A Palladium-Catalysed Allylic Alkylation Cascade: Towards the Total Synthesis of Thromboxanes A_2 and B_2

by
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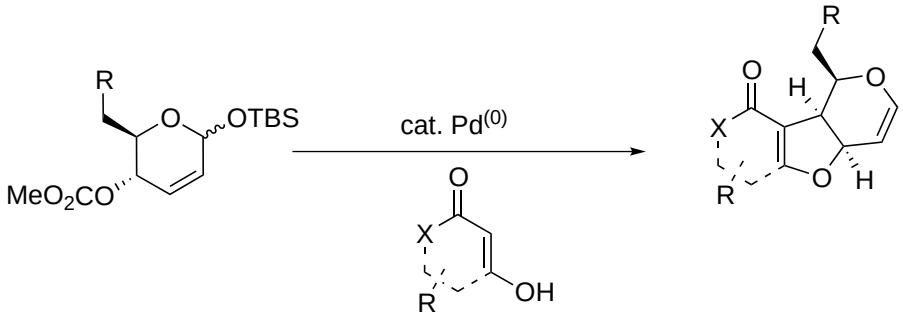
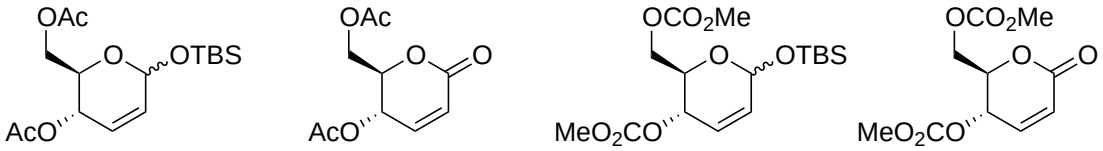
Abstract

The design and development of new chemical reactions is crucial to the ongoing success of organic synthesis research. In this work the scope and utility of a recently discovered regioselective palladium-catalysed allylic alkylation (Pd-AA) cascade was explored through increasing the range of non-symmetric pyran-based bis-electrophiles and β-dicarbonyl bis-nucleophiles that can be used in this reaction.



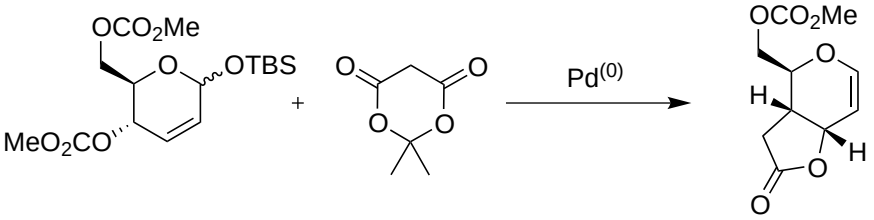
Four differentially protected tri-substituted dihydropyrans based on glucose were synthesised, including 2,3-unsaturated silyl glycosides and α,β-unsaturated lactones. These substrates were assessed as bis-electrophiles in the Pd-AA cascade. One silyl glycoside bis-electrophile, possessing a carbonate leaving group, was shown to be an excellent substrate for reaction with a number of cyclic bis-nucleophiles. Furthermore, a series of regioisomeric methylated 4-hydroxycoumarins were synthesised, tested and found to be equally effective as bis-nucleophiles in the Pd-AA cascade with both acyclic and cyclic bis-electrophiles.



Advances made during this research include a novel Ferrier reaction with silanol nucleophiles, which was found to produce silyl glycosides, albeit in low yields. Additionally, several Perlin aldehydes were generated by the Ferrier-type hydrolysis of 3,4,6-tri-*O*-acetyl-D-glucal and led to the discovery of discrepant structural assignments in the literature. Furthermore, a ^{13}C NMR shielding template was generated as a tool for the stereochemical assignment of tri-substituted dihydropyrans.

An extended variant of the Pd-AA cascade was achieved by employment of the bis-nucleophile Meldrum's acid with the optimal tri-substituted bis-electrophile in the presence of H_2O. The reaction afforded a γ-butyrolactone that could serve as a potential intermediate *en route* to the synthesis of the biologically interesting com-

pounds thromboxanes A_2 and B_2. This extended Pd-AA cascade, although currently unoptimised, is capable of performing five synthetic transformations in one-pot and holds the potential to improve on the current syntheses of the thromboxanes.



Acknowledgements

"Knowledge is in the end based on acknowledgement"
- Ludwig Wittgenstein

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Finally, I would like to thank my parents for everything over the last 23 years. I could not have achieved this without your support. It's no *New York Times* Best Seller, Mum, but it'll do.

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Glossary

AAA	asymmetric allylic alkylation
Ac	acetyl
acac	acetylacetonate
AD	assymetric dihydroxylation
a.k.a.	also known as
Allyl	CH_2CHCH_2-
apt.	apparent
aq.	aqueous
Ar	aromatic
Bn	benzyl
Boc	-$COOC(CH)_3$
br	broad
Bu	butyl
Bz	benzoyl
conc.	concentrated
COSY	correlation spectroscopy
d	doublet
dba	dibenzylidene acetone
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
Degr.	degradation
DIBALH	diisobutylaluminium hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
eq.	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
et al.	*et alia* (and others)

GFP	green fluorescent protein
glyme	1,2-dimethoxyethane
HMBC	heteronuclear multiple-bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
IC	inhibitory concentration
in vacuo	in vacuum
^{i}Pr	*iso*-propyl (-CH(CH_3)$_2$)
IR	infrared
L	ligand
LA	Lewis acid
LG	leaving group
m	multiplet
M	metal
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MK10	Montmorillonite clay
m	multiplet
m.p.	melting point
Ms	methanesulfonyl (a.k.a. mesyl)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu or Nuc	nucleophile
obs.	obscured
OD	optical density
O/N	overnight
P	protecting group
PCC	pyridinium chlorochromate
Pd-AA	palladium-catalysed allylic alkylation
PG	prostaglandin
PGG_2	prostaglandin endoperoxide G_2
PGH_2	prostaglandin endoperoxide H_2
PGI_2	prostacyclin

Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	Pyridinium *para*-toluenesulfonate
Pyr	pyridyl
q	quartet
quant.	quantitative
quint.	quintet
R_f	retention factor
rt	room temperature
s	singlet
sat.	saturated
SCPS	School of Chemical and Physical Sciences, Victoria University of Wellington
SM	starting material
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
TXA_2	thromboxane A_2
TXB_2	thromboxane B_2
UV	ultraviolet
vide infra	see below
vide supra	see above
Vis	visible
viz.	*videlicet* (namely)
w.r.t.	with respect to

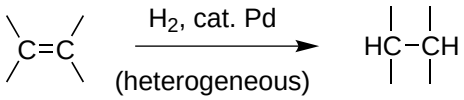
Chapter 1

Introduction

1.1 Palladium in Organic Synthesis

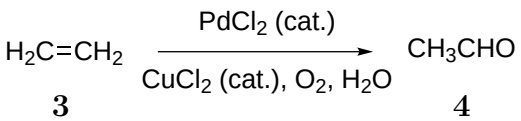
1.1.1 Introduction

Discovered by Wollaston in 1803 and named after the asteroid Pallas, palladium is a remarkable metal and has become one of the most useful tools in organic synthesis.[1] Since palladium is an expensive noble metal, its derivatives have mainly been employed as catalysts. Invention of the Wacker process in 1959 and its subsequent development represent one of the most important milestones in the history of organopalladium chemistry. The catalytic reduction or alkenes (Scheme 1.1) and Wacker oxidation of ethene (Scheme 1.2) demonstrated that palladium and its compounds can serve as catalysts for both oxidation and reduction.[2]



1 **2**

Scheme 1.1 Catalytic hydrogenation of alkenes with palladium



3 **4**

Scheme 1.2 Wacker oxidation of ethene

1.1.2 π-Allyl Palladium Complexes

Palladium has a great affinity for non-polar π-compounds such as alkenes, alkynes and even arenes.[2] Upon complexation with transition metals, π-compounds are rendered more reactive toward nucleophilic reagents.

Allyl palladium derivatives readily react with a wide variety of nucleophilic reagents to undergo nucleophilic substitution reactions, with palladium serving as a leaving group surrogate. The reaction of butadiene with $PdCl_2$ reported in 1957 most likely represents the first synthesis of allyl palladium complexes.[3] Early investigations of allyl palladiums mainly dealt with structural features and other purely organometallic aspects and it wasn't until Tsuji's work in 1965 that these compounds became prevalent in organic synthesis.[2]

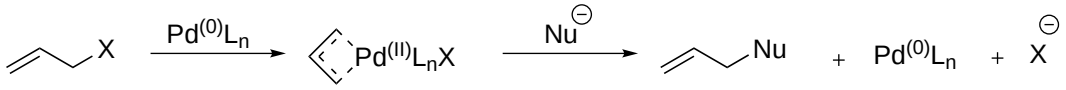
1.1.3 The Tsuji-Trost Reaction

Tsuji's extension of the Wacker process and proposal of its mechanism (nucleophilic attack of H_2O on ethylene complexed with Pd or Pd-complexed ethylene) led to the discovery of carbon-carbon bond formation between π-allylpalladium chloride (**5**) and diethyl sodiomalonate (**6**) to give the allylated malonate (**7**).[4] This reaction remained stoichiometric in palladium for a few years whereupon its catalytic version was discovered and subsequently extensively developed by Tsuji,[5] Trost,[6] and many others (Scheme 1.3). This reaction is now widely referred to as the Tsuji-Trost reaction and has become one of the most widely investigated areas of organopalladium chemistry.[2]

Original Stoichiometric Version

5 **6** **7**

Catalytic Version

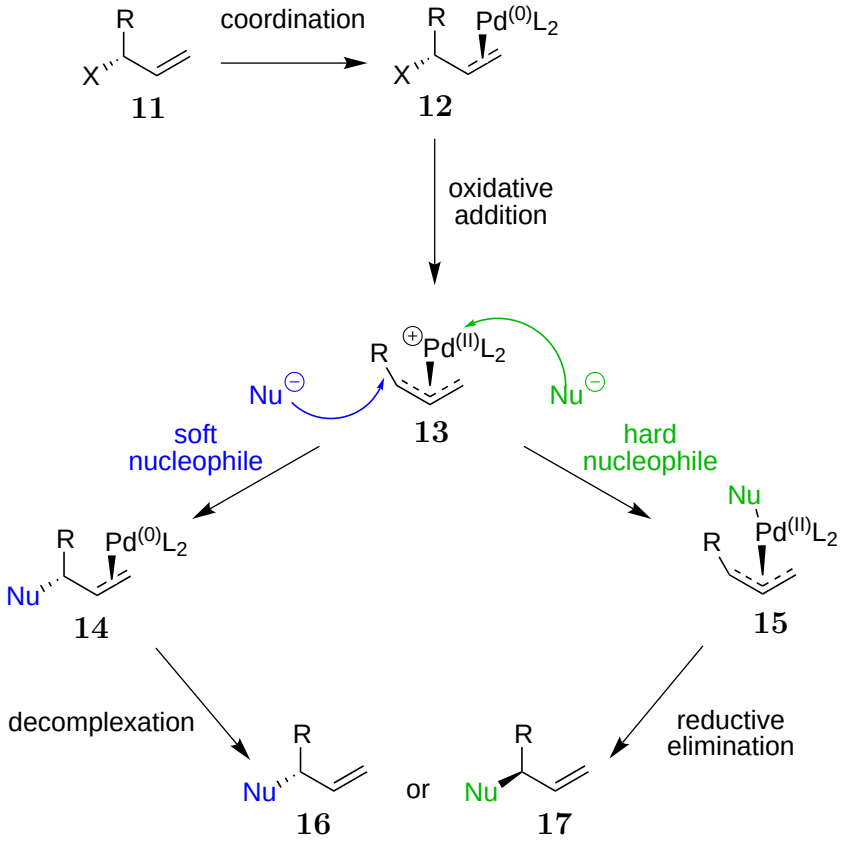


8 **9** **10**

Scheme 1.3 Development of the Tsuji-Trost reaction

Oxidative addition of allyl electrophiles to Pd has been shown to proceed with inversion.[7] This process is thought to involve π-complexation followed by intramolecular nucleophilic displacement of a leaving group by palladium with inversion. It is

now understood that there are two general mechanistic classes within Tsuji-Trost reactions and these are distinguished by the nature of the nucleophile.[8] "Hard" nucleophiles, defined as those derived from conjugate acids with pKa > 25, involve attack at Pd which is followed by reductive elimination to provide allylic substitution with overall inversion.[9] On the other hand, "soft" nucleophiles, defined as those derived from conjugate acids with pKa < 25, normally attack directly at the π-allyl ligands proceeding via inversion at the site of substitution and leading to substitution of allylic electrophiles with overall retention (Scheme 1.4).[6]

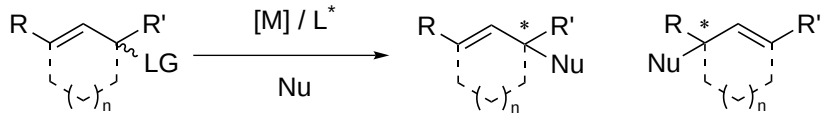


Scheme 1.4 Asymmetric induction in Tsuji-Trost reactions with the use of soft and hard nucleophiles

1.1.4 Asymmetric Allylic Alkylation Reactions

Transition metal-catalysed asymmetric allylic alkylation (AAA) reactions (Scheme 1.5) are enantioselective extensions of the Tsuji-Trost reaction and are unique and versatile for several reasons. The presence of a carbon-carbon double bond in the overall product is very advantageous to total synthesis as it provides great potential for further functionalisation.[10] These reactions also have numerous modes of enantiodiscrimination, which compares to most asymmetric reactions where there is only one. In AAA reactions both the electrophile and nucleophile may be prochiral in

which case the stereochemistry of positions resulting from either or both substrates can be controlled. Furthermore, AAA reactions have the potential to form many different types of bonds with the same catalyst. The electrophile is always an allylic carbon; however the nucleophilic centre may be H, N, O, S, C, etc., thereby providing access to C-H, C-N, C-O, C-S, C-C bonds from the same reaction type. Finally, the reaction may be altered to undergo net inversion or net retention mechanisms by changing the metal centre of the catalyst. While palladium involves a net retention via a double inversion path with "soft" nucleophiles and a net inversion path with "hard" nucleophiles (*vide supra*), many other metals have been found to catalyse allylic alkylation, e.g. Rh, Ru, Ir, Mo, W and Cu, by different mechanisms and with alternative stereochemical consequences.

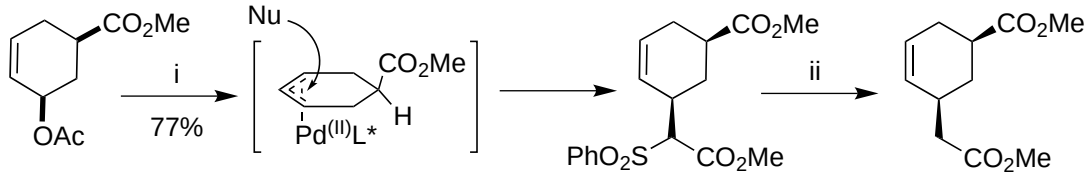


18 **19** **20**

M = Pd, Rh, Ir, Mo etc.
L* = chiral ligands

Scheme 1.5 Transition metal catalysed asymmetric allylic alkylation reaction

The first example of enantioselective palladium-catalysed allylic substitution with a stabilised nucleophile was reported in 1977.[11] When the racemic mixture **21** was treated with the sodium salt of methyl phenylsulfonylacetate in the presence of a palladium catalyst composed of $Pd(PPh_3)_4$ and chiral ligand (+)-DIOP, alkylation product **22** was produced in a 77% yield and desulfonylation of this product afforded **23** with 24% ee (Scheme 1.6). Since this achievement, a vast amount of work has been carried out to exploit the asymmetric capability of allylic alkylations.[8,12]



21 **22** **23**

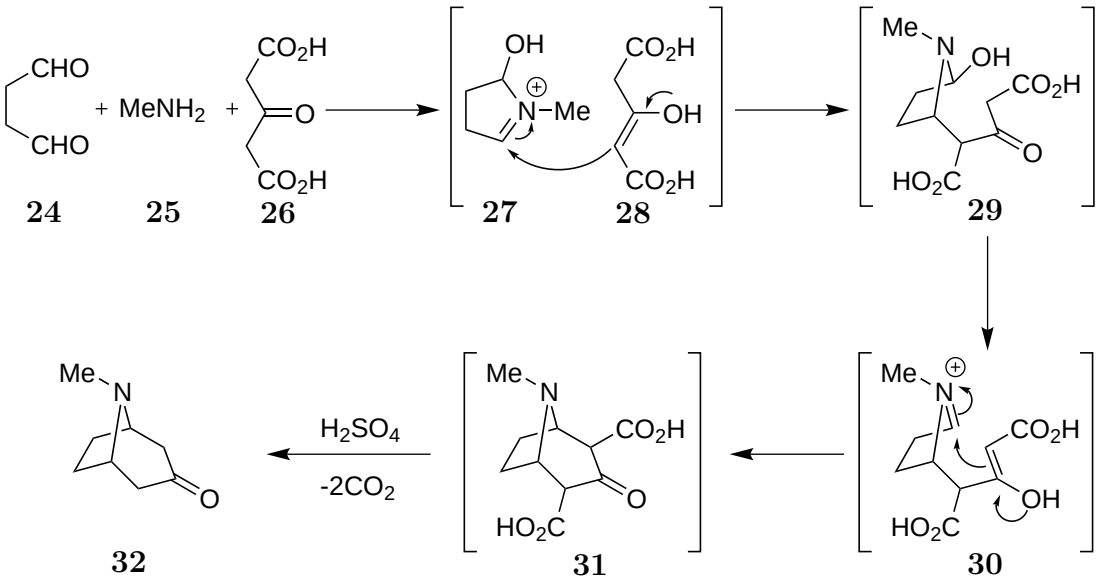
Reagents and Conditions: i) $NaCH(SO_2Ph)CO_2Me$, $Pd(PPh_3)_4$, (+)-DIOP; ii) 6% Na(Hg), Na_2HPO_4, MeOH.

Scheme 1.6 Enantioselective palladium-catalysed allylic substitution with a stabilised nucleophile

1.2 Allylic Alkylation Cascades

1.2.1 Cascade Reactions

In recent years, examination of biosynthesis as a means to guide synthetic strategy (a.k.a. biomimetic synthesis) has led to the use of cascade reactions.[13] Nature's synthetic transformations typically avoid protecting groups and many are cascade reaction sequences. Cascade (also known as domino, tandem, or sequential) reactions have been defined to be chemical processes in which at least two chemical reactions take place in a single operation without a change in the reaction conditions and where the latter transformations take place at the functionalities produces by the former bond forming reactions.[14,15] The benefits of cascade reactions are undeniable and include atom economy, alongside economies of time, labour, resource and waste management.[16] Additionally they are often accompanied by high levels of stereoselectivity.[13] Therefore, these impressive reactions can be considered a stepping stone on the path to "green chemistry" because the savings involved when several transformations are carried out in one synthetic operation can be significant.[17] These can include reducing several individual steps to a single process, with only one solvent system, workup procedure and purification.



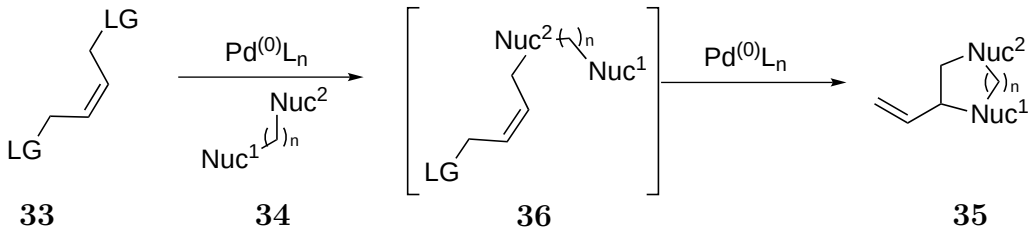
Scheme 1.7 Robinson's one pot synthesis of tropinone (**32**)

Cascade reactions not only improve the practical efficiency of a synthetic scheme but also enhance the aesthetic appeal of a proposed synthetic route by enabling the generation of complex molecules in a concise fashion. It is not surprising then that cascade reactions, whether intentionally or otherwise, have attracted the attention of organic chemists since the early days of total synthesis. Robinson's 1917 one pot synthesis of tropinone[18] (**32**) set the groundwork for the field of cascade reactions

(Scheme 1.7).[17] His elegant synthesis constructs tropinone from succindialdehyde (**24**), methylamine (**25**), and either acetone or its dicarboxylic acid derivative (**26**), through the consecutive action of both an intermolecular and intramolecular Mannich reaction, followed by double decarboxylation.

1.2.2 Palladium-Catalysed Allylic Alkylation (Pd-AA) Cascades

Palladium catalysts have proven to be reliable tools in a variety of cascade reactions. A generic Pd-AA cascade is one where an allyl bis-electrophile (**33**) is employed alongside a bis-nucleophile (**34**) in the presence of a $Pd^{(0)}$ species. As shown below, these annulation reactions can afford an array of vinyl substituted ring systems (**35**) (Scheme 1.8).



33 **34** **36** **35**

Scheme 1.8 General Pd-AA cascade

The problem with these reactions is in differentiating the two nucleophilic and electrophilic centres in order to gain regiochemical control. Figure 1.1 demonstrates the large number of regiochemical possibilities that can occur in the initial step alone of a Pd-AA cascade. In theory, either nucleophilic centre may attack one of two allylic systems at either terminus. The number of possibilities is further compounded by the second addition. Typically, this challenge is overcome by employment of symmetric bis-electrophiles or bis-nucleophiles, thereby reducing the number of product possibilities. However, this solution will not be appropriate for many synthetic targets.

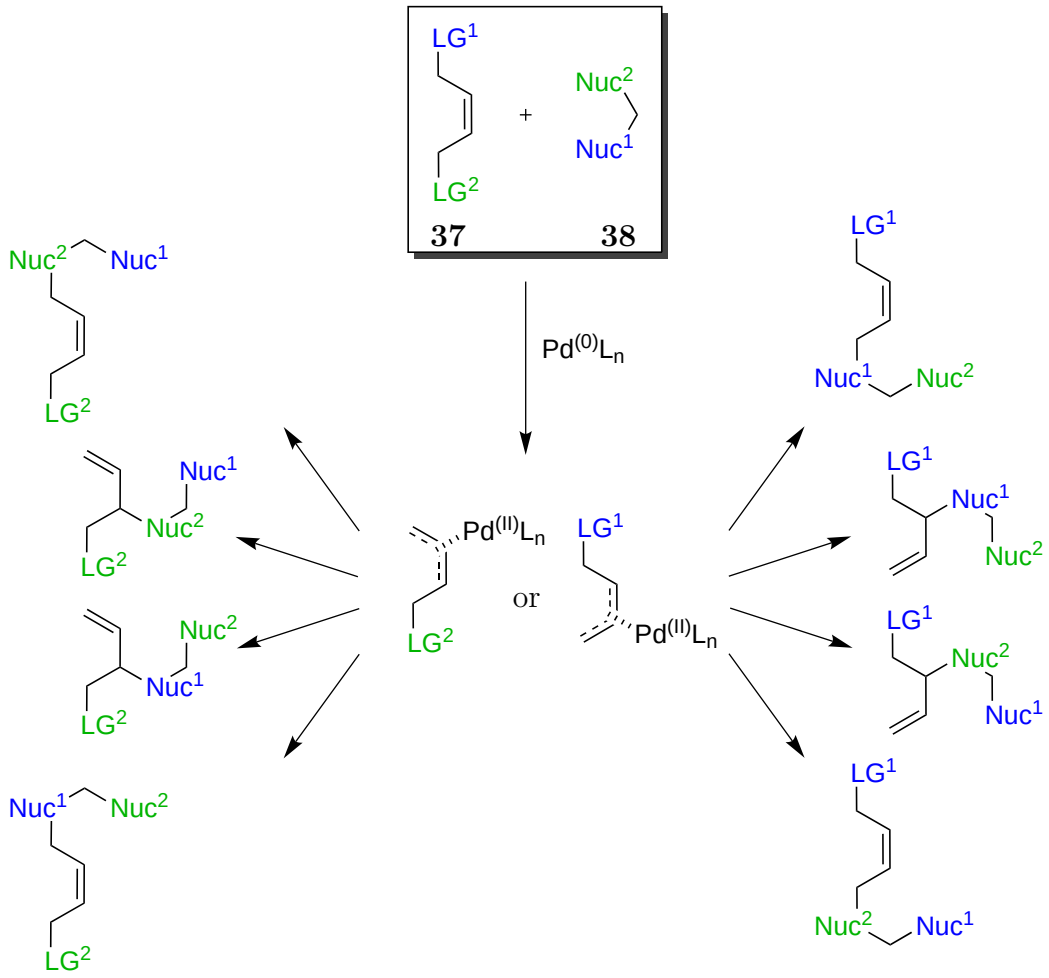
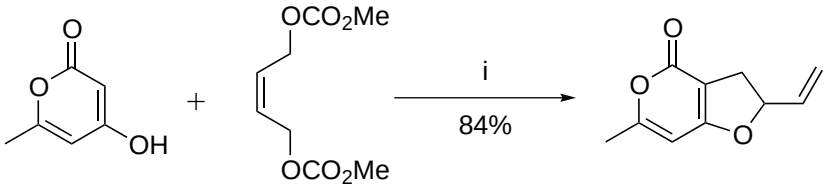


Figure 1.1 Regiochemical possibilities for the initial addition step of a Pd-AA cascade

1.2.3 Development of Pd-AA Cascades of Acyclic and Cyclic Bis-Electrophiles

During the course of research by a recently completed Ph.D. scholar in this group, Dr Mark Bartlett, into furanopyrone based natural products, a novel Pd-AA cascade was discovered. An initial model system involving 4-hydroxy-6-methyl-α-pyrone (**39**) and bis allyl carbonate (**40**) afforded vinyl-substituted furopyrone **41** in an 84% yield (Scheme 1.9).[19]

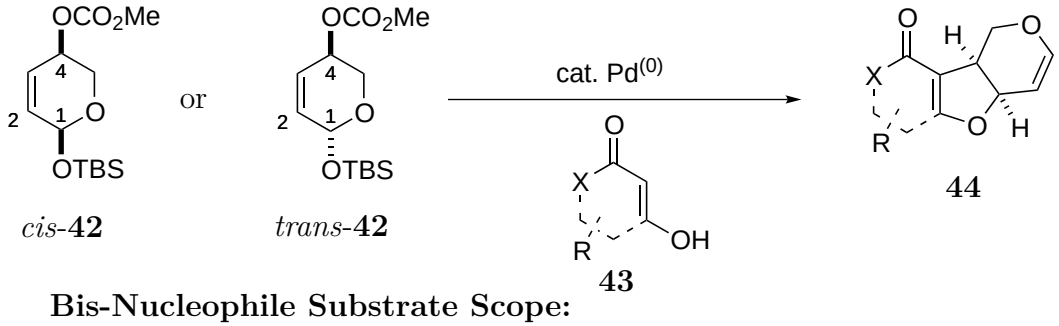


39 **40** **41**

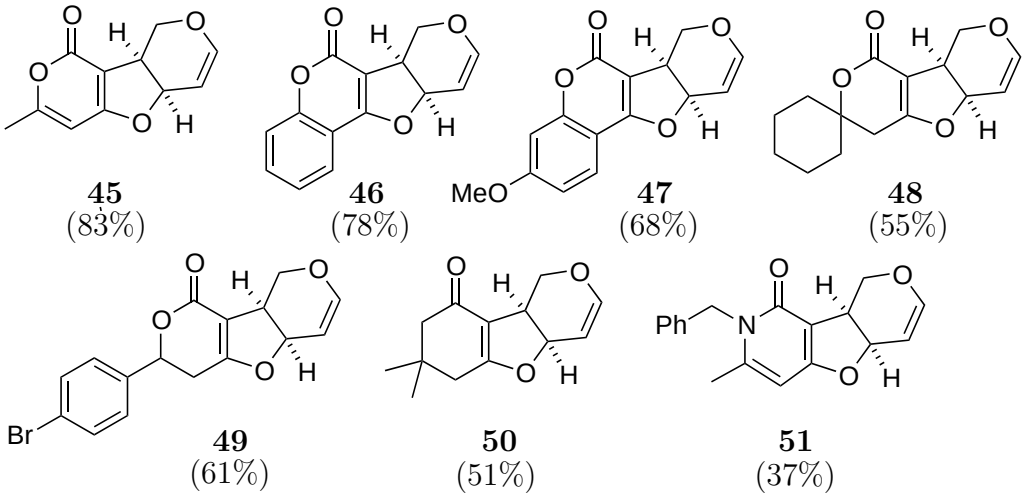
Reagents and Conditions: i) $Pd_2(dba)_3$, PPh_3, MeCN, NEt_3, 1 h, rt.

Scheme 1.9 Acyclic Pd-AA cascade

Further development of Pd-AA cascades on cyclic electrophiles led to the discovery that non-symmetric pyran substrates (*cis*-**42** or *trans*-**42**) can serve as effective bis-electrophiles with a variety of cyclic β-dicarbonyl nucleophiles (**43**) to provide a high degree of regio- and diastereoselectivity (Scheme 1.10). The combination of allylic carbonate and anomeric siloxy leaving groups provides control of the many possible regiochemical outcomes due to their differing capabilities as leaving groups. The anomeric siloxy group has a relatively low reactivity and both sterics and electronics lead to preferential ionisation of the allylic carbonate group. Furthermore, the presence of two inductively electron-withdrawing oxygen atoms at C-1 of the dihydropyran disfavours cationic character at the adjacent C-2. This has been proposed to cause an increase in the cationic character of C-4 in the initial π-allyl Pd intermediate, resulting in the preferential alkylation of C-4 over C-2.[20] Interestingly, it was also observed that the annulation proceeds stereoconvergently to give a *cis*-fused furopyran (**44**) irrespective of whether the starting material is *cis*- or *trans*-substituted.[21]

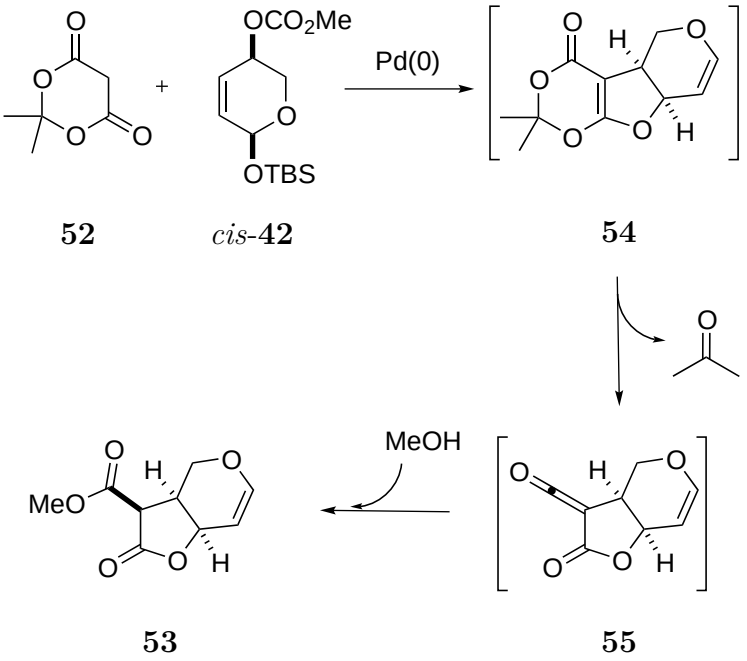


Bis-Nucleophile Substrate Scope:



Scheme 1.10 Stereoconvergent Pd-AA cascade of non-symmetric dihydropyrans with substrate scope

To investigate the scope of this method, a variety of cyclic β-dicarbonyl compounds were explored and found to be effective in the cascades (Scheme 1.10). Of particular note was the use of Meldrum's acid (**52**) which provided a γ-butyrolactone (**53**) via acetone extrusion/acyl ketene trapping sequence (Scheme 1.11). The product structure (**53**) has the potential to serve as a synthetic intermediate for the synthesis of natural products (*vide infra*).[21]



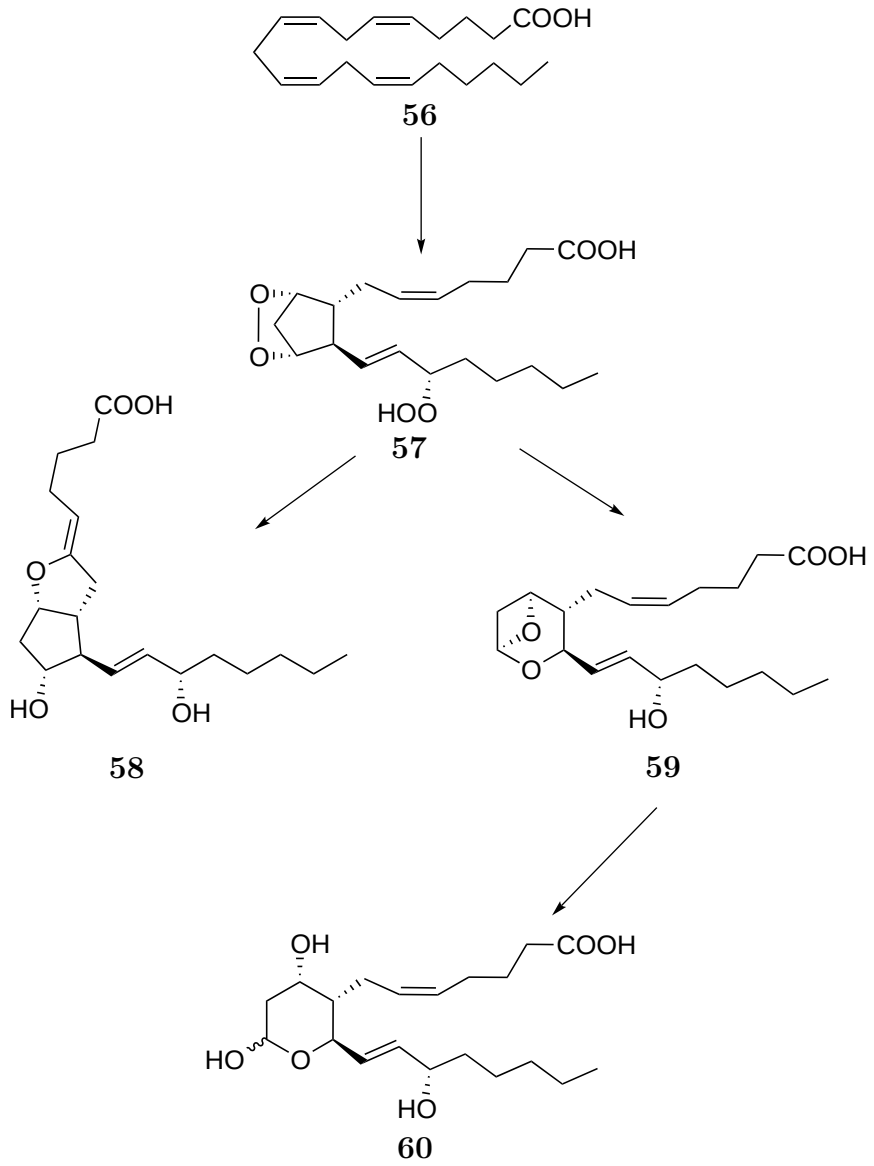
52 *cis*-**42** **54** **53** **55**

Scheme 1.11 Pd-AA cascade of a dihydropyran with Meldrum's acid

1.3 Prostaglandins

1.3.1 Discovery of Prostaglandins

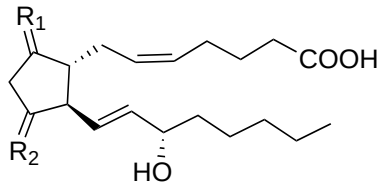
In the 1930s von Euler and Goldblatt independently discovered that lipid fractions isolated from both the genital glands and human semen exhibited vasodepressor and smooth muscle stimulating activity. The substances found to be responsible for this activity were provisionally termed "prostaglandins" due to the belief that they were produced in the prostate gland. In actual fact, it has been shown that prostaglandins (PGs) are, in general, produced from arachidonic acid (**56**) close to the site where they are to exert a tissue-specific effect, whereupon they are rapidly metabolised to less active materials.[22]



Scheme 1.12 Biosynthesis of the thromboxanes (**59**, **60**) and prostacyclin (**58**)

1.3.2 Structure Elucidation

The sequence of events by which arachidonic acid (**56**) is converted to PGG_2 (**57**) and from there to primary and secondary prostaglandins, their metabolites and other substances (Scheme 1.12) was elucidated and explored in depth in the middle of the twentieth century. It wasn't until 1960, when Bergstrom *et al.* isolated crystalline prostaglandin compounds, that the general structure of PGs was elucidated (Figure 1.2). Bergstrom's group discovered not only that prostaglandins are unsaturated, hydroxylated fatty acids with 20-carbon skeletons that always contain a 5-membered ring, but also demonstrated that these compounds were biosynthesised from polyunsaturated fatty acids e.g. arachidonic acid (**56**). Further work completed in this area by Samuelsson's group led to the discovery that the exocyclic oxygen atoms originated from the same molecule of oxygen and therefore a likely intermediate is an endoperoxide.[22]



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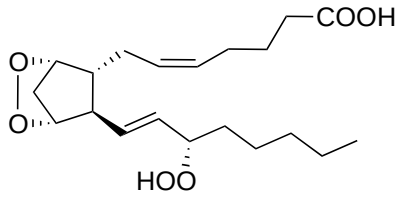
R_1 = O or α-OH, H
R_2 = O or α-OH, H

Figure 1.2 Structure of the prostaglandins

In 1973, Samuelsson isolated two endoperoxide containing prostaglandins; PGG_2 (**57**) and PGH_2 (**62**) (Figure 1.3), proving the earlier hypothesis. In contrast to the previously discovered prostaglandins, the endoperoxides have a short half-life, *ca.* 5 minutes, in biological systems.[22]



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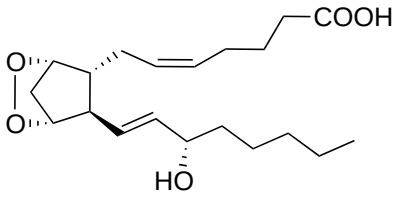

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Figure 1.3 Prostaglandin endoperoxides

1.3.3 Bioactivity of Prostaglandins

Since their discovery, it has been found that PGs contribute to a multitude of biological processes exhibiting a broad spectrum of activity and have therefore found a number of clinical uses. These include, but are not limited to, regulation of gastric acid secretion, promotion of the healing of peptic ulcers, regulation of ovarian function, induction of labour, termination of pregnancy, and treatment of asthma, inflammation and shock. PGs have also been examined as pro- and anti-inflammatories as, for example, overproduction of PGs in tissue is a main cause of rheumatoid arthritis, and treatment is based around inhibition of natural PG biosynthesis. Aspirin is known to reduce inflammation and alleviate pain by interfering with PG biosynthesis.[22]

1.4 Thromboxanes

1.4.1 Discovery of Thromboxanes

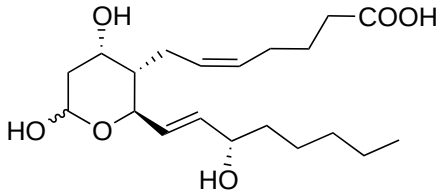
From the work carried out by Hamberg, Svensson and Samuelsson in 1974-1975, it was discovered that endoperoxide PGG_2 (**57**) is a precursor not only to the prostaglandins and prostacyclin PGI_2, (**58**) but also to another biologically interesting family of oxygenated heterocycles known as the thromboxanes.[23,24] Of particular note is the short-lived but extremely potent substance thromboxane A_2 (TXA_2) (**59**) (Scheme 1.12).[25,26]

1.4.2 Thromboxane A_2

TXA_2 (**59**) is a prostanoid signalling molecule generated by blood platelets and is known to have the opposite biological effect to PGI_2 (**58**). These two molecules are produced in the body to set up a delicate equilibrium: PGI_2 prevents platelets from aggregating and adhering to blood vessel walls and therefore causes smooth muscles (in particular, blood vessels) to relax, whereas TXA_2 induces platelets to clump, aggregate and adhere to blood vessels, causing the vessels to contract. TXA_2 therefore appears to be an important factor in blood clotting (thrombosis).[25,27] However, it has a half-life of only 30 seconds in aqueous solutions, in which the strained oxetane ring is rapidly hydrolysed, converting TXA_2 to thromboxane B_2 (TXB_2) (**60**).[28,29]

1.4.3 Thromboxane B_2

Unlike its precursor, TXB_2 is biologically inert as a platelet-aggregating agent. However, it has been demonstrated that TXB_2 can be converted to the biologically active TXA_2 (see Section 1.4.10).[30,31] Therefore TXB_2 is recognized as a valuable substance for study of a variety of biochemical processes which will aid in research aimed at reducing fatalities in patients at risk of thrombosis and heart attack.[27]

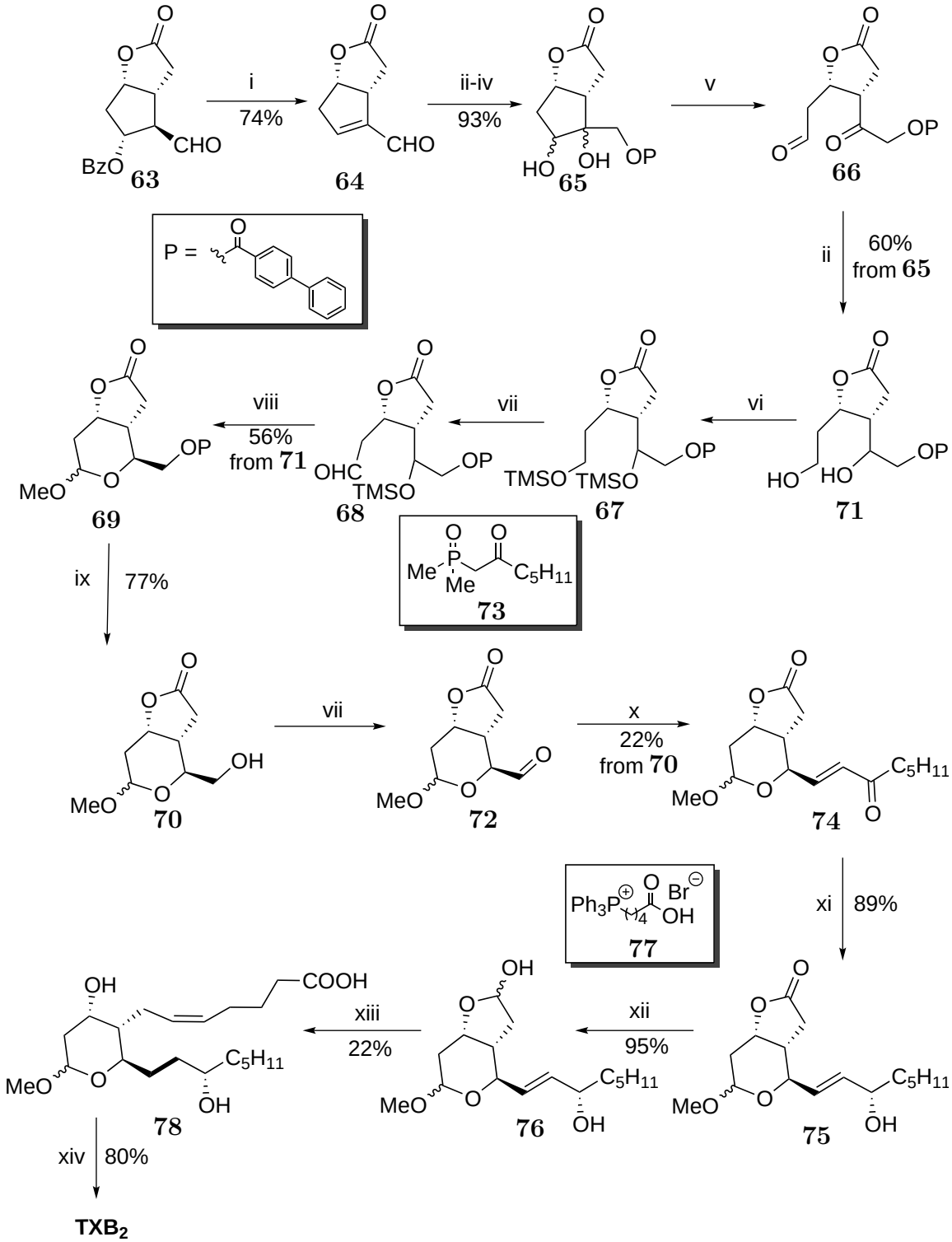


60

Figure 1.4 Thromboxane B_2

1.4.4 First Total Synthesis of Thromboxane B_2

The first total synthesis of TXB_2 was completed by Nelson and Jackson in 1976 whilst part of the then Upjohn Company (Scheme 1.13). The synthesis began with the benzoylated Corey aldehyde (**63**), a known and commercially available PG intermediate that was pioneered by Corey in his landmark syntheses of prostaglandins $F_{2\alpha}$ and E_2.[32,33] Upon treatment with Florisil® (an activated magnesium silicate gel), an α,β-unsaturated aldehyde (**64**) was obtained. After reduction of the aldehyde and protection of the resulting alcohol, dihydroxylation with osmium tetroxide produced a diol (**65**), which was then subsequently cleaved with paraperiodic acid, opening the cyclopentyl ring and leading to the unstable keto-aldehyde (**66**), which was immediately reduced with $NaBH_4$ and silylated. Selective deprotection of the primary TMS ether of **67**, followed by Collins oxidation afforded aldehyde **68**. Treatment with methanolic HCl afforded cyclic methyl acetal **69**, which was then deprotected to afford primary alcohol **70**. Primary alcohol oxidation allowed a Horner-Wadsworth-Emmons reaction to attach the first side chain, and reduction followed by a Wittig reaction afforded attachment of the second side-chain, finishing with hydrolysis to produce TXB_2 in less than 1% overall yield in 15 steps.[25]

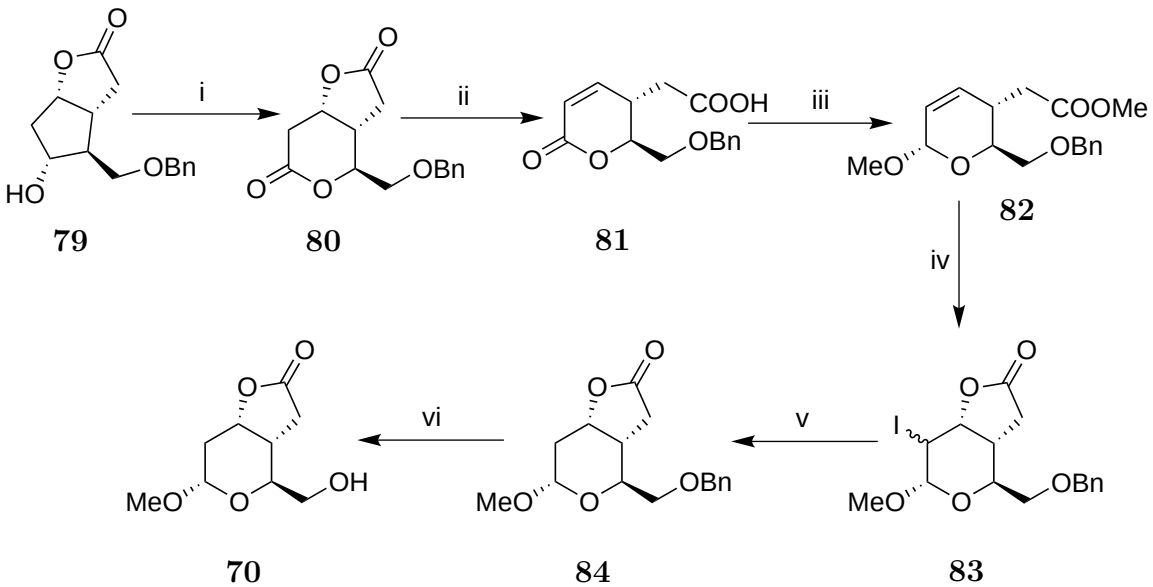


Reagents and Conditions: i) Florisil®; ii) $NaBH_4$; iii) *p*-PhC_6H_4COCl; iv) OsO_4-NMO; v) H_5IO_6; vi) Me_3SiCl; vii) Collins [O]; viii) HCl-MeOH; ix) NaOMe, MeOH; x) **73**, *t*BuOK, THF; xi) $Zn(BH_4)_2$; xii) DIBALH; xiii) DMSO, **77**; xiv) 85% H_3PO_4:H_2O:THF 1:10:10.

Scheme 1.13 First total synthesis of TXB_2 by the Upjohn Company

1.4.5 Syntheses of TXB_2 from Corey Prostanoid Intermediates

Since the first total synthesis there have been a number of reported syntheses of TXB_2. The Upjohn group developed another synthesis (Scheme 1.14) shortly after their original, which also started from another known Corey prostanoid intermediate (**79**), which allowed smoother formation of the 6-membered cyclic core of thromboxane. Jones' oxidation followed by a Baeyer-Villiger reaction with *m*-chloroperbenzoic acid gave a dilactone (**80**), which, when treated with a tertiary amine, led to the ring opened elimination product (**81**). Reduction of the remaining lactone with diisobutylaluminium hydride (DIBALH), esterification with diazomethane, followed by dissolution in methanolic HCl and addition of trimethyl orthoformate, afforded the cyclic methyl acetal (**82**). Saponification followed by iodolactonisation, reductive removal of the iodine from the intermediate iodolactone with tri-*n*-butyltin hydride and finally hydrogenation, afforded the deprotected γ-lactone intermediate (**70**) which could then be converted to TXB_2 using the known procedure. This method decreased the number of reaction steps to the intermediate from 9 to 7, mildly improving the efficiency of the synthetic route to TXB_2.[22,34]

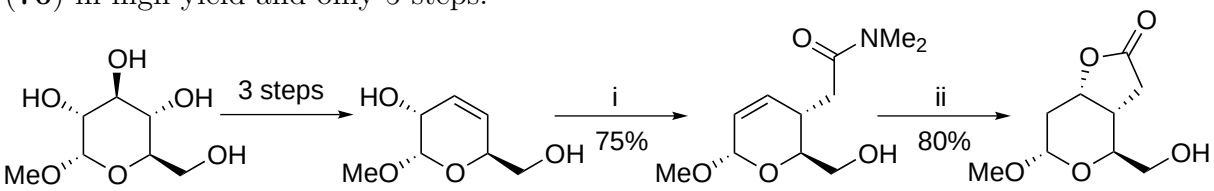


Reagents and Conditions: i) 1. Jones [O], 2. *m*CPBA; ii) tertiary amine *e.g.* 1,5-diazabicyclo undec-5-ene; iii) 1. DIBALH, 2. CH_2N_2, 3. MeOH / H^+ / $HC(OMe)_3$; iv) 1. NaOH, 2. CO_2, 3. I_2 / KI; v) Bu_3SnCl; vi) H_2, Pd / C.

Scheme 1.14 1976 formal total synthesis of TXB_2 by The Upjohn Company

1.4.6 Syntheses of TXB_2 from Carbohydrates

The Corey group produced a formal synthetic route to TXB_2 by utilising sugar chemistry (Scheme 1.15). Their simple and stereocontrolled route began with the optically active sugar precursor methyl α-D-glucoside (**85**) that was converted in a highly efficient manner, by a known procedure, to the unsaturated derivative (**86**). Claisen rearrangement, induced through heating with excess *N,N*-dimethylacetamide dimethylaminal in diglyme, resulted in stereospecific formation of the dimethyl amide (**87**). Treatment with iodine under hydrolytic conditions afforded the iodolactone, which could then be deiodinated with tributyltin hydride to produce the hydroxylactone (**70**) in high yield and only 5 steps.[35]



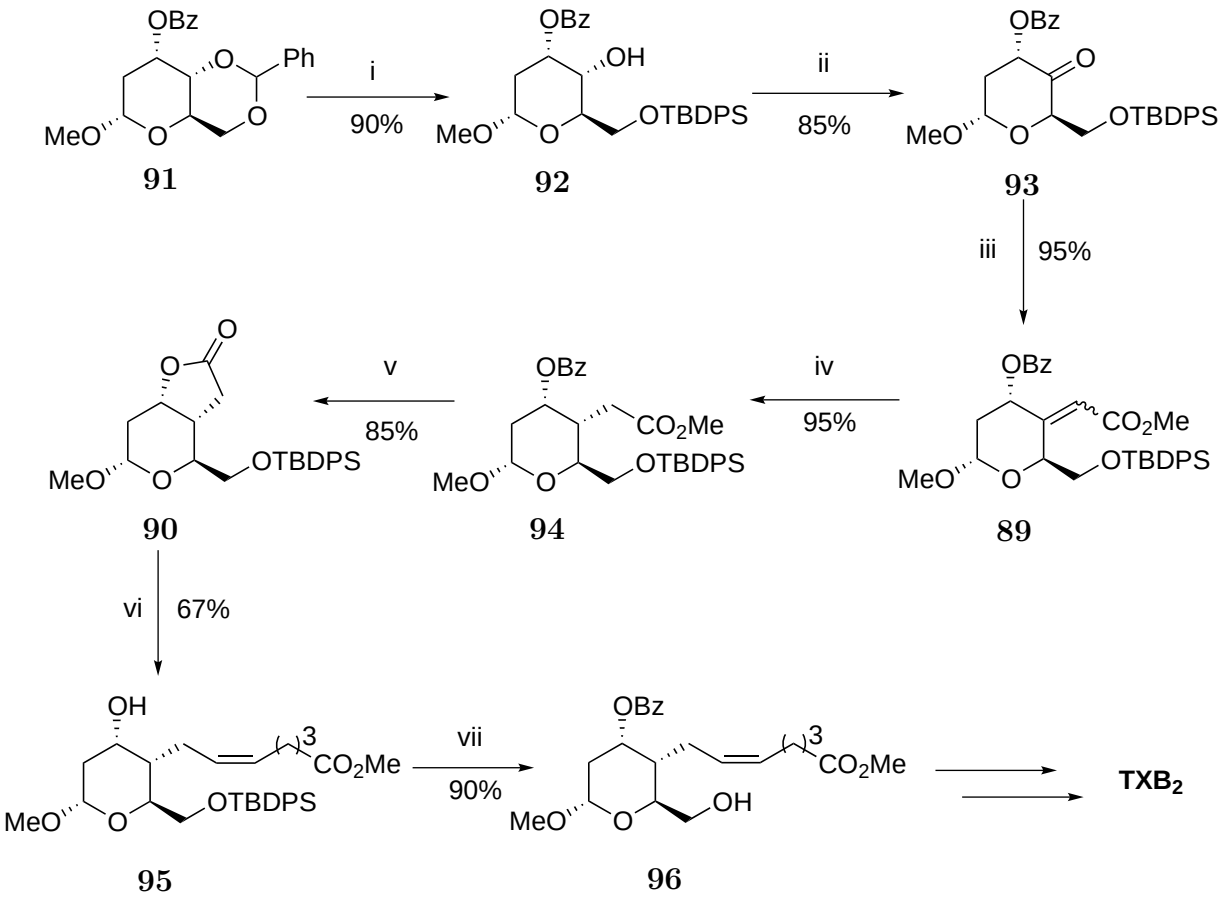
85 **86** **87** **70**

Reagents and Conditions: i) *N,N*-dimethylacetamide dimethylaminal, diglyme; ii) I_2, THF:H_2O, 2. Bu_3SnH.

Scheme 1.15 1977 synthesis of the thromboxane intermediate (**70**) from a sugar derivative

In 1977, Hanessian's group achieved a total synthesis of TXB_2 from the readily accessible D-glucose derivative methyl 4,6-*O*-benzylidene-2-deoxy-α-D-ribohexopyranoside (**88**) that exploited the compound's functionality and stereochemistry (Scheme 1.16). Hydrogenolysis, selective silylation of the primary alcohol and Pfitzner-Moffatt oxidation of the secondary alcohol followed by Horner-Wadsworth-Emmons condensation with the anion derived from trimethylphosphonoacetate and potassium tert-butoxide afforded a mixture of *E/Z* alkene isomers (**89**) in high overall yield. The mixture was then subjected to hydrogenation to remove the double bond, followed by debenzoylation to produce the γ-lactone (**90**). The remaining pathway to TXB_2 followed the known methodology for attachment of side-chains[25] resulting in a 12-step synthesis with a greatly improved overall yield of around 15%.[36]

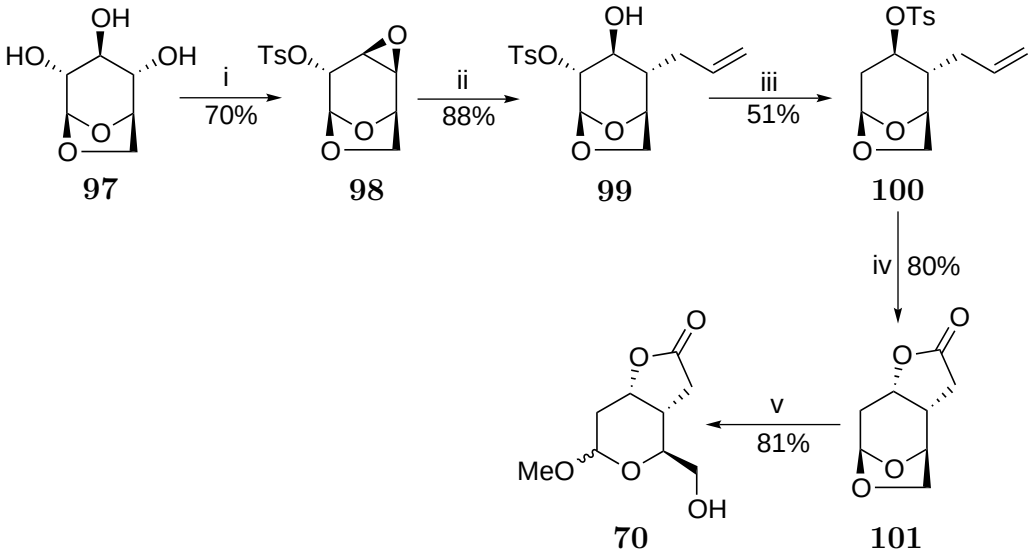
Alongside their other synthesis, the Corey group also developed a synthesis of TXB_2 in a racemic form in 12 steps with an overall yield of less than 10% which will not be commented on further.[26] In 1980, the work of Kelly and Roberts resulted in a synthesis of the bicyclic γ-lactone intermediate (**70**) of TXB_2 (Scheme 1.17). Starting with laevoglucosan (**97**), a cheap and readily available sugar derivative, allylation of an easily formed epoxide[37] (**98**) with a Grignard reagent afforded the TXB_2 intermediate (**70**) in six steps with an overall yield of around 20%.[38]



91 **92** **93** **89** **94** **90** **95** **96**

Reagents and Conditions: i) 1. $Pd(OH)_2/C$, H_2, 2. TBDPSCl; ii) EDCI, DMSO, pyridinium trifluoroacetate; iii) $(MeO)_2P(O)CH_2CO_2Me$, *t*BuOK; iv) $Pd(OH)_2/C$, H_2; v) K_2CO_3, MeOH; vi) 1. DIBALH, 2. $Ph_3PCH(CH_2)_3CO_2Li$, 3. CH_2N_2; vii) 1. BzCl, 2. Bu_4NF, THF.

