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Total Synthesis of the Chaetoquadrins

A thesis submitted in fulfilment of the

requirements for the degree of Doctor of Philosophy

By

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July 2013

Abstract

This thesis is concerned with the total synthesis of a family of natural products called the chaetoquadrins, isolated from ascomycete *Chaetomium quadrangulatum* that inhibit monoamine oxidase. Chaetoquadrins A–C (**1**–**3**, **Figure 1**) feature a chromone moiety fused to a 6,6-spiroketal. Inclusive in this interesting architecture are four chiral centres including an *anomerically* stabilised spiroketal centre.

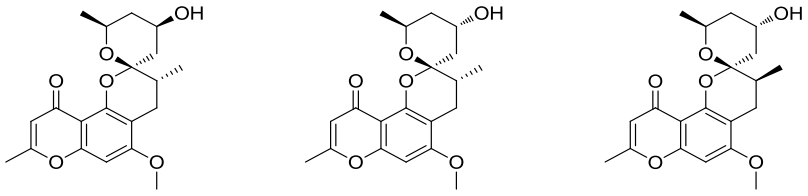

***Figure 1**. Chaetoquadrins A–C.*

The total synthesis of related bis-pyranone natural products chaetoquadrins H (**4**) and I (**5**) are also reported (**Figure 2**). As these natural products share a similar architecture to the aforementioned spiroketal chaetoquadrins, a similar strategy to that which enabled the total synthesis of chaetoquadrins A–C was employed in the total synthesis of chaetoquadrins H and I.

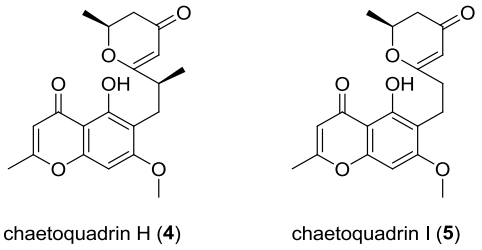

***Figure 2**. Chaetoquadrins H and I.*

Preface

All the work described was carried out by the author of this thesis, except for the work of others in which case due reference has been made to this in the text.

Some parts of this thesis have been published:

Kim, U. B.; Furkert, D. P.; Brimble, M. A. Total Synthesis of Chaetoquadrins A–C. *Org. Lett.* **2013**, *15*(3), 658–661. DOI: 10.1021/ol303482k

Kim, U. B.; Dalebrook, A. F.; Furkert, D. P.; Brimble, M. A. Total Synthesis of Chaetoquadrins H and I. *Synlett* **2013**, *24*(6), 723–726. DOI: 10.1055/s-0032-1318333

Acknowledgements

Working on the chaetoquadrins, I was able to play with chemicals for four, enjoyable years. During this time, every person I've encountered here at University of Auckland has afforded me kindness and unrestricted access to knowledge to which I have become so accustomed. Without this support, the work described here would not have been possible.

In this context I would like to first acknowledge my supervisor Professor **Margaret Brimble**:

Thank you for giving me the opportunity to work in your amazing research group. I cannot thank you enough for your guidance, patience, inspiration and time throughout this project despite my numerous short comings.

I would also like to acknowledge my co-supervisor Dr. David Barker. Thank you for always being available and for your support.

I would now like to thank other (past and present) members of the Brimble group:

Dr. Daniel P. Furkert's *stupendous wisdom* (chemistry and otherwise!) was invaluable in this journey and my safe passage of it. Thank you Dan.

Dr. Amanda Heapy, Dr. Sung Hyun Yang and Dr. Patrick O'Connor have generously taken their time to proof-read parts of this manuscript during its preparation (a challenging endeavour) and for this I am immensely grateful. And to Patrick: thank you for plucking me out from the undergraduate labs to the world of organic synthesis– and for your friendship.

Dr. Sung Hyun Yang has taught me multiples of practical lab skills which were vital in the execution of this project.

I am indebted to all the members of the Brimble group for their collective support and friendship. In particular I would like to acknowledge generous friendship of Dr. Jack Li-Yang Chen, Dr. Tsz-Ying Yuen and (soon to be Dr.) Kyo-yuan Hung. Thank you for making my time here all the more enjoyable. And to my glorious comrade Ivo- you are an amazing ally, friend and I was privileged to have you on my flanks.

I must make mention of the support staff: Thank you Tim and Anoma for the logistical efforts, without which I would have gone nowhere. And to Dr. Janice Choi- thank you especially for your advice, time and friendship- despite your busy schedule.

Finally, I owe my deepest gratitude and love to my parents, without whom the existence of myself (and this thesis in its current form) may be in question. I love you both!

Ubin Kim

Table of Contents

Abbreviations

Δ	reflux
δ	chemical shift
°C	degree Celsius
Ac	acetyl
aq	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
c	concentration
$CHCl_3$	chloroform
conc	concentrated
d	doublet
ee	enantiomeric excess
EI	electron impact
EOM	ethoxymethyl
ESI	electrospray ionisation
Et	ethyl
et al.	*et alii* (and others)
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
ie	*inter alia* (among other things)
Ipc	isopinocampheyl
^{i}Pr	isopropyl
IR	infra-red
J	coupling constant
L	litre
M	molar
m	multiplet or milli
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole
mp	melting point
Ms	mesylate
MW	microwave
NMR	nuclear magnetic resonance
PG	protecting group
pH	power of hydrogen
ppm	parts per million
py	pyridine
rt	room temperature

s	second(s)
t	triplet
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
Ts	tosylate
vide infra	see below
vide supra	see above

Chapter One

Introduction

1.0 Chaetoquadrins

Chaetoquadrins A–J (**1**–**11**, **Figure 3**) belong to a family of natural products isolated in 2002 and 2003 by Fujimoto and co-workers.[1-2] Isolated during a research program to identify monoamine oxidase (MAO) inhibitory compounds from an ascomycete *Chaetomium quadrangulatum*, they exhibit appreciable monoamine oxidase inhibitory activity against mouse liver MAO. Interestingly, chaetoquadrins A (**1**), B (**2**), G (**9**) and H (**4**) have also been isolated from the ascomycete *Chaetomium aureus* by Li and co-workers.[3] The chaetoquadrins, with the exception of 2-pyrone chaetoquadrin F, share the chromone (5-oxy-1,4-benzopyrone) motif possessing an internal phloroglucinol (1,3,5-benzenetriol) pattern.

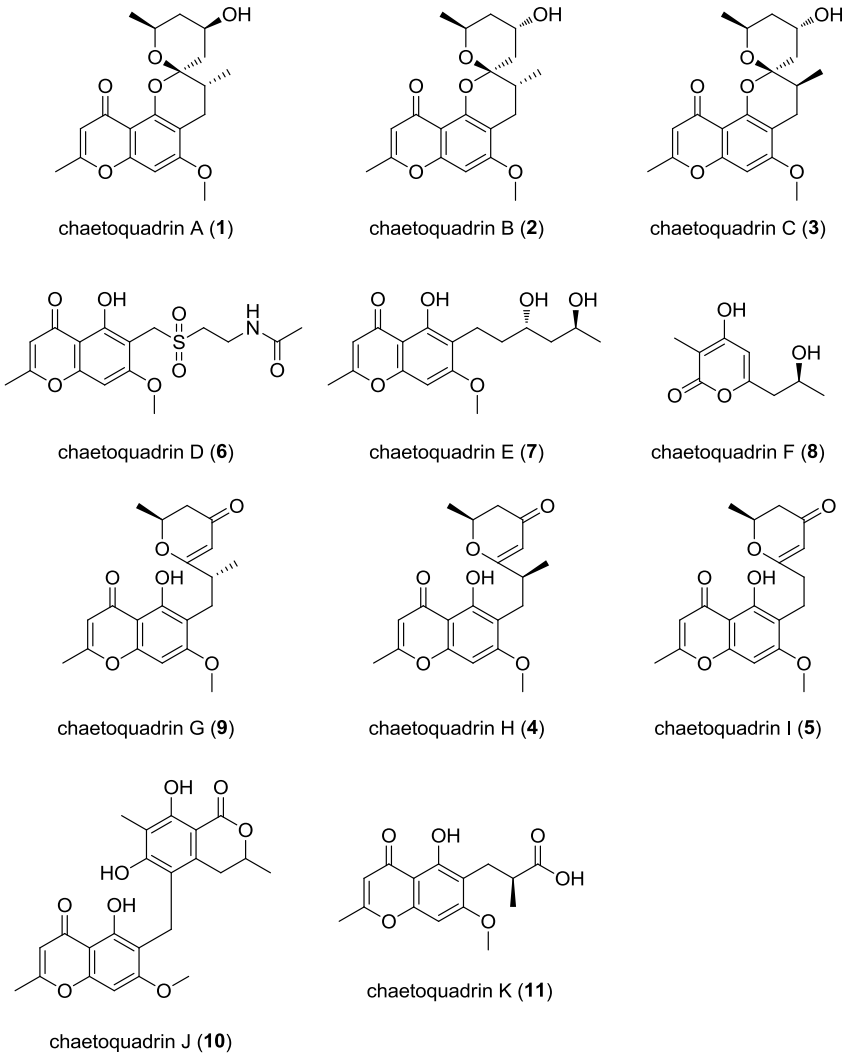

***Figure 3**. Chaetoquadrin natural products.*

As our research group has an interest in the synthesis of benzannulated spiroketal containing natural products,[4] the chaetoquadrins A–C (**1**–**3**) embodied a suitable synthetic target. Both

6,6-spiroketal (**12**) and chromone (**13**) moieties are described by Stockwell and co-workers as *privileged scaffolds* for library design and drug discovery (**Figure 4**).[5]

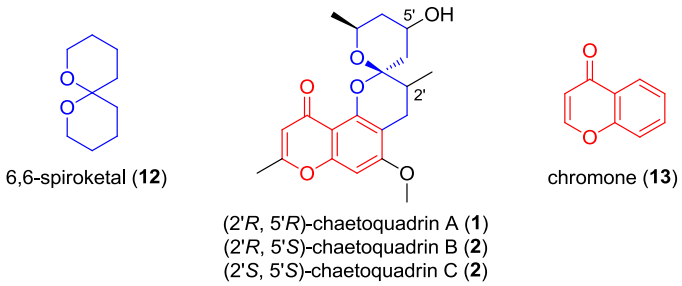

***Figure 4**. Privileged scaffolds: 6,6-spiroketal (**12**, left), chaetoquadrins A–C (**1**–**3**, middle) and chromone (**13**, right).*

In addition to this complex functionality, chaetoquadrins A–C (**1**–**3**) feature four chiral centres including an *anomerically* stabilised spiroketal centre. We proceeded to direct our synthetic effort towards these intriguing natural products with the aim of realising their total synthesis.

1.1 Monoamine neurotransmitters

The characteristics, instincts and mental states of humans are spawned by changes in the postsynaptic potential of a neuron caused by release of chemicals termed neurotransmitters.[6] Of these, catecholamine neurotransmitters such as dopamine (**14**), norepinephrine (**15**), epinephrine (**16**) and monoamine neurotransmitter serotonin (**17**) are of paramount interest as regulators of neurological well-being (**Figure 5**).

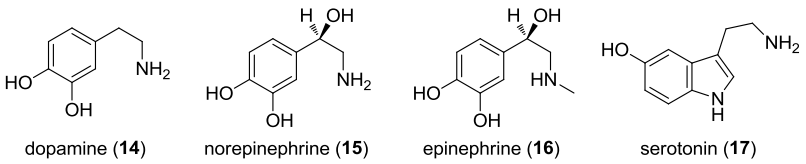

***Figure 5.** Selected catecholamine and monoamine neurotransmitters.*

As a neurotransmitter, dopamine (**14**) is responsible for major brain functions such as motor control, motivation and working memory as well as being an integral part of the brain reward system. Inefficient production of dopamine causes the primary symptoms associated with Parkinson's disease. Catecholamine norepinephrine (**15**) is implicated in alertness, arousal and attentive aspects of the mental faculty and like dopamine is involved in the reward system. Norepinephrine is thought to influence mood and depression; with increased levels of this neurotransmitter alleviating the worst symptoms. Catecholamine epinephrine (**16**) is a

neurotransmitter and a hormone that closely resembles norepinephrine; in its hormonal capacity it controls the "fight or flight" response. Monoamine serotonin (**17**) has a role in modulation of appetite, mood and aggression and as such serotonin receptors are a popular target for drugs that find use in psychiatry and neurology.[7]

The presence of these biogenic amines in the central nervous system may be surprising as many of the amines themselves cannot go through the blood brain barrier. It is known that amino acid precursors are transported across the blood barrier and absorbed into a neuron where appropriate enzymatic transformation yields the neurotransmitter amines. These amines are pooled and transported to nerve terminals and released upon stimulus (**Figure 6**).[7]

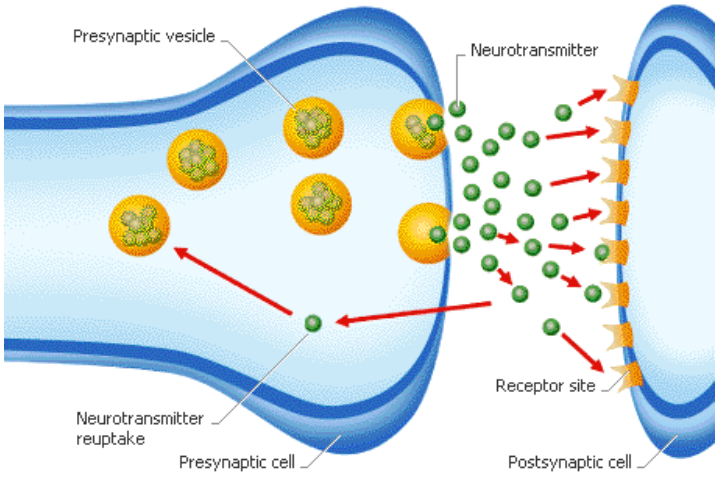

Figure 6. *Release of neurotransmitters.*

1.2 Monoamine oxidase

The level of monoamine neurotransmitters is regulated in the brain by the flavoenzyme monoamine oxidase (MAO). MAO is a FAD (Flavin adenine dinucleotide) dependent enzyme which catalyses aerobic oxidation of monoamines into an imine which then undergoes hydrolysis to yield the corresponding aldehyde, hydrogen peroxide and ammonia (**Reaction 1**).[8] It is by this mechanism that the levels of neurotransmitter amines are regulated and undesirable trace amines inactivated.[9]

$$RCH_2NH_2 + FAD + O_2 + H_2O \xrightarrow{MAO} RCHO + FADH_2 + H_2O_2 + NH_3$$

Reaction 1.

Initially given the name tyramine oxidase,[10] two distinct forms of monoamine oxidase were identified in humans; monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). They are two different proteins with 70% amino acid homology[11] and are most clearly differentiated by the different specificities shown towards substrates; hydrophilic substrates such as serotonin, norepinephrine and epinephrine are chiefly broken down by MAO-A while hydrophobic substrates such as phenylethylamine (**18**) (**Figure 7**) is favoured for oxidation in a reaction catalysed by MAO-B.[12] Both enzymes contain the essential Ser-Gly-Gly-Cys-Tyr sequence at which the FAD co-factor is bound. In terms of relative distribution of the two isoforms MAO-B is found to be the dominant isoform present in the human brain.[9,13]

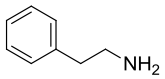

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Figure 7. *Example of a hydrophobic substrate, phenylethylamine.*

A. Monoamine oxidase B and ageing

Unlike other enzymes the activity of MAO-B increases with age, usually beginning at about 60. The activity of MAO-A remains constant throughout life.[9] The increased activity of MAO-B and the additional oxidative stress caused by increased levels of H_2O_2 can lead to neuronal degeneration and is thus implicated in the pathogenesis of neurological diseases such as Alzheimer's disease (*vide infra*).

1.3 Monoamine oxidase inhibitors

A. Use in treating depression

Since the 1950s monoamine oxidase inhibitors (MAOI) have found therapeutic use as antidepressants supported by the 'monoamine hypothesis'; a proposal that postulates depression to be a causal outcome of monoamine (noradrenaline and serotonin) deficit in the limbic regions of the brain.[14] Because these amines are principally degraded by MAO-A, inhibition of MAO-A has been one of the classical ways to treat depression. Irreversible MAO inhibitor iproniazid (**19**) was one of the first drugs used for this purpose.[15] Other drugs of this type include phenelzine (**20**) and tranylcypromine (**21**) (**Figure 8**).[16]

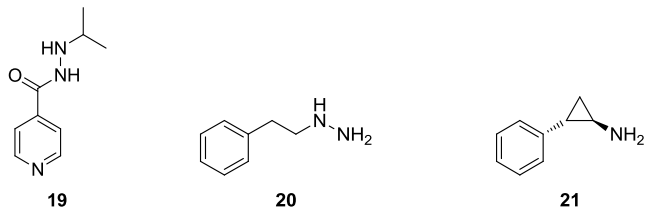

Figure 8. *Selected irreversible MAO inhibitors.*

Despite being effective, these 1st generation MAOI's are either discontinued or reserved as a 'last line of defence" because MAO-A is found in the gut as well as the central nervous system. Unrestrained inhibition of MAO-A entails high levels of exogenous vasopressor agents such as tyramine to be absorbed from tyramine rich foodstuffs. If the diet is not strictly controlled to reduce such intake, a resultant runaway absorption induces the potentially fatal hypertensive reaction (coined in context as "cheese reaction").[17] To address this shortcoming newer generations of MAO inhibitors are reversible and allow for tyramine to displace the drug from the enzyme when necessarily. Moreover, selective inhibition of MAO-B mitigates the danger from the 'cheese effect'. Due to low efficacy, low remission and high treatment-resistant rates of other types of anti-depressants[18] these new generation MAO inhibitors such as moclobemide (selective reversible MAO-A inhibitor, **22**) and selegiline (selective irreversible, MAO-B inhibitor, **23**) are valuable for treating depression (**Figure 9**).[15]

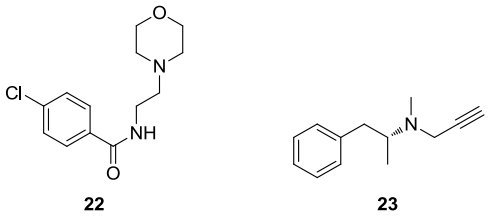

Figure 9. *Selected 2nd generation MAO inhibitors.*

B. Use in treating Parkinson's disease

MAOI's have therapeutic value for the treatment of neurodegenerative diseases outside their traditional anti-depressant role.[11] Of particular note are their potential for treating Parkinson's disease. Parkinson's disease is the onset of the degeneration of melanin-containing neurons often seen in elderly people,[13] caused by deficiency of dopamine in the striatum.[19] Because MAO-B is the predominant isoform in the brain and responsible for dopamine consumption, the selective inhibition of MAO-B allows for continued dopamine activity and thereby

enhances symptomatic motor benefits thus mitigating the symptoms of Parkinson's disease. An example includes the irreversible selective MAO-B inhibitor rasagiline (**24**, **Figure 10**).[13]

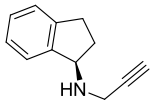

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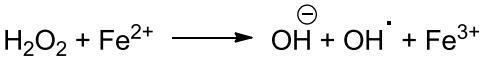
Figure 10. *Irreversible, selective MAO-B inhibitor rasagiline (**24**).*

Oxidative stress caused by generation of hydrogen peroxide by MAO in oxidation of amines has also been implicated in Parkinson's disease[20] and inhibition of MAO would therefore be appropriate for treatment of this disorder.

C. Oxidative stress and treatment of Alzheimer's Disease

The generation of hydrogen peroxide from oxidation of neurological amines by MAO have been detailed (*vide supra*) and this leads to considerable oxidative stress. It is proposed that inhibition of MAO will prevent the formation of peroxides and thus reduce the presence of neurotoxic free radicals that occur *via* the Fenton reaction involving ferrous ions (**Reaction 2**); the finding of accumulated iron in sites of neuron degeneration further supports this hypothesis.[21]



Reaction 2.

Because the pathogenesis of Alzheimer's disease (AD) involves Reactive Oxygen Species (ROS) and the overproduction of ROS leads to synaptic damage, molecules that inhibit MAO-B find use in AD treatment. An example is the hybrid drug ladostigil (**25**), inspired from both MAO inhibitor rasagiline (**24**) and rivastigmine (**26**), a cholinesterase inhibitor (**Figure 11**).[22]

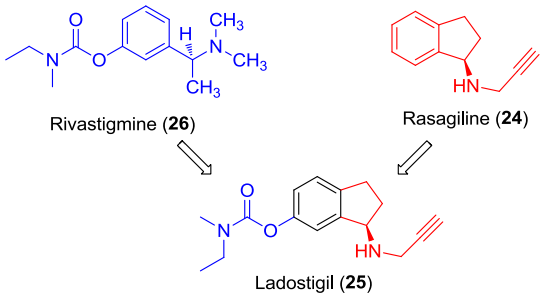


Figure 11. *Hybrid Alzheimer's drug ladostigil (**25**) inspired partly from MAO inhibitor rasagiline (**24**).*

D. Other neuroprotective activity and mechanisms

Synthetic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), (**27**, **Figure 12**) is used academically for inducing and studying symptoms of Parkinson's disease. When it was found that the effects of MPTP could be mitigated by MAO-B inhibitor selegiline (**23**) there was interest in finding neuroprotective benefits in MAOIs. Further studies however have deduced the neuroprotective mechanisms originally attributed to MAO inhibitors to be independent of MAO inhibitory activity.[23] For instance, it was found that selegiline (**23**) and other MAO-B inhibitors enhanced production of nitric oxide (NO) by the enzyme nitric oxide synthase, affording a protective effect on tissues by having an increased ratio of NO levels over O_2.[24]

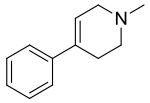


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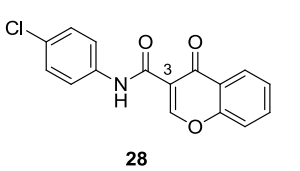
Figure 12. *MPTP (**27**), a synthetic neurotoxin.*

E. Chromones and monoamine oxidase inhibition

Recently it was recognised that chromone scaffolds (1,4-benzopyrone) which bear a carboxamide substituent in position C-3 (for example, **28**, **Figure 13**) act as selective MAO-B inhibitors with IC_{50} values in the nanomolar to micromolar range. Chromones which bear the same type of substituent in position C-2 are largely inactive (for example, **29**, **Figure 13**).[25] The structure of the spiroketal framework of chaetoquadrins A–C (±)-**30** is also shown for comparison.



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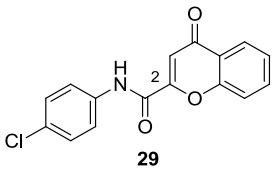
IC_{50}(hMAO-A) = *inactive*

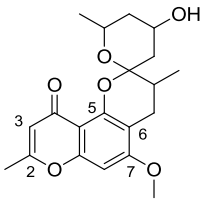
IC_{50}(hMAO-B) = 0.063 ± 0.0042 μM



29

IC_{50}(hMAO-A) = *inactive*

IC_{50}(hMAO-B) = *inactive*



(±)-**30**

Figure 13. *Chromones with biological activity (and inactivity) against hMAO.*

These and similar studies on chromones[26-31] have established that the chromone scaffold is an important pharmacophore for bioactive compounds that inhibit MAO. Chaetoquadrins A–C

(**1**–**3**) represent a unique C-5,6,7-trisubstituted subset of MAO inhibiting chromones which contain a spiroketal.

F. Conclusion

MAO inhibitors are able to induce a wide range of interesting therapeutic properties through increased levels of neurological amines and reduced oxidative stress. The subject of this thesis is concerned with the synthesis of a family of MOAI natural products named the chaetoquadrins which will be discussed in depth in the following sections and chapters.

1.4 Spiroketal chemistry

Spiroketals† are bicyclic ether systems with two oxygen atoms connected to a single quartnery carbon. As they are ubiquitous in nature and exhibit beneficial biological activity they have been the subject of several reviews[32,33,34,35,36,37] some of which have been published by our research group.[38,39,4,40] The majority of spiroketals found in nature feature a 6,6, a 6,5 or a 5,5 system[34] (**Figure 14**) although 7 membered and 4 membered spirocycles are also known.

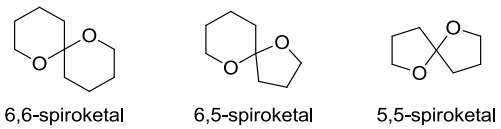


Figure 14. *Nominal spiroketal ring systems.*

The conformation adopted by spiroketals depends on several factors including the anomeric effect.[41] The anomeric effect is a stereoelectronic effect where the net stabilisation of a system is realised through the overlapping of the non-bonding oxygen orbital (HOMO) with the antibonding σ* orbital (LUMO) of the adjacent C–X bond. In a pyranoid ring, this requires the nonbonding electrons of the oxygen and the anti-bonding σ* orbital of the heteroatom to be arranged in a periplanar fashion. The anomeric heteroatom is required to adopt a sterically demanding axial orientation for this to occur (**Figure 15**).[34]

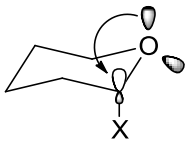


Figure 15. *Anomeric effect on a pyranoid system. Note that the generic heteroatom (represented here as X) is occupying an axial position, enabling the axial lone pair of the oxygen to donate into the C-X* ***σ***** orbital.*

Thus for a 6,6-spiroketal three conformations are possible (**Figure 16**); the bis-axial arrangement (**Figure 16**, A), whereby the lone pairs of both oxygens can effectively donate into the empty antibonding orbital of the C-O bond, representing two anomeric effects for the spiroketal. This is the thermodynamically most stable conformation and is commonly encountered in natural products including chaetoquadrin A (**Figure 16**, A2). An axial-equatorial arrangement is also possible (**Figure 16**, B) where only one oxygen lone pair can

† The spiroketal ring systems are also known as spiroacetals. The term "spiroketals" has been used throughout this thesis.

effectively donate into the empty antibonding orbital of a C-O bond. For the equatorial-equatorial spiroketal arrangement (**Figure 16**, C), no oxygen lone pairs can donate into any empty antibonding orbital of the C-O. This particular spiroketal is therefore non-anomeric.

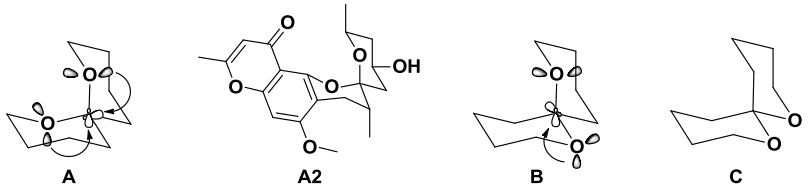


Figure 16. *The anomeric effect of spiroketals represented by a 6,6-spiroketal system.*
A*: double anomeric effect.* ***A2****: chaetoquadrin A.* ***B****: mono anomeric effect.* ***C****: no anomeric effect.*

Although the anomeric effect is a powerful predictor, during spiroketal construction other considerations[35] such as intramolecular hydrogen bonding[42] and chelation effects[43] also play an important role in determining the ultimate conformation of a spiroketal.

There are many methods reported in the literature for the synthesis of spiroketals and this thesis does not provide an exhaustive list. To illustrate some of the general methods available for the construction of spiroketals, a figure from a recent review on the "*Synthesis of 5,6- and 6,6-Spirocyclic Compounds*" written by our research group is reproduced here with permission (**Figure 17**).[44]

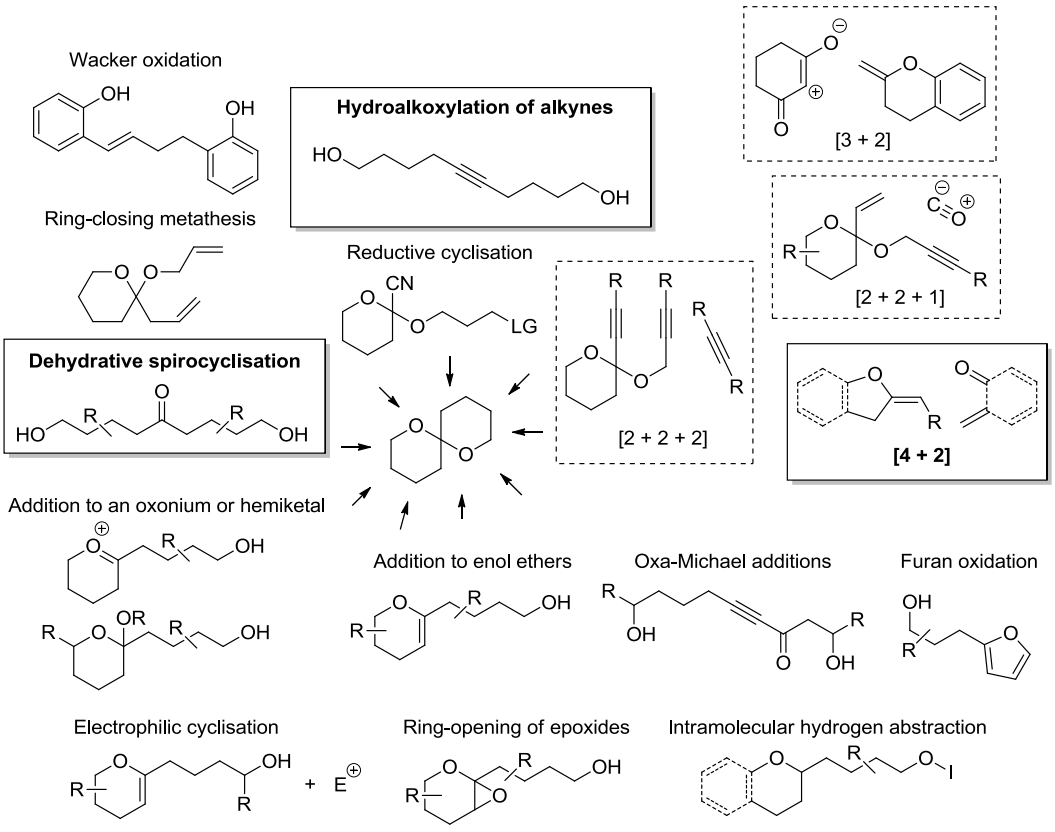
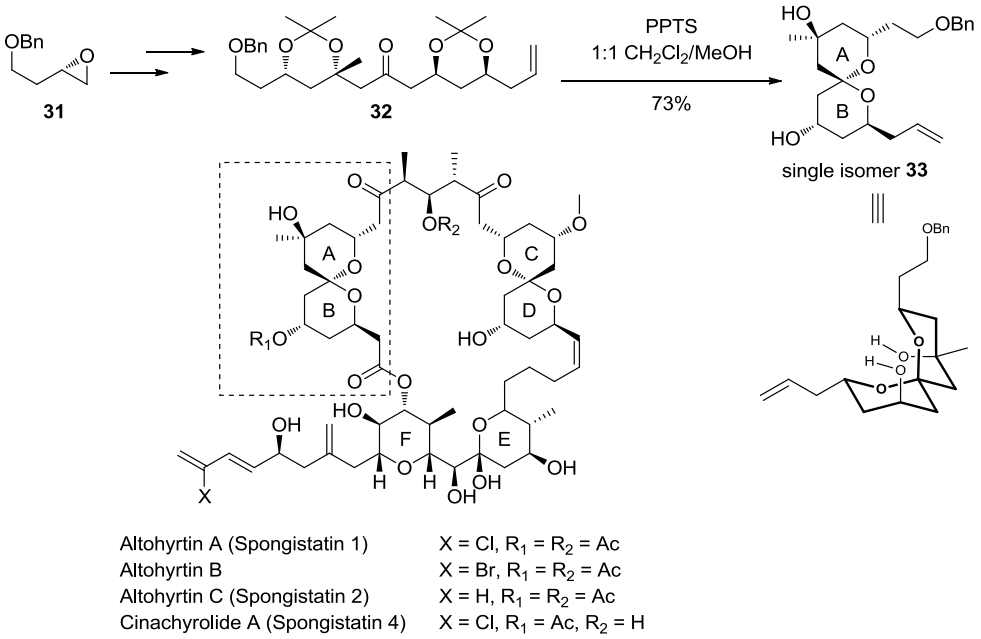


Figure 17. *Methods for the synthesis of spiroketals.*

Of these known methods, three specific methods (boxed in **Figure 17**) used in the recent synthesis of selected 6,6-, 6,5-, and 5,5-spiroketals will be presented in the following section. It is hoped that this brief discussion will also serve to illustrate some of the different factors which influence the ultimate stereochemistry adopted by a given spiroketal in the context of a practical, chemical synthesis.

A. Acid catalysed tandem deprotection-dehydrative cyclisation strategy: synthesis of the AB 6,6-spiroketal of spongistatin by Allais and Cossy

The acid catalysed, dehydrative diol deprotection/cyclisation sequence is by far the most common and general strategy used for the synthesis of spiroketals. Allais and Cossy executed this strategy to construct the AB spiroketal of spongistatin (**Scheme 1**).[45] Chiral epoxide **31** was elaborated to afford the protected linear spiroketal precursor **32**. Subjection of this precursor to pyridinium *p*-toluenesulfonate (PPTS) concomitantly deprotected the acetonide and the resultant diol cyclised on to the central carbonyl, forming the 6,6-spiroketal **33** as a single isomer which benefits from double anomeric stabilisation as present in the natural product.

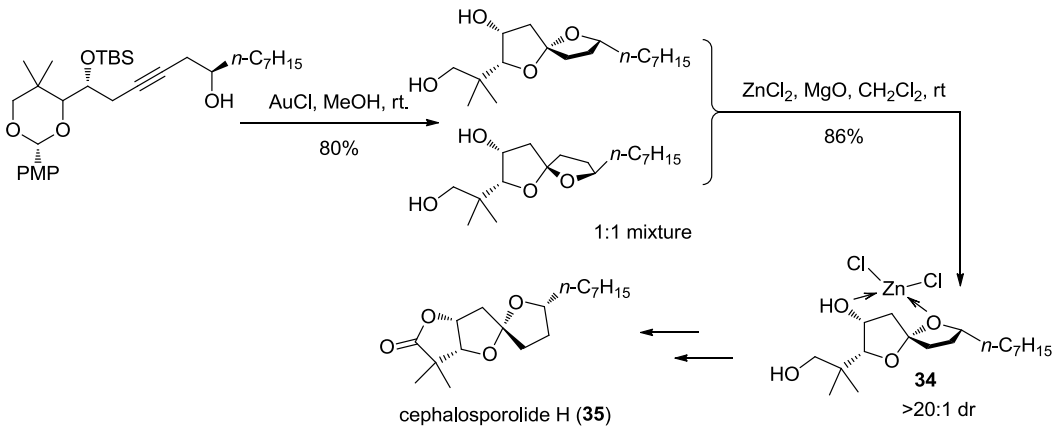


Scheme 1. *Synthesis of the AB 6,6-spiroketal of spongistatin by Allais and Cossy.*[45]

Like the above spongistatins, our synthetic targets chaetoquadrins A–C also feature a double anomerically stabilised 6,6-spiroketal.

B. Gold induced cycloisomerisation of alkyne and subsequent chelation control: synthesis of the 5,5-spiroketal of cephalosporolide H by Tlais and Dudley

In general, the absence of the anomeric effect in 5,5-spiroketals caused by geometrical constraints resulting from the pseudoaxial/pseudoequatorial relationship of substituents on less sterically defined conformations in five membered rings, mandate the spiroketals to be formed as a ~1:1 mixture of anomers as was the case for the Brimble synthesis of cephalosporolide E and F.[46] Targeting molecules in the same family, Tlais and Dudley[43] employed a gold induced cycloisomerisation to form the 5,5-spiroketal as a 1:1 anomeric mixture which when treated with $ZnCl_2$, formed the kinetically favoured spiroketal **34** resulting from chelation control. This spiroketal intermediate was then elaborated to cephalosporolide H (**35**) (**Scheme 2**).

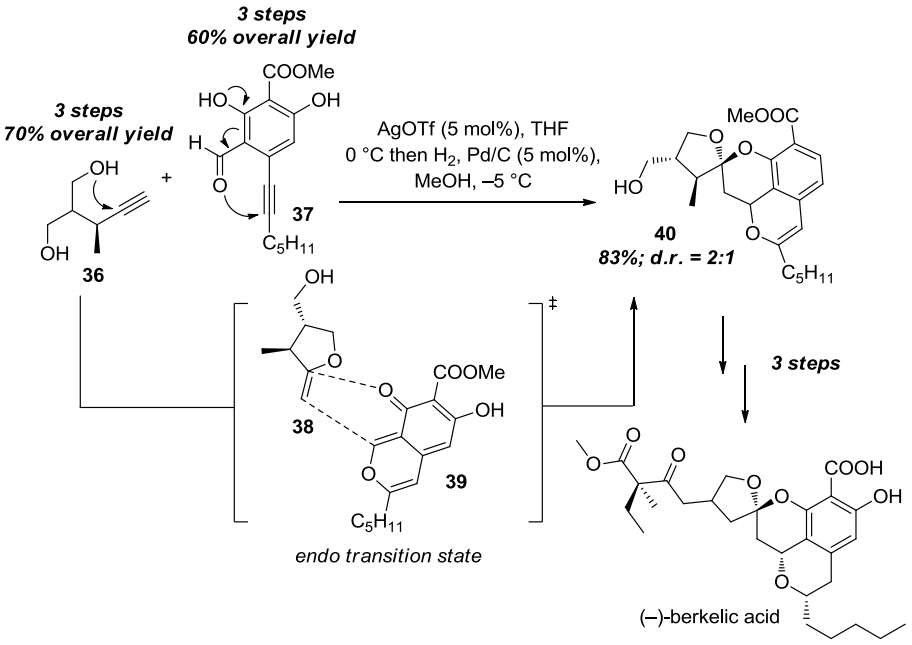


Scheme 2. *Synthesis of reported structure of cephalosporolide H (**35**) by Tlais and Dudley.*

C. Hetero Diels-Alder strategy: synthesis of the 5,6-spiroketal of berkelic acid by Fañanás and co-workers

Pettus and co-workers proposed to construct the chiral 5,6-spiroketal of berkelic acid using an inverse demand Diels-Alder reaction[47] and applied this methodology in 2010 to complete a total synthesis of berkelic acid.[48] Perhaps inspired by this work, in 2012 Fañanás and co-workers successfully executed a short (7 linear steps) gram-scale synthesis of berkelic acid relying on a similar hetero Diels-Alder reaction as the key step (**Scheme 3**).[49] From terminal acetylene **36** and aromatic aldehyde **37** the entire tricyclic core of berkelic acid was synthesised using an impressive silver-catalysed one-pot reaction *via in situ* formation of both *o*-quinonemethide **39** and enol ether **38**. The hetero Diels-Alder cycloaddition afforded 6,5-spiroketal **40** as a 2:1 diastereomeric mixture favouring the stereochemistry present in the

natural product. It is noteworthy that the stereochemistry present in the spiroketal system was dependent on the facial selectivity of the Diels-Alder reaction.



Scheme 3. *Diels Alder approach to 6,5-spiroketal of berkelic acid by Fañanás and co-workers.*

1.5 Chromone chemistry

In addition to the double anomerically stabilised 6,6-spiroketal, our target molecules chaetoquadrins A–C feature a chromone moiety fused to the spiroketal ring system. There are many methods available for construction of chromones reported in the literature and some of these methods are illustrated below (**Figure 18**).[50]

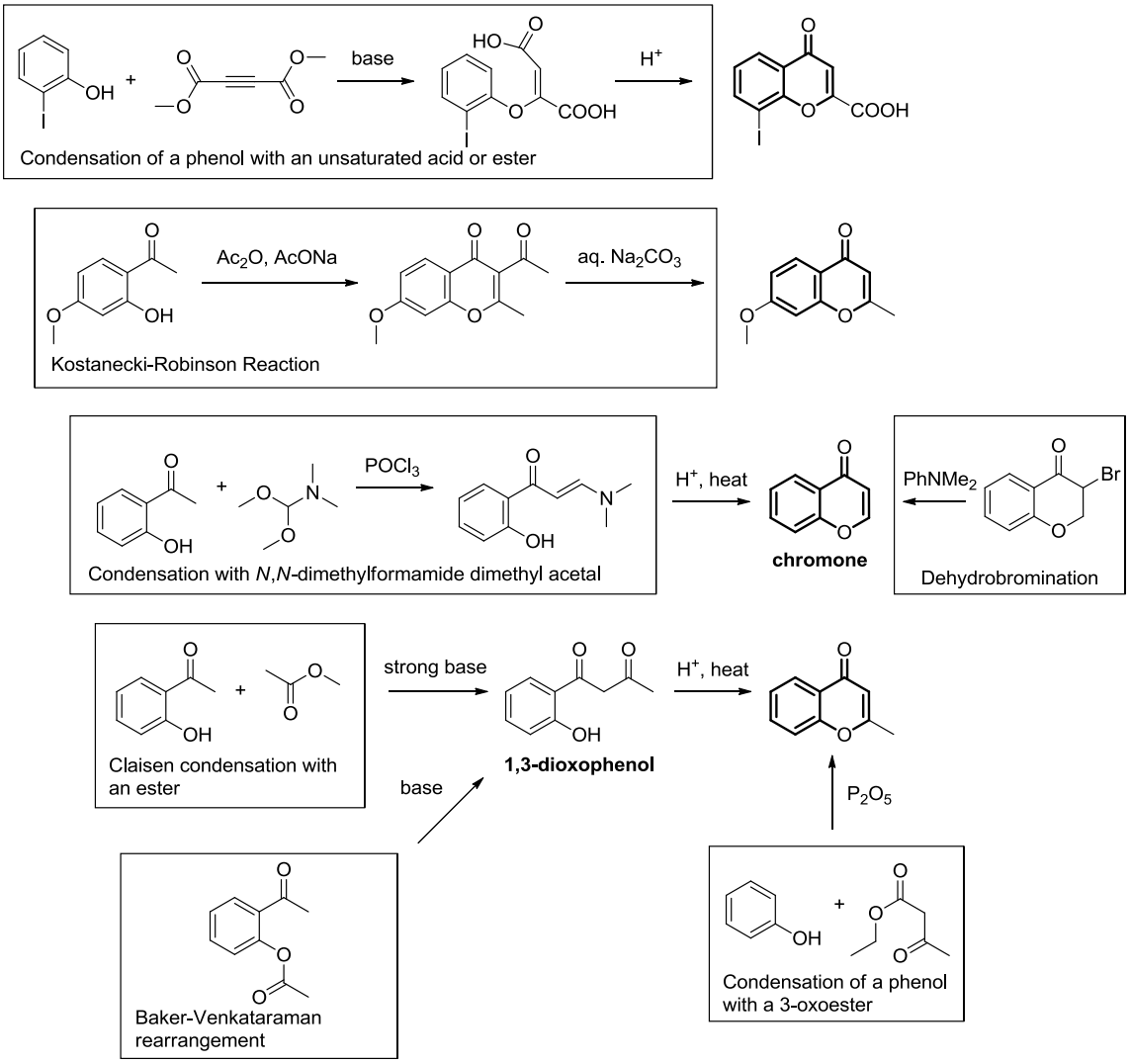
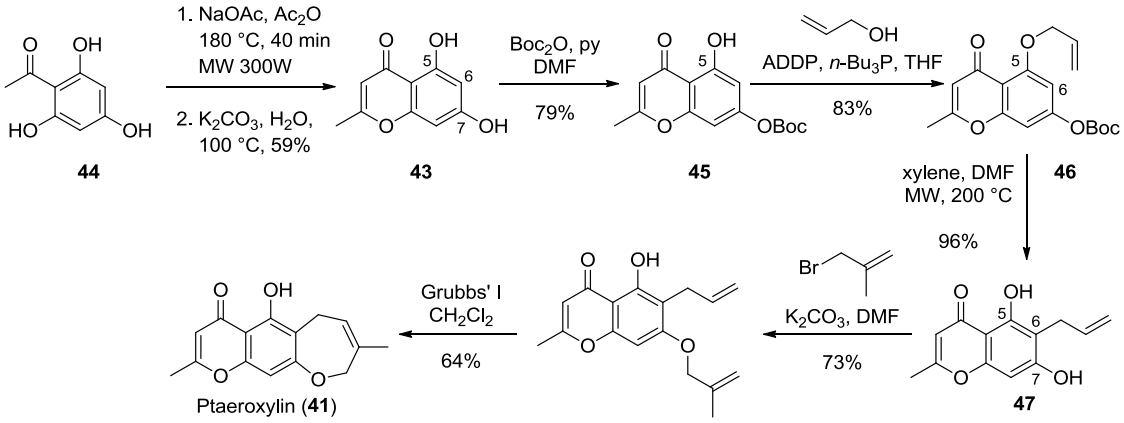


Figure 18. *Some selected methods for the synthesis of chromones.*

In the following section two syntheses of relevant chromone-containing natural products are detailed. First, the synthesis of the chromone natural product ptaeroxylin **41** (**Scheme 4**) by Moody and co-workers[51] is described followed by Li and Nicolaou's impressive synthesis of 1-*O*-methylforbesione **42** (**Scheme 5**).[52]

A. Synthesis of ptaeroxylin by Moody and co-workers

Ptaeroxylin **41** (**Scheme 4**) is a oxepino[3,2-g]chromone isolated from *Ptaeroxylon obliquumm*, commonly known as "sneezewood". To verify the original structural assignment of ptaeroxylin, Moody and co-workers undertook a short synthesis.[51] Noreugenin (**43**) was first prepared from 2,4,6-trihydroxyacetophenone (**44**) *via* microwave assisted Kostanecki–Robinson reaction. Next, a selective mono-Boc protection of chromone **43** (noreugenin) afforded Boc-protected noreugenin **45**. Allylation of the remaining phenol using Mitsunobu reaction with allyl alcohol, azodicarbonyldipiperidide (ADDP) and tri-*n*-butylphosphine afforded allyl phenyl ether **46** in high yield which underwent aromatic Claisen rearrangement to afford olefin **47**. The Boc protecting group was also cleaved under these reaction conditions. Selective alkylation of the C-7 phenol was followed by intramolecular RCM to afford the natural product **41**. This synthesis illustrates some strategies used in the course of our work directed towards the same heterocyclic framework; i. Selective alkylation of a C-7 phenol, ii. use of the C-5 phenol as a "handle" to create a C–C bond at C-6 using an aromatic Claisen rearrangement.



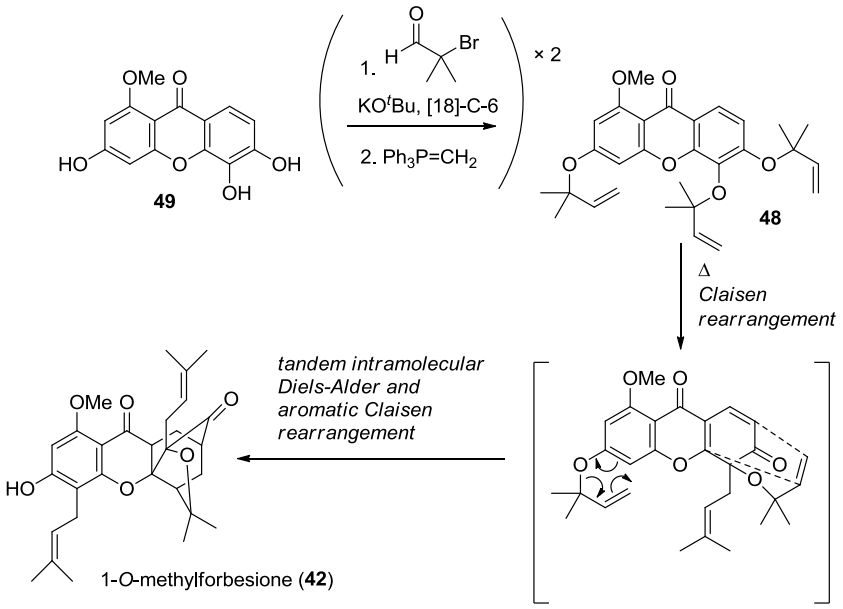
Scheme 4. *Synthesis of ptaeroxylin by Moody and co-workers.*

B. Synthesis of 1-O-methylforbesione by Li and Nicolaou

Li and Nicolaou employed a tandem Claisen rearrangement–intramolecular Diels-Alder sequence to rapidly complete the synthesis of the natural product 1-*O*-methylforbesione **42** (**Scheme 5**).[52] Construction of the Claisen precursor **48** was done in a stepwise fashion whereby the free phenols in the starting material **49** were all alkylated with *α*-bromoisobutyraldehyde followed by Wittig olefination. The alkylation–Wittig strategy is described to be efficient and high yielding and in this particular synthesis critical as other approaches to construct the phenyl aryl ether were unrewarding. The alkylation-Wittig-

Claisen strategy was used with success during our investigations (see **Chapter 3**, S**ection 3.2 B**, *vide infra*).

Subjection of the Claisen precursor **48** to heat effected the tandem aromatic Claisen rearrangement–Diels-Alder sequence which afforded the desired 1-*O*-methylforbesione (**42**) in 63% yield as the major product along with several regioisomers arising from the non regioselective Claisen rearrangement.



Scheme 5. *Synthesis of 1-O-methylforbesione by Li and Nicolaou.*

1.6 Proposed synthesis of chaetoquadrins A–C

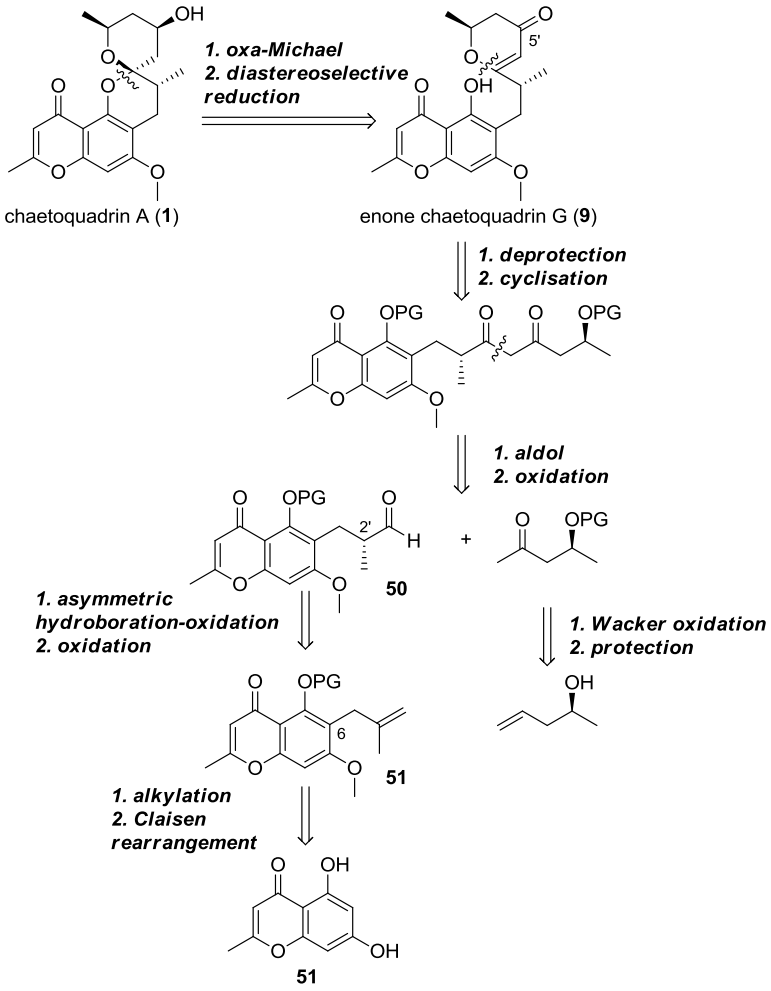
A. Aim of the present research

To the best of our knowledge none of the chaetoquadrins have been the subject of synthetic efforts to date. As alluded to in the previous sections our research aim was to achieve the first synthesis of the structurally complex spiroketal chaetoquadrins A–C.

B. First generation approach; Synthesis of the spiroketal chaetoquadrins A–C via enone chaetoquadrins G and H

It was thought that enone chaetoquadrin G (**9**) was a biosynthetic precursor to the spiroketal chaetoquadrin A (**1**). With this in mind, our original synthetic strategy hinged on completing the synthesis of enone chaetoquadrin G (**9**) *via* an aldol-oxidation-cyclisation sequence from aldehyde **50**, itself accessed by asymmetric hydroboration-oxidation chemistry from C-6 substituted 1,1-disubstituted terminal olefin **51** (**Scheme 6**). A key oxa-Michael reaction of

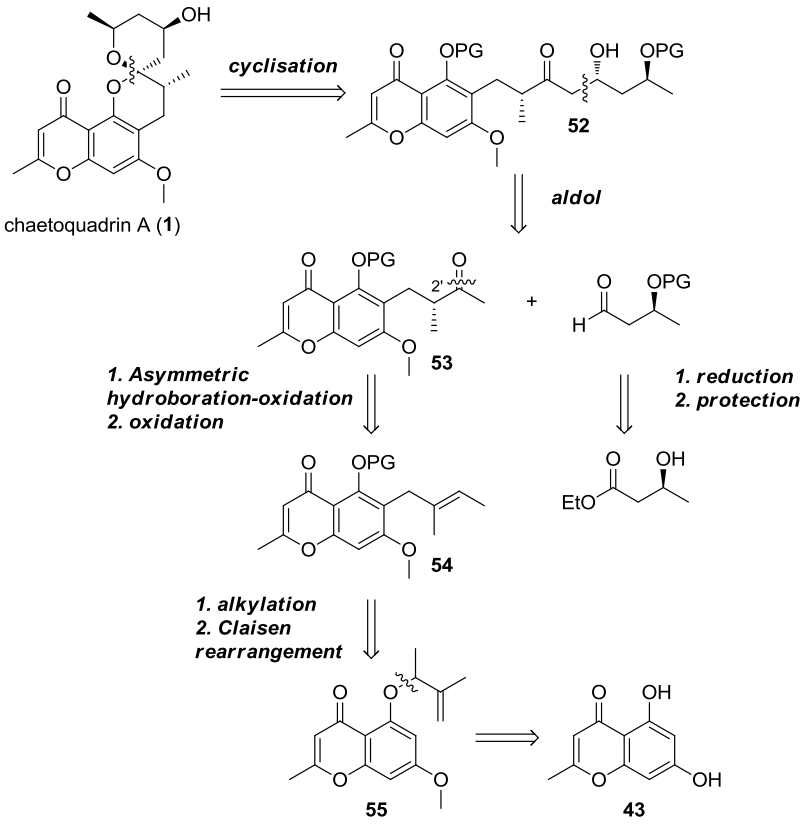
the enone chaetoquadrin G (**9**) was then proposed to access the spiroketal ring system. Subsequent diastereoselective reduction of the C-5´ ketone of **9** would then furnish the spiroketal natural product chaetoquadrin A (**1**).



Scheme 6. *First generation retrosynthetic analysis of chaetoquadrin A.*

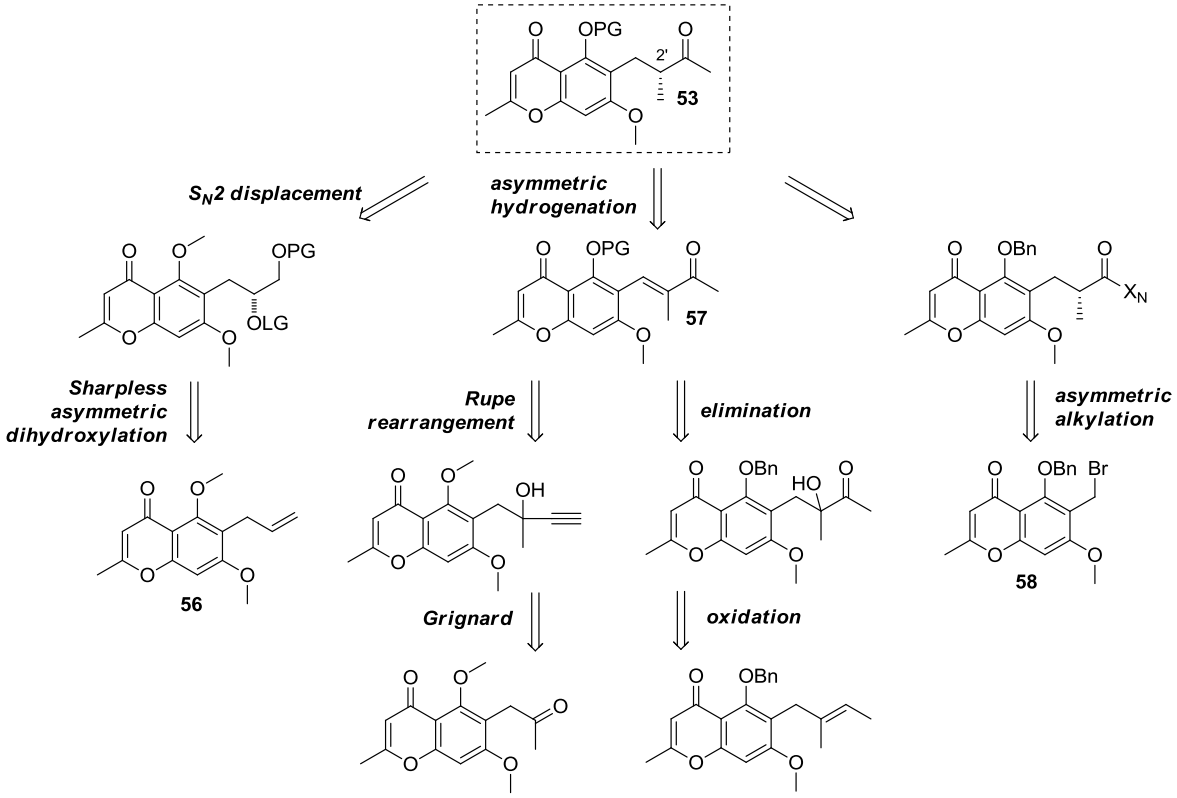
C. Second generation approach: Use of an natural aldol disconnection

Upon failure of our initial plan we re-examined the oxidation levels of the cyclisation precursor to reveal an alternative aldol disconnection from bis-hydroxy ketone **52** (**Scheme 7**). This convergent route would enable access to the spiroketal chaetoquadrins without the use of an enone intermediate. The required methyl ketone **53** was envisioned to be derived from asymmetric hydroboration-oxidation of trisubstituted olefin **54**. This olefin was to be accessed *via* Claisen rearrangement of the terminal olefin **55**, itself available from natural chromone noreugenin (**43**).



Scheme 7*. Second generation retrosynthetic analysis.*

Ultimately it was found that use of asymmetric hydroboration-oxidation to afford enantioenriched aldehyde **50** (**Scheme 6**) or ketone **53** (**Scheme 7**) was unsatisfactory although the synthetic strategy depicted was workable. Thus several alternative strategies to install the chiral centre at C-2′ in ketone **53** were investigated (**Scheme 8**).



Scheme 8. *Retrosynthetic analysis of α-chiral β-arylated carbonyl* ***53****.*

Firstly, we envisaged that chiral centre at C-2´ in ketone **53** could be prepared *via* an asymmetric Sharpless dihydroxylation of alkene **56**. The secondary alcohol in the resultant diol could be converted into a leaving group then displaced in an S_N2 fashion (**Scheme 8**). Alternatively, α,β–unsaturated carbonyl **57** was envisaged to be a suitable substrate for asymmetric hydrogenation. Finally, use of a chiral auxiliary to install the desired stereochemistry *via* an asymmetric alkylation reaction with benzyl bromide **58** was also a possibility.

After successful total synthesis of the spiroketal chaetoquadrins A–C (see **Chapter 4**, **Section 4.3** and **4.4**) we were also able to extend the established synthetic methodology to access other chaetoquadrins in the family including chaetoquadrins H and I. The retrosynthetic analysis of these compounds and their successful synthesis will be detailed in later sections (**see Chapter 4**, **Section 4.6** and **4.7**).

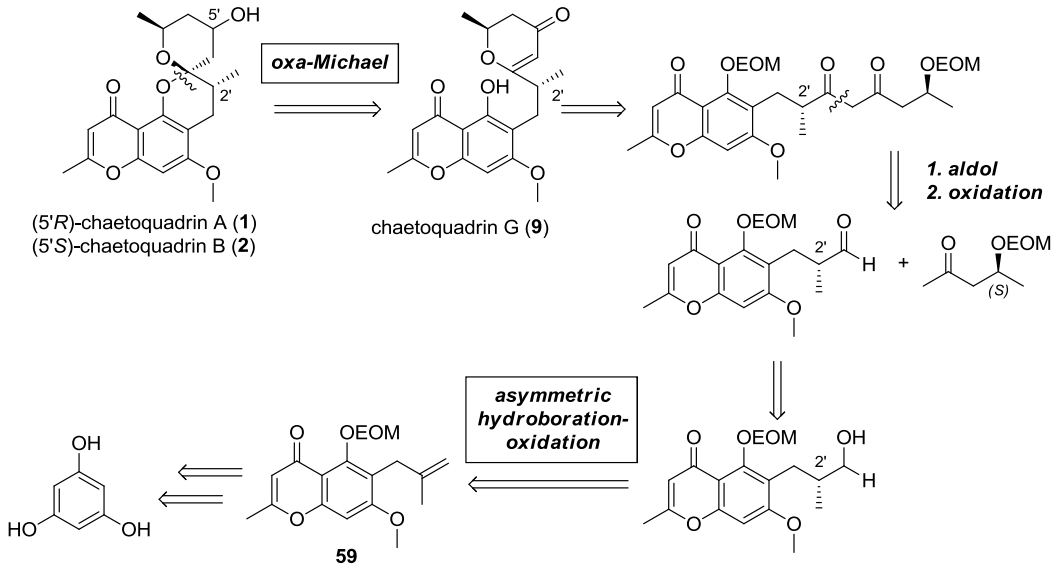
Chapter Two

Results and Discussion

Synthesis of (±)-chaetoquadrins G and H

2.0 Overview

Attention focused on the execution of a synthetic strategy towards the spiroketal chaetoquadrins based on two pivotal steps; i. construction of the spiroketal moiety of chaetoquadrins A (**1**) and B (**2**) *via* intramolecular oxa-Michael reaction on the bis-pyranone natural product **9** and ii. installation of the C-2′ stereocentre of chaetoquadrins A and B *via* use of asymmetric hydroboration-oxidation of 1,1-disubstituted terminal olefin **59** (**Scheme 9**). Unfortunately the C-2′ stereocentre of the chaetoquadrins was unable to be accessed *via* asymmetric hydroboration-oxidation of olefin **59**. Furthermore, although bis-pyranone natural product **9** was successfully synthesised in racemic form, the key intramolecular oxa-Michael reaction to access the spiroketal moiety of chaetoquadrins A and B proved difficult to execute. Faced with this failure, it was decided to modify the synthetic strategy which is discussed in **Chapter 3**.

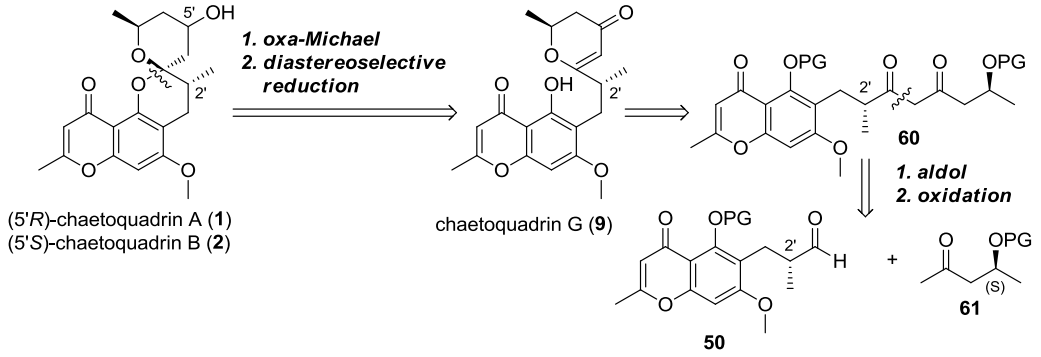


Scheme 9. *Initial synthetic strategy towards spiroketal chaetoquadrins. The key steps are highlighted.*

2.1 Retrosynthetic analysis of spiroketal chaetoquadrins via oxa-Michael disconnection to enone chaetoquadrins

It was thought that enone chaetoquadrin G (**9**) was a biosynthetic precursor to spiroketal chaetoquadrins A (**1**) and B (**2**). With this idea in mind, our original strategy hinged on the initial synthesis of enone chaetoquadrin G (**9**) (**Scheme 10**). Execution of a key intramolecular oxa-Michael reaction on chaetoquadrin G (**9**) would furnish a spiroketal which could then be elaborated to chaetoquadrin A (**1**) or B (**2**) *via* diastereoselective reduction.

Enone chaetoquadrin G (**9**) was envisaged to be accessible from the linear precursor 1,3-diketone **60** which could be assembled *via* aldol reaction between aldehyde **50** and ketone **61** followed by oxidation of the aldol adduct. While methyl ketone **61** could be made succinctly *via* protection and reduction of (*S*)-ethyl 3-hydroxybutanoate, initial attention was directed to the synthesis of aldehyde **50**.



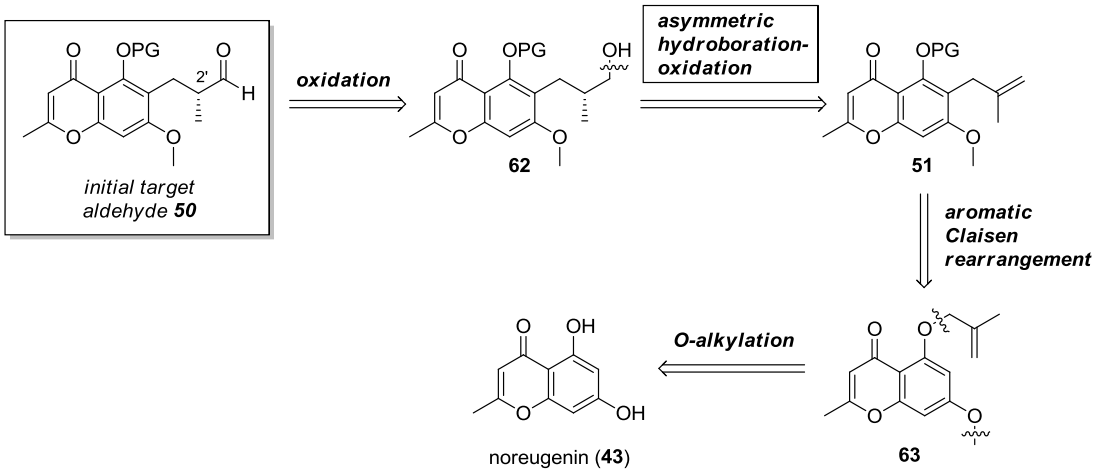
Scheme 10. *Retrosynthetic analysis of chaetoquadrins A (**1**), B (**2**) to aldehyde **50** and ketone **61**.*

2.2 Retrosynthetic analysis of aldehyde 50 via asymmetric hydroboration-oxidation strategy

A feasible retrosynthetic analysis for aldehyde **50** was required. To date there are only a few reported approaches to construct α-chiral β-arylated scaffolds.[53] We therefore foresaw the installation of the C-2′ stereogenic centre of aldehyde **50** to be a particular challenge.

At the start of this project, Soderquist *et al.* reported a new reagent based on the 10-substituted-9-borabicyclo[3.3.2]decane scaffold to tackle previously problematic asymmetric hydroboration-oxidations of 1,1-disubstituted terminal olefins.[54] We were excited to design our strategy based on this novel, newly reported reagent and perhaps be the first investigators to find application of this reagent in the setting of natural product synthesis. Aldehyde **50** was

therefore envisaged to be accessed *via* an asymmetric hydroboration-oxidation of 1,1-disubstituted terminal olefin **51** followed by oxidation of the resultant alcohol **62** (**Scheme 11**). The hydroboration precursor **51** was to be accessed *via* aromatic Claisen rearrangement of phenyl ether **63** which could be accessed *via O*-alkylation of noreugenin (**43**).

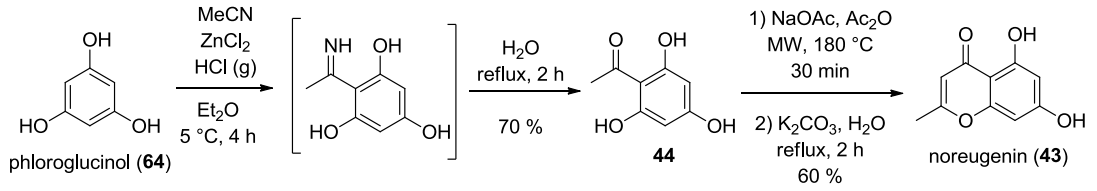


Scheme 11. *Retrosynthetic analysis of aldehyde **50**.*

Following this strategy to access the chaetoquadrins our initial objective was to construct aldehyde **50**.

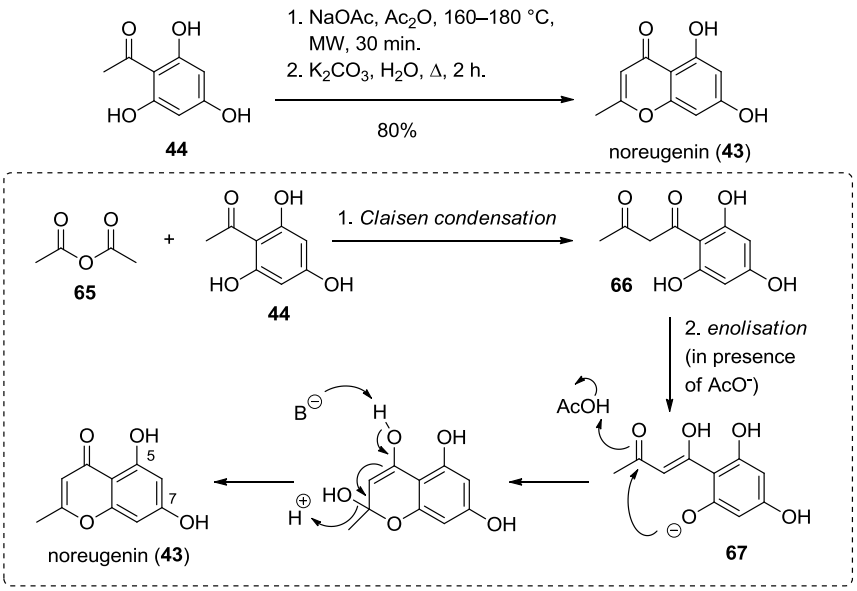
2.3 Chromone synthesis and aromatic Claisen rearrangement

Our synthetic effort initially required gram-scale access to chromone **43**. Known as noreugenin, this natural product could be accessed *via* Kostanecki-Robinson reaction[55] (referred to also as the Allan-Robinson reaction)[56] of 2,4,6-trihydroxyacetophenone (**44**) ($13 NZD/g, Sigma Aldrich, 2013). In the interest of economy we decided to start our synthesis one step further back using phloroglucinol (**64**) ($2 NZD/g) (**Scheme 12**). This compound could be acetylated on a 40 g scale using a literature protocol affording **43** in synthetically useful quantities.[57]



Scheme 12. *Synthesis of noreugenin (**43**).*

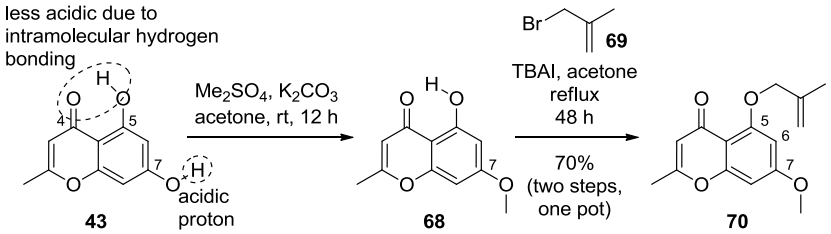
There are two procedures to transform 2,4,6-trihydroxyacetophenone **44** to noreugenin; the conventional thermal method (which requires strong bases such as NaH or LiH)[58-60] and the microwave method, where **44** is treated with sodium acetate and acetic anhydride under microwave irridation at 180 °C for 30 min followed by basic hydrolysis.[51] In our hands the use of the microwave method gave better results affording 60% of noreugenin over two steps. In contrast, the thermal method yielded only trace amounts of the desired product. The mechanistic details for this Kostanecki-Robinson synthesis are illustrated below (**Scheme 13**).[61] Claisen condensation between anhydride **65** and methyl ketone **44** delivers 1,3-dicarbonyl **66** which enolises to **67**. Subsequent cyclisation followed by dehydration affords the pyranone moiety of noreugenin (**43**). This microwave protocol was employed on a 2 g scale due to the limitation of the size of the microwave vessel available.



Scheme 13. *Reaction mechanism of Kostanecki-Robinson reaction for noreugenin synthesis.*

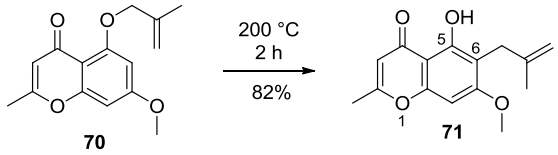
With gram quantities of noreugenin available, further functionalisation of the chromone could commence (**Scheme 14**). All the chromone-based chaetoquadrins (including the spiroketal chaetoquadrins A–C) feature a methylated phenol at C-7. The C-5 phenol meanwhile had to be functionalised to form an allyl ether in anticipation of the aromatic Claisen rearrangement. The intramolecular hydrogen bonding between the C-5 phenol and the C-4 carbonyl group effectively reduces the reactivity of the C-5 phenol. Selective *O*-alkylation of the C-7 phenol followed by *O*-alkylation of the C-5 phenol could be achieved on **43** using a one-pot procedure whereby the initial chemoselectivity was realised by conducting the reaction at room temperature using dimethyl sulfate and potassium carbonate in acetone for 12 h to

afford C-7 methylated chromone **68**. Heating this reaction mixture at reflux effected alkylation of the C-5 phenol after the addition of bromide **69** in the same pot. Following this strategy access to allyl phenyl ether **70** was enabled on a multi-gram scale.



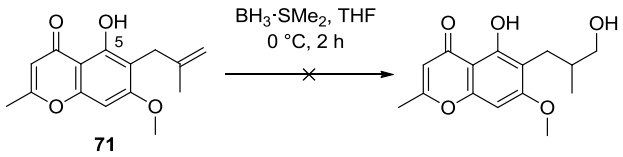
Scheme 14. *One pot synthesis of allyl ether **70**.*

The aromatic Claisen rearrangement is a [3,3]-sigmatropic rearrangement of an allyl phenyl ether effected at high temperatures to afford an *ortho*-substituted phenol. The thermal robustness of chromones have allowed this transformation to serve as a powerful tool to functionalise chromones at the C-6 position. Heating the Claisen precursor **70** neat and open to air at 200 °C for 2 h effected this rearrangement to afford olefin **71** in 82% yield (**Scheme 15**).



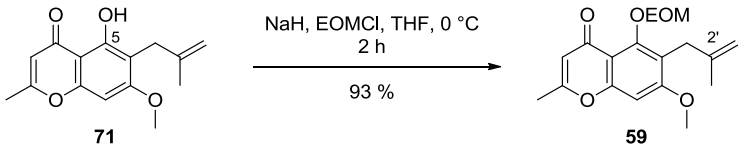
Scheme 15. *Aromatic Claisen rearrangement to afford C-6 substituted chromones.*

The successful Claisen rearrangement resulted in formation of a C-5 phenol **71**. Construction of the desired aldol partner aldehyde **50** mandated oxidation of the alkene **71**. Unfortunately hydroboration-oxidation of olefin **71** met with failure as the free phenol of **71** readily reacts with the borane, hindering this transformation (**Scheme 16**). Consequently, a protecting group for the C-5 phenol was required.



Scheme 16. *Failed hydroboration-oxidation reaction of olefin **71**.*

With the eventual one-pot acid catalysed tandem deprotection/cyclisation sequence in mind, acid labile ethoxymethyl ether (EOM) group was chosen as the C-5 phenol protecting group. Thus, treatment of phenol **71** with sodium hydride in the presence of chloromethyl ethyl ether (EOMCl) proceeded smoothly at 0 °C in 2 h to afford olefin **59** in 93% yield (**Scheme 17**).

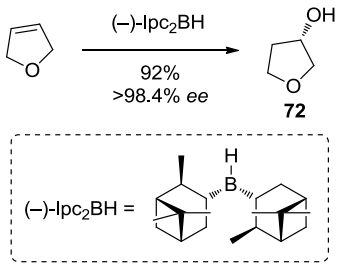


Scheme 17. *EOM protection of olefin **71**.*

With the protected olefin in hand, installation of the key chiral centre at C-2´ of chaetoquadrins using an asymmetric hydroboration-oxidation reaction was next envisaged.

2.4 Attempted asymmetric hydroboration-oxidation of olefins 59, 75 and synthesis of aldehyde (±)-78

Hydroboration-oxidation is a widely used reaction to afford alcohols from olefins using organoborane reagents. Use of an optically active borane such as diisopinocampheylborane (Ipc_2BH) enables asymmetric installation of the oxygen functionality, sometimes with remarkable efficacy as illustrated by the synthesis of furan alcohol **72** below (**Scheme 18**).[62]



Scheme 18. *Asymmetric hydroboration-oxidation with (–)–diisopinocampheylborane.*[62]

When planning to use asymmetric hydroboration-oxidation in synthesis it is desirable to examine the olefin (alkene) substrates which can be classified into different "types" (**Figure 19**) in order to predict their suitability as substrates for asymmetric hydroboration-oxidation.[63] The 2,5-dihydrofuran in the above example can be classified as a type II olefin which is known to give optimal results when using diisopinocampheylborane as the chiral borane reagent.[64]

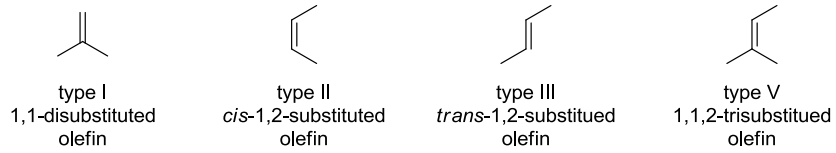
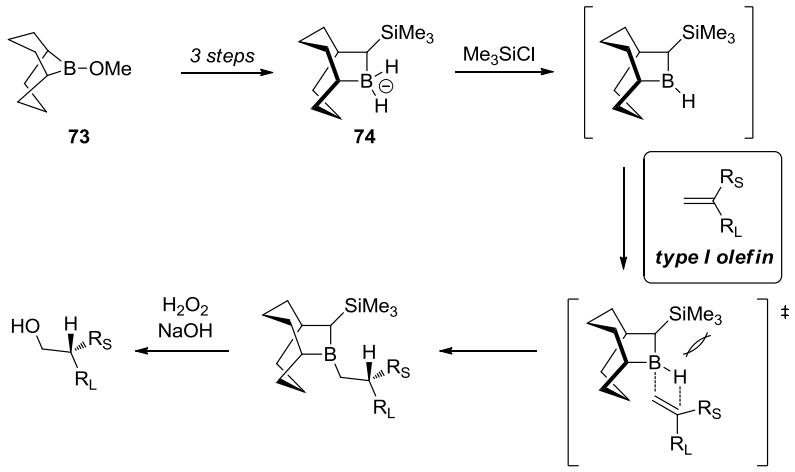


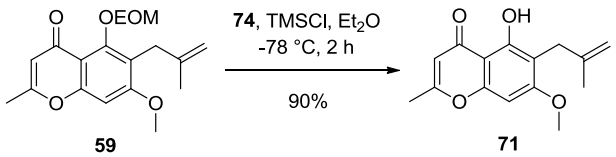
Figure 19. *Olefin (alkene) class.*

Notably, our olefin substrate **59** (**Scheme 17**) is a type I olefin. Olefins of this type (1,1-disubstitued terminal olefin) are known to be a notoriously poor substrates for asymmetric hydroboration-oxidation. As alluded to previously, Soderquist and co-workers recently developed a new asymmetric hydroboration reagent designed specifically to tackle type I olefins[54] (**Scheme 19**) a deed heralded by Aggarwal as the "*ultimate challenge in asymmetric synthesis*".[64] The novel reagent was prepared in 3 steps starting from *B*-methoxy-9-BBN (**73**) to afford hydride **74**, which in the presence of Me_3SiCl generates reactive borane *in situ* to facilitate hydroboration-oxidation of type I olefins.



Scheme 19. *Synthesis and use of hydride **74** by Soderquist et al.*[54]

Unfortunately, addition of hydride **74** to olefin **59** with TMSCl in Et_2O at –78 °C to room temperature for 2 h only resulted in deprotection of the EOM group to afford phenol **71** (**Scheme 20**).

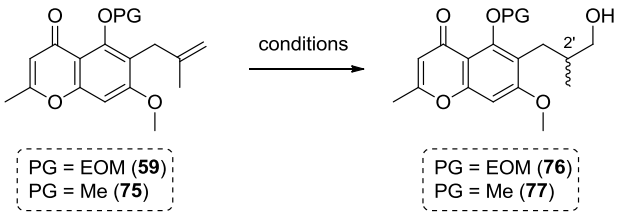


Scheme 20. *Attempted asymmetric hydroboration-oxidation of olefin **59** with hydride **74**.*

Faced with this setback H. C. Brown's traditional asymmetric hydroboration-oxidation reagents such as the diisopinocampheylborane[65] and monoisopinocampheylborane–TMEDA complex[66,67] were investigated using EOM-protected olefin **59** and methoxy-protected olefin **75**‡ to afford their respective alcohols **76** or **77** (**Table 1**).

As expected the *ultimate challenge* was unable to be overcome as no asymmetric induction was observed using type I olefins **59** and **75** (entries 1–4, 0% *ee*). Furthermore, the yields obtained for this transformation were disappointing.

Leaving this problem aside, subsequent synthetic steps were explored by using a racemic hydroboration-oxidation reaction. This was achieved by treating olefin **59** with $BH_3 \cdot SMe_2$ in THF at 0 °C for 2 h to afford alcohol **76** in 43% yield (entry 5).

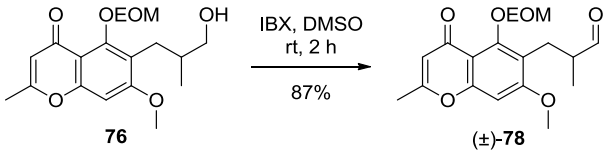


Entry	Protecting group	Conditions	Result
1	PG = EOM	(+)–TMEDA·2IpcBH$_2$	decomposition
		$BF_3 \cdot OEt_2$, THF, –30 °C to 0 °C, 2 h	
2	PG = Me	(+)–TMEDA·2IpcBH$_2$	23%, 0% *ee*
		$BF_3 \cdot OEt_2$, THF, –30 °C to 0 °C, 2 h	
3	PG = EOM	(+)–Ipc$_2$BH, THF, rt, 2 h	35%, 0% *ee*
4	PG = Me	(+)–Ipc$_2$BH, THF, rt, 2 h	31%, 0% *ee*
5	PG = EOM	$BH_3 \cdot SMe_2$, THF, 0 °C, 2 h	43%, 0% *ee*

Table 1. *Asymmetric hydroboration-oxidation of 1,1-disubstituted terminal olefin **59** and **75**.*

Oxidation of the newly formed primary alcohol **76** was accomplished by treatment with 2-Iodoxybenzoic acid (IBX) in DMSO (dimethyl sulfoxide) at rt for 2 h. This afforded corresponding aldehyde (±)-**78** in 87% yield, ready for assessment in the key aldol reaction (**Scheme 21**).

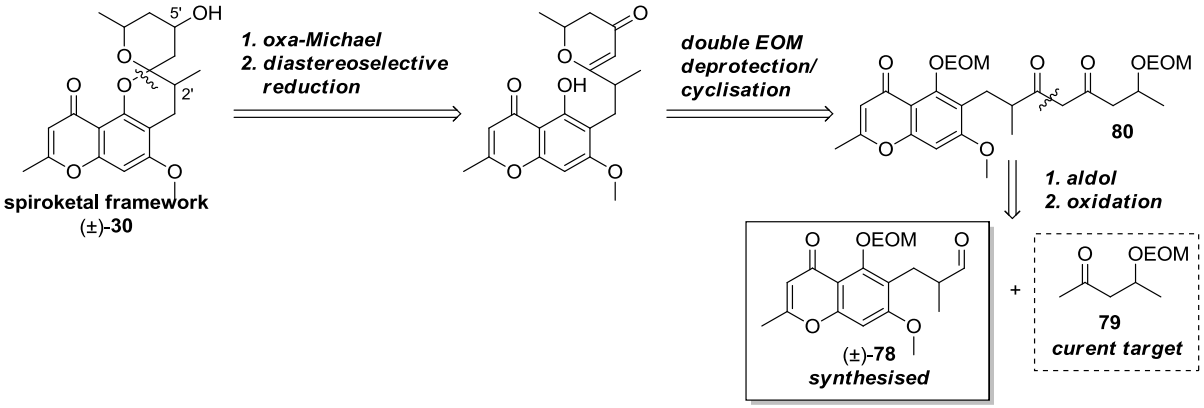
‡ Methoxy protected olefin **75** was prepared in 60% yield by treating free phenol **71** with methyl iodide, potassium carbonate in acetone at reflux for 24 h.



Scheme 21. *IBX oxidation of alcohol **76** to afford aldehyde (±)-**78**.*

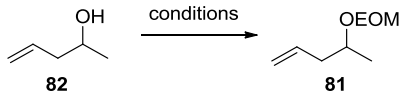
2.5 Synthesis of methyl ketone 79

With aldehyde (±)-**78** prepared in racemic form, methyl ketone coupling partner **79** was required in order to investigate the key aldol reaction for the synthesis of cyclisation precursor 1,3-diketone **80** (**Scheme 22**).



Scheme 22. *Retrosynthetic analysis of (±)-**30**.*

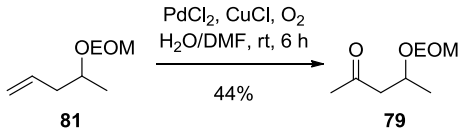
It was decided to prepare EOM-protected methyl ketone **79** anticipating the use of a double EOM deprotection/cyclisation sequence. Surprisingly, the synthesis of EOM-protected olefin **81** from **82** was not known in the literature and a quick optimisation study for its preparation was conducted (**Table 2**). Treatment of alcohol **82** with EOMCl and sodium hydride in THF at rt for 2 h afforded a complex mixture (entry 1). The use of EOMCl with Hünig's base (*N*,*N*-diisopropylethylamine, $^{i}Pr_2NEt$) using dichloromethane as solvent at 0 °C–rt for 12 h yielded protected alcohol **81** in 45% yield (entry 2). Changing the solvent to acetone gave a poorer yield (entry 3). Performing the reaction neat in the presence of Hünig's base for 2 h at rt only gave a slightly improved yield of 53% (entry 4). Finally, performing the reaction by changing the solvent to dichloromethane with added 4-dimethylaminopyridine (DMAP) as a catalyst in the presence of EOMCl and Hünig's base for 12 h at rt afforded the desired product in a satisfactory 86% yield (entry 5).



Entry	Conditions	Result
1	EOMCl, NaH, THF, rt, 2 h	complex mixture
2	EOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C–rt, 12 h	45%
3	EOMCl, $^{i}Pr_2NEt$, acetone, rt, 12 h	20%
4	EOMCl, $^{i}Pr_2NEt$, neat, rt, 2 h	53%
5	EOMCl, $^{i}Pr_2NEt$, DMAP (cat), CH_2Cl_2, 0 °C–rt, 12 h	86%

Table 2. *EOM protection of alcohol **82**.*

The Wacker oxidation of protected alcohol **81** using palladium chloride, copper (I) chloride and molecular oxygen bubbled through the reaction mixture using H_2O and DMF as solvent at rt for 6 h afforded the desired methyl ketone **79** in moderate yield (**Scheme 23**).



