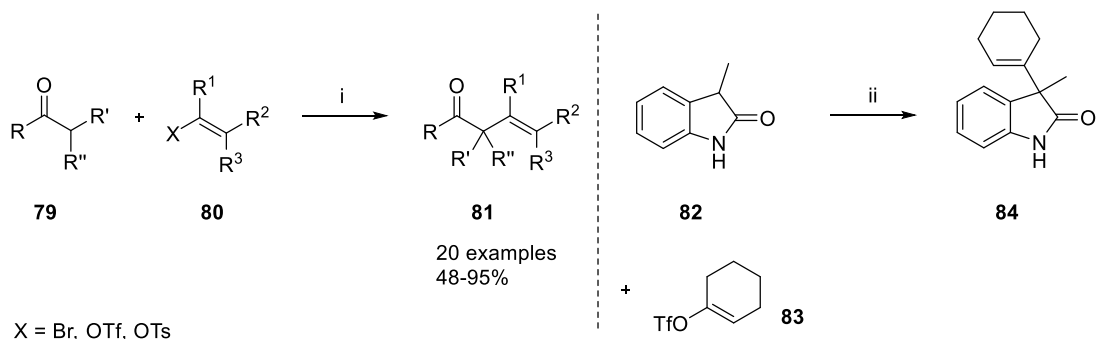
In this methodology, OBO ketone **5** is reacted with aryl halide **6** in the presence of a palladium catalyst and base. At the end of the reaction an additional arylation reaction or trapping with an electrophile may be performed leading to the synthesis of quaternary protected pyruvates. Deprotection of the OBO cage may be achieved simply by heating with PTSA for 3 h.



Scheme 10. Reagents and conditions: i) 5 mol% Pd(dtbpf)Cl₂, 2.5 eq. NaO^tBu, THF, heat; ii) additional arylation or electrophile trapping; iii) PTSA, EtOH, 90 °C, 3–8 h

Our first strategy for the synthesis of the (Z)–alkene fragment of the taiwanschirin family proposed to extend this reaction and apply it in the context of *alpha*–vinylation. In contrast to palladium–catalysed enolate arylation,^{23–25} vinylation reactions are relatively underexplored in the chemical literature.²⁶ There have been several notable recent reports, however, that gave promise to this approach. For example, in 2007, Faul disclosed a method for the *alpha*–vinylation of carbonyl compounds using [Pd(P^tBu₃)Br]₂ as the catalyst

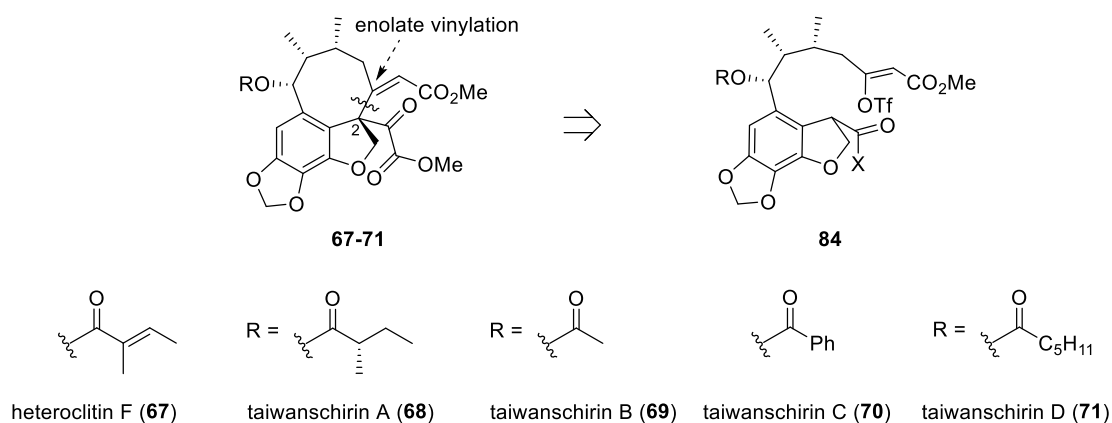
(Scheme 11).²⁷ The method was general and could be applied to vinyl bromides, triflates and tosylates. Significantly, a preliminary result for the enantioselective vinylation of amide **82** was presented, and alkene **84** was obtained in 38% yield and 40% ee.



Scheme 11. Reagents and conditions: i) 2.5 eq. LiHMDS, 2.5 mol% [Pd(P^tBu₃)Br]₂, toluene, 80 °C, 24 h; ii) 2.5 eq. LiHMDS, 2.5 mol% [Pd(P^tBu₃)Br]₂, (S)-MOP, toluene, 40 °C, 96 h, 38%, 40% ee

There are several examples of intramolecular *alpha*-vinylation reactions in the literature, many applied in complex environments in the total synthesis of natural products.²⁶ A later report by Helquist has also disclosed conditions for the low temperature vinylation of ketone enolates at 0 °C, an important advancement in the development of mild palladium-catalysis conditions.¹⁴

In light of this, we envisaged that the intramolecular transition metal cross coupling of a vinyl triflate and a protected pyruvate would provide an expeditious route towards these natural products (Scheme 12).

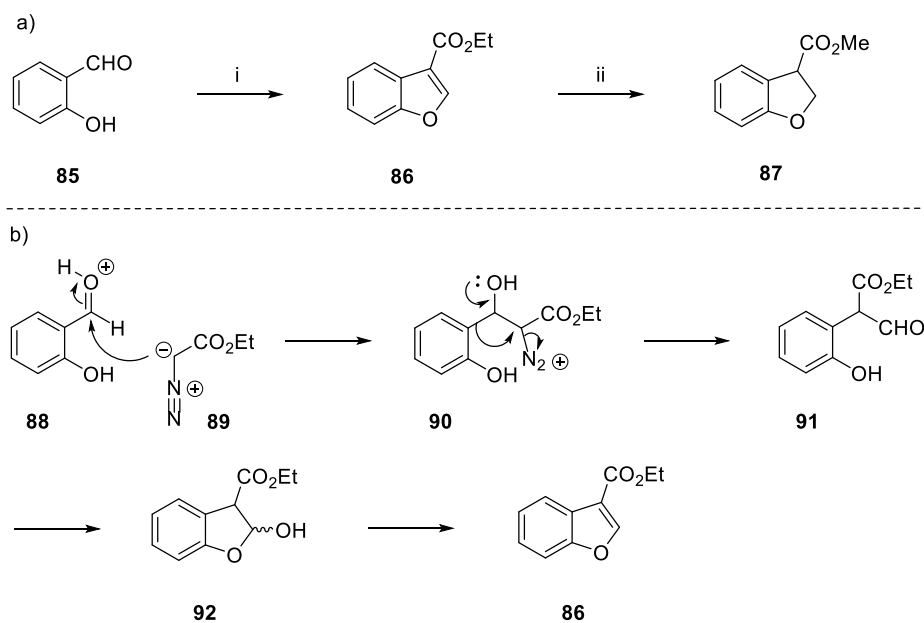


Scheme 12. heteroclitin F (**67**), taiwanschirins A–D (**68–71**), and proposed enolate vinylation

This project would therefore extend the methodology developed previously towards enolate vinylation and examine its applicability in a complex setting.

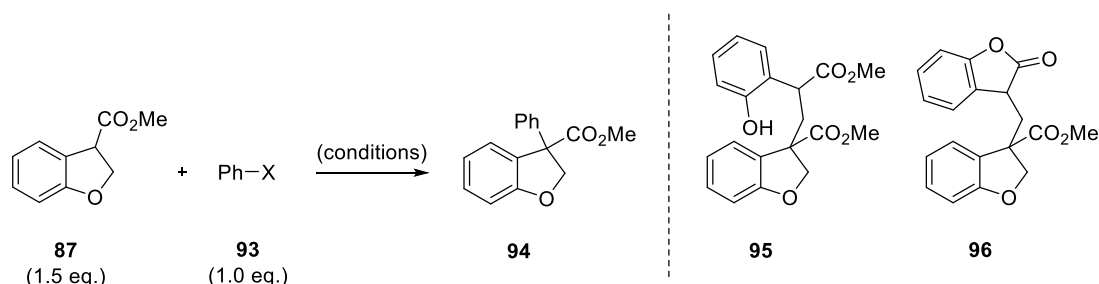
2.1.2 Arylation and vinylation of a model dihydrobenzofuran

Due to the prevalence of the dihydrobenzofuran motif in biologically active natural products, there are many different reported syntheses detailed in the literature.²⁹ A range of different strategies have been developed including: synthesis by intramolecular substitution;^{30,31} radical cyclisation;³² cycloaddition;³³ oxidative dimerization;³⁴ and from benzyne intermediates.³⁵ We were particularly drawn, however, to a report by Hossain describing the two-step synthesis of dihydrobenzofurans from 2-hydroxybenzaldehydes.³⁶ Following this protocol, 2-hydroxybenzaldehyde **85** was reacted with ethyl diazoacetate in the presence of tetrafluoroboric acid (Scheme 13). After treatment with concentrated sulfuric acid, benzofuran **86** was obtained in 85% yield. The reduction of benzofuran **86** using magnesium turnings in MeOH afforded dihydrobenzofuran **87** in 70% yield.



Scheme 13 a) Reagents and conditions: i) Ethyl diazoacetate, $\text{HBF}_4 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , rt, 30 min, then H_2SO_4 , 30 min, 85%; ii) Mg, MeOH, rt, 1 h, 70%; b) Proposed mechanism to show the formation of benzofuran **86**

With dihydrobenzofuran **87** in hand, we were now in a position to test the desired enolate arylation and vinylation reactions on a simple model substrate. A range of different arylation conditions were investigated in the first instance, because this reaction is more established than vinylation (Scheme 14).



Entry	X	Base ^a	Catalyst ^b	Solvent	T/ °C	t/h	Comment
1	OTf (97)	NaO ^t Bu	Pd(dtbpf)Cl ₂	THF	50	1	95 (20%)
2	OTf (97)	NaO ^t Bu	Pd(dtbpf)Cl ₂	THF	0	0.25	95 (72%)
3	—	NaO ^t Bu	—	THF	0	0.25	95 (99%)
4 ^c	OTf (97)	LiHMDS	Pd(dtbpf)Cl ₂	THF	0	0.25	95 (35%)
5 ^c	OTf (97)	LiHMDS	[P ^t Bu ₃ PdBr] ₂	THF	0	2	96 (38%)
6 ^c	Br (98)	LiHMDS	[P ^t Bu ₃ PdBr] ₂	Toluene	0	0.25	95 (66%)
7 ^c	Br (98)	LiHMDS	[P ^t Bu ₃ PdBr] ₂	Toluene	−78	1	95 (90%)
8 ^{c,d}	Br (98)	LiHMDS	[P ^t Bu ₃ PdBr] ₂	Toluene	−78 to 0	2	95 (60%)

Scheme 14. Attempted arylation of dihydrobenzofuran **87**

^a2.5 eq. Base ^b5 mol% Pd(dtbpf)Cl₂ and 2.5 mol% [P^tBu₃PdBr]₂. ^cStoichiometry reversed
In all cases order of addition: base, ester, catalyst then PhX (**93**) ^dElectrophile added neat

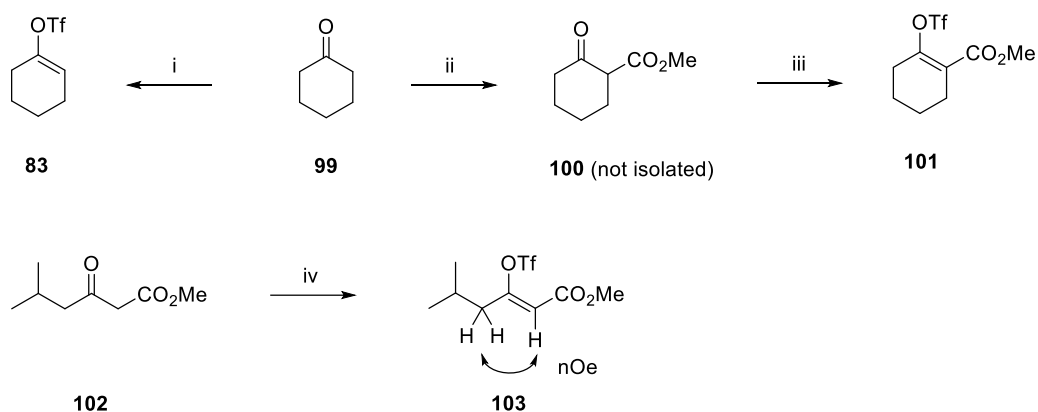
Initially we examined the conditions developed previously in the Donohoe group for the *alpha*-arylation of OBO *ortho*-ester protected pyruvate equivalents (Scheme 14, entry 1).⁶ Disappointingly, the desired arylated ester **94** was not observed. However, ester **95**, resulting from E1cB elimination followed by conjugate addition of a second benzofuran enolate, was isolated in 20% yield. In an effort to minimise elimination, the reaction temperature was lowered to 0 °C, however ester **95** was isolated in 72% yield (entry 2). Unsurprisingly, this reaction did not require the presence of a palladium catalyst in order to proceed, and ester **95**

was isolated in 99% yield when ester **87** was treated with base alone (entry 3). A change of base to LiHMDS also did not result in the formation of the desired product (entry 4). Subsequent conditions used the dimeric $[\text{Pd}^t\text{Bu}_3\text{PBr}]_2$ catalyst, reported by Hartwig to be a highly active catalyst or catalyst precursor for many catalytic processes including *alpha*-arylation.^{24,37,38}

However, in all instances competing E1cB elimination followed by conjugate addition was observed to form ester **95**, and lactone **96**, and no coupled product **94** was observed (entries 5–8).^{6,24,27,39}

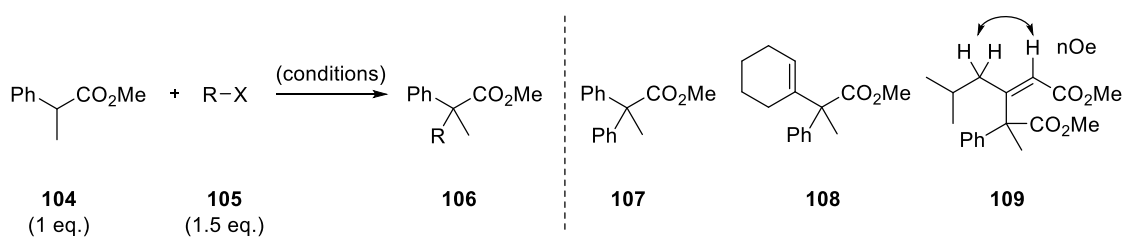
2.1.3 Vinylation of ester **87**

With enolate arylation proving unsuccessful, we then turned our attention towards the desired vinylation reaction. It was possible that enolate arylation was more challenging for this system than vinylation, so it seemed reasonable to investigate the desired vinylation with a range of triflates of varying complexity. Vinyl triflate **83** was synthesised in a single step from cyclohexanone **99** in 88% yield (Scheme 15). A more representative model vinyl triflate **101**, incorporating the enone as found in the taiwanschirin family, was synthesised in two steps in 51% overall yield.^{40,41} The most realistic model, triflate **103** was synthesised in order to test whether the proposed enolate vinylation reaction could be performed in a stereospecific manner, thereby preserving the (*Z*)-alkene geometry of the triflate starting material.⁴² The (*Z*)-configuration of triflate **103** was confirmed by the observation of nOe enhancements between the vinyl and methylene protons.



Scheme 15. Reagents and conditions: i) NaH, Tf₂O, CH₂Cl₂, 0 °C–rt, 2 h, 88%; ii) NaH, dimethyl carbonate, 1,4-dioxane, 130 °C, 2 h; iii) NaH, Tf₂O, CH₂Cl₂, 0 °C–rt, 2 h, 51% over 2 steps; iv) LiOTf, Et₂N^{*i*}Pr, Tf₂O, CH₂Cl₂, 0 °C, 2 h, 80%

A simpler model system, ester **104**, was then reacted with the range of electrophiles previously synthesised to test the feasibility of our proposal on a system in which the detrimental effects of rearrangement could be precluded (Scheme 16).



Entry	R-X	Base	Solvent	T/°C	t/h	Yield/comment
1	PhBr (98)	LiHMDS	THF	0 – rt	14	23%
2	PhBr (98)	NaHMDS	THF	0 – rt	14	0%
3	PhBr (98)	NaHMDS	Toluene	0 – rt	14	47%
4	PhOTf (97)	NaHMDS	Toluene	0 – rt	14	24% RSM
5	PhOTf (97)	NaHMDS	Toluene	0 – 80	14	44% RSM
6	83	NaHMDS	Toluene	0 – 80	14	14% ^a
7	101	NaHMDS	Toluene	0 – rt	1	Complex mixture
8	103	NaHMDS	Toluene	0 – rt	1	53%
9	103	NaHMDS	Toluene	0	1	31%
10 ^b	103	NaHMDS	Toluene	0 – rt	1	10%
11 ^c	103	NaHMDS	Toluene	0 – rt	1	RSM (57%)
12	103	NaO ^t Bu	THF	0 – rt	16	RSM (57%)

Scheme 16. Reagents and conditions: 2.5 eq. Base, 2.5 mol% [P^tBu₃PdBr]₂

^aIsolated as a 3:2 inseparable mixture of the desired product and ester **104** ^bNo [P^tBu₃PdBr]₂ catalyst

^c1.1 eq. base

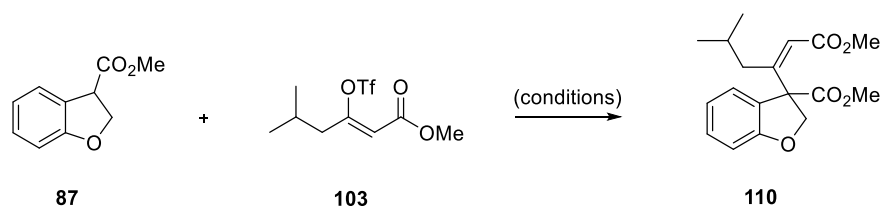
We were pleased to observe the arylation of ester **104** with bromobenzene **98** to afford a 23% yield of ester **107** (entry 1).²⁷ A change of base from LiHMDS to NaHMDS resulted in no product being observed with THF as the reaction solvent (entry 2). However, NaHMDS in toluene afforded a respectable 47% yield of the desired product.²⁴

Disappointingly, the optimised arylation conditions failed to promote a reaction with aryl triflate **97** (entries 4 and 5). However, reactivity was observed with triflate **83**, and a 14% yield of a 3:2 inseparable mixture of the desired cross-coupled product **108** and ester **87** was isolated (entry 6).

Ester **87** was then reacted with triflate **101**, however a complex mixture of products was observed (entry 7). Given the unsuccessful reaction of ester **87** with triflate **101**, we were surprised to observe the reaction with triflate **103** to afford alkene **109** in 53% yield (entry 8). Crucially, the (*Z*)-configuration of the alkene was preserved in the cross-coupled product, and was confirmed unambiguously by the observation of nOe enhancements.

A brief investigation revealed that a combination of NaHMDS (2.5 eq.), in toluene at 0 °C – rt afforded **109** in optimal yield. Interestingly, when the reaction was performed in the absence of a catalyst, alkene **109** was still isolated, albeit in only 10% yield (entry 10). Neither the use of fewer equivalents of base (entry 11), nor a change of base to NaO^tBu afforded the desired product in greater yield than the initial conditions (entry 12).

Encouraged by these preliminary results, we then looked towards the application of these conditions to the vinylation of our model dihydrobenzofuran, ester **87**. Disappointingly, however, a complex mixture of products was observed in the ¹H NMR of the crude reaction mixture (Scheme 17, entry 1). A range of cross-coupling conditions were investigated, however, as before only the product resulting from E1cB elimination followed by conjugate addition, ester **95**, was observed (entries 4 to 7).²⁴ Clearly the instability of the enolate derived from ester **87** was the root cause of this problem.

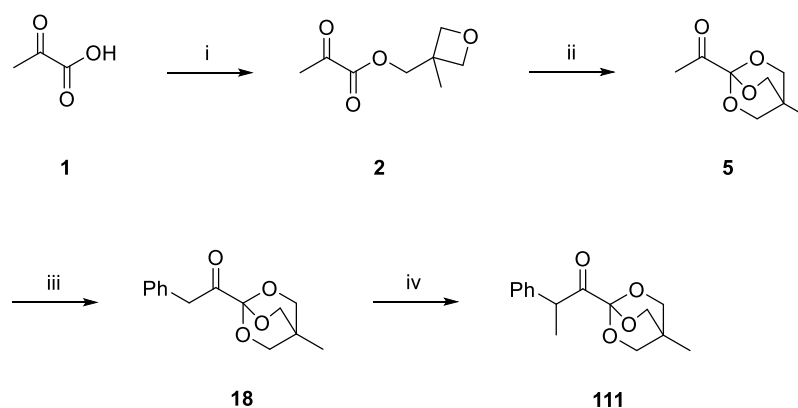


Entry	Catalyst	Ligand ^a	T/°C	Comment
1	[P ^t Bu ₃ PdBr] ₂	—	0	Complex mixture
2	[P ^t Bu ₃ PdBr] ₂	—	−78	Complex mixture
3 ^c	[P ^t Bu ₃ PdBr] ₂	—	−78	Complex mixture
4	Pd(dtbpf)Cl ₂ ^b	—	−78	95 (29%)
5	Pd(OAc) ₂ ^b	Q-Phos	−78	95 (30%)
6	Pd(OAc) ₂ ^b	S-Phos	−78	95 (20%)
7 ^{c,d}	—	—	−78	95 (53%)

Scheme 17. Reagents and conditions: 2.5 eq. NaHMDS, 2.5 mol% catalyst, toluene, 1 h

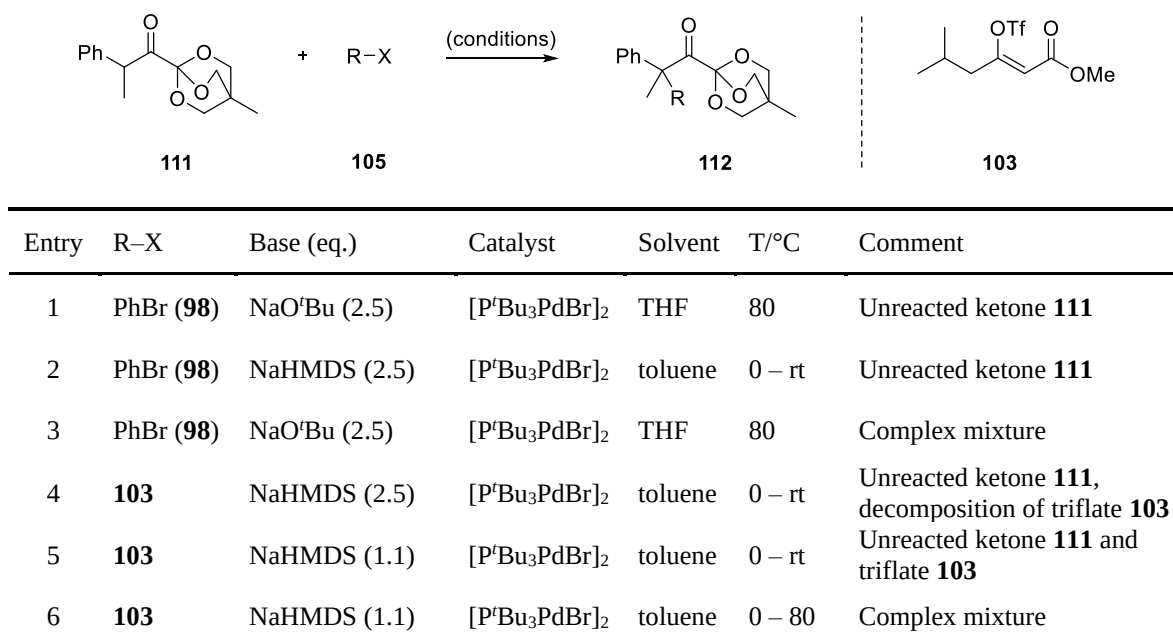
^a10 mol% ligand ^b5 mol% ^cElectrophile added neat at −78 °C ^dWarmed to 0 °C after 1 h as only SM observed

Our final model aimed to investigate the feasibility of an *alpha*-vinylation reaction of a tertiary-substituted OBO *ortho*-ester protected pyruvate, ketone **111**, in which elimination could not occur (Scheme 18). OBO ketone **5** was initially synthesised following a known procedure in 19% yield from pyruvic acid **1**.⁶ Subjection to the *alpha*-arylation conditions in the presence of bromobenzene furnished ketone **18** in 72% yield. Finally, lithiation with LiHMDS, followed by addition of MeI afforded the desired model ketone **111** in 75% yield.



Scheme 18. Reagents and conditions: i) oxalyl chloride, DMF, CH₂Cl₂, −40 °C, 3 h, then 3-oxetanemethanol, py, rt, 1 h, 67%; ii) BF₃·OEt₂, CH₂Cl₂, 0 °C, 16 h, 28%; iii) 5 mol% Pd(dtbpf)Cl₂, NaO^tBu, bromobenzene, THF, 50 °C, 24 h, 72%; iv) LiHMDS, **18**, THF, −78 °C, 30 min, then MeI, −78–rt, 16 h, 75%

With ketone **111** in hand we were now able to investigate the desired arylation and vinylation reaction. A variety of conditions were investigated, however, none of these resulted in either the arylation or vinylation of **111** (Scheme 19). Surprisingly, even application of the conditions found to be successful for the coupling of triflate **103** and ester **104** (Scheme 16) resulted in unreacted ketone **111** and triflate decomposition (entry 4). In an attempt to reduce the decomposition of triflate **103**, the amount of base in the reaction was reduced to 1.1 equivalents, however only unreacted starting materials were observed (entry 5). When the temperature was increased to 80 °C a complex mixture of products was observed after a reaction time of 1 h (entry 6).

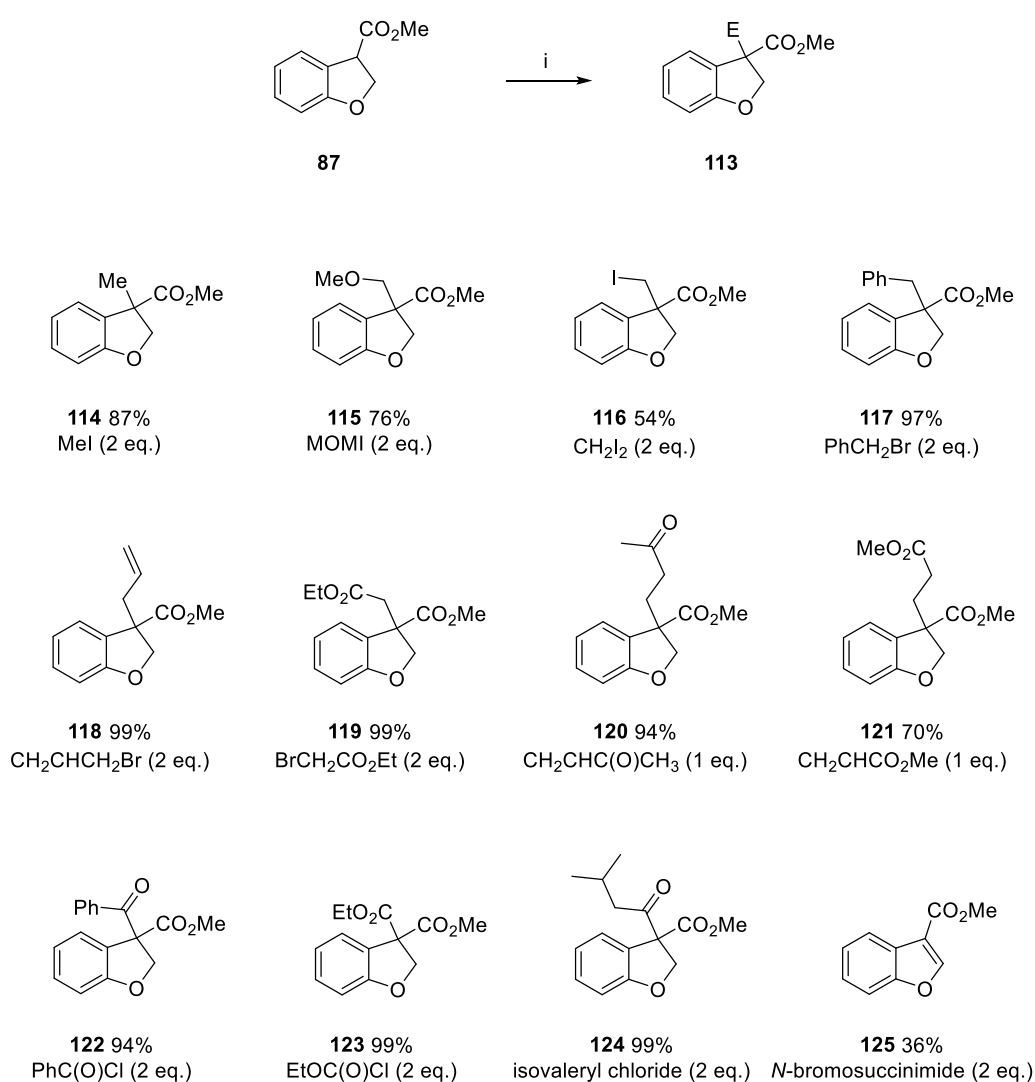


Scheme 19. Attempted arylation and vinylation of ketone **111**

2.1.4 Model studies: enolate functionalisation

With the palladium catalysed cross-coupling of ester **111** proving challenging, we then investigated the possibility that the enolate of ester **87** could be functionalised with more reactive electrophiles at low temperature in order to minimise undesired

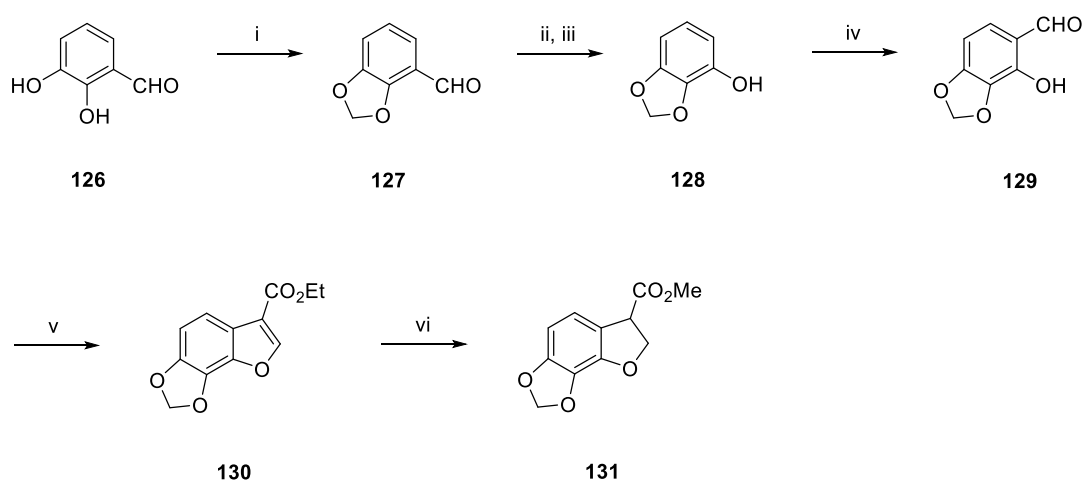
elimination processes. We were pleased to observe that ester **87** reacted with LiHMDS and a variety of electrophiles to afford a wide range of products (Scheme 20). Gratifyingly, neither rearrangement product ester **95**, nor lactone **96** were observed in any of the reactions conducted, provided that the temperature remained at $-78\text{ }^{\circ}\text{C}$ throughout. Surprisingly, the reaction of ester **87** with *N*-bromosuccinimide resulted in the formation of benzofuran **125**. Presumably the mechanism for this reaction involved the bromination of the enolate, followed by elimination to aromatise, thereby forming the benzofuran.



Scheme 20. Reagents and conditions: i) LiHMDS, **87**, THF, $-78\text{ }^{\circ}\text{C}$, 30 min, then electrophile, $-78\text{ }^{\circ}\text{C}$, 3 h

We were particularly interested in ketone **124**, formed from the reaction of ester **87** and isovaleryl chloride in 99% yield since it resembled the enone fragment of the taiwanschirin family of natural products, and the ketone carbonyl has the potential to be converted to the corresponding olefin. Preliminary Wittig and Peterson olefination attempts to install the enone motif were unsuccessful. However, there is scope for further investigation in this area including the application of Meyer–Schuster conditions previously reported for the olefination of ketones.⁴³

With conditions having now been found for the functionalisation of ester **87**, we then investigated whether this reactivity could be extended to a more realistic model incorporating the methylenedioxy motif, as present in our target family of natural products (Scheme 21).

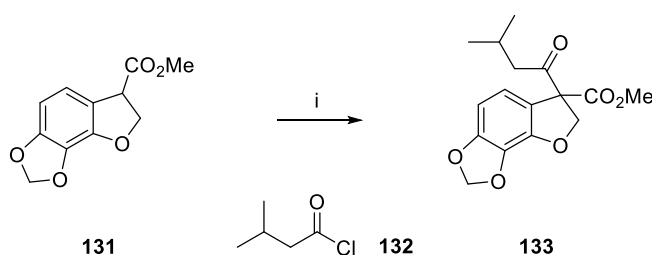


Scheme 21. Reagents and conditions: i) CH_2Br_2 , K_2CO_3 , 10 mol% CuO , DMF, 165 °C, 3 h, 100%; ii) MCPBA, CH_2Cl_2 , 40 °C, 16 h; iii) KOH, EtOH, rt, 2 h, 64% over 2 steps; iv) paraformaldehyde, MgCl_2 , Et_3N , THF, 85 °C, 6 h, 95%; v) Ethyl diazoacetate, $\text{HBF}_4 \cdot \text{OEt}_2$, rt, 30 min, then H_2SO_4 , rt, 30 min, 90%; vi) Mg, MeOH, rt, 1 h 82%

Commercially available 2,3-dihydroxybenzaldehyde **126** was reacted with dibromomethane in the presence of K_2CO_3 and 10 mol% CuO , as previously described in the literature, to afford aldehyde **127** in quantitative yield.⁴⁴ Subsequent reaction with MCPBA followed by ester hydrolysis under basic conditions afforded phenol **128** in 64% yield over 2 steps.

Application of the *ortho*-formylation conditions developed by Hansen provided access to aldehyde **129** in 95% yield.⁴⁵ This was then converted to benzofuran **130** in 90% yield with ethyl diazoacetate and tetrafluoroboric acid, followed by treatment with concentrated sulfuric acid. Finally, reduction using magnesium in methanol afforded the desired dihydrobenzofuran **131** in 82% yield.

The stability of the enolate of ester **131** at $-78\text{ }^{\circ}\text{C}$ was then confirmed by reaction with isovaleryl chloride **132**, affording ester **133** in 49% yield (Scheme 22).

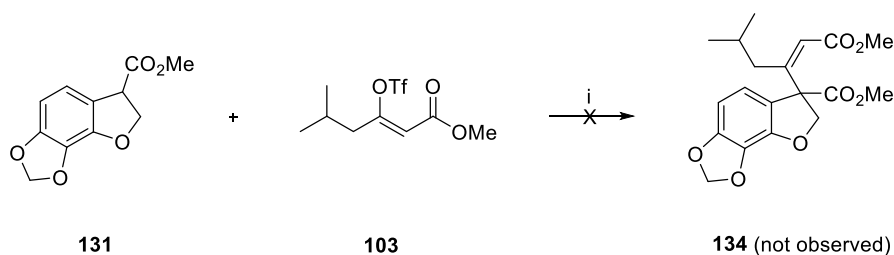


Scheme 22. Reagents and conditions: i) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 30 min, then isovaleryl chloride **132**, $-78\text{ }^{\circ}\text{C}$, 3 h, 49%

2.1.5 Strategies to combat elimination

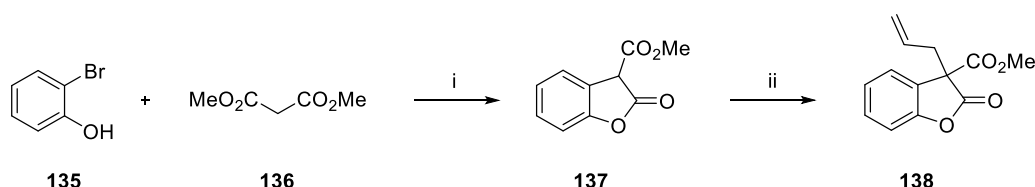
At this point we sought to devise a solution to the problematic elimination observed in our attempted enolate vinylation reaction of ester **87**. We postulated that incorporation of the methylenedioxy motif, present in our target family of natural products, may lead to increased enolate stability thereby reducing undesired elimination due to a negative inductive effect.

In order to test this hypothesis, ester **131** was then deprotonated with NaHMDS and reacted with triflate **103** in the presence of 2.5 mol% $[\text{P}^t\text{Bu}_3\text{PdBr}]_2$ at $-78\text{ }^{\circ}\text{C}$, according to the previously developed cross-coupling conditions (Scheme 16). Only unreacted starting material was observed by TLC after 1 h so the reaction temperature was increased to $0\text{ }^{\circ}\text{C}$ for a further hour (Scheme 23). Disappointingly, however, after warming to $0\text{ }^{\circ}\text{C}$ a complex mixture of products was observed by ^1H NMR.



Scheme 23. Reagents and conditions: i) 2.5 eq. NaHMDS, 2.5 mol% [P^tBu₃PdBr]₂, toluene, –78 °C, 1 h, then 0 °C, 1 h

The second strategy investigated to combat elimination involved the addition of a carbonyl group *alpha* to the phenolic oxygen, leading to the synthesis of ester **137** in 37% yield from 2-bromophenol **135** (Scheme 24).⁴⁶ Ester **137** was shown to react with allyl iodide, promoted by the addition of stoichiometric copper (I) bromide, as previously described in the literature to afford alkene **138** in 48% yield.⁴⁶ However, only unreacted starting material was observed when ester **137** was reacted with triflate **97** or bromobenzene **98** using a range of different palladium–catalysed arylation conditions. Arylation attempts with diphenyliodonium tetrafluoroborate⁴⁷ and copper(I) iodide catalysed vinylation⁴⁸ with *trans*-bromostyrene were also unsuccessful with unreacted starting material observed in each instance.

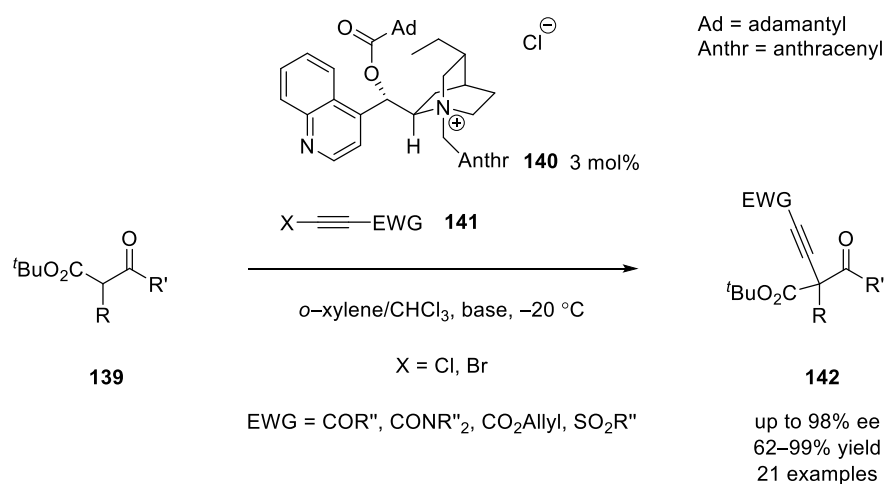


Scheme 24. Reagents and conditions: i) NaH, dioxane, rt, 10 min, then CuBr, 70 °C, 9 h, 37%; ii) LiHMDS, CuBr, THF, 10 min, then allyl iodide, rt, 3 h, 48%

2.1.6 Enolate alkynylation

Given the challenges associated with the vinylation of ester **87**, or derivatives thereof, we decided to revisit successful earlier work based on the low temperature reaction of ester **87** with electrophiles (Scheme 20). We were particularly drawn to a report by Jørgensen detailing the enantioselective *alpha*–alkynylation of cyclic *beta*–ketoesters using *beta*–

haloalkynes (Scheme 25).⁴⁹ In this work, *beta*-haloalkynes incorporating a variety of possible electron withdrawing groups are shown to undergo a conjugate addition–elimination reaction with cyclic *beta*-ketoesters under asymmetric phase–transfer conditions.

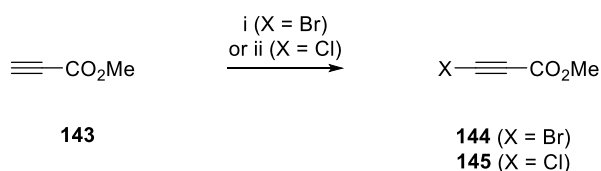


Scheme 25. Enantioselective *alpha*-alkynylation of *beta*-ketoesters⁴⁹

Earlier workers in the field have developed methodologies for the reaction of haloalkynes with ester enolates,^{50,51} and as partners in cycloaddition reactions with alkenes.^{52,53} There are several reports of acetylenic substitutions employing alternative classes of reagents in the literature, including notable work on hypervalent iodine reagents by Waser^{50,54} and lead triacetate reagents.⁵⁵ However, the application of these methodologies is limited due to the extended synthesis of reagents, toxicity issues, and relatively high molecular weight giving rise to low atom economy. The *beta*-haloalkyne reagents used by Jørgensen were therefore investigated as potential electrophiles under the conditions used previously for the reaction of ester **87** (Scheme 20).

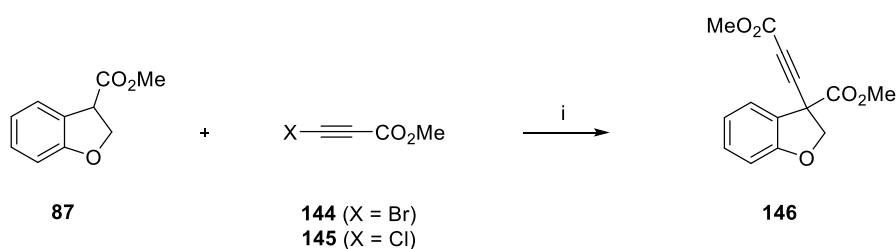
Bromoacetylene **144** was prepared in 76% yield by the reaction of *N*-bromosuccinimide with methylpropiolate.⁵⁶ The corresponding chloroacetylene **145** was initially prepared according to the procedure reported by Jørgensen, however this proved difficult to reproduce and

consistently low yields of the desired product were obtained.⁴⁹ This procedure was adapted to introduce a work up stage in which the crude mixture was partitioned between water and pentane. The use of pentane was crucial as this enabled the volatile product to be separated from the reaction solvent without significant loss.



Scheme 26. Reagents and conditions: i) *N*-bromosuccinimide, acetone, rt, 30 min, 76%; ii) ^tBuOCl, ^tBuOK, ^tBuOH, rt, 30 min, 60%

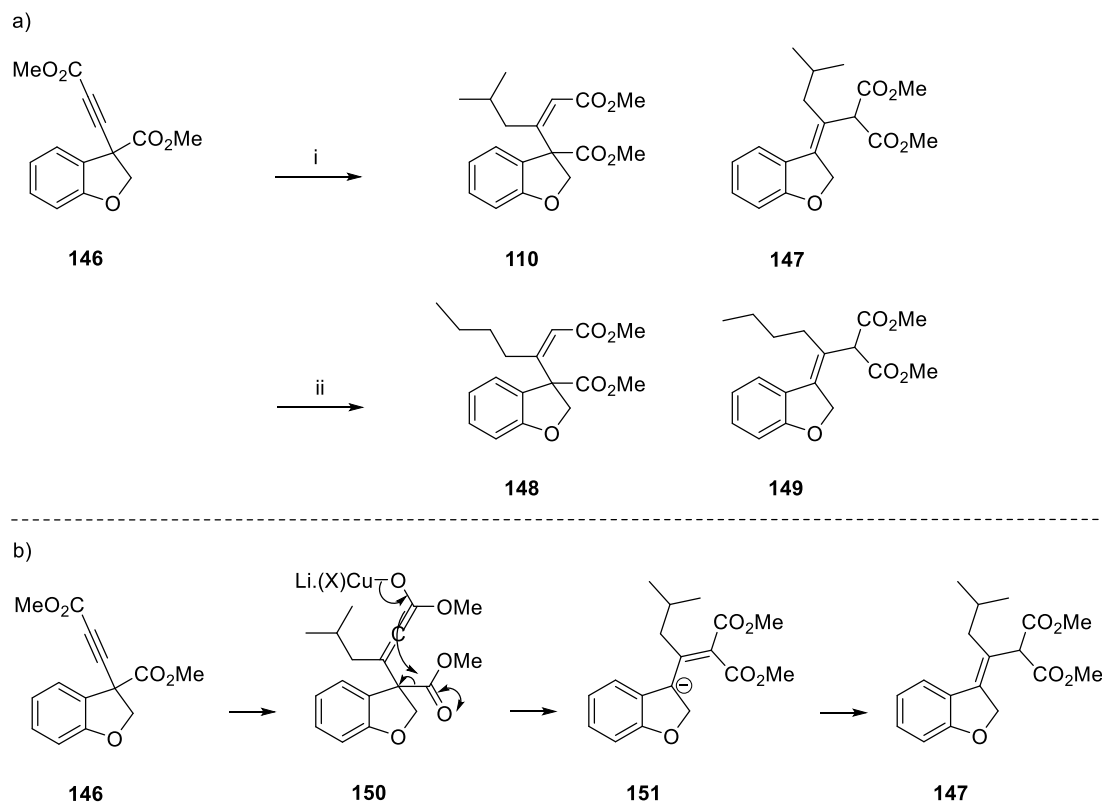
Pleasingly, ester **87** reacted with bromoacetylene **144** at $-78\text{ }^{\circ}\text{C}$ to afford alkyne **146** in 38% yield (Scheme 27). The use of chloroacetylene **145** resulted in a cleaner reaction profile and a considerably higher yield of 94%.



Scheme 27. Reagents and conditions: i) LiHMDS, **87**, THF, $-78\text{ }^{\circ}\text{C}$, 10 min, then **144**, 38%, or **145**, 94%

The successful synthesis of alkyne **146** in high yield represented a significant development in this work, and we could now explore known methods to functionalise the alkyne leading to trisubstituted olefins. For example, the addition of organocuprate reagents to ynones has been previously described in the literature as a method of accessing trisubstituted enones with overall *cis*-addition.⁵⁷ We initially examined the reactions of organocuprate reagents derived from Grignard reagents with alkyne **146**. In the case of isobutylmagnesium chloride, alkene **147** was isolated in 86% yield, and none of the desired alkene **110** was observed (Scheme 28a). We postulated that alkene **147** was formed from an intramolecular reaction

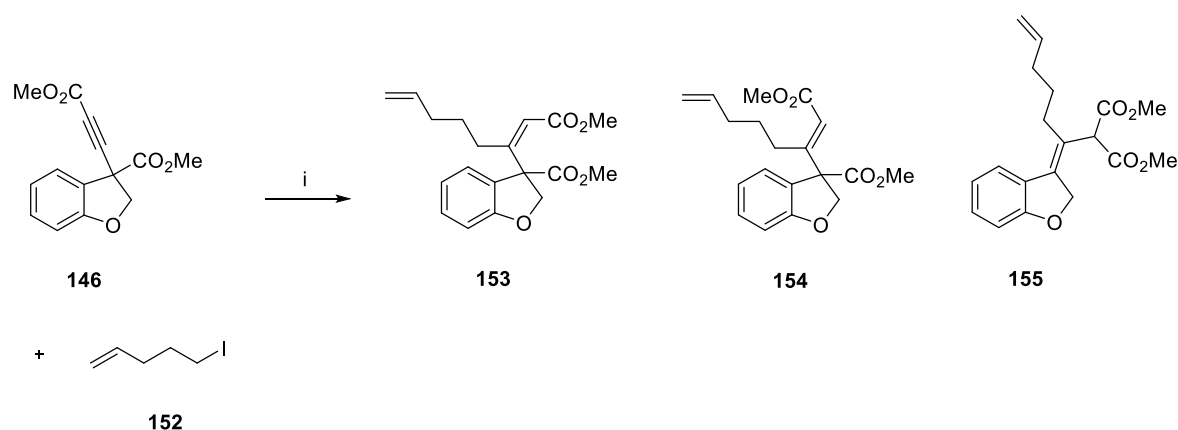
of extended enolate **150**, followed by alkene isomerisation (Scheme 28b). However, when butylmagnesium chloride was used, we were pleased to isolate alkene **148** in 38% yield. Moreover, alkene **148** was isolated as a single diastereomer and the (*Z*)-configuration was confirmed by nOe experiments.



Scheme 28. a) Reagents and conditions: i) 4 eq. *i*BuMgCl, 2 eq. CuI, THF, $-78-0^{\circ}\text{C}$, 1 h, then -78°C , **146**, 3 h, 86% **147** (**110** not observed); ii) 4 eq. *n*BuMgCl, 2 eq. CuI, THF, $-78-0^{\circ}\text{C}$, 1 h, then -78°C , **146**, 3 h, 38% **148**, 14% **149**; b) Proposed mechanism to show the formation of alkene **147**

We then looked towards the optimisation of this reaction and focussed our efforts on organocuprate reagents derived from the metal–halogen exchange of alkyl iodides. Using iodide **152** as a model substrate, metal–halogen exchange with *t*BuLi followed by subjection to the standard conditions to afford the desired (*Z*)-alkene **153** was isolated in 54% yield in addition to a 19% yield of the (*E*)-alkene **154** (Scheme 29, entry 1). An additional reaction time of 16 h at rt afforded alkene **155** in 53% yield (entry 2). This provided good evidence that longer reaction times favoured the formation of the undesired rearrangement product. Neither fewer equivalents of organocuprate reagent

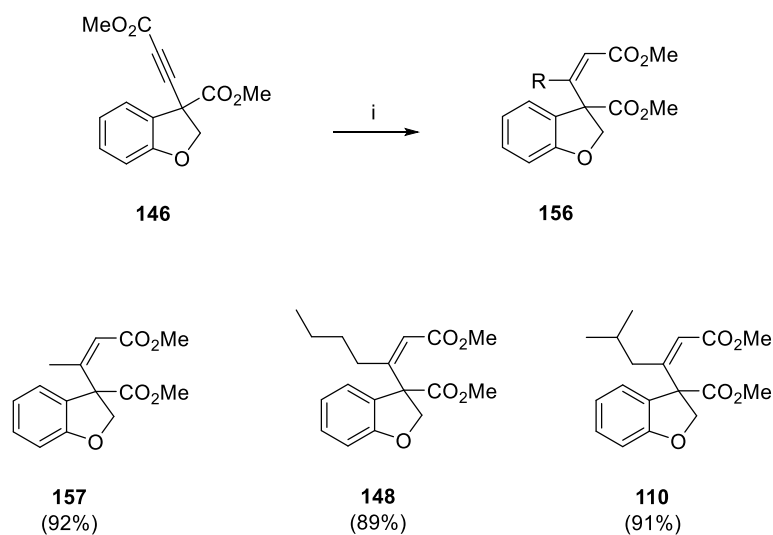
(entry 3), nor use of the corresponding bromide led to an increased yield of the (*Z*)-alkene (entry 4). We speculated, however, that the sat. aq. NH₄Cl solution used for quenching the reaction may freeze prematurely, leading to the reaction being quenched at higher temperature, thereby enabling the undesired formation of alkene **152**. Pleasingly, when the reaction was quenched with MeOH, alkene **153** was isolated in 55% yield and none of the undesired alkene **154** was observed (entry 5).



Entry	Change from standard conditions	% Yield 153	% Yield 154	% Yield 155
1	–	54	19	0
2	Additional reaction time rt, 16 h	0	0	53
3	1.2 eq. Organocuprate	38	36	0
4	5-bromopentane	24	0	0
5	MeOH quench	55	0	0

Scheme 29. Reagents and (standard) conditions: i) 4 eq. **152**, 8 eq. ^tBuLi, pentane/Et₂O 3:2, –78 °C, 2 eq. CuI, 10 min, then 0 °C, 1 h, then –78 °C, **146**, 30 min, NH₄Cl quench

Pleasingly, application of this new protocol to organocuprates derived from organolithium reagents resulted in the synthesis of several novel (*Z*)-enones in high yields. For example, the use of methyllithium afforded alkene **157** in 92% yield (Scheme 30).



Scheme 30. Reagents and conditions: 4 eq. RLi, 2 eq. CuI, THF, $-78 - 0\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C}$, **146**, 30 min

The (*Z*)-configuration of alkene **157** was confirmed by the clear observation of nOe enhancements between the allylic methyl group $\delta = 1.77$ (3H, d, $J = 1.6\text{ Hz}$, CH_3) and the olefinic proton $\delta = 5.93$ (1H, q, $J = 1.5\text{ Hz}$, $\text{C}=\text{CH}$) as shown below (Figure 2).

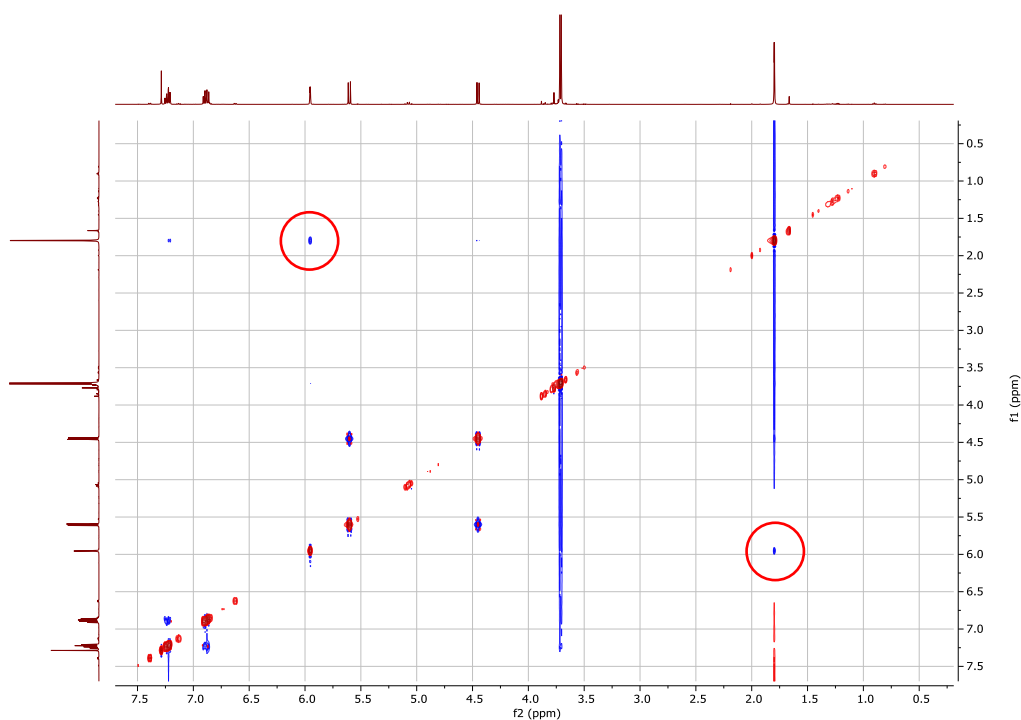


Figure 2. 2D NOESY spectrum of alkene **157**

Additionally, a crystal of alkene **157** was grown and an X-ray crystal structure obtained (Figure 3).

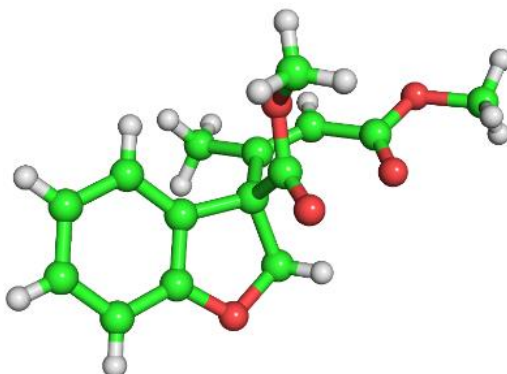


Figure 3. X-ray crystal structure of alkene **157**

We now had unequivocal proof of the (*Z*)-enone configuration and were in a position to progress our studies and investigate proposals for the synthesis of the 8-membered ring. Once we had devised a strategy for the closure of the 8-membered ring, we would be able to modify our cuprate reagent to include the two methyl stereocentres found in the structure of the taiwanschirin family.

2.2 8-Membered ring incorporation

8-Membered carbocyclic rings are present in a wide variety of natural products, with many exhibiting notable biological activities (Figure 4).⁵⁸ Perhaps one of the most significant classes of natural products is the diterpenoid family, including fusicoplagin A (**158**)⁵⁸ and taxol (**159**).^{59–61} Isolated from the Pacific yew tree, taxol (**159**) has found extensive application in the field of oncology and has been a longstanding target in the field of total synthesis.

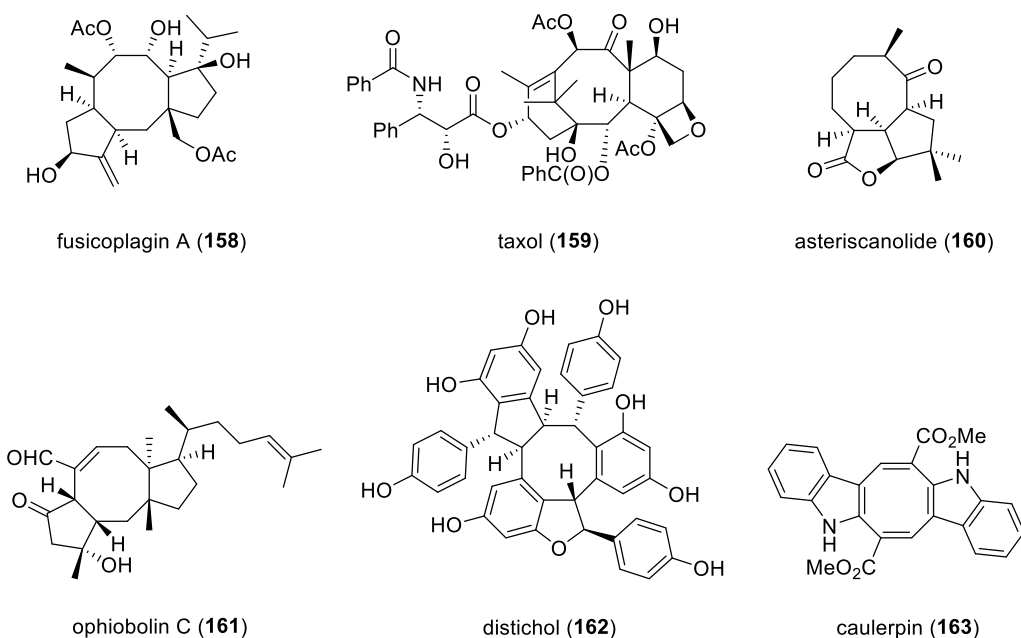


Figure 4. Natural products containing 8-membered rings

A range of different synthetic strategies have been devised for the synthesis of 8-membered rings, however their synthesis still remains challenging due to the presence of significant ring-strain and transannular interactions.⁵⁸ Spectroscopic techniques including NMR and IR, in addition to X-ray crystallography, have been used to identify the major conformations adopted by molecules featuring 8-membered rings within their structures. There are three main conformational families, the most important of which are detailed below (Figure 5).

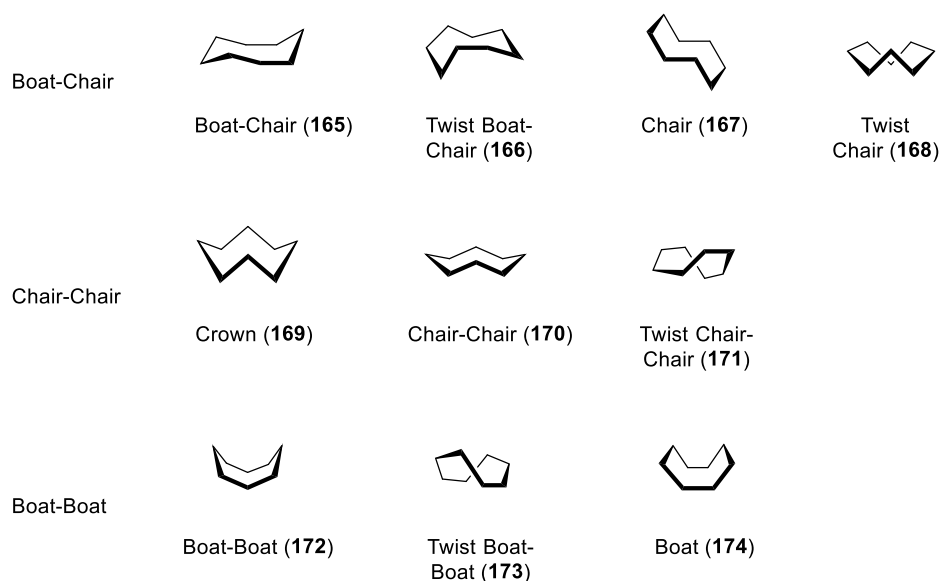


Figure 5. The major conformations of cyclooctane

Generally, the boat–chair conformation is the lowest in energy due to the minimisation of torsional strain and transannular interactions. At room temperature, cyclooctane exists predominantly in the boat–chair group of conformations (>94%). Due to the dominant nature of ring strain and transannular interactions, many of the strategies developed for the synthesis of smaller rings prove unsuccessful when applied to the synthesis of 8–membered rings. As a consequence of this, there has been a significant amount of effort devoted towards the development of new synthetic techniques for the synthesis of medium rings. A seminal review of the field, published in 1992 by Petasis, provided a comprehensive overview of the different strategies for the assembly of 8–membered rings in the context of natural product total synthesis.⁵⁸ In this work, methods are categorised to include intramolecular C–C bond formation reactions, ring expansions, and fragmentations.

In our studies towards the total synthesis of the taiwanschirin family of natural products, many methods for the synthesis of the 8–membered ring were explored. The first of these approaches is an intramolecular C–C bond formation reaction, a Friedel–Crafts acylation reaction.

2.2.1 Friedel–Crafts acylation

The Friedel–Crafts acylation reaction has been extensively used in the field of natural product chemistry.⁶² There are also many examples of intramolecular Friedel–Crafts acylation reactions used in the assembly of complex molecules, several of these are shown below (Figure 6).^{63–65}

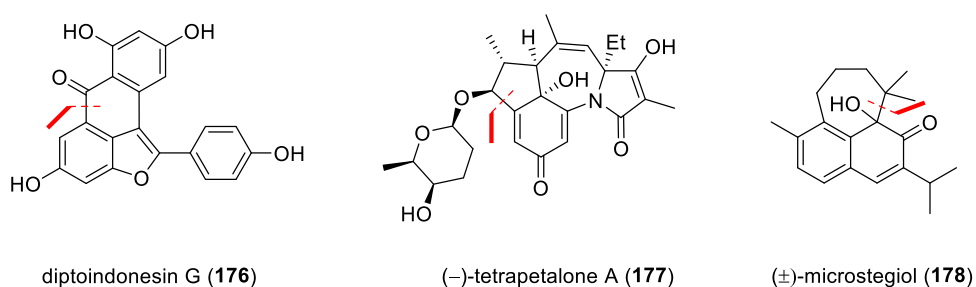
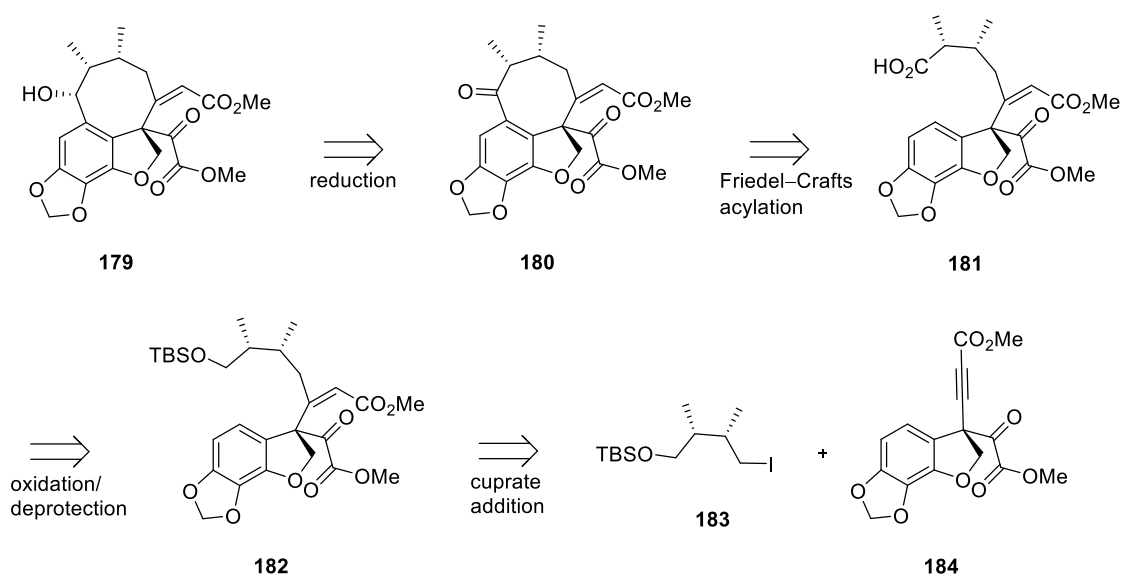


Figure 6. Intramolecular Friedel–Crafts reactions used in the assembly of natural products

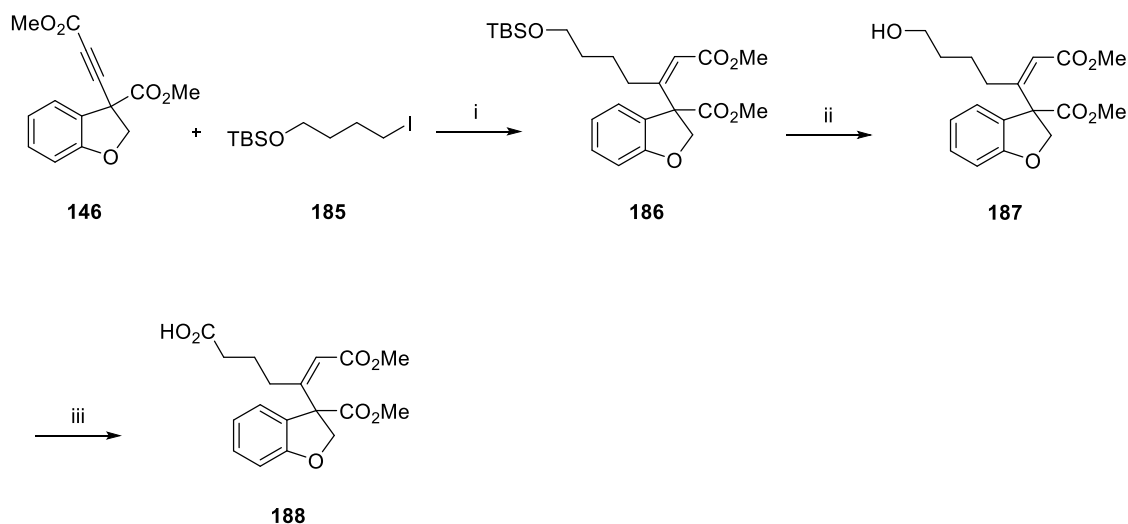
Our proposed retrosynthesis involved the formation of alcohol **179** from the reduction of ketone **180** (Scheme 31). Ketone **180** would be obtained from an intramolecular Friedel–Crafts acylation reaction of acid **181**. In turn, acid **181** was proposed to derive from the deprotection and oxidation of the primary alcohol present in alkene **182**, itself the product of the reaction of an organocuprate reagent derived from iodide **183**, with alkyne **184**.



Scheme 31. Proposed retrosynthesis involving a key intramolecular Friedel–Crafts acylation reaction

2.2.2 Synthesis of a model Friedel–Crafts acylation substrate

In order to investigate the feasibility of an intramolecular Friedel–Crafts reaction in the synthesis of the taiwanschirin family, the synthesis of a simplified model compound was necessary (Scheme 32).

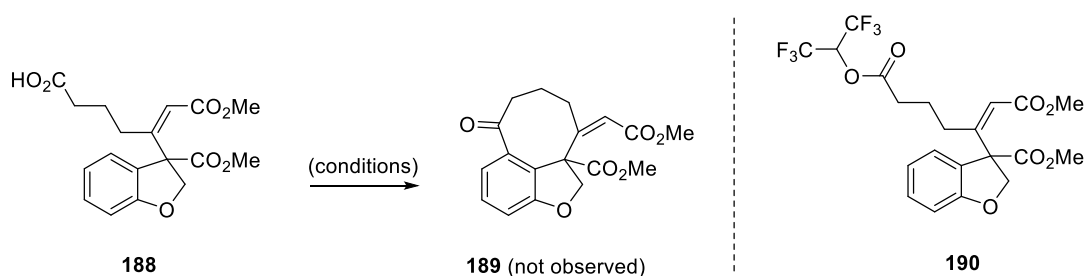


Scheme 32. Reagents and conditions: i) **185**, ^tBuLi, pentane/Et₂O 3:2, -78 °C, CuI, 10 min, then 0 °C, 1 h, then -78 °C, **146**, 30 min, 71%; ii) 10 mol% FeCl₃, MeOH, rt, 2 h, 91%; iii) 5 eq. CrO₃, H₂SO₄, acetone/water 2:1, rt, 1 h, 100%

Iodide **185**, synthesised in a ring-opening reaction from THF with TBSCl and KI, was treated with ^tBuLi and CuI to prepare an organocuprate reagent. The reaction with alkyne **146** furnished alkene **186** in 71% yield and as a single diastereomer. Deprotection of TBS-protected alcohol **186** using 10 mol% FeCl₃ in MeOH afforded alcohol **187** in 91% yield.⁶⁶ Initial attempts at the deprotection of alcohol **186** with TBAF at 0 °C resulted in a complex mixture of products. It was postulated that these conditions resulted in the formation of an alkoxide intermediate which could then undergo a variety of undesired reactions including transesterification and conjugate addition processes. Pleasingly, the oxidation of alcohol **187** to acid **188** under Jones' conditions proceeded cleanly to afford the desired product in quantitative yield on a scale of 50 mg. This reaction was also performed on a larger scale of 580 mg and a comparable yield of 83% was obtained. Crucially, the (Z)-

configuration of the alkene functional group present in acid **188** was confirmed by nOe measurements.

With acid **188** in hand, we were now in a position to investigate the key intramolecular Friedel–Crafts acylation reaction. A range of different conditions were investigated, all of which had been previously reported in the literature as promoting intramolecular Friedel–Crafts reactions (Scheme 33).



Entry	Reagents and Conditions	Comment
1	Oxalyl chloride, DMF, CH ₂ Cl ₂ , rt, 2 h, then 0 °C, AlCl ₃ , rt, 16 h	Complex mixture by ¹ H NMR
2	Cyanuric chloride, py, rt, 15 min, then AlCl ₃ , rt, 16 h	SM only by ¹ H NMR
3	MeSO ₃ H (0.2 M), P ₂ O ₅ , rt, 16 h	Complex mixture by ¹ H NMR
4	Oxalyl chloride, DMF, CH ₂ Cl ₂ , rt, 2 h, then HFIP, rt, 16 h	190 (27%)

Scheme 33. Attempted Friedel–Crafts acylation of acid **188**

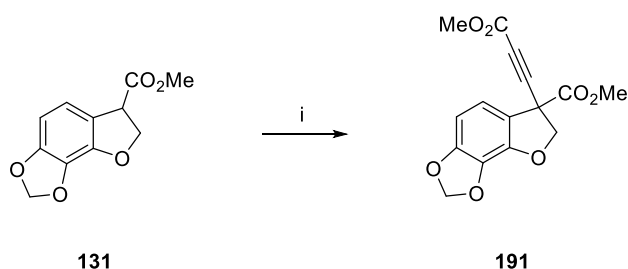
The first set of conditions investigated involved the reaction of acid **188** with oxalyl chloride in the presence of a catalytic amount of DMF to generate the corresponding acyl chloride. Subsequent addition of AlCl₃ was intended to promote the intramolecular Friedel–Crafts reaction, however in this case a complex mixture was observed by ¹H NMR (Scheme 33, entry 1).

An alternative set of conditions developed by Day employing cyanuric chloride and pyridine was also investigated (entry 2).⁶⁷ However, although the method was reported to successfully promote intramolecular Friedel–Crafts reactions in the literature, only starting material was observed. Methanesulfonic acid in combination with P₂O₅ was also unsuccessful and a complex mixture of products was observed in the ¹H NMR of the crude reaction mixture.⁶⁸

Recently, Aubé has reported the use of HFIP in the intramolecular Friedel–Crafts reactions of acyl chlorides.⁶⁹ Given the previous interest of the Donohoe group in the application of HFIP as a reaction solvent, and the possibility of milder reaction conditions when compared with strong Lewis acids, this seemed a promising set of conditions.^{70–73} However, when applied to this system, a 27% yield of HFIP ester **190** was obtained and none of the desired product was observed. This was surprising, as given the inherent low nucleophilicity of HFIP, it has only been reported to act as a nucleophile in the presence of highly reactive cationic species.^{72–74}

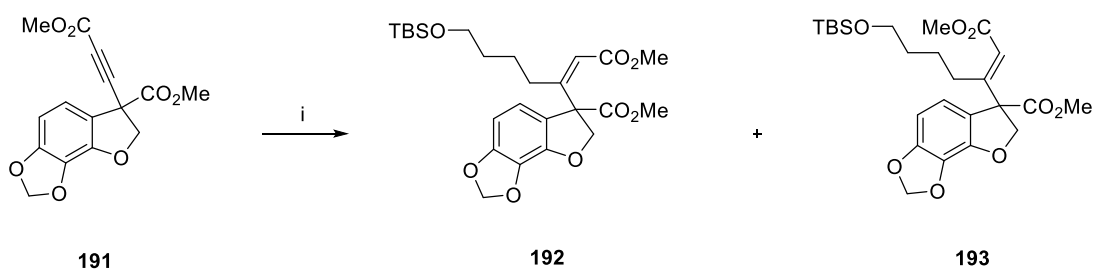
2.2.3 Synthesis of a more advanced acylation substrate

With the intramolecular Friedel–Crafts reaction of acid **188** proving unsuccessful, attention turned towards the synthesis of a model substrate incorporating the methylenedioxy motif as found in the target family of natural products. It was proposed that the oxygen substituents may stabilise the cationic intermediate formed in the Friedel–Crafts reaction by a mesomeric effect. In any case, this model would be a closer representation of the real system. To obtain the model compound required, ester **131**, prepared previously, was initially deprotonated with LiHMDS and reacted with chloroacetylene **145** to afford alkyne **191** in 68% yield (Scheme 34).



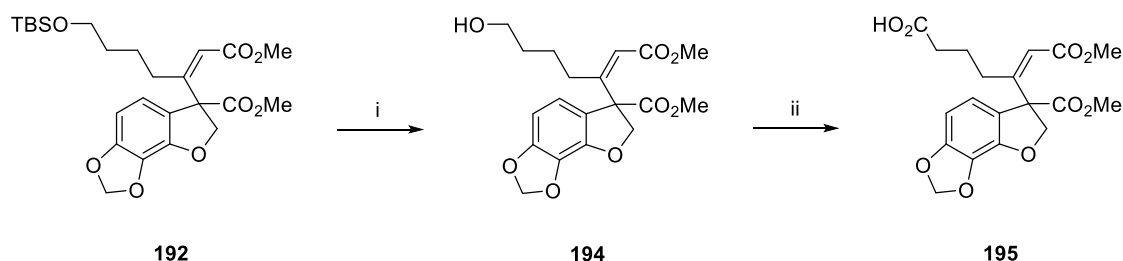
Scheme 34. Reagents and conditions: i) LiHMDS, **131**, THF, $-78\text{ }^{\circ}\text{C}$, 10 min, then **145**, $-78\text{ }^{\circ}\text{C}$, 1 h, 68%

Alkyne **191** was then reacted with the organocuprate reagent derived from iodide **185** (Scheme 35). Surprisingly, a mixture of alkene **192** and alkene **193** was observed. Fortunately, however, the two isomers were readily separable by column chromatography and the desired (*Z*)-alkene **192** was obtained in a modest 42% yield.



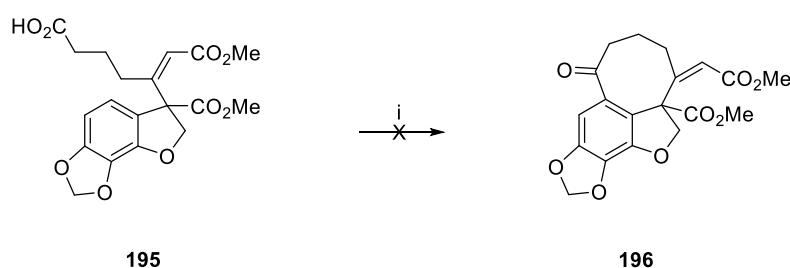
Scheme 35. Reagents and conditions: i) **185**, $t\text{-BuLi}$, pentane/ Et_2O 3:2, $-78\text{ }^{\circ}\text{C}$, CuI, 10 min, then $0\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C}$, **191**, 30 min, 42% **192** + 37% **193**

Deprotection of the TBS-protected alcohol **192** with 10 mol% FeCl_3 in MeOH afforded alcohol **194** in 99% yield (Scheme 36). Oxidation under Jones' conditions provided the desired carboxylic acid **195** in 64% yield.



Scheme 36. Reagents and conditions: i) 10 mol% FeCl_3 , MeOH, rt, 3 h, 99%; ii) 5 eq. CrO_3 , H_2SO_4 , acetone/water 2:1, rt, 2 h, 64%

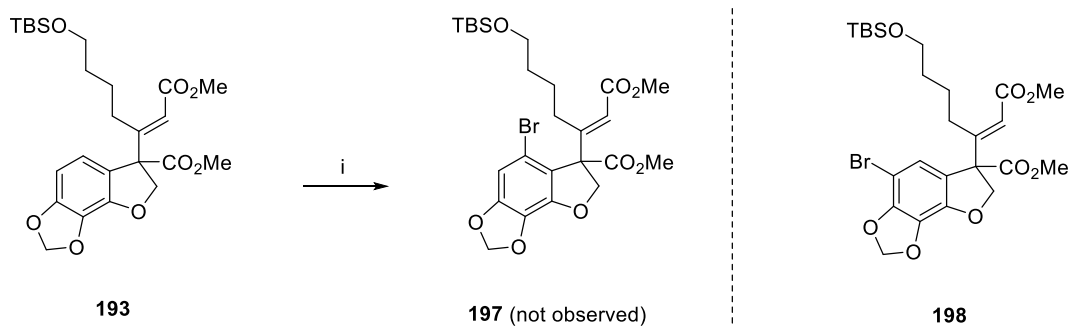
With acid **195** in hand, we were now able to investigate the proposed intramolecular Friedel–Crafts acylation reaction with a more realistic model substrate. Disappointingly, however, reaction with oxalyl chloride and DMF, followed by treatment with AlCl₃ resulted in the formation of a complex mixture of products (Scheme 37). Clearly, the development of milder reaction conditions was necessary in order to successfully synthesise the 8–membered ring present in the taiwanschirin family.



Scheme 37. Reagents and conditions: i) Oxalyl chloride, DMF, CH₂Cl₂, rt, 2 h, then 0 °C, AlCl₃, rt, 16 h

2.2.4 Halogenation of alkene **193**

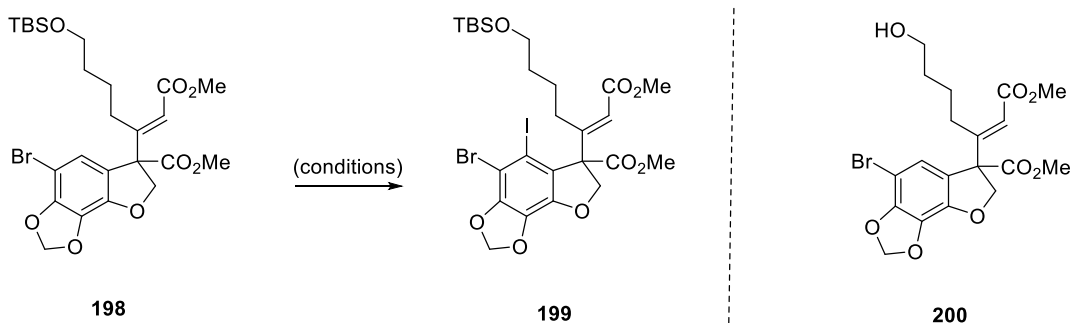
With the Friedel–Crafts approach proving unsuccessful, we now looked towards C–4 functionalisation of the benzofuran. It was postulated that a halogenation reaction could enable cross coupling reactions and other strategies to form the 8–membered ring. In order to test this hypothesis, the undesired side product of the organocuprate addition reaction, alkene **193**, was treated with *N*-bromosuccinimide in MeCN (Scheme 38). Alkene **193** was used to investigate this proposal due to the extended synthesis of alkene **192** (8 steps from commercially available aldehyde **126**).



Scheme 38. Reagents and conditions: i) *N*-bromosuccinimide, MeCN, rt, 16 h, 100% **198**

Bromination of the aromatic ring of alkene **193** was observed exclusively at the C-5 position rather than at C-4 to afford bromide **198** in 100% yield. Attempts were also made to form the dibromide via the treatment of bromide **198** with excess *N*-bromosuccinimide, both at rt and at 80 °C for 16 h, however only unreacted starting material was observed in each case. Treatment with bromine and iron powder in CH₂Cl₂ at 40 °C for 4 h led to decomposition.⁷⁵

An iodination approach was explored, and different conditions investigated (Scheme 39).



Entry	Reagents and Conditions	Comment
1	1.5 eq. <i>N</i> -iodosuccinimide, MeCN, 80 °C, 5 h	SM only by NMR
2	1.5 eq. <i>N</i> -iodosuccinimide, 1.5 eq. TMSOTf, MeCN, 80 °C, 5 h	Complex mixture
3	1.5 eq. DIH, H ₂ SO ₄ , EtOH, 1 h	69% 200
4	5 eq. ICl, CH ₂ Cl ₂ , 50 °C, 5 h	80% 200
5	3 eq. ICl, 1.5 eq. Ag ₂ SO ₄ , H ₂ SO ₄ , H ₂ O, 1 h	Decomposition
6	3 eq. ICl, 1.5 eq. Ag ₂ SO ₄ , H ₂ SO ₄ , EtOH, H ₂ O, 1 h	60% 200

Scheme 39. Iodination of alkene **198**

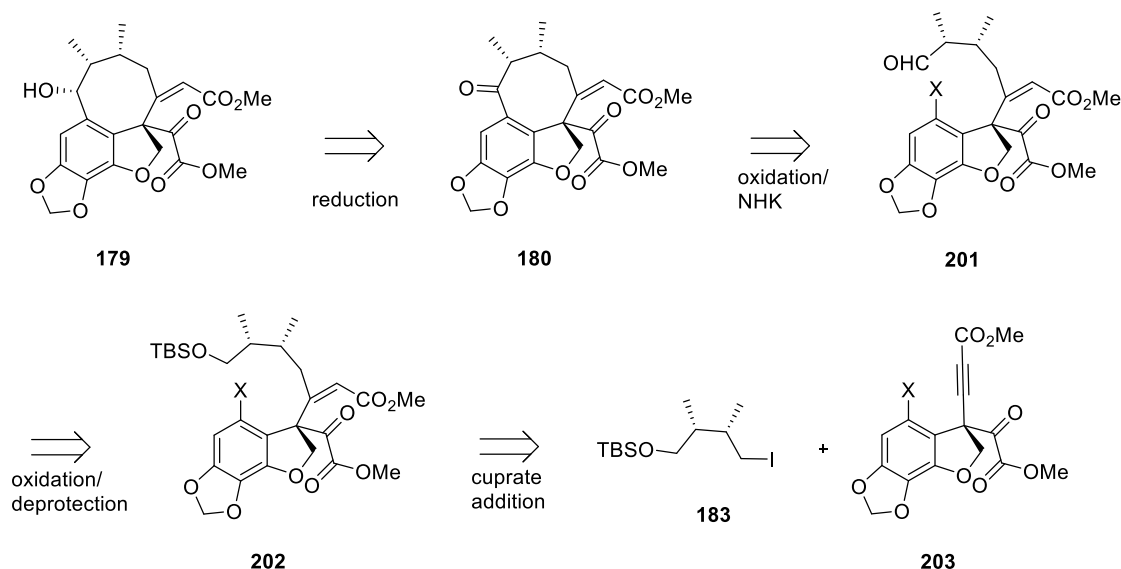
Bromide **198** was initially reacted with *N*-iodosuccinimide at 80 °C for 5 h, however only starting material was observed in the ¹H NMR of the crude reaction mixture (entry 1). More forcing iodination conditions employing a mixture of *N*-iodosuccinimide and TMSOTf were also investigated, however a complex mixture was obtained (Entry 2).⁷⁶ We postulated that this iodination reaction was particularly challenging due to steric hindrance present in the intermediate carbocation. In light of this, 1,3-diiodo-5,5-dimethylhydantoin (DIH) was explored as this has been reported in the literature as a highly active iodinating agent, even enabling the iodination of nitrobenzene.⁷⁷ Unfortunately, however, only deprotection of the TBS-protected alcohol was observed, and alcohol **200** was isolated in 69% yield (entry 3). ICl also resulted in deprotection of the alcohol and an 80% yield of alcohol **200** was obtained (entry 4). Highly active iodination conditions employing a combination of ICl and Ag₂SO₄ have been reported by Filiminov.⁷⁸ We were particularly interested in these conditions as Ag⁺ should sequester Cl⁻ as a solid precipitate, thereby minimising TBS-alcohol deprotection. However, application of these conditions to the iodination of bromide **198** resulted in decomposition (entry 5). Dilution of the reaction mixture with EtOH was also unsuccessful.

From the investigations described above, it was apparent that if halogenation at the C-4 position were desired, this must be achieved early in the synthesis. Our next strategy towards the formation of the 8-membered ring investigated this approach and developed a novel approach for the synthesis of C-4 halogenated dihydrobenzofurans.

2.2.5 Nozaki-Hiyama-Kishi coupling

The Nozaki-Hiyama-Kishi (NHK) reaction was first reported in 1977 using CrCl₃ and LiAlH₄ as the terminal reductant.⁷⁹ Independent work by the groups of Kishi,⁸⁰ and of Takai and Nozaki,⁸¹ identified the crucial role of catalytic nickel in this reaction. Due to its highly

chemoselective nature the NHK reaction has seen widespread application in the total synthesis of natural products. Moreover, this reaction has been employed in the late-stage synthesis of macrocyclic ring systems, suggesting the possibility of a new disconnection in the synthesis of the taiwanschirin family as detailed below (Scheme 40).⁸²



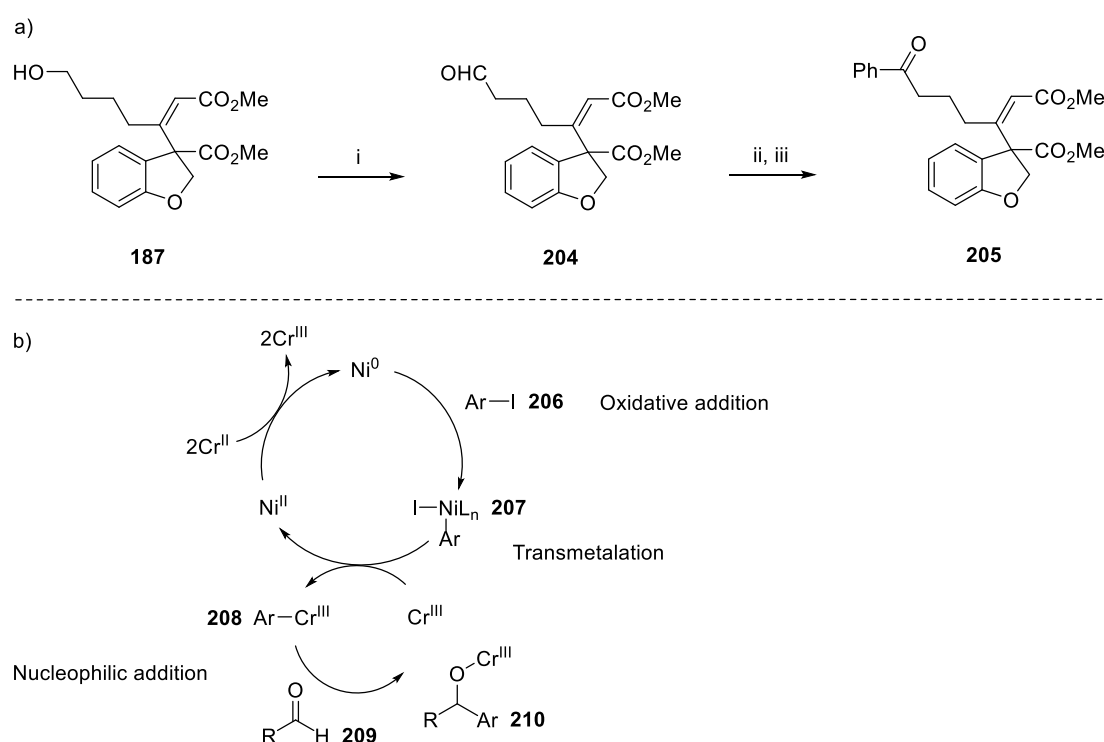
Scheme 40. Proposed retrosynthesis involving a key intramolecular NHK reaction (X = Br/I)

As shown above, alcohol **179** could be obtained by the reduction of ketone **180**, the precedent for which has already been described in the literature.⁸³ Ketone **180** derives from the intramolecular NHK reaction of aldehyde **201** followed by oxidation. The addition of a cuprate derived from iodide **183** to alkyne **203**, followed by deprotection and oxidation would afford the desired aldehyde **201**.

2.2.6 Synthesis of a model NHK substrate

In order to investigate the feasibility of this strategy, the previously synthesised alcohol **187** was oxidised with DMP to aldehyde **204** in 84% yield (Scheme 41a). Pleasingly, subjection of aldehyde **204** to NHK conditions in the presence of an excess of iodobenzene resulted in the disappearance of starting material by TLC after 3 h. Subsequent oxidation with DMP

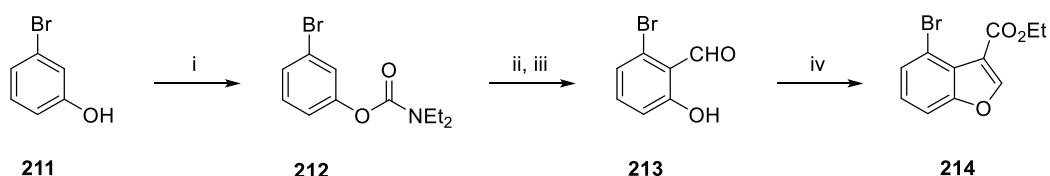
afforded ketone **205** in 89% yield over 2 steps. The proposed mechanism of the NHK reaction is shown below (Scheme 41b). The reaction is catalytic in nickel, and 2 equivalents of chromium (II) are initially required in order to reduce nickel (II) to nickel (0). Oxidative addition may then occur to afford intermediate **207**, which may then undergo a transmetalation process with chromium (III) to afford a more reactive organometallic species **208**. This may then attack aldehyde **209** in a nucleophilic addition reaction to afford chromium (III) alkoxide **210**.



Scheme 41. a) Reagents and conditions: i) DMP, NaHCO₃, CH₂Cl₂, rt, 1.5 h, 84%; ii) 5 eq. CrCl₂, 1 eq. NiCl₂, 10 eq. PhI, DMF, rt, 3 h; iii) DMP, NaHCO₃, CH₂Cl₂, rt, 1.5 h, 89% over 2 steps; b) Proposed NHK reaction mechanism

We then turned our attention to the synthesis of an intramolecular NHK substrate incorporating a bromine atom at the C-4 position. 3-Bromophenol **211** was deprotonated with NaH and reacted with diethylcarbamoyl chloride to form carbamate **212**. With this protecting group in place we were now able to perform a directed deprotonation using LDA in THF at -78 °C. Following reaction with DMF and subsequent deprotection under acidic

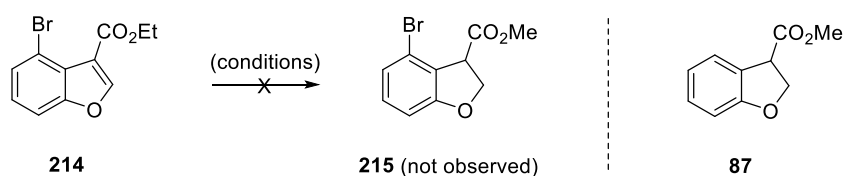
conditions, the desired aldehyde **213** was formed in 69% yield over 3 steps. Similarly to before, aldehyde **213** was then reacted with ethyl diazoacetate to afford benzofuran **214** in 84% yield.