Scheme 1.16 1977 synthesis of TXB_2 by Hanessian *et al.*

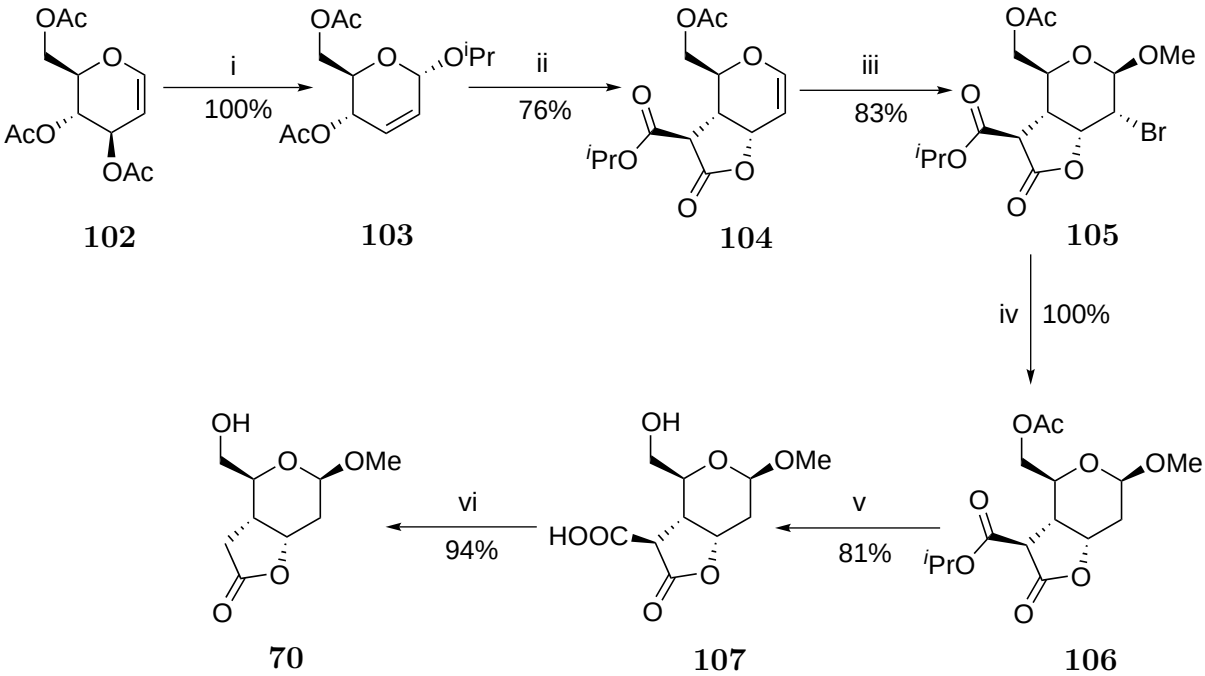


Reagents and Conditions: i) 1. TsCl, pyridine, 2. Na, MeOH; ii) AllylMgCl, CuI; iii) 1. $LiEt_3BH$, THF, 2. TsCl; iv) RuO_4, acetone-H_2O; v) Amberlyst (H^+), MeOH.

Scheme 1.17 1980 synthesis of the TXB_2 intermediate (**70**) from laevoglucosan (**97**)

1.4.7 Palladium-Assisted Synthesis of TXB_2

Research into the total synthesis of TXB_2 then slowed down quite significantly until 1989 when the Verdoorn group in South Africa significantly enhanced the efficiency of the synthesis by developing a short, facile route to the bicyclic γ-lactone intermediate (**70**) of TXB_2 (Scheme 1.18). Starting with tri-*O*-acetyl-D-glucal (**102**), a Ferrier rearrangement with isopropanol using catalytic $Pd(MeCN)Cl_2$ afforded the corresponding 2,3-unsaturated sugar derivative (**103**). Reacting the sugar with Meldrum's acid in the presence of catalytic $Pd(PPh_3)_4$ led to an unexpected cascade of reactions affording the protected unsaturated bicyclic γ-lactone (**104**). Introduction of the methoxy group at the C-1 position was achieved in high yield through bromination in methanol to afford **105** which was reductively debrominated affording the saturated furopyran (**106**) in an essentially quantitative yield. Through subsequent selective removal of the ester groups followed by decarboxylation, the desired bicyclic γ-lactone intermediate (**70**) was obtained in an overall yield of 48% in six steps.[39]



102 **103** **104** **105** **70** **107** **106**

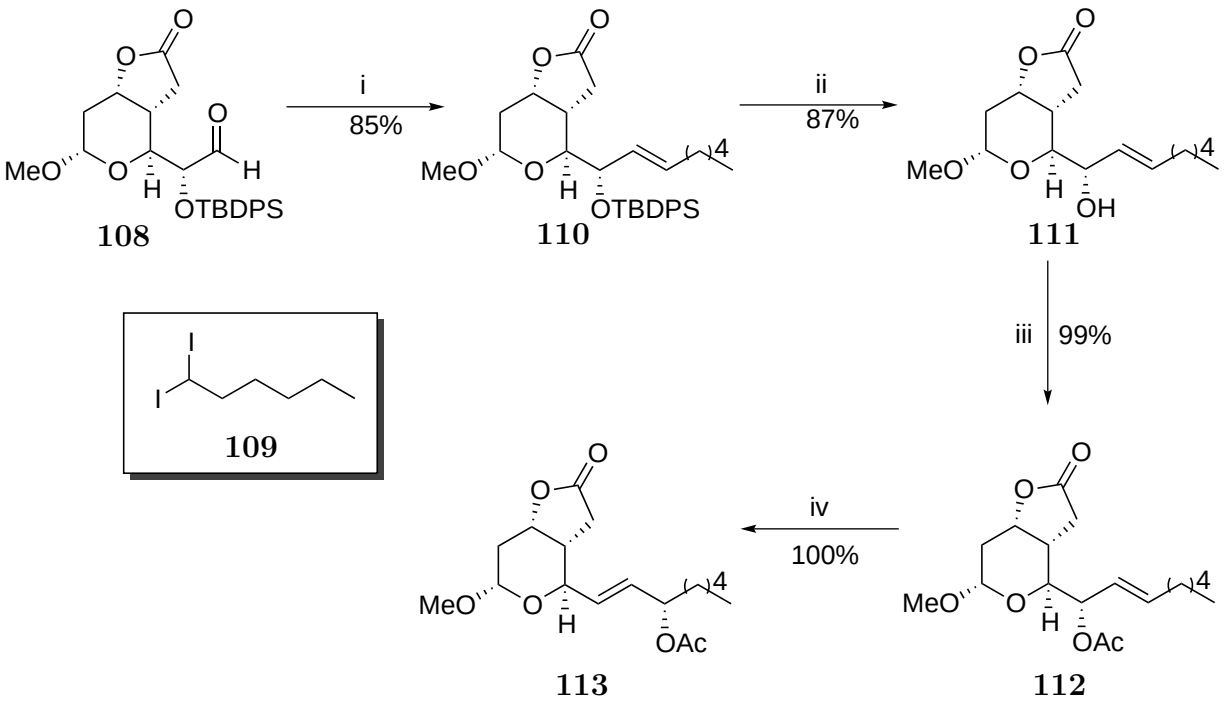
Reagents and Conditions: i) $Pd(MeCN)Cl_2$, $Cu(OTf)_2$, *i*PrOH; ii) Meldrum's acid, $Pd(PPh_3)_4$; iii) Br_2, MeOH; iv) Bu_3SnH, AIBN, toluene; v) NaOH aq., THF, vi) 170 °C.

Scheme 1.18 1989 palladium-assisted synthesis of the thromboxane intermediate (**70**)

1.4.8 Recent Synthetic Routes to TXB_2

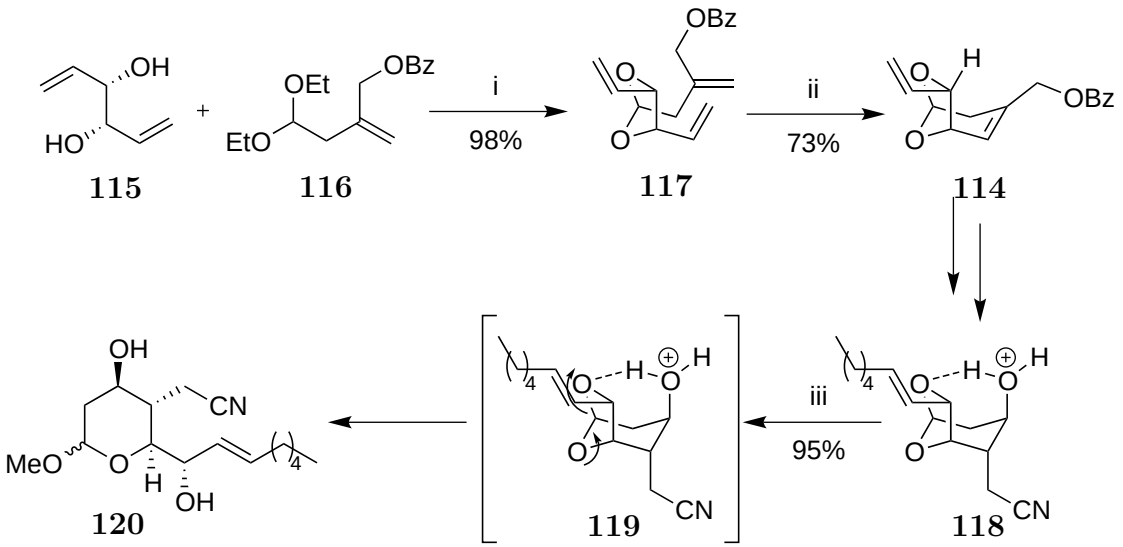
Since Verdoon's efficient synthesis, there have been a few elaborations on the total synthesis of TXB_2. One particular synthesis, reported in 1996,[40] involves a 22-step sequence and poor overall yield, employing (*R,R*)-tartaric acid as a chiral pool reagent. The synthesis provides a means to overcome the longstanding problem of establishing the chemistry of the C-15 hydroxyl group through employment of the Uchimoto method to introduce the *trans*-alkene bond of the C-5 side-chain, followed by palladium-catalysed allylic transposition of the acetate (Scheme 1.19).

Marvin and Burke carried out the most recent (2007) synthetic work on TXB_2. Their synthetic strategy involved an interesting ketalisation/ring-closing metathesis step (Scheme 1.20) to rapidly assemble the bicyclic acetal scaffold **114**, followed by functionalisation including employment of the Uchimoto/Pd catalysed allylic transposition methodology discussed above. However, this lengthy synthesis afforded TXB_2 in 16 steps from a C_2-symmetric diene diol with an overall yield of only 5%.[28]



Reagents and Conditions: i) **109**, $CrCl_2$, DMF, THF; ii) *n*-$Bu_4NF \cdot 3\,H_2O$, THF; iii) Ac_2O, pyridine; iv) $PdCl_2(MeCN)_2$ (cat.).

Scheme 1.19 Side-chain attachment method used in the 1996 synthesis of TXB_2



Reagents and Conditions: i) PPTS, benzene; ii) Grubbs 2nd generation catalyst (5.4 mol%), DCM, rt; iii) Amberlyst 15, MeOH, Δ.

Scheme 1.20 Key transformation of Marvin and Burke's 2007 synthesis of TXB_2

1.4.9 Summary of the Existing Total Syntheses of Thromboxane B_2

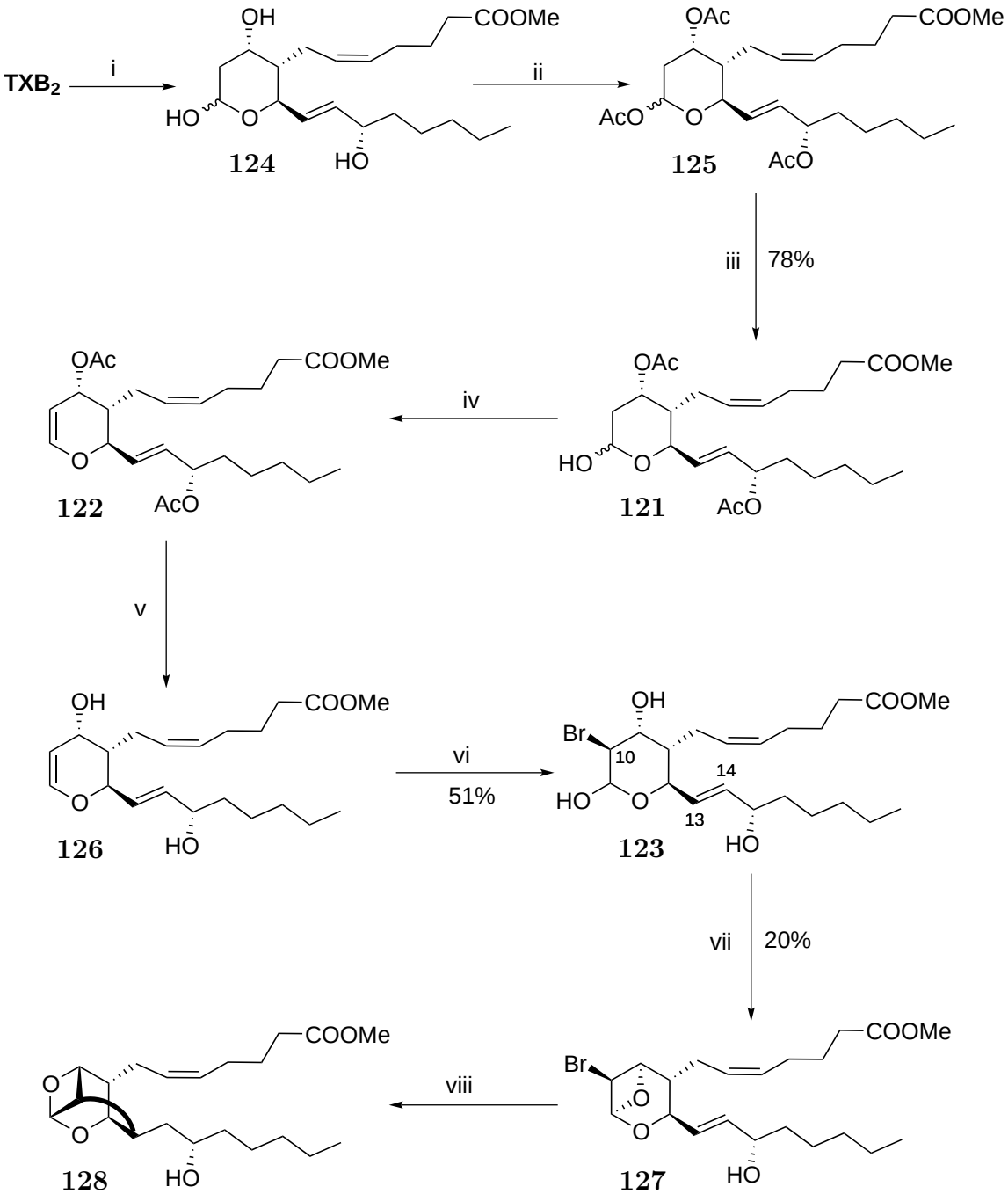
The use of Corey's lactone derivatives (e.g. **63** or **79**) provided a cornerstone for early syntheses of TXB_2, however it requires lengthy ring-opening and ring-closing sequences to convert the cyclopentane to a 6-membered ring. Examination of the structure of TXB_2 shows the presence of a 6-membered lactol and can be considered as a 2,4,6-trideoxy-D-ribo-hexopyranose in which positions 4 and 6 are the sites of *C*-branching and chain extension respectively.[36] Therefore it seems reasonable that the synthesis of this molecule should begin with a simple sugar or sugar derivative. This rationale is emphasised through the advances made in the synthetic efficiency of approaches to TXB_2 when carbohydrate based starting materials were employed (e.g. **85**, **91**, **97**, **102**). These compounds obviate the need to build up the cyclic motif and, when the sugar moiety is chosen correctly, provide the stereochemistry required for TXB_2.

The combination of carbohydrate-based chemistry and palladium catalysis afforded impressive results in Verdoorn's formal synthesis of TXB_2, which currently is the most efficient route to the TXB_2 intermediate (**70**). The methodology for attachment of the side-chains remains largely unchanged from the original prostaglandin procedure despite the issue of C-15 epimerisation. This was varied in 1996 with the successful demonstration of Pd-catalysed allylic transposition by Masaki *et al.*, and has since been the method of choice for the final stage of TXB_2 synthesis.

1.4.10 Total Synthesis of TXA_2

In 1985 Bhagwat *et al.* reported the first and, thus far, only synthesis of TXA_2 (**59**).[30,31] Their first attempt (Scheme 1.21) began with TXB_2 (**60**) which was esterified, peracetylated and selectively deacetylated at the more reactive anomeric centre to afford **121**. Dehydration to the unstable enol ether (**122**), deacetylation and immediate bromohydrin formation led to the 10-bromo-TXB_2 methyl ester (**123**). It was found that Mitsunobu cyclisation provided the oxetane ring in a low yield. Radical initiation however did not produce the desired debromination due to an interception of the intermediate C-10 free radical with the C-13, C-14 double bond.

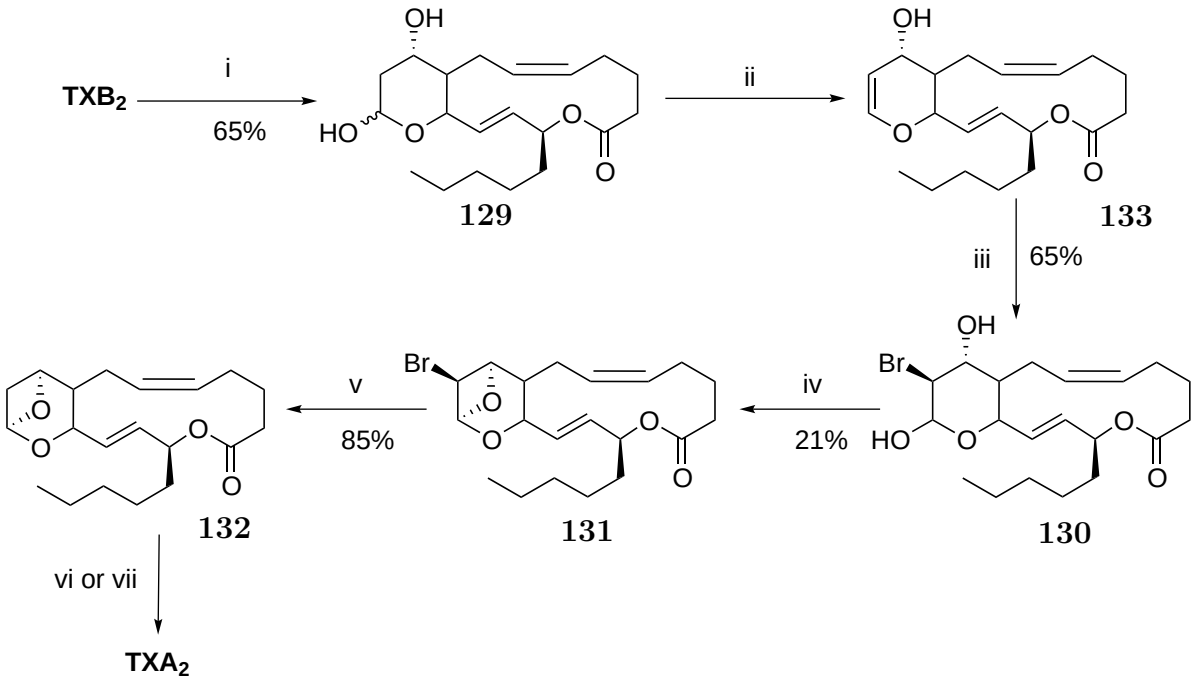
To overcome this problem, the allylic alcohol side-chain was anchored to the ester side-chain by formation of the 1,15-macrolactone (**129**), thereby inducing confor-



Reagents and Conditions: i) CH_2N_2, NEt_3; ii) Ac_2O, pyridine; iii) cat. KOMe, MeOH, -15 °C; iv) MsCl, NEt_3, DCM; v) K_2CO_3, MeOH; vi) NBS, H_2O, THF; vii) $(MeO)_3P$, DEAD, DCM; viii. Bu_3SnH, $h\nu$.

Scheme 1.21 Attempted synthesis of TXA_2 by Bhagwat *et al.* (1985)

mational restriction of the approach of the intermediate C-10 radical. Thus, TXB_2 was converted to the 1,15-macrolide using the Corey-Nicolaou procedure via the thiopyridyl ester. Dehydration at C-11 proceeded smoothly with the Mukaiyama reagent 2-chloro-1-methylpyridinium iodide, and immediate bromohydrin formation provided 10-bromo-1,15-anhydro-TXB_2 (**130**). Modified Mitsunobu etherification then provided the 10-bromo-TXA_2 derivative (**131**). A mild free-radical reduction with tributyltin hydride yielded the desired 1,15-anhydro-TXA_2 (**132**), which was then saponified, without loss of the bicyclic oxetane, and, upon dissolution in $MeOH/H_2O$ in the presence of NaOH, produced the sodium salt of TXA_2 (**59**). Likewise, **132** may also be opened in THF or Et_2O with Me_3SiOK to yield the potassium salt (Scheme 1.22).



Reagents and Conditions: i) 1. PyrSCOCl, NEt_3, Et_2O/DCM, 0 °C, 2. $PhCH_3$, 110 °C; ii) 2-chloro-1-methylpyridinium iodide, NEt_3, DCM; iii) NBS, Et_2O, H_2O; iv) DEAD, $(MeO)_3P$, DCM; v) Bu_3SnH; vi) $MeOH/H_2O$, NaOH; vii) THF or Et_2O, Me_3SiOK.

Scheme 1.22 Second generation route to TXA_2 by Bhagwat *et al.* (1985)

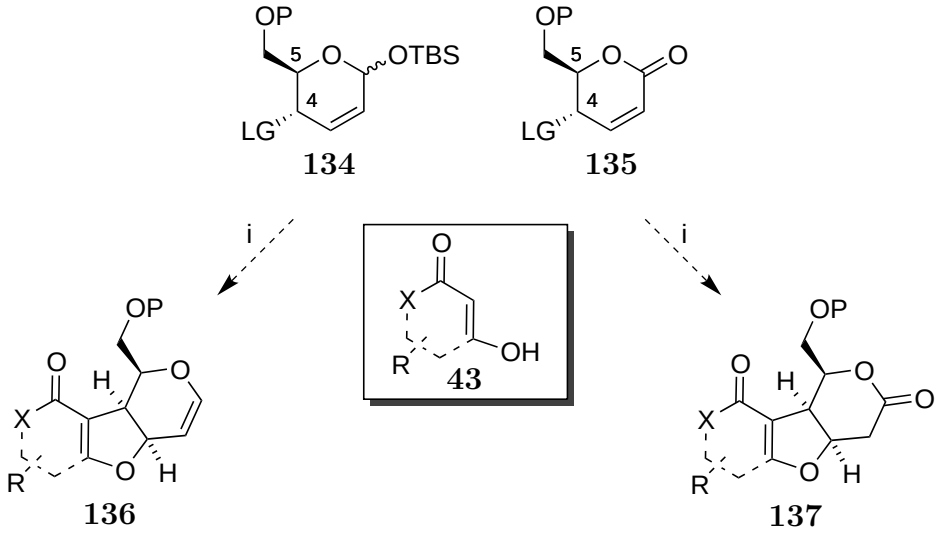
Whilst **132** is biologically inactive, the saponification reaction mixture displayed notable activity and reproduced the activities of natural platelet-derived TXA_2 in a variety of assays. Therefore it can be concluded that the sodium and potassium salts of synthetic TXA_2 are indistinguishable from natural TXA_2. Bhagwat *et al.* also noted that while TXA_2 is rapidly hydrolysed to TXB_2 in aqueous, high salt, neutral buffers, its stability is significantly enhanced at high pH. It was also found that the TXA_2 salts were able to be stored for more than a week if kept at −20 °C either as isolated solids or in basic methanol or THF solutions.[30,31]

1.5 Research Objectives

The research objectives of this project were two-fold. The first was to explore and expand the scope of Bartlett and Harvey's Pd-AA cascade reactions with dihydropyran substrates, and the second to improve on the current total syntheses of the thromboxanes through employing such reactions with Meldrum's acid, in a manner similar to Verdoorn, while developing synthetic efficiencies to achieve shorter 8- and 9-step syntheses of both TXA_2 and TXB_2, respectively.

1.5.1 Further Development of the Pd-AA Cascade

The first focus, to expand the scope of the Pd-AA cascade, was to be approached from two angles, namely the synthesis and testing of both new bis-electrophiles and new bis-nucleophiles. A variety of tri-substituted carbohydrate derived bis-electrophiles (Scheme 1.23) were targeted to extend the scope from Bartlett's di-substituted dihydropyrans. Furthermore, if these compounds were capable of undergoing the Pd-AA cascade efficiently, they would provide useful products due to the presence of a synthetic handle, capable of functionalisation, carried through from the C-5 substituent of the carbohydrate starting material.



LG = OAc or OCO_2Me
P = Ac or CO_2Me or TBS
Reagents and Conditions: i) cat. $Pd^{(0)}$, **43**.

Scheme 1.23 Planned bis-electrophiles and their corresponding Pd-AA cascade products

Two classes of compounds were selected for evaluation as bis-electrophiles: 2,3-

unsaturated glucosyl derivatives (**134**) and α,β-unsaturated lactones (**135**) (Scheme 1.23). Acetate and carbonate leaving groups at C-4 were considered due to the reported success of both in related cascades by Verdoorn and Bartlett, respectively. The choice of C-6 protecting group had more flexibility as it was assumed to not take part in the cascade and was left to be decided during synthesis. α,β-Unsaturated lactones were considered as starting materials for the Pd-AA cascades in order to investigate the potential of these alternative bis-electrophiles. Their increased planarity, when compared to the acetal derivatives, could aid in the initial π-allyl-Pd formation and then, after the initial alkylation at C-4, it was proposed that the cascade might be completed by Michael addition of the second centre of the bis-nucleophile to C-3. This would enhance the scope of the Pd-AA cascades by expanding both the type of bis-electrophile that can be used and also the type of product capable of being formed.

4-Hydroxycoumarins were found to be successful as bis-nucleophiles in Bartlett's scope studies, however only two examples had been tested (see Scheme 1.10, page 9). Therefore, the synthesis and testing of methylated 4-hydroxycoumarin regioisomers (Figure 1.5) was seen as an easy way to probe the effect the position of substitution has upon reactivity in Pd-AA cascades.

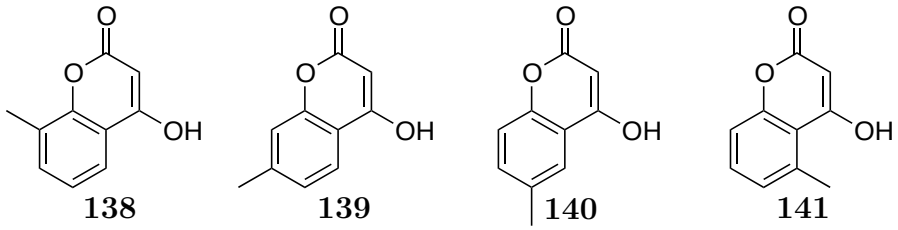
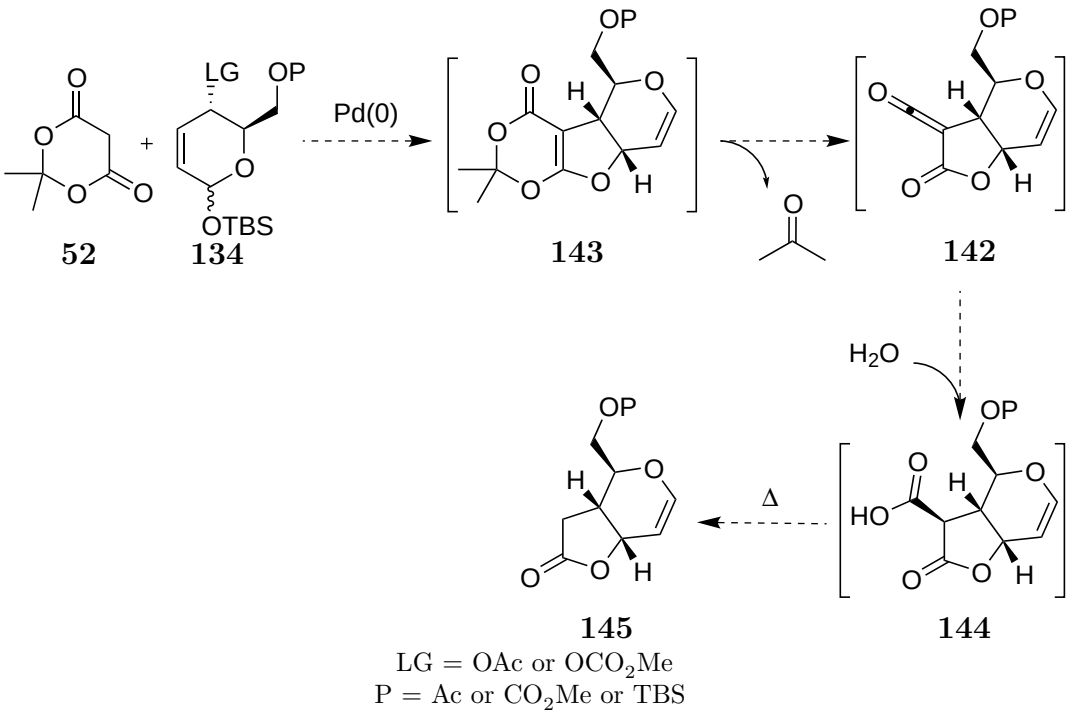


Figure 1.5 Planned bis-nucleophiles for Pd-AA cascade scope studies

1.5.2 Towards an Improved Synthesis of TXA_2 and TXB_2

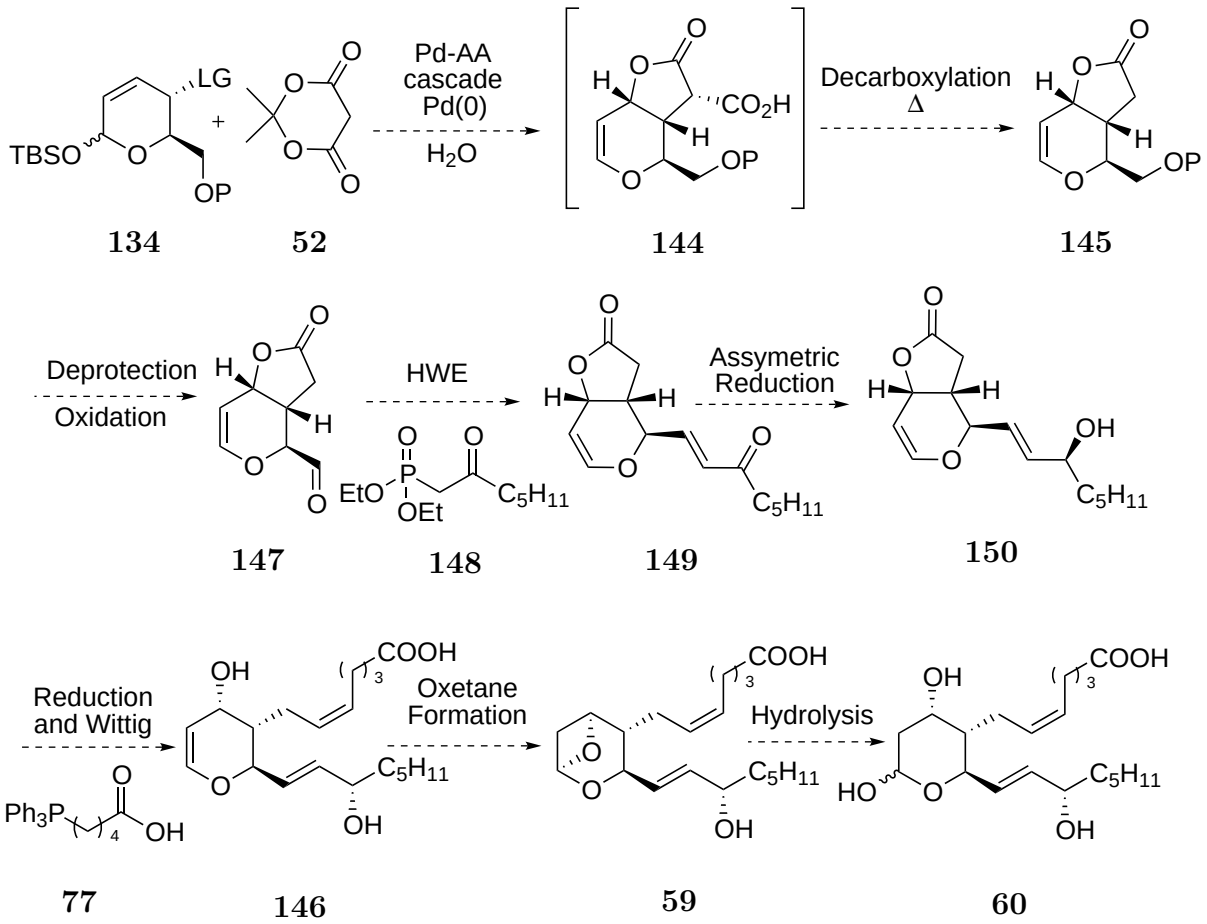
The second focus of this research was to employ the Pd-AA cascade to improve on the current syntheses of the thromboxanes. Using the most successful carbohydrate-derived bis-electrophile developed during the scope studies outlined in Section 1.5.1, an extended Pd-AA cascade with Meldrum's acid would incorporate a carboxylic acid from nucleophilic attack of the Meldrum's acid-derived ketene (**142**) with water. This functionality could be removed via *in situ* thermal decarboxylation to afford the bicyclic scaffold, of e.g. **70**, generated in several of the previous syntheses of thromboxanes (Scheme 1.24). Developing this multistep process into an efficient transformation would improve significantly upon Verdoorn's Pd-catalysed route. If

this endeavour was successful, a synthetic route towards both thromboxanes, *via* TXA_2, was planned to be worked on during the final stages of this project.



Scheme 1.24 Planned extension of the Pd-AA cascade with Meldrum's acid

The full synthetic plan (Scheme 1.25) towards the thromboxanes proposed exploitation of the extended Pd-AA cascade chemistry with Meldrum's acid, to produce the fused bicyclic core of a thromboxane intermediate (**145**) in one step. Optimisation of the traditional methods for side-chain attachment, namely Horner-Wadsworth-Emmons (HWE) Wittig reactions, and asymmetric ketone reduction, would then lead to a hydroxy-substituted dihydropyran (**146**). Lewis acid-promoted oxetane formation would produce TXA_2, followed by hydrolysis to afford TXB_2. The novel aspects of this proposed synthetic route to the thromboxanes are not only the extended Pd-AA cascade, but also retaining the glycal moiety throughout the process of side-chain attachment and the biomimetic approach to formation of TXA_2 prior to formation of TXB_2.



LG = OAc or OCO_2Me
P = Ac or CO_2Me or TBS

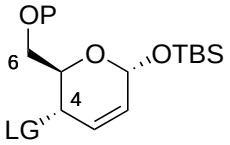
Scheme 1.25 Proposed synthetic plan of TXA_2 (**59**) and TXB_2 (**60**)

Chapter 2

Results and Discussion

2.1 Synthesis of Bis-Electrophiles

The Pd-AA cascade in the proposed synthetic plan (Scheme 1.25) required a trisubstituted dihydropyran as the bis-electrophile. Although based on the disubstituted pyrans employed by Bartlett, the design of the bis-electrophile remained flexible with respect to the choice of leaving group (LG) at C-4 and protecting group (P) at C-6 (Figure 2.1). Both acetates and carbonates were considered as potential leaving groups due to their success in Pd-AA cascades with Meldrum's acid as demonstrated by both Verdoorn[39] and Bartlett,[19] respectively. C-6 could either be differentially protected, for example as a silyl ether (*viz* **151** and **152**) or was selected to mimic the choice of C-4 leaving group, when applicable, in order to facilitate the synthesis (Figure 2.1).



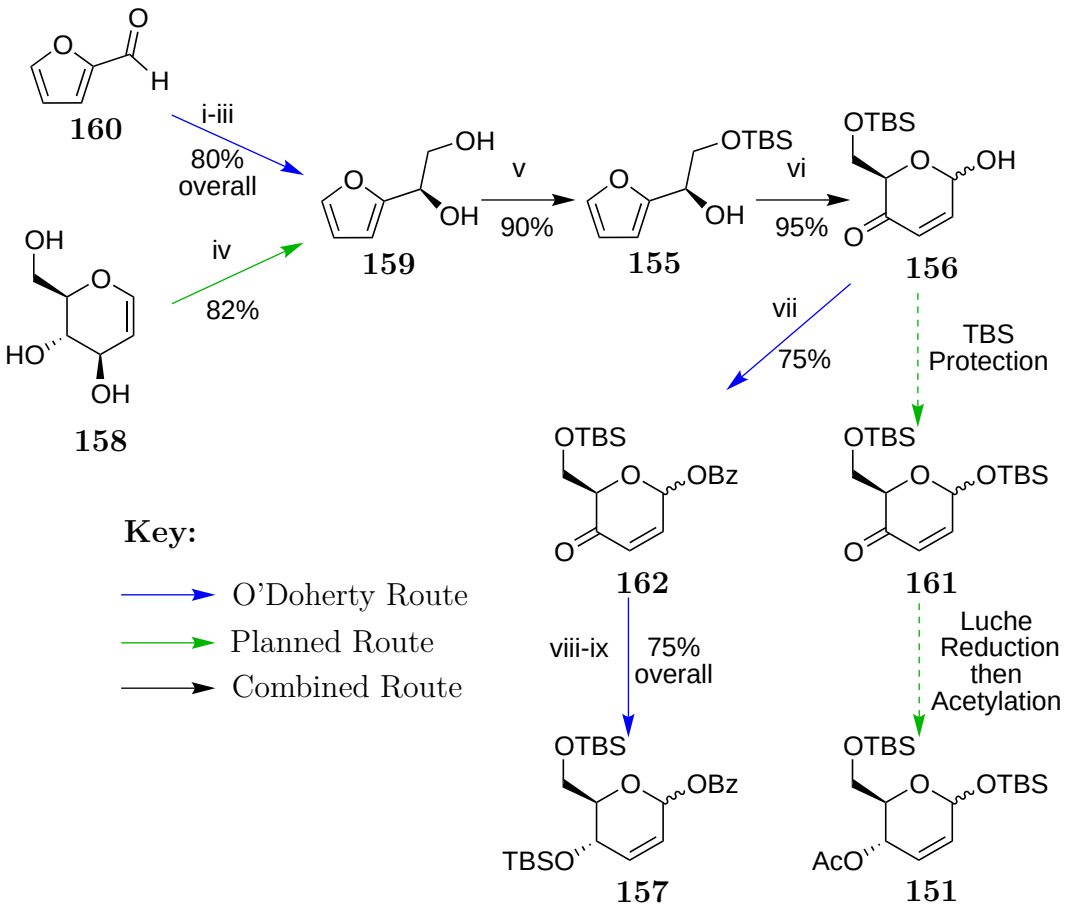
151: LG = OAc, OP = OTBS
152: LG = OCO_2Me, OP = OTBS
153: LG = OP = OAc
154: LG = OP = OCO_2Me

Figure 2.1 Design of tri-substituted dihydropyran bis-electrophiles

A flexible approach to starting material design was beneficial to this project in two ways. In developing more than one bis-electrophile to test, the scope and limitations of the Pd-AA cascade could be explored and the potential for optimisation in the current synthesis of the thromboxane intermediate core is increased. A variety of synthetic pathways were explored to achieve the synthesis of these bis-electrophiles.

2.1.1 Achmatowicz Route to Acetate Bis-Electrophile 151

The Achmatowicz rearrangement converts 2-hydroxyalkylfurans to the corresponding dihydropyrans, originally by reaction with Br_2/MeOH[41] and more recently with NBS,[42] *m*-CPBA[43] or *t*-BuOOH/VO(acac)$_2$.[44] O'Doherty used an Achmatowicz rearrangement of furfural derivative **155** with NBS to afford the 2,3-unsaturated sugar **156** *en route* to **157**.[42] Interception of this route by TBS protection of hemiacetal **156** could lead to the C-6 OTBS bis-electrophile **151** (see section 2.1.2 page 32). Starting from D-glucal (**158**), a synthetic route that merged with O'Doherty's was planned (Scheme 2.1). D-Glucal would be converted into the chiral substituted furan diol **159**, a transformation first reported by Gonzalez *et al.*[45] using the toxic metal salt $HgSO_4$ in concentrated H_2SO_4. A more recent publication by Babu *et al.*[46] demonstrated the use of relatively less toxic $InCl_3.3H_2O$ in acetonitrile for the same transformation. Employing this reaction as the inaugural step *en route* to **156** would shorten O'Doherty's synthesis by two steps (Scheme 2.1).



Reagents and Conditions: i) $TMSCH_2MgCl$; ii)1N HCl; iii)AD-mix α; iv) $InCl_3.3\,H_2O$ (10 mol%), MeCN; v) TBSCl, NEt_3, DMAP; vi) NBS, H_2O; vii) BzCl, NEt_3, DMAP; viii) $NaBH_4$, $CeCl_3$; ix) TBSCl, NEt_3, DMAP.

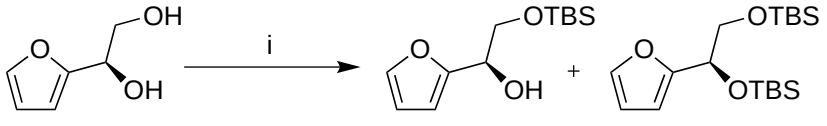
Scheme 2.1 Synthetic plan to bis-electrophile **151**

D-Glucal was prepared from tri-*O*-acetyl-D-glucal using NaOMe in methanol, therefore methanol was chosen as the initial solvent for screening reaction conditions.

In contrast to Babu's use of $InCl_3.3H_2O$, anhydrous $InCl_3$ was employed due to its availability in our lab at the time of investigation. This variation was met with failure, and even when the solvent was changed to acetonitrile only trace amounts of the desired product **159** were observed, according to NMR spectroscopy of the crude reaction mixture. It was then postulated that catalytic amounts of water seemed necessary for this reaction. However, upon testing this theory (Table 2.1 Entries 3-5) the yield of this reaction remained minimal. Increasing the temperature of the reaction slightly (Table 2.1 Entries 5-6) was thought to better reflect the ambient conditions of Babu *et al.*[47] This resulted in a mild increase in yield, however investigations of other Lewis acids were pursued.

Montmorillonite clay (MK10)[48] was shown to successfully promote this reaction by Yadav *et al.*,[47] however this result was not successfully replicated in this work (Table 2.1, Entry 7). A publication from 2007 found that $FeCl_3.6H_2O$ in acetonitrile at room temperature was capable of producing the furan diol in 82% yield.[49] Indeed, employing $FeCl_3.6H_2O$ as the Lewis acid afforded a highest yield of 71% but only when the reaction temperature was increased to reflux and water was added to the solvent mix. Increasing the catalyst loading resulted in complete degradation of the carbohydrate material present in the reaction mixture (Table 2.1, Entry 12).

The next synthetic step in this sequence was selective silyl protection of the primary alcohol of the furan diol. Two attempts at this reaction at both 0 and -78 °C produced a mixture of recovered starting material, mono- and di-protected products, with the major product in both reaction mixtures being the undesired latter. It was thought that perhaps TBSOTf was too reactive a silylating agent[50] so TBSCl, as used by O'Doherty, would overcome this problem (see section 2.1.1 page 29). However, a Darwinian approach to synthesis was employed in this project, and as another more successful pathway towards a C-4 acetate bis-electrophile (**153**) was being investigated concurrently with this one, the Achmatowicz route to the starting material was abandoned.

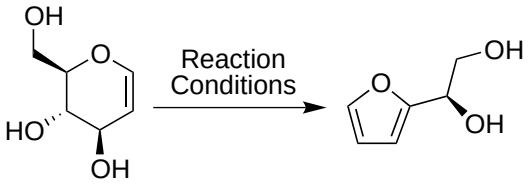


159 **155** **163**

Reagents and Conditions: i) TBSOTf (1 eq.), NEt_3 (1.5 eq), DCM, 0 °C–rt or –78 °C–rt.

Scheme 2.2 TBS protection of chiral furan diol **159**

Table 2.1 Optimisation of D-glucal (**158**) to chiral furan diol **159** reaction



158 **159**

Entry	**Lewis Acid**[a]	**Additives**	**Solvent**	**Temp**	**Time**	**Yield (%)**
1	$InCl_3$	-	MeOH	rt	O/N	SM
2	$InCl_3$	-	MeCN	rt	O/N	Min.
3	$InCl_3$	0.3 eq H_2O	MeCN	rt	O/N	< 2
4	$InCl_3$	0.3 eq + 4 drops H_2O	MeCN	rt	O/N	Min.
5	$InCl_3$	0.3 eq H_2O	MeCN	27 °C	2 days	9
6	$InCl_3$	-	MeCN	32 °C	O/N	16
7	MK10[b]	-	MeCN	27 °C	2 days	SM
8	$FeCl_3.6H_2O$	-	MeCN	32 °C	O/N	21
9	$FeCl_3.6H_2O$	-	MeCN	Δ	O/N	20
10	$FeCl_3.6H_2O$	-	MeCN	Δ	O/N	33
11	$FeCl_3.6H_2O$	-	14:1 MeCN:H_2O	Δ	O/N	71
12[c]	$FeCl_3.6H_2O$	-	MeCN	Δ	O/N	Degr.

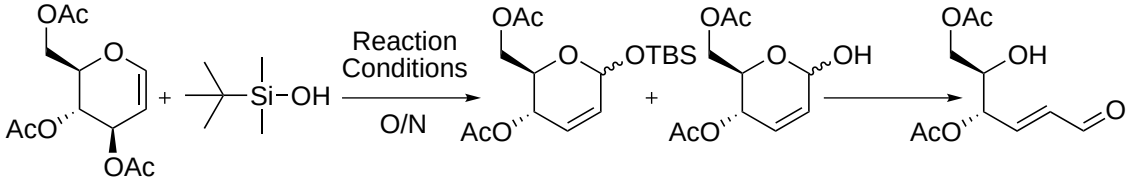
[a]Lewis acids added as 10 mol% except as otherwise indicated
[b]Montmorillonite K10 was used in a 300 $^{w}/_{w}$% loading
[c]50 mol% $FeCl_3.6\,H_2O$

2.1.2 Ferrier Approach to Diacetate Protected Bis-Electrophile 153

As discussed in subsection 1.4.9 (page 21), the cyclic core of the thromboxanes is a 2,4,6-trideoxy-D-ribo-hexopyranose, in which positions 4 and 6 are the sites of *C*-branching and chain extension, respectively.[36] Since oxygen groups can be easily functionalised, it seemed reasonable that the synthesis of this molecule should begin with a simple sugar or sugar derivative. The Ferrier reaction, a.k.a. Ferrier rearrangement, has been used as an effective means of converting glycals to 2,3-unsaturated glycosides[51] since its conception in 1962.[52] This would provide a C-2 deoxygenated species and was thought to provide an ideal approach to diacetate bis-electrophile **153**.

The correct stereochemistry at positions 4 and 5 of the Pd-AA starting material can be achieved through the use of readily available tri-*O*-acetyl-D-glucal (**102**), as exemplified in the formal thromboxane synthesis of Verdoorn *et al.*[39] The success of a siloxy anomeric leaving group in the Pd-AA cascade of Bartlett encouraged employment of a silanol nucleophile in the Ferrier reaction, where Verdoorn used *iso*-propanol. Despite the wide scope of the Ferrier reaction,[53] silanol nucleophiles are currently unreported in the literature. Therefore, exploring these nucleophiles in the Ferrier reaction could lead to a new avenue of research.

Table 2.2 Optimisation of Ferrier reaction of tri-*O*-acetyl-D-glucal (**102**) with TBSOH (**164**)

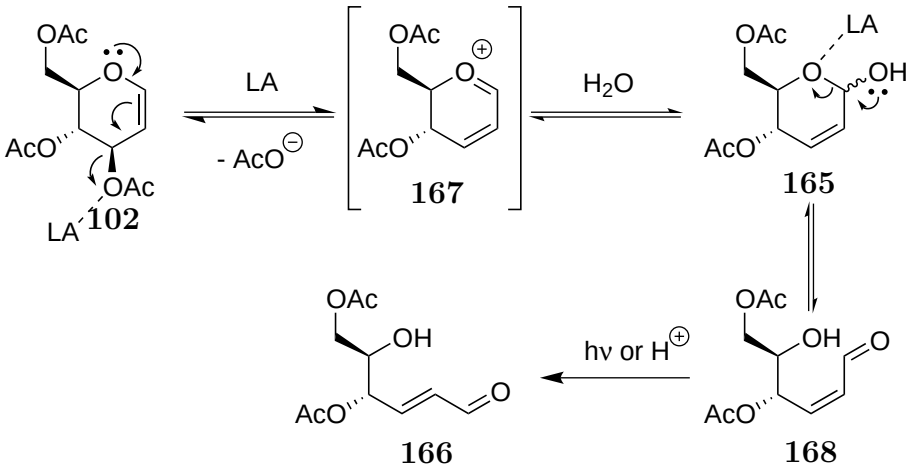


102 **164** **153** **165** **166**

Entry	Lewis Acid[a]	Solvent	Additives	Temp	Yield 153	Yield 165	Yield 166
1	$CeCl_3.7H_2O$	DCM	-	rt	-	-	-
2	$CeCl_3.7H_2O$	MeCN	-	Δ	5[b]	trace	30
3	$CeCl_3.7H_2O$	DCM	mol sieves	Δ	-	-	-
4	$CeCl_3.7H_2O$	MeCN	mol sieves	Δ	-	-	-
5	$InCl_3$	DCM	-	rt	4	3	15
6	MK10	DCM	mol sieves	rt	8	-	-
7	MK10	DCM	mol sieves	30 °C	14	-	-
8	MK10	DCM	mol sieves	Δ	32	-	-

[a]All Lewis acids in 10 mol% loading except MK10 which was used in a 300 $^{w}/_{w}$% loading
[b]Not identified as desired product until reisolated later in higher yield

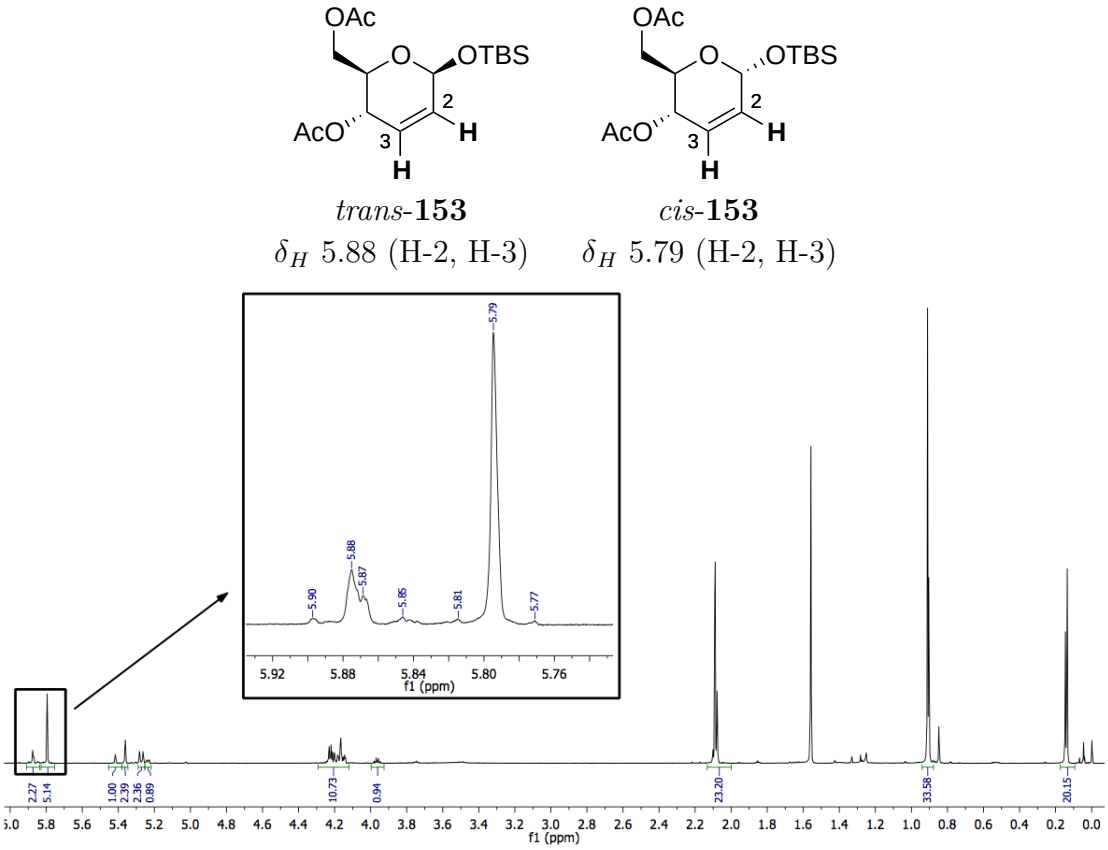
Investigation of the Ferrier reaction with silanols began with the preparation of *tert*-butyldimethylsilanol (TBSOH) (**164**) following a literature method[54] that proceeded without complications. The initial Ferrier reaction conditions (Table 2.2, Entry 1) were chosen based on work carried out by Yadav *et al.*[55] Their research demonstrated that tri-*O*-acetyl-D-glucal could undergo Ferrier reactions efficiently with a variety of alcohols (although silanols were not included in their examples) in the presence of catalytic amounts of $CeCl_3.7\,H_2O$ to afford the corresponding 2,3-unsaturated glycosides. Ambient conditions led to poor reactivity with TBSOH. When a higher temperature was employed, activity increased, however *trans*-aldehyde **166** was found to be the major product, characterised by a vicinal $^3J_{H,H}$ coupling constant of 16.0 Hz for the alkene protons (H-2, H-3) which is indicative of *trans* geometry (Table 2.2, Entry 2). This product was assumed to be generated via heterolytic cleavage of the C-3 acetyl group, a process most likely assisted by Lewis acid coordination, and subsequent nucleophilic attack by adventitious water at C-1 of the allyloxycarbenium **167**. After proton exchange, the α- and β-hemiacetals **165** would be produced (Scheme 2.3). Both anomers could then enter into an equilibrium with the open-chain *cis*-aldehyde **168** which can undergo essentially irreversible isomerisation to *trans*-aldehyde **166**. This transformation is well-documented in the literature, including computational studies on the mechanism.[56] Interestingly, Fraser-Reid proposed in 1970, after he too synthesised **166**, that the probable presence of this aldehyde in Emil Fischer's impure preparation of tri-*O*-acetyl-D-glucal (**102**) led to a positive test for an aldehyde function and, hence, the suffix "al" in the name glucal.[57]



Scheme 2.3 Formation of *trans*-aldehyde **166** from tri-*O*-acetyl-D-glucal

Alongside this major product, aldehyde **166**, the desired product was isolated in a 5% yield, however the assignment of structure was made difficult by the presence of two anomers whose H-2 and H-3 signals overlapped in the ^{1}H NMR spectrum. Specifically, two apparent singlets at 5.88 and 5.79 ppm were actually two pairs of heavily tenting doublets (Figure 2.2). It was only upon close examination of the ^{1}H

integration pattern, COSY and HSQC spectra that this product was determined to have the desired structure. Finally, mass spectrometry of the isolated compound gave m/z $[M+Na]^+ = 367.1549$ (calc. $C_{16}H_{28}O_6SiNa = 367.1547$), and is consistent with the assignment of **153**.



trans-**153**
δ_H 5.88 (H-2, H-3)

cis-**153**
δ_H 5.79 (H-2, H-3)

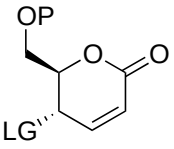
Figure 2.2 ^{1}H NMR spectrum of *cis*- and *trans*-**153**. Expansion showing pairs of heavily tenting doublets attributed to H-2 and H-3

To minimise the production of hemiacetals **165** and therefore aldehyde side-products, it seemed prudent to rigorously exclude water from the reaction and so the mixture of silanol **164** and Lewis acid was stirred with molecular sieves before addition of the glycal. By doing so, the reaction no longer produced the undesired products, however, it was then found to not proceed at all with $CeCl_3.7H_2O$ as the Lewis acid (Table 2.2, Entries 3-4). $ZnCl_2$ has been shown to be an efficient promoter of the Ferrier reaction,[58] however $ZnBr_2$ was tested instead due to its availability in our lab, but was found to be unsuccessful. Therefore, two other Lewis acids that have successfully been used in Ferrier reactions were tested, namely Montmorillonite K10 (MK10),[59] and $InCl_3$.[60] Both Lewis acids promoted the formation of the desired product, as a mixture with the side-products, albeit in low yields (e.g. Table 2.2, Entry 5). Control reactions, without addition of TBSOH, revealed that MK10 produced a reaction mixture with fewer side-products, and through the use of molecular sieves and increasing the reaction temperature, the optimised conditions for this reaction produced a yield of 32% (Table 2.2, Entries 6-8).

The scope of this reaction was briefly exlored with a different silanol as the nucleophile, namely *tert*-butyldiphenylsilanol (TBDPSOH). None of the desired product was found to form under the optimised conditions used with TBSOH, which could be due to the steric bulk of the nucleophile. Due to the poor yield after optimisation of this novel approach to diacetate bis-electrophile **153**, a more traditional route to the substrate was sought.

2.1.3 Oxidative Route to Diacetate Bis-Electrophile 172

As discussed in Section 1.5.1 (page 24), α,β-unsaturated lactones (*viz.* **135**, Figure 2.3) were proposed as an interesting variant of bis-electrophile. The increased planarity of these types of compounds, alongside their Michael acceptor properties, could lead to different reactivity or regioselectivity in the Pd-AA cascades, and therefore methods for their synthesis were sought.

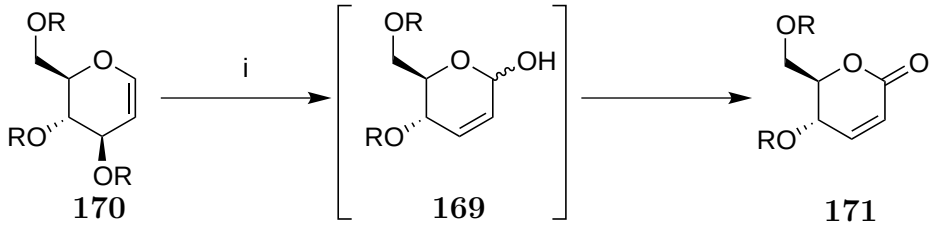


135

LG = OAc or OCO_2Me
P = Ac or CO_2Me

Figure 2.3 Design of α,β-unsaturated δ-lactone bis-electrophiles

Pyridinium chlorochromate (PCC) has historically been used for the conversion of glycals into α,β-unsaturated δ-lactones;[61] however, in 2004, Yadav *et al.* reported a mild and efficient protocol for this one-pot transformation using catalytic $InCl_3$ under aqueous conditions in combination with a stoichiometric amount of IBX as a novel reagent system.[62] Mechanistically, the reaction is initiated by $InCl_3$-induced allylic rearrangement of the glycal with water to form an intermediate 2,3-dideoxy-hex-2-enopyranose (**169**), which on subsequent oxidation by IBX results in the formation of the corresponding cyclic enoate in 76-82% yield.



170 **169** **171**

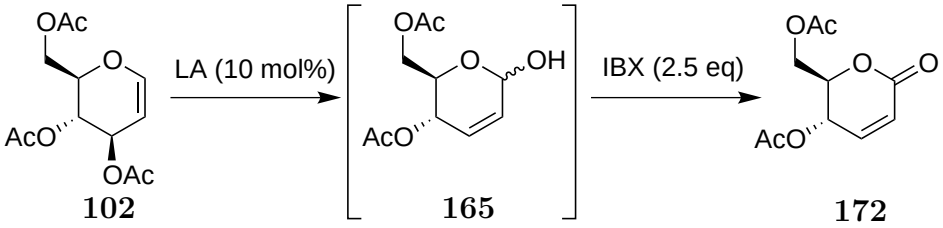
R = Ac, Allyl, Bn or Bz.
Reagents and Conditions: i) 10 mol% $InCl_3$, IBX, H_2O.

