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 (2*S*)-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 (2*S*)-2-[(benzyloxy)methyl]pyrrolidine in excellent yield.

DEDICATION

To my husband, dad and mom

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°	degree(s)
Δ	heat
(+)-	dextrorotatory
(-)-	levorotatory
(±)-	racemic
$[\alpha]_D^{20}$	specific rotation
1D	one dimentional
2D	two dimentional
Ac	acetyl
Ac_2O	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	^1H-^1H correlation spectroscopy

δ	chemical shift (NMR)
d	doublet (NMR spectroscopy)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
dd	doublet of doublets (NMR spectroscopy)
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
dec.	decomposition
DMSO	dimethyl sulfoxide (methyl sulfoxide)
dq	doublet of quartets (NMR spectroscopy)
dt	doublet of triplets (NMR spectroscopy)
EC_{50}	median effective concentration
ef	evaporative film (IR spectroscopy)
EI	electron impact ionization (mass spectroscopy)
equiv	equivalents
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol (ethyl alcohol)
Et_2O	ether (diethyl ether)
h	hour(s)
$h\nu$	irradiation (generally ultraviolet)
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence spectroscopy
HRMS	high-resolution mass spectroscopy
Hz	Hertz (cycles per second)

IBX	*ortho*-iodoxybenzoic acid
IC_{50}	median inhibition concentration
i-Pr	isopropyl
i-Pr_2EtN	*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

MS	mass spectroscopy
MTM	methylthiomethyl
MTPI	methyltriphenoxyphosphonium iodide
m/z	mass to charge ratio (mass spectroscopy)
μL	microliters
μmol	micromoles
NaOEt	sodium ethoxide
NaOMe	sodium methoxide
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect correlation spectroscopy
OAc	acetate
OMe	methoxy
$Pd(OAc)_2$	palladium (II) acetate
pH	the negative logarithm (log_{10}) of the hydronium ion concentration in moles per liter
Ph	phenyl
PhH	benzene
PP	pyrophosphate
ppm	parts per million (NMR spectroscopy)

Pr	propyl
q	quartet (NMR spectroscopy)
RCM	ring-closing metathesis
rel.	relative
R_f	retention factor (thin-layer chromatography)
rt	room temperature
s	singlet (NMR spectroscopy)
t	triplet (NMR spectroscopy)
t-Bu	*t*-butyl
td	triplet of doublets (NMR spectroscopy)
THF	tetrahydrofuran
THP	tetrahydropyranyl
TI	therapeutic index
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilylchloride (chlorotrimethylsilane)
UV	ultraviolet
v/v	volume by volume
w/v	weight by volume

PART ONE

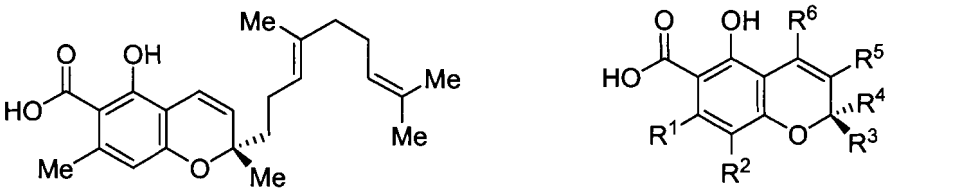
A MODULAR AND CONCISE TOTAL SYNTHESIS OF (±)-DAURICHROMENIC ACID AND ANALOGUES

CHAPTER ONE

GENERAL INTRODUCTION TO 2*H*-CHROMENES

1.1 Introduction

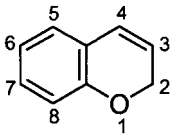
Part One of this thesis concerns the total synthesis of (±)-daurichromenic acid **1**, a 2*H*-chromene derivative, as well as a series of structural analogues **2** (Figure 1.1).



1 (±)-*Daurichromenic acid* **2** *Daurichromenic acid analogues*

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

2*H*-Chromenes, which are also known as 2*H*-1-benzopyrans, are an important family of oxygen heterocycles that have a benzo-fused 2*H*-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-dialkylchromene ring system.[1]



3

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

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

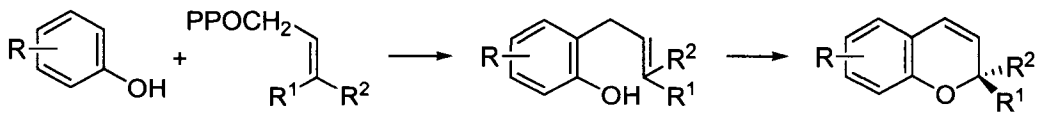
(1) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.

also been widely employed as useful intermediates in the synthesis of a wide range of natural products.[2] Moreover, the discovery of the photochromism of 2*H*-1-benzopyrans has sparked great interest in the synthesis and study of photochromic 2*H*-chromenes and a large number of patents have been issued in the past decade.[3]

1.2 Natural Occurrence and Biological Activities of 2*H*-Chromenes

2*H*-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.[4] 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).[5]

Scheme 1.1 Biosynthetic Pathway of 2*H*-Chromenes



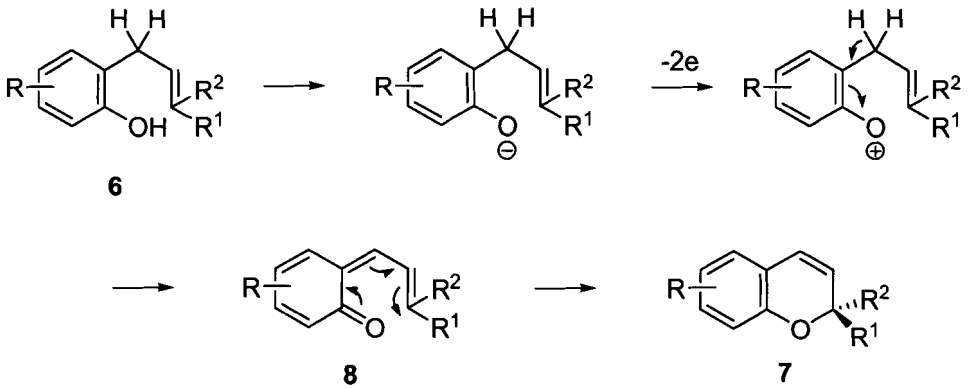
4 **5** **6** **7**

A variety of mechanisms have been proposed for the ring closure step.[6] 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

(2) Goujon, J. Y.; Zammattio, F.; Pagnoncelli, S.; Boursereau, Y.; Kirschleger, B. *Synlett* **2002**, 322.
(3) Becker, R. S.; Michl, J. *J. Am. Chem. Soc.* **1966**, *88*, 5931.
(4) Crombie, L.; Redshaw, S. D.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1411.
(5) Merlini, L. *Adv. Heterocycl. Chem.* **1975**, *18*, 159.
(6) See: ref 5 and references therein.

ortho-quinone methide **8** undergoes an electrocyclization reaction to afford the 2*H*-chromene **7** (Scheme 1.2).

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



As mentioned before, 2*H*-chromenes are key heterocyclic units in many natural polyoxygenated and biological active compounds. The 2*H*-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.[7,8] The 2*H*-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.[9,10] New discoveries regarding the biological activities of this class of compounds continue to be reported and some important examples are discussed herein.

(7) Doodeman, R.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **2000**, *41*, 5979.
(8) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.
(9) Cruz-Almanza, R.; Perez-Flores, F.; Lemini, C. *Heterocycles* **1994**, *37*, 759.
(10) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1318.

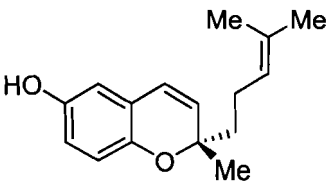
In 1976 Bowers and co-workers reported the discovery of the anti-juvenile hormones (anti-JH), precocene 1 **9** and precocene 2 **10** (Figure 1.3). These compounds were obtained from the crude lipid extract of the bedding plant *Ageratum houstonianum.*[11] These two simple 2*H*-chromene compounds induce 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.

9 *Precocene 1* **10** *Precocene 2*

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

Cordiachromen **11** [6-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromene] was isolated from the acetone extract of *Cordia alliodora*, an American tree known for its durability in marine use (Figure 1.4).[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, $CHCl_3$).[13] Cordiachromen **11** was found to have potent anti-inflamatory activities by the carrageena-induced rat paw edema assay. Racemic cordiachromen has been synthesized but the anti-inflamatory activity of this material was found to be less than that of the natural product.[14]

(11) Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science* **1976**, *193*, 542.
(12) Manners, G. D.; Jurd, L. *J. Chem. Soc., Perkin Trans. 1* **1977**, 405.
(13) Bouzbouz, S.; Goujon, J.-Y.; Deplanne, J.; Kirschleger, B. *Eur. J. Org. Chem.* **2000**, 3223.
(14) See: ref 13 and references therein.



11 *Cordiachromen*

Figure 1.4 Molecular structure of cordiachromen (11).

2*H*-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 2*H*-chromene **15** exhibited ED_{50} 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.

(15) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed.* **2000**, *39*, 734 and references therein.
(16) Subburaj, K.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 259.
(17) Banskota, A. H.; Tezuka, Y.; Prasain, J. K.; Matsushige, K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 896.

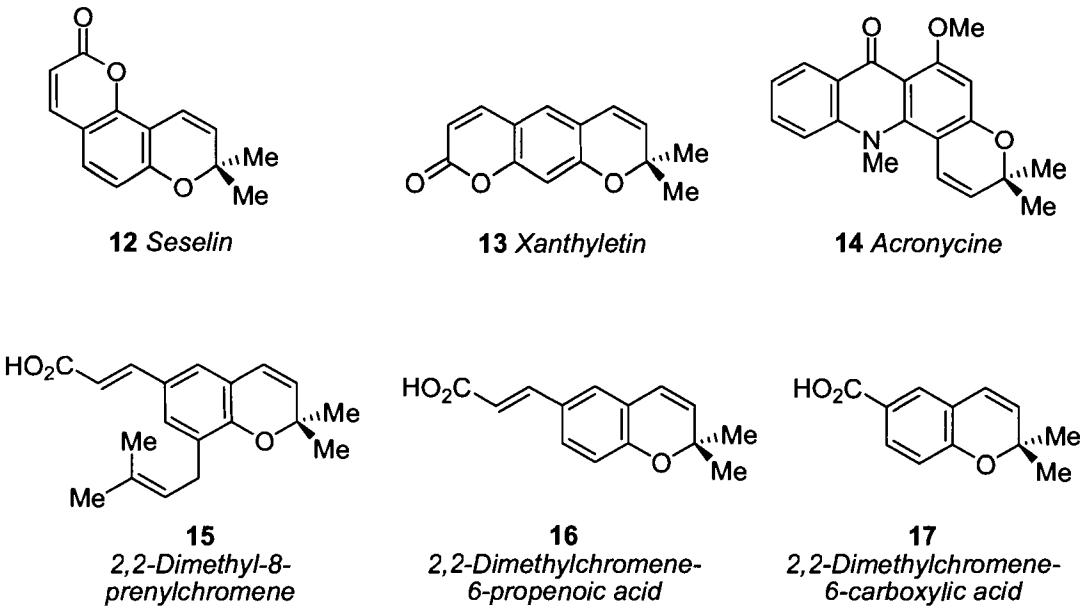


Figure 1.5 Molecular structures of 2*H*-chromene natural products (12-17).

In 1992, eight new coumarin compounds with 2*H*-chromene ring systems were isolated by anti-HIV bioassay guided fractionation of an extract of the tropical rainforest tree *Calophyllym lanigerum* var. *austrocoriaceum*.[18] 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.[19] 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.[20] While (+)-calanolide A **18** and (-)-calanolide B **19** were potent inhibitors of HIV-1, their respective enantiomers were devoid of antiviral activity.

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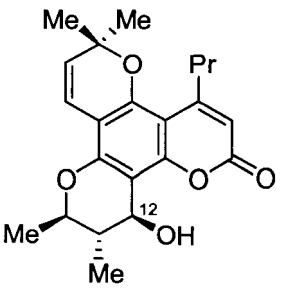
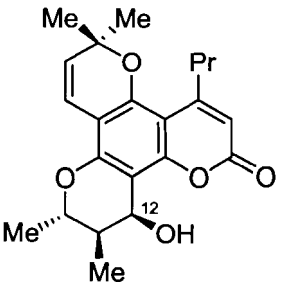
(18) Kashman, Y.; Gustafson, K. F.; Fuller, R. W.; Cardellina, J. H. II; McMahon, J. B.; Currens, M. J.; Buckheit, R. W, Jr.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735.
(19) McKee, T. C.; Fuller, R. W.; Covington, C. D.; Cardellina, J. H. II; Gulakowski, R. J.; Krepps, B. L.; McMahon, J. B.; Boyd, M. R. *J. Nat. Prod.* **1996**, *59*, 754.
(20) Galinis, D. L.; Fuller, R. W.; McKee, T. C.; Cardellina, J. H. II; Gulakowski, R. J.; McMahon, J. B.; Boyd, M. R. *J. Med. Chem.* **1996**, *39*, 4507 and references therein.



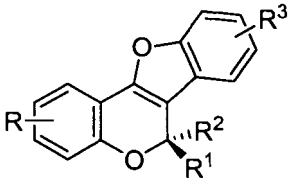
18 (+)-*Canalolide A*



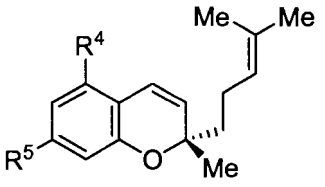
19 (-)-*Canalolide B*

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

The 2*H*-chromene moiety has also been found in large number of pterocarpenes **20** (Figure 1.7), which have been reported to posses anti-fungal, anti-tumor and potent activity against snake venom.[21] Many cannabichromene compounds **21** have shown anti-bacterial activities against Gram-positive, Gram-negative and acid-fast bacteria (Figure 1.7).[22]



20 *Pterocarpene*



21 *Cannabichromene*

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

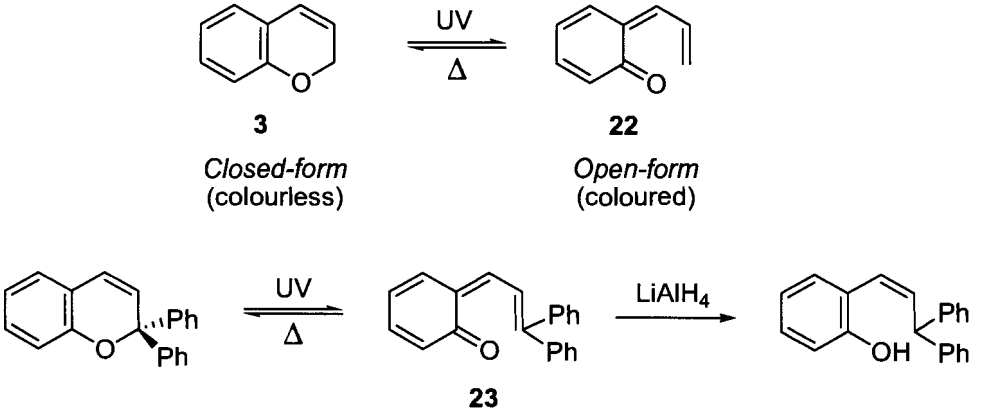
1.3 Photochromic Properties of 2*H*-1-Benzopyrans

The first account of photochromic 2*H*-1-benzopyrans was reported by Becker and Michl in 1966.[3] It was found that the simple 2*H*-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

(21) Murugesh, M. G.; Subburaj, K.; Trivedi, G. K. *Tetrahedron* **1996**, *52*, 2217 and references therein.
(22) Eisohly, H. N.; Turner, C. E.; Clark, A. M.; Eisohly, M. A. *J. Pharm. Sci.* **1982**, *71*, 1319.

the 2*H*-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 2*H*-1-Benzopyrans

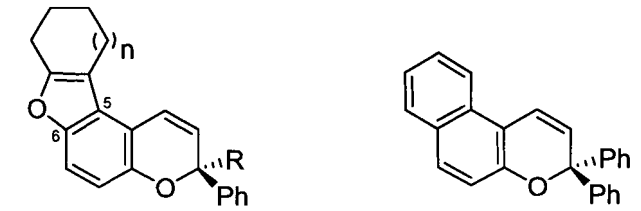


Research in the photochromic properties of 2*H*-1-benzopyrans has become increasingly active over the last decade due to the demand from industry for materials that undergo variable optical absorption. Extensive research has been carried out on the location and the nature of substituents on both rings of the 2*H*-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

(23) Kolc, J.; Becker, R. S. *J. Phys. Chem.* **1967**, *71*, 4045.
(24) van Gemert, B. In *Organic Photochromic and Thermochromic Compounds*; Crano, J. C.; Guglielmetti, R., Eds.; Plenum Press: New York, 1999; Vol. 1, pp 111-140.

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 2*H*-1-benzopyran derivatives **24** have been prepared by Pozzo and co-workers for the study of their potential industrial applications (Figure 1.8).[25] All of the compounds showed photochromic behaviour in toluene at room temperature. The electronic absorption spectra of the coloured-forms of these furan-fused 2*H*-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.



24 (n = 1, 2; R = Me, Ph) **25**

Figure 1.8 Molecular structures of furan-fused 2*H*-chromenes (24) and naphthopyran (25).

Additional examples of 2*H*-chromenes with extended annelation have included benzoindene-fused 2*H*-chromenes,[26] annulated coumarin systems,[27] fluorenone derived

(25) Pozzo, J.-L.; Samat, A.; Guglielmetti, R.; Lokshin, V.; Minkin, V. *Can. J. Chem.* **1996**, *74*, 1649.
(26) Martins, C. I.; Coelho, P. J.; Carvalho, L. M.; Oliveira-Campos, A. M. F.; Samat, A.; Guglielmetti, R. *Helv. Chim. Acta* **2003**, *86*, 570.
(27) Cerqueira, N. M. F. S. A.; Oliveira-Campos, A. M. F.; Coelho, P. J.; Melo de Carvalho, L. H.; Samat, A.; Guglielmetti, R. *Helv. Chim. Acta* **2002**, *85*, 442.

2*H*-chromenes[28] and benzothiophene derived 2*H*-chromenes.[29,30] Some representative compounds are illustrated below (Figure 1.9).

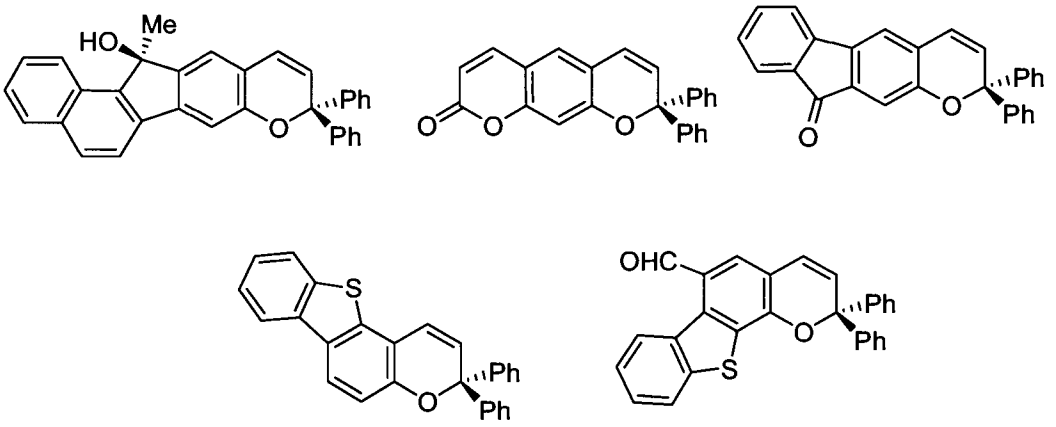
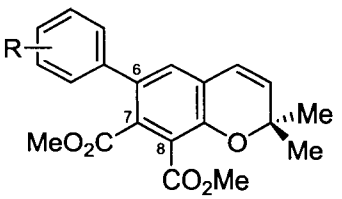


Figure 1.9 Representative examples of annelated 2*H*-1-benzopyrans.

Studies of substituent effects in photochromic 2*H*-chromenes have shown that the introduction of electron-withdrawing groups on the aromatic ring of the 2*H*-chromene improves the photochromic properties. Recently, Brun and co-workers reported the preparation of a new family of 6-aryl-2,2-dimethyl-2*H*-chromene derivatives **26** (Figure 1.10).[31] The photochromic studies on these compounds showed that variation of the C6-aryl substituents did not have much effect on the photochomic 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.

(28) Coelho, P. J.; Carvalho, L. M.; Rodrigues, S.; Oliveira-Campos, A. M. F.; Dubest, R.; Aubard, J.; Samat, A.; Guglielmetti, R. *Tetrahedron* **2002**, *58*, 925.
(29) Queiroz, M.-J. R. P.; Plasencia, P. M. S.; Dubest, R.; Aubard, J.; Guglielmetti, R. *Tetrahedron* **2003**, *59*, 2567.
(30) Oliveira, M. M.; Moustrou, C.; Carvalho, L. M.; Silva, J. A. C.; Samat, A.; Guglielmetti, R.; Dubest, R.; Aubard, J.; Oliveira-Campos, A. M. F. *Tetrahedron* **2002**, *58*, 1709.
(31) Maggiani, A.; Tubul, A.; Brun, P. *Helv. Chim. Acta* **2000**, *83*, 650.



26 (R = H, Ph, PhO, MeO, Br, Cl, 4-NO_2Ph)

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

1.4 Synthesis of 2*H*-Chromenes

The synthesis of 2*H*-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 2*H*-1-benzopyrans that exhibit improved photochromic properties.[24] The synthesis of 2*H*-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]

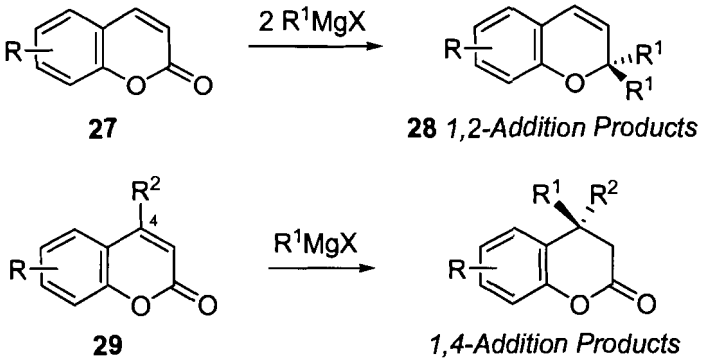
1.4.1 Synthesis of 2*H*-Chromenes From a Preformed Heteroatomic Ring

The reaction of coumarins **27** with a Grignard reagent, that affords 2,2-dialkyl-2*H*-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]

---

(32) a) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, pp 737-883. b) Levai, A.; Timar, T.; Sebok, P.; Eszenyi, T. *Heterocycles* **2000**, *53*, 1193.
(33) Shriner, R. L.; Sharp, A. G. *J. Org. Chem.* **1939**, *4*, 575.
(34) Tickle, R. W.; Melton, T.; Elvidge, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 569.

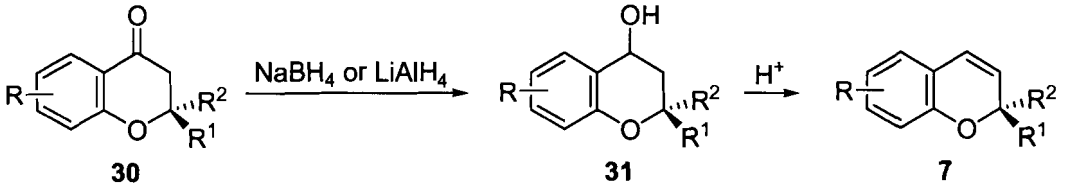
Scheme 1.4 Reaction of Coumarins with Grignard Reagents



(R = H, Me, MeO; R^1 = alkyl, alkenyl, aryl, heteroaryl)

The dehydration reaction of chromanols **31** is a convenient way to prepare 2*H*-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 2*H*-chromenes **7**.

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

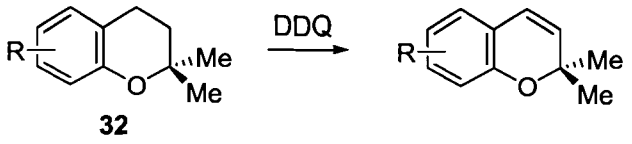


(R = H, acyloxy, alkoxy, alkyl, halogen, NO_2)

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-2*H*-chromene **10** (precocene 2, see: Figure 1.3).[35]

(35) Solladie, G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1996**, *52*, 2065.

Scheme 1.6 Oxidation Reaction of Chromans (32)

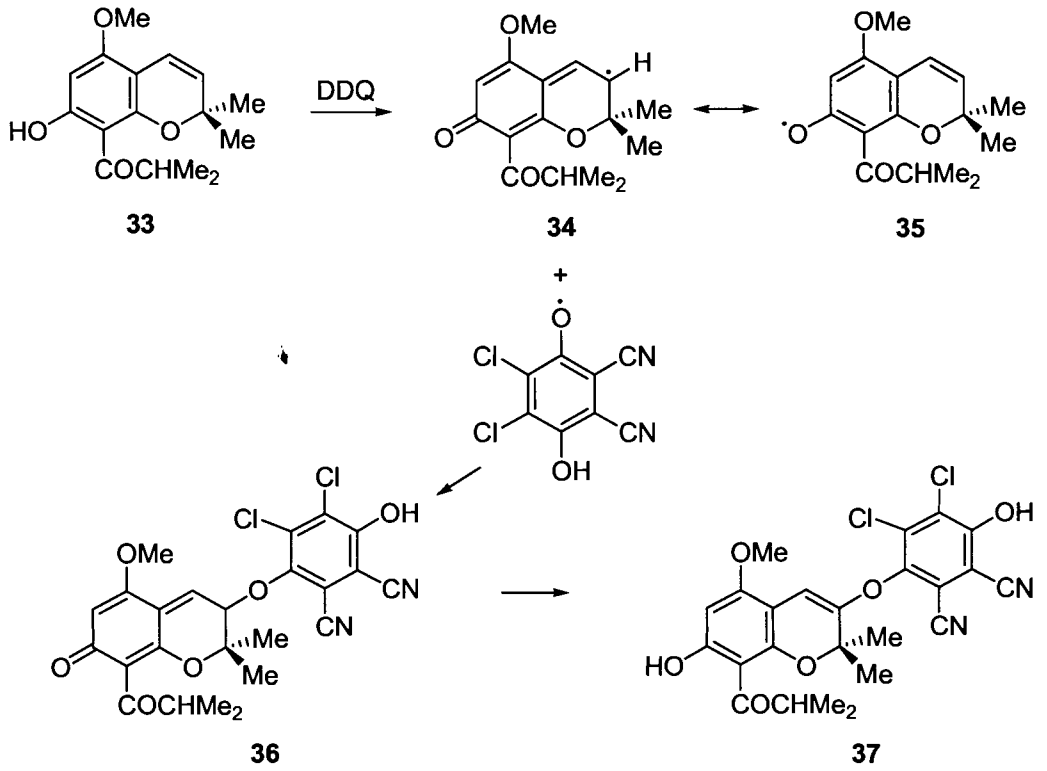


32

(R = H, Me, MeO)

It has been noted that chromenes could form adducts with DDQ which results in lower yields of the desired 2*H*-chromenes.[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



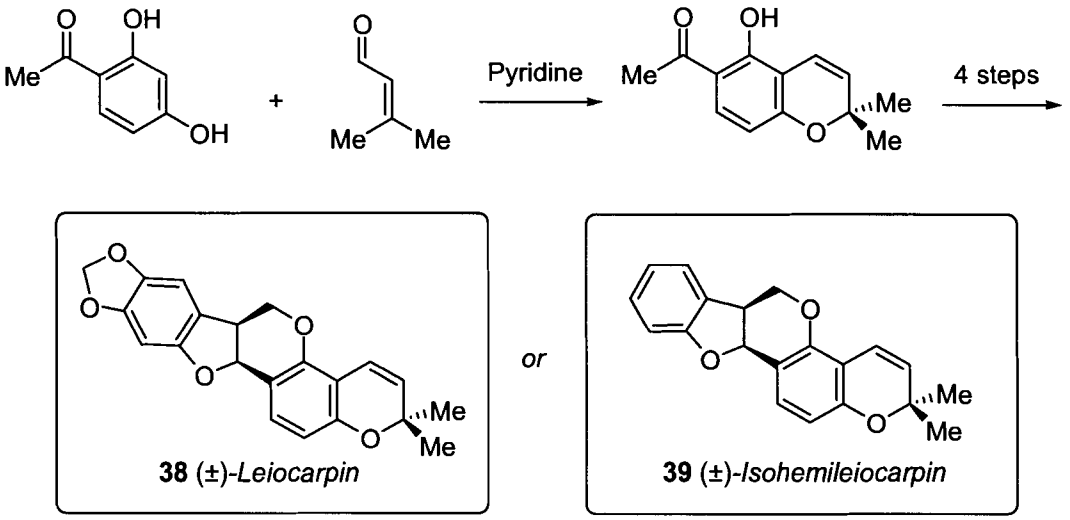
33 **34** **35**

36 **37**

1.4.2 Reaction of Phenols with α,β-Unsaturated Aldehydes

The base-promoted chromenylation reaction of phenols with α,β-unsaturated aldehydes has been a popular method to prepare 2*H*-chromenes.[36] Various bases such as *N,N*-dimethylphenylamine, trimethylamine and tributylamine, have been employed. Pyridine was found to offer the best result in most cases.[4,21,37,38,39] 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 (±)-isohemileiocarpin **39** (Scheme 1.8).[40] Moreover, the pyridine-catalyzed chromenylation reaction has frequently been found to be highly regioselective.

Scheme 1.8 Pyridine-Catalyzed Chromenylation Reaction

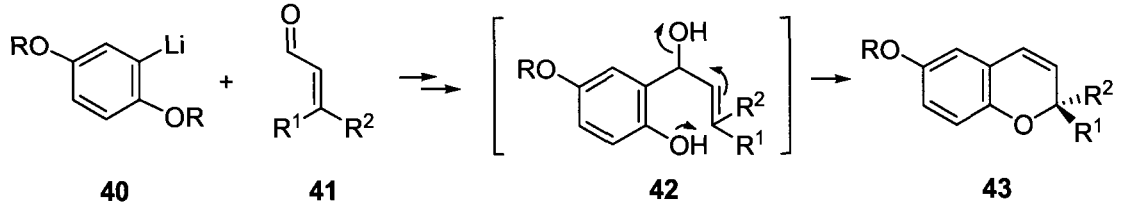


A series of 2,2-dialkyl-2*H*-1-benzopyrans have been synthesized using an aromatic lithiation reaction as a key step, followed by treatment with α,β-unsaturated aldehydes. Cruz-Almanza and co-workers have reported the synthesis of some 2*H*-

(36) Lamcharfi, E.; Menguy, L.; Zamarlik, H. *Synth. Commun.* **1993**, *23*, 3019.
(37) Clarke, D. G.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1973**, 580.
(38) Mahidol, C.; Tuntiwachwuttikul, P.; Reutrakul, V.; Taylor, W. C. *Aust. J. Chem.* **1984**, *37*, 1739.
(39) Hano, Y.; Itoh, M.; Koyama, N.; Nomura, T. *Heterocycles* **1984**, *22*, 1791.
(40) Narkhede, D. D.; Iyer, P. R.; Iyer, C. S. R. *Tetrahedron* **1990**, *46*, 2031.

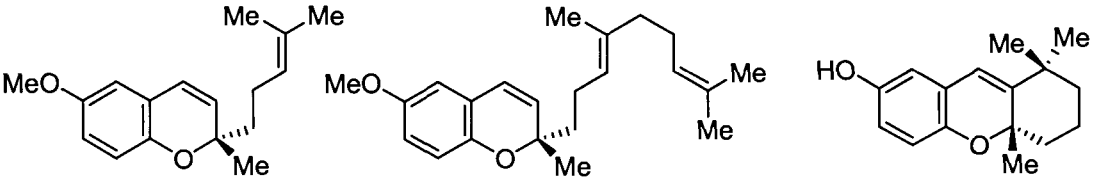
chromenes **43** by the 1,2-addition reaction of an appropriately protected arylithium compound **40** to an α,β-unsaturated aldehyde **41**, on subsequent deprotection and cyclization of the resultant carbinol **42** (Scheme 1.9).[9] Two natural product-related compounds *O*-methylcordiachromen **44** and *O*-methyldictyochromenol **45** as well as the tricyclic 2*H*-chromene **46** have been prepared by this method (Scheme 1.9).

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



40 **41** **42** **43**

(R = MOM, MTM, MEM, THP, CH_2Ph, Me)

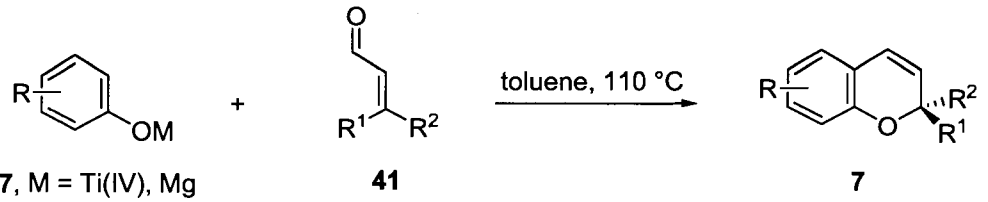


44, 29% **45**, 42% **46**, 38%

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

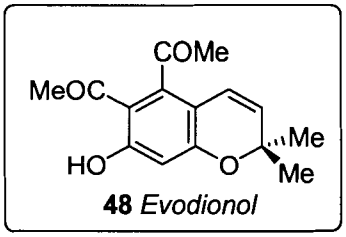
(41) Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem.* **1979**, *44*, 803.

Scheme 1.10 Reaction of Titanium or Magnesium Salts of Phenols with α,β-Unsatuated Aldehydes



47, M = Ti(IV), Mg **41** **7**

(R = H, Me, MeO, Ph, OH, NMe_2, COMe)

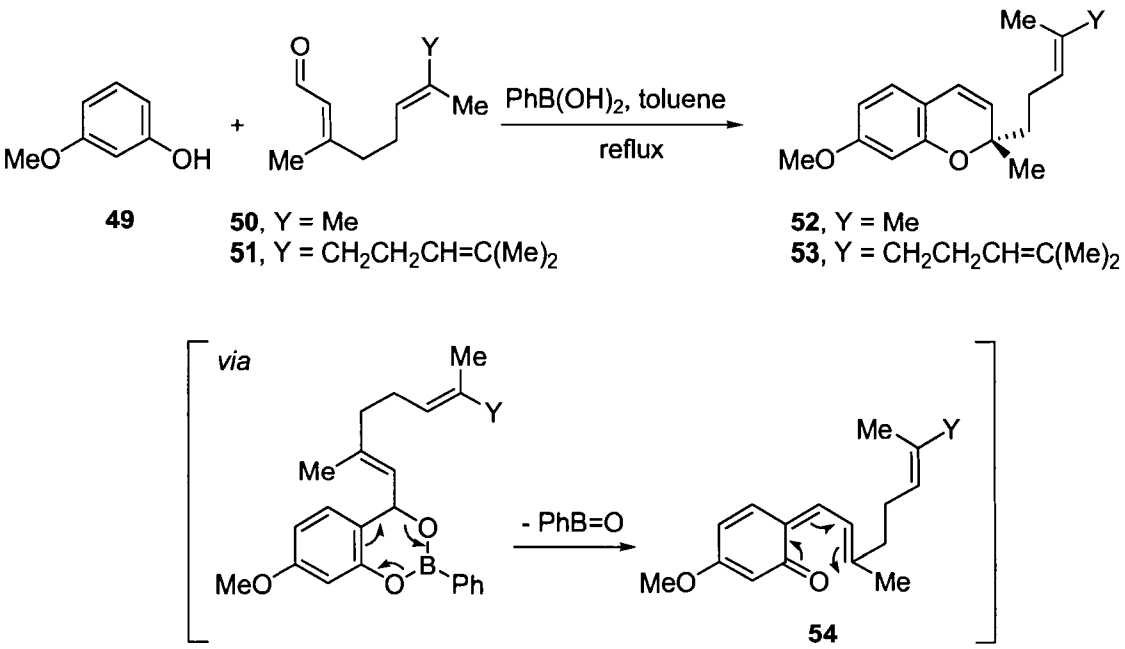


48 *Evodionol*

The phenylboronic acid-promoted condensation of phenols with α,β-unsaturated aldehydes has been found to be a convenient and mild method that complements classical routes for the synthesis of 2*H*-chromenes.[42] Reaction of 3-methoxyphenol **49** with citral **50** in the presence of phenyboronic acid in toluene afforded the cannabichromene analogue **52** in 45% yield. Similarly, with farnesal **51**, the 2*H*-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).

(42) Chauder, B. A.; Lopes, C. C.; Lopes, R. S. C.; da Silva, A. J. M.; Snieckus, V. *Synthesis* **1998**, 279 and references therein.

Scheme 1.11 Phenylboronic acid-Promoted Condensation of Phenols with α,β-Unsaturated Aldehydes

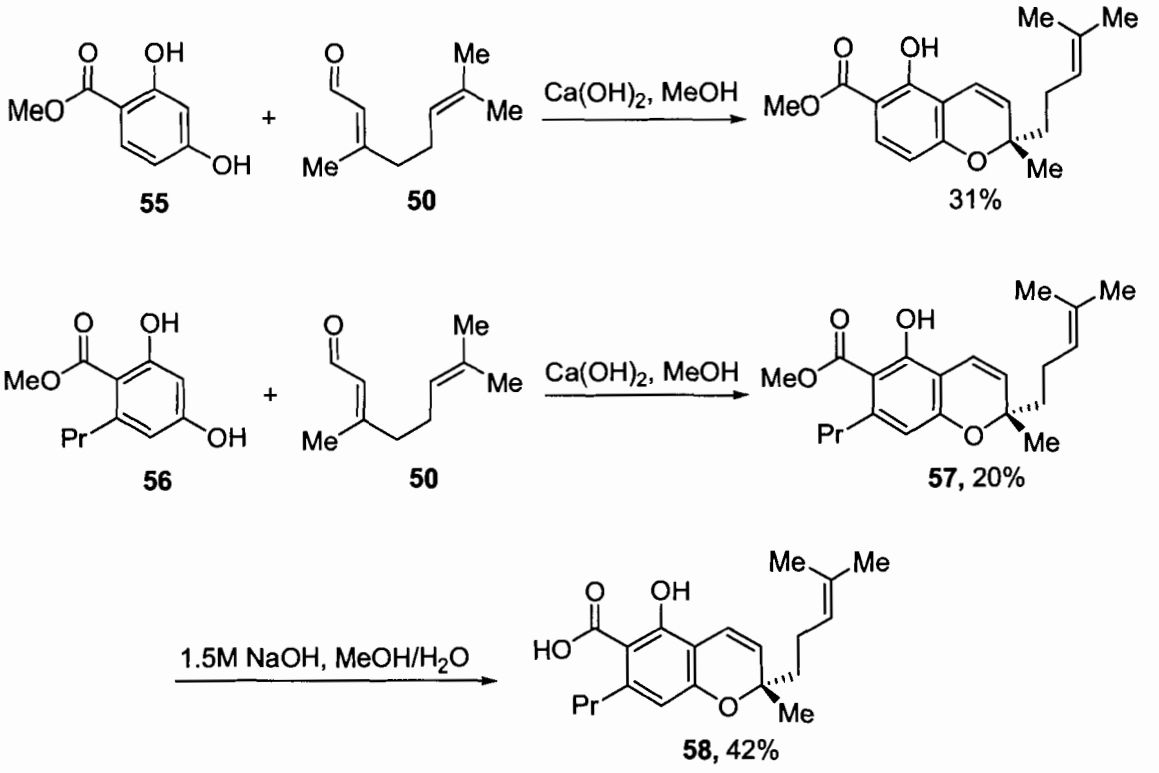


49 **50**, Y = Me; **51**, Y = $CH_2CH_2CH{=}C(Me)_2$ **52**, Y = Me; **53**, Y = $CH_2CH_2CH{=}C(Me)_2$ **54**

The use of calcium reagents in the chromenylation reaction of phenols with α,β-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.

(43) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768.

Scheme 1.12 Calcium Hydroxide-Mediated 2*H*-Chromene Formation Reactions

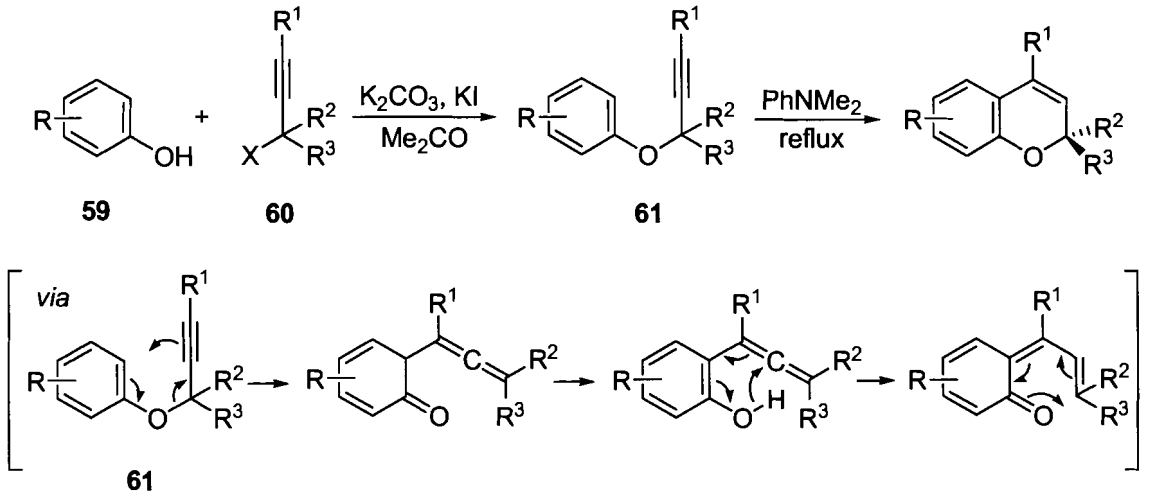


1.4.3 Rearrangement of Propargyl Ethers

A particularly useful synthesis of 2*H*-chromenes involves the thermal rearrangement of the corresponding aryl propagyl ether in a solvent of high boiling point such as *N,N*-diethylaniline (Scheme 1.13). The aryl propagyl 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-2*H*-chromenes and analogues.[44,45]

(44) Yamaguchi, S.; Ishibashi, M.; Akasaka, K.; Yokoyama, H.; Miyazawa, M.; Hirai, Y. *Tetrahedron Lett.* **2001**, *42*, 1091.