Scheme 23. *Wacker oxidation of olefin **81**.*

With the methyl ketone **79** and the aldehyde (±)-**78** in hand the key aldol coupling step to unite the aldehyde and ketone fragments was next investigated.

2.6 Successful synthesis of chaetoquadrins G and H (±)-85 and subsequent failure of the oxa-Michael reaction

*A. Use of a LDA mediated aldol reaction to synthesise β-hydroxyketone **83***

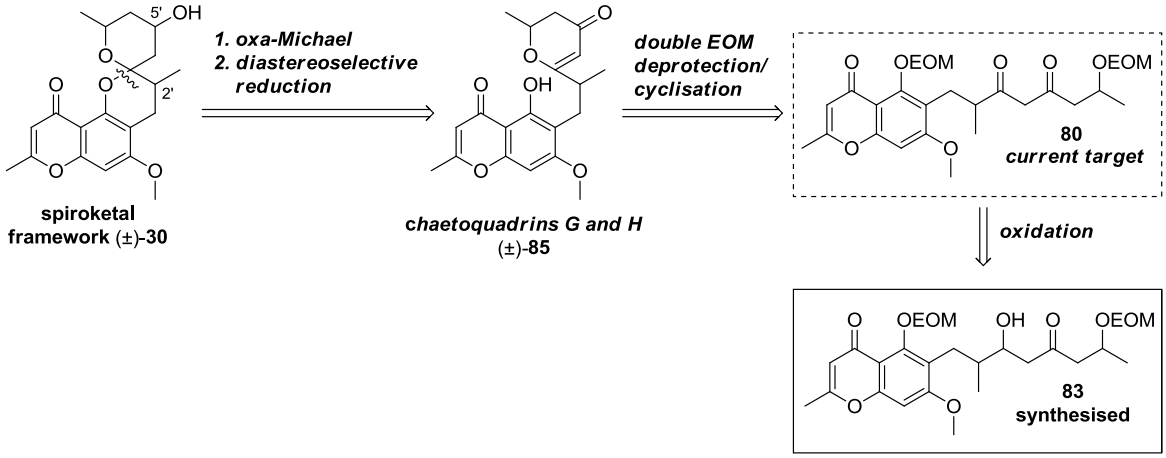
With aldehyde (±)-**78** and methyl ketone **79** in hand, the aldol reaction to prepare β-hydroxyketone **83** was next investigated (**Table 3**). The newly formed secondary alcohol would be directly oxidised to the corresponding ketone therefore stereocontrol of this step reaction was not required. It was pleasing to observe that the key aldol reaction could be effected in low yield using LDA (2 equivalents) in the presence of methyl ketone **79** (1 equivalent) and aldehyde (±)-**78** (1 equivalent) in THF at –78 °C for 2 h (entry 1). Repeating the aforementioned reaction conditions but with fewer molar equivalents of LDA (1 equivalent) using an overnight reaction time did not lead to any improvement (entry 2) nor did running the reaction under the same conditions with a shorter reaction time of 1 h (entry 3). Use of additional quantities of both ketone **79** (2.9 equivalents) and LDA (3 equivalents) relative to aldehyde (±)-**78** (1 equivalent) led to a dramatically improved yield of 60% (entry 4). This reaction was further optimised using ketone **79** (1.7 equivalents) with LDA (1.7 equivalents) and aldehyde (±)-**78** (1.0 equivalent) in THF at –78 °C for 4 h to give the desired product in an improved 76% yield (entry 5).

Entry	Conditions	Result
1	ketone **79** (1 eq), $^{i}Pr_2NH$ (2.2 eq), *n*-BuLi (2 eq), aldehyde (±)-**78** (1 eq), THF, –78 °C–rt, 2 h	15%
2	ketone **79** (1.2 eq), $^{i}Pr_2NH$ (1.1 eq), *n*-BuLi (1 eq), aldehyde (±)-**78** (1 eq), THF, –78 °C–rt, overnight	decomposition
3	ketone **79** (1 eq), $^{i}Pr_2NH$ (1.1 eq), *n*-BuLi (1 eq), aldehyde (±)-**78** (1 eq), THF, –78 °C–rt, 1 h	7.6%
4	ketone **79** (2.9 eq), $^{i}Pr_2NH$ (3.1 eq), *n*-BuLi (3 eq), aldehyde (±)-**78** (1 eq), THF, –78 °C–rt, 4 h	60%
5	ketone **79** (1.7 eq), $^{i}Pr_2NH$ (1.8 eq), *n*-BuLi (1.7 eq), aldehyde (±)-**78** (1 eq), THF, -78°C–rt, 4 h	76%

***Table 3.** Aldol reaction between aldehyde (±)-**78** and ketone **79** to form β-hydroxyketone **83**.*

*B. Oxidation of β-hydroxyketone **83** to access 1,3-diketone **80***

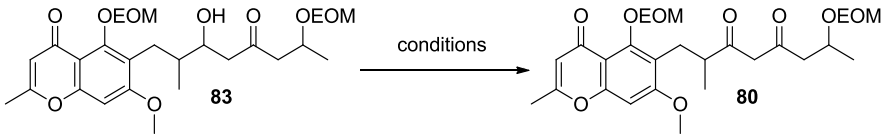
With the β-hydroxyketone **83** in hand, synthesis of the linear cyclisation precursor 1,3-diketone **80** by oxidation of **83** was next investigated (**Scheme 24**). A double EOM deprotection/cyclisation sequence on **80** was then envisaged to afford a mixture of bis-pyranone natural products chaetoquadrins G and H (±)-**85**.



Scheme 24. *Retrosynthetic analysis of (±)-**30**.*

Unexpectedly, the synthesis of 1,3-diketone **80** by oxidation of β-hydroxyketone **83** proved challenging. Our initial attempts to effect the oxidation of β-hydroxyketone **83** are tabulated below (**Table 4**). Treating β-hydroxyketone **83** with IBX in DMSO at 30 °C for 1 h only resulted in elimination (entry 1). The use of catalytic amounts of tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant in dichloromethane at rt for 1 h afforded the desired product in low yield (entry 2). Use of Corey-Kim oxidation conditions involved treating β-hydroxyketone **83** with NCS and Me_2S at –78 °C in dichloromethane for 1 h. This was followed by further addition of triethylamine (NEt_3) to afford a dimethylsulfonium dicarbonylmethylide. However, reductive desulfurisation with zinc-acetic acid in dichloromethane at 0 °C for 2 h led to decomposition of the material (entry 3). Treatment with a system of catalytic TEMPO, TBAI and a stoichiometric amount of oxone in toluene led to a complex mixture (entry 4). Parikh–Doering oxidation conditions using SO_3·pyridine, diisopropylamine and DMSO in dichloromethane at 0 °C also afforded a complex mixture of unwanted side-products (entry 5). Treatment of β-hydroxyketone **83** with Dess-Martin periodinane (DMP) with added pyridine as a buffer for 2 h at rt led to decomposition of the starting material. Better results were obtained using similar conditions and decreasing the reaction time to 40 seconds. This

afforded the desired product in 40% yield, albeit unreliably. In 2011 Beaudry and Bartlett[68] reported a specific protocol for oxidising β-hydroxyketones employing a mixture of IBX in EtOAc which is then heated at reflux. Although never attempted using this exact substrate, this protocol did indeed prove to be the optimal method to effect similar transformations and was used in the eventual successful stereoselective total synthesis of chaetoquadrin H (*vide infra*, see **Chapter 4**, **Section 4.6**).



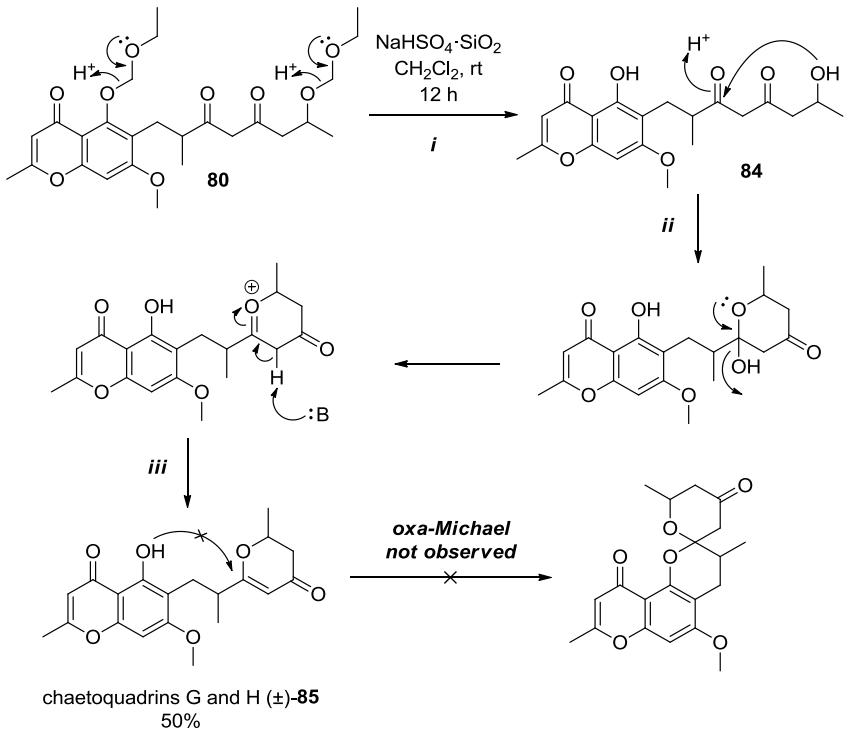
Entry	Conditions	Result
1	IBX (4 eq), DMSO, 30 °C, 1 h	elimination of alcoholic OEOM
2	TPAP (5 mol%), NMO (1.5 eq), CH_2Cl_2, rt, 1 h	< 10%
3	1) NEt_3, Me_2S, NCS, CH_2Cl_2, –78 °C, 1 h 2) Zn, AcOH, CH_2Cl_2, 0 °C, 2 h	decomposition
4	TEMPO (1 mol%), TBAI (2 mol%) oxone (2.2 eq), toluene, rt	complex mixture
5	SO_3·pyridine (3.3 eq), $^iPr_2NH$ (3.7 eq), CH_2Cl_2, DMSO, 0 °C	complex mixture
6	DMP (3 eq), pyridine (3 eq), CH_2Cl_2, rt, 2 h	decomposition
7	DMP (3 eq), pyridine (3 eq), CH_2Cl_2, rt, 40 sec	10-40%

Table 4. *Oxidation of β-hydroxyketone **83** to 1,3-diketone **80**.*

C. Synthesis of bis-pyranone natural products chaetoquadrins G and H

With 1,3-diketone **80** available albeit in low yield, it was nevertheless decided to complete the synthesis of the bis-pyranone natural products chaetoquadrin G and H (±)-**85** *en route* to the spiroketal chaetoquadrins. Towards this end, EOM-protected 1,3-diketone **80** was exposed to mildly acidic $NaHSO_4{\cdot}SiO_2$ reagent[69] in dichloromethane at rt for 12 h to successfully afford chaetoquadrins G and H as an inseparable racemic mixture (±)–**85** in ca. 50% yield. The $NaHSO_4{\cdot}SiO_2$ induced deprotection-cyclisation sequence represents a tandem cascade of the following reactions (**Scheme 25**); i. acid catalysed EOM deprotection of the aliphatic alcohol and aromatic phenol of **80** to afford deprotected linear precursor **84**; ii. nucleophilic attack of the aliphatic alcohol onto the C-3′ carbonyl to afford a hemiacetal; iii. a loss of the α-proton and elimination of the alcohol to afford the 4-pyranone moiety of the bis-pyranone chaetoquadrins G and H (±)–**85**. It should be noted that the weakly nucleophilic and hydrogen-bonded free phenol afforded after the initial EOM deprotection, does not participate

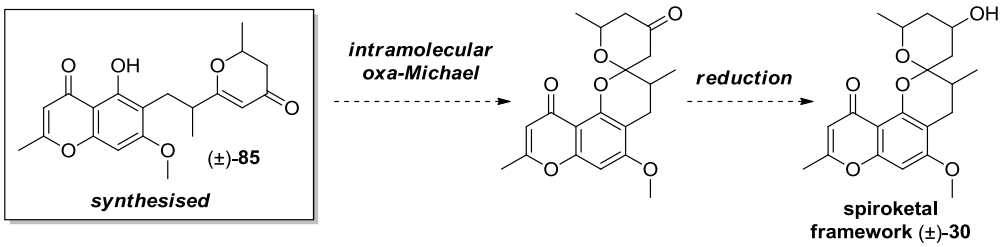
further in the reaction sequence and to our dismay could not be promoted to undergo an oxa-Michael reaction onto the pyranone. (*vide infra*).



Scheme 25. *Reaction mechanism of double deprotection-cyclisation-elimination sequence of 1,3-diketone* ***80*** *to afford chaetoquadrins G and H (±)–**85**.*

*D. Unsuccessful intramolecular oxa-Michael reaction of bis-pyranone (±)-**85***

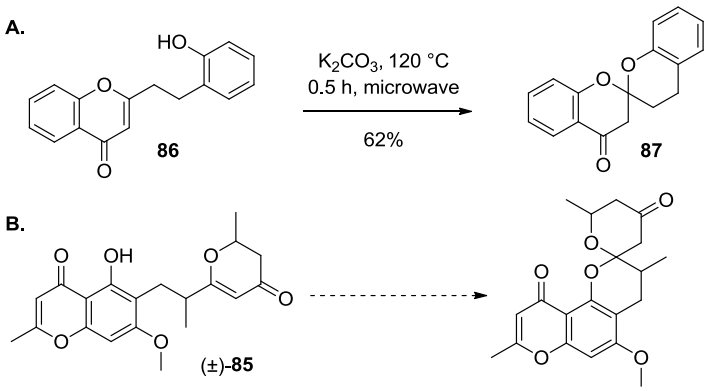
The bis-pyranone natural product mixture (±)-**85** was two synthetic steps from the desired spiroketal framework (±)-**30** of chaetoquadrins A–C (**Scheme 26**).



Scheme 26. *Remaining steps to spiroketal framework (±)-**30** of chaetoquadrins A–C.*

Examples of intramolecular oxa-Michael reactions are reported in the literature to effect spiroketal formation[70,71,72,73] and amongst them, the most comparable one to our desired transformation (**Scheme 27**, B) is the oxa-Michael addition of pyranone-phenol **86** using

potassium carbonate and microwave irradiation to form corresponding aromatic spiroketal **87** (**Scheme 27**, A). This specific example was established in our research group.[74]



***Scheme 27. A**. oxa-Michael reaction reported by Brimble et al.[74] **B**. Our desired transformation.*

There remains a difference between the two examples; the phenol in chaetoquadrins G and H (±)-**85** is hydrogen bonded to the chromone carbonyl as indicated by the distinctive phenol resonance in the ^{1}H NMR spectrum of chaetoquadrins G and H (**Figure 20**).

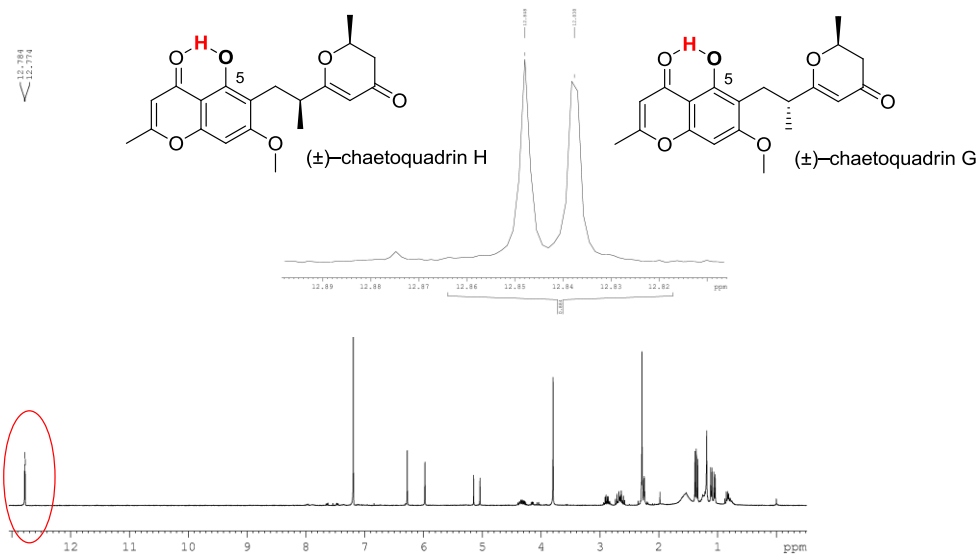
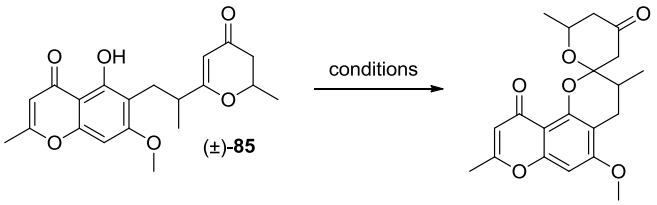


***Figure 20.** ^{1}H NMR spectrum of (±)-chaetoquadrin G and H mixture. Note the two distinct singlets at δ 12.8 ppm belonging to C-5 phenol of chaetoquadrin G and H, respectively.*

Nevertheless, the two examples in **Scheme 27** were considered to be similar enough to warrant an attempt at this reaction. Thus bis-pyranone (±)-**85** was loaded neat onto potassium carbonate and heated in a microwave at 150 °C for 0.5 h. Disappointingly, these reaction

conditions did not effect the desired transformation and only starting material was recovered (entry 1, **Table 5**).

Having met with this failure, a range of acidic and basic conditions were screened in an attempt to effect the desired oxa-Michael transformation. The disappointing results are summarised in the table below; treatment with sodium hydride in THF at 0 °C to rt overnight (entry 2), treatment with potassium hydride in THF at 0 °C to rt overnight (entry 3), use of silver (I) oxide in dichloromethane at 0 °C to rt overnight (entry 4) and treatment with trimethylphosphine in MeOH at 0 °C to rt overnight (entry 7) all resulted in no reaction. The treatment of (±)-**85** with mildly basic TBAF in THF at 0 °C for 1 h only resulted in decomposition of the starting material (entry 5) and use of *p*-toluenesulfonic acid (PTSA) in MeOH at 0 °C to rt was also unsuccessful (entry 6). The use of sodium borohydride in THF at 0 °C for 1 h (entry 8) and aqueous sodium hypochlorite in THF at 40 °C for 2 h (entry 9) led to decomposition of the starting material (±)-**85**.



Entry	Conditions	Result
1	K_2CO_3, 150 °C, MW, 30 min	no reaction
2	NaH, THF, 0 °C–rt, 12 h	no reaction
3	KH, THF, 0 °C–rt, 12 h	no reaction
4	Ag_2O, CH_2Cl_2, 0 °C–rt, 12 h	no reaction
5	TBAF, THF, 0 °C, 1 h	decomposition
6	PTSA, MeOH, 0 °C, 1 h	decomposition
7	PMe_3, MeOH, 0 °C–rt, 12 h	no reaction
8	$NaBH_4$, THF, 0 °C, 1 h	decomposition
9	$HClO_4$ (1 M, excess), THF, 40 °C, 2 h	decomposition

Table 5. *Failed attempts to effect the desired oxa-Michael transformation.*

The current synthetic investigation was thwarted at this key spiroketal-forming step. Additionally, effecting the aforementioned oxidation of the β-hydroxyketone **83** to 1,3-diketone **80** on a useful scale was also problematic. It was therefore decided to revise the synthetic strategy, which will be described in the following chapter.

2.7 Summary

A non-stereoselective racemic synthesis of chaetoquadrins G and H were accomplished using a Claisen rearrangement/aldol strategy. Attempts to secure the C-2´ stereocentre of aforementioned chaetoquadrins *via* means of an asymmetric hydroboration-oxidation reaction was unsuccessful, as was the attempt to form the spiroketal ring present in chaetoquadrins A–C *via* means of an oxa-Michael reaction.

Chapter Three

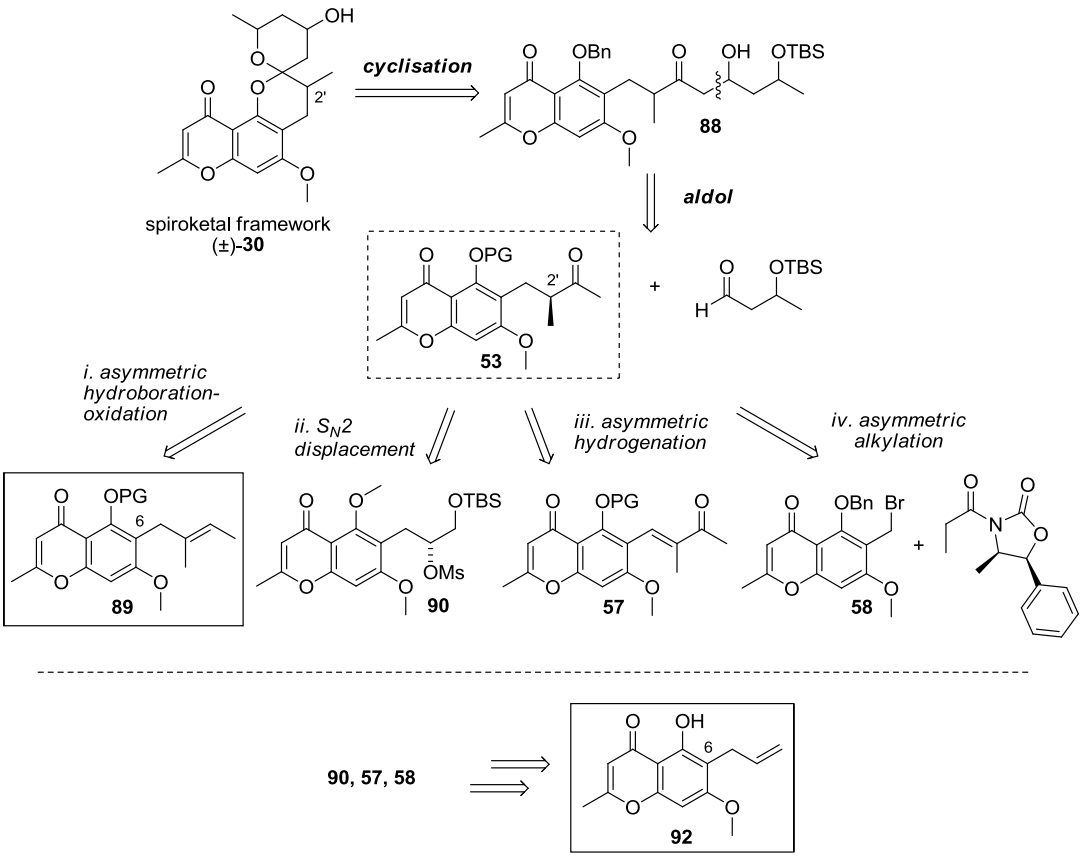
Results and Discussion

Synthesis of the spiroketal framework of the chaetoquadrins

3.0 Overview

In this chapter the construction of the spiroketal framework of chaetoquadrins A–C (±)-**30** from an appropriately protected cyclisation precursor **88** is discussed (**Scheme 28**). Several protecting groups were explored for the final stages of the synthesis and success was finally achieved using benzyl and TBS protecting groups.

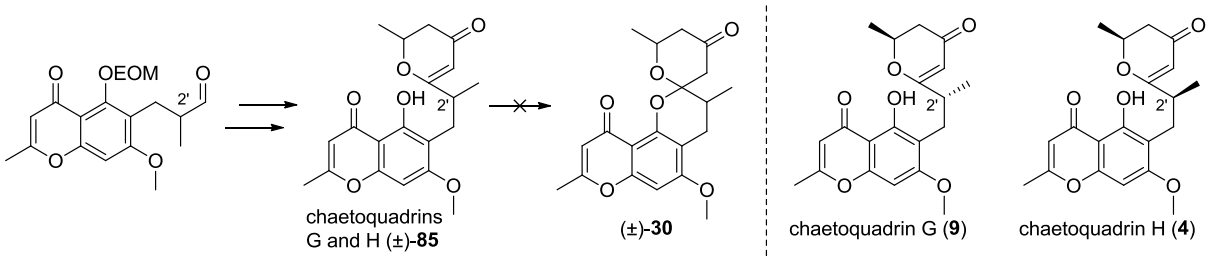
The installation of the C-2´ stereocentre in key intermediate **53** is also discussed in detail. Several different strategies were investigated including; i. asymmetric hydroboration-oxidation reaction of a trisubstituted olefin; ii. S_N2 displacement of secondary mesylate **90**; iii. asymmetric hydrogenation of conjugated ketone **57**; and iv. asymmetric alkylation of bromide **58** using a chiral auxiliary. The required substrates for execution of these strategies were derived from C-6 substituted allyl chromones **89** or **92** (highlighted) *via* alkylation-Claisen chemistry discussed in Chapter 2.



Scheme 28. *Various strategies to synthesise and install the C-2´stereocentre of (±)-**30**.*

3.1 S_N2 displacement strategy

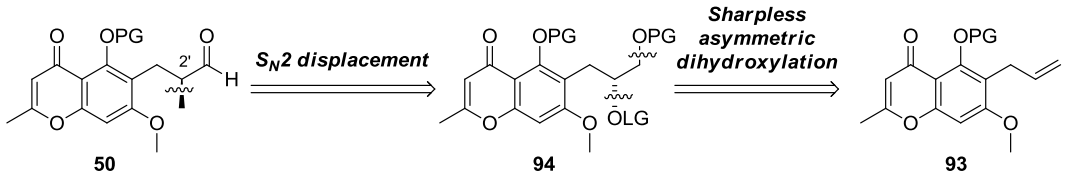
Faced with the failure to access the spiroketal ring system (±)-**30** of chaetoquadrins A, B and C *via* oxa-Michael reaction of (±)-**85** (**Scheme 29**), it was next decided to work towards stereoselective installation of the C-2′stereocentre of bis-pyranone chaetoquadrins G (**9**) and H (**4**).



Scheme 29. *Left: failed synthesis of spiroketal (±)-**30** via oxa-Michael reaction of (±)-**85**.*
*Right: structures of chaetoquadrin G (**9**) and H (**4**).*

A. Strategy

The initial synthetic intermediate required was enantioenriched aldehyde **50** (**Scheme 30**). It was envisaged to establish the required chirality at C-2′ in **50** *via* a Sharpless asymmetric dihydroxylation (SAD) of olefin **93** and displace the functionalised secondary alcohol of diol **94** with a methyl anion synthon such as dimethylcuprate *via* an S_N2 reaction.

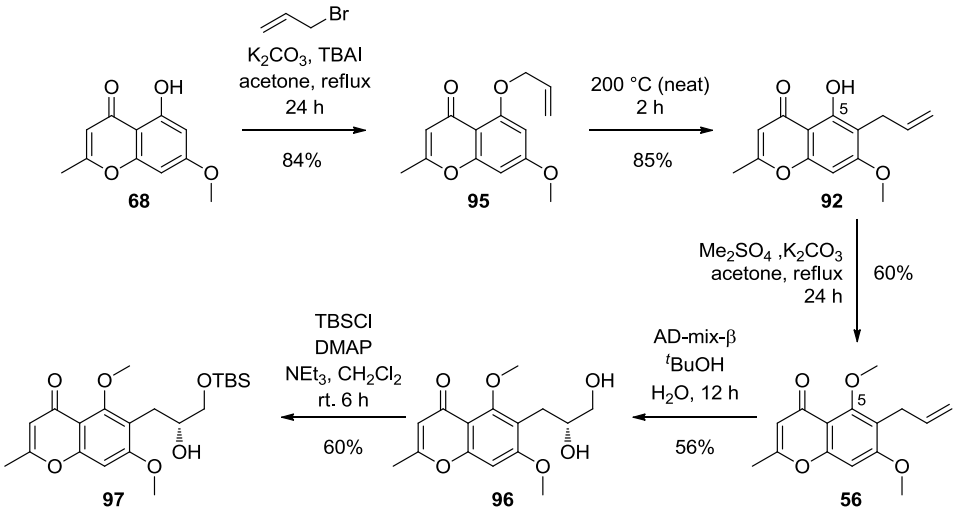


Scheme 30. *S_N2 displacement strategy. LG = leaving group. PG = protecting group.*

B. Attempted execution of the S_N2 displacement strategy

To access the enantioenriched aldehyde **50** by the aforementioned strategy, methylated noreugenin **68** was first alkylated by reaction with allyl bromide in the presence of tetrabutylammonium iodide in acetone heated at reflux for 24 h to afford allyl phenyl ether **95** (**Scheme 31**). Aromatic Claisen rearrangement was executed by heating **95** at 200 °C for 2 h to afford phenol **92**. It was decided to use the methoxy protecting group to protect the C-5 phenol in **92**. Use of a methoxy protecting group was rationalised by the robust nature of the

methoxy protecting group under a range of acidic, basic or thermal conditions. To this end, phenol **92** was alkylated using dimethyl sulfate and potassium carbonate in acetone at reflux for 24 h to afford C-5 methoxy protected olefin **56**, ready for the dihydroxylation reaction. Treatment of olefin **56** with AD-mix-β in ^{t}BuOH and H_2O afforded diol **96**.[§] Chemoselective protection of the primary alcohol of **96** was achieved with use of TBSCl, DMAP and triethylamine in dichloromethane at rt to afford TBS-protected alcohol **97** in 60% yield.

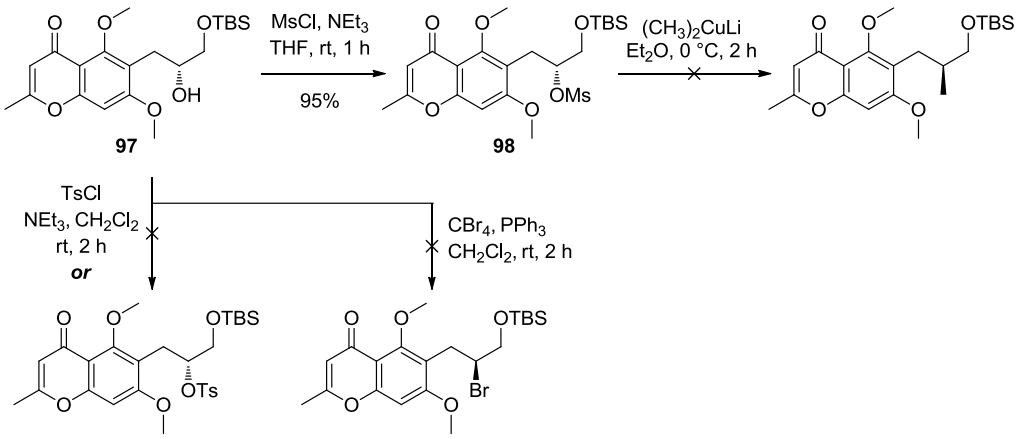


Scheme 31. *Synthesis of alcohol **97**.*

The secondary alcohol of **97** was required to effect conversion into a halide or a pseudohalide. Appel reaction of alcohol **97** using carbon tetrabromide and triphenylphosphine in dichloromethane at room temperature for 2 h was unsuccessful, yielding only starting material. Tosylation with 4-toluenesulfonyl chloride, triethylamine and dichloromethane at rt for 2 h was likewise unsuccessful.

Pleasingly, mesylation of the secondary alcohol was achieved in 95% yield using methanesulfonyl chloride and triethylamine in THF at room temperature in 1 h. It was therefore decided to use a mesylate as the leaving group for the key S_N2 displacement reaction. Unfortunately, treatment of mesylate (**98**) with dimethylcuprate in Et_2O at 0 °C failed to effect the desired transformation (**Scheme 32**).

[§] The *ee* of **96** from the SAD reaction and the subsequent compounds in **Schemes 31** and **32** were left undetermined in light of the failure of the S_N2 displacement reaction of mesylate **98** (see **Scheme 32**).



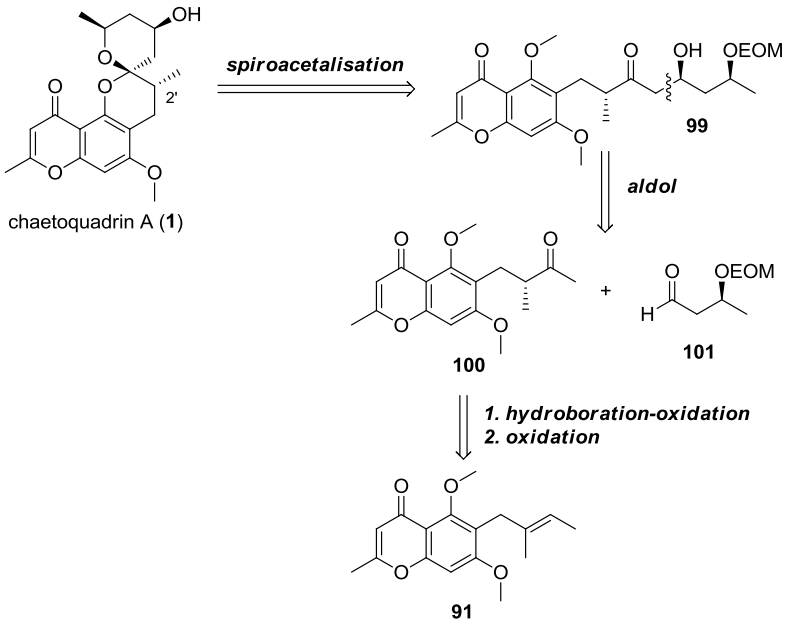
Scheme 32. *Unsuccessful displacement of mesylate* ***98*** *by dimethylcuprate.*

3.2 Trisubstituted olefin strategy

At this point there were two problems with the current synthesis: i. the stereocentre at C-2′ of chaetoquadrins A–C could not be installed; ii. the spiroketal moiety of the chaetoquadrins A–C could not be constructed using an intramolecular oxa-Michael reaction. The synthetic strategy was therefore revised (**Scheme 33**).

A. Strategy

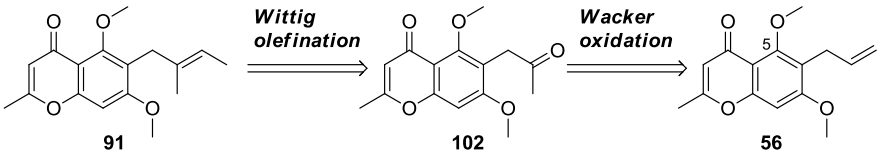
It was next envisaged to access spiroketal **1** from linear spiroketalisation precursor **99** which could be prepared directly by aldol reaction of methyl ketone **100** with aldehyde **101** thereby obviating the need for troublesome oxidative manipulations and avoiding the difficult intramolecular oxa-Michael reaction. It was thought that methyl ketone **100** could be accessed *via* asymmetric hydroboration-oxidation of trisubstituted olefin **91** (a type V alkene, see **Chapter 2**, **Section 2.4**). Accordingly, use of Masamune's borolane as the hydroborating reagent was proposed as it was known to give good asymmetric induction on type V alkenes (*vide infra*).



Scheme 33. *2nd generation retrosynthetic analysis of chaetoquadrin A (**1**).*

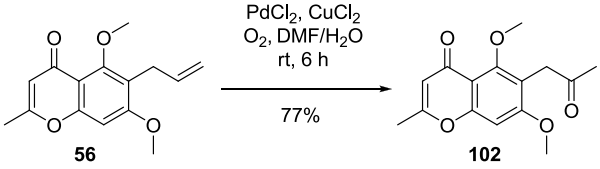
*B. Attempted synthesis of olefin **91** via Wittig olefination*

To access trisubstituted olefin **91** it was decided to effect a Wacker oxidation on olefin **56** to yield ketone **102**. Subsequent Wittig olefination could then be used to access trisubstituted olefin **91** (**Scheme 34**).



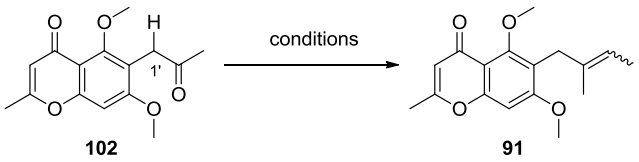
Scheme 34. *Retrosynthetic analysis of olefin **91**.*

Wacker oxidation of olefin **56** using $PdCl_2$, $CuCl_2$ and molecular oxygen in DMF/H_2O at rt for 6 h afforded the desired methyl ketone **102** in good yield (**Scheme 35**).



Scheme 35. *Synthesis of ketone **102** via Wacker oxidation.*

With ketone **102** in hand, trisubstituted olefin **91** was the next synthetic target. Wittig reaction of methyl ketone **102** with the ylide derived from ethyl triphenylphosphonium bromide proved troublesome. Use of KO^{t}Bu in toluene resulted in no reaction (entry 1, **Table 6**). Use of *n*-BuLi as base and THF as solvent at –78 °C to rt led to decomposition of the starting material after two days (entry 2). Extending the reaction time for 3 h while maintaining the temperature at 0 °C resulted in trace amounts of the desired product (entry 3) but the poor yield rendered this synthetic strategy impractical.

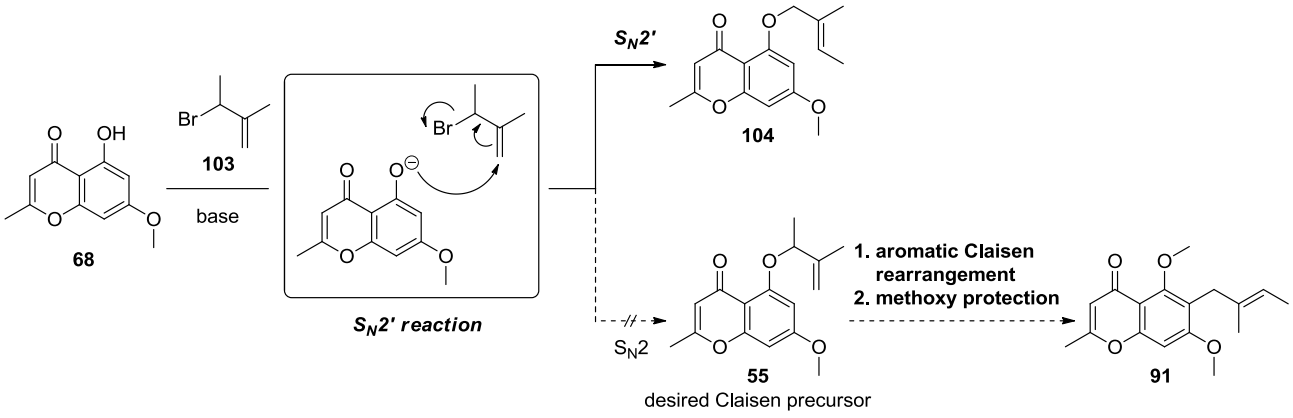


Entry	Conditions	Result
1	$EtPPh_3Br$, KO^{t}Bu, toluene, 0 °C to 75 °C, 2 h	no reaction
2	$EtPPh_3Br$, *n*-BuLi, THF, –78 °C to rt, 2 d	decomposition
3	$EtPPh_3Br$, *n*-BuLi, THF, 0 °C, 3 h	1–5%

Table 6. *Failed attempts to effect the desired Wittig reaction.*

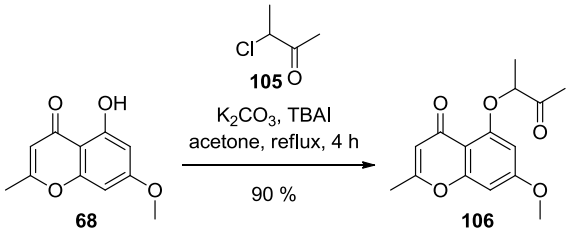
*C. Synthesis of olefin **91** via aromatic Claisen rearrangement*

Owing to the failure of the previous strategy a new route to the trisubstituted olefin **91** was devised whereby the olefin was to be accessed using an aromatic Claisen rearrangement. Synthesis of the Claisen precursor **55** necessitates the alkylation of methylated noreugenin **68** with bromide **103** (**Scheme 36**). This reaction would presumably proceed *via* a S_N2' mechanism and afford **104** containing the wrong substitution pattern.



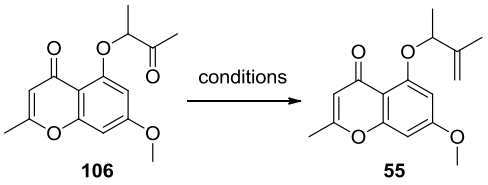
Scheme 36. *Envisaged alkylation of heterocycle **68** with bromide **104** may lead to a S_N2' type reaction.*

To circumvent this problem, methylated noreugenin **68** was first reacted with α-chloroketone **105** to afford alkylated carbonyl **106**. (**Scheme 37**).



Scheme 37. *Alkylation of **68** with α-chloroketone **105**.*

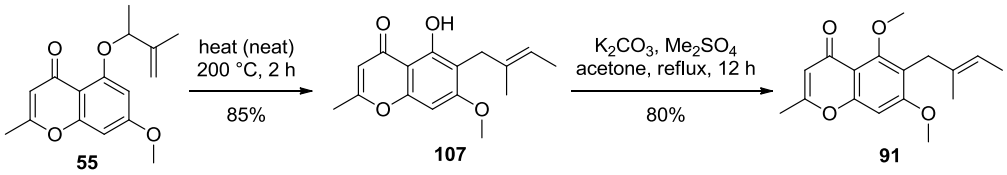
The carbonyl group was subsequently reacted *via* Wittig methylenation to afford the desired olefin in anticipitation of the aromatic Claisen rearrangement. The Wittig methylenation reaction required some degree of optimisation (**Table 7**). Use of methyl triphenylphosphonium iodide as the Wittig salt and KO^{t}Bu as base in THF with different reaction times in the presence of **106** led to poor to moderate yields of the desired product **55** (entries 1–4). Changing the base from KO^{t}Bu to NaH in THF afforded no desired product (entry 5) while use of *n*-BuLi in THF with methyl triphenyl phosphonium iodide for 24 h improved the yield to 46% (entry 6). The reaction was dramatically improved using methyl triphenylphosphonium bromide as the Wittig salt with KO^{t}Bu as the base in THF with reaction time of 12 h (entry 7). Excess base and Wittig salt was found to be critical to obtain an optimal yield of the desired olefin **55**.



Entry	Conditions	Result
1	KO^{t}Bu (3 eq), CH_3PPh_3I (3.5 eq), THF, 0 °C–rt, 12 h	decomposition
2	KO^{t}Bu (3 eq), CH_3PPh_3I (4 eq), THF, 0 °C–rt, 1 h	5%
3	KO^{t}Bu (3 eq), CH_3PPh_3I (4 eq), THF, 0 °C–rt, 20 sec	< 5%
4	KO^{t}Bu (1.1 eq), CH_3PPh_3I (3 eq), THF, 0 °C–rt, 12 h	25%
5	NaH (2 eq), CH_3PPh_3I (3 eq), THF, –78 °C–rt, 6 h	no reaction
6	*n*-BuLi (2 eq), CH_3PPh_3I (3 eq), THF, 24 h –78 °C–rt	46%
7	KO^{t}Bu (2.7 eq) CH_3PPh_3Br (3.6 eq), THF, rt, 12 h	89%

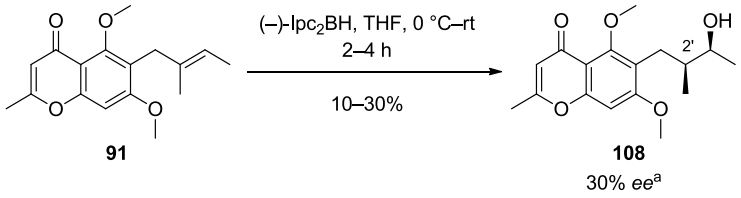
Table 7. *Wittig methylenation of carbonyl **106**.*

With the unmasked olefin **55** in hand, we next effected the aromatic Claisen rearrangement by heating olefin **55** to 200 °C to afford phenol **107** in 85% yield (**Scheme 38**). The free phenol was then protected by reaction with dimethyl sulfate and potassium carbonate in acetone under reflux for 12 h to afford methoxy protected trisubstituted olefin **91**.



Scheme 38. *Synthesis of OMe protected trisubstituted olefin **91**.*

With the desired olefin **91** in hand, asymmetric hydroboration-oxidation reaction was investigated. It was anticipated that (type V) olefin **91** would be more susceptible to chiral induction compared to our earlier attempts using (type I) olefin. The asymmetric hydroboration-oxidation of **91** with (–)-Ipc_2BH afforded the desired alcohol **108** with some asymmetric induction, albeit with a modest 30% *ee*. (**Scheme 39**).

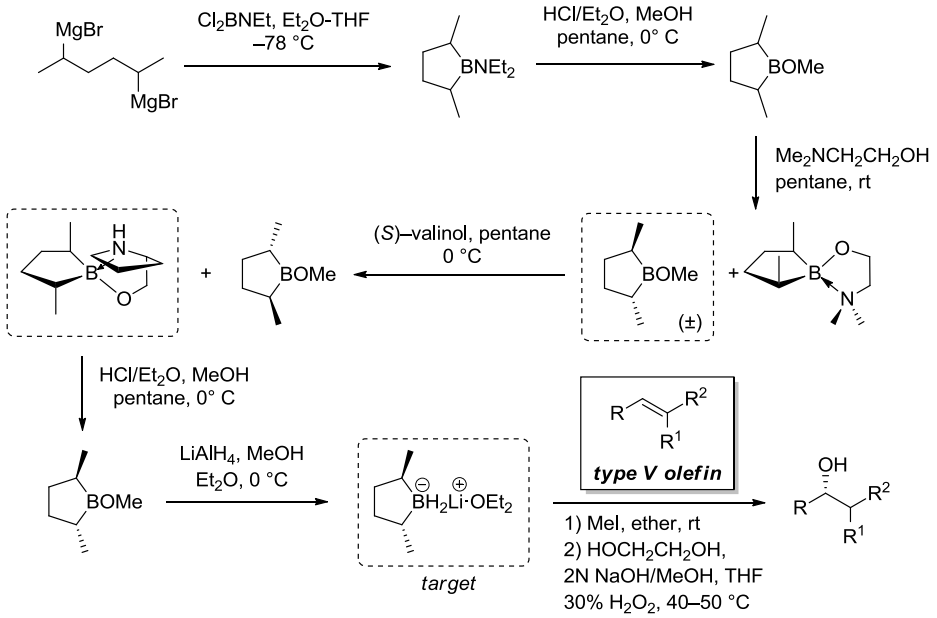


Scheme 39. *Asymmetric hydroboration-oxidation of olefin **91**.*

[a] Enantiomeric excess was calculated by HPLC analysis [chiralpak AD-H, hexanes : ^{i}PrOH (75:25)].

Unfortunately, material produced in this manner was not suitably enantioenriched to enable a stereoselective synthesis of the chaetoquadrins. It is known that the use of Masamune's C2-symmetric borolane affords excellent asymmetric induction with type V olefins and use of this reagent was considered.[63]

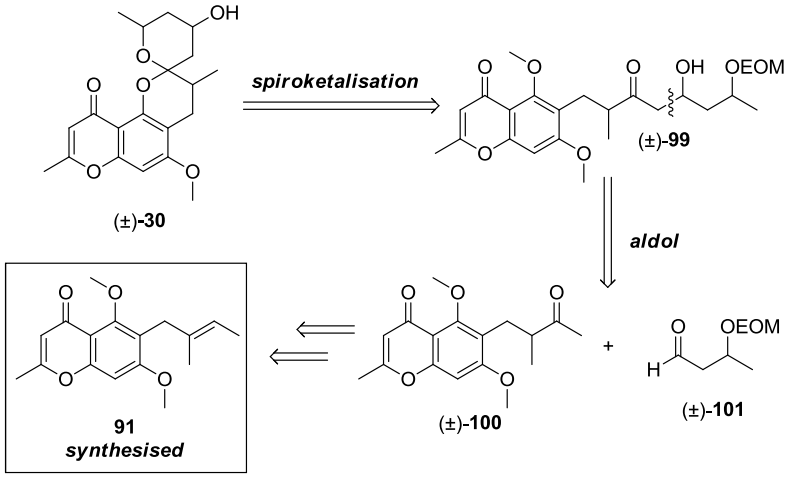
However it was ultimately decided not to use Masammune's borolane due to its lengthy preparation which involved separation of diastereoisomers and a resolution step (**Scheme 40**). Instead a new strategy was devised to install the stereogenic centre at C-2´ in the chaetoquadrins (*vide infra*).



Scheme 40. *Synthetic steps required to access Masamune's borolane and its reaction with a type V olefin.*[63]

D. Attempted racemic total synthesis of spiroketal chaetoquadrins using a C-5 methoxy protecting group

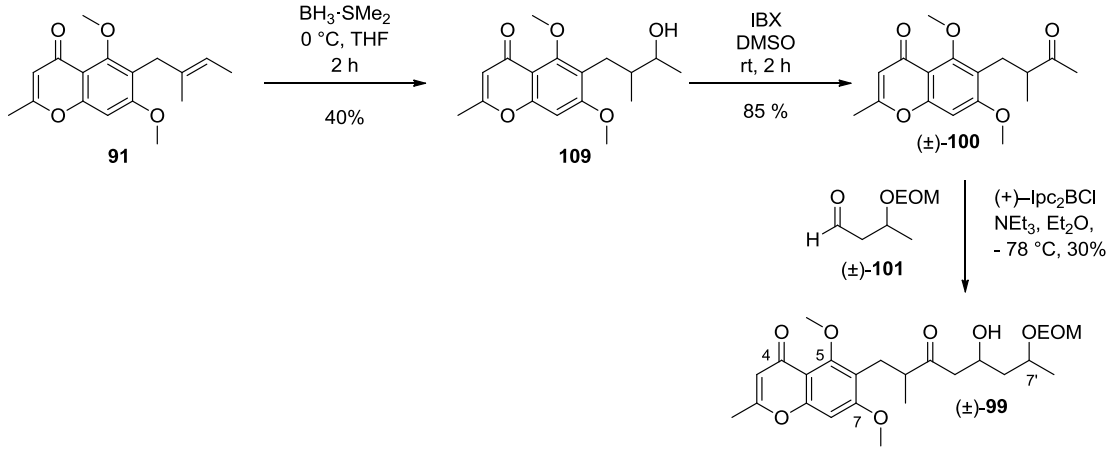
It was decided to proceed with the synthesis using racemic material with the aim of realising the synthesis of spiroketal (±)-**30**. Cyclisation precursor β-hydroxyketone (±)-**99** was to be derived from union of methyl ketone (±)-**100** and aldehyde (±)-**101**. Methyl ketone (±)-**100** would be derived from hydroboration-oxidation sequence of olefin **91** (**Scheme 41**).



Scheme 41. *Strategy for synthesis of spiroketal framework (±)-**30**.*

Towards this end, trisubstituted olefin **91** was treated with borane dimethylsulfide in THF at 0 °C for 2 h to afford secondary alcohol **109** which was oxidised with IBX in DMSO at rt to

afford methyl ketone (±)-**100** (**Scheme 42**). Aldol reaction between the ketone (±)-**100** and EOM-protected aldehyde (±)-**101** was effected by use of (+)-Ipc_2BCl and NEt_3 in Et_2O at –78 °C for 2 h to afford the desired β-hydroxyketone (±)-**99** in moderate yield.

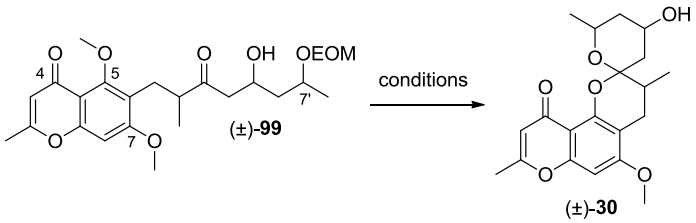


Scheme 42. *Synthesis of protected β-hydroxyketone (±)-**99**.*

β-Hydroxyketone (±)-**99** represents the fully functionalised linear precursor to the spiroketal chaetoquadrins. While the robustness of the methoxy protecting group at C-5 was advantageous during the early stage of the synthesis, it now had to be orthogonally deprotected in the presence of the C-7 methoxy group. It was thought that the intramolecular hydrogen bonding between C-5 phenol and C-4 carbonyl would provide a "thermodynamic sink" in favour of chemoselective deprotection of C-5 methoxy group over the C-7 methoxy group of (±)-**99**. Once C-5 methoxy deprotection was achieved, it was thought that the harsh conditions required for the aforementioned deprotection would also promote EOM deprotection of the aliphatic alcohol and the subsequent cyclisation.

Our deprotection attempts are tabulated below (**Table 8**). Complex mixtures were obtained, separated, and analysed by ^1H NMR thus allowing the following conclusions to be drawn. Use of $InCl_3$ in dichloromethane at –78 °C for 2 h failed to induce a reaction (entry 1). Replication of the previous reaction conditions using $AlCl_3$ as the Lewis acid was likewise unsuccessful (entry 2). Attempting the reaction at room temperature with $AlCl_3$ with ethanethiol additive in dichloromethane (entry 5) did afford the spiroketal but only in trace amounts. The ^1H NMR spectra of the spiroketal product matched the spectrum of chaetoquadrin B. Use of $BBr_3{\cdot}SMe_2$ at room temperature in dichloromethane for 1 h afforded the same spiroketal chaetoquadrin B (entry 3) but only in trace amounts. Cooling this reaction to –78 °C using $BBr_3{\cdot}SMe_2$ did not improve the reaction (entry 4) with no spiroketal being

formed. Use of aqueous hydrochloric acid heated at reflux led to decomposition of the starting material (entry 6). It was concluded at this point that chemoselective demethylation was impractical and a different protecting group for the C-5 phenol was considered.

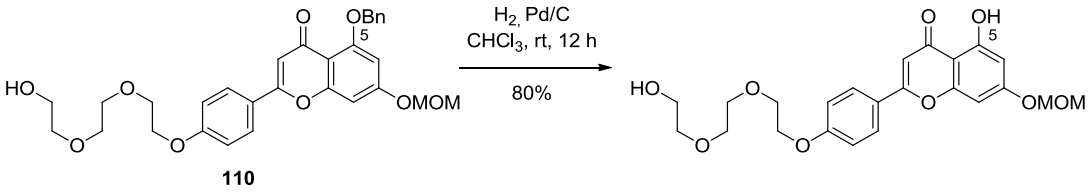


Entry	Conditions	Result
1	$InCl_3$, CH_2Cl_2, –78 °C , 2 h	no reaction
2	$AlCl_3$, CH_2Cl_2, –78 °C, 2 h	no reaction
3	$BBr_3 \cdot S(Me)_2$, CH_2Cl_2, rt, 1 h	complex mixture, trace spiroketal
4	$BBr_3 \cdot S(Me)_2$, CH_2Cl_2, –78 °C, 1 h	complex mixture
5	$AlCl_3$, CH_2Cl_2, rt, ethanethiol, 30 min	complex mixture, trace spiroketal
6	5N HCl (aq), rt, reflux, 12 h	decomposition

***Table 8**. Attempted deprotection of β-hydroxyketone (±)-**99**.*

E. The use of the benzyl (Bn) and di-tert-butylsilyl (TBS) protecting groups for synthesis of spiroketal chaetoquadrins

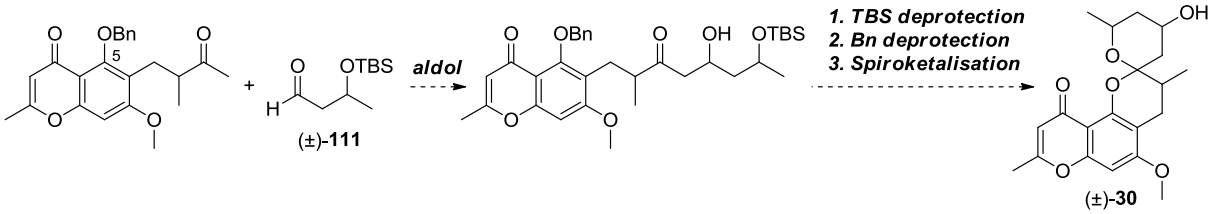
Use of a benzyl group was now envisaged to protect the C-5 phenol of the methyl ketone aldol partner. There was literature precedent in the context of flavonoid chemistry for successful debenzylation of a C-5 benzyl phenol (eg, deprotection of phenol **110**, **Scheme 43**) under reductive conditions.[75]



***Scheme 43.** Debenzylation of benzyl protected chromone **110** under reducing conditions.*

For the second aldehyde aldol partner, it was decided against using an EOM protecting group in light of the unsuccessful use of this protecting group thus far. A strictly orthogonal deprotection-cyclisation sequence was now desired to facilitate troubleshooting with deprotection and/or cyclisation steps. It was therefore decided to switch the EOM protecting

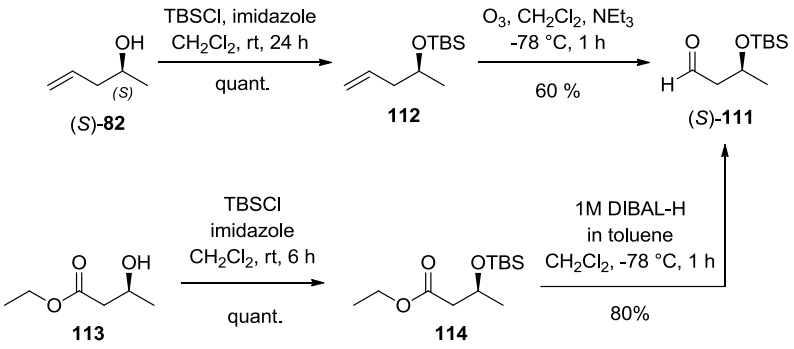
group to the di-*tert*-butylsilyl (TBS) protecting group for the aldehyde (*S*)-**111** aldol partner (**Scheme 44**).



Scheme 44. *Envisaged use of benzyl (Bn) and di-tert-butylsilyl (TBS) protecting groups for synthesis of (±)-**30**.*

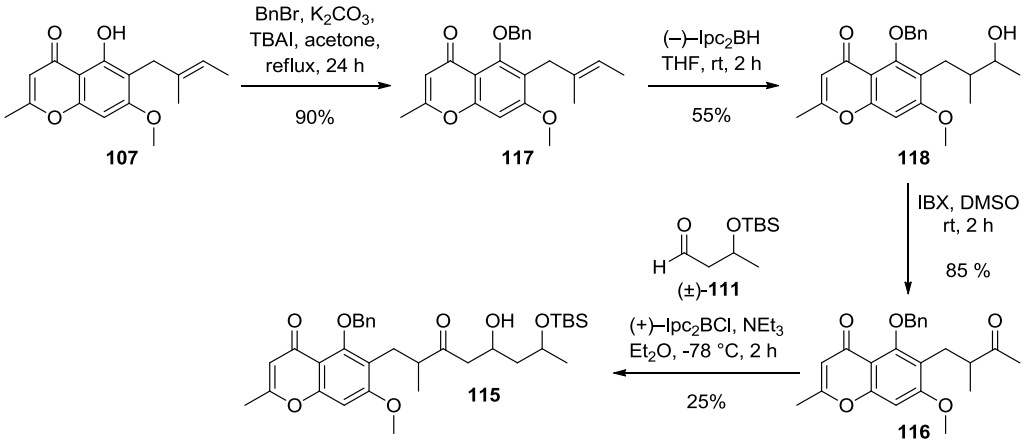
The TBS protecting group can be orthogonally cleaved in the presence of a benzyl group under mild conditions using fluoride anions. The deprotection mechanism is driven by the thermodynamic affinity for the formation of the Si-F bonds. Additionally, the TBS protecting group readily survives the reductive hydrogenolysis conditions used to effect debenzylation.

O-TBS protected aldehyde (*S*)-**111** was prepared using two complementary methods (**Scheme 45**). In the first method, commercially available alcohol (*S*)-**82** was protected *via* treatment with TBSCl and imidazole in dichloromethane to furnish **112**. Subsequently, TBS protected olefin **112** was cleaved by ozonolysis with ozone in dichloromethane at –78 °C to afford aldehyde (*S*)-**111**. Alternatively, TBS protection of commercially available ester **113** was achieved using TBSCl and imidazole in DMF at rt for 6 h to afford protected ester **114**. Subsequent DIBAL reduction of ester **114** in dichloromethane at –78 °C afforded the desired aldehyde (*S*)-**111**.[76] (±)-**111** could be prepared using the same methods, starting from racemic alcohol (±)-**82**.



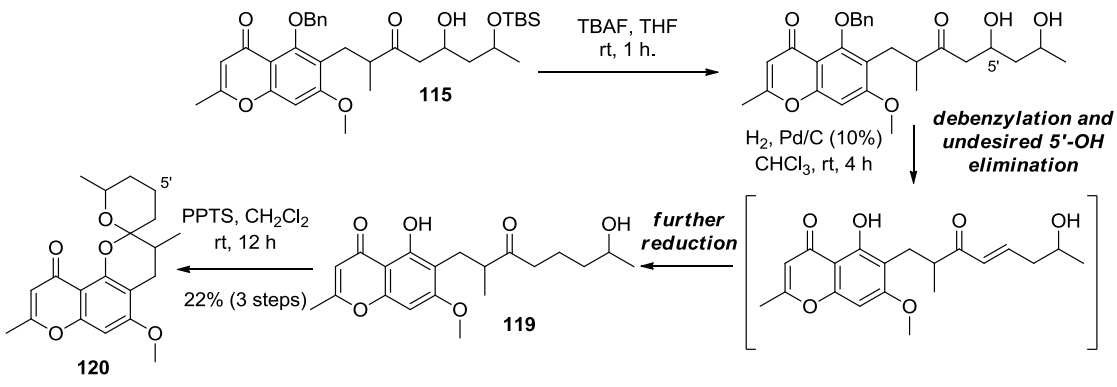
Scheme 45. *Synthesis of aldehyde (S)-**111**.*

With the TBS-protected aldehyde **111** in hand, aldol reaction of aldehyde **111** with benzyl protected methyl ketone **116** and the subsequent deprotection-spiroketalisation sequence using linear cyclisation precursor **115** had to be investigated (**Scheme 46**). Towards this end, phenol **107** was first protected as a benzyl ether by treatment with benzyl bromide, potassium carbonate and tetrabutylammonium iodide in acetone at reflux for 24 h to afford benzyl protected olefin **117** in good yield. Hydroboration-oxidation of the olefin **117** using (–)-Ipc_2BH in THF at rt for 2 h furnished secondary alcohol **118** in moderate yield with poor asymmetric induction (ca. ~20% *ee*). The optically active (–)-Ipc_2BH was used over optically inactive borane dimethylsulfide due to the superior yield delivered by (–)-Ipc_2BH in this particular hydroboration-oxidation reaction. As asymmetric induction was poor and not of concern, the chemical structures in this section will be drawn without indication of stereochemical information. Secondary alcohol **118** was oxidised with IBX in DMSO for 2 h to afford benzyl protected methyl ketone **116**. Boron mediated aldol reaction between TBS-protected aldehyde (±)-**111** and methyl ketone **116** was accomplished with the use of (+)-Ipc_2BCl, NEt_3 in Et_2O at –78 °C to afford the acyclic spiroketal precursor **115** as a complex mixture of several, inseparable diastereoisomers in moderate yield.



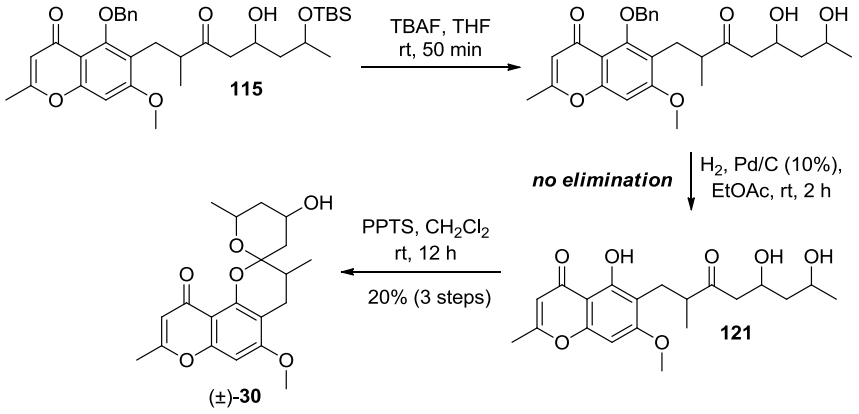
Scheme 46. *Synthesis of β-hydroxyketone **115**.*

With the Bn-protected β-hydroxyketone **115** in hand, the deprotection/cyclisation sequence was next investigated. The TBS protecting group of **115** was first deprotected by use of tetrabutylammonium fluoride in THF at rt for 1 h (**Scheme 47**). Subsequent debenzylation under reductive conditions using Pd/C (10%) and hydrogen gas in $CHCl_3$ afforded eliminated and reduced keto-diol **119**, which was cyclised directly using PPTS in dichloromethane at rt for 12 h. The spiroketal isolated was subsequently identified as C-5′ deoxy spiroketal **120**.



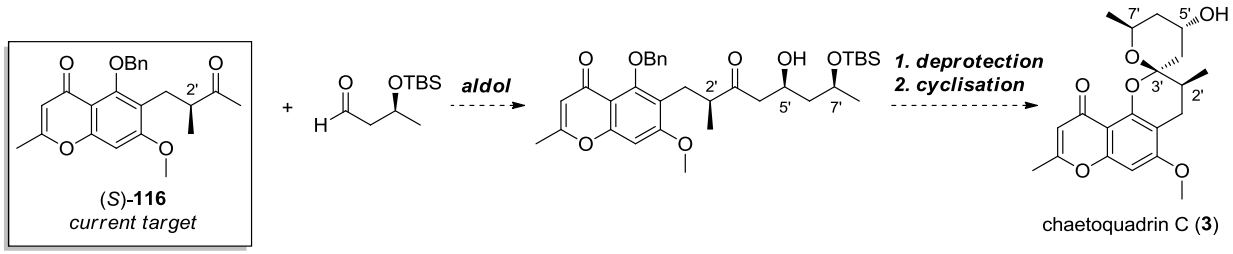
Scheme 47. *Synthesis of* ***120****.*

Fortunately, use of EtOAc as the solvent to effect the hydrogenolysis in the debenzylation reaction over Pd/C (10%) circumvented the undesired elimination reaction affording free phenol **121** which underwent cyclisation using PPTS in dichloromethane at rt for 12 h to furnish the desired spiroketal (±)-**30** in moderate yield (**Scheme 48**).



Scheme 48. *Synthesis of spiroketal (±)-****30****.*

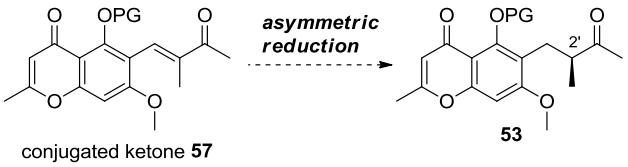
In conclusion, the use of TBS and benzyl groups in precursor **115** proved effective in accessing the spiroketal ring system of chaetoquadrins A–C. Execution of an asymmetric variant of the synthesis was next investigated. Our attention therefore was refocused on exploring methods to establish the C-2′stereocentre of the chaetoquadrins by investigating a method to prepare enantiopure methyl ketone (*S*)-**116** (**Scheme 49**).



Scheme 49. *Strategy for stereoselective synthesis of chaetoquadrin C (**3**) requires enantiopure preparation of (S)-**116**.*

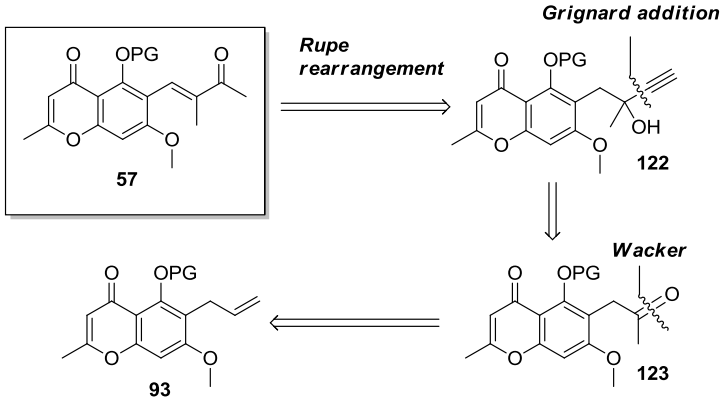
3.3 Attempted use of Rupe rearrangement to prepare conjugated ketone 57

Installation of the required stereocentre at C-2′ in ketone **53** *via* asymmetric reduction of a double bond present in the conjugated ketone **57** was next investigated. (**Scheme 50**).



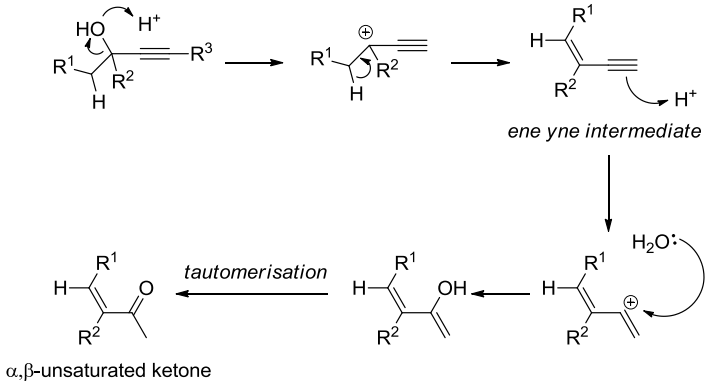
Scheme 50. *Proposed asymmetric reduction of conjugated ketone **57**.*

The first approach to the α,β-unsaturated ketone **57** involved preparation of hydroxyacetylene **122** that would undergo Rupe rearrangement to afford the desired α,β-unsaturated ketone **57**. Acetylene **122** was to be accessed *via* Grignard addition to ketone **123**. Wacker oxidation of olefin **93** would furnish ketone **123**. (**Scheme 51**).



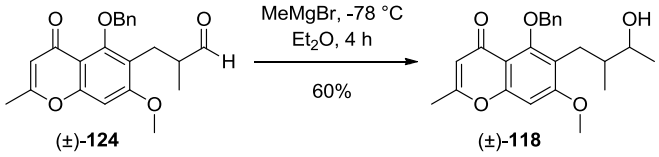
Scheme 51. *Retrosynthetic analysis of α,β-unsaturated ketone **57**.*

The Rupe rearrangement is an acid catalysed rearrangement of a tertiary (terminal) propargyl alcohol which bears a proton beta to the acetylene functionality.[16] Initial acid catalysed dehydration of the alcohol results in an enyne intermediate which is then re-hydrated to form an α,β-unsaturated ketone (**Scheme 52**).



Scheme 52. *Reaction mechanism of Rupe rearrangement.*

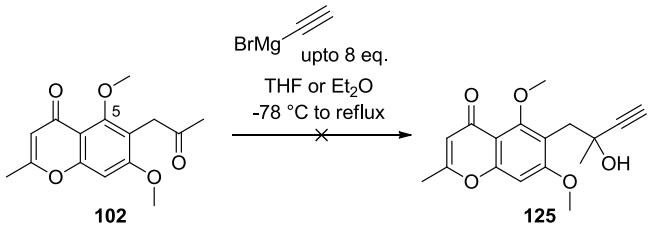
The potential incompatibility of the chromone heterocycle with a Grignard reagent was a concern due to the presence of an electrophilic pyranone moiety inherent in the chromone heterocycle. In order to investigate whether use of a Grignard reaction was possible on this system, a benzyl protected model aldehyde (±)-**124** was prepared and successfully alkylated with methyl magnesium bromide in Et_2O at –78 °C for 4 h to afford secondary alcohol (±)-**118** in 60% yield. (**Scheme 53**).



Scheme 53. *Successful Grignard reaction onto chromone aldehyde **124**.*

The synthesis of the acetylene **125** required for the Rupe rearrangement was now investigated (**Scheme 54**). For the preliminary investigation, methoxy protected methyl ketone **102** which was readily available from previous Wittig reaction studies was used (*vide supra*, **Section 3.2 A**). Upon success of the Rupe rearrangement it was planned to repeat the chemistry with a benzyl protecting group in place of the C-5 methoxy group. Disappointingly, addition of a vast excess of ethynylmagnesium bromide (up to 8 equivalents) to methyl ketone **102** in either

THF or Et_2O at reflux temperatures did not afford **125**. It was postulated that this lack of reactivity was due to the presence of acidic benzylic protons in methyl ketone **102**.

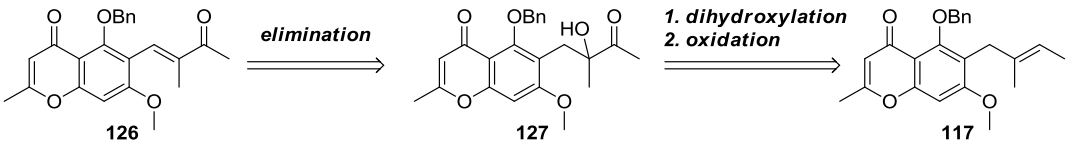


Scheme 54. *Unsuccessful Grignard reaction of methyl ketone **102**.*

3.4 Attempted synthesis of unsaturated ketone 126 via synthesis and elimination of acyloin 127 and 129

A. Strategy

Preparation of the required α,β–unsaturated ketone **126** *via* elimination of acyloin **127** was next considered (**Scheme 55**). Acyloin **127** itself could be prepared from dihydroxylation-oxidation sequence of trisubstituted olefin **117**.



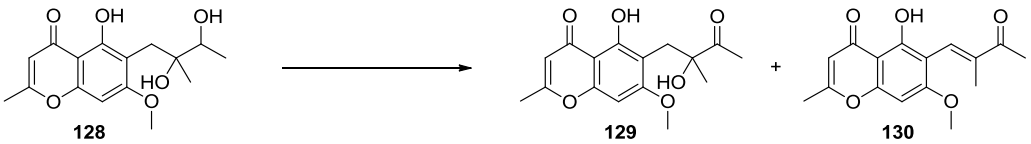
Scheme 55. *Retrosynthetic analysis of α,β unsaturated carbonyl **126**.*

*B. Synthesis of acyloin **129***

Interestingly, whereas dihydroxylation does not occur when the C-5 phenol moiety is protected with a benzyl protecting group, the reaction proceeds smoothly provided the phenol is unprotected to afford diol **128** from **107** suggesting some degree of intramolecular co-ordination with OsO_4. (**Scheme 56**).

Scheme 56. *Synthesis of diol **128**.*

The resulting diol **128** was oxidised under harsh conditions with the intention of simultaneously promoting the elimination of the tertiary alcohol. Unfortunately, neither un-buffered DMP oxidation nor IBX oxidation in hot DMSO (80 °C) for 12 h induced the elimination to take place to afford **130**. These reagents did however oxidise the secondary alcohol **128** to ketone **129** as desired (**Table 9**).

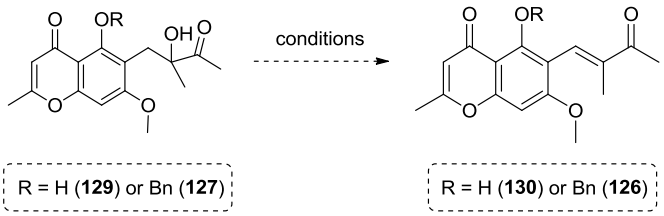


Entry	Conditions	Result
1	IBX (4 or 8 eq), DMSO, 80 °C, 12 h	**129** : 70%
2	DMP (3 eq), DCM, overnight, rt	**129** : 56%

Table 9. *Oxidation of diol **128**.*

*C. Attempted elimination of acyloin **129** and **127***

The next step required elimination of the tertiary alcohol in acyloin **129**. It was therefore desirable to introduce a leaving group on the tertiary alcohol to facilitate the elimination step (**Table 10**). Towards this end, acyloin **129** was acetylated using acetic anhydride with and without acid catalysis (entry 1, 3) without success. Exposure to concentrated sulfuric acid led only to partial decomposition of the starting material (entry 2). Mesylation of the tertiary alcohol using methanesulfonyl chloride and triethylamine in dichloromethane was also unsuccessful (entry 5). It was hoped that use of the non-nucleophilic base 1,8-diazabicycloundec-7-ene in THF at reflux may effect the desired transformation, however this was unsuccessful using both unprotected acyloin **129** and benzyl protected acyloin **127** (entries 4, 6).



Entry	Conditions	Result
1 (R = H)	Ac_2O, reflux, overnight	starting material
2 (R = H)	conc. H_2SO_4	starting material + decomposition
3 (R = H)	Ac_2O, H_2SO_4 (cat)	decomposition
4 (R = H)	DBU, THF, reflux, overnight	starting material
5 (R = Bn)	NEt_3, MsCl, CH_2Cl_2, 0 °C–reflux, overnight	starting material
6 (R = Bn)	DBU, THF, reflux, overnight	starting material

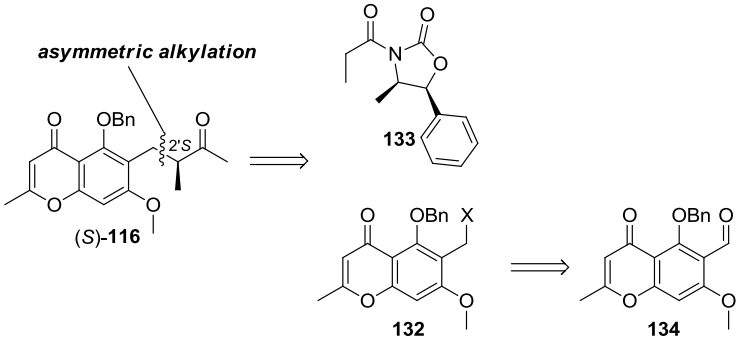
Table 10. *Attempted elimination of acyloin* ***129*** *and* ***127****.*

The failure to effect the key elimination of the acyloin required rethinking of the synthetic strategy. Attention turned away from the synthesis of α,β-unsaturated ketone **126** and a new approach to effect the enantioselective synthesis of the chaetoquadrins was investigated.

3.5 Use of a chiral auxiliary to effect asymmetric synthesis of imide 141

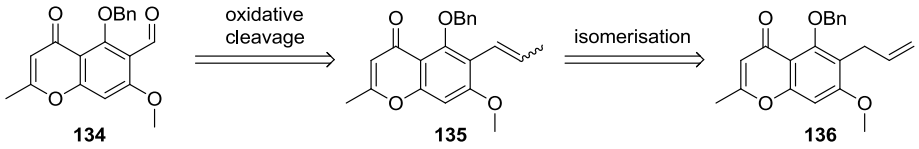
A. Strategy

In our third attempt to install the C-2′ stereocentre of methyl ketone (*S*)-**116**, methyl ketone was disconnected to a benzylic halide **132** and a chiral propionate fragment **133**. The benzylic halide was to be prepared from substituted benzylic aldehyde **134** (**Scheme 57**).



Scheme 57. *Retrosynthetic analysis of ketone (S)-****116****.*

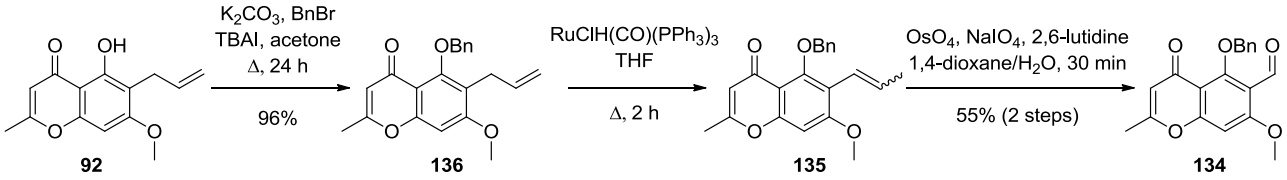
The required benzylic aldehyde **134** could be prepared by oxidative cleavage of conjugated olefin **135** which would be available from thermal isomerisation of protected allyl olefin **136**. (**Scheme 58**).



Scheme 58. *Retrosynthetic analysis of aldehyde **134**.*

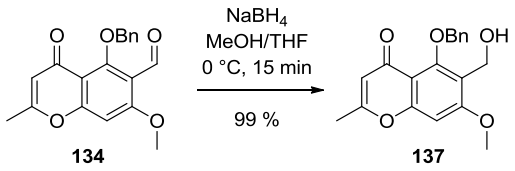
*B. Synthesis of bromide **58***

Towards this end, chromone **92** was treated with potassium carbonate, benzyl bromide and TBAI in acetone at reflux for 24 h to afford benzyl protected olefin **136**. Benzyl protected olefin **136** was then treated with $RuClH(CO)(PPh_3)_3$ in THF heated at reflux to afford the thermodynamically more stable conjugated olefin **135**.[77,78] A one-pot dihydroxylation-oxidative cleavage sequence was effected using catalytic osmium tetroxide, a stoichiometric amount of sodium periodate and 2,6-lutidine in aqueous 1,4-dioxane to afford aldehyde **134** in 55% yield over two steps (**Scheme 59**).



Scheme 59. *Synthesis of aldehyde **134**.*

Conversion of aldehyde **134** into a benzyl halide was next investigated in preparation for the introduction of the chiral auxiliary. Towards this end, aldehyde **134** was reduced with sodium borohydride in MeOH/THF at 0 °C for 15 min to afford benzyl alcohol **137** in good yield (**Scheme 60**).

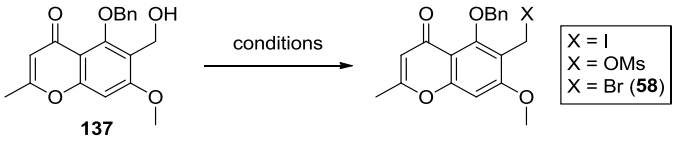


Scheme 60. *Synthesis of alcohol **137**.*

Subsequent conversion of alcohol **137** into a benzyl halide required extensive screening and optimisation of reaction conditions. Our attempts to effect this reaction are tabulated below (**Table 11**).

Alcohol **137** was first treated with phosphorus tribromide in Et_2O at 0 °C for 2 h to give the desired benzylic bromide **58** in poor yield (entry 1). The poor solubility of the starting material in this solvent was noted. Changing the solvent from Et_2O to dichloromethane and leaving the reaction to stir overnight resulted in decomposition (entry 2). Execution of an Appel reaction with iodine, triphenylphosphine and imidazole in dichloromethane was unsuccessful (entry 3). Repeating the same reaction conditions as used for entry 2 but limiting the reaction time to 2 h gave the desired product in poor yield (entry 4). Mesylation of the alcohol under standard conditions was unsuccessful (entry 5). It was suspected that the HBr present in phosphorus tribromide may have degraded the product. A small quantity of pyridine was therefore added to the reaction to serve as a buffer in the reaction with phosphorus tribromide. However, this afforded the desired product in only 31% yield after 3 h at 0 °C (entry 6). Decomposition of the starting material was observed when these reaction conditions were repeated and the reaction was allowed to run overnight (entry 7).

Effecting the bromination using NBS and triphenylphosphine was next attempted. This protocol delivered the desired bromide in 35% yield using $CHCl_3$ as solvent (entry 8) while use of DMF in place of $CHCl_3$ resulted in decomposition of the starting material (entry 9). In an attempt to solve the solubility problems, bromination with phosphorus tribromide was repeated in a 1:1 ether/tetrahydrofuran solvent system. This improved the yield of the desired bromide to 44% (entry 10). Finally use of phosphorus tribromide at 0 °C in 1:1 dichloromethane/THF afforded the desired product in excellent yield (entry 11).



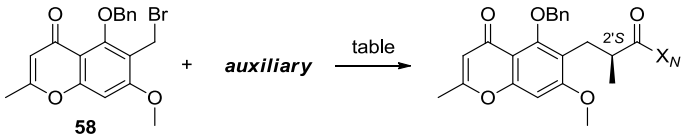
Entry	Conditions	Result
1	PBr_3, Et_2O, 0 °C, 2 h	20%
2	PBr_3, CH_2Cl_2, rt, overnight	decomposition
3	I_2, PPh_3, imidazole, CH_2Cl_2	no reaction
4	PBr_3, CH_2Cl_2, 0 °C, 2 h	23%
5	MsCl, NEt_3, 0 °C, LiBr, THF	no reaction
6	PBr_3, py, CH_2Cl_2, 0 °C, 3 h	31%
7	PBr_3, py, CH_2Cl_2, 0 °C, overnight	decomposition
8	NBS, PPh_3, CH_2Cl_2, 0 °C–rt, overnight	35%
9	NBS, PPh_3, DMF, 0 °C–rt, 1 h	decomposition
10	PBr_3, Et_2O/THF, 0 °C, 4 h	44%
11	PBr_3, CH_2Cl_2/THF, 0 °C, 4–6 h	80–99%

Table 11. *Reaction of alcohol* ***137****.*

C. Synthesis of imide ***141***

With benzyl bromide **58** in hand, alkylation with a chiral propionate fragment was next investigated (**Table 12**). Alkylation of valine-derived oxazolidinone **138** with bromide **58** using KO^{t}Bu was unsuccessful (entry 1).[79,80] This alkylation was realised in poor yield using NaHMDS as base (entry 2). The low yield obtained for this reaction and the difficulty experienced in the subsequent reductive cleavage step made use of this chiral propionate fragment **138** undesirable. Alkylation with phenylalanine-derived oxazolidinone **139** using NaHMDS as base in THF at –78 °C was unsuccessful (entry 3)[81] as was alkylation with *N*-propionyl pseudoephedrine **140** effected by LDA, LiCl in THF at –78 °C–0 °C (entry 4).[82,83]

To our delight alkylation of norephedrine-based auxiliary **133** with bromide **58** using NaHMDS as base and THF as solvent at –78 °C was successful (entry 5).[84]



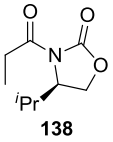
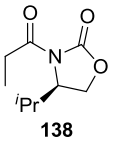
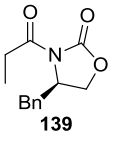
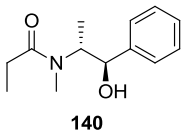
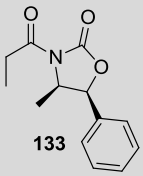
Entry	Auxiliary	Conditions	Result
1	 **138**	KO^{t}Bu, THF, –78 °C	no reaction
2	 **138**	NaHMDS, THF –78 °C	16%
3	 **139**	NaHMDS, THF –78 °C	no reaction
4	 **140**	LDA, LiCl, THF –78 °C – 0 °C	no reaction
5	 **133**	NaHMDS, THF –78 °C	51%

Table 12. *Alkylation of bromide* ***58*** *with a chiral propionate* ***133****.*

The resulting imide **141** formed colourless crystals during purification *via* flash column chromatography and an X-ray crystal structure was able to be obtained confirming that the newly established stereocentre had the *S* configuration (**Figure 21**).