Scheme 2.4 Yadav *et al.*'s one pot synthesis of α,β-unsaturated δ-lactones **171**

IBX was prepared via a literature method[63] but the initial attempt at replicating

Yadav's results was unsuccessful (Table 2.3, Entry 1). Due to the increased activity noted when $FeCl_3.6H_2O$ was employed as the Lewis acid in previous transformations of glycals (*vide supra*), it was tested as an alternative to $InCl_3$. This modification did result in greater consumption of starting material but only led to a complex mixture of products including, again, only trace amounts of product as seen by ^1H NMR of the crude reaction mixture (Table 2.3, Entry 2). Further modifications of Yadav's procedure were investigated, including variations in time, temperature, solvent system, and Lewis acid, however the reaction either produced complex mixtures or did not proceed at all, and only starting material (**102**) was retrieved (Table 2.3, Entry 3-8).

Table 2.3 Optimisation of IBX reaction



102 **165** **172**

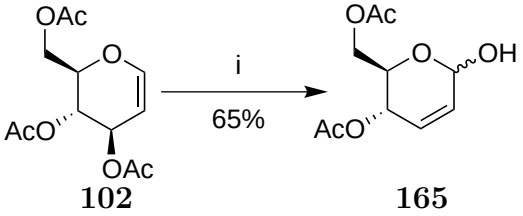
Entry	Lewis Acid[a]	Solvent	Temp	Time	Yield (**172**)
1	$InCl_3$	9:1 MeCN/H_2O	Δ	O/N	Min.
2	$FeCl_3.6H_2O$	9:1 MeCN/H_2O	Δ	O/N	Min.
3	$FeCl_3.6H_2O$	9:1 MeCN/H_2O	Δ	5 h	Min.
4	$InCl_3$	14:1 DMF/H_2O	rt	O/N	SM
5	$FeCl_3.6H_2O$	14:1 DMF/H_2O	rt	O/N	SM
6	$FeCl_3.6H_2O$	9:1 MeCN/H_2O	Δ	O/N	SM
7[b]	$InCl_3$	9:1 MeCN/H_2O	Δ	O/N	SM
8[b]	MK10	9:1 MeCN/H_2O	Δ	O/N	SM
9	-	H_2O	80 °C	2 h	0%[c] (54% **165**)
10[d]	-	H_2O	80 °C	O/N	0%[e]

[a]10 mol% Lewis acids added except for MK10 which was used in a 300 $^w/_w$% loading
[b]Stepwise addition of IBX
[c]19% *trans*-aldehyde **166**
[d]IBX added prior to addition of **102**
[e]Mainly *trans*-aldehyde **166**

It was imperative to improve conversion of **102** to the hemiacetal **165** in order to probe the ability of IBX to oxidise the anomeric hydroxyl group. Earlier work conducted by Baer *et al.*[64] demonstrated the ability to convert **102** to **165** in the absence of a Lewis acid in an 85% yield by simply heating **102** in water at 80 °C with vigorous stirring for 30 min. Incorporating this method with Yadav's IBX oxidation was met with mixed success. Upon heating **102** in water at 80 °C for 30 min., TLC showed almost complete conversion to a slower moving spot, whereupon 2.5 eq. of IBX was added to the mixture. After two hours, all starting material was consumed and the reaction was worked up and found to be predominantly hemiacetal **165**, although open-chain *trans*-aldehyde sideproducts (**166** and others)

were also observed (Table 2.3, Entry 9). A second attempt with a longer reaction time demonstrated that the IBX was not active towards oxidation of the anomeric hydroxyl of **165** (Table 2.3, Entry 10) in this manner because none of the desired lactone (**172**) was observed, and therefore different oxidising agents were pursued.

When deciding on alternative oxidising agents to try for this transformation, those previously used in allylic oxidations of α,β-unsaturated lactols were considered first; these included MnO_2,[65] Fétizon's reagent (Ag_2CO_3 on Celite™),[66] PCC[61,67] and Jones' reagent.[68] Firstly, however, formation of **165** needed to be improved. Attempts at improving the yield from 54% (Table 2.3, Entry 9) culminated in a highest isolated yield of 65%, achieved through increasing the reaction time to five hours and conducting the reaction in absence of light. Conducting the reaction in the dark suppresses production of *trans*-aldehyde side-products through light-induced irreversible isomerisation of the open-chain *cis*-aldehyde **168** to *trans*-aldehyde **166**, a process demonstated by Fraser-Reid *et al.*[69] (Scheme 2.5). Further comment and new insight on this reaction can be found in Section 2.1.4 (page 38).

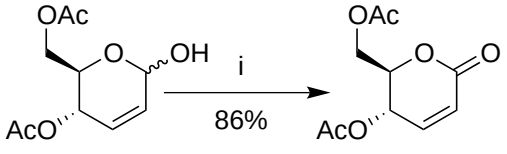


102 **165**

Reagents and Conditions: i) H_2O, dark, 80 °C, 5 h.

Scheme 2.5 Optimised conditions for conversion of **102** to hemiacetal **165**

With hemiacetal **165** in hand, the efficiency of both MnO_2 and Fétizon's reagent in the oxidation of this substrate were tested concurrently. Whilst the trial MnO_2 reaction returned all of the starting material hemiacetal, Fétizon's reagent delivered the desired α,β-unsaturated lactone bis-electrophile (**172**) cleanly in a 86% yield, without the need for further purification. The remarkable success of this reaction was accentuated by the lack of workup, with clean product accessible by filtration of the crude reaction mixture through Celite™. This result thereby obviated the need to probe the reactivity of other suggested oxidising agents.



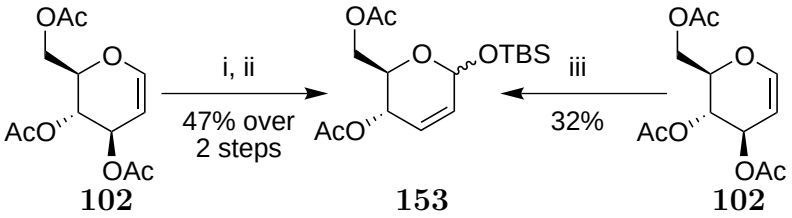
165 **172**

Reagents and Conditions: i) Fétizon's reagent, benzene, Δ, O/N.

Scheme 2.6 Oxidation of hemiacetal **165** to lactone **172** with Fétizon's reagent

Formation of hemiacetal **165** not only provided a clean pathway to lactone **172**,

but also uncovered a potentially facile route to the diacetate bis-electrophile **153** produced in low yield (32%) via the novel Ferrier reaction with TBSOH discussed in section 2.1.2 (page 32). TBS protection of the anomeric hydroxyl of **165** due to the absence of other hydroxyls on the substrate was expected to proceed relatively smoothly and, indeed, on treating **165** with TBSCl in the presence of DMAP, $AgNO_3$ and pyridine in DCM, the desired diacetate bis-electrophile **153** was isolated in a 73% yield. This modification improved the yield of formation of bis-electrophile **153** from glucal **102** with the two-step synthesis producing **153** in an overall yield of 47% (Scheme 2.7). No steps were taken to improve the efficiency of the TBS protection step, however this type of reaction is extremely common and in general found to be high-yielding,[70,71] therefore further work on this reaction is likely to meet few problems.



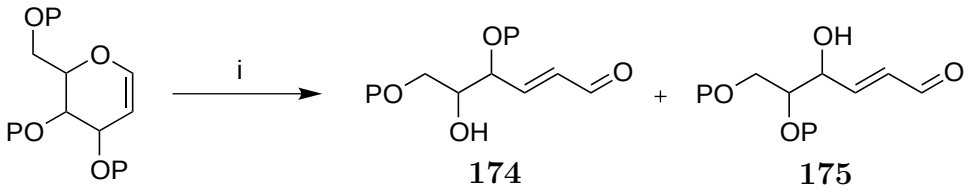
Reagents and Conditions: i) H_2O, dark, 80 °C, 5 h; ii) TBSCl, $AgNO_3$, pyridine, DCM; iii) TBSOH, MK10, DCM, Δ.

Scheme 2.7 Comparison of two successful syntheses of bis-electrophile **153**

2.1.4 New Insight on Perlin-Type Aldehydes

The formation of *trans*-aldehyde **166** from Ferrier reactions of **102** in the presence of water was noticed on more than one occasion during attempts to synthesise bis-electrophile **153**. This transformation is not new knowledge to the carbohydrate research community as such aldehydes have been noted numerous times.[72] However, when first developed into a synthetically useful transformation by Perlin, Lesage and Gonzalez in 1975 through the use of mercuric ion catalysis, alongside the major *trans*-aldehyde **166**, the trio also noticed another *trans*-aldehyde was produced. The aldehyde mixture was not purified but Perlin *et al.* assigned the new *trans*-aldehyde to be the product of acyl migration from C-4 to C-5 of aldehyde **166**. These aldehydes, alongside other δ-hydroxy-α,β-unsaturated aldehydes that can be synthesised in this manner, have since been referred to as the Perlin aldehydes, and the process by which they are made, Perlin hydrolysis (Scheme 2.8).

Interestingly, however, at the time that Perlin's paper appeared in 1975, a manuscript by Bert Fraser-Reid went to press outlining another synthesis of two *trans*-aldehydes isolated from the hydrolysis of tri-*O*-acetyl-D-glucal.[69] Fraser-Reid's ^{1}H NMR assignment of **166** mirrored that of Perlin's. On the other hand, the two chemists'



173 **174** **175**

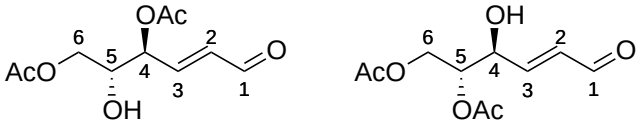
P = Ac, Bn, Me

Reagents and Conditions: i) $HgSO_4$, 1,4-dioxane, dil. H_2SO_4, rt, 2-3 hr.

Scheme 2.8 Perlin hydrolysis of alkyl protected glycals (**173**) to afford Perlin aldehydes **174** and **175**

assignments of the acyl migrated product (**176**), although similar, did not match. The most noticeable differences were between the assignments of H-2 and H-3 (Table 2.4). The variation in ^{1}H NMR shifts, coupled with results from the current work (*vide infra*), indicate that Perlin's assignment could be of another compound. This incongruency went without comment from Fraser-Reid despite him recognising Perlin's paper in a note added in proof at the end of the publication. This oversight could be due to the differing manner in which the two papers presented their ^{1}H NMR shifts, with Perlin reporting in delta (δ) and Fraser-Reid in tau (τ).

Table 2.4 Comparison of ^{1}H NMR data reported for *trans*-aldehydes **166** and **176**



166 **176**

Assigned Structure	Research	^{1}H NMR shifts (δ)					
		H-1	**H-2**	**H-3**	**H-4**	**H-5**	**H-6**
166	Perlin[a]	9.58	6.4	6.98	5.61	4.1	
	Fraser-Reid[b,c]	9.62	6.22	6.93	5.57	4.5 - 4.0	
	This work[d]	9.59	6.26	6.88	5.56	4.06	4.21
176	Perlin[a]	9.58	6.28	7.02	4.64	5.12	4.1
	Fraser-Reid[b,c]	9.62	6.37	6.86	4.6	5.1	4.4 - 4.0
	This work[d]	9.6	6.41	6.79	4.58	5.09	4.33

[a]Spectra recorded on a 100 MHz spectrometer.
[b]Spectra recorded on a 60 MHz spectrometer.
[c]Shifts converted from tau to delta with formula $\delta = 10 - \tau$.
[d]Spectra recorded on a 500 MHz spectrometer.

Since 1975, due to their high degree of functionality and well-defined chiral centres, Perlin aldehydes have been successfully utilised as chiral pool reagents in synthesis by various research groups.[72] It therefore seems surprising that since the original two spectroscopic assignments of the acyl migrated aldehyde (**176**), no new spectral data have been reported nor comment on the differing NMR data been made. Instead only references to Perlin's assignment of the compound have been reported. It would

appear that few chemists are aware of Fraser-Reid's 1975 paper, due to the lack of comment or reference to it in their own work, or perhaps the outdated use of τ by Fraser-Reid made quoting his data less favourable. In any case, it would seem that until now, no side-by-side comparison of the NMR data has been made.

During optimisation of the conversion of glucal **102** to hemiacetal **165** in this project, it was found that two major *trans*-aldehyde side-products were indeed formed. The highest yielding aldehyde was assigned as **166** and the spectral data matched those reported by both Perlin and Fraser-Reid. The next most abundant *trans*-aldehyde had ^{1}H NMR data that closely corresponded with those reported by Fraser-Reid for the structure of **176**. A compound with shifts closely corresponding to the aldehyde Perlin assigned to the structure of **176** was noticed in trace amounts along the baseline of the ^{1}H NMR of the crude reaction mixture, confirming that this compound could indeed be different from the aldehyde isolated by Fraser-Reid and in this work. 2D NMR data, unavailable to both Perlin and Fraser-Reid at their time of reporting, was used to confirm the assignment of structure **176** to the NMR shifts obtained on the aldehyde isolated in this work. Individual HMBC correlations between the acetate carbonyl carbons (δ 171.1 and δ 170.3) and H-5 (δ 5.08) and one H-6 (δ 4.34) of **176** in comparison to the HMBC correlations between the acetate carbonyl carbons and H-4 (δ 5.56) and one H-6 (δ 4.21) of **166** clearly demonstrate the connectivity of this aldehyde (Figure 2.4).

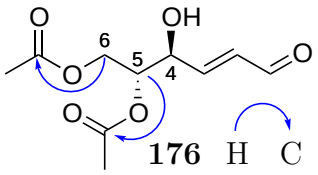


Figure 2.4 ^{1}H - ^{13}C HMBC correlations of **176**

Although noticed in trace amounts in this work, the compound which could be the aldehyde Perlin assigned to the structure of **176** was unfortunately not isolated. Therefore, conclusions about the structure of this aldehyde cannot yet be made, nor a definitive answer on whether Perlin's aldehyde has a different structure than the one he assigned his data to. However, based on the chemical shifts reported by Perlin, it is postulated that the compound could be aldehyde **177** (Figure 2.5) formed as a result of C-6 to C-5 acetyl migration of **166**.

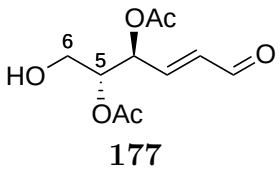
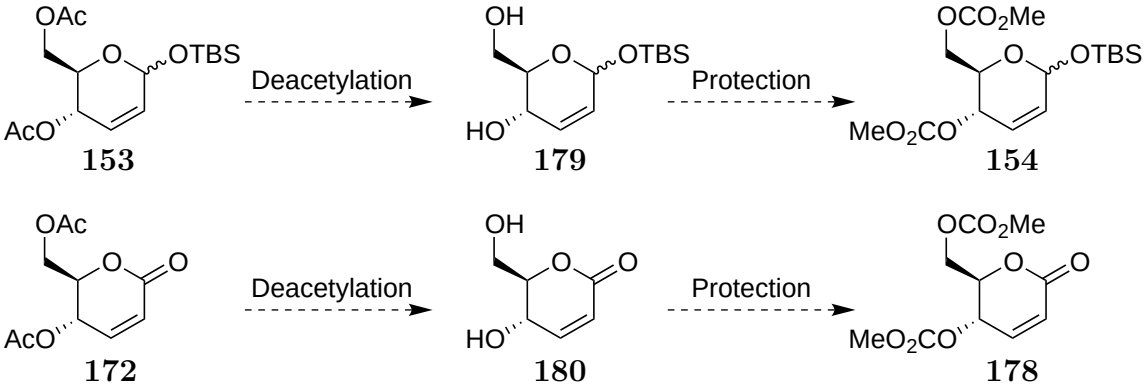


Figure 2.5 Proposed structure of the Perlin's misassigned aldehyde

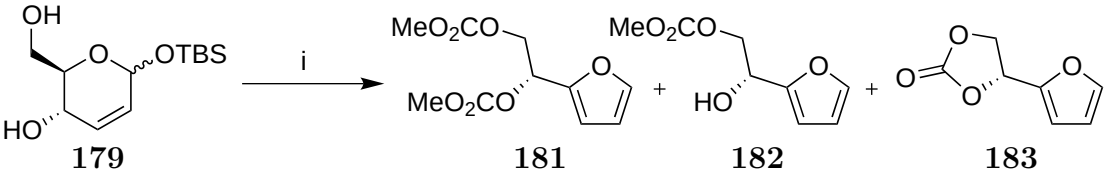
2.1.5 Synthesis of Dicarbonate Bis-Electrophiles 154 and 178

With two C-4 acetate bis-electrophiles synthesised, work on their carbonate analogues could begin. An initial route to these compounds (**154** and **178**) was envisioned through deprotection of the acetyl groups and subsequent carbonate protection of C-4 and C-6 of **153** and **172** (Scheme 2.9). Although this approach was not very synthetically efficient, it was seen as a way to gain quick access to these compounds so that they could be evaluated as bis-electrophiles in Pd-AA cascades. A more synthetically efficient route, where these compounds are generated directly from D-glucal is discussed later on in this section.



Scheme 2.9 Planned synthetic route from acetate bis-electrophiles **153** and **172** to carbonate bis-electrophiles **154** and **178**

Deprotection of **153** proceeded smoothly under basic conditions (NaOMe in methanol) delivering an anomeric mixture of diols (**179**) in an 85% yield. However, attempts to form dicarbonate **154** from the diols through protection with methyl chloroformate were unsuccessful. Examination of ^{1}H NMR spectra of crude reaction mixtures showed that, under the chosen conditions, no desired product formed; instead, formation of substituted furans dominated. The structures of these furans were distinguished in the ^{1}H NMR spectrum of the crude reaction mixture by their distinctive broad singlets around 7.40 ppm and, after isolation of each, their spectra matched those previously reported in the literature.[73]

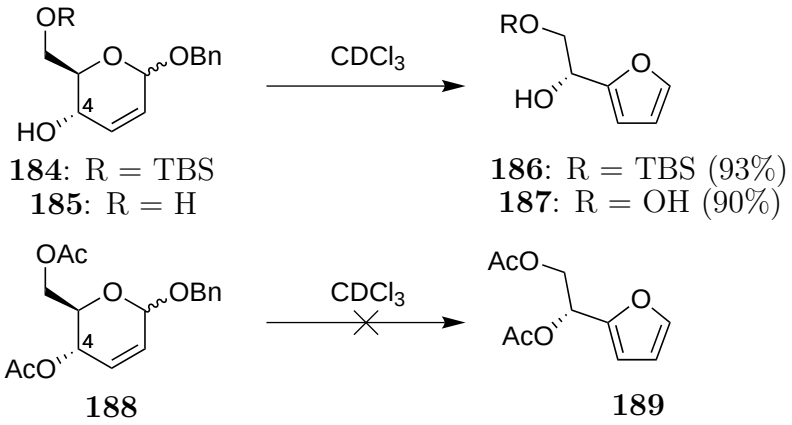


Reagents and Conditions: i) $ClCO_2Me$ (2.5 eq), DMAP (2.5 eq), THF, 0 °C or rt, O/N.

Scheme 2.10 Formation of furans **181**, **182** and **183** from diol **179**

The transformation of 2,3-unsaturated glycosides to furans has been documented

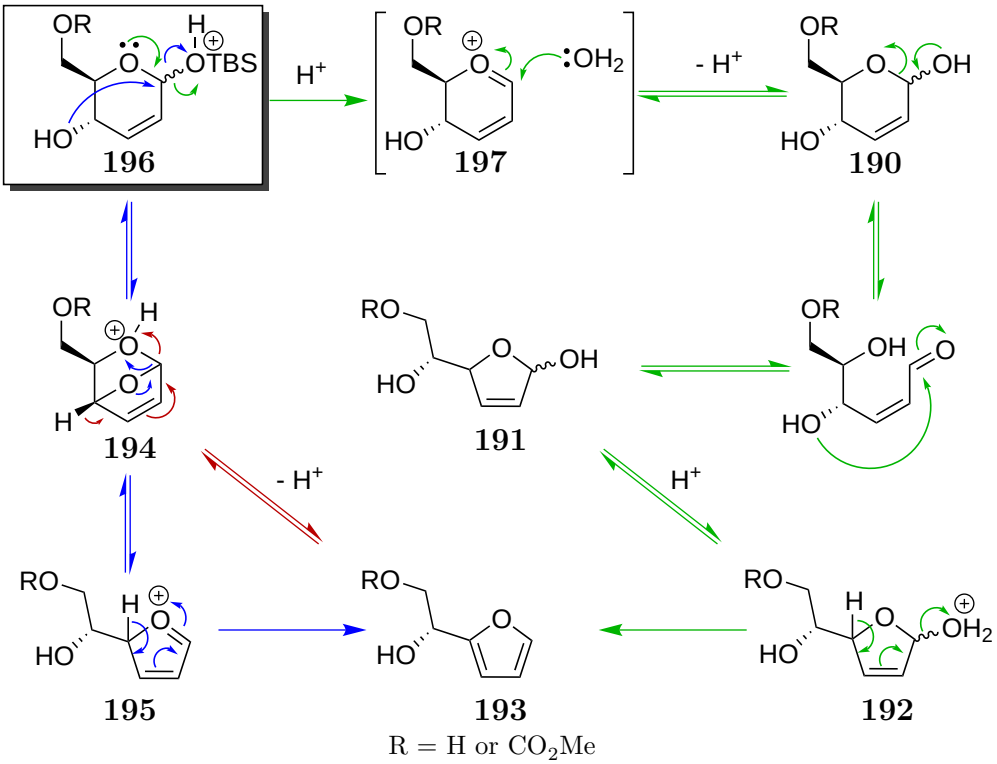
numerous times, including by Perlin when he observed rearrangement of D-glucal (**158**) in the presence of acid and catalytic mercuric sulfate, and also previously in our group by Dr Lynton Baird.[74] In Baird's research it was noted that when silyl ether **184** or diol **185** were left in $CDCl_3$ for extended periods of time, the compounds would convert to furans **186** and **187**, respectively. The stability of diacetate **188** in $CDCl_3$ however suggested that the presence of a free hydroxyl group at C-4 is necessary for this transformation (Scheme 2.11).



Scheme 2.11 Formation of furans from benzyl glycosides observed by Dr Lynton Baird

Three mechanisms for the formation of the observed furans in this work are proposed. The first (Scheme 2.12, green arrows) is consistent with Perlin and Baird's observations. Activation and elimination of the C-1 group and subsequent attack at the anomeric centre by trace amounts of water could give hemiacetal **190**. The free C-4 hydroxyl could then attack the carbonyl of the open-chain aldehyde to give dihydrofuran **191**. Protonation of the anomeric hydroxyl would activate hemiacetal **192** toward elimination, giving the stable furan **193**. The second mechanism (Scheme 2.12, blue arrows) deviates from mechanisms proposed by both Perlin and Baird, but is also plausible. Beginning with displacement of the C-1 OTBS by nucleophilic attack of the C-4 hydroxyl, ring opening of the corresponding bridged bicycle **194** to give furan **195** and subsequent elimination would afford the observed furan **193**. The third mechanism (Scheme 2.12, red arrows) begins with the same displacement of the C-1 OTBS as in the second mechanism but then a concerted formation of the furan is proposed over the previous step-wise mechanism. It is unknown whether protection of the C-6 hydroxyl occurs prior to or after rearrangement to the furan, and therefore both situations are considered in the case of all mechanisms.

The first proposed mechanism made it clear that trace amounts of water might be involved in the formation of the furan products, DCM was tested as a more suitable solvent than THF due to its lower miscibility with water. This variation did result

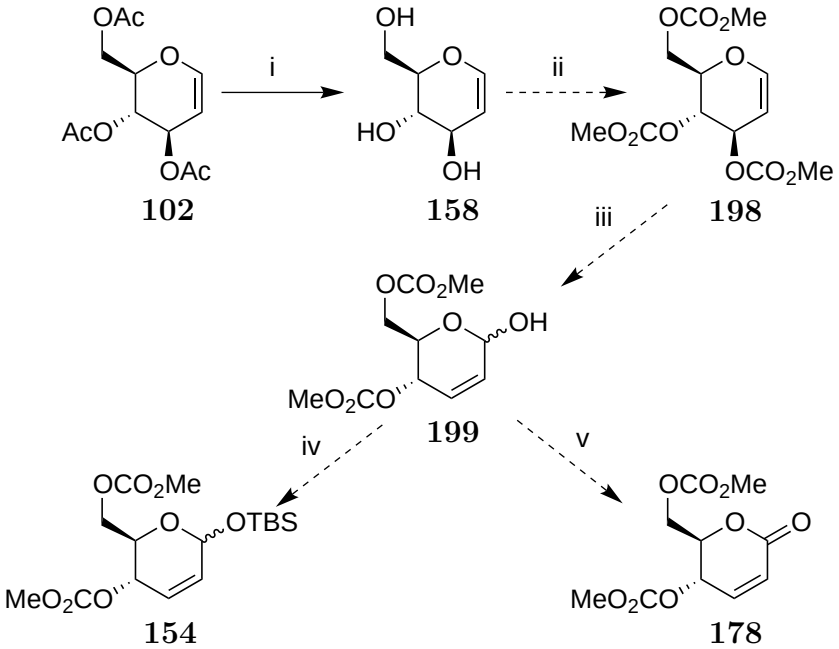


Scheme 2.12 Proposed mechanisms for the formation of furans from 2,3-unsaturated glycosides **196**

in decreased formation of furans, however also a decrease in consumption of starting materials and still no formation of the desired product.

The conversion of lactone **172** to **178** was also afflicted with difficulties. Deacetylation of the lactone using NaOMe in MeOH afforded a complex mixture of products whilst K_2CO_3 in MeOH led to a highly polar mixture of compounds that were unable to be isolated. These issues made it apparent that installation of methyl carbonate protecting groups would ideally be carried out prior to rearrangement of the glycal to give the 2,3-unsaturation. Therefore a more direct route to the carbonate bis-electrophiles **154** and **178** was proposed (Scheme 2.13).

Deacetylation of tri-*O*-acetyl-D-glucal (**102**) proceeded smoothly to give D-glucal (**158**) in 97% yield; however, conversion to tricarbonate glucal **198** through reaction with methyl chloroformate and stoichiometric DMAP, serving as both a catalyst and base, was consistently low. The desired tricarbonate product (**198**) was able to be isolated in 47-52% yields from crude reaction mixtures that also contained the 3,6- and 4,6-dicarbonate products. Longer reaction times, increasing equivalents of methyl chloroformate or using stoichiometric pyridine with catalytic DMAP afforded similar results. Purifying the mixture, combining the regioisomeric dicarbonate products and resubjecting them to the conditions produced further **198** in a 30% yield and the unreacted dicarbonate products could be re-isolated for further recycling. In all cases the 3,6-protected product was isolated in higher yields than



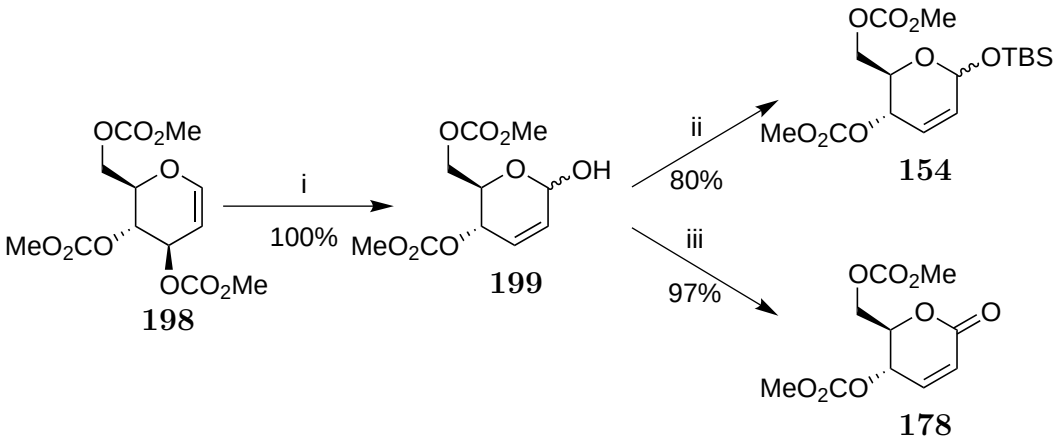
Reagents and Conditions: i) NaOMe, MeOH; ii) $ClCO_2Me$, DMAP, THF; iii) H_2O, 80 °C; iv) TBSCl, $AgNO_3$, pyridine, DCM; v) Fétizon's reagent, benzene.

Scheme 2.13 Planned route to dicarbonate bis-electrophiles **154** and **178**

the 4,6-protected product indicating that the issues surrounding this reaction could be due to steric hindrance induced upon dicarbonate formation.

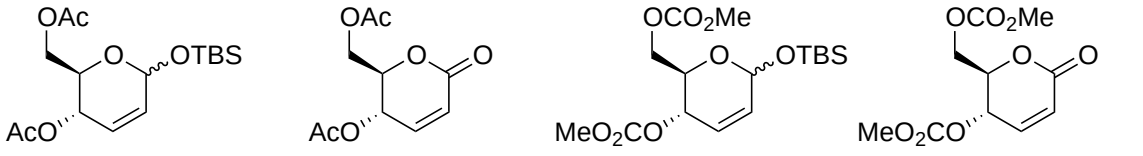
Despite the problems associated with the protection of D-glucal (**158**), the synthesis of the carbonate bis-electrophiles could be continued with the Ferrier-type allylic rearrangement of glucal **198** with water. As discussed earlier in section 2.1.3 (page 35), conversion of tri-*O*-acetyl-D-glucal (**102**) to diacetate hemiacetal **165** in hot water is a well established transformation, however the scope of this reaction has not been probed outside of glycals with C-3 acetate leaving groups. It was therefore pleasing to find that tri-*O*-(methoxycarbonyl)-D-glucal (**198**) could also undergo the transformation to hemiacetal **199**. More remarkably, the reaction was much more successful than its acetate equivalent, providing a quantitative yield, with no *trans*-aldehyde side-products, in a much shorter reaction time of only 30 minutes. Due to the only by-products of the reaction being methanol and carbon dioxide formed from the breakdown of the C-3 methylcarbonate leaving group, no workup was required except removal of water. Furthermore, the yield is quantitative, no organic solvents or metal promoters are used, there is no need for addition of reagents or catalysts , it is atom economical and requires only short reaction times. This reaction is therefore a wonderful example of the ideals of green chemistry.

Silyl protection of hemiacetal **199** with TBSCl proceeded smoothly providing carbonate bis-electrophile **154** in an 80% yield. Alternatively, oxidation of hemiacetal **199** with Fétizon's reagent afforded lactone **178** in 97% yield (Scheme 2.14), thereby completing the quartet of desired bis-electrophiles (Figure 2.6).



Reagents and Conditions: i) H_2O, 80 °C; ii) TBSCl, $AgNO_3$, pyridine, DCM; iii) Fétizon's reagent, benzene.

Scheme 2.14 Synthesis of carbonate bis-electrophiles **154** and **178** from glucal **198**



153	**172**	**154**	**178**
2 steps from **102**	2 steps from **102**	4 steps from **102**	4 steps from **102**
47% overall	56% overall	40% overall	49% overall

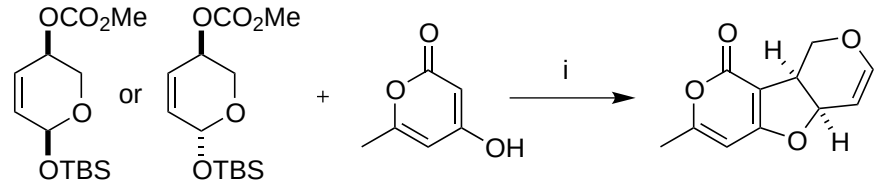
Figure 2.6 Bis-electrophiles synthesised from tri-*O*-acetyl-D-glucal (**102**)

2.2 Development of a ^{13}C NMR Shielding Profile for Tri-Substituted Dihydropyrans

Stereochemistry is known to play a significant role in governing the properties of compounds, including their chemical reactivity.[75] This is especially true for small ring compounds, such as those described in section 2.1, where the stereochemistry of the ring substituents also has a profound effect on the overall conformation of the compound,[76] a dominant factor in reactivity.[75] Indeed, upon developing the methodology of the Pd-AA cascade, Bartlett observed a notable difference in reactivity between *cis*- and *trans*-dihydropyran substrates *cis*-**42** and *trans*-**42**. Although both substrates were capable of undergoing the desired transformation to **45**, *trans*-**42** required a higher catalyst loading for efficient conversion to the product (Table 2.5).[19]

Two of the tri-substituted bis-electrophiles, **153** and **154**, prepared as described in section 2.1 (page 28), were isolated as anomeric mixtures. The stereoconvergent reaction of both dihydropyran diastereomers, demonstrated in Bartlett's work, sug-

Table 2.5 Comparison of reactivity of dihydropyrans *cis*-**42** and *trans*-**42** in a Pd-AA cascade



cis-**42** *trans*-**42** **39** **45**

Reagents and Conditions: i) $Pd(PPh_3)_4$, Toluene, rt., O/N.

Entry	Substrate	Cat. mol %	Yield
1	*cis*-**42**	5	83
2	*trans*-**42**	5	10
3	*trans*-**42**	20	74

gested that separation of the bis-electrophile diastereomers of **153** and **154** was probably unnecessary. However, due to the differing reaction conditions required by each diastereomer of **42**, it seemed prudent to determine the stereochemistry of the major and minor constituents of the bis-electrophile mixtures prior to testing them as substrates in the Pd-AA cascades.

The stereochemistry in question was that of the substituents at the anomeric centre, formed during the Ferrier reaction step. Although determination of the configurations at C-1 of 2,3-unsaturated products formed by Ferrier reactions is complex and depends upon many variables, substituted glucals when reacted with *O*-nucleophiles are generally assumed to give predominantly α-products.[53] This trend suggested that the major constituent of each of the bis-electrophile mixtures was the α-anomer and this is assumed to be true. However, an alternative method of analysis of the C-1 stereochemistry of these types of compounds was desired to allow for the assignment of tri-substituted dihydropyrans formed through non-Ferrier type reactions (e.g. the Achmatowicz route to **151**), or the assignment of 1:1, or near 1:1, mixtures of products of Ferrier reactions.

Stereochemical assignment of 3,6-dihydro-2*H*-pyrans is an interesting challenge due to the structural properties of the compounds. Planarity established by the unsaturation in the ring, accompanied by the ring oxygen, limit the information on the relative stereochemistry at C-1 and C-4 that could be taken from $^3J_{HH}$ coupling and also reduce the number of 1,3-diaxial relationships, thereby limiting the utility of NOE correlations. Bartlett noted these challenges and designed his own method of assigning the relative stereochemistry of C-1 and C-4 by analysis of axial shielding on the ring carbons.[19] He demonstrated that there is a clear difference in the ^{13}C chemical shifts of *cis*- and *trans*-dihydropyran diastereomers of type *cis*-**200** and *trans*-**200** (Figure 2.7). However, calculating the difference in chemical shift of each

ring carbon of the compounds ($\Delta\delta_C$) leads to a diagnostic shielding pattern which can allow for the assignment of relative stereochemistry. Thus, subtracting the ^{13}C NMR chemical shifts of *trans*-3,6-dihydro-2*H*-pyrans from the equivalent signals of the *cis*-diastereomer afforded a shielding pattern with positive values at positions C-1, C-3 and C-4 and negative values at positions C-2 and C-5.This diagnostic pattern, including the magnitudes of the differences, was found to fit well for a range of disubstituted substrates with oxygen-tethered substituents.

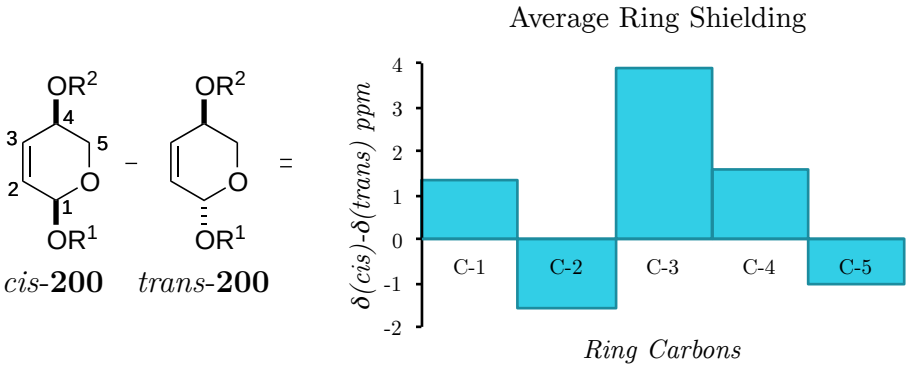
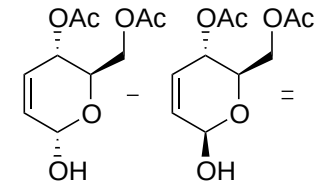
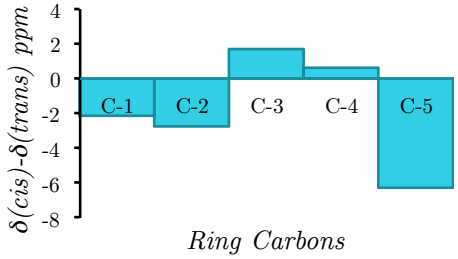
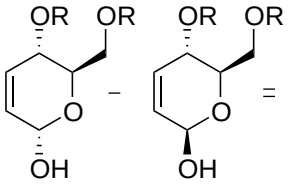
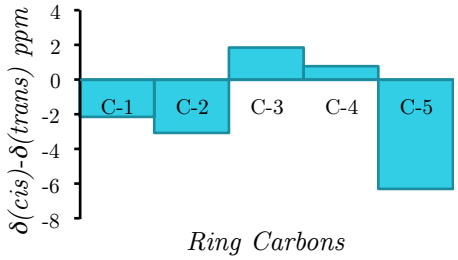
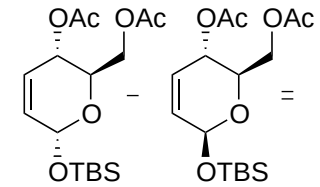
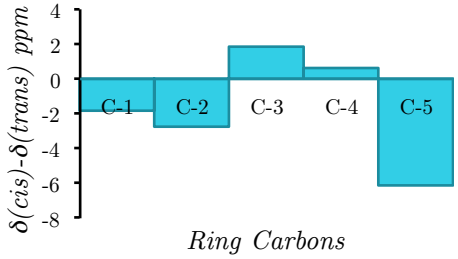
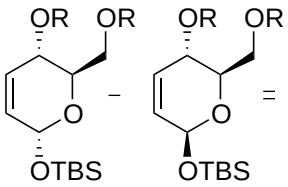
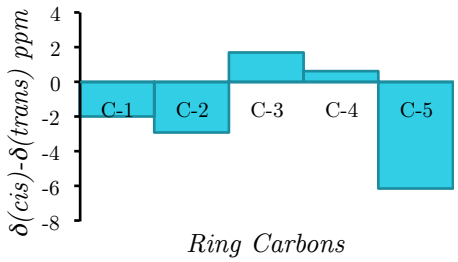
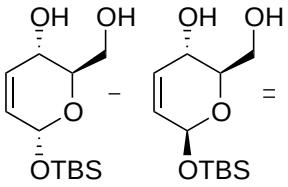
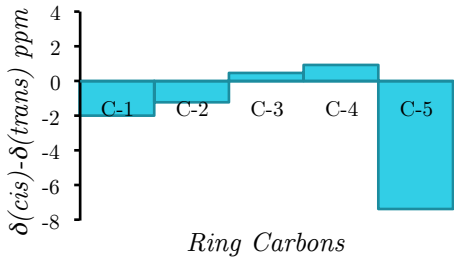


Figure 2.7 ^{13}C NMR shielding template for di-substituted dihydropyrans

With a limited number of examples to work with, Bartlett was unable to extend the template to more highly substituted ring systems. However with the accumulation of more examples and data in the present work, it was hoped that the methodology could be expanded. In section 2.1 a total of five anomeric mixtures of trisubstituted dihydropyran compounds were isolated. These compounds completed a pool of examples large enough that sufficient data was available for extension of the methodology.

Following Bartlett's method, ^{13}C NMR resonances of the ring carbons of all five trisubstituted dihydropyran mixtures synthesised in this work were assigned by analysis of their respective HSQC spectra. Next, the magnitude of axial shielding ($\Delta\delta_C$) was calculated by subtracting the ^{13}C shifts of each ring carbon in one diastereomer from those in their diastereomeric counterpart. It was noticed that, by subtracting the ^{13}C shifts of the minor product (assigned as the β-anomer or 1,4-*trans*-isomer) from those of the major product (assigned as the α-anomer or 1,4-*cis*-isomer), for all five dihydropyran mixtures, very similar shielding profiles were produced (Table 2.6). The profile produced from diol isomers *cis*- and *trans*-**179** deviates in the $\Delta\delta_C$ values of C-2 and C-3 to a minor extent when compared to the rest of the compounds. However this could be explained by the reduced conformational rigidity that comes with removal of the C-4 and C-6 protecting groups, which would effect the average shielding experienced by the ring carbons.

Table 2.6 Relative ^{13}C NMR shielding profiles of tri-substituted dihydropyrans synthesised in this project

Entry	Compounds	Relative Ring Shielding
1	 *cis*-**165** *trans*-**165**	
2	 *cis*-**199** *trans*-**199** R = CO_2Me	
3	 *cis*-**153** *trans*-**153**	
4	 *cis*-**154** *trans*-**154** R = CO_2Me	
5	 *cis*-**179** *trans*-**179**	

An average shielding template was therefore generated from the mean values of all five of these shielding profiles (Table 2.7, Figure 2.8). To some extent this new shielding template matches the shape of Bartlett's profile for disubstituted dihydropyrans for C-2 to C-5, however the deviation in sign of the average $\Delta\delta_C$ value of C-1 demonstrates that it was indeed necessary to develop a new profile for these more highly substituted dihydropyrans of type **201**.

Table 2.7 ^{13}C NMR shifts of *cis* and *trans* tri-substituted dihydropyrans and calculated $\Delta\delta_C$ values and average $\Delta\delta_C$ values

Cpd	**Substituents** $\mathbf{R^1, R^2, R^3}$	^{13}C NMR Shifts (*cis*, *trans*) (ppm) $\Delta\delta_C$ (***cis* - *trans***) **C-1**	**C-2**	**C-3**	**C-4**	**C-5**
165	H, Ac, Ac	88.7, 90.9	128.4, 131.2	129.0, 127.4	65.1, 64.5	66.8, 73.1
		-2.2	**-2.8**	**1.6**	**0.6**	**-6.3**
199	H, CO_2Me, CO_2Me	88.8, 90.9	128.6, 131.6	128.7, 126.9	68.6, 67.9	66.5, 72.8
		-2.2	**-3**	**1.8**	**0.7**	**-6.3**
153	TBS, Ac, Ac	89.1, 91.0	130.3, 133.0	127.0, 126.9	65.4, 64.8	66.8, 73.0
		-1.9	**-2.7**	**1.7**	**0.6**	**-6.2**
154	TBS, CO_2Me, CO_2Me	89.0, 91.0	130.7, 133.5	126.3, 124.7	68.8, 68.2	66.4, 72.6
		-2	**-2.8**	**1.6**	**0.6**	**-6.2**
179	TBS, H, H	89.0, 91.0	129.0, 130.1	131.2, 130.7	64.5, 63.5	71.1, 78.4
		-2	**-1.1**	**0.5**	**1**	**-7.3**
	Average $\Delta\delta_C$	**-2.1**	**-2.5**	**1.4**	**0.7**	**-6.5**

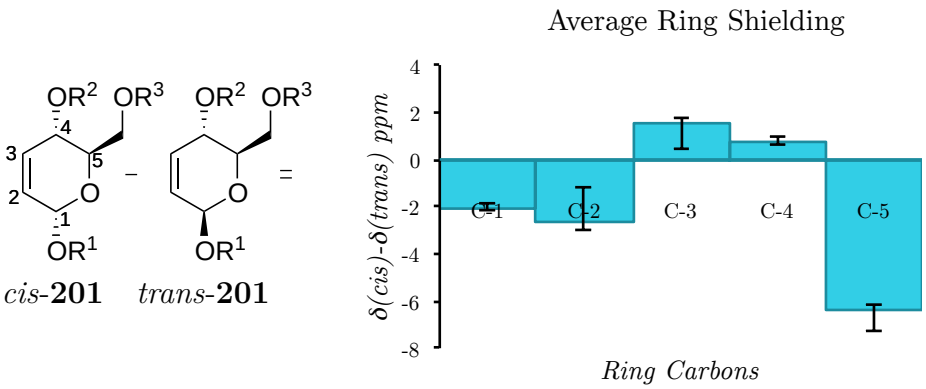


Figure 2.8 Average ^{13}C NMR shielding template of tri-substituted dihydropyrans **201**

To determine how applicable the average shielding template was for other similar compounds, additional spectral data of tri-substituted dihydropyrans were sought to analyse as comparisons. Although many compounds of this nature were found in the literature, ^{13}C NMR data of both *cis*- and *trans*-diastereomers were required, accompanied with either a full set of 2D NMR data or all carbon positions assigned to their NMR shifts. After a thorough search of available literature, no data that matched all the criteria were found. Therefore, a search of NMR data of compounds previously made within the research group was conducted and, even then, only two

compounds were found to have sufficient data for this study. The first compound, **202** (see Figure 2.9), was synthesised and isolated as a mixture of *cis*- and *trans*-diastereomers by Dr Lynton Baird during his PhD research.[74] With OTBS groups at C-4 and C-6 and an OBn group at C-1, this compound was seen as substantially different from the dihydropyrans produced in this work and therefore was a good compound for the assessment of the average shielding template. The second compound, **103** (see Figure 2.10), was synthesised as a mixture of *cis*- and *trans*-diastereomers by Dr Mark Bartlett during his PhD research.[19] Although similar to the compounds produced during this work, the anomeric isopropoxy group would also provide an extension to the scope of the template.

When compared to the average shielding template, the relative ring shielding profile produced by Baird's dihydropyran mixture (**202**) was found to fit extremely well, with all $\Delta\delta_C$ values matching in sign and magnitude (Figure 2.9). This provided evidence that the shielding template could fit well to a wide range of tri-substituted dihydropyrans.

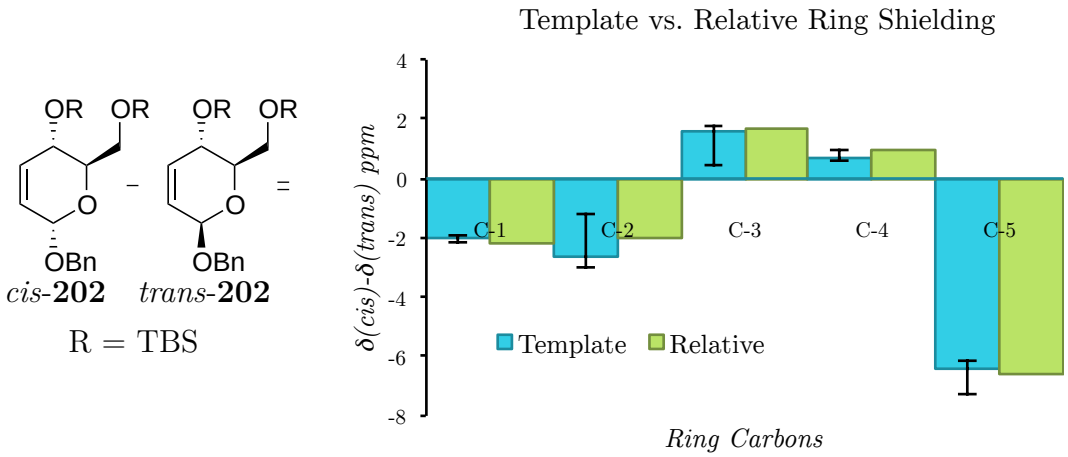


Figure 2.9 Comparison of ring shielding template versus relative ring shielding of tri-substituted dihydropyran **202**

Surprisingly, however, Bartlett's dihydropyran (**103**), although more closely related to the compounds produced in this work, did not fit the average shielding as well as did **202**. Significant deviations in magnitude for C-1, C-3 and C-5 were observed, although the general pattern of the template's silhouette remained (Figure 2.10). This example therefore made it clear that it is perhaps not the magnitudes of the $\Delta\delta_C$ values that should be taken into account but rather the sign and overall pattern of the profile produced. By doing so, it is believed that this template would provide additional evidence for stereochemical assignments of glucose-derived Ferrier products and also could be a useful tool for the stereochemical assignment of tri-substituted dihydropyrans formed through non-Ferrier type reactions.

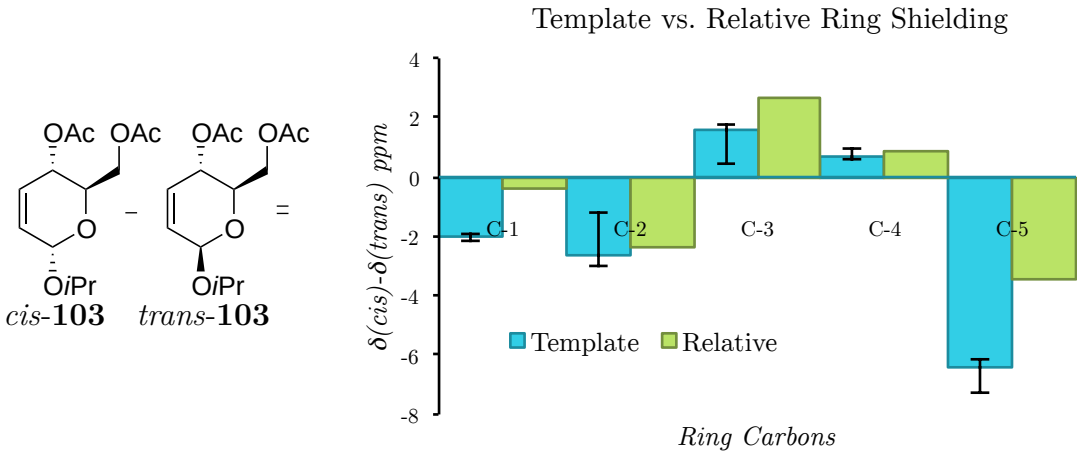
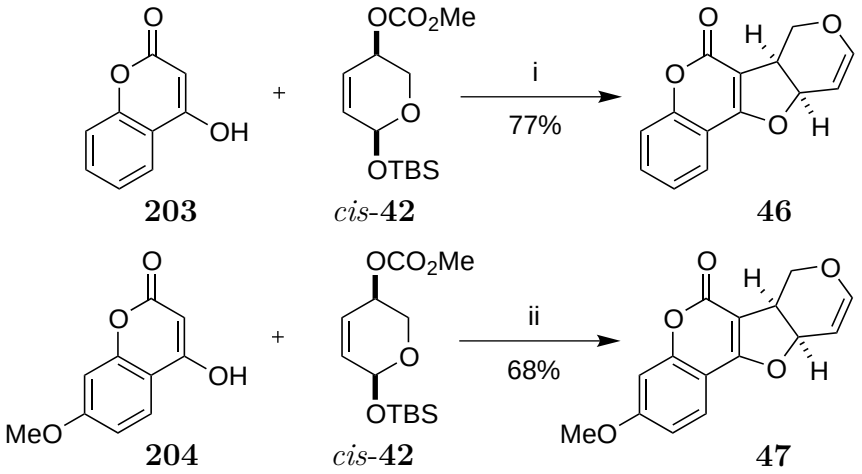


Figure 2.10 Comparison of ring shielding template versus relative ring shielding of tri-substituted dihydropyran **103**

2.3 Synthesis of Bis-Nucleophiles

2.3.1 Synthesis of Methyl Substituted 4-Hydroxycoumarins

During exploration of the scope of the earlier Pd-AA cascade, a variety of cyclic β-dicarbonyl bis-nucleophiles were tested by Bartlett (See Scheme 1.10, page 9). In general, it was found that nucleophiles with high enol content, such as α-pyrones and coumarins, yielded the best results. Two coumarins were tested in the Pd-AA cascade with bis-electrophile *cis*-**42**, namely 4-hydroxycoumarin (**203**) and 4-hydroxy-7-methoxycoumarin (**204**), and provided the desired pyranofurochromenone products **46** and **47** in 77% and 68% yields, respectively.

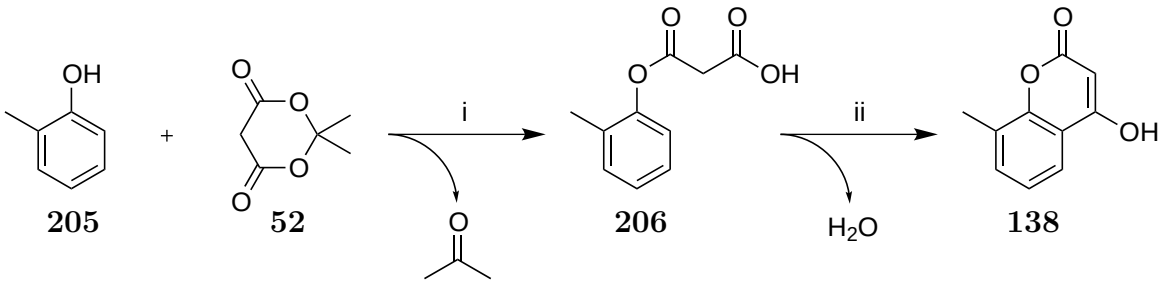


Reagents and Conditions: i) $Pd(PPh_3)_4$ (5 mol%), Toluene; ii) $Pd(PPh_3)_4$ (10 mol%), Toluene.

Scheme 2.15 Pd-AA cascade reactions of coumarin bis-nucleophiles **203** and **204**

To expand the scope of coumarin bis-nucleophiles in Pd-AA cascades, methylated

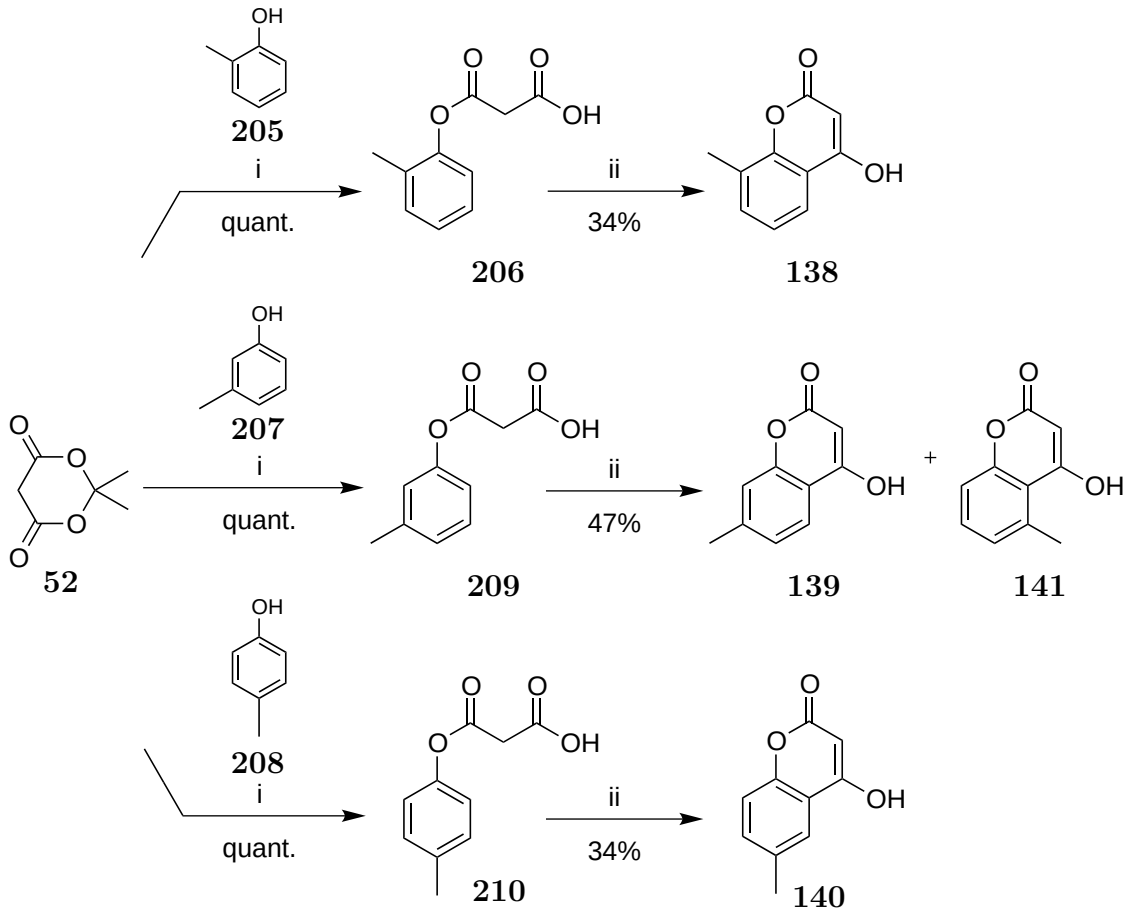
4-hydroxycoumarins were targeted as a means to probe regioisomeric effects of coumarins in the cascade. An attractive two-step one-pot literature method for the synthesis of 4-hydroxy-8-methylcoumarin from *o*-cresol and Meldrum's acid was reported by Moody *et al.*[77] This simple and efficient synthesis, first developed by Gao *et al.*[78] stood out from other literature methods for its solvent-free and atom-economic characteristics. The initiating step involved the neat reaction of *o*-cresol (**205**) and Meldrum's acid (**52**), whereupon expulsion of the sole by-product, acetone, provided the intermediate carboxylic acid **206** in quantitative yield. Evacuation to remove the acetone eliminated the need for a workup. The intermediate acid was treated immediately with Eaton's reagent, a dehydrating reagent readily prepared from P_2O_5 and methanesulfonic acid,[79] to afford the methylcoumarin **138**. Crystallisation of the crude reaction mixture then afforded the methylcoumarin **138** in a 98% yield according to Moody, although in only 60.5% yield by Gao.



Reagents and Conditions: i) 100 °C, 3h.; ii) Eaton's reagent, 70 °C, 4-5 h.

Scheme 2.16 One-pot synthesis of 4-hydroxy-8-methylcoumarin (**138**) from *o*-cresol (**205**)

Following this literature procedure in the current work successfully produced the desired methyl coumarin **138** from *o*-cresol (**205**). Purification by recrystallisation from 20% acetone in pentane, as reported in the literature,[77] yielded minimal coumarin from the crude reaction mixture, however, changing recrystallisation solvents to absolute ethanol, as recommended by Gao, increased the product yield to 34%. As no NMR analysis was carried out on the crude reaction mixture prior to recrystallisation nor on the mother liquor, no comment can be made on whether the differing results are due to the success of the reaction or isolation of the product. Nevertheless, the procedure was also found to be capable of producing the corresponding regioisomeric methylcoumarins from *m*- and *p*-cresol in similar isolated yields. However, *m*-cresol (**207**) yielded both possible regioisomers (**139** and **141**), which were isolated by recrystallisation as an inseparable 1.3:1 mixture (Scheme 2.17). Although not ideal, it was not seen as crucial to separate the two products because insight into the reactivity of each could still be monitored by ^{1}H NMR spectroscopy. Thus, four cyclic bis-nucleophiles were available for testing in the Pd-AA cascades.



Reagents and Conditions: i) 100 °C, 3h.; ii) Eaton's reagent, 70 °C, 4-5 h.