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

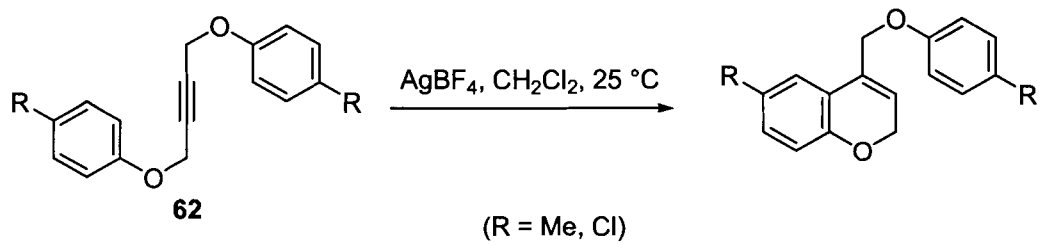


(X = Cl, Br or OAc; R = H, Me, MeO, Cl, CN, NO_2)

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 **62** with various hard Lewis acids (BCl_3, $ZnCl_2$) and soft Lewis acids (Ag^+, Hg^{2+}) (Scheme 1.14).[46] Recently, Oliveira-Campos and co-workers reported the syntheses of a series of novel 2*H*-chromenes by this approach using protic acid catalysts (*p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate) in their studies of photochromic 2*H*-chromenes.[27,28,30] 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.

(45) Fox, M. E.; Lennon, I. C.; Meek, G. *Tetrahedron Lett.* **2002**, *43*, 2899.
(46) Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *43*, 3856.

Scheme 1.14 Lewis Acid-Catalyzed Rearrangement of Phenyl Propargyl Ethers



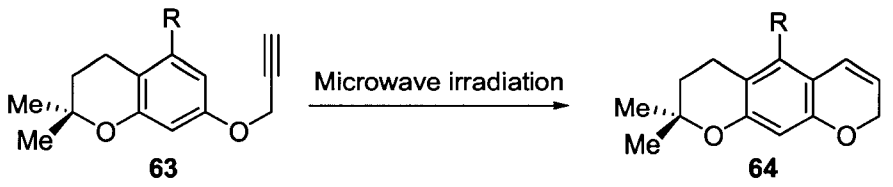
62

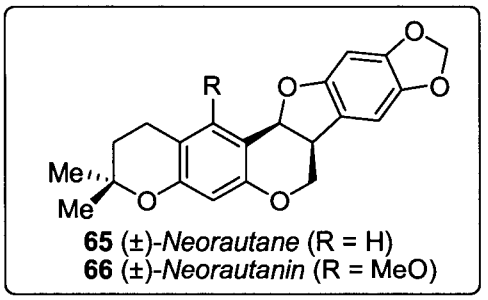
(R = Me, Cl)

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.[47] Subbugaj and co-workers have adopted this method and prepared 2*H*-chromenes **64** as key intermediates for the total synthesis of the natural products (±)-neorautane **65** and (±)-neorautanin **66** (Scheme 1.15).[48]

(47) a) Gigure, R. J.; Majetich, G.; Brady, T.L.; Dunca, S. M. *Tetrahedron Lett.* **1986**, *27*, 4945. b) Gigure, R. J.; Namen, A. M.; Lopez, B.O.; Arepally, A.; Ramos, D. E. *Tetrahedron Lett.* **1987**, *28*, 6533.
(48) Subburaj, K.; Katoch, R.; Murugesh, M. G.; Trivedi, G. K. *Tetrahedron* **1997**, *53*, 12621.

Scheme 1.15 Rearrangement of Phenyl Propargyl Ethers (63) by Microwave Irradiation



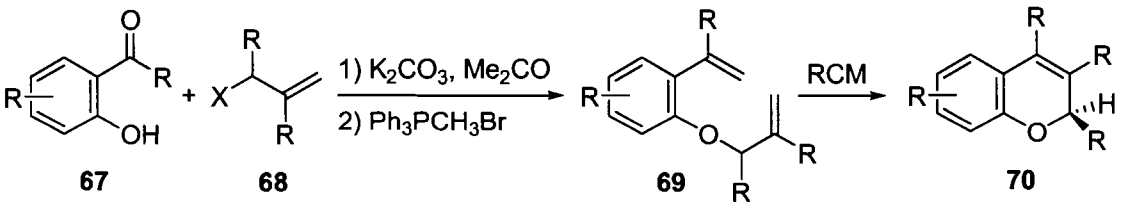


1.4.4 Ring-Closing Olefin Metathesis

Ring-closing olefin metathesis (RCM) has been developed into a practical and highly efficient procedure for preparation of a diverse array of 2*H*-chromene derivatives.[7,49] A series of substituted 2*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 [$Cl_2(PCy_3)_2Ru$=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.

(49) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488.
(50) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.

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



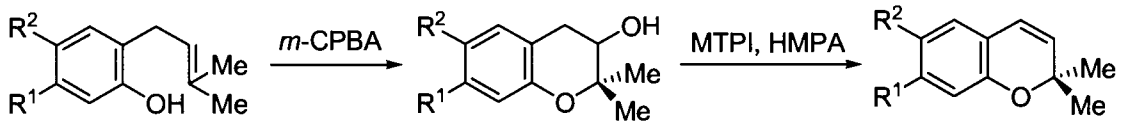
67 68 69 70

(R = H, alkyl, Cl, Br, NO_2, MeO)

1.4.5 Miscellaneous Methods

In addition to the methods discussed above, there are some miscellaneous syntheses of 2*H*-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 1 **9** (R^1 = MeO, R^2 = H) and 2 **10** (R^1 = MeO, R^2 = MeO) and two related 2*H*-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)



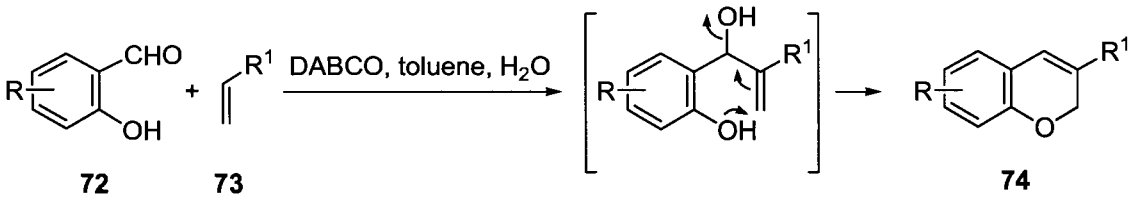
71

Recently Kaye and co-workers reported a convenient and general synthesis of 3-substituted 2*H*-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

(51) Cortes, M. J.; Haddad, G. R.; Valderrama, J. A. *Heterocycles* **1984**, *22*, 1951.

room temperature afforded the 3-substituted 2*H*-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)



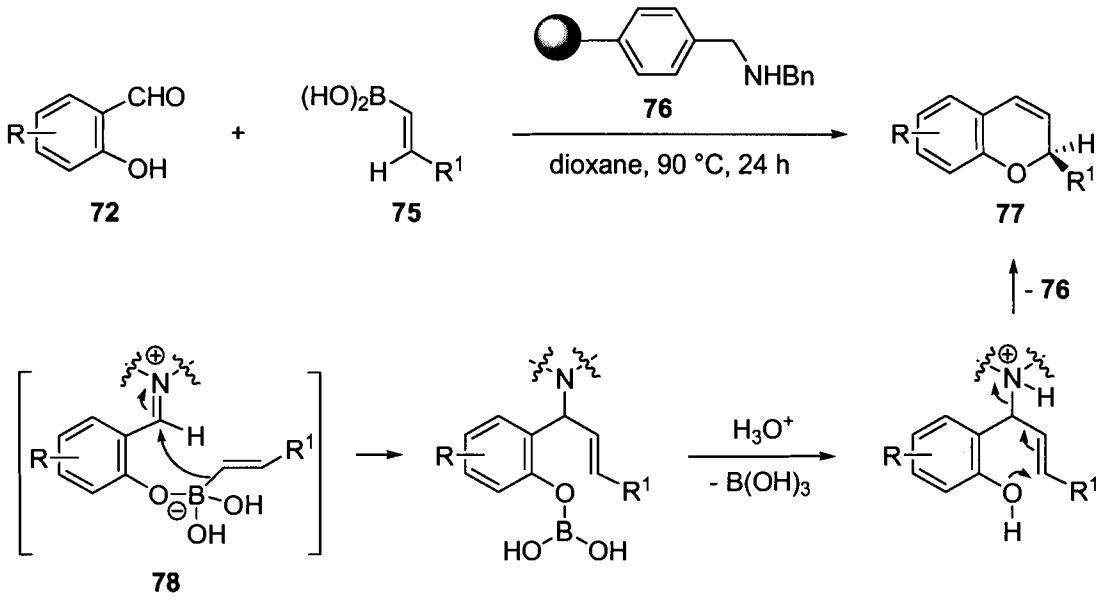
72 **73** **74**

(R = H, MeO, Cl, Br, NO_2; R^1 = COMe, COEt, SO_2Ph, COPh, CN)

A library of 2*H*-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).[52] 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).

(52) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063.

Scheme 1.19 Resin-Supported Base (76)-Catalyzed Condensation of Alkenyl Boronic Acid (75) and Salicylaldehyde Derivatives (72)



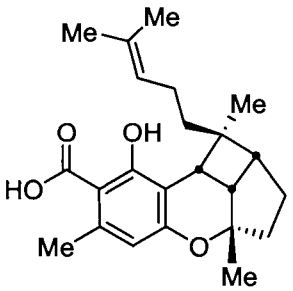
(R = H, OH, OMe, Cl, alkyl; R^1 = Ph, alkyl)

1.5 Research Project Overview

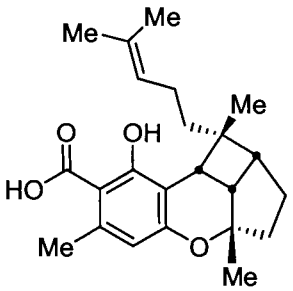
Recently, two novel chromane derivatives, rhododaurichromanic acid A **79** and B **80** as well as a known chromene derivative, daurichromenic acid **81**, were isolated from the methanol extract of the leaves and twigs of *Rhododendron dauricum*.[53] The plant is distributed in various parts of Asia 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 ($EC_{50} \leq 20$ μg/mL, TI > 5). Bioassay-guided fractionation and repetitive chromatography of the methanol extract afforded rhododaurichromanic acid A **79** and B

(53) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

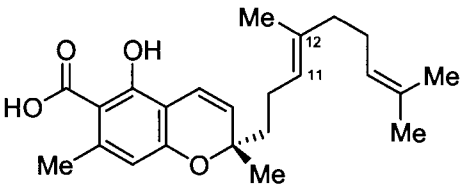
80 as well as the chromene derivative, daurichromenic acid **81**. The isolation of daurichromenic acid **81** has been reported previously by other researchers.[54]



79 *Rhododaurichromanic acid A*



80 *Rhododaurichromanic acid B*



81 *Daurichromenic acid*

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 μg/mL. Moreover, it exhibited

(54) Jpn. Kokai Tokkyo Koho, JP 82-28,080, 1982.

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 rhododaurichomanic 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**.

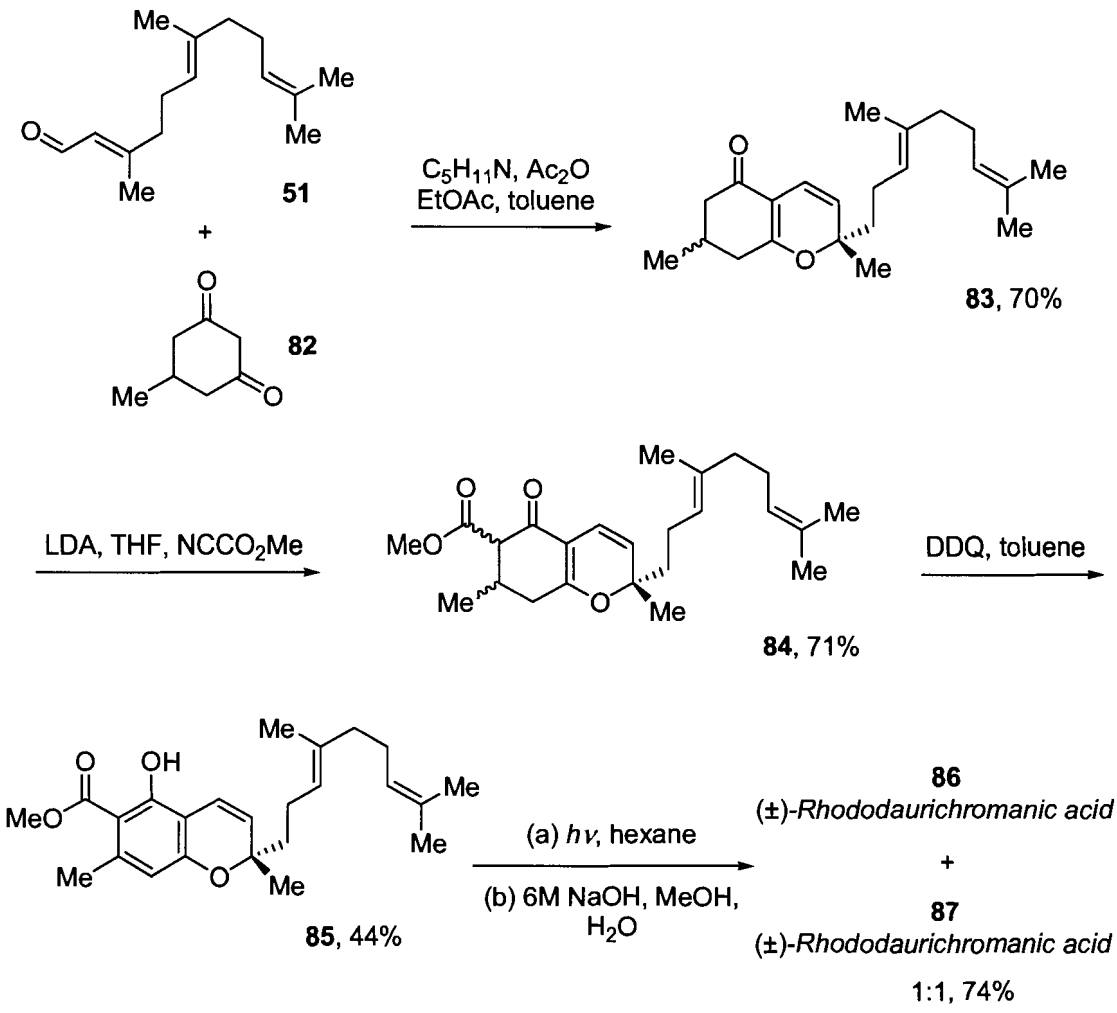
The total syntheses of methyl (±)-daurichromenic acid ester **85** as well as (±)-rhododaurichromanic acid A **86** and B **87** were reported by Hsung and co-workers

(55) Hu, H.; Harrison T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.

(Scheme 1.20).[56] 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 2*H*-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 (±)-rhodaurichromanic acid A **86** and B **87**.

(56) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.

Scheme 1.20 Synthesis of Methyl (±)-Daurichromenic Ester (85) as well as (±)-Rhododaurichromanic Acid A (86) and B (87) by Hsung *et al.*[56]

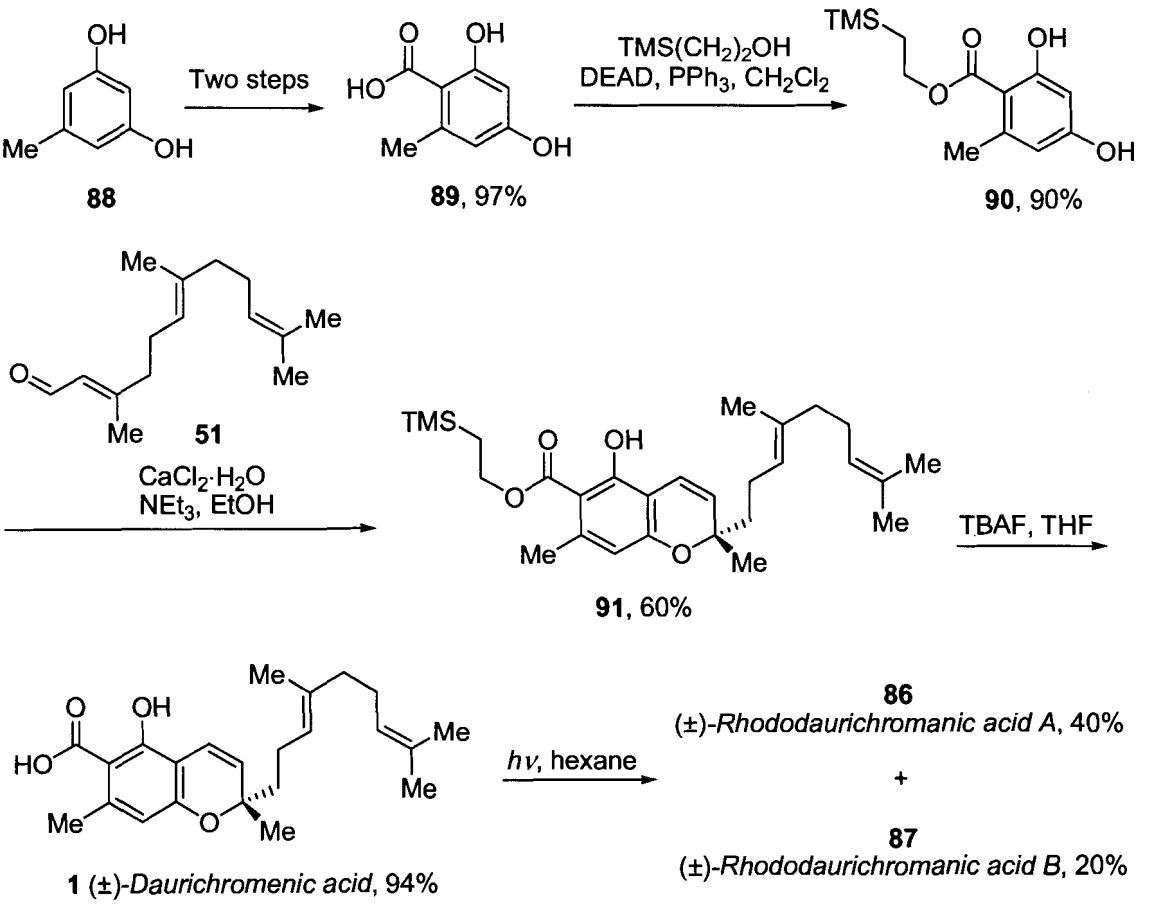


More recently, an efficient and concise total synthesis of (±)-daurichromenic acid **1** has been reported by Jin and co-workers.[57] The carboxylic acid **89** was obtained in two steps from commercially available orcinol **88**. The latter compound was converted to the corresponding *β*-trimethylsilyl 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

(57) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.

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 1.11).[53] 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 2*H*-pyrans **94** by a dehydrogenation (oxidation/aromatization) reaction and a subsequent ester hydrolysis reaction of the resultant aromatic ester **93**.

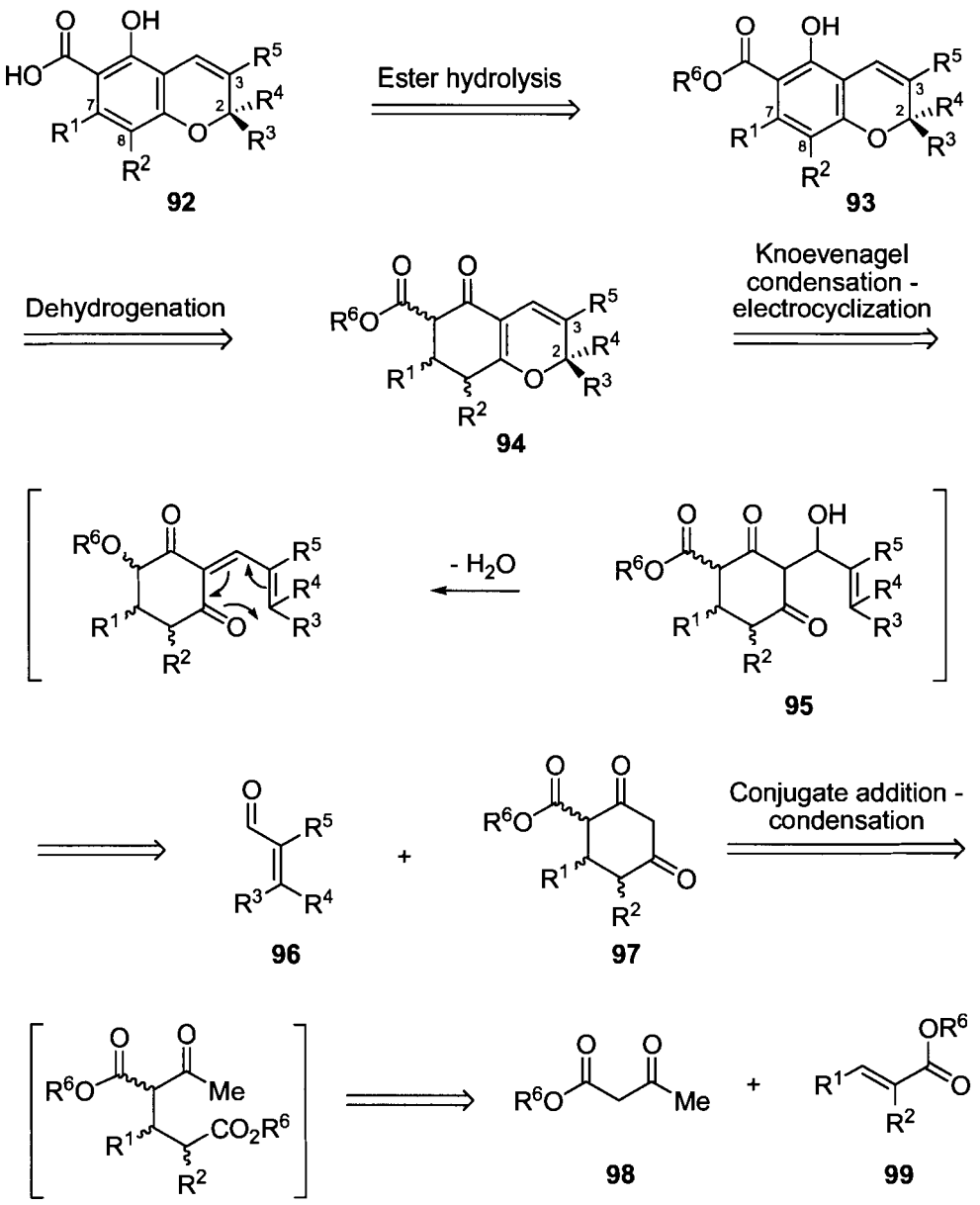


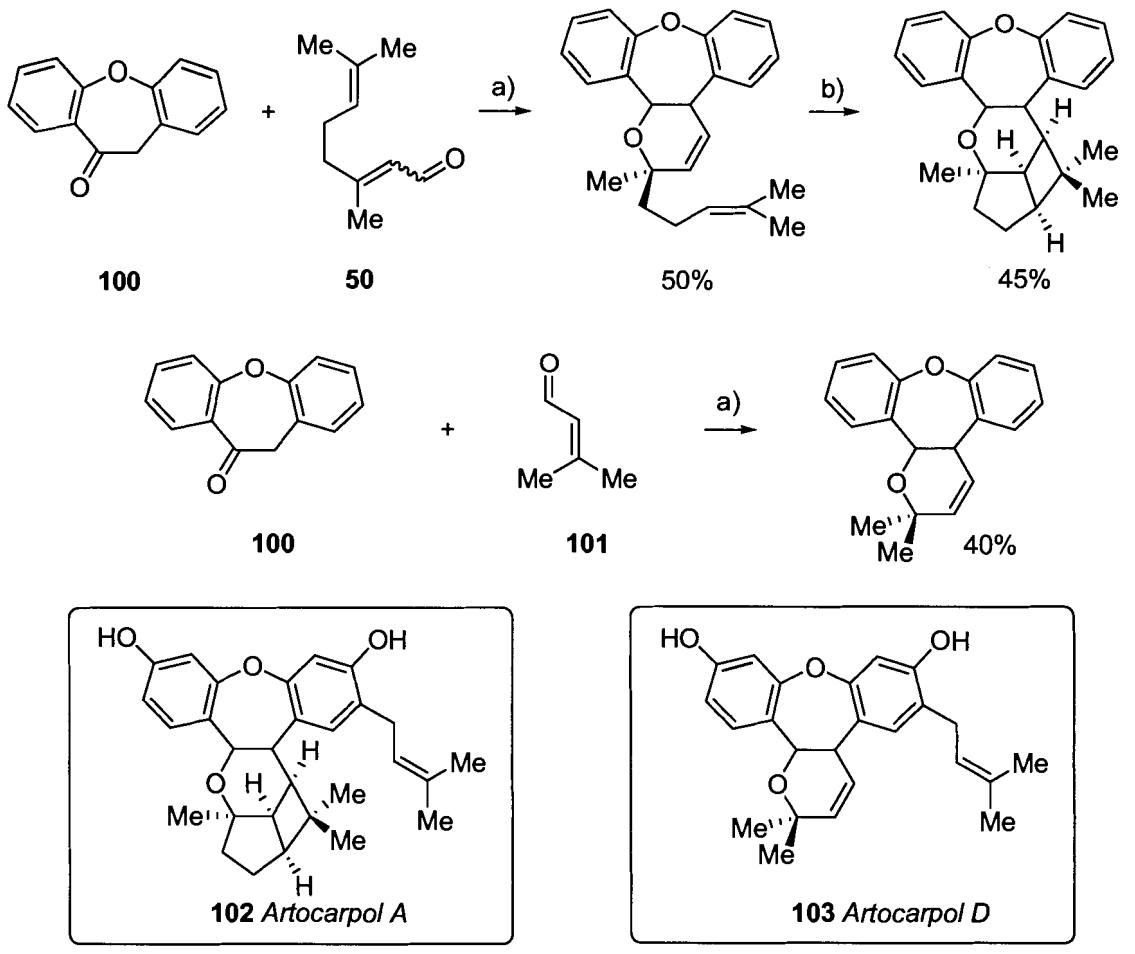
Figure 2.1 Retrosynthetic analysis of (±)-daurichromenic acid and analogues (92).

The 2*H*-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

electrocyclization reaction.[56,58] 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 α,β-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 β-hydroxycarbonyl intermediates **95** or the related Mannich products. A subsequent dehydration reaction of these intermediates **95** followed by concomitant 6π-electrocyclization reaction would furnish the 2*H*-pyrans **94**. A variety of substituents could potentially be introduced at C2 and C3 in the 2*H*-pyrans **94** in this step of the synthesis by using a series of C3- and C2-substituted α,β-unsaturated aldehydes **96**. Recently, our research group has reported a related condensation reaction of the dibenzo-oxepinone **100** with senecialdedyde **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]

(58) For a review on the formation of *2H*-pyrans from 1,3-dicarbonyl compounds and α,β-unsaturated aldehydes *via* the Knoevenagel condensation reaction, see: (a) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Heathcock, C. H., Vol. Ed.; Pergamon Press: Oxford, 1992; Vol 2, p. 341. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729 and references therein.
(59) Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911.

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



[a] Reagents and conditions: a) allylamine (6 equiv), $MgSO_4$, THF, reflux, 8 h; b) benzophenone, PhH, $h\nu$, 24 h.

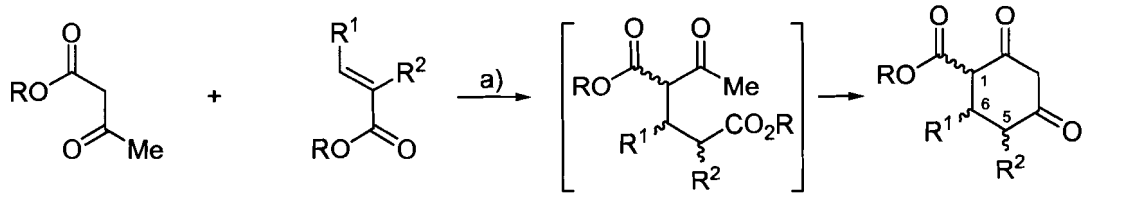
The 1,3-cyclohexanedione precursors **97** could be prepared from the alkyl acetoacetates **98** and a series of α,β-unsaturated esters **99** by employment of a conjugate addition and concomitant intramolecular condensation reaction (Figure 2.1). Various substituents could potentially be introduced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

well as a series of C7 or C8-monosubstitued and C7,C8-disubstituted (±)-daurichomenic acid analogues.

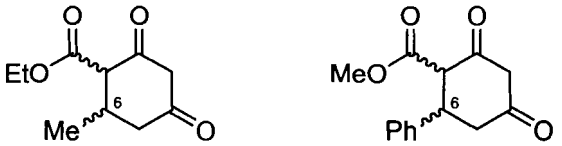
2.2 Preparation of 1,3-Cyclohexanediones

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.[60,61] The typical method involves the combination of the monoanion of a β-ketoester (alkyl acetoacetate) with an α,β-unsaturated ester by sequential Michael addition and Dieckmann condensation reactions.[61] In this study, two 1,3-cyclohexanediones **104** and **105** were prepared by employment of this process (Scheme 2.2).

Scheme 2.2 Michael Addition and Concomitant Dieckmann Condensation Reactions[a]



Alkyl acetoacetates *α,β-Unsaturated esters* *1,3-Cyclohexanediones*



104, 81% **105**, 61%

1,3-Cyclohexanediones

[a] Reagents and conditions: a) NaOR, ROH, reflux, **104** (R = Me) 24 h, **105** (R = Ph) 66 h.

(60) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. *Tetrahedron* **1972**, *28*, 4395.
(61) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.

The 1,3-cyclohexanedione **104** was prepared from ethyl acetoacetate and ethyl crotonate on reaction with sodium ethoxide in 81% yield.[62,63] The product gave satisfactory elemental analysis and the molecular ion was observed by mass spectrometry (CI, M + H). The ^{1}H NMR spectrum of this compound showed a small broad singlet at ~ δ 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 ^{13}C NMR spectrum of this product was complex and so only the major signals are reported in the experimental section (see: *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.[62,64] The ^{1}H NMR spectrum of this compound showed resonance signals at ~ δ 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 ^{1}H NMR spectrum (broad singlet at ~ δ 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 α,β-unsaturated methyl esters (methyl methacrylate, methyl 1-cyclohexene-1-carboxylate and methyl acrylate,

(62) Gould, S. J.; Cheng, X.-C. *Tetrahedron* **1993**, *49*, 11135.
(63) Gaucher, G. M.; Shepherd, M. G. *Biochem. Prep.* **1971**, *13*, 70.
(64) Piskov, V. B.; Kasperovich, V. P. *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.

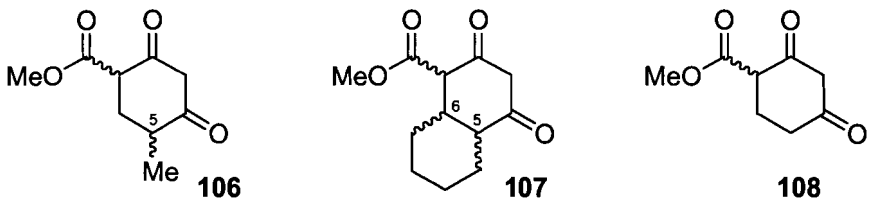


Figure 2.2 Molecular structures of 1,3-cyclohexanediones (106-108).

2.3 Preparation of 2*H*-Pyrans

The second step toward the total synthesis of (±)-daurichromenic acid and a series of analogues was to prepare the 2*H*-pyran derivatives **94** (5-oxo-5,6,7,8-tetrahydro-2*H*-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.[65]

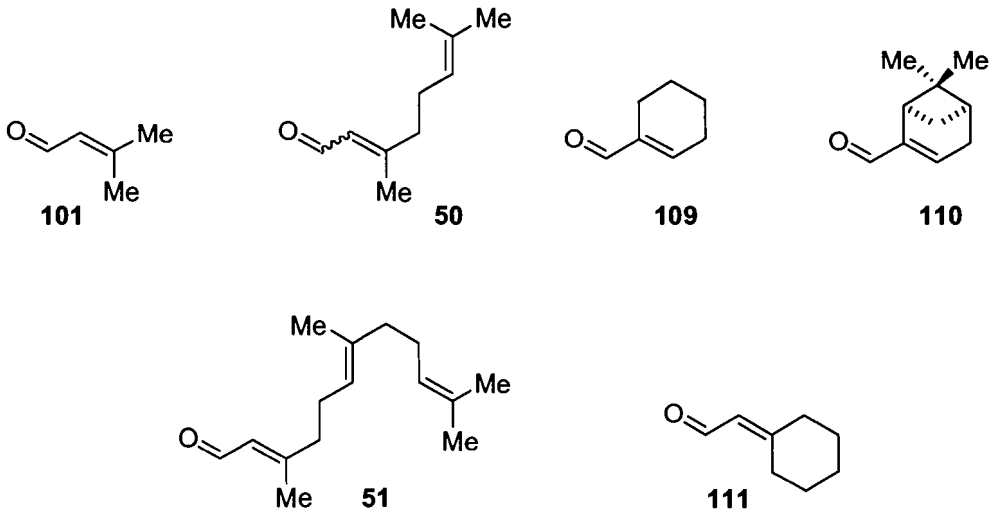
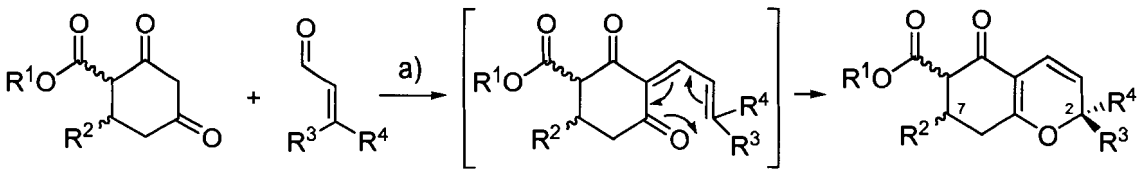


Figure 2.3 α,β-Unsaturated aldehyde precursors.

Condensation of the ethyl crotonate-derived 1,3-cyclohexanedione **104** in methanol with senecialdehyde **101**, citral **50**, *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 ~ 3 h, afforded the expected substituted 2*H*-pyrans **112a-114a** and the spirocyclic 2*H*-pyran **115** (Scheme 2.3).[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 *trans,trans*-farnesal **51** (at room temperature for ~ 16 h).

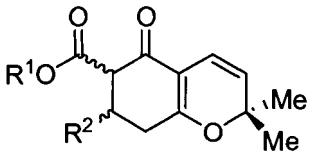
(65) (a) Mason, T. J.; Harrison, M. J.; Hall, J. A.; Sargent, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 1849. (b) Dauben W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
(66) Tietze, L. F.; von Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683.

Scheme 2.3 Knoevenagel Condensation-Electrocyclization Reaction Products (112-115)[a]

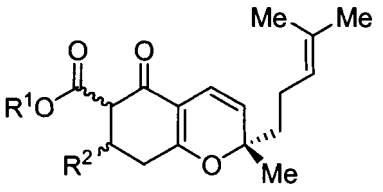


1,3-Cyclohexanediones and α,β-Unsaturated Aldehydes

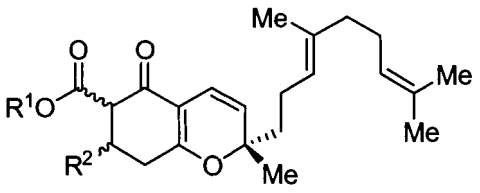
2H-Pyrans



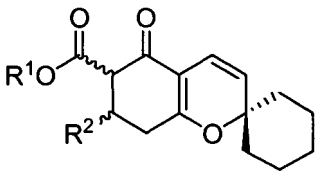
112a (R^1 = Et, R^2 = Me, 75%)
112b (R^1 = Me, R^2 = Ph, 72%)



113a (R^1 = Et, R^2 = Me, 90%)
113b (R^1 = Me, R^2 = Ph, 65%)



114a (R^1 = Et, R^2 = Me, 87%)
114b (R^1 = Me, R^2 = Ph, 68%)



115 (R^1 = Et, R^2 = Me, 63%)

2H-Pyrans

[a] Reagents and conditions: a) 5 mol % $H_2NCH_2CH_2NH_2$, 10 mol % AcOH, MeOH, rt, 3-16 h.

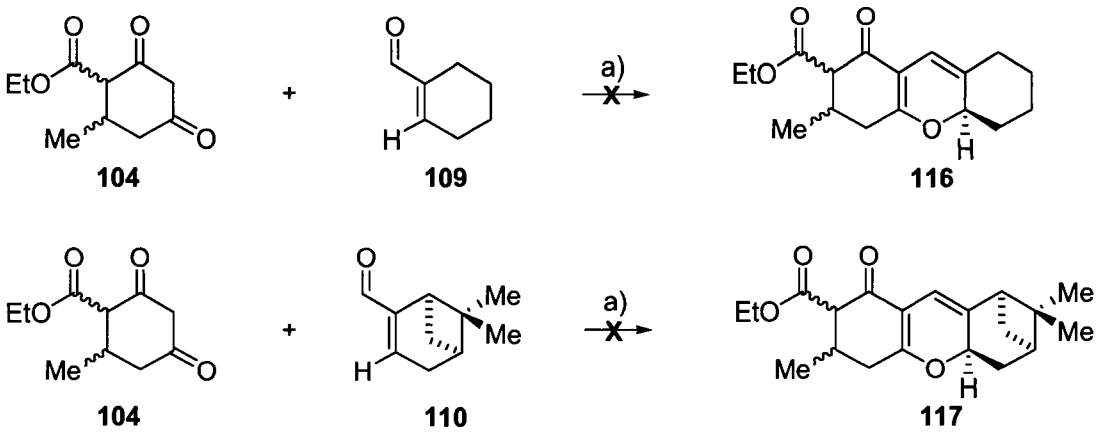
All of the 2*H*-pyran derivatives **112-115** were isolated as inseparable mixtures of diastereoisomers in good to excellent yield (63-90%). The complete characterization data for these compounds is presented in the experimental section (see: *Chapter Four*). The ^{1}H NMR spectra of C7-methyl substituted 2*H*-pyrans **112a-114a** contained two doublets at ~ δ4.8 and 6.7 ppm that correspond to two protons and at ~ δ5.2 and 6.5 ppm for the corresponding C7-phenyl substituted 2*H*-pyrans **112b-114b**. These signals were assigned

as the alkene protons at C3 and C4, which confirmed the incorporation of the 2*H*-pyran ring. COSY NMR spectra were recorded for the citral and *trans,trans*-farnesal derived 2*H*-pyrans **113a** and **114a** in order to assign the remaining signals in the ^{1}H NMR spectra of these compounds. The ^{1}H NMR spectrum of *trans,trans*-farnesal derived 2*H*-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 2*H*-pyrans in the ^{13}C 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 2*H*-pyran **112b** (R^1= Me, R^2 = 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)[a]



[a] Reagents and conditions: a) 5 mol % $H_2NCH_2CH_2NH_2$, 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.

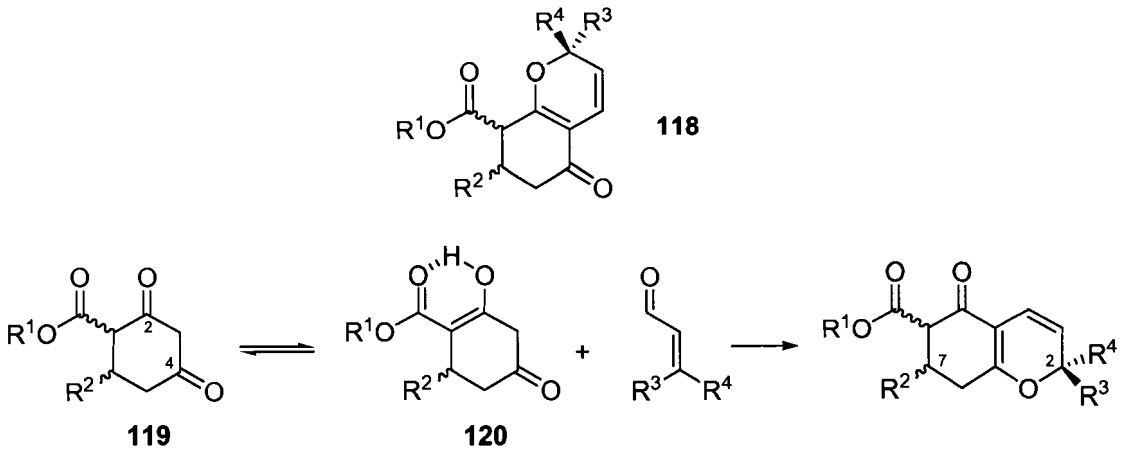
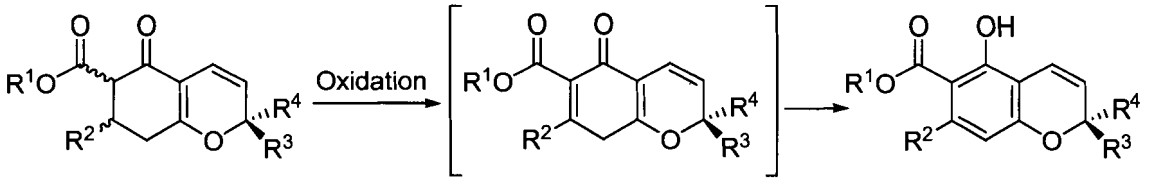


Figure 2.4 Plausible regioisomeric Knoevenagel condensation-electrocyclization reaction products (118) and mechanistic rationale.

2.4 Preparation of Daurichromenic Ethyl Ester and Analogues

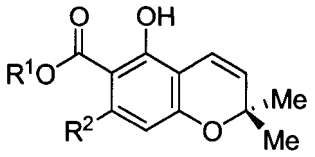
The next step of the synthesis was to install the aromatic ring in (±)-daurichromenic acid and a series of analogues. The process would involve dehydrogenation of the products of the latter reactions (the 2*H*-pyrans **112-115**) to introduce an additional carbon-carbon double bond in the six-membered ketoester ring. Subsequent tautomerization of the resultant dienone would lead to a stable aromatic ring. Although methods for the dehydrogenation of ketones to form α,β-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 *syn*-elimination of phenylselenic acid.

