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The synthesis of Open Chain Pancratistatin Analogues

Warren Thompson

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the Degree of Master of Science

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Declaration

I declare that the work presented in this dissertation was carried out exclusively by myself under the supervision of Prof. W.A.L. van Otterlo. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



Warren Thompson
February 2010

Abstract

(+)-Pancratistatin is a medicinally useful compound which has been isolated from plants belonging to the Amaryllidaceae plant family. The deceptively simple looking pancratistatin is in fact a complicated molecule; it has six contiguous stereocenters of which four belong to alcohol groups and the other two make up a *trans* B-C ring junction. In addition, it consists of three fused rings. The medicinal properties and the synthetic challenges set by pancratistatin have attracted the attentions of many synthetic groups.

Herein are reported approaches to the synthesis of C-*seco* pancratistatin analogues. D(-)-tartaric acid was used as the starting material as it contains two of the four stereocenters found in pancratistatin.

Organocuprate and rhodium-catalyzed reactions were successfully employed to install one of the two stereocenters required for the *trans* B-C junction. The rhodium catalysed addition reactions were found to be more efficient: they were easier to set up, the work up was a simple filtration, high conversions and *anti*-selectivity were observed. The *anti*-selective addition was proved by means of obtaining a crystal structure of 3-((4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylpropanoic acid - a carboxylic acid derivative of an addition product.

Confirmation of the resulting compound, resulting from the attempted ring closure via an isocyanate intermediate - formed through a Curtius rearrangement of an azide - to complete the *trans* B-C junction has proved, through NMR analysis, to be inconclusive. Unfortunately, this result meant that the synthesis was halted one step away from the formation of a protected open chain pancratistatin analogue.

Good progress was made towards the synthesis of open chain pancratistatin analogues and it is said with great optimism that the analogues will eventually be made.

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My daily laboratory routine was made enjoyable through the interactions with all of the members of the Wits Organic Group. A special thank you to all of the past and present Lab 321 members: Tanya, Jenny, Darren, Pavel, Rafique, Candice, James and Matt. Mundane work routines were always brightened by the presence of the above mentioned souls. In addition, I was mentored by three foreign post-doc students. An invaluable amount of organic chemistry was patiently taught to me by these gentle and intelligent souls. Thank you Pavel, Uma and Rafique.

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I thank my parents for their continuous support and believe in me. Wes, thank you for being such a tough brother and for making me want to be the brother you can look up to.

List of abbreviations

Ac	acetyl
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
BTMSA	bis(trimethylsilyl)acetylene
cat.	catalytic
cm^{-1}	wavenumber
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
Et	ethyl
hr	hour
Hz	Hertz, s^{-1}
IBX	2-iodoxybenzoic acid
IR	infrared
Me	methyl
min	minutes
mp.	melting point
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
rt	room temperature
SMEAH	sodium bis(2-methoxyethoxy) aluminum hydride
TBAF	tetrabutylammonium fluoride

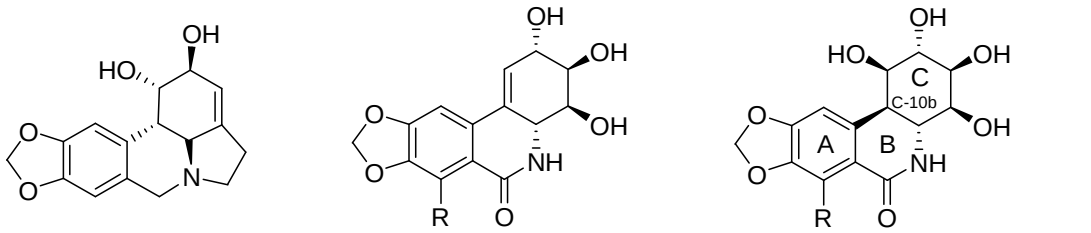
TBS	*tert*-butyldimethylsilyl
TIPS	triisopropylsilyl

Chapter 1: Introduction

1.1 The Amaryllidaceae alkaloids

Historically the Amaryllidaceae plant family has always been a source of medicinally useful compounds; over 30 species have been used to treat cancer in ancient times. The use of Amaryllidaceae family plants can be traced back to the fourth century BC. Hippocrates of Cos used oil extracted from the daffodil *Narciclasus poeticus* to treat patients with uterine cancer. Incidentally South Africa and Andean South America is host to a wide variety of plants belonging to the Amaryllidaceae family.[1]

In 1877, the first Amaryllidaceae alkaloid, lycorine **1** (**Figure 1**) was isolated from *Narcissus pseudonarcissus.*[2] Lycorine has been shown to possess anticancer and antiviral activity.[3] Furthermore from the bulbs of *Lycoris radiate,* the antineoplastics lycoricidine **2** and narciclasine **3** (**Figure 1**) were isolated in 1968.[4]



1 lycorine

2 R = H, lycoricidine
3 R = OH, narciclasine
4 R = H, 7-deoxynarciclasine

5 R = OH, (+)-pancratsistatin
6 R = H, (+)-7-deoxypancratistatin

Figure 1 Medicinally useful compounds belonging to the Amaryllidaceae family



In 1984, Pettit and co-workers isolated (+)-pancratistatin **5** (**Figure 1**) from the spider lily *Pancratium littoralle.*[5] During biological evaluation, pancratistatin has shown activity as an antiviral[6], antiparasitic[7] and anticancer agent.[8,9,10,11] As an anti-cancer agent, pancratistatin has shown excellent *in vitro* and *in-vivo* activity against: leukaemia, pancreas, breast, lung, colon and prostate cancer cell lines.[8,9] A few

years later, (+)-7-deoxypancratistatin **6** (**Figure 1**) was isolated from *Haemanthus kalbreyeri* by Ghosal and co-workers.[12] As with (+)-pancratistatin, (+)-7-deoxypancratistatin has also been shown to possess useful medicinal properties.

Examining the etymology of the word pancratistatin it's no surprise as to how medicinally powerful the compound is. The word pancratistatin comes from the Latin word *pancratistatinum* which means an "all-powerful breaker or stopper".[13] The plant from which pancratistatin was isolated, *Pancratium littoralle,* translates from latin as "all powerful from the shore of a lake". The Latin word *pancratium* is the offspring of the Greek word *pankration* which means "victory by any and all means". The word, *pankration,* was used to describe ancient Greek wrestling matches which were fought to the death or until total surrender of one of the opponents – gouging and biting were forbidden from these contests!

1.2 Medicinal properties of pancratistatin and 7-deoxypancratistatin

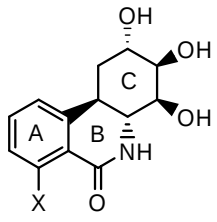
Cancer still plagues modern civilisation and despite enormous efforts to cure the disease there is still no single cure which effectively singles out cancerous cells. Currently Western medicine predominately makes use of gentotoxic treatments such as chemotherapy, radiotherapy and immunotherapy. These treatments involve damaging the DNA of cancerous cells which then initiates apoptosis - programmed cell death. These treatments can not selectively damage cancerous cells and the apoptosis of healthy cells is unavoidable.[14] There is even the possibility that by damaging healthy DNA secondary cancers are created.[14]

Pancratistatin **5** and 7-deoxypancratisatin **6** (**Figure 1**) showed very good efficacy against the US National Cancer Institute (NCI) human cell lines,[8,9,10,11] with pancratistatin being the most active anticancer agent of the two.[15] Pancratistatin has also shown activity as an antiviral[6] and antiparasitic[7] agent. In fact, 7-deoxypancratistatin and pancratistatin are two of only three agents which showed activity in a Japanese encephalitis virus-infected mouse model.[6] Importantly, pancratistatin has also been shown to selectively induce

apoptosis in cancerous cells.[13] Although the mechanism by which pancratistatin is able to induce apoptosis is unknown, the site of action is likely to be the mitochondria of the infected cells.[13] Interestingly, it is believed that the difference in the mitochondria of healthy *vs.* cancerous cells is one of the main causes for the development of cancers.[16]

Although medicinally useful Amaryllidaceae alkaloids have been isolated, their potential to be used has been hampered due to their low natural abundance. It is thus the onus of synthetic chemists to attempt to synthesise these natural products - in an efficient manner - so as to allow for extended medical trials and ultimately their prospective use on humans. Pancratistatin has been used in pre-clinical trials as an anticancer agent for two decades; this long time frame is attributable to pancratistatin's low natural abundance and lack of viable synthetic routes; an eloquent review of nine of the better total syntheses of pancratistatin has been prepared by Kornienko.[17]

A lot of energy has been spent towards identifying pancratistatin's pharmacophore and mode of medicinal action by the groups of Pettit *et al*.,[18] Faculty *et al.* [13,19] and Rinner *et al.*[20] So far it has been discovered that for a pancratistatin analogue to be effective in inducing apoptosis in cancer cells it is necessary that there is: a 2,3,4-triol cyclitol ring (Ring C), a full phenanthridone nucleus (Ring A, B and C), *trans* fused B-C rings and an alcohol group or a proton at the A-7 position **7** (**Figure 2**). It was only through the synthesis and testing of a great variety of pancratistatin analogues that these groups were able to suggest a minimum pharmacophore; the suggested structural requirements must be held in mind if one wants to synthesise a useful anticancer pancratistatin analogue. It is thus obvious that there is not very much that can be changed from the original pancratistatin molecule for an analogue to be effective.

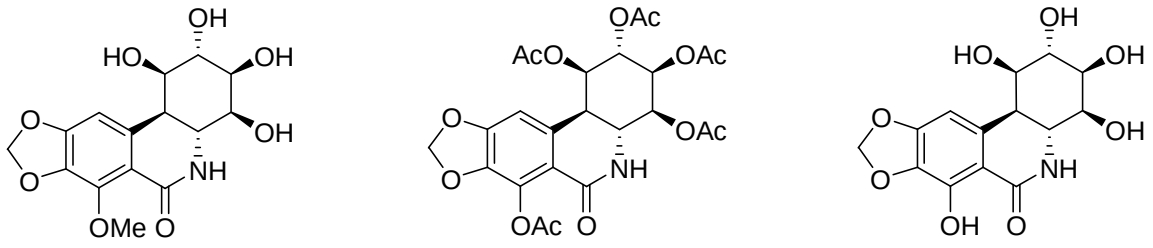


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Figure 2 The minimum pharmacophore of pancratistatin

1.3 Isolation of pancratistatin

In 1984 Pettit's group isolated pancratistatin from the bulbs of the Hawaiian plant, *Pancratium littorale.*[5] In this study the bulb portion of the plant was extracted with dichloromethane-methanol-water. A bioassay using the PS *in vivo* system showed that a compound in the water fraction showed antineoplastic activity. Pancratistatin was then extracted from the aqueous phase using *n*-butanol. Purification was achieved using selective solubility properties and gel permeation chromatography on Sephadex-20. 6.5 g (0.028%) of pure pancratistatin **10** (**Figure 3**) was eventually isolated from 45 kg of the bulbs used. Pancratistatin was converted to the monomethyl **8** (**Figure 3**) which was subsequently re-crystallized from 95% aqueous ethanol and a crystal structure was obtained. In addition the penta-acetate protected pancratistatin **9** (**Figure 3**) was also made. Spectroscopic data of **8, 9** and **10** together with the crystal structure of **8** was used to assign the structure of pancratistatin as **10**. At this point in time they were not confident about assigning the absolute stereochemistry of pancratistatin – although what they hypothesised did in fact turn out to be the correct assignment. Pettit's group also showed that the pancratistatin isolated was useful in combating marine P-388 lymphocytic leukaemia.[5]



8 **9** **10**

Figure 3 The structure of pancratistatin and its derivatives *assigned* by Pettit

In 1986 Pettit isolated narciclasine **3** and 7-deoxynarciclasine **4** (**Figure 1**) from the bulbs of *Pancratium littorale.*[8] In addition, the isolation of pancratistatin **5** (**Figure 1**) from the bulbs of the plant was slightly improved from 0.028% to 0.039%.

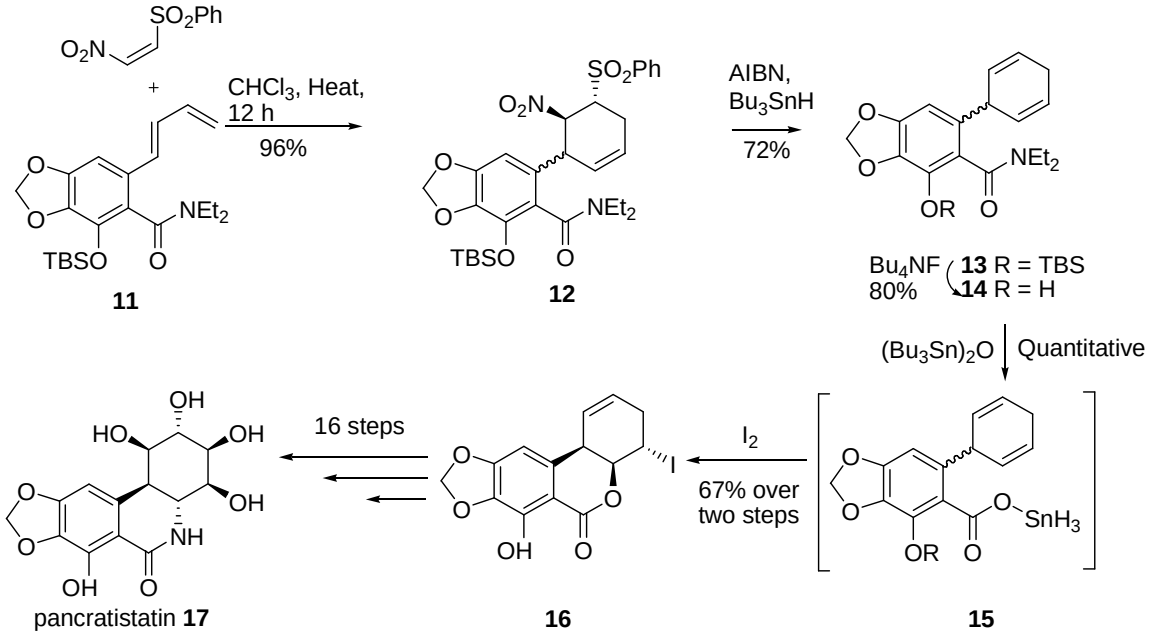
It was also shown that pancratistatin **5** was effective against the P-388 *in vitro* cell line and murine M-5076 ovary sarcoma.[8] It was becoming apparent that pancratistatin **5** (**Figure 1**) was a potential medicinal champion of the Amaryllidaceae plant alkaloids and deserved greater interest from the scientific community. In 1999 Khan *et al.* published methodology of re-extracting pancratistatin from human plasma. The experiments conducted provided a greater insight into pancratistatin's stability in human blood plasma. A solid-phase extraction and HPLC assay were used to recover as much as 90% of the pancratistatin which had been infused for up to five days in human blood plasma.[19] From a medicinal point of view; the information gathered showed that pancratistatin was stable for up to five days, in different concentrations, in human blood plasma. From a practical point of view this would mean that re-extracted pancratistatin could be used for several trials; this would be very useful in light of its low availability. In 2005, Pettit was able to extract pancratistatin (0.041%) from the Texas grasshopper *Brachystola magna*. In addition, they were able to obtain the first crystal structure of pancratistatin.[21] The medicinal potential of pancratistatin along with the low isolation yields prompted the need for a viable synthesis of pancratistatin.

1.4 Synthetic strategies towards pancratistatin – a brief history

A comprehensive set of reviews has been published describing the syntheses of Amaryllidaceae anticancer agents; especially with regard to pancratistatin, 7-deoxypancratistatin, narciclasine and lycoricidine.[2,22,23,24,25,26] Recently Kornienko published a comparative review of the nine total syntheses of pancratistatin published up until 2008.[17]

In 1989 the first racemic pancratistatin synthesis was achieved by Danishefsky and Lee (**Scheme 1**).[27] Their synthesis was an arduous 27 steps and they were able to achieve an overall yield of 0.16%. The first key step was the Diels-Alder reaction between the butadiene group found on compound **11** and a β-nitrovinyl sulfone to yield the sulfonyl nitro compound **12 (Scheme 1**). The hexadiene **13** (**Scheme 1**) was then successfully made using tri-*n*-butyltin hydride to initiate the elimination.

Halolactonisation, using a variety of methods, of the hexadiene **13** (**Scheme 1**) was unsuccessful. They cited the repulsion between the large OTBS and amide group as preventing the halolactonisation from occurring. However once the TBS protecting group was removed, **14** (**Scheme 1**) was still resistant to halolactonisation. It was thus decided that the nucleophilicity of the carboxamido linkage was not strong enough for the reaction to occur. A way to improve the nucleophilicity was via the stannylation of the phenolic group.[28] This was achieved by reacting **14** with bis(tributyltin)oxide to from the stannyl ether **15** (**Scheme 1**). Iodine dissolved in THF converted the stannyl ether **15** to **16** and eventually racemic pancratistatin **17** (**Scheme 1**) over an additional sixteen steps.

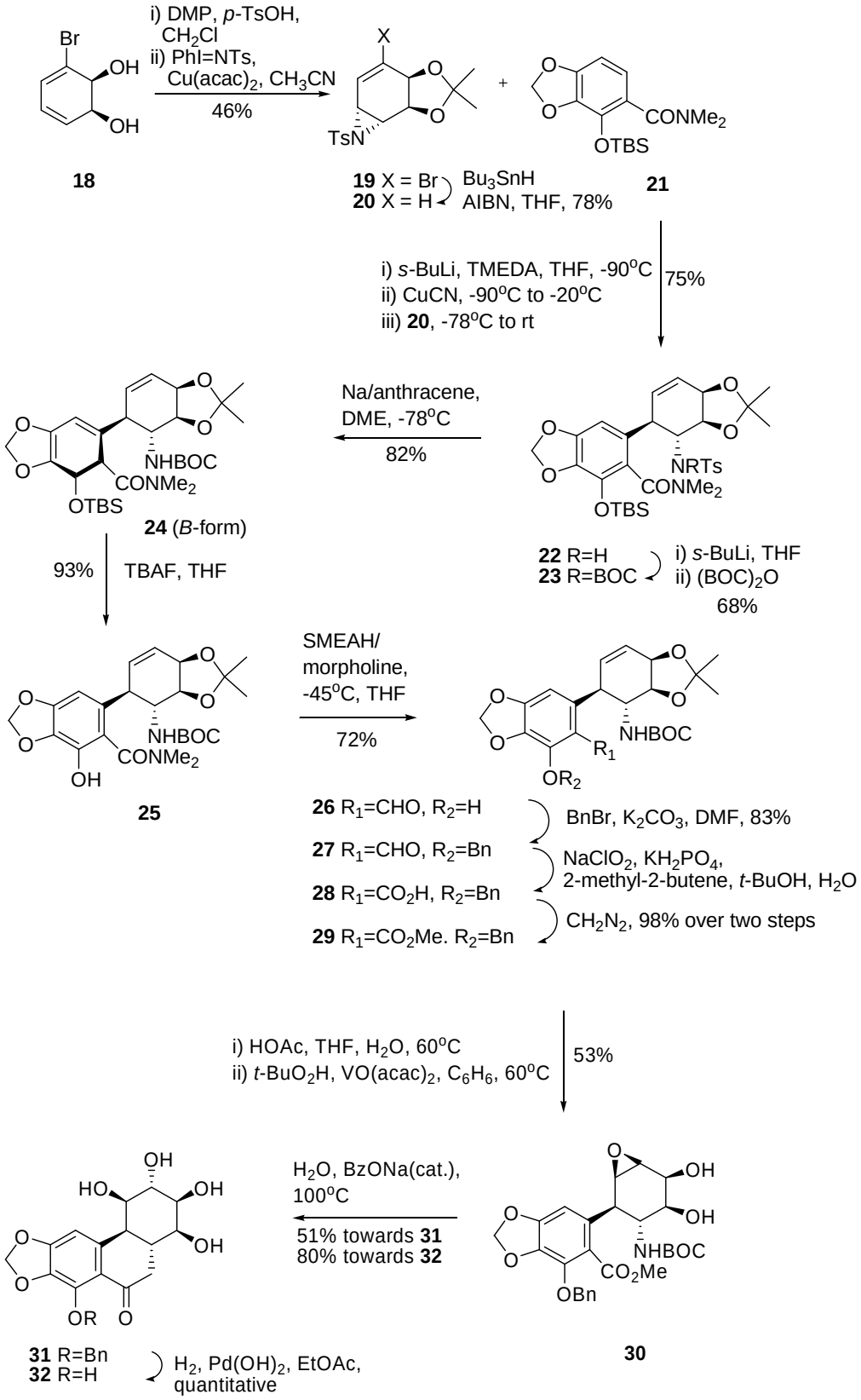


Scheme 1 Key steps in Danishefsky's racemic synthesis of pancratistatin.

In 1995 Hudlicky's group reported the first asymmetric synthesis of pancratistatin (**Scheme 2**).[29] The synthesis was an economical 13 steps and had an overall yield of 2%. Hudlicky started with the commercially available (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol **18** (**Scheme 2**) which was prepared from the oxidation of bromo-benzene using the bacteria *Pseudomonas putida.*[36] This important starting material already contained the *cis*-diol unit found in pancratistatin.

The next challenge was to attach an aryl group to the diol unit which retained the stereochemistry required at the C-10b position of pancratistatin. This was achieved by making a lithium cyanocuprate of the aryl moiety **21** (**Scheme 2**) and reacting this with the *cis*-diol unit **20** (**Scheme 2**). At this point Hudlicky was looking forward to completing the phenanthridone core via a transamidation reaction. Unfortunately it was found that the position of the tosyl group on the amine relative to the dimethylamide **22** (**Scheme 2**) (180°) was not conducive to transamidation to form the cyclized phenanthridone core. This unexpected result added a further six steps to the synthesis. Subsequently, the tosyl group was replaced by a BOC group to form compound **23** (**Scheme 2**). The research group's luck then got worse as the instalment of the BOC group caused problems later as it hindered the α-face of ring C to epoxidation; unfortunately it was necessary to remove the BOC group prior to epoxidation and have it reinstalled after epoxidation.

A lucky break was finally granted during an attempted opening of the epoxide using a catalytic amount of sodium benzoate to yield the required *trans*-diol. A remarkable set of results occurred if the reaction was allowed to proceed over six days: the epoxide was opened, both the BOC and benzyl protecting groups were removed and furthermore there was ring closure to furnish pancratistatin **32** (**Scheme 2**). If the reaction was allowed to react for a shorter period of time of two days, the reaction yielded the benzylated analogue **31** (**Scheme 2**).

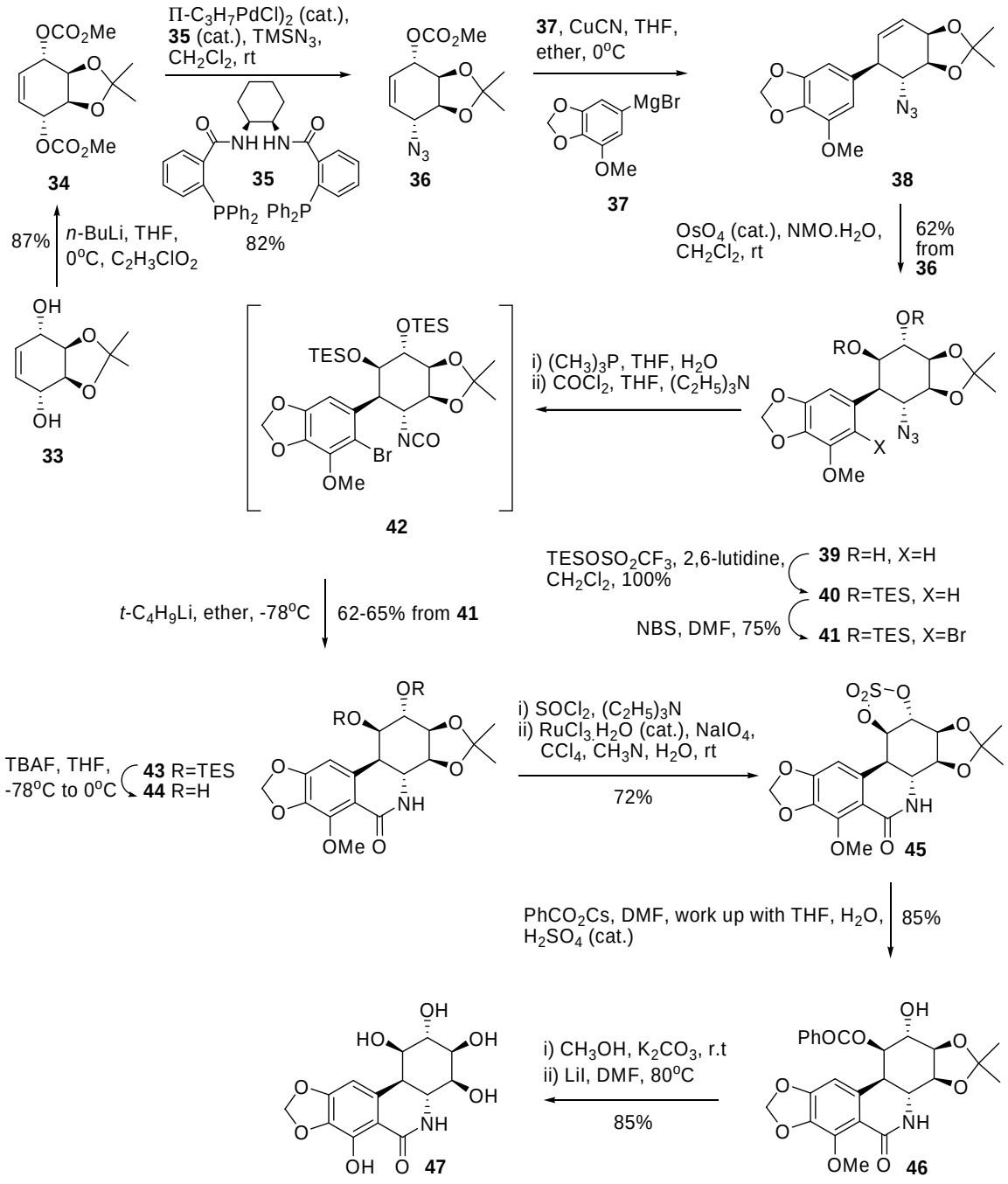


Scheme 2 The first asymmetric synthesis of pancratistatin

Later that year Trost and Pulley reported another asymmetric synthesis (**Scheme 3**).[31] Their synthesis consisted of 20 steps and had an impressive overall yield of 11%. Similarly to Hudlicky's synthesis, Trost started with a *cis* diol starting material **33** (**Scheme 3**). The treatment of **33** with *n*-butyl lithium, followed by quenching with methyl chloroformate yielded the symmetrical dicarbonate **34** (**Scheme** 3). Desymmetrisation of **34** with trimethylsilyl azide was then achieved by using catalytic amounts of both π-allylpalladium chloride and ligand **35** to yield the azide **36** (**Scheme 3**).

Formation of the C-10b stereochemistry was again problematic; the addition of the aryl moiety, using organocuprate chemistry, did not proceed as expected. The researchers suggested that the arylcuprate was probably not stable enough for the reaction to occur. Trost was eventually able to introduce the necessary stereochemistry by reacting Grignard **37** with azide **36**, in the presence of cuprous cyanide to yield azide **38** (**Scheme 3**).

Another pitfall in their synthesis was in the unexpected non-intramolecular ring closure of the isocyanate intermediate formed from compound **39** (**Scheme 3**). It was suggested that acetonide oxygens – a σ-nucleophile - were more nucleophilic than the aryl ring – a π-nucleophile - and hence more willing to attack the isocyanate formed. Unfortunately, Trost did not either characterize or report the compound that formed as a result of the attempted formation of the isocyanate and the expected ring closure of compound **39**. The problem was circumvented by converting the aryl ring into a stronger σ-nucleophile via the introduction of bromine onto the aryl ring **42** (**Scheme 3**). The late addition of a bromine atom to the aryl ring added an additional eight steps and as a result the number of total synthetic steps was almost doubled. The rest of the synthesis proceeded smoothly towards synthetic pancratistatin **47** (**Scheme 3**).

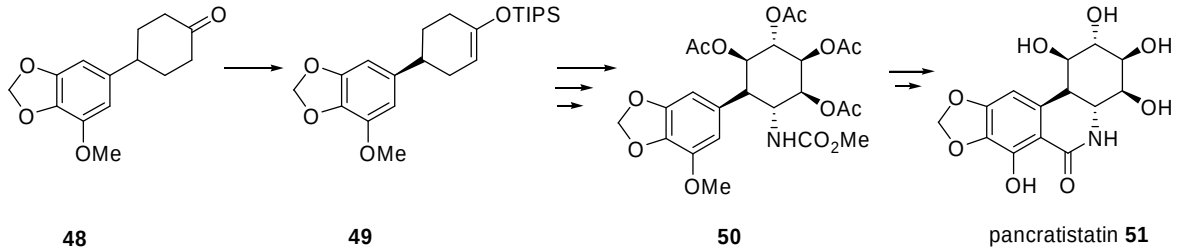


Scheme 3 Trost's asymmetric synthesis of pancratistatin

In 1998 Magnus, starting with *o*-vanillin, reported the synthesis of pancratistatin utilising 22 steps and an overall yield of 1.5% (**Scheme 4**).[32] Magnus used a β-

azidobistriisopropylsilyl enol ether functionalization of **48** to **49** (**Scheme 4**) to install the required stereochemistry at the C-10b position.

The TIPS protecting group "trapped" the enantiomer shown in 95% yield with >85% ee. Bischler-Napieralski chemistry was then performed on **50** to give an acetate protected phenanthridone skeleton and eventually pancratistatin **51** (**Scheme 4**).



48 **49** **50** pancratistatin **51**

Scheme 4 Key steps in Magnus's pancratistatin synthesis

A number of additional synthetic approaches towards pancratistatin have been reported. These include a synthesis by Rigby's group who used an aryl enamide photocyclisation reaction as his key step to form the *trans* B-C ring. His synthesis was 22 steps with an overall yield of 0.35%.[33] Pettit's group used a novel approach whereby they used (+)-narciclasine as a pre-cursor to (+)-pancratistatin.[34] (+)-Narciclasine is readily available from some Amaryllidaceae plants and relatively easier to synthesise. From (+)-naciclasine they were able to synthesise (+)-pancratistatin in 10 steps with a 3.6% total yield. More recently Madsen's group reported the use of two strategies towards the synthesis of 7-deoxypancratistatin.[35] Both strategies employ the use of carbohydrate starting materials, D-ribose and D-xylose, and ring closing metathesis to form ring C. Several groups have successfully synthesised pancratistatin however no synthesis to date is scaleable. In addition Trost's synthesis is still the highest yielding. The major difficulties in synthesising pancratistatin are the inclusion of the six contiguous stereocenters and the stereochemistry required for the *trans* B-C ring junction. All the syntheses share the following commonalities: there are many protecting and deprotecting steps and that it is evident that addition reactions play an important role in producing the required stereochemistry at site C-10b. It is clear from Trost and Hudlicky's work that the instalment of the stereochemistry at the C-10b site is problematic.

The challenges unveiled during the reported syntheses of pancratistatin encouraged our investigation into the minimum structural requirements of pancratistatin to be a useful medicinal agent. It was hopeful that an efficient synthesis of medicinally potent pancratistatin analogues would emerge. In the next section, synthetic work towards the synthesis of pancratistatin analogues will be discussed.

1.5 Pancratistatin analogues

In 2004 Kornienko and Nadein published the synthesis of various 1-aryl-1-deoxyconduritols F analogues **52** (**Figure 4**);[36] possible precursors of pancratistatin and 7-deoxypancratistatin.

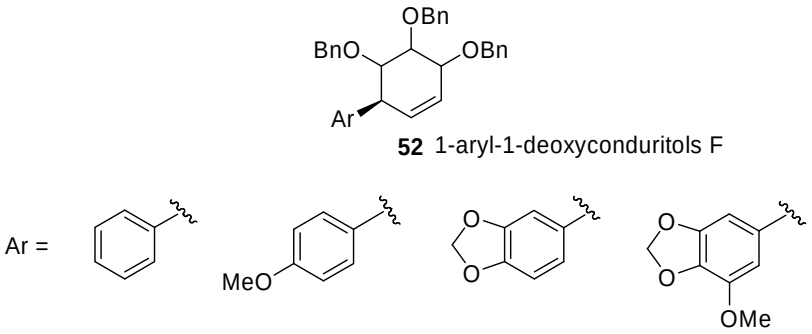
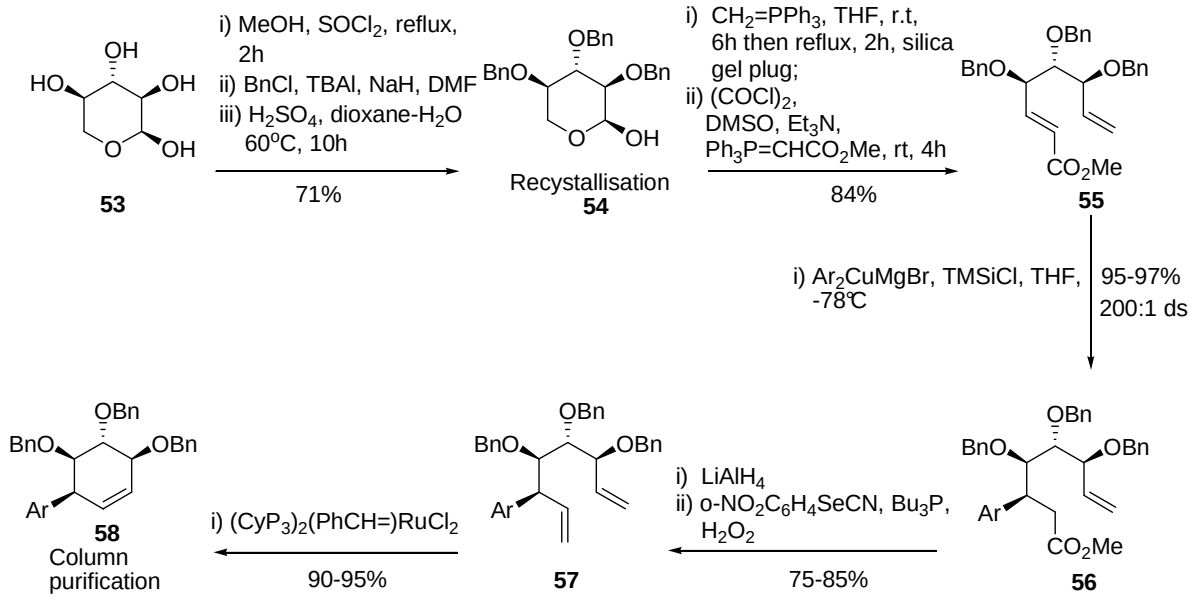


Figure 4 1-aryl-1-deoxyconduritols F analogues synthesised by Kornienko

The researchers started by converting D-xylose **53** into the benzyl-protected **54** (**Scheme 5**). Diene **55** (**Scheme 5**) was then made using oxidation and Wittig reactions. A highly *anti*-selective organocuprate addition was then employed to yield **56** (**Scheme 5**); this was a useful way of installing the stereochemistry required at the C-10b site of pancratistatin. Reduction, followed by ring closing metathesis (RCM) then yielded the 1-aryl-1-deoxyconduritol F **58** (**Scheme 5**).



Scheme 5 Kornienko's synthesis of 1-aryl-1-deoxyconduritols F analogues

Kornienko then went on to publish two more papers describing the use of a organocuprate addition reaction in this area: the *anti*-selective additions to acyclic γ-alkoxy-α,β-enoates,[37] the *syn*-selective additions to acyclic γ-amino and γ-carbamato-α,β-enoates.[38] As will be discussed later, these results would be of interest as it was our intention to apply the same chemistry to a similar acyclic γ-alkoxy-α,β-enoate substituent. Their synthesis was practical and efficient in that only 9 steps were required, column chromatography was employed only twice and many of the steps were accomplished in one pot.

Later in 2006 Kornienko collaborated with a host of individuals to expand on their group's work done in 2004, towards the synthesis of 1-aryl-1-deoxyconduritols F. RCM and the useful *anti*-selective arylcuprate addition were again employed successfully. They were able to synthesise 15 B-*seco* pancratistatin analogues in which ring B of pancratistatin was open (**Figure 5**).[39] Unfortunately none of them showed any potential as cytotoxic, apoptososis inducing or growth inhibitors against leukaemia and adenocarcinoma cell lines. Each analogue had at least four of the stereocenters, including the important C-10b stereochemistry, found in pancratistatin.

It was suggested that the full phenanthridone skeleton and the complete B-C ring junction of pancratistatin was necessary for pancratistatin to exhibit cytotoxity.

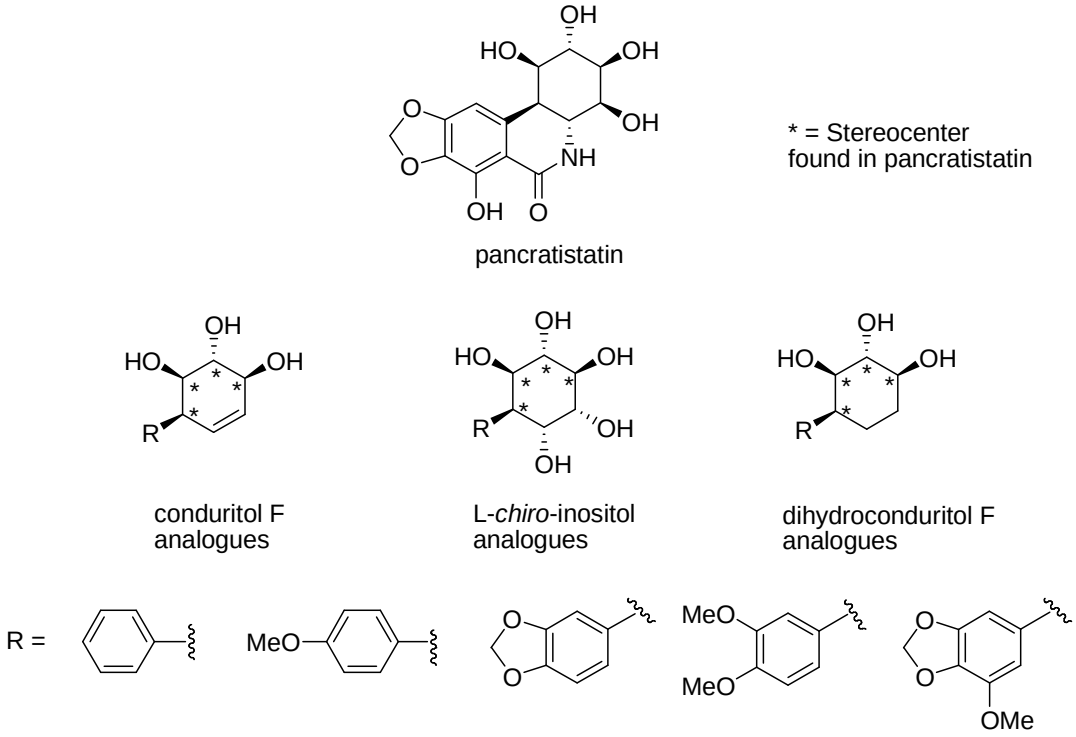
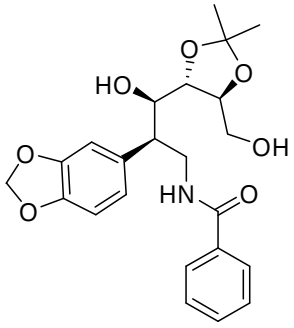
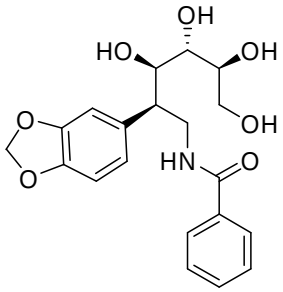


Figure 5 Kornienko's B-*seco* pancratistatin analogues

Furthermore work done by McNulty and co-workers towards the synthesis of B,C-*seco* pancratistatin analogues **59** and **60** (**Figure 6**), also showed that the compounds synthesised had little activity in inducing apoptosis in human cancer cells, further evidence that the B and C rings need to be complete for a pancratistatin analogue to exhibit efficient activity against cancer cells.[40]



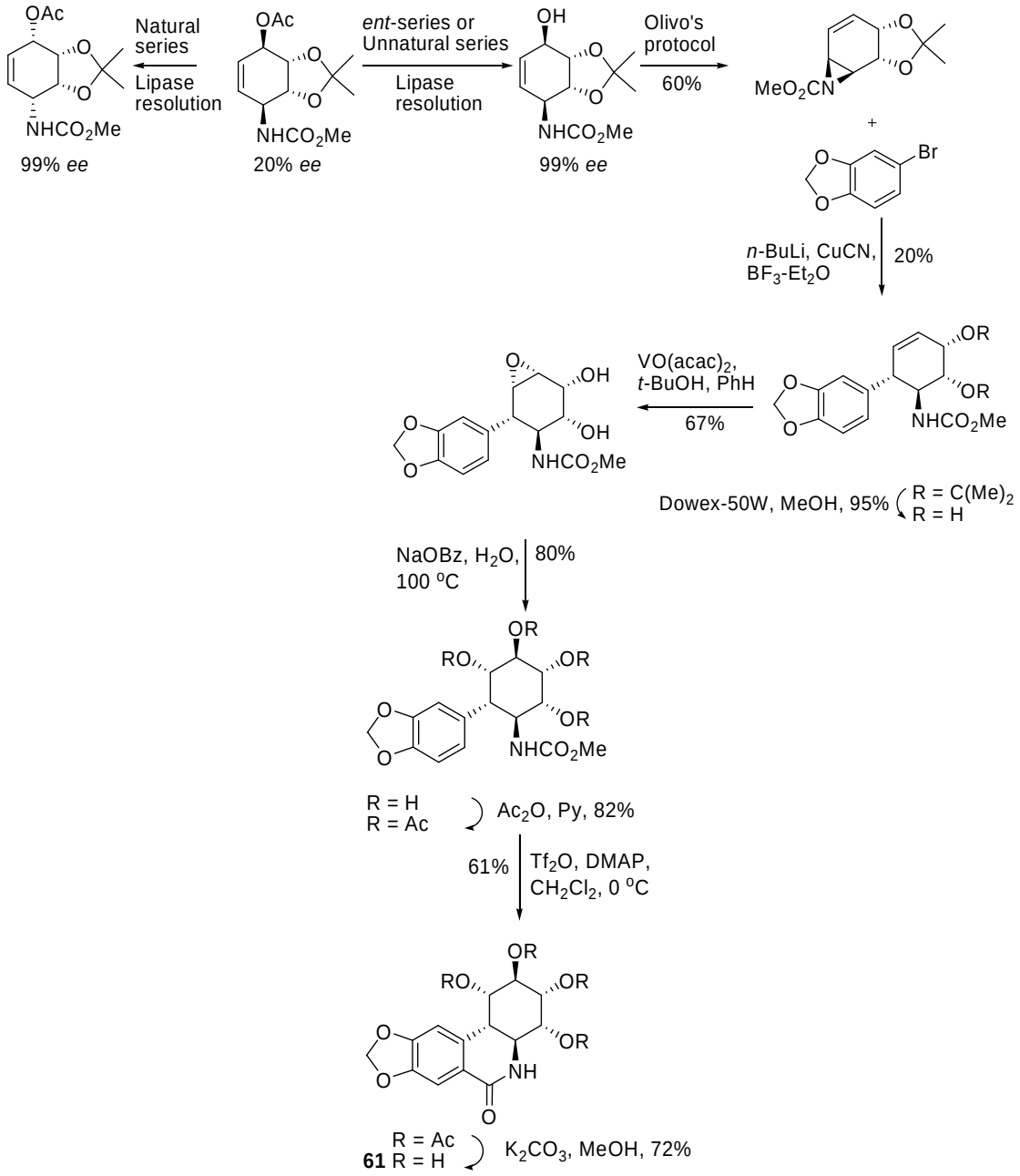
59



60

Figure 6 McNulty's work towards B,C-*seco* pancratistatin analogues

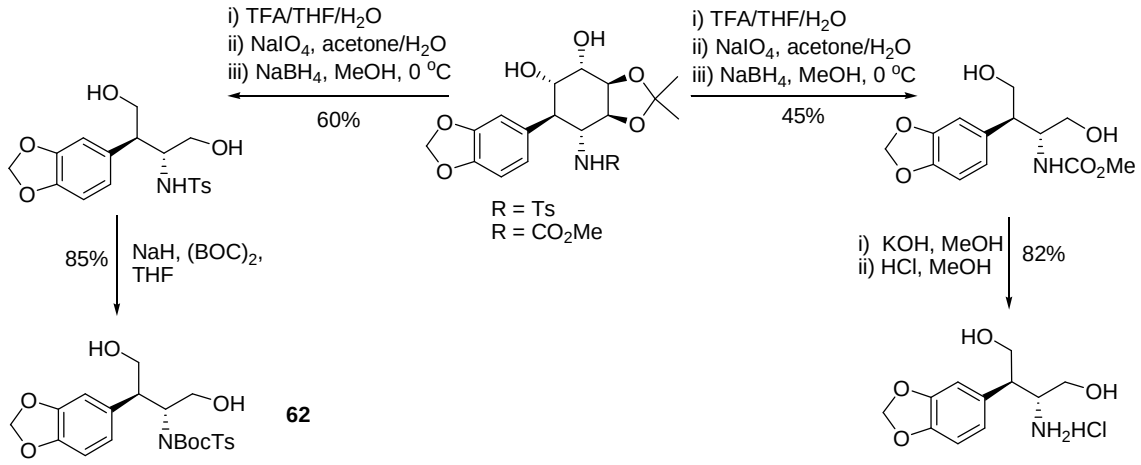
In addition to the total synthesis of pancratistatin, Hudlicky along with a number of his fellow researchers have invested a considerable amount of energy into the synthesis of pancratistatin and 7-deoxypancratistatin analogues. The biological testing of these analogues has provided useful insight into pancratistatin's pharmacophore. Several syntheses of these analogues shall be discussed briefly.