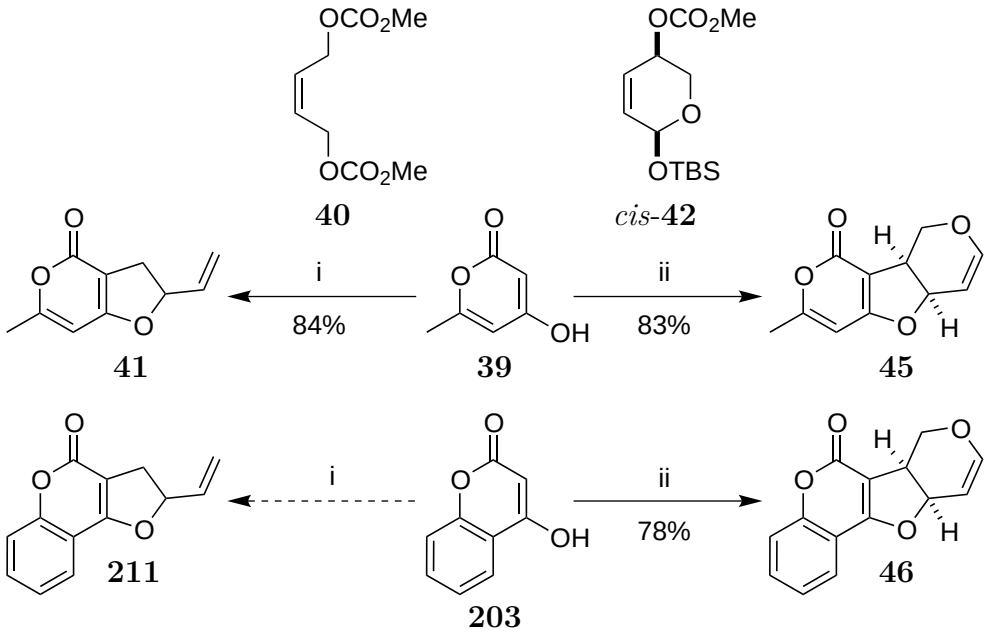
Scheme 2.17 Synthesis of methylcoumarins **138**, **139**, **141**, and **140**

2.4 Pd-AA Cascades with Prepared Substrates

2.4.1 Technical Challenges of Pd-AA Cascades and Initial Exploration

Prior to testing the prepared substrates, it was necessary to gain competence in carrying out the experimentally challenging Pd-AA cascades by achieving consistency in results of known reactions. Consistent experimental technique was essential in order to maximise the validity of any results gained. This was achieved through repeating Pd-AA cascades on substrates already tested by Bartlett and comparing the results with those obtained previously.

Existing[19] Pd-AA cascades were used as a platform to learn the Pd-AA cascade techniques, namely coumarin **203** with pyran bis-electrophile *cis*-**42**, and pyrone **39** with acyclic bis-electrophile **40**. This also opened up the possibility to test coumarin **203** as a substrate in the acyclic Pd-AA cascade (Scheme 2.18).



Reagents and Conditions: i) **40**, $Pd_2(dba)_3$, PPh_3, NEt_3, MeCN, rt,1h; ii) *cis*-**42**, $Pd(PPh_3)_4$, toluene, rt, O/N.

Scheme 2.18 Bartlett's Pd-AA results for synthesis of **45**, **41** and **46** and planned synthesis of **211**

After a few attempts at the synthesis of **41**, it became apparent just how sensitive these cascades were to modifications in experimental technique and also to subtle changes in the integrity of solvents or reagents. The initial runs of the Pd-AA cascade were met with inconsistent results, from low conversion to no reaction at all. In general, this was seen as a direct result of the sensitivity of the catalyst.

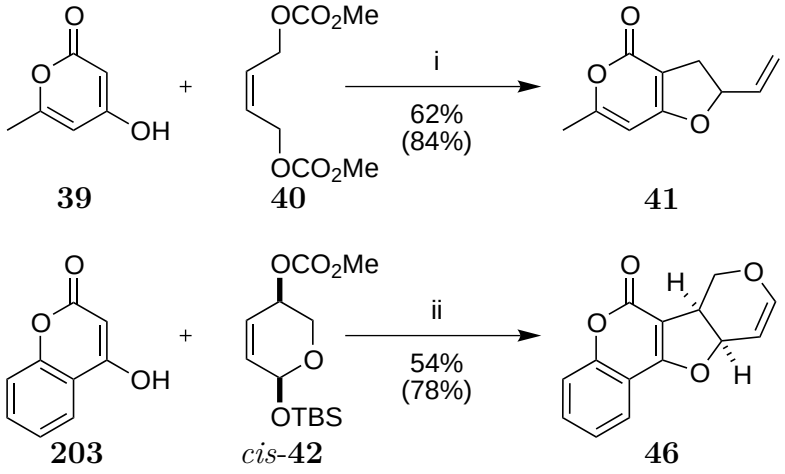
With the exception of some novel air-stable palladium catalysts, organopalladium chemistry typically requires rigorously inert conditions due to the tendency for palladium complexes to decompose upon reaction with oxygen or moisture.[2] $Pd_2(dba)_3$ is a useful source of Pd(0) as, in contrast to $Pd(PPh_3)_4$, it is insensitive to oxygen and so special care in handling and storage is unnecessary. When $Pd_2(dba)_3$ is in solution in the presence of phosphine ligands, L, dba dissociates and allows the formation of the active species, PdL_2, in the reaction mixture.[80] An attractive aspect of these Pd-AA cascades is that they can be successfully performed without the use of expensive equipment or special glassware.

In order to achieve consistent and reliable results, the following techniques were deemed necessary. Firstly, all glassware used in the reactions, or in preparation of the reactions, were thoroughly cleaned and heated to 600 °C with a heat gun under high vacuum and then immediately placed under an inert atmosphere of either argon or nitrogen. Secondly, all solvents and liquids were degassed by sparging with argon or nitrogen for a minimum of 20 minutes, and then, when required, transferred into the reaction flask via needles that had been dried in an oven overnight and cooled in a dessicator prior to use. The quality of solvent was also found to be a contributing player in the success of the reactions and freshly distilled solvents were found to produce the best results, while solvents of poorer quality produced lower yields or completely inhibited consumption of the bis-electrophiles. For overnight reactions, rubber septa with minimal previous use were beneficial for eliminating contamination by air and moisture. Furthermore, after all reagents were added, all gas lines were removed and the septum was secured and doubly sealed with insulation tape, forming, as much as possible, a closed system. This last technique was deemed safe in this instance on small scale, due to the possibility of only a small pressure build up, as only a stoichiometric amount of CO_2 gas is produced from the carbonate leaving groups.

Purging the reaction vessel was one of the more interesting technical challenges faced upon performing the cascades. Prior to the addition of reagents, a Schlenk line was used to purge the reaction vessel under oil-pump vacuum. However, upon adding the catalyst and bis-nucleophile, the high pressure of the nitrogen line* in conjunction with the light weight of the catalyst material made purging the vessel with a Schlenk line detrimental to the success of the reaction. In most cases the catalyst would get blown upwards into the septum, thereby making the true catalyst loading in the reaction mixture unknown. Controlling the speed of introduction of the gas in the purge was best done by the use of a nitrogen-balloon connected via a glass tube and tap setup, a consequence of the lower pressure of the balloon.

*The pressure of the reticulated gas in the building where labwork was conducted was abnormally high.

Employing the above techniques and Bartlett's methods on the reported cascades eventually led to consistent results; however, in both cases, the yields gained were lower than those reported by Bartlett (Scheme 2.19). This result emphasises the degree of sensitivity of these reactions where, despite considerable efforts, reproducibility of yields between researchers is limited. However, because the relative magnitude of the yields matched the reactivity difference in substrates seen by Bartlett, and as they were also high enough for synthetic purposes, it was possible to attempt extending the scope to include the reaction of hydroxycoumarin **203** with dicarbonate **40**.



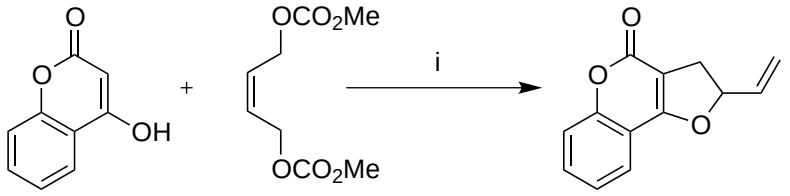
Reported yields[19] shown in brackets

Reagents and Conditions: i) $Pd_2(dba)_3$, PPh_3, NEt_3, MeCN, rt,1h; ii) $Pd(PPh_3)_4$, toluene, rt, O/N.

Scheme 2.19 Comparison of reported yields with yields obtained in this work for selected Pd-AA cascades

Using Bartlett's optimised conditions for Pd-AA cascades with acyclic bis-electrophile **40**, the reaction of hydroxycoumarin **203** successfully produced the desired product **211** in a modest 52% yield, thereby adding to the scope of the reaction (Table 2.8). This yield compared well with Bartlett's results that showed the hydroxycoumarin produced a lower yield than methylpyrone **39** when subjected to the same conditions (*viz.* Scheme 2.18). To ensure that the conditions were optimal, a small study of catalyst loadings and reaction concentration revealed that, indeed, decreasing catalyst loading or increasing reaction concentration were detrimental to the success of this reaction (Table 2.8).

Table 2.8 Effect of changes to reaction variables on yield of Pd-AA cascade product **211**: catalyst loading and reaction concentration



203 **40** **211**

Reagents and Conditions: i) $Pd_2(dba)_3$, PPh_3, NEt_3, MeCN, rt, 1h.

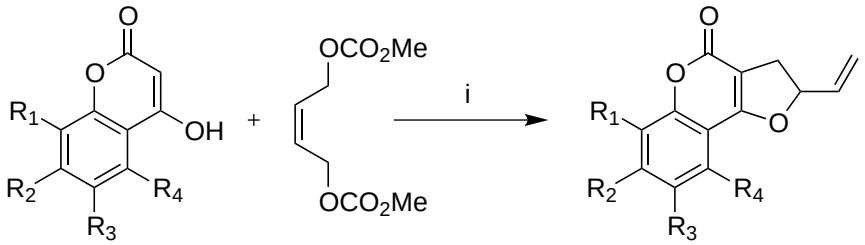
Reaction Variables		**Conc. (40) (M)**		
		0.05	0.10	0.20
Mol % Pd	20	52%	41%	-
	10	47%	32%	26%
	5	43%	-	-

2.4.2 Reactions of Methylcoumarins with Acyclic and Cyclic Bis-Electrophiles

The synthesis of a variety of methylated 4-hydroxycoumarins (see Section 2.3.1, page 51) allowed for exploration of their ability to act as bis-nucleophiles in the Pd-AA cascades with both acyclic and cyclic bis-electrophiles, **40** and *cis*-**42**, respectively. All four coumarins were found to successfully produce the corresponding vinyl-substituted products when introduced to acyclic bis-electrophile **40** and the optimised conditions associated with it. The yields summarised in Table 2.9 demonstrate that the position of the aromatic methyl substituent provides little deviation in the reactivity of the compounds towards the cascades. This is emphasised by the consistency in the ratio of the starting material and product regioisomers during the reaction of the *m*-cresol derived coumarins **139** and **141** (Table 2.9, Entry 2). Despite achieving only modest yields for all three reactions, no further optimisation studies were performed. It is highly likely, given the variance in yields between previously reported work and this work as discussed in the previous section, that higher yields can be achieved for these reactions.

When subjecting the methylated 4-hydroxycoumarins to Bartlett's optimised conditions for the reaction with *cis*-**42**, ^{1}H NMR of the crude reaction mixtures showed that no reaction occurred for any of the substrates. It was noticed that solubility of the coumarins was limited in toluene and therefore a mixed solvent system of 3:1 toluene:DMF was tested. This modification was chosen as it was found to be moderately successful with the 4-hydroxypyridinone substrate which was similarly insoluble in earlier scope studies performed by Bartlett (Scheme 1.10). Indeed, in the presence of DMF, the substrates were completely soluble and TLC analysis

Table 2.9 Expansion of Pd-AA cascades with dicarbonate bis-electrophile **40** to include methylcoumarins



212 **40** **213**

Reagents and Conditions: i) $Pd_2(dba)_3$, PPh_3, NEt_3, MeCN, rt, 1h.

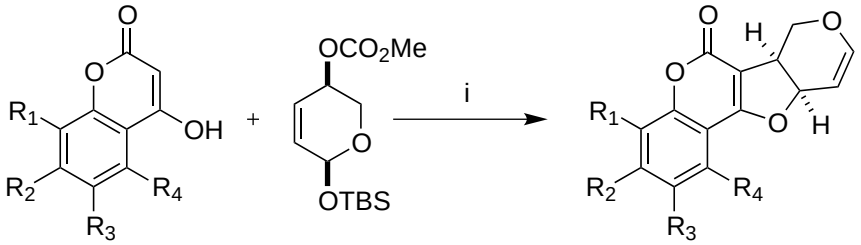
Entry	Bis-Nucleophile	Substituents				Yield
		R_1	R_2	R_3	R_4	
1	**138**	Me	H	H	H	51%
2[a]	**139**+**141**	H	Me/H	H	H/Me	46%[b]
3	**140**	H	H	Me	H	46%

[a]Reaction performed on a 1.3:1 mixture of **139**:**141**
[b]Composed of a 1.3:1 mixture of **214**:**215**

showed complete consumption of the bis-electrophile *cis*-**42**. However, after flash column chromatography, the desired products were isolated in only low yields (Table 2.10, Entries 4-6). The necessity of the methylated 4-hydroxycoumarins to have a different solvent system than 4-hydroxycoumarin (**203**) was surprising due to the minimal structural differences in the compounds. Furthermore, the mixed solvent system induced a negative effect on the Pd-AA cascade of 4-hydroxycoumarin (**203**), lowering the yield from 54% (see Scheme 2.19) to 22% (Table 2.10, Entry 7).

The low yields obtained upon modification of the solvent system was unexpected and contradicted the exceptionally clean ^{1}H NMR of the crude reaction mixtures (e.g. Figure 2.11, blue spectrum), all of which showed no starting material remained, instead revealing only peaks that correlated to the desired product, PPh_3, and the cleaved TBS group. It therefore seemed apparent that compounds remained on the column after isolation of the desired product. The polar compounds that remained on the column after purification of the reaction of **138** with *cis*-**42** (Table 2.10, Entry 4) were eluted with EtOAc and ^{1}H NMR showed the presence of compounds with shifts around 3.8-4.2 ppm and a multiplet at 2.0 ppm that were absent from the ^{1}H NMR spectrum of the crude reaction mixture. Purification of the EtOAc-eluted fractions by flash column chromatography afforded the main component, characterised as a hemiacetal (**219**) (red spectrum Figure 2.11). This demonstrated that the desired products were susceptible to hydrolysis on the column, potentially acid-promoted hydrolysis due to the slightly acidic nature of silica gel.

Table 2.10 Optimisation of expansion of Pd-AA cascades with dihydropyran bis-electrophile *cis*-**42** to include methylcoumarins



212 *cis*-**42** **216**

Reagents and Conditions: i) $Pd(PPh_3)_4$, Solvent, rt, O/N.

Entry	Solvent	Bis-Nucleophile	Substituents				Yield
			R_1	R_2	R_3	R_4	
1	Toluene	**138**	Me	H	H	H	0%[a]
2[b]	Toluene	**139** + **141**	H	Me/H	H	H/Me	0%[a]
3	Toluene	**140**	H	H	Me	H	0%[a]
4	Toluene:DMF 3:1	**138**	Me	H	H	H	39%
5[b]	Toluene:DMF 3:1	**139** + **141**	H	Me/H	H	H/Me	30%[c]
6	Toluene:DMF 3:1	**140**	H	H	Me	H	25%
7	Toluene:DMF 3:1	**203**	H	H	H	H	22%
8[d]	Toluene:DMF 3:1	**140**	H	H	Me	H	<10%
9[e]	Toluene:DMF 3:1	**138**	Me	H	H	H	49%
10[e]	Toluene:DMF 3:1	**140**	H	H	Me	H	47%

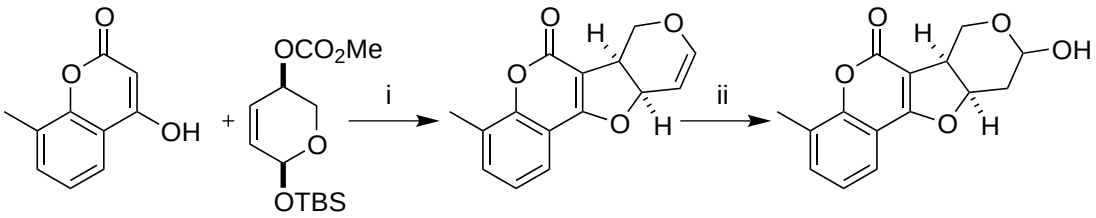
[a] ^{1}H NMR of the crude reaction mixture showed unreacted starting material and no desired product

[b] Reaction performed on a 1.3:1 mixture of **139**:**141**

[c] Composed of a 1.3:1 mixture of **217**:**218**

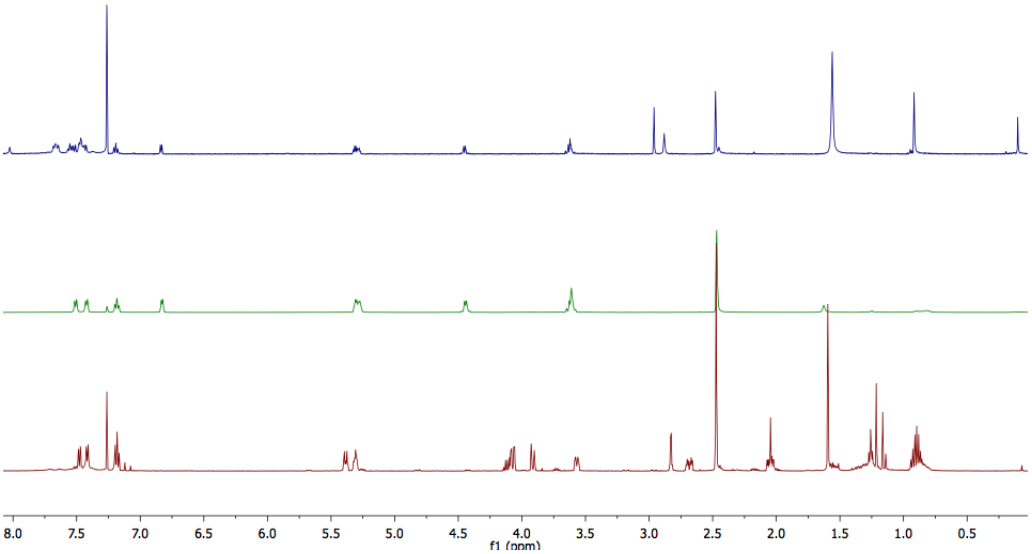
[d] Purified by alumina gel column chromatography

[e] Purified by column chromatography with solvent containing 1% NEt_3



138 *cis*-**42** **220** **219**

Reagents and Conditions: i) $Pd(PPh_3)_4$, 3:1 toluene:DMF, rt, O/N; ii) silica column.



Key: Blue spectrum = crude reaction mixture of Pd-AA cascade of **138** and *cis*-**42**, Green spectrum = purified desired product (**220**), Red spectrum = purified degradation product (**219**)

Figure 2.11 Comparison of ^{1}H NMR spectra of Pd-AA cascade crude reaction mixture (blue), desired product **220** (green), and by-product **219** (red)

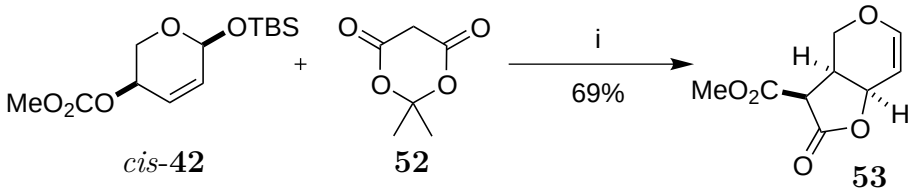
Two methods were tested to suppress this mode of degradation. The first replaced silica with alumina as the stationary phase, tested with a crude mixture of the reaction of *p*-cresol derived coumarin **140** and resulted in poor separation and low isolated yields (<10%) of desired product. The second method was to treat the silica gel with organic base prior to use in column chromatography and then to use a solvent system containing a low percentage of base during elution. This method was tested on a crude mixture of the reaction of **138**. The column was packed with a slurry of silica prepared from a solution of 1% NEt_3 in petroleum ether, and then eluted with 10-20% EtOAc in the NEt_3-treated petroleum ether. This was a more successful purification method, resulting in an increase in the isolated yield of desired product **220** from 39% to 49%. An EtOAc elution, performed after isolation of the desired product, demonstrated that this method did suppress the formation of hemiacetal **219** through the absence of peaks that correspond to this degradation product in the ^{1}H NMR spectrum.

Overall, the yields of desired products obtained from the reactions of the methylated 4-hydroxycoumarins with *cis*-**42** reflected the observation, noted earlier with the acyclic variant, that the placement of the aromatic methyl does not affect the reactivity of the coumarins towards the Pd-AA cascade. The consistency of yields of around 50% for the Pd-AA cascades with *cis*-**42**, at first glance might appear significant, suggesting, perhaps, that these compounds may require two equivalents of coumarin substrate as in the acyclic conditions. However, the simplicity of the ^{1}H NMR spectrum of the crude reaction mixture would indicate that the modest yields are not a result of suboptimal reaction conditions, but instead a problem with purification technique, and further work is required in this area.

2.4.3 Reactions of Tri-Substituted Bis-Electrophiles

Finding a carbohydrate-derived bis-electrophile that was capable of undergoing a Pd-AA cascade with Meldrum's acid, in the same manner as does dihydropyran *cis*-**42** (Scheme 2.20), was crucial to the success of the thromboxane synthesis. In this way, the bicyclic core of the thromboxane intermediate would be constructed in a facile manner, providing a strong foundation for the proposed synthetic route to the thromboxanes.

Of the four bis-electrophiles prepared in section 2.1 (*viz.* page 28), **154** was the closest in functionality to *cis*-**42** and, therefore, was tested first in a Pd-AA cascade with Meldrum's acid. Investigations began with conditions based on an unoptimised version of Bartlett's cascade, namely employing one equivalent of Meldrum's acid

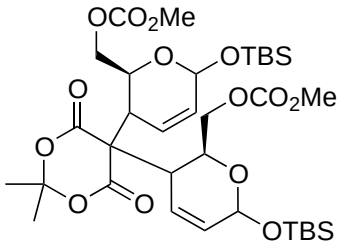


cis-**42** **52** **53**

Reagents and Conditions: i) 5 eq. of **52**, $Pd(PPh_3)_4$ (10 mol%), THF:MeOH 10:1, rt, O/N.

Scheme 2.20 Bartlett's synthesis of **53** from *cis*-**42** with Meldrum's acid (**52**)

and toluene as the solvent (Table 2.11, Entry 1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the reaction had proceeded with good conversion in that a distinctive doublet was observed at 6.64 ppm corresponding to the enol ether proton at C-1 of the desired product (**221**). Isolation of the desired product was unsuccessful, however, as it was co-eluted with unreacted Meldrum's acid. Therefore an isolated yield of **221** was unable to be quoted for these conditions. One compound was isolated and was identified as bis-adduct **222** (Figure 2.12) formed through double addition of the bis-electrophile to Meldrum's acid. Due to the small amount of material obtained, no stereochemical assignment was made. However, on the basis that the Pd-AA mechanism was followed overall retention of configuration at C-4 is assumed. Furthermore, a single relative stereochemical realationship at C-1 is proposed based on the identical NMR signals from both pyran rings. An excess (5 equiv.) of Meldrum's acid was added to suppress the formation of bis-adduct **222** (Table 2.11, Entry 2). This reaction did not proceed at all, which is puzzling.

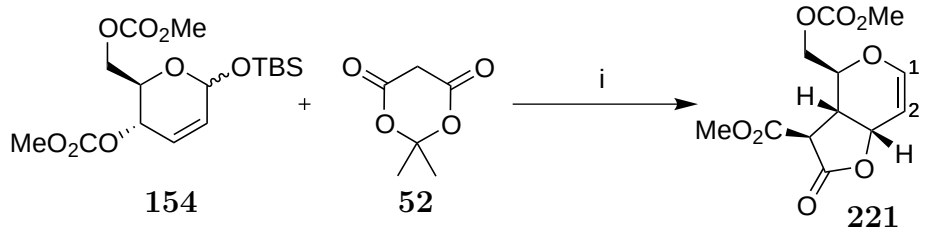


222

Figure 2.12 Bis-adduct formed in Pd-AA cascade of **154** with Meldrum's acid

Adoption of Bartlett's conditions (Table 2.11, Entry 3) resulted in formation of the desired product; however, isolation was again unsuccessful for the aforementioned reason. It was also noticed that the reaction proceeded with limited conversion and **154** was able to be regenerated in 32% yield. Retaining the mixed solvent system (THF/MeOH) and reverting back to addition of a single equivalent of Meldrum's acid (Table 2.11, Entry 4) decreased the conversion of the reaction, with 53% of starting material **154** recovered from the reaction mixture; however, the reduction in the amount of Meldrum's acid in the crude reaction mixture allowed for the observation of a small dark spot appearing just below the characterstic pink spot of Meldrum's acid on a TLC plate of the reaction mixture when stained with anisaldehyde dip. With excess charring the dark spot was completely disguised by the Meldrum's acid

Table 2.11 Optimisation of Pd-AA cascade of bis-electrophile **154** with Meldrum's acid (**52**)



154 **52** **221**

Reagents and Conditions: i) catalyst, solvent, MeOH (5 eq.), rt, O/N

Entry	Catalyst (Mol% Pd)	Solvent	Equiv. 52	Yield
1	$Pd(PPh_3)_4$ (5)	Toluene	1	0%[a,b]
2	$Pd(PPh_3)_4$ (5)	Toluene	5	0%[c]
3	$Pd(PPh_3)_4$ (5)	THF:MeOH 10:1	5	0% [a,d]
4	$Pd(PPh_3)_4$ (5)	THF:MeOH 10:1	1	18% [e]
5	$Pd(PPh_3)_4$ (15)	Toluene	5	**62%**
6	$Pd_2(dba)_3$ / PPh_3 (15)	Toluene	5	13% [f]
7	$Pd(PPh_3)_4$ (20)	Toluene	5	36%[f]
8[g]	$Pd(PPh_3)_4$ (15)	Toluene	5	17%[f,g]

[a]Desired product was observed in ^{1}H NMR of crude reaction mixture, but was lost in isolation

[b]Bis adduct **222** isolated in 7% yield (*w.r.t.* **154**)

[c] ^{1}H NMR of the crude reaction mixture showed unreacted starting materials and no desired product

[d]**154** recovered in 32% yield

[e]**154** recovered in 53% yield

[f]Poor conversion

[g]Reaction performed at 30-40 °C

spot. Careful chromatography allowed the compound correlating to the dark spot to be isolated separately from Meldrum's acid and it was found to be the desired product. The formation of **221** was evident from signals at δ 6.64 and δ 5.13 in the ^{1}H NMR spectrum attributed to H-1 and H-2 respectively. The *R*-stereochemistry at C-5 of **221** was assigned through a positive NOE correlation between H-5 (δ 3.57) and H-8 (δ 4.38). While this assignment appears surprising at first glance, a 3D model makes it evident that these protons can be in close proximity in only this stereoisomer (Figure 2.13). Circumstantially, NOE correlations between H-1 and H-5, and H-1 and H-7 were not observed.

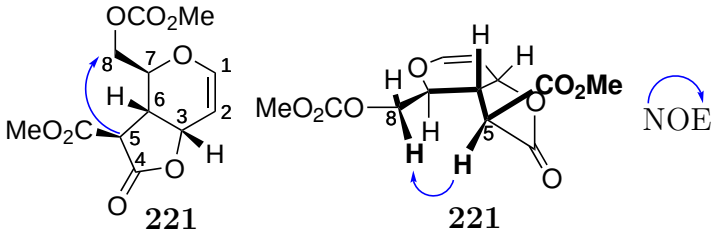
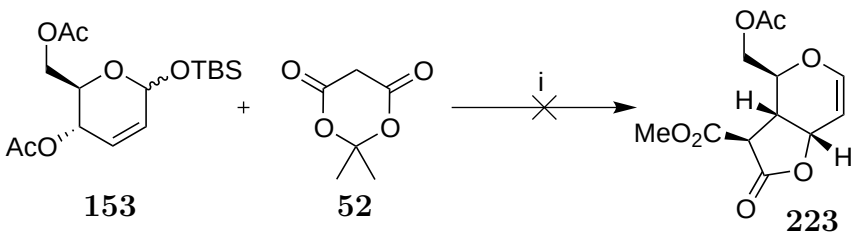


Figure 2.13 NOE correlation used to determine stereochemistry of Pd-AA cascade product **221**

Entries 1, 3 and 4 (Table 2.11) revealed that bis-addition can be suppressed by either the use of excess Meldrum's acid or by the use of THF:MeOH as a solvent, and using excess equivalents of Meldrum's acid or toluene as a solvent increases conversion of the reaction. The conditions chosen for the next step of the optimisation, were based of these observations in conjunction with an increased catalyst loading to combat the decreased reactivity assumed to accompany the use of a mixture of 1,4-*cis*- and *trans*-isomers of **154** (Table 2.11, Entry 5) (see also section 2.2 page 45). ^{1}H NMR spectroscopy of the crude reaction mixture showed complete consumption of starting material **154** with very minimal evidence of undesired side products. The desired product (**221**) was then isolated in a 62% yield, and these conditions were found to give reproducible yields of 55-62% when repeated. Additional modifications of the reaction conditions, namely the use of a different catalyst system (Entry 6), a further increase in catalyst loading (Entry 7), or increasing reaction temperature (Entry 8) were all found to have negative effects on the conversion and yield of the reaction.

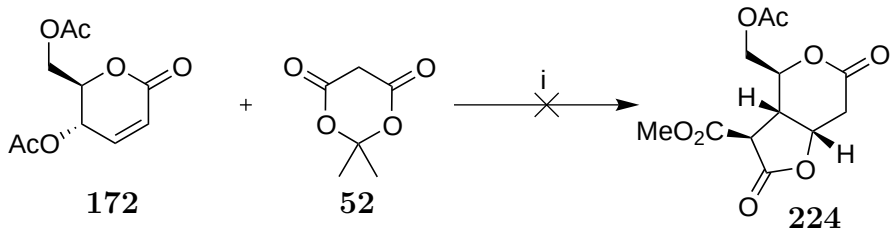


Reagents and Conditions: i) $Pd(PPh_3)_4$ (15 mol%), MeOH (5 eq.) toluene, rt, O/N.

Scheme 2.21 Unsuccessful Pd-AA cascade of bis-electrophile **153** with Meldrum's acid (**52**)

The acetate analogue of **154** (**153**), was found to be unreactive under the previously optimised Pd-AA conditions (Scheme 2.21). The ^{1}H NMR spectrum of the crude reaction mixture showed that the reaction did not proceed at all, displaying only unreacted starting material. This result, although unsurprising given the poor performance of acetates in Pd-AA cascades in Bartlett's research, was incongruent with previous results including those reported by Verdoorn *et al.*[39] The variation in C-1 leaving group of the substrate appears to be the only way in which Verdoorn's research deviates with respect to this reaction and so the complete lack of reactivity was surprising. Exploration of reaction conditions in an attempt to provide complimentary results to Verdoorn's was not undertaken due to the success of the carbonate variant (**154**) in this reaction and the time constraints of this project.

α,β-Unsaturated lactone bis-electrophile **172** was unreactive towards the Pd-AA cascade with Meldrum's acid (Scheme 2.22), despite the modification of reaction conditions to better suit the nature of the substrate. These modifications included lowering the catalyst loading as this was required to combat the anomeric mixtures used previously, and also addition of NaH to generate an equivalent of methoxide for the attack on the ketene at the end of the reaction. The modifications were ineffective and the cascade failed to proceed, allowing all of starting material **172** to be recovered from the crude reaction mixture.



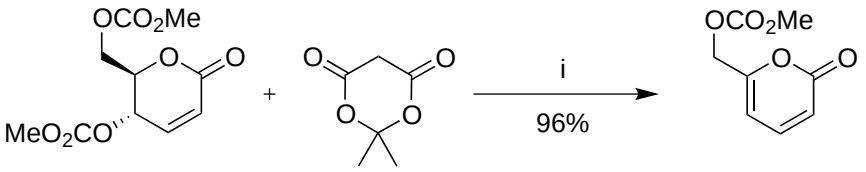
172 **52** **224**

Reagents and Conditions: i) $Pd(PPh_3)_4$ (5 mol%), NaH (1.1 eq.), MeOH (5 eq.) toluene, rt, O/N.

Scheme 2.22 Unsuccessful Pd-AA cascade of acetate bis-electrophile **172** with Meldrum's acid (**52**)

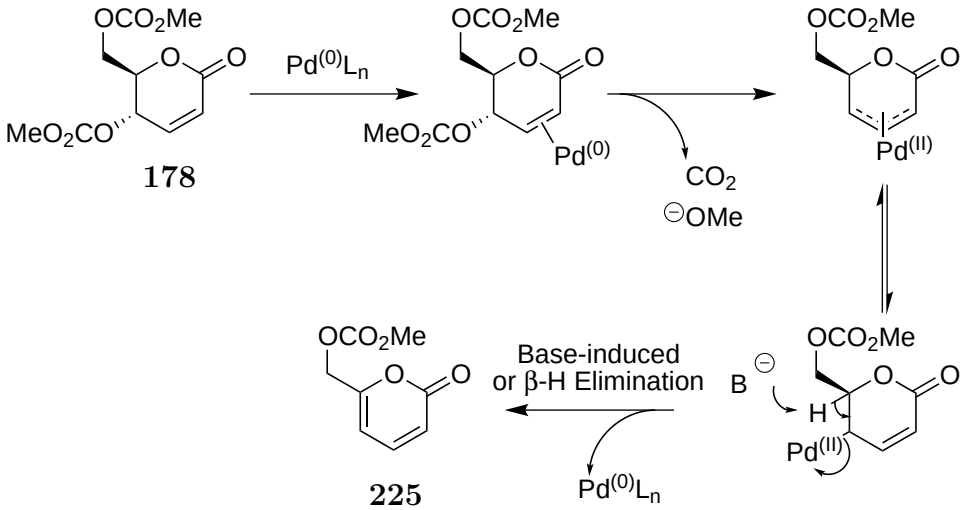
On the other hand, carbonate bis-electrophile **178**, when subjected to the appropriate Pd-AA cascade conditions (Scheme 2.23), was found to be extremely reactive, with TLC analysis showing complete consumption of **178** after only 2.5 hours. ^{1}H NMR spectroscopy of the crude reaction mixture, however, showed clearly that **178** had not reacted with the Meldrum's acid. Instead, it had undergone a transformation in a high yield to one product that, upon purification, was found to be 2*H*-pyran-2-one **225**. An intense colour change from yellow to red-orange of the reaction mixture was observed. This could indicate that the formation of this compound is a palladium-assisted process. A plausible mechanism could involve the initial π-allyl Pd formation anticipated for the desired reaction. Then, instead of C-4 alkylation by Meldrum's acid, either β-hydride elimination or base induced elimination of H-5 followed by dissociation of Pd, would form the observed pyranone

(**225**) (Scheme 2.24). The observed colour change could be caused by complexation of the diene to palladium. The lack of reactivity of the acetate analogue (**172**) is consistent with either mechanism but could be a consequence of the less reactive C-4 acetate leaving group retarding the process, by inhibiting formation of the initial π-allyl Pd complex. The base involved in deprotonation of C-5 could be methoxide or Meldrum's acid. Performing this reaction without Meldrum's acid would be required to test the proposed mechanisms.



Reagents and Conditions: i) $Pd(PPh_3)_4$ (5 mol%), MeOH (5 eq.) toluene, rt, 2.5 h.

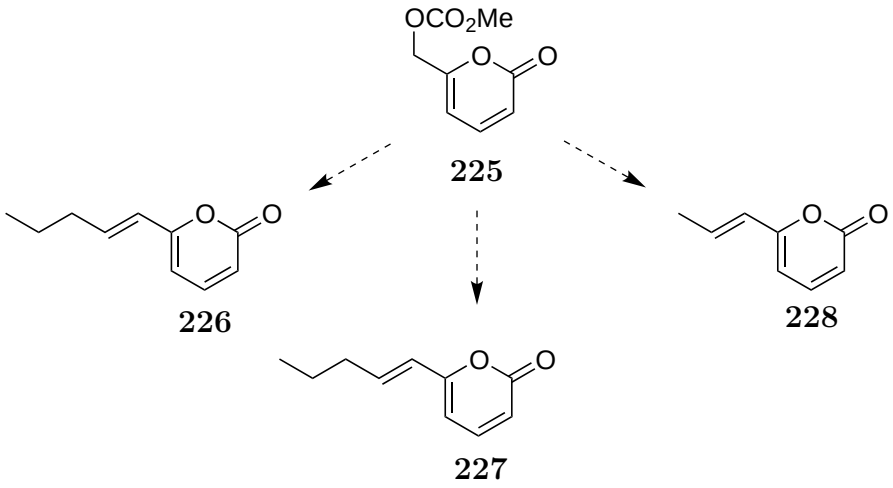
Scheme 2.23 Unexpected elimination reaction of lactone **178** under Pd-AA cascade conditions



Scheme 2.24 Possible mechanism for the formation of 2*H*-pyran-2-one **225**

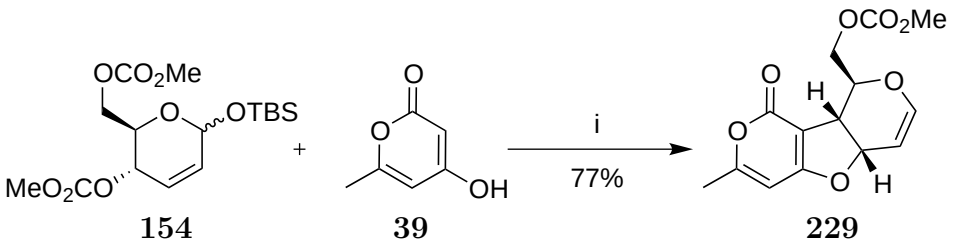
The facile and high yielding synthesis of pyranone **225** could be promoted by the conjugation inherent to the 2*H*-pyran-2-one (a.k.a. α-pyrone) structure. Nature provides further evidence for the favoured formation of these compounds, as this type of ring system has been found in a plethora of compounds isolated from plants, animals, marine organisms, bacteria, insects and fungi. Some 2*H*-pyran-2-one derivatives have been found to display a wide range of cytotoxic, neurotoxic and phytotoxic properties whilst others have been used as synthetic precursors to pharmacologically active compounds such as HIV protease inhibitors, antifungals, anticonvulsants, antimicrobials, pheromones, natural pigments, antitumour agents, and plant growth regulators.[81,82] In particular, pyranone **225** provides access to 6-alkylpyran-2-ones, examples of which include 6-pentylpyran-2-one (**226**) that exhibits tyrosinase inhibitory activity with an IC_{50} value of 0.8 μM and has been in the treatment of hyperpigmentation diseases,[83] 6-(1-penten-1-yl)-pyran-2-one (**227**) which has been

identified as a queen pheromone of the red fire ant,[84] and 6-propenylpyran-2-one (**228**), known as sibirinone, which was isolated from a culture of *Hypomyces semitranslucens*[85](Scheme 2.25). It should be noted that although this research does provide a new synthetic route to this important class of compounds, the pathway does not hold many advantages over the traditional strategies for the synthesis of 2*H*-pyran-2-ones, and will find limited use due to its atom and step inefficiency.



Scheme 2.25 Examples of 6-alkylpyran-2-ones accessible from 2*H*-pyran-2-one **225**

To conclude the scope studies of the tri-substituted bis-electrophiles, the most successful bis-electrophile, carbonate **154**, was reacted with the pyrone and coumarin bis-nucleophiles, **39** and **203**. These reactions, performed by Dr Mark Bartlett, provided the desired products in good and excellent yields, demonstrating that their reactivity is comparable and sometimes, in the case of the cascade with hydroxycoumarin **203**, greater than their C-5 unsubstituted analogue, *cis*-**42** (2.4.3).

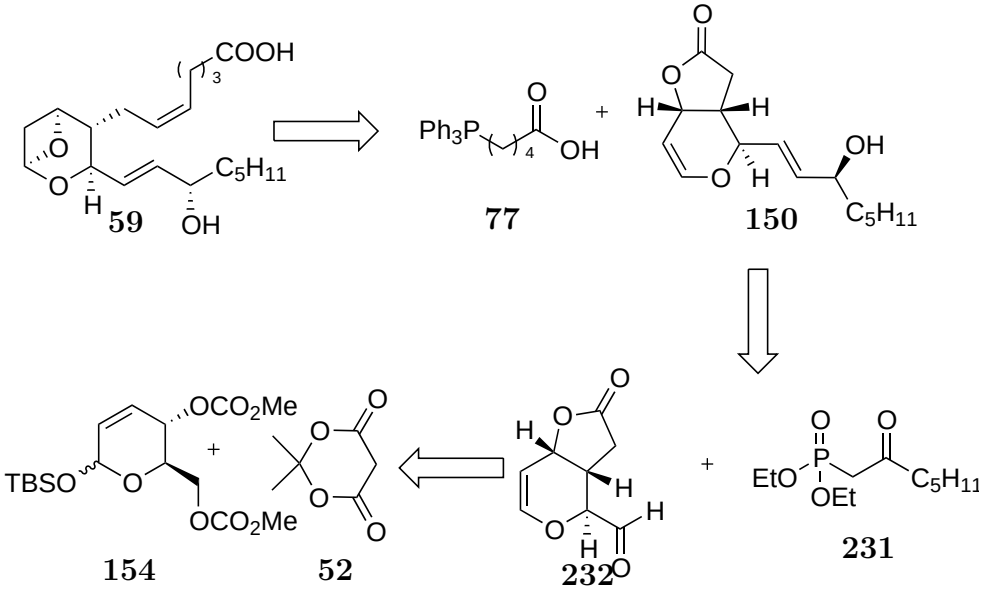


Reagents and Conditions: i) $Pd(PPh_3)_4$ (15 mol%), toluene, rt, O/N.

Scheme 2.26 Pd-AA cascades of pyrone **39** and coumarin **203** with bis-electrophile **154**

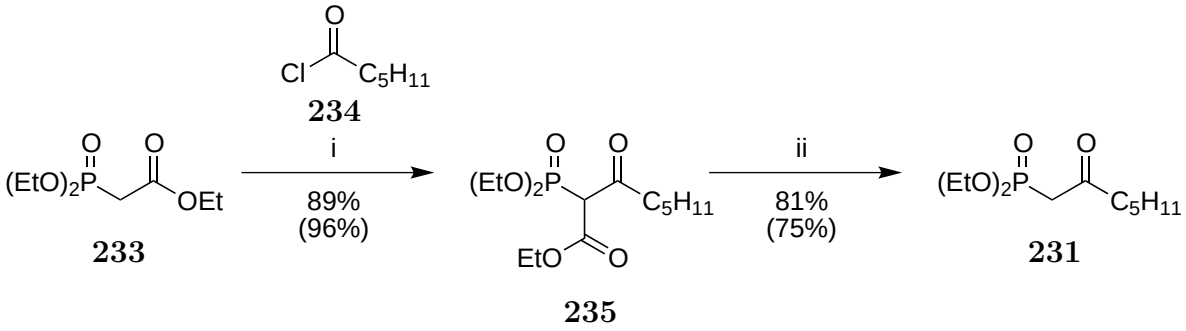
2.5 Progress Towards the Synthesis of Thromboxanes A_2 and B_2

The final aim of this project was to employ a Pd-AA cascade with a tri-substituted dihydropyran bis-electrophile to form the core of the thromboxane intermediates, and in doing so, work towards improved total syntheses of the thromboxanes. A retrosynthesis of the proposed synthetic plan in Section 1.5.2 shows that three compounds were required in the early stages of the synthesis, namely Meldrum's acid, bis-electrophile **154** and HWE reagent **231** (Scheme 2.27).



Scheme 2.27 Retrosynthesis of TXA_2 (**59**) to starting materials: Meldrum's acid (**52**), **154** and **231**

Both Meldrum's acid and bis-electrophile **154** were accessible and so the synthesis of the HWE reagent, diethyl (hexanoylmethyl)phosphonate (**231**), to be used in the attachment of the first thromboxane side-chain, was made a priority. A literature method[86] for the synthesis of **231** was successfully followed with only minor variations in the experimental procedure. The synthesis, developed by Kurangi *et al.* involved acylation of triethyl phosphonoacetate (**233**) with hexanoyl chloride (**234**) in the presence of $MgCl_2$ and NEt_3, followed by hydrolysis in water with *p*-TsOH and decarboxylation (Scheme 2.28). In contrast to Kurangi's procedure, where intermediate **235** was produced in a 96% yield and judged as pure by observation of a single spot on TLC after aqueous workup, column chromatography was required when the reaction was carried out in this work to remove by-products detected by ^{1}H NMR of the crude reaction mixture. The intermediate (**235**) was able to be isolated in an 89% yield; however, when subjected to the second step of the procedure for the reported three hours, the desired product was isolated in a low 38% yield after column chromatography, much less than Kurangi's 75%. Reaction conversion appeared to be the issue, and when the reaction was repeated and left to react overnight, phosphonate **231** was able to be produced in an 81% yield after extraction with diethyl ether without the need for further purification. Coincidentally, the modifications to Kurangi's procedure implemented in this work did not change the outcome of the synthesis of **231** as both procedures required the use of one column and resulted in an overall yield of 72% over two steps.



Reported yields[86] shown in brackets
Reagents and Conditions: i) $MgCl_2$, NEt_3, toluene, 6 h, rt; ii) *p*-TsOH, H_2O, Δ.

Scheme 2.28 Synthesis of HWE reagent **231** with comparative yields from the reported procedure

The desired bicyclic thromboxane intermediate **232** deviates only slightly from the bicyclic Pd-AA cascade product **221** generated from Meldrum's acid and trisubstituted bis-electrophile **154** (Figure 2.14). The formation of this compound was therefore envisioned to be achievable through a one-pot synthesis involving a Pd-AA cascade of **154** with Meldrum's acid to produce the usual ketene intermediate. An equivalent of water added to the reaction mixture could then quench the ketene to form carboxylic acid **236** that, by warming up the reaction mixture, would undergo thermal decarboxylation to provide **232** (see Scheme 1.24).

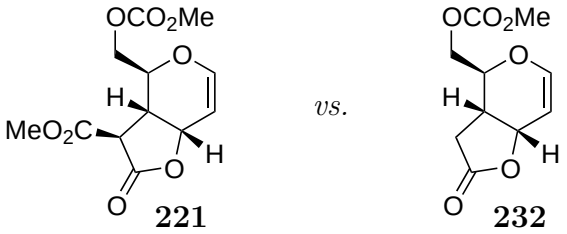
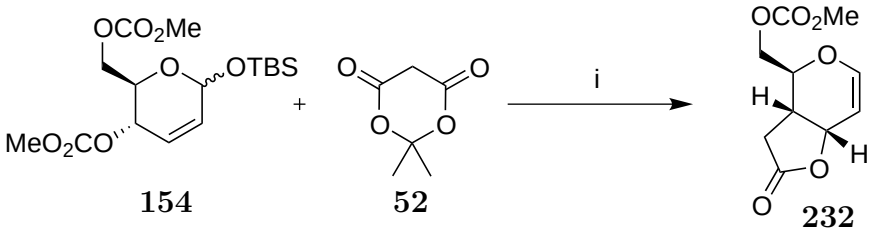


Figure 2.14 Comparison in Pd-AA cascade product **221** and planned thromboxane intermediate **232**

Investigation of this process began with the reaction of Meldrum's acid with **154** under the optimised conditions for the formation of **221** with the addition of five equivalents of water (Table 2.12, Entry 1) to determine whether the presence of water in the reaction hindered the activity of the catalyst. Gratifyingly, peaks correlating to ester **221** were detected in the ^{1}H NMR of the crude reaction mixture with good conversion, but no other products were observed. Repeating the reaction without methanol resulted in complete recovery of starting materials (Table 2.12, Entry 2). It was postulated that the poor miscibility of water in toluene reduced its availability for the use in the Pd-AA cascade, thereby hindering the process. When acetonitrile was employed as a more water-miscible solvent (Table 2.12, Entry 3), the reaction was found to proceed and give both **221** and **232**, although the reaction suffered from poor conversion of starting material **154**. As the reaction mixture was subjected to only mild heating during evaporation of the solvent *in vacuo* during work up, it was a great surprise to discover that the product isolated from this reaction was in fact the decarboxylated product **232**. This is in contrast to the procedure reported by Verdoorn,[39] where a temperature of 170 °C was required for decarboxylation of a similar substrate (**107**) to occur. The presence of **237** was indicated through the similarity of signals compared to **221** together with the new signals attributed to the H-5 ABX system at δ 2.87 (dd, J = 18.0, 8.5 Hz) and δ 2.48 (dd, J = 18.0, 2.0 Hz). Unfortunately, the decarboxylated compound **232** was isolated as the major component of a mixture of unidentified compounds of similar polarity and therefore only an estimated yield is able to be reported and is based on integrations of the ^{1}H NMR spectrum of the product mixture (Table 2.12, Entry 3).

A small increase in the equivalents of water (Table 2.12, Entry 4) resulted in a small increase in yield of the desired product. Employing water as a co-solvent with THF (Table 2.12, Entry 5) gave extremely promising results upon analysis of integrations of the peaks in the ^{1}H NMR of the crude reaction mixture, but a disappointingly poor yield of **232** was isolated. This isolated yield is considered to not reflect the true result for this set of reaction conditions and optimisation of this reaction would benefit from its repetition. Finally, using water as the solvent, and employing

Table 2.12 Exploration of Pd-AA cascade of **154** and Meldrum's acid (**52**) in presence of water



154 **52** **232**

Reagents and Conditions: i) catalyst (15 mol%), solvent, Meldrum's acid (5 eq.), H_2O, MeOH, rt, O/N

Entry	Catalyst	Solvent	Eq. H_2O	Eq. MeOH	Yield (232)
1	$Pd(PPh_3)_4$	Toluene	5	5	0%[a]
2	$Pd(PPh_3)_4$	Toluene	5	0	0%[b]
3	$Pd(PPh_3)_4$	MeCN	5	0	<5%[c]
4	$Pd(PPh_3)_4$	MeCN	20	0	9%
5	$Pd(PPh_3)_4$	THF:H_2O 9:1	-	0	7%[d]
6	$PdCl_2$	H_2O	-	0	0%[b]

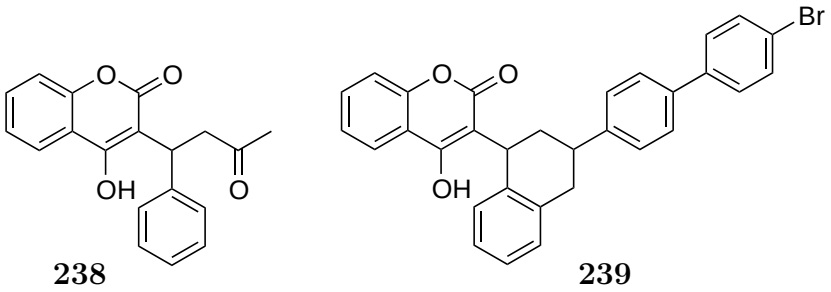
[a]Sole product identified as **221** by analysis of ^{1}H NMR of crude reaction mixture
[b] ^{1}H NMR of the crude reaction mixture showed only unreacted starting materials
[c]**232** isolated as the major component of a mixture of products
[d]Isolated yield of **232** inconsistent with integrations of ^{1}H NMR of the crude reaction mixture

water-soluble $PdCl_2$ as the catalyst, gave no desired product or consumption of starting material, potentially as a result of the poor solubility of starting materials (Table 2.12, Entry 6). Time constraints of this project have meant that this research has been halted. However, future plans for the development of this reaction are discussed in Section 3.4.

Further optimisation of this reaction is required and therefore work could not begin on attachment of the first side-chain with HWE reagent **231**. However, the current results show promise for the extended Pd-AA cascade as an efficient transformation *en route* to the synthesis of the Thromboxanes. The formation of product **232**, even in low yields, differentiates this research from Verdoorn's, and establishes a new extension to Bartlett's Pd-AA cascade, carrying out a remarkable five-steps in one-pot.

2.6 Bioactivity of Selected Pd-AA Cascade Products

4-Hydroxycoumarins are well established as a class of compounds that demonstrates significant bioactivity.[87] These structural motifs can be found in many well-known bioactive compounds with examples including the anticogulant drug Warfarin[88] (**238**) and the rodenticide Brodifacoum[89] (**239**) (Figure 2.15). Bartlett noted the potential for bioactivity in the compounds produced in the Pd-AA cascades and submitted several for testing of their cytotoxicity against HL-60, a human leukemia cell line. The results of the studies showed a variety of cytotoxicities and an interesting trend became apparent. Whilst the products of cascades formed with disubstituted dihydropyran bis-electrophile *cis*-**42** showed limited to no cytoxicity against HL-60, the products of the cascades formed from the tri-substituted dihydropyran (**154**), namely **229** and **230**, were found to be active with IC_{50} values of 21 and 25 μM, respectively.[19]



238 **239**

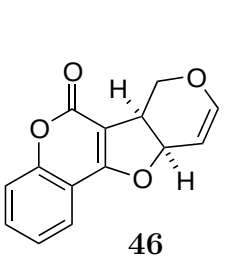
Figure 2.15 4-Hydroxycoumarin derived bioactive compounds: Warfarin (**238**) and Brodifacoum (**239**)

A variety of Pd-AA cascade products synthesised in this work were therefore tested against the human promyelocytic leukemia HL-60 cell line and the human ovarian cancer 1A9 cell line. Their cytostatic activities were determined using MTT cell proliferation assays (n = 1-3 experiments).[90] The most active compounds prepared by Bartlett (**229** and **230**) were also tested against the 1A9 cell line. Unsurprisingly, **229** and **230**, were found to show cytotoxicity against 1A9. On the other hand, the products of Pd-AA cascades; with acyclic precursor **40**, *viz.* **211**, **240**, **214**, **215** and **241**, were all inactive against the cell lines at the concentrations tested. Interestingly, the products formed from Meldrum's acid, **221** and **232**, were also found to be inactive, demonstrating that the presence of a carbonate moiety on the dihydropyran does not solely determine the cytotoxicity of a Pd-AA cascade product (Table 2.13).

Bartlett also submitted several Pd-AA cascade products for testing of their antibacterial activity against *E. coli*, *S. aureus* and *M. smegmatis*.[19] However only products

formed from bis-electrophile *cis*-**42** were tested. Of the compounds tested, one, **46**, was found to display antibacterial activity against *S. aureus*. With an IC_{90} value of 1.35 mM, the activity was not high, but based on the trend noted from the HL-60 cytotoxicity studies, analogues with carbonate substituents on the dihydropyran ring showed promise for increasing antibacterial activity. Therefore, **230**, **45** and **229** were submitted for assessment of their antibacterial activity to compare with that displayed by **46**. Bacterial growth was measured using optical density (OD) and resazurin reduction for *E. coli* and *S. aureus*. Cell growth of *M. smegmatis*, in addition to resazurin and OD, was measured with green fluorescent protein (GFP) expression to infer inhibitory activity of the selected compounds. Whilst methylpyrone-derived **45** was found to show no antibacterial activity at the concentrations tested, the carbonate analogue, **229**, showed activity against *S. aureus*, complying with the observed trend. Unfortunately, **230** was found to be inactive at the highest concentration able to be tested, 0.5 mM, due to the limited availability of the compound, and so a comparison with **46** cannot be made.

Table 2.13 Bioactivity of selected Pd-AA cascade products



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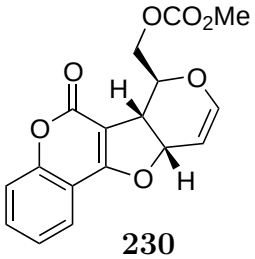

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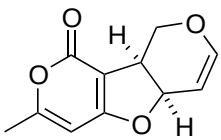

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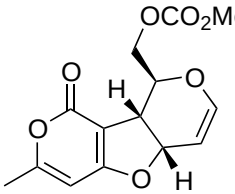
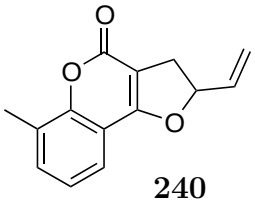


229



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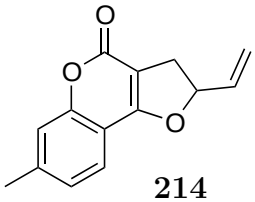

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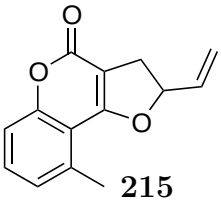

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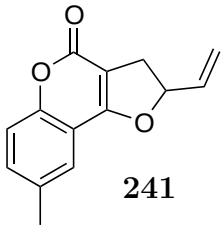

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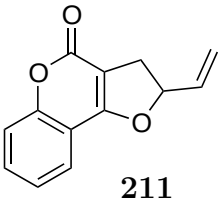
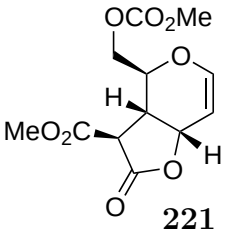
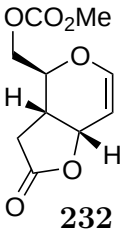


211



221



232

Compound	**Cytotoxicity**[a] (IC_{50})		**Antibacterial**[b] (IC_{90})		
	HL-60 (μM)	1A9 (μM)	*E. coli*	*S. aureus*	*M. smegmatis*
46[c]	>100	-	*inactive*	1.35 mM	*inactive*
230[c]	25	30[d]	*inactive*	*inactive*	*inactive*
45[c]	>250	-	*inactive*	*inactive*	*inactive*
229[c]	21	30[e]	*inactive*	0.5 mM	*inactive*
240	>250	-	-	-	-
214, **215**[f]	>250	-	-	-	-
241	>250	>250	-	-	-
211	>250	>100	-	-	-
221	-	-	-	-	-
232	-	-	-	-	-

[a]Cytotoxicity testing was performed by Arun Kanakkanthara and Deepanjan Ghosh.
[b]Antibacterial screening was performed by Nathaniel Dasyam.
[c]Compound synthesised by Dr Mark Bartlett.
[d]Average of 3 consistent values; standard deviation = 4.5 μM.
[e]Average of 3 consistent values; standard deviation = 0.9 μM.
[f]Compounds tested as a 1.3:1 mixture of **214**:**215**.

Chapter 3

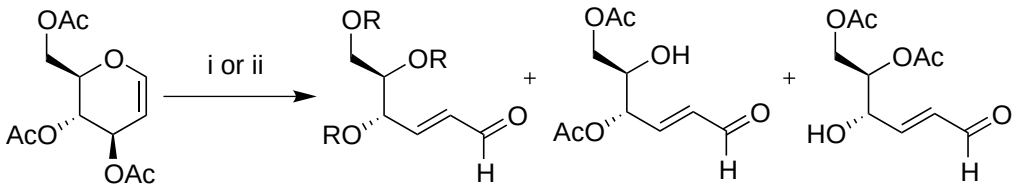
Future Work and Conclusion

Throughout this thesis, there have been indications of further work that could be explored. These aspects are outlined below alongside research that was not able to be carried out due to the time constraints of the project.