Scheme 2.5 Dehydrogenation Reaction Products (121-124)

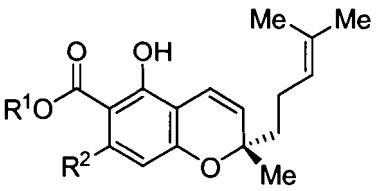


2H-Pyrans

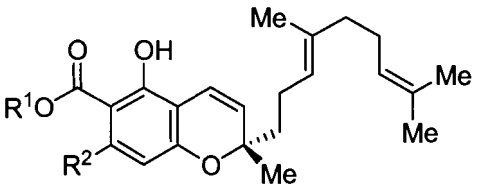
Daurichromenic ester and analogues



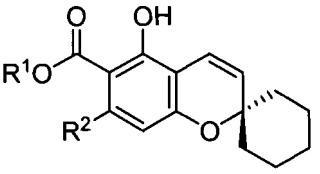
121a (R^1 = Et, R^2 = Me)
121b (R^1 =Me, R^2 = Ph)



122a (R^1 = Et, R^2 = Me)
122b (R^1 =Me, R^2 = Ph)



123a (R^1 = Et, R^2 = Me)
123b (R^1 =Me, R^2 = Ph)



124 (R^1 = Et, R^2 = Me)

Daurichromenic ester and analogues

2.4.1 Halogenation-Dehalohydrogenation

Reaction of the senecialdehyde-derived 2*H*-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 δ 6.35 ppm (aromatic proton) and a singlet at δ 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*-

(68) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814.

chlorosuccinimide (NCS) was used under similar reaction conditions.[69] However, treatment of the farnesal-derived 2*H*-pyran **114a** (R^1 = Et, R^2 = 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 2*H*-pyrans **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 2*H*-pyran **112a** (R^1 = Et, R^2 = Me) when cupric chloride,[70] palladium acetate,[71] cerium ammonium nitrate[72] 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 2*H*-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.

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(69) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh S. *J. Org. Chem.* **1983**, *48*, 3439.
(70) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635.
(71) Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186.
(72) Evans, P. A.; Longmire, J. M.; Modi, D. P. *Tetrahedron Lett.* **1995**, *36*, 3985.
(73) Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110.
(74) Li, A.; Peng, X.; Bie, P.; Wu, T.; Pan, X.; Yang, T.-K. *J. Chem. Res. (S)* **2001**, 328.
(75) Kawamoto, A.; Uda, H.; Harada, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3279.
(76) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *J. Org. Chem.* **1990**, *55*, 3158.

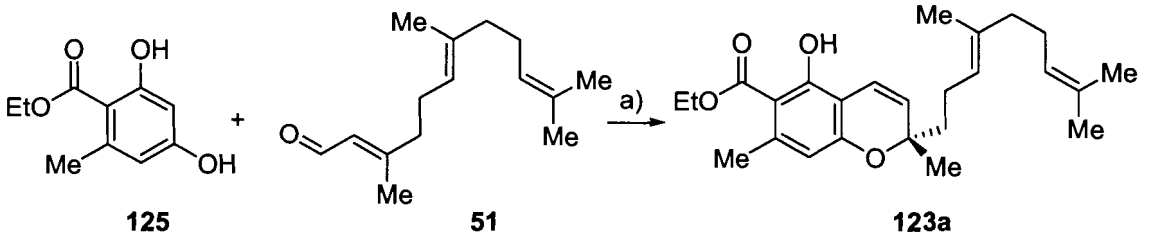
The oxidation reaction of the citral-derived 2*H*-pyran **113a** (R^1 = Et, R^2 = Me) employing cupric chloride,[70] TEMPO,[73] or allyl diethylphosphate/palladium acetate[78] afforded more complex reaction mixtures and lower yields (< 30%) than the corresponding oxidation reactions of the senecialdehyde-derived 2*H*-pyran **112a** (R^1 = Et, R^2 = Me) under similar reaction conditions. Other oxidizing reagents such as selenium dioxide,[79,80] molecular oxygen[81] and cerium ammonium nitrate[72] 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 B_2[83] 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 2*H*-pyran **113a** (R^1 = Et, R^2 = 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 ^1H 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 2*H*-pyran **114a** (R^1 = Et, R^2 = Me) proved to be considerably more problematic using a direct dehydrogenation approach. A majority of the dehydrogenation methods discussed above afforded complex

(77) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W. Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.-I.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7530.
(78) Guijarro, D.; Mancheno, B.; Yus, M. *Tetrahedron* **1994**, *50*, 8551.
(79) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.
(80) Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* **1960**, *82*, 1235.
(81) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.
(82) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 993.
(83) Lu, C.; Bucher, G.; Sander, W. *ChemPhysChem* **2004**, *5*, 47.

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 ^1H NMR spectrum (a singlet at δ 6.18 ppm for the aromatic proton and a singlet at δ 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)[57] and is the direct precursor of (±)-daurichromenic acid **1**. The ^1H 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 (±)-Dauchromenic Acid Precursor (123a) by Jin *et al.*[a]



125 51 123a

[a] Reagents and conditions: a) $CaCl_2 \cdot 2H_2O$, NEt_3, EtOH, microwave irradiation, 20 x 1 min, 70%.

(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.[85] 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.[72] Deprotonation of the senecialdehyde-derived 2*H*-pyran **112a** (R^1 = Et, R^2 = Me) with lithium *N,N*-diisopropylamide (prepared *in situ* from *N,N*-diisopropylamine and *n*-butyllithium 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).[86] However, the aromatization reaction of the citral and farnesal-derived 2*H*-pyrans **113a** and **114a** (R^1 = Et, R^2 = 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.[72,87] The use of a sub-stoichiometric amount of palladium acetate, using a combination of palladium acetate and DDQ (0.5 equiv in each case),

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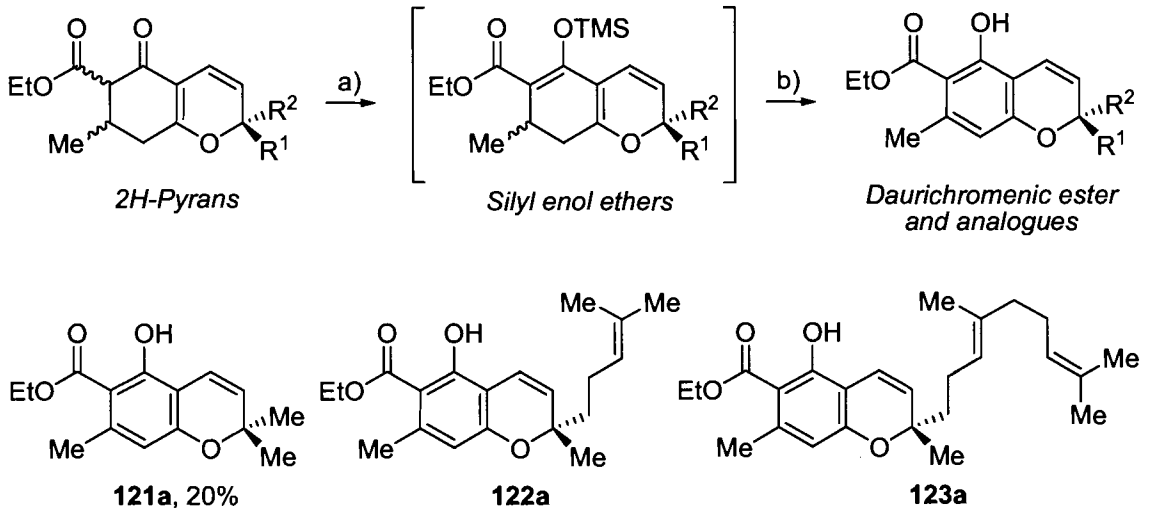
(85) (a) Larock, R. C.; Hightower, T. R. *Tetrahedron Lett.* **1995**, *36*, 2423. (b) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971. (c) Fleming, I; Paterson, I. *Synthesis* **1979**, 736. (d) Jung, M. E.; Pan, Y.-G. *J. Org. Chem.* **1977**, *42*, 3961.
(86) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(87) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 996.

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

Scheme 2.7 Aromatization Reactions of the 2*H*-Pyrans (112a-114a) *via* the Corresponding Trimethyl Silyl Enol Ethers[a]



Daurichromenic ester and analogues

[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.

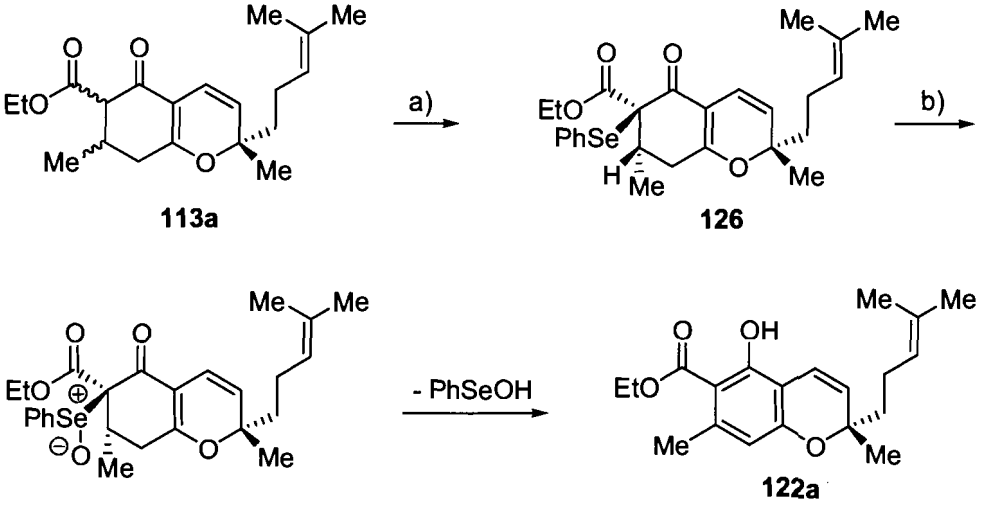
2.4.4 *syn*-Elimination of Phenylselenic Acid

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

(88) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443.
(89) (a) Chapdelaine, D.; Belzile, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5669. (b) Crich, D.; Barba, G. R. *Org. Lett.* **2000**, *2*, 989.

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 α-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_2O) 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 = Me, R^2 = 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 *syn*-Elimination of Phenylselenic Acid[a]

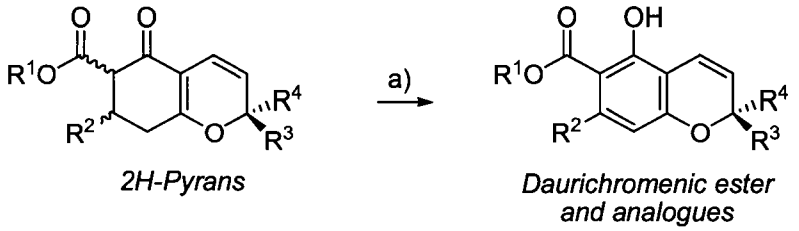


[a] Reagents and conditions: a) base then PhSeX (X = Cl, Br), THF; b) H_2O_2 (30% w/v), CH_2Cl_2.

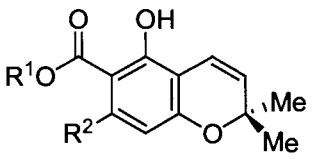
(90) Christoffers, J.; Mann, A. *Eur. J. Org. Chem.* **2000**, 1977.
(91) Meyer, C.; Piva, O.; Pete, J.-P. *Tetrahedron* **2000**, *56*, 4479.

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** (R^1= Et, R^2 = 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 2*H*-pyran precursor with DDQ on heating at reflux in toluene.[56] 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.

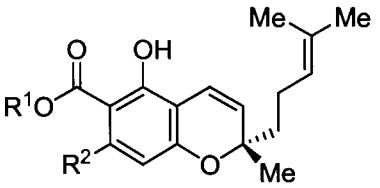
Scheme 2.9 Oxidation/Aromatisation Reactions of 2*H*-Pyrans (112-115) with DDQ[a]



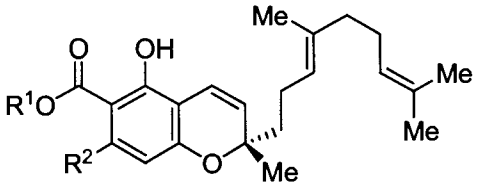
2H-Pyrans → *Daurichromenic ester and analogues*



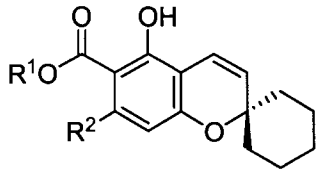
121a (R^1 = Et, R^2 = Me, 43%)
121b (R^1 = Me, R^2 = Ph, 35%)



122a (R^1 = Et, R^2 = Me, 27%)
122b (R^1 = Me, R^2 = Ph, 10%)



123a (R^1 = Et, R^2 = Me, 11%)
123b (R^1 = Me, R^2 = Ph, 6%)



124 (R^1 = Et, R^2 = Me, 35%)

Daurichromenic ester and analogues

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

2.5 Preparation of (±)-Daurichromenic Acid and Analogues

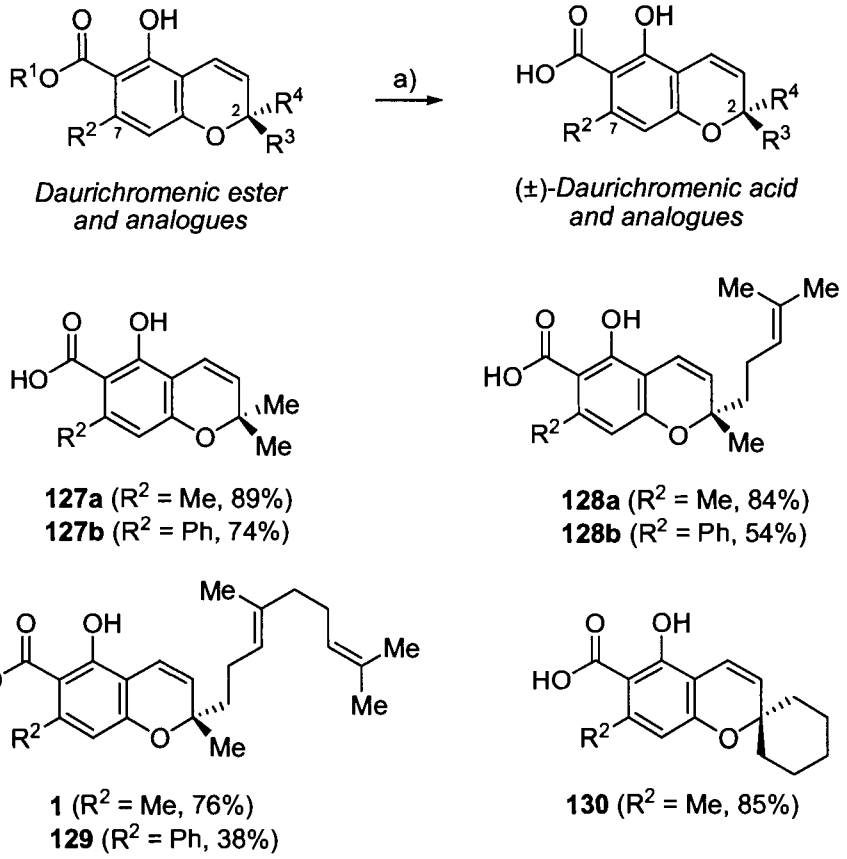
Various reagents and conditions were examined in order to effect the hydrolysis reaction of the products obtained in the latter reactions (the ethyl ester of daurichromenic acid and a series of analogues). The hydrolysis reaction under acidic conditions [*e.g.* concentrated sulphuric acid[62] and hydrochloric 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

(92) Severin, T.; Bruck, B.; Adhikary, P. *Chem. Ber.* **1966**, *99*, 3097.

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.[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**.[56] Jin and co-workers also commented in their synthesis of (±)-daurichromenic acid that the hydrolysis (3M NaOH, MeOH, H_2O, 40 °C) of the ethyl ester of (±)-daurichromenic acid (**1**) was slow and afforded the product in relatively low yield (40%).[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).[93] The use of other solvent systems for this hydrolysis reaction, such as acetone, DME or methanol,[94] proved to be inefficient. These reactions were also low yielding due to the undesirable and relatively facile decarboxylation reaction.

(93) Elix, J. A.; Whitton, A. A. *Aust. J. Chem.* **1989**, *42*, 1969.
(94) van Laak, K.; Scharf, H.-D. *Tetrahedron* **1989**, *45*, 5511.

Scheme 2.10 Synthesis of (±)-Daurichromenic Acid (1) and Analogues (127-130)[a]

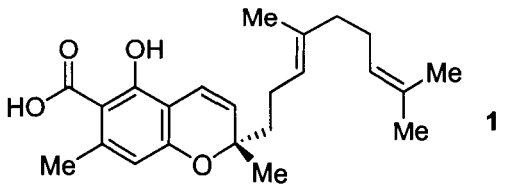


[a] Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 °C, ~ 16 h.

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 ~ δ 176 ppm for the C7-methyl substituted products **1**, **127a**, **128a** and **130** and ~ δ 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 ~ 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 δ 11.66 ppm as a sharp singlet. Two doublets at δ 5.48 and 6.74 ppm were observed for the alkene protons on the pyran ring. The aromatic proton signal was observed at δ 6.24 ppm. The two vinylic protons on the side chain corresponded to the multiplet at δ 5.09 ppm. The signals for the allylic protons were observed at ~ δ 1.9-2.20 ppm. The benzylic methyl group was observed as a singlet at δ 2.54. The remaining alkyl signals were located in the upfield region (δ 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]



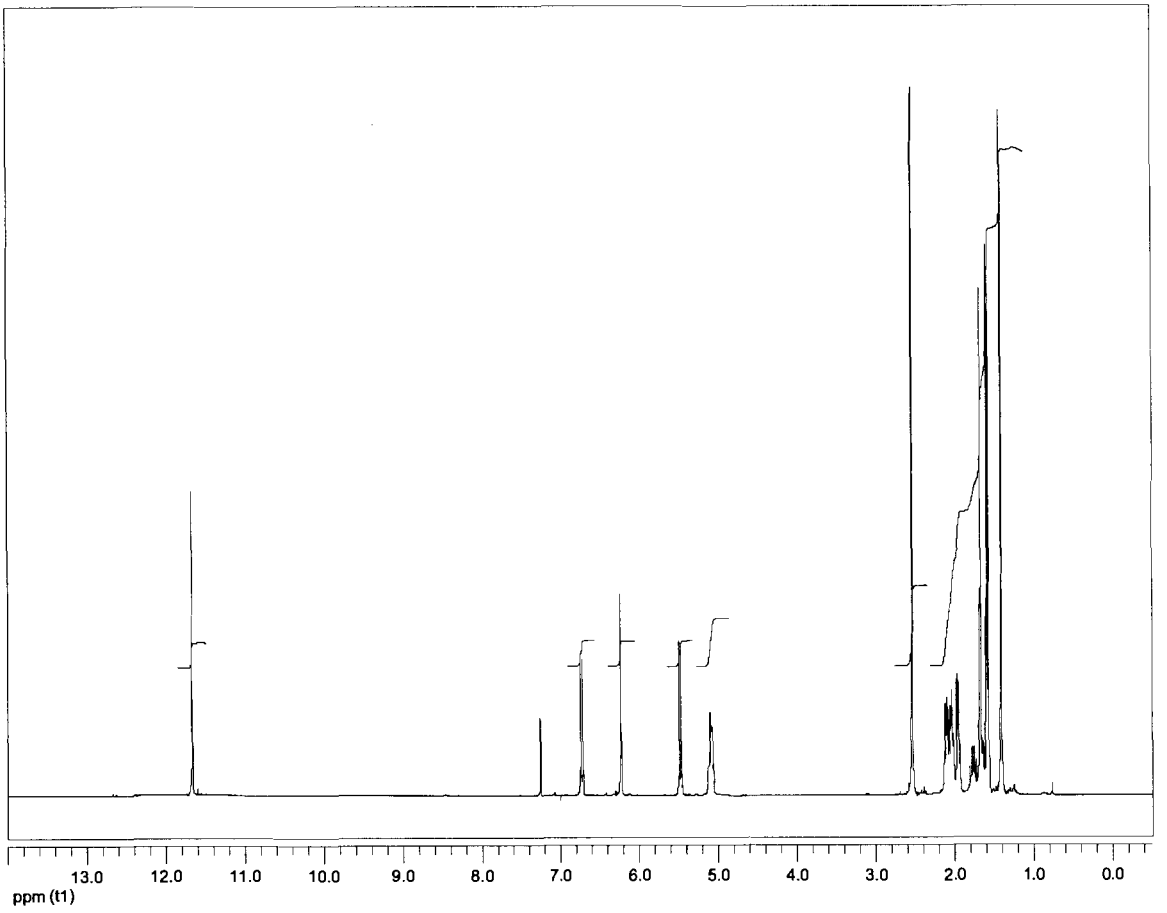
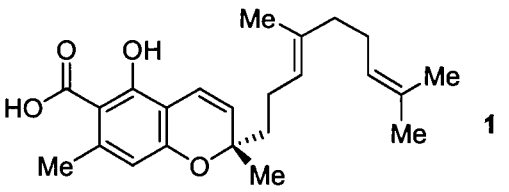


Figure 2.5 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of synthetic (±)-daurichromenic acid (1).

The ^{13}C NMR spectrum of (±)-daurichromenic acid **1** is presented below (Figure 2.6). Thirteen resonance signals were observed in the downfield region (δ 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 (δ 16-81 ppm). The ^{13}C NMR spectroscopic data were again in full agreement with the reported values of the natural product.[53]



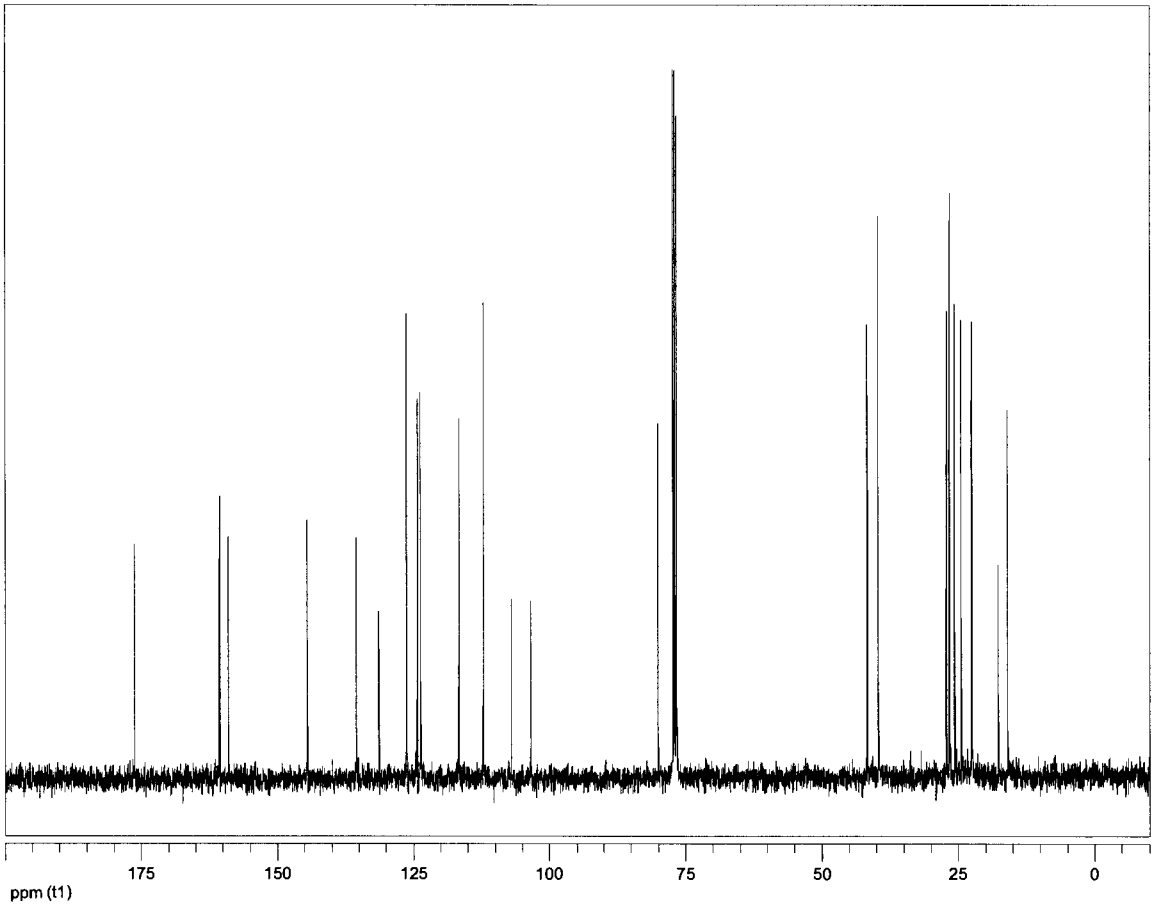


Figure 2.6 ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of synthetic (±)-daurichromenic acid (1).

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 2*H*-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 2*H*-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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(95) Kato, T.; Kimura, H. *Chem. Pharm. Bull.* **1977**, *25*, 2692.
(96) Brown, J. C.; Mandal. A. K.; Kulkarni, S. U. *J. Org. Chem.* **1977**, *42*, 1392.

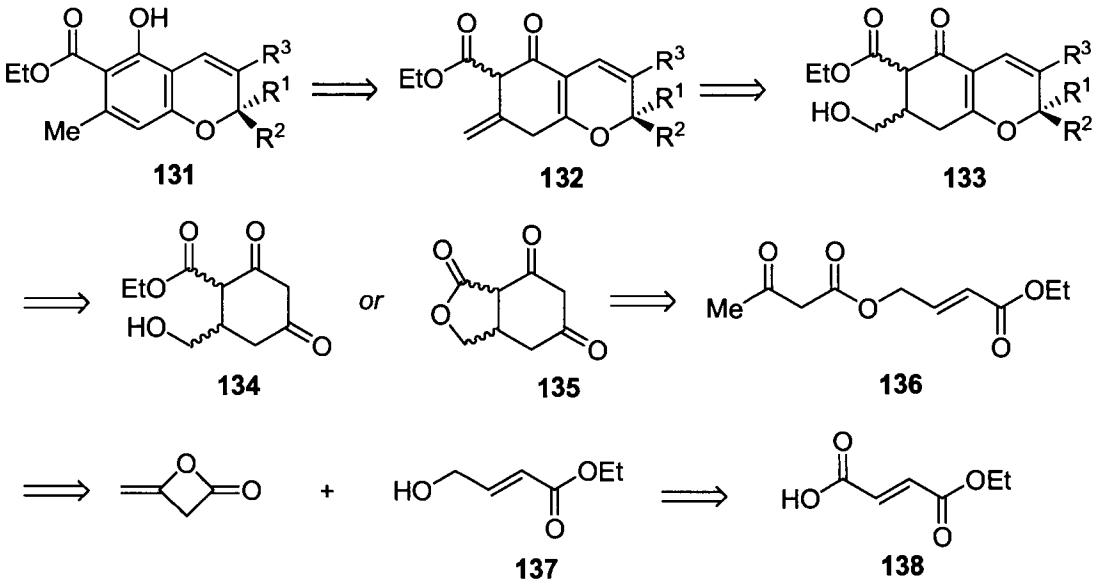
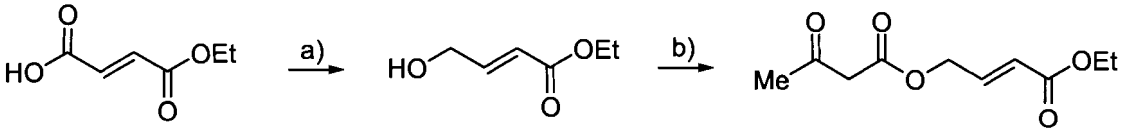


Figure 2.7 Alternative retrosynthetic analysis of (±)-daurichromenic ester and analogues (131).

Reduction of fumaric acid monoethyl ester **138** with borane dimethylsulfide complex (BMS) in THF afforded ethyl 4-hydroxybut-2-enoate **137** chemoselectively (41% yield).[97] 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 α,β-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 δ 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.

(97) Wilson, P. D. Ph.D. Thesis, University of Manchester, Manchester, UK, 1993.

Scheme 2.11 Synthesis of Ethyl (*E*)-4-Acetoacetoxycrotonate (136)[a]



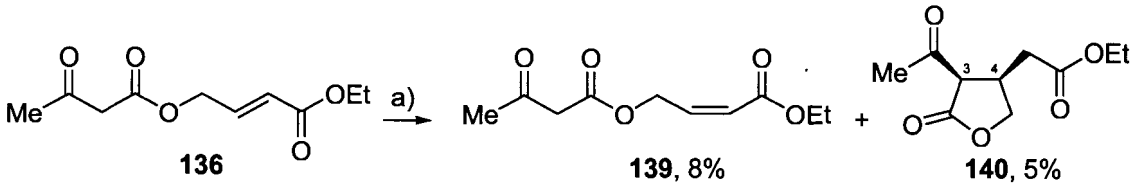
138 **137** **136**

[a] Reagents and conditions: a) BMS, THF, rt, 22 h, 41%; b) diketene, PhH, Et_3N cat., reflux, 2.5 h, 83%.

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.[95] 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 δ 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.[98]

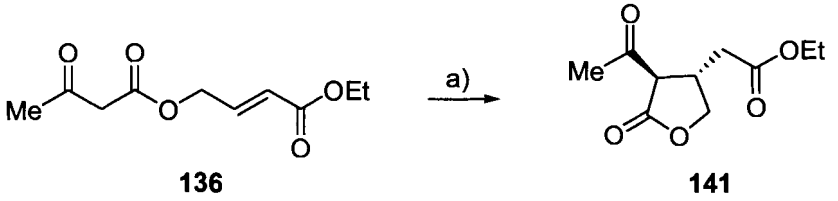
Scheme 2.12 *Z*-Isomerization Product (139) and Intramolecular Michael Addition Product (140)[a]



[a] 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 γ-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]



[a] Reagents and conditions: a) NaOEt, EtOH, reflux, 1 day, 13%.

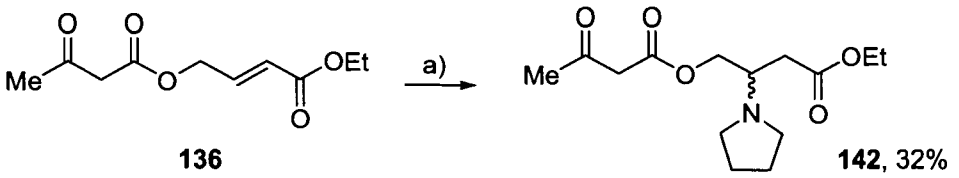
(98) Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*; 6th ed.; Wiley: New York, 1998; p. 186.

A related procedure that involved an intermolecular Michael addition and Dieckmann condensation reaction has been reported in the literature.[99] 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-acetoacetoxycrotonate **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-acetoacetoxycrotonate **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-acetoacetoxycrotonate **136** with pyrrolidine (1 equiv) in THF at 0 °C for 10 min followed by the addition of acetic acid (1 equiv).[100] 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 ^{1}H NMR data, which showed signals at δ1.76 (4H, 2 x pyrrolidine-C*H*$_2$) and 2.63 ppm (4H, 2 x pyrrolidine-C*H*$_2$). Further proof of the structure **142** came from the ^{13}C NMR spectrum in which the correct number of signals with the expected chemical shifts was observed (Scheme 2.14).

(99) Zimmerman, H. Z.; St. Clair, J. D. *J. Org. Chem.* **1989**, *54*, 2125.
(100) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425.

Scheme 2.14 Conjugate Addition Product (142)[a]



136 **142**, 32%

[a] 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 2*H*-pyran derivatives **143** (Figure 2.8). Tautomerization of the resultant dienones would install the aromatic ring in the esters **131**. The 2*H*-pyrans **143** could be prepared from 1,3-cyclohexanedione **144** and various α,β-unsaturated aldehydes in the same manner as reported above (5 mol % 1,2-ethylenediammmonium diacetate, MeOH, rt).[66] 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

(101) Nishizuka, T.; Hirosawa, S.; Kondo, S.; Ikeda, D.; Takeuchi, T. *J. Antibiotics* **1997**, *50*, 755.
(102) Bentley, P. H.; Hunt, E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2222.

intramolecular condensation reaction. The required Diels-Alder adduct **145** could be prepared from cyclopentadiene **147** and ethyl 2-butynoate **146**.[103]

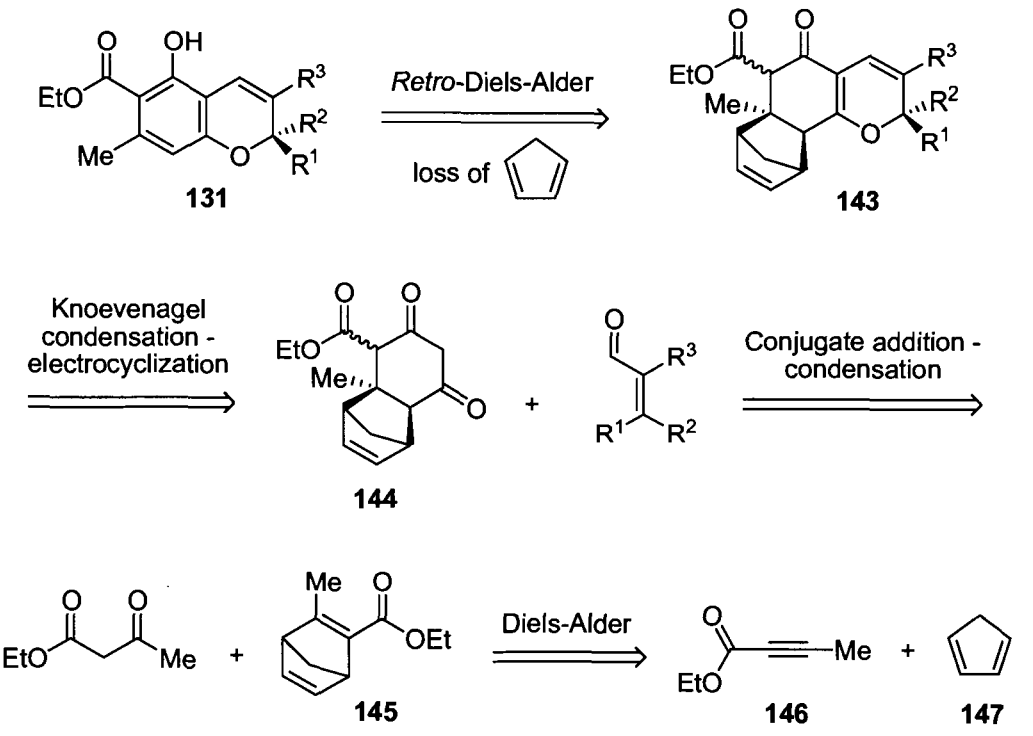
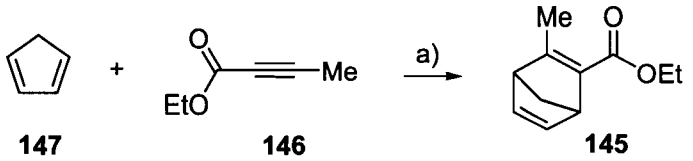


Figure 2.8 Alternative retrosynthetic analysis of (±)-daurichromenic ester and analogues (131).

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*).

(103) Gibson, T.; Barneis, Z. J. *Tetrahedron Lett.* **1972**, *22*, 2207.

Scheme 2.15 Diels-Alder Product (145)[a]

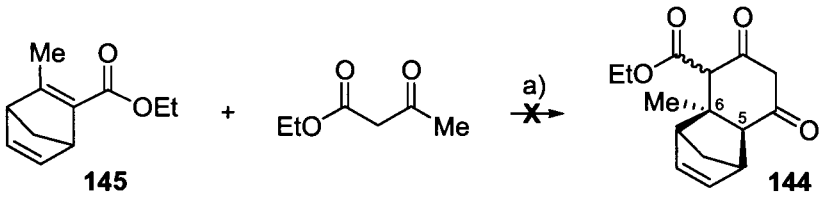


147 146 145

[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[a]



145 144

[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 *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.

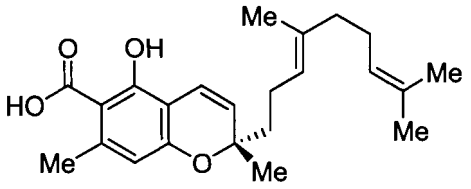
Additional synthetic studies have also been investigated to improve the synthesis as well as to prepare further structural analogues. The results of these studies are discussed in the following chapter.

CHAPTER THREE

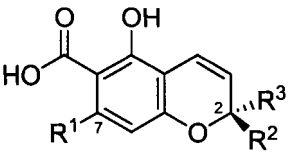
SYNTHESIS OF ADDITIONAL DAURICHROMENIC ACID ANALOGUES: RESULTS AND DISCUSSION

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).



1 (±)-*Daurichromenic acid*



Daurichromenic acid analogues

Figure 3.1 Molecular structures of (±)-daurichromenic acid (1) and analogues.

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 2*H*-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 2*H*-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 2*H*-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 2*H*-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).[104,105,106,107]

(104) Lamcharfi, E.; Menguy, L.; Zamarlik, H. *Synth. Commun.* **1993**, *23*, 3019.
(105) Saimoto, H.; Ogo, Y.; Komoto, M.; Morimoto, M.; Shigemasa, Y. *Heterocycles* **2001**, *55*, 2051.
(106) Talley, J. J. *Synthesis* **1983**, 845.
(107) Bissada, S.; Lau, C. K.; Bernstein, M. A.; Dufresne, C. *Can. J. Chem.* **1994**, *72*, 1866.

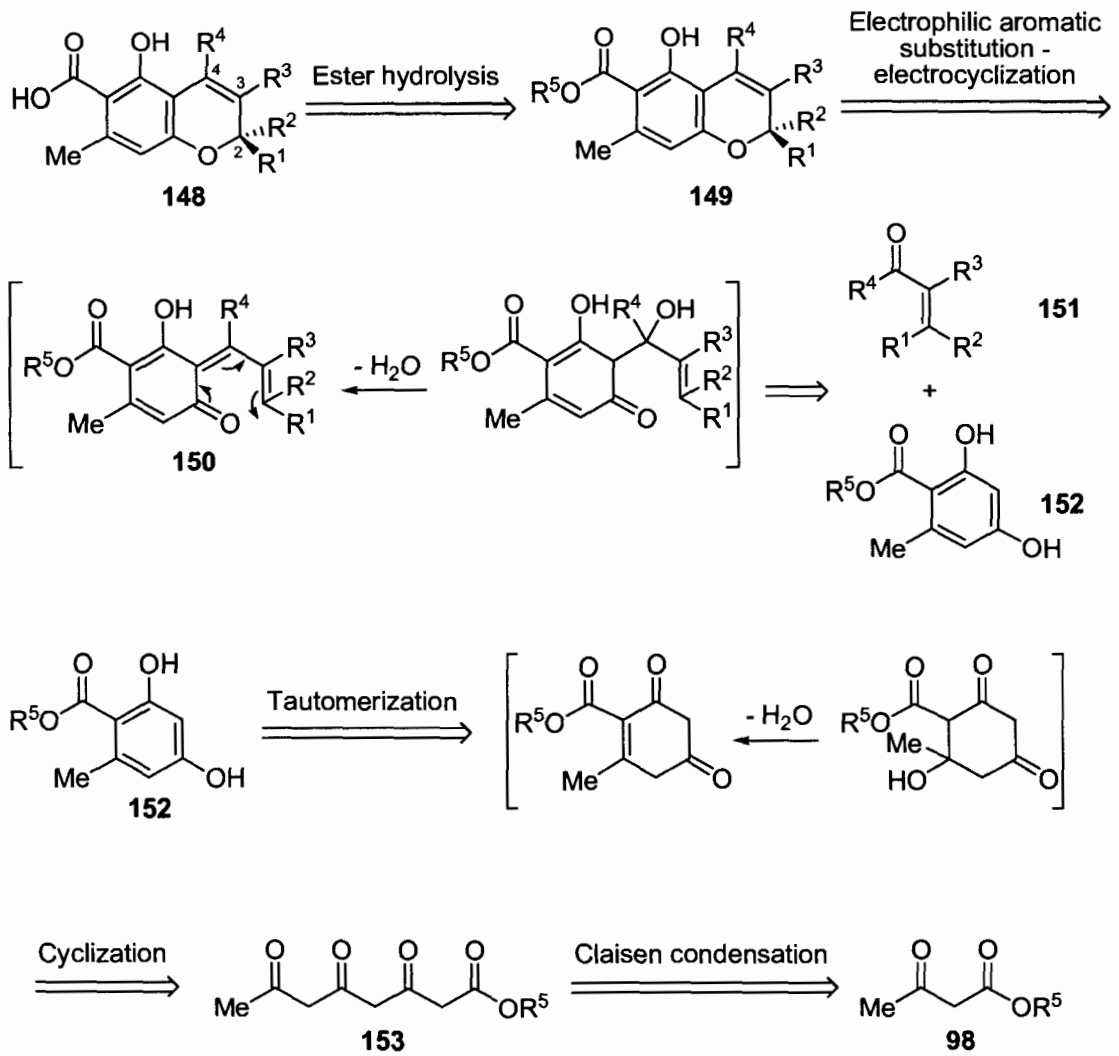


Figure 3.2 Retrosynthetic analysis of (±)-daurichromenic acid and analogues (148).

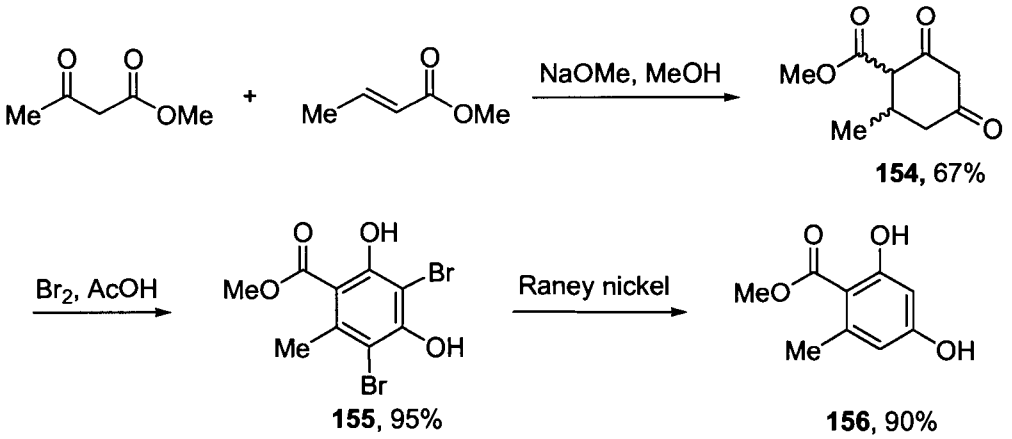
The desired phenols **152** are esters of a known compound, orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) that is a natural product of considerable biochemical interest.[108] The synthesis of orsellinic acid and derivatives has been well studied and a common approach is *via* the cyclization of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

(108) Harris, T, M.; Murphy, G. P.; Poje, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 7733.

