CHEMICAL STUDIES OF NECIC ACID ANALOGUES

BY

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Submitted to Rhodes University
in fulfilment of the requirements
for the degree of

Master of Science

Department of Chemistry
Rhodes University
Grahamstown

December
1996

"without informations we are nothing. But with informations we can go anywhere in the world, we are like turtles, our houses always on our backs. You learn to paint, you can paint anywhere. A sculptor, a musician, a painter; they need no permits. Only their heads. Our world must be inside our heads. That is the only safe way."

A Perfect Spy
John le Carré

"You will find it takes patience, care, thoughtfulness, and some feeling for the route you are travelling, together with some open-mindedness about where and when you will arrive. Adding these things successfully to your curiosity, you become a scientist."

Crystals and Crystal Growing
Alan Holden and Phylis Morrison

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ACKNOWLEDGEMENTS

I wish to start with thanks to my co-supervisors; Prof. P.T. Kaye for his support and interest in my work, and Dr J.R. Liddell for introducing me to the world of *Senecio* alkaloids.

I am deeply indebted to Warner Molema (proof-reading), Catherine Logie (*Senecio* alkaloid expertise), Ross Robinson (Baylis-Hillman info.), Melanie Evans (general info.), Philip Deane (general dogsbody) and everyone in the lab. for their years of input, support, jokes and database of knowledge.

Many thanks to Mr Aubrey Sonemann for low resolution mass spectroscopy and Dr Philip Boshoff (Cape Technikon) for high resolution mass spectroscopy.

Financial support from Rhodes University and FRD, with the aid of Mrs M. van Hille, was greatly appreciated.

Lastly, my deepest gratitude to my parents, brother and sister for their support in times of trouble.

ABBREVIATIONS

CDI	-	1,1-carbonyldiimidazole
DABCO	-	1,4-diazabicyclo[2.2.2]octane
d.e.	-	diastereomeric excess
NMR	-	nuclear magnetic resonance
PLC	-	preparative layer chromatography
RDS	-	rate determining step
SMM	-	sodium methylmercaptan
TLC	-	thin layer chromatography
TSC	-	transition state complex

ABSTRACT

Various aldehydes have been reacted with methyl acrylate under Baylis-Hillman conditions, using DABCO as a catalyst, to afford a range of α-substituted acrylic esters containing an allylic hydroxy group. Selected Baylis-Hillman products have been brominated, hydrolysed and acetylated to afford substrates for the synthesis of necic acid analogues.

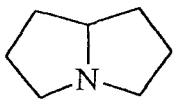
The diastereo- and regioselectivity of nucleophilic attack, using sodium methylmercaptan, on the Baylis-Hillman products and selected brominated derivatives was investigated. The allylic hydroxy compounds favour conjugate addition with the generation of a new chiral centre, while the allylic bromo derivatives favour substitution (S_N and S_N') with consequent loss of chirality.

(*E*)-2-Isopropylcrotonic acid, a vital precursor in the synthesis of all stereoisomers of trachelanthic and viridifloric acid, was synthesised in an attempt to obtain the necic acid components required for total alkaloid synthesis of lycopsamine and its derivatives. This precursor and salicylic acid were then used to prepare esters of retronecine, a dihydroxy necine base obtained *via* extraction and consequent hydrolysis of retrorsine.

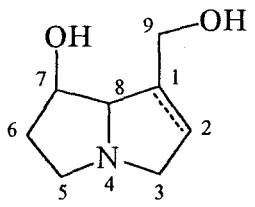
1 INTRODUCTION

The word alkaloid was first used to describe all organic bases, including the natural alkali-like substances which occur in plants. F. W. A. Serturner isolated the first alkaloid, morphine, in pure form from opium in 1816, and described it as "basic, salt-forming and ammonia-like." He used the term "organic alkali" from which the name alkaloid was derived.[1] A more modern and less rigid definition of alkaloids refers to naturally occuring, relatively complex, basic substances which exhibit some physiological action.[2]

Pyrrolizidine alkaloids are a class of alkaloids characterised by a bridged "dipyrrole-like"[3] structure **(1)**. It was not until the early 20th Century that interest developed in this particular class of compounds. They were linked to a series of poisonings in livestock and humans due to crops contaminated with alkaloid-containing *Senecio* plants.[3] Alkaloids, in general, have been used and abused for centuries as both medicinals and poisons.[1]



(1)



(2)

Following their ignominious discovery, pyrrolizidine alkaloids are commonly referred to as *Senecio* alkaloids. This can be somewhat misleading in that although 149 pyrrolizidine alkaloid containing *Senecio* species have been identified some 460 other species, distributed

among 110 genera of 19 plant families, have also been shown to contain pyrrolizidine alkaloids.[4] These plants may be found all over the world but mostly as members of botanical families such as the Compositae, Boraginaceae and Leguminosae (Table 1).

Senecio alkaloids have generally been isolated from plants although some have been detected in insects that are able to utilise the alkaloids, obtained in their diets, for defence or as pheromones.[3] *Senecio* alkaloids are reputed to be distasteful to vertebrate and invertebrate predators,[7] and some ant species produce their own alkaloids as defence mechanisms.[8]

On the whole, *Senecio* alkaloids are of considerable economic importance, both in South Africa and all over the world, due to their known hepatotoxicity and carcinogenicity to humans and grazing animals. Recently, medical interest in *Senecio* alkaloids has intensified as they are a human health hazard in herbal teas and medicines, honey and milk.[9] Concern has now arisen that even low levels (1-4 ppm) of some of these alkaloids can induce tumors.[10]

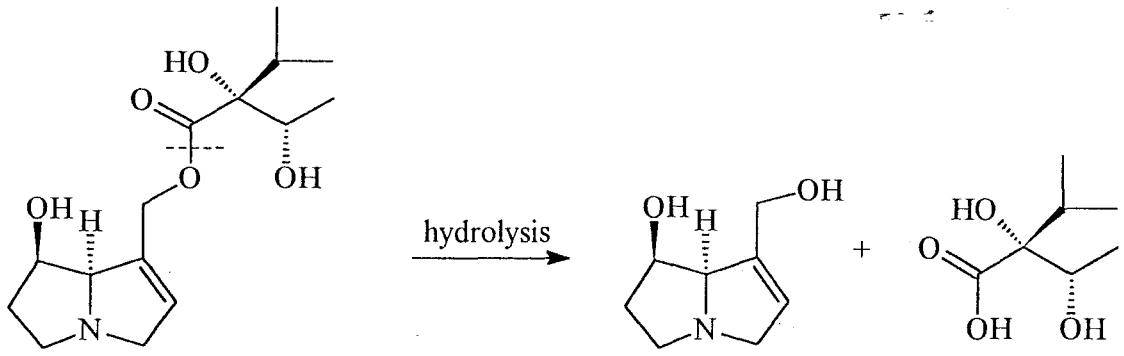
Most *Senecio* alkaloids consist of a dihydroxy "necine base", which may be unsaturated between carbons 1 and 2 **(2)**, and a necic acid, *e.g.*, indicine **(3)**, when hydrolysed, yields retronecine **(4)** and (-)-trachelanthic acid **(5)** (Scheme 1). Many of these alkaloids are mono- or diesters of the necine base; the latter frequently occur as macrocyclic diesters, *e.g.*, retrorsine **(6)**. Particular necine bases and necic acids may be obtained by hydrolysing the appropriate alkaloid ester. The necic acids are usually highly branched and oxygenated, and many of them are not found in any other plant or animal source, *e.g.*, integerrinecic acid **(7)**.

Table 1 Botanical distribution of *Senecio* alkaloids[4,5,6]

Family	Genus
Apocynaceae	*Alafia, Anodendron, Parsonia, Strophanthus, Tabernaemontana, Urechites*
Boraginaceae/ Ehretiaceae	*Alkanna, Amsinkia, Anchusa, Arnebia, Asperugo, Borago, Caccinia, Cerinthe, Cordia, Cryptantha, Cynoglossum, Echium, Ehretia, Hackelia, Heliotropium, Lappula, Lindelofia, Lithospermum, Macrotomia, Mertensia, Messerschmidia, Moltikiopsis, Myosotis, Neatostema, Omphalodes, Omosma, Paracaryum, Paracynoglossum, Rindera, Solenanthus, Symphytum, Tournefortia, Trachelanthus, Trichodesma, Turneforcia, Ulegbekia*
Celastraceae	*Bhesa*
Compositae/ Asteraceae	*Adenostyles, Ageratum, Arnica, Brachyglottis, Cacalia, Chersodoma, Chromolaena, Cirsium, Conoclinium, Crassocephalum, Doronicum, Echinaceae, Emilia, Erechtites, Eupatorium, Farfugium, Gynura, Homogyne, Jacmaia, Kleinia, Liatris, Ligularia, Nardosmia, Notonia, Packera, Petasites, Schismus, Senecio, Syneilesis, Tussilago, Werneria*
Convolvulaceae	*Ipomoea*
Elaeocarpaceae	*Aristotelia*
Euphorbiaceae	*Phyllanthus, Securinega*
Gramineae	*Festuca, Lolium, Thelepogon*
Leguminosae/ Fabaceae	*Adenocarpus, Alexa, Buchenroedera, Castanospermum, Crotalaria, Cytisus, Laburnum, Lotononis, Onosma*
Linaceae	*Hugonia*
Orchidaceae	*Chysis, Doritus, Hammarbya, Kingiella, Liparis, Malaxis, Phalaenopsis, Vanda, Vandopsis*
Papaveraceae	*Glaucium*
Ranunculaceae	*Caltha, Trollius*
Rhizophoraceae	*Cassiopourea*
Santalaceae	*Thesium*
Sapotaceae	*Mimusops, Planchonella*
Scrophulariaceae	*Castillega, Melampyrum, Pedicularis*

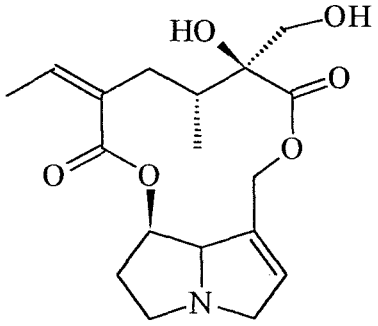
The challenge in necic acid synthesis lies in the highly branched and oxygenated nature of many of these acids. Usually, many stereoisomers are possible with only one being found to occur naturally, and this, not necessarily the most stable isomer.[8] The earlier syntheses of

necic acids involved the preparation of all possible stereoisomers in order to unambiguously determine the absolute configuration of the naturally occuring necic acid. More recent work on necic acid synthesis has involved highly stereospecific syntheses of predetermined products, where only one or two of the stereoisomers are targeted.



(3) **(4)** **(5)**

Scheme 1



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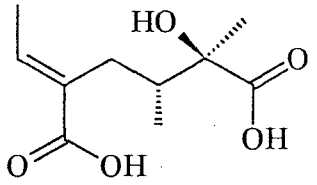


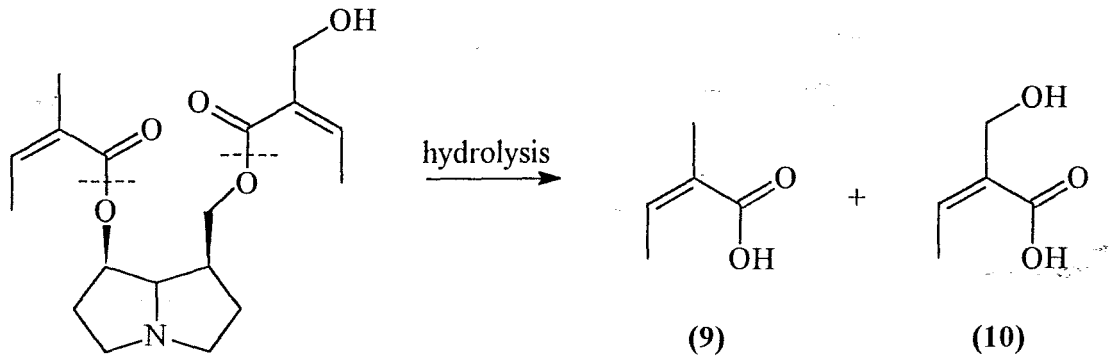
(7)

Necic acids exist as 5-, 6-, 7-, 8-, 9-, 10- and 11-carbon membered types, as well as glycosides of a selected few. Most exist as C-10 dicarboxylic acids present in macrocyclic diesters. The following review is an attempt to highlight interesting and common trends in the synthesis of some necic acids rather than provide an exhaustive treatment of an extensive literature.