Scheme 42. Reagents and conditions: i) NaH, diethylcarbamoyl chloride, THF, rt, 16 h; ii) LDA, THF, $-78\text{ }^{\circ}\text{C}$, 30 min, then DMF, $-78\text{ }^{\circ}\text{C}$, 30 min; iii) 2 M HCl (aq.), $0\text{ }^{\circ}\text{C}$, 20 min, 69% over 3 steps; iv) Ethyl diazoacetate, $\text{HBF}_4\cdot\text{OEt}_2$, rt, 30 min, then H_2SO_4 , rt, 30 min, 84%

With benzofuran **214** in hand, it was now subjected to the standard magnesium-promoted reduction conditions (Scheme 43, entry 1). Disappointingly, bromide **215** was not observed in the reaction mixture, however de-brominated dihydrobenzofuran **87** was isolated in 23% yield. Presumably the formation of a highly reactive Grignard species was in direct competition with the desired reduction process, leading to the complex reaction profile. Carrying out the reaction at $0\text{ }^{\circ}\text{C}$ resulted in only starting material being observed by ^1H NMR spectroscopy (entry 2).

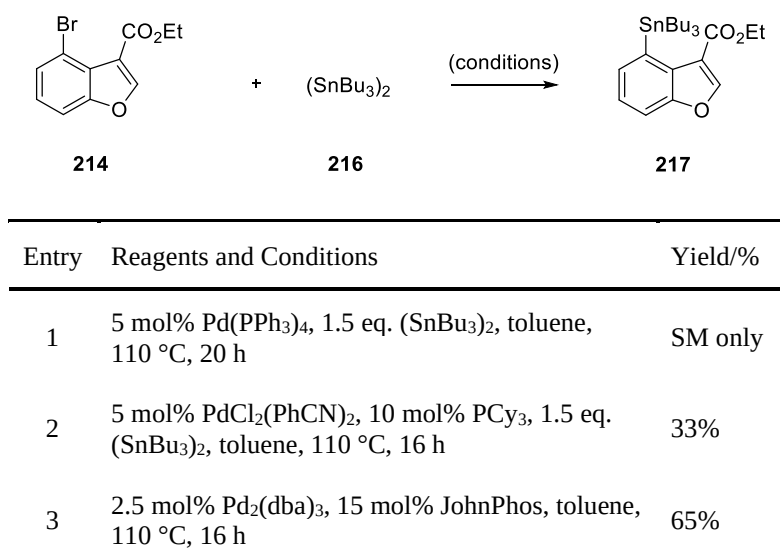
A variety of different conditions, previously shown to reduce benzofuran compounds in the literature, were also investigated as detailed below. Surprisingly the use of palladium-catalysed hydrogenation conditions (entries 3 and 4) failed to afford the desired product, even the de-brominated benzofuran was not observed by ^1H NMR spectroscopy.⁸⁴ Both triethylsilane in the presence of trifluoroacetic acid (TFA),⁸⁵ and samarium(II) iodide also resulted in only starting material being observed by ^1H NMR spectroscopy of the crude reaction mixtures (entries 5 and 6).⁸⁶



Entry	Reagents and Conditions	Comment
1	5 eq. Mg, MeOH, rt, 1 h	87 (23%)
2	5 eq. Mg, MeOH, 0 °C, 1 h	SM only by ¹ H NMR
3	10 mol% Pd/C, 10 mol% PhSH, H ₂ , MeOH, rt, 16 h	SM only by ¹ H NMR
4	10 mol% Pd/C, H ₂ , MeOH, rt, 16 h	SM only by ¹ H NMR
5	5 eq. Et ₃ SiH, TFA, rt, 16 h	SM only by ¹ H NMR
6	5 eq. Sm, 1.7 eq. I ₂ , MeOH/DMA 3:1, rt, 16 h	SM only by ¹ H NMR

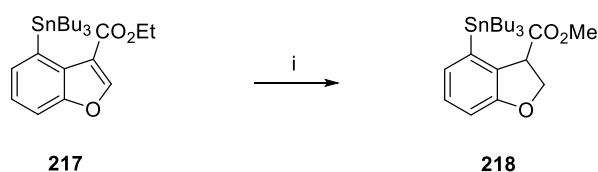
Scheme 43. Attempted reduction of benzofuran **214**

In order to overcome this problem, a palladium–catalysed stannylation reaction to convert the aryl bromide to the tributylstannane was proposed. Initially only starting material was observed by ¹H NMR when Pd(PPh₃)₄ was used as the catalyst (Scheme 44, entry 1).⁸⁷ However, a change of conditions to those developed previously by Hanson for the stannylation of indole derivatives resulted in a 33% yield of the desired product (entry 2).⁸⁸ Pleasingly, the use of 2.5 mol% Pd₂(dba)₃ in combination with 15 mol% JohnPhos resulted in a satisfactory 65% yield (entry 3).



Scheme 44. Stannylation of benzofuran **214**

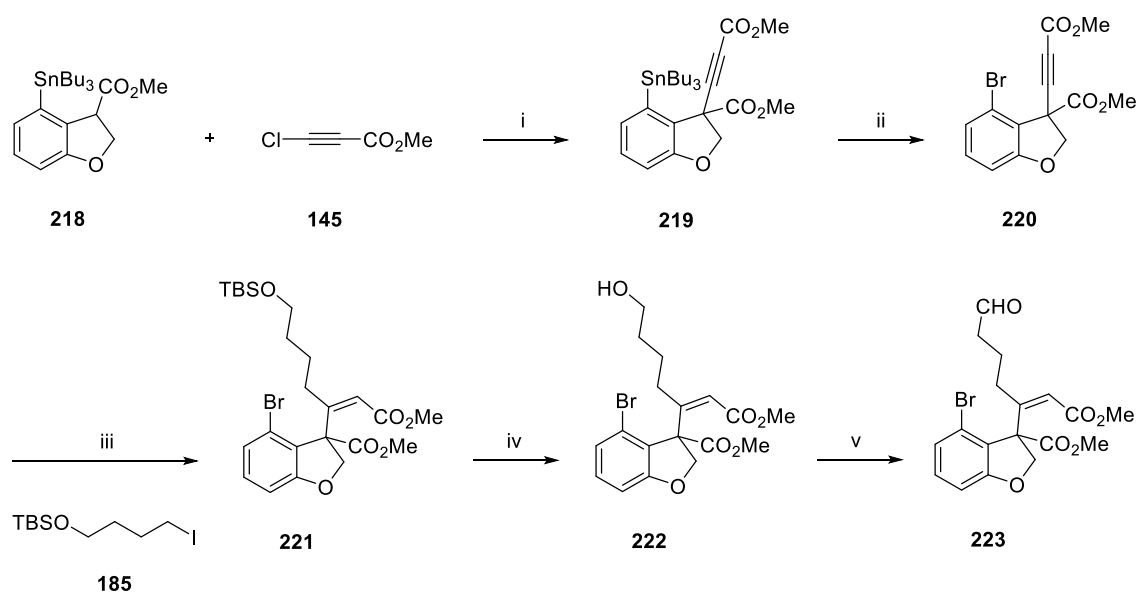
With stannane **217** in hand, we were now able to test the key magnesium mediated reduction step. We were pleased to observe the formation of stannane **218** in 92% yield when the reaction was performed on a scale of 670 mg (Scheme 45). Furthermore, a comparable yield of 84% was achieved when the reaction was scaled up to 1.6 g. Crucially, heating at 70 °C was necessary in order for complete transesterification to occur to form the methyl ester.



Scheme 45. Reagents and conditions: i) Mg, MeOH, rt, 4 h then 70 °C, 1 h, 92%

The successful stannylation–reduction sequence represented an important advance towards the synthesis of the 8–membered ring; it was now possible to synthesise dihydrobenzofuran compounds with functionality at the C–4 position.

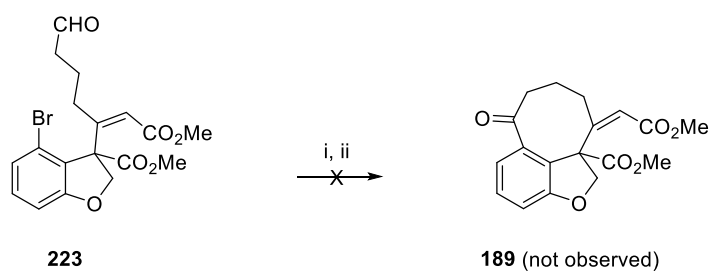
Subjection of stannane **218** to the previously developed alkynylation reaction conditions afforded alkyne **219** in a modest 48% yield (Scheme 46).



Scheme 46. Reagents and conditions: i) LiHMDS, **218**, THF, $-78\text{ }^{\circ}\text{C}$, 10 min, then **145**, $-78\text{ }^{\circ}\text{C}$, 1 h, 48%; ii) *N*-bromosuccinimide, THF, rt, 1 h, 56%; iii) **185**, $t\text{-BuLi}$, pentane/ Et_2O 3:2, $-78\text{ }^{\circ}\text{C}$, CuI , 10 min, then $0\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C}$, **220**, 30 min, 57% + 31% RSM; iv) 10 mol% FeCl_3 , MeOH, rt, 1.5 h, 92%; v) DMP, NaHCO_3 , CH_2Cl_2 , rt, 2 h, 66%

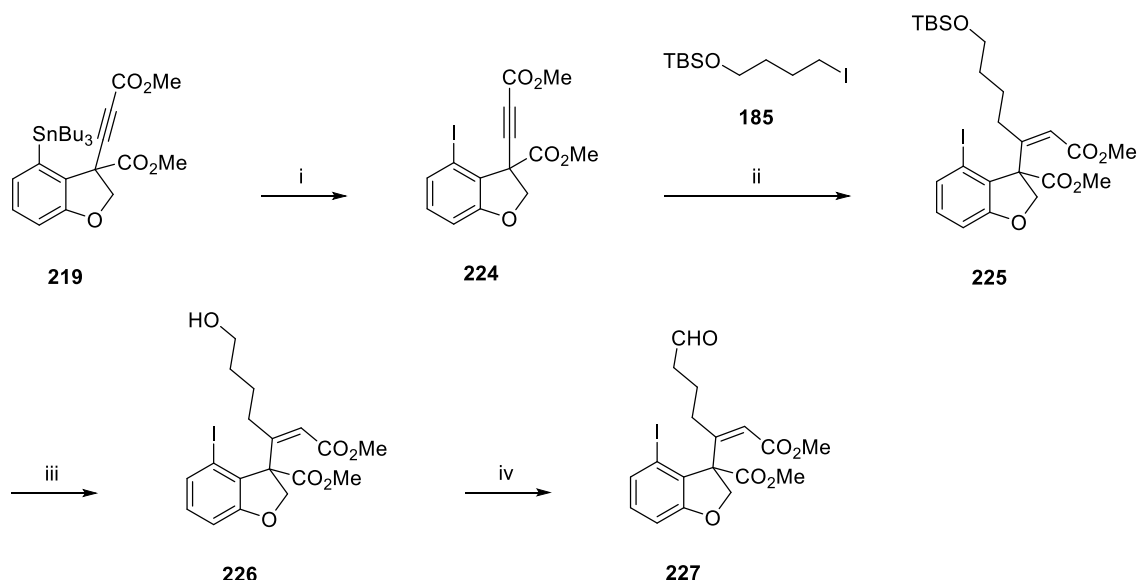
Subsequent metal–halogen exchange of stannane **219** in the presence of *N*-bromosuccinimide proceeded smoothly to afford bromide **220** in 56% yield. Using the previously developed procedure for the addition of cuprate reagents to alkynes, alkene **221** was synthesised from alkyne **220** as a single diastereomer in 57% yield. A 31% yield of recovered starting material was also obtained, suggesting the potential to optimise this reaction further. The lower than expected yield was attributed to the relatively small scale of the reaction (61 mg of alkyne **220**). The TBS–protected alcohol was treated with FeCl_3 in MeOH to afford alcohol **222** in 92% yield. Oxidation using DMP afforded the desired model aldehyde **223** in 66% yield.

With aldehyde **223** in hand we were now able to investigate the proposed intramolecular NHK reaction. Disappointingly, application of standard NHK conditions employed in the literature, followed by oxidation with DMP resulted in the formation of a complex mixture (Scheme 47).^{89,90}



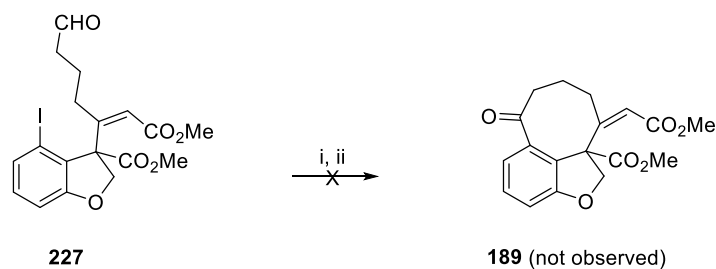
Scheme 47. Reagents and conditions: i) 5 eq. CrCl_2 , 1 eq. NiCl_2 , DMF, rt, 6 h, then 50 °C, 10 h; ii) DMP, NaHCO_3 , CH_2Cl_2 , rt, 3 h

With the NHK reaction of aldehyde **223** proving unsuccessful, we now pursued the synthesis of the corresponding iodide. We postulated that aryl bromide reduction was rate-limiting, therefore a change to the corresponding iodide should promote the reaction. Stannane **219** was cleanly converted to iodide **224** in 87% yield with iodine in chloroform at room temperature (Scheme 48). The following cuprate addition also progressed cleanly to afford alkene **225** in 64% yield as a single diastereomer. TBS-deprotection with FeCl_3 in MeOH afforded alcohol **226** in 81% yield, which was subsequently oxidised with DMP to afford aldehyde **227** in 51% yield.



Scheme 48. Reagents and conditions: i) I_2 , CHCl_3 , rt, 1 h, 87%; ii) **185**, $^t\text{BuLi}$, pentane/ Et_2O 3:2, -78 °C, 10 min, CuI , then 0 °C, 1 h, then -78 °C, **224**, 30 min, 64%; iii) 10 mol% FeCl_3 , MeOH, rt, 3 h, 81%; iv) DMP, NaHCO_3 , CH_2Cl_2 , rt, 2 h, 51%

Disappointingly, aldehyde **227** was also unsuccessful as a substrate in the NHK reaction with only starting material observed by ^1H NMR, even after heating at 50 °C for 16 h (Scheme 49). Attempts were also made to generate the aryl anion via a lithium–halogen exchange reaction employing $t\text{BuLi}$, followed by a DMP oxidation. However, only starting material was observed in this case.



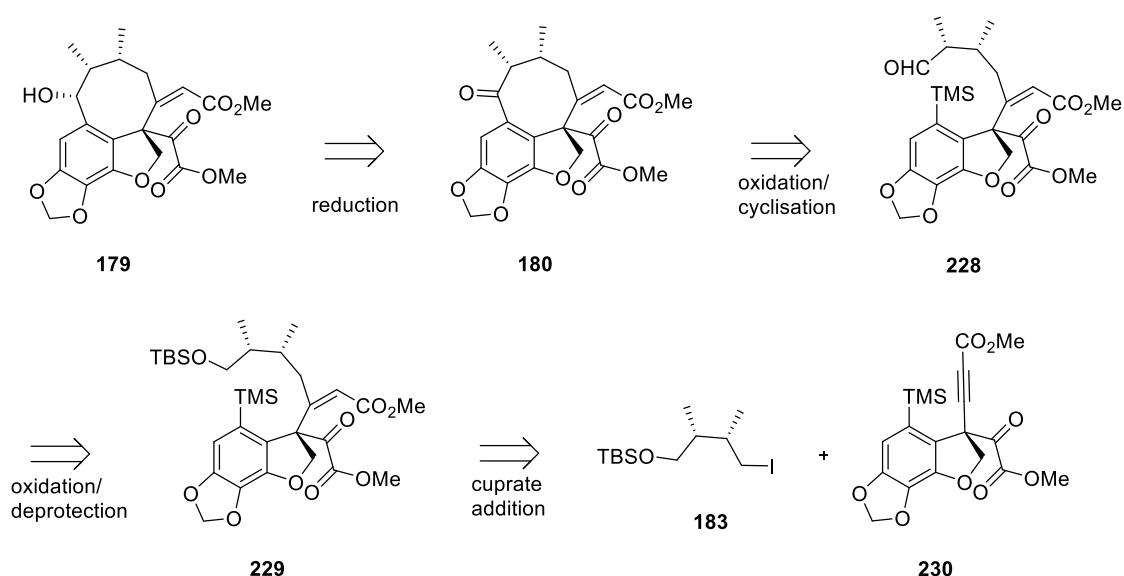
Scheme 49. Reagents and conditions: i) 5 eq. CrCl_2 , 1 eq. NiCl_2 , DMF, rt, 6 h, then 50 °C, 16 h; ii) DMP, NaHCO_3 , CH_2Cl_2 , rt, 3 h

Overall, two novel approaches towards the 8–membered ring are presented above based on a key NHK cyclisation reaction. Neither the use of an aryl bromide, nor an aryl iodide resulted in the formation of the desired product. However, studies leading to the synthesis of these key model substrates have provided access to C–4 functionalised dihydrofurans that may be used in other cyclisation strategies.

2.2.7 Aryl silane coupling

With the intramolecular NHK reaction proving challenging, we now turned our attention towards an alternative strategy. Aryl silanes captured our attention due to their relative stability and well documented reactivity, particularly in the case of Hiyama and Hiyama–Denmark cross coupling reactions.^{91,92} Previously, a palladium–catalysed stannylation reaction had been developed (Scheme 44). If a similar reaction could be applied to the synthesis of aryl silanes then it should be possible to access an aryl silane model compound with which cyclisation strategies could be investigated.

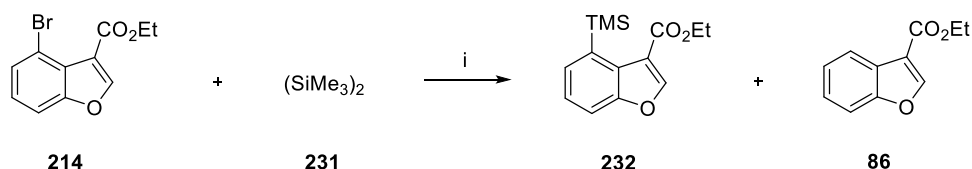
As was the case for the previous retrosynthesis (Scheme 40), alcohol **179** was intended to derive from ketone **180**, itself the product of an oxidation reaction (Scheme 50). The key step in this retrosynthesis involved an intramolecular coupling reaction between an aryl silane and an aldehyde. Recent work by O'Shea has reported the use of TMSOK and Bu₄NCl as successfully promoting the reaction of aryl silanes with aldehydes.⁹³ Application of these conditions to aldehyde **228** followed by oxidation with DMP would lead to the synthesis of ketone **180**. Alternatively, it was proposed that the addition of Lewis acids could promote this reaction, via activation of the aldehyde functional group.



Scheme 50. Proposed retrosynthesis involving a key aryl silane cyclisation reaction

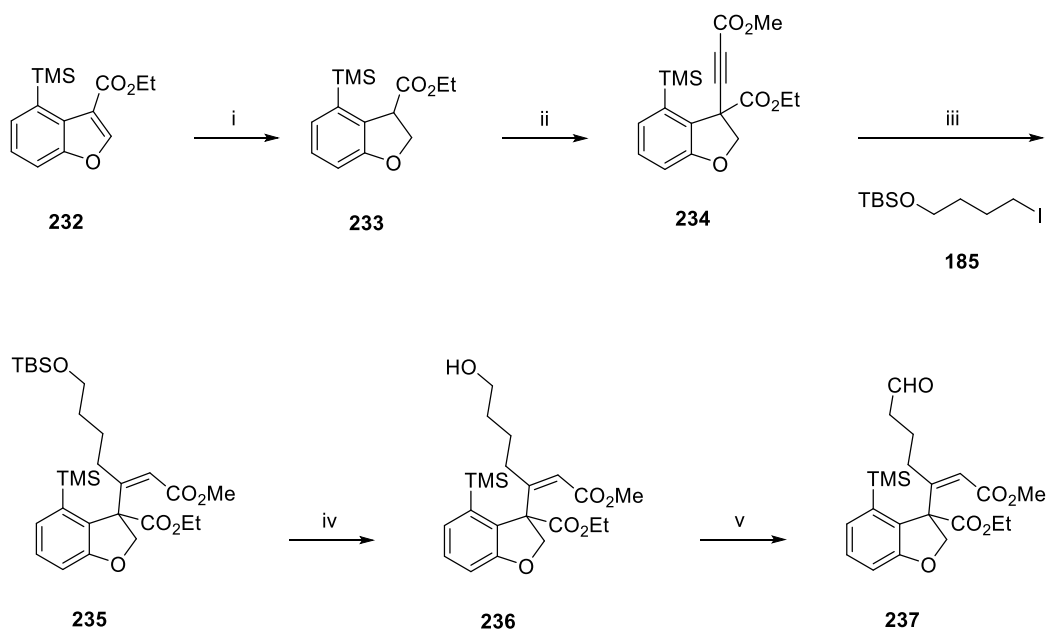
2.2.8 Synthesis of a model aryl silane

With a proposed retrosynthesis defined, a model substrate was now required in order to test the key aryl silane coupling reaction. Starting with the previously synthesised ester **214**, application of conditions developed by Gooßen for the catalytic silylation of aryl bromides afforded the aryl silane **232** in 58% yield in addition to a 9% yield of the de-brominated benzofuran **86** (Scheme 51).⁹⁴



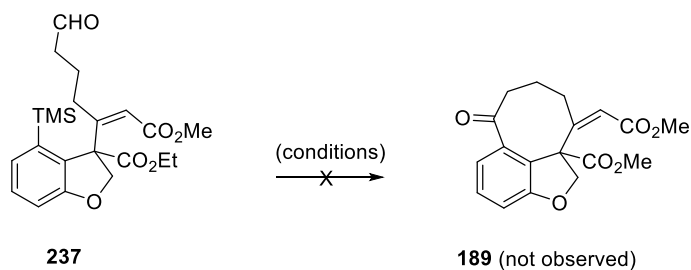
Scheme 51. Reagents and conditions: i) 1.2 eq. **231**, 1.5 mol% Pd₂(dba)₃, 9 mol% JohnPhos, 5 eq. KF, 2 eq. H₂O, DMPU, 100 °C, 16 h, 58% **232**, 9% **86**

Subjection of aryl silane **232** to the reduction conditions afforded ester **233** in quantitative yield (Scheme 52). It is notable that transesterification to the methyl ester was not observed, presumably this was unfavourable as the small scale of the reaction limited the reaction temperature. The alkynylation reaction of ester **233** proceeded smoothly to afford alkyne **234** in 69% yield. The reaction of alkyne **234** with an organocuprate reagent derived from iodide **185** led to the formation of alkene **235** as a single diastereomer in 72% yield. Finally, deprotection of the TBS-protected alcohol **236** and subsequent oxidation with DMP afforded the desired aldehyde **237** in 92% and 89% yield respectively.



Scheme 52. Reagents and conditions: i) Mg, MeOH, rt, 1 h, 100%; ii) LiHMDS, **233**, THF, –78 °C, 10 min, then **145**, –78 °C, 1 h, 69%; iii) **185**, ^tBuLi, pentane/Et₂O 3:2, –78 °C, 10 min, CuI, then 0 °C, 1 h, then –78 °C, **235**, 30 min, 72%; iv) 10 mol% FeCl₃, MeOH, rt, 2 h, 92%; v) DMP, NaHCO₃, CH₂Cl₂, rt, 2 h, 89%

With aldehyde **237** in hand we now looked towards the formation of the 8-membered ring. Disappointingly, application of the conditions developed previously by O'Shea were unsuccessful and a complex mixture of products was obtained (Scheme 52, entry 1).⁹³ TBAF was also investigated as an alternative fluoride source, however this also resulted in a complex mixture (entry 2). With the aim of exploiting the reactivity of the aryl silane through the π -system rather than the σ -system as attempted previously, aldehyde **237** was stirred at rt with 2 eq. $\text{BF}_3 \cdot \text{OEt}_2$ for 16 h (entry 3). Disappointingly, however, only unreacted starting material was observed under these conditions. Heating the reaction mixture at 40 °C also failed to result in the formation of the desired product (entry 4).

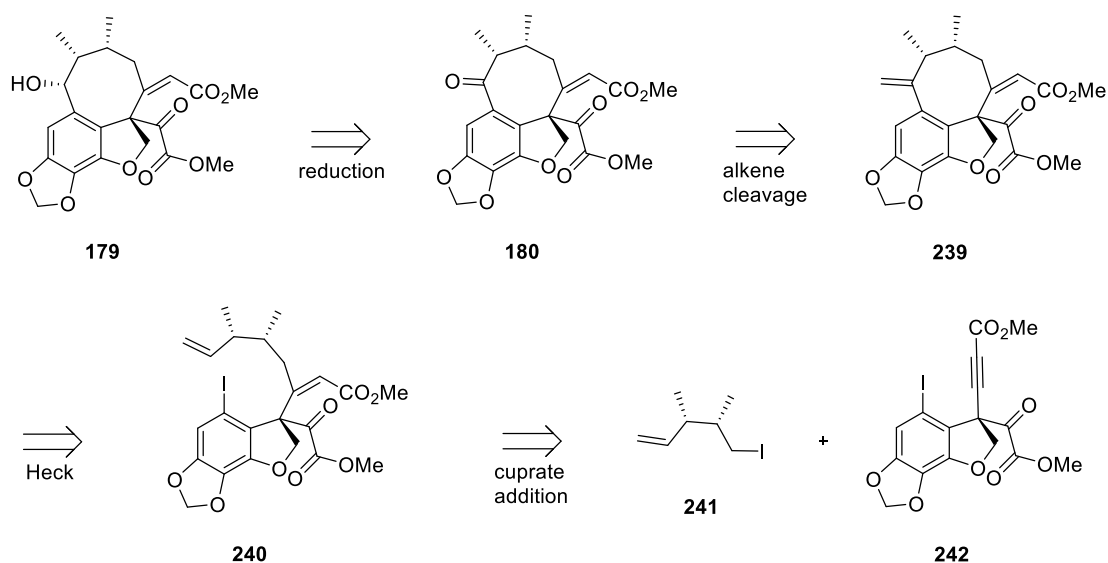


Entry	Reagents and Conditions	Comment
1	1.5 eq. TMSOK, 1.5 eq. Bu_4NCl , THF, 0 °C – rt, 2 h, then 1.5 eq. DMP, 2.5 eq. NaHCO_3 , CH_2Cl_2 , rt, 2 h	Complex mixture
2	1.5 eq. TBAF, THF, 0°C, 1 h, then 1.5 eq. DMP, 2.5 eq. NaHCO_3 , CH_2Cl_2 , rt, 2 h	Complex mixture
3	1.5 eq. $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , rt, 16 h	SM only
4	1.5 eq. $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , rt, 24 h	SM only

Scheme 53. Attempted cyclisation of aldehyde **237**

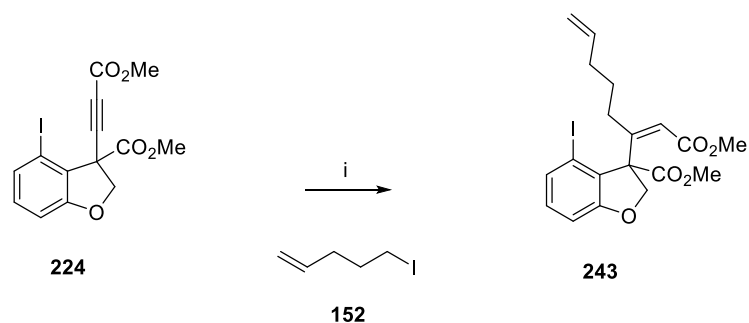
2.2.9 Heck cross-coupling

With *in situ* anion formation proving problematic, we now looked towards a milder method of forming the 8-membered ring found in the taiwanschirin family. Previously we had developed a method for the incorporation of a halide at the C-4 position of the aromatic ring. As a consequence of this, the initial NHK cyclisation proposal was refined to feature a Heck cross-coupling reaction as the key disconnection (Scheme 54). In this route, the initial reaction of an organocuprate derived from iodide **241** with alkyne **242** would form alkene **240**. An intramolecular Heck cyclisation reaction would allow access to ketone **180** after either an ozonolysis or osmium-promoted dihydroxylation/periodate cleavage reaction.



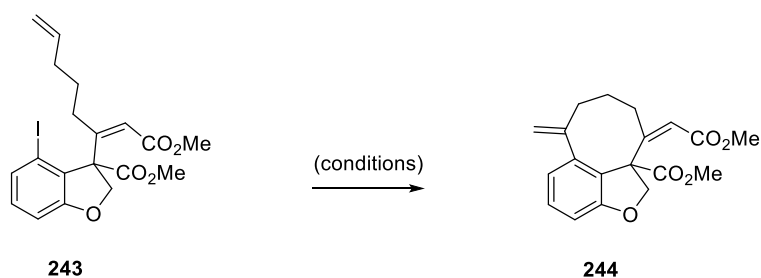
Scheme 54. Proposed retrosynthesis involving a key intramolecular Heck reaction

In order to synthesise a model compound with which to investigate the feasibility of a Heck cross-coupling reaction, iodide **152** was treated with t BuLi and CuI to generate a cuprate reagent, and reacted with the previously synthesised alkyne **224** (Scheme 55). Although alkene **243** was isolated in a modest 45% yield, the key Heck cyclisation step could now be tested.



Scheme 55. Reagents and conditions: i) **152**, ^tBuLi, pentane/Et₂O 3:2, –78 °C, 10 min, CuI, then 0 °C, 1 h, then –78 °C, **224**, 30 min, 45%

The conditions chosen for this step were modified slightly from those previously shown to catalyse intramolecular Heck reactions in the literature.⁹⁵ Initially, high catalyst and ligand loadings were used due to the small scale of the reaction and the limited availability of the starting material (9 steps from 3-bromophenol **211**). Pleasingly, the intramolecular Heck reaction proceeded smoothly to afford alkene **244** in 61% yield in a reaction time of only 1 h (Scheme 56, entry 1). Lowering the catalyst and ligand loadings resulted in an increase in the yield of the reaction to 81% (entry 2).



Entry	Reagents and Conditions	Yield/%
1	50 mol% Pd(OAc) ₂ , 2 eq. PPh ₃ , 10 eq. Et ₃ N, MeCN, 80 °C, 1 h	61%
2	10 mol% Pd(OAc) ₂ , 40 mol% PPh ₃ , 10 eq. Et ₃ N, MeCN, 80 °C, 1 h	81%

Scheme 56. Heck cyclisation of iodide **243**

The reaction was regioselective, affording the *exo*-isomer exclusively, and the undesired 9-*endo*-trig cyclisation product was not observed in the ^1H NMR of the crude reaction mixture (Figure 7).

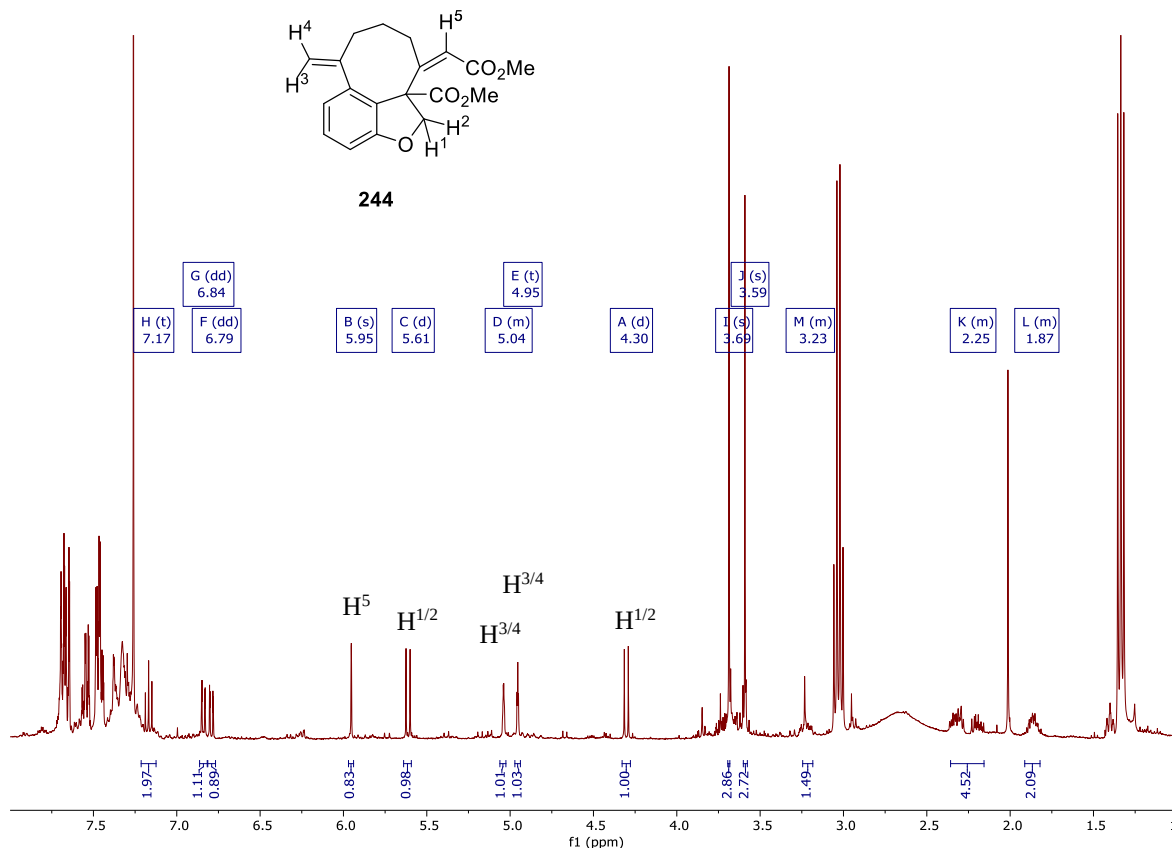
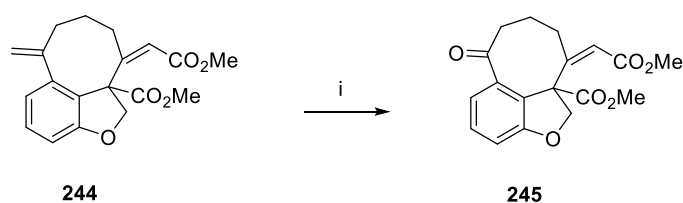


Figure 7. ^1H NMR of the crude Heck cyclisation reaction mixture

The identity of the reaction product was confirmed unambiguously through ^1H NMR analysis. Conclusively, the two olefinic protons, $\delta = 5.04$ (1H, m, $\text{C}=\text{CH}_3\text{H}_4$ or $\text{C}=\text{CH}_3\text{H}_4$) and $\delta = 4.95$ (1H, t, $J = 1.8$ Hz, $\text{C}=\text{CH}_3\text{H}_4$ or $\text{C}=\text{CH}_3\text{H}_4$) clearly correlate to the same carbon ($\delta = 115.8$) in the 2D HMBC spectrum. This confirms the 8-*exo*-trig selectivity leading to the formation of an 8-membered ring. In the case of the 9-*endo*-trig regioisomer, these two olefinic protons would correlate to two *different* carbon nuclei. Furthermore, the presence of the 8-membered ring was confirmed by an HMBC correlation from the geminal olefinic protons to the quaternary aromatic carbon nucleus.

In order to install the stereo-defined benzylic alcohol featured in the taiwanschirin family of natural products, we planned to convert the exocyclic alkene into a ketone followed by hydride reduction. Model alkene **244** was therefore reacted with OsO₄ in the presence of NaIO₄. This dihydroxylation–periodate cleavage reaction afforded ketone **245** in 69% yield, representing the most structurally similar compound to the taiwanschirin family synthesised so far in this work. Overall, ketone **245** was synthesised in 4% yield over 11 steps from 3-bromophenol **211**.

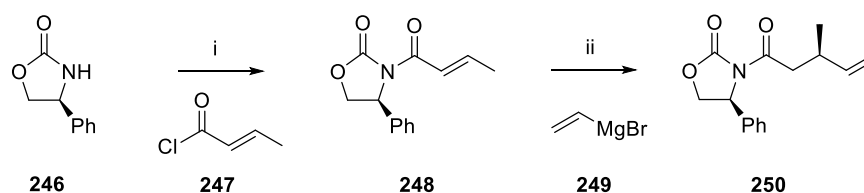


Scheme 57. Reagents and conditions: 5 mol% OsO₄, 5 eq. NaIO₄, THF/H₂O 2:1, rt, 2 h, 69%

2.2.10 Synthesis of iodide **241**

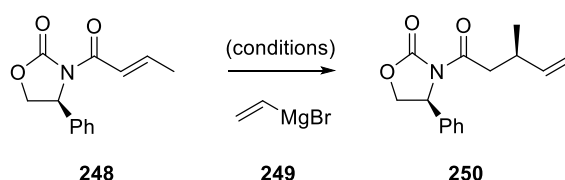
In order to install the two contiguous methyl stereocentres present in the 8-membered ring of the taiwanschirn family, we envisaged the synthesis of chiral iodide **241** (Scheme 54). The late-stage installation of a fragment incorporating these two stereocentres was highly desirable as it would lead to a highly convergent approach.

In order to access iodide **241**, Evans' auxiliary **246** was deprotonated and reacted with crotonyl chloride **247** to afford oxazolidinone **248** in quantitative yield on 100 mmol scale (Scheme 58).⁹⁶ Following literature precedent, a cuprate reagent was formed from vinylmagnesium bromide **249** and reacted with oxazolidinone **248** at –40 °C to afford oxazolidinone **250** in 93% yield, 9:1 dr.⁹⁷



Scheme 58. Reagents and conditions: i) n BuLi, THF, -78°C , 15 min, then crotonyl chloride, -78°C , 30 min, then rt, 15 min, 100%; ii) CuBr·SMe₂, vinylmagnesium bromide **249**, THF, -40°C , 10 min, then **248**, 5 min, 60% after recrystallisation, dr $\geq 95:5$

Several attempts were made to optimise the cuprate addition reaction, however none of these resulted in either an increase in yield or, more importantly, dr (Scheme 59).^{98,99}



Entry	Reagents and Conditions	Isolated Yield/Comment	dr ^a
1	3.5 eq. 249 , 0.88 eq. CuBr·SMe ₂ , -40°C	93%	9:1
2	3.5 eq. 249 , 0.88 eq. CuBr·SMe ₂ , -78°C	Full conversion	6.3:1
3	3.5 eq. 249 , 0.88 eq. CuBr·SMe ₂ , 2 eq. Et ₂ AlCl, -78°C	Full conversion	3.7:1
4	3.5 eq. 249 , 0.88 eq. CuBr·SMe ₂ , 1.1 eq. Yb(OTf) ₃ , -78°C	Decomposition	–
5	1.05 eq. 249 , 1.2 eq. TMEDA, 1.1 eq. TMSCl, -30°C	1,2-Addition to carbamate	–

Scheme 59. Optimisation of Grignard addition to oxazolidinone **248**; ^aDetermined by ^1H NMR spectroscopy of the crude reaction mixture

It was postulated that a lower reaction temperature would lead to an improvement in the selectivity of the reaction, however the dr decreased to 6.3:1 as determined by ^1H NMR of the crude reaction mixture (entry 2). The addition of strongly chelating Lewis acids was also explored, including Et₂AlCl and Yb(OTf)₃ (entries 3 and 4).⁹⁸ Despite full conversion being observed in the case of Et₂AlCl, the reaction was only moderately selective, with a dr of 3.7. However, when Yb(OTf)₃ was used we were surprised to observe complete decomposition with neither starting material nor either diastereomer of the desired product being observed

in the ^1H NMR of the crude material. Alternative literature conditions were also investigated involving the use of the Grignard reagent in the presence of TMEDA and TMSCl at $-30\text{ }^\circ\text{C}$ (entry 5).⁹⁹ However, none of the desired was isolated in this instance, only 1,2-addition to the carbamate was observed.

Ultimately, the decision was made to retain the initial reaction conditions and develop conditions for the recrystallisation of oxazolidinone **250**. Initially this was found to be challenging due to the relatively low melting point of oxazolidinone **250** at $82\text{ }^\circ\text{C}$. However, after a brief screen of solvents it was found that a combination of MTBE in pentane enabled recrystallisation of oxazolidinone **250** to a purity of $\geq 95:5$ dr. Although successive recrystallisations were required, overall oxazolidinone **250** was obtained in 60% yield when the reaction was performed on a scale of 57 mmol.

The absolute stereochemistry of oxazolidinone **250** was initially confirmed by the close agreement of specific rotation value measured $[\alpha]_{\text{D}}^{25} +42$ (c 1.0, CHCl_3) compared to $[\alpha]_{\text{D}}^{20} +49$ (c 1.04, CHCl_3) reported in the literature.⁹⁸ Furthermore, the structure of oxazolidinone **250** was confirmed unequivocally by X-ray crystallography (Figure 8).

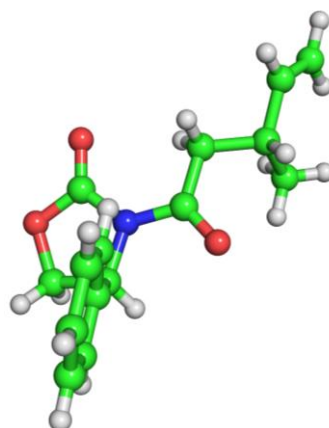
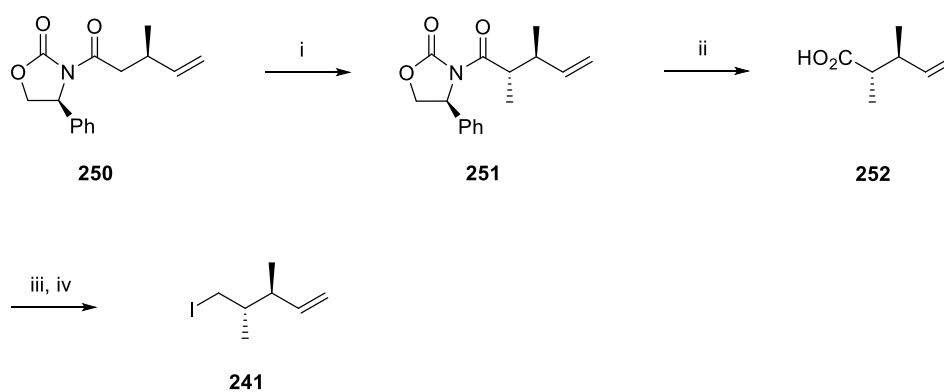


Figure 8. X-ray crystal structure of oxazolidinone **250**

With oxazolidinone **250** in hand, we then investigated the installation of the second stereocentre via a diastereoselective enolate alkylation reaction.⁹⁷ Initial conditions involving the deprotonation of oxazolidinone **250** at $-78\text{ }^{\circ}\text{C}$, reaction with methyl iodide and quenching at $-78\text{ }^{\circ}\text{C}$ afforded only starting material (Scheme 60). It was found that warming to room temperature for a period of 2 h was necessary for the enolate of **250** to fully react. With these conditions now optimised, oxazolidinone **250** was alkylated to afford oxazolidinone **251** in 76% yield.



Scheme 60. Reagents and conditions: i) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 15 min, then MeI, $-78\text{ }^{\circ}\text{C}$, 15 min, then rt, 2 h, 76%; ii) H_2O_2 , LiOH, THF/water 1:1, rt, 2 h, 67%; iii) LiAlH_4 , Et_2O , rt, 2 h; iv) I_2 , PPh_3 , imidazole, CH_2Cl_2 , rt, 16 h, 75% over 2 steps

Methods for the removal of Evans auxiliary are well documented in the literature. In our case, conditions for the direct cleavage of oxazolidinone **251** and subsequent reduction to the alcohol with LiBH_4 were unsuccessful.⁹⁷ Direct attack of the auxiliary carbonyl was observed and this by-product proved extremely challenging to separate from the desired product. However, the use of hydrogen peroxide and LiOH afforded the carboxylic acid in 67% yield.⁹⁷ This was subsequently reduced with LiAlH_4 to the alcohol and converted to the desired iodide under Appel conditions in 75% yield over 2 steps.

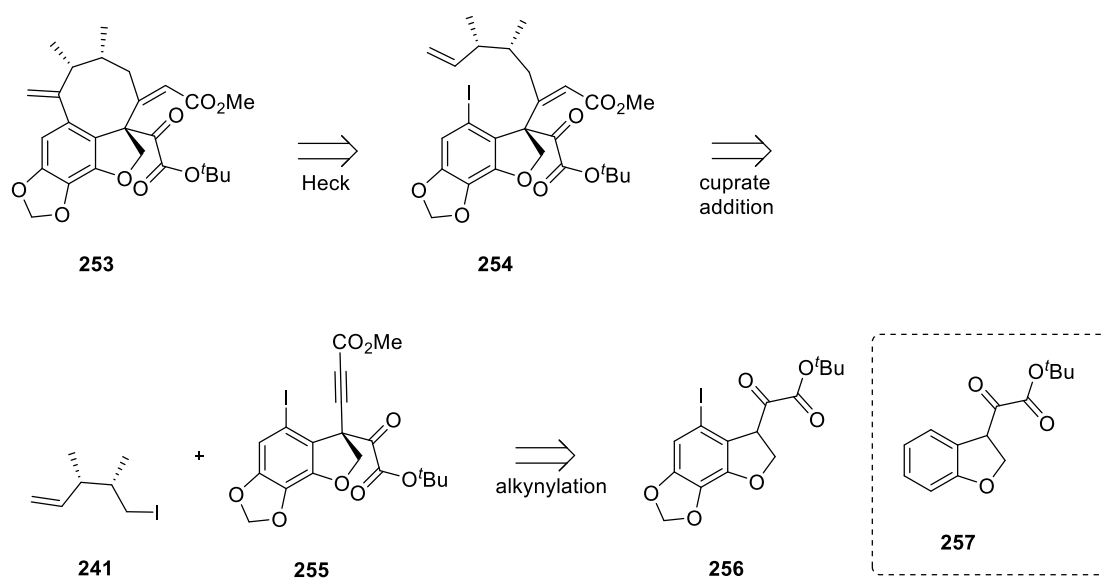
Overall, iodide **241** was synthesised in 23% yield over 6 steps. This represented an important advancement for the project as there now existed the means to assemble the natural product

incorporating both the 8-membered ring and the two contiguous stereocentres. We could now progress towards the development of a method for the synthesis of the pyruvate functional group. Upon solving this final problem, we could then look towards completing the total synthesis of the taiwanschirin family of natural products.

2.3 Pyruvate incorporation

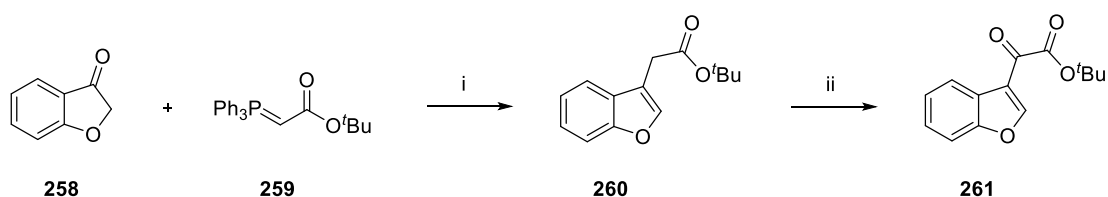
With methods developed for the synthesis of the (*Z*)-enone and incorporation of the 8-membered ring, we now turned our attention to the final major synthetic challenge in the synthesis of the taiwanschirin family, the pyruvate functional group.

Our planned retrosynthesis involved a key Heck cyclisation reaction of alkene **254** to form alkene **253**. Alkene **254** in turn would be accessed from alkyne **255** and the organocuprate reagent formed from iodide **241**. To prepare alkyne **255**, we envisaged an alkynylation of *tert*-butyl protected pyruvate **256**. Owing to the extended synthesis of pyruvate **256**, we looked towards the synthesis of pyruvate **257** as a simple model compound with which our hypothesis could be tested.



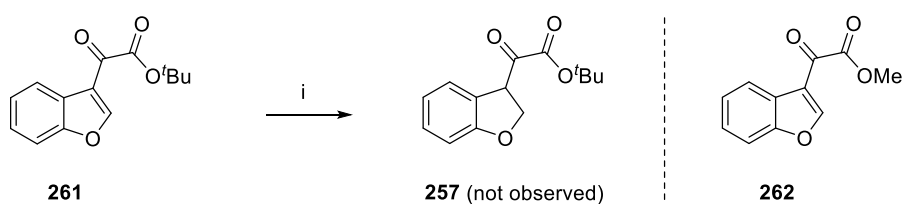
Scheme 61. Proposed retrosynthesis of alkene **253**

In order to prepare pyruvate **257**, ketone **258** was reacted with the commercially available phosphorus ylide **259** to afford benzofuran **260** in 66% yield (Scheme 62).¹⁰⁰ Subsequent oxidation of benzofuran **260** with SeO₂ afforded pyruvate **261** in 91% yield.¹⁰⁰



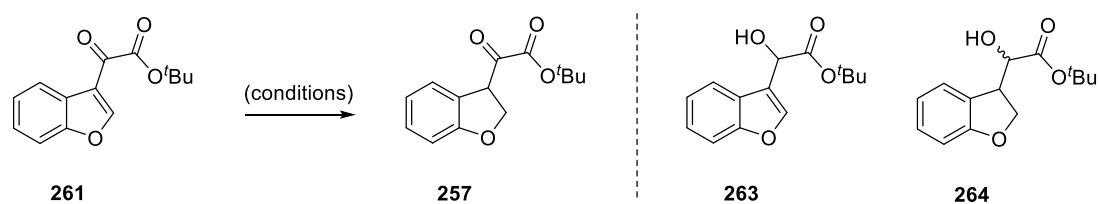
Scheme 62. Reagents and conditions: i) Toluene, 130 °C, 16 h, 66%; ii) SeO₂, dioxane, 115 °C, 16 h, 91%

With pyruvate **261** in hand, we now needed to reduce the benzofuran ring to obtain the desired dihydrobenzofuran **257**. Initially, magnesium in methanol was investigated for this reaction as these conditions proved highly effective for the reduction of benzofurans featuring ester functional groups in previous model studies (Scheme 13). Disappointingly, however, only transesterification to methyl pyruvate **262** was observed in addition to a 53% isolated recovery of the unsaturated benzofuran starting material **261** (Scheme 63).



Scheme 63. Reagents and conditions: i) Mg, MeOH, rt, 1 h, 34% **261**, 53% **262**

With the reduction of benzofuran **261** using magnesium and methanol proving unsuccessful, we then investigated hydrogenation conditions (Scheme 64).



Entry	Reagents and Conditions	Time/h	NMR Ratio 257:263:264 ^{a,b}	Isolated Yield 257/%	Isolated Yield 264 ^b /%
1	H ₂ , 10 wt% Pearlman's, MeOH, rt	1	1:2.2:1.4	22	—
2	H ₂ , 10 wt% PdO, MeOH, rt	1	1.7:2.3:1	33	—
3	H ₂ , 10 wt% Pd/C, MeOH, rt	1	1:5.2:3.2	—	—
4	H ₂ , 10 wt% Pearlman's, MeOH, rt	16	—	—	99

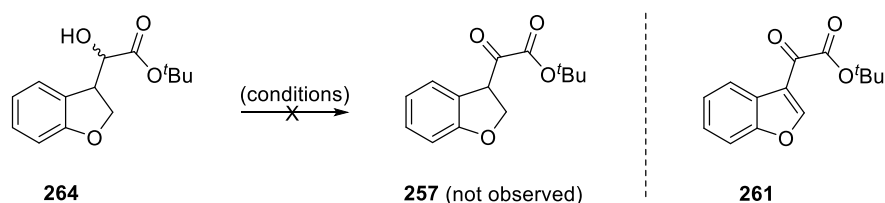
Scheme 64. Attempted reduction of benzofuran **261**

^aDetermined by ¹H NMR, ^bObserved as an equimolar mixture of diastereomers

The use of Pearlman's catalyst resulted in the formation of a mixture of the desired pyruvate **257**, alcohol **263** arising from carbonyl reduction, and an equimolar mixture of diastereomers of the over-reduced product, ester **264** (entry 1). Pyruvate **267** was isolated in a modest 22% yield. A change of catalyst to PdO afforded a greater selectivity for the desired product, however the isolated yield of pyruvate **257** was only marginally higher at 33% (entry 2). Pd/C resulted in preferential carbonyl reduction, and none of the desired pyruvate was isolated (entry 3). Disappointingly, the reaction proved challenging to perform on a larger scale, and over-reduction was frequently observed despite constant monitoring by TLC. Consequently, we decided to allow the reaction to go to completion and then oxidise alcohol **264** to pyruvate **257**. This reduction reaction was high yielding, with alcohol **264** obtained in 99% yield (entry 4).

To obtain the desired pyruvate, it was necessary to oxidise alcohol **264**. We were surprised to find that this was a particularly challenging transformation, and although a range of

different oxidants were investigated, only complex mixtures of products or the over-oxidised product, benzofuran **261** was observed (Scheme 65). We postulated that this was due to the detrimental effects of E1cB processes similar to those observed previously in this work.

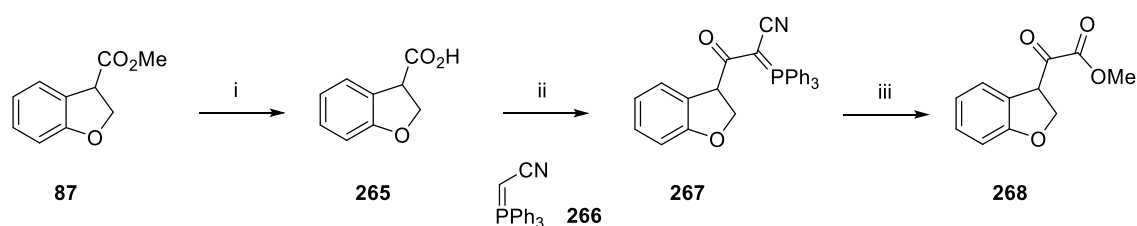


Entry	Reagents and Conditions	Comment	Yield 261 /%
1	DMP, NaHCO ₃ , rt, 16 h	–	17
2	IBX, DMSO, rt, 16 h	Complex mixture	5
3	Oxalyl chloride, DMSO, CH ₂ Cl ₂ , –78 °C, 1 h	Complex mixture	–
4	PCC, rt, 3 h	Complex mixture	–
5	TEMPO, PIDA, rt, 16 h	–	33
6	MnO ₂ , rt, 16 h	Complex mixture, 17% 264 isolated	6

Scheme 65. Attempted oxidation of alcohol **264**

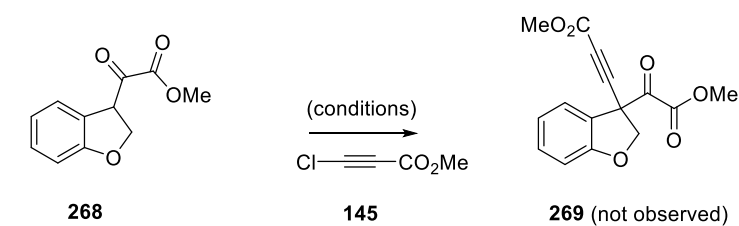
2.3.1 Cyanophosphorane **266**

At this stage an alternative pyruvate synthesis was proposed from ester **87**, using cyanophosphorane **266** as a pyruvate equivalent (Scheme 66). Ester hydrolysis afforded acid **265** in 98% yield, and coupling with cyanophosphorane **266** led to the synthesis of cyanoketophosphorane **267**. Cyanoketophosphorane **267** was then oxidised with DMDO following a literature procedure to afford pyruvate **268** in 72% yield.¹⁰¹



Scheme 66. Reagents and conditions: i) Na_2CO_3 , THF/ H_2O 1:1, rt, 16 h, 98%; ii) EDC·HCl, DMAP, CH_2Cl_2 , 16 h, 56% iii) DMSO, MeOH, rt, 1 h, 72%

With pyruvate **268** in hand we could now investigate the proposed alkynylation reaction to prepare the (*Z*)-enone fragment of the taiwanschirin family. Initial conditions using LiHMDS at -78°C failed to result in the formation of the desired alkyne product, and only starting material was observed (Scheme 67, entry 1). Increasing the reaction temperature to 0°C after alkyne addition resulted in only starting material being observed (entry 2). KHMDS was then investigated as we hypothesised that the less strongly coordinating potassium cation may form a more reactive enolate. However, although several temperatures were investigated, complex mixtures of products were observed in each instance (entries 3 and 4). NaHMDS was also explored, although a similarly complex mixture was obtained when the reaction was carried out at -78°C .

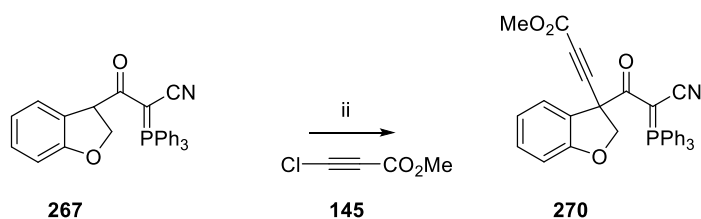


Entry	Reagents and Conditions	Comment
1	LiHMDS, $-78\text{ }^{\circ}\text{C}$, THF, 2 h	SM only
2	LiHMDS, $-78 - 0\text{ }^{\circ}\text{C}$, THF, 2 h	SM only
3	KHMDS, $-78 - 0\text{ }^{\circ}\text{C}$, THF, 2 h	Complex mixture
4	KHMDS, $-78\text{ }^{\circ}\text{C}$, THF, 2 h	Complex mixture
5	NaHMDS, $-78\text{ }^{\circ}\text{C}$, THF, 2 h	Complex mixture

Scheme 67. Attempted alkylation of pyruvate **268**

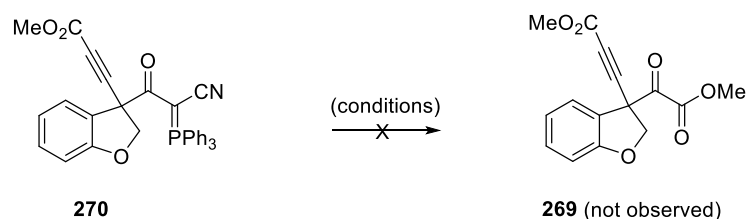
2.3.2 Alkylation of cyanoketophosphorane **267**

At this point we pursued an alternative strategy in which cyanoketophosphorane **267** could be alkylated directly, then oxidised with DMDO to reveal the methyl pyruvate at a later stage. Pleasingly, cyanoketophosphorane **267** reacted cleanly with chloroacetylene **145** to afford alkyne **270** in 90% yield (Scheme 68). A change of reaction solvent from THF to DMF was found to be necessary due to the poor solubility of cyanoketophosphorane **267** in THF at low temperature.



Scheme 68. Reagents and conditions: i) LiHMDS, **267**, DMF, $-40\text{ }^{\circ}\text{C}$, 10 min, then **145**, $-40\text{ }^{\circ}\text{C}$, 30 min, 90%

Disappointingly, the attempted oxidation of alkyne **270** with DMDO was unsuccessful and only starting material was observed (Scheme 69, entry 1). Surprisingly, the use of ozone also returned only starting material (entry 2). The use of TFDO, a significantly stronger oxidant than DMDO, resulted in the formation of a complex mixture of products and the desired pyruvate was not observed (entry 3).¹⁰²



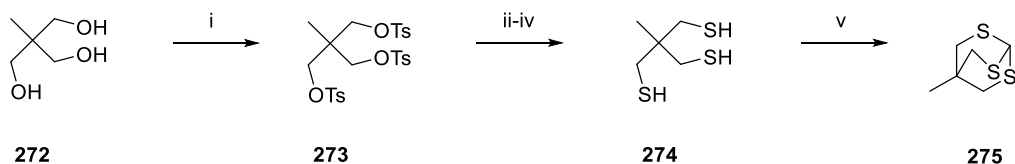
Entry	Reagents and Conditions	Comment
1	DMDO, MeOH, rt, 2 h	SM only
2	Ozone, -78 °C, 15 min	SM only
3 ^a	TFDO, MeOH, MeCN	Complex mixture

Scheme 69. Attempted oxidation of cyanoketophosphorane **270**

With the oxidation of cyanoketophosphorane **267** shown to be possible, but that of alkyne **270** unfavourable, we decided to investigate the oxidation of alternative functional groups to access the pyruvate group.

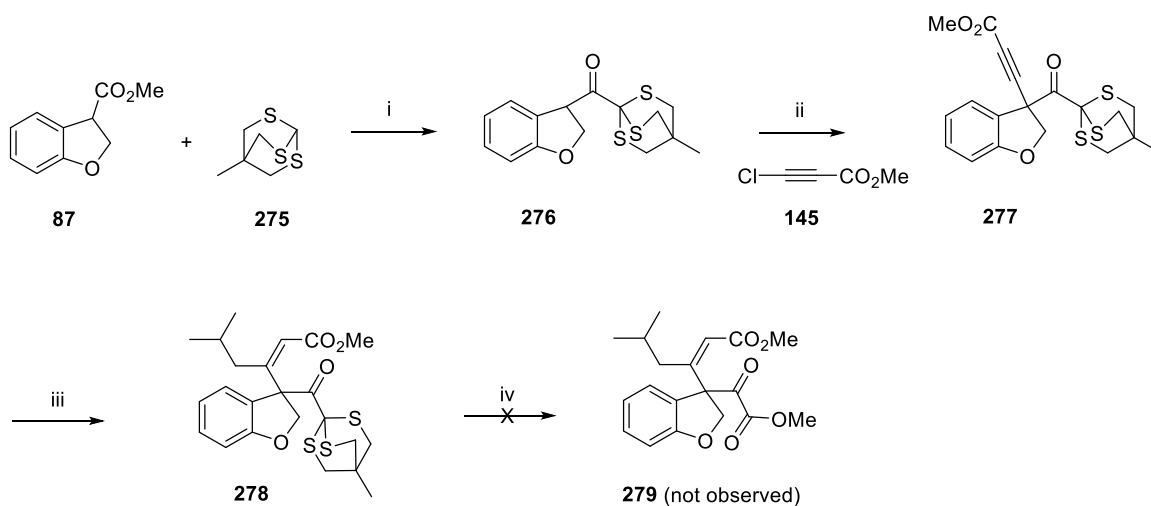
2.3.3 Thioether cleavage

In 2008, Kutateladze reported the synthesis of thioether cages in the investigation of photolabile tags (Scheme 70).¹⁰³ We noted the similarity of this group to OBO ketone **5** used by the Donohoe group previously. Conditions are known for the cleavage of thioether cages such as these, and it was postulated that this group could be used to install a masked pyruvate group that could be deprotected at a later stage.



Scheme 70. Reagents and conditions: i) TsCl, py, 0 °C – rt, 16 h, 100%; ii) NaSH·9H₂O, S, DMF, 80 °C, 1 h, then **273**, 100 °C, 4 h; iii) Cu, toluene, 115 °C, 16 h; iv) Zn, HCl, EtOH, rt, 24 h, 94% over 3 steps; v) trimethylorthoformate, PTSA, toluene, 115 °C, 24 h, 54%

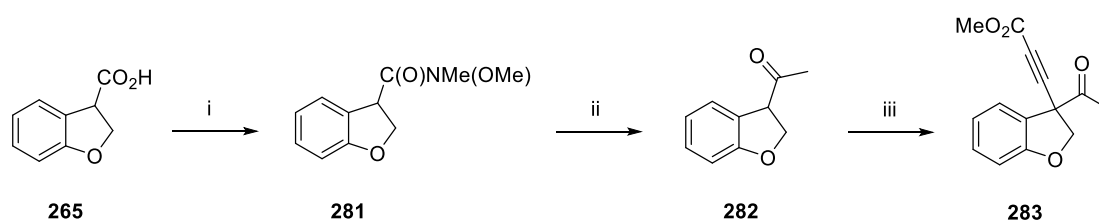
With thioether **275** in hand, we were then able to deprotonate and react it with ester **87** to afford thioether **276** in 76% yield (Scheme 71). The alkynylation reaction proceeded smoothly to afford alkyne **277** in 54% yield. However, upon scaling this reaction, the yields became highly variable, and in some instances, there was no product observed at all. With sufficient quantities of alkyne **277** to investigate our proposal, we performed the cuprate addition reaction to afford the desired enone **278** in a modest 22% yield. Disappointingly, subjection of enone **278** to the literature conditions for thioether deprotection using HgO failed to afford any of the desired product.¹⁰⁴



Scheme 71. Reagents and conditions: i) **275**, ⁿBuLi, THF, –78 °C, 10 min, then **87**, 30 min, 76%; ii) LiHMDS, **276**, THF, –78 °C, 10 min, then **145**, –78 °C, 30 min, 54%; iii) ^tBuLi, CuI, THF, –78 – 0 °C, 1 h, then –78 °C, **277**, 30 min, 22%; iv) HgO, HBF₄, KI, then H₂SO₄, MeOH

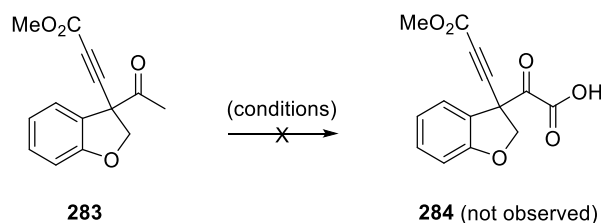
2.3.4 Ketone oxidation

With early incorporation of the pyruvate functional group proving problematic, we looked towards a late-stage approach. One well-precedented strategy for the preparation of pyruvates is the oxidation of ketones. In order to synthesise a model compound with which to investigate this approach, amide **281** was prepared in quantitative yield from acid **265** (Scheme 72). The addition of methylmagnesium bromide to amide **281** afforded ketone **282** in 96% yield. Finally, the alkynylation reaction provided alkyne **283** in a modest 37% yield, and we were now able to investigate the oxidation reaction.



Scheme 72. Reagents and conditions: i) EDC·HCl, DMAP, HNMe(OMe)·HCl, Et₃N, CH₂Cl₂, rt, 16 h, 100%; ii) MeMgBr, THF, 0 °C, 1 h, 96%; iii) LiHMDS, **282**, THF, –78 °C, 10 min, then **145**, 30 min, 37%

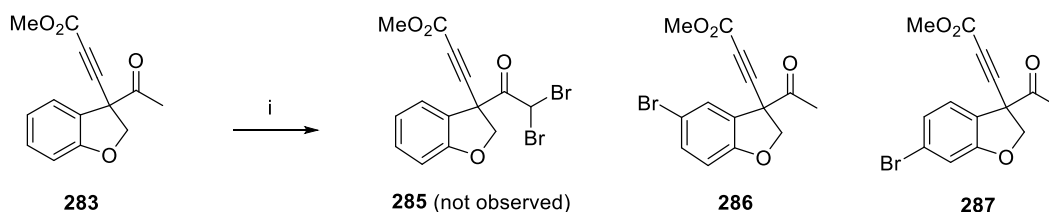
Unfortunately, the oxidation of ketone **283** using SeO₂ in the presence of pyridine at 115 °C resulted in complete decomposition. When the reaction was performed at the lower temperature of 85 °C overnight, only starting material was observed.¹⁰⁵



Scheme 73. Reagents and conditions: SeO₂, pyridine, 16 h, 115 °C or 85 °C

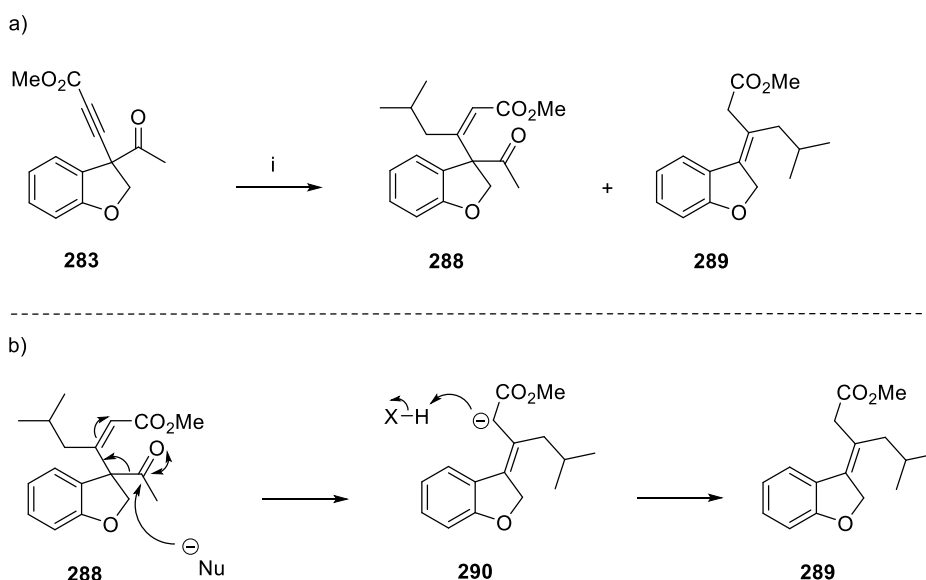
Bromination of ketone **283** was also explored as a potential approach towards pyruvate **259**. If dibromide **285** could be formed from the bromination of ketone **283** then it was postulated that a Kornblum oxidation would afford the desired pyruvate. However, when ketone **283**

was subjected to the bromination conditions reported in the literature, none of the desired dibromide was isolated and only aromatic bromination was observed to afford the two regioisomeric aryl bromides **286** and **287**.¹⁰⁶



Scheme 74. Reagents and conditions: i) Benzyltrimethylammonium tribromide, CH₂Cl₂/MeOH 5:2, rt, 16 h, **286** 61%, **287** 35 %

Ketone **283** was reacted with a cuprate reagent derived from $i\text{BuLi}$ to afford enone **288** in 16% yield (Scheme 75a). There were several by-products of this reaction, however the only other compound that could be isolated cleanly and fully characterised was alkene **289**, isolated in 10% yield after purification by column chromatography. The proposed mechanism shown below to explain the formation of alkene **289** involves an initial nucleophilic attack of enone **288**, followed by protonation (Scheme 75b)

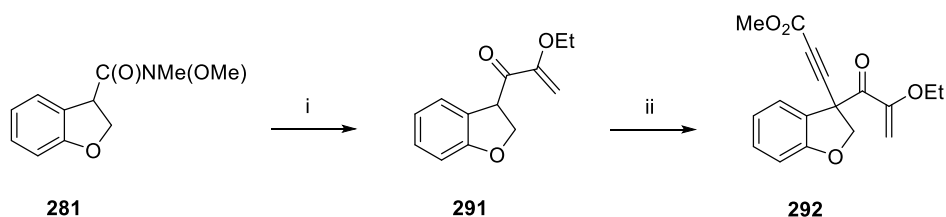


Scheme 75. a) Reagents and conditions: i) *i*BuLi, CuI, THF, $-78 - 0\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C}$, **283**, 30 min, 16% **288** and 10% **289**; b) Proposed mechanism to show the formation of alkene **289**

Ketone **288** was treated with several different oxidising conditions in an effort to oxidise the ketone to a carboxylic acid. The conditions investigated included SeO₂/pyridine and KMnO₄, although none of these were successful.

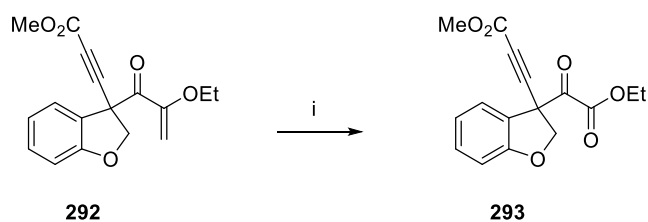
2.3.5 Alkene oxidation

At this point we decided to explore whether alkene oxidation could offer a more viable approach towards the pyruvate group found in the taiwanschirin family. To investigate this hypothesis ethyl vinyl ether was deprotonated at –78 °C with ^tBuLi and reacted with amide **281** to form alkene **291** in 75% yield (Scheme 76).¹⁰⁷ Subsequent lithiation and reaction with chloroacetylene **145** afforded alkene **292** in 19% yield.



Scheme 76. Reagents and conditions: i) Ethyl vinyl ether, ^tBuLi, THF, –78 – 0 °C, 15 min, then –78 °C, **281**, 2 h, 75%; ii) LiHMDS, **291**, THF, –78 °C, 10 min, then **145**, –78 °C, 1 h, 19%

We were pleased to observe that alkene **292** reacted cleanly with ozone at –78 °C to afford pyruvate **293**, as observed by ¹H NMR analysis of the crude reaction mixture (Scheme 77 and Figure 9).¹⁰⁸ Clear evidence for the success of this transformation was demonstrated by the disappearance of the alkene resonances: $\delta = 5.33$ (1H, $J = 2.7$ Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$) and 4.58 (1H, 2.7 Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), and the downfield shift of the ethyl ester resonances. Disappointingly, however, pyruvate **293** proved to be highly unstable and rapidly decomposed upon purification by silica chromatography. Neither the addition of triethylamine to the column eluent system, nor the use of phosphate–doped silica resolved this issue.



Scheme 77. Reagents and conditions: i) Ozone, CH₂Cl₂, -78 °C, 10 min, full conversion by ¹H NMR

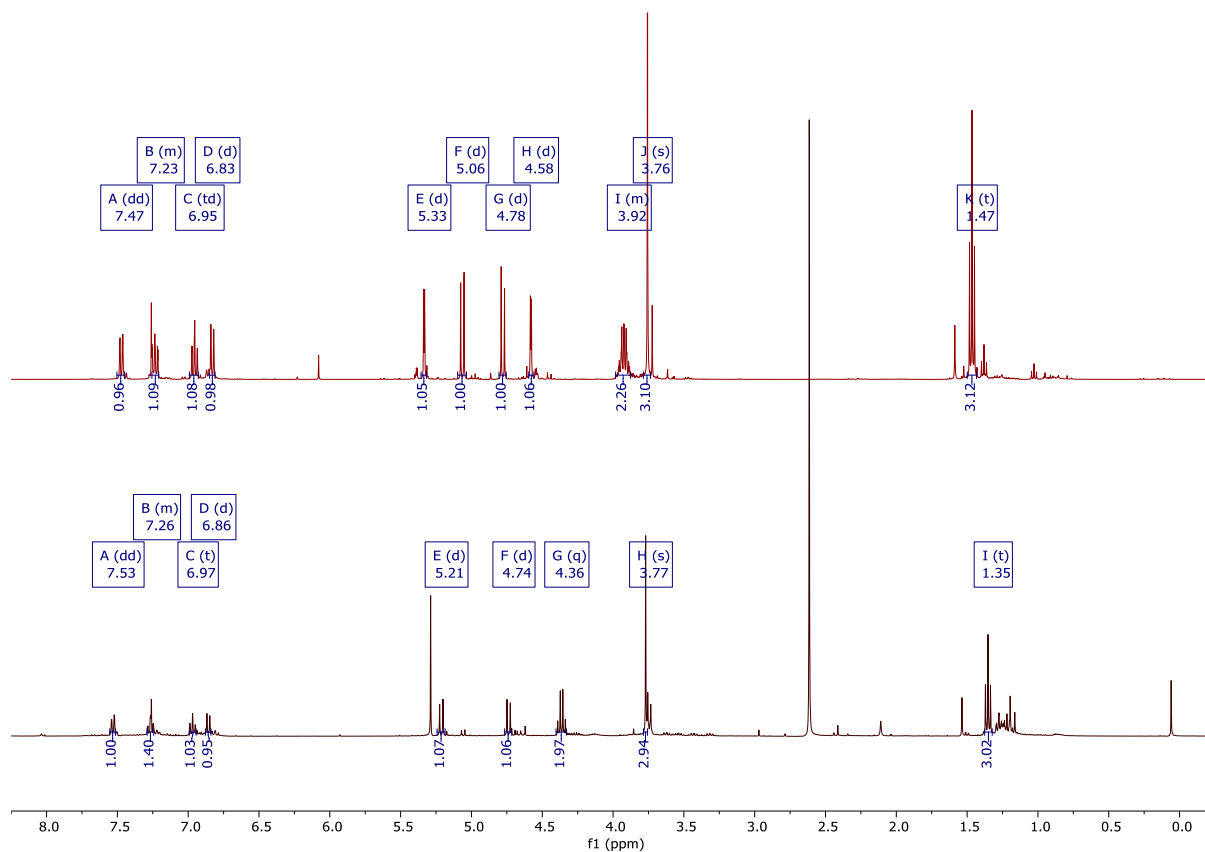
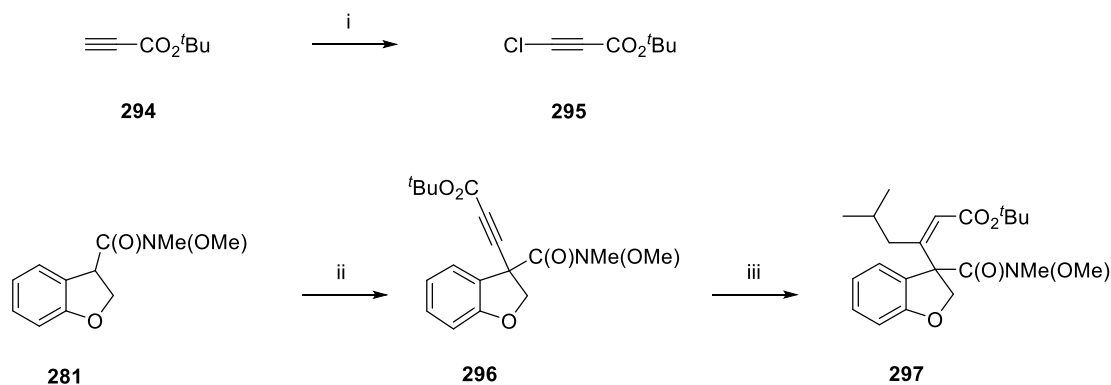


Figure 9. ¹H NMR spectra showing alkene **292** (red) and crude pyruvate **293** (black)

We postulated that the instability of pyruvate **293** was due to the close proximity of the electron-withdrawing alkyne and pyruvate functional groups. In order to refine this proposed route towards the pyruvate group, we decided to first install the (less electron-deficient) enone, and then unmask the pyruvate functional group. Since the enone is *alpha* to the pyruvate group in the natural product family isolated from nature, we felt that this was a more viable approach.

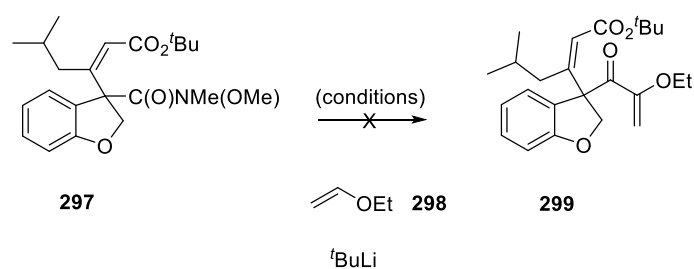
In our first approach we decided to synthesise *tert*-butyl protected ester **296** and react the Weinreb amide functional group with deprotonated ethyl vinyl ether to form the desired alkene. (Scheme 78).



Scheme 78. Reagents and conditions: i) tBuOCl , tBuOK , tBuOH , rt, 30 min, 48%; ii) LiHMDS , **281**, THF, -78°C , 10 min, then **295**, -78°C , 1 h, 85%; iii) tBuLi , CuI , THF, $-78 - 0^\circ\text{C}$, 1 h, then -78°C , **296**, 30 min, 52%

Chloroacetylene **295** was initially prepared in 48% yield in a single step from commercially available alkyne **294**.⁴⁸ This acetylene cleanly reacted with the anion formed *in situ* from amide **281** to form alkyne **296** in 85% yield. The cuprate addition reaction afforded enone **297** in 52% yield.

With enone **297** in hand we could then investigate the desired reaction with deprotonated ethyl vinyl ether.¹⁰⁷ Disappointingly, although several different conditions were tested none of the desired product was observed (Scheme 79).



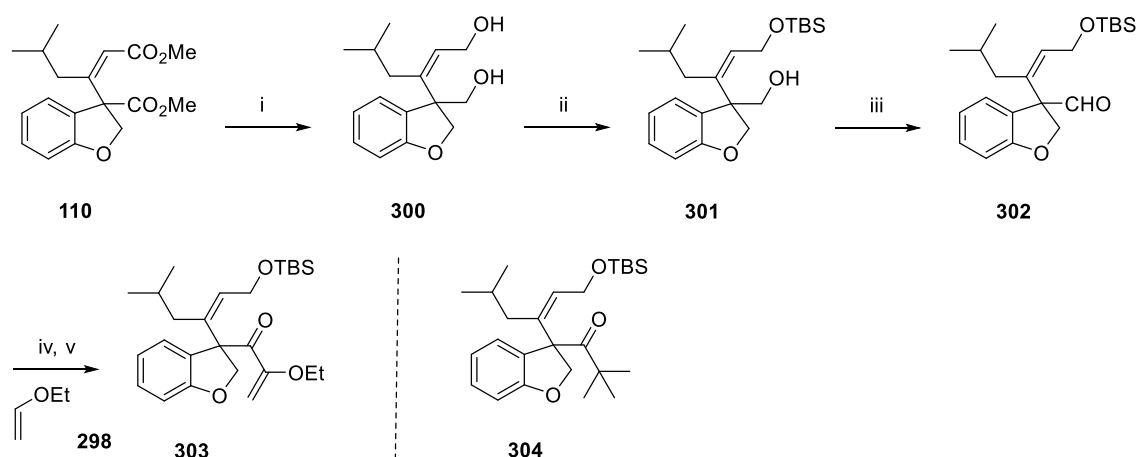
Entry	eq. $t\text{BuLi}$	eq. 298	T/ $^{\circ}\text{C}$	Comment
1	2.7	3	-78	SM only
2	2.7	3	-78 – rt	SM only
3	9	10	-78	Complex mixture

Scheme 79. Attempted organolithium addition

We attributed the failure of this attempted nucleophilic acyl substitution reaction to steric bulk and lack of reactivity of the tertiary Weinreb amide. In order to resolve this issue, we then modified our proposed synthesis so that a more reactive aldehyde was used as the electrophile to react with deprotonated ethyl vinyl ether **298**.

2.3.6 Selective alcohol protection

In this approach, we intended to fully reduce ester **110** and then selectively protect the least sterically hindered alcohol (Scheme 80). This would then enable the other alcohol to be oxidised to form aldehyde **302** that would then react with deprotonated ethyl vinyl ether **298**.

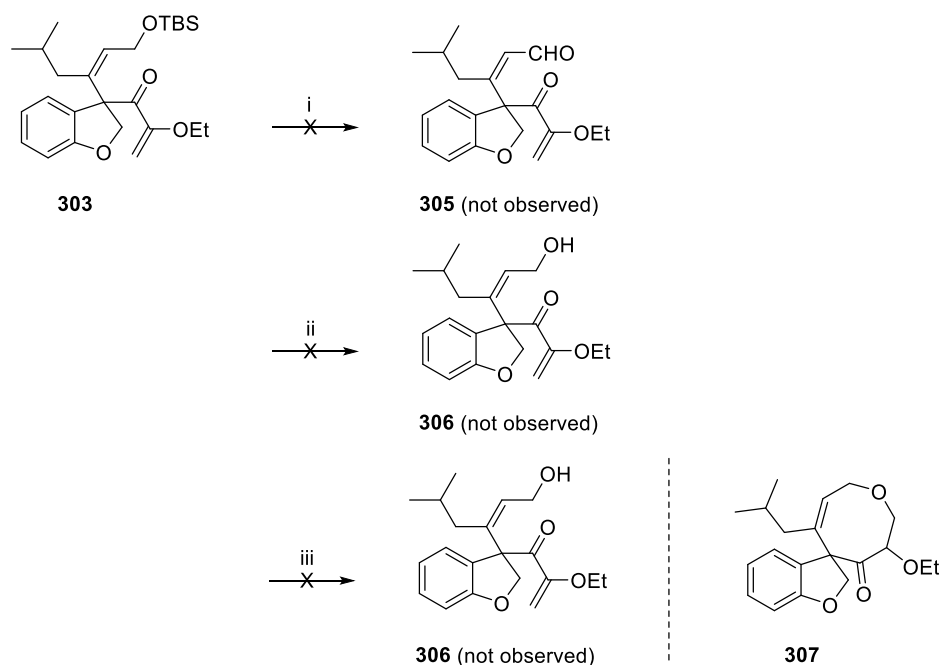


Scheme 80. Reagents and conditions: i) LiAlH_4 , THF, rt, 1 h, 95%; ii) TBSCl, imidazole, CH_2Cl_2 , 15 min, 76%; iii) DMP, NaHCO_3 , CH_2Cl_2 , rt, 1 h, 90%; iv) **298**, $t\text{-BuLi}$, THF, $-78 - 0^\circ\text{C}$, 10 min, then **302**, -78°C , 1 h; v) DMP, NaHCO_3 , CH_2Cl_2 , rt, 1 h, 65% over 2 steps

Firstly, the reaction of previously prepared ester **110** with LiAlH_4 afforded diol **300** in 95% yield. The less sterically hindered alcohol was protected with TBSCl to afford alcohol **301** in 76% yield, which was in turn oxidised with DMP to form aldehyde **302** in 90% yield. Crucially, aldehyde **302** reacted cleanly with deprotonated ethyl vinyl ether **298**, and subsequent oxidation afforded the desired enone **303** in 65% yield over 2 steps. It was necessary that the deprotonation of ethyl vinyl ether **298** occurred at 0°C over a period of 10 min, as 30 min at -78°C resulted in incomplete deprotonation. Instead of the desired enone **303** being isolated, ketone **304** was isolated in 87% yield, resulting from the direct addition of $t\text{-BuLi}$ to aldehyde **302**.

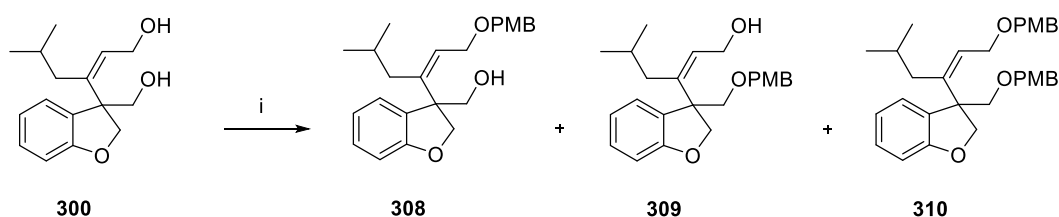
With enone **303** in hand, we then investigated a one-pot deprotection-oxidation procedure developed by Paterson employing DDQ (Scheme 81).¹⁰⁹ Unfortunately, despite previous reported success using TBS-protected allylic alcohols as substrates, in our hands only starting material was obtained when this method was applied to enone **303**. Deprotection using FeCl_3 in MeOH, conditions previously found to be successful on other substrates, resulted in the formation of a complex mixture of products.⁶⁶ Finally, the use of TBAF was explored, however, instead of forming alcohol **306**, macrocyclic ether **307** was

isolated in 70% yield as a 1:1 mixture of diastereoisomers. The treatment of macrocyclic ether **307** with a range of bases including DBU, ^tBuOK and NaOEt resulted in either no reaction or complex mixtures of products.



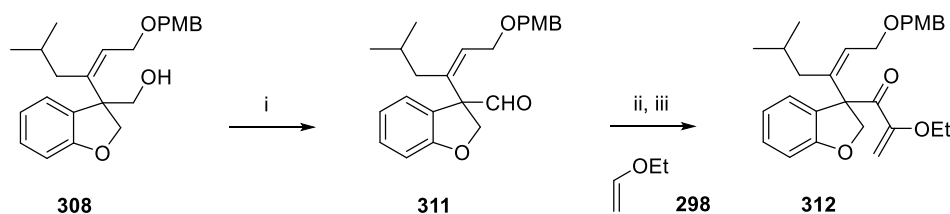
Scheme 81. Reagents and conditions: i) DDQ, phosphate buffer, rt, 2 h; ii) 10 mol% FeCl₃, MeOH, rt, 2 h; iii) TBAF, THF, 0 °C – rt, 1 h, 70% **307**

Since TBS-deprotection proved problematic, we then attempted a PMB protecting group strategy. Consequently, diol **300** was reacted with PMBTCA in the presence of catalytic PPTS (Scheme 82). Surprisingly, the reaction was complex and a mixture of mono- and doubly-protected alcohol products was obtained. Pleasingly, however, after careful separation by column chromatography, the desired alcohol **308** was isolated in 16% yield, thereby enabling the investigation of this approach.



Scheme 82. Reagents and conditions: i) PMBTCA, 10 mol% PPTS, CH₂Cl₂, rt, 1 h, 16% **308**, 14% **309**, 29% **310**

Alcohol **308** was oxidised with DMP to form aldehyde **311** in 50% yield (Scheme 83). This was then converted into enone **312** in 50% yield over 2 steps, via a reaction with ethyl vinyl ether **298**, followed by oxidation with DMP.



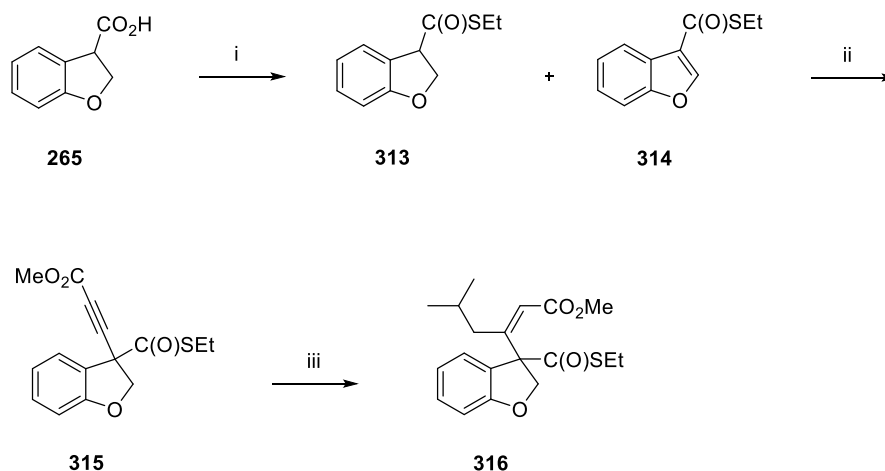
Scheme 83. Reagents and conditions: i) DMP, NaHCO₃, CH₂Cl₂, rt, 1 h, 50%; ii) **298**, 'BuLi, THF, -78 – 0 °C, 10 min, then **311**, -78 °C, 1 h; iii) DMP, NaHCO₃, CH₂Cl₂, rt, 1 h, 50% over 2 steps

With enone **312** in hand, we were then able to investigate potential deprotection strategies. Disappointingly, although several conditions investigated, including treatment with DDQ, none of these resulted in the clean deprotection of the PMB group.

2.3.7 Thioester reduction

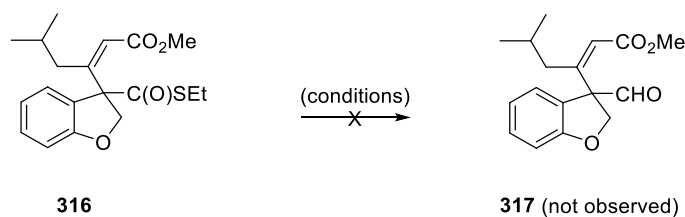
Several reports have detailed the reduction of thioesters to obtain aldehydes.^{110–112} With this in mind, we proposed that we could selectively reduce a thioester in the presence of an ester. The newly formed aldehyde could then react with deprotonated ethyl vinyl ether, and, following DMP oxidation, would afford the desired enone. Accordingly, acid **265** was coupled with thioethanol to afford thioester **313** in 92% yield, in addition to benzofuran **314** in 3% yield (Scheme 84). Thioester **313** was deprotonated with LiHMDS and reacted with

chloroacetylene **145** at $-78\text{ }^{\circ}\text{C}$ to afford alkyne **315** in 99% yield. The addition of a cuprate reagent derived from $i\text{BuLi}$ afforded enone **316** in 72% yield.



Scheme 84. Reagents and conditions: i) EDC·HCl, DMAP, CH_2Cl_2 , 16 h, 92% **313** and 3% **314**; ii) LiHMDS, **313**, THF, $-78\text{ }^{\circ}\text{C}$, 10 min, then **145**, $-78\text{ }^{\circ}\text{C}$, 30 min, 99%; iii) $i\text{BuLi}$, CuI, THF, $-78 - 0\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C}$, **315**, 30 min, 72%

Having successfully prepared enone **316**, we could then explore potential reduction conditions (Scheme 85). Initially, Et_3SiH was used as the terminal reductant in combination with a Pd/C catalyst.¹¹⁰ At room temperature no reaction was observed over 16 h, and an increased temperature of $80\text{ }^{\circ}\text{C}$ also had no effect on the reaction, with only starting material being observed by ^1H NMR (entries 1 and 2). The reaction was re-attempted using Lindlar's catalyst, and since the reaction was attempted on a small scale, one equivalent was used to promote the reaction (entries 3 and 4).¹¹¹ Similarly to before, only starting material was observed in each case. The final set of catalytic palladium conditions investigated used Bu_3SnH as the hydrogen source, however these were also not effective (entries 5 and 6).¹¹² We postulated that the quaternary-substituted thioester group was simply too sterically hindered to enable the sulfur atom to coordinate to the catalyst surface, therefore inhibiting reduction. NaBH_4 was also investigated as a reducing agent, however no reaction was observed (entry 7).