Scheme 6 Hudlicky's synthesis of *ent*-7-deoxypancratistatin

In 2002 Hudlicky and fellow researchers were successful in synthesising *ent*-7-deoxypancratistatin **61** (**Scheme 6**).[20] The compound showed activity, with GI_{50} values of 2.0 - 3.4 $\mu g.ml^{-1}$, against: CNS SF-295, colon KM 20L2, lung NCI-H460, melanoma SK-MEL-5, ovary OVCAR-3 and renal A498 human cancer cell lines, and the marine leukaemia P388 cancer cell line.

The activity observed was ten fold less than that of 7-deoxypancratistatin, which exhibited GI_{50} values of 0.22 - 0.47 µg.ml^{-1} against the same cancer cell lines. The results highlighted the importance of the four alcohol groups on ring C to have the correct stereochemistry.

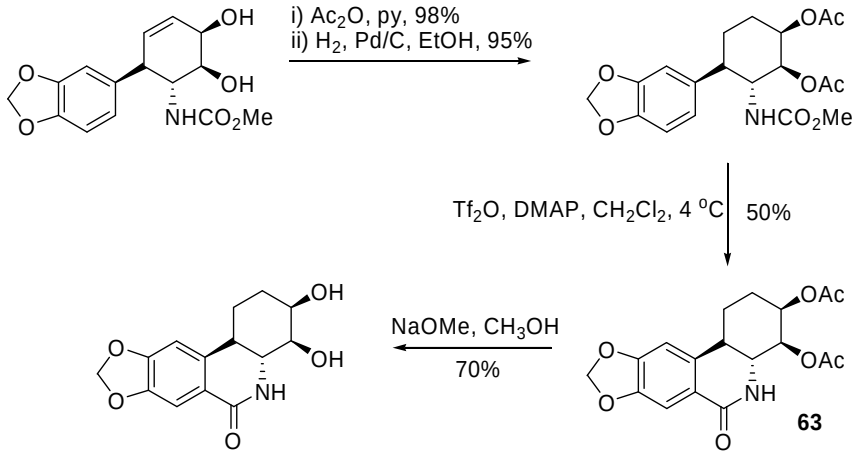


Scheme 7 Truncated analogues of 7-deoxypancratistatin

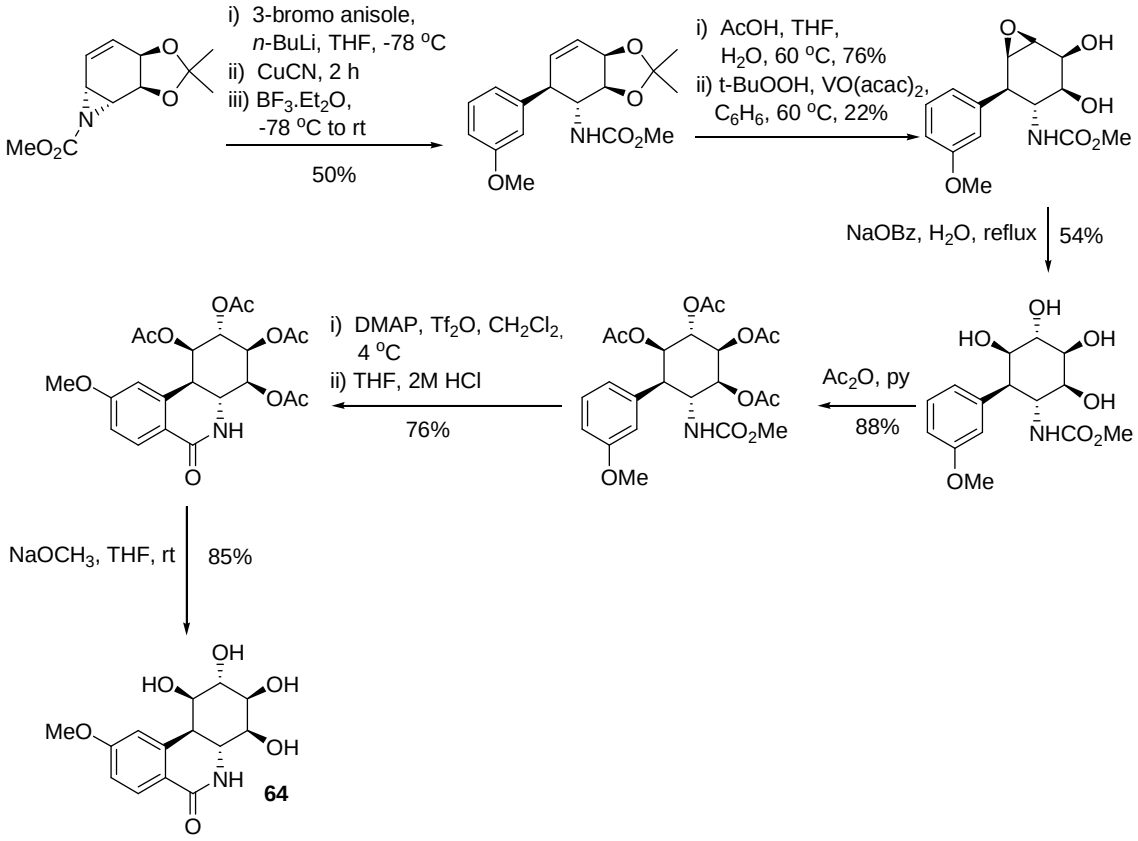
In addition to the *ent*-7-deoxypancratistatin synthesis, the researchers also described the synthesis of truncated, B,C-*seco*, 7-deoxypancratistatin analogues (**Scheme 7**).[20] It was found that only the truncated analogue **62** (**Scheme 7**) showed activity; GI_{50} values of 5.3 µg.ml^{-1} and 8.5 µg.ml^{-1} were recorded for the pancreas-a BX-PG-3 and lung NCI-H460 cancer cell lines, respectively. From these results, similarly to the findings of McNulty and his fellow researchers,[40] it was shown that it was necessary for the B and C ring to be complete for 7-deoxypancratistatin to be active.

In 2004 Hudlicky along with Rinner and Pettit published the synthesis of 7-deoxypancratistatin analogues whereby the oxygen constituents were different on either ring A or C.[11] It was found that the analogue **63** (**Scheme 8**)**,** missing the *trans* diol unit on ring C, was only active against murine P388 lymphocytic leukemia; its activity was a 100 fold less than pancratistatin. Only the analogue having all four alcohol units on ring C **64** (**Scheme 9**) showed activity against both murine P388 lymphocytic leukemia and human cancer cell lines.

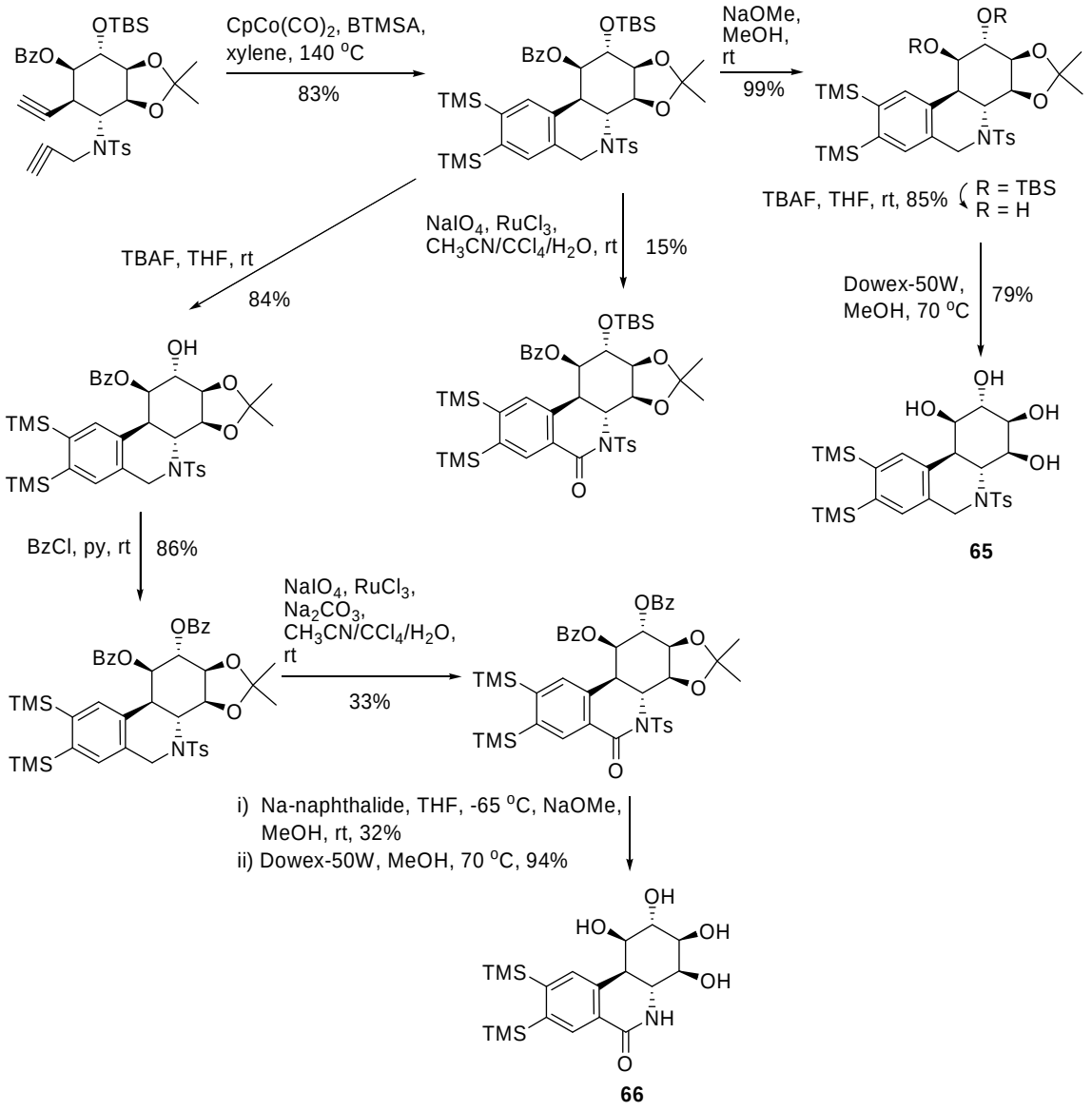
Analogue **64** (**Scheme 9**) displayed activities about a 100 fold less than pancratistatin across the cell lines. Their findings highlighted the importance of having a fully oxygenated ring C. In addition, it could be proposed that the alcohol units, especially the *trans* diol unit, of ring C are more important for activity relative to the dioxole unit of ring A.



Scheme 8 Pancratistatin analogues missing the *trans* diol unit on ring C which were active against murine P388 lymphocytic leukemia

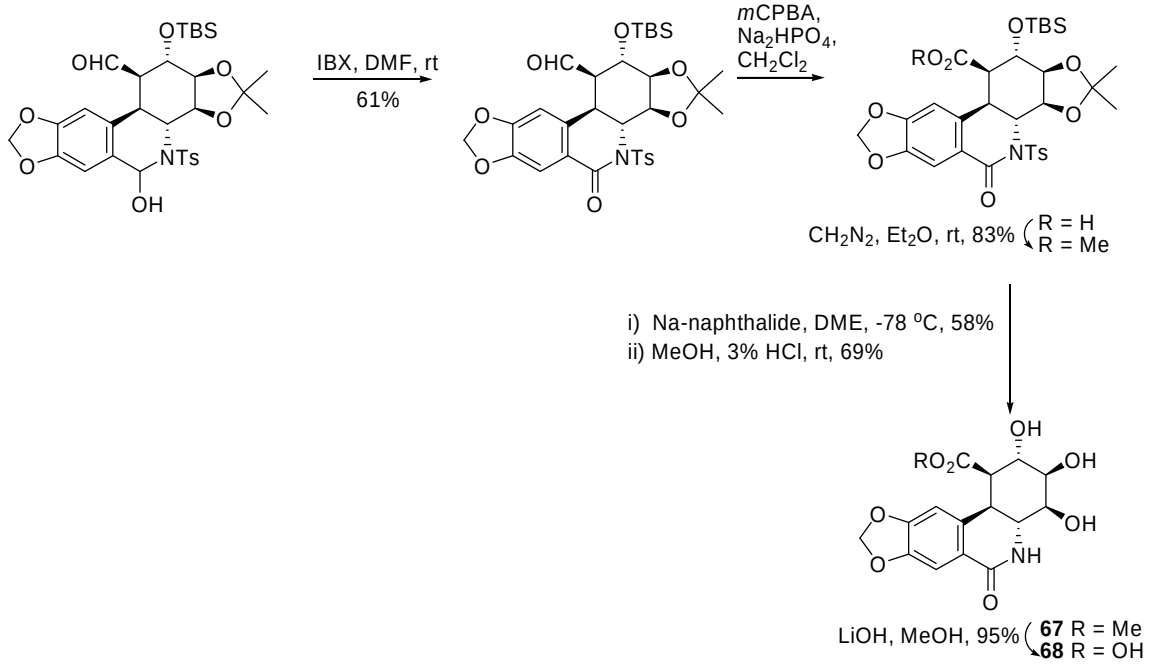


Scheme 9 Synthesis of a pancratistatin analogue that was active against both P388 lymphocytic leukemia and human cancer cell lines



Scheme 10 Hudlicky's synthesis of pancratistatin analogues without a dioxole unit on ring A

The importance of the dioxole unit on ring A was tested in 2005 by Hudlicky *et al.*[22] Their work generated some very interesting results. It was found that analogue **65** (**Scheme 10**), lacking the dioxole unit and amide moiety, was ten fold less active than 7-deoxypancratistatin against several cancer cell lines. Analogue **66** (**Scheme 10**), lacking a dioxole unit, also showed similar activities to that of compound **65**.



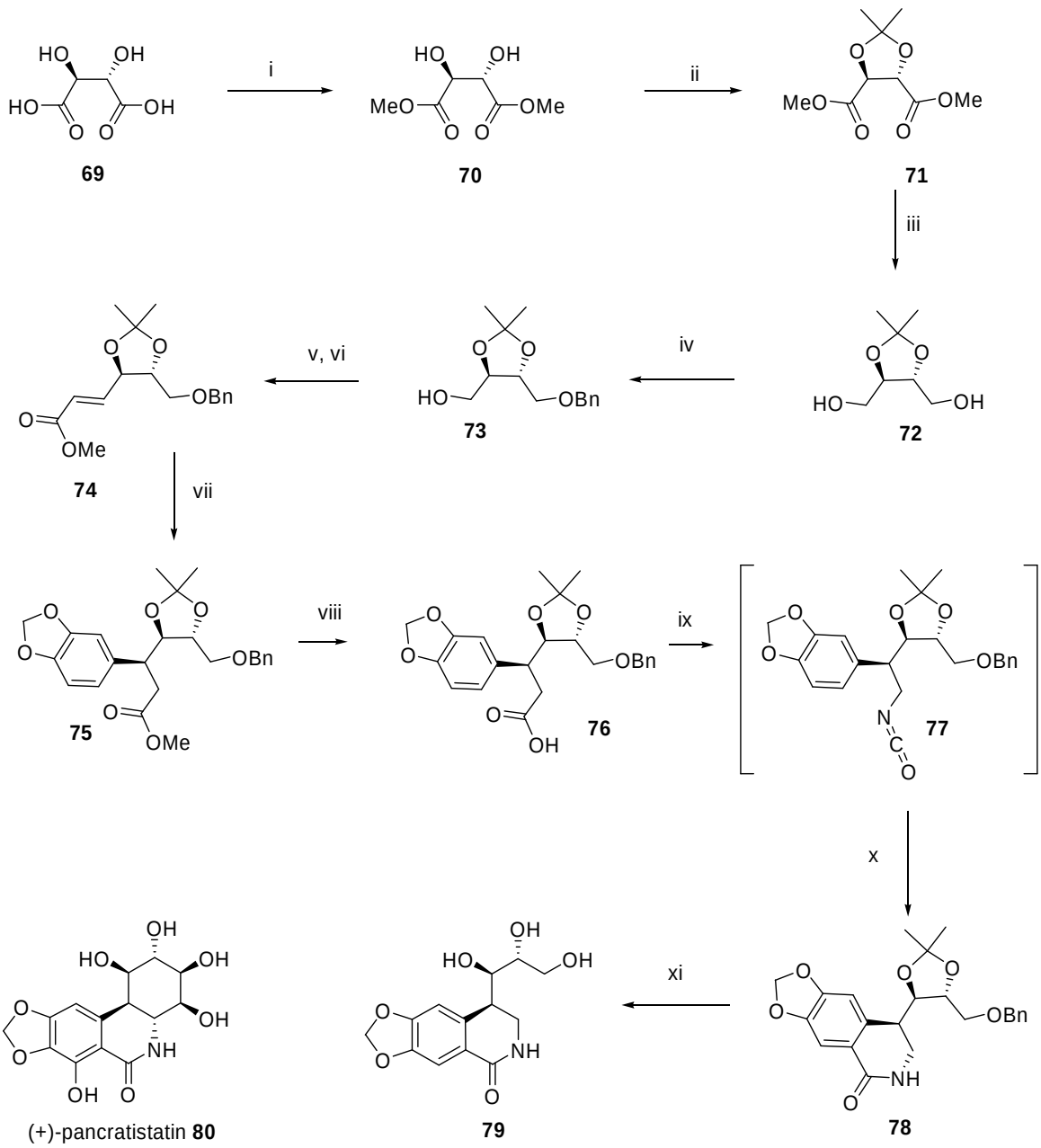
Scheme 11 Hudlicky's work towards a 7-deoxypancratistatin analogue with a modified *trans* diol unit

In 2008 Hudlicky reported the synthesis of a 7-deoxypancratistatin analogue with a modified *trans* diol unit.[23] They replaced one of the alcohol groups with an ester and a carboxylic acid towards compounds **67** and **68** (**Scheme 11**) respectively. Their biological testing results are pending.

To our knowledge no pancratistatin analogues have been made and biologically tested with an open C ring. It would thus be of interest to investigate the synthesis of these analogues.

1.6 Aims of the project

Our aim was to synthesise C-*seco*-pancratistatin analogues or to be more precise C-*seco*-7-deoxypancratistatin analogues. The synthesis would start with the readily available D(-)-tartaric acid **69** (**Scheme 12**). The starting material was chosen as it is readily available, relatively inexpensive and contains the two *trans* alcohol groups as found on ring C of pancratistatin. It was our intention to synthesise enantiomerically pure analogues using the innate stereochemistry of tartaric acid. Our analogues would have the open cyclitol ring C of pancratistatin. Key steps initially envisaged would be the arylcuprate addition (vii, **Scheme 12**) and the isocyanate formation and ring closure (ix, x). As discussed previously the highly *anti*-selective aryl additions were successfully used by Kornienko's group towards the synthesis of pancratistatin analogues.[36,39] We would be using this methodology in attempting to add the aryl groups to a acyclic γ-alkoxy-α,β-enoate with the same *R*-stereochemistry of the C-10b position of pancratistatin.



Scheme 12 The synthetic strategy we planned to use

In brief, the synthesis would start with the esterfication of D(-)-tartaric acid **69** to afford diol **70** (**Scheme 12**). The diol would then be protected with an acetonide group to yield ester **71** (**Scheme 12**). The reduction of the two ester groups would then lead to the diol **72** (**Scheme 12**). The protection of one primary alcohol with a benzyl group would result in compound **73** (**Scheme 12**)**.**

The mono benzyl **73** would then undergo a Swern oxidation and Horner-Wadsworth reaction to yield the enoate **74** (**Scheme 12**). Kornienko's *anti*-selective organocuprate chemistry would then be implemented to install ring A in compound **75** (**Scheme 12**).

The use of a rhodium catalyst for the *anti*-addition of the aryl group would also be attempted as a synthetic alternative. The functional group inter-conversion of the ester to a carboxylic acid **76** (**Scheme 12**) would then follow suite. The formation of the azide, a subsequent Curtius rearrangement to the isocyanate would follow from the carboxylic acid to form either the stable isocyanate intermediate **77** or the ring closed product **78** (**Scheme 12**). Deprotection of the acetonide and benzyl protecting groups would then finally furnish a C-*seco* pancratistatin analogue **79** (**Scheme 12**).

The first five steps of the proposed synthesis have been fairly well documented in the literature and little concern was placed on these steps. However the aryl additions and subsequent attempted ring closure of the isocyanate intermediate would prove to be new and exciting territory.

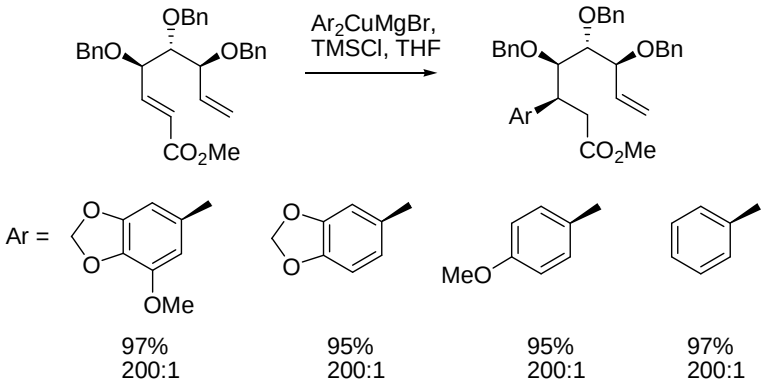
1.7 Aryl additions by metal-mediated 1,4-additions

It was our intention to test Kornienko's *anti*-selective arylcuprate additions on our γ-alkoxy-α,β-enoates. With this in mind, copper-mediated organo additions will be briefly reviewed, as well as a rhodium-mediated addition reaction

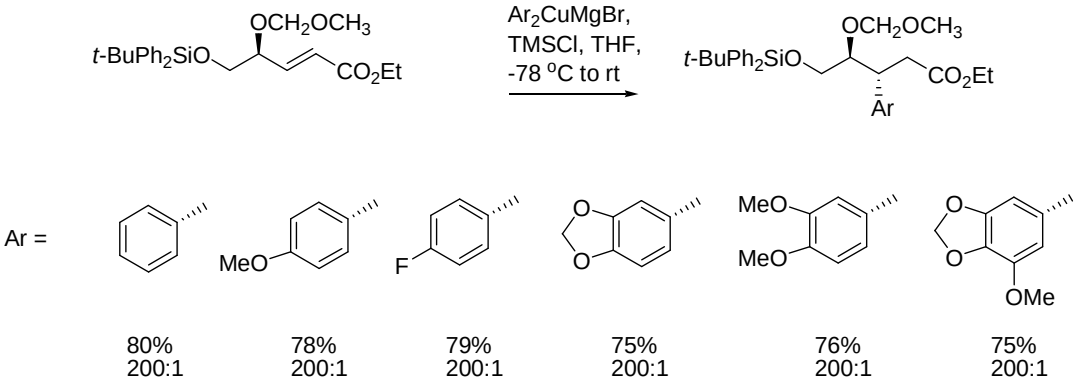
1.7.1 Organocuprate addition reactions

Organocopper reagents are used in a broad spectrum of applications in organic synthesis; they are commonly used to add carbon, hydrogen and heteroatom nucleophiles.[41] Organo copper reagents have been used for the 1,4-addition of acylic and cyclic nucleophiles to acylic α,β-unsaturated enoates.[41] With regard to stereoselectivity, it has been proposed that the flexability of open ring systems - such as acyclic α,β-unsaturated enoates – do not have high selectivities with respect to 1,4-additions using organocopper reagents.[41]

In addition, it has been suggested that selectivities observed during the copper-mediated 1,4-additions to acylic α,β-unsaturated enoates, is dependant on the group in the γ position.[41] Fortunately, with respect to the work discussed herein, Kornienko *et al.* successfully employed organocopper reagents to mediate the *anti* addition of aryl groups to γ-alkoxy-α,β-enoates (**Scheme 14 and 15**).[36,39] Kornienko proposed that the *anti* selectivity observed could be predicted using a reductive elimination model (**Figure 7**).[37]



Scheme 14 Kornienko's use of organocopper chemistry



Scheme 15 Kornienko's use of organocopper chemistry

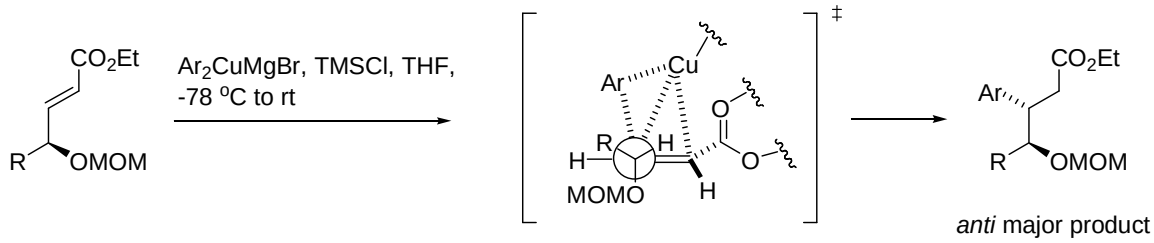
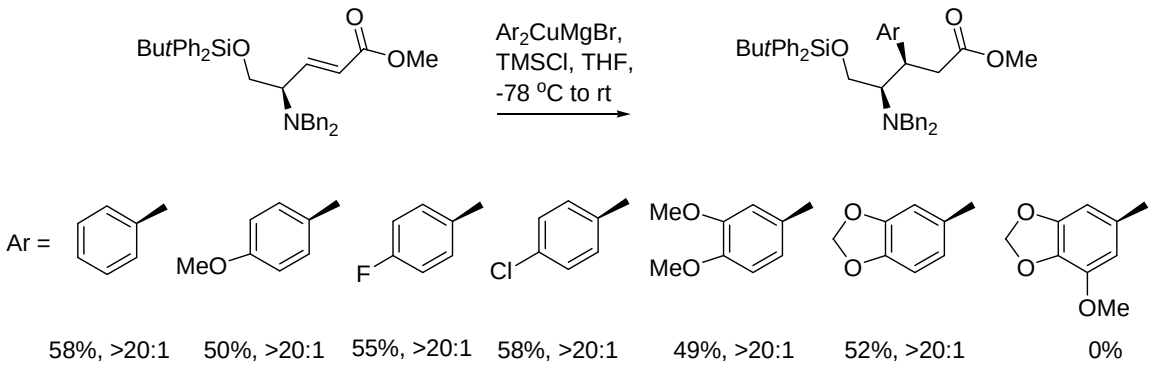
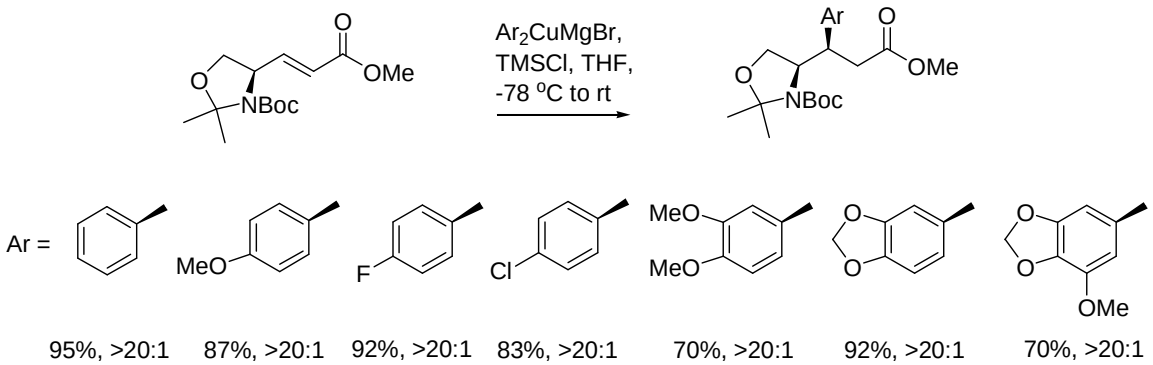


Figure 7 Kornienko's reductive elimination model

Kornienko and fellow researchers validated the use of the reductive elimination model (**Figure 8**) when they correctly predicted the *syn*-selective arylcuprate additions to acyclic γ-amino- and γ-carbamato-α,β-unsaturated enoates (**Scheme 16** and **17**).[38]



Scheme 16 Kornienko's *syn*-selective arylcuprate additions



Scheme 17 Kornienko's *syn*-selective arylcuprate additions

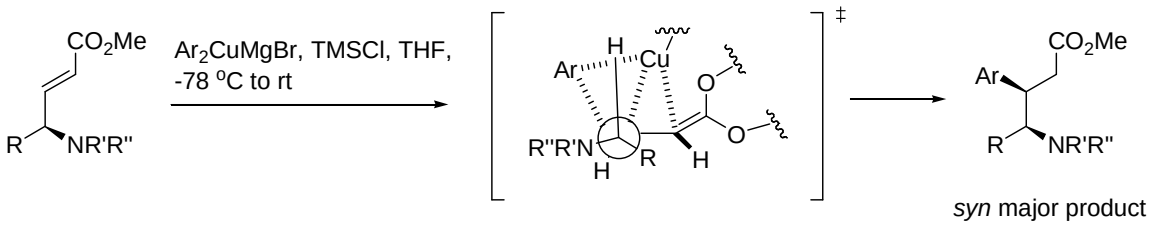


Figure 8 Reductive elimination model used to predict the outcome of the *syn*-selective arylcuprate additions

1.7.2 Rhodium catalyzed reaction

In 1997, Miyaura reported the rhodium catalysed conjugate addition of both aryl and alkenyl boronic acids to acyclic and cyclic enones.[42] In this work 3 mol % $Rh(acac)(CO)_2$ and 1,4-bis-(diphenylphosphino)butane (dppb) was used to catalyse the addition of a variety of aryl boronic acids to numerous enones at 50°C in aqueous solvent. A year later, Hayashi and Miyaura published work concerning the rhodium catalysed asymmetric 1,4-addition of aryl boronic acids.[43] In their paper they achieved high enantioselectivity and impressive yields. Miyaura's investigation into using a rhodium catalyst for the addition of boronic acids to enones prompted other groups to investigate various other rhodium catalysts and reaction conditions for the addition of boronic acids to: α,β-unsaturated ketones[43], α,β-unsaturated esters[44] and α,β-unsaturated amides.[45]

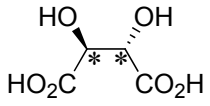
More importantly for our work, Segura and Csaky recently published a paper describing the use of a catalytic amount of $[(cod)RhCl]_2$ for the *anti*-addition of aryl- and alkenylboronic acids to acyclic γ,δ-oxy-α,β-unsaturated enoates.[46] The chemistry described in this paper is very useful as: the rhodium catalyst and boronic acids are stable when exposed to oxygen and water, the reactions can be done in aqueous solvents at low temperatures and high enantioselectivity and conversions are possible.

Chapter 2: Results and discussion

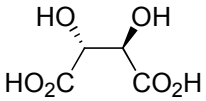
2.1 Preparation of open chain pancratistatin analogues

2.1.1 The 'Natural' trial synthesis

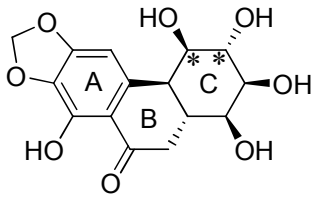
Similarly to Hudlicky and Trost's pancratistatin syntheses,[28,30] it was our intention to use the inherent *trans* diol stereochemistry - the 2*S*,3*S* stereocenters of D(-)-tartaric acid **69** (**Figure 9**) - towards the synthesis of enantiomerically pure, open chain pancratistatin analogues. L(+)-tartaric acid **81** (**Figure 9**) was initially used as the starting material for a 'trial' synthesis. L(+)-tartaric acid is less expensive than D(-)-tartaric acid and was readily available in our laboratory. L(+)-tartaric acid or 'Natural' tartaric acid is found commonly in grapes and its potassium hydrogen tartrate salt sometimes precipitates out of wines. In addition it was anticipated that chemistry used on the two tartaric enantiomers would yield similar results.



D(-)-tartaric acid
'Unnatural'
69



L(+)-tartaric acid
'Natural'
81

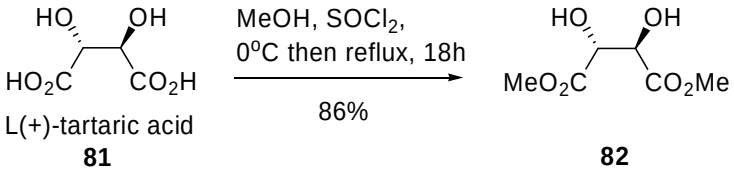


(+)-pancratistatin
* = equivalent stereocenters

Figure 9 The starting materials we intended to use towards the synthesis of pancratistatin analogues

2.1.1.1 Synthesis of ester 82

The synthesis started with the esterification of L(+)-tartaric acid **81** (**Scheme 18**). L(+)-tartaric acid **81** was thus dissolved in methanol and thionyl chloride was cautiously added drop-wise over one hour at 0°C. [24] The reaction mixture was then heated at reflux for eighteen hours. No purification was necessary, removal of the solvent *in vacuo* yielded ester **82** (**Scheme 18**) as a light yellow oil with a respectable 86% conversion.



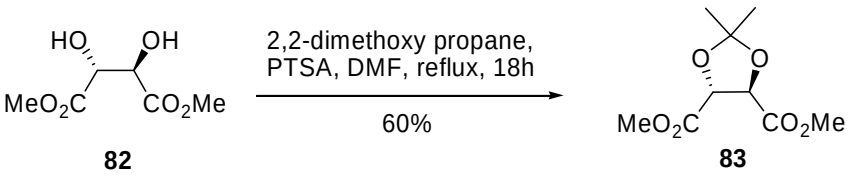
Scheme 18

The ^{1}H NMR spectrum of **82** (**Scheme 18**) indicated a singlet at 3.9 ppm integrating for 6 hydrogen atoms, this shift was attributable to the presence of the two ester methyl groups. The chemical shift compared favourably with the literature which reported the same chemical shift at 3.8 ppm.[47] In addition, the *trans*-diol gave rise to a broad signal integrating for two protons at 3.5 ppm on the ^{1}H NMR of **82**. A signal at 170.0 ppm on the ^{13}C NMR spectrum of **82** was characteristic of the two carbonyl groups. The literature reported the carbonyl groups giving rise to a signal at 173.0 ppm.[47] Two signals at 51.1 ppm (*lit.*[47] 52.7 ppm) on the ^{13}C NMR spectrum of **82** confirmed the presence of the two methoxy functionalities.

2.1.1.2 Protection of the diol unit with an acetonide protecting group

The next step involved the protection of diol **82** with an acetonide protecting group towards **83** (**Scheme 19**). Diol **82** was dissolved in DMF and then heated at reflux for eighteen hours in the presence of 2,2-dimethoxy propane and a catalytic amount of *p*-toluene sulphonic acid monohydrate (PTSA).[25] The solvent was removed *in vacuo* and the resulting red residue was washed with sodium hydrogen carbonate and extracted with chloroform.

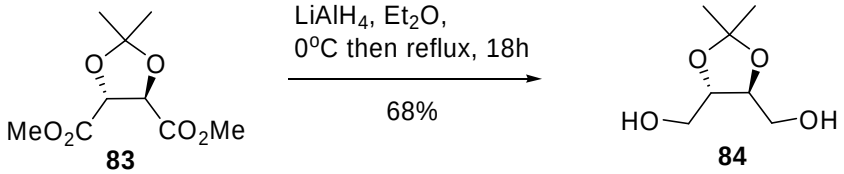
The removal of the solvent *in vacuo* and subsequent distillation (bp 130°C at 6 mmHg vs. *lit.*[48] bp 82 – 90 °C) yielded the acetonide-protected product **83** (**Scheme 19**) , as a dark orange oil, with a reasonable 60% yield.



Scheme 19

Inspection of the ^{1}H NMR spectrum of **83** (**Scheme 19**) indicated**:** the newly added acetonide functionality giving rise to a signal integrating for 6 protons at 1.5 ppm (*lit.*[48] 1.5 ppm), the absence of the diol signal - evident as a broad peak at 3.51 ppm in the ^{1}H NMR spectrum of **82** (**Scheme 19**). In addition, there was a singlet at 3.83 ppm in compound **83**'s ^{1}H NMR spectrum which could be assigned to the two methoxy groups. The literature reported the same signal at 3.80 ppm.[48] The ^{13}C NMR spectrum of **83** included: a carbonyl chemical shift at 170.4 ppm (*lit.*[48] 169.9 ppm), a chemical shift at 114.2 ppm (*lit.*[48] 113.7 ppm) which was assigned to the CH group of the acetonide and the two methyl groups of the acetonide protecting-group gave rise to a signal at 26.6 ppm (*lit.*[48] 26.2 ppm).

2.1.1.3 Reduction of diester 83 towards diol 84



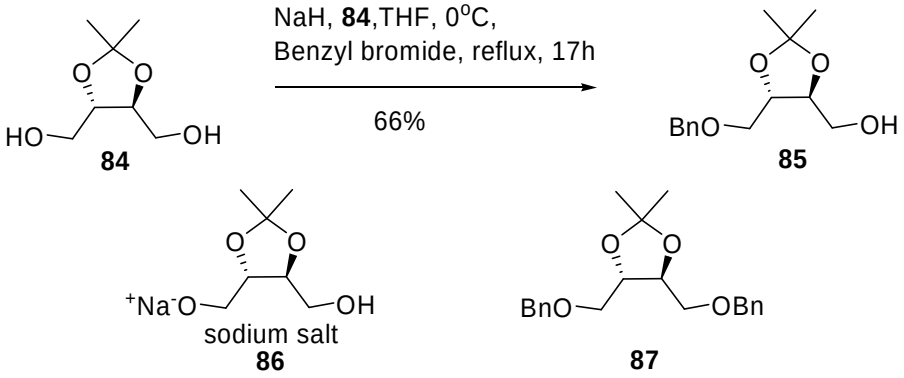
Scheme 20

The third step in this synthetic sequence was the reduction of the ester groups to their corresponding primary alcohols.

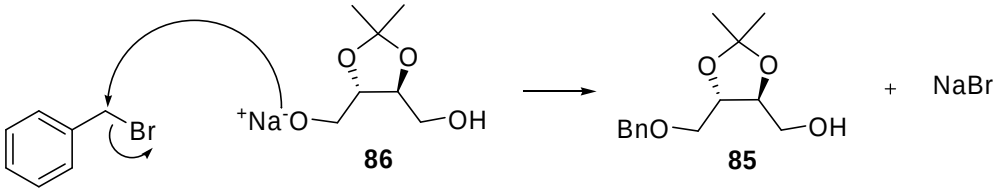
The ubiquitous reducing agent lithium aluminium hydride (LAH),[26] was successfully employed to reduce diester **83** to the diol **84** (**Scheme 20**). To this end, LAH in diethyl ether was vigorously heated at reflux for 30 min. and then cooled to room temperature. Ester **83** was dissolved in diethyl ether and added drop-wise to the LAH/Et_2O mixture cooled to 0°C, over one hour. The reaction mixture was then heated at reflux. The standard acid work-up was not employed as we were concerned that under acidic conditions the acetonide-protecting group may be cleaved. Instead a somewhat messy base work-up was employed. It is possible that some of the diol product was lost during the work-up stage as extraction of the organic products proved to be difficult. Purification was achieved by way of a silica gel plug and a 68% yield of the desired compound, an opaque semi-solid, was achieved. It was later found, in attempts to remove the acetonide, that the acetonide-protecting group was resilient to acids; ethereal hydrochloric acid was unable to remove the acetonide. It is thus suggested that the acid work-up be tested for future reactions. The following evidence for the formation of compound **84** was seen in its ^{1}H NMR spectrum. A broad signal integrating for 2 H's at 3.01 ppm on the ^{1}H spectrum of **84** indicated the presence of the two alcohol groups. The obvious absence of the esters methyl groups, a singlet at 3.86 ppm integrating for six H's on the ^{1}H NMR spectrum of **83**, provided further evidence for the formation of diol **84**. A multiplet signal, integrating for two protons, at 3.97 ppm was assigned to the two CH groups beta to the two alcohol groups. Furthermore, the presence of the two CH_2 groups alpha to the alcohol groups gave rise to a multiplet signal, integrating for four protons, at 3.75 ppm on the ^{1}H NMR spectrum of **84**. Examination of the literature validated the ^{1}H NMR spectrum of compound **84** further by the inclusion of the following signals: the two CH groups beta to the alcohol groups gave rise to a multiplet at 3.94 ppm, and the CH_2 groups alpha to the two alcohol groups gave rise to a multiplet signal at 3.71 ppm.[48] The absence of the carbonyl peaks, seen at 170.4 ppm on the ^{13}C NMR spectrum of ester **83,** provided further evidence for the successful reduction of ester **83** towards diol **84**.

2.1.1.4 Mono protection of diol 84

Diol **84** was then converted into the mono-benzyl protected alcohol **85 (Scheme 21).**[49] Initially, sodium salt **86** (**Scheme 21**) was prepared by treating diol **84** with sodium hydride in the presence of THF at 0°C. It was anticipated that the addition of 1.2 equivalents of sodium hydride would result in the kinetically favourable mono-sodium salt **86** (**Scheme 22**). The strongly nucleophillic oxygen of the sodium salt would then be expected to readily attack the electrophillic methylene group α to the bromine atom to yield the mono-protected product **85** (**Scheme 22**).



Scheme 21



Scheme 22

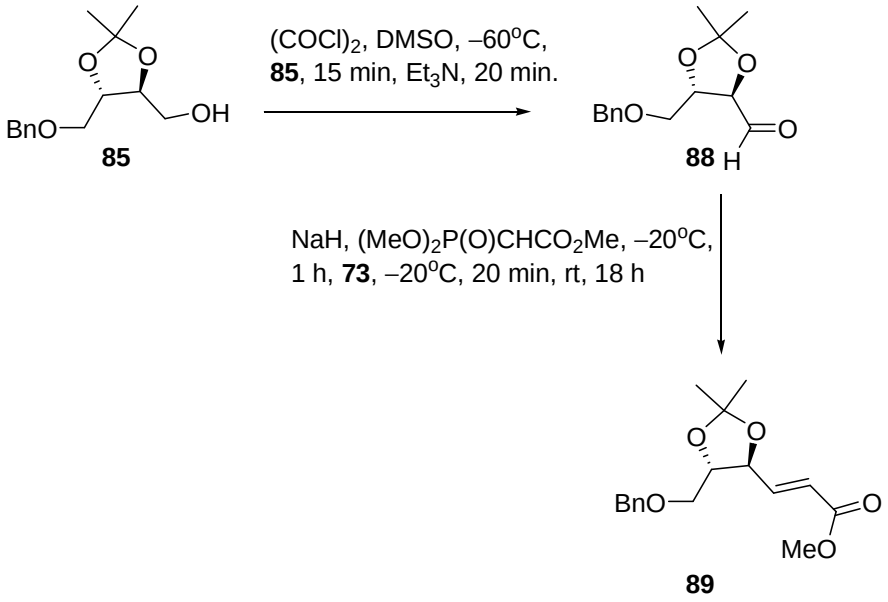
Upon addition of the sodium hydride to diol **84** (**Scheme 21**), the formation of a salt was indicated by the evolution of a cream coloured precipitate. Benzyl bromide was then added and the reaction mixture heated at reflux to complete the mono protection sequence. Column chromatography then yielded the mono-protected alcohol **85** (S**cheme 21**), a light yellow oil, with a moderate yield of 66%.