1.1 Necic Acid Syntheses

1.1.1 C-5 Acids

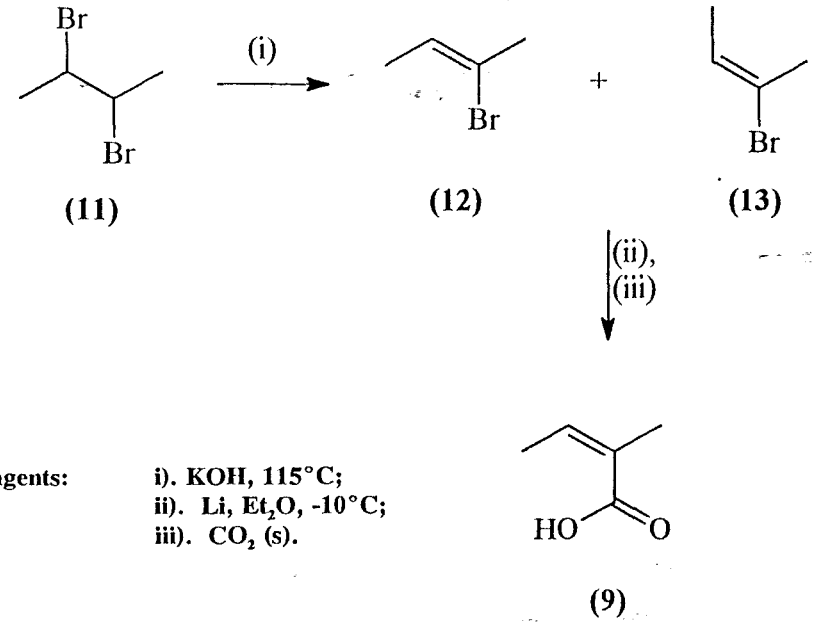
Angelic (**9**) and sarracinic acid (**10**) comprise the pentanecic acid moieties of the senecio alkaloid sarracine (**8**) (Scheme 2).[11] Tiglic acid,[12-14] is the more stable (*E*)-isomer of angelic acid and is typically utilised as the starting material in a conversion to angelic acid,[14] although stereoselective synthesis of angelic acid may be prefered.[15,16]



(**8**) (**9**) (**10**)

Scheme 2

Dreiding and Pratt[16] synthesised angelic acid (**9**) *via* carboxylation of the vinyllithium derivative obtained from (*E*)-2-bromo-2-butene. This method was found to be stereospecific (*E*:*Z*::91:9) and the conditions were mild, preventing isomerisation to the more stable tiglic acid (Scheme 3).

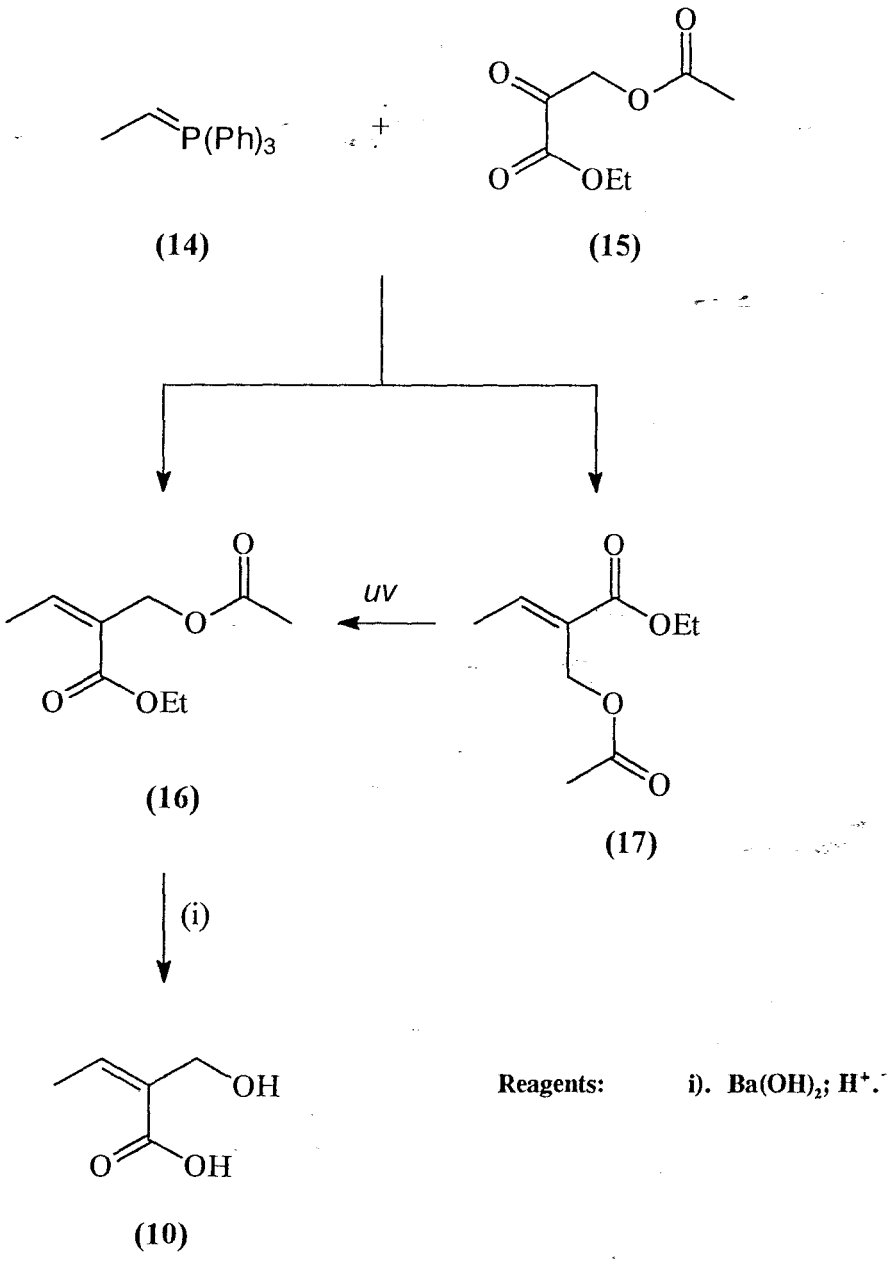


Scheme 3

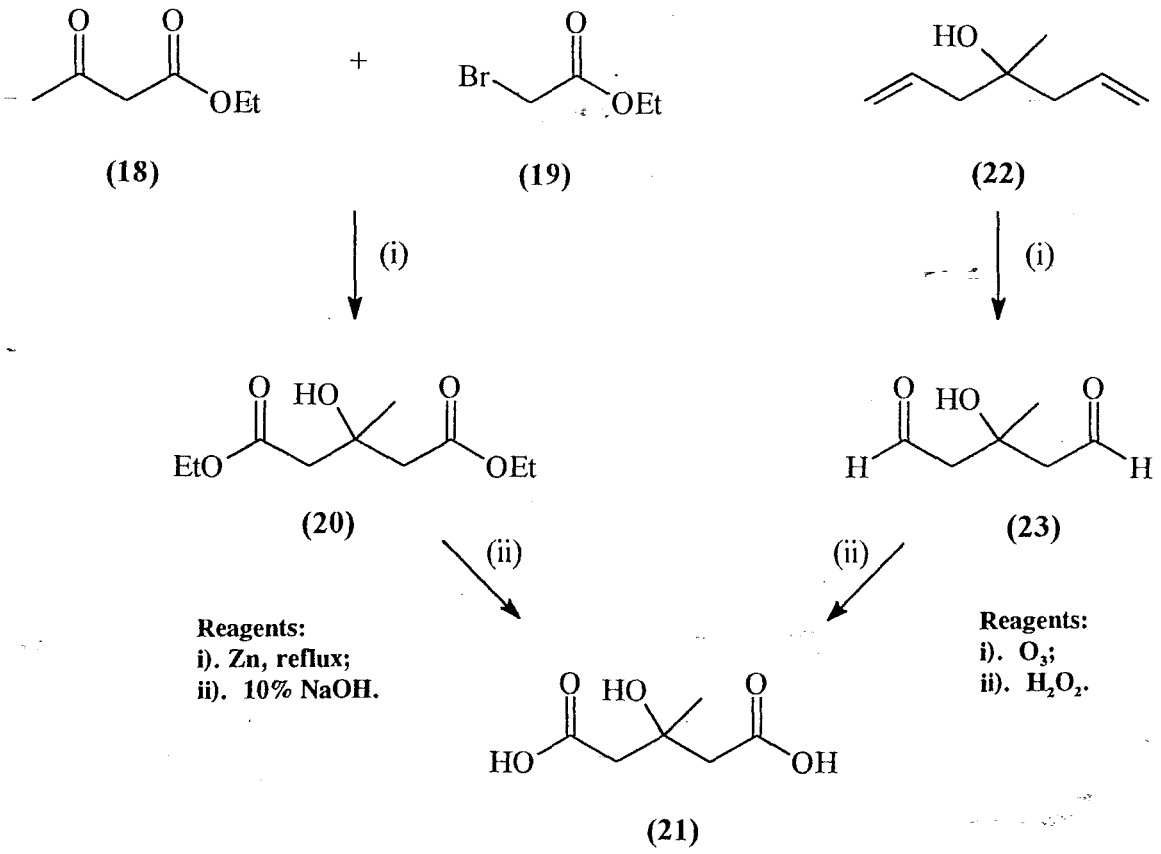
Sarracinic acid **(10)** was synthesised by Edwards, Matsumoto and Hase[17] (Scheme 4) using a highly reactive ylid **(14)** similar to that described by House and Rasmusson[13] in their synthesis of angelic and tiglic acid. Sarracinic acid was found to be analogous to angelic acid in being the (*Z*)-isomer.

1.1.2 C-6 Acids

Dicrotaline, from which dicrotalic acid **(21)** is obtained by hydrolysis, was isolated from *Crotalaria dura* and *Crotalaria globifera*.[18] Adams and Van Duuren[19] followed the method of Nieuland and Daly[20] and synthesised dicrotalic acid from ethyl acetoacetate **(18)** and ethyl bromoacetate **(19)** as shown in Scheme 5, while Brown, Devlin and Robins[21] followed the method of Klosterman and Smith[22] by starting from diallylmethylcarbinol **(22)** (Scheme 5).

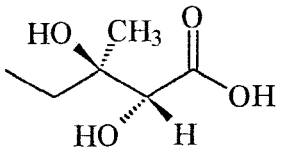


Scheme 4



Scheme 5

2,3-Dihydroxy-3-methylpentanoic acid **(24)**, the necic acid component of strigosine, and all its isomers were synthesised by Crout and Whitehouse[23] by dihydroxylating unsaturated precursors using various oxidising agents, including $KMnO_4$, OsO_4 and WO_3/H_2O_2.