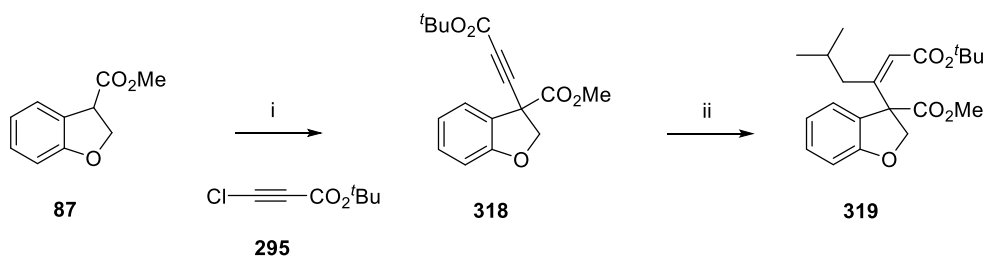


Entry	Reagents and Conditions	Comment
1	5 eq. Et ₃ SiH, 10 mol% Pd/C, acetone, rt, 16 h	SM only
2	5 eq. Et ₃ SiH, 10 mol% Pd/C, acetone, 80 °C, 16 h	SM only
3	5 eq. Et ₃ SiH, 1 eq. Lindlar, acetone, rt, 16 h	SM only
4	5 eq. Et ₃ SiH, 1 eq. Lindlar, acetone, 80 °C, 16 h	SM only
5	2 eq. Bu ₃ SnH, 50 mol% Pd(PPh ₃) ₄ , toluene, 80 °C, 16 h	SM only
6	2 eq. Bu ₃ SnH, 50 mol% PdCl ₂ (PPh ₃) ₂ , toluene, 80 °C, 16 h	SM only
7	2.2 eq. NaBH ₄ , MeOH, rt, 16 h	SM only

Scheme 85. Attempted reduction of thioester **316**

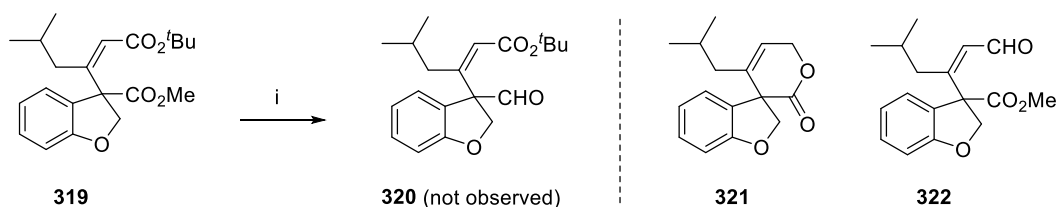
2.3.8 Selective ester reduction

With the reduction of thioester **316** proving unsuccessful, we postulated that a protecting group strategy could be used to achieve the selective reduction of one ester group over another. To this end, ester **87** was reacted with *tert*-butyl chloroacetylene **295** to afford alkyne **318** in quantitative yield (Scheme 86). The addition of a cuprate reagent afforded enone **319** in 83% yield and provided us with an ideal substrate with which to investigate this hypothesis.



Scheme 86. Reagents and conditions: i) LiHMDS, **87**, THF, $-78\text{ }^{\circ}\text{C}$, 10 min, then **295**, $-78\text{ }^{\circ}\text{C}$, 30 min, 100%; ii) $t\text{BuLi}$, CuI, THF, $-78 - 0\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C}$, **318**, 30 min, 83%

Ester **319** was then carefully treated with 1.2 equivalents of DIBAL-H at $-78\text{ }^{\circ}\text{C}$ in an attempt to selectively reduce the methyl ester in the presence of the *tert*-butyl ester (Scheme 87).



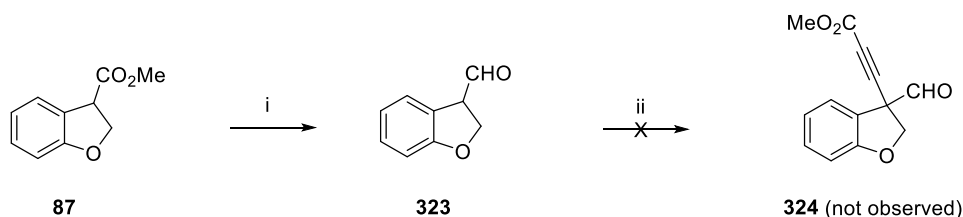
Scheme 87. Reagents and conditions: i) DIBAL-H, toluene, $-78\text{ }^{\circ}\text{C}$, 1.5 h, 38% **321**, 3% **322** and 36% RSM

Disappointingly, however, instead of reducing the methyl ester, the *tert*-butyl ester was almost completely reduced to the alcohol which presumably then cyclised to form lactone **321** in 38% yield. We postulated that coordination of DIBAL-H to the *tert*-butyl ester was more favourable due to the steric hindrance of the quaternary substituted methyl ester. A trace amount of the intermediate aldehyde **322** was isolated, in addition to a 36% yield of recovered starting material.

2.3.9 Alkynylation of aldehyde and imine derivatives

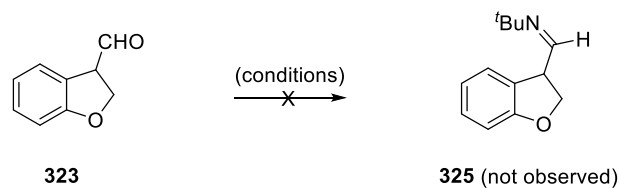
Although direct reduction of the methyl ester to the aldehyde was not feasible, we decided to investigate a potential direct aldehyde alkynylation to afford the desired product (Scheme 88). To this end, ester **87** was reduced with DIBAL-H to afford aldehyde **323** in

74% yield. This reaction was highly variable in terms of yield and product purity, and in some instances the product was contaminated with a large quantity of inseparable by-products. Nevertheless, a 74% yield (330 mg) provided enough material for us to investigate our hypothesis. Disappointingly, the direct alkynylation of aldehyde **323** failed to afford any of the desired alkyne product **324**, and a complex mixture was obtained (Scheme 88).



Scheme 88. Reagents and conditions: i) DIBAL-H, toluene, $-78\text{ }^\circ\text{C}$, 30 min, 74%; ii) LiHMDS, **323**, THF, $-78\text{ }^\circ\text{C}$, 10 min, then **145**, $-78\text{ }^\circ\text{C}$, 30 min,

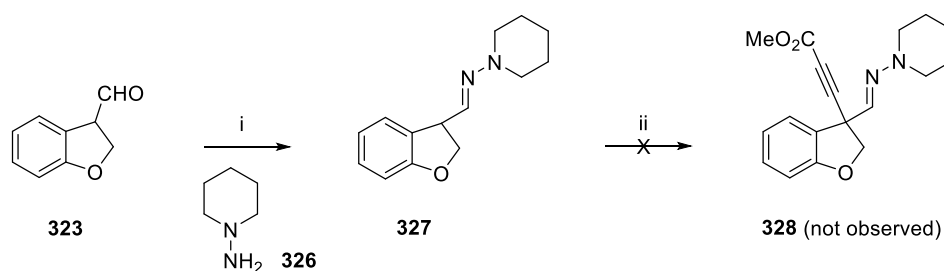
As we were unable to alkynylate aldehyde **323** directly, we decided to investigate the possibility of the alkynylation of an imine derivative of aldehyde **323**, which may later be hydrolysed to the aldehyde. We first attempted to prepare imine **325** via the reaction of aldehyde **323** with *tert*-butylamine under a range of conditions (Scheme 89).¹¹³ Unfortunately, none of these conditions afforded the desired imine product and complex mixtures were observed in nearly all cases.



Entry	Reagents and Conditions	Comment
1	3 eq. ^t BuNH ₂ , MgSO ₄ , CH ₂ Cl ₂ , rt, 16 h	SM only
2	3 eq. ^t BuNH ₂ , MgSO ₄ , CH ₂ Cl ₂ , 40 °C, 16 h	Complex mixture
3	3 eq. ^t BuNH ₂ , 4 Å molecular sieves, CH ₂ Cl ₂ , rt, 16 h	Complex mixture
4	3 eq. ^t BuNH ₂ , 3 eq. trimethyl orthoformate, CH ₂ Cl ₂ , rt, 16 h	Complex mixture
5	3 eq. ^t BuNH ₂ , 3 eq. Ti(O ⁱ Pr) ₄ , CH ₂ Cl ₂ , rt, 16 h	Complex mixture

Scheme 89. Attempted formation of imine **325**

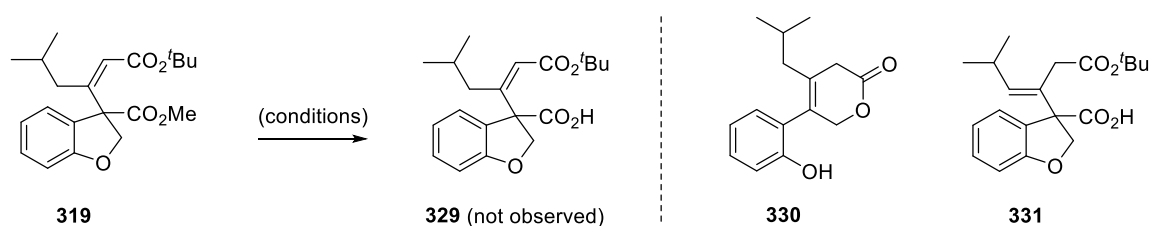
Hydrazone formation was later attempted and afforded more promising results, with hydrazone **327** synthesised in 67% yield (Scheme 90). However, when subjected to the alkynylation conditions, only starting material was observed. The reaction was also attempted using LDA as the base, however a complex mixture of products was observed in the ¹H NMR spectrum of the crude reaction mixture.



Scheme 90. Reagents and conditions: i) MgSO₄, CH₂Cl₂, rt, 16 h; ii) LiHMDS, **327**, THF, –78 °C, 10 min, then **145**, –78 °C, 30 min

2.3.10 Carboxylic acid derivatives

In an alternative strategy to that attempted in Section 2.3.8, the previously synthesised ester **319** was subjected to hydrolysis conditions. In an attempt to selectively form the carboxylic acid from the methyl ester in the presence of the *tert*-butyl ester, several approaches were explored (Scheme 91).

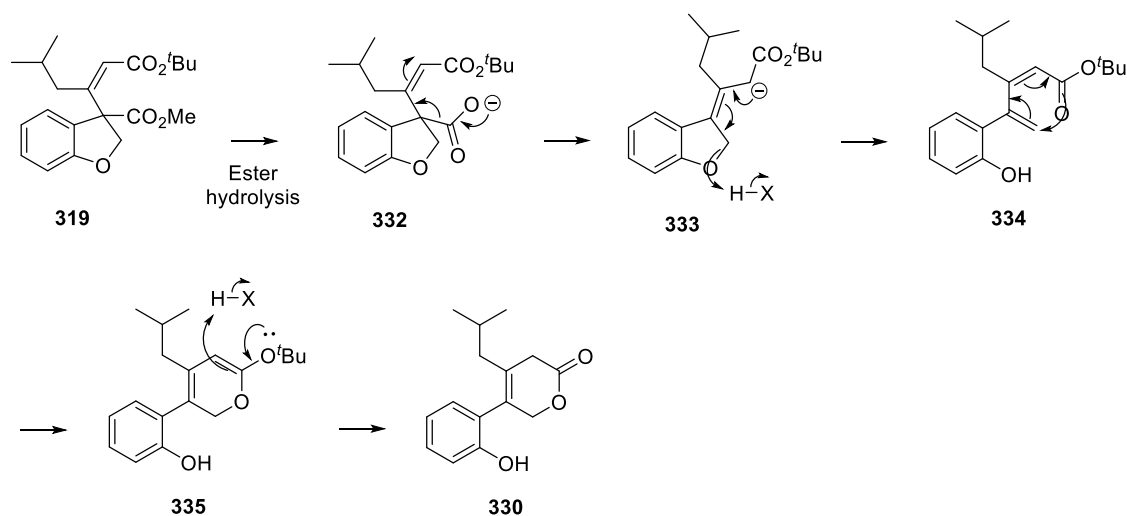


Entry	Reagents and Conditions	Comment
1	Me ₃ SnOH, DCE, 80 °C, 16 h	SM only
2	3 eq. LiOH, THF/H ₂ O/MeOH (3:1:1), rt, 16 h	SM only
3	3 eq. LiOH, THF/H ₂ O/MeOH (3:1:1), 80 °C, 16 h	20% 330 and 25% 331

Scheme 91. Attempted reduction of thioester **319**

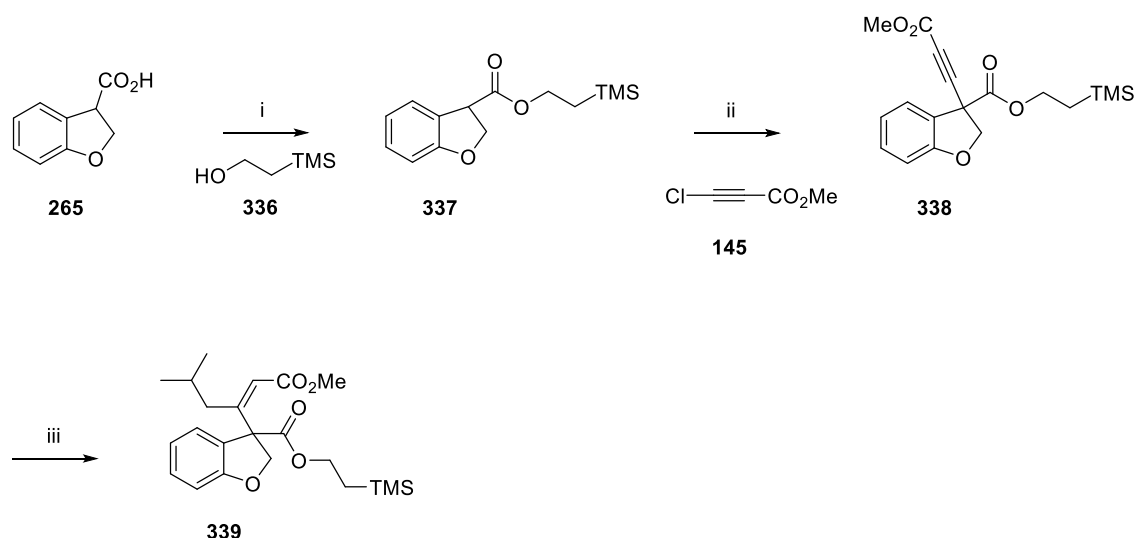
Initially, Me₃SnOH was investigated as it has been reported by Nicolaou to be highly effective in the cleavage of methyl esters under mild conditions.¹¹⁴ However, in our case, heating at 80 °C for 16 h resulted in only starting material being observed (entry 1). LiOH was then explored as an alternative reagent, but no reaction was observed at room temperature (entry 2). More forcing conditions were then used, and the reaction was heated to 80 °C for 16 h. None of the desired product was observed in this reaction, however lactone **330** and carboxylic acid **331** were isolated in 20% and 25% yield respectively. A proposed mechanism to explain the formation of lactone **330** is shown in Scheme 92. The mechanism initially involves an ester hydrolysis and a decarboxylation reaction to afford enolate **333**, followed by E1cB elimination and an electrocyclization reaction,

presumably made possible due to the extended heating of this reaction. Finally, the protonation of enol ether **335** affords lactone **330**.



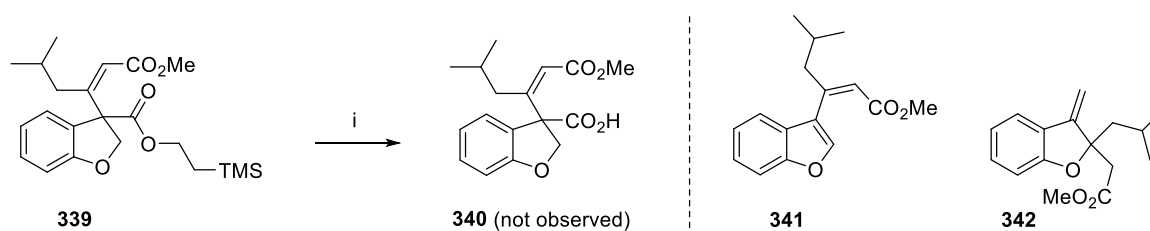
Scheme 92. Proposed mechanism to show the formation of lactone **330**

With our previous approach proving unsuccessful, we postulated that the ester group of the dihydrobenzofuran could be protected with a cleavable auxiliary. After alkynylation and cuprate addition, this group could then be removed to reveal the carboxylic acid that could then be further manipulated. Accordingly, carboxylic acid **265** was reacted with alcohol **336** to afford ester **337** in 88% yield (Scheme 93). Ester **337** was then subjected to our alkynylation conditions to synthesise alkyne **338** in 96% yield. Finally, cuprate addition afforded enone **339** in 89% yield.



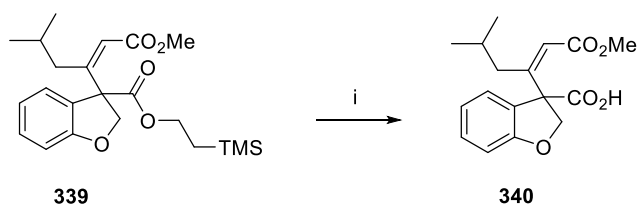
Scheme 93. Reagents and conditions: i) EDC·HCl, DMAP, CH₂Cl₂, 16 h, 88%; ii) LiHMDS, **337**, THF, -78 °C, 10 min, then **145**, -78 °C, 30 min, 96%; iii) *t*BuLi, CuI, THF, -78 – 0 °C, 1 h, then -78 °C, **338**, 30 min, 89%

With enone **339** in hand, we were then able to attempt the removal of the 2-(trimethylsilyl)ethyl group. Initial attempts using TBAF at room temperature failed to afford any of the desired product, and only starting material was observed. However, under more forcing conditions, involving heating at 75 °C for 16 h, the reaction afforded benzofuran **341** and alkene **342** in 39% and 34% yield respectively (Scheme 94).



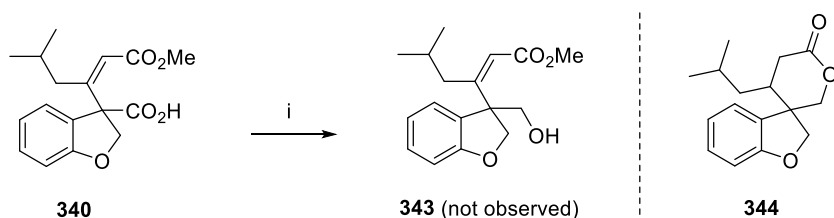
Scheme 94. Reagents and conditions: i) TBAF, THF, 75 °C, 16 h, 39% **341** and 34% **342**

Superior conditions, however, were found involving the use of TFA and CH₂Cl₂ to deprotect ester **339**, and the desired carboxylic acid **340** was formed in 90% yield (Scheme 95).¹¹⁵



Scheme 95. Reagents and conditions: i) $\text{CH}_2\text{Cl}_2/\text{TFA}$, (3:1), 0 °C – rt, 16 h, 90%

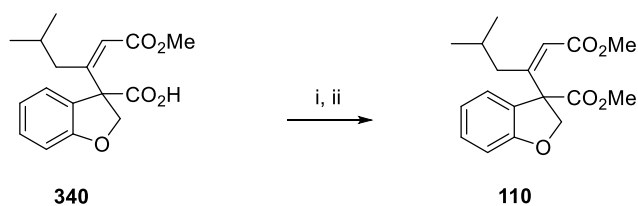
Successful ester deprotection was a significant development in the project because it demonstrated the possibility that one carbonyl group may be manipulated in the presence of the other. With carboxylic acid **340** in hand, we then attempted to use a borane reduction to reduce carboxylic acid **340** to alcohol **343** (Scheme 96).



Scheme 96. Reagents and conditions: i) $\text{BH}_3 \cdot \text{DMS}$, THF, rt, 2 h, 50% **344**

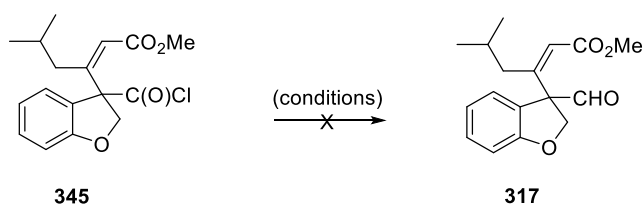
Disappointingly, however, none of the desired alcohol **343** was observed, and only lactone **344** was isolated in 50% yield. It was postulated that lactone **344** arose from the reduction of carboxylic acid **340** to alcohol **343**, which then underwent a lactonisation reaction. Several different conditions were used to quench the reaction, as a precaution against lactonisation during the work-up. However, none of these proved successful and alcohol **343** was never observed.

We then attempted to obtain aldehyde **317** via the conversion of carboxylic acid **340** to an acyl chloride, followed by a Rosenmund reduction.¹¹⁶ First, carboxylic acid **340** was reacted with oxalyl chloride and reacted with MeOH to prove that we had successfully formed the acyl chloride (Scheme 97).



Scheme 97. Reagents and conditions: i) Oxalyl chloride, DMF, CH₂Cl₂, 0 °C – rt, 2 h; ii) MeOH, rt, 16 h, 68%

We were pleased to observe that ester **110** was isolated in 68% yield after purification by column chromatography. In light of this, we prepared a batch of acyl chloride **345** and subjected it to hydrogenation conditions using a range of catalysts (Scheme 98).

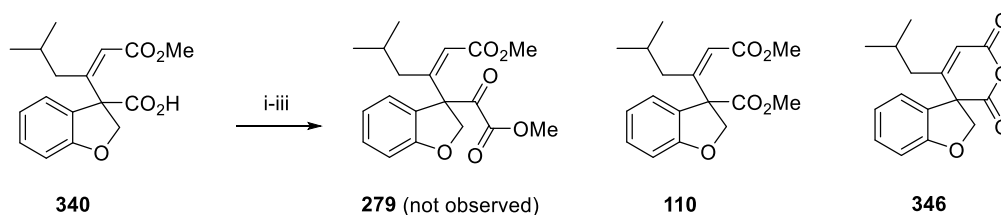


Entry	Catalyst	Comment	Entry	Catalyst	Comment
1 ^a	Pd/C 10R487	Complex mixture	7	Evonik 2	Complex mixture
2 ^a	Pd/C 10T755	Complex mixture	8	Evonik 3	Complex mixture
3 ^a	Pd/C 5R452	Complex mixture	9	Evonik 4	Complex mixture
4 ^a	Pd(S)/C A103023–5	Complex mixture	10	Evonik 5	Complex mixture
5 ^a	Pd/BaSO ₄ A308053–5	Complex mixture	11	Evonik 6	Complex mixture
6	Evonik 1	Complex mixture			

Scheme 98. Reagents and conditions: 5 bar H₂, 10 wt% catalyst, THF, rt, 16 h
^aSourced from Johnson Matthey®

Although a wide range of palladium catalysts were used, none of these resulted in the reduction of the acyl chloride and complex mixtures were observed in all cases.

A literature report by Photis detailed the synthesis of a methyl pyruvate from the acid hydrolysis of an acyl cyanide, itself derived from an acyl chloride.¹¹⁷ We were intrigued by the possibility that we could synthesise the pyruvate fragment of the taiwanschirin family following this approach, and so we applied these reported conditions to our model system (Scheme 99).



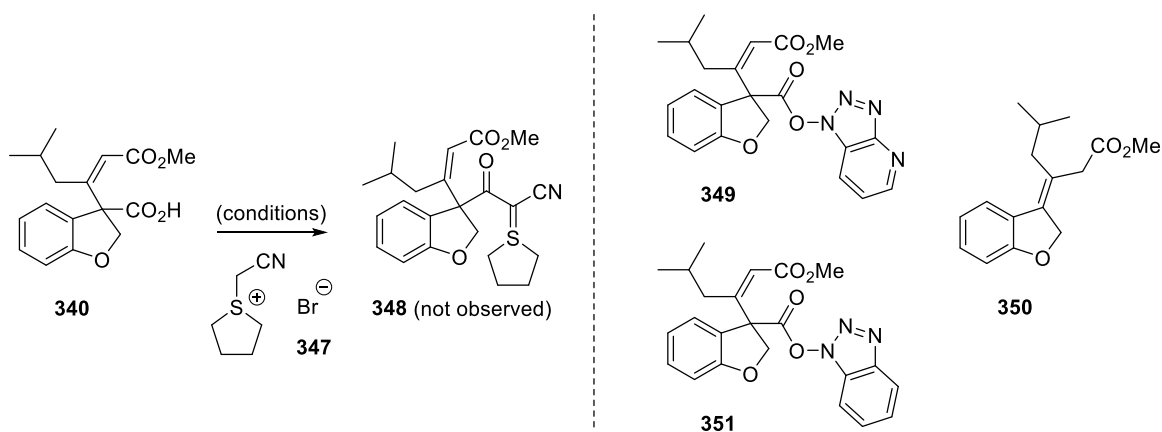
Scheme 99. Reagents and conditions: i) Oxalyl chloride, DMF, CH₂Cl₂, 0 °C – rt, 2 h; ii) 2 eq. CuCN, MeCN, 85 °C, 1 h; iii) H₂SO₄, NaBr, MeOH, 70 °C, 30 min, 34% **340**, 50% **110**, 3% **346**

Unfortunately, however, none of the desired pyruvate was observed, and instead significant quantities of carboxylic acid **340** and ester **110** were isolated, in addition to trace amounts of anhydride **346**. We postulated that the mechanism of this reaction involved the formation of the acyl chloride initially, followed by demethylation of the methyl ester by cyanide. The carboxylate could then cyclise onto the acyl chloride to form anhydride **346**, which was subsequently opened by MeOH to afford carboxylic acid **340**. Ester **110** could either form from the attack of MeOH on the acyl chloride, assuming incomplete reaction with cyanide, or from the esterification of carboxylic acid **340** under the highly acidic reaction conditions.

2.3.11 Cyanoketothiane formation

With the reactions of the acyl chloride derived from carboxylic acid **340** proving unsuccessful, we decided to revisit an earlier approach towards the pyruvate fragment. Previously, in Section 2.3.1 and 2.3.2, we explored the use of cyanoketophosphoranes, however alkyne **270** could not be oxidised successfully to afford the desired pyruvate **269**.

We postulated that steric bulk was responsible. In order to test this hypothesis, we investigated the use of a less sterically bulky pyruvate equivalent, salt **347**, prepared in a single step from tetrahydrothiophene and bromoacetonitrile (Scheme 100).¹¹⁸

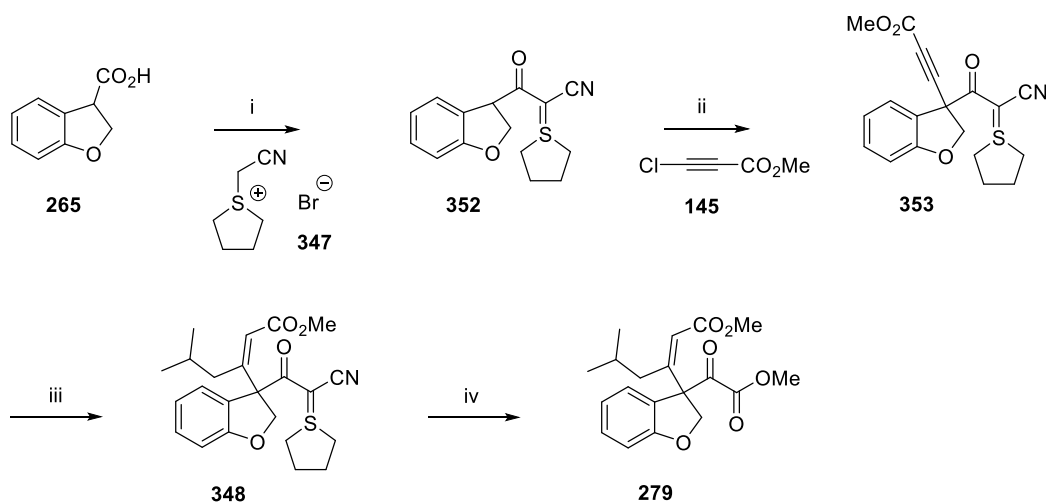


Entry	Reagents and Conditions	Comment/Yield
1	EDC·HCl, DMAP, DIPEA, CH ₂ Cl ₂ , rt, 16 h	Complex mixture
2	EDC·HCl, HOBT, DIPEA, CH ₂ Cl ₂ , rt, 16 h	Complex mixture
3	HATU, DMAP, DIPEA, CH ₂ Cl ₂ , rt, 16 h	98% 349
4	HBTU, DMAP, DIPEA, CH ₂ Cl ₂ , rt, 16 h	60% 351
5	BOPCl, DMAP, DIPEA, CH ₂ Cl ₂ , rt, 16 h	Complex mixture
6	PyBOP, DMAP, DIPEA, CH ₂ Cl ₂ , rt, 16 h	67% 351
7	CDI, DIPEA, CH ₂ Cl ₂ , rt, 16 h	SM only
8	DCC, DMAP, DIPEA, CH ₂ Cl ₂ , rt, 16 h	74% 350
9	CMDT, DMAP, morpholine, CH ₂ Cl ₂ , rt, 16 h	SM only

Scheme 100. Attempted coupling of acid **340**

Initially, acid **340** was reacted with cyanothiane **347** in the presence of a variety of coupling reagents in an attempt to form enone **348** (Scheme 100). However, in most cases only recovered starting material or a complex mixture was observed. When HATU was employed, adduct **351** was isolated in 98% yield (entry 3). Similarly, adduct **351** was isolated when HBTU and PyBOP were used as coupling agents (entries 4 and 6).

The order of events was now reversed to allow coupling before alkylation and organocuprate addition (Scheme 101).



Scheme 101. Reagents and conditions: i) EDC·HCl, DIPEA, DMAP, CH₂Cl₂, rt, 16 h, 68%; ii) LDA, **352**, THF, −78 °C, 10 min, then **145**, −78 °C, 30 min, 60%; iii) *t*BuLi, CuI, THF, −78 – 0 °C, 1 h, then −78 °C, **353**, 5 min, 79%; iv) O₃, CH₂Cl₂/MeOH 4:1, −78 °C, 10 min, 34%

Pleasingly, the reaction of acid **265** with cyanothiane **347** in the presence of EDC·HCl proceeded smoothly to provide cyanoketothiane **352** in 68% yield. Cyanoketothiane **352** was subsequently deprotonated with LiHMDS and reacted with chloroacetylene **145** to afford alkyne **353** in 35% yield. A range of different bases were explored to optimise this reaction, including NaHMDS and KHMDS. Eventually, the optimal conditions were found to be LDA at −78 °C, affording alkyne **353** in 60% isolated yield.

The addition of an organocuprate reagent derived from *t*BuLi to alkyne **353** afforded enone **348** in 79% yield (Scheme 101). The (*Z*)-configuration of enone **348** was confirmed by extensive nOe measurements, as was conducted previously. We were delighted to observe that enone **348** reacted with ozone at −78 °C in the presence of methanol, to form the desired pyruvate in 34% yield. ¹³C NMR data provided key evidence for the presence of the pyruvate functional group, for example the ketone resonance at $\delta = 187.7$ (C(O)CO₂CH₃)

and the appearance of the methyl ester signal at $\delta = 167.0$ (CO_2CH_3) (Figure 11). The methyl ester was also observed in the ^1H NMR spectrum at $\delta = 3.71$ (3H , s, CO_2CH_3) (Figure 11).

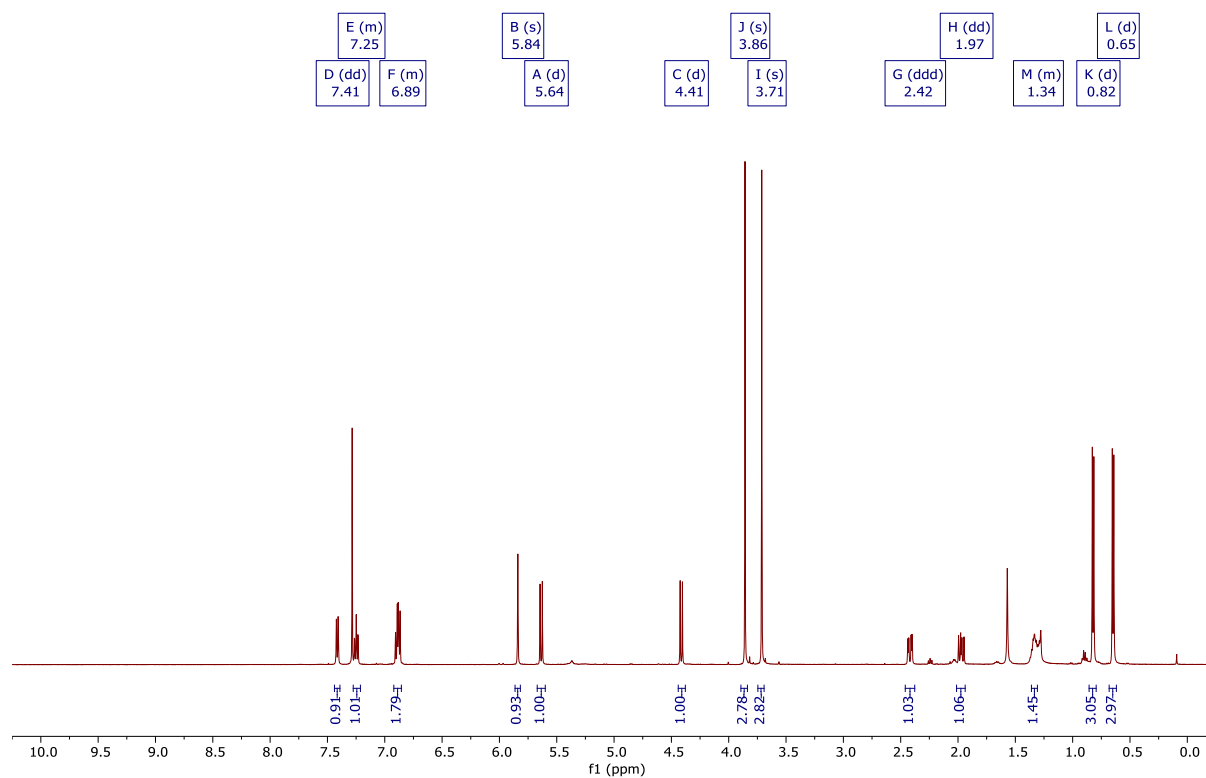


Figure 10. ^1H NMR spectrum of pyruvate **279**

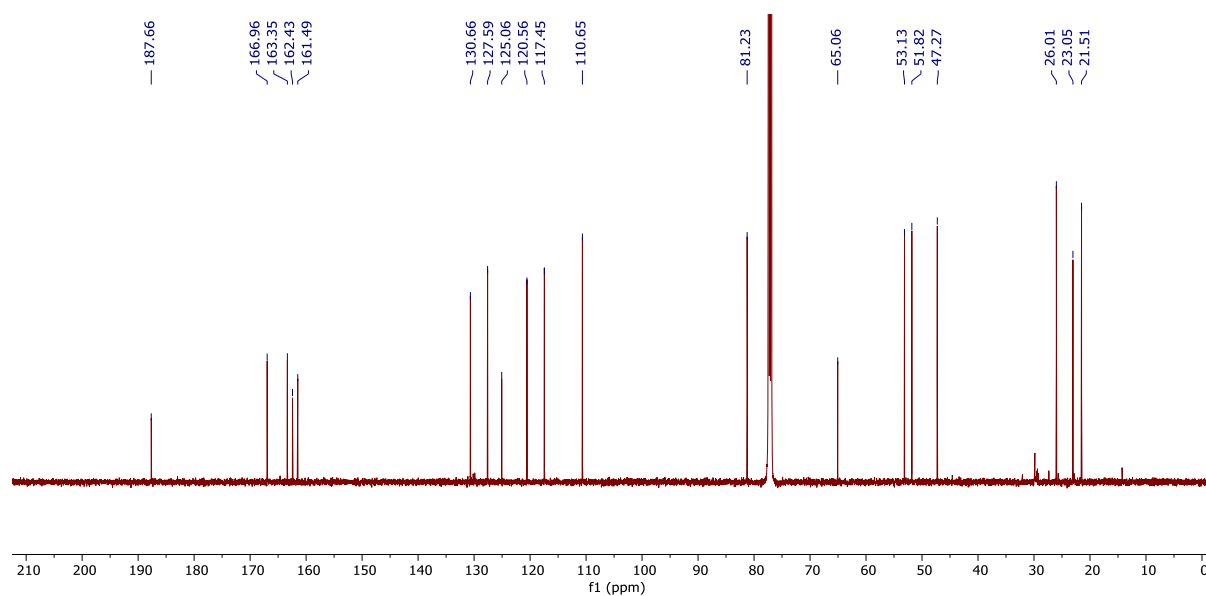


Figure 11. ^{13}C NMR spectrum of pyruvate **279**

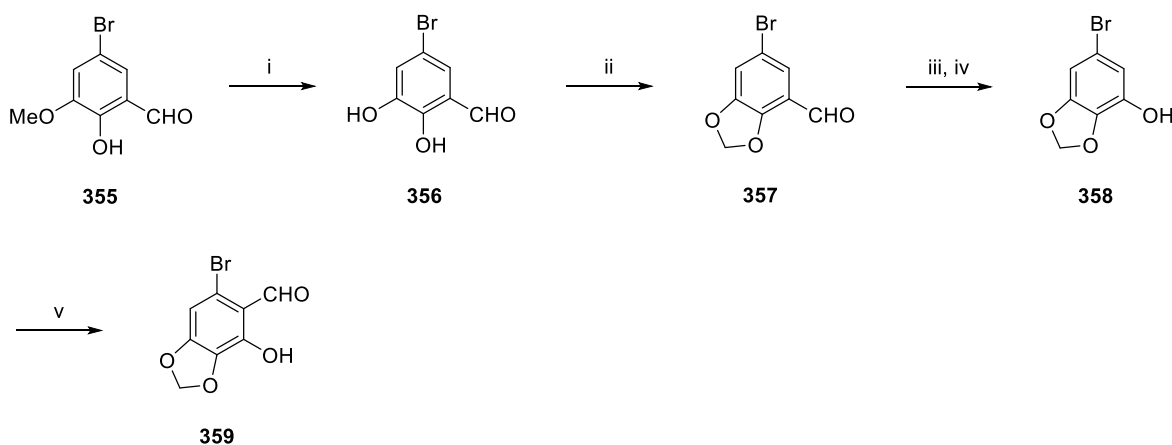
A pyruvate group had now been introduced in a model substrate incorporating a (*Z*)-enone, benzofuran core and the branched aliphatic sidechain found in the structure of the taiwanschirin family (Figure 10 and 11). This was a significant breakthrough for the project, and work could now begin towards the total synthesis of this family of natural products, incorporating the methods devised to overcome the difficulties associated with the synthesis of the four key structural fragments.

2.4 Towards the taiwanschirin family

2.4.1 Benzofuran synthesis

With completed model studies demonstrating the incorporation of all key structural fragments, we now devised an approach towards the total synthesis of the taiwanschirin family.

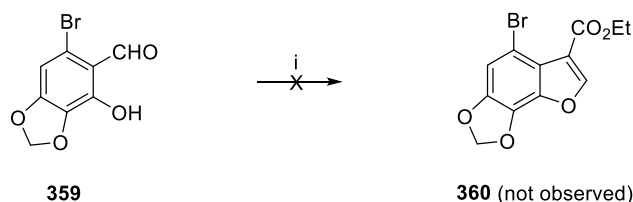
In order to prepare the dihydrobenzofuran core required for our synthesis, commercially available phenol **355** was reacted with BBr_3 to afford diphenol **356** in 98% yield (Scheme 102). The success of this reaction was demonstrated by the loss of the key methyl resonance $\delta = 3.93$ (3H, s, OCH_3) in the ^1H NMR spectrum. As before, for the preparation of aldehyde **127** (Section 1.2.4), aldehyde **356** was treated with dibromomethane in the presence of K_2CO_3 and CuO to form the methylenedioxy group found in aldehyde **357**. A subsequent Baeyer–Villiger oxidation employing MCPBA, followed by base-promoted ester hydrolysis afforded phenol **358** in 71% yield over 2 steps.⁴⁴



Scheme 102. Reagents and conditions: i) BBr_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$ – rt, 16 h, 98%; ii) CH_2Br_2 , K_2CO_3 , 10 mol% CuO , DMF, $165\text{ }^\circ\text{C}$, 3 h, 77%; iii) MCPBA, CH_2Cl_2 , $40\text{ }^\circ\text{C}$, 16 h; iv) KOH , EtOH, rt, 2 h, 71% over 2 steps; v) paraformaldehyde, MgCl_2 , Et_3N , THF, $85\text{ }^\circ\text{C}$, 16 h, 39%

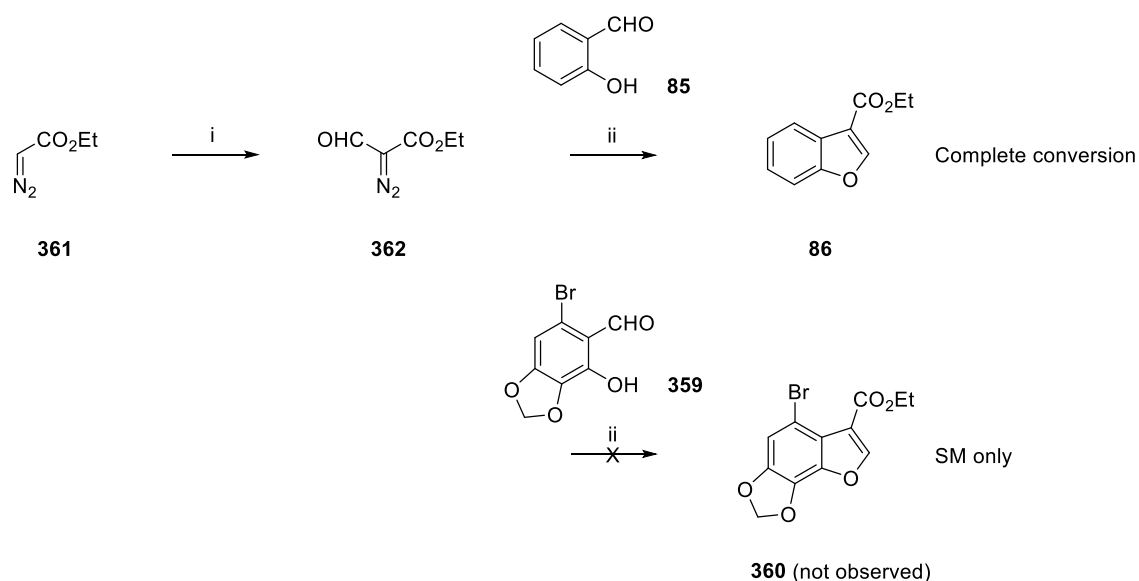
The formylation reaction was lower yielding for phenol **358** (39%) compared to 95% for phenol **128**, the substrate differing only in the presence of the bromine atom. However, it seemed reasonable that the formation of aldehyde **359** should be challenging due to the increase in steric clash upon forming a penta-substituted aromatic ring.

With aldehyde **359** in hand, we were now able to attempt to form the benzofuran with the conditions applied previously employing ethyl diazoacetate and $\text{HBF}_4 \cdot \text{OEt}_2$.³⁶ Disappointingly, however, none of the desired product was observed under these standard conditions (Scheme 103). Analysis by TLC after the reaction of aldehyde **359** with ethyl diazoacetate and $\text{HBF}_4 \cdot \text{OEt}_2$ confirmed consumption of the starting material. However, upon treatment with conc. H_2SO_4 , ^1H NMR analysis of the crude material showed an absence of resonances around $\delta = 6$ ppm, corresponding to a loss of the methylenedioxy group.



Scheme 103. Reagents and conditions: i) Ethyl diazoacetate, $\text{HBF}_4 \cdot \text{OEt}_2$, rt, 30 min, then H_2SO_4 , rt, 30 min, 0%

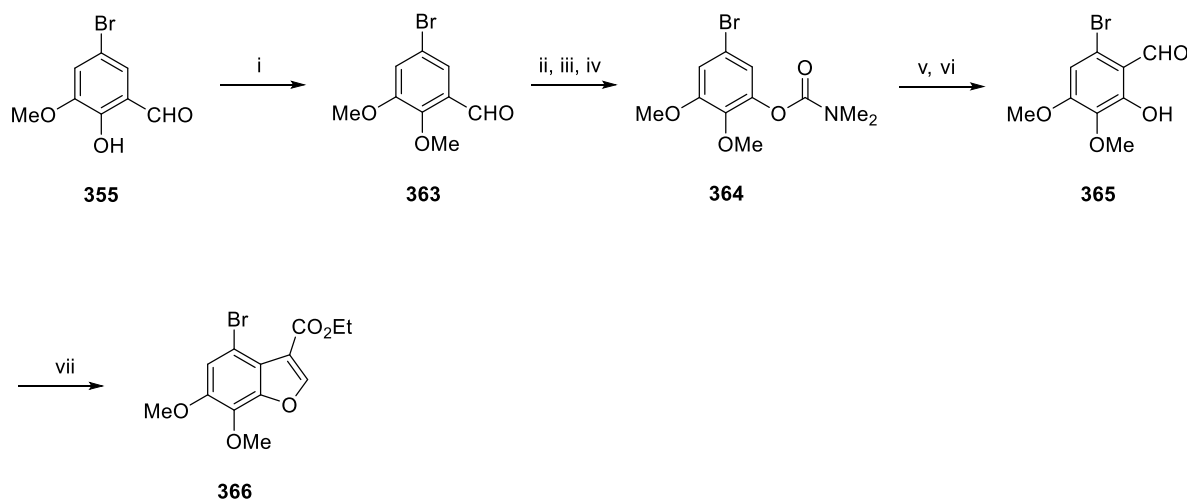
We hypothesised that this functional group was unable to survive strongly acidic conditions, and therefore we decided to investigate alternative, neutral reaction conditions developed for this transformation by Yao (Scheme 104).¹¹⁹



Scheme 104. Reagents and conditions: i) DMF, SOCl_2 , 40 °C, 16 h, then ethyl diazoacetate, AcOH, rt, 16 h, 28%; ii) 2.5 mol% $[\text{RhCp}^*\text{Cl}_2]_2$, 20 mol% AgNTf_2 , DCE, 60 °C, 16 h

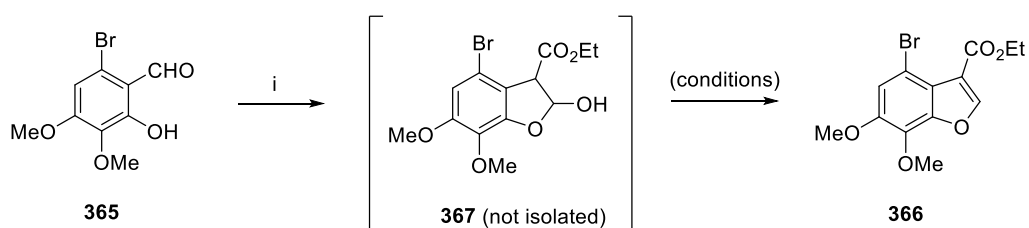
Accordingly, ethyl diazoacetate **361** was formylated using DMF and SOCl_2 to afford aldehyde **362**. Subjection of 2-hydroxybenzaldehyde **85** to the conditions developed by Yao resulted in complete conversion to the desired product by ^1H NMR. However, when aldehyde **359** was used as the substrate, only starting material was observed and none of the desired product. At this time, we decided to investigate an alternative route using two methoxy groups in lieu of the methylenedioxy. We postulated that methoxy groups should display greater resistance towards acidic conditions, thereby permitting the formation of the benzofuran. After the benzofuran had been installed, the methoxy groups would be deprotected to afford the diphenol which could then react with dibromoethane to form the desired methylenedioxy group. To this end, phenol **355** was reacted with Me_2SO_4 in the presence of K_2CO_3 to afford aldehyde **363** in quantitative yield (Scheme 105). Subsequent Baeyer–Villiger oxidation and ester cleavage, followed by reaction with carbamyl chloride, afforded carbamate **364** in 62% yield over 3 steps. *Ortho*–lithiation with LDA and quenching with DMF, followed by carbamate deprotection afforded aldehyde **365**

in a modest 22% yield over 2 steps. We were pleased to observe that the benzofuran cyclisation proceeded smoothly to afford benzofuran **366** in 63% yield over 2 steps.



Scheme 105. Reagents and conditions: i) Me_2SO_4 , K_2CO_3 , 40 °C, 1 h, 100%; ii) MCPBA, CH_2Cl_2 , 40 °C, 16 h; iii) KOH, EtOH, rt, 2 h; iv) NaH, carbamyl chloride, DMF, rt, 16 h, 62% over 3 steps; v) LDA, THF, –78 °C, 1.5 h, DMF, rt, 2 h; vi) 2 M HCl, 1 h, 22% over 2 steps; vii) Ethyl diazoacetate, $\text{HBF}_4\cdot\text{OEt}_2$, rt, 30 min, then H_2SO_4 , 70 °C, 1 h, 63%

Upon scaling up the reaction to afford the benzofuran, mixtures of the desired product and the undesired de-brominated product were observed. We postulated that this was due to the presence of strong acid, so we sought to develop a milder alternative set of conditions for this transformation (Scheme 106).

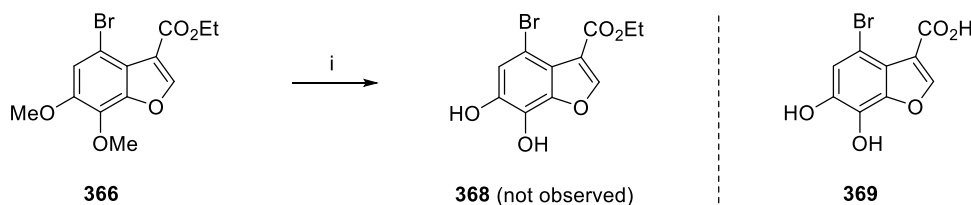


Entry	Reagents and Conditions	Comment
1	Ethyl diazoacetate, $\text{HBF}_4\cdot\text{OEt}_2$, rt, 30 min, then $\text{Sc}(\text{OTf})_3$, Et_3N , CH_2Cl_2 , rt, 5 h	No product observed
2	Ethyl diazoacetate, $\text{HBF}_4\cdot\text{OEt}_2$, rt, 30 min, then MsCl , Et_3N , CH_2Cl_2 , rt, 5 h	26%
3	Ethyl diazoacetate, $\text{HBF}_4\cdot\text{OEt}_2$, rt, 30 min, then Ms_2O , pyridine, CH_2Cl_2 , rt, 5 h	53%

Scheme 106. Reagents and conditions: i) Ethyl diazoacetate, $\text{HBF}_4\cdot\text{OEt}_2$, rt, 30 min

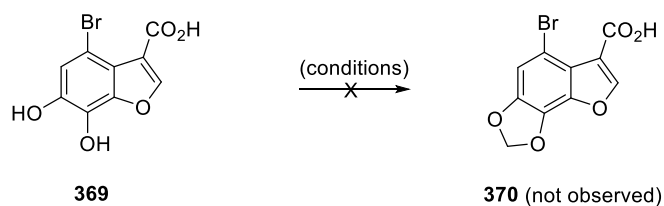
We were surprised to observe that the use of the oxophilic Lewis acid, $\text{Sc}(\text{OTf})_3$, failed to result in the formation of any of the desired product, especially given that it was employed in a similar elimination reaction previously within our research group (entry 1).¹²⁰ MsCl resulted in the first hit, with the desired product isolated in 26% yield (entry 2). Substitution of MsCl for Ms_2O resulted in a near doubling of the yield to 53% (entry 3).

With benzofuran **366** in hand, we then attempted to deprotect the methoxy groups using BBr_3 . Although BBr_3 did indeed reveal the diphenol, it also resulted in ester hydrolysis, thereby forming carboxylic acid **369** in 92% yield (Scheme 107).



Scheme 107. i) BBr_3 , CH_2Cl_2 , 0 °C – rt, 30 min, 92%

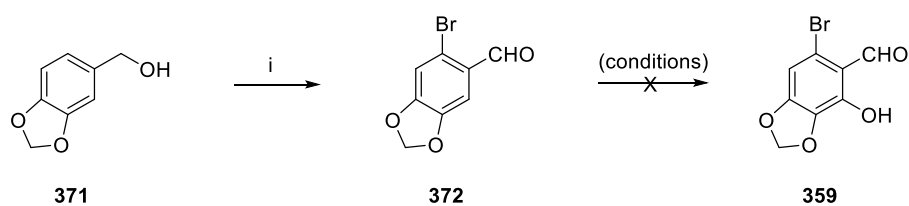
Several attempts employing ethanol and various acids failed to result in esterification. Therefore, we attempted to form the methylenedioxy group from the diphenol acid **369** (Scheme 108). Several different conditions were explored, investigating different temperatures, bases and electrophiles, however none of these resulted in the formation of the desired product.



Entry	Reagents and Conditions	Comment
1	K ₂ CO ₃ , 10 mol% CuO, CH ₂ I ₂ , DMF, 150 °C, 16 h	Complex mixture
2	K ₂ CO ₃ , 10 mol% CuO, CH ₂ I ₂ , DMF, 85 °C, 16 h	SM only
3	Cs ₂ CO ₃ , 10 mol% CuO, CH ₂ Br ₂ , DMF, 85 °C, 16 h	Complex mixture

Scheme 108. Attempted formation of methylenedioxy functional group

With this approach seeming less viable, we returned to scale up our initial route with the intention of later applying our newly developed elimination conditions (Scheme 106). Unfortunately, however, scaling up the Baeyer–Villiger/ester hydrolysis reactions proved to be prohibitively difficult, and dramatically lower yields were obtained on large scale. For example, a 4% yield was recorded on a scale of 24 g. A series of investigations revealed the Baeyer–Villiger reaction to be the problematic transformation, although modifications to the reaction conditions: temperature, reaction time etc. all failed to result in an improved yield on a scale greater than a couple of grams. Furthermore, the *meta*-chloroperbenzoic acid by-product proved challenging to remove from phenol **358**. In order to progress through the synthesis, we required a route that was capable of delivering large amounts of clean material to the frontline. With this in mind, we turned our attention towards an alternative method of preparing aldehyde **359** (Scheme 109).



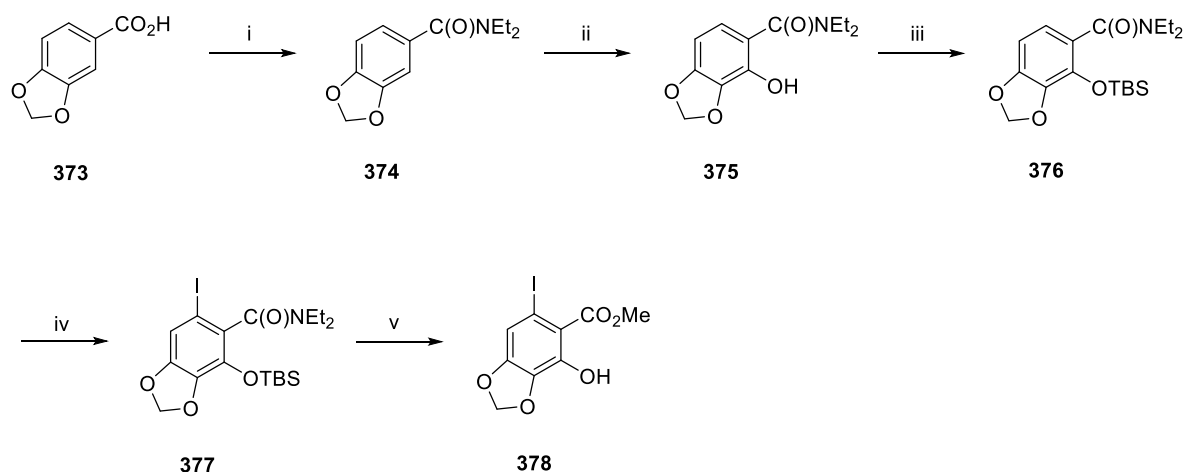
Entry	Reagents and Conditions	Comment
1	5 mol% [RuCl ₂ (<i>p</i> -cymene) ₂], 1.5 eq. PIFA, DCE, 100 °C, 16 h	Complex mixture
2	ⁿ BuLi, <i>N,N,N'</i> -trimethylethylenediamine, –20 °C, THF, 372 , 30 min, LDA, 30 min, B(OMe) ₃ , 0 °C, 1 h, AcOH, H ₂ O ₂ , rt, 1 h	Complex mixture

Scheme 109. Reagents and conditions: i) DBDMH, CH₂Cl₂, rt, 30 min, 52%

Commercially available piperonyl alcohol **371** was initially reacted with DBDMH using the conditions developed by Zou to afford aldehyde **372** in 52% yield on a scale of 20 mmol.¹²¹ We postulated that aldehyde **372** could be transformed into the desired intermediate, aldehyde **359** by the application of an aldehyde-directed ruthenium (II)-catalysed C–H oxidation reaction recently reported by Ackermann.¹²² However, application of these conditions failed to result in the formation of any of the desired product, and a complex mixture was observed (entry 1). A second attempt involved the use of a transient directing group developed by Einhorn (entry 2).¹²³ In this approach, a secondary amine was deprotonated with ⁿBuLi and reacted with aldehyde **372**. The subsequent addition of LDA was intended to effect *ortho*-lithiation which, upon reaction with B(OMe)₃ and H₂O₂/AcOH, would result in an overall *ortho*-hydroxylation reaction. Key to this approach developed by Einhorn was the chelating effect of the amine transient directing group. Disappointingly, however, a complex mixture of products was observed by ¹H NMR.

At this moment we devised an alternative approach towards the dihydrobenzofuran heterocycle based on the initial steps developed by Madsen towards the total synthesis of pancratistatin (Scheme 110).¹²⁴ Piperonylic acid **373** was transformed to the acyl chloride

with SOCl_2 and reacted with diethylamine to afford amide **374** in quantitative yield. *Ortho*-lithiation was achieved with $^s\text{BuLi}$ and subsequent reaction with $\text{B}(\text{OMe})_3$ and $\text{H}_2\text{O}_2/\text{NaOH}$ afforded phenol **375** in 85% yield (36 g). TBS-protection was easily performed on large scale, and in a single reaction 107 g of amide **376** was synthesised, representing a 93% yield. Although amide **376** had a melting point of $65\text{ }^\circ\text{C}$, thereby hindering purification by recrystallisation, it was found that due to the reasonable polarity difference between amide **376** and phenol **375**, the entire reaction mixture could be purified by column chromatography in a single batch. *Ortho*-lithiation and subsequent reaction with iodine afforded iodide **377** in 66% yield. Although bromination was attempted initially, this gave rise to complex mixtures of products and only small quantities of the desired bromide could be isolated cleanly. However, the reaction of the aryl anion with iodine was a far cleaner reaction, and it was found that it was necessary to use 1.05 eq. of iodine in order to avoid over-iodination of amide **376**. Finally, a small quantity of iodide **377** was reacted with Me_3OBF_4 to afford ester **378** in 87% yield. We anticipated that either iodide **377** or ester **378** could be transformed into the iodide analogue of aldehyde **359**.

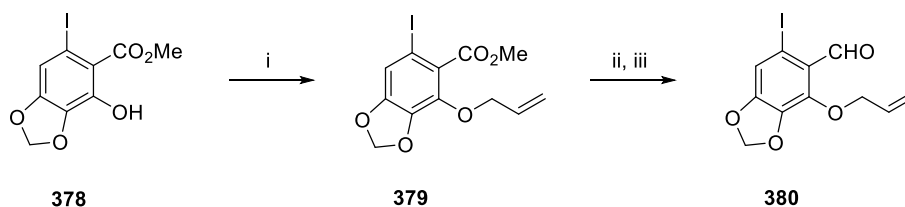


Scheme 110. Reagents and conditions: i) SOCl_2 , $90\text{ }^\circ\text{C}$, 2 h, $0\text{ }^\circ\text{C}$, diethylamine, rt, 16 h, 100%; ii) $^s\text{BuLi}$, N,N,N',N' -tetramethylethylenediamine, THF, $-78\text{ }^\circ\text{C}$, 1 h, $\text{B}(\text{OMe})_3$, rt, 1 h, H_2O_2 , NaOH , rt, 16 h, 85%; iii) TBSCl , imidazole, rt, 1 h, 93%; iv) $^s\text{BuLi}$, N,N,N',N' -tetramethylethylenediamine, THF, $-78\text{ }^\circ\text{C}$, 1 h, I_2 , $-78\text{ }^\circ\text{C}$, 1 h, then rt, 1 h, 66%; v) $\text{Me}_3\text{OBF}_4\cdot\text{OEt}_2$, Na_2HPO_4 , MeCN , $0\text{ }^\circ\text{C}$, then rt, 12 h, NaHCO_3 , 6 h, 87%

Initial attempts explored the reduction of the amide functional group of iodide **377** to the aldehyde using Schwartz reagent,¹²⁵ or the alcohol with Super Hydride®. However, in both these reactions none of the desired product was observed. In the case of Super Hydride®, evidence for iodide reduction in the form of aromatic doublet resonances was observed in the ¹H NMR spectrum of the crude reaction mixture. Strongly reducing conditions employing NaI, ZnI₂ and NaH reported by Takita in 2019 for the reduction of amides to alcohols resulted in only starting material by ¹H NMR when applied to iodide **377**.¹²⁶

Ester **378** was reacted with LiAlH₄ in an attempt to form the alcohol, however complex mixtures were observed in addition to iodide loss by ¹H NMR. Another strategy involved a LiOH promoted ester hydrolysis to the carboxylic acid. This reaction proceeded cleanly to the desired product, as confirmed by the loss of the characteristic methyl ester resonance $\delta = 3.96$ (3H, s, CO₂CH₃) in the ¹H NMR spectrum. However, subsequent attempts to reduce the carboxylic acid to the alcohol using BH₃·DMS proved unsuccessful and complex mixtures were observed.

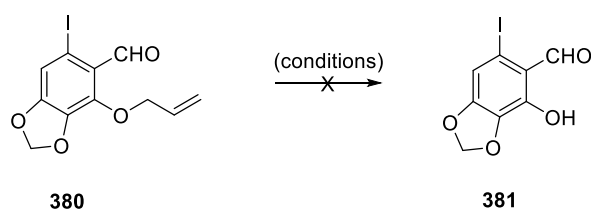
At this point we decided to explore the use of a protecting group to enable the reduction of the ester in the presence of the phenol functional group. Accordingly, ester **378** was reacted with allyl iodide in the presence of K₂CO₃ to afford ester **379** in 95% yield (Scheme 111).



Scheme 111. Reagents and conditions: i) Allyl iodide, K₂CO₃, DMF, 70 °C, 1 h, 95%; ii) DIBAL–H, CH₂Cl₂/toluene, –78 °C – rt, 1 h; iii) DMP, NaHCO₃, CH₂Cl₂, 44% over 2 steps

Initial attempts at the reduction of ester **379** using NaBH₄ proved ineffective, with starting material only being observed. However, it was soon found that DIBAL–H was able to

rapidly reduce the ester down to the alcohol at $-78\text{ }^{\circ}\text{C}$. Although efforts were made to stop the reduction at the aldehyde oxidation level, none of these proved fruitful. When a single equivalent of DIBAL-H was used and delivered carefully to the reaction mixture by dripping down the inside walls of the flask deeply submerged in a dry ice bath, a 1:1 mixture of alcohol and ester **379** was obtained. As a consequence of this it was resolved that an excess should be used and the alcohol immediately oxidised back up to the aldehyde using DMP. This reaction proceeded smoothly and afforded the desired aldehyde **380** in 44% yield over 2 steps. However, although several literature reported methods for allyl deprotection were attempted using aldehyde **380**, none of these resulted in the formation of the desired product (Scheme 112).

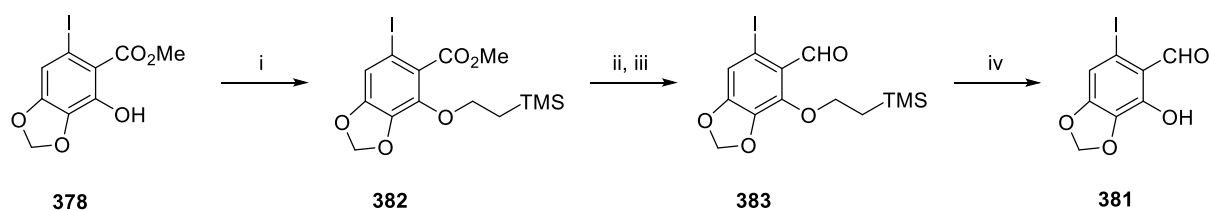


Entry	Reagents and Conditions	Comment
1	20 mol% Pd/C, NH_4HCO_2 , MeOH, $70\text{ }^{\circ}\text{C}$, 16 h	SM only
2	TiCl_4 , Bu_4NI , CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$ – rt, 16 h	Complex mixture
3	5 mol% OsO_4 , NaIO_4 , NMO, $60\text{ }^{\circ}\text{C}$, 16 h	Complex mixture

Scheme 112. Attempted deprotection of aldehyde **380**

In the case of Pd/C and ammonium formate, only starting material was observed after heating in MeOH at $70\text{ }^{\circ}\text{C}$ for 4 h (entry 1).¹²⁷ TiCl_4 and Bu_4NI resulted in complete decomposition of the starting material (entry 2),¹²⁸ similarly to the application of catalytic OsO_4 in the presence of NMO and NaIO_4 (entry 3).¹²⁹

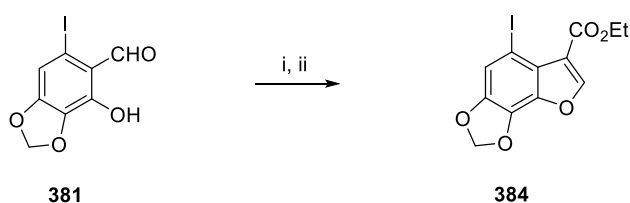
As a consequence of the allyl group proving difficult to remove, we decided to explore an alternative protecting group (Scheme 113).



Scheme 113. Reagents and conditions: i) 2-(trimethylsilyl)ethanol, DIAD, PPh₃, THF, 0 °C – rt, 16 h, 87%; ii) DIBAL–H, CH₂Cl₂/toluene, –78 °C – rt, 1 h; iii) DMP, NaHCO₃, CH₂Cl₂, 58% over 2 steps; iv) ZnBr₂, MeNO₂, rt, 16 h, 91%

Ester **378** was subjected to Mitsunobu reaction conditions to afford ester **382** in 87% yield. Pleasingly, this reaction could be carried out on large scale with around 16 g of product produced in each batch. Subsequent DIBAL–H reduction and DMP oxidation afforded aldehyde **384** in 58% yield over 2 steps. Deprotection using ZnBr₂ in MeNO₂ afforded the desired aldehyde **381** in 91% yield after purification by column chromatography.¹³⁰

With aldehyde **381** in hand, we were then able to apply our newly developed benzofuran cyclisation conditions (Scheme 114).



Scheme 114. Reagents and conditions: i) Ethyl diazoacetate, HBF₄·OEt₂, rt, 30 min; ii) Ms₂O, pyridine, CH₂Cl₂, rt, 16 h, 54% over 2 steps

We were delighted to observe that aldehyde **381** underwent a clean reaction with ethyl diazoacetate, followed by elimination with Ms₂O and pyridine, to form benzofuran **384** in 54% yield (780 mg) over 2 steps. Formation of the benzofuran was confirmed by the disappearance of the aldehyde resonance $\delta = 9.89$ (1H, s, CHO) in the ¹H NMR spectrum, and the appearance of an aromatic signal at $\delta = 8.06$ (1H, s, ArH), characteristic of the newly formed benzofuran. Benzofuran **384** was a highly crystalline solid, and it was a facile process to obtain large crystals by slow evaporation from an ethereal solution. The structure

of benzofuran **384**, and crucially the substitution of the iodide functional group, was confirmed unequivocally by X-ray crystallography (Figure 12).

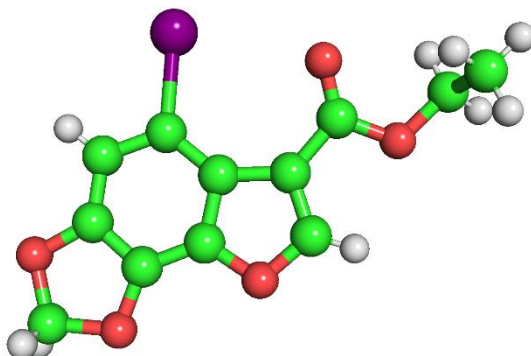
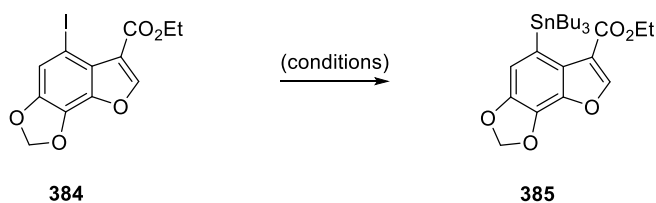


Figure 12. X-ray crystal structure of benzofuran **384**

2.4.2 Stannylation of benzofuran **384**

With a method for the preparation of benzofuran **384** in hand, we were now able to progress with our planned synthesis and convert the iodide into a stannane (Scheme 115).



Entry	Reagents and conditions	Scale/mmol	Yield
1	i PrMgCl·LiCl, THF, $-20\text{ }^{\circ}\text{C}$, 30 min, then $-78\text{ }^{\circ}\text{C}$, Bu_3SnCl , rt, 1 h,	0.14	21%
2	1.3 eq. $(\text{Bu}_3\text{Sn})_2$, 2.5 mol% $\text{Pd}_2(\text{dba})_3$, 15 mol% JohnPhos, dioxane, $110\text{ }^{\circ}\text{C}$, 2 h	0.22	43%
3	1.3 eq. $(\text{Bu}_3\text{Sn})_2$, 20 mol% $\text{Pd}_2(\text{dba})_3$, 60 mol% JohnPhos, dioxane, $110\text{ }^{\circ}\text{C}$, 3 h	0.28	45%
4	1.3 eq. $(\text{Bu}_3\text{Sn})_2$, 20 mol% $\text{Pd}_2(\text{dba})_3$, 60 mol% JohnPhos, dioxane (degassed with bubbling Ar), $110\text{ }^{\circ}\text{C}$, 2.5 h	0.94	64%
5	1.3 eq. $(\text{Bu}_3\text{Sn})_2$, 20 mol% $\text{Pd}_2(\text{dba})_3$, 60 mol% JohnPhos, dioxane (degassed with bubbling Ar), $110\text{ }^{\circ}\text{C}$, 3.5 h	1.89	65%

Scheme 115. Synthesis of stannane **385**

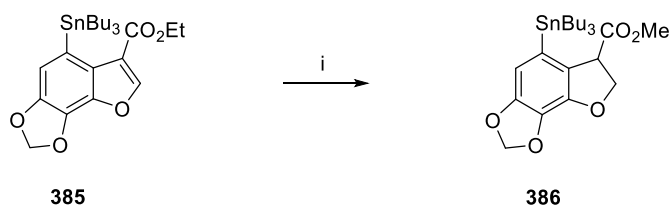
Previous attempts at the optimisation of the stannylation reaction using different palladium catalysts and ligands proved unsuccessful, so we decided to explore an alternative strategy. Based on literature precedent, benzofuran **384** was treated with Turbo Grignard at $-20\text{ }^{\circ}\text{C}$, followed by reaction with Bu_3SnCl at $-78\text{ }^{\circ}\text{C}$ and warming to room temperature (entry 1).¹³¹ However, a complex mixture of products was obtained, and the desired stannane **385** could only be isolated in 21% yield after column chromatography.

Application of the previously developed catalytic palladium conditions for the stannylation reaction afforded a 43% yield of the desired stannane product **385** (entry 2).⁸⁸ In the ^1H NMR spectra of the crude material, it was observed that there was often a significant amount of starting material. Interestingly, prolonged reaction times did not force the reaction to completion, and conversely, product decomposition was often observed. In an attempt to force the reaction to completion, the loadings of the pre-catalyst and ligand were increased to 20 and 60 mol% respectively. However, despite this significant increase in loading, the isolated yield remained essentially unchanged at 45% (entry 3).

A breakthrough was obtained when the dioxane solvent was degassed under bubbling argon prior to use in the reaction. Under these conditions the yield dramatically increased to 64% (entry 4). Furthermore, this reaction could reliably be carried out on large scale, with a 65% yield obtained on a scale of 1.89 mmol (entry 5).

2.4.3 Reduction of stannane **385**

With stannane **385** in hand, we could now perform the magnesium-mediated reduction reaction to afford the dihydrobenzofuran (Scheme 116). Pleasingly, this reaction worked well on large scale and a 92% yield of stannane **386** was obtained on a scale of 1.2 mmol (640 mg).

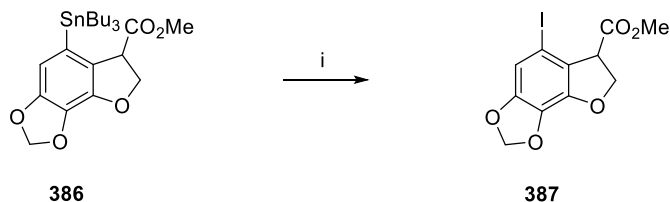


Scheme 116. Reagents and conditions: i) Mg, MeOH, 1 h, 92%

In previous work on model substrates, in order to achieve complete transesterification in this reaction, the mixture was often heated at 70 °C for a period of 30 min to 1 h. However, with this substrate it was found that this led to decomposition, and in some cases mixtures of methyl and ethyl esters were carried through in order to obtain the maximum yield. Fortunately, a future ester hydrolysis step meant that ultimately this mixture was inconsequential. However, on significantly large scale, i.e. over 1 mmol, the heat given out by the reaction was sufficient to promote complete transesterification to the methyl ester product.

2.4.4 Tin–iodine exchange

Tin–iodine exchange was achieved by the titration of a 0.1 M solution of iodine in CHCl₃ into a solution of stannane **386** at 0 °C (Scheme 117). Pleasingly, this reaction was extremely simple to perform, and proceeded rapidly, with instantaneous decolourisation of the iodine solution upon addition to stannane **386**.



Scheme 117. Reagents and conditions: i) I₂, CHCl₃, 0 °C – rt, 100%

Conventional TLC eluent systems using Et₂O or EtOAc in combination with pentane failed to separate the desired iodide product from the tin impurities. However, it was quickly found that the use of CH₂Cl₂ enabled the successful purification of iodide **387** to afford the product in quantitative yield after column chromatography. Furthermore, the structure of iodide **387** was confirmed unequivocally by X-ray crystallography (Figure 13).

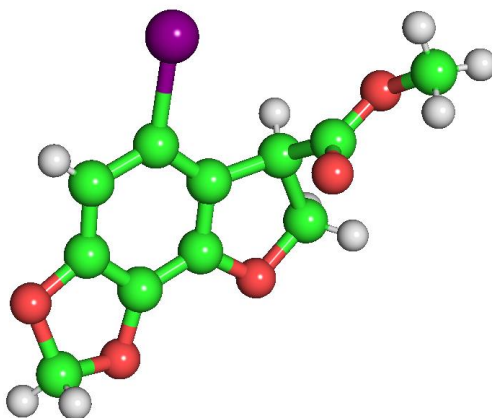
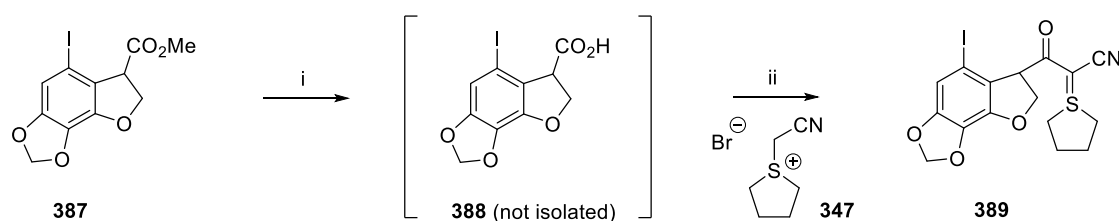


Figure 13. X-ray crystal structure of iodide **387**

2.4.5 Ylide formation

In order to prepare the ylide required for the alkynylation reaction, ester hydrolysis was attempted using Me₃SnOH as reported by Nicolaou.¹³² However, only starting material was observed after heating at reflux in DCE for 16 h. Similarly, the use of pig liver esterase also only resulted in starting material after an overnight reaction in a phosphate buffer (pH = 8).¹³³ With a change of conditions, the ester functional group of iodide **387** was successfully hydrolysed using NaOH in MeOH/CH₂Cl₂ (Scheme 118).¹³⁴ This reaction proceeded cleanly to the desired product, as confirmed by the loss of the characteristic methyl ester resonance $\delta = 3.77$ (3H, s, CO₂CH₃) in the ¹H NMR spectrum. The crude carboxylic acid product was then subjected to amide coupling conditions with salt **347**. Carboxylic acid **388** was found to be very insoluble in almost all organic solvents, with the

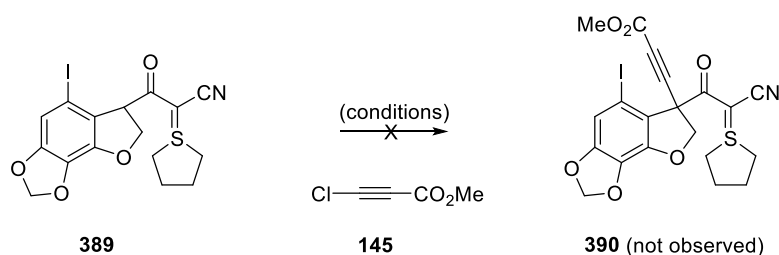
notable exception of DMF. For this reason, the decision was taken to carry forward this acid as the crude mixture, and purify the product of the coupling reaction. In previous model studies, EDC·HCl had been used, however it was found that this was not a suitable coupling agent in this reaction as none of the desired product was observed.¹¹⁸ A brief optimisation found T3P[®] to be the optimal coupling agent, affording a 37% yield of the desired product, ylide **389**, over 2 steps.



Scheme 118. Reagents and conditions: i) NaOH, CH₂Cl₂/MeOH (9:1), 0 °C–rt, 16 h; ii) T3P[®], DIPEA, DMAP, DMF, rt, 16 h, 37% over 2 steps

2.4.6 Alkynylation

With ylide **389** successfully synthesised, we could now examine the key alkynylation reaction (Scheme 119). This was a key step in the synthesis of the taiwanschirin family of natural products, however, despite a range of conditions investigated, none afforded the desired alkyne product.

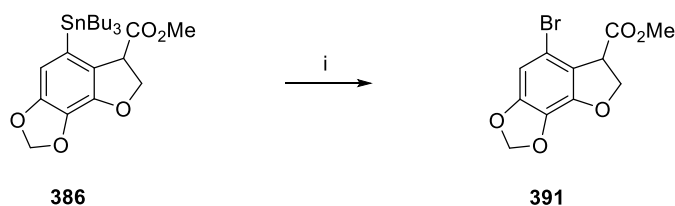


Entry	Reagents and Conditions	Comment
1	LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 5 min, then 145 , $-78\text{ }^{\circ}\text{C}$, 30 min	SM only
2	LDA, DMF, $-78\text{ }^{\circ}\text{C}$, 5 min, then 145 , $-78\text{ }^{\circ}\text{C}$, 2 h	SM only
3	LDA, DMF, $-40\text{ }^{\circ}\text{C}$, 5 min, then 145 , $0\text{ }^{\circ}\text{C}$, 2 h	Complex mixture with approximately 50% SM by ^1H NMR

Scheme 119. Attempted synthesis of alkyne **390**

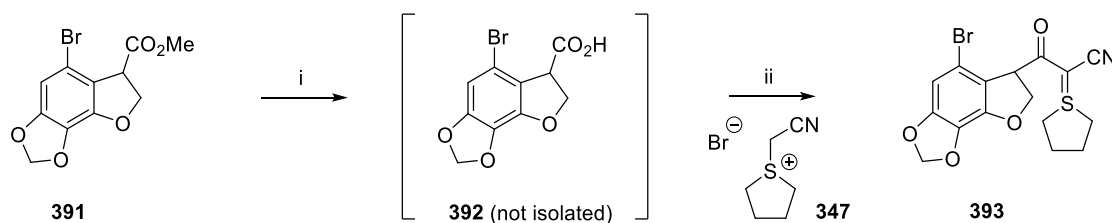
Application of the standard conditions developed previously resulted only in the isolation of starting material (entry 1). It was noticed that the solubility of ylide **389** was poor in THF at $-78\text{ }^{\circ}\text{C}$, so a change of solvent was made to DMF. LDA had also afforded positive results for this reaction on the model system, and so these combined conditions were applied for the second attempt at this reaction (entry 2). However, these conditions also failed to afford any of the desired product. We postulated that lack of reactivity of the anion was an issue, so the temperature of the reaction, upon addition of the electrophile, was increased to $0\text{ }^{\circ}\text{C}$ (entry 3). Although the amount of starting material was observed to decrease in the ^1H NMR spectrum of the crude reaction material, complex mixtures of impurities were beginning to form, and there were no characteristic doublets indicating traces of alkyne **390**.

In light of the challenges faced with this alkynylation reaction, it was postulated that the reason for the markedly differing reactivity between ylide **389** and model ylide **352** was the presence of the bulky iodide substituent. In light of this, we decided to investigate the reactivity of the bromide analogue of ylide **389** (Scheme 120).



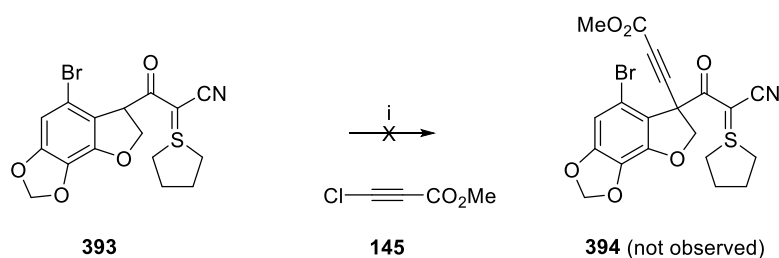
Scheme 120. Reagents and conditions: i) *N*-bromosuccinimide, THF, 0 °C – rt, 98%

Stannane **386** was reacted with *N*-bromosuccinimide to afford bromide **391** in 98% yield (Scheme 120). Similarly to the sequence followed previously, bromide **391** was hydrolysed with NaOH to yield a crude carboxylic acid that was then subjected to a coupling reaction using T3P® (Scheme 121).



Scheme 121. Reagents and conditions: i) NaOH, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1), 0 °C – rt, 16 h; ii) T3P®, DIPEA, DMAP, DMF, rt, 16 h, 25% over 2 steps

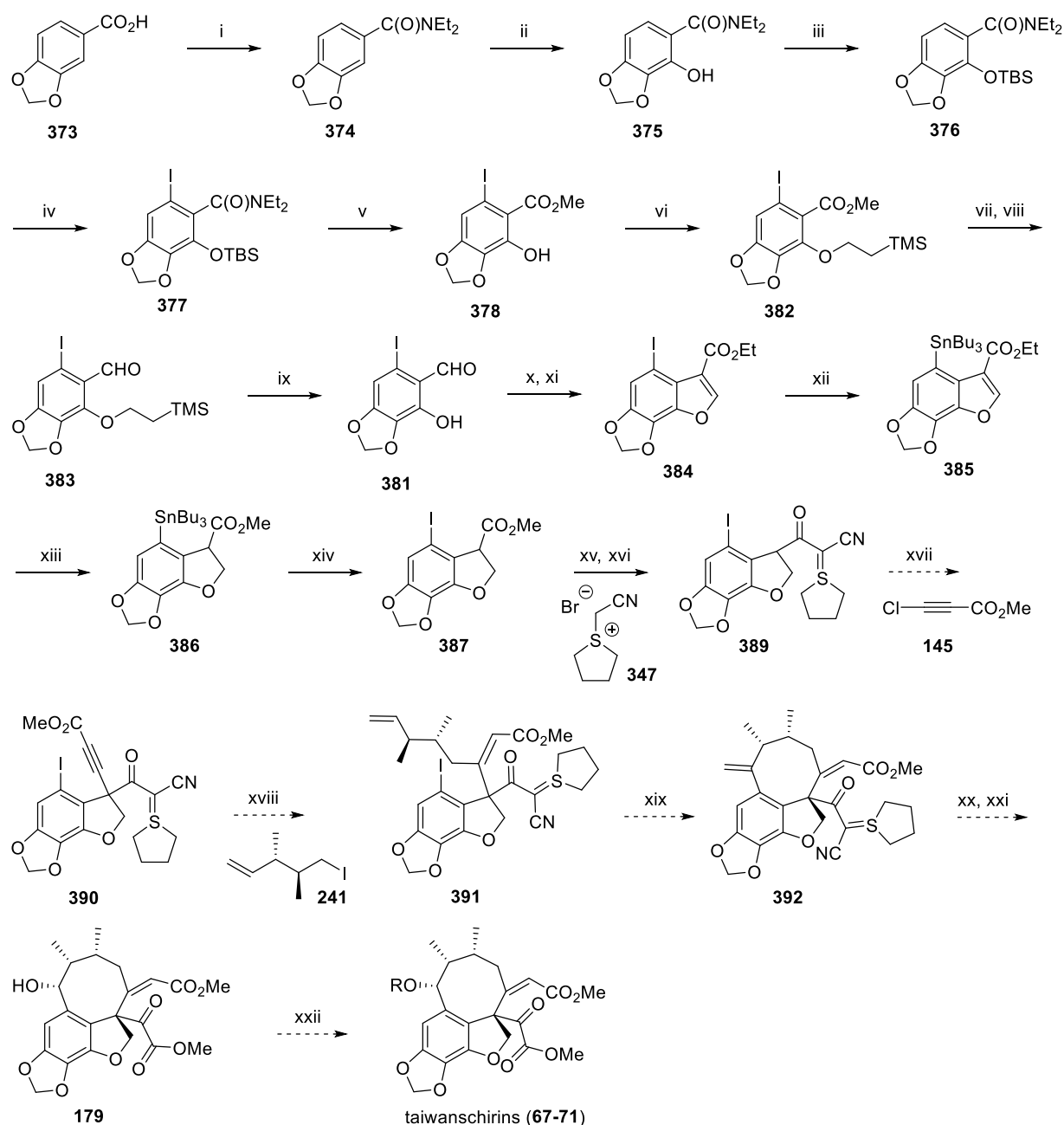
The resulting product, ylide **393**, was formed in 25% yield over 2 steps, and we could now investigate the key alkynylation reaction using this substrate. Disappointingly, however, the use of the newly synthesised ylide resulted in a complex mixture of products being formed when a reaction temperature of –40 °C was used for the initial deprotonation, followed by warming to 0 °C upon addition of the chloroacetylene electrophile **145** (Scheme 122).



Scheme 122. Reagents and conditions: i) LDA, DMF, –40 °C, 5 min, then **145**, 0 °C, 3 h

Chapter 3: Conclusion and future work

With the alkynylation step proving problematic, it was unfortunately not possible to advance with our synthesis of the taiwanschirin family. However, the plan for the completion of the total synthesis, had this stage been possible, is detailed below (Scheme 123).



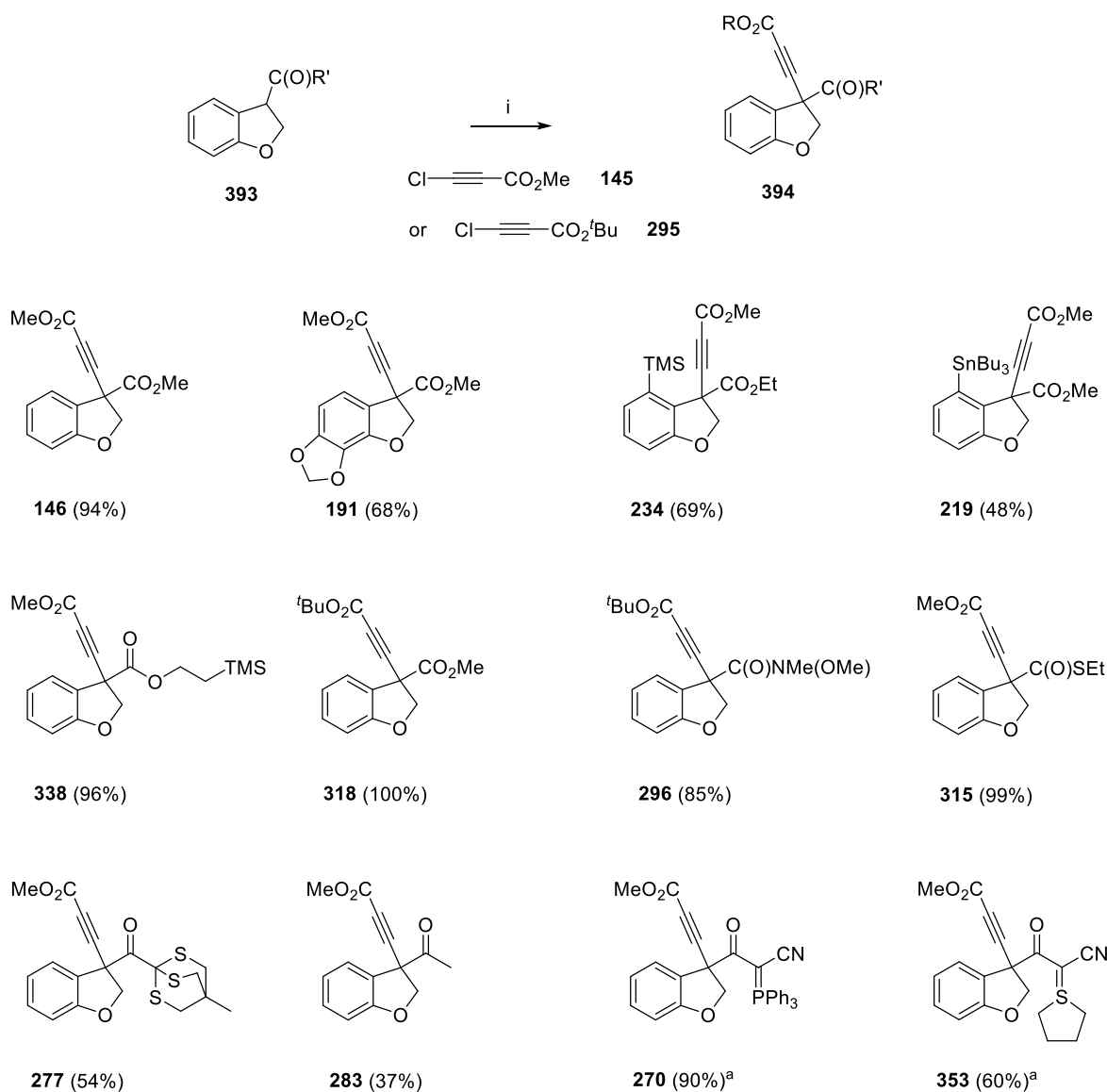
Scheme 123. Reagents and conditions: i) SOCl_2 , 90 °C, 2 h, 0 °C, diethylamine, rt, 16 h, 100%; ii) $^s\text{BuLi}$, N,N,N',N' -tetramethylethylenediamine, THF, -78 °C, 1 h, $\text{B}(\text{OMe})_3$, rt, 1 h, H_2O_2 , NaOH, rt, 16 h, 85%; iii) TBSCl, imidazole, rt, 1 h, 93%; iv) $^s\text{BuLi}$, N,N,N',N' -tetramethylethylenediamine, THF, -78 °C, 1 h, I_2 , -78 °C, 1 h, then rt, 1 h, 66%; v) $\text{Me}_3\text{OBF}_4 \cdot \text{OEt}_2$, Na_2HPO_4 , MeCN, 0 °C, then rt, 12 h, NaHCO_3 , 6 h, 87%; vi) 2-(trimethylsilyl)ethanol, DIAD, PPh_3 , THF, 0 °C – rt, 16 h, 87%; vii) DIBAL-H, $\text{CH}_2\text{Cl}_2/\text{toluene}$, -78 °C – rt, 1 h; viii) DMP, NaHCO_3 , CH_2Cl_2 , 58% over 2 steps; ix) ZnBr_2 , MeNO_2 , rt, 16 h, 91%; x) ethyl diazoacetate, $\text{HBF}_4 \cdot \text{OEt}_2$, rt, 30 min; xi) Ms_2O , pyridine, CH_2Cl_2 , rt, 16 h, 54% over 2 steps; xii) $(\text{Bu}_3\text{Sn})_2$,

20 mol% Pd₂(dba)₃, 60 mol% JohnPhos, 1,4-dioxane, 110 °C, 3.5 h, 65%; xiii) Mg, MeOH, rt, 1 h, 92%; xiv) I₂, CHCl₃, 0 °C – rt, 100%; xv) NaOH, CH₂Cl₂/MeOH (9:1), 0 °C – rt, 16 h; xvi) T3P®, DIPEA, DMAP, DMF, rt, 16 h, 37% over 2 steps; xvii) LDA, DMF, –40 °C, 5 min, then **145**, –40 °C, 30 min; xviii) **241**, ^tBuLi, pentane/Et₂O (3:2), –78 °C, 10 min, CuI, then 0 °C, 1 h, then –78 °C, **390**, 5 min; xix) 10 mol% Pd(OAc)₂, 40 mol% PPh₃, 10 eq. Et₃N, MeCN, 80 °C, 1 h; xx) O₃, CH₂Cl₂/MeOH (4:1), –78 °C, 10 min; xxi) NaBH₄, MeOH, 0 °C – rt, 1 h; xxii) R(O)Cl, py, CH₂Cl₂, 0 °C – rt, 16 h

In this sequence, the alkynylation reaction would be proceeded by the addition of a cuprate reagent derived from iodide **241**. Following a palladium–catalysed Heck cyclisation, we planned to separate the two diastereomers and retain ylide **392**. The structure of this intermediate would need to be confirmed unambiguously by X–ray crystallography, morphology permitting. However, if it were not possible to crystallise ylide **392**, it may be possible to synthesise a crystalline derivative, for example the osmate ester.¹³⁵

With ylide **392** in hand, a dual ozonolysis of the exocyclic alkene and the ylide functional groups would afford the desired ketone and methyl pyruvate. This would then be reduced to alcohol **179**, for example using NaBH₄. Finally, reaction with the appropriate acyl chloride or acid anhydride would afford the five different members of the taiwanschirin family in a highly convergent approach.