The ^{1}H NMR spectrum of compound **85** (**Scheme 21**) provided the following evidence: a signal integrating for five protons at 7.32 ppm which could be assigned to the benzyl group and a singlet integrating for two protons at 4.58 ppm which were assigned to the benzyl's methylene group.

A relatively small quantity of the bi-protected product **87** (**Scheme 21**) was also retrieved off the column, indicating that either the kinetically unfavourable bi-sodium salt had formed or that some of the starting material had not been converted into a mono-sodium salt and was thus bi-protected. The formation of the unexpected salt illustrates the inherent bellicosity of certain organic molecules.

2.1.1.5 Attempted Swern and Wittig reaction towards α,β-enoate 89

The attempted Swern oxidation and sequential Wittig reaction[50] of **85** towards enoate **89** (**Scheme 23**) did not proceed with any confidence; attempts would yield the starting material **85**. It was then decided to investigate other possible *in-situ* oxidation\addition reactions which would serve our purposes.



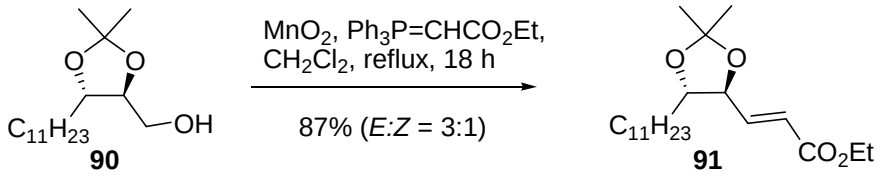
Scheme 23

2.1.2 Tandem oxidation process (TOP)

2.1.2.1 The used of manganese dioxide and a stable Wittig reagent – Taylor's method

In the 1990's Taylor successfully used activated manganese dioxide and stabilized Wittig (ylide) reagents in a variety of tandem oxidation processes (TOP).[51-54] Since this discovery manganese dioxide has been employed successfully in TOPs. These include: the use of non- and semi-stabilized ylides to yield α,β-unsaturated aldehydes and β-unsaturated di-bromo compounds,[55,56] the use of sulphur ylides to yield cyclopropane products[57] and the conversion of amines and *O*-alkyl hydroxylamines towards imines and oximes respectively.[58,59]

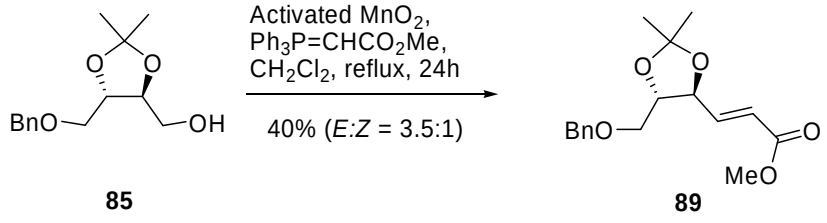
Historically, activated manganese dioxide was used for the oxidation of activated (benzylic\allylic\propargylic) primary alcohols to afford aldehydes. It was believed that activated manganese dioxide was unable to oxidize un-activated primary alcohols.[60] Taylor used the oxidizing ability of activated manganese dioxide in tandem or *in-situ* with a stabilized Wittig reagent to trap the aldehyde formed. In this way the researchers were able to perform a TOP on 'semi' activated and completely un-activated primary alcohols.[61] The non-toxicity of activated manganese dioxide, ease of reaction and work-up – a simple filtration - made this chemistry desirable for our synthesis. A representative example pertinent to our work is the TOP of the un-activated alcohol **90** towards enoate **91** (**Scheme 24**).[62]



Scheme 24

Using Taylor's methodology it was possible to isolate enoate **89** (**Scheme 25)** as a bright yellow oil, with a 40% yield and *E:Z* ratio of 3.5:1.[61] The *E:Z* ratio was determined by comparing the *E* isomer's ^{1}H NMR spectrum's signal – the proton alpha to the ester group - height to that of the *Z* isomer's ^{1}H NMR spectrum signal height – again, the proton alpha to the ester group. Examination of **89**'s (**Scheme 25**) ^{1}H NMR spectrum showed that: the spectrum did not contain a signal for an alcohol group - a broad singlet integrating for one proton at 2.42 ppm on the ^{1}H NMR spectrum of **85**, and the methyl group of the newly added ester was accountable for a singlet at 3.67 ppm (*lit.*[63] 3.75 ppm) integrating for three protons. In addition two double doublets, each integrating for one proton, at 6.87 ppm and 6.00 ppm, indicated the presence of the alkene functionality. The signals assigned to the two alkene protons compared favourably with the literature values of 6.92 ppm and 6.11 ppm for the respective protons.[63] In addition, the coupling constants that were calculated for compound **89**'s alkene proton alpha to the ester group and beta proton were J = 15.7, 5.3 Hz and J = 15.7, 0.7 Hz respectively. These values corresponded relatively well with the literature values of J = 15.5, 5.4 Hz and J = 15.5, 1.6 Hz for the equivalent protons.[63]

The yield over two steps was promising but the *E:Z* ratio was not high enough for our synthesis. It should be noted that the activated manganese dioxide that was used was not freshly prepared and was probably in need of purification.



85 **89**

Scheme 25

2.1.2.2 Pyridinium chlorochromate and the stable Wittig reagent – from Corey to Shet

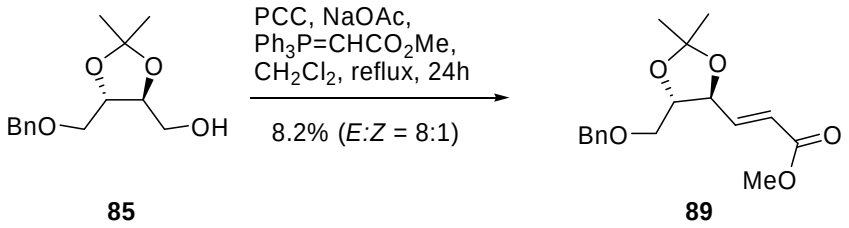
We next turned to the use of pyridinium chlorochromate (PCC) as an oxidizing agent. In 1975 Corey reported the use of PCC for an oxidizing agent of primary and secondary alcohols towards their corresponding carbonyls.[64] The use of PCC in a TOP with a stable Wittig reagent was recently documented by Bressette and Glover.[65] Although the process was not truly *in-situ,* it still took place sequentially in 'one pot'.

In the same year, Shet *et al.* reported the first proper *in-situ* use of PCC and a stable Wittig reagent for the conversion of a number of activated and un-activated primary alcohols into their aldehydes with a contiguous *E:Z* ratio of 9:1 for all of their TOP reactions.[66]

The *in-situ* Shet-type TOP was applied in our case.[66] Alcohol **85** (**Scheme 26**) was thus treated with PCC buffered with sodium acetate at room temperature and stirred for ten minutes. Subsequently the stable Wittig reagent, methyl (triphenylphosphoranylidene)acetate, was added and the reaction mixture was stirred at room temperature for twenty hours.

The reaction mixture was then filtered through celite and the enoate **89** (**Scheme 26**) isolated by way of column chromatography. A yield of 8.2% was truly disappointing as it was a severe payoff against an improved *E:Z* ratio of 8:1.

Analysis of the ^{1}H NMR spectrum of **89** (**Scheme 26**) showed: the removal of the alcohol group by the absence of the alcohol signal. In addition, two new signals, double doublets at 6.87 ppm (*lit.*[63] 6.92 ppm) and 6.00 ppm (*lit.*[63] 6.11), indicated the presence of the alkene functionality. The methyl group of the ester was also accounted for by a singlet at 3.67 ppm (*lit.*[63] 3.75) integrating for three protons. As mentioned, there was a much improved *E:Z* ratio. Interestingly, the ratio is very close to that reported by Shet *et al.* (E:Z = 9:1) and it could be proposed that this is the *E:Z* ratio limit of this type of TOP.

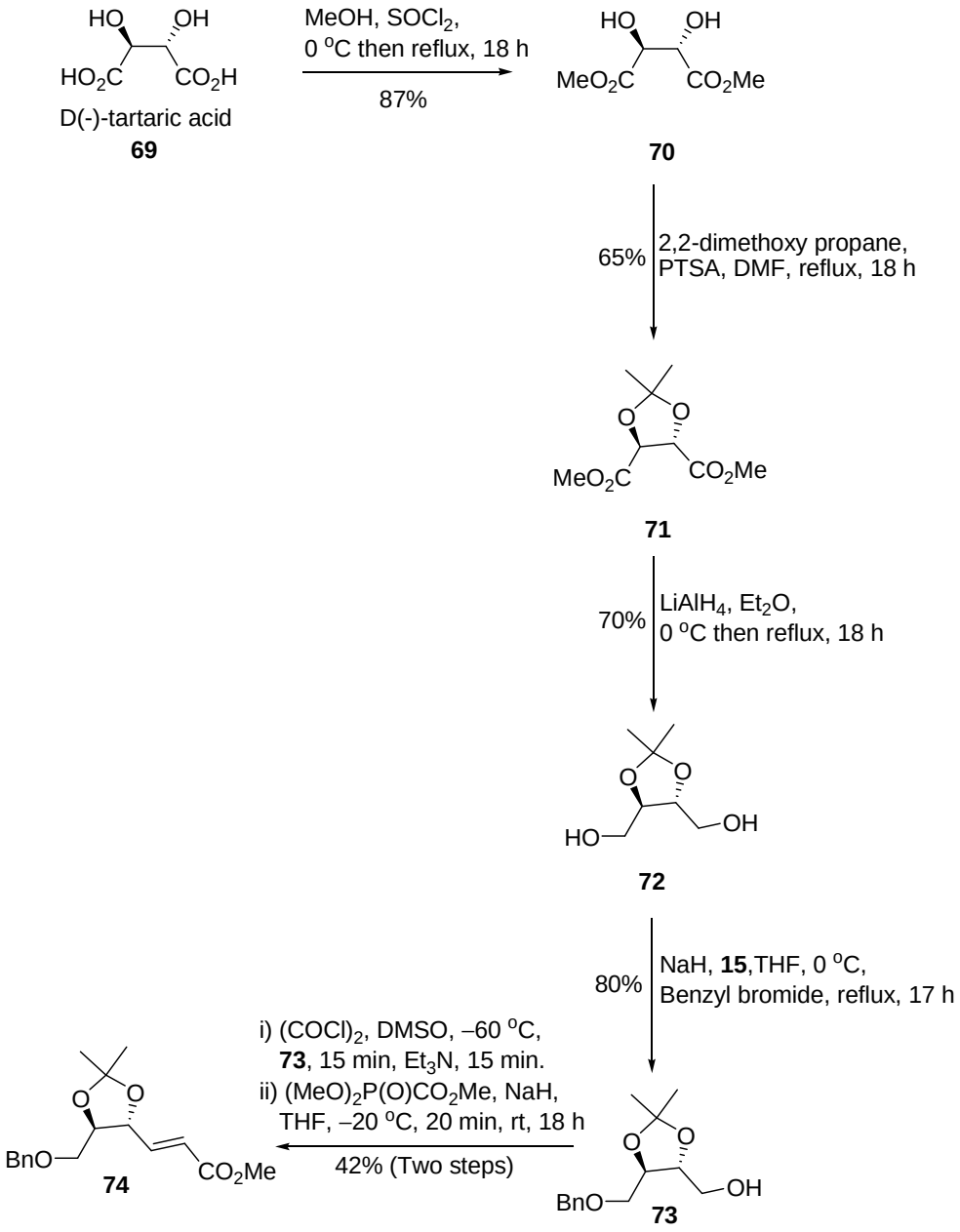


85 **89**

Scheme 26

2.1.3 The successful synthesis of α,β-unsaturated enoate 74

The disappointing *E:Z* ratios observed for the MnO_2 and PCC TOPs redirected attentions towards the use of the Swern-Wittig reaction. In addition, the arrival of fresh oxalyl chloride and DMSO allowed for the testing of the sequential Swern-Wittig reaction.[50] At this point, the 'trial' synthesis ended and efforts were directed into using the 'unnatural' D(-)-tartaric acid **69** (**Scheme 27**). D(-)-tartaric acid contains the correct stereochemical elements required for the synthesis of a pancratistatin analogue; namely the correct stereochemistry for the *trans* diol unit found on ring C of pancratistatin. Now starting with the 'unnatural' tartaric acid **69**; we repeated all of the steps that have previously been described - barring the activated manganese and PCC TOPs. This has been illustrated in **Scheme 27** and will be briefly discussed. Diester **70** (**Scheme 27**) was produced and isolated, with an 87 % yield, in exactly the same way as the 'natural' diester **70**. Examination of the ^{1}H and ^{13}C NMR spectrum of **70** included the following signals: a singlet, integrating for six protons, at 3.59 ppm (*lit.*[67] 3.87 ppm) which was assigned to the two newly added methyl groups, and a carbonyl signal at 172.3 ppm.



Scheme 27

The acetonide protection of diester **70** proceeded smoothly to yield compound **71** (**Scheme 27**) with a slightly improved yield of 65 % relative to the 'natural' acetonide protection yield of 60 % towards compound **83** (**Scheme 19**). The ^{1}H NMR spectrum signals of compound **71** corrsponded well with literature values. The signal at 4.81 ppm (*lit.*[67] 4.80 ppm) was assigned to the two protons alpha to their adjacent ester groups.

A singlet integrating for six protons at 1.49 ppm (*lit.*[67] 1.50 ppm) was attributable to the presence of the two newly added methyl groups of the acetonide-protecting group. A signal in the ^{13}C NMR spectrum of compound **71** (**Scheme 27**) occurring at 114.2 ppm was a clear indication of the presence of the O-CH-O bridge of the acetonide-protecting group. The reduction of the ester groups towards their corresponding primary alcohols to produce diol **72** (**Scheme 27**) with a 70 % yield, proceeded more smoothly than the reduction of **83** towards diol **84** (**Scheme 20**). The major reason being the experience gained from extracting diol from the work up mixture in the manufacture of diol **84**. The ^{1}H NMR spectrum of **72** included the following signals: a multiplet in the range of 3.67 – 3.78 (*lit.*[67] 3.69 – 3.82), integrating for four protons which was assigned to the two CH_2 groups alpha to the primary alcohol groups, and a triplet, J = 5.55 Hz, signal at 3.09 ppm which integrated for two protons – this signal was assigned to the two primary alcohol protons. The shifts recorded for compound **72** were in agreement with the literature and the synthesis proceeded to the last of the known chemistry steps – the mono-protection of diol **72** towards compound **73** (**Scheme 27**). The chemistry used was again the same as that applied in the synthesis of mono-protected compound **85** (**Scheme 22**) . The formation of compound **73** was validated by the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum had a multiplet integrating for five protons in the range of 7.26 – 7.34 ppm, this signal was a clear indication of the presence of the five aromatic protons belonging to the benzyl-protecting group. A review of the literature showed this same shift to occur in the range of 7.31 – 7.40 ppm.[68] A singlet at 4.58 ppm (*lit.*[68] 4.60 ppm) was assigned to the CH_2 group bridging the alcohol and aryl group. The ^{1}H NMR spectrum of **73** also showed the existence of an AB system; signals at 3.77 ppm and 3.72 ppm, each integrating for a single proton and with J = 11.5, 4.2 Hz and J = 7.5 Hz respectively, could be assigned to the CH_2 group alpha to the newly protected alcohol. The coupling constants recorded did not agree well with literature values of J = 4.4, 2.2 Hz and J = 5.6 Hz.[68] However the shift positions did correspond fairly well with literature values of 3.74 ppm and 3.64 ppm.[68]

Our synthesis proceeded on towards the Swern-Wittig reaction. The Swern reagent was prepared by stirring oxalyl chloride with DMSO for ten minutes at -60°C.

Alcohol **69** (**Scheme 27**) was then added carefully and the reaction mixture stirred for fifteen minutes at -60°C before triethylamine was added. The reaction mixture was then warmed to room temperature and the solvent was hastily removed *in-vacuo.* The characteristic stench of dimethyl sulphide was evident to many unfortunate colleagues - a great victory! The yellow coloured aldehyde was promptly added to the prepared Wittig reagent at -20°C and stirred for one hour. The Wittig reagent was synthesised by treating trimethyl phosphonoacetate with sodium hydride for one hour at -20°C. The desired enoate **74** (S**cheme 27**) was obtained after purification by column chromatography. A reasonable yield of 42%, over two steps, and ^{1}H NMR spectrum analysis of compound **74** indicated that an *E:Z* = 25:1 was achieved. This was in contrast with the low *E:Z* ratios observed for the activated manganese and PCC TOPs.

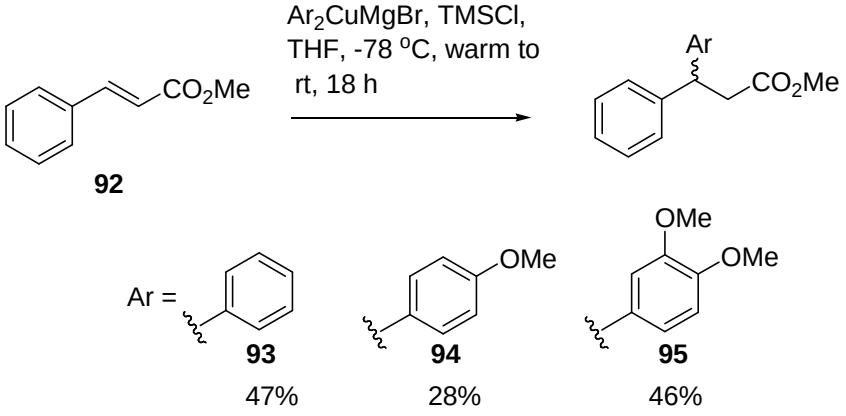
The elimination of the alcohol group was shown by the absence of the alcohol signal. In addition, there were two double of doublets in the ^{1}H NMR spectrum of compound **74** (**Scheme 27**) at 6.91 and 6.11 ppm, each integrating for one proton; these signals corresponded to the presence of the alkene functionality. Coupling constants of J = 15.7, 5.6 Hz and J = 15.7, 1.4 Hz were recorded for the two alkene protons. The methyl group of the ester was accountable for a singlet integrating for three protons at 3.73 ppm. A chemical shift at 166.29 ppm on the ^{13}C spectrum of **74** was assigned to the carbonyl group of the ester.

All of the compounds made up until this point have been previously synthesised by other research groups. We now left the known behind and set our vision towards the synthesis of a series of novel compounds. So far, in six steps we had achieved a 13.3% conversion of D(-)-tartaric acid towards enoate **74** (**Scheme 27**).

2.1.4 The use of arylcuprates for the installation of aryl groups

As mentioned in the introduction, Kornienko used highly *anti*-selective organocuprate conjugate additions to install the stereochemistry equivalent to the C-10b position of pancratistatin.[36,38,39]

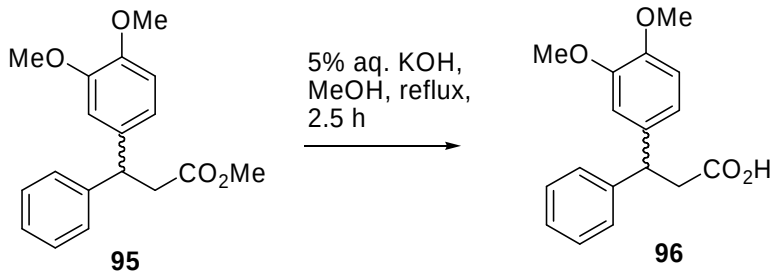
Before testing his approach on our enoate **74** (**Scheme 27**) we cautiously decided to do a set of trial organocuprate additions on a model substrate, the system α,β-unsaturated methyl cinnamate **92** (**Scheme 28**). The general procedure used was as follows. The aryl Grignard reagent was made by combining the appropriate aryl bromide compound with magnesium turnings, in THF, at room temperature. The organocopper reagent was then completed by way of the cannulation of the Grignard reagent into a suspension of copper (I) iodide in THF at -78°C. The reaction mixture was subsequently stirred for one hour. Trimethylsilyl chloride (TMSCl) and the enoate methyl cinnamate **92** were then cannulated into the organocopper reagent. The reaction was allowed to warm to room temperature and stirred for eighteen hours.[38] **Scheme 28** shows the arylbromide utilised in the study and the yields obtained.



Scheme 28

Although the yields were nothing to boast about, the trial reactions served as good practice for the substrate required in this synthesis. It must be noted that the organocuprate conjugate addition reactions were relatively laborious; work ups were difficult and purification always involved the separation of several compounds with similar polarity including large amounts of biaryl compounds which formed due to the large excess of cuprate reagent; 5 mol equivalents of cuprate reagent were used.

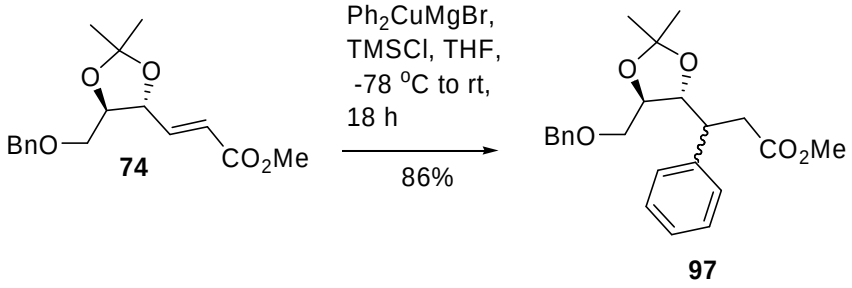
The ^{1}H NMR spectrum of compound **93** (**Scheme 28**) included the following signals: a multiplet integrating for ten protons was attributable to the aromatic protons, a doublet integrating for two protons at 3.06 ppm was assigned to the CH_2 group alpha to the ester. From the ^{1}H NMR spectrum of compound **94** (**Scheme 28**) we could assign: a multiplet integrating for nine protons at 7.21 ppm to the aromatic protons, a triplet integrating for one proton at 4.50 ppm to the proton beta to the ester, a singlet integrating for three protons at 3.75 ppm for the methoxy group. The difficulty experienced in purifying the conjugate addition products peaked when we were unable to purify compound **95 (Scheme 28**), despite several attempts to obtain a reasonable ^{1}H NMR spectrum. It was thus necessary to convert ester **95** into its carboxylic acid **96 (Scheme 29**)**-** using a 5% aqueous potassium hydroxide solution. The ^{1}H NMR spectrum of **96** included the following signals: a broad singlet integrating for one proton at 9.54 ppm due to the carboxylic acid functionality and two singlets integrating for three protons each at 3.81 and 3.79 ppm which were assigned to the two methoxy groups. The functional group conversion of the ester to the carboxylic acid also served as practice for a similar future transformation.



Scheme 29

2.1.5 Testing Kornienko's cuprate chemistry on α,β-enoate 74

Considering the results of the organocuprate additions performed on methyl cinnamate **92** (**Scheme 28**); the search was on for an alternative reaction which would afford the same conjugate addition with high stereoselectivity and good conversions. However, in the meanwhile the organocuprate chemistry was used on the α,β-unsaturated enoate **74** (**Scheme 30**). The methodology used was identical to that described for the organocuprate additions performed on methyl cinnamate **92**. It was possible to isolate the addition product **97** (**Scheme 30**) with a respectable yield of 86%. The ^{1}H NMR spectrum of compound **97** had a chemical shift integrating for ten protons between 7.13 ppm and 7.28 ppm; this indicated the presence of the newly added phenyl group. The two double of doublets at 6.91 and 6.11 ppm – accountable for the alkene protons in enoate **74** – were not present in the ^{1}H NMR spectrum of product **97**. A multiplet integrating for two protons at 2.81 ppm on the ^{1}H NMR spectrum of addition compound **97** confirmed the presence of the new CH_2 group α to the ester. At this point no attempts were made to validate the stereochemistry of the addition product. The ^{1}NMR spectrum of compound **97** did indicate that there was a very large diastereomeric excess in the range of 200:1. Considering Kornienko's findings,[37] it could be proposed that it was very probable that the *anti*-addition did in fact occur.



Scheme 30

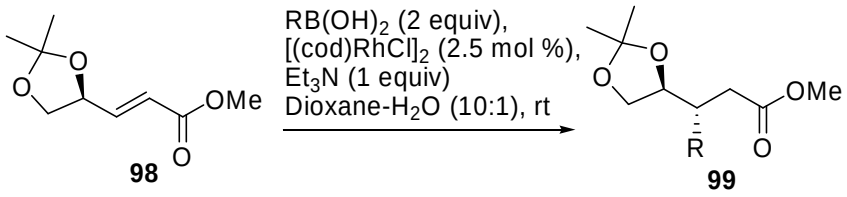
As mentioned previously, the cuprate addition reaction proved to be tedious: the work up was difficult and laborious and the reaction requires several processes to take place at low temperatures. Unlike the trial organocuprate reactions, the purification was not as problematic as only two compounds had to be resolved via column chromatography.

This is where all affairs with organocuprate chemistry ended. It has been shown – contrary to previous findings – that α,β-unsaturated enolates that contain a γ-oxygen are not amicable substrates towards conjugate additions; this is because the γ-oxygen – being an electron donor – makes the β-position of the enoate less electrophillic.[69]

A search of the literature provided a more a far more attractive, affable and expensive prospect for the 1,4-addition to the γ-alkoxy-α,β-enoate used in this synthesis. Her name was rhodium and dressed in the appropriate ligands she was elegant and useful.

2.1.6 Rhodium (I) – a lascivious catalyst

The use of Rh(I) catalysts for the *anti*-addition of aryl boronic acids to acyclic α,β-unsaturated enoates was discussed in the introduction. In 2007, Csaky and Segura reported the use of a Rh(I) catalyst for the addition of a number of aryl- and alkenylboronic acids to γ,δ-oxygen-substituted-αβ-unsaturated acyclic enoates.[46] They found that the conjugate additions proceeded with high *anti*-selectivity and impressive yields. They also reported that the high stereoselectivities were because the additions were substrate controlled; the δ-oxygen, if protected, yielded highly *anti*-selective products. A representative example of their work is shown in **Scheme 31.**



Scheme 31

Csaky and Segura proposed that the rate determining step of the catalytic cycle, and the step responsible for the diastereosectivity, to be the formation of the oxo-π-allyl-Rh^{I} intermediate. In addition, they proposed two transition state models as shown in **Figure 10**. In building their two models, steric hindrance was minimized by the lack of co-ordination between the rhodium metal and the OR_1 and OR_2 groups – in our case this would be the acetonide protected oxygens.

They proposed that the diastereoselection was occurring at either transition state model **I** or **II** (**Figure 10**) and calculated that transition state model **I** was energetically more favourable than transition state **II**. Their reasoning being, in model **I** the nucleophile would enter anti-periplanar to the lowest σ^*-lying orbital of the γ-C-OR_1 bond, while in model **II** the nucleophile would enter anti-periplanar to the γ-C-OR_2 bond. Model **I** can also clearly be used to rationalize the *anti*-selective products.[46]

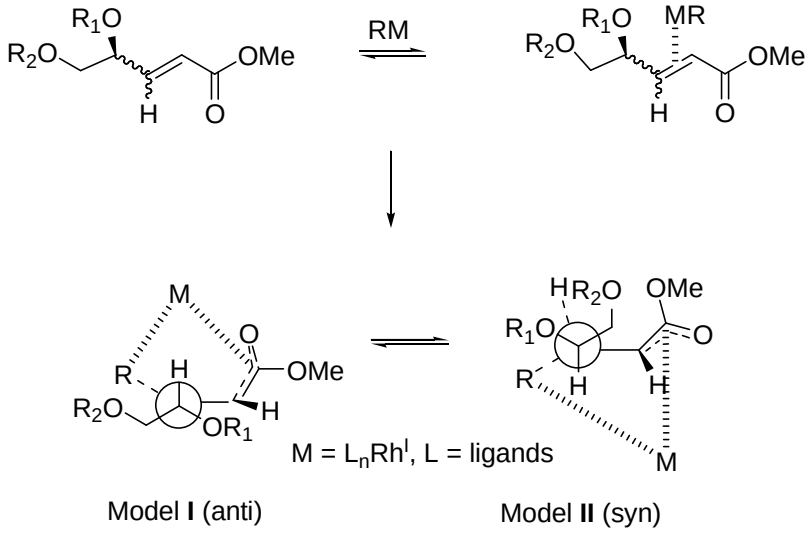
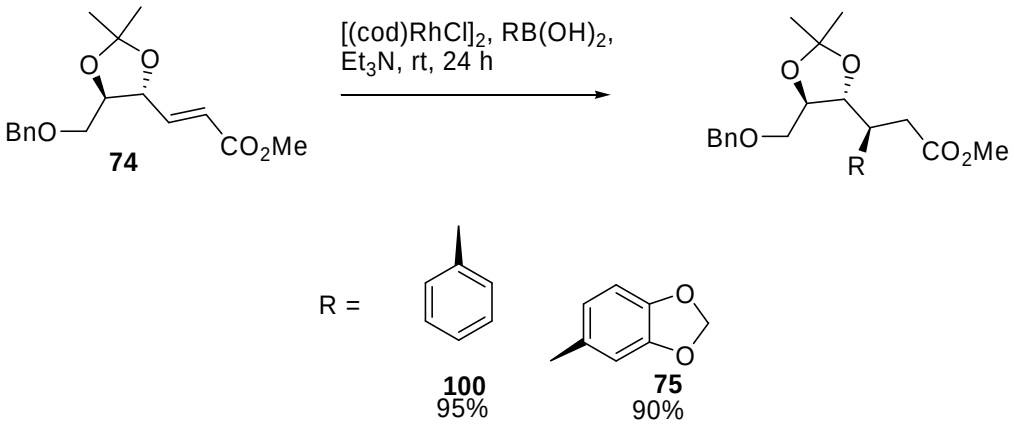


Figure 10 Segura's transition state models

This was great news for us as we were attempting additions on a similar compound and also required an *anti*-selective addition.



Scheme 32

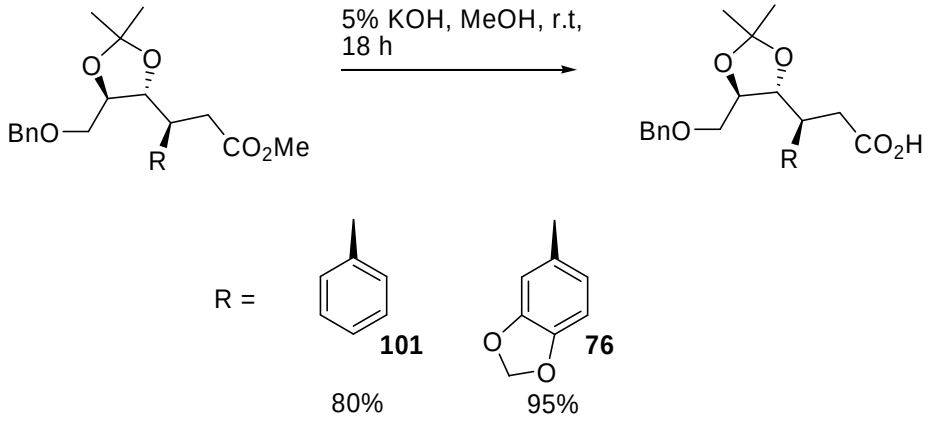
The rhodium catalysed 1,4-additions were relatively - compared to the organocuprate reactions - easy to perform. Addition compound **100** (**Scheme 32**) was prepared in the following manner: a dry mixture of phenylboronic acid and the Rh(I) catalyst was initially made, enoate **74** (**Scheme 32**) was dissolved in 1,4-dioxane:H_2O (10:1) and was then added to the dry mixture and lastly triethylamine was added. The reaction mixture was stirred at room temperature for 24 hours under an argon atmosphere. The reaction mixture was subsequently dried onto silica gel and compound **100** isolated by means of column chromatography. A respectable yield of 95% was achieved and ^{1}H and ^{13}C NMR analysis showed no evidence of the existence of another diastereomer. At this point it was not possible to determine if the reaction proceeded with *anti*- or conversely with *syn*-selctivity. The subsequent formation and x-ray structure determination of a carboxylic acid derivative **101** (**Figure 11**) of addition product **100** proved that the Rh(I) catalysed reaction proceeded with *anti*-selectivity – this will be discussed in the next section. The ^{1}H NMR spectrum of addition product **100** had a multiplet in the range of 7.15 – 7.29 ppm integrating for 10 protons; these protons could be assigned to both the benzyl-protecting group and the newly added aryl group. The signals at 6.91 and 6.11 ppm on the ^{1}H NMR spectrum of starting material **74**, which were assigned to the alkene protons of enoate, were no longer present in the ^{1}H NMR spectrum of compound **100**. Instead there was: a multiplet signal at 2.80 ppm integrating for one proton - the single proton at the CH-aryl junction, and a double of doublets signal at 2.68 ppm integrating for two protons – the CH_2 group α to the ester. The addition compound **75** (**Scheme 32**) was made in exactly the same way as compound **100**; the obvious difference being the use of 3,4-(methylene dioxy)-phenyl boronic acid as the source of the aryl group to be added to enoate **74** towards compound **75** and slightly less Rh(I) catalyst was used. The ^{1}H NMR spectrum of **75** did not contain the alkene signals found in the ^{1}H NMR spectrum of compound **74**. The CH_2 functionality of the dioxole group gave rise to a double of doublets at 5.89 ppm on the ^{1}H NMR spectrum of **75**. In addition, there was a multiplet integrating for three protons, in the range of 6.60 – 6.68 ppm, this chemical shift could assigned to the newly added aryl group's protons. The ^{1}H and ^{13}C NMR spectra of compound **75** did not indicate the presence of a diastereomer.

The production of **75** and **100** (95%, 90%) using 4.2 and 2.7 mol % Rh(I) catalyst respectively, the appropriate aryl boronic acid and triethylammine proceeded efficiently, with high stereoselectivity and conversion. This was in agreement with the results of Csaky and Segura.[46]

2.1.7 Functional group inter-conversion – hydrolysis of the ester functionalities

The next important step in the synthesis necessitated the hydrolysis of the ester functionalities. Fortunately the inter-conversion had been employed successfully on compound **95** towards acid **96** (**Scheme 29**).[70] Ester **100** (**Scheme 32**) was dissolved in methanol before a 5% aqueous potassium hydroxide solution was added.[70] The reaction mixture was stirred overnight at room temperature under a room atmosphere. A base-acid work up – starting with sodium hydrogen carbonate and finally 10% hydrochloric acid - was employed to retrieve and purify the desired acid **101** (**Scheme 33**) with a decent yield of 80%. The ^{1}H NMR spectrum of carboxylic acid **101** no longer contained a shift - a singlet integrating for three protons at 3.52 ppm on the ^{1}H NMR spectrum of compound **100** – which indicated the presence of the ester's CH_3 group present on ester **100**. In addition, there was a broad peak at 9.00 ppm on the ^{1}H NMR spectrum of acid **101**; this signal corresponded to the newly formed alcohol functionality of the carboxylic acid. Ester **75** (**Scheme 32**) was also stirred in a mixture of methanol and 5% aqueous potassium hydroxide to yield carboxylic acid **76** (**Scheme 33**).[70] Acid **76** was, like compound **101**, retrieved and purified - with an excellent 95% yield - through a base-acid work up; similarly using sodium hydrogen carbonate and 10% hydrochloric acid. The ^{1}H NMR spectrum of compound **76** did not contain an ester chemical shift as found on the ^{1}H NMR of compound **75**. A broad signal, assigned to the carboxylic acid's alcohol group, was evident on the ^{1}H NMR spectrum of acid **76** at 9.00 ppm.

In subsequent attempts, the work up was simplified; the methanol was removed *in vacuo* and the resulting residue was washed with water and extracted with ethyl acetate to yield carboxylic acids **76** and **101** (**Scheme 33**) with reasonable purity.



Scheme 33

2.1.8 Confirmation of the anti-selectivity for the Rh(I) catalysed additions

Re-crystallization of **101** (**Scheme 33**) in hexane allowed for a crystal structure to be obtained. Looking at the CH-protons coloured in blue and green (**Figure 11**), it can be clearly seen that the Rh(I) catalysed 1,4-additions had proceeded with *anti*-selectivity. The rhodium catalysed reaction had shown itself to be a useful alternative to the organocuprate chemistry previously used. In addition, the Rh(I) catalysed 1,4-addition proved to be a novel method of installing aromatic groups with the stereochemistry required for site C-10b of pancratistatin.

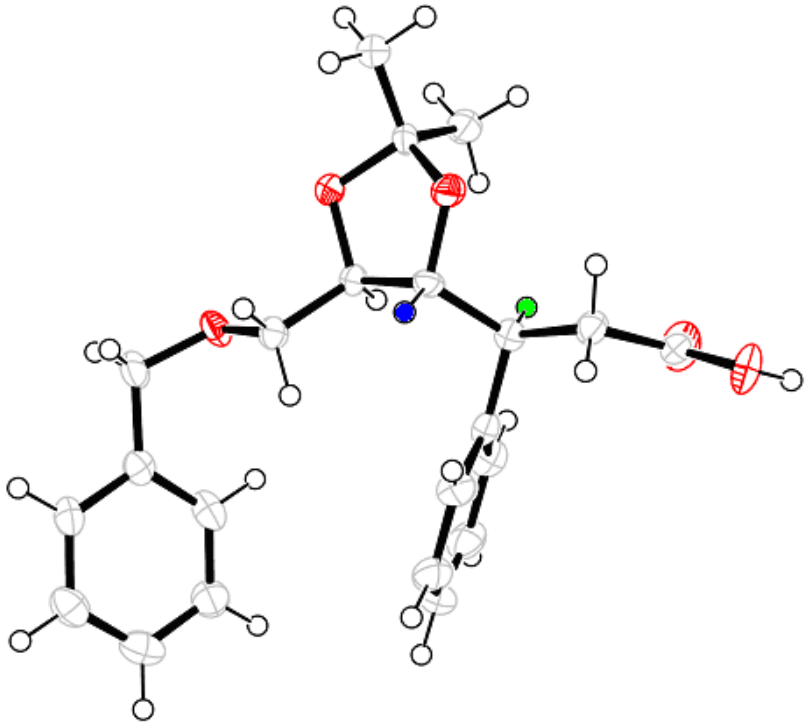


Figure 11 Crystal structure obtained for compund **101**

The *anti*-selectivity observed complemented the findings of Csaky and Segura.[46] Csaky and Segura's transition state model **I** (**Figure 12**) could also be used to predict the *anti*-selectivity observed for the Rh(I) catalysed 1,4-additions to σ,γ-alkoxy α,β-unsaturated enoate **102** (**Figure 12**).

Looking at transition state model **I** and **II** (**Figure 12**) it could also be proposed that - due to the steric hindrance resulting from the interaction of the benzyl protecting group and ester functionality - transition state model **II** is energetically less favourable than transition state model **I**. Model **I** can again be used in this case to rationalize the *anti*-selective products.[46]

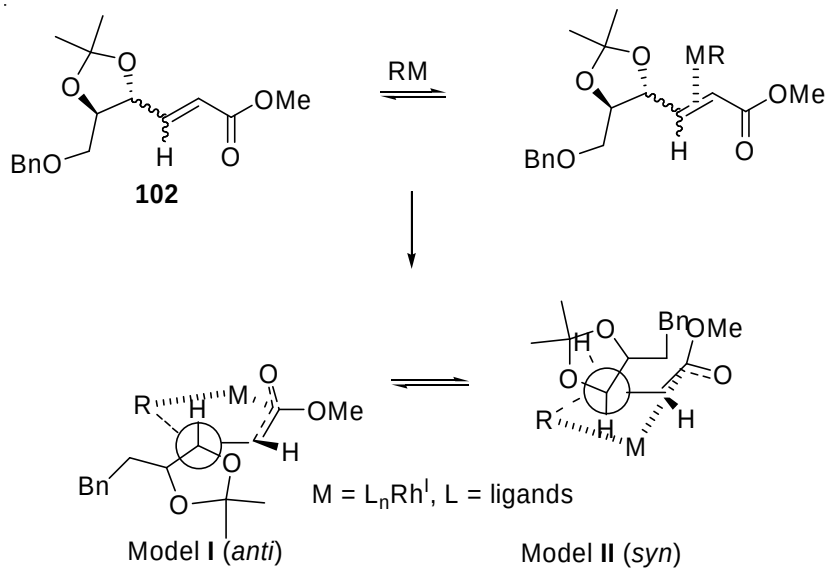
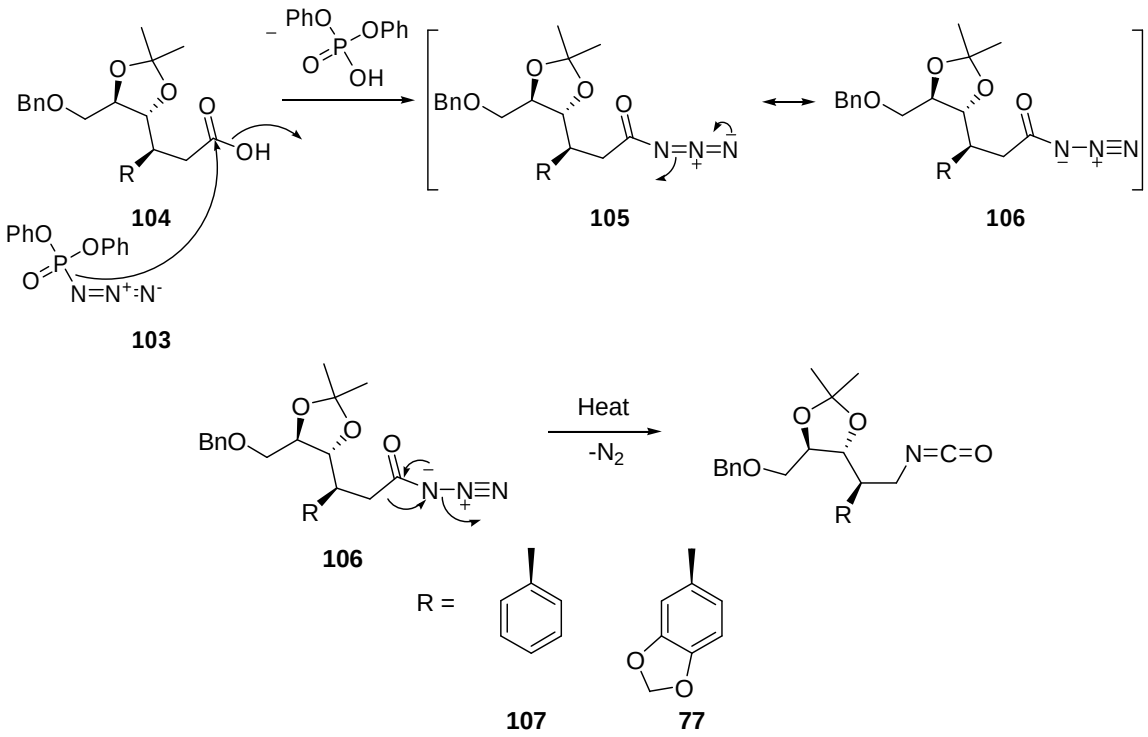


Figure 12 Segura's transition state models

2.1.9 Completing the open chain through a ring

With the two carboxylic acids **76** and **101** (**Scheme 33**) in hand the completion of ring B of pancratistatin could be attempted. The plan envisaged was, using diphenyl phosphoryl azide (DPPA) as the azide transfer agent, to initially convert the carboxylic acids into their corresponding azides. Finally, it was hoped, that subsequent heating would then promote a Curtius rearrangement to afford the isocyanate intermediates **77** and **106** (**Scheme 34**). **Scheme 34** illustrates the *possible* mechanisms by which the azide is formed and the subsequent Curtius rearrangement.