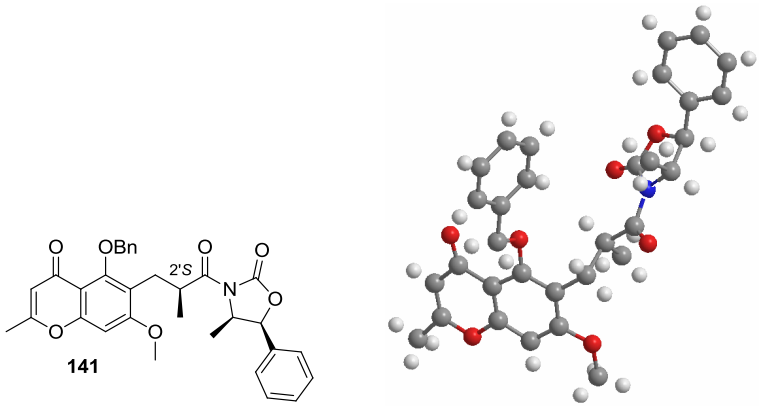
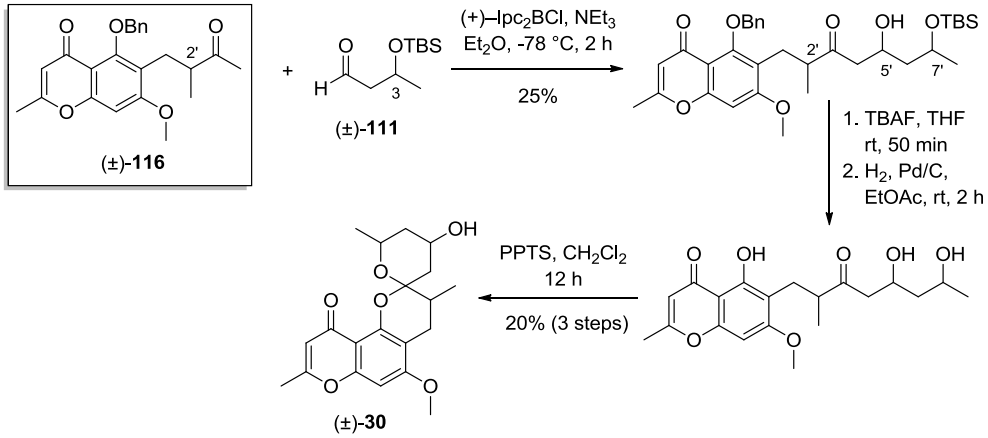


Figure 21. *Left: Structural formula of imide* ***141****. Right: X-ray crystal structure of imide* ***141****.*

Thus a reliable, scalable method to form the key stereocentre at C-2′ in imide **141** was secured. This stereocentre in imide **141** served ultimately as the origin of C-2′ stereocentre in spiroketal chaetoquadrins. In the course of this research multigram quantities of this intermediate **141** were prepared.

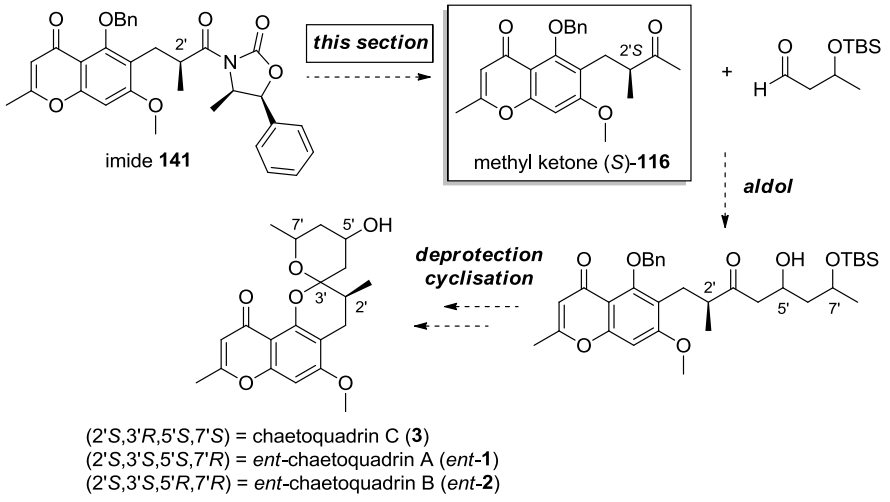
*D. Synthesis of methyl ketone (S)-**116***

The racemic synthesis of spiroketal (±)-**30** had been accomplished starting from racemic methyl ketone (±)-**116** (**Scheme 61**. Also see **Chapter 3**, **Section 3.2 D**).



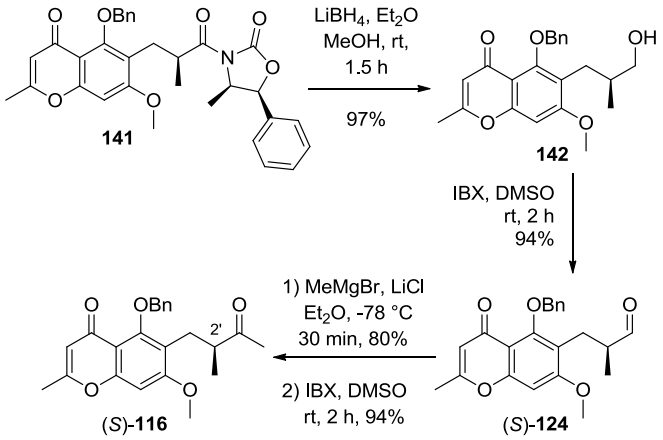
Scheme 61. *Synthesis of (±)-**30**.*

In order to execute a stereoselective synthesis of chaetoquadrin natural products it was now necessary to convert imide **141** to enantiopure methyl ketone (*S*)-**116** (**Scheme 62**).



Scheme 62. *Synthesis of (S)-**116** in the context of the spiroketal chaetoquadrin synthesis.*

Towards this end, the imide auxiliary was cleaved from **141** under reductive conditions using $LiBH_4$ and MeOH in Et_2O at room temperature for 1.5 h to afford primary alcohol **142** in excellent yield (97%) (**Scheme 63**). To obtain a good yield it was important that the reducing reagent was added slowly, typically over 1.5 h and in several portions. IBX oxidation of primary alcohol **142** in DMSO at room temperature for 2 h afforded the corresponding aldehyde (*S*)-**124** in 94% yield. Following this step, Grignard reaction using methyl magnesium bromide and excess lithium chloride (6 equivalents) in Et_2O at –78 °C for 30 min afforded the corresponding secondary alcohol in 80% yield. It was pleasing to observe that under these conditions the nucleophilic attack of the Grignard reagent at the pyranone did not take place. IBX oxidation of the secondary alcohol in DMSO at room temperature for 2 h afforded the desired methyl ketone (*S*)-**116** in 94% yield.



Scheme 63. *Synthesis of methyl ketone (S)-**116**.*

With the methyl ketone (*S*)-**116** in hand, the subsequent chapter explores the pivotal asymmetric boron aldol reaction and elaboration of aldol adducts into several chaetoquadrin natural products.

3.6 Summary

A racemic synthesis of chaetoquadrins A–C and chiral auxiliary-mediated stereoselective synthesis of imide **114** was accomplished. Aforementioned imide **114** was successfully converted into methyl ketone **116** in four high yielding steps in anticipation of a stereoselective synthesis of chaetoquadrins A–C.

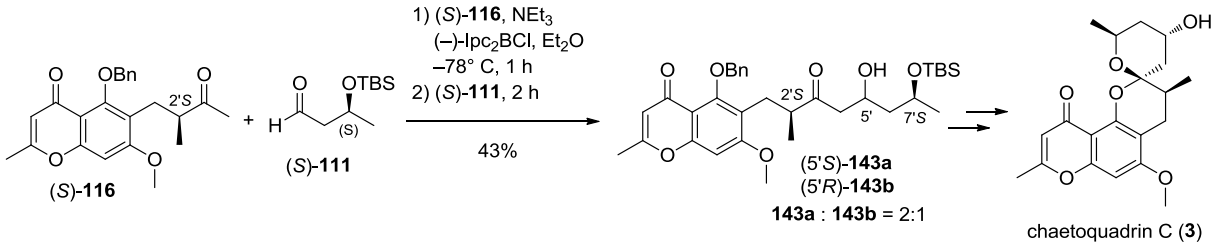
Chapter Four

Results and Discussion

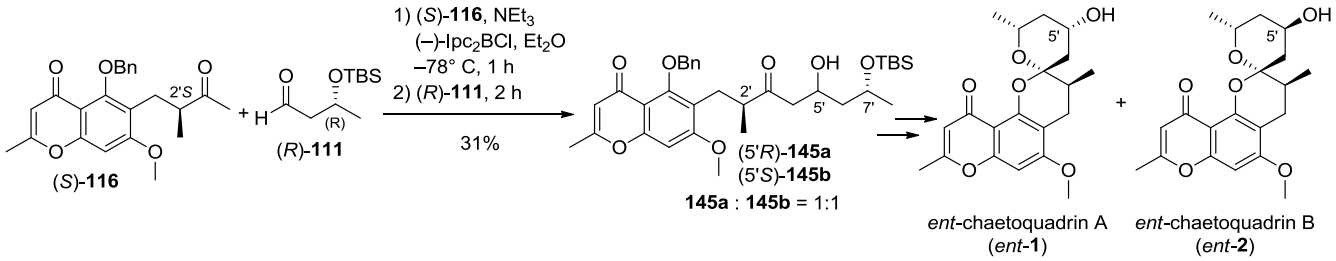
The total synthesis of the chaetoquadrins

4.0 Overview

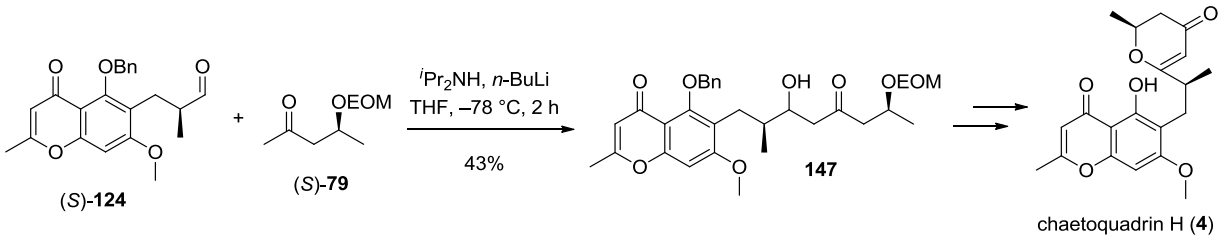
In this chapter the successful total syntheses of chaetoquadrins C (**3**), *ent*-A (*ent*-**1**) & *ent*-B (*ent*-**2**), H (**4**) and I (**5**) are detailed (**Schemes 64**, **65**, **66** and **67** respectively).



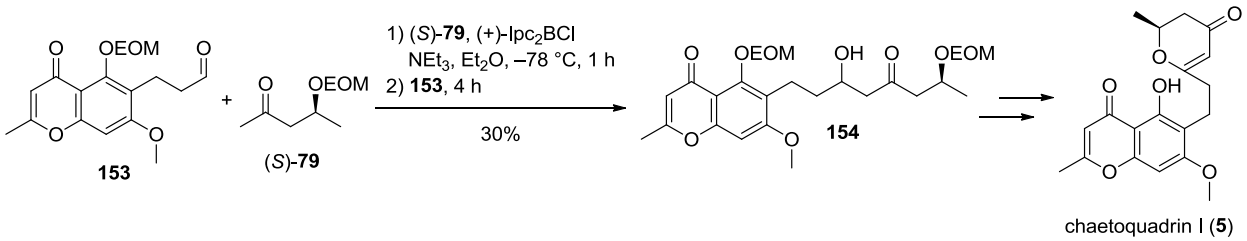
Scheme 64. *Synthesis of chaetoquadrin C (**3**).*



Scheme 65. *Synthesis of ent-chaetoquadrins A (ent-**1**) and B (ent-**2**).*



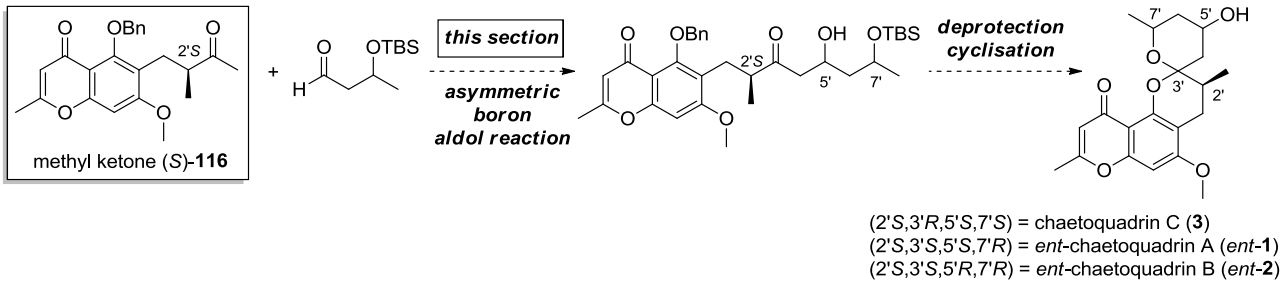
Scheme 66. *Synthesis of chaetoquadrin H (**4**).*



Scheme 67. *Synthesis of chaetoquadrin I (**5**).*

4.2 Asymmetric Paterson aldol reaction

With methyl ketone (*S*)-**116** in hand, stereoselective synthesis of chaetoquadrin natural products required the execution of an asymmetric boron aldol reaction followed by a deprotection–cyclisation sequence (**Scheme 68**).



Scheme 68. *Strategy towards chaetoquadrin natural products.*

The reaction between optically active diisopinocampheyl (Ipc_2) boron enolate and an aldehyde to yield a β-hydroxyketone is known as the Paterson aldol reaction. Mechanistically, the reaction takes advantage of the 'conformational lock' afforded by the sterically demanding isopinocampheyl (Ipc) ligands, thereby leading to predictable asymmetric induction. With a *Z* (–)-Ipc_2 boron enolate the standard Zimmerman-Traxler transition state can be invoked where the serious steric interaction between the enolate side chain (R^2) and the (–)-Ipc ligand is entirely minimised (**Figure 22**, Top). In consideration of the chair transition states, *Si*-face attack of the aldehyde is favoured.

However, when using an (–)-Ipc_2 boron enolate derived from an unsubstituted methyl ketone, this trend is reversed and *Re*-face attack is now observed. This has been rationalised with a different, boat transition state where minimisation of the steric interaction between the bulky enolate substituent (R^1) and the (–)-Ipc ligand now dominates (**Figure 22**, Bottom).[85]

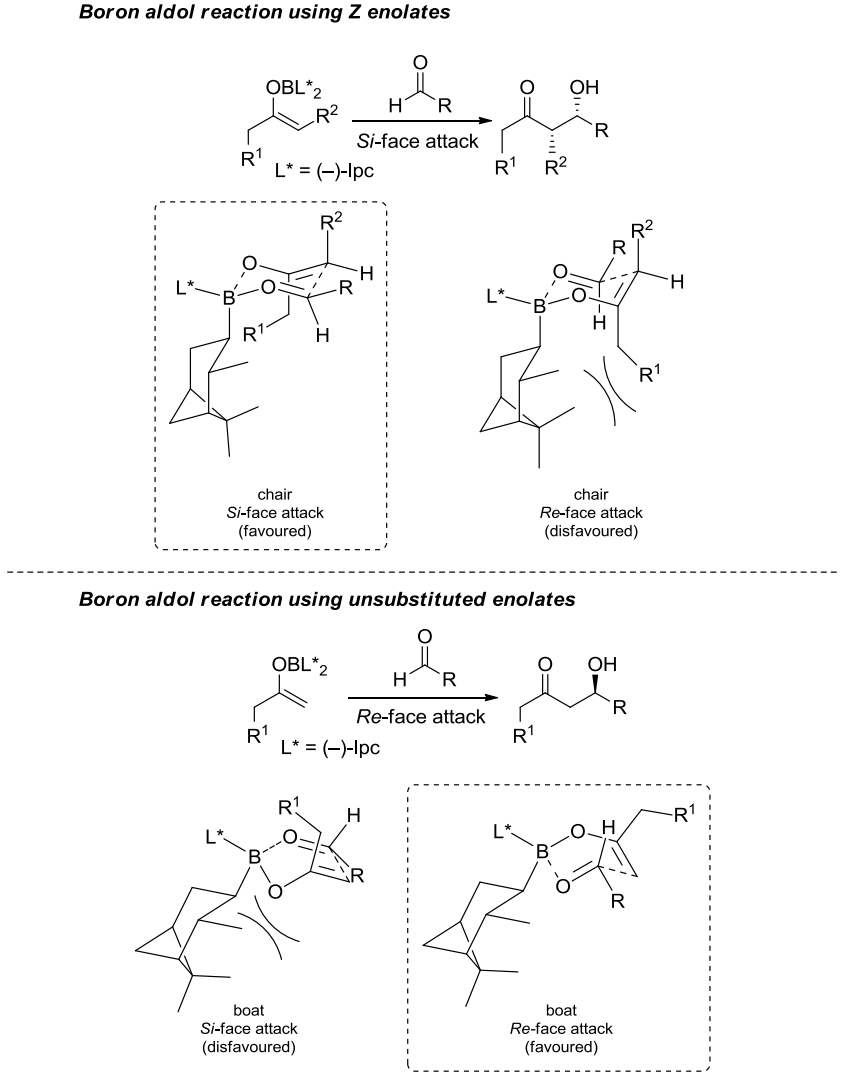


Figure 22. *Possible transition states of the Paterson aldol reaction.*

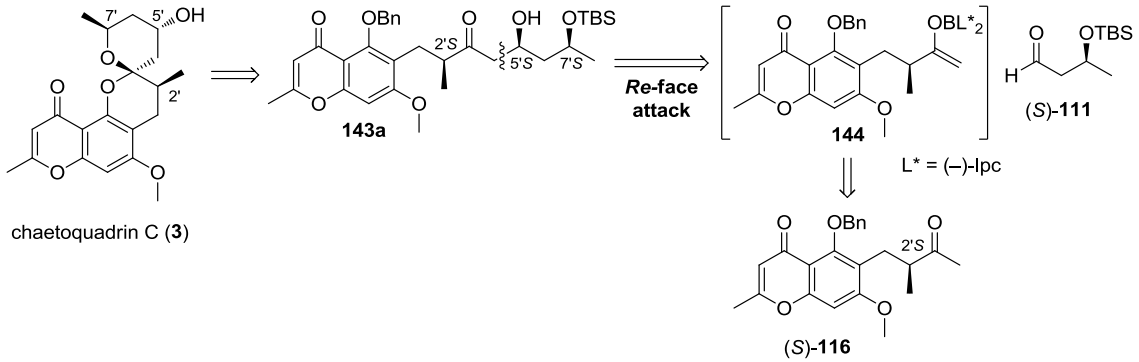
As our aldol reaction partner (*S*)-**116** is a methyl ketone, it was anticipated that our boron aldol reaction would proceed *via* the boat transition state as illustrated in **Figure 22**. The enantioselectivity of this reaction could be reversed by using the (+)-Ipc ligand. A literature search to investigate the expected diastereoselectivity of aldol reactions between α-chiral unsubstituted boron enolates and β-alkoxy aldehydes revealed that no such examples of this reaction type had been reported to date.

Despite questions remaining over the diastereomeric outcome of the proposed aldol reaction, a decision was made to progress with the synthesis. We were motivated by the assured success of the remaining steps which had already been explored on the racemate (see **Chapter 3**, **Section 3.2 D**). With the C-2′ stereocentre of **116** set as *S*, it was now required to execute the boron aldol reaction with the correct facial selectivity.

4.3 Asymmetric total synthesis of chaetoquadrin C (3)

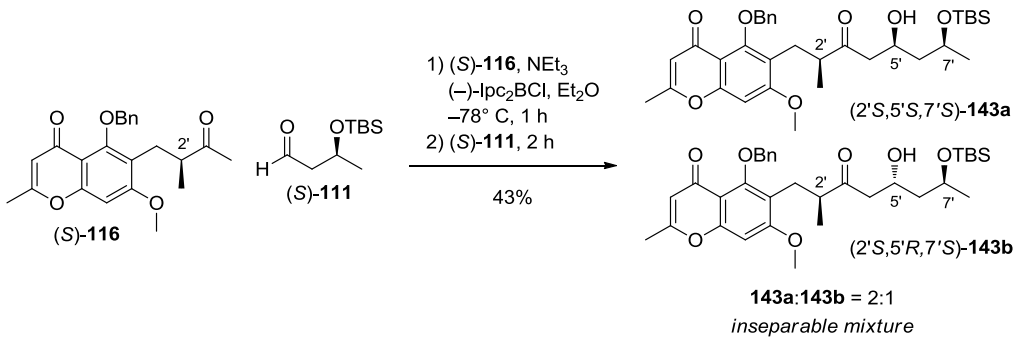
*A. Synthesis of β-hydroxyketone **143a** and **143b***

Chaetoquadrin C (**3**) was chosen as the initial target as it had the highest inhibitory activity against mouse liver MAO. In order to complete the stereoselective synthesis of chaetoquadrin C (**3**) the correct Ipc ligand for the boron aldol reaction had to be chosen. The protected linear precursor **143a** to chaetoquadrin C (**3**) required the stereocentre at C-5′ to be *S* (**Scheme 69**). Thus, *Re* face attack by the boron enolate **144** was required on aldehyde (*S*)-**111**. It was therefore anticipated that the use of (–)-Ipc ligand would give the desired stereochemical outcome.



Scheme 69. *Retrosynthetic analysis of chaetoquadrin C (**3**).*

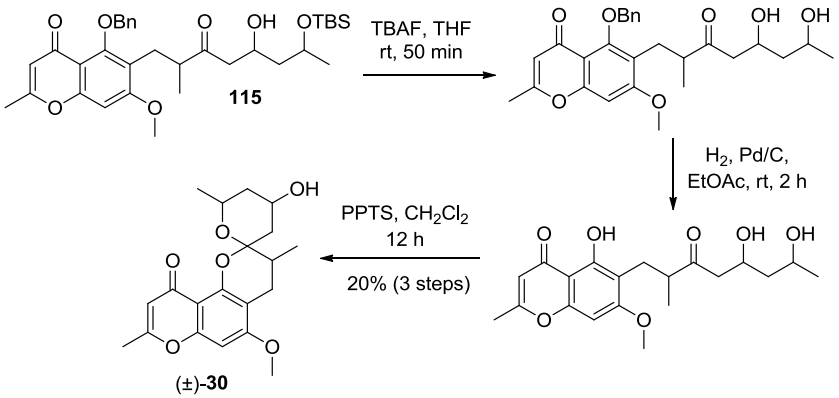
With this information in hand, methyl ketone (*S*)-**116** was treated with triethylamine and (–)-Ipc_2BCl in Et_2O at –78 °C for 1 h to first form the requisite boron enolate *in situ.* TBS-aldehyde (*S*)-**111** was then added and the reaction was stirred for 2 h to afford β-hydroxyketones **143a** and **143b** as a 2:1 mixture of inseparable diastereoisomers in 43% yield (**Scheme 70**). At this point the exact stereochemistry of the β-hydroxyketones was not able to be determined. However, subsequent conversion of the linear precursors to chaetoquadrin C (*vide infra*) established that β-hydroxyketone **143a** was the major product in this reaction.



Scheme 70. *Asymmetric boron aldol reaction between methyl ketone (S)-**116** and aldehyde (S)-**111**.*

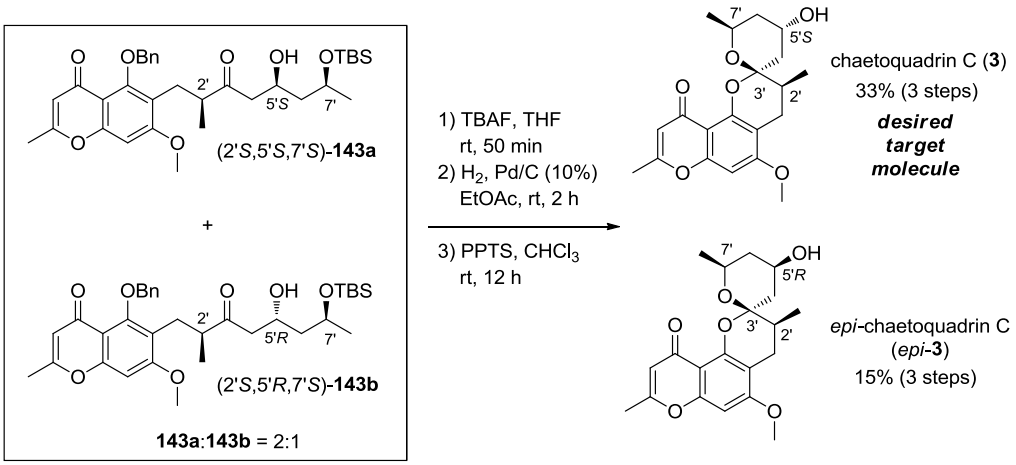
*B. Elaboration of β-hydroxyketones **143a** and **143b** into chaetoquadrin C (**3**) and epi-chaetoquadrin C (epi-**3**) via a deprotection-cyclisation sequence*

The synthetic manipulation of racemic cyclisation precursor **115** to the desired spiroketal (±)-**30** was previously accomplished by TBS deprotection, debenzylation and PPTS–catalysed cyclisation (**Scheme 71**. Also see **Chapter 3**, **Section 3.2 D**).



***Scheme 71.** Previously accomplished synthesis of spiroketal (±)-**30**.*

With the benzyl and TBS-protected diastereomeric mixture of β-hydroxyketones **143a** and **143b** in hand, the aforementioned protocol to elaborate the β-hydroxyketones into the desired spiroketals was now applied (**Scheme 72**). The 2:1 mixture of β-hydroxyketones **143a** and **143b** was first treated with TBAF in THF at rt for 50 min. The crude product from this reaction was then taken up in EtOAc and reacted under a hydrogen atmosphere in the presence of Pd/C (10%) for 2 h. Finally the deprotected linear precursor was reacted with PPTS in $CHCl_3$ for 12 h to afford two bright UV active spots on the TLC plate. Purification of these spots gave chaetoquadrin C (**3**) in 33% yield over three steps as well as an unreported spiroketal (*epi*-**3**) in 15% yield over three steps. These spiroketals **3** and *epi*-**3** were obtained in ca. 2:1 ratio in favour of chaetoquadrin C (**3**) thereby establishing that the aforementioned aldol reaction had proceeded mainly with the desired facial selectivity.



Scheme 72. *Synthesis of chaetoquadrin C (**3**).*

The ^{13}C NMR spectroscopic data for the synthetic sample of chaetoquadrin C (**3**) were in full agreement with those reported for the natural product. The presence of a spiroketal was established by the characteristic quaternary resonance at δ_C 101.1 ppm.

Interestingly for the ^{1}H NMR analysis, chemical shifts in the synthetic material consistently differed from the reported values by 0.07 ppm. It is hypothesised that calibration to silicone grease (δ_H 0.07 ppm) in place of the standard TMS resonance (δ_H 0.00 ppm) may have been performed by the isolation chemists which may explain this consistent discrepancy between the synthetic material and the natural product.

Although α_D values were not reported for chaetoquadrin C (**3**), the CD spectra obtained from our synthetic sample (**Figure 23**) matched the one reported for the natural product (**Figure 24**), confirming the absolute stereochemistry of chaetoquadrin C as depicted. The α_D of the synthetic material was: $[[\alpha]_D^{20}$ -6.67 (*c* 0.30, $CHCl_3$)].

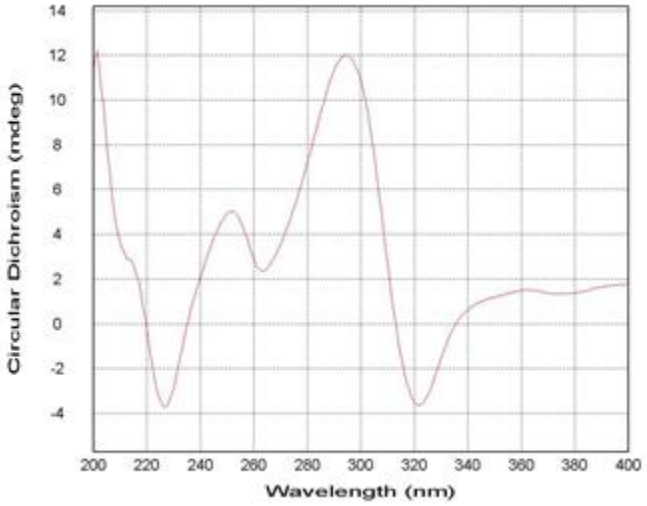


Figure 23. *CD spectrum of synthetic chaetoquadrin C (**3**) in MeOH.*

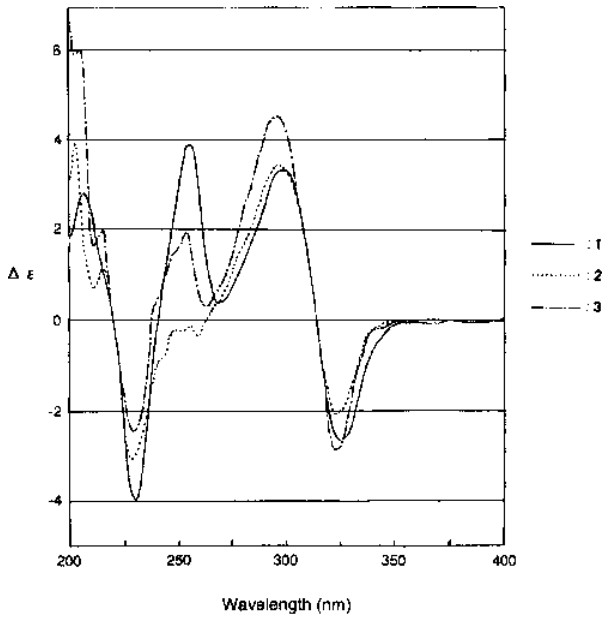
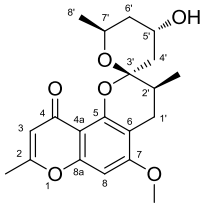


Figure 24. *CD Spectrum of chaetoquadrins A (**1**), B (**2**), and C (**3**) in MeOH as reported by Fujimoto et al. Chaetoquadrin C (**3**) is illustrated with an alternating dotted and dashed line, "– • – • – • – ".*

The direct comparison of the reported ^{1}H NMR and ^{13}C NMR data for chaetoquadrin C (**3**) to those of our synthetic sample is tabulated below (**Table 13**).



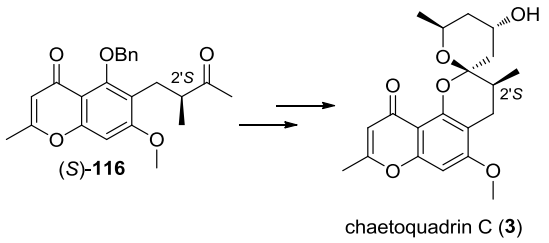
chaetoquadrin C (**3**)

Comparison of ^{1}H NMR of natural product to synthetic material			
Position	Natural chaetoquadrin C	Synthetic chaetoquadrin C	Δ
2'-CH$_3$	1.03 (3H, d, 6.6)	1.10 (3H, d, 6.8)	-0.07
8'	0.94 (3H, d, 6.1)	1.01 (3H, d, 6.3)	-0.07
6'	1.84 (ddd, 14.0, 2.2, 2.2), 1.38 (ddd, 14.0, 2.2, 2.2)	1.87-1.94 (m), 1.41-1.51 (m)	-
2'	1.89 (qdd, 6.6, 12.4, 6.0)	1.94-2.00 (m)	-
2-CH$_3$	2.21 (3H, s)	2.28 (3H, s)	-0.07
4'	2.03 (d, 16.4), 1.98 (d, 16.4)	1.99-2.13 (m)	-
1'	2.55 (dd, 16.8, 6.0), 2.30 (dd, 16.8, 12.4)	2.62 (dd, 16.7, 5.8), 2.37 (dd, 16.7, 12.3)	-0.07
7-OCH$_3$	3.82 (3H, s)	3.89 (3H, s)	-0.07
7'	4.03 (dqd, 12.0, 6.1, 2.2)	4.11 (dqd, 12.1, 6.0, 2.0)	-0.08
5'	4.12 (ddd, 11.9, 3.2, 2.2)	4.19 (ddd, 11.9, 3.3, 2.3)	-0.07
3	5.92 (s)	5.99 (s)	-0.07
5'-OH	6.44 (d, 11.9)	6.51 (d, 11.8)	-0.05
8	6.36 (s)	6.42 (s)	-0.07
Comparison of ^{13}C NMR of natural product to synthetic material			
Position	Natural chaetoquadrin C	Synthetic chaetoquadrin C	Δ
2'-CH$_3$	16.0	16.0	0.0
2-CH$_3$	19.9	19.9	0.0
8'	21.4	21.4	0.0
1'	23.5	23.5	0.0
2'	33.3	33.4	-0.1
4'	35.9	35.9	0.0
6'	40.1	40.2	-0.1
7-OCH$_3$	55.8	55.8	0.0
7'	62.4	62.4	0.0
5'	63.8	63.8	0.0
8	91.3	91.3	0.0
3'	101.1	101.1	0.0
6	109.2	109.3	-0.1
4a	108.0	108.1	-0.1
3	111.5	111.5	0.0
5	150.8	150.8	0.0
8a	157.9	158.0	-0.1
7	160.8	160.8	0.0
2	163.4	163.4	0.0
4	177.6	177.6	0.0

Table 13. *^{1}H NMR and ^{13}C NMR data of synthetic and natural chaetoquadrin C (**3**) in $CDCl_3$.*

4.4 Asymmetric total synthesis of ent-chaetoquadrin B (ent-2) and ent-chaetoquadrin A (ent-1)

With the synthesis of chaetoquadrin C (**3**) successfully accomplished from methyl ketone (*S*)-**116** (**Scheme 73**), our attention turned to the synthesis of chaetoquadrins B (**2**) and A (**1**).



Scheme 73. *Synthesis of chaetoquadrin C (**3**). The C-2´stereocentre of **3** was derived directly from (S)-**116**.*

The C-2´ stereocentre in chaetoquadrins A (**1**) and B (**2**) was set as *R* (**Figure 25**). As the C-2´ stereocentre of the prepared methyl ketone (*S*)-**116** was set as *S*, it was decided to synthesise both *enantiomers* of chaetoquadrins A (*ent*-**1**) and B (*ent*-**2**) in order to confirm the relative and absolute stereochemistry of the chaetoquadrins with material on hand. In the following discussion the synthesis of *ent*-chaetoquadrin B (*ent*-**2**) is presented first (**Section 4.4, A**), followed by the synthesis of *ent*-chaetoquadrin A (*ent*-**1**) (**Section 4.4, C**).

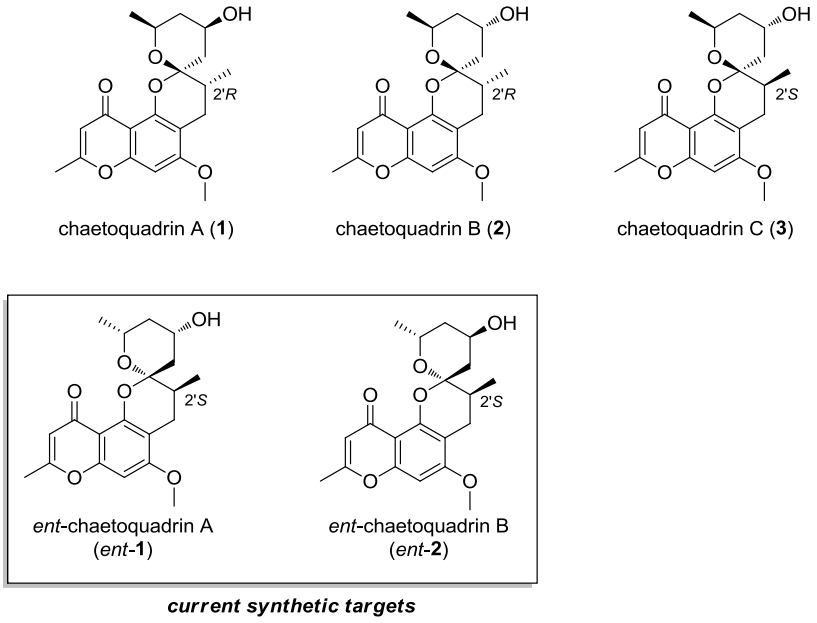
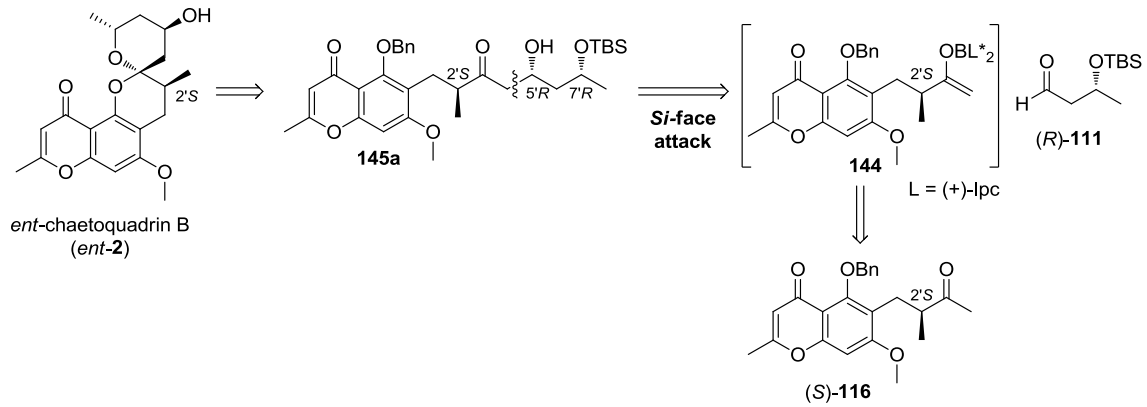


Figure 25. *Structures of ent-chaetoquadrin A (ent-**1**), ent-chaetoquadrin B (ent-**2**) are shown as synthetic targets for this section. Structures of chaetoquadrins A–C (**1–3**) are also shown.*

*A. Retrosynthetic analysis of ent-chaetoquadrin B (ent-**2**)*

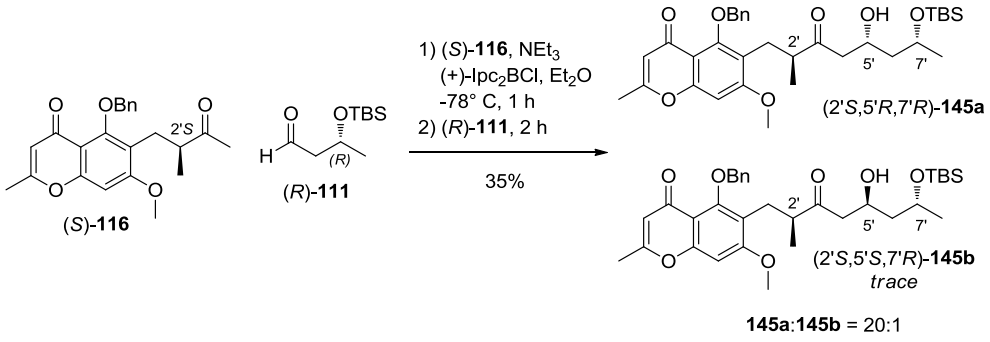
The retrosynthetic analysis for *ent*-chaetoquadrin B (*ent*-**2**) is illustrated below (**Scheme 74**). The protected linear precursor **145a** to *ent*-chaetoquadrin B (*ent*-**2**) required the C-5′ stereocentre to be of the *R* configuration. *Si* face attack on aldehyde (*R*)-**111** by the boron enolate **144** was required. It was therefore recognised that use of the (+)-Ipc ligand would give the desired stereochemical outcome.



Scheme 74. *Retrosynthetic analysis for ent-chaetoquadrin B (ent-**2**).*

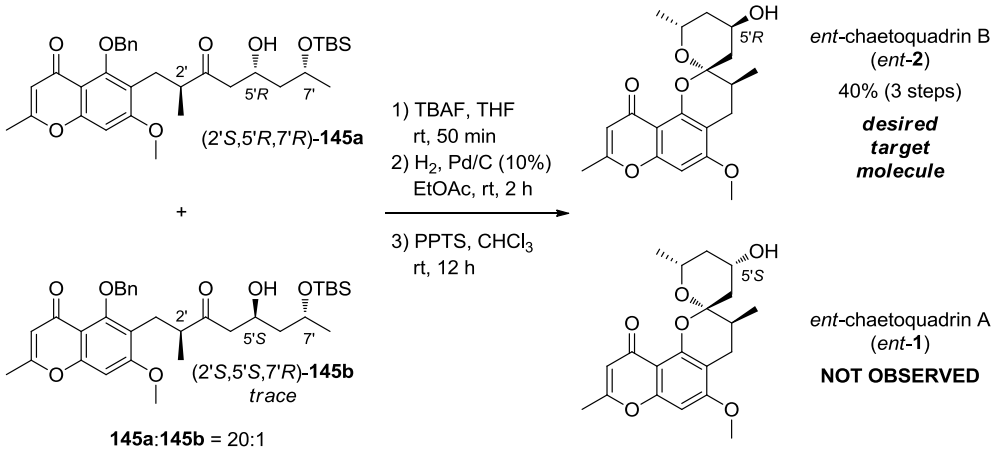
*B. Reaction of methyl ketone (S)-**116** with (+)-Ipc$_2$BCl and aldehyde (R)-**111** and synthesis of ent-chaetoquadrin B (ent-**2**)*

To prepare *ent*-chaetoquadrin B (*ent*-**2**), methyl ketone (*S*)-**116** was next treated with triethylamine and (+)-Ipc$_2$BCl in Et_2O at –78 °C for 1 h (**Scheme 75**). After formation of the boron enolate, (*R*)-TBS aldehyde **111** was added and the reaction was stirred for 2 h. Pleasingly, this aldol reaction afforded β-hydroxyketone **145a** in 35% yield. Close inspection of the ^{1}H NMR spectra of the aldol adduct established the diastereoselectivity of this reaction to be approximately 20:1. Although the exact stereochemistry of the β-hydroxyketone (**145a**) was not able to be determined at this point, subsequent conversion of β-hydroxyketone **145a** to *ent*-chaetoquadrin B (*ent*-**2**) established the stereochemistry of **145a** to be 2′*S*, 5′*R*, 7′*R*. Thus aldol reaction between ketone (*S*)-**116** and aldehyde (*R*)-**111** mediated by (+)–Ipc$_2$BCl had proceeded with excellent facial selectivity.



Scheme 75. *Asymmetric boron aldol reaction between methyl ketone (S)-**116** and aldehyde (R)-**111**.*

Application of the previously established deprotection/cyclisation protocol (*vide supra*) afforded *ent*-chaetoquadrin B (*ent*-**2**) as the sole spiroketal product in 40% yield over three steps (**Scheme 76**).



Scheme 76. *Synthesis of ent-chaetoquadrin B (ent-**2**).*

Although α_D values for chaetoquadrin B were also unreported, CD spectra comparison could be made between the synthetic sample and the natural product to establish the absolute stereochemistry. This analysis established that the enantiomer of chaetoquadrin B (*ent*-**2**) had been successfully prepared, as the CD spectrum of the synthetic material (**Figure 26**) was a mirror image to the one reported for the natural product chaetoquadrin B (**Figure 27**).

The α_D value recorded for synthetic chaetoquadrin B was $[\alpha]_D^{20}$ +19.3 (*c* 0.46, $CHCl_3$).

Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) for the synthetic sample of chaetoquadrin B (**2**) were in full agreement with those recorded for the natural product.

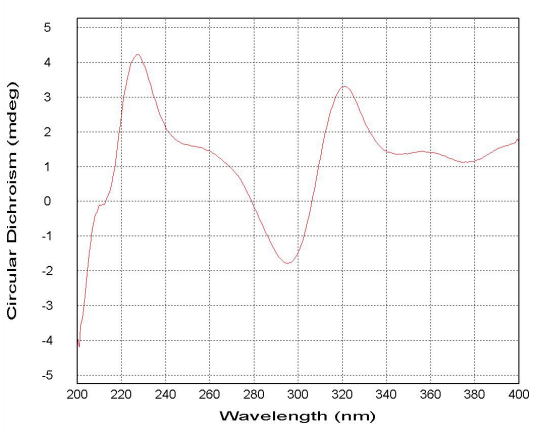


Figure 26. *CD spectrum of ent-chaetoquadrin B (ent-**2**) in MeOH.*

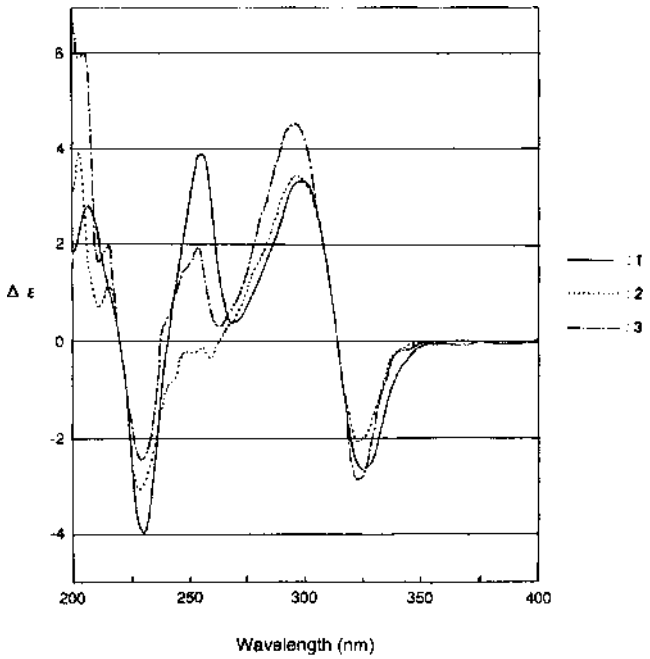
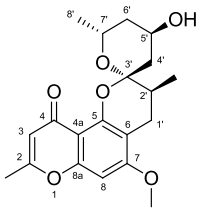


Figure 27. *CD Spectrum of chaetoquadrins A (**1**), B (**2**), and C (**3**) in MeOH as reported by Fujimoto et al. Chaetoquadrin B (**2**) is illustrated with a dotted line "· · · ·".*

The comparison of the reported ^{1}H NMR and ^{13}C NMR data for *ent*-chaetoquadrins B (*ent*-**2**) are tabulated below (**Table 14**).



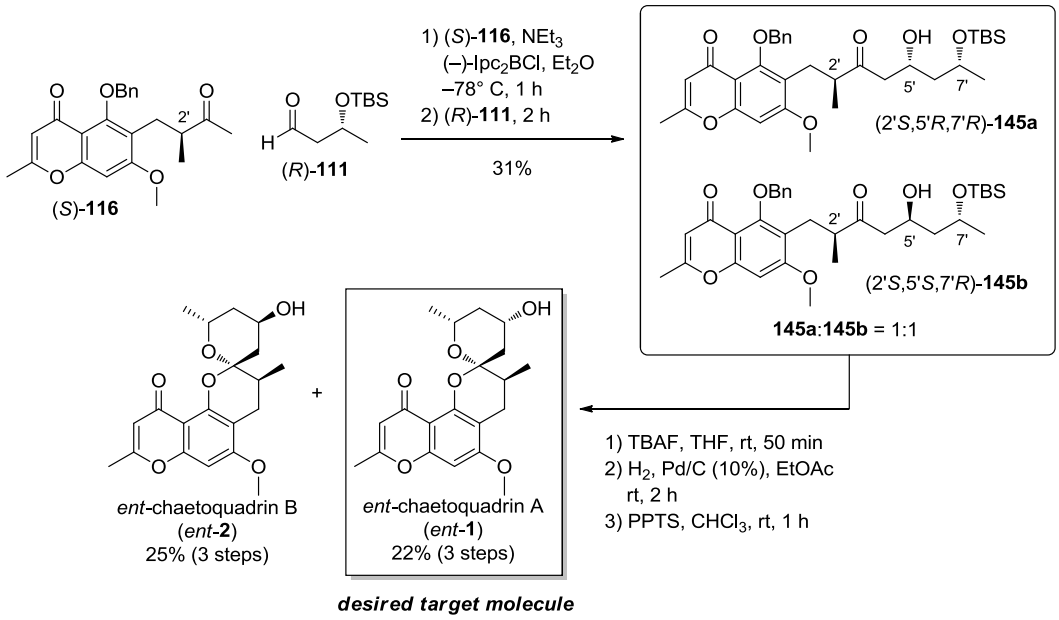
ent-chaetoquadrin B (*ent*-**2**)

Comparison of ^{1}H NMR of natural product to synthetic material			
Position	Natural chaetoquadrin B	Synthetic *ent*-chaetoquadrin B	Δ
2'-CH$_3$	0.95 (3H, d, 7.0)	0.95 (3H, d, 7.0)	0.00
8'	1.04 (3H, d, 6.1)	1.03 (3H, d, 6.2)	0.01
6'	1.92 (ddd, 13.8, 4.5, 2.2), 1.49 (ddd, 13.8, 11.9, 3.0)	1.86-1.97 (m), 1.49 (ddd, 13.8, 12.0, 3.2)	0.00, 0.00
2'	2.05 (qdd, 7.0, 6.5, 1.6)	2.04 (qdd, 7.0, 6.5, 1.6)	0.01
2-CH$_3$	2.29 (3H, s)	2,29 (3H, d, 0.73)	0.00
4'	2.35 (dd, 14.3, 2.0), 1.65 (dd, 14.3, 4.1)	2.36 (dd, 14.2, 2.2), 1.63 (dd, 14.2, 4.1)	-0.01, 0.02
1'	2.92 (dd, 16.7, 6.5), 2.40 (dd, 16.7, 1.6)	2.92 (dd, 16.7, 6.6), 2.40 (dd, 16.8, 1.6)	0.00, 0.00
7-OCH$_3$	3.90 (3H, s)	3.89 (3H, s)	0.01
7'	4.14 (m)	4.07-4.23 (m)	0.00
5'	4.17 (m)	4.07-4.23 (m)	0.00
3	6.00 (s)	6.00 (d, 0.73)	0.00
5'-OH	6.32 (d, 11.7)	6.29 (d, 11.4)	0.03
8	6.46 (s)	6.45 (s)	0.01
Comparison of ^{13}C NMR of natural product to synthetic material			
Position	Natural chaetoquadrin B	Synthetic *ent*-chaetoquadrin B	Δ
2'-CH$_3$	15.3	15.3	0.0
2-CH$_3$	19.9	19.9	0.0
8'	21.4	21.5	-0.1
1'	23.3	23.4	-0.1
2'	32.3	32.3	0.0
4'	36.7	36.8	-0.1
6'	39.9	40.0	-0.1
7-OCH$_3$	55.8	55.8	0.0
7'	62.5	62.6	-0.1
5'	63.5	63.7	-0.2
8	91.5	91.5	0.0
3'	100.5	100.6	-0.1
6	107.2	107.2	0.0
4a	107.9	108.0	-0.1
3	111.5	111.6	-0.1
5	150.3	150.4	-0.1
8a	157.9	158.0	-0.1
7	161.7	161.7	0.0
2	163.4	163.4	0.0
4	177.6	177.6	0.0

Table 14. *^{1}H NMR and ^{13}C NMR data of synthetic ent-chaetoquadrin B (ent-**2**) and natural chaetoquadrin B in $CDCl_3$.*

*C. Reaction of methyl ketone (S)-**116** with (–)-Ipc$_2$BCl and aldehyde (R)-**111** and synthesis of ent-chaetoquadrin A (ent-**1**)*

With the synthesis of *ent*-chaetoquadrin B (*ent*-**2**) accomplished, our attention now turned to the synthesis of *ent*-chaetoquadrin A (*ent*-**1**). Synthesis of *ent*-chaetoquadrin A (*ent*-**1**) required use of (–)-Ipc ligand in the aldol reaction. When reaction of methyl ketone (*S*)-**116** and aldehyde (*R*)-**111** was mediated with (–)-Ipc$_2$BCl in Et_2O at –78 °C for 2 h, a 1:1 inseparable mixture of diastereoisomers **145a** and **145b** was obtained in 31% yield (**Scheme 77**). Elaboration of the β-hydroxyketone mixture to the spiroketals *via* deprotection/cyclisation protocol afforded both *ent*-chaetoquadrin A (*ent*-**1**) and *ent*-chaetoquadrin B (*ent*-**2**) in similar amounts, indicating that the aldol reaction had proceeded with poor selectivity. Gratifyingly, the two natural products having assumed it's cyclised conformation, could at this point be separated *via* preparative TLC.



Scheme 77. *Synthesis of ent-chaetoquadrin A (ent-**1**) and ent-chaetoquadrin B (ent-**2**).*

CD spectra comparison between synthetic *ent*-chaetoquadrin A (*ent*-**1**, **Figure 28**) and the natural product (**Figure 29**) established that the enantiomer of chaetoquadrin A had been prepared. The α_D value for the natural chatoquadrin A was not reported. For synthetic *ent*-chaetoquadrin A, the α_D value was $[\alpha]_D^{20}$ +17.0 (*c* 0.1 $CHCl_3$).

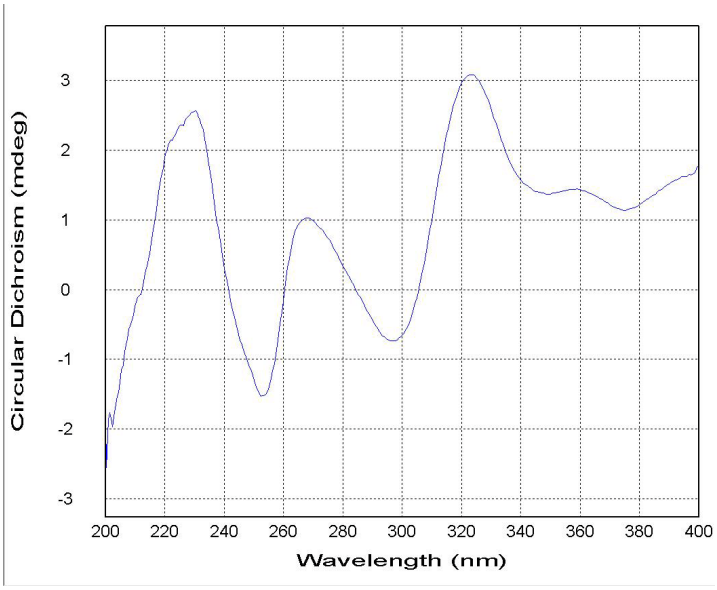


Figure 28. *CD spectrum of ent-chaetoquadrin A (ent-**1**) in MeOH.*

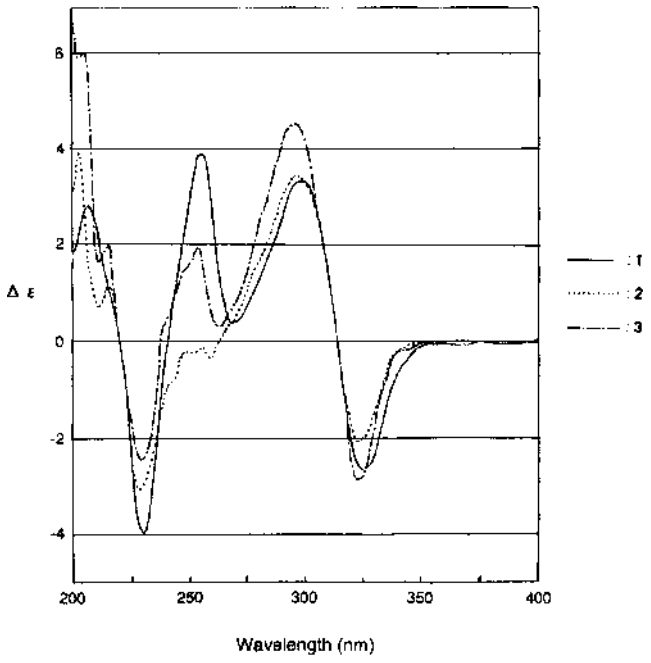
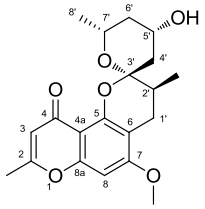


Figure 29. *CD Spectrum of chaetoquadrins A (**1**), B (**2**), and C (**3**) in MeOH as reported by Fujimoto et al. Chaetoquadrin A (**1**) is illustrated with line, "——".*

A comparison of the reported ^{1}H NMR and ^{13}C NMR data for *ent*-chaetoquadrins A (*ent*-**1**) are tabulated below (**Table 15**).



ent-chaetoquadrin A (**1**).

Comparison of ^{1}H NMR of natural product to synthetic material			
Position	Natural chaetoquadrin A	Synthetic *ent*-chaetoquadrin A	Δ
2'-CH$_3$	1.00 (3H, d, 7.1)	0.99 (3H, d, 7.0)	0.01
8'	1.08 (3H, d, 6.8)	1.07 (3H, d, 6.3)	0.01
6'	2.04 (ddd, 12.0, 6.8, 3.0), 1.25 (ddd, 12.0, 12.0, 12.0)	2.04 (ddd, 12.4, 6.8, 2.0), 1.25–12.7 (m)	0, -0.01
2'	2.11 (qdd, 7.1, 6.6, 3.2)	2.11 (qdd. 7.1, 6.8, 3.1)	0.00
2-CH$_3$	2.28 (3H, s)	2.28 (3H, d, 0.7)	0.00
4'	2.43 (ddd, 12.7, 4.8, 1.7), 1.32 (dd, 12.7, 11.2)	2.43 (ddd, 12.5, 4.7, 1.8), 1.32 (dd, 12.5, 11.1)	0.00, 0.00
1'	2.91 (dd, 16.9, 6.6), 2.39 (16.9, 3.2)	2.91 (dd, 16.8, 6.6), 2.37 (16.8, 3.3)	0.00, 0.02
7-OCH$_3$	3.89 (3H, s)	3.88 (3H, s)	0.01
7'	4.00 (dqd, 12.0, 6.8, 3.0)	4.01 (dqd, 12.1, 6.4, 2.9)	-0.01
5'	4.67 (ddd, 12.0, 11.2, 4.8)	4.60-4.74 (m)	-
3	5.94 (s)	5.93 (d, 0.7)	0.01
5'-OH	-	-	-
8	6.42 (s)	6.42 (s)	0.00
Comparison of ^{13}C NMR of natural product to synthetic material			
Position	Natural chaetoquadrin A	Synthetic *ent*-chaetoquadrin A	Δ
2'-CH$_3$	15.6	15.6	0.0
2-CH$_3$	19.8	19.8	0.0
8'	21.4	21.4	0.0
1'	24.2	24.2	0.0
2'	32.5	32.5	0.0
4'	39.4	39.4	0.0
6'	42.4	42.4	0.0
7-OCH$_3$	55.7	55.7	0.0
7'	66.6	66.6	0.0
5'	64.5	64.5	0.0
8	91.2	91.2	0.0
3'	101.4	101.4	0.0
6	107.3	107.3	0.0
4a	108.3	108.4	-0.1
3	111.8	111.8	0.0
5	151.3	151.3	0.0
8a	158.0	158.0	0.0
7	161.4	161.4	0.0
2	162.9	162.9	0.0
4	177.4	177.3	0.1

Table 15. *^{1}H NMR and ^{13}C NMR data of ent-chaetoquadrin A (**1**) and natural chaetoquadrin A in $CDCl_3$.*

4.5 Assignment of the unknown stereocentres present in the spiroketal chaetoquadrins using NMR spectra data

In chaetoquadrins *ent*-A (*ent*-**1**), *ent*-B (*ent*-**2**) and C (**3**) there are four stereocentres present around the 6,6-spiroketal ring system. While stereocentres at C-7′ and C-2′ of the spiroketal chaetoquadrins were derived from known starting materials (**Figure 30**), stereocentres at C-5′ and C-3′ were introduced during the asymmetric aldol reaction and spiroketalisation reaction respectively. Thus the identities of C-5′ and C-3′ stereocentres were not known from the outset.

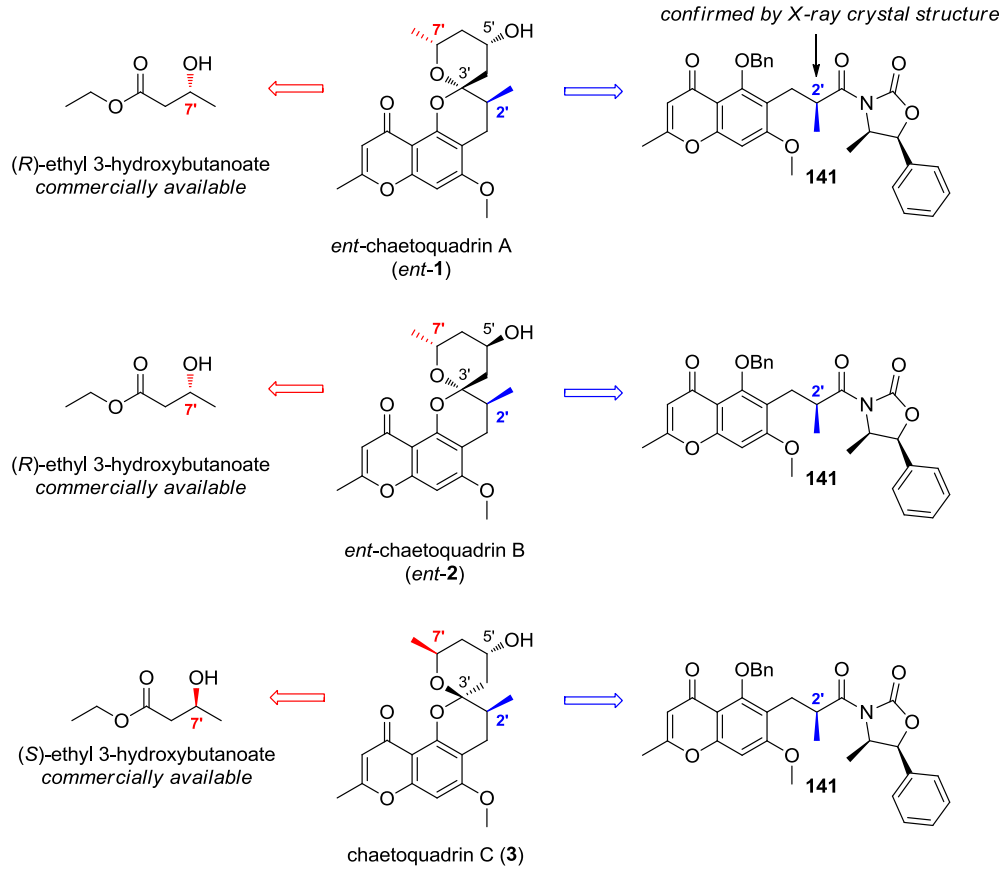


Figure 30. *In spiroketal chaetoquadrins, chiral information at stereocentres C-7′ and C-2′ was derived from commercially available starting materials and synthetic intermediates confirmed by X-ray crystallography.*

With synthesis of spiroketal chaetoquadrins complete and spectral data in hand, it was possible to assign the remaining C-5′ and C-3′ stereocentres of spiroketal chaetoquadrins.

A. Assignment of C-5′ stereocentre in chaetoquadrins ent-A, ent-B and C.

As mentioned, the C-7′ stereocentre in chaetoquadrins *ent*-A, *ent*-B and C was derived from known starting materials (*vide supra*). It was possible to use this stereocentre as a lynchpin to assign C-5′ stereocentre which in turn could be used to determine the C-3′ stereocentre. For *ent*-chaetoquadrin A (*ent*-**1**) a key 1,3-diaxial nOe correlation was observed between H-5′ and H-7′ indicating a *syn*-relationship between the two nuclei (**Figure 31**).

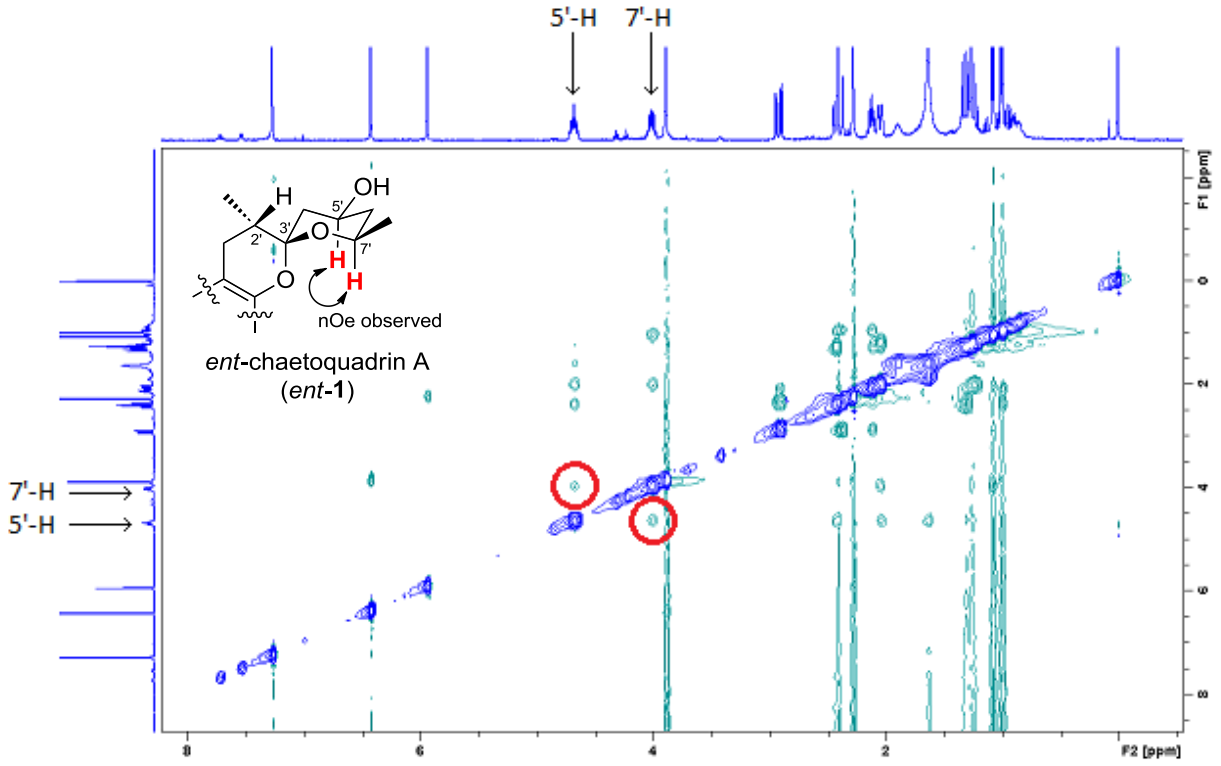


Figure 31. *NOSEY spectrum of ent-**1**. nOe correlation between H-5′ and H-7′ is highlighted.*

This correlation was missing in the nOe spectra of *ent*-chaetoquadrins B (*ent*-**2**) and C (**3**) indicating a *trans*-relationship between the H-5′ and H-7′ (**Figure 32**).

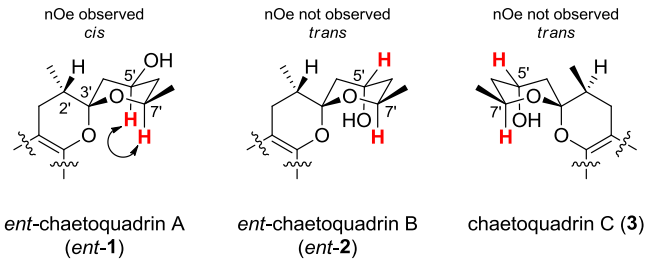


Figure 32. *1,3-diaxial nOe correlation between H-5′ and H-7′ is observed in ent-**1** (indicative of a syn relationship) but not observed in ent-**2** and **3** (indicative of a trans relationship).*

The stereochemical assignment at C-5′ was further supported by the H-5′ resonance in the ^{1}H NMR spectrum of the spiroketal chaetoquadrins. For *ent*-chaetoquadrin B (*ent*-**2**) and chaetoquadrin C (**3**) H-5′ resonated as a multiplet at δ 4.17 ppm and δ 4.12 ppm respectively. For *ent*-chaetoquadrin A (*ent*-**1**) however, H-5′ resonated further downfield at δ 4.67 ppm due to the 1,3-diaxial interaction between H-5′ and O1 (**Figure 33** & **Figure 34**).[86]

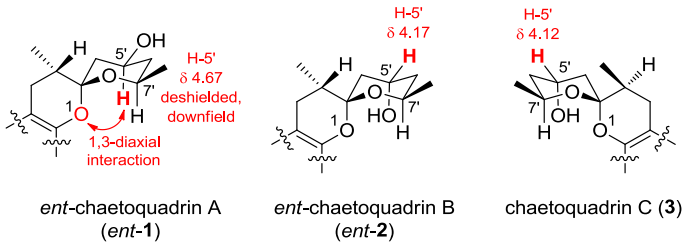


Figure 33. *1,3-Diaxial interaction between H-5′ and O1 is possible in ent-chaetoquadrin A (ent-**1**) resulting in the comparatively downfield resonance of H-5′.*

B. Assignment of C-3′ stereocentre in chaetoquadrins A–C.

With the C-5′–C-7′ relative stereochemistry established in the spiroketal chaetoquadrins, it was now possible to establish the stereochemistry at C-3′.

In a typical ^{1}H NMR experiment in deuterated chloroform, aliphatic alcohols resonate at δ 0.5–4.0 ppm as a broad signal. However, if the alcohol is able to participate in an intramolecular hydrogen bonding interaction, the –O*H* typically resonates as a sharp and distinctive signal.

The 5′-O*H* proton resonated strongly as a sharp doublet in *ent*-chaetoquadrin B (*ent*-**2**) and chaetoquadrin C (**3**) at δ 6.32 ppm (J = 11.7) and δ 6.44 ppm (J = 11.9) respectively (**Figure 34**). Meanwhile, this signal was missing from chaetoquadrin A. These data suggestes that the C-3′ stereochemistry for *ent*-chaetoquadrin B (*ent*-**2**) and chaetoquadrin C (**3**) must orientate 5′-O*H* proton to point inwards towards the chromone to enable intramolecular hydrogen bonding, giving rise to the observable sharp signals in the ^{1}H NMR spectrum. For *ent*-chaetoquadrin A (*ent*-**1**) however, the C-3′ stereocentre must orientate the 5′-O*H* proton outward and away from the chromone. Thus for chaetoquadrins *ent*-A and *ent*-B, the C-3′ stereocentre is *S* whilst for chaetoquadrin C, the C-3′ stereocentre is *R*.

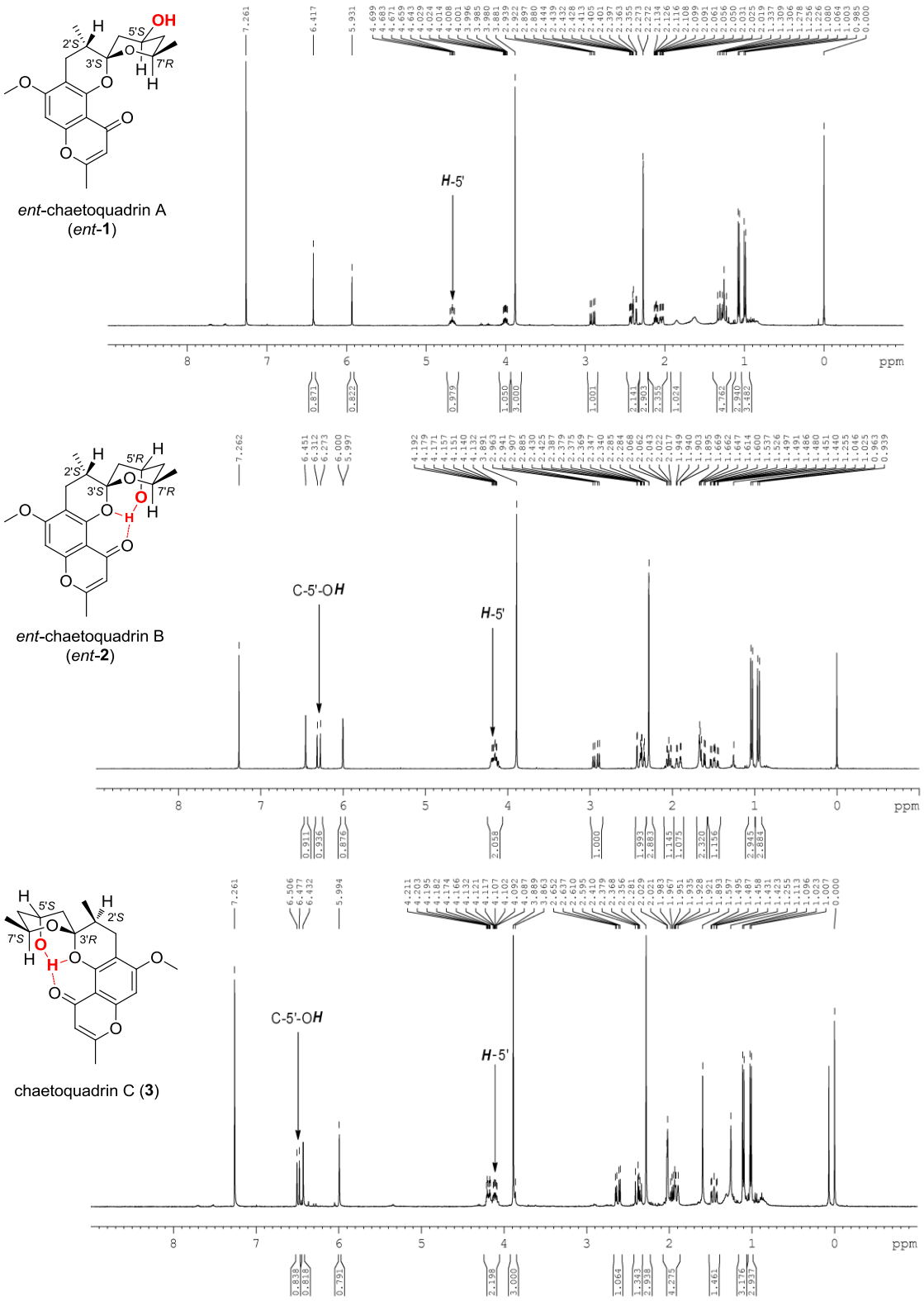


Figure 34. *Structures and ^{1}H NMR spectra of chaetoquadrins ent-A (ent-**1**, top), ent-B (ent-**2**, middle) and C (**3**, bottom). In chaetoquadrins ent-B (ent-**2**) and C (**3**) the intramolecular hydrogen bonding is highlighted with a dotted line. In chaetoquadrin A (**1**) the 5'-OH proton points away from the chromone. The H-5' resonances for the chaetoquadrins are also highlighted.*

In our synthesis, the remaining C-2′ stereocentre was derived from a synthetic intermediate whose stereochemical identity was confirmed by X-ray crystallography (*vide supra*). Accordingly, chaetoquadrins *ent*-A (*ent*-**1**), *ent*-B (*ent*-**2**) and C (**3**) possess the absolute stereochemistry as depicted below (**Figure 35**).

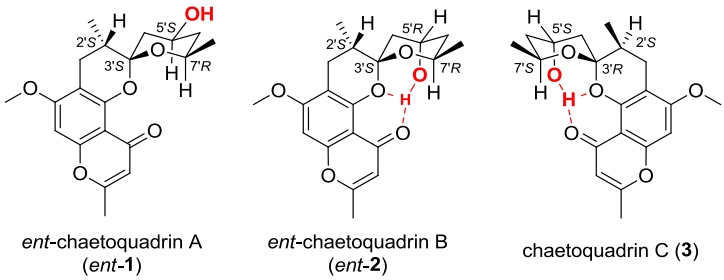
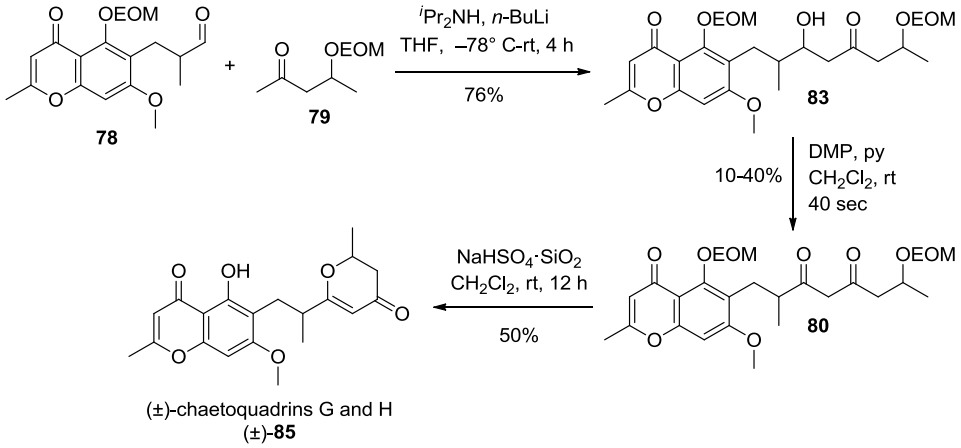


Figure 35. *Structures of chaetoquadrins ent-A (ent-**1**), ent-B (ent-**2**) and C (**3**) synthesised in this work. Intramolecular hydrogen bonding present in chaetoquadrins B and C is highlighted.*

4.6 Total synthesis of chaetoquadrin H (4)

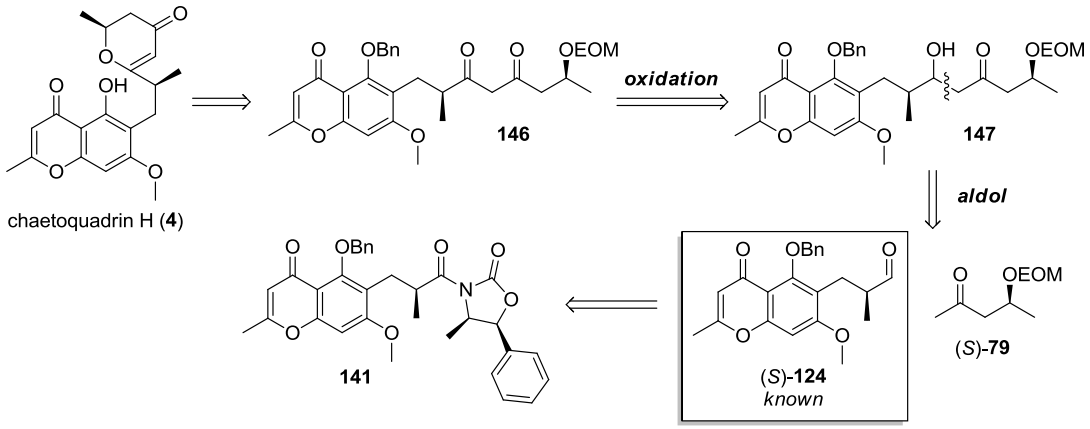
The successful stereoselective total synthesis of the spiroketal chaetoquadrins prompted us to turn our attention to other members of the chaetoquadrin family. The racemic syntheses of (±)-chaetoquadrin G and H have been described (*vide supra*, **Chapter 2**, **Section 2.6**) as an inseparable mixture of the two natural products (**Scheme 78**).



Scheme 78*. Previous synthesis of (±)-chaetoquadrin G and H (±)-**85**.*

Our asymmetric synthesis of imide **141** enabled the synthesis of chiral aldehyde **124** (*vide supra*, **Section 4.1.1**) which could be substituted into the aforementioned racemic synthesis of (±)-chaetoquadrin G and H (±)-**85** thereby facilitating the asymmetric synthesis of chaetoquadrin H (**4**).

The retrosynthetic analysis of chaetoquadrin H (**4**) is illustrated below and hinges on deprotection/cyclisation sequence of **146**, which is derived from aldol product **147**. Aldol product **147** could be accessed by aldol union of aldehyde (*S*)-**124** and ketone (*S*)-**79** (**Scheme 79**).

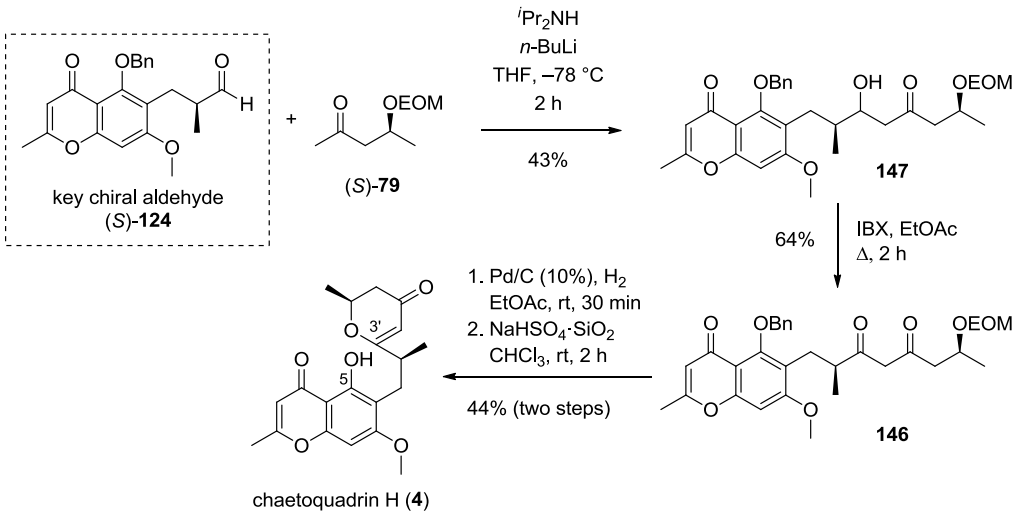


Scheme 79. *Retrosynthetic analysis of chaetoquadrin H (**4**).*

Based on our prior experience with racemic material, the $NaHSO_4 \cdot SiO_2$ catalysed EOM deprotection/cyclisation strategy was investigated.

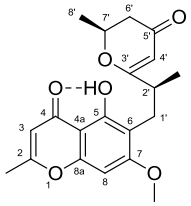
The LDA mediated aldol reaction between benzyl protected aldehyde (*S*)-**124** and EOM-protected methyl ketone (*S*)-**79** in THF at –78 °C for 2 h afforded β-hydroxyketone **147** in moderate yield (**Scheme 80**). Subsequent oxidation of the β-hydroxyketone, initially a problem that hindered our synthetic efforts, was now resolved by employing the recently published protocol for oxidation of β-hydroxyketones using IBX in EtOAc heated at reflux.[68]

Oxidation of β-hydroxyketone **147** using IBX in EtOAc heated at reflux for 2 h gave the desired 1,3-dicarbonyl **146** in 64% yield (crude) which was used in the next step without purification. Hydrogenolysis of the benzyl protecting group was achieved using Pd/C (10%) and EtOAc as solvent under a hydrogen atmosphere. The crude keto alcohol was then treated with $NaHSO_4 \cdot SiO_2$ in $CHCl_3$ at rt for 2 h to effect the acid catalysed EOM deprotection/cyclisation sequence. This reaction sequence afforded enantiopure chaetoquadrin H (**4**) in 44% yield over two steps.



Scheme 80. *Total synthesis of chaetoquadrin H (**4**).*

Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) for the synthetic sample of chaetoquadrin H (**4**) were in full agreement with that recorded for the natural product (**Table 16**). Comparison of the α_D for the synthetic sample [$[\alpha]_D^{20}$ –41.3 (*c* 0.15, $CHCl_3$)] with that of the natural product [lit. $[\alpha]_D^{20}$ –57.2 (*c* 0.2, $CHCl_3$)] established the absolute stereochemistry of chaetoquadrin H (**4**) as depicted. In the ^{1}H NMR spectrum, the 5-OH phenolic proton resonated strongly as a sharp singlet at δ_H 12.85 ppm, establishing the presence of the typical intramolecular hydrogen bonding observed in 5-hydroxy chromones. In the ^{13}C NMR spectrum, the C-3′ quaternary centre of pyranone resonated at δ_C 181.3 ppm.



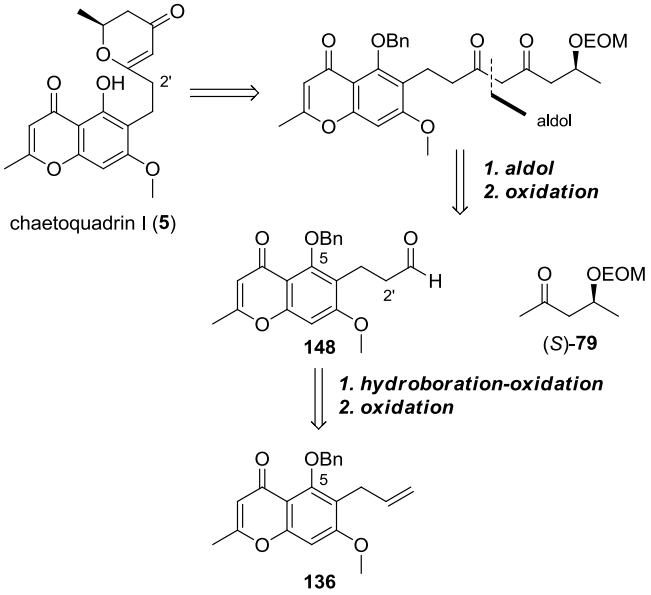
chaetoquadrin H (**4**)

Comparison of ^{1}H NMR of natural product to synthetic material			
Position	Natural chaetoquadrin H	Synthetic chaetoquadrin H	Δ
2-CH_3	2.35 (3H, s)	2.35 (3H, s)	0.00
3	6.04 (s)	6.04 (s)	0.00
7-OCH_3	3.86 (3H, s)	3.87 (3H, s)	-0.01
8	6.34 (s)	6.34 (s)	0.00
1'	2.70 (dd, 12.0, 6.4) 2.97 (dd, 12.0, 7.6)	2.71 (m) 2.97 (m)	-0.01 0.00
2'	2.73 (m)	2.72 (m)	0.01
2'-CH_3	1.17 (3H, d, 6.8)	1.17 (3H, d, 6.7)	0.00
4'	5.11 (s)	5.11 (s)	0.00
6'	2.32 (2H, m)	2.32 (2H, m)	0.00
7'	4.37 (m)	4.37 (m)	0.00
8'	1.44 (3H, d, 6.4)	1.44 (3H, d, 6.5)	0.00
5-OH	unreported	12.85 (s)	-
Comparison of ^{13}C NMR of natural product to synthetic material			
Position	Natural chaetoquadrin H	Synthetic chaetoquadrin H	Δ
2	166.5	166.6	-0.1
2-CH_3	20.4	20.6	-0.2
3	108.9	109.1	-0.2
4	182.5	182.7	-0.2
4a	105.0	105.2	-0.2
5	159.0	159.2	-0.2
6	110.6	110.8	-0.2
7	163.2	163.4	-0.2
7-OCH_3	55.8	56.0	-0.2
8	89.3	89.5	-0.2
8a	156.8	157.0	-0.2
1'	27.1	27.3	-0.2
2'	38.9	39.1	-0.2
2'-CH_3	17.4	17.6	-0.2
3'	181.1	181.3	-0.2
4'	103.1	103.3	-0.2
5'	193.6	193.7	-0.1
6'	42.7	42.9	-0.2
7'	75.6	75.8	-0.2
8'	20.3	20.5	-0.2

Table 16. *^{1}H NMR and ^{13}C NMR data of natural and synthetic chaetoquadrin H (**4**) in $CDCl_3$.*

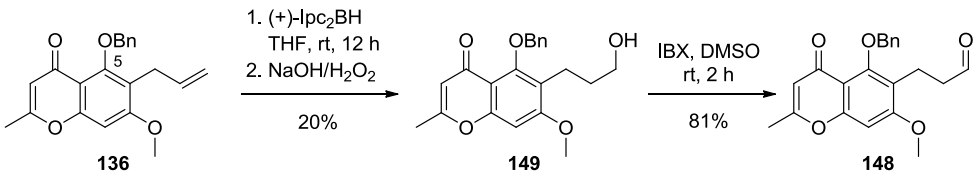
4.7 Total synthesis of chaetoquadrin I (5)

Bis-pyranone chaetoquadrin I (**5**) bears a structural similarity to chaetoquadrin H (**4**). A notable difference is the absence of the C-2´ methyl group. Thus, preparation of C-2´–unsubstituted aldehyde **148** would enable the synthesis of chaetoquadrin I (**5**) (**Scheme 81**). It was envisaged that the unsubstituted aldehyde **148** could be derived from hydroboration-oxidation of previously prepared olefin **136**. The benzyl protecting group was selected for the C-5 phenol protection in view of its successful use in the spiroketal and chaetoquadrin H (**4**) synthesis.



Scheme 81. *Retrosynthetic analysis of chaetoquadrin I (**5**).*

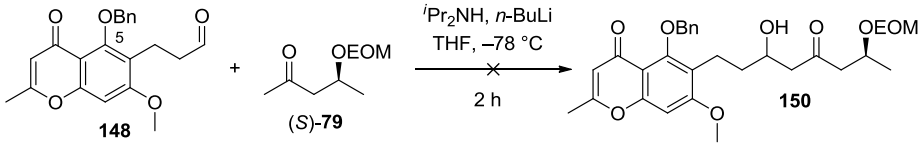
Olefin **136** was subjected to hydroboration-oxidation by treatment with (+)-Ipc_2BH in THF at rt for 12 h to afford alcohol **149** in 20% yield. IBX oxidation of alcohol **149** in DMSO at rt for 2 h afforded aldehyde **148** in 80% yield (**Scheme 82**).