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-cyclohexanedione derivatives) which are readily available from the base-catalyzed condensation of α,β-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 preparared 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]



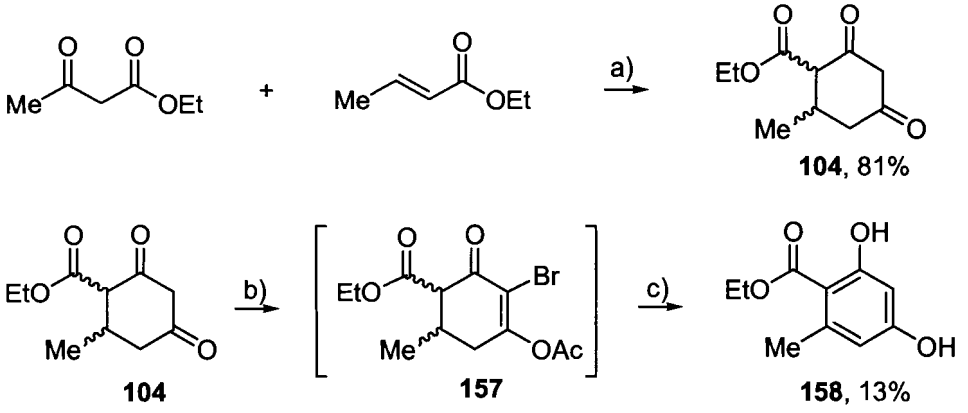
However, in our hands the debromination reaction of the orsellinate derivative **155** with Raney nickel in aqueous sodium hydroxide (2M) proved to be ineffective.[111] No reaction was observed after the reaction mixture was stirred at room temperature for

(109) Sargent, M. V.; Vogel, P.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1986.
(110) Santesson, J. *Acta Chem. Scand.* **1970**, *24*, 3373.
(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.[112] 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)[a]

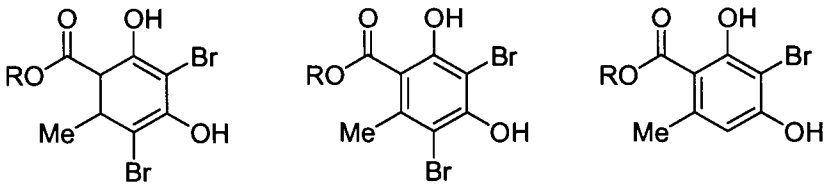


[a] Reagents and conditions: a) NaOEt, EtOH, reflux, 24 h; b) Br_2, Ac_2O, AcOH, 12 °C to reflux, 2 h; c) HBr (aq, 50% w/v), H_2O, reflux, 2 h.

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

(112) Dyke, H. J.; Elix, J. A.; Marcuccio, S. M.; Whitton, A. A. *Aust. J. Chem.* **1987**, *40*, 431.

the bromination products of dihydroorsellinate.[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.



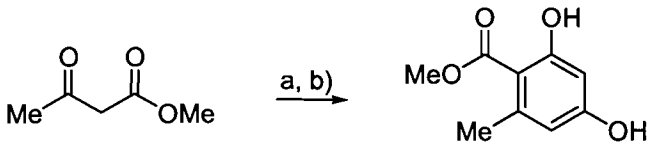
159 **160** **161**

(R = Me, Et)

Figure 3.3 Reported bromination products of 1,6-dihydroorsellinate (104).

In view of the difficulty encountered in this bromination-debromination approach an alternative preparation was attempted. Using a modified version of Barton's protocol,[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).[114]

Scheme 3.3 One-Pot Synthesis of Methyl Orsellinate (156)[a]



156, 46%

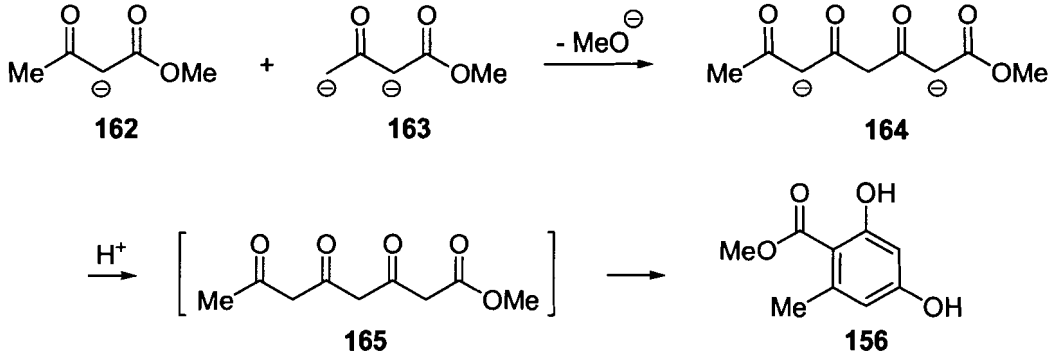
[a] Reagents and conditions: a) NaH, *n*-BuLi, 0 °C to reflux, 40 h; b) 6M HCl (aq), rt, 16 h.

(113) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2272.
(114) Chiarello, J.; Joullie, M. M. *Tetrahedron* **1988**, *44*, 41.

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.[114] The ^{1}H and ^{13}C NMR spectroscopic data were also consistent with those reported in the literature.[114]

The mechanism of this reaction has been established.[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** (mono-deprotonation 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)



162 **163** **164** **165** **156**

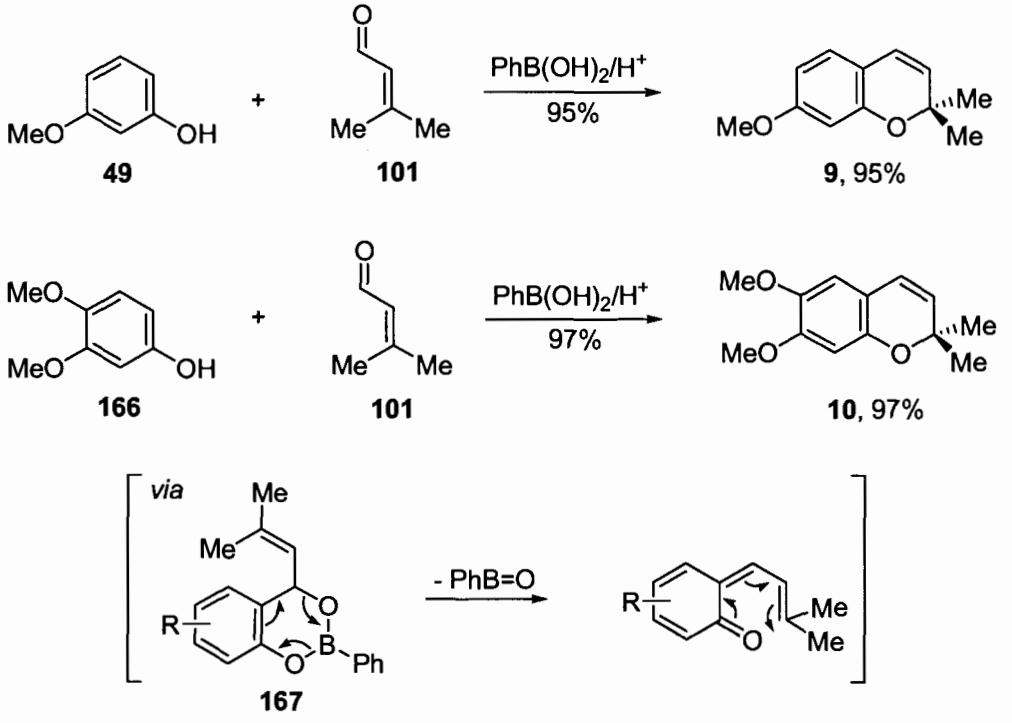
3.3 Preparation of 2*H*-Chromenes

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

(115) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(116) Hill, J. E.; Harris, T. M. *Synth. Commun.* **1982**, *12*, 621.

yields.[104,105,117] However, Bissada and co-workers have reported the synthesis of the anti-juvenile hormones precocene 1 **9** and 2 **10** (see also: Figure 1.3) *via* the 2-phenyl-4*H*-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).[107] 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.[42]

Scheme 3.5 Phenylboronic Acid-Mediated Synthesis of Precocene 1 (9) and 2 (10)[107]

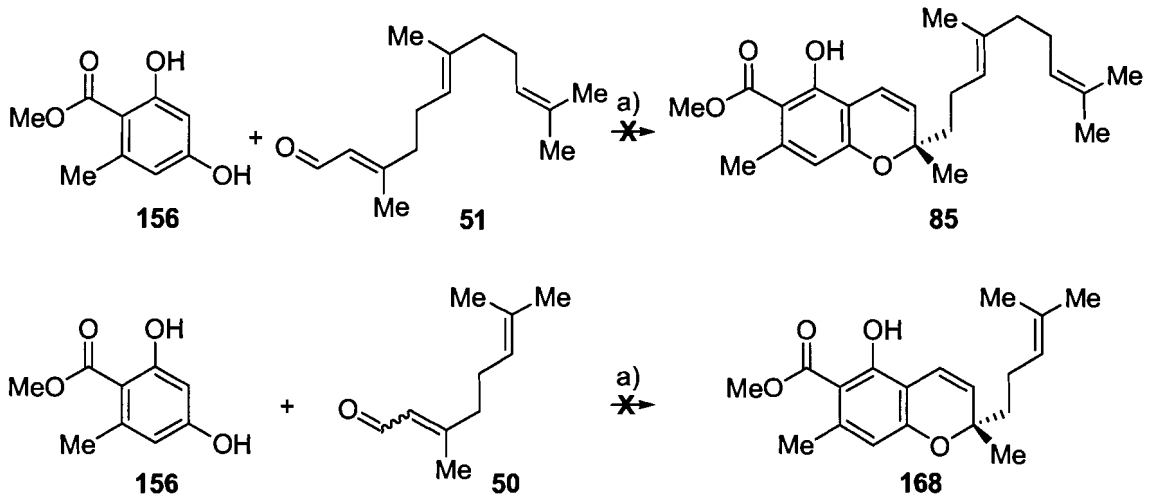


In the first instance, *trans,trans*-farnesal **51** (2 equiv, prepared from commercially available *trans,trans*-farnesol on oxidation with pyridinium dichromate; see: *Chapter Two*) was reacted with methyl orsellinate **156** in the presence of phenylboronic acid (1.6

(117) Subburaj, K.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 259.

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 2*H*-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.

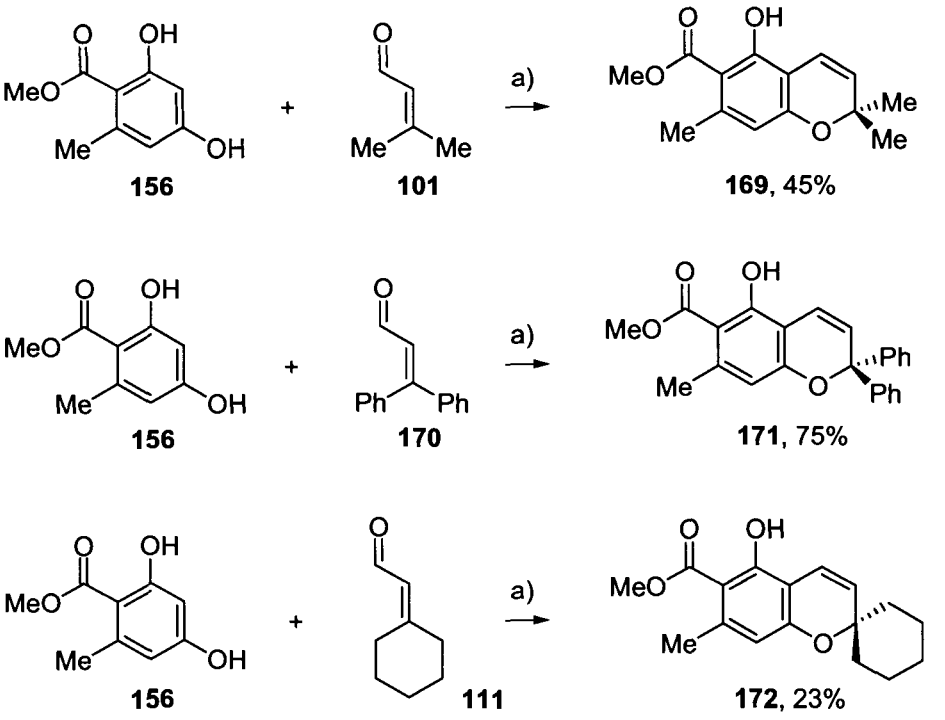
Scheme 3.6 Attempted Preparation of 2*H*-Chromenes (85) and (168)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 24 h.

However, further experiments have proved that C2-disubstituted 2*H*-chromene derivatives can be prepared employing this synthetic method when α,β-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**, β-phenylcinnamaldehyde **170** and cyclohexylideneacetaldehyde **111** in the presence of phenylboronic acid and propionic acid afforded the expected 2,2-disubstituted 2*H*-chromene derivatives **169**, **171** and **172** in 23-75% yield (Scheme 3.7).

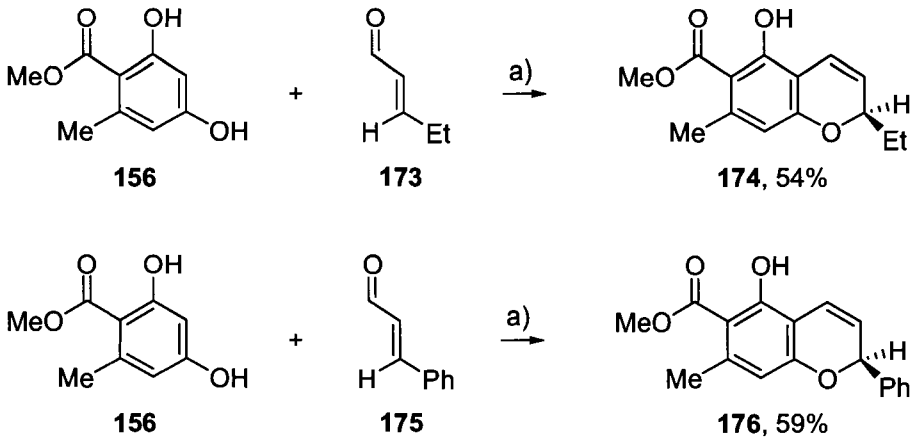
Scheme 3.7 Phenylboronic Acid-Mediated Synthesis of 2*H*-Chromenes (169), (171) and (172)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 16-24 h.

Following the same procedure discussed above, two C2-monosubstituted 2*H*-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).

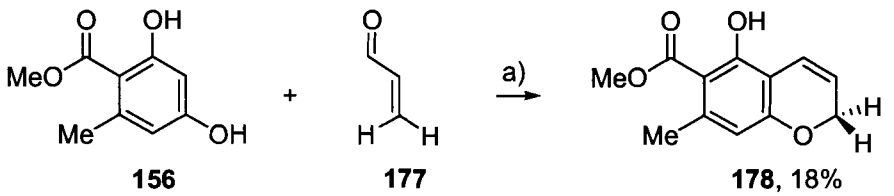
Scheme 3.8 Phenylboronic Acid-Mediated Synthesis of C2-Monosubstituted 2*H*-Chromenes (174) and (176)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 20-24 h.

This method was then extended to prepare a 2*H*-chromene derivative with no substituents at the C2 and C3 positions. Reaction of methyl orsellinate **156** with acrolein **177** afforded the expected 2*H*-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 2*H*-Chromene (178)[a]

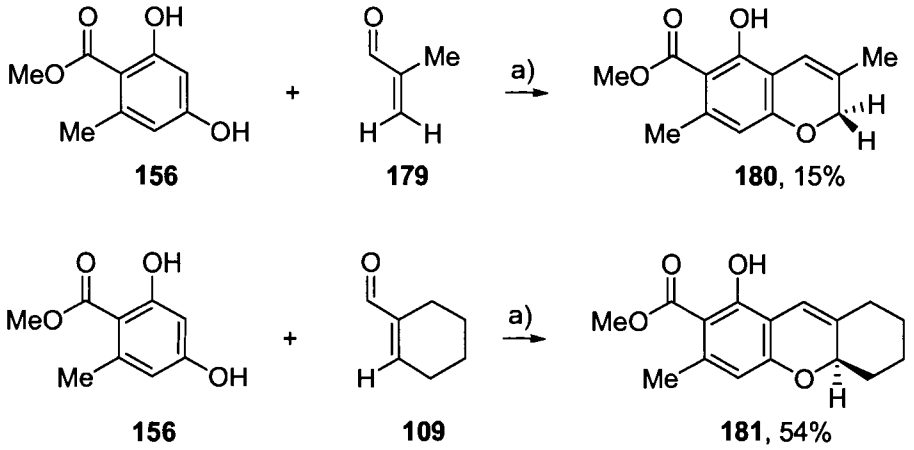


[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 24 h.

The success of these reactions demonstrated that a variety of 2*H*-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 2*H*-

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 2*H*-chromene derivatives was also successful. The tricyclic 2*H*-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 2*H*-Chromenes (180) and (181)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 20-24 h.

All of the 2*H*-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 ~ 1650 cm^{-1} (C=O) was observed in the IR spectrum of each compound. The ^1H NMR spectrum of each compound showed a characteristic singlet at ~ δ6.2 ppm for the aromatic proton, a doublet at ~ δ6.7 ppm for the C4-alkene proton and at ~ δ5.5 ppm for the C3-alkene proton (where it was applicable) as well as a singlet at ~ δ12 ppm for the hydrogen-bonded phenolic proton. Of note, the spectroscopic data of the senecialdehyde

derived 2*H*-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.

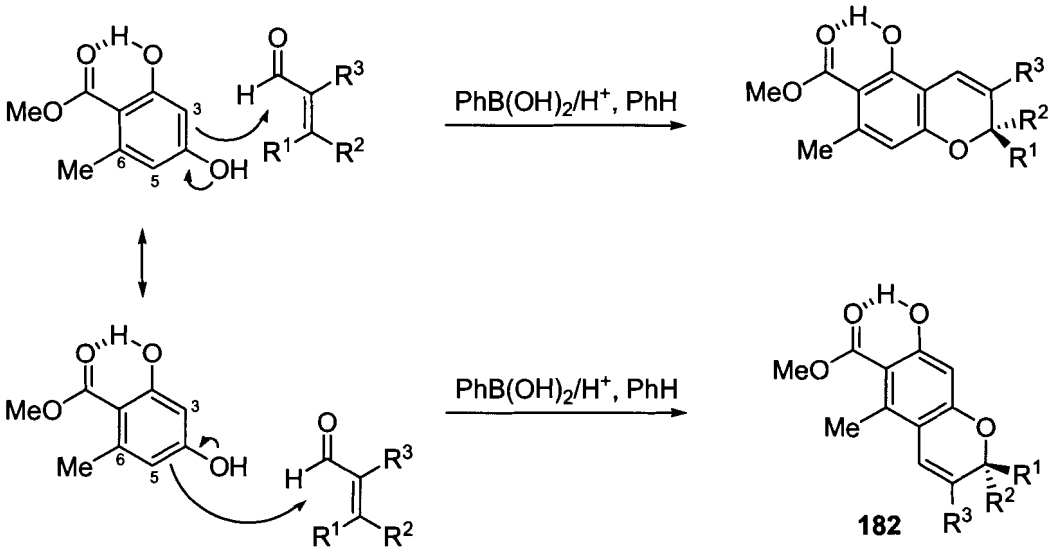
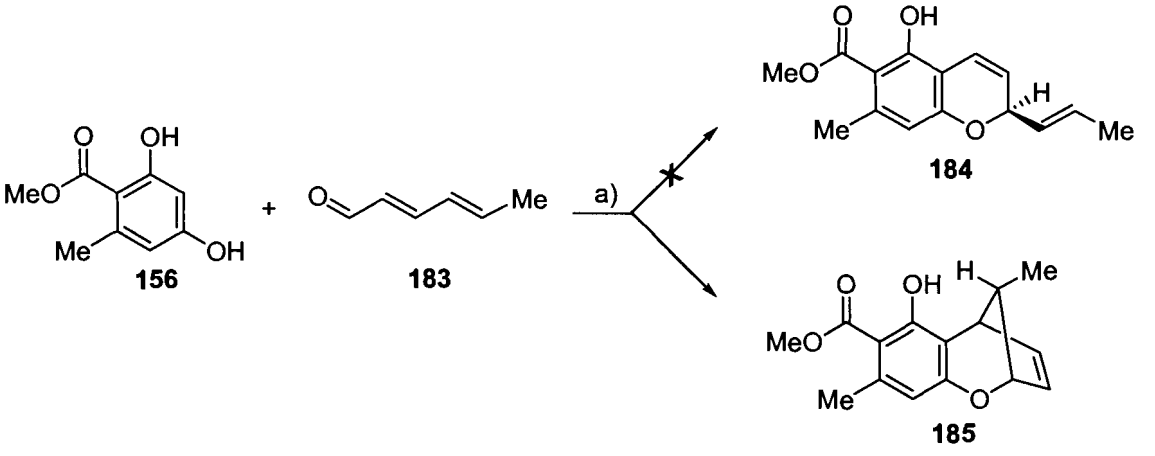


Figure 3.4 Rationalization of the regioselectivity of the phenylboronic acid-mediated 2*H*-chromene formation reaction.

In light of the success of this method for the direct preparation of various C2- and C3-substituted 2*H*-chromene derivatives, the reactions of methyl orsellinate **156** with

conjugate dienals were examined. Treatment of methyl orsellinate **156** with sorbic aldehyde (*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*H*-chromene derivative **184**. However, the ^{1}H and ^{13}C NMR spectra of this compound did not resemble those of the other 2*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 *trans,trans*-2,4-Hexadienal (183)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, 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

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

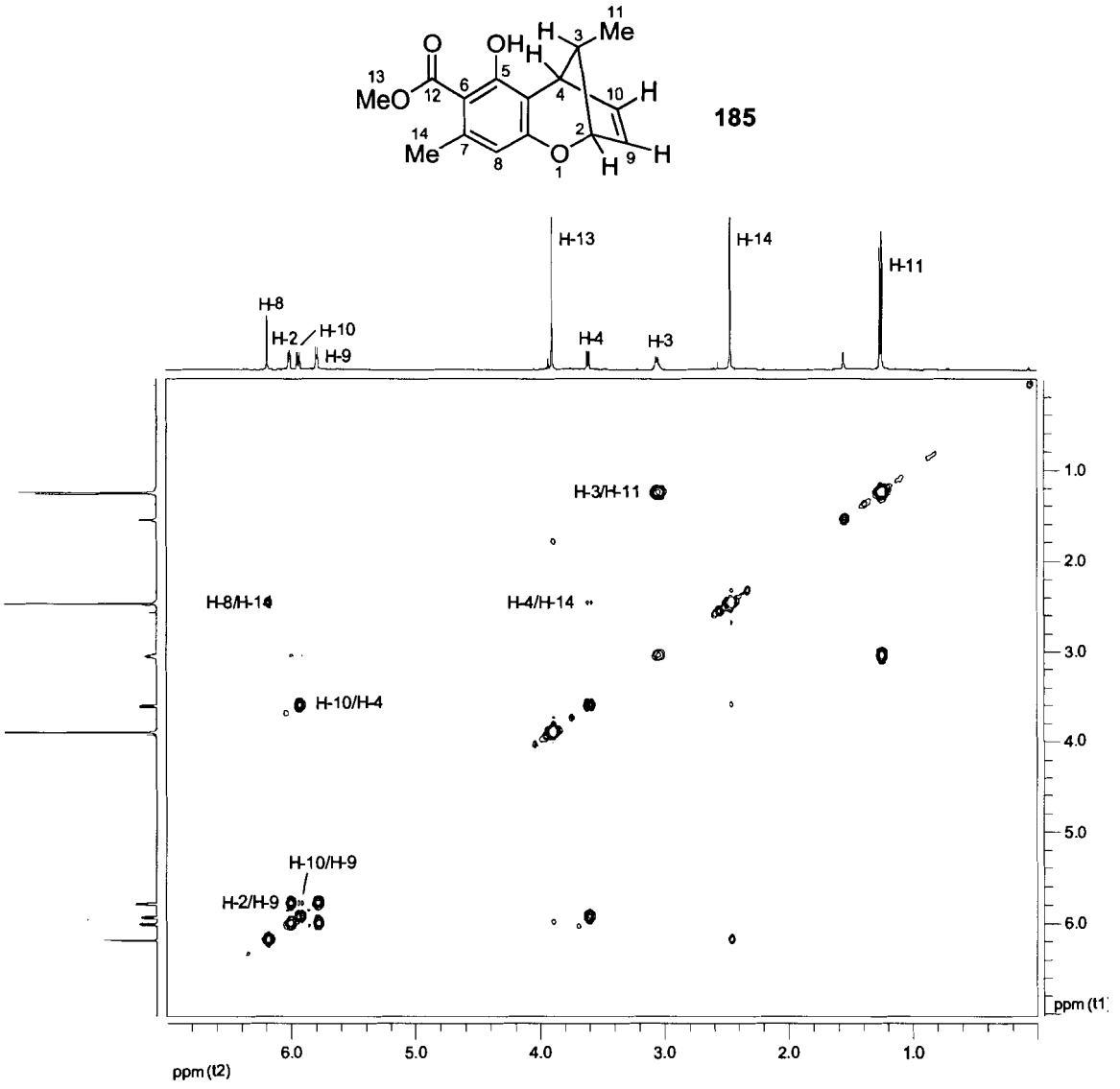


Figure 3.5 A section of the COSY NMR spectrum (500 MHz, $CDCl_3$) of the tricyclic phenol derivative (185).

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).

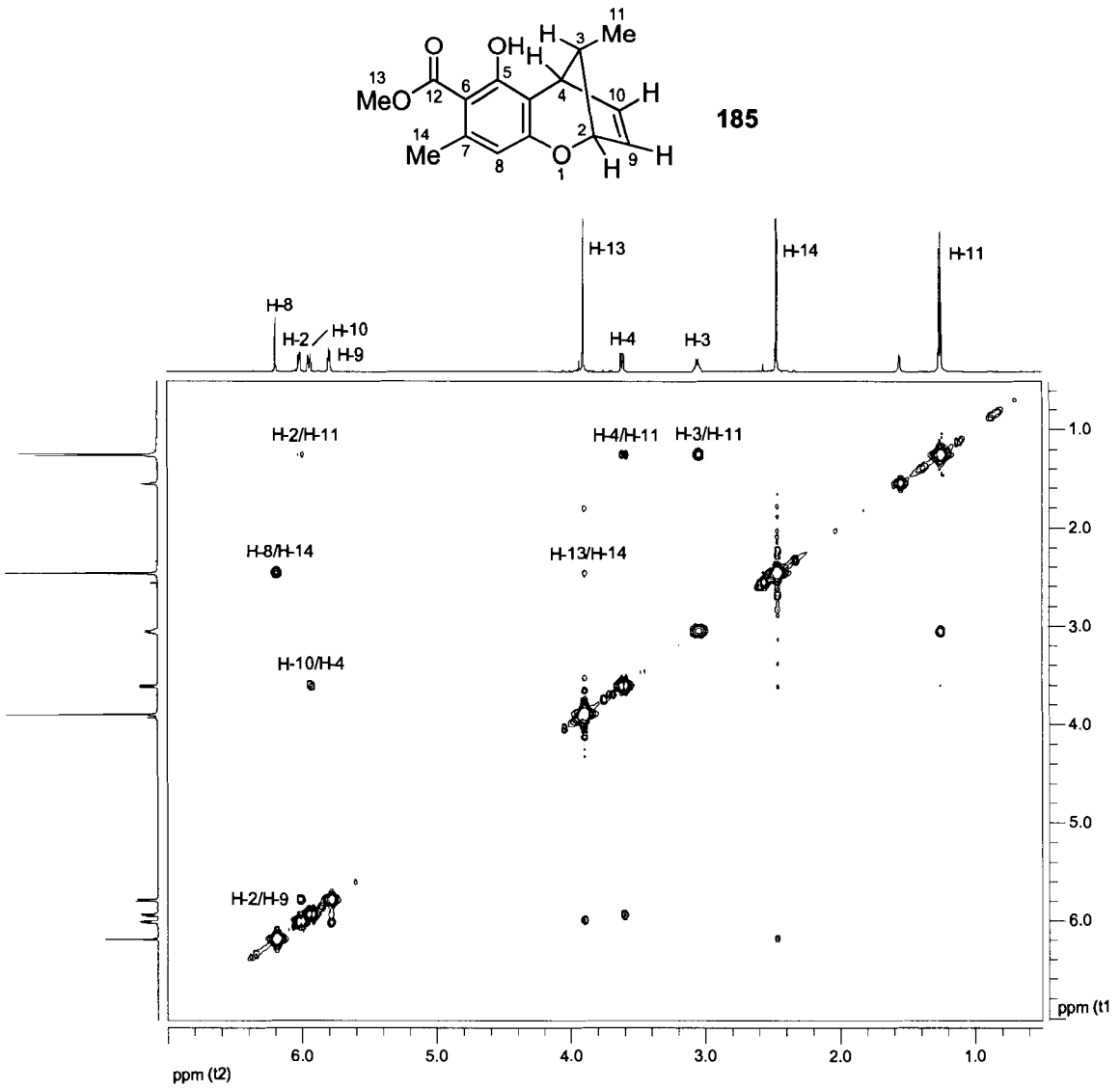


Figure 3.6 A section of the NOESY NMR spectrum (500 MHz, $CDCl_3$) of the tricyclic phenol derivative (185).

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).

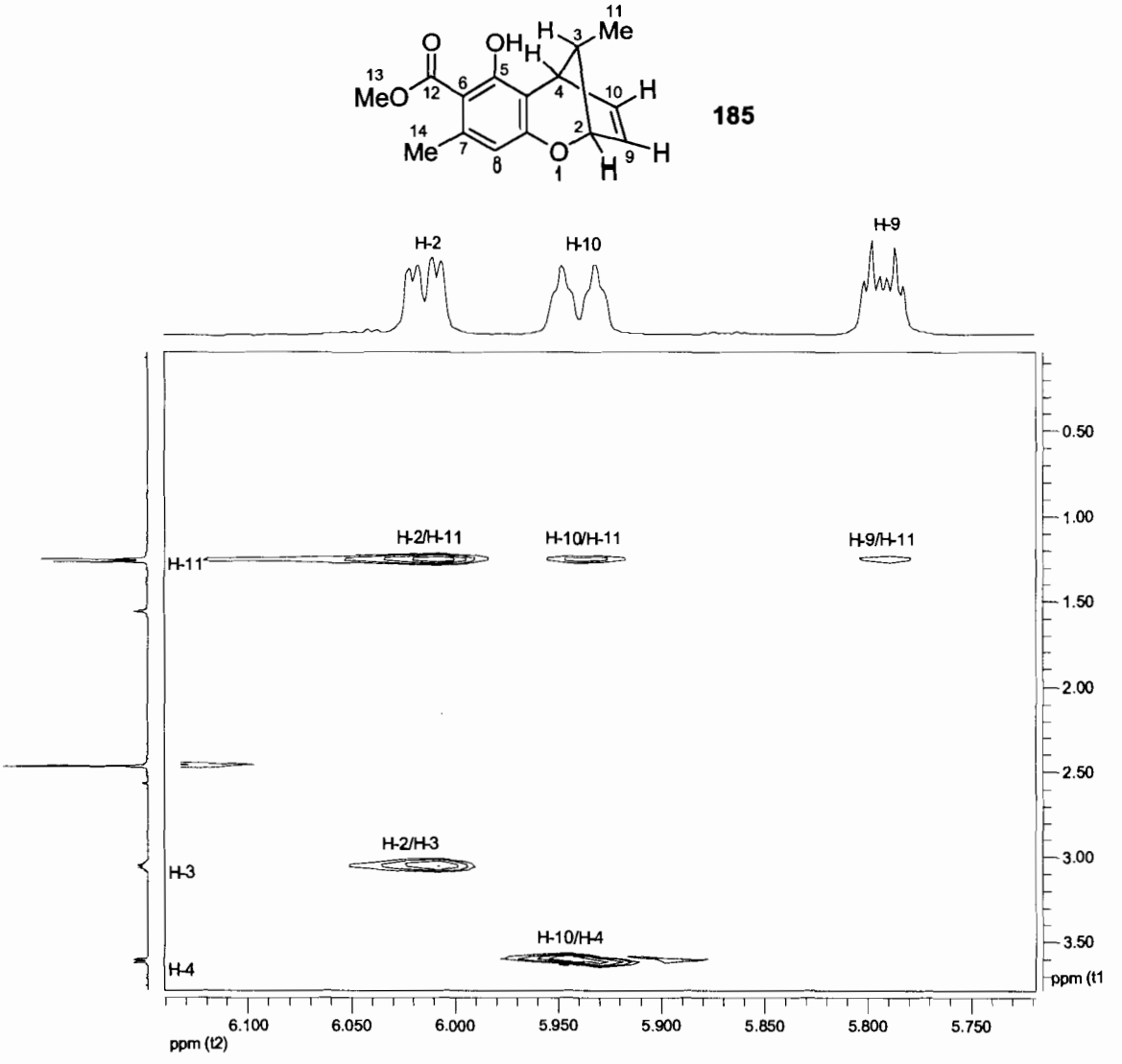


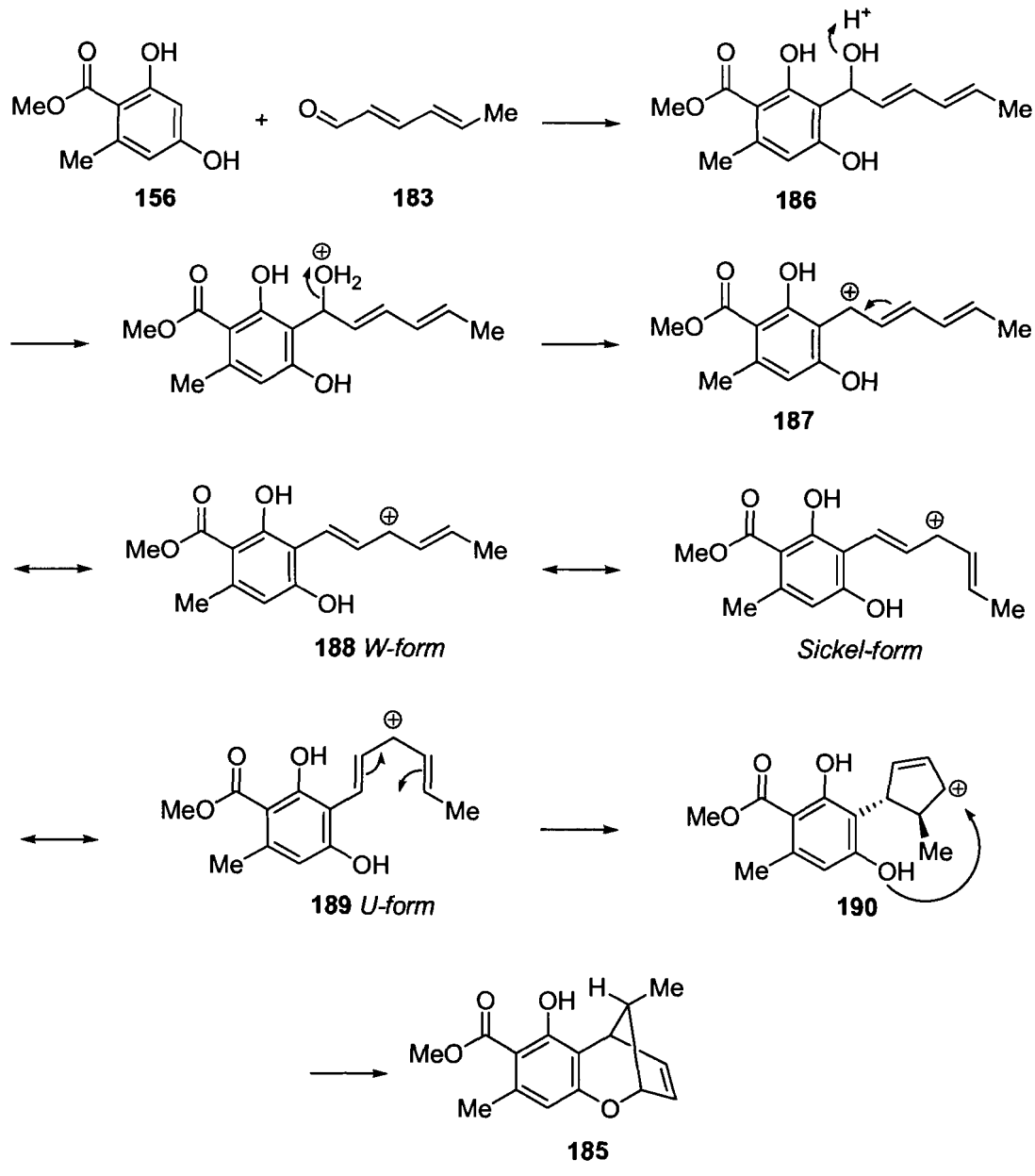
Figure 3.7 An expansion of the NOESY NMR spectrum (500MHz, $CDCl_3$) of the tricyclic phenol derivative (185).

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**.[118] 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.[119] The latter ring closure reaction should proceed in a conrotatory manner under thermal conditions to afford the cyclopentenyl cation intermediate **190**.[120] 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.

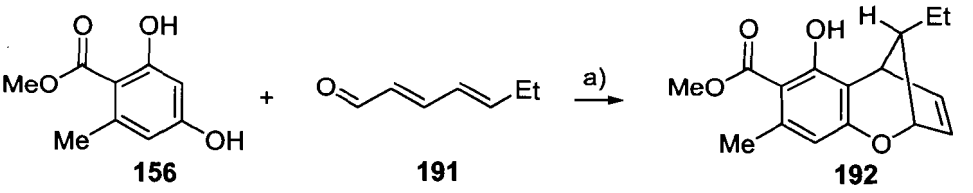
(118) Chiu, N. W. K.; Sorensen, T. S. *Can. J. Chem.* **1973**, *51*, 2776.
(119) Bladek, R.; Sorensen, T. S. *Can. J. Chem.* **1972**, *50*, 2806.
(120) Campbell, P. H.; Chiu, N. W. K.; Deugau, K.; Miller, I. J.; Sorensen, T. S. *J. Am. Chem. Soc.* **1969**, *91*, 6404.

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 *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 *trans,trans*-2,4-Heptadienal (191)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 24 h, 20%.

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).

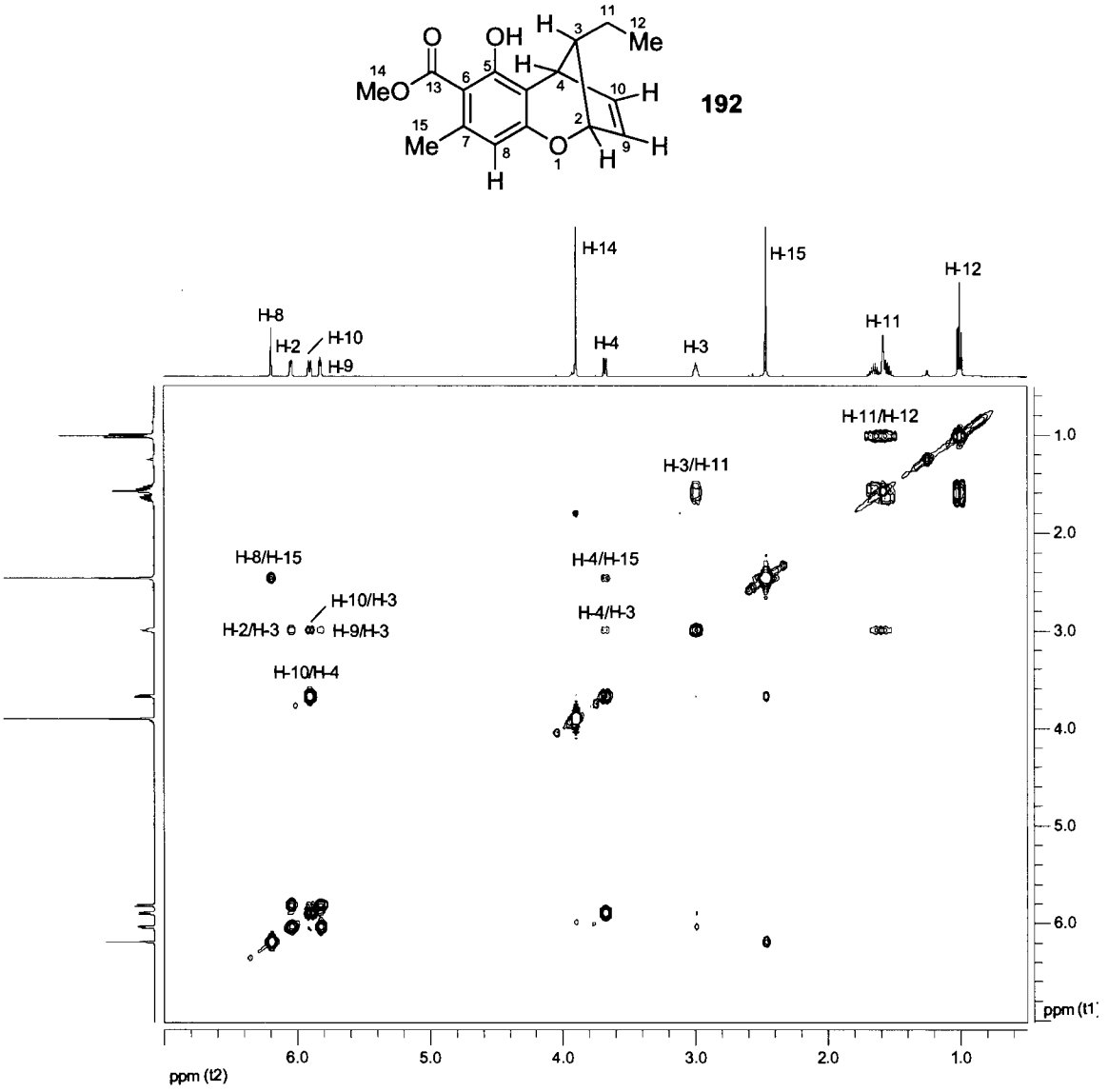


Figure 3.8 A section of the COSY NMR spectrum (500 MHz, $CDCl_3$) of the tricyclic phenol derivative (192).

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, δ106.1 ppm) and proton H8.