In this work, an alkynylation reaction using chloroacetylene **145** was initially developed, and the scope of this reaction was demonstrated using a large range of different enolate nucleophiles. This reaction enabled us to continue with our investigations into forming the (Z)–enone, and was a major breakthrough in this work. A summary of the different products of this newly developed enolate alkynylation reaction is presented below (Scheme 124).



Scheme 124. Reagents and conditions: i) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 5 min, then **145** or **295**, $-78\text{ }^{\circ}\text{C}$, 30 min

^aReagents and conditions: i) LiHMDS, DMF, $-40\text{ }^{\circ}\text{C}$, 5 min, then **145**, $-40\text{ }^{\circ}\text{C}$, 30 min

As shown in Scheme 124, the alkynylation reaction afforded good yields for ester substrates featuring electron donating groups including methylenedioxy (**191**), trimethylsilyl (**234**) and tributylstannyl (**219**), affording the product alkynes in 68%, 69% and 48% yields respectively. The highest yields, however, were obtained from dihydrobenzofuran esters that were not substituted on the aromatic ring, for example ester **146** and **338** obtained in 94% and 96% yields. It was also found that the alkynylation reaction could be performed with the *tert*-butyl chloroacetylene **295** to afford ester **318** and amide **296** in 100% and

85% yields. A model thioester was also found to display high reactivity, affording alkyne **315** in near quantitative yield. An unprecedented reactivity was obtained with thioether **276** to obtain alkyne **277** in 54% yield. The reaction with ketone **282** afforded alkyne **283** in 37% yield, and a high yield was obtained for cyanoketophosphorane **267** to synthesise alkyne **270** in 90% yield. Finally, cyanoketothiane **352** underwent the alkynylation reaction to afford alkyne **353** in 60% yield. This model study ultimately concluded in the successful synthesis of the pyruvate fragment of the taiwanschirin family.

With the alkynylation reaction developed, we then progressed to carry out cuprate addition reactions to form the (*Z*)-enone fragment of the taiwanschirin family. Further work established methods for macrocycle incorporation and pyruvate installation. Finally, an approach to the heterocyclic core was developed and the planned synthesis successfully completed up to step 16 inclusive. Overall, ylide **389** was synthesised in 2.4% yield over 16 steps from commercially available piperonylic acid **373**. This work describes the first studies towards a family of highly structurally complex natural products, and represents a significant advancement in this field of research.

Chapter 4: Experimental

4.1 Experimental techniques

General: All glassware was flame-dried under vacuum and reactions carried out under argon atmosphere unless otherwise noted. Compounds were named based on IUPAC guidelines using ChemDraw software and atom numbering may not be consistent with this name. This is for clarity in assignment and consistency between different classes of molecules.

Solvents and reagents: CH₂Cl₂, THF, toluene, Et₂O, acetonitrile and MeOH were dried by filtration through an activated alumina purification column under a positive pressure of nitrogen. When required, CH₂Cl₂ was degassed by bubbling an inert gas (argon or nitrogen) through the solvent for 15–30 min. All other solvents and reagents requiring purification were purified using standard laboratory techniques. Reagents obtained from commercial sources (Acros Organics, Alfa Aesar, Apollo Scientific, Fluorochem, Sigma Aldrich, TCI) were used as supplied unless otherwise stated.

Chromatography: Flash column chromatography (FCC) was performed using Merck Geduran silica gel 60 (40–63 µm). The solvent systems employed are quoted in parentheses. Reactions and column chromatography were monitored by thin layer chromatography (TLC) analysis using Merck Kieselgel 60 F254 0.25 mm precoated aluminium backed plates. Product spots were visualised under UV light (λ_{max} = 254 nm) and stained with basic potassium permanganate solution, phosphomolybdic acid solution or acidic vanillin solution as deemed appropriate for the compound.

NMR spectroscopy: ¹H and ¹³C nuclear magnetic resonance spectra (NMR) were recorded on Bruker spectrometers at 400 MHz or 500 MHz (for ¹H NMR), at 101 MHz or 126 MHz (for ¹³C NMR), at 377 MHz or 471 MHz (for ¹⁹F NMR), and at 126 MHz (for ³¹P NMR) as specified. Chemical shifts (δ) are reported relative to residual protic solvent peaks or

tetramethylsilane (TMS) internal standard and quoted in parts per million (ppm) to the nearest 0.01 ppm for ^1H NMR and 0.1 ppm for ^{13}C NMR, ^{19}F NMR and ^{31}P NMR. ^{19}F NMR and ^{31}P NMR spectra were not externally referenced. Coupling constants (J) are quoted in Hertz (Hz) to the nearest 0.1 Hz for ^1H NMR. Signal splittings are recorded as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m). Structural assignments were based on COSY, HSQC, HMBC, DEPT, and NOESY experiments.

Mass spectrometry: High resolution mass spectra (HRMS) under electrospray ionisation (ESI) or field ionisation (FI) were recorded on a Bruker MicroTof or a Thermo Exactive orbitrap spectrometer. HRMS under chemical ionisation (CI) or electron ionisation (EI) conditions were recorded on a Waters LCT Premier or an Agilent 7200 quadrupole time of flight (Q-ToF) spectrometer. HRMS under matrix assisted laser desorption/ionisation (MALDI) were recorded on a Waters MALDI micro MX spectrometer. Masses are reported as a ratio of mass to charge in Daltons and are given to four decimal places.

Infrared spectroscopy: Fourier transformation infrared spectra (FTIR) were recorded on a Bruker Tensor 27 FT-IR spectrometer equipped with Attenuated Total Reflectance sampling accessory as evaporated films or powders. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Polarimetry: Specific optical rotations were recorded on a Schmidt-Haensch UniPol 2000 polarimeter at the sodium D line ($\lambda = 589.3 \text{ nm}$) in CHCl_3 and are quoted in the units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Solution concentrations are given in units of $10^{-2} \text{ g mL}^{-1}$.

Melting points: Melting points (m.p.) were obtained using a Leica VMTG heated stage microscope and are uncorrected.

4.2 General procedures

General Procedure A: reaction of ester **87** with electrophiles

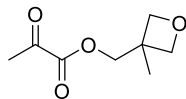
To a stirred solution of ester **87** (1.0 eq.) in THF (8.8 mL mmol⁻¹) at -78 °C was added LHMDS (1 M in THF, 1.2 eq.). After 30 min the electrophile (2.0 eq.) was added dropwise and the reaction mixture was stirred at -78 °C for 3 h. Sat. aq. NH₄Cl (3 mL) was added and the mixture extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over Mg₂SO₄ and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound.

General Procedure B: arylation and vinylation using NaHMDS^{24,27}

To a stirred solution of NaHMDS (0.6 M in toluene, 2.5 eq.) and additional toluene (0.25 mL) at 0 °C was added ester **8** (1.0 eq.) in toluene (3.3 mL mmol⁻¹). After 20 min [P^tBu₃PdBr]₂ (0.025 eq.) was added followed by the electrophile (1.5 eq.) in toluene (2.2 mL mmol⁻¹). The reaction mixture was stirred at rt for the stated time. Sat. aq. NH₄Cl (2 mL) was added and the mixture extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over Mg₂SO₄ and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound.

4.3 Experimental details

(3-Methyloxetan-3-yl)methyl 2-oxopropanoate (2)⁶



2

To a solution of pyruvic acid (13.9 mL, 200 mmol) and DMF (310 μ L, 4.00 mmol) in CH_2Cl_2 (400 mL) was added dropwise oxalyl chloride (18.6 mL, 220 mmol) over 1 h. The solution was stirred for 3 h at rt before being cooled to -40°C . A solution of 3-oxetanemethanol (19.9 mL, 200 mmol) in pyridine (40.0 mL, 500 mmol) was added dropwise over 30 min and the reaction mixture warmed to rt. After 1 h HCl (6 M aq., 100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×200 mL). The combined organic phase was washed with brine (200 mL), dried over MgSO_4 and concentrated *in vacuo*. Distillation of the residue (bp 124°C , 25 mbar) afforded the title compound as a colourless oil (23.1 g, 67%).

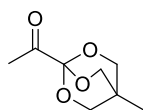
$R_f = 0.4$ (Et_2O).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) $\delta = 4.48$ (2H, d, $J = 6.2$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{OCH}_\text{A}\text{H}_\text{B}$), 4.38 (2H, d, $J = 6.2$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{OCH}_\text{A}\text{H}_\text{B}$), 4.32 (2H, s, CO_2CH_2), 2.44 (3H, s, $\text{CH}_3\text{C}(\text{O})$), 1.33 (3H, s, CCH_3).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) $\delta = 191.2$ ($\text{C}(\text{O})\text{CO}_2$), 160.8 ($\text{C}(\text{O})\text{CO}_2$), 79.4 (CH_2OCH_2), 70.5 (CO_2CH_2), 39.2 (CCH_3), 26.8 ($\text{CH}_3\text{C}(\text{O})$), 21.0 (CCH_3).

Analytical data are in accordance with those previously reported for this compound.⁶

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (5)⁶



5

To a solution of pyruvate **2** (8.76 g, 50.9 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added BF₃·OEt₂ (1.88 mL, 15.3 mmol) over 10 min. The reaction mixture was stirred at 0 °C for 16 h and Et₃N (2.10 mL, 15.3 mmol) was added. The solution was concentrated *in vacuo* and the crude product filtered through a pad of silica using CH₂Cl₂ as the eluent to afford the title compound as a white solid (2.43 g, 28%).

*R*_f = 0.2 (CH₂Cl₂).

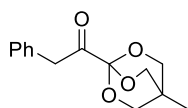
m.p. 109 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 3.98 (6H, s, OCH₂ × 3), 2.24 (3H, s, CH₃C(O)), 0.84 (3H, s, (CH₃C)).

¹³C NMR (CDCl₃, 101 MHz) δ = 196.6 (CH₃C(O)), 103.5 (CO₃), 73.2 (OCH₂ × 3), 31.0 (CH₃C), 24.6 (CH₃C(O)), 14.3 (CH₃C).

Analytical data are in accordance with those previously reported for this compound.⁶

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-phenylethan-1-one (18)⁶



18

To a solution of OBO ketone **5** (1.38 g, 8.00 mmol), Pd(dtbpf)Cl₂ (261 mg, 400 μ mol) and bromobenzene (927 μ L, 8.8 mmol) in THF (70 mL) was added NaO^tBu (2 M THF, 10.0 mL). The reaction mixture was heated at 50 °C for 24 h before sat. aq. NH₄Cl (20 mL) was added. The mixture was diluted with Et₂O (50 mL) and the layers separated. The aqueous layer was

extracted with Et₂O (3 × 60 mL), and the combined organic phase was washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 70:30 to 50:50) afforded the title compound as a white solid (1.43 g, 72%).

R_f = 0.2 (Pentane:EtOAc, 70:30).

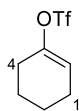
m.p. 116 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 7.35 – 7.14 (5H, m, ArH × 5), 4.03 (6H, s, OCH₂ × 3), 3.97 (2H, s, CH₂), 0.87 (3H, s, CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 195.7 (CH₃C(O)), 133.5 (C_{Ar}), 130.0 (C_{Ar}H × 2), 128.5 (C_{Ar}H × 2), 127.0 (C_{Ar}H), 103.9 (CO₃), 73.2 (OCH₂ × 3), 43.2 (CH₂), 31.1 (CH₃C), 14.3 (CH₃C).

Analytical data are in accordance with those previously reported for this compound.⁶

Cyclohex-1-en-1-yl trifluoromethanesulfonate (**83**)⁴¹



83

To a solution of cyclohexanone **94** (1.04 mL, 10.0 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added NaH (480 mg, 12.0 mmol, 60 wt% in mineral oil). After 30 min, Tf₂O (2.02 mL, 12.0 mmol) was added dropwise and the reaction mixture was stirred at rt for 2 h. Sat. aq. NH₄Cl (20 mL) was added and the mixture extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 99:1) afforded the title compound as a colourless oil (2.02 g, 88%).

$R_f = 0.2$ (Pentane:Et₂O, 99:1).

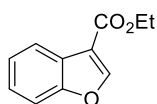
¹H NMR (CDCl₃, 400 MHz) δ = 5.75 (1H, t, J = 4.1 Hz, C=CH), 2.36 – 2.27 (2H, m, C(4)H₂), 2.23 – 2.12 (2H, m, C(1)H₂), 1.84 – 1.71 (2H, m, C(3)H₂), 1.65 – 1.52 (2H, m, C(2)H₂).

¹³C NMR (CDCl₃, 101 MHz) δ = 149.5 (C=CH), 118.7 (q, J = 320.1 Hz, CF₃), 118.6 (C=CH), 27.7 (C4), 24.0 (C1), 22.8 (C3), 21.1 (C2).

¹⁹F NMR (CDCl₃, 377 MHz) δ = –74.1.

Analytical data are in accordance with those previously reported for this compound.¹³⁶

Ethyl benzofuran-3-carboxylate (**86**)³⁶



86

To a solution of salicylaldehyde **85** (6.10 g, 50.0 mmol) and HBF₄·OEt₂ (680 μ L, 5.00 mmol) in CH₂Cl₂ (12 mL) at 0 °C was added dropwise a solution of ethyl diazoacetate (8.42 mL, 80 mmol) in CH₂Cl₂ (80 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 30 min and then concentrated *in vacuo*. After nitrogen evolution had ceased, conc. H₂SO₄ (3.00 mL) was added and the reaction mixture was stirred at room temperature for 30 min. CH₂Cl₂ (100 mL) was added followed by solid NaHCO₃ until gas evolution had ceased. The solution was washed successively with water (50 mL), 1 M aq. NaOH (50 mL) and sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil (8.05 g, 85%).

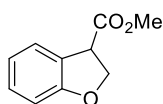
$R_f = 0.2$ (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 8.26 (1H, s, ArH), 8.07 (1H, ddd, J = 6.0, 3.2, 0.7 Hz, ArH), 7.60 – 7.47 (1H, m, ArH), 7.42 – 7.30 (2H, m, ArH $\times$ 2), 4.41 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 1.43 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 163.5 (CO₂CH₂CH₃), 155.7 (C_{Ar}), 151.0 (C_{Ar}H), 125.3 (C_{Ar}H), 124.7 (C_{Ar}), 124.2 (C_{Ar}H), 122.1 (C_{Ar}H), 114.8 (C_{Ar}), 111.8 (C_{Ar}H), 60.7 (CO₂CH₂CH₃), 14.5 (CO₂CH₂CH₃).

Analytical data are in accordance with those previously reported for this compound.³⁶

Methyl 2,3-dihydrobenzofuran-3-carboxylate (**87**)¹³⁷



87

Mg turnings (1.96 g, 80.7 mmol) were added to a solution of ester **86** (3.07 g, 16.1 mmol) in MeOH (107 mL). After 1 h the reaction mixture was evaporated to dryness and re-dissolved in CH₂Cl₂ (200 mL). The solution was washed successively with sat. aq. NH₄Cl (100 mL), sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil (2.01 g, 70%).

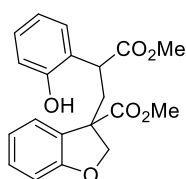
$R_f = 0.25$ (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 7.38 (1H, dt, J = 7.4, 1.3 Hz, ArH), 7.23 – 7.14 (1H, m, ArH), 6.89 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.86 – 6.80 (1H, m, ArH), 4.93 (1H, dd, J = 9.2, 6.6 Hz, CH_AH_B), 4.66 (1H, t, J = 9.2 Hz, CH_AH_B), 4.34 (1H, dd, J = 9.7, 6.5 Hz, CH), 3.78 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 171.7 (CO₂CH₃), 159.9 (C_{Ar}), 129.5 (C_{Ar}H), 125.4 (C_{Ar}H), 124.2 (C_{Ar}), 120.7 (C_{Ar}H), 110.0 (C_{Ar}H), 72.5 (CH_AH_B), 52.6 (CO₂CH₃), 47.2 (CH).

Analytical data are in accordance with those previously reported for this compound.¹³⁷

Methyl 3-(2-(2-hydroxyphenyl)-3-methoxy-3-oxopropyl)-2,3-dihydrobenzofuran-3-carboxylate (95)



95

To a stirred solution of NaO^tBu (375 μ L, 750 μ mol, 2 M in THF) and additional THF (2.5 mL) at 0 °C was added ester **87** (54 mg, 300 μ mol) in THF (1 mL). The reaction mixture was stirred at 0 °C for 15 min. Sat. aq. NH₄Cl (2 mL) was added and the mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound as a colourless oil (53 mg, 99%, 1.7:1 dr).

R_f = 0.2 (Pentane:Et₂O, 60:40).

IR (film) ν_{max} /cm⁻¹ 3417, 2953, 1802, 1733, 1596, 1506, 1480, 1233, 753.

HRMS: (CI⁺) Found [M⁺] = 357.1334, C₂₀H₂₁O₆ requires 357.1333.

Major Diastereomer

¹H NMR (CDCl₃, 400 MHz) δ = 7.31 – 7.27 (1H, m, ArH), 7.18 (1H, s, OH), 7.14 – 7.04 (2H, m, ArH $\times$ 2), 6.91 (1H, d, *J* = 8.0 Hz, ArH), 6.85 – 6.77 (3H, m, ArH $\times$ 3), 6.69 (1H, d, *J* = 8.1 Hz, ArH), 4.59 (1H, d, *J* = 9.6 Hz, OCH_AH_B), 3.99 (1H, d, *J* = 9.5 Hz, OCH_AH_B),

3.84 – 3.76 (1H, m, CH), 3.64 (3H, s, CO₂CH₃), 3.62 (3H, s, CO₂CH₃), 2.99 (1H, dd, *J* = 14.3, 6.4 Hz, CH_AH_B), 2.39 (1H, dd, *J* = 14.2, 7.8 Hz, CH_AH_B).

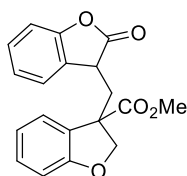
¹³C NMR (CDCl₃, 101 MHz) δ = 175.9 (CO₂CH₃), 173.1 (CO₂CH₃), 159.3 (C_{Ar}), 154.6 (C_{Ar}), 130.0 (C_{Ar}H), 129.9 (C_{Ar}H), 129.6 (C_{Ar}H), 128.2 (C_{Ar}), 124.9 (C_{Ar}H), 124.0 (C_{Ar}), 121.2 (C_{Ar}H), 120.9 (C_{Ar}H), 117.9 (C_{Ar}H), 110.2 (C_{Ar}H), 77.6 (OCH_AH_B), 56.0 (C_{Ar}C), 53.0 (CO₂CH₃), 52.9 (CO₂CH₃), 45.2 (CH), 39.3 (CH_AH_B).

Minor Diastereomer

¹H NMR (CDCl₃, 400 MHz) δ = 7.32 – 7.26 (1H, m, ArH), 7.15 – 7.04 (2H, m, ArH $\times$ 2), 6.98 (1H, d, *J* = 7.6 Hz, ArH), 6.85 – 6.76 (3H, m, ArH $\times$ 2), 6.76 – 6.72 (1H, m, ArH), 5.02 (1H, d, *J* = 9.5 Hz, OCH_AH_B), 4.39 (1H, d, *J* = 9.5 Hz, OCH_AH_B), 3.78 – 3.72 (1H, m, CH), 3.49 (3H, s, CO₂CH₃), 3.41 (3H, s, CO₂CH₃), 2.77 (1H, dd, *J* = 14.5, 7.3 Hz, CH_AH_B), 2.61 (1H, dd, *J* = 14.3, 6.4 Hz, CH_AH_B).

¹³C NMR (CDCl₃, 101 MHz) δ = 176.0 (CO₂CH₃), 172.8 (CO₂CH₃), 159.6 (C_{Ar}), 154.7 (C_{Ar}), 130.0 (C_{Ar}H), 129.9 (C_{Ar}H), 129.4 (C_{Ar}H), 127.6 (C_{Ar}), 125.5 (C_{Ar}H), 123.9 (C_{Ar}), 121.0 (C_{Ar}H), 120.9 (C_{Ar}H), 117.8 (C_{Ar}H), 110.3 (C_{Ar}H), 77.1 (OCH_AH_B), 55.8 (C_{Ar}C), 52.9 (CO₂CH₃), 52.8 (CO₂CH₃), 44.4 (CH), 39.4 (CH_AH_B).

Methyl 3-((2-oxo-2,3-dihydrobenzofuran-3-yl)methyl)-2,3-dihydrobenzofuran-3-carboxylate (96)



96

To a stirred solution of LiHMDS (750 μ L, 750 μ mol, 1 M in THF) and additional THF (0.75 mL) at 0 °C was added ester **87** (54 mg, 300 μ mol) in THF (1 mL). After 20 min

[P^tBu₃PdBr]₂ (5.8 mg, 7.5 μmol) was added followed by triflate **97** (102 mg, 450 μmol) in THF (1 mL). The reaction mixture was stirred at 0 °C for 2 h. Sat. aq. NH₄Cl (2 mL) was added and the mixture extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound as a colourless oil (19 mg, 38%, 1:1 dr). The two diastereomers were indistinguishable by ¹H NMR so are quoted here together.

R_f = 0.4 (Pentane:Et₂O, 60:40).

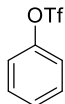
¹H NMR (CDCl₃, 500 MHz) δ = 7.33 (1H, dd, *J* = 7.6, 1.4 Hz, Ar*H*), 7.31 – 7.27 (1H, m, Ar*H*), 7.25 – 7.19 (2H, m, Ar*H* × 2), 7.17 – 7.12 (2H, m, Ar*H* × 2), 7.07 – 7.03 (2H, m, Ar*H* × 2), 7.03 – 6.98 (3H, m, Ar*H* × 3), 6.90 – 6.82 (3H, m, Ar*H* × 3), 6.78 (2H, d, *J* = 7.9 Hz, Ar*H* × 2), 5.15 (1H, d, *J* = 9.7 Hz, OCH_AH_B), 4.98 (1H, d, *J* = 9.6 Hz, OCH_AH_B), 4.66 (1H, d, *J* = 9.8 Hz, OCH_AH_B), 4.53 (1H, d, *J* = 9.6 Hz, OCH_AH_B), 3.76 – 3.72 (1H, m, CH), 3.71 (3H, s, CO₂CH₃), 3.66 (3H, s, CO₂CH₃), 3.61 (1H, t, *J* = 5.9 Hz, CH), 2.79 (1H, dd, *J* = 14.6, 7.2 Hz, CH_AH_B), 2.68 (1H, dd, *J* = 14.6, 4.9 Hz, CH_AH_B), 2.41 (2H, ddd, *J* = 14.6, 6.7, 1.1 Hz, CH_AH_B × 2).

¹³C NMR (CDCl₃, 126 MHz) δ = 176.8 (CO₂C_{Ar}), 176.8 (CO₂C_{Ar}), 172.7 (CO₂CH₃), 172.5 (CO₂CH₃), 159.7 (C_{Ar}), 159.6 (C_{Ar}), 153.5 (C_{Ar}), 153.5 (C_{Ar}), 130.2 (C_{Ar}H), 130.1 (C_{Ar}H), 129.6 (C_{Ar}H), 129.1 (C_{Ar}H), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (C_{Ar}), 124.7 (C_{Ar}H), 124.4 (C_{Ar}H), 124.4 (C_{Ar}H), 124.3 (C_{Ar}H), 124.2 (C_{Ar}H), 121.1 (C_{Ar}H), 121.0 (C_{Ar}H), 115.3 (C_{Ar}H), 110.8 (C_{Ar}H), 110.8 (C_{Ar}H), 110.5 (C_{Ar}H), 110.4 (C_{Ar}H), 78.6 (OCH_AH_B), 78.6 (OCH_AH_B), 56.0 (C_{Ar}C), 55.4 (C_{Ar}C), 53.0 (CO₂CH₃), 52.9 (CO₂CH₃), 40.6 (CH), 39.9 (CH), 39.5 (CH_AH_B), 39.4 (CH_AH_B).

IR (film) ν_{max}/cm⁻¹ 2954, 1802, 1732, 1596, 1480, 1462, 1232, 1128, 753.

HRMS: (EI⁺) Found [M⁺] = 324.1001; C₁₉H₁₆O₅ requires 324.0992.

Phenyl trifluoromethanesulfonate (97)¹³⁸



97

To a solution of phenol (2.35 g, 25 mmol) in CH₂Cl₂ (25 mL) at 0 °C was added pyridine (4.00 mL, 50 mmol). Tf₂O (5.05 mL, 30 mmol) in CH₂Cl₂ (10 mL) was added dropwise and the reaction mixture stirred at rt for 4 h. HCl (1 M aq., 10 mL) was added and the layers separated. The organic layer was washed with sat. aq. NaHCO₃ (20 mL), brine (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane) afforded the title compound as a colourless oil (5.06 g, 90%).

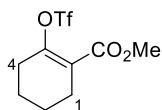
R_f = 0.4 (Pentane).

¹H NMR (CDCl₃, 400 MHz) δ = 7.52 – 7.45 (2H, m, ArH $\times$ 2), 7.45 – 7.39 (1H, m, ArH), 7.34 – 7.27 (2H, m, ArH $\times$ 2).

¹³C NMR (CDCl₃, 101 MHz) δ = 149.8 (C_{Ar}), 130.4 (C_{Ar}H $\times$ 2), 128.5 (C_{Ar}H), 121.5 (C_{Ar}H $\times$ 2), 118.9 (q, *J* = 320.7 Hz, CF₃)

¹⁹F NMR (CDCl₃, 377 MHz) δ = –73.0.

Analytical data are in accordance with those previously reported for this compound.¹³⁸

Methyl 2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (101)⁴¹**101**

To a solution of NaH (1.77 g, 43.3 mmol, 60 wt% in mineral oil) in 1,4-dioxane (20 mL), was added dropwise a solution of cyclohexanone (1.93 mL, 18.8 mmol) in 1,4-dioxane (5 mL). The reaction mixture was heated at 130 °C for 2 h then cooled to rt and water (50 mL) and Et₂O (50 mL) were added and the layers separated. The aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was passed through a pad of Celite[®] using (Pentane:Et₂O, 80:20) as the eluent, and concentrated *in vacuo*. To the crude product (2.03 g, 13.0 mmol) in CH₂Cl₂ (65 mL) at 0 °C was added NaH (624 mg, 15.6 mmol, 60 wt% in mineral oil). After 45 min, Tf₂O (2.62 mL, 15.6 mmol) was added dropwise and the reaction mixture was stirred at rt for 2 h. Sat. aq. NH₄Cl (20 mL) was added and the mixture extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil (2.79 g, 51% over 2 steps).

*R*_f = 0.3 (Pentane:Et₂O, 90:10).

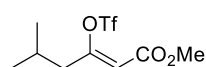
¹H NMR (CDCl₃, 400 MHz) δ = 3.80 (3H, s, CO₂CH₃), 2.47 (2H, tt, *J* = 5.9, 2.6 Hz, C(1)H₂), 2.40 (2H, ddd, *J* = 8.9, 6.0, 2.5 Hz, C(4)H₂), 1.84 – 1.73 (2H, m, C(2)H₂), 1.72 – 1.61 (2H, m, C(3)H₂).

¹³C NMR (CDCl₃, 101 MHz) δ = 165.3 (CO₂CH₃), 151.9 (C=CCO₂CH₃), 123.0 (C=CCO₂CH₃), 118.5 (q, J = 319.6 Hz, CF₃), 52.3 (CO₂CH₃), 28.7 (C₄), 26.2 (C₁), 22.4 (C₂), 21.1 (C₃).

¹⁹F NMR (CDCl₃, 377 MHz) δ = -74.8.

Analytical data are in accordance with those previously reported for this compound.⁴¹

Methyl (Z)-5-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hex-2-enoate (103)⁴²



103

To a solution of methyl 5-methyl-3-oxohexanoate (2.37 g, 15 mmol) in CH₂Cl₂ (30 mL) was added LiOTf (4.68 g, 30.0 mmol). The solution was cooled to 0 °C and Et₂N^{*i*}Pr (2.87 mL, 16.5 mmol) was added dropwise over 10 min. After 20 min, Tf₂O (2.78 mL, 16.5 mmol) was added dropwise over 30 min and the reaction mixture was stirred for 1 h at 0 °C. Sat. aq. NH₄Cl (20 mL) was added and the mixture extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was washed successively with HCl (1 M aq., 2 × 30 mL), water (30 mL) and brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Et₂O (50 mL) was added to the resulting semisolid and the solution filtered and washed with further Et₂O to obtain the crude product as a pale yellow oil. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 93:7) afforded the title compound as a colourless oil (3.47 g, 80%).

R_f = 0.4 (Pentane:Et₂O, 80:20).

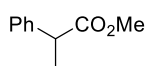
¹H NMR (CDCl₃, 400 MHz) δ = 5.74 (1H, s, C=CH), 3.77 (3H, s, CO₂CH₃), 2.24 (2H, d, J = 7.2 Hz, CH₂), 1.95 (1H, dt, J = 13.6, 6.8 Hz, CH(CH₃)₂), 0.96 (6H, d, J = 6.6 Hz, CH(CH₃)₂).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 162.9 (CO_2CH_3), 158.4 (COSO_2CF_3), 118.5 (q, J = 319.9 Hz, CF_3), 112.5 ($\text{C}=\text{CH}$), 52.1 (CO_2CH_3), 43.8 (CH_2), 25.9 ($\text{CH}(\text{CH}_3)_2$), 22.0 ($\text{CH}(\text{CH}_3)_2$).

^{19}F NMR (CDCl_3 , 377 MHz) δ = -74.8 .

Analytical data are in accordance with those previously reported for this compound.⁴²

Methyl 2-phenylpropanoate (104)



104

To a solution of LiHMDS (3.01 g, 18.0 mmol) in THF (75 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise methyl phenylacetate (2.11 mL, 15.0 mmol). After 30 min methyl iodide (1.87 mL, 30.0 mmol) was added dropwise and the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 3 min, then rt for 1 h. Sat. aq. NH_4Cl (20 mL) was added and the mixture extracted with Et_2O ($3 \times 50\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 97:3) afforded the title compound as a colourless oil (2.27 g, 92%).

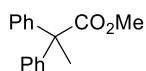
R_f = 0.5 (Pentane: Et_2O , 80:20).

^1H NMR (CDCl_3 , 400 MHz) δ = 7.24 – 7.07 (5H, m, $\text{ArH} \times 5$), 3.59 (1H, q, J = 7.1 Hz, CH), 3.52 (3H, d, J = 1.1 Hz, CO_2CH_3), 1.37 (3H, d, J = 7.2, CH_3).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 175.1 (CO_2CH_3), 140.6 (C_{Ar}), 128.7 ($\text{C}_{\text{ArH}} \times 2$), 127.6 ($\text{C}_{\text{ArH}} \times 2$), 127.2 (C_{ArH}), 52.1 (CO_2CH_3), 45.5 (CH), 18.7 (CH_3).

Analytical data are in accordance with those previously reported for this compound.¹³⁹

Methyl 2,2-diphenylpropanoate (**107**)



107

Ester **104** (49 mg, 300 μ mol) and bromobenzene (71 mg, 450 μ mol) were subjected to general procedure B and stirred at rt for 16 h. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil (34 mg, 47%).

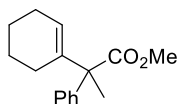
R_f = 0.5 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 7.34 – 7.19 (10H, m, ArH $\times$ 10), 3.74 (3H, s, CO₂CH₃), 1.94 (3H, s, CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 175.8 (CO₂CH₃), 144.5 (C_{Ar} $\times$ 2), 128.2 (C_{ArH} $\times$ 4), 128.1 (C_{ArH} $\times$ 4), 127.0 (C_{ArH} $\times$ 2), 56.7 (C(CH₃)), 52.6 (CO₂CH₃), 27.3 (C(CH₃)).

Analytical data are in accordance with those previously reported for this compound.¹⁴⁰

Methyl 2-(cyclohex-1-en-1-yl)-2-phenylpropanoate (**108**)



108

Ester **104** (49 mg, 300 μ mol) and triflate **83** (104 mg, 450 μ mol) were subjected to general procedure B and stirred at rt for 16 h. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 96:4) afforded an inseparable 3:2 mixture of the title compound and ester **104** as a colourless oil (15 mg, 14%).

R_f = 0.5 (Pentane:Et₂O, 80:20).

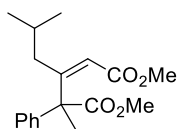
¹H NMR (CDCl₃, 500 MHz) δ = 7.37 – 7.20 (5H, m, ArH $\times$ 5), 5.49 – 5.45 (1H, m, C=CH), 3.70 (3H, s, CO₂CH₃), 2.15 – 2.09 (2H, m, C(4)H₂), 1.93 – 1.86 (2H, m, C(3)H₂), 1.68 (3H, s, CH₃), 1.64 – 1.60 (2H, m, C(2)H₂), 1.59 – 1.57 (2H, m, C(1)H₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 177.4 (CO₂CH₃), 144.8 (C_{Ar}), 143.1 (C=CH), 126.8 (C_{Ar}H), 126.7 (C_{Ar}H $\times$ 2), 125.7 (C_{Ar}H $\times$ 2), 124.4 (C=CH), 57.6 (CCH₃), 52.3 (CO₂CH₃), 26.5 (C3), 25.7 (C4), 24.2 (CCH₃), 23.3 (C2), 22.3 (C1).

IR (film) ν_{max} /cm⁻¹ 2930, 1730, 1447, 1238, 1147, 699.

HRMS: (APCI⁺) Found [M + H]⁺ = 245.1536; C₁₆H₂₁O₂ requires 245.1536.

Dimethyl (Z)-3-isobutyl-4-methyl-4-phenylpent-2-enedioate (**109**)



109

Ester **104** (49 mg, 300 μ mol) and triflate **103** (131 mg, 450 μ mol) were subjected to general procedure B and stirred at rt for 16 h. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil (49 mg, 53%).

R_f = 0.2 (Pentane:Et₂O, 95:5).

¹H NMR (CDCl₃, 500 MHz) δ = 7.35 – 7.27 (4H, m, ArH $\times$ 4), 7.26 – 7.23 (1H, m, ArH), 5.68 (1H, s, C=CH), 3.74 (3H, s, CO₂CH₃), 3.66 (3H, s, CHCO₂CH₃), 2.66 (2H, dd, J = 7.4, 4.3 Hz, CH₂), 1.77 (3H, s, CH₃), 1.68 – 1.53 (1H, m, CH(CH₃)₂), 0.85 (6H, dd, J = 6.6, 1.3 Hz, CH(CH₃)₂).

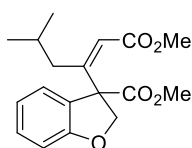
¹³C NMR (CDCl₃, 126 MHz) δ = 174.5 (CO₂CH₃), 167.3 (CHCO₂CH₃), 161.8 (C=CH), 142.4 (C_{Ar}), 128.3 (C_{Ar}H $\times$ 2), 128.0 (C_{Ar}H $\times$ 2), 127.3 (C_{Ar}H), 121.3 (C=CH), 59.3 (CCH₃).

52.6 (CO₂CH₃ or CHCO₂CH₃), 51.2 (CO₂CH₃ or CHCO₂CH₃), 38.5 (CH₂), 28.4 (CH(CH₃)₂), 25.1 (CH₃), 22.3 (CH(CH₃)₂).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 1723, 1632, 1459, 1234, 1197, 1156, 700.

HRMS: (APCI⁺) Found [M + H]⁺ = 305.1747; C₁₈H₂₅O₄ requires 305.1747.

Methyl (Z)-3-(1-methoxy-5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (110)



110

To a solution of CuI (76 mg, 400 μmol) in THF (1.5 mL) at -78°C was added *i*BuLi (470 μL , 800 μmol , 1.7 M in hexane). The mixture was stirred vigorously at 0°C for 1 h before being cooled to -78°C . A solution of alkyne **146** (52 mg, 200 μmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78°C for 3 h. Sat. aq. NH₄Cl (2 mL) was added and the mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil and a single diastereomer (58 mg, 91%).

R_f = 0.3 (Pentane:Et₂O, 70:30).

¹H NMR (CDCl₃, 500 MHz) δ = 7.24 – 7.16 (2H, m, ArH $\times$ 2), 6.86 (1H, td, *J* = 7.6, 1.1 Hz, ArH), 6.82 (1H, d, *J* = 8.1 Hz, ArH), 5.83 (1H, s, C=CH), 5.60 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.40 (1H, d, *J* = 9.8 Hz, CH_AH_B), 3.68 (3H, s, CO₂CH₃), 3.68 (3H, s, CO₂CH₃), 2.15 (1H, ddd, *J* = 14.2, 5.1, 1.2 Hz, C=CCH_AH_B), 1.83 (1H, ddd, *J* = 14.2, 8.6, 1.1 Hz,

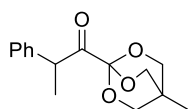
C=CCH_AH_B), 1.36 – 1.22 (1H, m, CH(CH₃)_A(CH₃)_B), 0.76 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.61 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.8 (CO₂CH₃), 166.6 (CO₂CH₃), 161.6 (C=CH), 160.9 (C_{Ar}), 130.3 (C_{Ar}H), 126.4 (C_{Ar}), 126.0 (C_{Ar}H), 120.4 (C_{Ar}H), 118.3 (C=CH), 110.5 (C_{Ar}H), 82.4 (CH_AH_B), 61.6 (C_{Ar}C), 52.9 (CO₂CH₃), 51.5 (CO₂CH₃), 47.1 (C=CCH_AH_B), 26.0 (CH(CH₃)_A(CH₃)_B), 22.8 (CH(CH₃)_A(CH₃)_B), 21.6 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2955, 1735, 1715, 1481, 1234, 975, 753.

HRMS: (ESI⁺) Found [M + H]⁺ = 319.1534; C₁₈H₂₃O₅ requires 319.1540.

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-phenylpropan-1-one (111)



111

To a solution of LiHMDS (1 M in THF, 2.40 mL, 2.40 mmol) in THF (7.6 mL) at –78°C was added dropwise ketone **18** (497 mg, 2.00 mmol) in THF (3.0 mL). The reaction mixture was stirred for 30 min at –78°C before MeI (250 μ L, 4.00 mmol) was added. After a further 30 min at –78°C, the reaction was stirred at rt for 16 h before sat. aq. NH₄Cl (20 mL) was added. The mixture was diluted with Et₂O (20 mL) and the layers separated. The aqueous layer was extracted with Et₂O (3 $\times$ 60 mL), and the combined organic phase was washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 70:30) afforded the title compound as a white solid (393 mg, 75%).

R_f = 0.3 (Pentane:EtOAc, 70:30).

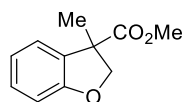
m.p. 77 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 7.21 – 7.17 (4H, m, ArH $\times$ 4), 7.16 – 7.09 (1H, m, ArH), 4.32 (1H, q, J = 7.1 Hz, CH), 3.86 (6H, s, OCH₂ $\times$ 3), 1.35 (3H, d, J = 7.1 Hz, CHCH₃), 0.74 (3H, s, CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 199.0 (CH₃C(O)), 140.2 (C_{Ar}), 128.5 (C_{Ar}H $\times$ 2), 128.3 (C_{Ar}H $\times$ 2), 126.9 (C_{Ar}H), 104.2 (CO₃), 73.1 (OCH₂ $\times$ 3), 46.1 (CH), 31.0 (CH₃C), 19.2 (CHCH₃), 14.4 (CH₃C).

Analytical data are in accordance with those previously reported for this compound.⁶

Methyl 3-methyl-2,3-dihydrobenzofuran-3-carboxylate (114)



114

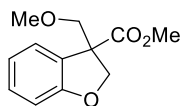
Ester **87** (54 mg, 300 μ mol) and methyl iodide (37 μ L, 600 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil (50 mg, 87%).

R_f = 0.4 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 7.32 (1H, d, J = 7.5 Hz, ArH), 7.19 (1H, t, J = 7.7 Hz, ArH), 6.91 (1H, t, J = 7.5 Hz, ArH), 6.82 (1H, d, J = 8.0 Hz, ArH), 5.07 (1H, d, J = 9.1 Hz, CH_AH_B), 4.26 (1H, d, J = 9.1 Hz, CH_AH_B), 3.73 (3H, s, CO₂CH₃), 1.62 (3H, s, CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 174.3 (CO₂CH₃), 159.5 (C_{Ar}), 130.8 (C_{Ar}), 129.4 (C_{Ar}H), 124.4 (C_{Ar}H), 120.9 (C_{Ar}H), 110.1 (C_{Ar}H), 80.1 (CH_AH_B), 52.8 (CO₂CH₃), 52.4 (C_{Ar}C), 24.6 (CH₃).

Analytical data are in accordance with those previously reported for this compound.¹⁴¹

Methyl 3-(methoxymethyl)-2,3-dihydrobenzofuran-3-carboxylate (115)**115**

Ester **87** (54 mg, 300 μmol) and iodomethyl methyl ether (55 μL , 600 μmol) were subjected to general procedure A. Purification by flash column chromatography (SiO_2 , Pentane: CH_2Cl_2 , 50:50 to 0:100) afforded the title compound as a colourless oil (51 mg, 76%).

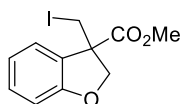
$R_f = 0.4$ (Pentane: CH_2Cl_2 , 50:50).

^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.34$ (1H, d, $J = 7.5$ Hz, ArH), 7.20 (1H, t, $J = 7.8$ Hz, ArH), 6.88 (1H, t, $J = 7.5$ Hz, ArH), 6.82 (1H, d, $J = 8.1$ Hz, ArH), 5.09 (1H, d, $J = 9.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.60 (1H, d, $J = 9.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.98 (1H, d, $J = 8.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{OCH}_3$), 3.78 (3H, s, CO_2CH_3), 3.52 (1H, d, $J = 8.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{OCH}_3$), 3.35 (3H, s, OCH_3).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 172.0$ (CO_2CH_3), 159.9 (C_Ar), 130.1 ($\text{C}_\text{Ar}\text{H}$), 125.6 (C_Ar), 124.8 ($\text{C}_\text{Ar}\text{H}$), 120.7 ($\text{C}_\text{Ar}\text{H}$), 110.2 ($\text{C}_\text{Ar}\text{H}$), 76.9 ($\text{CH}_\text{A}\text{H}_\text{B}\text{OCH}_3$), 76.3 ($\text{CH}_\text{A}\text{H}_\text{B}$), 59.5 (CO_2CH_3), 57.8 ($\text{C}_\text{Ar}\text{C}$), 52.9 (CO_2CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2989, 2896, 1736, 1481, 1220, 1103, 751.

HRMS: (APCI $^+$) Found $[\text{M} + \text{H}]^+ = 223.0966$; $\text{C}_{12}\text{H}_{15}\text{O}_4$ requires 223.0965.

Methyl 3-(iodomethyl)-2,3-dihydrobenzofuran-3-carboxylate (116)

116

Ester **87** (54 mg, 300 μ mol) and diiodomethane (48 μ L, 600 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97:3) afforded the title compound as a colourless oil (62 mg, 54%).

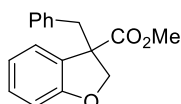
R_f = 0.4 (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 7.33 (1H, d, J = 7.8 Hz, ArH), 7.28 – 7.20 (1H, m, ArH), 6.91 (1H, t, J = 7.5 Hz, ArH), 6.82 (1H, d, J = 8.1 Hz, ArH), 5.14 (1H, d, J = 9.8 Hz, CH_AH_B), 4.46 (1H, d, J = 10.5 Hz, CH_AH_B), 3.87 (1H, d, J = 9.9 Hz, CH_AH_BI), 3.82 (3H, s, CO₂CH₃), 3.32 (1H, d, J = 9.9 Hz, CH_AH_BI).

¹³C NMR (CDCl₃, 101 MHz) δ = 170.9 (CO₂CH₃), 159.8 (C_{Ar}), 130.7 (C_{Ar}H), 126.8 (C_{Ar}), 124.2 (C_{Ar}H), 121.1 (C_{Ar}H), 110.9 (C_{Ar}H), 79.4 (CH_AH_B), 57.9 (C_{Ar}C), 53.3 (CO₂CH₃), 10.6 (CH₂I).

IR (film) ν_{max} /cm⁻¹ 2952, 1734, 1478, 1229, 749.

HRMS: (APCI⁺) Found [M + H]⁺ = 318.9824; C₁₁H₁₂IO₃ requires 318.9826.

Methyl 3-benzyl-2,3-dihydrobenzofuran-3-carboxylate (117)

117

Ester **87** (54 mg, 300 μ mol) and benzyl bromide (71 μ L, 600 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 98:2 to 95:5) afforded the title compound as a colourless oil (78 mg, 97%).

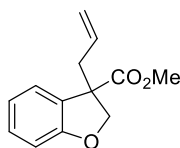
$R_f = 0.5$ (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 400 MHz) $\delta = 7.42$ (1H, d, $J = 7.5$ Hz, ArH), 7.31 – 7.25 (3H, m, ArH $\times$ 2), 7.22 (1H, t, $J = 7.7$ Hz, ArH), 7.05 (2H, dd, $J = 7.0, 2.3$ Hz, ArH $\times$ 2), 6.95 (1H, t, $J = 7.5$ Hz, ArH), 6.81 (1H, d, $J = 8.0$ Hz, ArH), 4.92 (1H, d, $J = 9.5$ Hz, CH_AH_B), 4.54 (1H, d, $J = 9.4$ Hz, CH_AH_B), 3.76 (3H, s, CO₂CH₃), 3.51 (1H, d, $J = 13.6$ Hz, Bn–CH_AH_B), 3.13 (1H, d, $J = 13.7$ Hz, Bn–CH_AH_B).

¹³C NMR (CDCl₃, 101 MHz) $\delta = 172.9$ (CO₂CH₃), 159.6 (C_{Ar}), 136.3 (C_{Ar}), 129.7 (C_{Ar}H), 129.7 (C_{Ar}H), 128.5 (C_{Ar}H $\times$ 2), 128.5 (C_{Ar}), 127.2 (C_{Ar}H), 125.2 (C_{Ar}H), 120.8 (C_{Ar}H $\times$ 2), 110.2 (C_{Ar}H), 76.7 (CH_AH_B), 57.8 (C_{Ar}C), 52.6 (CO₂CH₃), 44.1 (Bn–CH₂).

Analytical data are in accordance with those previously reported for this compound.¹⁴¹

Methyl 3-allyl-2,3-dihydrobenzofuran-3-carboxylate (118)



118

Ester **87** (54 mg, 300 μ mol) and allyl iodide (55 μ L, 600 μ mol), freshly distilled from CaH₂, were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97:3) afforded the title compound as a colourless oil (65 mg, 99%).

$R_f = 0.5$ (Pentane:Et₂O, 80:20).

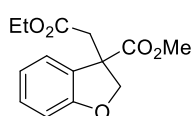
¹H NMR (CDCl₃, 400 MHz) $\delta = 7.37$ (1H, d, $J = 7.6$ Hz, ArH), 7.19 (1H, t, $J = 7.7$ Hz, ArH), 6.91 (1H, t, $J = 7.5$ Hz, ArH), 6.81 (1H, d, $J = 8.0$ Hz, ArH), 5.70 – 5.56 (1H, m, CH=CH_AH_B), 5.14 (2H, d, $J = 5.9$ Hz, CH=CH_AH_B), 5.10 (1H, s, CH=CH_AH_B), 5.02 (1H, d, $J = 9.3$ Hz, CH_AH_B), 4.42 (1H, d, $J = 9.4$ Hz, CH_AH_B), 3.76 (3H, s, CO₂CH₃), 2.87 (1H, dd, $J = 13.9, 7.0$ Hz, CH_AH_BCH), 2.60 (1H, dd, $J = 13.9, 7.3$ Hz, CH_AH_BCH).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 173.0 (CO_2CH_3), 159.7 (C_{Ar}), 132.5 ($\text{CH}=\text{CH}_{\text{A}}\text{H}_{\text{B}}$), 129.6 ($\text{C}_{\text{Ar}}\text{H}$), 128.2 (C_{Ar}), 124.7 ($\text{C}_{\text{Ar}}\text{H}$), 120.8 ($\text{C}_{\text{Ar}}\text{H}$), 119.4 ($\text{CH}=\text{CH}_{\text{A}}\text{H}_{\text{B}}$), 110.1 ($\text{C}_{\text{Ar}}\text{H}$), 77.0 ($\text{CH}_{\text{A}}\text{H}_{\text{B}}$), 56.3 ($\text{C}_{\text{Ar}}\text{C}$), 52.7 (CO_2CH_3), 42.7 ($\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{CH}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 1734, 1481, 1217, 1021, 981, 751.

HRMS: (APCI $^{+}$) Found $[\text{M} + \text{H}]^{+}$ = 219.1016; $\text{C}_{13}\text{H}_{15}\text{O}_3$ requires 219.1016.

Methyl 3-(2-ethoxy-2-oxoethyl)-2,3-dihydrobenzofuran-3-carboxylate (**119**)



119

Ester **87** (54 mg, 300 μmol) and ethyl bromoacetate (67 μL , 600 μmol) were subjected to general procedure A. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (79 mg, 99%).

R_f = 0.3 (Pentane: Et_2O , 80:20).

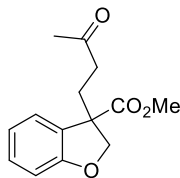
^1H NMR (CDCl_3 , 400 MHz) δ = 7.24 – 7.15 (2H, m, $\text{ArH} \times 2$), 6.87 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.82 (1H, d, J = 8.1 Hz, ArH), 5.30 (1H, dd, J = 9.8, 1.0 Hz, $\text{CH}_{\text{A}}\text{H}_{\text{B}}$), 4.44 (1H, d, J = 9.8 Hz, $\text{CH}_{\text{A}}\text{H}_{\text{B}}$), 4.15 (2H, q, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.73 (3H, s, CO_2CH_3), 3.41 (1H, d, J = 17.2 Hz, $\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{CO}_2\text{CH}_2\text{CH}_3$), 2.74 (1H, d, J = 17.2 Hz, $\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{CO}_2\text{CH}_2\text{CH}_3$), 1.25 (3H, t, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 172.5 (CO_2CH_3), 170.9 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 159.7 (C_{Ar}), 130.1 ($\text{C}_{\text{Ar}}\text{H}$), 127.6 (C_{Ar}), 123.9 ($\text{C}_{\text{Ar}}\text{H}$), 120.9 ($\text{C}_{\text{Ar}}\text{H}$), 110.4 ($\text{C}_{\text{Ar}}\text{H}$), 79.1 ($\text{CH}_{\text{A}}\text{H}_{\text{B}}$), 61.1 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 53.9 ($\text{C}_{\text{Ar}}\text{C}$), 53.0 (CO_2CH_3), 42.7 ($\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{CO}_2\text{CH}_2\text{CH}_3$), 14.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2982, 1728, 1481, 1224, 751.

HRMS: (APCI⁺) Found $[M + H]^+ = 265.1069$; C₁₄H₁₇O₅ requires 265.1071.

Methyl 3-(3-oxobutyl)-2,3-dihydrobenzofuran-3-carboxylate (120)



120

Ester **87** (54 mg, 300 μ mol) and 3-buten-2-one (25 μ L, 300 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 60:40) afforded the title compound as a colourless oil (70 mg, 94%).

R_f = 0.2 (Pentane:Et₂O, 60:40).

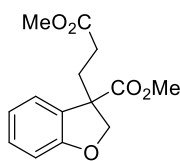
¹H NMR (CDCl₃, 400 MHz) δ = 7.34 (1H, dd, J = 7.5, 1.5 Hz, ArH), 7.18 (1H, ddd, J = 8.1, 7.4, 1.4 Hz, ArH), 6.90 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.80 (1H, d, J = 8.1 Hz, ArH), 4.98 (1H, d, J = 9.4 Hz, CH_AH_B), 4.31 (1H, d, J = 9.4 Hz, CH_AH_B), 3.73 (3H, s, CO₂CH₃), 2.50 – 2.14 (4H, m, CH₂CH₂C(O)CH₃ and CH₂CH₂C(O)CH₃), 2.08 (3H, s, C(O)CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 207.1 (C(O)CH₃), 173.2 (CO₂CH₃), 159.6 (C_{Ar}), 129.7 (C_{Ar}H), 127.7 (C_{Ar}), 125.0 (C_{Ar}H), 121.0 (C_{Ar}H), 110.1 (C_{Ar}H), 77.5 (CH_AH_B), 55.7 (C_{Ar}C), 52.8 (CO₂CH₃), 38.7 (CH₂CH₂C(O)CH₃), 31.7, (CH₂CH₂C(O)CH₃) 30.1 (C(O)CH₃).

IR (film) ν_{max} /cm⁻¹ 2954, 1728, 1715, 1481, 1226, 978, 752.

HRMS: (APCI⁺) Found $[M + H]^+ = 249.1121$; C₁₄H₁₇O₄ requires 249.1121.

Methyl 3-(3-methoxy-3-oxopropyl)-2,3-dihydrobenzofuran-3-carboxylate (121)



121

Ester **87** (54 mg, 300 μ mol) and methyl acrylate (24 μ L, 300 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 60:40 to 50:50) afforded the title compound as a colourless oil (56 mg, 70%).

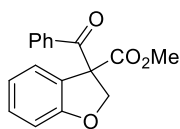
R_f = 0.2 (Pentane:Et₂O, 50:50).

¹H NMR (CDCl₃, 400 MHz) δ = 7.35 (1H, dd, J = 7.5, 1.4 Hz, ArH), 7.23 – 7.15 (1H, m, ArH), 6.90 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.81 (1H, d, J = 8.0 Hz, ArH), 5.00 (1H, d, J = 9.4 Hz, CH_AH_B), 4.36 (1H, d, J = 9.4 Hz, CH_AH_B), 3.75 (3H, s, CO₂CH₃), 3.63 (3H, s, CO₂CH₃), 2.43 – 2.15 (4H, m, CH₂CH₂CO₂CH₃ and CH₂CH₂CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 172.9, 172.9 (CO₂CH₃ $\times$ 2), 159.6 (C_{Ar}), 129.7 (C_{Ar}H), 127.5 (C_{Ar}), 124.9 (C_{Ar}H), 120.9 (C_{Ar}H), 110.1 (C_{Ar}H), 77.3 (CH_AH_B), 55.8 (C_{Ar}C), 52.8 (CO₂CH₃), 51.8 (CO₂CH₃), 32.9 (CH₂CH₂CO₂CH₃), 29.6 (CH₂CH₂CO₂CH₃).

IR (film) ν_{max} /cm⁻¹ 2953, 1731, 1481, 1226, 983, 752.

HRMS: (APCI⁺) Found [M + H]⁺ = 265.1070; C₁₄H₁₇O₅ requires 265.1071.

Methyl 3-benzoyl-2,3-dihydrobenzofuran-3-carboxylate (122)**122**

Ester **87** (54 mg, 300 μmol) and benzoyl chloride (70 μL , 600 μmol) were subjected to general procedure A. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (80 mg, 94%).

$R_f = 0.2$ (Pentane: Et_2O , 90:10).

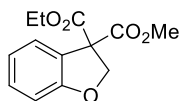
^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.82 - 7.76$ (2H, m, $\text{ArH} \times 2$), 7.59 (1H, tt, $J = 7.3, 1.8$ Hz, ArH), 7.53 – 7.44 (3H, m, $\text{ArH} \times 3$), 7.31 – 7.26 (1H, m, ArH), 6.98 (1H, td, $J = 7.5, 1.0$ Hz, ArH), 6.87 (1H, d, $J = 8.1$ Hz, ArH), 5.55 (1H, d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.79 (1H, d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.74 (3H, s, CO_2CH_3).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 192.6$ ($\text{C}(\text{O})\text{C}_6\text{H}_5$), 170.3 (CO_2CH_3), 160.0 (C_Ar), 134.3 (C_Ar), 133.8 ($\text{C}_\text{Ar}\text{H}$), 130.6 ($\text{C}_\text{Ar}\text{H}$), 129.1 ($\text{C}_\text{Ar}\text{H} \times 2$), 128.8 ($\text{C}_\text{Ar}\text{H} \times 2$), 127.8 ($\text{C}_\text{Ar}\text{H}$), 123.5 (C_Ar), 121.0 ($\text{C}_\text{Ar}\text{H}$), 110.2 ($\text{C}_\text{Ar}\text{H}$), 75.8 ($\text{CH}_\text{A}\text{H}_\text{B}$), 67.7 ($\text{C}_\text{Ar}\text{C}$), 53.6 (CO_2CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 1739, 1689, 1481, 1256, 1237, 750, 700.

HRMS: (APCI $^+$) Found $[\text{M} + \text{H}]^+ = 283.0965$; $\text{C}_{17}\text{H}_{15}\text{O}_4$ requires 283.0965.

3-Ethyl 3-methyl benzofuran-3,3(2H)-dicarboxylate (123)



123

Ester **87** (54 mg, 300 μ mol) and ethyl chloroformate (57 μ L, 600 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (75 mg, 100%).

R_f = 0.2 (Pentane:Et₂O, 80:20).

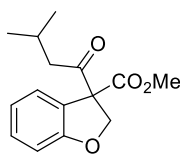
¹H NMR (CDCl₃, 400 MHz) δ = 7.53 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.25 (1H, ddd, J = 8.1, 7.4, 1.4 Hz, ArH), 6.95 (1H, td, J = 7.6, 1.0 Hz, ArH), 6.84 (1H, d, J = 8.2 Hz, ArH), 5.00 (1H, s, CH_AH_B), 5.00 (1H, s, CH_AH_B), 4.26 (2H, q, J = 7.1 Hz, CH₂CH₃), 3.80 (3H, s, CO₂CH₃), 1.28 (3H, t, J = 7.1 Hz, CH₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 169.2, 168.5 (C(O)CH₃), (C(O)CH₂CH₃), 160.1 (C_{Ar}), 130.6 (C_{Ar}H), 126.8 (C_{Ar}H), 123.3 (C_{Ar}), 121.0 (C_{Ar}H), 110.3 (C_{Ar}H), 76.1 (CH_AH_B), 63.5 (C_{Ar}C), 62.6 (CO₂CH₂CH₃), 53.5 (CO₂CH₃), 14.1 (CO₂CH₂CH₃).

IR (film) $\nu_{\max}$ /cm⁻¹ 2983, 1736, 1481, 1242, 1094, 984, 751.

HRMS: (APCI⁺) Found [M + H]⁺ = 251.0915; C₁₃H₁₅O₅ requires 251.0914.

Methyl 3-(3-methylbutanoyl)-2,3-dihydrobenzofuran-3-carboxylate (124)



124

Ester **87** (535 mg, 3.00 mmol) and isovaleryl chloride (732 μ L, 6.00 mmol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97:3) afforded the title compound as a colourless oil (710 mg, 90%).

R_f = 0.4 (Pentane:Et₂O, 80:20).

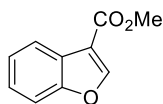
¹H NMR (CDCl₃, 400 MHz) δ = 7.55 (1H, dd, J = 7.6, 1.3 Hz, ArH), 7.28 (1H, td, J = 7.9, 7.5, 1.4 Hz, ArH), 6.98 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.88 (1H, d, J = 8.1 Hz, ArH), 4.97 (1H, s, CH_AH_B), 4.97 (1H, s, CH_AH_B), 3.83 (3H, s, CO₂CH₃), 2.42 (2H, d, J = 7.0 Hz, CH₂), 2.23 – 2.06 (1H, m, CH), 0.87 (3H, d, J = 4.3 Hz, CH(CH₃)_A(CH₃)_B), 0.85 (3H, d, J = 4.3 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 101 MHz) δ = 202.6 (C(O)CH₂), 169.5 (CO₂CH₃), 160.5 (C_{Ar}), 130.7 (C_{Ar}H), 126.6 (C_{Ar}H), 123.4 (C_{Ar}), 121.2 (C_{Ar}H), 110.6 (C_{Ar}H), 75.0 (CH_AH_B), 70.1 (C_{Ar}C), 53.3 (CO₂CH₃), 47.2 (CH₂), 24.2 (CH), 22.4 (CH(CH₃)_A(CH₃)_B), 22.4 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\max}$ /cm⁻¹ 2957, 1745, 1719, 1481, 1264, 983, 752.

HRMS: (EI⁺) Found [M⁺] = 262.1208, C₁₅H₁₈O₄ requires 262.1200.

Methyl benzofuran-3-carboxylate (**125**)



125

Ester **87** (54 mg, 300 μ mol) and *N*-bromosuccinimide (107 mg, 600 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil (19 mg, 36%).

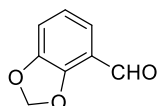
*R*_f = 0.2 (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 8.26 (1H, s, ArH), 8.12 – 8.03 (1H, m, ArH), 7.57 – 7.50 (1H, m, ArH), 7.41 – 7.32 (2H, m, ArH $\times$ 2), 3.95 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 164.0 (C(O)CH₃), 155.7 (C_{Ar}), 151.1 (C_{Ar}H), 125.4 (C_{Ar}H), 124.7 (C_{Ar}), 124.3 (C_{Ar}H), 122.1 (C_{Ar}H), 114.6 (C_{Ar}), 111.8 (C_{Ar}H), 51.8 (CO₂CH₃).

Analytical data are in accordance with those previously reported for this compound.¹⁴²

Benzo[d][1,3]dioxole-4-carbaldehyde (**127**)⁴⁴



127

A solution of 2,3-dihydroxybenzaldehyde **126** (5.00 g, 36.2 mmol), CuO (288 mg, 3.62 mmol), K₂CO₃ (5.50 g, 39.8 mmol) and CH₂Br₂ (3.05 mL, 43.4 mmol) in DMF (40 mL) was heated at 165 °C for 3 h. The reaction mixture was filtered through Celite[®] and washed with EtOAc (150 mL). The filtrate was washed with sat. aq. LiCl (100 mL), sat. aq. K₂CO₃ (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 93:7 to 80:20) afforded the title compound as a pale yellow oil (5.43 g, 100%).

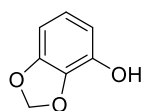
$R_f = 0.2$ (Pentane:Et₂O, 93:7).

¹H NMR (CDCl₃, 400 MHz) δ = 10.11 (1H, s, CHO), 7.27 (1H, dt, J = 8.0, 0.9 Hz, ArH), 7.02 (1H, dt, J = 7.8, 1.0 Hz, ArH), 6.93 (1H, t, J = 7.9 Hz, ArH), 6.13 (2H, s, CH₂).

¹³C NMR (CDCl₃, 101 MHz) δ = 188.1 (CHO), 149.3 (C_{Ar}), 149.0 (C_{Ar}), 121.8 (C_{Ar}H), 121.2 (C_{Ar}H), 119.4 (C_{Ar}), 113.5 (C_{Ar}H), 102.6 (CH₂).

Analytical data are in accordance with those previously reported for this compound.⁴⁴

Benzo[d][1,3]dioxol-4-ol (128)⁴⁴



128

To a solution of aldehyde **127** (5.34 g, 5.6 mmol) in CH₂Cl₂ (120 mL) was added MCPBA (10.0 g, 40.7 mmol, 70 wt. %). The reaction mixture was heated at reflux for 16 h, filtered through Celite[®] and washed with CH₂Cl₂ (200 mL). The filtrate was washed with sat. aq. NaHCO₃ (3 × 100 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in ethanolic KOH solution (5 wt.%, 100 mL) and stirred at rt for 2 h. The reaction mixture was acidified to pH 2 with HCl (1 M aq.), diluted with H₂O (100 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a white solid (3.15 g, 64%).

$R_f = 0.1$ (Pentane:Et₂O, 90:10).

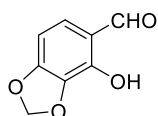
m.p. 61 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 6.73 (1H, t, J = 8.1 Hz, ArH), 6.50 (1H, d, J = 4.0 Hz, ArH), 6.49 – 6.43 (1H, m, ArH), 5.96 (2H, s, CH₂), 4.98 (1H, s, OH).

¹³C NMR (CDCl₃, 101 MHz) δ = 148.8 (C_{Ar}), 139.6 (C_{Ar}), 134.1 (C_{Ar}), 122.4 (C_{Ar}H), 111.0 (C_{Ar}H), 102.1 (C_{Ar}H), 101.3 (C_{Ar}H).

Analytical data are in accordance with those previously reported for this compound.⁴⁴

4-Hydroxybenzo[d][1,3]dioxole-5-carbaldehyde (**129**)⁴⁵



129

To a solution of phenol **128** (1.97 g, 14.3 mmol) in THF (140 mL) was added MgCl₂ (2.72 g, 28.5 mmol), Et₃N (3.98 mL, 28.5 mmol) and paraformaldehyde (1.28 g, 42.8 mmol). The reaction mixture was heated at 85 °C for 6 h and HCl (1 M aq., 100 mL) was added. The solution was extracted with Et₂O (3 × 100 mL) and the organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by recrystallisation from EtOH afforded the title compound as a white solid (2.24 g, 95%).

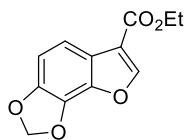
R_f = 0.1 (Pentane:Et₂O, 90:10).

m.p. 112 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 10.99 (1H, s, CHO), 9.73 (1H, s, OH), 7.16 (1H, d, J = 8.2 Hz, ArH), 6.58 (1H, d, J = 8.2 Hz, ArH), 6.11 (2H, s, CH₂).

¹³C NMR (CDCl₃, 101 MHz) δ = 195.2 (CHO), 155.3 (C_{Ar}), 145.6 (C_{Ar}), 134.3 (C_{Ar}), 130.6 (C_{Ar}H), 118.4 (C_{Ar}), 103.0 (CH₂), 102.1 (C_{Ar}H).

Analytical data are in accordance with those previously reported for this compound.⁴⁵

Ethyl [1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (130)

130

To a solution of aldehyde **129** (100 mg, 600 μmol) and $\text{HBF}_4 \cdot \text{OEt}_2$ (8 μL , 60 μmol) in CH_2Cl_2 (5 mL) at 0 $^\circ\text{C}$ was added dropwise a solution of ethyl diazoacetate (120 μL , 960 μmol) in CH_2Cl_2 (3 mL) over a period of 5 min. The reaction mixture was stirred at room temperature for 30 min and then concentrated *in vacuo* after nitrogen evolution had ceased. THF (3 mL) and conc. H_2SO_4 (30 μL) was added and the reaction mixture was stirred at room temperature for 30 min. CH_2Cl_2 (10 mL) was added followed by solid NaHCO_3 until gas evolution had ceased. The solution was washed successively with water (10 mL), 1 M aq. NaOH (10 mL) and sat. aq. NaCl (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (126 mg, 90%).

$R_f = 0.2$ (Pentane: Et_2O , 95:5).

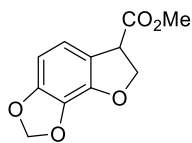
$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ = 8.16 (1H, s, ArH), 7.55 (1H, d, $J = 8.3$ Hz, ArH), 6.96 (1H, d, $J = 8.3$ Hz, ArH), 6.09 (2H, s, CH_2), 4.39 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 1.41 (3H, t, $J = 7.1$ Hz, CH_2CH_3).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ = 163.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 151.0 (C_{ArH}), 146.9 (C_{Ar}), 139.3 (C_{Ar}), 131.1 (C_{Ar}), 122.0 (C_{Ar}), 115.4 (C_{Ar}), 114.3 (C_{ArH}), 106.7 (C_{ArH}), 102.2 (CH_2), 60.8 (CH_2CH_3), 14.5 (CH_2CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2926, 1717, 1487, 1271, 1086, 801.

HRMS: (EI^+) Found $[\text{M}^+] = 234.0530$; $\text{C}_{12}\text{H}_{10}\text{O}_5$ requires 234.0523.

Methyl 6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (131)¹³⁷



131

Mg turnings (110 mg, 4.54 mmol) were added to a solution of benzofuran **130** (200 mg, 908 μ mol) in MeOH (6 mL). After 1 h the reaction mixture was evaporated to dryness and re-dissolved in CH₂Cl₂ (20 mL). The solution was washed successively with sat. aq. NH₄Cl (20 mL), sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (166 mg, 82%).

R_f = 0.3 (Pentane:Et₂O, 80:20).

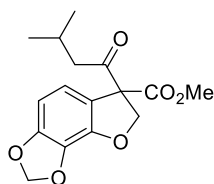
¹H NMR (CDCl₃, 400 MHz) δ = 6.85 (1H, dd, J = 7.9, 1.2 Hz, ArH), 6.43 (1H, d, J = 7.9 Hz, ArH), 6.05 – 5.86 (2H, m, CH₂), 5.01 (1H, dd, J = 9.3, 6.3 Hz, CH), 4.73 (1H, t, J = 9.3 Hz, CH_AH_B), 4.28 (1H, ddd, J = 9.4, 6.2, 1.2 Hz, CH_AH_B), 3.77 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 171.7 (CO₂CH₃), 150.1 (*C*_{Ar}), 142.6 (*C*_{Ar}), 130.5 (*C*_{Ar}), 120.7 (*C*_{Ar}), 117.7 (*C*_{Ar}H), 101.8 (CH₂), 101.6 (*C*_{Ar}H), 74.7 (CH_AH_B), 52.8 (CO₂CH₃), 47.0 (CH).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2900, 1735, 1470, 1250, 1192, 1069, 1025.

HRMS: (APCI⁺) Found $[M + H]^+ = 223.0600$; C₁₁H₁₁O₅ requires 223.0601.

Methyl 6-(3-methylbutanoyl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (133)



133

Ester **131** (10 mg, 45 μ mol) and isovaleryl chloride **132** (11 μ L, 90 μ mol) were subjected to general procedure A. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (6.7 mg, 49%).

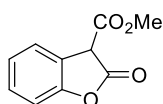
R_f = 0.3 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 500 MHz) δ = 7.01 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.50 (1H, d, *J* = 8.1 Hz, Ar*H*), 5.98 (2H, q, *J* = 1.4 Hz, CH₂), 5.03 (1H, d, *J* = 9.8 Hz, CH_AH_B), 5.00 (1H, d, *J* = 9.8 Hz, CH_AH_B), 3.81 (3H, s, CO₂CH₃), 2.39 (2H, dd, *J* = 6.8, 1.5 Hz, CH₂), 2.19 – 2.07 (1H, m, CH), 0.85 (3H, d, *J* = 4.7 Hz, CH(CH₃)_A(CH₃)_B), 0.83 (3H, d, *J* = 4.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 126 MHz) δ = 202.7 (C(O)CH₂), 169.5 (CO₂CH₃), 150.9 (C_{Ar}), 143.2 (C_{Ar}), 130.7 (C_{Ar}), 119.8 (C_{Ar}), 119.3 (C_{Ar}H), 102.1 (C_{Ar}H), 102.1 (CH₂), 77.0 (CH_AH_B), 69.6 (C_{Ar}C), 53.3 (CO₂CH₃), 47.1 (CH₂), 24.2 (CH), 22.4 (CH(CH₃)_A(CH₃)_B), 22.4 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2958, 1744, 1719, 1473, 1371, 1253, 1194.

HRMS: (APCI⁺) Found [M + H]⁺ = 307.1172; C₁₆H₁₉O₆ requires 307.1176.

Methyl 2-oxo-2,3-dihydrobenzofuran-3-carboxylate (137)⁴⁶

137

To a solution of 2-bromophenol **135** (1.50 g, 8.67 mmol) and dimethyl malonate **136** (1.37 g, 10.4 mmol) in dioxane (30 mL) was added NaH (763 mg, 19.1 mmol, 60% in mineral oil). The reaction mixture was stirred for 10 min and CuBr (1.49 g, 10.4 mmol) was added. The reaction mixture was heated at 70 °C for 9 h. The solution was cooled to 0 °C and partitioned between EtOAc (100 mL) and HCl (1 M aq., 50 mL). The layers were separated and the organic layer was washed successively with H₂O (50 mL) and brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Volatile impurities were removed by distillation (200 °C, 0.1 mbar) to afford the residual title compound as a yellow oil (608 mg, 37%).

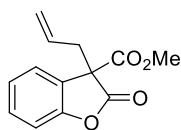
*R*_f = 0.3 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 7.43 – 7.35 (2H, m, ArH $\times$ 2), 7.20 (1H, td, *J* = 7.6, 1.0 Hz, ArH), 7.14 (1H, d, *J* = 7.8 Hz, ArH), 4.68 (1H, s, CH), 3.83 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 169.5 (CO₂CH₃ or CO₂C_{Ar}), 165.7 (CO₂CH₃ or CO₂C_{Ar}), 154.2 (C_{Ar}), 130.4 (C_{Ar}H), 125.1 (C_{Ar}H), 124.8 (C_{Ar}H), 122.2 (C_{Ar}), 111.3 (C_{Ar}H), 53.7 (CO₂CH₃), 50.2 (CH).

Analytical data are in accordance with those previously reported for this compound.⁴⁶

Methyl 3-allyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (138)⁴⁶



138

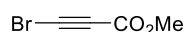
To a stirred solution of ester **137** (48 mg, 250 μ mol) in THF (2.2 mL) at rt was added LiHMDS (1 M in THF, 300 μ L, 300 μ mol) and CuBr (43 mg, 300 μ mol). After 10 min allyl iodide (46 μ L, 500 μ mol) was added dropwise and the reaction mixture was stirred at rt for 3 h. Sat. aq. NH_4Cl (3 mL) was added and the mixture extracted with Et_2O (3×20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 93:7) afforded the title compound as a colourless oil (28 mg, 48%).

$R_f = 0.4$ (Pentane: Et_2O , 70:30).

^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.36$ (1H, ddd, $J = 8.1, 7.6, 1.5$ Hz, ArH), 7.33 – 7.28 (1H, m, ArH), 7.19 (1H, td, $J = 7.6, 1.0$ Hz, ArH), 7.15 – 7.08 (1H, m, ArH), 5.50 – 5.36 (1H, m, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.10 (1H, dq, $J = 17.0, 1.4$ Hz, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.04 (1H, ddt, $J = 10.1, 1.7, 0.9$ Hz, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.72 (3H, s, CO_2CH_3), 3.09 – 3.02 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$), 3.02 – 2.94 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 172.8$ (CO_2CH_3 or $\text{CO}_2\text{C}_\text{Ar}$), 168.1 (CO_2CH_3 or $\text{CO}_2\text{C}_\text{Ar}$), 153.5 (C_Ar), 130.2 ($\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 130.0 ($\text{C}_\text{Ar}\text{H}$), 126.2 (C_Ar), 124.7 ($\text{C}_\text{Ar}\text{H}$), 124.1 ($\text{C}_\text{Ar}\text{H}$), 121.3 ($\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 111.1 ($\text{C}_\text{Ar}\text{H}$), 58.4 (CCO_2CH_3), 53.6 (CO_2CH_3), 39.0 ($\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$).

Analytical data are in accordance with those previously reported for this compound.⁴⁶

Methyl 3-bromopropiolate (144)⁵⁶

144

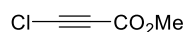
To a solution of *N*-bromosuccinimide (4.89 g, 27.5 mmol) in acetone (80 mL) was added methyl propiolate (2.22 mL, 25.0 mmol). The reaction mixture was stirred for 30 min and the solvent removed *in vacuo*. The residue was re-dissolved in Et₂O (100 mL) and filtered through Celite[®]. Distillation of the residue (bp 28 °C, 5 mbar) afforded the title compound as a colourless oil (3.12 g, 76%).

*R*_f = 0.5 (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 3.76 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 152.9 (CO₂CH₃), 72.6 (C≡CBr), 53.1 (C≡CBr), 53.0 (CO₂CH₃).

Analytical data are in accordance with those previously reported for this compound.⁵⁶

Methyl 3-chloropropiolate (145)⁴⁹

145

To a solution of methyl propiolate **143** (10.2 mL, 115 mmol) and ^tBuOCl (12.4 g, 115 mmol) in ^tBuOH (20 mL) was added portion-wise ^tBuOK (1.28 mg, 11.5 mmol). The reaction mixture was stirred at rt for 30 min, then water (30 mL) and pentane (50 mL) was added. The two layers were separated and the organic layer washed with brine (20 mL), dried over Mg₂SO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil (8.10 g, 60%).

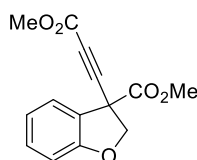
$R_f = 0.5$ (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) $\delta = 3.78$ (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) $\delta = 152.9$ (CO₂CH₃), 68.7 (C $\equiv$ CCl), 61.8 (C $\equiv$ CCl), 53.2 (CO₂CH₃).

Analytical data are in accordance with those previously reported for this compound.¹⁴³

Methyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)-2,3-dihydrobenzofuran-3-carboxylate
(146)



146

To a stirred solution of ester **87** (261 mg, 1.46 mmol) in THF (13 mL) at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (1.75 mL, 1.75 mmol, 1 M in THF). After 10 min chloroacetylene **145** (260 mg, 2.19 mmol) in THF (500 μL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Sat. aq. NH₄Cl (3 mL) was added and the mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (357 mg, 94%).

$R_f = 0.3$ (Pentane:Et₂O, 70:30).

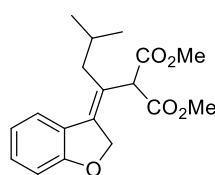
¹H NMR (CDCl₃, 400 MHz) $\delta = 7.46$ (1H, dd, $J = 7.6, 1.4$ Hz, ArH), 7.29 – 7.23 (1H, m, ArH), 6.96 (1H, td, $J = 7.6, 1.0$ Hz, ArH), 6.86 (1H, d, $J = 8.2$ Hz, ArH), 5.22 (1H, d, $J = 9.2$ Hz, CH_AH_B), 4.71 (1H, d, $J = 9.2$ Hz, CH_AH_B), 3.83 (3H, s, CO₂CH₃), 3.78 (3H, s, CO₂CH₃).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 168.4 (CO_2CH_3), 159.4 (C_{Ar}), 153.6, 131.0 (C_{ArH}), 125.2 (C_{ArH}), 125.2 (C_{Ar}), 121.7 (C_{ArH}), 110.9 (C_{ArH}), 84.4 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 79.1 ($\text{CH}_\text{A}\text{H}_\text{B}$), 75.8 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 54.2 (C_{ArC}), 53.1 (CO_2CH_3), 51.1 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 2243, 1746, 1717, 1597, 1480, 1281, 1236, 750.

HRMS: (APCI $^+$) Found $[\text{M} + \text{H}]^+ = 261.0756$; $\text{C}_{14}\text{H}_{13}\text{O}_5$ requires 261.0758.

Dimethyl (Z)-2-(1-(benzofuran-3(2H)-ylidene)-3-methylbutyl)malonate (147**)⁵⁷**



147

To a solution of CuI (76 mg, 400 μmol) in THF (1 mL) at -78°C was added $i\text{PrMgCl}$ (400 μL , 800 μmol , 2.0 M in Et_2O). The mixture was stirred vigorously at 0°C for 1 h before being cooled to -78°C . A solution of alkyne **146** (52 mg, 200 μmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78°C for 3 h. Sat. aq. NH_4Cl (2 mL) was added and the mixture extracted with Et_2O (3×20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 85:15) afforded the title compound as a colourless oil and a single diastereomer (55 mg, 86%).

$R_f = 0.2$ (Pentane: Et_2O , 80:20).

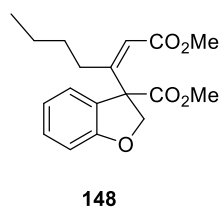
^1H NMR (CDCl_3 , 400 MHz) δ = 7.57 (1H, dd, $J = 7.9, 1.3$ Hz, ArH), 7.19 (1H, ddd, $J = 8.4, 7.5, 1.3$ Hz, ArH), 6.90 (1H, td, $J = 7.6, 1.1$ Hz, ArH), 6.86 (1H, dd, $J = 8.1, 1.0$ Hz, ArH), 5.09 (2H, t, $J = 1.4$ Hz, OCH_2), 4.14 (1H, s, CH), 3.76 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 2.49 (2H, dt, $J = 7.6, 1.5$ Hz, CH_2), 2.00 – 1.90 (1H, m, $\text{CH}(\text{CH}_3)_2$), 0.99 (6H, d, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 168.1 ($\text{CO}_2\text{CH}_3 \times 2$), 164.8 (C_{Ar}), 137.7 ($\text{C}_{\text{Ar}}\text{C}=\text{C}$), 130.1 ($\text{C}_{\text{Ar}}\text{H}$), 125.3 (C_{Ar}), 125.2 ($\text{C}_{\text{Ar}}\text{H}$), 122.8 ($\text{C}_{\text{Ar}}\text{C}=\text{C}$), 120.6 ($\text{C}_{\text{Ar}}\text{H}$), 110.8 ($\text{C}_{\text{Ar}}\text{H}$), 74.2 (OCH_2), 57.7 (CH), 52.9 ($\text{CO}_2\text{CH}_3 \times 2$), 41.3 (CH_2), 27.6 ($\text{CH}(\text{CH}_3)_2$), 22.4 ($\text{CH}(\text{CH}_3)_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2870, 1735, 1476, 1466, 1235, 1150, 748.

HRMS: (EI^+) Found $[\text{M}]^+ = 318.1470$; $\text{C}_{18}\text{H}_{22}\text{O}_5$ requires 318.1462.

Methyl (Z)-3-(1-methoxy-1-oxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate
(148)⁵⁷



To a solution of CuI (76 mg, 400 μmol) in THF (1.5 mL) at -78°C was added $n\text{BuLi}$ (320 μL , 800 μmol , 2.5 M in hexane). The mixture was stirred vigorously at 0°C for 1 h before being cooled to -78°C . A solution of alkyne **146** (52 mg, 200 μmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78°C for 3 h. Sat. aq. NH_4Cl (2 mL) was added and the mixture extracted with Et_2O (3×20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 85:15) afforded the title compound as a colourless oil and a single diastereomer (57 mg, 89%).

$R_f = 0.3$ (Pentane: Et_2O , 70:30).

^1H NMR (CDCl_3 , 500 MHz) δ = 7.22 (1H, td, $J = 7.7, 1.4$ Hz, ArH), 7.18 (1H, dd, $J = 7.6, 1.3$ Hz, ArH), 6.87 (1H, td, $J = 7.6, 1.1$ Hz, ArH), 6.84 (1H, d, $J = 8.2$ Hz, ArH), 5.86 (1H, t, $J = 1.4$ Hz, $\text{C}=\text{CH}$), 5.60 (1H, d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.41 (1H, d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$),

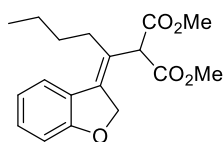
3.68 (6H, s, CO₂CH₃ × 2), 2.16 – 2.07 (1H, m, C=CCH_AH_B), 2.01 – 1.93 (1H, m, C=CCH_AH_B), 1.33 – 1.09 (4H, m, CH₂ × 2), 0.73 (3H, t, *J* = 7.1 Hz, CH₃).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.8 (CO₂CH₃), 166.9 (CO₂CH₃), 163.1 (C=CH), 160.9 (C_{Ar}), 130.3 (C_{Ar}H), 126.3 (C_{Ar}), 125.9 (C_{Ar}H), 120.5 (C_{Ar}H), 116.8 (C=CH), 110.5 (C_{Ar}H), 82.4 (CH_AH_B), 61.8 (C_{Ar}C), 52.9 (CO₂CH₃), 51.5 (CO₂CH₃), 37.2 (C=CCH_AH_B), 30.0 (CH₂), 22.3 (CH₂), 13.8 (CH₃).

IR (film) ν_{max} /cm⁻¹ 2955, 1734, 1715, 1481, 1228, 974, 753.

HRMS: (EI⁺) Found [M⁺] = 318.1462; C₁₈H₂₂O₅ requires 318.1462.

Dimethyl (Z)-2-(1-(benzofuran-3(2H)-ylidene)pentyl)malonate (149)⁵⁷



149

To a solution of CuI (76 mg, 400 μ mol) in THF (1 mL) at –78 °C was added ⁿBuMgCl (400 μ L, 800 μ mol, 2.0 M in THF). The mixture was stirred vigorously at 0 °C for 1 h before being cooled to –78 °C. A solution of alkyne **146** (52 mg, 200 μ mol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at –78 °C for 3 h. Sat. aq. NH₄Cl (2 mL) was added and the mixture extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil and a single diastereomer (9 mg, 14%).

¹H NMR (CDCl₃, 400 MHz) δ = 7.41 (1H, d, *J* = 7.9, ArH), 7.22 (1H, m, ArH), 7.02 (1H, dd, *J* = 7.5, 1.4 Hz, ArH), 6.95 – 6.91 (1H, m, ArH), 5.11 (2H, s, OCH₂), 4.08 (1H, s, CH),

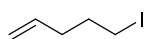
3.76 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 2.52 (2H, t, $J = 8.0$ Hz, $\text{C}=\text{CCH}_2$), 1.89 – 1.74 (2H, m, CH_2CH_3), 1.68 – 1.60 (2H, m, $\text{C}=\text{CCH}_2\text{CH}_2$), 0.81 (3H, t, $J = 7.2$ Hz, CH_3).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 166.9$ ($\text{CO}_2\text{CH}_3 \times 2$), 163.1 (C_{Ar}), 136.4 ($\text{C}_{\text{Ar}}\text{C}=\text{C}$), 130.1 ($\text{C}_{\text{Ar}}\text{H}$), 126.3 (C_{Ar}), 124.8 ($\text{C}_{\text{Ar}}\text{H}$), 123.5 ($\text{C}_{\text{Ar}}\text{H}$), 121.0 ($\text{C}_{\text{Ar}}\text{H}$), 116.8 ($\text{C}_{\text{Ar}}\text{C}=\text{C}$), 74.2 (OCH_2), 57.0 (CH), 52.8 (CO_2CH_3), 40.3, 40.3, ($\text{C}=\text{CCH}_2\text{CH}_2$), (CH_2CH_3), 31.3 ($\text{C}=\text{CCH}_2$), 13.7 (CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2872, 1735, 1715, 1480, 1228, 1150, 751.

HRMS: (CI^+) Found $[\text{M} + \text{H}]^+ = 319.1546$, $\text{C}_{18}\text{H}_{23}\text{O}_5$ requires 319.1540.

5-Iodopent-1-ene (152)¹⁴⁴



152

To a solution of 4-penten-1-ol (1.03 mL, 10.0 mmol) in CH_2Cl_2 (30 mL) was added PPh_3 (3.41 g, 13.0 mmol) and imidazole (885 mg, 13.0 mmol). The mixture was cooled to 0 °C and iodine (3.05 g, 12.0 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C and then concentrated *in vacuo*. Pentane (150 mL) was added and the mixture was filtered through Celite[®]. Distillation of the residue (bp 50 °C, 30 mbar) afforded the title compound as a colourless oil (1.30 g, 67%).

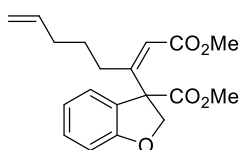
$R_f = 0.7$ (Pentane: Et_2O , 90:10).

^1H NMR (CDCl_3 , 400 MHz) $\delta = 5.75$ (1H, ddt, $J = 17.0, 10.1, 6.7$ Hz, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.08 (1H, dq, $J = 17.1, 1.7$ Hz, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.02 (1H, ddt, $J = 10.2, 2.0, 1.2$ Hz, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.19 (2H, t, $J = 6.9$ Hz, CH_2I), 2.21 – 2.11 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 1.91 (2H, p, $J = 6.9$ Hz, $\text{CH}_2\text{CH}_2\text{I}$).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 136.7 ($\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 116.1 ($\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 34.4 ($\text{CH}_2\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 32.6 ($\text{CH}_2\text{CH}_2\text{I}$), 6.5 (CH_2I).

Analytical data are in accordance with those previously reported for this compound.¹⁴⁴

Methyl (Z)-3-(1-methoxy-1-oxoocta-2,7-dien-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (153)⁵⁷



153

To a solution of iodide **152** (157 mg, 800 μmol) in pentane (3 mL) and Et_2O (2 mL) at -78°C was added $^t\text{BuLi}$ (940 μL , 1.6 mmol, 1.7 M in pentane). After 10 min CuI (76 mg, 400 μmol) was added and the mixture was stirred vigorously at 0°C for 1 h before being cooled to -78°C . A solution of alkyne **146** (52 mg, 200 μmol) in Et_2O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78°C for 30 min. Methanol (0.5 mL) was added and the mixture partitioned between water (15 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 92:8) afforded the title compound as a colourless oil and a single diastereomer (37 mg, 55%).

R_f = 0.3 (Pentane: Et_2O , 70:30).

^1H NMR (CDCl_3 , 500 MHz) δ = 7.24 – 7.20 (1H, m, ArH), 7.18 (1H, dd, J = 7.6, 1.4 Hz, ArH), 6.87 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.84 (1H, d, J = 8.1 Hz, ArH), 5.87 (1H, t, J = 1.4 Hz, $\text{C}=\text{CH}$), 5.60 (1H, d, J = 9.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 5.58 – 5.50 (1H, m, $\text{CH}_2=\text{CH}$), 4.91 –

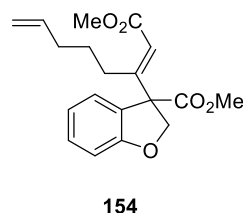
4.81 (2H, m, CH₂=CH), 4.41 (1H, d, *J* = 9.8 Hz, CH_AH_B), 3.68 (6H, s, CO₂CH₃ × 2), 2.12 (1H, m, C=CCH_AH_B), 1.99 (1H, m, C=CCH_AH_B), 1.93 – 1.79 (2H, m, CH₂=CHCH₂), 1.44 – 1.33 (1H, m, CH₂=CHCH₂CH_AH_B), 1.31 – 1.25 (1H, m, CH₂=CHCH₂CH_AH_B).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.7 (CO₂CH₃), 166.8 (CO₂CH₃), 162.9 (C=CH), 160.8 (C_{Ar}), 137.8 (CH₂=CH), 130.4 (C_{Ar}H), 126.3 (C_{Ar}), 126.0 (C_{Ar}H), 120.5 (C_{Ar}H), 117.0 (C=CH), 115.3 (CH₂=CH), 110.6 (C_{Ar}H), 82.5 (CH_AH_B), 61.7 (C_{Ar}C), 52.9 (CO₂CH₃), 51.5 (CO₂CH₃), 36.9 (C=CCH_AH_B), 33.2 (CH₂=CHCH₂), 27.1 (CH₂=CHCH₂CH_AH_B).

IR (film) ν_{max} /cm⁻¹ 2980, 2360, 2341, 1734, 1717, 1481, 1231, 754.

HRMS: (ESI⁺) Found [M + Na]⁺ = 353.1360; C₁₉H₂₂O₅Na requires 353.1359.

Methyl (*E*)-3-(1-methoxy-1-oxoocta-2,7-dien-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (154**)⁵⁷**



To a solution of iodide **152** (157 mg, 800 μ mol) in pentane (3 mL) and Et₂O (2 mL) at –78 °C was added ^tBuLi (940 μ L, 1.6 mmol, 1.7 M in pentane). After 10 min CuI (76 mg, 400 μ mol) was added and the mixture was stirred vigorously at 0 °C for 1 h before being cooled to –78 °C. A solution of alkyne **146** (52 mg, 200 μ mol) in Et₂O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at –78 °C for 30 min. Sat. aq. NH₄Cl (1 mL) was added and the mixture partitioned between water (15 mL) and Et₂O (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O,

92:8) afforded the title compound (13 mg, 19%) as a colourless oil, in addition to alkene **153** (36 mg, 54%), separable by column chromatography.

$R_f = 0.7$ (Pentane:Et₂O, 70:30).