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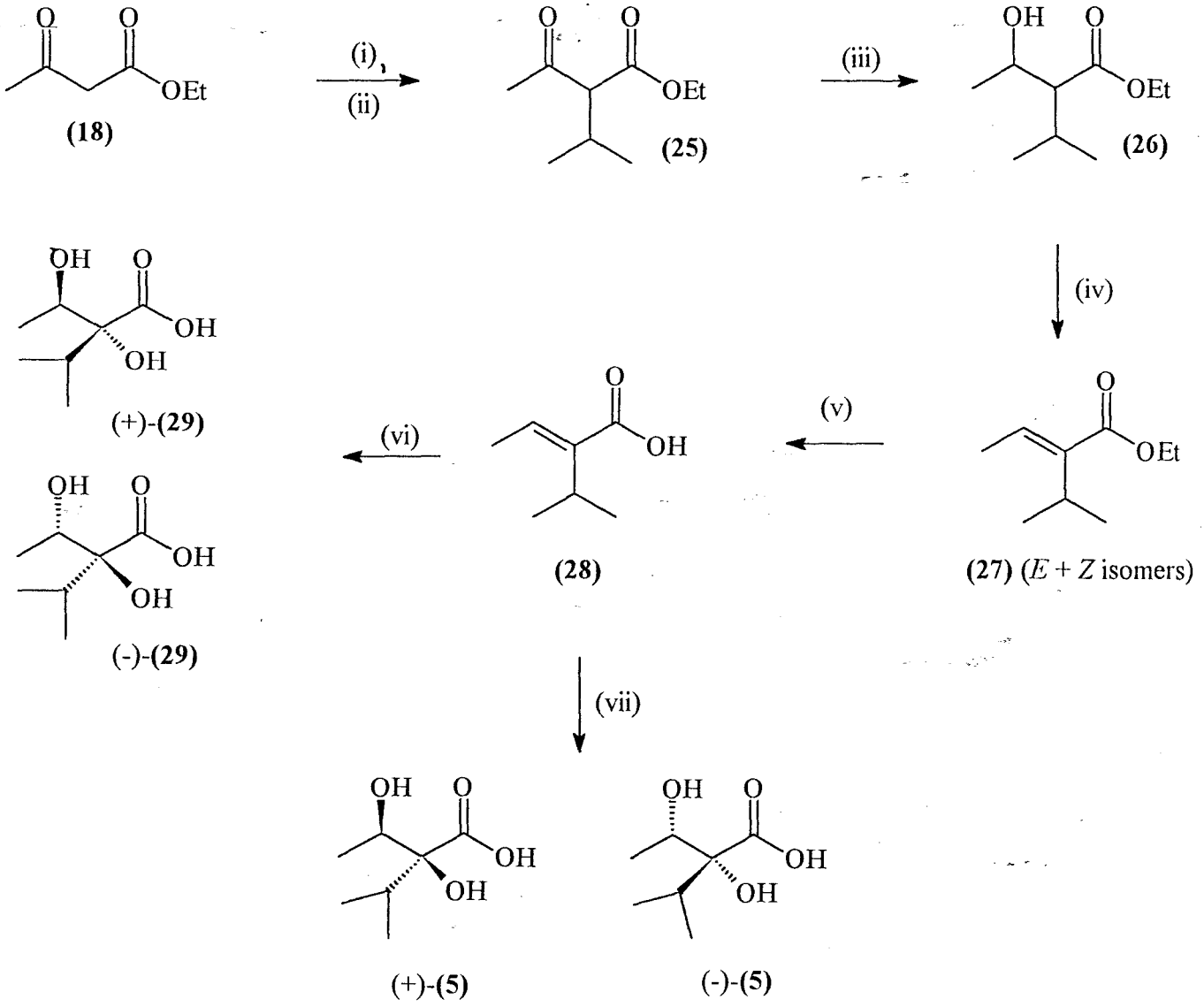
1.1.3 C-7 Acids

Trachelanthic **(5)** and viridifloric **(29)** acid are common necic acids and are found in many *Senecio* alkaloids, which differ only in the necine base. Initial work on these acids was directed towards the resolution of the enantiomers obtained using diastereoselective dihydroxylation reagents,[9,24-27] and is illustrated by the reactions of (*E*)-2-isopropylcrotonic acid **(28)** reported by Kotchetkov *et al.*[27] and shown in Scheme 6.

Niwa *et al.* decided to use a starting material and fix, with known stereochemistry, one hydroxy group and then introduce the other hydroxy group stereospecifically.[28-30] This involved the coupling of acetaldehyde to the enolate of the readily accessible, homochiral lactone **(30)** to form (-)-trachelanthic **(5)** and (+)-viridifloric **(29)** acids (Scheme 7).

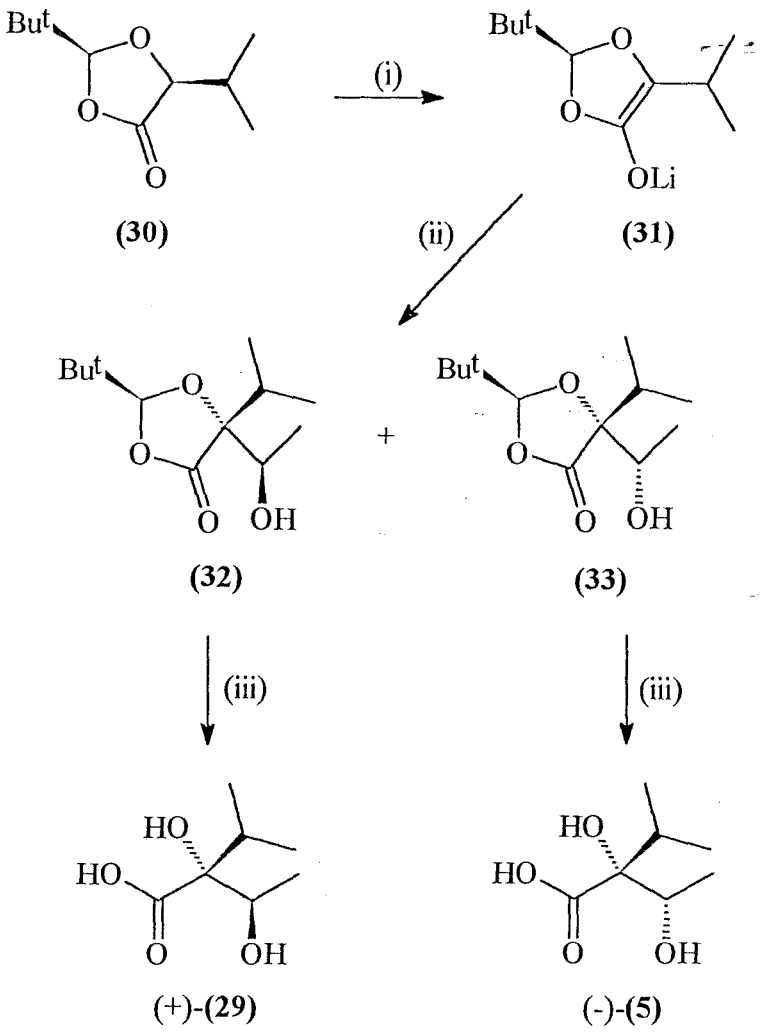
A novel synthesis of 1,2-diols was explored by Sato, Kato, Gokyu and Fujisawa[31] and extended to the synthesis of (-)-trachelanthic acid **(5)**. 1,2-Asymmetric induction by the nucleophilic addition of organometallics to chiral α-alkoxycarbonyl compounds was efficiently utilised in their synthesis of the 1,2-diols (Scheme 8).

Latifolic acid, another C-7 acid and present in latifoline,[32] was synthesised by Matsumoto, Okabe and Fukui.[33] All stereoisomers were synthesised from dimethyl 1-acetyl-2-methyl-succinate **(39)** in order to establish the configuration of naturally occuring latifolic acid **(47)** (Scheme 9).



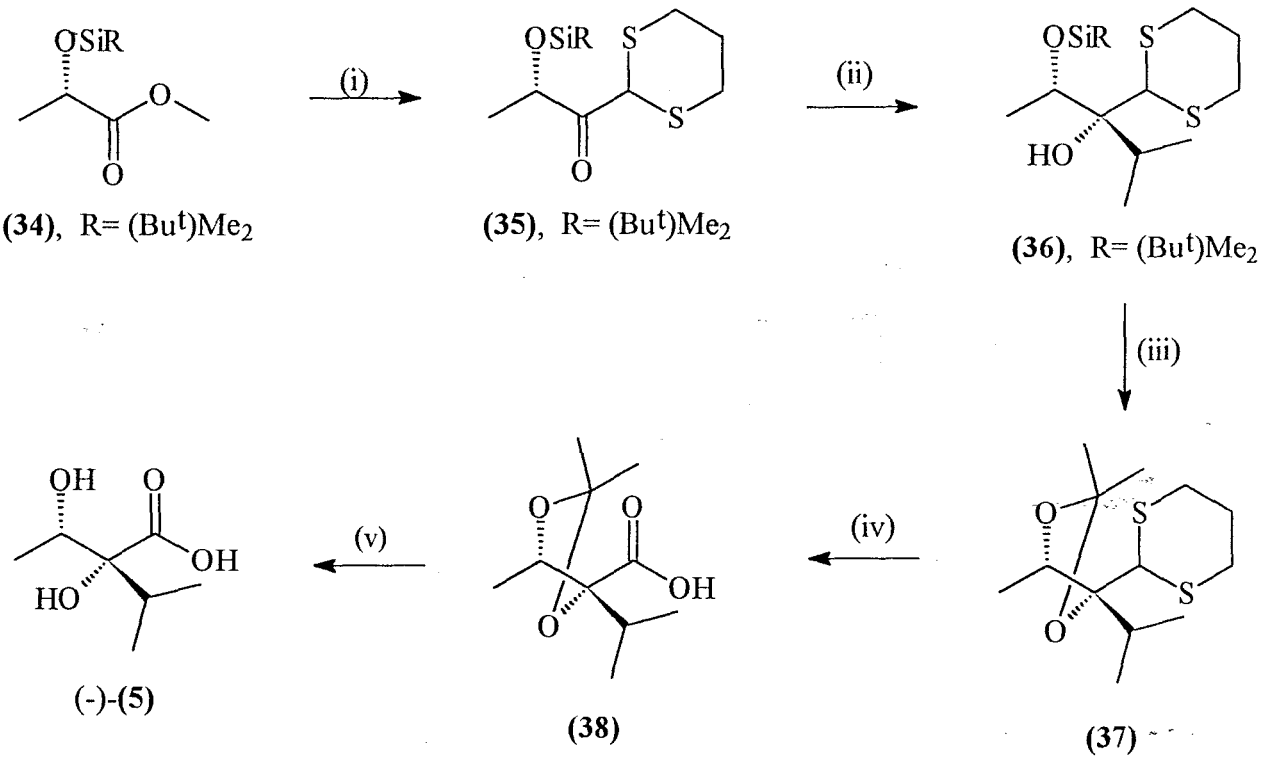
Reagents: **i). NaH, EtOH; ii). Pr^iBr; iii). Raney Ni, 1800psi, 100°C; iv). P_2O_5, benzene; v). KOH; vi). WO_3, 30% H_2O_2; vii). OsO_4, chloric acid.**

Scheme 6



Reagents: **i). LDA, THF, -100°C, 1h; ii). Acetaldehyde, -100°C; iii). 1M HCl, reflux, 3h.**