3.1 Future Work on Perlin Aldehydes and Synthesis of Hemiacetals (Section 2.1)

The discovery of the incongruencies in the assignment of the struture of *trans*-aldehyde **176** was an interesting exercise and demonstrated just how important it is to fully characterise compounds even when they have been reported in the literature. Although it is clear from the evidence discussed in Section 2.1.4 that the NMR shifts corresponding to a *trans*-aldehyde reported by Fraser-Reid in 1975, and again in this work, are correctly assigned to the structure of Perlin aldehyde **176**, the structure of Perlin's aldehyde (**242**) remains unclear. Therefore a small project for future work could be the synthesis and characterisation of aldehyde **242**. This could be done through either the repetition of Perlin's 1975 reaction involving $HgSO_4$ or, as demonstrated in this research, the less toxic heating of tri-*O*-acetyl-D-glucal in boiling water in the presence of light to aid formation of aldehyde products (Scheme 3.1).

Formation of the Perlin aldehydes was not a desired outcome in this research and yet, when working towards the synthesis of diacetate bis-electrophiles (**153** and **172**), they were repeatedly isolated as by-products. In particular, the synthesis of intermediate hemiacetal **165** suffered because of facile ring-opening to form these aldehydes



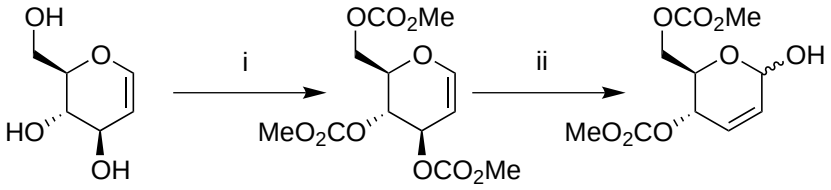
102 **242** **166** **176**

Reagents and Conditions: i) (Perlin Hydrolysis) $HgSO_4$, 1,4-dioxane, dil.H_2SO_4, rt, 2-3 hr; or ii) H_2O, Δ, O/N.

Scheme 3.1 Synthesis of Perlin aldehydes for the isolation and characterisation of Perlin's misassigned aldehyde **242**

and so only moderate yields of **165** were achieved. It was therefore surprising that the hydrolysis of tri-*O*-(methoxycarbonyl)-D-glucal (**198**) was not similarly plagued by the formation of aldehyde by-products. In contrast, the reaction afforded the desired hemiacetal (**199**) in quantitative yields in only half an hour and required no work up. A computational study on the differences between the acetate and carbonate versions of this reaction could provide some insight as to why diacetate hemiacetal **165** has a greater affinity to ring open and rearrange to aldehyde products than its carbonate analogue (**199**).

Secondly, the transformation of 3,4,6-tri-*O*-(methoxycarbonyl)-D-glucal (**198**) to hemiacetal **199** could become a useful high-yielding synthetic transformation, however the low yielding synthesis of the starting material, **198**, from D-glucal (**158**) is currently a limiting factor. Therefore, further optimisation of the protection of D-glucal with methyl chloroformate would need to be carried out in future research (Scheme 3.2) to make this a more attractive pathway than its acetate analogue.



158 **198** **199**

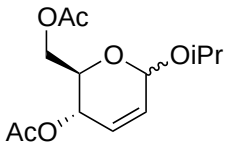
Reagents and Conditions: i) $ClCO_2Me$; ii) H_2O, 80 °C, 30 mins.

Scheme 3.2 Synthesis of hemiacetal **199** from D-glucal (**158**)

3.2 Future Work on ^{13}C NMR Shielding Profile (Section 2.2)

The ^{13}C NMR shielding profile developed in Section 2.2 was found to fit well for a range of tri-substituted glucose-derived dihydropyrans. However, while diacetylated dihydropyran **103** (Figure 3.1) was found to fit the silhouette of the profile, it devi-

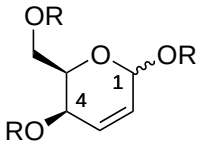
ated in the magnitude of the $\Delta\delta_C$ values. Future work could involve the synthesis of other dihydropyrans with C-1 isopropyl ether substituents to explore the scope of this discrepancy and extend the analytical method to a broader range of compounds. In addition to this, computational studies on the effects of C-1 isopropxy groups on the overall conformation of the dihydropyrans, when compared to the silyl and other C-1 substituted compounds used in this study, may provide useful information.



103

Figure 3.1 Bartlett's tri-substituted dihydropyran **103**

Furthermore, an extension of this study that would enhance this method of analysis would be exploring the shielding profile of galactose-derived dihydropyrans (**243**, Figure 3.2). The configurational difference at C-4 would allow determination of whether the profile is consistent for all compounds with a *cis- vs trans*-relationship between C-1 and C-4, or whether a new profile needs to be developed to account for the altered C-4 - C-5 stereochemical relationship.

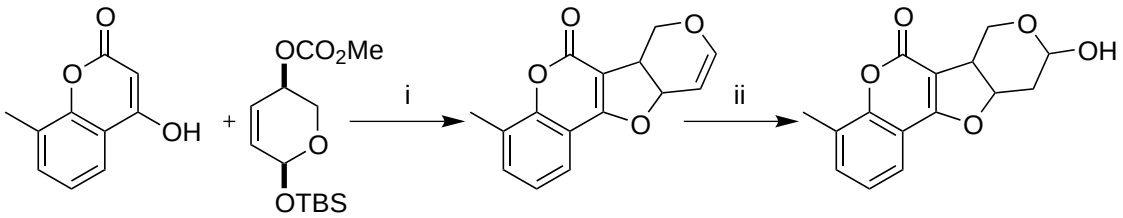


243

Figure 3.2 Galactose-derived tri-substituted dihydropyrans

3.3 Future Work on Pd-AA Cascades (Section 2.4)

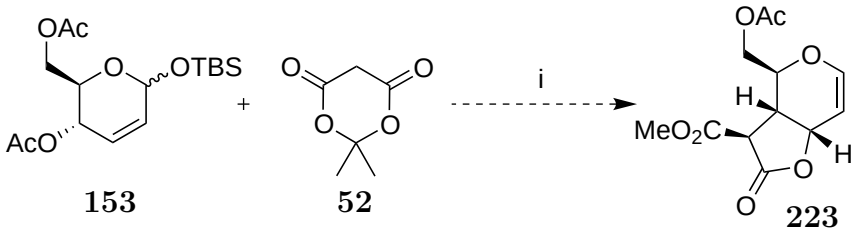
Isolation of the desired products from the Pd-AA cascades of the methylated 4-hydroxy-coumarins with Bartlett's disubstituted dihydropyran *cis*-**42** (such as in Scheme 3.3) were only achieved in modest yields in this project, despite the observation of extremely clean ^{1}H NMR spectra of the crude reaction mixtures (see Section 2.4.2). The identification and suppression of one of the undesired products (**219**), which formed during purification, increased the isolated yields marginally. However, the chromatographic procedure needs to be improved so that the isolated yields better represent the apparently near-quantitative conversion observed. Future work could involve the use of an alternative solid phase for chromatography of the cascade products. This would require determination of the current reasons for the poor mass balance from silica gel column chromatography.



Reagents and Conditions: i) $Pd(PPh_3)_4$, 3:1 toluene:DMF, rt, O/N; ii) silica column.

Scheme 3.3 Degradation of Pd-AA cascade product **220** to **219**

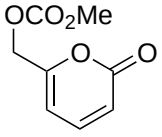
Other avenues for future work inspired by the scope studies of the Pd-AA cascades could be in developing conditions that allow for the C-4 acetate bis-electrophile **153** to successfully undergo a Pd-AA cascade with Meldrum's acid (Scheme 3.4). Verdoorn's success with a similar diacetate substrate[39] suggests that this transformation should work and therefore investigating the reactivity of **153** under a variety of Pd-AA cascade conditions might extend the scope of the Pd-AA cascade with Meldrum's acid (Scheme 3.4). If unsuccessful, it might be useful to repeat Verdoorn's 1989 synthesis and probe whether the results of this Pd-catalysed reaction are reproducible.



Reagents and Conditions: i) $Pd^{(0)}$ cat.

Scheme 3.4 Proposed investigation of the Pd-AA cascade of diacetate hemiacetal **153** with Meldrum's acid

On a different note, testing the bioactivity of pyranone **225** (Figure 3.3), formed by the Pd-AA cascade of carbonate bis-electrophile **178** with Meldrum's acid, could be a sensible pursuit. Section 2.4.3 described a number of similar mono-substituted pyranones, which have been found to show bioactivity in a variety of assays.[81] In addition to this, the presence of a carbonate substitutent was demonstrated to increase the activity of compounds tested in Section 2.6. Therefore, pyranone **225** has the potential to show good bioactivity.

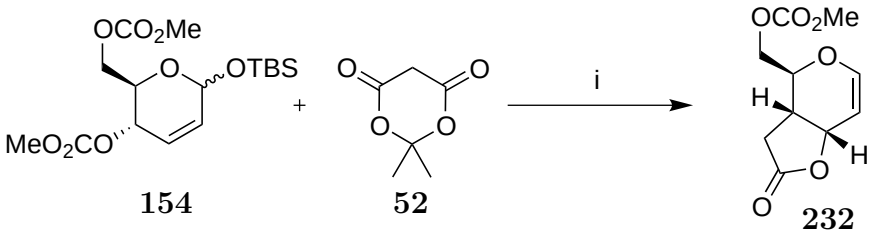


225

Figure 3.3 2*H*-pyran-2-one **225**

3.4 Future Work on Thromboxane Synthesis (Section 2.5)

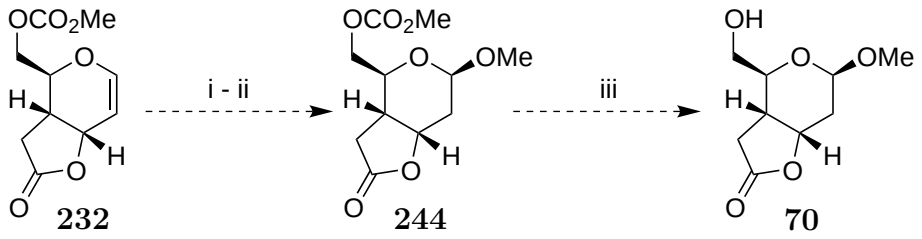
The work carried out in this project towards the synthesis of the thromboxanes showed promise for improving on the current synthetic routes. However, this research was not able to be continued to fruition due to time constraints. There is definitely potential for future work towards either formal or total syntheses of the thromboxanes, through employment of the extended Pd-AA cascade of **154** with Meldrum's acid (**52**) and water (Scheme 3.5). Optimisation of this cascade would be required and could be explored through the use of other Pd catalysts, especially those known to perform catalysis in the presence of water, e.g. $Pd(OAc)_2$ and $PdCl_2$, in conjunction with different organic-aqueous solvent mixtures e.g. MeCN:H_2O or DMF:H_2O and phase-transfer catalysts. In addition, carrying out an NMR scale reaction of the current optimised conditions would reveal if the decarboxylation step occurs prior to heating or upon concentration *in vacuo* during workup. If it is found to not undergo decarboxylation at room temperature then probing the effects of temperature on the reaction would be beneficial to its optimisation.



Reagents and Conditions: i) catalyst (15 mol%), solvent, Meldrum's acid (5 eq.), H_2O.

Scheme 3.5 Extended Pd-AA cascade of **154** with Meldrum's acid and water.

If the extended Pd-AA cascade is developed into an efficient transformation, a formal total synthesis of the thromboxane intermediate **70** could be achieved in only a few steps from **232**, and would clearly demonstrate the synthetic utility of this reaction (Scheme 3.6). The proposed total synthesis of the thromboxanes should also be approached as a goal for future research, as it would be interesting to determine whether the glycal moiety can be retained throughout the synthesis, thereby providing the potential to synthesise TXA_2 as the primary target *en route* to TXB_2. This would be the first instance of an approach to TXA_2 from a precursor other than TXB_2.



Reagents and Conditions: i) Br_2, MeOH; ii) Bu_3SnH, AIBN, toluene; iii) K_2CO_3, MeOH.

Scheme 3.6 Proposed formal total synthesis of thromboxane intermediate **70**

3.5 Concluding Remarks

The objectives of this project, *i.e.* to explore both the scope and utility of the recently discovered Pd-AA cascade, were successfully achieved. A series of regioisomeric methylated 4-hydroxycoumarins were tested and found to be equally effective as substrates in the Pd-AA cascade with both acyclic and cyclic bis-electrophiles. Furthermore, four differentially protected bis-electrophiles based on glucose were synthesised and tested as Pd-AA cascade substrates. The carbonate bis-electrophile **154** was shown to be an excellent substrate for reaction with a number of cyclic bis-nucleophiles which afforded products that were found to have antibacterial activity and bioactivity against two human cancer cell lines. In addition, bis-electrophile **154** was used in an extension of the Pd-AA cascade with Meldrum's acid in the presence of water. The resulting reaction showed the capacity to perform five synthetic transformations in one-pot. This extended cascade is currently in the early stages of optimisation, and has the potential to improve on the current syntheses of the thromboxanes.

During this project, a number of other interesting discoveries were made. The first was the development of a novel Ferrier reaction with silanol nucleophiles that produced diacetate bis-electrophile **153** in one step. Secondly, incongruent NMR data of Perlin's aldehyde **242** was uncovered through close evaluation of spectroscopic data reported in the literature, accompanied by the 1D and 2D NMR spectroscopic analysis of Perlin aldehydes synthesised in this work. Finally, Bartlett's ^{13}C NMR shielding profile for the stereochemical assignments of dihydropyrans was expanded with the development of an average shielding profile for glucose-derived tri-substituted dihydropyrans.

This project has explored and extended a variety of avenues of organic synthesis, and has set the platform for future research in a number of areas. Most importantly, this project has demonstrated the exciting area of chemistry that has opened up upon the development of the Pd-AA cascade. It remains to be seen whether this cascade will improve on the synthesis of the thromboxanes, yet the groundwork has been laid.

The Pd-AA cascade holds the potential for providing efficient and elegant syntheses of numerous synthetic targets and will undoubtedly find many future applications.

Chapter 4

Experimental

4.1 General Experimental

Unless otherwise stated, the following conditions apply. All reactions were performed in oven-dried glassware with magnetic stirring under an atmosphere of argon or nitrogen. Moisture- and oxygen-sensitive liquids and solutions were transferred using a stainless steel syringe. Before use, solvents were refluxed over the appropriate drying agent and distilled under nitrogen: tetrahydrofuran (THF) from sodium benzophenone ketyl radical; dichloromethane (DCM), acetonitrile (MeCN) and triethylamine (NEt_3) from calcium hydride; methanol (MeOH) and toluene from sodium. Anhydrous *N,N*-dimethylformamide (DMF) and acetic anhydride were used as purchased, without further purification. All other reagents were of commercial quality and used as received, without further purification.

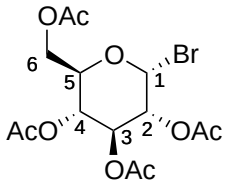
Analytical thin layer chromatography (TLC) was performed using plastic-backed pre-coated silica TLC plates (Polygram SilG/UV254). Visualisation was achieved by UV irradiation (254 nm) or by heating after treatment with a potassium permanganate dip (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL of 10% aqueous NaOH solution and 200 mL of water) or *p*-anisaldehyde dip (0.7 mL *p*-anisaldehyde, 9.5 mL conc. H_2SO_4, 2.7 mL acetic acid and 250 mL of EtOH). The purification of products by flash column chromatography was conducted using silica gel 60 (220-240 mesh) with the solvent systems indicated. ^{1}H NMR spectra were recorded a Varian Unity Inova 500 spectrometer at 500 MHz, a Varian DirectDrive 600 spectrometer at 600 MHz or a Varian Inova 300 at 300 MHz. Data are listed as follows: chemical shift in ppm using, as internal standard, chloroform (7.26 ppm) or water (4.79 ppm) or dimethylsulfoxide (DMSO) (2.50 ppm), multiplicity [s = singlet, d = doublet, t = triplet, q

= quartet, quint = quintet, m = multiplet or overlap of non-equivalent resonances, br = broad, apt. = apparent, obs. = (partially) obscured], integration, peak assignment. ^{13}C NMR spectra were recorded on a Varian Unity Inova 500 spectrometer at 125 MHz or a Varian DirectDrive 600 spectrometer at 150 MHz and the data listed as follows: chemical shift in ppm using chloroform as internal standard (77.0 ppm) or DMSO (39.5 ppm), multiplicity, peak assignment. The assignments of signals are exclusively based on atom connectivity and spatial relationships are derived from 2D NMR correlations (NOESY, ^{1}H/^{1}H-COSY, ^{1}H/^{13}C-HMBC and ^{1}H/^{13}C-HSQC). IR bands were measured as either a thin film on a Bruker FT-IR Tensor 27 spectrometer with ATR sampling accessory or a sold or thin film on a Bruker ALPHA FT-IR spectrometer or as a KBr disc on a Perkin-Elmer Spectrum One FT-IR spectrometer. High-resolution mass spectrometry (HRMS) was performed on an Agilent 6530 Accurate-Mass Q-TOF LC/MS mass spectrometer with Agilent Jet Stream ESI source. Melting points were measured on a Gallenkamp melting point apparatus with samples in a melting tube and are uncorrected. Optical rotations were measured on an Autopol II polarimeter from Rudolph Research Analytical. The structure of each compound is presented with the corresponding method of preparation and spectroscopic data.

4.2 Experimental Methods and Characterisation

4.2.1 Experimental Details for Section 2.1.1

Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (245)



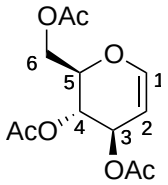
245

Using a modification of Kozikowski's procedure,[91] a magnetically stirred solution of D-glucose **246** (150 mg, 0.8 mmol) in acetic anhydride (76 mL, 804.0 mmol) was treated dropwise with conc. perchloric acid (0.45 mL, 6.9 mmol). Additional D-glucose **246** (19.50 g, 108.2 mmol) was added slowly over one hour, at a rate that maintained a temperature of $40-50\,^{\circ}$C. Upon complete addition of D-glucose, the solution was allowed to cool to room temperature, then treated with a 33% (w/w) solution of hydrobromic acid in acetic acid (93 mL, 0.517 mmol). After 90 minutes, the solution was diluted with dichloromethane (180 mL) and washed with

ice-cold water (2 x 100 mL), then cold sat. sodium bicarbonate solution (6 x 80 mL). The organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated to afford crude tetra-*O*-acetyl-α-D-glucopyranosyl bromide **245** as a white solid (43.68 g, 106.2 mmol, 96%) that was used without purification. Spectral data matched those which have been previously reported.[92]

^{1}H-NMR: (500 MHz; $CDCl_3$) δ_H 6.61 (d, J = 4.0 Hz, 1H, H-1), 5.56 (t, J = 10.0 Hz, 1H, H-3), 5.16 (t, J = 10.0 Hz, 1H, H-4), 4.84 (dd, J = 10.0, 4.0 Hz, 1H, H-2), 4.33 (dd, J = 12.5, 4.0 Hz, 1H, H-6a), 4.30 (m, 1H, H-5), 4.13 (dd, J = 12.5, 2.0 Hz, 1H, H-6b), 2.100 (s, 3H, CH_3CO), 2.096 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 170.5 (C, $CH_3\underline{C}O$), 169.83 (C, $CH_3\underline{C}O$), 169.77 (C, $CH_3\underline{C}O$), 169.4 (C, $CH_3\underline{C}O$), 86.5 (CH, C-1), 72.1 (CH, C-5), 70.6 (CH, C-2), 70.1 (CH, C-3), 67.1 (CH, C-4), 60.9 (CH_2, C-6), 20.66 (CH_3, $\underline{C}H_3CO$), 20.64 (CH_3, $\underline{C}H_3CO$), 20.61 (CH_3, $\underline{C}H_3CO$), 20.54 (CH_3, $\underline{C}H_3CO$).

Tri-*O*-acetyl-D-glucal (102)



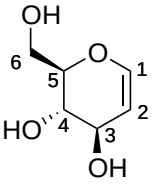
102

A mechanically stirred dispersion of zinc dust (47.92 g, 733.1 mmol) in water (150 mL) was cooled to 0 °C, diluted with acetic acid (150 mL), then treated dropwise with a solution of glucosyl **245** in diethyl ether (150 mL) over one hour. The reaction was allowed to warm to room temperature and left to proceed overnight. The solution was filtered, then diluted with dichloromethane (200 mL). The solution was washed successively with water (3 x 60 mL), sat. sodium bicarbonate solution (4 x 50 mL), then brine (60 mL). The organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated to provide **102** as a white solid (26.3 g, 96.6 mmol, 91%). Spectral data matched those which have been previously reported.[93]

R$_f$ 0.3 (25% EtOAc / pet. ether); $[\alpha]_D^{23}$ -19.32 (c 0.98, CH_2Cl_2); **m.p.** 55.6 – 56.2 °C (lit.[94] **m.p.** 50 – 52 °C); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.47 (d, J = 6.0 Hz, 1H, H-1), 5.34 (m, 1H, H-3), 5.23 (dd, J = 7.5, 6.0 Hz, 1H, H-4), 4.85 (dd, J = 6.5, 3.5 Hz, 1H, H-2), 4.40 (dd, J = 12.0, 6.0 Hz, 1H, H-6a), 4.26 (m, 1H, H-5), 4.20 (dd, J = 12.0, 3.0 Hz, 1H, H-6b), 2.10 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 170.6 (C, $CH_3\underline{C}O$), 170.4 (C, $CH_3\underline{C}O$), 169.6 (C, $CH_3\underline{C}O$), 145.6 (CH, C-1), 99.0 (CH, C-2), 73.9 (CH, C-5), 67.4 (CH, C-3), 67.2 (CH, C-4), 61.4 (CH, C-6), 21.0 (CH_3, $\underline{C}H_3CO$), 20.8 (CH_3, $\underline{C}H_3CO$), 20.7 (CH_3, $\underline{C}H_3CO$); **IR:** ν_{max} 2959, 1731, 1647, 1370, 1208, 1024, 900

cm^{-1}.

D-Glucal (158)

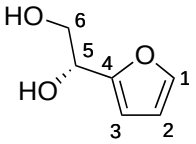


158

Sodium (77 mg, 0.033 mmol) was added to methanol (60 mL) and allowed to react. This was followed by addition of protected glucal **102** (2.75 g, 0.01 mol). The reaction was stirred at room temp for 10 minutes and then the solution was concentrated to provide crude D-glucal **158**. The crude product was treated with methanol (2 mL), then successively diluted with acetone (10 mL) and diethyl ether (20 mL), which led to the precipitation of impurities. The solution was filtered and conentrated to afford **158** (1.33 g, 90%) as a very viscous orange oil. Spectral data matched those which have been previously reported.[91]

^{1}H-NMR: (500 MHz; D_2O) δ_H 6.36 (dd, J = 6.0, 1.5 Hz, 1H, H-1), 4.74 (dd, J = 6.0, 2.0 Hz, 1H, H-2), 4.17 (dt, J = 7.0, 2.0 Hz, 1H, H-3), 3.82 (complex m, 3H, H-5, 6-a, 6-b), 3.62 (dd, J = 9.0, 7.0 Hz, 1H, H-4); **^{13}C-NMR:** (125 MHz; D_2O) δ_C 143.7 (CH, C-1), 102.8 (CH, C-2), 78.1 (CH, C-5), 68.7 (CH, C-4), 68.3 (CH, C-3), 60.0 (CH_2, C-6).

(1*R*)-1-(2-Furanyl)-1,2-ethanediol (159)



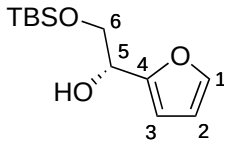
159

To a solution of D-glucal **158** (93 mg, 0.638 mmol) in 14:1 acetonitrile:water (2.8 mL:0.2 mL) was added $FeCl_3 \cdot 6\,H_2O$ (17 mg, 0.064 mmol). The reaction was heated at reflux overnight then quenched with saturated aqueous $NaHCO_3$ solution, extracted with DCM (3 x 20 mL), dried with anhydrous Na_2SO_4 and concentrated to produce **159** (58 mg, 0.453 mmol, 71%) as a colourless oil. Spectral data matched those which have been previously reported.[47]

^{1}H-NMR: (500 MHz; $CDCl_3$) δ_H 7.40 (s, 1H, H-1), 6.36 (dd, J = 3.0, 1.5 Hz, 1H, H-2), 6.33 (apt. d, J = 3.5 Hz, 1H, H-3), 4.82 (t, J = 10.0 Hz, 1H, H-5), 3.89 (m, 2H, H-6a, 6b), 2.50 (br s, J = 5.0 Hz, 1H, OH), 2.04 (br s, J = 6.3 Hz, 1H, OH). **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 153.5 (CH, C-4), 142.4 (CH, C-1), 110.3 (CH, C-3), 107.1 (CH, C-2), 68.3 (CH, C-5), 65.1 (CH_2, C-6).

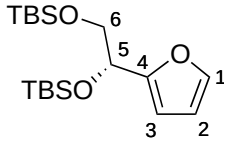
(1*R*)-1-(2-furanyl)-2-*tert*-butyldimethylsiloxyethan-ol (155) and (1*R*)- 1-(2-furanyl)-1,2-di-*tert*-butyldimethylsiloxyethane (163)

A solution of diol **159** (100 mg, 0.781 mmol) in DCM (5 mL) and NEt_3 (850 μL, 1.17 mmol) was cooled to -78 °C and TBSOTf (238 muL, 0.781 mmol) was added. The reaction was left to warm to room temperature overnight. On return, the reaction was diluted with DCM (10 mL), quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with DCM (3 x 25 mL), dried with anhydrous Na_2SO_4 and concentrated to afford a mixture of products as a colourless oil (376 mg). Chromatography of the oil (5 - 15% EtOAc / pet. ether) afforded the desired product **155** (70 mg, 0.289 mmol, 37%) and di-protected furan **163** (68 mg, 0.191 mmol, 24%) as colourless oils. Spectral data of **155** matched those which have been previously reported.[95]



155

R*f* 0.3 (20% EtOAc / pet. ether); $[\alpha]_D^{26.4}$ +17.19 (*c* 1.015, CH_2Cl_2); (lit.[96] $[\alpha]_D^{21.0}$ +15.9 (*c* 1.37, CH_2Cl_2)); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.37 (s, 1H, H-1), 6.34-6.30 (complex m, 2H, H-2,3), 4.76 (dd, J = 7.0, 4.0 Hz, 1H, H-5), 3.88-3.81 (complex m, 2H, H-6a, 6b), 2.84 (d, J = 4.0 Hz, 1H, OH), 0.90 (s, 9H, $OSiC(CH_3)_3$), 0.07 (s, 3H, $OSiCH_3$), 0.06 (s, 3H, $OSiCH_3$), ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 153.6 (C, C-4), 142.0 (CH, C-1), 110.2 (CH, C-3), 107.0 (CH, C-2), 68.3 (CH, C-5), 65.6 (CH_2, C-6), 25.8 (CH_3, $OSiC(\underline{C}H_3)_3$), 18.3 (C, $OSi(\underline{C}H_3)_3$), -5.4 (CH_3, $OSi\underline{C}H_3$), -5.5 (CH_3, $OSi\underline{C}H_3$); **IR:** (Film from $CDCl_3$) ν_{max} 3437, 2954, 2930, 2885, 2858, 1472, 1464, 1255, 1148, 1117, 1006, 837, 778 cm^{-1}.

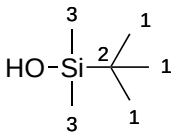


163

^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.34 (t, J = 1.0 Hz, 1H, H-1), 6.30 (dd, J = 3.0, 1.5 Hz, 1H, H-2), 6.22 (d, J = 3.0 Hz, 1H, H-3), 4.72 (t J = 6.5 Hz, 1H, H-5), 3.80 (dd J = 10.0, 6.0 Hz, 1H, H-6a), 3.75 (dd J = 10.0, 7.0 Hz, 1H, H-6b), 0.86 (s, 9H, $OSiC(CH_3)_3$), 0.85 (s, 9H, $OSiC(CH_3)_3$), 0.06 (s, 3H, $OSiCH_3$), 0.01 (s, 3H, $OSiCH_3$), -0.01 (s, 3H, $OSiCH_3$), -0.03 (s, 3H, $OSiCH_3$).

4.2.2 Experimental Details for Section 2.1.2

tert-Butyldimethylsilanol (164)

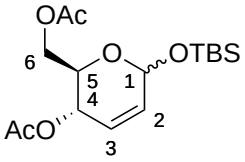


164

Following a literature method,[54] a solution of TBSCl (402 mg, 2.66 mmol) in Et_2O (8 mL) was added dropwise to an ice-cold solution of KOH (146 mg, 2.60 mmol) in a mixture of H_2O (4 mL) and MeOH (1 mL). The acidic solution was then neutralised by addition of aq. KOH solution. The reaction was stirred for 10 minutes and then extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the desired product **164** (291 mg, 2.20 mmol, 83%) as a colourless oil. Spectral data matched those which have been previously reported.[97]

^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 1.45 (br s, OH), 0.91 (s, 9H, H-1), 0.10 (s, 6H, H-3); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 25.6 (CH_3, C-1), 18.0 (C, C-2), -3.6 (CH_3, C-3); **IR:** (Film from $CDCl_3$) ν_{max} 3299, 2955, 2929, 2857, 1471, 1464, 1254, 832, 770, 668 cm^{-1}.

4,6-Di-*O*-acetyl-1-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-erythro-hex-2-enopyranoside (153)



153

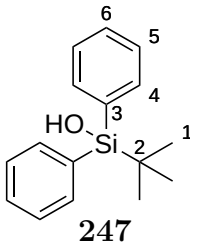
Method A Molecular sieves were stirred in DCM (10 mL) for 5 minutes, whereupon TBSOH (81 mg, 0.612 mmol) was added and the solution was stirred for a further 5 minutes. 3,4,6-Tri-*O*-acetyl-D-glucal (**102**) (166 mg, 0.610 mmol) and Montmorillonite K10 (572 mg) were added and the reaction was heated at reflux overnight. The reaction mixture was filtered through Celite™, washed with dichloromethane, and concentrated to give the crude product as a yellow oil. Chromatography of the oil (10% EtOAc / pet. ether) afforded a 1.7:1 α:β anomeric mixture of **153** (67 mg, 0.198 mmol, 32%) as a colourless oil.

Method B TBSCl (936 mg, 6.21 mmol) was added to a solution of hemiacetal **165** (1.3 g, 5.65 mmol), $AgNO_3$ (1.05 g 6.21 mmol) and pyridine (502 μL, 6.21 mmol) in DCM (50 mL) and left to react overnight. The solution was filtered through Celite™,

washed with DCM (50 mL) and then the organic extract was extracted with aq. sat. $CuSO_4$ solution (2 x 50 mL) to afford the crude product as a colourless oil. Chromatography of this oil (10% EtOAc / pet. ether) afforded a 2:1 α:β anomeric mixture of **153** (1.43 g, 4.15 mmol, 73%) as a colourless oil.

R_f 0.6 (20% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H **Major anomer (α):** 5.79 (complex m, 2H, H-2, 3), 5.36 (s, 1H, H-1), 5.27 (d, J = 9.5 Hz, 1H, H-4), 4.24-4.14 (obs. m, 3H, H-5, 6a, 6b), 2.09 (s, 6H, CH_3CO), 0.91 (s, 9H, $OSiC(CH_3)_3$), 0.14 (s, 6H, $OSiCH_3$); **Minor Anomer (β):** 5.87 (complex m, 2H, H-2, 3), 5.42 (s, 1H, H-1), 5.24 (dt, J = 6.0, 2.0 Hz, 1H, H-4), 4.24-4.14 (obs. m, 2H, H-6a, 6b), 3.96 (dd, J = 12.0, 5.5 Hz, 1H, H-5), 2.076 (s, 3H, CH_3CO), 2.075 (s, 3H, CH_3CO), 0.90 (s, 9H, $OSiC(CH_3)_3$), 0.15 (s, 6H, $OSiCH_3$); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C **Major anomer (α):** 170.9 (C, $CH_3\underline{C}O$), 170.34 (C, $CH_3\underline{C}O$), 130.3 (CH, C-2), 127.0 (CH, C-3), 89.1 (CH, C-1), 66.8 (CH, C-5), 65.4 (CH, C-4), 63.3 (CH_2, C-6), 25.6 (CH_3, $OSiC(\underline{C}H_3)_3$), 21.0 (CH_3, $\underline{C}H_3CO$), 20.8 (CH_3, $\underline{C}H_3CO$), 18.0 (C, $OSi(\underline{C}H_3)_3$), -4.4 (CH_3, $OSi\underline{C}H_3$), -5.3 (CH_3, $OSi\underline{C}H_3$); **Minor Anomer (β):** 170.7 (C, $CH_3O\underline{C}O$), 170.30 (C, $CH_3O\underline{C}O$), 133.0 (CH, C-2), 125.3 (CH, C-3), 91.0 (CH, C-1), 73.0 (CH, C-5), 64.8 (CH, C-4), 63.4 (CH_2, C-6), 25.7 (CH_3, $OSiC(\underline{C}H_3)_3$), 21.0 (CH_3, $\underline{C}H_3CO$), 20.8 (CH_3, $\underline{C}H_3CO$), 18.0 (C, $OSi(\underline{C}H_3)_3$), -4.1 (CH_3, $OSi\underline{C}H_3$), -5.0 (CH_3, $OSi\underline{C}H_3$); **IR:** (Film from $CDCl_3$) ν_{max} 2955, 2930, 2897, 2858, 1743, 1370, 1225, 1033, 838, 781 cm^{-1}; **HRMS:** m/z $C_{16}H_{28}NaO_6Si^+$ $[M+Na]^+$ calcd 367.1547, found 367.1549.

tert-Butyldiphenylsilanol (247)



247

A solution of TBDPSCl (100 mg, 0.364 mmol) in Et_2O (8 mL) was added dropwise to an ice-cold solution of KOH (20 mg, 0.364 mmol) in a mixture of H_2O (4 mL) and MeOH (1 mL). The acidic solution was then neutralised by addition of aq. KOH solution. The reaction was stirred for 5 hours and then extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the desired product **247** (47 mg, 2.20 mmol, 50%) as a white solid. Spectral data matched those which have been previously reported.[97]

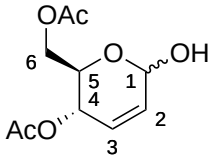
m.p. 63.8 – 65.2 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.72 (d, J = 6.5 Hz, 4H, H-4), 7.44-7.37 (complex m, 6H, H-5, 6), 2.15 (br s, 1H, OH), 1.08 (s, 9H, H-1); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 135.1 (C, C-3), 134.8 (CH, C-4), 129.6 (CH, C-

6), 127.7 (CH, C-5), 26.5 (CH_3, C-1), 19.0 (C, C-2); **IR:** (Film from $CDCl_3$) ν_{max} 3619, 3417, 3071, 2957, 2930, 2890, 2857, 1471, 1428, 1113, 819, 699, 608 cm^{-1}.

4.2.3 Experimental Details for Section 2.1.3

4,6-Di-*O*-acetyl-2,3-dideoxy-D-erythro-hex-2-enopyranose (165) and (2*E*, 4*S*,5*R*)-4,6-di-*O*-acetyl-5-hydroxy-hex-2-enal (166) and (2*E*,4*S*,5*R*)-5,6-diacetate-4-hydroxy-hex-2-enal (176)

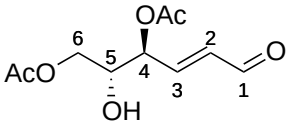
Under atmospheric conditions, in the dark, tri-*O*-acetyl-D-glucal (**102**) (1.99 mg, 7.30 mmol) was dissolved in 50 mL H_2O and the mixture was heated to 80 °C whereupon all solid dissolved. After 5 hours the reaction mixture was cooled to room temperature, extracted with ethyl acetate (3 x 50 mL), dried with anhydrous $MgSO_4$, and concentrated to afford a crude 20:12:1 mixture of **165**:**166**:**176** . Chromatographic separation (25% - 50% EtOAc / pet. ether) afforded a 2:1 α:β anomeric mixture of **165** (1.00 g, 4.34 mmol, 60%), **166** (504 mg, 2.19 mmol, 30%) and **176** (44 mg, 0.19 mmol, 3%) as colourless oils. Spectral data of all three matched those reported previously.[64, 45, 69]



165

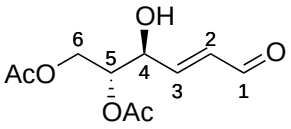
R_f 0.5 (50% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H **Major Anomer (α):** 5.89-5.84 (m, 2H, H-2,3), 5.43 (br s, 1H, H-1), 5.27 (d, J = 9.0 Hz, 1H, H-4), 4.25-4.15 (complex m, 3H, H-5, 6a, 6b), 3.67 (d, J = 5.0 Hz, 1H, OH), 2.08 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO); **Minor Anomer (β):** 5.94-5.89 (m, 2H, H-2,3), 5.42 (br s, 1H, H-1), 5.24 (d, J = 7.0 Hz, 1H, H-4), 4.25-4.17 (complex m, 2H, H-6a, 6b), 3.94 (ddd, J = 7.0, 5.5, 4.5 Hz, 1H, H-5), 3.84 (d, J = 7.5 Hz, 1H, OH), 2.07 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C **Major Anomer (α):** 171.0 (C, $CH_3\underline{C}O$), 170.34 (C, $CH_3\underline{C}O$), 129.0 (CH, C-3), 128.4 (CH, C-2), 88.7 (CH, C-1), 66.8 (CH, C-5), 65.1(CH, C-4), 63.0 (CH_2, C-6), 20.93 (CH_3, $\underline{C}H_3CO$), 20.75 (CH_3, $\underline{C}H_3CO$); **Minor Anomer (β):** 170.9 (C, $CH_3\underline{C}O$), 170.30 (C, $CH_3\underline{C}O$), 131.2 (CH, C-3), 127.4 (CH, C-2), 90.9 (CH, C-1), 73.1 (CH, C-5), 64.5 (CH, C-4), 63.3 (CH_2, C-6), 20.90 (CH_3, $\underline{C}H_3CO$), 20.76 (CH_3, $\underline{C}H_3CO$); **IR:** (Film from CH_2Cl_2) ν_{max} 3433, 2953, 1736, 1370, 1221, 1029, 1018 cm^{-1};

R_f 0.3 (60% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 9.59 (d, J = 7.5



166

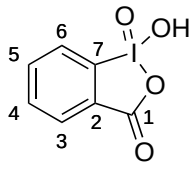
Hz, 1H, H-1), 6.88 (dd, J = 16.0, 5.0 Hz, 1H, H-3), 6.26 (dd, J = 16.0, 7.5 Hz, 1H, H-2), 5.56 (apt. t, J = 5.0 Hz, 1H, H-4), 4.21 (d, J = 4.5 Hz, 2H, H-6a, 6b), 4.06 (dd, J = 11.0, 5.5 Hz, H-5), 2.67 (br s, 1H, OH), 2.16 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 192.6 (CH, C-1), 171.3 (C, $CH_3\underline{C}O$), 169.5 (C, $CH_3\underline{C}O$), 149.6 (CH, C-3), 133.2 (CH, C-2), 72.3 (CH, C-4), 71.1 (CH, C-5), 64.7 (CH_2, C-6), 20.76 (CH_3, $\underline{C}H_3CO$), 20.75 (CH_3, $\underline{C}H_3CO$); **IR:** (Film from $CDCl_3$) ν_{max} 3470, 1740, 1690, 1373, 1225, 1042 cm^{-1}.



176

R_f 0.4 (60% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 9.60 (d, J = 7.5 Hz, 1H, H-1), 6.79 (dd, J = 16.0, 4.0 Hz, 1H, H-3), 6.41 (dd, J = 16.0, 8.0 Hz, 1H, H-2), 5.08 (obs. m, 1H, H-5), 4.58 (obs. m, 1H, H-4), 4.34 (obs.m, 2H, H-6a, 6b), 3.02 (br s, 1H, OH), 2.11 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 192.9 (CH, C-1), 171.1 (C, $CH_3\underline{C}O$), 170.3 (C, $CH_3\underline{C}O$), 152.4 (CH, C-3), 132.9 (CH, C-2), 73.4 (CH, C-5), 70.0 (CH, C-4), 61.8 (CH_2, C-6), 20.9 (CH_3, $\underline{C}H_3CO$), 20.7 (CH_3, $\underline{C}H_3CO$); **IR:** (Film from $CDCl_3$) ν_{max} 3467, 2959, 1734, 1689, 1370, 1218, 1037 cm^{-1}.

2-Iodoxybenzoic Acid (IBX) (248)



248

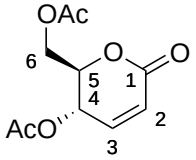
Following a literature procedure,[63] under atmospheric conditions, 2-iodobenzoic acid (3.49 g, 0.014 mol) was added in one portion to a solution of Oxone (25.99 g, 0.042 mol) in deionized water (200 mL) The reaction mixture was warmed to 70 °C for 3 h. The suspension was then cooled to 0 °C and left at this temperature for 30 mins with slow stirring. The mixture was filtered through a sintered-glass funnel, and the solid was washed with ice-cold water (50 mL) and acetone (50 mL). The solid was left to dry in a dessicator for 5 days to give the desired product **248** (2.5 g, 8.93 mmol, 63%) as a white powder. *CAUTION!* IBX is explosive under impact or sporadically upon heating to >200 °C.[98]

m.p. 226.1 – 226.4 °C (lit.[63] **m.p.** 232 – 233 °C).

Fétizon's reagent

Following a literature procedure,[99] Celite™ (2.00 g) was purified by washing successively with methanol containing 10% HCl solution (100 mL) and then with distilled water until neutral and then oven-dried overnight. The purified Celite™ (1 g) was added to a solution of silver nitrate (1.14 g, 6.71 mmol) in distilled water (6.7 mL). A solution of $Na_2CO_3.10\,H_2O$ (1.02 g, 3.56 mmol) in distilled water (10 mL) was then added slowly to the resulting homogeneous suspension and stirred vigorously for 15 mins. The yellow-green precipitate formed was then filtered off and dried on a rotary evaporator over six hours. The resulting grey solid, Fétizon's reagent, was stored in a dessicator under vacuum in the dark. According to the literature,[99] the reagent contains approx. 1 mmol of Ag_2CO_3 per 0.57 g.

4,6-Di-*O*-acetyl-2,3-dideoxy-D-erythro-hex-2-enono-1,5-lactone (172)



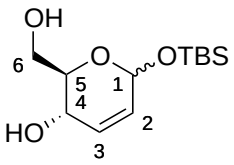
172

To a solution of **165** (280 mg, 1.22 mmol) in benzene (13 mL) at 50 °C was added Fétizon's reagent **249** (0.72 g, 1.26 mmol). The solution was then heated at reflux overnight. The resulting black suspension was cooled to room temperature, filtered through Celite™, washed with ethyl acetate (50 mL) and concentrated to give **172** (240 mg, 1.05 mmol, 86%) as a colourless oil. Spectral data matched those which have been previously reported.[62]

$\mathbf{R_f}$ 0.5 (50% EtOAc / pet. ether); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.79 (dd, J = 10.0, 3.0 Hz, 1H, H-3), 6.12 (dd, J = 10.0, 1.5 Hz, 1H, H-2), 5.54 (ddd, J = 8.0, 3.0, 2.0 Hz, 1H, H-4), 4.66 (ddd, J = 8.0, 4.5, 3.5 Hz, 1H, H-5), 4.35 (dd, J = 12.5, 4.5 Hz, 1H, H-6a), 4.27 (dd, J = 12.5, 4.0 Hz, 1H, H-6b), 2.15 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 170.4 (C, $CH_3\underline{C}O$), 169.7 (C, $CH_3\underline{C}O$), 161.1 (C, C-1), 143.2 (CH, C-3), 122.4 (CH, C-2), 77.3 (CH, C-5), 63.4 (CH, C-4), 62.0 (CH, C-6), 20.72 (CH_3, $\underline{C}H_3CO$), 20.67 (CH_3, $\underline{C}H_3CO$); **IR:** (Film from CH_2Cl_2) ν_{max} 2958, 1736, 1371, 1221, 1113, 1047, 818 cm^{-1}.

4.2.4 Experimental Details for Section 2.1.5

***tert*-Butyldimethylsilyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (179)**



179

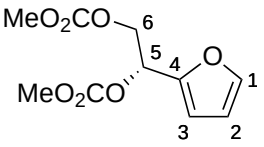
Sodium (10 mg, 0.435 mmol) was added to methanol (2 mL) and allowed to react. This was followed by addition of a solution of **165** (280 mg, 0.813 mmol) in methanol (2 mL). The reaction was stirred at room temp for 15 minutes and then the solution was concentrated to afford the crude product as a viscous yellow oil. Chromatography of the oil (1:1 hexanes:ethyl acetate) afforded a 1.7:1 α:β anomeric mixture of **179** (179 mg, 0.688 mmol, 85%) as a colourless oil.

$\mathbf{R_f}$ 0.3 (40% EtOAc / pet. ether); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H **Major anomer (α):** 5.88 (d, J = 10.0 Hz, 1H, H-3), 5.72 (dt, J = 10.0, 2.5 Hz, 1H, H-2), 5.33 (s, 1H, H-1), 4.23 (m, 1H, H-4), 3.86-3.71 (obs. m, 3H, H-5, 6a, 6b), 1.89 (t, J = 6.0 Hz, 1H, OH), 1.84 (obs. m, 1H, OH), 0.90 (s, 9H, $OSiC(CH_3)_3$), 0.13 (s, 6H, $OSiCH_3$); **Minor Anomer (β):** 5.96 (ddd, J = 10.3, 3.5, 1.5 Hz, 1H, H-3), 5.77 (dt, J = 10.0, 1.5 Hz, 1H, H-2), 5.43 (s, 1H, H-1), 4.16 (m, 1H, H-4), 3.86-3.71 (obs. m, 3H, H-5, 6a, 6b), 2.37 (t, J = 6.5 Hz, 1H, OH), 1.84 (obs. m, 1H, OH), 0.93 (s, 9H, $OSiC(CH_3)_3$), 0.16 (s, 6H, $OSiCH_3$); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C **Major anomer (α):** 131.2 (CH, C-3), 129.0 (CH, C-2), 89.0 (CH, C-1), 71.1 (CH, C-5), 64.5 (CH, C-4), 63.0 (CH_2, C-6), 25.68 (CH_3, $OSiC(\underline{C}H_3)_3$), 18.0 (C, $OSi(\underline{C}H_3)_3$), -4.3(CH_3, $OSi\underline{C}H_3$), -5.3 (CH_3, $OSi\underline{C}H_3$); **Minor Anomer (β):** 130.7 (CH, C-3), 130.1 (CH, C-2), 91.0 (CH, C-1), 78.4 (CH, C-5), 63.5 (CH, C-4), 63.4 (CH_2, C-6), 25.69 (CH_3, $OSiC(\underline{C}H_3)_3$), 18.1 (C, $OSi(\underline{C}H_3)_3$), -4.1 (CH_3, $OSi\underline{C}H_3$), -4.9 (CH_3, $OSi\underline{C}H_3$); **IR:** (Film from $CDCl_3$) ν_{max} 3362, 2954, 2929, 2895, 2857, 1253, 1030, 999, 875, 837, 780 cm^{-1}; **HRMS:** m/z $C_{12}H_{25}O_4Si^+$ $[M+H]^+$ calcd 261.1517, found 261.1514.

(1*R*)-1-(2-furanyl)-2-(methoxycarbonyl)ethan-ol (182) and (4*R*)-4-(2-furanyl)-1,3-dioxolan-2-one) (183) and (1*R*)-1-(2-furanyl)-1,2-di-(methoxycarbonyl)ethane (181)

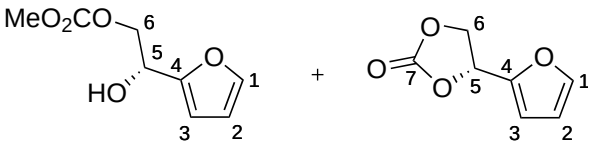
A solution of diol **179** (67 mg, 0.258 mmol) in THF (5 mL) was cooled to 0 °C and DMAP (79 mg, 0.647 mmol) and methyl chloroformate (50 μL, 0.652 mmol) was added. The reaction was allowed to warm to room temperature overnight and then the solution was concentrated to afford a yellow oil. Chromatography of the oil (20 -

30% EtOAc / pet. ether) afforded three undesired furan products; diprotected furan **181** (17 mg, 0.071 mmol, 28%) as a colourless oil and a 1.4:1 mixture of **182** and **183** (11 mg, 0.062 mmol, 24%) as a colourless oil. Spectral data of **183** matched those which have been previously reported.[73]



181

$\mathbf{R_f}$ 0.6 (30% EtOAc / pet. ether); $[\alpha]_D^{23.0}$ +89.50 (*c* 0.9, CH_2Cl_2); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.42 (s, 1H, H-1), 6.48 (d, J = 3.0 Hz, 1H, H-3), 6.37 (dd, J = 3.0, 2.0 Hz, 1H, H-2), 5.95 (dd, J = 8.0, 4.0 Hz, 1H, H-5), 4.57 (dd, J = 12.0, 8.5 Hz, 1H, H-6a), 4.52 (dd, J = 12.0, 4.0 Hz, 1H, H-6b), 3.80 (s, 3H, CH_3OCO), 3.79 (s, 3H, CH_3OCO); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 155.3 (C, $CH_3O\underline{C}O$), 154.9 (C, $CH_3O\underline{C}O$), 148.1 (CH, C-4), 143.4 (CH, C-1), 110.5 (CH, C-2), 110.4 (CH, C-3), 70.0 (CH, C-5), 66.4 (CH_2, C-6), 55.12 (CH_3, $\underline{C}H_3OCO$), 55.10 (CH_3, $\underline{C}H_3OCO$); **IR:** (Film from CH_2Cl_2) ν_{max} 2960, 1745, 1441, 1279, 1239, 938, 787, 749 cm^{-1}; **HRMS:** *m/z* $C_{10}H_{16}NO_7^+$ $[M+NH_4]^+$ calcd 262.0921, found 262.0922.



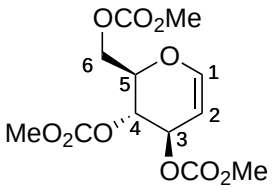
182 **183**

$\mathbf{R_f}$ 0.2 (40% EtOAc / pet. ether); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H **182**: 7.40 (s, 1H, H-1), 6.36 (m, 2H, H-2, 3), 5.00 (br s, 1H, H-5), 4.45-4.43 (obs. m, 2H, H-6a, 6b), 3.81 (s, 3H, CH_3OCO), 2.49 (br s, 1H, OH); **183**: 7.52 (s, 1H, H-1), 6.58 (d, J = 2.5 Hz, 1H, H-2), 6.43 (dd, J = 3.0, 2.0 Hz, 1H, H-3), 5.69 (t, J = 8.0 Hz, 1H, H-5), 4.69 (complex m, 2H, H-6a, 6b); **IR:** (Film from CH_2Cl_2) ν_{max} 3469, 3127, 2961, 1796, 1747, 1444, 1269, 1168, 1151, 1067 cm^{-1}.

3,4,6 Tri-*O*-methoxycarbonyl-D-glucal (198) and 3,6-di-*O*-methoxycarbonyl-D-glucal (250) and 4,6-di-*O*-methoxycarbonyl-D-glucal (251)

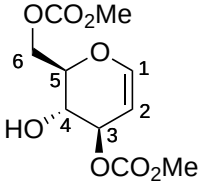
To a solution of D-glucal **158** (1.87 g, 12.8 mmol) in THF (150 mL) at 0 °C was added DMAP (5.01 g, 41.0 mmol), followed by methyl chloroformate (3.1 mL, 41.0 mmol). The reaction was allowed to warm to room temperature and left to proceed overnight. The solution was filtered through Celite™, washed with dichloromethane (50 mL), and concentrated to give the crude products **198**:**250**:**251** as an off-white solid in 8:1:1 ratio. Chromatography of the solid (30% EtOAc / pet. ether) afforded **198** (2.15 g, 6.70 mmol, 52%) as a white solid, **250** (517 mg, 1.97 mmol, 15%) as a colourless oil and **251** (300 mg, 1.14 mmol, 9%) as a colourless oil in a combined

yield of 76%.



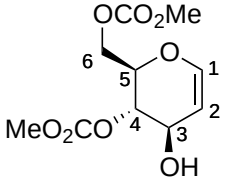
198

R$_f$ 0.45 (30% EtOAc / pet. ether); $[\alpha]_D^{21}$ -23.4 (*c* 1.085, CH_2Cl_2); **m.p.** 66.1 – 66.9 °C; ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.48 (d, J = 6.0 Hz, 1H, H-1), 5.22 (t, J = 4.0 Hz, 1H, H-3), 5.09 (t, J = 6.5 Hz, 1H, H-4), 4.94 (dd, J = 6.0, 3.5 Hz, 1H, H-2), 4.47 (dd, J = 12.0, 6.0 Hz, 1H, H-6a), 4.36 (complex m, 1H, H-5), 4.32 (dd, J = 12.0, 4.0 Hz, 1H, H-6b), 3.82 (s, 3H, CH_3OCO), 3.80 (s, 3H, CH_3OCO), 3.79 (s, 3H, CH_3OCO); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 155.4 (C, $CH_3O\underline{C}O$), 154.9 (C, $CH_3O\underline{C}O$), 154.5 (C, $CH_3O\underline{C}O$), 146.0 (CH, C-1), 97.9 (CH, C-2), 73.4 (CH, C-5), 70.7 (CH, C-4), 70.2 (CH, C-3), 64.7 (CH_2, C-6), 55.4 (CH_3, $\underline{C}H_3OCO$), 55.1 (CH_3, $\underline{C}H_3OCO$), 55.0 (CH_3, $\underline{C}H_3OCO$); **IR:** (KBr) ν_{max} 3012, 2962, 1758, 1736, 1654, 1447, 1318, 1267, 1244, 1097, 955, 937 cm^{-1}; **HRMS:** *m/z* $C_{12}H_{16}O_{10}Na^+$ $[M+Na]^+$ calcd 343.0636, found 343.0642.



250

R$_f$ 0.28 (30% EtOAc / pet. ether); $[\alpha]_D^{26.0}$ +38.42 (*c* 1.26, CH_2Cl_2); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.44 (d, J = 6.5 Hz, 1H, H-1), 5.20 (d, J = 6.5 Hz, 1H, H-3), 4.79 (dd, J = 6.0, 2.5 Hz, 1H, H-2), 4.56 (dd, J = 12.0, 4.0 Hz, 1H, H-6a), 4.48 (dd, J = 12.0, 2.0 Hz, 1H, H-6b), 4.02 (ddd, J = 10.0, 4.0, 2.0 Hz, 1H, H-5), 3.95 (ddd, J = 10.5, 6.5, 3.5 Hz, 1H, H-4), 3.82 (s, 6H, CH_3OCO), 3.44 (d, J = 3.5 Hz, 1H, OH); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 156.4 (C, $CH_3O\underline{C}O$), 156.1 (C, $CH_3O\underline{C}O$), 146.3 (CH, C-1), 98.8 (CH, C-2), 76.2 (CH, C-5), 76.1 (CH, C-3), 66.9 (CH, C-4), 65.7 (CH_2, C-6), 55.2 (CH_3, $\underline{C}H_3OCO$), 55.2 (CH_3, $\underline{C}H_3OCO$); **IR:** (Film from CH_2Cl_2) ν_{max} 3436, 2960, 1749, 1443, 1270, 1050, 790 cm^{-1}; **HRMS:** *m/z* $C_{10}H_{14}O_8Na^+$ $[M+Na]^+$ calcd 285.0581, found 285.0584.

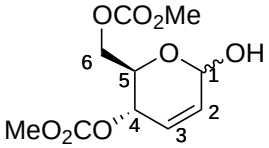


251

R$_f$ 0.14 (30% EtOAc / pet. ether); $[\alpha]_D^{26}$ +43.45 (*c* 1.065, CH_2Cl_2); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.40 (d, J = 5.5 Hz, 1H, H-1), 4.51 (obs. m, 2H, H-2,4), 4.44-4.39 (m, 3H, H-3,6a,6b), 4.19 (ddd, J = 8.5, 5.5, 3.0 Hz, 1H, H-5), 3.84 (s, 3H,

CH_3OCO), 3.80 (s, 3H, CH_3OCO) 2.44 (d, J = 5.5 Hz, 1H, OH); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 155.6 (C, $CH_3O\underline{C}O$), 155.5 (C, $CH_3O\underline{C}O$), 144.1 (CH, C-1), 102.5 (CH, C-2), 74.9 (CH, C-4), 73.4 (CH, C-5), 66.8 (CH, C-3), 65.3 (CH_2, C-6), 55.5 (CH_3, $\underline{C}H_3OCO$), 55.1 (CH_3, $\underline{C}H_3OCO$); **IR:** (Film from CH_2Cl_2) ν_{max} 3497, 2961, 1749, 1650, 1443, 1259 cm^{-1}; **HRMS:** *m/z* $C_{10}H_{14}O_8Na^+$ $[M+Na]^+$ calcd 285.0581, found 285.0583.

4,6-Di-*O*-(methoxycarbonyl)-2,3-dideoxy-D-erythro-hex-2-eno-pyranose (199)

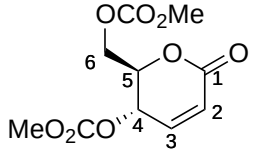


199

A solution of tricarbonate **198** (590 mg, 1.84 mmol) in H_2O was stirred at 80 °C for 30 minutes. The solution was then cooled to room temperature and concentrated to afford a 3:1 α:β anomeric mixture of **199** (470 mg, 1.79 mmol, 97%) as a colourless oil.

R$_f$ 0.43 (50% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H **Major Anomer (α):** 6.02 - 5.89 (obs. m, 2H, H-2,3), 5.46 (br s, 1H, H-1), 5.17 (d, J = 10.0 Hz, 1H, H-4), 4.38 (dd, J = 12.0, 2.0 Hz, 1H, H-6a), 4.29 (dd, J = 12.0, 5.0 Hz, 1H, H-6b), 4.25-4.22 (obs. m, 1H, H-5), 3.82 (s, 3H, CH_3OCO), 3.80 (s, 3H, CH_3OCO), 2.99 (d, J = 5.0 Hz, 1H, OH); **Minor Anomer (β):** 6.02 - 5.89 (obs. m, 2H, H-2,3), 5.46 (br s, 1H, H-1), 5.13 (d, J = 6.5 Hz, 1H, H-4), 4.35 (obs. m, 1H, H-6a), 4.25-4.22 (obs. m, 1H, H-6b), 4.05 (dt, J = 10.0, 5.0 Hz, 1H, H-5), 3.81 (s, 3H, CH_3OCO), 3.80 (s, 3H, CH_3OCO), 3.10 (d, J = 8.0 Hz, 1H, OH); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C **Major Anomer (α):** 155.6 (C, $CH_3O\underline{C}O$), 155.03 (C, $CH_3O\underline{C}O$), 128.7 (CH, C-3), 128.6 (CH, C-2), 88.8 (CH, C-1), 68.6 (CH, C-4), 66.5 (CH, C-5), 66.3 (CH_2, C-6), 55.21 (CH_3, $\underline{C}H_3OCO$), 55.00 (CH_3, $\underline{C}H_3OCO$); **Minor Anomer (β):** 155.5 (C, $CH_3O\underline{C}O$), 154.99 (C, $CH_3O\underline{C}O$), 131.6 (CH, C-2), 126.9 (CH, C-3), 90.9 (CH, C-1), 72.8 (CH, C-5), 67.9 (CH, C-4), 66.6 (CH_2, C-6), 55.17 (CH_3, $\underline{C}H_3OCO$), 55.04 (CH_3, $\underline{C}H_3OCO$); **IR:** (Film from $CDCl_3$) ν_{max} 3479, 3010, 2961, 1749, 1444, 1264, 1016 cm^{-1}; **HRMS:** *m/z* $C_{10}H_{14}O_8Na^+$ $[M+Na]^+$ calcd 285.0581, found 285.0583.