Scheme 82*. Synthesis of aldehyde **148**.*

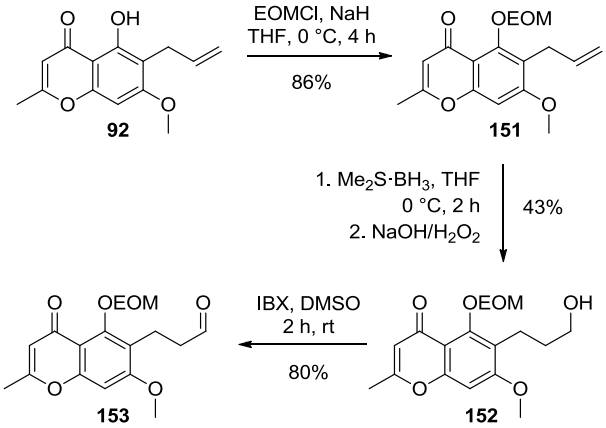
Similar to the chaetoquadrin H (**4**) synthesis, it was decided to investigate the reaction of EOM-protected methyl ketone (*S*)-**79** with benzyl protected aldehyde **148**. To our surprise the LDA

mediated aldol reaction between benzyl protected aldehyde **148** and EOM-protected methyl ketone (*S*)-**79** to afford **150** was unsuccessful (**Scheme 83**).



Scheme 83. *Unsuccessful aldol reaction between aldehyde **148** and ketone (S)-**79**.*

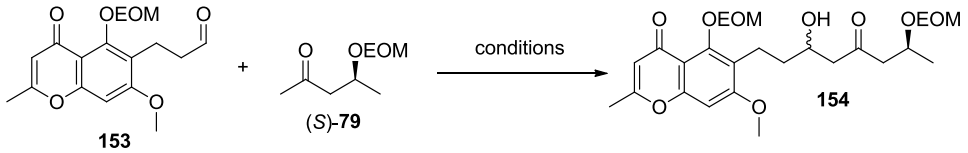
In light of this failure it was decided to investigate the use of the EOM protecting group for the C-5 phenol of the aldehyde coupling partner similar to its use in the early stages of our investigation when the double EOM deprotection/cyclisation sequence was executed (*vide supra*, **Chapter 2**, **Section 2.6 C**). Olefin **92** was therefore treated with EOMCl and NaH at 0 °C in THF for 4 h to afford EOM-protected olefin **151** in 86% yield. Hydroboration-oxidation with borane dimethylsulfide complex in THF at 0 °C for 2 h afforded alcohol **152** in 43% yield which was oxidised with IBX in DMSO at rt for 2 h to furnish EOM-protected aldehyde **153** in 80% yield (**Scheme 84**).



Scheme 84. *Synthesis of aldehyde **153***

The key aldol reaction was again investigated between aldehyde **153** and ketone (*S*)-**79**. Unfortunately use of LDA in THF at –78 °C for 4 h failed to afford the desired product (**Table 17**, entry 1). Alternative aldol conditions were explored to form the key β-hydroxyketone **154**. Use of KHMDS in THF at –78 °C for 2 h enabled the desired reaction to take place but it was also accompanied by elimination of the newly formed β-hydroxyketone (entry 2). The Mukaiyama aldol reaction was next investigated in which a TMS enol ether derived from ketone (*S*)-**79** was required to react with aldehyde **153** in the presence of $BF_3 \cdot OEt_2$. However TMS enol ether formation using TMSOTf and 2,6-lutidine in dichloromethane at 0 °C was unsuccessful, leading only to isolation of starting material

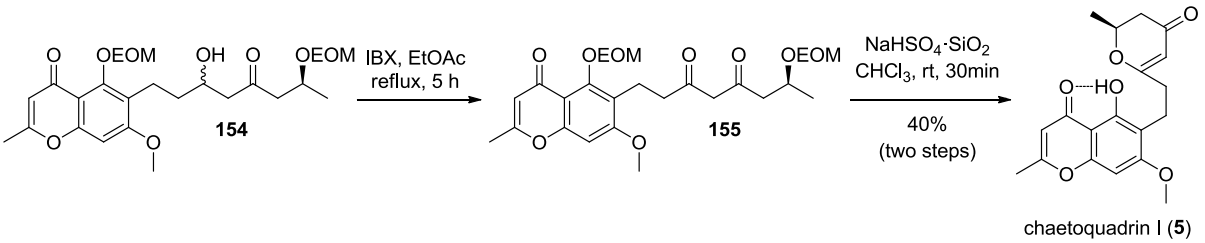
(entry 3). A boron aldol coupling was next investigated to unite aldehyde **153** and ketone (*S*)-**79** using (+)-Ipc_2BCl and triethylamine in Et_2O at –78 °C for 4 h. Pleasingly, these conditions afforded the desired β-hydroxyketone **154** in 30% yield (entry 4).



Entry	Conditions	Result
1	ketone (*S*)-**79** (3 eq), $^{i}Pr_2NH$ (3.1 eq), *n*-BuLi (3 eq), aldehyde **153** (1 eq), THF, –78 °C-rt, 4 h	decomposition
2	ketone (*S*)-**79** (1 eq), KHMDS (1 eq), aldehyde **153** (1 eq), THF, –78 °C, 1.5 h	elimination of the β-hydroxyketone
3	ketone (*S*)-**79** (1 eq), TMSOTf (1.7 eq), 2,6-lutidine (3 eq), CH_2Cl_2, 0 °C-rt, 1 h	no reaction
4	i. ketone (*S*)-**79**, (+)-Ipc_2BCl, Et_3N, Et_2O, –78 °C, 1 h ii. aldehyde **153**, 4 h	30%

Table 17. *Aldol reaction between aldehyde **153** and ketone (S)-**79**.*

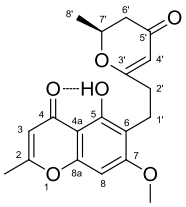
With β-hydroxyketone **154** in hand, IBX oxidation of **154** in EtOAc heated at reflux for 5 h afforded the desired 1,3-diketone **155**. Subjection of crude 1,3-diketone **155** to $NaHSO_4 \cdot SiO_2$ afforded chaetoquadrin I (**5**) in 40% yield over two steps (**Scheme 85**).



Scheme 85. *Synthesis of chaetoquadrin I (**5**).*

Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) for the synthetic sample of chaetoquadrin I (**5**) were in full agreement with those reported for the natural product (**Table 18**). Comparison of the α_D for the synthetic sample [$[\alpha]_D^{20}$ –10.8 (*c* 0.05, $CHCl_3$)] with that of the natural product [lit. $[\alpha]_D^{20}$ –40.8 (*c* 0.05, $CHCl_3$)] established the absolute stereochemistry of chaetoquadrin I as depicted, although the magnitude of the optical rotation value did differ considerably. The reason for this discrepancy may lie in the dilute concentration used to measure the optical rotation values. In the isolation report it was stated that not enough chaetoquadrin I was isolated to allow for biological testing.

In the ^{1}H NMR spectrum of chaetoquadrin I the 5-OH phenolic proton resonated as a sharp singlet at δ_H 12.8 ppm, establishing the presence of intramolecular hydrogen bonding. In the ^{13}C NMR spectrum, the C-3′ quaternary centre of pyranone resonated at δ_C 177.8 ppm.



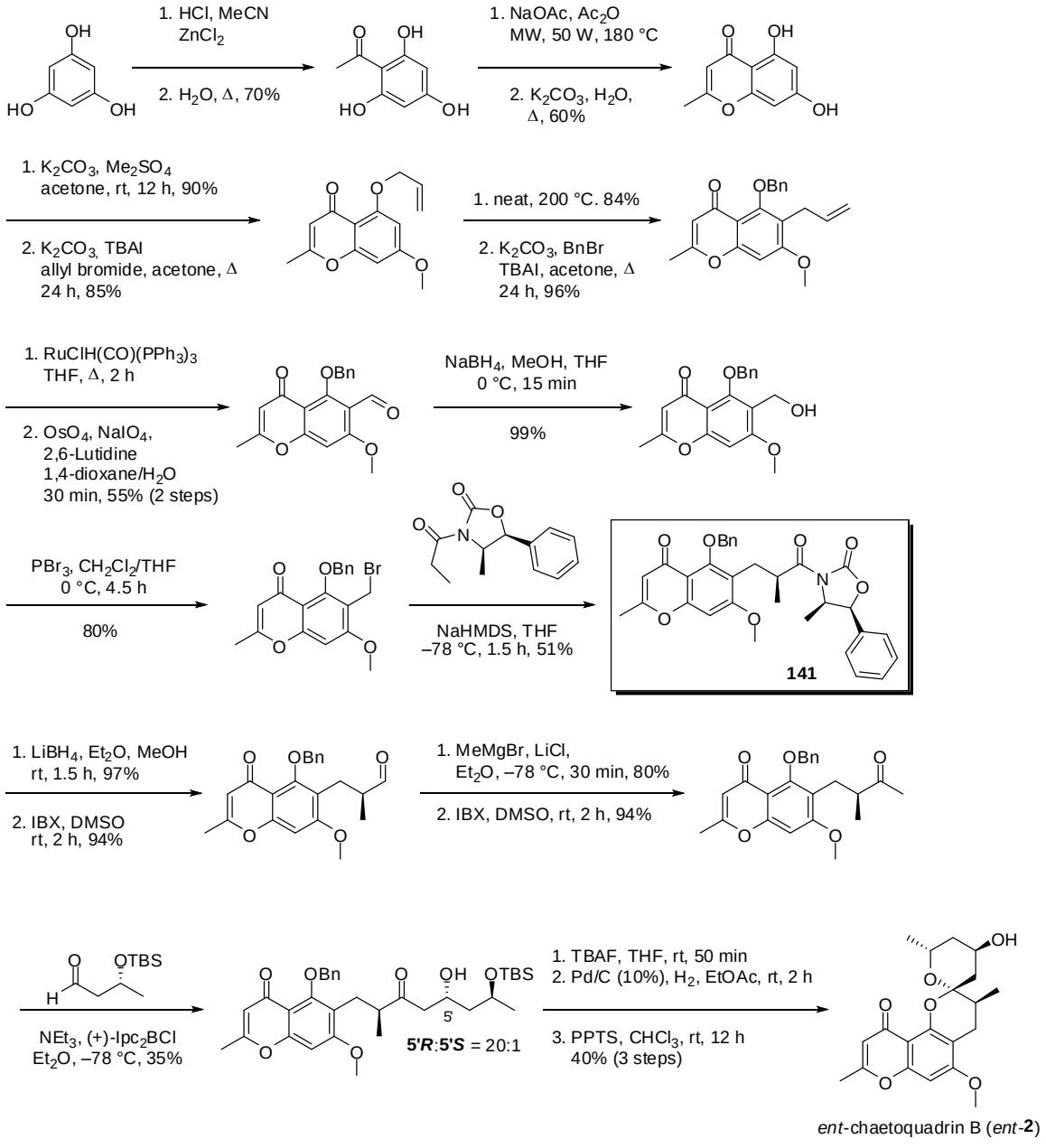
chaetoquadrin I (**5**)

Comparison of ^{1}H NMR of natural product to synthetic material			
Position	Natural chaetoquadrin I	Synthetic chaetoquadrin I	Δ
2-CH_3	2.35 (3H, s)	2.36 (3H, s)	-0.01
3	6.04 (s)	6.05 (s)	-0.01
7-OCH_3	3.88 (3H, s)	3.88 (3H, s)	0.00
8	6.36 (s)	6.36 (s)	0.00
1'	2.92 (2H, m)	2.93 (2H, m)	-0.01
2'	2.46 (2H, ddd, 7.8, 7.8, 2.8)	2.46 (2H, m)	0.00
4'	5.21 (s)	5.22 (s)	-0.01
6'	2.34 (2H, m)	2.36 (2H, m)	-0.02
7'	4.45 (m)	4.45 (m)	0.00
8'	1.44 (3H, d, 6.0)	1.44 (3H, d, 6.1)	0.00
5-OH	unreported	12.8	-
Comparison of ^{13}C NMR of natural product to synthetic material			
Position	Natural chaetoquadrin I	Synthetic chaetoquadrin I	Δ
2	166.5	166.6	-0.1
2-CH_3	20.4	20.6	-0.2
3	109.0	109.1	-0.1
4	182.5	182.6	-0.1
4a	105.1	105.2	-0.1
5	158.9	159.0	-0.1
6	111.1	111.3	-0.2
7	163.0	163.2	-0.2
7-OCH_3	55.9	56.0	-0.1
8	89.4	89.5	-0.1
8a	156.8	157.0	-0.2
1'	19.4	19.6	-0.2
2'	33.6	33.8	-0.2
3'	177.6	177.8	-0.2
4'	104.1	104.2	-0.1
5'	193.3	193.5	-0.2
6'	42.7	42.8	-0.1
7'	75.6	75.8	-0.2
8'	20.4	20.6	-0.2

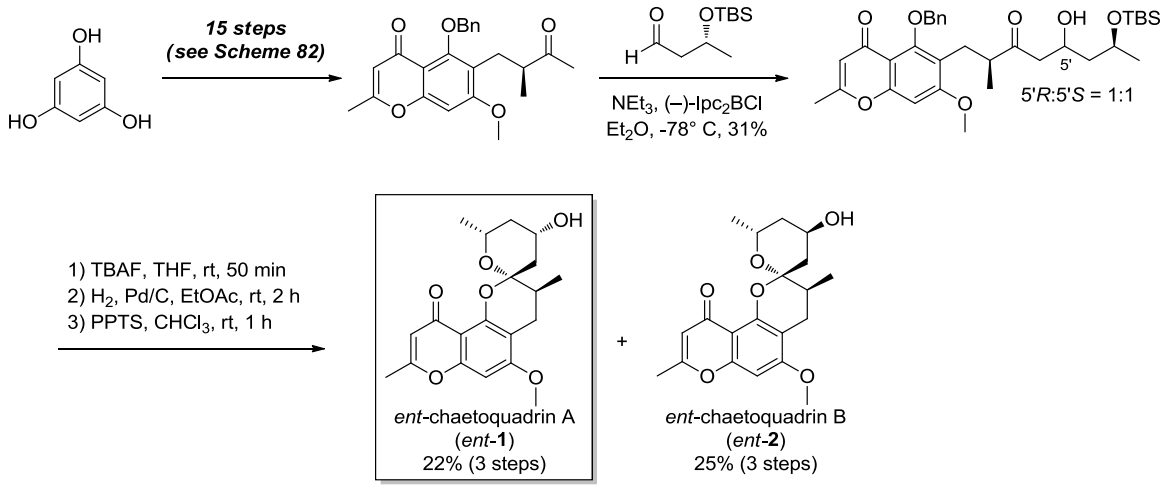
Table 18. *^{1}H NMR and ^{13}C NMR interpretation of chaetoquadrin I (**5**).*

4.8 Summary of the syntheses of chaetoquadrins

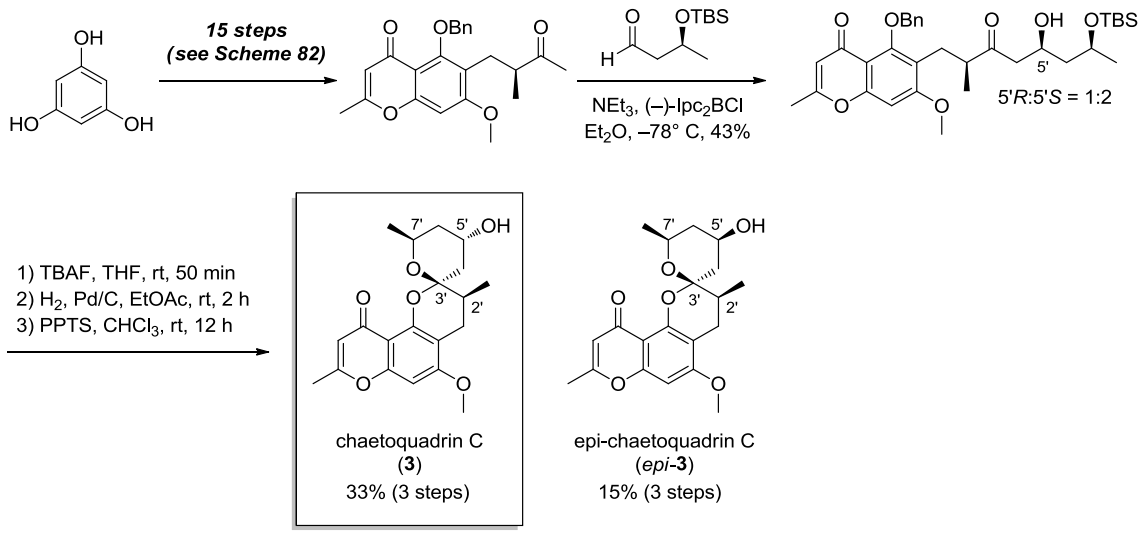
In conclusion five natural products (chaetoquadrins C (**3**), *ent*-A (*ent*-**1**), *ent*-B (*ent*-**2**), H, (**4**) and I (**5**)) have been prepared here for the first time. Presented are the synthetic schemes that illustrate the total syntheses of *ent*-chaetoquadrin B (*ent*-**2**) (**Scheme 86**), *ent*-chaetoquadrin A (*ent*-**1**) (**Scheme 87**), chaetoquadrin C (**3**) (**Scheme 88**), H (**4**) (**Scheme 89**) and I (**5**) (**Scheme 90**). In **Scheme 86**, imide **141** represents the common intermediate required for the synthesis of chaetoquadrins *ent*-A, *ent*-B, C and H.



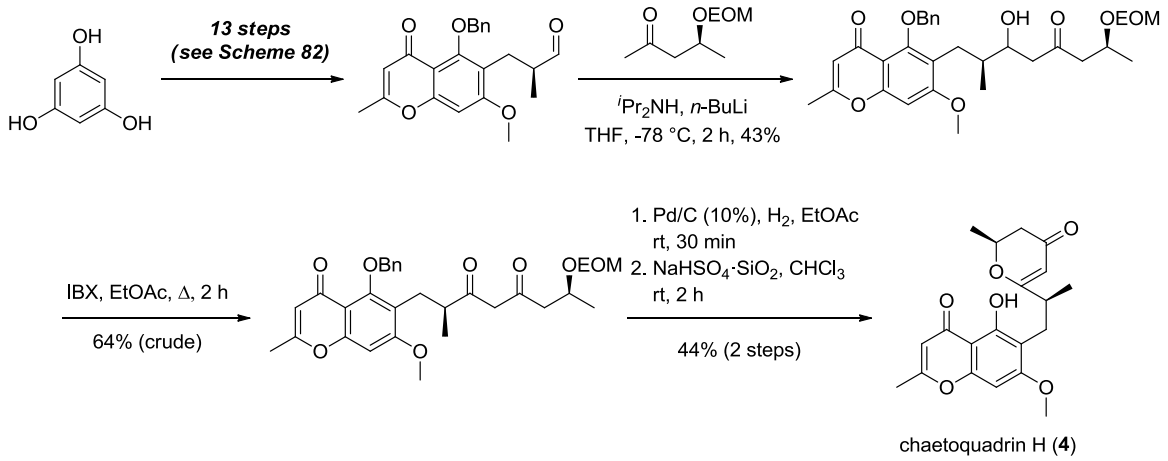
Scheme 86. *Total synthesis of ent-chaetoquadrin B (ent-**2**).*



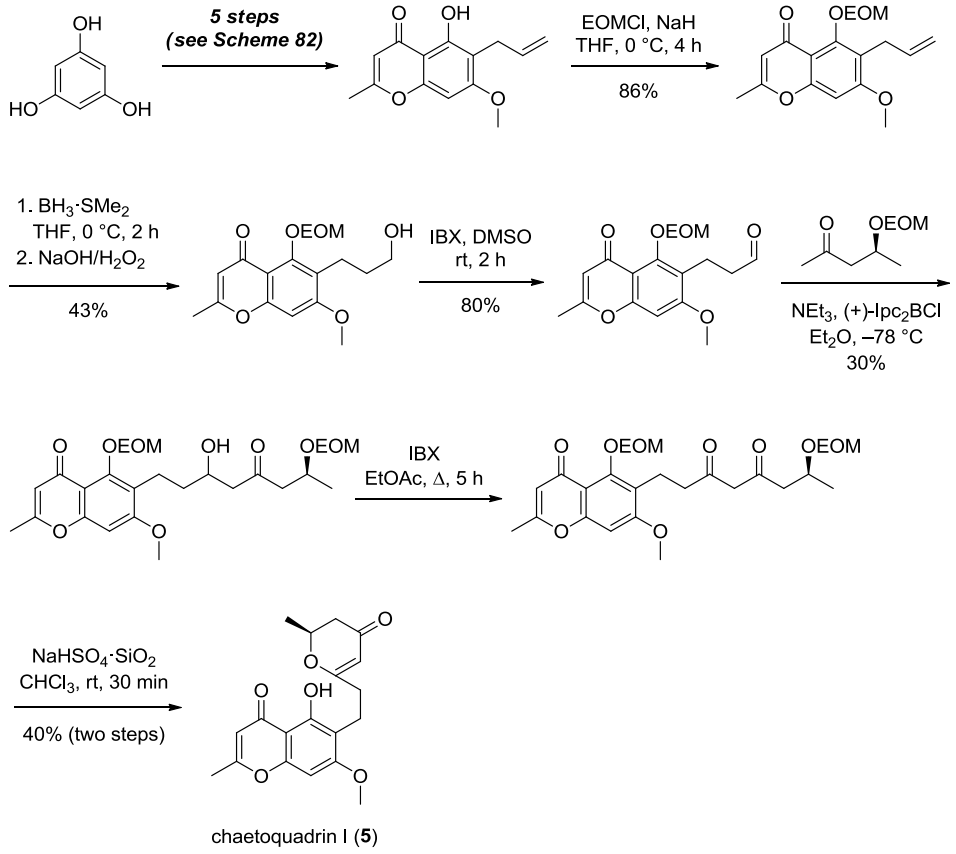
Scheme 87. *Total synthesis of ent-chaetoquadrin A (ent-**1**).*



Scheme 88. *Total synthesis of chaetoquadrin C (**3**).*



Scheme 89. *Total synthesis of chaetoquadrin H (**4**).*

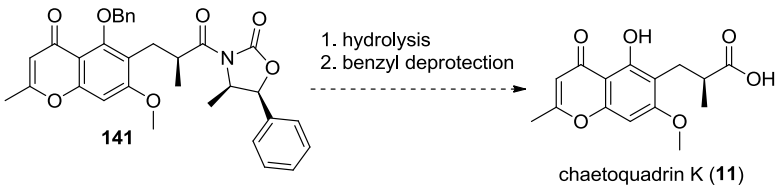


Scheme 90. *Total synthesis of chaetoquadrin I (**5**).*

4.9 Future work

*A. Total synthesis of chaetoquadrin K (**11**)*

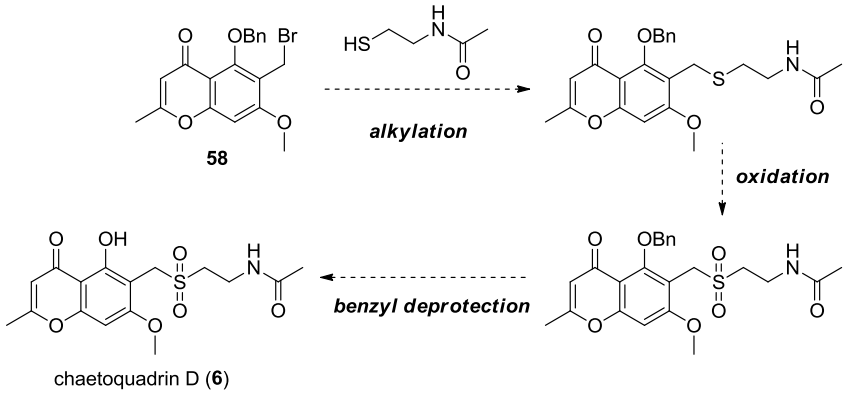
Chaetoquadrin K (**11**) is a carboxylic acid which could conceivably be prepared using the methodology presented herein. Therefore, hydrolysis and benzyl deprotection of the known imide **141** (**Scheme 91**) should furnish the target. Experimentally, use of Pd/C (10%) and hydrogen gas should effect deprotection while lithium hydroxide in THF should enable hydrolysis of the imide to furnish the carboxylic acid natural product chaetoquadrin K (**11**).



Scheme 91. *Proposed synthesis of chaetoquadrin K (**11**).*

*B. Total synthesis of chaetoquadrin D (**6**)*

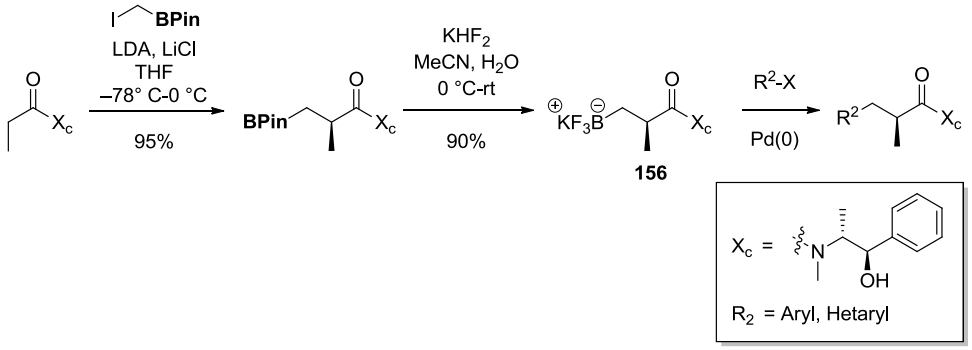
Chaetoquadrin D (**6**) is an interesting sulfur containing chromone. It could be made in three steps from known bromide **58** (**Scheme 92**). The pivotal *S*-alkylation onto the benzylic bromide **58** may be problematic due to the propensity of thiols to participate in 1,4-conjugate additions. An undesired side-reaction may therefore be the 1,4-conjugate addition of the thiol onto the pyranone of chromone-bromide **58**.



Scheme 92. *Proposed synthesis of chaetoquadrin D (**6**).*

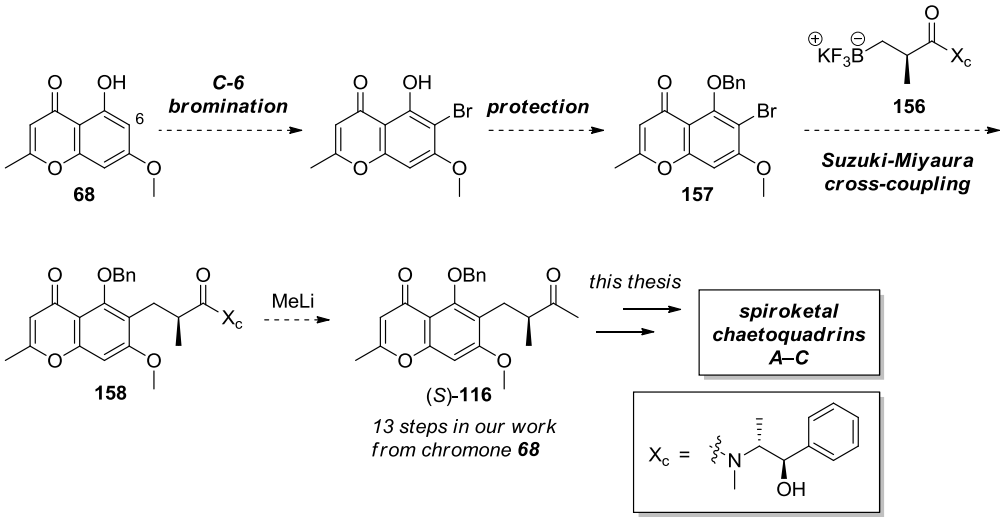
*C. Suzuki−Miyaura cross-coupling of bromide **157** and potassium β-trifluoroboratoamide **156** for synthesis of methyl ketone (S)-**116***

Molander and co-workers recently reported successful Suzuki-Miyaura cross-coupling reactions between aryl halides and enantiomerically enriched potassium β-trifluoroboratoamides (for example, **156**, **Scheme 93**) derived from pseudoephedrine for construction of α-chiral β-arylated carbonyl compounds.[53]



Scheme 93. *Preparation of α-chiral β-trifluoroboratoamide **156** as reported by Molander et al.*[53]

If regioselective C-6 bromination of chromone **68** could be achieved (**Scheme 94**), application of the aforementioned Suzuki−Miyaura cross-coupling methodology may be possible to enable construction of methyl ketone (*S*)-**116** by reacting protected bromide **157** with potassium β-trifluoroboratoamide **156** to afford α-chiral imide **158**. Imide **158** could then be elaborated into methyl ketone (*S*)-**116**, significantly reducing the number of steps required to synthesise chaetoquadrins A–C.



Scheme 94. *Proposed synthesis of methyl ketone (S)-**116** by use of Suzuki-Miyaura cross-coupling reaction.*

Chapter Five

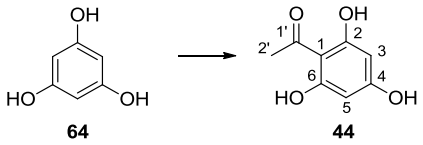
Experimental

5.1 General methods

Unless stated, all solvents and reagents were used as supplied from commercial sources. Tetrahydrofuran was freshly distilled over sodium and benzophenone ketyl. Dichloromethane and diisopropylethylamine were freshly distilled over calcium hydride. Lithium chloride was dried for >24 h in an oven (110 ° C) prior to use. Analytical thin layer chromatography (TLC) was performed using Kieselgel F_{254} 0.2 mm (Merck) silica plates with visualisation by ultraviolet irradiation (254 nm) followed by staining with potassium permanganate or vanillin. Flash column chromatography was performed using Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were measured on a Perkin Elmer 341 polarimeter at wavelength 589 nm and are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX300 or Bruker DRX400 spectrophotometer at ambient temperature. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to the chloroform ($CDCl_3$, δ 7.26), dimethylsulfoxide (DMSO-*d6*, δ 2.50) or methanol (CD_3OD, δ 3.31) peak. The multiplicities of ^{1}H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. All coupling constants *J* are reported in Hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode and assignments were determined using DEPT sequences. ^{13}C NMR chemical shifts are reported in ppm relative to the chloroform ($CDCl_3$, δ 77.16), dimethylsulfoxide (DMSO-*d6*, δ 39.5) or methanol (CD_3OD, δ 49.0) peak. Mass spectra were recorded on a Bruker microTOF QII (electrospray ionisation, ESI) mass spectrometer.

5.2 Synthesis of (±)-chaetoquadrins G and H (±-85)

1-(2,4,6-trihydroxyphenyl)ethanone, **phloroacetophenone** (**44**)



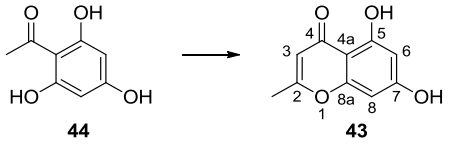
This compound **44** was prepared from phloroglucinol **64** by the method reported in the literature.[87]

δ_H (400 MHz, CD_3OD) 5.80 (2H, s, H-3, H-6), 2.60 (3H, s, H-2′).

δ_C (100 MHz, CD_3OD) 204.6 (C, C-1′), 166.3 (C, C-4), 165.9 (C, C-2, C-6), 105.6 (C, C-1), 95.6 (CH, C-3, C-6), 32.7 (CH_3, C-2′).

The ^{1}H NMR and ^{13}C NMR data obtained was in agreement with that reported in the literature.[57]

5,7-dihydroxy-2-methyl-4*H*-chromen-4-one, **noreugenin** (**43**)



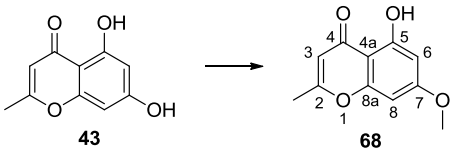
This compound was prepared from phloroacetophenone **44** by the method reported in the literature.[51]

δ_H (400 MHz, $(CD_3)_2SO$) 12.8 (1H, s, C-5-O*H*), 6.32 (1H, d, *J* 1.9, H-8), 6.13–6.18 (2H, m, H-3, H-6), 2.34 (3H, s, C-2-CH_3).

δ_C (100 MHz, $(CD_3)_2SO$) 181.7 (C, C-4), 167.6 (C, C-7), 164.2 (C, C-5), 161.5 (C, C-8a), 157.8 (C, C-2), 107.9 (CH, C-3), 103.3 (C, C-4a), 98.7 (CH, C-6), 93.7 (CH, C-8), 19.9 (CH_3, C-2-*C*H_3).

The ^{1}H NMR and ^{13}C NMR data obtained were in agreement with that reported in the literature.[51]

5-hydroxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**68**)



To a solution of noreugenin **43** (0.28 g, 1.5 mmol) in acetone (30 mL) was added K_2CO_3 (0.23 g, 1.7 mmol) followed by dropwise addition of Me_2SO_4 (0.14 mL, 1.5 mmol). The reaction mixture was stirred for 12 h. Upon completion of the reaction, the reaction mixture was acidified with 12% HCl (aq) and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified *via* flash column chromatography (1:3.5, EtOAc–Hexanes) to afford the *title compound* (0.27 g, 90%) as a white solid.

mp: 109–113 °C (lit: 106–108 °C).

δ_H (400 MHz, $CDCl_3$) 12.70 (1H, s, C-5-O*H*), 6.35 (1H, d, *J* 2.2, H-8), 6.32 (1H, d, *J* 2.2, H-6), 6.02 (1H, s, H-3), 3.85 (3H, s, C-7-OCH_3), 2.34 (3H, s, C-2-CH_3).

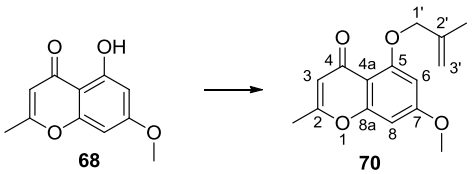
δ_C (100 MHz, $CDCl_3$) 182.6 (C, C-4), 166.9 (C, C-7), 165.5 (C, C-5), 162.3 (C, C-8a), 158.2 (C, C-2), 108.9 (CH, C-3), 105.4 (C, C-4a), 98.0 (CH, C-6), 92.6 (CH, C-8), 55.9 (CH_3, C-7-O*C*H_3), 20.3 (CH_3, C-2-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 3087, 2932, 2846, 1664, 1507, 1439, 1114, 1077, 840, 745.

HRMS (ESI+) found $[M+H]^+$ 207.0652 $C_{11}H_{11}O_4^+$ requires 207.0652.

The ^1H NMR and ^{13}C NMR data obtained were in agreement with that reported in the literature.[88]

5-(2′-methylallyl)oxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**70**)



To a solution of chromone **68** (537 mg, 2.61 mmol) in acetone (50 mL) was added K_2CO_3 (1.4 g, 10.13 mmol), 3-bromo-2-methylprop-1-ene (0.7 g, 5.23 mmol) and TBAI (40 mg, 0.11 mmol). The reaction mixture was stirred under reflux for 48 h. Upon completion of the reaction, the reaction mixture was filtered through Celite® and solvent was removed *in vacuo* to furnish a yellow oil which solidified partially upon standing. This crude product was dissolved in minimal amount of CH_2Cl_2 and purified *via* flash column chromatography (1:1.5, EtOAc–Hexanes) to afford the *title compound* (521 mg, 78%) as white solid.

mp: 85–90 °C.

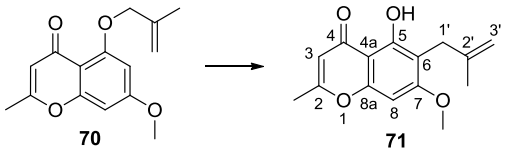
δ_H (300 MHz, $CDCl_3$) 6.34 (1H, d, *J* 2.3, H-8), 6.26 (1H, d, *J* 2.3, H-6), 5.91 (1H, s, H-3), 5.33 (1H, s, H_A-3′), 4.96–5.01 (1H, m, H_B-3′), 4.46 (2H, s, H-1′), 3.80 (3H, s, C-7-OC$\underline{H}_3$), 2.21 (3H, s, C-2-C$\underline{H}_3$), 1.83 (3H, s, C-2′-C$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$) 177.1 (C, C-4), 163.6 (C, C-2), 162.8 (C, C-7), 160.0 (C, C-8a), 159.7 (C, C-5), 139.7 (C, C-2′), 112.7 (CH_2, C-3′), 111.9 (CH, C-3), 109.1 (C, C-4a), 97.0 (CH, C-6), 92.8 (CH, C-8), 72.4 (CH_2, C-1′), 55.6 (CH_3, C-7-O$\underline{C}H_3$), 19.7 (CH_3, C-2-$\underline{C}H_3$), 19.3 (CH_3, C-2′-$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 1654, 1609, 1342, 1162, 1095, 523.

HRMS (ESI+) found $[M+H]^+$ 261.1124 $C_{15}H_{17}O_4^+$ requires 261.1121.

5-hydroxy-7-methoxy-2-methyl-6-(2′-methylallyl)-4*H*-chromen-4-one (**71**)



Allyl phenyl ether **70** (111 mg, 0.427 mmol) was heated to 200 °C to form a brown melt. The melt was stirred at this temperature for 2 h then cooled to rt. The brown solid was then dissolved in minimum amount of CH_2Cl_2 and purified *via* flash column chromatography (1:2, EtOAc–Hexanes) to yield the *title compound* as an off white solid (912 mg, 82%).

mp: 96.2–97.0 °C.

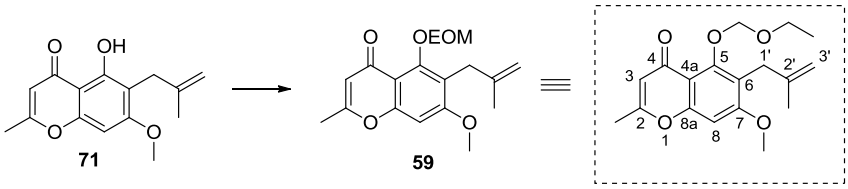
δ_H (300 MHz, $CDCl_3$) 12.82 (1H, s, C-5-O*H*), 6.38 (1H, s, H-8), 6.04 (1H, s, H-3), 4.71 (1H, s, H_A-3′), 4.53 (1H, s, H_B-3′), 3.87 (3H, s, C-7-OC*H*$_3$), 3.35 (2H, s, H-1′), 2.35 (3H, s, C-2-C*H*$_3$), 1.80 (3H, s, C-2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 182.6 (C, C-4), 166.5 (C, C-2), 163.5 (C, C-7), 159.0 (C, C-8a), 156.9 (C, C-5), 144.1 (C, C-2′), 111.1 (C, C-6), 109.7 (CH_2, C-3′), 109.0 (CH, C-3), 105.2 (C, C-4a), 89.5 (CH, C-8), 56.0 (CH_3, C-7-O*C*H$_3$), 30.0 (CH_2, C-1′), 23.0 (CH_3, C-2′-*C*H$_3$), 20.5 (CH_3, C-2-*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} 1626, 1494, 1114, 1091, 836, 812, 622.

HRMS (ESI+) found $[M+H]^+$ 261.1114, $C_{15}H_{17}O_4^+$ requires 261.1121.

5-(ethoxymethoxy)-7-methoxy-2-methyl-6-(2′-methylallyl)-4*H*-chromen-4-one (**59**)



To a chilled solution of phenol **71** (0.912 g, 3.51 mmol) in THF (10 mL) at 0 °C was added sodium hydride (60% w/w in mineral oil, 0.351 g, 8.87 mmol), chloromethyl ethyl ether (0.33 mL, 3.51 mmol) and stirred at this temperature for 2 h. Upon completion of the reaction as monitored by TLC analysis, reaction mixture was quenched by addition of brine (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* and purified *via* flash column chromatography (1:2, EtOAc–Hexanes) to afford the *title compound* (1.00 g, 90%) as a pale yellow solid.

mp: 103–104 °C.

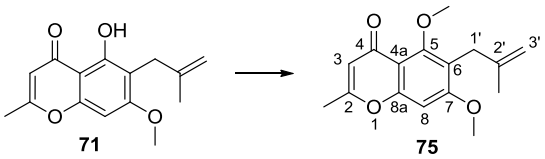
δ_H (300 MHz, $CDCl_3$) 6.63 (1H, s, H-8), 5.99 (1H, s, H-3), 5.17 (2H, s, C-5-OC$\underline{H}_2$OCH$_2$CH$_3$), 4.69 (1H, s, H_A-3′), 4.41 (1H, s, H_B-3′), 3.87 (3H, s, C-7-OC$\underline{H}_3$), 3.85 (2H, q, *J* 7.0, C-5-OCH$_2$OC$\underline{H}_2$CH$_3$), 3.46 (2H, s, H-1′), 2.29 (3H, s, C-2-C$\underline{H}_3$), 1.79 (3H, s, C-2′-C$\underline{H}_3$), 1.25 (3H, t, *J* 7.0, C-5-OCH$_2$OCH$_2$C$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$) 177.1 (C, C-4), 163.4 (C, C-2), 162.3 (C, C-7), 158.4 (C, C-8a), 155.7 (C, C-5), 144.1 (C, C-2′), 120.5 (C, C-6), 111.7 (CH, C-3), 111.4 (C, C-4a), 110.0 (CH$_2$, C-3′), 100.4 (CH$_2$, C-5-O$\underline{C}$H$_2$OCH$_2$CH$_3$), 95.3 (CH, C-8), 65.6 (CH$_2$, C-5-OCH$_2$O$\underline{C}$H$_2$CH$_3$), 56.1 (CH$_3$, C-7-O$\underline{C}$H$_3$), 31.4 (CH$_2$, C-1′), 23.2 (CH$_3$, C-2′-$\underline{C}$H$_3$), 20.0 (CH$_3$, C-2-$\underline{C}$H$_3$), 15.3 (CH$_3$, C-5-OCH$_2$OCH$_2$$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 3091, 2907, 1653, 1628, 1211, 1171, 1092, 1054.

HRMS (ESI+) found $[M+Na]^+$ 341.1372, $C_{18}H_{22}NaO_5^+$ requires 341.1359.

5,7-dimethoxy-2-methyl-6-(2′-methylallyl)-4*H*-chromen-4-one (**75**)



To a solution of phenol **71** (40 mg, 0.15 mmol) in acetone (1 mL) were added K_2CO_3 (85 mg, 0.62 mmol) and methyl iodide (0.019 mL, 0.31 mmol). The reaction mixture was heated at reflux and stirred for 24 h. The mixture was then filtered through Celite®, concentrated *in vacuo* and the residue was purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to afford the *title compound* (25 mg, 60%) as a yellow oil.

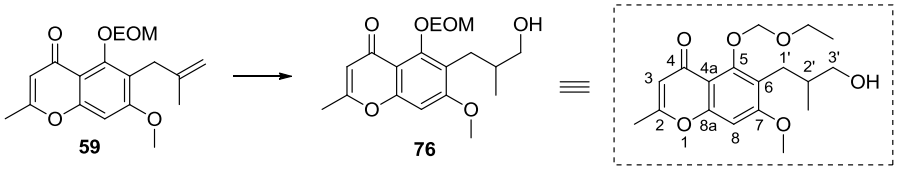
δ_H (400 MHz, $CDCl_3$) 6.63 (1H, s, H-8), 6.02 (1H, d, *J* 0.9, H-3), 4.67–4.71 (1H, m, H_A-3′), 4.37–4.42 (1H, m, H_B-3′), 3.87 (3H, s, C-7-OC*H*$_3$), 3.83 (3H, s, C-5-OC*H*$_3$), 3.38 (2H, s, H-1′), 2.30 (3H, d, *J* 0. 9, C-2-C*H*$_3$), 1.80 (3H, s, C-2′-C*H*$_3$).

δ_C (100 MHz, $CDCl_3$) 177.0 (C, C-4), 163.3 (C, C-2), 162.3 (C, C-7), 158.5 (C, C-8a), 158.3 (C, C-5), 114.9 (C, C-2′), 120.3 (C, C-6), 112.1 (C, C-4a), 111.9 (CH, C-3), 109.9 (CH_2, C-3′). 95.2 (CH, C-8), 62.5 (CH_3, C-5-O*C*H$_3$), 56.1 (CH_3, C-7-O*C*H$_3$), 30.9 (CH_2, C-1′), 23.3 (CH_3, C-2′-*C*H$_3$), 20.0 (CH_3, C-2-*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} 3083, 2930, 2842, 1655, 1601, 1456, 1387, 1339, 1202, 1177, 1113, 1086.

HRMS (ESI+) found $[M+Na]^+$ 297.1090, $C_{16}H_{18}NaO_4^+$ requires 297.1097.

5-(ethoxymethoxy)-6-(3′-hydroxy-2′-methylpropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**76**)



To a chilled solution of olefin **59** (225 mg, 0.707 mmol) in THF (4 mL) at 0 °C was added borane-dimethyl sulphide complex (0.07 mL, 1.06 mmol) and stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by dropwise addition of 1M NaOH (aq) (0.5 mL) and 30% aq. H_2O_2 solution (0.5 mL). The mixture was then diluted with brine (5 mL) and immediately extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (2.5:1, EtOAc–Hexanes) to afford the *title compound* (102 mg, 43%) as yellow oil.

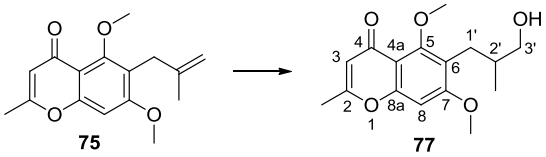
δ_H (300 MHz, $CDCl_3$) 6.65 (1H, s, H-8), 6.00 (1H, d, *J* 0.6, H-3), 5.21 (1H, d, *J* 6.8, C-5-OC$\underline{H_A}$H$_B$OCH$_2$CH$_3$), 5.16 (1H, d, *J* 6.8, C-5-OCH$_A$$\underline{H_B}OCH_2CH_3$), 3.90 (3H, s, C-7-OC$\underline{H}_3$), 3.82–3.93 (2H, m, C-5-OCH$_2$OC$\underline{H}_2$CH$_3$), 3.38 (2H, d, *J* 4.5, H-3′), 2.65–2.87 (2H, m, H-1′), 2.30 (3H, d, *J* 0.6, C-2-C$\underline{H}_3$), 1.89–2.02 (1H, m, H-2′), 1.26 (3H, t, *J* 7.1, C-5-OCH$_2$OCH$_2$C$\underline{H}_3$), 1.00 (3H, d, *J* 6.9, H-2′-C$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$) 177.1 (C, C-4), 163.6 (C, C-2), 162.1 (C, C-7), 158.2 (C, C-8a), 155.6 (C, C-5), 121.3 (C, C-6), 111.7 (CH, C-3), 111.4 (C, C-4a), 100.7 (CH_2, C-5-O$\underline{C}$H$_2$OCH$_2$CH$_3$), 95.5 (CH, C-8), 66.6 (CH_2, C-3′), 66.0 (CH_2, C-5-OCH$_2$O$\underline{C}$H$_2$CH$_3$), 56.1 (CH_3, C-7-O$\underline{C}$H$_3$), 35.9 (CH, C-2′), 26.7 (CH_2, C-1′), 20.0 (CH_3, C-2′-$\underline{C}$H$_3$), 17.5 (CH_3, C-2-$\underline{C}$H$_3$), 15.3 (CH_3, C-5-OCH$_2$OCH$_2$$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 2928, 1661, 1604, 1451, 1343, 1133, 1053, 992.

HRMS (ESI+) found $[M+Na]^+$ 359.1454, $C_{18}H_{24}NaO_6^+$ requires 359.1465.

6-(3′-hydroxy-2′-methylpropyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**77**)



To a stirred solution of olefin **75** (118 mg, 0.431 mmol) in THF (2 mL) was added (+)-Ipc_2BH (123 mg, 0.430 mmol). The reaction mixture was stirred for 2 h. Methanol (0.1 mL) was then added followed by 1 M NaOH (aq) (0.2 mL), 30% aq. H_2O_2 solution (0.2 mL) and brine (5 mL). Reaction mixture was then extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (2.5:1, EtOAc–Hexanes) to yield the *title compound* (41 mg, 32%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 6.61 (1H, s, H-8), 5.99 (1H, s, H-3), 3.86 (3H, s, C-7-OC$\underline{H}_3$), 3.83 (3H, s, C-5-OC$\underline{H}_3$), 3.34 (2H, d, *J* 4.6, H-3′), 2.51–2.77 (2H, m, H-1′), 2.19–2.42 (1H, m, H-2′), 2.26 (3H, s, C-2-C$\underline{H}_3$), 0.96 (3H, d, *J* 6.8, C-2′-C$\underline{H}_3$).

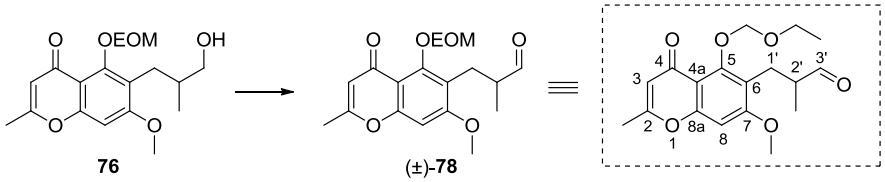
δ_C (75 MHz, $CDCl_3$) 176.8 (C, C-4), 163.3 (C, C-2), 162.3 (C, C-7), 162.1 (C, C-5), 158.1 (C, C-8a), 157.8 (C, C-6), 120.7 (C, C-4a), 111.7 (CH, C-3), 95.3 (CH, C-8), 66.5 (CH_2, C-3′), 62.3 (CH_3, C-5-O$\underline{C}H_3$), 55.9 (CH_3, C-7-O$\underline{C}H_3$), 35.9 (CH, C-2′), 26.0 (CH_2, C-1′), 19.8 (CH_3, C-2-$\underline{C}H_3$), 17.3 (CH_3, C-2′-$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 2941, 2253, 1655, 1602, 1457, 1423, 1389, 1343, 1261, 1203, 1059, 904, 724.

HRMS (ESI+) $[M+H]^+$ 293.1376, $C_{16}H_{21}O_5^+$ requires 293.1384.

1′-(5-(ethoxymethoxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)-2′-methylpropan-3′-al

(±)-**78**



To a solution of alcohol **76** (104 mg, 0.309 mmol) in DMSO (3 mL) was added 2-iodoxybenzoic acid (300 mg, 1.07 mmol) and reaction mixture was stirred at rt for 3 h. Saturated aqueous $Na_2S_2O_3$ (8 mL) was added followed by the addition of EtOAc (20 mL). The layers were separated then the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield the *title compound* (90 mg, 87%) as a colourless oil.

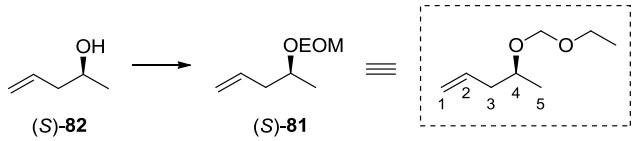
δ_H (300 MHz, $CDCl_3$) 9.63 (1H, d, *J* 1.8, H-3′), 6.61 (1H, s, H-8), 5.98 (1H, s, H-3), 5.17 (2H, s, C-5-OC$\underline{H_2}$OCH$_2$CH$_3$), 3.85 (3H, s, C-7-OC$\underline{H_3}$), 3.81 (2H, q, *J* 7.0, C-5-OCH$_2$OC$\underline{H_2}$CH$_3$), 3.09 (1H, dd, *J* 13.9, 7.38, H_A-1′), 2.90 (1H, dd, *J* 13.9, 7.38, H_B-1′), 2.62–2.77 (1H, m, H-2′), 2.28 (3H, s, C-2-CH$_3$), 1.23 (3H, t, *J* 7.2, C-5-OCH$_2$OCH$_2$C$\underline{H_3}$), 1.04 (3H, d, *J* 7.1, C-2′-C$\underline{H_3}$).

δ_C (75 MHz, $CDCl_3$) 204.9 (CH, C-3′), 176.9 (C, C-4), 163.6 (C, C-2), 161.7 (C, C-7), 158.4 (C, C-8a), 156.0 (C, C-5), 119.3 (C, C-6), 111.5 (CH, C-3), 111.1 (C, C-4a), 100.6 (CH$_2$, C-5-O$\underline{C}$H$_2$OCH$_2$CH$_3$), 95.3 (CH, C-8), 65.6 (CH$_2$, C-5-OCH$_2$O$\underline{C}$H$_2$CH$_3$), 55.9 (CH$_3$, C-7-O$\underline{C}$H$_3$), 46.3 (CH, C-2′), 24.7 (CH$_2$, C-1′), 19.8 (CH$_3$, C-2-$\underline{C}$H$_3$), 15.1 (CH$_3$, C-5-OCH$_2$OCH$_2\underline{C}$H$_3$), 13.3 (CH$_3$, C-2′-$\underline{C}$H$_3$).

IR: ν_{max} (film)/cm^{-1} 2943, 1723, 1658, 1603, 1494, 1446, 1389, 1342, 1203, 1177, 990.

HRMS (ESI+) found $[M+Na]^+$ 357.1312, $C_{18}H_{22}NaO_6^+$ requires 357.1309.

(*S*)-4-(ethoxymethoxy)pent-1-ene (*S*)-**81**



(*S*)-**82** (*S*)-**81**

To a chilled solution of alcohol (*S*)-**82** (1.07 g, 12.4 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added $^{i}Pr_2NEt$ (6.5 mL, 37.3 mmol), DMAP (0.23 g, 2.48 mmol), and chloromethyl ethyl ether (1.78 mL, 18.6 mmol). The reaction mixture was allowed to warm to rt and stirred at this temperature for 12 h. The reaction mixture was subsequently quenched with addition of saturated aqueous NH_4Cl (10 mL) and layers separated. Organic layer was washed with saturated aqueous NH_4Cl (4 × 5 mL), concentrated *in vacuo* and purified *via* flash column chromatography (20:1, Pentane–Et_2O) to afford the *title compound* (1.55 g, 86%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 5.71–5.89 (1H, m, H-2), 5.00–5.12 (2H, m, H-1), 4.65–4.75 (2H, m, C-4-OC*H*$_2$OCH$_2$CH$_3$), 3.70–3.83 (1H, m, H-4), 3.54–3.66 (2H, m, C-4-OCH$_2$OC*H*$_2$CH$_3$), 2.12–2.38 (2H, m, H-3), 1.20 (3H, t, *J* 7.2, C-4-OCH$_2$OCH$_2$C*H*$_3$), 1.16 (3H, d, *J* 6.2, H-5).

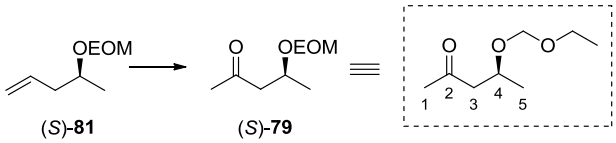
δ_C (75 MHz, $CDCl_3$) 135.0 (CH, C-2), 117.0 (CH_2, C-1), 93.5 (CH_2, C-4-O*C*H$_2$OCH$_2$CH$_3$), 72.6 (CH, C-4), 63.2 (CH_2, C-4-OCH$_2$O*C*H$_2$CH$_3$), 41.5 (CH_2, C-3), 20.1 (CH_3, C-5), 15.2 (CH_3, C-4-OCH$_2$OCH$_2$*C*H$_3$).

$[\alpha]_D^{20}$ +1.64 (c 4.2, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 3672, 2980, 2903, 1396, 1241, 1061, 886.

HRMS (ESI+) found $[M+Na]^+$ 167.1042, $C_8H_{16}NaO_2^+$ requires 167.1043.

(*S*)-4-(ethoxymethoxy)pentan-2-one (*S*)-**79**



(*S*)-**81** (*S*)-**79**

To a solution of olefin (*S*)-**81** (100 mg, 0.69 mmol) in a mixture of DMF (2 mL) and H_2O (1.32 mL) was added palladium(II) chloride (30 mg, 0.35 mmol) and copper (I) chloride (82 mg, 0.83 mmol). Oxygen gas was bubbled through the solution for 6 h. The reaction mixture was then filtered through Celite®, diluted with Et_2O (10 mL) and brine (10 mL) and layers separated. The aqueous layer was further extracted with Et_2O (3 × 5 mL), washed with brine (10 mL), concentrated *in vacuo* and purified *via* flash column chromatography (10:1, Pentane– Et_2O) to afford the *title compound* (49 mg, 44%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 4.63–4.69 (2H, m, C-4-OC*H*$_2$OCH$_2$CH$_3$), 4.09–4.22 (1H, m, H-4), 3.54 (2H, q, *J* 7.1, C-4-OCH$_2$OC*H*$_2$CH$_3$), 2.73 (1H, dd, *J* 16.0, 7.5, H_A-3), 2.43 (1H, dd, *J* 16.0, 5.2, H_B-3), 2.14 (3H, s, H-1), 1.18 (3H, d, *J* 6.4, H-5), 1.17 (3H, t, *J* 7.1, C-4-OCH$_2$OCH$_2$C*H*$_3$).

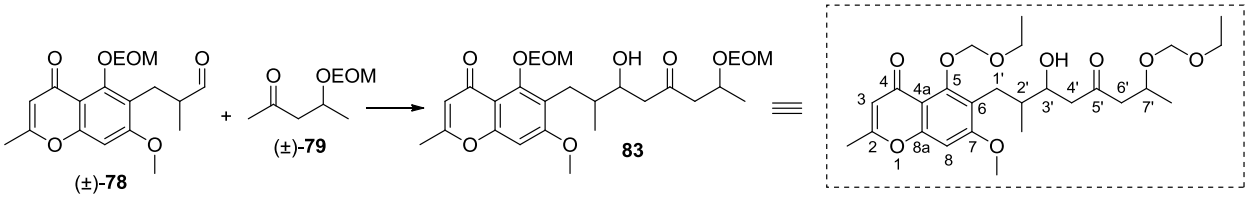
δ_C (75 MHz, $CDCl_3$) 207.1 (C, C-2), 93.9 (CH_2, C-4-O*C*H$_2$OCH$_2$CH$_3$), 69.8 (CH, C-4), 63.4 (CH_2, C-4-OCH$_2$O*C*H$_2$CH$_3$), 51.1 (CH_2, C-3), 31.0 (CH_3, C-1), 20.7 (CH_3, C-5), 15.1 (CH_3, C-4-OCH$_2$OCH$_2$*C*H$_3$).

$[\alpha]_D^{20}$ +21.1 (c 3.0, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 2975, 2932, 1716, 1381, 1102, 1032, 844.

HRMS (ESI+) found $[M+Na]^+$ 183.0994, $C_8H_{16}NaO_3^+$ requires 183.0992.

5-(ethoxymethoxy)-6-(7′-(ethoxymethoxy)-3′-hydroxy-2′-methyl-5′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**83**)[§]



To a solution of distilled diisopropylamine (0.09 mL, 0.66 mmol) in THF (4 mL) cooled to –78 °C was added *n*-BuLi (1.6 M in Hexanes, 0.4 mL, 0.62 mmol). The mixture was stirred for 1 h at –78 °C then warmed to 0 °C and stirred at this temperature for 10 min then cooled back to –78 °C. Meanwhile, mixture of ketone (±)-**79** (100 mg, 0.62 mmol) in THF (4 mL) was cooled to –78 °C and added to the reaction mixture *via* cannula. Upon complete addition of the ketone (±)-**79** mixture, solution of aldehyde (±)-**78** (125 mg, 0.37 mmol) in THF (4 mL) was cooled to –78 °C and was added to the mixture *via* cannula. The mixture was allowed to warm to rt and stirred for 4 h. The reaction mixture was then quenched with saturated NH_4Cl (6 mL) at 0 °C, extracted with EtOAc (3 × 5 mL), dried over $MgSO_4$ and purified *via* flash column chromatography (2.5:1, EtOAc–Hexanes) to afford the *title compound* (109 mg, 60%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 6.59–6.68 (1H, m), 5.99 (1H, m), 5.09–5.25 (2H, m), 4.06–4.31 (1H, m), 3.89 (3H, s), 3.79–3.95 (2H, m), 2.39–2.93 (6H, m), 2.30 (3H, s), 1.81–1.98 (2H, m), 1.10–1.32 (7H, m), 0.80–0.98 (3H, m).

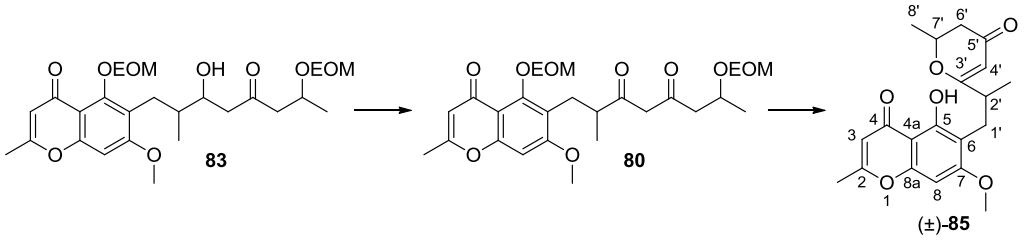
δ_C (75 MHz, $CDCl_3$) 209.5, 200.6, 177.1, 163.6, 163.5, 162.1, 158.3, 155.8, 143.8, 143.5, 132.6, 121.1, 111.7, 100.7, 100.6, 95.6, 95.5, 95.3, 94.0, 93.9, 71.6, 69.8, 69.7, 69.6, 69.0, 65.9, 63.5, 63.4, 56.2, 56.0, 51.3, 51.1, 48.4, 48.3, 47.1, 44.3, 38.6, 38.1, 38.0, 38.0, 27.7, 26.4, 20.8, 20.0, 18.4, 15.4, 15.3.

IR: ν_{max} (film)/cm^{-1} 3475, 2972, 2930, 1654, 1660, 1445, 1341, 1048, 989, 845.

HRMS (ESI+) found $[M+H]^+$ 495.2569, $C_{26}H_{39}NaO_9^+$ requires 495.2589.

[§] Note: To test the viability of our synthetic route, this compound was made without asymmetric control and isolated as a complicated mixture of inseparable diastereoisomers. Accordingly, peaks remain unassigned.

(±)–chaetoquadrin G and H (±)-**85**



To a solution of β-hydroxyketone **83** (52 mg, 0.106 mmol) in CH_2Cl_2 (10 mL) was added pyridine (25 mg, 0.317 mmol) and Dess-Martin periodinane (134 mg, 0.317 mmol). The reaction mixture was stirred for 30 seconds followed by the addition of H_2O (20 mL). The layers were separated and organic layer was dried with $MgSO_4$. The solvent was removed *in vacuo* to afford the crude aldehyde **80** which was used directly in the next step.

To a solution of crude aldehyde **80** in CH_2Cl_2 (2 mL) was added $NaHSO_4 \cdot SiO_2$ (20 mg) and the reaction mixture stirred for 2 h. The reaction mixture was filtered through cotton wool and the filtrate loaded directly onto a preparative TLC plate and purified (EtOAc–hexanes, 2:1) to afford the *title compound* (7 mg, ca 50% over two steps) as a yellow oil.

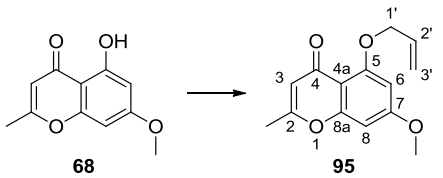
δ_H (300 MHz, $CDCl_3$) 12.85 (1H, s, C-5-O*H*), 12.84 (1H, s*, C-5-O*H*), 6.34 (1H, s, H-8), 6.04 (1H, s, H-3), 5.22 (1H, s*, H-4′) 5.11 (1H, s, H-4′), 4.29–4.45 (1H, m, H-7′), 3.87 (3H, s, C-7-OC*H*$_3$), 2.89–3.05 (1H, m, H-1′), 2.63–2.81 (2H, m, H-2′), 2.35 (3H, s, C-2-C*H*$_3$), 2.24–2.42 (2H, m, H-6′), 1.44 (3H, d, *J* 6.5, H-8′), 1.41 (3H, d*, *J* 6.0, H-8′) 1.17 (3H, d, *J* 6.7, C-2′-C*H*$_3$), 1.12 (3H, d*, *J* 6.8, C-2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 193.7 (C, C-5′), 193.5 (C*, C-5′), 182.7 (C, C-4), 182.5 (C*, C-4), 181.3 (C, C-3′), 181.1 (C*, C-3′), 166.6 (C, C-2), 166.4 (C*, C-2), 163.4 (C, C-7), 163.2 (C*, C-7), 159.2 (C, C-5), 159.1 (C*, C-5), 157.0 (C, C-8a), 110.8 (C, C-6), 109.1 (CH, C-3), 105.2 (C, C-4a), 103.3 (CH, C-4′), 102.1 (CH*, C-4′), 89.5 (CH, C-8), 89.4 (CH*, C-8), 75.8 (CH, C-7′), 75.6 (CH*, C-7′), 56.0 (CH_3, C-7-O*C*H$_3$), 42.9 (CH_2, C-6′), 42.8 (CH_2*, C-6′), 39.1 (CH, C-2′), 38.5 (CH*, C-2′), 27.3 (CH_2, C-1′), 20.6 (CH_3, C-2-*C*H$_3$), 20.5 (CH_3, C-8′), 17.6 (CH_3, C-2′-*C*H$_3$), 17.4 (CH_3*, C-2′-*C*H$_3$).

The ^{1}H NMR and ^{13}C NMR data obtained was in agreement with that reported in the literature.[1-2] Note: Non-asterisk peaks denote those arising from chaetoquadrin H. Asterisks denote peaks arising from chaetoquadrin G.

5.3 Synthesis of mesylate 98

5-(allyloxy)-7-methoxy-2-methyl-4*H*-chromen-4-one (**95**)



To a solution of eugenin **68** (0.10 g, 0.48 mmol) in acetone (6 mL) were added K_2CO_3 (0.2 g, 1.5 mmol), allyl bromide (0.12 g, 0.99 mmol) and TBAI (0.02 g, 0.054 mmol). The reaction mixture was heated at reflux and stirred for 24 h. The mixture was then filtered through Celite®, concentrated *in vacuo* and the brown residue was purified *via* flash column chromatography (1.1:1, EtOAc–Hexanes) to afford the *title compound* (0.1 g, 85%) as a yellow oil.

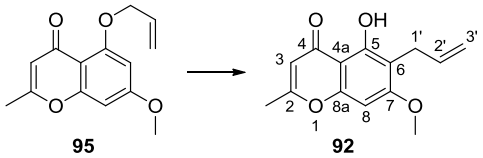
δ_H (300 MHz, CDCl3) 6.40 (1H, d, *J* 2.6, H-8), 6.32 (1H, d, *J* 2.2, H-6), 6.09 (1 H, ddt, *J* 17.2, 10.7, 4.7, H-2′), 5.97 (1H, d, *J* 0.7, H-3), 5.67 (1H, ddt, *J* 17.2, 1.8, 1.7, H_A-3′), 5.33 (1H, ddt, *J* 10.6, 1.8, 1.5, H_B-3′), 4.63 (2H, dt, *J* 4.7, 1.8, H-1′), 3.85 (3H, s, C-7-OC*H*$_3$), 2.26 (3H, d, *J* 0.7, C-2-C*H*$_3$).

δ_C (75 MHz, CDCl3) 177.3 (C, C-4), 163.6 (C, C-2), 162.9 (C, C-7), 160.1 (C, C-8a), 159.8 (C, C-5), 132.3 (CH, C-2′), 117.7 (CH_2, C-3′), 112.0 (CH, C-3), 109.3 (C, C-4a), 97.3 (CH, C-6), 93.0 (CH, C-8), 69.8 (CH_2, C-1′), 55.7 (CH_3, C-7-O*C*H$_3$), 19.8 (CH_3, C-2-*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} 2924, 1655, 1602, 1572, 1390, 1335, 1161, 1084, 927, 821.

HRMS (ESI+) found $[M+Na]^+$ 269.0789 $C_{14}H_{14}NaO_4^+$ requires 269.0784.

6-allyl-5-hydroxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**92**)



Allyl phenyl ether **95** (0.58 g, 2.4 mmol) was heated to 200 °C to form a brown melt. The melt was stirred at this temperature for 2 h then cooled to rt. The brown solid was then dissolved in minimum amount of CH_2Cl_2 and purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to afford the *title compound* (0.49 g, 84%) as a light yellow solid.

mp: 94.2–95.6 °C.

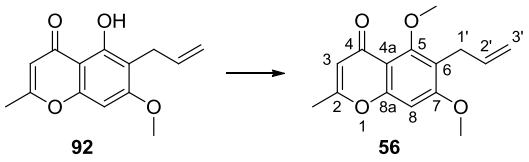
δ_H (300 MHz, $CDCl_3$) 12.81 (1H, s, C-5-O*H*), 6.37 (1H, s, C-8), 6.03 (1H, d, *J* 0.6, C-3), 5.95 (1H, ddt, *J* 17.2, 10.2, 6.1, C-2′), 4.93–5.06 (2H, m, C-3′), 3.88 (3H, s, C-7-OCH_3), 3.40 (2H, dt, *J* 6.2, 1.5, C-1′), 2.34 (3H, d, *J* 0.6, C-2-CH_3).

δ_C (75 MHz, $CDCl_3$) 182.6 (C, C-4), 166.5 (C, C-2), 163.3 (C, C-7), 158.8 (C, C-5), 156.9 (C, C-8a), 136.0 (CH, C-2′), 114.6 (CH_2, C-3′), 111.0 (C, C-6), 109.1 (CH, C-3), 105.3 (C, C-4a), 89.6 (CH, C-8), 56.1 (CH_3, C-6-OCH_3), 26.4 (CH_2, C-1′), 20.6 (CH_3, C-2-CH_3)

IR: ν_{max} (film)/cm^{-1} 1656, 1624, 1590, 1492, 1447, 1407, 1202. 1135, 960, 845.

HRMS (ESI+) found $[M+H]^+$ 247.0959 $C_{14}H_{15}O_4^+$ requires 247.0965.

6-allyl-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**56**)



To a solution of phenol **92** (1.43 g, 5.81 mmol) in acetone (70 mL) were added K_2CO_3 (2.5 g, 18 mmol) and dimethyl sulfate (0.67 mL, 7.06 mmol). The reaction mixture was heated at reflux and stirred for 24 h. The mixture was then filtered through Celite®, concentrated *in vacuo* and the brown residue was purified *via* flash column chromatography (1:1.5, EtOAc–Hexanes) to afford the *title compound* (1.19 g, 79%) as a white solid.

mp: 89–91 °C.

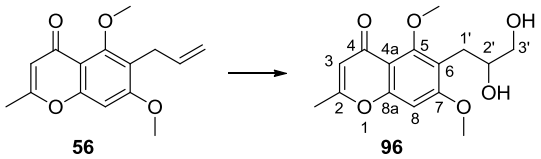
δ_H (400 MHz, $CDCl_3$) 6.62 (1H, s, H-8), 6.01 (1H, s, H-3), 5.90–6.00 (1H, m, H-2′), 4.90–5.03 (2H, m, H-3′), 3.89 (3H, s, C-7-OC$\underline{H}_3$), 3.86 (3H, s, C-5-OC$\underline{H}_3$), 3.43–3.47 (2H, m, H-1′), 2.29 (3H, s, H-9).

δ_C (100 MHz, $CDCl_3$) 176.9 (C, C-4), 163.3 (C, C-2), 162.1 (C, C-7), 158.4 (C, C-5), 158.0 (C, C-8a), 136.8 (CH, C-2′), 120.3 (C, C-4a), 115.0 (CH_2, C-3′), 112.1 (C, C-6), 111.8 (CH, C-3), 95.3 (CH, C-8), 62.6 (CH_3, C-5-O$\underline{C}H_3$), 56.1 (CH_3, C-7-O$\underline{C}H_3$), 27.5 (CH_2, C-1′), 20.0 (CH_3, C-2-$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 2927, 1656, 1602, 1456, 1339, 1200, 1131, 1115, 1075, 824.

HRMS (ESI+) found $[M+H]^+$ 261.1119 $C_{15}H_{17}O_4^+$ requires 261.1121.

6-(2′,3′-dihydroxypropyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**96**)



A mixture of ^{t}BuOH (8.3 mL), H_2O (10 mL) and AD-mix-β (3.0 g) was cooled in an ice water bath. Olefin **56** (0.55 g, 2.11 mmol) was added and the reaction mixture was allowed to warm to rt and stirred at this temperature for 12 h. Sodium sulphite (4 g) was then added and stirred for further 45 min. The reaction mixture was diluted with EtOAc (10 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with brine (2 × 10 mL). The organic extracts were then dried with $MgSO_4$ and concentrated *in vacuo* to afford *title compound* (346 mg, 56%) as a white solid.

mp: 137.3–138.2 °C.

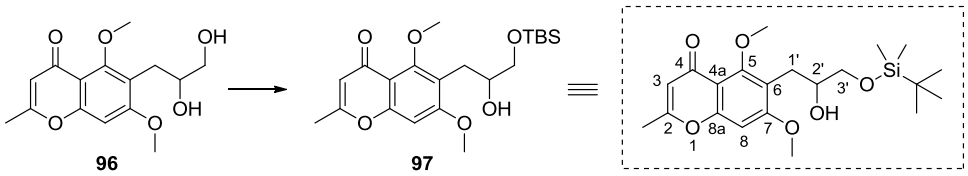
δ_H (300 MHz, $CDCl_3$) 6.66 (1H, s, H-8), 6.03 (1H, s, H-3), 3.91 (3H, s, C-7-OC$\underline{H}_3$), 3.88 (3H, s, C-5-OC$\underline{H}_3$), 3.87–3.92 (1H, m, H-2′), 3.42–3.65 (2H, m, C-3′), 2.84–3.05 (2H, m, C-1′), 2.31 (3H, s, C-2-C$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$) 176.7 (C, C-4), 163.6 (C, C-2), 161.9 (C, C-7), 158.5 (C, C-5), 158.0 (C, C-8a), 118.0 (C, C-4a), 111.9 (C, C-6), 111.7 (CH, C-3), 95.6 (CH, C-8), 71.7 (CH, C-2′), 66.0 (CH_2, C-3′), 62.3 (CH_3, C-5-$\underline{C}H_3$), 56.1 (CH_3, C-7-O$\underline{C}H_3$), 27.0 (CH_2, C-1′), 19.8 (CH_3, C-2-$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 3376, 1651, 1597, 1389, 1343, 1202, 1120, 1086.

HRMS (ESI+) found $[M+H]^+$ 295.1184 $C_{15}H_{19}O_6^+$ requires 295.1176.

6-(3′-((*tert*-butyldimethylsilyl)oxy)-2′-hydroxypropyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**97**)



To a solution of alcohol **96** (323 mg, 1.10 mmol) in CH_2Cl_2 (8 mL) was added DMAP (5.3 mg, 0.04 mmol), NEt_3 (0.18 mL, 1.32 mmol) and *tert*-butyldimethylsilyl chloride (182 mg, 1.21 mmol). The reaction mixture was stirred for 6 h, and then diluted with H_2O (20 mL) and CH_2Cl_2 (10 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (1.5:1, EtOAc–Hexanes) to afford the *title compound* (267 mg, 60%) as a colourless oil.

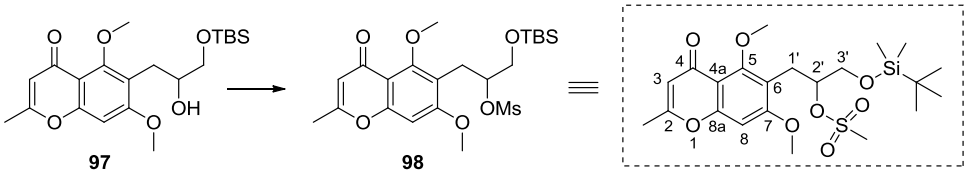
δ_H (400 MHz, $CDCl_3$) 6.64 (1H, s, H-8), 6.02 (1H, s, H-3), 3.89 (3H, s, C-7-OC$\underline{H}_3$), 3.88 (3H, s, C-5-OC$\underline{H}_3$), 3.81–3.89 (1H, m, H-2′), 3.55–3.64 (2H, m, C-3′), 2.83–2.98 (2H, m, C-1′), 2.30 (3H, s, C-2-C$\underline{H}_3$), 0.92 (9H, s, C-3′-OSi$(CH_3)_2$C(C$\underline{H}_3)_3$), 0.08 (3H, s, C-3′-OSi(C$\underline{H}_3)_2$C$(CH_3)_3$), 0.07 (3H, s, C-3′-OSi(C$\underline{H}_3)_2$C$(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$) 176.9 (C, C-4), 163.4 (C, C-2), 162.2 (C, C-7), 158.5 (C, C-5), 158.4 (C, C-8a), 118.8 (C, C-4a), 112.0 (C, C-6), 111.9 (CH, C-3), 95.4 (CH, C-8), 71.8 (CH, C-2′), 67.2 (CH_2, C-3′), 62.3 (CH_3, C-5-O$\underline{C}H_3$), 56.0 (CH_3, C-7-O$\underline{C}H_3$), 27.1 (CH_2, C-1′), 26.0 (CH_3, C-3′-OSi$(CH_3)_2$C($\underline{C}H_3)_3$), 19.9 (CH_3, C-2-$\underline{C}H_3$), 18.4 (C, C-3′-OSi$(CH_3)_2\underline{C}(CH_3)_3$), -5.22 ($CH_3$, C-3′-OSi($\underline{C}H_3)_2C(CH_3)_3$), -5.25 ($CH_3$, C-3′-OSi($\underline{C}H_3)_2C(CH_3)_3$).

IR: ν_{max} (film)/cm^{-1} 2942, 2858, 1657, 1602, 1388, 1341, 1202, 1122, 841.

HRMS (ESI+) found $[M+H]^+$ 409.2033 $C_{21}H_{33}O_6Si^+$ requires 409.2041.

3′-((*tert*-butyldimethylsilyl)oxy)-1′-(5,7-dimethoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)propan-2′-yl methanesulfonate (**98**)



To a solution of alcohol **97** (183 mg, 0.45 mmol) in THF (10 mL) was added NEt_3 (0.13 mL, 0.90 mmol) and methanesulfonyl chloride (0.035 mL, 0.45 mmol) and the mixture stirred at rt for 1 h. Brine (20 mL) and EtOAc (10 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (1.5:1, EtOAc–Hexanes) to afford the *title compound* (206 mg, 95%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 6.64 (1H, s, H-8), 6.02 (1H, s, H-3), 4.93–5.02 (1H, m. H-2′), 3.92 (3H, s, C-7-OC$\underline{H}_3$), 3.90 (3H, s, C-5-OC$\underline{H}_3$), 3.81 (1H, dd, *J* 11.4, 6.34, H_A-3′), 3.73 (1H, dd, *J* 11.4, 4.0, H_B-3′), 3.21 (1H, dd, *J* 14.0, 8.3, H_A-1′), 2.97 (1H, dd, *J* 14.0, 5.9, H_B-1′), 2.81 (3H, s, C-2′-S(O)$_2$C$\underline{H}_3$), 2.30 (3H, s, C-2-C$\underline{H}_3$), 0.90 (9H, s, C-3′-OSi(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), 0.07 (3H, s, C-3′-OSi(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$), 0.06 (3H, s, C-3′-OSi(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$).

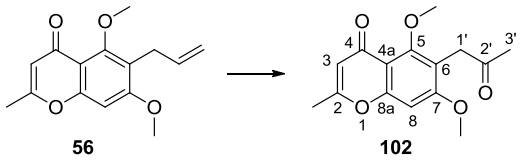
δ_C (100 MHz, $CDCl_3$) 176.8 (C, C-4), 163.5 (C, C-2), 162.3 (C, C-7), 158.9 (C, C-5), 158.8 (C, C-8a), 116.6 (C, C-4a), 112.02 (C, C-6), 111.98 (CH, C-3), 95.4 (CH, C-8), 83.1 (CH, C-2′), 65.2 (CH$_2$, C-3′), 62.5 (CH$_3$, C-5-O$\underline{C}$H$_3$), 56.2 (CH$_3$, C-7-O$\underline{C}$H$_3$), 38.2 (CH$_3$, C-2′-OS(O)$_2\underline{C}$H$_3$), 26.0 (CH$_3$, C-3′-OSi(CH$_3$)$_2$C($\underline{C}$H$_3$)$_3$), 25.7 (CH$_2$, C-1′), 20.0 (CH$_3$, C-2-$\underline{C}$H$_3$), 18.5 (C, C-3′-OSi(CH$_3$)$_2\underline{C}$(CH$_3$)$_3$), -5.24 (CH$_3$, C-3′-OSi($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), -5.29 (CH$_3$, C-3′-OSi($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$).

IR: ν_{max} (film)/cm^{-1} 29.9, 2857, 1657, 1603, 1461, 1388, 1340, 1202, 1174, 1124, 1083, 918.

HRMS (ESI+) found $[M+H]^+$ 487.1808 $C_{22}H_{35}O_8Si^+$ requires 487.1816.

5.4 Synthesis of ketone 102

5,7-dimethoxy-2-methyl-6-(2′-oxopropyl)-4*H*-chromen-4-one (**102**)



To a solution of olefin **56** (129 mg, 0.50 mmol) in a mixture of DMF (1.43 mL) and H_2O (0.94 mL) was added palladium(II) chloride (21 mg, 0.118 mmol) and copper(I) chloride (59 mg, 0.44 mmol). Oxygen gas was bubbled through the solution for 6 h. The reaction mixture was then filtered through Celite®, diluted with Et_2O (5 mL) and brine (5 mL) and the layers separated. The aqueous layer was further extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), concentrated *in vacuo* and purified *via* flash column chromatography (4:1, EtOAc–Hexanes) to afford the *title compound* (106 mg, 77%) as a white solid.

mp: 56.5–58.2 °C.

δ_H (400 MHz, $CDCl_3$) 6.64 (1H, s, H-8), 6.03 (1H, s, H-3), 3.87 (3H, s, C-7-OC$\underline{H}_3$), 3.82 (3H, s, C-5-OC$\underline{H}_3$), 3.80 (2H, s, H-1′), 2.30 (3H, s, C-2-C$\underline{H}_3$), 2.22 (3H, s, H-3′).

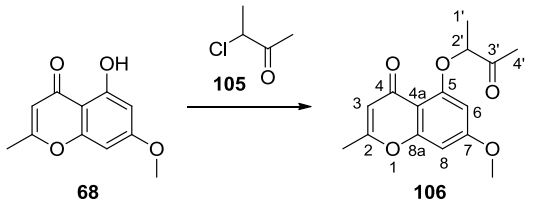
δ_C (100 MHz, $CDCl_3$) 206.4 (C, C-3′), 176.9 (C, C-4), 163.6 (C, C-2), 161.8 (C, C-7), 159.0 (C, C-5), 158.4 (C, C-8a), 116.0 (C, C-6), 112.1 (C, C-4a), 111.9 (CH, C-3), 95.4 (CH, C-8), 62.5 (CH_3, C-5-O$\underline{C}H_3$), 56.2 (CH_3, C-7-O$\underline{C}H_3$), 38.4 (CH_2, C-1′), 29.7 (CH_3, C-3′), 20.0 (CH_3, C-2-$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 2945, 1717, 1653, 1601, 1458, 1422, 1387, 1338, 1114, 1084, 846.

HRMS (ESI+) found $[M+Na]^+$ 299.0901 $C_{15}H_{16}O_5Na^+$ requires 299.0890.

5.5 Synthesis of β-hydroxyketone (±)-99

7-methoxy-2-methyl-5-((3′-oxobutan-2′-yl)oxy)-4*H*-chromen-4-one (**106**)



To a solution of chromone **68** (450 mg, 2.18 mmol) in acetone (10 mL) was added K_2CO_3 (900 mg, 6.55 mmol), α-chlorocarbonyl **105** (465 mg, 4.37 mmol) and TBAI (80 mg, 0.22 mmol). The reaction mixture was heated at reflux and stirred at this temperature for 4 h. The reaction mixture was then filtered through Celite®, concentrated *in vacuo* and the residue was purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to afford the *title compound* (540 mg, 90%) as a white solid.

mp: 112–114 °C.

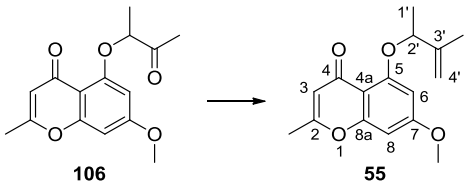
δ_H (300 MHz, $CDCl_3$) 6.45 (1H, d, *J* 2.2, H-8), 6.23 (1H, d, *J* 2.2, H-6), 5.96 (1H, s, H-3), 4.63 (1H, q, *J* 6.9, H-2′), 3.83 (3H, s, C-7-OC*H*$_3$), 2.34 (3H, s, H-4′), 2.27 (3H, s, C-2-C*H*$_3$), 1.55 (3H, d, *J* 6.9, C-2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 210.1 (C, C-2′), 177.0 (C, C-4), 163.7 (C, C-2), 163.3 (C, C-7), 160.3 (C, C-5), 158.4 (C, C-8a), 112.1 (CH, C-3), 109.7 (C, C-4a), 99.1 (CH, C-6), 94.2 (CH, C-8), 81.1(CH, C-1′), 55.8 (CH_3, C-7-O*C*H_3), 25.3 (CH_3, C-3′), 19.9 (CH_3, C-2-*C*H_3), 17.1 (CH_3, C-1′-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 2975, 1713, 1658, 1609, 1430, 1391, 1340, 1202, 1162, 1095, 1045, 928, 849.

HRMS (ESI+) found $[M+H]^+$ 277.1073 $C_{15}H_{17}O_5^+$ requires 277.1071.

7-methoxy-2-methyl-5-((3′-methylbut-3′-en-2′-yl)oxy)-4*H*-chromen-4-one (**55**)



To a solution of methyl triphenyl phosphonium bromide (5.16 g, 14.5 mmol) in THF (28 mL) was added KO^{t}Bu (1.22 g, 10.8 mmol) and stirred at rt for 12 h. A solution of ketone **106** (1.12 g, 4.06 mmol) in THF (16 mL) was then added to the reaction mixture and stirred for further 30 min. The reaction was quenched with addition of brine (30 mL) and reaction mixture extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine (20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to afford the *title compound* (1.00 g, 89%) as a yellow oil.

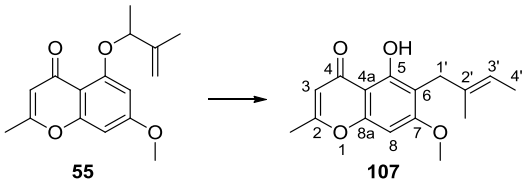
δ_H (300 MHz, $CDCl_3$) 6.38 (1H, d, *J* 2.4, H-8), 6.32 (1H, d, *J* 2.4, H-6), 5.93 (1H, d, *J* 0.6, H-3), 5.07–5.13 (1H, m, H_A-4′), 4.89–4.95 (1H, m, H_B-4′), 4.78 (1H, q, *J* 6.4, H-2′), 3.83 (3H, s, C-7-OC$\underline{H}_3$), 2.25 (3H, d, *J* 0.6, C-2-C$\underline{H}_3$), 1.79 (3H, s, C-3′-C$\underline{H}_3$), 1.56 (3H, d, *J* 6.4, C-2′-C$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$) 177.1 (C, C-4), 163.3 (C, C-2), 162.6 (C, C-7), 160.0 (C, C-5), 159.1 (C, C-8a), 145.2 (C, C-3′), 112.3 (CH_2, C-4′), 111.9 (CH, C-3), 109.6 (C, C-4a), 98.8 (CH, C-6), 92.8 (CH, C-8), 79.1 (CH, C-2′), 55.5 (CH_3, C-7-O$\underline{C}H_3$), 20.2 (CH_3, C-1′), 19.7 (CH_3, C-2-C$\underline{H}_3$), 17.3 (C-3′-$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 2980, 1660, 1608, 1441, 1392, 1341, 1202, 1161, 1087, 910, 825, 730.

