A MODULAR AND CONCISE TOTAL SYNTHESIS OF (±)-DAURICHROMENIC ACID AND ANALOGUES

AND

A NEW METHOD FOR THE MILD AND SELECTIVE MONO-DEALKYLATION OF TERTIARY AMINES

by

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ABSTRACT

This thesis consists of two parts. Part One concerns the total synthesis of (±)-daurichromenic acid and a series of structural analogues. Daurichromenic acid, a natural product isolated from the leaves and twigs of *Rhododendron dauricum*, has potent anti-HIV activity. A concise synthetic route was designed whereby the target molecule was prepared in four steps from *trans*,*trans*-farnesal, ethyl crotonate and ethyl acetoacetate. Furthermore, the modular nature of the synthetic route allowed for the preparation of a variety of structural analogues of the natural product. Although the overall yield of this route was relatively low, significant quantities of analytically pure materials have been obtained for subsequent biological evaluation.

Two alternative routes were explored in order to circumvent a problematic dehydrogenation/aromatization step encountered in this route. In these instances, attempts were made to install the aromatic ring of the target compound through migration of a carbon-carbon double bond and *via a retro*-Diels-Alder reaction.

Moreover, a strategy employing a phenylboronic acid-promoted condensation reaction of methyl orsellinate and *α*,*β*-unsaturated aldehydes as the key step was also developed. This provided additional access to a series of structural analogues of (±)-daurichromenic acid from commercially available starting materials.

In Part Two of the thesis, a new procedure for the mono-dealkylation of tertiary amines is described. Attempted oxidation of a known hydroxy crown ether derivative, 2,3,9,10-dibenzo-6-hydroxy-16-crown-5, under modified Swern conditions resulted in
the unexpected formation of a diethylamide as the major reaction product. Based on this initial observation, a novel and facile means was developed for the mono-dealkylation of a series of tertiary amines using a monoester of oxalyl chloride as the cleaving agent. The experiments also demonstrated that various alkyl groups could be cleaved and the selectivity of the bond breaking process was: benzyl > allyl > methyl > heterocyclic ring.

The chemoselectivity of this new dealkylation procedure was demonstrated by performing the selective removal of the N-benzyl group of (2S)-1-benzyl-2-[(benzyloxy)methyl]pyrrolidine. The reaction proceeded cleanly and resulted in the isolation of the desired amide product in 83% yield. Subsequent hydrolysis of the amide product afforded (2S)-2-[(benzyloxy)methyl]pyrrolidine in excellent yield.
DEDICATION

To my husband, dad and mom
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LIST OF ABBREVIATIONS

° degree(s)
Δ heat
(+)- dextrorotatory
(-)- levorotatory
(±)- racemic
$[\alpha]_D^{20}$ specific rotation
1D one dimensional
2D two dimensional
Ac acetyl
Ac$_2$O acetic anhydride
AcOH acetic acid
Anal. elemental microanalysis
aq aqueous
Ar aryl
BMS borane dimethylsulfoxide complex
Bn benzyl
Calcd. calculated (elemental analysis)
cat. catalytic (amount)
CI chemical ionization (mass spectroscopy)
cm$^{-1}$ wavenumbers (IR spectroscopy)
COSY $^1$H-$^1$H correlation spectroscopy
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>chemical shift (NMR)</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR spectroscopy)</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]-undec-7-ene</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets (NMR spectroscopy)</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-p-benzoquinone</td>
</tr>
<tr>
<td>dec.</td>
<td>decomposition</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide (methyl sulfoxide)</td>
</tr>
<tr>
<td>dq</td>
<td>doublet of quartets (NMR spectroscopy)</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets (NMR spectroscopy)</td>
</tr>
<tr>
<td>EC₅₀</td>
<td>median effective concentration</td>
</tr>
<tr>
<td>ef</td>
<td>evaporative film (IR spectroscopy)</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization (mass spectroscopy)</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol (ethyl alcohol)</td>
</tr>
<tr>
<td>Et₂O</td>
<td>ether (diethyl ether)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>ℎν</td>
<td>irradiation (generally ultraviolet)</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence spectroscopy</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (cycles per second)</td>
</tr>
</tbody>
</table>
IBX  ortho-iodoxybenzoic acid
IC$_{50}$  median inhibition concentration
$i$-Pr  isopropyl
$i$-$i$-$i$-$i$-Pr$_2$EtN  $N,N$-diisopropylethylamine (Hünig’s base)
IR  infrared (infrared spectroscopy)
$J$  coupling constant (NMR)
LDA  lithium $N,N$-diisopropylamide
lit.  literature value for a physical or spectroscopic property
m  multiplet (NMR spectroscopy)
M  molecular ion (mass spectroscopy)
M  molarity of a solution
$m$-$CPBA$  $m$-chloroperoxybenzoic acid
Me  methyl
MeCN  acetonitrile (methyl cyanide)
MEM  2-methoxyethoxymethyl
MeOH  methanol (methyl alcohol)
mg  milligram
MHz  megahertz (NMR field strength)
min  minute(s)
mL  milliliters
mmol  millimoles
mol  moles
MOM  methoxymethyl
MPO  4-methoxypyridine-$N$-oxide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>MTM</td>
<td>methylthiomethyl</td>
</tr>
<tr>
<td>MTPI</td>
<td>methyltriphenoxyphosphonium iodide</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio (mass spectroscopy)</td>
</tr>
<tr>
<td>µL</td>
<td>microliters</td>
</tr>
<tr>
<td>µmol</td>
<td>micromoles</td>
</tr>
<tr>
<td>NaOEt</td>
<td>sodium ethoxide</td>
</tr>
<tr>
<td>NaOMe</td>
<td>sodium methoxide</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>$^1$H NMR</td>
<td>proton nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>carbon nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect correlation spectroscopy</td>
</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
</tr>
<tr>
<td>OMe</td>
<td>methoxy</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>palladium (II) acetate</td>
</tr>
<tr>
<td>pH</td>
<td>the negative logarithm ($\log_{10}$) of the hydronium ion concentration in moles per liter</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhH</td>
<td>benzene</td>
</tr>
<tr>
<td>PP</td>
<td>pyrophosphate</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million (NMR spectroscopy)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectroscopy)</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>rel.</td>
<td>relative</td>
</tr>
<tr>
<td>$R_t$</td>
<td>retention factor (thin-layer chromatography)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectroscopy)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>t-Bu</td>
<td>t-butyl</td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets (NMR spectroscopy)</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyranyl</td>
</tr>
<tr>
<td>TI</td>
<td>therapeutic index</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride (chlorotrimethylsilane)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>v/v</td>
<td>volume by volume</td>
</tr>
<tr>
<td>w/v</td>
<td>weight by volume</td>
</tr>
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</table>
PART ONE

A MODULAR AND CONCISE TOTAL SYNTHESIS OF (±)-DAURICHROMENIC ACID AND ANALOGUES
CHAPTER ONE

GENERAL INTRODUCTION TO 2H-CHROMENES

1.1 Introduction

Part One of this thesis concerns the total synthesis of (±)-daurichromenic acid 1, a 2H-chromene derivative, as well as a series of structural analogues 2 (Figure 1.1).

![Molecular structures of (±)-daurichromenic acid (1) and analogues (2).]

Figure 1.1 Molecular structures of (±)-daurichromenic acid (1) and analogues (2).

2H-Chromenes, which are also known as 2H-1-benzopyrans, are an important family of oxygen heterocycles that have a benzo-fused 2H-pyran ring system 3 (Figure 1.2). These compounds are widely distributed in nature and almost every class of natural phenolic compounds include members that feature a 2,2-dialkylicchromene ring system.

![2H-Chromene ring system (3).]

Figure 1.2 2H-Chromene ring system (3).

2H-Chromenes have been studied extensively as a consequence of their widespread natural occurrence and extremely diverse biological properties. They have

---

also been widely employed as useful intermediates in the synthesis of a wide range of natural products. Moreover, the discovery of the photochromism of 2H-1-benzopyrans has sparked great interest in the synthesis and study of photochromic 2H-chromenes and a large number of patents have been issued in the past decade.

1.2 Natural Occurrence and Biological Activities of 2H-Chromenes

2H-Chromenes are constituents of a considerable number of natural phenolic compounds including flavanoids, coumarins, rotenoids, stilbenoids and chromene glycosides. The number of these types of compounds that are discovered increases every year. Surprisingly, studies on their biosynthetic pathways have been sparse. It is believed that essentially all natural 2,2-dialkylchromenes are derived in vivo by alkylation reactions of a phenol 4 or a related precursor with an allyl pyrophosphate 5 (Scheme 1.1).

Scheme 1.1 Biosynthetic Pathway of 2H-Chromenes

A variety of mechanisms have been proposed for the ring closure step. The most widely accepted hypothesis involves the abstraction of a hydride ion from the benzylic position of the isoprenylated phenol 6 by a quinone-like enzyme cofactor. The resultant

---

(6) See: ref 5 and references therein.
ortho-quinone methide 8 undergoes an electrocyclization reaction to afford the 2H-chromene 7 (Scheme 1.2).

Scheme 1.2 Proposed Mechanism for the Ring Closure Reaction to Form 2H-Chromenes

As mentioned before, 2H-chromenes are key heterocyclic units in many natural polyoxygenated and biological active compounds. The 2H-chromene ring system is a common feature of many tannins and polyphenols found in teas, fruits, vegetables and red wines, and these compounds have become increasingly important as a result of their reported health-promoting effects.\textsuperscript{7,8} The 2H-chromene nucleus has also been found in many naturally-occurring pharmacological active compounds. These compounds have been found to have anti-depressant, anti-hypertensive as well as anti-ischaemic properties and their uses in treatment of diseases dates back thousands of years.\textsuperscript{9,10} New discoveries regarding the biological activities of this class of compounds continue to be reported and some important examples are discussed herein.

\textsuperscript{9} Cruz-Almanza, R.; Perez-Flores, F.; Lemini, C. Heterocycles 1994, 37, 759.
In 1976 Bowers and co-workers reported the discovery of the anti-juvenile hormones (anti-JH), precocene 1 \(9\) and precocene 2 \(10\) (Figure 1.3). These compounds were obtained from the crude lipid extract of the bedding plant \textit{Ageratum houstonianum}.\(^\text{11}\) These two simple \(2H\)-chromene compounds induce precocious metamorphosis and sterilization in several insect orders. Precocene 2 \(10\) is about ten-fold more active than precocene 1 \(9\). This discovery initiated a new area of research on environmentally benign and insect-specific pesticides.

![Molecular structures of precocene 1 (9) and 2 (10).](image)

**Figure 1.3** Molecular structures of precocene 1 (9) and 2 (10).

Cordiachromen \(11\) \(\text{[6-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromene]}\) was isolated from the acetone extract of \textit{Cordia alliodora}, an American tree known for its durability in marine use (Figure 1.4).\(^\text{12}\) The same compound was later isolated from other plant sources and was shown to be optically active \(([\alpha]_D = +2.8, c = 0.025, \text{CHCl}_3)\).\(^\text{13}\) Cordiachromen \(11\) was found to have potent anti-inflammatory activities by the carrageena-induced rat paw edema assay. Racemic cordiachromen has been synthesized but the anti-inflammatory activity of this material was found to be less than that of the natural product.\(^\text{14}\)

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(14) See: ref 13 and references therein.
Figure 1.4 Molecular structure of cordiachromen (11).

2H-Chromene compounds, such as seselin 12, xanthyletin 13 and acronycine 14, have been shown to exhibit anti-cancer activities (Figure 1.5).15,16 2,2-Dimethyl-8-prenylchromene 15, 2,2-dimethylchromene-6-propenoic acid 16 and 2,2-dimethylchromene-6-carboxylic acid 17 were recently isolated from the methanolic extract of Brazilian propolis, a resinous hive product collected by honeybees from parts of plants (Figure 1.5).17 These compounds were tested against human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma for their in vitro cytotoxicity. The C8-prenylated 2H-chromene 15 exhibited ED50 values of 46.86 μg/mL (HT-1080) and 50.22 μg/mL (colon 26-L5). The remaining two chromene carboxylic acids 16 and 17, that were also isolated, were found to be inactive.

In 1992, eight new coumarin compounds with 2H-chromene ring systems were isolated by anti-HIV bioassay guided fractionation of an extract of the tropical rainforest tree *Calophyllum lanigerum* var. *austrorcoriaceum*. Of these compounds, (+)-calanolide A 18 showed potent activity against HIV-1 replication in human T-lymphoblastic (CEM-SS) cells with EC$_{50}$ value of 2.7 µM and IC$_{50}$ value of 13.0 µM. (-)-Calanolide B 19 showed a potency similar to that of (+)-calanolide A 18 (Figure 1.6). These discoveries have defined a new subclass of non-nucleoside HIV-1 reverse transcriptase inhibitors. Subsequent studies on the structure-activity relationship of this type of compounds showed that the 12-β-hydroxyl group is essential for anti-HIV activity. While (+)-calanolide A 18 and (-)-calanolide B 19 were potent inhibitors of HIV-1, their respective enantiomers were devoid of antiviral activity.

---

Figure 1.6 Molecular structures of (+)-canalolide A (18) and (-)-canalolide B (19).

The 2H-chromene moiety has also been found in large number of pterocarpenes 20 (Figure 1.7), which have been reported to possess anti-fungal, anti-tumor and potent activity against snake venom. Many cannabichromene compounds 21 have shown antibacterial activities against Gram-positive, Gram-negative and acid-fast bacteria (Figure 1.7).  

Figure 1.7 Basic structures of pterocarpene (20) and cannabichromene (21).

1.3 Photochromic Properties of 2H-1-Benzopyrans

The first account of photochromic 2H-1-benzopyrans was reported by Becker and Michl in 1966. It was found that the simple 2H-chromene 3 and over twenty five analogues underwent colourless to coloured conversion upon irradiation with UV light (Scheme 1.3). Gradual disappearance of the colour was observed as the temperature was increased. A mechanistic rationalisation for these transformations was proposed in which

the 2H-chromene undergoes a reversible ring opening reaction on irradiation with UV light that leads to the open-form 22. The molecule then can revert to the ring-closed form 3 via a thermal pathway. This mechanism was later confirmed by the reduction of the open-form 23 with lithium aluminium hydride at low temperature.23

Scheme 1.3 Mechanism of Photochromism of 2H-1-Benzopyrans

Research in the photochromic properties of 2H-1-benzopyrans has become increasingly active over the last decade due to the demand from industry for materials that undergo variable optical absorption. Extensive research has been carried out on the location and the nature of substituents on both rings of the 2H-1-benzopyrans in order to determine their influence on the photochromic properties. The results from these studies have been reviewed.24 These compounds were reported to be, in general, less photochromic than naphthopyrans that had the same substituents, and were found to be less fatigue resistant. Further improvement of photochromic properties could be achieved by annelation of the aromatic ring with heteroaromatic moieties and the addition of bulky

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substituents at the C2-position. The incorporation of phenyl groups at this position also allowed for extended conjugation.

A series of C5,C6-furan annelated 2H-1-benzopyran derivatives 24 have been prepared by Pozzo and co-workers for the study of their potential industrial applications (Figure 1.8). All of the compounds showed photochromic behaviour in toluene at room temperature. The electronic absorption spectra of the coloured-forms of these furan-fused 2H-1-benzopyran derivatives 24 extended over a much larger range of wavelengths than the corresponding naphthopyran 25. The open-forms of C2-diphenyl compounds exhibited a deeper colour and a bathochromic shift in the visible spectra than the corresponding monoaryl substituted compounds.

![Figure 1.8 Molecular structures of furan-fused 2H-chromenes (24) and naphthopyran (25).](image)

Additional examples of 2H-chromenes with extended annelation have included benzoindene-fused 2H-chromenes,\(^{(26)}\) annulated coumarin systems,\(^{(27)}\) fluorenone derived

---


2H-chromenes\textsuperscript{28} and benzothiophene derived 2H-chromenes.\textsuperscript{29,30} Some representative compounds are illustrated below (Figure 1.9).

![Representative examples of annelated 2H-1-benzopyrans.](image)

Figure 1.9 Representative examples of annelated 2H-1-benzopyrans.

Studies of substituent effects in photochromic 2H-chromenes have shown that the introduction of electron-withdrawing groups on the aromatic ring of the 2H-chromene improves the photochromic properties. Recently, Brun and co-workers reported the preparation of a new family of 6-aryl-2,2-dimethyl-2H-chromene derivatives 26 (Figure 1.10).\textsuperscript{31} The photochromic studies on these compounds showed that variation of the C6-aryl substituents did not have much effect on the photochromic properties. The introduction of two methoxycarbonyl groups, at C7 and C8, onto the aromatic ring led to the formation of more stable coloured-forms upon irradiation with UV light, and thus prolonged colouration.

\textsuperscript{29} Queiroz, M.-J. R. P.; Plasencia, P. M. S.; Dubest, R.; Aubard, J.; Guglielmetti, R. \textit{Tetrahedron} 2003, 59, 2567.
26 (R = H, Ph, PhO, MeO, Br, Cl, 4-NO2Ph)

Figure 1.10 Molecular structures of 6-aryl-2,2-dimethylchromene derivatives (26).

1.4 Synthesis of 2H-Chromenes

The synthesis of 2H-chromenes has been an active area of research due to the widespread natural occurrence and diverse range of biological properties of these compounds. Many procedures have been developed in the last few decades and new synthetic methods continue to be reported. In addition, the great commercial success of photochromic plastic ophthalmic lenses in the last decade has also generated interest in new synthetic 2H-1-benzopyrans that exhibit improved photochromic properties. The synthesis of 2H-chromenes has been reviewed and some of the important procedures as well as a selection of newly developed methods are discussed in this section.5,32

1.4.1 Synthesis of 2H-Chromenes From a Preformed Heteroatomic Ring

The reaction of coumarins 27 with a Grignard reagent, that affords 2,2-dialkyl-2H-chromenes 28, has been known for a long time (Scheme 1.4).33 However, the method is limited to coumarins that do not have substituents that would react with the organometalic reagent, such as carbonyl or nitro groups. 1,4-Addition has been observed as a side reaction which occurs more commonly with C4-substituted coumarins 29.34

Scheme 1.4 Reaction of Coumarins with Grignard Reagents

![Reaction of Coumarins with Grignard Reagents](image)

(R = H, Me, MeO; R' = alkyl, alkenyl, aryl, heteroaryl)

The dehydration reaction of chromanols 31 is a convenient way to prepare 2H-chromenes (Scheme 1.5).\(^{21}\) The chromanols can be easily obtained on reduction of chroman-4-ones 30 with reducing agents such as sodium borohydride and lithium aluminium hydride. Subsequent dehydration of the hydroxy intermediate 30 on treatment with acid then affords the desired 2H-chromenes 7.

Scheme 1.5 Preparation of 2H-Chromenes (7) from Chromanols (31)

![Preparation of 2H-Chromenes from Chromanols](image)

(R = H, acyloxy, alkoxy, alkyl, halogen, NO\(_2\))

Direct oxidation of chromans to chromenes can be achieved by using a quinone as the oxidizing agent, such as chloranil or DDQ (Scheme 1.6). This procedure was used by Solladie and co-workers for the preparation of 6,7-dimethoxy-2,2-dimethyl-2H-chromene 10 (precocene 2, see: Figure 1.3).\(^{35}\)

Scheme 1.6 Oxidation Reaction of Chromans (32)

![Scheme 1.6](image)

(R = H, Me, MeO)

It has been noted that chromenes could form adducts with DDQ which results in lower yields of the desired 2H-chromenes.\textsuperscript{32a} It was proposed that the charge transfer complex between the chromene 33 and DDQ breaks down by a one-electron process to afford the semiquinone radical 34 and the phenoxy radical 35. The p-quinoneallide 36 rearranges to give the 3-substituted chromene 37 (Scheme 1.7).

Scheme 1.7 Reaction of Chromene (33) with DDQ

![Scheme 1.7](image)
1.4.2 Reaction of Phenols with $\alpha,\beta$-Unsaturated Aldehydes

The base-promoted chromenylation reaction of phenols with $\alpha,\beta$-unsaturated aldehydes has been a popular method to prepare $2H$-chromenes. Various bases such as $N,N$-dimethylphenylamine, trimethylamine and tributylamine, have been employed. Pyridine was found to offer the best result in most cases. This method has found widespread application in the synthesis of natural products, such as in the total synthesis of the natural products (±)-leiocarpin 38 and (±)-isohelemileiocarpin 39 (Scheme 1.8). Moreover, the pyridine-catalyzed chromenylation reaction has frequently been found to be highly regioselective.

Scheme 1.8 Pyridine-Catalyzed Chromenylation Reaction

A series of 2,2-dialkyl-$2H$-1-benzopyrans have been synthesized using an aromatic lithiation reaction as a key step, followed by treatment with $\alpha,\beta$-unsaturated aldehydes. Cruz-Almanza and co-workers have reported the synthesis of some $2H$-

---

chromenes 43 by the 1,2-addition reaction of an appropriately protected arylithium compound 40 to an $\alpha,\beta$-unsaturated aldehyde 41, on subsequent deprotection and cyclization of the resultant carbinol 42 (Scheme 1.9). Two natural product-related compounds $O$-methylcordiachromen 44 and $O$-methylidictyochromenol 45 as well as the tricyclic $2H$-chromene 46 have been prepared by this method (Scheme 1.9).

**Scheme 1.9 Preparation of $2H$-Chromenes via Aromatic Lithiation Reaction**

Titanium or magnesium salts of phenols 47 have also been reacted with $\alpha,\beta$-unsaturated aldehydes 41 (Scheme 1.10). This method has provided a facile synthesis of a number of naturally occurring $2H$-chromenes, such as precocenes 1 9 and 2 10 as well as evodionol 48. Recently, Oliveira and co-workers have reported the preparation of a series of photochromic benzothiophene-fused $2H$-1-benzopyrans by this approach.30

---

Scheme 1.10 Reaction of Titanium or Magnesium Salts of Phenols with \( \alpha,\beta \)-Unsaturated Aldehydes

\[
\begin{align*}
\text{toluene, } 110^\circ C & \\
\text{R} & = \text{H, Me, MeO, Ph, OH, NMe}_2, \text{COMe}
\end{align*}
\]

The phenylboronic acid-promoted condensation of phenols with \( \alpha,\beta \)-unsaturated aldehydes has been found to be a convenient and mild method that complements classical routes for the synthesis of 2H-chromenes.\(^{42}\) Reaction of 3-methoxyphenol 49 with citral 50 in the presence of phenylboronic acid in toluene afforded the cannabichromene analogue 52 in 45% yield. Similarly, with farnesal 51, the 2H-chromene derivative 53 was obtained in 80% yield. It was proposed that the reaction proceeds through an ortho-quinone methide intermediate 54 (Scheme 1.11).

Scheme 1.11 Phenylboronic acid-Promoted Condensation of Phenols with $\alpha,\beta$-Unsaturated Aldehydes

The use of calcium reagents in the chromenylation reaction of phenols with $\alpha,\beta$-unsaturated aldehydes has also been examined.\(^{43}\) The synthesis of two natural product analogues has been achieved through an aldol-type reaction of phenolic anions, derived from 2,4-dihydroxybenzoates 55 and 56, with citral 50 in the presence of calcium hydroxide (Scheme 1.12). Hydrolysis of ester 57 afforded (±)-cannabichromevarinic acid 58 in 42% yield.

1.4.3 Rearrangement of Propargyl Ethers

A particularly useful synthesis of 2H-chromenes involves the thermal rearrangement of the corresponding aryl propargyl ether in a solvent of high boiling point such as \(N,N\)-diethylaniline (Scheme 1.13). The aryl propargyl ether 61 can be conveniently prepared from a phenol derivative 59 and a C3-halogenated alkyne 60. The reaction is proposed to proceed via a Claisen-like [3,3]-sigmatropic rearrangement followed by a [1,5]-sigmatropic shift. An electrocyclization reaction then completes the process. This approach has found widespread application in the synthesis of naturally occurring 2,2-dimethyl-2H-chromenes and analogues.\(^{44,45}\)

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Scheme 1.13 Preparation of 2H-Chromenes via Rearrangement of Propargyl Ethers

\[
\begin{align*}
\text{R} & \text{OH} + \text{R}^1 \text{R}^2 \text{X} \rightarrow \text{R} \text{O} \text{R}^3 \text{R}^2 \text{R}^1 \rightarrow \text{R} \text{C} \text{R}^3 \text{R}^2 \text{R}^1 \rightarrow \text{R} \text{O} \text{R}^3 \text{R}^2 \text{R}^1
\end{align*}
\]

(X = Cl, Br or OAc; R = H, Me, MeO, Cl, CN, NO₂)

The rearrangement of phenyl propargyl ethers can also be catalyzed by acid. Early examples included the acid-catalyzed rearrangement of 1,4-bis(aryloxy)-2-butynes with various hard Lewis acids (BCl₃, ZnCl₂) and soft Lewis acids (Ag⁺, Hg²⁺) (Scheme 1.14). Recently, Oliveira-Campos and co-workers reported the syntheses of a series of novel 2H-chromenes by this approach using protic acid catalysts (p-toluenesulfonic acid or pyridinium p-toluenesulfonate) in their studies of photochromic 2H-chromenes. As compared to the thermal process, these reactions can be conducted at substantially lower temperatures and can show rate increases of up to ten-times that of the thermal process.

Scheme 1.14 Lewis Acid-Catalyzed Rearrangement of Phenyl Propargyl Ethers

![Reaction Scheme]

(R = Me, Cl)

The rearrangement of phenyl propargyl ethers can also be achieved on irradiation with microwaves. Unlike the conventional thermal process, this method takes place over a short period of time and results in higher isolated yields of the desired reaction products.\(^\text{47}\) Subbugaj and co-workers have adopted this method and prepared 2H-chromenes 64 as key intermediates for the total synthesis of the natural products (±)-neorautane 65 and (±)-neorautanin 66 (Scheme 1.15).\(^\text{48}\)


1.4.4 Ring-Closing Olefin Metathesis

Ring-closing olefin metathesis (RCM) has been developed into a practical and highly efficient procedure for preparation of a diverse array of 2\textit{H}-chromene derivatives.\(^{7,49}\) A series of substituted 2\textit{H}-chromenes 70 were prepared in high yields (79-99%) by the ring-closing metathesis reaction of the 2-styrenyl allyl ethers 69 using a ruthenium carbene catalyst \([\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}]\) (Scheme 1.16).\(^{50}\) The 2-styrenyl allyl ethers 69 were prepared easily by allylation of the substituted salicylaldehydes or 2-hydroxy aryl ketones 67 with allyl bromide 68 in the presence of potassium carbonate and acetone followed by a Wittig olefination reaction.

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Scheme 1.16 Preparation of 2H-Chromenes via Ring-Closing Olefin Metathesis

![Chemical structure](image)

(R = H, alkyl, Cl, Br, NO2, MeO)

1.4.5 Miscellaneous Methods

In addition to the methods discussed above, there are some miscellaneous syntheses of 2H-chromenes reported in the chemical literature that are facile and might have the potential for further applications. Cortes and co-workers reported the total synthesis of natural products precocenes 19 (R' = MeO, R2 = H) and 210 (R' = MeO, R2 = MeO) and two related 2H-chromenes in modest to good yield (45-81%). This was achieved by the oxidative cyclization of the o-isoprenylphenols 71 with m-chloroperbenzoic acid (m-CPBA) in dichloromethane at 0°C and subsequent dehydration reactions with methyltriphenoxyphosphonium iodide (MTPI) in HMPA (Scheme 1.17).51

Scheme 1.17 Oxidative Cyclization of ortho-Isoprenylphenols (71)

![Chemical structure](image)

Recently Kaye and co-workers reported a convenient and general synthesis of 3-substituted 2H-chromene derivatives 74 by a 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed reaction (Scheme 1.18).10 Treatment of salicylaldehyde 72 with the activated alkenes 73 in the presence of DABCO (0.8 equiv) in a mixture of toluene and water at

room temperature afforded the 3-substituted 2H-chromenes 74 in 10-87% yield. The process is believed to be initiated by a Baylis-Hillman reaction.

**Scheme 1.18 DABCO-Catalyzed Reaction of Salicylaldehydes (72) and Activated Alkenes (73)**

![Scheme 1.18](image)

(R = H, MeO, Cl, Br, NO₂; R¹ = COMe, COEt, SO₂Ph, COPh, CN)

A library of 2H-chromenes 77 has also been synthesized in good to excellent yields (85-96%) via the condensation reaction of the alkenyl boronic acids 75 and salicylaldehyde derivatives 72 using the resin-supported base 76 as a catalyst (40 mol % relative to aldehyde). The key step of the process is considered to be a variation of a Mannich reaction and the intermediate 78 is assembled by imminium ion formation and coordination of the phenolate oxygen to the boronic acid (Scheme 1.19).

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1.5 Research Project Overview

Recently, two novel chromane derivatives, rhododaurichromanic acid A 79 and B 80 as well as a known chromene derivative, daurichromenic acid 81, were isolated from the methanol extract of the leaves and twigs of *Rhododendron dauricum*. The plant is distributed in various parts of Asia and has been used for medicinal purposes in China. During the screening of plant derived natural products for novel anti-HIV agents, the methanol extract of the leaves and twigs of *Rhododendron dauricum* showed potent anti-HIV activity (EC\textsubscript{50} ≤ 20 μg/mL, TI > 5). Bioassay-guided fractionation and repetitive chromatography of the methanol extract afforded rhododaurichromanic acid A 79 and B...
80 as well as the chromene derivative, daurichromenic acid 81. The isolation of daurichromenic acid 81 has been reported previously by other researchers.\(^{54}\)

![Molecular structures of rhododaurichromanic acid A (79), rhododaurichromanic acid B (80) and daurichromenic acid (81).](image)

**Figure 1.11 Molecular structures of rhododaurichromanic acid A (79), rhododaurichromanic acid B (80) and daurichromenic acid (81).**

The molecular structure and absolute stereochemistry of rhododaurichromanic acid A 79 was established by spectroscopic means and X-ray crystallography. The molecular structure and absolute stereochemistry of rhododaurichromanic acid B 80 and daurichromenic acid 81 were established indirectly as daurichromenic acid 81 can be converted to rhododaurichromanic acid A 79 and B 80 by a photochemical transformation. It was assumed that the *trans* C11-C12 double bond of daurichromenic acid 81 was isomerised to *cis* under the reaction conditions prior to the photochemical cyclization reaction that afforded rhododaurichromanic acid B 80.

Daurichromenic acid 81 was shown to have potent anti-HIV activity against acutely infected H9 cells with an EC\(_{50}\) value of 0.00567 \(\mu\)g/mL. Moreover, it exhibited

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low inhibition to uninfected H9 cells (IC$_{50}$ = 21.1 µg/mL) and thus exhibited a good therapeutic index (TI) value of 3,710. Rhododaurichromanic acid A 79 also showed relatively potent anti-HIV activity (EC$_{50}$ = 0.37 µg/mL, TI = 91.9) whereas rhododaurichromanic B 80 was inactive.

Rhododaurichromanic acid A 79 and daurichromenic acid 81 represent a new class of anti-HIV agents and therefore the total synthesis of daurichromenic acid and a series of structural analogues is of scientific importance. We designed a modular and concise synthetic plan for the preparation of (+)-daurichromenic acid 1 and structural analogues from readily available starting materials. This short synthesis (four-steps) afforded (+)-daurichromenic acid 1 and a series of structural analogues.$^{55}$ The detailed results and discussion of this study are presented in Chapter Two of this thesis. In addition, alternative routes were also explored and one particular route, complementary to the previous one, was successful and provided additional access to a series of structural analogues of (+)-daurichromenic acid. The details of this study are presented in Chapter Three of this thesis.

The discovery of these new anti-HIV agents, that was reported by Kashiwada and co-workers,$^{53}$ has attracted attention from other researchers. Two papers have been published recently regarding the total synthesis of (+)-daurichromenic acid 1 and (+)-rhododaurichromanic acid A 86 and B 87.

The total syntheses of methyl (+)-daurichromenic acid ester 85 as well as (+)-rhododaurichromanic acid A 86 and B 87 were reported by Hsung and co-workers

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Condensation and concomitant electrocyclization of trans,trans-farnesal 51 with the symmetrical 1,3-cyclohexanedione 82 on heating with piperidine and acetic anhydride afforded the 2H-pyran 83. The lithium enolate of the latter compound was reacted with methyl cyanoformate to afford the ester 84. A dehydrogenation reaction of ester 84 with DDQ led to the formation of methyl (±)-daurichromenic ester 85. Unfortunately, these researchers were not able to identify suitable reaction conditions to effect the hydrolysis reaction of the methyl ester 85 in order to complete a total synthesis of (±)-daurichromenic acid 1. However, subsequent photochemical cyclization and saponification of methyl (±)-daurichromenic ester 85 afforded a mixture of (±)-rhodaurichromatic acid A 86 and B 87.

Scheme 1.20 Synthesis of Methyl (±)-Daurichromenic Ester (85) as well as (±)-Rhododaurichromanic Acid A (86) and B (87) by Hsung et al.\textsuperscript{56}

More recently, an efficient and concise total synthesis of (±)-daurichromenic acid 1 has been reported by Jin and co-workers.\textsuperscript{57} The carboxylic acid 89 was obtained in two steps from commercially available orcinol 88. The latter compound was converted to the corresponding β-trimethylsilyl ethyl ester 90 in 90% yield. The β-trimethylsilyl ethyl ester 90 was then condensed with trans,trans-farnesal 51 on heating in microwave oven. Subsequent deprotection of the product of this reaction, the ester 91, with tetra-n-butylammonium fluoride (TBAF) afforded (±)-daurichromenic acid 1 in 94% yield. The

photochemical reaction of (±)-daurichromenic acid 1 in hexane afforded a mixture of rhododaurichromanic acid A 86 (40%) and B 87 (20%).

Scheme 1.21 Synthesis of (±)-Daurichromenic Acid (1) by Jin et al. 57

The two syntheses discussed above bear some similarity to the synthetic routes for the total synthesis of (±)-daurichromenic acid 1 that we have investigated. However, the modular nature of our synthetic routes has allowed for the preparation of not only the natural product but also a variety of structural analogues. Furthermore, the biological evaluation of (±)-daurichromenic acid 1 and the analogues has potential to provide insight into the mode of action of this natural product and perhaps lead to the discovery of new and potent anti-HIV compounds.
CHAPTER TWO
SYNTHESIS OF (±)-DAURICHRomeNIC ACID AND ANALOGUES: RESULTS AND DISCUSSION

2.1 Introduction

As described in Chapter One, daurichromenic acid 81, as well as two novel chromane derivatives, rhododaurichromanic acid A 79 and B 80, were isolated recently from the leaves and twigs of *Rhododendron dauricum* (see: Figure 1.1). Of particular note, daurichromenic acid 81 was shown to have potent anti-HIV activity [EC$_{50}$ = 0.00567 µg/mL, therapeutic index (TI) = 3,710]. Rhododaurichromanic acid A 79 also showed relatively potent anti-HIV activity [EC$_{50}$ = 0.37µg/mL, TI = 91.9] whereas rhododaurichromanic acid B 80 was inactive. Thus, daurichromenic acid was selected as a target for total synthesis. In addition, the designed route would be amenable to the synthesis of a series of structural analogues of this biologically active natural product.

The retrosynthetic analysis of the target compounds 92 is illustrated below (Figure 2.1). It was conceived that (±)-daurichromenic acid and a series of analogues 92 could be prepared from the 2H-pyrans 94 by a dehydrogenation (oxidation/aromatization) reaction and a subsequent ester hydrolysis reaction of the resultant aromatic ester 93.
Figure 2.1 Retrosynthetic analysis of (±)-daurichromenic acid and analogues (92).

The 2H-pyrans 94 could be prepared in a convergent manner from the unsymmetrical 1,3-cyclohexanediones 97 and a series of α,β-unsaturated aldehydes 96 employing a well-established Knoevenagel condensation and concomitant
The Knoevenagel condensation refers to reactions of aldehydes or ketones with active methylene compounds, such as malonates and acetoacetates, in the presence of a base to give alkylidene- or benzylidene-dicarbonyl compounds (Knoevenagel condensation product). In this case, treatment of 1,3-cyclohexanediones 97 with the \( \alpha,\beta \)-unsaturated aldehydes 96 in the presence of at least a catalytic amount of a base (e.g. amines) would lead to the formation of the \( \beta \)-hydroxycarbonyl intermediates 95 or the related Mannich products. A subsequent dehydration reaction of these intermediates 95 followed by concomitant \( 6\pi \)-electrocyclization reaction would furnish the 2H-pyrans 94. A variety of substituents could potentially be introduced at C2 and C3 in the 2H-pyrans 94 in this step of the synthesis by using a series of C3- and C2-substituted \( \alpha,\beta \)-unsaturated aldehydes 96. Recently, our research group has reported a related condensation reaction of the dibenzo-oxepinone 100 with senecialdehyde 101 and citral 50 (Scheme 2.1). This reaction was employed as the key step in the synthesis of the polycyclic ring systems of artocarpol A 102 and D 103.\(^{59}\)

Scheme 2.1 Condensation Reaction of the Oxepinone (100) with Senecialdehyde (101) and Citral (50)*

Reagents and conditions: a) allylamine (6 equiv), MgSO4, THF, reflux, 8 h; b) benzophenone, PhH, hν, 24 h.

The 1,3-cyclohexanedione precursors 97 could be prepared from the alkyl acetoacetates 98 and a series of α,β-unsaturated esters 99 by employment of a conjugate addition and concomitant intramolecular condensation reaction (Figure 2.1). Various substituents could potentially be introduced at the C5 and C6 positions in the 1,3-cyclohexanediones 97 and thus allow for the formation of (±)-daurichromenic acid 1 as
2.2 Preparation of 1,3-Cyclohexanediones

There have been a number of reports on the preparation of 1,3-cyclohexanediones as useful intermediates for the total synthesis of a wide range of natural products.\textsuperscript{60,61} The typical method involves the combination of the monoanion of a $\beta$-ketoester (alkyl acetoacetate) with an $\alpha,\beta$-unsaturated ester by sequential Michael addition and Dieckmann condensation reactions.\textsuperscript{61} In this study, two 1,3-cyclohexanediones 104 and 105 were prepared by employment of this process (Scheme 2.2).