Scheme 7

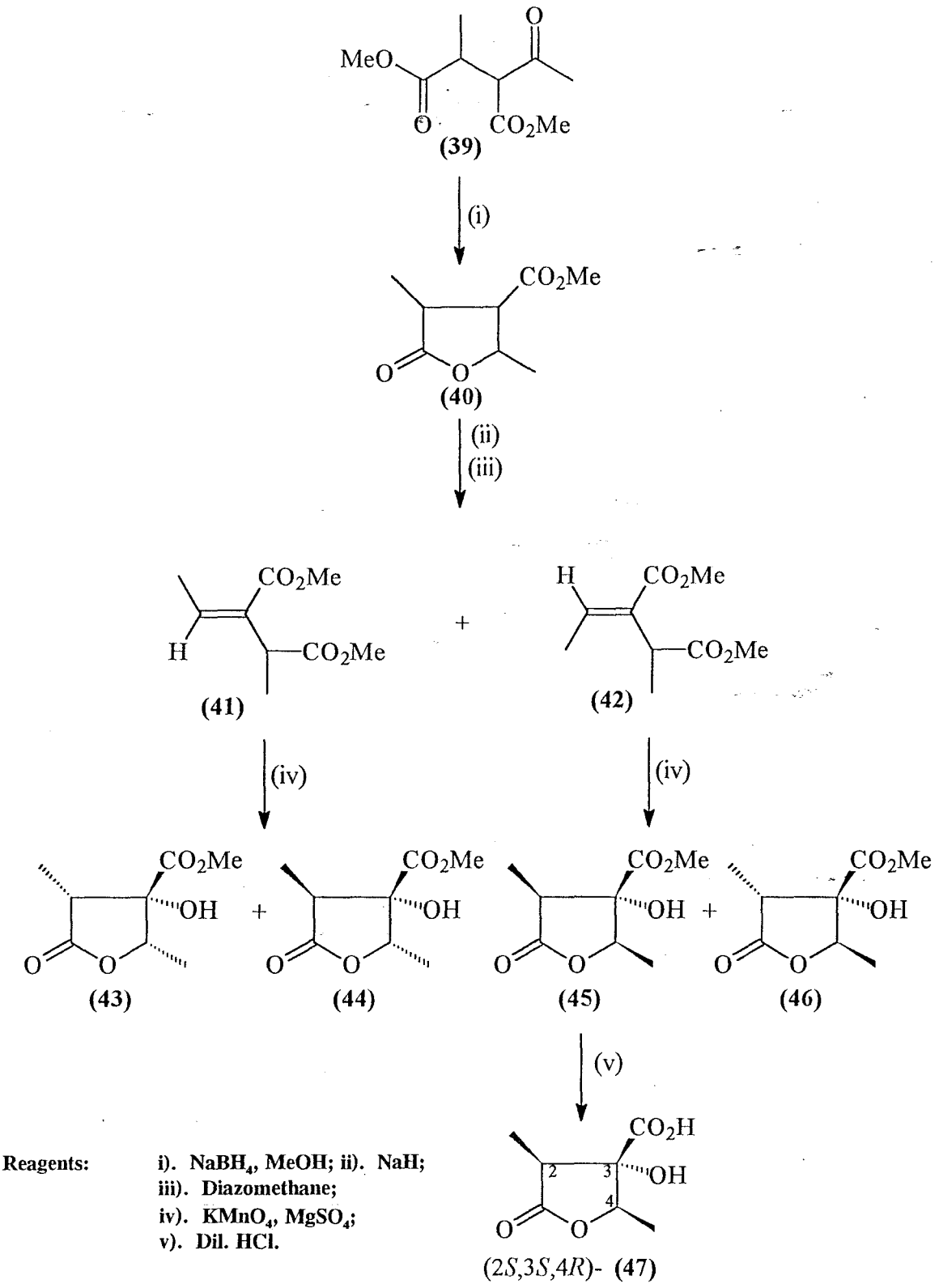


(34), R= $(Bu^t)Me_2$ **(35)**, R= $(Bu^t)Me_2$ **(36)**, R= $(Bu^t)Me_2$

(37) **(38)** (-)-(5)

Reagents: **i). 2-Lithio-1,3-dithiane, THF, -90 to -30°C, 3h; ii). $LiPr^i$, Et_2O; iii). HF, 2,2-dimethoxypropane; iv). Pyridinium dichromate; v). F_3CCO_2H.**

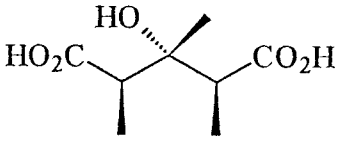
Scheme 8


MeO
O
O
CO2Me
(39)
(i)
CO2Me
O
O
(40)
(ii)
(iii)
CO2Me
H
CO2Me
(41)
+
H
CO2Me
CO2Me
(42)
(iv)
(iv)
CO2Me
OH
O
O
(43)
+
CO2Me
OH
O
O
(44)
CO2Me
OH
O
O
(45)
+
CO2Me
OH
O
O
(46)
(v)
CO2H
2
3
OH
4
O
O
(2S,3S,4R)- (47)
Reagents:
i). NaBH4, MeOH; ii). NaH;
iii). Diazomethane;
iv). KMnO4, MgSO4;
v). Dil. HCl.

Scheme 9

1.1.4 C-8 Acids

The C-8 necic acids consist of the isomers fulvinic **(48)** and crispatic acid **(49)** (isolated as the alkaloid esters fulvine and crispatine respectively, from *Crotalaria* plants[34]) and monocrotalic acid. Monocrotalic acid is obtained from the hydrolysis of monocrotaline, which is also extracted from various *Crotalaria* species.[35] Matsumoto *et al.*[36] set out to synthesise all stereoisomers of monocrotalic acid in order to establish the stereochemistry of the naturally occuring acid. This was accomplished by comparison of the γ-lactone of monocrotalic acid **(50)** with the synthetic analogues.



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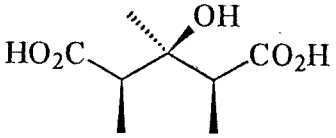

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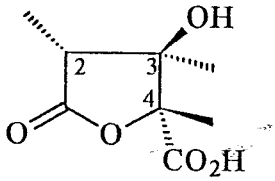
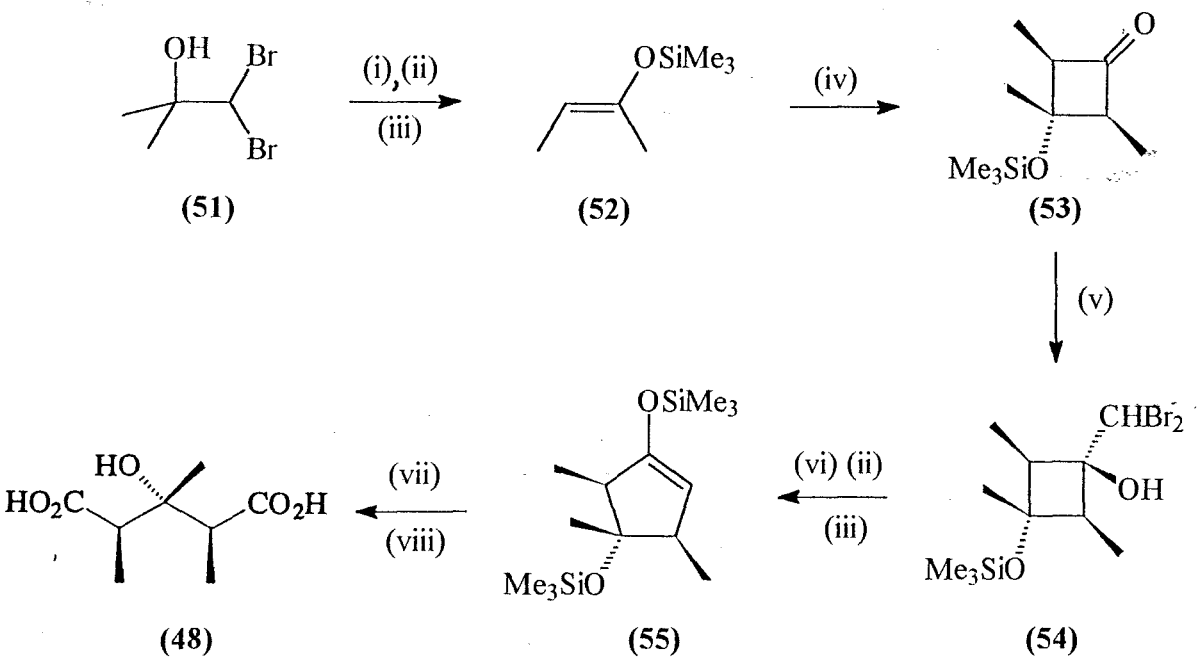


(2*R*,3*R*,4*R*)-**(50)**

This work was followed by the stereospecific synthesis of naturally occuring monocrotalic acid by Niwa *et al.*[37] and Honda *et al.*[38] Each route employed more than 12 steps, resulting in low overall yields. Ingenuity and an impressive array of stereospecific reactants and reagents were used to obtain the monocrotalic acid. Niwa *et al.*[37] started with a fixed hydroxy stereochemistry and introduced the desired (*R*)-configuration at C-2, whereas Honda *et al.*[38] relied on the established *cis*-dihydroxylation using osmium tetroxide to introduce the (*R*)-configurations at C-3 and C-4.

All six possible stereoisomers (including 2 *meso* forms) of fulvinic **(48)** and crispatic acid **(49)** were synthesised by Matsumoto *et al.*[39]. The naturally occuring acids were found to be optically inactive[34] and were thus assigned the *meso* structures **(48)** and **(49)**. The Reformatsky reaction[20,40] was utilised in the synthesis of the acids. This method proved to be non-selective and required purification *via* repeated column chromatography on silica gel to separate the isomers. Vedejs and Larsen[41] decided that this approach was impractical and proposed a new synthesis of fulvinic acid using organometallic and organosilicon reagents (Scheme 10). Features of general interest include the synthesis of the thermodynamically unstable **(52)** followed by the selective cycloaddition of methyl ketene to **(52)**.



Reagents: **i). 2 eq. BuLi, -78°C; ii). -45°C; iii). Me_3SiCl; iv). Methyl ketene; v). CH_2Br_2, LDA; vi). BuLi, -78°C; vii). O_3; viii). HCO_3H.**

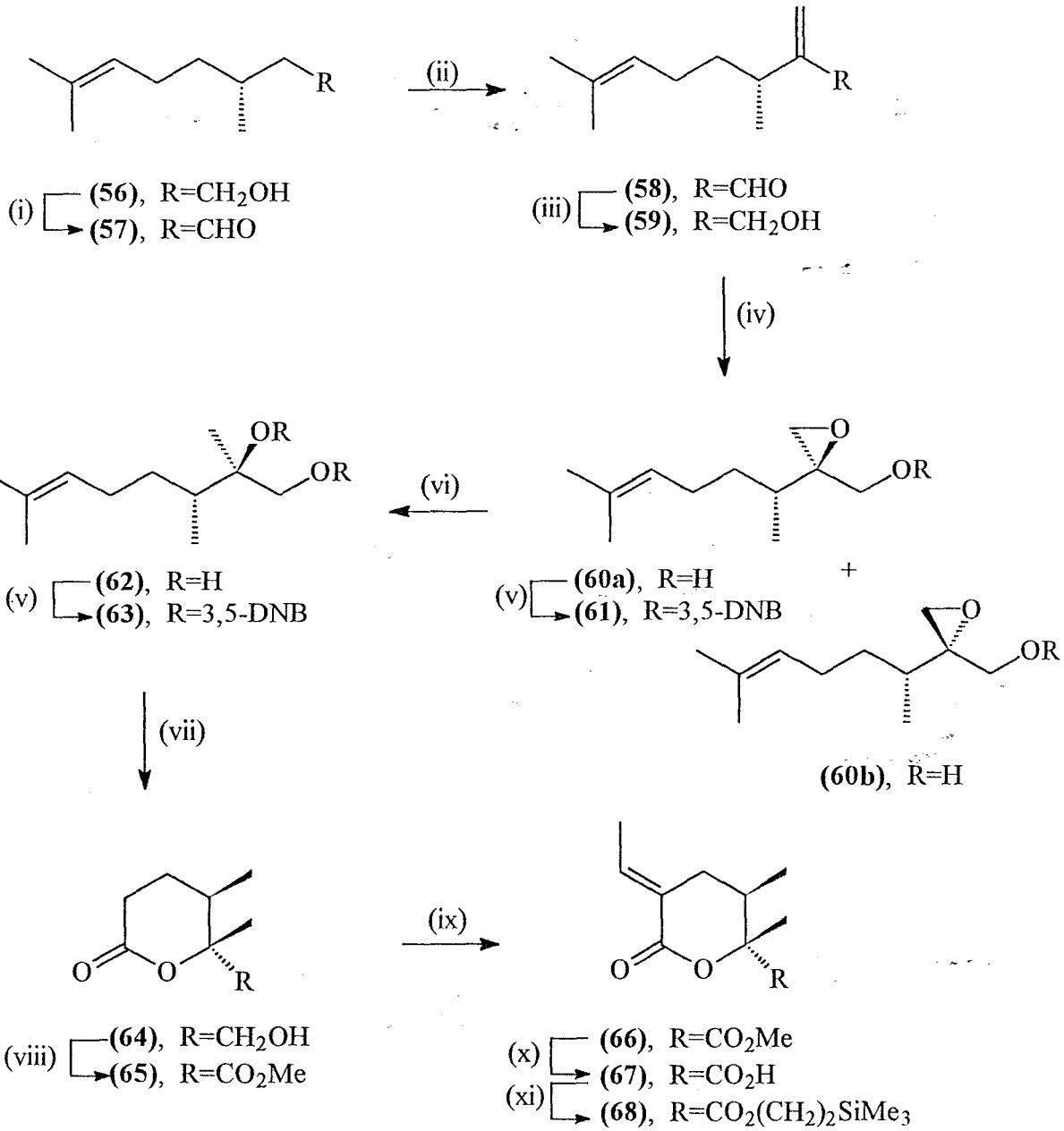
Scheme 10

1.1.5 C-10 Acids

The greatest *Senecio* alkaloid toxicity is shown by macrocyclic dilactonic alkaloids[42] containing C-10 acids. It is therefore not surprising that numerous syntheses have been developed for C-10 necic acids as precursors in total alkaloid synthesis.