HRMS (ESI+) found $[M+Na]^+$ 297.1104 $C_{16}H_{18}NaO_4^+$ requires 297.1097.

5-hydroxy-7-methoxy-2-methyl-6-(2′-methylbut-2′-en-1′-yl)-4*H*-chromen-4-one (**107**)



Allyl phenyl ether **55** (0.625 g, 2.28 mmol) was heated to 200 °C to form a brown melt. The melt was stirred at this temperature for 2 h then cooled to rt. The brown solid was then dissolved in minimum amount of CH_2Cl_2 and purified *via* flash column chromatography (1:3, EtOAc–Hexanes) to yield the *title compound* as an off white solid (0.531 g, 85%).

mp: 112.1–112.2 °C.

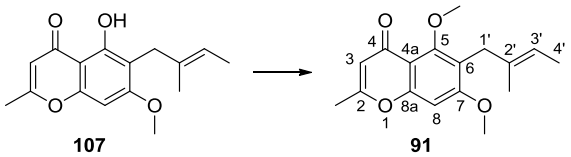
δ_H (300 MHz, $CDCl_3$) 12.8 (1H, s, C-5-O*H*), 6.36 (1H, s, H-8), 6.02 (1H, s, H-3), 5.06 (1H, qq, *J* 6.7, 1.52, H-3′), 3.85 (3H, s, C-7-OCH_3), 3.30 (2H, s, H-1′), 2.34 (3H, s, C-2-CH_3), 1.66 (3H, s, C-2′-CH_3), 1.54 (3H, dd, *J* 6.7, 1.10, H-4′).

δ_C (75 MHz, $CDCl_3$) 182.4 (C, C-4), 166.3 (C, C-2), 163.5 (C, C-7), 158.9 (C, C-5), 156.7 (C, C-8a), 133.6 (C, C-2′), 117.8 (CH, C-3′), 111.3 (C, C-6), 108.9 (CH, C-3), 105.0 (C, C-4a), 89.4 (CH, C-8), 55.9 (CH_3, C-7-O*C*H_3), 31.1 (CH_2, C-1′), 20.4 (CH_3, C-2-*C*H_3), 16.2 (CH_3, C-2′-*C*H_3), 13.4 (CH_3, C-4′).

IR: ν_{max} (film)/cm^{-1} 2919, 1656, 1491, 1445, 1409, 1381, 1340, 1202, 1115, 1092, 953, 844, 804.

HRMS (ESI+) found $[M+Na]^+$ 297.1097 $C_{16}H_{18}NaO_4^+$ requires 297.1097.

5,7-dimethoxy-2-methyl-6-(2′-methylbut-2′-en-1′-yl)-4*H*-chromen-4-one (**91**)



To a solution of olefin **107** (0.79 g, 2.88 mmol) in acetone (35 mL) were added K_2CO_3 (1.2 g, 8.62 mmol) and dimethyl sulfate (0.13 mL, 2.88 mmol). The reaction mixture was heated at reflux and stirred for 24 h. The mixture was then filtered through Celite®, concentrated *in vacuo* and the brown residue was purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to afford the *title compound* (0.66 g, 80%) as a white solid.

mp: 88–91 °C.

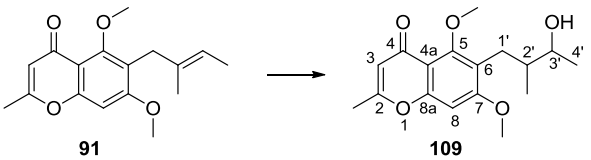
δ_H (300 MHz, $CDCl_3$) 6.62 (1H, s, H-8), 6.00 (1H, d, *J* 0.7, H-3), 4.97 (1H, q, *J* 6.8, H-3′), 3.86 (3H, s, C-7-OC$\underline{H}_3$), 3.81 (3H, s, C-5-OC$\underline{H}_3$), 3.35 (2H, s, H-1′), 2.29 (3H, s, C-2-C$\underline{H}_3$), 1.65 (3H, s, C-2′-C$\underline{H}_3$), 1.52 (3H, dd, *J* 6.8, 0.74, H-4′).

δ_C (75 MHz, $CDCl_3$) 176.7 (C, C-4), 163.0 (C, C-2), 162.2 (C, C-7), 162.1 (C, C-5), 158.1 (C, C-8a), 134.1 (C, C-2′), 120.3 (C, C-6), 118.0 (CH, C-3′), 111.7 (C, C-4a), 111.5 (CH, C-3), 94.9 (CH, C-8), 62.1 (CH_3, C-5-O$\underline{C}H_3$), 55.8 (CH_3, C-7-O$\underline{C}H_3$), 31.7 (CH_2, C-1′), 19.7 (CH_3, C-2-$\underline{C}H_3$), 16.3 (CH_3, C-2′-$\underline{C}H_3$), 13.2 (CH_3, C-4′).

IR: ν_{max} (film)/cm^{-1} 2924, 2244, 1653, 1599, 1456, 1439, 1420, 1387, 1338, 1202, 1177, 1114, 1085, 1020, 950, 908.

HRMS (ESI+) found $[M+Na]^+$ 311.1251 $C_{17}H_{20}NaO_4^+$ requires 311.1254.

6-(3′-hydroxy-2′-methylbutyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**109**)[**]



To a chilled solution of olefin **91** (273 mg, 0.95 mmol) in THF (4 mL) at 0 °C was added borane-dimethyl sulphide complex (0.09 mL, 0.95 mmol) and stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by dropwise addition of 1 M NaOH (aq) (1 mL) and 30% aq. H_2O_2 solution (1 mL). The mixture was then diluted with brine (10 mL) and immediately extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* and purified *via* flash column chromatography (2:1, EtOAc–Hexanes) to yield the *title compound* (115 mg, 40%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 6.64 (1H, s*), 6.63 (1H, s), 3.91 (3H, s*), 3.89 (3H, s), 3.88 (3H, s*), 3.86 (3H, s), 3.60–3.69 (1H, m), 3.50–3.59 (1H, m*), 2.53–2.83 (2H, m*), 2.30 (3H, s*), 2.29 (3H, s), 1.72–1.91 (1H, m*), 1.19 (3H, d, *J* 6.3), 1.08 (3H, d*, *J* 6.4), 0.94 (3H, d*, *J* 6.9), 0.83 (3H, d, *J* 6.8).

δ_C (100 MHz, $CDCl_3$) 177.0 (C), 176.9 (C*), 163.5 (C), 163.4 (C*), 162.2 (C), 162.1 (C*), 158.24 (C), 158.20 (C*), 158.1 (C), 121.4 (C), 121.0 (C*), 112.0 (C), 111.9 (CH), 111.88 (CH*), 95.49 (CH), 95.24 (CH*), 72.0 (CH), 68.2 (CH*), 62.5 (CH_3), 62.2 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 41.2 (CH), 39.6 (CH), 27.1 (CH_2), 25.9 (CH_2*), 20.0 (CH_3), 19.98 (CH_3*), 19.9 (CH_3), 15.6 (CH_3), 13.5 (CH_3*).

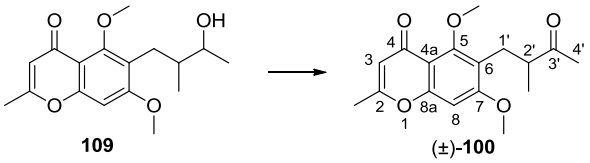
Note: Asterisks denote peaks arising from one of the two compounds posessing an diastoisomeric releationship.

IR: ν_{max} (film)/cm^{-1} 1655, 1601, 1342, 1202, 1132, 576, 555.

HRMS (ESI+) found $[M+Na]^+$ 329.1353 $C_{17}H_{22}NaO_5^+$ requires 329.1359.

[**] Note: To test the viability of our synthetic route, this compound was made without asymmetric control and was isolated as mixture of inseparable diastereoisomers. Accordingly, peaks remain unassigned.

5,7-dimethoxy-2-methyl-6-(2′-methyl-3′-oxobutyl)-4*H*-chromen-4-one (±)-**100**



To a solution of phenol **109** (120 mg, 0.39 mmol) in DMSO (10 mL) was added 2-iodoxybenzoic acid (439 mg, 1.57 mmol) and the reaction mixture was stirred at rt for 2 h. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added followed by the addition of EtOAc (30 mL). The layers were separated then the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield the *title compound* (101 mg, 85%) as a colourless oil.

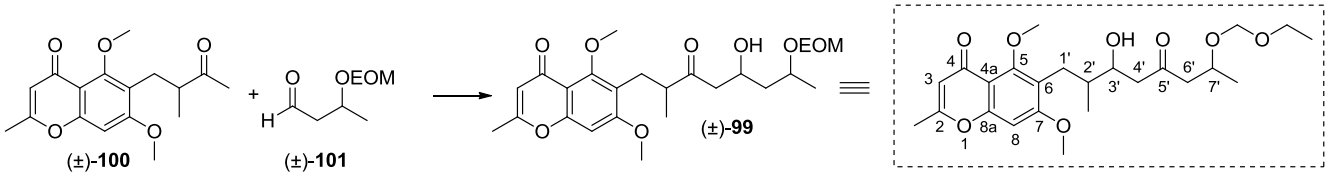
δ_H (300 MHz, $CDCl_3$) 6.62 (1H, s, H-8), 6.03 (1H, d, *J* 0.7, H-3), 3.88 (3H, s, C-7-OC*H*$_3$), 3.86 (3H, s, C-5-OC*H*$_3$), 2.79–2.91 (1H, m, H-2′), 2.70–3.05 (2H, m, H-1′), 2.30 (3H, d, *J* 0.7, C-2-C*H*$_3$), 2.17 (3H, s, H-4′), 1.01 (3H, d, *J* 6.6, C-2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 212.5 (C, C-3′), 176.9 (C, C-4), 163.5 (C, C-2), 162.2 (C, C-7), 158.5 (C, C-5), 158.4 (C, C-8a), 111.9 (C, C-6), 112.0 (C, C-4a), 111.9 (CH, C-3), 95.3 (CH, C-8), 62.3 (CH_3, C-5-O*C*H$_3$), 56.0 (CH_3, C-7-O*C*H$_3$), 47.1 (CH, C-2′), 28.2 (CH_3, C-4′), 26.0 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H$_3$), 15.7 (CH_3, C-2′-*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} : 3670, 2978, 2903, 1709, 1656, 1602, 1420, 1388, 1340, 1125, 1066.

HRMS (ESI+) found $[M+Na]^+$ 327.1207 $C_{17}H_{20}NaO_5^+$ requires 327.1203.

6-(7′-(ethoxymethoxy)-3′-hydroxy-2′-methyl-5′-oxooctyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (±)-**99**[††]



A two necked round bottom flask was charged with (+)-Ipc_2BCl (250 mg, 0.78 mmol) and placed under high vacuum for 1 h to remove traces of HCl. Et_2O (4 mL) was added and mixture was cooled to –78 °C. NEt_3 (0.12 mL, 0.85 mmol) was added followed by a solution of ketone (±)-**100** (70 mg, 0.23 mmol) in Et_2O (1 mL + 1 mL washings). The resultant white suspension was warmed to 0 °C and stirred for 1 h. The reaction mixture was cooled to –78 °C and aldehyde (±)-**101** (67 mg, 0.46 mmol) in Et_2O (1 mL) was added. The reaction mixture was stirred at –78 °C for 4 h then quenched by addition of pH 7 buffer solution (2 mL), MeOH (1 mL) and 30% aq. H_2O_2 solution (1 mL) and warmed to rt and stirred vigorously for 2 h. The mixture was then diluted with H_2O (10 mL) and EtOAc (5 mL), the layers separated and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified *via* flash column chromatography (1:2, EtOAc–Hexanes) to afford the *title compound* (31 mg, 30%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 6.59–6.65, 6.03, 4.63–4.78, 4.10–4.39, 3.92–4.06, 3.91, 3.89, 3.88, 3.86, 3.85, 3.48–3.71, 2.70–2.99, 2.50–2.71, 2.30, 1.14–1.26, 1.00, 0.75–0.92.

δ_C (75 MHz, $CDCl_3$) 215.1, 214.5, 176.7, 163.4, 163.2, 162.1, 161.9, 158.4, 158.1, 158.0, 121.3, 120.0, 111.9, 111.8, 95.3, 95.1, 94.0, 93.2, 72.1, 71.9, 70.5, 66.4, 66.3, 64.3, 63.5, 63.4, 62.2, 62.1, 55.9, 55.8, 47.9, 47.8, 46.6, 43.8, 43.5, 41.0, 31.9, 29.7, 29.3, 25.8, 25.7, 22.7, 20.7, 20.2, 19.9, 19.8, 15.5, 15.4, 15.1.

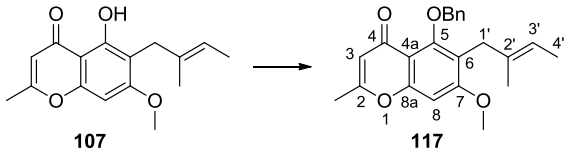
IR: ν_{max} (film)/cm^{-1} 3462, 2926, 1706, 1656, 1601, 1457, 1388, 1342, 1130, 1037.

HRMS (ESI+) found $[M+Na]^+$ 473.2130 $C_{24}H_{34}NaO_8^+$ requires 473.2146.

[††] Note: To test the viability of our synthetic route, this compound was made without asymmetric control and was isolated as complicated mixture of inseparable diastereoisomers. Accordingly, peaks remain unassigned.

5.6 Synthesis of secondary alcohol 118

5-(benzyloxy)-7-methoxy-2-methyl-6-(2′-methylbut-2′-en-1′-yl)-4*H*-chromen-4-one (**117**)



To a solution of olefin **107** (180 mg, 0.657 mmol) in acetone (5 mL) were added K_2CO_3 (273 mg, 1.97 mmol), benzyl bromide (0.12 mL, 0.986 mmol) and TBAI (15 mg, 0.041 mmol). The reaction was heated at reflux and stirred at this temperature for 24 h. The reaction mixture was then cooled to rt, filtered through Celite®, then the filtrate was concentrated *in vacuo* and purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to afford the *title compound* (214 mg, 90%) as a white solid.

mp: 66–68 °C.

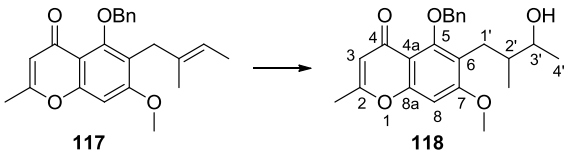
δ_H (300 MHz, $CDCl_3$) 7.53–7.65 (2H, m, CH, C-5-OCH_2Ar-*H*), 7.27–7.44 (3H, m, C-5-OCH_2Ar-*H*), 6.65 (1H, s, H-8), 6.04 (1H, d, *J* 1.0, H-3), 4.94 (2H, s, C-5-O*C*H_2Ar), 4.85–5.00 (1H, m, H-3′), 3.87 (3H, s, C-7-O*C*H_3), 3.32 (2H, s, H-1′), 2.31 (3H, s, C-2-*C*H_3), 1.61 (3H, s, C-2′-*C*H_3), 1.50 (3H, dd, *J* 6.6, 1.0, H-4′).

δ_C (75 MHz, $CDCl_3$) 177.1 (C, C-4), 163.3 (C, C-2), 162.5 (C, C-7), 158.4 (C, C-8a), 157.0 (C, C-5), 137.8 (C, C-5-OCH_2*Ar*), 134.5 (C, C-2′), 128.9 (CH, C-5-OCH_2*Ar*-H), 128.4 (CH, C-5-OCH_2*Ar*-H), 128.0 (CH, C-5-OCH_2*Ar*-H), 121.0 (C, C-4a), 118.1 (CH, C-3′), 112.4 (C, C-6), 111.9 (CH, C-3), 95.4 (CH, C-8), 76.6 (CH_2, C-5-O*C*H_2Ar), 56.1 (CH_3, C-7-O*C*H_3), 32.3 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H_3), 16.7 (CH_3, C-2′-*C*H_3), 13.5 (CH_3, C-4′).

IR: ν_{max} (film)/cm^{-1} 3051, 2917, 1654, 1598, 1202, 1116, 1080.

HRMS (ESI+) found $[M+Na]^+$ 387.1560 $C_{23}H_{24}NaO_4^+$ requires 387.1567.

5-(benzyloxy)-6-(3′-hydroxy-2′-methylbutyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**118**)



To a solution of olefin **117** (500 mg, 1.74 mmol) in THF (5 mL) was added (–)-Ipc_2BH (972 mg, 3.47 mmol). The reaction mixture was stirred for 2 h. The reaction mixture was then diluted with brine (15 mL), EtOAc (20 mL) and layers then separated. The organic layer were then washed with brine (3 × 5 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (3:1, EtOAc–Hexanes) to yield the *title compound* (294 mg, 55%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 7.56–7.66 (2H, m, CH, C-5-OCH_2Ar-*H*), 7.29–7.46 (3H, m, CH, C-5-OCH_2Ar-*H*), 6.68 (1H, s, H-8), 6.06 (1H, d, *J* 0.7, H-3), 5.10 (1H, d, *J* 9.9, CH, C-5-OCH_2Ar), 4.87 (1H, d, *J* 9.9, C-5-OCH_2Ar), 3.91 (3H, s, C-7-OCH_3), 3.41–3.56 (1H, m, H-3′), 2.47–2.71 (2H, m, H-1′), 2.32 (3H, d, *J* 0.7, C-2-CH_3), 1.65–1.79 (1H, m, H-2′), 1.00 (3H, d, *J* 6.6, H-4′), 0.87 (3H, d, *J* 6.7, C-2′-CH_3).

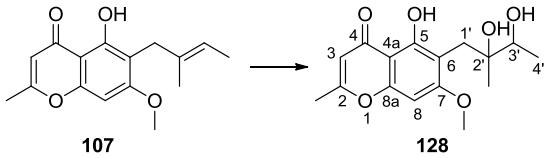
δ_C (75 MHz, $CDCl_3$) 177.0 (C, C-4), 163.5 (C, C-2), 162.2 (C, C-7), 158.3 (C, C-8a), 156.7 (C, C-5), 137.1 (C, C-5-OCH_2*Ar*), 129.1 (CH, C-5-OCH_2*Ar*-H), 128.7 (CH C-5-OCH_2*Ar*-H), 128.5 (CH C-5-OCH_2*Ar*-H), 121.4 (C, C-4a), 112.3 (C, C-6), 111.9 (CH, C-3), 95.7 (CH, C-8), 77.0 (CH_2, C- C-5-O*C*H_2Ar), 67.8 (CH, C-3′), 56.2 (CH_3, C-7-O*C*H_3), 39.4 (CH, C-2′), 27.4 (CH_2, C-1′), 20.0 (CH_3, C-4-*C*H_3), 19.8 (CH_3, C-2-*C*H_3), 13.4 (CH_3, C-2′-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 2968, 2245, 1654, 1600, 1444, 1343, 1069, 910.

HRMS (ESI+) found $[M+Na]^+$ 405.1665 $C_{23}H_{26}NaO_5^+$ requires 405.1672.

5.7 Synthesis of acyloin 127

6-(2′,3′-dihydroxy-2′-methylbutyl)-5-hydroxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**128**)



To a solution of olefin **107** (405 mg, 1.48 mmol) in a mixture of THF : acetone : pH 7 buffer solution (2:2:2. v/v, 5 mL) was added *N*-methylmorpholine *N*-oxide (225 mg, 1.92 mmol) and osmium tetroxide (2.5% w/v in ^{t}BuOH, 1.2 mL, 0.12 mmol). After stirring for 12 h, sodium bisulfite (0.61 g, 5.87 mmol) in H_2O (20 mL) was added and solution was stirred for 10 min, diluted with brine (20 mL) and extracted with EtOAc (2 × 30 mL). The organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (3:1, EtOAc–Hexanes) to afford the *title compound* (273 mg, 60%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 13.42 (1H, s, C-5-O*H*), 6.43 (1H, s, H-8), 6.08 (1H, d, *J* 0.7, H-3), 3.90 (3H, s, C-7-OC*H*$_3$), 3.57–3.69 (1H, m, H-3′), 2.93 (2H, s, H-1′), 2.37 (3H, d, *J* 0.7, C-2-C*H*$_3$), 1.20 (3H, d, *J* 6.2, H-4′), 1.06 (3H, s, C-2′-C*H*$_3$).

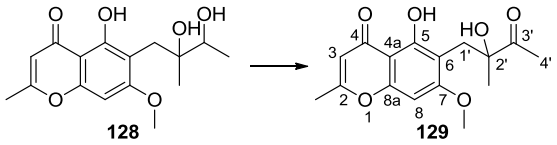
δ_C (75 MHz, $CDCl_3$) 182.6 (C, C-4), 167.0 (C, C-2), 163.6 (C, C-7), 159.3 (C, C-5), 157.0 (C, C-8a), 109.4 (C, C-5a), 109.1 (CH, C-3), 105.2 (C, C-6), 90.2 (CH, C-8), 77.4 (C, C-2′), 72.9 (CH, C-3′), 56.1 (CH_3, C-7-O*C*H$_3$), 31.6 (CH_2, C-1′), 20.6 (CH_3, C-2′-*C*H$_3$), 20.6 (CH_3, C-2-*C*H$_3$), 16.9 (CH_3, C-4′).

IR: ν_{max} (film)/cm^{-1} 3521, 2985, 1652, 1628, 1586, 1400, 1345, 1209, 1135, 1100, 830.

HRMS (ESI+) found $[M+H]^+$ 309.1321, $C_{16}H_{21}O_6^+$ requires 309.1333.

5-hydroxy-6-(2′-hydroxy-2′-methyl-3′-oxobutyl)-7-methoxy-2-methyl-4*H*-chromen-4-one

(**129**)



To a solution of alcohol **128** (53 mg, 0.17 mmol) in DMSO (3 mL) was added 2-iodoxybenzoic acid (193 mg, 0.69 mmol). The reaction mixture was heated to 80 °C and stirred at this temperature for 12 h. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added followed by the addition of EtOAc (20 mL). The layers were separated then the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield the *title compound* (37 mg, 70%) as a colourless oil.

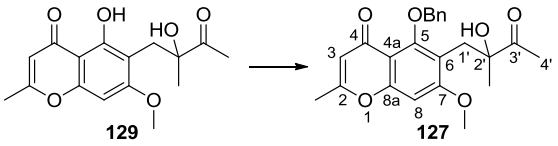
δ_H (300 MHz, $CDCl_3$) 13.16 (1H, s, C-5-O*H*), 6.38 (1H, s, H-8), 6.07 (1H, d, *J* 0.8, H-3), 3.85 (3H, s, C-7-OC*H*$_3$), 3.17 (1H, d, *J* 13.8, H_A-1′), 3.02 (1H, d, *J* 13.8, H_B-1′), 2.36 (3H, d, *J* 0.8, C-2-C*H*$_3$), 2.29 (3H, s, H-4′), 1.39 (3H, s, C-2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 212.8 (C, C-3′), 182.4 (C, C-4), 166.8 (C, C-2), 163.5 (C, C-7), 159.5 (C, C-5), 157.1 (C, C-8a), 108.9 (CH, C-3), 107.8 (C, C-4a), 105.0 (C, C-6), 89.8 (CH, C-8), 79.9 (C, C-2′), 55.8 (CH_3, C-7-O*C*H$_3$), 31.9 (CH_2, C-1′), 24.8 (CH_3, C-4′), 24.6 (CH_3, C-2′-*C*H$_3$), 20.4 (CH_3, C-2-*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} 3485, 2930, 1711, 1659, 1622, 1589, 1494, 1449, 1344, 1205, 1129, 846.

HRMS (ESI+) found $[M+H]^+$ 307.1158, $C_{16}H_{19}O_6^+$ requires 307.1176.

5-(benzyloxy)-6-(2′-hydroxy-2′-methyl-3′-oxobutyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**127**)



To a solution of phenol **129** (48 mg, 0.16 mmol) in acetone (5 mL) were added K_2CO_3 (87 mg, 0.63 mmol), benzyl bromide (80 mg, 0.47 mmol) and TBAI (15 mg, 0.04 mmol). The reaction was heated at reflux and stirred at this temperature for 24 h. The reaction mixture was then cooled to rt, filtered through Celite®, then the filtrate was concentrated *in vacuo* and purified *via* flash column chromatography (3:1, EtOAc–Hexanes) to afford the *title compound* (47 mg, 76%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 7.56–7.62 (2H, m, C-5-OCH$_2$Ar-*H*), 7.30–7.43 (3H, m, C-5-OCH$_2$Ar-*H*), 6.66 (1H, s, H-8), 6.06 (1H, d, *J* 0.7, H-3), 5.12 (1H, d, *J* 10.0, C-5-OC*H*$_2$Ar), 5.00 (1H, d, *J* 10.0, C-5-OC*H*$_2$Ar), 3.85 (1H, s, C-2′-O*H*), 3.84 (3H, s, C-7-O*C*H$_3$), 3.12 (1H, d, *J* 13.8, H$_A$-1′), 2.86 (1H, d, *J* 13.8, H$_B$-1′), 2.32 (3H, d, *J* 0.7, C-2-C*H*$_3$), 2.12 (3H, s, H-4′), 1.25 (3H, s, C-2′-C*H*$_3$).

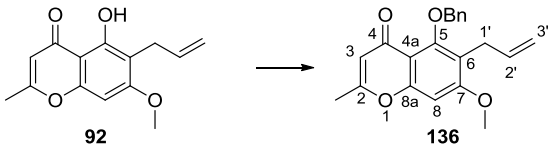
δ_C (75 MHz, $CDCl_3$) 213.0 (C, C-3′), 176.7 (C, C-4), 163.4 (C, C-2), 162.0 (C, C-7), 158.7 (C, C-5), 157.3 (C, C-8a), 137.1 (C, C-5-OCH$_2$*Ar*), 129.0 (CH, C-5-OCH$_2$*Ar*-H), 128.5 (CH, C-5-OCH$_2$*Ar*-H), 128.3 (CH, C-5-OCH$_2$*Ar*-H), 116.9 (C, C-6), 112.1 (C, C-4a), 111.8 (CH, C-3), 95.6 (CH, C-8), 79.4 (C, C-2′), 76.9 (CH$_2$, C-5-O*C*H$_2$Ar), 55.7 (CH$_3$, C-7-O*C*H$_3$), 32.6 (CH$_2$, C-1′), 24.7 (CH$_3$, C-2′-*C*H$_3$), 24.6 (CH$_3$, C-4′), 19.9 (CH$_3$, C-2-*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} 1712, 1656, 1602, 1443, 1393, 1342, 1204, 1125.

HRMS (ESI+) found $[M+H]^+$ 397.1624, $C_{23}H_{25}O_6^+$ requires 397.1646.

5.8 Synthesis of chaetoquadrins A (1), ent-B (ent-2), ent-C (ent-3) and deoxy-spiroketal 120

6-allyl-5-(benzyloxy)-7-methoxy-2-methyl-4*H*-chromen-4-one (**136**)



To a solution of phenol **92** (1.0 g, 4.1 mmol) in acetone (44 mL) were added K_2CO_3 (1.7 g, 12.2 mmol), benzyl bromide (0.73 mL, 6.1 mmol) and TBAI (0.15 g, 0.41 mmol). The reaction was heated at reflux and stirred at this temperature for 12 h. The reaction mixture was then cooled to rt, K_2CO_3 (0.56 g, 4.1 mmol) was added then the reaction mixture was heated at reflux and stirred at this temperature for a further 12 h. The reaction mixture was then cooled to rt, filtered through Celite®, then the filtrate was concentrated *in vacuo* and purified *via* flash column chromatography (1:2.5, EtOAc–Hexanes) to afford the *title compound* as a light yellow oil (1.3 g, 96%) which solidified upon standing.

mp: 55.8–56.0 °C.

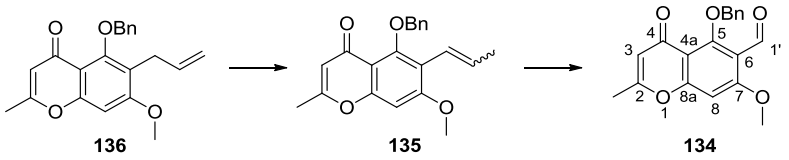
δ_H (400 MHz, $CDCl_3$) 7.60–7.65 (2H, m, C-5-OCH_2Ar-*H*), 7.29–7.42 (3H, m, C-5-OCH_2Ar-*H*), 6.64 (1H, s, H-8), 6.03 (1H, s, H-3), 5.86–5.98 (1H, m, H-2′), 4.98 (2H, s, H-3′), 4.92–4.96 (2H, m, C-5-O*C*H_2Ar), 3.89 (3H, s, C-7-O*C*H_3), 3.43 (2H, td, *J* 6.2, 1.5, H-1′), 2.31 (3H, s, C-2-*C*H_3).

δ_C (100 MHz, $CDCl_3$) 177.0 (C, C-4), 163.4 (C, C-2), 162.1 (C, C-7), 158.4 (C, C-5), 156.5 (C, C-8a), 137.6 (C, C-5-OCH_2*Ar*), 136.6 (CH, C-2′), 128.8 (CH, C-5-OCH_2*Ar*-H), 128.4 (CH, C-5-OCH_2*Ar*-H), 128.0 (CH, C-5-OCH_2*Ar*-H), 120.5 (C, C-6), 115.0 (CH_2, C-3′), 112.3 (C, C-4a), 111.8 (CH, C-3), 95.4 (CH, C-8), 76.7 (CH_2, C-5-O*C*H_2Ar), 56.0 (CH_3, C-7-O*C*H_3), 27.7 (CH_2, C-1′), 19.9 (CH_3, C-2-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 2924, 1653, 1599, 1443, 1388, 1201, 1131, 997, 911, 699.

HRMS (ESI+) found $[M+Na]^+$ 359.1255 $C_{21}H_{20}NaO_4^+$ requires 359.1254.

5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehyde (**134**)



To a solution of olefin **136** (2.71 g, 8.06 mmol) in THF (200 mL) was added $RuClH(CO)(PPh_3)_3$ (0.27 g, 0.28 mmol) and the reaction heated at reflux for 3 h. The solvent was removed *in vacuo* to yield a black residue (**135**) which was carried on to the next step without further purification.

To a solution of the crude material **135** (2.74 g) in 1,4-dioxane (47.8 mL) and H_2O (23.8 mL) were added 2,6-lutidine (1.86 mL, 16.1 mmol), OsO_4 (2.5% in ^tBuOH, 46.78 mg, 0.18 mmol) and $NaIO_4$ (6.9 g, 32.3 mmol). After stirring for 30 min, H_2O (60 mL) and EtOAc (120 mL) were added. The organic layer was washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* flash column chromatography (1:1, EtOAc–Hexanes) afforded the *title compound* (1.43 g, 55%) as a white solid.

mp: 122–123 °C.

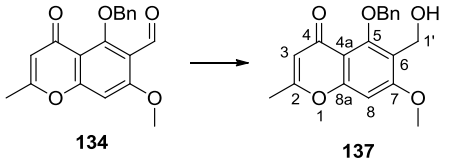
δ_H (300 MHz, $CDCl_3$) 10.28 (1H, s, H-1′), 7.51–7.59 (2H, m, C-5-OCH_2Ar-*H*), 7.30–7.42 (3H, m, C-5-OCH_2Ar-*H*), 6.68 (1H, s, H-8), 6.07 (1H, d, *J* 0.7, H-3), 5.14 (2H, s, C-5-OCH_2Ar), 3.96 (3H, s, C-7-OCH_3), 2.34 (3H, d, *J* 0.7, C-2-CH_3).

δ_C (75 MHz, $CDCl_3$) 188.8 (C, C-1′), 176.3 (C, C-4), 164.0 (C, C-2), 163.9 (C, C-7), 163.5 (C, C-5), 162.5 (C, C-8a), 135.9 (C, C-5-OCH_2*Ar*), 129.5 (CH, C-5-OCH_2*Ar*-H), 128.79 (CH, C-5-OCH_2*Ar*-H), 128.75 (CH, C-5-OCH_2*Ar*-H), 117.9 (C, C-4), 112.3 (CH, C-3), 112.2 (C, C-6), 96.5 (CH, C-8), 79.2 (CH_2, C-5-O*C*H_2Ar), 56.6 (CH_3, C-7-O*C*H_3), 20.0 (CH_3, C-2-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 1693, 1660, 1595, 1349, 1203, 1120, 826, 701.

HRMS (ESI+) found $[M+Na]^+$ 347.0882 $C_{19}H_{16}NaO_5^+$ requires 347.0890.

5-(benzyloxy)-6-(hydroxymethyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**137**)



A solution of aldehyde **134** (630 mg, 1.94 mmol) in THF:MeOH (1:1, 50 mL) was cooled to 0 °C. $NaBH_4$ (73.4 mg, 1.94 mmol) was added portionwise and the reaction stirred for 5 min. Saturated aqueous NH_4Cl (10 mL) was then added and reaction mixture was warmed to rt. The reaction mixture was concentrated roughly to a quarter of its volume *in vacuo*. To the concentrate were added H_2O (50 mL) and the aqueous layer extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* (631 mg, 99%) as a white solid which was used without further purification.

mp: 136.2–137.5 °C.

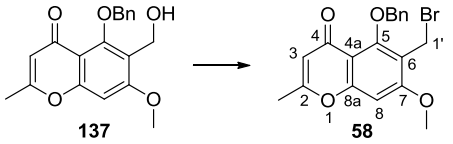
δ_H (300 MHz, $CDCl_3$) 7.52–7.61 (2H, m, C-5-OCH_2Ar-*H*), 7.31–7.44 (3H, m, C-5-OCH_2Ar-*H*), 6.68 (1H, s, H-8), 6.07 (1H, s, H-3), 5.07 (2H, s, C-5-O*C*H_2Ar), 4.65 (2H, d, *J* 6.7, H-1′), 3.93 (3H, s, C-7-O*C*H_3), 2.33 (3H, s, C-2-*C*H_3), 2.02 (1H, t, *J* 6.7, C-1′-O*H*).

δ_C (75 MHz, $CDCl_3$) 177.0 (C, C-4), 163.7 (C, C-2), 162.1 (C, C-7), 159.5 (C, C-5), 157.3 (C, C-8a), 137.0 (C, C-5-OCH_2*Ar*), 129.3 (CH, C-5-OCH_2Ar-*H*), 128.8 (CH, C-5-OCH_2Ar-*H*), 128.6 (CH, C-5-OCH_2Ar-*H*), 121.3 (C, C-6), 112.2 (C, C-4a), 112.0 (CH, C-3), 95.8 (CH, C-8), 78.1 (CH_2, C-5-O*C*H_2Ar), 56.3 (CH_3, C-7-O*C*H_3), 54.7 (CH_2, C-1′), 20.1 (CH_3, C-2-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 3401, 2926, 1655, 1601, 1445, 1389, 1341, 1202, 1122, 1084, 1015, 833, 730, 701.

HRMS (ESI+) found $[M+Na]^+$ 349.1040 $C_{19}H_{18}NaO_5^+$ requires 349.1046.

5-(benzyloxy)-6-(bromomethyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**58**)



To a solution of alcohol **137** (341 mg, 1.04 mmol) in THF:DCM (20 mL, 1:1) was added PBr_3 (204 mg, 71.5 µL, 0.75 mmol) over a period of 3.5 h at 0 °C. The reaction mixture was then stirred for further 1 h at this temperature. Saturated aqueous $NaHCO_3$ (20 mL) was added, the reaction mixture warmed to rt and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography using Merck Silica gel 60 (0.015-0.040 mm) (1:1, EtOAc–Hexanes) to give the *title compound* (326 mg, 80%) as a white solid.

mp: 135.2–136.0 °C.

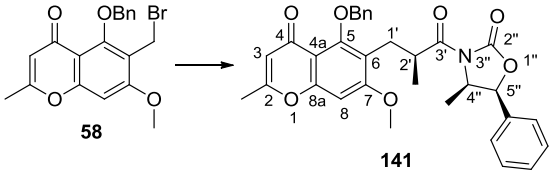
δ_H (400 MHz, $CDCl_3$) 7.69–7.73 (2H, m, C-5-OCH_2Ar-*H*), 7.33–7.45 (3H, m, C-5-OCH_2Ar-*H*), 6.67 (1H, s, H-8), 6.05 (1H, s, H-3), 5.18 (2H, s, C-5-O*C*H_2Ar), 4.64 (2H, s, H-1′), 3.98 (3H, s, C-7-O*C*H_3), 2.32 (3H, s, C-2-*C*H_3).

δ_C (100 MHz, $CDCl_3$) 176.7 (C, C-4), 163.7 (C, C-2), 161.8 (C, C-7), 159.9 (C, C-5), 157.8 (C, C-8a), 137.1 (C, C-5-OCH_2*Ar*), 129.3 (CH, C-5-OCH_2*Ar*-H), 128.6 (CH, C-5-OCH_2*Ar*-H), 128.4 (CH, C-5-OCH_2*Ar*-H), 119.0 (C, C-6), 112.5 (C, C-5a), 112.0 (CH, C-3), 96.0 (CH, C-8), 76.7 (CH_2, C-5-O*C*H_2Ar), 56.5 (CH_3, C-7-O*C*H_3), 22.4 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H_3).

IR: ν_{max} (film)/cm^{-1} 3056, 2244, 1652, 1597, 1445, 1360, 1199, 1164, 906, 830, 728.

HRMS (ESI+) found $[M+Na]^+$ 411.0198 $C_{19}H_{17}BrNaO_4^+$ requires 411.0202.

(4″*R*,5″*S*)-3-((*S*)-3-(5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)-2′-methylpropanoyl)-4″-methyl-5″-phenyloxazolidin-2″-one (**141**)



(4*R*,5*S*)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (295 mg, 1.26 mmol) was dissolved in THF (5.2 mL) and the solution cooled to –78 °C. NaHMDS (1.0 M in THF, 1.73 mL, 1.73 mmol) was added and reaction mixture was stirred for 1 h. A solution of bromide **58** (385 mg, 0.992 mmol) in THF (2.6 mL) was added *via* cannula and the reaction mixture was stirred for a further 30 min at –78 °C. The reaction was then quenched by addition of H_2O (20 mL) and warmed to rt. The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Purification *via* flash column chromatography (1:1.5, EtOAc–Hexanes) afforded the *title compound* (350 mg, 51%) as a white solid.

mp: 149.2–151.5 °C.

δ_H (300 MHz, $CDCl_3$) 7.58–7.66 (2H, m, Ar-*H*), 7.20–7.44 (8H, m, Ar-*H*), 6.65 (1H, s, H-8), 6.03 (1H, d, *J* 0.7, H-3), 5.58 (1H, d, *J* 7.3, H-5″), 4.98 (2H, m, C-5-OC*H*$_2$Ar), 4.70 (1H, dq, *J* 13.6, 6.8, H-4″), 4.02–4.17 (1H, m, H-2′), 3.91 (3H, s, C-7-OC*H*$_3$), 2.98 (2H, m, H-1′), 2.32 (3H, s, C-2-C*H*$_3$), 1.12 (3H, d, *J* 7.0, C-2′-C*H*$_3$), 0.79 (3H, d, *J* 6.7, C-4″-C*H*$_3$).

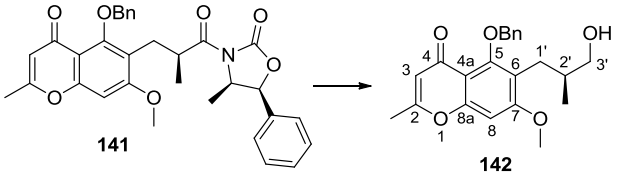
δ_C (75 MHz, $CDCl_3$) 176.93 (C, C-4), 176.91 (C, C-3′), 163.3 (C, C-2), 162.5 (C, C-7), 158.7 (C, C-5), 157.1 (C, C-8a), 152.7 (C, C-2″), 137.5 (C, *Ar*), 133.7 (C, *Ar*), 129.0 (CH, *Ar*-H), 128.78 (CH, *Ar*-H), 128.76 (CH, *Ar*-H), 128.5 (CH, *Ar*-H), 128.0 (CH, *Ar*-H), 125.8 (CH, *Ar*-H), 119.8 (C, C-6), 112.2 (C, C-4a), 111.9 (CH, C-3), 95.4 (CH, C-8), 78.9 (CH, C-5″), 76.7 (CH_2, C-5-O*C*H$_2$Ar), 56.0 (CH_3, C-7-O*C*H$_3$), 55.2 (CH, C-4″), 37.4 (CH, C-2′), 26.6 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H$_3$), 17.5 (CH_3, C-2′-*C*H$_3$), 14.6 (CH_3, C-4″-*C*H$_3$).

$[\alpha]_D^{20}$ -9.2 (*c* 0.53, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 2931, 1780, 1700, 1657, 1602, 1342, 1200, 1125, 961, 701.

HRMS (ESI+) found $[M+Na]^+$ 564.2000. $C_{32}H_{31}NNaO_7$ requires 564.1993.

(*S*)-5-(benzyloxy)-6-(3′-hydroxy-2′-methylpropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**142**)



To a solution of imide **141** (219 mg, 0.40 mmol) in THF (4 mL) and Et_2O (6 mL) were added $LiBH_4$ (8 mg, 0.37 mmol) then MeOH (30 µL). The reaction mixture was stirred for 2.5 h. MeOH (30 µL) was then added and reaction mixture was stirred for a further 1 h followed by further addition of $LiBH_4$ (2 mg, 0.092 mmol)[‡‡] and stirred for additional 1.5 h. The reaction mixture was quenched by the addition of a 1:1 mixture of brine and saturated NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (2:1, EtOAc–Hexanes) to yield the *title compound* (145 mg, 97%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 7.58–7.64 (2H, m, C-5-OCH_2Ar-*H*), 7.29–7.45 (3H, m, C-5-OCH_2Ar-*H*), 6.67 (1H, s, H-8), 6.05 (1H, d, *J* 0.7, H-3), 5.07 (1H, d, *J* 9.9, C-5-OC*H*$_2$Ar), 4.90 (1H, d, *J* 9.9, C-5-OC*H*$_2$Ar), 3.90 (3H, s, C-7-OC*H*$_3$), 3.21–3.36 (2H, m, H-3′), 2.65 (1H, dd, *J* 13.1, 8.54, H_A-1′), 2.54 (1H, dd, *J* 13.1, 5.9, H_B-1′), 2.32 (3H, d, *J* 0.7, C-2-C*H*$_3$), 1.96 (1H, m, C-3′-O*H*), 1.87 (1H, m, H-2′), 0.93 (3H, d, *J* 6.8, C-2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 177.0 (C, C-4), 163.5 (C, C-2), 162.2 (C, C-7), 158.3 (C, C-5), 156.6 (C, C-8a), 137.1 (C, C-5-OCH_2*Ar*), 129.0 (CH, C-5-OCH_2*Ar*-H), 128.6 (CH, C-5-OCH_2*Ar*-H), 128.4 (CH, C-5-OCH_2*Ar*-H), 121.3 (C, C-6), 112.2 (C, C-4a), 111.9 (CH, C-3), 95.6 (CH, C-8), 77.0 (CH_2, C-5-O*C*H_2Ar), 66.4 (CH_2, C-3′), 56.1 (CH_3, C-7-O*C*H_3), 36.0 (CH, C-2′), 26.4 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H_3), 17.4 (CH_3, C-2′-*C*H_3).

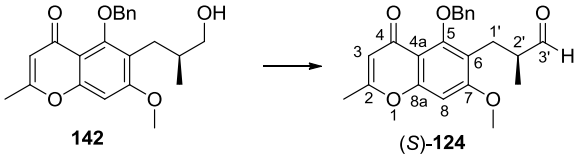
$[\alpha]_D^{20}$ +21.4 (*c* 0.7, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 3390, 2960, 2941, 2860, 1654, 1599, 1446, 1389, 1342, 1260, 1202, 1179, 1063, 837, 737, 700.

HRMS (ESI+) found $[M+H]^+$ 369.1690. $C_{22}H_{25}O_5$ requires 369.1697.

[‡‡] The alternating addition of $LiBH_4$ and MeOH as described was found to be imperative in achieving a high yield for this transformation

(*S*)-1′-(5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)-2′-methylpropan-3′-al (*S*)-**124**



To a solution of alcohol **142** (144 mg, 0.39 mmol) in DMSO (4.8 mL) was added 2-iodoxybenzoic acid (329 mg, 1.17 mmol) and the reaction mixture was stirred at rt for 3 h. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added followed by the addition of EtOAc (30 mL). The layers were separated then the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield the *title compound* (135 mg, 94%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 9.55 (1H, d, *J* 1.9, H-3′), 7.52–7.57 (2H, m, C-5-OCH_2Ar-*H*), 7.30–7.41 (3H, m, C-5-OCH_2Ar-*H*), 6.65 (1H, s, H-8), 6.06 (1H, d, *J* 0.8, H-3), 5.03 (1H, d, *J* 10.5, C-5-OCH_2Ar), 4.99 (1H, d, *J* 10.5, C-5-OCH_2Ar), 3.87 (3H, s, C-7-OCH_3), 2.91 (1H, dd, *J* 13.2, 7.1, H_A-1′), 2.72 (1H, dd, *J* 13.2, 7.5, H_B-1′), 2.54–2.65 (1H, m, H-2′), 2.32 (3H, s, C-2-CH_3), 0.97 (3H, d, *J* 6.9, C-2′-CH_3).

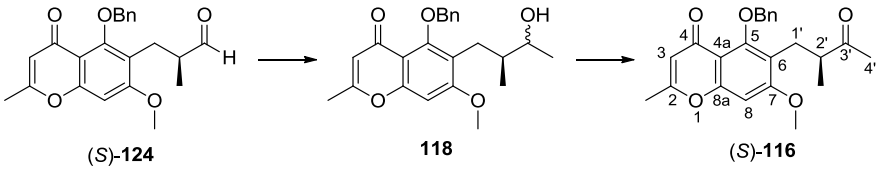
δ_C (100 MHz, $CDCl_3$) 204.9 (CH, C-3′), 177.0 (C, C-4), 163.6 (C, C-2), 161.9 (C, C-7), 158.7 (C, C-5), 157.1 (C, C-8a), 137.4 (C, C-5-OCH_2*Ar*), 128.8 (CH, C-5-OCH_2*Ar*-H), 128.6 (CH, C-5-OCH_2*Ar*-H), 128.3 (CH, C-5-OCH_2*Ar*-H), 119.6 (C, C-6), 112.3 (C, C-4a), 112.0 (CH, C-3), 95.5 (CH, C-8), 77.1 (CH_2, C-5-O*C*H_2Ar), 56.0 (CH_3, C-7-O*C*H_3), 46.6 (CH, C-2′), 24.6 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H_3), 13.5 (CH_3, C-2′-*C*H_3).

$[\alpha]_D^{20}$ +15.1 (*c* 1.4, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 1722, 1655, 1601, 1444, 1340, 1202, 1125, 1061, 701.

HRMS (ESI+) found $[M+Na]^+$ 389.1335 $C_{22}H_{22}NaO_5^+$ requires 389.1359.

(*S*)-5-(benzyloxy)-7-methoxy-2-methyl-6-(2′-methyl-3′-oxobutyl)-4*H*-chromen-4-one (*S*)-**116**



To a solution of aldehyde (*S*)-**124** (135 mg, 0.37 mmol) in THF (8.7 mL) was added LiCl (98 mg, 2.32 mmol) and the reaction mixture cooled to –78 °C. MeMgBr (3 M in Et_2O, 0.2 mL, 0.6 mmol) was added and the reaction mixture stirred for 30 min. Upon completion of the reaction as monitored by TLC, saturated aqueous Rochelle's salt (10 mL) was added and the reaction mixture warmed to rt. Brine (10 mL) was added and reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the corresponding secondary alcohol **118** (111 mg, 0.29 mmol, 80%) as a colourless oil that was taken onto the next step without further purification.

To the solution of crude alcohol **118** (111 mg, 0.29 mmol) in DMSO (3.5 mL) was added 2-iodoxybenzoic acid (243 mg, 0.87 mmol) and the reaction mixture stirred for 3 h. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added followed by the addition of EtOAc (30 mL). The layers were separated and the organic layer washed with saturated aqueous $Na_2S_2O_3$ (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the *title compound* (82 mg, 94%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.54–7.60 (2H, m, C-5-OCH_2Ar-*H*), 7.30–7.41 (3H, m, C-5-OCH_2Ar-*H*), 6.65 (1H, s, H-8), 6.06 (1H, d, *J* 0 .7, H-3), 4.99 (2H, m, C-5-OCH_2OAr), 3.87 (3H, s, C-7-OCH_3), 2.76–2.87 (2H, m, H-1′), 2.66–2.75 (1H, m, H-2′), 2.32 (3H, s, C-2-CH_3), 2.01 (3H, s, H-4′), 0.93 (3H, d, *J* 7.0, C-2′-CH_3).

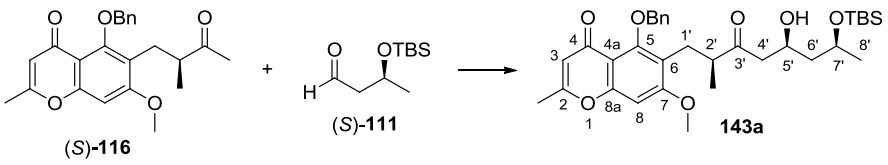
δ_C (100 MHz, $CDCl_3$) 212.6 (C, C-3′), 177.0 (C, C-4), 163.5 (C, C-2), 162.2 (C, C-7), 158.5 (C, C-5), 157.1 (C, C-8a), 137.4 (C, C-5-OCH_2*Ar*), 129.0 (CH, C-5-OCH_2*Ar*-H), 128.6 (CH, C-5-OCH_2*Ar*-H), 128.3 (CH, C-5-OCH_2*Ar*-H), 120.3 (C, C-4a), 112.3 (C, C-6), 111.9 (CH, C-3), 95.4 (CH, C-8), 77.0 (CH_2, C-5-O*C*H_2Ar-H), 56.0 (CH_3, C-7-O*C*H_3), 47.0 (CH, C-2′), 28.1 (CH_3, C-4′), 26.3 (CH_2, C-1′), 20.0 (CH_3, C-2-*C*H_3), 15.7 (CH_3, C-2′-*C*H_3).

$[\alpha]_D^{20}$ +28.1 (*c* 0.7, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 2934, 1708, 1654, 1600, 1443, 1388, 1339, 1202, 1124, 1084, 1062, 844.

HRMS (ESI+) found $[M+Na]^+$ 403.1502 $C_{23}H_{24}NaO_5^+$ requires 403.1516.

5-(benzyloxy)-6-((2′*S*,5′*S*,7′*S*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**143a**)



General procedure for the aldol reaction:

A two necked round bottom flask was charged with (–)-Ipc_2BCl (44 mg, 0.22 mmol) and placed under high vacuum for 1 h to remove traces of HCl. Et_2O (1 mL) was added and mixture was cooled to –78 °C. NEt_3 (0.04 mL, 0.27 mmol) was added followed by a solution of ketone (*S*)-**116** (15 mg, 0.039 mmol) in Et_2O (1 mL + 1 mL washings). The resultant white suspension was warmed to 0 °C and stirred for 1 h. The reaction mixture was cooled to –78 °C and aldehyde (*S*)-**111** (80 mg, 0.39 mmol) in Et_2O (1 mL) was added. The reaction mixture was stirred at –78 °C for 2 h then quenched by addition of pH 7 buffer solution (2 mL), MeOH (1 mL) and 30% aq. H_2O_2 solution (1 mL) and warmed to rt and stirred vigorously for 2 h. The mixture was then diluted with H_2O (10 mL) and EtOAc (5 mL), the layers separated and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified *via* flash column chromatography (1:1, EtOAc–Hexanes) to yield an inseparable 2:1 mixture of (5′*S*)-**143a** and (5′*R*)-**143b** as a colourless oil (10 mg, 43%).

Major diastereomer (5′*S*)-**143a** (obtained by substraction of signals due to minor isomer):

δ_H (300 MHz, $CDCl_3$) 7.52–7.62 (2H, m), 7.28–7.43 (3H, m), 6.64 (1H, s), 6.06 (1H, d, *J* 0.7), 5.01 (1H, d, *J* 10.3), 4.95 (1H, d, *J* 10.3), 3.99–4.18 (2H, m), 3.874 (3H, s), 3.51 (1H, br s, OH), 2.62–2.90 (3H, m), 2.38–2.60 (2H, m), 2.32 (3H, d, *J* 0.7), 1.31–1.57 (2H, m), 1.15 (3H, d, *J* 6.0), 0.93 (3H, d, *J* 6.6), 0.88 (9H, s), 0.08 (6H, s).

δ_C (75 MHz, $CDCl_3$) 214.7 (C, C-3′), 176.99 (C, C-4), 163.5 (C, C-2), 162.1 (C, C-7), 158.6 (C, C-5), 157.1 (C, C-8a), 137.4 (C, C-5-OCH_2*Ar*), 129.0 (CH, C-5-OCH_2*Ar*-H), 128.62 (CH, C-5-OCH_2*Ar*-H), 128.28 (CH, C-5-OCH_2*Ar*-H), 120.2 (C, C-4a), 112.3 (C, C-6), 111.9 (CH, C-3), 95.4 (CH, C-8), 76.95 (CH_2, C-5-O*C*H_2Ar-H), 68.3 (CH, C-7′), 66.6 (CH, C-5′), 56.0 (CH_3, C-7-O*C*H_3), 48.1 (CH_2, C-4′), 46.7 (CH, C-2′), 45.8 (CH_2, C-6′), 26.2 (CH_2, C-1′), 26.0 (CH_3, C-7′-OSi(CH_3)$_2$C(*C*H_3)$_3$), 24.0 (CH_3, C-8′), 20.0 (CH_3, C-2-*C*H_3), 18.10 (C, C-7′-

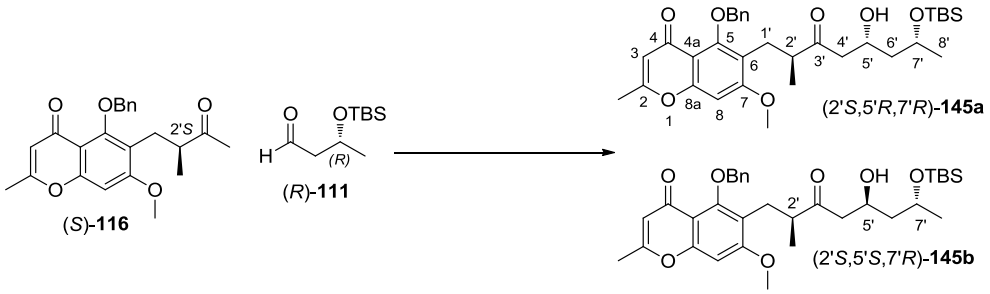
$OSi(CH_3)_2\underline{C}(CH_3)_3$), 15.6 ($CH_3$, C-2′-$\underline{C}H_3$), -3.99 ($CH_3$, C-7′-$OSi(\underline{C}H_3)_2C(CH_3)_3$), -4.63 ($CH_3$, C-7′-$OSi(\underline{C}H_3)_2C(CH_3)_3$).

IR: ν_{max} (film)/cm^{-1} (mixture of diastereoisomers) 3465, 2596, 2931, 2857, 1706, 1656, 1601, 1446, 1389, 1341, 1256, 1202, 1128, 1079, 1003, 834, 776, 700.

HRMS (ESI+) found $[M+Na]^+$ 605.2908 $C_{33}H_{46}NaO_7Si^+$ requires 605.2905.

5-(benzyloxy)-6-((2′*S*,5′*R*,7′*R*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**145a**)

5-(benzyloxy)-6-((2′*S*,5′*S*,7′*R*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**145b**)



Using (–)-Ipc$_2$BCl: the general procedure for the aldol reaction was followed using ketone (*S*)-**116** (72 mg, 0.189 mmol), aldehyde (*R*)-**111** (240 mg, 1.19 mmol) and (–)-Ipc$_2$BCl (179 mg, 0.558 mmol) to yield an inseparable 1:1 mixture of (5′*R*)-**145a** and (5′*S*)-**145b** as a colourless oil (34 mg, 31%).

Using (+)-Ipc$_2$BCl: the general procedure for the aldol reaction was followed using ketone (*S*)-**116** (37 mg, 0.097 mmol), aldehyde (*R*)-**111** (196 mg, 0.969 mmol) and (+)-Ipc$_2$BCl (94 mg, 0.292 mmol) to yield an inseparable 20:1 mixture of (5′*R*)-**145a** and (5′*S*)-**145b** as a colourless oil (20 mg, 35%).

For (5′*R*)-**145a**

δ_H (300 MHz, $CDCl_3$) 7.54–7.61 (2H, m, C-5-OCH$_2$Ar-*H*), 7.28–7.43 (3H, m, C-5-OCH$_2$Ar-*H*), 6.64 (1H, s, H-8), 6.06 (1H, s, H-3), 5.02 (1H, d, *J* 10.1, C-5-OC*H*$_2$Ar), 4.95 (1H, d, *J* 10.1, C-5-OC*H*$_2$Ar), 4.04–4.16 (1H, m, H-5′), 3.95–4.10 (1H, m, H-7′), 3.87 (3H, s, C-7-OC*H*$_3$), 3.50 (1H, br s, C-5′-O*H*), 2.75–2.89 (2H, m, H-1′), 2.63–2.75 (1H, m, H-2′), 2.37–2.54 (2H, m, H-4′), 2.32 (3H, s, C-2-C*H*$_3$), 1.31–1.66 (2H, m, H-6′), 1.15 (3H, d, *J* 6.1, H-8′), 0.92 (3H, d, *J* 6.6, C-2′-C*H*$_3$), 0.88 (9H, s, C-7′-OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.08 (6H, s, C-7′-OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$).

δ_C (75 MHz, $CDCl_3$) 214.7 (C, C-3′), 177.0 (C, C-4), 163.5 (C, C-2), 162.2 (C, C-7), 158.6 (C, C-5), 157.1 (C, C-8a), 137.4 (C, C-5-OCH$_2$*Ar*), 129.0 (CH, C-5-OCH$_2$*Ar*-H), 128.7 (CH, C-5-OCH$_2$*Ar*-H), 128.3 (CH, C-5-OCH$_2$*Ar*-H), 120.2 (C, C-6), 112.3 (C, C-4a), 111.9 (CH, C-3), 95.5 (CH, C-8), 77.0 (CH$_2$, C-5-O*C*H$_2$Ar), 68.2 (CH, C-7′), 66.6 (CH, C-5′), 56.0 (CH$_3$, C-7-O*C*H$_3$), 48.1 (CH$_2$, C-4′), 46.6 (CH, C-2′), 45.7 (CH$_2$, C-6′), 26.3 (CH$_2$, C-1′), 26.0 (CH$_3$,

C-7′-OSi(CH_3)$_2$C(<u>*C*</u>H$_3$)$_3$), 24.1 (CH_3, C-8′), 20.0 (CH_3, C-2-<u>*C*</u>H$_3$), 18.1 (C, C-7′-OSi(CH_3)$_2$<u>*C*</u>(CH_3)$_3$), 15.6 (CH_3, C-2′-<u>*C*</u>H$_3$), -3.96 (CH_3, C-7′-OSi(<u>*C*</u>H$_3$)$_2$C(CH_3)$_3$), -4.63 (CH_3, C-7′-OSi(<u>*C*</u>H$_3$)$_2$C(CH_3)$_3$).

IR: ν_{max} (film)/cm^{-1} (20:1 mixture of **145a** and **145b**) 2959, 2929, 2856, 1706, 1657, 1602, 1449, 1079, 835, 777.

HRMS (ESI+) found [M+Na]$^+$ 605.2891. $C_{33}H_{46}NaO_7Si^+$ requires 605.2905.

For (5′*S*)-**145b**

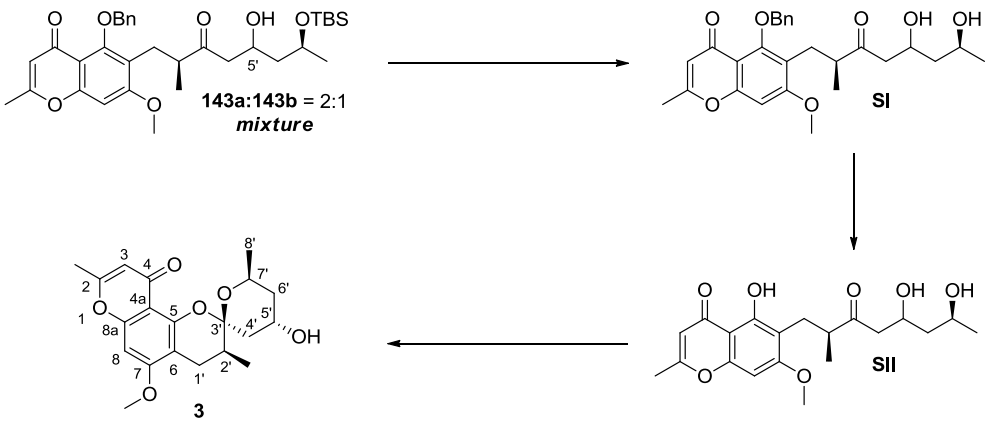
δ_H (300 MHz, $CDCl_3$) 7.54–7.61 (2H, m, C-5-OCH$_2$Ar-<u>*H*</u>), 7.28–7.43 (3H, m, C-5-OCH$_2$Ar-<u>*H*</u>), 6.64 (1H, s, H-8), 6.06 (1H, s, H-3), 5.02 (1H, d, *J* 10.1, C-5-OC<u>*H*</u>$_2$Ar), 4.95 (1H, d, *J* 10.1, C-5-OC<u>*H*</u>$_2$Ar), 4.18–4.30 (1H, m, H-5′), 3.95–4.16 (1H, m, H-7′), 3.87 (3H, s, C-7-OC<u>*H*</u>$_3$), 3.45 (1H, br s, C-5′-O<u>*H*</u>), 2.75–2.89 (2H, m, H-1′), 2.63–2.75 (1H, m, H-2′), 2.37–2.54 (2H, m, H-4′), 2.32 (3H, s, C-2-C<u>*H*</u>$_3$), 1.31–1.66 (2H, m, H-6′), 1.18 (3H, d, *J* 6.3, H-8′), 0.92 (3H, d, *J* 6.6, C-2′-C<u>*H*</u>$_3$), 0.90 (9H, s, C-7′-OSi(CH_3)$_2$C(C<u>*H*</u>$_3$)$_3$), 0.08 (6H, s, C-7′-OSi(C<u>*H*</u>$_3$)$_2$C(CH_3)$_3$).

δ_C (75 MHz, $CDCl_3$) 215.1 (C, C-3′), 177.0 (C, C-4), 163.5 (C, C-2), 162.2 (C, C-7), 158.6 (C, C-5), 157.1 (C, C-8a), 137.4 (C, C-5-OCH$_2$<u>*Ar*</u>), 129.0 (CH, C-5-OCH$_2$<u>*Ar*</u>-H), 128.7 (CH, C-5-OCH$_2$<u>*Ar*</u>-H), 128.3 (CH, C-5-OCH$_2$<u>*Ar*</u>-H), 120.2 (C, C-6), 112.3 (C, C-4a), 111.9 (CH, C-3), 95.5 (CH, C-8), 77.0 (CH_2, C-5-O<u>*C*</u>H$_2$Ar), 66.3 (CH, C-7′), 64.5 (CH, C-5′), 56.0 (CH_3, C-7-O<u>*C*</u>H$_3$), 48.3 (CH_2, C-4′), 46.7 (CH, C-2′), 45.2 (CH_2, C-6′), 26.2 (CH_2, C-1′), 26.0 (CH_3, C-7′-OSi(CH_3)$_2$C(<u>*C*</u>H$_3$)$_3$), 23.9 (CH_3, C-8′), 20.0 (CH_3, C-2-<u>*C*</u>H$_3$), 18.2 (C, C-7′-OSi(CH_3)$_2$<u>*C*</u>(CH_3)$_3$), 15.5 (CH_3, C-2′-<u>*C*</u>H$_3$), -4.35 (CH_3, C-7′-OSi(<u>*C*</u>H$_3$)$_2$C(CH_3)$_3$), -4.74 (CH_3, C-7′-OSi(<u>*C*</u>H$_3$)$_2$C(CH_3)$_3$).

IR: ν_{max} (film)/cm^{-1} (1:1 mixture of **145a** and **145b**) 2957, 2930, 2856, 1657, 1602, 1448, 1389, 1341, 1257, 1203, 1078, 835.

HRMS (ESI+) found [M+Na]$^+$ 605.2896 $C_{33}H_{46}NaO_7Si$ requires 605.2905.

chaetoquadrin C (**3**)



To a solution of a 2:1 mixture of (5′*S*)-**143a** and (5′*R*)-**143b** (10 mg, 0.017 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.03 mL, 0.03 mmol) and the reaction mixture was stirred for 50 min. The reaction mixture was then quenched by the addition of brine (10 mL), diluted with EtOAc (10 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude alcohol **SI** (crude mass: 11 mg) was used directly in the next step.

The crude alcohol **SI** (11 mg) was taken up in EtOAc (1 mL) and 10% Pd/C (25 mg) and stirred under H_2 atmosphere for 2 h. The reaction was filtered through cotton wool and the solvent removed *in vacuo*. The crude phenol **SII** (crude mass: 10 mg) was used directly in the next step.

Crude phenol **SII** (10 mg) was dissolved in $CHCl_3$ (1 mL). PPTS (2 mg) was added and the reaction mixture was stirred for 12 h. The reaction mixture was then directly loaded on to a preparative TLC plate (2:1, EtOAc–CH_2Cl_2) to yield chaetoquadrin C (2 mg, 33% over 3 steps).

For proton and carbon data comparison to the natural sample please see **Chapter 4**, **Section 4.3 B**.

δ_H (400 MHz, $CDCl_3$) 6.42 (1H, s, H-8), 6.51 (1H, d, *J* 11.8, C-5'-O*H*), 5.99 (1H, s, H-3), 4.19 (1H, ddd, *J* 11.9, 3.3, 2.3, H-5'), 4.11 (1H, dqd, *J* 12.1, 6.0, 2.0, H-7'), 3.89 (3H, s, C-7-OC*H*$_3$), 2.62 (1H, dd, *J* 16.7, 5.8, H_A-1'), 2.37 (1H, dd, *J* 16.7, 12.3, H_B-1') 1.99–2.13 (2H, m, H-4'), 2.28 (3H, s, C-2-C*H*$_3$), 1.94–2.00 (2H, m, H-2'), 1.87–1.94 (1H, m, H_A-6'), 1.41–1.51 (1H, m, H_B-6'), 1.01 (3H, d, *J* 6.3, H-8'), 1.10 (3Hm d, *J* 6.8, C-2'-C*H*$_3$).

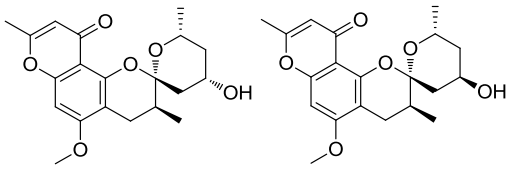
δ_C (100 MHz, $CDCl_3$) 177.6 (C, C-4), 163.4 (C, C-2), 160.8 (C, C-7), 158.0 (C, C-8a), 150.8 (C, C-5), 111.5 (CH, C-3), 108.1 (C, C-4a), 109.3 (C, C-6), 101.1 (C, C-3'), 91.3 (CH, C-8), 63.8 (CH, C-5'), 62.4 (CH, C-7'), 55.8 (CH_3, C-7-O<u>*C*</u>H_3), 40.2 (CH_2, C-6'), 35.9 (CH_2, C-4'), 33.4 (CH, C-2'), 23.5 (CH_2, C-1'), 21.4 (CH_3, C-8'), 19.9 (CH_3, C-2-<u>*C*</u>H_3), 16.0 (CH_3, 2'-<u>*C*</u>H_3).

$[\alpha]_D^{20}$ -6.67 (*c* 0.30, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 3415, 2933, 1657, 1607, 1453, 1389, 1345, 1203, 1060.

HRMS (ESI+) found $[M+H]^+$ 361.1657 $C_{20}H_{25}O_6^+$ requires 361.1646.

ent-chaetoquadrin A (*ent*-**1**) and B (*ent*-**2**)



ent-**1** *ent*-**2**

The same procedure described for **3** was followed using a 1:1 mixture of (5′*R*)-**145a** and (5′*S*)-**145b**

(34 mg, 0.058 mmol) to yield *ent*-chaetoquadrin A (*ent*-**1**) (4.6 mg, 22% over 3 steps) and *ent*-chaetoquadrin B (*ent*-**2**) (5.2 mg, 25% over 3 steps).

For proton and carbon data comparison to the natural sample please see **Chapter 4**, **Section 4.4 B** and **C**.

For *ent*-**1**:

δ_H (400 MHz, $CDCl_3$) 6.42 (1H, s, H-8), 5.93 (1H, d, *J* 0.7), 4.60–4.74 (1H, m, H-5'), 4.01 (1H, dqd, *J* 12.1, 6.4, 2.9), 3.88 (3H, s, C-7-OC$\underline{H}_3$), 2.91 (1H, dd, *J* 16.8, 6.6, H_A-1'), 2.37 (1H, dd, *J* 16.8, 3.3, H_B-1'), 2.43 (1H, ddd, *J* 12.5, 4.7, 1.8, H_A-4'), 1.32 (1H, dd, *J* 12.5, 11.1, H_B-4'), 2.28 (3H, d, *J* 0.7, C-2-C$\underline{H}_3$), 2.11 (1H, qdd, *J* 7.1, 6.8, 3.1, H-2'), 2.04 (1H, ddd, *J* 12.4, 6.8, 2.0, H_A-6'), 1.25–1.27 (1H, m, H_B-6'), 1.07 (3H, d, *J* 6.3, H-8'), 0.99 (3H, d, *J* 7.0, C-2'-C$\underline{H}_3$).

δ_C (100 MHz, $CDCl_3$) 177.3 (C, C-4), 162.9 (C, C-2), 161.4 (C, C-7), 158.0 (C, C-8a), 151.3 (C, C-5), 111.8 (CH, C-3), 108.4 (C, C-4a), 107.3 (C, C-6), 101.4 (C, C-3'), 91.2 (CH, C-8), 64.5 (CH, C-5'), 66.6 (CH, C-7'), 55.7 (CH_3, C-7-O$\underline{C}H_3$), 42.4 (CH_2, C-6'), 39.4 (CH_2, C-4'), 32.5 (CH, C-2'), 24.2 (CH_2, C-1'), 21.4 (CH_3, C-8'), 19.8 (CH_3, 2-$\underline{C}H_3$), 15.6 (CH_3, 2'-$\underline{C}H_3$).

$[\alpha]_D^{20}$ +17.0 (*c* 0.1 $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 2967, 2930, 1654, 1603, 1450, 1384, 1343, 1260, 1108, 1084, 1033, 803.

HRMS (ESI+) found $[M+H]^+$ 361.1649 $C_{20}H_{25}O_6^+$ requires 361.1646.

For *ent*-**2**:

δ_H (300 MHz, $CDCl_3$) 6.45 (1H, s, H-8), 6.29 (1H, d, *J* 11.4, C-5'-O$\underline{H}$), 6.00 (1H, d, *J* 0.7, H-3), 4.07–4.23 (2H, m, H-5', H-7'), 3.89 (3H, s, C-7-OC$\underline{H}_3$), 2.29 (1H, dd, *J* 16.7, 6.6, H_A-1'),

2.40 (1H, dd, *J* 16.8, 1.6, H_B-1'), 2.36 (1H, dd, *J* 14.2, 2.2, H_A-4'), 1.63 (1H, dd, *J* 14.2, 4.1, H_B-4'), 2.29 (3H, d, *J* 0.7, C-2-C$\underline{H}_3$), 2.04 (1H, qdd, *J* 7.0, 6.5, 1.6, H-2'), 1.86–1.97 (1H, m, H_A-6'), 1.49 (1H, ddd, *J* 13.8, 12.0, 3.2, H_B-6'), 1.03 (3H, d, *J* 6.2, H-8'), 0.95 (3H, d, *J* 7.0, C-2'-C$\underline{H}_3$).

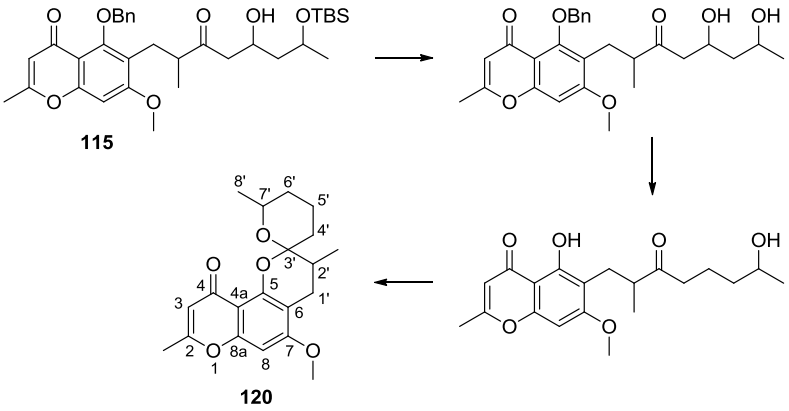
δ_C (75 MHz, $CDCl_3$) 177.6 (C, C-4), 163.4 (C, C-2), 161.7 (C, C-7), 158.0 (C, C-8a), 150.4 (C, C-5), 111.6 (C, C-3), 108.0 (C, C-4a), 107.2 (C, C-6), 100.6 (C, C-3'), 91.5 (CH, C-8), 63.7 (CH, C-5'), 62.6 (CH, C-7'), 55.8 (CH_3, C-7-O$\underline{C}H_3$), 40.0 (CH_2, C-6'), 36.8 (CH_2, C-4'), 32.3 (CH, C-2'), 23.4 (CH_2, C-1'), 21.5 (CH_3, C-8'), 19.9 (CH_3, 2-$\underline{C}H_3$), 15.3 (CH_3, 2'-$\underline{C}H_3$).

$[\alpha]_D^{20}$ +19.3 (*c* 0.46, $CHCl_3$).

IR: ν_{max} (film)/cm^{-1} 3420, 2970, 2928, 1654, 1605, 1452, 1344, 1204.

HRMS (ESI+) found $[M+Na]^+$ 383.1463. $C_{20}H_{24}NaO_6$ requires 383.1465.

deoxy-spiroketal **120**[§§]



The same procedure described for **3** was followed using **115** (20 mg, 0.034 mmol). For the second (debenzylation) step, $CHCl_3$ was used in place of EtOAc to afford deoxy-spiroketal **120** (2.5 mg, 22% over 3 steps) as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 6.37–6.42, 5.94, 3.93–4.06, 3.88, 2.82–3.00, 2.51–2.72, 2.30–2.47, 2.26, 1.99–2.15, 1.85–1.99, 1.63–1.84, 0.73–1.81, 0.07.

δ_C (75 MHz, $CDCl_3$) 177.5, 162.8, 161.5, 160.8, 158.2, 152.3, 152.1, 133.4, 129.6, 127.7, 112.0, 111.9, 109.4, 108.8, 107.6, 100.4, 100.3, 91.1, 90.9, 67.8, 67.6, 55.8, 33.7, 33.2, 32.9, 30.8, 30.3, 29.8, 24.5, 24.4, 22.0, 21.9, 20.0, 18.8, 18.7, 16.1, 15.7.

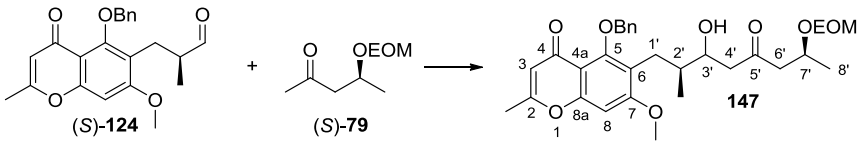
IR: ν_{max} (film)/cm^{-1} 2926, 1660, 1608, 1450, 1343, 1203, 1085.

HRMS (ESI+) found $[M+H]^+$ 345.1695 $C_{20}H_{25}O_5^+$ requires 345.1697.

[§§] Note: To test the viability of our synthetic route, this compound was made without asymmetric control and was isolated as complicated mixture of inseparable diastereoisomers. Accordingly, peaks remain unassigned.

5.9 Synthesis of chaetoquadrin H (4)

5-(benzyloxy)-6-((2′*S*,7′*S*)-7′-(ethoxymethoxy)-3′-hydroxy-2′-methyl-5′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**147**) [***]



A solution of diisopropylamine (0.04 mL, 0.25 mmol) in THF (1 mL) was cooled to -78° C. *n*-BuLi (0.15 mL, 0.24 mmol, 1.6 M in hexanes) was carefully added *via* syringe and the mixture stirred for 1 h at the same temperature. The reaction mixture was then warmed to 0° C for 10 min, then cooled to -78 °C. A solution of ketone (*S*)-**79** (39 mg, 0.24 mmol) in THF (1 mL) was cooled to -78 °C and added to the LDA mixture *via* cannula, maintaining the temperature of all of the reactants at -78 °C. The solution of aldehyde (*S*)-**124** (36 mg, 0.11 mmol) in THF (1 mL) was then cooled to -78 °C and added to the mixture dropwise *via* cannula. The reaction mixture was stirred at this temperature for 2 h. Saturated aqueous NH_4Cl (4 mL) was added and reaction mixture was allowed to warm to rt. The reaction mixture was extracted with EtOAc (3 × 4 mL) and the combined organic extracts washed with brine (6 mL), dried over $MgSO_4$ and purified *via* flash column chromatography (EtOAc–hexanes, 1.5:1) to yield β-hydroxy ketone **147** (22 mg, 43%) as an inseparable mixture of diastereomers (1:1) and as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.56–7.66 (2H, m), 7.29–7.44 (3H, m), 6.67 (0.5H, s*), 6.65 (0.5H, s), 6.05 (0.5H, s*), 6.04 (0.5H, s), 4.99–5.09 (1H, m), 4.87–4.95 (1H, m), 4.59–4.69 (2H, m), 4.07–4.19 (1H, m), 3.90 (1.5H, s*), 3.88 (1.5H, s), 3.76–3.87 (1H, m), 3.47–3.59 (2H, m), 2.32 (1.5H, s*), 2.31 (1.5H, s), 2.23–2.71 (6H, m), 1.73–1.98 (2H, m), 1.14–1.22 (6H, m), 0.84 (1.5H, d, *J* 6.8*) ,0.78 (1.5H, d, *J* 7.1).

δ_C (100 MHz, $CDCl_3$) 210.7 (C*), 209.6 (C), 177.0 (C*), 176.9 (C), 163.5 (C*), 163.4 (C), 162.3 (C*), 162.2 (C), 158.4 (C*), 158.3 (C), 156.8 (C*), 156.7 (C), 137.5 (C*), 137.2 (C), 129.1 (CH*), 129.0 (CH), 128.6 (CH*), 128.5 (CH), 128.3 (CH*), 128.2 (CH), 121.4 (C*), 121.0 (C), 112.2 (C), 111.9 (CH), 95.7 (CH*), 95.4 (CH), 93.9 (CH_2*), 93.8 (CH_2), 77.0

[***] Note: This compound was made as a mixture of two inseparable diastereoisomers. Accordingly, peaks remain unassigned.

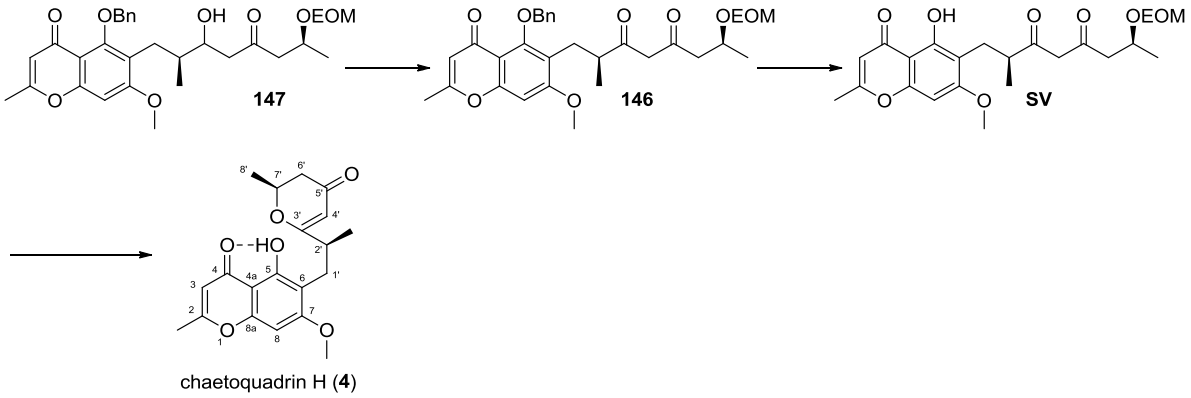
(CH_2), 71.2 (CH*), 69.7 (CH*), 69.6 (CH), 69.0 (CH), 63.4 (CH_2*), 63.3 (CH_2), 56.1 (CH_3*), 56.0 (CH_3), 50.9 (CH_2*), 50.8 (CH_2), 48.1 (CH_2*), 46.6 (CH_2), 38.6 (CH*), 38.1 (CH), 27.3 (CH_2*), 25.9 (CH_2), 20.7 (CH_3*), 20.0 (CH_3), 15.4 (CH_3), 15.2 (CH_3*), 15.1 (CH_3), 13.7 (CH_3).

Note: Asterisks denote peaks arising from one of the two compounds posessing an diastoisomeric releationship with respect to the C-3' stereocentre.

IR (film): 2971, 2932, 1709, 1655, 1600, 1444, 1389, 1341, 1202, 1129, 1034 cm^{-1}.

HRMS (ESI+) found $[M+H]^+$ 527.2622. $C_{30}H_{39}O_8^+$ requires 527.2639.

chaetoquadrin H (**4**)



To a solution of β-hydroxyketone **147** (22 mg, 0.04 mmol) in EtOAc (1 mL) was added 2-iodoxybenzoic acid (38 mg, 0.14 mmol) and the reaction mixture heated at reflux for 2 h. The reaction mixture was then allowed to cool to rt and filtered through a plug of cotton wool. Solvent was removed *in vauco* to afford the crude ketone **146** (14 mg, 64%) as a colourless oil.

Crude 1,3-diketone **146** (10 mg, 0.02 mmol) was taken up in EtOAc (1 mL), 10% Pd/C (16 mg) was added and the reaction mixture stirred under an atmosphere of H_2 for 30 min. The reaction was filtered through cotton wool and the solvent removed *in vacuo* to afford crude phenol **SV**.

The crude phenol **SV** was dissolved in $CHCl_3$ (1 mL). $NaHSO_4 \cdot SiO_2$ (15 mg) was added and the mixture stirred for 2 h. The reaction mixture was filtered through cotton wool and the filtrate loaded directly onto a preparative TLC plate and purified (EtOAc–hexanes, 3:1) to yield chaetoquadrin H (**4**) (3 mg, 44% over two steps).

$[\alpha]_D^{20}$ -41.3 (*c* 0.15 $CHCl_3$) [lit.[2] $[\alpha]_D^{20}$ -57.2 (*c* 0.2 $CHCl_3$)].

δ_H (300 MHz, $CDCl_3$) 12.85 (1H, s, C-5-O*H*), 6.34 (1H, s, H-8), 6.04 (1H, s, H-3), 5.11 (1H, s, H-4′), 4.29–4.45 (1H, m, H-7′), 3.87 (3H, s, C-7-OC*H*$_3$), 2.89–3.05 (1H, m, H-1′), 2.63–2.81 (2H, m, H-2′), 2.35 (3H, s, C-2-C*H*$_3$), 2.24–2.42 (2H, m, H-6′), 1.44 (3H, d, *J* 6.5, H-8′), 1.17 (3H, d, *J* 6.7, 2′-C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 193.7 (C, C-5′), 182.7 (C, C-4), 181.3 (C, C-3′), 166.6 (C, C-2), 163.4 (C, C-7), 159.2 (C, C-5), 157.0 (C, C-8a), 110.8 (C, C-6), 109.1 (CH, C-3), 105.2 (C, C-4a), 103.3 (CH, C-4′), 89.5 (CH, C-8), 75.8 (CH, C-7′), 56.0 (CH_3, C-7-O*C*H$_3$), 42.9 (CH_2, C-6′),

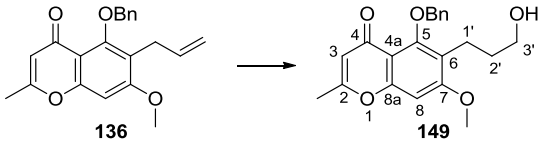
39.1 (CH, C-2′), 27.3 (CH_2, C-1′), 20.6 (CH_3, C-2-$\underline{C}H_3$), 20.5 (CH_3, C-8′), 17.6 (CH_3, C-2′-$\underline{C}H_3$).

IR (film): 2935, 1661, 1598, 1494, 1449, 1343, 1127 cm^{-1}.

HRMS (ESI+) found $[M+H]^+$ 359.1487. $C_{20}H_{23}O_6^+$ requires 359.1489.

5.10 Synthesis of chaetoquadrin I (5)

5-(benzyloxy)-6-(3′-hydroxypropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**149**)



To a stirred solution of olefin **136** (0.286 g, 0.851 mmol) in THF (3 mL) was added (+)-Ipc_2BH (0.243 g, 0.849 mmol). The reaction mixture was stirred for 12 h whereupon solid (+)-Ipc_2BH disappeared. The organoborane was treated with methanol (0.1 mL) followed by 1 M NaOH (aq) (0.5 mL), 30% aq. H_2O_2 solution (0.5 mL) and brine (3 mL). The reaction mixture was then extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified *via* flash column chromatography (2:1, EtOAc–Hexanes) to yield the *title compound* (61 mg, 20%) as a colourless oil.

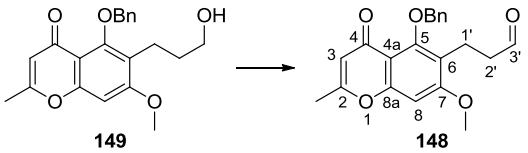
δ_H (400 MHz, $CDCl_3$) 7.58–7.65 (2H, m, C-5-OCH_2Ar-*H*), 7.29–7.45 (3H, m, C-5-OCH_2Ar-*H*), 6.66 (1H, s, H-8), 6.05 (1H, s, H-3), 4.99 (2H, s, C-5-OCH_2Ar), 3.90 (3H, s, C-7-OCH_3), 3.45 (2H, t, *J* 5.9, H-3′), 2.73 (2H, t, *J* 7.0, H-1′), 2.32 (3H, s, 2-CH_3), 1.65–1.75 (2H, m, H-2′).

δ_C (100 MHz, $CDCl_3$) 177.0 (C, C-4), 163.5 (C, C-2), 162.1 (C, C-7), 158.3 (C, C-5), 156.4 (C, C-8a), 137.2 (C, C-5-OCH_2Ar), 129.0 (CH, C-5-OCH_2Ar-H), 128.6 (CH, C-5-OCH_2Ar-H), 128.3 (CH, C-5-OCH_2Ar-H), 121.9 (C, C-6), 112.2 (C, C-4a), 111.9 (CH, C-3), 95.6 (CH, C-8), 77.1 (CH_2, C-5-OCH_2Ar), 61.6 (CH_2, C-3′), 56.1 (CH_3, C-7-OCH_3), 32.0 (CH_2, C-2′), 20.0 (CH_3, C-2-CH_3), 19.3 (CH_2, C-1′).

IR: ν_{max} (film)/cm^{-1} 2945, 2862, 1655, 1600, 1449, 1391, 1342, 1125.