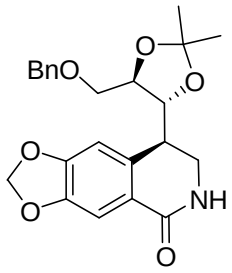


Scheme 34 Curtius rearrangements

The electron pair in the phosphorous-nitrogen bond of DPPA **103** (**Scheme 34**) attacks the electrophillic carbonyl of carboxylic acid **104** (**Scheme 34**) resulting in the alcohol group being liberated. The resulting intermediates **105** and **106** (**Scheme 34**) have azide functionalities which can resonate between one another as shown in S**cheme 34**. The Curtius rearrangement – initiated by heat - can be justified by the rearrangement of electron density of resonance structure **106**. The lone pair on the nitrogen atom attacks the electrophillic carbonyl and forces the electron pair of the carbon-carbonyl bond to move onto the initiating nitrogen atom. Finally, there is the expulsion of nitrogen gas, resulting in isocyanates **77** and **107** (**Scheme 34**). It was anticipated that the intramolecular ring closure of the isocyanate to furnish ring B of pancratistatin would require a catalytic amount of Lewis acid.[70]

2.1.10 Attempted Ring Closure using isocyanate chemistry

Compound **76** (**Scheme 33**) was treated with diphenyl phosphoryl azide (DPPA) and triethyl ammine at 0°C for ten minutes, followed by the addition of the Lewis acid - aluminium trichloride - and heating for 18 hours.[70] TLC analysis indicated the presence of two compounds before the subsequent addition of the Lewis catalyst and heating. There were however no additional 'spots' formed after the treatment with aluminium trichloride. The reaction was worked up and only one characterizable product was isolated via silica gel chromatography.



78

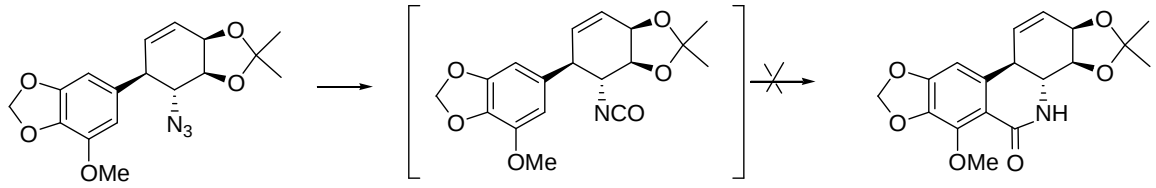
Figure 13 Desired compound

Unfortunately it was not possible to isolate the desired compound **78** (**Figure 13**). Analysis of the ^{1}H NMR spectrum indicated that a compound with the majority of the carbon backbone present in compound **78** was indeed present in our unknown compound. There was no longer a broad carboxylic acid's OH signal present on the ^{1}H NMR spectrum – a broad singlet integrating for one proton at 9.00 ppm on the ^{1}H NMR spectrum of compound **76** (**Scheme 33**). The two methyl groups belonging to the acetonide protecting group were still present as was indicated by two signals each integrating for three protons at 1.43 and 1.45 ppm on the ^{1}H NMR spectrum of the unknown compound. The benzyl protecting group's CH_2 gave rise to a singlet signal integrating for two protons at 4.35 ppm on the ^{1}H NMR spectrum of the attempted ring closure product. The CH_2 group alpha to the benzyl protected oxygen gave rise to a double doublet at 2.98 ppm on the ^{1}H NMR spectrum of the attempted ring closed product. The majority of the expected peaks required for compound **78** were included in the ^{1}H NMR spectrum of the attempted ring closed product.

However, the aromatic region of the ^{1}H NMR spectrum of the unknown compound did not correlate well with the expected signals that compound **78** (**Figure 13**) would have given rise to. Firstly, there was always an extra proton present in the aromatic region. In addition, there was a broad triplet signal integrating for one proton at 5.47 ppm that could be assigned to the proton attached to the nitrogen atom. Unfortunately, the ^{13}C NMR spectrum did not resolve anything as there was only one change from the ^{13}C NMR spectrum of the carboxylic acid starting material **76** (**Scheme 33**) and that was the shift of the carbonyl group's peak from 171.2 ppm to 156.13 ppm. Otherwise all of the other ^{13}C NMR spectrum peaks of our unknown compound were in the very same positions as they had been for the ^{13}C NMR spectrum of compound **76**. Analysis of all of the data was extremely frustrating as there was a lot of evidence supporting the existence of a compound with the majority of the carbon backbone found in compound **78**. However, no firm conclusions could be made. Mass spectroscopy indicated the presence of a compound with the mass of compound **78**. However there were other peaks present showing compounds with higher molecular masses. The reaction was repeated without the presence of aluminium trichoride and the exact same compounds were isolated as discussed above.[71]

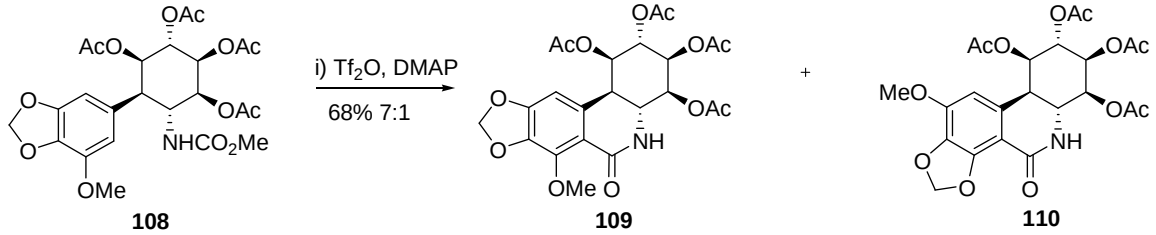
The same chemistry was attempted on the less activated carboxylic acid **101** (**Scheme 33**) and very similar results were observed. The only difference being that the mass spectrum of the attempted ring closed product from compound **101** did not indicate the presence of the desired ring closed product.

This was not such a bad result; in Trost's first synthesis of pancratistatin they were unable to promote an intramolecular ring closure via the isocyanate to form ring B (**Scheme 35**).[31] They reasoned that the acetonide protected oxygen atoms were more reactive (nucleophillic), relative to the aryl carbon, towards the isocyanate. This was a shortcoming in their synthesis and several steps were added to their synthesis as a result – see Chapter 1:Introduction, *1.4 Synthetic strategies towards pancratistatin – a brief history* (**Scheme 3)**.

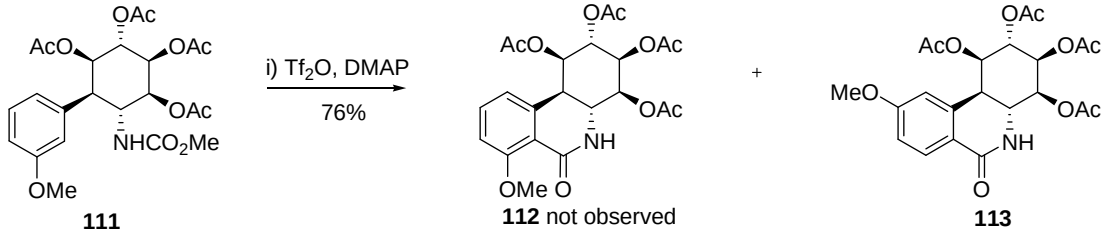


Scheme 35 Trost's failed use of isocyanate chemistry towards the synthesis of pancratistatin

The literature showed several other examples of when the Curtius rearrangement did not proceed as expected. Similarly to our findings; Magnus's group reported two inseparable regio-isomers **109** and **110** (7:1) when they attempted Bischler-Napieralski chemistry on **108** to furnish ring B of pancratistatin (**Scheme 36**).[32] The *ortho* position relative to the methoxy group was the most favourable position for ring closure. Three giants of the pancratistatin world: Hudlicky, Pettit and Rinner, did not experience – although un-expectantly - regio-selectivity when they attempted the modified Bischler-Napieralski chemistry on the methoxy compound **111** (**Scheme 37**)**.**[73] They suggested that steric control was at play where the *para* position was sterically – although less electronically – favourable for attack.

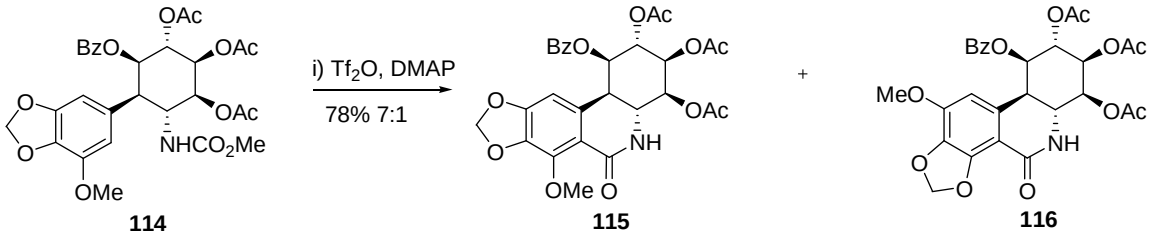


Scheme 36 Magnus's inseparable regio-isomers



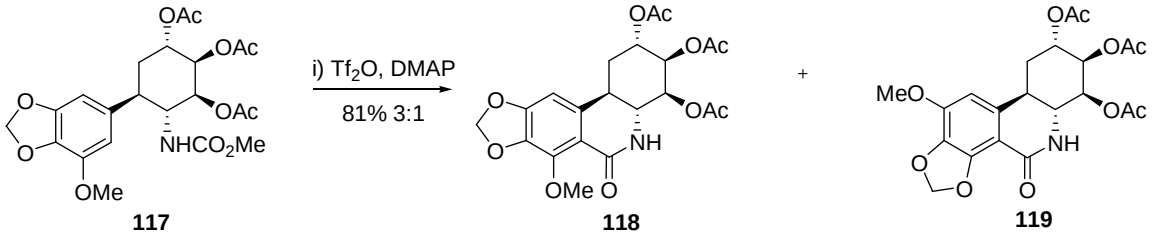
Scheme 37 Hudlicky's outcome of the modified Bischler-Napieralski reaction

In 2002, Kim's group reported a very similar result to Magnus; they found that the modified Bischler-Napieralski reaction on **114** also yielded two inseparable isomers **115** and **116** (7:1) (**Scheme 38**).[74] Later in 2007, Cho reported the formation of the two inseparable regio-isomers **118** and **119** (3:1) (**Scheme 39**).[72] In lieu of what three of the four groups found, it was no big surprise that we would also experience regio-selectivity when attempting the intramolecular ring closure of **76** (**Scheme 33**).



114 **115** **116**

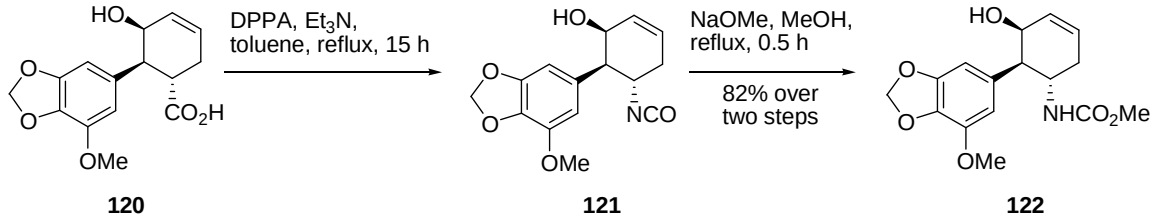
Scheme 38 Kim's findings using Bischler-Napieralski chemistry



117 **118** **119**

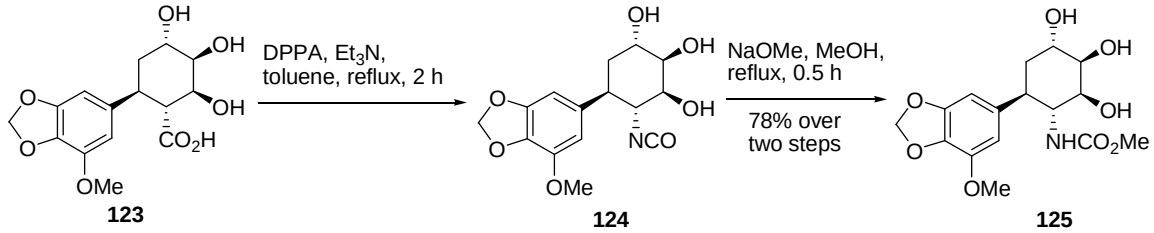
Scheme 39 Cho's inseperable isomers

Interestingly Kim and Cho also used diphenyl phosphoryl azide and heat to convert carboxylic acids **120** and **123** (**Scheme 40** and **41**) into their corresponding isocyanates **121** and **124** (**Scheme 40** and **41**) respectively. The isocyanates formed were stable and were then converted into their corresponding carbamates **122** and **125** (**Scheme 40** and **41**). This is a possible alternative to using the Curtius rearrangement to ring close isocynates **77** and **107** (**Scheme 34**).



120 **121** **122**

Scheme 40 Kim's use of DPPA chemistry



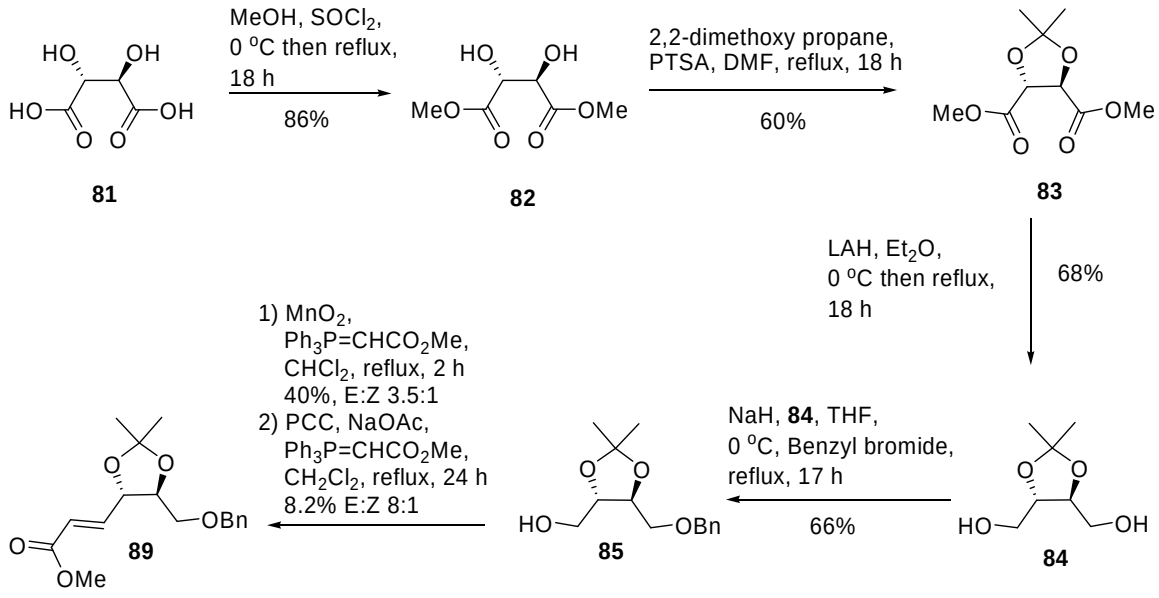
123 **124** **125**

Scheme 41 Cho's use of DPPA chemistry

Chapter 3: Future Work and Conclusions

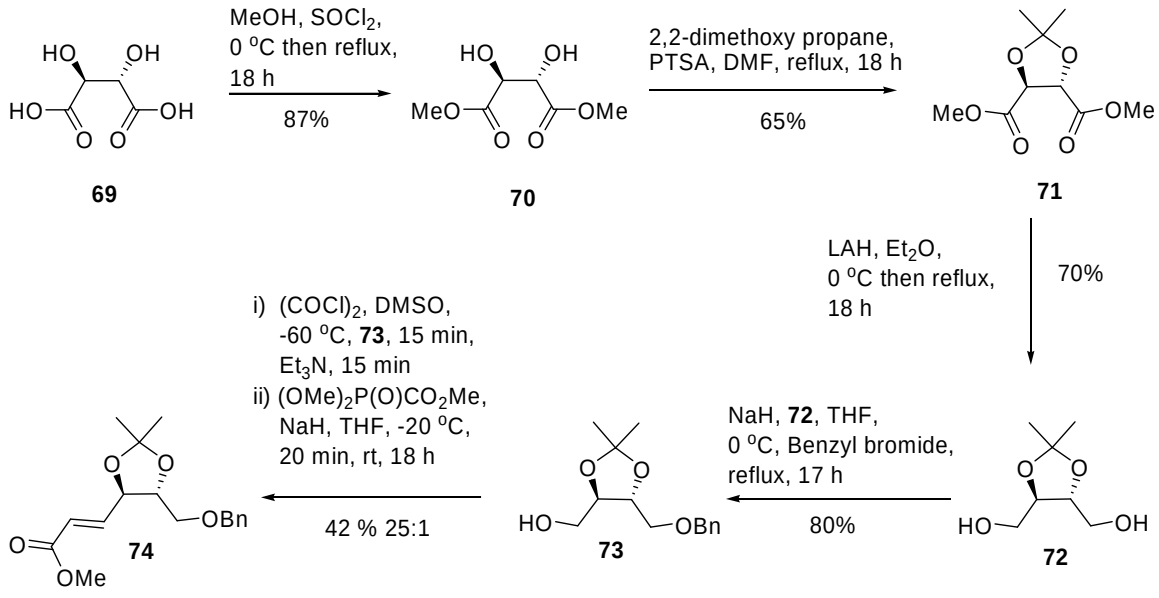
3.1 Synthetic Successes

The synthesis of all the known compounds starting with the natural tartaric acid **81** up until enoate **89** (**Scheme 42**) proceeded with great success. Starting with the natural tartaric acid **81** it was possible to synthesise the benzyl mono-protected compound **85** with an overall yield of 23%. One distillation and two column purification steps were used up until the isolation of compound **85**. It was anticipated that the use of the standard acid work up, using hydrochloric acid, for the reduction of compound **83** to diol **84** would cleave the acetonide protecting group. Subsequent attempts at removing the acteonide protecting group using hydrochloric acid did not work. It is thus suggested that instead of the somewhat tedious base work up that an acid work up be attempted for reduction of ester **83** to diol **84**. It is anticipated that a higher yield will be achieved due to the simplified extraction procedure expected when an acid work up is employed. The use of both the activated manganese oxide and pyridium chlorochromate reactions either provided relatively disappointing yields and/or E:Z ratios. None the less they were interesting reactions to attempt. In addition it is suggested that both these reactions be re-attempted using fresh activated manganese oxide and pyridium chlorochromate. In addition, the encouraging yield from the activated manganese TOP, it's the low toxicity and simplicity of reaction set-up could make it a potentially useful reaction.



Scheme 42 Synthetic successes starting with natural tartaric acid

The experience gained from the trial synthesis - using natural tartaric acid - was used to great effect for the attempted synthesis of pancratistatin analogues using the unnatural tartaric acid **69** (**Scheme 43**). Yields were improved for all the steps up until the production of the mono protected compound **73** (**Scheme 43**) and a total yield of 36% was achieved over the four steps.



Scheme 43 Synthetic successes starting with unnatural tartaric acid

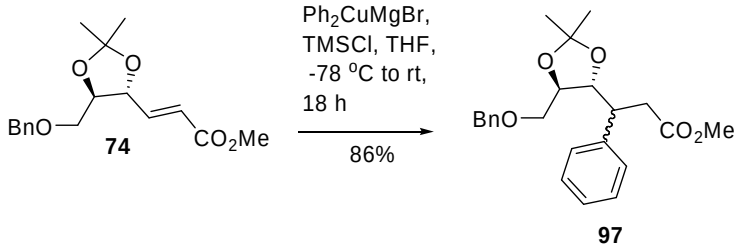
The Swern reaction – using fresh oxalyl chloride and dry triethylamine – proved to be great success. A respectable yield of 40% was achieved over the two steps as well as a decent E:Z ratio of 25:1 (Ratio calculated using the ^{1}H NMR spectrum of **74**). All of the reported chemistry thus far could be readily repeated with great confidence.

3.2 1,4-additions using a Rhodium catalyst and Cuprate chemistry

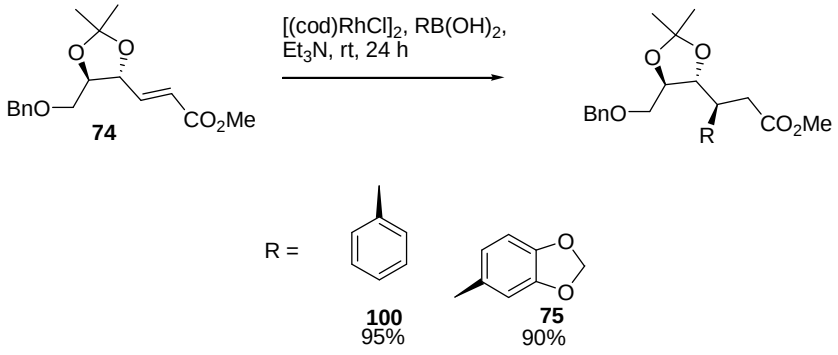
The addition of the aryl ring – ring A of pancratistatin – needed to take place with a high level of stereochemistry. Both the rhodium and organo cuprate chemistry were employed with a high level of stereo selectivity. The organo cuprate reaction was difficult to set up as low reaction temperatures and two cannulations were necessary. In addition, the purification of the desired compound **97** (**Scheme 44**) was tedious. However the reaction was an interesting and challenging task and a success in that a high yield of 86% was achieved with no evidence of stereoisomers being present in the product **97**'s ^{1}H NMR spectrum. Unfortunately a crystal structure was not obtained to indicate if the steroselctivity took place in an *anti*- or *syn*-selective fashion. It could be proposed from

the work done by Kornienko on similar systems, that the aromatic ring did add in an *anti* selective fashion.[37] However more solid evidence is needed to back this claim.

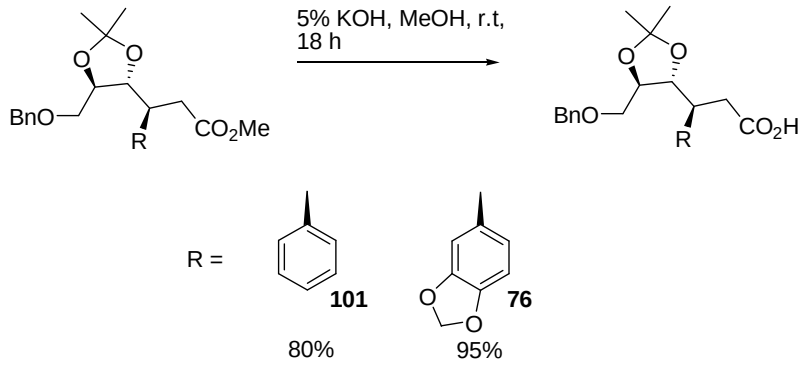
The rhodium catalysed 1,4-addition yielded a number of useful results (**Scheme 45**). Firstly, the reaction was a pleasure to set up as the reagents had to simply be mixed and stirred at room temperature in the presence of the starting material **74** (**Scheme 45**). The purification of the desired compounds **75** and **100** (**Scheme 45**) was readily done via silica gel column chromatography. Impressive yields and stereo-selectivity (ee >200:1) was achieved for both the production of compound **75** (90%) and compound **100** (95%). The *anti*-selective model proposed by Csaky was confirmed by our results as it was possible to obtain a crystal structure of compound **101** (**Figure 11**).[46] It is said with great confidence that the rhodium catalysed reaction was more efficient in terms of it's ease of set up and it is advised that this reaction be used for the installation of ring A on any future pancratistatin analogues produced.



Scheme 44 The successful use of organocuprate chemistry



Scheme 45 The successful use of a Rhodium catalysed reaction

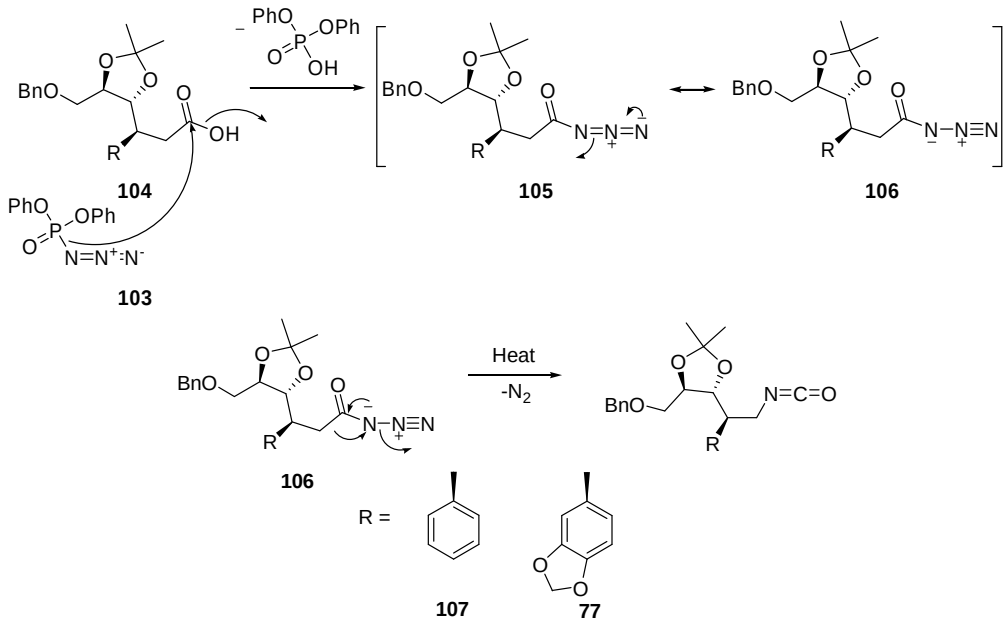


Scheme 46

Starting with tartaric acid it was possible to isolate compound **76** with an overall yield of 11% and compound **101** with a yield of 10% (**Scheme 46**).

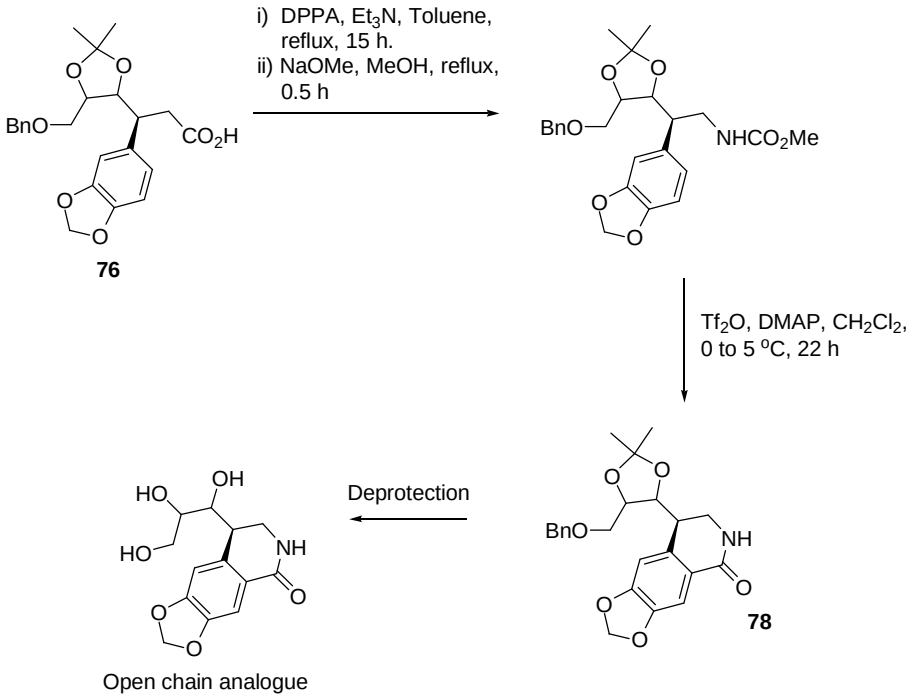
3.3The attempted ring closure to furnish Ring B of our analogues

Unfortunately it was not possible to identify the outcome of the ring closure reaction via an isocyanate intermediate and Curtius rearrangement. There is evidence to suggest that the isocyanate intermediates did in fact form from the characteristic N=C=O peak found on the IR of both the isocyanate compounds **77** and **107** (**Scheme 47**). However, the ^{1}H and ^{13}C NMR spectra of the isolated compounds from the attempted ring closure did not conclusively indicate that ring closure had taken place to furnish the protected analogues.



Scheme 47 Attempted ring-closure via an isocyanate intermediate and Curtius rearrangement

It is thus suggested than alternative chemistry such as Banwell's modified Bischler-Napieralski cyclization be attempted (**Scheme 48**). This is a useful synthetic alternative as the reaction could proceed from the carboxylic acids **76** and **101** (**Scheme 46**).



Scheme 48 An alternative for the ring closure is to try make use of Banwell's modified Bischler-Napieralski cyclization chemistry

Chapter 4: Experimental Procedures

4.1 General experimental procedures

4.1.1 Purification of solvents reagents

All solvents used for reactions and preparative chromatography were distilled prior to use. Where necessary, they were also dried by standard methods as recommended by Perrin *et al.*[75] Tetrahydrofuran, was distilled from the sodium benzophenone ketyl radical; dichloromethane and triethylammine from calcium hydride; toluene from sodium; chloroform was dried from passage through basic alumina (ICN Adsorbentien, ICN Alumina Super I). Where necessary, solvents were stored over activated molecular sieves (4 Å) under nitrogen atmosphere. Unless otherwise noted, other reagents were obtained from commercial sources and used without purification.

4.1.2 Chromatographic separations

The R_f values quoted are for analytical thin layer chromatography (TLC) on aluminium backed Mackerey-Nagel Alugram Sil G/UV_{254} plates pre-coated 0.25 mm silica gel 60, detection by UV-adsorbtion. Preparative column chromatography was carried out on both wet and dry-packed columns using Macherey-Nagel Kieselgel 60 silica gel (particle size 0.063-0.020 mm) as the adsorbent. Mixtures of EtOAc and hexane or MeOH and CH_2Cl_2 were used as the mobile phase.

4.1.3 Spectroscopic and physical data

All melting points were obtained on a Reichert hot-stage microscope, and are uncorrected.

^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE 300 (300.13 MHz) or a Bruker 400 (400.13 MHz) spectrometer.

Spectra were recorded in deuterated chloroform ($CDCl_3$) and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, the internal standard; coupling constants are given in Hertz. Splitting patterns are designated as “s”, “d”, “t”, “q” and “m” indicating “singlet”, “doublet”, “triplet”, “quartet” and “multiplet” respectively. NMR data are reported as follows: chemical shift (integration of signal, splitting pattern, coupling constant(s), assignment).

^{13}C NMR (^{1}H decoupled) spectra were recorded on a Bruker ADVANCE 300 (75.47 MHz) or Bruker 400 (100.63 MHz) spectrometer. Spectra were recorded in $CDCl_3$ and chemical shifts are reported in ppm relative to the central signal of $CDCl_3$, taken as δ 77.00.

Infrared (IR) spectra were recorded on a Bruker IFS-25 Fourier Transform spectrometer. The signals are reported on the wavenumber scale (ν/cm^{-1}). Signals were designated as “s”, “m”, “w” and “br”; indicating “strong”, “medium”, “weak” and “broad” respectively. IR spectra data are reported as follows: wavenumber (intensity, assignment).

High resolution mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer.

Optical rotations were measured on a Jasco DIP 3-70 instrument at 19 °C at the sodium D line, and $[\alpha]_D$ are given in $deg.cm^2.g^{-1}$.

4.1.4 Crystal structure solution and refinement

Intensity data were collected at 20 °C on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3 °. Data reduction was carried out using the program *SAINT+* and adsorption corrections were made using the program *SADABS.*[76] The crystal structure was solved by direct methods using *SHELXTL*.[77]

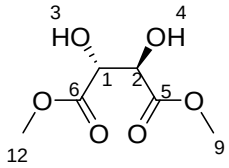
Non hydrogen atoms were first refined isotropically followed by an anistropic refinement by full matrix least squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material generated using *SHELXTL* and *PLATON*.[78]

4.1.5 Other general procedures

The term "*in vacuo*" refers to the removal of solvent by rotary evaporation, followed by removal of the residual solvent at the oil pump's pressure (*ca*. 0.1-1 Torr) at ambient temperature or with heat applied from a hair dryer until constant mass was achieved.

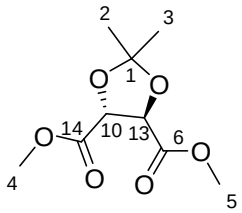
4.2 Experimental procedures

4.2.1 Synthesis of (2R,3R)-Dimethyl 2,3-dihydroxysuccinate 82



In a flame dried, 100 cm^3 round-bottom flask fitted with a condenser, L(+)-tartaric acid (20.00 g, 133 mmol) was dissolved in anhydrous methanol (60 cm^3). The solution was then placed in an ice-bath and cooled to 0 °C. Thionyl chloride (50.5 cm^3, 82.00 g, 689 mmol, 5.2 equiv.) was added drop-wise over 1 h to the cooled solution. The reaction mixture was allowed to warm up to room temperature and subsequently heated at reflux for 18 hours. The reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo.* The resulting orange-yellow residue was washed with distilled water (40 cm^3) and extracted with ethyl acetate (3 × 40 cm^3). The combined organic extracts were then dried with anhydrous Na_2SO_4 and solvent then removed *in vacuo,* to yield a light yellow oil (20.48 g, 86%). $\mathbf{R_f}$ = 0.7 (5% $CH_3OH/CHCl_3$); **IR :** ν_{max}- (cm^{-1}) = 3480 (s, br, OH), 1735 (s, C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 4.54 (2H, s, 1-CH and 2-CH), 3.82 (6H, d, J = 1.5 Hz, 9-CH_3 and 12-CH_3), 3.51 (2H, bs, 3-OH and 4-OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 170.0 (C-5 and C-6), 70.2 (C-1 or C-2), 70.2 (C-1 or C-2), 51.14 (C-9 or C-12), 51.12 (C-9 or C-12).

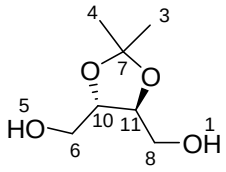
4.2.2 Synthesis of (4R,5R)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 83



(2*R*,3*R*)-Dimethyl 2,3-dihydroxysuccinate **82** (20.4 g, 114 mmol) was dissolved distilled DMF (60 cm^3). 2,2-Dimethoxy propane (160 cm^3 , 1.13 mol, 10 equiv.) and a catalytic amount of *p*-toluene sulphonic acid monohydrate (1.30 g, 6.85 mmol, 16.6 mol %) was added to the solution. The reaction mixture was then heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature and the organic solvents were removed *in vacuo* until approximately 50 cm^3 of a dark red solution remained. 50 cm^3 4% aqueous $NaHCO_3$ solution was added and the organic material extracted with $CHCl_3$ (6 × 50 cm^3). The organic extracts were combined, dried using anhydrous Na_2SO_4 and the solvent removed *in vacuo* to yield a dark red-orange liquid. The desired compound (15.9

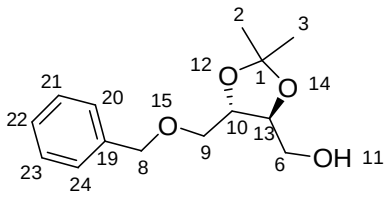
g, 60 %), a light yellow oil, was obtained via distillation (bp = 130 °C at 6 mbar). $\mathbf{R_f}$ = 0.9 (5% $CH_3OH/CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 4.81 (2H, s, 10-CH and 13-CH), 3.83 (6H, s, 4-CH_3 and 5-CH_3), 1.49 (6H, s, 2-CH_3 and 3-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 170.4 (C-6 and C-14), 114.2 (C-1), 77.3 (C-10 and C-13), 53.1 (C-4 and C-5), 26.6 (C-2 and C-3).

4.2.3 Synthesis of [(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol 84



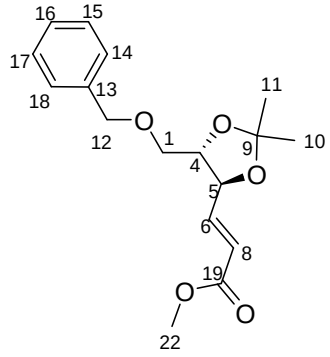
A mixture of $LiAlH_4$ (5.75 g, 151 mmol, 2.2 equiv.) in anhydrous Et_2O (90 cm^3) was heated vigorously at reflux for 30 min. It is important to note that the mixture needed to be stirred vigorously and that all glassware and the Et_2O be free of water. The mixture was then cooled to room temperature. (4*R*,5*R*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **83** (15.0 g, 68.5 mmol) was dissolved in anhydrous Et_2O (90 cm^3) and added drop-wise to the $LAlH_4$-Et_2O mixture over 1 h. The reaction mixture was subsequently heated at reflux for 18 h. On cooling, the reaction mixture was quenched, by with the cautious addition of H_2O (10 cm^3), 4M NaOH (25 cm^3) and finally H_2O (20 cm^3). The grey colloidal solid that formed was allowed to dry overnight. The resulting solid grey reaction mixture was subsequently ground to a powder and the organic compounds were removed by passing hot Et_2O through the powder. The organic extracts were removed *in vacuo*. The desired product (7.54 g, 68%) was then obtained by column chromatography. The undesired compounds were initially removed from the column using 5% $MeOH/CH_2Cl_2$ and the desired compound was eluted from the column using MeOH. It was necessary to remove silica from the effluent using CH_2Cl_2 and filtration. $\mathbf{R_f}$ = 0.15 (5% $CH_3OH/CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 3.94 – 3.97 (2H, m, 10-CH and 11-CH), 3.69 – 3.79 (4 H, m, 6-CH_2 and 8-CH_2), 3.01 (2H, bs, 1-OH and 5-OH), 1.42 (6H, s, 3-CH_3 and 4-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 109.7 (C-7), 78.7 (C-10 and C-11), 62.5 (C-6 and C-8), 27.4 (C-3 and C-4).

4.2.4 Synthesis of ((4S,5S)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 85



A suspension of NaH (0.739 g, 18.4 mmol, 1.2 equiv.) in THF (20 cm^3) was made and cooled to 0 °C. [(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol **84** (2.5 g, 15 mmol) was dissolved in THF (10 cm^3) and added cautiously over 15 min. to the suspension. The reaction mixture was then warmed to and stirred at room temperature for 1 h. Further portions of THF (2 × 30 cm^3) were added to break up the suspension and assist the stirring. The precipitate, sodium (4*S*,5*R*)-5-Carboxy-2-methyl-1,3-dioxolane-4-carboxylate, was evidently forming. Benzyl bromide (2.0 cm^3, 2.9 g, 17 mmol, 1.1 equiv.) was dissolved in THF (10 cm^3) and added to the reaction mixture over a period of 10 min. The reaction mixture was then stirred for 17 h at room temperature. The formation of a white salt, NaBr, was observed. The reaction was quenched with saturated NH_4Cl (50 cm^3) and saturated NaCl (40 cm^3). Extraction of the organic solutes was done using Et_2O (2 × 50cm^3). The organic extracts were then combined and dried using Na_2SO_4 and the solvent removed *in vacuo* to yield a yellow oil. The undesired side-products were removed using silica gel column chromatography (15% ethyl acetate/hexane) and the desired product, a light yellow oil (2.56 g, 66%), was eluted from the column (5% MeOH/CH_2Cl_2). Using an isovannilin staining dip, the product could be clearly seen on a TLC plate as a blue spot. $\mathbf{R_f}$ = 0.1 (20% EtOAc/Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.26 – 7.37 (5H, m, 5 × **A**-H's), 4.58 (2H, s, 8-CH_2), 4.03 (1H, td, J = 8.1, 5.3 Hz, 10-CH), 3.94 (1H, td, J = 8.3, 4.3 Hz, 13-CH), 3.76 (1H, dd, J = 11.7, 4.1 Hz, 6-CH_2), 3.70 (1H, d, J = 4.9 Hz, 6-CH_2), 3.7 (1H, d, J = 5.0 Hz, 8-CH_2), 3.56 (1H, dd, J = 9.9, 5.6 Hz, 8-CH_2), 2.42 (1H, s, 11-OH), 1.41 (6H, s, 2-CH_3 and 3-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 137.9 (C-19), 128.9 (C-21 and C-23), 128.3 (C-22), 128.2 (C-20 and C-24), 109.8 (C-1), 80.1 (C-13), 76.9 (C-10), 74.1 (C-8), 70.8 (C-9), 62.8 (C-6), 27.4 (C-2 and C-3).

4.2.5 Synthesis of (E)-Methyl 3-((4R,5S)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate 89



Method 1

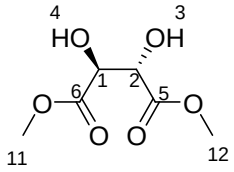
A solution of [(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)]methanol **85** (0.086 g, 0.343 mmol), 90% (triphenylphosphoranylidene)acetate (0.139 g, 0.375 mmol, 1.1 equiv.) and CH_2Cl_2 (10 cm^3) was prepared. Activated 90% manganese oxide (0.331 g, 3.43 mmol, 10 equiv.) was added to the solution and the reaction mixture was heated to reflux. After 4 h a further portion of activated manganese oxide (0.166 mg, 1.71 mmol) was added to the reaction mixture. The reaction mixture was heated at reflux for 24 h. The reaction mixture was then filtered through celite and the organic solvent removed *in vacuo*. Silica gel chromatography (20% EtOAc/hexane) was used to purify the product (0.042 g, 40%). *E*:*Z* = 3.5:1; $\mathbf{R_f}$ = 0.4 (20% EtOAc/hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.18 - 7.28 (5H, m, 5 × A-H's), 6.84 (1H, dd, J = 15.7, 5.3 Hz, 6-CH), 5.95 (1H, dd, J = 15.7, 0.7 Hz, 8-CH), 4.52 (2H, s, 12-CH_2), 4.36 (1H, dd, J = 8.3, 5.4 Hz, 5-CH), 3.88 (1H, td, J = 8.8, 4.5 Hz, 4-CH), 3.67 (3H, s, 22-CH_3), 3.56 (2H, d, J = 4.8 Hz, 1-CH_2), 1.37 (6H, d, J = 7.3 Hz, 10-CH_3 and 11-CH_3).

Method 2

A suspension of PCC (0.261 g, 1.18 mmol, 1.5 equiv.), sodium acetate (0.985 g, 1.18 mmol, 1.5 equiv.) and CH_2Cl_2 (10 cm^3) was made. A solution of [(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)]methanol **85** (0.200 g, 0.792 mmol) in CH_2Cl_2 (5 cm^3) was added to the suspension. The reaction mixture was then stirred for 10 min. before 90% (triphenylphosphoranylidene)acetate (0.278 mg, 0.792 mmol, 1 equiv.) was added. The reaction mixture was then stirred at room temperature for 20 h. A further portion of PCC (0.087 g, 0.393 mmol, 0.5 equiv.) was added and the reaction mixture was stirred for a further 6 h. The reaction mixture was subsequently filtered

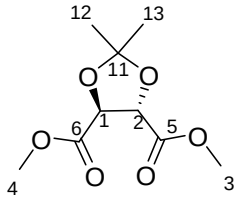
through celite and the organic solvent removed *in vacuo*. Purification was performed using silica gel column chromatography (20% EtOAc/hexane) to yield the desired product as clear oil (0.020 g, 8.2%). *E*:*Z* = 8:1. $\mathbf{R_f}$ = 0.4 (20% EtOAc/hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.19 – 7.30 (5H, m, 5 × A-H's), 6.84 (1H, dd, J = 15.7, 5.3 Hz, 6-CH), 5.95 (1H, dd, J = 15.7, 0.70 Hz, 8-CH), 4.52 (2H, s, 12-CH_2), 4.36 (1H, dd, J = 7.4, 6.2 Hz, 5-CH), 3.73 – 3.90 (1H, m, 4-CH), 3.67 (3H, s, 22-CH_3), 3.56 (2H, d, J = 4.7 Hz, 1-CH_2), 1.37 (6H, d, J = 7.3 Hz, 10-CH_3 and 11-CH_3).