The necic acids isolated from (-)-integerrimine,[43-45] (+)-usaramine[45,46] and nemorensine[47] were all synthesised starting from (*R*)-(+)-β-citronellol **(56)**. White *et al.*[43-47] found this to be a valuable synthon for the introduction of new stereogenic centres and the functionality required in the target acids. The preparation of (+)-interriginecic acid, in protected form **(69)**,[43] illustrates the synthetic dexterity of White et al. and the utility of (*R*)-(+)-β-citronellol (Scheme 11).

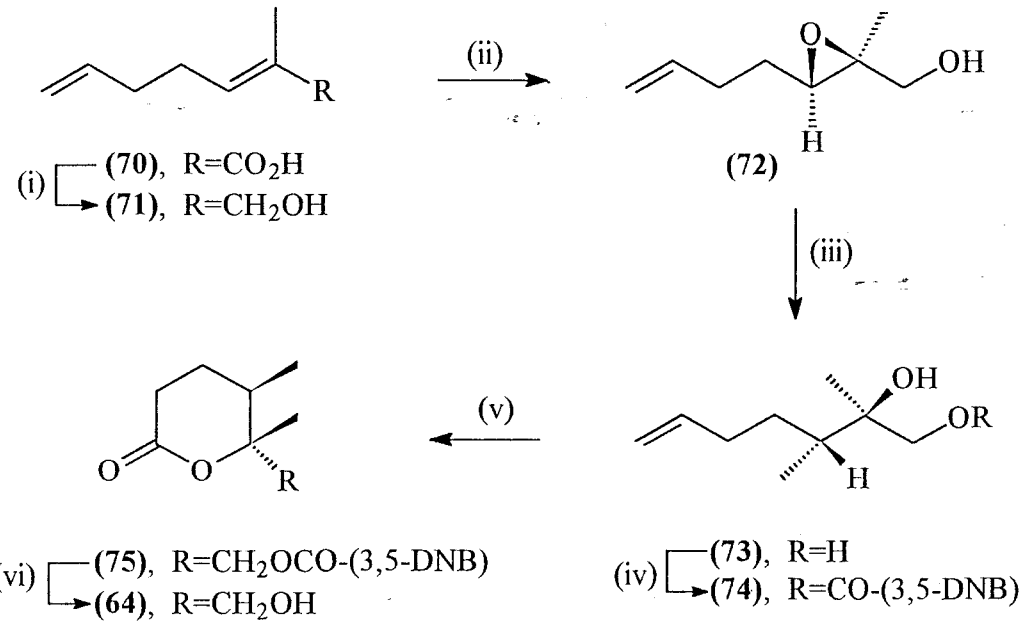
Narasaka *et al.* chose to start from 2-methyl-2-cyclopentenone in their quest for integerrinecic acid;[48-50] whereas Niwa *et al.* preferred (*E*)-2-methylhepta-2,6-dienoic acid **(70)** as starting material (Scheme 12).[42,51,52] Reduction, followed by Sharpless asymmetric epoxidation[53] gave an epoxide **(72)** which underwent stereospecific and regioselective ring opening with trimethylaluminium, to furnish the 1,2-diol **(73)**. The diol was protected and the terminal alkene was cleaved with $RuCl_3$-$NaIO_4$. Treatment with *p*-toluenesulphonic acid afforded the lactone **(75)** which yielded the lactone alcohol **(64)** after methanolysis. Subsequent oxidation, alkylation and hydrolysis, gave the desired integerrinecic acid **(7)** as the *o*-(methylthio)methyl protected ether; the protecting group being chosen for its ease of application, stability and ease of removal.



Reagents:

i). Pyridinium chlorochromate;
ii). CH_2=NMe_2I, LDA, MeI, $NaHCO_3$;
iii). $NaBH_4$, $CeCl_3$;
iv). Cumene hydroperoxide, diisopropyl (-)-tartrate, $Ti(OPr^i)_4$;
v). $3,5\text{-}(NO_2)_2C_6H_3COCl$, DMAP;
vi). $LiAlH_4$;
vii). $RuCl_3$, $NaIO_4$, K_2CO_3, 5% HCl;
viii). $RuCl_3$, H_5IO_6, CH_2N_2;
ix). Acetaldehyde, LDA, HMPA;
x). LiOH, 0°C;
xi). $Me_3Si(CH_2)_2OH$, 2-chloro-1-methylpyridinium iodide;
xii). LiOH, H_2O_2;
xiii). $Me_2(Bu^t)SiOSO_2CF_3$, 2,6-lutidine, 0°C.

Scheme 11



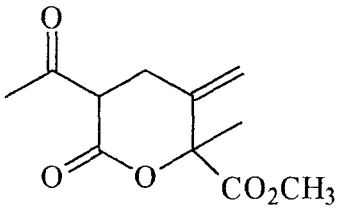
Reagents: **i). $LiAlH_4$; ii). Bu^tOOH, (+)-DET, $Ti(OPr^i)_4$, -25°C; iii). $AlMe_3$, 0°C; iv). $3,5\text{-}(NO_2)_2C_6H_3COCl$, 0°C; v). $RuCl_3$, $NaIO_4$, *p*-TsOH; vi). NaOMe.**

Scheme 12

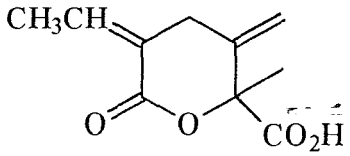
Culvenor and Geissman synthesised integerrinecic acid as the lactone and photochemically isomerised it to senecic acid lactone,[54] while Lee, Jackson and Wiemer used the Horner-Wadsworth-Emmons condensation of α-phosphono lactones with acetaldehyde or propionaldehyde to give predominantly either integerrinecic acid or senecic acid lactone, depending on the conditions.[55]

During the synthesis of senecic and integerrinecic acid, Edwards *et al.*[56] discovered that the intermediate, dimethyl 5-acetyl-2-hydroxy-2-methyl-3-methylenehexanedioate could be used as its γ-lactone **(76)**, to synthesise seneciphyllic acid **(77)**.[57] The acids were not resolved but

were isolated as the *racemic*-lactones.

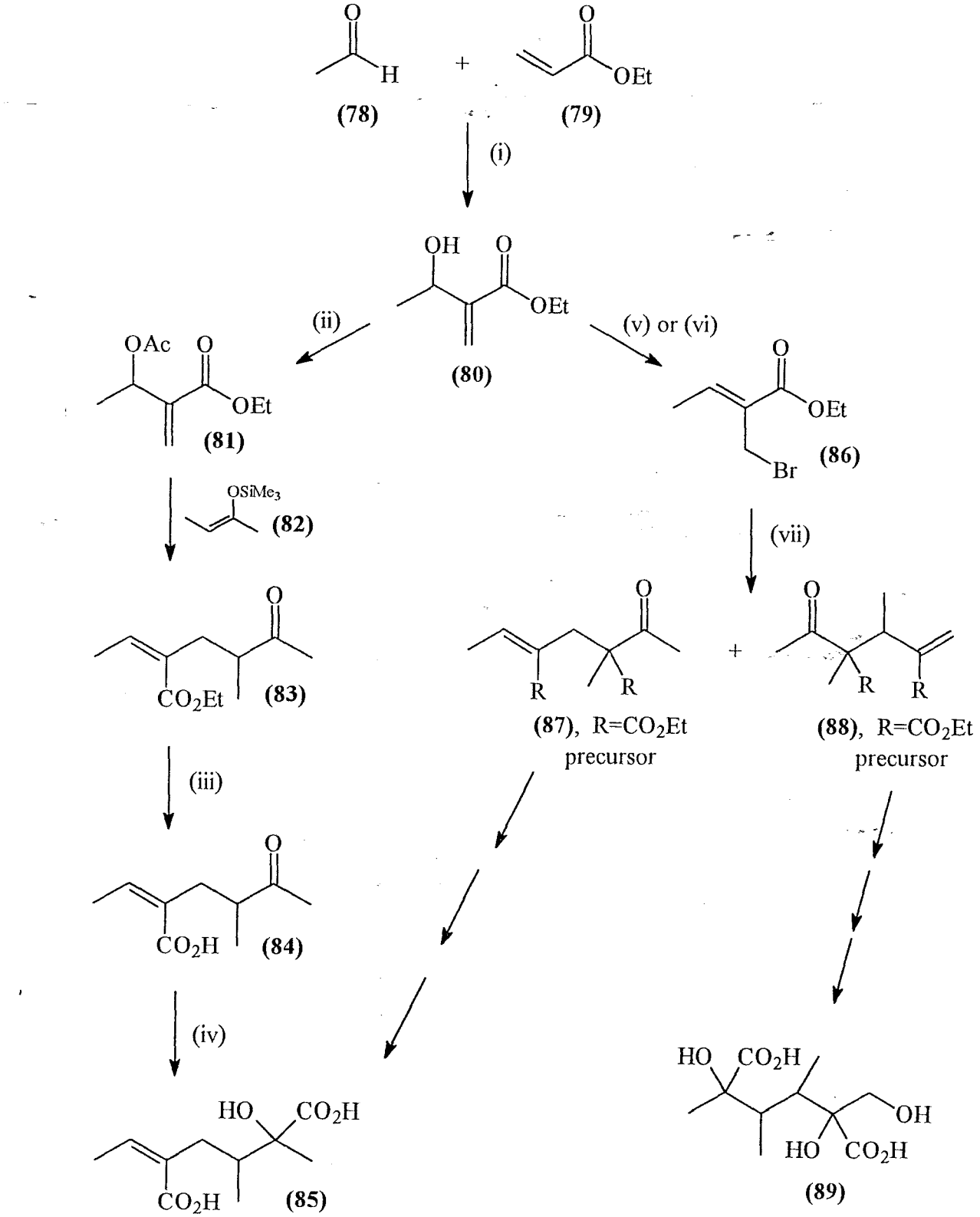


(76)



(77)

Drewes and Emslie achieved a convenient five step synthesis of racemic integerrinecic acid **(85)** from ethyl acrylate **(79)**.[58] The β-hydroxy ester **(80)** was obtained *via* the DABCO catalysed coupling of acetaldehyde **(78)** and ethyl acrylate **(79)** (Scheme 13). The hydroxy ester was be converted to the allylic bromo ester **(86)** utilising either of two methods. The acetylated hydroxy and bromo esters, **(81)** and **(86)** respectively, contain an allylic leaving group making them susceptible to nucleophilic substitution at the allylic position (S_N) or at the vinylic position followed by rearrangement (S_N'). These possibilities were investigated further[59-64] since many necic acids or precursors may be synthesised by varying the regioselectivity of the nucleophilic displacement, *viz.*, sceleranecic acid **(89)**,[58] retronecic acid[59,60] and senecivernecic acid.[59]

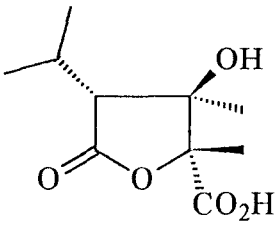


Scheme 13

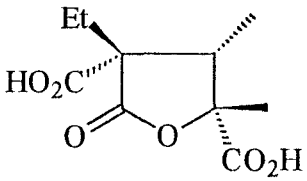
Reagents: **i). DABCO; ii). Ac_2O; iii). KOH, HCl; iv). NaCN, H_2SO_4; v). H_2SO_4, HBr; vi). NBS, Me_2S; vii). $MeCOCH(Me)CO_2Et$.**

Axillaridine was isolated from the seeds of *Crotalaria axillaris* Ait by Crout in 1969.[65] All stereoisomers of the necic acid component were synthesised by Matsumoto *et al.*[66] utilising a phosphorane to obtain the skeleton of the structure. This approach was similar to the methods employed by Edwards *et al.*[17] and House *et al.*[13] in the synthesis of C-5 acids.