HRMS (ESI+) found $[M+Na]^+$ 377.1364, $C_{21}H_{22}NaO_5^+$ requires 377.1359.

1′-(5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)propan-3′-al (**148**)



To a solution of alcohol **149** (62 mg, 0.18 mmol) in DMSO (3 mL) was added 2-iodoxybenzoic acid (196 mg, 0.70 mmol) and reaction mixture was stirred at rt for 2 h. Saturated aqueous $Na_2S_2O_3$ (8 mL) was added followed by the addition of EtOAc (20 mL). The layers were separated then the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield the *title compound* (50 mg, 81%) as a colourless oil.

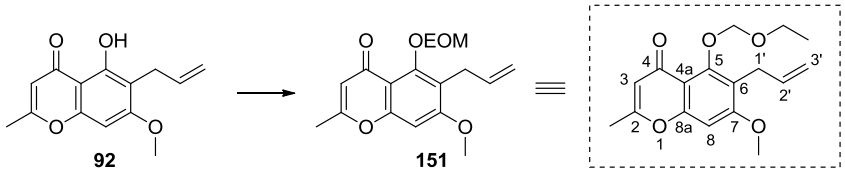
δ_H (300 MHz, $CDCl_3$) 9.66 (1H, t, *J* 1.7, H-3′), 7.50–7.57 (2H, m, C-5-OCH_2Ar-*H*), 7.28–7.42 (3H, m, C-5-OCH_2Ar-*H*), 6.64 (1H, s, H-8), 6.05 (1H, d, *J* 0.7, H-3), 5.01 (2H, s, C-5-OCH_2Ar), 3.88 (3H, s, C-7-OCH_3), 2.91 (2H, t, *J* 7.3, H-1′), 2.40–2.50 (2H, m, H-2′), 2.32 (3H, s, C-2-CH_3).

δ_C (75 MHz, $CDCl_3$) 202.4 (CH, C-3′), 177.0 (C, C-4), 163.6 (C, C-2), 161.9 (C, C-7), 158.6 (C, C-5), 156.6 (C, C-8a), 137.3 (C, C-5-OCH_2*Ar*), 129.0 (CH, C-5-OCH_2*Ar*-H), 128.6 (CH, C-5-OCH_2*Ar*-H), 128.3 (CH, C-5-OCH_2*Ar*-H), 120.8 (C, C-6), 112.3 (C, C-4a), 111.9 (CH, C-3), 95.5 (CH, C-8), 77.3 (CH_2, C-5-O*C*H_2Ar), 56.0 (CH_3, C-7-O*C*H_3), 43.5 (CH_2, C-2′), 20.0 (CH_3, C-2-*C*H_3), 16.6 (CH_2, C-1′).

IR: ν_{max} (film)/cm^{-1} 2945, 1721, 1656, 1603, 1445, 1389, 1340, 1121.

HRMS (ESI+) found $[M+Na]^+$ 375.1190, $C_{21}H_{20}NaO_5^+$ requires 375.1203.

6-allyl-5-(ethoxymethoxy)-7-methoxy-2-methyl-4*H*-chromen-4-one (**151**)



To a chilled solution of phenol **92** (1.1 g, 4.47 mmol) in THF (50 mL) at 0 °C was added sodium hydride (60% w/w in mineral oil, 0.715 g, 17.9 mmol) and chloromethyl ethyl ether (0.46 mL, 4.92 mmol) and the reaction mixture was stirred at this temperature for 4 h. Brine (40 mL) was then added and the reaction mixture was extracted with EtOAc (3 × 30 mL). Organic extracts were then washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* (1.16 g, 86%) as a white solid.

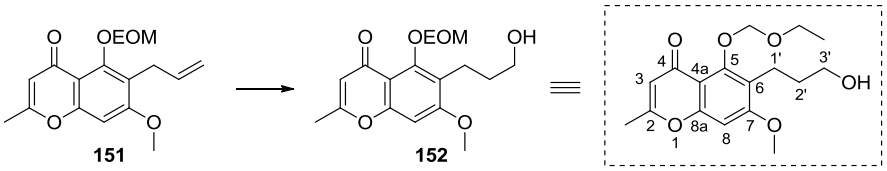
δ_H (300 MHz, $CDCl_3$) 6.63 (1H, s, H-8), 6.00 (1H, d, *J* 0.7, H-3), 5.87–6.05 (1H, m, H-2′), 5.18 (2H, s, C-5-OC$\underline{H}_2$OCH$_2$CH$_3$), 4.90–5.07 (2H, m, H-3′), 3.89 (3H, s, C-7-OC$\underline{H}_3$), 3.87 (2H, q, *J* 7.0, C-5-OCH$_2$OC$\underline{H}_2$CH$_3$), 3.52 (2H, dt, *J* 6.2, 1.5, H-1′), 2.29 (3H, d, *J* 0.7, C-2-C$\underline{H}_3$), 1.25 (3H, t, *J* 7.0, C-5-OCH$_2$OCH$_2$C$\underline{H}_3$).

δ_C (75 MHz, $CDCl_3$) 177.0 (C, C-4), 163.3 (C, C-2), 161.9 (C, C-7), 158.2 (C, C-5), 155.2 (C, C-8a), 136.2 (CH, C-2′), 120.4 (C, C-6), 114.8 (CH$_2$, C-3′), 111.5 (CH, C-3′), 111.2 (C, C-4a), 100.4 (CH$_2$, C-5-OCH$_2$O$\underline{C}$H$_2$CH$_3$), 95.2 (CH, C-8), 65.5 (CH$_2$, C-5-OCH$_2$O$\underline{C}$H$_2$CH$_3$), 55.9 (CH$_3$, C-7-O$\underline{C}$H$_3$), 27.8 (CH$_2$, C-1′), 19.9 (CH$_3$, C-2-$\underline{C}$H$_3$), 15.2 (CH$_3$, C-5-OCH$_2$OCH$_2\underline{C}$H$_3$).

IR: ν_{max} (film)/cm^{-1} 2925, 2857, 1659, 1604, 1447, 1343, 1203, 1136.

HRMS (ESI+) found $[M+Na]^+$ 327.1209, $C_{17}H_{20}NaO_5^+$ requires 327.1203.

5-(ethoxymethoxy)-6-(3′-hydroxypropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**152**)



To a chilled solution of olefin **151** (608 mg, 2.0 mmol) in THF (10 mL) at 0 °C was added borane-dimethyl sulphide complex (0.12 mL, 2.0 mmol) and stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by dropwise addition of 1 M NaOH (aq) (1 mL) and 30% aq. H_2O_2 solution (1 mL). The mixture was then diluted with brine (10 mL) and immediately extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* and purified *via* flash column chromatography (2:1, EtOAc–Hexanes) to yield the *title compound* (274 mg, 43%) as a colourless oil.

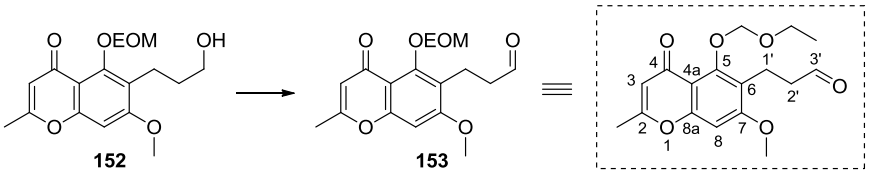
δ_H (300 MHz, $CDCl_3$) 6.64 (1H, s, H-8), 6.00 (1H, d, *J* 0.7, H-3), 5.20 (2H, s, C-5-OC*H*$_2$OCH$_2$CH$_3$), 3.91 (3H, s, C-7-OC*H*$_3$), 3.88 (2H, q, *J* 7.1, C-5-OCH$_2$OC*H*$_2$CH$_3$), 3.55 (2H, t, *J* 6.0, H-3′), 2.88 (2H, t, *J* 7.1, H-1′), 2.30 (3H, d, *J* 0.7, C-2-C*H*$_3$), 1.73–1.89 (2H, m, H-2′), 1.26 (3H, t, *J* 7.2, C-5-OCH$_2$OCH$_2$C*H*$_3$).

δ_C (75 MHz, $CDCl_3$) 176.9 (C, C-4), 163.5 (C, C-2), 161.9 (C, C-7), 158.1 (C, C-8a), 155.2 (C, C-5), 121.8 (C, C-6), 111.6 (CH, C-3), 111.2 (C, C-4a), 100.5 (CH$_2$, C-5-O*C*H$_2$OCH$_2$CH$_3$), 95.3 (CH, C-8), 65.8 (CH$_2$, C-5-OCH$_2$O*C*H$_2$CH$_3$), 61.7 (CH$_2$, C-3′), 56.0 (CH$_3$, C-7-O*C*H$_3$), 31.8 (CH$_2$, C-2′), 19.9 (CH$_3$, C-2-*C*H$_3$), 19.3 (CH$_2$, C-1′), 15.2 (CH$_3$, C-5-OCH$_2$OCH$_2$*C*H$_3$).

IR: ν_{max} (film)/cm^{-1} 3375, 3313, 2980, 1699, 1491, 1243, 1163, 1056.

HRMS (ESI+) found $[M+Na]^+$ 345.1321, $C_{17}H_{22}NaO_6^+$ requires 345.1309.

1′-(5-(ethoxymethoxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)propan-3′-al (**153**)



To a solution of alcohol **152** (274 mg, 0.851 mmol) in DMSO (12 mL) was added 2-iodoxybenzoic acid (862 mg, 3.08 mmol) and reaction mixture was stirred at rt for 2 h. Saturated aqueous $Na_2S_2O_3$ (20 mL) was added followed by addition of EtOAc (30 mL). The layers were separated then the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 × 15 mL), dried with $MgSO_4$ and concenterated *in vacuo* to yield the *title compound* (217 mg, 80%) as a colourless oil.

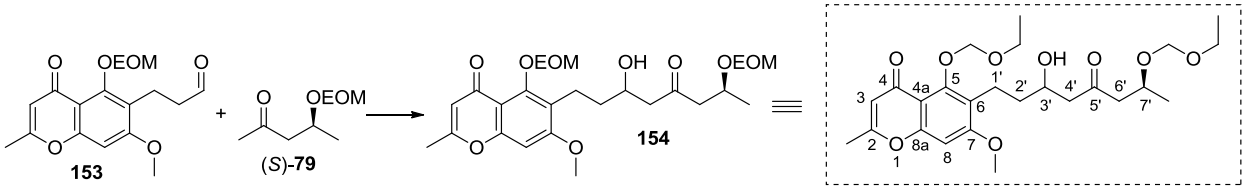
δ_H (400 MHz, $CDCl_3$) 9.82 (1H, t, *J* 1.6, H-3′), 6.63 (1H, s, H-8), 6.00 (1H, s, H-3), 5.18 (2H, s, C-5-OC$\underline{H_2}$OCH$_2$CH$_3$), 3.89 (3H, s, C-7-OC$\underline{H_3}$), 3.82 (2H, q, *J* 7.0, C-5-OCH$_2$OC$\underline{H_2}$CH$_3$), 3.09 (2H, t, *J* 7.5, H-1′), 2.64–2.71 (2H, dt, *J* 7.5, 1.6, H-2′), 2.30 (3H, s, 2-C$\underline{H_3}$), 1.24 (3H, t, *J* 7.0, C-5-OCH$_2$OCH$_2$C$\underline{H_3}$).

δ_C (100 MHz, $CDCl_3$) 202.4 (CH, C-3′), 176.9 (C, C-4), 163.5 (C, C-2), 161.5 (C, C-7), 158.3 (C, C-5), 155.5 (C, C-8a), 120.6 (C, C-6), 111.5 (CH, C-3), 111.1 (C, C-4a), 100.6 (CH$_2$, C-5-O$\underline{C}$H$_2$OCH$_2$CH$_3$), 95.3 (CH, C-8), 65.6 (CH$_2$, C-5-OCH$_2$O$\underline{C}$H$_2$CH$_3$), 55.9 (CH$_3$, C-7-O$\underline{C}$H$_3$), 43.4 (CH$_2$, C-2′), 19.8 (CH$_3$, C-2-$\underline{C}$H$_3$), 16.6 (CH$_2$, C-1′), 15.1 (CH$_3$, C-5-OCH$_2$OCH$_2$$\underline{C}H_3$).

IR: ν_{max} (film)/cm^{-1} 2975, 1720, 1654, 1602, 1446, 1388, 1341, 1177, 1060, 989.

HRMS (ESI+) found $[M+Na]^+$ 343.1147, $C_{17}H_{20}NaO_6^+$ requires 343.1152.

5-(ethoxymethoxy)-6-((7′*S*)-7′-(ethoxymethoxy)-3′-hydroxy-5′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**154**)[†††]



A two necked round bottom flask was charged with (+)-Ipc_2BCl (210 mg, 0.66 mmol) and placed under high vacuum for 1 h to remove traces of HCl. Et_2O (2 mL) was added and mixture was cooled to –78 °C. NEt_3 (0.1 mL, 0.72 mmol) was added followed by a solution of ketone (*S*)-**79** (100 mg, 0.63 mmol) in Et_2O (1 mL). The resultant white suspension was warmed to 0 °C and stirred for 40 min. The reaction mixture was cooled to –78 °C and aldehyde **153** (100 mg, 0.31 mmol) in Et_2O (2 mL) was added. The reaction mixture was stirred at –78 °C for 4 h then quenched by addition of aqueous pH 7 buffer solution (1 mL), MeOH (0.5 mL) and 30% aq. H_2O_2 solution (0.5 mL), warmed to rt and stirred for 1 h. The mixture was then diluted with H_2O (10 mL) and EtOAc (10 mL), the layers separated and the aqueous layer further extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified *via* flash column chromatography (EtOAc–hexanes, 2:1) to yield the *title compound* (44 mg, 30%) as an inseparable mixture of diastereomers (1:1) and as a colourless oil.

δ_H (300 MHz, $CDCl_3$) 6.63 (1H, s), 5.99 (1H, s), 5.12–5.23 (2H, m), 4.63–4.72 (2H, m), 4.11–4.28 (1H, m), 3.93–4.04 (1H, m), 3.89 (3H, s), 3.81–3.92 (2H, m), 3.55 (2H, q, *J* 7.2), 2.69–2.98 (3H, m), 2.40–2.63 (3H, m), 2.29 (3H, s), 1.60–1.78 (2H, m), 1.13–1.30 (9H, m).

δ_C (75 MHz, $CDCl_3$) 209.7 (C*), 209.6 (C), 177.0 (C), 163.5 (C), 161.8 (C), 158.1 (C), 155.2 (C), 122.0 (C), 111.5 (CH), 111.2 (C), 100.5 (CH_2), 95.3 (CH), 93.8 (CH_2*), 93.7 (CH_2), 69.7 (CH*), 69.6 (CH), 67.3 (CH*), 67.2 (CH), 65.7 (CH_2), 63.3 (CH_2), 56.0 (CH_3), 51.0 (CH_2*), 50.9 (CH_2), 50.5 (CH_2*), 50.4 (CH_2), 36.0 (CH_2*), 35.9 (CH_2), 20.6 (CH_3), 19.9 (CH_3), 19.6 (CH_2), 15.2 (CH_3), 15.0 (CH_3).

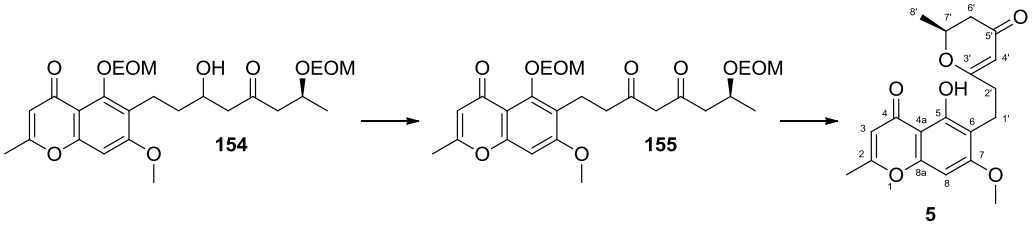
[†††] Note: this compound was isolated as a mixture of inseparable diastereoisomers. Accordingly, peaks remain unassigned.

Note: Asterisks denote peaks arising from one of the two compounds posessing an diastoisomeric releationship with respect to the C-3' stereocentre.

IR: ν_{max} (film)/cm^{-1} 2974, 1709, 1655, 1600, 1446, 1388, 1341, 1260, 1177, 1107, 1046, 990 cm^{-1}.

HRMS (ESI+) found $[M+Na]^+$ 481.2417, $C_{25}H_{37}NaO_9^+$ requires 481.2432.

chaetoquadrin I (**5**)



To a solution of β-hydroxyketone **154** (19 mg, 0.04 mmol) in EtOAc (2 mL) was added 2-iodoxybenzoic acid (100 mg, 0.36 mmol) and the reaction mixture heated at reflux for 5 h. The reaction mixture was then allowed to cool to rt and filtered through a plug of cotton wool. The solvent was removed *in vacuo* to give the 1,3-diketone **155** which was dissolved in $CHCl_3$ (1 mL). $NaHSO_4 \cdot SiO_2$ (20 mg) was added and the reaction mixture stirred for 1 h. The reaction mixture was filtered through cotton wool and the filtrate loaded directly onto a preparative TLC plate (EtOAc–hexanes, 2:1) to yield chaetoquadrin I (**5**) (5.5 mg, 40% over two steps).

$[\alpha]_D^{20}$ -10.8 (*c* 0.05 $CHCl_3$) [lit.[2] $[\alpha]_D^{20}$ -40.8 (*c* 0.05 $CHCl_3$)].

δ_H (300 MHz, $CDCl_3$): 12.8 (1H, s, C-5-O*H*), 6.36 (1H, s, H-8), 6.05 (1H, s. H-3), 5.22 (1H, s, H-4′), 4.38–4.53 (1H, m, H-7′), 3.88 (3H, s, C-7-OC*H*$_3$), 2.83–3.02 (2H, m, H-1′), 2.43–2.50 (2H, m, H-2′), 2.36 (3H, s, C-2-C*H*$_3$), 2.33–2.39 (2H, m, H-6′), 1.44 (3H, d, *J* 6.1, H-8′).

δ_C (75 MHz, $CDCl_3$): 193.5 (C, C-5′), 182.6 (C, C-4), 177.8 (C, C-3′), 166.6 (C, C-2), 163.2 (C, C-7), 159.0 (C, C-5), 157.0 (C, C-8a), 111.3 (C, C-6), 109.1 (CH, C-3), 105.2 (C, C-4a), 104.2 (CH, C-4′), 89.5 (CH, C-8), 75.8 (CH, C-7′), 56.0 (CH_3, C-7-O*C*H$_3$), 42.8 (CH_2, C-6′), 33.8 (CH_2, C-2′-*C*H$_3$), 20.6 (CH_3, C-8′), 20.6 (CH_3, C-2-*C*H$_3$), 19.6 (CH_2, C-1′).

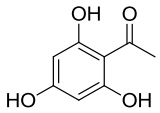
IR: ν_{max} (film)/cm^{-1} 2928, 1660, 1493, 1448, 1343, 1174 cm^{-1}.

HRMS (ESI+) found $[M+H]^+$ 345.1341, $C_{19}H_{21}O_6^+$ requires 345.1333.

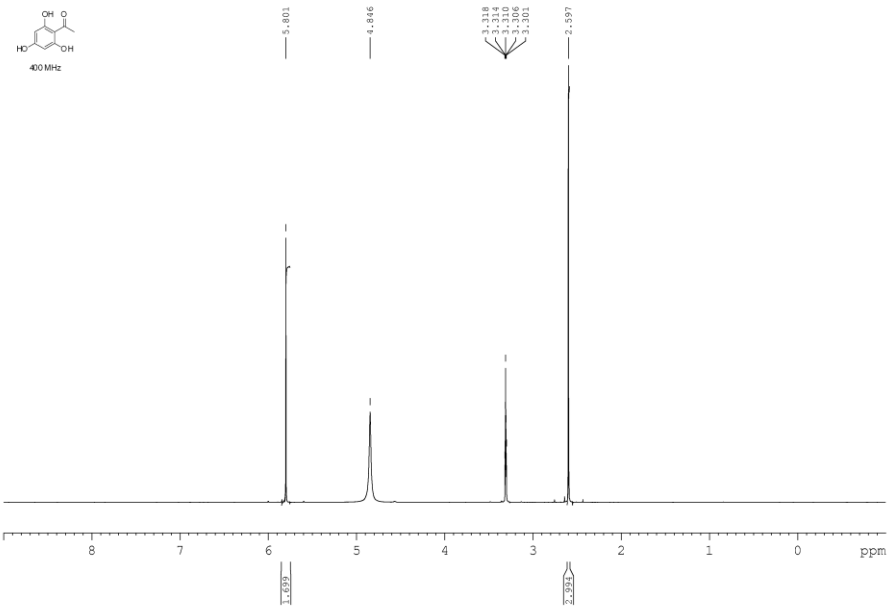
Appendices

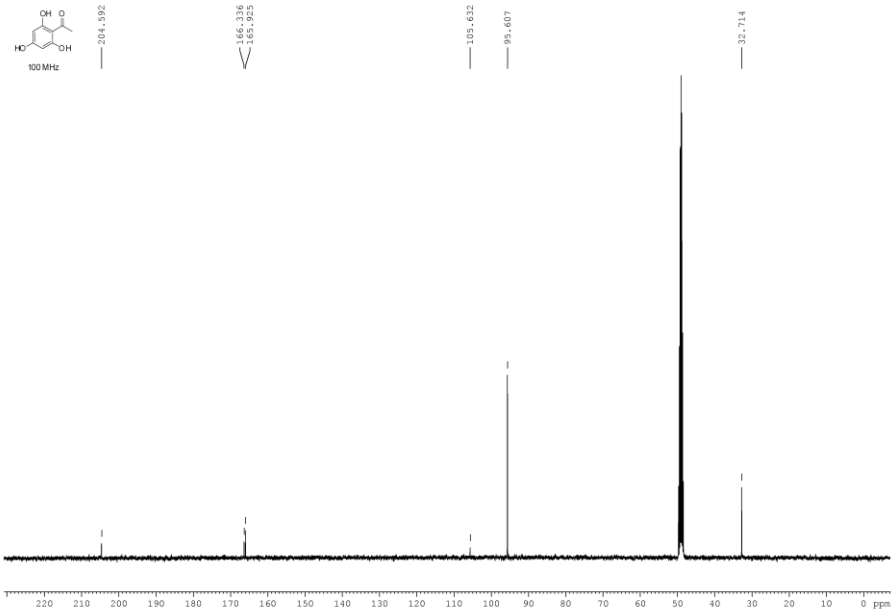
A. NMR spectra of compounds

1-(2,4,6-trihydroxyphenyl)ethanone, **phloroacetophenone** (**44**)

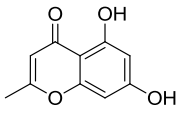


44

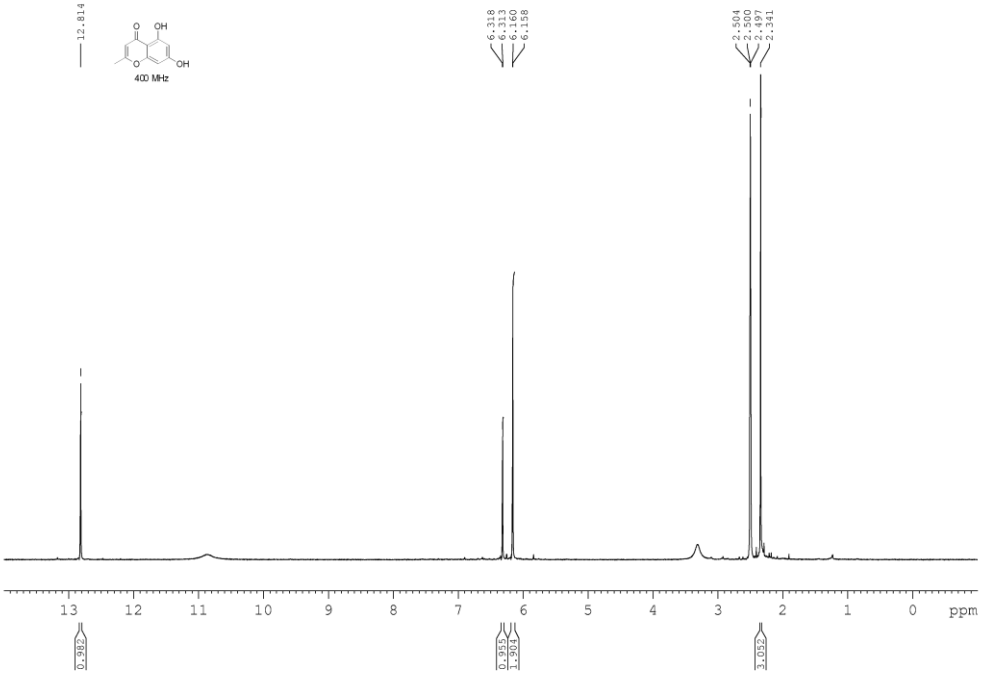


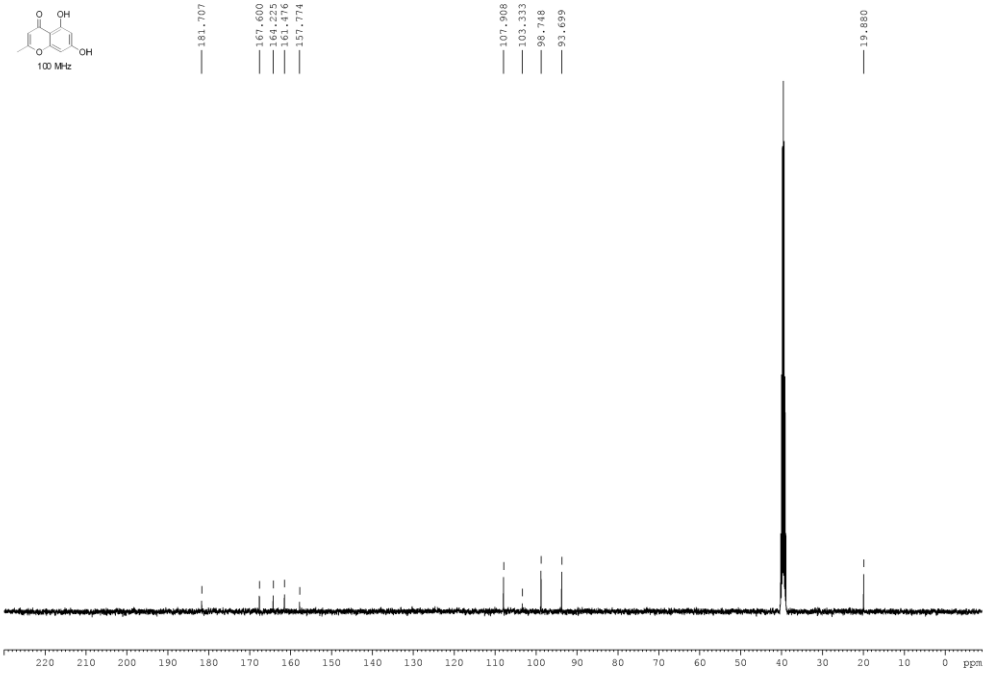


5,7-dihydroxy-2-methyl-4*H*-chromen-4-one , **noreugenin** (**43**)

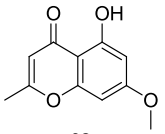


43

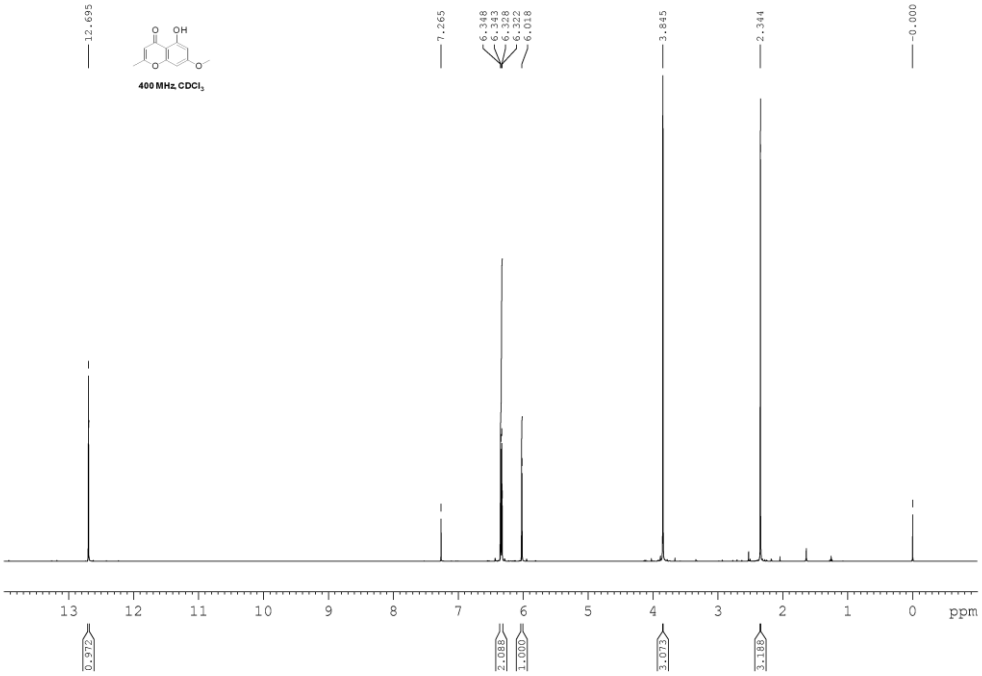


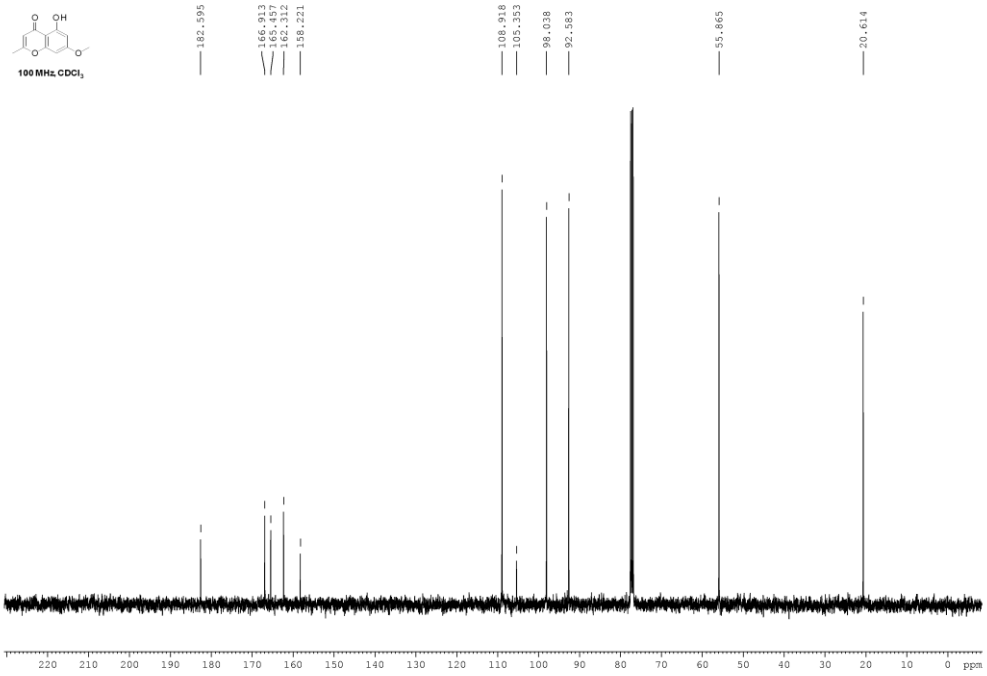


5-hydroxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**68**)

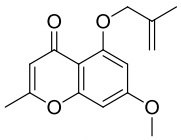


68

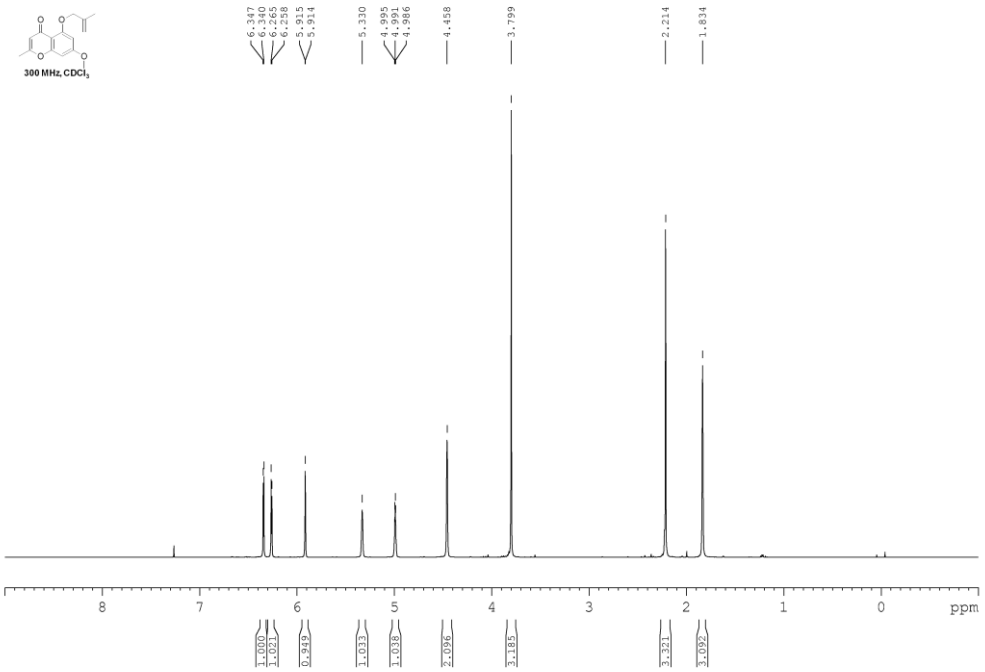


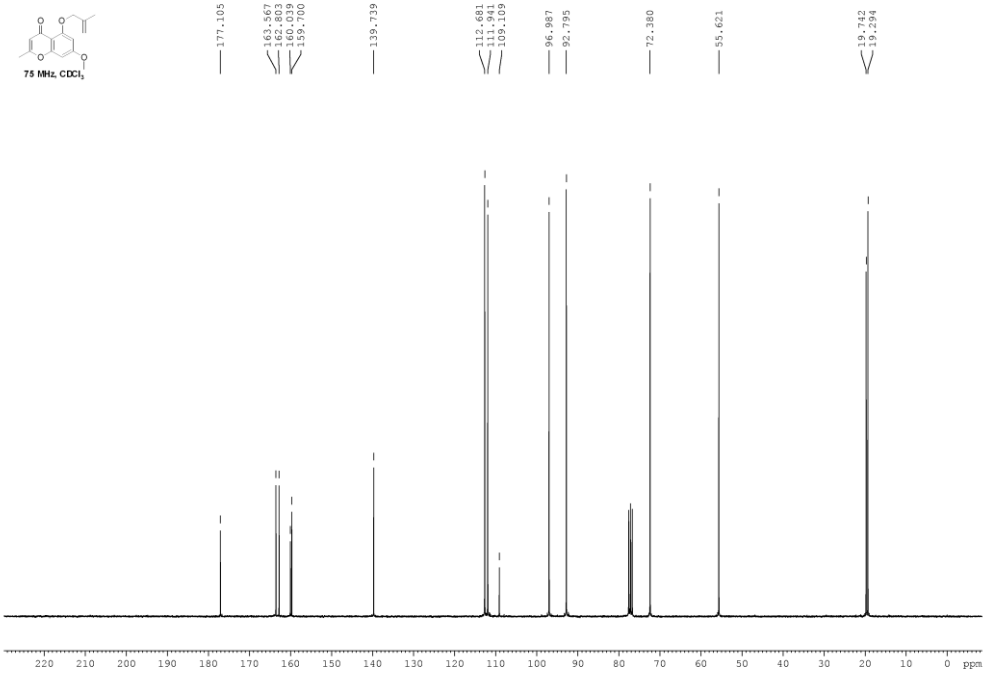


5-(2′-methylallyl)oxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**70**)

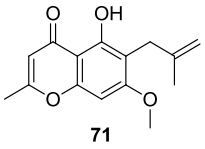


70

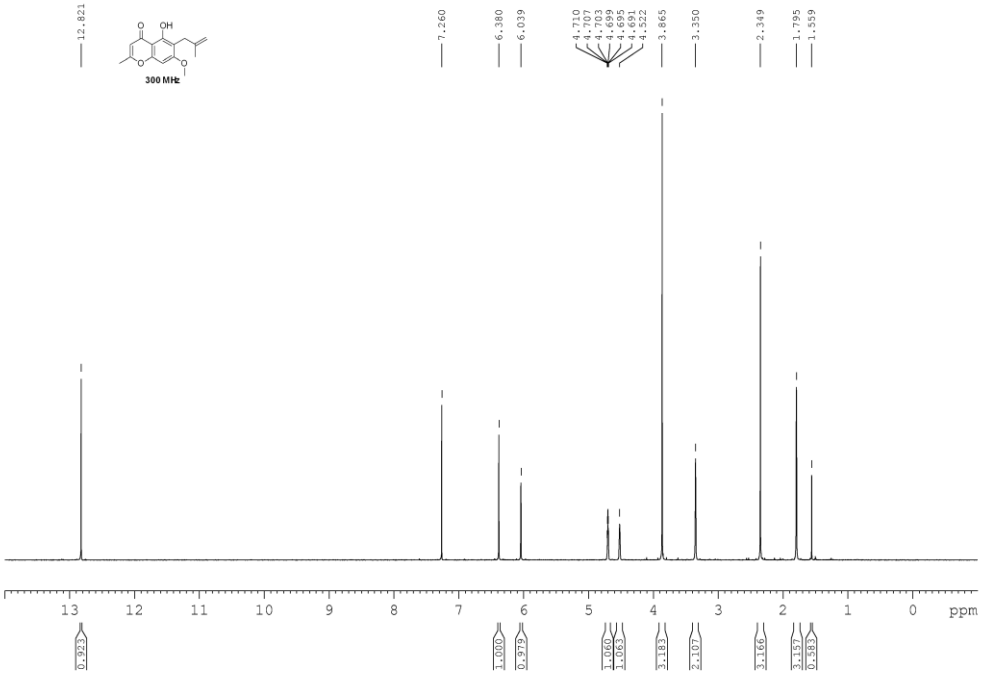


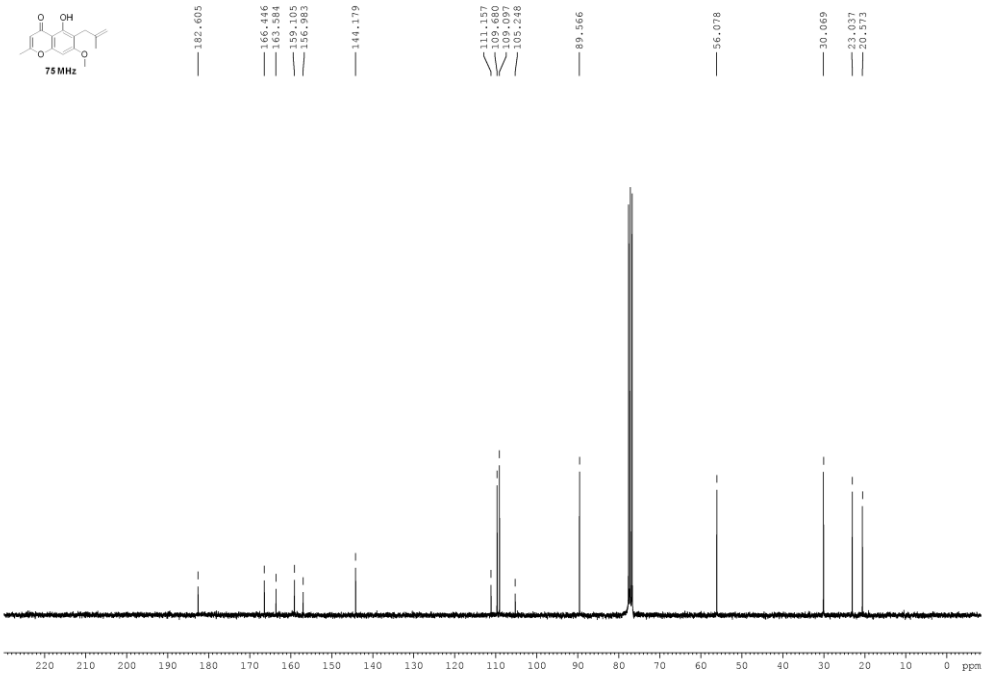


5-hydroxy-7-methoxy-2-methyl-6-(2′-methylallyl)-4*H*-chromen-4-one (**71**)

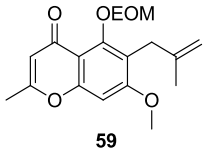


71

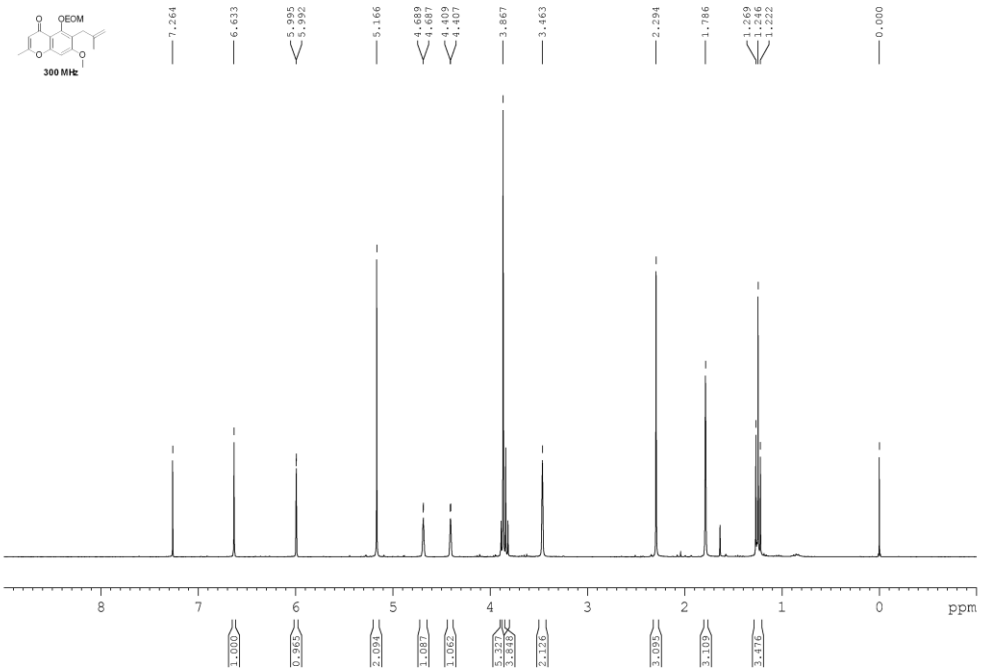


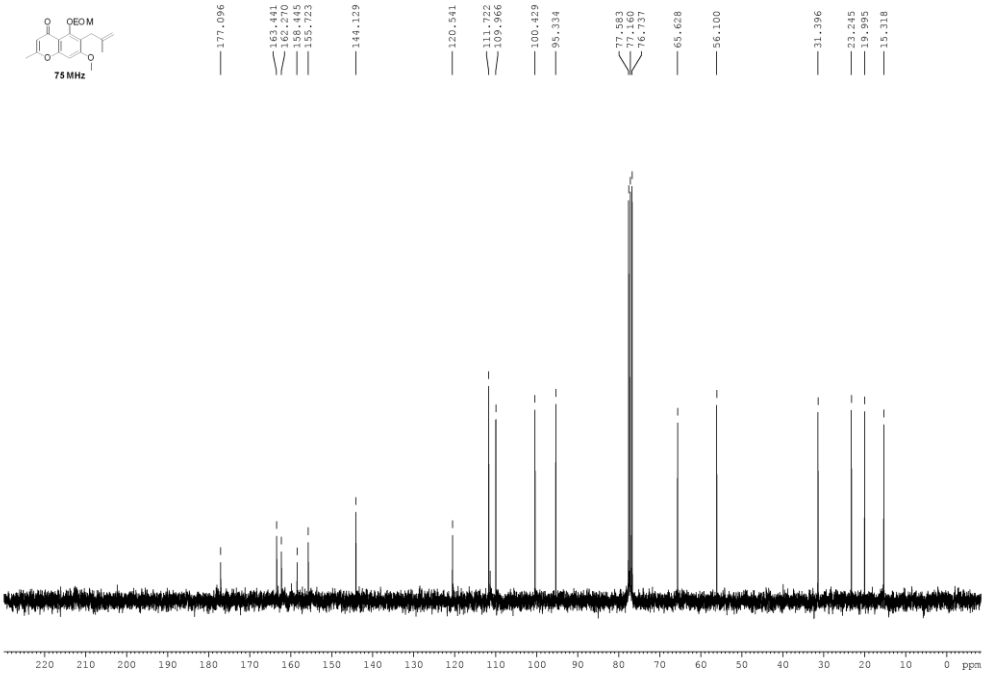


5-(ethoxymethoxy)-7-methoxy-2-methyl-6-(2′-methylallyl)-4*H*-chromen-4-one (**59**)

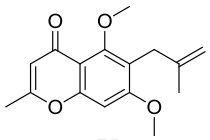


59

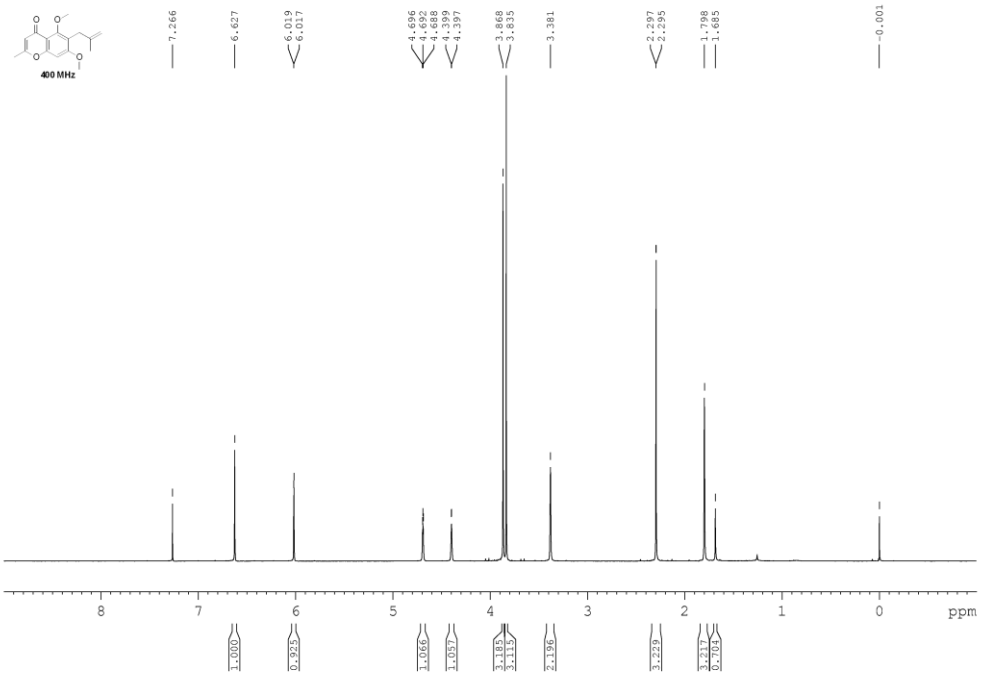


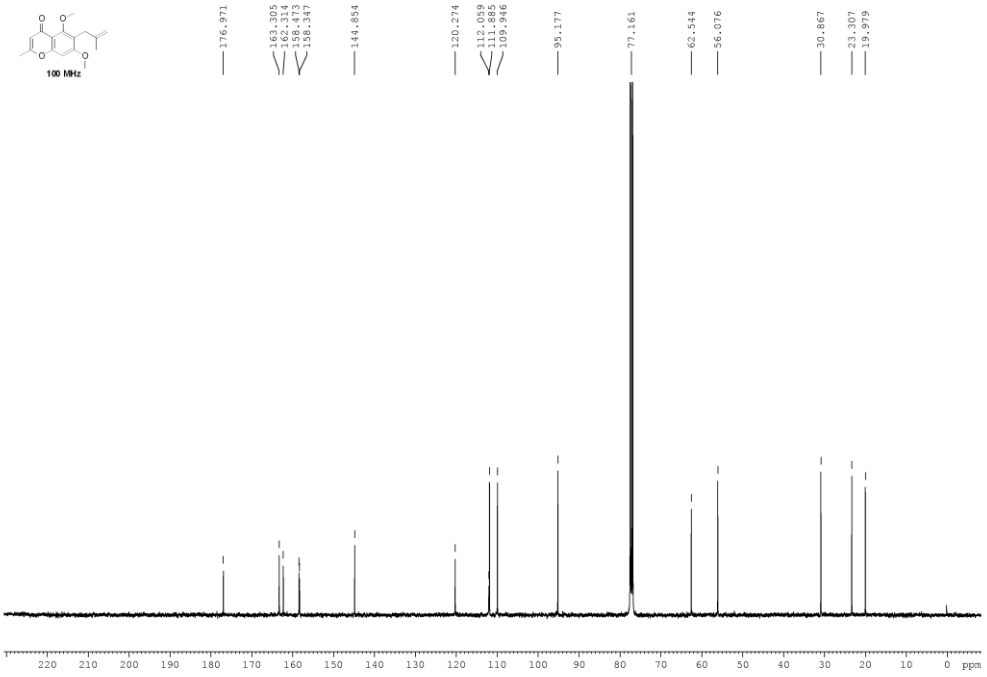


5,7-dimethoxy-2-methyl-6-(2′-methylallyl)-4*H*-chromen-4-one (**75**)

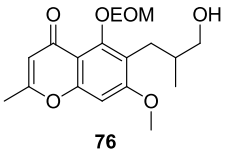


75

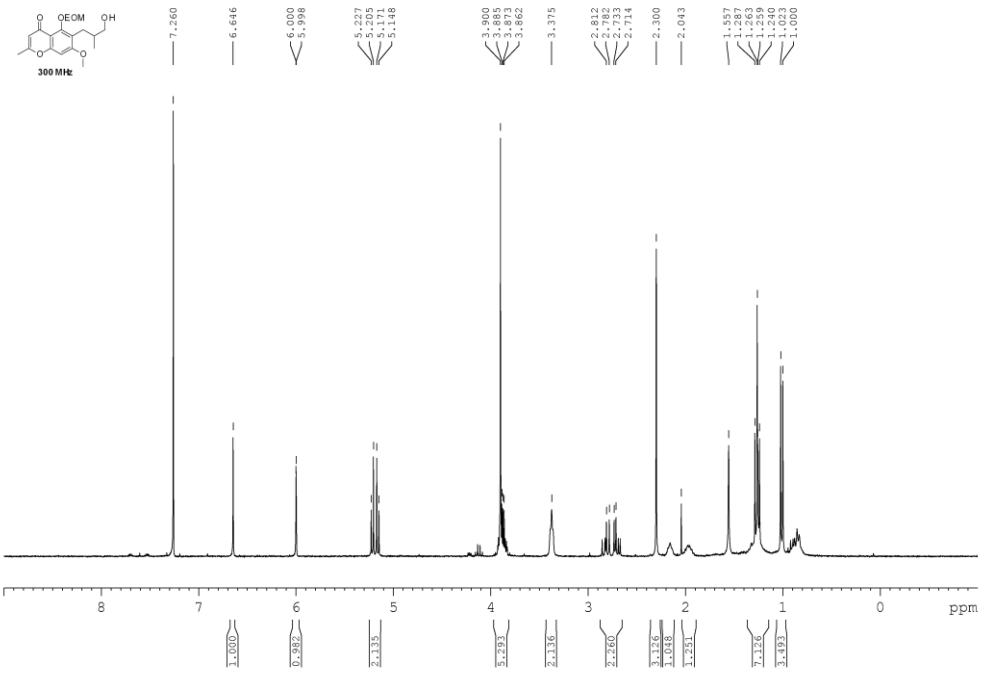


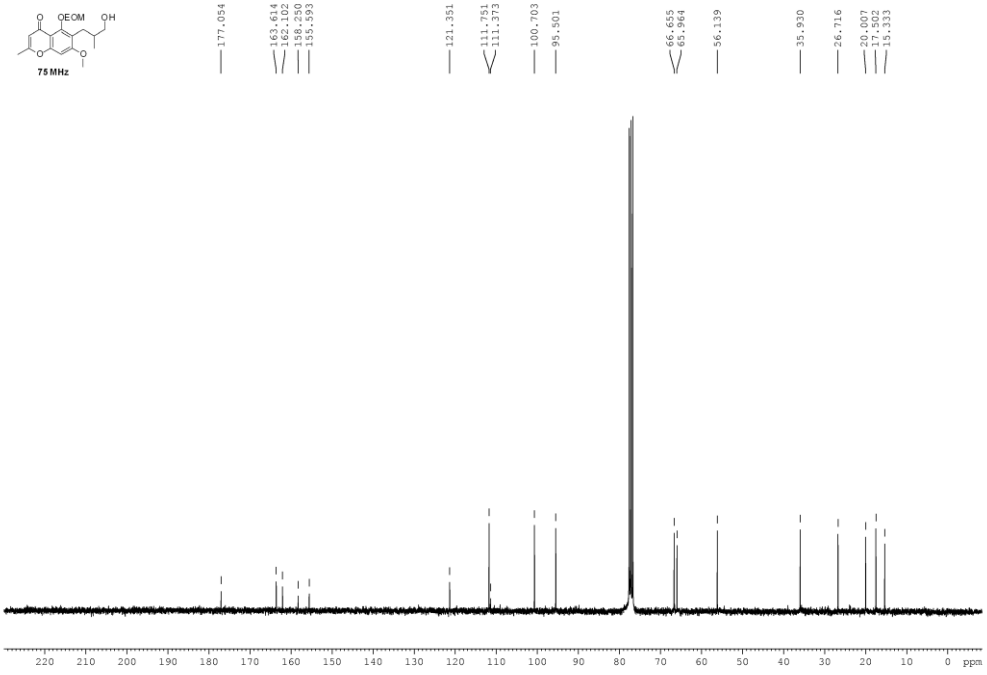


5-(ethoxymethoxy)-6-(3′-hydroxy-2′-methylpropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**76**)

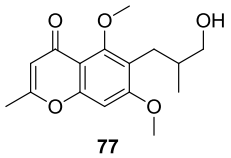


76

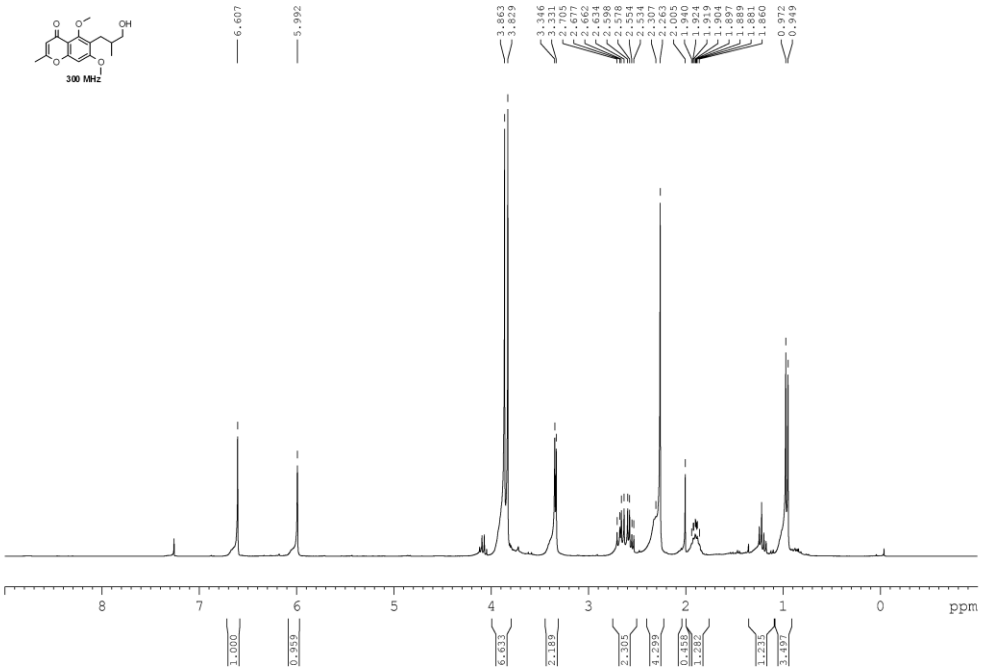


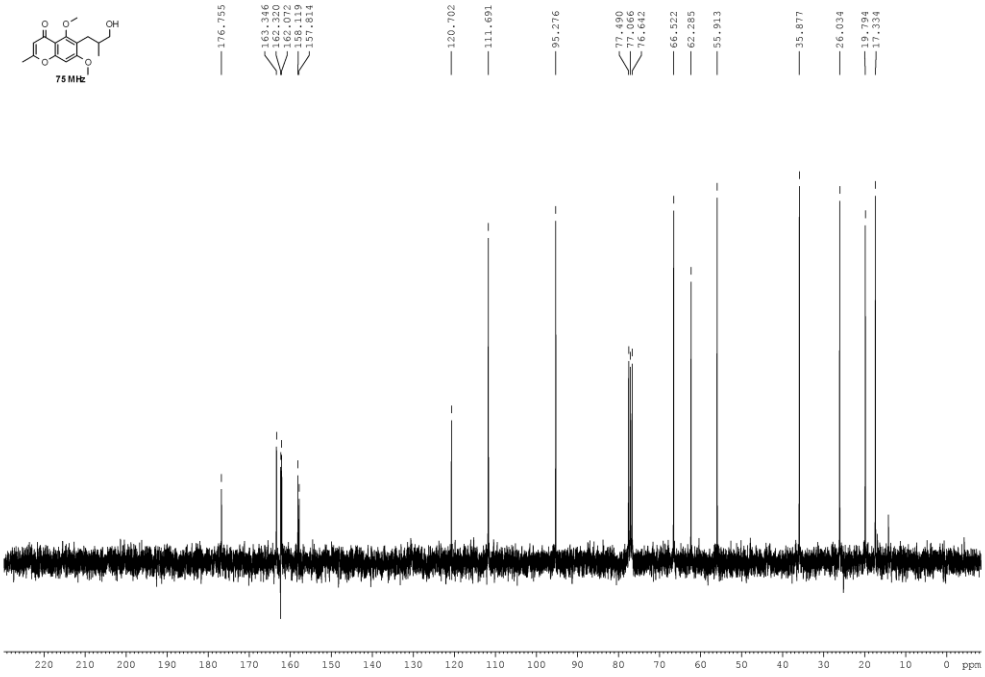


6-(3′-hydroxy-2′-methylpropyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**77**)



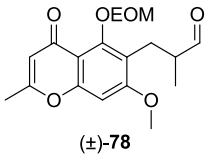
77



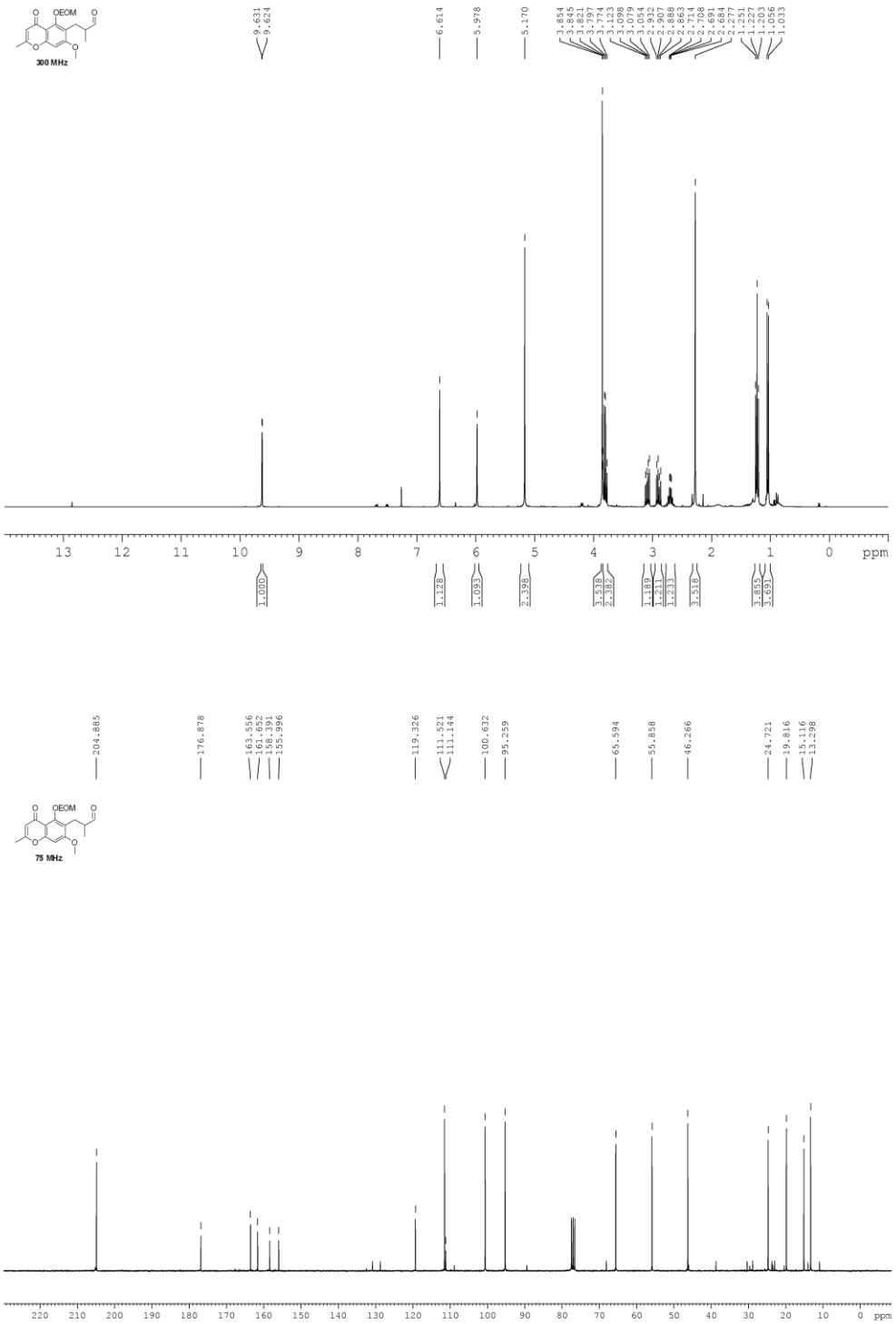


1′-(5-(ethoxymethoxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)-2-methylpropan-3-′al

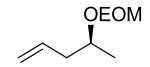
(±)-**78**



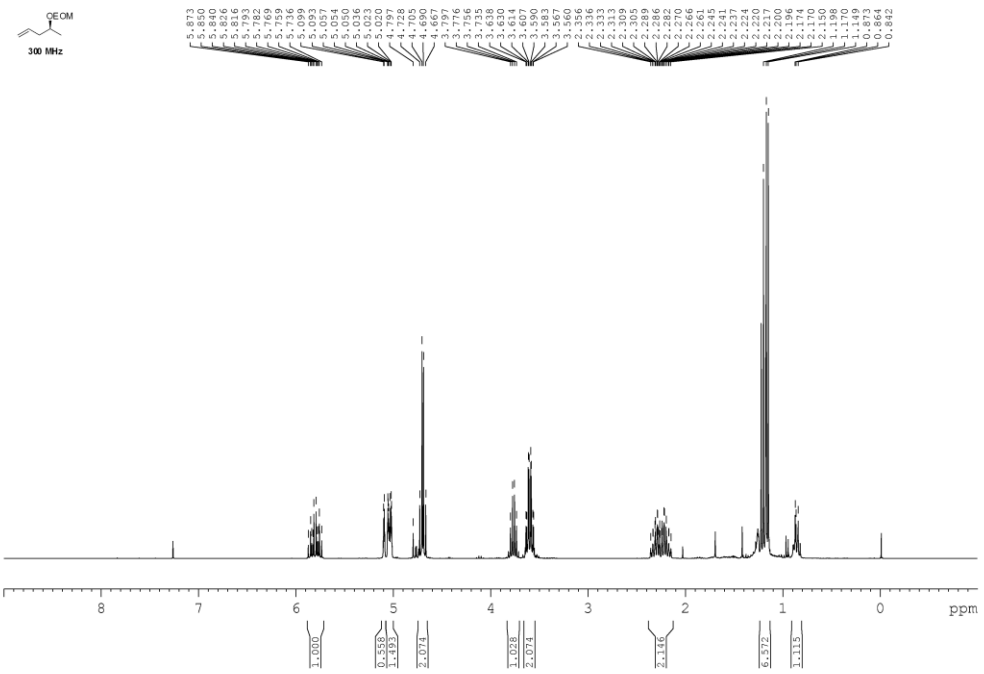
(±)-**78**

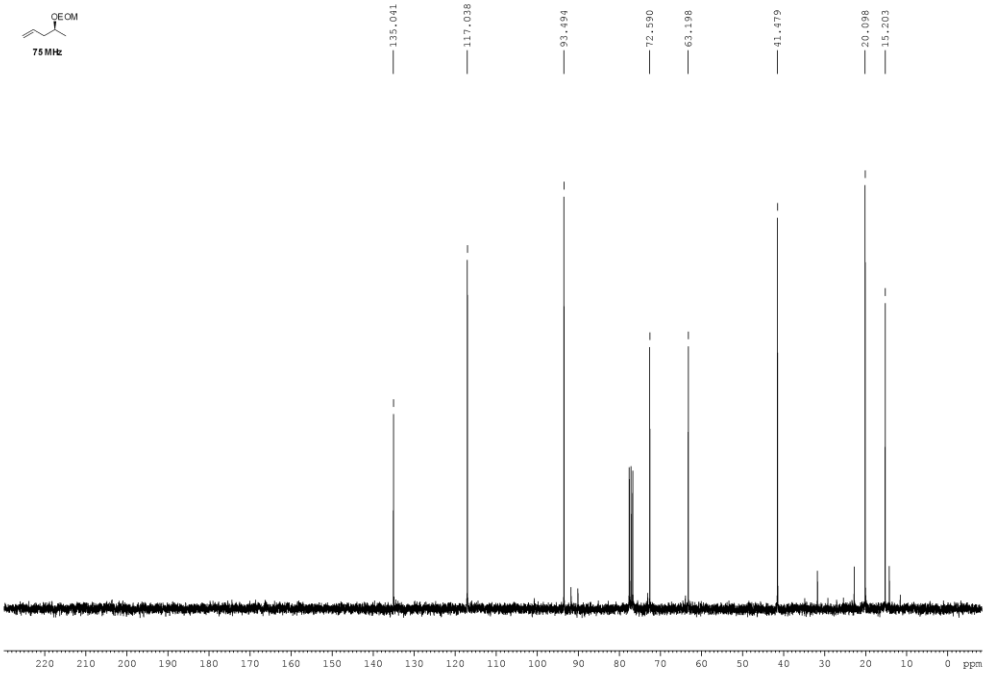


(*S*)-4-(ethoxymethoxy)pent-1-ene (*S*)-**81**

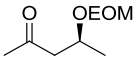


(*S*)-**81**

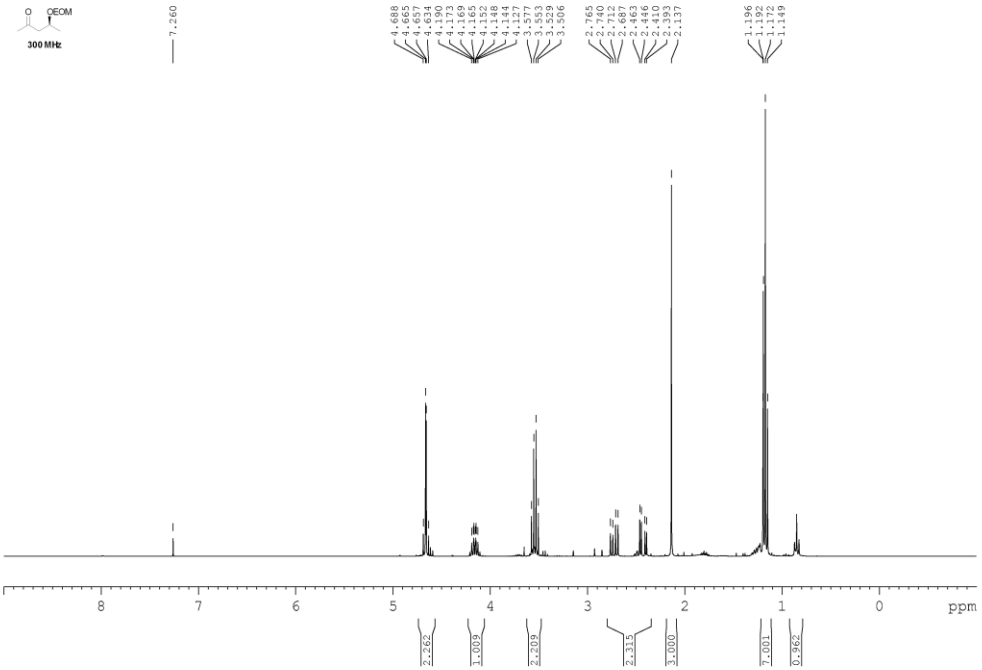


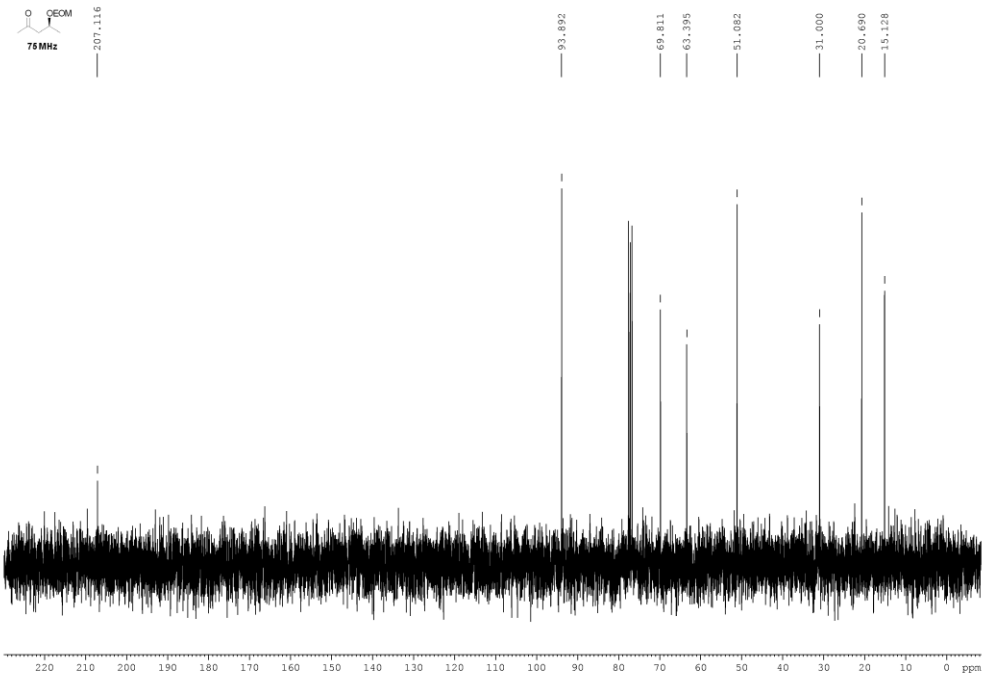


(*S*)-4-(ethoxymethoxy)pentan-2-one (*S*)-**79**

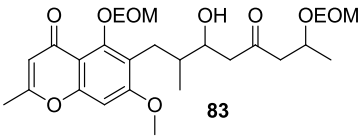


(*S*)-**79**

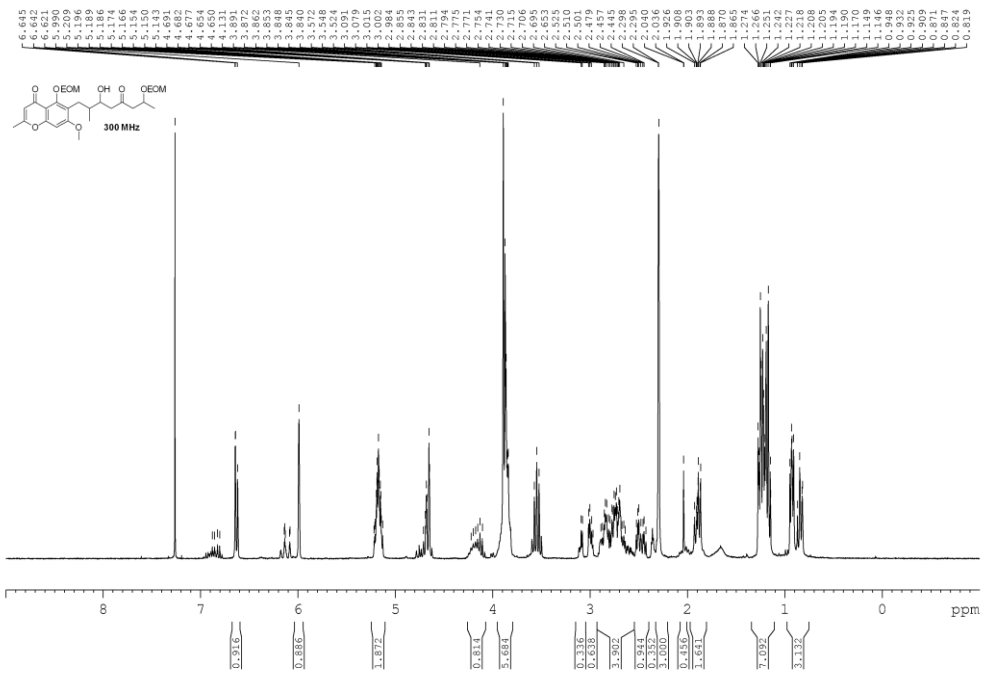


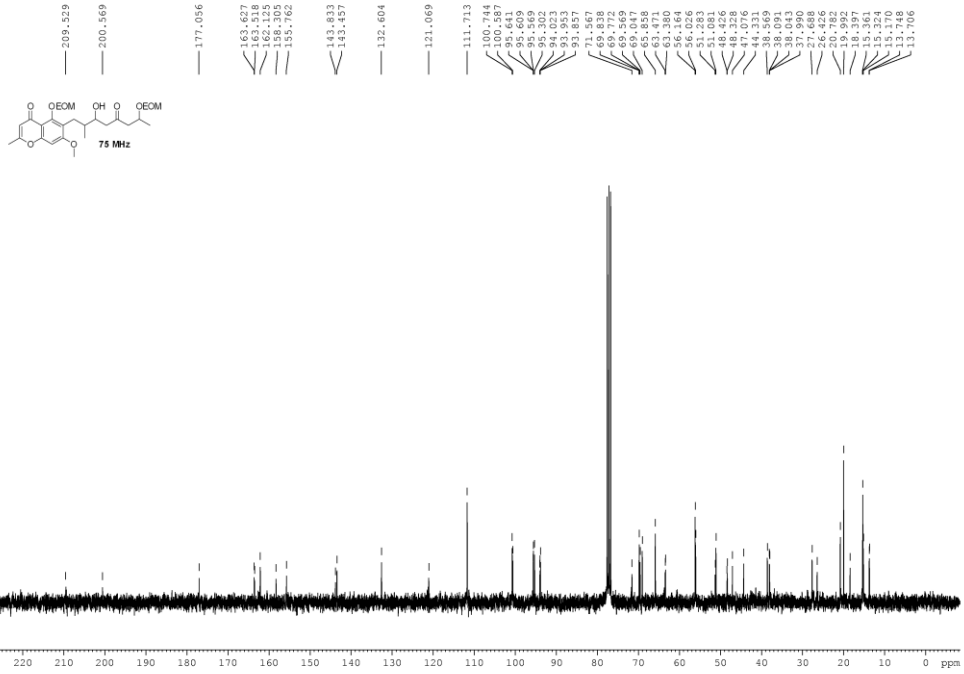


5-(ethoxymethoxy)-6-(7′-(ethoxymethoxy)-3′-hydroxy-2′-methyl-5′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**83**)

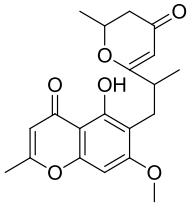


83

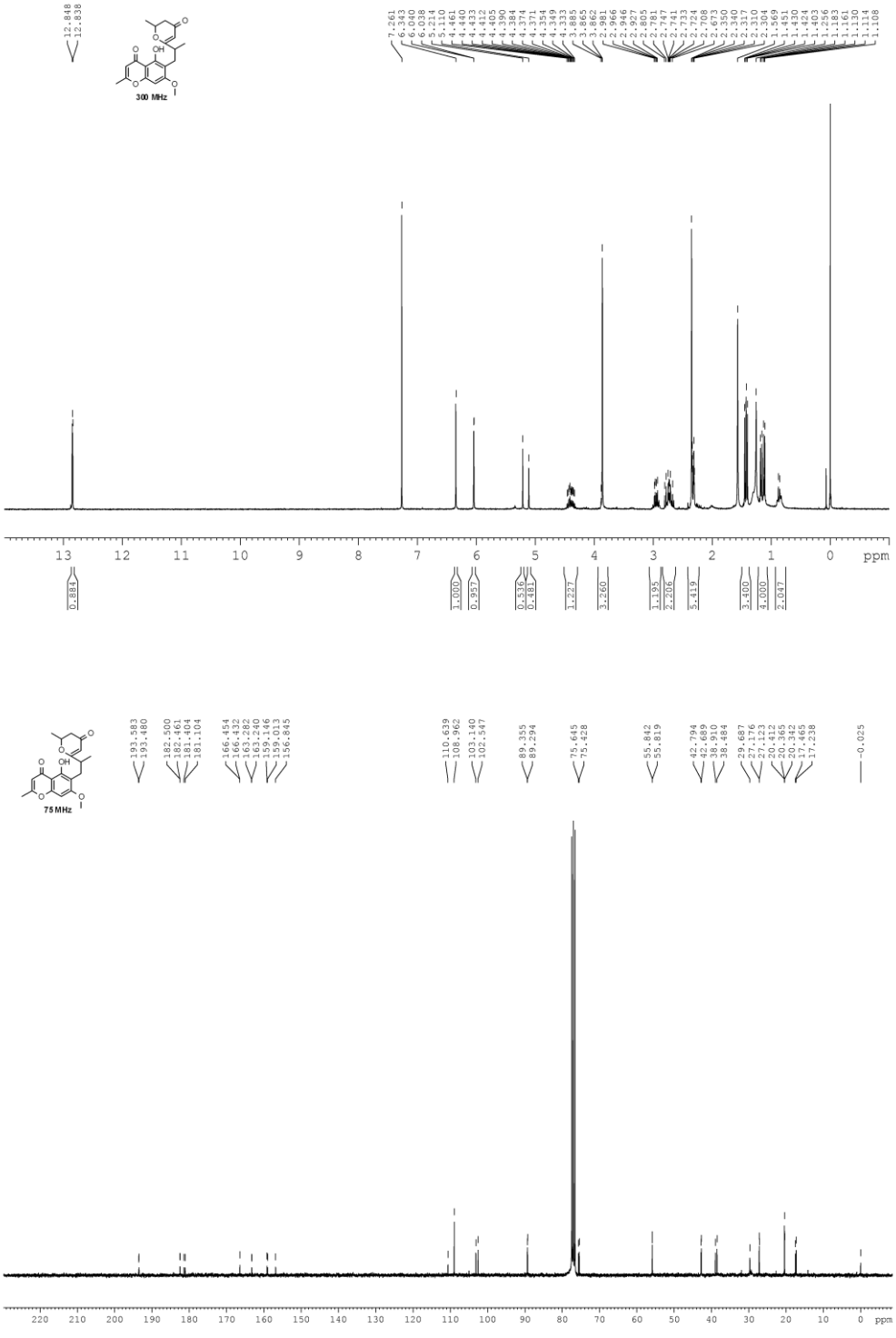




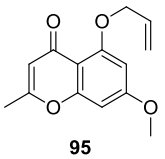
(±)–chaetoquadrin G and H (±)-**85**



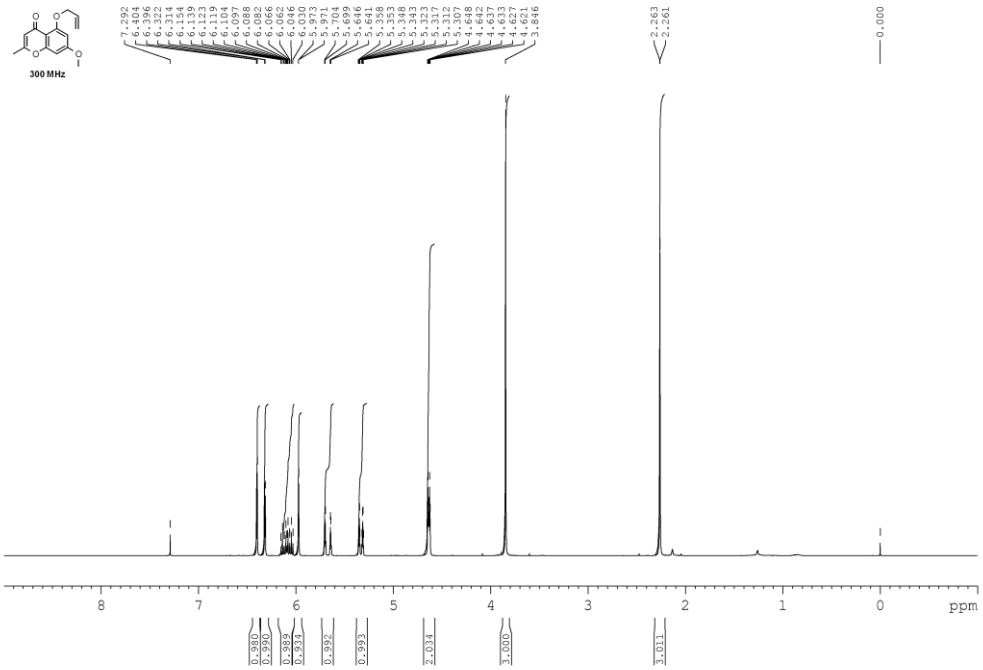
(±)-**85**

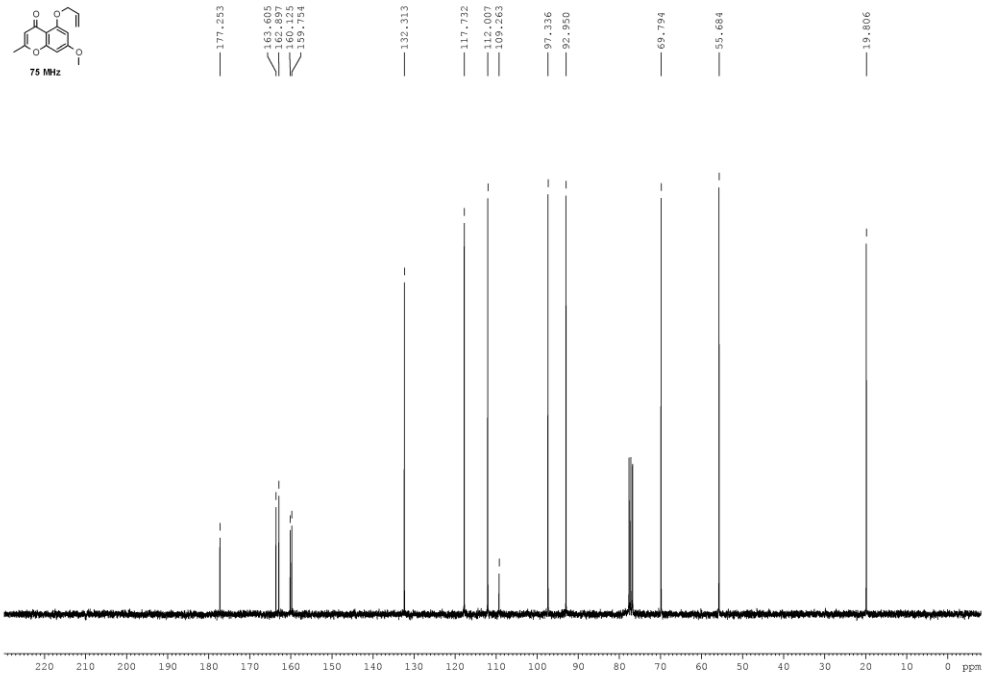


5-(allyloxy)-7-methoxy-2-methyl-4*H*-chromen-4-one (**95**)

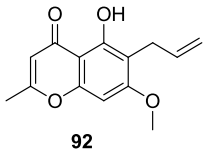


95

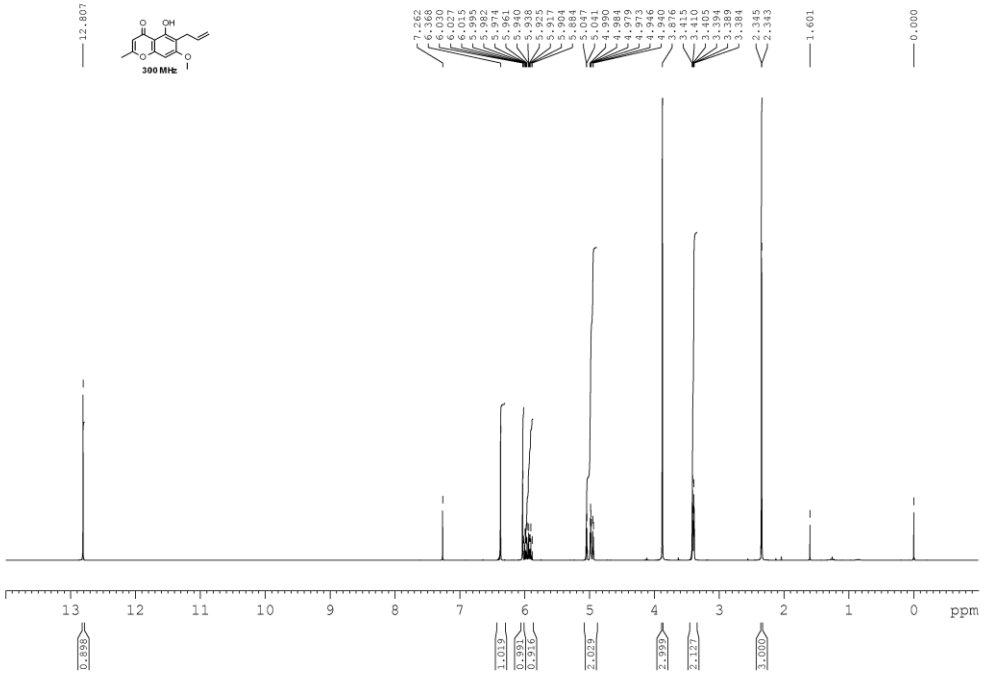


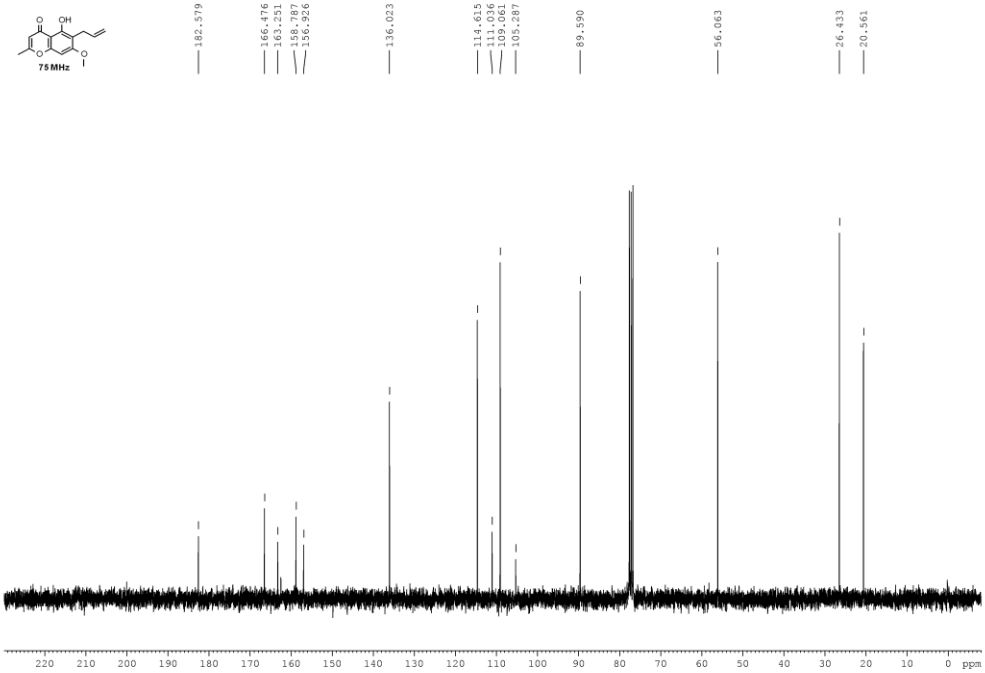


6-allyl-5-hydroxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**92**)