4,6-Di-*O*-(methoxycarbonyl)-2,3-dideoxy-D-erythro-hex-2-enono-1,5-lactone (178)

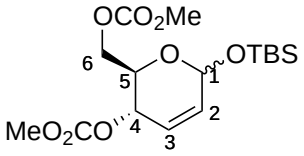


178

A solution of **199** (240 mg, 0.916 mmol) in benzene (10 mL) was heated to 50 °C at which point Fétizon's reagent (1.04 g, 1.832 mmol) was added. The solution was then heated to reflux overnight. The black solution was cooled to room temperature, filtered through Celite™, washed with EtOAc (50 mL) and concentrated to give the crude product as a yellow oil. Chromatography of the oil (30% EtOAc / pet. ether) afforded **178** (232 mg, 0.89 mmol, 97%) as a white solid.

R$_f$ 0.5 (40% EtOAc / pet. ether) **m.p.** 111 – 112.3 °C; $[\alpha]_D^{24}$ +92.09 (*c* 1.06, CH_2Cl_2); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.86 (dd, J = 10.0, 2.5 Hz, 1H, H-3), 6.13 (dd, J = 10.0, 1.0 Hz, 1H, H-2), 5.47 (d, J = 8.0 Hz, 1H, H-4), 4.70 (dt, J = 8.0, 4.0 Hz, 1H, H-5), 4.42 (d, J = 3.5 Hz, 2H, H-6), 3.86 (s, 3H, CH_3OCO), 3.81 (s, 3H, CH_3OCO); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 160.7 (C, C1), 155.2 (C, CH_3OCO), 154.5 (C, CH_3OCO), 142.7 (CH, C-3), 122.4 (CH, C-2), 76.7 (CH, C-5, (observed by HSQC)), 66.8 (CH, C-4), 65.3 (CH, C-6), 55.7 (CH_3, $\underline{C}H_3OCO$), 55.3 (CH_3, $\underline{C}H_3OCO$); **IR:** ν_{max} 2962, 1746, 1443, 1261, 1231, 994, 788 cm^{-1}; **HRMS:** *m/z* $C_{10}H_{12}O_8Na^+$ $[M+Na]^+$ calcd 283.0424, found 283.0427.

4,6-Di-*O*-(methoxycarbonyl)-1-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-erythro-hex-2-enopyranoside (154)



154

A solution of **199** (250 mg, 0.95 mmol) in DCM (10 mL) and pyridine (85 μL, 1.05 mmol) was cooled to 0 °C. Silver nitrate (178 mg, 1.05 mmol) was added and after all solid was dissolved TBSCl (158 mg, 1.05 mmol) was added and the reaction was allowed to warm to room temperature and left to proceed overnight. The solution was filtered through Celite™, washed with DCM (50 mL) and concentrated to give the crude product and pyridine as a white semi-crystalline solid. Chromatography of the solid (10% EtOAc / pet. ether) afforded a 3:2 α:β anomeric mixture of **252** (287 mg, 0.76 mmol, 80%) as a colourless oil.

R$_f$ 0.9 (30% EtOAc / pet. ether); **^{1}H-NMR:** (600 MHz; $CDCl_3$) δ_H **Major Anomer (α):** 5.86 (d, J = 10.8 Hz, 1H, H-3), 5.80 (dt, J = 10.8, 2.4 Hz, 1H, H-2), 5.35 (d, J = 1.8 Hz, 1H, H-1), 5.16 (dd, J = 9.6, 0.6 Hz, 1H, H-4), 4.36 - 4.26 (obs. m, 2H, H-6), 4.19 (ddd, J = 9.6, 4.8, 3.0 Hz, 1H, H-5), 3.81 (s, 3H, CH_3OCO), 3.78 (s, 3H, CH_3OCO), 0.89 (s, 9H, $OSiC(CH_3)_3$), 0.12 (s, 3H, $OSiCH_3$), 0.11 (s, 3H, $OSiCH_3$); **Minor Anomer (β):** 5.93 (ddd, J = 10.2, 2.4, 1.0 Hz, 1H, H-3), 5.89 (d, J = 10.2 Hz, 1H, H-2), 5.40 (d, J = 1.2 Hz, 1H, H-1), 5.10 (dd, J = 6.6, 1.2 Hz, 1H, H-4), 4.36 - 4.26 (obs. m, 2H, H-6), 4.03 (apt. q, J = 5.7 Hz, 1H, H-

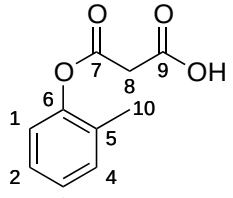
5), 3.80 (s, 3H, CH_3OCO), 3.79 (s, 3H, CH_3OCO), 0.89 (s, 9H, $OSiC(CH_3)_3$), 0.13 (s, 3H, $OSiCH_3$), 0.12 (s, 3H, $OSiCH_3$); **^{13}C-NMR:**(150 MHz; $CDCl_3$) δ_C **Major Anomer (α):** 155.7 (C, $CH_3O\underline{C}O$), 155.08 (C, $CH_3O\underline{C}O$), 130.7 (CH, C-2), 126.3 (CH, C-3), 89.0 (CH, C-1), 68.8 (CH, C-4), 66.41 (CH, C-5), 66.35 (CH_2, C-6), 55.14 (CH_3, $\underline{C}H_3OCO$), 54.89 (CH_3, $\underline{C}H_3OCO$), 25.6 (CH_3, $OSiC(\underline{C}H_3)_3$), 17.95 (C, $OSi(\underline{C}H_3)_3$), -4.5 (CH_3, $OSi\underline{C}H_3$), -5.4 (CH_3, $OSi\underline{C}H_3$); **Minor Anomer (β):** 155.5 (C, $CH_3O\underline{C}O$), 155.06 (C, $CH_3O\underline{C}O$), 133.5 (CH, C-2), 124.7 (CH, C-3), 91.0 (CH, C-1), 72.6 (CH, C-5), 68.2 (CH, C-4), 66.6 (CH_2, C-6), 55.07 (CH_3, $\underline{C}H_3OCO$), 54.94 (CH_3, $\underline{C}H_3OCO$), 25.7 (CH_3, $OSiC(\underline{C}H_3)_3$), 17.98 (C, $OSi(\underline{C}H_3)_3$), -4.1 (CH_3, $OSi\underline{C}H_3$), -5.1 (CH_3, $OSi\underline{C}H_3$); **IR:** (Film from $CDCl_3$) ν_{max} 2957, 2931, 2858, 1749, 1442, 1248, 1020, 838, 704, 675 cm^{-1}; **HRMS:** *m/z* $C_{16}H_{28}O_8SiNa^+$ $[M+Na]^+$ calcd 399.1446, found 399.1452.

4.2.5 Experimental Details for Section 2.3.1

Synthesis of 3-oxo-3-phenoxypropanoic acids

Following a literature method,[77] a mixture of cresol (6.94 mmol) and Meldrum's acid (6.94 mmol) was heated at 110 °C for 3 h. After cooling to room temperature overnight, the acetone formed was removed under vacuum to give the desired phenoxypropanoic acid in a quantitative yield that was used without further purification.

3-(2-Methylphenoxy)-3-oxo-propanoic acid (206)

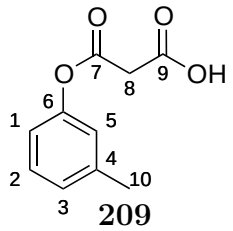


206

The reaction was performed with *o*-cresol (0.75 g, 6.94 mmol) according to the above method to afford **206** as a brown solid. This is a known compound[77] however no spectral data was available for comparison in the literature.

^{1}H-NMR: (500 MHz; $CDCl_3$) δ_H 7.26-7.17 (obs. m, 3H, H-1,2,3), 7.05 (d, J = 8.5, 1H, H-4), 3.72 (s, 2H, H-8), 2.24 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 170.5 (C, C-9), 164.8 (C, C-7), 149.0 (C, C-6), 131.3 (CH, C-2), 130.0 (C, C-5), 127.0 (CH, C-3), 126.6 (CH, C-1), 121.6 (CH, C-4) 40.7 (CH_2, C-8), 16.1 (CH_3, C-10).

3-(3-Methylphenoxy)-3-oxo-propanoic acid (209)

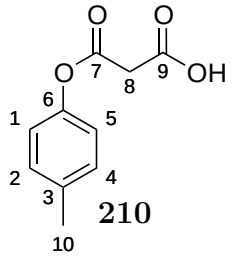


209

The reaction was performed with *m*-cresol (0.73 mL, 6.94 mmol) according to the above method to afford **209** as a pale-yellow oil. This is a known compound[100] however no spectral data was available for comparison in the literature.

^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.29 (d, J = 8.0 Hz, 1H, H-2), 7.08 (d, J = 7.5 Hz, 1H, H-1), 6.95 (s, 1H, H-5), 6.94 (d, J = 12.0 Hz, 1H, H-3), 3.69 (s, 2H, H-8), 2.37 (s, 3H, H-10); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 165.5 (C, C-9), 155.4 (C, C-7), 150.2 (C, C-6), 139.9 (C, C-4), 129.3 (CH, C-2), 127.2 (CH, C-1), 121.8 (CH, C-5), 118.2 (CH, C-3), 40.7 (CH_2, C-8), 21.3 (CH_3, C-10).

3-(4-Methylphenoxy)-3-oxo-propanoic acid (210)



210

The reaction was performed with *p*-cresol (0.75 g, 6.94 mmol) according to the above method to afford **210** as an off-white solid. This is a known compound[101] however no spectral data was available for comparison in the literature.

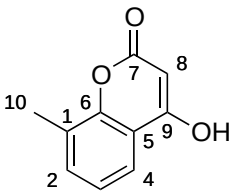
^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.20 (d, J = 8.5 Hz, 2H, H-2), 7.02 (d, J = 8.5 Hz, 2H, H-3), 3.68 (s, 2H, H-5), 2.35 (s, 3H, H-7); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 165.7 (C, C-7), 148.0 (C, C-5), 136.2 (C, C-4), 130.1 (CH, C-2), 120.9 (CH, C-3), 40.5 (CH_2, C-6), 20.9 (CH_3, C-8).

Synthesis of 4-Hydroxymethylcoumarins

Following a literature method,[77] Eaton's reagent (prepared from P_2O_5 (1.68 g) dissolved in methanesulfonic acid (10 mL))[79] (7.6 mL) was added to the 3- oxo- 3-phenoxypropanoic acid (6.94 mmol) and the reaction mixture was heated at 70 °C with constant stirring for 5 h. After cooling to room temperature the reaction mixture was poured into ice-cooled water (80 mL) with vigorous stirring. The aqueous solution was stirred for 30 min at 0 °C and then filtered. The solid was washed with

cold water, dried under high vacuum, and purified by recrystallisation from absolute ethanol to afford the desired 4-hydroxymethyl-coumarin as a solid.

4-Hydroxy-8-methylcoumarin (138)

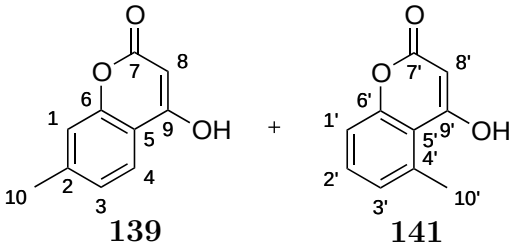


138

The above reaction was performed with **206** (1.35 g, 6.94 mmol) to afford **138** as a beige semi-crystalline solid (420 mg, 2.38 mmol, 34%). Spectral data matched those which have been previously reported[77]

m.p. 241.4 – 243.6 °C (lit.[77] **m.p.** 238 – 239 °C); ^{1}**H-NMR:** (500 MHz; DMSO-d_6) δ_{H} 12.44 (s, 1H, OH), 7.65 (d, J = 7.5 Hz, 1H, H-4), 7.50 (d, J = 7.5 Hz, 1H, H-2), 7.23 (t, J = 7.5 Hz, 1H, H-3), 5.58 (s, 1H, H-8), 2.34 (s, 3H, H-10); ^{13}**C-NMR:** (125 MHz; DMSO-d_6) δ_{C} 166.4 (C, C-9), 162.3 (C, C-7), 152.3 (C, C-6), 134.1 (CH, C-2), 125.7 (C, C-1), 123.8 (CH, C-3), 121.3 (CH, C-4), 116.0 (C, C-5), 91.2 (CH, C-8), 15.7 (CH_3, C-10).

4-Hydroxy-7-methylcoumarin (139) and 4-hydroxy-5-methylcoumarin (141)



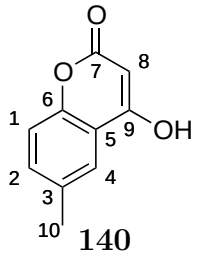
139 **141**

The above reaction was performed with **209** (1.35 g, 6.94 mmol) to afford a 1.3:1 mixture of **139**:**141** as a beige solid (580 mg, 3.29 mmol, 47%). Spectral data of **141** matched those which have been previously reported.[77]

m.p. 193.9 – 198.9 °C; (**139** lit.[102] **m.p.** 222 – 223 °C); (**141** lit.[77] **m.p.** 238 – 239 °C); ^{1}**H-NMR:** (500 MHz; DMSO-d_6) δ_{H} **139:** 12.41 (s, 1H, OH), 7.68 (d, J = 8.0 Hz, 1H, H-4), 7.19 - 7.15 (m, 2H, H-1,3), 5.52 (s, 1H, H-8), 2.49 (s, 3H, H-10); **141:** 12.36 (s, 1H, OH'), 7.46 (t, J = 7.5 Hz, 1H, H-2'), 7.19 - 7.15 (m, 1H, H-1'), 7.10 (d, J = 6.5 Hz, 1H, H-3'), 5.54 (s, 1H, H-8'), 2.66 (s, 3H, H-10'); ^{13}**C-NMR:** (125 MHz; DMSO-d_6) δ_{C} **139:** 166.3 (C, C-9), 162.5 (C, C-7), 154.1 (C, C-6), 143.9 (C, C-2), 125.5 (CH, C-1), 123.4 (CH, C-4), 116.8 (CH, C-3), 113.7 (C, C-5), 90.6

(CH, C-8), 21.6 (CH_3, C-10). **141:** 169.1 (C, C-9'), 161.9 (C, C-7'), 155.5 (C, C-6'), 137.6 (C, C-4'), 132.2 (CH, C-2'), 127.6 (CH, C-3'), 115.2 (CH, C-1'), 114.7 (C, observed by HMBC, C-5'), 91.6 (CH, C-8'), 23.1 (CH_3, C-10').

4-Hydroxy-6-methylcoumarin (140)



140

The above reaction was performed with **210** (1.35 g, 6.94 mmol) to afford **140** as a brown semi-crystalline solid (410 mg, 2.33 mmol, 34%). Spectral data matched those which have been previously reported.[78]

m.p. 270.7 – 272.0 °C (lit.[103] **m.p.** 261 – 264 °C); ^{1}**H-NMR:** (500 MHz; DMSO-d_6) δ_H 12.44 (s, 1H, OH), 7.60 (s, 1H, H-4), 7.45 (d, J = 8.5 Hz, 1H, H-1), 7.25 (d, J = 8.5 Hz, 1H, H-2), 5.55 (s, 1H, H-8), 2.31 (s, 3H, H-10); ^{13}**C-NMR:** (125 MHz; DMSO-d_6) δ_C 166.1 (C, C-9), 162.5 (C, C-7), 152.1 (C, C-6), 134.0 (CH, C-4), 133.6 (C, C-3), 123.2 (CH, C-1), 116.6 (CH, C-2), 115.9 (C, C-5), 91.4 (CH, C-8), 20.8 (CH_3, C-10).

4.2.6 Experimental Details for Sections 2.4.1 and 2.4.2

Pd-AA cascade with Acyclic Substrate (Method A): β-Dicarbonyl bis-nucleophile (2.3 eq.), PPh_3 (0.4 eq.) and $Pd_2(dba)_3$ (0.1 eq.) were combined in a reaction vessel which was then evacuated and back filled with nitrogen. Acetonitrile (*ca.* 0.05 M *w.r.t* **40**), degassed by sparging with nitrogen for approx. 20 minutes) was added, followed by addition of both *Z*-but-2-ene-1,4-diyl dimethyl dicarbonate (**40**)* (1.0 eq.) and NEt_3 (1.0 eq.) via syringe. After 1 hour the reaction mixture was concentrated and purified by flash column chromatography (10% then 25% EtOAc / pet. ether).

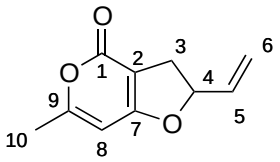
Pd-AA cascade with Cyclic Substrate (Method B): β-Dicarbonyl bis-nucleophile (1.0 eq.) and $Pd(PPh_3)_4$ (0.05 eq.) were combined in a reaction vessel which was then evacuated and back filled with nitrogen. Toluene (*ca.* 0.05 M), degassed by sparging with nitrogen for approx. 20 minutes) was added, followed by addition of cis-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-*2H*-pyran-3-yl methyl

*Compound **40** was provided by Dr Mark Bartlett.

carbonate (*cis*-**42**)[†] (1.0 eq.) via syringe. The reaction was stirred overnight at room temperature before being concentrated and purified by flash column chromatography (10 - 20% EtOAc / pet. ether).

Pd-AA cascade with Cyclic Substrate (Method C): β-Dicarbonyl bis-nucleophile (1.0 eq.) and $Pd(PPh_3)_4$ (0.05 eq.) were combined in a reaction vessel which was then evacuated and back filled with nitrogen. Toluene/DMF (3:1, *ca.* 0.05 M), degassed by sparging with nitrogen for approx. 20 minutes) was added, followed by addition of cis-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-*2H*-pyran-3-yl methyl carbonate (*cis*-**42**)[†] (1.0 eq.) via syringe. The reaction was stirred overnight at room temperature before being concentrated and purified by flash column chromatography (10 - 20% EtOAc / (1% NEt_3 / pet. ether)).

6-Methyl-2-vinyl-2*H*-furo[3,2-*c*]pyran-4(3*H*)-one (41)

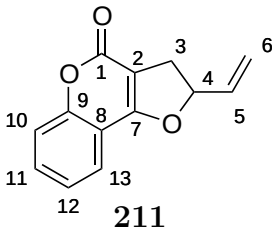


41

The Pd-AA cascade reaction was performed with 4-hydroxy-6-methyl-2-pyrone (90 mg, 0.714 mmol) according Method A. The product (**41**) was purified as a colourless oil (33 mg, 0.185 mmol, 59% yield). Spectral data matched those which have been previously reported.[19]

R*f* 0.25 (40% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 5.95 (obs. m, 1H, H-5), 5.93 (br s, 1H, H-8), 5.38-5.32 (m, 2H, H-4, 6a), 5.28 (d, J = 10.5 Hz, 1H, H-6b) 3.21 (dd, J = 15.0, 10.0 Hz, 1H, H-3a), 2.80 (dd, J = 15.0, 7.5 Hz, 1H, H-3b), 2.25 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 171.2 (C, C-7), 165.3 (C, C-1), 162.3 (C, C-9), 135.5 (CH, C-5), 118.1 (CH_2, C-6), 99.0 (C, C-2), 95.7 (CH, C-8), 86.8 (CH, C-4), 31.6 (CH_2, C-3), 20.3 (CH_3, C-10); **IR:** (Film from $CDCl_3$) ν_{max} 3088, 2927, 1718, 1637, 1581, 1452, 1418, 1256, 1166, 1109, 977, 924, cm^{-1}.

2-Vinyl-2*H*-furo[3,2-*c*]chromen-6(6bH)-one (211)



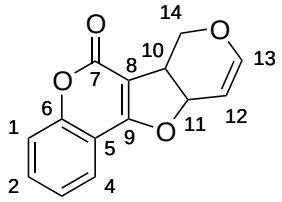
211

[†] *cis*-**42** was provided on separate occasions by Dr Mark Bartlett and Stephen Tat.

The Pd-AA cascade reaction was performed with 4-hydroxycoumarin (116 mg, 0.715 mmol) according to Method A. The product (**211**) was purified as an off white solid (35 mg, 0.164 mmol, 52%).

R$_f$ 0.3 (25% EtOAc / pet. ether); **m.p.** 116.8 – 119.1 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.69 (d, J = 7.5 Hz, 1H, H-13), 7.57 (t, J = 8.0 Hz, 1H, H-12), 7.39 (d, J = 8.0 Hz, 1H, H-10), 7.30 (td, J = 7.5, Hz, 1H, H-11), 6.06 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H, H-5), 5.55 (dt, J = 10.0, 7.5 Hz, 1H, H-4), 5.47 (dt, J = 17.0, 1.5 Hz, 1H, H-6a), 5.36 (dt, J = 10.5, 1.0 Hz, 1H, H-6b), 3.39 (dd, J = 15.0, 10.0 Hz, 1H, H-3a), 2.99 (dd, J = 15.0, 7.5 Hz, 1H, H-3b); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 166.4 (C, C-7), 160.6 (C, C-1), 155.0 (C, C-9), 135.5 (CH, C-5), 132.4 (CH, C-12), 124.0 (CH, C-11), 122.7 (CH, C-13), 118.4 (CH_2, C-6), 117.0 (CH, C-10), 112.5 (C, C-8), 101.8 (C, C-2), 87.3 (CH, C-4), 32.7(CH_2, C-3); **IR:** ν_{max} 3050, 2990, 1710, 1638, 1497, 1409, 1247, 1018, 893, 749, 732 cm^{-1}; **HRMS:** *m/z* $C_{13}H_{10}NaO_3^+$ $[M+Na]^+$ calcd 237.0522, found 237.0526.

2,3-Dihydro-8-vinyl-4*H*-furo[3,2-c]chromen-6(6bH)-one (46)

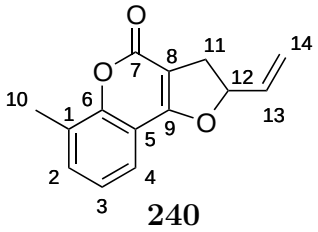


46

The Pd-AA cascade reaction was performed with 4-hydroxycoumarin (45 mg, 0.278 mmol) according to Method B. The product (**46**) was purified as a white solid (36 mg, 0.150 mmol, 54%). Spectral data matched those which have been previously reported.[19]

R$_f$ 0.5 (30% EtOAc / pet. ether) **m.p.** 159.6 – 162.0 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.67 (dd, J = 8.0, 1.5, 1H, H-4), 7.58 (td, J = 8.5, 1.5 Hz, 1H, H-3), 7.38 (d, J = 8.5 Hz, 1H, H-1), 7.28 (t, J = 7.5 Hz, 1H, H-2), 6.84 (d, J = 5.5 Hz, 1H, H-13), 5.32-5.28 (m, 2H, H-12,11), 4.44 (dd, J = 9.5, 3.5 Hz, 1H, H-14a), 3.67-3.59 (m, 2H, H-14b, 10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 167.7 (C, C-9), 160.4 (C, C-7), 155.1 (C, C-6), 150.8 (CH, C-13), 132.9 (CH, C-3), 124.0 (CH, C-2), 123.0 (CH. C-4), 117.1 (CH, C-1), 112.6 (C, C-5), 102.6 (C, C-8), 98.4 (CH, C-12), 79.2 (CH, C-11), 64.7 (CH_2, C-14), 37.7 (CH, C-10); **IR:** ν_{max} 3070, 2951, 1706, 1636, 1413, 1234, 1158, 1064, 1031, 830, 753 cm^{-1}; **HRMS:** *m/z* $C_{14}H_{11}O_4^+$ $[M+H]^+$ calcd 243.0652, found 243.0659.

2,3-Dihydro-4-methyl-8-vinyl-4*H*-furo[3,2-c]chromen-6(6bH)-one (240)

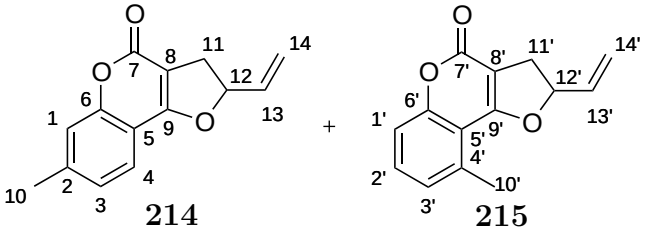


240

The Pd-AA cascade reaction was performed with **138** (126 mg, 0.176 mmol) according to Method A. The product (**240**) was purified as a pale-yellow solid (37 mg, 0.162 mmol, 51%).

R$_f$ 0.6 (30% EtOAc / pet. ether); **m.p.** 69.2 – 75.1 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.52 (d, J = 8.0 Hz, 1H, H-4), 7.41 (d, J = 7.0 Hz, 1H, H-2), 7.19 (t, J = 7.5 Hz, 1H, H-3), 6.05 (ddd, J = 17.0, 10.5, 7.0 Hz, 1H, H-13), 5.53 (dt, J = 10.0, 7.5 Hz, 1H, H-12), 5.46 (d, J = 17.0 Hz, 1H, H-14a), 5.34 (d, J = 10.5 Hz, 1H, H-14b), 3.39 (dd, J = 15.0, 10.0 Hz, 1H, H-11a), 2.98 (dd, J = 15.0, 7.5 Hz, 1H, H-11b), 2.48 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 166.8 (C, C-9), 160.8 (C, C-7), 153.4 (C, C-6), 135.6 (CH, C-13), 133.7 (CH, C-2), 126.5 (C, C-1), 123.5 (CH, C-3), 120.3 (CH, C-4), 118.2 (CH_2, C-14), 112.2 (C, C-5), 101.5 (C, C-8), 87.2 (CH, C-12), 32.7 (CH_2, C-11), 16.0 (CH_3, C-10); **IR:** (Film from CH_2Cl_2) ν_{max} 3061, 2987, 2925, 2865, 1713, 1640, 1606, 1581, 1489, 1395, 1184, 93, 746 cm^{-1}; **HRMS:** m/z $C_{14}H_{13}O_3^+$ $[M+H]^+$ calcd 229.0860, found 229.0859.

2,3-Dihydro-3-methyl-8-vinyl-4*H*-furo[3,2-c]chromen-6(6bH)-one (214) and 2,3-dihydro-2-methyl-8-vinyl-4*H*-furo[3,2-c]chromen-6(6bH)-one (215)



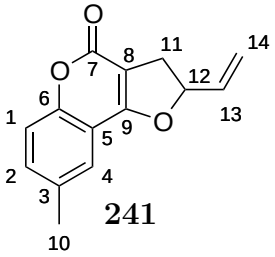
214 + **215**

The Pd-AA cascade reaction was performed with a 1.3:1 mixture of **139** and **141** (126 mg, 0.176 mmol) according to Method A. The products (**214** and **215**) were purified as a 1.3:1 mixture as a pale yellow solid (33 mg, 0.146 mmol, 46%).

R$_f$ 0.6 (30% EtOAc / pet. ether); **m.p.** 76.2 – 79.4 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H **253:** 7.55 (d, J = 8.0 Hz, 1H, H-4), 7.19 (obs. m, 1H, H-3), 7.10 (d, J = 7.5 Hz, 1H, H-1), 6.05 (obs. m, 1H, H-13), 5.52 (obs. m, 1H, H-12), 5.45 (d, J = 17.0 Hz, 1H, H-14a), 5.34 (d, J = 8.5 Hz, 1H, H-14b), 3.37 (dd, J = 15.0, 10.5 Hz, 1H, H-11a), 2.96 (dd, J = 15.0, 7.5 Hz, 1H, H-11b), 2.46 (s, 3H, H-10); **254:** 7.40 (t, J = 8.0 Hz, 1H, H-1), 7.22 (obs. m, 1H, H-4), 7.04 (d, J = 7.5 Hz, 1H, H-3), 6.05 (obs. m, 1H, H-13), 5.52 (obs. m, 1H, H-12), 5.43 (d, J = 17.0 Hz, 1H,

H-14a), 5.32 (d, J = 10.5 Hz, 1H, H-14b), 3.34 (dd, J = 15.0, 10.5 Hz, 1H, H-11a), 2.93 (dd, J = 15.0, 7.5 Hz, 1H, H-11b), 2.68 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C **253:** 166.6 (C, C-9), 160.9 (C, C-7), 155.2 (C, C-6), 143.7 (C, C-2), 135.6 (CH, C-13), 125.2 (CH, C-1), 122.3 (CH, C-4), 118.3 (CH_2, C-14), 117.1 (C, C-3), 110.0 (C, C-5) 101.0 (C, C-8), 87.2 (CH, C-12), 32.6 (CH_2, C-11), 21.9 (CH_3, C-10); **254:** 167.8 (C, C-9), 160.6 (C, C-7), 155.9 (C, C-6), 136.2 (C, C-4), 135.7 (CH, C-13), 131.6 (CH, C-2), 126.3 (CH, C-3), 117.6 (CH_2, C-14), 114.9 (CH, C-1), 111.9 (C, C-5), 101.9 (C, C-8), 86.7 (CH, C-12), 32.1 (CH_2, C-11), 21.3 (CH_3, C-10); **IR:** (Film from CH_2Cl_2) ν_{max} 3060, 2929, 2864, 1713, 1628, 1603, 1386, 1205, 1044, 1022, 903 cm^{-1}; **HRMS:** m/z $C_{14}H_{13}O_3$ $[M+H]^+$ calcd 229.0859, found 229.0864.

2,3-Dihydro-3-methyl-8-vinyl-4*H*-furo[3,2-c]chromen-6(6bH)-one (241)



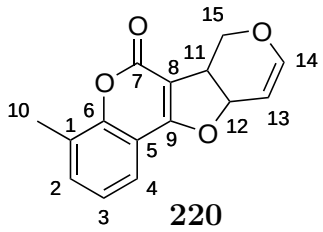
241

The Pd-AA cascade reaction was performed with **140** (126 mg, 0.176 mmol) according to Method A. The product (**241**) was purified to give a beige solid (34 mg, 0.148 mmol, 46%).

R$_f$ 0.6 (30% EtOAc / pet. ether); **m.p.** 95.9 – 98.2 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.47 (s, 1H, H-4), 7.37 (d, J = 8.5 Hz, 1H, H-1), 7.28 (d, J = 9.5 Hz, 1H, H-2), 6.05 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H, H-13), 5.53 (dt, J = 10.0, 7.5 Hz, 1H, H-12), 5.46 (d, J = 17.0 Hz, 1H, H-14a), 5.35 (d, J = 10.5 Hz, 1H, H-14b), 3.38 (dd, J = 15.0, 10.0 Hz, 1H, H-11a), 2.97 (dd, J = 15.0, 7.5 Hz, 1H, H-11b), 2.42 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 166.4 (C, C-9), 160.9 (C, C-7), 153.2 (C, C-6), 135.5 (CH, C-13), 133.7 (C, C-3), 133.5 (CH, C-4), 122.4 (CH, C-1), 118.3 (CH_2, C-14), 116.7 (CH, C-2), 112.2 (C, C-5), 101.7 (C, C-8), 87.2 (CH, C-12), 32.7 (CH_2, C-11), 20.8 (CH_3, C-10); **IR:** (Film from CH_2Cl_2) ν_{max} 3059, 2989, 2926, 2866, 1712, 1643, 1610, 1576, 1499, 1438, 1427, 1397, 1205, 1100, 926 cm^{-1}; **HRMS:** m/z $C_{14}H_{13}O_3$ $[M+H]^+$ calcd 229.0859, found 229.0864.

cis-(±)-4-Methyl-7,10a-dihydropyrano[3',4':4,5]furo[3,2-c]chromen-6(6bH)-one (220)

The Pd-AA cascade reaction was performed with **138** (31 mg, 0.176 mmol) according to Method C. The product (**220**) was purified as a a cream coloured semi-crystalline solid (22 mg, 0.086 mmol, 49%).

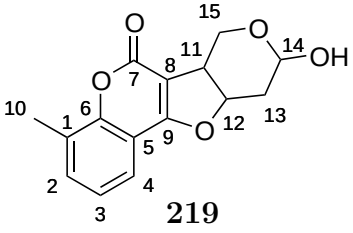


220

R*f* 0.5 (20% EtOAc / pet. ether); **m.p.** 152.1 – 153.5 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.52 (d, J = 7.5 Hz, 1H, H-4), 7.43 (d, J = 7.5 Hz, 1H, H-2), 7.19 (t, J = 7.5 Hz, 1H, H-3), 6.84 (d, J = 6.0 Hz, 1H, H-14), 5.33-5.27 (complex m, 2H, H-12, 13), 4.45 (d, J = 6.0 Hz, 1H, H-15a), 3.66-3.59 (m, 2H, H-11, 15b), 2.47 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 168.1 (C, C-9), 160.5 (C, C-7), 153.5 (C, C-6), 150.8 (CH, C-14), 134.1 (CH, C-2), 126.6 (C, C-1), 123.6 (CH, C-3), 120.6 (CH, C-4), 112.3 (C, C-5), 102.4 (C, C-8), 98.5 (CH, C-13), 79.1(CH, C-12), 64.8 (CH_2, C-15), 37.7 (CH, C-11), 16.0 (CH_3, C-10); **IR:** (Film from $CDCl_3$) ν_{max} 3064, 2923, 1716, 1642, 1397, 1238, 831, 755 cm^{-1}; **HRMS:** *m/z* $C_{15}H_{13}O_4^+$ $[M+H]^+$ calcd 257.0808, found 257.0813.

cis-(±)-4-Methyl-7,10a-tetrahydro-2-hydroxy-2*H*-pyrano[4',5':4,5]furo[3,2-c]chromen-6(6bH)-one (219)

The Pd-AA cascade reaction was performed with **138** (31 mg, 0.176 mmol) according to Method B. Column chromatography (10 - 20% EtOAc / pet. ether) afforded the product (**220**) as a a cream semi-crystalline solid (18 mg, 0.070 mmol, 39%). Elution of the column with EtOAc afforded an orange oil (22 mg). Column chromatography (50% EtOAc / pet. ether) afforded **219** as a red solid (9 mg, 0.033 mmol, 19%).

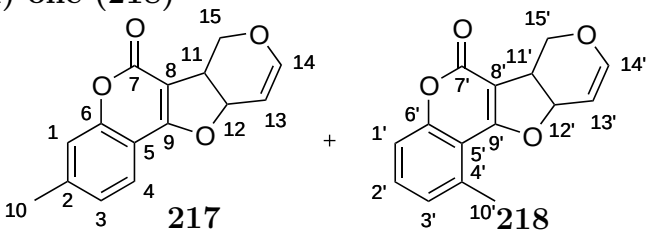


219

R*f* 0.26 (50% EtOAc / pet. ether); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.49 (d, J = 7.0 Hz, 1H, H-4), 7.42 (d, J = 7.5 Hz, 1H, H-2), 7.19 (t, J = 8.0 Hz, 1H, H-3), 5.39 (dt, J = 9.5, 3.5 Hz, 1H, H-12) 5.32 (m, 1H, H-14), 4.09 (m, 1H, H-15a), 3.92 (dd, J = 12.5, 2.5 Hz, 1H, H-15b), 3.58 (ddd, J = 9.5, 3.5, 2.0 Hz, 1H, H-11), 2.86 (d, J = 3.5 Hz, 1H, OH), 2.69 (ddd, J = 16.0, 5.5, 3.5 Hz, 1H, H-13a), 2.48 (s, 3H, H-10), 2.05 (ddd, J = 16.0, 7.5, 3.5 Hz, 1H, H-13b); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 167.9 (C, C-9), 160.6 (C, C-7), 153.6 (C, C-6), 133.8 (CH, C-2), 126.6 (C, C-1), 123.5 (CH, C-3), 120.4 (CH, C-4), 112.1 (C, C-5), 103.4 (C, C-8), 89.9 (CH, C-14), 82.9 (CH, C-12), 58.2 (CH_2, C-15), 39.2 (CH, C-11), 31.0 (CH_2, C-13), 16.0 (CH_3, C-10); **IR:** (Film from $CDCl_3$) ν_{max} 3400, 2958, 2926, 1713, 1643, 1399, 1203, 1036,

754 cm^{-1}; **HRMS:** *m/z* $C_{15}H_{15}O_5^+$ $[M+H]^+$ calcd 275.0914, found 275.0916.

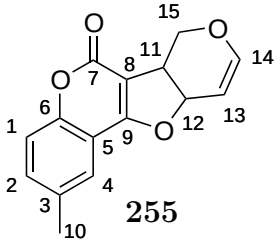
***cis*-(±)-3-Methyl-7,10a-dihydropyrano[3',4':4,5]furo[3,2-c]chromen-6(6bH)-one (217) and *cis*-(±)-1-methyl-7,10a-dihydropyrano[3',4':4,5]furo[3,2-c] chromen-6(6bH)-one (218)**



The Pd-AA cascade reaction was performed with a 1.3:1 mixture of **139** and **141** (49 mg, 0.278 mmol) according to Method C. Column chromatography (10 - 20% EtOAc / pet. ether) afforded the products (**217** and **218**) in a 1.3:1 mixture as a light-brown semi-crystalline solid (20 mg, 0.078 mmol, 30%).

R_f 0.4 (20% EtOAc / pet. ether); **m.p.** 158.2 – 169.5 °C; **^{1}H-NMR:** (300 MHz; $CDCl_3$) δ_H **217:** 7.54 (d, J = 8.1 Hz, 1H, H-4), 7.18 (s, 1H, H-3), 7.11 (d, J = 8.1 Hz, 1H, H-1), 6.83 (d, J = 5.7 Hz, 1H, H-14), 5.29 (obs. m, 2H, H-12,13), 4.43 (obs. m, 1H, H-15a), 3.59 (obs. m, 2H, H-11,15b), 2.46 (s, 3H, H-10); **218:** 7.41 (t, J = 7.8 Hz, 1H, H-2), 7.21 (m, 1H, H-1), 7.05 (d, J = 7.5 Hz, 1H, H-3), 6.83 (d, J = 5.7 Hz, 1H, H-14), 5.29 (obs. m, 2H, H-12,13), 4.43 (obs. m, 1H, H-15a), 3.59 (obs. m, 2H, H-11,15b), 2.67 (s, 3H, H-10); **IR:** (Film from CH_2Cl_2) ν_{max} 3065, 2927, 1700, 1635, 1617, 1603, 1244, 1028, 841, 741 cm^{-1}; **HRMS:** *m/z* $C_{15}H_{13}O_4^+$ $[M+H]^+$ calcd 257.0808, found 257.0812. ^{13}C NMR data was not obtained on this mixture of compounds.

***cis*-(±)-2-Methyl-7,10a-dihydropyrano[3',4':4,5]furo[3,2-c]chromen-6(6bH)-one (255)**



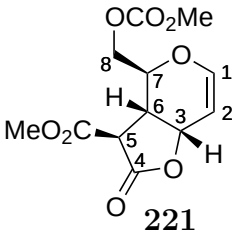
The Pd-AA cascade reaction was performed with **140** (31 mg, 0.176 mmol) according to Method C. The product (**255**) was purified as a light brown semi-crystalline solid (21 mg, 0.082 mmol, 47%)

R_f 0.4 (20% EtOAc / pet. ether); **m.p.** 158.0 – 161.6 °C; **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.46 (s, 1H, H-4), 7.38 (d, J = 8.5 Hz, 1H, H-2), 7.27 (obs. d, 1H, H-1), 6.83 (d, J = 5.5 Hz, 1H, H-14), 5.31-5.27 (complex m, 2H, H-13,12), 4.44 (dd,

J = 10.0, 4.0 Hz, 1H, H-15a), 3.66-3.58 (complex m, 2H, H-15b, 11), 2.41 (s, 3H, H-10); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 167.6 (C, C-9), 160.5 (C, C-7), 153.3 (C, C-6), 150.8 (CH, C-14), 133.89 (CH, C-2), 133.87 (C, C-3), 122.6 (CH, C-4), 116.8 (CH, C-1), 112.3 (C, C-5), 102.5 (C, C-8), 98.5 (CH, C-13), 79.1 (CH, C-12), 64.8 (CH_2, C-15), 37.8 (CH, C-11), 20.8 (CH_3, C-10); **IR:** (Film from $CDCl_3$) ν_{max} 3069, 2926, 1717, 1644, 1238, 1069, 838, 766 cm^{-1}; **HRMS:** m/z $C_{15}H_{13}O_4^+$ $[M+H]^+$ calcd 257.0808, found 257.0813.

4.2.7 Experimental Details for Section 2.4.3

Methyl (methyl (3*R*, 3a*S*, 4*R*, 7a*R*)-2*H*-2-oxo-3,3a,4,7a-tetrahydrofuro[3,2-c]pyran-3-carbox-4-yl)carbonate (221)

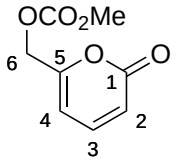


221

Meldrum's acid (96 mg, 0.664 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) were combined in a reaction vessel which was then evacuated and back-filled with nitrogen. Toluene (1.5 mL, degassed by sparging with nitrogen for approx. 20 minutes) and MeOH (27 μL, degassed by sparging with nitrogen for approx. 20 minutes) were added, followed by addition of a solution of **252** (50 mg, 0.133 mmol) in toluene (0.5 mL). The reaction was left at room temperature overnight then concentrated. Chromatography of the resulting brown oil (10% - 25% EtOAc / pet. ether) afforded **221** (23 mg, 0.080 mmol, 61%) as a colourless oil.

R$_f$ 0.3 (30% EtOAc / pet. ether); $[\alpha]_D^{25.3}$ +71.41 (c 0.36, CH_2Cl_2); **^{1}H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.64 (dd, J = 6.3, 0.9 Hz, 1H, H-1), 5.13 (dd, J = 6.0, 3.9 Hz, 1H, H-2), 5.05 (ddd, J = 6.3, 4.2, 0.9 Hz, 1H, H-3), 4.38 (d, J = 4.2 Hz, 2H, H-8), 3.92 (dt, J = 8.7, 4.2 Hz, 1H, H-7), 3.84 (s, 3H, CH_3OCO), 3.81 (s, 3H, CH_3OCO), 3.57 (d, J = 4.5 Hz, 1H, H-5), 3.08 (ddd, J = 9.0, 6.3, 4.5 Hz, 1H, H-6); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 169.7 (C, C-4), 166.7 (C, $CH_3O\underline{C}O$), 155.4 (C, $CH_3O\underline{C}O$), 147.7 (CH, C-1), 98.6 (CH, C-2), 71.2 (CH, C-7), 70.6 (CH, C-3), 66.2 (CH_2, C-8), 55.3 (CH_3, $\underline{C}H_3OCO$), 53.5 (CH_3, $\underline{C}H_3OCO$), 49.4 (CH, C-5), 38.6 (CH, C-6); **IR:** (Film from CH_2Cl_2) ν_{max} 3007, 2959, 2925, 1776, 1736, 1649, 1441, 1266, 1242, 1166, 935 cm^{-1}; **HRMS:** m/z $C_{12}H_{15}O_8^+$ $[M+H]^+$ calcd 287.0761, found 287.0765.

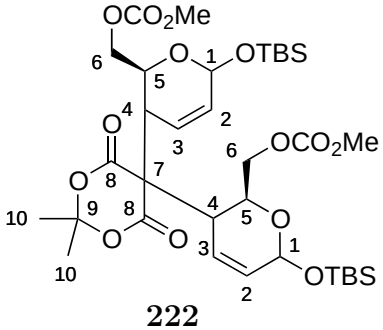
Methyl-2-hydroxymethyl-2*H*-pyran-6-one carbonate (225)



Meldrum's acid (22 mg, 0.154 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.001 mmol) were combined in a reaction vessel which was then evacuated and back filled with nitrogen. Toluene (2 mL, degassed by sparging with nitrogen for approx. 20 minutes) and MeOH (31 μL, degassed by sparging with nitrogen for approx. 20 minutes) were added, followed by addition of a solution of **178** (40 mg, 0.154 mmol). The reaction was left at room temperature for 2.5 hours then concentrated. Chromatography of the resulting orange oil (25 - 40% EtOAc / pet. ether) afforded **225** (27 mg, 0.148 mmol, 96%) as a white solid.

R*f* 0.2 (40% EtOAc / pet. ether); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 7.31 (dd, J = 9.0, 7.0 Hz, 1H, H-2), 6.27 (complex m, 2H, H-3, 4), 4.90 (s, 1H, H-6), 3.84 (s, 3H, CH_3OCO); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 161.1 (C, C-1), 158.2 (C, C-5), 155.0 (C, $CH_3O\underline{C}O$), 142.8 (CH, C-2), 115.9 (CH, C-3) 104.0 (CH, C-4) 64.6 (CH_2, C-6), 55.4 (CH_3, $\underline{C}H_3OCO$); **IR:** (Film from CH_2Cl_2) ν_{max} 3094, 3068, 2969, 1737, 1646, 1563, 1451, 1278 cm^{-1}; **HRMS:** *m/z* $C_8H_8NaO_5^+$ $[M+Na]^+$ calcd 207.0264, found 207.0264.

5,5-Bis-(6-*O*-(methoxycarbonyl)-1-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-D-erythro-hex-2-enopyranos-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (222)



222

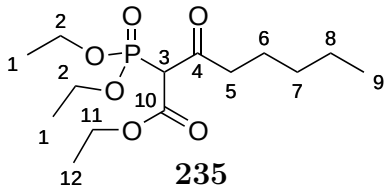
Meldrum's acid (23 mg, 0.159 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) were combined in a reaction vessel which was then evacuated and back filled with nitrogen. Toluene (1.5 mL, degassed by sparging with nitrogen for approx. 20 minutes) and MeOH (32 μL, degassed by sparging with nitrogen for approx. 20 minutes) were added, followed by addition of a solution of **252** (60 mg, 0.159 mmol) in toluene (1.5 mL). The reaction was left at room temperature for 2 hours then concentrated. Chromatography of the resulting yellow oil (5% - 20% EtOAc / pet. ether) afforded **222** (4 mg, 0.005 mmol, 7%) as a colourless oil.

R*f* 0.5 (20% EtOAc / pet. ether); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 5.99 (m, 4H,

H-2, 3), 5.13 (s, 2H, H-1), 4.39 (dd, J = 11.0, 5.5 Hz, 2H, H-6a), 4.16 (dd, J = 11.0, 8.0 Hz, 2H, H-6b), 4.05 (m, 2H, H-5), 3.77 (s, 6H, CH_3OCO), 2.93 (d, J = 4.5 Hz, 2H, H-4), 1.78 (s, 6H, H-10), 0.87 (s, 18H, $OSiC(CH_3)_3$), 0.10 (s, 6H, $OSiCH_3$), 0.09(s, 6H, $OSiCH_3$); **^{13}C-NMR:** (125 MHz; $CDCl_3$) δ_C 165.3 (C, C-7), 155.4 (C, $CH_3O\underline{C}O$), 132.9 (CH, C-2), 120.8 (CH, C-3), 106.3 (C, C-9), 87.8 (CH, C-1) 69.1 (CH, C-5), 67.8 (CH_2, C-6), 57.8 (CH_3, $\underline{C}H_3OCO$), 54.9 (C, C-8), 39.9 (CH, C-4), 29.7 (CH_3, C-10), 25.6 (CH_3, $OSiC(\underline{C}H_3)_3$), 17.9 (C, $OSi(\underline{C}H_3)_3$), -4.3 (CH_3, $OSi\underline{C}H_3$), -5.3 (CH_3, $OSi\underline{C}H_3$); **IR:** (Film from CH_2Cl_2) ν_{max} 2956, 2931, 2901, 2859, 1751, 1270, 1030 cm^{-1}; **HRMS:** m/z $C_{34}H_{60}NO_{14}Si_2^+$ $[M+NH_4]^+$ calcd 762.3547, found 762.3546.

4.2.8 Experimental Details for Section 2.5

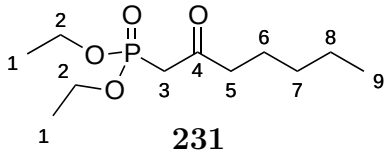
Ethyl 2-Diethoxyphosphoryl-3-oxo-octanoate (235)



235

Using a literature method,[86] a solution of hexanoyl chloride (104 μL, 0.743 mmol) in toluene (0.4 mL) was added dropwise to a cold solution (5 °C) of triethyl phosphonoacetate (149 μL, 0.743 mmol), $MgCl_2$ (71 mg, 0.743 mmol), and NEt_3 (0.3 mL, 2.15 mmol) in toluene (2.2 mL). The reaction was stirred for 6 hours under nitrogen at room temperature and then quenched by addition of an ice-cold solution of 10% H_2SO_4 (2.2 mL) and stirred for 5 minutes. The two layers were separated and the aqueous layer was extracted with EtOAc (4 x 25 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. Chromatography of the resulting yellow oil (20% - 40% EtOAc / pet. ether) afforded the desired product **235** (371 mg, 0.659 mmol, 89%) observed as a complex mixture of tautomers by ^{1}H NMR, which was used immediately.

Diethyl (hexanoylmethyl)phosphonate (231)



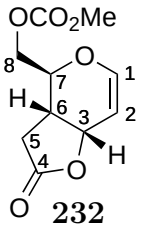
231

Using a literature method,[86] a solution of **235** (88 mg, 0.273 mmol) and p-toluenesulfonic acid monohydrate (2.6 mg, 0.013 mmol) in H_2O was heated under reflux overnight. The reaction mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the desired product **231**

(55 mg, 0.220 mmol, 81%) as a colourless oil. Spectral data matched those which have been previously reported.[86]

R_f 0.2 (40% EtOAc / pet. ether); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 4.15 (m, 4H, H-2), 3.08 (d, J = 23.0 Hz, 2H, H-3), 2.62 (t, J = 7.5 Hz, 2H, H-5), 1.59 (q, J = 7.5 Hz, 2H, H-6), 1.34 (t, J = 7.0 Hz, 6H, H-1), 1.31-1.26 (m, 4H, H-7,8), 0.89 (t, J = 7.0 Hz, 3H, H-9); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 202.3 (C, J = 6.3 Hz, C-4), 62.5 (CH_2, J = 6.6 Hz, C-2), 44.1 (CH_2, C-5), 42.4 (CH_2, J = 126.5 Hz, C-3), 31.1 (CH_2, C-7), 23.1 (CH_2, C-6), 22.4 (CH_2, C-8), 16.3 (CH_3, J = 6.3 Hz, C-1), 13.9 (CH_3, C-9); **IR:** (Film from CH_2Cl_2) ν_{max} 2958, 2931, 2872, 1715, 1252, 1022, 965 cm^{-1}.

Methyl (3*R*, 3a*S*, 4*R*, 7a*R*)-2*H*-2-oxo-3,3a,4,7a-tetrahydrofuro[3,2-c]pyran-4-yl carbonate (232)



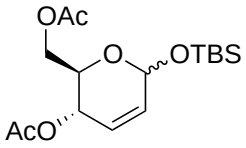
232

Meldrum's acid (96 mg, 0.664 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) were combined in a reaction vessel which was then evacuated and back filled with nitrogen. MeCN (1.5 mL, degassed by sparging with nitrogen for approx. 20 minutes) was added, followed by addition of a solution of **252** (50 mg, 0.133 mmoL) in MeCN (0.5 mL). Distilled H_2O (48 μL, degassed by sparging with nitrogen for approx. 20 minutes) was added vi syringe and then the reaction was left at room temperature overnight then concentrated. Chromatography of the resulting brown oil (10% - 30% EtOAc / pet. ether) afforded **232** (3 mg, 0.013 mmol, 10%) as a colourless oil.

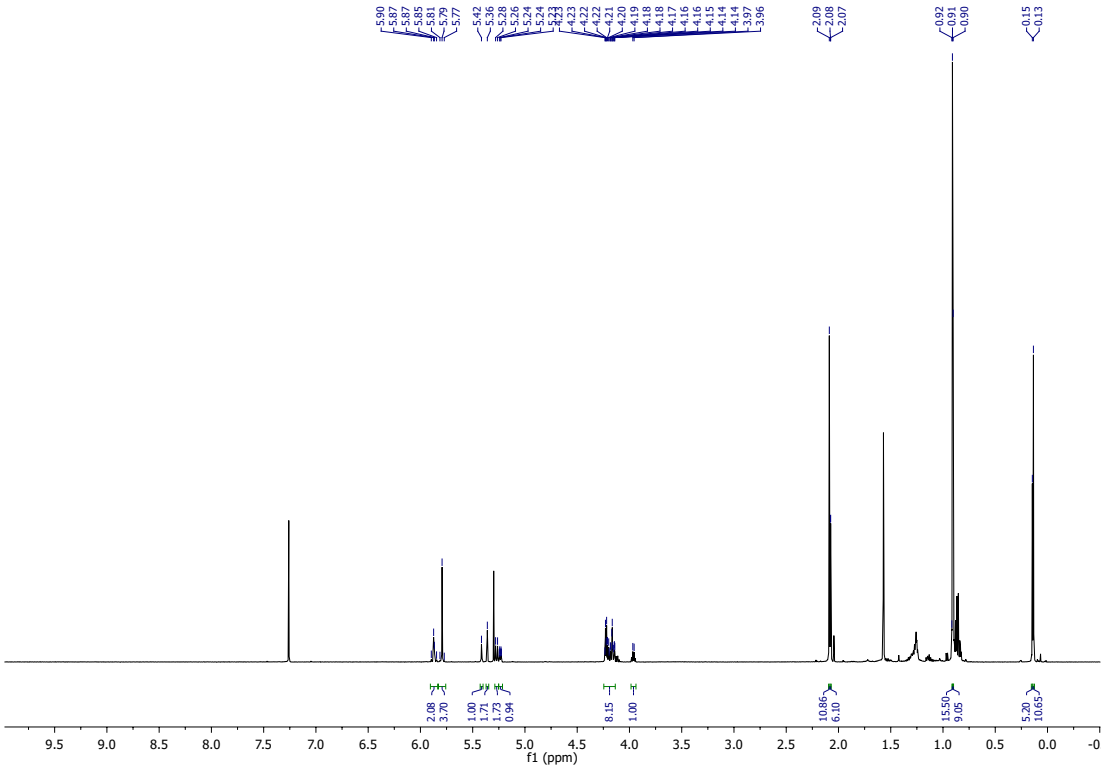
R_f 0.2 (30% EtOAc / pet. ether); $[\alpha]_D^{25.3}$ +8.40 (c 0.60, CH_2Cl_2); ^{1}**H-NMR:** (500 MHz; $CDCl_3$) δ_H 6.70 (d, J = 6.5 Hz, 1H, H-1), 5.18 (t, J = 4.5 Hz, 1H, H-2), 4.85 (t, J = 5.0 Hz, 1H, H-3), 4.34 (dd, J = 12.0, 2.5 Hz, 1H, H-8a), 4.32 (dd, J = 12.0, 5.0 Hz, 1H, H-8b), 3.82 (s, 3H, CH_3OCO), 3.82-3.76 (m, 1H, H-7), 2.87 (dd, J = 18.0, 8.5 Hz, 1H, H-5a), 2.74-2.70 (m, 1H, H-6), 2.48 (dd, J = 18.0, 2.0 Hz, 1H, H-5b); ^{13}**C-NMR:** (125 MHz; $CDCl_3$) δ_C 174.7 (C, C-4), 162.8 (C, $CH_3O\underline{C}O$), 148.5 (CH, C-1), 98.7 (CH, C-2), 72.1 (CH, C-7), 71.2 (CH, C-3), 66.4 (CH_2, C-8), 55.2 (CH_3, $\underline{C}H_3OCO$), 34.3 (CH, C-6), 31.8 (CH_2, C-5); **IR:** (Film from CH_2Cl_2) ν_{max} 3006, 2960, 2928, 1746, 1647, 1443, 1272, 1241, 1168, 935 cm^{-1}; **HRMS:** m/z $C_{10}H_{13}O_6^+$ $[M+H]^+$ calcd 229.0707, found 229.0710.