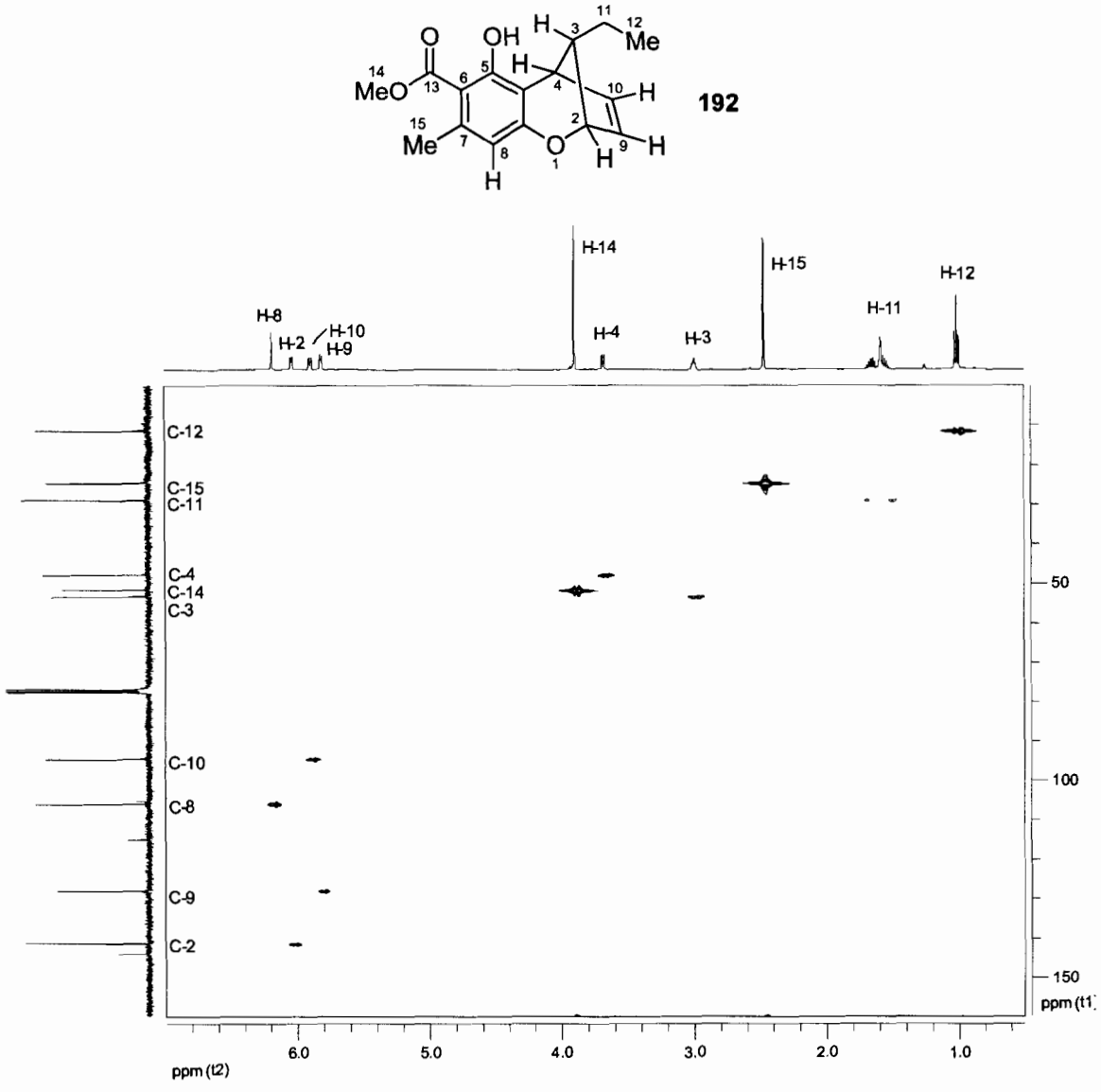
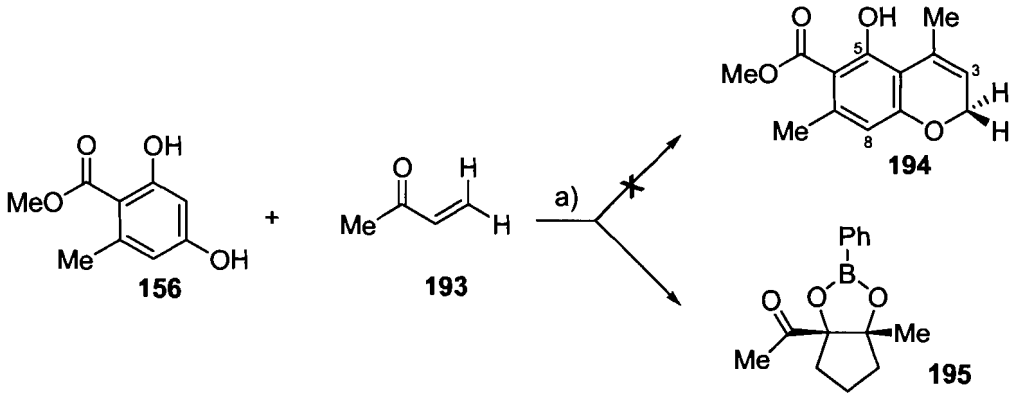


Figure 3.9 A section of the HMQC NMR spectrum (500 MHz, $CDCl_3$) of the tricyclic phenol derivative (192).

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

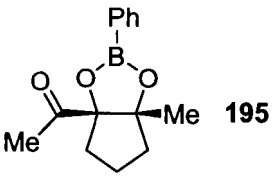
variety of α,β-unsaturated aldehydes. It was also of synthetic interest to examine the potential application of this one-pot procedure in the reaction of methyl orsellinate **156** with α,β-unsaturated ketones in order to prepare C4-substituted (±)-daurichromenic acid analogues. Heating methyl orsellinate **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 derivetive **194**. In addition, the ^{1}H NMR spectrum did not show signals that were characteristic of the 2*H*-chromenes [*e.g.* the C3-alkene proton (~ δ 6.2 ppm), C8-aromatic proton (~ δ 6.7 ppm) and the C5-phenolic proton (~ δ 12 ppm)]. Instead, five aromatic protons at δ 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)[a]



[a] Reagents and conditions: a) $PhB(OH)_2$, $CH_3CH_2CO_2H$, benzene, reflux, 48 h, 44%.

The incorporation of the phenylboronic moiety in the product was evident from the distinctive broad multiplet signal at δ 127.5 ppm in the ^{13}C NMR spectrum, which corresponded to the aromatic carbon that was coupled to the adjacent boron atom (Figure 3.10).



195

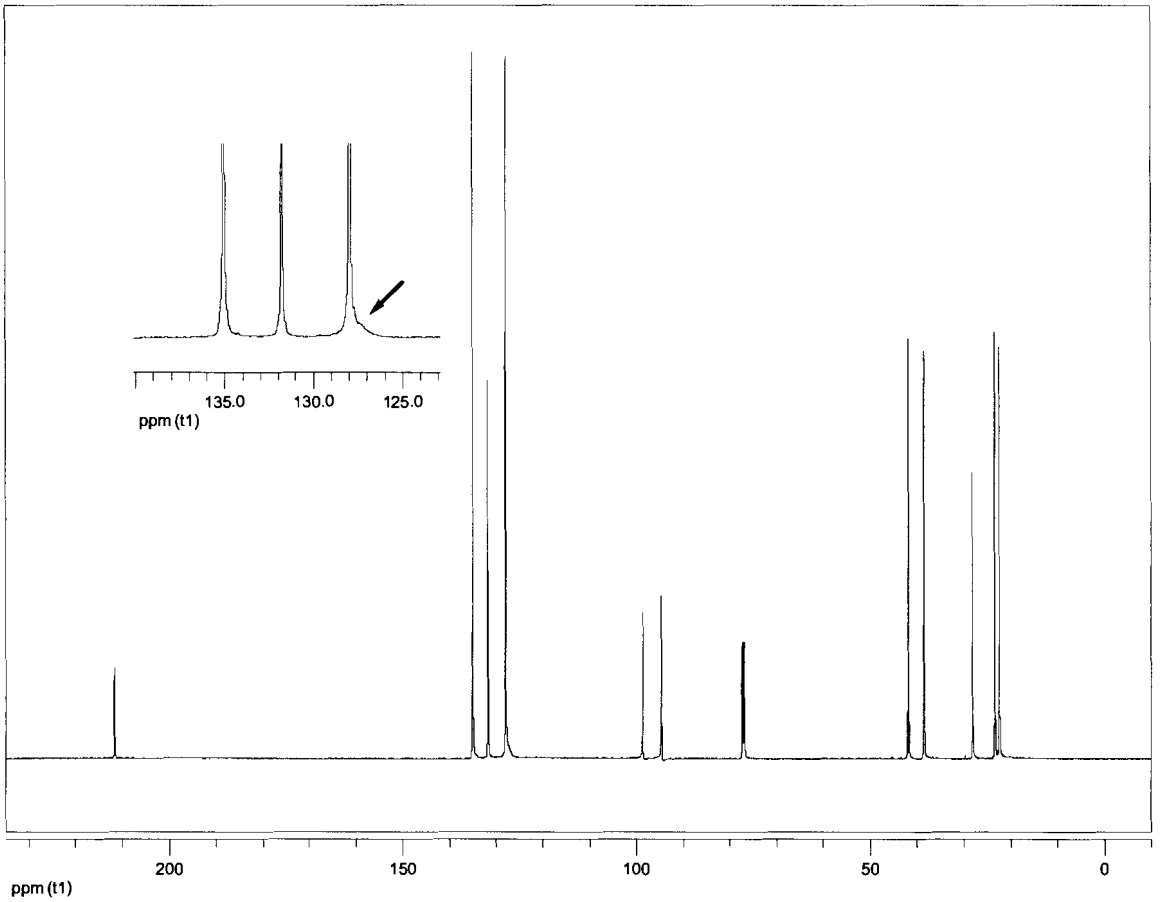


Figure 3.10 A section of the ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the cyclic phenylboronate ester (195).

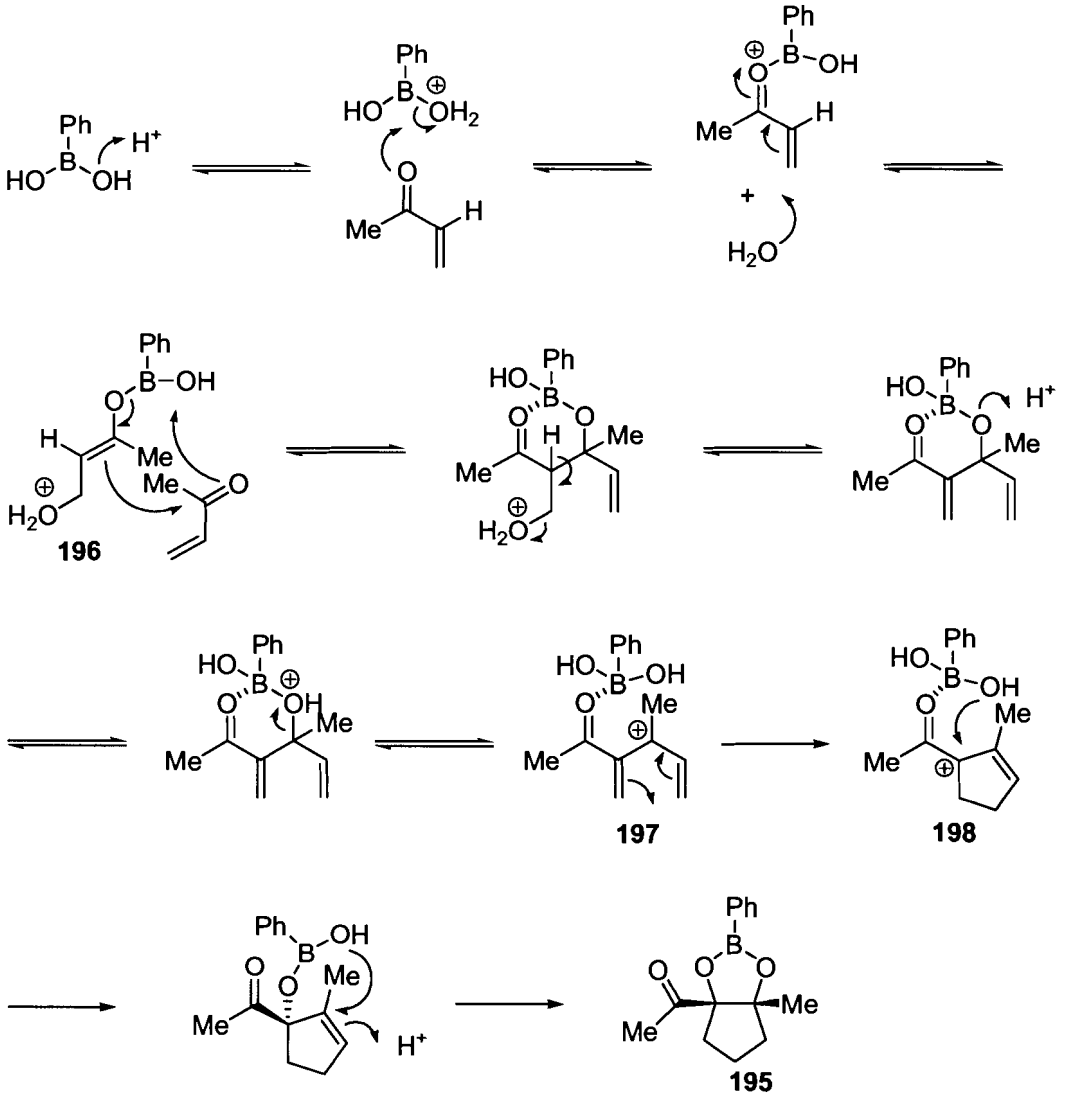
An improvement in the yield of the phenylboronate ester product **195** (80%) was obtained when the reaction was performed in the absence of methyl orsellinate **156** and

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.

Scheme 3.15 Mechanism for the Formation of the Phenylboronate Ester (195)

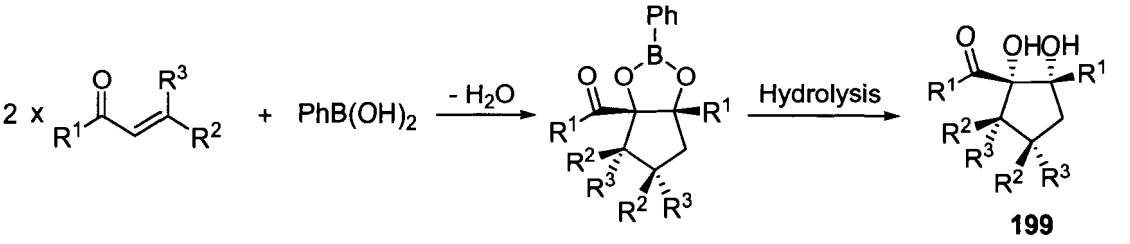


The two key steps of this unprecedented reaction involved in the proposed mechanism, a Baylis-Hillman reaction and a cyclization reaction of 1,4-pentadienyl cation, provide a notable consecutive carbon-carbon bond-forming reaction. Furthermore, phenylboronate esters have been widely used as protecting groups for diols in organic synthesis and their hydrolysis have been reported to take place under simple and mild conditions.[122] It was considered that this new reaction might have potential as a means to

(122) Seltzman, H. H.; Fleming, D. N.; Hawkins, G. D.; Carroll, F. I. *Tetrahedron Lett.* **2000**, *41*, 3589.

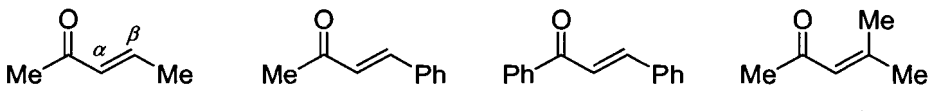
effect the stereo-controlled synthesis of substituted *syn*-cyclopentyl-1,2-diols **199** (Scheme 3.16).

Scheme 3.16 Proposed Synthesis of *syn*-Cyclopentyl-1,2-diols (199)



Thus, the applicability of this one-pot reaction was examined by varying the structure of the α,β-unsaturated ketone substrate. A series of commercially available α,β-unsaturated ketones including 3-penten-2-one **200**, *trans*-4-phenyl-3-buten-2-one **201**, *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 β-substituted α,β-unsaturated ketones in Baylis-Hillman reactions in the chemical literature.[121,123]

(123) Further experiments with various α,β-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.



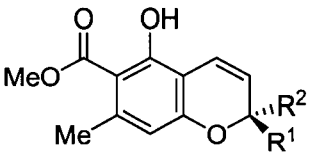
200 **201** **202** **203**

Figure 3.11 Selected α,β-unsaturated ketone precursors (200-203).

3.4 Preparation of Daurichromenic Acid Analogues

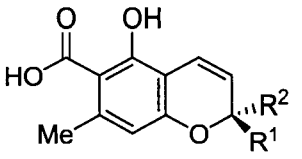
With a variety of 2*H*-chromenes in hand, the stage was now set for the preparation of daurichromenic acid analogues by the employment of the hydrolysis reaction discussed in *Chapter Two* of this thesis. Thus, saponification of the C2-dimethyl 2*H*-chromene derivative **169** and the spiropyran derivative **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 2*H*-Chromenes[a]

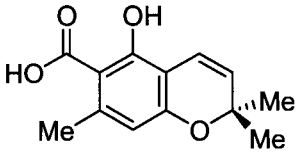


2,2-Disubstituted 2H-chromenes

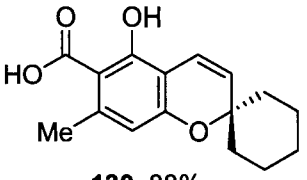
a)



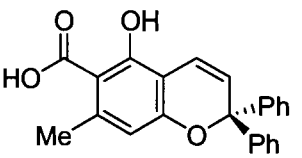
2,2-Disubstituted daurichromenic acid analogues



127a, 83%



130, 88%



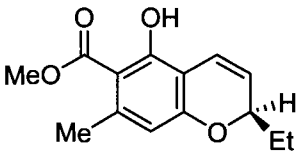
204

2,2-Disubstituted daurichromenic acid analogues

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

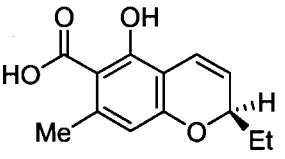
The hydrolysis reaction of the 2-ethyl 2*H*-chromene derivative **174** under similar reaction conditions afforded the desired 2*H*-chromene-6-carboxylic acid **205** in 53% yield (Scheme 3.18). Attempted hydrolysis of the 2-phenyl 2*H*-chromene derivative **176** using the same method afforded a complex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

Scheme 3.18 Saponification Reactions of C2-Monosubstituted 2*H*-Chromenes[a]

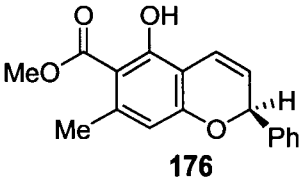


174

a)

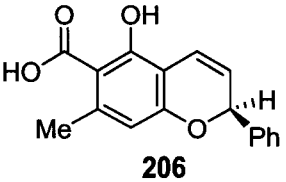


205, 53%



176

a)

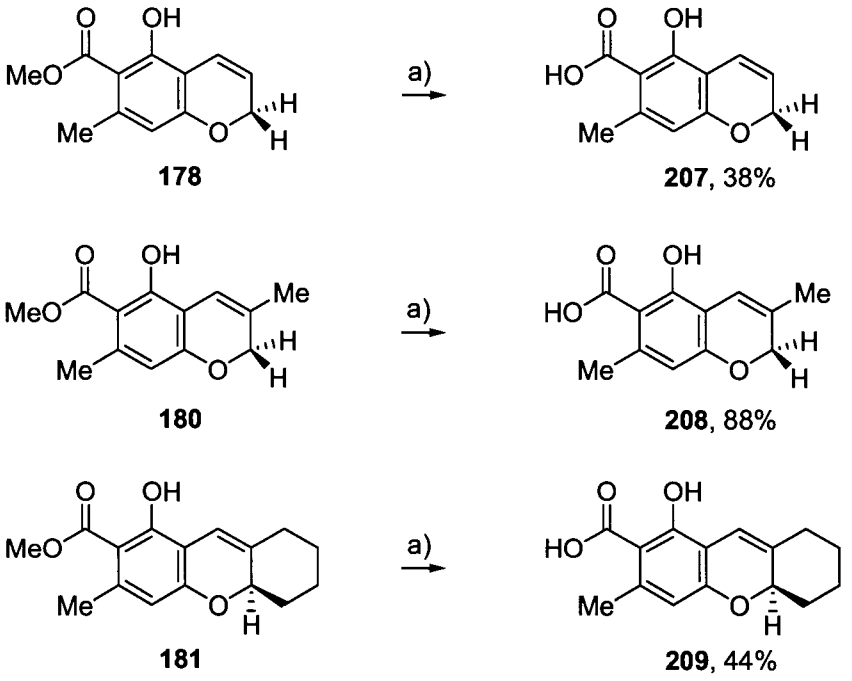


206

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

The 2*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*H*-chromene esters **180** and **181** following the same procedure afforded the desired 2*H*-chromene-6-carboxylic acid derivatives **208** and **209** in 88% and 44% yield, respectively.

Scheme 3.19 Preparation of 2*H*-Chromene-6-carboxylic acids (207-209)[a]



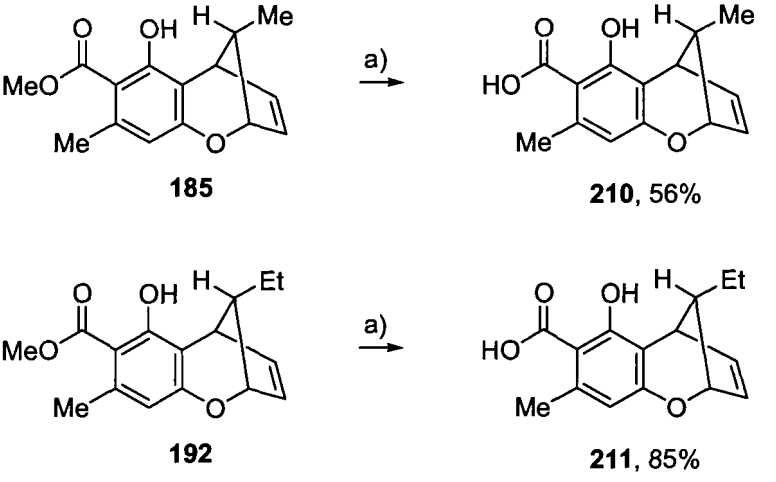
[a] Reagents and conditions: a) 5M NaOH (aq), DMSO, 80 °C, ~ 16 h.

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 Four*). The IR spectrum of each compound showed a strong absorption band at ~ 1630cm^{-1} (C=O). The absence of the ester methyl signals in the ^{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)[a]



[a] 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 α,β-unsaturated aldehydes. The key step of this extremely concise synthesis involved the phenylboronic acid-promoted condensation reaction of methyl orsellinate **156** and the α,β-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 (±)-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 *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 *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 2*H*-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 β-substituted α,β-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

(124) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heinemann: Oxford, 1997.
(125) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

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 (δ) 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 [$(CD_3)_2CO$] 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 [$(CD_3)_2SO$] were 2.50 and 39.52 ppm for ^{1}H and ^{13}C NMR spectra, respectively. The reference values used for deuterated methanol (CD_3OD) were 3.31 and 49.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively. The reference values used for deuterated benzene (C_6D_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.

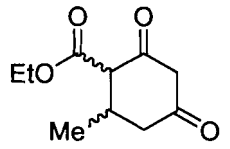
Low-resolution mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer. The mode of ionization used was chemical ionization (CI) with

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)[62,63]

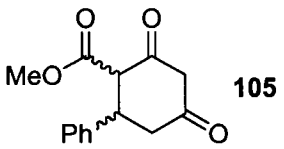


104

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 *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 *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.[63] **M.p.** 88-90 °C, benzene/petroleum ether); **^{1}H NMR** (400 MHz, C_6D_6) δ 0.73 (d, J = 6.6 Hz, 3H, CH_3CH), 1.00 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.78 (dd, J = 17.6, 11.3 Hz, 1H, CHC*H*H), 2.24 (dd, J = 17.6, 4.7 Hz, 1H,

CHCH*H*), 2.41 (m, 1H, CH_3CH), 2.91 (d, J = 11.3 Hz, 1H, $CHCO_2Et$), 4.05 (m, 2*H*, CH_3CH_2), 5.84 (s, 2*H*, $COCH_2CO$); **^{13}C NMR** (101 MHz, C_6D_6) δ (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** (CI) *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]

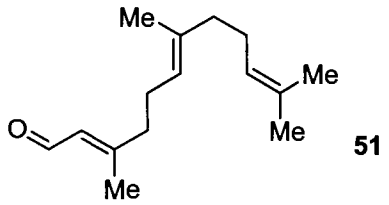


105

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, $(CD_3)_2CO$) δ 2.60 (dd, J = 17.4, 4.7 Hz, 1H,

PhCHC*H*H), 2.87 (dd, J = 17.4, 11.9 Hz, 1H, PhCHCH*H*), 3.46 (s, 3H, CH_3), 3.66 (m, 1H, PhC*H*), 3.78 (d, J = 12.5 Hz, 1H, C*H*CO$_2$Me), 5.42 (s, 2*H*, COCH_2CO), 7.22-7.46 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) 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 $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.09; H, 5.84.

4.2.3 *trans,trans*-Farnesal (51)[56,57]

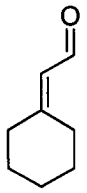


51

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. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.58 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.97 (m, 2H, CH_2), 2.04 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.23 (m, 4H, 2 x CH_2), 5.06 (m, 2H, CH_2CH), 5.87 (d, J = 8.1 Hz, 1H, C*H*CHO), 9.98 (d, J = 8.1 Hz, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) 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** (CI) *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)[65]

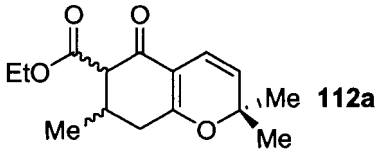


111

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. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.60-1.77 (m, 6H, 3 x CH_2), 2.29 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 5.82 (d, J = 8.3 Hz, 1H, CHCHO), 10.02 (d, J = 8.3 Hz, 1H, CHO); **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 26.3, 28.3, 28.6, 29.8, 38.2, 125.5, 190.7, 212.1; **IR** (ef) 2929, 1677, 1449, 1223, 1142, 1121 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 141 (100), 125 (M + H, 25).

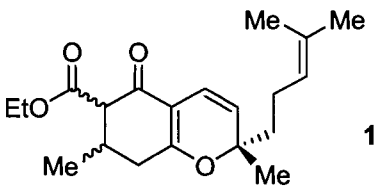
4.2.5 2,2,7-Trimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylic acid ethyl ester (112a)



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. **^{1}H NMR** (400 MHz, C_6D_6) δ 0.68 (d, J = 6.7 Hz, 3H, CH_3CH), 0.91 (t, J = 7.7 Hz, 3H, CH_3CH_2), 1.13 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.78 (dd, J = 16.3, 9.9 Hz, 1H, CH_3CHCHH), 2.29 (m, 1H, CH_3CH), 2.42 (dd, J = 16.3, 4.4 Hz, 1H, CH_3CHCHH), 2.92 (d, J = 8.1 Hz, 1H, $CHCO_2Et$), 3.94 (m, 2H, CH_3CH_2), 4.87 (d, J = 9.9 Hz, 1H, CH=CH), 6.77 (d, J = 9.9 Hz, 1H, CH=CH); **^{13}C NMR** (101 MHz, C_6D_6) δ 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; **IR** (ef) 2976, 1739, 1654, 1593, 1416, 1323, 1254, 1152 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 265 (M + H, 100); **Anal.** Calcd. for $C_{15}H_{20}O_3$: C, 68.16; H, 7.63. Found: C, 67.82; H, 7.82.

4.2.6 (±)-2,7-Dimethyl-2-(4-methyl-3-pentenyl)-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylic acid ethyl ester (113a)

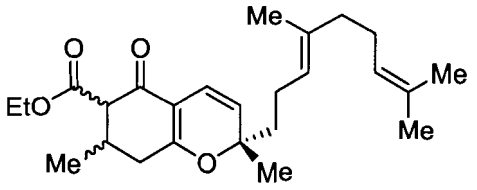


113a

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 *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* **113a** (743 mg, 90%) as a pale yellow oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 0.77 (d, J = 6.4 Hz, 3H, CH_3CH), 1.07 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.15 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.63 (m, 2H, CH_2CH_2), 1.71 (s, 3H, CH_3), 2.10 (m, 4H, CH_3CHCH_2 and CH_2CH_2), 2.43 (m, 1H, CH_3CH), 2.94 (d, J = 11.7 Hz, 1H, $CHCO_2Et$), 4.15 (m, 2H, CH_3CH_2), 4.83 (d, J = 10.1 Hz, 1H, CH=CH), 5.17 (m, 1H, $(CH_3)_2C=CH$), 6.78 (d, J = 10.1 Hz, 1H, CH=CH); **^{13}C NMR** (101 MHz, C_6D_6) δ (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; **IR** (ef) 2968, 1739, 1655, 1597, 1415, 1326,

1255, 1158 cm^{-1}; **MS** (CI) *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)

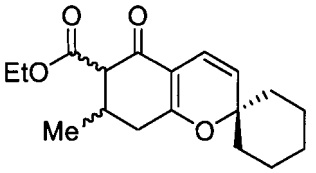


114a

To a mixture of 1,2-ethylenediamine (20 μL, 0.30 mmol) and acetic acid (34 μL, 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 *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 *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_6D_6) δ 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 (apparant s, 6H, 2 x CH_3), 1.63 (m, 2H, CH_2CH$_2$), 1.67 (s, 3H, CH_3), 2.02 (m, 2H, CH$_3$CHCH_2), 2.08 (m, 4H, allylic-CH_2), 2.17 (m, 2H, allylic-CH_2), 2.38 (m, 1H, CH$_3$C*H*), 2.88 (d, J = 11.6 Hz, 1H, C*H*CO$_2$Et), 4.09 (m, 2H, CH$_3$CH_2), 4.80 (d, J = 10.1 Hz, 1H, C*H*=CH), 5.20 (m, 2H, CH$_3$C=C*H* and (CH$_3$)$_2$C=C*H*), 6.73 (d, J = 10.1 Hz, 1H, CH=C*H*); **^{13}C NMR** (101 MHz, C_6D_6) δ (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-2*H*-chromene-6-carboxylic acid ethyl ester (115)

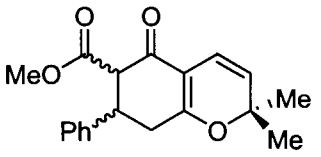


115

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, 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. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 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); **^{13}C NMR** (101 MHz, $CDCl_3$) δ (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** (CI) *m/z* (rel. intensity) 305 (M + H, 100); **FAB HRMS** Calcd. for $C_{18}H_{24}O_4$ *m/z*: 304.1675. Found *m/z*: 304.1670.

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

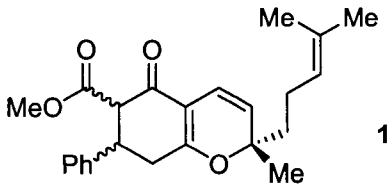


112b

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, C_6D_6) δ 1.39 (s, 3H, C*H*$_3$), 1.45 (s, 3H, C*H*$_3$), 2.67 (m, 2H, PhCHC*H*$_2$), 3.57 (s, 3H, CO_2CH_3), 3.70 (m, 2H, PhC*H* and C*H*CO_2Me), 5.29 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.41 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.24-7.31 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, C_6D_6) 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** (CI) *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-methyl-3-pentenyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylic acid ethyl ester (113b)

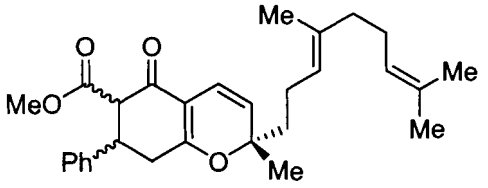


113b

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_6D_6) δ 1.36 (s, 3H, C*H*$_3$), 1.58-1.80 (m, 2H, C*H*$_2$CH$_2$), 1.60 (s, 3H, C*H*$_3$), 1.67 (s, 3H, C*H*$_3$), 2.04 (m, 2H, CH$_2$C*H*$_2$), 2.67 (m, 2H, PhCHC*H*$_2$), 3.57 (s, 3H, C*H*$_3$O), 3.69 (m, 2H, PhC*H* and C*H*CO$_2$Me), 5.08 (m, 1H, (CH$_3$)$_2$C=C*H*), 5.25 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.46 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.25-7.31 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, C_6D_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** (CI) *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)

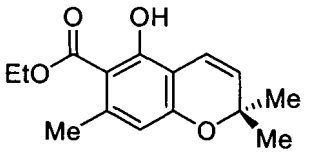


114b

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, *trans,trans*-farnesal **51** (1.01 g, 4.60 mmol) was added. After 16 h, the solvent was removed *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 *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_6D_6) δ 1.36 (s, 3H, CH_3), 1.53-1.85 (m, 2H, CH_2CH$_2$), 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_3O), 3.69 (m, 2H, PhC*H* and C*H*CO$_2$Me), 5.08 (m, 2H, CH$_3$C=C*H* and (CH$_3$)$_2$C=C*H*), 5.25 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.46 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.24-7.32 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, C_6D_6) δ (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,

188.9, 189.0; **IR** (ef) 2968, 1746, 1655, 1596, 1415, 1349, 1260, 1158 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 449 (M + H, 100), 391 (6), 247 (7), 203 (8); **Anal.** Calcd. for $C_{29}H_{36}O_4$: C, 77.64; H, 8.09. Found: C, 77.81; H, 8.25.

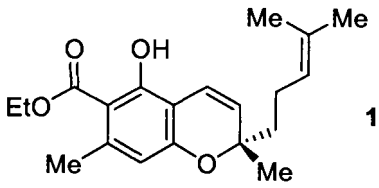
4.2.12 5-Hydroxy-2,2,7-trimethyl-2*H*-chromene-6-carboxylic acid ethyl ester (121a)



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_6D_6) δ 0.83 (t, J = 7.0 Hz, 3H, CH_3CH_2), 1.25 (s, 6H, 2 x CH_3), 2.30 (s, 3H, CH_3), 3.88 (q, J = 7.0 Hz, 2H, CH_3CH_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); **^{13}C NMR** (101 MHz, C_6D_6) δ 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.

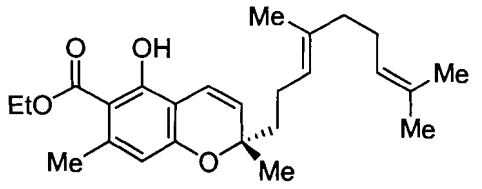
4.2.13 (±)-5-Hydroxy-2,7-dimethyl-2-(4-methyl-3-pentenyl)-2*H*-chromene-6-carboxylic acid ethyl ester (122a)



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, $CDCl_3$) δ 1.38 (s, 3H, C*H*$_3$), 1.40 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.53-1.80 (m, 2H, C*H*$_2$CH$_2$), 1.56 (s, 3H, C*H*$_3$), 1.65 (s, 3H, C*H*$_3$), 2.08 (m, 2H, CH$_2$C*H*$_2$), 2.47 (s, 3H, C*H*$_3$), 4.38 (q, J = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 5.08 (m, 1H, (CH$_3$)$_2$C=C*H*), 5.46 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.18 (s, 1H, Ar*H*), 6.73 (d, J = 10.1 Hz, 1H, CH=C*H*), 12.07 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *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.

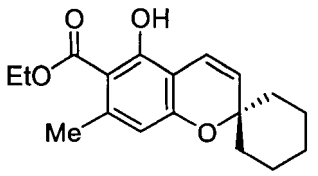
4.2.14 (±)-5-Hydroxy-2,7-dimethyl-2-(4,8-dimethyl-3*E*,7-nonadienyl)- 2*H*-chromene-6-carboxylic acid ethyl ester (123a)



123a

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. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.39 (s, 3H, C*H*$_3$), 1.40 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.56 (s, 3H, C*H*$_3$), 1.59 (s, 3H, C*H*$_3$), 1.67 (s, 3H, C*H*$_3$), 1.65-1.75 (m, 2H, C*H*$_2$CH$_2$), 1.95 (m, 2H, allylic-C*H*$_2$), 2.03 (m, 2H, allylic-C*H*$_2$), 2.09 (m, 2H, allylic-C*H*$_2$), 2.47 (s, 3H, C*H*$_3$), 4.38 (q, J = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 5.09 (m, 2H, (CH$_3$)$_2$C=C*H* and (CH$_3$)C=C*H*), 5.47 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.18 (s, 1H, Ar*H*), 6.73 (d, J = 10.1 Hz, 1H, CH=C*H*), 12.07 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.16; H, 8.61.

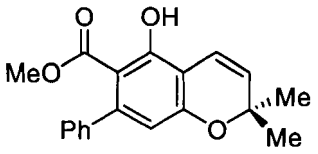
4.2.15 5-Hydroxy-7-methyl-2-spirocyclohexyl-2*H*-chromene-6-carboxylic acid ethyl ester (124)



124

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; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H, CH_3CH_2), 1.53 (m, 6H, cyclohexyl-CH_2), 1.72 (m, 2H, cyclohexyl-CH_2), 1.91 (m, 2H, cyclohexyl-CH_2), 2.48 (s, 3H, CH_3), 4.39 (q, J = 7.0 Hz, 2H, CH_3CH_2O), 5.56 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.24 (s, 1H, Ar*H*), 7.04 (d, J = 10.1 Hz, 1H, CH=C*H*), 12.81 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ14.3, 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 $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.70; H, 7.53.

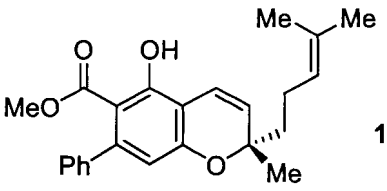
4.2.16 5-Hydroxy-2,2-dimethyl-7-phenyl-2*H*-chromene-6-carboxylic acid methyl ester (121b)



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, $CDCl_3$) δ 1.46 (s, 6H, 2 x C*H*$_3$), 3.44 (s, 3H, C*H*$_3$O), 5.59 (d, J = 9.9 Hz, 1H, C*H*=CH), 6.27 (s, 1H, Ar*H*), 6.75 (d, J = 9.9 Hz, 1H, CH=C*H*), 7.20-7.31 (m, 5H, Ar*H*), 11.43 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *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.

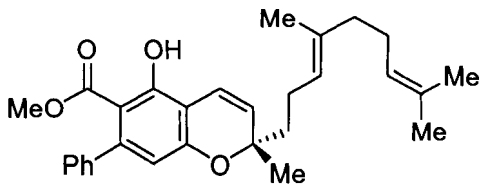
4.2.17 (±)-5-Hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-7-phenyl-2*H*-chromene-6-carboxylic acid methyl ester (122b)



122b

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; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.42 (s, 3H, C*H*$_3$), 1.57 (s, 3H, C*H*$_3$), 1.65 (s, 3H, C*H*$_3$), 1.65-1.76 (m, 2H, C*H*$_2$CH$_2$), 2.10 (m, 2H, CH$_2$C*H*$_2$), 3.44 (s, 3H, C*H*$_3$O), 5.09 (t, J = 7.1 Hz, 1H, (CH$_3$)$_2$C=C*H*), 5.54 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.26 (s, 1H, Ar*H*), 6.79 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.20-7.31 (m, 5H, Ar*H*), 11.42 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ17.8, 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** (CI) *m/z* (rel. intensity) 379 (M + H, 47), 347 (20), 295 (100), 263 (59); **Anal.** Calcd. for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found: C, 76.23; H, 7.06.

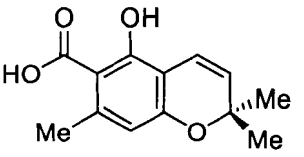
4.2.18 (±)-5-Hydroxy-2-methyl-2-(4,8-dimethyl-3*E*,7-nonadienyl)- 7-phenyl-2*H*-chromene-6-carboxylic acid methyl ester (123b)



123b

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, $CDCl_3$) δ 1.42 (s, 3H, C*H*$_3$), 1.57 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 1.66 (s, 3H, C*H*$_3$), 1.65-1.76 (m, 2H, C*H*$_2$CH$_2$), 1.95 (m, 2H, allylic-C*H*$_2$), 2.04 (m, 2H, allylic-C*H*$_2$), 2.12 (m, 2H, allylic-C*H*$_2$), 3.44 (s, 3H, C*H*$_3$O), 5.09 (m, 2H, CH$_3$C=C*H* and (CH$_3$)$_2$C=C*H*), 5.54 (d, J = 10.2 Hz, 1H, C*H*=CH), 6.26 (s, 1H, Ar*H*), 6.79 (d, J = 10.2 Hz, 1H, CH=C*H*), 7.21-7.32 (m, 5H, Ar*H*), 10.09 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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, 1558, 1438, 1323, 1270, 1196 cm^{-1}; **MS** (CI) *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.

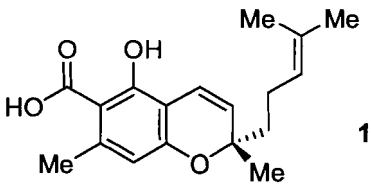
4.2.19 5-Hydroxy-2,2,7-trimethyl-2*H*-chromene-6-carboxylic acid (127a)



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, $CDCl_3$) δ 1.44 (s, 6H, 2 x C*H*$_3$), 2.52 (s, 3H, C*H*$_3$), 5.52 (d, J = 10.1 Hz, 1H, C*H*=CH) 6.23 (s, 1H, Ar*H*), 6.68 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.6 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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, - 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.

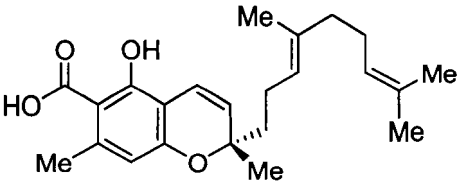
4.2.20 (±)-5-Hydroxy-2,7-dimethyl-2-(4-methyl-3-pentenyl)-2*H*-chromene-6-carboxylic acid (128a)



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, $CDCl_3$) δ 1.40 (s, 3H, C*H*$_3$), 1.57 (s, 3H, C*H*$_3$), 1.66 (s, 3H, C*H*$_3$), 1.59-1.82 (m, 2H, C*H*$_2$CH$_2$), 2.08 (m, 2H, CH$_2$C*H*$_2$), 5.08 (m, 1H, (CH$_3$)$_2$C=C*H*), 5.48 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.23 (s, 1H, Ar*H*), 6.73 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.71 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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 $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 70.15; H, 7.78.

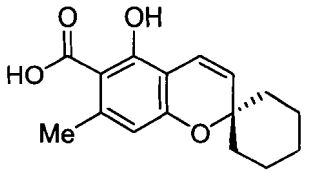
4.2.21 (±)-Daurichromenic acid (1)



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}H NMR** (400 MHz, $CDCl_3$) δ 1.41 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.66-1.77 (m, 2H, CH_2CH_2), 1.95 (m, 2H, allylic-CH_2), 1.97 (m, 2H, allylic-CH_2), 2.04-2.12 (m, 2H, allylic-CH_2), 2.54 (s, 3H, CH_3), 5.09 (m, 2H, CH_3C=C*H* and $(CH_3)_2C$=C*H*), 5.48 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.24 (s, 1H, Ar*H*), 6.74 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.66 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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; **IR** (ef) 2966, 1621, 1455, 1268, 1177 cm^{-1}; **MS** (CI) *m/z* 327 (M + H, - CO_2, 100), 175 (9); **Anal.** Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.30; H, 8.18.