4.2.6 Synthesis of (2S,3S)-Dimethyl 2,3-dihydroxysuccinate 70



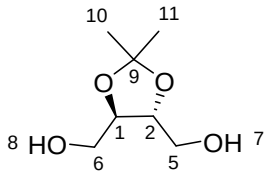
In a flame-dried round bottom flask fitted with a condenser, D-(-)-tartaric acid (20.0 g, 133 mmol) was dissolved in anhydrous methanol (80 cm^3). The solution was placed in an ice-bath and cooled to 0 °C. Thionyl chloride (50.5 cm^3, 82 g, 689.2 mmol, 5.2 equiv.) was added drop-wise over 1 h to the cooled solution. The reaction mixture was allowed to warm up to room temperature and subsequently heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature and the solvents were removed *in vacuo.* The resulting orange-yellow residue was washed with distilled water (40 cm^3) and extracted with ethyl acetate (3 × 40 cm^3). The organic extracts were dried with anhydrous Na_2SO_4 and the organic solvent was removed *in vacuo* to yield a light yellow oil (20.64 g, 87%). $\mathbf{R_f}$ = 0.7 (5% $CH_3OH/CHCl_3$); **IR :** $\nu_{max}(cm^{-1})$ = 3480 (s, br, OH), 1735 (s, C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 4.33 (2H, s, 1-CH and 2-CH), 3.59 (6H, s, 11-CH_3 and 12-CH_3), 3.43 (2H, bs, 3-OH and 4-OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 172.3 (C-5 and C-6), 72.5 (C-1 and C-2), 53.3 (C-11 and C-12); ESIMS *m/z* (relative intensity) 179 (M^+ +1, 4), 172 (8), 129 (10), 73 (32).

4.2.7 Synthesis of (4S,5S)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 71



(2*S*,3*S*)-Dimethyl 2,3-dihydroxysuccinate **70** (20.4 g, 114 mmol) was dissolved in distilled DMF (60 cm^3). 2,2-dimethoxy propane (160 cm^3, 1.13 mol) and a catalytic amount of *p*-toluene sulphonic acid monohydrate (1.30 g, 6.85 mmol) was added to the solution. The reaction mixture was heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature before the organic solvents were removed *in vacuo* until approximately 50 cm^3 of a dark red solution remained. 4% aqueous $NaHCO_3$ solution (50 cm^3) was added and the organic material extracted with $CHCl_3$ (6 × 50 cm^3). The organic extracts were combined, dried using anhydrous Na_2SO_4 and the solvent removed *in vacuo* to yield a dark orange liquid. The desired compound (15.7 g, 65 %), a light yellow oil, was obtained via distillation (bp = 130 °C at 6 mbar). $[\alpha]^{25}_D$ + 41.8, EtOAc, *c* = 54 $mg.ml^{-1}$ (*lit.*[79] $[\alpha]^{20}_D$ + 44.0, no solvent); $\mathbf{R_f}$ = 0.9 (5% $CH_3OH/CHCl_3$); **IR :** $\nu_{max}(cm^{-1})$ = 1740 (s, C=O), 1206 (s, C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 4.81 (2H, s, 1-CH and 2-CH), 3.83 (6H, s, 3-CH_3 and 4-CH_3), 1.49 (6H, s, 12-CH_3 and 13-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 170.4 (C-5 and C-6), 114.2 (C-11), 77.3 (C-1 and C-2), 53.1 (C-3 and C-4), 26.7 (C-12 and C-13); ESIMS *m/z* (relative intensity) 179 (M^+ +1, 4),

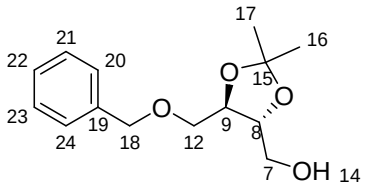
4.2.8 Synthesis of [(4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol 72



A mixture of $LiAlH_4$ (5.75 g, 151.4 mmol) and anhydrous Et_2O (90 cm^3) was heated vigorously at reflux for 30 min. It is important to note that the mixture needs to be stirred vigorously and that all glassware and the Et_2O be free of water. The mixture was then allowed to cool to room temperature. (4*S*,5*S*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **71** (14.96 g, 68.5 mmol) was dissolved in anhydrous Et_2O (90 cm^3) and added drop-wise over 1 h. The reaction mixture was subsequently heated at reflux for 18 h. On cooling, the reaction mixture was quenched, by carefully adding H_2O (10 cm^3), 4M NaOH (25 cm^3) and finally H_2O (20 cm^3). The resulting grey colloidal matter that formed was allowed to dry overnight. The resulting solid grey was then

ground to a powder. The organic compounds were removed by passing hot Et_2O through the powder and finally the Et_2O was removed *in vacuo*. The desired product (7.69 g, 70%) was obtained by column chromatography. The undesirable compounds were removed from the column using 5% MeOH/CH_2Cl_2 and the desired compound was eluted from the column using MeOH. It was necessary to remove silica from the effluent with CH_2Cl_2 and filtration. $[\alpha]^{25}_D$ -9.6, EtOAc, *c* = 60 mg.ml^{-1} (*lit.*[80] $[\alpha]^{26}_D$ – 4.8, $CHCl_3$, *c* = 10 mg.ml^{-1}); $\mathbf{R_f}$ = 0.9 (5% $CH_3OH/CHCl_3$); IR : ν_{max}(cm^{-1}) = 3389 (s, b, OH), 1215 (s, C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 3.97 (2H, tt, J = 2.7, 1.56 Hz, 1-CH and 2-CH), 3.67 – 3.78 (4 H, m, 5-CH_2 and 6-CH_2), 3.09 (2H, t, J = 5.7 Hz, 7-OH and 8-OH), 1.42 (6H, s, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 107.5 (C-9), 70.5 (C-1 and C-2), 60.4 (C-5 and C-6), 25.2 (C-10 and C-11).

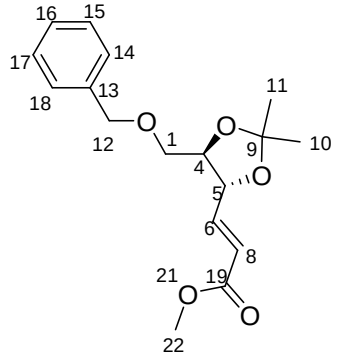
4.2.9 Synthesis of ((4R,5R)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 73



A suspension of NaH (0.739 g, 18.4 mmol, 1.2 equiv.) in THF (20 cm^3) was made and cooled to 0 °C. [(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol **72** (7.5 g, 46.2 mmol) was dissolved in THF (30 cm^3) and added cautiously over 1 h to the suspension. The reaction mixture was then warmed to, and stirred at room temperature for 1 h. Further portions of THF (2 × 30 cm^3) were added to break up the suspension and assist stirring. The precipitate, sodium [(4*R*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanolate, was evidently forming. Benzyl bromide (6.0 cm^3, 8.7 g, 50 mmol, 1.1 equiv.) was dissolved in THF (25 cm^3) and added to the reaction mixture over a period of 10 min. The reaction mixture was stirred for 20 h at room temperature and the formation of a white salt, NaBr, was observed. The reaction was quenched with saturated aqueous NH_4Cl solution (40 cm^3) and saturated NaCl solution (40 cm^3). Extraction was accomplished using Et_2O (4 × 50 cm^3) and the extracts were combined and dried using Na_2SO_4 and the solvent removed *in vacuo*. This yielded a yellow oil. The unwanted side products were removed via silica gel column chromatography (15% Ethyl acetate/Hexane) and the desired product, a light yellow oil

(10.13 g, 80%), was eluted from the column (5% MeOH/CH_2Cl_2). Using an isovanilin staining dip, the product could be clearly seen on a TLC plate as a blue spot. $[\alpha]^{25}_D$ + 1.7, EtOAc, *c* = 23 mg.ml^{-1} (*lit.*[81] $[\alpha]^{26}_D$ – 9.3, $CHCl_3$, *c* = 14.4 mg.ml^{-1}); $\mathbf{R_f}$ = 0.1 (20% EtOAc/Hexane); IR : ν_{max}(cm^{-1}) = 3466 (s, b, OH), 1214 (s, C-O), 1497 (w, C=C aromatic); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.26 – 7.34 (5H, m, 5 * A-H's), 4.58 (2H, s, 18-CH_2), 4.02 – 4.15 (1H, m, 9-CH), 3.91 – 3.99 (1H, m, 8-CH), 3.77 (1H, dd, J = 11.5, 4.2 Hz, 7-CH_2), 3.72 (1H, d, J = 7.5 Hz, 7CH_2), 3.68 (1H, d, J = 5.2 Hz, 12-CH_2), 3.55 (1H, dd, J = 9.9, 5.7 Hz, 12-CH_2), 2.32 - 2.36 (1H, m, 14-OH), 1.41 (6H, s, 16-CH_3 and 17-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 137.6 (C-19), 128.5 (C-21 and C-23), 127.9 (C-22), 127.8 (C-20 and C-24), 109.4 (C-15), 79.7 (C-8), 76.6 (C-9), 73.7 (C-18), 70.4 (C-12), 62.5 (C-7), 27.0 (C-16 or C-17), 27.0 (C-16 or C-17); **HRMS**: Found [M-CH_3]$^+$, 237.1128. $C_{13}H_{17}O_4$ requires *M* 237.1132; *m/z* (EI) 237 ([M-CH_3]$^+$, 2%), 235 (2), 221 (11).

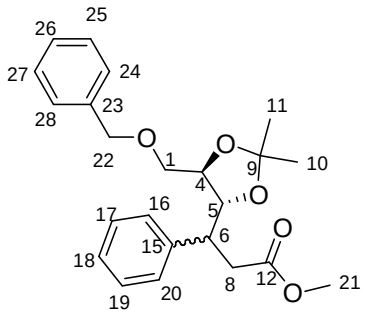
4.2.10 Synthesis of (E)-Methyl 3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate 74



Oxalyl chloride (8.24 cm^3, 11.8 g, 92 mmol, 2 equiv.) was dissolved in anhydrous CH_2Cl_2 (50 cm^3) and cooled to -60 °C. A solution of dimethyl sulphoxide (DMSO) (13.2 cm^3, 14.5 g, 4 equiv.) in and anhydrous CH_2Cl_2 (50 cm^3) was carefully added drop-wise, over a period of 10 min, to the oxalyl chloride solution. Furthermore, a solution of [(4*R*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol **73** (11.7 g, 46.3 mmol) in anhydrous CH_2Cl_2 (50 cm^3) was then added. The reaction mixture was stirred for 15 min. before triethyl amine (32.3 cm^3, 23.4 g, 231 mmol, 5.1 equiv.) was added. The reaction mixture was then slowly warmed to room temperature over 10 min. The organic solvent was removed *in vacuo* to yield a bright yellow oil. A quantitative yield was assumed and the crude aldehyde was used without delay. A suspension of 60% sodium hydride (2.4 g, 60 mmol) in anhydrous THF (50 cm^3) was stirred at -20 °C for 10 min. Trimethyl phosphonoacetate (8.7 cm^3, 10.9 g, 60 mmol,

1.3 equiv.), dissolved in THF (30 cm^3), was then added to the suspension at -20 °C. The reaction mixture was stirred at -20 °C for 1 h. Further portions of THF were added to assist stirring; as more precipitate had formed. The aldehyde, [(4*S*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, was dissolved in THF (20 cm^3) and added to the reaction mixture. The mixture was stirred at -20 °C for 1 h before being allowed to warm slowly to room temperature overnight. The THF was removed *in vacuo*. H_2O (50 cm^3) was then added to the yellow residue and the organic material extracted with EtOAc (3 × 70 cm^3). The organic extracts were dried using Na_2SO_4 and the solvent removed *in vacuo*. The desired product was purified by silica gel column chromatography (15% EtOAc/hexane) to yield a bright yellow oil (5.9 g, 42% over two steps) *E*:*Z* = 25:1 . $[\alpha]^{25}_D$ + 22.2 (MeOH, *c* = 21 $mg.ml^{-1}$) $\mathbf{R_f}$ = 0.33 (15% EtOAc/Hexane); IR : $\nu_{max}(cm^{-1})$ = 1726 (s, C=O), 1664 (w, C=C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.26 – 7.37 (5H, m, Aromatic H's), 6.91 (1H, dd, J = 15.7, 5.6 Hz, 6-CH), 6.11 (1H, dd, J = 15.7, 1.4 Hz, 8-CH), 4.58 (2H, s, 12-CH_2), 4.43 (1H, ddd, J = 8.3, 5.4, 1.3 Hz, 5-CH), 3.95 (1H, td, J = 8.5, 4.8 Hz, 4-CH), 3.73 (3H, s, 22-CH_3), 3.63 (2H, dd, J = 4.5, 0.9 Hz, 1-CH_2), 1.44 (6H, d, J = 7.3, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 166.3 (C-19), 144.4 (C-6), 137.7 (C-13), 128.3 (C-15 and C-17), 127.7 (C-16), 127.6 (C-14 and C-18), 121.9 (C-8), 110.1 (C-9), 79.5 (C-5), 77.4 (C-4), 73.6 (C-12), 69.2 (C-1), 51.6 (C-22), 26.9 (C-10 or C-11), 26.6 (C-10 or C-11).

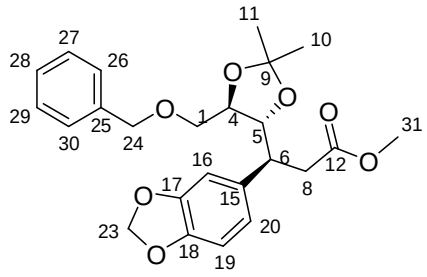
4.2.11 Synthesis of Methyl 3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylpropanoate 97



Magnesium turnings (0.388 g, 16 mmol, 10 equiv.) was added to anhydrous THF (15 cm^3). Phenyl bromide (1.7 cm^3, 2.49 g, 16 mmol, 10 equiv.) dissolved in anhydrous THF (5 cm^3) was then added. The reaction mixture was left to stand without stirring for approximately 20 min. Stirring was started once one could feel heat being generated by the reaction mixture. The reaction was stirred for approximately 30 min. or until the reaction mixture cooled down - indicating the reaction was complete. Copper

iodide (1.52 g, 8 mmol, 5 equiv.) was mixed with anhydrous THF (15 cm^3) and cooled to -65 °C. Please note that the copper (I) iodide was purified using hot THF flushing. The Grignard previously prepared was then cannulated into the cooled copper (I) iodide/THF mixture. The reaction mixture was stirred for 1 h at -60 °C. (E)-methyl 3-((4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate **74** (0.490 g, 1.6 mmol) was dissolved in anhydrous THF (15 cm^3) and cannulated to the reaction mixture. The reaction mixture was warmed slowly to room temperature and stirred for 20 h. Saturated aqueous NH_4Cl solution (3 × 50 cm^3) was used to quench the reaction and EtOAc (3 × 50 cm^3) was used to extract the organic component. The organic extracts were combined and dried with Na_2SO_4 and the solvent removed *in vacuo*. The product (1.72 g, 86%) was isolated using silica gel column chromatography (10% EtOAc/hexane) as yellow tinted clear oil. $\mathbf{R_f}$ = 0.45 (15% EtOAc/hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.15 – 7.28 (10H, m, 10 × A-H's), 4.28 (2H, d, J = 1.1 Hz, 22-CH_2), 3.88 – 3.98 (2H, m, 1-CH_2), 3.53 (3H, s, 21-CH_3), 3.26 (1H, ddd, J = 9.5, 8.7, 5.1 Hz, 5-CH), 3.06 (1H, dd, J = 15.7, 5.0 Hz, 4-CH), 2.76 – 2.85 (2H, m, 8-CH_2), 2.68 (1H, dd, J = 15.7, 9.9 Hz, 6-CH), 1.43 (6H, d, 6.1 Hz, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 173.4 (C-12), 139.8 (C-15), 138.4 (C-23), 129.9 (C-17 and C-19), 129.1 (C-18), 128.7 (C-16 and C-20), 128.5 (C-25 and C-27), 128.0 (C-26), 127.9 (C-24 and C-28), 109.7 (C-9), 80.5 (C-5), 80.4 (C-4), 73.6 (C-22), 70.7 (C-1), 51.9 (C-21), 47.2 (C-8), 38.6 (C-6), 27.6 (C-10 or C-11), 27.5 (C-10 or C-11); **HRMS**: Found $[M\text{-}CH_3]^+$, 369.1697. $C_{22}H_{25}O_5$ requires *M* 369.1697; *m/z* (EI) 369 ($[M\text{-}CH_3]^+$, 100%), 366 (44), 364 (6), 359 (10), 355 (40).

4.2.12 Synthesis of Methyl 3-(benzo[d][1,3]dioxol-5-yl)-3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate 75

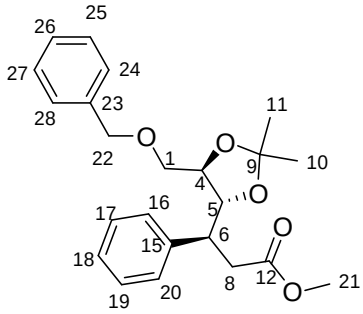


A mixture of 3,4-(Methylene dioxy)-phenyl boronic acid (0.539 g, 3.6 mmol, 2 equiv.) and $[(cod)RhCl]_2$ (0.035 g, 0.060 mmol, 4.2 mol %) was made.

Methyl (2E)-6-O-(1,3-cyclohexadien-1-ylmethyl)-2,3-dideoxy-4,5-O-(1-methylethylidene)-L-erythro-hex-2-enonate **74** (0.5 g, 1.6 mmol) was dissolved in,

thoroughly degassed 1,4-dioxane/H_2O (10:1) (5 cm^3), and added to the solid mixture. Triethyl amine (0.3 cm^3, 1.8 mmol, 1.1 equiv) was then added to the above mixture. The reaction mixture was stirred for 18 h. The solvents were removed *in vacuo* and the crude product dried onto silica. The product (0.627 g, 90%), an orange-yellow oil, was purified by silica gel column chromatography (15% EtOAc/hexane). $[\alpha]^{25}_D$ + 50.7 (MeOH, *c* = 13 $mg.ml^{-1}$); $\mathbf{R_f}$ = 0.42 (20% EtOAc/hexane); IR : $\nu_{max}(cm^{-1})$ = 1735 (s, C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.18 – 7.36 (5H, m, 5 × A-H's), 6.60 – 6.68 (3H, m, 16-CH, 19-CH and 20-CH), 5.90 (1H, m, 23-CH_2), 5.88 (1H, m, 23-CH_2), 4.36 (2H, s, 24-CH_2), 3.85 – 3.94 (2H, m, 1-CH_2), 3.55 (3H, s, 31-CH_3), 3.18 (1H, dt, J = 9.8, 9.7, 4.8 Hz, 5-CH), 3.01 (1H, dd, J = 15.7, 4.7 Hz, 4-CH), 2.94 (2H, t, J = 3.67 Hz, 8-CH_2), 2.59 (1H, dd, J = 15.7, 10.1 Hz, 6-CH), 1.42 (6H, d, J = 5.6 Hz, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 172.4 (C-12), 147.8 (C-17), 146,7 (C-18), 137.9 (C-25), 133.2 (C-15), 128.2 (C-27 and C-29), 127.5 (C-28), 127.5 (C-26 and C-30), 121.4 (C-20), 109.2 (C-19), 108.4 (C-16), 108.2 (C-9), 100.9 (C-23), 80.1 (C-5), 79.9 (C-4), 73.2 (C-24), 70.4 (C-1), 51.5 (C-31), 46.4 (C-8), 38.3 (C-6), 27.2 (C-10 or C-11), 27.2 (C-10 or C-11).

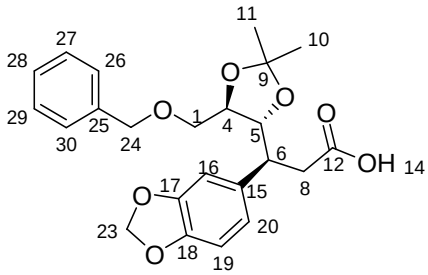
4.2.13 Synthesis of Methyl 3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylpropanoate 100



A mixture of phenylboronic acid (0.394 g, 3.3 mmol, 2 equiv.) and $[(cod)RhCl]_2$ (0.022 g, 0.044 mmol, 2.7 mol %) was made. (E)-Methyl 3-((4*R*,5*R*)-5 (benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate **74** (0.5 g, 1.6 mmol) was dissolved in, thoroughly degassed, 90% 1,4-dioxane/H_2O (5 cm^3) and added to the boronic acid and rhodium catalyst mixture. Triethyl amine (0.25 cm^3, 1.8 mmol, 1.1 equiv) was added to the above mixture. The reaction mixture was stirred for 18 h. The solvents were removed *in vacuo* and the crude product dried onto silica. The product (0.590 g, 95%), a yellow oil, was purified by silica gel column chromatography (15% EtOAc/hexane). $[\alpha]^{25}_D$ + 37.9 (MeOH, *c* = 11 $mg.ml^{-1}$); $\mathbf{R_f}$ = 0.40 (20% EtOAc/Hexane); IR : $\nu_{max}(cm^{-1})$ = 1736 (s, C=O) 1496 (w, C=C aromatic); **^{1}H NMR**

(300 MHz, $CDCl_3$): δ_H = 7.15 – 7.29 (10H, m, 10 × A-H's), 4.27 (2H, s, 22-CH_2), 3.88 – 3.97 (2H, m, 1-CH_2), 3.52 (3H, s, 21-CH_3), 3.26 (1H, dt, J = 9.2, 8.8, 5.1 Hz, 5-CH), 3.06 (1H, dd, J = 15.7, 4.9 Hz, 4-CH), 2.79 – 2.82 (2H, m, 8-CH_2), 2.68 (1H, dd, J = 15.7, 9.9 Hz, 6-CH), 1.43 (6H, d, J = 6.3 Hz, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 171.4 (C-12), 138.3 (C-15), 136.9 (C-23), 128.2 (C-17 and C-19), 127.6 (C-18), 127.1 (C-16 and C-20), 126.9 (C-25 and C-27), 126.5 (C-26), 126.4 (C-24 and C-28), 108.10 (C-9), 78.9 (C-5), 78.9 (C-4), 72.1 (C-22), 69.2 (C-1), 50.4 (C-21), 45.7 (C-8), 37.1 (C-6), 26.1 (C-10 or C-11).

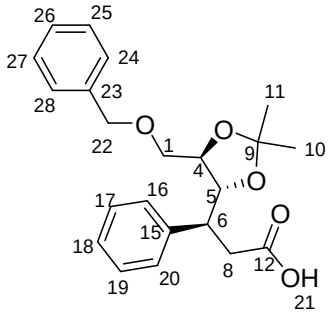
4.2.14 Synthesis of 3-(Benzo[d][1,3]dioxol-5-yl)-3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoic acid 76



Methyl 3-(benzo[d][1,3]dioxol-5-yl)-3-((4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate **75** (0.460 g, 1.1 mmol) was dissolved in MeOH (30 cm^3). 5% aqueous KOH solution (20 cm^3) was added to the reaction mixture. The reaction mixture was stirred for 18 h at room temperature. The organic solvent was removed *in vacuo*. Saturated aqueous $NaHCO_3$ solution (50 cm^3) was added to the pale yellow residue and washed with Et_2O (50 cm^3). The aqueous extract was collected and cooled to 0 °C. 10% aqueous HCl solution was carefully added to the aqueous extract until the mixture was acidified – acidity was monitored with pH paper. The desired carboxylic acid (0.420 g, 95%) was extracted with EtOAc (3 × 50 cm^3) and dried over Na_2SO_4 and the solvent was finally removed *in vacuo*. $[\alpha]^{25}_D$ + 25.8 (MeOH, *c* = 16 $mg.ml^{-1}$) $\mathbf{R_f}$ = 0 (20% EtOAc/hexane); IR : $\nu_{max}(cm^{-1})$ = ; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = ≈ 9.00 (1H, bs, 14-OH), 7.17 – 7.32 (5H, m, 5 × A-H's), 6.58 – 6.65 (3H, m, 16-CH, 19-CH and 20-CH), 5.89 (1H, m, 23-CH_2), 5.87 (1H, m, 23-CH_2), 4.35 (2H, s, 24-CH_2), 3.82 – 3.93 (2H, m, 1-CH_2), 3.13 (1H, dt, J = 9.4, 9.2, 5.2 Hz, 5-CH), 3.03 (1H, dd, J = 16.0, 4.0 Hz, 4-CH), 2.91 (2H, d, J = 3.9, 8-CH_2), 2.58 (1H, dd, J = 15.8, 9.9 Hz, 6-CH), 1.40 (6H, d, J = 2.3 Hz, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 171.2 (C-12), 147.8 (C-17), 146.7 (C-18), 137.9 (C-25), 132.9 (C-15), 128.2 (C-27 and

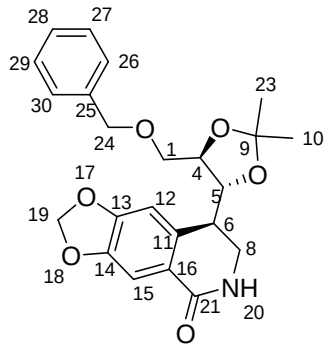
C-29), 127.5 (C-28), 127.5 (C-26 and C-30), 121.3 (C-20), 109.3 (C-19), 108.4 (C-16), 108.2 (C-9), 100.9 (C-23), 79.9 (C-5), 79.9 (C-4), 73.2 (C-24), 70.3 (C-1), 46.2 (C-8), 38.3 (C-6), 27.1 (C-10 and C-11).

4.2.15 Synthesis of 3-((4R,5R)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylpropanoic acid 101



Methyl 3-((4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylpropanoate **100** (0.300 g, 0.78 mmol) was dissolved in MeOH (10 cm^3). 5% aqueous KOH solution (20 cm^3) was added to the reaction mixture. The reaction mixture was stirred for 18 h at room temperature. The organic solvent was removed *in vacuo*. Saturated aqueous $NaHCO_3$ solution (50 cm^3) was added to the pale yellow residue and washed with Et_2O (50 cm^3). The aqueous extract was collected and cooled to 0 °C. 5% aqueous HCl solution was carefully added to the aqueous extract until the mixture was slightly acidic – pH was monitored using pH indicator paper. The desired carboxylic acid (0.230 g, 80%) was extracted with EtOAc (3 × 50 cm^3) and dried with Na_2SO_4 and the solvent removed *in vacuo*. $[\alpha]^{25}_D$ + 38.3 MeOH, *c* = 5 $mg.ml^{-1}$); $\mathbf{R_f}$ = 0 (20% EtOAc/hexane); IR : $\nu_{max}(cm^{-1})$ = 3219 (s, b, OH), 1725 (s, C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = ≈ 9.00 (1H, s, 21-OH), 7.13 – 7.32 (10H, m, 10 × A-H's), 4.27 (2H, s, 22-CH_2), 3.87 – 3.96 (2H, m, 1-CH_2), 3.22 (1H, dt, J = 9.3, 8.9, 5.5 Hz, 5-CH), 3.09 (1H, dd, J = 15.9, 3.5 Hz, 4-CH), 2.68 (1H, dd, J = 15.9, 10.4 Hz, 6-CH), 1.41 (6H, d, J = 3.7 Hz, 10-CH_3 and 11-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 178.9 (C-12), 140.2 (C-15), 139.1 (C-23), 129.8 (C-17 and C-19), 129.4 (C-18), 129.2 (C-16 and C-20), 128.7 (C-25 and C-27), 128.7 (C-26), 128.6 (C-24 and C-28), 110.4 (C-9), 81.2 (C-5), 81.1 (C-4), 74.3 (C-22), 71.3 (C-1), 47.7 (C-8), 39.3 (C-6), 28.3 (C-10 and C-11).

4.2.16 Attempted Synthesis of Ring Closed Compound 78



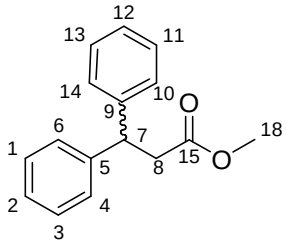
All glassware was flame dried and anhydrous solvents used. 3-(Benzo[d][1,3]dioxol-5-yl)-3-((4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoic acid **76** (0.550 g, 1.3 mmol) was dissolved in toluene (20 $cm^{3)}$. The solution was cooled to 0 °C before DPPA (0.411 g, 0.3 cm^3, 1.5 mmol, 1.1 equiv) and triethyl amine (0.268 g, 0.4 cm^3, 2.6 mmol, 2 equiv) was added. The presence of gas bubbles indicated that N_2 gas was being evolved and hence the formation of the isocyanate intermediate The reaction mixture was stirred at 0 °C for 10 min. At this point an IR was run to determine if the isocyanate had indeed formed.

IR : $\nu_{max}(cm^{-1})$ = 2166 (m, NCO)

The reaction mixture was then allowed to warm to room temperature and subsequently heated to 110 °C. The reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and the toluene removed *in vacuo*. The residue was washed with 0.1 N aqueous NaOH solution (50 cm^3) and extracted with EtOAc (3 × 50 cm^3). The extracts were dried over Na_2SO_4 and the solvent removed *in vacuo*. The unknown compound (0.200 g), an opaque gum, was purified by silica gel column chromatography (20% EtOAc/hexane). $[\alpha]^{25}_D$ + 81.9 (EtOAc, *c* = 14 $mg.ml^{-1}$); $\mathbf{R_f}$ = 35 (20% EtOAc/hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.28-6.61 (8 × Aromatic protons), 5.87 (1H, m, 19-CH_2), 5.85 (1H, m, 19-CH_2), 5.47 (1H, t, J = 5.3, 5.3 Hz, 20-NH), 4.35 (2H, s, 24-CH_2), 3.99 (1H, m, 5-CH), 3.90 (1H, ddd, J = 7.9, 5.5, 2.76 Hz, 4-CH), 3.75 (1H, ddd, J = 13.6, 6.9, 5.6 Hz, 6-CH), 3.46 (1H, ddd, J = 13.7, 7.4, 6.36 Hz, 8-CH_2), 2.98 (1H, dd, J = 10.6, 2.8 Hz, 1-CH_2), 2.90 (1H, dd, J= 10.6, 5.5 Hz, 1-CH_2), 2.81 (1H, m, 8-CH_2), 1.45 (3H, s, 23-CH_3), 1.43 (3H, s, 10-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C = 156.13 (Unknown), 148.09 (C-14), 147.10 (C-13), 137.81 (C-25), 131.26 (C-11), 128.25 (C-27 and C-29), 127.54 (C-28, C-26 and C-30), 121.42 (C-16), 109.52

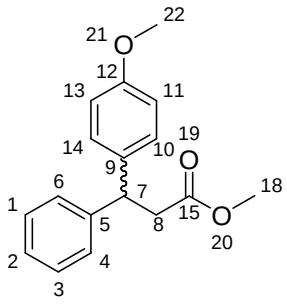
(C-15), 108.67 (C-12), 107.94 (C-9), 101.14 (C-3), 80.09 (C-5), 79.96 (C-4), 73.26 (C-24), 70.03 (C-1), 49.38 (C-8), 44.70 (C-6), 27.22 (C-10 or C-23), 27.04 (C-10 or C-23)

4.2.18 Synthesis of Methyl 3,3-diphenylpropanoate 93



Magnesium turnings (0.763 g, 31.4 mmol, 10 equiv.) were added to anhydrous THF (15 cm^3). Phenyl bromide (3.3 cm^3, 4.84 g, 30.8 mmol, 10 equiv.), dissolved in anhydrous THF (5 cm^3) was then added. The reaction mixture was subsequently left to stand without stirring for approximately 20 min. Stirring only started when heat was generated by the reaction mixture. The reaction was stirred for approximately 30 min. or until the reaction mixture cooled down, indicating the reaction was complete. In a separate vessel copper (I) iodide (2.68 g, 14.1 mmol, 5 equiv.) was added to anhydrous THF (15 cm^3) and cooled to -65 °C. The Grignard, previously prepared, was then cannulated to the cooled copper (I) iodide/THF mixture. The reaction mixture was stirred for one h at -60 °C. Methyl cinnamate (0.5 g, 3.1 mmol) was dissolved in anhydrous THF (15 cm^3) and cannulated to the organocopper reagent mixture. The reaction mixture was warmed slowly to room temperature and stirred for 20 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 × 50 cm^3) followed by the extraction of organic components using EtOAc (3 × 50 cm^3). The organic extracts were combined and dried with Na_2SO_4 and the solvent removed *in vacuo*. The product (0.350 g, 47%) was isolated using silica gel column chromatography (20% EtOAc/hexane) as a clear oil. $\mathbf{R_f}$ = 0.15 (20% EtOAc/Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.14 – 7.29 (10H, m, 10 × A-H's), 4.55 (1H, t, J = 8.0 Hz, 7-CH), 3.55 (3H, s, 18-CH_3), 3.06 (2H, d, J = 8.0 Hz, 8-CH_2).

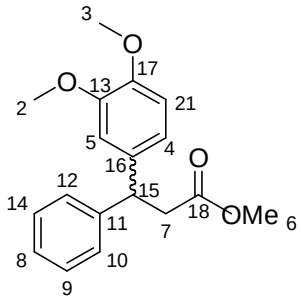
4.2.19 Synthesis of Methyl 3-(4-methoxyphenyl)-3-phenylpropanoate 94



Magnesium turnings (0.755 g, 31.0 mmol, 10 equiv.) was added to anhydrous THF (15 cm^3). 1-Bromo anisole (3.85 cm^3, 5.76 g, 30.8 mmol, 10 equiv.) dissolved in anhydrous THF (15 cm^3) was then added. The reaction mixture was subsequently left to stand

without stirring for approximately 20 min. Stirring was only started when heat was generated by the reaction mixture. The reaction was stirred for approximately 30 min. or until the reaction mixture cooled down, indicating the reaction was complete. In a separate vessel copper (I) iodide (2.96 g, 15.5 mmol, 5 equiv.) was added to anhydrous THF (15 cm^3) and cooled to -65 °C. The Grignard, previously prepared, was then cannulated to the cooled copper (I) iodide/THF mixture. The reaction mixture was subsequently stirred for 1 h at -60 °C. Methyl cinnamate (0.5 g, 3.1 mmol) was dissolved in anhydrous THF (15 cm^3) and cannulated to the organocopper reagent mixture. The reaction mixture was warmed slowly to room temperature and stirred for 20 h. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl solution (3 × 50 cm^3) and the organic components extracted with EtOAc (3 × 50 cm^3). The organic extracts were combined and dried with Na_2SO_4 and the solvent removed *in vacuo*. The product **76** (0.230 mg, 28%) was isolated as a clear oil using silica gel column chromatography (20% EtOAc/hexane). The desired product was purified further by re-crystallisation using EtOAc. $\mathbf{R_f}$ = 0.5 (20% EtOAc/hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.12 – 7.29 (9H, m, 9 × A-H's), 4.50 (1H, t, J = 7.99 Hz, 7-CH), 3.75 (3H, s, 22-CH_3), 3.56 (3H, s, 18-CH_3), 3.02 (2H, d, J = 8.0 Hz, 8-CH_2).

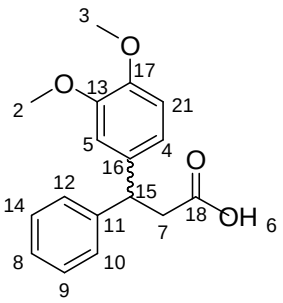
4.2.20 Synthesis of Methyl 3-(3,4-dimethoxyphenyl)-3-phenylpropanoate 95



Magnesium turnings (0.750 g, 30.8 mmol, 10 equiv.) was added to anhydrous THF (15 cm^3). 4-bromo veratrole (4.47 cm^3, 6.7 g, 30.7 mmol, 10 equiv.) dissolved in anhydrous THF (15 cm^3) was then added. The reaction mixture was subsequently left to stand without stirring for approximately 20 min. Stirring was only started when heat was generated by the reaction mixture. The reaction was stirred for approximately 30 min. or until the reaction mixture cooled down, indicating the reaction was complete. In a separate vessel copper (I) iodide (2.93 g, 15.4 mmol, 5 equiv.) was mixed with anhydrous THF (15 cm^3) and cooled to -65 °C. The Grignard, prepared previously, was then cannulated to the cooled copper (I) iodide/THF mixture. The reaction mixture was stirred for 1 h at -60 °C. Methyl cinnamate (0.5g, 3.1

mmol) was dissolved in anhydrous THF (15 cm^3) and cannulated to the organocopper reagent mixture. The reaction mixture was warmed slowly to room temperature and stirred for 20 h. The reaction was quenched with saturated aqueous NH_4Cl solution (3 × 50 cm^3) and the organic products extracted with EtOAc (3 × 50 cm^3). The organic extracts were combined and dried with Na_2SO_4 and the solvent removed *in vacuo*. The addition ester product, methyl 3-(3,4-dimethoxyphenyl)-3-phenylpropanoate, (320 mg, 46%) was isolated with impurities with using silica gel column chromatography. Despite several re-purification attempts, a clean spectrum was not obtained and it was decided to use the impure product in the next reaction.

4.2.21 Synthesis of 3-(3,4-Dimethoxyphenyl)-3-phenylpropanoic acid 96

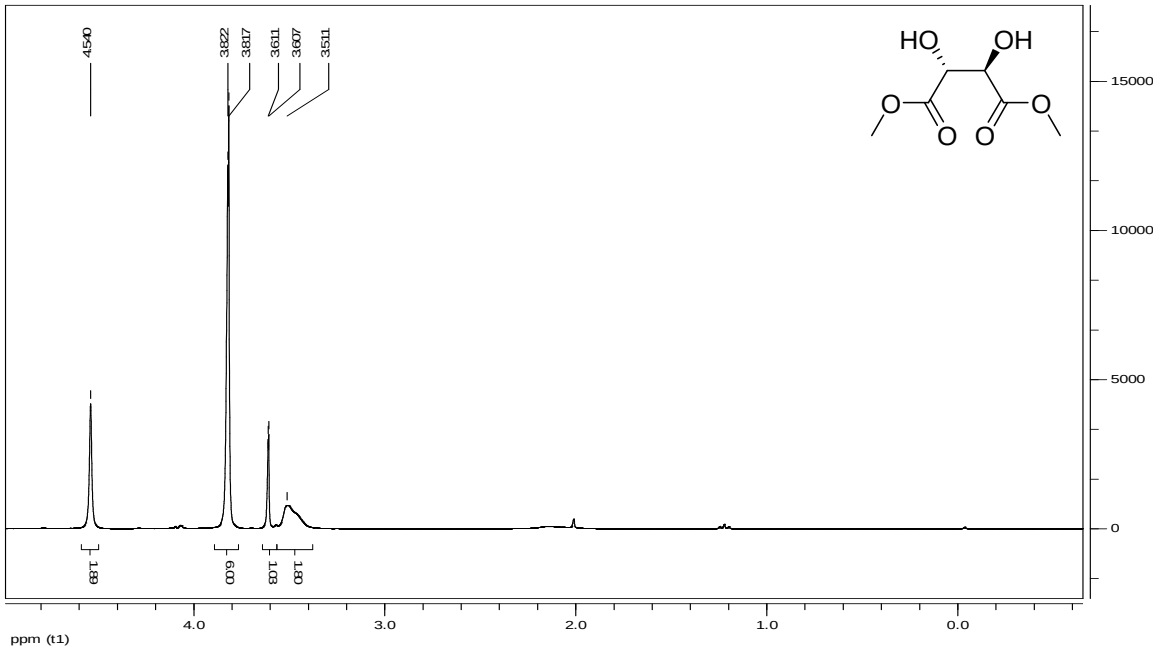


A mixture of Methyl 3-(3,4-dimethoxyphenyl)-3-phenylpropanoate (0.320 g, 1.1 mmol) **95**, 5% aqueous NaOH solution (15 cm^3) and MeOH (25 cm^3) was heated at reflux for 2.5 h. The solvent was subsequently removed *in vacuo*. The residue was then washed with distilled water (25 cm3) and extracted with Et_2O (3 × 50 cm^3). The desired compound **79** was purified using column chromatography (40% EtOAc/Hexane) as clear crystals (0.060 g, 6.8%). $\mathbf{R_f}$ = 0.27 (40% EtOAc/hexane); **^{1}H NMR** (300 MHz, CDCl3): δ_H = 9.54 (1H, bs, 6-OH), 7.17 – 7.29 (5H, m, 5 × A-H's), 6.71 – 6.77 (3H, m, 4-CH, 5-CH and 21-CH), 4.47 (1H, t, J = 7.9 Hz, 15-CH), 3.81 (3H, s, 2-CH_3 or 3-CH_3), 3.79 (3H, s, 2-CH_3 or 3-CH_3), 3.04 (2H, d, J = 7.9 Hz, 7-CH_2).