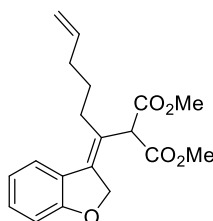
¹H NMR (CDCl₃, 500 MHz) δ = 7.41 (1H, d, J = 7.6 Hz, ArH), 7.28 – 7.20 (1H, m, ArH), 6.95 (1H, t, J = 7.5 Hz, ArH), 6.84 (1H, d, J = 8.0 Hz, ArH), 5.82 – 5.68 (1H, m, CH₂=CH), 5.62 (1H, s, C=CH), 5.25 (1H, d, J = 9.4, 0.9 Hz, CH_AH_B), 5.04 – 4.92 (2H, m, CH₂=CH), 4.41 (1H, d, J = 9.4, 0.9 Hz, CH_AH_B), 3.77 (3H, s, CO₂CH₃), 3.66 (3H, s, CO₂CH₃), 2.59 – 2.49 (2H, m, C=CCH₂), 2.13 – 2.02 (2H, m, CH₂=CHCH₂), 1.56 – 1.39 (2H, m, CH₂=CHCH₂CH₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.3 (CO₂CH₃), 166.4 (CO₂CH₃), 160.8 (C=CH), 160.5 (C_{Ar}), 138.1 (CH₂=CH), 130.5 (C_{Ar}H), 127.3 (C_{Ar}H), 124.9 (C_{Ar}), 121.1 (C_{Ar}H), 118.5 (C=CH), 115.2 (CH₂=CH), 110.6 (C_{Ar}H), 78.3 (CH_AH_B), 65.1 (C_{Ar}C), 53.1 (CO₂CH₃), 51.4 (CO₂CH₃), 34.4 (CH₂=CHCH₂), 30.8 (C=CCH_AH_B), 28.7 (CH₂=CHCH₂CH_AH_B).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2980, 1737, 1722, 1640, 1481, 1225, 1171, 754.

HRMS: (ESI⁺) Found $[M + H]^+ = 331.1541$; C₁₉H₂₃O₅ requires 331.1540.

Dimethyl (Z)-2-(1-(benzofuran-3(2H)-ylidene)hex-5-en-1-yl)malonate (**155**)⁵⁷



155

To a solution of iodide **152** (157 mg, 800 μmol) in pentane (3 mL) and Et₂O (2 mL) at -78°C was added ^tBuLi (940 μL , 1.6 mmol, 1.7 M in pentane). After 10 min CuI (76 mg, 400 μmol) was added and the mixture was stirred vigorously at 0°C for 1 h before being

cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **146** (52 mg, 200 μmol) in Et_2O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Methanol (0.5 mL) was added and the mixture partitioned between water (15 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 92:8) afforded the title compound as a colourless oil and a single diastereomer (37 mg, 55%).

$R_f = 0.3$ (Pentane: Et_2O , 70:30).

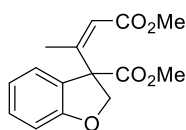
^1H NMR (CDCl_3 , 500 MHz) $\delta = 7.42$ (1H, d, $J = 7.8\text{ Hz}$, ArH), 7.20 (1H, t, $J = 7.7\text{ Hz}$, ArH), 6.92 (2H, t, $J = 7.6\text{ Hz}$, ArH), 6.86 (1H, d, $J = 8.0\text{ Hz}$, ArH), 5.86 (1H, ddt, $J = 17.0$, 10.3, 6.8 Hz, $\text{CH}_2=\text{CH}$), 5.11 (2H, s, OCH_2), 5.10 – 5.00 (2H, m, $\text{CH}_2=\text{CH}$), 4.08 (1H, s, CH), 3.76 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 2.58 – 2.49 (2H, m, $\text{C}=\text{CCH}_2$), 2.17 (2H, q, $J = 7.2\text{ Hz}$, $\text{CH}_2=\text{CHCH}_2$), 1.60 – 1.53 (2H, m, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$).

^{13}C NMR (CDCl_3 , 126 MHz) $\delta = 168.0$ ($\text{CO}_2\text{CH}_3 \times 2$), 164.9 (C_{Ar}), 138.1 ($\text{CH}_2=\text{CH}$), 136.7 ($\text{C}=\text{CCH}_2$), 130.2 (C_{ArH}), 124.8 (C_{ArH}), 124.8 (C_{ArH}), 123.0 ($\text{C}=\text{CCH}_2$), 121.0 (C_{ArH}), 115.4 ($\text{CH}_2=\text{CH}$), 110.7 (C_{ArH}), 74.2 (OCH_2), 57.0 (CH), 52.9 ($\text{CO}_2\text{CH}_3 \times 2$), 34.1 ($\text{CH}_2=\text{CHCH}_2$), 30.9 ($\text{C}=\text{CCH}_2$), 26.5 ($\text{CH}_2=\text{CHCH}_2\text{CH}_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 1736, 1467, 1435, 1233, 1151, 749.4.

HRMS: (CI^+) Found $[\text{M} + \text{H}]^+ = 31.1545$, $\text{C}_{19}\text{H}_{23}\text{O}_5$ requires 331.1540.

Methyl (Z)-3-(4-methoxy-4-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-3-carboxylate
(157)⁵⁷



157

To a solution of CuI (143 mg, 753 μ mol) in THF (2 mL) at $-78\text{ }^{\circ}\text{C}$ was added MeLi (940 μ L, 1.51 mmol, 1.6 M in Et₂O). The mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **146** (98 mg, 377 μ mol) in THF (1.5 mL + 0.5 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h. Sat. aq. NH₄Cl (3 mL) was added and the mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil and a single diastereomer (96 mg, 92%).

R_f = 0.2 (Pentane:Et₂O, 80:20).

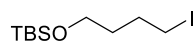
¹H NMR (CDCl₃, 400 MHz) δ = 7.20 (2H, ddd, J = 15.8, 7.7, 1.3 Hz, ArH $\times$ 2), 6.90 – 6.85 (1H, m, ArH), 6.86 – 6.82 (1H, m, ArH), 5.93 (1H, q, J = 1.5 Hz, C=CH), 5.58 (1H, d, J = 9.7 Hz, CH_AH_B), 4.42 (1H, d, J = 9.7 Hz, CH_AH_B), 3.69 (3H, s, CO₂CH₃), 3.68 (3H, s, CO₂CH₃), 1.77 (3H, d, J = 1.6 Hz, CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 171.5 (CO₂CH₃), 166.5 (CO₂CH₃), 160.5 (C=CH), 159.0 (C_{Ar}), 130.3 (C_{Ar}H), 126.6 (C_{Ar}), 125.9 (C_{Ar}H), 120.5 (C_{Ar}H), 117.9 (C=CH), 110.6 (C_{Ar}H), 81.9 (CH_AH_B), 61.5 (C_{Ar}C), 52.9 (CO₂CH₃), 51.5 (CO₂CH₃), 25.7 (CH₃).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 1732, 1717, 1481, 1230, 1154, 753.

HRMS: (APCI⁺) Found $[M + H]^+ = 277.1069$; C₁₅H₁₇O₅ requires 277.1071.

***tert*-Butyl(4-iodobutoxy)dimethylsilane (**185**)**¹⁴⁵



185

A solution of TBSCl (3.01 g, 20.0 mmol), NaI (6.00 g, 40.0 mmol) and THF (4.10 mL, 50.0 mmol) in MeCN (40 mL) was heated at 55 °C for 16 h. Water (20 mL) was added and the mixture extracted with Et₂O (3 × 100 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Distillation of the residue (bp 86 °C, 0.4 mbar) afforded the title compound as a colourless oil (5.08 g, 81%).

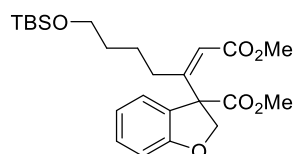
*R*_f = 0.2 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 3.63 (2H, t, *J* = 6.1 Hz, OCH₂), 3.22 (2H, t, *J* = 7.0 Hz, CH₂I), 1.90 (2H, p, *J* = 7.1 Hz, CH₂CH₂I), 1.65 – 1.56 (2H, m, OCH₂CH₂), 0.88 (9H, s, TBS–C(CH₃)₃), 0.04 (6H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 62.1 (OCH₂), 33.7 (OCH₂CH₂), 30.3 (CH₂CH₂I), 26.1 (TBS–C(CH₃)₃), 18.4 (TBS–C(CH₃)₃), 7.2 (CH₂I), –5.2 (TBS–Si(CH₃)₂).

Analytical data are in accordance with those previously reported for this compound.¹⁴⁵

Methyl (Z)-3-(7-((*tert*-butyldimethylsilyl)oxy)-1-methoxy-1-oxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (186**)**⁵⁷



186

To a solution of iodide **185** (676 mg, 2.15 mmol) in pentane (8.1 mL) and Et₂O (5.4 mL) at –78 °C was added ^tBuLi (2.53 mL, 4.30 mmol, 1.7 M in pentane). After 10 min CuI (205 mg, 1.08 mmol) was added and the mixture was stirred vigorously at 0 °C for 1 h before being

cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **146** (140 mg, 538 μmol) in Et_2O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Methanol (1 mL) was added and the mixture partitioned between water (15 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 92:8) afforded the title compound as a colourless oil and a single diastereomer (170 mg, 71%).

$R_f = 0.3$ (Pentane: Et_2O , 70:30).

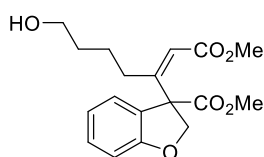
^1H NMR (CDCl_3 , 500 MHz) $\delta = 7.22$ (1H, td, $J = 7.7, 1.4\text{ Hz}$, ArH), 7.18 (1H, dd, $J = 7.7, 1.4\text{ Hz}$, ArH), 6.86 (1H, td, $J = 7.5, 1.0\text{ Hz}$, ArH), 6.83 (1H, d, $J = 8.2\text{ Hz}$, ArH), 5.87 (1H, t, $J = 1.4\text{ Hz}$, C=CH), 5.60 (1H, d, $J = 9.8\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.41 (1H, d, $J = 9.7\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.68 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 3.44 (2H, td, $J = 6.1, 2.2\text{ Hz}$, OCH_2), 2.18 – 1.92 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.39 – 1.32 (2H, m, OCH_2CH_2), 1.32 – 1.21 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 0.86 (9H, s, TBS– $\text{C}(\text{CH}_3)_3$), -0.00 (6H, s, TBS– $\text{Si}(\text{CH}_3)_2$).

^{13}C NMR (CDCl_3 , 126 MHz) $\delta = 171.7$ (CO_2CH_3), 166.9 (CO_2CH_3), 162.8 (C=CH), 160.8 (C_Ar), 130.4 ($\text{C}_\text{Ar}\text{H}$), 126.3 (C_Ar), 125.9 ($\text{C}_\text{Ar}\text{H}$), 120.5 ($\text{C}_\text{Ar}\text{H}$), 116.8 (C=CH), 110.6 ($\text{C}_\text{Ar}\text{H}$), 82.4 ($\text{CH}_\text{A}\text{H}_\text{B}$), 62.8 (OCH_2), 61.8 ($\text{C}_\text{Ar}\text{C}$), 52.9 (CO_2CH_3), 51.5 (CO_2CH_3), 37.2 ($\text{CH}_2\text{C}=\text{CH}$), 32.3 (OCH_2CH_2), 26.1 (TBS– $\text{C}(\text{CH}_3)_3$), 24.2 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), 18.5 (TBS– $\text{C}(\text{CH}_3)_3$), -5.2 (TBS– $\text{Si}(\text{CH}_3)_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2981, 2889, 1734, 1717, 1481, 1229, 1149, 1093, 835.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 471.2173$; $\text{C}_{24}\text{H}_{36}\text{O}_6\text{NaSi}$ requires 471.2173.

Methyl (Z)-3-(7-hydroxy-1-methoxy-1-oxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (187)⁶⁶



187

To a solution of alkene **146** (231 mg, 515 μmol) in MeOH (3.4 mL) was added FeCl_3 (8 mg, 52 μmol). The reaction mixture was stirred at rt for 2 h then filtered through a plug of silica using EtOAc as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 60:40) afforded the title compound as a colourless oil 157 mg, 91%).

$R_f = 0.3$ (Pentane:EtOAc, 50:50).

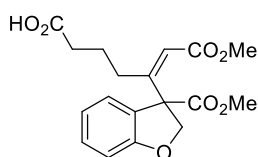
^1H NMR (CDCl_3 , 500 MHz) $\delta = 7.25 - 7.20$ (1H, m, ArH), 7.19 (1H, dd, $J = 7.6, 1.4$ Hz, ArH), 6.88 (1H, td, $J = 7.5, 1.0$ Hz, ArH), 6.84 (1H, d, $J = 8.2$ Hz, ArH), 5.88 (1H, t, $J = 1.4$ -Hz, C=CH), 5.60 (1H, d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.41 (1H, d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.68 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 3.45 (2H, q, $J = 5.8$ Hz, CH_2OH), 2.19 – 1.96 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.45 – 1.32 (2H, m, OCH_2CH_2), 1.36 – 1.23 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.22 – 1.17 (1H, m, OH).

^{13}C NMR (CDCl_3 , 126 MHz) $\delta = 171.7$ (CO_2CH_3), 166.8 (CO_2CH_3), 162.6 (C=CH), 160.9 (C_Ar), 130.4 (C_ArH), 126.3 (C_Ar), 125.9 (C_ArH), 120.5 (C_ArH), 117.1 (C=CH), 110.6 (C_ArH), 82.5 ($\text{CH}_\text{A}\text{H}_\text{B}$), 62.3 (CH_2OH), 61.7 (C_ArC), 52.9 (CO_2CH_3), 51.6 (CO_2CH_3), 37.2 ($\text{CH}_2\text{C}=\text{CH}$), 32.1 (OCH_2CH_2), 24.1 ($\text{OCH}_2\text{CH}_2\text{CH}_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3659, 2981, 2889, 1733, 1715, 1382, 1234, 1150.

HRMS: (EI^+) Found $[\text{M}]^+ = 334.1401$; $\text{C}_{18}\text{H}_{22}\text{O}_6$ requires 334.1411.

(Z)-7-Methoxy-5-(3-(methoxycarbonyl)-2,3-dihydrobenzofuran-3-yl)-7-oxohept-5-enoic acid (188)¹⁴⁶



188

To a solution of alcohol **187** (50 mg, 150 μ mol) in acetone (1 mL) at 0 °C was added dropwise a solution of CrO₃ (75 mg, 750 μ mol) in H₂SO₄ (150 μ L) and water (500 μ L). The reaction mixture was stirred at rt for 1 h and *i*PrOH (500 μ L) was added followed by water (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, CHCl₃:MeOH, 97:3) afforded the title compound as a colourless oil (52 mg, 100%).

*R*_f = 0.3 (CHCl₃:MeOH, 90:10).

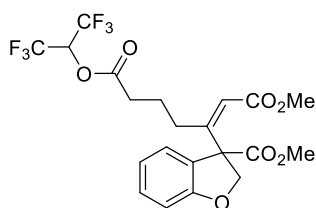
¹H NMR (CDCl₃, 400 MHz) δ = 10.17 (1H, br. s, CO₂H), 7.25 – 7.19 (1H, m, ArH), 7.17 (1H, d, *J* = 7.6 Hz, ArH), 6.90 – 6.81 (2H, m, ArH $\times$ 2), 5.88 (1H, s, C=CH), 5.59 (1H, d, *J* = 9.9 Hz, CH_AH_B), 4.41 (1H, d, *J* = 9.9 Hz, CH_AH_B), 3.68 (6H, s, CO₂CH₃ $\times$ 2), 2.23 – 1.97 (4H, m, CH₂C=CH and CH₂CO₂H), 1.81 – 1.46 (2H, m, CH₂CH₂CO₂H).

¹³C NMR (CDCl₃, 101 MHz) δ = 178.7 (CO₂H), 171.6 (CO₂CH₃), 166.7 (CO₂CH₃), 161.7 (C=CH), 160.8 (C_{Ar}), 130.5 (C_{Ar}H), 126.1 (C_{Ar}), 125.8 (C_{Ar}H), 120.7 (C_{Ar}H), 117.6 (C=CH), 110.7 (C_{Ar}H), 82.5 (CH_AH_B), 61.7 (C_{Ar}C), 52.9 (CO₂CH₃), 51.6 (CO₂CH₃), 36.4 (CH₂C=CH), 33.2 (CH₂CO₂H), 22.9 (CH₂CH₂CO₂H).

IR (film) ν_{max} /cm⁻¹ 2952, 1711, 1481, 1231, 755.

HRMS: (ESI⁻) Found [M – H]⁻ = 347.1136; C₁₈H₁₉O₇ requires 347.1136.

7-(1,1,1,3,3,3-Hexafluoropropan-2-yl) 1-methyl (Z)-3-(3-(methoxycarbonyl)-2,3-dihydrobenzofuran-3-yl)hept-2-enedioate (190)⁶⁹



190

To a solution of acid **188** (30 mg, 86 μ mol) in CH_2Cl_2 (500 μ L) was added DMF (1 drop) followed by oxalyl chloride (15 μ L, 170 μ mol). The reaction mixture was stirred at rt for 1.5 h then the solvent was removed using a balloon with exit needle followed by high vacuum. HFIP (500 μ L, 4.7 mmol) was added under argon and the reaction mixture stirred at rt for 16 h and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 85:15) afforded the title compound as a colourless oil (12 mg, 27%).

R_f = 0.3 (Pentane:EtOAc, 85:15).

^1H NMR (CDCl_3 , 500 MHz) δ = 7.23 (1H, t, J = 7.9 Hz, ArH), 7.17 (1H, d, J = 7.6 Hz, ArH), 6.88 (1H, t, J = 7.3 Hz, ArH), 6.85 (1H, d, J = 8.7 Hz, ArH), 5.86 (1H, s, C=CH), 5.71 (1H, hept, J = 6.1 Hz, $\text{CO}_2\text{CH}(\text{CF}_3)_2$), 5.59 (1H, d, J = 9.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.42 (1H, d, J = 9.9 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.70 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 2.35 (2H, t, J = 7.4 Hz, $\text{CH}_2\text{CO}_2\text{CH}(\text{CF}_3)_2$), 2.23 – 1.98 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.74 – 1.57 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}(\text{CF}_3)_2$).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 171.5 ($\text{CO}_2\text{CH}(\text{CF}_3)_2$), 169.7 (CO_2CH_3), 166.6 (CO_2CH_3), 161.2 (C=CH), 160.8 (C_Ar), 130.6 ($\text{C}_\text{Ar}\text{H}$), 126.0 (C_Ar), 125.7 ($\text{C}_\text{Ar}\text{H}$), 120.7 ($\text{C}_\text{Ar}\text{H}$), 117.7 (C=CH), 110.8 ($\text{C}_\text{Ar}\text{H}$), 82.6 ($\text{CH}_\text{A}\text{H}_\text{B}$), 66.5 (hept, J = 34.5 Hz, $\text{CO}_2\text{CH}(\text{CF}_3)_2$), 61.6 ($\text{C}_\text{Ar}\text{C}$),

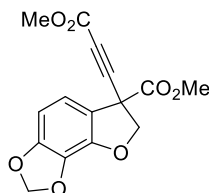
53.0 (CO₂CH₃), 51.7 (CO₂CH₃), 36.2 (CH₂C=CH), 32.5 (CH₂CO₂CH(CF₃)₂), 22.6 (CH₂CH₂CO₂CH(CF₃)₂).

¹⁹F NMR (CDCl₃, 471 MHz,) $\delta = -73.4$.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 1781, 1736, 1720, 1482, 1287, 1227, 1201, 1110.

HRMS: (ESI⁺) Found [M + Na]⁺ = 521.1003; C₂₄H₂₄O₆Na requires 521.1005.

Methyl 6-(3-methoxy-3-oxoprop-1-yn-1-yl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (191)



191

To a stirred solution of ester **131** (67 mg, 302 μmol) in THF (2.1 mL) at -78°C was added LiHMDS (360 μL , 360 μmol , 1 M in THF). After 10 min, chloroacetylene **145** (54 mg, 450 μmol) in THF (500 μL) was added dropwise and the reaction mixture was stirred at -78°C for 1 h. Sat. aq. NH₄Cl (3 mL) was added and the mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (53 mg, 68%).

R_f = 0.3 (Pentane:Et₂O, 70:30).

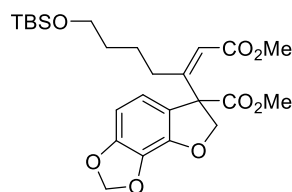
¹H NMR (CDCl₃, 400 MHz) δ = 6.95 (1H, d, J = 8.1 Hz, ArH), 6.49 (1H, d, J = 8.1 Hz, ArH), 5.98 (1H, d, J = 1.5 Hz, OCH_AH_BO), 5.96 (1H, d, J = 1.4 Hz, OCH_AH_BO), 5.26 (1H, d, J = 9.2 Hz, CH_AH_B), 4.76 (1H, d, J = 9.2 Hz, CH_AH_B), 3.82 (3H, s, CO₂CH₃), 3.77 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 168.3 (CO₂CH₃), 153.6 (CO₂CH₃), 151.1 (C_{Ar}), 142.2 (C_{Ar}), 130.8 (C_{Ar}), 121.6 (C_{Ar}), 117.8 (C_{Ar}H), 102.6 (C_{Ar}H), 102.2 (OCH_AH_BO), 84.1 (C $\equiv$ CCO₂CH₃), 80.9 (CH_AH_B), 75.8 (C $\equiv$ CCO₂CH₃), 54.2 (C_{Ar}C), 53.1 (CO₂CH₃), 50.8 (CO₂CH₃).

IR (film) ν_{max} /cm⁻¹ 3032, 1747, 1717, 1653, 1472, 1250, 1068.

HRMS: (APCI⁺) Found [M + H]⁺ = 306.0659; C₁₅H₁₃O₇ requires 305.0656.

Methyl (Z)-6-(7-((tert-butyldimethylsilyl)oxy)-1-methoxy-1-oxohept-2-en-3-yl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (192**)⁵⁷**



192

To a solution of iodide **185** (723 mg, 2.30 mmol) in pentane (8.7 mL) and Et₂O (5.8 mL) at -78 °C was added ^tBuLi (2.71 mL, 4.60 mmol, 1.7 M in pentane). After 10 min CuI (219 mg, 1.15 mmol) was added and the mixture was stirred vigorously at 0 °C for 1 h before being cooled to -78 °C. A solution of alkyne **191** (175 mg, 575 μ mol) in Et₂O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78 °C for 30 min. Methanol (1 mL) was added and the mixture partitioned between water (50 mL) and Et₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil and a single diastereomer (119 mg, 42%).

$R_f = 0.3$ (Pentane:Et₂O, 70:30).

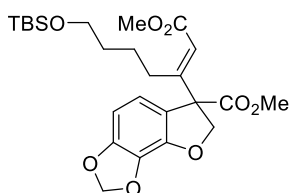
¹H NMR (CDCl₃, 400 MHz) δ = 6.66 (1H, d, J = 8.0 Hz, ArH), 6.42 (1H, d, J = 8.1 Hz, ArH), 5.97 (2H, s, OCH₂O), 5.87 (1H, s, C=CH), 5.68 (1H, d, J = 9.8 Hz, CH_AH_B), 4.48 (1H, d, J = 9.8 Hz, CH_AH_B), 3.68 (6H, s, CO₂CH₃ × 2), 3.49 (2H, t, J = 5.9 Hz, OCH₂), 2.20 – 1.94 (2H, m, CH₂C=CH), 1.53 – 1.18 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 0.87 (9H, s, TBS–C(CH₃)₃), 0.01 (6H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 101 MHz) δ = 171.6 (CO₂CH₃), 166.9 (CO₂CH₃), 162.6 (C=CH), 150.5 (C_{Ar}), 143.6 (C_{Ar}), 130.7 (C_{Ar}), 122.8 (C_{Ar}), 118.5 (C_{Ar}H), 116.9 (C=CH), 102.0 (OCH₂O), 101.5 (C_{Ar}H), 84.5 (CH_AH_B), 62.8 (OCH₂), 61.6 (C_{Ar}C), 52.9 (CO₂CH₃), 51.6 (CO₂CH₃), 37.0 (CH₂C=CH), 32.3 (OCH₂CH₂), 26.1 (TBS–C(CH₃)₃), 24.2 (OCH₂CH₂CH₂), 18.5 (TBS–C(CH₃)₃), –5.2 (TBS–Si(CH₃)₂).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2952, 2931, 2858, 1734, 1717, 1498, 1255, 1225, 1092, 837, 777.

HRMS: (ESI⁺) Found $[M + H]^+ = 493.2253$; C₂₅H₃₇O₈Si requires 493.2252.

Methyl (*E*)-6-(7-((tert-butyldimethylsilyl)oxy)-1-methoxy-1-oxohept-2-en-3-yl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (193**)⁵⁷**



193

To a solution of iodide **185** (723 mg, 2.30 mmol) in pentane (8.7 mL) and Et₂O (5.8 mL) at –78 °C was added ^tBuLi (2.71 mL, 4.60 mmol, 1.7 M in pentane). After 10 min CuI (219 mg, 1.15 mmol) was added and the mixture was stirred vigorously at 0 °C for 1 h before being cooled to –78 °C. A solution of alkyne **191** (175 mg, 575 μ mol) in Et₂O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at –78 °C for 30 min. Methanol (1 mL)

was added and the mixture partitioned between water (50 mL) and Et₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil and a single diastereomer (104 mg, 37%).

R_f = 0.5 (Pentane:Et₂O, 70:30).

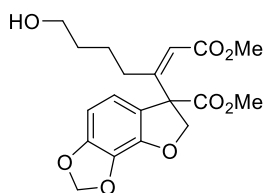
¹H NMR (CDCl₃, 500 MHz) δ = 6.88 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.48 (1H, d, *J* = 8.1 Hz, Ar*H*), 5.96 (2H, q, *J* = 1.5 Hz, OCH₂O), 5.63 (1H, s, C=CH), 5.31 (1H, d, *J* = 9.4 Hz, CH_AH_B), 4.49 (1H, d, *J* = 9.4 Hz, CH_AH_B), 3.76 (3H, s, CO₂CH₃), 3.66 (3H, s, CO₂CH₃), 3.58 (2H, t, *J* = 6.2 Hz, OCH₂), 2.61 – 2.46 (2H, m, CH₂C=CH), 1.56 – 1.40 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 0.88 (9H, s, TBS–C(CH₃)₃), 0.03 (6H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.0 (CO₂CH₃), 166.2 (CO₂CH₃), 160.6 (C=CH), 150.5 (C_{Ar}), 143.1 (C_{Ar}), 130.5 (C_{Ar}), 121.2 (C_{Ar}), 119.7 (C_{Ar}H), 118.4 (C=CH), 101.9 (C_{Ar}H), 101.9 (OCH₂O), 79.9 (CH_AH_B), 64.7 (C_{Ar}C), 62.7 (OCH₂), 53.0 (CO₂CH₃), 51.2 (CO₂CH₃), 33.4 (OCH₂CH₂), 31.0 (CH₂C=CH), 26.1 (OCH₂CH₂CH₂), 26.0 (TBS–C(CH₃)₃), 18.3 (TBS–C(CH₃)₃), –5.3 (TBS–Si(CH₃)₂).

IR (film) ν_{max} /cm^{–1} 2952, 2930, 2857, 1737, 1721, 1652, 1473, 1253, 1211, 1095, 1061, 836.

HRMS: (ESI⁺) Found [M + H]⁺ = 493.2252; C₂₅H₃₇O₈Si requires 493.2252.

Methyl (Z)-6-(7-hydroxy-1-methoxy-1-oxohept-2-en-3-yl)-6,7-dihydro-[1,3]dioxolo[4,5-g]benzofuran-6-carboxylate (194)⁶⁶



194

To a solution of alkene **193** (82 mg, 170 μmol) in MeOH (4 mL) was added FeCl_3 (3.0 mg, 17 μmol). The reaction mixture was stirred at rt for 3 h then filtered through a plug of silica using EtOAc as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:Et₂O, 20:80) afforded the title compound as a colourless oil (62 mg, 99%).

R_f = 0.4 (Pentane:Et₂O, 0:100).

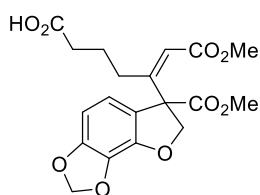
¹H NMR (CDCl_3 , 500 MHz) δ = 6.65 (1H, d, J = 7.9 Hz, ArH), 6.41 (1H, d, J = 8.0 Hz, ArH), 5.95 (2H, dd, J = 4.8, 1.4 Hz, OCH₂O), 5.86 (1H, t, J = 1.5 Hz, C=CH), 5.65 (1H, d, J = 9.8 Hz, CH_AH_B), 4.47 (1H, d, J = 9.8 Hz, CH_AH_B), 3.66 (6H, s, CO₂CH₃ $\times$ 2), 3.52 – 3.47 (2H, m, CH₂OH), 2.20 – 1.96 (2H, m, CH₂C=CH), 1.47 – 1.30 (4H, m, CH₂CH₂OH and CH₂CH₂CH₂OH).

¹³C NMR (CDCl_3 , 101 MHz) δ = 171.5 (CO₂CH₃), 166.8 (CO₂CH₃), 162.4 (C=CH), 150.5 (C_{Ar}), 143.5 (C_{Ar}), 130.7, 122.7, 118.4 (C_{Ar}H), 117.1 (C=CH), 101.9 (OCH₂O), 101.5 (C_{Ar}H), 84.5 (CH_AH_B), 62.4 (CH₂OH), 61.5 (C_{Ar}C), 52.9 (CO₂CH₃), 51.5 (CO₂CH₃), 36.9 (CH₂C=CH), 32.1 (CH₂CH₂OH), 24.0 (CH₂CH₂CH₂OH).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3405, 2951, 1733, 1714, 1651, 1635, 1500, 1256, 1227, 1058, 1027.

HRMS: (ESI⁺) Found $[\text{M} + \text{Na}]^+ = 401.1206$; C₁₉H₂₂O₈Na requires 401.1207.

(Z)-7-Methoxy-5-(6-(methoxycarbonyl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-yl)-7-oxohept-5-enoic acid (195)¹⁴⁶



195

To a solution of alcohol **194** (40 mg, 110 μmol) in acetone (1 mL) at 0 °C was added dropwise a solution of CrO_3 (53 mg, 530 μmol) in H_2SO_4 (150 μL) and water (500 μL). The reaction mixture was stirred at rt for 2 h and *i*PrOH (500 μL) was added followed by water (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , CHCl_3 :MeOH, 95:5) afforded the title compound as a colourless oil (27 mg, 64%).

R_f = 0.4 (CHCl_3 :MeOH, 90:10).

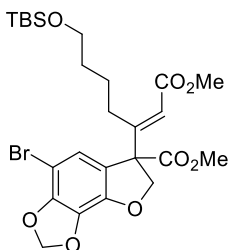
^1H NMR (CDCl_3 , 500 MHz) δ = 6.65 (1H, d, J = 8.0, 1.9 Hz, ArH), 6.41 (1H, d, J = 8.0, 1.8 Hz, ArH), 5.97 (2H, s, OCH_2O), 5.88 (1H, s, $\text{C}=\text{CH}$), 5.66 (1H, d, J = 9.9 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.49 (1H d, J = 9.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.68 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 2.23 (2H, t, J = 7.3, 3.6 Hz, $\text{CH}_2\text{CO}_2\text{H}$), 2.18 – 1.99 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.72 – 1.54 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 178.4 (CO_2H), 171.4 (CO_2CH_3), 166.7 (CO_2CH_3), 161.6, 150.6, 143.5, 130.8, 122.6, 118.4 ($\text{C}_\text{Ar}\text{H}$), 117.6 ($\text{C}=\text{CH}$), 102.0 (OCH_2O), 101.6 ($\text{C}_\text{Ar}\text{H}$), 84.6 ($\text{CH}_\text{A}\text{H}_\text{B}$), 61.5 ($\text{C}_\text{Ar}\text{C}$), 53.0 (CO_2CH_3), 51.7 (CO_2CH_3), 36.2 ($\text{CH}_2\text{C}=\text{CH}$), 33.2 ($\text{CH}_2\text{CO}_2\text{H}$), 23.0 ($\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 1720, 1711, 1501, 1255, 1228, 1090, 756.

HRMS: (ESI⁻) Found [M – H]⁻ = 391.1037; C₁₉H₁₉O₉ requires 391.1035.

Methyl (E)-4-bromo-6-(7-((tert-butyldimethylsilyl)oxy)-1-methoxy-1-oxohept-2-en-3-yl)-6,7-dihydro-[1,3]dioxolo[4,5-g]benzofuran-6-carboxylate (198)



198

To a solution of alkene **193** (57 mg, 120 μmol) in MeCN (6 mL) was added *N*-bromosuccinimide (21 mg, 120 μmol). The reaction mixture was stirred at rt for 16 h then concentrated *in vacuo*. Et₂O (30 mL) and water (30 mL) were added and the layers separated. The aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil (66 mg, 100%).

*R*_f = 0.4 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 500 MHz) δ = 7.03 (1H, s, ArH), 6.05 (2H, s, OCH₂O), 5.60 (1H, s, C=CH), 5.30 (1H, d, *J* = 9.4 Hz, CH_AH_B), 4.51 (1H, d, *J* = 9.5 Hz, CH_AH_B), 3.79 (3H, s, CO₂CH₃), 3.68 (3H, s, CO₂CH₃), 3.59 (2H, t, *J* = 6.2 Hz, OCH₂), 2.54 (2H, dd, *J* = 9.0, 7.0 Hz, CH₂C=CH), 1.50 – 1.19 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 0.89 (9H, s, TBS–C(CH₃)₃), 0.04 (6H, s, TBS–Si(CH₃)₂).

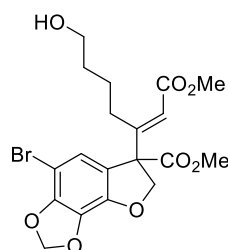
¹³C NMR (CDCl₃, 126 MHz) δ = 170.7 (CO₂CH₃), 166.2 (CO₂CH₃), 160.1 (C=CH), 148.4 (C_{Ar}), 142.7 (C_{Ar}), 131.1 (C_{Ar}), 123.1 (C_{Ar}), 122.5 (C_{Ar}H), 118.8 (C=CH), 102.5 (OCH₂O),

92.6 (C_{Ar}), 80.3 (CH_AH_B), 64.7 (C_{ArC}), 62.9 (OCH_2), 53.4 (CO_2CH_3), 51.4 (CO_2CH_3), 33.5 (OCH_2CH_2), 31.1 ($CH_2C=CH$), 26.3 ($OCH_2CH_2CH_2$), 26.1 (TBS- $C(CH_3)_3$), 18.5 (TBS- $C(CH_3)_3$), -5.2 (TBS-Si(CH_3)₂).

IR (film) ν_{max}/cm^{-1} 2953, 2930, 2857, 1740, 1724, 1451, 1255, 1208, 1097, 1069, 836.

HRMS: (ESI⁺) Found $[M + H]^+ = 571.1357$; $C_{25}H_{36}O_8BrSi$ requires 571.1357.

Methyl (*E*)-4-bromo-6-(7-hydroxy-1-methoxy-1-oxohept-2-en-3-yl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (200)⁷⁷



200

To a solution of alkene **198** (10 mg, 18 μ mol) in EtOH (1 mL) at 0 °C was added 1,3-diiodo-5,5-dimethylimidazolidine-2,4-dione (7.0 mg, 18 μ mol) followed by conc. H_2SO_4 (50 μ L). The reaction mixture was stirred at rt for 1 h then Et₂O (30 mL) and water (30 mL) were added and the layers separated. The aqueous layer was extracted with Et₂O (3 $\times$ 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:Et₂O, 20:80) afforded the title compound as a colourless oil (66 mg, 100%).

R_f = 0.4 (Pentane:Et₂O, 80:20).

¹H NMR ($CDCl_3$, 500 MHz) δ = 7.04 (1H, s, ArH), 6.09 – 6.02 (2H, m, OCH_2O), 5.62 (1H, s, $C=CH$), 5.30 (1H, d, J = 9.5 Hz, CH_AH_B), 4.52 (1H, d, J = 9.5 Hz, CH_AH_B), 3.81 (3H, s,

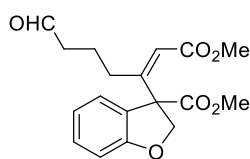
CO₂CH₃), 3.69 (5H, s, CO₂CH₃ and CH₂OH), 2.61 – 2.43 (2H, m, CH₂C=CH), 2.07 (1H, s, OH), 1.62 – 1.56 (5H, m, CH₂CH₂OH and CH₂CH₂CH₂OH).

¹³C NMR (CDCl₃, 126 MHz) δ = 170.7 (CO₂CH₃), 166.5 (CO₂CH₃), 160.6 (C=CH), 148.4 (C_{Ar}), 142.7 (C_{Ar}), 131.2 (C_{Ar}), 122.8 (C_{Ar}), 122.5 (C_{Ar}H), 118.5 (C=CH), 102.5 (OCH₂O), 92.6 (C_{Ar}), 80.2 (CH_AH_B), 64.8 (C_{Ar}C), 61.3 (CH₂OH), 53.4 (CO₂CH₃), 51.6 (CO₂CH₃), 32.4 (CH₂CH₂OH), 30.2 (CH₂C=CH), 25.5 (CH₂CH₂CH₂OH).

IR (film) ν_{max} /cm⁻¹ 2951, 1721, 1647, 1451, 1206, 1068, 929.

HRMS: (ESI⁺) Found [M + H]⁺ = 457.0491; C₁₉H₂₂BrO₈ requires 457.0493.

Methyl (Z)-3-(1-methoxy-1,7-dioxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (204)¹⁴⁷



204

To a solution of alcohol **187** (67 mg, 200 μ mol) in CH₂Cl₂ (2 mL) at 0 °C was added NaHCO₃ (40 mg, 480 μ mol) and Dess–Martin periodinane (127 mg, 300 μ mol). The reaction mixture was stirred at rt for 1.5 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 50:50) afforded the title compound as a colourless oil (56 mg, 84%).

R_f = 0.8 (Pentane:EtOAc, 50:50).

¹H NMR (CDCl₃, 500 MHz) δ = 9.54 (1H, t, *J* = 1.5 Hz, CHO), 7.25 – 7.19 (1H, m, ArH), 7.16 (1H, dd, *J* = 7.6, 1.3 Hz, ArH), 6.87 (1H, td, *J* = 7.5, 1.0 Hz, ArH), 6.83 (1H, d, *J* = 8.3 Hz, ArH), 5.87 (1H, t, *J* = 1.4 Hz, C=CH), 5.59 (1H, d, *J* = 9.9 Hz, CH_AH_B), 4.41 (1H,

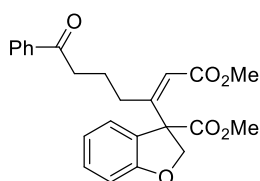
d, $J = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.68 (3H, s, CO_2CH_3), 3.68 (3H, s, CO_2CH_3), 2.29 – 2.23 (2H, m, CH_2CHO), 2.19 – 1.92 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.67 – 1.47 (2H, m, $\text{CH}_2\text{CH}_2\text{CHO}$).

^{13}C NMR (CDCl_3 , 126 MHz) $\delta = 201.5$ (CHO), 171.5 (CO_2CH_3), 166.6 (CO_2CH_3), 161.7 ($\text{C}=\text{CH}$), 160.8 (C_Ar), 130.5 ($\text{C}_\text{Ar}\text{H}$), 126.1 (C_Ar), 125.8 ($\text{C}_\text{Ar}\text{H}$), 120.6 ($\text{C}_\text{Ar}\text{H}$), 117.5 ($\text{C}=\text{CH}$), 110.7 ($\text{C}_\text{Ar}\text{H}$), 82.5 ($\text{CH}_\text{A}\text{H}_\text{B}$), 61.6 ($\text{C}_\text{Ar}\text{C}$), 52.9 (CO_2CH_3), 51.6 (CO_2CH_3), 43.0 (CH_2CHO), 36.5 ($\text{CH}_2\text{C}=\text{CH}$), 20.3 ($\text{CH}_2\text{CH}_2\text{CHO}$).

IR (film) $\nu_\text{max}/\text{cm}^{-1}$ 2952, 1717, 1633, 1594, 1481, 1229, 1147, 756.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 355.1153$; $\text{C}_{18}\text{H}_{20}\text{O}_6$ requires 355.1152.

Methyl (Z)-3-(1-methoxy-1,7-dioxo-7-phenylhept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (205)¹⁴⁸



205

Aldehyde **204** (20 mg, 60 μmol) was dissolved in DMF (500 μL), degassed with three freeze–pump–thaw cycles and warmed to rt before addition of iodobenzene (67 μL , 600 μmol), CrCl_2 (37 mg, 300 μmol) and NiCl_2 (8 mg, 60 μmol). The reaction mixture was stirred at room temperature for 3 h before addition of water (3 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude alcohol was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. NaHCO_3 (12 mg, 144 μmol) and Dess–Martin periodinane (38 mg, 90 μmol) was added and the reaction mixture stirred at rt for 1 h. Hexane (10 mL) was added and the mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*.

Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 65:35) afforded the title compound as a colourless oil (22 mg, 71%).

R_f = 0.4 (Pentane:EtOAc, 70:30).

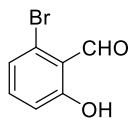
¹H NMR (CDCl₃, 500 MHz) δ = 7.87 – 7.82 (2H, m, ArH), 7.57 – 7.50 (1H, m, ArH), 7.43 (2H, t, J = 7.8 Hz, ArH $\times$ 2), 7.24 – 7.17 (2H, m, ArH $\times$ 2), 6.86 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.83 (1H, d, J = 8.0 Hz, ArH), 5.94 (1H, t, J = 1.4 Hz, C=CH), 5.61 (1H, d, J = 9.8 Hz, CH_AH_B), 4.44 (1H, d, J = 9.8 Hz, CH_AH_B), 3.69 (6H, s, CO₂CH₃ $\times$ 2), 2.79 (2H, t, J = 7.3 Hz, CH₂C(O)), 2.30 – 2.00 (2H, m, CH₂C=CH), 1.84 – 1.63 (2H, m, CH₂CH₂C(O)).

¹³C NMR (CDCl₃, 126 MHz) δ = 199.4 (C(O)CH₂), 171.6 (CO₂CH₃), 166.8 (CO₂CH₃), 162.0 (C=CH), 160.8 (C_{Ar}), 136.8 (C_{Ar}), 133.2 (C_{Ar}H), 130.4 (C_{Ar}H), 128.7 (C_{Ar}H), 128.1 (C_{Ar}H), 126.2 (C_{Ar}), 125.9 (C_{Ar}H), 120.6 (C_{Ar}H), 117.4 (C=CH), 110.7 (C_{Ar}H), 82.5 (CH_AH_B), 61.7 (C_{Ar}C), 52.9 (CO₂CH₃), 51.6 (CO₂CH₃), 37.7 (C(O)CH₂), 36.7 (CH₂C=CH), 22.5 (C(O)CH₂CH₂).

IR (film) ν_{max} /cm⁻¹ 2951, 1736, 1715, 1685, 1481, 1228, 754.

HRMS: (ESI⁺) Found [M + Na]⁺ = 431.1465; C₂₄H₂₄O₆Na requires 431.1465.

2-Bromo-6-hydroxybenzaldehyde (213)¹⁴⁹



213

To a suspension of NaH (1.20 g, 30.0 mmol, 60 wt% in mineral oil) in THF (30 mL) at rt was added dropwise 3-bromophenol (2.60 g, 15.0 mmol) in THF (5 mL). The solution was stirred for 15 min and diethylcarbonyl chloride (2.76 mL, 30.0 mmol) was added in THF (3 mL). The reaction mixture was stirred for 16 h and water (30 mL) was added at 0 °C.

After warming to rt, Et₂O (30 mL) was added and the layers separated. The aqueous layer was extracted with Et₂O (3 × 20 mL) and the combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Separately, diisopropylamine (3.15 mL, 22.5 mmol) in THF (30 mL) was cooled to 0 °C and ⁿBuLi (9.00 mL, 22.5 mmol, 2.5 M hexanes) was added dropwise and the solution stirred for 30 min at 0 °C, then cooled to –78 °C. The residue from the previous step was dissolved in THF (5 mL) and added dropwise to the solution. The reaction mixture was stirred at –78 °C for 30 min, then DMF (3.48 mL, 45.0 mmol) was added dropwise. The mixture was stirred for a further 30 min at –78 °C, then 30 min at rt. The reaction mixture was cooled to 0 °C and HCl (15 mL, 30 mmol, 2 M aq.) was added. The solution was stirred at rt for 20 min and KOH (20 mL, 40 mmol, 2 M aq.) was added followed by Et₂O (100 mL). The two layers were separated and HCl (25 mL, 50 mmol, 2 M aq.) was added to the aqueous layer followed by Et₂O (100 mL). The layers were again separated and the aqueous layer extracted with Et₂O (3 × 100 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound (2.07 g, 69%) with no further purification necessary.

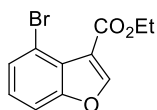
R_f = 0.7 (Pentane:Et₂O, 80:20).

m.p. 55 °C

¹H NMR (CDCl₃, 400 MHz) δ = 12.00 (1H, s, CHO), 10.35 (1H, d, *J* = 0.6 Hz, OH), 7.35 (1H, dd, *J* = 8.5, 7.8 Hz, ArH), 7.18 (1H, dd, *J* = 7.8, 1.0 Hz, ArH), 6.96 (1H, dt, *J* = 8.5, 0.8 Hz, ArH).

¹³C NMR (CDCl₃, 101 MHz) δ = 198.0 (CHO), 164.1 (C_{Ar}), 137.7 (C_{Ar}H), 127.6 (C_{Ar}), 124.6 (C_{Ar}H), 118.0 (C_{Ar}H).

Analytical data are in accordance with those previously reported for this compound.¹⁴⁹

Ethyl 4-bromobenzofuran-3-carboxylate (214)³⁶**214**

To a solution of aldehyde **213** (2.00 g, 9.94 mmol) and $\text{HBF}_4 \cdot \text{OEt}_2$ (137 μL , 995 μmol) in CH_2Cl_2 (10 mL) at rt was added dropwise a solution of ethyl diazoacetate (1.97 mL, 15.9 mmol) in CH_2Cl_2 (20 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 30 min and then concentrated *in vacuo* after nitrogen evolution had ceased. conc. H_2SO_4 (2.00 mL) was added and the reaction mixture was stirred at room temperature for 30 min. CH_2Cl_2 (30 mL) was added followed by solid NaHCO_3 until gas evolution had ceased. The solution was washed successively with water (30 mL), 1 M aq. NaOH (20 mL) and sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (2.26 g, 84%).

$R_f = 0.7$ (Pentane: Et_2O , 60:40).

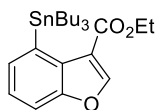
m.p. 45 $^\circ\text{C}$

^1H NMR (CDCl_3 , 400 MHz) δ = 8.21 (1H, s, ArH), 7.55 (1H, dd, $J = 7.8, 0.9$ Hz, ArH), 7.50 (1H, dd, $J = 8.3, 0.9$ Hz, ArH), 7.21 (1H, t, $J = 8.1$ Hz, ArH), 4.40 (2H, q, $J = 7.1$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.41 (3H, t, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 162.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 156.3 (C_{Ar}), 151.4 (C_{ArH}), 129.5 (C_{ArH}), 126.3 (C_{ArH}), 124.6 (C_{Ar}), 115.8 (C_{Ar}), 114.3 (C_{Ar}), 111.2 (C_{ArH}), 61.3 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2982, 1734, 1559, 1126, 897, 761.

HRMS: (APCI⁺) Found $[\text{M}]^+ = 268.9811$; $\text{C}_{11}\text{H}_{10}\text{O}_3\text{Br}$ requires 268.9808.

Ethyl 4-(tributylstannyl)benzofuran-3-carboxylate (217)⁸⁸**217**

To a solution of benzofuran **214** (81 mg, 300 μmol) in dioxane (2 mL) in a microwave vial was added successively $\text{Pd}_2(\text{dba})_3$ (7.0 mg, 7.5 μmol), JohnPhos (13 mg, 45 μmol) and bis(tributyltin) **216** (230 μL , 450 μmol). The reaction mixture was heated at 110 $^\circ\text{C}$ for 16 h, filtered through Celite[®] and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_3N , 99:1) afforded the title compound as a colourless oil (93 mg, 65%).

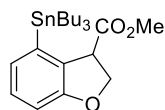
R_f = 0.8 (Pentane: Et_2O , 95:5).

^1H NMR (CDCl_3 , 400 MHz) δ = 8.23 (1H, s, ArH), 7.52 (1H, dd, J = 7.1, 1.0 Hz, ArH), 7.48 (1H, dd, J = 8.3, 1.0 Hz, ArH), 7.31 (1H, dd, J = 8.3, 7.0 Hz, ArH), 4.36 (2H, q, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.58 – 1.46 (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 1.39 (3H, t, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.32 (6H, q, J = 7.3 Hz, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 1.17 – 1.02 (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 0.87 (9H, t, J = 7.3 Hz, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 163.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 155.2 (C_{Ar}), 150.9 (C_{ArH}), 137.1 (C_{Ar}), 133.6 (C_{ArH}), 130.9 (C_{Ar}), 124.6 (C_{ArH}), 115.8 (C_{Ar}), 111.6 (C_{ArH}), 60.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 29.3 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 27.6 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 14.6 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 13.9 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 12.6 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2922, 2871, 2853, 1720, 1405, 1280, 1139, 766.

HRMS: (APCI[−]) Found $[\text{M} - \text{H}]^-$ = 479.1609; $\text{C}_{23}\text{H}_{35}\text{O}_3\text{Sn}$ requires 479.1614.

Methyl 4-(tributylstannyl)-2,3-dihydrobenzofuran-3-carboxylate (218)¹³⁷**218**

Mg turnings (170 mg, 6.99 mmol) were added to a solution of benzofuran **217** (670 mg, 1.40 mmol) in MeOH (9 mL) at rt. After 4 h the reaction was heated at 70 °C for 1 h. CH₂Cl₂ (100 mL) and water (100 mL) were added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 100 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O:Et₃N, 95:4.5:0.5) afforded the title compound as a colourless oil (621 mg, 92%).

*R*_f = 0.3 (Pentane:Et₂O, 95:5).

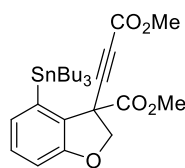
¹H NMR (CDCl₃, 400 MHz) δ = 7.15 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.03 – 6.90 (1H, m, Ar*H*), 6.79 (1H, dd, *J* = 8.0, 1.1 Hz, Ar*H*), 4.85 (1H, dd, *J* = 9.2, 3.2 Hz, CH_AH_B), 4.57 (1H, t, *J* = 9.2 Hz, CH_AH_B), 4.13 (1H, dd, *J* = 9.1, 3.1 Hz, CH), 3.70 (3H, s, CO₂CH₃), 1.55 – 1.43 (6H, m, SnCH₂CH₂CH₂CH₃ × 3), 1.39 – 1.28 (6H, m, SnCH₂CH₂CH₂CH₃ × 3), 1.16 – 0.98 (6H, m, SnCH₂CH₂CH₂CH₃ × 3), 0.89 (9H, t, *J* = 7.3 Hz, SnCH₂CH₂CH₂CH₃ × 3).

¹³C NMR (CDCl₃, 101 MHz) δ = 172.6 (CO₂CH₃), 159.3 (*C*_{Ar}), 140.0 (*C*_{Ar}), 131.6 (*C*_{Ar}), 129.4 (*C*_{Ar}H), 128.8 (*C*_{Ar}H), 110.1 (*C*_{Ar}H), 73.1 (CH_AH_B), 52.7 (CO₂CH₃), 49.2 (CH), 29.3 (SnCH₂CH₂CH₂CH₃ × 3), 27.6 (SnCH₂CH₂CH₂CH₃ × 3), 13.8 (SnCH₂CH₂CH₂CH₃ × 3), 10.4 (SnCH₂CH₂CH₂CH₃ × 3).

IR (film) ν_{max} /cm⁻¹ 2955, 2922, 2871, 2852, 1735, 1569, 1421, 1246, 1213, 982, 775.

HRMS: (ESI⁺) Found [M + Na]⁺ = 491.1583; C₂₂H₃₆O₃NaSn requires 491.1579.

Methyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)-4-(tributylstannyl)-2,3-dihydrobenzofuran-3-carboxylate (219)



219

To a stirred solution of ester **218** (657 mg, 1.41 mmol) in THF (12 mL) at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (1.69 mL, 1.69 mmol, 1 M in THF). After 10 min chloroacetylene **145** (250 mg, 2.11 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Sat. aq. NH_4Cl (5 mL) was added and the mixture extracted with Et_2O ($3 \times 50\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O : Et_3N , 93:6.5:0.5) afforded the title compound as a colourless oil (368 mg, 48%).

$R_f = 0.2$ (Pentane: Et_2O , 95:5).

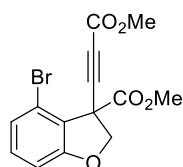
^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.20$ (1H, t, $J = 7.2\text{ Hz}$, ArH), 7.06 (1H, dd, $J = 7.3, 1.1\text{ Hz}$, ArH), 6.81 (1H, dd, $J = 8.0, 1.2\text{ Hz}$, ArH), 4.89 (1H, d, $J = 9.1\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.72 (1H, d, $J = 9.1\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.79 (3H, s, CO_2CH_3), 3.77 (3H, s, CO_2CH_3), $1.58 - 1.43$ (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), $1.36 - 1.28$ (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), $1.21 - 1.04$ (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 0.89 (9H, t, $J = 7.3\text{ Hz}$, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 169.6$ ($\text{CO}_2\text{CH}_2\text{CH}_3$), 159.3 (C_Ar), 153.5 (CO_2CH_3), 140.5 (C_Ar), 131.9 (C_Ar), 130.5 ($\text{C}_\text{Ar}\text{H}$), 129.6 ($\text{C}_\text{Ar}\text{H}$), 110.6 ($\text{C}_\text{Ar}\text{H}$), 85.1 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 80.1 ($\text{CH}_\text{A}\text{H}_\text{B}$), 77.5 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 53.8 (CO_2CH_3), 53.2 ($\text{C}_\text{Ar}\text{C}$), 52.8 (CO_2CH_3), 29.2 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 27.5 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 13.7 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 11.1 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2924, 2871, 2853, 2242, 1746,

HRMS: (ESI⁺) Found $[\text{M} + \text{H}]^+ = 551.1815$; $\text{C}_{26}\text{H}_{39}\text{O}_5\text{Sn}$ requires 551.1814.

Methyl 4-bromo-3-(3-methoxy-3-oxoprop-1-yn-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (220)



220

To a solution of stannane **219** (200 mg, 360 μmol) in THF (3.6 mL) at 0 °C was added *N*-bromosuccinimide (78 mg, 440 μmol). The reaction mixture was stirred at rt for 2 h. Water (30 mL) was added and the mixture extracted with Et₂O (3 $\times$ 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10 to 80:20) afforded the title compound as a yellow oil (69 mg, 56%).

$R_f = 0.3$ (Pentane:Et₂O, 70:30).

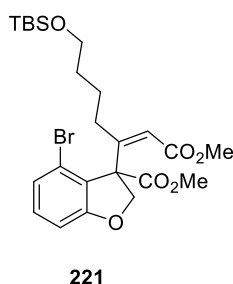
¹H NMR (CDCl₃, 400 MHz) δ = 7.15 – 7.05 (2H, m, ArH $\times$ 2), 6.83 (1H, dd, J = 7.7, 1.3 Hz, ArH), 4.91 (1H, d, J = 9.0 Hz, CH_AH_B), 4.84 (1H, d, J = 9.1 Hz, CH_AH_B), 3.84 (3H, s, CO₂CH₃), 3.77 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 168.6 (CO₂CH₃), 160.9 (CO₂CH₃), 153.6 (C_{Ar}), 132.1 (C_{Ar}H), 126.0 (C_{Ar}), 125.7 (C_{Ar}H), 119.4 (C_{Ar}), 109.9 (C_{Ar}H), 82.5 (C $\equiv$ CCO₂CH₃), 80.9 (CH_AH_B), 77.8 (C $\equiv$ CCO₂CH₃), 54.1 (CO₂CH₃), 53.3 (C_{Ar}C), 53.0 (CO₂CH₃).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2246, 1746, 1717, 1583, 1436, 1288, 1246, 887.

HRMS: (ESI⁺) Found $[\text{M} + \text{Na}]^+ = 360.9683$; $\text{C}_{14}\text{H}_{11}\text{O}_5\text{BrNa}$ requires 360.9682.

Methyl (Z)-4-bromo-3-(7-((tert-butyldimethylsilyl)oxy)-1-methoxy-1-oxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (221)⁵⁷



To a solution of iodide **185** (230 mg, 720 μ mol) in pentane (2.7 mL) and Et₂O (1.8 mL) at $-78\text{ }^{\circ}\text{C}$ was added ^tBuLi (850 μ L, 1.44 mmol, 1.7 M in pentane). After 10 min CuI (69 mg, 360 μ mol) was added and the mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **220** (61 mg, 180 μ mol) in Et₂O (0.5 mL + 0.2 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Methanol (0.5 mL) was added and the mixture partitioned between water (50 mL) and Et₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10 to 80:20) afforded the title compound as a colourless oil and a single diastereomer (54 mg, 57%) in addition to recovered alkyne **220** (19 mg, 31%).

$R_f = 0.4$ (Pentane:Et₂O, 60:40).

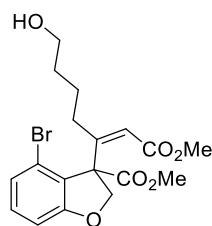
¹H NMR (CDCl₃, 400 MHz) δ = 7.10 – 7.00 (2H, m, ArH $\times$ 2), 6.80 (1H, dd, J = 7.8, 1.2 Hz, ArH $\times$ 2), 5.94 (1H, t, J = 1.5 Hz, C=CH), 5.53 (1H, d, J = 9.7 Hz, CH_AH_B), 4.52 (1H, d, J = 9.6 Hz, CH_AH_B), 3.68 (6H, d, J = 1.1 Hz, CO₂CH₃ $\times$ 2), 3.45 (2H, t, J = 5.5 Hz, OCH₂), 2.40 – 1.93 (2H, m, CH₂C=CH), 1.45 – 1.26 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 0.85 (9H, s, TBS-C(CH₃)₃), -0.00 (6H, s, TBS-Si(CH₃)₂).

¹³C NMR (CDCl₃, 101 MHz) δ = 170.6 (CO₂CH₃), 167.1 (CO₂CH₃), 162.6 (C_{Ar}), 160.4 (C=CH), 131.4 (C_{Ar}H), 127.2 (C_{Ar}), 125.6 (C_{Ar}H), 120.4 (C_{Ar}), 117.9 (C=CH), 109.8 (C_{Ar}H), 84.5 (CH_AH_B), 63.3 (C_{Ar}C), 62.8 (OCH₂), 52.6 (CO₂CH₃), 51.5 (CO₂CH₃), 36.3 (CH₂C=CH), 32.3 (OCH₂CH₂), 26.1 (TBS–C(CH₃)₃), 24.4 (OCH₂CH₂CH₂), 18.5 (TBS–C(CH₃)₃), –5.2 (TBS–Si(CH₃)₂).

IR (film) $\nu_{\max}$ /cm^{–1} 2951, 2857, 1738, 1715, 1436, 1255, 1232, 1213, 1096, 887, 837, 775.

HRMS: (ESI⁺) Found [M + H]⁺ = 527.1462; C₂₄H₃₆O₆BrSi requires 527.1459.

Methyl (Z)-4-bromo-3-(7-hydroxy-1-methoxy-1-oxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (222)⁶⁶



222

To a solution of alkene **221** (52 mg, 99 μ mol) in MeOH (2 mL) was added FeCl₃ (2.0 mg, 10 μ mol). The reaction mixture was stirred at rt for 1.5 h then filtered through a plug of silica using EtOAc as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 60:40) afforded the title compound as a colourless oil (37 mg, 92%).

R_f = 0.4 (Pentane:EtOAc, 50:50).

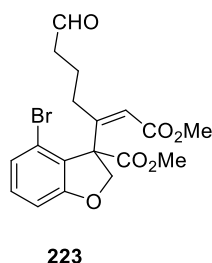
¹H NMR (CDCl₃, 400 MHz) δ = 7.16 – 6.95 (2H, m, ArH $\times$ 2), 6.81 (1H, dd, J = 7.8, 1.3 Hz, ArH), 5.95 (1H, d, J = 1.5 Hz, C=CH), 5.52 (1H, d, J = 9.7 Hz, CH_AH_B), 4.53 (1H, d, J = 9.7 Hz, CH_AH_B), 3.68 (6H, s, CO₂CH₃ $\times$ 2), 3.54 – 3.40 (2H, m, CH₂OH), 2.39 – 1.96 (2H, m, CH₂C=CH), 1.52 – 1.21 (5H, m, OCH₂CH₂, OCH₂CH₂CH₂ and OH).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 170.6 (CO_2CH_3), 167.1 (CO_2CH_3), 162.6 ($\text{C}=\text{CH}$), 160.3 (C_{Ar}), 131.5 (C_{ArH}), 127.2 (C_{Ar}), 125.6 (C_{ArH}), 120.4 (C_{Ar}), 118.1 ($\text{C}=\text{CH}$), 109.8 (C_{ArH}), 84.7 (CH_{AHB}), 63.2 (C_{ArC}), 62.4 (CH_2OH), 52.7 (CO_2CH_3), 51.6 (CO_2CH_3), 36.3 ($\text{CH}_2\text{C}=\text{CH}$), 32.1 (OCH_2CH_2), 24.4 ($\text{OCH}_2\text{CH}_2\text{CH}_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3399, 2949, 1733, 1712, 1437, 1254, 1233, 1215, 886.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 435.0411$; $\text{C}_{18}\text{H}_{21}\text{O}_6\text{BrNa}$ requires 435.0414.

Methyl (Z)-4-bromo-3-(1-methoxy-1,7-dioxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (223)¹⁴⁷



To a solution of alcohol **222** (35 mg, 85 μmol) in CH_2Cl_2 (1 mL) at 0 $^\circ\text{C}$ was added NaHCO_3 (18 mg, 210 μmol) and Dess–Martin periodinane (60 mg, 130 μmol). The reaction mixture was stirred at rt for 2 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 75:25) afforded the title compound as a colourless oil (23 mg, 66%).

R_f = 0.7 (Pentane: EtOAc , 50:50).

^1H NMR (CDCl_3 , 400 MHz) δ = 9.59 (1H, t, J = 1.4 Hz, CHO), 7.13 – 7.01 (2H, m, $\text{ArH} \times 2$), 6.82 (1H, dd, J = 7.8, 1.2 Hz, ArH), 5.96 (1H, t, J = 1.5 Hz, $\text{C}=\text{CH}$), 5.53 (1H, d, J = 9.7 Hz, CH_{AHB}), 4.53 (1H, d, J = 9.8 Hz, CH_{AHB}), 3.69 (3H, s, CO_2CH_3), 3.68 (3H, s,

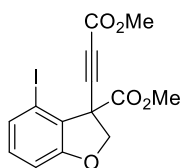
CO₂CH₃), 2.41 – 1.98 (4H, m, CH₂C=CH and CH₂CHO), 1.71 – 1.57 (2H, m, CH₂CH₂CHO).

¹³C NMR (CDCl₃, 101 MHz) δ = 201.4 (CHO), 170.5 (CO₂CH₃), 166.9 (CO₂CH₃), 162.5 (C_{Ar}), 159.3 (C=CH), 131.6 (C_{Ar}H), 127.0 (C_{Ar}), 125.7 (C_{Ar}H), 120.4 (C_{Ar}), 118.5 (C=CH), 109.9 (C_{Ar}H), 84.6 (CH_AH_B), 63.2 (C_{Ar}C), 52.7 (CO₂CH₃), 51.7 (CO₂CH₃), 43.1 (CH₂CHO), 35.6 (CH₂C=CH), 20.5 (CH₂CH₂CHO).

IR (film) ν_{max} /cm⁻¹ 2951, 1716, 1438, 1255, 1234, 979, 886.

HRMS: (ESI⁺) Found [M + Na]⁺ = 433.0259; C₁₈H₁₉O₆BrNa requires 433.0258.

Methyl 4-iodo-3-(3-methoxy-3-oxoprop-1-yn-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (224)



224

To a solution of stannane **219** (100 mg, 190 μ mol) in CHCl₃ (10 mL) was added dropwise iodine (9.5 mL, 228 μ mol, 0.024 M in CHCl₃). The reaction mixture was stirred for 1 h and sat. aq. Na₂S₂O₃ (10 mL) was added. The mixture was extracted with CHCl₃ (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (64 mg, 87%).

R_f = 0.3 (Pentane:Et₂O, 70:30).

¹H NMR (CDCl₃, 400 MHz) δ = 7.35 (1H, dd, J = 7.8, 1.0 Hz, ArH), 6.96 (1H, t, J = 8.0 Hz, ArH), 6.87 (1H, dd, J = 8.2, 1.1 Hz, ArH), 4.89 (1H, d, J = 9.1 Hz, CH_AH_B), 4.85 (2H, d, J = 9.1 Hz, CH_AH_B), 3.86 (3H, s, CO₂CH₃), 3.79 (3H, s, CO₂CH₃).

$R_f = 0.3$ (Pentane:Et₂O, 80:20).

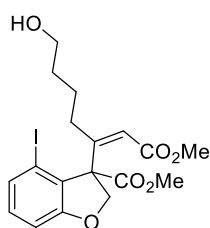
¹H NMR (CDCl₃, 400 MHz) δ = 7.32 (1H, dd, J = 7.6, 1.3 Hz, ArH), 6.91 – 6.82 (2H, m, ArH $\times$ 2), 5.96 (1H, t, J = 1.5 Hz, C=CH), 5.51 (1H, d, J = 9.7 Hz, CH_AH_B), 4.51 (1H, d, J = 9.8 Hz, CH_AH_B), 3.69 (3H, s, CO₂CH₃), 3.68 (3H, s, CO₂CH₃), 3.46 (2H, dt, J = 8.0, 3.0 Hz, OCH₂), 2.41 – 1.93 (2H, m, CH₂C=CH), 1.55 – 1.30 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 0.86 (9H, s, TBS–C(CH₃)₃), 0.00 (6H, d, J = 0.9 Hz, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 170.5 (CO₂CH₃), 167.2 (CO₂CH₃), 161.9 (C_{Ar}), 159.5 (C=CH), 132.7 (C_{Ar}H), 131.5 (C_{Ar}), 130.3 (C_{Ar}H), 118.3 (C=CH), 110.7 (C_{Ar}H), 93.1 (C_{Ar}), 84.0 (CH_AH_B), 64.3 (C_{Ar}C), 62.8 (OCH₂), 52.5 (CO₂CH₃), 51.5 (CO₂CH₃), 36.7 (CH₂C=CH), 32.3 (OCH₂CH₂), 26.1 (TBS–C(CH₃)₃), 24.5 (OCH₂CH₂CH₂), 18.5 (TBS–C(CH₃)₃), –5.2 (TBS–Si(CH₃)₂).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2950, 2857, 1736, 1716, 1459, 1254, 1231, 1098, 837.

HRMS: (ESI⁺) Found $[M + H]^+ = 597.1138$; C₂₄H₃₅O₆INaSi requires 597.1140.

Methyl (Z)-3-(7-hydroxy-1-methoxy-1-oxohept-2-en-3-yl)-4-iodo-2,3-dihydrobenzofuran-3-carboxylate (226)⁶⁶



226

To a solution of alkene **225** (54 mg, 94 μmol) in MeOH (2 mL) was added FeCl₃ (1.5 mg, 9.4 μmol). The reaction mixture was stirred at rt for 3 h then filtered through a plug of silica using EtOAc as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 70:30 to 50:50) afforded the title compound as a colourless oil (35 mg, 81%).

$R_f = 0.4$ (Pentane:EtOAc, 50:50).

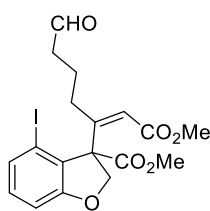
^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.27$ (1H, dd, $J = 7.5, 1.3$ Hz, ArH), 6.89 – 6.76 (2H, m, $\text{ArH} \times 2$), 5.91 (1H, t, $J = 1.5$ Hz, $\text{C}=\text{CH}$), 5.44 (1H, d, $J = 9.7$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.45 (1H, d, $J = 9.7$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.63 (3H, s, CO_2CH_3), 3.62 (3H, s, CO_2CH_3), 3.49 – 3.36 (2H, m, CH_2OH), 2.35 – 1.95 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.42 – 1.25 (5H, m, OCH_2CH_2 , $\text{OCH}_2\text{CH}_2\text{CH}_2$ and OH).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 170.5$ (CO_2CH_3), 167.1 (CO_2CH_3), 161.9 ($\text{C}=\text{CH}$), 159.4 (C_Ar), 132.7 ($\text{C}_\text{Ar}\text{H}$), 131.5 ($\text{C}_\text{Ar}\text{H}$), 130.4 (C_Ar), 118.6 ($\text{C}=\text{CH}$), 110.7 ($\text{C}_\text{Ar}\text{H}$), 93.2 (C_Ar), 84.1 ($\text{CH}_\text{A}\text{H}_\text{B}$), 64.2 ($\text{C}_\text{Ar}\text{C}$), 62.4 (CH_2OH), 52.5 (CO_2CH_3), 51.6 (CO_2CH_3), 36.7 ($\text{CH}_2\text{C}=\text{CH}$), 32.2 (OCH_2CH_2), 24.4 ($\text{OCH}_2\text{CH}_2\text{CH}_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3447, 2949, 1733, 1713, 1568, 1434, 1253, 1233, 869.

HRMS: (EI^-) Found $[\text{M}]^- = 460.0379$; $\text{C}_{18}\text{H}_{21}\text{IO}_6$ requires 460.0377.

Methyl (Z)-4-iodo-3-(1-methoxy-1,7-dioxohept-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (227**)¹⁴⁷**



227

To a solution of alcohol **226** (33 mg, 72 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added NaHCO_3 (15 mg, 180 μmol) and Dess–Martin periodinane (51 mg, 110 μmol). The reaction mixture was stirred at rt for 2 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column

chromatography (SiO₂, Pentane:Et₂O, 70:30) afforded the title compound as a colourless oil (17 mg, 51%).

*R*_f = 0.8 (Pentane:EtOAc, 50:50).

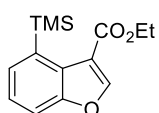
¹H NMR (CDCl₃, 400 MHz) δ = 9.60 (1H, t, *J* = 1.4 Hz, CHO), 7.34 (1H, dd, *J* = 7.6, 1.2 Hz, ArH), 6.94 – 6.83 (2H, m, ArH $\times$ 2), 5.98 (1H, t, *J* = 1.5 Hz, C=CH), 5.51 (1H, d, *J* = 9.7 Hz, CH_AH_B), 4.52 (1H, d, *J* = 9.7 Hz, CH_AH_B), 3.69 (6H, s, CO₂CH₃ $\times$ 2), 2.42 – 1.99 (4H, m, CH₂C=CH and CH₂CHO), 1.74 – 1.59 (2H, m, CH₂CH₂CHO).

¹³C NMR (CDCl₃, 101 MHz) δ = 201.4 (CHO), 170.3 (CO₂CH₃), 167.0 (CO₂CH₃), 161.9 (C_{Ar}), 158.5 (C=CH), 132.8 (C_{Ar}H), 131.6 (C_{Ar}H), 130.2 (C_{Ar}), 119.0 (C=CH), 110.8 (C_{Ar}H), 93.1 (C_{Ar}), 84.1 (CH_AH_B), 64.2 (C_{Ar}C), 52.6 (CO₂CH₃), 51.6 (CO₂CH₃), 43.1 (CH₂CHO), 36.0 (CH₂C=CH), 20.6 (CH₂CH₂CHO).

IR (film) ν_{max} /cm⁻¹ 2950, 1717, 1632, 1568, 1434, 1253, 1233, 869.

HRMS: (ESI⁺) Found [M + Na]⁺ = 481.0119; C₁₈H₁₉O₆INa requires 481.0119.

Ethyl 4-(trimethylsilyl)benzofuran-3-carboxylate (**232**)⁹⁴



232

To a solution of bromide **214** (140 mg, 500 μ mol) in degassed DMPU (1.6 mL) was added tris(dibenzylideneacetone)dipalladium(0) (7.0 mg, 7.5 μ mol), JohnPhos (13 mg, 45 μ mol) and KF (150 mg, 2.5 mmol). The reaction mixture was stirred for 5 min at rt and water (18 μ L, 1.0 mmol) and hexamethyldisilane **231** (120 μ L, 600 μ mol) were added successively. The reaction mixture was heated at 100 °C for 16 h and hexane (40 mL) was added. The organic layer was washed with sat. aq. LiCl (3 $\times$ 20 mL), dried over MgSO₄ and

concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 99:1) afforded the title compound as a pale yellow oil (76 mg, 58%).

R_f = 0.8 (Pentane: Et₂O, 90:10).

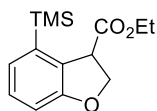
¹H NMR (CDCl₃, 400 MHz) δ = 8.26 (1H, s, ArH), 7.59 (1H, dd, *J* = 7.2, 1.1 Hz, ArH), 7.54 (1H, dd, *J* = 8.3, 1.1 Hz, ArH), 7.34 (1H, dd, *J* = 8.3, 7.3 Hz, ArH), 4.38 (2H, q, *J* = 7.1 Hz, CO₂CH₂CH₃), 1.39 (3H, t, *J* = 7.1 Hz, CO₂CH₂CH₃), 0.40 (9H, s, TMS-Si(CH₃)₃).

¹³C NMR (CDCl₃, 126 MHz) δ = 163.5 (CO₂CH₂CH₃), 155.6 (C_{Ar}), 151.4 (C_{Ar}H), 135.1 (C_{Ar}), 131.7 (C_{Ar}H), 128.0 (C_{Ar}), 124.6 (C_{Ar}H), 116.6 (C_{Ar}), 112.8 (C_{Ar}H), 60.7 (CO₂CH₂CH₃), 14.6 (CO₂CH₂CH₃), 1.3 (TMS-Si(CH₃)₃).

IR (film) ν_{max} /cm⁻¹ 2981, 2958, 1732, 1556, 1401, 1144, 842, 764.

HRMS: (APCI⁺) Found [M + H]⁺ = 263.1090; C₁₄H₁₉O₃Si requires 263.1098.

Ethyl 4-(trimethylsilyl)-2,3-dihydrobenzofuran-3-carboxylate (233)¹³⁷



233

To a solution of benzofuran **232** (70 mg, 270 μ mol) in MeOH (2.0 mL) was added freshly ground Mg turnings (32 mg, 1.30 mmol). The reaction was stirred at rt for 1 h before sat. aq. NH₄Cl (5 mL) was added followed by water (20 mL) and Et₂O (30 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a white solid (70 mg, 100%).

R_f = 0.4 (Pentane:Et₂O, 90:10).

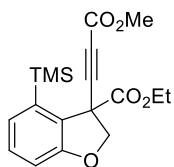
¹H NMR (CDCl₃, 400 MHz) δ = 7.20 (1H, t, J = 7.8 Hz, ArH), 7.05 (1H, d, J = 8.5 Hz, ArH), 6.86 (1H, d, J = 8.0 Hz, ArH), 4.74 (1H, dt, J = 9.3, 2.5 Hz, CH_AH_B), 4.60 (1H, t, J = 9.2 Hz, CH_AH_B), 4.25 (1H, dt, J = 9.4, 2.5 Hz, CH), 4.17 (2H, q, J = 7.2 Hz, CO₂CH₂CH₃), 1.25 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 0.29 (9H, s, TMS-Si(CH₃)₃).

¹³C NMR (CDCl₃, 126 MHz) δ = 172.8 (CO₂CH₂CH₃), 159.8 (C_{Ar}), 137.9 (C_{Ar}), 129.4 (C_{Ar}), 129.0 (C_{Ar}H), 127.0 (C_{Ar}H), 110.9 (C_{Ar}H), 74.0 (CH_AH_B), 61.5 (CO₂CH₂CH₃), 48.5 (CH), 14.3 (CO₂CH₂CH₃), -0.3 (TMS-Si(CH₃)₃).

IR (film) ν_{max} /cm⁻¹ 2956, 2899, 1732, 1571, 1422, 1249,

HRMS: (APCI⁺) Found [M + H]⁺ = 265.1258; C₁₄H₂₁O₃Si requires 265.1255.

Ethyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)-4-(trimethylsilyl)-2,3-dihydrobenzofuran-3-carboxylate (234)



234

To a stirred solution of ester **235** (310 mg, 1.17 mmol) in THF (10 mL) at -78 °C was added LiHMDS (1.41 mL, 1.41 mmol, 1 M in THF). After 10 min chloroacetylene **145** (208 mg, 1.76 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. Sat. aq. NH₄Cl (5 mL) was added and the mixture extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (280 mg, 69%).

R_f = 0.2 (Pentane:Et₂O, 90:10).

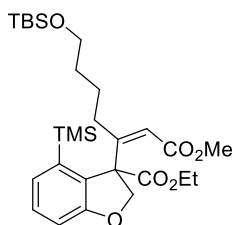
¹H NMR (CDCl₃, 400 MHz) δ = 7.04 (1H, t, *J* = 3.8 Hz, ArH), 6.93 (1H, dd, *J* = 7.5, 1.2 Hz, ArH), 6.66 (1H, dd, *J* = 7.9, 1.2 Hz, ArH), 4.55 (2H, s, CH_AH_B and CH_AH_B), 4.09 – 3.98 (2H, m, CO₂CH₂CH₃), 3.55 (3H, s, CO₂CH₃), 1.07 (3H, t, *J* = 7.1 Hz, CO₂CH₂CH₃), 0.11 (9H, s, TMS-Si(CH₃)₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 169.7 (CO₂CH₂CH₃), 159.8 (C_{Ar}), 153.7 (CO₂CH₃), 138.4 (C_{Ar}), 129.9 (C_{Ar}H), 129.8 (C_{Ar}), 128.6 (C_{Ar}H), 111.6 (C_{Ar}H), 85.6 (CH_AH_B), 81.1 (C≡CCO₂CH₃), 78.2 (C≡CCO₂CH₃), 63.1 (CO₂CH₂CH₃), 53.0 (CO₂CH₃), 52.8 (C_{Ar}C), 14.1 (CO₂CH₂CH₃), 0.5 (TMS-Si(CH₃)₃).

IR (film) ν_{max} /cm⁻¹ 2956, 2244, 1742, 1719, 1283, 1249, 839.

HRMS: (ESI⁺) Found [M + Na]⁺ = 369.1129; C₁₈H₂₂O₅NaSi requires 369.1129.

Ethyl (Z)-3-(7-((tert-butyldimethylsilyl)oxy)-1-methoxy-1-oxohept-2-en-3-yl)-4-(trimethylsilyl)-2,3-dihydrobenzofuran-3-carboxylate (235)⁵⁷



235

To a solution of iodide **185** (152 mg, 485 μ mol) in pentane (1.8 mL) and Et₂O (1.2 mL) at –78 °C was added ^tBuLi (570 μ L, 570 μ mol, 1.7 M in pentane). After 10 min CuI (46.0 mg, 242 μ mol) was added and the mixture was stirred vigorously at 0 °C for 1 h before being cooled to –78 °C. A solution of alkyne **234** (42.0 mg, 121 μ mol) in Et₂O (0.5 mL + 0.2 mL) was added dropwise and the reaction mixture stirred at –78 °C for 30 min. Methanol (0.5 mL) was added and the mixture partitioned between water (15 mL) and Et₂O (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$

20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil and a single diastereomer (47 mg, 72%).

R_f = 0.6 (Pentane:Et₂O, 80:20).

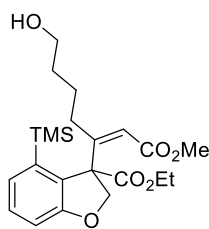
¹H NMR (CDCl₃, 500 MHz) δ = 7.19 (1H, t, *J* = 7.7 Hz, ArH), 7.09 (1H, dd, *J* = 7.5, 1.2 Hz, ArH), 6.85 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 5.87 (1H, t, *J* = 0.8 Hz, C=CH), 5.60 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.35 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.25 – 3.95 (2H, m, CO₂CH₂CH₃), 3.66 (3H, s, CO₂CH₃), 3.43 (2H, t, *J* = 6.1 Hz, OCH₂), 2.17 – 1.86 (2H, m, CH₂C=CH), 1.41 – 1.26 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 1.19 (3H, t, *J* = 7.2 Hz, CO₂CH₂CH₃), 0.85 (9H, s, TBS–C(CH₃)₃), 0.26 (9H, s, TMS–Si(CH₃)₃), –0.01 (6H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.2 (CO₂CH₂CH₃), 167.3 (CO₂CH₃), 161.0 (C_{Ar}), 160.8 (C=CH), 139.1 (C_{Ar}), 130.9 (C_{Ar}), 129.3 (C_{Ar}H), 128.0 (C_{Ar}H), 117.2 (C=CH), 111.5 (C_{Ar}H), 82.4 (CH_AH_B), 63.0 (C_{Ar}C), 62.8 (OCH₂), 61.7 (CO₂CH₂CH₃), 51.5 (CO₂CH₃), 37.5 (CH₂C=CH), 32.5 (OCH₂CH₂), 26.1 (TBS–C(CH₃)₃), 24.2 (OCH₂CH₂CH₂), 18.5 (TBS–C(CH₃)₃), 14.1 (CO₂CH₂CH₃), 1.0 (TMS–Si(CH₃)₃), –5.2 (TBS–Si(CH₃)₂).

IR (film) ν_{max} /cm^{–1} 2952, 2931, 1736, 1716, 1255, 1223, 1098, 839.

HRMS: (APCI⁺) Found [M + H]⁺ = 535.2900; C₂₈H₄₇O₆Si₂ requires 535.2906.

Ethyl (Z)-3-(7-hydroxy-1-methoxy-1-oxohept-2-en-3-yl)-4-(trimethylsilyl)-2,3-dihydrobenzofuran-3-carboxylate (236)⁶⁶



236

To a solution of alkene **235** (44 mg, 82 μ mol) in MeOH (2 mL) was added FeCl₃ (1.0 mg, 8.2 μ mol). The reaction mixture was stirred at rt for 2 h then filtered through a plug of silica using EtOAc as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 70:30) afforded the title compound as a colourless oil (32 mg, 92%).

*R*_f = 0.6 (Pentane:EtOAc, 1:1).

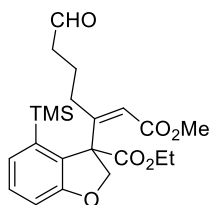
¹H NMR (CDCl₃, 400 MHz) δ = 7.20 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.10 (1H, d, *J* = 7.4 Hz, Ar*H*), 6.86 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.89 (1H, t, *J* = 1.2 Hz, C=CH), 5.61 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.37 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.25 – 3.95 (2H, m, CO₂CH₂CH₃), 3.66 (3H, s, CO₂CH₃), 3.51 – 3.36 (2H, m, CH₂OH), 2.18 – 1.90 (2H, m, CH₂C=CH), 1.47 – 1.24 (4H, m, OCH₂CH₂ and OCH₂CH₂CH₂), 1.19 (3H, t, *J* = 7.2 Hz, CO₂CH₂CH₃), 0.26 (9H, s, TMS–Si(CH₃)₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 171.1 (CO₂CH₂CH₃), 167.3 (CO₂CH₃), 161.0 (C_{Ar}), 160.8 (C=CH), 139.2 (C_{Ar}), 130.9 (C_{Ar}), 129.4 (C_{Ar}H), 128.0 (C_{Ar}H), 117.5 (C=CH), 111.5 (C_{Ar}H), 82.7 (CH_AH_B), 62.9 (C_{Ar}C), 62.3 (CH₂OH), 61.7 (CO₂CH₂CH₃), 51.5 (CO₂CH₃), 37.5 (CH₂C=CH), 32.2 (CH₂CH₂OH), 24.3 (CH₂CH₂CH₂OH), 14.1 (CO₂CH₂CH₃), 1.0 (TMS–Si(CH₃)₃).

IR (film) ν_{max} /cm^{–1} 3430, 2950, 1734, 1715, 1633, 1566, 1435, 1254, 1224, 840.

HRMS: (APCI[−]) Found $[M - H]^- = 419.1892$; $C_{22}H_{31}O_6Si$ requires 419.1895.

Ethyl (Z)-3-(1-methoxy-1,7-dioxohept-2-en-3-yl)-4-(trimethylsilyl)-2,3-dihydrobenzofuran-3-carboxylate (237)¹⁴⁷



237

To a solution of alcohol **236** (30 mg, 71 μ mol) in CH_2Cl_2 (1 mL) at 0 °C was added $NaHCO_3$ (15 mg, 180 μ mol) and Dess–Martin periodinane (47 mg, 110 μ mol). The reaction mixture was stirred at rt for 2 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:Et₂O, 65:35) afforded the title compound as a colourless oil (27 mg, 89%).

$R_f = 0.7$ (Pentane:EtOAc, 70:30).

¹H NMR ($CDCl_3$, 500 MHz) δ = 9.51 (1H, s, CHO), 7.20 (1H, t, $J = 7.7$ Hz, ArH), 7.10 (1H, d, $J = 7.4$ Hz, ArH), 6.86 (1H, d, $J = 8.1$ Hz, ArH), 5.89 (1H, t, $J = 1.4$ Hz, C=CH), 5.61 (1H, d, $J = 9.7$ Hz, CH_AH_B), 4.37 (1H, d, $J = 9.6$ Hz, CH_AH_B), 4.25 – 3.95 (2H, m, $CO_2CH_2CH_3$), 3.67 (3H, s, CO_2CH_3), 2.33 – 2.21 (2H, m, CH_2CHO), 2.18 – 1.85 (2H, m, $CH_2C=CH$), 1.67 – 1.56 (2H, m, CH_2CH_2CHO), 1.19 (3H, t, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 0.25 (9H, s, TMS–Si(CH_3)₃).

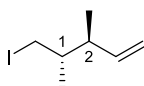
¹³C NMR ($CDCl_3$, 101 MHz) δ = 201.5 (CHO), 171.0 ($CO_2CH_2CH_3$), 167.2 (CO_2CH_3), 160.9 (C_{Ar}), 160.0 (C=CH), 139.1 (C_{Ar}), 130.7 (C_{Ar}), 129.4 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 117.8 (C=CH), 111.6 ($C_{Ar}H$), 82.7 (CH_AH_B), 62.8 ($C_{Ar}C$), 61.8 ($CO_2CH_2CH_3$), 51.6 (CO_2CH_3),

43.1 (CH₂CHO), 36.8 (CH₂C=CH), 20.4 (CH₂CH₂CHO), 14.1 (CO₂CH₂CH₃), 0.9 (TMS–Si(CH₃)₃).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 2900, 1732, 1633, 1566, 1414, 1254, 1225, 841.

HRMS: (APCI⁺) Found $[M + H]^+ = 419.1888$; C₂₂H₃₁O₆Si requires 419.1884.

(3S,4S)-5-Iodo-3,4-dimethylpent-1-ene (241)¹⁵⁰



241

To a solution of acid **240** (40 mg, 310 μmol) in Et₂O (2 mL) at 0 °C was added LiAlH₄ (36 mg, 940 μmol). The reaction mixture was stirred for 1 h at rt and water (10 mL) was added followed by Et₂O (30 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude residue was re-dissolved in CH₂Cl₂ (2 mL). Iodine (160 mg, 620 μmol), PPh₃ (160 mg, 620 μmol) and imidazole (42 mg, 620 μmol) were added and the reaction mixture was stirred at rt overnight. Water (10 mL) and sat. aq. Na₂S₂O₃ (10 mL) were added followed by CH₂Cl₂ (30 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane) afforded the title compound as a colourless oil (70 mg, 75% over two steps).

R_f = 0.8 (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 500 MHz) δ = 5.73 – 5.59 (1H, m, CH₂=CH), 5.12 – 4.95 (2H, m, CH₂=CH), 3.26 – 3.10 (2H, m, CH₂I), 2.33 – 2.24 (1H, m, C(2)H), 1.55 – 1.48 (1H, m, C(1)H), 1.01 (3H, d, *J* = 6.8 Hz, C(2)HCH₃), 0.96 (3H, d, *J* = 6.7 Hz, C(1)HCH₃).

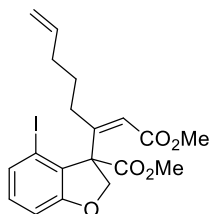
¹³C NMR (CDCl₃, 126 MHz) δ = 140.6 (CH₂=CH), 115.3 (CH₂=CH), 42.1 (C(2)H), 40.1 (C(1)H), 18.0 (C(2)HCH₃), 17.2 (C(1)HCH₃), 15.4 (CH₂I).

IR (film) ν_{max} /cm⁻¹ 2917, 2849, 1739, 1463, 1243.

HRMS: Ion not found.

$[\alpha]_D^{25}$ -11 (c 1.0, CHCl₃).

Methyl (Z)-4-iodo-3-(1-methoxy-1-oxoocta-2,7-dien-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (243)⁵⁷



243

To a solution of iodide **152** (282 mg, 1.44 mmol) in pentane (5.3 mL) and Et₂O (3.7 mL) at -78 °C was added ^tBuLi (1.69 mL, 1.6 mmol, 1.7 M in pentane). After 10 min CuI (137 mg, 720 μmol) was added and the mixture was stirred vigorously at 0 °C for 1 h before being cooled to -78 °C. A solution of alkyne **224** (139 mg, 360 μmol) in Et₂O (0.5 mL + 0.2 mL) was added dropwise and the reaction mixture stirred at -78 °C for 1.5 h. Methanol (0.5 mL) was added and the mixture partitioned between water (15 mL) and Et₂O (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil and a single diastereomer (74 mg, 45%).

$R_f = 0.5$ (Pentane:Et₂O, 60:40).

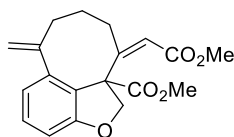
¹H NMR (CDCl₃, 400 MHz) δ = 7.26 (1H, dd, J = 7.5, 1.3 Hz, ArH), 6.86 – 6.75 (2H, m, ArH $\times$ 2), 5.90 (1H, t, J = 1.4 Hz, C=CH), 5.55 – 5.47 (1H, m, CH_AH_B=CH), 5.44 (1H, d, J = 9.7 Hz, CH_AH_B), 4.86 – 4.77 (2H, m, CH₂=CH), 4.45 (1H, d, J = 9.7 Hz, CH_AH_B), 3.62 (3H, s, CO₂CH₃), 3.61 (3H, s, CO₂CH₃), 2.32 – 1.92 (2H, m, CH₂C=CH), 1.92 – 1.74 (2H, m, CH₂=CHCH₂), 1.44 – 1.20 (2H, m, CH₂=CHCH₂CH₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 170.5 (CO₂CH₃), 167.1 (CO₂CH₃), 161.9 (C=CH), 159.7 (C_{Ar}), 137.7 (CH₂=CH), 132.7 (C_{Ar}H), 131.4 (C_{Ar}H), 130.4, 118.5 (C=CH), 115.3 (CH₂=CH), 110.6 (C_{Ar}H), 93.2 (C_{Ar}), 84.1 (CH_AH_B), 64.3 (C_{Ar}C), 52.5 (CO₂CH₃), 51.5 (CO₂CH₃), 36.5 (C=CCH₂), 33.2 (CH₂=CHCH₂), 27.5 (CH₂=CHCH₂CH₂).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2949, 1735, 1714, 1634, 1594, 1434, 1253, 1230, 870.

HRMS: (ESI⁺) Found $[M + \text{Na}]^+ = 479.0326$; C₁₉H₂₁O₅INa requires 479.0326.

Methyl (Z)-10-(2-methoxy-2-oxoethylidene)-6-methylene-7,8,9,10-tetrahydro-1H-cycloocta[cd]benzofuran-10a(6H)-carboxylate (244)¹⁵¹



244

To a solution of alkene **243** (24 mg, 53 μmol) in MeCN (1 mL) was added triphenylphosphine (5.5 mg, 21 μmol), Pd(OAc)₂ (1.2 mg, 5.3 μmol) and Et₃N (73 μL , 530 μmol). The reaction mixture was heated at 80 °C for 2 h. EtOAc (20 mL) was added and the reaction mixture filtered through Celite[®]. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil and a single diastereomer (14 mg, 81%).

$R_f = 0.5$ (Pentane:Et₂O, 60:40).

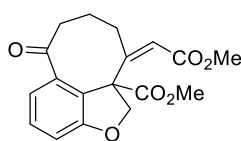
¹H NMR (CDCl₃, 400 MHz) δ = 7.17 (1H, t, J = 7.9 Hz, ArH), 6.84 (1H, dd, J = 7.6, 1.1 Hz, ArH), 6.79 (1H, dd, J = 8.1, 1.1 Hz, ArH), 5.95 (1H, s, C=CH), 5.61 (1H, d, J = 9.7 Hz, CH_AH_B), 5.06 – 5.02 (1H, m, C=CH_AH_B), 4.96 (1H, t, J = 1.8 Hz, C=CH_AH_B), 4.30 (1H, d, J = 9.7 Hz, CH_AH_B), 3.69 (3H, s, CO₂CH₃), 3.59 (3H, s, CO₂CH₃), 3.28 – 3.18 (1H, m, CH_AH_BC=CH), 2.39 – 2.15 (3H, m, CH₂C=CH₂ and CH_AH_BC=CH), 1.94 – 1.78 (2H, m, CH₂CH₂C=CH₂).