Edwards and Matsumoto synthesised trichodesmic acid lactone,[67] which had been isolated from trichodesmine[68], *via* stereospecific dihydroxylation using osmium tetroxide and confirmed the stereochemistry of the naturally occuring acid to be as shown in structure **(90)**. Kiyooka, Hase and Edwards synthesised retusaminic acid[69] and resolved the diastereomers to assign structure **(91)** to the lactone of the naturally occuring acid.

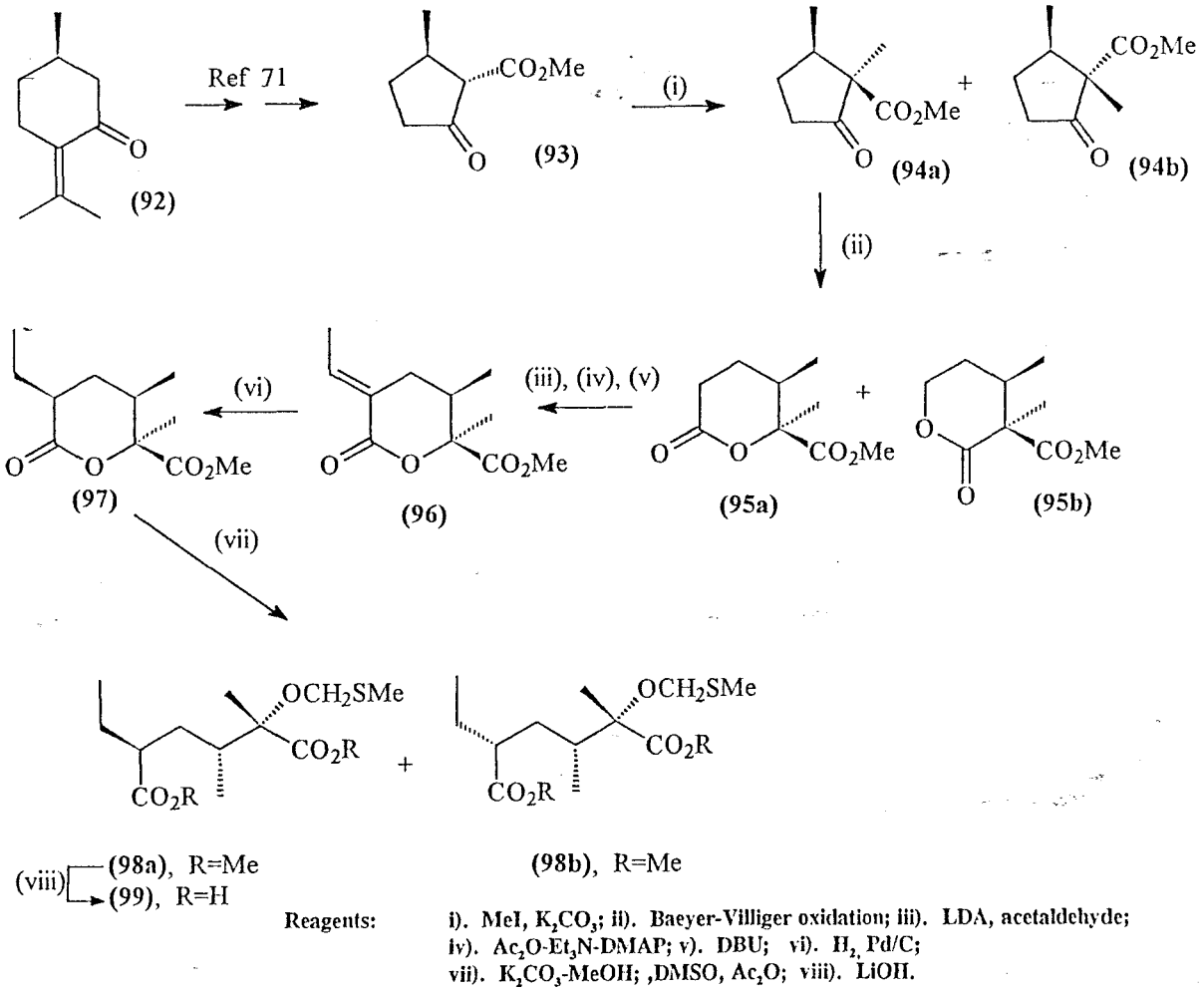


(90)



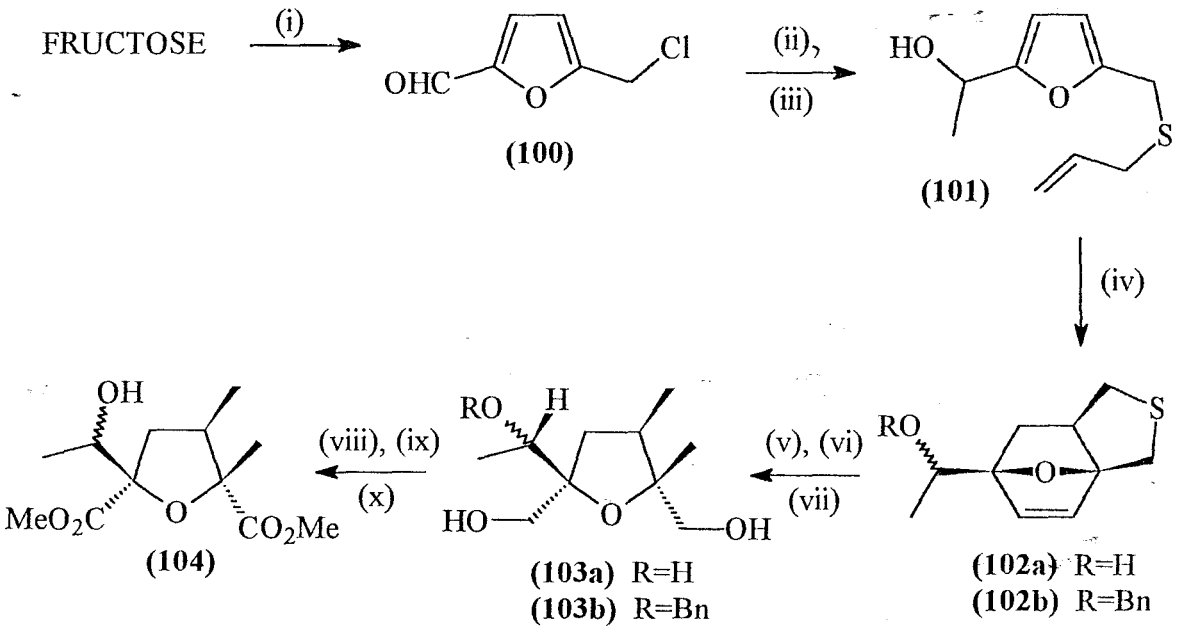
(91)

Niwa *et al.* set out to synthesise yamataimine[70] which required generation of the known necic acid derivative **(99)** (Scheme 14). Readily available (*R*)-(+)-pulegone **(92)** was converted to the intermediate **(93)**, which was alkylated and oxidised to the required lactone **(95a)**. A three-step sequence afforded compound **(96)** which was then subjected to catalytic hydrogenation to yield the lactone **(97)** as the sole product. Ring opening with DMSO followed by base hydrolysis provided the acid derivative **(99)**.



Scheme 14

Röder *et al.*[72] synthesised nemorensic acid in the open-chain form starting from 3-methyl-2-butenoic acid, while Klein and Shanklin made use of an intramolecular cycloaddition of a furfuryl allyl sulphide **(101)** to synthesise (±)-nemorensic acid[73] and the dimethyl ester of (±)-jaconecic acid **(104)** (Scheme 15).[74] The synthesis proceeds *via* a substituted tetrahydrofuran intermediate, followed by elimination of sulphur and hydrogenation to obtain the required carbon skeleton.



Reagents: i). $MgCl_2$, HCl; ii). $HSCH_2CH{=}CH_2$, Et_3N; iii). CH_3Li; iv). Δ; v). BnBr, NaH, Bu_4NI; vi). O_3, $NaBH_4$; vii). Raney Ni, viii). Jones oxidation; ix). CH_2N_2; x). H_2, Pd.

Scheme 15

1.2 Nucleophilic Reactions of α,ß-Unsaturated Carbonyl Systems

1.2.1 Nucleophilic Addition

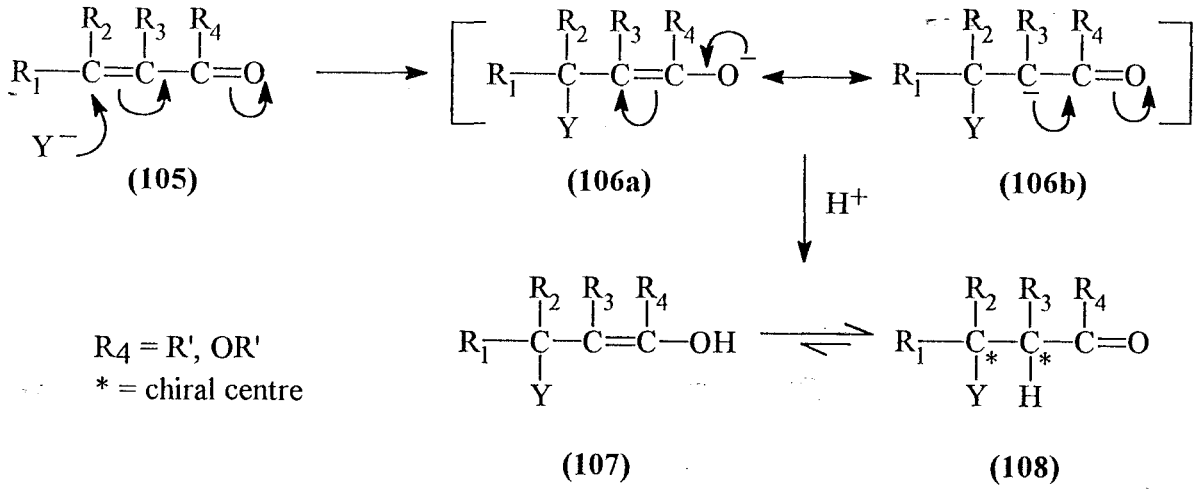
Nucleophilic addition to α,ß-unsaturated aldehydes, ketones and related compounds may involve attack at the carbonyl carbon (1,2-addition) or attack at the alkene double bond (1,4-addition or conjugate addition). Conjugate addition, in which the attacking nucleophile is a carbanion, is specifically referred to as a Michael reaction.[75,76]

1.2.1.1 The Michael Reaction

The synthetic importance of the Michael addition lies in its use as a stepping-up reaction. It is usually base-catalysed (to generate the carbanion) and reversible, and the rate determining step (RDS) is believed to involve the formation of the carbon-carbon bond (Scheme 16).[76] Nucleophilic reagents do not normally attack C-C double bonds unless adjacent functionalities (usually electron withdrawing) enhance the nucleophilicity of the double bond *e.g.* CHO > COR > CO_2R > CN > NO_2.[76] This enhancement of the double bond reactivity is not surprising as nucleophilic attack must result in a resonance-stabilised enolate anion, the carbonyl functionality most commonly activating alkenes for nucleophilic attack. Competing reactions may arise and 1,2-addition (to the C=O or C≡N group) may predominate.

Traditionally, the Michael reaction has been limited to protic solvents with catalytic amounts of base. This is no longer the case where better yields with fewer side reactions may be obtained using an equimolar amount of base to generate a preformed enolate. The

stereoselectivity of the reaction is also enhanced.[77] The Michael reaction yields two new chiral centres (*) with suitably substituted reactants (Scheme 16) and the products may thus comprise two pairs of enantiomers.