\textbf{Scheme 2.2 Michael Addition and Concomitant Dieckmann Condensation Reactions\textsuperscript{a}}

\texttt{Reagents and conditions: a) NaOR, ROH, reflux, 104 (R = Me) 24 h, 105 (R = Ph) 66 h.}

\textsuperscript{a} Reagents and conditions: a) NaOR, ROH, reflux, 104 (R = Me) 24 h, 105 (R = Ph) 66 h.

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\textsuperscript{(60) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. Tetrahedron 1972, 28, 4395.}
The 1,3-cyclohexanedione 104 was prepared from ethyl acetoacetate and ethyl crotonate on reaction with sodium ethoxide in 81% yield.\textsuperscript{62,63} The product gave satisfactory elemental analysis and the molecular ion was observed by mass spectrometry (CI, M + H). The \textsuperscript{1}H NMR spectrum of this compound showed a small broad singlet at \( \delta 9.3 \) ppm (OH) and the IR spectrum had an absorption at 3175 cm\(^{-1}\) (OH) indicating the product was a mixture of keto and enol forms. The \textsuperscript{13}C NMR spectrum of this product was complex and so only the major signals are reported in the experimental section (see: \textit{Chapter Four}).

The 1,3-cyclohexanedione 105 was prepared in a similar manner from methyl acetoacetate and methyl cinnamate on reaction with sodium methoxide in 61% yield.\textsuperscript{62,64} The \textsuperscript{1}H NMR spectrum of this compound showed resonance signals at \( \sim \delta 7.3 \) ppm corresponding to five protons and confirmed the presence of the C6-phenyl substituent. The existence of a mixture of enol ester and keto ester forms of the product was also evident from the \textsuperscript{1}H NMR spectrum (broad singlet at \( \sim \delta 10.2 \) ppm ) and IR spectrum (broad peak at 3630 cm\(^{-1}\)).

The successful preparation of the two 1,3-cyclohexanediones 104 and 105 demonstrated that a variety of substituents could potentially be introduced at C7 in the daurichromenic acid analogues. Unfortunately, attempts to prepare the C5-substituted, C5,C6-disubstituted or the mono-substituted cyclohexanediones 106-108 from methyl acetoacetate and the corresponding commercially available \( \alpha,\beta \)-unsaturated methyl esters (methyl methacrylate, methyl 1-cyclohexene-1-carboxylate and methyl acrylate,

\textsuperscript{(63) Gaucher, G. M.; Shepherd, M. G. \textit{Biochem. Prep.} 1971, 13, 70.}
\textsuperscript{(64) Piskov, V. B.; Kasperovich, V. P. \textit{J. Org. Chem. USSR} 1985, 21, 1088.}
respectively) by this direct one-pot procedure proved to be unsuccessful (Figure 2.2). Polymerisation and self-condensation reactions of the starting materials occurred preferentially under these conditions.

![Molecular structures of 1,3-cyclohexanediones (106-108).](image)

**Figure 2.2 Molecular structures of 1,3-cyclohexanediones (106-108).**

### 2.3 Preparation of 2H-Pyrans

The second step toward the total synthesis of (+)-daurichromenic acid and a series of analogues was to prepare the 2H-pyran derivatives 94 (5-oxo-5,6,7,8-tetrahydro-2H-chromene-6-carboxylates) by a tandem Knoevenagel condensation-electrocyclization reaction of the 1,3-cyclohexanediones 96 and the α,β-unsaturated aldehydes 98 (see: Figure 2.1). The α,β-unsaturated aldehydes selected for this study included commercially available 3-methyl-2-butenal (senecialdehyde) 101, 3,7-dimethyl-2,6-octadienal (citral, E:Z = ~ 2:1) 50, cyclohexene-1-carboxaldehyde 109 and (-)-myrtenal 110. In addition, trans,trans-farnesal 51 was prepared from commercially available trans,trans-farnesol on oxidation with pyridinium dichromate (buffered with sodium bicarbonate) in 96% yield.56,57 The latter aldehyde was required for the total synthesis of (+)-daurichromenic acid 1. Cyclohexylideneacetaldehyde 111 was also prepared in 39% overall yield from cyclohexanone, on addition of vinyl magnesium bromide and
subsequent oxidation of the resultant tertiary allylic alcohol with pyridinium chlorochromate.\textsuperscript{65}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.3}
\caption{\textit{\alpha,\beta}-Unsaturated aldehyde precursors.}
\end{figure}

Condensation of the ethyl crotonate-derived 1,3-cyclohexanedione 104 in methanol with senecialdehyde 101, citral 50, \textit{trans,trans}-farnesal 51 and cyclohexylideneacetaldehyde 111, at room temperature in the presence of 5 mol \% of 1,2-ethylenediammonium diacetate [freshly prepared from ethylenediamine (5 mol \%) and acetic acid (10 mol \%)] for \textasciitilde3 h, afforded the expected substituted 2\textit{H}-pyrans 112a-114a and the spirocyclic 2\textit{H}-pyran 115 (Scheme 2.3).\textsuperscript{66} The tandem Knoevenagel condensation-electrocyclization reaction was also used to prepare the phenyl-substituted derivatives 112b-114b from the methyl cinnamate-derived 1,3-cyclohexanedione 105 and senecialdehyde 101, citral 50, and \textit{trans,trans}-farnesal 51 (at room temperature for \textasciitilde16 h).

Scheme 2.3 Knoevenagel Condensation-Electrocyclization Reaction Products (112-115)\textsuperscript{a}

\[ \text{1,3-Cyclohexanediones and } \alpha,\beta-\text{Unsaturated Aldehydes} \]

\[ \begin{array}{c}
R^1 \quad O \quad \text{R}^2 \\
\text{O} \quad \text{R}^3 \quad \text{R}^4
\end{array} + \begin{array}{c}
\text{C} \quad \text{R}^2 \quad \text{Me, 75%)}
\text{O} \quad \text{R}^3 \quad \text{R}^4
\end{array} \rightarrow \begin{array}{c}
\text{O} \quad \text{Me, 75%)}
\text{O} \quad \text{R}^3 \quad \text{R}^4
\end{array}
\]

Reagents and conditions: a) 5 mol % H\textsubscript{2}NCH\textsubscript{2}CH\textsubscript{2}NH\textsubscript{2}, 10 mol % AcOH, MeOH, rt, 3-16 h.

All of the 2H-pyran derivatives 112-115 were isolated as inseparable mixtures of diastereoisomers in good to excellent yield (63-90%). The complete characterization data for these compounds is presented in the experimental section (see: Chapter Four). The \textsuperscript{1}H NMR spectra of C7-methyl substituted 2H-pyrans 112a-114a contained two doublets at \( \delta \) 4.8 and 6.7 ppm that correspond to two protons and at \( \delta \) 5.2 and 6.5 ppm for the corresponding C7-phenyl substituted 2H-pyrans 112b-114b. These signals were assigned
as the alkene protons at C3 and C4, which confirmed the incorporation of the 2H-pyran ring. COSY NMR spectra were recorded for the citral and trans,trans-farnesal derived 2H-pyrans 113a and 114a in order to assign the remaining signals in the 1H NMR spectra of these compounds. The 1H NMR spectrum of trans,trans-farnesal derived 2H-pyran 114a was very similar to that of the corresponding methyl ester reported by Hsung and co-workers in their synthesis of methyl (±)-daurichromenic ester.67 The signals of the diastereomeric 2H-pyrans in the 13C NMR spectra were difficult to distinguish and therefore only the major signals are reported in the experimental section (see: Chapter Four). The purity of products 112-115 was confirmed by elemental analysis. However, satisfactory elemental analysis results could not be obtained for the senecialdehyde derived 2H-pyran 112b (R' = Me, R'' = Ph) or the spiropyran 115. As a result, the exact masses of these compounds were determined by high resolution mass spectroscopy (FAB HRMS) to confirm the molecular formula of these compounds.

This series of efficient reactions demonstrated that a variety of substituents can be introduced at C2 and C7 in the daurichromenic acid analogues. However, the condensation reaction of 1,3-cyclohexanedione 104 with cyclohexene-1-carboxaldehyde 109 and (-)-myrtenal 110, under these reaction conditions, afforded complex mixtures of products from which it was not possible to isolate the corresponding tricyclic and tetracyclic (C2,C3-disubstituted) analogues 116 and 117 (Scheme 2.4).

(67) See: ref 56 (Supplementary Material).
Scheme 2.4 Attempted Condensation-Electrocyclization Reaction of 1,3-Cyclohexanedione (104) with Cyclohexene-1-carboxaldehyde (109) and (-)-Myrtenal (110)\textsuperscript{a}

\[
\begin{align*}
\text{EtO} & \quad \text{Me} \\
\text{104} & \quad + \\
\text{109} & \quad \xrightarrow{\text{a})} \\
\text{116} & \quad \text{Me} \\
\text{EtO} & \quad \text{Me} \quad \text{Me} \\
\text{104} & \quad + \\
\text{110} & \quad \xrightarrow{\text{a})} \\
\text{117} & \quad \text{Me} \quad \text{Me}
\end{align*}
\]

\textsuperscript{a} Reagents and conditions: a) 5 mol % H$_2$NCH$_2$CH$_2$NH$_2$, 10 mol % AcOH, MeOH, rt, 5 h (116) and 28 h (117).

Of note, the regioisomeric products 118 were not isolated nor were any spectroscopic data obtained from crude reaction products to indicate that these potential products were formed in these Knoevenagel condensation-electrocyclization reactions (Figure 2.4). The regioselectivity of this reaction could possibly be attributed to the equilibrium of the keto ester 119 and enol ester 120. The latter structure contains an intramolecular hydrogen bond between the enol hydrogen and the ester carbonyl oxygen within a six-membered ring. This would render the C2-carbonyl less available for the electrocyclization process.
2.4 Preparation of Daurichromenic Ethyl Ester and Analogues

The next step of the synthesis was to install the aromatic ring in (±)-daurichromenic acid and a series of analogues. The process would involve dehydrogenation of the products of the latter reactions (the 2H-pyrans 112-115) to introduce an additional carbon-carbon double bond in the six-membered ketoester ring. Subsequent tautomerization of the resultant dienone would lead to a stable aromatic ring. Although methods for the dehydrogenation of ketones to form $\alpha$$\beta$-unsaturated ketones have been well-studied, limited applications have been found in the literature for dehydrogenation/aromatization reactions in more complex systems. Thus, a broad spectrum of reagents and conditions were screened in order to effect this dehydrogenation/aromatisation process and the methods studied herein can be categorized in terms of halogenation-dehalohydrogenation, direct dehydrogenation, oxidation of silyl enol ethers and $\text{syn}$-elimination of phenylselenic acid.

Figure 2.4 Plausible regioisomeric Knoevenagel condensation-electrocyclization reaction products (118) and mechanistic rationale.
2.4.1 Halogenation-Dehalohydrogenation

Reaction of the senecialdehyde-derived $2H$-pyran 112a ($R^1 = Et$, $R^2 = Me$) at 0 °C in carbon tetrachloride with bromine (1 equiv) and acetic acid followed by elimination of hydrogen bromide at reflux afforded the desired aromatized product 121a in 30% yield.\(^{68}\) The appearance of a singlet at $\delta$ 6.35 ppm (aromatic proton) and a singlet at $\delta$ 12.81 (hydrogen-bonded phenolic OH) in the $^1$H NMR spectrum as well as an absorption at 3431 cm\(^{-1}\) (phenolic OH) in the IR spectrum confirmed the aromatic ring had been installed successfully. A lower yield (20%) was obtained for this reaction when $N$-
chlorosuccinimide (NCS) was used under similar reaction conditions. However, treatment of the farnesal-derived 2H-pyran 114a (R¹ = Et, R² = Me) with NCS afforded a complex mixture of products from which it was not possible to obtain the desired analytically pure daurichromenic ethyl ester 123a. The use of N-bromosuccinimide (NBS) as an alternative reagent did not improve the situation.

2.4.2 Direct Dehydrogenation

A variety of oxidizing reagents and different reaction conditions were screened in order to convert the 2H-pyran 112-115 to the corresponding daurichromenic ethyl ester and analogues 121-124. Low yields (< 30%) were obtained for the oxidation reaction of the senecialdehyde-derived 2H-pyran 112a (R¹ = Et, R² = Me) when cupric chloride,70 palladium acetate,71 cerium ammonium nitrate72 or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)73 were used as oxidizing agents according to literature procedures. It was found that a better yield (43%) could be obtained by heating this 2H-pyran derivative 112a with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at reflux in benzene for 4 h. Further attempts to optimise the reaction conditions, including changing the solvent (e.g. MeOH)74, the addition of an acid catalyst (e.g. p-toluenesulfonic acid),75 substituting chloranil for DDQ,76 or regulating the pH of the reaction by adding pH 7 buffer,77 all proved to be less productive.

The oxidation reaction of the citral-derived 2H-pyran 113a (R' = Et, R2 = Me) employing cupric chloride,70 TEMPO,73 or allyl diethylphosphate/palladium acetate78 afforded more complex reaction mixtures and lower yields (< 30%) than the corresponding oxidation reactions of the senecialdehyde-derived 2H-pyran 112a (R' = Et, R2 = Me) under similar reaction conditions. Other oxidizing reagents such as selenium dioxide,79,80 molecular oxygen81 and cerium ammonium nitrate72 were also employed for this reaction. However, these reagents caused extensive decomposition of the starting material. The hypervalent iodine (V) complex, o-iodoxybenzoic acid/4-methoxypyridine N-oxide (IBX/MPO)82 and vitamin B283 as oxidizing agents, proved to be unreactive. It was found again that a better yield (27%) of the desired product could be obtained by heating the citral-derived 2H-pyran 113a (R' = Et, R2 = Me) with DDQ at reflux in benzene for 16 h. The molecular ion was observed for the product of this reaction (CI, M + H) and correct elemental analysis was obtained. In addition, a characteristic absorption in the IR spectrum (3402 cm⁻¹, phenolic OH) and signals in the 'H NMR spectrum (a singlet at δ 6.18 ppm for the aromatic proton and a singlet at δ 12.07 ppm for phenolic OH) confirmed the presence of the highly functionalized aromatic ring.

The aromatization reaction of the farnesal-derived 2H-pyran 114a (R' = Et, R2 = Me) proved to be considerably more problematic using a direct dehydrogenation approach. A majority of the dehydrogenation methods discussed above afforded complex

mixtures of reaction products. It proved to be difficult to isolate the desired analytically pure aromatized product 123a by extensive chromatography. However, oxidation with DDQ in benzene at reflux once again offered a better result. In this case, the desired product 123a was isolated in analytically pure form in 11% yield. The compound showed a characteristic absorption in the IR spectrum (3316 cm\(^{-1}\), phenolic OH) and characteristic signals in the \(^1\)H NMR spectrum (a singlet at \(\delta 6.18\) ppm for the aromatic proton and a singlet at \(\delta 12.07\) ppm for hydrogen-bonded phenolic OH) confirming the presence of the aromatic ring. Of note, this aromatic ester 123a has been prepared previously by microwave irradiation of the phenol 125 and trans,trans-farnesal 51 (Scheme 2.6)\(^{87}\) and is the direct precursor of (±)-daurichromenic acid 1. The \(^1\)H and \(^{13}\)C NMR spectral data of our synthetic material was completely consistent with the data reported by Jin and co-workers.\(^{84}\)

**Scheme 2.6 Synthesis of (±)-Daurichromenic Acid Precursor (123a) by Jin et al.\(^a\)**

\[\text{EtO} \quad \text{OH} \quad \text{Me} \quad \text{Me} \]
125

\[\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{OH} \quad \text{Me} \quad \text{Me} \]
51

\[\text{EtO} \quad \text{OH} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
123a

\(^a\) Reagents and conditions: a) CaCl\(_2\)-2H\(_2\)O, NEt\(_3\), EtOH, microwave irradiation, 20 x 1 min, 70\%.

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\(^{84}\) See: ref 57 (Supplementary Material).
2.4.3 Dehydrosilylation of Silyl Enol Ethers

The conversion of ketones into enones via the oxidation of silyl enol ether derivatives has been widely used. This approach generally involves the formation of the silyl enol ether of a ketone by reacting the corresponding enolate with trialkylsilyl chlorides or bromides and a subsequent palladium (II)-mediated oxidation reaction. This sequential approach has been reported to be more selective and afford higher yields than more classical methods. Deprotonation of the senecialdehyde-derived 2H-pyran 112a (R1 = Et, R2 = Me) with lithium N,N-diisopropylamide (prepared in situ from N,N-diisopropylamine and n-butylithium at 0 °C) followed by treatment of the resultant enolate with trimethylsilyl chloride (−78 °C to room temperature) afforded the corresponding silyl enol ether, which was subjected immediately to an oxidation reaction employing a stoichiometric amount of palladium acetate in acetonitrile. The desired aromatized product 121a was obtained in 20% yield after chromatography (Scheme 2.7). However, the aromatization reaction of the citral and farnesal-derived 2H-pyran 113a and 114a (R1 = Et, R2 = Me) using this method afforded complex mixtures of products and purification of the desired products proved to be problematic (only a mixture of compounds could be isolated). It was observed in all the above cases that hydrolysis of the silyl enol ethers occurred under the reaction conditions and resulted in the recovery of significant quantity of the starting materials. This issue has been commented on in the literature. The use of a sub-stoichiometric amount of palladium acetate, using a combination of palladium acetate and DDQ (0.5 equiv in each case),

proved to be less effective.\textsuperscript{88} In addition, the use of cerium ammonium nitrate as the oxidizing agent resulted in extensive decomposition of the silyl enol ether.\textsuperscript{72}

**Scheme 2.7 Aromatization Reactions of the 2H-Pyrans (112a-114a) via the Corresponding Trimethyl Silyl Enol Ethers\textsuperscript{a}**

\[\text{2H-Pyrans} \rightarrow \text{Silyl enol ethers} \rightarrow \text{Daurichromenic ester and analogues}\]

\[\text{121a, 20\%} \rightarrow \text{122a} \rightarrow \text{123a}\]

\textit{Daurichromenic ester and analogues}

\textsuperscript{a} Reagents and conditions: a) LDA, THF, -78 °C, 30 min then TMSCl, -78 °C to rt, 1.5 h; b) Pd(OAc)$_2$, MeCN, rt, 16 h.

2.4.4 \textit{syn}-Elimination of Phenylselenic Acid

The dehydrogenation of ketones via the formation of the corresponding $\alpha$-phenylseleno-ketones followed by oxidation to the selenoxide intermediates, that results in subsequent \textit{syn}-elimination of phenylselenic acid, has been used extensively for the synthesis of $\alpha\beta$-unsaturated ketones.\textsuperscript{89} Following a literature procedure, the citral-derived 2H-pyran 113a ($R^1 = \text{Et}, R^2 = \text{Me}$) was deprotonated with sodium hydride in tetrahydrofuran at 0 °C and the resultant enolate was treated with phenylselenenyl

chloride (1.2 equiv).\(^{90}\) A complex mixture of products was obtained and it was unclear if the phenylseleno-ketone 126 had indeed been formed. A second attempt to install the \(\alpha\)-phenylselenenyl group was made by employing lithium \(N,N\)-diisopropylamide as the base followed by treatment with phenylselenenyl bromide. Again, the crude reaction mixture was complex by TLC. In addition, the oxidation reaction of the crude product of this reaction with hydrogen peroxide (30\% w/v in H\(_2\)O) in dichloromethane afforded a complex mixture of products and the desired product was not isolated by chromatographic means. Treatment of the citral-derived 2\(H\)-pyran 113a (\(R^1 = \text{Me}, R^2 = \text{Ph}\)) with pyridine and phenylselenenyl bromide also afforded a complex mixture of products and phenylselenenyl bromide was the only pure product that was isolated (Scheme 2.8).\(^{91}\)

**Scheme 2.8** Dehydrogenation of the 2\(H\)-Pyran (113a) via the \(\text{syn}\)-Elimination of Phenylselenic Acid\(^a\)

\[
\begin{align*}
\text{113a} & \xrightarrow{\text{a})} \text{126} \\
\text{122a} & \xrightarrow{- \text{PhSeOH}} \text{122a}
\end{align*}
\]

\(^a\) Reagents and conditions: a) base then PhSeX (\(X = \text{Cl, Br}\)), THF; b) \(\text{H}_2\text{O}_2\) (30\% w/v), CH\(_2\)Cl\(_2\).

Based on the results obtained from all of the attempted dehydrogenation/aromatisation reactions, the optimal conditions for the dehydrogenation/aromatisation step involved the use of DDQ in benzene at reflux (Scheme 2.9). Daurichromenic ethyl ester 123a and a series of analogues 121-124 were thus obtained in low to moderate yield (6-43%). In this case, the aromatic ethyl ester 123a (R¹ = Et, R² = Me), which is the direct precursor of (±)-daurichromenic acid 1, was isolated in 11% yield. Hsung and co-workers have reported that the corresponding methyl ester can be obtained by dehydrogenation of the related 2H-pyran precursor with DDQ on heating at reflux in toluene. In our hands, these reaction conditions caused extensive decomposition of the starting material. Of note, these oxidation reactions with DDQ could be performed on a relatively large scale and significant quantities of the desired analytically pure reaction products were isolated chromatographically.
Scheme 2.9 Oxidation/Aromatisation Reactions of 2H-Pyrans (112-115) with DDQ$^a$

Reagents and conditions: a) DDQ, PhH, reflux, 4-16 h.

2.5 Preparation of (±)-Daurichromenic Acid and Analogues

Various reagents and conditions were examined in order to effect the hydrolysis reaction of the products obtained in the latter reactions (the ethyl ester of daurichromenic acid and a series of analogues). The hydrolysis reaction under acidic conditions [e.g. concentrated sulphuric acid$^{62}$ and hydrochloric acid (20% w/v) in dioxane$^{92}$] resulted in decomposition of the starting materials. No reaction was observed when the senecialdehyde derived ethyl ester 121a was stirred with lithium hydroxide in aqueous solution.

THF at room temperature for 16 h. The saponification reactions of the methyl and ethyl ester of (±)-daurichromenic acid have been reported to be problematic due to a facile decarboxylation reaction of the product.\textsuperscript{56,57} Hsung and co-workers reported that they were not able to identify suitable reaction conditions to effect the hydrolysis of the methyl ester of (±)-daurichromenic acid in order to complete a total synthesis of (±)-daurichromenic acid 1.\textsuperscript{56} Jin and co-workers also commented in their synthesis of (±)-daurichromenic acid that the hydrolysis (3M NaOH, MeOH, H\textsubscript{2}O, 40 °C) of the ethyl ester of (±)-daurichromenic acid (1) was slow and afforded the product in relatively low yield (40%).\textsuperscript{57} Following considerable experimentation, it was eventually found that these aromatic ortho-hydroxy esters could be saponified with an aqueous 5M solution of sodium hydroxide (~ 10 equiv) in dimethylsulfoxide (DMSO) on heating at 80 °C for ~16 h (Scheme 2.10).\textsuperscript{93} The use of other solvent systems for this hydrolysis reaction, such as acetone, DME or methanol,\textsuperscript{94} proved to be inefficient. These reactions were also low yielding due to the undesirable and relatively facile decarboxylation reaction.

\textsuperscript{94} van Laak, K.; Scharf, H.-D. Tetrahedron 1989, 45, 5511.
Scheme 2.10 Synthesis of (±)-Daurichromenic Acid (1) and Analogues (127-130)\textsuperscript{a}

\[ \text{Daurichromenic ester and analogues} \]

\[ \text{(+)-Daurichromenic acid and analogues} \]

\[ \text{1 (R}^2\text{ = Me, 76%)} \]
\[ \text{129 (R}^2\text{ = Ph, 38%)} \]

\[ \text{127a (R}^2\text{ = Me, 89%)} \]
\[ \text{127b (R}^2\text{ = Ph, 74%)} \]

\[ \text{128a (R}^2\text{ = Me, 84%)} \]
\[ \text{128b (R}^2\text{ = Ph, 54%)} \]

\[ \text{130 (R}^2\text{ = Me, 85%)} \]

\( \text{a Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 °C, \sim 16 h.} \)

The latter procedure afforded significant quantities of the corresponding carboxylic acids and completed the total synthesis of the desired target compounds (±)-daurichromenic acid 1 and the structural analogues 127-130. (±)-Daurichromenic acid 1 was isolated in 76% yield and the analogues 127-130 were isolated in moderate to high yield (38-89%). The undesired decarboxylation reaction occurred more extensively in the hydrolysis reactions of the C7-phenyl substituted esters 121b-123b and resulted in lower yields of the corresponding carboxylic acids 127b, 128b and 129 (38-74%).
All of the products were fully characterized and the spectroscopic data are presented in the experimental section (see: Chapter Four). Molecular masses of each compound were obtained by mass spectroscopy (CI or MALDI-TOF). The absence of the ester proton signals in the $^1$H NMR spectra confirmed the successful hydrolysis of the ester functional group. The carbonyl carbon of the carboxylic acid function appeared at $\delta$ 176 ppm for the C7-methyl substituted products 1, 127a, 128a and 130 and $\delta$ 175 ppm for the C7-phenyl substituted products 127b, 128b and 129 in their $^{13}$C NMR spectra. The IR spectra of these compounds showed strong absorption bands at $\sim$ 1630 cm$^{-1}$ (C=O). The purity of these products was confirmed by elemental analysis. However, satisfactory elemental analysis could not be obtained for the trans,trans-farnesal-derived, C7-phenyl substituted (±)-daurichromenic acid analogue 129. In this case, the exact mass was obtained by FAB HRMS in order to confirm the molecular formula of the product.

The $^1$H NMR spectrum of the target molecule, (±)-daurichromenic acid 1, is presented below (Figure 2.5). The signal for the hydrogen bonded phenolic proton appeared at $\delta$ 11.66 ppm as a sharp singlet. Two doublets at $\delta$ 5.48 and 6.74 ppm were observed for the alkene protons on the pyran ring. The aromatic proton signal was observed at $\delta$ 6.24 ppm. The two vinylic protons on the side chain corresponded to the multiplet at $\delta$ 5.09 ppm. The signals for the allylic protons were observed at $\sim$ $\delta$ 1.9-2.20 ppm. The benzylic methyl group was observed as a singlet at $\delta$ 2.54. The remaining alkyl signals were located in the upfield region ($\delta$ 1.4-1.8 ppm). Moreover, the $^1$H NMR spectroscopic data were in full agreement with the reported values for the natural product.$^{53}$
Figure 2.5 $^1$H NMR spectrum (400 MHz, CDCl$_3$) of synthetic ($\pm$)-daurichromenic acid (1).

The $^{13}$C NMR spectrum of ($\pm$)-daurichromenic acid 1 is presented below (Figure 2.6). Thirteen resonance signals were observed in the downfield region ($\delta$ 103-177 ppm). These included signals that corresponded to the carboxylic acid group, the alkene carbons of the pyran ring, two tri-substituted double bonds and the penta-substituted aromatic ring. The remaining ten carbons of the molecule can be attributed to signals in the upfield
region ($\delta$ 16-81 ppm). The $^{13}$C NMR spectroscopic data were again in full agreement with the reported values of the natural product.$^{53}$

![Figure 2.6 $^{13}$C NMR spectrum (101 MHz, CDCl$_3$) of synthetic (±)-daurichromenic acid (1).](image)

2.6 Alternative Strategies for the Installation of the Aromatic Ring in (±)-Daurichromenic Acid and Analogues

As discussed in the previous sections, difficulties were encountered in the formation of the aromatic ring in (±)-daurichromenic acid and analogues via the
dehydrogenation (oxidation/aromatisation) reaction of the 2H-pyran precursors 112-115. Various dehydrogenation conditions either led to no reaction, caused extensive decomposition of the starting materials or resulted in isolation of the desired reaction products in relatively low yield. Alternative strategies were considered and investigated in an effort to circumvent this problem.

2.6.1 *Via Isomerization of a Carbon-Carbon Double Bond*

It was envisioned that the aromatic ring of the daurichromenic ester and related analogues 131 could be installed through the isomerization of the exo-cyclic double bond of the ketoesters 132 to an endo-cyclic carbon-carbon double bond. Subsequent tautomerization of the resultant dienones would lead to the formation of the aromatic ring of the target compounds. The exo-cyclic ketoesters 132 could be obtained by a dehydration reaction of the 7-hydroxymethyl 2H-pyran derivatives 133. The latter compounds could be prepared *via* a tandem Knoevenagel condensation-electrocyclization reaction of the 1,3-cyclohexanedione 134 or 135 and α,β-unsaturated aldehydes. The 1,3-cyclohexanedione precursors 134 or 135 could in turn be prepared from the intramolecular conjugate addition and concomitant condensation reaction of the known compound, ethyl 4-acetoacetoxycrotonate 136.95 This ester can be prepared in two steps from commercially available fumaric acid monoethyl ester 138 (Figure 2.7).96

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Reduction of fumaric acid monoethyl ester 138 with borane dimethylsulfide complex (BMS) in THF afforded ethyl 4-hydroxybut-2-enoate 137 chemoselectively (41% yield). The IR spectrum of this alcohol showed absorptions at 3445 cm\(^{-1}\) (OH) as well as at 1719 cm\(^{-1}\) (C=O) and 1661 cm\(^{-1}\) (C=C), which are characteristic for \(\alpha,\beta\)-unsaturated esters. Nucleophilic addition of this alcohol to diketene in benzene afforded the desired ethyl 4-acetoacetoxycrotonate 136 in 83% yield. The IR spectrum of this compound showed no absorption for a hydroxyl group and the \(^{13}\)C NMR spectrum contained three carbonyl resonance signals at \(\delta\) 165.8, 166.5 and 200.1 ppm confirming the incorporation of the acetoacetyl unit. The two vinylic proton signals had a large coupling constant of 15.8 Hz that confirmed the E-configuration of the carbon-carbon double bond.

Various reagents and conditions were examined in order to effect the intramolecular Michael addition and concomitant condensation reaction of ester 136. Initially, the reaction was carried out with sodium ethoxide in ethanol at room temperature for 1.5 h. Two compounds were isolated from the complex reaction mixture that had formed. These two compounds had the same molecular mass as the starting material 136. The \(^1\)H NMR spectrum of one of these compounds was very similar to that of the starting material with two doublets at \(\delta 5.20\) (1H) and 7.17 ppm (1H). The structure of this compound was determined to be ethyl (Z)-4-acetoacetoxycrotonate 139. The Z-configuration of the double bond was supported by the relatively small coupling constant (6.4 Hz) in the \(^1\)H NMR spectrum. The \(^1\)H NMR spectrum of the second compound showed the presence of ethyl ester proton signals that indicated that it was not the desired lactone 135. The lack of evidence in the IR and \(^1\)H NMR spectra for the presence of a hydroxyl group ruled out the possibility that 6-hydroxymethyl ester 134 had formed. In addition, the \(^1\)H NMR spectrum of the product showed no signals that corresponded to alkene protons, which suggested that the conjugate addition had indeed occurred. With the aid of 2D COSY and HMQC correlations, the structure of the product was assigned as 3-acetyl-4-(ethoxycarbonyl)methyltetrahydrofuran-2-one 140 (Scheme 2.12). Furthermore, the \(^1\)H
NMR spectrum of this compound showed a coupling constant of 8.1 Hz for the C3 and C4 protons, which indicated the cis orientation of the two substituents on the lactone ring.\(^9\)

Scheme 2.12 Z-Isomerization Product (139) and Intramolecular Michael Addition Product (140)\(^a\)

\[\text{Reagents and conditions: a) NaOEt, EtOH, rt, 1.5 h.}\]

When this reaction was carried out at reflux for 1 day a single major product was isolated. This compound had a different \(R_f\) value by TLC from the two compounds discussed above. It also had the same molecular mass as the starting material 136. On careful examination of the 1D and 2D (COSY and HMQC) NMR spectroscopic data it was concluded that the diastereoisomer of the \(\gamma\)-lactone 140 had formed. The structure of this product, compound 141, is shown below (Scheme 2.13).

Scheme 2.13 Intramolecular Michael Addition Product (141)\(^a\)

\[\text{Reagents and conditions: a) NaOEt, EtOH, reflux, 1 day, 13%}\]

A related procedure that involved an intermolecular Michael addition and Dieckmann condensation reaction has been reported in the literature. This prompted us to examine the use of potassium tert-butoxide as the base for the intended intramolecular reactions of ester 136. However, no reaction was observed after ethyl (E)-4-acetoacetoxyacrylate 136 was stirred in a suspension of potassium tert-butoxide (1 equiv) in ether for 8 h at 0 °C. Higher temperature (room temperature) and extended reaction time (6 h) proved to be ineffective. Activation of potassium tert-butoxide with 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane, 8 mol %) resulted in the isolation of two products. The spectroscopic data of these two compounds were identical to those of ethyl (Z)-4-acetoacetoxyacrylate 139 and γ-lactone 140 as illustrated above (Scheme 2.12).

A further attempt to effect the desired intramolecular conjugate addition and concomitant condensation reaction was carried out by treatment of ethyl (E)-4-acetoacetoxyacrylate 136 with pyrrolidine (1 equiv) in THF at 0 °C for 10 min followed by the addition of acetic acid (1 equiv). The reaction mixture was then stirred at room temperature for 19 h. A colourless liquid was isolated as the major product of this reaction after flash chromatography on silica gel. This compound had a molecular mass of 285, which suggested the incorporation of a pyrrolidine moiety had occurred. This was confirmed by the 1H NMR data, which showed signals at δ 1.76 (4H, 2 x pyrrolidine-CH2) and 2.63 ppm (4H, 2 x pyrrolidine-CH2). Further proof of the structure 142 came from the 13C NMR spectrum in which the correct number of signals with the expected chemical shifts was observed (Scheme 2.14).

---


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Scheme 2.14 Conjugate Addition Product (142)*

\[
\text{\begin{align*}
\text{Me} & \quad \text{O} \quad \text{O} \quad \text{Me} \\
\text{O} & \quad \text{C} \quad \text{C} \quad \text{OEt} \quad \text{a)} \\
136 & \quad 142, 32\%
\end{align*}}
\]

* Reagents and conditions: a) pyrrolidine, AcOH, rt, 19 h.

Additional methods employing LDA\(^{101}\) or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)\(^{102}\) for the intended tandem intramolecular cyclization reactions caused extensive polymerisation of the starting material 136. This route was abandoned at this point after numerous attempts had failed to deliver either of the key intermediates, the 1,3-cyclohexanediones 134 or 135.

2.6.2 *Via a Retro-Diels-Alder Reaction*

It was envisioned that the aromatic ring in (±)-daurichromenic acid and related analogues could potentially be installed *via* a retro-Diels-Alder reaction of 2H-pyran derivatives 143 (Figure 2.8). Tautomerization of the resultant dienones would install the aromatic ring in the esters 131. The 2H-pyran 143 could be prepared from 1,3-cyclohexanedione 144 and various \(\alpha,\beta\)-unsaturated aldehydes in the same manner as reported above (5 mol % 1,2-ethylenediammonium diacetate, MeOH, rt).\(^{56}\) The 1,3-cyclohexanedione precursor 144 could in turn be prepared from ethyl acetoacetate and the Diels-Alder adduct 145 employing a conjugate addition and concomitant

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intramolecular condensation reaction. The required Diels-Alder adduct 145 could be prepared from cyclopentadiene 147 and ethyl 2-butynoate 146.\(^{103}\)

![Diagram showing the retrosynthetic analysis of (±)-daurichromenic ester and analogues (131).]

**Figure 2.8 Alternative retrosynthetic analysis of (±)-daurichromenic ester and analogues (131).**

The Diels-Alder reaction of ethyl 2-butynoate 146 and dicyclopentadiene on heating at reflux for 16 h afforded the known bicyclic ester 145 as a colourless oil in 83% yield. A molecular ion was observed by mass spectroscopy (MALDI-TOF). The \(^1\)H and \(^13\)C NMR spectra were consistent with the formation of the desired product (see: Chapter Four).


63
Scheme 2.15 Diels-Alder Product (145)

\[
\begin{align*}
\text{147} + \text{146} & \xrightarrow{\text{a)}} \quad \text{145}
\end{align*}
\]

\(^a\) Reagents and conditions: a) reflux, 16 h, 83%.

Unfortunately, the desired conjugate addition and concomitant intramolecular Dieckmann condensation of ethyl acetoacetate and the Diels-Alder adduct 145 proved to be ineffective following the procedure discussed previously for the preparation of 1,3-cyclohexanediones 104 and 105 (Scheme 2.16). A complex mixture was obtained after the reaction was stirred at reflux for 44 h in an ethanolic solution of sodium ethoxide. The mass spectrum of the crude reaction products did not contain a peak corresponding to the desired 1,3-cyclohexanedione 144. This result was in agreement with our earlier finding that it was not possible to prepare C5,C6-disubstituted cyclohexanediones by this direct one-pot procedure (Section 2.2).

Scheme 2.16 Attempted Conjugate Addition-Concomitant Condensation Reaction

\[
\begin{align*}
\text{145} + \text{146} & \xrightarrow{\text{a)}} \quad \text{144}
\end{align*}
\]

\(^a\) Reagents and conditions: a) NaOEt, EtOH, reflux, 44 h.

2.7 Conclusion

A modular and concise total synthesis of (±)-daurichromenic acid 1 has been accomplished in four steps from \textit{trans,trans}-farnesal 51, ethyl acetoacetate and ethyl crotonate. The synthetic route was also adapted to prepare a series of daurichromenic
acid analogues in which a variety of substituents were introduced at C2 and C7. However, the synthesis of C5-substituted, C5,C6-disubstituted or mono-substituted 1,3-cyclohexandiones 106-108 was unsuccessful and so the C8-substituted or the corresponding less substituted daurichromenic acid analogues could not be prepared. Although the overall yield of the route was relatively low (in the case of derivatives that had substituents that incorporated carbon-carbon double bonds), significant quantities of analytically pure materials have been prepared for subsequent biological evaluation. It is hoped that these studies will provide insight into the structure-activity relationships of this potent anti-HIV lead compound.

Two alternative routes were explored in attempt to circumvent the somewhat problematic dehydrogenation/aromatisation step. The key step of the first alternative route was to install the aromatic ring in (±)-daurichromenic acid and analogues via the isomerization of a carbon-carbon double bond (see: Figure 2.7). This route proved to be ineffective as difficulties were encountered in the synthesis of one of the key intermediates, the 1,3-cyclohexanedione 134 or 135. A second alternative route was designed in order to install the aromatic ring of the target compounds by a retro-Diels-Alder reaction (see: Figure 2.8). This route was discontinued as attempts to prepare the 1,3-cyclohexanedione intermediate 144 were unsuccessful.