¹³C NMR (CDCl₃, 126 MHz) δ = 171.0 (CO₂CH₃), 166.5 (CO₂CH₃), 162.7 (C_{Ar}), 160.8 (C=CH), 148.4 (C_{Ar}), 141.3 (C=CH₂), 130.1 (C_{Ar}H), 123.9, 121.9 (C_{Ar}H), 119.3 (C=CH), 115.8 (C=CH₂), 109.7 (C_{Ar}H), 81.9 (CH_AH_B), 62.4 (C_{Ar}C), 52.4 (CO₂CH₃), 51.5 (CO₂CH₃), 34.6 (CH₂C=CH₂), 34.1 (CH_AH_BC=CH), 28.5 (CH₂CH₂C=CH₂).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2950, 1738, 1716, 1573, 1435, 1256, 1230, 1145.

HRMS: (ESI⁺) Found $[M + \text{Na}]^+ = 351.1203$; C₁₉H₂₀O₅Na requires 351.1203.

Methyl (Z)-10-(2-methoxy-2-oxoethylidene)-6-oxo-7,8,9,10-tetrahydro-1H-cycloocta[cd]benzofuran-10a(6H)-carboxylate (245)¹⁵²



245

To a solution of alkene **244** (13 mg, 40 μmol) in THF (1.2 mL) and water (0.6 mL) was added OsO₄ (500 μg , 2.0 μmol) and NaIO₄ (42 mg, 200 μmol). The reaction mixture was stirred for 2 h then sat. aq. Na₂SO₃ (30 mL) was added followed by EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and

concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 70:30) afforded the title compound as a colourless oil (9 mg, 69%).

R_f = 0.5 (Pentane:Et₂O, 60:40).

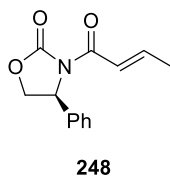
¹H NMR (CDCl₃, 400 MHz) δ = 7.53 (1H, dd, *J* = 7.8, 1.2 Hz, ArH), 7.31 (1H, t, *J* = 7.9 Hz, ArH), 7.07 (1H, dd, *J* = 8.1, 1.2 Hz, ArH), 6.05 (1H, s, C=CH), 5.72 (1H, d, *J* = 9.7 Hz, CH_AH_B), 4.21 (1H, d, *J* = 9.7 Hz, CH_AH_B), 4.09 – 3.96 (1H, m, CH_AH_BC=CH), 3.71 (3H, s, CO₂CH₃), 3.63 (3H, s, CO₂CH₃), 2.68 – 2.59 (1H, m, CH_AH_BC=CH), 2.53 – 2.39 (2H, m, CH₂C=CH), 2.08 – 1.88 (2H, m, CH₂CH₂C(O)).

¹³C NMR (CDCl₃, 110 MHz) δ = 201.3 (C(O)CH₂), 170.8 (CO₂CH₃), 166.2 (CO₂CH₃), 161.6 (C_{Ar}), 158.7 (C=CH), 136.9 (C_{Ar}), 130.4 (C_{Ar}H), 125.3 (C_{Ar}), 123.1 (C_{Ar}H), 120.1 (C=CH), 115.5 (C_{Ar}H), 79.4 (CH_AH_B), 63.3 (C_{Ar}C), 52.9 (CO₂CH₃), 51.7 (CO₂CH₃), 39.2 (CH_AH_BC=CH), 33.7 (CH₂C=CH), 25.5 (CH₂CH₂C(O)).

IR (film) ν_{max} /cm⁻¹ 2952, 1733, 1716, 1673, 145, 1232, 1155.

HRMS: (ESI⁺) Found [M + Na]⁺ = 353.0996; C₁₈H₁₈O₆Na requires 353.0996.

(*S,E*)-3-(But-2-enoyl)-4-phenyloxazolidin-2-one (**248**)⁹⁶



To a solution of (*S*)-(+)-4-phenyl-2-oxazolidinone **246** (16.3 g, 100 mmol) in THF (600 mL) at –78 °C was added ^{*n*}BuLi (48 mL, 120 mmol, 2.5 M hexanes). The solution was stirred for 15 min and crotonyl chloride **247** (11.5 mL, 120 mmol) was added. The reaction mixture was stirred at –78 °C for 30 min then 15 min at rt. Sat. aq. NH₄Cl (100 mL) was added followed by water (100 mL) and Et₂O (200 mL). The two layers were separated and the

aqueous layer was extracted with Et₂O (3 × 300 mL). The organic layer was washed with brine (200 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound as a white solid used without further purification (23.1 g, 100%).

*R*_f = 0.8 (Pentane:EtOAc, 50:50).

m.p. 75 °C.

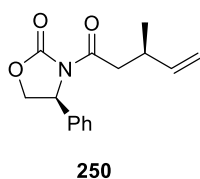
¹H NMR (CDCl₃, 400 MHz) δ = 7.41 – 7.23 (6H, m, ArH × 5, CH=CHCH₃), 7.14 – 7.03 (1H, m, CH=CHCH₃), 5.46 (1H, dd, *J* = 8.8, 3.9 Hz, NCH), 4.67 (1H, t, *J* = 8.8 Hz, CH_AH_B), 4.24 (1H, dd, *J* = 9.0, 3.9 Hz, CH_AH_B), 1.92 (3H, dd, *J* = 6.9, 1.7 Hz, CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 164.5 (NC(O)CH), 153.8 (OC(O)N), 147.2 (CH=CHCH₃), 139.2 (C_{Ar}), 129.2 (C_{Ar}H), 128.6 (C_{Ar}H), 126.0 (C_{Ar}H), 121.8 (CH=CHCH₃), 70.0 (CH_AH_B), 57.8 (NCH), 18.5 (CH₃).

$[\alpha]_D^{25}$ +110 (*c* 1.0, CHCl₃).

Analytical data are in accordance with those previously reported for this compound.⁹⁶

(*S*)-3-((*R*)-3-Methylpent-4-enoyl)-4-phenyloxazolidin-2-one (**250**)⁹⁷



To a solution of CuBr·DMS (10.3 g, 50.2 mmol) in THF (300 mL) at –40 °C was added dropwise vinylmagnesium bromide (200 mL, 200 mmol, 1 M in THF). The solution was stirred for 10 min then a solution of oxazolidinone **248** (13.2 g, 57.1 mmol) in THF (48 mL) was added as rapidly as possible. The reaction mixture was stirred vigorously for 5 min and sat. aq. NH₄Cl (100 mL) was added followed by Et₂O (200 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 × 300 mL). The organic layer

was washed with brine (200 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by recrystallisation (MTBE/pentane) afforded the title compound as a white solid $\geq 95:5$ dr (8.88 g, 60%).

$R_f = 0.4$ (Pentane: Et_2O , 50:50).

m.p. 82 °C.

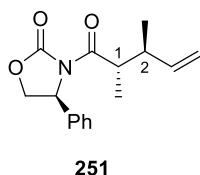
^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.41 - 7.26$ (5H, m, $\text{ArH} \times 5$), 5.82 – 5.70 (1H, m, $\text{CH}_2=\text{CH}$), 5.43 (1H, dd, $J = 8.7, 3.7$ Hz, NCH), 4.99 – 4.85 (2H, m, $\text{CH}_2=\text{CH}$), 4.68 (1H, t, $J = 8.8$ Hz, $\text{OCH}_\text{A}\text{H}_\text{B}$), 4.27 (1H, dd, $J = 8.9, 3.7$ Hz, $\text{OCH}_\text{A}\text{H}_\text{B}$), 3.08 (1H, dd, $J = 15.9, 6.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.84 (1H, dd, $J = 15.9, 7.4$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.77 – 2.65 (1H, m, CH), 1.02 (3H, d, $J = 6.7$ Hz, CH_3).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 171.7$ (NC(O)CH), 153.8 (OC(O)N), 142.5 ($\text{CH}_2=\text{CH}$), 139.2 (C_Ar), 129.3 ($\text{C}_\text{Ar}\text{H}$), 128.8 ($\text{C}_\text{Ar}\text{H}$), 126.1 ($\text{C}_\text{Ar}\text{H}$), 113.5 ($\text{CH}_2=\text{CH}$), 70.0 ($\text{OCH}_\text{A}\text{H}_\text{B}$), 57.8 (NCH), 41.9 ($\text{CH}_\text{A}\text{H}_\text{B}$), 34.0 (CH), 19.8 (CH_3).

$[\alpha]_\text{D}^{25} +42$ (c 1.0, CHCl_3).

Analytical data are in accordance with those previously reported for this compound.¹⁵³

(S)-3-((2S,3S)-2,3-Dimethylpent-4-enoyl)-4-phenyloxazolidin-2-one (251)⁹⁷



To a solution of LiHMDS (13.9 mL, 13.9 mmol, 1 M in THF) in THF (30 mL) at -78 °C was added dropwise a solution of oxazolidinone **250** (3.00 g, 11.6 mmol) in THF (14 mL). The reaction mixture was stirred for 15 min at -78 °C. MeI (1.44 mL, 23.2 mmol) was added and the reaction stirred at -78 °C for 15 min, then 2 h at rt. Sat. aq. NH_4Cl (5 mL) and water

(20 mL) were added followed by Et₂O (50 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a white solid (2.41 g, 76%).

R_f = 0.5 (Pentane:Et₂O, 50:50).

m.p. 82 °C.

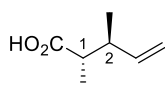
¹H NMR (CDCl₃, 400 MHz) δ = 7.42 – 7.26 (5H, m, ArH × 5), 5.72 – 5.61 (1H, m, CH₂=CH), 5.43 (1H, dd, *J* = 8.7, 3.5 Hz, NCH), 5.07 – 4.97 (2H, m, CH₂=CH), 4.67 (1H, t, *J* = 8.8 Hz, OCH_AH_B), 4.24 (1H, dd, *J* = 8.9, 3.5 Hz, OCH_AH_B), 3.78 – 3.67 (1H, m, C(1)H), 2.54 – 2.41 (1H, m, C(2)H), 1.04 (3H, d, *J* = 0.8 Hz, C(1)H₃), 1.03 (3H, d, *J* = 1.1 Hz, C(2)H₃).

¹³C NMR (CDCl₃, 126 MHz) δ = 176.0 (NC(O)CH), 153.6 (OC(O)N), 140.9 (CH₂=CH), 139.4 (C_{Ar}), 129.3 (C_{Ar}H), 128.8 (C_{Ar}H), 125.8 (C_{Ar}H), 115.3 (CH₂=CH), 69.9 (OCH_AH_B), 57.9 (NCH), 42.6 (CH), 40.8 (CH), 18.9 (CH₃), 15.4 (CH₃).

[α]_D²⁵ +78 (*c* 1.0, CHCl₃).

Analytical data are in accordance with those previously reported for this compound.⁹⁷

(2S,3S)-2,3-Dimethylpent-4-enoic acid (252)⁹⁷



252

To a solution of oxazolidinone **251** (250 mg, 900 μ mol) in water (6 mL) and THF (6 mL) at 0 °C was added H₂O₂ (390 μ L, 3.4 mmol, 30% aq.) followed by LiOH·H₂O (71 mg,

1.7 mmol). The reaction mixture was stirred vigorously for 2 h then the two layers were separated. The aqueous layer was acidified to pH = 2 with HCl (1 M, aq.) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (78 mg, 67%).

R_f = 0.2 (Pentane:Et₂O, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 5.65 (1H, ddd, *J* = 17.1, 10.3, 8.2 Hz, CH₂=CH), 5.10 – 5.01 (2H, m, CH₂=CH), 2.54 – 2.41 (1H, m, C(1)*H*), 2.39 – 2.30 (1H, m, C(2)*H*), 1.13 (3H, d, *J* = 6.9 Hz, C(2)HCH₃), 1.07 (3H, d, *J* = 6.8 Hz, C(1)HCH₃).

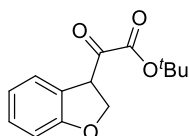
¹³C NMR (CDCl₃, 110 MHz) δ = 182.8 (CO₂H), 140.6 (CH₂=CH), 115.5 (CH₂=CH), 45.1 (C2), 40.9 (C1), 18.5 (C(1)HCH₃), 14.5 (C(2)HCH₃).

IR (film) ν_{max} /cm⁻¹ 3466, 2974, 2936, 1708, 1460, 1198, 917, 773.

HRMS: (ESI⁻) Found [M – H]⁻ = 127.0762; C₇H₁₁O₂ requires 127.0765.

[α]_D²⁵ –21 (*c* 1.0, CHCl₃).

***tert*-Butyl (*E*)-2-(benzofuran-3(2*H*)-ylidene)-2-hydroxyacetate (257)**



257

To a solution of benzofuran **261** (49 mg, 200 μ mol) in MeOH (2.0 mL) was added PdO (4.9 mg, 40 μ mol). The reaction mixture was stirred vigorously for 1 h under a hydrogen atmosphere before being filtered through Celite[®]. Concentration *in vacuo* followed by purification by flash column chromatography (SiO₂, Pentane:Et₂O, 96:4) afforded the title

compound as a colourless oil (16 mg, 33%). N.B. the title compound was observed entirely as the enol form by NMR.

R_f = 0.3 (Pentane:Et₂O, 95:5).

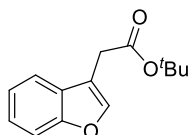
¹H NMR (CDCl₃, 400 MHz) δ = 7.94 (1H, dd, *J* = 7.7, 1.3 Hz, *ArH*), 7.26 – 7.20 (1H, m, *ArH*), 6.96 (1H, td, *J* = 7.5, 1.0 Hz, *ArH*), 6.87 (1H, d, *J* = 8.1 Hz, *ArH*), 6.05 (1H, s, *OH*), 5.32 (2H, s, *CH*₂), 1.59 (9H, s, CO₂C(CH₃)₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 164.1 (CO₂C(CH₃)₃ or C=C(OH)), 163.4 (CO₂C(CH₃)₃ or C=C(OH)), 132.3 (*C*_{Ar}), 130.9 (*C*_{Ar}H), 126.9 (*C*_{Ar}H), 124.9 (*C*_{Ar}), 123.1 (C=C(OH)), 121.2 (*C*_{Ar}H), 109.7 (*C*_{Ar}H), 84.1 (CO₂C(CH₃)₃), 74.4 (*CH*₂), 28.4 (CO₂C(CH₃)₃).

IR (film) ν_{max} /cm⁻¹ 2933, 1726, 1680, 1192, 1146, 753.

HRMS: (ESI⁺) Found [M + Na]⁺ = 271.0941; C₁₄H₁₆O₄Na requires 271.0941.

***tert*-Butyl 2-(benzofuran-3-yl)acetate (260)¹⁰⁰**



260

2,3-Dihydrobenzo[*b*]furan-3-one (738 mg, 5.5 mmol) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane (2.28 g, 6.05 mmol) in toluene (18.0 mL) were heated at 130 °C for 16 h. Concentration *in vacuo* followed by purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97.5:2.5) afforded the title compound as a pale yellow oil (841 g, 66%).

$R_f = 0.4$ (Pentane:Et₂O, 90:10).

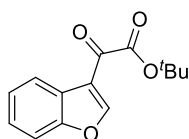
¹H NMR (CDCl₃, 400 MHz) δ = 7.62 (1H, s, ArH), 7.60 – 7.56 (1H, m, ArH), 7.48 (1H, d, J = 8.3 Hz, ArH), 7.30 (1H, td, J = 7.7, 1.6 Hz, ArH), 7.28 – 7.22 (1H, m, ArH), 3.62 (2H, d, J = 1.1 Hz, CH₂), 1.47 (9H, s, CO₂C(CH₃)₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 170.1 (CO₂C(CH₃)₃), 155.3 (C_{Ar}), 142.8 (C_{Ar}H), 127.9 (C_{Ar}), 124.5 (C_{Ar}H), 122.6 (C_{Ar}H), 119.9 (C_{Ar}H), 113.8 (C_{Ar}), 111.6 (C_{Ar}H), 81.4 (CO₂C(CH₃)₃), 31.3 (CH₂), 28.2 (CO₂C(CH₃)₃).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2979, 1731, 1478, 1145, 1068, 745.

HRMS: (APCI⁺) Found $[M + H]^+ = 233.1173$; C₁₄H₁₇O₃ requires 233.1172.

***tert*-Butyl 2-(benzofuran-3-yl)-2-oxoacetate (261)¹⁰⁰**



261

A solution of benzofuran **260** (820 mg, 3.53 mmol) and SeO₂ (783 mg, 7.06 mmol) in dioxane (11.8 mL) was heated to 115 °C for 16 h. The reaction was diluted with Et₂O (30 mL) and filtered through Celite[®]. Concentration *in vacuo* followed by purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97.5:2.5) afforded the title compound as a pale yellow solid (790 g, 91%).

$R_f = 0.4$ (Pentane:Et₂O, 90:10).

m.p. 65 °C.

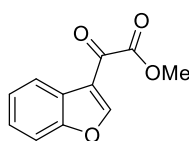
¹H NMR (CDCl₃, 400 MHz) δ = 8.81 (1H, s, ArH), 8.33 – 8.23 (1H, m, ArH), 7.62 – 7.51 (1H, m, ArH), 7.45 – 7.33 (2H, m, ArH $\times$ 2), 1.64 (9H, s, CO₂C(CH₃)₃).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 179.8 ($\text{C}(\text{O})\text{CO}_2\text{C}(\text{CH}_3)_3$), 160.6 ($\text{C}(\text{O})\text{CO}_2\text{C}(\text{CH}_3)_3$), 155.6 (C_{ArH}), 155.2 (C_{Ar}), 126.2 (C_{ArH}), 125.1 (C_{ArH}), 124.5 (C_{Ar}), 123.0 (C_{ArH}), 118.8 (C_{Ar}), 111.7 (C_{ArH}), 84.5 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 28.0 ($\text{CO}_2\text{C}(\text{CH}_3)_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2981, 1738, 1663, 1626, 1285, 1150, 1125, 1087, 755.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 269.0784$; $\text{C}_{14}\text{H}_{14}\text{O}_4\text{Na}$ requires 269.0784.

Methyl 2-(benzofuran-3-yl)-2-oxoacetate (**262**)¹³⁷



262

To a solution of benzofuran **261** (49 mg, 200 μmol) in MeOH (2.0 mL) was added freshly ground Mg turnings (24 mg, 1.00 mmol). The reaction was stirred at rt for 1 h before sat. aq. NH_4Cl (5 mL) was added followed by water (20 mL) and Et_2O (30 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 95:5) afforded the title compound as a white solid (14 mg, 34%).

R_f = 0.2 (Pentane: Et_2O , 95:5).

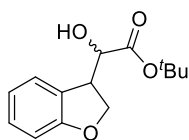
m.p. 65 $^\circ\text{C}$.

^1H NMR (CDCl_3 , 400 MHz) δ = 8.91 (1H, s, ArH), 8.33 – 8.24 (1H, m, ArH), 7.61 – 7.54 (1H, m, ArH), 7.47 – 7.38 (2H, m, $\text{ArH} \times 2$), 3.99 (3H, s, CO_2CH_3).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 178.1 ($\text{C}(\text{O})\text{CO}_2\text{CH}_3$), 161.6 ($\text{C}(\text{O})\text{CO}_2\text{CH}_3$), 156.3 (C_{Ar}), 155.3 (C_{ArH}), 126.4 (C_{ArH}), 125.2 (C_{ArH}), 124.3 (C_{Ar}), 123.0 (C_{ArH}), 118.8 (C_{ArH}), 111.8 (C_{Ar}), 53.4 (CO_2CH_3).

Analytical data are in accordance with those previously reported for this compound.¹⁵⁴

***tert*-Butyl 2-(2,3-dihydrobenzofuran-3-yl)-2-hydroxyacetate (**264**)**



264

To a solution of benzofuran **261** (246 mg, 1.00 mmol) in MeOH (10.0 mL) was added Pd/C (24.6 mg, 10 wt%). The reaction mixture was stirred vigorously for 16 h under a hydrogen atmosphere before being filtered through Celite[®]. Concentration *in vacuo* followed by purification by flash column chromatography (SiO₂, Pentane:Et₂O, 96:4) afforded the title compound as a colourless oil (248 mg, 99%, 1.4:1 dr).

*R*_f = 0.3 (Pentane:Et₂O, 95:5).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3485, 2979, 1725, 1483, 1235, 1158, 1099, 751.

HRMS: (ESI⁺) Found [M + Na]⁺ = 273.1098; C₁₄H₁₈O₄Na requires 273.1097.

Major Diastereomer

¹H NMR (CDCl₃, 500 MHz) δ = 7.28 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.18 – 7.11 (1H, m, Ar*H*), 6.85 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.78 (1H, t, *J* = 7.5 Hz, Ar*H*), 4.60 – 4.58 (1H, m, α), 4.58 – 4.56 (1H, m, CH_AH_B), 4.31 (1H, dd, *J* = 4.6, 3.4 Hz, CH(OH)), 3.93 – 3.83 (1H, m, CH), 3.19 (1H, d, *J* = 4.6 Hz, OH), 1.37 (9 H, s, CO₂C(CH₃)₃)

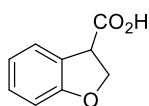
¹³C NMR (CDCl₃, 126 MHz) δ = 172.4 (CO₂C(CH₃)₃), 160.7 (C_{Ar}), 129.1 (C_{Ar}H), 126.1 (C_{Ar}), 125.1 (C_{Ar}H), 120.5 (C_{Ar}H), 109.6 (C_{Ar}H), 83.5 (CO₂C(CH₃)₃), 72.4 (CH(OH)), 72.0 (CH_AH_B), 46.2 (CH), 27.8 (CO₂C(CH₃)₃).

Minor Diastereomer

¹H NMR (CDCl₃, 500 MHz) δ = 7.20 (1H, d, J = 7.4 Hz, ArH), 7.18 – 7.11 (1H, m, ArH), 6.85 (1H, t, J = 7.4 Hz, ArH), 6.78 (1H, t, J = 7.5 Hz, ArH), 4.65 – 4.60 (1H, m, CH_AH_B), 4.56 – 4.52 (1H, m, CH_AH_B) 4.22 (1H, dd, J = 6.3, 4.6 Hz, CH(OH)), 3.93 – 3.83 (1H, m, CH), 3.00 (1H, d, J = 6.2 Hz, OH), 1.42 (9 H, s, CO₂C(CH₃)₃)

¹³C NMR (CDCl₃, 126 MHz) δ = 172.4 (CO₂C(CH₃)₃), 160.9 (C_{Ar}), 129.1 (C_{Ar}H), 125.5 (C_{Ar}), 125.5 (C_{Ar}H), 120.5 (C_{Ar}H), 109.8 (C_{Ar}H), 83.3 (CO₂C(CH₃)₃), 73.2 (CH_AH_B), 72.3 (CH(OH)), 46.3 (CH), 27.9 (CO₂C(CH₃)₃).

2,3-Dihydrobenzofuran-3-carboxylic acid (265)



265

To a solution of ester **87** (535 mg, 3.00 mmol) in EtOH (20 mL) at rt was added a solution of Na₂CO₃ (1.00 g, 9.43 mmol) in water (10 mL). The reaction mixture was stirred for 1.5 h. HCl (5 M aq., 5 mL) was added and excess EtOH removed *in vacuo*. Et₂O (50 mL) and water (20 mL) were added and the layers separated. To the organic layer was added sat. aq. Na₂CO₃ (15 mL). the layers were separated and the aqueous layer was acidified with HCl (5 M aq.) until pH = 3. Et₂O (30 mL) was added and the layers separated. The aqueous layer was extracted with Et₂O (3 × 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound (266 mg, 54%) as a white solid with no further purification necessary.

R_f = 0.2 (CHCl₃:MeOH, 95:5).

m.p. 94 °C

¹H NMR (CDCl₃, 400 MHz) δ = 9.93 (1H, br. s, CO₂H), 7.41 (1H, d, J = 7.5 Hz, ArH), 7.24 – 7.17 (1H, m, ArH), 6.91 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.84 (1H, d, J = 7.9 Hz, ArH), 4.92 (1H, dd, J = 9.3, 6.3 Hz, CH_AH_B), 4.67 (1H, t, J = 9.5 Hz, CH_AH_B), 4.37 (1H, dd, J = 9.7, 6.3 Hz, CH).

¹³C NMR (CDCl₃, 126 MHz) δ = 177.4 (CO₂H), 159.9 (C_{Ar}), 129.9 (C_{Ar}H), 125.6 (C_{Ar}H), 123.6 (C_{Ar}), 121.0 (C_{Ar}H), 110.2 (C_{Ar}H), 72.3 (CH_AH_B), 47.1 (CH).

Analytical data are in accordance with those previously reported for this compound.¹³⁷

2-(Triphenyl- λ^5 -phosphaneylidene)acetonitrile (266)¹⁵⁵



266

To a solution of (cyanomethyl)triphenylphosphonium chloride (4.00 g, 11.8 mmol) in CH₂Cl₂ (60 mL) was added dropwise Et₃N (4.13 mL, 29.6 mmol). The reaction mixture was stirred for 30 min then water (30 mL) was added. The two layers were separated and the organic layer was washed with water (30 mL) once more. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Purification by recrystallisation (CHCl₃/pentane) afforded the title compound as a beige solid (3.00 g, 84%).

R_f = 0.1 (CHCl₃:MeOH, 95:5).

m.p. 195 °C

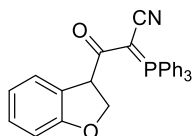
¹H NMR (CDCl₃, 400 MHz) δ = 7.63 – 7.38 (15H, m, ArH $\times$ 15), 1.55 (1H, s, CH).

¹³C NMR (CDCl₃, 126 MHz) δ = 132.6 (d, J = 10.0 Hz, C_{Ar}H $\times$ 6), 132.5 (d, J = 2.9 Hz, C_{Ar}H $\times$ 3), 129.0 (d, J = 12.6 Hz, C_{Ar}H $\times$ 6), 127.2 (d, J = 91.6 Hz, (C_{Ar} $\times$ 3), –2.2 (d, J = 135.9 Hz, CH).

³¹P NMR (162 MHz, CDCl₃) δ = 23.1.

Analytical data are in accordance with those previously reported for this compound.¹⁵⁵

3-(2,3-Dihydrobenzofuran-3-yl)-3-oxo-2-(triphenyl- λ^5 -phosphaneylidene)propanenitrile (267)¹⁰¹



267

To a solution of acid **265** (34 mg, 210 μ mol) in CH_2Cl_2 (1 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (60 mg, 310 μ mol), 4-(dimethylamino)pyridine (3.0 mg, 21 μ mol) and ylide **266** (75 mg, 250 μ mol). The reaction mixture was stirred at rt for 16 h, diluted with CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 60:40) afforded the title compound as a white solid (52 mg, 56%).

R_f = 0.6 (Pentane:EtOAc, 40:60).

m.p. 224 $^\circ\text{C}$

^1H NMR (CDCl_3 , 400 MHz) δ = 7.65 – 7.45 (15H, m, $\text{ArH} \times 15$), 7.14 (1H, t, J = 7.7 Hz, ArH), 6.90 (1H, t, J = 7.5 Hz, ArH), 6.77 (1H, d, J = 7.9 Hz, ArH), 5.08 (1H, dd, J = 9.3, 6.1 Hz, CH), 4.91 (1H, dd, J = 8.7, 6.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.66 (1H, t, J = 9.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 193.3 (d, J = 3.9 Hz, $\text{C}(\text{O})\text{C}=\text{P}$), 160.1 (C_Ar), 133.6 (d, J = 10.1 Hz, $\text{C}_\text{Ar}\text{H} \times 6$), 133.3 (d, J = 3.1 Hz, $\text{C}_\text{Ar}\text{H} \times 3$), 129.2 (d, J = 12.8 Hz, $\text{C}_\text{Ar}\text{H} \times 6$), 128.7 ($\text{C}_\text{Ar}\text{H}$), 127.2 ($\text{C}\equiv\text{N}$), 125.1 ($\text{C}_\text{Ar}\text{H}$), 122.8 (d, J = 93.6 Hz, $\text{C}_\text{Ar} \times 3$), 122.6 (d, J =

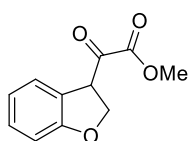
16.0 Hz, C_{Ar}), 120.2 (C_{ArH}), 109.7 (C_{ArH}), 72.9 (CH_{AHB}), 50.6 (d, $J = 7.3$ Hz, CH), 48.2 (d, $J = 125.6$ Hz, C(O)C=P).

^{31}P NMR (162 MHz, $CDCl_3$) $\delta = 20.5$.

IR (film) ν_{max}/cm^{-1} 3003, 2173, 1595, 1481, 1108, 747, 666.

HRMS: (ESI⁺) Found $[M + H]^+ = 448.1457$; $C_{29}H_{23}O_2NP$ requires 448.1461.

Methyl 2-(2,3-dihydrobenzofuran-3-yl)-2-oxoacetate (**268**)¹⁰¹



268

To a solution of dihydrobenzofuran **267** (22 mg, 50 μ mol) in acetone (1 mL) and MeOH (1 mL) was added dropwise freshly prepared DMDO (0.11 M in acetone, 910 μ L, 100 μ mol). The reaction mixture was stirred for 1 h and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 80:20) afforded the title compound as a colourless oil (7 mg, 72%). N.B. the title compound was observed entirely as the enol form by NMR.

$R_f = 0.4$ (Pentane:EtOAc, 70:30).

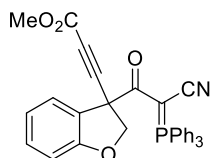
^1H NMR ($CDCl_3$, 400 MHz) $\delta = 7.96$ (1H, dd, $J = 7.8, 1.4$ Hz, ArH), 7.30 – 7.23 (1H, m, ArH), 6.97 (1H, td, $J = 7.6, 1.0$ Hz, ArH), 6.88 (1H, d, $J = 8.1$ Hz, ArH), 5.89 (1H, s, OH), 5.35 (2H, s, CH_2), 3.95 (3H, s, CO_2CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) $\delta = 165.1$ (CO_2CH_3), 163.7 (C_{Ar}), 131.3 (C_{ArH}), 131.1 ($C=C(OH)$), 127.1 (C_{ArH}), 125.1 ($C=C(OH)$), 124.6 (C_{Ar}), 121.2 (C_{ArH}), 109.9 (C_{ArH}), 74.3 (CH_2), 53.2 (CO_2CH_3).

IR (film) ν_{max}/cm^{-1} 3457, 3374, 2959, 2941, 1700, 1674, 1469, 1238, 970, 759.

HRMS: (APCI⁺) Found $[M + H]^+ = 207.0652$; C₁₁H₁₁O₄ requires 207.0652.

Methyl 3-(3-(2-cyano-2-(triphenyl- λ^5 -phosphaneylidene)acetyl)-2,3-dihydrobenzofuran-3-yl)propiolate (270)



270

To a stirred solution of cyanoketophosphorane **267** (180 mg, 400 μ mol) in DMF (8 mL) at -40°C was added LiHMDS (480 μ L, 480 μ mol, 1 M in THF). After 10 min chloroacetylene **145** (72 mg, 600 μ mol) in DMF (0.5 mL) was added dropwise and the reaction mixture was stirred at -40°C for 2 h. Sat. aq. NH₄Cl (5 mL) was added and the mixture extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. LiCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 70:30) afforded the title compound as a pale yellow solid (190 mg, 90%).

R_f = 0.65 (Pentane:EtOAc, 40:60).

m.p. 91 $^\circ\text{C}$

¹H NMR (CDCl₃, 400 MHz) δ = 7.79 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.65 – 7.44 (15H, m, ArH $\times$ 15), 7.25 – 7.18 (1H, m, ArH), 7.01 – 6.92 (1H, m, ArH), 6.81 (1H, d, J = 8.4 Hz, ArH), 5.27 (1H, d, J = 9.0 Hz, CH_AH_B), 4.82 (1H, d, J = 8.9 Hz, CH_AH_B), 3.76 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 126 MHz) δ = 187.3 (d, J = 3.9 Hz, C(O)C=P), 159.6 (C_{Ar}), 154.1 (CO₂CH₃), 133.6 (d, J = 9.8 Hz, C_{Ar}H $\times$ 6), 133.4 (d, J = 2.9 Hz, C_{Ar}H $\times$ 3), 130.0 (C_{Ar}H), 129.3 (d, J = 13.1 Hz, C_{Ar}H $\times$ 6), 126.9 (C $\equiv$ N), 126.6 (C_{Ar}H), 122.6 (d, J = 93.5 Hz, C_{Ar} $\times$

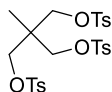
3), 121.3 ($C_{Ar}H$), 120.5 (d, $J = 14.3$ Hz, C_{Ar}), 110.3 ($C_{Ar}H$), 86.2 ($C\equiv CCO_2CH_3$), 79.2 (CH_AH_B), 77.3 ($C\equiv CCO_2CH_3$), 54.8 (d, $J = 6.9$ Hz, $C_{Ar}C$), 52.9 (CO_2CH_3), 47.7 (d, $J = 125.0$ Hz, $C(O)C=P$).

^{31}P NMR (162 MHz, $CDCl_3$) $\delta = 22.8$.

IR (film) ν_{max}/cm^{-1} 3010, 2235, 2179, 1714, 1653, 1460, 1276, 1236, 750.

HRMS: (ESI⁺) Found $[M + H]^+ = 530.1516$; $C_{33}H_{25}O_4NP$ requires 530.1516.

2-Methyl-2-((tosyloxy)methyl)propane-1,3-diyl bis(4-methylbenzenesulfonate) (273)¹⁰³



273

To a solution of 1,1,1-tris(hydroxymethyl)ethanol **272** (4.00 g, 3.3 mmol) in pyridine (40 mL) at 0 °C was added *p*-toluenesulfonyl chloride (25.4 g, 133 mmol). The reaction mixture was stirred for 16 h then Et_2O (200 mL) was added followed by HCl (6 M aq., 400 mL). The two layers were separated and the organic layer was washed with sat. aq. NaCl (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound (19.4 g, 100 %) as a white solid with no further purification necessary.

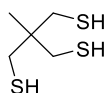
$R_f = 0.5$ (Pentane: Et_2O , 70:30).

m.p. 107 °C.

^1H NMR ($CDCl_3$, 400 MHz) $\delta = 7.70$ (6H, d, $J = 8.4$ Hz, $ArH \times 6$), 7.35 (6H, d, $J = 8.1$ Hz, $ArH \times 6$), 3.76 (6H, s, $CH_2 \times 3$), 2.46 (9H, s, $CH_3 \times 3$), 0.88 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 110 MHz) $\delta = 145.5$ ($C_{Ar} \times 3$), 132.0 ($C_{Ar} \times 3$), 130.2 ($C_{Ar}H \times 6$), 128.0 ($C_{Ar}H \times 6$), 69.9 ($CH_2 \times 3$), 39.5 (CH_3C), 21.8 ($CH_3 \times 3$), 16.2 (CH_3).

Analytical data are in accordance with those previously reported for this compound.¹⁰³

2-(Mercaptomethyl)-2-methylpropane-1,3-dithiol (274)¹⁰³**274**

A solution of NaSH·9H₂O (3.88 g, 47.1 mmol) and S (2.63 g, 82.2 mmol) in DMF (50 mL) was heated at 80 °C for 1 h. Tosylate **273** (6.40 g, 11.0 mmol) was added and the reaction mixture was heated at 100 °C for 4 h. The reaction was cooled and the solvent removed by distillation under reduced pressure. Toluene (50 mL) and Cu (4.73 g, 74.4 mmol) were added and the mixture was heated at 115 °C for 16 h. The reaction mixture was filtered through Celite[®] and washed with toluene (70 mL). The solvent was reduced *in vacuo* to approximately 50 mL then EtOH (50 mL) and Zn (10.6 g, 162 mmol) were added followed by conc. HCl (40 mL) dropwise. The reaction mixture was stirred at rt for 24 h. Water (100 mL) was added and the layers separated. The aqueous layer was washed with EtOAc (3 × 50 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound (1.74 g, 94 %) as a pale yellow oil with no further purification necessary.

R_f = 0.4 (Pentane:EtOAc, 50:50).

¹H NMR (CDCl₃, 400 MHz) δ = 2.60 (6H, d, J = 8.7 Hz, CH₂ × 3), 1.22 (3H, t, J = 8.8 Hz, SH × 3), 1.00 (3H, s, CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 39.2 (CH₃C), 31.8 (CH₂ × 3), 21.5 (CH₃).

Analytical data are in accordance with those previously reported for this compound.¹⁰³

4-Methyl-2,6,7-trithiabicyclo[2.2.2]octane (275)¹⁰³



275

A solution of thiol **274** (1.70 g, 10.1 mmol), trimethylorthoformate (1.87 mL, 17.1 mmol) and PTSA (85 mg, 500 μ mol) in toluene (50 mL) was heated at 115 °C for 24 h. Sat. aq. NaHCO₃ (50 mL) was added and the two layers separated. The aqueous layer was washed with Et₂O (3 $\times$ 50 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound (1.04 g, 54 %) as a white solid.

*R*_f = 0.3 (Pentane:Et₂O, 90:10).

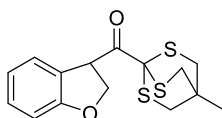
m.p. 130 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 4.60 (1H, s, CH), 3.03 (6H, s, CH₂ $\times$ 3), 1.22 (3H, s, CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 38.2 (CH), 34.3 (CH₂ $\times$ 3), 30.9 (CH₃), 28.4 (CH₃C).

Analytical data are in accordance with those previously reported for this compound.¹⁰³

(2,3-Dihydrobenzofuran-3-yl)(4-methyl-2,6,7-trithiabicyclo[2.2.2]octan-1-yl)methanone (276)



276

To a solution of thioether **275** (750 mg, 4.21 mmol) in THF (15 mL) at –78 °C was added dropwise ⁿBuLi (1.85 mL, 740 μ mol, 2.5 M hexanes) and the reaction mixture stirred for 10 min. A solution of ester **87** (600 mg, 3.36 mmol) in THF (2 mL) was added and the

reaction mixture stirred for a further 20 min at $-78\text{ }^{\circ}\text{C}$. Sat. aq. NH_4Cl (10 mL) was added followed by water (50 mL) and the mixture extracted with Et_2O ($3 \times 50\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 80:20) afforded the title compound as a pale yellow oil (824 mg, 76%).

m.p. $130\text{ }^{\circ}\text{C}$.

R_f = 0.2 (Pentane: Et_2O , 80:20).

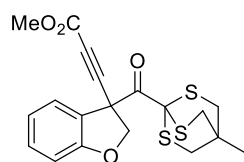
^1H NMR (CDCl_3 , 400 MHz) δ = 7.29 (1H, dt, J = 7.8, 1.3 Hz, ArH), 7.21 – 7.14 (1H, m, ArH), 6.91 – 6.80 (2H, m, ArH $\times$ 2), 5.41 – 5.30 (1H, m, CH), 4.79 (1H, dd, J = 9.7, 8.9 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.58 (1H, dd, J = 8.9, 7.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.17 – 3.06 (6H, m, $\text{CH}_2 \times 3$), 1.31 (3H, s, CH_3).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 200.7 ($\text{C}(\text{O})$), 160.8 (C_Ar), 129.6 (C_ArH), 126.3 (C_Ar), 125.7 (C_ArH), 121.0 (C_ArH), 110.1 (C_ArH), 74.9 ($\text{CH}_\text{A}\text{H}_\text{B}$), 65.7 ($\text{C}(\text{O})\text{C}$), 50.5 (CH), 35.9 ($\text{CH}_2 \times 3$), 30.2 (CH_3), 29.7 (CH_3C).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2957, 2914, 1715, 1481, 1459, 1233, 1119, 983, 752.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 325.0386$; $\text{C}_{15}\text{H}_{17}\text{O}_2\text{S}_3$ requires 325.0385.

Methyl 3-(3-(4-methyl-2,6,7-trithiabicyclo[2.2.2]octane-1-carbonyl)-2,3-dihydrobenzofuran-3-yl)propionate (277)



277

To a stirred solution of ketone **276** (200 mg, 618 μmol) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (928 μL , 928 μmol , 1 M in THF). After 10 min chloroacetylene **145** (88 mg,

743 μmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Sat. aq. NH_4Cl (5 mL) and water (20 mL) were added and the mixture extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 65:35) afforded the title compound as a colourless oil (136 mg, 54%).

$R_f = 0.2$ (Pentane: Et_2O , 60:40).

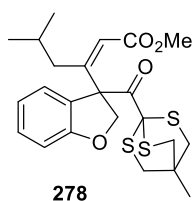
$^1\text{H NMR}$ (CDCl_3 , 400 MHz) $\delta = 7.51$ (1H, dd, $J = 7.8, 1.4\text{ Hz}$, ArH), $7.28 - 7.24$ (2H, m, $\text{ArH} \times 2$), 6.96 (1H, td, $J = 7.6, 1.0\text{ Hz}$, ArH), 6.85 (1H, d, $J = 8.0\text{ Hz}$, ArH), 5.52 (1H, d, $J = 9.7\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.80 (1H, d, $J = 9.6\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.77 (3H, s, CO_2CH_3), 3.06 (6H, s, $\text{CH}_2 \times 3$), 1.26 (3H, s, CH_3).

$^{13}\text{C NMR}$ (CDCl_3 , 110 MHz) $\delta = 194.5$ ($\text{C}(\text{O})$), 160.0 (CO_2CH_3), 153.6 (C_Ar), 131.0 ($\text{C}_\text{Ar}\text{H}$), 126.8 ($\text{C}_\text{Ar}\text{H}$), 125.4 (C_Ar), 121.7 ($\text{C}_\text{Ar}\text{H}$), 110.7 ($\text{C}_\text{Ar}\text{H}$), 83.9 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 79.8 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 79.6 ($\text{CH}_\text{A}\text{H}_\text{B}$), 64.4 ($\text{C}_\text{Ar}\text{C}$), 56.5 ($\text{C}(\text{O})\text{C}$), 53.0 (CO_2CH_3), 36.5 ($\text{CH}_2 \times 3$), 29.7 (CH_3), 29.5 (CH_3C).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 1722, 1596, 1479, 1463, 1174, 1020, 749.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 407.0440$; $\text{C}_{19}\text{H}_{19}\text{O}_4\text{S}_3$ requires 407.0439.

Methyl (Z)-5-methyl-3-(3-(4-methyl-2,6,7-trithiabicyclo[2.2.2]octane-1-carbonyl)-2,3-dihydrobenzofuran-3-yl)hex-2-enoate (278)⁵⁷



To a solution of CuI (38 mg, 200 μ mol) in THF (2 mL) at -78 $^{\circ}$ C was added *i*BuLi (235 μ L, 400 μ mol, 1.7 M in pentane). The reaction mixture was stirred vigorously at 0 $^{\circ}$ C for 1 h before being cooled to -78 $^{\circ}$ C. A solution of chloroacetylene **145** (41 mg, 100 μ mol) in Et₂O (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78 $^{\circ}$ C for 30 min. Methanol (1 mL) was added and the mixture partitioned between water (15 mL) and Et₂O (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 70:30) afforded the title compound as a colourless oil and a single diastereomer (170 mg, 71%).

R_f = 0.2 (Pentane:Et₂O, 70:30).

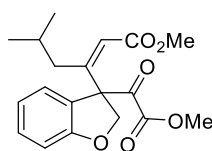
¹H NMR (CDCl₃, 500 MHz) δ = 7.32 – 7.26 (1H, m, ArH), 7.14 (1H, d, J = 7.6 Hz, ArH), 6.90 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.83 (1H, d, J = 8.1 Hz, ArH), 6.37 (1H, d, J = 10.6 Hz, CH_AH_B), 5.88 (1H, s, C=CH), 4.56 (1H, d, J = 10.6 Hz, CH_AH_B), 3.70 (3H, s, CO₂CH₃), 3.06 (3H, dd, J = 11.4, 2.0 Hz, SCH_AH_B $\times$ 3), 2.76 (3H, dd, J = 11.5, 2.2 Hz, SCH_AH_B $\times$ 3), 2.04 (1H, dd, J = 13.9, 5.0 Hz, C=CCH_AH_B), 1.78 (1H, ddd, J = 14.1, 8.4, 1.0 Hz, C=CCH_AH_B), 1.20 (1H, m, CH), 1.15 (3H, s, CH₃), 0.74 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.59 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 196.0 (C(O)), 166.1 (CO₂CH₃), 163.0 (C=CH), 162.8 (C_{Ar}), 131.5 (C_{Ar}H), 128.0 (C_{Ar}H), 123.8 (C_{Ar}), 120.1 (C_{Ar}H), 118.9 (C=CH), 110.2 (C_{Ar}H), 82.2 (CH_AH_B), 69.2 (C_{Ar}C), 64.7 (C(O)C), 51.7 (CO₂CH₃), 47.7 (CH_AH_BC=CH), 37.1 (CH₂ × 3), 29.6 (CH₃), 29.2 (CH₃C), 26.2 (CH(CH₃)_A(CH₃)_B), 22.9 (CH(CH₃)_A(CH₃)_B), 21.7 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2955, 2915, 1712, 1479, 1232, 1209, 1162, 753, 732.

HRMS: (ESI⁺) Found [M + H]⁺ = 465.1220; C₂₃H₂₉O₄S₃ requires 465.1222.

Methyl (Z)-3-(3-(2-methoxy-2-oxoacetyl)-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-enoate (279)¹⁵⁶



279

Ozone was bubbled through a solution of ylide **348** (7 mg, 17 μmol) in CH₂Cl₂ (1.6 mL) and MeOH (0.4 mL) at –78 °C until an intense blue colour persisted. Dimethylsulfide (500 μL , 6.8 mmol) was added and the solution stirred at rt for 1 h. The mixture was concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 90:10) afforded the title compound as a pale yellow oil and a single diastereomer (2 mg, 34%).

*R*_f = 0.2 (Pentane:EtOAc, 90:10).

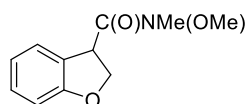
¹H NMR (CDCl₃, 500 MHz) δ = 7.41 (1H, d, *J* = 7.6 Hz, ArH), 7.28 – 7.21 (1H, m, ArH), 6.92 – 6.86 (2H, m, ArH × 2), 5.84 (1H, s, C=CH), 5.64 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.41 (1H, d, *J* = 9.9 Hz, CH_AH_B), 3.86 (3H, s, C(O)CO₂CH₃), 3.71 (3H, s, CO₂CH₃), 2.42 (1H, ddd, *J* = 14.3, 4.5, 1.1 Hz), 1.97 (1H, ddd, *J* = 14.4, 9.1, 1.0 Hz), 1.36 – 1.31 (1H, m), 0.82 (3H, d, *J* = 6.6 Hz), 0.65 (3H, d, *J* = 6.6 Hz).

¹³C NMR (CDCl₃, 126 MHz) δ = 187.7 (C(O)CO₂CH₃), 167.0 (CO₂CH₃), 163.4 (C=CH), 162.4 (C(O)CO₂CH₃), 161.5 (C_{Ar}), 130.7 (C_{Ar}H), 127.6 (C_{Ar}H), 125.1 (C_{Ar}), 120.6 (C_{Ar}H), 117.5 (C=CH), 110.7 (C_{Ar}H), 81.2 (CH_AH_B), 65.1 (C_{Ar}C), 53.1 (C(O)CO₂CH₃), 51.8 (CO₂CH₃), 47.3 (CH_AH_BC=CH), 26.0 (CH(CH₃)_A(CH₃)_B), 23.1 (CH(CH₃)_A(CH₃)_B), 21.5 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2956, 1733, 1717, 1684, 1480, 1326, 1214, 1166, 1127, 756.

HRMS: (ESI⁺) Found [M + Na]⁺ = 369.1309; C₁₉H₂₂O₆Na requires 369.1309.

***N*-Methoxy-*N*-methyl-2,3-dihydrobenzofuran-3-carboxamide (281)¹⁰¹**



281

To a solution of acid **265** (240 mg, 1.46 mmol) in CH₂Cl₂ (12 mL) at rt was added *N*-O-dimethylhydroxylamine hydrochloride (178 mg, 1.82 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (450 mg, 2.35 mmol), 4-(dimethylamino)pyridine (25 mg, 200 μ mol) and Et₃N (254 μ L, 1.82 mmol). The reaction mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 65:35) afforded the title compound as a pale yellow oil (303 mg, 100%).

R_f = 0.15 (Pentane:EtOAc, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 7.30 (1H, d, *J* = 7.1 Hz, Ar*H*), 7.15 (1H, td, *J* = 7.8, 1.4 Hz, Ar*H*), 6.85 (1H, td, *J* = 7.5, 1.1 Hz, Ar*H*), 6.82 (1H, d, *J* = 8.8 Hz, Ar*H*), 4.93 – 4.84 (1H,

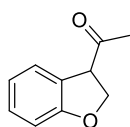
m, CH_AH_B), 4.74 – 4.65 (2H, m, CH_AH_B and CH), 3.75 (3H, s, $N(CH_3)OCH_3$), 3.27 (3H, s, $N(CH_3)OCH_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.3 ($C(O)N(CH_3)OCH_3$), 160.3 (C_{Ar}), 129.3 ($C_{Ar}H$), 125.7 (C_{Ar}), 125.5 ($C_{Ar}H$), 120.7 ($C_{Ar}H$), 110.0 ($C_{Ar}H$), 73.2 (CH_AH_B), 61.5 ($N(CH_3)OCH_3$), 45.1 (CH), 32.8 ($N(CH_3)OCH_3$).

IR (film) ν_{max}/cm^{-1} 2940, 1664, 1437, 1234, 753.

HRMS: (ESI^+) Found $[M + Na]^+ = 230.0788$; $C_{11}H_{13}O_3NNa$ requires 230.0788.

1-(2,3-Dihydrobenzofuran-3-yl)ethan-1-one (282)¹⁵⁷



282

To a solution of amide **281** (300 mg, 1.45 mmol) in THF (25 mL) at 0 °C was added dropwise $MeMgBr$ (724 μL , 2.17 mmol, 3.0 M in Et_2O). The reaction mixture was stirred for 2 h and sat. aq. NH_4Cl (10 mL) was added. The mixture was diluted with Et_2O (70 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3×30 mL) and the combined organic phase was washed with sat. aq. $NaCl$ (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 85:15) afforded the title compound as a pale yellow oil (226 mg, 96%).

R_f = 0.8 (Pentane: $EtOAc$, 1:1).

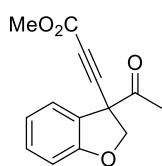
^1H NMR ($CDCl_3$, 400 MHz) δ = 7.22 (1H, d, J = 7.2, 1.2 Hz, ArH), 7.16 – 7.10 (1H, m, ArH), 6.83 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.78 (1H, d, J = 8.1, 0.9 Hz, ArH), 4.86 (1H, dd, J = 9.4, 5.0 Hz, CH_AH_B), 4.52 (1H, t, J = 9.3 Hz, CH), 4.21 (1H, dd, J = 9.3, 4.9 Hz, CH_AH_B), 2.19 (3H, s, CH_3).

¹³C NMR (CDCl₃, 126 MHz) δ = 205.0 (C(O)CH₃), 160.3 (C_{Ar}), 129.8 (C_{Ar}H), 125.0 (C_{Ar}H), 124.7 (C_{Ar}), 120.9 (C_{Ar}H), 110.5 (C_{Ar}H), 72.2 (CH_AH_B), 55.8 (CH), 27.5 (CH₃).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3049, 2917, 1713, 1594, 1481, 1461, 1357, 1231, 1168, 751.

HRMS: (APCI⁺) Found [M + H]⁺ = 163.0753; C₁₀H₁₁O₂ requires 163.0754.

Methyl 3-(3-acetyl-2,3-dihydrobenzofuran-3-yl)propiolate (**283**)



283

To a stirred solution of ketone **282** (6.0 mg, 37 μmol) in THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (44 μL , 44 μmol , 1 M in THF). After 10 min chloroacetylene **145** (7.0 mg, 56 μmol) in THF (0.2 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Sat. aq. NH₄Cl (1 mL) was added and the mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (8.0 mg, 87%).

R_f = 0.2 (Pentane:Et₂O, 80:20).

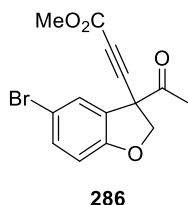
¹H NMR (CDCl₃, 400 MHz) δ = 7.36 (1H, dd, J = 7.6, 1.3 Hz, ArH), 7.24 – 7.14 (1H, m, ArH), 6.95 – 6.86 (1H, m, ArH), 6.79 (1H, d, J = 8.7 Hz, ArH), 5.17 (1H, d, J = 9.0 Hz, CH_AH_B), 4.52 (1H, d, J = 9.0 Hz, CH_AH_B), 3.72 (3H, s, CO₂CH₃), 2.37 (3H, s, C(O)CH₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 198.1 (C(O)CH₃), 159.7 (CO₂CH₃), 153.5 (C_{Ar}), 131.0 (C_{Ar}H), 125.2 (C_{Ar}), 124.6 (C_{Ar}H), 121.7 (C_{Ar}H), 111.2 (C_{Ar}H), 84.4 (C $\equiv$ CCO₂CH₃), 74.2 (CH_AH_B), 57.3 (C $\equiv$ CCO₂CH₃), 53.1 (CO₂CH₃), 47.8 (C_{Ar}C), 25.4 (C(O)CH₃).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2955, 2918, 2238, 1720, 1480, 1277, 1238, 751.

HRMS: (ESI⁺) Found [M + Na]⁺ = 267.0629; C₁₄H₁₂O₄NaSi requires 267.0628.

Methyl 3-(3-acetyl-5-bromo-2,3-dihydrobenzofuran-3-yl)propiolate (286)¹⁰⁶



To a solution of ketone **283** (24 mg, 100 μmol) in CH₂Cl₂ (1 mL) and MeOH (400 μL) at rt was added benzyltrimethylammonium tribromide (82 mg, 210 μmol). The reaction mixture was stirred at rt for 18 h. Et₂O (20 mL) and water (20 mL) were added and the layers separated. The aqueous layer was extracted with Et₂O (2 × 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (20 mg, 61%).

R_f = 0.18 (Pentane:Et₂O, 80:20).

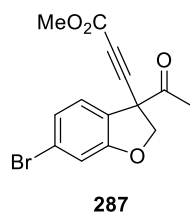
¹H NMR (CDCl₃, 400 MHz) δ = 7.52 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.36 (1H, dd, *J* = 8.6, 2.1 Hz, Ar*H*), 6.75 (1H, d, *J* = 8.6 Hz, Ar*H*), 5.24 (1H, d, *J* = 9.0 Hz, CH_AH_B), 4.61 (1H, d, *J* = 9.1 Hz, CH_AH_B), 3.81 (3H, s, CO₂CH₃), 2.46 (3H, s, C(O)CH₃).

¹³C NMR (CDCl₃, 126 MHz) δ = 197.4 (C(O)CH₃), 158.9 (C_{Ar}), 153.3 (CO₂CH₃), 133.9 (C_{Ar}H), 127.5 (C_{Ar}H), 127.4 (C_{Ar}), 113.3 (C_{Ar}H), 112.8 (C_{Ar}), 83.4 (C≡CCO₂CH₃), 78.1 (CH_AH_B), 77.8 (C≡CCO₂CH₃), 57.1 (C_{Ar}C), 53.2 (CO₂CH₃), 25.5 (C(O)CH₃).

IR (film) ν_{max}/cm⁻¹

HRMS: (APCI⁻) Found [M]⁻ = 320.9767; C₁₄H₁₀BrO₄ requires 320.9768.

Methyl 3-(3-acetyl-6-bromo-2,3-dihydrobenzofuran-3-yl)propiolate (287)¹⁰⁶



To a solution of ketone **283** (24 mg, 100 μ mol) in CH_2Cl_2 (1 mL) and MeOH (400 μ L) at rt was added benzyltrimethylammonium tribromide (82 mg, 210 μ mol). The reaction mixture was stirred at rt for 18 h. Et_2O (20 mL) and water (20 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (2×30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 85:15) afforded the title compound as a colourless oil (11 mg, 35%).

$R_f = 0.2$ (Pentane: Et_2O , 80:20).

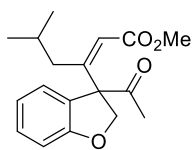
^1H NMR (CDCl_3 , 400 MHz) δ = 7.41 (1H, d, J = 2.1 Hz, ArH), 7.36 (1H, dd, J = 8.6, 2.1 Hz, ArH), 6.75 (1H, d, J = 8.6 Hz, ArH), 5.58 (1H, d, J = 9.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.56 (1H, d, J = 9.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.90 (3H, s, CO_2CH_3), 2.45 (3H, s, $\text{C}(\text{O})\text{CH}_3$).

^{13}C NMR (CDCl_3 , 126 MHz) δ = 197.7 ($\text{C}(\text{O})\text{CH}_3$), 163.8 (CO_2CH_3), 159.8 (C_Ar), 134.0 ($\text{C}_\text{Ar}\text{H}$), 130.1 ($\text{C}_\text{Ar}\text{H}$), 128.2 (C_Ar), 126.2 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 112.7 ($\text{C}_\text{Ar}\text{H}$), 112.0 (C_Ar), 109.9 ($\text{C}\equiv\text{CCO}_2\text{CH}_3$), 78.2 ($\text{CH}_\text{A}\text{H}_\text{B}$), 71.7 ($\text{C}_\text{Ar}\text{C}$), 53.8 (CO_2CH_3), 26.3 ($\text{C}(\text{O})\text{CH}_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 2926, 1738, 1723, 1476, 1260, 1243, 1172.

HRMS: (APCI $^-$) Found $[\text{M} - \text{H}]^- = 320.9769$; $\text{C}_{14}\text{H}_{10}\text{BrO}_4$ requires 320.9768.

Methyl (Z)-3-(3-acetyl-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-enoate (288)⁵⁷



288

To a solution of CuI (229 mg, 1.20 mmol) in THF (3.6 mL) at $-78\text{ }^{\circ}\text{C}$ was added $t\text{BuLi}$ (1.41 mL, 2.40 mmol, 1.7 M in pentane). The mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **283** (147 mg, 600 μmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. MeOH (0.5 mL) was added followed by water (30 mL), and the mixture was extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil and a single diastereomer (20 mg, 16%).

$R_f = 0.4$ (Pentane:Et₂O, 80:20).

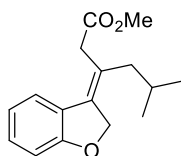
¹H NMR (CDCl₃, 400 MHz) δ = 7.25 – 7.20 (1H, m, ArH), 7.10 (1H, dd, J = 7.6, 1.4 Hz, ArH), 6.88 (1H, dd, J = 7.5, 1.1 Hz, ArH), 6.85 (1H, d, J = 8.1 Hz, ArH), 5.85 (1H, t, J = 1.2 Hz, C=CH), 5.55 (1H, d, J = 10.6 Hz, CH_AH_B), 4.44 (1H, d, J = 10.5 Hz, CH_AH_B), 3.67 (3H, s, CO₂CH₃), 2.23 (3H, s, C(O)CH₃), 2.23 – 2.18 (1H, m, CH_AH_BC=CH), 1.93 – 1.84 (1H, m, CH_AH_BC=CH), 1.27 (1H, m, J = 8.8, 6.7, 4.9 Hz, CH), 0.77 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.62 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 202.7 (C(O)CH₃), 166.9 (CO₂CH₃), 163.0 (C_{Ar}), 161.4 (C=CH), 130.5 (C_{Ar}H), 126.8 (C_{Ar}H), 125.2 (C_{Ar}), 120.6 (C_{Ar}H), 117.9 (C=CH), 110.5 (C_{Ar}H), 81.7 (CH_AH_B), 68.3 (C_{Ar}C), 51.5 (CO₂CH₃), 47.6 (CH_AH_BC=CH), 26.4 (C(O)CH₃), 25.9 (CH), 22.9 (CH(CH₃)_A(CH₃)_B), 21.6 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 1710, 1626, 1592, 1480, 1461, 1228, 1210, 1153, 753.

HRMS: (ESI⁺) Found $[M + H]^+ = 361.2007$; C₂₁H₂₉O₅ requires 361.2010.

Methyl (E)-3-(benzofuran-3(2H)-ylidene)-5-methylhexanoate (289)⁵⁷



289

To a solution of CuI (229 mg, 1.20 mmol) in THF (3.6 mL) at $-78\text{ }^{\circ}\text{C}$ was added ^tBuLi (1.41 mL, 2.40 mmol, 1.7 M in pentane). The mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **283** (147 mg, 600 μmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. MeOH (0.5 mL) was added followed by water (30 mL), and the mixture was extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil and a single diastereomer (7 mg, 10%).

R_f = 0.7 (Pentane:Et₂O, 80:20).

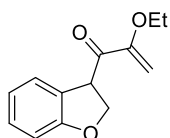
¹H NMR (CDCl₃, 400 MHz) δ = 7.42 (1H, d, J = 7.8 Hz, ArH), 7.11 – 7.05 (1H, m, ArH), 6.82 (1H, td, J = 7.6, 1.2 Hz, ArH), 6.77 (1H, d, J = 8.1 Hz, ArH), 5.07 (2H, t, J = 1.3 Hz, CH₂O), 3.63 (3H, s, CO₂CH₃), 3.38 (2H, t, J = 1.4 Hz, CH₂CO₂CH₃), 1.97 – 1.92 (2H, m, CH₂C=C), 1.88 – 1.78 (1H, m, CH), 0.88 (6H, d, J = 5.6 Hz, CH(CH₃)₂).

¹³C NMR (CDCl₃, 110 MHz) δ = 171.7 (CO₂CH₃), 164.6 (C_{Ar}), 134.7 (CH₂C=C), 129.5 (C_{Ar}H), 125.4 (C_{Ar}), 124.0 (C_{Ar}H), 123.3 (CH₂C=C), 120.8 (C_{Ar}H), 110.5 (C_{Ar}H), 74.7 (CH₂O), 52.1 (CO₂CH₃), 45.5 (CH₂C=C), 37.6 (CH₂CO₂CH₃), 27.0 (CH), 22.7 (CH(CH₃)₂).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 2869, 1736, 1476, 1261, 1223, 1157, 997, 748.

HRMS: (ESI⁺) Found $[M + \text{Na}]^+ = 283.1304$; $\text{C}_{16}\text{H}_{20}\text{O}_3\text{Na}$ requires 283.1305.

1-(2,3-dihydrobenzofuran-3-yl)-2-ethoxyprop-2-en-1-one (291)¹⁰⁷



291

To a solution of ethyl vinyl ether **288** (287 μL , 3.00 mmol) in THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ was added ^tBuLi (1.71 mL, 2.90 mmol, 1.7 M in pentane). After 15 min at $0\text{ }^{\circ}\text{C}$, a solution of amide **281** (207 mg, 1.00 mmol) in THF (10 mL) was added dropwise at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred at rt for 2 h. Sat. aq. NH_4Cl (20 mL) was added and the mixture partitioned between water (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O ($3 \times 50\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (163 mg, 75%).

$R_f = 0.7$ (Pentane: Et_2O , 80:20).

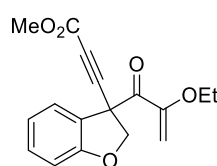
¹H NMR (CDCl_3 , 400 MHz) δ = 7.24 (1H, d, $J = 7.5\text{ Hz}$, ArH), 7.15 (1H, t, $J = 7.6\text{ Hz}$, ArH), 6.84 (1H, td, $J = 7.6, 1.1\text{ Hz}$, ArH), 6.81 (1H, d, $J = 8.1\text{ Hz}$, ArH), 5.31 (1H, d, $J = 2.5\text{ Hz}$, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.00 (1H, dd, $J = 9.3, 6.1\text{ Hz}$, CH), 4.96 (1H, dd, $J = 8.7, 6.1\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.65 (1H, t, $J = 9.0\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.54 (1H, d, $J = 2.6\text{ Hz}$, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.00 – 3.88 (2H, m, OCH_2CH_3), 1.47 (3H, t, $J = 7.0\text{ Hz}$, OCH_2CH_3).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 193.9 ($\text{C}(\text{O})$), 160.3 (C_{Ar}), 156.7 ($\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 129.3 ($\text{C}_{\text{Ar}}\text{H}$), 125.6 ($\text{C}_{\text{Ar}}\text{H}$), 124.9 (C_{Ar}), 120.5 ($\text{C}_{\text{Ar}}\text{H}$), 110.1 ($\text{C}_{\text{Ar}}\text{H}$), 92.7 ($\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 72.1 ($\text{CH}_\text{A}\text{H}_\text{B}$), 64.2 (OCH_2CH_3), 49.4 (CH), 14.5 (OCH_2CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2980, 1709, 1609, 1480, 1231, 1080, 1058, 1080, 1058, 750.

HRMS: Ion not found.

Methyl 3-(3-(2-ethoxyacryloyl)-2,3-dihydrobenzofuran-3-yl)propiolate (**292**)



292

To a stirred solution of ketone **291** (87 mg, 400 μmol) in THF (2.3 mL) at -78°C was added LiHMDS (480 μL , 480 μmol , 1 M in THF). After 10 min chloroacetylene **145** (71 mg, 600 μmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at -78°C for 1 h. Sat. aq. NaHCO_3 (2 mL) was added and the mixture extracted with Et_2O (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 75:25) afforded the title compound as an orange oil (22 mg, 19%).

R_f = 0.3 (Pentane: Et_2O , 70:30).

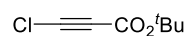
^1H NMR (CDCl_3 , 400 MHz) δ = 7.47 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.26 – 7.21 (1H, m, ArH), 6.95 (1H, td, J = 7.6, 1.1 Hz, ArH), 6.83 (1H, d, J = 8.1 Hz, ArH), 5.33 (1H, d, J = 2.7 Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.06 (1H, d, J = 9.4 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.78 (1H, d, J = 9.4 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.58 (1H, d, J = 2.7 Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.92 (2H, dd, J = 7.1, 5.3 Hz, OCH_2CH_3), 3.76 (3H, s, CO_2CH_3), 1.47 (3H, t, J = 7.0 Hz, OCH_2CH_3).

¹³C NMR (CDCl₃, 101 MHz) δ = 187.6 (C(O)), 159.9 (C_{Ar}), 155.5 (CO₂CH₃), 153.7 (C=CH_AH_B), 130.4 (C_{Ar}H), 126.7 (C_{Ar}H), 124.5 (C_{Ar}), 121.3 (C_{Ar}H), 110.4 (C_{Ar}H), 94.7 (C=CH_AH_B), 85.4 (C $\equiv$ CCO₂CH₃), 78.5 (CH_AH_B), 76.6 (C $\equiv$ CCO₂CH₃), 64.5 (OCH₂CH₃), 54.5, 52.8 (CO₂CH₃), 14.1 (OCH₂CH₃).

IR (film) ν_{max} /cm⁻¹ 2982, 2238, 1714, 1607, 1479, 1273, 1236, 751.

HRMS: Ion not found.

***tert*-Butyl 3-chloropropiolate (295)⁴⁹**



295

To a solution of *tert*-butyl propiolate **294** (1.26 g, 10.0 mmol) and ^tBuOCl (1.09 g, 10.0 mmol) in ^tBuOH (5 mL) was added portionwise ^tBuOK (112 mg, 1.00 mmol). The reaction mixture was stirred at rt for 1 h, then filtered through Celite[®] and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane) afforded the title compound as a colourless oil (768 mg, 48%).

R_f = 0.7 (Pentane:Et₂O, 90:10).

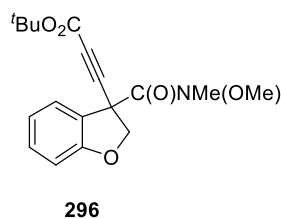
¹H NMR (CDCl₃, 400 MHz) δ = 1.48 (9H, s, CO₂C(CH₃)₃).

¹³C NMR (CDCl₃, 101 MHz) δ = 151.4 (CO₂C(CH₃)₃), 84.3 (CO₂C(CH₃)₃), 66.1 (C $\equiv$ CCl), 63.2 (C $\equiv$ CCl), 28.0 (CO₂C(CH₃)₃).

IR (film) ν_{max} /cm⁻¹ 2982, 2927, 2218, 1714, 1274, 1258, 1157.

HRMS: Ion not found

***tert*-Butyl 3-(3-(methoxy(methyl)carbamoyl)-2,3-dihydrobenzofuran-3-yl)propiolate**
(296)



To a stirred solution of amide **281** (207 mg, 1.00 mmol) in THF (8 mL) at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (1.20 mL, 1.20 mmol, 1 M in THF). After 10 min chloroacetylene **295** (241 mg, 1.50 mmol) in THF (0.6 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Sat. aq. NaHCO_3 (2 mL) was added and the mixture extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 75:25) afforded the title compound as a colourless oil (282 mg, 85%).

$R_f = 0.7$ (Pentane: EtOAc , 50:50).

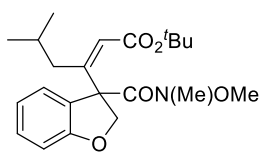
^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.54$ (1H, dd, $J = 7.5, 1.1\text{ Hz}$, ArH), 7.25 – 7.19 (1H, m, ArH), 6.95 (1H, td, $J = 7.5, 1.0\text{ Hz}$, ArH), 6.83 (1H, d, $J = 8.2\text{ Hz}$, ArH), 5.09 (1H, d, $J = 9.3\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.76 (1H, d, $J = 9.2\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.85 (3H, s, $\text{C(O)N(CH}_3\text{)OCH}_3$), 3.24 (3H, s, $\text{C(O)N(CH}_3\text{)OCH}_3$), 1.47 (9H, s, $\text{CO}_2\text{C(CH}_3\text{)}_3$).

^{13}C NMR (CDCl_3 , 101 MHz) $\delta = 167.8$ ($\text{C(O)N(CH}_3\text{)OCH}_3$), 159.8 ($\text{CO}_2\text{C(CH}_3\text{)}_3$), 152.6 (C_Ar), 130.4 (C_ArH), 127.1 (C_ArH), 125.8 (C_Ar), 121.4 (C_ArH), 110.5 (C_ArH), 83.9 ($\text{C}\equiv\text{CCO}_2\text{C(CH}_3\text{)}_3$), 83.5 ($\text{C}\equiv\text{CCO}_2\text{C(CH}_3\text{)}_3$), 79.7 ($\text{CH}_\text{A}\text{H}_\text{B}$), 77.4 (C_ArC), 61.1 ($\text{C(O)N(CH}_3\text{)OCH}_3$), 50.6 ($\text{CO}_2\text{C(CH}_3\text{)}_3$), 33.6 ($\text{C(O)N(CH}_3\text{)OCH}_3$), 28.1 ($\text{CO}_2\text{C(CH}_3\text{)}_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2980, 2940, 2234, 1704, 1671, 1479, 1461, 1395, 1287, 1240, 1152, 752.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 332.1493$; $\text{C}_{18}\text{H}_{25}\text{O}_5\text{N}$ requires 332.1493.

***tert*-Butyl (Z)-3-(3-(methoxy(methyl)carbamoyl)-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-enoate (297)⁵⁷**



297

To a solution of CuI (152 mg, 800 μ mol) in THF (3 mL) at -78 $^{\circ}$ C was added *t*BuLi (941 μ L, 1.60 mmol, 1.7 M in hexane). The mixture was stirred vigorously at 0 $^{\circ}$ C for 1 h before being cooled to -78 $^{\circ}$ C. A solution of alkyne **296** (133 mg, 400 μ mol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at -78 $^{\circ}$ C for 3 h. Sat. aq. NH_4Cl (2 mL) was added and the mixture extracted with Et_2O (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 75:25) afforded the title compound as a colourless oil and a single diastereomer (80 mg, 52%).

R_f = 0.4 (Pentane: Et_2O , 50:50).

^1H NMR (CDCl_3 , 500 MHz) δ = 7.54 (1H, dd, J = 7.7, 1.4 Hz, ArH), 7.18 (1H, ddd, J = 8.1, 7.3, 1.4 Hz, ArH), 6.90 (1H, td, J = 7.6, 1.1 Hz, ArH), 6.79 (1H, d, J = 8.0 Hz, ArH), 5.74 (1H, s, C=CH), 5.10 (1H, d, J = 9.7 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.59 (1H, d, J = 9.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.61 (3H, s, C(O)N(CH₃)OCH₃), 3.20 (3H, s, C(O)N(CH₃)OCH₃), 2.81 (2H, d, J = 7.3 Hz, CH₂), 1.46 (9H, s, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 1.42 – 1.34 (1H, m, CH), 0.82 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.62 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

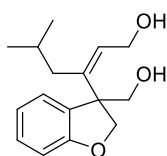
^{13}C NMR (CDCl_3 , 101 MHz) δ = 172.9 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 166.1 (C(O)N(CH₃)OCH₃), 160.4 (C=CH), 157.9 (C_Ar), 129.9 (C_ArH), 128.0 (C_ArH), 126.1 (C_Ar), 120.7 (C_ArH), 119.8 (C=CH), 110.2 (C_ArH), 80.4 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 78.2 ($\text{CH}_\text{A}\text{H}_\text{B}$), 64.1 (C_ArC), 59.7 (C(O)N(CH₃)OCH₃),

37.1 (CH₂), 33.6 (C(O)N(CH₃)OCH₃), 28.3 (CO₂C(CH₃)₃), 27.2 (CH(CH₃)_A(CH₃)_B), 22.3 (CH(CH₃)_A(CH₃)_B), 22.1 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 1711, 1661, 1479, 1366, 1141, 752, 732.

HRMS: (ESI⁺) Found [M + Na]⁺ = 412.2096; C₂₂H₃₁O₅NNa requires 412.2094.

(Z)-3-(3-(Hydroxymethyl)-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-en-1-ol (300)



300

To a solution of ester **110** (48 mg, 150 μmol) in THF (2 mL) at 0 °C was added LiAlH₄ (46 mg, 1.2 mmol). The reaction mixture was stirred for 1 h at rt and water (5 mL) was added followed by Et₂O (30 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (37 mg, 95%).

R_f = 0.4 (Et₂O).

¹H NMR (CDCl₃, 400 MHz) δ = 7.16 – 7.10 (2H, m, ArH $\times$ 2), 6.83 (1H, td, J = 7.4, 1.0 Hz, ArH), 6.76 (1H, dd, J = 8.3, 1.0 Hz, ArH), 5.44 (1H, t, J = 7.0 Hz, C=CH), 4.61 (1H, d, J = 8.8 Hz, CH_AH_B), 4.35 (1H, d, J = 8.8 Hz, CH_AH_B), 3.88 – 3.55 (4H, m, CH₂OH and C=CCH₂OH), 1.96 (2H, d, J = 6.9 Hz, CH₂), 1.59 – 1.54 (1H, m, OH), 1.33 (1H, s, OH), 1.30 – 1.19 (1H, m, CH), 0.79 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.69 (3H, d, J = 6.5 Hz, CH(CH₃)_A(CH₃)_B).

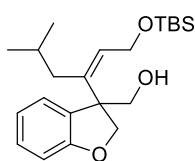
¹³C NMR (CDCl₃, 126 MHz) δ = 160.5 (C=CH), 142.8 (C_{Ar}), 130.5 (C=CH), 130.3 (C_{Ar}), 129.5 (C_{Ar}H), 125.0 (C_{Ar}H), 120.7 (C_{Ar}H), 110.3 (C_{Ar}H), 81.0 (CH_AH_B), 67.8 (CH₂OH),

59.8 (C=CCH₂OH), 55.8 (C_{Ar}C), 46.3 (CH₂), 27.2 (CH), 22.4 (CH(CH₃)_A(CH₃)_B), 22.2 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3358, 2954, 1594, 1482, 1459, 1232, 1013, 983, 751.

HRMS: (ESI⁺) Found [M + Na]⁺ = 285.1460; C₁₆H₂₂O₃Na requires 285.1472.

(Z)-(3-(1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-yl)methanol (301)



301

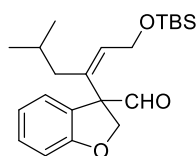
To a solution of diol **300** (340 mg, 1.30 mmol) in CH₂Cl₂ (13 mL) was added *tert*-butyldimethylsilyl chloride (235 mg, 1.56 mmol), (4-dimethylamino)pyridine (16 mg, 130 μ mol) and imidazole (106 mg, 1.56 mmol). The reaction mixture was stirred at rt for 15 min and water (30 mL) was added. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil (373 mg, 76%).

R_f = 0.2 (Pentane:Et₂O, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 7.21 – 7.15 (2H, m, ArH $\times$ 2), 6.89 (1H, td, J = 7.4, 1.0 Hz, ArH), 6.81 (1H, dd, J = 8.4, 1.0 Hz, ArH), 5.46 (1H, t, J = 6.5 Hz, C=CH), 4.65 (1H, d, J = 8.7 Hz, CH_AH_B), 4.43 (1H, d, J = 8.7 Hz, CH_AH_B), 3.93 – 3.63 (4H, m, CH₂OH and C=CCH₂OTBS), 1.99 (2H, d, J = 7.0 Hz, CH₂), 1.75 (1H, dd, J = 8.6, 5.5 Hz, OH), 1.35 – 1.26 (1H, m, CH), 0.87 – 0.81 (12H, m, TBS–C(CH₃)₃ and CH(CH₃)_A(CH₃)_B), 0.75 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), –0.01 (6H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 110 MHz) δ = 160.5 (C=CH), 140.8 (C_{Ar}), 131.6 (C=CH), 130.2 (C_{Ar}), 129.3 (C_{Ar}H), 125.2 (C_{Ar}H), 120.6 (C_{Ar}H), 110.1 (C_{Ar}H), 80.7 (CH_AH_B), 67.8 (CH₂OH), 60.3 (C=CCH₂OTBS), 55.8 (C_{Ar}C), 46.3 (CH₂), 27.3 (CH), 26.0 (TBS-C(CH₃)₃), 22.4 (CH(CH₃)_A(CH₃)_B), 22.3 (CH(CH₃)_A(CH₃)_B), 18.4 (TBS-C(CH₃)₃), -5.1 (TBS-Si(CH₃)₂).
IR (film) ν_{max} /cm⁻¹ 3440, 2954, 2858, 1594, 1482, 1460, 1252, 1082, 1047, 835, 776, 749.
HRMS: (ESI⁺) Found [M + Na]⁺ = 399.2325; C₂₂H₃₆O₃NaSi requires 399.2326.

(Z)-3-(1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carbaldehyde (302)¹⁴⁷



302

To a solution of alcohol **301** (248 mg, 659 μ mol) in CH₂Cl₂ (2 mL) at 0 °C was added NaHCO₃ (42 mg, 500 μ mol) and Dess–Martin periodinane (142 mg, 300 μ mol). The reaction mixture was stirred at rt for 1 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 98:2) afforded the title compound as a colourless oil (223 mg, 90%).

*R*_f = 0.7 (Pentane:Et₂O, 70:30).

¹H NMR (CDCl₃, 400 MHz) δ = 9.55 (1H, s, CHO), 7.24 – 7.20 (1H, m, ArH), 7.18 (1H, d, *J* = 7.5 Hz, ArH), 6.91 (1H, t, *J* = 7.5 Hz, ArH), 6.83 (1H, d, *J* = 8.0 Hz, ArH), 5.63 (1H, t, *J* = 6.2 Hz, C=CH), 5.34 (1H, d, *J* = 9.1 Hz, CH_AH_B), 4.31 (1H, d, *J* = 9.1 Hz, CH_AH_B), 3.93 – 3.80 (2H, m, C=CH₂OTBS), 2.13 – 1.85 (2H, m, CH₂), 1.37 – 1.28 (1H, m, CH), 0.87 (9H,

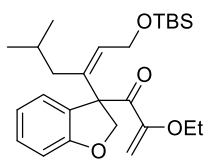
s, TBS–C(CH₃)₃), 0.82 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.69 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.02 (6H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 110 MHz) δ = 192.7 (CHO), 160.5 (C=CH), 136.9 (C_{Ar}), 132.7 (C=CH), 130.3 (C_{Ar}H), 126.2 (C_{Ar}H), 124.5 (C_{Ar}), 120.8 (C_{Ar}H), 110.7 (C_{Ar}H), 76.4 (CH_AH_B), 65.1 (C_{Ar}C), 60.0 (C=CCH₂OTBS), 46.0 (CH₂), 26.3 (CH), 26.1 (TBS–C(CH₃)₃), 22.6 (CH(CH₃)_A(CH₃)_B), 21.8 (CH(CH₃)_A(CH₃)_B), 18.5 (TBS–C(CH₃)₃), –5.2 (TBS–Si(CH₃)₂).

IR (film) ν_{max} /cm^{–1} 2954, 2857, 1725, 1480, 1462, 1238, 1052, 836.

HRMS: (ESI⁺) Found [M + Na]⁺ = 397.2167; C₂₂H₃₄O₃SiNa requires 397.2169.

(Z)-1-(3-(1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-yl)-2-ethoxyprop-2-en-1-one (303)^{107,147}



303

To a solution of ethyl vinyl ether (140 μ L, 1.5 mmol) in THF (3 mL) at –78 °C was added ^tBuLi (1.81 mL, 3.08 mmol, 1.7 M in pentane). After 10 min at 0 °C, 1.35 mL of this solution was added dropwise to a solution of aldehyde **302** (64 mg, 170 μ mol) at 0 °C and the reaction mixture was stirred at rt for 30 min. Sat. aq. NH₄Cl (10 mL) was added and the mixture partitioned between water (10 mL) and Et₂O (30 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. To the crude product in CH₂Cl₂ (2 mL) at 0 °C was added NaHCO₃ (36 mg, 430 μ mol) and Dess–Martin periodinane (120 mg, 260 μ mol). The reaction mixture was stirred at rt for 1 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂,

Pentane:Et₂O, 98:2) afforded the title compound as a colourless oil (49 mg, 65% over 2 steps).

R_f = 0.2 (Pentane:Et₂O, 98:2).

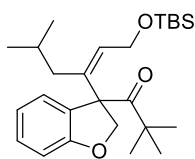
¹H NMR (CDCl₃, 400 MHz) δ = 7.50 (1H, d, J = 7.8 Hz, ArH), 7.19 – 7.12 (1H, m, ArH), 6.83 (1H, t, J = 7.6 Hz, ArH), 6.78 (1H, d, J = 8.0 Hz, ArH), 5.45 (1H, d, J = 9.0 Hz, CH_AH_B), 5.33 (1H, t, J = 6.5 Hz, C=CH), 5.31 (1H, d, J = 2.2 Hz, C=CH_AH_B), 4.46 (1H, d, J = 2.4 Hz, C=CH_AH_B), 4.26 (1H, d, J = 9.0 Hz, CH_AH_B), 3.98 – 3.74 (4H, m, OCH₂CH₃ and C=CHCH₂OTBS), 2.40 (1H, dd, J = 14.6, 5.0 Hz, CH_AH_BC=CH), 1.84 (1H, dd, J = 14.2, 8.9 Hz, CH_AH_BC=CH), 1.46 (3H, t, J = 7.0 Hz, OCH₂CH₃), 1.33 – 1.22 (1H, m, CH), 0.87 (9H, s, TBS–C(CH₃)₃), 0.80 (3H, d, J = 6.5 Hz, CH(CH₃)_A(CH₃)_B), 0.65 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.02 (3H, s, TBS–Si(CH₃)_A(CH₃)_B), 0.01 (3H, s, TBS–Si(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 192.4 (C(O)), 160.9 (C=CH), 156.7 (C(O)C=CH₂), 139.1 (C_{Ar}), 129.8 (C_{Ar}H), 129.0 (C=CH), 128.2 (C_{Ar}H), 125.5 (C_{Ar}), 120.3 (C_{Ar}H), 110.5 (C_{Ar}H), 94.2 (C=CH_AH_B), 78.7 (CH_AH_B), 64.6 (C_{Ar}C), 64.1 (OCH₂CH₃), 60.0 (C=CHCH₂OTBS), 46.6 (CH_AH_BC=CH), 26.1 (CH), 26.0 (TBS–C(CH₃)₃), 23.1 (CH(CH₃)_A(CH₃)_B), 21.7 (CH(CH₃)_A(CH₃)_B), 18.3 (TBS–C(CH₃)₃), 14.4 (OCH₂CH₃), –5.1 (TBS–Si(CH₃)_A(CH₃)_B), –5.1 (TBS–Si(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm^{–1} 2954, 2929, 1698, 1606, 1477, 1294, 1055, 836.

HRMS: (ESI⁺) Found [M + Na]⁺ = 467.2587; C₂₆H₄₀O₄SiNa requires 467.2588

(Z)-1-(3-(1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-yl)-2,2-dimethylpropan-1-one (304)^{107,147}



304

To a solution of ethyl vinyl ether (140 μ L, 1.5 mmol) in THF (3 mL) -78 $^{\circ}$ C was added t BuLi (1.81 mL, 3.08 mmol, 1.7 M in pentane). After 30 min at -78 $^{\circ}$ C, 1.4 mL of this solution was added dropwise to a solution of aldehyde **302** (64 mg, 170 μ mol) at 0 $^{\circ}$ C and the reaction mixture was stirred at rt for 30 min. Sat. aq. NH_4Cl (10 mL) was added and the mixture partitioned between water (10 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. To the crude product in CH_2Cl_2 (2 mL) at 0 $^{\circ}$ C was added NaHCO_3 (36 mg, 430 μ mol) and Dess–Martin periodinane (120 mg, 260 μ mol). The reaction mixture was stirred at rt for 1 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 50:50) afforded the title compound as a colourless oil (64 mg, 87% over 2 steps).

R_f = 0.6 (Pentane: Et_2O , 95:5).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ = 7.37 (1H, dd, J = 7.7, 1.3 Hz, ArH), 7.21 – 7.13 (1H, m, ArH), 6.86 (1H, td, J = 7.6, 1.1 Hz, ArH), 6.80 (1H, d, J = 8.0 Hz, ArH), 5.43 (1H, t, J = 6.9 Hz, C=CH), 5.36 (1H, d, J = 9.3 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.29 (1H, d, J = 9.1 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.95 – 3.81 (2H, m, C=CH CH_2OTBS), 2.28 (1H, dd, J = 14.4, 5.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.88 (1H, dd, J = 13.7, 8.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.35 – 1.26 (1H, m, CH), 1.18 (9H, s, $\text{C}(\text{O})\text{C}(\text{CH}_3)_3$),

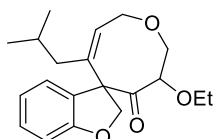
0.88 (9H, s, TBS-C(CH₃)₃), 0.80 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.68 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.04 (3H, s, TBS-Si(CH₃)_A(CH₃)_B), 0.03 (3H, s, TBS-Si(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 210.8 (C(O)C(CH₃)₃), 160.9 (C=CH), 138.8 (C_{Ar}), 130.5 (C=CH), 129.8 (C_{Ar}H), 127.6 (C_{Ar}H), 126.4 (C_{Ar}), 120.2 (C_{Ar}H), 110.8 (C_{Ar}H), 79.5 (CH_AH_B), 67.6 (C_{Ar}C), 60.1 (C=CHCH₂OTBS), 46.6 (CH_AH_BC=CH), 45.9 (C(O)C(CH₃)₃), 29.6 (C(O)C(CH₃)₃), 26.2 (CH), 26.0 (TBS-C(CH₃)₃), 22.8 (CH(CH₃)_A(CH₃)_B), 21.7 (CH(CH₃)_A(CH₃)_B), 18.3 (TBS-C(CH₃)₃), -5.0 (TBS-Si(CH₃)_A(CH₃)_B), -5.1 (TBS-Si(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2955, 1687, 1477, 1461, 1250, 1087, 1051, 835, 750.

HRMS: (ESI⁺) Found [M + Na]⁺ = 453.2795 ; C₂₆H₄₂O₃SiNa requires 453.2795.

(Z)-3'-Ethoxy-6'-isobutyl-2',3'-dihydro-2*H*,4'*H*,8'*H*-spiro[benzofuran-3,5'-oxocin]-4'-one (307)



307

To a solution of alkene **303** (13 mg, 29 μ mol) in THF (2 mL) at 0 °C was added dropwise TBAF (58 μ mol, 58 μ mol, 1 M in THF). The solution was stirred at 0 °C for 15 min then warmed to rt and stirred for 1 h. Sat. aq. NaHCO₃ (2 mL) was added followed by water (20 mL) and Et₂O (20 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10) afforded the title compound as a colourless oil

(6.7 mg, 70%, 1:1 dr). The two diastereomers were indistinguishable by ^1H NMR so are quoted here together.

$R_f = 0.7$ (Pentane:Et₂O, 40:60).

^1H NMR (CDCl₃, 500 MHz) δ = 7.23 (1H, dd, J = 7.5, 1.4 Hz, ArH), 7.13 (2H, td, J = 7.6, 1.4 Hz, ArH $\times$ 2), 7.08 (1H, td, J = 7.8, 1.5 Hz, ArH), 6.83 (1H, t, J = 7.4 Hz, ArH), 6.77 (1H, t, J = 7.2 Hz, ArH), 6.70 (1H, d, J = 8.0 Hz, ArH), 6.67 (1H, d, J = 8.0 Hz, ArH), 5.67 – 5.61 (1H, m, C=CH), 5.63 – 5.58 (1H, m, C=CH), 4.91 (1H, d, J = 9.9 Hz, CH_AH_B), 4.74 (1H, d, J = 9.7 Hz, CH_AH_B), 4.61 – 4.52 (3H, m, C=CHCH_AH_B $\times$ 2 and CH_AH_B), 4.49 – 4.41 (1H, m, C=CHCH_AH_B), 4.38 – 4.30 (2H, m, OCH_AH_BCH(OCH₂CH₃) and C=CHCH_AH_B), 4.20 – 4.15 (2H, m, CH_AH_B and OCH_AH_BCH(OCH₂CH₃)), 4.06 (1H, d, J = 2.6 Hz, OCH_AH_BCH(OCH₂CH₃)), 3.92 (1H, d, J = 2.7 Hz, OCH_AH_BCH(OCH₂CH₃)), 3.60 – 3.36 (4H, m, OCH₂CH₃ $\times$ 2), 3.36 (1H, s, CHC(O)), 3.33 (1H, s, CHC(O)), 1.96 – 1.85 (2H, m, CH_AH_BC=CH $\times$ 2), 1.85 – 1.74 (1H, m, CH), 1.73 – 1.61 (2H, m, CH_AH_BC=CH $\times$ 2), 1.55 – 1.50 (1H, m, CH), 1.13 (3H, t, J = 7.0 Hz, OCH₂CH₃), 0.93 (3H, t, J = 7.0 Hz, OCH₂CH₃), 0.84 (3H, d, J = 6.5 Hz, CH(CH₃)_A(CH₃)_B), 0.80 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.78 (3H, d, J = 6.8 Hz, CH(CH₃)_A(CH₃)_B), 0.67 (3H, d, J = 6.4 Hz, CH(CH₃)_A(CH₃)_B).

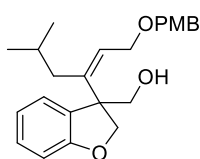
^{13}C NMR (CDCl₃, 126 MHz) δ = 162.0 (C=CH), 160.7 (C=CH), 160.2 (C(O)), 160.0 (C(O)), 136.1 (C_{Ar}), 135.0 (C_{Ar}), 129.6 (C_{Ar}), 128.8 (C_{Ar}H), 128.7 (C_{Ar}H), 127.8 (C_{Ar}), 127.2 (C_{Ar}H), 126.6 (C_{Ar}H), 120.3 (C=CH), 120.0 (C_{Ar}H), 119.8 (C_{Ar}H), 119.3 (C=CH), 109.1 (C_{Ar}H), 108.8 (C_{Ar}H), 97.3 (CHC(O)), 96.6 (CHC(O)), 85.7 (OCH_AH_BCH(OCH₂CH₃)), 84.6 (OCH_AH_BCH(OCH₂CH₃)), 77.4 (CH_AH_B), 75.0 (CH_AH_B), 63.8 (OCH₂CH₃), 63.6 (OCH₂CH₃), 62.3 (C=CHCH_AH_B), 61.7 (C=CHCH_AH_B), 57.6 (C_{Ar}C), 57.2 (C_{Ar}C), 41.9 (CH_AH_BC=CH), 41.3 (CH_AH_BC=CH), 26.2 (CH), 25.4 (CH), 23.0 (CH(CH₃)_A(CH₃)_B), 22.7

(CH(CH₃)_A(CH₃)_B), 22.2 (CH(CH₃)_A(CH₃)_B), 22.2 (CH(CH₃)_A(CH₃)_B), 14.1 (OCH₂CH₃), 13.9 (OCH₂CH₃).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 2927, 1629, 1596, 1482, 1460, 1239, 1147, 1107, 975, 835, 750.

HRMS: (ESI⁺) Found $[M + H]^+ = 353.1724$; C₂₀H₂₆O₄Na requires 353.1723.

(Z)-(3-(1-((4-Methoxybenzyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-yl)methanol (308)¹⁵⁸



308

To a solution of diol **300** (230 mg, 890 μmol) in CH₂Cl₂ (9 mL) was added 4-methoxybenzyl-2,2,2-trichloroacetimidate (280 mg, 980 μmol) and pyridinium *p*-toluenesulfonate (22 mg, 89 μmol). The reaction mixture was stirred at rt for 1 h. Sat. aq. NaHCO₃ (10 mL) was added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15 to 1:1) afforded the title compound as a colourless oil (54 mg, 16%).

R_f = 0.5 (Pentane:Et₂O, 60:40).