Scheme 16

Diastereoselectivity requires that the process afford one of the enantiomeric pairs exclusively or predominantly, as a racemic mixture. Enantioselectivity (predominant formation of one of the four possible diastereomers) may be attained when one or both components are chiral, as well as by using a chiral catalyst.[77]

Michael reactions may also be applied to α,ß-unsaturated alkyne systems and due to their greater susceptibility to nucleophilic attack, non-activated alkynes may also act as substrates in this reaction.[77] In closely related $TiCl_4$-catalysed reactions, silyl enol ethers and allylic silanes (Sakurai reaction[78]) add to α,ß-unsaturated ketones and esters.

1.2.2 Nucleophilic Substitution Reactions

Nucleophilic substitution reactions are ionic or polar reactions which involve the displacement of a leaving group (X) in alkyl derivatives (RX) by nucleophilic reagents (Y:). Alkyl halides are the chief substrates involved in S_N reactions although derivatives such as alcohols, ethers and esters are also important. The reactivity of a substrate RX to substitution by a nucleophile Y: depends upon the nature of R, X and Y as well as the solvent used.

1.2.2.1 S_N Mechanisms

There are two main types of S_N mechanism and these differ in the sequence of bond breaking and bond making, *viz.* S_N1 and S_N2. In the S_N1 mechanism the reaction is a two step process involving:- (i) slow unimolecular dissociation of RX to form R^+ and (ii) a fast reaction between R^+ and Y:. In the S_N2 mechanism attack of Y: at the carbon occurs simultaneously with the loss of X^- in a one-step, bimolecular process.[79]

1.2.2.2 Nucleophilic Substitution in Allylic Systems

Allylic substrates may undergo direct displacement of the leaving group (S_N) or displacement with allylic rearrangement (S_N') (Figure 1). The unimolecular process (S_N1') involves distinctly separate ion pairs although they do not usually exist in that form. It is assumed that the leaving group X^- remains close to the carbon from which it left, thereby increasing its electrophilicity and susceptibility to nucleophilic attack. A product spread results favouring the starting arrangement due to the presence of the leaving group. An increase in solvent polarity may decrease and even eliminate the product spread by solubilizing the X^- and

removing its influence on the allylic cation.[80]

Allylic substitution may also proceed *via* a bimolecular (S_N2') mechanism both under normal S_N2 conditions as well as when the normal mode of attack is sterically hindered. An increase in nucleophile size may also favour an S_N2' over S_N2 mechanism. In S_N2' reactions, nucleophiles tend to favour attack from the *syn* side (Y: enters side that X^- departs) resulting in a predictable stereochemistry for the products.[80] There is evidence for and against a true S_N2' mechanism (concerted movement of 3 pairs of electrons) and Bordwell[81] contends that the sequence is not necessarily concerted.

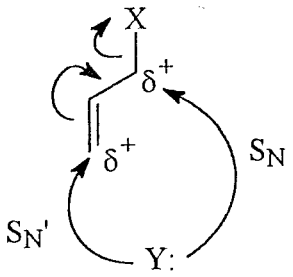


Figure 1

1.2.2.3 Solvent Effects

Solvents may have a marked effect on the rate and/or mechanism of S_N reactions. An increase in the polarity of the solvent and/or its ion-solvating ability may greatly increase the rate of an S_N1 reaction. This aids (stabilises) the formation of the R^+ and X^- ions in the RDS. An

increase in solvent polarity may also aid a change in reaction mechanism from S_N2 to S_N1.

S_N2 reaction rates may be increased by limiting the H-bonded solvation of the nucleophile in polar hydroxylic solvents. Polar non-hydroxylic solvents such as DMF and DMSO decrease the solvation strength and increase the reaction rate by inducing a more powerful and effective nucleophile. This may also have the desired effect of changing a reaction mechanism from S_N1 to S_N2.

1.2.2.4 The Entering Nucleophile (Y:)

The attacking nucleophile does not directly influence the rate of an S_N1 reaction as it is not involved in the RDS. In S_N2 reactions, however, the strength of the nucleophile plays a large role in the rate of the reaction. The stronger the nucleophile the faster the reaction (see solvent effects). Nucleophilicity is affected by a number of factors including steric effects. Soft bases (low electronegativity, high polarisability and easily oxidised), such as RS^-, I^- and SCN^-, promote nucleophilicity for a given degree of basicity. In general, however, the stronger the base the more powerful the nucleophile: $EtO^- > PhO^- > MeCO_2^-$.[82]

Mechanisms may be predetermined according to which nucleophile is used, *e.g.*, S_N1 with H_2O: may become S_N2 with OH^-. The size and electronegativity govern the polarisability and hence nucleophilicity of the attacking atom in the nucleophile,

e.g., $I^- > Br^- > Cl^-$ and $RS^- > RO^-$.[82]

1.2.2.5 The Leaving Group (X)

The leaving group has a profound effect on the rate of both S_N1 and S_N2 reactions as the breaking of the R-X bond is involved in the RDS of both. The breaking of the R-X bond is influenced by:- (i) the R-X bond strength; (ii) polarisation of the bond; (iii) stability of X^-; and (iv) the degree of stabilisation, through solvation, of the incipient anion X^- in the transition state for either S_N1 or S_N2 reactions.

In general, the weaker X^- is as a base, the better it will be as a leaving group, *e.g.* I^- is a good entering and leaving group whereas stronger bases (as leaving groups) are more difficult to displace, *e.g.*, HO^-, RO^- and H_2N^-. Modification of the leaving group, by protonation for example, may encourage displacements that are normally difficult or impossible.[82]

1.3 PREVIOUS RESEARCH AND AIMS OF THE PRESENT INVESTIGATION

The synthesis of *Senecio* alkaloids continues to recieve attention, and a key step in such syntheses is typically the esterification of the hydroxylated necine base with various necic acids to afford monoester-, diester- and macrocyclic diester alkaloids. The Baylis-Hillman reaction has been used previously to prepare precursors for a number of necic acids and the Baylis-Hillman products themselves are susceptible to a number of interesting transformations. Thus, various Baylis-Hillman products, or their derivatives, have been shown to undergo intramolecular cyclisation (to indolizidines, coumarins and chromenes), or nucleophilic attack involving S_N, S_N' or conjugate adduct reactions. These developments have provided the background for the present studies, the aims of which have been as follows:

i) Synthesis of unsaturated and hydroxylated esters and acids as possible necic acid precursors *via* the Baylis-Hillman reaction.

ii) An investigation of the diastereo- and regioselectivity of thiomethylation of Baylis-Hillman products and derivatives.

iii) Synthesis of (E)-2-isopropylcrotonic acid as a precursor to (±)-trachelanthic and (±)-viridifloric acids.

iv) The synthesis of *Senecio* alkaloid analogues by coupling various acids to the isolated necine base, retronecine.

2 DISCUSSION

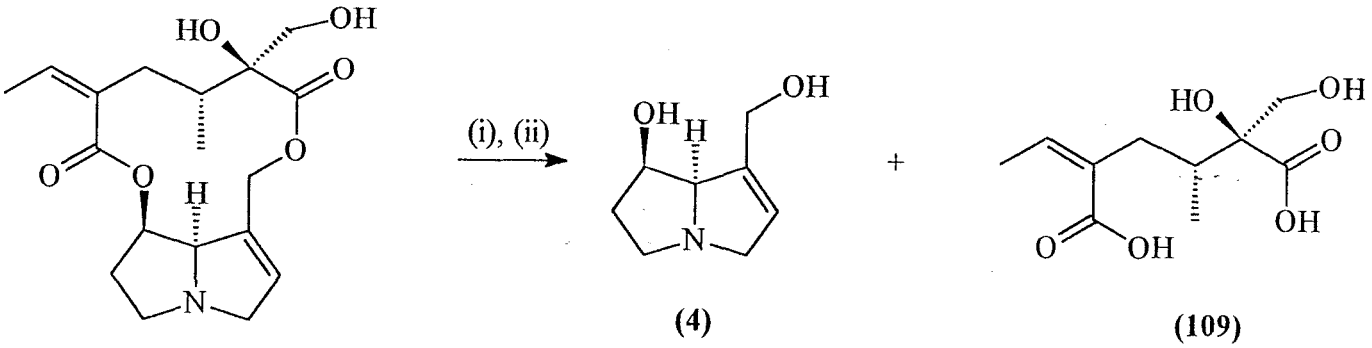
The discussion which follows covers the isolation of retronecine from *Senecio orthonnoflorus* (Section 2.1), use of the Baylis-Hillman reaction to prepare necic acid analogues and precursors (Section 2.3), bromination (Section 2.3) and thiomethylation studies of the Baylis-Hillman products and derivatives (Section 2.4), synthesis of 2-alkenoic acids as necic acid analogues (Section 2.5), the preparation of 2-isopropylcrotonic acid as a necic acid precursor (Section 2.6) and, finally, the esterification of retronecine to give *Senecio* alkaloid analogues (Section 2.7).

2.1 Acquisition of Retronecine

Senecio plants are notorious for their pyrrolizidine alkaloid content and have been studied extensively in order to determine the specific alkaloids they contain. In this study, attention has been given to the alkaloidal content of *Senecio orthonnoflorus*. *Senecio orthonnoflorus*, which belongs to the genus *Senecio* and the family Compositae (Table 1; p. 3), is a fleshy perennial herb with thong-like flowering stems and bright yellow flowers. It is found in a region stretching north-east from Humansdorp, Uitenhage and Grahamstown to Queenstown and the Amatolas in the Eastern Cape. It grows in grassland, often on steep slopes and among rocky outcrops. The herb flowers between December and February,[83] and the *Senecio orthonnoflorus* utilised was collected in February 1993 from One Oak Farm in the Bedford/Adelaide District in the Eastern Cape. Flowering *Senecio* plants are reputed to have

a higher alkaloid content.[84] The alkaloidal material was isolated following the flow diagram in Figure 2 and found to be pure retrorsine **(6)** (1.4%), an alkaloid comprising the necine base, retronecine **(4)**, and the necic acid, isatinecic acid **(109)** (Scheme 17).

The extraction of retrorsine proved to be straight-forward and the purity of the alkaloid obtained makes *Senecio orthonnoflorus* a highly desirable and reliable source of retrorsine **(6)** and hence retronecine **(4)**. Hydrolysis of retrorsine **(6)** using barium hydroxide[5] (Scheme 17) afforded pure retronecine **(4)** (84.6%), ^{1}H NMR spectra of which are shown in Figure 3. The necine base was subsequently used in esterification studies.



(6) **(4)** **(109)**

Reagents: i) $Ba(OH)_2$;
ii) 1M HCl.