Additional synthetic studies have also been investigated to improve the synthesis as well as to prepare further structural analogues. The results of these studies are discussed in the following chapter.
3.1 Introduction

In Chapter Two, the total synthesis of (+)-daurichromenic acid 1, which was accomplished in four steps from trans,trans-farnesal 51, ethyl acetate and ethyl crotonate, was described. This synthetic route was also adapted to prepare a series of structural analogues with various substituents at the C2 and C7 positions (Figure 3.1).

![Figure 3.1 Molecular structures of (+)-daurichromenic acid (1) and analogues.](image)

Some difficulties were encountered in this route in that the formation of the aromatic ring in (+)-daurichromenic acid and related analogues via a dehydrogenation (oxidation/aromatisation) reaction of the 2H-pyran intermediates 121-124 was problematic. Various dehydrogenation conditions (employing for example: chloranil, DDQ, NCS, NBS, molecular bromine, ortho-iodoxybenzoic acid, anhydrous copper(II) chloride as reagents) either led to no reaction, caused extensive decomposition of the starting materials or resulted in isolation of the desired reaction products in relatively low yield. Similarly, attempted oxidation of the corresponding silyl enol ether or
phenylselenide derivative of these substrates was low yielding. These results prompted us to investigate alternative routes that would provide a more efficient synthesis for (±)-daurichromenic acid 1 and a series of structural analogues.

Of the many protocols that are available for the synthesis of 2H-chromenes the condensation of α,β-unsaturated carbonyl compounds with phenols has received much attention (for an overview, see: Chapter One). This approach provides a direct and facile means to prepare 2H-chromenes. Thus, we devised a route for the synthesis of (±)-daurichromenic acid and related structural analogues based on this reaction and the details of this study are discussed in this chapter.

It was envisioned that the esters of (±)-daurichromenic acid and a series of analogues 149 could be prepared by the electrophilic aromatic substitution reactions of the phenols 152 and α,β-unsaturated carbonyl compounds 151 followed by the electrocyclization of the resultant ortho-quinone methide intermediates 150. This approach is well documented for the preparation of 2H-chromenes and would potentially allow for the installation of various substituents at C2, C3 and C4 positions in (±)-daurichromenic acid analogues 148 (Figure 3.2).

---

The desired phenols 152 are esters of a known compound, orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) that is a natural product of considerable biochemical interest.\(^\text{108}\) The synthesis of orsellinic acid and derivatives has been well studied and a common approach is via the cyclization of polyketoesters 153, which in turn can be prepared by the Claisen condensation reaction of alkyl acetoacetates 98.

---

3.2 Preparation of Methyl Orsellinate

A widely applicable route to prepare orsellinic acid and related compounds involves the oxidation of the corresponding dihydro compounds (1,3-cyclohexanediione derivatives) which are readily available from the base-catalyzed condensation of \( \alpha,\beta \)-unsaturated esters and alkyl acetoacetates (see: Chapter Two). Sargent and co-workers have reported the synthesis of methyl orsellinate 156 via the oxidation reaction of methyl 1,6-dihydroorsellinate 154, which was prepared from methyl acetoacetate and methyl crotonate on reaction with sodium methoxide.\(^{109}\) The reaction of the methyl ester 154 with bromine (3 equiv) in acetic acid afforded the aromatic dibromo compound 155. The subsequent debromination of compound 155 led to the formation of methyl orsellinate 156 (Scheme 3.1).\(^{110}\)

**Scheme 3.1 Synthesis of Methyl Orsellinate (156) by Sargent et al.\(^{109}\)**

![Synthesis of Methyl Orsellinate (156) by Sargent et al.\(^{109}\)](attachment)

However, in our hands the debromination reaction of the orsellinate derivative 155 with Raney nickel in aqueous sodium hydroxide (2M) proved to be ineffective.\(^{111}\) No reaction was observed after the reaction mixture was stirred at room temperature for

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\(^{(111)}\) The orsellinate derivative 155 was prepared and characterized by Ms. Peggy M. Paduraru.
22 h. Additional Raney nickel and extended reaction time (8 h) did not improve the situation. The starting material 155 was recovered almost quantitatively after a standard workup.

The oxidation reaction of ethyl 1,6-dihydroorsellinate 104 (prepared from ethyl acetoacetate and ethyl crotonate, on reaction with sodium ethoxide, in 81% yield; see: Chapter Two) following a more recent procedure developed by Dyke and co-workers was also performed. Reaction of ethyl 1,6-dihydroorsellinate 104 with bromine (1 equiv) in the presence of acetic anhydride afforded a complex mixture of products, which was then heated at reflux for 2 h. Selective hydrolysis of the resultant aromatic ester under acidic condition afforded the desired product, ethyl orsellinate 158, in low yield (13%) after purification by flash chromatography on silica gel.

Scheme 3.2 Oxidation Reaction of Ethyl 1,6-Dihydroorsellinate (104)*

![Scheme 3.2 Oxidation Reaction of Ethyl 1,6-Dihydroorsellinate (104)](image)

* Reagents and conditions: a) NaOEt, EtOH, reflux, 24 h; b) Br₂, Ac₂O, AcOH, 12 °C to reflux, 2 h; c) HBr (aq, 50% w/v), H₂O, reflux, 2 h.

The low yield of this method might be attributable to the unselective nature of the bromination reaction. Some confusion is apparent in the chemical literature concerning

the bromination products of dihydroorsellinate.\textsuperscript{109,110} As well as the mono-bromo intermediate 157 shown above (Scheme 3.2), compounds 159-161 have also been reported as products of the bromination reaction of ethyl and methyl 1,6-dihydroorsellinate (Figure 3.3). In some cases a mixture of brominated products were isolated.

![Figure 3.3 Reported bromination products of 1,6-dihydroorsellinate (104).](image)

In view of the difficulty encountered in this bromination-debromination approach an alternative preparation was attempted. Using a modified version of Barton's protocol,\textsuperscript{113} the base-promoted self-condensation reaction of methyl acetoacetate with sodium hydride (1.5 equiv) and n-butyllithium (1.0 equiv) in tetrahydrofuran afforded directly methyl orsellinate 156 in 46% yield (Scheme 3.3).\textsuperscript{114}

**Scheme 3.3 One-Pot Synthesis of Methyl Orsellinate (156)\textsuperscript{a}**

\[\text{MeC(\text{O})C(\text{O})Me} \xrightarrow{\text{a, b)}\text{MeO}^+} \text{156, 46\%}\]

\(\text{a Reagents and conditions: a) NaH, } n\text{-BuLi, } 0^\circ\text{C to reflux, 40 h; b) 6M HCl (aq), rt, 16 h.}\)

The expected molecular mass was observed for this reaction product by mass spectroscopy (CI). The melting point of the product was comparable to the reported literature value.\textsuperscript{114} The $^1$H and $^{13}$C NMR spectroscopic data were also consistent with those reported in the literature.\textsuperscript{114}

The mechanism of this reaction has been established.\textsuperscript{108,115,116} It is believed that the reaction goes through the polyketoester intermediate 165, which is generated by the Claisen condensation reaction of the monoanion of methyl acetoacetate 167 (monodeprotonation by sodium hydride) with the strongly nucleophilic dianion of methyl acetoacetate 163 (generated by deprotonation of the corresponding monoanion with $n$-butyllithium). The subsequent aldol condensation of intermediate 165 under acidic condition then affords methyl orsellinate 156.

Scheme 3.4 Reaction Mechanism for the Formation of Methyl Orsellinate (156)

![Chemical reaction diagram]

3.3 Preparation of 2H-Chromenes

As mentioned earlier, the synthesis of 2H-chromene ring systems utilizing the reaction of phenols with $\alpha,\beta$-unsaturated aldehydes has been widely explored. Often the base-catalyzed reactions require extended reaction times and afforded the products in low

yields. However, Bissada and co-workers have reported the synthesis of the anti-juvenile hormones precocene 1 and 2 (see also: Figure 1.3) via the 2-phenyl-4H-1,3,2-benzodioxaborin intermediates 167 which were prepared by the condensation reactions of phenylboronic acid, senecialdehyde 101 and the corresponding phenols 49 and 166 (Scheme 3.5). The mildness of these reaction conditions and efficiency of this method over other Lewis acid- and base-induced processes prompted us to examine the application of this method for the synthesis of (±)-daurichromenic acid and a series of analogues.

Scheme 3.5 Phenylboronic Acid-Mediated Synthesis of Precocene 1 (9) and 2 (10)

In the first instance, trans,trans-farnesal 51 (2 equiv, prepared from commercially available trans,trans-farnesol on oxidation with pyridinium dichromate; see: Chapter Two) was reacted with methyl orsellinate 156 in the presence of phenylboronic acid (1.6...
equiv) and 30 mol % of propionic acid in benzene at reflux. Unfortunately, this reaction afforded a complex mixture of products from which the desired C2-disubstituted 2H-chromene product 85, the direct precursor of (±)-daurichromenic acid 1, was not isolated (Scheme 3.6). The reaction of citral 50 with methyl orsellinate 156 under similar reaction conditions also proved to be unsuccessful. A complex mixture was obtained and the desired product 168 was not isolated.

Scheme 3.6 Attempted Preparation of 2H-Chromenes (85) and (168)$^a$

\[ \text{Scheme 3.6 Attempted Preparation of 2H-Chromenes (85) and (168)$^a$} \]

$^a$ Reagents and conditions: a) PhB(OH)$_2$, CH$_3$CH$_2$CO$_2$H, benzene, reflux, 24 h.

However, further experiments have proved that C2-disubstituted 2H-chromene derivatives can be prepared employing this synthetic method when $\alpha,\beta$-unsaturated aldehydes that do not contain additional isolated carbon-carbon double bonds were employed as substrates. The reactions of methyl orsellinate 156 with senecialdehyde 101, $\beta$-phenylcinnamaldehyde 170 and cyclohexylideneacetaldehyde 111 in the presence of phenylboronic acid and propionic acid afforded the expected 2,2-disubstituted 2H-chromene derivatives 169, 171 and 172 in 23-75% yield (Scheme 3.7).
Scheme 3.7 Phenylboronic Acid-Mediated Synthesis of 2H-Chromenes (169), (171) and (172)

Reagents and conditions: a) PhB(OH)₂, CH₃CH₂CO₂H, benzene, reflux, 16-24 h.

Following the same procedure discussed above, two C₂-monosubstituted 2H-chromene derivatives 174 and 176 were prepared in 54% and 59% yield, respectively, on reaction of methyl orsellinate 156 with trans-2-pentenal 173 and trans-cinnamaldehyde 175 (Scheme 3.8).
Scheme 3.8 Phenylboronic Acid-Mediated Synthesis of C2-Monosubstituted 2H-Chromenes (174) and (176)\textsuperscript{a}

\[
\begin{align*}
\text{MeO} & \begin{array}{c}
\text{Me} \vphantom{\text{O}} \\
\text{OH} \\
\text{OH}
\end{array} & \text{O} & \begin{array}{c}
\text{Et} \\
\text{H} \\
\text{Me}
\end{array} & \rightarrow & \text{MeO} & \begin{array}{c}
\text{Me} \vphantom{\text{O}} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Et} \\
\text{H} \\
\text{Me}
\end{array} \\
156 & \text{173} & \rightarrow & 174, 54\%
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \begin{array}{c}
\text{Me} \vphantom{\text{O}} \\
\text{OH} \\
\text{OH}
\end{array} & \text{O} & \begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{Me}
\end{array} & \rightarrow & \text{MeO} & \begin{array}{c}
\text{Me} \vphantom{\text{O}} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{Me}
\end{array} \\
156 & \text{175} & \rightarrow & 176, 59\%
\end{align*}
\]

\textsuperscript{a} Reagents and conditions: a) PhB(OH)\textsubscript{2}, CH\textsubscript{3}CH\textsubscript{2}CO\textsubscript{2}H, benzene, reflux, 20-24 h.

This method was then extended to prepare a 2H-chromene derivative with no substituents at the C2 and C3 positions. Reaction of methyl orsellinate 156 with acrolein 177 afforded the expected 2H-chromene 178 in 18% yield (Scheme 3.9). The low yield of this reaction as compared to the previous cases might be attributable to the facile polymerisation of the starting material, acrolein 177, under these reaction conditions.

Scheme 3.9 Preparation of 2H-Chromene (178)\textsuperscript{a}

\[
\begin{align*}
\text{MeO} & \begin{array}{c}
\text{Me} \vphantom{\text{O}} \\
\text{OH} \\
\text{OH}
\end{array} & \text{O} & \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H}
\end{array} & \rightarrow & \text{MeO} & \begin{array}{c}
\text{Me} \vphantom{\text{O}} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H}
\end{array} \\
156 & \text{177} & \rightarrow & 178, 18\%
\end{align*}
\]

\textsuperscript{a} Reagents and conditions: a) PhB(OH)\textsubscript{2}, CH\textsubscript{3}CH\textsubscript{2}CO\textsubscript{2}H, benzene, reflux, 24 h.

The success of these reactions demonstrated that a variety of 2H-chromene derivatives with various substituents at C2 could be prepared by this direct one-pot procedure. Further exploration of this method using methyl orsellinate 156 and methacrolein 179 as starting materials led to the isolation of the C3-substituted 2H-
chromene derivative 180 in 15% yield. The low yield of this reaction might again be due to polymerisation of the starting material 179 (Scheme 3.10). Application of this method to the preparation of C2,C3-disubstitued 2H-chromene derivatives was also successful. The tricyclic 2H-chromene derivative 181 was isolated in 54% yield by the reaction of methyl orsellinate 156 and 1-cyclohexene-1-carboxaldehyde 109 (Scheme 3.10). Of note, the corresponding ethyl ester of this derivative could not be prepared by the procedure described in Chapter Two.

Scheme 3.10 Phenylboronic Acid-Mediated Synthesis of 2H-Chromenes (180) and (181)\textsuperscript{a}

\[ \text{Reagents and conditions: a) PhB(OH)\textsubscript{2}, CH\textsubscript{3}CH\textsubscript{2}CO\textsubscript{2}H, benzene, reflux, 20-24 h.} \]

All of the 2H-chromenes prepared in this study were fully characterized and the data are reported in the experimental section (see: Chapter Four). A strong absorption band at \( \sim 1650 \text{ cm}^{-1} \) (C=O) was observed in the IR spectrum of each compound. The \(^1\text{H}\) NMR spectrum of each compound showed a characteristic singlet at \( \sim \delta 6.2 \text{ ppm} \) for the aromatic proton, a doublet at \( \sim \delta 6.7 \text{ ppm} \) for the C4-alkene proton and at \( \sim \delta 5.5 \text{ ppm} \) for the C3-alkene proton (where it was applicable) as well as a singlet at \( \sim \delta 12 \text{ ppm} \) for the hydrogen-bonded phenolic proton. Of note, the spectroscopic data of the senecialdehyde
derived $2H$-chromene 169 and the spiropyran 172 were in full agreement with the data obtained for the corresponding ethyl esters that were prepared and previously discussed in Chapter Two of this thesis.

It is interesting to note that this boronic acid-catalyzed condensation reaction was highly regioselective at C3 of the aromatic ring and only a single regioisomer was isolated in each of the reactions discussed above. This finding is in accordance with the conclusion reached in the literature that for molecules containing both hydrogen-bonded and free hydroxyl groups, only the latter hydroxyl group (which is more nucleophilic) is involved in chromene formation.$^{32a}$ Further regiochemical control of this reaction can be rationalized in that the C6-methyl substituent blocks attack at C5 and so the isomeric compound 182 is not formed.

![Figure 3.4 Rationalization of the regioselectivity of the phenylboronic acid-mediated $2H$-chromene formation reaction.](image)

In light of the success of this method for the direct preparation of various C2- and C3-substituted $2H$-chromene derivatives, the reactions of methyl orsellinate 156 with
conjugate dienals were examined. Treatment of methyl orsellinate 156 with sorbic aldehyde (\textit{trans,trans}-2,4-hexadienal) 183 in the presence of phenylboronic acid and propionic acid afforded a white solid as the major product. This compound had a molecular mass that corresponded to the expected 2\textit{H}-chromene derivative 184. However, the \textit{^1}H and \textit{^{13}C} NMR spectra of this compound did not resemble those of the other 2\textit{H}-chromenes that were prepared under similar reaction conditions. Careful analysis of the 1D NMR spectra in combination with 2D COSY and NOESY NMR data indicated that the product was the tricyclic compound 185.

**Scheme 3.11 Reaction of Methyl Orsellinate (156) with \textit{trans,trans}-2,4-Hexadienal (183)**

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{MeO} & \quad \text{OH} \\
\text{Me} \quad \text{OH}
\end{align*}
\]
\begin{align*}
\text{156} & \quad + \quad \text{O} \quad \text{O} \quad \text{Me} \\
\text{183} & \quad \text{Me} \quad \text{Me}
\end{align*}

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{MeO} & \quad \text{Me}
\end{align*}
\]
\begin{align*}
\text{OH} & \quad \text{H} \\
\text{H} & \quad \text{Me}
\end{align*}

\[
\begin{align*}
\text{184} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
\begin{align*}
\text{OH} & \quad \text{H} \\
\text{H} & \quad \text{Me}
\end{align*}

\[
\begin{align*}
\text{185} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\textit{a} Reagents and conditions: a) PhB(OH)$_2$, CH$_3$CH$_2$CO$_2$H, benzene, reflux, 40 h, 14%.

A section of the COSY NMR spectrum of this tricyclic compound 185 is presented below (Figure 3.5). Correlations were observed between the protons of the C11-methyl substituent and the bridge hydrogen (H3). The aromatic proton (H8) and the methyl substituent (C14) were also coupled. Furthermore, the protons of the alkene moiety (H9 and H10) also showed correlations with the adjacent bridgehead protons (H2

79
and H4). A notable long range correlation was also observed between the benzylic protons of C14 and the bridgehead proton (H4).

Figure 3.5 A section of the COSY NMR spectrum (500 MHz, CDCl3) of the tricyclic phenol derivative (185).

A section of the NOESY NMR spectrum of this compound is also presented below (Figure 3.6). A correlation was observed between the bridge proton (H3) and the protons of the methyl substituent (H11). The aromatic protons of the methyl substituent (H14) also showed an NOE contact with the protons of the methyl ester (H13).
Figure 3.6 A section of the NOESY NMR spectrum (500 MHz, CDCl₃) of the tricyclic phenol derivative (185).

The presence of the NOE contacts between the protons of the methyl substituent (C11) and the vinylic protons (H9 and H10) indicated that the methyl substituent is located on the same side of the molecule as H9 and H10. This was further supported by the absence of the NOE correlations between the bridge proton (H3) and the vinylic protons (H9 and H10) in the NOESY spectrum (see also: Figure 3.7).
Figure 3.7 An expansion of the NOESY NMR spectrum (500MHz, CDCl₃) of the tricyclic phenol derivative (185).

A mechanism of this interesting reaction could involve the phenylboronic acid-promoted electrophilic aromatic substitution reaction of the aldehyde 183 and the phenol 156. This would afford the intermediate alcohol 186, which upon protonation, could lose a molecule of water to form the benzylic and allylic carbocation intermediate 187. Subsequent migration of the double bond of this carbocation would then generate the
pentadienyl cation 188. Literature reports indicate that there are three possible planar structures of a pentadienyl cation and it is believed that the most stable "W-form" 188 (the all-trans form) undergoes conformational changes leading to the "U-form" 189 which can undergo a 4π-electrocyclization reaction. The latter ring closure reaction should proceed in a conrotatory manner under thermal conditions to afford the cyclopentenyl cation intermediate 190. Subsequent intramolecular nucleophilic addition of the hydroxyl group at C4 of the aromatic ring would account for the formation of the tricyclic phenol product 185. The stereochemical outcome of this proposed reaction mechanism is in full agreement with the NOESY spectroscopic data of the isolated product.

Scheme 3.12 Proposed Reaction Mechanism for the Formation of the Tricyclic Phenol Derivative (185)

In view of this discovery, an analogous reaction of methyl orsellinate 156 with $\text{trans,trans-2,4-heptadienal}$ 191 was carried out under similar reaction conditions. The expected tricyclic phenol derivative 192 was isolated in 20% yield (Scheme 3.13).
Scheme 3.13  Phenylboronic Acid-Mediated Reaction of Methyl Orsellinate (156) with \textit{trans,trans}-2,4-Heptadienal (191)

\begin{align*}
\text{Scheme 3.13} \quad \text{Phenylboronic Acid-Mediated Reaction of Methyl Orsellinate (156) with \textit{trans,trans}-2,4-Heptadienal (191)}^{a}\nonumber
\end{align*}

\begin{align*}
\text{Reagents and conditions: } a) \text{ PhB(OH)}_2, \text{ CH}_3\text{CH}_2\text{CO}_2\text{H, benzene, reflux, 24 h, 20\%.}
\end{align*}

A section of the COSY spectrum of this compound is presented below (Figure 3.8). A correlation was observed between the methylene protons (H11) and the methyl protons (H12). The bridge proton (H3) showed a series of expected correlations with the methylene protons (H11), the bridgehead protons (H4 and H2), and the alkene protons (H9 and H10). The bridgehead proton (H4) also showed correlations with the benzylic methyl protons (H15) and the alkene proton (H10). As expected, the aromatic proton (H8) was again coupled to the benzylic methyl protons (H15).
Figure 3.8 A section of the COSY NMR spectrum (500 MHz, CDCl₃) of the tricyclic phenol derivative (192).

A section of the HMQC spectrum is also provided (Figure 3.9). Correlations were observed between the primary carbons C12 (δ 11.7 ppm), C15 (δ 24.8 ppm), C14 (δ 51.8 ppm) and the protons H12, H15 and H14, respectively. The secondary carbon C11 (δ 29.2 ppm) was coupled to H11, as expected. The three tertiary carbons C2 (δ 141.3 ppm), C3 (δ 53.5 ppm) and C4 (δ 48.0 ppm) showed individual correlations with H2, H3 and H4. Correlations were also observed between the alkene carbons C9 (δ 128.1 ppm),
C10 (δ 94.5 ppm) and protons H9 and H10, respectively. A correlation was also observed between the aromatic carbon (C8, δ 106.1 ppm) and proton H8.

Figure 3.9 A section of the HMQC NMR spectrum (500 MHz, CDCl₃) of the tricyclic phenol derivative (192).

The results discussed in this section have demonstrated that various substituents can be introduced at the C2 and C3 positions in (±)-daurichromenic acid analogues utilizing a facile phenylboronic acid-promoted reaction of methyl orsellinate 156 and a
variety of \( \alpha,\beta \)-unsaturated aldehydes. It was also of synthetic interest to examine the potential application of this one-pot procedure in the reaction of methyl orsellinate 156 with \( \alpha,\beta \)-unsaturated ketones in order to prepare C4-substituted (±)-daurichromenic acid analogues. Heating methyl orsellinate 156, methyl vinyl ketone 193 (MVK) and phenylboronic acid in the presence of propionic acid in benzene at reflux afforded a white solid as the major product. The mass spectrum of this compound did not contain a molecular ion corresponding to the expected 2\( H \)-chromene derivative 194. In addition, the \( ^1H \) NMR spectrum did not show signals that were characteristic of the 2\( H \)-chromenes [e.g. the C3-alkene proton (\( \sim \delta 6.2 \) ppm), C8-aromatic proton (\( \sim \delta 6.7 \) ppm) and the C5-phenolic proton (\( \sim \delta 12 \) ppm)]. Instead, five aromatic protons at \( \delta 7.42 \) (2H), 7.52 (1H) and 7.86 (2H) ppm were observed that suggested a phenyl group from phenylboronic acid had been incorporated into the product. Careful analysis of the 1D and 2D (COSY and HMQC) NMR data led to the assignment of the product as the cyclic phenylboronate ester derivative 195 (Scheme 3.14).

**Scheme 3.14 Phenylboronic Acid-Mediated Reaction of Methyl Orsellinate (156) with Methyl Vinyl Ketone (193)**

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{OH} & \quad \text{OH} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{156} & \quad + \quad \text{193} \\
\quad & \quad \text{194} \\
\quad & \quad \text{195}
\end{align*}
\]

\( ^a \) Reagents and conditions: a) PhB(OH)$_2$, CH$_3$CH$_2$CO$_2$H, benzene, reflux, 48 h, 44%.
The incorporation of the phenylboronic moiety in the product was evident from the distinctive broad multiplet signal at \( \delta \) 127.5 ppm in the \(^{13}\text{C}\) NMR spectrum, which corresponded to the aromatic carbon that was coupled to the adjacent boron atom (Figure 3.10).

![Diagram of cyclic phenylboronate ester 195](image)

**Figure 3.10** A section of the \(^{13}\text{C}\) NMR spectrum (126 MHz, CDCl\(_3\)) of the cyclic phenylboronate ester (195).

An improvement in the yield of the phenylboronate ester product 195 (80%) was obtained when the reaction was performed in the absence of methyl orsellinate 156 and
MVK 193 was used as the limiting reagent. A third experiment, using a stoichiometric ratio of starting materials, resulted in the isolation of the boronate ester product 195 in a relatively lower yield (65%). This suggested that a minimum of 1.25 equivalents of phenylboronic acid relative to MVK 193 is required to maintain a good yield (~ 80%) of this interesting product 195.

A mechanism for this unexpected reaction is illustrated below (Scheme 3.15). Under the acidic reaction conditions, nucleophilic attack of the carbonyl oxygen of methyl vinyl ketone 193 to the protonated form of phenylboronic acid generates water, which in turn could serve as a promoter for the subsequent self-coupling reaction of MVK, a process akin to the well known Baylis-Hillman reaction.\(^{121}\) This process involves the Michael-type nucleophilic addition of water to the phenylboronic acid-activated methyl vinyl ketone species to produce a borinic acid intermediate 196. This intermediate then undergoes nucleophilic attack onto another molecule of MVK in an aldol fashion. Subsequent elimination of water completes this Baylis-Hillman reaction. The next step of the process could involve the departure of the phenylboronic acid moiety to generate a 1,4-pentadienyl cation 197, which could undergo an electrocyclization reaction and result in the formation of the cyclopentenyl cation 198. Nucleophilic addition of phenylboronic acid to this carbocation and addition of the hydroxyl group to the alkene double bond would furnish the final product, the cyclic phenylboronate ester 195.

\(^{121}\) The Baylis-Hillman reaction has been studied extensively as an important carbon-carbon bond forming reaction. For a recent review of Baylis-Hillman reaction, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Chem. Rev. 2003, 103, 811.
The two key steps of this unprecedented reaction involved in the proposed mechanism, a Baylis-Hillman reaction and a cyclization reaction of 1,4-pentadienyl cation, provide a notable consecutive carbon-carbon bond-forming reaction. Furthermore, phenylboronate esters have been widely used as protecting groups for diols in organic synthesis and their hydrolysis have been reported to take place under simple and mild conditions.\(^\text{122}\) It was considered that this new reaction might have potential as a means to

effect the stereo-controlled synthesis of substituted \textit{syn}-cyclopentyl-1,2-diols (199) (Scheme 3.16).

\textbf{Scheme 3.16 Proposed Synthesis of \textit{syn}-Cyclopentyl-1,2-diols (199)}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{2 x \[2 \times R^1 R^3 + \text{PhB(OH)}_2 \rightarrow \text{PhB(OH)}_2 \rightarrow \text{Hydrolysis} \rightarrow R^1 R^3 \]}};
\node (b) at (0,2) {\textbf{2 x \[2 \times R^1 R^3 \]}};
\node (c) at (2,2) {\textbf{PhB(OH)}_2};
\node (d) at (4,2) {\textbf{Hydrolysis}};
\node (e) at (6,2) {\textbf{R^1 R^3 \]}};
\end{tikzpicture}
\end{center}

Thus, the applicability of this one-pot reaction was examined by varying the structure of the \(\alpha\beta\)-unsaturated ketone substrate. A series of commercially available \(\alpha\beta\)-unsaturated ketones including 3-penten-2-one 200, \textit{trans}-4-phenyl-3-buten-2-one 201, \textit{trans}-chalcone 202 and 4-methyl-3-penten-2-one 203 were selected (Figure 3.11). Unfortunately, these ketones proved to be unreactive towards phenylboronic acid and the desired phenylboronate ester products were not isolated. These results are consistent with the fact that there are very few reports of the use of \(\beta\)-substituted \(\alpha\beta\)-unsaturated ketones in Baylis-Hillman reactions in the chemical literature.\textsuperscript{121,123}

\textsuperscript{(123)} Further experiments with various \(\alpha\beta\)-unsaturated ketones were carried out by Ms. Neenah Navasero. Phenyl vinyl ketone, (4-methoxy)phenyl vinyl ketone and 5-phenylpent-1-en-3-one proved to be unreactive. The reaction of cyclohex-2-enone resulted in the isolation of an unrelated self-condensation product in 45\% yield.

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3.4 Preparation of Daurichromenic Acid Analogues

With a variety of 2\(H\)-chromenes in hand, the stage was now set for the preparation of daurichromenic acid analogues by the employment of the hydrolysis reaction discussed in Chapter Two of this thesis. Thus, saponification of the C2-dimethyl 2\(H\)-chromene derivative 169 and the spiropyran derivative 172 with an aqueous 5M solution of sodium hydroxide (~ 10 equiv) in dimethylsulfoxide (DMSO) on heating at 80 °C for ~ 16 h afforded the desired daurichromenic acid analogues 127a and 130 in good yields (83% and 88%, respectively). Unfortunately, the hydrolysis reaction of the corresponding 2,2-diphenyl 2\(H\)-chromene derivative 171 under similar reaction conditions resulted in decomposition of the starting material and the desired 2\(H\)-chromene-6-carboxylic acid 204 was not isolated (Scheme 3.17).
Scheme 3.17  Saponification Reactions of 2,2-Disubstituted 2H-Chromenes$^a$

![Diagram showing saponification reactions of 2,2-disubstituted 2H-chromenes to produce daurichromenic acid analogues.]

$^a$ Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 °C, ~ 16 h.

The hydrolysis reaction of the 2-ethyl 2H-chromene derivative 174 under similar reaction conditions afforded the desired 2H-chromene-6-carboxylic acid 205 in 53% yield (Scheme 3.18). Attempted hydrolysis of the 2-phenyl 2H-chromene derivative 176 using the same method afforded a complex mixture of products from which the desired product 206 was not isolated.

Scheme 3.18  Saponification Reactions of C2-Monosubstituted 2H-Chromenes$^a$

![Diagram showing saponification reactions of C2-monosubstituted 2H-chromenes to produce daurichromenic acid analogues.]

$^a$ Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 °C, ~ 16 h.
The 2\textit{H}-chromene-6-carboxylic acid 207 was obtained in 38\% yield from the hydrolysis reaction of the corresponding methyl ester 178 (Scheme 3.19). The saponification reactions of the remaining two C3-substituted 2\textit{H}-chromene esters 180 and 181 following the same procedure afforded the desired 2\textit{H}-chromene-6-carboxylic acid derivatives 208 and 209 in 88\% and 44\% yield, respectively.

\textbf{Scheme 3.19 Preparation of 2\textit{H}-Chromene-6-carboxylic acids (207-209)\textsuperscript{a}}

\begin{align*}
\text{MeO} & \quad \text{OH} & \quad \text{MeO} & \quad \text{OH} & \quad \text{MeO} & \quad \text{OH} \\
\text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{O} \\
178 & \quad \text{a)} & \quad 207, 38\% & \quad \text{a)} & \quad 208, 88\% & \quad \text{a)} & \quad 209, 44\% \\
\end{align*}

\textsuperscript{a} Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 \degree C, \sim 16 h.

All of the products isolated from the hydrolysis reactions discussed above were fully characterized and the data are reported in the experimental section (see: Chapter \textit{Four}). The IR spectrum of each compound showed a strong absorption band at \sim 1630\textsuperscript{1}/\text{cm} (C=O). The absence of the ester methyl signals in the \textsuperscript{1}H NMR spectra of these products confirmed the success of the hydrolysis reaction. No other significant changes
were observed in the $^1$H NMR chemical shifts of these carboxylic acids as compared to the corresponding methyl esters.

These reaction conditions were also employed in the hydrolysis of the two tricyclic phenols 185 and 192 (Scheme 3.20). The expected C3-methyl substituted carboxylic acid derivative 210 was isolated in 56% yield while the corresponding C3-ethyl substituted carboxylic acid derivative 211 was obtained in a higher yield (85%).

**Scheme 3.20 Hydrolysis Reactions of Tricyclic Phenols (185) and (192)**

![Scheme 3.20](image)

Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 °C, ~ 16 h.

Both products were fully characterized and the data are again presented in the experimental section (see: Chapter Four). The melting point measurement for these compounds showed that the C3-methyl carboxylic acid derivative 210 decomposed at 178 °C and the C3-ethyl derivative 211 decomposed at a higher temperature (194 °C). The absence of the ester signals in the $^1$H and $^{13}$C NMR spectra of these compounds provided evidence for the success of the hydrolysis reactions. No significant changes in chemical shifts were observed for the remaining signals of these compounds as compared to the corresponding methyl ester precursors. The molecular ion of these compounds was
observed by mass spectroscopy (CI or MALDI-TOF) and satisfactory elemental analysis was obtained for both products.

3.5 Conclusion

The synthesis of a number of daurichromenic acid analogues has been accomplished in three steps from methyl acetoacetate and a series of readily available \( \alpha,\beta \)-unsaturated aldehydes. The key step of this extremely concise synthesis involved the phenylboronic acid-promoted condensation reaction of methyl orsellinate \( 156 \) and the \( \alpha,\beta \)-unsaturated aldehydes, which has allowed for the successful introduction of a variety of substituents at the C2 and C3 positions in the daurichromenic acid analogues. This synthetic route is complementary to the one previously discussed, which employed an oxidation/aromatization step for the total synthesis of \( (\pm) \)-daurichromenic acid \( 1 \) and a series of structural analogues (see: Chapter Two). Significant quantities of analytically pure materials were again prepared. It is hoped that the subsequent biological evaluation of these additional daurichromenic acid analogues will provide further information for the structure-activity relationship study of this natural product which is a potent anti-HIV lead compound.

Two interesting reactions were discovered in the course of these studies. An unexpected tricyclic phenol derivative \( 185 \) was isolated from the phenylboronic acid-mediated condensation reaction of methyl orsellinate \( 156 \) and \( \textit{trans,trans} \)-2,4-hexadienal \( 183 \). The corresponding C3-ethyl substituted tricyclic phenol derivative \( 192 \) was also obtained from the reaction of methyl orsellinate \( 156 \) and \( \textit{trans,trans} \)-2,4-heptadienal \( 191 \) under similar conditions. A mechanism of the reaction was proposed that involved a cyclization reaction of a pentadienyl cation as the key step (see: Scheme 3.12). The
hydrolysis of these two tricylic compounds has led to the formation of the corresponding carboxylic acids 210 and 211. The biological evaluation of these two acids will perhaps provide some insight into the significance of the 2H-pyran ring on the anti-HIV activity of daurichromenic acid 81.

A novel cyclic phenylboronate ester derivative 195 was obtained by the phenylboronic acid-promoted condensation reaction of methyl orsellinate 156 and methyl vinyl ketone 193, a reaction intended for the preparation of the C4-methyl substituted daurichromenic ester derivative 194. The reaction also occurred in the absence of methyl orsellinate 156. A reaction mechanism was proposed and the key steps involved a Baylis-Hillman reaction followed by the cyclization of the pentadienyl cation intermediate 197 (see: Scheme 3.15). Preliminary results indicated that the extension of this method to other \( \beta \)-substituted \( \alpha,\beta \)-unsaturated ketones was not possible. However, it is believed that this approach could have potential in the development of a facile synthesis of syn-cyclopentyl-1,2-diols if alternative reaction conditions could be identified. The results of this study will be reported in due course.
CHAPTER FOUR

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA CONCERNING

CHAPTER TWO AND THREE

4.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware. The reaction temperatures stated were those of the external bath.

Diethyl ether (ether) and tetrahydrofuran (THF) were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene and dichloromethane were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. Methanol was dried over magnesium methoxide and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied.\(^{124}\) Brine refers to a saturated aqueous solution of sodium chloride.

Column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh).\(^ {125}\) Thin layer chromatography (TLC) was performed using Merck silica gel 60 F\(_{254}\) plates. Visualisation was achieved with an ultraviolet lamp, on treatment with a solution of \(p\)-anisaldehyde (2.6% v/v), acetic acid (1.0 % v/v) and

concentrated sulfuric acid (3.5% v/v) in 95% ethanol and subsequent heating or by treatment with iodine preabsorbed on silica gel.

Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected.

All proton and carbon nuclear magnetic resonance spectra ($^1$H and $^{13}$C NMR, respectively) were recorded using a Bruker AMX 400 FT spectrometer (operating frequencies: $^1$H, 400.13 MHz; $^{13}$C, 100.61 MHz), a Varian AS500 spectrometer (operating frequencies: $^1$H, 499.77 MHz; $^{13}$C, 125.67 MHz) or a Bruker AMX 600 FT spectrometer (operating frequencies: $^1$H, 600.14 MHz; $^{13}$C, 150.92 MHz) at ambient temperature. Chemical shifts ($\delta$) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated acetone [(CD$_3$)$_2$CO] were 2.09 and 30.60 ppm for $^1$H and $^{13}$C NMR spectra, respectively. The reference values used for deuterated chloroform (CDCl$_3$) were 7.26 and 77.16 ppm for $^1$H and $^{13}$C NMR spectra, respectively. The reference values used for deuterated dimethyl sulfoxide [(CD$_3$)$_2$SO] were 2.50 and 39.52 ppm for $^1$H and $^{13}$C NMR spectra, respectively. The reference values used for deuterated methanol (CD$_3$OD) were 3.31 and 49.00 ppm for $^1$H and $^{13}$C NMR spectra, respectively. The reference values used for deuterated benzene (C$_6$D$_6$) were 7.15 and 128.02 ppm for $^1$H and $^{13}$C NMR spectra, respectively.

Infrared spectra (IR) were recorded either as KBr pellets (KBr) or as evaporated films (ef) using a Perkin Elmer 599B IR spectrophotometer.

Low-resolution mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer. The mode of ionization used was chemical ionization (CI) with
isobutane. Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF) were recorded on a PerSeptive Biosystems Voyager-DE mass spectrometer using 2,4-dihydroxybenzoic acid as the matrix. High-resolution mass spectra using fast atom bombardment (FAB HRMS) were recorded on a Kratos Concept IH mass spectrometer.

Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer.

4.2 Experimental Procedures and Characterization Data Concerning Chapter Two

4.2.1 6-Methyl-2,4-dioxo-cyclohexanecarboxylic acid ethyl ester (104)\textsuperscript{62,63}

\[
\begin{align*}
\text{EtO} & \quad \text{Me} \\
\text{O} & \\
\text{O} & \quad \text{104}
\end{align*}
\]

To an ethanolic solution of sodium ethoxide [prepared from sodium (0.970 g, 42.4 mmol) and dry ethanol (50 mL)] was added ethyl acetoacetate (5.4 mL, 42 mmol) and ethyl crotonate (5.3 mL, 43 mmol) dropwise at room temperature. The reaction mixture was then heated at reflux for 66 h. After cooling, the solvent was removed \textit{in vacuo} and the solid residue was dissolved in water (50 mL). The resultant aqueous solution was washed with ether (50 mL), cooled to 0 °C, acidified with concentrated hydrochloric acid to pH < 4 and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo} to afford the title compound 104 (6.80 g, 81%) as a cream-coloured solid. M.p. 99-101 °C, ethyl acetate (lit.\textsuperscript{63} M.p. 88-90 °C, benzene/petroleum ether);

\textsuperscript{1}H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) \textsuperscript{63} δ 0.73 (d, \textit{J} = 6.6 Hz, 3H, CH\textsubscript{3}CH), 1.00 (t, \textit{J} = 7.2 Hz, 3H, CH\textsubscript{3}CH\textsubscript{2}), 1.78 (dd, \textit{J} = 17.6, 11.3 Hz, 1H, CHCHH), 2.24 (dd, \textit{J} = 17.6, 4.7 Hz, 1H,
CHCHH), 2.41 (m, 1H, CH$_3$CH), 2.91 (d, $J = 11.3$ Hz, 1H, CHCO$_2$Et), 4.05 (m, 2H, CH$_3$CH$_2$), 5.84 (s, 2H, COCH$_2$CO); $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ (mixture of isomers - major signals reported) 14.3, 14.4, 19.9, 21.7, 27.5, 28.9, 42.7, 46.1, 47.0, 57.5, 61.0, 62.0, 62.9, 103.8, 167.6, 168.7, 171.6, 198.9, 202.1, 206.2; IR (KBr) 3175 (broad), 2990, 1733, 1630, 1566, 1461, 1448, 1219, 1176 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 199 (M + H, 100); Anal. Calcd. for C$_{10}$H$_{14}$O$_4$: C, 60.59; H, 7.12; Found: C, 60.74; H, 7.18.

4.2.2 2,4-Dioxo-6-phenyl-cyclohexanecarboxylic acid methyl ester (105)$^{62,64}$

![Image of the compound](attachment:image.png)

To a methanolic solution of sodium methoxide [prepared from sodium (830 mg, 36.1 mmol) and dry methanol (30 mL)] was added methyl acetoacetate (3.5 mL, 32 mmol) at room temperature. After 30 min, the resultant clear solution was cooled to 0 °C and methyl cinnamate (4.75 g, 29.3 mmol) was added. The reaction mixture was then heated at reflux for 48 h. After cooling, the solvent was removed in vacuo and the resultant yellow solid residue was dissolved in water (50 mL) and washed with ether (50 mL). The aqueous layer was then acidified with concentrated hydrochloric acid to pH < 4 and the white solid precipitate was collected by filtration and washed with water (2 x 15 mL). The filtrate was then extracted with ether (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to afford a pale yellow solid residue. The combined crude reaction product was then recrystallized from acetone/hexanes to afford the title compound 105 (4.36 g, 61%) as a white solid. M.p. 155-157 °C, acetone/hexanes (lit.$^{64}$ M.p. 168-169 °C, ethanol/ethyl acetate); $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) $\delta$ 2.60 (dd, $J = 17.4$, 4.7 Hz, 1H,
PhCHCHH), 2.87 (dd, J = 17.4, 11.9 Hz, 1H, PhCHCHH), 3.46 (s, 3H, CH₃), 3.66 (m, 1H, PhCH), 3.78 (d, J = 12.5 Hz, 1H, CHCO₂Me), 5.42 (s, 2H, COCH₂CO), 7.22-7.46 (m, 5H, ArH); ¹³C NMR (101 MHz, (CD₃)₂CO) δ (observed signals) 30.8, 38.4, 44.8, 52.7, 60.0, 105.1, 129.0, 129.3, 130.4, 143.4, 171.9; IR (KBr) 2948, 1736, 1618, 1595, 1541, 1236, 1150 cm⁻¹; MS (CI) m/z (rel. intensity) 247 (M + H, 100), 215 (9); Anal. Calcd.

for C₁₄H₂₄O₄: C, 68.28; H, 5.73. Found: C, 68.09; H, 5.84.

4.2.3 trans,trans-Farnesal (51)⁵⁶,⁵⁷

To a solution of commercially available trans,trans-farnesol (Aldrich, 3.40 mL, 13.4 mmol) in dichloromethane (50 mL) was added pyridinium dichromate (6.64 g, 14.6 mmol) and sodium bicarbonate (1.71 g, 16.9 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 16 h. The dark brown reaction mixture was then filtered through a pad of celite with dichloromethane (100 mL). The filtrate was concentrated in vacuo to afford the crude product that was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the title compound 51 (2.88 g, 96%) as a colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.58 (s, 3H, CH₃), 1.60 (s, 3H, CH₃), 1.67 (s, 3H, CH₃), 1.97 (m, 2H, CH₂), 2.04 (m, 2H, CH₂), 2.17 (s, 3H, CH₃), 2.23 (m, 4H, 2 x CH₂), 5.06 (m, 2H, CH₂CH), 5.87 (d, J = 8.1 Hz, 1H, CHCHO), 9.98 (d, J = 8.1 Hz, 1H, CHO); ¹³C NMR (101 MHz, CDCl₃) δ 16.2, 17.7, 17.8, 25.79, 25.83, 26.7, 39.8, 40.7, 122.6, 124.2, 127.5, 131.6, 136.7, 164.0, 191.4; IR
(ef) 2966, 2917, 1673, 1634, 1444, 1382, 1194, 1120 cm⁻¹; MS (Cl) m/z (rel. intensity) 221 (M + H, 79), 203 (100), 177 (21), 163 (12), 137 (33), 123 (14), 109 (18).

4.2.4 Cyclohexylideneacetaldehyde (111)

To a solution of vinylmagnesium bromide (1M in hexanes, 45.0 mL, 45.0 mmol) was added a solution of freshly distilled cyclohexanone (3.1 mL, 30 mmol) in tetrahydrofuran (12 mL) dropwise at 0 °C. The reaction mixture was then heated at reflux for 16 h. After cooling, the reaction was quenched with a saturated aqueous solution of ammonium chloride (45 mL) and extracted with ether (3 x 80 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The reaction product (3.58 g) was then dissolved in dichloromethane (100 mL) and pyridinium chlorochromate (12.3 g, 56.8 mmol) was added at room temperature. The resultant mixture was stirred for 16 h and then ether (200 mL) was added. The organic layer was decanted and washed with an aqueous solution of sodium hydroxide (5% w/v, 2 x 100 mL), hydrochloric acid (0.5M, 2 x 100 mL), a saturated aqueous solution of sodium bicarbonate (30 mL), brine (50 ml) and dried over anhydrous sodium sulfate. The organic layer was concentrated in vacuo and the crude product was purified by flash chromatography using ether/hexanes (10%) as the eluant to afford the title compound 111 (1.45 g, 39%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.60-1.77 (m, 6H, 3 x CH₂), 2.29 (m, 2H, CH₂), 2.71 (m, 2H, CH₂), 5.82 (d, J = 8.3 Hz, 1H, CHCHO), 10.02 (d, J = 8.3 Hz, 1H, CHO); ¹³C NMR (101 MHz,
4.2.5 2,2,7-Trimethyl-5-oxo-5,6,7,8-tetrahydro-2H-chromene-6-carboxylic acid ethyl ester (112a)

To a mixture of 1,2-ethylenediamine (9.0 µL, 0.13 mmol) and acetic acid (16 µL, 0.28 mmol) in dry methanol (5 mL) was added the ester 104 (545 mg, 2.75 mmol) at room temperature. After 30 min, commercially available senecialdehyde 101 (Aldrich, 240 µL, 2.49 mmol) was added. After 3 h, the solvent was removed in vacuo and the yellow residue was dissolved in ethyl acetate (10 mL) and washed with water (2 x 5 mL), a saturated aqueous solution of sodium bicarbonate (2 x 5 mL) and then brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 112a (493 mg, 75%) as a pale yellow oil.

\[ \text{1H NMR} \ (400 \text{ MHz, } \text{C}_6\text{D}_6) \ \delta 0.68 \ (d, \ J = 6.7 \text{ Hz, } \text{3H}, \text{CH}_2\text{CH}), 0.91 \ (t, \ J = 7.7 \text{ Hz, } \text{3H}, \text{CH}_3\text{CH}_2), 1.13 \ (s, \ 3\text{H}, \text{CH}_3), 1.16 \ (s, \ 3\text{H}, \text{CH}_3), 1.78 \ (dd, \ J = 16.3, 9.9 \text{ Hz, } \text{1H}, \text{CH}_3\text{CHCHHH}), 2.29 \ (m, \ 1\text{H}, \text{CH}_3\text{CH}), 2.42 \ (dd, J = 16.3, 4.4 \text{ Hz, } \text{1H}, \text{CH}_3\text{CHCHHH}), 2.92 \ (d, J = 8.1 \text{ Hz, } \text{1H}, \text{CHCO}_2\text{Et}), 3.94 \ (m, \ 2\text{H}, \text{CH}_3\text{CH}_2), 4.87 \ (d, J = 9.9 \text{ Hz, } \text{1H}, \text{CH=CH}), 6.77 \ (d, J = 9.9 \text{ Hz, } \text{1H}, \text{CH=CH}); \ \text{13C NMR} \ (101 \text{ MHz, } \text{C}_6\text{D}_6) \ \delta 14.2, 19.4, 27.8, 28.4, 31.7, 42.7, 53.0, 60.9, 80.0, 111.4, 116.3, 123.8, 164.9, 170.1, 191.8; \ \text{IR (ef)} \ 2976, 1739, 1654, 1593, 1416, 1323, 1254, 1152 \text{ cm}^{-1}; \ \text{MS} \ (\text{Cl}) \ m/z \ (\text{rel. intensity}) 265 \ (\text{M + H}, 100);

\text{Anal. Calcd. for } C_{15}H_{20}O_3: \text{C}, 68.16; \text{H}, 7.63. \text{Found: C}, 67.82; \text{H}, 7.82.
4.2.6  (+)-2,7-Dimethyl-2-(4-methyl-3-pentenyl)-5-oxo-5,6,7,8-tetrahydro-2H-chromene-6-carboxylic acid ethyl ester (113a)

To a mixture of 1,2-ethylenediamine (9.0 µL, 0.13 mmol) and acetic acid (16 µL, 0.28 mmol) in dry methanol (5 mL) was added the ester 104 (545 mg, 2.75 mmol) at room temperature. After 30 min, commercially available citral 50 (Aldrich, 3,7-dimethyl-2,6-octadienal [E:Z = ~ 2:1], 430 µL, 2.51 mmol) was added. After 3 h, the solvent was removed \textit{in vacuo} and the yellow residue was dissolved in ethyl acetate (10 mL) and washed with water (2 x 5 mL), a saturated aqueous solution of sodium bicarbonate (2 x 5 mL) and then brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated \textit{in vacuo} and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 113a (743 mg, 90%) as a pale yellow oil. \textbf{1H NMR} (400 MHz, C₆D₆) \( \delta \) 0.77 (d, \( J = 6.4 \) Hz, 3H, CH₃CH), 1.07 (t, \( J = 7.1 \) Hz, 3H, CH₂CH₂), 1.15 (s, 3H, CH₃), 1.59 (s, 3H, CH₃), 1.63 (m, 2H, CH₂CH₂), 1.71 (s, 3H, CH₃), 2.10 (m, 4H, CH₃CHCH₂ and CH₂CH₂), 2.43 (m, 1H, CH₃CH), 2.94 (d, \( J = 11.7 \) Hz, 1H, CHCO₂Et), 4.15 (m, 2H, CH₃CH₂CH₂), 4.83 (d, \( J = 10.1 \) Hz, 1H, CH=CH), 5.17 (m, 1H, (CH₃)₂C=CH), 6.78 (d, \( J = 10.1 \) Hz, 1H, CH=CH); \textbf{13C NMR} (101 MHz, C₆D₆) \( \delta \) (mixture of isomers - major signals reported) 14.3, 17.6, 19.5, 19.6, 22.8, 23.1, 25.8, 27.2, 27.4, 30.9, 31.0, 35.2, 35.3, 41.9, 60.6, 60.7, 82.46, 82.51, 109.6, 109.7, 117.0, 117.1, 121.8, 124.25, 124.28, 131.8, 169.9, 170.0, 170.10, 170.14, 188.9, 189.0; \textbf{IR} (ef) 2968, 1739, 1655, 1597, 1415, 1326,
1255, 1158 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 333 (M + H, 100); Anal. Calcd. for C\(_{20}\)H\(_{28}\)O\(_4\): C, 72.26; H, 8.49. Found: C, 72.36; H, 8.55.

4.2.7 (±)-2,7-Dimethyl-2-(4,8-dimethyl-3\(E\),7-nonadienyl)-5-oxo-5,6,7,8-tetrahydro-2\(H\)-chromene-6-carboxylic acid ethyl ester (114a)

To a mixture of 1,2-ethylenediamine (20 \(\mu\)L, 0.30 mmol) and acetic acid (34 \(\mu\)L, 0.59 mmol) in dry methanol (10 mL) was added the ester 104 (1.16 g, 5.83 mmol) at room temperature. After 30 min, \(trans,trans\)-farnesal 51 (1.17 g, 5.30 mmol) was added. After 3 h, the solvent was removed \textit{in vacuo} and the yellow residue was dissolved in ethyl acetate (20 mL) and washed with water (2 x 10 mL), a saturated aqueous solution of sodium bicarbonate (2 x 10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated \textit{in vacuo} and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 114a (1.85 g, 87%) as a pale yellow oil. \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.72 (d, \(J = 6.4\) Hz, 3H, \(CH_3CH\)), 1.02 (t, \(J = 7.1\) Hz, 3H, \(CH_3CH_2\)), 1.10 (s, 3H, \(CH_3\)), 1.57 (apparent s, 6H, 2 x \(CH_3\)), 1.63 (m, 2H, \(CH_2CH_2\)), 1.67 (s, 3H, \(CH_3\)), 2.02 (m, 2H, \(CH_3CHCH_2\)), 2.08 (m, 4H, allylic-\(CH_2\)), 2.17 (m, 2H, allylic-\(CH_2\)), 2.38 (m, 1H, \(CH_3CH\)), 2.88 (d, \(J = 11.6\) Hz, 1H, \(CHCO_2Et\)), 4.09 (m, 2H, \(CH_3CH_2\)), 4.80 (d, \(J = 10.1\) Hz, 1H, \(CH=CH\)), 5.20 (m, 2H, \(CH_3C=CH\) and \((CH_3)_2C=CH\)), 6.73 (d, \(J = 10.1\) Hz, 1H, \(CH=CH\)); \(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\) (mixture of isomers - major signals reported) 14.3, 16.0, 17.7, 19.5, 22.7, 23.0, 27.1, 30.8, 35.2, 40.1, 60.6, 60.8, 82.4, 82.5, 109.6, 109.7, 117.0,
117.1, 124.07, 124.11, 124.7, 124.8, 131.31, 131.34, 135.7, 169.8, 170.0, 170.08, 170.13, 188.9, 190.0; IR (ef) 2967, 1739, 1655, 1597, 1415, 1326, 1254, 1157 cm\(^{-1}\); MS (CI) 
\(m/z\) (rel. intensity) 401 (M + H, 100); FAB HRMS Calcd. for \(C_{25}H_{36}O_4\) \(m/z\): 400.2614. Found \(m/z\): 400.2611.

4.2.8 7-Methyl-5-oxo-2-spirocyclohexyl-5,6,7,8-tetrahydro-2H-chromene-6-carboxylic acid ethyl ester (115)

![Chemical Structure](image)

To a mixture of 1,2-ethylenediamine (9.0 \(\mu\)L, 0.13 mmol) and acetic acid (16 \(\mu\)L, 0.28 mmol) in dry methanol (5 mL) was added the ester 104 (545 mg, 2.75 mmol) at room temperature. After 30 min, cyclohexylideneacetaldehyde 111 (310.2 mg, 2.50 mmol) was added. After 3 h, the solvent was removed in vacuo and the yellow residue was dissolved in ethyl acetate (10 mL) and washed with water (2 x 5 mL), a saturated aqueous solution of sodium bicarbonate (2 x 5 mL) and then brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 115 (483 mg, 63%) as a pale yellow oil. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.09 (d, \(J = 6.4\) Hz, 3H, \(CH_3CH\)), 1.22-1.74 (m, 8H, cyclohexyl-\(CH_2\)), 1.30 (t, \(J = 7.0\) Hz, 3H, \(CH_3CH_2\)), 1.79-1.97 (m, 2H, cyclohexyl-\(CH_2\)), 2.13 (dd, \(J = 17.4, 11.0\) Hz, 1H, \(CH_3CHCHH\)), 2.46-2.61 (m, 2H, \(CH_3CHCHH\)), 3.20 (d, \(J = 8.2\) Hz, 1H, \(CHCO_2Et\)), 4.24 (m, 2H, \(CH_3CH_2\)), 5.28 (d, \(J = 10.1\) Hz, 1H, \(CH=CH\)), 6.38 (d, \(J = 10.1\) Hz, 1H, \(CH=CH\)); \(^13C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) (mixture of isomers - major signals reported) 14.3, 18.5, 19.8, 20.4, 20.6, 21.0, 25.0, 30.2, 31.6, 35.6, 36.3, 36.8, 40.9,
42.8, 50.5, 53.1, 61.4, 81.6, 111.3, 115.8, 116.3, 123.5, 123.9, 166.2, 169.3, 170.5, 193.4, 194.6; IR (ef) 2934, 1738, 1660, 1596, 1414, 1322, 1238, 1151 cm⁻¹; MS (Cl) m/z (rel. intensity) 305 (M + H, 100); FAB HRMS Calcd. for C₁₈H₂₄O₄ m/z: 304.1675. Found m/z: 304.1670.

4.2.9 2,2-Dimethyl-5-oxo-7-phenyl-5,6,7,8-tetrahydro-2H-chromene-6-carboxylic acid methyl ester (112b)

\[
\begin{array}{c}
\text{MeO} \\
/ \backslash \\
/ \backslash \\
\text{Ph} \\
/ \backslash \\
/ \backslash \\
\text{Me} \\
\end{array}
\]

112b

To a mixture of 1,2-ethylenediamine (35 µL, 0.52 mmol) and acetic acid (59 µL, 1.0 mmol) in dry methanol (20 mL) was added the ester 105 (2.46 g, 10.0 mmol) at room temperature. After 30 min, senecialdehyde 101 (900 µL, 9.33 mmol) was added. After 16 h, the solvent was removed in vacuo and the yellow residue was dissolved in ethyl acetate (40 mL) and washed with water (2 x 20 mL), a saturated aqueous solution of sodium bicarbonate (2 x 20 mL) and then brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 112b (2.07 g, 72%) as a pale yellow oil. \(^1\)H NMR (400 MHz, C₆D₆) δ 1.39 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 2.67 (m, 2H, PhCH₂), 3.57 (s, 3H, CO₂CH₃), 3.70 (m, 2H, PhCH and CHCO₂Me), 5.29 (d, J = 10.1 Hz, 1H, CH=CH), 6.41 (d, J = 10.1 Hz, 1H, CH=CH), 7.24-7.31 (m, 5H, ArH); \(^1\)³C NMR (101 MHz, C₆D₆) δ 28.5, 28.9, 35.8, 42.0, 52.1, 59.2, 80.8, 115.6, 123.5, 127.2, 127.6, 128.9, 140.7, 170.1, 170.4, 189.0, 192.6; IR (ef) 2975, 1744, 1655, 1592, 1415, 1318, 1259, 1138; MS (Cl) m/z (rel.
intensity) 313 (M + H, 100); FAB HRMS Calcd. for C_{19}H_{20}O_{4} m/z: 312.1362. Observed m/z: 312.1365.

4.2.10 (±)-2-Methyl-2-(4-methy1-3-pentenyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-2H-chromene-6-carboxylic acid ethyl ester (113b)

To a mixture of 1,2-ethylenediamine (17 μL, 0.25 mmol) and acetic acid (30 μL, 0.52 mmol) in dry methanol (20 mL) was added the ester 105 (1.23 g, 5.00 mmol) at room temperature. After 30 min, citral 50 (790 μL, 4.61 mmol) was added. After 16 h, the solvent was removed in vacuo and the yellow residue was dissolved in ether (30 mL) and washed with water (2 x 15 mL), a saturated aqueous solution of sodium bicarbonate (2 x 15 mL) and then brine (15 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 113b (1.15 g, 65%) as a pale yellow oil. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 1.36 (s, 3H, CH$_3$), 1.58-1.80 (m, 2H, CH$_2$CH$_2$), 1.60 (s, 3H, CH$_3$), 1.67 (s, 3H, CH$_3$), 2.04 (m, 2H, CH$_2$CH$_2$), 2.67 (m, 2H, PhCHCH$_2$), 3.57 (s, 3H, CH$_3$O), 3.69 (m, 2H, PhCH and CHCO$_2$Me), 5.08 (m, 1H, (CH$_3$)$_2$C=CH), 5.25 (d, J = 10.1 Hz, 1H, CH=CH), 6.46 (d, J = 10.1 Hz, 1H, CH=CH), 7.25-7.31 (m, 5H, ArH); $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ (mixture of isomers - major signals reported) 17.8, 22.5, 22.9, 25.8, 27.6, 27.8, 35.7, 35.8, 41.86, 41.91, 42.1, 52.2, 59.1, 59.2, 83.4, 83.5, 116.2, 116.3, 122.3, 123.6, 127.3, 127.6, 129.0, 132.2, 140.7, 170.2, 170.7, 170.8, 188.9, 189.0, 192.5; IR (ef) 2968, 1746, 1656, 1596,
1415, 1349, 1260, 1158 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 381 (M + H, 100), 323 (23);

**Anal.** Calcd. for C\(_{24}\)H\(_{28}\)O\(_4\): C, 75.76; H, 7.42. Found: C, 75.43; H, 7.70.

### 4.2.11 (±)-2-Methyl-2-(4,8-dimethyl-3\(E\),7-nonadienyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-2\(H\)-chromene-6-carboxylic acid methyl ester (114b)

![Structure of 114b](image)

To a mixture of 1,2-ethylenediamine (17 \(\mu\)L, 0.25 mmol) and acetic acid (30 \(\mu\)L, 0.52 mmol) in dry methanol (20 mL) was added the ester 105 (1.23 g, 5.00 mmol) at room temperature. After 30 min, \textit{trans,trans}-farnesal 51 (1.01 g, 4.60 mmol) was added. After 16 h, the solvent was removed \textit{in vacuo} and the yellow residue was dissolved in ether (60 mL) and washed with water (2 x 30 mL), a saturated aqueous solution of sodium bicarbonate (2 x 30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated \textit{in vacuo} and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 114b (1.40 g, 68%) as a pale yellow oil. 

**\(^1^H\) NMR** (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 1.36 (s, 3H, CH\(_3\)), 1.53-1.85 (m, 2H, CH\(_2\)CH\(_2\)), 1.59 (s, 6H, 2 x CH\(_3\)), 1.68 (s, 3H, CH\(_3\)), 2.01 (m, 6H, allylic-CH\(_2\)), 2.67 (m, 2H, PhCHCH\(_2\)), 3.57 (s, 3H, CH\(_3\)O), 3.69 (m, 2H, PhCH and CHCO\(_2\)Me), 5.08 (m, 2H, CH\(_3\)C=CH and (CH\(_3\))\(_2\)C=CH), 5.25 (d, \(J = 10.1\) Hz, 1H, CH=CH), 6.46 (d, \(J = 10.1\) Hz, 1H, CH=CH), 7.24-7.32 (m, 5H, ArH); **\(^{13}\)C NMR** (101 MHz, C\(_6\)D\(_6\)) \(\delta\) (mixture of isomers - major signals reported) 16.1, 17.8, 22.3, 22.7, 25.8, 26.8, 27.5, 27.8, 35.7, 35.9, 39.8, 41.9, 52.2, 59.1, 59.2, 83.46, 83.50, 109.4, 109.5, 116.2, 116.3, 122.4, 123.5, 124.4, 127.2, 127.6, 129.0, 131.6, 135.9, 140.7, 170.2, 170.6, 170.8, 111
5-Hydroxy-2,2,7-trimethyl-2H-chromene-6-carboxylic acid ethyl ester (121a)

To a solution of the ester 112a (460 mg, 1.74 mmol) in benzene (10 mL) was added DDQ (595 mg, 2.61 mmol) at room temperature. The dark green reaction mixture was then heated at reflux for 4 h. The resultant dark red solution was cooled to room temperature and filtered through a pad of basic alumina with ethyl acetate (100 mL). Upon removal of the solvent in vacuo, the residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 121a (196 mg, 43%) as a white solid. M.p. 109-110 °C, ethyl acetate/hexanes; \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.83 (t, \(J = 7.0\) Hz, 3H, CH\(_3\)CH\(_2\)), 1.25 (s, 6H, 2 x CH\(_3\)), 2.30 (s, 3H, CH\(_3\)), 3.88 (q, \(J = 7.0\) Hz, 2H, CH\(_3\)CH\(_2\)), 5.18 (d, \(J = 10.0\) Hz, 1H, CH=CH), 6.35 (s, 1H, ArH), 7.04 (d, \(J = 10.0\) Hz, 1H, CH=CH), 12.81 (s, 1H, OH); \(^1^3\)C NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\) 13.9, 24.6, 28.2, 61.0, 77.2, 105.7, 108.0, 112.3, 117.1, 127.4, 143.0, 158.1, 160.9, 172.3; IR (KBr) 3431, 2977, 1650, 1561, 1381, 1127 cm\(^{-1}\); MS (CI) \(m/z\) (rel. intensity) 263 (M + H, 100); Anal. Calcd. for C\(_{15}\)H\(_{18}\)O\(_4\): C, 68.68; H, 6.92. Found: C, 68.46; H, 7.08.
4.2.13 (±)-5-Hydroxy-2,7-dimethyl-2-(4-methyl-3-pentenyl)-2H-chromene-6-carboxylic acid ethyl ester (122a)

To a solution of the ester 113a (120 mg, 0.360 mmol) in benzene (3 mL) was added DDQ (123 mg, 0.540 mmol) at room temperature. The reaction mixture was then heated at reflux for 8 h. On cooling, the resultant dark red solution was filtered through a pad of basic alumina with ethyl acetate (30 mL). The solvent was removed in vacuo and the residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the title compound 122a (18 mg, 15%) as a white solid. M.p. 67-68 °C, ethyl acetate/hexanes; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.38 (s, 3H, CH$_3$), 1.40 (t, $J$ = 7.1 Hz, 3H, CH$_3$CH$_2$), 1.53-1.80 (m, 2H, CH$_2$CH$_2$), 1.56 (s, 3H, CH$_3$), 1.65 (s, 3H, CH$_3$), 2.08 (m, 2H, CH$_2$CH$_2$), 2.47 (s, 3H, CH$_3$), 4.38 (q, $J$ = 7.1 Hz, 2H, CH$_3$CH$_2$O), 5.08 (m, 1H, (CH$_3$)$_2$C=CH), 5.46 (d, $J$ = 10.1 Hz, 1H, CH=CH), 6.18 (s, 1H, ArH), 6.73 (d, $J$ = 10.1 Hz, 1H, CH=CH), 12.07 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.4, 17.7, 22.8, 24.7, 25.8, 27.1, 41.7, 61.3, 79.8, 105.2, 107.2, 111.8, 117.0, 124.1, 126.4, 131.9, 142.9, 157.9, 159.9, 172.1; IR (KBr) 3402, 2977, 1649, 1568, 1268, 1173 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 331 (M + H, 100), 285 (10), 247 (10); Anal. Calcd. for C$_{20}$H$_{26}$O$_4$: C, 72.70; H, 7.93. Found: C, 72.56; H, 8.00.
4.2.14 (±)-5-Hydroxy-2,7-dimethyl-2-(4,8-dimethyl-3E,7-nonadienyl)-2H-chromene-6-carboxylic acid ethyl ester (123a)

![Chemical Structure](image)

To a solution of the ester 114a (580 mg, 1.46 mmol) in benzene (16 mL) was added DDQ (497 mg, 2.20 mmol) at room temperature. The reaction mixture was then heated at reflux for 16 h. On cooling, the resultant mixture was filtered through a pad of basic alumina with ethyl acetate (160 mL). The solvent was removed in vacuo and the dark red residue was purified by flash chromatography using ethyl acetate/hexanes (2%) as the eluant to afford the title compound 123a (63 mg, 11%) as a yellow oil. **'H NMR** (400 MHz, CDCl₃) δ 1.39 (s, 3H, CH₃), 1.40 (t, J = 7.1 Hz, 3H, CH₃CH₂), 1.56 (s, 3H, CH₃), 1.59 (s, 3H, CH₃), 1.67 (s, 3H, CH₃), 1.65-1.75 (m, 2H, CH₂CH₂), 1.95 (m, 2H, allylic-CH₂), 2.03 (m, 2H, allylic-CH₂), 2.09 (m, 2H, allylic-CH₂), 2.47 (s, 3H, CH₃), 4.38 (q, J = 7.1 Hz, 2H, CH₂CHO), 5.09 (m, 2H, (CH₃)₂C=CH and (CH₃)C=CH), 5.47 (d, J = 10.1 Hz, 1H, CH=CH), 6.18 (s, 1H, ArH), 6.73 (d, J = 10.1 Hz, 1H, CH=CH), 12.07 (broad s, 1H, OH); **'C NMR** (101 MHz, CDCl₃) δ 14.4, 16.1, 17.8, 22.7, 24.7, 25.8, 26.8, 27.1, 39.8, 41.7, 61.3, 79.8, 105.2, 107.2, 111.8, 117.0, 123.9, 124.5, 126.4, 131.5, 135.6, 142.9, 157.9, 159.9, 172.1; **IR** (ef) 3316, 2971, 1650, 1566, 1453, 1377, 1270, 1174 cm⁻¹; **MS** (CI) m/z 399 (M + H, 100), 353 (38), 249 (14), 209 (5); **Anal.** Calcd. for C₂₅H₃₄O₄: C, 75.34; H, 8.60. Found: C, 75.16; H, 8.61.
4.2.15 5-Hydroxy-7-methyl-2-spirocyclohexyl-2H-chromene-6-carboxylic acid ethyl ester (124)

![Chemical structure of 124](image)

To a solution of the ester 115 (338 mg, 1.11 mmol) in benzene (6 mL) was added DDQ (379 mg, 1.67 mmol) at room temperature. The resultant dark green reaction mixture was then heated at reflux for 16 h. The resultant dark red solution was then cooled to room temperature and filtered through a pad of basic alumina with ethyl acetate (60 mL). Upon removal of the solvent *in vacuo*, the residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 124 (118 mg, 35%) as a white solid. **M.p.** 100-102 °C, ethyl acetate/hexanes;  

**^1H NMR** (400 MHz, CDCl₃) δ 1.40 (t, J = 7.0 Hz, 3H, CH₃CH₂), 1.53 (m, 6H, cyclohexyl-CH₂), 1.72 (m, 2H, cyclohexyl-CH₂), 1.91 (m, 2H, cyclohexyl-CH₂), 2.48 (s, 3H, CH₃), 4.39 (q, J = 7.0 Hz, 2H, CH₃CH₂O), 5.56 (d, J = 10.1 Hz, 1H, CH=CH), 6.24 (s, 1H, ArH), 7.04 (d, J = 10.1 Hz, 1H, CH=CH), 12.81 (s, 1H, OH);  

**^13C NMR** (101 MHz, CDCl₃) δ 14.3, 21.4, 24.6, 25.4, 36.4, 61.3, 77.9, 105.3, 108.2, 112.1, 116.9, 127.1, 142.8, 157.5, 159.9, 172.0;  

**IR** (KBr) 3422, 29723, 1641, 1618, 1564, 1396, 1257, 1167 cm⁻¹;  

**MS** (CI) m/z (rel. intensity) 303 (M + H, 100);  

**Anal.** Calcd. for C₁₈H₂₂O₄: C, 71.50; H, 7.33. Found: C, 71.70; H, 7.53.
4.2.16 5-Hydroxy-2,2-dimethyl-7-phenyl-2H-chromene-6-carboxylic acid methyl ester (121b)

To a solution of the ester 112b (1.93 g, 6.18 mmol) in benzene (60 mL) was added DDQ (2.11 g, 9.28 mmol) at room temperature. The reaction mixture was then heated at reflux for 16 h. The reaction was cooled to room temperature and filtered through a pad of basic alumina with ethyl acetate (400 mL). The solvent was removed in vacuo and the resultant dark red residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the title compound 121b (675 mg, 35%) as a white solid. M.p. 83-85 °C, ethyl acetate/hexanes; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.46 (s, 6H, 2 x CH$_3$), 3.44 (s, 3H, CH$_3$O), 5.59 (d, $J = 9.9$ Hz, 1H, CH=CH), 6.27 (s, 1H, ArH), 6.75 (d, $J = 9.9$ Hz, 1H, CH=CH), 7.20-7.31 (m, 5H, ArH), 11.43 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 28.5, 51.5, 77.5, 104.8, 108.4, 112.1, 116.3, 126.9, 127.6, 128.1, 128.4, 143.0, 146.1, 157.2, 158.7, 171.7; IR (KBr) 3316, 2985, 1655, 1617, 1558, 1442, 1319, 1250, 1119 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 311 (M + H, 100), 295 (7), 279 (8), 263 (13); Anal. Calcd. for C$_{19}$H$_{18}$O$_4$: C, 73.53; H, 5.85. Found: C, 73.43; H, 5.92.
To a solution of the ester 113b (1.02 g, 2.07 mmol) in benzene (20 mL) was added DDQ (919 mg, 4.02 mmol) at room temperature. The reaction mixture was then heated at reflux for 16 h. The reaction was cooled to room temperature and filtered through a pad of basic alumina with ethyl acetate (200 mL). The solvent was removed *in vacuo* and the resultant dark red residue was purified by flash chromatography using ethyl acetate/hexanes (8%) as the eluant to afford the title compound 122b (101 mg, 10%) as a white solid. **M.p.** 89-91 °C, ethyl acetate/hexanes; **¹H NMR** (400 MHz, CDCl₃) δ 1.42 (s, 3H, CH₃), 1.57 (s, 3H, CH₃), 1.65 (s, 3H, CH₃), 1.65-1.76 (m, 2H, CH₂CH₂), 2.10 (m, 2H, CH₂CH₂), 3.44 (s, 3H, CH₃O), 5.09 (t, J = 7.1 Hz, 1H, (CH₃)₂C=CH), 5.54 (d, J = 10.1 Hz, 1H, CH=CH), 6.26 (s, 1H, ArH), 6.79 (d, J = 10.1 Hz, 1H, CH=CH), 7.20-7.31 (m, 5H, ArH), 11.42 (s, 1H, OH); **¹³C NMR** (101 MHz, CDCl₃) δ 17.8, 22.8, 25.8, 27.2, 41.7, 51.5, 80.0, 104.6, 108.2, 111.9, 116.8, 124.0, 126.9, 127.3, 127.6, 128.1, 132.0, 143.0, 146.1, 157.5, 158.7, 171.7; **IR** (KBr) 3320, 2969, 1656, 1615, 1558, 1439, 1323, 1271, 1115 cm⁻¹; **MS (Cl)** m/z (rel. intensity) 379 (M + H, 47), 347 (20), 295 (100), 263 (59); **Anal. Calcd.** for C₂₄H₂₆O₄: C, 76.17; H, 6.92. Found: C, 76.23; H, 7.06.
To a solution of the ester 114b (1.29 g, 2.87 mmol) in benzene (28 mL) was added DDQ (978 mg, 4.31 mmol) at room temperature. The dark green reaction mixture was then heated at reflux for 16 h. The resultant dark red solution was then cooled to room temperature and filtered through a pad of basic alumina with ethyl acetate (250 mL). Upon removal of the solvent in vacuo, the residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 123b (74 mg, 6%) as a white solid. M.p. 72-74 °C, ethyl acetate/hexanes; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.42 (s, 3H, CH$_3$), 1.57 (s, 3H, CH$_3$), 1.58 (s, 3H, CH$_3$), 1.66 (s, 3H, CH$_3$), 1.65-1.76 (m, 2H, CH$_2$CH$_2$), 1.95 (m, 2H, allylic-CH$_2$), 2.04 (m, 2H, allylic-CH$_2$), 2.12 (m, 2H, allylic-CH$_2$), 3.44 (s, 3H, CH$_3$O), 5.09 (m, 2H, CH$_3$C=CH and (CH$_3$)$_2$C=CH), 5.54 (d, $J$ = 10.2 Hz, 1H, CH=CH), 6.26 (s, 1H, ArH), 6.79 (d, $J$ = 10.2 Hz, 1H, CH=CH), 7.21-7.32 (m, 5H, ArH), 10.09 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 16.1, 17.8, 22.7, 25.8, 26.8, 27.2, 39.8, 41.7, 51.5, 80.0, 104.6, 108.2, 111.9, 116.8, 123.9, 124.5, 126.9, 127.3, 127.6, 128.1, 131.5, 135.7, 143.0, 146.1, 157.5, 158.7, 171.7; IR (KBr) 2923, 1656, 1615, 1580, 1438, 1323, 1270, 1196 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 447 (M + H, 100), 415 (71), 365 (5), 323 (11), 297 (89), 263 (35), 257 (43), 191 (8), 109 (7); Anal. Calcd. for C$_{29}$H$_{34}$O$_4$: C, 78.00; H, 7.67. Found: C, 77.95; H, 7.65.
4.2.19 5-Hydroxy-2,2,7-trimethyl-2H-chromene-6-carboxylic acid (127a)

To a solution of the ester 121a (22 mg, 0.080 mmol) in DMSO (0.4 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 170 μL, 0.85 mmol) at room temperature. The reaction mixture was then heated at 80 °C for 16 h. On cooling, the dark brown reaction mixture was diluted with water (1.5 mL) and the resultant solution was washed with ether (1 mL). The aqueous layer was then acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with dichloromethane (3 x 2 mL). The combined dichloromethane extracts were washed with water (2 x 1 mL) and brine (2 mL), dried over anhydrous sodium sulfate and then concentrated in vacuo. The crude product was purified by flash chromatography using methanol/dichloromethane (3%) as the eluant to afford the title compound 127a (18 mg, 89%) as a white solid. M.p. 154-155 °C, methanol/dichloromethane; $^1$H NMR (400 MHz, CDCl₃) δ 1.44 (s, 6H, 2 x CH₃), 2.52 (s, 3H, CH₃), 5.52 (d, J = 10.1 Hz, 1H, CH=CH) 6.23 (s, 1H, ArH), 6.68 (d, J = 10.1 Hz, 1H, CH=CH), 11.6 (broad s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl₃) δ 24.5, 28.5, 29.8, 77.6, 107.4, 112.4, 116.4, 125.7, 127.5, 144.5, 158.5, 160.7, 176.1; IR (KBr) 2969, 1638, 1617, 1457, 1275, 1123 cm⁻¹; MS (CI) m/z (rel. intensity) 235 (M + H, 79), 191 (M + H, - CO₂, 100); Anal. Calcd. for C₁₃H₁₄O₄: C, 66.66; H, 6.02. Found: C, 66.90; H, 6.03.
4.2.20 (±)-5-Hydroxy-2,7-dimethyl-2-(4-methyl-3-pentenyl)-2H-chromene-6-carboxylic acid (128a)

To a solution of the ester 122a (66 mg, 0.20 mmol) in DMSO (0.7 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 400 μL, 2.0 mmol) at room temperature. The reaction was then heated at 80 °C for 16 h. After cooling, water (1 mL) was added and the resultant solution was washed with ether (1.5 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 2 mL), brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (1%) as the eluant to afford the title compound 128a (35 mg, 57%) as a pale yellow solid. M.p. 108-110 °C, methanol/dichloromethane; \(^1\)H NMR (400 MHz, CDCl₃) δ 1.40 (s, 3H, CH₃), 1.57 (s, 3H, CH₃), 1.66 (s, 3H, CH₃), 1.59-1.82 (m, 2H, CH₂CH₂), 2.08 (m, 2H, CH₂CH₂), 5.08 (m, 1H, (CH₃)₂C=CH), 5.48 (d, J = 10.1 Hz, 1H, CH=CH), 6.23 (s, 1H, ArH), 6.73 (d, J = 10.1 Hz, 1H, CH=CH), 11.71 (broad s, 1H, OH); \(^1^3\)C NMR (101 MHz, CDCl₃) δ 17.8, 22.8, 24.6, 25.8, 27.3, 41.8, 80.2, 103.6, 107.2, 112.3, 116.8, 124.0, 126.4, 132.0, 144.5, 159.1, 160.8, 176.0; IR (KBr) 2969, 1619, 1456, 1269, 1177 cm\(^{-1}\); MS (MALDI-TOF) m/z 303 (M + H); Anal. Calcd. for C₁₈H₂₂O₄: C, 71.50; H, 7.33. Found: C, 70.15; H, 7.78.
4.2.21 (±)-Daurichromenic acid (1)

To a solution of the ester 123a (400 mg, 1.00 mmol) in DMSO (5 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 2.0 mL, 10 mmol) at room temperature. The reaction was then heated at 80 °C for 16 h. On cooling, water (2 mL) was added and the resultant solution was washed with ether (5 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (3%) as the eluant to afford the title compound 1 (252 mg, 68%) as a light brown syrup. 