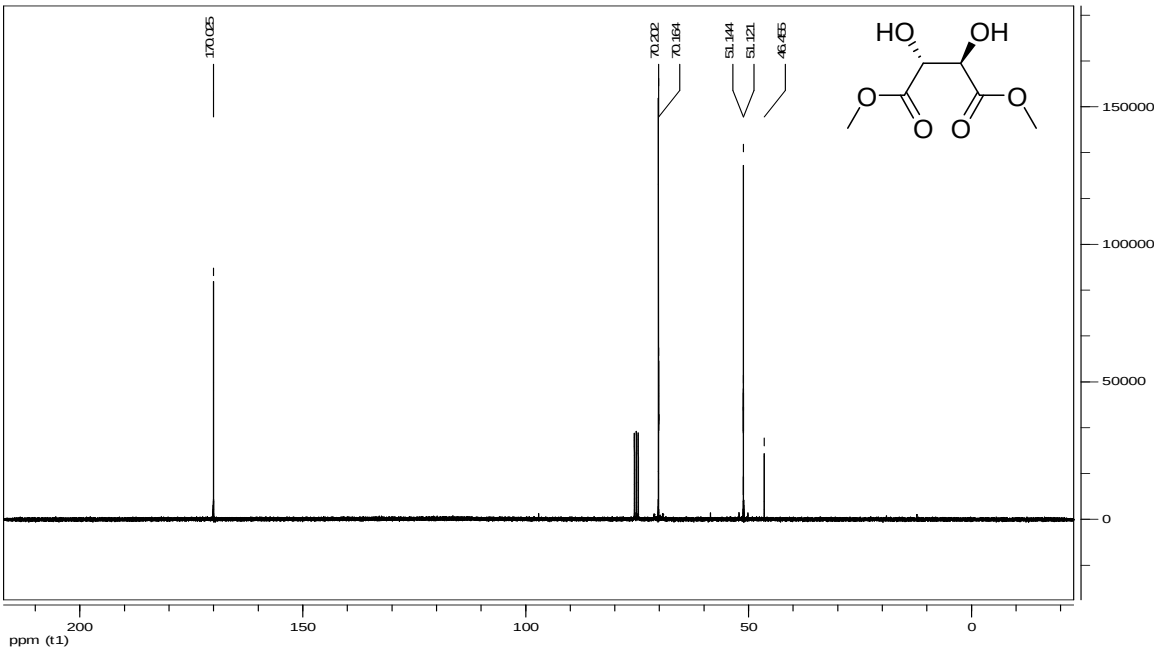
Appendix

A1.1: ^{1}H and ^{13}C NMR spectra for compounds successfully synthesised

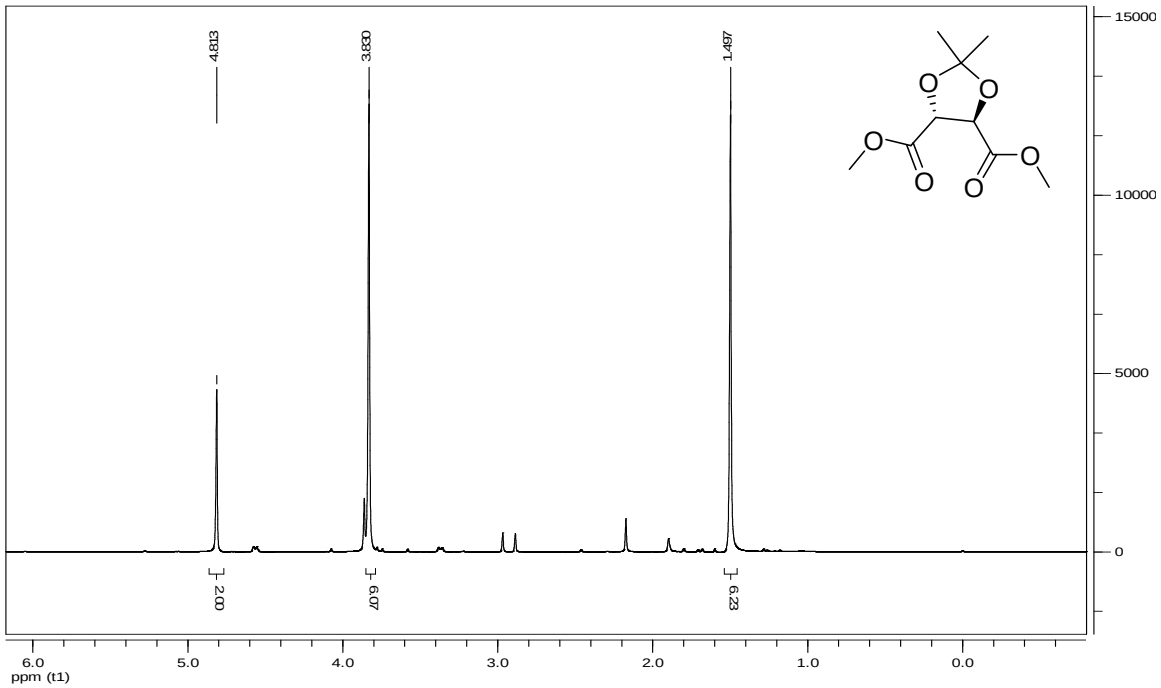
A1.1.1 ^{1}H NMR spectrum of **82**



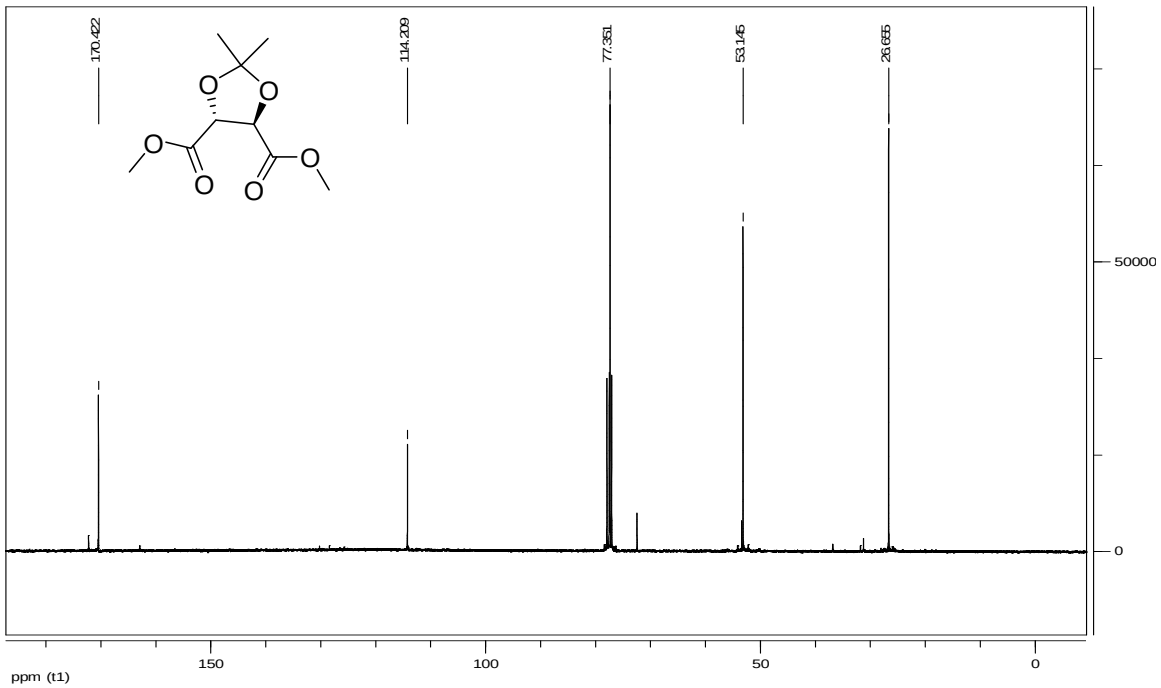
A1.1.2 ^{13}C NMR spectrum of **82**



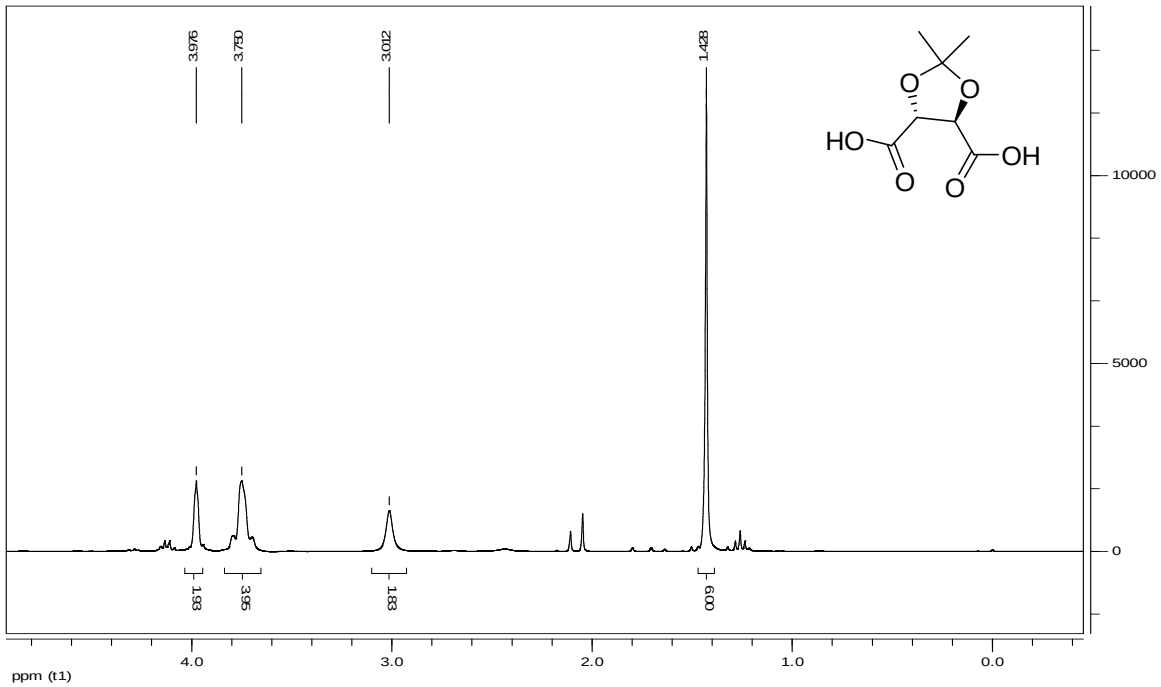
A1.2.1 ^{1}H NMR spectrum of **83**



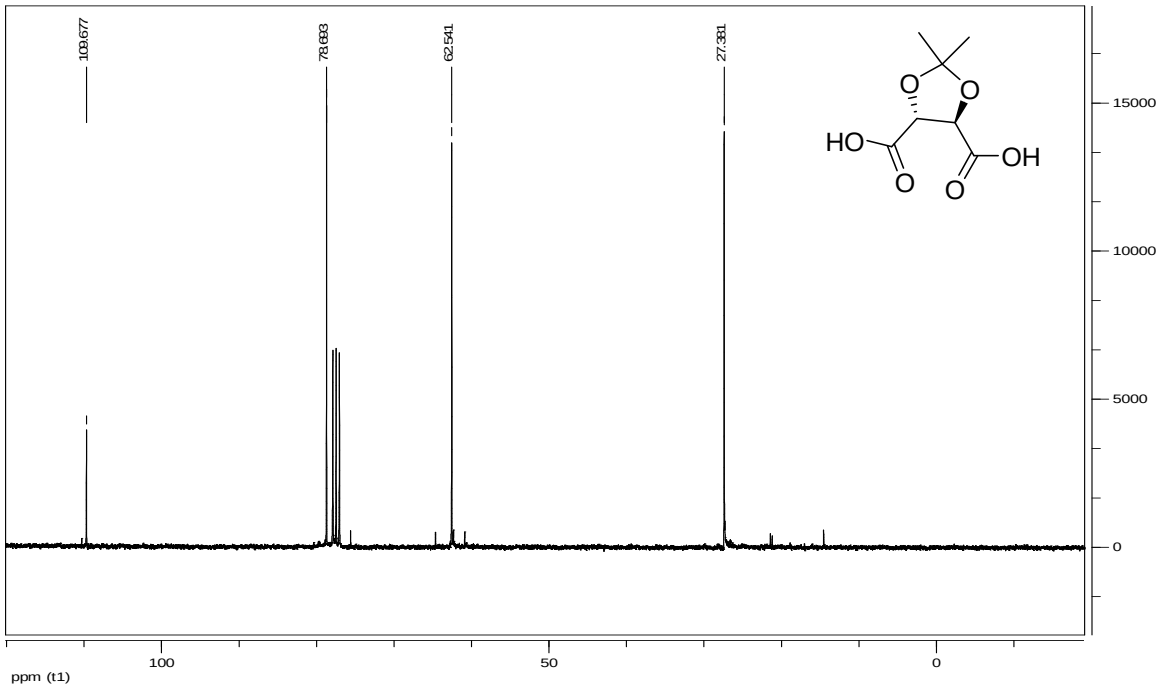
A1.2.2 ^{13}C spectrum of **83**



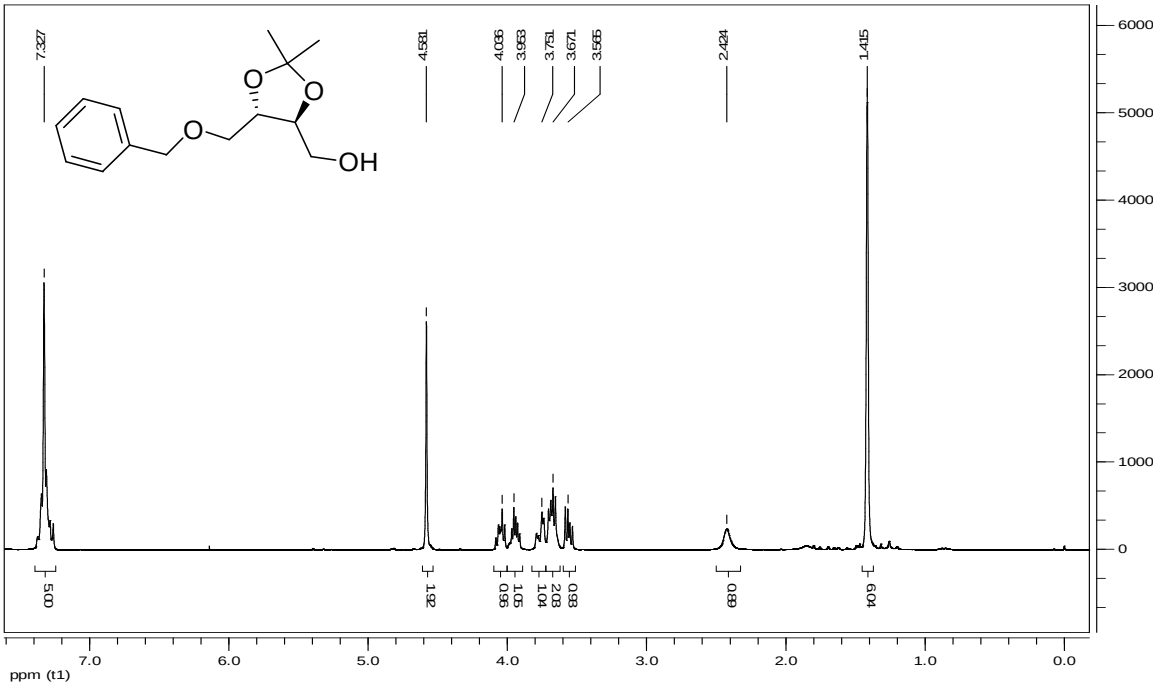
A1.3.1 ^{1}H NMR spectrum of **84**



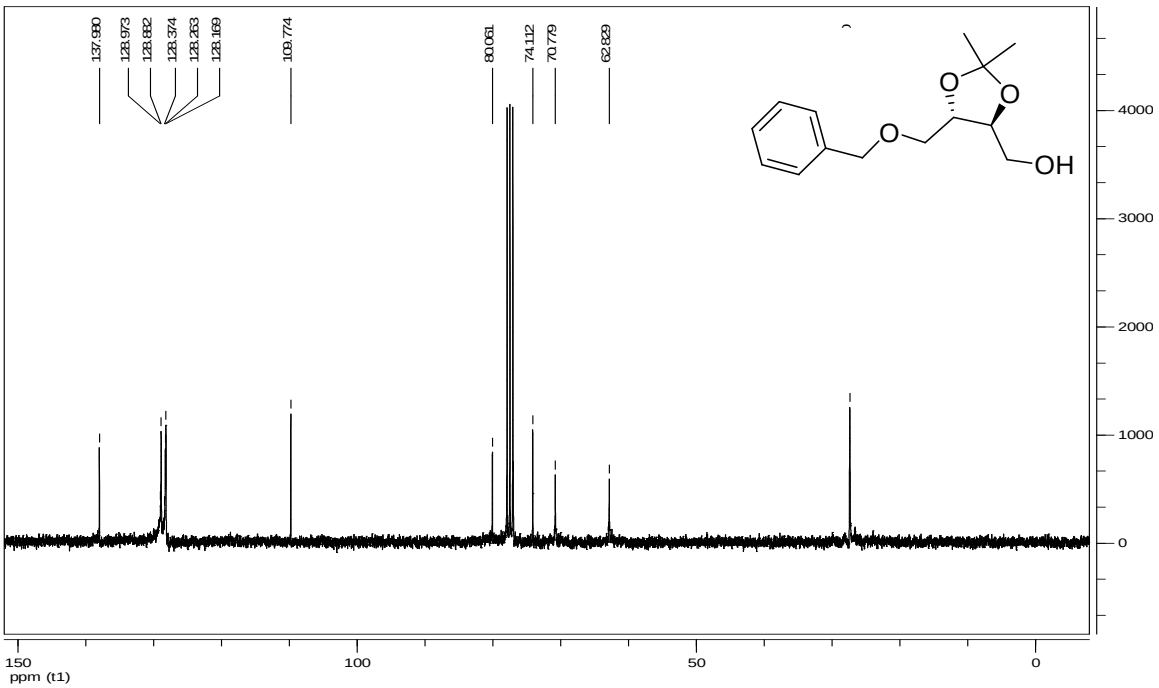
A1.3.2 ^{13}C NMR spectrum of **84**



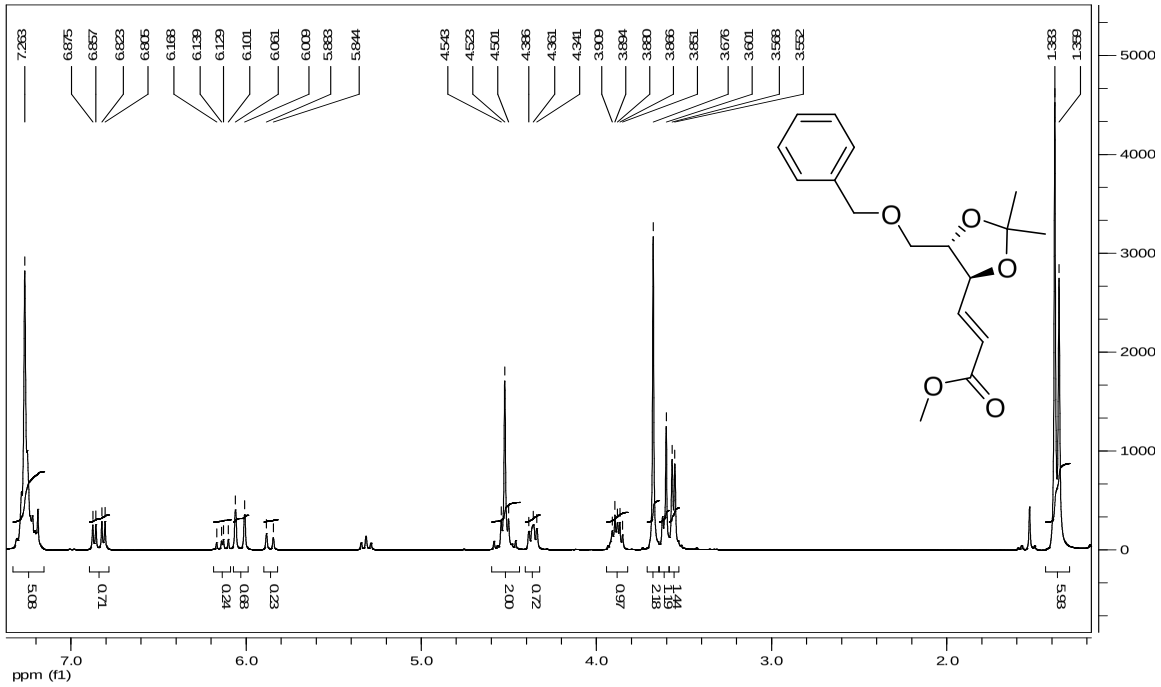
A1.4.1 ^{1}H NMR spectrum of **85**



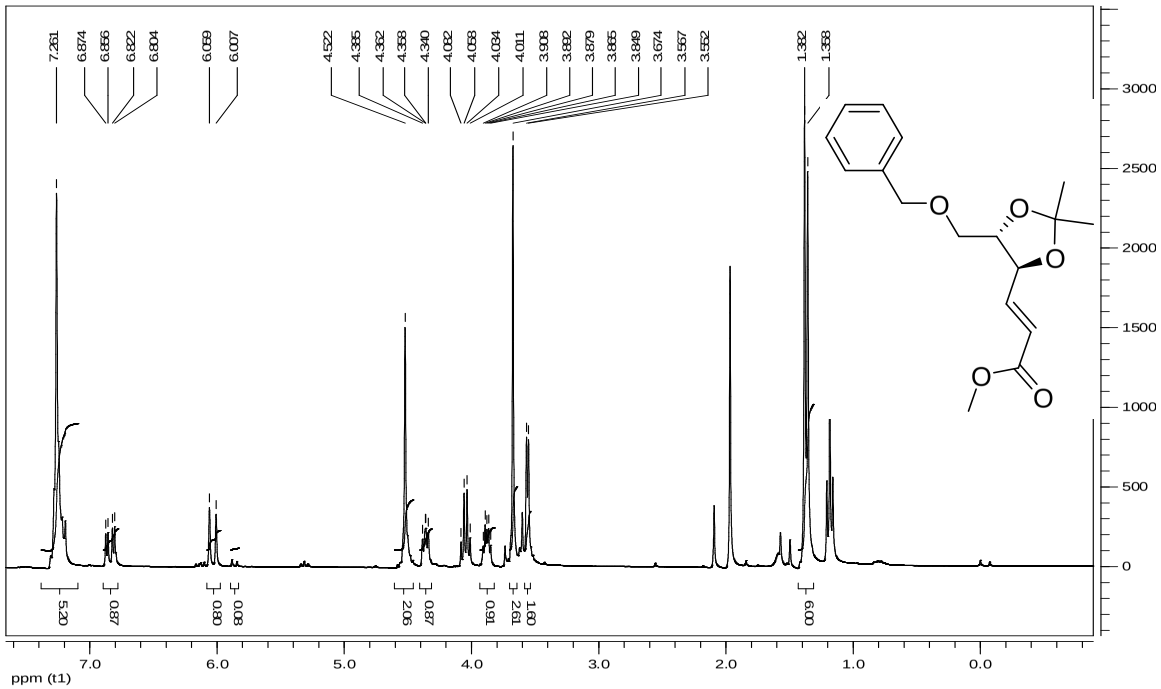
A1.4.2 ^{13}C NMR spectrum of **85**



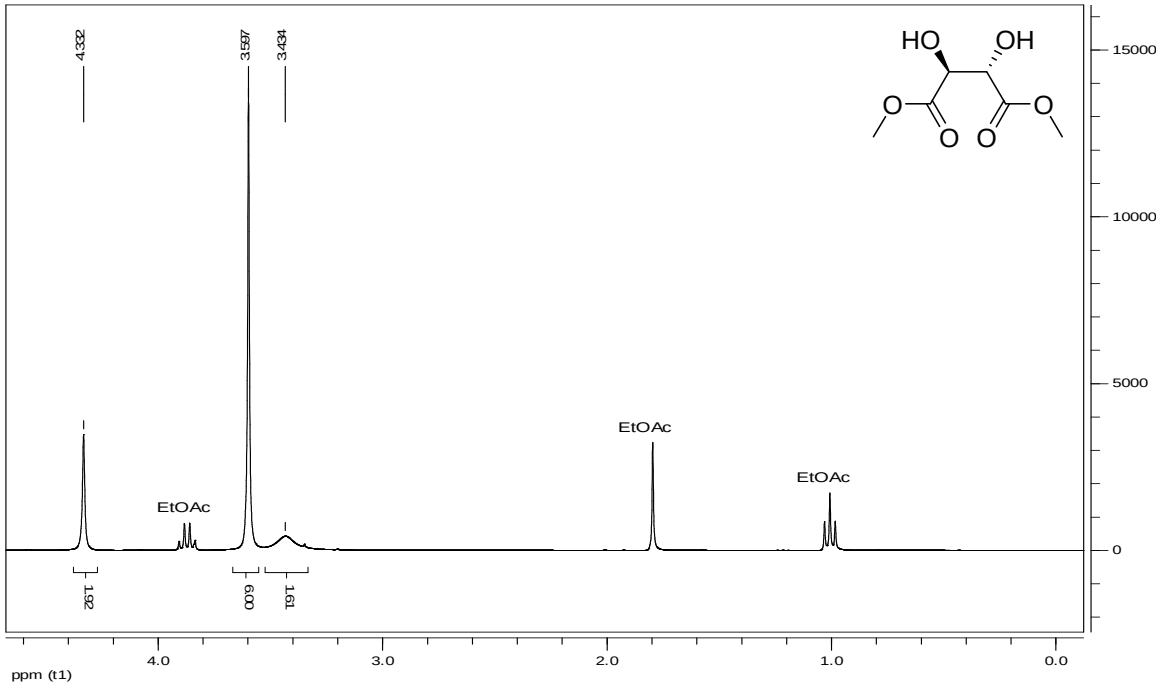
A1.5.1 ^{1}H NMR spectrum of **89** (MnO_2 TOP method)



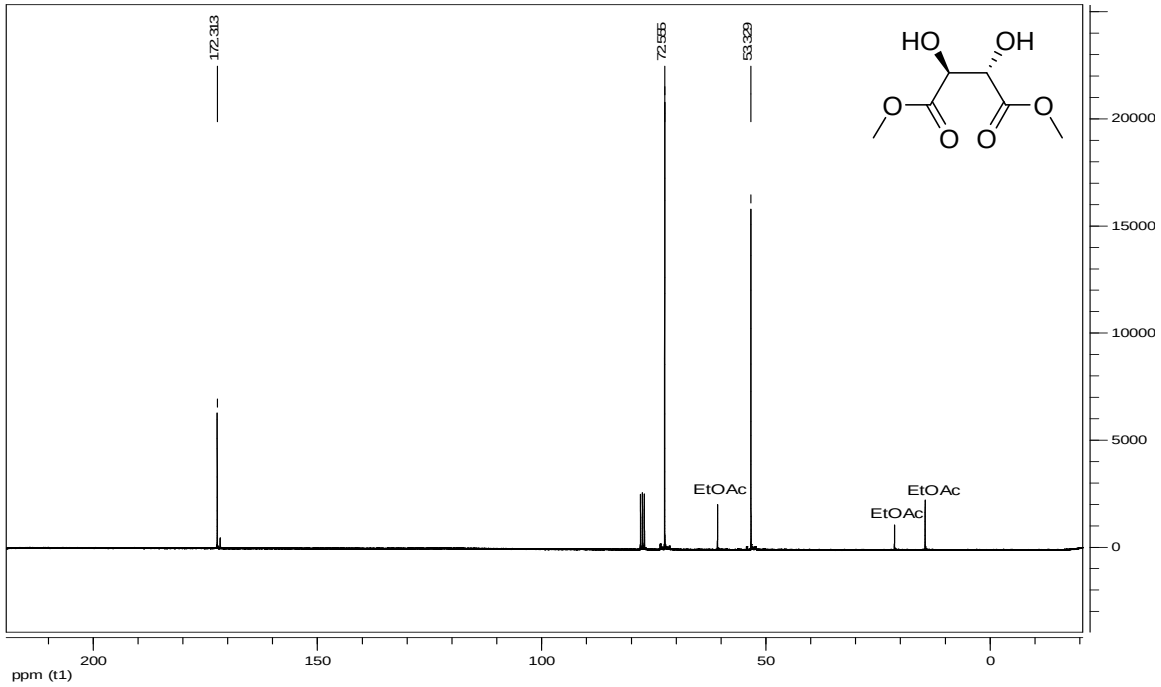
A1.6.1 ^{1}H NMR spectrum of **89** (PCC TOP method)