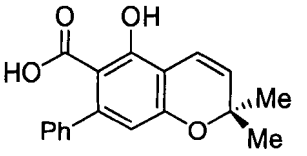
4.2.22 5-Hydroxy-7-methyl-2-spirocyclohexyl-*2H*-chromene-6-carboxylic acid (130)



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, $CDCl_3$) δ 1.36 (m, 1H, cyclohexyl-C*H*$_2$), 1.54 (m, 5H, cyclohexyl-C*H*$_2$), 1.73 (m, 2H, cyclohexyl-C*H*$_2$), 1.92 (m, 2H, cyclohexyl-C*H*$_2$), 2.53 (s, 3H, C*H*$_3$), 5.57 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.28 (s, 1H, Ar*H*), 6.69 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.68 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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, 1250 1184, 1128 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 275 (M + H, 7), 231 (M + H - CO_2, 100); **Anal.** Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.32; H, 6.63.

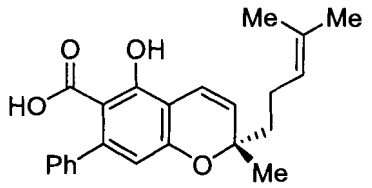
4.2.23 5-Hydroxy-2,2-dimethyl-7-phenyl-*2H*-chromene-6-carboxylic acid (127b)



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; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.46 (s, 6H, 2 x C*H*$_3$), 5.59 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.25 (s, 1H, Ar*H*), 6.72 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.26-7.36 (m, 5H, Ar*H*), 11.46 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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, 1610, 1454, 1282, 1193, 1123 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 297 (M + H, 48), 279 (6), 253 (M + H, - CO_2, 100), 237 (10), 197 (12); **Anal.** Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.64; H, 5.64.

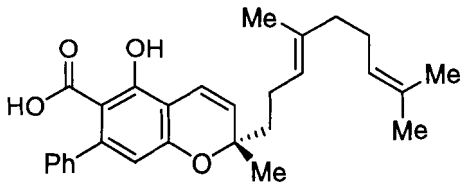
4.2.24 (±)-5-Hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-7-phenyl-2*H*-chromene-6-carboxylic acid (128b)



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_2CH_2), 2.10 (m, 2H, CH_2CH_2), 5.09 (m, 1H, $(CH_3)_2C=CH$), 5.53 (d, J = 10.1 Hz, 1H, CH=CH), 6.24 (s, 1H, Ar*H*), 6.76 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.26-7.36 (m, 5H, Ar*H*), ~ 9.5 (broad s, 1H, CO_2H), 11.46 (s, 1H, O*H*); **^{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** (CI) *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.

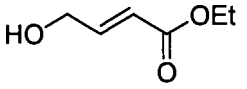
4.2.25 (±)-5-Hydroxy-2-methyl-2-(4,8-dimethyl-3*E*,7-nonadienyl)-7-phenyl-2*H*-chromene-6-carboxylic acid (129)



129

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. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.41 (s, 3H, C*H*$_3$), 1.56 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 1.67 (s, 3H, C*H*$_3$), 1.67-1.76 (m, 2H, C*H*$_2$CH$_2$), 1.95 (m, 2H, allylic-C*H*$_2$), 2.03 (m, 2H, allylic-C*H*$_2$), 2.11 (m, 2H, allylic-C*H*$_2$), 5.09 (m, 2H, CH_3C=C*H* and $(CH_3)_2C$=C*H*), 5.52 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.18 (s, 1H, Ar*H*), 6.76 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.19-7.23 (m, 5H, Ar*H*), ~ 11.8 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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, - CO_2, 100), 256 (20), 239 (6); **FAB HRMS** Calcd. for $C_{28}H_{32}O_4$ - CO_2 *m/z*: 388.2402. Found *m/z*: 388.2408.

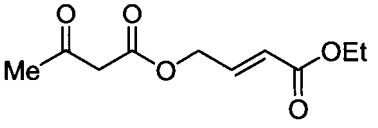
4.2.26 Ethyl 4-hydroxybut-2-enoate (137)[97]



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_3CH_2), 4.20 (q, J = 7.1 Hz, 2H, CH_3CH_2), 4.35 (m, 2H, CH_2OH), 6.09 (dt, J = 15.7, 2.1 Hz, 1H, C*H*=CH), 7.03 (dt, J = 15.7, 4.0 Hz, 1H, CH=C*H*); **^{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 $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.40; H, 7.81.

4.2.27 Ethyl (*E*)-4-acetoacetoxycrotonate (136)[95]

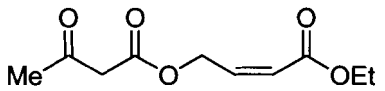


136

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

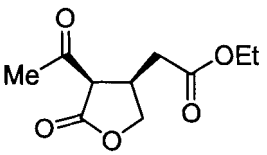
concentrated *in vacuo*. The crude product was purified by flash chromatography using ether/hexanes (25%) as the eluant to afford the *title compound* **136** (954 mg, 83%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H, CH_3CH_2), 2.29 (s, 3H, CH_3CO), 3.53 (s, 2H, $COCH_2CO$), 4.21 (q, J = 7.1 Hz, 2H, CH_3CH_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, $CDCl_3$) δ 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-ethoxycarbonylmethyltetrahydrofuran-2-one (140)



139

and



140

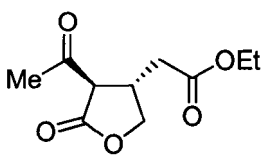
To an ethanolic solution of sodium ethoxide [prepared from sodium (11.7 mg, 0.509 mmol) and dry ethanol (2 mL)] was added ethyl (*E*)-4-acetoacetoxycrotonate **136** (100 mg, 0.467 mmol) and the resultant mixture was stirred for 1.5 h at room temperature. The reaction mixture was then neutralized with 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-ethoxycarbonylmethyltetahydrofuran-2-one **140** (5 mg, 5%) as a colourless oil.

Characterization data for ethyl (*Z*)-4-acetoacetoxycrotonate **139**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H, CH_3CH_2), 2.30 (s, 3H, CH_3CO), 3.19 (dd, J = 7.1, 1.7 Hz, 2H, OCH_2), 3.55 (s, 2H, $COCH_2CO$), 4.15 (q, J = 7.1 Hz, 2H, CH_3CH_2), 5.20 (td, J = 7.1, 6.4 Hz, 1H, C*H*=CH), 7.17 (dt, J = 6.4, 1.7 Hz, 1H, CH=C*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *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, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H, CH_3CH_2), 2.46 (s, 3H, CH_3CO), 2.51 (m, 2H, CH_2CO_2), 3.39 (m, 1H, CH_2CHCH_2), 3.56 (d, J = 8.1 Hz, 1H, COC*H*), 3.99 (dd, J = 9.2, 7.5 Hz, 1H, OC*H*H), 4.14 (q, J = 7.1 Hz, 2H, CH_3CH_2), 4.57 (dd, J = 9.2, 8.0 Hz, 1H, OCH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *m/z* (rel. intensity) 215 (M + H, 100), 197 (8), 171 (27).

4.2.29 (±)-*trans*-3-Acetyl-4-ethoxycarbonyl-methyltetrahydrofuran-2-one (141)

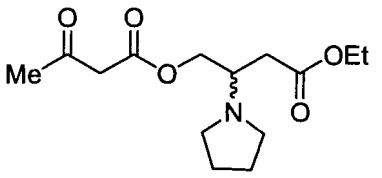


141

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-ethoxycarbonylmethyltetahydrofuran-2-one **141** (26 mg, 13%) as colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H, CH_3CH_2), 2.19 (s, 3H, CH_3CO), 2.39 (dd, J = 17.0, 3.3 Hz, 1H, $CHHCO_2$), 3.03 (dd, J = 17.0, 10.6 Hz, 1H, $CHHCO_2$), 3.60 (m, 1H, CH_2CHCH_2), 4.19 (m, 3H, OC*H*H and CH_3CH_2), 4.55 (apparent t, J = 9.8 Hz, 1H, OCH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *m/z* (rel. intensity) 215 (M + H, 100), 197 (15), 169 (16).

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

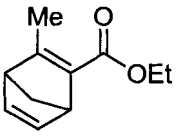


142

To a solution of ester **136** (100 mg, 0.467 mmol) in THF (1 mL) was added pyrrolidine (39 μL, 0.47 mmol) at 0 °C. After 10 min, acetic acid (27 μL, 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, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.76 (m, 4H, 2 x CH_2CH_2N), 2.27 (s, 3H, CH_3CO), 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_2CH_2N), 3.19 (m, 1H, NC*H*), 3.48 (s, 2H, $COCH_2CO$), 4.14 (q, J = 7.1 Hz, 2H, CH_3CH_2), 4.21 (dd, J = 11.5, 5.3 Hz, 1H, OC*H*H), 4.35 (dd, J = 11.5, 4.8 Hz, 1H, OCH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *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]



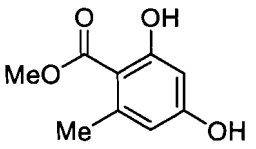
145

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, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.95 (apparent td, J = 6.4, 1.5 Hz, 1H, C*H*H), 2.05 (apparent td, J = 6.4, 1.5 Hz, 1H, CH*H*), 2.22 (s, 3H, CH_3), 3.40 (m, 1H, C*H*), 3.88 (m, 1H, C*H*), 4.17 (m, 2H, CH_3CH_2), 6.73 (dd, J = 5.0, 3.0 Hz, C*H*=CH), 6.89 (dd, J = 5.0, 3.0 Hz, CH=C*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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]

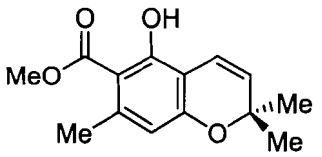


156

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); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49 (s, 3H, CH_3), 3.92 (s, 3H, CH_3O), 6.23 (d, J = 2.4 Hz, 1H, Ar*H*), 6.28 (d, J = 2.4 Hz, 1H, Ar*H*), 11.76 (s, 2H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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}; **MS** (CI) *m/z* (rel. intensity) 183 (M + H, 100); **Anal.** Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.08; H, 5.56.

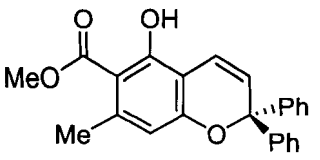
4.3.2 5-Hydroxy-2,2,7-trimethyl-2*H*-chromene-6-carboxylic acid methyl ester (169)



169

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 μL, 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 *in vacuo*. The yellow solid residue was purified by flash chromatography using ethyl acetate/hexanes (3%) as the eluant to afford the *title compound* **169** (112 mg, 45%) as a white solid. **M.p.** 51-53 °C, ethyl acetate/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.43 (s, 6H, 2 x CH_3), 2.46 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 5.52 (d, J = 10.0 Hz, 1H, C*H*=CH), 6.20 (s, 1H, Ar*H*), 6.69 (d, J = 10.0 Hz, 1H, CH=C*H*), 11.98 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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; **IR** (ef) 2972, 1646, 1615, 1562, 1439, 1267, 1155, 1096 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 (M + H, 100).

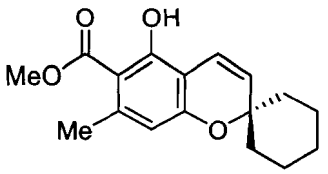
4.3.3 5-Hydroxy-7-methyl-2,2-diphenyl-2*H*-chromene-6-carboxylic acid methyl ester (171)



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 *μ*L, 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, $CDCl_3$) δ 2.45 (s, 3H, CH_3), 3.90 (s, 3H, CH_3O), 6.05 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.35 (s, 1H, Ar*H*), 6.99 (d, J = 10.1 Hz, 1H, CH=C*H*), 7.29, 7.40 (m, 10H, Ar*H*), 12.00 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *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.

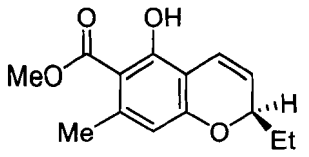
4.3.4 5-Hydroxy-7-methyl-2-spirocyclohexyl-2*H*-chromene-6-carboxylic acid methyl ester (172)



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, C*H*$_3$), 3.91 (s, 3H, C*H*$_3$O), 5.56 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.24 (s, 1H, Ar*H*), 6.69 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.96 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ21.4, 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.

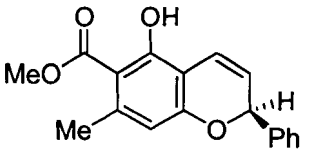
4.3.5 (±)-2-Ethyl-5-hydroxy-7-methyl-2*H*-chromene-6-carboxylic acid methyl ester (174)



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, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H, CH_3CH_2), 1.75 (m, 2H, CH_3CH_2), 2.46 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 4.83 (m, 1H, OC*H*), 5.57 (dd, J = 10.1, 3.1 Hz, 1H, C*H*=CH), 6.20 (s, 1H, Ar*H*), 6.76 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.97 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ9.1, 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** (CI) *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.

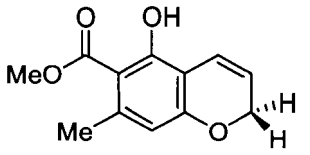
4.3.6 (±)-5-Hydroxy-7-methyl-2-phenyl-2*H*-chromene-6-carboxylic acid methyl ester (176)



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, $CDCl_3$) δ 2.44 (s, 3H, C*H*$_3$), 3.92 (s, 3H, C*H*$_3$O), 5.71 (dd, J = 10.1, 3.4 Hz, 1H, C*H*=CH), 5.92 (dd, J = 3.4, 1.3 Hz, 1H, PhC*H*), 6.20 (s, 1H, Ar*H*), 6.93 (dd, J = 10.1, 1.3 Hz, 1H, CH=C*H*), 7.35-7.44 (m, 5H, Ar*H*), 12.02 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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** (CI) *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.

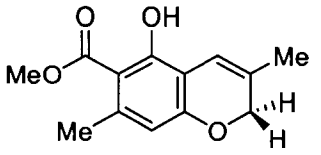
4.3.7 5-Hydroxy-7-methyl-2*H*-chromene-6-carboxylic acid methyl ester (178)



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; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.45 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 4.83 (dd, J = 3.5, 1.8 Hz, 2H, OCH_2), 5.65 (dt, J = 10.1, 3.5 Hz, 1H, CH=CH), 6.17 (s, 1H, Ar*H*), 6.77 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.96 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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** (CI) *m/z* (rel. intensity) 221 (M + H, 100); **IR** (ef) 3436 (broad), 2940, 1650, 1617, 1563, 1453, 1271, 1165, 1130 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 221 (M + H, 100); **Anal.** Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.40; H, 5.49.

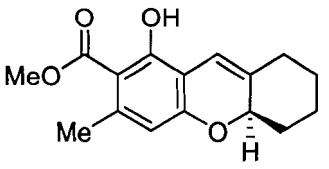
4.3.8 5-Hydroxy-3,7-dimethyl-2*H*-chromene-6-carboxylic acid methyl ester (180)



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, $CDCl_3$) δ 1.80 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 4.69 (s, 2H, OCH_2), 6.17 (s, 1H, Ar*H*), 6.51 (s, 1H, *H*C=C), 11.91 (s, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 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** (CI) *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.

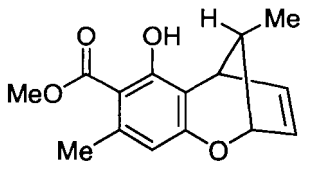
4.3.9 (±)-5-Hydroxy-7-methyl-2,3-butano-2*H*-chromene-6-carboxylic acid methyl ester (181)



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, $CDCl_3$) δ 1.40 (m, 2H, C*H*$_2$), 1.70 (m, 2H, C*H*$_2$), 1.88 (m, 1H, C*H*H), 2.05 (m, 1H, CH*H*), 2.17 (m, 1H, C*H*H), 2.43 (s, 3H, C*H*$_3$), 2.47 (m, 1H, CH*H*), 3.90 (s, 3H, C*H*$_3$O), 4.95 (m, 1H, OC*H*), 6.10 (s, 1H, Ar*H*), 6.39 (s, 1H, *H*C=C), 11.90 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ24.4, 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.

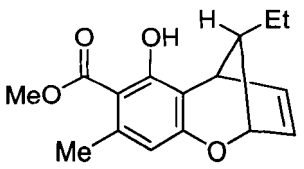
4.3.10 (±)-3,4-Dihydro-5-hydroxy-3,7-dimethyl-2,4-etheno-2*H*-chromene-6-carboxylic acid methyl ester (185)



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. **M.p.** 75-77 °C, ethyl acetate/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.26 (d, J = 7.2 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 Hz, 1H, CH=CH), 5.94 (apparent dt, J = 8.4, 2.2 Hz, 1H, CH=CH), 6.02 (dd, J = 5.7, 2.3 Hz, 1H, OCH), 6.19 (s, 1H, ArH), 11.77 (s, 1H, OH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 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; **IR** (ef) 2955, 1654, 1632, 1588, 1439, 1289, 1277, 1149, 1011 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 261 (M + H, 100), 229 (10).

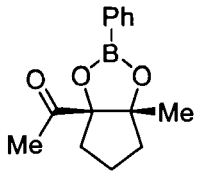
4.3.11 (±)-3-Ethyl-3,4-dihydro-5-hydroxy-7-dimethyl-2,4-etheno-2*H*-chromene-6-carboxylic acid methyl ester (192)



192

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, $CDCl_3$) δ 1.01 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.49-1.73 (m, 2H, CH_3CH_2), 2.47 (s, 3H, CH_3), 3.00 (m, 1H, CH_2CH), 3.68 (d, J = 7.9 Hz, 1H, ArCH), 3.90 (s, 3H, CH_3O), 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, $CDCl_3$) δ 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** (CI) *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.

4.3.12 (±)-1-(Tetrahydro-3a-methyl-2-phenyl-3a*H*-cyclopenta[*d*][1,3,2]dioxaborol-6a-yl)-ethanone (195)



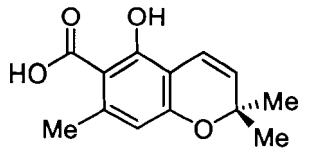
195

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; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (s, 3H, C*H*$_3$), 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, C*H*$_3$CO), 7.42 (m, 2H, Ar*H*), 7.52 (m, 1H, Ar*H*), 7.86 (m, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 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** (CI) *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 μL, 1.50 mmol, 1.25 equiv), phenylboronic acid (146 mg, 1.20 mmol, 1 equiv) and propionic acid (16 μL, 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 μL, 1.50 mmol, 2 equiv), phenylboronic acid (91.5 mg, 0.750 mmol, 1 equiv) and propionic acid (16 μL, 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.

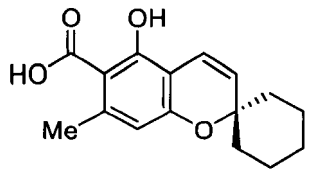
4.3.13 5-Hydroxy-2,2,7-trimethyl-2*H*-chromene-6-carboxylic acid (127a) - prepared from methyl ester (169)[55]



127a

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, $CDCl_3$) δ 1.44 (s, 6H, 2 x C*H*$_3$), 2.52 (s, 3H, C*H*$_3$), 5.52 (d, J = 10.1 Hz, 1H, C*H*=CH) 6.23 (s, 1H, Ar*H*), 6.68 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.6 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 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, - 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.

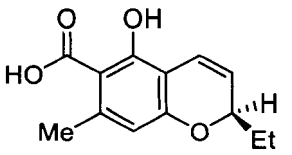
4.3.14 5-Hydroxy-7-methyl-2-spirocyclohexyl-2*H*-chromene-6-carboxylic acid (130) - prepared from methyl ester (172)



130

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. **M.p.** 144 °C (dec.), methanol/dichloromethane [lit.[55] **M.p.** 144 °C (dec.), methanol/dichloromethane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (m, 1H, cyclohexyl-C*H*$_2$), 1.54 (m, 5H, cyclohexyl-C*H*$_2$), 1.73 (m, 2H, cyclohexyl-C*H*$_2$), 1.92 (m, 2H, cyclohexyl-C*H*$_2$), 2.53 (s, 3H, C*H*$_3$), 5.57 (d, J = 10.1 Hz, 1H, C*H*=CH), 6.28 (s, 1H, Ar*H*), 6.69 (d, J = 10.1 Hz, 1H, CH=C*H*), 11.68 (broad s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ21.4, 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; **IR** (ef) 3408 (broad), 2933, 1636, 1458, 1283, 1268, 1250 1184, 1128 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 275 (M + H, 7), 231 (M + H, - CO_2, 100); **Anal.** Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.32; H, 6.63.

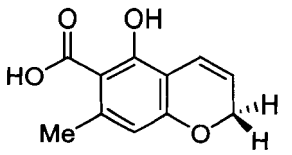
4.3.15 (±)-2-Ethyl-5-hydroxy-7-methyl-2*H*-chromene-6-carboxylic acid (205)



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_3CH_2), 1.77 (m, 2H, CH_3CH_2), 2.54 (s, 3H, CH_3), 4.86 (m, 1H, OC*H*), 5.58 (dd, J = 10.1, 3.4 Hz, 1H, C*H*=CH), 6.24 (s, 1H, Ar*H*), 6.76 (dd, J = 10.1, 1.2 Hz, 1H, CH=C*H*), 11.66 (broad s, 1H, O*H*); **^{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** (CI) *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.

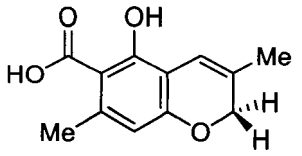
4.3.16 5-Hydroxy-7-methyl-2*H*-chromene-6-carboxylic acid (207)



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_3OD) δ2.48 (s, 3H, C*H*$_3$), 4.79 (dd, J = 3.4, 1.8 Hz, 2H, OC*H*$_2$), 5.68 (dt, J = 10.1, 3.4 Hz, 1H, C*H*=CH), 6.17 (s, 1H, Ar*H*), 6.71 (d, J = 10.1 Hz, 1H, CH=C*H*); **^{13}C NMR** (101 MHz, CD_3OD) δ24.4, 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.

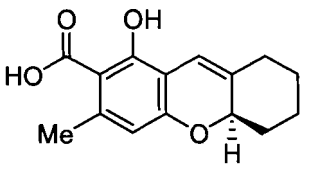
4.3.17 5-Hydroxy-3,7-dimethyl-2*H*-chromene-6-carboxylic acid (208)



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, $(CD_3)_2SO$) δ1.80 (s, 3H, C*H*$_3$), 2.45 (s, 3H, C*H*$_3$), 4.70 (s, 2H, OC*H*$_2$), 6.25 (s, 1H, Ar*H*), 6.42 (s, 1H, C*H*=C); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$) δ18.8, 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, 1269, 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-butano-2*H*-chromene-6-carboxylic acid (209)

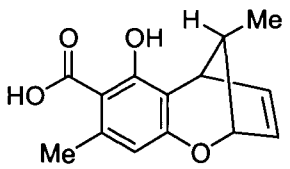


209

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; **^{1}H NMR** (400 MHz, $CDCl_3$ and CD_3OD) δ1.12-1.39 (m, 2H, C*H*$_2$), 1.50-1.68 (m, 2H, C*H*$_2$), 1.69-1.79 (m, 1H, C*H*H), 1.90 (m, 1H, CH*H*), 2.02 (m, 1H, C*H*H), 2.24-2.36 (m, 1H, CH*H*), 2.31 (s, 3H, C*H*$_3$), 4.79 (m, 1H, OC*H*), 5.94 (s, 1H, C*H*=C), 6.21 (s, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$ and CD_3OD) δ23.7, 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; **IR** (KBr) 3446 (broad), 2934, 1635, 1595, 1455, 1263, 1178 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 261 (M + H, 46), 217 (M + H, - CO_2, 100); **Anal.** Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.02. Found: C, 69.48; H, 6.39.

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

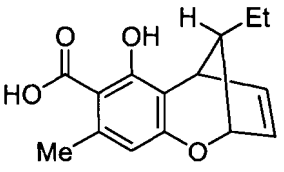


210

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, $(CD_3)_2CO$) δ 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); **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ 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-2*H*-chromene-6-carboxylic acid (211)



211

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 μL, 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; **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 1.05 (t, J = 7.4 Hz, 3H, CH_3CH_2), 1.62 (m, 2H, CH_3CH_2), 2.57 (s, 3H, CH_3), 2.98 (m, 1H, CH_2CH), 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); **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) 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** (CI) *m/z* (rel. intensity) 261 (M + H, 100), 243 (7), 217 (M + H, - CO_2, 47); **Anal.** Calcd. for $C_{15}H_{16}O_4$: 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

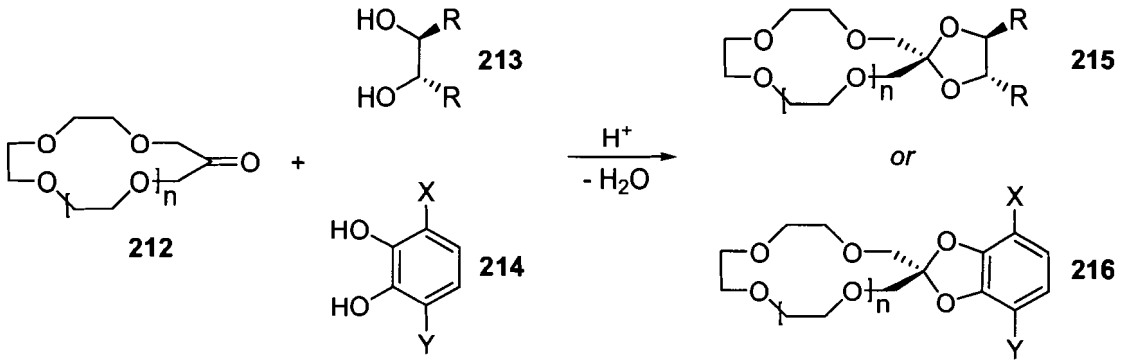
GENERAL INTRODUCTION TO *N*-DEALKYLATION REACTIONS OF TERTIARY AMINES

5.1 Research Project Overview

The project described herein stemed 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 C_2-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]

(126) For a recent review, see: Fuhrhop, J.-H.; Wang, T. *Chem. Rev.* **2004**, *104*, 2901.

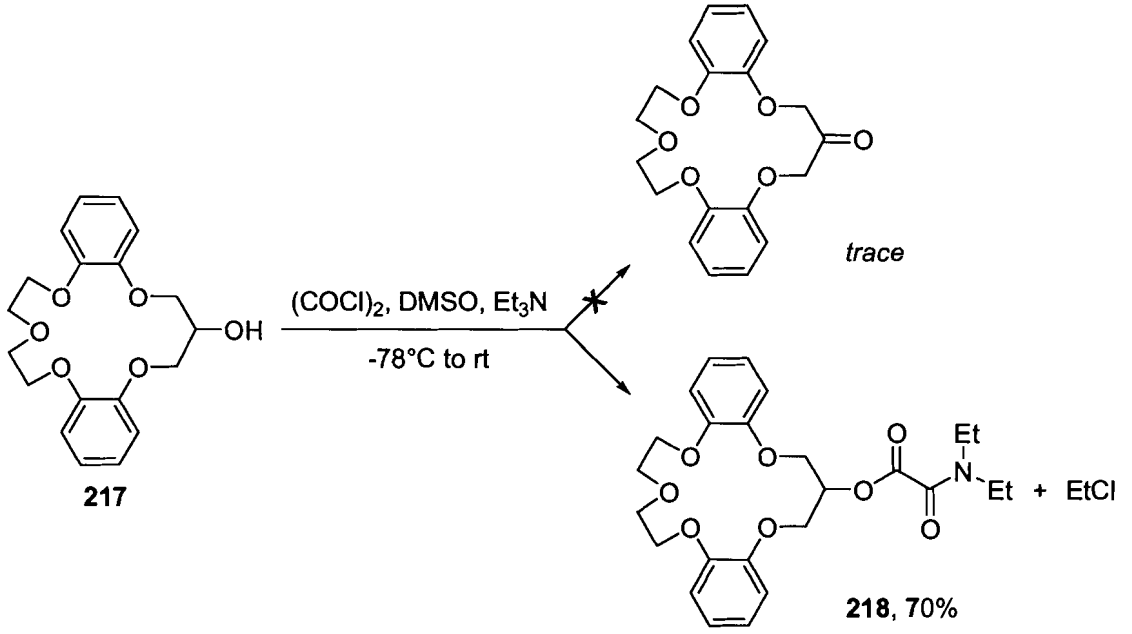
Scheme 5.1 Proposed Synthesis of Oxo-Crown Ether Acetals (215) and (216)



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.[127] In this reaction, one of the alkyl substituents of triethylamine was cleaved, presumably *via* the loss of ethyl chloride.[128]

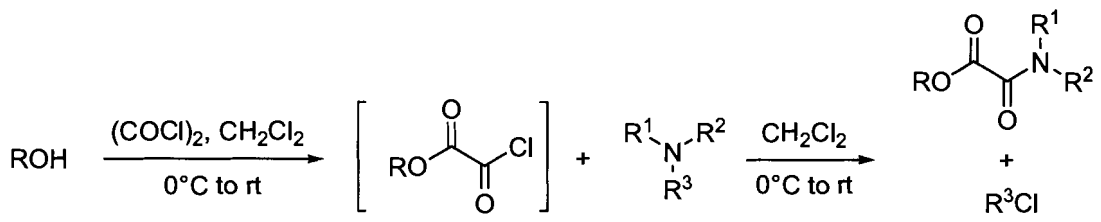
(127) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(128) Heo, G. S.; Bartsch, R. A.; Schlobohm, L. L.; Lee, J. G. *J. Org. Chem.* **1981**, *46*, 3574.

Scheme 5.2 Formation of Amide (218) *via* the Dealkylation of Triethylamine



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



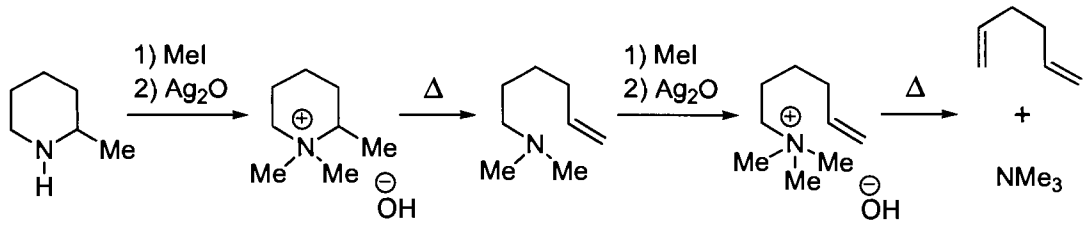
In the subsequent section, a brief overview of the methods that have been used to dealkylate tertiary amines is presented.

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]

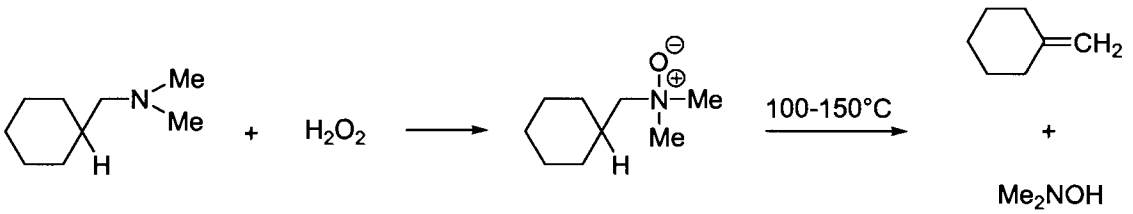
(129) Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325.
(130) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.
(131) March, J. *Advanced Organic Chemistry; Reactions, Mechanisms, and Structure*; 4th ed.; Wiley-Interscience: New York, 1992; p. 1016.

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).[132]

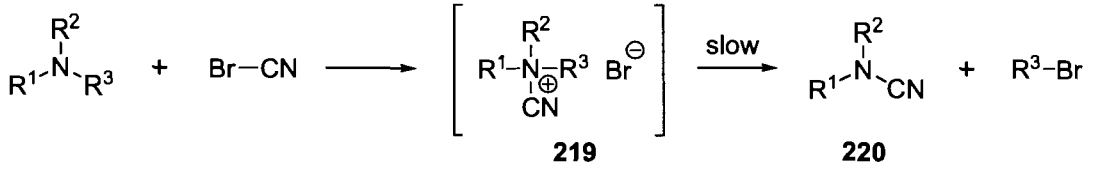
Scheme 5.5 An Example of the Cope Elimination Reaction



The cleavage of tertiary amines with various reagents, such as cyanogen bromide, phosgene and chlorofomates, has been investigated over the past century.[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.[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.[134]

(132) Solomons, T. W. G. *Organic Chemistry*; 5th ed.; Wiley: New York, 1992; p. 866.
(133) Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.
(134) Fodor, G.; Abidi, S.; Carpenter, T. C. *J. Org. Chem.* **1974**, *39*, 1507.

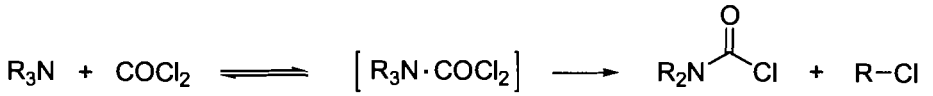
Scheme 5.6 The von Braun Reaction



219 **220**

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.[135]

Scheme 5.7 Dealkylation of Trialkylamines with Phosgene

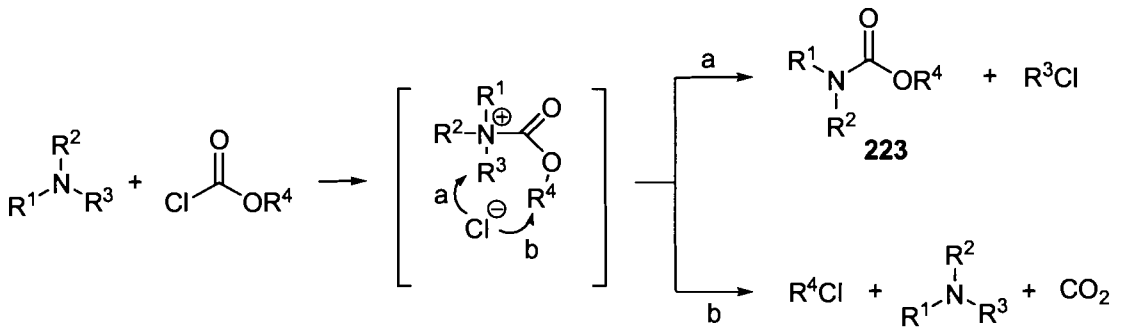


221 **222**

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.[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.

(135) Strepikheev, Y. A.; Perlova, T. G.; Zhivechkova, L. A. *J. Org. Chem. USSR* **1968**, *4*, 1826.
(136) Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc. C* **1967**, 2015.

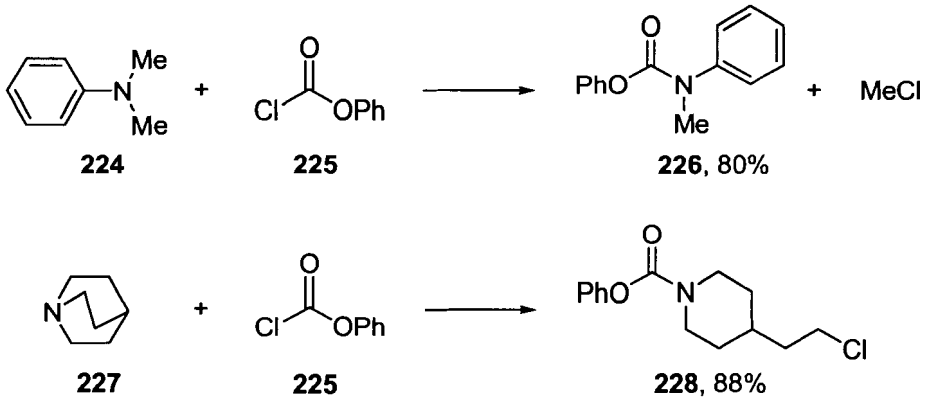
Scheme 5.8 Dealkylation of Tertiary Amines with Chloroformate Reagents



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.[137] An improved procedure was later reported by Hobson and McCluskey using phenyl chloroformate **225** as the cleavage reagent.[136] 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.

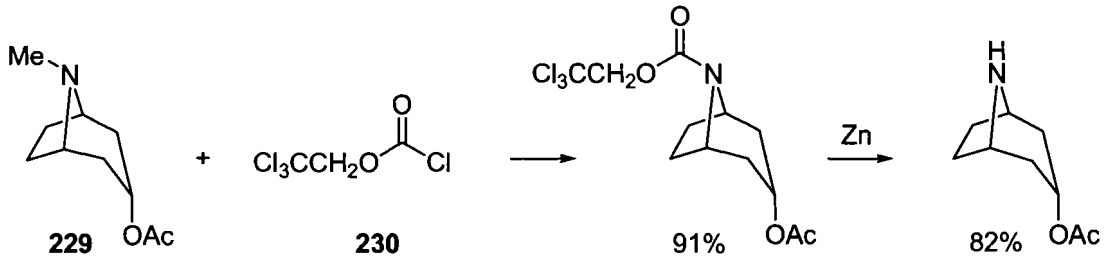
(137) Campbell, J. A. *J. Org. Chem.* **1957**, *22*, 1259.

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



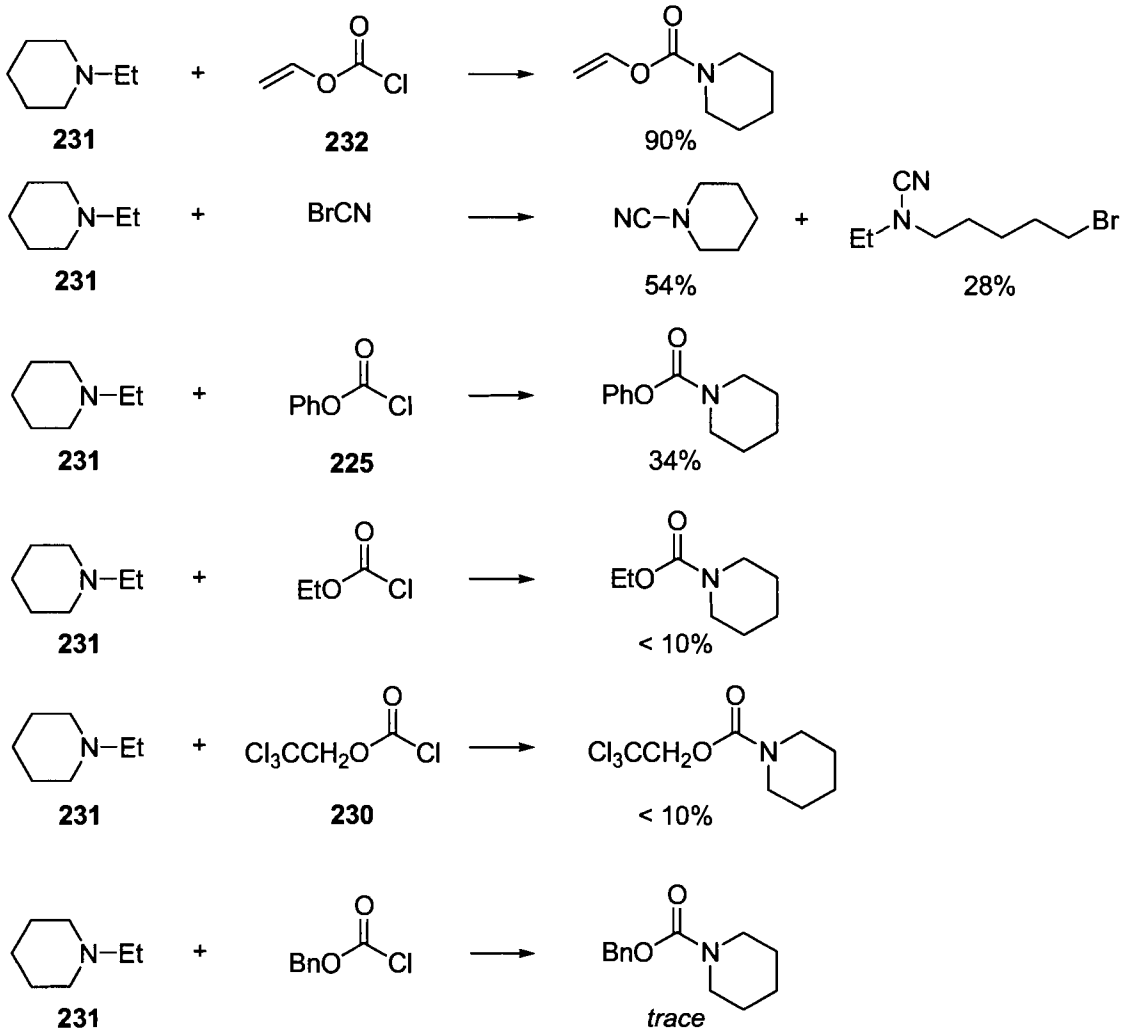
To avoid the problem encountered in the hydrolysis of the ethyl or phenyl carbamate products, Montzka and co-workers demonstrated that 2,2,2-trichloroethyl carbonochloridate **230** could be used to dealkylate tertiary methylamines.[129] The resultant trichloroethyl carbamate derivatives were easily 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)



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).

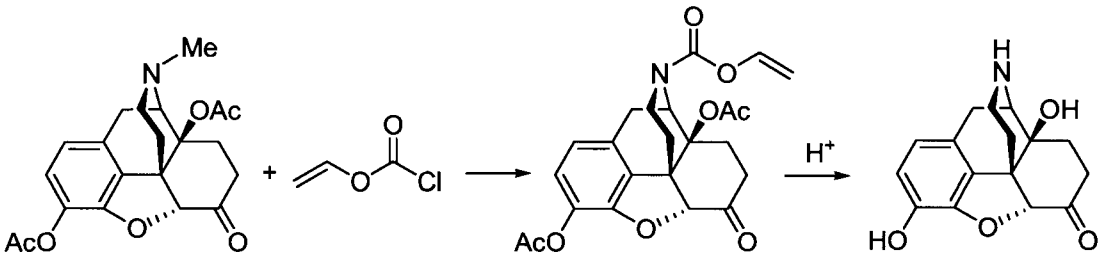
Scheme 5.11 Dealkylation of *N*-Ethylpiperidine (231) with Various Reagents



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 ($OCH{=}CH_2$). Vinyl chloroformate **232** (VOCCl) was also employed in an improved synthesis of noroxymorphone **235**, a precusor 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)



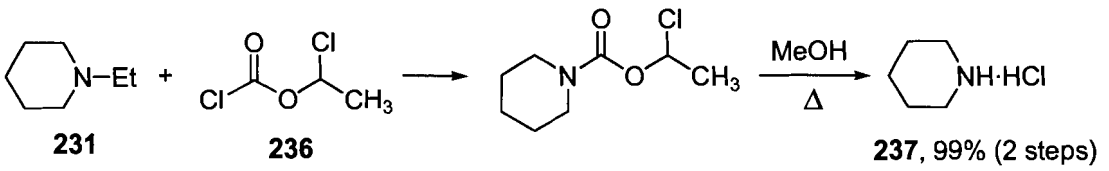
233 **232** **234** **235** *Noroxymorphone*

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.[138] The selectivity of these reactions was established as *N*-debenzylation > *N*-deallylation > *N*-demethylation.