Appendix

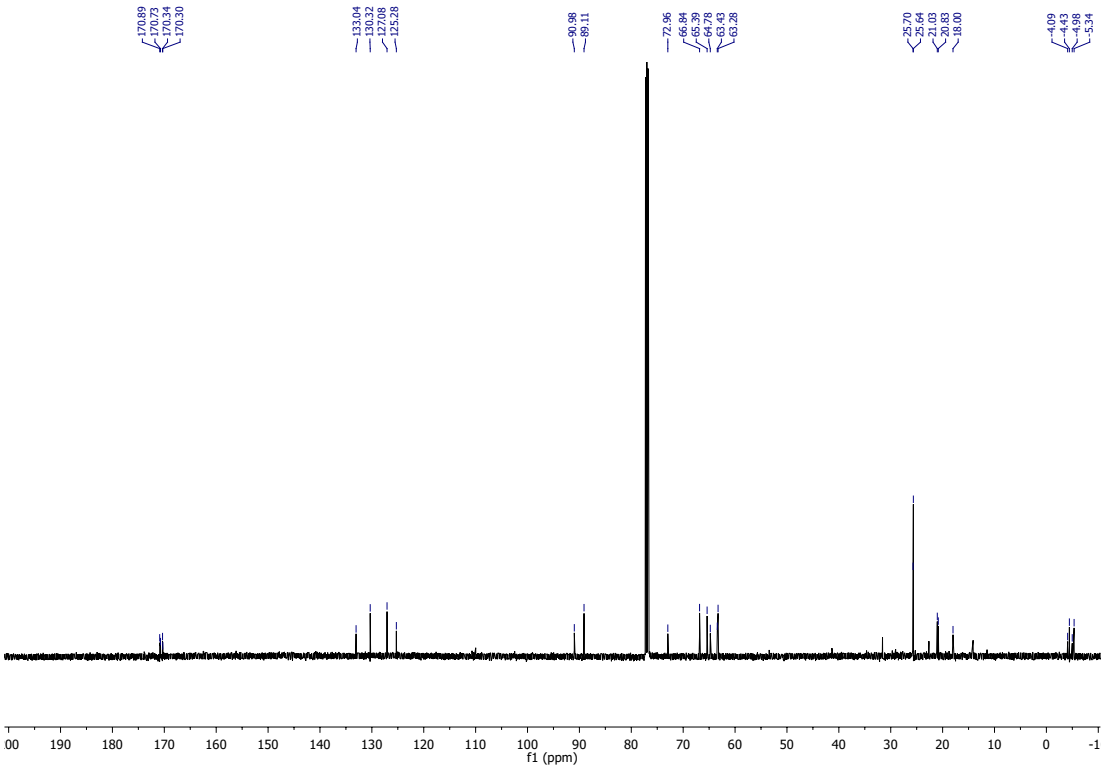
Spectra of New and Selected Compounds



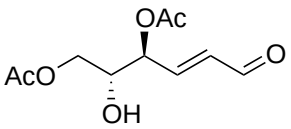
153



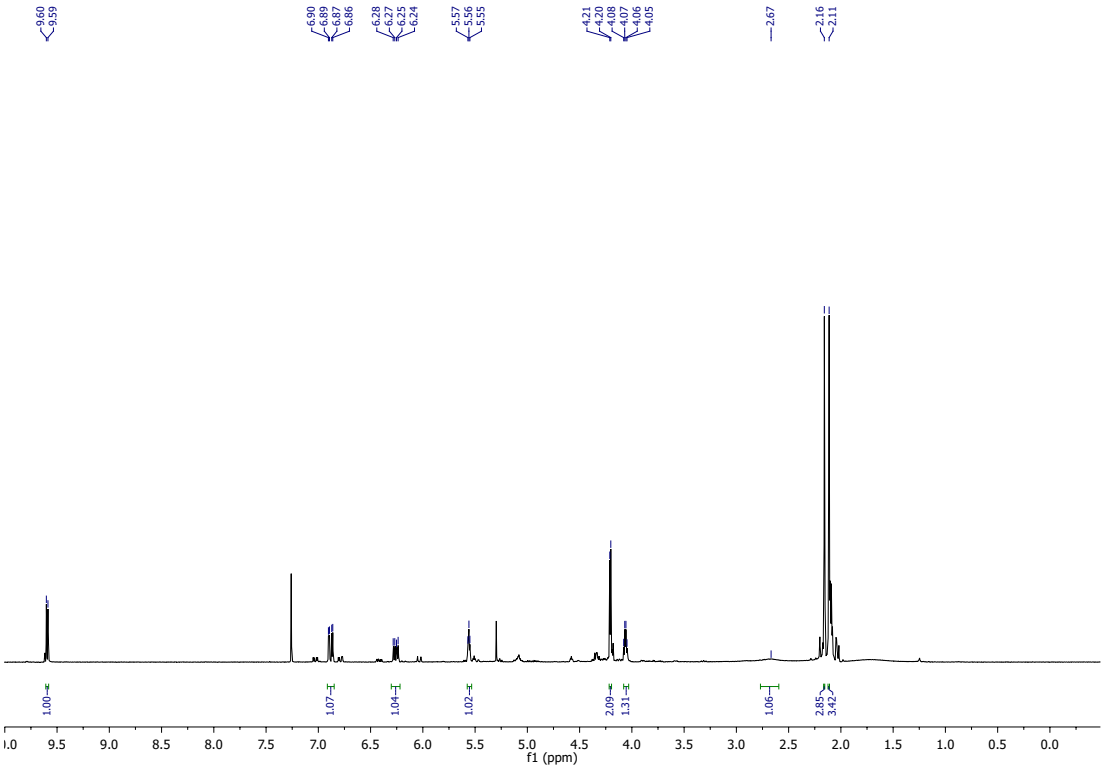
^{1}H-NMR spectrum of **153** (500 MHz, $CDCl_3$)



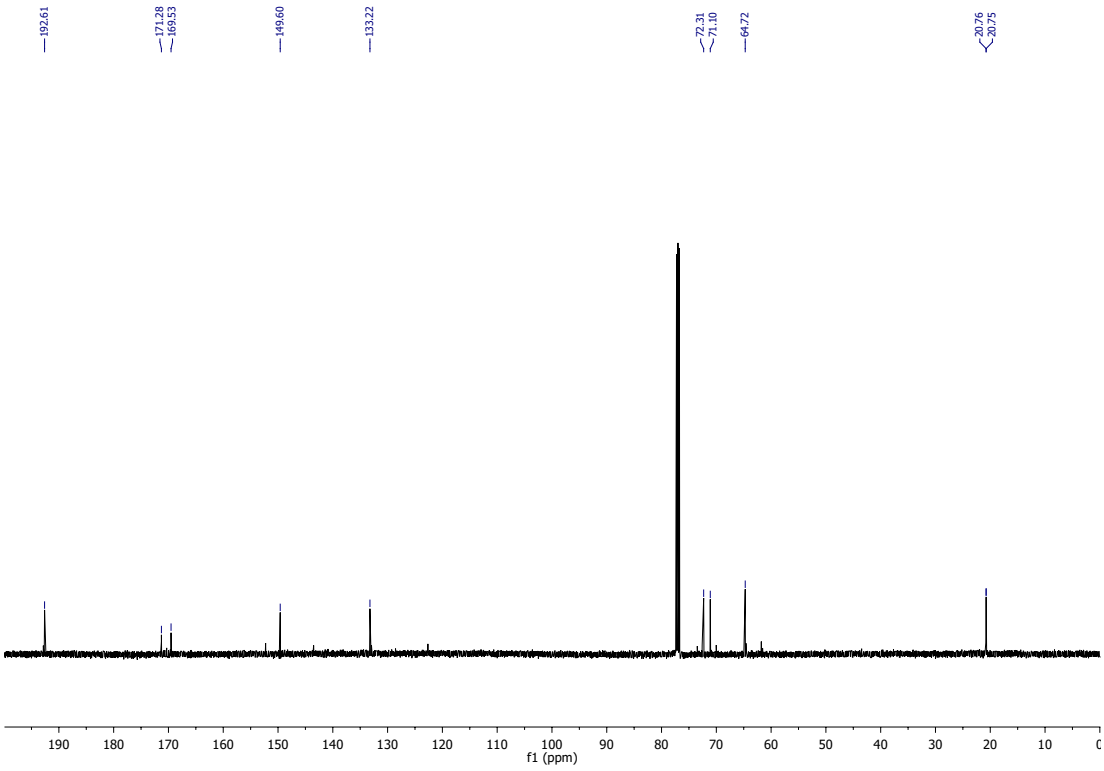
^{13}C-NMR spectrum of **153** (500 MHz, $CDCl_3$)



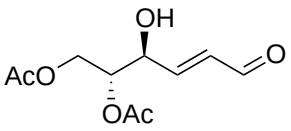
166



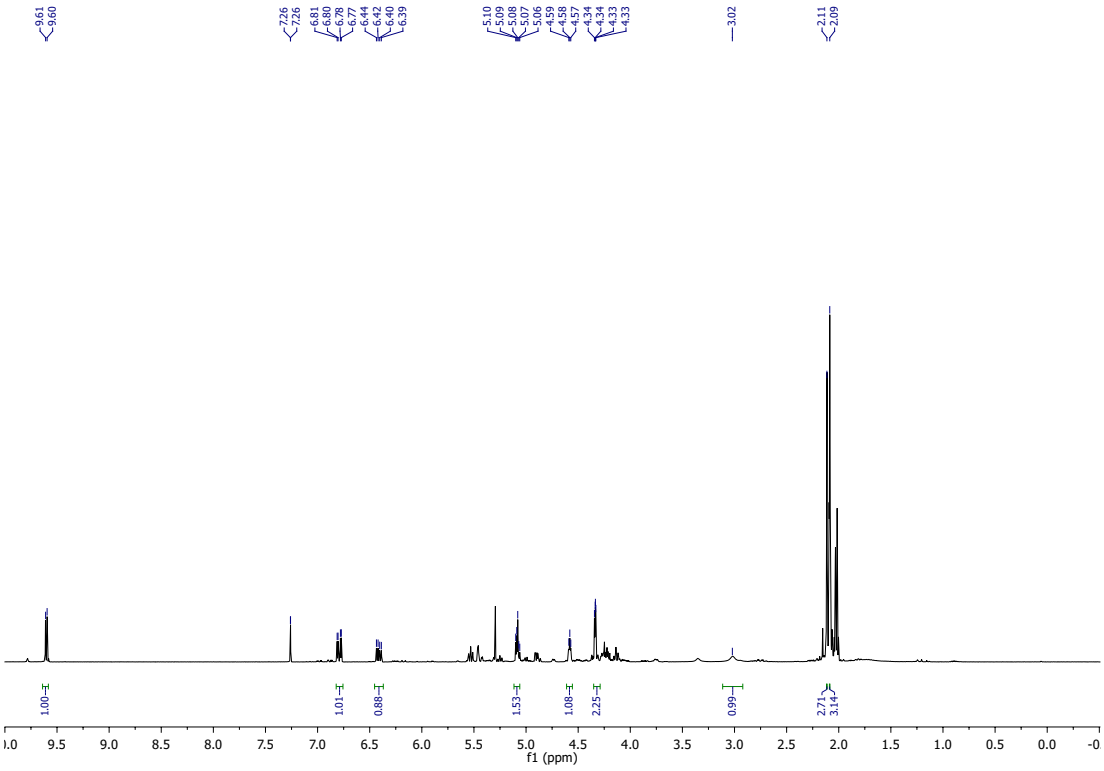
^{1}H-NMR spectrum of **166** (500 MHz, $CDCl_3$)



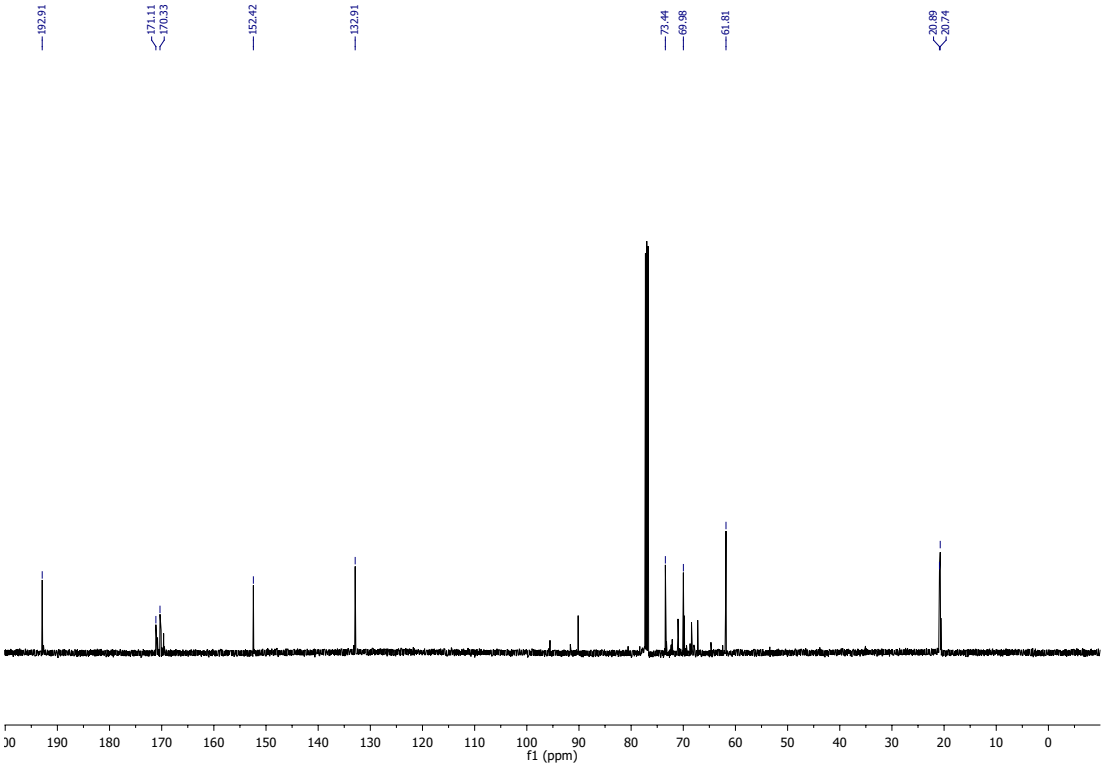
^{13}C-NMR spectrum of **166** (500 MHz, $CDCl_3$)



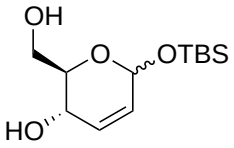
176



^{1}H-NMR spectrum of **176** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **176** (500 MHz, $CDCl_3$)



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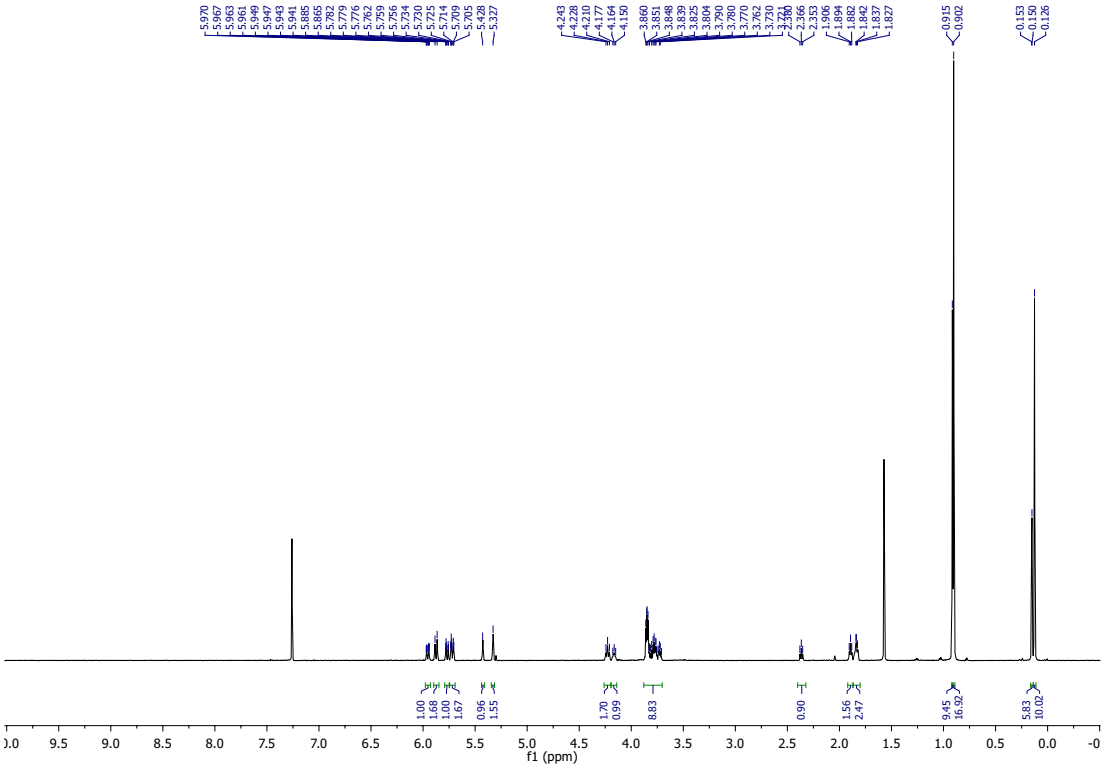
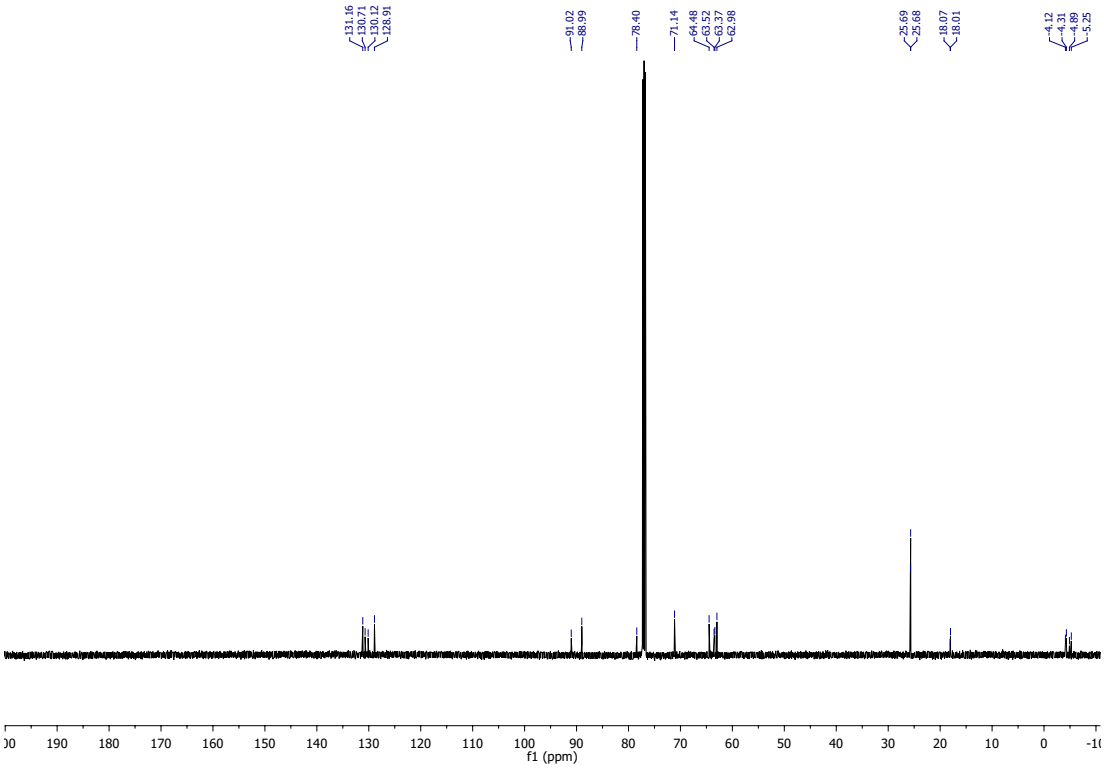
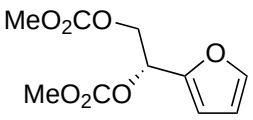


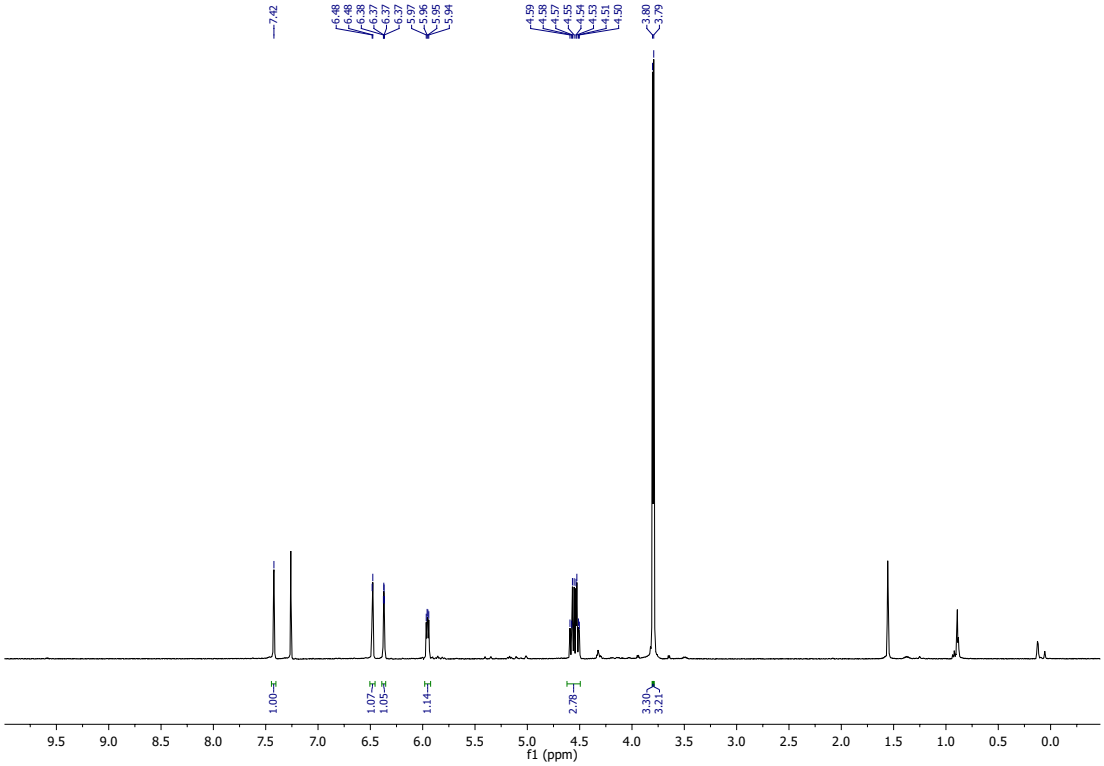
^{1}H-NMR spectrum of **179** (500 MHz, $CDCl_3$)



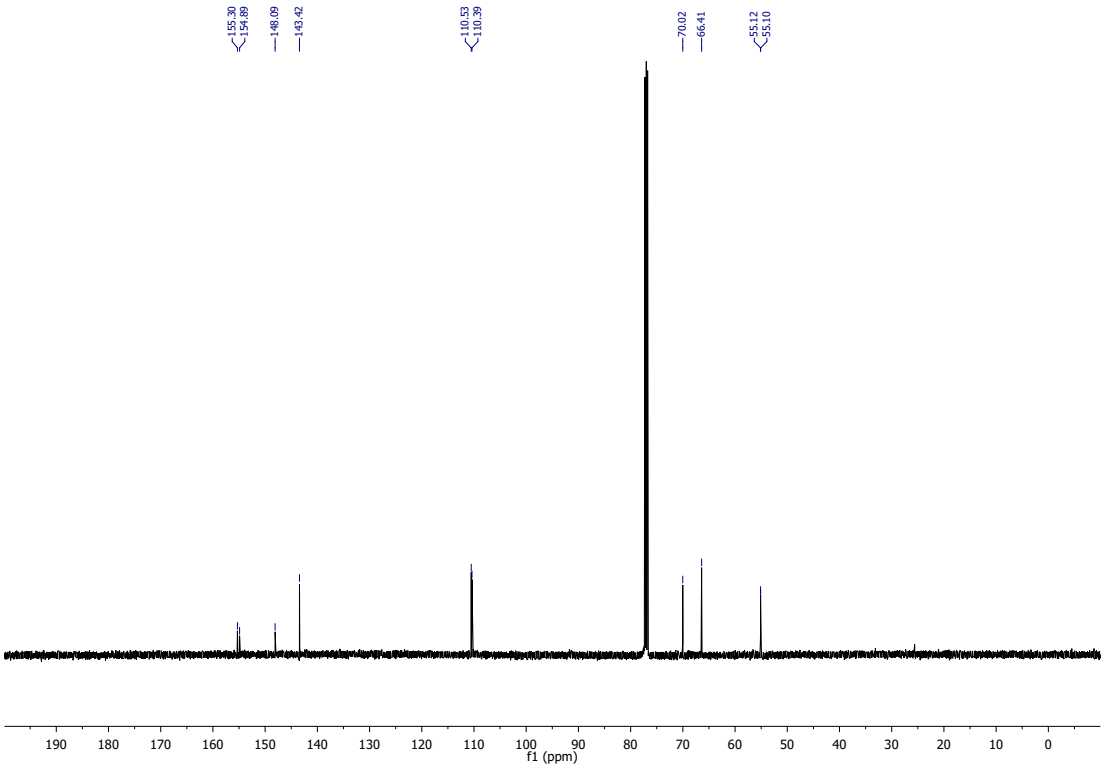
^{13}C-NMR spectrum of **179** (500 MHz, $CDCl_3$)



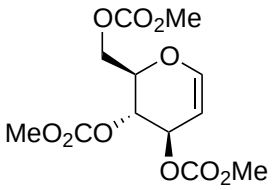
181



^{1}H-NMR spectrum of **181** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **256** (500 MHz, $CDCl_3$)



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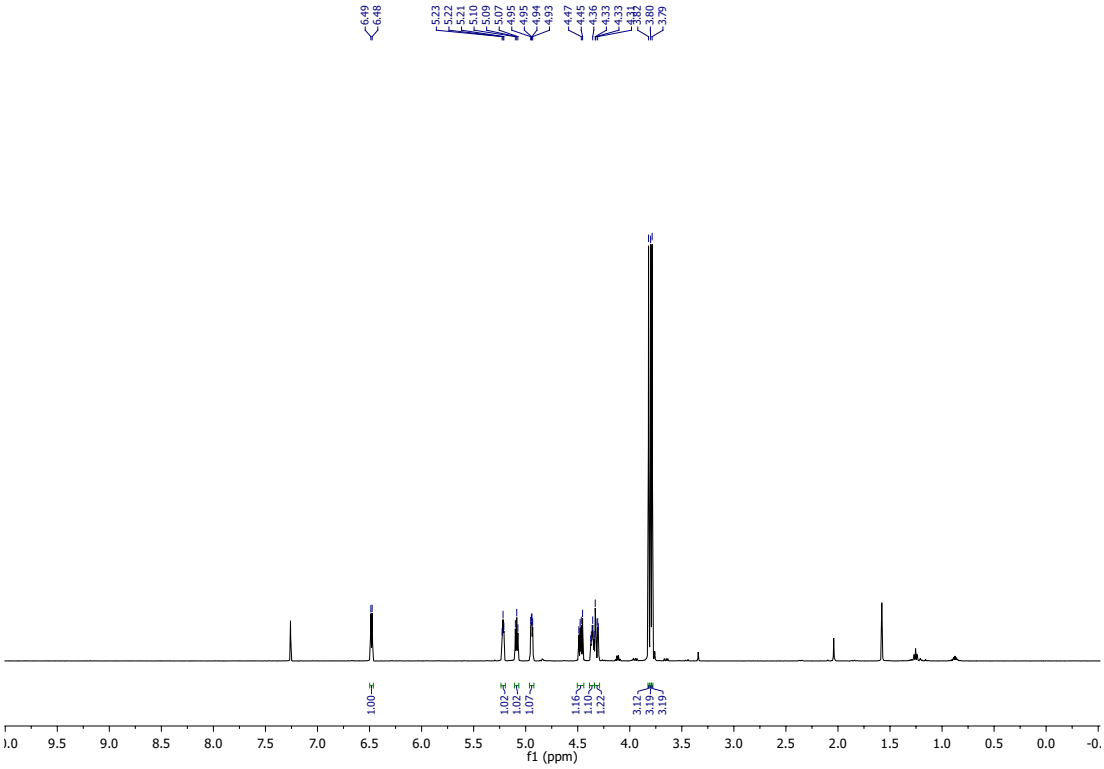
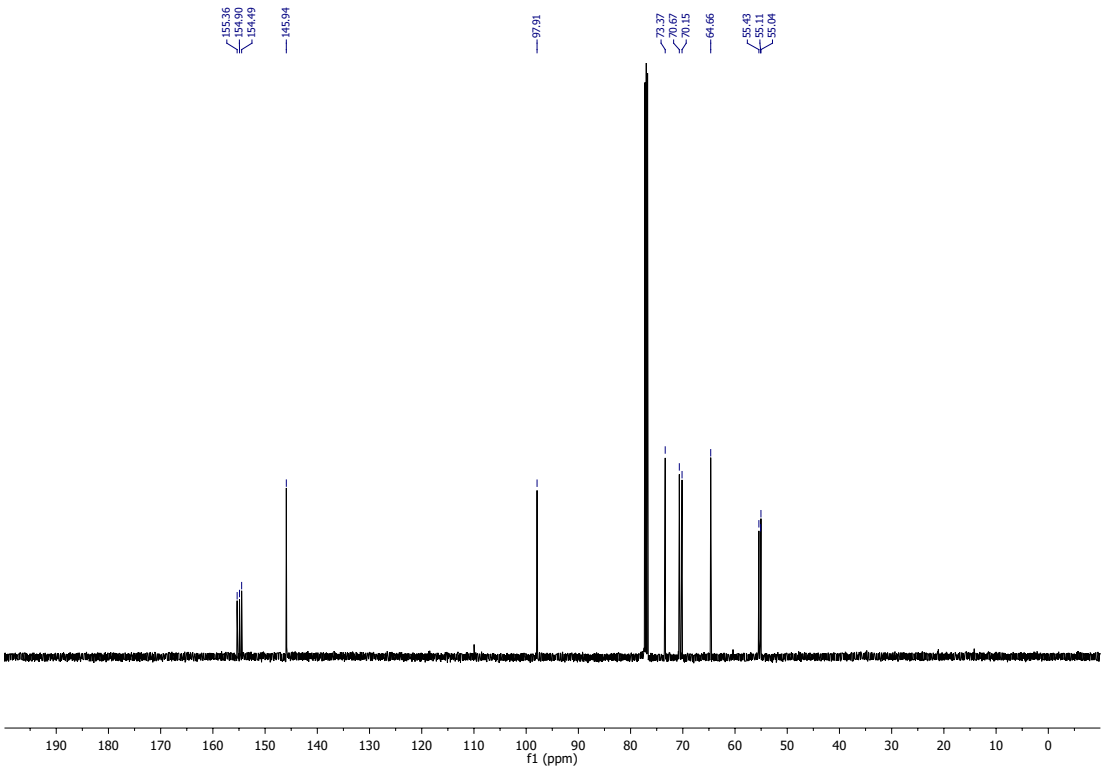
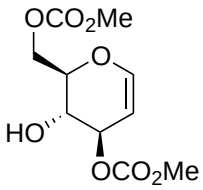


^{1}H-NMR spectrum of **198** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **198** (500 MHz, $CDCl_3$)



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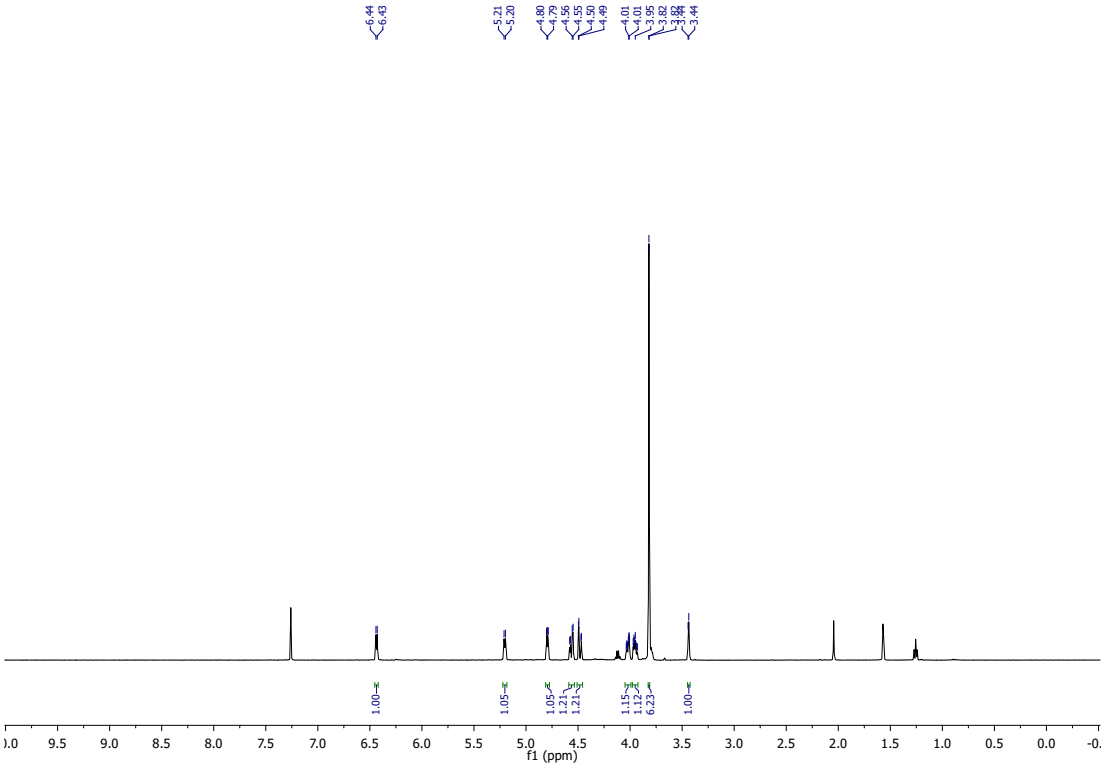
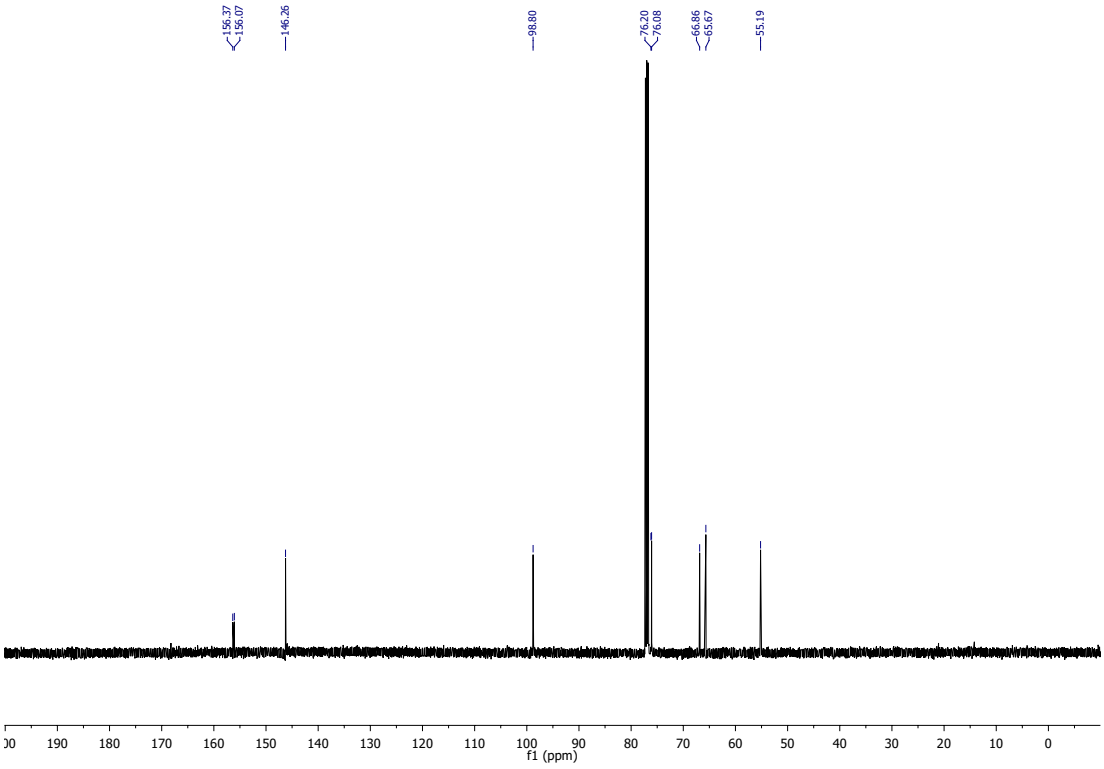
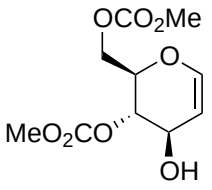


^{1}H-NMR spectrum of **250** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **250** (500 MHz, $CDCl_3$)



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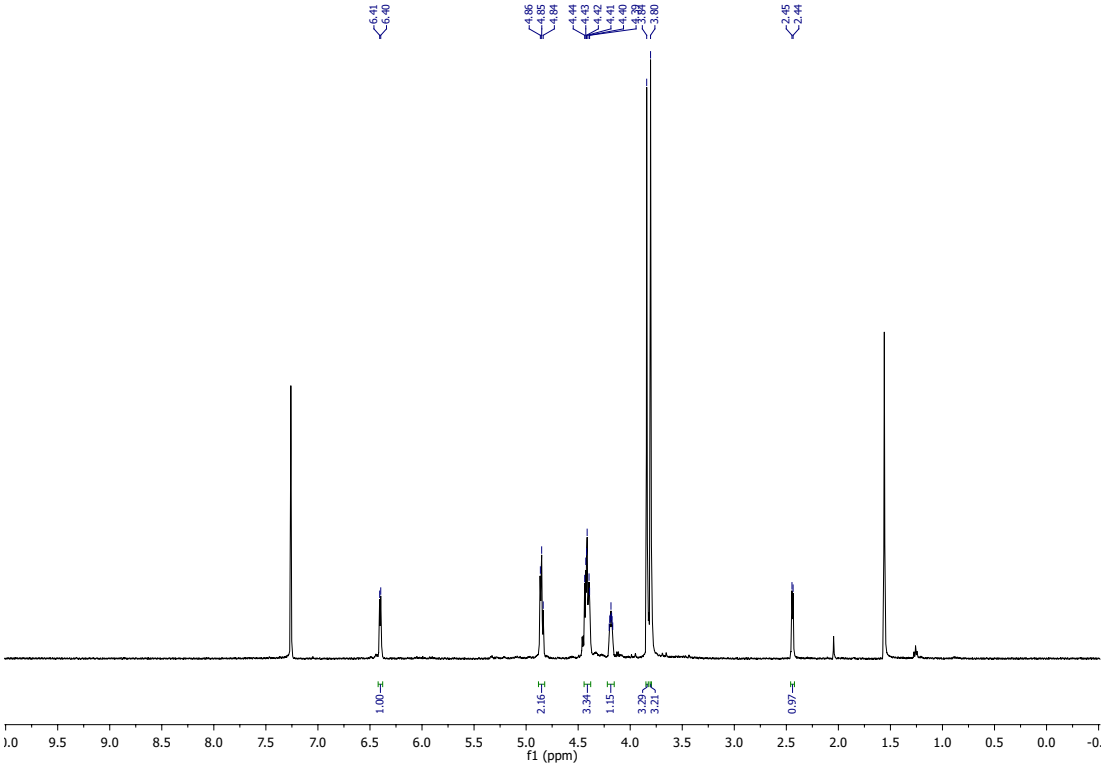
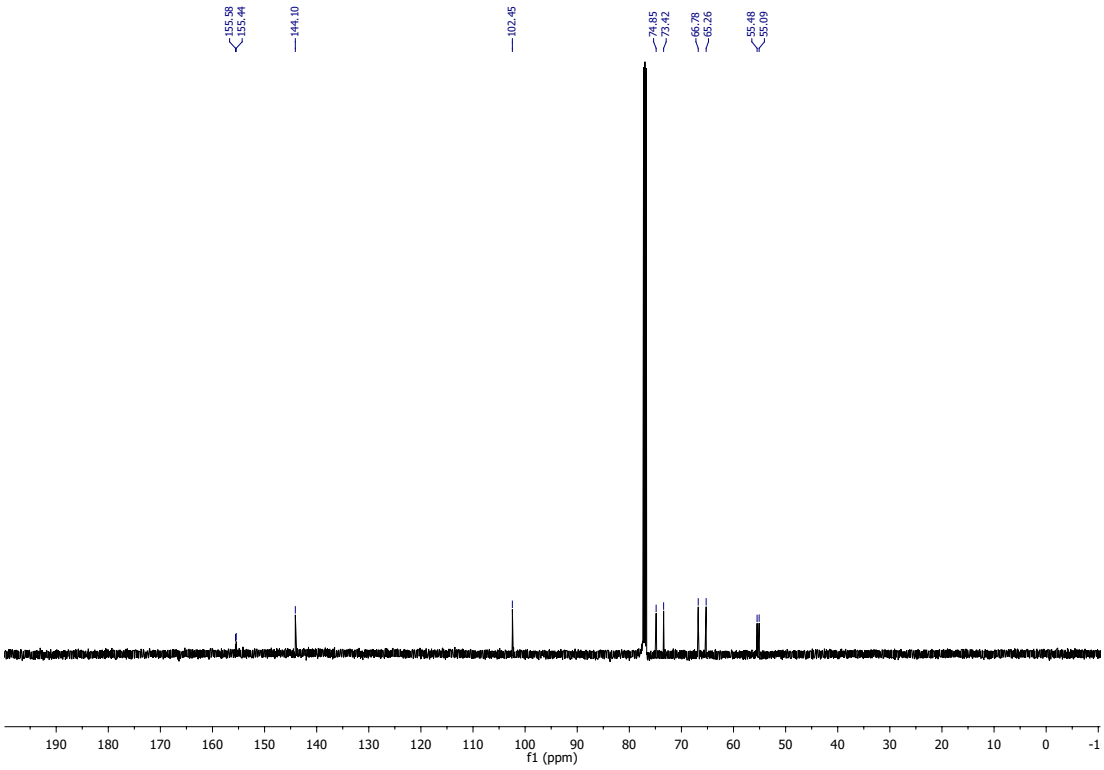
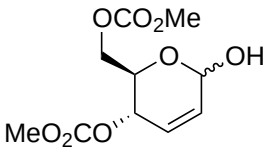


^{1}H-NMR spectrum of **251** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **251** (500 MHz, $CDCl_3$)



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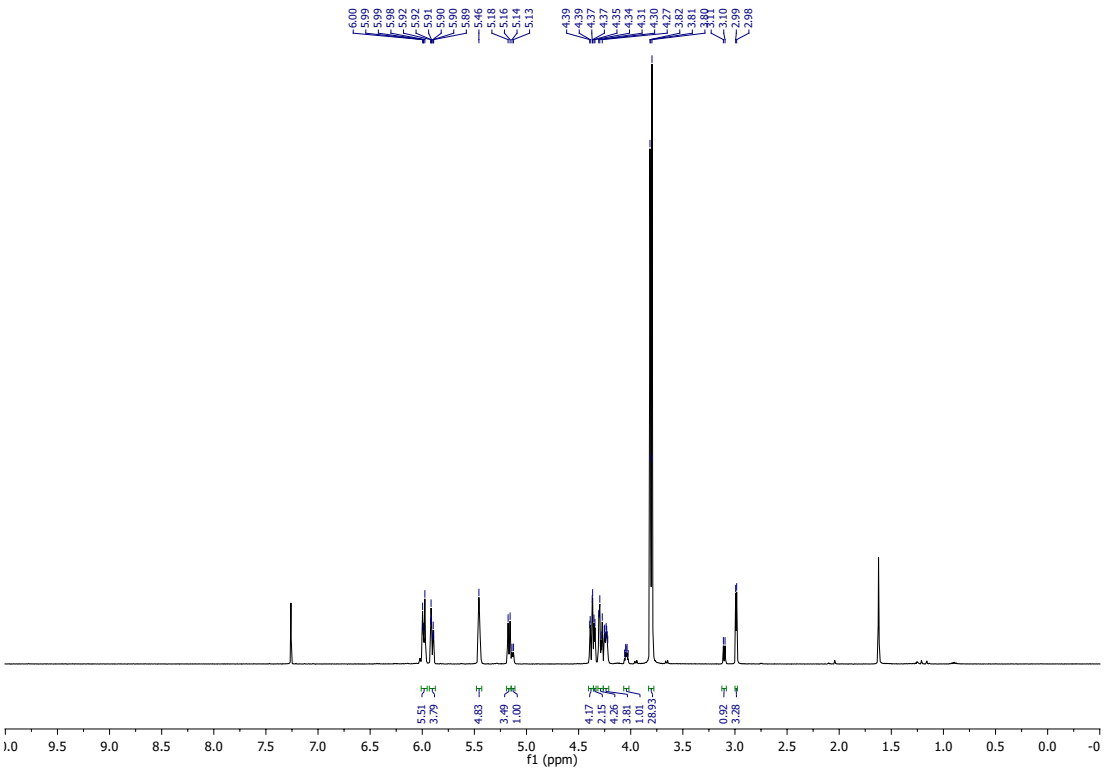
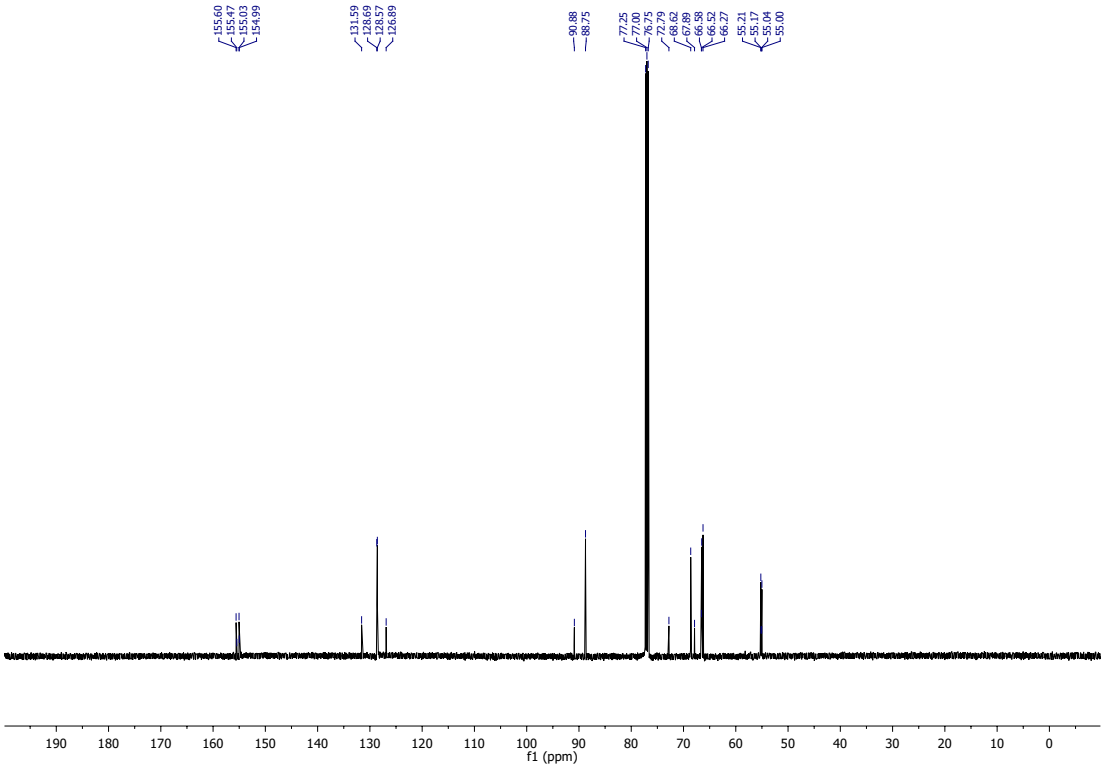
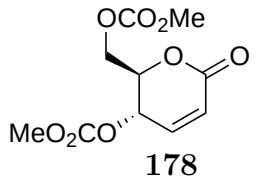


^{1}H-NMR spectrum of **199** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **199** (500 MHz, $CDCl_3$)



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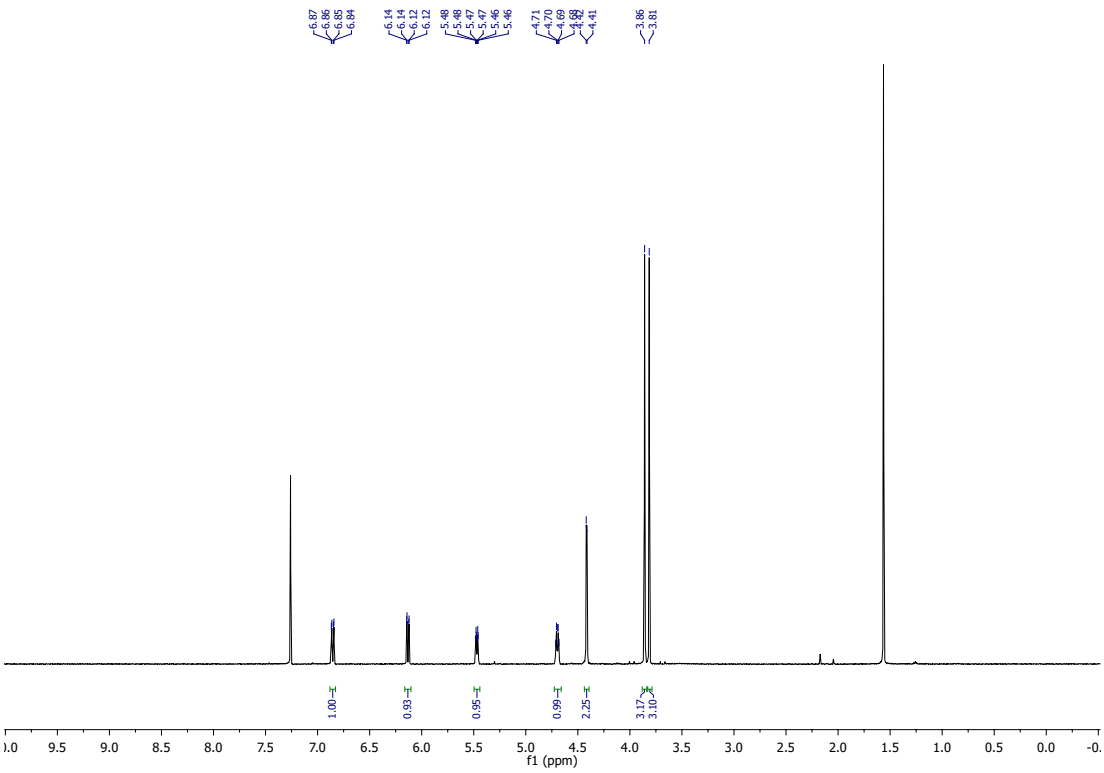
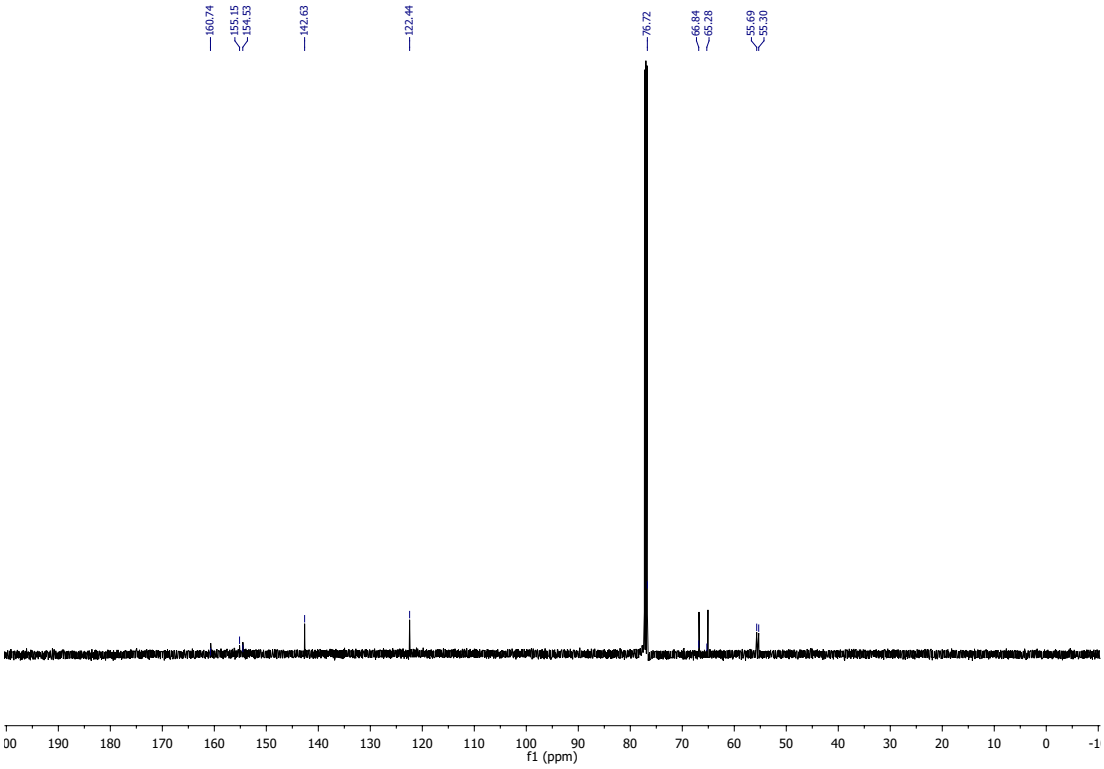
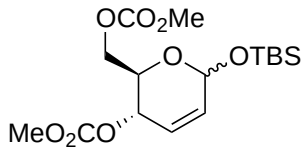


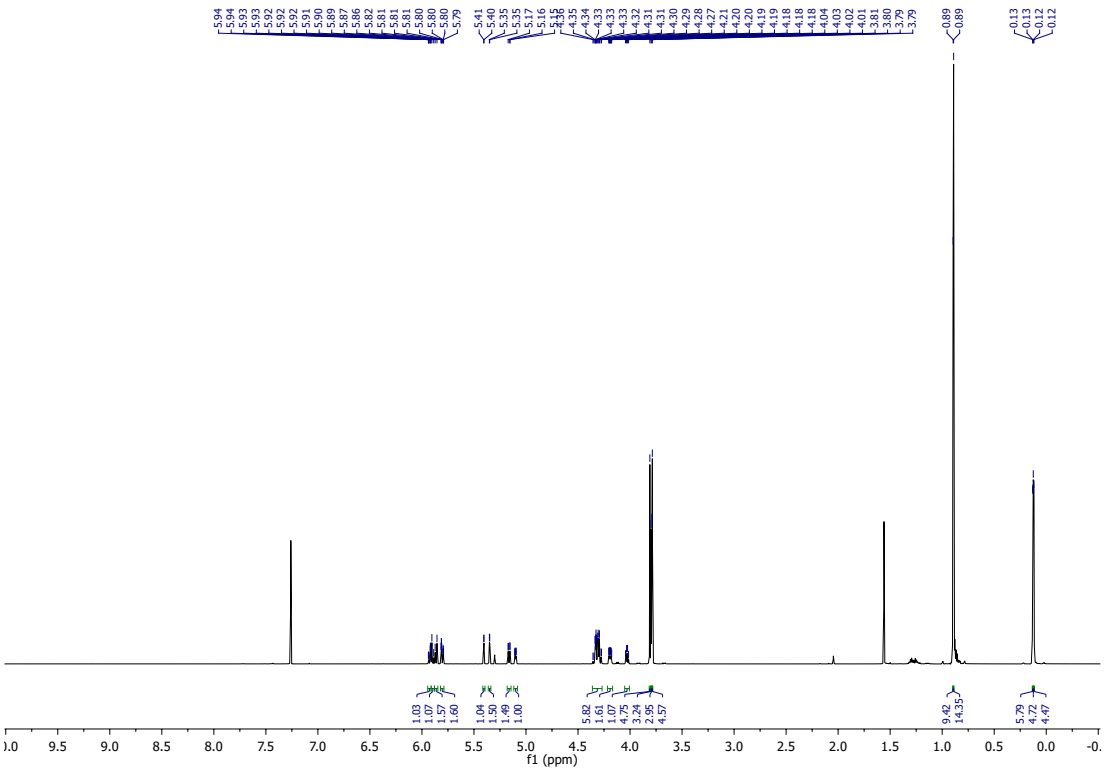
^{1}H-NMR spectrum of **178** (500 MHz, $CDCl_3$)



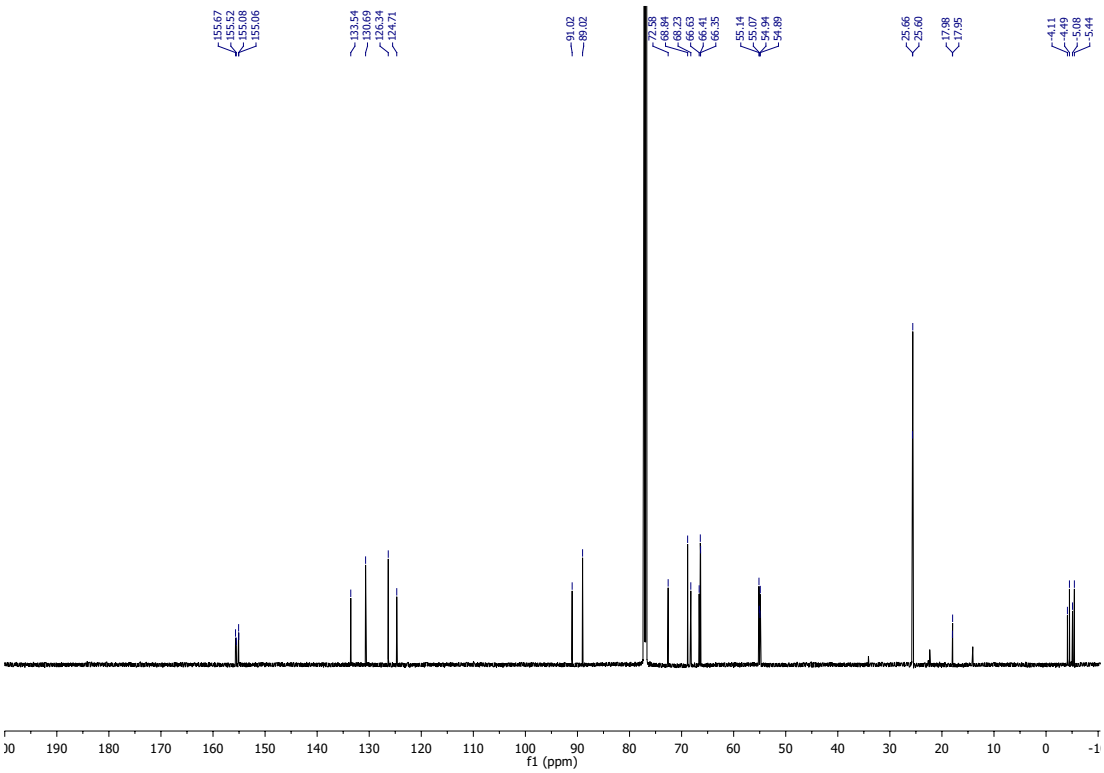
^{13}C-NMR spectrum of **178** (500 MHz, $CDCl_3$)



154

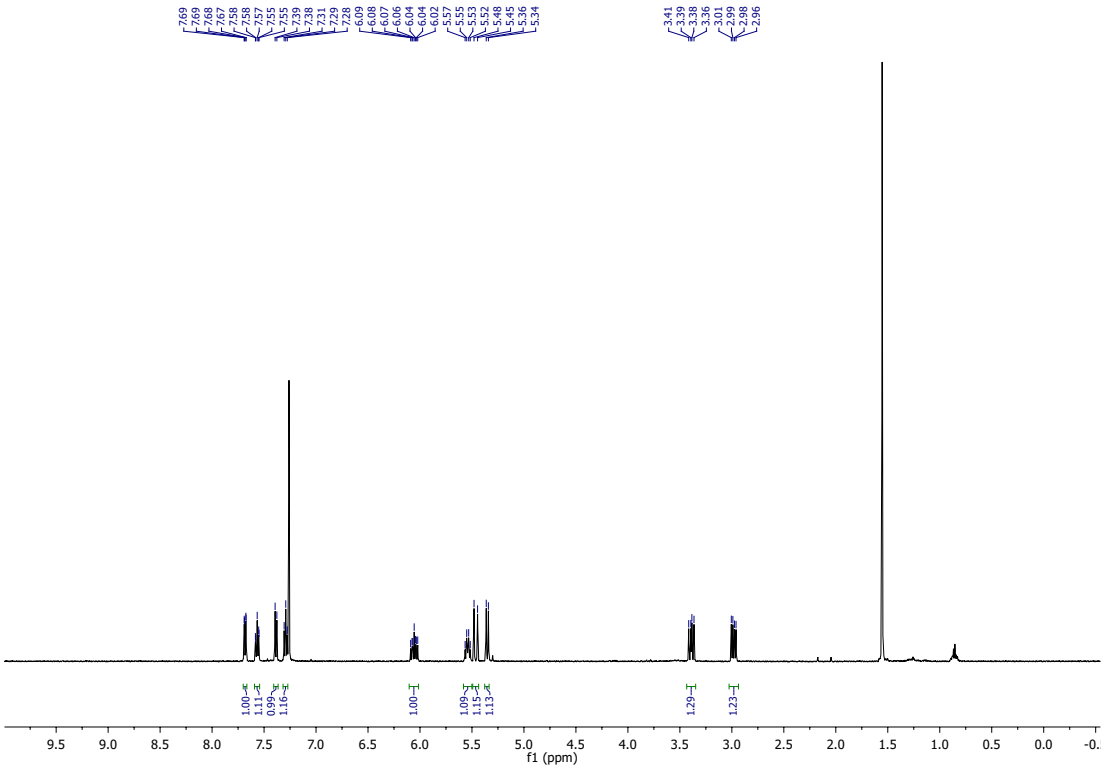


^{1}H-NMR spectrum of **154** (600 MHz, $CDCl_3$)