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 1.41 (s, 3H, \(\text{CH}_3\)), 1.57 (s, 3H, \(\text{CH}_3\)), 1.59 (s, 3H, \(\text{CH}_3\)), 1.67 (s, 3H, \(\text{CH}_3\)), 1.66-1.77 (m, 2H, \(\text{CH}_2\text{CH}_2\)), 1.95 (m, 2H, allylic-\(\text{CH}_2\)), 1.97 (m, 2H, allylic-\(\text{CH}_2\)), 2.04-2.12 (m, 2H, allylic-\(\text{CH}_2\)), 2.54 (s, 3H, \(\text{CH}_3\)), 5.09 (m, 2H, \(\text{CH}_3\text{C}=\text{CH}\) and (\(\text{CH}_3\))\(_2\text{C}=\text{CH}\)), 5.48 (d, \(J = 10.1\) Hz, 1H, \(\text{CH}=\text{CH}\)), 6.24 (s, 1H, ArH), 6.74 (d, \(J = 10.1\) Hz, 1H, \(\text{CH}=\text{CH}\)), 11.66 (s, 1H, \(\text{OH}\)); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 16.1, 17.8, 22.7, 24.6, 25.8, 26.8, 27.3, 39.8, 41.8, 80.3, 103.7, 107.2, 112.4, 116.8, 123.9, 124.5, 126.5, 131.5, 135.7, 144.7, 159.2, 160.8, 176.4; \(\text{IR}\) (ef) 2966, 1621, 1455, 1268, 1177 cm\(^{-1}\)); \(\text{MS}\) (Cl) \(m/z\) 327 (M + H, - CO\(_2\), 100), 175 (9); \textit{Anal.} Calcd. for C\(_{23}\)H\(_{30}\)O\(_4\): C, 74.56; H, 8.16. Found: C, 74.30; H, 8.18.
4.2.22 5-Hydroxy-7-methyl-2-spirocyclexy1-2H-chromene-6-carboxylic acid (130)

To a solution of ester 124 (91 mg, 0.30 mmol) in DMSO (1.6 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 600 μL, 3.00 mmol) at room temperature. The reaction was heated at 80 °C for 16 h. On cooling, water (1 mL) was added and the resultant solution was washed with ether (2 x 3 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (3%) as the eluant to afford the title compound 130 (70 mg, 85%) as a white solid. M.p. 144 °C (dec.); $^1$H NMR (400 MHz, CDCl₃) δ 1.36 (m, 1H, cyclohexyl-CH₂), 1.54 (m, 5H, cyclohexyl-CH₂), 1.73 (m, 2H, cyclohexyl-CH₂), 1.92 (m, 2H, cyclohexyl-CH₂), 2.53 (s, 3H, CH₃), 5.57 (d, J = 10.1 Hz, 1H, CH=CH), 6.28 (s, 1H, ArH), 6.69 (d, J = 10.1 Hz, 1H, CH=CH), 11.68 (broad s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl₃) δ 21.4, 24.6, 25.4, 36.5, 78.4, 103.9, 108.2, 112.6, 116.8, 127.3, 144.5, 158.8, 160.8, 176.0; IR (ef) 3408 (broad), 2933, 1636, 1458, 1283, 1268, 1184, 1128 cm⁻¹; MS (Cl) m/z (rel. intensity) 275 (M + H, 7), 231 (M + H - CO₂, 100); Anal. Calcd. for C₁₆H₁₈O₄: C, 70.06; H, 6.61. Found: C, 70.32; H, 6.63.
4.2.23 5-Hydroxy-2,2-dimethyl-7-phenyl-2H-chromene-6-carboxylic acid (127b)

To a solution of the ester 121b (470 mg, 1.00 mmol) in DMSO (7 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 2.0 mL, 10 mmol) at room temperature. The reaction was then heated at 80 °C for 16 h. On cooling, water (3 mL) was added and the resultant solution was washed with ether (5 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant dark brown residue was purified by flash chromatography using methanol/dichloromethane (3%) as the eluant and the product was then recrystallized from dichloromethane/hexanes to afford the title compound 127b (346 mg, 74%) as a white solid. **M.p.** 182-184 °C, dichloromethane/hexanes; **1H NMR** (400 MHz, CDCl₃) δ 1.46 (s, 6H, 2 x CH₃), 5.59 (d, J = 10.1 Hz, 1H, CH=CH), 6.25 (s, 1H, ArH), 6.72 (d, J = 10.1 Hz, 1H, CH=CH), 7.26-7.36 (m, 5H, ArH), 11.46 (s, 1H, OH); **13C NMR** (101 MHz, CDCl₃) δ 28.6, 77.9, 102.9, 108.5, 112.7, 116.1, 127.6, 128.0, 128.3, 128.4, 142.0, 146.7, 158.1, 160.0, 174.3; **IR** (KBr) 2973, 1642, 1454, 1282, 1193, 1123 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 297 (M + H, 48), 279 (6), 253 (M + H, - CO₂, 100), 237 (10), 197 (12); **Anal.** Calcd. for C₁₈H₁₆O₄: C, 72.96; H, 5.44. Found: C, 72.64; H, 5.64.
4.2.24 (±)-5-Hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-7-phenyl-2H-chromene-6-carboxylic acid (128b)

To a solution of the ester 122b (430 mg, 1.00 mmol) in DMSO (5 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 2.0 mL, 10 mmol) at room temperature. The reaction mixture was then heated at 80 °C for 16 h. On cooling, water (2 mL) was added and the resultant solution was washed with ether (5 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant dark brown residue was purified by flash chromatography using methanol/dichloromethane (2%) as the eluant to afford the title compound 128b (256 mg, 54%) as a light brown syrup.

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.42 (s, 3H, CH$_3$), 1.57 (s, 3H, CH$_3$), 1.65 (s, 3H, CH$_3$), 1.65-1.77 (m, 2H, CH$_2$CH$_2$), 2.10 (m, 2H, CH$_2$CH$_2$), 5.09 (m, 1H, (CH$_3$)$_2$C=CH), 5.53 (d, J = 10.1 Hz, 1H, CH=CH), 6.24 (s, 1H, ArH), 6.76 (d, J = 10.1 Hz, 1H, CH=CH), 7.26-7.36 (m, 5H, ArH), ~ 9.5 (broad s, 1H, CO$_2$H), 11.46 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 17.7, 22.8, 25.8, 27.3, 41.8, 80.4, 102.8, 108.2, 112.6, 116.6, 123.9, 127.2, 127.4, 127.9, 128.3, 132.1, 142.2, 147.0, 158.5, 159.9, 175.0; IR (ef) 3579 (broad), 2970, 1645, 1613, 1445, 1272, 1186, 1112 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 321 (M + H, - CO$_2$, 100); Anal. Calcd. for C$_{23}$H$_{24}$O$_4$: C, 75.80; H, 6.64. Found: C, 75.47; H, 6.83.
4.2.25 (±)-5-Hydroxy-2-methyl-2-(4,8-dimethyl-3E,7-nonadienyl)-7-phenyl-2H-chromene-6-carboxylic acid (129)

\[
\text{HO} - \text{CH}_2 - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{C}_2 \text{H}_5 - \text{COOH}
\]

To a solution of the ester 123b (175 mg, 0.393 mmol) in DMSO (2 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 0.79 mL, 4.0 mmol) at room temperature. The reaction mixture was then heated at 80 °C for 16 h. On cooling, water (2 mL) was added and the resultant solution was washed with ether (2 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 2 mL), brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant dark brown residue was then purified by flash chromatography using methanol/dichloromethane (4%) as the eluant to afford the title compound 129 (82 mg, 38%) as a brown syrup. ¹H NMR (400 MHz, CDCl₃) δ 1.41 (s, 3H, CH₃), 1.56 (s, 3H, CH₃), 1.58 (s, 3H, CH₃), 1.67 (s, 3H, CH₃), 1.67-1.76 (m, 2H, CH₂CH₂), 1.95 (m, 2H, allylic-CH₂), 2.03 (m, 2H, allylic-CH₂), 2.11 (m, 2H, allylic-CH₂), 5.09 (m, 2H, CH₃C=CH and (CH₃)₂C=CH), 5.52 (d, J = 10.1 Hz, 1H, CH=CH), 6.18 (s, 1H, ArH), 6.76 (d, J = 10.1 Hz, 1H, CH=CH), 7.19-7.23 (m, 5H, ArH), ~ 11.8 (broad s, 1H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 16.1, 17.8, 22.3, 22.7, 25.8, 26.8, 27.1, 39.8, 41.7, 79.8, 108.1, 111.8, 117.2, 123.9, 124.5, 126.9, 127.6, 128.4, 131.5, 135.6, 142.9, 146.6, 148.8, 152.7, 157.2, 159.2, 164.5, 175.1; IR (ef) 3424 (broad), 2968, 1650, 1613, 1444, 1269, 1190, 1110 cm⁻¹; MS (CI) m/z (rel. intensity) 389 (M + H - CO₂, 100), 256 (20), 239 (6); FAB HRMS Calcd. for C₂₈H₃₂O₄ - CO₂ m/z: 388.2402. Found m/z: 388.2408.
4.2.26 Ethyl 4-hydroxybut-2-enoate (137)

To a solution of fumaric acid monoethyl ester 138 (3.60 g, 25.0 mmol) in THF (13 mL) was added borane-methyl sulfide complex (10.1M, 2.5 mL, 25 mmol) at -18 °C. The resultant solution was allowed to warm to room temperature and was stirred for 22 h. The reaction mixture was then cooled to 0 °C and water (15 mL) and potassium carbonate (6.0 g) were added. The resultant mixture was extracted with ether (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using ether/hexanes (20 - 60%) as the eluant to afford the title compound 137 (1.34 g, 41%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.28 (t, J = 7.1 Hz, 3H, CH$_3$CH$_2$), 4.20 (q, J = 7.1 Hz, 2H, CH$_3$CH$_2$), 4.35 (m, 2H, CH$_2$OH), 6.09 (dt, J = 15.7, 2.1 Hz, 1H, CH=CH), 7.03 (dt, J = 15.7, 4.0 Hz, 1H, CH=CH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 14.4, 60.6, 62.0, 120.4, 146.9, 166.6; IR (ef) 3445 (broad), 2925, 1719, 1661, 1277, 1177, 1098; MS (MALDI-TOF) m/z 153 (M + Na); Anal. Calcd. for C$_6$H$_{10}$O$_3$: C, 55.37; H, 7.74. Found: C, 55.40; H, 7.81.

4.2.27 Ethyl (E)-4-acetoacetoxycrotonate (136)

To a solution of ethyl 4-hydroxybut-2-enoate 137 (700 mg, 5.38 mmol) in benzene (4 mL) was added diketene (415 μL, 5.38 mmol) and a drop of triethylamine at room temperature. The resultant solution was heated at reflux for 2.5 h and then
concentrated in vacuo. The crude product was purified by flash chromatography using ether/hexanes (25%) as the eluant to afford the title compound 136 (954 mg, 83%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.29 (t, $J = 7.1$ Hz, 3H, CH$_3$CH$_2$), 2.29 (s, 3H, CH$_3$CO), 3.53 (s, 2H, COCH$_2$CO), 4.21 (q, $J = 7.1$ Hz, 2H, CH$_3$CH$_2$), 4.81 (dd, $J = 4.7$, 1.9 Hz, 2H, OCH$_2$), 6.05 (dt, $J = 15.8$, 1.9 Hz, 1H, CH=CH), 6.92 (dt, $J = 15.8$, 4.7 Hz, 1H, CH=CH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.4, 30.4, 49.9, 60.8, 63.5, 123.0, 140.3, 165.8, 166.5, 200.1; IR (neat) 2982, 1747, 1720, 1666, 1277, 1181, 1150, 1034; MS (CI) $m/z$ (rel. intensity) 215 (M + H, 82), 169 (42), 131 (13), 115 (100); Anal. Calcd. for C$_{10}$H$_{14}$O$_5$: C, 56.07; H, 6.59. Found: C, 56.18; H, 6.79.

4.2.28 Ethyl (Z)-4-acetoacetoxycrotonate (139) and (±)-cis-3-Acetyl-4-ethoxy-carbonylmethyltetrahydrofuran-2-one (140)

To an ethanolic solution of sodium ethoxide [prepared from sodium (11.7 mg, 0.509 mmol) and dry ethanol (2 mL)] was added ethyl (E)-4-acetoacetoxycrotonate 136 (100 mg, 0.467 mmol) and the resultant mixture was stirred for 1.5 h at room temperature. The reaction mixture was then neutralized with solid carbon dioxide and concentrated in vacuo. The residue was dissolved in water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using ethyl acetate/hexanes (10%) as the eluant to afford ethyl (Z)-4-acetoacetoxycrotonate 139.
(8 mg, 8%) and (±)-cis-3-acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one 140 (5 mg, 5%) as a colourless oil.

Characterization data for ethyl (Z)-4-acetoacetoxycrotonate 139: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.27\) (t, \(J = 7.1\) Hz, 3H, CH\(_3\)CH\(_2\)), 2.30 (s, 3H, CH\(_3\)CO), 3.19 (dd, \(J = 7.1, 1.7\) Hz, 2H, OCH\(_2\)), 3.55 (s, 2H, COCH\(_2\)CO), 4.15 (q, \(J = 7.1\) Hz, 2H, CH\(_3\)CH\(_2\)), 5.20 (td, \(J = 7.1, 6.4\) Hz, 1H, CH=CH), 7.17 (dt, \(J = 6.4, 1.7\) Hz, 1H, CH=CH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 14.3, 21.6, 30.5, 49.7, 61.1, 106.9, 135.9, 163.9, 170.9, 199.5;\) IR (ef) 3400 (broad), 2986, 1734, 1627, 1324, 1226, 1145, 1088; MS (Cl) \(m/z\) (rel. intensity) 215 (M + H, 100), 131 (52); Anal. Calcd. for C\(_{10}\)H\(_{14}\)O\(_5\): C, 56.07; H, 6.59. Found: C, 56.05; H, 6.58.

Characterization data for (±)-cis-3-acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one 140: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.26\) (t, \(J = 7.1\) Hz, 3H, CH\(_3\)CH\(_2\)), 2.46 (s, 3H, CH\(_3\)CO), 2.51 (m, 2H, CH\(_2\)CO\(_2\)), 3.39 (m, 1H, CH\(_2\)CHCH\(_2\)), 3.56 (d, \(J = 8.1\) Hz, 1H, COCH\(_3\)), 3.99 (dd, \(J = 9.2, 7.5\) Hz, 1H, OCH\(_2\)), 4.14 (q, \(J = 7.1\) Hz, 2H, CH\(_3\)CH\(_2\)), 4.57 (dd, \(J = 9.2, 8.0\) Hz, 1H, OCH\(_2\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 14.3, 29.9, 33.6, 36.3, 58.3, 61.2, 71.4, 170.9, 171.8, 199.8;\) IR (ef) 3521 (broad), 2983, 1776, 1722, 1373, 1192, 1160, 1032; MS (Cl) \(m/z\) (rel. intensity) 215 (M + H, 100), 197 (8), 171 (27).

4.2.29 (±)-trans-3-Acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one (141)

To an ethanolic solution of sodium ethoxide [prepared from sodium (21.6 mg, 0.939 mmol) and dry ethanol (2 mL)] was added ethyl (E)-4-acetoacetoxycrotonate 136
(200 mg, 0.935 mmol) at 0 °C. The resultant solution was then heated at reflux for 1 day. Upon cooling, the reaction mixture was concentrated in vacuo and the resultant residue was dissolved in water (5 mL). The aqueous solution was then acidified to pH ~ 5 with hydrochloric acid (10% w/v) and was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using ethyl acetate/hexanes (20%) as the eluant to afford (±)-trans-3-acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one 141 (26 mg, 13%) as colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.28 (t, $J$ = 7.1 Hz, 3H, CH$_3$CH$_2$), 2.19 (s, 3H, CH$_3$CO), 2.39 (dd, $J$ = 17.0, 3.3 Hz, 1H, CH$_2$CO$_2$), 3.03 (dd, $J$ = 17.0, 10.6 Hz, 1H, CH$_2$CO$_2$), 3.60 (m, 1H, CH$_2$CHCH$_3$), 4.19 (m, 3H, OCH$_2$ and CH$_3$CH$_2$), 4.55 (apparent t, $J$ = 9.8 Hz, 1H, OCH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.55, 14.58, 38.3, 38.8, 59.8, 76.1, 104.6, 165.9, 170.2, 177.7; IR (ef) 3309 (broad), 2980, 1734, 1702, 1638, 1387, 1222, 1090; MS (Cl) m/z (rel. intensity) 215 (M + H, 100), 197 (15), 169 (16).

4.2.30 (±)-Ethyl 4-acetoacetoxy-3-pyrrolidinylbutanoate (142)

![Chemical Structure](image)

To a solution of ester 136 (100 mg, 0.467 mmol) in THF (1 mL) was added pyrrolidine (39 $\mu$L, 0.47 mmol) at 0 °C. After 10 min, acetic acid (27 $\mu$L, 0.47 mmol) was added dropwise and the resultant solution was stirred at room temperature for 19 h. The reaction mixture was then concentrated in vacuo and the residue was dissolved in ethyl acetate (4 mL), washed with hydrochloric acid (1M, 2 x 0.5 mL), a saturated
aqueous solution of sodium bicarbonate (2 x 0.5 mL), brine (1 mL), dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using methanol/dichloromethane (3%) as the eluant to afford the title compound 142 (42 mg, 32%) as colourless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.25 (t, $J = 7.1$ Hz, 3H, CH$_3$CH$_2$), 1.76 (m, 4H, 2 x CH$_2$CH$_2$N), 2.27 (s, 3H, CH$_3$CO), 2.50 (dd, $J = 15.5$, 7.5 Hz, 1H, CHHCO$_2$), 2.61 (dd, $J = 15.5$, 5.5 Hz, 1H, CHHCO$_2$), 2.63 (m, 4H, 2 x CH$_2$CH$_2$N), 3.19 (m, 1H, NCH), 3.48 (s, 2H, COCH$_2$CO), 4.14 (q, $J = 7.1$ Hz, 2H, CH$_3$CH$_2$), 4.21 (dd, $J = 11.5$, 5.3 Hz, 1H, OCHH), 4.35 (dd, $J = 11.5$, 4.8 Hz, 1H, OCHH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.3, 23.6, 30.3, 35.1, 50.2, 50.6, 58.0, 60.8, 65.8, 167.2, 172.0, 200.5; IR (ef) 2970, 2805, 1732, 1361, 1245, 1179, 1150, 1034; MS (Cl) $m/z$ (rel. intensity) 286 (M + H, 100), 202 (16), 184 (34).

4.2.31 Ethyl 3-methylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (145)$^{103}$

![145]

A mixture of ethyl 2-butynoate 146 (1.0 mL, 8.9 mmol) and dicyclopentadiene (1.8 mL, 13 mmol) was heated at reflux for 20 h. Upon cooling, the reaction mixture was purified by flash chromatography using ethyl acetate/hexanes (1%) as the eluant to afford the title compound 145 (0.98 g, 62%) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.29 (t, $J = 7.1$ Hz, 3H, CH$_3$CH$_2$), 1.95 (apparent td, $J = 6.4$, 1.5 Hz, 1H, CHH), 2.05 (apparent td, $J = 6.4$, 1.5 Hz, 1H, CHH), 2.22 (s, 3H, CH$_3$), 3.40 (m, 1H, CH), 3.88 (m, 1H, CH), 4.17 (m, 2H, CH$_3$CH$_2$), 6.73 (dd, $J = 5.0$, 3.0 Hz, CH=CH), 6.89 (dd, $J = 5.0$, 3.0 Hz, CH=CH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.5, 17.3, 51.2, 58.3, 59.8, 71.1,
138.5, 140.5, 144.2, 166.2, 169.6; IR (ef) 2975, 1703, 1636, 1567, 1415, 1254, 1153 cm⁻¹; MS (MALDI-TOF) m/z 178 (M).

4.3 Experimental Procedures and Characterization Data Concerning Chapter Three

4.3.1 2,4-Dihydroxy-6-methylbenzoic acid methyl ester (156)¹¹⁴

To a stirred suspension of sodium hydride (620 mg, 25.8 mmol; prewashed with hexanes) in THF (10 mL) at 0 °C was added methyl acetoacetate (1.9 mL, 18 mmol). The resultant mixture was then cooled to -78 °C and a solution of n-butyllithium (2.5M in hexanes, 6.60 mL, 16.5 mmol) was added dropwise over 2 h. The reaction mixture was allowed to warm slowly to room temperature over 16 h and was then heated at reflux for 24 h. On cooling to room temperature, the resultant mixture was acidified with hydrochloric acid (6M) to pH ~ 2 and stirred at room temperature for 16 h. The reaction mixture was then extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using ethyl acetate/hexanes (20%) as the eluant to afford the title compound 156 (720 mg, 46%) as a white crystalline solid. M.p. 133-135 °C, ethyl acetate/hexanes (lit.¹¹⁴ M.p. 136-138 °C, ethyl acetate/hexane); ¹H NMR (400 MHz, CDCl₃) δ 2.49 (s, 3H, CH₃), 3.92 (s, 3H, CH₂), 6.23 (d, J = 2.4 Hz, 1H, ArH), 6.28 (d, J = 2.4 Hz, 1H, ArH), 11.76 (s, 2H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 24.4, 52.0, 101.4, 105.8, 111.5, 144.1, 160.4, 165.5, 172.3; IR (KBr) 3369
(broad), 2990, 1652, 1610, 1445, 1266, 1112 cm\(^{-1}\); \textbf{MS (CI)} \(m/z\) (rel. intensity) 183 (M + H, 100); \textbf{Anal.} Calcd. for C\(_9\)H\(_{10}\)O\(_4\): C, 59.34; H, 5.53. Found: C, 59.08; H, 5.56.

4.3.2 5-Hydroxy-2,2,7-trimethyl-2\(H\)-chromene-6-carboxylic acid methyl ester (169)

\begin{center}
\textbf{OH} \\
\textbf{MeO} \\
\textbf{Me} \\
\textbf{Me} \\
\textbf{169}
\end{center}

A solution of senecialdehyde 101 (168 mg, 2.00 mmol), the ester 156 (182 mg, 1.00 mmol), phenylboronic acid (195 mg, 1.60 mmol) and propionic acid (23 \(\mu\)L, 0.30 mmol) in benzene (2 mL) was heated at reflux for 16 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20\% w/v, 2 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (3\%) as the eluant to afford the \textit{title compound} 169 (112 mg, 45\%) as a white solid. \textbf{M.p.} 51-53 °C, ethyl acetate/hexanes; \textbf{\(^1\text{H NMR}\)} (400 MHz, CDCl\(_3\)) \(\delta\) 1.43 (s, 6H, 2 x CH\(_3\)), 2.46 (s, 3H, CH\(_3\)), 3.91 (s, 3H, CH\(_3\)O), 5.52 (d, \(J = 10.0\) Hz, 1H, CH=CH), 6.20 (s, 1H, ArH), 6.69 (d, \(J = 10.0\) Hz, 1H, CH=CH), 11.98 (s, 1H, OH); \textbf{\(^{13}\text{C NMR}\)} (101 MHz, CDCl\(_3\)) \(\delta\) 24.5, 28.3, 51.8, 77.3, 105.1, 107.3, 111.9, 116.5, 127.4, 142.8, 157.6, 159.9, 172.5; \textbf{IR} (ef) 2972, 1646, 1615, 1562, 1439, 1267, 1155, 1096 cm\(^{-1}\); \textbf{MS (CI)} \(m/z\) (rel. intensity) 249 (M + H, 100).
4.3.3 5-Hydroxy-7-methyl-2,2-diphenyl-2H-chromene-6-carboxylic acid methyl ester (171)

A solution of β-phenylcinnamaldehyde 170 (740 mg, 3.60 mmol), the ester 156 (328 mg, 1.80 mmol), phenylboronic acid (345 mg, 2.80 mmol) and propionic acid (39 μL, 0.52 mmol) in benzene (4 mL) was heated at reflux for 24 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 4 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 8 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using dichloromethane/ether (30%) as the eluant to afford the title compound 171 (491 mg, 75%) as a white solid. M.p. 133-135 °C, dichloromethane/ether; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.45 (s, 3H, CH$_3$), 3.90 (s, 3H, CH$_2$O), 6.05 (d, $J$ = 10.1 Hz, 1H, CH=CH), 6.35 (s, 1H, ArH), 6.99 (d, $J$ = 10.1 Hz, 1H, CH=CH), 7.29, 7.40 (m, 10H, ArH), 12.00 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 24.6, 52.0, 83.5, 105.7, 107.6, 111.9, 117.7, 125.7, 127.1, 127.7, 128.28, 143.4, 144.8, 156.9, 160.1, 172.4; IR (KBr) 3061, 2953, 1651, 1619, 1566, 1446, 1271, 1159, 1117 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 373 (M + H, 100); Anal. Calcd. for C$_{24}$H$_{20}$O$_4$: C, 77.40; H, 5.41. Found: C, 77.66; H, 5.49.
4.3.4 5-Hydroxy-7-methyl-2-spirocyclohexyl-2H-chromene-6-carboxylic acid methyl ester (172)

A solution of cyclohexylideneacetaldehyde 111 (321 mg, 2.59 mmol), the ester 156 (236 mg, 1.29 mmol), phenylboronic acid (252 mg, 2.06 mmol) and propionic acid (29 μL, 0.39 mmol) in benzene (3 mL) was heated at reflux for 24 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 3 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 172 (86 mg, 23%) as a white solid. M.p. 82-84 °C, ethyl acetate/hexanes; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.36 (m, 1H, cyclohexyl-H), 1.54 (m, 5H, cyclohexyl-H), 1.72 (m, 2H, cyclohexyl-H), 1.90 (m, 2H, cyclohexyl-H), 2.46 (s, 3H, CH$_3$), 3.91 (s, 3H, CH$_3$O), 5.56 (d, $J$ = 10.1 Hz, 1H, CH=CH), 6.24 (s, 1H, ArH), 6.69 (d, $J$ = 10.1 Hz, 1H, CH=CH), 11.96 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 21.4, 24.5, 25.4, 36.4, 51.9, 78.1, 105.2, 108.2, 112.1, 116.9, 127.2, 142.8, 157.7, 159.9, 172.5; IR (ef) 3385 (broad), 2928, 1651, 1622, 1439, 1272, 1166, 1021 cm$^{-1}$; MS (CI) $m/z$ (rel. intensity) 289 (M + H, 100); Anal. Calcd. for C$_{17}$H$_{20}$O$_4$: C, 70.81; H, 6.99. Found: C, 70.55; H, 7.09.
4.3.5 (±)-2-Ethyl-5-hydroxy-7-methyl-2H-chromene-6-carboxylic acid methyl ester (174)

A solution of trans-2-pentenal 173 (780 µL, 7.97 mmol), the ester 156 (728 mg, 4.00 mmol), phenylboronic acid (781 mg, 6.40 mmol) and propionic acid (89 µL, 1.2 mmol) in benzene (9 mL) was heated at reflux for 24 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 9 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residual yellow oil was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 174 (530 mg, 54%) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.01 (t, $J$ = 7.3 Hz, 3H, CH$_3$CH$_2$), 1.75 (m, 2H, CH$_3$CH$_2$), 2.46 (s, 3H, CH$_3$), 3.91 (s, 3H, CH$_3$O), 4.83 (m, 1H, OCH), 5.57 (dd, $J$ = 10.1, 3.1 Hz, 1H, CH=CH), 6.20 (s, 1H, ArH), 6.76 (d, $J$ = 10.1 Hz, 1H, CH=CH), 11.97 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 9.1, 24.5, 28.8, 51.9, 77.0, 105.3, 107.9, 111.5, 118.3, 122.2, 142.9, 158.3, 159.8, 172.5; IR (ef) 3401 (broad), 2969, 1652, 1622, 1454, 1268, 1163 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 249 (M + H, 100); Anal. Calcd. for C$_{14}$H$_{16}$O$_4$: C, 67.73; H, 6.50. Found: C, 67.58; H, 6.58.
4.3.6 (±)-5-Hydroxy-7-methyl-2-phenyl-2H-chromene-6-carboxylic acid methyl ester (176)

A solution of trans-cinnamaldehyde 175 (120 μL, 0.952 mmol), the ester 156 (83.0 mg, 0.460 mmol), phenylboronic acid (89.0 mg, 0.730 mmol) and propionic acid (10 μL, 0.13 mmol) in benzene (1 mL) was heated at reflux for 20 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 1 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 3 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 176 (80 mg, 59%) as a white solid. M.p. 79-81 °C, ethyl acetate/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.44 (s, 3H, CH\(_3\)), 3.92 (s, 3H, CH\(_3\)O), 5.71 (dd, \(J = 10.1, 3.4\) Hz, 1H, CH=CH), 5.92 (dd, \(J = 3.4, 1.3\) Hz, 1H, PhCH), 6.20 (s, 1H, ArH), 6.93 (dd, \(J = 10.1, 1.3\) Hz, 1H, CH=CH), 7.35-7.44 (m, 5H, ArH), 12.02 (s, 1H, OH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 24.6, 52.0, 77.7, 105.7, 107.5, 111.6, 118.2, 121.5, 127.3, 128.7, 128.9, 140.6, 143.4, 157.5, 159.9, 172.5; IR (ef) 3321 (broad), 2940, 1651, 1619, 1453, 1255, 1158, 1117 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 297 (M + H, 100); Anal. Calcd. for C\(_{18}\)H\(_{16}\)O\(_4\): C, 72.96; H, 5.44. Found: C, 72.69; H, 5.57.
4.3.7 5-Hydroxy-7-methyl-2H-chromene-6-carboxylic acid methyl ester (178)

A solution of acrolein 177 (240 µL, 3.59 mmol), the ester 156 (323 mg, 1.77 mmol), phenylboronic acid (345 mg, 2.80 mmol) and propionic acid (39 µL, 0.52 mmol) in benzene (4 mL) was heated at reflux for 24 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 4 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 8 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (5%) as the eluant to afford the title compound 178 (71 mg, 18%) as a white solid. **M.p.** 52-54 °C, ethyl acetate/hexanes; **¹H NMR** (400 MHz, CDCl₃) δ 2.45 (s, 3H, CH₃), 3.91 (s, 3H, CH₂O), 4.83 (dd, J = 3.5, 1.8 Hz, 2H, OCH₂), 5.65 (dt, J = 10.1, 3.5 Hz, 1H, CH=CH), 6.17 (s, 1H, ArH), 6.77 (d, J = 10.1 Hz, 1H, CH=CH), 11.96 (s, 1H, OH); **¹³C NMR** (101 MHz, CDCl₃) δ 24.5, 51.9, 66.0, 105.6, 108.3, 111.3, 118.4, 118.9, 143.03, 158.5, 159.7, 172.4; **IR (ef)** 3436 (broad), 2940, 1650, 1617, 1563, 1453, 1271, 1165, 1130 cm⁻¹; **MS (Cl) m/z** (rel. intensity) 221 (M + H, 100); **IR (ef)** 3436 (broad), 2940, 1650, 1617, 1563, 1453, 1271, 1165, 1130 cm⁻¹; **MS (Cl) m/z** (rel. intensity) 221 (M + H, 100); **Anal.** Calcd. for C₁₂H₁₂O₄: C, 65.45; H, 5.49. Found: C, 65.40; H, 5.49.
4.3.8 5-Hydroxy-3,7-dimethyl-2H-chromene-6-carboxylic acid methyl ester (180)

A solution of methacrolein 179 (methacrylaldehyde, 140 mg, 2.00 mmol), the ester 156 (182 mg, 1.00 mmol), phenylboronic acid (195 mg, 1.60 mmol) and propionic acid (23 μL, 0.30 mmol) in benzene (2 mL) was heated at reflux for 20 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 2 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the title compound 180 (36 mg, 15%) as a white solid. M.p. 96-98 °C, ethyl acetate/hexanes; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.80 (s, 3H, CH\(_3\)), 2.45 (s, 3H, CH\(_3\)), 3.91 (s, 3H, CH\(_3\)O), 4.69 (s, 2H, OCH\(_2\)), 6.17 (s, 1H, ArH), 6.51 (s, 1H, HC=C), 11.91 (s, 1H, OH); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 19.2, 24.5, 52.0, 69.6, 105.7, 108.6, 111.0, 113.3, 127.8, 141.8, 157.1, 159.1, 172.6; IR (ef) 2928, 1647, 1611, 1572, 1437, 1272, 1161 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 235 (M + H, 100); Anal. Calcd. for C\(_{13}\)H\(_{14}\)O\(_4\): C, 66.66; H, 6.02. Found: C, 66.83; H, 5.93.
4.3.9 (±)-5-Hydroxy-7-methyl-2,3-butano-2H-chromene-6-carboxylic acid methyl ester (181)

A solution of 1-cyclohexene-1-carboxaldehyde 109 (910 µL, 7.98 mmol), the ester 156 (728 mg, 4.00 mmol), phenylboronic acid (781 mg, 6.40 mmol) and propionic acid (89 µL, 1.2 mmol) in benzene (9 mL) was heated at reflux for 24 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 9 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using dichloromethane/ether (30%) as the eluant to afford the title compound 181 (530 mg, 54%) as a yellow solid.