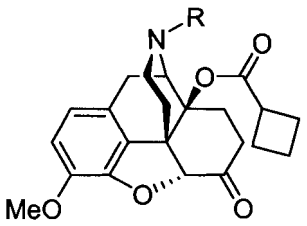
The use of the inexpensive reagent α-chloroethyl chloroformate **236** for the dealkylation of tertiary amines was reported by Olofson and Martz in 1984.[139] This new process was illustrated by converting *N*-ethylpiperidine **231** to piperidine hydrochloride **237** in 99% yield (Scheme 5.13). This method was adopted in the synthesis of analgesic nalbuphine **240**.[139] The key intermediate **239** was obtained in essentially quantitative yield on *N*-demethylation of compound **238**.

(138) Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233.
(139) Olofson, R. A.; Martz, J. T. *J. Org. Chem.* **1984**, *49*, 2081.

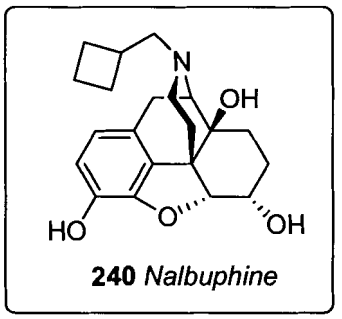
Scheme 5.13 ***N*-Dealkylation of Tertiary Amines with α-Chloroethyl Chloroformate (236)**



231 **236** **237**, 99% (2 steps)



238 (R = Me)
239 (R = H·HCl)

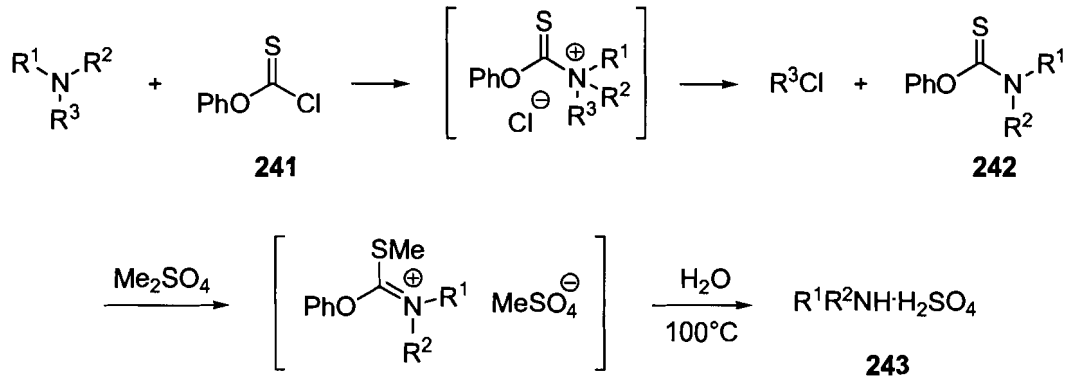


240 *Nalbuphine*

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.

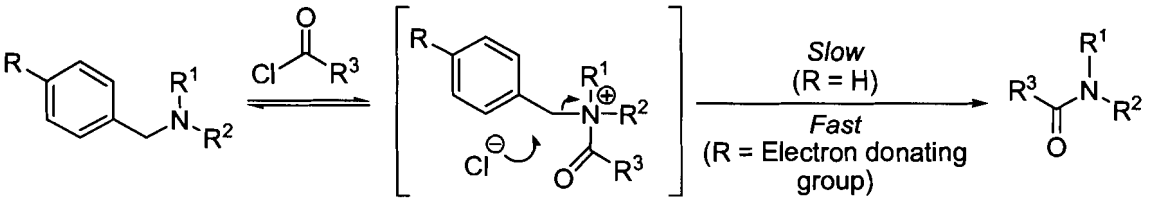
(140) Millan, D. S.; Prager, R. H. *Tetrahedron Lett.* **1998**, *39*, 4387.
(141) Millan, D. S.; Prager, R. H. *Aust. J. Chem.* **1999**, *52*, 841.

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



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).[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

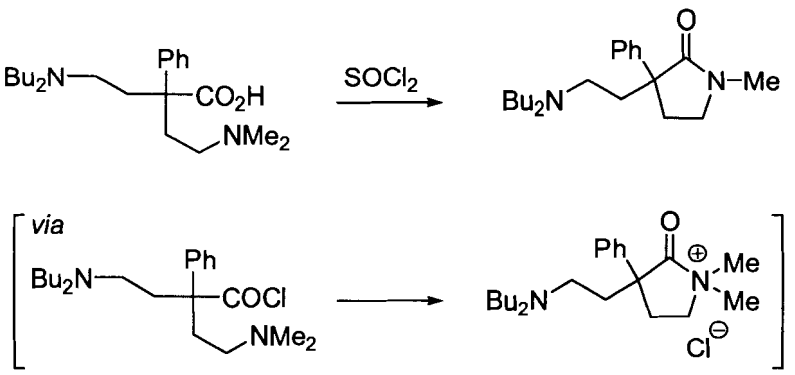


Variants of the above reaction are known in which the dealkylation process is favoured by the intramolecular nucleophilic attack of a tertiary amine on an acid chloride. For example, Clarke and co-workers have examined the reactions of γ-dialkylamino carboxylic acids with thionyl chloride (Scheme 5.16).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

(142) Miller, M. W.; Vice, S. F.; McCombie, S. W. *Tetrahedron Lett.* **1998**, *39*, 3429.

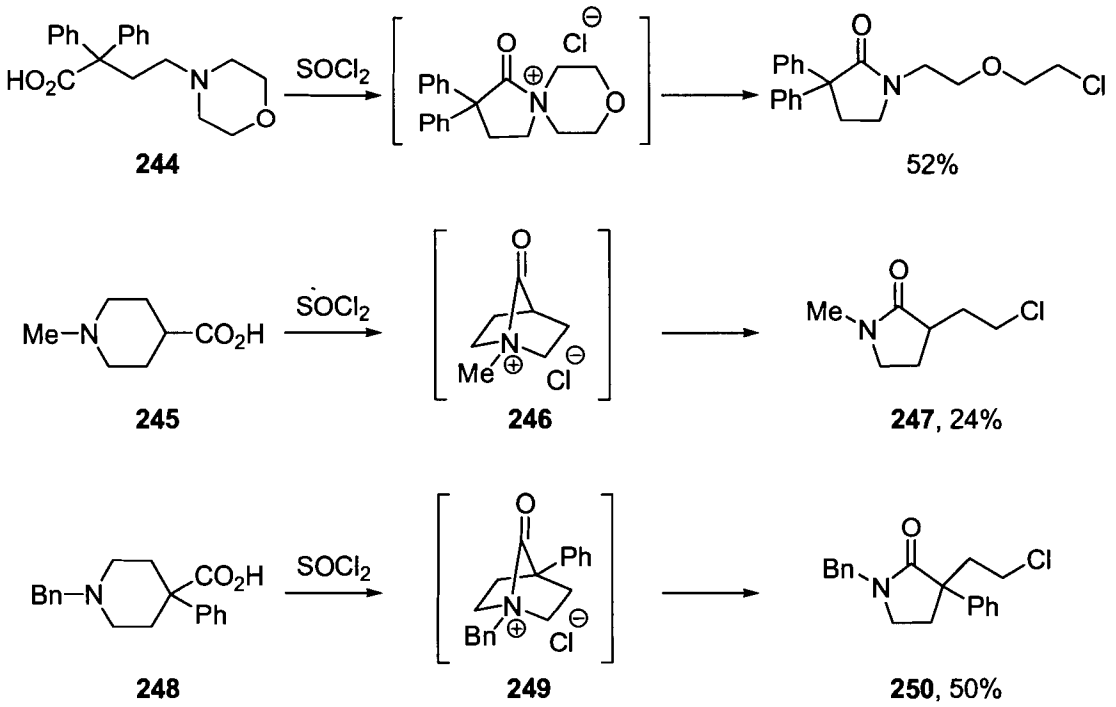
corresponding acid halide *in situ* that then undergoes an intramolecular dealkylation reaction.

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 (*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 stablization energy that is associated with the 7-keto-1-azabicyclo[2.2.1]heptane ring system in the reaction intermediates **246** and **249**.

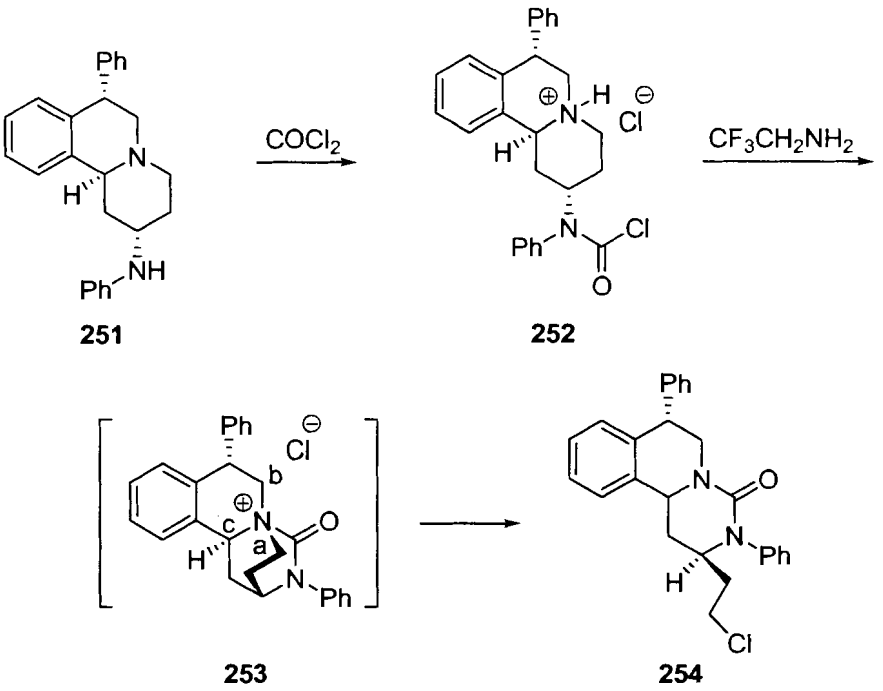
Scheme 5.17 Dealkylation of Nitrogen Heterocycles with Thionyl Chloride



A related reaction was later reported by Maryanoff and co-workers for the intramolecular rearrangement of the quinolizidine system **251** (Scheme 5.18).[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.

(143) Maryanoff, B. E.; Molinari, A. J.; Wooden, G. P.; Olofson, R. A. *Tetrahedron Lett.* **1982**, *23*, 2829.
(144) Maryanoff, B. E.; Molinari, A. J.; McComsey, D. F.; Maryanoff, C. A. *J. Org. Chem.* **1983**, *48*, 5074.

Scheme 5.18 Intramolecular Rearrangement of Quinolizidine Derivative (251)



251 **252** **253** **254**

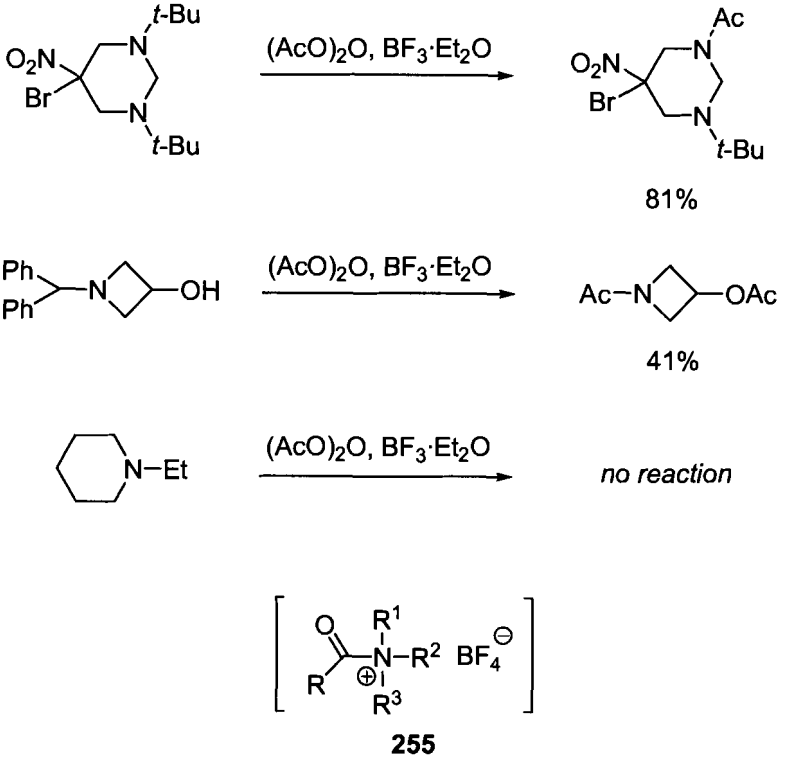
The bicyclic ammonium ion intermediate **253** had three possible sites (*a*, *b* or *c*) for cleavage by nucleophilic (S_N1 or S_N2) attack of chloride ion. However, the urea **254** was formed exclusively in this reaction which indicated that regiospecific fragmentation of the ammonium ion intermediate **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.[145] 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

(145) Dave, P. R.; Kumar, K. A.; Duddu, R. *J. Org. Chem.* **2000**, *65*, 1207.

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).

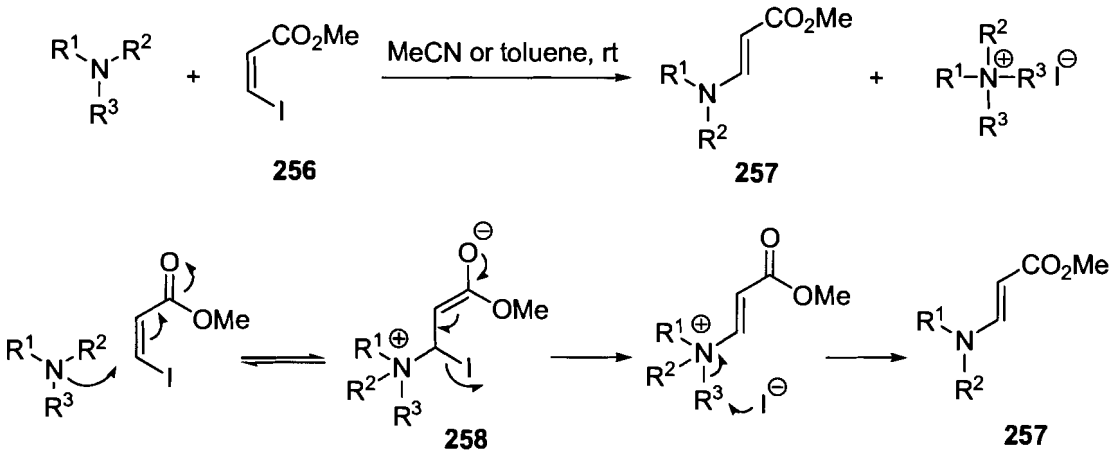
Scheme 5.19 Dealkylation of Tertiary Amines with Acetic Anhydride



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]

(146) Maw, G.; Thirsk, C.; Whiting, A. *Tetrahedron Lett.* **2001**, *42*, 8387.

Scheme 5.20 Dealkylation of Tertiary Amines with (*Z*)-Iodoacrylate (256)



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 menthioned 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).[127] Instead of isolating the expected ketone product, the amide **218** was isolated as the major product in 70% yield (see: Scheme 5.2).

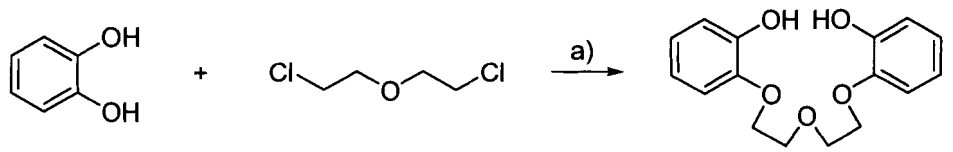
Based on this interesting experimental observation, a mild and selective method for the mono-dealkylation of tertiary amines has been developed and the results of this study are reported herein.

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).[147]

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



259 **260** **261**

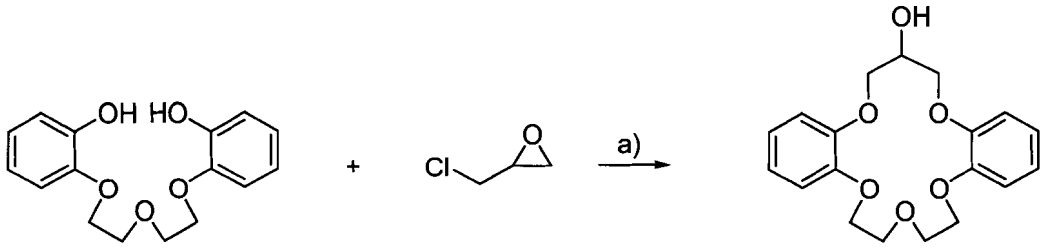
[a] Reagents and conditions: a) NaOH, H_2O, reflux, 48 h, 40%.

The melting point of the product **261** was in agreement with the literature reported value and a molecular ion was observed by mass spectroscopy (CI).[147] The ^{1}H NMR spectrum of the product showed signals for the ethylene protons at δ 3.87 ppm (4H) and 4.22 ppm (4H). The aromatic protons were observed at δ 6.77-7.03 ppm (8H) and the phenolic protons at δ 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).[148]

(147) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564.
(148) Tuarsheva, Z. O.; Mamedova, Y. G.; Shabanov, A. L.; Sidakova, G. A. *J. Org. Chem. USSR* **1984**, *20*, 363.

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



[a] Reagents and conditions: a) NaOH, H_2O, 50 °C, 5 h, 44%.

The melting point obtained for the product was again in agreement with the literature reported value.[148] 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}H NMR spectrum of this product along with the presence of the alcohol hydroxyl proton signal at δ 3.29 ppm confirmed the formation of the crown alcohol **217**.

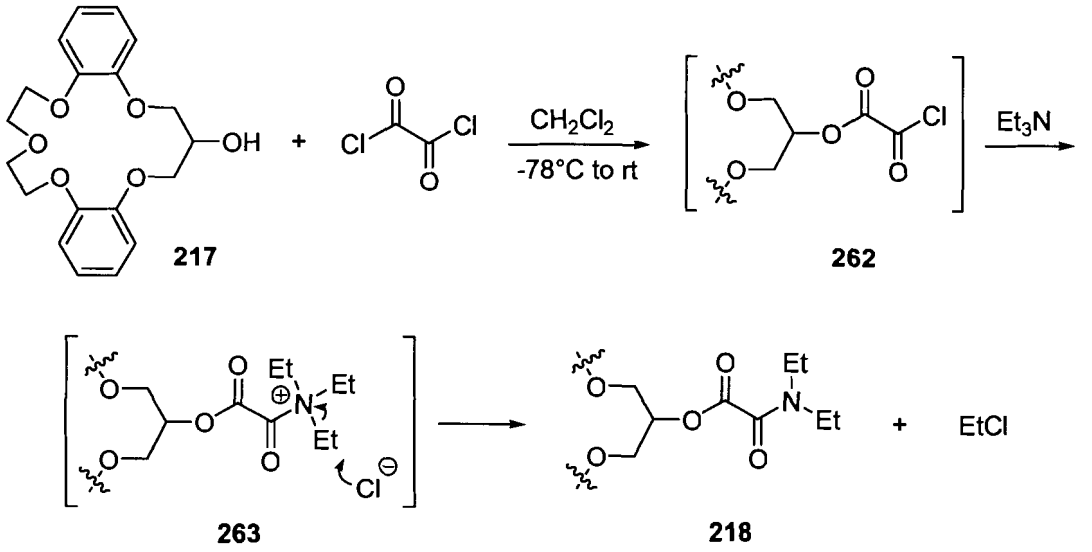
6.3 *N*-Dealkylation of Tertiary Amines with Hydroxy Crown Ether (217) and Oxalyl Chloride

The original *N*-dealkylation reaction of triethylamine was discovered in the attempted oxidation reaction of the crown alcohol **217** under modified Swern conditions.[127] 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**.

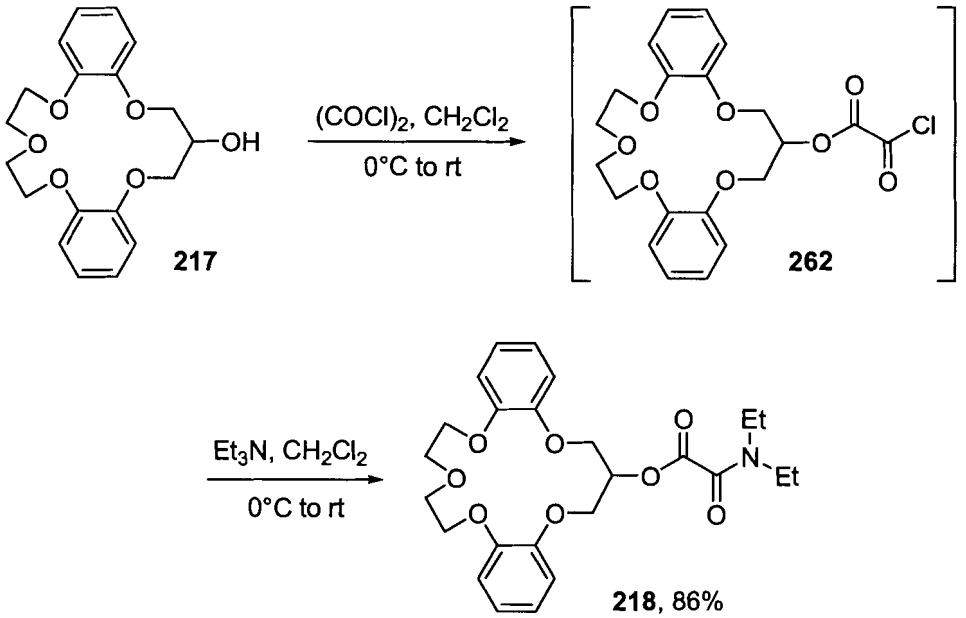
This reaction pathway bears some analogy to the well established acylative dealkylation reaction of tertiary amines with chloroformates that affords carbamate reaction products.[142] It is believed that electron-withdrawing groups attached to the acyl carbons enhance the reactivity of the cholorformate reagents.[130] In this case, the chlorocarbonyl formate intermediate **262** is activated by an adjacent carbonyl group.

Scheme 6.3 Proposed Mechanism for the Formation of Amide (218)

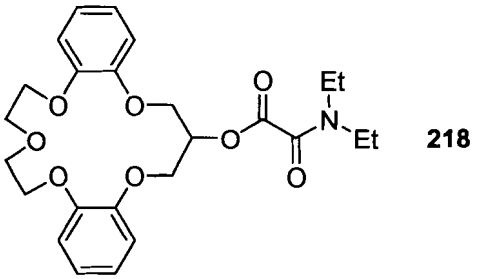


Following these preliminary studies, a practically simpler procedure was developed to perform this mono-dealkylation reaction. This procedure (**Method A**) involved treatment of the crown alcohol **217** (1 equiv) with excess oxalyl chloride (3 equiv) in dichloromethane at 0 °C. The reaction mixture was then concentrated *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.

Scheme 6.4 ***N*-Dealkylation Reaction of Triethylamine Using *Method A***



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 ^1H NMR spectrum of this compound is presented below (Figure 6.1). The spectrum contained multiplets at δ 6.81-7.04 ppm (8H, aromatic), δ 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 δ 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.



218

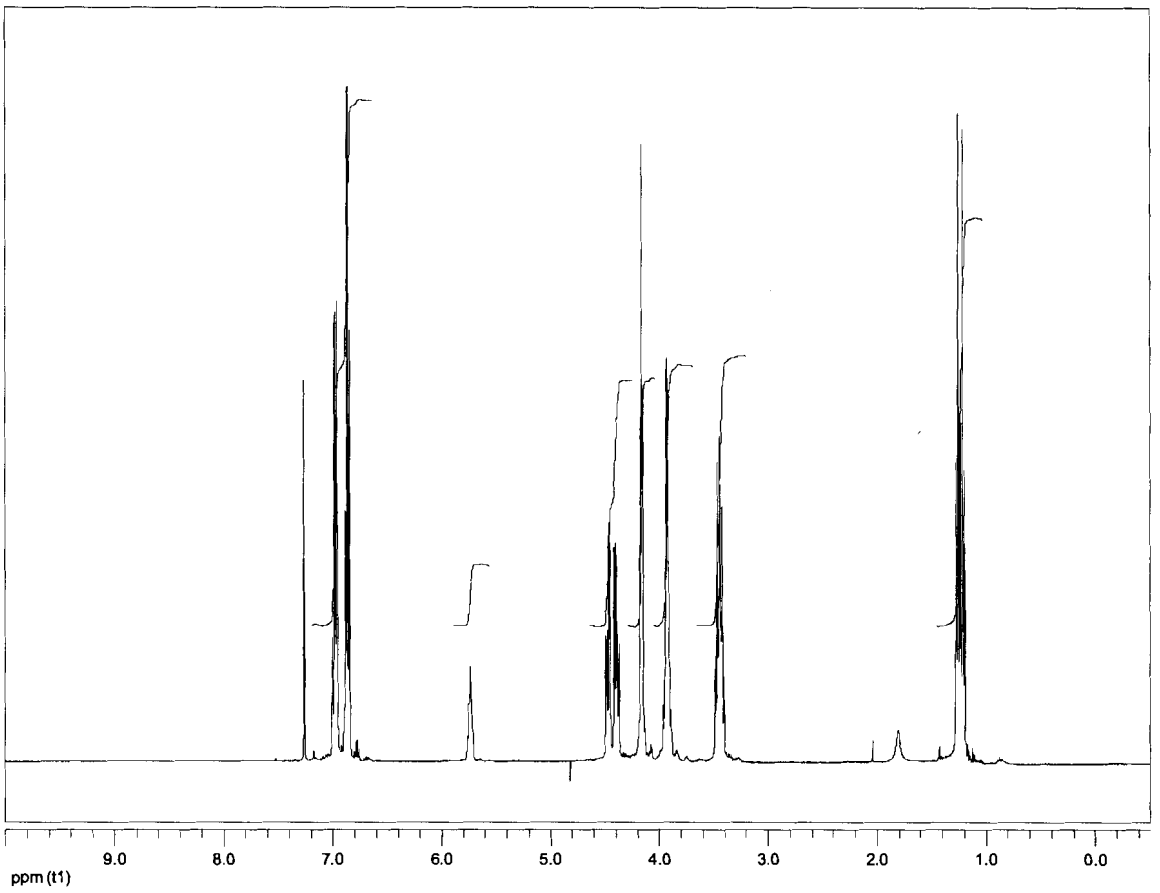
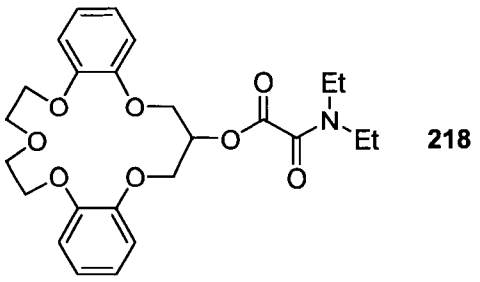


Figure 6.1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of amide (218).

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 δ 121 and 151 ppm. Two peaks were observed at low field (δ 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 (δ 12-74 ppm).



218

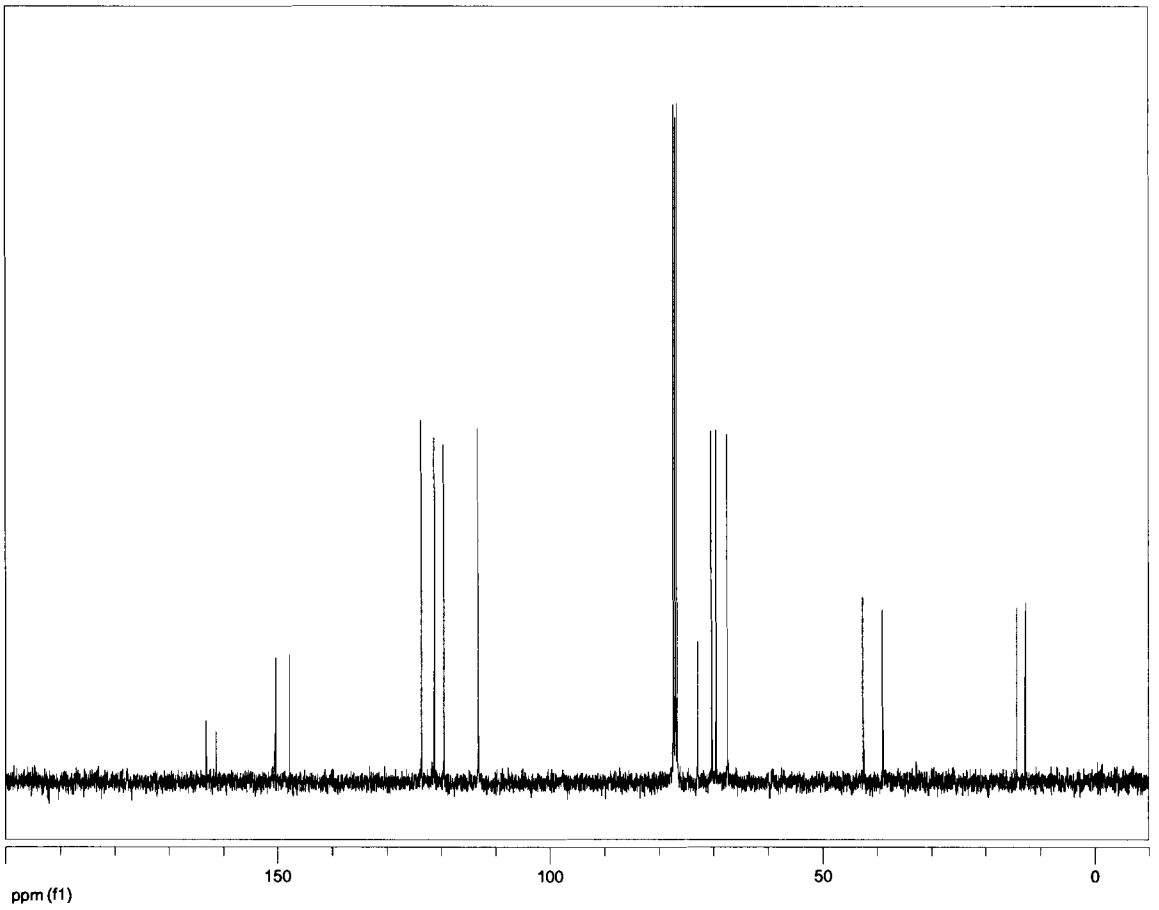


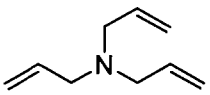
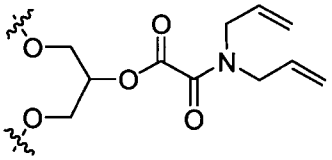
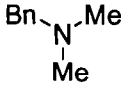
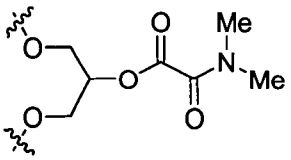
Figure 6.2 ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of amide (218).

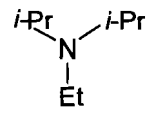
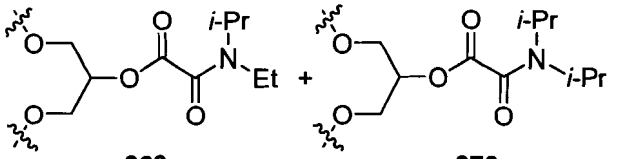
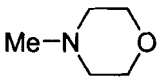
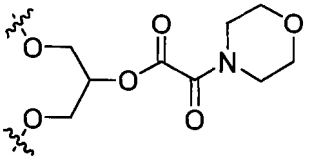
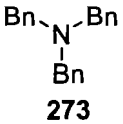
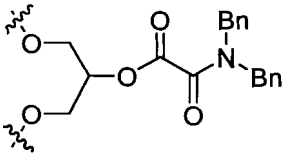
It was found that a variety of tertiary amines could be mono-dealkylated under these reaction conditions (**Method A**, Table 6.1). A mono-deallylation reaction occurred readily with triallylamine **264** and afforded the corresponding amide **265** in 88% yield (Entry 1). When dimethylbenzylamine **266** 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*-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*)

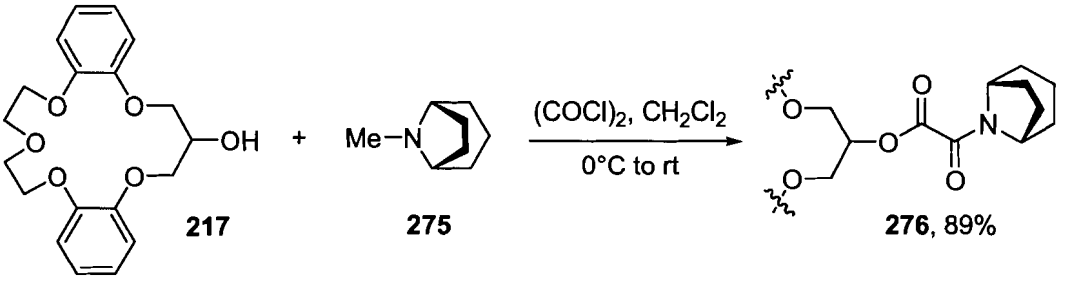
Entry	Tertiary Amine	Product	Yield
1	 **264**	 **265**	88%
2	 **266**	 **267**	90%

Entry	Tertiary Amine	Product	Yield
3	 **268**	 **269** **270**	**269**, 74% **270**, 8%
4	 **271**	 **272**	63%
5	 **273**	 **274**	0%

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 α-chloroethyl chloroformate **236** as the cleavage reagent.[149]

Scheme 6.5 ***N*-Dealkylation of Tropane (275) and Tropine Acetate (229)**[149]

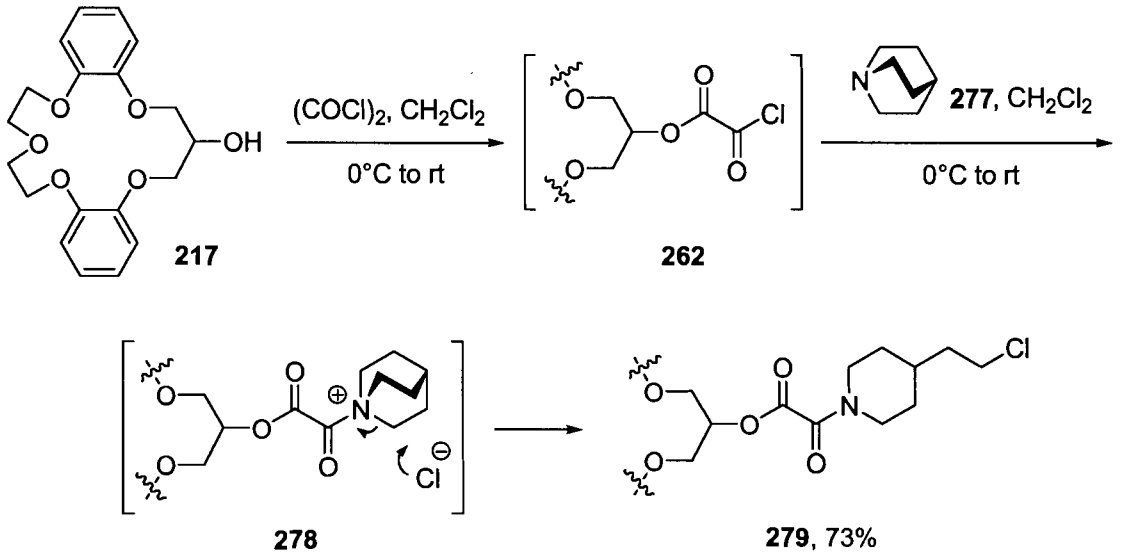


In order to gain further insight into the reaction mechanism, quinuclidine **277** was also subjected to these reaction conditions. Subsequent isolation and characterization of the major product of this reaction confirmed indirectly our hypothesis that ethylchloride was lost in the original reaction 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

(149) Koreeda, M.; Luengo, J. I. *J. Org. Chem.* **1984**, *49*, 2081.

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)



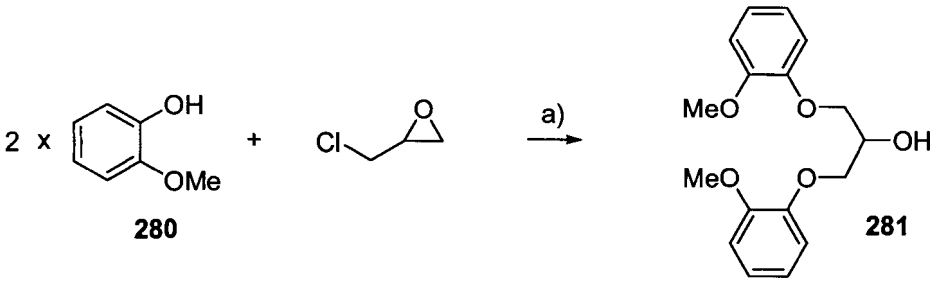
All of the *N*-dealkylation products discussed above were fully characterized. The molecular mass of each compound was obtained by mass spectroscopy (CI or MALDI-TOF). Elemental analysis was also obtained for each product and the results are presented in the experimental section (see: *Chapter Seven*). The IR spectrum of each compound showed strong absorption bands at ~ 1750 and 1650 cm^{-1} confirming the presence of the two carbonyl functions in each product. The ^1H NMR spectra of these compounds showed signals at ~ δ6.8 (8H, aromatic), 3.9 (4H, 2 x ArOCH_2) and 4.2 ppm [4H, (CH_2)$_2$O]. Two doublet of doublets were observed at ~ δ 4.4 ppm for the OCH(CH_2)$_2$ protons in the crown ether moiety. The ^{13}C signals for the carbonyl carbons were observed between δ160 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 ^1H

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]

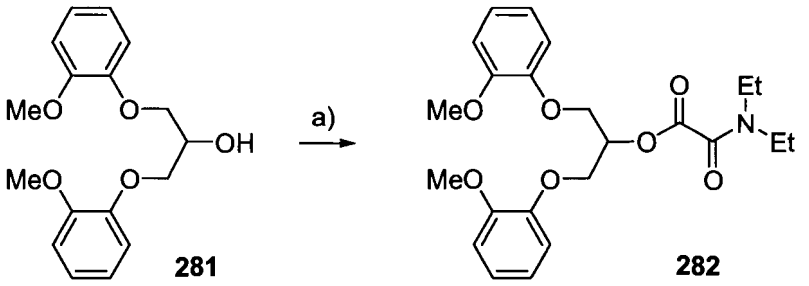


[a] Reagents and conditions: a) NaOH, H_2O, 50 °C to rt, 16 h, 76%.

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.

(150) Hayashita, T.; Goo, M.-J.; Lee, J. C.; Kim, J. S.; Krzykawski, J.; Bartsch, R. A. *Anal. Chem.* **1990**, *62*, 2283.

Scheme 6.8 Dealkylation Reaction of Triethylamine with Alcohol (281)[a]

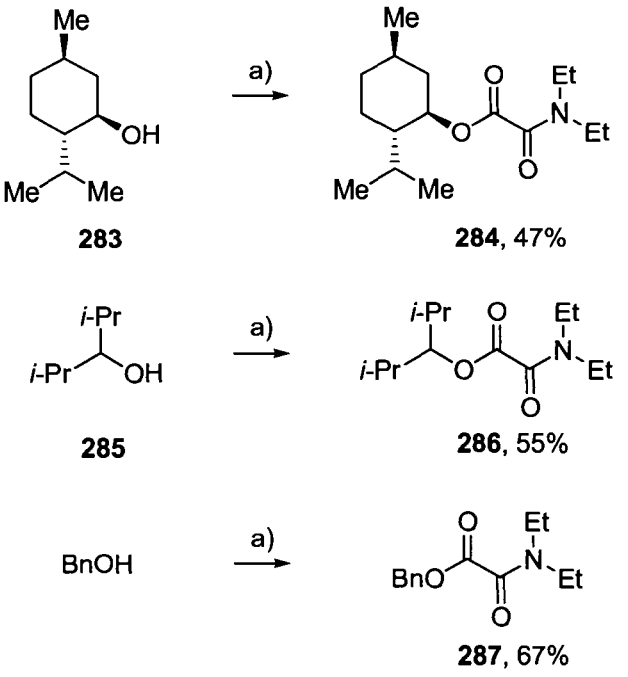


281 **282**

[a] Reagents and conditions: a) $(COCl)_2$, CH_2Cl_2, 0 °C to rt, 1 h then Et_3N, CH_2Cl_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**).

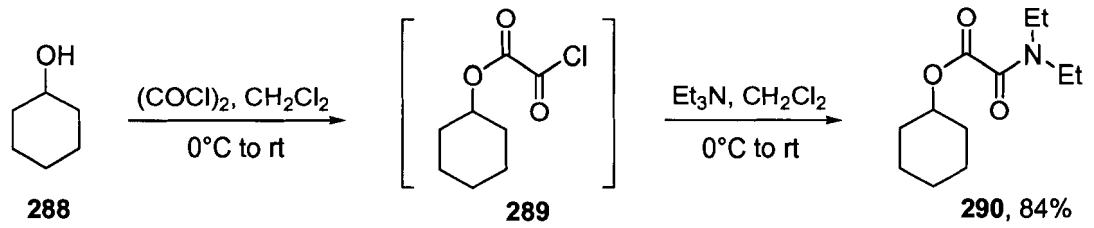
Scheme 6.9 Dealkylation Reactions of Triethylamine with Various Alcohols



[a] Reagents and conditions: a) $(COCl)_2$, CH_2Cl_2, 0 °C to rt, 1 h then Et_3N, CH_2Cl_2, 0 °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**.