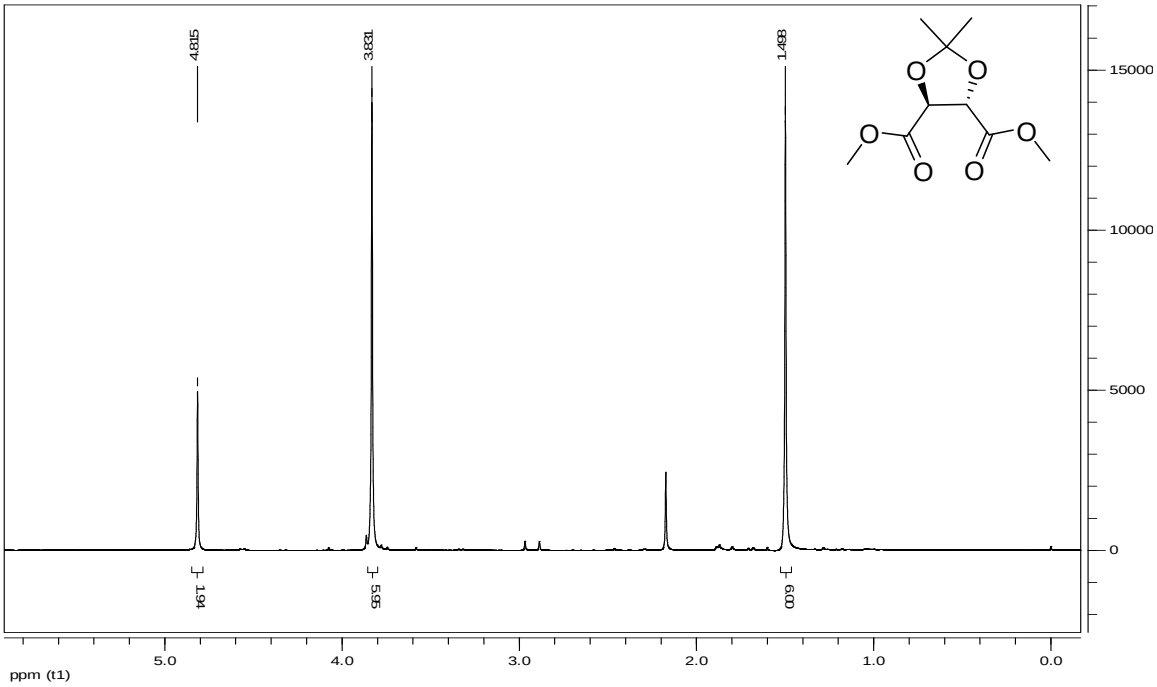
A1.7.1 ^{1}H NMR spectrum of **70**



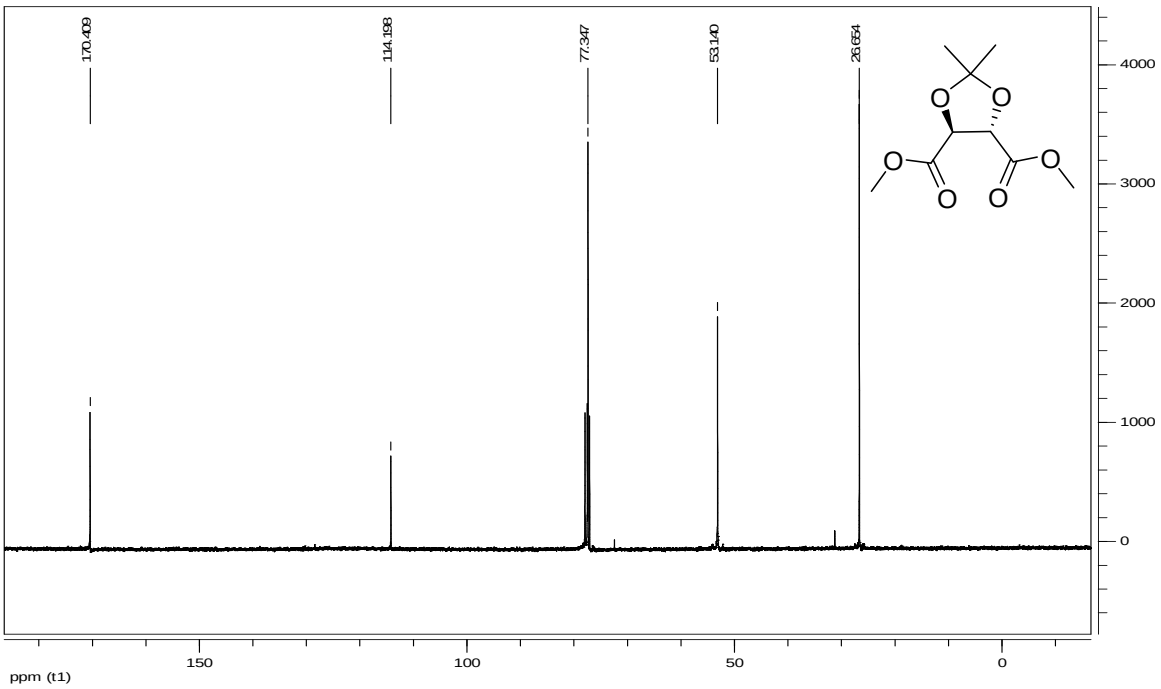
A1.7.2 ^{13}C NMR spectrum of **70**



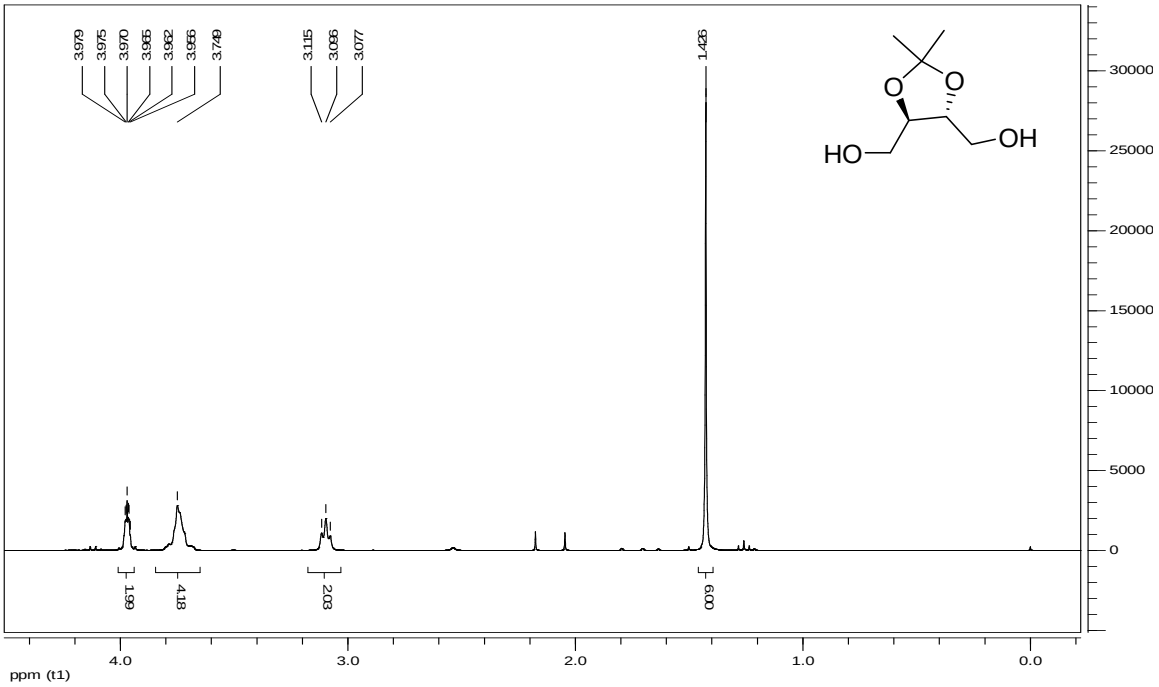
A1.8.1 ^{1}H NMR spectrum of **71**



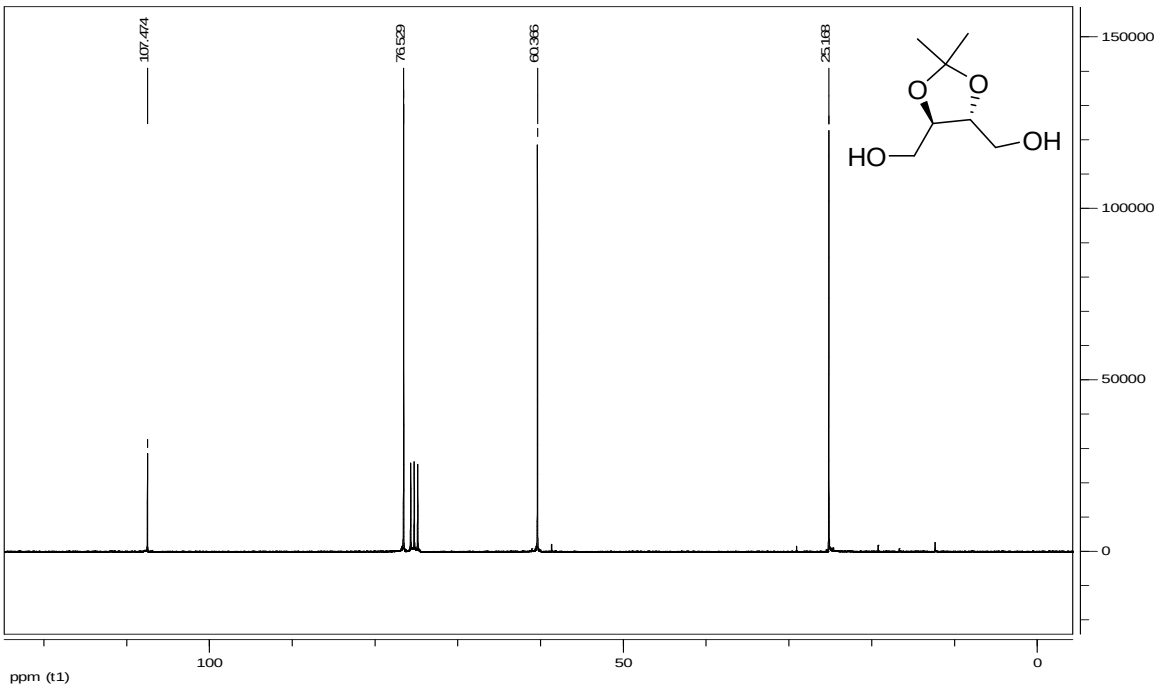
A1.8.2 ^{13}C NMR spectrum of **71**



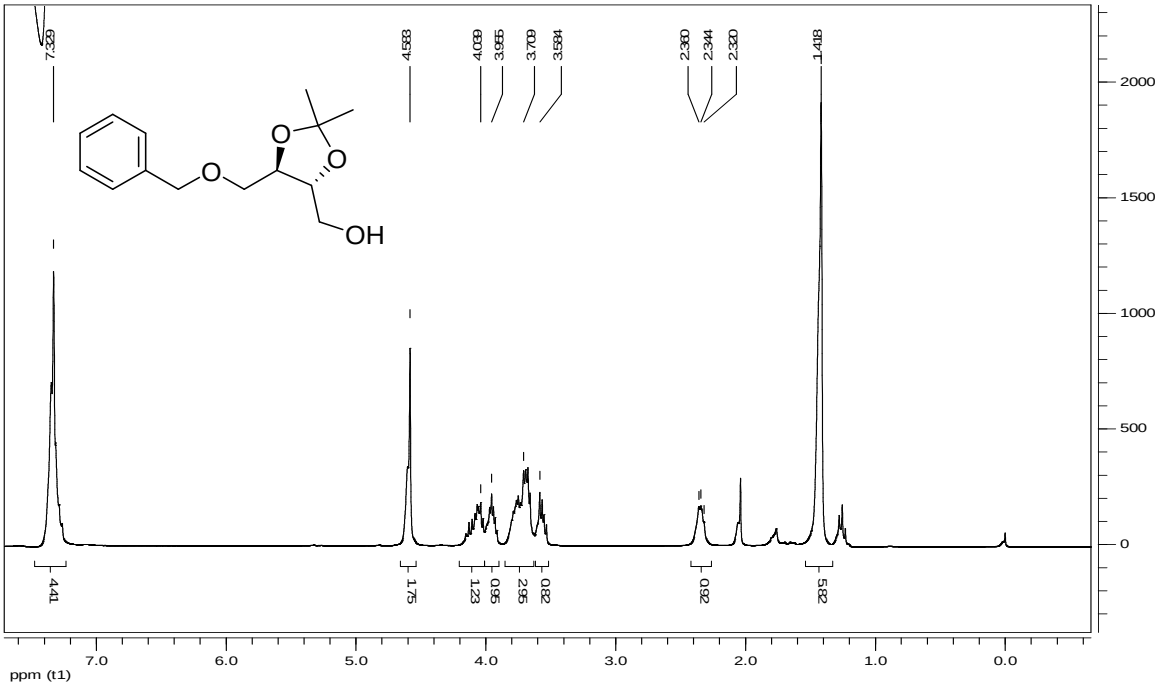
A1.9.1 ^{1}H NMR spectrum of **72**



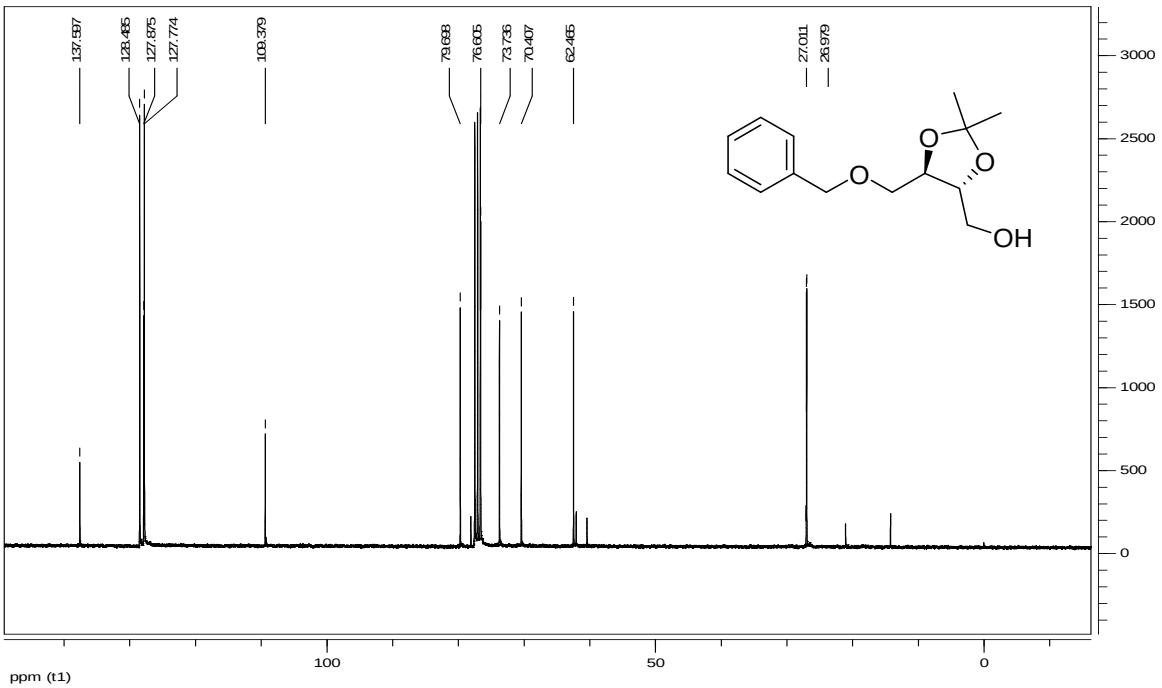
A1.9.2 ^{13}C NMR spectrum of **72**



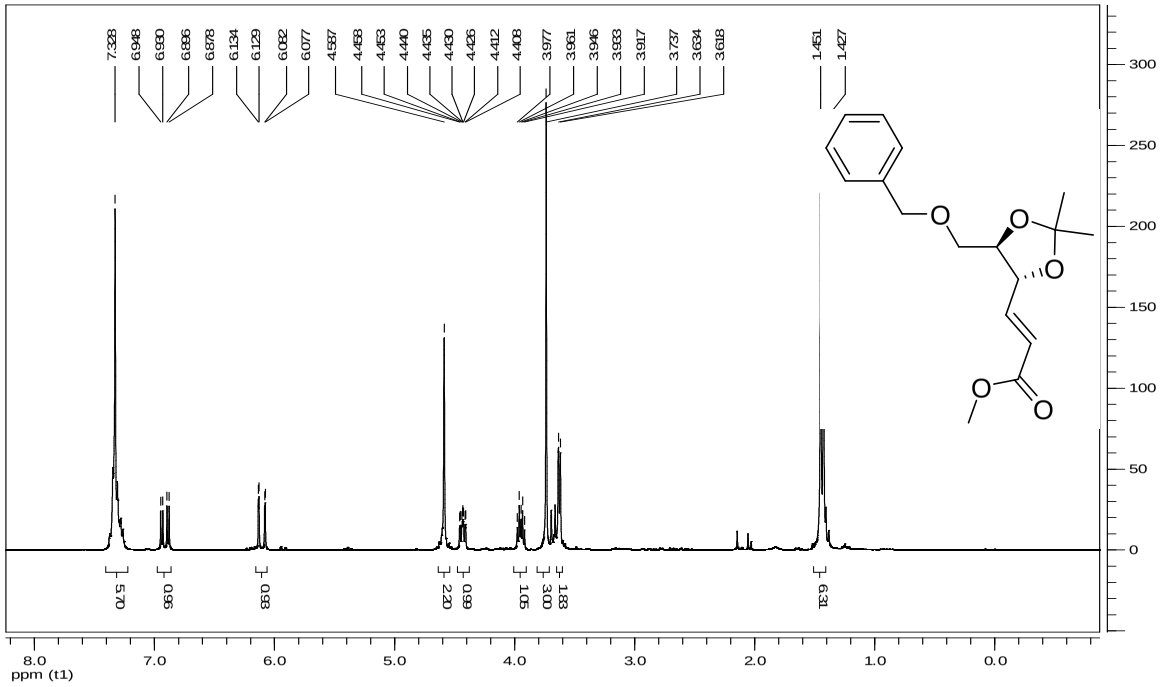
A1.10.1 ^{1}H NMR spectrum of **73**



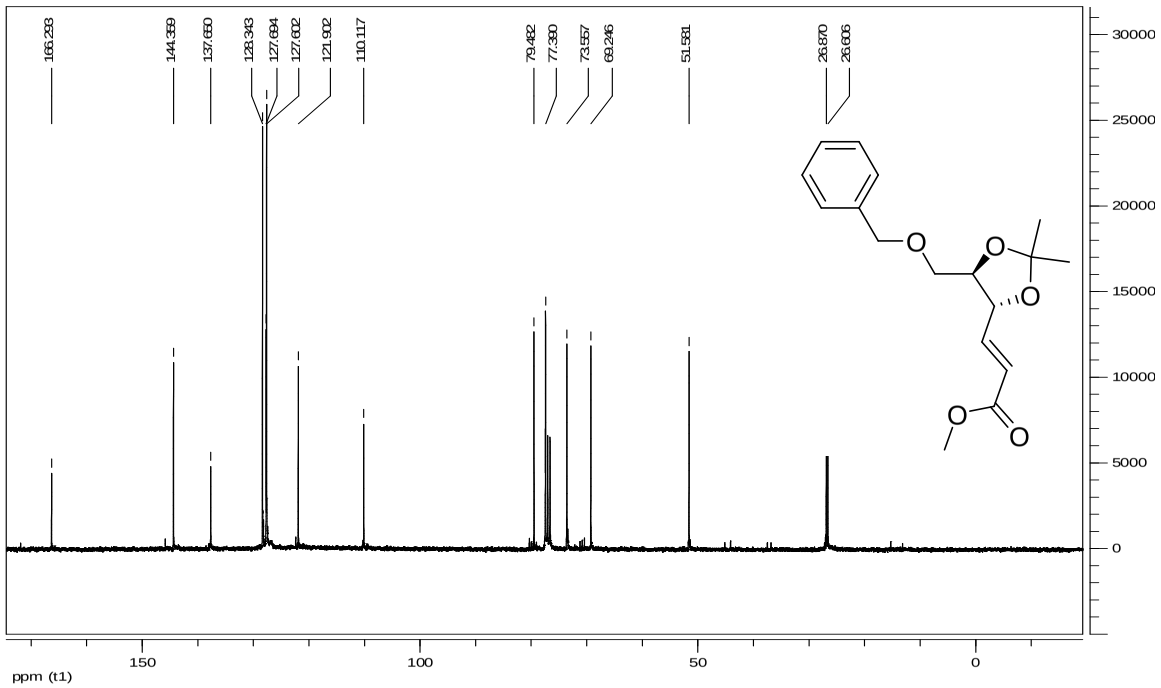
A1.10.2 ^{13}C NMR spectrum of **73**



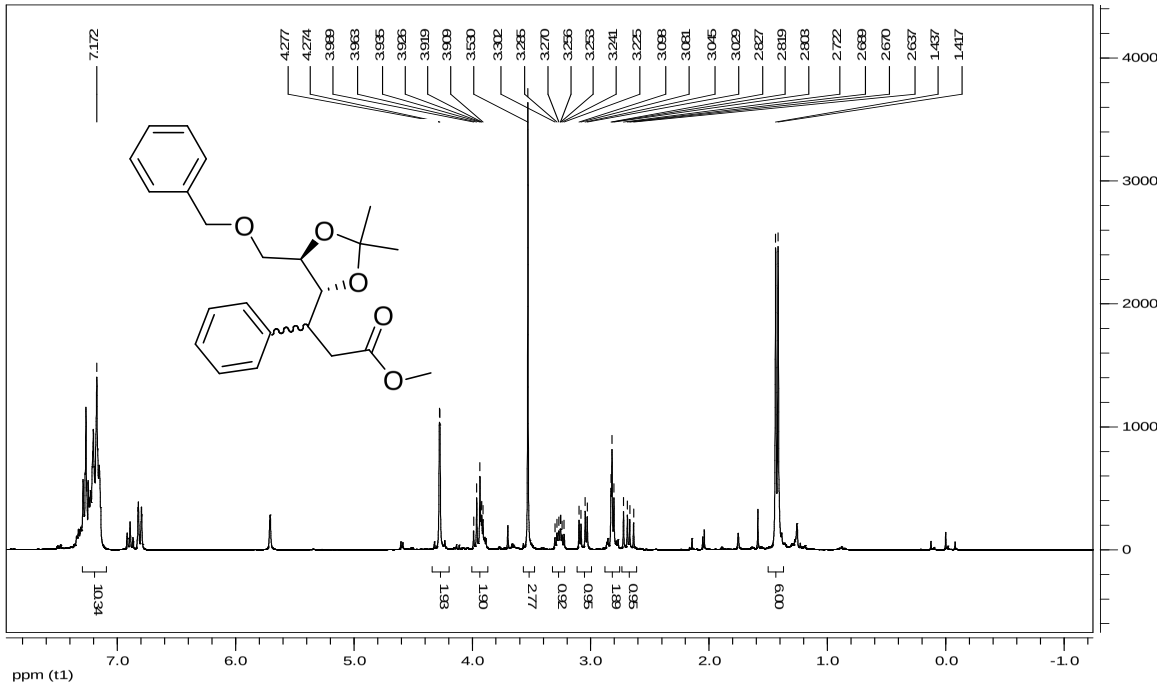
A1.11.1 ^{1}H NMR spectrum of **74**



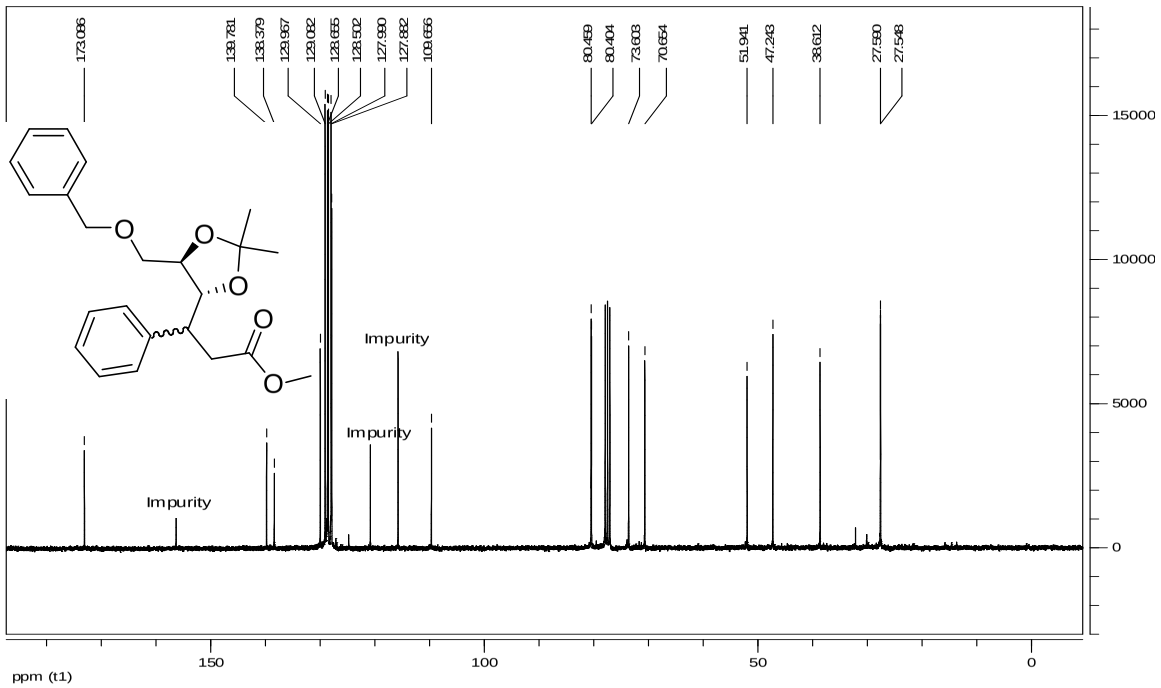
A1.11.2 ^{13}C NMR spectrum of **74**



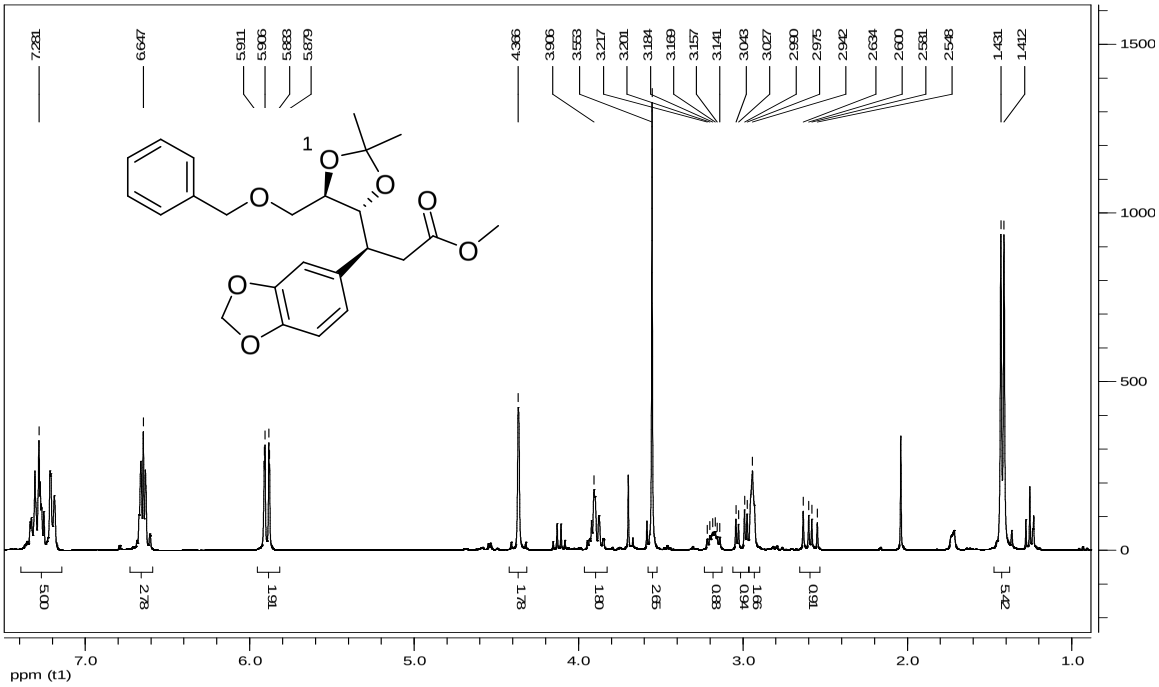
A1.12.1 ^{1}H NMR spectrum of **97**



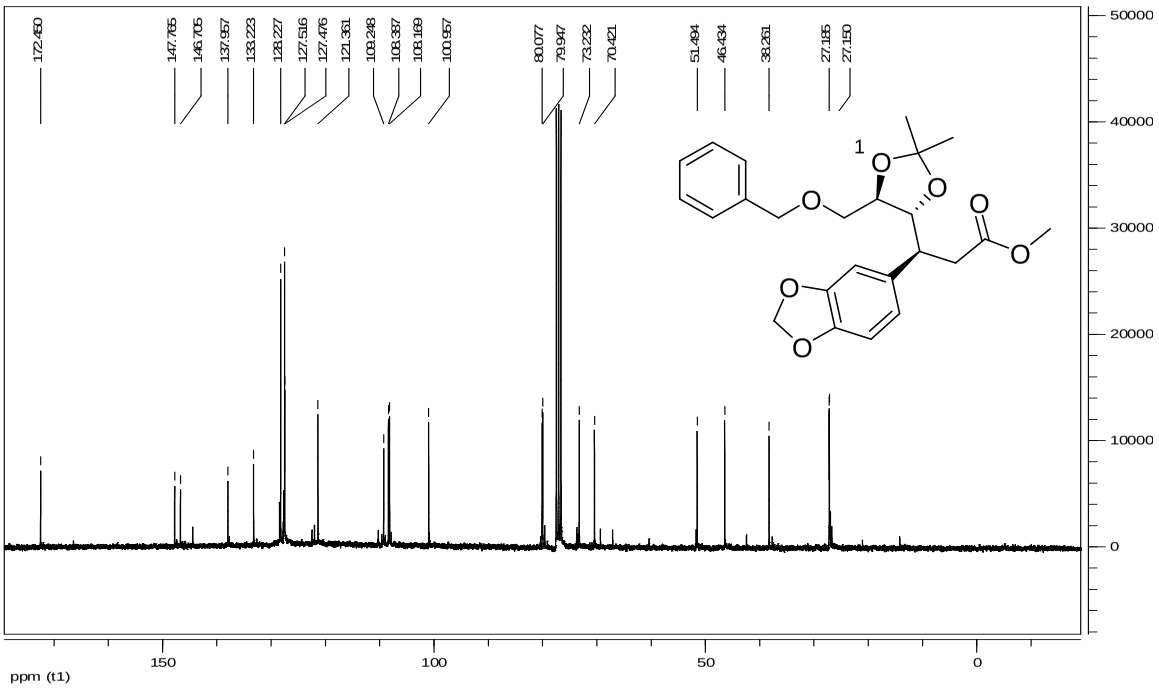
A1.12.2 ^{13}C NMR spectrum of **97**



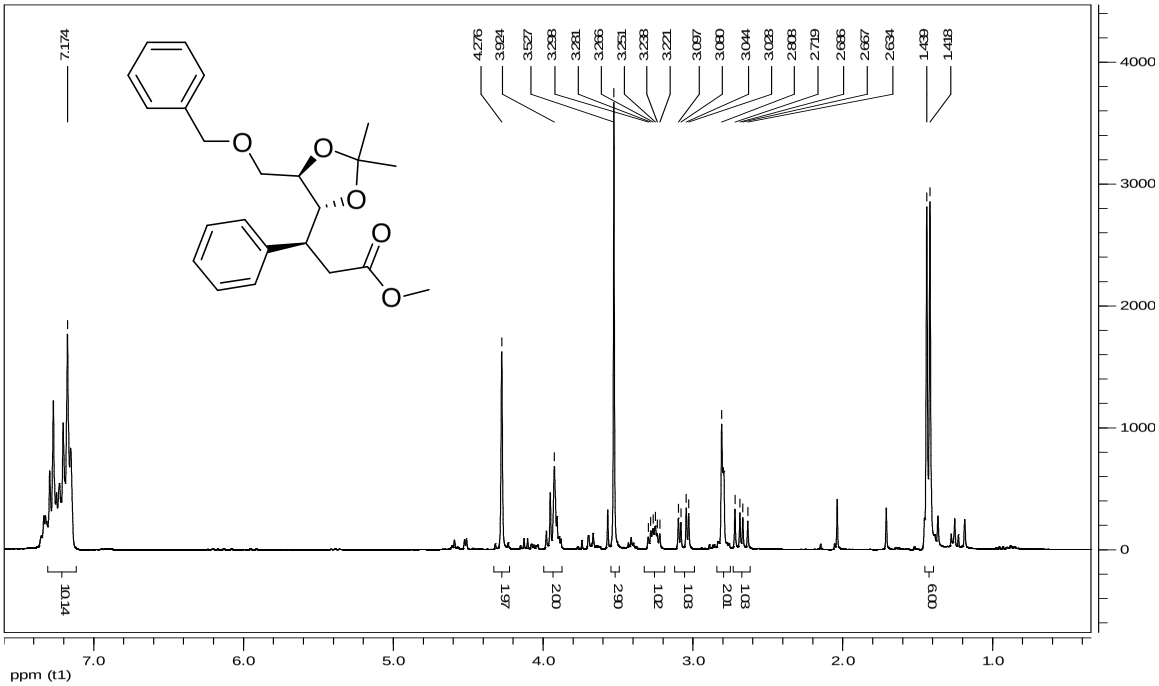
A1.13.1 ^{1}H NMR spectrum of **75**



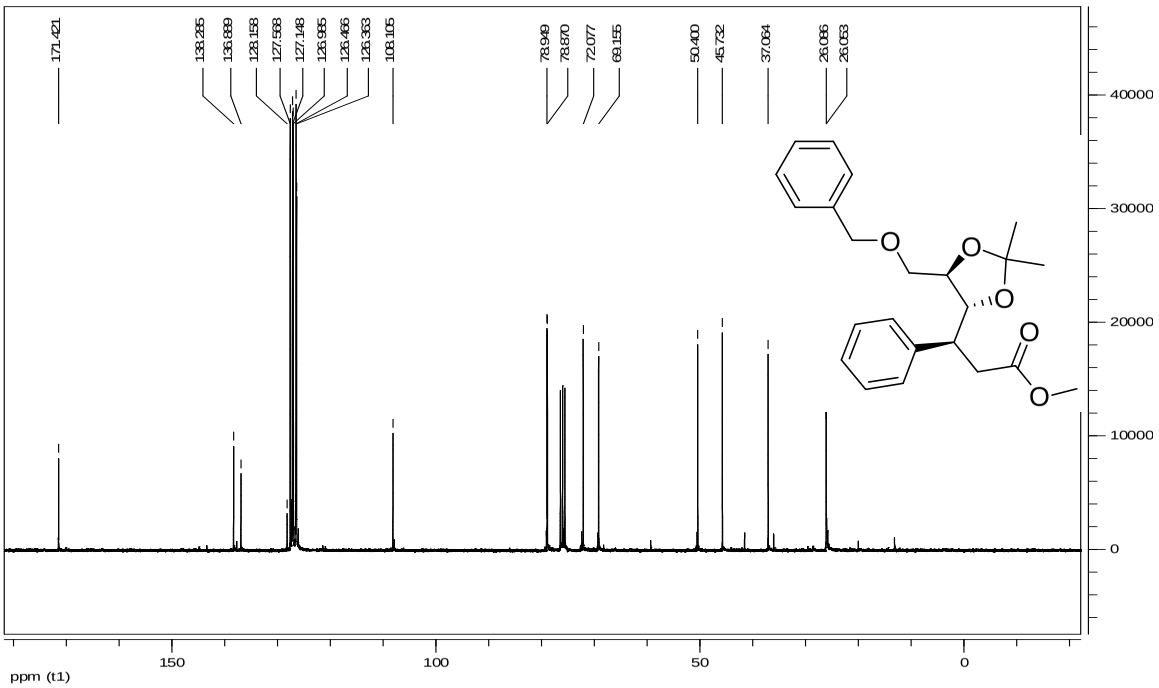
A1.13.2 ^{13}C NMR spectrum of **75**



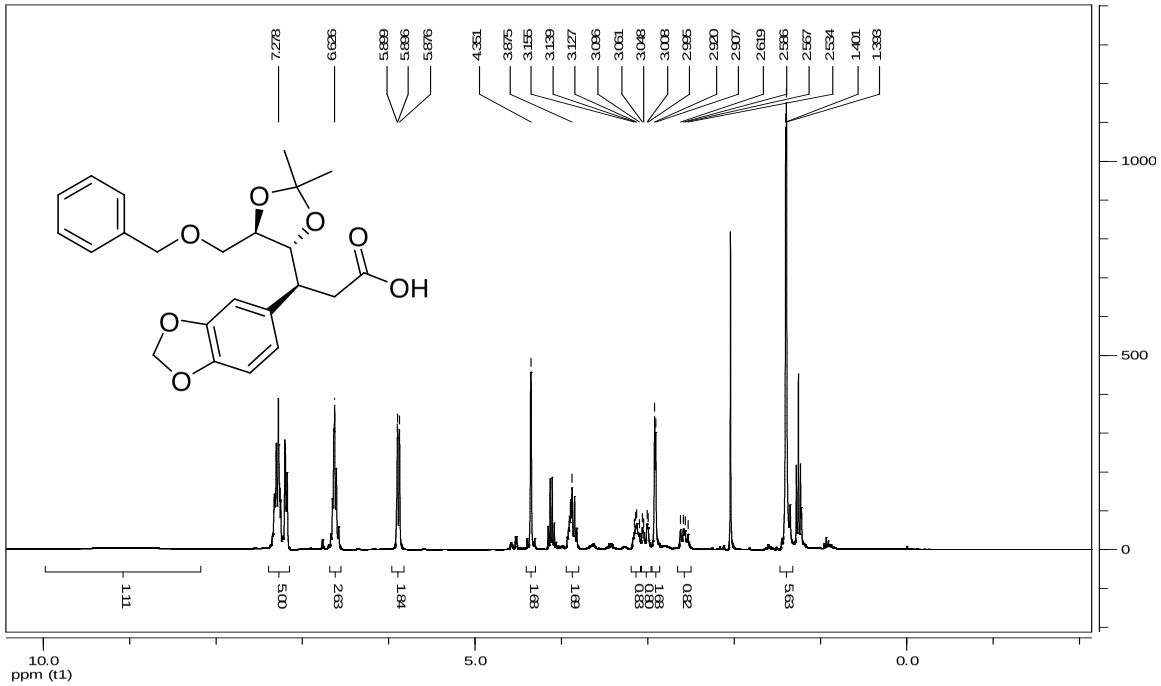
A1.14.1 ^{1}H NMR spectrum of **100**



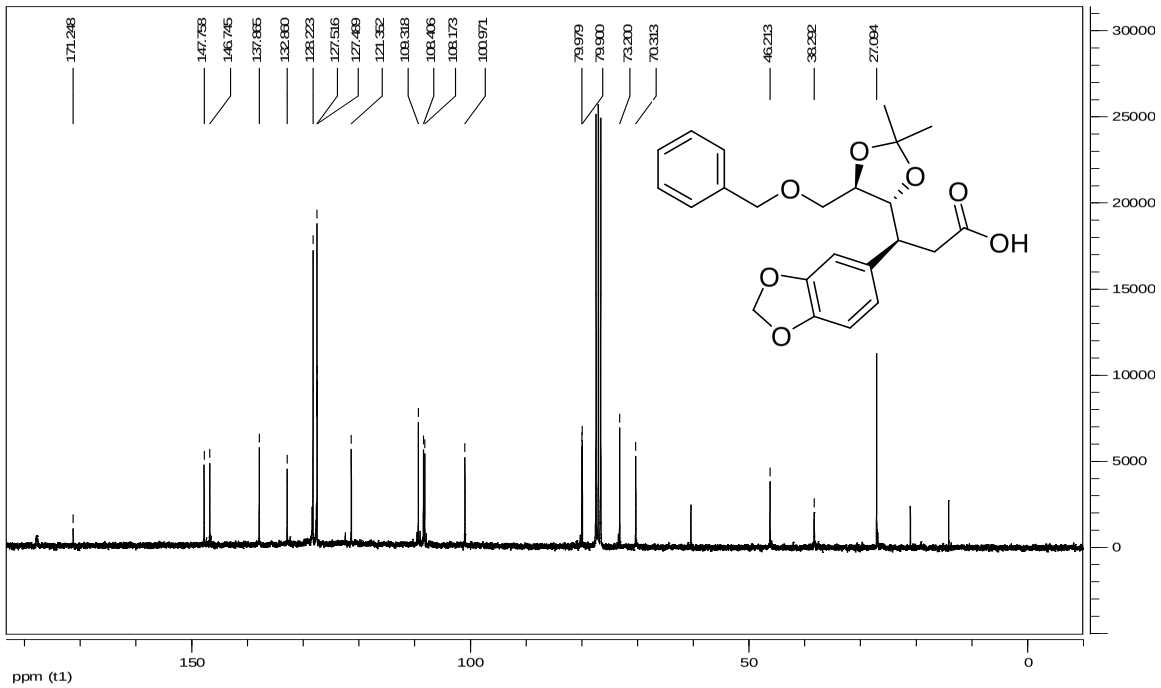
A1.14.2 ^{13}C NMR spectrum of **100**



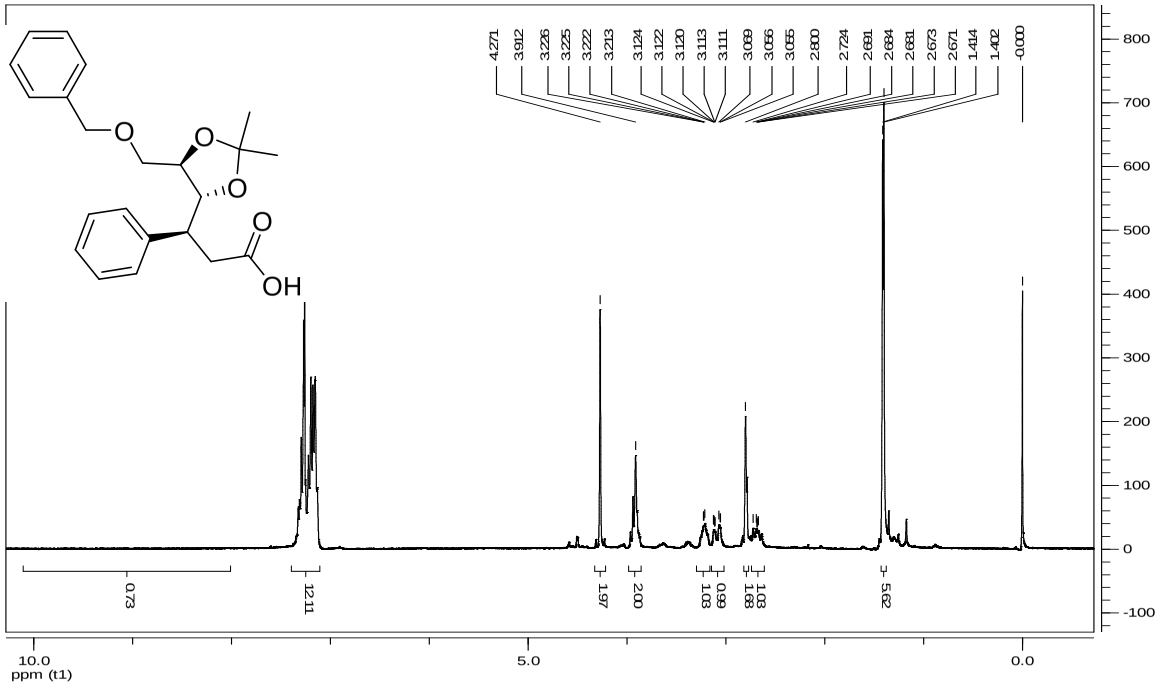
A1.15.1 ^{1}H NMR spectrum of **76**



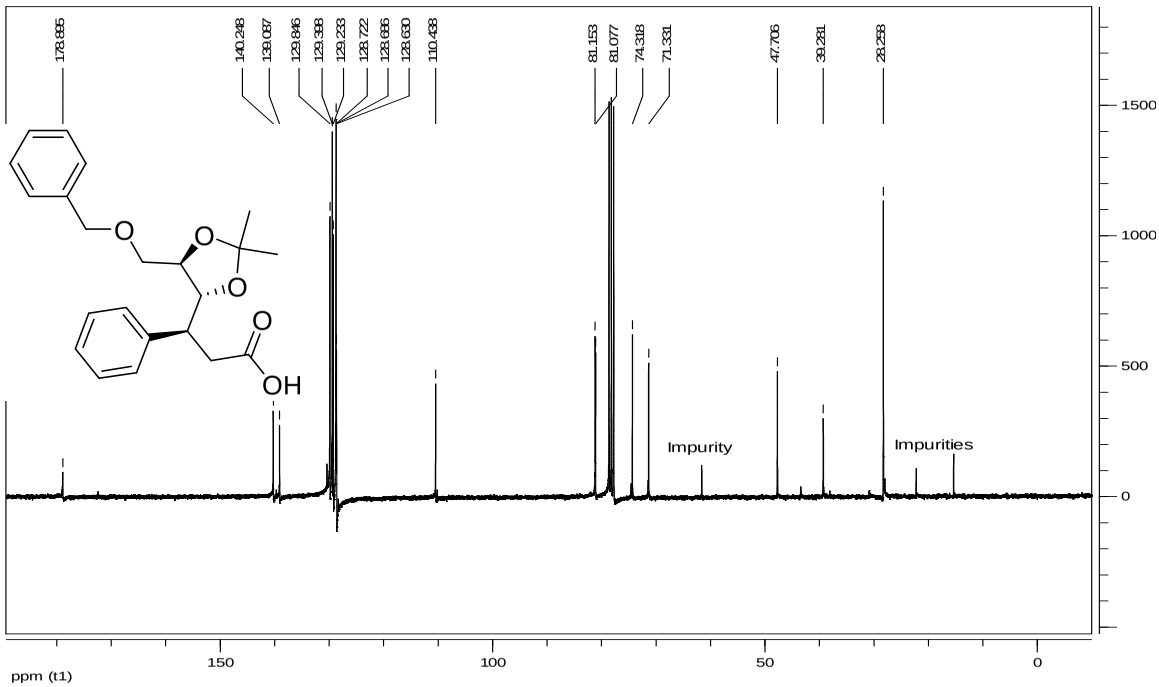
A1.15.2 ^{13}C NMR spectrum of **76**



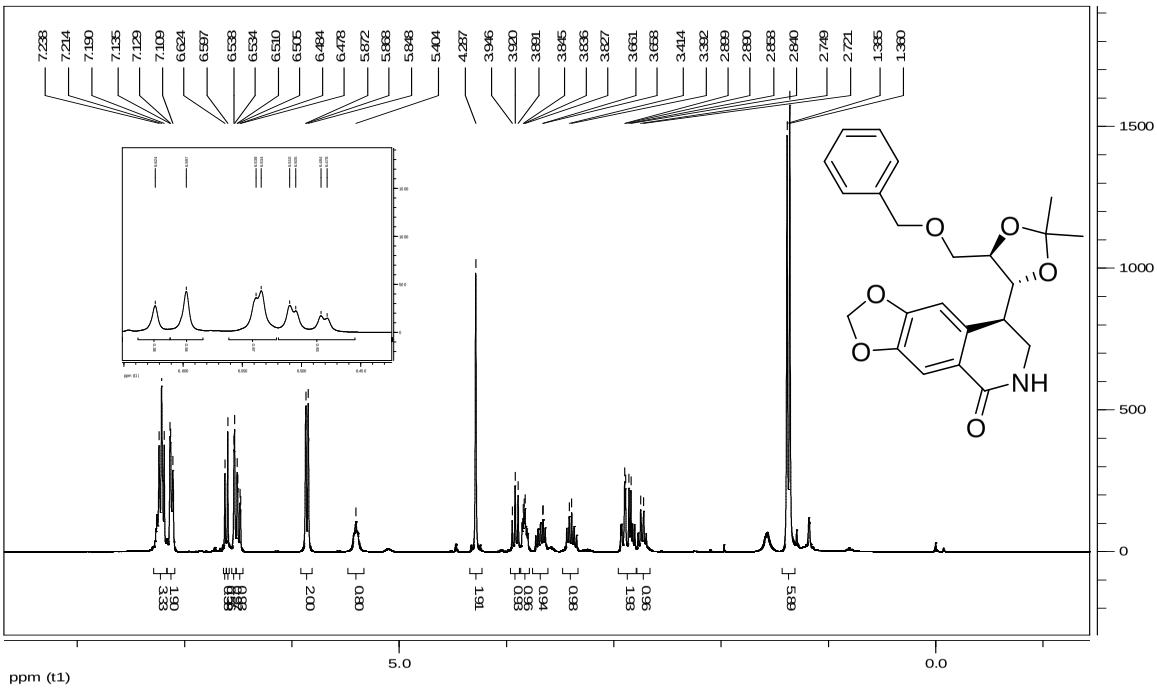
A1.16.1 ^{1}H NMR spectrum of **101**



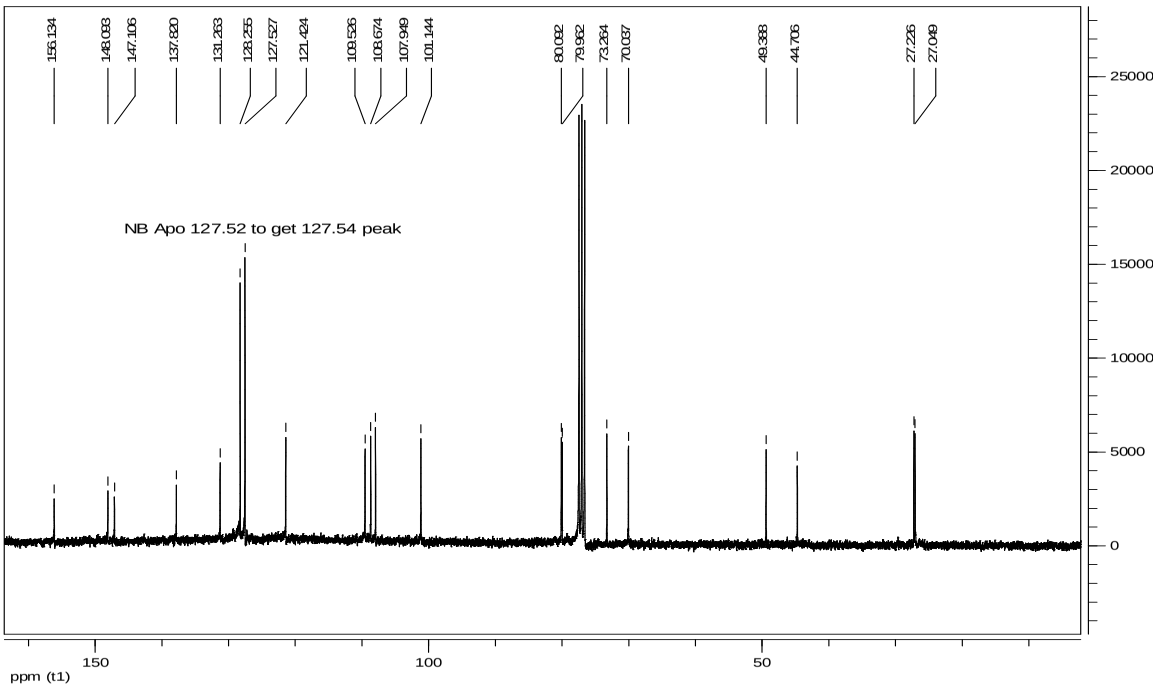
A1.16.2 ^{13}C NMR spectrum of **101**



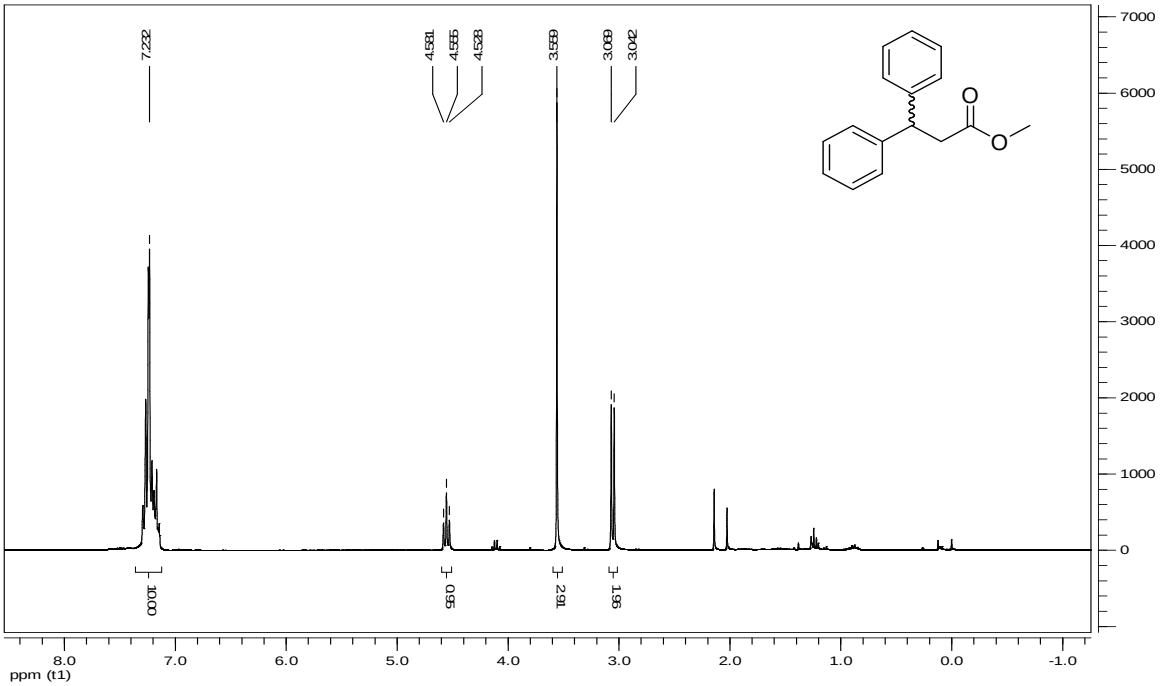
A1.17.1 ^{1}H NMR spectrum of **78** (Attempted ring closure product)



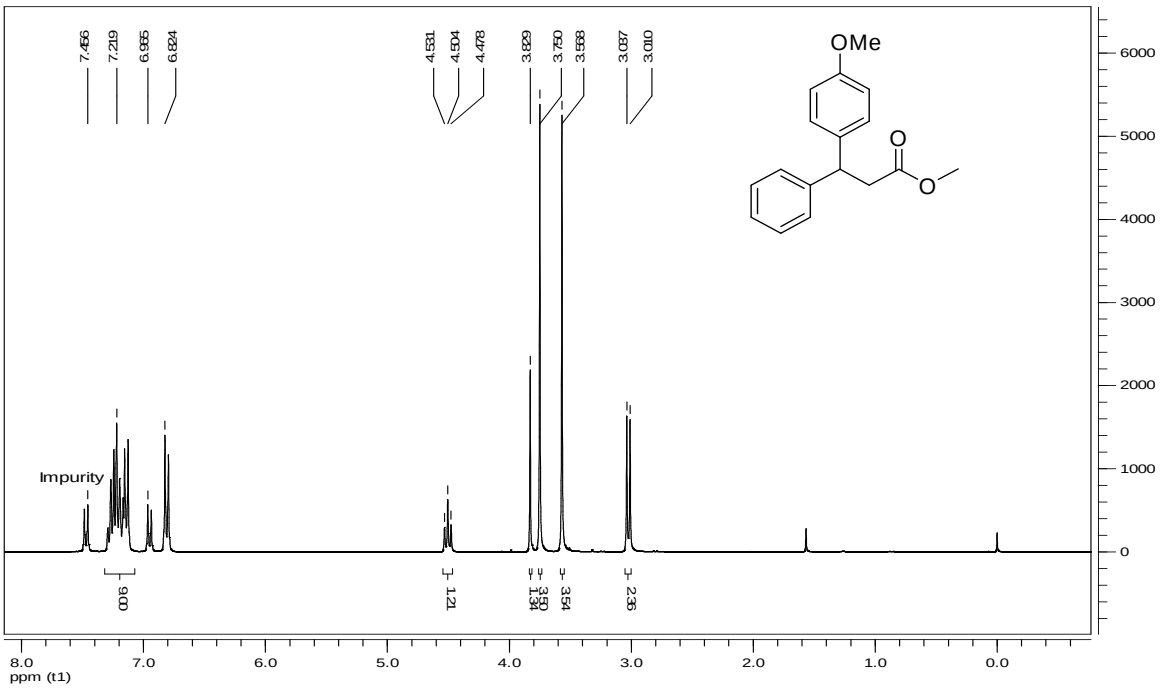
A1.17.2 ^{13}C NMR spectrum of **78** (Attempted ring closure product)



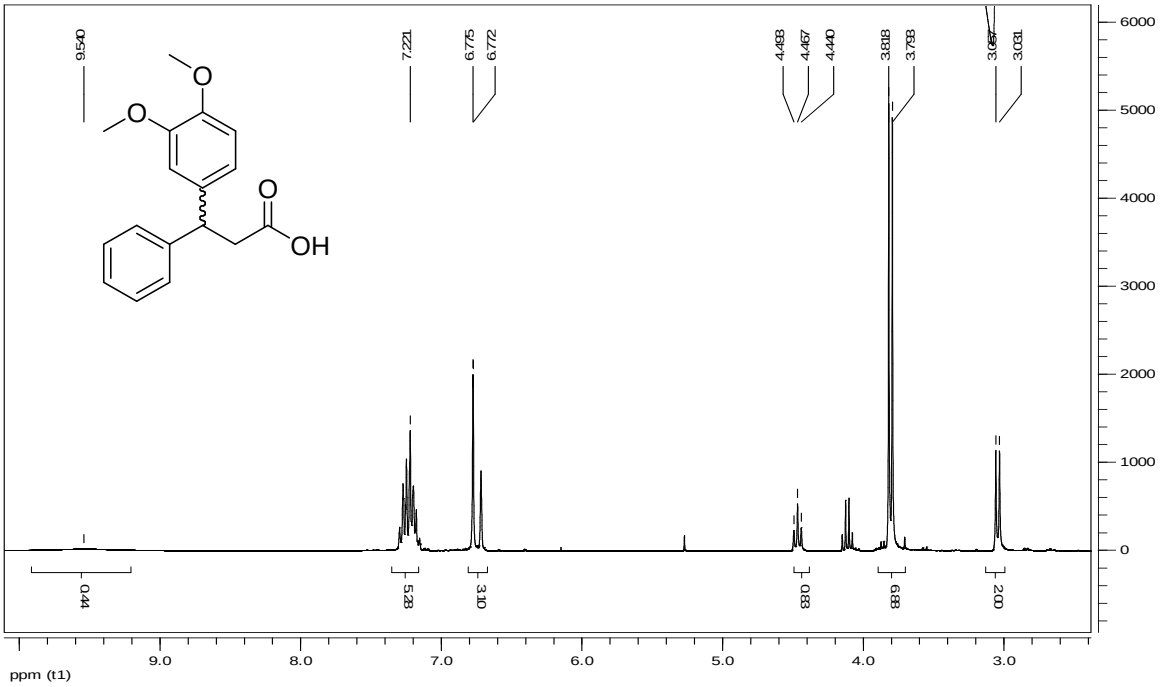
A1.19.1 ^{1}H NMR spectrum of **93**



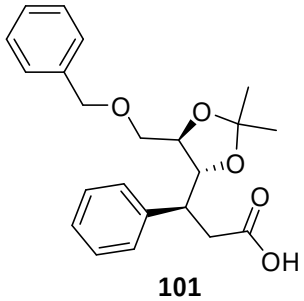
A1.20.1 ^{1}H NMR spectrum of **94**



A1.21.1 ^{1}H NMR spectrum of **96**



A2.1: Single crystal data and structure for 3-((4R,5R)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylpropanoic acid **101**



101

Table A2.1.1 Crystal data and structure refinement for **101**

Identification code	**101**	
Empirical formula	C10 H10 N O	
Formula weight	160.19	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.9680(6) Å	□= 90°.
	b = 20.466(2) Å	□= 97.854(4)°.
	c = 16.2314(18) Å	□ = 90°.
Volume	1963.9(4) Å^3	
Z	3	
Density (calculated)	0.406 Mg/m^3	
Absorption coefficient	0.026 mm^{-1}	
F(000)	255	
Crystal size	0.32 x 0.07 x 0.07 mm^3	
Theta range for data collection	1.27 to 25.00°.	
Index ranges	-7<=h<=6, -24<=k<=24, -19<=l<=14	
Reflections collected	12158	
Independent reflections	6885 [R(int) = 0.0647]	

Completeness to theta = 25.00°	99.8 %
Max. and min. transmission	0.9981 and 0.9916
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6885 / 1 / 487
Goodness-of-fit on F^2	0.932
Final R indices [I>2sigma(I)]	R1 = 0.0601, wR2 = 0.0721
R indices (all data)	R1 = 0.1238, wR2 = 0.0877
Absolute structure parameter	0.1(10)
Largest diff. peak and hole	0.195 and -0.185 e.$Å^{-3}$

Table A2.1.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **101**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(96)	857(6)	908(2)	1145(2)	31(1)
C(95)	4748(6)	1414(2)	1320(2)	34(1)
C(97)	-7056(7)	1030(2)	-4412(2)	41(1)
C(98)	-10368(6)	1165(2)	-3619(3)	45(1)
O(4)	1975(4)	1671(1)	2234(2)	28(1)
O(9)	-60(4)	3322(1)	382(2)	29(1)
O(7)	-2387(4)	1978(1)	-260(2)	39(1)
O(1)	-8713(4)	2078(1)	-4241(2)	29(1)
O(10)	-9218(4)	3387(1)	-4645(2)	31(1)
O(3)	1335(4)	2044(1)	918(2)	26(1)
O(2)	-6677(4)	1593(1)	-3119(2)	28(1)
O(6)	8415(4)	2460(2)	3769(2)	42(1)
C(009)	4060(6)	3353(2)	2930(2)	24(1)
O(5)	7022(4)	2242(1)	4938(2)	38(1)
C(011)	-7492(6)	2581(2)	-3742(2)	20(1)
O(8)	-640(4)	2240(1)	-1341(2)	37(1)
C(013)	-132(6)	3093(2)	1204(2)	25(1)
C(014)	4093(6)	2616(2)	2871(2)	22(1)