M.p. 110-112 °C, dichloromethane/ether; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.40 (m, 2H, \(CH_2\)), 1.70 (m, 2H, \(CH_2\)), 1.88 (m, 1H, \(CHH\)), 2.05 (m, 1H, \(CHH\)), 2.17 (m, 1H, \(CHH\)), 2.43 (s, 3H, \(CH_3\)), 2.47 (m, 1H, \(CHH\)), 3.90 (s, 3H, \(CH_3O\)), 4.95 (m, 1H, OCH), 6.10 (s, 1H, ArH), 6.39 (s, 1H, \(HC=C\)), 11.90 (s, 1H, \(OH\)); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 24.4, 24.6, 27.0, 33.3, 35.4, 51.8, 78.1, 105.1, 107.0, 109.8, 110.8, 134.8, 141.8, 157.4, 159.0, 172.5; IR (ef) 3420 (broad), 2935, 1651, 1622, 1439, 1272, 1166, 1021 cm\(^{-1}\); MS (CI) \(m/z\) (rel. intensity) 275 (M + H, 100); Anal. Calcd. for C\(_{16}\)H\(_{18}\)O\(_4\): C, 70.06; H, 6.61. Found: C, 69.87; H, 6.79.
4.3.10 (±)-3,4-Dihydro-5-hydroxy-3,7-dimethyl-2,4-etheno-2H-chromene-6-carboxylic acid methyl ester (185)

A solution of sorbic aldehyde 183 (trans,trans-2,4-hexadienal, 440 µL, 3.99 mmol), the ester 156 (364 mg, 2.00 mmol), phenylboronic acid (390 mg, 3.20 mmol) and propionic acid (44 µL, 0.59 mmol) in benzene (4 mL) was heated at reflux for 40 h with a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 4 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the title compound 185 (71 mg, 14%) as a white solid. 

\[ \text{M.p.} \ 75-77 \ {^\circ}\text{C}, \text{ethyl acetate/hexanes; } ^1\text{H NMR} (600 MHz, CDCl}_3 \ \delta 1.26 (d, J = 7.2 \text{ Hz}, 3H, CH}_3), 2.47 (s, 3H, CH}_3), 3.06 (m, 1H, CH}_3CH), 3.61 (m, 1H, ArCH), 3.90 (s, 3H, CH}_3O), 5.79 (apparent dt, J = 5.7, 2.1 \text{ Hz}, 1H, CH=CH), 5.94 (apparent dt, J = 8.4, 2.2 \text{ Hz}, 1H, CH=CH), 6.02 (dd, J = 5.7, 2.3 \text{ Hz}, 1H, OCH), 6.19 (s, 1H, ArH), 11.77 (s, 1H, OH); \ ^{13}\text{C NMR} (151 MHz, CDCl}_3) \ \delta 22.0, 24.8, 47.1, 50.2, 51.9, 94.8, 106.1, 114.2, 115.0, 127.3, 143.5, 144.0, 161.0, 163.5, 172.5; \ \text{IR} (\text{ef}) 2955, 1654, 1632, 1588, 1439, 1289, 1277, 1149, 1011 \text{ cm}^{-1}; \ \text{MS} (\text{Cl}) m/z (\text{rel. intensity}) 261 (M + H, 100), 229 (10). \]
A solution of trans,trans-2,4-heptadienal 191 (250 µL, 2.00 mmol), the ester 156 (182 mg, 1.00 mmol), phenylboronic acid (195 mg, 1.60 mmol) and propionic acid (22 µL, 0.30 mmol) in benzene (2 mL) was heated at reflux for 24 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 2 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using dichloromethane/hexanes (40%) as the eluant to afford the title compound 192 (53 mg, 20%) as a white solid. M.p. 81-83 °C, dichloromethane/hexanes; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.01 (t, \(J = 7.5\) Hz, 3H, CH\(_3\)CH\(_2\)), 1.49-1.73 (m, 2H, CH\(_3\)CH\(_2\)), 2.47 (s, 3H, CH\(_3\)), 3.00 (m, 1H, CH\(_2\)CH), 3.68 (d, \(J = 7.9\) Hz, 1H, ArCH), 3.90 (s, 3H, CH\(_3\)O), 5.82 (apparent dt, \(J = 5.9, 2.0\) Hz, 1H, CH=CH), 5.90 (apparent dt, \(J = 8.3, 2.0\) Hz, 1H, CH=CH), 6.04 (dd, \(J = 5.9, 2.4\) Hz, 1H, OCH), 6.19 (s, 1H, ArH), 11.75 (s, 1H, OH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 11.7, 24.8, 29.2, 48.0, 51.8, 53.5, 94.5, 105.5, 106.1, 114.9, 128.1, 141.3, 143.9, 161.0, 163.5, 172.5; IR (ef) 2961, 1652, 1632, 1586, 1458, 1437, 1276, 1267, 1193, 1011 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 275 (M + H, 100), 243 (7); Anal. Calcd. for C\(_{16}\)H\(_{18}\)O\(_4\): C, 70.06; H, 6.61. Found: C, 70.41; H, 6.79.
Method A: A solution of methyl vinyl ketone 193 [MVK, 500 µL, 6.01 mmol, 2 equiv (1.25 equiv in regard to phenylboronic acid)], the ester 156 (546 mg, 3.00 mmol, 1 equiv), phenylboronic acid (585 mg, 4.80 mmol, 1.6 equiv) and propionic acid (66 µL, 0.89 mmol) in benzene (7 mL) was heated at reflux for 48 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 7 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the title compound 195 (321 mg, 44%) as a white solid. M.p. 48-50 °C, ethyl acetate/hexanes; \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.35 (s, 3H, CH\(_3\)), 1.62-1.82 (m, 3H, cyclopentyl-\( H \)), 1.93 (m, 1H, cyclopentyl-\( H \)), 2.07 (m, 1H, cyclopentyl-\( H \)), 2.28 (m, 1H, cyclopentyl-\( H \)), 2.34 (s, 3H, CH\(_3\)CO), 7.42 (m, 2H, Ar\( H \)), 7.52 (m, 1H, Ar\( H \)), 7.86 (m, 2H, Ar\( H \)); \( ^{13}C \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 22.5, 23.5, 28.2, 38.5, 41.5, 94.6, 98.6, 127.5 (broad), 128.0, 131.8, 135.1, 211.7; IR (ef) 2968, 1714, 1604, 1498, 1362, 1127 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 245 (M + H, 100), 227 (10), 201 (24), 186 (6), 141 (9), 123 (30); Anal. Calcd. for C\(_{14}\)H\(_{17}\)BO\(_3\): C, 68.89; H, 7.02. Found: C, 68.69; H, 7.11.
**Method B:** A solution of the MVK 193 (125 $\mu$L, 1.50 mmol, 1.25 equiv), phenylboronic acid (146 mg, 1.20 mmol, 1 equiv) and propionic acid (16 $\mu$L, 0.21 mmol) in benzene (2 mL) was heated at reflux for 16 h in Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 2 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the *title compound* 195 (146 mg, 80%) as a white solid.

**Method C:** A solution of MVK 193 (125 $\mu$L, 1.50 mmol, 2 equiv), phenylboronic acid (91.5 mg, 0.750 mmol, 1 equiv) and propionic acid (16 $\mu$L, 0.21 mmol) in benzene (2 mL) was heated at reflux for 16 h in a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and an aqueous solution of ammonium acetate (20% w/v, 2 mL) was added. The resultant mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the *title compound* 195 (118 mg, 65%) as a white solid.
4.3.13 5-Hydroxy-2,2,7-trimethyl-2H-chromene-6-carboxylic acid (127a) - prepared from methyl ester (169)\(^{55}\)

![](image)

To a solution of the ester 169 (87.2 mg, 0.351 mmol) in dimethylsulfoxide (DMSO, 2 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 700 µL, 3.50 mmol) at room temperature. The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (1 mL) was added and the resultant solution was washed with ether (2 x 1 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 1 mL), brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (2%) as the eluant to afford the title compound 127a (68 mg, 83%) as a white solid. **M.p.** 154-155 °C, methanol/dichloromethane (lit.\(^{55}\) M.p. 154-155 °C, methanol/dichloromethane); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.44 (s, 6H, 2 x CH\(_3\)), 2.52 (s, 3H, CH\(_3\)), 5.52 (d, \(J = 10.1\) Hz, 1H, CH=CH) 6.23 (s, 1H, ArH), 6.68 (d, \(J = 10.1\) Hz, 1H, CH=CH) 11.6 (broad s, 1H, OH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 24.5, 28.5, 29.8, 77.6, 107.4, 112.4, 116.4, 125.7, 127.5, 144.5, 158.5, 160.7, 176.1; **IR** (KBr) 2969, 1638, 1617, 1457, 1275, 1123 cm\(^{-1}\); **MS** (Cl) \(m/z\) (rel. intensity) 235 (M + H, 79), 191 (M + H, - CO\(_2\), 100); **Anal.** Calcd. for C\(_{13}\)H\(_{14}\)O\(_4\): C, 66.66; H, 6.02. Found: C, 66.90; H, 6.03.
4.3.14 5-Hydroxy-7-methyl-2-spirocyclohexyl-2H-chromene-6-carboxylic acid (130) - prepared from methyl ester (172)

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{OH} & \\
\end{align*}
\]

To a solution of the ester 172 (61.4 mg, 0.210 mmol) in DMSO (1 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 420 µL, 2.10 mmol) at room temperature. The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (1 mL) was added and the resultant solution was washed with ether (2 x 3 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 3 mL), brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (2%) as the eluant to afford the title compound 130 (51 mg, 88%) as a white solid. \textbf{M.p.} 144 °C (dec.), methanol/dichloromethane [lit.\textsuperscript{55} M.p. 144 °C (dec.), methanol/dichloromethane]; \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.36 (m, 1H, cyclohexyl-\(CH_2\)), 1.54 (m, 5H, cyclohexyl-\(CH_2\)), 1.73 (m, 2H, cyclohexyl-\(CH_2\)), 1.92 (m, 2H, cyclohexyl-\(CH_2\)), 2.53 (s, 3H, \(CH_3\)), 5.57 (d, \(J = 10.1\ Hz\), 1H, \(CH=CH\)), 6.28 (s, 1H, Ar\(H\)), 6.69 (d, \(J = 10.1\ Hz\), 1H, \(CH=CH\)), 11.68 (broad s, 1H, OH); \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 21.4, 24.6, 25.4, 36.5, 78.4, 103.9, 108.2, 112.6, 116.8, 127.3, 144.5, 158.76, 160.8, 176.0; \textbf{IR} (ef) 3408 (broad), 2933, 1636, 1458, 1283, 1268, 1250 1184, 1128 cm\(^{-1}\); \textbf{MS} (Cl) \(m/z\) (rel. intensity) 275 (M + H, 7), 231 (M + H\(_2\) - CO\(_2\), 100); \textbf{Anal. Calcd. for} \(C_{16}H_{18}O_4:\) C, 70.06; H, 6.61. Found: C, 70.32; H, 6.63.
4.3.15 (±)-2-Ethyl-5-hydroxy-7-methyl-2H-chromene-6-carboxylic acid (205)

To a solution of the ester 174 (293 mg, 1.18 mmol) in DMSO (6 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 2.40 mL, 11.8 mmol). The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (3 mL) was added and the resultant solution was washed with ether (2 x 5 ml). The aqueous layer was then acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (2%) as the eluant to afford the title compound 205 (147 mg, 53%) as a white solid. M.p. 129-130 °C, methanol/dichloromethane; $^{1}$H NMR (400 MHz, CDCl$_3$) δ 1.02 (t, J = 7.3 Hz, 3H, CH$_3$CH$_2$), 1.77 (m, 2H, CH$_3$CH$_2$), 2.54 (s, 3H, CH$_3$), 4.86 (m, 1H, OCH), 5.58 (dd, J = 10.1, 3.4 Hz, 1H, CH=CH), 6.24 (s, 1H, ArH), 6.76 (dd, J = 10.1, 1.2 Hz, 1H, CH=CH), 11.66 (broad s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 8.9, 24.5, 28.8, 76.7, 103.9, 107.8, 112.0, 118.0, 122.2, 144.6, 159.3, 160.5, 176.2; IR (KBr) 3435 (broad), 2971, 2940, 1647, 1616, 1455, 1258, 1178, 1137 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 235 (M + H, 100), 191 (M + H - CO$_2$, 23); Anal. Calcd. for C$_{13}$H$_{14}$O$_4$: C, 66.66; H, 6.02. Found: C, 66.40; H, 6.24.
4.3.16 5-Hydroxy-7-methyl-2H-chromene-6-carboxylic acid (207)

To a solution of the ester 178 (40.0 mg, 0.182 mmol) in DMSO (1 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 360 μL, 1.80 mmol). The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (1 mL) was added and the resultant solution was washed with ether (1 mL). The aqueous layer was then acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted with dichloromethane (3 x 3 mL). The combined organic extracts were washed with water (2 x 3 mL), brine (3 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then recrystallized from methanol to afford the title compound 207 (14 mg, 38%) as a white solid. M.p. 178 °C (dec.), methanol; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 2.48 (s, 3H, CH\(_3\)), 4.79 (dd, \(J = 3.4, 1.8\) Hz, 2H, OCH\(_2\)), 5.68 (dt, \(J = 10.1, 3.4\) Hz, 1H, CH=CH), 6.17 (s, 1H, ArH), 6.71 (d, \(J = 10.1\) Hz, 1H, CH=CH); \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 24.4, 66.8, 106.6, 109.3, 111.8, 119.5, 119.6, 144.8, 159.8, 161.3, 175.1; IR (ef) 3432 (broad), 2938, 1623, 1456, 1266, 1182, 1138 cm\(^{-1}\); MS (CI) \(m/z\) (rel. intensity) 207 (M + H, 100), 163 (M + H, - CO\(_2\), 15); Anal. Calcd. for C\(_{11}\)H\(_{10}\)O\(_4\): C, 64.07; H, 4.89. Found: C, 63.95; H, 4.99.
4.3.17 5-Hydroxy-3,7-dimethyl-2H-chromene-6-carboxylic acid (208)

To a solution of the ester 180 (86.3 mg, 0.369 mmol) in DMSO (2 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 740 μL, 3.70 mmol). The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (1 mL) was added and the resultant solution was washed with ether (3 ml). The aqueous layer was then acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted with ether (3 x 5 mL). The combined organic extracts were washed with water (2 x 3 mL), brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The pale yellow crude product was recrystallized from dichloromethane to afford the title compound 208 (71 mg, 88%) as a white solid. M.p. 190 °C (dec.), dichloromethane; $^1$H NMR (500 MHz, (CD$_3$)$_2$SO) $\delta$ 1.80 (s, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 4.70 (s, 2H, OCH$_2$), 6.25 (s, 1H, ArH), 6.42 (s, 1H, CH=C); $^{13}$C NMR (126 MHz, (CD$_3$)$_2$SO) $\delta$ 18.8, 23.7, 68.7, 105.8, 107.9, 110.3, 112.2, 128.7, 141.7, 156.2, 158.5, 173.8; IR (KBr) 2944, 2853, 1619, 1572, 1456, 1281, 1176 cm$^{-1}$; MS (MALDI-TOF) $m/z$ 243 (M + Na), 221 (M + H), 177 (M +H, - CO$_2$); Anal. Calcd. for C$_{12}$H$_{12}$O$_4$: C, 65.45; H, 5.49. Found: C, 65.32; H, 5.45.

4.3.18 (±)-5-Hydroxy-7-methyl-2,3-butan-2H-chromene-6-carboxylic acid (209)

To a solution of the ester 181 (365 mg, 1.36 mmol) in DMSO (7 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 2.70 mL, 13.6 mmol). The reaction
mixture was then stirred at 80 °C for 16 h. Upon cooling, water (3 mL) was added and the resultant solution was washed with ether (5 mL). The aqueous layer was then acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was recrystallized from dichloromethane to afford the title compound 209 (154 mg, 44%) as a white solid. M.p. 198 °C (dec.), dichloromethane; \(^\text{\textsuperscript{1}H NMR}\) (400 MHz, CDCl\(_3\) and CD\(_3\)OD) \(\delta\) 1.12-1.39 (m, 2H, CH\(_2\)), 1.50-1.68 (m, 2H, CH\(_2\)), 1.69-1.79 (m, 1H, CHH), 1.90 (m, 1H, CHH), 2.02 (m, 1H, CHH), 2.24-2.36 (m, 1H, CHH), 2.31 (s, 3H, CH\(_3\)), 4.79 (m, 1H, OCH), 5.94 (s, 1H, CH=CH), 6.21 (s, 1H, ArH); \(^\text{\textsuperscript{13}C NMR}\) (101 MHz, CDCl\(_3\) and CD\(_3\)OD) \(\delta\) 23.7, 24.1, 26.6, 32.9, 35.0, 77.7, 104.8, 106.5, 109.4, 110.1, 134.4, 142.4, 156.91, 158.8, 173.8; \(\text{IR (KBr)}\) 3446 (broad), 2934, 1635, 1595, 1455, 1263, 1178 cm\(^{-1}\); \(\text{MS (Cl)}\) m/z (rel. intensity) 261 (M + H, 46), 217 (M + H, - CO\(_2\), 100); \(\text{Anal. Calcd. for} \ C_{15}H_{16}O_4: \ C, 69.22; \ H, 6.02. \) \(\text{Found:} \ C, 69.48; \ H, 6.39.\)

4.3.19 (±)-3,4-Dihydro-5-hydroxy-3,7-dimethyl-2,4-etheno-2H-chromene-6-carboxylic acid (210)

![Chemical Structure](image)

To a solution of the ester 185 (35.6 mg, 0.137 mmol) in DMSO (1 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 270 μL, 1.35 mmol) at room temperature. The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (1 mL) was added and the resultant solution was washed with ether (2 x 1 mL). The aqueous layer was acidified with hydrochloric acid (6M) to pH ~ 2 and was extracted
with ether (3 x 3 mL). The combined organic extracts were washed with water (2 x 1 mL), brine (3 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The dark brown crude product was then recrystallized from dichloromethane to afford the title compound 210 (19 mg, 56%) as a beige solid. M.p. 178 °C (dec.), dichloromethane; \(^1\)H NMR (500 MHz, (CD\(_3\))\(_2\)CO) \(\delta\) 1.27 (d, \(J = 7.1\) Hz, 3H, \(CH_3\)), 2.57 (s, 3H, \(CH_3\)), 3.04 (m, 1H, \(CH_3CH\)), 3.64 (dd, \(J = 8.3, 2.0\) Hz, 1H, ArCH), 5.85 (apparent dt, \(J = 5.6, 2.0\) Hz, 1H, \(CH=CH\)), 6.01 (apparent dt, \(J = 8.3, 2.2\) Hz, 1H, \(CH=CH\)), 6.10 (dd, \(J = 5.6, 2.4\) Hz, 1H, OCH), 6.25 (s, 1H, ArH), \(~\)12.3 (broad s, 1H, OH); \(^1^3\)C NMR (126 MHz, (CD\(_3\))\(_2\)CO) \(\delta\) 22.8, 25.4, 48.6, 51.5, 96.1, 106.3, 107.2, 116.3, 129.1, 144.3, 146.0, 163.2, 165.3, 175.1; IR (ef) 3044, 2959, 1641, 1613, 1466, 1301, 1267, 1171 cm\(^{-1}\); MS (MALDI-TOF) \(m/z\) 269 (M + Na), 247 (M + H). Anal. Calcd. for C\(_{14}\)H\(_{14}\)O\(_4\): C, 68.28; H, 5.73. Found: C, 68.20; H, 5.82.

4.3.20 (±)-3-Ethyl-3,4-dihydro-5-hydroxy-7-methyl-2,4-etheno-2H-chromene-6-carboxylic acid (211)

![211](image)

To a solution of the ester 192 (75.6 mg, 0.276 mmol) in DMSO (1.5 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 550 \(\mu\)L, 2.75 mmol). The reaction mixture was then stirred at 80 °C for 16 h. Upon cooling, water (1 mL) was added and the resultant solution was washed with ether (1 mL). The aqueous layer was then acidified with hydrochloric acid (6M) to pH \(~\)2 and was extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were washed with water (2 x 1 mL), brine (3 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The brown crude
product was then recrystallized from methanol to afford the *title compound* 211 (62 mg, 85%) as a white solid. **M.p.** 194 °C (dec.), methanol; **¹H NMR** (400 MHz, (CD₃)₂CO) δ 1.05 (t, J = 7.4 Hz, 3H, CH₃CH₂), 1.62 (m, 2H, CH₃CH₂), 2.57 (s, 3H, CH₃), 2.98 (m, 1H, CH₂CH), 3.71 (dd, J = 8.0, 1.3 Hz, 1H, ArCH), 5.87 (apparent dt, J = 5.8, 2.2 Hz, 1H, CH=CH), 5.97 (apparent dt, J = 8.0, 2.2 Hz, 1H, CH=CH), 6.11 (dd, J = 5.8, 2.2 Hz, 1H, OCH), 6.25 (s, 1H, ArH); **¹³C NMR** (126 MHz, (CD₃)₂CO) δ 12.7, 25.4, 30.8, 49.2, 55.1, 95.8, 106.4, 107.1, 116.2, 129.9, 142.2, 145.9, 163.0, 165.3, 175.1; **IR** (KBr) 3447 (broad), 2959, 1619, 1468, 1265, 1170, 1012 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 261 (M + H, 100), 243 (7), 217 (M + H - CO₂, 47); **Anal.** Calcd. for C₁₅H₁₆O₄: C, 69.22; H, 6.20. Found: C, 69.51; H, 6.31.
PART TWO

A NEW METHOD FOR THE MILD AND SELECTIVE MONO-DEALKYLATION OF TERTIARY AMINES
CHAPTER FIVE

GENERAL INTRODUCTION TO N-DEALKYLATION REACTIONS OF TERTIARY AMINES

5.1 Research Project Overview

The project described herein stemmed from an unprecedented discovery that we made in a target-oriented research project that concerned the chemistry of oxo-crown ethers 212. Our research group was interested in the preparation of the corresponding acetals of oxo-crown ethers (e.g. 215 and 216) by their experimentally simple acid-catalyzed condensation reaction with diols (Scheme 5.1). This would offer a direct means to prepare chiral crown ethers 215 from C₂-symmetric diols 213 (R = various substituents) for their use as chiral ligands for asymmetric synthesis, and monomeric building blocks 216 from substituted catechol 214 (X and Y = substituents that can engage in directional hydrogen-bonding interactions) for the assembly of ion channel mimics.126

Scheme 5.1 Proposed Synthesis of Oxo-Crown Ether Acetals (215) and (216)

Attempted oxidation of the known hydroxy crown ether 217 under modified Swern conditions at -78 °C with oxalyl chloride (1.5 equiv), DMSO (2.6 equiv) and triethylamine (5.0 equiv) resulted in the isolation of the amide 218 as the major product in 70% yield after flash chromatography on silica gel. In this reaction, one of the alkyl substituents of triethylamine was cleaved, presumably via the loss of ethyl chloride.

Based on this initial observation, a project was designed to investigate this reaction and to develop a new synthetic procedure for the selective mono-dealkylation of tertiary amines. Preliminary experimental results established that the dealkylation reaction of triethylamine with hydroxy crown ether 217 and oxalyl chloride could be carried out in the absence of DMSO. A novel and facile method was then established for the mono-dealkylation of tertiary amines using a series of monoesters of oxalyl chloride as the cleavage reagent (Scheme 5.3). Moreover, the scope and selectivity of the reaction was also examined and the reaction mechanism was investigated. The hydrolysis of the resultant amide reaction products was demonstrated by employment of standard literature procedures. The results of these studies are reported in the following two chapters.
Scheme 5.3 A New Method for the Mild and Selective Mono-Dealkylation of Tertiary Amines

\[
\text{ROH} \underset{(\text{COCl})_2, \text{CH}_2\text{Cl}_2}{\text{0°C to rt}} \rightarrow \left[ \begin{array}{c}
\text{Cl} \\
\text{RO} \\
\text{O} \\
\end{array} \right] + \begin{array}{c}
\text{R}^1 \\
\text{N} \\
\text{R}^2 \\
\text{R}^3 \\
\end{array} \underset{\text{CH}_2\text{Cl}_2}{\text{0°C to rt}} \rightarrow \begin{array}{c}
\text{O} \\
\text{RO} \\
\text{O} \\
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \text{Cl} \\
\end{array}
\]

In the subsequent section, a brief overview of the methods that have been used to dealkylate tertiary amines is presented.

5.2 N-Dealkylation Reactions of Tertiary Amines

The selective removal of an alkyl group from a tertiary nitrogen centre has been studied extensively for a variety of purposes, e.g. the degradative structural analysis of alkaloids\(^{129}\) and more importantly, for the selective cleavage of protecting groups of amines in natural product total synthesis.\(^{130}\) Many reagents and methods have been developed for the dealkylation of tertiary amines. The earliest related reaction was discovered by Hofmann in the mid-19th century (Scheme 5.4). In this reaction, a quaternary ammonium hydroxide salt is heated to effect its decomposition to afford an alkene. This classic reaction has been used to determine the molecular structure of amines, especially alkaloids.\(^{131}\)

Scheme 5.4 An Example of the Hofmann Elimination Reaction

The Cope elimination of N-oxides also affords alkenes on heating and constitutes a method for the dealkylation of tertiary amines (Scheme 5.5).\(^\text{132}\)

Scheme 5.5 An Example of the Cope Elimination Reaction

The cleavage of tertiary amines with various reagents, such as cyanogen bromide, phosgene and chlorofomates, has been investigated over the past century.\(^\text{133}\) The dealkylation of tertiary amines using cyanogen bromide (von Braun reaction) has found many applications in both synthetic chemistry and in the degradative structural analysis of alkaloids.\(^\text{134}\) The reaction was reported to proceed through an N-cyanoammonium salt intermediate 219, which decomposes to give the disubstituted cyanamide 220 (Scheme 5.6). The study of the kinetics of this reaction has shown that the formation of the quaternary ammonium intermediate 219 is a fast process. The slow step is the decomposition of this intermediate 219. N-cyanoammonium salt intermediates 219 have also been isolated and analysed by NMR spectroscopy.\(^\text{134}\)

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Strepkheev and co-workers have studied the reaction of phosgene with tertiary amines (Scheme 5.7). The complex 221 was proposed as a reaction intermediate that decomposes to afford the carbamoyl chloride 222. In this reaction, one of the alkyl groups on nitrogen is cleaved and eliminated as the corresponding alkyl halide. When triethylamine was used, the products were isolated in > 90% yield. In the case of tribenzylamine no C-N bond cleavage was observed.\textsuperscript{135}

\textbf{Scheme 5.7 Dealkylation of Trialkylamines with Phosgene}

\begin{equation}
\begin{align*}
\text{R}_3\text{N} + \text{COCl}_2 & \rightleftharpoons [\text{R}_3\text{N-COCl}_2] & \rightarrow \text{R}_2\text{N-Cl} + \text{R-Cl}
\end{align*}
\end{equation}

In recent years the classic dealkylation reaction of tertiary amines with cyanogen bromide (the von Braun reaction) has been replaced by the use of chloroformate (carbonochloridate) reagents, which have proven to be more efficient and selective.\textsuperscript{136}

The generally accepted reaction sequence is illustrated below (Scheme 5.8). The reaction could proceed via the nucleophilic attack of the chloride ion on one of the substituents of nitrogen atom (path a) leading to the formation of the carbamate ester 223. However, this dealkylation reaction can be accompanied by a decarboxylation reaction that regenerates the original trialkylamine.

Scheme 5.8 Dealkylation of Tertiary Amines with Chloroformate Reagents

The use of a number of chloroformate reagents has been reported in the chemical literature. Campbell reported the dealkylation of trialkylamines with ethyl chloroformate in boiling benzene. An improved procedure was later reported by Hobson and McCluskey using phenyl chloroformate 225 as the cleavage reagent. Employing this method, dimethylaniline 224 and quinuclidine 227 were converted to the corresponding carbamates 226 and 228 in good yields (Scheme 5.9). However, the hydrolysis of the resultant carbamates has been reported to often require the use of strong base or acid and extended reaction times.

---

Scheme 5.9 Dealkylation of Tertiary Amines with Phenyl Chloroformate (225)

[Chemical structures and reactions]

To avoid the problem encountered in the hydrolysis of the ethyl or phenyl carbamate products, Montzka and co-workers demonstrated that 2,2,2-trichloroethyl carbonochloridate 230 could be used to dealkylate tertiary methylamines.\(^{129}\) The resultant trichloroethyl carbamate derivatives were easily cleaved with zinc in acetic acid or methanol. For an example, the dealkylation of acetyltropine 229 was achieved in 75% overall yield (Scheme 5.10).

Scheme 5.10 Dealkylation of Acetyltropine with Trichloroethyl Carbonochloridate (230)

[Chemical structures and reactions]

In 1977, Olofson and co-workers introduced a mild procedure for the selective dealkylation of tertiary amines with vinyl chloroformate 232.\(^{130}\) The reactivity of vinyl chloroformate 232 towards tertiary amines was compared with existing dealkylating reagents by performing a series of reactions with N-ethylpiperidine 231 (Scheme 5.11).
The high yield (90%) obtained with vinyl chloroformate 232 was attributed to the enhanced electrophilicity of the acyl carbon which is attached to a relatively electron withdrawing ethenoxyl group (OCH=CH₂). Vinyl chloroformate 232 (VOCCl) was also employed in an improved synthesis of noroxymorphone 235, a precursor of the narcotic antagonist drug naloxone (Scheme 5.12). The oxymorphone derivative 233 was N-demethylated with VOCCl 232 in dichloroethane at reflux and resulted in the formation of the N-VOC compound 234 in essentially quantitative yield. Subsequent hydrolysis of the latter compound under acidic conditions afforded noroxymorphone 235 in 98% yield.
The previous synthesis of noroxymorphone 235 was accomplished in 20% overall yield using the von Braun reaction (cyanogen bromide).

Scheme 5.12 Synthesis of Noroxymorphone (235)

The order of cleavage of different substituents on nitrogen has been examined by Kapnang and Charles through a sequence of competitive reactions between various tertiary amines and known chloroformates. The selectivity of these reactions was established as N-debenzylation > N-deallylation > N-demethylation.

The use of the inexpensive reagent α-chloroethyl chloroformate 236 for the dealkylation of tertiary amines was reported by Olofson and Martz in 1984. This new process was illustrated by converting N-ethylpiperidine 231 to piperidine hydrochloride 237 in 99% yield (Scheme 5.13). This method was adopted in the synthesis of analgesic nalbuphine 240. The key intermediate 239 was obtained in essentially quantitative yield on N-demethylation of compound 238.

---

Scheme 5.13  *N*-Dealkylation of Tertiary Amines with α-Chloroethyl Chloroformate (236)

Scheme 5.13  *N*-Dealkylation of Tertiary Amines with α-Chloroethyl Chloroformate (236)

\[ 
\text{N-Et} + \text{ClO}_2\text{C}-\text{CH}_3 \rightarrow \text{N-O-C}=\text{CH}_3 \xrightarrow{\text{MeOH} \Delta} \text{NH-HCl} 
\]

The use of the readily available reagent phenyl chlorothionoformate 241 for the dealkylation of tertiary amines has also been investigated (Scheme 5.14).\(^{140,141}\) Dialkyl thiocarbamate products 242 were isolated in 9-98% yield. The selectivity of the cleavage process for different alkyl groups from a tertiary nitrogen centre was established as the following: benzyl ≥ t-butyl > allyl > cyclohexyl > ethyl > methyl > heterocyclic ring. The thiocarbamates 242 could be converted into the secondary amine salts 243 on treatment with dimethyl sulfate, followed by hydrolysis with water.

Scheme 5.14 Dealkylation of Tertiary Amines with Phenyl Chlorothionoformate (241)

\[
\begin{align*}
R_1^1 N^1 R^2_1 + PhOCl & \rightarrow \left[ \begin{array}{c} \text{PhO} \text{N}^1 R^1_1 \text{R}^2_2 \text{Cl} \\ \text{R}^2_3 \end{array} \right] \rightarrow R^3\text{Cl} + \text{PhO} \text{N}^1 R^1_1 \\
\text{Me}_2\text{SO}_4 & \rightarrow \left[ \begin{array}{c} \text{MeSO}_4 \text{N}^1 R^1_1 \text{MeSO}_4 \\ \text{R}^2_2 \end{array} \right] \rightarrow H_2O \rightarrow R^1_1 R^2_2 \text{NH}_{2}\text{SO}_4 
\end{align*}
\]

The use of acid chlorides as reagents for the dealkylation of tertiary amines is less common and the reaction process with these reagents is less facile. Miller and co-workers reported the dealkylation reactions of tertiary benzylamines using various acid chlorides (Scheme 5.15).\(^\text{(142)}\) Electron donating groups on the \(N\)-benzyl substituents were found to facilitate the cleavage process. However, the application of this method remains limited to the cleavage of tertiary benzylamines.

Scheme 5.15 Debenzylation of Tertiary Amines with Acid Chlorides

\[
\begin{align*}
\text{R}^2_2 \text{N}^1 \text{R}^1_1 \text{Cl} \rightarrow \left[ \begin{array}{c} \text{R}^2_2 \text{N}^1 \text{R}^1_1 \text{Cl} \\ \text{R}^3_3 \end{array} \right] & \rightarrow \text{Fast} \quad (R = \text{Electron donating group}) \\
& \rightarrow \text{Slow} \quad (R = \text{H}) \\
& \rightarrow \text{R}^3_3 \text{N}^1 \text{R}^1_1 \text{R}^2_2 \text{O}
\end{align*}
\]

Variants of the above reaction are known in which the dealkylation process is favoured by the intramolecular nucleophilic attack of a tertiary amine on an acid chloride. For example, Clarke and co-workers have examined the reactions of \(\gamma\)-dialkylamino carboxylic acids with thionyl chloride (Scheme 5.16). This procedure generates the

corresponding acid halide \textit{in situ} that then undergoes an intramolecular dealkylation reaction.

\textbf{Scheme 5.16 Intramolecular Dealkylation of Tertiary Amines with Acid Chlorides}

When nitrogen heterocycles such as 244 were subjected to these reaction conditions, ring-opened products were formed exclusively (Scheme 5.17). In contrast to the intermolecular reactions, the N-methyl or N-benzyl substituted 4-carboxypiperidines (\textit{e.g.} 245 and 248) formed azabicyclic intermediates which gave rise to the pyrrolidone products 247 and 250. The N-demethylated or N-debenzylated products were not observed. This selectivity was attributed to angle strain and the loss of the amide resonance stabilization energy that is associated with the 7-keto-1-azabicyclo[2.2.1]heptane ring system in the reaction intermediates 246 and 249.
A related reaction was later reported by Maryanoff and co-workers for the intramolecular rearrangement of the quinolizidine system 251 (Scheme 5.18).\textsuperscript{143,144} They found that when reacted with phosgene in the presence of the non-nucleophilic amine base, 2,2,2-trifluoroethylamine, the secondary amine 251 was converted to the ammonium salt 252. This rearrangement process involved an intramolecular acylation reaction with the carbamyl chloride group of the free basic nitrogen, followed by cleavage of a carbon-nitrogen bond.

Scheme 5.18 Intramolecular Rearrangement of Quinolizidine Derivative (251)

The bicyclic ammonium ion intermediate 253 had three possible sites (a, b or c) for cleavage by nucleophilic (S_N1 or S_N2) attack of chloride ion. However, the urea 254 was formed exclusively in this reaction which indicated that regiospecific fragmentation of the ammonium ion intermediate 253 through path a had occurred. The cleavage at sites b and c were considered improbable because they would lead to strained bicyclic ureas.

Recent progress on acylative dealkylation of tertiary amines has included the use of acetic anhydride as a cleavage reagent. In this case, a catalytic amount of boron trifluoride diethyl etherate is required. Secondary, tertiary and benzyl groups were cleaved preferentially from tertiary nitrogen centres (Scheme 5.19). However, tertiary amines bearing only simple primary alkyl substituents were unreactive. Based on these findings a N-acyltrialkylammonium salt intermediate similar to salt 255 was proposed

which underwent nucleophilic (S_N1-like) cleavage of a C-N bond with selective loss of the alkyl group that would form the most stable carbocation (Scheme 5.19).

Scheme 5.19  Dealkylation of Tertiary Amines with Acetic Anhydride

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{Br} \quad \text{N} \quad \text{t-Bu} \\
\xrightarrow{(\text{AcO})_2\text{O}, \text{BF}_3\text{Et}_2\text{O}} \\
\text{O}_2\text{N} & \quad \text{Br} \quad \text{N} \quad \text{Ac} \quad \text{t-Bu} \\
& \quad 81\% \\
\text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{H} \quad \text{O} \\
\xrightarrow{(\text{AcO})_2\text{O}, \text{BF}_3\text{Et}_2\text{O}} \\
\text{Ac} \quad \text{N} \quad \text{OAc} \\
& \quad 41\% \\
\text{N} \quad \text{Et} \\
\xrightarrow{(\text{AcO})_2\text{O}, \text{BF}_3\text{Et}_2\text{O}} \\
& \quad \text{no reaction} \\
\end{align*}
\]

In addition to this recent report, new reagents and methods continue to be discovered. For example, Whiting and co-workers have reported an unusual process for the dealkylation of tertiary amines with \( (Z) \)-iodoacrylate 256 (Scheme 5.20). In this reaction, the tertiary amines underwent a concomitant Michael addition-dealkylation reaction producing the \( (E) \)-dialkylamino acrylates 257 in essentially quantitative yield.\(^{146}\)

A mechanism was proposed for the formation of these adducts. The first step of the reaction involved a Michael addition of the amine to the acrylate 256 forming an ammonium propenolate zwitterion intermediate 258. This intermediate would then rapidly lose iodide, which in turn attacked one of the substituents on the ammonium nitrogen centre to complete the dealkylation process.
CHAPTER SIX

A NEW METHOD FOR THE MILD AND SELECTIVE MONO-DEALKYLATION OF TERTIARY AMINES: RESULTS AND DISCUSSION

6.1 Introduction

As mentioned in the previous chapter, a new N-dealkylation reaction of triethylamine was discovered in an attempted oxidation reaction of the known hydroxy crown ether derivative 217 under modified Swern conditions at -78 °C using oxalyl chloride (1.5 equiv), DMSO (2.6 equiv) and triethylamine (5.0 equiv). Instead of isolating the expected ketone product, the amide 218 was isolated as the major product in 70% yield (see: Scheme 5.2).

Based on this interesting experimental observation, a mild and selective method for the mono-dealkylation of tertiary amines has been developed and the results of this study are reported herein.

6.2 Preparation of Hydroxy Crown Ether (217)

The hydroxy crown ether 217, that was initially required for another research project in our laboratory, was prepared in two steps from catechol 259 and bis(2-chloroethyl)ether 260. Deprotonation of catechol 259 with sodium hydroxide in water followed by the nucleophilic attack on bis(2-chloroethyl) ether 260 afforded the desired
bis[2-(ortho-hydroxyphenoxy)ethyl] ether 261 in 40% yield after recrystallization (Scheme 6.1).\textsuperscript{147}

**Scheme 6.1 Preparation of bis[2-(ortho-Hydroxyphenoxy)ethyl] Ether (261)**

\[ \begin{array}{ccc}
\text{OH} & + & \text{Cl}\xrightarrow{a) NaOH, H}_2\text{O, reflux, 48 h, 40%} \text{OH} \\
\text{259} & & \text{260} \\
\end{array} \]

\textsuperscript{a} Reagents and conditions: a) NaOH, H\textsubscript{2}O, reflux, 48 h, 40%.

The melting point of the product 261 was in agreement with the literature reported value and a molecular ion was observed by mass spectroscopy (Cl).\textsuperscript{147} The \textsuperscript{1}H NMR spectrum of the product showed signals for the ethylene protons at \( \delta \) 3.87 ppm (4H) and 4.22 ppm (4H). The aromatic protons were observed at \( \delta \) 6.77-7.03 ppm (8H) and the phenolic protons at \( \delta \) 7.57 ppm (2H), which confirmed the molecular structure of the product 261.