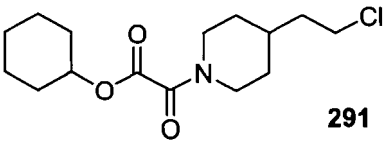
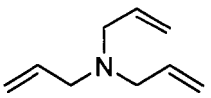
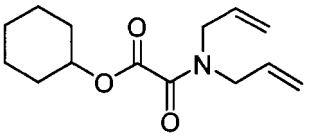
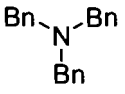
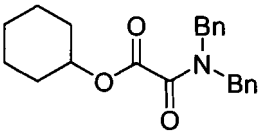
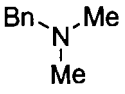
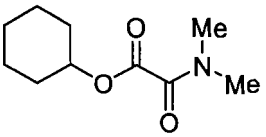
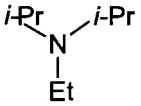
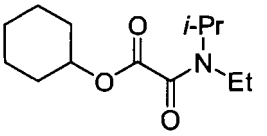
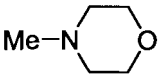
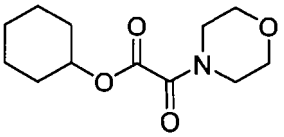
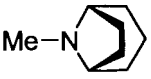
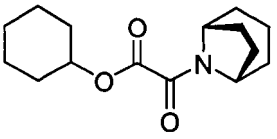
Scheme 6.10 ***N*-Dealkylation Reaction of Triethylamine with Cyclohexanol-Derived Chlorocarbonyl Formate (289)**



288 **289** **290**, 84%

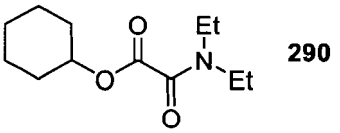
Employing **Method B**, the experimental results obtained from the dealkylation reactions of a number of tertiary amines bearing different alkyl groups are summarized below (Table 6.2). Among the compounds studied, quinuclidine **277** was transformed to the expected amide **291** in 66% yield (Entry 1). Triallylamine **264** was dealkylated easily to afford the corresponding amide **292** in 81% yield (Enty 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

Entry	Tertiary amine	Product	Yield
1	 **277**	 **291**	66%
2	 **264**	 **292**	81%
3	 **273**	 **293**	9%
4	 **266**	 **294**	90%
5	 **268**	 **295**	69%
6	 **271**	 **296**	46%
7	 **275**	 **297**	92%

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 ^1H NMR spectra showed signals at δ 1.1-1.9 ppm (10H, 5 x cyclohexyl-CH_2) and at δ 4.9 ppm (*H*CO). The two carbonyl carbons appeared at ~ δ 162 and 164 ppm in the ^{13}C NMR spectra. As expected, the dealkylation product **295** from Hünig's base **268** exhibited two sets of signals in the ^1H and ^{13}C NMR spectra corresponding to the two conformationally restricted rotamers of the product.

A representiative ^1H 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 δ 1.14-1.94 ppm corresponding to the cyclohexyl-CH_2 protons. The remaining proton on the cyclohexyl ring (*H*CO) was at δ 4.95 ppm.



290

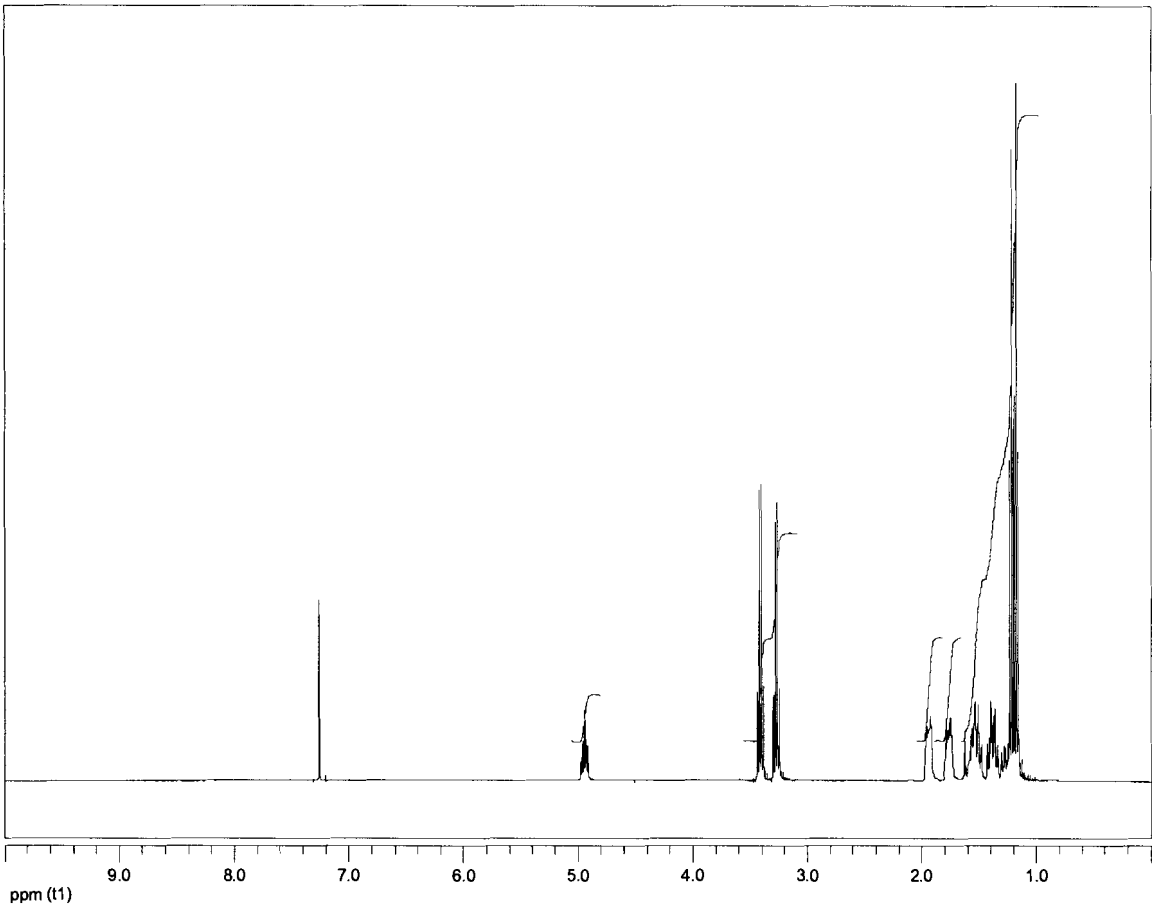
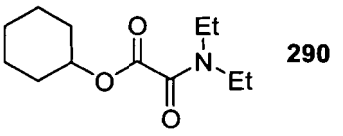


Figure 6.3 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of amide (290).

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.



290

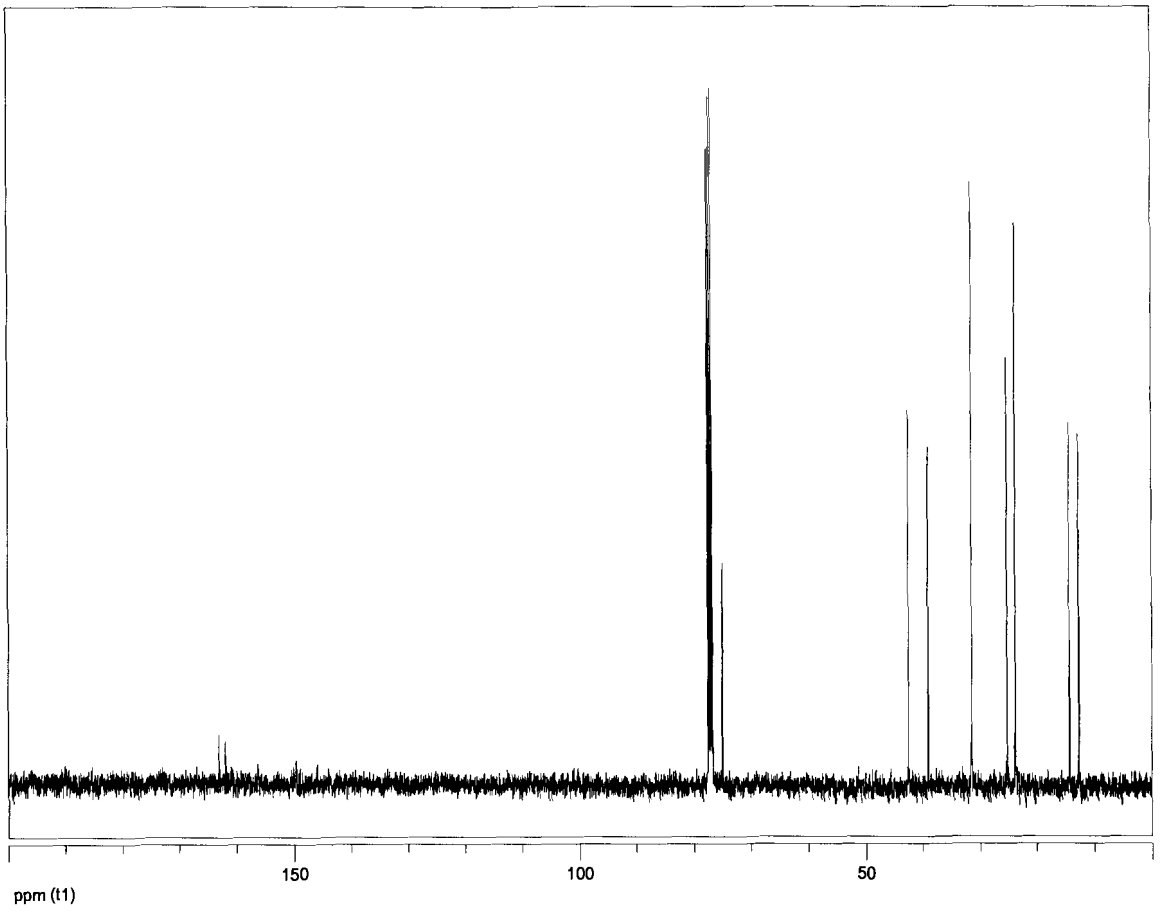


Figure 6.4 ^{13}C **NMR spectrum (101 MHz, $CDCl_3$) of amide (290).**

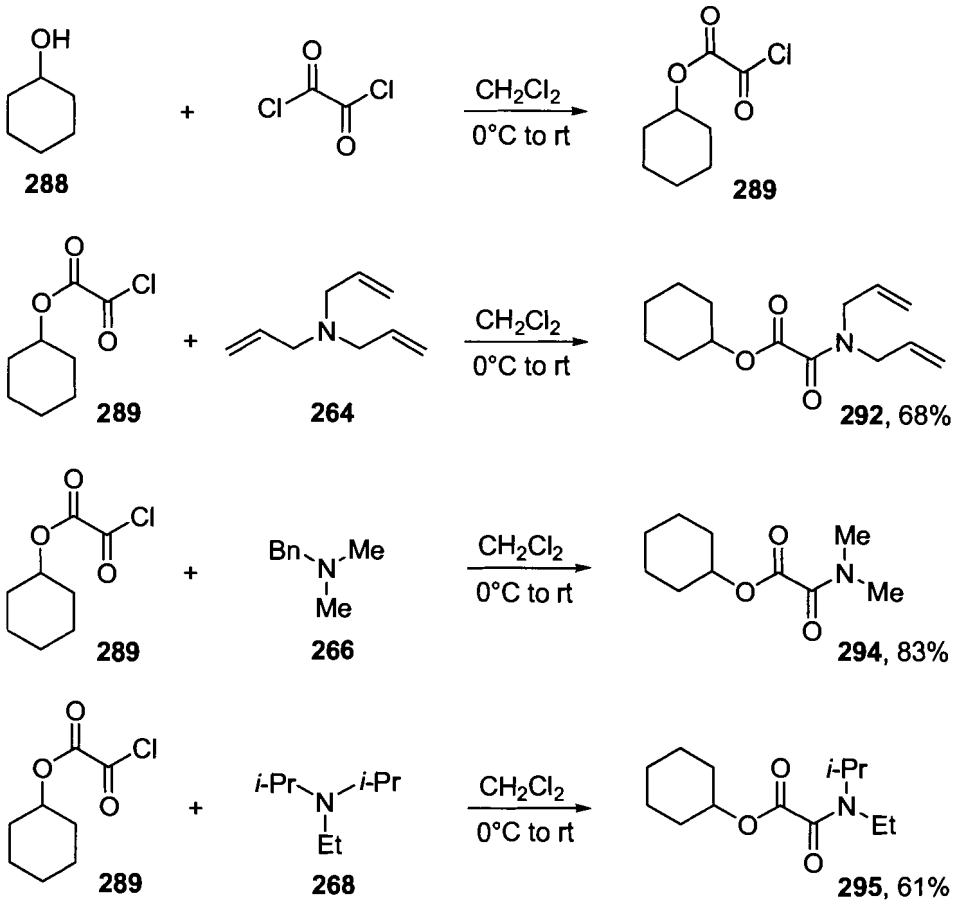
6.5 Dealkylation Reaction with Pre-made Monoesters of Oxalyl Chloride

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.[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 *in vacuo* and the corresponding amide was isolated by flash chromatography. Employing this method, the dealkylation reaction of triallyamine **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**.

(151) Attempted distillation of the crude product under high vacuum resulted in decomposition.

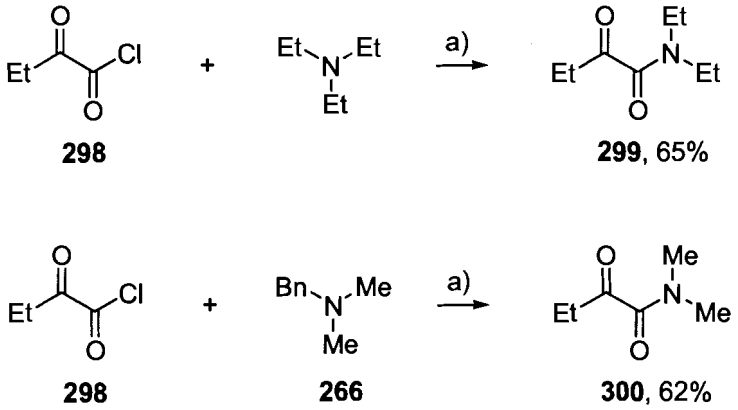
Scheme 6.11 Dealkylation of Tertiary Amines with Pre-made Chlorocarbonyl Formate (289)



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]



[a] Reagents and conditions: a) CH_2Cl_2, 0 °C to rt, 1 h.

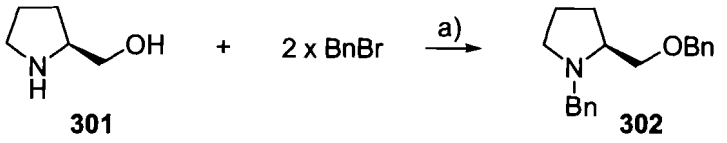
These results clearly demonstrated that the dealkylation reaction with freshly prepared cyclohexyl chlorocarbonyl formate **289** (**Method B**) is a higher yielding procedure.

6.6 Dealkylation of (2*S*)-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 (2*S*)-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-pyrrolidinemethanol **301** with excess benzylbromide on deprotonation with sodium hydride (Scheme 6.13).[152] The product **302** was fully characterized and the ^{1}H NMR spectrum of the product showed signals at δ 7.19-7.41 ppm (10H, aromatic) confirming the incorporation of the two benzyl groups in the product.

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



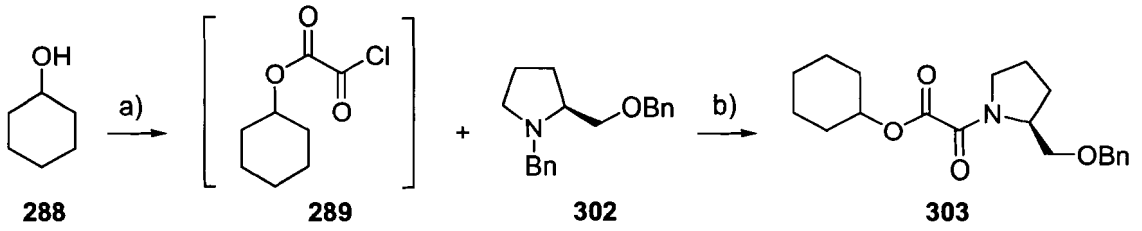
301 **302**

[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.

(152) Benerab, A.; Comoy, C.; Guilaumet, G. *Heterocycles* **1994**, *38*, 1641.

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



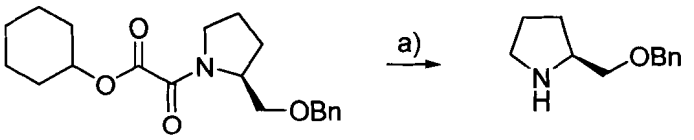
288 **289** **302** **303**

[a] Reagents and conditions: a) $(COCl)_2$, CH_2Cl_2, 0 °C to rt, 1 h; b) CH_2Cl_2, 0 °C to rt, 1 h, 83%.

Amide hydrolysis can be achieved with acid or base-catalysis.[145] In the case of (2*S*)-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 ^1H NMR spectrum confirmed the successful hydrolysis of the amide function in the starting material **303**.

(153) Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 7920.

Scheme 6.15 Hydrolysis of Amide (303)[a]



303 **304**

[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 (2*S*)-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.[154]

(154) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; Wiley: New York, 1999; pp 494-653.

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.[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 a ultraviolet lamp, treatment with a solution of *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 (δ) 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_6D_6) were 7.15 and 128.02 ppm for ^{1}H and ^{13}C NMR spectra, respectively.

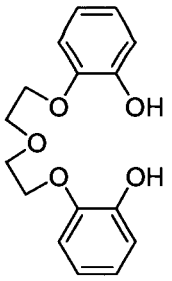
Infrared spectra (IR) were recorded as either KBr discs (KBr) or as evaporated films (ef) using a Perkin Elmer 599B IR spectrophotometer.

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 α-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

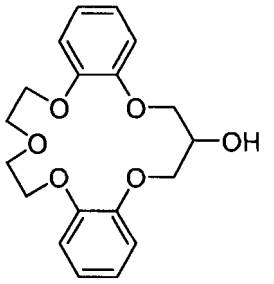
7.2.1 *bis*[2-(*ortho*-Hydroxyphenoxy)ethyl] ether (261)[147]



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.[147] **M.p.** 83-85 °C, after sublimation); **^{1}H NMR** ($CDCl_3$) δ3.87 (m, 4H, $(CH_2)_2O$), 4.22 (m, 4H, 2 x $ArOCH_2$), 6.77-7.03 (m, 8H, Ar*H*), 7.57 (broad s, 2H, O*H*); **^{13}C NMR** ($CDCl_3$) δ69.7, 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** (CI) *m/z* (rel. intensity) 291 (M + H, 100), 181 (14), 137 (8).

7.2.2 2,3,9,10-Dibenzo-6-hydroxy-16-crown-5 (217)[148]



217

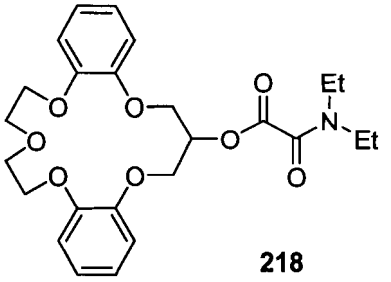
To a solution of sodium hydroxide (2.06 g, 51.6 mmol) in water (500 mL) was added *bis*[2-(*ortho*-hydroxyphenoxy)ethyl] ether **261** (7.50 g, 25.8 mmol) at room temperature. The resultant mixture was heated at 90-100 °C until a homogeneous solution was obtained. The resultant colourless solution was 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.[148] **M.p.** 122-123 °C, octane); **^{1}H NMR** ($CDCl_3$) δ 3.29 (broad s, 1H, O*H*), 3.93 (apparent t, J = 4.3 Hz, 4H, 2 x ArOCH_2), 4.18 (m, 4H, 2 x ArOCH_2CH_2), 4.25 (m, 4H, (CH_2)$_2$O), 4.36 (m, 1H, *H*COH), 6.85-7.03 (m, 8H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 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** (CI) *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.

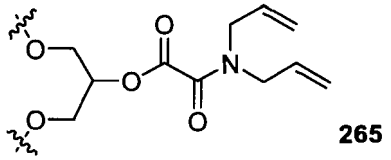
7.2.4 Reaction of alcohol (217) with triethylamine



218

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. **^{1}H NMR** ($CDCl_3$) δ 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), 3.46 (q, J = 7.3 Hz, 2H, NCH_2), 3.93 (m, 4H, 2 x $ArOCH_2CH_2$), 4.16 (m, 4H, $(CH_2)_2O$), 4.39 (dd, J = 10.8, 6.5 Hz, 2H, 2 x ArOC*H*H), 4.47 (dd, J = 10.8, 4.3 Hz, 2H, 2 x ArOCH*H*), 5.74 (m, 1H, *H*CO), 6.81-7.04 (m, 8H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 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** (CI) *m/z* (rel. intensity) 474 (M + H, 100), 329 (5), 175 (5); **Anal.** Calcd. for $C_{25}H_{31}NO_8$: 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)

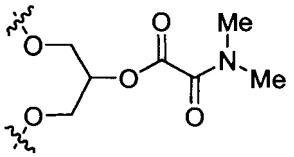


265

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; **^{1}H NMR** ($CDCl_3$) δ3.91 (m, 4H, 2 x ArOCH_2CH_2), 3.99 (apparent d, J = 6.0 Hz, 2H, NCH_2), 4.03 (apparent d, J = 6.1 Hz, 2H, NCH_2), 4.16 (m, 4H, (CH_2)$_2$O), 4.38 (dd, J = 10.8, 6.4 Hz, 2H, 2 x ArOC*H*H), 4.47 (dd, J = 10.8, 4.3 Hz, 2H, 2 x ArOCH*H*), 5.17-5.29 (m, 4H, 2 x CH=CH_2), 5.69-5.90 (m, 3H, *H*CO and 2 x C*H*=CH$_2$), 6.81-6.91 (m, 4H, Ar*H*), 6.91-7.04 (m, 4H, Ar*H*); **^{13}C NMR** ($CDCl_3$) 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, 1129, 788 cm^{-1}; **MS** (MALDI-TOF) *m/z* 520 (M + Na), 498 (M + H); **Anal.** Calcd. for $C_{27}H_{31}NO_8$: 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)

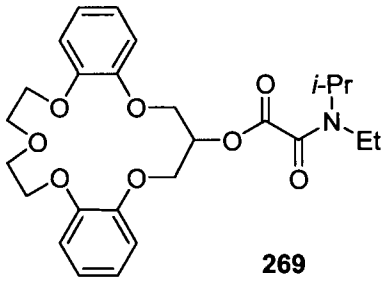


267

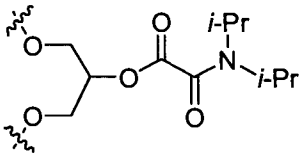
Method A. Employing alcohol **217** (100 mg, 0.289 mmol), oxalyl chloride (76 μL, 0.87 mmol) and *N,N*-dimethylbenzylamine **266** (130 μL, 0.865 mmol). Flash chromatography using methanol/dichloromethane (5%) as the eluant afforded the *product* **267** (113 mg, 90%) as a colourless oil. **^{1}H NMR** ($CDCl_3$) δ3.01 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.92 (m, 4H, 2 x ArOCH_2CH_2), 4.16 (m, 4H, (CH_2)$_2$O), 4.39 (dd, J = 10.8, 6.4 Hz, 2H, 2 x ArOC*H*H), 4.47 (dd, J = 10.8, 3.9 Hz, 2H, 2 x ArOCH*H*), 5.75 (m, 1H, *H*CO), 6.82-6.90 (m, 4H, Ar*H*), 6.93-7.02 (m, 4H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ34.1, 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)



269

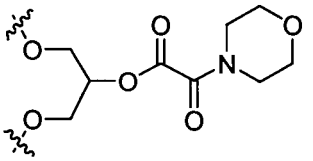


270

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; **^{1}H NMR** (C_6D_6) δ(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_3CH_2), 3.35 (m, 4H, 2 x $ArOCH_2CH_2$), 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 $ArOCH_2CH_2$), 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_6D_6) δ14.5, 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 $C_{26}H_{33}NO_8$: C, 64.05; H, 6.82; N, 2.87. Found: C, 63.86; H, 6.88; N, 2.78. *Minor product* **270**: **^{1}H NMR** ($CDCl_3$) δ 1.25 (d, J = 6.4 Hz, 6H, $(CH_3)_2CH$), 1.49 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 3.52 (m, 1H, $CH(CH_3)_2$), 3.93 (m, 5H, 2 x $ArOCH_2CH_2$ and $CH(CH_3)_2$), 4.17 (m, 4H, $(CH_2)_2O$), 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}C NMR** ($CDCl_3$) δ 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^{-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)

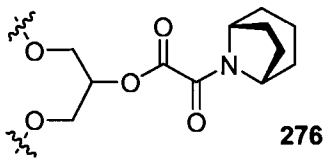


272

Method A. Employing the alcohol **217** (100 mg, 0.289 mmol), oxalyl chloride (76 μL, 0.87 mmol) and *N*-methylmorpholine **271** (95 μL, 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}H NMR** ($CDCl_3$) δ 3.52-3.77 (m, 8H, $N(CH_2CH_2)_2O$), 3.91 (m, 4H, 2 x $ArOCH_2CH_2$), 4.16 (m, 4H, $(CH_2)_2O$), 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}C NMR** ($CDCl_3$) δ 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^{-1}; **MS** (MALDI-TOF) *m/z* 526 (M + K), 510 (M + Na),

488 (M + H); **Anal.** Calcd. for $C_{25}H_{29}NO_9$: C, 61.59; H, 6.00; N, 2.87. Found: C, 61.39; H, 5.97; N, 2.69.

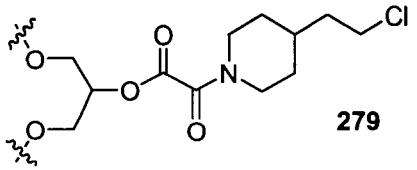
7.2.9 Reaction of alcohol (217) with tropane (275)



276

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_2CH$_2$), 4.17 (m, 4H, (CH_2)$_2$O), 4.41 (m, 4H, NC*H*, ArOCH_2 and ArOC*H*H), 4.51 (dd, J = 10.8, 4.1 Hz, 1H, ArOCH*H*), 4.69 (m, 1H, NC*H*), 5.72 (m, 1H, *H*CO), 6.83-6.91 (m, 4H, Ar*H*), 6.93 (m, 4H, Ar*H*); **^{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.

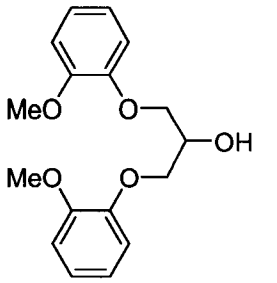
7.2.10 Reaction of alcohol (217) with quinuclidine (277)



279

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** ($CDCl_3$) δ 1.26 (m, 2H, CH_2CH_2Cl), 1.68-1.92 (m, 5H, $(CH_2)_2CHCH_2$), 2.73 (td, J = 13.1, 2.8 Hz, 1H, NC*H*H), 3.14 (td, J = 13.1, 2.8 Hz, 1H, NCH*H*), 3.57 (t, J = 6.6 Hz, 2H, CH_2Cl), 3.93 (m, 5H, 2 x $ArOCH_2CH_2$ and NC*H*H), 4.17 (m, 4H, $(CH_2)_2O$), 4.35 (dd, J = 10.7, 6.4 Hz, 1H, ArOC*H*H), 4.38 (dd, J = 10.7, 5.5 Hz, 1H, ArOCH*H*), 4.42 (dd, J = 10.7, 4.6 Hz, 1H, ArOC*H*H), 4.44 (dd, J = 10.7, 4.3 Hz, 1H, ArOCH*H*), 4.54 (m, 1H, NC*H*H), 5.74 (m, 1H, *H*CO), 6.82-6.91 (m, 4H, Ar*H*), 6.92-7.03 (m, 4H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 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.

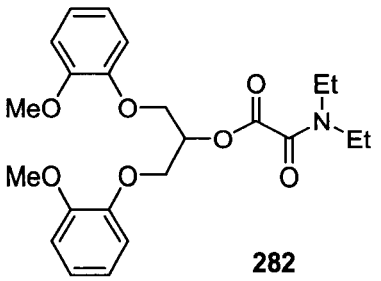
7.2.11 1,3-*bis*(*ortho*-Methoxyphenoxy)-2-propanol (281)[150]



281

To a solution of sodium hydroxide (323 mg, 8.06 mmol) in water (40 mL) was added 2-methoxyphenol **280** (890 μl, 8.09 mmol) at 90 °C. Once a homogeneous solution was obtained, the reaction mixture was cooled to 50 °C and epichlorohydrin (320 μl, 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 NMR** ($CDCl_3$) δ 3.29 (broad s, 1H, O*H*), 3.85 (s, 6H, 2 x OCH_3), 4.20 (m, 4H, 2 x ArOCH_2), 4.41 (m, 1H, *H*COH), 6.84-6.93 (m, 4H, Ar*H*), 6.94-7.02 (m, 4H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 56.0, 68.8, 71.2, 112.2, 115.5, 121.1, 122.3, 148.3, 150.1; **IR** (ef) 3477 (broad), 2935, 2836, 1592, 1505, 1454, 1254, 1124, 743 cm^{-1}; **MS** (CI) *m/z* (rel. intensity), 305 (M + H, 100), 181 (36), 163 (80).

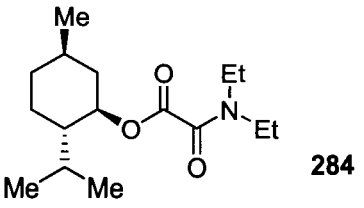
7.2.12 Reaction of 1,3-*bis*(*ortho*-methoxyphenoxy)-2-propanol (281) with triethylamine



282

Method A. Employing 1,3-*bis*(*ortho*-methoxyphenoxy)-2-propanol **281** (100 mg, 0.329 mmol), oxalyl chloride (86 μL, 0.99 mmol) and triethylamine (140 μL, 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** ($CDCl_3$) δ1.15 (m, 6H, 2 x CH_3CH_2), 3.33 (q, J = 7.0 Hz, 2H, CH_3CH_2), 3.41 (q, J = 7.2 Hz, 2H, CH_3CH_2), 3.82 (s, 6H, 2 x CH_3O), 4.36 (dd, J = 10.9, 6.01 Hz, 2H, 2 x ArOC*H*H), 4.41 (dd, J = 10.9, 5.0 Hz, 2H, 2 x ArOCH*H*), 5.80 (m, 1H, *H*CO), 6.84-6.93 (m, 4H, Ar*H*), 6.93-7.04 (m, 4H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ12.7, 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

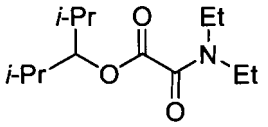


284

Method A. Employing (-)-menthol **283** (200 mg, 1.28 mmol), oxalyl chloride (330 μL, 3.78 mmol) and triethylamine (540 μL, 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** ($CDCl_3$) δ0.79 (d, J = 7.1 Hz, 3H, CH_3CH), 0.90 (d, J = 7.1 Hz, 3H, CH_3CH), 0.92 (d, J = 6.7 Hz, 3H, $CH_3CH(CH_2)_2$), 1.10 (m, 2H, cyclohexyl-CH_2), 1.20 (m, 7H, 2 x CH_2CH_3 and $CH_3CH(CH_2)_2$), 1.49 (m, 2H, cyclohexyl-CH_2), 1.70 (m, 2H, cyclohexyl-CH_2), 1.96 (m, 1H, $(CH_3)_2CH$), 2.07 (m, 1H, OCHC*H*), 3.28 (q, J = 7.1 Hz, 2H, CH_3CH_2), 3.41 (m, 2H, CH_3CH_2), 4.87 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ 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 $C_{16}H_{29}NO_3$: 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

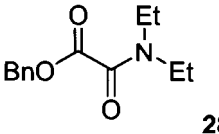


286

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** ($CDCl_3$) δ0.93 (d, J = 6.7 Hz, 6H, $(CH_3)_2CH$), 0.95 (d, J = 6.7 Hz, 6H, $(CH_3)_2CH$), 1.19 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.23 (t, J = 7.2 Hz, 3H, CH_3CH_2), 2.00 (m, 2H, 2 x $(CH_3)_2CH$), 3.33 (q, J = 7.2 Hz, 2H, CH_3CH_2), 3.43 (q, J = 7.2 Hz, 2H, CH_3CH_2), 4.76 (t, J = 6.1 Hz, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ 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 $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 63.90; H, 10.31; N, 5.95.

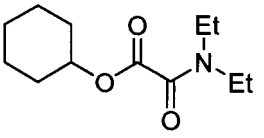
7.2.15 Reaction of benzylalcohol with triethylamine



287

Method A. Employing benzylalcohol (190 μL, 1.84 mmol), oxalyl chloride (530 μL, 5.57 mmol) and triethylamine (780 μL, 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** ($CDCl_3$) δ 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, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 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 $C_{12}H_{15}NO_3$: 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

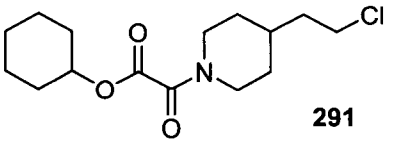


290

Method A. Employing cyclohexanol **288** (210 μL, 1.99 mmol), oxalyl chloride (520 μL, 5.96 mmol) and triethylamine (840 μL, 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** ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.22 (t, J = 7.2 Hz, 3H, CH_3CH_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_3CH_2), 3.41 (q, J = 7.2 Hz, 2H, CH_3CH_2), 4.95 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ 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 $C_{12}H_{21}NO_3$: 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)

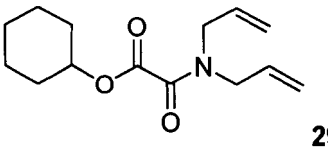


291

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** ($CDCl_3$) δ 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, NC*H*H), 3.10 (td, J = 13.3, 2.8 Hz, 1H, NCH*H*), 3.58 (t, J = 6.6 Hz, 2H, CH_2Cl), 3.63 (m, 1H, NC*H*H), 4.51 (m, 1H, NCH*H*), 4.95 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ 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** (ef) 2927, 2856,

1733, 1659, 1455, 1266, 1205, 1180, 1009 cm^{-1}; **MS** (MALDI-TOF) *m/z* 302 (M + H); **Anal.** Calcd. for $C_{15}H_{24}ClNO_3$: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.61; H, 8.14; N, 4.80.

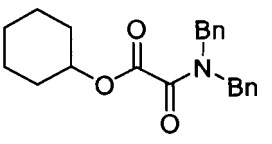
7.2.18 Reaction of cyclohexanol (288) with triallylamine (264)



292

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. **^{1}H NMR** ($CDCl_3$) 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, NCH_2), 3.99 (d, J = 6.2 Hz, 2H, NCH_2), 4.95 (m, 1H, *H*CO), 5.15-5.33 (m, 4H, 2 x CH=CH_2), 5.69-5.84 (m, 2H, 2 x C*H*=CH_2); **^{13}C NMR** ($CDCl_3$) 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 $C_{14}H_{21}NO_3$: 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)

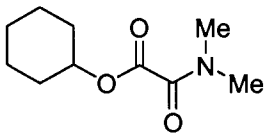


293

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; **^{1}H NMR** ($CDCl_3$) 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, PhC*H*$_2$), 4.48 (s, 2H, PhC*H*$_2$), 4.96 (m, 1H, *H*CO), 7.18-7.42 (m, 10H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 23.7, 25.3, 31.4, 46.1, 50.3, 75.5, 128.0, 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** (CI) *m/z* (rel. intensity) 352 (M + H, 100), 270 (17), 178 (12), 91 (37); **Anal.** Calcd. for $C_{22}H_{25}NO_3$: 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)



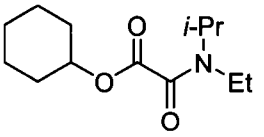
294

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; **^{1}H NMR** ($CDCl_3$) 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, NC*H*$_3$), 3.00 (s, 3H, NC*H*$_3$), 4.95 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) 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-

TOF) *m/z* 238 (M + K), 222 (M + Na), 200 (M + H); **Anal.** Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.01; H, 8.66; N, 6.87.

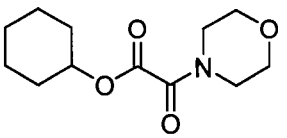
7.2.21 Reaction of cyclohexanol (288) with *N,N*-diisopropylethylamine (268)



295

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** ($CDCl_3$), δ(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_3CH_2), 3.79 (septet, J = 6.6 Hz, 1H, $(CH_3)_2CH$), 4.95 (m, 1H, *H*CO); (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_3CH_2), 4.46 (septet, J = 6.9 Hz, 1H, $(CH_3)_2CH$), 4.95 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ14.5, 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 $C_{13}H_{23}NO_3$: 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)

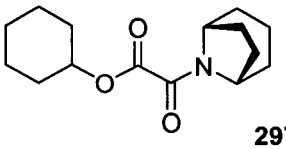


296

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 NMR** ($CDCl_3$) δ 1.14-1.47 (m, 3H), 1.47-1.62 (m, 3H), 1.76 (m, 2H), 1.92 (m, 2H), 3.44 (m, 2H, NCH_2), 3.61-3.79 (m, 6H, NCH_2 and O(CH_2)$_2$), 4.95 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ 23.7, 25.2, 31.4, 41.7, 46.4, 66.5, 66.7, 75.4, 160.6, 162.2; **IR** (ef) 2937, 2859, 1738, 1665, 1449, 1293, 1271, 1205, 1117 cm^{-1}; **MS** (MALDI-TOF) *m/z* 280 (M + K), 264 (M + Na); **Anal.** Calcd. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.83; H, 8.09; N, 6.00.

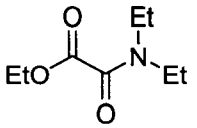
7.2.23 Reaction of cyclohexanol (288) with tropane (275)



297

Method B. Employing cyclohexanol **288** (170 μL, 1.61 mmol), oxalyl chloride (430 μL, 4.93 mmol) and tropane **275** (200 μL, 1.49 mmol). Flash chromatography using dichloromethane as the eluant afforded the *product* **297** (365 mg, 92%) as a white solid. **M.p.** 50-52 °C, dichloromethane; **^{1}H NMR** ($CDCl_3$) δ 1.17-2.08 (m, 20H), 4.16 (m, 1H, NC*H*), 4.65 (m, 1H, NC*H*), 4.93 (m, 1H, *H*CO); **^{13}C NMR** ($CDCl_3$) δ 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** (KBr) 2937, 2859, 1733, 1655, 1454, 1244, 1203, 1165 cm^{-1}; **MS** (MALDI-TOF) *m/z* 304 (M + K), 288 (M + Na), 266 (M + H); **Anal.** Calcd. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.69; H, 8.85; N, 5.10.

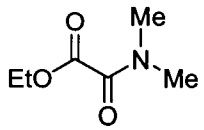
7.2.24 Reaction of ethyl chlorooxoacetate (298) with triethylamine



299

To a solution of commercially available ethyl chlorooxoacetate **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 *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* **299** (180 mg, 65%) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 1.21 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3CH_2O), 3.27 (q, J = 7.2 Hz, 2H, NCH_2CH_3), 3.41 (q, J = 7.2 Hz, 2H, NCH_2CH_3), 4.32 (q, J = 7.2 Hz, 2H, CH_3CH_2O); **^{13}C NMR** ($CDCl_3$) 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^{-1}; **MS** (CI) *m/z* (rel. intensity) 174 (M + H, 100); **Anal.** Calcd. for $C_8H_{15}NO_3$: 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 chlorooxoacetate (298) with *N,N*-dimethylbenzylamine (266)

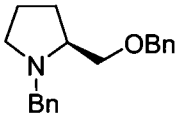


300

To a solution of commercially available ethyl chlorooxoacetate **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 *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. **^{1}H NMR** ($CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H, CH_3CH_2), 2.98 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3), 4.33 (q, J = 7.2 Hz, 2H, CH_3CH_2); **^{13}C NMR** ($CDCl_3$) 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** (CI) *m/z* (rel. intensity) 146 (M + H, 100); **Anal.** Calcd. for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.46; H, 7.58; N, 9.46.

7.2.26 (2*S*)-1-Benzyl-2-[(benzyloxy)methyl]pyrrolidine (302)[155]



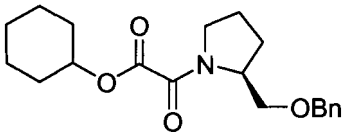
302

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 (2*S*)-(+)-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. $[\alpha]_D^{20}$ -65 (*c* 0.9, chloroform); **^{1}H NMR** ($CDCl_3$) δ 1.56-1.79 (m, 3H, $CHCHHCH_2$), 1.94 (m, 1H, $CHCHHCH_2$), 2.21 (m, 1H, $NCHH$), 2.77 (m, 1H, NCH), 2.92 (m, 1H, $NCHH$), 3.40

(155) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098.

(m, 2H, OC*H*HCH and NC*H*HPh), 3.53 (dd, J = 9.2, 5.2 Hz, 1H, OCH*H*CH), 4.13 (d, J = 12.9 Hz, 1H, NCH*H*Ph), 4.53 (s, 2H, PhCH_2O), 7.19-7.41 (m, 10H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ 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 (2*S*)-1-benzyl-2-[(benzyloxy)methyl]-pyrrolidine (302)

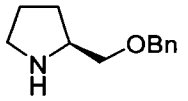


303

Method B. Employing cyclohexanol **288** (110 μL, 1.04 mmol), oxalyl chloride (270 μL, 3.10 mmol) and (2*S*)-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. $[\alpha]_D^{20}$ - 80 (*c* 1.0, chloroform); **^{1}H NMR** ($CDCl_3$) δ (rotamer a, ~ 50%) 1.13-2.14 (m, 14H), 3.35 (m, 2H, OCH_2CH), 3.54 (m, 2H, NCH_2), 4.44 (m, 1H, NC*H*), 4.52 (apparent d, J = 2.2 Hz, 2H, PhCH_2), 4.93 (m, 1H, *H*CO), 7.23-7.39 (m, 5H, Ar*H*); (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, OC*H*HCH), 3.69 (dd, J = 9.5, 3.2 Hz, 1H, OCH*H*CH), 4.30 (m, 1H, NC*H*), 4.48 (apparent d, J = 4.7 Hz, 2H, PhCH_2), 4.85 (m, 1H, *H*CO), 7.23-7.39 (m, 5H, Ar*H*); **^{13}C NMR** ($CDCl_3$) δ (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 (2*S*)-2-[(Benzyloxy)methyl]pyrrolidine (304)



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. $[\alpha]_D^{20}$ - 9.2 (*c* 1.3, chloroform), lit.[156] $[\alpha]_D^{20}$ -0.6 (*c* 2.0, benzene); **^{1}H NMR** ($CDCl_3$) δ 1.46 (m, 1H, $CHCH_2CHH$), 1.65-1.92 (m, 3H, $CHCH_2CHH$), 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** ($CDCl_3$) δ 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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