C(015)	1963(6)	2365(2)	2321(2)	22(1)
C(016)	1775(6)	2616(2)	1416(2)	20(1)
C(017)	-4632(6)	2028(2)	-1554(2)	31(1)
C(018)	-5285(6)	3191(2)	-2063(2)	22(1)
C(019)	4425(6)	2287(2)	3724(2)	26(1)
C(020)	2265(6)	1502(2)	1409(2)	25(1)
C(021)	2379(7)	3673(2)	3285(2)	32(1)
C(022)	-2345(7)	2107(2)	-1053(2)	25(1)
C(023)	5669(7)	3728(2)	2618(2)	32(1)
C(024)	-4994(6)	2484(2)	-2308(2)	28(1)
C(025)	3961(7)	4715(2)	3006(3)	40(1)
C(026)	-10860(7)	3895(2)	-4801(2)	32(1)
C(027)	-10157(7)	4528(2)	-4367(2)	29(1)
C(028)	2332(7)	4346(2)	3323(3)	38(1)
C(029)	-1929(7)	3731(2)	100(2)	35(1)
C(030)	-8953(7)	3182(2)	-3806(2)	29(1)
C(031)	-7031(7)	3381(2)	-1626(2)	35(1)
C(032)	-1825(7)	4397(2)	492(2)	26(1)
C(033)	-3757(7)	4782(2)	428(2)	33(1)
C(034)	6822(7)	2346(2)	4130(3)	29(1)
C(035)	230(7)	5279(2)	1228(3)	36(1)
C(036)	-8214(7)	1458(2)	-3845(2)	27(1)
C(037)	-5980(8)	4498(2)	-1709(3)	48(1)
C(038)	167(7)	4661(2)	894(3)	36(1)
C(039)	-7060(6)	2254(2)	-2897(2)	23(1)
C(040)	-3879(8)	3669(2)	-2299(2)	38(1)
C(041)	-11509(7)	4827(2)	-3865(2)	31(1)
C(042)	-3699(7)	5401(2)	758(2)	36(1)
C(043)	-7375(7)	4031(2)	-1455(3)	42(1)
C(044)	5635(8)	4403(2)	2663(3)	39(1)
C(045)	-7458(8)	5401(2)	-4053(3)	44(1)
C(046)	-8096(7)	4817(2)	-4452(3)	38(1)
C(047)	-1695(7)	5655(2)	1164(3)	40(1)
C(048)	-8879(8)	5695(2)	-3556(3)	43(1)
C(049)	-10908(8)	5410(2)	-3464(3)	37(1)

C(050)	-4243(9)	4320(2)	-2125(3)	47(1)

Table A2.1.3 Bond lengths [Å] and angles [°] for **101**

C(96)-C(020)	1.507(5)
C(96)-H(96A)	0.9800
C(96)-H(96B)	0.9800
C(96)-H(96C)	0.9800
C(95)-C(020)	1.519(5)
C(95)-H(95A)	0.9800
C(95)-H(95B)	0.9800
C(95)-H(95C)	0.9800
C(97)-C(036)	1.505(5)
C(97)-H(97A)	0.9800
C(97)-H(97B)	0.9800
C(97)-H(97C)	0.9800
C(98)-C(036)	1.508(5)
C(98)-H(98A)	0.9800
C(98)-H(98B)	0.9800
C(98)-H(98C)	0.9800
O(4)-C(020)	1.415(4)
O(4)-C(015)	1.429(4)
O(9)-C(013)	1.420(4)
O(9)-C(029)	1.420(4)
O(7)-C(022)	1.317(4)
O(7)-H(7)	0.8400
O(1)-C(036)	1.436(4)
O(1)-C(011)	1.443(4)
O(10)-C(030)	1.413(4)
O(10)-C(026)	1.427(4)
O(3)-C(016)	1.427(4)
O(3)-C(020)	1.432(4)
O(2)-C(036)	1.418(4)
O(2)-C(039)	1.427(4)
O(6)-C(034)	1.205(4)

C(009)-C(023)	1.380(5)
C(009)-C(021)	1.388(5)
C(009)-C(014)	1.511(5)
O(5)-C(034)	1.319(4)
O(5)-H(5)	0.8400
C(011)-C(030)	1.503(5)
C(011)-C(039)	1.517(5)
C(011)-H(011)	1.0000
O(8)-C(022)	1.208(4)
C(013)-C(016)	1.503(5)
C(013)-H(01A)	0.9900
C(013)-H(01B)	0.9900
C(014)-C(019)	1.527(5)
C(014)-C(015)	1.538(5)
C(014)-H(014)	1.0000
C(015)-C(016)	1.545(5)
C(015)-H(015)	1.0000
C(016)-H(016)	1.0000
C(017)-C(022)	1.499(5)
C(017)-C(024)	1.532(5)
C(017)-H(01C)	0.9900
C(017)-H(01D)	0.9900
C(018)-C(040)	1.377(5)
C(018)-C(031)	1.394(5)
C(018)-C(024)	1.516(5)
C(019)-C(034)	1.496(5)
C(019)-H(01E)	0.9900
C(019)-H(01F)	0.9900
C(021)-C(028)	1.379(5)
C(021)-H(021)	0.9500
C(023)-C(044)	1.383(5)
C(023)-H(023)	0.9500
C(024)-C(039)	1.527(5)
C(024)-H(024)	1.0000
C(025)-C(044)	1.366(5)
C(025)-C(028)	1.384(6)

C(025)-H(025)	0.9500
C(026)-C(027)	1.507(5)
C(026)-H(02A)	0.9900
C(026)-H(02B)	0.9900
C(027)-C(041)	1.367(5)
C(027)-C(046)	1.389(5)
C(028)-H(028)	0.9500
C(029)-C(032)	1.502(5)
C(029)-H(02C)	0.9900
C(029)-H(02D)	0.9900
C(030)-H(03A)	0.9900
C(030)-H(03B)	0.9900
C(031)-C(043)	1.380(6)
C(031)-H(031)	0.9500
C(032)-C(038)	1.385(5)
C(032)-C(033)	1.389(5)
C(033)-C(042)	1.373(5)
C(033)-H(033)	0.9500
C(035)-C(038)	1.374(5)
C(035)-C(047)	1.375(5)
C(035)-H(035)	0.9500
C(037)-C(050)	1.362(6)
C(037)-C(043)	1.367(6)
C(037)-H(037)	0.9500
C(038)-H(038)	0.9500
C(039)-H(039)	1.0000
C(040)-C(050)	1.385(5)
C(040)-H(040)	0.9500
C(041)-C(049)	1.382(5)
C(041)-H(041)	0.9500
C(042)-C(047)	1.386(5)
C(042)-H(042)	0.9500
C(043)-H(043)	0.9500
C(044)-H(044)	0.9500
C(045)-C(048)	1.386(5)
C(045)-C(046)	1.388(6)

C(045)-H(045)	0.9500
C(046)-H(046)	0.9500
C(047)-H(047)	0.9500
C(048)-C(049)	1.371(5)
C(048)-H(048)	0.9500
C(049)-H(049)	0.9500
C(050)-H(050)	0.9500

C(020)-C(96)-H(96A)	109.5
C(020)-C(96)-H(96B)	109.5
H(96A)-C(96)-H(96B)	109.5
C(020)-C(96)-H(96C)	109.5
H(96A)-C(96)-H(96C)	109.5
H(96B)-C(96)-H(96C)	109.5
C(020)-C(95)-H(95A)	109.5
C(020)-C(95)-H(95B)	109.5
H(95A)-C(95)-H(95B)	109.5
C(020)-C(95)-H(95C)	109.5
H(95A)-C(95)-H(95C)	109.5
H(95B)-C(95)-H(95C)	109.5
C(036)-C(97)-H(97A)	109.5
C(036)-C(97)-H(97B)	109.5
H(97A)-C(97)-H(97B)	109.5
C(036)-C(97)-H(97C)	109.5
H(97A)-C(97)-H(97C)	109.5
H(97B)-C(97)-H(97C)	109.5
C(036)-C(98)-H(98A)	109.5
C(036)-C(98)-H(98B)	109.5
H(98A)-C(98)-H(98B)	109.5
C(036)-C(98)-H(98C)	109.5
H(98A)-C(98)-H(98C)	109.5
H(98B)-C(98)-H(98C)	109.5
C(020)-O(4)-C(015)	109.8(3)
C(013)-O(9)-C(029)	111.9(3)
C(022)-O(7)-H(7)	109.5
C(036)-O(1)-C(011)	108.8(3)

C(030)-O(10)-C(026)	111.8(3)
C(016)-O(3)-C(020)	107.0(3)
C(036)-O(2)-C(039)	106.7(3)
C(023)-C(009)-C(021)	117.9(4)
C(023)-C(009)-C(014)	121.1(4)
C(021)-C(009)-C(014)	121.0(4)
C(034)-O(5)-H(5)	109.5
O(1)-C(011)-C(030)	107.5(3)
O(1)-C(011)-C(039)	101.7(3)
C(030)-C(011)-C(039)	116.7(3)
O(1)-C(011)-H(011)	110.2
C(030)-C(011)-H(011)	110.2
C(039)-C(011)-H(011)	110.2
O(9)-C(013)-C(016)	108.0(3)
O(9)-C(013)-H(01A)	110.1
C(016)-C(013)-H(01A)	110.1
O(9)-C(013)-H(01B)	110.1
C(016)-C(013)-H(01B)	110.1
H(01A)-C(013)-H(01B)	108.4
C(009)-C(014)-C(019)	112.5(3)
C(009)-C(014)-C(015)	110.6(3)
C(019)-C(014)-C(015)	112.0(3)
C(009)-C(014)-H(014)	107.1
C(019)-C(014)-H(014)	107.1
C(015)-C(014)-H(014)	107.1
O(4)-C(015)-C(014)	112.0(3)
O(4)-C(015)-C(016)	103.7(3)
C(014)-C(015)-C(016)	112.8(3)
O(4)-C(015)-H(015)	109.4
C(014)-C(015)-H(015)	109.4
C(016)-C(015)-H(015)	109.4
O(3)-C(016)-C(013)	109.2(3)
O(3)-C(016)-C(015)	104.4(3)
C(013)-C(016)-C(015)	112.8(3)
O(3)-C(016)-H(016)	110.1
C(013)-C(016)-H(016)	110.1

C(015)-C(016)-H(016)	110.1
C(022)-C(017)-C(024)	112.8(3)
C(022)-C(017)-H(01C)	109.0
C(024)-C(017)-H(01C)	109.0
C(022)-C(017)-H(01D)	109.0
C(024)-C(017)-H(01D)	109.0
H(01C)-C(017)-H(01D)	107.8
C(040)-C(018)-C(031)	117.9(4)
C(040)-C(018)-C(024)	120.6(4)
C(031)-C(018)-C(024)	121.4(4)
C(034)-C(019)-C(014)	111.2(3)
C(034)-C(019)-H(01E)	109.4
C(014)-C(019)-H(01E)	109.4
C(034)-C(019)-H(01F)	109.4
C(014)-C(019)-H(01F)	109.4
H(01E)-C(019)-H(01F)	108.0
O(4)-C(020)-O(3)	104.5(3)
O(4)-C(020)-C(96)	109.3(3)
O(3)-C(020)-C(96)	107.9(3)
O(4)-C(020)-C(95)	111.5(3)
O(3)-C(020)-C(95)	110.4(3)
C(96)-C(020)-C(95)	112.9(3)
C(028)-C(021)-C(009)	120.7(4)
C(028)-C(021)-H(021)	119.6
C(009)-C(021)-H(021)	119.6
O(8)-C(022)-O(7)	123.6(3)
O(8)-C(022)-C(017)	124.5(4)
O(7)-C(022)-C(017)	111.8(3)
C(009)-C(023)-C(044)	121.4(4)
C(009)-C(023)-H(023)	119.3
C(044)-C(023)-H(023)	119.3
C(018)-C(024)-C(039)	110.3(3)
C(018)-C(024)-C(017)	112.3(3)
C(039)-C(024)-C(017)	109.0(3)
C(018)-C(024)-H(024)	108.4
C(039)-C(024)-H(024)	108.4

C(017)-C(024)-H(024)	108.4
C(044)-C(025)-C(028)	119.1(4)
C(044)-C(025)-H(025)	120.4
C(028)-C(025)-H(025)	120.4
O(10)-C(026)-C(027)	113.7(3)
O(10)-C(026)-H(02A)	108.8
C(027)-C(026)-H(02A)	108.8
O(10)-C(026)-H(02B)	108.8
C(027)-C(026)-H(02B)	108.8
H(02A)-C(026)-H(02B)	107.7
C(041)-C(027)-C(046)	118.1(4)
C(041)-C(027)-C(026)	121.0(4)
C(046)-C(027)-C(026)	120.9(4)
C(021)-C(028)-C(025)	120.5(5)
C(021)-C(028)-H(028)	119.7
C(025)-C(028)-H(028)	119.7
O(9)-C(029)-C(032)	114.4(3)
O(9)-C(029)-H(02C)	108.6
C(032)-C(029)-H(02C)	108.6
O(9)-C(029)-H(02D)	108.6
C(032)-C(029)-H(02D)	108.6
H(02C)-C(029)-H(02D)	107.6
O(10)-C(030)-C(011)	107.3(3)
O(10)-C(030)-H(03A)	110.3
C(011)-C(030)-H(03A)	110.3
O(10)-C(030)-H(03B)	110.3
C(011)-C(030)-H(03B)	110.3
H(03A)-C(030)-H(03B)	108.5
C(043)-C(031)-C(018)	121.0(4)
C(043)-C(031)-H(031)	119.5
C(018)-C(031)-H(031)	119.5
C(038)-C(032)-C(033)	117.7(4)
C(038)-C(032)-C(029)	122.4(4)
C(033)-C(032)-C(029)	119.8(4)
C(042)-C(033)-C(032)	121.2(4)
C(042)-C(033)-H(033)	119.4

C(032)-C(033)-H(033)	119.4
O(6)-C(034)-O(5)	123.0(4)
O(6)-C(034)-C(019)	124.9(4)
O(5)-C(034)-C(019)	112.1(4)
C(038)-C(035)-C(047)	120.5(4)
C(038)-C(035)-H(035)	119.7
C(047)-C(035)-H(035)	119.7
O(2)-C(036)-O(1)	105.7(3)
O(2)-C(036)-C(97)	108.8(3)
O(1)-C(036)-C(97)	109.0(3)
O(2)-C(036)-C(98)	110.5(3)
O(1)-C(036)-C(98)	109.2(3)
C(97)-C(036)-C(98)	113.3(4)
C(050)-C(037)-C(043)	120.0(5)
C(050)-C(037)-H(037)	120.0
C(043)-C(037)-H(037)	120.0
C(035)-C(038)-C(032)	121.3(4)
C(035)-C(038)-H(038)	119.4
C(032)-C(038)-H(038)	119.4
O(2)-C(039)-C(011)	101.7(3)
O(2)-C(039)-C(024)	108.0(3)
C(011)-C(039)-C(024)	116.9(3)
O(2)-C(039)-H(039)	109.9
C(011)-C(039)-H(039)	109.9
C(024)-C(039)-H(039)	109.9
C(018)-C(040)-C(050)	120.6(5)
C(018)-C(040)-H(040)	119.7
C(050)-C(040)-H(040)	119.7
C(027)-C(041)-C(049)	122.1(4)
C(027)-C(041)-H(041)	119.0
C(049)-C(041)-H(041)	119.0
C(033)-C(042)-C(047)	120.4(4)
C(033)-C(042)-H(042)	119.8
C(047)-C(042)-H(042)	119.8
C(037)-C(043)-C(031)	119.9(5)
C(037)-C(043)-H(043)	120.0

C(031)-C(043)-H(043)	120.0
C(025)-C(044)-C(023)	120.3(5)
C(025)-C(044)-H(044)	119.8
C(023)-C(044)-H(044)	119.8
C(048)-C(045)-C(046)	119.7(4)
C(048)-C(045)-H(045)	120.1
C(046)-C(045)-H(045)	120.1
C(045)-C(046)-C(027)	120.7(4)
C(045)-C(046)-H(046)	119.7
C(027)-C(046)-H(046)	119.7
C(035)-C(047)-C(042)	118.9(4)
C(035)-C(047)-H(047)	120.5
C(042)-C(047)-H(047)	120.5
C(049)-C(048)-C(045)	119.9(4)
C(049)-C(048)-H(048)	120.1
C(045)-C(048)-H(048)	120.1
C(048)-C(049)-C(041)	119.5(4)
C(048)-C(049)-H(049)	120.3
C(041)-C(049)-H(049)	120.3
C(037)-C(050)-C(040)	120.5(5)
C(037)-C(050)-H(050)	119.7
C(040)-C(050)-H(050)	119.7

Symmetry transformations used to generate equivalent atoms:

Table A2.1.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **101**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(96)	35(3)	25(3)	30(3)	-2(2)	-3(2)	2(2)
C(95)	30(3)	34(3)	37(3)	-8(2)	0(2)	7(2)
C(97)	41(3)	42(3)	36(3)	-15(2)	-7(2)	7(2)
C(98)	39(3)	43(3)	49(3)	3(3)	-6(3)	-12(3)
O(4)	39(2)	25(2)	18(2)	0(1)	2(1)	0(2)
O(9)	36(2)	30(2)	20(2)	5(2)	4(1)	15(2)
O(7)	33(2)	60(2)	21(2)	9(2)	-4(1)	-4(2)
O(1)	35(2)	21(2)	27(2)	-2(1)	-12(1)	0(1)
O(10)	48(2)	25(2)	18(2)	1(1)	-3(1)	10(2)
O(3)	31(2)	25(2)	21(2)	-2(1)	-3(1)	3(1)
O(2)	33(2)	18(2)	29(2)	0(1)	-9(1)	-5(1)
O(6)	28(2)	64(2)	35(2)	-1(2)	8(2)	-1(2)
C(009)	20(2)	32(3)	19(2)	-1(2)	0(2)	-1(2)
O(5)	29(2)	58(2)	23(2)	4(2)	-7(1)	-6(2)
C(011)	22(2)	19(2)	18(2)	-3(2)	-1(2)	1(2)
O(8)	25(2)	54(2)	31(2)	3(2)	1(1)	-8(2)
C(013)	30(3)	25(3)	19(2)	3(2)	2(2)	2(2)
C(014)	18(2)	26(2)	22(2)	-1(2)	6(2)	1(2)
C(015)	25(2)	19(2)	23(2)	-3(2)	6(2)	4(2)
C(016)	16(2)	24(3)	20(3)	0(2)	3(2)	0(2)
C(017)	34(2)	28(3)	27(2)	7(2)	-9(2)	-4(2)
C(018)	24(2)	23(2)	18(2)	-1(2)	-2(2)	-4(2)
C(019)	26(2)	27(3)	25(2)	0(2)	0(2)	-4(2)
C(020)	28(3)	25(3)	19(3)	-2(2)	-3(2)	7(2)
C(021)	33(3)	33(3)	31(3)	-4(2)	5(2)	-2(2)
C(022)	32(3)	19(2)	21(3)	2(2)	-3(2)	-1(2)

C(023)	31(3)	42(3)	26(3)	-3(2)	8(2)	-2(2)
C(024)	29(2)	31(3)	22(3)	4(2)	0(2)	-9(2)
C(025)	48(3)	22(3)	46(3)	-3(2)	-6(3)	3(3)
C(026)	40(3)	26(3)	27(3)	4(2)	-7(2)	8(2)
C(027)	34(3)	26(3)	24(3)	3(2)	-4(2)	6(2)
C(028)	39(3)	40(3)	34(3)	-12(2)	3(2)	6(3)
C(029)	41(3)	33(3)	27(3)	5(2)	-5(2)	13(2)
C(030)	43(3)	23(3)	20(2)	-1(2)	0(2)	1(2)
C(031)	38(3)	35(3)	31(3)	-5(2)	5(2)	-8(2)
C(032)	30(3)	29(3)	20(2)	7(2)	6(2)	2(2)
C(033)	24(3)	36(3)	35(3)	4(2)	-2(2)	5(2)
C(034)	37(3)	23(3)	24(3)	-3(2)	-6(2)	1(2)
C(035)	33(3)	30(3)	45(3)	2(2)	2(2)	-6(2)
C(036)	27(3)	26(3)	25(3)	-1(2)	-8(2)	2(2)
C(037)	83(4)	29(3)	32(3)	-10(2)	10(3)	-6(3)
C(038)	29(3)	34(3)	43(3)	8(2)	5(2)	7(2)
C(039)	28(2)	18(2)	20(2)	-1(2)	-1(2)	-3(2)
C(040)	58(3)	39(3)	21(3)	-7(2)	15(2)	-17(3)
C(041)	41(3)	22(3)	30(3)	2(2)	7(2)	0(2)
C(042)	35(3)	38(3)	38(3)	5(2)	13(2)	9(2)
C(043)	31(3)	45(3)	49(3)	-13(3)	4(2)	-1(3)
C(044)	44(3)	34(3)	36(3)	1(3)	-2(2)	-16(3)
C(045)	41(3)	45(3)	43(3)	3(3)	-2(3)	-7(3)
C(046)	34(3)	43(3)	37(3)	1(3)	3(2)	8(3)
C(047)	52(3)	26(3)	44(3)	1(2)	14(3)	3(3)
C(048)	70(4)	25(3)	32(3)	0(2)	-5(3)	-2(3)
C(049)	55(3)	32(3)	26(3)	0(2)	12(2)	5(3)
C(050)	87(4)	27(3)	28(3)	-4(2)	13(3)	-20(3)

Table A2.1.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **101.**

	x	y	z	U(eq)
H(96A)	1050	791	574	46
H(96B)	-740	1004	1173	46
H(96C)	1344	543	1517	46
H(95A)	4890	1298	743	52
H(95B)	5391	1064	1692	52
H(95C)	5563	1822	1466	52
H(97A)	-8107	932	-4915	61
H(97B)	-6578	621	-4125	61
H(97C)	-5729	1257	-4565	61
H(98A)	-11406	1072	-4127	67
H(98B)	-11078	1473	-3273	67
H(98C)	-10018	758	-3310	67
H(7)	-1084	2025	3	58
H(5)	8386	2279	5145	56
H(011)	-6027	2675	-3952	24
H(01A)	-1599	2877	1240	30
H(01B)	34	3464	1599	30
H(014)	5421	2495	2588	26
H(015)	590	2501	2568	27
H(016)	3237	2819	1314	24
H(01C)	-5807	2118	-1193	37
H(01D)	-4814	1570	-1747	37
H(01E)	3409	2493	4082	31
H(01F)	4015	1820	3660	31
H(021)	1249	3427	3505	39

H(023)	6826	3519	2367	39
H(024)	-3639	2454	-2607	33
H(025)	3915	5178	3026	48
H(02A)	-12293	3746	-4620	38
H(02B)	-11155	3975	-5408	38
H(028)	1172	4559	3569	46
H(02C)	-3333	3512	214	42
H(02D)	-2022	3783	-510	42
H(03A)	-10444	3082	-3634	35
H(03B)	-8225	3531	-3440	35
H(031)	-7997	3059	-1443	42
H(033)	-5144	4615	152	39
H(035)	1614	5447	1505	43
H(037)	-6223	4946	-1595	57
H(038)	1517	4409	941	43
H(039)	-8443	2282	-2614	27
H(040)	-2649	3552	-2583	46
H(041)	-12904	4628	-3789	37
H(042)	-5040	5656	707	43
H(043)	-8580	4154	-1160	50
H(044)	6781	4651	2455	46
H(045)	-6054	5598	-4121	52
H(046)	-7111	4612	-4787	46
H(047)	-1651	6082	1395	48
H(048)	-8447	6094	-3279	52
H(049)	-11894	5611	-3127	45
H(050)	-3273	4646	-2298	56

Table A2.1.6. Torsion angles [°] for **101**

C(036)-O(1)-C(011)-C(030)	-145.1(3)
C(036)-O(1)-C(011)-C(039)	-22.0(4)
C(029)-O(9)-C(013)-C(016)	174.7(3)
C(023)-C(009)-C(014)-C(019)	117.9(4)
C(021)-C(009)-C(014)-C(019)	-63.5(4)
C(023)-C(009)-C(014)-C(015)	-116.1(4)

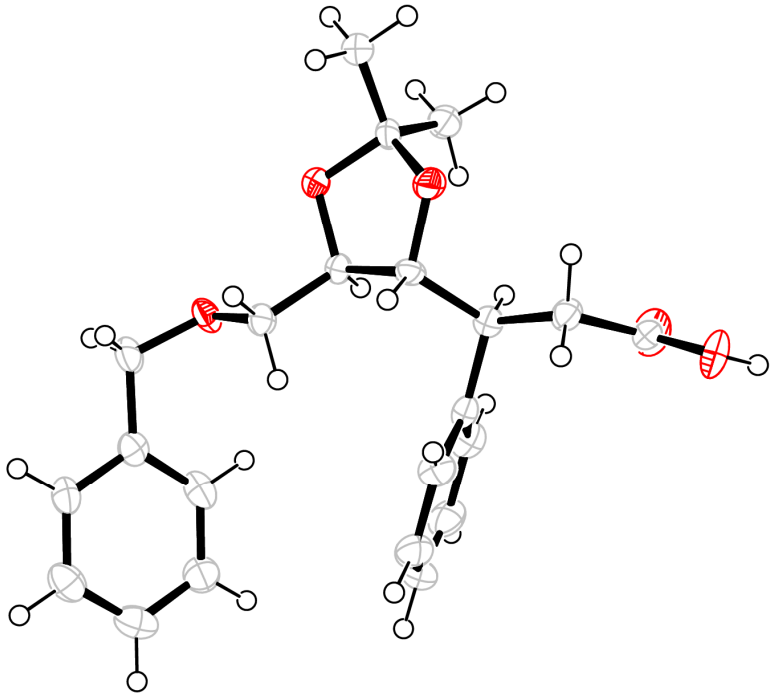
C(021)-C(009)-C(014)-C(015)	62.6(5)
C(020)-O(4)-C(015)-C(014)	-110.5(3)
C(020)-O(4)-C(015)-C(016)	11.5(4)
C(009)-C(014)-C(015)-O(4)	178.4(3)
C(019)-C(014)-C(015)-O(4)	-55.3(4)
C(009)-C(014)-C(015)-C(016)	61.8(4)
C(019)-C(014)-C(015)-C(016)	-171.8(3)
C(020)-O(3)-C(016)-C(013)	-147.0(3)
C(020)-O(3)-C(016)-C(015)	-26.1(4)
O(9)-C(013)-C(016)-O(3)	-68.0(4)
O(9)-C(013)-C(016)-C(015)	176.4(3)
O(4)-C(015)-C(016)-O(3)	9.1(4)
C(014)-C(015)-C(016)-O(3)	130.5(3)
O(4)-C(015)-C(016)-C(013)	127.5(3)
C(014)-C(015)-C(016)-C(013)	-111.1(4)
C(009)-C(014)-C(019)-C(034)	-74.7(4)
C(015)-C(014)-C(019)-C(034)	159.9(3)
C(015)-O(4)-C(020)-O(3)	-27.7(4)
C(015)-O(4)-C(020)-C(96)	-143.0(3)
C(015)-O(4)-C(020)-C(95)	91.5(4)
C(016)-O(3)-C(020)-O(4)	33.6(4)
C(016)-O(3)-C(020)-C(96)	149.7(3)
C(016)-O(3)-C(020)-C(95)	-86.4(3)
C(023)-C(009)-C(021)-C(028)	0.0(6)
C(014)-C(009)-C(021)-C(028)	-178.7(3)
C(024)-C(017)-C(022)-O(8)	-33.6(6)
C(024)-C(017)-C(022)-O(7)	149.8(4)
C(021)-C(009)-C(023)-C(044)	0.7(6)
C(014)-C(009)-C(023)-C(044)	179.4(4)
C(040)-C(018)-C(024)-C(039)	-114.9(4)
C(031)-C(018)-C(024)-C(039)	62.4(5)
C(040)-C(018)-C(024)-C(017)	123.3(4)
C(031)-C(018)-C(024)-C(017)	-59.5(5)
C(022)-C(017)-C(024)-C(018)	-72.0(4)
C(022)-C(017)-C(024)-C(039)	165.4(3)
C(030)-O(10)-C(026)-C(027)	67.0(4)

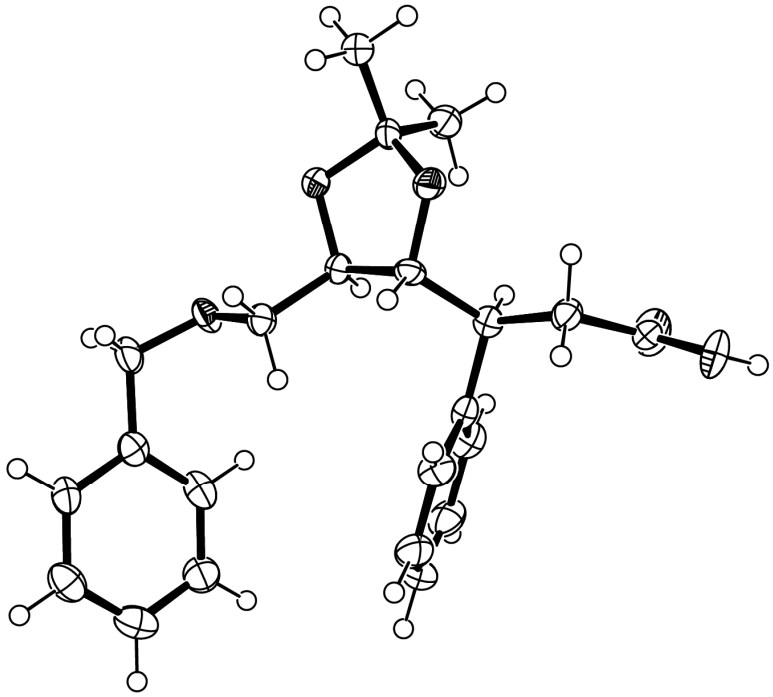
O(10)-C(026)-C(027)-C(041)	-125.8(4)
O(10)-C(026)-C(027)-C(046)	52.8(5)
C(009)-C(021)-C(028)-C(025)	0.1(6)
C(044)-C(025)-C(028)-C(021)	-0.8(6)
C(013)-O(9)-C(029)-C(032)	72.9(4)
C(026)-O(10)-C(030)-C(011)	170.9(3)
O(1)-C(011)-C(030)-O(10)	-63.9(4)
C(039)-C(011)-C(030)-O(10)	-177.3(3)
C(040)-C(018)-C(031)-C(043)	1.7(6)
C(024)-C(018)-C(031)-C(043)	-175.6(3)
O(9)-C(029)-C(032)-C(038)	18.2(6)
O(9)-C(029)-C(032)-C(033)	-164.4(4)
C(038)-C(032)-C(033)-C(042)	-0.4(6)
C(029)-C(032)-C(033)-C(042)	-178.0(4)
C(014)-C(019)-C(034)-O(6)	-20.0(6)
C(014)-C(019)-C(034)-O(5)	161.7(3)
C(039)-O(2)-C(036)-O(1)	25.3(4)
C(039)-O(2)-C(036)-C(97)	142.2(3)
C(039)-O(2)-C(036)-C(98)	-92.8(4)
C(011)-O(1)-C(036)-O(2)	-0.7(4)
C(011)-O(1)-C(036)-C(97)	-117.5(3)
C(011)-O(1)-C(036)-C(98)	118.2(3)
C(047)-C(035)-C(038)-C(032)	-0.5(7)
C(033)-C(032)-C(038)-C(035)	0.7(6)
C(029)-C(032)-C(038)-C(035)	178.2(4)
C(036)-O(2)-C(039)-C(011)	-38.4(4)
C(036)-O(2)-C(039)-C(024)	-162.0(3)
O(1)-C(011)-C(039)-O(2)	36.2(3)
C(030)-C(011)-C(039)-O(2)	152.9(3)
O(1)-C(011)-C(039)-C(024)	153.5(3)
C(030)-C(011)-C(039)-C(024)	-89.8(4)
C(018)-C(024)-C(039)-O(2)	178.9(3)
C(017)-C(024)-C(039)-O(2)	-57.3(4)
C(018)-C(024)-C(039)-C(011)	65.1(4)
C(017)-C(024)-C(039)-C(011)	-171.1(3)
C(031)-C(018)-C(040)-C(050)	-1.9(6)

C(024)-C(018)-C(040)-C(050)	175.5(4)
C(046)-C(027)-C(041)-C(049)	1.7(6)
C(026)-C(027)-C(041)-C(049)	-179.6(4)
C(032)-C(033)-C(042)-C(047)	-0.1(7)
C(050)-C(037)-C(043)-C(031)	-0.5(7)
C(018)-C(031)-C(043)-C(037)	-0.6(6)
C(028)-C(025)-C(044)-C(023)	1.4(6)
C(009)-C(023)-C(044)-C(025)	-1.4(7)
C(048)-C(045)-C(046)-C(027)	0.9(6)
C(041)-C(027)-C(046)-C(045)	-1.6(6)
C(026)-C(027)-C(046)-C(045)	179.8(4)
C(038)-C(035)-C(047)-C(042)	0.0(7)
C(033)-C(042)-C(047)-C(035)	0.3(7)
C(046)-C(045)-C(048)-C(049)	-0.3(6)
C(045)-C(048)-C(049)-C(041)	0.5(6)
C(027)-C(041)-C(049)-C(048)	-1.2(6)
C(043)-C(037)-C(050)-C(040)	0.4(7)
C(018)-C(040)-C(050)-C(037)	0.9(7)

Symmetry transformations used to generate equivalent atoms:

A2.1.7. ORTEP diagrams of **101**





References:

1. Viladomat, F.; Bastida, J.; Codina, C.; Nair, J.J.; Cambell, W.E. In *Recent Research Developments in Phytochemistry*; Research Signpost Publishers; Trivandrum, **1997**, Vol. 1, 131.
2. Cook, J.W.; Loudon, J.D. In *The Alkaloids*; Manske, R.H.F.; Holmes, H.L Academic Press; New York; **1952**, Vol. 2, 331.
3. Hoshino, O. In *The Alkaloids*; Manske, R.H.F. Academic Press; New York; **1998**, Vol. 51, 323.
4. Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull*. **1968**, 16, 1860.
5. Pettit, G.R.; Gaddamidi, V.; Cragg, G.M.; Herald, D.L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun*. **1984**, 1693.
6. Gabrielsen, B.; Monath, T.P.; Huggins, J.W.; Kefauver, D.F.; Pettit, G.R.; Groszek, G.; Hollingshead, M.; Kirsi, J.J.; Shannon, W.M.; Shubert, E.M.; Dare, J.; Ugarkar, B.; Ussery, M.A.; Phelan, M.J. *J. Nat. Prod.* **1992**, 55, 1569.

7. Quarzane-Amara, M.; Franetich, J.F.; Mazier, D.; Pettit, G.R.; Meijer, L.; Doerig, C.; Desportes-Livage, I. *Antimicrob. Agents Chemother*. **2001**, 45, 3409.
8. Pettit, G.R.; Gaddamidi, V.; Herald, D.L.; Singh, S.B.; Cragg, G.M.; Schmidt, J.M.; Boettner, F.E.; Williams, M.; Sagawa, Y. *J. Nat. prod.* **1986**, 49, 995.
9. Pettit, G.R.; Pettit, G.R. III.; Backhaus, R.A.; Boyd, M.R.; Meerow, A.W. *J. Nat. Prod.* **1993**, 56, 1682.
10. Pettit, G.R.; Orr, B.; Ducki, S. *Anti-Cancer Drug Des.* **2000**, 15, 389.
11. Rinner, U.; Hillebrenner, H.L.; Adams, D.R.; Hudlicky, T.; Pettit, G.R.; *Bioorg. Med. Chem. Lett.*. **2004**, 14, 2911.
12. Yuan, H.; Mutaomba, M.; Prinz, I.; Gottlieb, R. *Mitochondrion*. **2001**, 1, 61.
13. Green, D.; Kroener, G. *Science*. **2004**, 305, 626.
14. Boose, G.; Stopper, H. *Tox. Lett.* **2000**, 116, 7.
15. Hudlicky, T.; Moser, M.; Banfield, S.C.; Rinner, U.; Chapuis, J.C.; Pettit, G.R. *Can. J. Chem*. **2006**, 84, 1313.
16. Modica-Naoolitano, J.; Singh, K. *Exp. Rev. Mol. Med.* 11 April, **2002**.
17. Manpadi, M.; Kornienko, A. *Organic preprations and procedures*. **2008**, 40 (2), 107.
18. Pettit, G.R.; Freeman, S.; Simpson, M.J.; Thompson, M.A.; Boyd, M.R.; Williams, M.D.; Pettit, G.R. III.; Doubek, D.L. *Anti-Cancer Drug Res.* **1995**, 10, 243.
19. a) McNulty, J.; Mao, R.; Mo, R.; Wolf, S.; Pettit, G.R.; Herald, D.L.; Boyd, M.R. *Bioorg. Med. Chem. Lett*. **2001**, 11, 169. b) McNulty, J.; Larichev, V.; Pandey, S. *Bioorg. Med. Chem.* **2005**, 15, 5315.
20. Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T.A.; Pettit, G.R. *J. Org. Chem.* **2002**, 67, 8726.
21. Pettit, G.R.; Meng, Y.; Herald, D.L.; Knight, J.C.; Day, J.F. *J. Nat. Prod.* **2005**, 68, 1256.
22. Moser, M.; Sun, X.; Hudlicky, T. *Org. Lett.* **2005**, Vol. 27, 25, 5669.
23. Collins, J.; Drouin, M.; Sun, X.; Rinner, U. ; Hudlicky, T. *Org. Lett.* **2008**, Vol. 10, 3, 361.

24. Kim, M.; Bae, S.J.; So, S.M.; Yoo, H.T.; Chang, S.K.; Lee, J.H.; Kang, J. *Org. Lett.* **2001**, Vol. 3, 15, 2349.
25. De Napoli, L.; Messere, A.; Palomba, D.; Piccialli, G.; Evidente, A. *J. Org. Chem.* **2000**, 65, 3432.
26. Yamamoto, Y. ; Kobayashi, K. ; Okano, H. ; Kadato, I. *J. Org. Chem.* **1992**, 26, 7003.
27. Danishefsky, S.; Lee, J.Y. *J. Am. Chem. Soc.* **1989**, 111, 4829.
28. Poller, R.C. In *Comprehensive Organic Chemistry.* Pergamon Press. Oxford. **1979**, Vol. 3, 1073.
29. Tian, X.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc.* **1995**, 117, 3643.
30. Gibson, D.T.; Hensley, M.; Yosioka, H.; Mabry, T.J. *Biochemistry*. **1970**, 9, 1626.
31. Trost, B.; Pulley, S.R. *J. Am. Chem. Soc.* **1995**, 117, 10143.
32. Magnus, P.; Sebhat, I.K. *Tetrahedron*. **1998**, 54, 15509.
33. Rigby, J.H.; Maharoof, U.S.M.; Mateo, M.E. *J. Am. Chem. Soc.* **2000**, 122, 6624.
34. Pettit, G.R.; Melody, N.; Herald, D.L. *J. Org. Chem.* **2001**, 66, 2583.
35. Håkansson, A.E.; Palmelund, A.; Holm, H.; Madsen, R. *Chem. Eur. J.* **2006**, 12, 3243.
36. Nadein, O.N.; Kornienko, A. *Org. Lett.* **2004**, 6, 831.
37. Manpadi, M.; Kornienko, A. *Tetrahedron Lett.* **2005**, 46, 4433.
38. Rastogi, S.K.; Kornienko, A. *Tetrahedron: Asymmetry*. **2006**, 17, 3170.
39. Kireev, A.S.; Nadein, O.N.; Agustin, V.; Bush, N.E.; Evidente, A.; Manpadi, M.; Ogasawara, M.A.; Rastogi, S.K.; Rogelj, S.; Shors, S.T.; Kornienko, A. *J. Org. Chem.* **2006**, 71, 5694.
40. McNulty, J.; Nair, J.J.; Griffin, C.; Pandey, S. *J. Nat. Prod.* **2008**, 71, 357.
41. Breit, B.; Schmidt., Y. *Chem. Rev.* **2008**, 108, 2928.
42. Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics*. **1997**, 16, 4229.
43. Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, 120, 5579.
44. Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry*. **1999**, 10, 4047.

45. Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, 66, 8944.
46. Segura, A.; Csáky, A.G. *Org. Lett.* **2007**, 9, 3667.
47. Gawonski, J.; Gawranska, K.; Rychlewska, P.U.; Watiajtis, B.; Rychlewski, J.; Hoffmann, M.; Szarecka, A. *Tetrahedron*. **1997**, 53, 6113.
48. Khanapure, S.P.; Najafi, N.; Manna, S.; Yang, J.J.; Rokach, J. *J. Org. Chem.* **1985**, 60, 7548 .
49. Fox, D.T.; Poulter, C.D. *J. Org. Chem.* **2005**, 70, 1978.
50. Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, 66, 8199.
51. Taylor, R.J.K.; Alcarez, L.; Kapfer-eyer, I.; Macdonald, G.; Wei, X.; Lewis, N.J. *Synthesis*. **1998**, 775.
52. Macdonald, G.; Alcarez, L.; Wei, X.; Lewis, N.J.; Taylor, R.J.K. *Tetrahedron*. **1998**, 54, 9823.
53. Alcarez, L.; Macdonald, G.; Ragot, J.; Lewis, N.J.; Taylor, R.J.K. *J. Org. Chem*. **1998**, 63, 3526.
54. Alcarez, L.; Macdonald, G.; Ragot, J.; Lewis, N.J.; Taylor, R.J.K. *Tetrahedron*. **1999**, 55, 3707.
55. Blackburn, L.; Pei, C.; Taylor, R.J.K. *Synlett*. **2002**, 215.
56. Ranatunge, R.R.; Augustyniak, M.; Bandarage, U.K.; Earl, R.A.; Ellis, J.L.; Garvey, D.S.; Janero, D.R.; Letts, L.G.; Martino, A.M.; Murty, M.G.; Richardson, S.K.; Schroeder, J.D.; Shumway, M.J.; Tam, S.W.; Trocha, A.M.; Young, D.V. *J. Med. Chem*. **2004**, 47, 2180.
57. Oswald, M.F.; Raw, S.A.; Taylor, R.J.K. *Org. Lett.* **2004**, 6, 3997.
58. Blackburn, L.; Taylor, R.J.K. *Org. Lett*. **2001**, 3, 1637.
59. Kanno, H.; Taylor, R.J.K. *Synlett*. **2002**, 1287.
60. Fatiadi, A.J. *Synthesis*. 1976, 65 and 133. *Encyclopedia of Reagents for Organic Synthesis,* ed. L.A. Paquette, Willey, Chichester. **1995**, vol. 5, 3229.
61. Blackburn, L.; Wei, X.; Taylor, R.J.K. *Chem. Commun.* **1999**, 1337.
62. Wilfred, C.D.; Taylor, R.J.K. *Synthetic Commun.* **2005**, 35, 2859.
63. Pak, C.S.; Lee, E.; Lee, G.H.; *J. Org. Chem.* **1993**, 58, 1523.
64. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 31, 2647.

65. Bressette, A.R.; Glover, L.C. *Synlett.* **2004**, 738-740.

66. Shet, J.; Desai, V.; Tilve, S. *Synthesis*. **2004**, 11, 1859.

67. Kim, B.M.; Bae, S.J.; So, S.M.; Yoo, H.T.; Chang, S.K.; Lee, J.H.; Kang, J. *Org. Lett.* **2001**, Vol. 3, No. 15, 2349.

68. Fox, D.T.; Poulter, C.D. *J. Org. Chem*. **2005**, 70, 1978.

69. Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P.A. *Tetrahedron*. **1995**, 51, 12843.

70. Reed, P.E.; Katzenellenbogen, J.A. *J. Med. Chem.* **1991**, 34, 1162.

71. Bondinell, W.E.; Chapin, F.W.; Girard, G.R.; Kaiser, C.; Krog, A.J.; Pavloff, A.M.; Schwartz, M.S.; Silvestri, J.S.; Vaidya. P.D.; Lam, B. L.; Wellman, G. R.; Pendleton, R. G. *J. Med. Chem.* **1980**, 23, 506.

72. Shin, I.; Choi, E.; Cho, C. *Angew. Chem. Int. Ed.* **2007**, 46, 2303.

73. Rinner, U.; Hillebrenner, H.L.; Adams, D.R.; Hudlicky, T.; Pettit, G.R. *Bioorg. Med, Chem. Lett.* **2004**, 14, 2911.

74. Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett*. **2002**, 8, 1343.

75. Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory chemicals*. Pergamon Press, Oxford, **1998**.

76. Bruker, in '*SAINT*+ Version 6.02 (includes XPREP and SADABS)', Madison, Wisconsin, USA, **1999**.

77. Bruker, in '*SHELXTL* Version 5.1 (includes XS, XL, XP and XSHELL)', Madison, Wisconsin, USA, **1999**.

78. Spek, A.L. *J. Appl. Cryst.* **2003**, 36, 7.