The bis[2-(ortho-hydroxyphenoxy)ethyl] ether 261 was then heated with sodium hydroxide in water at 90-100 °C and then reacted with epichlorohydrin at 50 °C for 5 h. The known hydroxy crown ether 217 was isolated in 44% yield as a white solid after flash chromatography on silica gel (Scheme 6.2).\textsuperscript{148}

Scheme 6.2 Preparation of the Known Hydroxy Crown Ether (217)

\[ \text{Reagents and conditions: a) NaOH, H}_2\text{O, 50 °C, 5 h, 44%}. \]

The melting point obtained for the product was again in agreement with the literature reported value. A molecular ion was observed by mass spectroscopy (CI) and the elemental analysis obtained for this compound was satisfactory. The disappearance of the phenolic proton signal in the \(^1\text{H} \) NMR spectrum of this product along with the presence of the alcohol hydroxyl proton signal at \( \delta 3.29 \text{ ppm} \) confirmed the formation of the crown alcohol 217.

6.3 \textit{N-Dealkylation of Tertiary Amines with Hydroxy Crown Ether (217) and Oxalyl Chloride}

The original \textit{N}-dealkylation reaction of triethylamine was discovered in the attempted oxidation reaction of the crown alcohol 217 under modified Swern conditions. However, preliminary experimental results revealed that this dealkylation process could be carried out in the absence of DMSO.

The proposed mechanism of this reaction is illustrated below (Scheme 6.3). The crown alcohol 217 reacts with oxalyl chloride to generate the chlorocarbonyl formate intermediate 262, which then undergoes an acylative dealkylation reaction with triethylamine via the quarternary ammonium salt 263 to give the amide product 218.
This reaction pathway bears some analogy to the well established acylative dealkylation reaction of tertiary amines with chloroformates that affords carbamate reaction products.\textsuperscript{142} It is believed that electron-withdrawing groups attached to the acyl carbons enhance the reactivity of the chloroformate reagents.\textsuperscript{130} In this case, the chlorocarbonyl formate intermediate 262 is activated by an adjacent carbonyl group.

\textbf{Scheme 6.3 Proposed Mechanism for the Formation of Amide (218)}

Following these preliminary studies, a practically simpler procedure was developed to perform this mono-dealkylation reaction. This procedure (Method A) involved treatment of the crown alcohol 217 (1 equiv) with excess oxalyl chloride (3 equiv) in dichloromethane at 0 °C. The reaction mixture was then concentrated \textit{in vacuo} to remove hydrogen chloride and excess oxalyl chloride. The resultant residue was then resuspended in dichloromethane and treated with triethylamine (3 equiv) at 0 °C. The reaction mixture was then allowed to warm to room temperature over the course of 1 hour and following concentration, the amide 218 was isolated by flash chromatography on silica gel in 86% yield.
The product of this reaction, the compound 218, was fully characterized. The molecular ion of the compound was observed by mass spectroscopy (CI) and the elemental analysis data were in agreement with the proposed structure. Two carbonyl absorptions were evident at 1741 and 1657 cm\(^{-1}\) in the IR spectrum confirming the formation of the amide product. The \(^1\)H NMR spectrum of this compound is presented below (Figure 6.1). The spectrum contained multiplets at \(\delta\) 6.81-7.04 ppm (8H, aromatic), \(\delta\) 3.93 (4H, 2 x ArOCH\(_2\)) and 4.16 ppm [4H, (CH\(_2\)\(_2\))O]. The two methylene groups in the crown ether moiety appeared as two doublet of doublets at \(\delta\) 4.39 and 4.47 ppm. The protons of the two ethyl substituents on the nitrogen atom corresponded to two sets of a triplet and a quartet with a coupling constant of 7.3 Hz.
Figure 6.1 $^1$H NMR spectrum (400 MHz, CDCl$_3$) of amide (218).

The $^{13}$C NMR spectrum of this compound 218 is also presented below (Figure 6.2). The signals for the aromatic carbon atoms appeared between $\delta$ 121 and 151 ppm. Two peaks were observed at low field ($\delta$ 161.5 and 163.3 ppm), which were characteristic for carbonyl carbons. The remaining carbon atoms in the molecule corresponded to resonance signals in the upper field ($\delta$ 12-74 ppm).
It was found that a variety of tertiary amines could be mono-dealkylated under these reaction conditions (Method A, Table 6.1). A mono-deallylation reaction occurred readily with triallylamine 264 and afforded the corresponding amide 265 in 88% yield (Entry 1). When dimethylbenzylamine 266 was subjected to these reaction conditions the benzyl group was cleaved exclusively and gave rise to the amide 267 in good yield (90%, Entry 2). An interesting observation was made, in that an isopropyl group was cleaved in
preference to an ethyl group when Hünig's base \((N,N\text{-diisopropylethylamine})\) 268 was employed as the reaction substrate (Entry 3). This selective cleavage reaction suggests that for a secondary alkyl group the reaction occurs via a relatively facile \(S_N1\) process. This finding is in agreement with the result reported by Maw and co-workers in which the dealkylation reaction of Hünig's base 268 was performed with methyl \((Z)\)-iodoacrylate.\(^{146}\) In this reaction, the loss of isopropyl group occurred exclusively (93%).

The cyclic tertiary amine, \(N\)-methyl morpholine 271 has been used frequently as a substrate in the study of \(N\)-dealkylation reactions.\(^{141}\) In most cases the methyl group was lost preferentially and this was found to be the case in this instance (Entry 4). The sterically hindered amine, tribenzylamine 273 was found to be unreactive under these conditions (Entry 5). This observation is in agreement with the findings reported by Strepkheev and co-workers in their study of the reactions of phosgene with tertiary amines.\(^{135}\)

**Table 6.1 Mono-Dealkylation of Various Tertiary Amines Using Chlorocarbonyl Formate (262) as the Cleavage Reagent (Method A)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tertiary Amine</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{264})</td>
<td>(\text{265})</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{266})</td>
<td>(\text{267})</td>
<td>90%</td>
</tr>
</tbody>
</table>
In view of the cost and in some cases the limited availability of the tertiary amine starting materials, a general procedure was subsequently developed in which the tertiary amine was used as the limiting reagent. In this method (Method B), oxalyl chloride (3.3 equiv) was dissolved in dry dichloromethane and cooled to 0 °C. The crown alcohol 217 (1.1 equiv) was then added and the reaction mixture was allowed to warm to room temperature over 1 h. The volatiles were then removed in vacuo and the resultant solid residue was redissolved in dichloromethane. The tertiary amine (1 equiv) was then added at 0 °C and the reaction mixture was again allowed to warm to room temperature. After 1 h the reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography.
As mentioned in Chapter Five of this thesis, the selective dealkylation of tertiary amines is of particular importance in the synthesis of complex organic molecules. Therefore it was of synthetic interest to test this new dealkylation method with more structurally complex tertiary amines. Tropane 275 was selected as a substrate and it was found that the methyl group could be cleaved preferentially under these reaction conditions (Method B). This finding was similar to the results reported in the literature for the dealkylation of the structurally related tertiary amine, tropine acetate 229, using \(\alpha\)-chloroethyl chloroformate 236 as the cleavage reagent.\(^{149}\)

**Scheme 6.5 N-Dealkylation of Tropane (275) and Tropine Acetate (229)**\(^{149}\)

\[
\begin{align*}
\text{Oxalyl chloride} + \text{Tropine acetate} & \quad \xrightarrow{\Delta} \quad \text{Tropine acetate} \text{Ac}
\end{align*}
\]

In order to gain further insight into the reaction mechanism, quinuclidine 277 was also subjected to these reaction conditions. Subsequent isolation and characterization of the major product of this reaction confirmed indirectly our hypothesis that ethyl chloride was lost in the original reaction with triethylamine. A plausible mechanism for this process is depicted below (Scheme 6.6). On reaction of the crown alcohol 217 with oxalyl chloride, the resultant ester 262 reacted with quinuclidine 277 to afford the ionic material.

intermediate 278. Subsequent nucleophilic attack of the chloride counterion then effected the dealkylation reaction. In this case, the alkyl halide function was retained in the reaction product 279.

Scheme 6.6 Dealkylation Reaction of Quinuclidine (277)

\[
\begin{align*}
\text{217} & \quad \text{(COCl)}_2, \text{CH}_2\text{Cl}_2 \quad 0^\circ\text{C to rt} \quad \text{Cl}^- \\
\text{Cl}^- & \quad \text{278} \quad \text{262} \quad \text{N} \quad \text{277, CH}_2\text{Cl}_2 \quad 0^\circ\text{C to rt} \\
\text{279, 73%} & \quad \text{O} \quad \text{Cl} \\
\end{align*}
\]

All of the \(N\)-dealkylation products discussed above were fully characterized. The molecular mass of each compound was obtained by mass spectroscopy (CI or MALDI-TOF). Elemental analysis was also obtained for each product and the results are presented in the experimental section (see: Chapter Seven). The IR spectrum of each compound showed strong absorption bands at \(\sim 1750\) and \(1650\ \text{cm}^{-1}\) confirming the presence of the two carbonyl functions in each product. The \(^1\text{H}\) NMR spectra of these compounds showed signals at \(\sim \delta 6.8\) (8H, aromatic), 3.9 (4H, 2 x ArOCH\(_2\)) and 4.2 ppm [4H, \((CH_2)_2O\)]. Two doublet of doublets were observed at \(\sim \delta 4.4\) ppm for the OCH\((CH_2)_2\) protons in the crown ether moiety. The \(^{13}\text{C}\) signals for the carbonyl carbons were observed between \(\delta 160\) ppm and 164 ppm. Of note, in the case of the dealkylation reaction of Hünig’s base 268, the amide product 269 showed two sets of signals in the \(^1\text{H}\)
and $^{13}$C NMR spectra indicating the existence of the two conformationally restricted rotamers of the reaction product.

6.4 $N$-Dealkylation of Tertiary Amines with Various Alcohols

In light of the promising results discussed above, efforts were then directed to identify the potential utility of other alcohols that could be used in this novel dealkylation process in order to optimize the reaction conditions. A closely related derivative of the original crown ether, 1,3-bis(ortho-methoxyphenoxy)-2-propanol 281, was selected in the first instance. The preparation of this compound involved heating 2-methoxyphenol 281 with sodium hydroxide at 90 °C followed by reaction with epichlorohydrin between 50 °C and room temperature. The expected alcohol 281 was isolated in 76% yield as a white solid. The characterization data of this compound was in agreement with those reported in the literature.150

Scheme 6.7 Preparation of 1,3-bis(ortho-Methoxyphenoxy)-2-propanol (281)$^a$

$^a$ Reagents and conditions: a) NaOH, H$_2$O, 50 °C to rt, 16 h, 76%.

Alcohol 281 was then used for the dealkylation reaction of triethylamine (Method A). The expected amide 282 was isolated in 43% yield after flash chromatography on silica gel.

Scheme 6.8 Dealkylation Reaction of Triethylamine with Alcohol (281)\textsuperscript{a}

\begin{align*}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{OH} \\
\text{281}
\end{array}
\quad \xrightarrow{a)} \quad
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{O} \\
\text{Et} \\
\text{282}
\end{array}
\end{align*}

\textsuperscript{a} Reagents and conditions: a) (COCl)\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1 h then Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1 h, 43%.

This result demonstrated that various alcohols could potentially be used in this dealkylation process. Further experiments were performed in which a series of commercially available alcohols including (-)-menthol 283, 2,4-dimethyl-3-pentanol 285 and benzylalcohol were used to effect the dealkylation reaction. The corresponding amides 284, 286 and 287 were obtained in 47-67\% yield (Method A).
Scheme 6.9 Dealkylation Reactions of Triethylamine with Various Alcohols

Reagents and conditions: a) \((\text{COCl})_2, \text{CH}_2\text{Cl}_2, 0 ^{\circ}\text{C to rt, 1 h then Et}_3\text{N, CH}_2\text{Cl}_2, 0 ^{\circ}\text{C to rt, 1 h.}\)

In continued efforts to search for an effective and simple commercially available alcohol for this dealkylation reaction we discovered that cyclohexanol 288 afforded the corresponding product 290 in similar yield (84%, Method A and B, Scheme 6.10) as was found in the reaction with the hydroxy crown alcohol 217. These results encouraged us to investigate the ease, selectivity and yields of the dealkylation reactions of various readily available tertiary amines using the cyclohexanol-derived chlorocarbonyl formate 289.
Employing Method B, the experimental results obtained from the dealkylation reactions of a number of tertiary amines bearing different alkyl groups are summarized below (Table 6.2). Among the compounds studied, quinuclidine 277 was transformed to the expected amide 291 in 66% yield (Entry 1). Triallylamine 264 was dealkylated easily to afford the corresponding amide 292 in 81% yield (Entry 2). Interestingly, although tribenzylamine 273 was found to be unreactive to the dealkylation reaction with the hydroxy crown alcohol 217, the debenzylated product 293 was isolated, albeit in a low yield (9%), in this instance (Entry 3). This improved reactivity might be attributable to the smaller size of the monoester intermediate 289 formed from cyclohexanol and oxalyl chloride, which would impose less steric hindrance to nucleophilic attack by the amine 273. In the case of the less bulky amine, dimethylbenzylamine 266, debenzylation occurred readily and the amide product 294 was isolated in good yield (90%, Entry 4). In addition, the loss of an isopropyl group occurred preferentially in the dealkylation reaction of Hünig’s base 268 (Entry 5). Similar findings were observed when the hydroxy crown ether 217 was used (Table 6.1). Furthermore, the methyl substituent of the cyclic tertiary amines, N-methylmorpholine 271 (Entry 6) and tropane 275 (Entry 7) were cleaved exclusively and resulted in the isolation of the corresponding amides 296 and 297 in 46% and 92% yield, respectively.
Table 6.2 Mono-Dealkylation of Various Tertiary Amines Using Cyclohexanol Derived Chlorocarbonyl Formate (289) as the Cleavage Reagent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tertiary amine</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="277" alt="Tertiary amine" /></td>
<td><img src="291" alt="Product" /></td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td><img src="264" alt="Tertiary amine" /></td>
<td><img src="292" alt="Product" /></td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td><img src="273" alt="Tertiary amine" /></td>
<td><img src="293" alt="Product" /></td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td><img src="266" alt="Tertiary amine" /></td>
<td><img src="294" alt="Product" /></td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td><img src="268" alt="Tertiary amine" /></td>
<td><img src="295" alt="Product" /></td>
<td>69%</td>
</tr>
<tr>
<td>6</td>
<td><img src="271" alt="Tertiary amine" /></td>
<td><img src="296" alt="Product" /></td>
<td>46%</td>
</tr>
<tr>
<td>7</td>
<td><img src="275" alt="Tertiary amine" /></td>
<td><img src="297" alt="Product" /></td>
<td>92%</td>
</tr>
</tbody>
</table>
All of the amide products obtained from the dealkylation reactions with cyclohexanol and oxalyl chloride were again fully characterized. The molecular mass of each compound was determined by mass spectroscopy (CI or MALDI-TOF). Elemental analysis was performed on each product and the results were found to be satisfactory. Two strong absorption bands at ~ 1730 and 1660 cm\(^{-1}\) were observed in each of the IR spectra, which are characteristic of two carbonyl groups. The \(^{1}\text{H}\) NMR spectra showed signals at \(\delta 1.1-1.9\) ppm (10H, 5 x cyclohexyl-\(\text{CH}_2\)) and at \(\delta 4.9\) ppm (HCO). The two carbonyl carbons appeared at ~ \(\delta 162\) and 164 ppm in the \(^{13}\text{C}\) NMR spectra. As expected, the dealkylation product 295 from Hünig's base 268 exhibited two sets of signals in the \(^{1}\text{H}\) and \(^{13}\text{C}\) NMR spectra corresponding to the two conformationally restricted rotamers of the product.

A representative \(^{1}\text{H}\) NMR spectrum of amide 290 is presented below (Figure 6.3). The signals for the ethyl substituents on nitrogen appeared as two sets of a triplet and a quartet with a coupling constant of 7.2 Hz. A group of multiplets were observed at \(\delta 1.14-1.94\) ppm corresponding to the cyclohexyl-\(\text{CH}_2\) protons. The remaining proton on the cyclohexyl ring (HCO) was at \(\delta 4.95\) ppm.
Figure 6.3 $^1$H NMR spectrum (400 MHz, CDCl$_3$) of amide (290).

The $^{13}$C NMR spectrum of this amide 290 is presented below (Figure 6.4). Two distinctive signals appeared at low field (δ 161.9 and 163.1 ppm) that corresponded to the two carbonyl carbons of the molecule.
**Figure 6.4** $^{13}$C NMR spectrum (101 MHz, CDCl$_3$) of amide (290).

### 6.5 Dealkylation Reaction with Pre-made Monoesters of Oxalyl Chloride

In an attempt to further simplify the dealkylation procedure, the cyclohexanol derived cleavage reagent 289 was prepared by the reaction of cyclohexanol and oxalyl chloride (3 equiv) in dichloromethane at 0 °C to room temperature. After 1 h, the volatiles were removed *in vacuo* and the residue was left on the high vacuum overnight. The crude product was then stored as a stock solution in dichloromethane in the
refrigerator under nitrogen.\textsuperscript{151} A portion of this stock solution (1.5 equiv relative to the amine) was transferred by syringe into the reaction flask and the temperature was adjusted to 0 °C. A tertiary amine was then added under nitrogen. The resultant mixture was allowed to warm to room temperature and stirred for 1 h. The volatiles were removed \textit{in vacuo} and the corresponding amide was isolated by flash chromatography. Employing this method, the dealkylation reaction of triallylamine 264, dimethylbenzylamine 266 and Hünig's base 268 proceeded cleanly and selectively as expected (Scheme 6.11). However, the yields of these reactions were slightly lower than the corresponding reactions with the freshly prepared chlorocarbonyl formate 289 using Method B.

\textsuperscript{151} Attempted distillation of the crude product under high vacuum resulted in decomposition.
Scheme 6.11 Dealkylation of Tertiary Amines with Pre-made Chlorocarbonyl Formate (289)

The decrease in reaction yields might be attributable to the instability of this chlorocarbonyl formate reagent 289 in dichloromethane as colouration of the stock solution was observed soon after the solution was prepared. For comparison purposes, the commercially available mono-ethyl ester of oxalyl chloride was also used in the dealkylation reactions. Thus, ethyl chlorooxoacetate 298 (1.1 equiv) was dissolved in dichloromethane and cooled to 0 °C and triethylamine was then added. The reaction was allowed to warm to room temperature over 1 h and then was concentrated in vacuo. The amide product 299 was isolated in 65% yield after flash chromatography. When N,N-dimethylbenzylamine 266 was subjected to these reaction conditions, the benzyl group
was cleaved as expected and the corresponding amide product 300 was obtained in 62% yield.

Scheme 6.12 Reaction of Ethyl Chlorooxoacetate (298) with Triethylamine and N,N-Dimethylbenzylamine (266)$^a$

![Chemical Structures](image)

$^a$ Reagents and conditions: a) CH$_2$Cl$_2$, 0 °C to rt, 1 h.

These results clearly demonstrated that the dealkylation reaction with freshly prepared cyclohexyl chlorocarbonyl formate 289 (Method B) is a higher yielding procedure.

6.6 Dealkylation of (2S)-1-Benzyl-2-[(benzyloxy)methyl]pyrrolidine

With the new method for the selective dealkylation of tertiary amines established, our final goal was to examine the chemoselectivity of this method with tertiary amines in the presence of other potential dealkylation sites and to identify suitable reaction conditions in order to obtain the corresponding secondary amines. Towards these ends, a benzyl ether compound containing both a tertiary benzylamine and a benzyl ether moiety was considered and so (2S)-1-benzyl-2-[(benzyloxy)methyl]pyrrolidine 302 was selected as the substrate for investigation.
The substrate 302 was prepared in 85% yield by the reaction of (S)-(+)−2-pyrroldinemethanol 301 with excess benzylbromide on deprotonation with sodium hydride (Scheme 6.13). The product 302 was fully characterized and the $^1$H NMR spectrum of the product showed signals at $\delta$ 7.19-7.41 ppm (10H, aromatic) confirming the incorporation of the two benzyl groups in the product.

Scheme 6.13 Preparation of (2S)-1-Benzyl-2-[(benzyloxy)methyl]pyrrolidine (302)$^a$

![Scheme 6.13](image)

$^a$ Reagents and conditions: a) NaH, THF, rt, 16 h, 85%.

The dealkylation reaction of the substrate 302 was carried out employing cyclohexanol 288 and oxalyl chloride (Method B). The $N$-benzyl group in the starting material was cleaved successfully while the benzyl ether moiety was unaffected (Scheme 6.14). The expected amide product 303 was isolated in 83% yield after flash chromatography on silica gel. The mass spectrum of the product contained a molecular ion (MALDI-TOF) and the elemental analysis was found to be satisfactory. The IR spectrum of the product exhibited two strong absorption bands at 1731 and 1659 cm$^{-1}$ confirming the presence of the two carbonyl groups in the molecule. The $^1$H NMR spectrum showed signals for the cyclohexyl protons (11H) and aromatic protons (5H), confirming one of the two benzyl groups in the starting material 302 had been cleaved. Further evidence of the formation of the amide product 303 came from the two sets of signals in the NMR spectra that corresponded to the two rotameric forms of the product.

Scheme 6.14 Dealkylation of (2S)-1-Benzyl-2-[(benzyloxy)methyl]pyrrolidine (302)$^a$

\[
\begin{array}{c}
\text{OH} \quad \text{a)} \\
\text{288} \quad \text{[OCCl$_2$]} \quad \text{b)} \quad \text{N-Obn} \\
\text{289} \quad \text{302} \quad \text{303}
\end{array}
\]

$^a$ Reagents and conditions: a) (COCl)$_2$, CH$_2$Cl$_2$, 0 °C to rt, 1 h; b) CH$_2$Cl$_2$, 0 °C to rt, 1 h, 83%.

Amide hydrolysis can be achieved with acid or base-catalysis.$^{145}$ In the case of (2S)-1-benzyl-2-[(benzyloxy)methyl]pyrrolidine, the hydrolysis reaction was achieved in good yield (95%) by heating compound 302 at reflux in 10% aqueous KOH (Scheme 6.15). The secondary amine product 304 was fully characterized and the data were in accordance with those reported in the literature.$^{153}$ A peak corresponding to the molecular ion was observed in the mass spectrum (MALDI-TOF) and the elemental analysis results were again satisfactory. Evidence of an N-H bond present in the product was provided by a broad absorption band at 3343 cm$^{-1}$ in the IR spectrum. The absence of the cyclohexyl signals and the appearance of the NH signal (δ 3.19 ppm, broad) in the $^1$H NMR spectrum confirmed the successful hydrolysis of the amide function in the starting material 303.

---

Scheme 6.15  Hydrolysis of Amide (303)\textsuperscript{a}

\[
\begin{array}{c}
\text{303} \\
\text{304}
\end{array}
\]

\textsuperscript{a} Reagents and conditions: a) KOH (aq, 10\% w/v), reflux, 3.5 h, 95%.

6.7  Conclusion

A novel and facile method for the mono-dealkylation of tertiary amines has been developed using a monoester of oxalyl chloride as the cleavage reagent. A variety of alcohols were examined and cyclohexanol was found to be the most effective, simple and inexpensive reagent to effect this selective dealkylation process. The scope of this reaction was assessed with various cyclic and acyclic tertiary amines (Table 6.2) and the results clearly demonstrate that this method is mild, selective and has a broad potential. The selectivity of the cleavage process for common alkyl groups from tertiary nitrogen centres was established as the following: benzyl > allyl > methyl > heterocyclic ring.

The use of this new dealkylation method for selective N-debenzylation in the presence of benzyl ether was demonstrated. The selective removal of the N-benzyl group of (2S)-1-benzyl-2-[(benzyloxy)methyl]pyrrolidine 302 proceeded smoothly which resulted in the isolation of the desired amide product 303 in 83\% yield. In addition, hydrolysis of the amide product under basic conditions afforded the desired secondary amine product 304 in excellent yield (95\%).
In summary, the method discussed herein provides a useful means for the mild and selective dealkylation of tertiary amines. This process should have wide applicability and provide an alternate and efficient means to deprotect amines.\(^\text{154}\)

CHAPTER SEVEN

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA CONCERNING CHAPTER SIX

7.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware, unless indicated otherwise. The reaction temperatures stated were those of the external bath.

Tetrahydrofuran (THF) was dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Dichloromethane was dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied.\textsuperscript{124} Brine refers to a saturated aqueous solution of sodium chloride.

Column chromatography (“flash chromatography”) was carried out using Merck silica gel 60 (230 to 400 mesh).\textsuperscript{125} Thin layer chromatography (TLC) was performed using Merck silica gel 60 F\textsubscript{254} plates. Visualisation was achieved with a ultraviolet lamp, treatment with a solution of \textit{p}-anisaldehyde (2.6\% v/v), acetic acid (1.1\% v/v) and sulfuric acid (3.5\% v/v) in 95\% ethanol and on subsequent heating or by exposure to iodine preabsorbed on silica.
Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected.

Optical rotations were measured using a Perkin-Elmer 341 digital polarimeter at room temperature.

All proton and carbon nuclear magnetic resonance spectra ($^1$H and $^{13}$C NMR, respectively) were recorded using a Bruker AMX 400 FT spectrometer (operating frequencies: $^1$H, 400.13 MHz; $^{13}$C, 100.61 MHz) at ambient temperature. Chemical shifts ($\delta$) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform (CDCl$_3$) were 7.26 and 77.16 ppm for $^1$H and $^{13}$C NMR spectra, respectively. The reference values used for deuterated benzene (C$_6$D$_6$) were 7.15 and 128.02 ppm for $^1$H and $^{13}$C NMR spectra, respectively.

Infrared spectra (IR) were recorded as either KBr discs (KBr) or as evaporated films (ef) using a Perkin Elmer 599B IR spectrophotometer.

Low-resolution mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer. The mode of ionization used was chemical ionization (CI) with isobutane. Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF) were recorded on a PerSeptive Biosystems Voyager-DE mass spectrometer using $\alpha$-cyano-4-hydroxycinnamic acid as the matrix.

Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer.
7.2 Experimental Procedures and Characterization Data

7.2.1 bis-[2-(ortho-Hydroxyphenoxy)ethyl] ether (261)

To a stirred solution of catechol 259 (3.60 g, 327 mmol) and sodium hydroxide (4.43 g, 111 mmol) in water (260 mL) at reflux was added bis(2-chloroethyl) ether (6.30 mL, 53.7 mmol) over 3 h. The reaction mixture was heated for an additional 48 h and then allowed to cool to room temperature. The reaction product was isolated by filtration, washed with water (2 x 50 mL) and recrystallized from benzene to afford the title compound 261 (9.57 g, 40%) as a white solid. M.p. 83-85 °C, benzene (lit. M.p. 83-85 °C, after sublimation); $^1$H NMR (CDCl$_3$) $\delta$ 3.87 (m, 4H, $\text{CH}_2$O), 4.22 (m, 4H, 2 x ArOCH$_2$), 6.77-7.03 (m, 8H, ArH), 7.57 (broad s, 2H, OH); $^{13}$C NMR (CDCl$_3$) $\delta$ 69.7, 70.0, 116.2, 116.4, 120.3, 123.7, 145.9, 147.7; IR (KBr) 3321 (broad), 2945, 2885, 1597, 1503, 1461, 1267, 1115, 737 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 291 (M + H, 100), 181 (14), 137 (8).
To a solution of sodium hydroxide (2.06 g, 51.6 mmol) in water (500 mL) was added bis[2-(ortho-hydroxyphenoxy)ethyl] ether 261 (7.50 g, 25.8 mmol) at room temperature. The resultant mixture was heated at 90-100 °C until a homogeneous solution was obtained. The resultant colourless solution was cooled to 50 °C and epichlorohydrin (2.0 mL, 26 mmol) was added over 3 h. The reaction mixture was then heated at 50 °C for an additional 5 h and then allowed to cool to room temperature. The resultant suspension was filtered and the solid product was dissolved in dichloromethane (50 mL) and washed with water (2 x 10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was then purified by flash column chromatography using ether as the eluant to afford the title compound 217 (3.90 g, 44%) as a white solid. M.p. 121-123 °C, ether (lit. M.p. 122-123 °C, octane); \(^1\text{H NMR}\) (CDCl\(_3\)) \(\delta\) 3.29 (broad s, 1H, OH), 3.93 (apparent t, \(J = 4.3\) Hz, 4H, 2 x ArOCH\(_2\)), 4.18 (m, 4H, 2 x ArOCH\(_2\)CH\(_2\)), 4.25 (m, 4H, (CH\(_2\))\(_2\)O), 4.36 (m, 1H, HCOH), 6.85-7.03 (m, 8H, ArH); \(^{13}\text{C NMR}\) (CDCl\(_3\)) \(\delta\) 68.1, 69.8, 69.8, 73.3, 114.2, 118.8, 121.8, 123.3, 148.8, 150.3; IR (KBr) 3406 (broad), 2927, 2870, 1594, 1507, 1452, 1258, 1123, 735 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 347 (M + H, 100), 181 (8), 175 (5), 137 (6); Anal. Calcd. for C\(_{19}\)H\(_{22}\)O\(_6\): C, 65.88; H, 6.40. Found: C, 65.57; H, 6.41.
7.2.3 General Procedures for the Mono-Dealkylation of Tertiary Amines

**Method A.** To a solution of oxalyl chloride (76 µL, 0.87 mmol) in dichloromethane (4 mL) was added a solution of the appropriate alcohol (0.289 mmol) in dichloromethane (1 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature over 1 h. The volatiles (hydrogen chloride and excess oxalyl chloride) were then removed *in vacuo*. The resultant residue was dissolved in dichloromethane (5 mL), cooled to 0 °C and the appropriate amine (0.867 mmol) was then added. The reaction mixture was then allowed to warm to room temperature over 1 h. The volatiles were again removed *in vacuo* to afford the crude products which were purified by flash chromatography.

**Method B.** To a solution of oxalyl chloride (430 µL, 4.93 mmol) in dry dichloromethane (6 mL) was added the appropriate alcohol (1.65 mmol) in dichloromethane (1 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature over 1 h. The volatiles were then removed *in vacuo* and the residue was dissolved in dichloromethane (7 mL) and the resultant solution was cooled to 0 °C. The appropriate amine (1.50 mmol) was then added and the reaction mixture was again allowed to warm to room temperature over 1 h. The reaction mixture was then concentrated *in vacuo* and the crude products which were purified by flash chromatography.
7.2.4 Reaction of alcohol (217) with triethylamine

Method A. Employing alcohol 217 (100 mg, 0.289 mmol), oxalyl chloride (76 μL, 0.87 mmol) and triethylamine (120 μL, 0.861 mmol). Flash chromatography using ether as the eluant afforded the product 218 (78 mg, 86%) as a colourless oil. \( ^1H \text{NMR} \) (CDCl\(_3\)) \( \delta \) 1.21 (t, \( J = 7.3 \) Hz, 3H, CH\(_3\)), 1.25 (t, \( J = 7.3 \) Hz, 3H, CH\(_3\)), 3.43 (q, \( J = 7.3 \) Hz, 2H, NCH\(_2\)), 4.16 (m, 4H, 2 x ArOCH\(_2\)CH\(_2\)), 4.39 (dd, \( J = 10.8, 6.5 \) Hz, 2H, 2 x ArOCHH), 4.47 (dd, \( J = 10.8, 4.3 \) Hz, 2H, 2 x ArOCHH), 5.74 (m, 1H, HCO), 6.81-7.04 (m, 8H, ArH); \( ^{13}C \text{NMR} \) (CDCl\(_3\)) \( \delta \) 12.7, 14.4, 39.0, 42.6, 67.6, 69.7, 70.5, 73.1, 113.3, 119.6, 121.4, 123.7, 147.9, 150.6, 161.5, 163.3; \( IR \) (ef) 2979, 2881, 1741, 1657, 1596, 1499, 1453, 1259, 1129, 737 cm\(^{-1}\); \( MS \) (Cl) m/z (rel. intensity) 474 (M + H, 100), 329 (5), 175 (5); Anal. Calcd. for C\(_{25}\)H\(_{31}\)NOS: C, 63.41; H, 6.60; N, 2.96. Found: C, 63.50; H, 5.55; N, 2.79.

7.2.5 Reaction of alcohol (217) with triallylamine (264)

Method A. Employing the alcohol 217 (100 mg, 0.289 mmol), oxalyl chloride (76 μL, 0.87 mmol) and triallylamine 264 (150 μL, 0.864 mmol). Flash chromatography using ethyl acetate/hexanes (40%) as the eluant afforded the product 265 (246 mg, 88%)
as a white solid. **M.p.** 79-81 °C, ethyl acetate/hexanes; **^1H NMR** (CDCl₃) δ 3.91 (m, 4H, 2 x ArOCH₂CH₂), 3.99 (apparent d, J = 6.0 Hz, 2H, NCH₂), 4.03 (apparent d, J = 6.1 Hz, 2H, NCH₂), 4.16 (m, 4H, (CH₂)₂O), 4.38 (dd, J = 10.8, 6.4 Hz, 2H, 2 x ArOCHH), 4.47 (dd, J = 10.8, 4.3 Hz, 2H, 2 x ArOCHH), 5.17-5.29 (m, 4H, 2 x CH=CH₂), 5.69-5.90 (m, 3H, HCO and 2 x CH=CH₂), 6.81-6.91 (m, 4H, ArH); **^13C NMR** (CDCl₃) δ 46.1, 49.8, 67.6, 69.7, 70.4, 73.3, 113.3, 118.8, 119.3, 119.7, 121.4, 123.8, 131.7, 132.5, 147.9, 150.6, 161.7, 162.8; **IR** (ef) 2959, 2872, 1731, 1661, 1458, 1298, 1229, 788 cm⁻¹; **MS** (MALDI-TOF) m/z 520 (M + Na), 498 (M + H); **Anal.** Calcd. for C₂₇H₃₁N₀₈: C, 65.18; H, 6.28; N, 2.82. Found: C, 64.79; H, 6.39; N, 2.71.

7.2.6 Reaction of alcohol (217) with N,N-dimethylbenzylamine (266)

![Chemical Structure](image)

**Method A.** Employing alcohol 217 (100 mg, 0.289 mmol), oxalyl chloride (76 μL, 0.87 mmol) and N,N-dimethylbenzylamine 266 (130 μL, 0.865 mmol). Flash chromatography using methanol/dichloromethane (5%) as the eluant afforded the product 267 (113 mg, 90%) as a colourless oil. **^1H NMR** (CDCl₃) δ 3.01 (s, 3H, CH₃), 3.12 (s, 3H, CH₃), 3.92 (m, 4H, 2 x ArOCH₂CH₂), 4.16 (m, 4H, (CH₂)₂O), 4.39 (dd, J = 10.8, 6.4 Hz, 2H, 2 x ArOCHH), 4.47 (dd, J = 10.8, 3.9 Hz, 2H, 2 x ArOCHH), 5.75 (m, 1H, HCO), 6.82-6.90 (m, 4H, ArH), 6.93-7.02 (m, 4H, ArH); **^13C NMR** (CDCl₃) δ 34.1, 37.3, 67.6, 69.7, 70.5, 73.2, 113.3, 119.6, 121.4, 123.8, 147.9, 150.6, 161.8, 163.0; **IR** (ef) 2928, 2876, 1742, 1664, 1596, 1499, 1454, 1258, 1223, 1124, 749 cm⁻¹; **MS** (MALDI-
TOF) m/z 468 (M + Na), 446 (M + H); Anal. Calcd. for C_{23}H_{27}NO_8: C, 62.01; H, 6.11; N, 3.14. Found: C, 62.19; H, 6.35; N, 2.95.

7.2.7 Reaction of alcohol (217) with N,N-diisopropylethylamine (268)

Method A. Employing the alcohol 217 (100 mg, 0.289 mmol), oxalyl chloride (76 μL, 0.87 mmol) and N,N-diisopropylethylamine 268 (150 μL, 0.861 mmol). Repetitive flash chromatography using methanol/dichloromethane (1%) and then ether/hexanes (80%) as eluants afforded the major product 269 (104 mg, 74%) as a white solid and the minor product 270 (11 mg, 8%) as a colourless oil. Major product 269:

M.p. 69-71 °C, ether/hexanes; \(^1H\) NMR (C\(_6\)D\(_6\)) \(\delta\) (rotamer a, ~ 67%) 0.87 (d, \(J = 6.7\) Hz, 6H, \((CH_3)_2CH\)), 1.04 (t, \(J = 7.1\) Hz, 3H, \(CH_3CH_2\)), 3.01 (q, \(J = 7.1\) Hz, 2H, \(CH_2CH_2\)), 3.35 (m, 4H, 2 x ArOCH\(_2\)CH\(_2\)), 3.65 (m, 4H, \((CH_2)_2O\)), 4.12 (septet, \(J = 6.7\) Hz, 1H, CH(CH\(_3\))\(_2\)), 4.16-4.32 (m, 4H, 2 x ArOCH\(_2\)), 5.87 (m, 1H, HCO), 6.61 (d, \(J = 8.0\) Hz, 2H, ArH), 6.72-6.93 (m, 6H, ArH); (rotamer b, ~ 33%) 0.89 (d, \(J = 7.0\) Hz, 6H, \((CH_3)_2CH\)), 1.04 (t, \(J = 7.1\) Hz, 3H, \(CH_3CH_2\)), 3.11 (q, \(J = 7.1\) Hz, 2H, \(CH_3CH_2\)), 3.35 (m, 4H, 2 x ArOCH\(_2\)CH\(_2\)), 3.65 (m, 4H, \((CH_2)_2O\)), 4.16-4.32 (m, 5H, 2 x ArOCH\(_2\) and CH(CH\(_3\))\(_2\)), 5.87 (m, 1H, HCO), 6.61 (d, \(J = 7.95\) Hz, 2H, ArH), 6.72-6.93 (m, 6H, ArH); \(^{13}C\) NMR (C\(_6\)D\(_6\)) \(\delta\) 14.5, 16.6, 20.0, 21.0, 34.9, 39.4, 46.4, 49.8, 67.7, 69.5, 70.8, 73.1, 113.4, 119.9, 121.5, 123.5, 148.8, 151.0, 162.0, 164.1; IR (ef) 2925, 2880, 1740, 1653, 1596, 1499, 1453, 1259, 1204, 1117, 749 cm\(^{-1}\); MS (MALDI-TOF) m/z 510 (M + Na), 488 (M + H);
Anal. Calcd. for C_{26}H_{33}N_{08}: C, 64.05; H, 6.82; N, 2.87. Found: C, 63.86; H, 6.88; N, 2.78. *Minor product 270*: \^1H NMR (CDCl\textsubscript{3}) \\delta 1.25 (d, J = 6.4 Hz, 6H, (CH\textsubscript{3})\textsubscript{2}CH), 1.49 (d, J = 6.9 Hz, 6H, (CH\textsubscript{3})\textsubscript{2}CH), 3.52 (m, 1H, CH(CH\textsubscript{3})\textsubscript{2}), 3.93 (m, 5H, 2 x ArOCH\textsubscript{2}CH\textsubscript{2} and CH(CH\textsubscript{3})\textsubscript{2}), 4.17 (m, 4H, (CH\textsubscript{2})\textsubscript{2}O), 4.37 (dd, J = 10.8, 6.4 Hz, 2H, 2 x ArOCHH), 4.46 (dd, J = 10.8, 4.4 Hz, 2H, 2 x ArOCHH), 5.71, (m, 1H, HCO), 6.82-6.90 (m, 4H, ArH), 6.90-7.02 (m, 4H, ArH); \(^{13}\text{C} NMR (CDCl\textsubscript{3}) \delta 20.23, 20.87, 46.03, 50.89, 67.69, 69.73, 70.38, 72.76, 113.41, 119.54, 121.43, 123.67, 148.00, 150.56, 161.55, 163.34; IR (ef) 2974, 2875, 1740, 1655, 1596, 1499, 1453, 1259, 1203, 1117, 750 cm\textsuperscript{-1}; MS (MALDI-TOF) m/z 524 (M + Na), 502 (M + H), 501 (M).