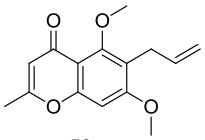


92

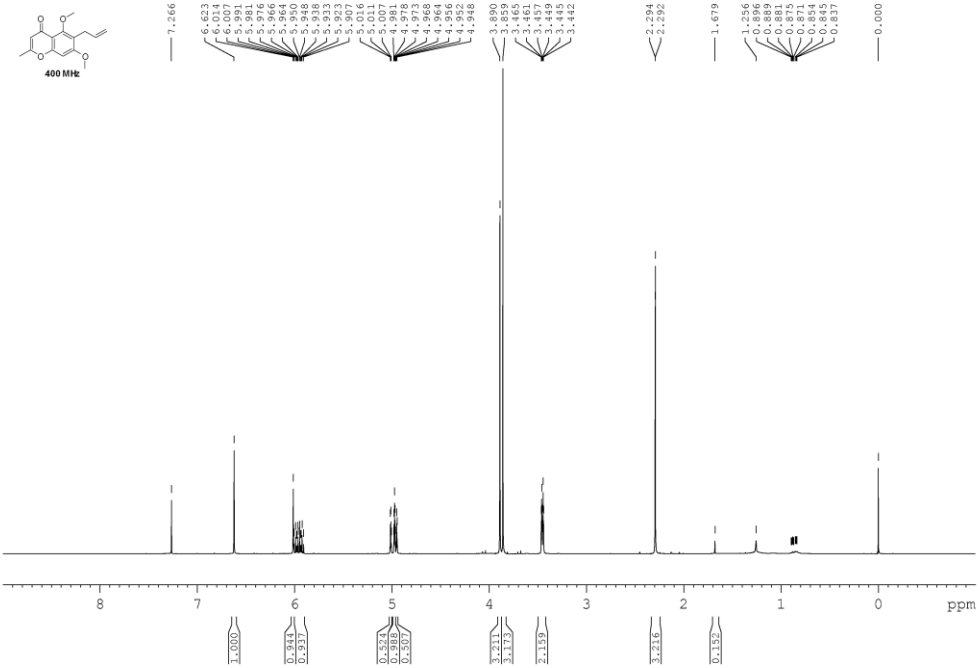


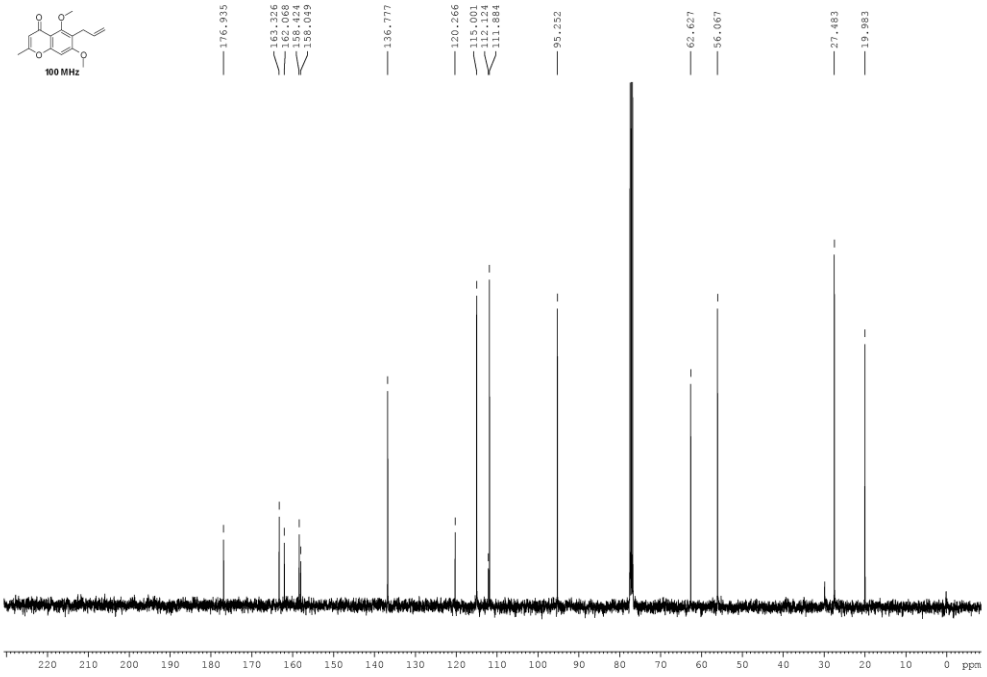


6-allyl-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**56**)

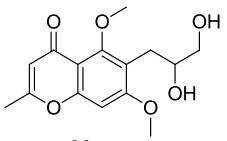


56

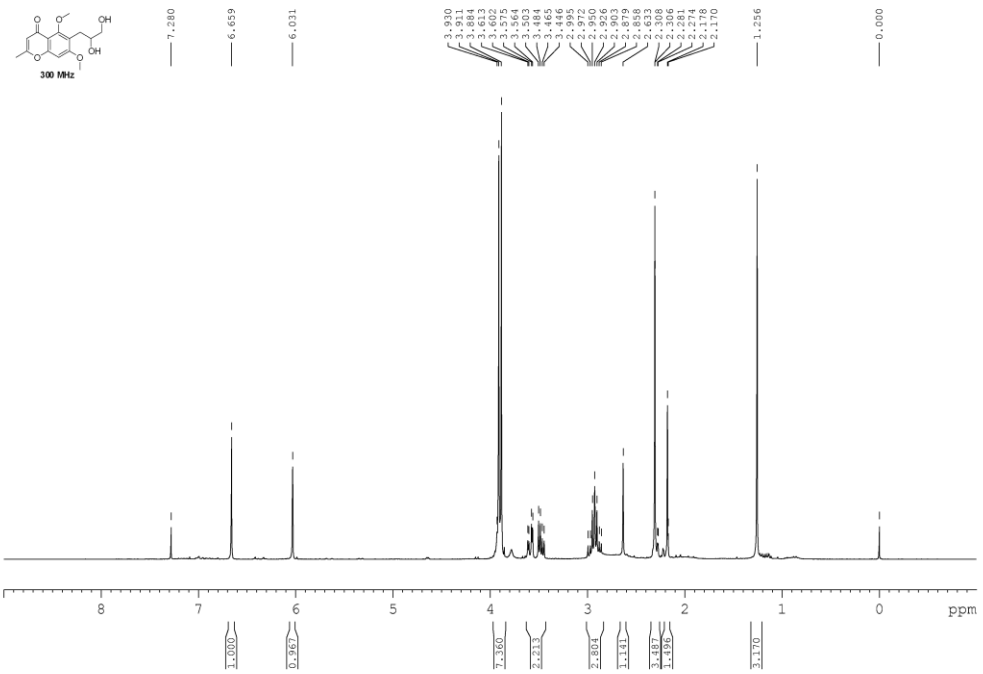


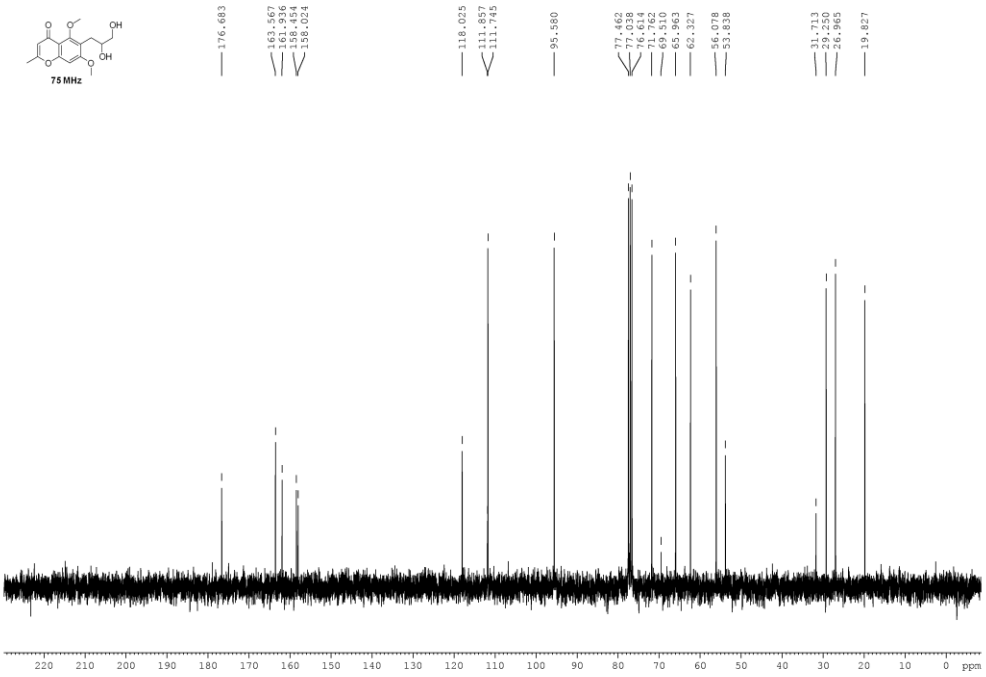


6-(2′,3′-dihydroxypropyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**96**)

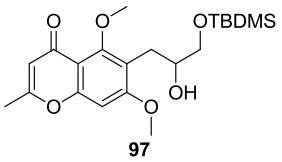


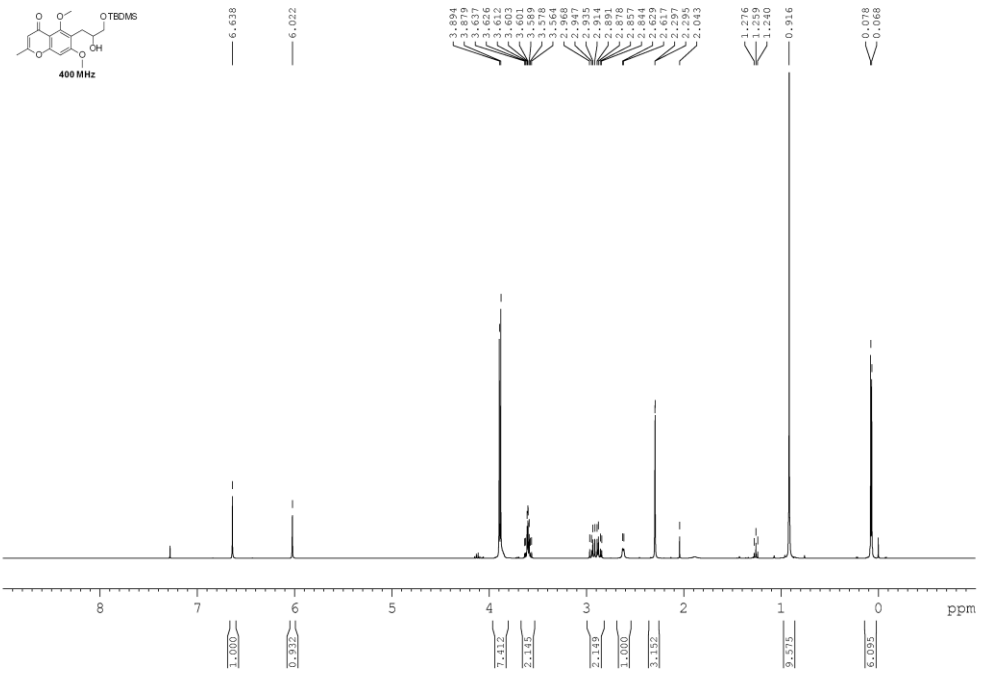
96

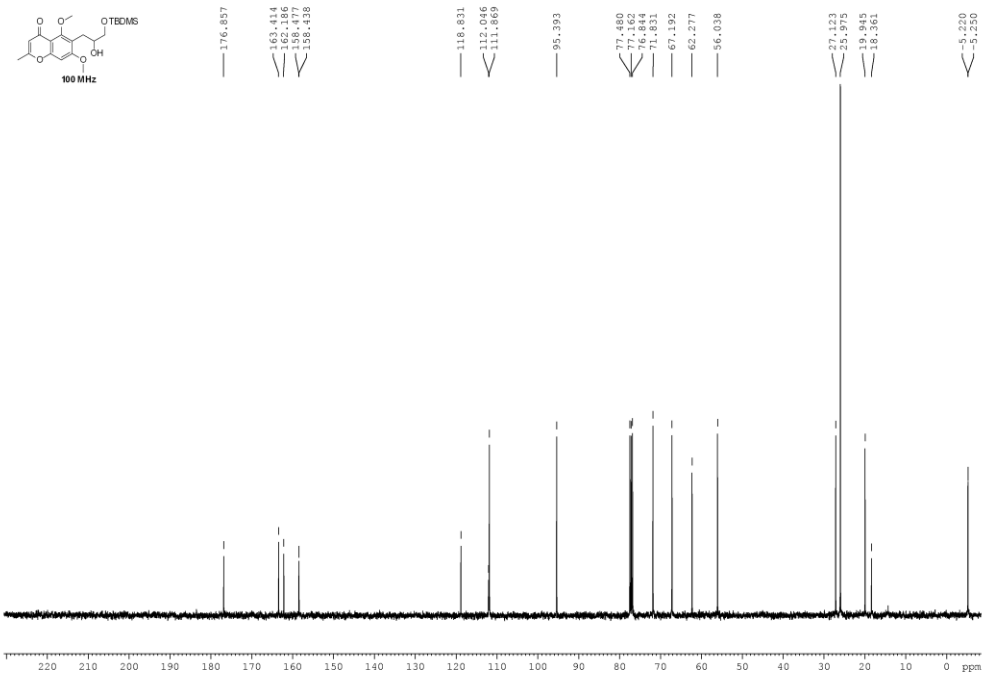




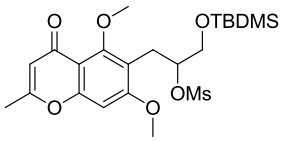
6-(3′-((*tert*-butyldimethylsilyl)oxy)-2′-hydroxypropyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**97**)



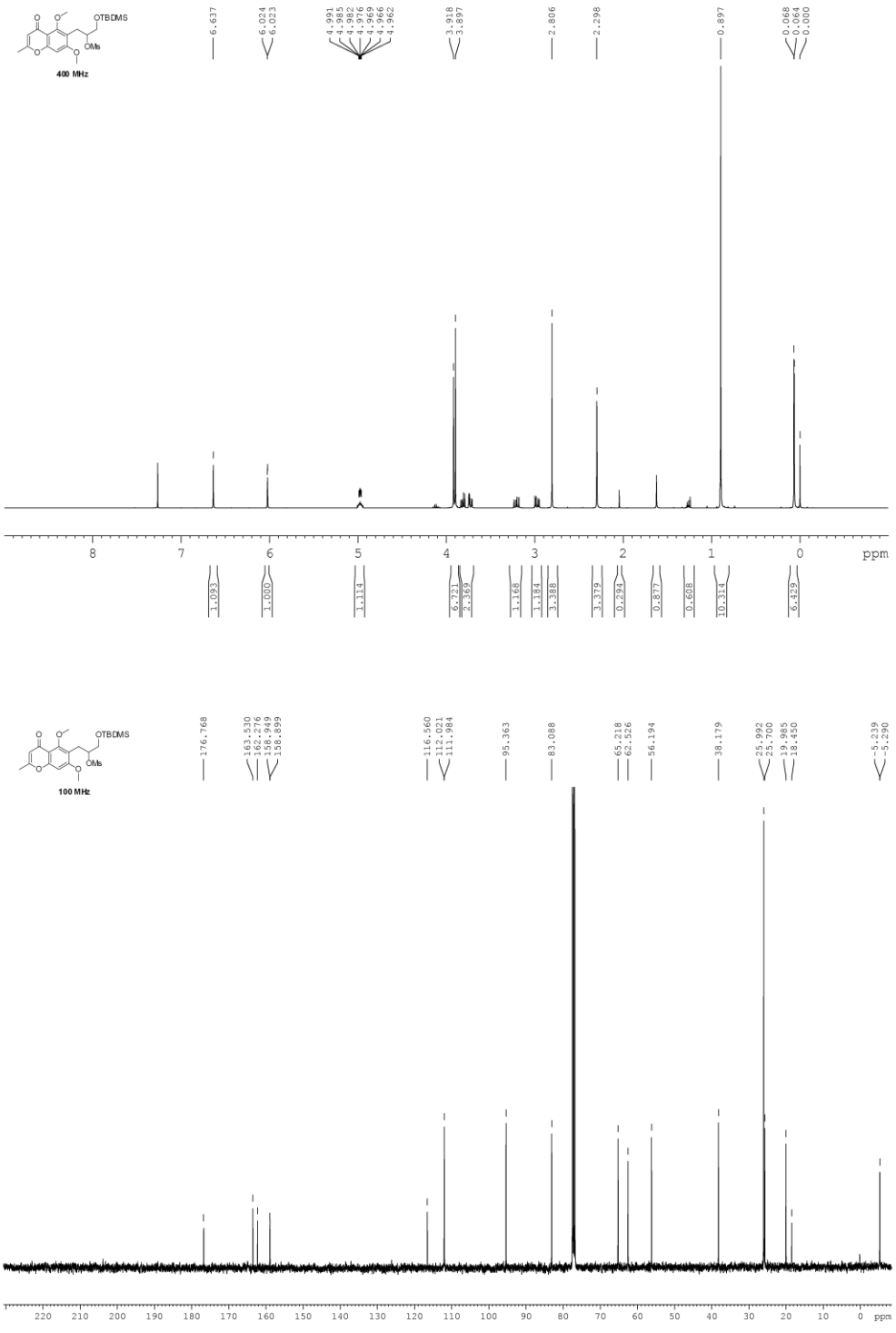




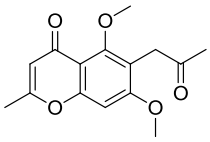
3′-((*tert*-butyldimethylsilyl)oxy)-1′-(5,7-dimethoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)propan-2′-yl methanesulfonate (**98**)



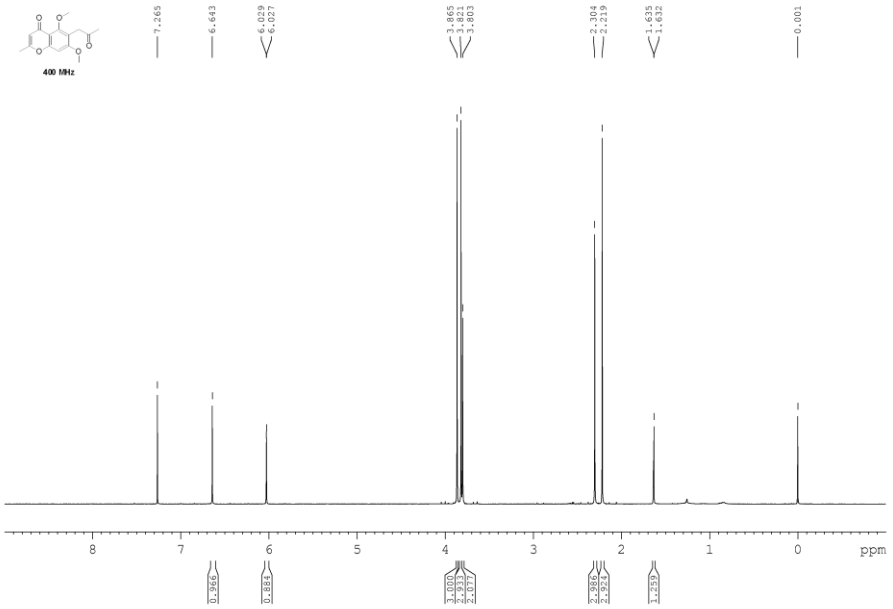
98

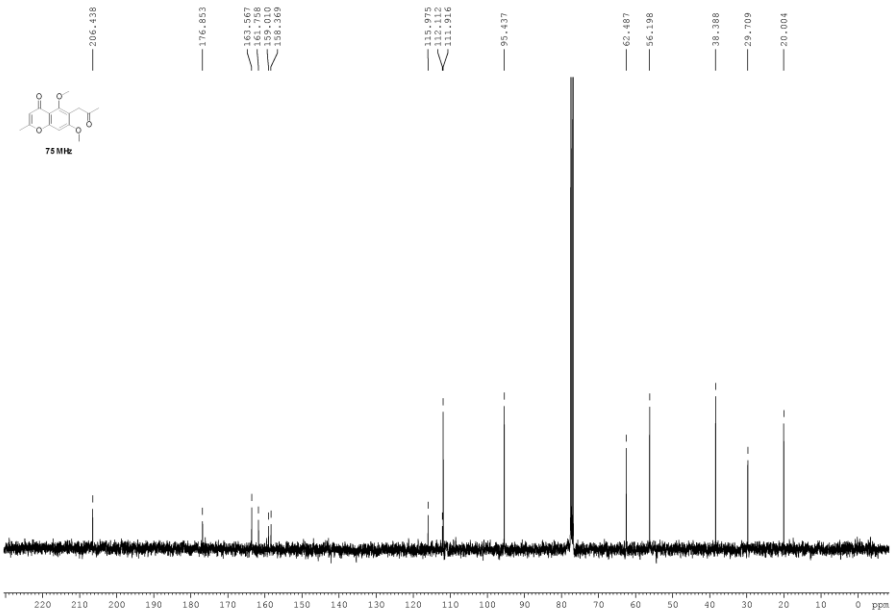


5,7-dimethoxy-2-methyl-6-(2′-oxopropyl)-4*H*-chromen-4-one (**102**)

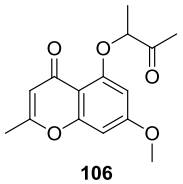


102

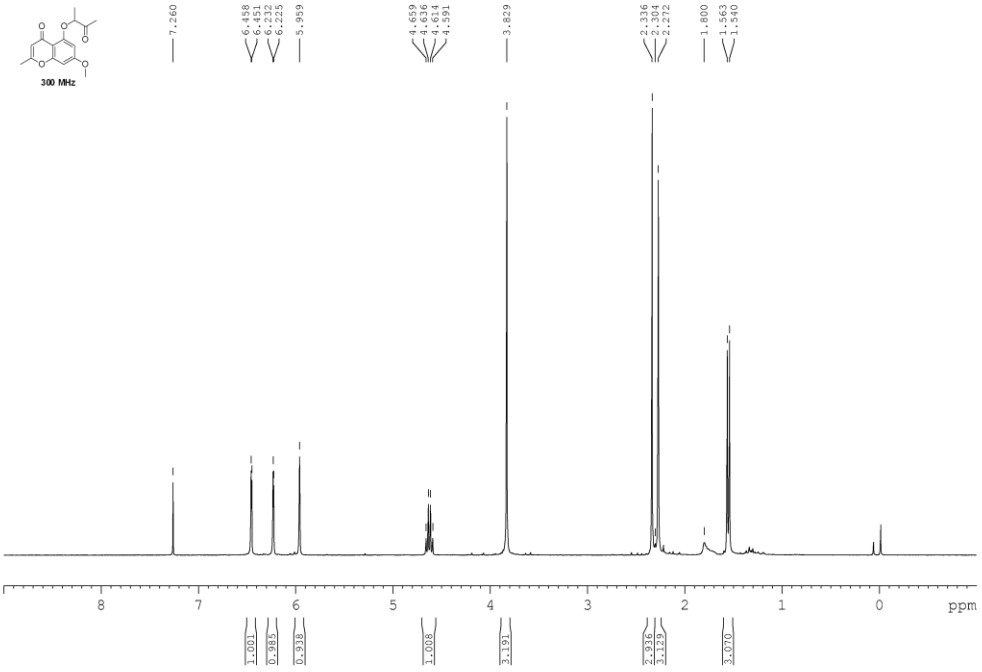


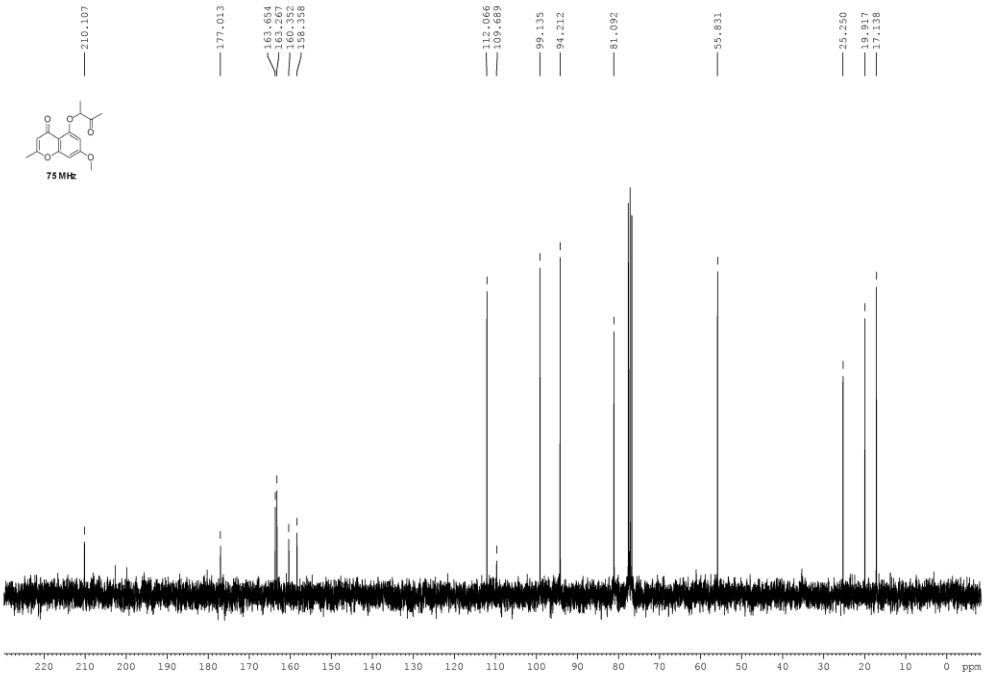


7-methoxy-2-methyl-5-((3′-oxobutan-2′-yl)oxy)-4*H*-chromen-4-one (**106**)

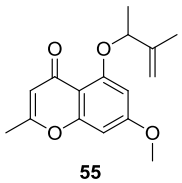


106

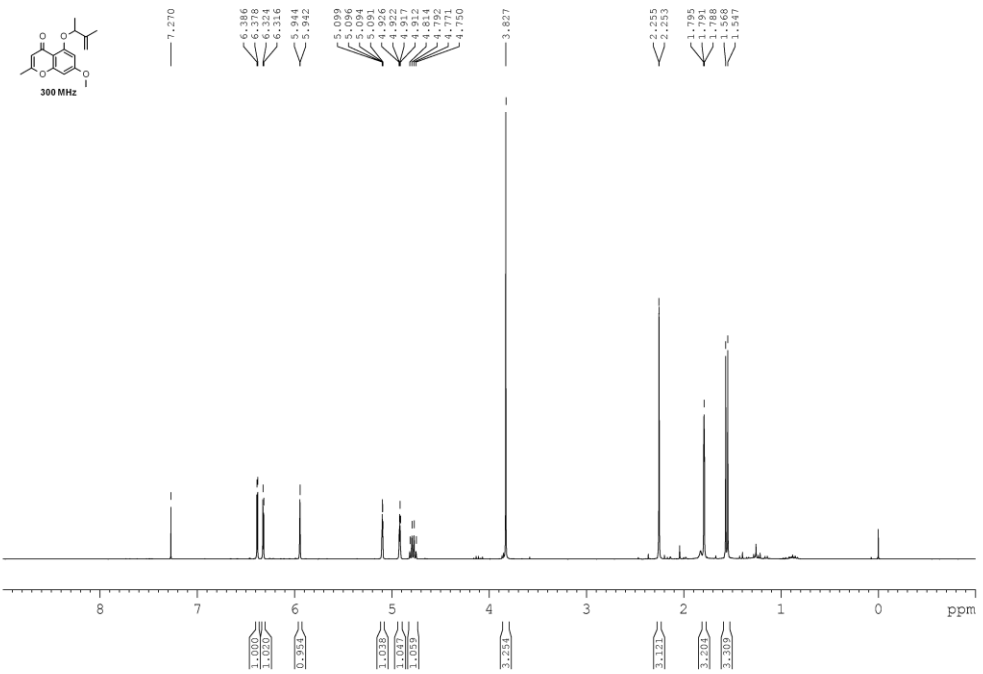


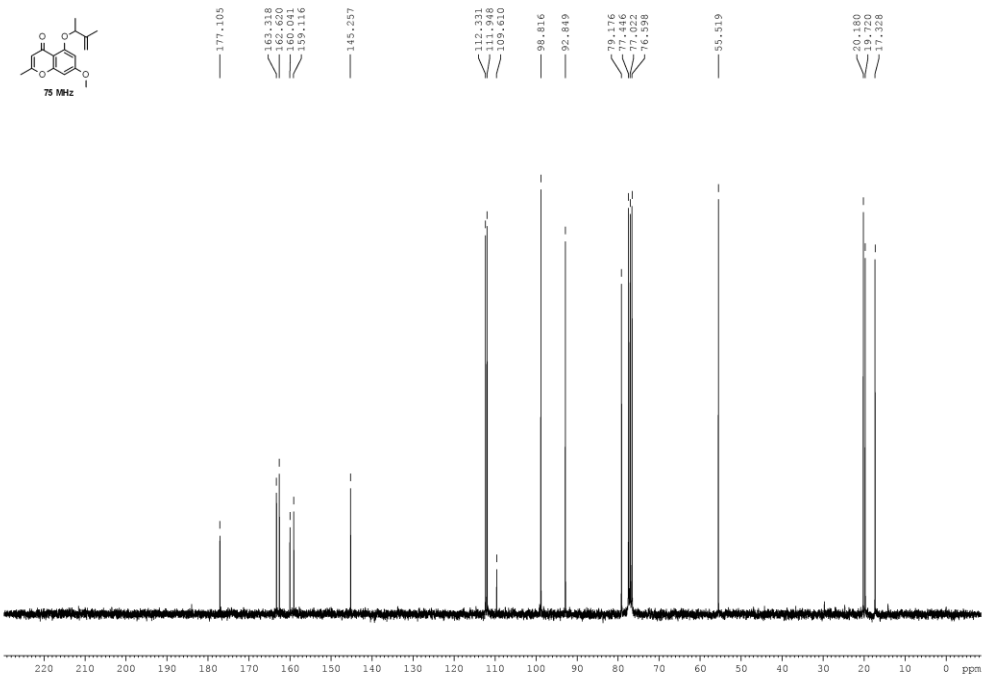


7-methoxy-2-methyl-5-((3′-methylbut-3′-en-2′-yl)oxy)-4*H*-chromen-4-one (**55**)

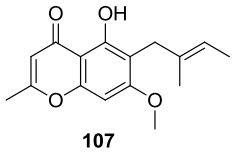


55

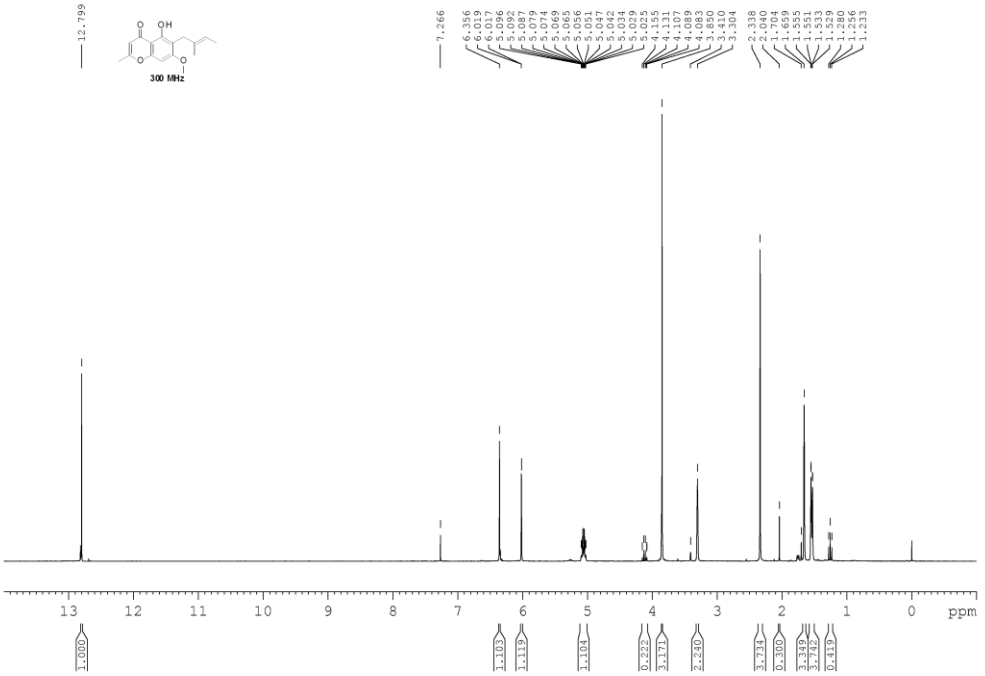


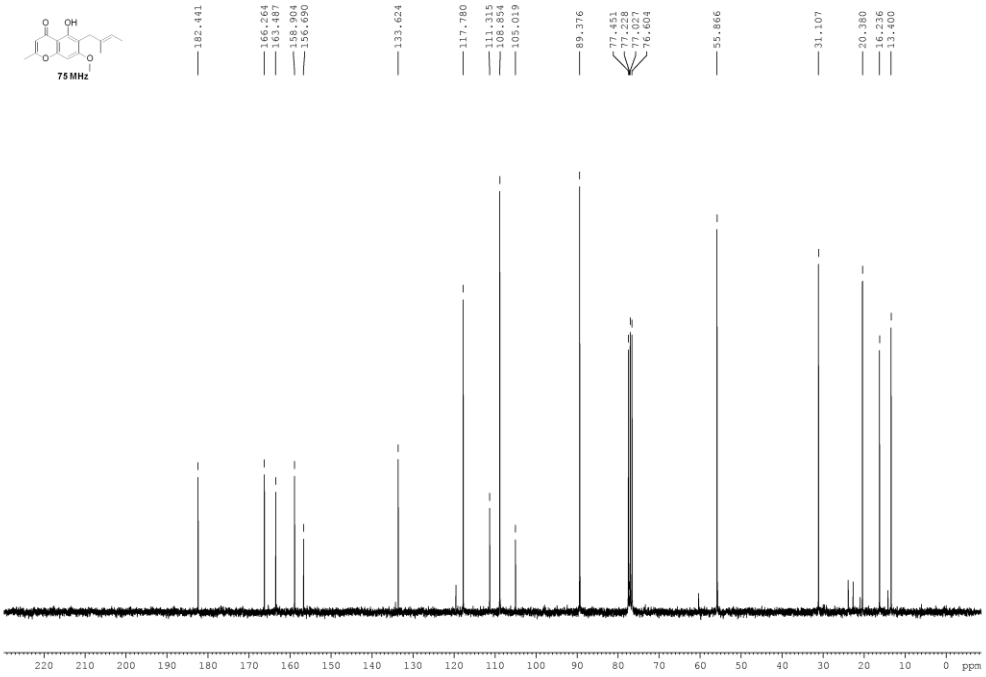


5-hydroxy-7-methoxy-2-methyl-6-(2′-methylbut-2′-en-1′-yl)-4*H*-chromen-4-one (**107**)

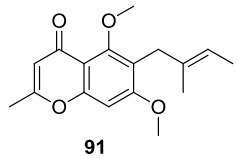


107

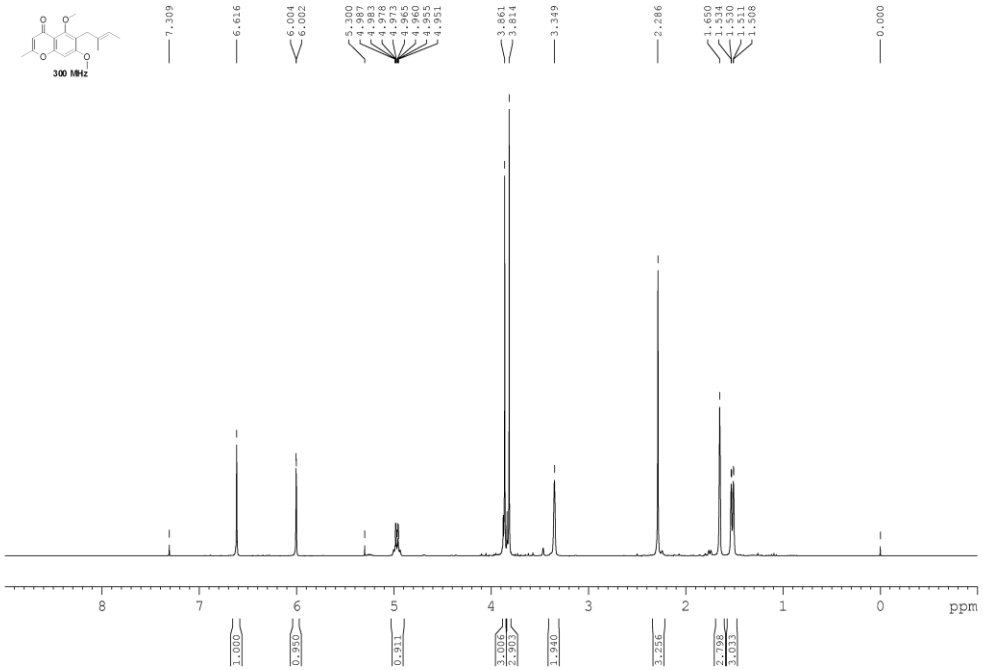


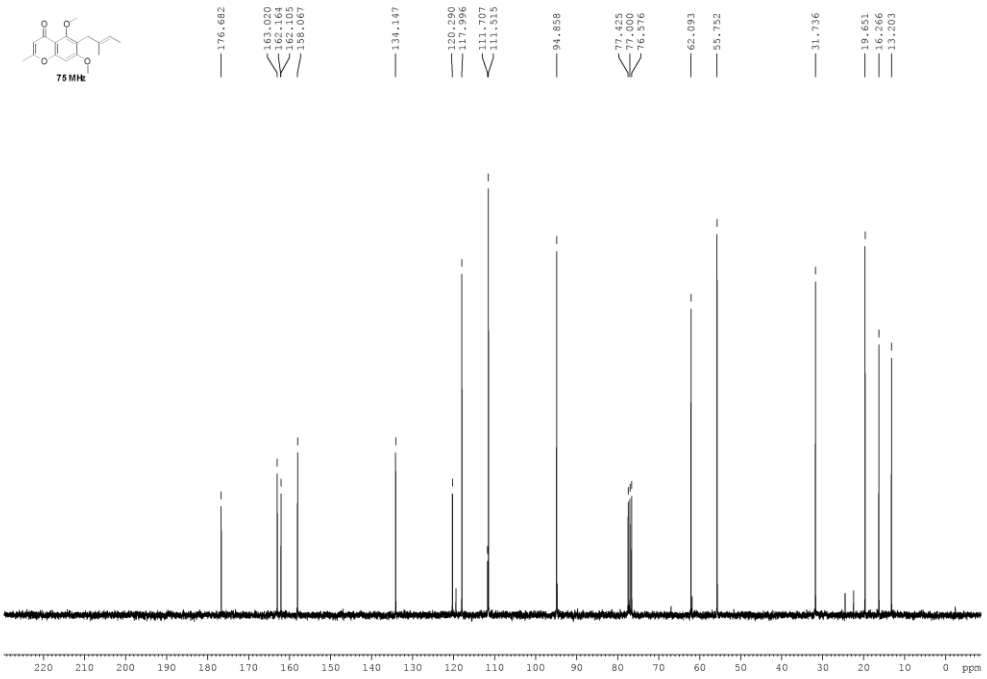


5,7-dimethoxy-2-methyl-6-(2′-methylbut-2′-en-1′-yl)-4*H*-chromen-4-one (**91**)

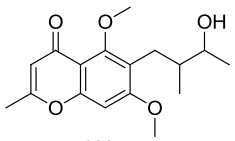


91

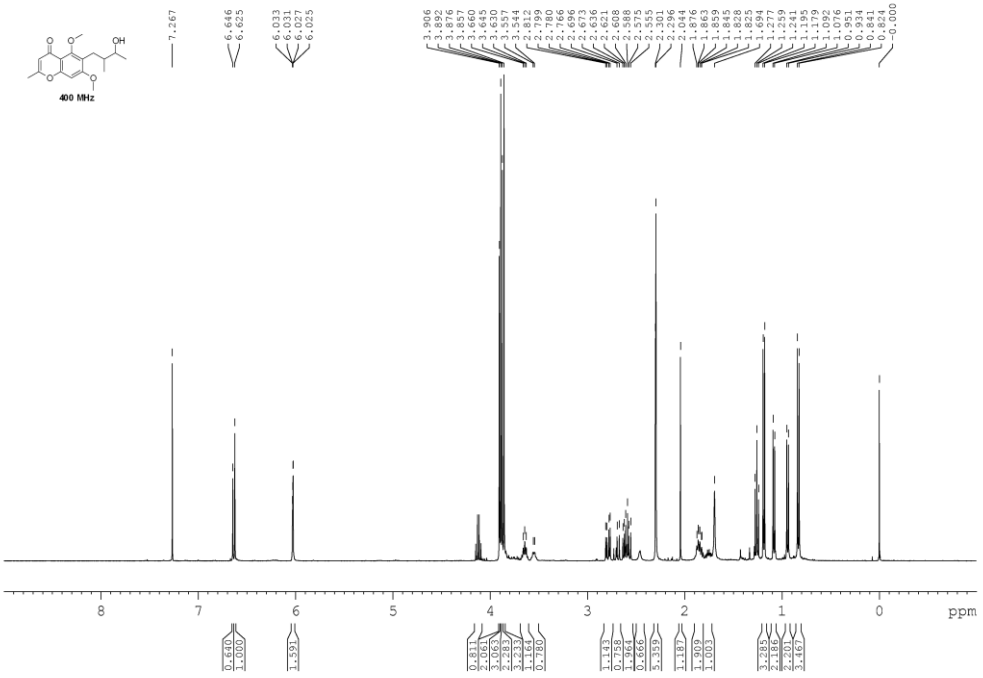


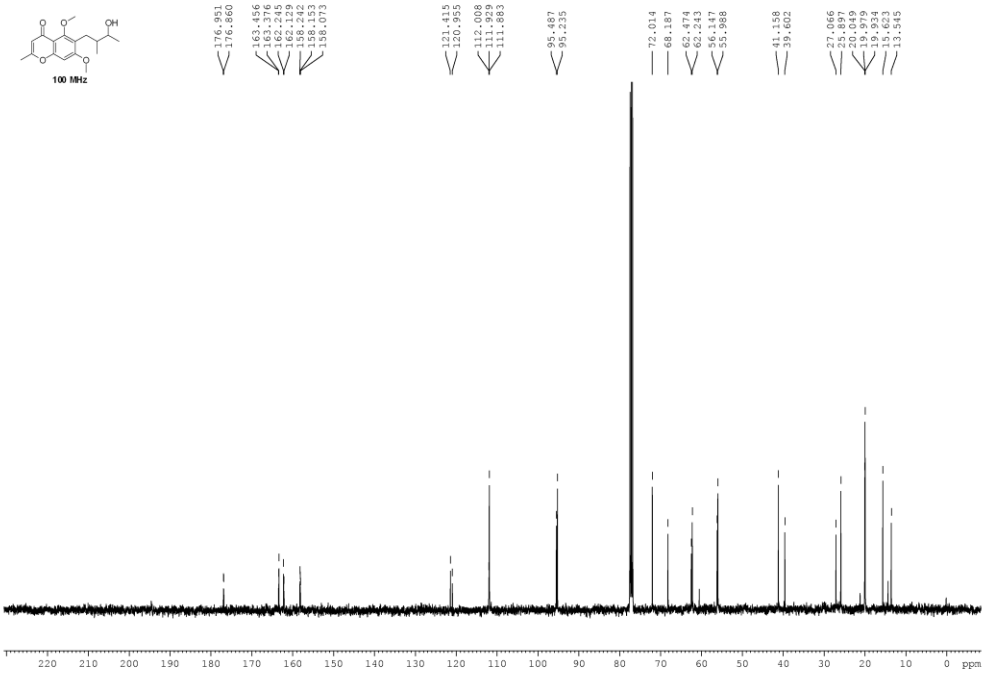


6-(3′-hydroxy-2′-methylbutyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (**109**)

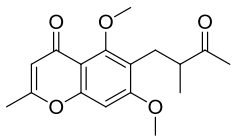


109

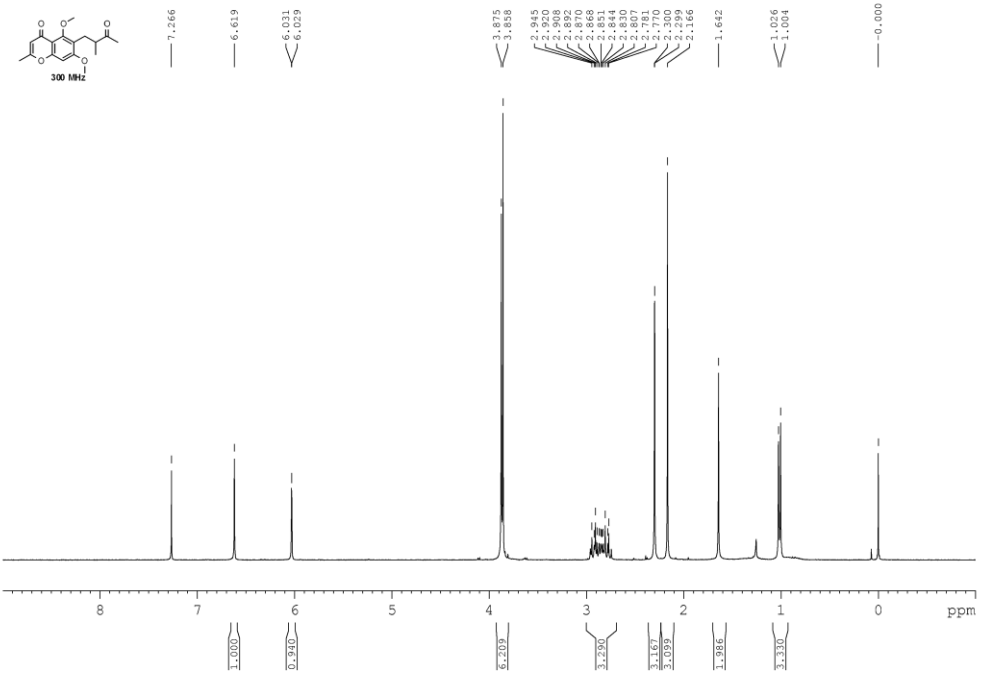


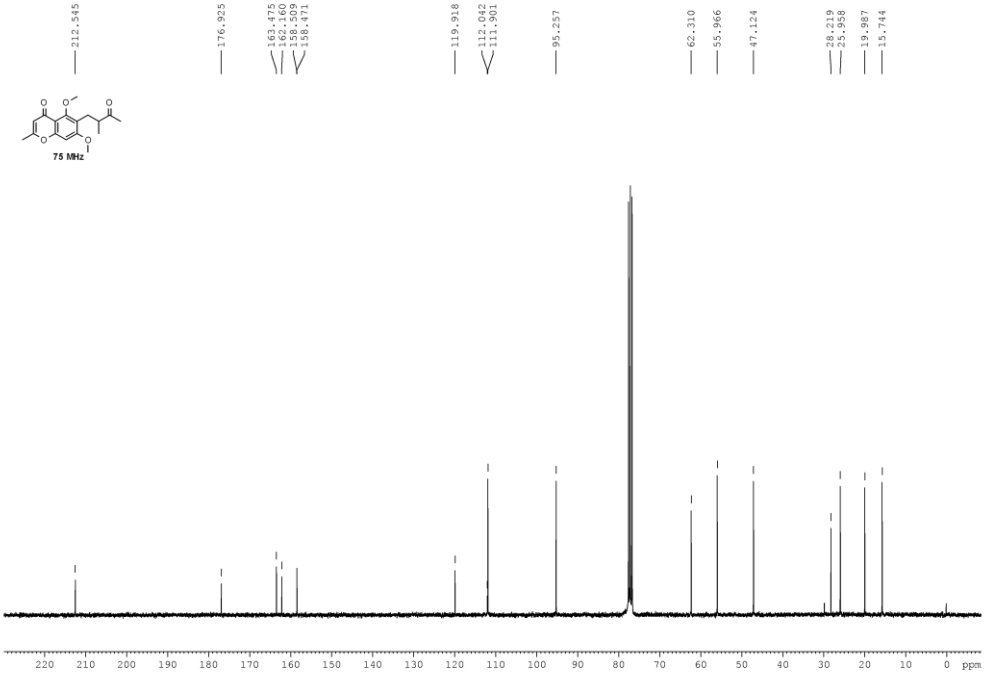


5,7-dimethoxy-2-methyl-6-(2′-methyl-3′-oxobutyl)-4*H*-chromen-4-one (±)-**100**

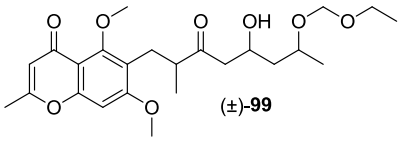


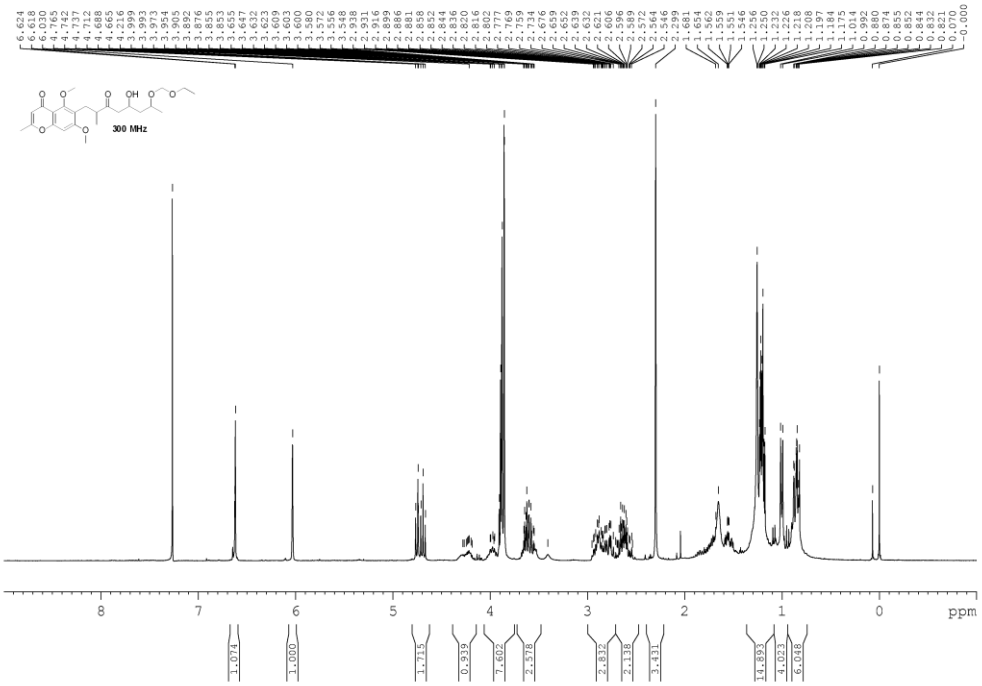
(±)-**100**

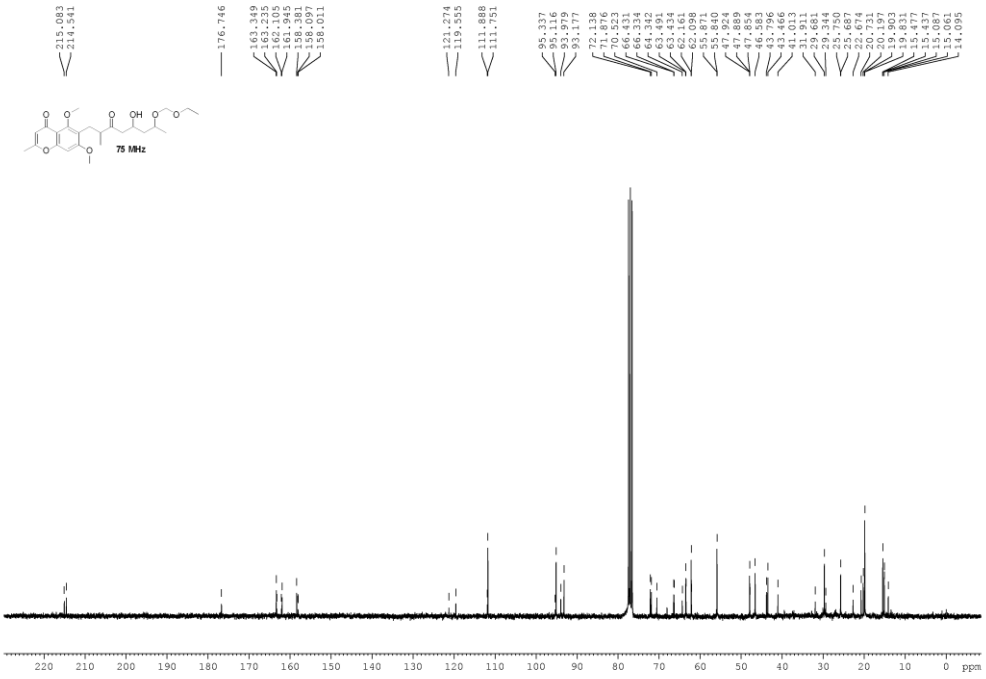




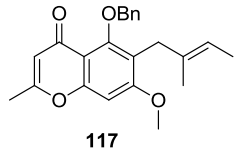
6-(7′-(ethoxymethoxy)-3′-hydroxy-2′-methyl-5′-oxooctyl)-5,7-dimethoxy-2-methyl-4*H*-chromen-4-one (±)-**99**



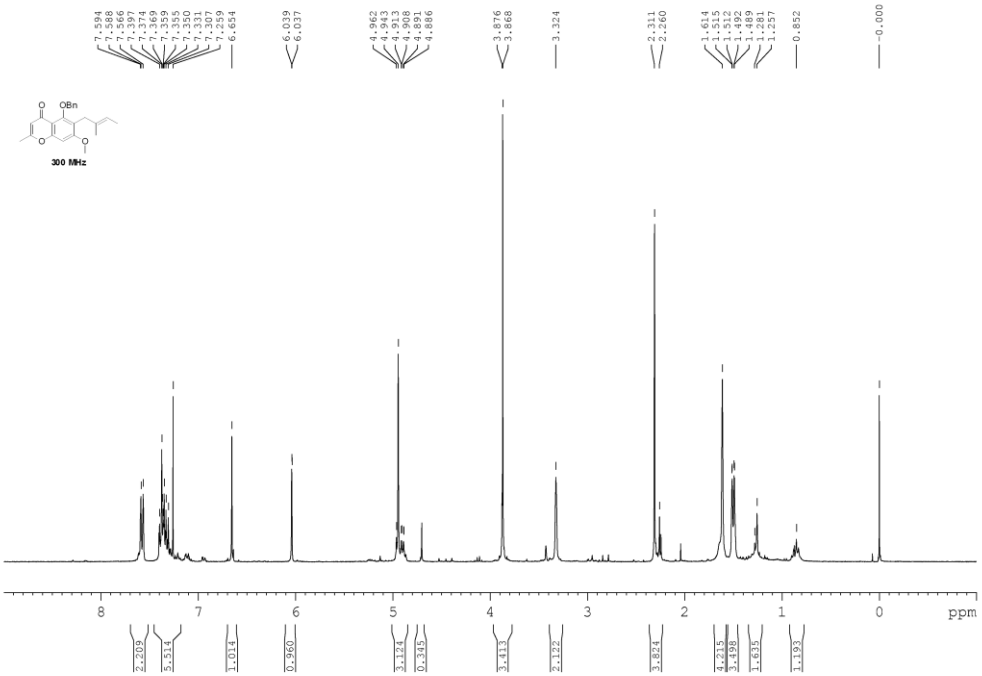


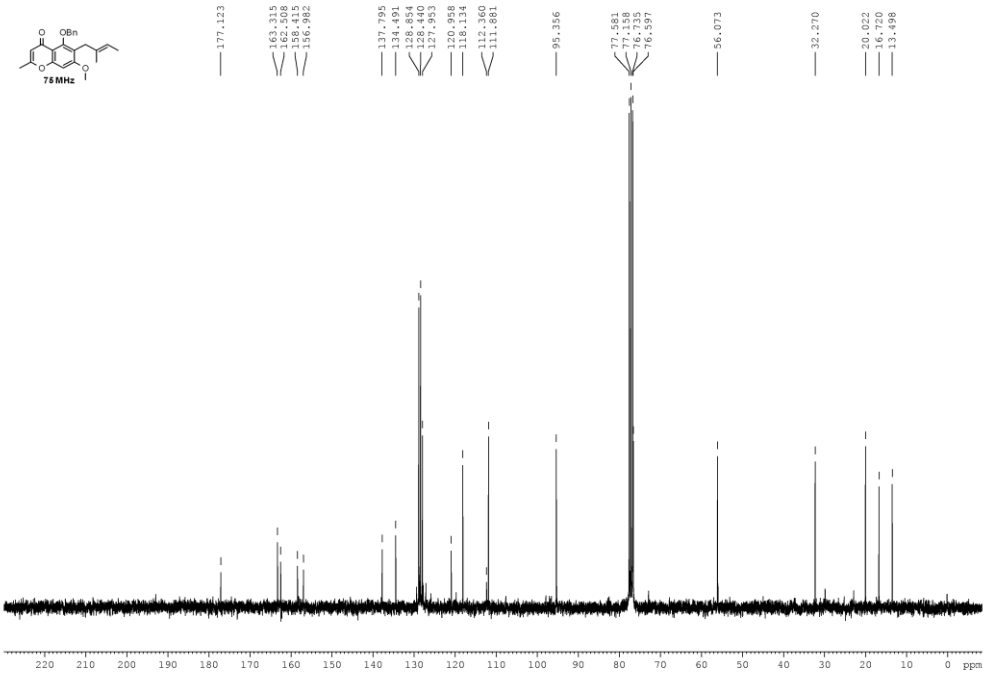


5-(benzyloxy)-7-methoxy-2-methyl-6-(2′-methylbut-2′-en-1′-yl)-4*H*-chromen-4-one (**117**)

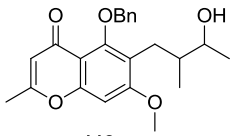


117

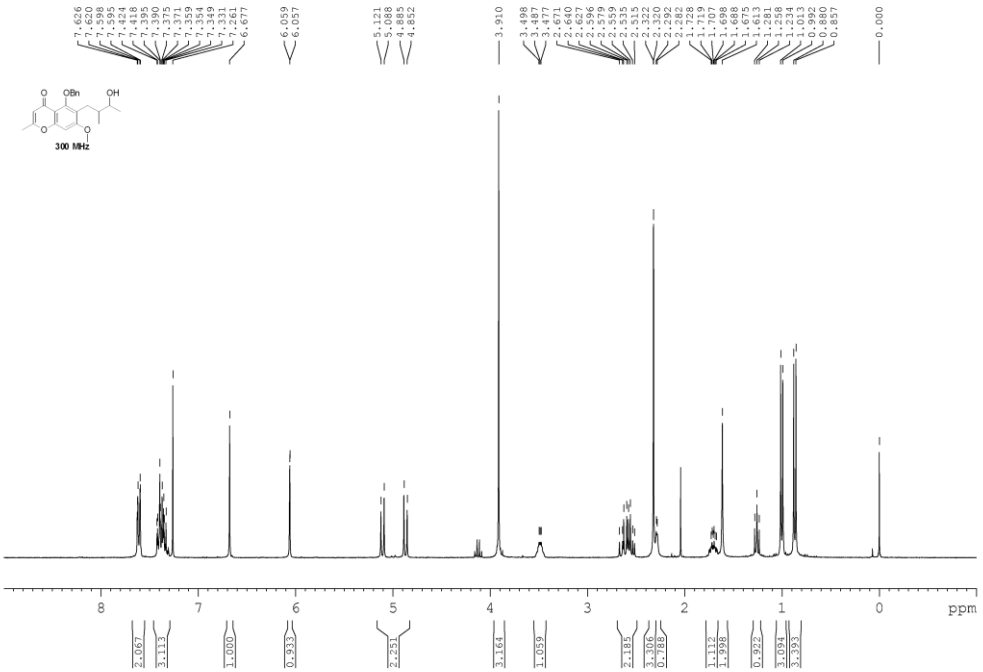


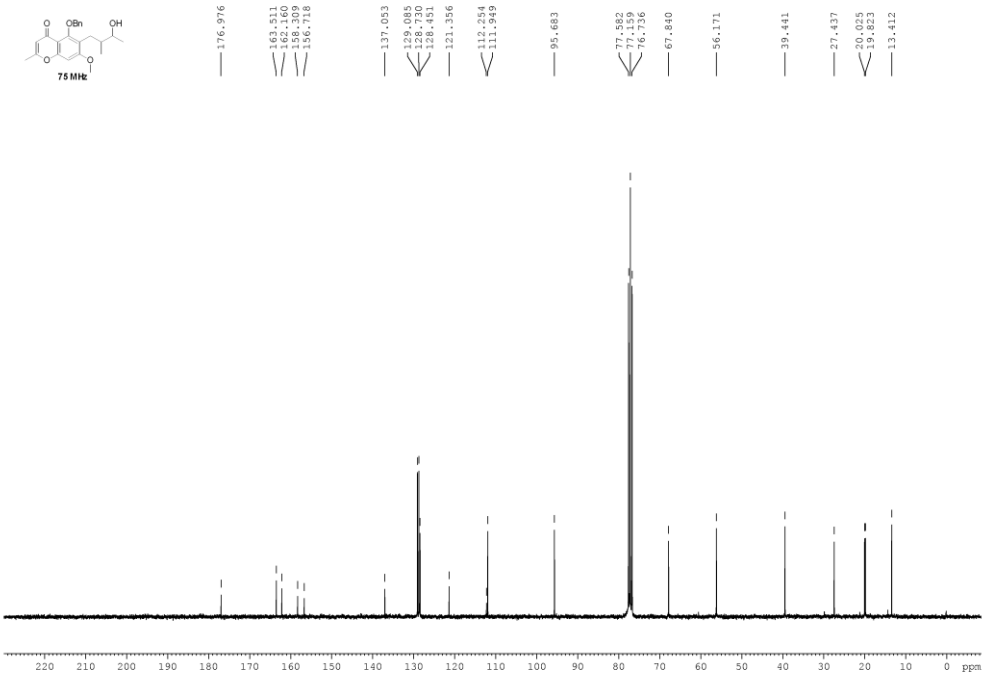


5-(benzyloxy)-6-(3′-hydroxy-2′-methylbutyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**118**)

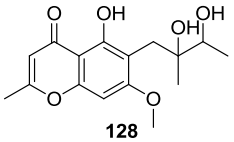


118

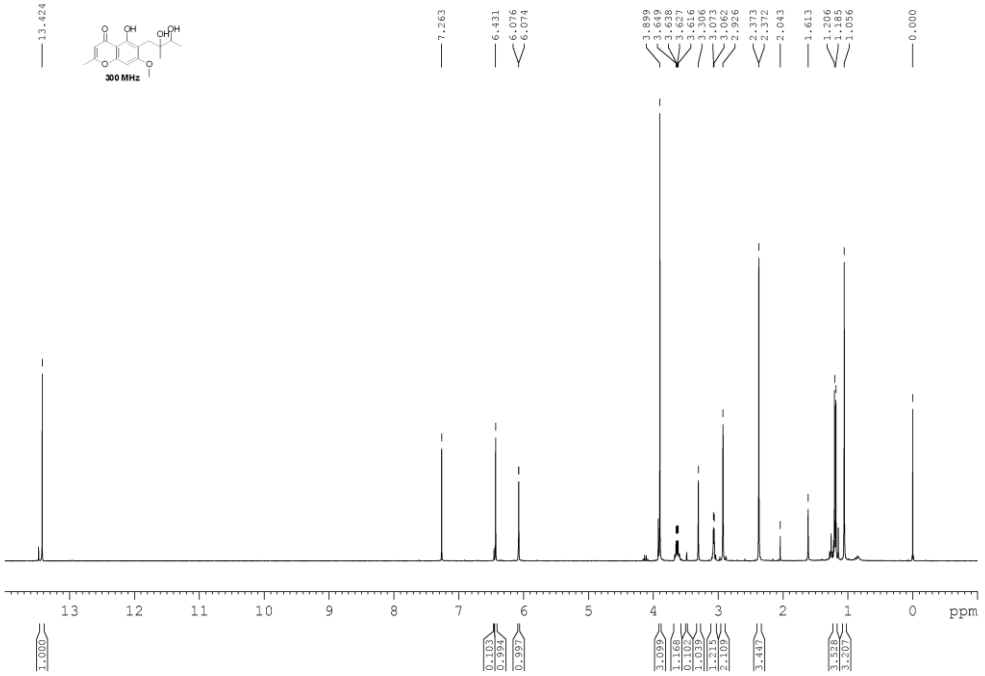


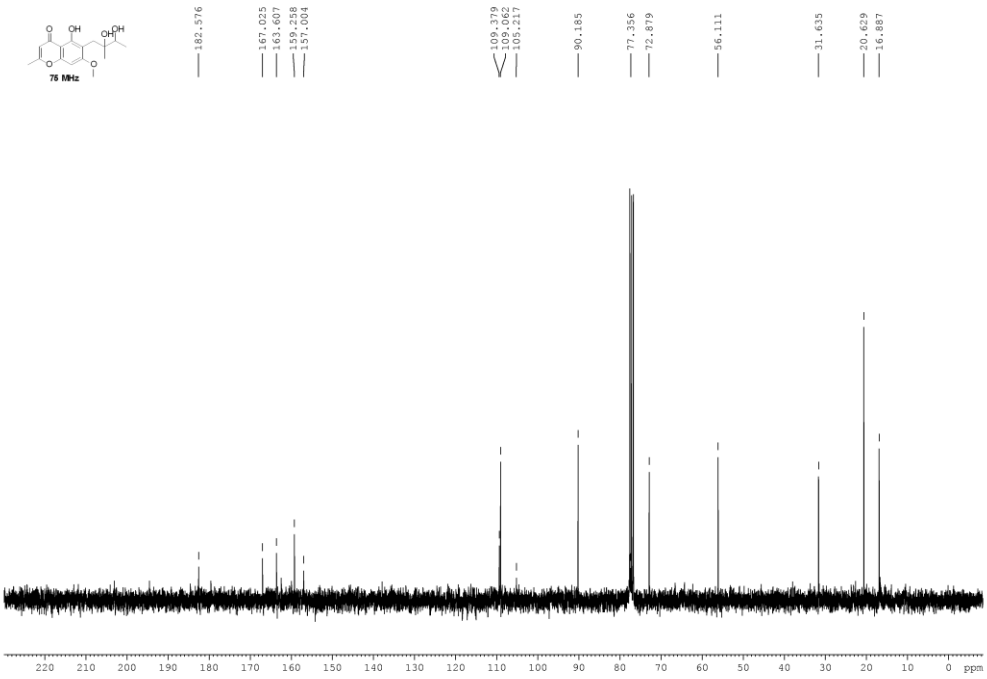


6-(2′,3′-dihydroxy-2′-methylbutyl)-5-hydroxy-7-methoxy-2-methyl-4*H*-chromen-4-one (**128**)

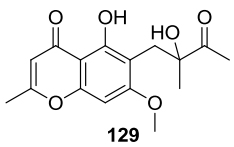


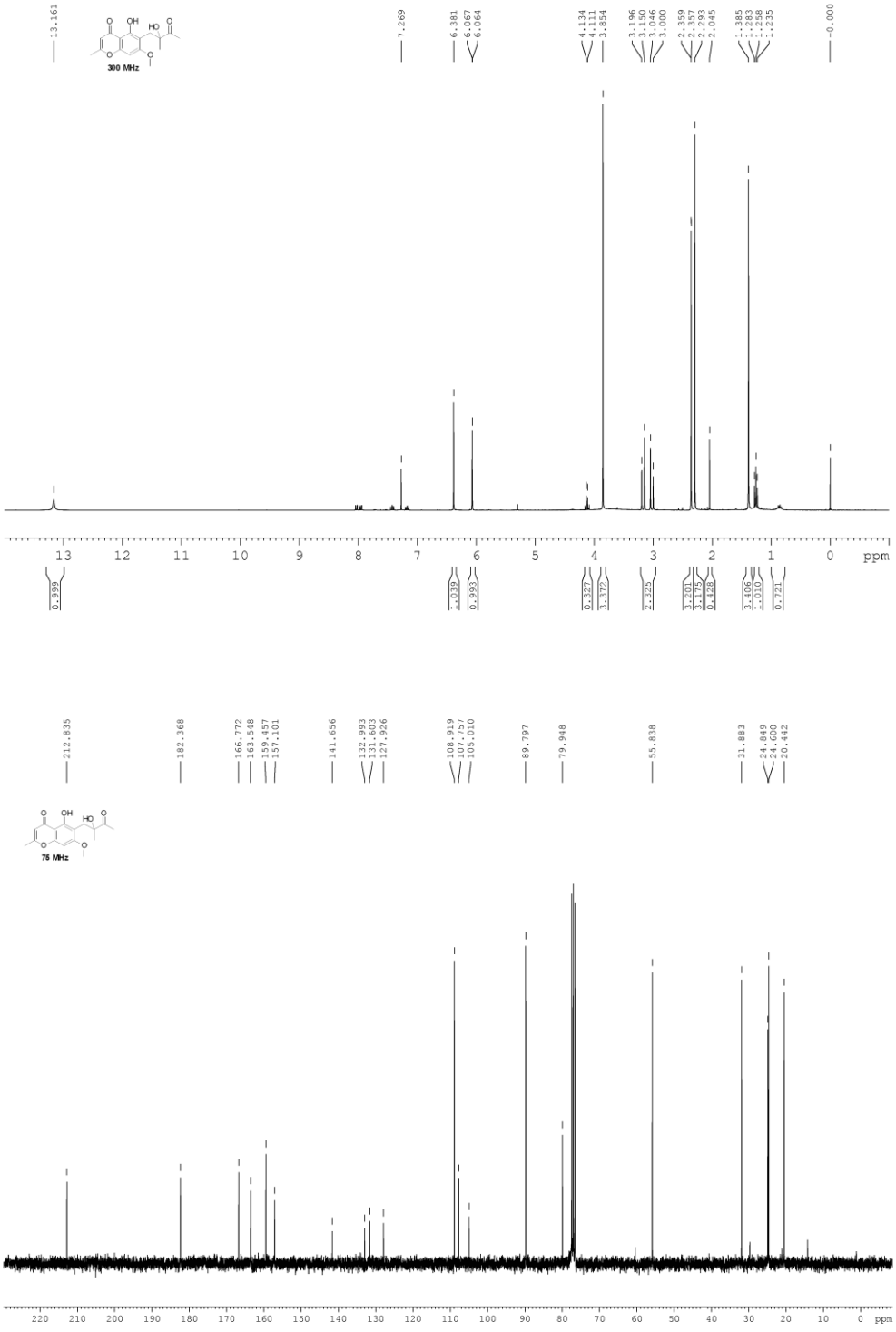
128



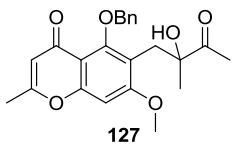


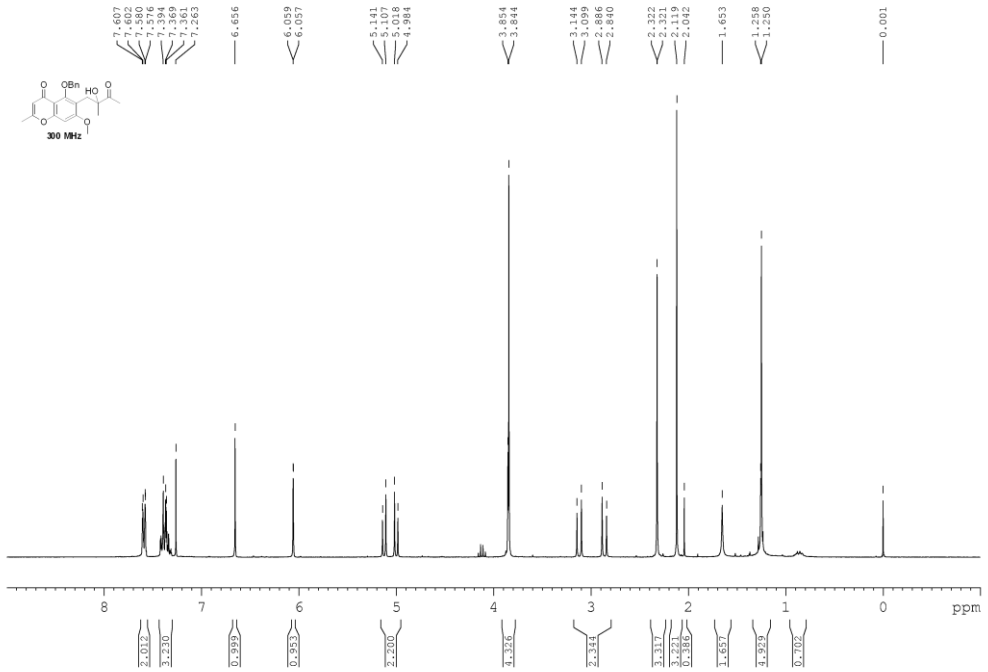
5-hydroxy-6-(2′-hydroxy-2′-methyl-3′-oxobutyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**129**)

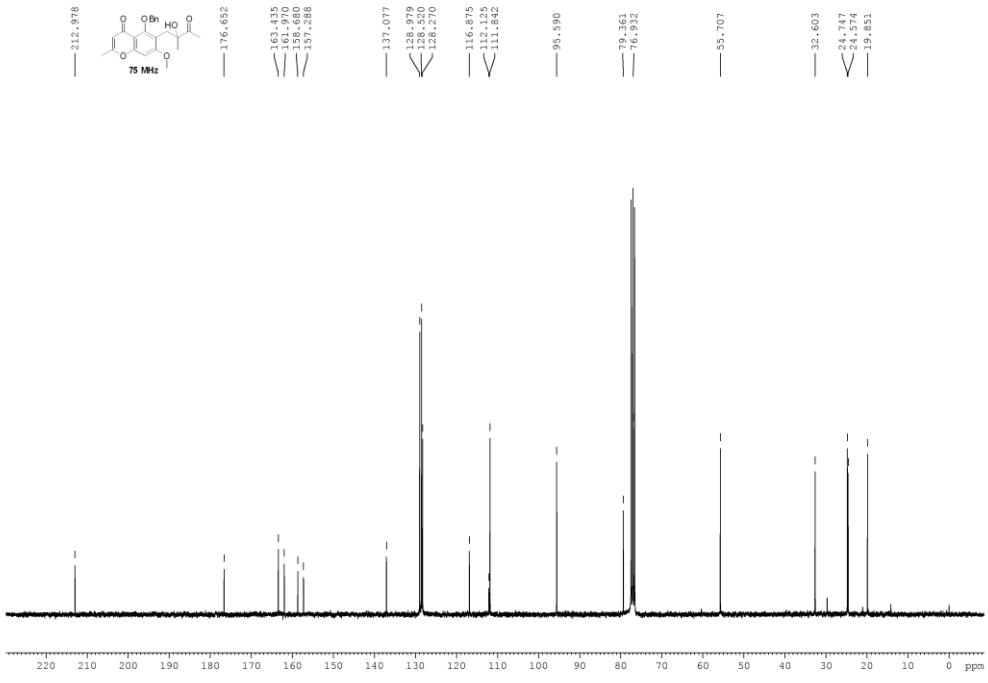




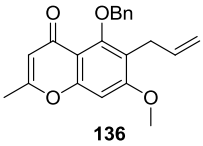
5-(benzyloxy)-6-(2′-hydroxy-2′-methyl-3′-oxobutyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**127**)

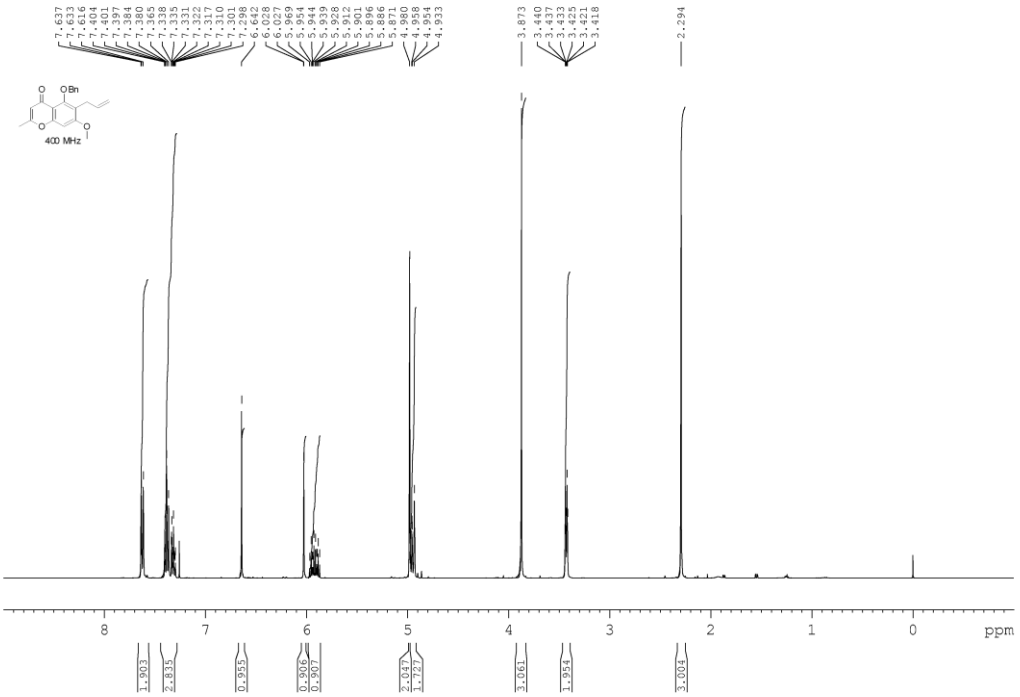


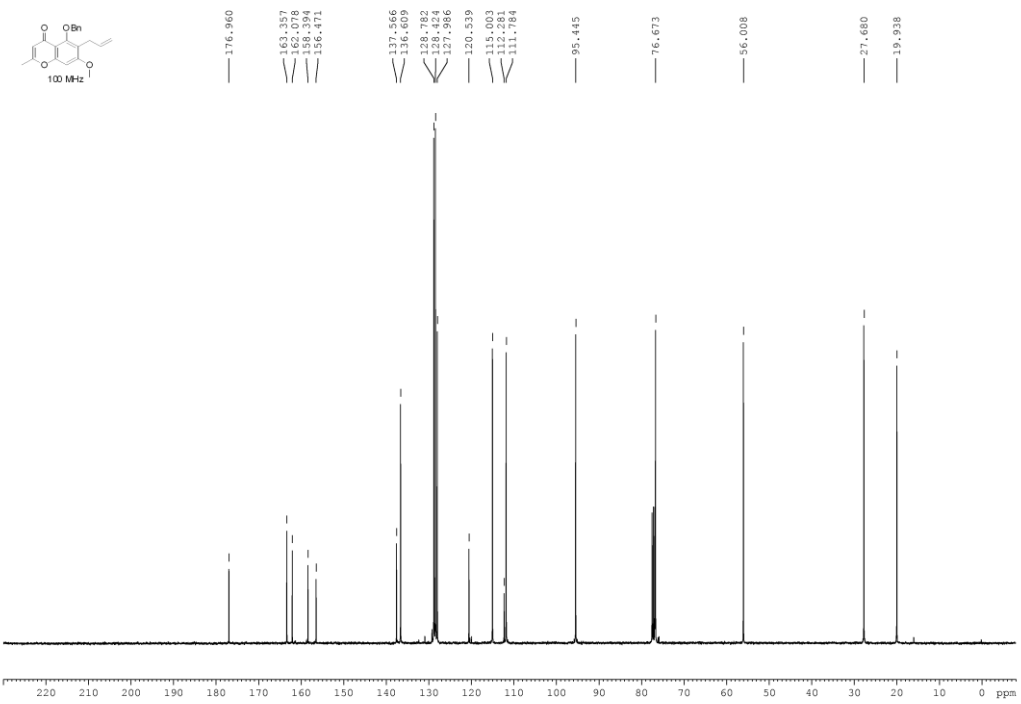




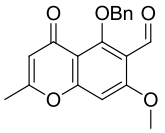
6-allyl-5-(benzyloxy)-7-methoxy-2-methyl-4*H*-chromen-4-one (**136**)



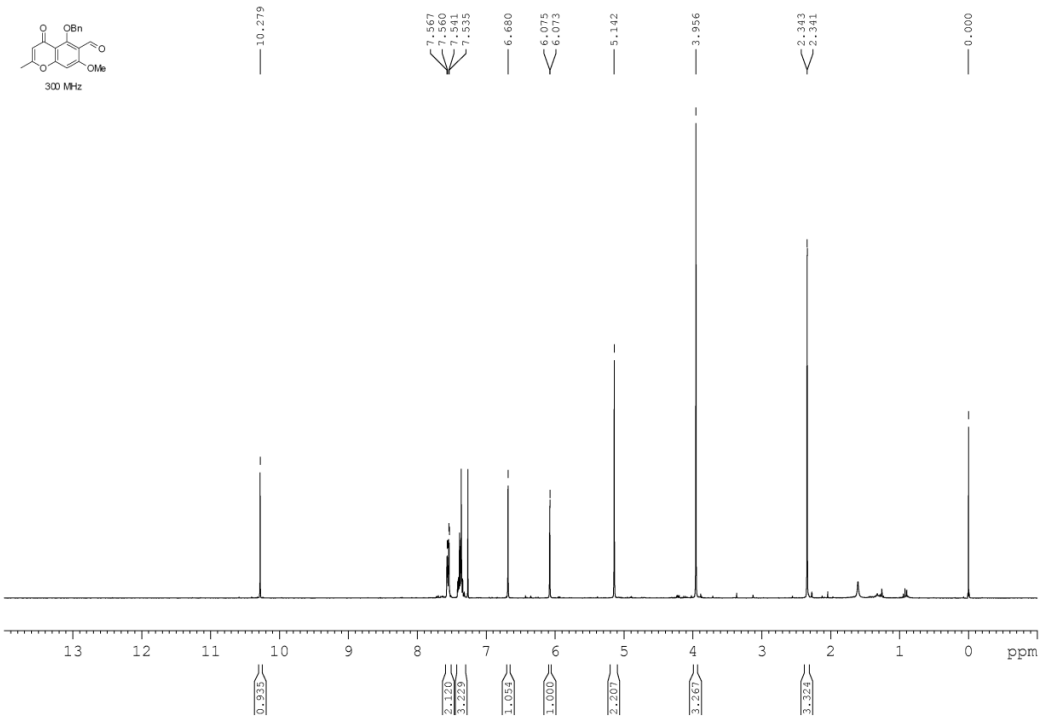


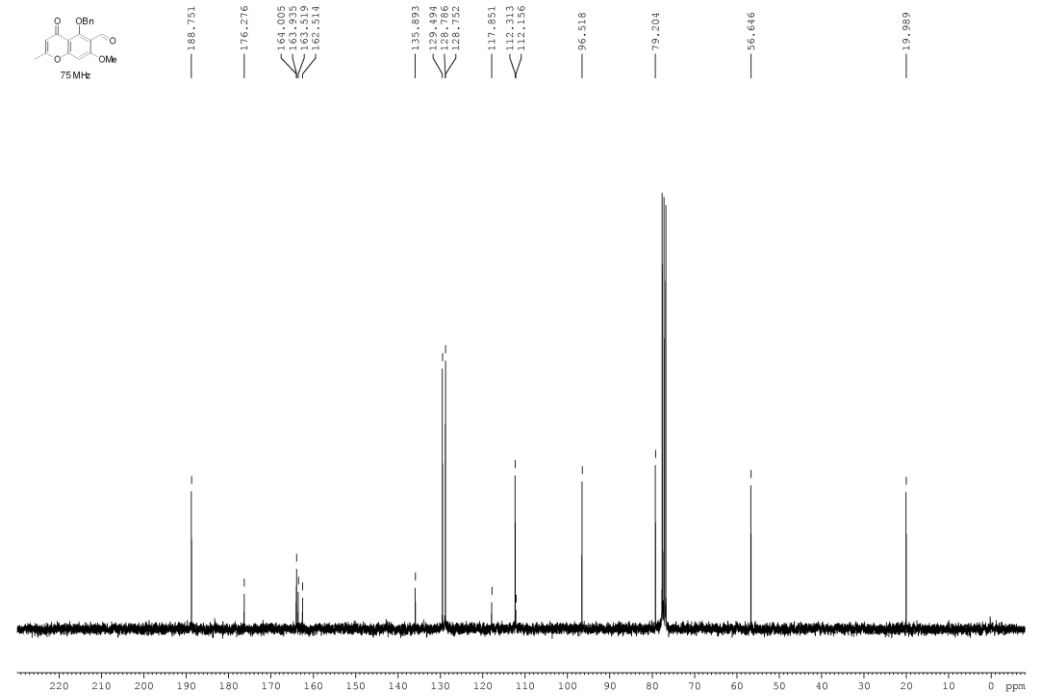


5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehyde (**134**)