¹H NMR (CDCl₃, 400 MHz) δ = 7.23 – 7.16 (4H, m, ArH $\times$ 4), 6.89 – 6.84 (3H, m, ArH $\times$ 3), 6.80 (1H, d, J = 8.3 Hz, ArH), 5.53 (1H, t, J = 6.9 Hz, C=CH), 4.61 (1H, d, J = 8.7 Hz, CH_AH_B), 4.40 (1H, d, J = 8.7 Hz, CH_AH_B), 4.34 – 4.27 (2H, m, PMB–CH₂), 3.84 (1H, dd, J = 11.3, 5.1 Hz, CH_AH_BOH), 3.80 (3H, s, PMB–OCH₃), 3.76 – 3.66 (2H, m, CH₂OPMB), 3.63 (1H, dd, J = 10.8, 8.6 Hz, CH_AH_BOH), 2.06 – 1.94 (2H, m, CH₂C=CH), 1.79 (1H, dd,

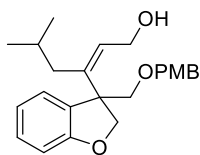
$J = 8.5, 5.3$ Hz, *OH*), 1.32 – 1.24 (1H, m, *CH*), 0.84 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.74 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

^{13}C NMR (CDCl_3 , 126 MHz) $\delta = 160.5$ (C_{Ar}), 159.4 ($\text{C}=\text{CH}$), 143.3 (C_{Ar}), 130.1 (C_{Ar}), 130.0 (C_{Ar}), 129.7 ($\text{C}_{\text{ArH}} \times 2$), 129.3 (C_{ArH}), 128.2 ($\text{C}=\text{CH}$), 125.3 (C_{ArH}), 120.6 (C_{ArH}), 113.9 ($\text{C}_{\text{ArH}} \times 2$), 110.1 (C_{ArH}), 80.7 ($\text{CH}_\text{A}\text{H}_\text{B}$), 72.5 ($\text{PMB}-\text{CH}_2$), 67.7 ($\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$), 66.8 (CH_2OPMB), 55.9 (C_{ArC}), 55.4 ($\text{PMB}-\text{OCH}_3$), 46.4 ($\text{CH}_2\text{C}=\text{CH}$), 27.1 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 22.3 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3430, 2954, 1723, 1513, 1482, 1459, 1247, 1034, 825, 752.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 405.2041$; $\text{C}_{24}\text{H}_{30}\text{O}_4\text{Na}$ requires 405.2047.

(*Z*)-3-(3-(((4-Methoxybenzyl)oxy)methyl)-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-en-1-ol (309**)¹⁵⁸**



309

To a solution of diol **300** (230 mg, 890 μmol) in CH_2Cl_2 (9 mL) was added 4-methoxybenzyl-2,2,2-trichloroacetimidate (280 mg, 980 μmol) and pyridinium *p*-toluenesulfonate (22 mg, 89 μmol). The reaction mixture was stirred at rt for 1 h. Sat. aq. NaHCO_3 (10 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with brine (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 85:15 to 1:1) afforded the title compound as a colourless oil (49 mg, 14%).

$R_f = 0.4$ (Pentane:Et₂O, 60:40).

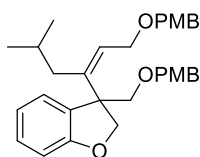
¹H NMR (CDCl₃, 500 MHz) $\delta = 7.21 - 7.09$ (4H, m, ArH $\times$ 4), 6.87 – 6.78 (4H, m, ArH $\times$ 4), 5.44 (1H, t, $J = 6.9$ Hz, C=CH), 4.59 (1H, d, $J = 8.9$ Hz, CH_AH_B), 4.43 – 4.30 (3H, m, CH_AH_B and PMB–CH₂), 3.80 – 3.74 (2H, m, CH₂OH), 3.79 (3H, s, PMB–OCH₃), 3.59 (1H, d, $J = 9.1$ Hz, CH_AH_BOPMB), 3.51 (1H, d, $J = 9.2$ Hz, CH_AH_BOPMB), 2.08 – 1.96 (2H, m, CH₂C=CH), 1.47 (1H, t, $J = 5.4$ Hz, OH), 1.39 – 1.31 (1H, m, CH), 0.82 (3H, d, $J = 6.6$ Hz, CH(CH₃)_A(CH₃)_B), 0.77 (3H, d, $J = 6.6$ Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 126 MHz) $\delta = 159.8$ (C_{Ar}), 159.3 (C=CH), 142.6 (C_{Ar}), 131.9 (C_{Ar}), 130.5 (C=CH), 129.9 (C_{Ar}), 129.5 (C_{Ar}H $\times$ 2), 128.9 (C_{Ar}H), 125.7 (C_{Ar}H), 120.4 (C_{Ar}H), 113.9 (C_{Ar}H $\times$ 2), 109.8 (C_{Ar}H), 81.2 (CH_AH_B), 75.0 (CH_AH_BOPMB), 73.2 (PMB–CH₂), 59.7 (CH₂OH), 55.4 (PMB–OCH₃), 54.4 (C_{Ar}C), 46.3 (CH₂C=CH), 27.3 (CH), 22.5 (CH(CH₃)_A(CH₃)_B), 22.2 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3369, 2954, 1724, 1693, 1612, 1513, 1482, 1459, 1246, 1034, 831, 752.

HRMS: (ESI⁺) Found $[M + \text{Na}]^+ = 405.2041$; C₂₄H₃₀O₄Na requires 405.2047.

(Z)-3-(1-((4-Methoxybenzyl)oxy)-5-methylhex-2-en-3-yl)-3-(((4-methoxybenzyl)oxy)methyl)-2,3-dihydrobenzofuran (310)¹⁵⁸



310

To a solution of diol **300** (230 mg, 890 μmol) in CH₂Cl₂ (9 mL) was added 4-methoxybenzyl-2,2,2-trichloroacetimidate (280 mg, 980 μmol) and pyridinium *p*-toluenesulfonate (22 mg, 89 μmol). The reaction mixture was stirred at rt for 1 h. Sat. aq. NaHCO₃ (10 mL) was added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄

and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (130 mg, 29%).

R_f = 0.4 (Pentane:Et₂O, 70:30).

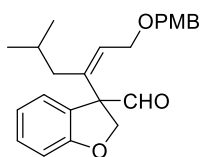
¹H NMR (CDCl₃, 400 MHz) δ = 7.32 – 7.29 (1H, m, ArH), 7.21 – 7.15 (4H, m, ArH $\times$ 4), 7.13 (2H, d, J = 8.6 Hz, ArH $\times$ 2), 6.91 (1H, d, J = 8.7 Hz, ArH), 6.88 – 6.84 (5H, m, ArH $\times$ 5), 6.80 (1H, d, J = 8.0 Hz, ArH), 5.47 (1H, t, J = 6.4 Hz, C=CH), 4.58 (1H, d, J = 8.7 Hz, CH_AH_B), 4.41 – 4.31 (3H, m, CH_AH_B and PMB–CH₂), 4.26 – 4.19 (2H, m, PMB–CH₂), 3.82 (3H, s, PMB–OCH₃), 3.81 (3H, s, PMB–OCH₃), 3.69 – 3.57 (3H, m, C=CHCH₂ and CH_AH_BOPMB), 3.50 (1H, d, J = 9.3 Hz, CH_AH_BOPMB), 2.08 – 2.00 (2H, m, CH₂C=CH), 1.42 – 1.34 (1H, m, CH), 0.84 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.79 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 159.9 (C=CH), 159.2 (C_{Ar}), 159.2 (C_{Ar}), 142.8 (C_{Ar}), 130.4 (C_{Ar}), 130.1 (C_{Ar}), 129.5 (C_{Ar}H $\times$ 2), 129.3 (C_{Ar}H $\times$ 2), 128.6 (C=CH), 128.6 (C_{Ar}), 125.9 (C_{Ar}H $\times$ 2), 120.2 (C_{Ar}H), 113.9 (C_{Ar}H), 113.8 (C_{Ar}H $\times$ 2), 113.8 (C_{Ar}H), 109.6 (C_{Ar}H), 80.8 (CH_AH_B), 74.7 (CH_AH_BOPMB), 73.1 (PMB–CH₂), 72.2 (PMB–CH₂), 67.0 (C=CHCH₂), 55.3 (PMB–OCH₃), 55.3 (PMB–OCH₃), 54.3 (C_{Ar}C), 46.3 (CH₂C=CH), 27.2 (CH), 22.5 (CH(CH₃)_A(CH₃)_B), 22.3 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm^{–1} 2954, 2864, 1612, 1512, 1244, 1173, 1085, 1034, 819, 751.

HRMS: (ESI⁺) Found [M + Na]⁺ = 525.2613; C₃₂H₃₈O₅Na requires 525.2612.

(Z)-3-(1-((4-Methoxybenzyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carbaldehyde (311)¹⁴⁷



311

To a solution of alcohol **308** (52 mg, 140 μ mol) in CH_2Cl_2 (2 mL) at 0 $^\circ\text{C}$ was added NaHCO_3 (29 mg, 340 μ mol) and Dess–Martin periodinane (97 mg, 200 μ mol). The reaction mixture was stirred at rt for 1 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 80:20) afforded the title compound as a colourless oil (26 mg, 50%).

R_f = 0.7 (Pentane: Et_2O , 60:40).

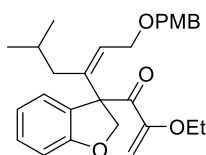
^1H NMR (CDCl_3 , 400 MHz) δ = 9.37 (1H, s, CHO), 7.18 – 7.12 (3H, m, $\text{ArH} \times 3$), 7.07 (1H, dd, J = 7.7, 1.4 Hz, ArH), 6.85 – 6.78 (3H, m, $\text{ArH} \times 3$), 6.74 (1H, d, J = 8.1 Hz, ArH), 5.59 (1H, t, J = 6.5 Hz, $\text{C}=\text{CH}$), 5.08 (1H, d, J = 9.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.28 – 4.18 (3H, m, $\text{CH}_\text{A}\text{H}_\text{B}$ and $\text{PMB}-\text{CH}_2$), 3.74 (3H, s, $\text{PMB}-\text{CH}_3$), 3.72 – 3.61 (2H, m, CH_2OPMB), 2.04 – 1.98 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.75 (1H, dd, J = 14.1, 8.4 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.29 – 1.19 (1H, m, CH), 0.73 (3H, d, J = 6.6 Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.58 (3H, d, J = 6.6 Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 192.6 (CHO), 160.8 (C_Ar), 159.5 ($\text{C}=\text{CH}$), 139.7 (C_Ar), 130.4 (C_Ar), 129.9 ($\text{C}_\text{ArH} \times 2$), 129.7 (C_Ar), 128.2 ($\text{C}=\text{CH}$), 126.6 (C_ArH), 124.2, 120.8 (C_ArH), 114.0 ($\text{C}_\text{ArH} \times 2$), 110.6 (C_ArH), 77.4 ($\text{CH}_\text{A}\text{H}_\text{B}$), 72.8 ($\text{PMB}-\text{CH}_2$), 66.6 (CH_2OPMB), 65.2 (C_ArC), 55.4 ($\text{PMB}-\text{OCH}_3$), 46.3 ($\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 26.1 (CH), 22.8 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 21.7 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2867, 1722, 1671, 1613, 1514, 1479, 1462, 1248, 1035, 754.

HRMS: (ESI⁺) Found $[M + \text{Na}]^+ = 403.1880$; $\text{C}_{24}\text{H}_{28}\text{O}_4\text{Na}$ requires 403.1880.

(Z)-2-Ethoxy-1-(3-(1-((4-methoxybenzyl)oxy)-5-methylhex-2-en-3-yl)-2,3-dihydrobenzofuran-3-yl)prop-2-en-1-one (312)^{107,147}



312

To a solution of ethyl vinyl ether (140 μL , 1.5 mmol) in THF (3 mL) $-78\text{ }^\circ\text{C}$ was added $t\text{BuLi}$ (1.81 mL, 3.08 mmol, 1.7 M in pentane). After 10 min, 1.35 mL of this solution was added dropwise to a solution of aldehyde **311** (64 mg, 170 μmol) at $0\text{ }^\circ\text{C}$ and the reaction mixture was stirred at rt for 30 min. Sat. aq. NH_4Cl (10 mL) was added and the mixture partitioned between water (10 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. To the crude product in CH_2Cl_2 (2 mL) at $0\text{ }^\circ\text{C}$ was added NaHCO_3 (36 mg, 430 μmol) and Dess–Martin periodinane (120 mg, 260 μmol). The reaction mixture was stirred at rt for 1 h and hexane (10 mL) was added. The mixture was filtered through Celite[®] using hexane as the eluent and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 98:2) afforded the title compound as a colourless oil (49 mg, 65% over 2 steps).

$R_f = 0.2$ (Pentane: Et_2O , 98:2).

^1H NMR (CDCl_3 , 400 MHz) δ = 7.49 (1H, dd, $J = 7.8, 1.4\text{ Hz}$, ArH), 7.24 – 7.20 (2H, m, ArH $\times 2$), 7.19 – 7.14 (1H, m, ArH), 6.90 – 6.86 (2H, m, ArH $\times 2$), 6.83 (1H, td, $J = 7.5$,

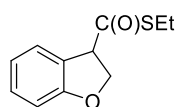
1.1 Hz, *ArH*), 6.79 (1H, d, $J = 8.1$ Hz, *ArH*), 5.43 – 5.38 (2H, m, C=CH and $\text{CH}_\text{A}\text{H}_\text{B}$), 5.29 (1H, d, $J = 2.4$ Hz, C=CH $\text{A}\text{H}_\text{B}$), 4.44 (1H, d, $J = 2.3$ Hz, C=CH $\text{A}\text{H}_\text{B}$), 4.33 (2H, s, PMB-CH₂), 4.24 (1H, d, $J = 9.0$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.93 – 3.88 (1H, m, C=CHCH $\text{A}\text{H}_\text{B}$ OPMB), (4H, m, PMB-CH₃ and C=CHCH $\text{A}\text{H}_\text{B}$ OPMB), 3.77 – 3.72 (2H, m, OCH₂CH₃), 2.42 (1H, dd, $J = 14.8, 4.1$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.87 (1H, dd, $J = 14.2, 8.9$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.45 (3H, t, $J = 7.0$ Hz, CH₂CH₃), 1.28 – 1.25 (1H, m, CH), 0.80 (3H, d, $J = 6.5$ Hz, CH(CH₃)_A(CH₃)_B), 0.64 (3H, d, $J = 6.6$ Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 192.4 (C(O)), 160.9 (C=CH), 159.4 (C_{Ar}), 156.7 (C(O)C=CH₂), 141.7 (C_{Ar}), 130.4 (C_{Ar}), 129.8 (C_{Ar}H), 129.6 (C_{Ar}H $\times$ 2), 128.2 (C_{Ar}H), 125.6 (C=CH), 125.4 (C_{Ar}), 120.3 (C_{Ar}H), 113.9 (C_{Ar}H $\times$ 2), 110.5 (C_{Ar}H), 94.2 (C=CH $\text{A}\text{H}_\text{B}$), 78.7 (CH $\text{A}\text{H}_\text{B}$), 72.3 (PMB-CH₂), 66.7 (OCH₂CH₃), 64.6 (C=CHCH $\text{A}\text{H}_\text{B}$ OPMB), 64.1 (C_{Ar}C), 55.4 (PMB-CH₃), 46.7 (CH $\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 26.0 (CH), 23.1 (CH(CH₃)_A(CH₃)_B), 21.7 (CH(CH₃)_A(CH₃)_B), 14.4 (OCH₂CH₃).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 1723, 1607, 1513, 1477, 1295, 1247, 1059, 1030, 994, 753.

HRMS: (ESI⁺) Found $[\text{M} + \text{Na}]^+ = 473.2298$; C₂₈H₃₄O₅Na requires 473.2299.

S-Ethyl 2,3-dihydrobenzofuran-3-carbothioate (313)¹⁰¹



313

To a solution of acid **265** (1.0 g, 6.1 mmol) in CH₂Cl₂ (30 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.8 g, 9.1 mmol), 4-(dimethylamino)pyridine (74 mg, 610 μmol) and thioethanol (1.8 mL, 24 mmol). The reaction mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (30 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL)

and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97:3) afforded the title compound as a colourless oil (1.2 g, 92%).

$R_f = 0.7$ (Pentane:Et₂O, 70:30).

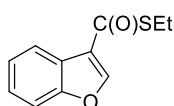
¹H NMR (CDCl₃, 400 MHz) δ = 7.40 (1H, d, J = 7.6 Hz, ArH), 7.26 – 7.20 (1H, m, ArH), 6.93 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.87 (1H, d, J = 7.9 Hz, ArH), 4.92 (1H, dd, J = 9.4, 5.6 Hz, CH_AH_B), 4.68 (1H, t, J = 9.4 Hz, CH_AH_B), 4.47 (1H, dd, J = 9.2, 5.7 Hz, CH), 2.95 (2H, q, J = 7.4 Hz, CH₂CH₃), 1.29 (3H, t, J = 7.4 Hz, CH₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 198.5 (C(O)), 160.4 (C_{Ar}), 129.9 (C_{Ar}H), 125.7 (C_{Ar}H), 124.4 (C_{Ar}), 120.8 (C_{Ar}H), 110.3 (C_{Ar}H), 73.2 (CH_AH_B), 55.9 (CH), 23.9 (CH₂CH₃), 14.7 (CH₂CH₃).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2981, 1678, 1480, 1460, 1232, 971, 748.

HRMS: (ESI⁺) Found $[M + Na]^+ = 209.0633$; C₁₁H₁₃O₂SNa requires 209.0631.

S-Ethyl benzofuran-3-carbothioate (**314**)¹⁰¹



314

To a solution of acid **265** (1.0 g, 6.1 mmol) in CH₂Cl₂ (30 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.8 g, 9.1 mmol), 4-(dimethylamino)pyridine (74 mg, 610 μ mol) and thioethanol (1.8 mL, 24 mmol). The reaction mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (30 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄

and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97:3) afforded the title compound as a colourless oil (37 mg, 3%).

R_f = 0.8 (Pentane:Et₂O, 70:30).

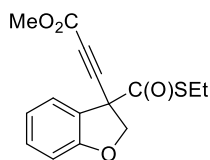
¹H NMR (CDCl₃, 400 MHz) δ = 8.31 (1H, s, ArH), 8.18 – 8.11 (1H, m, ArH), 7.56 – 7.49 (1H, m, ArH), 7.41 – 7.33 (2H, m, ArH $\times$ 2), 3.12 (2H q, J = 7.4 Hz, CH₂CH₃), 1.38 (3H, t, J = 7.4 Hz, CH₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 185.4 (C(O)), 155.7 (C_{Ar}), 149.6 (C_{Ar}H), 125.7 (C_{Ar}H), 124.6 (C_{Ar}H), 123.8 (C_{Ar}), 122.4 (C_{Ar}), 122.4 (C_{Ar}H), 111.8 (C_{Ar}H), 23.1 (CH₂CH₃), 15.1 (CH₂CH₃).

IR (film) ν_{max} /cm⁻¹ 2981, 1678, 1480, 1460, 1232, 971, 748.

HRMS: (ESI⁺) Found [M + Na]⁺ = 207.0477; C₁₁H₁₁O₂SNa requires 207.0474.

Methyl 3-(3-((ethylthio)carbonyl)-2,3-dihydrobenzofuran-3-yl)propiolate (**315**)



315

To a stirred solution of thioester **313** (208 mg, 1.00 mmol) in THF (7 mL) at -78 °C was added LiHMDS (1.20 mL, 1.20 mmol, 1 M in THF). After 10 min chloroacetylene **145** (178 mg, 1.50 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. Sat. aq. NH₄Cl (5 mL) was added and the mixture extracted with Et₂O (3 $\times$ 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 93:7) afforded the title compound as a colourless oil (288 mg, 99%).

$R_f = 0.25$ (Pentane:Et₂O, 90:10).

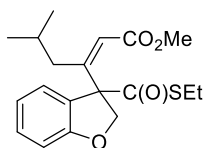
¹H NMR (CDCl₃, 400 MHz) δ = 7.47 (1H, dd, J = 7.5, 1.4 Hz, ArH), 7.30 – 7.26 (1H, m, ArH), 6.97 (1H, td, J = 7.6, 1.0 Hz, ArH), 6.87 (1H, d, J = 8.1 Hz, ArH), 5.13 (1H, d, J = 9.2 Hz, CH_AH_B), 4.68 (1H, d, J = 9.2 Hz, CH_AH_B), 3.79 (3H, s, CO₂CH₃), 2.92 (2H, q, J = 7.4 Hz, CH₂CH₃), 1.26 (3H, t, J = 7.4 Hz, CH₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 195.5 (C(O)SCH₂CH₃), 160.0 (C_{Ar}), 153.5 (CO₂CH₃), 131.2 (C_{Ar}H), 125.7 (C_{Ar}), 125.2 (C_{Ar}H), 121.7 (C_{Ar}H), 111.0 (C_{Ar}H), 84.2 (C≡CCO₂CH₃), 79.5 (CH_AH_B), 78.0 (C≡CCO₂CH₃), 58.2 (C_{Ar}C), 53.1 (CO₂CH₃), 24.8 (CH₂CH₃), 14.3 (CH₂CH₃).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2954, 2239, 1716, 1681, 1478, 1273, 1235, 942, 749.

HRMS: (ESI⁺) Found $[M + H]^+ = 291.0687$; C₁₅H₁₅O₄S requires 291.0686.

Methyl (Z)-3-(3-((ethylthio)carbonyl)-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-enoate (316)⁵⁷



316

To a solution of CuI (476 mg, 2.50 mmol) in THF (11 mL) at $-78\text{ }^{\circ}\text{C}$ was added ^{*i*}BuLi (2.94 mL, 4.99 mmol, 1.7 M in pentane). The mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **315** (260 mg, 1.25 mmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. MeOH (0.5 mL) was added followed by water (30 mL), and the mixture was extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column

chromatography (SiO₂, Pentane:Et₂O, 96:4) afforded the title compound as a colourless oil and a single diastereomer (315 mg, 72%).

R_f = 0.5 (Pentane:Et₂O, 75:25).

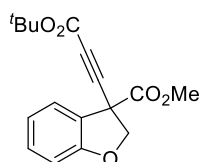
¹H NMR (CDCl₃, 500 MHz) δ = 7.38 (1H, dd, *J* = 7.6, 1.4 Hz, Ar*H*), 7.24 – 7.18 (1H, m, Ar*H*), 6.87 (1H, td, *J* = 7.5, 1.0 Hz, Ar*H*), 6.82 (1H, d, *J* = 8.1 Hz, Ar*H*), 5.93 (1H, s, C=CH), 5.67 (1H, d, *J* = 10.1 Hz, CH_AH_B), 4.43 (1H, d, *J* = 10.1 Hz, CH_AH_B), 3.69 (3H, s, CO₂CH₃), 2.91 – 2.80 (2H, m, CH₂CH₃), 2.28 (1H, ddd, *J* = 14.0, 4.6, 1.2 Hz, CH_AH_BC=CH), 1.87 (1H, ddd, *J* = 13.9, 9.0, 1.0 Hz, CH_AH_BC=CH), 1.28 – 1.22 (1H, m, CH), 1.19 (3H, t, *J* = 7.4 Hz, CH₂CH₃), 0.77 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.61 (3H, d, *J* = 6.7 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 197.2 (C(O)SCH₂CH₃), 166.1 (CO₂CH₃), 160.9 (C_{Ar}), 160.6 (C=CH), 130.4 (C_{Ar}H), 126.4 (C_{Ar}H), 126.3 (C_{Ar}), 121.0 (C=CH), 120.2 (C_{Ar}H), 110.5 (C_{Ar}H), 82.2 (CH_AH_B), 68.5 (C_{Ar}C), 51.6 (CO₂CH₃), 47.5 (CH_AH_BC=CH), 26.2 (CH), 24.4 (CH₂CH₃), 23.0 (CH(CH₃)_A(CH₃)_B), 21.4 (CH(CH₃)_A(CH₃)_B), 14.7 (CH₂CH₃).

IR (film) ν_{max} /cm⁻¹ 2956, 1717, 1685, 1479, 1461, 1236, 1208, 1155, 752.

HRMS: (ESI⁺) Found [M + Na]⁺ = 371.1288; C₁₉H₂₄O₄SNa requires 371.1288.

Methyl 3-(3-(tert-butoxy)-3-oxoprop-1-yn-1-yl)-2,3-dihydrobenzofuran-3-carboxylate
(318)



318

To a stirred solution of ester **87** (248 mg, 1.39 mmol) in THF (11 mL) at –78 °C was added LiHMDS (1.67 mL, 1.67 mmol, 1 M in THF). After 10 min chloroacetylene **295** (335 mg,

2.09 mmol) in THF (1 mL) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Sat. aq. NaHCO_3 (2 mL) was added and the mixture extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (420 mg, 100%).

$R_f = 0.3$ (Pentane: EtOAc , 90:10).

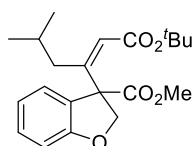
$^1\text{H NMR}$ (CDCl_3 , 500 MHz) $\delta = 7.48$ (1H, dd, $J = 7.6, 1.2\text{ Hz}$, ArH), $7.27 - 7.23$ (1H, m, ArH), 6.96 (1H, td, $J = 7.6, 1.0\text{ Hz}$, ArH), 6.85 (1H, d, $J = 8.1\text{ Hz}$, ArH), 5.21 (1H, d, $J = 9.2\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.70 (1H, d, $J = 9.2\text{ Hz}$, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.82 (3H, s, CO_2CH_3), 1.48 (9H, s, $\text{CO}_2\text{C}(\text{CH}_3)_3$).

$^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) $\delta = 168.7$ (CO_2CH_3), 159.4 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 152.3 (C_Ar), 130.9 ($\text{C}_\text{Ar}\text{H}$), 125.5 (C_Ar), 125.4 ($\text{C}_\text{Ar}\text{H}$), 121.7 ($\text{C}_\text{Ar}\text{H}$), 110.8 ($\text{C}_\text{Ar}\text{H}$), 84.1 ($\text{C}\equiv\text{CCO}_2\text{C}(\text{CH}_3)_3$), 81.5 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 79.2 ($\text{CH}_\text{A}\text{H}_\text{B}$), 77.4 ($\text{C}\equiv\text{CCO}_2\text{C}(\text{CH}_3)_3$), 54.1 (CO_2CH_3), 51.0 ($\text{C}_\text{Ar}\text{C}$), 28.1 ($\text{CO}_2\text{C}(\text{CH}_3)_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2981, 2240, 1747, 1707, 1480, 1291, 1251, 1153, 837, 752.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 325.1047$; $\text{C}_{17}\text{H}_{18}\text{O}_5\text{Na}$ requires 325.1057.

Methyl (Z)-3-(1-(tert-butoxy)-5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (319)⁵⁷



319

To a solution of CuI (510 mg, 2.68 mmol) in THF (13 mL) at $-78\text{ }^{\circ}\text{C}$ was added $i\text{BuLi}$ (3.15 mL, 5.36 mmol, 1.7 M in pentane). The mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h

before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **318** (405 mg, 1.34 mmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. MeOH (0.5 mL) was added followed by water (30 mL), and the mixture was extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 92:8) afforded the title compound as a colourless oil and a single diastereomer (403 mg, 83%).

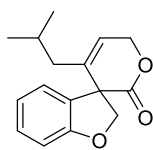
R_f = 0.6 (Pentane:Et₂O, 70:30).

¹H NMR (CDCl₃, 400 MHz) δ = 7.23 – 7.19 (1H, m, ArH), 7.19 – 7.15 (1H, m, ArH), 6.88 – 6.81 (2H, m, ArH $\times$ 2), 5.76 (1H, t, J = 1.1 Hz, C=CH), 5.63 (1H, d, J = 9.9 Hz, CH_AH_B), 4.41 (1H, d, J = 9.9 Hz, CH_AH_B), 3.67 (3H, s, CO₂CH₃), 2.10 (1H, ddd, J = 14.4, 5.1, 1.2 Hz, CH_AH_BC=CH), 1.79 (1H, ddd, J = 14.2, 8.6, 1.1 Hz, CH_AH_BC=CH), 1.47 (9H, s, CO₂C(CH₃)₃), 1.35 – 1.26 (1H, m, CH), 0.77 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.60 (3H, d, J = 6.5 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 172.0 (CO₂CH₃), 166.0 (C_{Ar}), 161.0 (C=CH), 158.7 (CO₂C(CH₃)₃), 130.2 (C_{Ar}H), 126.7 (C_{Ar}), 126.0 (C_{Ar}H), 120.6 (C=CH), 120.4 (C_{Ar}H), 110.5 (C_{Ar}H), 82.4 (CH_AH_B), 80.7 (CO₂C(CH₃)₃), 61.4 (C_{Ar}C), 52.8 (CO₂CH₃), 46.9 (CH_AH_BC=CH), 28.2 (CO₂C(CH₃)₃), 26.0 (CH), 22.9 (CH(CH₃)_A(CH₃)_B), 21.7 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 2932, 1737, 1704, 1480, 1368, 1238, 1144, 752.

HRMS: (ESI⁺) Found $[\text{M} + \text{H}]^+ = 361.2007$; C₂₁H₂₉O₅ requires 361.2010.

4'-Isobutyl-2*H*,2'*H*,6'*H*-spiro[benzofuran-3,3'-pyran]-2'-one (321)**321**

To a solution of alkene **319** (54 mg, 150 μ mol) in toluene (2 mL) at -78 $^{\circ}$ C was added dropwise DIBAL-H (180 μ L, 180 μ mol, 1 M in toluene). The reaction mixture was stirred at -78 $^{\circ}$ C for 1.5 h then sat. aq. NH_4Cl (5 mL) was added followed by Et_2O (30 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 60:40) afforded the title compound as a colourless oil (15 mg, 38%).

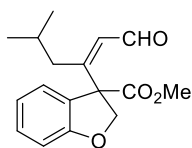
$R_f = 0.2$ (Pentane: Et_2O , 60:40).

^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.21$ (1H, td, $J = 7.7, 1.4$ Hz, ArH), 7.08 – 7.01 (1H, m, ArH), 6.90 – 6.84 (2H, m, $\text{ArH} \times 2$), 5.77 – 5.70 (1H, m, $\text{C}=\text{CH}$), 5.20 – 4.92 (2H, m, CO_2CH_2), 5.06 (1H, d, $J = 9.2$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.61 (1H, d, $J = 9.2$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.90 – 1.70 (2H, m, $\text{CH}_2\text{C}=\text{CH}$), 1.66 – 1.59 (1H, m, CH), 0.82 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.75 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 171.6$ (CO_2CH_2), 160.1 (C_Ar), 136.6 ($\text{C}=\text{CH}$), 130.2 (C_ArH), 129.0 (C_Ar), 123.9 (C_ArH), 121.2 (C_ArH), 117.5 ($\text{C}=\text{CH}$), 110.5 (C_ArH), 78.3 ($\text{CH}_\text{A}\text{H}_\text{B}$), 68.7 (CO_2CH_2), 56.0 (C_ArC), 40.5 ($\text{CH}_2\text{C}=\text{CH}$), 26.0 (CH), 22.5 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 22.4 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 1729, 1596, 1481, 1461, 1210, 929, 750.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 259.1330$; $\text{C}_{16}\text{H}_{19}\text{O}_3$ requires 253.1329.

Methyl (Z)-3-(5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate**(322)****322**

To a solution of alkene **319** (54 mg, 150 μ mol) in toluene (2 mL) at -78 $^{\circ}$ C was added dropwise DIBAL-H (180 μ L, 180 μ mol, 1 M in toluene). The reaction mixture was stirred at -78 $^{\circ}$ C for 1.5 h then sat. aq. NH_4Cl (5 mL) was added followed by Et_2O (30 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 80:20) afforded the title compound as a colourless oil (2 mg, 3%).

$R_f = 0.3$ (Pentane: Et_2O , 70:30).

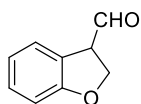
^1H NMR (CDCl_3 , 400 MHz) $\delta = 9.58$ (1H, d, $J = 5.5$ Hz, CHO), 7.33 (1H, dd, $J = 7.7$, 1.4 Hz, ArH), 7.27 (1H, m, $J = 9.2$ Hz, ArH), 6.09 (1H, d, $J = 5.5$ Hz, ArH), 6.97 – 6.92 (1H, m, ArH), 6.88 (1H, d, $J = 8.1$ Hz,), 6.09 (1H, d, $J = 5.5$ Hz, C=CH), 5.60 (1H, d, $J = 9.6$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.44 (1H, d, $J = 9.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.76 (3H, s, CO_2CH_3), 2.25 (1H, dd, $J = 14.6$, 5.7 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.99 (1H, dd, $J = 14.6$, 8.0 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 0.97 – 0.88 (1H, m, CH), 0.83 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.72 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 190.1$ (CHO), 171.8 (CO_2CH_3), 162.9 (C=CH), 160.6 (C_Ar), 130.7 ($\text{C}_\text{Ar}\text{H}$), 128.1 (C=CH), 126.4 ($\text{C}_\text{Ar}\text{H}$), 125.8 (C_Ar), 121.0 ($\text{C}_\text{Ar}\text{H}$), 110.8 ($\text{C}_\text{Ar}\text{H}$), 81.5 ($\text{CH}_\text{A}\text{H}_\text{B}$), 62.0 ($\text{C}_\text{Ar}\text{C}$), 53.4 (CO_2CH_3), 47.0 ($\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 26.2 (CH), 22.7 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 21.9 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2957, 1735, 1672, 1592, 1481, 1461, 1222, 975, 836, 753.

HRMS: (ESI⁺) Found $[M + H]^+ = 259.1330$; C₁₆H₁₉O₃ requires 259.1329.

2,3-Dihydrobenzofuran-3-carbaldehyde (323)



323

To a solution of ester **87** (535 mg, 3.00 mmol) in toluene (15 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise DIBAL-H (3.30 mL, 3.30 mmol, 1 M in toluene) over 10 min. The reaction mixture was stirred for 30 min and MeOH (1 mL) was added followed by water (50 mL) and Et₂O (50 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 60:40) afforded the title compound as a colourless oil (331 mg, 74%).

$R_f = 0.2$ (Pentane:Et₂O, 60:40).

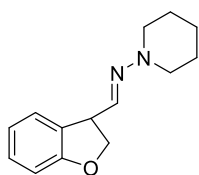
¹H NMR (CDCl₃, 500 MHz) δ = 9.73 (1H, d, $J = 2.2$ Hz, CHO), 7.33 (1H, d, $J = 7.5$ Hz, ArH), 7.26 (1H, t, $J = 8.1$ Hz, ArH), 6.96 (1H, td, $J = 7.4, 1.0$ Hz, ArH), 6.88 (1H, d, $J = 7.8$ Hz, ArH), 5.01 (1H, dd, $J = 9.5, 5.5$ Hz, CH_AH_B), 4.68 (1H, t, $J = 9.5$ Hz, CH_AH_B), 4.27 – 4.21 (1H, m, CH).

¹³C NMR (CDCl₃, 126 MHz) δ = 197.0 (CHO), 160.4 (C_{Ar}), 130.1 (C_{Ar}H), 125.3 (C_{Ar}H), 122.2 (C_{Ar}), 121.2 (C_{Ar}H), 110.4 (C_{Ar}H), 69.9 (CH_AH_B), 54.8 (CH).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2897, 2825, 1722, 1595, 1481, 1461, 1231, 841, 751.

HRMS: (ESI⁻) Found $[M - H]^- = 147.0448$; C₉H₇O₂ requires 147.0452.

(E)-1-(2,3-Dihydrobenzofuran-3-yl)-N-(piperidin-1-yl)methanimine (327)¹¹³



327

To a solution of aldehyde **323** (200 mg, 1.35 mmol) in CH₂Cl₂ (6 mL) was added MgSO₄ (244 mg, 2.00 mmol) and 1-aminopiperidine **326** (437 μ L, 4.05 mmol). The reaction mixture was stirred at rt overnight, filtered through Celite[®] and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 80:20) afforded the title compound as a colourless oil (209 mg, 67%).

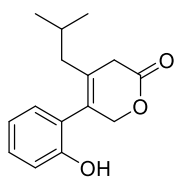
R_f = 0.4 (Pentane:Et₂O, 60:40).

¹H NMR (CDCl₃, 400 MHz) δ = 7.20 (1H, d, *J* = 7.3 Hz, Ar*H*), 7.18 – 7.13 (1H, m, Ar*H*), 6.88 (1H, td, *J* = 7.5, 1.1 Hz, Ar*H*), 6.84 (1H, d, *J* = 6.6 Hz, CHN), 6.81 (1H, d, *J* = 8.0 Hz, Ar*H*), 4.75 (1H, t, *J* = 9.3 Hz, CH_AH_B), 4.46 (1H, dd, *J* = 9.0, 7.5 Hz, CH_AH_B), 4.38 – 4.30 (1H, m, CH), 2.99 – 2.94 (4H, m, CH₂N $\times$ 2), 1.74 – 1.66 (4H, m, CH₂CH₂N $\times$ 2), 1.53 – 1.47 (2H, m, CH₂CH₂CH₂N).

¹³C NMR (CDCl₃, 110 MHz) δ = 160.2 (C_{Ar}), 137.4 (CHN), 129.0 (C_{Ar}H), 128.2 (C_{Ar}), 125.3 (C_{Ar}H), 120.9 (C_{Ar}H), 109.9 (C_{Ar}H), 74.9 (CH_AH_B), 52.6 (CH₂N $\times$ 2), 46.5 (CH), 25.3 (CH₂CH₂N $\times$ 2), 24.2 (CH₂CH₂CH₂N $\times$ 2).

IR (film) ν_{max} /cm⁻¹ 2981, 2936, 1597, 1481, 1459, 1228, 1082, 969, 751.

HRMS: (ESI⁺) Found [M + H]⁺ = 231.1494; C₁₄H₁₉ON₂ requires 231.1492.

5-(2-Hydroxyphenyl)-4-isobutyl-3,6-dihydro-2H-pyran-2-one (330)**330**

To a solution of ester **319** (22 mg, 60 μ mol) in THF (600 μ L), MeOH (200 μ L) and water (200 μ L) was added LiOH $\cdot$ H₂O (8.0 mg, 180 μ mol). The reaction mixture was stirred at 80 $^{\circ}$ C for 16 h then sat. aq. NH₄Cl (30 mL) was added followed by EtOAc (30 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, CHCl₃:MeOH, 95:5) afforded the title compound as a colourless oil (3.0 mg, 20%).

R_f = 0.3 (Pentane:Et₂O, 70:30).

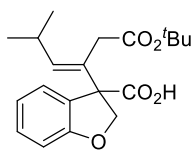
¹H NMR (CDCl₃, 400 MHz) δ = 7.55 (1H, d, J = 7.9 Hz, ArH), 7.20 – 7.16 (1H, m, ArH), 6.94 – 6.89 (1H, m, ArH), 6.89 – 6.83 (1H, m, ArH), 5.16 (2H, s, CH₂O), 3.09 (2H, s, CH₂CO₂), 2.46 (2H, d, J = 7.5, 1.5 Hz, CH₂C=C), 2.02 – 1.95 (1H, m, CH), 1.02 (6H, d, J = 6.6 Hz, CH(CH₃)₂).

¹³C NMR (CDCl₃, 110 MHz) δ = 176.2 (CO₂CH₂), 164.8 (C_{Ar}), 135.2 (CH₂C=C), 129.6 (C_{Ar}H), 125.3 (C_{Ar}), 124.6 (C_{Ar}H), 123.2 (CH₂C=C), 120.6 (C_{Ar}H), 110.6 (C_{Ar}H), 74.5 (CH₂O), 41.9 (CH₂C=C), 41.0 (CO₂CH₂), 27.5 (CH), 22.7 (CH(CH₃)₂).

IR (film) ν_{max} /cm⁻¹ 3081, 2958, 1705, 1478, 1147, 750.

HRMS: (ESI⁺) Found [M + H]⁺ = 269.1145; C₁₅H₁₈O₃Na requires 269.1148.

(E)-3-(1-(*tert*-Butoxy)-5-methyl-1-oxohex-3-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylic acid (331)



331

To a solution of ester **319** (22 mg, 60 μ mol) in THF (600 μ L), MeOH (200 μ L) and water (200 μ L) was added LiOH $\cdot$ H₂O (8.0 mg, 180 μ mol). The reaction mixture was stirred at 80 $^{\circ}$ C for 16 h then sat. aq. NH₄Cl (30 mL) was added followed by EtOAc (30 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, CHCl₃:MeOH, 95:5) afforded the title compound as a colourless oil (5.2 mg, 25%).

R_f = 0.3 (Pentane:Et₂O, 70:30).

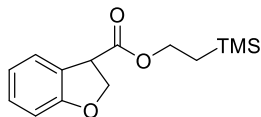
¹H NMR (CDCl₃, 400 MHz) δ = 7.38 (1H, d, J = 7.6 Hz, ArH), 7.26 – 7.22 (1H, m, ArH), 6.94 – 6.89 (1H, m, ArH), 6.89 – 6.83 (1H, m, ArH), 5.39 (1H, d, J = 9.8 Hz, C=CH), 5.23 (1H, d, J = 9.2 Hz, CH_AH_B), 4.50 (1H, d, J = 9.1 Hz, CH_AH_B), 3.18 (1H, d, J = 16.8 Hz, CH_AH_BC=CH), 2.94 (1H, d, J = 16.8 Hz, CH_AH_BC=CH), 2.55 – 2.47 (1H, m, CH), 1.43 (9H, s, C(CH₃)₃), 0.98 (3H, d, J = 6.5 Hz, CH(CH₃)_A(CH₃)_B), 0.94 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 176.1 (CO₂H), 171.8 (CO₂C(CH₃)₃), 160.5 (C_{Ar}), 141.2 (C=CH), 130.2 (C_{Ar}H), 129.7 (C=CH), 126.9 (C_{Ar}H), 126.0 (C_{Ar}), 120.8 (C_{Ar}H), 110.5 (C_{Ar}H), 81.9 (CO₂C(CH₃)₃), 80.2 (CH_AH_B), 63.6 (C_{Ar}C), 36.1 (CH_AH_BC=CH), 28.2 (CH), 28.0 (CO₂C(CH₃)₃), 22.5 (CH(CH₃)_A(CH₃)_B), 22.3 (CH(CH₃)_A(CH₃)_B).

IR (film) $\nu_{\max}$ /cm⁻¹ 2919, 1708, 1463, 1243, 836, 751.

HRMS: (ESI⁺) Found [M + H]⁺ = 369.1671; C₂₀H₂₆O₅Na requires 369.1673.

2-(Trimethylsilyl)ethyl 2,3-dihydrobenzofuran-3-carboxylate (337)¹⁰¹



337

To a solution of acid **265** (1.0 g, 6.1 mmol) in CH₂Cl₂ (30 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.8 g, 9.1 mmol), 4-(dimethylamino)pyridine (74 mg, 610 μmol) and 2-(trimethylsilyl)ethanol **336** (1.8 mL, 12 mmol). The reaction mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (30 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 97:3) afforded the title compound as a colourless oil (1.4 g, 88%).

*R*_f = 0.4 (Pentane:Et₂O, 90:10).

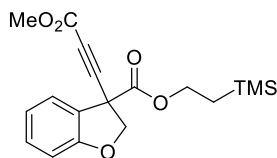
¹H NMR (CDCl₃, 400 MHz) δ = 7.39 (1H, d, *J* = 7.5 Hz, *ArH*), 7.21 – 7.15 (1H, m, *ArH*), 6.89 (1H, td, *J* = 7.4, 1.0 Hz, *ArH*), 6.82 (1H, d, *J* = 7.8 Hz, *ArH*), 4.93 (1H, dd, *J* = 9.2, 6.7 Hz, *CH_AH_B*), 4.66 (1H, t, *J* = 9.8 Hz, *CH_AH_B*), 4.31 (1H, dd, *J* = 9.5, 6.2 Hz, CO₂CH₂), 4.25 (2H, td, *J* = 8.8, 0.9 Hz, *CH*), 1.08 – 0.99 (2H, m, CO₂CH₂CH₃), 0.05 (9H, s, TMS–(CH₃)₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 171.4 (CO₂CH₂), 159.9 (*C_{Ar}*), 129.5 (*C_{Ar}H*), 125.4 (*C_{Ar}H*), 124.5 (*C_{Ar}*), 120.7 (*C_{Ar}H*), 110.0 (*C_{Ar}H*), 72.6 (*CH_AH_B*), 64.0 (*CH*), 47.4 (CO₂CH₂), 17.6 (CO₂CH₂CH₃), –1.4 (TMS–(CH₃)₃).

IR (film) *v*_{max}/cm^{–1} 2954, 1732, 1597, 1482, 1235, 1172, 857, 749.

HRMS: (ESI⁺) Found [M + Na]⁺ = 207.1074; C₁₄H₂₀O₃SiNa requires 207.1074.

2-(Trimethylsilyl)ethyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (338)



338

To a stirred solution of ester **337** (529 mg, 2.00 mmol) in THF (15 mL) at -78°C was added LiHMDS (2.40 mL, 2.40 mmol, 1 M in THF). After 10 min chloroacetylene **145** (356 mg, 3.00 mmol) in THF (0.5 mL) was added dropwise and the reaction mixture was stirred at -78°C for 1 h. Sat. aq. NH₄Cl (5 mL) was added and the mixture extracted with Et₂O (3 $\times$ 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil (667 mg, 96%).

R_f = 0.6 (Pentane:Et₂O, 75:25).

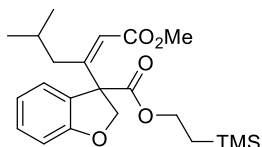
¹H NMR (CDCl₃, 400 MHz) δ = 7.47 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.28 – 7.23 (1H, m, ArH), 6.96 (1H, td, J = 7.6, 1.0 Hz, ArH), 6.85 (1H, d, J = 8.1 Hz, ArH), 5.21 (1H, d, J = 9.2 Hz, CH_AH_B), 4.70 (1H, d, J = 9.1 Hz, CH_AH_B), 4.33 – 4.26 (2H, m, CO₂CH₂), 3.77 (3H, s, CO₂CH₃), 1.12 – 0.97 (2H, m, CO₂CH₂CH₂), 0.04 (9H, s, TMS–(CH₃)₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 167.9 (CO₂CH₃), 159.5 (CO₂CH₂), 153.7 (C_{Ar}), 130.9 (C_{Ar}H), 125.4 (C_{Ar}), 125.2 (C_{Ar}H), 121.7 (C_{Ar}H), 110.8 (C_{Ar}H), 84.8 (C $\equiv$ CCO₂CH₃), 79.1 (CH_AH_B), 75.8 (C $\equiv$ CCO₂CH₃), 65.9 (CO₂CH₂), 53.0 (CO₂CH₃), 51.2 (C_{Ar}C), 17.4 (CO₂CH₂CH₂), -1.4 (TMS–(CH₃)₃).

IR (film) ν_{max} /cm^{−1} 2954, 2243, 1739, 1718, 1480, 1278, 1235, 1174, 858, 836, 750.

HRMS: (ESI⁺) Found [M + Na]⁺ = 369.1130; C₁₈H₂₂O₅NaSi requires 369.1129.

2-(Trimethylsilyl)ethyl (Z)-3-(1-methoxy-5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (339)⁵⁷



339

To a solution of CuI (705 mg, 3.70 mmol) in THF (14 mL) at $-78\text{ }^{\circ}\text{C}$ was added *i*BuLi (4.35 mL, 7.39 mmol, 1.7 M in pentane). The mixture was stirred vigorously at $0\text{ }^{\circ}\text{C}$ for 1 h before being cooled to $-78\text{ }^{\circ}\text{C}$. A solution of alkyne **145** (640 mg, 1.85 mmol) in THF (0.75 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. MeOH (0.5 mL) was added followed by water (30 mL), and the mixture was extracted with Et₂O (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a colourless oil and a single diastereomer (664 mg, 89%).

*R*_f = 0.2 (Pentane:Et₂O, 95:5).

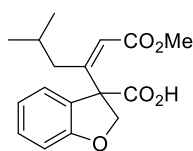
¹H NMR (CDCl₃, 400 MHz) δ = 7.20 (2H, dt, *J* = 7.5, 1.2 Hz, Ar*H*), 6.86 (2H, td, *J* = 7.4, 1.0 Hz, Ar*H* $\times$ 2), 6.82 (1H, dd, *J* = 8.4, 1.1 Hz, Ar*H*), 5.82 (1H, t, *J* = 1.1 Hz, C=CH), 5.62 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.41 (1H, d, *J* = 9.8 Hz, CH_AH_B), 4.24 – 4.11 (2H, m, CO₂CH₂), 3.68 (3H, s, CO₂CH₃), 2.16 (1H, ddd, *J* = 14.2, 5.0, 1.2 Hz, CH_AH_BC=CH), 1.82 (1H, ddd, *J* = 14.0, 8.5, 0.8 Hz, CH_AH_BC=CH), 1.34 – 1.23 (1H, m, CH), 1.02 – 0.86 (2H, m, CO₂CH₂CH₂), 0.76 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), 0.61 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B), -0.01 (9H, s, TMS-(CH₃)₃).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 171.4 (CO_2CH_3), 166.6 (CO_2CH_2), 161.7 ($\text{C}=\text{CH}$), 161.0 (C_{Ar}), 130.2 (C_{ArH}), 126.6 (C_{ArH}), 126.0 (C_{ArH}), 120.3 (C_{ArH}), 118.3 ($\text{C}=\text{CH}$), 110.5 (C_{ArH}), 82.5 ($\text{CH}_\text{A}\text{H}_\text{B}$), 64.2 (CO_2CH_2), 61.7 (C_{ArC}), 51.5 (CO_2CH_3), 47.3 ($\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 26.0 (CH), 22.9 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 21.6 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 17.3 ($\text{CO}_2\text{CH}_2\text{CH}_2$), -1.5 ($\text{TMS}-(\text{CH}_3)_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 1718, 1629, 1594, 1481, 1208, 859, 836, 751.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 427.1911$; $\text{C}_{22}\text{H}_{32}\text{O}_5\text{NaSi}$ requires 427.1911.

(Z)-3-(1-Methoxy-5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylic acid (340)¹¹⁵



340

A solution of ester **339** (512 mg, 1.27 mmol) in trifluoroacetic acid (2 mL) and CH_2Cl_2 (6 mL) was stirred for 16 h. CH_2Cl_2 (30 mL) was added followed by water (30 mL) and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , CHCl_3 :MeOH, 95:5) afforded the title compound as a colourless oil (347 mg, 90%).

$R_f = 0.2$ (CHCl_3 :MeOH, 95:5).

^1H NMR (CDCl_3 , 400 MHz) δ = 9.02 (1 H, s, CO_2H), 7.29 – 7.19 (2H, m, $\text{ArH} \times 2$), 6.90 – 6.80 (2H, m, $\text{ArH} \times 2$), 5.82 (1H, s, $\text{C}=\text{CH}$), 5.56 (1H, d, $J = 9.9$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.39 (1H, d, $J = 9.9$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.62 (3H, s, CO_2CH_3), 2.11 (1H, dd, $J = 14.2, 5.0$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$),

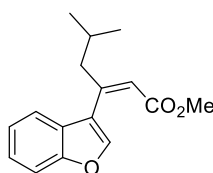
1.81 (1H, dd, $J = 14.2, 8.5$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.30 – 1.22 (1H, m, CH), 0.75 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.61 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 176.7$ (CO_2H), 166.8 (CO_2CH_3), 161.0 ($\text{C}=\text{CH}$), 160.9 (C_Ar), 130.6 (C_ArH), 126.2 (C_ArH), 125.9 (C_Ar), 120.5 (C_ArH), 118.6 ($\text{C}=\text{CH}$), 110.6 (C_ArH), 82.3 ($\text{CH}_\text{A}\text{H}_\text{B}$), 61.5 (C_ArC), 51.6 (CO_2CH_3), 47.0 ($\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 26.0 (CH), 22.8 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 21.6 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2957, 1713, 1481, 1238, 1210, 1156, 961, 753.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 305.1384$; $\text{C}_{17}\text{H}_{21}\text{O}_5\text{Si}$ requires 305.1384.

Methyl (Z)-3-(benzofuran-3-yl)-5-methylhex-2-enoate (341)



341

To a solution of alkene **339** (81 mg, 200 μmol) in THF (2 mL) was added TBAF (1.00 mL, 1.00 mmol, 1 M in THF). The reaction mixture was heated at 75 $^\circ\text{C}$ for 16 h. Sat. aq. NH_4Cl (5 mL) was added and the layers separated. The mixture was extracted with Et_2O (3×50 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (10 mg, 39%).

$R_f = 0.5$ (Pentane: Et_2O , 75:25).

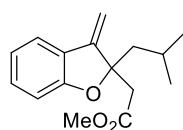
^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.85 - 7.81$ (1H, m, ArH), 7.81 (1H, s, ArH), 7.55 – 7.50 (1H, m, ArH), 7.39 – 7.29 (2H, m, $\text{ArH} \times 2$), 6.40 (1H, s, $\text{C}=\text{CH}$), 3.77 (3H, s, CO_2CH_3), 3.03 (2H, d, $J = 7.4$ Hz, CH_2), 1.96 – 1.82 (1H, m, CH), 0.94 (6H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_2$).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 167.2 (CO_2CH_3), 156.1 (C_{Ar}), 151.5 ($\text{C}=\text{CH}$), 144.7 (C_{ArH}), 125.4 (C_{Ar}), 125.1 (C_{ArH}), 123.6 (C_{ArH}), 122.9 (C_{Ar}), 121.2 (C_{ArH}), 116.9 (C_{ArH}), 112.1 ($\text{C}=\text{CH}$), 51.2 (CO_2CH_3), 39.8 (CH_2), 29.0 (CH), 22.7 ($\text{CH}(\text{CH}_3)_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 1716, 1621, 1452, 1173, 1124, 746.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 259.1330$; $\text{C}_{16}\text{H}_{19}\text{O}_3$ requires 259.1329.

Methyl 2-(2-isobutyl-3-methylene-2,3-dihydrobenzofuran-2-yl)acetate (**342**)



342

To a solution of alkene **339** (81 mg, 200 μmol) in THF (2 mL) was added TBAF (1.0 mL, 1.0 mmol, 1 M in THF). The reaction mixture was heated at 75 $^{\circ}\text{C}$ for 16 h. Sat. aq. NH_4Cl (5 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a colourless oil (9.0 mg, 34%).

R_f = 0.4 (Pentane: Et_2O , 75:25).

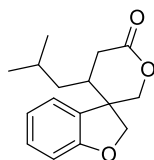
^1H NMR (CDCl_3 , 400 MHz) δ = 7.40 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.25 – 7.19 (1H, m, ArH), 6.89 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.85 (1H, d, J = 8.1 Hz, ArH), 5.48 (1H, d, J = 0.9 Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.84 (1H, d, J = 0.8 Hz, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.55 (3H, s, CO_2CH_3), 2.81 (1H, d, J = 14.9 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2\text{CH}_3$), 2.71 (1H, d, J = 14.9 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2\text{CH}_3$), 2.02 – 1.94 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.77 – 1.68 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}$ and CH), 0.89 (3H, d, J = 3.0 Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.87 (3H, d, J = 3.1 Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

¹³C NMR (CDCl₃, 110 MHz) δ = 169.9 (CO₂CH₃), 161.2 (C_{Ar}), 149.8 (C=CH_AH_B), 130.9 (C_{Ar}H), 126.1 (C_{Ar}), 121.2 (C_{Ar}H), 120.7 (C_{Ar}H), 110.6 (C_{Ar}H), 100.9 (C=CH_AH_B), 90.6 (COC_{Ar}), 51.7 (CO₂CH₃), 48.3 (CH_AH_B), 45.7 (CH_AH_BCO₂CH₃), 24.7 (CH), 24.3 (CH(CH₃)_A(CH₃)_B), 24.3 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2954, 1737, 1465, 1240, 1197, 1014, 875, 748.

HRMS: (ESI⁺) Found [M + Na]⁺ = 283.1305; C₁₆H₂₀O₃Na requires 283.1305.

4'-isobutyl-4',5'-Dihydro-2H,2'H,6'H-spiro[benzofuran-3,3'-pyran]-6'-one (344)¹⁵⁹



344

To a solution of acid **340** (91 mg, 300 μ L) in THF (2 mL) was added BH₃·DMS (85 μ L, 900 μ mol). The reaction mixture was stirred for 1 h then additional BH₃·DMS (85 μ L, 900 μ mol) was added. After a further 1 h water (20 mL) was added followed by EtOAc (20 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 20 mL) and the combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 70:30) afforded the title compound as a colourless oil and a single diastereomer (39 mg, 50%).

R_f = 0.4 (Pentane:Et₂O, 60:40).

¹H NMR (CDCl₃, 400 MHz) δ = 7.18 – 7.12 (1H, m, ArH), 6.93 (1H, dd, *J* = 7.6, 1.4 Hz, ArH), 6.86 (1H, td, *J* = 7.4, 1.0 Hz, ArH), 6.77 (1H, d, *J* = 8.0 Hz, ArH), 4.54 – 4.36 (2H, m, OCH₂), 4.26 (2H, s, CO₂CH₂), 2.87 (1H, dd, *J* = 18.5, 6.0 Hz, CH_AH_BCO₂), 2.39 – 2.28 (1H, m, CH), 2.14 (1H, dd, *J* = 18.5, 12.3 Hz, CH_AH_BCO₂), 1.50 – 1.40 (1H, m,

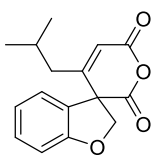
$\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 1.08 – 1.00 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.91 (1H, ddd, $J = 13.5$, 10.5, 2.9 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.76 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.72 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 169.8$ (CO_2CH_2), 160.5 (C_Ar), 130.0 ($\text{C}_\text{Ar}\text{H}$), 126.6 (C_Ar), 122.9 ($\text{C}_\text{Ar}\text{H}$), 121.1 ($\text{C}_\text{Ar}\text{H}$), 110.3 ($\text{C}_\text{Ar}\text{H}$), 76.4 (CO_2CH_2), 74.3 (OCH_2), 48.9 ($\text{C}_\text{Ar}\text{C}$), 39.8 ($\text{CH}_\text{A}\text{H}_\text{B}\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 36.2 (CH), 33.9 ($\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2$), 24.6 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 23.9 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 21.0 ($\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 1741, 1597, 1481, 1461, 1244, 1218, 1180, 1057, 1021, 753.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 261.1485$; $\text{C}_{16}\text{H}_{21}\text{O}_3$ requires 261.1487.

4'-isobutyl-2H,2'H,6'H-Spiro[benzofuran-3,3'-pyran]-2',6'-dione (346)¹¹⁷



346

To a solution of carboxylic acid **340** (30 mg, 100 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added oxalyl chloride (17 μL , 200 μmol) followed by DMF (1 drop). The reaction mixture was stirred for 1 h at rt then concentrated *in vacuo*. After drying under high vacuum for 1 h MeCN (1 mL) was added followed by CuCN (18 mg, 200 μL) and the reaction mixture was heated at 85 °C for 1 h. The mixture was concentrated *in vacuo* and filtered through Celite[®] with Et_2O . The filtrate was concentrated *in vacuo* and conc. H_2SO_4 (0.5 mL) was added followed by MeOH (0.5 mL) and NaBr (1.0 mg, 10 μmol). The reaction mixture was heated at 70 °C for 30 min then poured onto ice and diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated

in vacuo. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 80:20) afforded the title compound as a colourless oil (1 mg, 3%).

R_f = 0.2 (Pentane:EtOAc, 80:20).

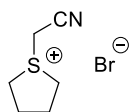
¹H NMR (CDCl₃, 400 MHz) δ = 7.48 – 7.41 (1H, m, ArH), 7.25 – 7.21 (2H, m, ArH $\times$ 2), 6.13 (1H, t, J = 1.5 Hz, ArH), 4.68 (1H, d, J = 11.1 Hz, CH_AH_B), 4.39 (1H, d, J = 11.1 Hz, CH_AH_B), 2.12 – 2.03 (1H, m, CH_AH_BC=CH), 1.89 – 1.81 (1H, m, CH_AH_BC=CH), 1.54 – 1.51 (1H, m, CH), 0.77 (2H, d, J = 3.6 Hz, CH(CH₃)_A(CH₃)_B), 0.75 (2H, d, J = 3.5 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 172.8 (C_{Ar}CCO₂), 162.7 (C=CHCO₂), 157.0 (C_{Ar}), 153.1 (C_{Ar}), 131.0 (C_{Ar}H), 125.5 (C_{Ar}), 125.3 (C_{Ar}H), 124.7 (C_{Ar}H), 119.0 (C=CH), 111.7 (C_{Ar}H), 71.7 (CH_AH_B), 52.0 (C_{Ar}C), 42.6 (CH_AH_BC=CH), 25.4 (CH), 22.4 (CH(CH₃)_A(CH₃)_B), 22.2 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2956, 1741, 1597, 1481, 1461, 1244, 1218, 1180, 1057, 1021, 753.

HRMS: (ESI⁺) Found [M + H]⁺ = 273.1122; C₁₆H₁₇O₄ requires 273.1121.

1-(Cyanomethyl)tetrahydro-1H-thiophen-1-ium Bromide (347)¹¹⁸



347

To a solution of tetrahydrothiophene (4.80 mL, 54.0 mmol) was added dropwise bromoacetonitrile (3.40 mL, 49.0 mmol). The reaction mixture was stirred at rt for 16 h and the resulting solid was quickly broken into smaller pieces using a spatula. The powder was triturated with Et₂O (3 $\times$ 5 mL), then collected and dried under high vacuum to afford the title compound as a white solid (8.52 g, 84%).

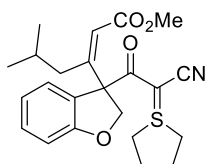
m.p. 70 °C.

¹H NMR (MeOD, 400 MHz) δ = 4.87 (2H, s, CH₂CN), 4.07 – 3.83 (4H, m, CH₂S), 2.73 – 2.43 (4H, m, CH₂CH₂S).

¹³C NMR (MeOD, 101 MHz) δ = 118.8 (CN), 112.8 (CH₂CN), 46.6 (CH₂S), 30.1 (CH₂CH₂S).

Analytical data are in accordance with those previously reported for this compound.¹¹⁸

Methyl (Z)-3-(3-(2-cyano-2-(tetrahydro-1 λ ⁴-thiophen-1-ylidene)acetyl)-2,3-dihydrobenzofuran-3-yl)-5-methylhex-2-enoate (348)⁵⁷



348

To a solution of CuI (32 mg, 170 μ mol) in THF (0.7 mL) at –78 °C was added *i*BuLi (200 μ L, 340 μ mol, 1.7 M in hexane). The mixture was stirred vigorously at 0 °C for 1 h before being cooled to –78 °C. A solution of alkyne **353** (15 mg, 42 μ mol) in THF (0.5 mL + 0.25 mL) was added dropwise and the reaction mixture stirred at –78 °C for 5 min. MeOH (1 mL) was added followed by water (20 mL) and the mixture extracted with EtOAc (3 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, EtOAc) afforded the title compound as an orange oil and a single diastereomer (14 mg, 79%).

R_f = 0.2 (EtOAc).

¹H NMR (CDCl₃, 500 MHz) δ = 7.54 (1H, dd, *J* = 7.8, 1.4 Hz, ArH), 7.19 – 7.12 (1H, m, ArH), 6.84 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 6.78 (1H, d, *J* = 8.1 Hz, ArH), 5.90 (1H, s, C=CH), 5.83 (1H, d, *J* = 9.4 Hz, CH_AH_B), 4.29 (1H, d, *J* = 9.5 Hz, CH_AH_B), 3.64 (3H, s, CO₂CH₃),

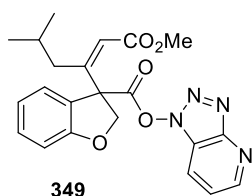
3.49 – 3.18 (4H, m, S(CH₂CH₂)_A(CH₂CH₂)_B and S(CH₂CH₂)_A(CH₂CH₂)_B), 2.66 – 2.53 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B), 2.05 – 1.91 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B), 1.24 – 1.19 (1H, m, CH), 0.79 (3H, d, *J* = 6.5 Hz, CH(CH₃)_A(CH₃)_B), 0.56 (3H, d, *J* = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 187.7 (C(O)), 166.4 (CO₂CH₃), 162.3 (C_{Ar}), 160.8 (C=CH), 129.7 (C_{Ar}H), 127.6 (C_{Ar}), 126.4 (C_{Ar}H), 121.2 (CN), 120.2 (C_{Ar}H), 119.6 (C=CH), 110.3 (C_{Ar}H), 81.2 (CH_AH_B), 64.9 (C_{Ar}C), 51.3 (CO₂CH₃), 50.1 (C=S), 48.3 (CH_AH_BC=CH), 43.4 (S(CH₂CH₂)_A(CH₂CH₂)_B), 43.3 (S(CH₂CH₂)_A(CH₂CH₂)_B), 28.6 (S(CH₂CH₂)_A(CH₂CH₂)_B), 28.6 (S(CH₂CH₂)_A(CH₂CH₂)_B), 26.2 (CH(CH₃)_A(CH₃)_B), 23.3 (CH(CH₃)_A(CH₃)_B), 21.3 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2956, 2239, 2164, 1715, 1593, 1480, 1238, 1205, 1156, 752, 731.

HRMS: (ESI⁺) Found [M + Na]⁺ = 436.1544; C₂₃H₂₇O₄NNaS requires 436.1553.

1*H*-[1,2,3]Triazolo[4,5-*b*]pyridin-1-yl (*Z*)-3-(1-methoxy-5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (349**)¹⁰¹**



To a solution of acid **340** (21 mg, 70 μ mol) in CH₂Cl₂ (1 mL) was added HATU (42 mg, 110 μ mol), 4-(dimethylamino)pyridine (1 mg, 7 μ mol), DIPEA (19 μ L, 110 μ mol), and salt **347** (23 mg, 110 μ mol). The reaction mixture was stirred at rt for 16 h, diluted with CH₂Cl₂ (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash

column chromatography (SiO₂, Pentane:EtOAc, 80:20) afforded the title compound as a white solid (58 mg, 98%).

R_f = 0.2 (Pentane:EtOAc, 80:20).

m.p. 70 °C

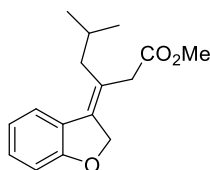
¹H NMR (CDCl₃, 400 MHz) δ = 8.65 (1H, d, J = 4.5, 1.4 Hz, ArH), 8.36 (1H, dd, J = 8.4, 1.4 Hz, ArH), 7.79 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.40 – 7.30 (2H, m, ArH $\times$ 2), 7.08 (1H, td, J = 7.6, 1.1 Hz, ArH), 6.90 (1H, dd, J = 8.3, 1.0 Hz, ArH), 6.07 (1H, d, J = 1.2 Hz, C=CH), 5.74 (1H, d, J = 10.1 Hz, CH_AH_B), 4.62 (1H, d, J = 10.1 Hz, CH_AH_B), 3.91 (3H, s, CO₂CH₃), 2.27 (1H, ddd, J = 14.4, 5.2, 1.3 Hz, CH_AH_BC=CH), 1.96 (1H, ddd, J = 14.3, 8.5, 1.0 Hz, CH_AH_BC=CH), 1.47 – 1.36 (1H, m, CH), 0.82 (3H, d, J = 6.5 Hz, CH(CH₃)_A(CH₃)_B), 0.67 (3H, d, J = 6.6 Hz, CH(CH₃)_A(CH₃)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 167.2 (CO₂N), 166.9 (CO₂CH₃), 161.0 (C=CH), 159.2 (C_{Ar}), 151.8 (C_{Ar}H), 140.8 (C_{Ar}), 134.9 (C_{Ar}), 131.3 (C_{Ar}H), 129.3 (C_{Ar}H), 126.9 (C_{Ar}H), 124.4 (C_{Ar}), 121.3 (C_{Ar}H), 120.8 (C_{Ar}H), 119.9 (C=CH), 110.9 (C_{Ar}H), 82.6 (CH_AH_B), 60.6 (C_{Ar}C), 52.3 (CO₂CH₃), 46.7 (CH_AH_BC=CH), 26.2 (CH), 22.8 (CH(CH₃)_A(CH₃)_B), 21.6 (CH(CH₃)_A(CH₃)_B).

IR (film) ν_{max} /cm⁻¹ 2957, 1822, 1709, 1630, 1594, 1481, 1463, 1237, 1214, 1164, 753.

HRMS: (ESI⁺) Found [M + Na]⁺ = 261.1485; C₂₂H₂₃O₅N₄ requires 261.1487.

Methyl (Z)-3-(benzofuran-3(2H)-ylidene)-5-methylhexanoate (350)¹⁰¹



350

To a solution of acid **340** (21 mg, 70 μmol) in CH_2Cl_2 (1 mL) was added DCC (2.0 mg, 110 μmol), 4-(dimethylamino)pyridine (1.0 mg, 7 μmol), DIPEA (19 μL , 110 μmol), and salt **347** (23 mg, 110 μmol). The reaction mixture was stirred at rt for 16 h, diluted with CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 80:20) afforded the title compound as a colourless oil (13 mg, 74%).

R_f = 0.7 (Pentane:Et₂O, 60:40).

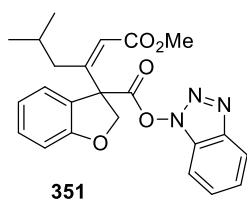
¹H NMR (CDCl_3 , 400 MHz) δ = 7.53 (1H, d, J = 7.8 Hz, ArH), 7.18 – 7.12 (1H, m, ArH), 6.91 – 6.86 (1H, m, ArH), 6.86 (1H, d, J = 8.0 Hz, ArH), 5.14 (2H, t, J = 1.3 Hz, OCH_2), 3.69 (3H, s, CO_2CH_3), 3.05 (2H, t, J = 1.1 Hz, $\text{CH}_2\text{CO}_2\text{CH}_3$), 2.42 (2H, dt, J = 7.4, 1.5 Hz, $\text{CH}_2\text{C}=\text{C}$), 2.02 – 1.92 (1H, m, CH), 0.99 (6H, d, J = 6.6 Hz, $\text{CH}(\text{CH}_3)_2$).

¹³C NMR (CDCl_3 , 110 MHz) δ = 171.1 (CO_2CH_3), 164.6 (C_{Ar}), 134.5 (C_{Ar}), 129.3 (C_{ArH}), 125.3 ($\text{OCH}_2\text{C}=\text{C}$), 124.4 (C_{ArH}), 123.8 ($\text{OCH}_2\text{C}=\text{C}$), 120.4 (C_{ArH}), 110.4 (C_{ArH}), 74.5 (OCH_2), 52.0 (CO_2CH_3), 41.8 ($\text{CH}_2\text{C}=\text{C}$), 41.2 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 27.4 (CH), 22.6 ($\text{CH}(\text{CH}_3)_2$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2954, 1734, 1475, 1465, 1232, 1157, 1024, 998, 835, 744.

HRMS: (ESI⁺) Found $[\text{M} + \text{Na}]^+ = 283.1303$; $\text{C}_{16}\text{H}_{20}\text{O}_3\text{Na}$ requires 283.1305.

1H-Benzo[d][1,2,3]triazol-1-yl (Z)-3-(1-methoxy-5-methyl-1-oxohex-2-en-3-yl)-2,3-dihydrobenzofuran-3-carboxylate (351)¹⁰¹



To a solution of acid **340** (21 mg, 70 μ mol) in CH_2Cl_2 (1 mL) was added PyBOP (57 mg, 110 μ mol), 4-(dimethylamino)pyridine (1 mg, 7 μ mol), DIPEA (19 μ L, 110 μ mol), and salt **347** (23 mg, 110 μ mol). The reaction mixture was stirred at rt for 16 h, diluted with CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 85:15) afforded the title compound as a white solid (20 mg, 98%).

R_f = 0.3 (Pentane:EtOAc, 80:20).

m.p. 153 $^\circ\text{C}$

^1H NMR (CDCl_3 , 400 MHz) δ = 8.02 (1H, d, J = 8.4 Hz, ArH), 7.55 (1H, d, J = 7.6 Hz, ArH), 7.46 (1H, t, J = 7.7, 6.5 Hz, ArH), 7.41 – 7.33 (3H, m, ArH $\times$ 3), 7.08 (1H, t, J = 7.6 Hz, ArH), 6.97 – 6.93 (1H, m, ArH), 6.03 (1H, s, C=CH), 5.83 (1H, d, J = 10.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.56 (1H, d, J = 10.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.86 (3H, s, CO_2CH_3), 2.26 (1H, dd, J = 14.4, 5.3 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.97 (1H, dd, J = 14.4, 8.5 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{C}=\text{CH}$), 1.42 (1H, dtt, J = 13.2, 6.6, 1.3 Hz, CH), 0.83 (3H, d, J = 6.6 Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 0.68 (3H, d, J = 6.6 Hz, $\text{CH}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

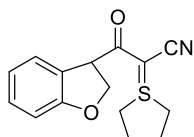
^{13}C NMR (CDCl_3 , 110 MHz) δ = 167.3 (CO_2N), 167.2 (CO_2CH_3), 161.2 (C=CH), 159.9 (C_Ar), 143.6 (C_Ar), 131.5 ($\text{C}_\text{Ar}\text{H}$), 128.8 (C_Ar), 128.6 ($\text{C}_\text{Ar}\text{H}$), 126.3 ($\text{C}_\text{Ar}\text{H}$), 124.8 ($\text{C}_\text{Ar}\text{H}$),

124.4 (C_{Ar}), 121.3 (C_{ArH}), 120.5 (C_{ArH}), 119.5 ($C=CH$), 111.2 (C_{ArH}), 109.0 (C_{ArH}), 81.7 (CH_{AHB}), 60.8 (C_{ArC}), 52.2 (CO_2CH_3), 46.7 ($CH_{AHB}C=CH$), 26.2 (CH), 22.8 ($CH(CH_3)_A(CH_3)_B$), 21.7 ($CH(CH_3)_A(CH_3)_B$).

IR (film) ν_{max}/cm^{-1} 2955, 1806, 1700, 1631, 1597, 1487, 1462, 1237, 1217, 1157, 743.

HRMS: (ESI⁺) Found $[M + Na]^+ = 444.1530$; $C_{23}H_{23}O_5N_3Na$ requires 444.1530.

3-(2,3-Dihydrobenzofuran-3-yl)-3-oxo-2-(tetrahydro-1 λ^4 -thiophen-1-ylidene)propanenitrile (352)¹¹⁸



352

To a solution of acid **265** (1.77 g, 10.8 mmol) in CH_2Cl_2 (50 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (3.10 g, 16.2 mmol), 4-(dimethylamino)pyridine (132 mg, 1.08 mmol) and salt **347** (2.25 g, 10.8 mmol). The reaction mixture was stirred at rt for 16 h, diluted with CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 30 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , $CHCl_3$:MeOH, 60:40) afforded the title compound as a beige solid (2.30 g, 78%).

R_f = 0.3 ($CHCl_3$:MeOH, 95:5).

m.p. 153 °C.

¹H NMR ($CDCl_3$, 400 MHz) δ = 7.36 (1H, dt, J = 7.8, 1.3 Hz, ArH), 7.20 – 7.06 (1H, m, ArH), 6.83 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.79 (1H, d, J = 8.1 Hz, ArH), 4.89 (1H, dd, J = 8.5, 5.7 Hz, CH_{AHB}), 4.74 (1H, dd, J = 9.3, 5.6 Hz, CH), 4.62 (1H, dd, J = 9.4, 8.5 Hz,

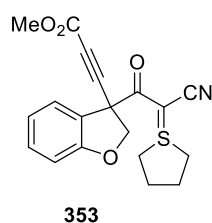
$\text{CH}_\text{A}\text{H}_\text{B}$), 3.44 – 3.25 (4H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$ and $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 2.70 – 2.51 (2H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 2.09 – 1.95 (2H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 189.1 ($\text{C}(\text{O})$), 160.2 (C_Ar), 129.0 (C_ArH), 127.0 (C_Ar), 124.9 (C_ArH), 120.8 (CN), 120.5 (C_ArH), 109.9 (C_ArH), 73.2 ($\text{CH}_\text{A}\text{H}_\text{B}$), 53.4 ($\text{C}=\text{S}$), 50.2 (CH), 45.0 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 44.9 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 28.7 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 28.6 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$).

IR (film) $\nu_\text{max}/\text{cm}^{-1}$ 2957, 2160, 1977, 1588, 1482, 1236, 1155, 961, 766.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 296.0715$; $\text{C}_{15}\text{H}_{15}\text{O}_2\text{NNaS}$ requires 296.0716.

Methyl 3-(3-(2-cyano-2-(tetrahydro-1 λ^4 -thiophen-1-ylidene)acetyl)-2,3-dihydrobenzofuran-3-yl)propiolate (353)



To a stirred solution of cyanoketothiane **352** (50 mg, 180 μmol) in THF (1 mL) at -78°C was added LDA (220 μL , 220 μmol , 1 M in THF). After 10 min chloroacetylene **145** (32 mg, 270 μmol) in THF (0.6 mL) was added dropwise and the reaction mixture was stirred at -78°C for 30 min. Sat. aq. NH_4Cl (5 mL) and water (20 mL) were added and the mixture extracted with EtOAc (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , CHCl_3 :MeOH, 99:1) afforded the title compound as a colourless oil (38 mg, 60%).

$R_f = 0.2$ (CHCl₃:MeOH, 98.5:1.5).

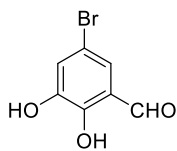
¹H NMR (CDCl₃, 400 MHz) δ = 7.69 (1H, dd, J = 7.6, 1.3 Hz, ArH), 7.24 – 7.18 (1H, m, ArH), 6.95 (1H, td, J = 7.5, 1.0 Hz, ArH), 6.82 (1H, d, J = 8.1 Hz, ArH), 5.25 (1H, d, J = 8.9 Hz, CH_AH_B), 4.72 (1H, d, J = 8.9 Hz, CH_AH_B), 3.77 (3H, s, CO₂CH₃), 3.43 – 3.26 (4H, m, S(CH₂CH₂)_A(CH₂CH₂)_B and S(CH₂CH₂)_A(CH₂CH₂)_B), 2.65 – 2.47 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B), 2.11 – 2.02 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 183.3 (C(O)), 159.6 (C_{Ar}), 154.0 (CO₂CH₃), 130.3 (C_{Ar}H), 126.8 (C_{Ar}), 126.1 (C_{Ar}H), 121.5 (C_{Ar}H), 119.1 (CN), 110.6 (C_{Ar}H), 85.8 (C $\equiv$ CCO₂CH₃), 79.6 (CH_AH_B), 77.5 (C $\equiv$ CCO₂CH₃), 54.5 (C_{Ar}C), 54.0 (C=S), 53.0 (CO₂CH₃), 45.0 (S(CH₂CH₂)_A(CH₂CH₂)_B), 44.8 (S(CH₂CH₂)_A(CH₂CH₂)_B), 28.6 (S(CH₂CH₂)_A(CH₂CH₂)_B), 28.6 (S(CH₂CH₂)_A(CH₂CH₂)_B).

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2955, 2235, 2170, 1714, 1596, 1480, 1274, 1236, 1154, 752.

HRMS: (ESI⁺) Found $[M + H]^+ = 356.0953$; C₁₉H₁₈O₄NS requires 356.0951.

5-Bromo-2,3-dihydroxybenzaldehyde (**356**)¹⁶⁰



356

To a solution of 5-bromo-2-hydroxy-3-methoxybenzaldehyde **355** (3.38 g, 14.6 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added dropwise BBr₃ (43.8 mL, 43.8 mmol, 1 M in CH₂Cl₂). The reaction mixture was stirred at rt for 16 h then cooled to 0 °C. Sat. aq. NaHCO₃ (50 mL) was added followed by NaOH (1 M, aq.) until pH = 9. CH₂Cl₂ (100 mL) was added and the two layers separated. The aqueous layer was acidified with HCl (2 M, aq.) to pH = 2 then extracted with EtOAc (3 $\times$ 100 mL). The combined organic phase was washed with sat. aq.

NaCl (100 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound as a white solid used without further purification (3.11 g, 98%).

R_f = 0.10 (Pentane:Et₂O, 10:90).

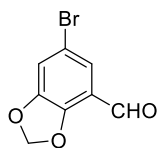
m.p. 124 °C

¹H NMR (CDCl₃, 400 MHz) δ = 11.03 (1H, s, CHO), 9.82 (1H, s, OH), 7.31 (1H, d, *J* = 2.2 Hz, ArH), 7.27 (1H, d, *J* = 2.3 Hz, ArH), 5.80 (1H, s, OH).

¹³C NMR (CDCl₃, 110 MHz) δ = 195.8 (CHO), 147.8 (C_{Ar}), 146.1 (C_{Ar}), 126.3 (C_{Ar}H), 124.6 (C_{Ar}H), 121.3 (C_{Ar}), 111.9 (C_{Ar}).

Analytical data are in accordance with those previously reported for this compound.¹⁶⁰

6-Bromobenzo[d][1,3]dioxole-4-carbaldehyde (357)⁴⁴



357

A solution of aldehyde **356** (3.07 g, 14.2 mmol), CuO (123 mg, 1.42 mmol), K₂CO₃ (2.15 g, 15.6 mmol) and CH₂Br₂ (1.19 mL, 17.0 mmol) in DMF (28 mL) was heated at 165 °C for 3 h. The reaction mixture was filtered through Celite[®] and washed with EtOAc (150 mL). The filtrate was washed with sat. aq. LiCl (100 mL), sat. aq. K₂CO₃ (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 80:20) afforded the title compound as a white solid (2.50 g, 77%).

R_f = 0.4 (Pentane:Et₂O, 60:40).

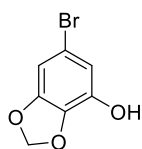
m.p. 109 °C

¹H NMR (DMSO-*d*₆, 500 MHz) δ = 9.96 (1H, s, CHO), 7.45 (1H, d, *J* = 2.0 Hz, ArH), 7.40 (1H, d, *J* = 2.0 Hz, ArH), 6.26 (2H, s, CH₂).

¹³C NMR (DMSO-*d*₆, 126 MHz) δ = 187.3 (CHO), 150.3 (*C*_{Ar}), 148.6 (*C*_{Ar}), 122.9 (*C*_{Ar}H), 119.4 (*C*_{Ar}), 116.1 (*C*_{Ar}H), 112.6 (*C*_{Ar}), 103.9 (CH₂).

Analytical data are in accordance with those previously reported for this compound.¹⁶¹

6-Bromobenzo[*d*][1,3]dioxol-4-ol (**358**)⁴⁴



358

To a solution of aldehyde **357** (1.95 g, 8.52 mmol) in CH₂Cl₂ (30 mL) was added MCPBA (1.77 g, 10.2 mmol, 70 wt. %). The reaction mixture was heated at reflux for 16 h, filtered through Celite[®] and washed with CH₂Cl₂ (150 mL). The filtrate was washed with sat. aq. NaHCO₃ (3 × 100 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in ethanolic KOH solution (5 wt.%, 25 mL) and stirred at rt for 2 h. The reaction mixture was acidified to pH 2 with HCl (1 M aq.), diluted with H₂O (100 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 75:25) afforded the title compound as a yellow solid (1.31 g, 71%).

R_f = 0.4 (Pentane:Et₂O, 60:40).

m.p. 100 °C.

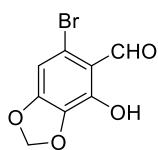
¹H NMR (CDCl₃, 400 MHz) δ = 6.67 (1H, d, *J* = 1.8 Hz, ArH), 6.62 (1H, d, *J* = 1.8 Hz, ArH), 5.96 (2H, s, CH₂).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 149.5 (C_{Ar}), 140.0 (C_{Ar}), 133.9 (C_{Ar}), 114.4 (C_{ArH}), 113.4 (C_{Ar}), 105.9 (C_{ArH}), 102.1 (CH_2).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3392, 1632, 1467, 1060, 1018, 927, 773.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 293.9349$; $\text{C}_7\text{H}_4\text{O}_3\text{Br}$ requires 293.9349.

6-Bromo-4-hydroxybenzo[d][1,3]dioxole-5-carbaldehyde (359)⁴⁵



359

To a solution of phenol **358** (1.13 g, 5.21 mmol) in THF (52 mL) was added MgCl_2 (991 mg, 10.4 mmol), Et_3N (1.45 mL, 10.4 mmol) and paraformaldehyde (469 mg, 15.6 mmol). The reaction mixture was heated at 85 °C for 16 h and HCl (30 mL, 1 M aq.) was added. The solution was extracted with Et_2O (3×100 mL) and the organic layer was washed with brine (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Toluene) afforded the title compound as a yellow solid (500 mg, 39%).

R_f = 0.1 (Pentane: Et_2O , 90:10).

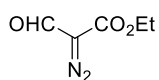
m.p. 155 °C.

^1H NMR (CDCl_3 , 400 MHz) δ = 11.97 (1H, s, CHO), 10.14 (1H, s, OH), 6.78 (1H, s, ArH), 6.11 (2H, s, CH_2).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 197.0 (CHO), 155.0 (C_{Ar}), 147.7 (C_{Ar}), 134.4 (C_{Ar}), 122.2 (C_{Ar}), 114.8 (C_{Ar}), 107.3 (C_{ArH}), 103.4 (CH_2).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3392, 1632, 1467, 1060, 1018, 927, 773.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 244.9445$; $\text{C}_8\text{H}_6\text{O}_4\text{Br}$ requires 244.9444.

Ethyl 2-diazo-3-oxopropanoate (362)¹¹⁹**362**

To DMF (1.40 mL, 18.0 mmol) was added dropwise SOCl₂ (1.30 mL, 18.0 mmol). The reaction mixture was heated at 40 °C for 16 h then concentrated *in vacuo* to afford a solid. The solid was dissolved in CHCl₃ (8 mL) and cooled to 0 °C. Ethyl diazoacetate (4.40 mL, 36.0 mmol) was added and the reaction mixture stirred at rt for 1 h. The reaction was concentrated *in vacuo* and Et₂O (10 mL) was added. The precipitate was filtered and dissolved in AcOH (4 mL). The reaction was stirred for 16 h then diluted with Et₂O (20 mL) and water (20 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 85:15) afforded the title compound as a beige solid (794 mg, 28%).

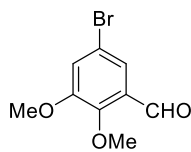
R_f = 0.3 (SiO₂, Pentane:EtOAc, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 9.69 (1H, s, CHO), 4.35 (2H, q, *J* = 7.1 Hz, CO₂CH₂CH₃), 1.34 (3H, t, *J* = 7.1 Hz, CO₂CH₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 181.4 (CHO), 161.4 (CO₂CH₂CH₃), 62.1 (CO₂CH₂CH₃), 14.5 (CO₂CH₂CH₃).

Analytical data are in accordance with those previously reported for this compound.¹⁶²

5-Bromo-2,3-dimethoxybenzaldehyde (363)



363

To a solution of NaH (400 mg, 10.0 mmol, 60 wt% in mineral oil) in THF (30 mL) was added 5-bromo-2-hydroxy-methoxybenzaldehyde (1.16 g, 5.00 mmol). The reaction mixture was stirred at rt for 10 min before the addition of dimethylsulfate (1.42 mL, 15.0 mmol). The reaction was heated at 40 °C for 1 h then and water (20 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 90:10) afforded the title compound as a white solid (1.22 g, 100%).

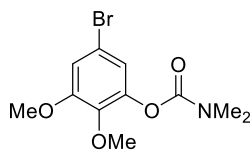
m.p. 80 °C.

R_f = 0.2 (SiO₂, Pentane:EtOAc, 90:10).

¹H NMR (CDCl₃, 400 MHz) δ = 10.27 (1H, s, CHO), 7.46 (1H, d, *J* = 2.4 Hz, ArH), 7.16 (1H, d, *J* = 2.4 Hz, ArH), 3.90 (3H, s, OCH₃), 3.84 (3H, s, OCH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 188.8 (CHO), 154.0 (C_{Ar}), 152.1 (C_{Ar}), 130.7 (C_{Ar}), 122.0 (C_{Ar}H), 121.2 (C_{Ar}H), 117.1 (C_{Ar}), 62.6 (OCH₃), 56.5 (OCH₃).

Analytical data are in accordance with those previously reported for this compound.¹⁶³

5-Bromo-2,3-dimethoxyphenyl dimethylcarbamate (364)¹⁴⁹**364**

To a solution of aldehyde **363** (2.04 g, 8.2 mmol) in CH₂Cl₂ (28 mL) was added MCPBA (1.72 g, 9.99 mmol, 70 wt. %). The reaction mixture was heated at reflux for 16 h, filtered through Celite[®] and washed with CH₂Cl₂ (100 mL). The filtrate was washed with sat. aq. NaHCO₃ (3 × 100 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in ethanolic KOH solution (5 wt.%, 20 mL) and stirred at rt for 2 h. The reaction mixture was acidified to pH 2 with HCl (1 M aq.), diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to afford a crude phenol. To this solid was added DMF (24 mL) and NaH (584 mg, 14.6 mmol, 60 wt% in mineral oil) at rt. The reaction mixture was stirred for 10 min then dimethyl carbonyl chloride (1.34 mL, 14.6 mmol) was added dropwise and the reaction mixture stirred at rt for 16 h. Water (50 mL) was added and the mixture extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 60:40) afforded the title compound as a pale yellow oil (1.56 g, 62% over 3 steps).

R_f = 0.2 (Pentane:Et₂O, 60:40).

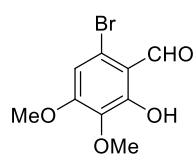
¹H NMR (CDCl₃, 400 MHz) δ = 6.91 (1H, d, *J* = 2.3 Hz, ArH), 6.90 (1H, d, *J* = 2.3 Hz, ArH), 3.85 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.11 (3H, s, N(CH₃)_A(CH₃)_B), 3.01 (3H, s, N(CH₃)_A(CH₃)_B).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 154.4 ($\text{C}(\text{O})$), 154.2 (C_{Ar}), 145.6 (C_{Ar}), 141.2 (C_{Ar}), 119.2 (C_{ArH}), 115.3 (C_{Ar}), 113.5 (C_{ArH}), 61.0 (OCH_3), 56.5 (OCH_3), 37.0 ($\text{N}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), 36.7 ($\text{N}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2941, 1724, 1589, 1380, 1155, 1095, 1000, 852, 752.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 304.0179$; $\text{C}_{11}\text{H}_{15}\text{O}_4\text{N}^{79}\text{Br}$ requires 304.0180.

6-Bromo-2-hydroxy-3,4-dimethoxybenzaldehyde (**365**)¹⁴⁹



365

To a solution of diisopropylamine (1.53 mL, 10.9 mmol) in THF (15 mL) at 0 °C was added dropwise $n\text{BuLi}$ (4.40 mL, 10.9 mmol, 2.5 M hexanes). The reaction was cooled to $-78\text{ }^\circ\text{C}$ and carbamate **364** (1.45 g, 4.77 mmol) in THF (4 mL) was added dropwise. The reaction mixture was stirred at rt for 1.5 h then DMF (1.70 mL, 21.9 mmol) was added. After 2 h at rt, HCl (2 M aq., 15 mL) was added and the reaction stirred for a further 1 h at rt. Water (50 mL) was added followed by EtOAc (50 mL), the layers were separated and the aqueous layer was extracted with EtOAc ($3 \times 50\text{ mL}$). The combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 90:10) afforded the title compound as a yellow solid (276 mg, 22% over 2 steps).

R_f = 0.2 (Pentane:Et₂O, 90:10).

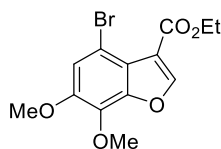
m.p. 75 °C.

^1H NMR (CDCl_3 , 400 MHz) δ = 10.12 (1H, s, CHO), 6.78 (1H, s, ArH), 3.95 (3H, s, OCH_3), 3.88 (3H, s, OCH_3).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 196.8 (CHO), 159.2 (C_{Ar}), 158.2 (C_{Ar}), 136.1 (C_{Ar}), 123.4 (C_{Ar}), 113.7 (C_{Ar}), 109.5 (C_{ArH}), 61.0 (OCH_3), 56.7 (OCH_3).

Analytical data are in accordance with those previously reported for this compound.¹⁶⁴

Ethyl 4-bromo-6,7-dimethoxybenzofuran-3-carboxylate (366)³⁶



366

To a solution of aldehyde **365** (157 mg, 600 μmol) and $\text{HBF}_4 \cdot \text{OEt}_2$ (8 μL , 60 μmol) in CH_2Cl_2 (1 mL) at 0 $^\circ\text{C}$ was added dropwise a solution of ethyl diazoacetate (148 μL , 1.20 mmol) in CH_2Cl_2 (1 mL) over a period of 5 min. The reaction mixture was stirred at room temperature for 30 min and then concentrated *in vacuo* after nitrogen evolution had ceased. Conc. H_2SO_4 (200 μL) was added and the reaction mixture was heated at 70 $^\circ\text{C}$ for 1 h. CH_2Cl_2 (10 mL) was added followed by solid NaHCO_3 until gas evolution had ceased. The solution was filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 90:10) afforded the title compound as a yellow solid (124 mg, 63%).

m.p. 60 $^\circ\text{C}$

R_f = 0.5 (Pentane: Et_2O , 40:60).