### 7.2.8 Reaction of alcohol (217) with N-methylmorpholine (271)

**Method A.** Employing the alcohol 217 (100 mg, 0.289 mmol), oxalyl chloride (76 \( \mu \)L, 0.87 mmol) and N-methylmorpholine 271 (95 \( \mu \)L, 0.86 mmol). Flash chromatography using methanol/dichloromethane (3\%) as the eluant afforded the *product 272* (86 mg, 63\%) as a white solid. M.p. 143-145 °C, methanol/dichloromethane; \(^1\text{H} NMR (CDCl\textsubscript{3}) \delta 3.52-3.77 (m, 8H, N(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}O), 3.91 (m, 4H, 2 x ArOCH\textsubscript{2}CH\textsubscript{2}), 4.16 (m, 4H, (CH\textsubscript{2})\textsubscript{2}O), 4.40 (dd, J = 10.8, 5.9 Hz, 2H, 2 x ArOCHH), 4.44 (dd, J = 10.8, 4.4 Hz, 2H, 2 x ArOCHH), 5.75 (m, 1H, HCO), 6.82-6.90 (m, 4H, ArH), 6.91-7.02 (m, 4H, ArH); \(^{13}\text{C} NMR (CDCl\textsubscript{3}) \delta 41.8, 46.6, 66.5, 66.9, 67.6, 69.6, 70.4, 73.5, 113.4, 119.5, 121.4, 123.8, 147.8, 150.5, 160.2, 162.4; IR (ef) 2926, 2873, 1744, 1661, 1596, 1499, 1452, 1258, 1188, 1115, 750 cm\textsuperscript{-1}; MS (MALDI-TOF) m/z 526 (M + K), 510 (M + Na), 501 (M + Na).
488 (M + H); Anal. Calcd. for C_{23}H_{29}NO_{9}: C, 61.59; H, 6.00; N, 2.87. Found: C, 61.39; H, 5.97; N, 2.69.

7.2.9 Reaction of alcohol (217) with tropane (275)

Method B. Employing the alcohol 217 (381 mg, 1.10 mmol), oxalyl chloride (290 µL, 3.32 mmol) and tropane 275 (140 µL, 1.04 mmol). Flash chromatography using methanol/dichloromethane (1%) as the eluant afforded the product 276 (456 mg, 89%) as a white solid. M.p. 127-129 °C, methanol/dichloromethane; $^1$H NMR (CDCl$_3$) δ 1.48-2.12 (m, 10H), 3.93 (m, 4H, 2 x ArOCH$_2$CH$_2$), 4.17 (m, 4H, (CH$_2$)$_2$O), 4.41 (m, 4H, NCH, ArOCH$_2$ and ArOCHH), 4.51 (dd, $J$ = 10.8, 4.1 Hz, 1H, ArOCHH), 4.69 (m, 1H, NCH), 5.72 (m, 1H, HCO), 6.83-6.91 (m, 4H, ArH), 6.93 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$) δ 16.8, 26.9, 28.4, 31.1, 33.0, 52.4, 56.3, 67.6, 69.7, 70.2, 70.5, 73.2, 113.3, 119.7, 121.4, 123.6, 123.7, 148.0, 150.5, 150.6, 156.3, 162.6; IR (ef) 2926, 2872, 1741, 1652, 1499, 1454, 1258, 1199, 751 cm$^{-1}$; MS (MALDI-TOF) m/z 534 (M + Na), 512 (M + H); Anal. Calcd. for C$_{28}$H$_{33}$NO$_8$: C, 65.74; H, 6.50; N, 2.74. Found: C, 65.79; H, 6.75; N, 2.63.
7.2.10 Reaction of alcohol (217) with quinuclidine (277)

Method B. Employing alcohol 217 (343 mg, 0.990 mmol), oxalyl chloride (260 μL, 2.98 mmol) and quinuclidine 277 (100 mg, 0.900 mmol). Flash chromatography using ether as the eluant afforded the product 279 (358 mg, 73%) as a white solid. M.p. 75-76 °C, ether; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.26 (m, 2H, CH\(_2\)CH\(_2\)Cl), 1.68-1.92 (m, 5H, (CH\(_2\))\(_2\)CHCH\(_2\)), 2.73 (td, \(J = 13.1, 2.8\) Hz, 1H, NCHH), 3.14 (td, \(J = 13.1, 2.8\) Hz, 1H, NCHH), 3.57 (t, \(J = 6.6\) Hz, 2H, CH\(_2\)Cl), 3.93 (m, 5H, 2 x ArOCH\(_2\)CH\(_2\) and NCHH), 4.17 (m, 4H, (CH\(_2\))\(_2\)O), 4.35 (dd, \(J = 10.7, 6.4\) Hz, 1H, ArOCHH), 4.38 (dd, \(J = 10.7, 5.5\) Hz, 1H, ArOCHH), 4.42 (dd, \(J = 10.7, 4.6\) Hz, 1H, ArOCHH), 4.44 (dd, \(J = 10.7, 4.3\) Hz, 1H, ArOCHH), 4.54 (m, 1H, NCHH), 5.74 (m, 1H, HCO), 6.82-6.91 (m, 4H, ArH), 6.92-7.03 (m, 4H, ArH); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 31.0, 32.0, 33.2, 38.7, 41.5, 42.2, 46.6, 67.6, 69.7, 70.4, 70.6, 73.2, 113.3, 119.5, 119.7, 121.4, 123.8, 123.8, 147.8, 150.5, 160.2, 163.1; IR (ef) 2930, 2875, 1743, 1658, 1597, 1499, 1454, 1258, 1223, 1122, 732 cm\(^{-1}\); MS (MALDI-TOF) \(m/z\) 586 (M + K), 570 (M + Na), 548 (M + H); Anal. Calcd. for C\(_{28}\)H\(_{34}\)ClNO\(_8\): C, 61.37; H, 6.25; N, 2.56. Found: C, 61.66; H, 6.45; N, 2.31.
To a solution of sodium hydroxide (323 mg, 8.06 mmol) in water (40 mL) was added 2-methoxyphenol 280 (890 \mu l, 8.09 mmol) at 90 °C. Once a homogeneous solution was obtained, the reaction mixture was cooled to 50 °C and epichlorohydrin (320 \mu l, 4.09 mmol) was added dropwise. The reaction mixture was allowed to cool to room temperature overnight and then was extracted with dichloromethane (3 x 80 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Flash chromatography of the crude product using ether/hexanes (80%) as the eluant afforded the title compound 281 (930 mg, 76%) as a white solid. M.p. 69-71 °C, ether/hexanes (lit. 5 M.p. 69-71 °C, ethyl acetate);

\[ {^1}H \text{ NMR (CDCl}_3) \delta 3.29 \text{ (broad s, 1H, O}H\text{), 3.85 \text{ (s, 6H, 2 x OCH}_3\text{), 4.20 \text{ (m, 4H, 2 x ArOCH}_2\text{), 4.41 \text{ (m, 1H, HCOH), 6.84-6.93 \text{ (m, 4H, ArH), 6.94-7.02 \text{ (m, 4H, ArH);}}}_{13}\text{C NMR (CDCl}_3) \delta 56.0, 68.8, 71.2, 112.2, 115.5, 121.1, 122.3, 148.3, 150.1; IR (ef) 3477 \text{ (broad), 2935, 2836, 1592, 1505, 1454, 1254, 1124, 743 cm}^{-1}; MS (Cl) m/z \text{ (rel. intensity), 305 (M}+\text{H, 100), 181 (36), 163 (80).}} \]
7.2.12 Reaction of 1,3-bis(ortho-methoxyphenoxy)-2-propanol (281) with triethylamine

Method A. Employing 1,3-bis(ortho-methoxyphenoxy)-2-propanol 281 (100 mg, 0.329 mmol), oxalyl chloride (86 \( \mu L \), 0.99 mmol) and triethylamine (140 \( \mu L \), 1.00 mmol). Flash chromatography using ether/hexanes (70%) as the eluant afforded the product 282 (61 mg, 43%) as a colourless oil. 

$^1$H NMR (CDCl$_3$) $\delta$ 1.15 (m, 6H, 2 x CH$_3$CH$_2$), 3.33 (q, $J = 7.0$ Hz, 2H, CH$_3$CH$_2$), 3.41 (q, $J = 7.2$ Hz, 2H, CH$_2$CH$_2$), 3.82 (s, 6H, 2 x CH$_3$O), 4.36 (dd, $J = 10.9$, 6.01 Hz, 2H, 2 x ArOCHH), 4.41 (dd, $J = 10.9$, 5.0 Hz, 2H, 2 x ArOCHH), 5.80 (m, 1H, HCO), 6.84-6.93 (m, 4H, ArH), 6.93-7.04 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ 12.7, 14.2, 39.0, 42.6, 56.0, 68.0, 72.1, 112.4, 115.1, 121.1, 122.5, 148.0, 150.1, 161.2, 162.9; IR (ef) 2954, 2872, 1731, 1661, 1459, 1298, 1229, 1216, 1129, 788 cm$^{-1}$; MS (MALDI-TOF) $m/z$ 470 (M + K), 454 (M + Na), 432 (M + H); Anal. Calcd. for C$_{23}$H$_{29}$NO$_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.28; H, 6.81; N, 3.27.

7.2.13 Reaction of (-)-menthol (283) with triethylamine

Method A. Employing (-)-menthol 283 (200 mg, 1.28 mmol), oxalyl chloride (330 \( \mu L \), 3.78 mmol) and triethylamine (540 \( \mu L \), 3.87 mmol). Flash chromatography
using ether/hexanes (40%) as the eluant afforded the product 284 (129 mg, 47%) as a
colourless oil. \( [\alpha]_{D}^{20} = 51 \) (c 1.0, chloroform); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 0.79 (d, \( J = 7.1 \) Hz, 3H, CH\(_3\)CH), 0.90 (d, \( J = 7.1 \) Hz, 3H, CH\(_2\)CH), 0.92 (d, \( J = 6.7 \) Hz, 3H, CH\(_3\)CH(CH\(_2\))\(_2\)), 1.10 (m, 2H, cyclohexyl-CH\(_2\)), 1.20 (m, 7H, 2 x CH\(_2\)CH\(_3\) and CH\(_3\)CH(CH\(_2\))\(_2\)), 1.49 (m, 2H, cyclohexyl-CH\(_2\)), 1.70 (m, 2H, cyclohexyl-CH\(_2\)), 1.96 (m, 1H, (CH\(_3\))\(_2\)CH), 2.07 (m, 1H, OCHCH\(_3\)), 3.28 (q, \( J = 7.1 \) Hz, 2H, CH\(_3\)CH\(_2\)), 3.41 (m, 2H, CH\(_3\)CH\(_2\)), 4.87 (m, 1H, HCO); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 12.7, 14.4, 16.1, 20.9, 22.1, 23.4, 26.1, 31.6, 34.2, 39.0, 40.6, 42.5, 46.9, 76.4, 161.9, 163.3; IR (ef) 2959, 2872, 1731, 1660, 1456, 1298, 1216, 1128 cm\(^{-1}\); MS (MALDI-TOF) m/z 322 (M + K), 306 (M + Na), 284 (M + H); Anal. Calcd. for C\(_{16}\)H\(_{29}\)N\(_2\)O\(_3\): C, 67.81; H, 10.31; N, 4.94. Found: C, 67.59; H, 10.30; N, 4.98.

7.2.14 Reaction of 2,4-dimethyl-3-pentanol (285) with triethylamine

Method A. Employing 2,4-dimethyl-3-pentanol 285 (240 µL, 1.71 mmol), oxalyl
chloride (450 µL, 5.16 mmol) and triethylamine (720 µL, 5.17 mmol). Flash
chromatography using dichloromethane as the eluant afforded the product 286 (228 mg,
55%) as a pale yellow oil. \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 0.93 (d, \( J = 6.7 \) Hz, 6H, (CH\(_3\))\(_2\)CH), 0.95
(d, \( J = 6.7 \) Hz, 6H, (CH\(_3\))\(_2\)CH), 1.19 (t, \( J = 7.2 \) Hz, 3H, CH\(_3\)CH\(_2\)), 1.23 (t, \( J = 7.2 \) Hz, 3H,
CH\(_3\)CH\(_2\)), 2.00 (m, 2H, 2 x (CH\(_3\))\(_2\)CH), 3.33 (q, \( J = 7.2 \) Hz, 2H, CH\(_3\)CH\(_2\)), 3.43 (q, \( J =
7.2 \) Hz, 2H, CH\(_3\)CH\(_2\)), 4.76 (t, \( J = 6.1 \) Hz, 1H, HCO); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 12.7, 14.5,
17.3, 19.6, 29.7, 38.9, 42.4, 85.3, 162.1, 164.0; IR (ef) 2970, 2876, 1733, 1658, 1465,
1297, 1229, 1122 cm\(^{-1}\); **MS** (MALDI-TOF) \(m/z\) 266 (M + Na); **Anal.** Calcd. for C\(_{13}\)H\(_{25}\)N\(_{3}\): C, 64.16; H, 10.36; N, 5.76. Found: C, 63.90; H, 10.31; N, 5.95.

### 7.2.15 Reaction of benzylalcohol with triethylamine

![Chemical Structure](image)

**Method A.** Employing benzylalcohol (190 \(\mu\)L, 1.84 mmol), oxalyl chloride (530 \(\mu\)L, 5.57 mmol) and triethylamine (780 \(\mu\)L, 5.60 mmol). Flash chromatography using dichloromethane as the eluant afforded the product **287** (290 mg, 67\%) as a pale yellow oil. **\(^1\)H NMR** (CDCl\(_3\)) \(\delta\) 1.12 (t, \(J = 7.2\) Hz, 3H, \(CH_3CH_2\)), 1.16 (t, \(J = 7.2\) Hz, 3H, \(CH_3CH_2\)), 3.19 (q, \(J = 7.2\) Hz, 2H, \(CH_3CH_2\)), 3.40 (q, \(J = 7.2\) Hz, 2H, \(CH_3CH_2\)), 5.29 (s, 2H, PhCH\(_2\)), 7.31-7.44 (m, 5H, ArH); **\(^{13}\)C NMR** (CDCl\(_3\)) \(\delta\) 12.6, 14.2, 39.1, 42.5, 67.5, 128.8, 128.987, 161.3, 163.2; **IR** (ef) 2959, 2872, 1732, 1661, 1458, 1297, 1215, 1128, 788 cm\(^{-1}\); **MS** (MALDI-TOF) \(m/z\) 258 (M + Na), 236 (M + H); **Anal.** Calcd. for C\(_{12}\)H\(_{15}\)N\(_{3}\): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.51; H, 7.32; N, 5.97.

### 7.2.16 Reaction of cyclohexanol (288) with triethylamine

![Chemical Structure](image)

**Method A.** Employing cyclohexanol **288** (210 \(\mu\)L, 1.99 mmol), oxalyl chloride (520 \(\mu\)L, 5.96 mmol) and triethylamine (840 \(\mu\)L, 6.03 mmol). Flash chromatography using dichloromethane as the eluant afforded the product **290** (381 mg, 84\%) as a white solid.
Method B. Employing cyclohexanol 288 (120 µL, 1.14 mmol), oxalyl chloride (290 µL, 3.32 mmol) and triethylamine (140 µL, 1.00 mmol). Flash chromatography using dichloromethane as the eluant afforded the product 290 (192 mg, 84%) as a white solid. M.p. 25-26 °C, dichloromethane; $^1$H NMR (CDCl$_3$) $\delta$ 1.18 (t, $J = 7.2$ Hz, 3H, CH$_3$CH$_2$), 1.22 (t, $J = 7.2$ Hz, 3H, CH$_3$CH$_2$), 1.14-1.31 (m, 3H, cyclohexyl-H), 1.31-1.61 (m, 3H, cyclohexyl-H), 1.76 (m, 2H, cyclohexyl-H), 1.94 (m, 2H, cyclohexyl-H), 3.27 (q, $J = 7.2$ Hz, 2H, CH$_3$CH$_2$), 3.41 (q, $J = 7.2$ Hz, 2H, CH$_3$CH$_2$), 4.95 (m, 1H, HCO); $^{13}$C NMR (CDCl$_3$) $\delta$ 12.7, 14.3, 23.8, 25.3, 31.5, 39.0, 42.5, 75.0, 161.9, 163.1; IR (KBr) 2958, 2872, 1732, 1661, 1458, 1215, 1128 cm$^{-1}$; MS (MALDI-TOF) m/z 250 (M + Na), 228 (M + H); Anal. Calcd. for C$_{12}$H$_{21}$N$_2$O$_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.58; H, 9.35; N, 6.40.

7.2.17 Reaction of cyclohexanol (288) with quinuclidine (277)

Method B. Employing cyclohexanol 288 (110 µL, 1.04 mmol), oxalyl chloride (260 µL, 2.98 mmol) and quinuclidine 277 (100 mg, 0.899 mmol). Flash chromatography using dichloromethane as the eluant afforded the product 291 (179 mg, 66%) as a white solid. M.p. 47-49 °C, dichloromethane; $^1$H NMR (CDCl$_3$) $\delta$ 1.11-1.45 (m, 5H), 1.47-1.63 (m, 3H), 1.64-1.99 (m, 9H), 2.69 (td, $J = 13.1$, 2.8 Hz, 1H, NCHH), 3.10 (td, $J = 13.3$, 2.8 Hz, 1H, NCHH), 3.58 (t, $J = 6.6$ Hz, 2H, CH$_2$Cl), 3.63 (m, 1H, NCHH), 4.51 (m, 1H, NCHH), 4.95 (m, 1H, HCO); $^{13}$C NMR (CDCl$_3$) $\delta$ 23.7, 25.3, 30.9, 31.5, 32.0, 33.2, 38.6, 41.4, 42.2, 46.4, 75.1, 160.6, 162.9; IR (cf) 2927, 2856,
1733, 1659, 1455, 1266, 1205, 1180, 1009 cm⁻¹; MS (MALDI-TOF) m/z 302 (M + H); Anal. Calcd. for C₁₃H₂₅ClNO₃: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.61; H, 8.14; N, 4.80.

7.2.18 Reaction of cyclohexanol (288) with triallylamine (264)

Method B. Employing cyclohexanol 288 (170 µL, 1.61 mmol), oxalyl chloride (430 µL, 4.93 mmol) and triallylamine 264 (260 µL, 1.50 mmol). Flash chromatography using dichloromethane as the eluant afforded the product 292 (377 mg, 81%) as a colourless oil. ¹H NMR (CDCl₃) δ 1.18-1.44 (m, 3H), 1.46-1.64 (m, 3H), 1.75 (m, 2H), 1.92 (m, 2H), 3.84 (d, J = 5.8 Hz, 2H, NCH₂), 3.99 (d, J = 6.2 Hz, 2H, NCH₂), 4.95 (m, 1H, HCO), 5.15-5.33 (m, 4H, 2 x CH=CH₂), 5.69-5.84 (m, 2H, 2 x CH=CH₂); ¹³C NMR (CDCl₃) δ 23.8, 25.3, 31.4, 46.2, 49.6, 75.3, 118.8, 119.1, 131.7, 132.4, 162.1, 162.6; IR (ef) 2936, 2859, 1733, 1664, 1448, 1277, 1200, 1129, 1005 cm⁻¹; MS (MALDI-TOF) m/z 274 (M + Na), 252 (M + H); Anal. Calcd. for C₁₄H₂₁NO₃: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.06; H, 8.53; N, 5.63.

7.2.19 Reaction of cyclohexanol (288) with tribenzylamine (273)

Method B. Employing cyclohexanol 288 (170 µL, 1.61 mmol), oxalyl chloride (430 µL, 4.93 mmol) and tribenzylamine 273 (431 mg, 1.50 mmol). Flash
chromatography using dichloromethane/hexanes (70%) as eluant afforded the product 293 (46 mg, 9%) as a white solid. **M.p.** 65-67 °C, dichloromethane/hexanes; **¹H NMR** (CDCl₃) δ 1.14-1.41 (m, 3H), 1.41-1.62 (m, 3H), 1.71 (m, 2H), 1.88 (m, 2H), 4.32 (s, 2H, PhCH₂), 4.48 (s, 2H, PhCH₂), 4.96 (m, 1H, HCO), 7.18-7.42 (m, 10H, ArH); **¹³C NMR** (CDCl₃) δ 23.7, 25.3, 31.4, 46.1, 50.3, 75.5, 128.0, 128.4, 128.7, 128.9, 129.0, 135.1, 135.7, 162.8, 162.9; **IR** (ef) 2934, 2859, 1732, 1661, 1453, 1259, 1183, 701 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 352 (M + H, 100), 270 (17), 178 (12), 91 (37); **Anal. Calcd.** for C₂₂H₂₅N₂O₃: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.92; H, 7.35; N, 4.12.

7.2.20 Reaction of cyclohexanol (288) with N,N-dimethylbenzylamine (266)

![Chemical Structure](attachment:image.png)

**Method A.** Employing cyclohexanol 288 (210 µL, 1.99 mmol), oxalyl chloride (520 µL, 5.96 mmol) and N,N-dimethylbenzylamine 266 (900 µL, 5.99 mmol). Flash chromatography using dichloromethane as the eluant afforded the product 294 (368 mg, 92%) as a white solid.

**Method B.** Employing cyclohexanol 288 (170 µL, 1.61 mmol), oxalyl chloride (430 µL, 4.93 mmol) and N,N-dimethylbenzylamine 266 (230 µL, 1.53 mmol). Flash chromatography using dichloromethane as the eluant afforded the product 294 (269 mg, 90%) as a white solid. **M.p.** 44-46 °C, dichloromethane; **¹H NMR** (CDCl₃) δ 1.17-1.45 (m, 3H), 1.45-1.60 (m, 3H), 1.75 (m, 2H), 1.93 (m, 2H), 2.97 (s, 3H, NCH₃), 3.00 (s, 3H, NCH₃), 4.95 (m, 1H, HCO); **¹³C NMR** (CDCl₃) δ 23.7, 25.3, 31.4, 34.1, 37.1, 75.1, 162.2, 162.9; **IR** (KBr) 2936, 2860, 1737, 1665, 1453, 1238, 1120 cm⁻¹; **MS** (MALDI-
7.2.21 Reaction of cyclohexanol (288) with N,N-diisopropylethylamine (268)

Method B. Employing cyclohexanol 288 (170 μL, 1.61 mmol), oxalyl chloride (430 μL, 4.93 mmol) and N,N-diisopropylethylamine 268 (260 μL, 1.49 mmol). Flash chromatography using dichloromethane as the eluant afforded the product 295 (249 mg, 69%) as a pale yellow oil. \(^1\)H NMR (CDCl\(_3\)), \(\delta\) (rotamer a, ~ 67%) 1.18-1.45 (m, 12H), 1.46-1.63 (m, 3H), 1.76 (m, 2H), 1.93 (m, 2H), 3.30 (q, \(J = 7.2\) Hz, 2H, CH\(_3\)CH\(_2\)), 3.79 (septet, \(J = 6.6\) Hz, 1H, (CH\(_3\))\(_2\)CH), 4.95 (m, 1H, HCO); (rotamer b, ~ 33%) 1.18-1.45 (m, 12H), 1.46-1.63 (m, 3H), 1.76 (m, 2H), 1.93 (m, 2H), 3.25 (q, \(J = 7.2\) Hz, 2H, CH\(_3\)CH\(_2\)), 4.46 (septet, \(J = 6.9\) Hz, 1H, (CH\(_3\))\(_2\)CH), 4.95 (m, 1H, HCO); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 14.5, 16.7, 20.3, 21.3, 23.8, 23.9, 25.3, 31.5, 31.5, 35.1, 39.1, 46.2, 50.1, 74.8, 75.0, 162.1, 163.4; IR (ef) 2938, 2860, 1733, 1655, 1453, 1227, 1115 cm\(^{-1}\); MS (MALDI-TOF) \(m/z\) 264 (M + Na), 242 (M + H); Anal. Calcd. for C\(_{13}\)H\(_{23}\)N\(_2\)O\(_3\): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.97; H, 9.73; N, 5.83.

7.2.22 Reaction of cyclohexanol (288) with N-methylmorpholine (271)

Method B. Employing cyclohexanol 288 (170 μL, 1.61 mmol), oxalyl chloride (430 μL, 4.93 mmol) and N-methylmorpholine 271 (170 μL, 1.55 mmol). Flash
chromatography using methanol/dichloromethane (1%) as the eluant afforded the product 296 (166 mg, 46%) as a colourless oil. \( ^{1}H \text{NMR (CDCl}_{3} \delta 1.14-1.47 \text{ (m, 3H), 1.47-1.62 \text{ (m, 3H), 1.76 \text{ (m, 2H), 1.92 \text{ (m, 2H), 3.44 \text{ (m, 2H, NCH}_{2} \text{), 3.61-3.79 \text{ (m, 6H, NCH}_{2} \text{ and O(CH}_{2} \text{)_{2}}, 4.95 \text{ (m, 1H, HCO); ^{13}C \text{NMR \text{(CDCl}}_{3} \delta 23.7, 25.2, 31.4, 41.7, 46.4, 66.5, 66.7, 75.4, 160.6, 162.2; IR \text{(ef) 2937, 2859, 1738, 1665, 1449, 1293, 1271, 1205, 1117 \text{ cm}^{-1}; \text{MS (MALDI-TOF) m/z 280 (M + K), 264 (M + Na); Anal. Calcd. for C}_{12}\text{H}_{19}\text{N}_{0}4: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.83; H, 8.09; N, 6.00.}

**7.2.23 Reaction of cyclohexanol (288) with tropane (275)**

\[
\begin{align*}
\text{O} & \text{O} \\
\text{N} & \text{N} \\
\end{align*}
\]

**Method B.** Employing cyclohexanol 288 (170 \( \mu \text{L, 1.61 mmol}), \text{oxalyl chloride} (430 \( \mu \text{L, 4.93 mmol}) \text{and tropane 275 (200 \( \mu \text{L, 1.49 mmol}). \text{Flash chromatography using dichloromethane as the eluant afforded the product 297 (365 mg, 92%) as a white solid. M.p.} 50-52 \ ^\circ\text{C, dichloromethane; ^{1}H \text{NMR (CDCl})_{3} \delta 1.17-2.08 \text{ (m, 20H), 4.16 \text{ (m, 1H, NCH), 4.65 \text{ (m, 1H, NCH), 4.93 \text{ (m, 1H, HCO); ^{13}C \text{NMR \text{(CDCl}}_{3} \delta 16.8, 23.8, 25.3, 26.9, 28.4, 31.0, 31.5, 32.9, 52.3, 56.2, 75.0, 156.7, 162.5; IR \text{(KBr) 2937, 2859, 1733, 1655, 1454, 1244, 1203, 1165 \text{ cm}^{-1}; \text{MS (MALDI-TOF) m/z 304 (M + K), 288 (M + Na), 266 (M + H); Anal. Calcd. for C}_{15}\text{H}_{23}\text{N}_{0}3: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.69; H, 8.85; N, 5.10.}}

215
7.2.24 Reaction of ethyl chlorooxocacetate (298) with triethylamine

\[ \text{EtO} \text{C} = \text{O} \text{Et} \]

To a solution of commercially available ethyl chlorooxocacetate 298 (Aldrich, 190 μL, 1.70 mmol) in dichloromethane (7 mL) was added triethylamine (210 μL, 1.51 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h and then the volatiles were removed \textit{in vacuo}. The pale yellow residue was then passed through a pad of silica using methanol/dichloromethane (1%) as the eluant to afford the \textit{product} 299 (180 mg, 65%) as a pale yellow oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}) δ 1.17 (t, J = 7.2 Hz, 3H, NCH\textsubscript{2}CH\textsubscript{3}), 1.21 (t, J = 7.2 Hz, 3H, NCH\textsubscript{2}CH\textsubscript{3}), 1.35 (t, J = 7.2 Hz, 3H, CH\textsubscript{3}CH\textsubscript{2}O), 3.27 (q, J = 7.2 Hz, 2H, NCH\textsubscript{2}CH\textsubscript{3}), 3.41 (q, J = 7.2 Hz, 2H, NCH\textsubscript{2}CH\textsubscript{3}), 4.32 (q, J = 7.2 Hz, 2H, CH\textsubscript{3}CH\textsubscript{2}O); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ 12.6, 14.1, 14.3, 39.1, 42.6, 62.0, 161.6, 163.4; IR (ef) 2982, 2940, 1738, 1659, 1463, 1447, 1229, 1214, 1127, 1021 cm\textsuperscript{-1}; MS (CI) m/z (rel. intensity) 174 (M + H, 100); \textbf{Anal.} Calcd. for C\textsubscript{8}H\textsubscript{13}NO\textsubscript{3}: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.37; H, 8.89; N, 8.18.

7.2.25 Reaction of ethyl chlorooxocacetate (298) with N,N-dimethylbenzylamine (266)

\[ \text{EtO} \text{C} = \text{O} \text{NMe} \]

To a solution of commercially available ethyl chlorooxocacetate 298 (Aldrich, 190 μL, 1.70 mmol) in dichloromethane (7 mL) was added N,N-dimethylbenzylamine 266 (230 μL, 1.53 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h and then the volatiles were removed \textit{in vacuo}. The pale yellow
residue was then passed through a pad of silica using methanol/dichloromethane (1%) as the eluant to afford the product **300** (135 mg, 62%) as a pale yellow oil. **1H NMR** (CDCl₃) δ 1.35 (t, J = 7.2 Hz, 3H, CH₃CH₂), 2.98 (s, 3H, NCH₃), 3.01 (s, 3H, NCH₃), 4.33 (q, J = 7.2 Hz, 2H, CH₃CH₂); **13C NMR** (CDCl₃) δ 14.1, 34.2, 37.2, 62.1, 161.9, 163.1; **IR** (ef) 2984, 2940, 1740, 1665, 1509, 1449, 1278, 1244, 1121, 1014 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 146 (M + H, 100); **Anal. Calcd.** for C₆H₁₁NO₃: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.46; H, 7.58; N, 9.46.

**7.2.26 (2S)-1-Benzyl-2-[(benzyl oxy)methyl]pyrrolidine (302)**

![302]

To a stirred suspension of sodium hydride (60% w/w in mineral oil, 261 mg, 10.9 mmol, pre-washed with hexanes) in THF (4 mL) was added a solution of (2S)-(−)-2-pyrrolidinemethanol **301** (500 mg, 4.94 mmol) in THF (3 mL) at room temperature. After the evolution of hydrogen had stopped, benzylbromide (1.20 mL, 10.1 mmol) was added and then the reaction mixture was stirred overnight. The reaction mixture was then diluted with ether (5 mL), was washed with water (5 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL) and then dried over anhydrous potassium carbonate and concentrated *in vacuo*. Flash chromatography using ethyl acetate/hexanes (5%) as the eluant afforded the *title compound* **302** (1.17 g, 85%) as a yellow oil. [α]_D^20 = −65 (c 0.9, chloroform); **1H NMR** (CDCl₃) δ 1.56-1.79 (m, 3H, CHCHHCH₂), 1.94 (m, 1H, CHCHH/CH₂), 2.21 (m, 1H, NCHH), 2.77 (m, 1H, NCH), 2.92 (m, 1H, NCHH), 3.40

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(m, 2H, OCHHCH and NCHHPh), 3.53 (dd, $J = 9.2, 5.2$ Hz, 1H, OCHHCH), 4.13 (d, $J = 12.9$ Hz, 1H, NCHHPh), 4.53 (s, 2H, PhCH$_2$O), 7.19-7.41 (m, 10H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ 22.9, 28.8, 54.8, 59.9, 63.2, 73.5, 74.3, 126.9, 127.6, 127.8, 128.3, 128.5, 129.1, 138.7, 139.9; IR (ef) 3027, 2959, 2871, 2790, 1494, 1453, 1209, 1098, 735, 697 cm$^{-1}$; MS (MALDI-TOF) $m/z$ 282 (M + H); Anal. Calcd. for C$_{19}$H$_{23}$NO: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.44; H, 8.33; N, 5.10.

7.2.27 Reaction of cyclohexanol (288) with (2S)-1-benzyl-2-[(benzyloxy)methyl]-pyrrolidine (302)

![Chemical Structure](image)

Method B. Employing cyclohexanol 288 (110 µL, 1.04 mmol), oxalyl chloride (270 µL, 3.10 mmol) and (2S)-1-benzyl-2-[(benzyloxy)methyl]pyrrolidine 302 (270 mg, 0.940 mmol). Flash chromatography using acetone/hexanes (5%) as the eluant afforded the product 303 (269 mg, 83%) as a pale yellow oil. [α]$^20$ - 80 (c 1.0, chloroform); $^1$H NMR (CDCl$_3$) $\delta$ (rotamer a, ~50%) 1.13-2.14 (m, 14H), 3.35 (m, 2H, OCH$_2$CH), 3.54 (m, 2H, NCH$_2$), 4.44 (m, 1H, NCH), 4.52 (apparent d, $J = 2.2$ Hz, 2H, PhCH$_2$), 4.93 (m, 1H, HCO), 7.23-7.39 (m, 5H, ArH); (rotamer b, ~50%) 1.13-2.14 (m, 14H), 3.44-3.64 (m, 2H, NCH$_2$), 3.61 (dd, $J = 9.5, 6.2$ Hz, 1H, OCHHCH), 3.69 (dd, $J = 9.5, 3.2$ Hz, 1H, OCHHCH), 4.30 (m, 1H, NCH), 4.48 (apparent d, $J = 4.7$ Hz, 2H, PhCH$_2$), 4.85 (m, 1H, HCO), 7.23-7.39 (m, 5H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ (two rotamers) 21.8, 23.9, 23.9, 24.4, 25.3, 27.6, 28.6, 31.4, 31.4, 31.5, 46.1, 48.0, 57.2, 57.3, 69.5, 71.5, 73.4, 75.1, 75.2, 127.6, 127.7, 127.8, 127.9, 128.5, 128.6, 137.9, 138.5, 159.8, 162.2, 162.3; IR (ef) 2939, 2860, 1731, 1659, 1451, 1233, 1183, 1101, 738, 698 cm$^{-1}$; MS (MALDI-TOF) $m/z$ 368
(M + Na), 346 (M + H); Anal. Calcd. for C_{20}H_{27}NO_{4}: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.94; H, 8.14; N, 4.12.

7.2.28 (2S)-2-[(Benzyloxy)methyl]pyrrolidine (304)

\[ \text{304} \]

The amide 303 (600 mg, 1.74 mmol) was heated at reflux in an aqueous solution of potassium hydroxide (10% w/v, 10 mL) for 3.5 h. On cooling, the reaction mixture was extracted with ether (3 x 10 mL) and the combined organic extracts were washed with brine (15 mL), dried over anhydrous potassium carbonate and concentrated in vacuo. The crude product was purified by flash chromatography using dichloromethane:methanol:triethylamine (95:4:1) as the eluant to afford the title compound 304 (314 mg, 95%) as a colourless oil. $\left[ \alpha \right]_{D}^{20} = 9.2$ (c 1.3, chloroform), lit.$^{156}$ $\left[ \alpha \right]_{D}^{20} = 0.6$ (c 2.0, benzene); $^1$H NMR (CDCl$_3$) $\delta$ 1.46 (m, 1H, CHCH$_2$CHH), 1.65-1.92 (m, 3H, CHCH$_2$CHH), 2.91 (m, 1H, NCHH), 3.00 (m, 1H, NCHH), 3.19 (broad s, 1H, NH), 3.37 (m, 1H, NCH), 3.41 (dd, $J = 8.9$, 6.9 Hz, 1H, OCHHCH), 3.50 (dd, $J = 8.9$, 4.3 Hz, 1H, OCHHCH), 4.54 (s, 2H, PhCH$_2$), 7.27-7.38 (m, 5H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ 25.2, 27.9, 46.5, 58.1, 73.3, 73.4, 127.7, 127.9, 128.5, 138.5; IR (ef) 3343 (broad), 2957, 2867, 1496, 1453, 1402, 1205, 1100, 737, 698 cm$^{-1}$; MS (MALDI-TOF) $m/z$ 191 (M); Anal. Calcd. for C$_{12}$H$_{17}$NO: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.14; H, 9.14; N, 7.35.

$^{156}$ Bernauer, K.; Chuard, T.; Stoeckli-Evans, H. Helv. Chim. Acta 1993, 76, 2263. A range of specific rotations, recorded in a variety of different solvents, for this compound have been reported elsewhere in the chemical literature. We observed, that on recording this measurement in water, that the rotation does not remain constant over a 24 h period.
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