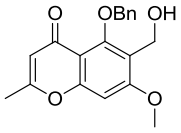


134

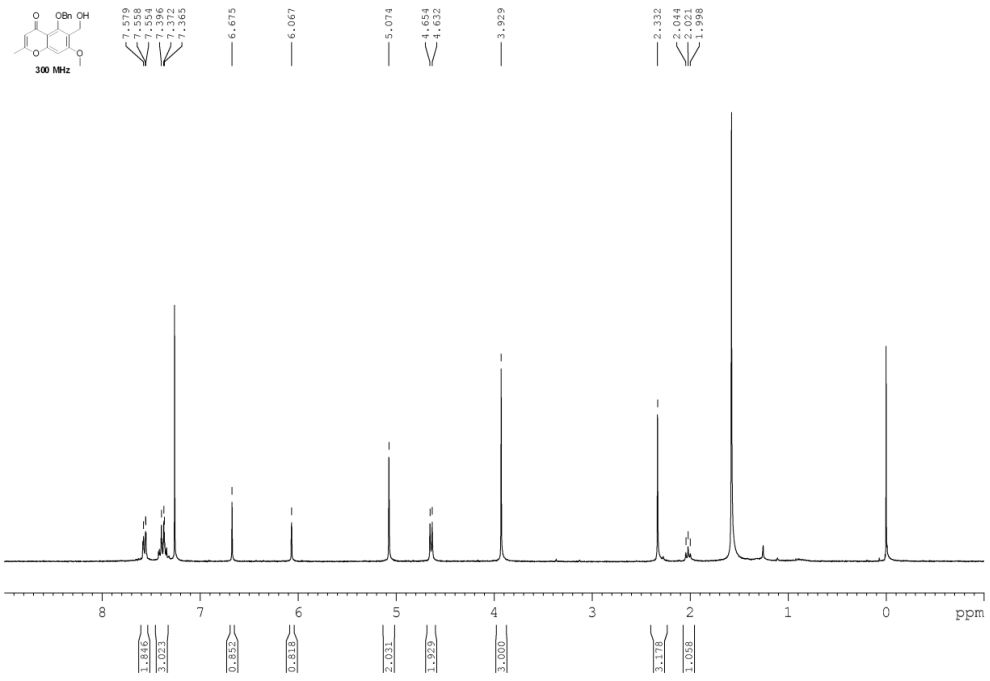


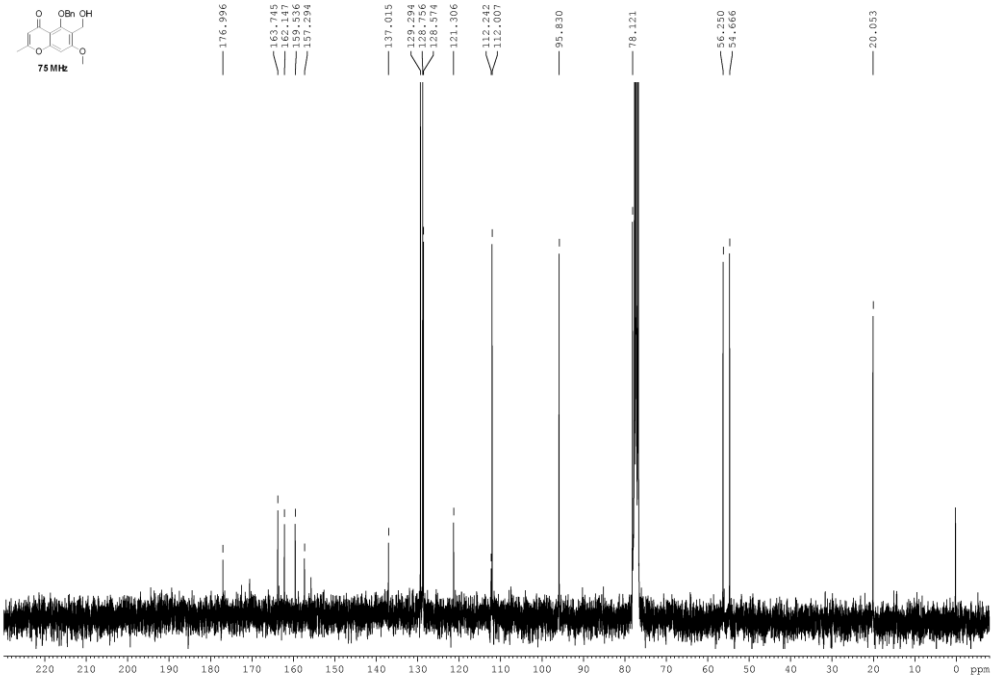


5-(benzyloxy)-6-(hydroxymethyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**137**)

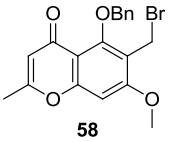


137

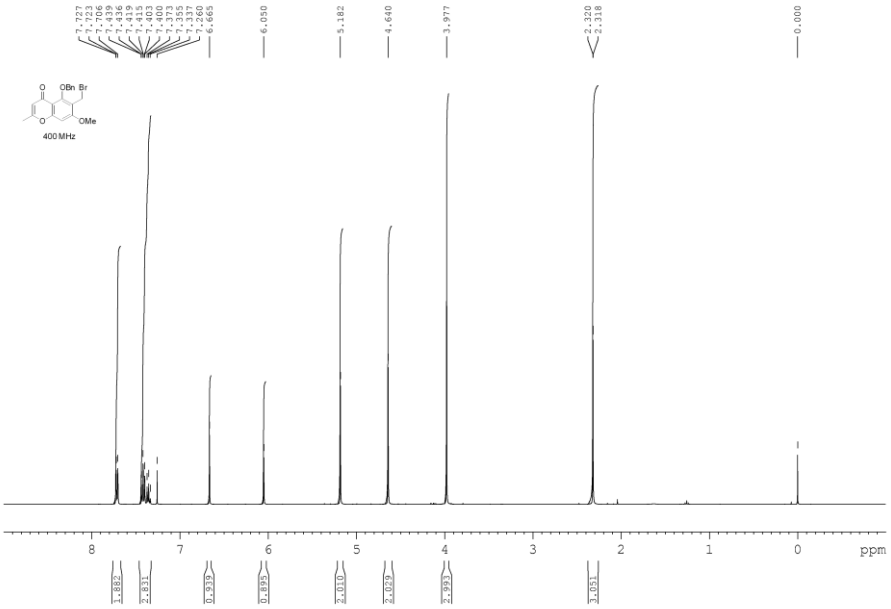


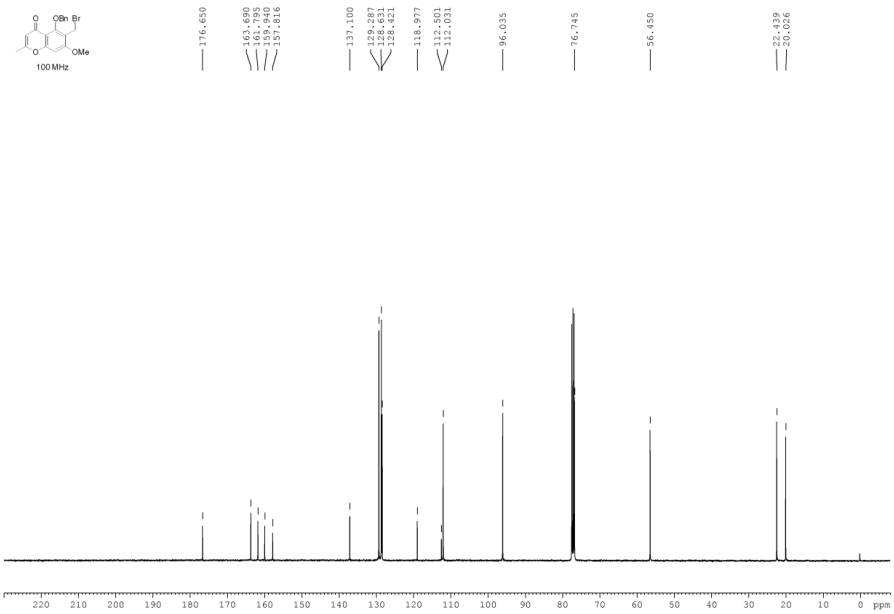


5-(benzyloxy)-6-(bromomethyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**58**)

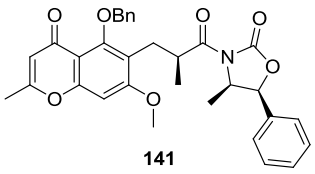


58

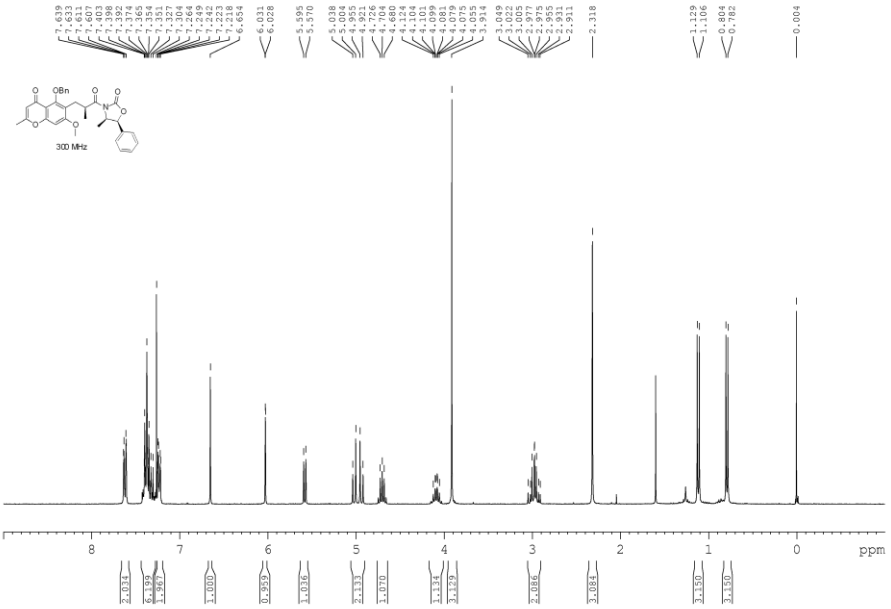


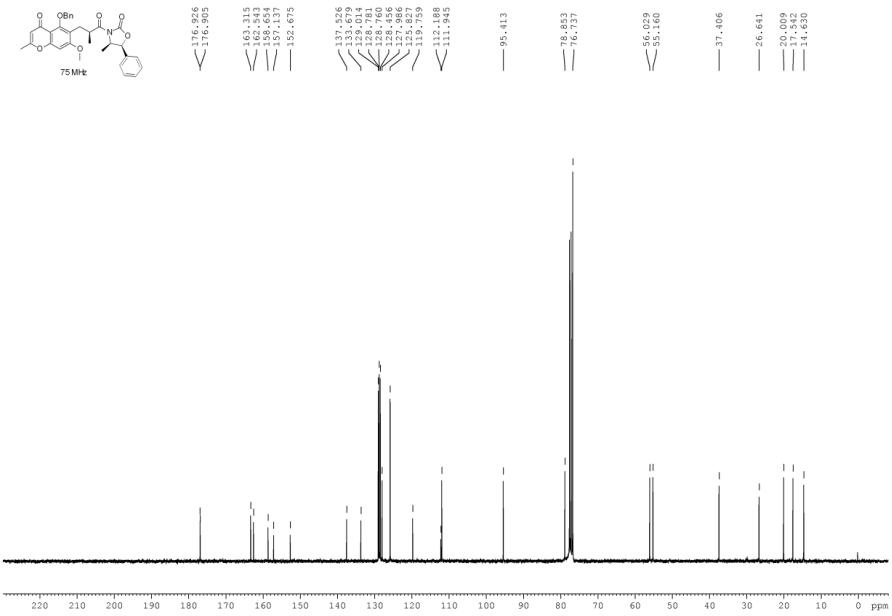


(4″*R*,5″*S*)-3-((*S*)-3-(5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)-2′-methylpropanoyl)-4″-methyl-5″-phenyloxazolidin-2″-one (**141**)

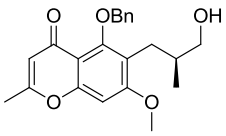


141

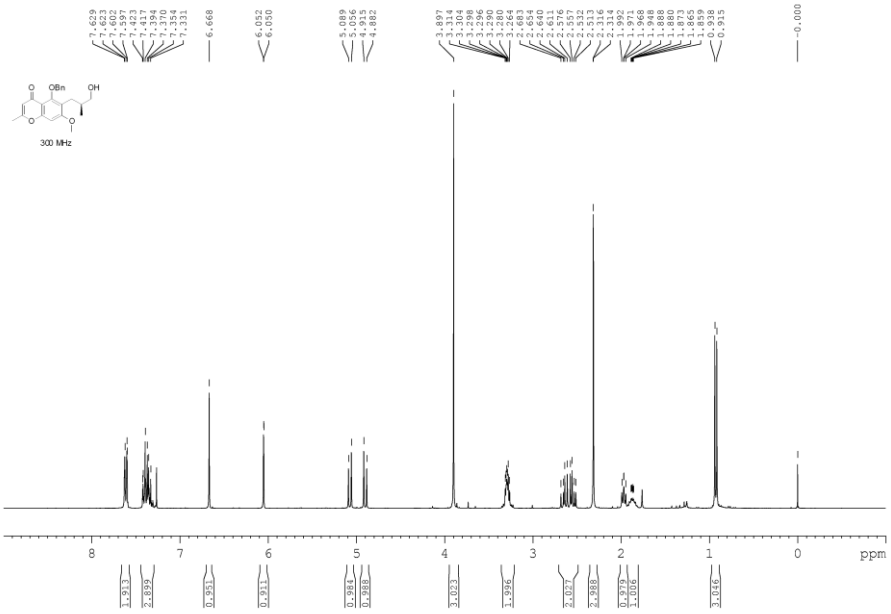


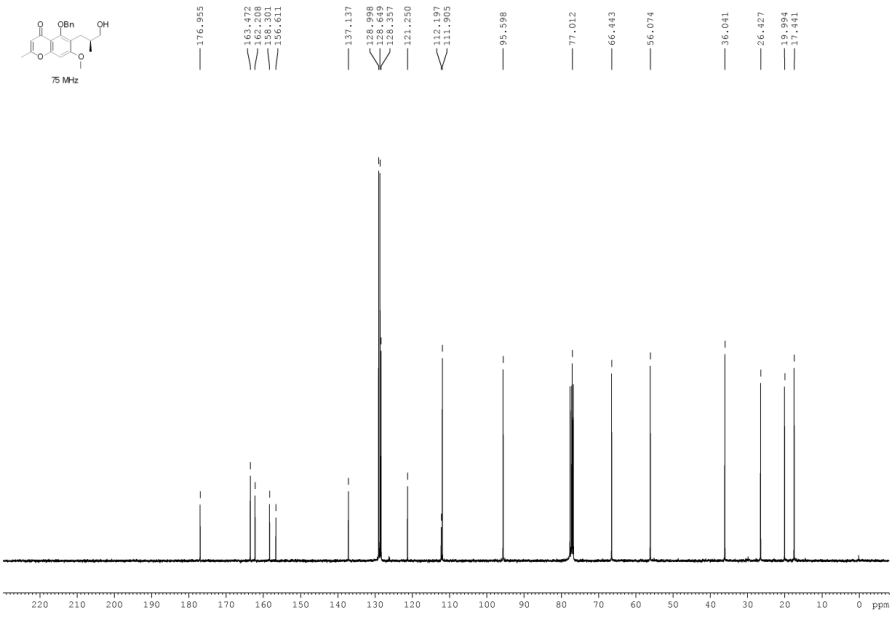


(*S*)-5-(benzyloxy)-6-(3′-hydroxy-2′-methylpropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**142**)

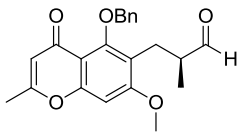


142

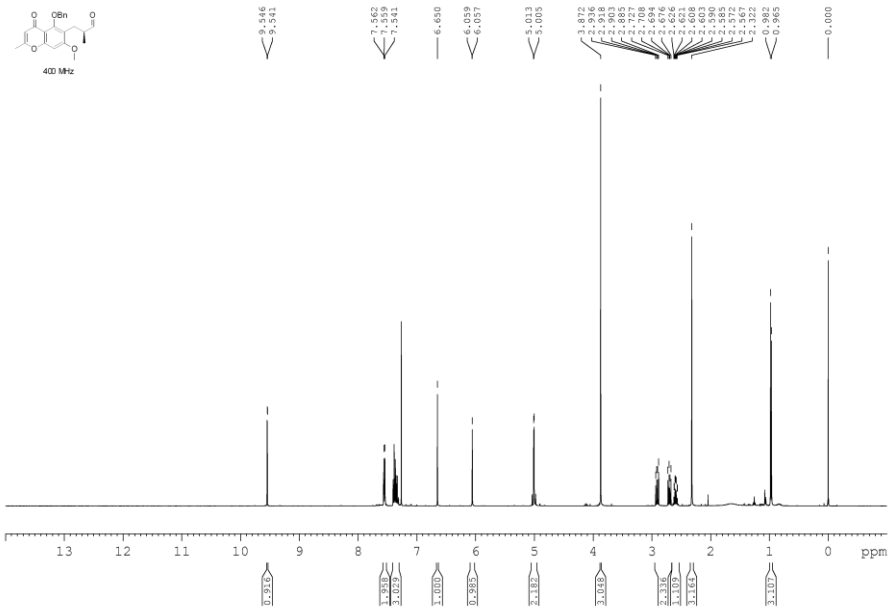


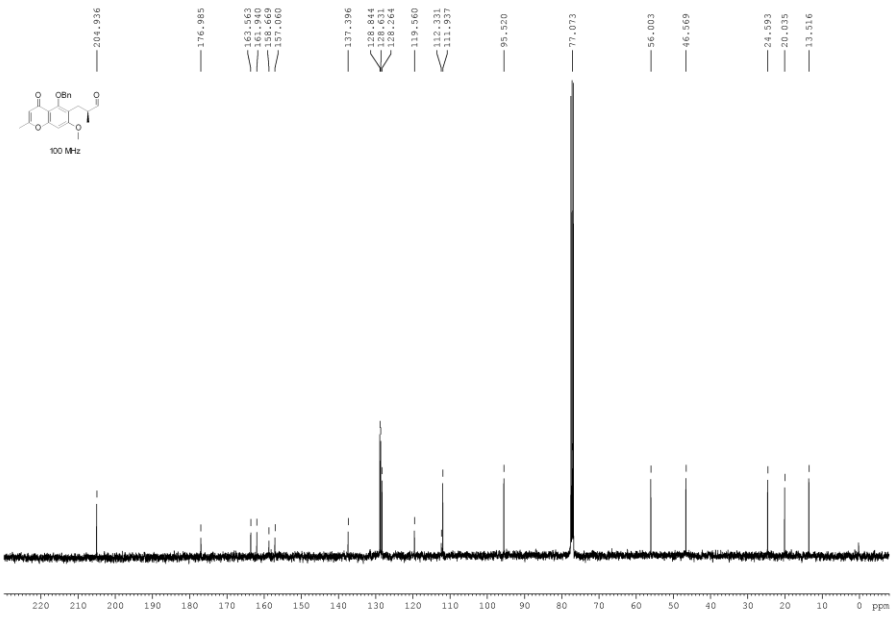


(*S*)-1′-(5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)-2′-methylpropan-3′-al

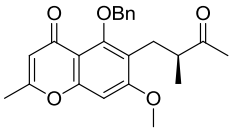


(*S*)-**124** (*S*)-**124**

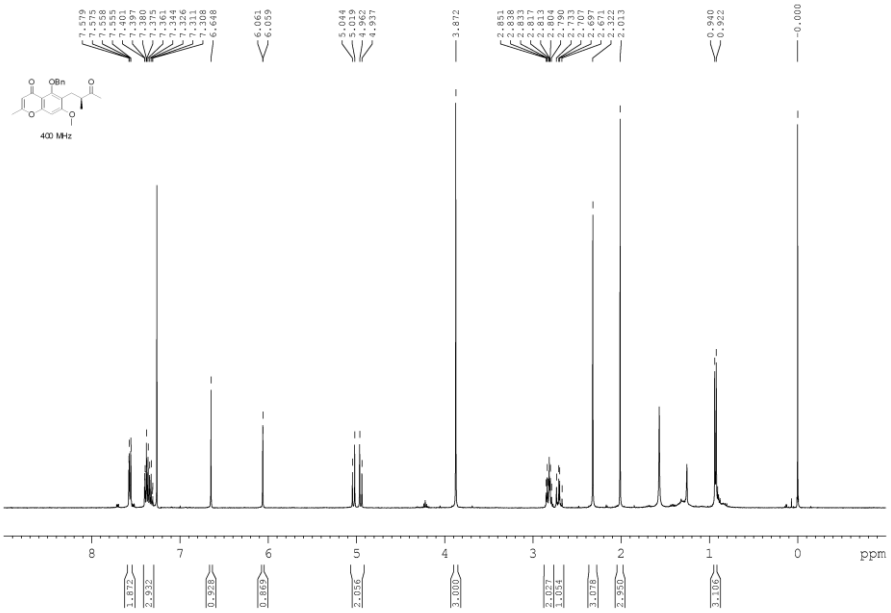


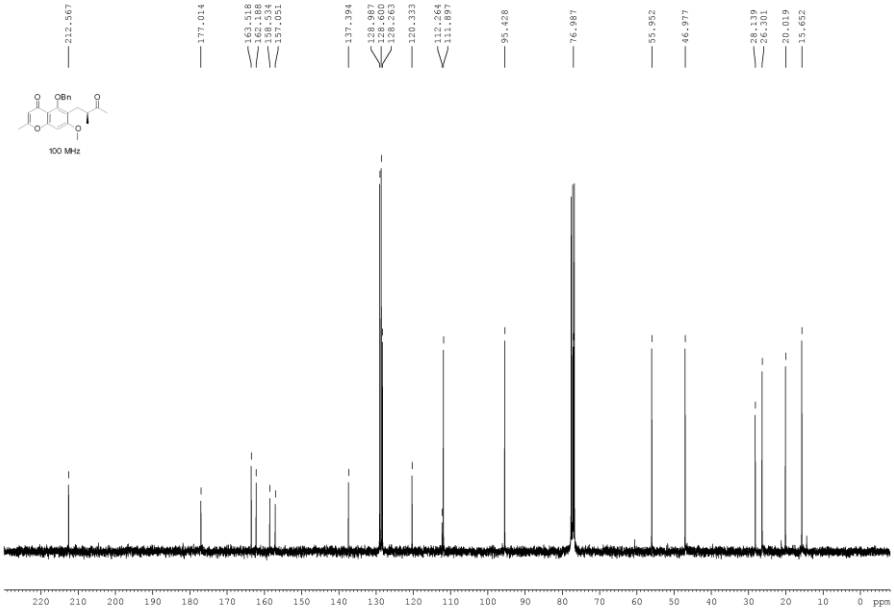


(*S*)-5-(benzyloxy)-7-methoxy-2-methyl-6-(2′-methyl-3′-oxobutyl)-4*H*-chromen-4-one (*S*)-**116**



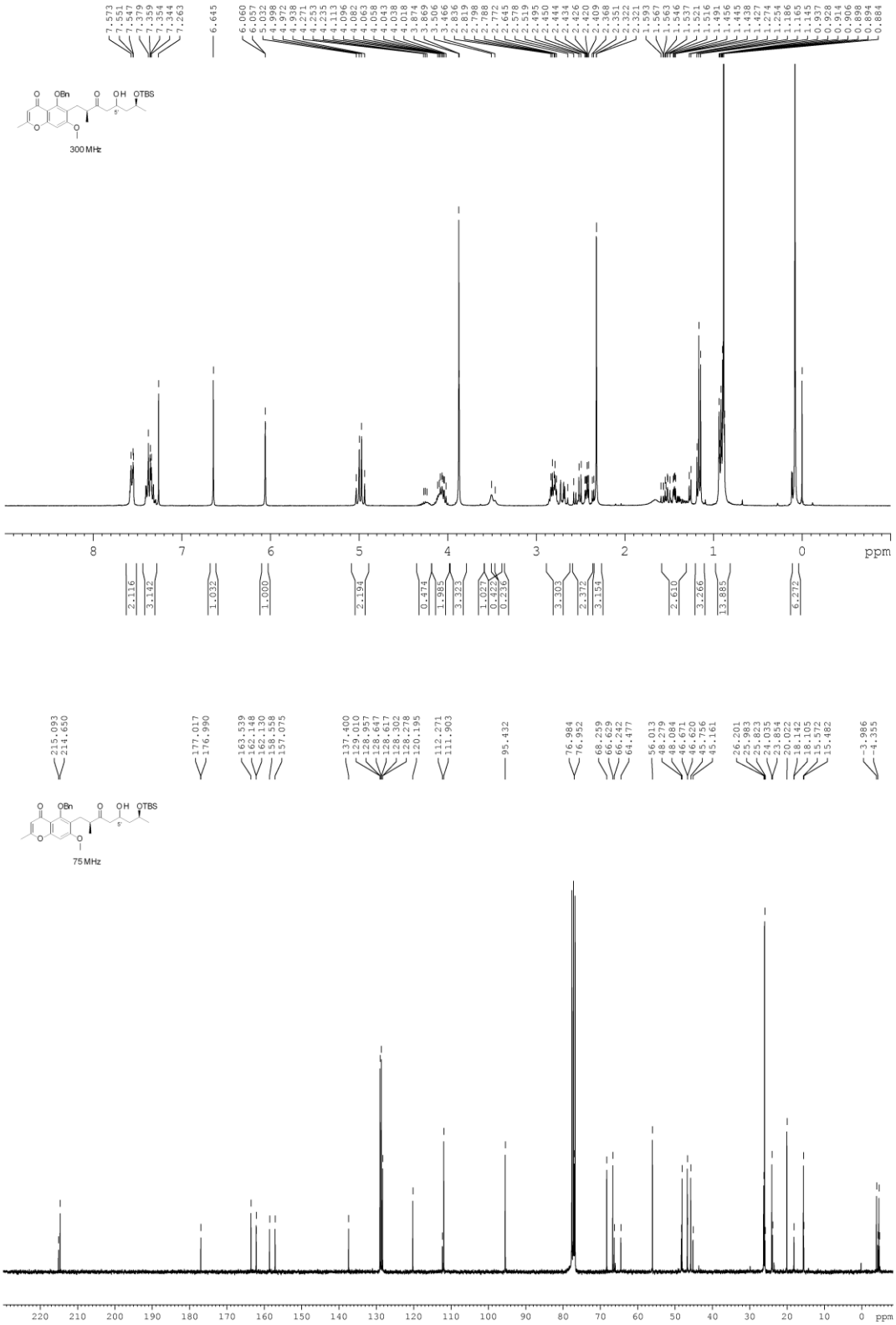
(*S*)-**116**





5-(benzyloxy)-6-((2′*S*,5′*S*,7′*S*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**143a**)

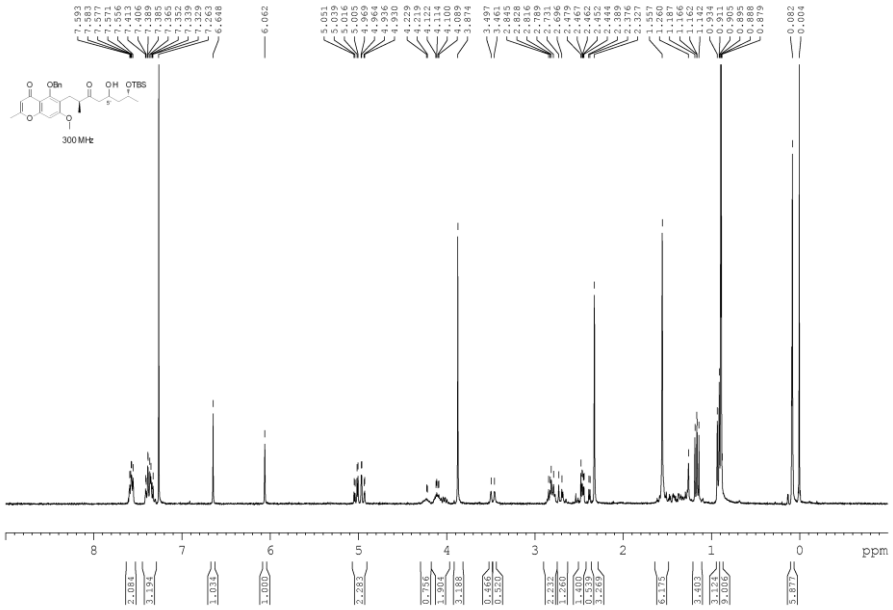
(5′*S*)-**143a:** (5′*R*)-**143b**: = 2:1 mixture

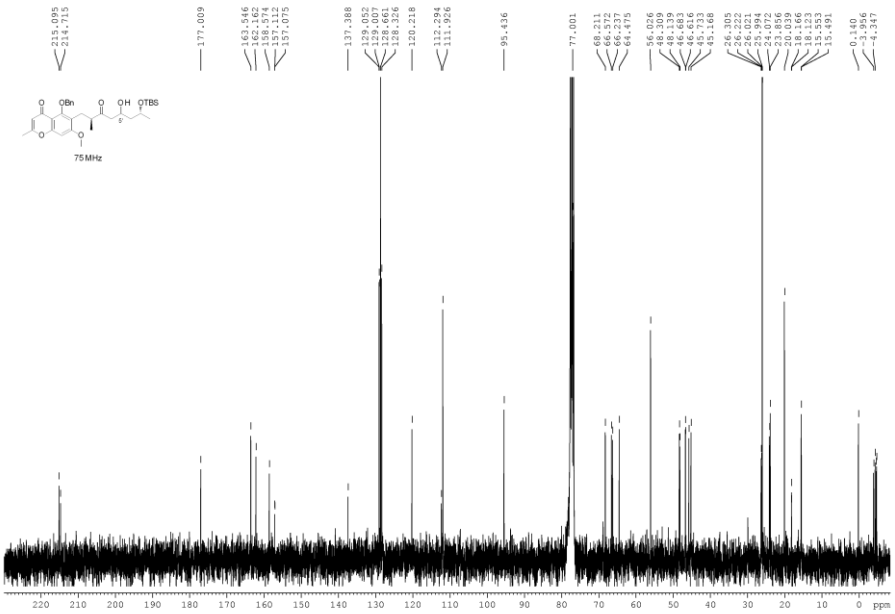


5-(benzyloxy)-6-((2′*S*,5′*R*,7′*R*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**145a**)

5-(benzyloxy)-6-((2′*S*,5′*S*,7′*R*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**145b**)

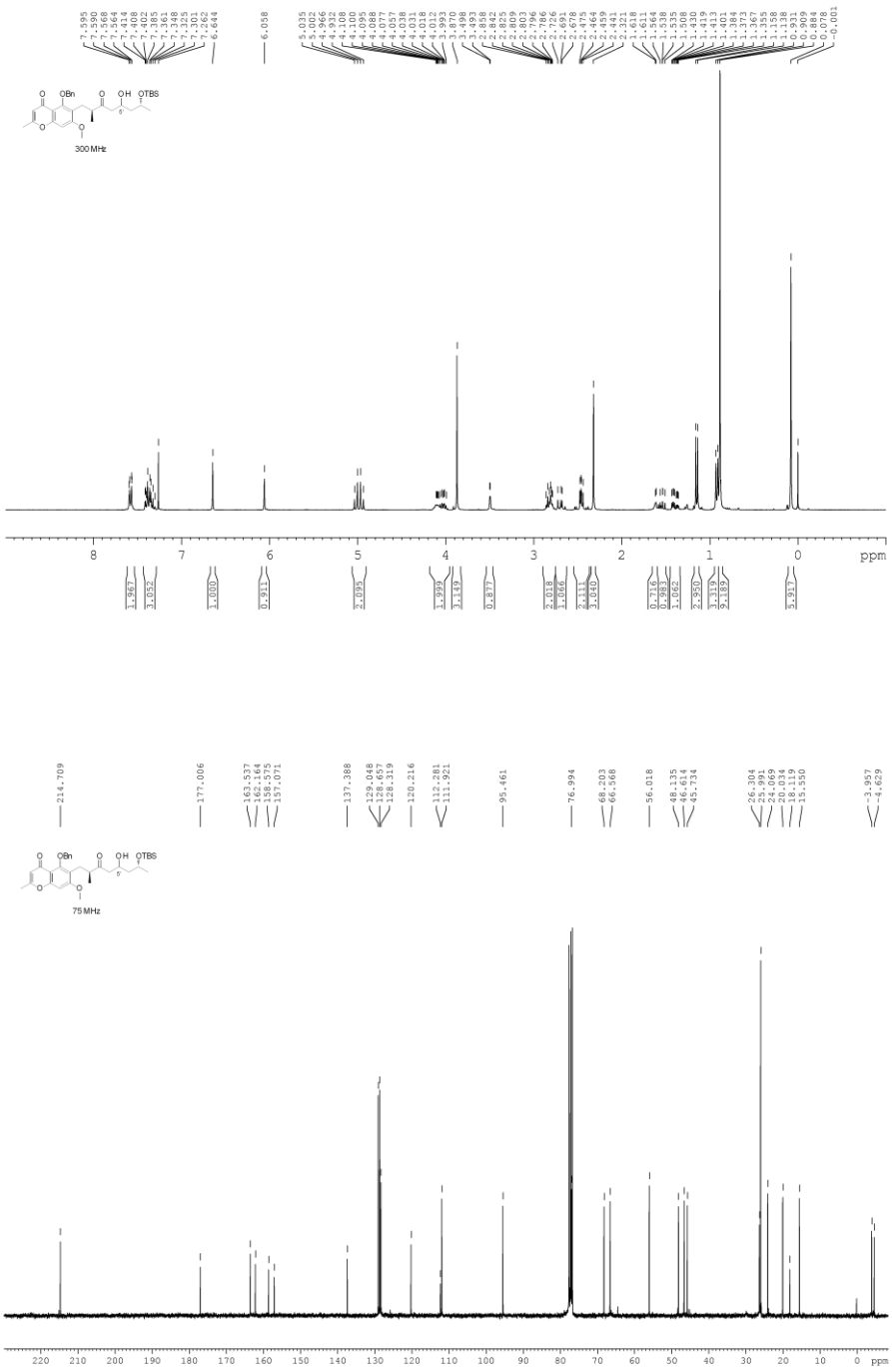
1:1 mixture of (5′*R*)-**145a** and (5′*S*)-**145b**



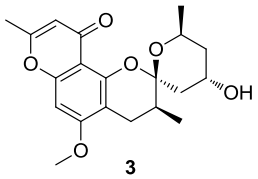


5-(benzyloxy)-6-((2′*S*,5′*R*,7′*R*)-7′-((*tert*-butyldimethylsilyl)oxy)-5′-hydroxy-2′-methyl-3′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**145a**)

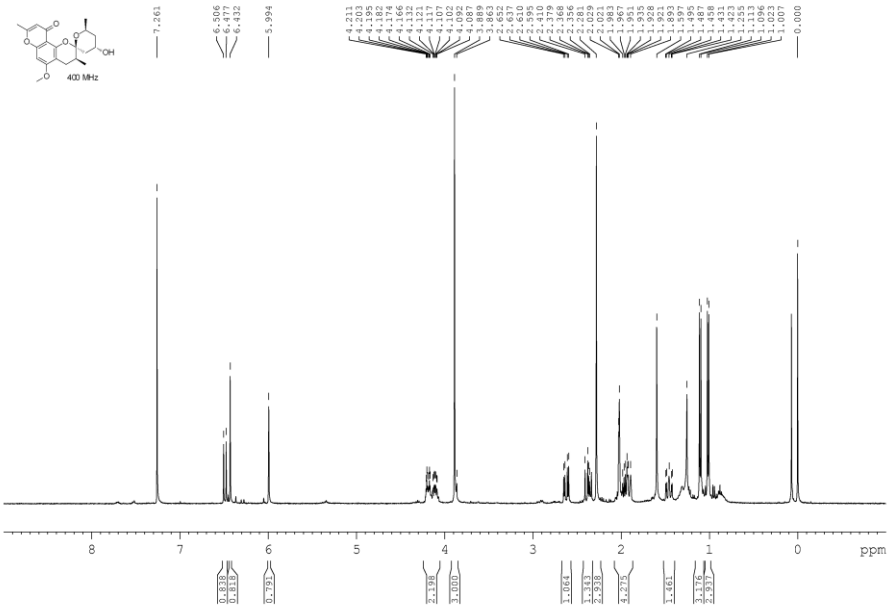
20:1 mixture of (5′*R*)-**145a** and (5′*S*)-**145b**

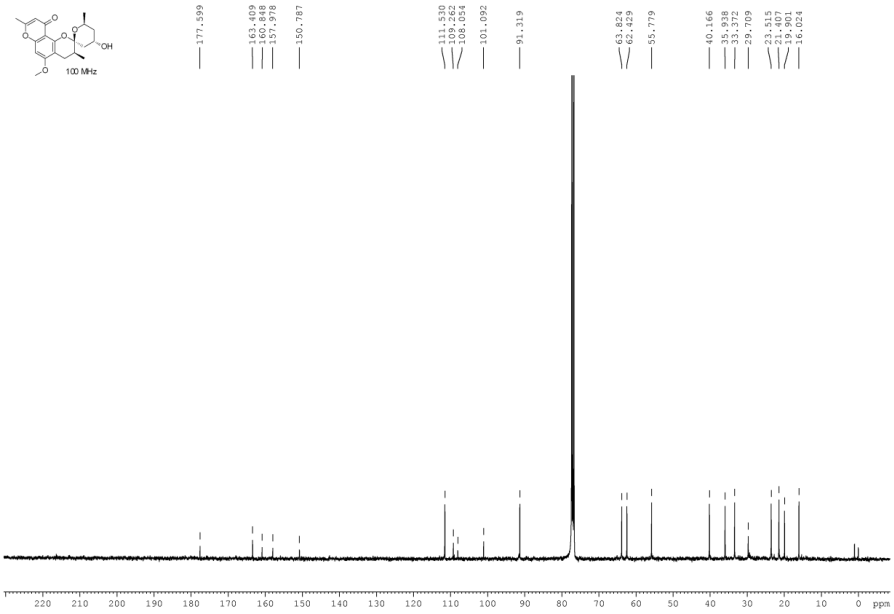


chaetoquadrin C (**3**)

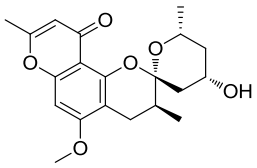


3

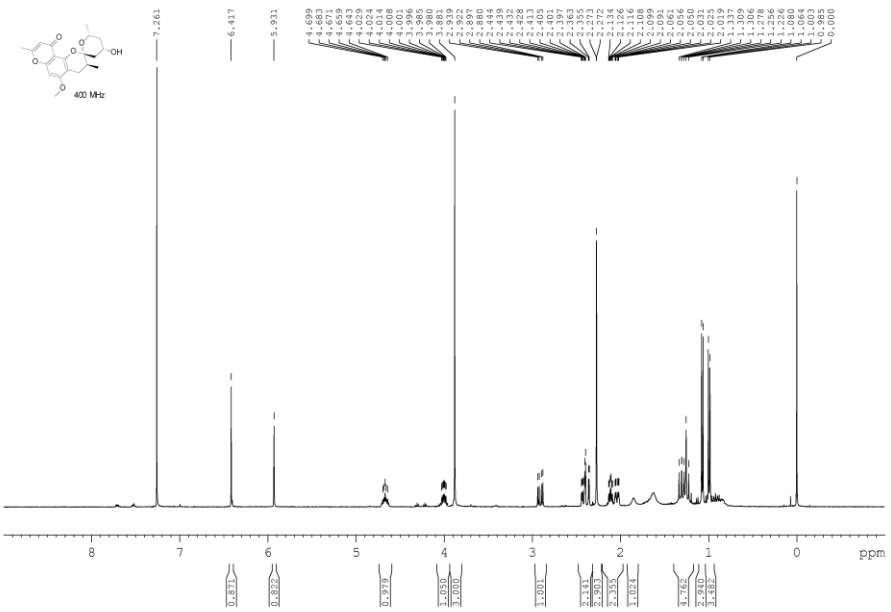


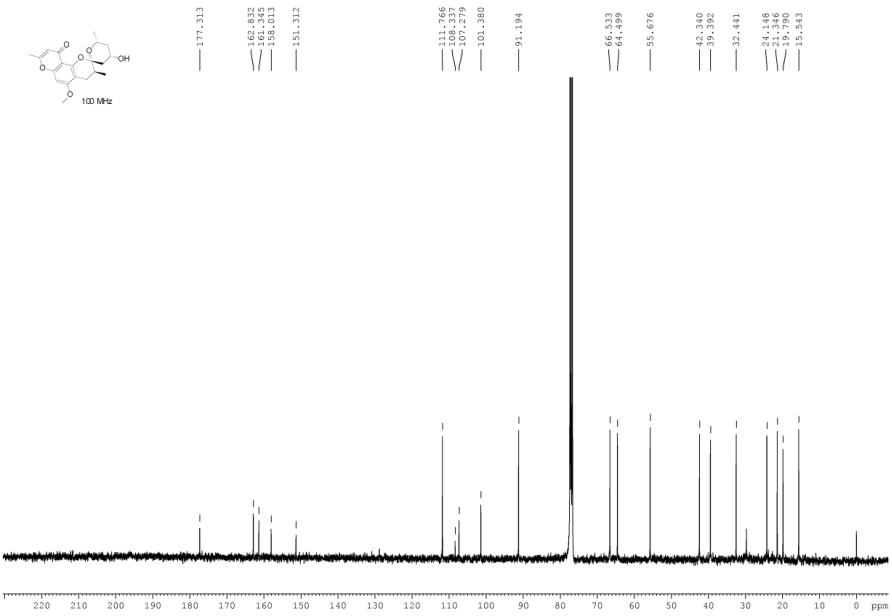


ent-chaetoquadrin A (*ent*-**1**)

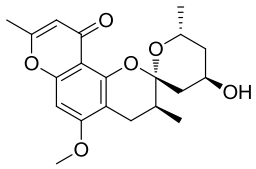


ent-**1**

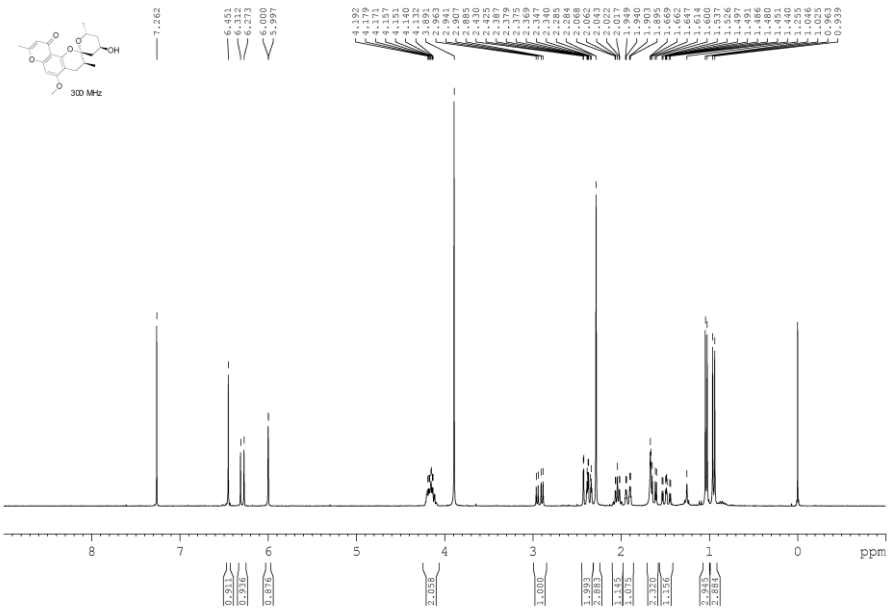


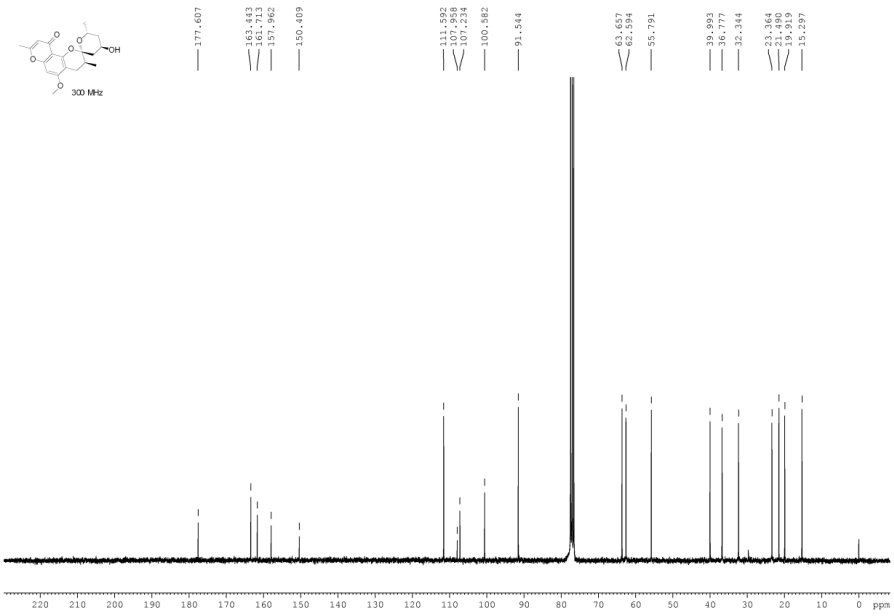


ent-chaetoquadrin B (*ent*-**2**)

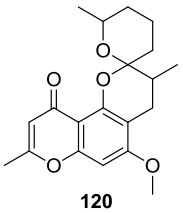


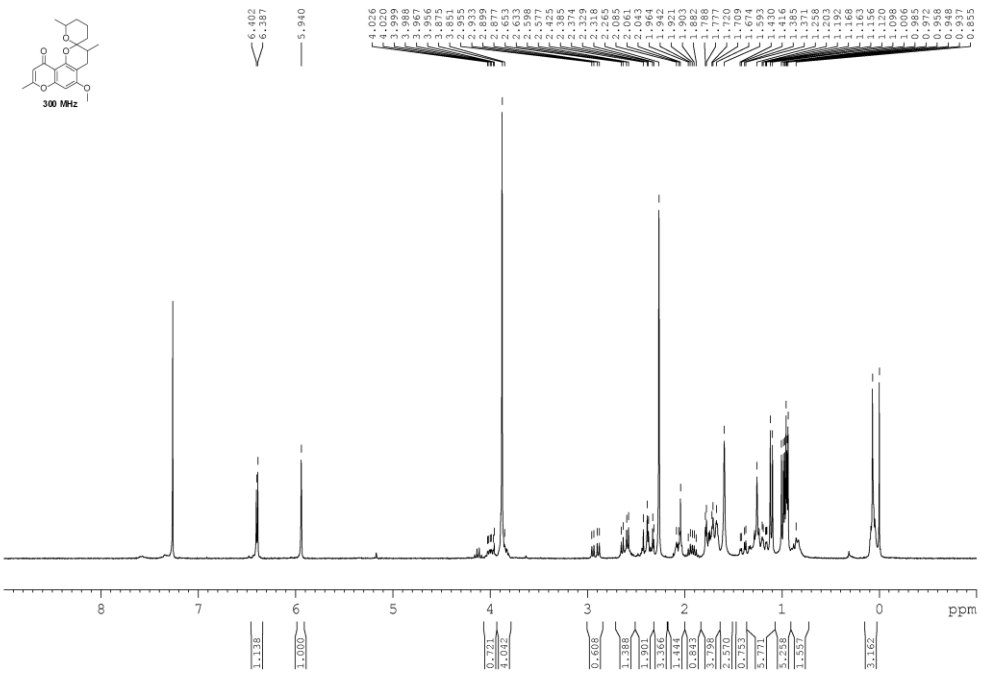
ent-**2**

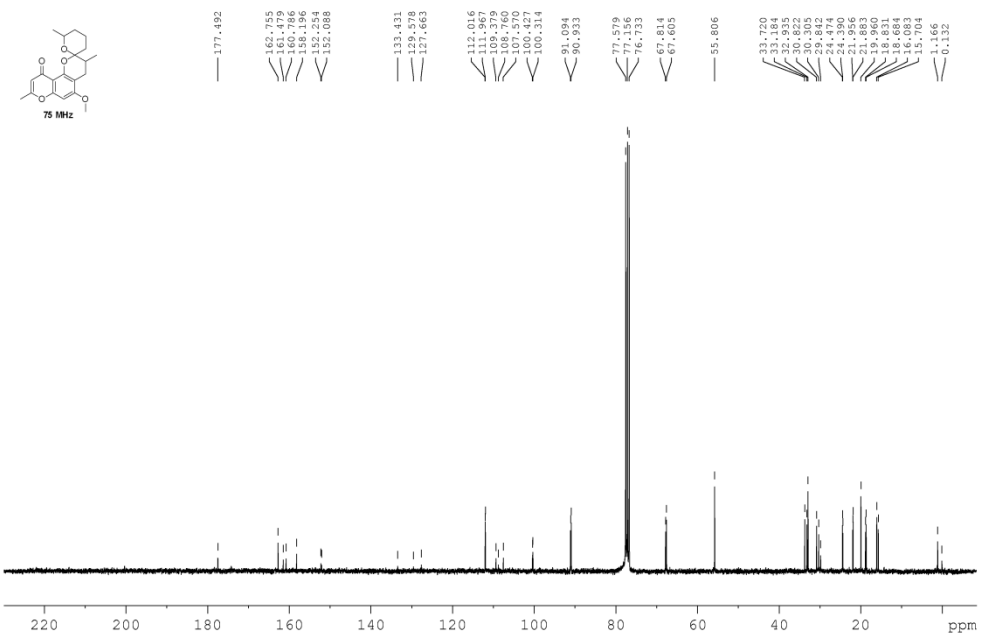




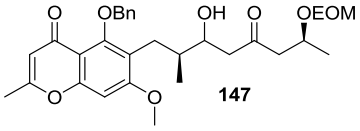
deoxy-spiroketal **120**

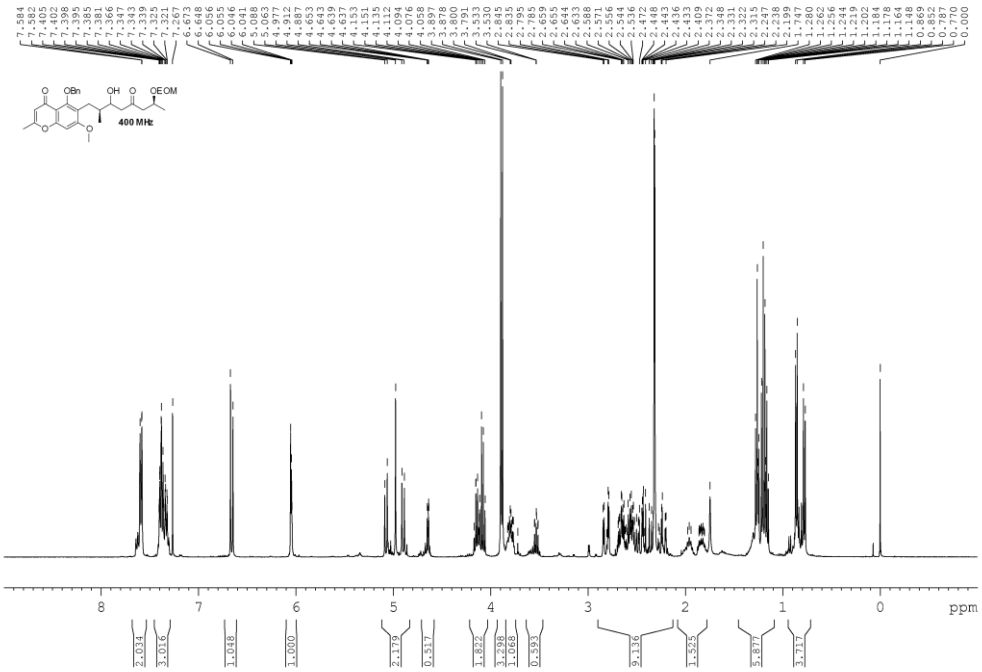


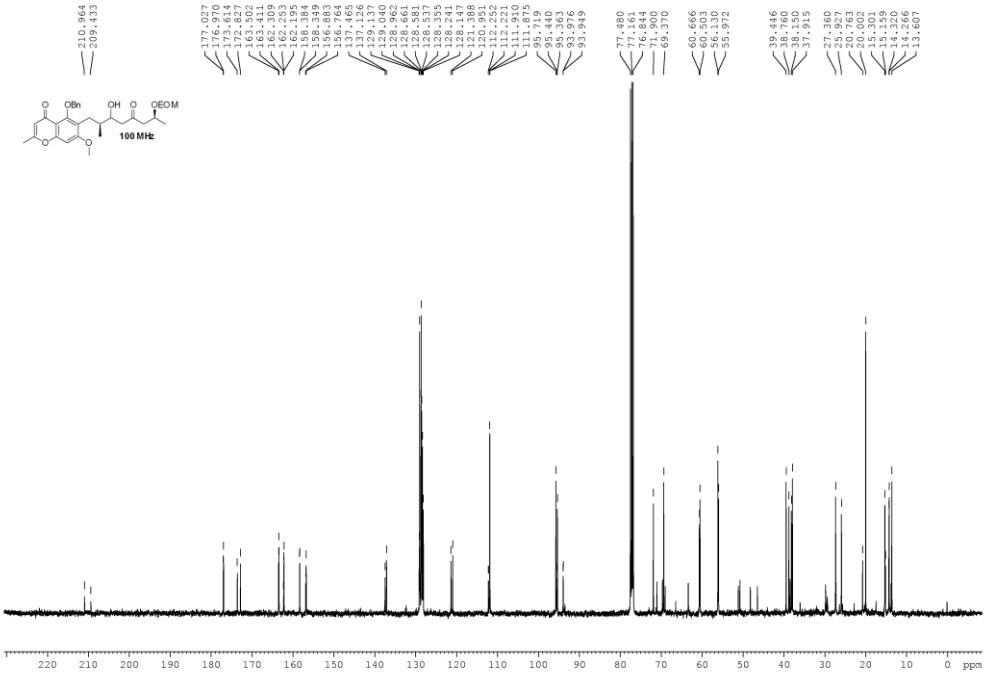




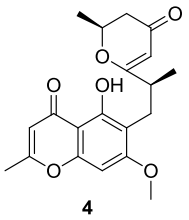
5-(benzyloxy)-6-((2′*S*,7′*S*)-7′-(ethoxymethoxy)-3′-hydroxy-2′-methyl-5′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**147**)



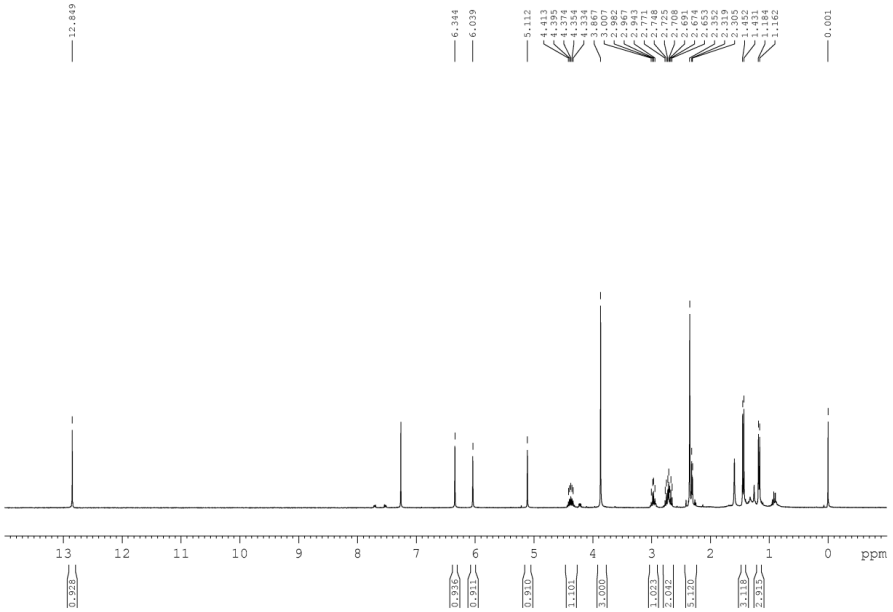


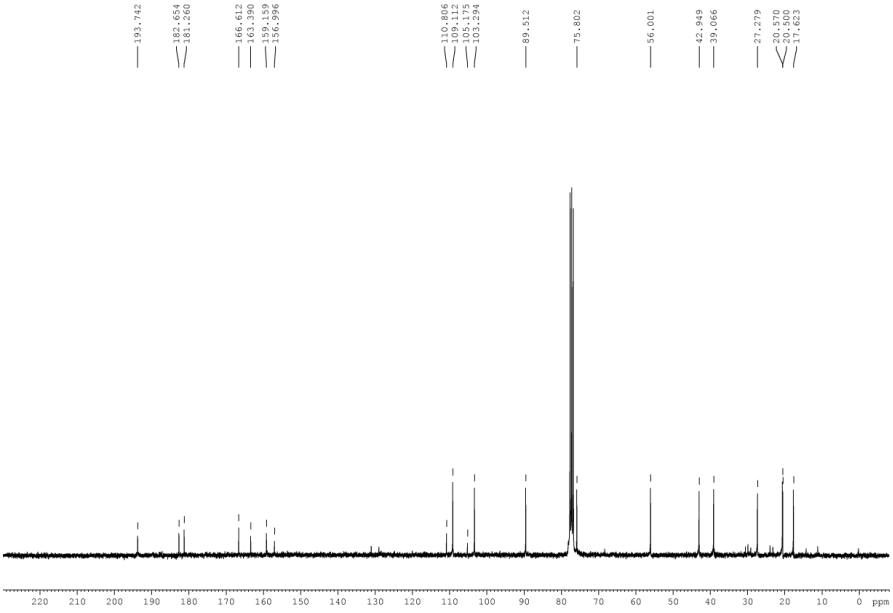


chaetoquadrin H (**4**)

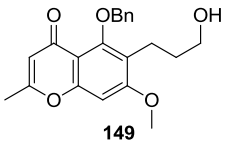


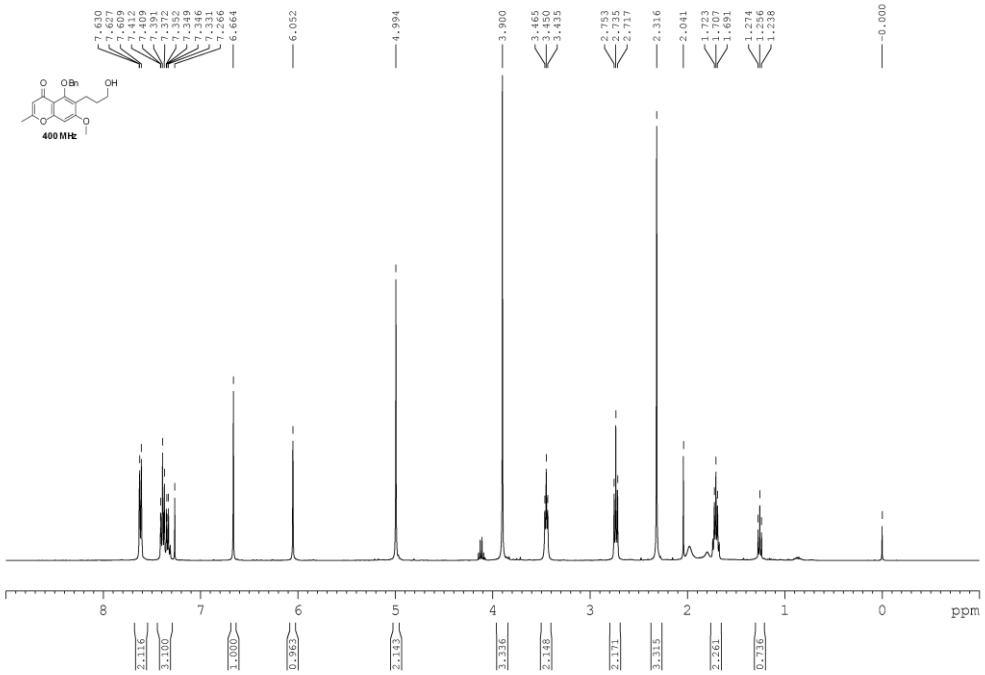
4

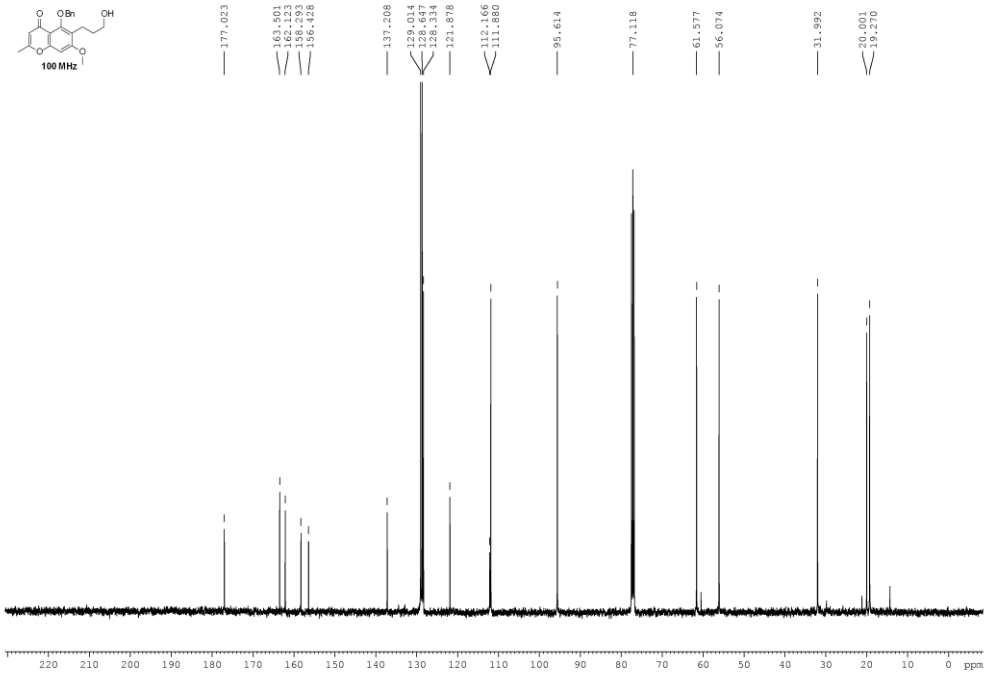




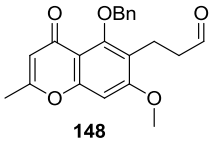
5-(benzyloxy)-6-(3′-hydroxypropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**149**)



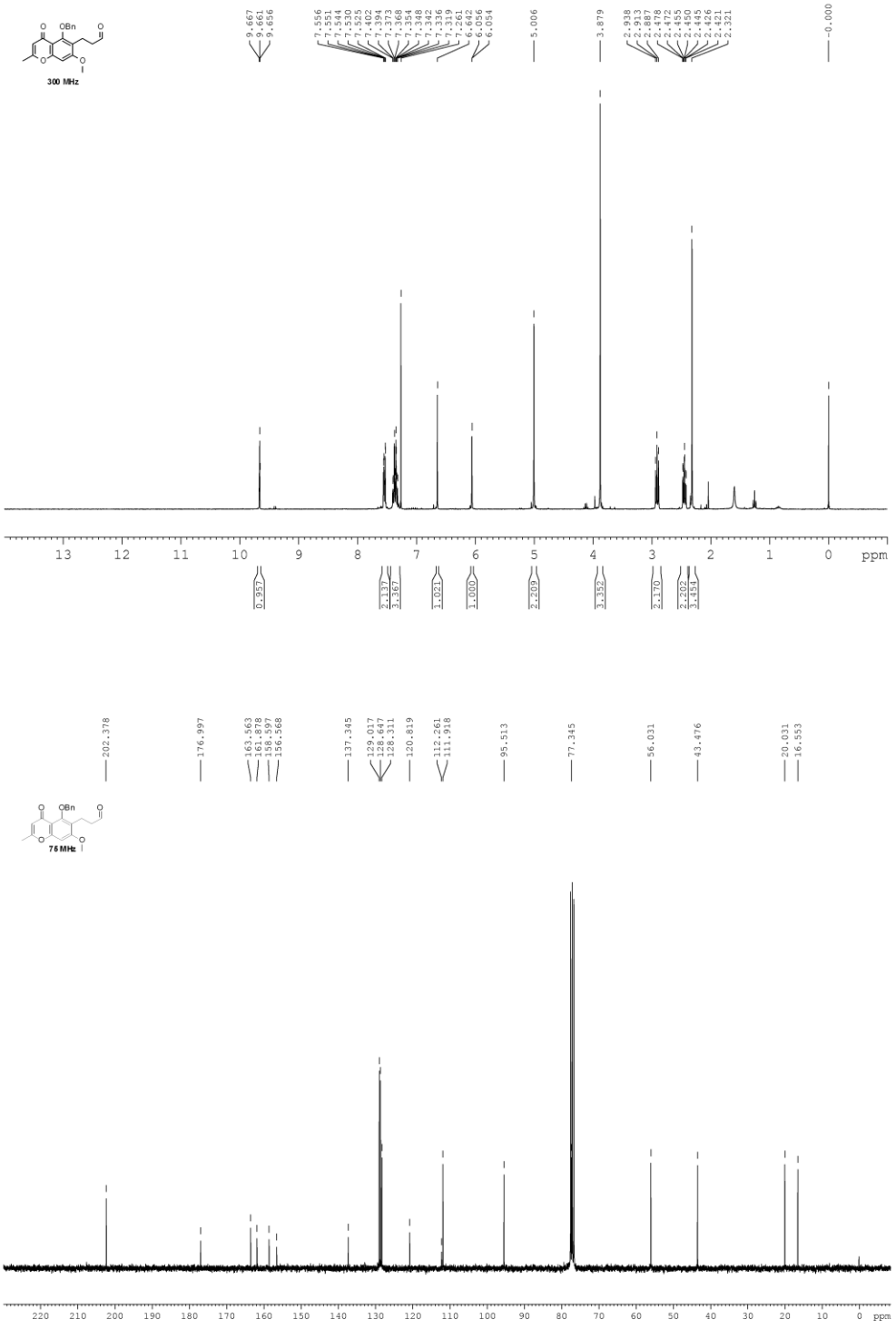




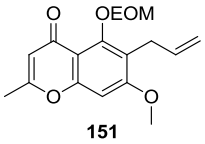
1′-(5-(benzyloxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)propan-3′-al (**148**)



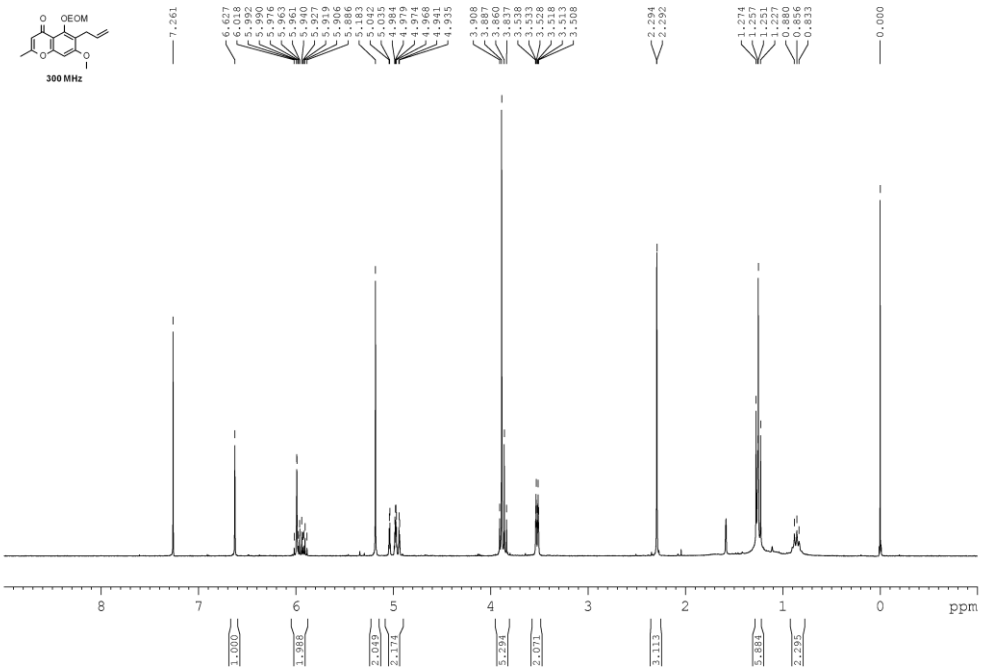
148

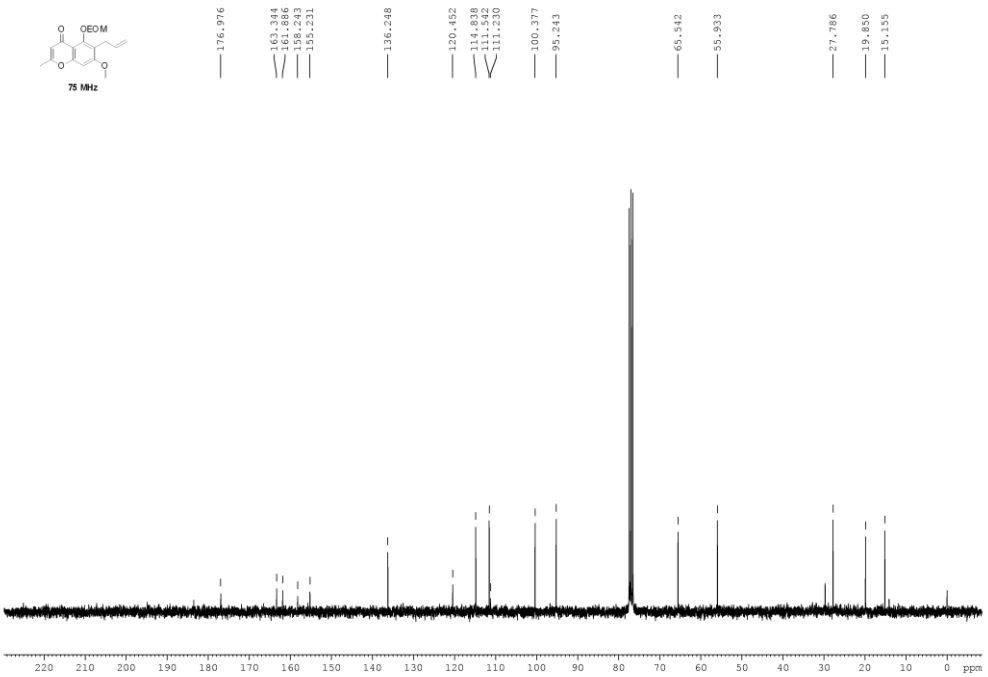


6-allyl-5-(ethoxymethoxy)-7-methoxy-2-methyl-4*H*-chromen-4-one (**151**)

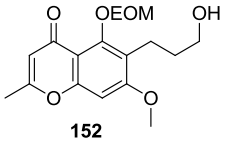


151

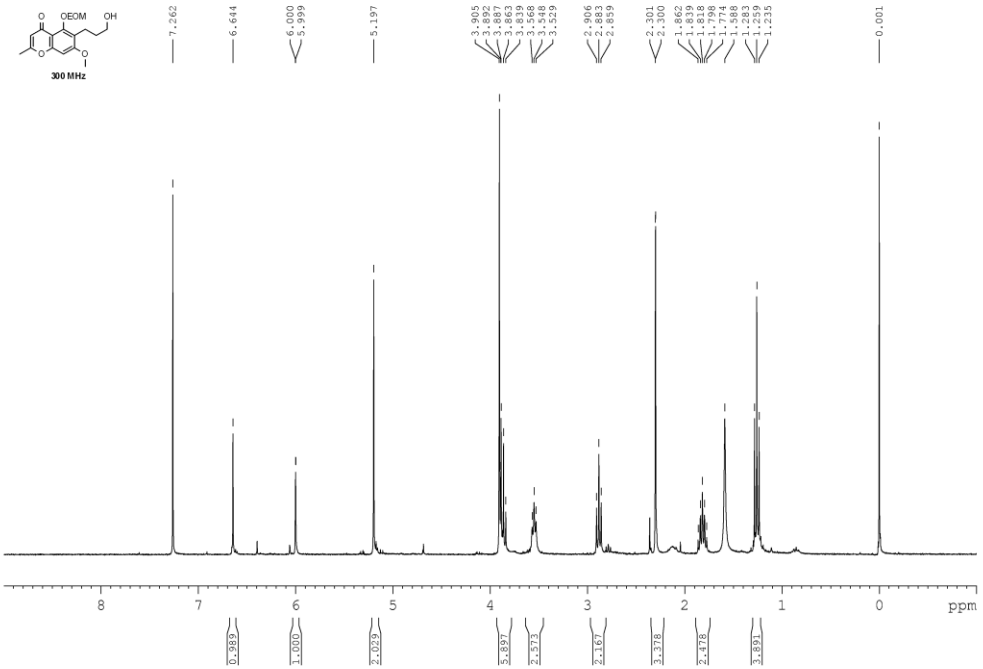


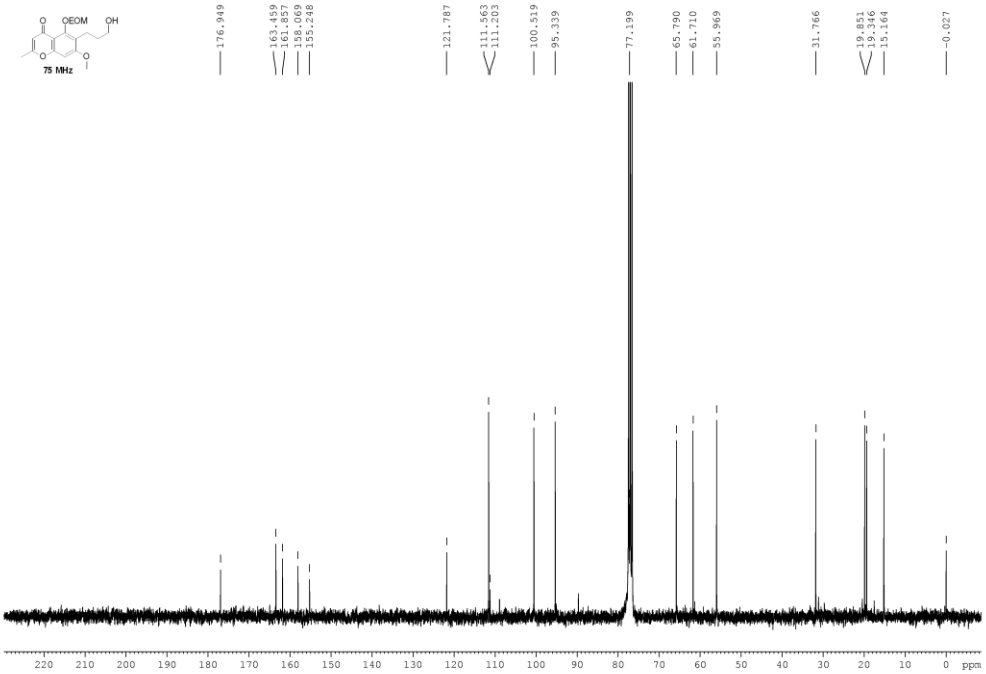


5-(ethoxymethoxy)-6-(3′-hydroxypropyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**152**)

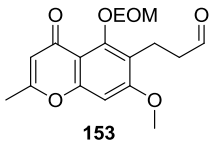


152

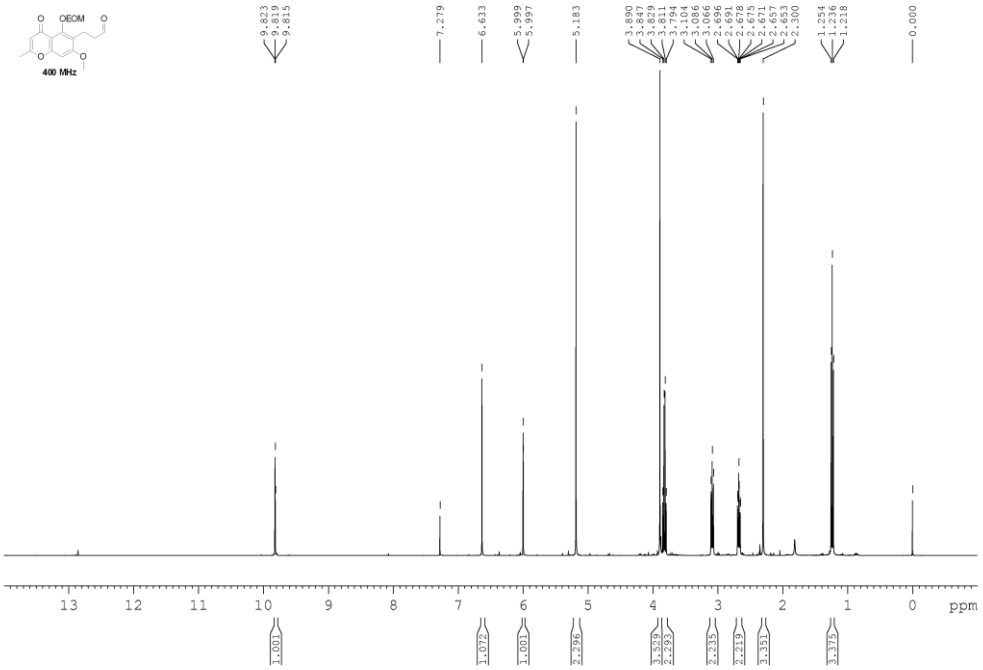


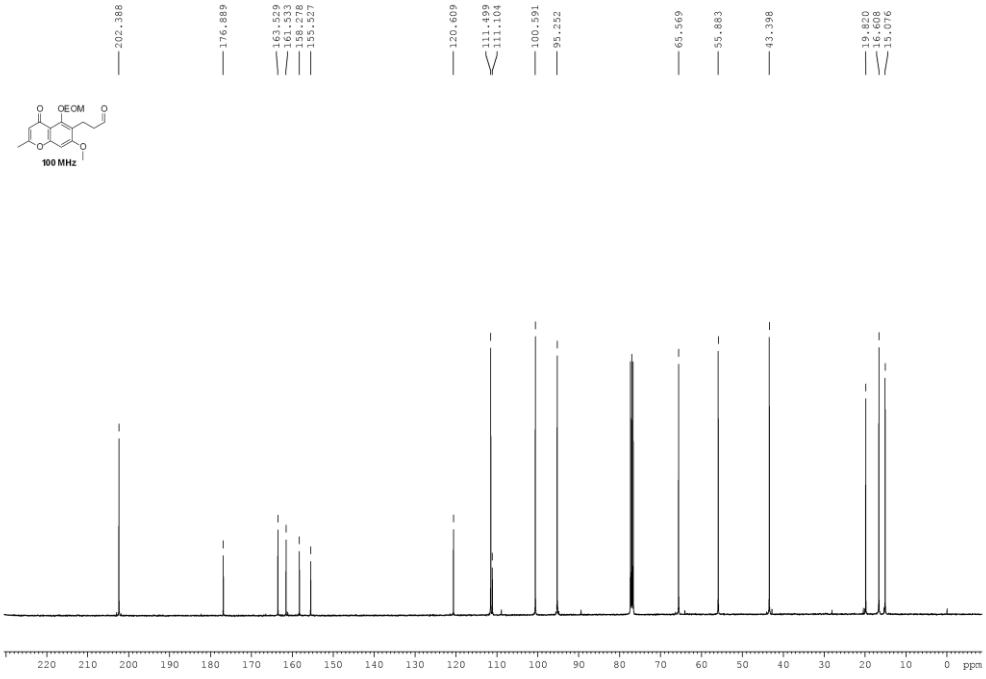


1′-(5-(ethoxymethoxy)-7-methoxy-2-methyl-4-oxo-4*H*-chromen-6-yl)propan-3′-al (**153**)

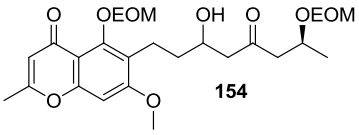


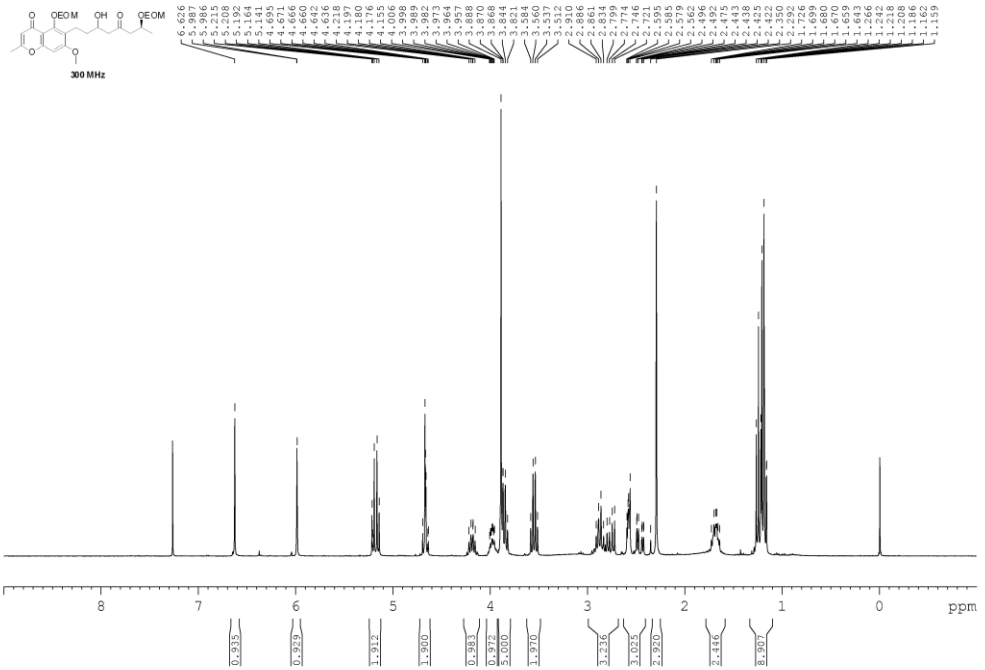
153

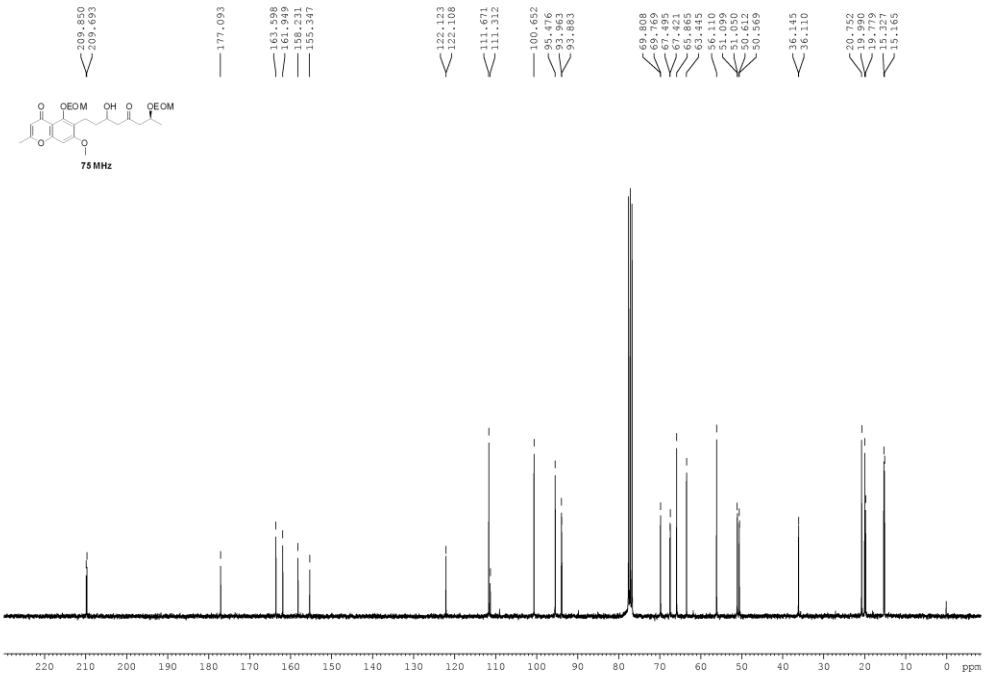




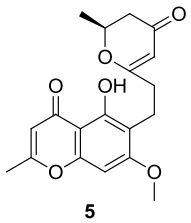
5-(ethoxymethoxy)-6-((7′*S*)-7′-(ethoxymethoxy)-3′-hydroxy-5′-oxooctyl)-7-methoxy-2-methyl-4*H*-chromen-4-one (**154**)



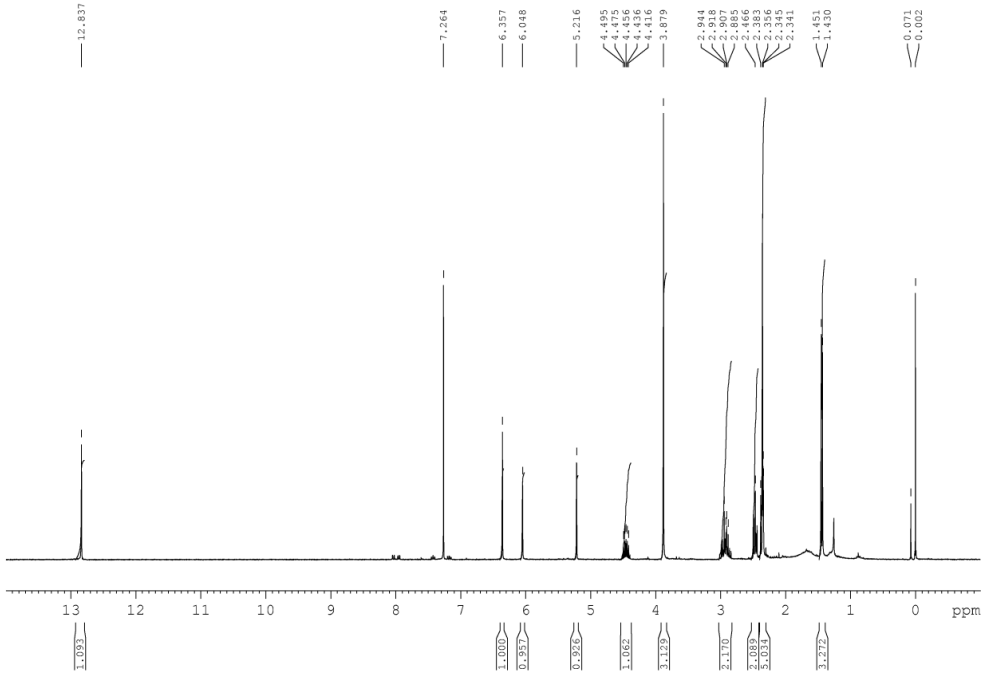


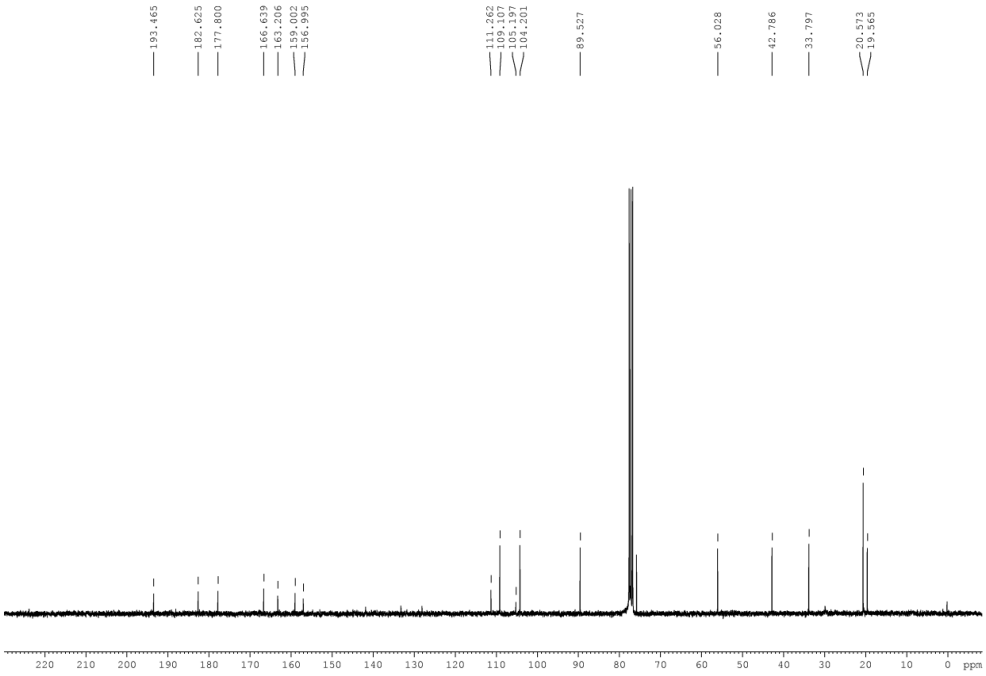


chaetoquadrin I (**5**)



5





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