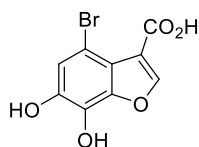
^1H NMR (CDCl_3 , 400 MHz) δ = 8.13 (1H, s, ArH), 7.18 (1H, s, ArH), 4.39 (2H, q, J = 7.1 Hz, CH_2CH_3), 4.09 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 1.41 (3H, t, J = 7.1 Hz, CH_2CH_3).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 162.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 150.9 (C_{ArH}), 149.8 (C_{Ar}), 149.0 (C_{Ar}), 134.2 (C_{Ar}), 119.9 (C_{Ar}), 116.0 (C_{ArH}), 115.7 (C_{Ar}), 106.2 (C_{Ar}), 61.4 (OCH_3), 61.1 (CH_2CH_3), 57.3 (OCH_3), 14.4 (CH_2CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2937, 1732, 1501, 1260, 1106, 1025, 842.

HRMS: (ESI⁺) Found $[M + H]^+ = 329.0019$; C₁₃H₁₄O₅⁷⁹Br requires 329.0019.

4-Bromo-6,7-dihydroxybenzofuran-3-carboxylic acid (369)¹⁶⁰



369

To a solution of ester **366** (120 mg, 365 μmol) in CH₂Cl₂ (1 mL) at 0 °C was added dropwise BBr₃ (2.92 mL, 2.92 mmol, 1 M in CH₂Cl₂). The reaction mixture was stirred at rt for 30 min then cooled to 0 °C. Sat. aq. NaHCO₃ (5 mL) was added followed by water (20 mL) and the two layers separated. The aqueous layer was extracted with EtOAc (3 $\times$ 20 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound as a brown solid (91 mg, 92%).

R_f = 0.05 (CHCl₃:MeOH, 90:10).

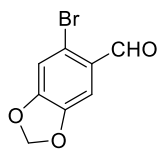
m.p. 184 °C.

¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.44 (1H, s, ArH), 7.04 (1H, s, ArH).

¹³C NMR (DMSO-*d*₆, 110 MHz) δ = 163.1 (CO₂H), 150.7 (C_{Ar}H), 146.3 (C_{Ar}), 144.1 (C_{Ar}), 130.6 (C_{Ar}), 118.2 (C_{Ar}H), 117.4 (C_{Ar}), 115.6 (C_{Ar}), 100.0 (C_{Ar}).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3234, 1711, 1682, 1519, 1238, 1198, 1146, 1108, 1019, 715.

HRMS: (ESI⁺) Found $[M + Na]^+ = 294.9426$; C₉H₅O₅Na⁷⁹Br requires 294.9213.

6-Bromobenzo[d][1,3]dioxole-5-carbaldehyde (372)¹²¹**372**

To a solution of piperonyl alcohol (3.05 g, 20.0 mmol) in CH₂Cl₂ (100 mL) was added portionwise DBDMH (11.4 g, 40 mmol). The reaction mixture was stirred at rt for 30 min then water (100 mL) was added and the two layers were separated. The aqueous layer was washed with CH₂Cl₂ (2 × 100 mL) and the combined organic phase was washed with sat. aq. NaCl (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 95:5) afforded the title compound as a yellow solid (2.37 g, 52%).

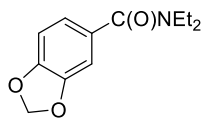
m.p. 130 °C.**R_f** = 0.2 (Pentane:EtOAc, 95:5).

¹H NMR (CDCl₃, 400 MHz) δ = 10.18 (1H, s, CHO), 7.36 (1H, s, ArH), 7.06 (1H, s, ArH), 6.08 (2H, s, OCH₂O).

¹³C NMR (CDCl₃, 110 MHz) δ = 190.2 (CHO), 153.3 (C_{Ar}), 148.1 (C_{Ar}H), 127.9 (C_{Ar}), 121.6 (C_{Ar}H), 113.3 (C_{Ar}), 108.0 (C_{Ar}), 102.7 (OCH₂O).

Analytical data are in accordance with those previously reported for this compound.¹²¹

***N,N*-Diethylbenzo[*d*][1,3]dioxole-5-carboxamide (374)¹²⁴**



374

A solution of piperonylic acid (25.0 g, 151 mmol) in thionyl chloride (110 mL, 1.50 mol) was heated at 90 °C for 2 h then cooled to rt. The excess thionyl chloride was removed *in vacuo* and then CH₂Cl₂ (150 mL) was added followed by diethylamine (62.0 mL, 602 mmol) at 0 °C. The reaction mixture was stirred at rt overnight and then water (200 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 100 mL) and the combined organic phase was washed with sat. aq. NaCl (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 70:30) afforded the title compound as a colourless oil (33.3 g, 100%).

m.p. 65 °C.

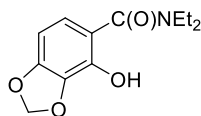
R_f = 0.5 (Pentane:EtOAc, 75:25).

¹H NMR (CDCl₃, 400 MHz) δ = 6.81 – 6.76 (2H, m, ArH × 2), 6.74 – 6.69 (1H, m, ArH), 5.88 (2H, s, OCH₂O), 3.31 (4H, s, CH₂CH₃ × 2), 1.16 – 1.01 (6H, m, CH₂CH₃ × 2).

¹³C NMR (CDCl₃, 110 MHz) δ = 170.5 (C(O)), 148.2 (C_{Ar}), 147.4 (C_{Ar}), 130.8 (C_{Ar}), 120.3 (C_{Ar}H), 108.0 (C_{Ar}H), 107.2 (C_{Ar}H), 101.2 (OCH₂O), 43.2, 39.5, (CH₂CH₃ × 2), 13.4 (CH₂CH₃ × 2).

Analytical data are in accordance with those previously reported for this compound.¹²⁴

***N,N*-Diethyl-4-hydroxybenzo[*d*][1,3]dioxole-5-carboxamide (375)¹²⁴**



375

To a solution of amide **374** (39.2 g, 177 mmol) and *N,N,N',N'*-tetramethylethylenediamine (34.5 mL, 230 mmol) in THF (440 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise $^s\text{BuLi}$ (177 mL, 230 mmol). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then B(OMe)_3 (27.6 mL, 248 mmol) was added and then warmed to rt. After 1 h, NaOH (175 mL, 350 mmol, 2 M aq.) was added, followed by H_2O_2 (36.0 mL, 350 mmol, 30% aq.) dropwise. The reaction mixture was stirred at rt overnight then acidified to $\text{pH} = 3$ with HCl (2 M, aq.). EtOAc (200 mL) was added and the two layers separated. The aqueous layer was washed with EtOAc ($2 \times 200\text{ mL}$) and the combined organic phase was washed with sat. aq. NaCl (100 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 40:60) afforded the title compound as a yellow oil (35.8 g, 85%).

$R_f = 0.4$ (Pentane: EtOAc , 50:50).

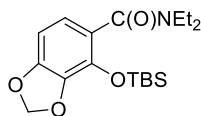
^1H NMR (CDCl_3 , 400 MHz) $\delta = 6.82$ (1H, d, $J = 8.3\text{ Hz}$, ArH), 6.38 (1H, d, $J = 8.3\text{ Hz}$, ArH), 5.98 (2H, s, OCH_2O), 3.48 (4H, q, $J = 7.1\text{ Hz}$, $\text{CH}_2\text{CH}_3 \times 2$), 1.24 (6H, t, $J = 7.1\text{ Hz}$, $\text{CH}_2\text{CH}_3 \times 2$).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 171.5$ (C(=O)), 151.1 (C_{Ar}), 143.7 (C_{Ar}), 135.7 (C_{Ar}), 122.0 (C_{ArH}), 115.1 (C_{Ar}), 102.3 (OCH_2O), 100.1 (C_{ArH}), 42.7 ($\text{CH}_2\text{CH}_3 \times 2$), 13.8 ($\text{CH}_2\text{CH}_3 \times 2$).

Analytical data are in accordance with those previously reported for this compound.¹²⁴

4-((*tert*-Butyldimethylsilyl)oxy)-*N,N*-diethylbenzo[*d*][1,3]dioxole-5-carboxamide

(376)¹²⁴



376

To a solution of phenol **375** (77.4 g, 326 mmol) in CH₂Cl₂ (1 litre) at 0 °C was added *tert*-butyldimethylsilyl chloride (54.1 g, 359 mmol) and imidazole (44.4 g, 652 mmol). The reaction mixture was stirred for 1 h before water (500 mL) was added. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 200 mL). The combined organic phase was washed with sat. aq. NaCl (200 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 90:10 to 25:75) afforded the title compound as a white solid (107 g, 93%).

R_f = 0.7 (Pentane:EtOAc, 50:50).

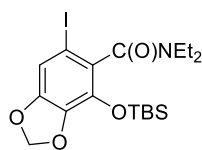
m.p. 65 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 6.68 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.51 (1H, d, *J* = 8.0 Hz, Ar*H*), 5.93 (2H, s, OCH₂O), 3.59 – 3.43 (2H, m, CH₂CH₃), 3.34 – 3.05 (2H, m, CH₂CH₃), 1.23 (3H, t, *J* = 7.2 Hz, CH₂CH₃), 1.02 (3H, t, *J* = 7.1 Hz, CH₂CH₃), 0.95 (9H, s, TBS–C(CH₃)₃), 0.21 (3H, s, TBS–Si(CH₃)₂), 0.19 (3H, s, TBS–Si(CH₃)₂).

¹³C NMR (CDCl₃, 110 MHz) δ = 168.6 (C(O)), 149.1 (C_{Ar}), 137.1 (C_{Ar}), 135.6 (C_{Ar}), 125.7 (C_{Ar}), 121.0 (C_{Ar}H), 102.7 (C_{Ar}H), 101.1 (OCH₂O), 43.1 (CH₂CH₃), 39.6 (CH₂CH₃), 25.8 (TBS–C(CH₃)₃), 18.4 (TBS–C(CH₃)₃), 14.2 (CH₂CH₃), 13.4 (CH₂CH₃), –4.3 (TBS–Si(CH₃)₂).

Analytical data are in accordance with those previously reported for this compound.¹²⁴

4-((*tert*-Butyldimethylsilyl)oxy)-N,N-diethyl-6-iodobenzo[*d*][1,3]dioxole-5-carboxamide (377)¹²⁴



377

To a solution of amide **376** (43.2 g, 123 mmol) and *N,N,N',N'*-tetramethylethylenediamine (24.0 mL, 160 mmol) in THF (300 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise $^s\text{BuLi}$ (123 mL, 160 mmol). The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then I_2 (32.8 g, 129 mmol) in THF (50 mL) was added slowly and the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h then rt. After 1 h, H_2O (200 mL) was added, followed by sat. aq. NH_4Cl (200 mL). EtOAc (200 mL) was added and the two layers separated. The aqueous layer was washed with EtOAc ($2 \times 400\text{ mL}$) and the combined organic phase was washed with sat. aq. NaCl (300 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O , 85:15) afforded the title compound as a white solid (38.9 g, 66%).

m.p. $66\text{ }^{\circ}\text{C}$.

R_f = 0.7 (Pentane:EtOAc, 50:50).

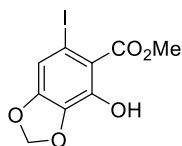
^1H NMR (CDCl_3 , 400 MHz) δ = 6.91 (1H, s, ArH), 5.95 (1H, d, J = 1.4 Hz, $\text{OCH}_\text{A}\text{H}_\text{BO}$), 5.91 (1H, d, J = 1.4 Hz, $\text{OCH}_\text{A}\text{H}_\text{BO}$), 3.91 – 3.78 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BCH}_3$) and 3.24 – 3.08 (3H, m, CH_2CH_3 and $\text{CH}_\text{A}\text{H}_\text{BCH}_3$), 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.11 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.93 (9H, s, $\text{TBS}-\text{C}(\text{CH}_3)_3$), 0.22 (3H, s, $\text{TBS}-\text{Si}(\text{CH}_3)_2$), 0.18 (3H, s, $\text{TBS}-\text{Si}(\text{CH}_3)_2$).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 167.6 ($\text{C}(\text{O})$), 149.5 (C_Ar), 137.7 (C_Ar), 136.1 (C_Ar), 130.7 (C_Ar), 112.7 (C_ArH), 101.5 (OCH_2O), 82.4 (C_Ar), 43.2 (CH_2CH_3), 39.5 (CH_2CH_3), 25.7

(TBS-C(CH₃)₃), 18.4 (TBS-C(CH₃)₃), 14.0 (CH₂CH₃), 12.7 (CH₂CH₃), -4.0 (TBS-Si(CH₃)_A(CH₃)_B), -4.5 (TBS-Si(CH₃)_A(CH₃)_B).

Analytical data are in accordance with those previously reported for this compound.¹²⁴

Methyl 4-hydroxy-6-iodobenzo[d][1,3]dioxole-5-carboxylate (378)¹²⁴



378

To a solution of amide **377** (27.4 g, 57.4 mmol) and Na₂HPO₄ (12.2 g, 86.1 mmol) in MeCN (300 mL) at 0 °C was added slowly Me₃OBf₄ (25.5 g, 72.2 mmol). The reaction mixture was stirred at rt for 12 h then cooled to 0 °C once more and sat. aq. NaHCO₃ (250 mL) was added in addition to NaHCO₃ (24.1 g, 287 mmol). After 6 h at rt, water (300 mL) and EtOAc (300 mL) were added and the layers separated. The aqueous layer was washed with EtOAc (2 × 200 mL) and the combined organic phase was washed with sat. aq. NaCl (300 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, toluene:EtOAc, 90:10) afforded the title compound as a white solid (16.0 g, 87%).

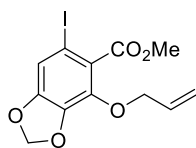
R_f = 0.5 (Pentane:EtOAc, 40:60).

m.p. 158 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 10.96 (1H, s, OH), 7.19 (1H, s, ArH), 6.07 (2H, s, OCH₂O), 3.96 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 168.8 (CO₂CH₃), 152.8 (C_{Ar}), 147.0 (C_{Ar}), 135.8 (C_{Ar}), 115.6 (C_{Ar}H), 112.7 (C_{Ar}), 103.1 (OCH₂O), 84.8 (C_{Ar}), 52.0 (CO₂CH₃).

Analytical data are in accordance with those previously reported for this compound.¹²⁴

Methyl 4-(allyloxy)-6-iodobenzo[d][1,3]dioxole-5-carboxylate (379)**379**

To a solution of phenol **378** (140 mg, 430 μmol) in DMF (2 mL) was added K_2CO_3 (297 mg, 2.15 mmol) and allyl iodide (118 μL , 1.29 μmol). The reaction mixture was heated at 70 $^\circ\text{C}$ for 1 h then cooled to rt. Water (50 mL) and EtOAc (50 mL) were added and the two layers were separated. The aqueous layer was washed with EtOAc (2×50 mL) and the combined organic phase was washed with sat. aq. LiCl (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 95:5) afforded the title compound as a pale yellow oil (148 mg, 95%).

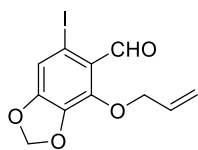
$R_f = 0.3$ (Pentane:EtOAc, 96:4).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) $\delta = 6.96$ (1H, s, ArH), 6.01 – 5.89 (3H, m, OCH_2O and $\text{HC}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.33 (1H, dq, $J = 17.2, 1.5$ Hz, $\text{HC}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.23 (1H, dq, $J = 10.5, 1.3$ Hz, $\text{HC}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.71 (2H, dt, $J = 5.6, 1.4$ Hz, OCH_2), 3.91 (3H, s, CO_2CH_3).

$^{13}\text{C NMR}$ (CDCl_3 , 110 MHz) $\delta = 167.6$ (CO_2CH_3), 150.8 (C_Ar), 140.0 (C_Ar), 137.4 (C_Ar), 133.1 ($\text{C}=\text{CH}_2$), 128.1 (C_Ar), 118.4 ($\text{C}=\text{CH}_2$), 113.5 (C_ArH), 102.0 (OCH_2O), 81.2 (C_Ar), 73.2 (OCH_2), 52.9 (CO_2CH_3).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2950, 1732, 1616, 1464, 1438, 1341, 1259, 1130, 1082, 1033, 934.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 384.9541$; $\text{C}_{12}\text{H}_{11}\text{O}_5\text{INa}$ requires 384.9543.

4-(Allyloxy)-6-iodobenzo[d][1,3]dioxole-5-carbaldehyde (380)¹⁴⁷**380**

To a solution of ester **379** (36 mg, 100 μ mol) in CH_2Cl_2 (1 mL) at -78°C was added dropwise DIBAL-H (120 μ L, 120 μ mol, 1 M in toluene). The reaction mixture was stirred at rt for 1 h then CHCl_3 (50 mL) was added followed by sat. aq. Rochelle's salt (50 mL). The mixture was stirred vigorously for 1 h and the two layers were separated. The aqueous layer was washed with CHCl_3 (2×50 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was re-dissolved in CH_2Cl_2 (1 mL) and NaHCO_3 (11 mg, 140 μ mol) was added. The reaction mixture was cooled to 0°C and Dess-Martin periodinane (38 mg, 90 μ mol) was added before being stirred at rt for 12 h. CH_2Cl_2 (20 mL) and water (10 mL) were added, and the layers separated. The aqueous layer was washed with CH_2Cl_2 (2×10 mL) and the combined organic phase was washed with sat. aq. NaCl (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 90:10) afforded the title compound as a pale yellow oil (15 mg, 44% over 2 steps).

$R_f = 0.4$ (Pentane:EtOAc, 80:20).

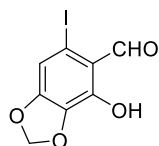
$^1\text{H NMR}$ (CDCl_3 , 400 MHz) $\delta = 10.08$ (1H, s, CHO), 7.20 (1H, s, ArH), 6.05 (2H, s, OCH_2O), 6.03 – 5.96 (1H, m, $\text{HC}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.40 (1H, dq, $J = 17.2, 1.5$ Hz, $\text{HC}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.28 (1H, dq, $J = 10.3, 1.2$ Hz, $\text{HC}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.80 (2H, dt, $J = 5.8, 1.4$ Hz, OCH_2).

$^{13}\text{C NMR}$ (CDCl_3 , 110 MHz) $\delta = 190.4$ (CHO), 153.8 (C_Ar), 144.8 (C_Ar), 138.3 (C_Ar), 132.8 ($\text{HC}=\text{CH}_2$), 122.8 (C_Ar), 119.1 ($\text{HC}=\text{CH}_2$), 116.6 ($\text{C}_\text{Ar}\text{H}$), 102.6 (OCH_2O), 87.5 (C_Ar), 73.8 (OCH_2).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 2897, 1688, 1601, 1467, 1330, 1264, 1251, 1087, 1039, 859, 838.

HRMS: (ESI⁺) Found $[M + H]^+ = 354.9437$; C₁₁H₉O₄INa requires 354.9438.

4-Hydroxy-6-iodobenzo[d][1,3]dioxole-5-carbaldehyde (381)¹³⁰



381

To a solution of aldehyde **383** (1.20 g, 3.06 mmol) in nitromethane (10 mL) at 0 °C was added ZnBr₂ (2.76 g, 12.2 mmol). The reaction mixture was stirred at rt for 16 h then water (50 mL) and EtOAc (50 mL) were added and the layers separated. The aqueous layer was washed with EtOAc (2 × 50 mL) and the combined organic phase was washed with sat. aq. NaCl (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 96:4) afforded the title compound as a yellow solid (815 mg, 91%).

m.p. 100 °C.

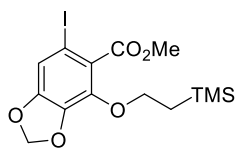
R_f = 0.3 (Pentane:EtOAc, 96:4).

¹H NMR (CDCl₃, 400 MHz) δ = 12.07 (1H, s, OH), 9.89 (1H, s, CHO), 7.08 (1H, s, ArH), 6.11 (2H, s, OCH₂O).

¹³C NMR (CDCl₃, 110 MHz) δ = 201.5 (CHO), 155.2 (C_{Ar}), 147.7 (C_{Ar}), 135.6 (C_{Ar}), 116.0 (C_{Ar}), 113.9 (C_{Ar}H), 103.4 (OCH₂O), 94.6 (C_{Ar}).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2916, 1650, 1500, 1476, 1425, 1258, 1087, 1047, 968, 615.

HRMS: (ESI⁺) Found $[M + H]^+ = 292.9306$; C₈H₆O₄I requires 292.9305.

Methyl 6-iodo-4-(2-(trimethylsilyl)ethoxy)benzo[d][1,3]dioxole-5-carboxylate (382)¹³⁰**382**

To a solution of phenol **378** (8.00 g, 24.8 mmol) in THF (125 mL) was added triphenylphosphine (9.78 g, 37.3 mmol) followed by 2-(trimethylsilyl)ethanol (5.34 mL, 37.3 mmol). The solution was cooled to 0 °C and diisopropyl azodicarboxylate (7.34 mL, 37.3 mmol) was added dropwise. The reaction mixture was stirred at rt overnight and water (300 mL) and EtOAc (200 mL) were added and the layers separated. The aqueous layer was washed with EtOAc (2 × 200 mL) and the combined organic phase was washed with sat. aq. NaCl (300 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, pentane:EtOAc, 95:5) afforded the title compound as a pale yellow solid (16.0 g, 87%).

m.p. 38 °C.

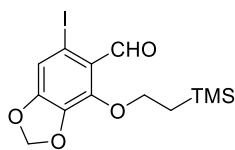
R_f = 0.7 (Pentane:EtOAc, 80:20).

¹H NMR (CDCl₃, 400 MHz) δ = 6.93 (1H, s, ArH), 5.95 (2H, s, OCH₂O), 4.35 – 4.24 (2H, m, OCH₂CH₂), 3.90 (3H, s, CO₂CH₃), 1.12 – 1.00 (2H, m, OCH₂CH₂), 0.03 (9H, s, TMS–Si(CH₃)₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 167.7 (CO₂CH₃), 150.8 (C_{Ar}), 140.3 (C_{Ar}), 137.3 (C_{Ar}), 128.2 (C_{Ar}), 113.0 (C_{Ar}H), 101.9 (OCH₂O), 81.1 (C_{Ar}), 70.9 (OCH₂CH₂), 52.9 (CO₂CH₃), 18.7 (OCH₂CH₂), –1.3 (TMS–Si(CH₃)₃).

IR (film) ν_{max} /cm^{–1} 2951, 1735, 1614, 1461, 1439, 1256, 1082, 1038, 859, 838.

HRMS: (ESI⁺) Found [M + Na]⁺ = 444.9937; C₁₄H₁₉O₅INaSi requires 444.9939.

6-Iodo-4-(2-(trimethylsilyl)ethoxy)benzo[d][1,3]dioxole-5-carbaldehyde (383)¹⁴⁷**383**

To a solution of ester **382** (3.92 g, 10.0 mmol) in CH₂Cl₂ (80 mL) at -78 °C was added dropwise DIBAL-H (24 mL, 24.0 mmol, 1 M in toluene). The reaction mixture was stirred at rt for 1 h then CHCl₃ (50 mL) was added followed by sat. aq. Rochelle's salt (75 mL). The mixture was stirred vigorously overnight and the two layers were separated. The aqueous layer was washed with CHCl₃ (2 × 70 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was re-dissolved in CH₂Cl₂ (100 mL) and NaHCO₃ (2.52 g, 30.0 mmol) was added. The reaction mixture was cooled to 0 °C and Dess-Martin periodinane (6.36 g, 26.3 mmol) was added before being stirred at rt for 36 h. Water (100 mL) was added and the layers separated. The aqueous layer was washed with CH₂Cl₂ (2 × 100 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:EtOAc, 95:5) afforded the title compound as a pale yellow solid (2.27 g, 58% over 2 steps).

R_f = 0.8 (Pentane:EtOAc, 80:20).

m.p. 87 °C.

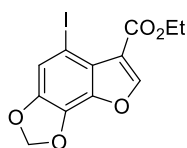
¹H NMR (CDCl₃, 400 MHz) δ = 10.08 (1H, s, CHO), 7.19 (1H, s, ArH), 6.04 (2H, s, OCH₂O), 4.43 – 4.32 (2H, m, OCH₂CH₂), 1.21 – 1.11 (2H, m, OCH₂CH₂), 0.05 (9H, s, TMS-Si(CH₃)₃).

^{13}C NMR (CDCl_3 , 110 MHz) δ = 190.3 (CHO), 153.8 (C_{Ar}), 145.5 (C_{Ar}), 138.2 (C_{Ar}), 122.9 (C_{Ar}), 116.3 (C_{ArH}), 102.4 (OCH_2O), 86.9 (C_{Ar}), 71.5 (OCH_2CH_2), 18.9 (OCH_2CH_2), -1.3 ($\text{TMS-Si}(\text{CH}_3)_3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 2897, 1688, 1601, 1467, 1330, 1264, 1251, 1087, 1039, 859, 838.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 393.0016$; $\text{C}_{13}\text{H}_{18}\text{O}_4\text{ISi}$ requires 393.0014.

Ethyl 5-iodo-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (384**)³⁶**



384

To a solution of aldehyde **381** (1.43 g, 4.90 mmol) and HBF_4 (68 μL , 5.00 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of ethyl diazoacetate (1.81 mL, 14.7 mmol) in CH_2Cl_2 (10 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 30 min and then concentrated *in vacuo* after nitrogen evolution had ceased. The crude residue was passed through a pad of silica (Pentane:EtOAc, 75:25) and the solvent collected and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 $^\circ\text{C}$. Ms_2O (2.55 g, 14.6 mmol) and pyridine (2.38 mL, 29.4 mmol) were added and the reaction mixture was stirred at rt for 16 h. Water (20 mL) was added and the layers separated. The aqueous layer was washed with CH_2Cl_2 (2×50 mL) and the combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane:EtOAc, 96:4) afforded the title compound as a white solid (779 mg, 54% over 2 steps).

R_f = 0.8 (Pentane:EtOAc, 50:50).

m.p. 88 $^\circ\text{C}$.

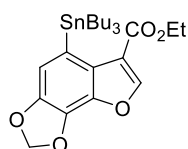
¹H NMR (CDCl₃, 400 MHz) δ = 8.06 (1H, s, ArH), 7.42 (1H, s, ArH), 6.11 (2H, s, OCH₂O), 4.41 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 1.42 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 162.4 (CO₂CH₂CH₃), 150.4 (C_{Ar}H), 147.8 (C_{Ar}), 139.2 (C_{Ar}), 132.4 (C_{Ar}), 124.9 (C_{Ar}), 118.3 (C_{Ar}H), 117.3 (C_{Ar}), 103.0 (OCH₂O), 71.8 (C_{Ar}), 61.4 (CO₂CH₂CH₃), 14.4 (CO₂CH₂CH₃).

IR (film) ν_{max} /cm⁻¹ 2983, 1650, 1500, 1476, 1425, 1258, 1087, 1047, 968.

HRMS: (ESI⁺) Found [M + Na]⁺ = 382.9386; C₁₂H₉O₅INa requires 382.9387.

Ethyl 5-(tributylstannyl)-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (**385**)⁸⁸



385

To a solution of benzofuran **385** (680 mg, 1.89 mmol) in 1,4-dioxane (17 mL) in a microwave vial was added successively Pd₂(dba)₃ (43 mg, 47 μ mol), JohnPhos (84 mg, 282 μ mol) and bis(tributyltin) (1.24 mL, 2.45 mmol). The reaction mixture was heated at 110 °C for 3.5 h, filtered through Celite[®] and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, Pentane:Et₃N, 99.5:0.5) afforded the title compound as a colourless oil (641 mg, 65%).

R_f = 0.8 (Pentane:Et₂O, 60:40).

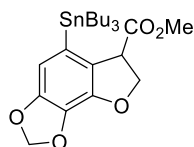
¹H NMR (CDCl₃, 400 MHz) δ = 8.15 (1H, s, ArH), 7.14 (1H, s, ArH), 6.07 (2H, s, OCH_AH_BO), 4.34 (2H, q, J = 7.1 Hz, CO₂CH₂CH₃), 1.56 – 1.43 (6H, m, SnCH₂CH₂CH₂CH₃ $\times$ 3), 1.38 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.35 – 1.25 (6H, m, SnCH₂CH₂CH₂CH₃ $\times$ 3), 1.16 – 0.97 (6H, m, SnCH₂CH₂CH₂CH₃ $\times$ 3), 0.86 (9H, t, J = 7.3 Hz, SnCH₂CH₂CH₂CH₃ $\times$ 3).

^{13}C NMR (CDCl_3 , 101 MHz) δ = 163.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 151.0 (C_{ArH}), 146.5 (C_{Ar}), 139.4 (C_{Ar}), 131.4 (C_{Ar}), 128.3 (C_{Ar}), 127.8 (C_{Ar}), 116.3 (C_{Ar}), 114.8 (C_{ArH}), 101.9 (OCH_2O), 60.6 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 29.3 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 27.6 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 14.6 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 13.9 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 12.8 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2920, 1719, 1481, 1254, 1136, 1049.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 547.1475$; $\text{C}_{24}\text{H}_{36}\text{O}_5\text{NaSn}$ requires 547.1477.

Methyl 5-(tributylstannyl)-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate
(386)¹³⁷



386

Mg turnings (297 mg, 12.3 mmol) were added to a solution of ester **385** (640 mg, 1.22 mmol) in MeOH (13 mL). After 1 h the reaction mixture was diluted with CHCl_3 (100 mL) and water (100 mL) and the two layers separated. The aqueous layer was washed with CH_2Cl_2 (2×100 mL) and the combined organic phase was washed with sat. aq. NaCl (100 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , Pentane: Et_2O : Et_3N , 94.5:5:0.5) afforded the title compound as a colourless oil (573 mg, 92%).

R_f = 0.2 (Pentane: Et_2O , 95:5).

^1H NMR (CDCl_3 , 400 MHz) δ = 6.51 (1H, s, ArH), 5.95 (1H, d, J = 1.5 Hz, $\text{OCH}_\text{A}\text{H}_\text{BO}$), 5.92 (1H, d, J = 1.5 Hz, $\text{OCH}_\text{AH}\text{BO}$), 4.92 (1H, dd, J = 9.2, 2.9 Hz, CH_AHB), 4.63 (1H, t, J = 9.1 Hz, CH_AHB), 4.06 (1H, dd, J = 8.9, 2.8 Hz, CH), 3.70 (3H, s, CO_2CH_3), 1.57 – 1.42 (6H,

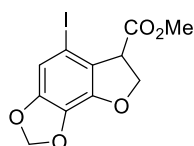
m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 1.38 – 1.28 (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 1.15 – 0.96 (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 0.89 (9H, t, $J = 7.3$ Hz, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 172.6$ (CO_2CH_3), 149.8 (C_{Ar}), 142.5 (C_{Ar}), 131.0 (C_{Ar}), 130.8 (C_{Ar}), 127.8 (C_{Ar}), 108.8 (C_{ArH}), 101.5 (OCH_2O), 75.2 (CH_AHB), 52.7 (CO_2CH_3), 48.9 (CH), 29.2 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 27.5 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 13.8 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$), 10.4 ($\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \times 3$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 1738, 1366, 1229, 1217, 1073.

HRMS: (ESI^+) Found $[\text{M} + \text{Na}]^+ = 525.1480$; $\text{C}_{23}\text{H}_{36}\text{O}_5\text{NaSn}$ requires 535.1477.

Methyl 5-iodo-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (**387**)



387

To a solution of stannane **386** (30 mg, 57 μmol) in CHCl_3 (1 mL) at 0 $^\circ\text{C}$ was added dropwise iodine (630 μL , 63 μmol , 0.1 M in CHCl_3). The reaction mixture was stirred for 20 min and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) was added followed by CHCl_3 (20 mL). The layers were separated and the aqueous layer was extracted with CHCl_3 (2×20 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , CH_2Cl_2) afforded the title compound as a white solid (20 mg, 100%).

m.p. 65 $^\circ\text{C}$.

R_f = 0.2 (Pentane:EtOAc, 95:5).

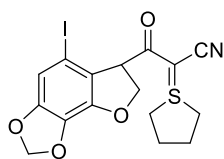
¹H NMR (CDCl₃, 400 MHz) δ = 6.80 (1H, s, ArH), 5.98 (1H, d, J = 1.3 Hz, OCH_AH_BO), 5.95 (1H, d, J = 1.4 Hz, OCH_AH_BO), 4.83 – 4.73 (2H, m, CH_AH_B and CH_AH_B), 4.12 (1H, dd, J = 9.0, 4.9 Hz, CH), 3.77 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 171.6 (CO₂CH₃), 151.0 (C_{Ar}), 142.5 (C_{Ar}), 131.6 (C_{Ar}), 126.2 (C_{Ar}), 111.1 (C_{Ar}H), 102.4 (OCH₂O), 80.3 (C_{Ar}), 75.2 (CH_AH_B), 52.8 (CO₂CH₃), 51.8 (CH).

IR (film) ν_{max} /cm⁻¹ 3000, 1738, 1650, 1470, 1377, 1217, 1203, 1077.

HRMS: (ESI⁺) Found [M + Na]⁺ = 370.9387; C₁₁H₉O₅NaI requires 370.9387.

3-(5-Iodo-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-yl)-3-oxo-2-(tetrahydro-1 λ -thiophen-1-ylidene)propanenitrile (389)^{118,134}



389

To a solution of ester **387** (33 mg, 9.5 μ mol) in CH₂Cl₂ (900 μ L) at 0 °C was added NaOH (19 mg, 475 μ mol) in MeOH (200 μ L). The reaction mixture was stirred at rt for 16 h then a phosphate buffer (20 mL, pH = 2.1, 0.1 M) was added followed by CH₂Cl₂ (30 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude solid was dissolved in DMF (1 mL) and salt **330** (56 mg, 270 μ mol) followed by T3P[®] (161 μ L, 270 μ mol, 50% in EtOAc) and DIPEA (141 μ L, 810 μ mol) were added. The reaction mixture was stirred for 16 h then water (20 mL) was added followed by EtOAc (30 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*.

Purification by flash column chromatography (SiO₂, CHCl₃:MeOH, 98:2) afforded the title compound as a colourless oil (14.1 mg, 35% over 2 steps).

R_f = 0.2 (Pentane:EtOAc, 95:5).

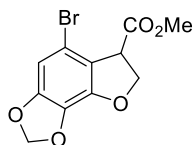
¹H NMR (CDCl₃, 400 MHz) δ = 6.74 (1H, s, ArH), 5.95 (1H, d, J = 1.4 Hz, OCH_AH_BO), 5.91 (1H, d, J = 1.5 Hz, OCH_AH_BO), 4.81 (1H, t, J = 8.6 Hz, CH), 4.64 – 4.54 (2H, m, CH_AH_B and CH_AH_B), 3.61 – 3.44 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B), 3.44 – 3.32 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B), 2.71 – 2.58 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B), 2.11 – 1.97 (2H, m, S(CH₂CH₂)_A(CH₂CH₂)_B).

¹³C NMR (CDCl₃, 110 MHz) δ = 188.7 (C(O)), 150.7 (C_{Ar}), 143.0 (C_{Ar}), 131.4 (C_{Ar}), 128.4 (C_{Ar}), 120.6 (CN), 110.7 (C_{Ar}H), 102.2 (OCH₂O), 80.0 (C_{Ar}), 76.3 (OCH_AH_B), 54.9 (C=S), 53.8 (CH), 44.6 (S(CH₂CH₂)_A(CH₂CH₂)_B), 43.7 (S(CH₂CH₂)_A(CH₂CH₂)_B), 28.8 (S(CH₂CH₂)_A(CH₂CH₂)_B), 28.7 (S(CH₂CH₂)_A(CH₂CH₂)_B).

IR (film) ν_{max} /cm⁻¹ 2921, 2167, 1648, 1595, 1472, 1423, 1251, 1075, 1035.

HRMS: (ESI⁺) Found [M + H]⁺ = 443.9759; C₁₆H₁₅O₄NSI requires 443.9761.

Methyl 5-bromo-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (**391**)



391

To a solution of stannane **386** (211 mg, 413 μ mol) in THF (5 mL) at 0 °C was added *N*-bromosuccinimide (81 mg, 454 μ mol). The reaction mixture was stirred for 1 h and sat. aq. Na₂S₂O₃ (10 mL) was added followed by EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 $\times$ 20 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*.

Purification by flash column chromatography (SiO₂, Pentane:Et₂O, 85:15) afforded the title compound as a colourless oil (122 mg, 98%).

*R*_f = 0.3 (Pentane:EtOAc, 80:20).

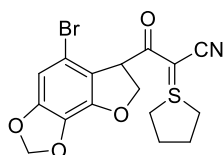
¹H NMR (CDCl₃, 400 MHz) δ = 6.60 (1H, s, ArH), 5.99 (1H, d, *J* = 1.3 Hz, OCH_AH_BO), 5.97 (1H, d, *J* = 1.4 Hz, OCH_AH_BO), 4.85 – 4.73 (2H, m, CH_AH_B and CH_AH_B), 4.23 (1H, dd, *J* = 9.0, 4.9 Hz, CH), 3.77 (3H, s, CO₂CH₃).

¹³C NMR (CDCl₃, 110 MHz) δ = 171.7 (CO₂CH₃), 151.1 (C_{Ar}), 143.1 (C_{Ar}), 130.5 (C_{Ar}), 122.0 (C_{Ar}), 110.1 (C_{Ar}), 105.5 (C_{Ar}H), 102.5 (OCH₂O), 75.9 (CH_AH_B), 52.8 (CO₂CH₃), 49.2 (CH).

IR (film) ν_{max} /cm⁻¹ 2954, 1739, 1653, 1472, 1435, 1256, 1196, 1078.

HRMS: (ESI⁺) Found [M + Na]⁺ = 322.9526; C₁₁H₉O₅NaBr requires 322.9526.

3-(5-Bromo-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-yl)-3-oxo-2-(tetrahydro-1 λ ⁴-thiophen-1-ylidene)propanenitrile (393)^{118,134}



393

To a solution of ester **391** (121 mg, 402 μ mol) in CH₂Cl₂ (4 mL) at 0 °C was added NaOH (80 mg, 2.00 mmol) in MeOH (1 mL). The reaction mixture was stirred at rt for 16 h then a phosphate buffer (20 mL, pH = 2.1, 0.1 M) was added followed by CH₂Cl₂ (30 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude solid was dissolved in DMF (2.5 mL) and salt **347** (252 mg, 1.21 mmol) followed by T3P[®] (720 μ L, 1.21 mmol, 50% in EtOAc) and DIPEA

(631 μ L, 1.21 mmol) were added. The reaction mixture was stirred for 16 h then water (20 mL) was added followed by EtOAc (30 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 , CHCl_3 :MeOH, 98:2) afforded the title compound as a colourless oil (41 mg, 26% over 2 steps).

$R_f = 0.2$ (Pentane:EtOAc, 95:5).

^1H NMR (CDCl_3 , 400 MHz) $\delta = 6.74$ (1H, s, ArH), 5.95 (1H, d, $J = 1.4$ Hz, $\text{OCH}_\text{A}\text{H}_\text{BO}$), 5.91 (1H, d, $J = 1.5$ Hz, $\text{OCH}_\text{A}\text{H}_\text{BO}$), 4.81 (1H, t, $J = 8.6$ Hz, CH), 4.64 – 4.54 (2H, m, $\text{CH}_\text{A}\text{H}_\text{B}$ and $\text{CH}_\text{A}\text{H}_\text{B}$), 3.61 – 3.44 (2H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 3.44 – 3.32 (2H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 2.71 – 2.58 (2H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 2.11 – 1.97 (2H, m, $\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$).

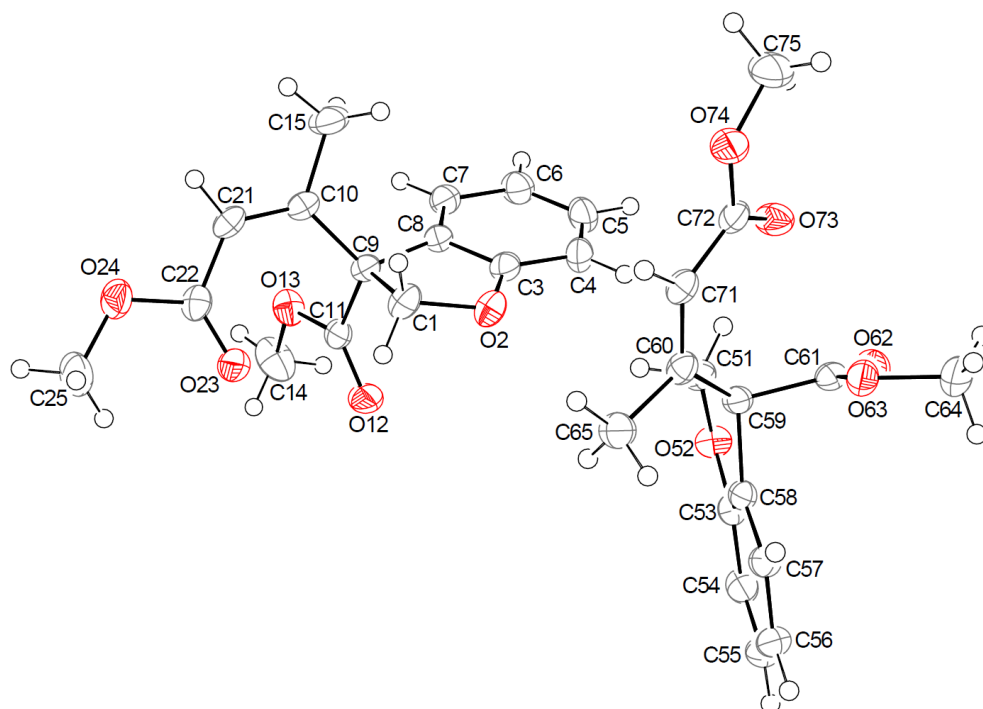
^{13}C NMR (CDCl_3 , 110 MHz) $\delta = 188.5$ ($\text{C}(\text{O})$), 150.6 (C_Ar), 143.5 (C_Ar), 130.3 (C_Ar), 124.1 (C_Ar), 120.4 (CN), 109.5 ($\text{C}_\text{Ar}\text{H}$), 105.0 (C_Ar), 102.2 (OCH_2O), 76.8 ($\text{OCH}_\text{A}\text{H}_\text{B}$), 54.8 ($\text{C}=\text{S}$), 51.4 (CH), 44.8 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 43.9 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 28.7 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$), 28.6 ($\text{S}(\text{CH}_2\text{CH}_2)_\text{A}(\text{CH}_2\text{CH}_2)_\text{B}$).

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2981, 2169, 1595, 1474, 1379, 1253, 1151, 1076, 755.

HRMS: (ESI^+) Found $[\text{M} + \text{H}]^+ = 395.9900$; $\text{C}_{16}\text{H}_{15}\text{O}_4\text{NSBr}$ requires 395.9900.

4.4 Supplementary CIF data

Methyl (Z)-3-(4-methoxy-4-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-3-carboxylate (157)



The structure contains two molecules in the asymmetric unit. The numbering scheme has been offset by 50 between the two molecules.

Table 1. Crystal data and structure refinement

Identification code	7002	
Empirical formula	C ₁₅ H ₁₆ O ₅	
Formula weight	276.29	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P c a 21	
Unit cell dimensions	a = 14.0413(3) Å	$\alpha = 90^\circ$

	$b = 7.0334(2) \text{ \AA}$	$\beta = 90^\circ$
	$c = 27.4163(9) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$2707.58(13) \text{ \AA}^3$	
Z	8	
Density (calculated)	1.355 Mg/m^3	
Absorption coefficient	0.851 mm^{-1}	
F(000)	1167.994	
Crystal size	$0.21 \times 0.18 \times 0.03 \text{ mm}^3$	
Theta range for data collection	$3.224 \text{ to } 76.653^\circ$	
Index ranges	$-10 \leq h \leq 17, -8 \leq k \leq 8, -34 \leq l \leq 33$	
Reflections collected	13755	
Independent reflections	5388 [R(int) = 0.027]	
Completeness to theta = 76.653°	99.6%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.72	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5386 / 1 / 362	
Goodness-of-fit on F^2	0.9983	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0355, wR2 = 0.0906$	
R indices (all data)	$R1 = 0.0391, wR2 = 0.0950$	
Absolute structure parameter	$-0.05(9)$	
Largest diff. peak and hole	$0.25 \text{ and } -0.18 \text{ e.\AA}^{-3}$	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U (eq)
C(1)	5946(2)	3292(3)	5000(1)	33
O(2)	6778(1)	3733(2)	5293(1)	35
C(3)	7029(1)	5560(3)	5189(1)	31
C(4)	7755(2)	6552(3)	5425(1)	37
C(5)	7943(2)	8380(3)	5266(1)	40
C(6)	7437(2)	9202(3)	4886(1)	37
C(7)	6718(1)	8191(3)	4651(1)	31

C(8)	6509(1)	6368(3)	4812(1)	26
C(9)	5844(1)	4843(3)	4605(1)	25
C(10)	4796(1)	5401(3)	4552(1)	27
C(11)	6354(1)	4275(3)	4133(1)	27
O(12)	7007(1)	3174(2)	4121(1)	40
O(13)	6063(1)	5331(2)	3755(1)	34
C(14)	6657(2)	5196(4)	3323(1)	50
C(15)	4480(2)	7148(3)	4822(1)	42
C(21)	4143(1)	4361(3)	4316(1)	30
C(22)	4310(1)	2520(3)	4076(1)	29
O(23)	5024(1)	1571(2)	4098(1)	37
O(24)	3533(1)	1990(2)	3824(1)	41
C(25)	3561(2)	124(4)	3604(1)	51
C(51)	8188(1)	1771(3)	6459(1)	28
O(52)	9065(1)	1376(2)	6196(1)	31
C(53)	9323(1)	−444(3)	6311(1)	26
C(54)	10080(1)	−1388(3)	6097(1)	32
C(55)	10267(1)	−3231(3)	6258(1)	34
C(56)	9721(1)	−4076(3)	6620(1)	32
C(57)	8974(1)	−3080(3)	6839(1)	29
C(58)	8773(1)	−1255(3)	6675(1)	24
C(59)	8093(1)	271(2)	6871(1)	24
C(60)	7051(1)	−315(3)	6938(1)	27
C(61)	8609(1)	912(3)	7333(1)	27
O(62)	9253(1)	2040(2)	7333(1)	36
O(63)	8345(1)	−106(2)	7721(1)	33
C(64)	8956(2)	83(4)	8146(1)	45
C(65)	6731(1)	−2083(3)	6675(1)	36
C(71)	6407(1)	712(3)	7181(1)	29
C(72)	6570(1)	2551(3)	7419(1)	29
O(73)	7263(1)	3552(2)	7375(1)	36
O(74)	5818(1)	3030(2)	7696(1)	40
C(75)	5842(2)	4906(4)	7915(1)	53

Table 3. Bond lengths [Å] and angles [°]

C(1)–O(2)	1.452(2)	C(1)–C(9)–C(10)	109.71(15)
C(1)–C(9)	1.543(3)	C(8)–C(9)–C(10)	116.26(15)
C(1)–H(12)	0.977	C(1)–C(9)–C(11)	111.40(16)
C(1)–H(11)	0.97	C(8)–C(9)–C(11)	102.17(14)
O(2)–C(3)	1.363(3)	C(10)–C(9)–C(11)	115.82(16)
C(3)–C(4)	1.395(3)	C(9)–C(10)–C(15)	116.57(17)

C(3)–C(8)	1.387(3)	C(9)–C(10)–C(21)	124.38(17)
C(4)–C(5)	1.383(3)	C(15)–C(10)–C(21)	118.83(18)
C(4)–H(41)	0.93	C(9)–C(11)–O(12)	123.23(19)
C(5)–C(6)	1.387(3)	C(9)–C(11)–O(13)	111.57(15)
C(5)–H(51)	0.928	O(12)–C(11)–O(13)	124.67(19)
C(6)–C(7)	1.394(3)	C(11)–O(13)–C(14)	114.89(18)
C(6)–H(61)	0.957	O(13)–C(14)–H(141)	104.8
C(7)–C(8)	1.388(3)	O(13)–C(14)–H(142)	107.4
C(7)–H(71)	0.964	H(141)–C(14)–H(142)	110
C(8)–C(9)	1.531(3)	O(13)–C(14)–H(143)	111.7
C(9)–C(10)	1.529(2)	H(141)–C(14)–H(143)	109.6
C(9)–C(11)	1.532(3)	H(142)–C(14)–H(143)	112.8
C(10)–C(15)	1.502(3)	C(10)–C(15)–H(152)	108.8
C(10)–C(21)	1.339(3)	C(10)–C(15)–H(153)	111
C(11)–O(12)	1.201(2)	H(152)–C(15)–H(153)	110.1
C(11)–O(13)	1.338(3)	C(10)–C(15)–H(151)	110.5
O(13)–C(14)	1.450(2)	H(152)–C(15)–H(151)	108.4
C(14)–H(141)	0.963	H(153)–C(15)–H(151)	108
C(14)–H(142)	0.973	C(10)–C(21)–C(22)	125.97(17)
C(14)–H(143)	0.965	C(10)–C(21)–H(211)	117.6
C(15)–H(152)	0.958	C(22)–C(21)–H(211)	116.4
C(15)–H(153)	0.995	C(21)–C(22)–O(23)	126.63(18)
C(15)–H(151)	0.962	C(21)–C(22)–O(24)	110.17(17)
C(21)–C(22)	1.472(3)	O(23)–C(22)–O(24)	123.19(19)
C(21)–H(211)	0.933	C(22)–O(24)–C(25)	116.40(18)
C(22)–O(23)	1.205(2)	O(24)–C(25)–H(252)	105.5
C(22)–O(24)	1.344(2)	O(24)–C(25)–H(253)	108
O(24)–C(25)	1.445(3)	H(252)–C(25)–H(253)	111.5
C(25)–H(252)	0.984	O(24)–C(25)–H(251)	110.9
C(25)–H(253)	0.996	H(252)–C(25)–H(251)	111.5
C(25)–H(251)	0.948	H(253)–C(25)–H(251)	109.4
C(51)–O(52)	1.453(2)	O(52)–C(51)–C(59)	107.68(15)
C(51)–C(59)	1.553(3)	O(52)–C(51)–H(512)	108.7
C(51)–H(512)	0.961	C(59)–C(51)–H(512)	113.1
C(51)–H(511)	0.977	O(52)–C(51)–H(511)	108.2
O(52)–C(53)	1.367(2)	C(59)–C(51)–H(511)	109.3
C(53)–C(54)	1.383(3)	H(512)–C(51)–H(511)	109.8
C(53)–C(58)	1.385(3)	C(51)–O(52)–C(53)	106.79(15)
C(54)–C(55)	1.394(3)	O(52)–C(53)–C(54)	123.68(19)
C(54)–H(541)	0.926	O(52)–C(53)–C(58)	113.89(17)
C(55)–C(56)	1.387(3)	C(54)–C(53)–C(58)	122.40(18)
C(55)–H(551)	0.925	C(53)–C(54)–C(55)	117.21(19)
C(56)–C(57)	1.398(3)	C(53)–C(54)–H(541)	120.2

C(56)–H(561)	0.968	C(55)–C(54)–H(541)	122.5
C(57)–C(58)	1.389(3)	C(54)–C(55)–C(56)	121.37(19)
C(57)–H(571)	0.96	C(54)–C(55)–H(551)	119.9
C(58)–C(59)	1.534(2)	C(56)–C(55)–H(551)	118.8
C(59)–C(60)	1.531(2)	C(55)–C(56)–C(57)	120.49(19)
C(59)–C(61)	1.527(3)	C(55)–C(56)–H(561)	119.5
C(60)–C(65)	1.506(3)	C(57)–C(56)–H(561)	120
C(60)–C(71)	1.336(3)	C(56)–C(57)–C(58)	118.44(19)
C(61)–O(62)	1.202(2)	C(56)–C(57)–H(571)	120.6
C(61)–O(63)	1.335(3)	C(58)–C(57)–H(571)	120.9
O(63)–C(64)	1.455(2)	C(57)–C(58)–C(53)	120.06(17)
C(64)–H(641)	0.978	C(57)–C(58)–C(59)	131.30(18)
C(64)–H(642)	0.992	C(53)–C(58)–C(59)	108.11(16)
C(64)–H(643)	0.969	C(58)–C(59)–C(51)	99.63(15)
C(65)–H(652)	0.963	C(58)–C(59)–C(60)	116.65(14)
C(65)–H(653)	0.977	C(51)–C(59)–C(60)	110.65(15)
C(65)–H(651)	0.987	C(58)–C(59)–C(61)	101.59(14)
C(71)–C(72)	1.467(3)	C(51)–C(59)–C(61)	111.24(15)
C(71)–H(711)	0.941	C(60)–C(59)–C(61)	115.72(16)
C(72)–O(73)	1.207(2)	C(59)–C(60)–C(65)	116.79(16)
C(72)–O(74)	1.343(2)	C(59)–C(60)–C(71)	124.15(17)
O(74)–C(75)	1.450(3)	C(65)–C(60)–C(71)	118.86(17)
C(75)–H(752)	0.94	C(59)–C(61)–O(62)	123.56(18)
C(75)–H(753)	0.933	C(59)–C(61)–O(63)	111.73(15)
C(75)–H(751)	0.968	O(62)–C(61)–O(63)	124.18(18)
O(2)–C(1)–C(9)	108.15(16)	C(61)–O(63)–C(64)	115.20(17)
O(2)–C(1)–H(12)	106.6	O(63)–C(64)–H(641)	107.4
C(9)–C(1)–H(12)	110	O(63)–C(64)–H(642)	112.7
O(2)–C(1)–H(11)	108.7	H(641)–C(64)–H(642)	111.7
C(9)–C(1)–H(11)	109.4	O(63)–C(64)–H(643)	107.6
H(12)–C(1)–H(11)	113.8	H(641)–C(64)–H(643)	107.2
C(1)–O(2)–C(3)	107.12(16)	H(642)–C(64)–H(643)	110
O(2)–C(3)–C(4)	124.34(19)	C(60)–C(65)–H(652)	110.2
O(2)–C(3)–C(8)	113.92(18)	C(60)–C(65)–H(653)	109.1
C(4)–C(3)–C(8)	121.7(2)	H(652)–C(65)–H(653)	109.7
C(3)–C(4)–C(5)	117.3(2)	C(60)–C(65)–H(651)	109.6
C(3)–C(4)–H(41)	120.8	H(652)–C(65)–H(651)	111.2
C(5)–C(4)–H(41)	121.9	H(653)–C(65)–H(651)	107
C(4)–C(5)–C(6)	121.8(2)	C(60)–C(71)–C(72)	126.39(17)
C(4)–C(5)–H(51)	119.5	C(60)–C(71)–H(711)	119.2
C(6)–C(5)–H(51)	118.8	C(72)–C(71)–H(711)	114.4
C(5)–C(6)–C(7)	120.4(2)	C(71)–C(72)–O(73)	126.53(18)
C(5)–C(6)–H(61)	121	C(71)–C(72)–O(74)	110.50(16)

C(7)–C(6)–H(61)	118.6	O(73)–C(72)–O(74)	122.96(19)
C(6)–C(7)–C(8)	118.5(2)	C(72)–O(74)–C(75)	116.34(17)
C(6)–C(7)–H(71)	121	O(74)–C(75)–H(752)	109.6
C(8)–C(7)–H(71)	120.5	O(74)–C(75)–H(753)	104.7
C(7)–C(8)–C(3)	120.33(18)	H(752)–C(75)–H(753)	112.3
C(7)–C(8)–C(9)	131.12(18)	O(74)–C(75)–H(751)	110.1
C(3)–C(8)–C(9)	108.09(17)	H(752)–C(75)–H(751)	110.1
C(1)–C(9)–C(8)	100.30(15)	H(753)–C(75)–H(751)	109.8

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic

displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	29(1)	33(1)	39(1)	8(1)	−4(1)	1(1)
O(2)	31(1)	38(1)	34(1)	7(1)	−6(1)	3(1)
C(3)	27(1)	36(1)	28(1)	−3(1)	1(1)	6(1)
C(4)	32(1)	50(1)	29(1)	−6(1)	−8(1)	4(1)
C(5)	32(1)	47(1)	41(1)	−15(1)	−5(1)	−4(1)
C(6)	32(1)	33(1)	45(1)	−6(1)	−1(1)	−4(1)
C(7)	28(1)	29(1)	35(1)	−2(1)	−1(1)	1(1)
C(8)	23(1)	29(1)	26(1)	−3(1)	0(1)	2(1)
C(9)	22(1)	24(1)	29(1)	1(1)	1(1)	2(1)
C(10)	23(1)	29(1)	30(1)	3(1)	3(1)	4(1)
C(11)	18(1)	31(1)	33(1)	−5(1)	1(1)	−4(1)
O(12)	23(1)	44(1)	52(1)	−16(1)	4(1)	3(1)
O(13)	32(1)	44(1)	26(1)	−1(1)	4(1)	−7(1)
C(14)	53(1)	63(2)	33(1)	−7(1)	16(1)	−20(1)
C(15)	28(1)	38(1)	61(2)	−9(1)	6(1)	8(1)
C(21)	18(1)	36(1)	37(1)	5(1)	2(1)	2(1)
C(22)	21(1)	37(1)	30(1)	3(1)	2(1)	−6(1)
O(23)	26(1)	36(1)	49(1)	−9(1)	−4(1)	0(1)
O(24)	25(1)	54(1)	44(1)	−6(1)	−4(1)	−4(1)
C(25)	33(1)	59(2)	60(2)	−18(1)	−5(1)	−13(1)
C(51)	25(1)	27(1)	33(1)	0(1)	1(1)	0(1)
O(52)	30(1)	29(1)	34(1)	3(1)	6(1)	0(1)
C(53)	25(1)	26(1)	27(1)	−3(1)	−3(1)	−2(1)
C(54)	26(1)	39(1)	31(1)	−6(1)	3(1)	−3(1)
C(55)	28(1)	38(1)	36(1)	−10(1)	1(1)	6(1)
C(56)	30(1)	28(1)	39(1)	−3(1)	−3(1)	5(1)
C(57)	26(1)	27(1)	32(1)	−2(1)	−1(1)	0(1)

C(58)	19(1)	27(1)	28(1)	−5(1)	−1(1)	−1(1)
C(59)	21(1)	22(1)	28(1)	−2(1)	0(1)	1(1)
C(60)	21(1)	26(1)	33(1)	2(1)	−3(1)	−2(1)
C(61)	20(1)	30(1)	31(1)	−4(1)	1(1)	4(1)
O(62)	24(1)	38(1)	45(1)	−11(1)	−1(1)	−5(1)
O(63)	29(1)	41(1)	28(1)	−2(1)	−3(1)	4(1)
C(64)	43(1)	59(2)	33(1)	−4(1)	−12(1)	14(1)
C(65)	25(1)	32(1)	52(1)	−8(1)	−1(1)	−5(1)
C(71)	18(1)	34(1)	35(1)	2(1)	−1(1)	−1(1)
C(72)	20(1)	37(1)	31(1)	−1(1)	−3(1)	5(1)
O(73)	28(1)	32(1)	48(1)	−8(1)	5(1)	−2(1)
O(74)	25(1)	52(1)	42(1)	−12(1)	5(1)	3(1)
C(75)	35(1)	66(2)	59(2)	−26(1)	7(1)	7(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$).

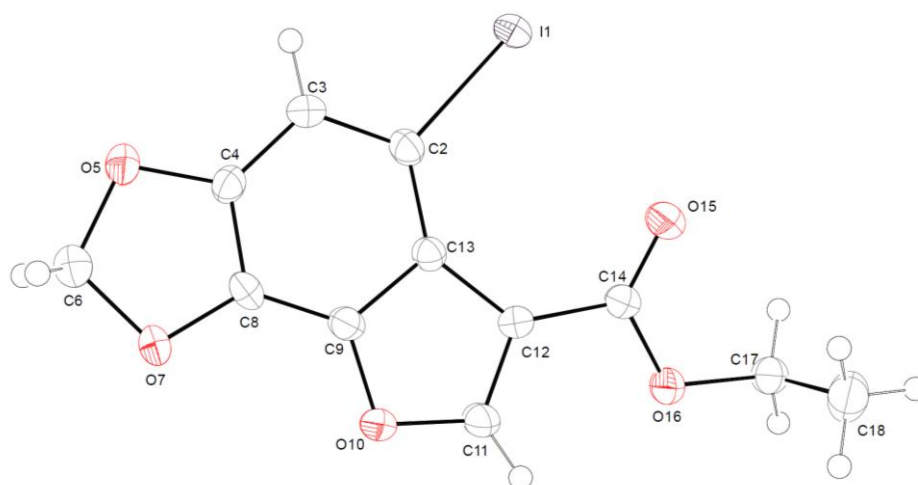
	x	y	z	U(eq)
H(12)	5398	3328	5220	41
H(11)	6042	2068	4844	39
H(41)	8099	5993	5677	44
H(51)	8422	9079	5416	49
H(61)	7561	10481	4785	43
H(71)	6361	8753	4387	37
H(152)	3800	7228	4807	63
H(153)	4694	7109	5168	63
H(151)	4742	8272	4674	62
H(211)	3522	4830	4304	37
H(252)	3163	217	3309	76
H(253)	3291	−800	3842	77
H(251)	4195	−230	3526	77
H(512)	8212	3054	6578	34
H(511)	7657	1633	6231	34
H(541)	10447	−788	5863	38
H(551)	10772	−3904	6127	41
H(561)	9871	−5356	6725	38
H(571)	8612	−3643	7099	35
H(652)	6047	−2189	6687	54
H(653)	7019	−3193	6830	54
H(651)	6962	−2052	6335	54
H(711)	5776	269	7202	35
H(752)	5257	5522	7863	81

H(753)	5960	4685	8245	80
H(751)	6357	5646	7776	80
H(141)	6350	5999	3086	74
H(142)	7279	5710	3407	75
H(143)	6688	3911	3202	74
H(641)	8610	−438	8425	66
H(642)	9160	1414	8205	67
H(643)	9509	−717	8094	68

Table 6. Hydrogen bonds [$\text{\AA}$ and $^\circ$].

D–H...A	d(D–H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
C(21)–H(211)...O(12)#1	0.93	2.6	3.506(3)	164
C(25)–H(253)...O(12)#2	1	2.57	3.486(3)	152

Ethyl 5-iodo-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate (384)



Crystal system	Triclinic
Space group	P $\bar{1}$
Unit cell dimensions	$a = 7.7465(5) \text{ \AA}$ $\alpha = 84.138(5)^\circ$ $b = 8.1535(5) \text{ \AA}$ $\beta = 68.292(6)^\circ$ $c = 10.1679(6) \text{ \AA}$ $\gamma = 80.401(5)^\circ$
Volume	$587.74(7) \text{ \AA}^3$
Z	2
Density (calculated)	2.035 Mg/m^3
Absorption coefficient	21.542 mm^{-1}
F(000)	348
Crystal size	$0.04 \times 0.02 \times 0.02 \text{ mm}^3$
Theta range for data collection	4.685 to 77.115° .
Index ranges	$-8 \leq h \leq 9$, $-8 \leq k \leq 10$, $-12 \leq l \leq 12$
Reflections collected	4664
Independent reflections	2433 [R(int) = 0.031]
Completeness to theta = 73.259°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.65 and 0.46
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2431 / 0 / 163
Goodness-of-fit on F^2	0.9991
Final R indices [I > 2sigma(I)]	R1 = 0.0297, wR2 = 0.0722
R indices (all data)	R1 = 0.0337, wR2 = 0.0756
Largest diff. peak and hole	0.80 and $-0.62 \text{ e.\AA}^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	1879(1)	2124(1)	11804(1)	30
C(2)	3204(6)	3490(5)	9937(4)	25
C(3)	4591(6)	2529(5)	8893(5)	26
C(4)	5530(6)	3329(5)	7619(4)	24

O(5)	6905(5)	2599(4)	6454(4)	37
C(6)	7433(7)	3926(6)	5410(5)	33
O(7)	6249(5)	5441(4)	5981(3)	33
C(8)	5163(6)	5007(5)	7329(4)	24
C(9)	3799(6)	5929(5)	8365(4)	23
O(10)	3282(4)	7608(4)	8272(3)	28
C(11)	1897(6)	7995(5)	9539(5)	29
C(12)	1505(6)	6643(5)	10438(4)	23
C(13)	2782(5)	5218(5)	9700(4)	21
C(14)	57(6)	6795(5)	11867(5)	26
O(15)	−135(6)	5758(4)	12820(4)	48
O(16)	−1038(4)	8285(4)	11983(3)	29
C(17)	−2540(6)	8591(6)	13344(5)	31
C(18)	−1885(7)	9379(7)	14314(6)	41

Table 3. Bond lengths [Å] and angles [°]

I(1)–C(2)	2.099(4)	C(3)–C(4)–C(8)	123.8(4)
C(2)–C(3)	1.393(6)	O(5)–C(4)–C(8)	109.7(4)
C(2)–C(13)	1.409(6)	C(4)–O(5)–C(6)	105.8(3)
C(3)–C(4)	1.386(6)	O(5)–C(6)–O(7)	108.1(3)
C(3)–H(31)	0.927	O(5)–C(6)–H(61)	109.8
C(4)–O(5)	1.375(5)	O(7)–C(6)–H(61)	108.8
C(4)–C(8)	1.375(6)	O(5)–C(6)–H(62)	109.9
O(5)–C(6)	1.434(5)	O(7)–C(6)–H(62)	109.3
C(6)–O(7)	1.442(5)	H(61)–C(6)–H(62)	110.8
C(6)–H(61)	0.972	C(6)–O(7)–C(8)	105.3(3)
C(6)–H(62)	0.97	C(4)–C(8)–O(7)	111.1(4)
O(7)–C(8)	1.363(5)	C(4)–C(8)–C(9)	117.6(4)
C(8)–C(9)	1.365(6)	O(7)–C(8)–C(9)	131.2(4)
C(9)–O(10)	1.365(5)	C(8)–C(9)–O(10)	125.5(4)
C(9)–C(13)	1.414(5)	C(8)–C(9)–C(13)	122.4(4)
O(10)–C(11)	1.363(5)	O(10)–C(9)–C(13)	112.1(4)
C(11)–C(12)	1.358(5)	C(9)–O(10)–C(11)	105.5(3)
C(11)–H(111)	0.917	O(10)–C(11)–C(12)	112.7(4)
C(12)–C(13)	1.462(5)	O(10)–C(11)–H(111)	122.8
C(12)–C(14)	1.473(6)	C(12)–C(11)–H(111)	124.5
C(14)–O(15)	1.202(5)	C(11)–C(12)–C(13)	106.6(4)
C(14)–O(16)	1.349(5)	C(11)–C(12)–C(14)	121.3(4)
O(16)–C(17)	1.454(5)	C(13)–C(12)–C(14)	132.1(4)
C(17)–C(18)	1.500(7)	C(12)–C(13)–C(9)	103.1(3)
C(17)–H(171)	0.979	C(12)–C(13)–C(2)	139.3(4)

C(17)–H(172)	0.966	C(9)–C(13)–C(2)	117.6(4)
C(18)–H(181)	0.962	C(12)–C(14)–O(15)	125.6(4)
C(18)–H(182)	0.961	C(12)–C(14)–O(16)	110.8(3)
C(18)–H(183)	0.962	O(15)–C(14)–O(16)	123.7(4)
I(1)–C(2)–C(3)	113.9(3)	C(14)–O(16)–C(17)	116.4(3)
I(1)–C(2)–C(13)	125.3(3)	O(16)–C(17)–C(18)	111.0(4)
C(3)–C(2)–C(13)	120.8(4)	O(16)–C(17)–H(171)	108.1
C(2)–C(3)–C(4)	117.8(4)	C(18)–C(17)–H(171)	109
C(2)–C(3)–H(31)	121.9	O(16)–C(17)–H(172)	109.8
C(4)–C(3)–H(31)	120.4	C(18)–C(17)–H(172)	110.2
C(3)–C(4)–O(5)	126.6(4)	H(171)–C(17)–H(172)	108.7

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic

displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	37(1)	22(1)	24(1)	5(1)	–3(1)	–6(1)
C(2)	25(2)	25(2)	21(2)	1(2)	–5(2)	–7(2)
C(3)	31(2)	19(2)	27(2)	2(2)	–9(2)	–2(2)
C(4)	26(2)	22(2)	23(2)	–5(2)	–5(2)	–3(2)
O(5)	41(2)	26(2)	27(2)	–4(1)	5(1)	–3(1)
C(6)	40(2)	30(2)	25(2)	–2(2)	–6(2)	–4(2)
O(7)	40(2)	28(2)	20(2)	–1(1)	3(1)	–4(1)
C(8)	25(2)	28(2)	17(2)	3(2)	–6(2)	–8(2)
C(9)	25(2)	22(2)	22(2)	3(2)	–8(2)	–5(2)
O(10)	33(2)	20(1)	25(2)	3(1)	–3(1)	–2(1)
C(11)	28(2)	24(2)	26(2)	4(2)	–4(2)	3(2)
C(12)	27(2)	19(2)	23(2)	0(2)	–8(2)	–2(2)
C(13)	20(2)	22(2)	21(2)	0(2)	–6(2)	–4(2)
C(14)	28(2)	23(2)	23(2)	1(2)	–7(2)	–1(2)
O(15)	60(2)	31(2)	28(2)	6(1)	4(2)	9(2)
O(16)	29(2)	26(2)	24(2)	0(1)	–2(1)	0(1)
C(17)	27(2)	27(2)	28(2)	0(2)	0(2)	0(2)
C(18)	43(3)	42(3)	35(3)	–10(2)	–7(2)	–8(2)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$).

	x	y	z	U(eq)
H(31)	4897	1394	9037	32
H(61)	8731	4058	5208	40
H(62)	7253	3699	4555	40
H(111)	1306	9059	9748	35
H(171)	−3567	9348	13178	37
H(172)	−2993	7558	13773	37
H(181)	−2899	9566	15207	62
H(182)	−1461	10415	13881	62
H(183)	−857	8645	14460	62

Methyl 5-iodo-6,7-dihydro-[1,3]dioxolo[4,5-*g*]benzofuran-6-carboxylate

(387)

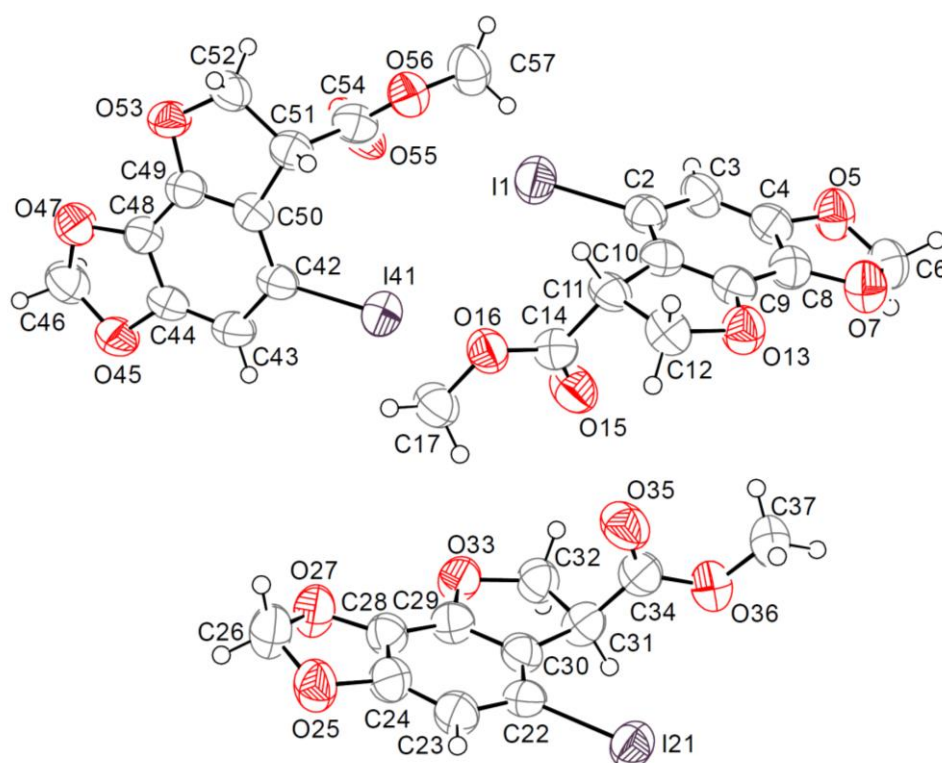


Table 1. Crystal data and structure refinement

Identification code	7306
Empirical formula	C ₁₁ H ₉ IO ₅
Formula weight	348.09
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P $\bar{1}$
Unit cell dimensions	a = 4.86700(10) Å α =
99.5462(18)°	b = 13.7255(3) Å β =
	92.0699(19)°
	c = 26.2381(5) Å γ = 90.148(2)°
Volume	1727.29(6) Å ³
Z	6
Density (calculated)	2.008 Mg/m ³
Absorption coefficient	21.959 mm ⁻¹
F(000)	1008
Crystal size	0.36 × 0.06 × 0.02 mm ³
Theta range for data collection	3.930 to 76.215°.
Index ranges	−6 ≤ h ≤ 6, −17 ≤ k ≤ 16, −32 ≤ l ≤ 32
Reflections collected	41081
Independent reflections	7146 [R(int) = 0.064]
Completeness to theta = 74.691°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.64 and 0.04
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7146 / 0 / 461
Goodness-of-fit on F ²	0.9999
Final R indices [I > 2sigma(I)]	R1 = 0.0966, wR2 = 0.2704
R indices (all data)	R1 = 0.0985, wR2 = 0.2721
Largest diff. peak and hole	4.06 and −0.92 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	4506(2)	3107(1)	2867(1)	73
C(2)	4080(20)	2962(8)	2062(5)	56
C(3)	2240(30)	3588(8)	1842(5)	61
C(4)	1990(20)	3395(8)	1309(5)	57
O(5)	345(19)	3893(7)	997(3)	70
C(6)	370(30)	3329(10)	499(5)	68
O(7)	2714(19)	2672(7)	483(3)	69
C(8)	3390(20)	2666(9)	995(4)	59
C(9)	5110(20)	2075(8)	1223(5)	58
C(10)	5480(20)	2229(8)	1755(5)	59
C(11)	7300(20)	1426(8)	1895(4)	54
C(12)	8280(30)	923(9)	1360(5)	63
O(13)	6628(19)	1320(6)	970(3)	66
C(14)	5670(20)	713(8)	2161(4)	56
O(15)	3330(19)	493(7)	2050(4)	78
O(16)	7177(17)	352(6)	2512(3)	61
C(17)	5710(30)	−337(10)	2764(5)	69
I(21)	4742(2)	−4142(1)	588(1)	67
C(22)	4630(20)	−3829(7)	1395(4)	55
C(23)	6420(30)	−4347(8)	1692(5)	61
C(24)	6320(30)	−4086(9)	2213(5)	64
O(25)	7800(20)	−4479(7)	2586(3)	73
C(26)	7310(30)	−3869(12)	3057(5)	76
O(27)	4870(20)	−3281(7)	2981(3)	73
C(28)	4560(20)	−3364(8)	2459(4)	56
C(29)	2870(20)	−2889(8)	2162(4)	57
C(30)	2930(20)	−3105(8)	1626(4)	56
C(31)	1090(20)	−2400(9)	1400(4)	60
C(32)	−220(30)	−1825(9)	1888(5)	64
O(33)	1125(18)	−2142(6)	2338(3)	64
C(34)	2610(20)	−1730(9)	1110(5)	61
O(35)	4790(20)	−1353(7)	1247(4)	79
O(36)	1230(20)	−1576(7)	680(4)	79
C(37)	2560(40)	−964(12)	378(6)	92
I(41)	−648(2)	1468(1)	3783(1)	71
C(42)	−390(20)	1617(7)	4586(4)	55

C(43)	−2070(30)	1016(8)	4845(5)	64
C(44)	−1820(30)	1188(8)	5377(5)	60
O(45)	−3110(20)	707(6)	5712(3)	70
C(46)	−2600(30)	1297(10)	6217(5)	74
O(47)	−161(19)	1878(7)	6180(3)	68
C(48)	−70(30)	1890(8)	5657(4)	59
C(49)	1540(20)	2464(8)	5399(4)	57
C(50)	1330(20)	2338(8)	4870(4)	53
C(51)	3120(20)	3093(8)	4691(5)	59
C(52)	4550(30)	3596(9)	5211(5)	63
O(53)	3287(17)	3203(6)	5625(3)	61
C(54)	1420(30)	3849(8)	4456(5)	63
O(55)	−880(20)	4082(9)	4576(6)	108
O(56)	2722(18)	4225(6)	4099(3)	66
C(57)	1240(30)	4927(11)	3855(6)	78

Table 3. Bond lengths [Å] and angles [°]

I(1)–C(2)	2.090(12)	C(11)–C(12)–O(13)	106.9(9)
C(2)–C(3)	1.414(16)	C(11)–C(12)–H(122)	110.1
C(2)–C(10)	1.379(17)	O(13)–C(12)–H(122)	110.1
C(3)–C(4)	1.380(17)	C(11)–C(12)–H(121)	110.3
C(3)–H(31)	0.926	O(13)–C(12)–H(121)	109.7
C(4)–O(5)	1.384(14)	H(122)–C(12)–H(121)	109.7
C(4)–C(8)	1.384(16)	C(12)–O(13)–C(9)	107.2(9)
O(5)–C(6)	1.405(16)	C(11)–C(14)–O(15)	123.3(11)
C(6)–O(7)	1.453(15)	C(11)–C(14)–O(16)	112.2(9)
C(6)–H(62)	0.967	O(15)–C(14)–O(16)	124.4(11)
C(6)–H(61)	0.969	C(14)–O(16)–C(17)	113.5(9)
O(7)–C(8)	1.372(14)	O(16)–C(17)–H(171)	109
C(8)–C(9)	1.361(16)	O(16)–C(17)–H(173)	110.1
C(9)–C(10)	1.383(17)	H(171)–C(17)–H(173)	109.5
C(9)–O(13)	1.367(14)	O(16)–C(17)–H(172)	109.1
C(10)–C(11)	1.497(16)	H(171)–C(17)–H(172)	109.3
C(11)–C(12)	1.550(17)	H(173)–C(17)–H(172)	109.7
C(11)–C(14)	1.529(15)	I(21)–C(22)–C(23)	118.7(8)
C(11)–H(111)	0.979	I(21)–C(22)–C(30)	119.9(8)
C(12)–O(13)	1.457(15)	C(23)–C(22)–C(30)	121.4(10)
C(12)–H(122)	0.963	C(22)–C(23)–C(24)	116.0(10)
C(12)–H(121)	0.969	C(22)–C(23)–H(231)	121.8
C(14)–O(15)	1.189(14)	C(24)–C(23)–H(231)	122.2
C(14)–O(16)	1.319(14)	C(23)–C(24)–O(25)	127.8(11)

O(16)–C(17)	1.442(14)	C(23)–C(24)–C(28)	123.7(11)
C(17)–H(171)	0.964	O(25)–C(24)–C(28)	108.4(10)
C(17)–H(173)	0.961	C(24)–O(25)–C(26)	106.1(10)
C(17)–H(172)	0.959	O(25)–C(26)–O(27)	108.0(10)
I(21)–C(22)	2.092(11)	O(25)–C(26)–H(262)	109.8
C(22)–C(23)	1.415(16)	O(27)–C(26)–H(262)	109.7
C(22)–C(30)	1.371(16)	O(25)–C(26)–H(261)	109.6
C(23)–C(24)	1.357(17)	O(27)–C(26)–H(261)	109.9
C(23)–H(231)	0.928	H(262)–C(26)–H(261)	109.9
C(24)–O(25)	1.377(14)	C(26)–O(27)–C(28)	103.9(9)
C(24)–C(28)	1.403(16)	C(24)–C(28)–O(27)	110.6(10)
O(25)–C(26)	1.401(16)	C(24)–C(28)–C(29)	118.5(10)
C(26)–O(27)	1.462(17)	O(27)–C(28)–C(29)	130.9(10)
C(26)–H(262)	0.973	C(28)–C(29)–C(30)	120.2(10)
C(26)–H(261)	0.971	C(28)–C(29)–O(33)	125.9(10)
O(27)–C(28)	1.359(14)	C(30)–C(29)–O(33)	113.8(10)
C(28)–C(29)	1.355(16)	C(29)–C(30)–C(22)	120.1(10)
C(29)–C(30)	1.389(16)	C(29)–C(30)–C(31)	108.8(10)
C(29)–O(33)	1.364(13)	C(22)–C(30)–C(31)	131.0(10)
C(30)–C(31)	1.500(15)	C(30)–C(31)–C(32)	101.9(9)
C(31)–C(32)	1.549(17)	C(30)–C(31)–C(34)	113.2(9)
C(31)–C(34)	1.495(18)	C(32)–C(31)–C(34)	112.0(10)
C(31)–H(311)	0.976	C(30)–C(31)–H(311)	109.5
C(32)–O(33)	1.460(14)	C(32)–C(31)–H(311)	110.2
C(32)–H(321)	0.97	C(34)–C(31)–H(311)	109.8
C(32)–H(322)	0.974	C(31)–C(32)–O(33)	107.6(9)
C(34)–O(35)	1.196(15)	C(31)–C(32)–H(321)	109.4
C(34)–O(36)	1.339(15)	O(33)–C(32)–H(321)	109.6
O(36)–C(37)	1.416(18)	C(31)–C(32)–H(322)	110.2
C(37)–H(372)	0.96	O(33)–C(32)–H(322)	110.6
C(37)–H(371)	0.962	H(321)–C(32)–H(322)	109.5
C(37)–H(373)	0.96	C(32)–O(33)–C(29)	107.5(9)
I(41)–C(42)	2.083(12)	C(31)–C(34)–O(35)	124.5(11)
C(42)–C(43)	1.425(15)	C(31)–C(34)–O(36)	112.6(11)
C(42)–C(50)	1.393(15)	O(35)–C(34)–O(36)	122.9(12)
C(43)–C(44)	1.378(17)	C(34)–O(36)–C(37)	116.1(12)
C(43)–H(431)	0.927	O(36)–C(37)–H(372)	109.3
C(44)–O(45)	1.356(13)	O(36)–C(37)–H(371)	109.8
C(44)–C(48)	1.383(16)	H(372)–C(37)–H(371)	109.4
O(45)–C(46)	1.446(17)	O(36)–C(37)–H(373)	109.2
C(46)–O(47)	1.442(16)	H(372)–C(37)–H(373)	109.7
C(46)–H(461)	0.973	H(371)–C(37)–H(373)	109.4
C(46)–H(462)	0.965	I(41)–C(42)–C(43)	120.0(8)

O(47)–C(48)	1.377(14)	I(41)–C(42)–C(50)	119.7(8)
C(48)–C(49)	1.379(16)	C(43)–C(42)–C(50)	120.2(10)
C(49)–C(50)	1.371(16)	C(42)–C(43)–C(44)	115.9(10)
C(49)–O(53)	1.367(13)	C(42)–C(43)–H(431)	122
C(50)–C(51)	1.497(14)	C(44)–C(43)–H(431)	122.1
C(51)–C(52)	1.560(17)	C(43)–C(44)–O(45)	127.7(10)
C(51)–C(54)	1.523(17)	C(43)–C(44)–C(48)	123.8(10)
C(51)–H(511)	0.978	O(45)–C(44)–C(48)	108.4(10)
C(52)–O(53)	1.444(13)	C(44)–O(45)–C(46)	105.5(9)
C(52)–H(521)	0.97	O(45)–C(46)–O(47)	106.6(10)
C(52)–H(522)	0.964	O(45)–C(46)–H(461)	110
C(54)–O(55)	1.206(16)	O(47)–C(46)–H(461)	109.9
C(54)–O(56)	1.320(15)	O(45)–C(46)–H(462)	110
O(56)–C(57)	1.427(15)	O(47)–C(46)–H(462)	110.7
C(57)–H(572)	0.959	H(461)–C(46)–H(462)	109.5
C(57)–H(571)	0.96	C(46)–O(47)–C(48)	102.8(9)
C(57)–H(573)	0.959	C(44)–C(48)–O(47)	111.5(10)
I(1)–C(2)–C(3)	119.3(9)	C(44)–C(48)–C(49)	119.3(11)
I(1)–C(2)–C(10)	119.6(8)	O(47)–C(48)–C(49)	129.2(10)
C(3)–C(2)–C(10)	121.0(11)	C(48)–C(49)–C(50)	119.4(10)
C(2)–C(3)–C(4)	114.8(10)	C(48)–C(49)–O(53)	125.7(10)
C(2)–C(3)–H(31)	122.5	C(50)–C(49)–O(53)	114.8(10)
C(4)–C(3)–H(31)	122.7	C(42)–C(50)–C(49)	121.4(10)
C(3)–C(4)–O(5)	126.7(10)	C(42)–C(50)–C(51)	130.1(10)
C(3)–C(4)–C(8)	124.9(11)	C(49)–C(50)–C(51)	108.5(9)
O(5)–C(4)–C(8)	108.3(10)	C(50)–C(51)–C(52)	101.5(9)
C(4)–O(5)–C(6)	106.0(9)	C(50)–C(51)–C(54)	111.6(9)
O(5)–C(6)–O(7)	107.7(10)	C(52)–C(51)–C(54)	109.9(9)
O(5)–C(6)–H(62)	110	C(50)–C(51)–H(511)	111
O(7)–C(6)–H(62)	109.8	C(52)–C(51)–H(511)	111.5
O(5)–C(6)–H(61)	109.8	C(54)–C(51)–H(511)	111
O(7)–C(6)–H(61)	110	C(51)–C(52)–O(53)	107.7(9)
H(62)–C(6)–H(61)	109.5	C(51)–C(52)–H(521)	109.6
C(6)–O(7)–C(8)	103.6(9)	O(53)–C(52)–H(521)	110.1
C(4)–C(8)–O(7)	110.9(10)	C(51)–C(52)–H(522)	110.1
C(4)–C(8)–C(9)	118.3(11)	O(53)–C(52)–H(522)	109.8
O(7)–C(8)–C(9)	130.8(11)	H(521)–C(52)–H(522)	109.6
C(8)–C(9)–C(10)	119.9(11)	C(52)–O(53)–C(49)	106.9(9)
C(8)–C(9)–O(13)	125.6(11)	C(51)–C(54)–O(55)	124.1(11)
C(10)–C(9)–O(13)	114.5(10)	C(51)–C(54)–O(56)	113.1(10)
C(9)–C(10)–C(2)	121.0(11)	O(55)–C(54)–O(56)	122.7(12)
C(9)–C(10)–C(11)	107.7(10)	C(54)–O(56)–C(57)	116.3(10)
C(2)–C(10)–C(11)	130.9(11)	O(56)–C(57)–H(572)	109.6

C(10)–C(11)–C(12)	102.5(9)	O(56)–C(57)–H(571)	109.7
C(10)–C(11)–C(14)	110.7(9)	H(572)–C(57)–H(571)	109.3
C(12)–C(11)–C(14)	111.9(9)	O(56)–C(57)–H(573)	109.6
C(10)–C(11)–H(111)	110.5	H(572)–C(57)–H(573)	109.3
C(12)–C(11)–H(111)	110.2	H(571)–C(57)–H(573)	109.3
C(14)–C(11)–H(111)	110.9	C(11)–C(12)–O(13)	106.9(9)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic

displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U11	U22	U33	U23	U13	U12
I(1)	88(1)	73(1)	57(1)	11(1)	−2(1)	8(1)
C(2)	49(5)	52(5)	69(6)	15(5)	−5(4)	−5(4)
C(3)	67(7)	54(6)	66(6)	19(5)	9(5)	11(5)
C(4)	52(5)	55(5)	68(6)	16(5)	9(5)	−2(4)
O(5)	76(5)	78(5)	60(4)	18(4)	9(4)	21(4)
C(6)	58(6)	81(8)	70(7)	27(6)	1(5)	6(6)
O(7)	75(5)	73(5)	61(4)	16(4)	11(4)	25(4)
C(8)	51(5)	65(6)	61(6)	14(5)	4(4)	−3(5)
C(9)	55(6)	52(5)	69(6)	13(5)	3(5)	−5(4)
C(10)	57(6)	54(6)	66(6)	13(5)	−2(5)	−16(5)
C(11)	47(5)	52(5)	67(6)	19(4)	4(4)	−10(4)
C(12)	57(6)	64(6)	72(7)	19(5)	7(5)	5(5)
O(13)	72(5)	68(5)	60(4)	13(4)	4(4)	12(4)
C(14)	48(5)	55(5)	64(6)	7(4)	0(4)	2(4)
O(15)	65(5)	79(6)	98(7)	38(5)	−7(5)	−8(4)
O(16)	63(4)	61(4)	63(4)	20(3)	−2(3)	0(3)
C(17)	68(7)	66(7)	76(7)	22(6)	2(6)	−7(6)
I(21)	77(1)	70(1)	53(1)	4(1)	1(1)	3(1)
C(22)	60(6)	45(5)	58(5)	6(4)	1(4)	−7(4)
C(23)	64(6)	56(6)	64(6)	10(5)	2(5)	11(5)
C(24)	67(7)	60(6)	64(6)	13(5)	−9(5)	7(5)
O(25)	82(6)	73(5)	65(5)	18(4)	−3(4)	23(4)
C(26)	82(9)	89(9)	60(7)	17(6)	−5(6)	12(7)
O(27)	84(6)	79(5)	54(4)	10(4)	0(4)	23(5)
C(28)	58(6)	56(5)	55(5)	11(4)	5(4)	2(4)
C(29)	54(6)	55(5)	61(6)	7(4)	4(4)	5(4)
C(30)	57(6)	53(5)	61(6)	16(4)	−2(4)	−9(4)
C(31)	52(6)	63(6)	61(6)	3(5)	−5(4)	11(5)
C(32)	61(6)	68(7)	64(6)	15(5)	−3(5)	0(5)

O(33)	70(5)	63(4)	58(4)	4(3)	−3(3)	16(4)
C(34)	60(6)	57(6)	66(6)	10(5)	−3(5)	14(5)
O(35)	69(6)	78(6)	97(7)	35(5)	−11(5)	−17(5)
O(36)	96(7)	80(6)	66(5)	26(4)	−5(5)	−2(5)
C(37)	141(16)	79(9)	61(7)	25(6)	−11(8)	2(9)
I(41)	79(1)	75(1)	58(1)	10(1)	−5(1)	0(1)
C(42)	51(5)	45(5)	69(6)	12(4)	0(4)	−5(4)
C(43)	66(7)	52(5)	72(7)	9(5)	1(5)	−12(5)
C(44)	64(6)	48(5)	69(6)	15(5)	4(5)	−12(5)
O(45)	75(5)	65(5)	72(5)	17(4)	7(4)	−20(4)
C(46)	82(9)	66(7)	76(8)	20(6)	15(6)	−5(6)
O(47)	72(5)	75(5)	60(4)	16(4)	9(4)	−13(4)
C(48)	65(6)	50(5)	61(6)	9(4)	−6(5)	0(5)
C(49)	56(6)	51(5)	65(6)	10(4)	−1(5)	−1(4)
C(50)	46(5)	52(5)	62(6)	13(4)	6(4)	2(4)
C(51)	51(5)	56(6)	69(6)	12(5)	6(5)	−3(4)
C(52)	58(6)	61(6)	73(7)	22(5)	5(5)	−11(5)
O(53)	61(4)	57(4)	63(4)	7(3)	3(3)	−15(3)
C(54)	63(7)	52(6)	73(7)	7(5)	9(5)	1(5)
O(55)	69(6)	102(8)	177(12)	85(8)	30(7)	26(6)
O(56)	68(5)	65(5)	67(5)	18(4)	3(4)	6(4)
C(57)	92(10)	73(8)	73(8)	20(6)	8(7)	23(7)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$).

	x	y	z	U(eq)
H(31)	1298	4089	2040	73
H(62)	545	3758	244	82
H(61)	−1318	2947	428	82
H(111)	8867	1708	2114	65
H(122)	10198	1069	1328	76
H(121)	8010	214	1318	76
H(171)	6982	−629	2984	103
H(173)	4291	−2	2969	103
H(172)	4908	−846	2507	103
H(231)	7567	−4839	1538	73
H(262)	8883	−3433	3161	92
H(261)	6988	−4273	3320	92
H(311)	−315	−2771	1172	72
H(321)	80	−1122	1902	76
H(322)	−2189	−1963	1878	76

H(372)	1306	−826	108	138
H(371)	3129	−354	592	138
H(373)	4141	−1298	228	138
H(431)	−3249	537	4665	76
H(461)	−4144	1730	6308	88
H(462)	−2319	873	6473	88
H(511)	4458	2779	4449	70
H(521)	4287	4305	5254	75
H(522)	6485	3452	5211	75
H(572)	2456	5452	3805	117
H(571)	−226	5196	4068	117
H(573)	488	4611	3526	117

Table 6. Hydrogen bonds [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
C(17)–H(172)...O(33)	0.96	2.53	3.353(17)	144
C(23)–H(231)...O(5)#1	0.93	2.49	3.411(17)	171
C(26)–H(262)...O(47)#2	0.97	2.57	3.372(17)	139
C(32)–H(322)...O(35)#3	0.97	2.43	3.036(17)	120
C(43)–H(431)...O(45)#4	0.93	2.52	3.436(17)	172

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