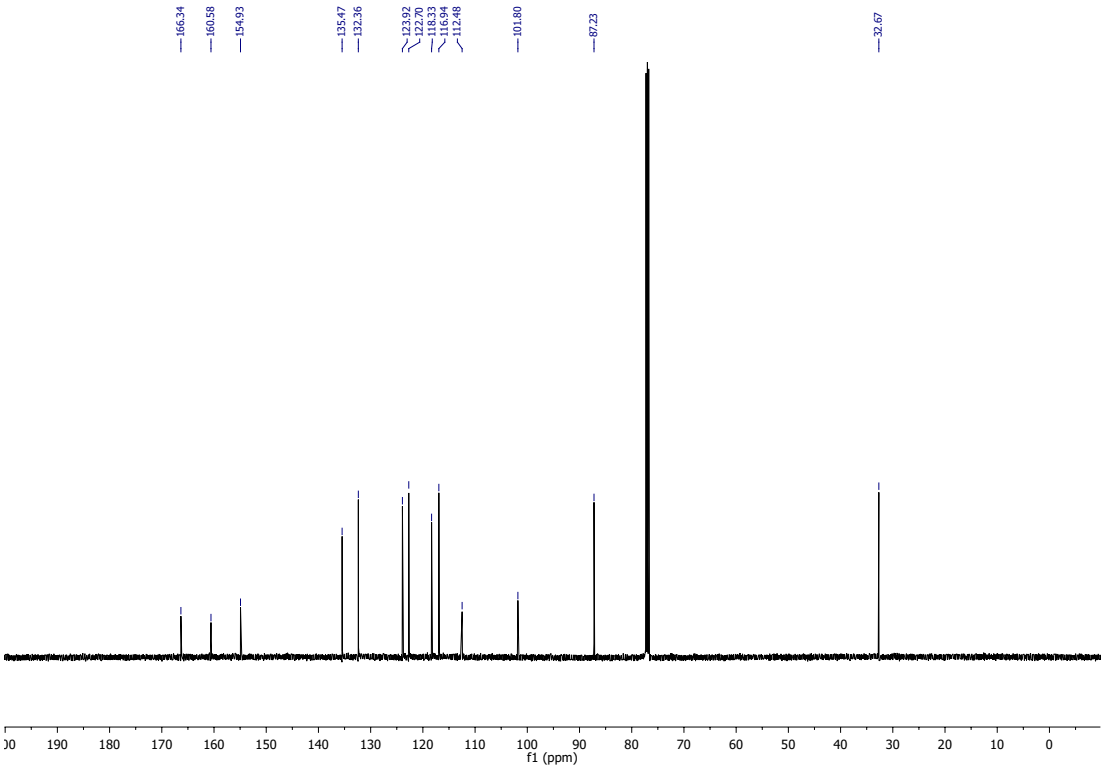


^{13}C-NMR spectrum of **154** (600 MHz, $CDCl_3$)

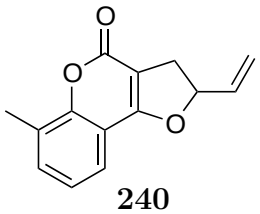
211



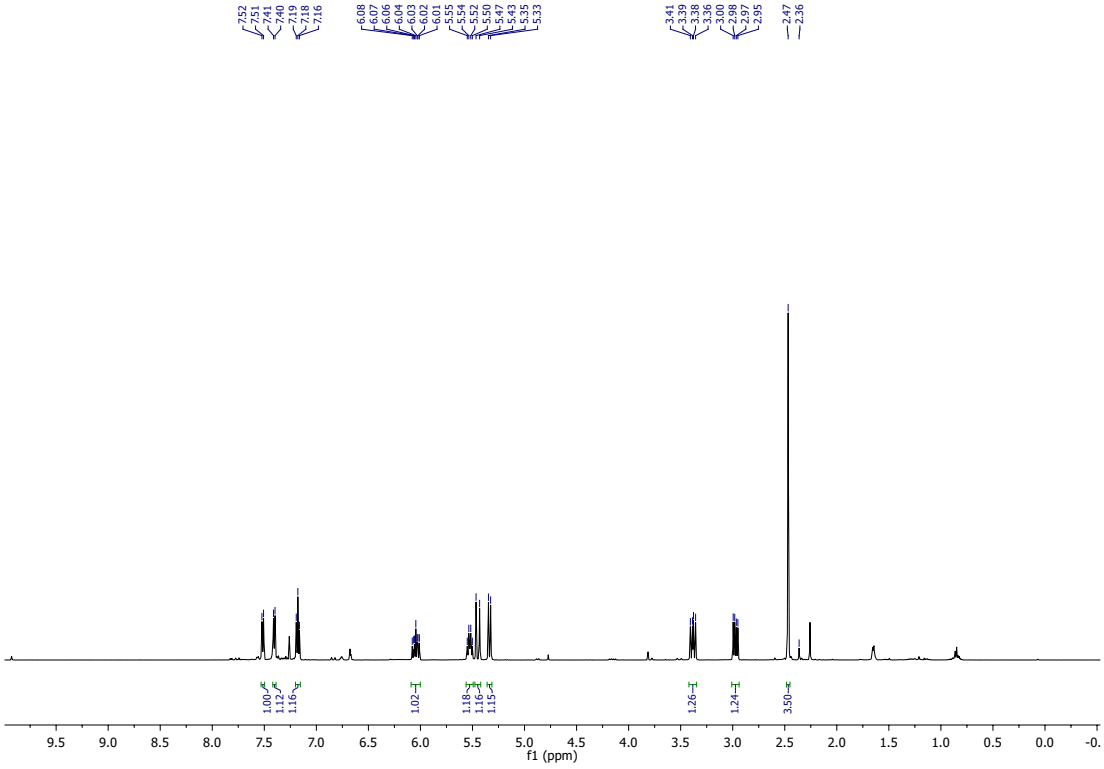
^{1}H-NMR spectrum of **211** (500 MHz, $CDCl_3$)



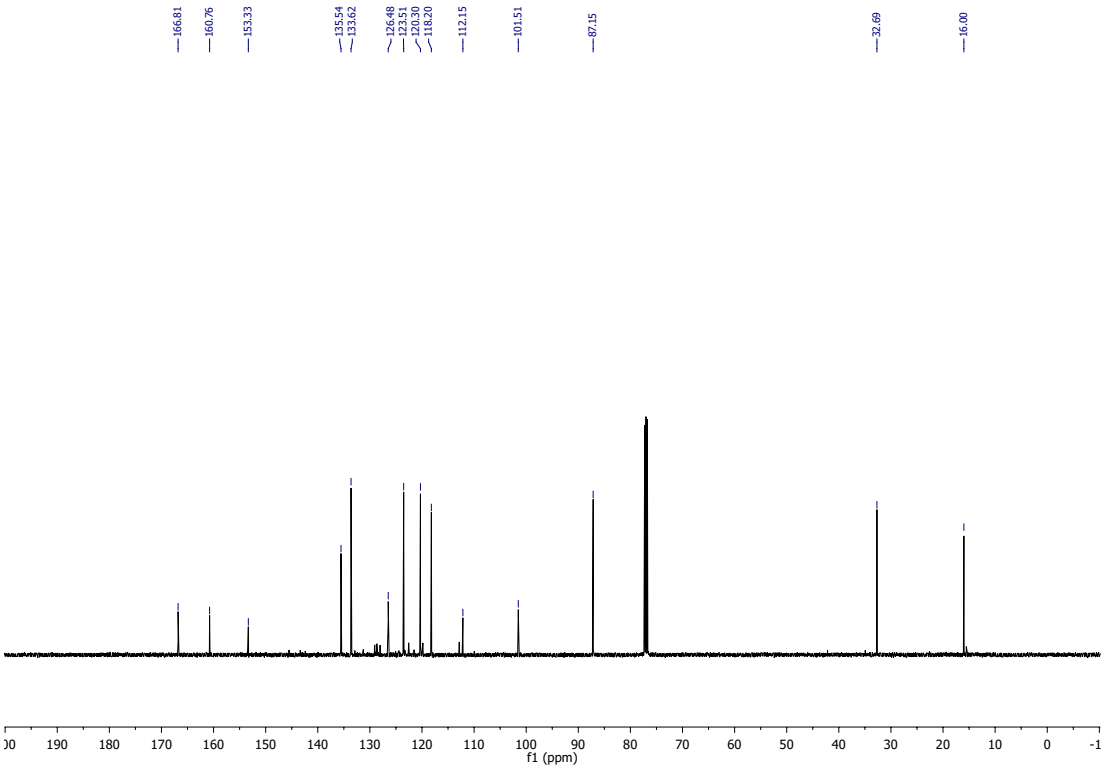
^{13}C-NMR spectrum of **211** (500 MHz, $CDCl_3$)



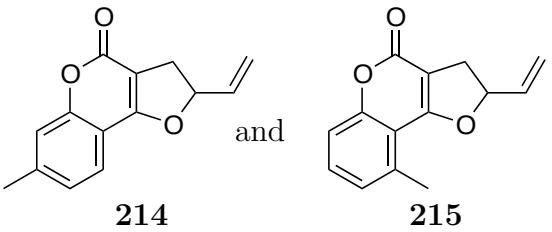
240



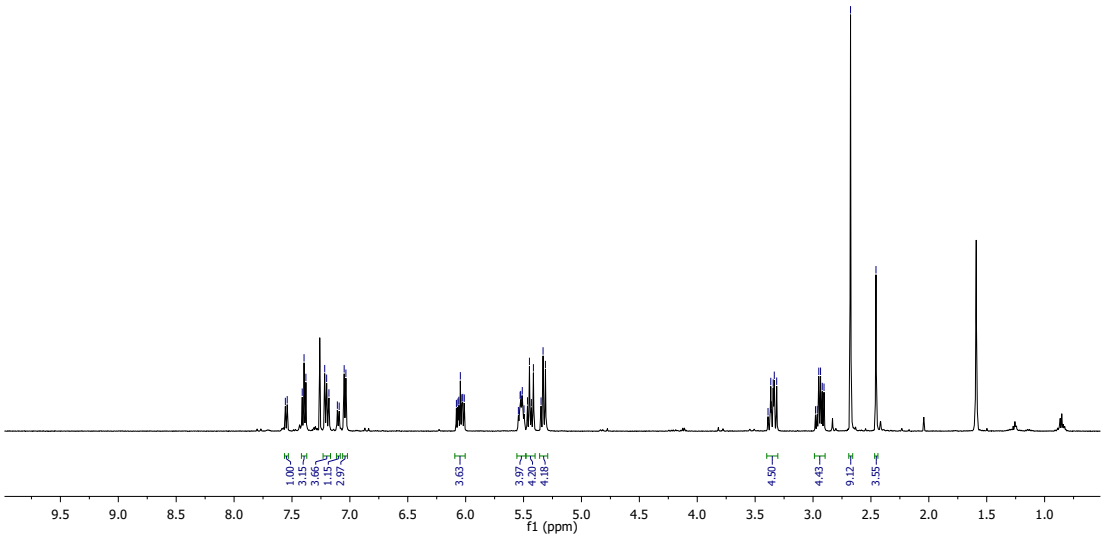
^{1}H-NMR spectrum of **240** (500 MHz, $CDCl_3$)



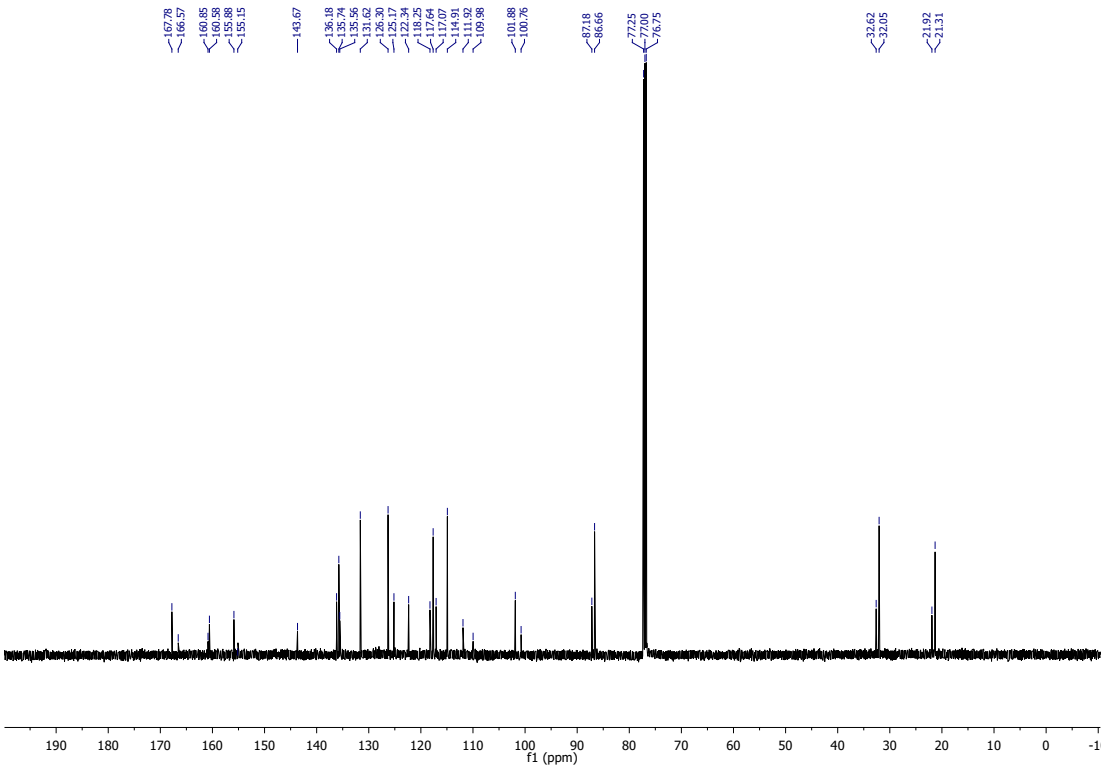
^{13}C-NMR spectrum of **240** (500 MHz, $CDCl_3$)



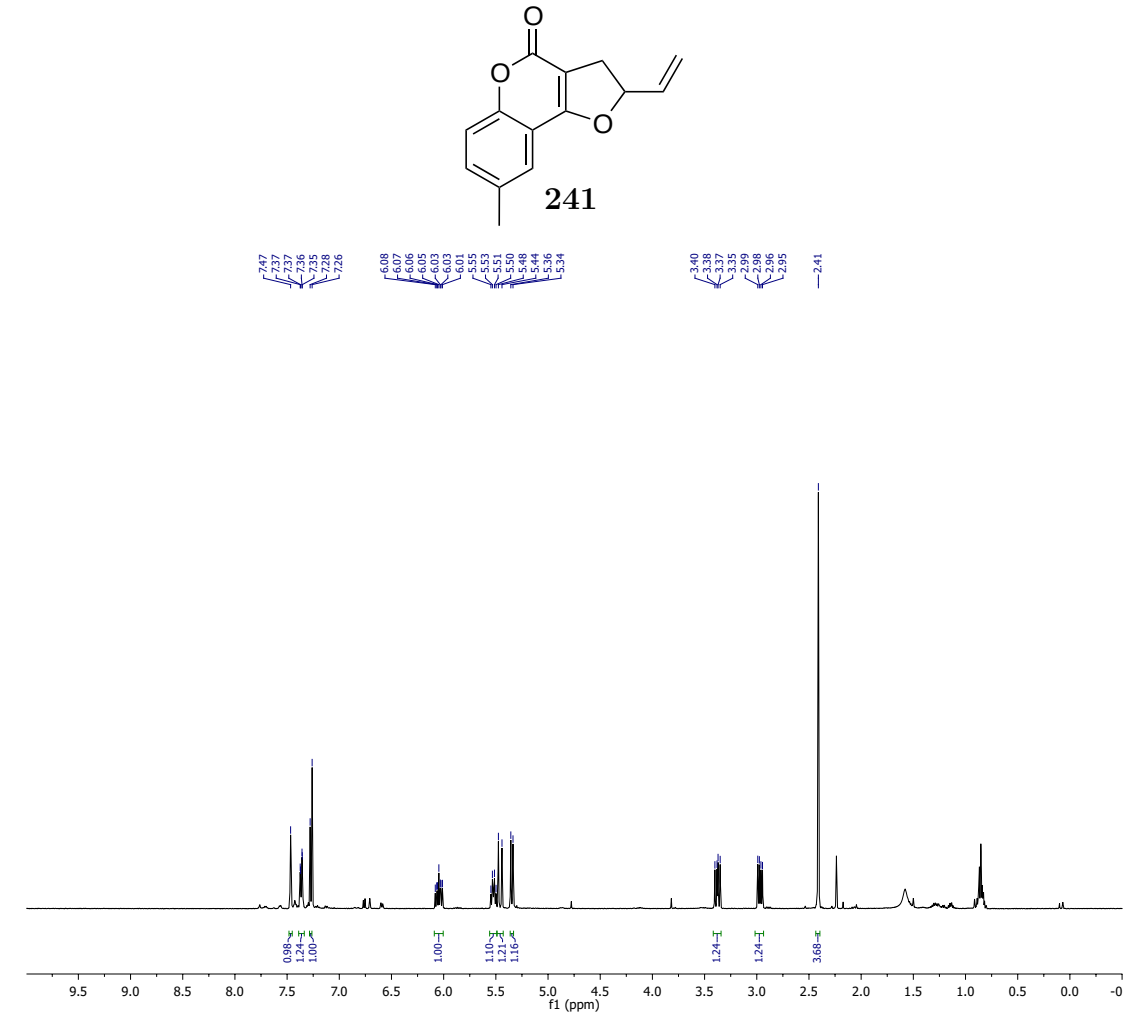
214 and **215**



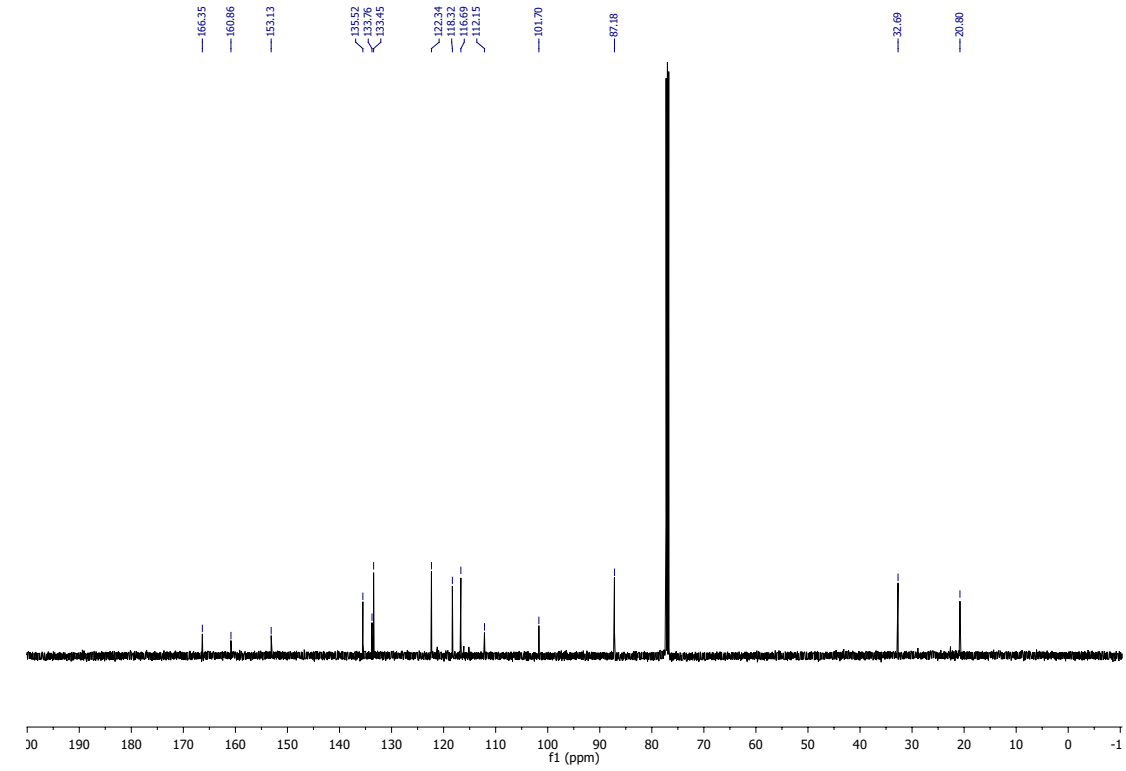
^{1}H-NMR spectrum of **214** and **215** (500 MHz, $CDCl_3$)



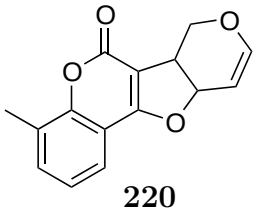
^{13}C-NMR spectrum of **214** and **215** (500 MHz, $CDCl_3$)



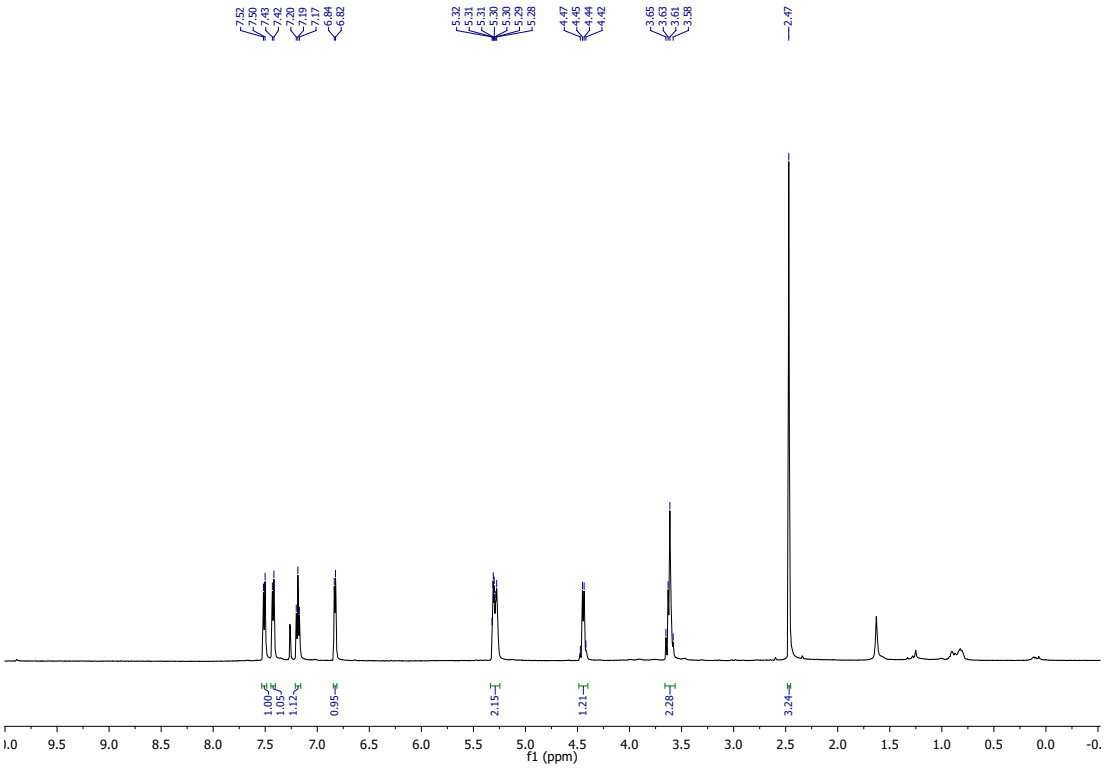
^{1}H-NMR spectrum of **241** (500 MHz, $CDCl_3$)



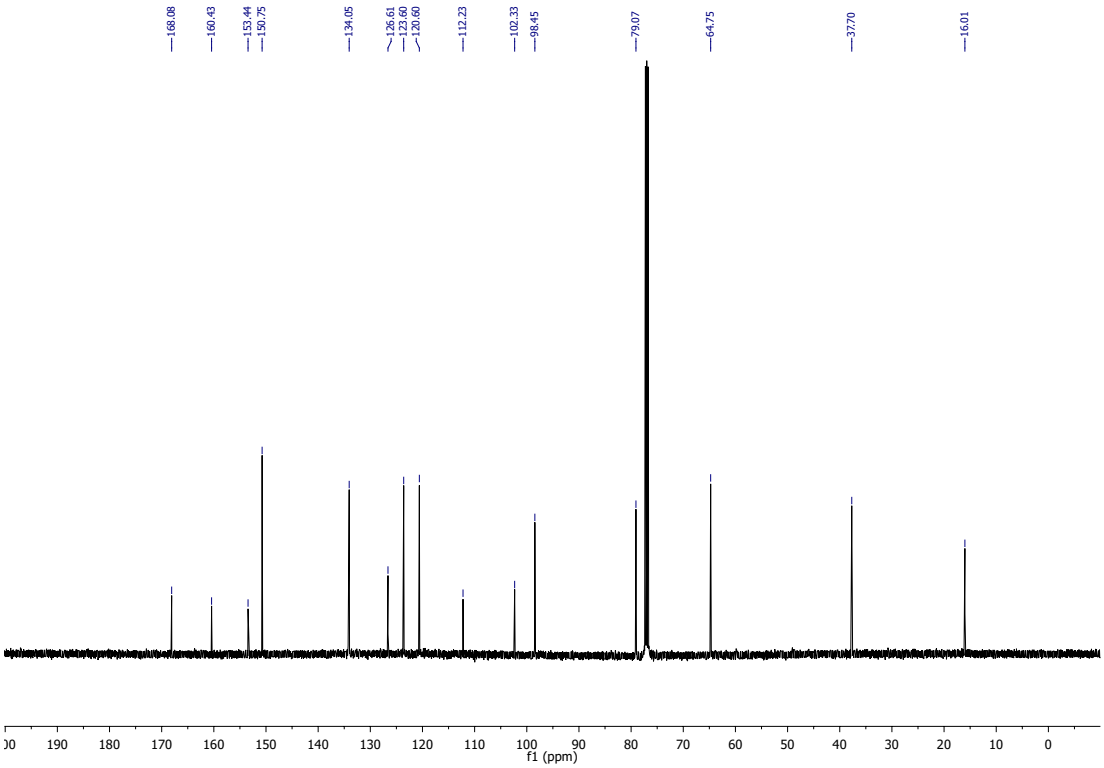
^{13}C-NMR spectrum of **241** (500 MHz, $CDCl_3$)



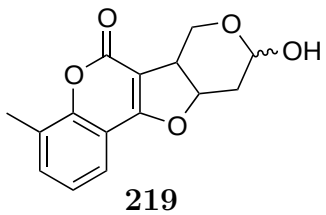
220



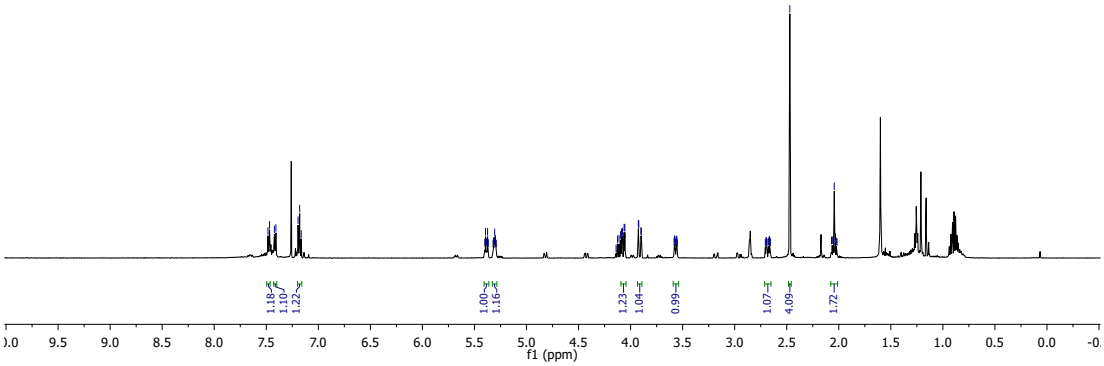
^{1}H-NMR spectrum of **220** (500 MHz, $CDCl_3$)



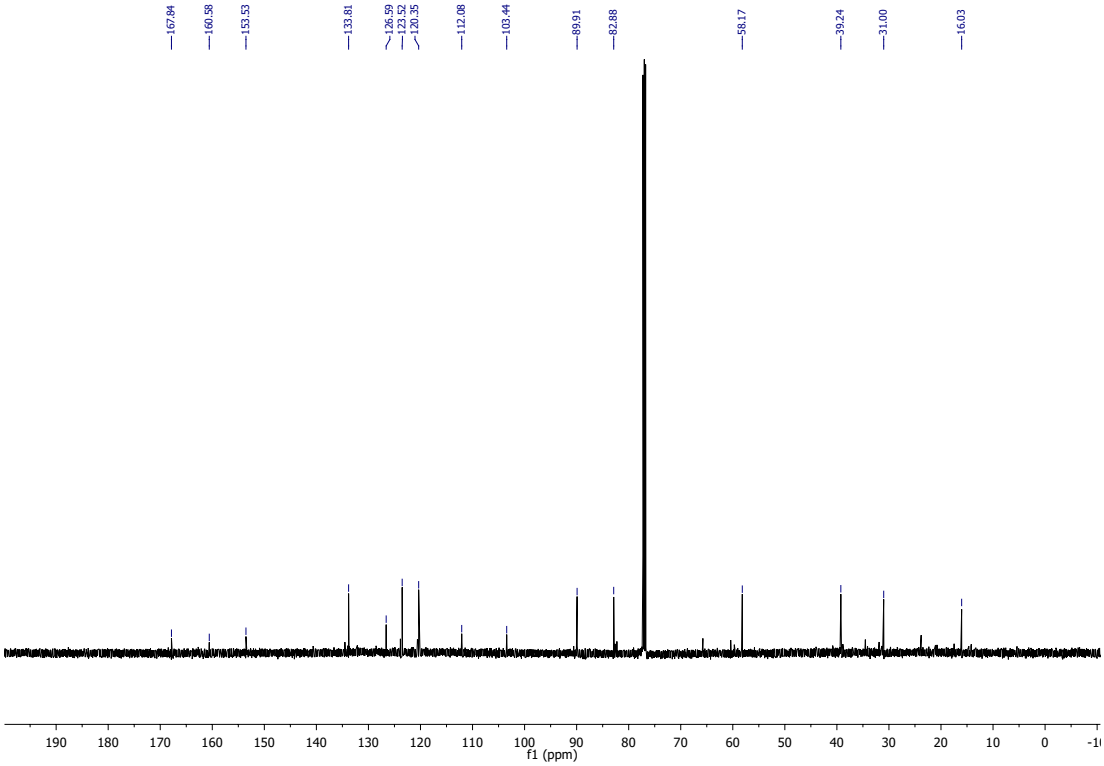
^{13}C-NMR spectrum of **220** (500 MHz, $CDCl_3$)



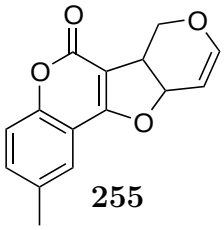
219



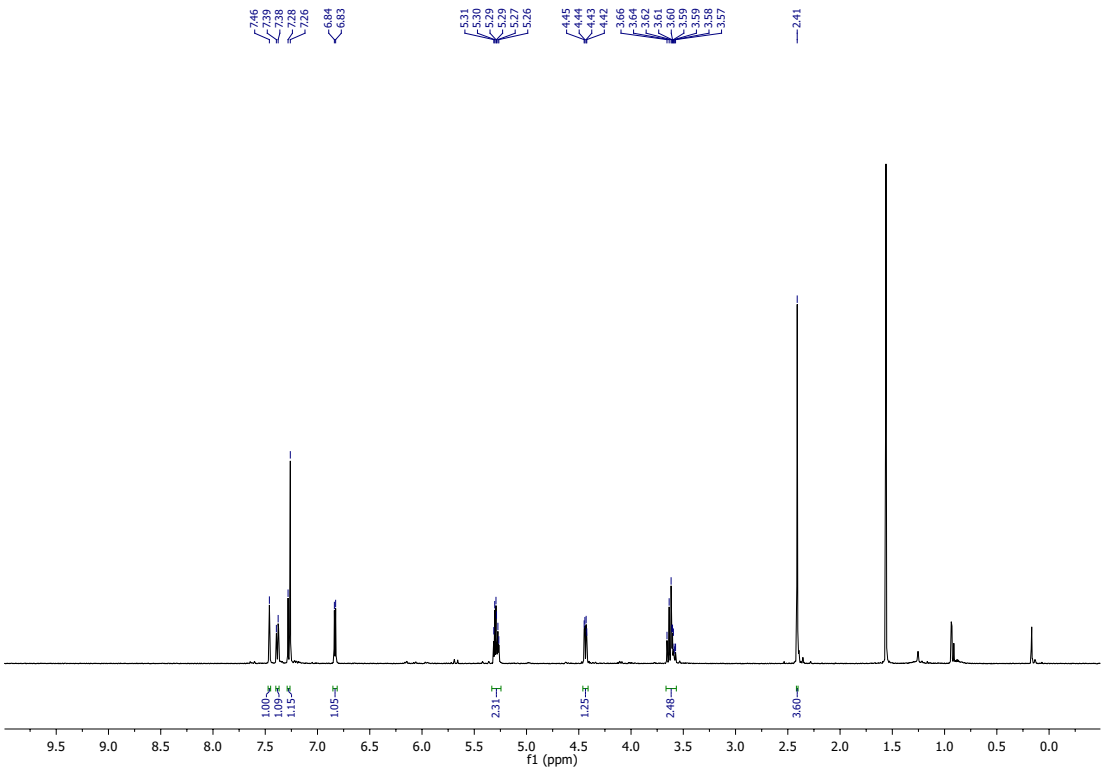
^{1}H-NMR spectrum of **219** (500 MHz, $CDCl_3$)



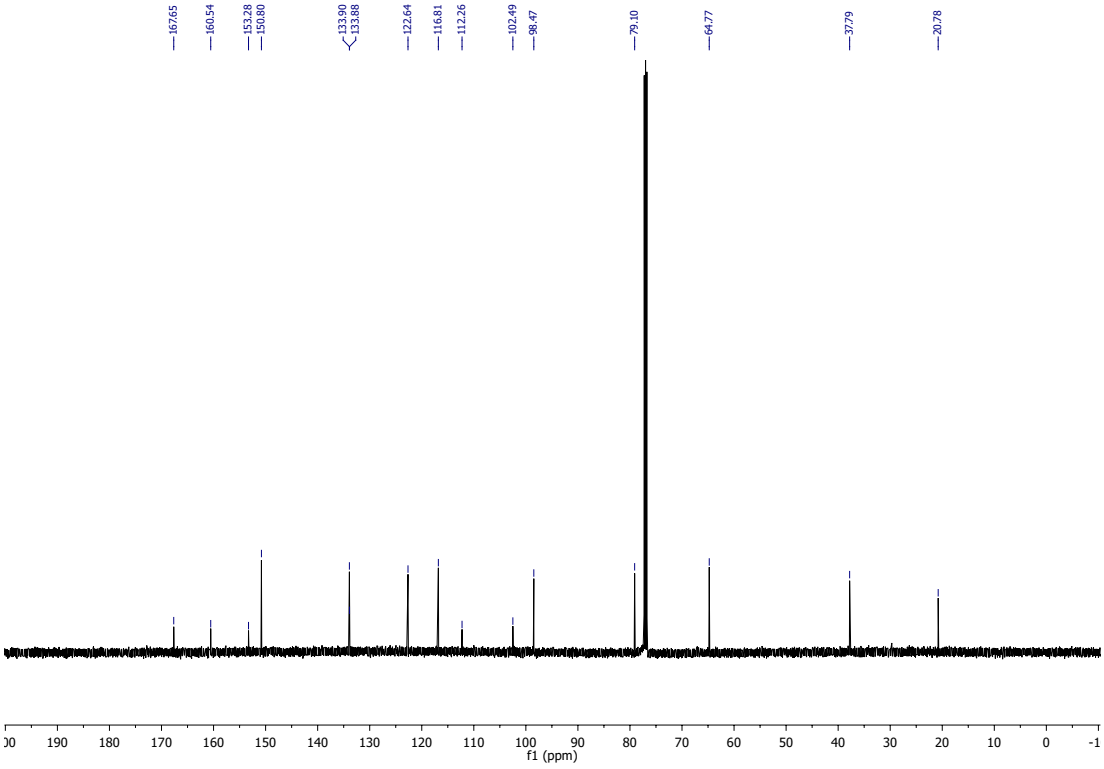
^{13}C-NMR spectrum of **219** (500 MHz, $CDCl_3$)



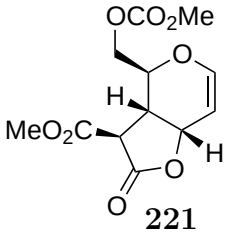
255



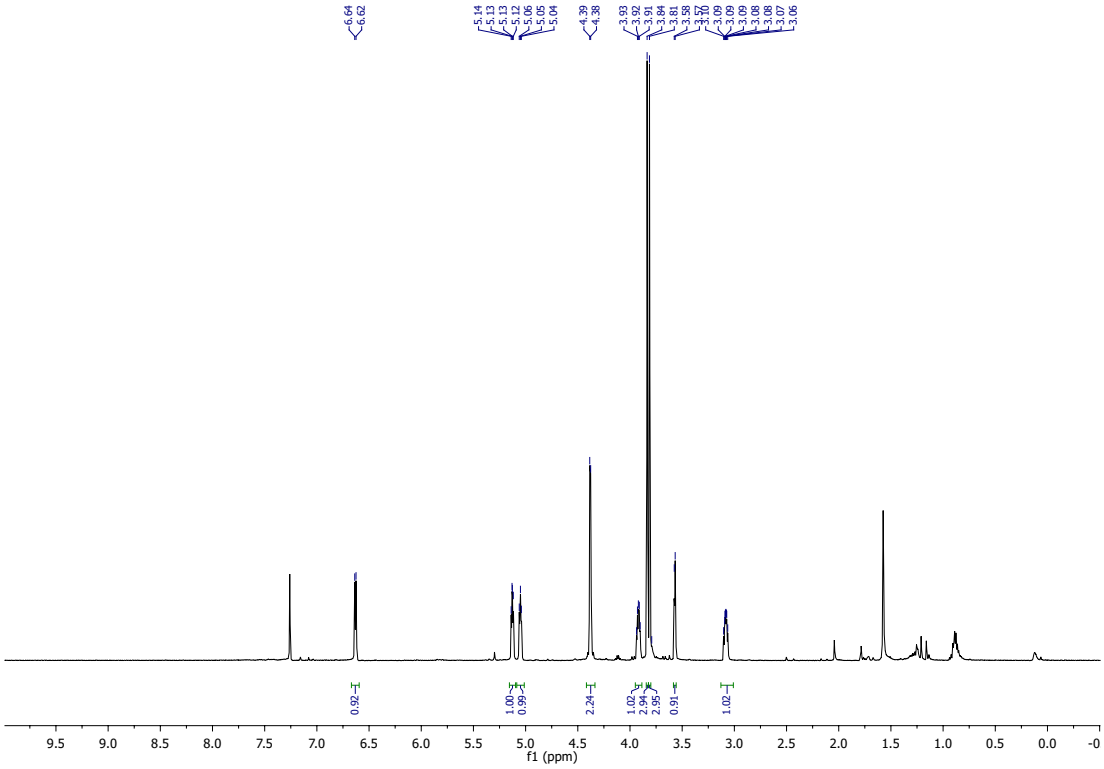
^{1}H-NMR spectrum of **255** (500 MHz, $CDCl_3$)



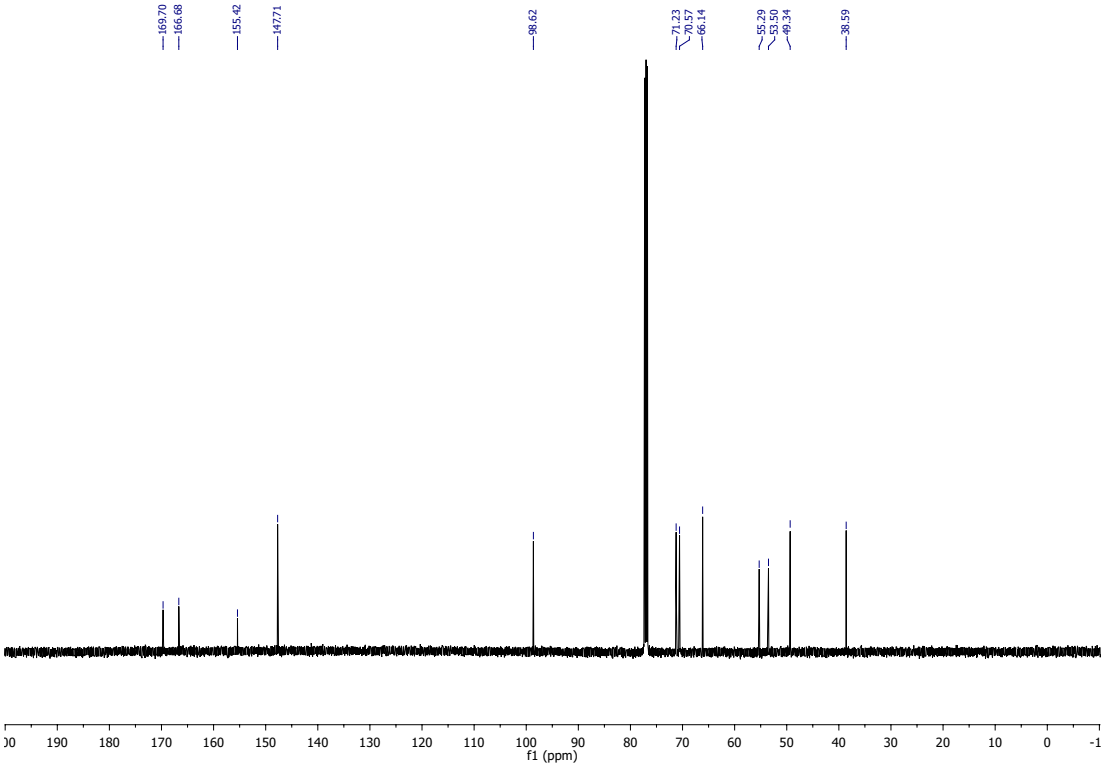
^{13}C-NMR spectrum of **255** (500 MHz, $CDCl_3$)



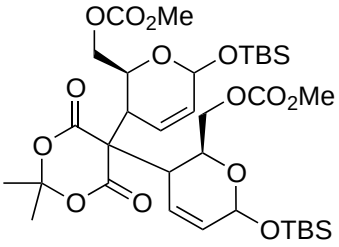
221



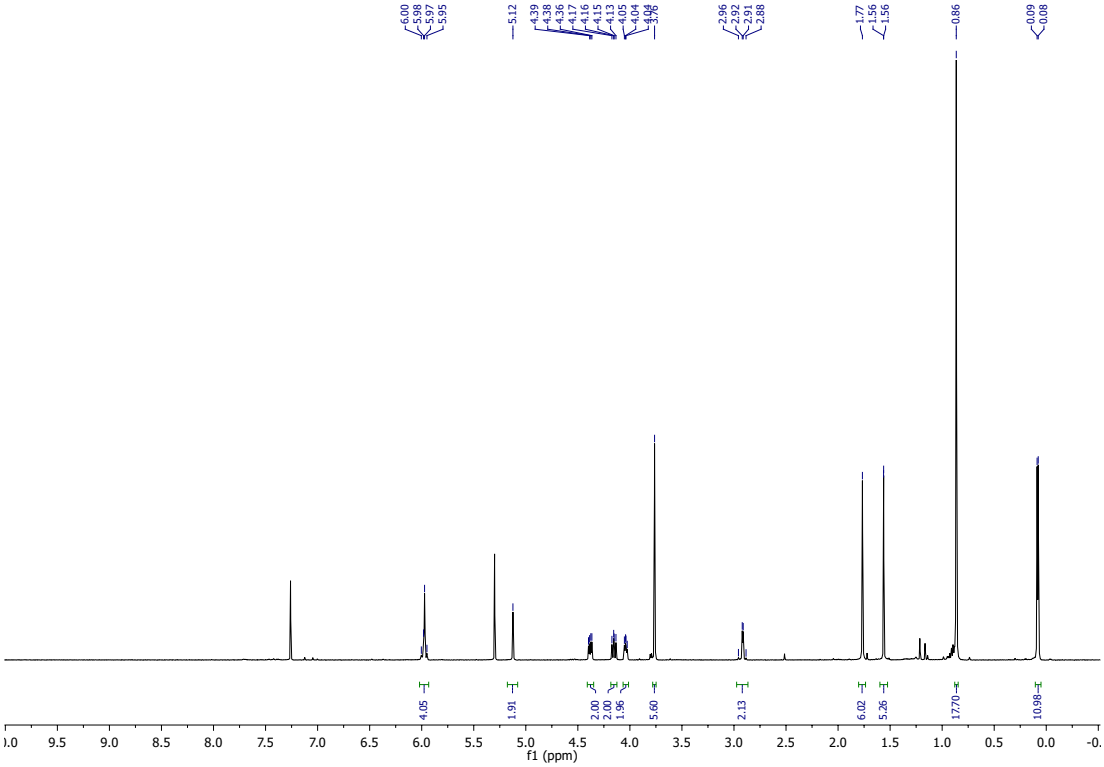
^{1}H-NMR spectrum of **221** (500 MHz, $CDCl_3$)



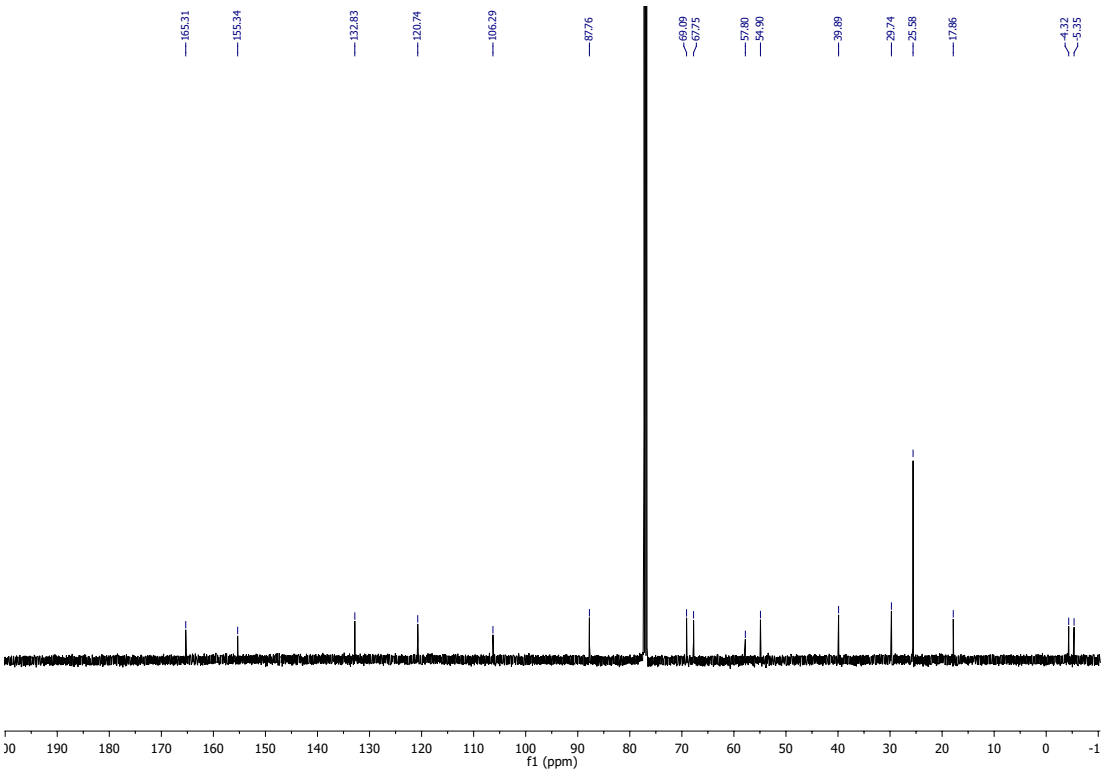
^{13}C-NMR spectrum of **221** (500 MHz, $CDCl_3$)



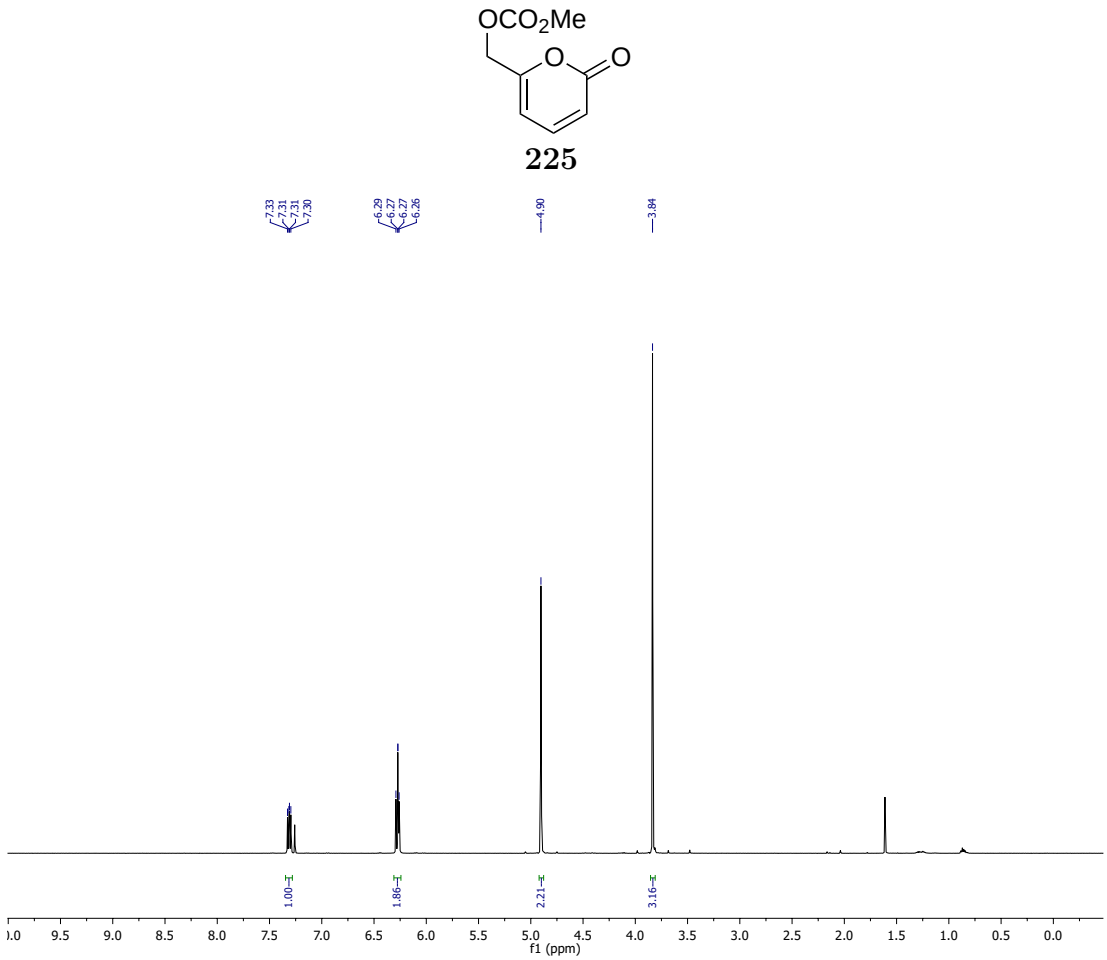
222



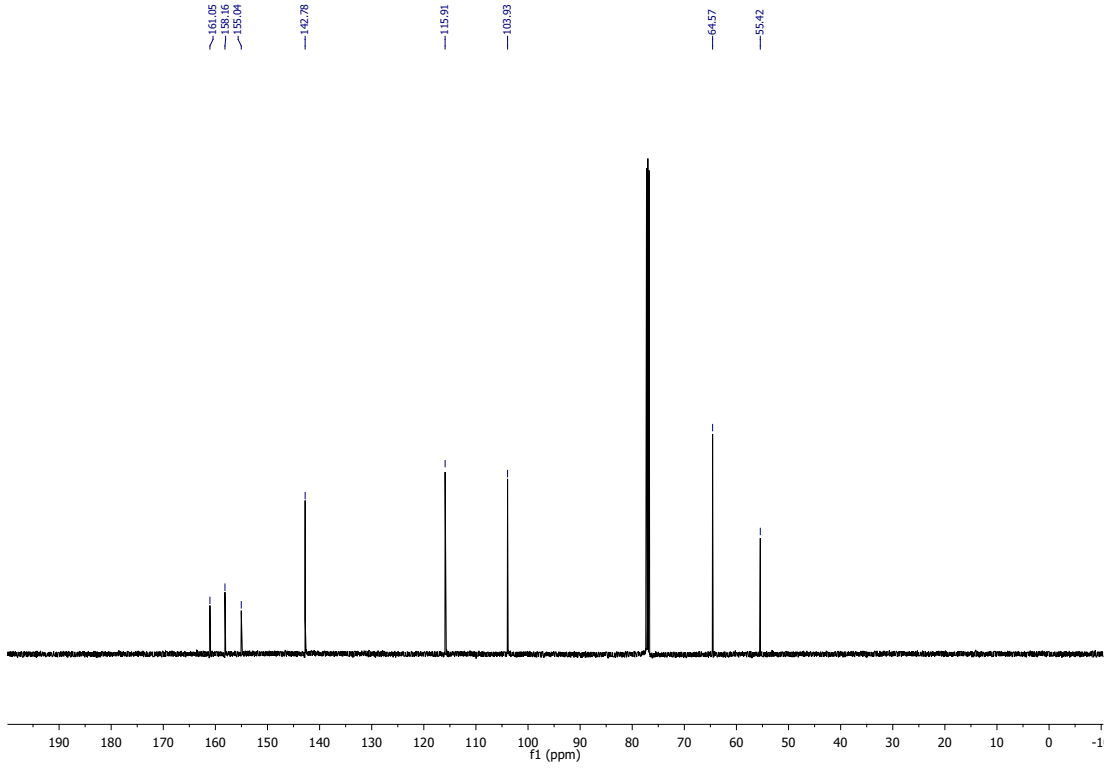
^{1}H-NMR spectrum of **222** (500 MHz, $CDCl_3$)



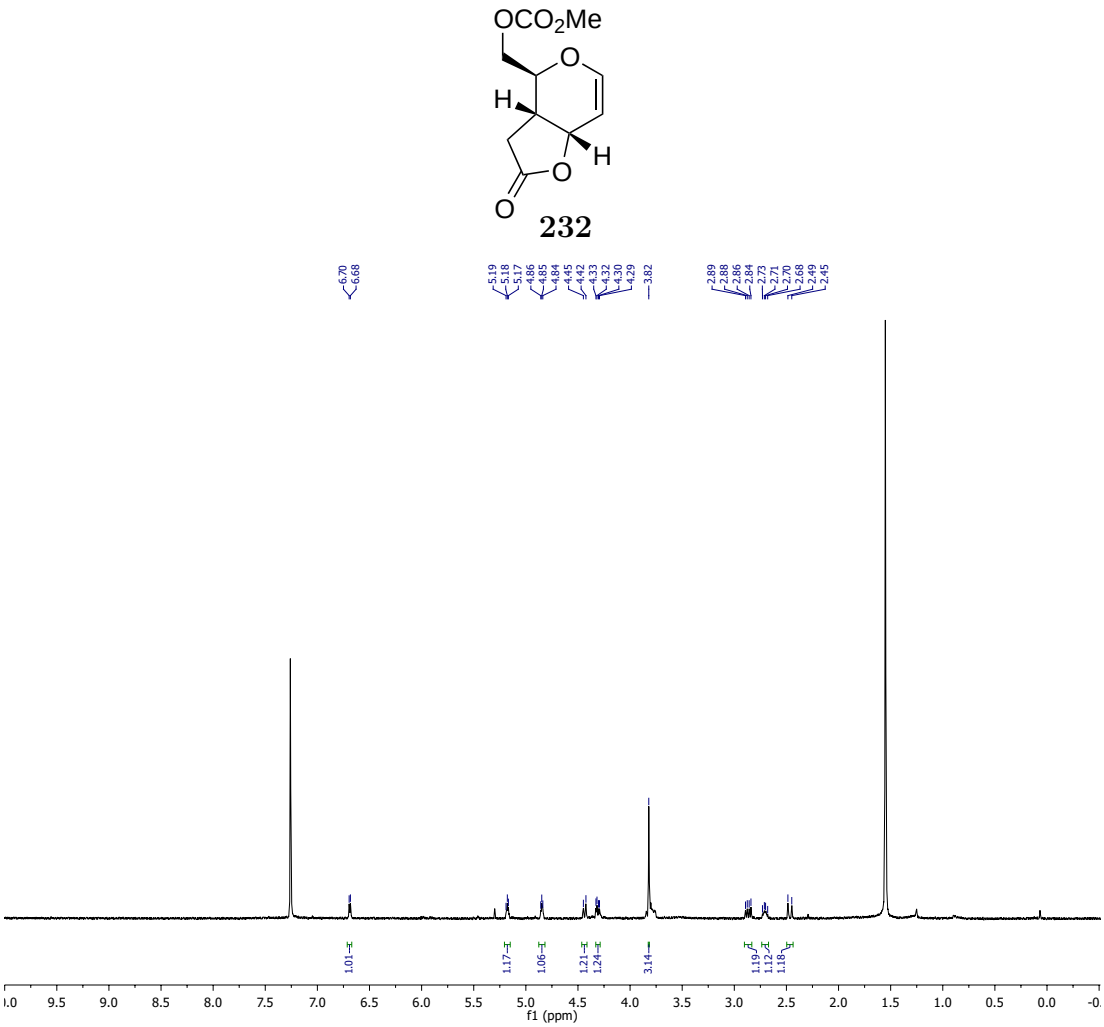
^{13}C-NMR spectrum of **222** (500 MHz, $CDCl_3$)



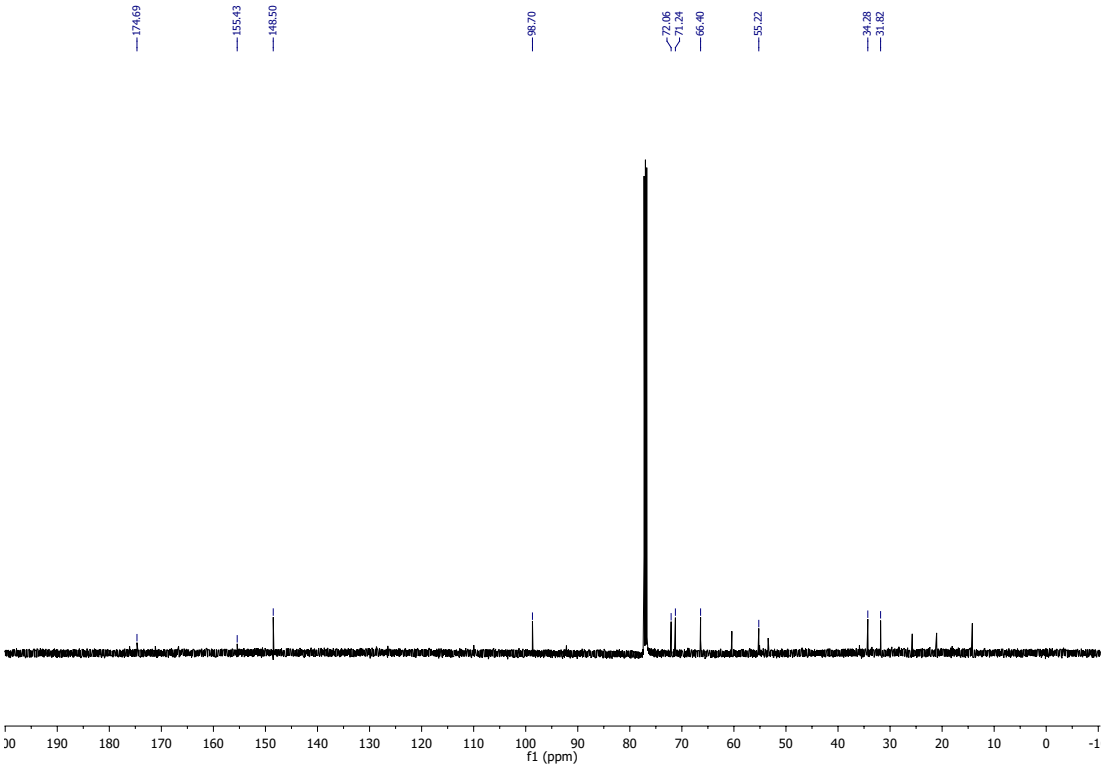
^{1}H-NMR spectrum of **225** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **225** (500 MHz, $CDCl_3$)



^{1}H-NMR spectrum of **232** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **232** (500 MHz, $CDCl_3$)

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