Scheme 17

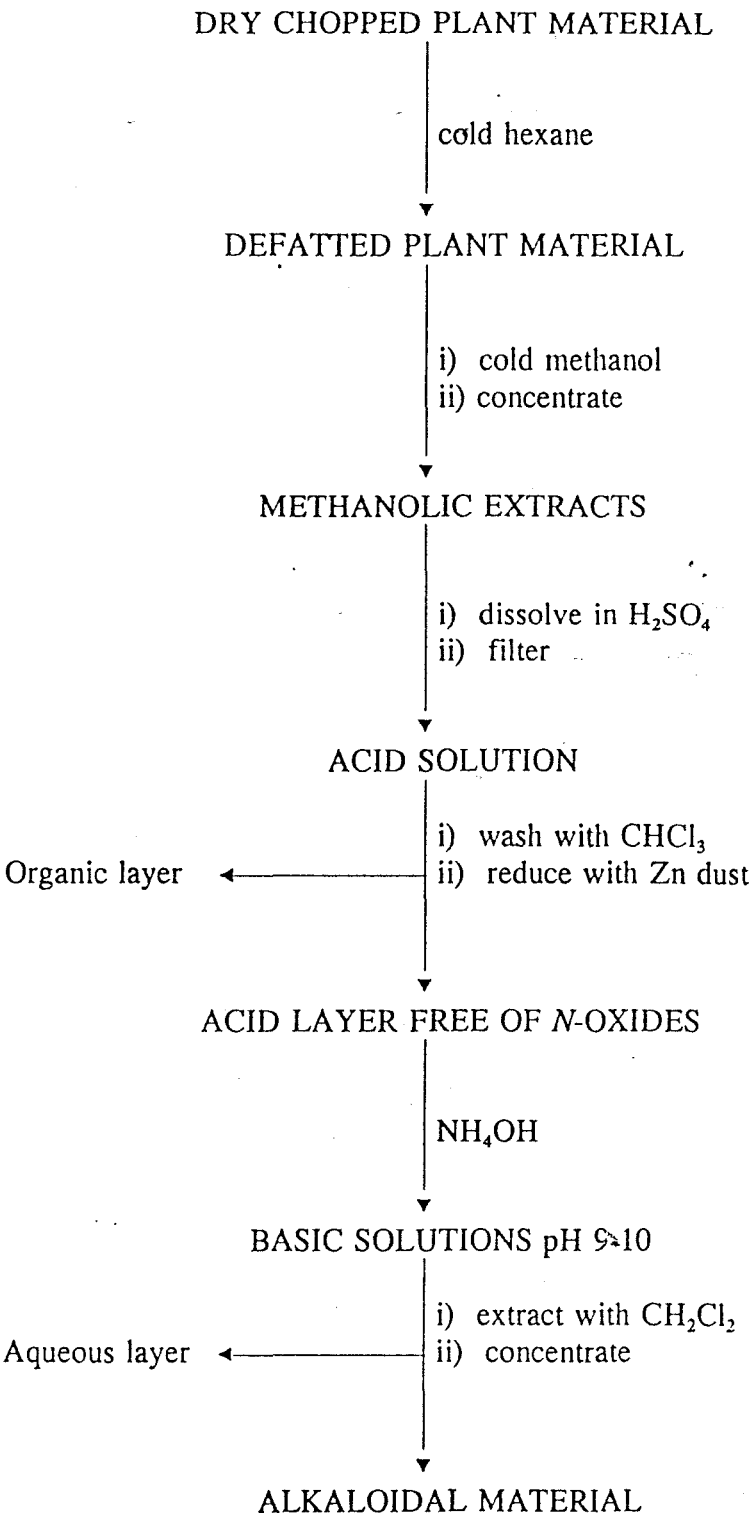


Figure 2. Flow diagram for extraction of alkaloidal material from *Senecio orthonnoflorus*[2]

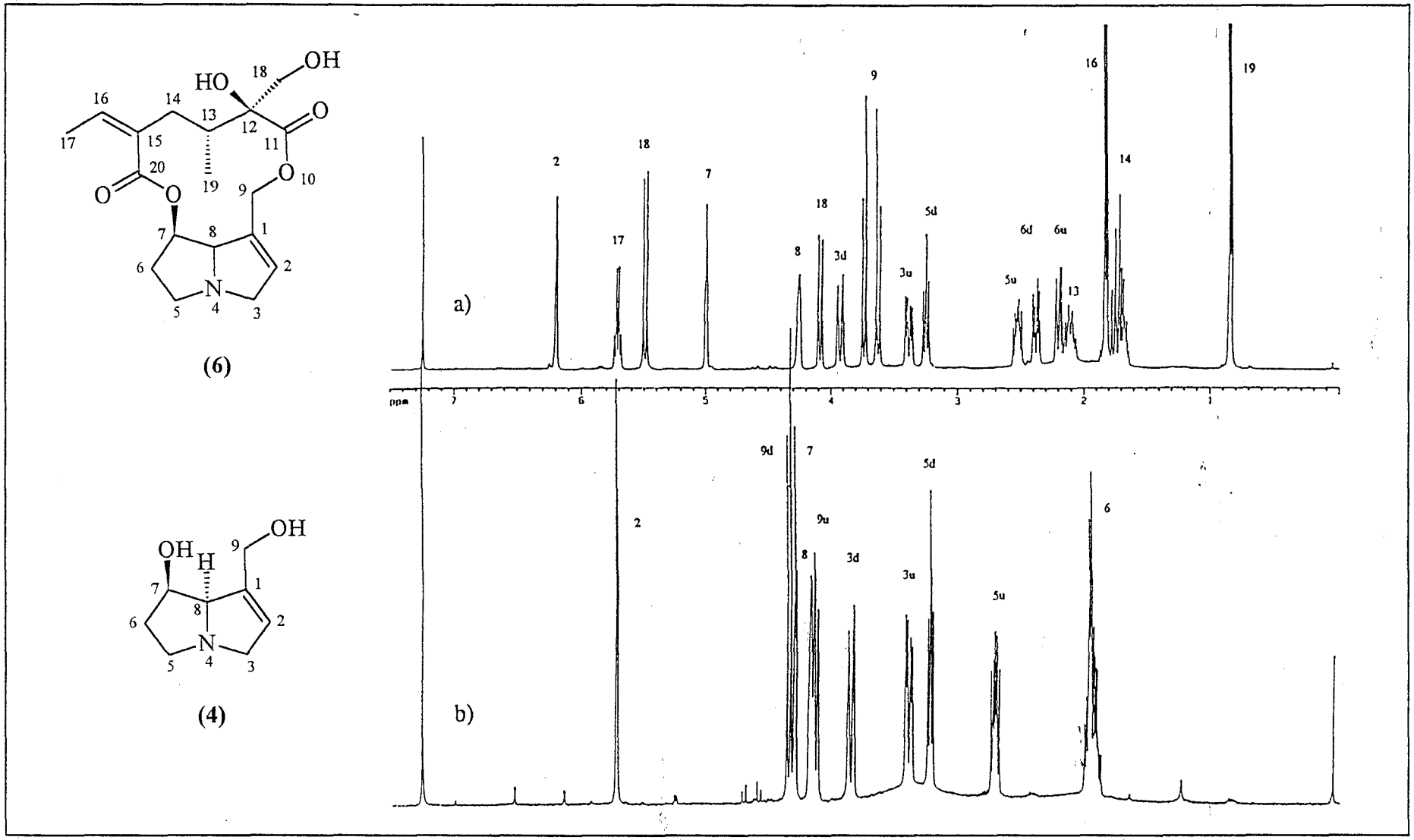
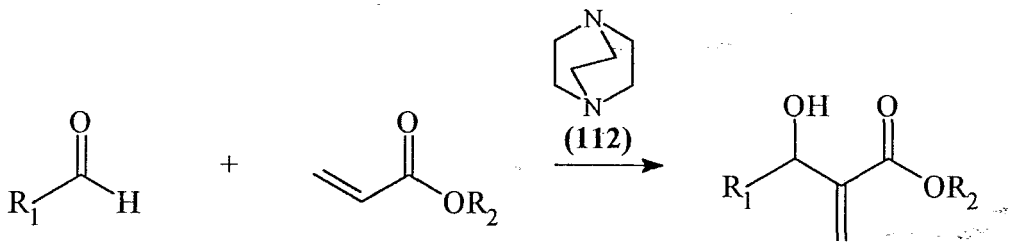


Figure 3. 400 MHz ^{1}H NMR spectra of a) retrorsine (**6**) and b) retronecine (**4**). The notation (d=downfield; u=upfield) refers to relative shifts of geminal protons.

2.2 Synthesis of 3-Hydroxy-2-methylenealkanoate Esters using the Baylis-Hillman Reaction.

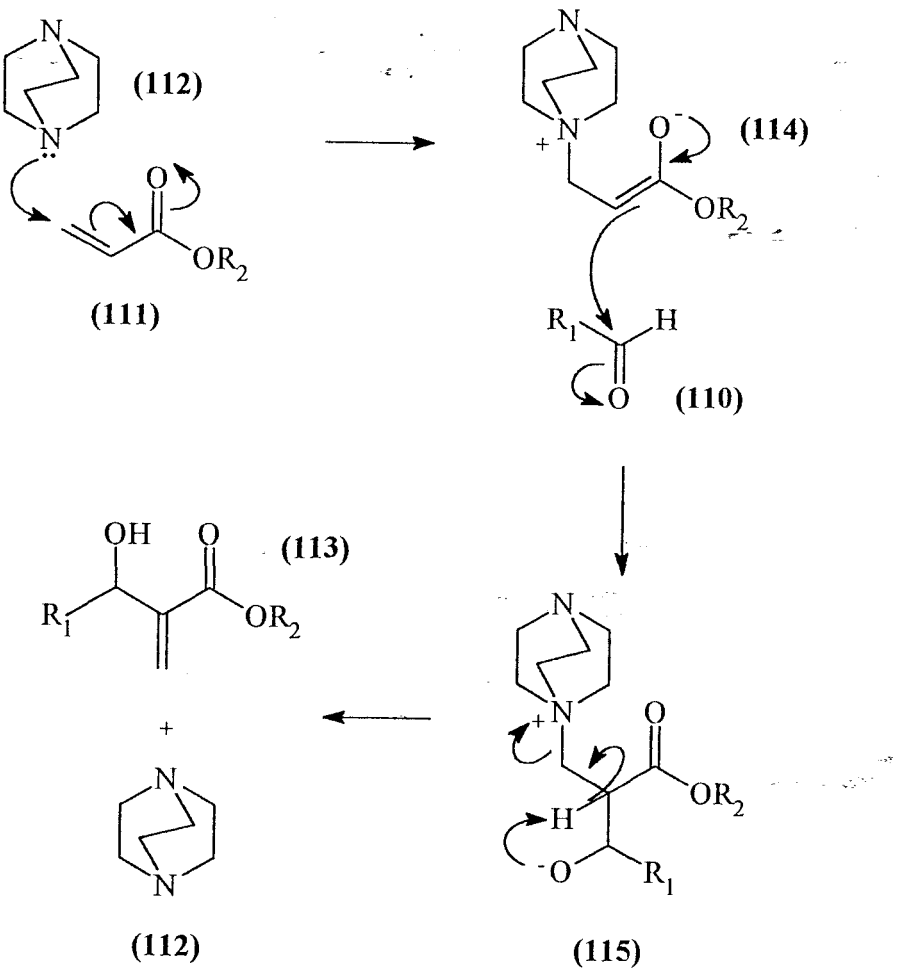
A. B. Baylis and M. E. D. Hillman patented a reaction between α,ß-unsaturated esters, nitriles, amides or ketones with a number of different aldehydes in 1972.[85] This reaction, which is catalysed by tertiary amines, is now commonly referred to as the Baylis-Hillman reaction[86] (Scheme 18). The most widely used catalysts are DABCO **(112)** and quinuclidine, with the reaction proceeding with or without solvent.



(110) **(111)** **(113)**

Scheme 18

In the Baylis-Hillman reaction the α,ß-unsaturated moiety acts as a nucleophilic vinyl anion equivalent with the product containing both the α,ß-unsaturated functionality and a new 3-hydroxy functionality. These multifunctional products are useful synthetic precursors which have been utilised in the preparation of necic acids,[58-60] coumarins[87] and indolizines[88] and other systems. Mechanistic studies indicate that the reaction proceeds *via* a zwitterionic enolate intermediate[86] **(114)** which then attacks the aldehyde as shown in Scheme 19.

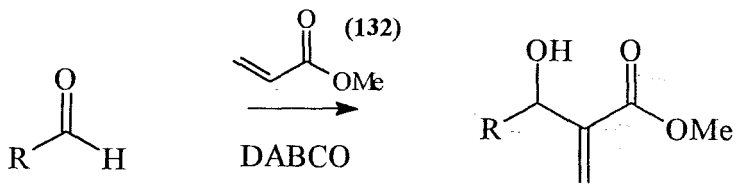


Scheme 19

In the present study, a variety of aldehydes **(116-123)** were treated with methyl acrylate **(132)** and DABCO (Table 2) with a view to obtaining a series of Baylis-Hillman products which could be elaborated to necic acid analogues. The reactions proceeded without difficulty, but the products **(124-131)** were prone to polymerisation on work-up and, following distillation, the yields tended to be low. The reaction with benzaldehyde **(121)** only proceeded once the aldehyde had been washed with sodium bicarbonate to remove the oxidised impurity, benzoic

acid. The progress of the reactions can easily be followed by ^{1}H NMR spectroscopy since the unsaturated reactants and products differ markedly in the vinyl region (5-7ppm) as shown in Figure 3.

Table 2 Results of the Baylis-Hillman reaction of various aldehydes with methyl acrylate



Substrate	R	Product	Yield %
116	H	124	not purified
117	Me	125	22.4
118	Et	126	42.7
119	Pr^i	127	27.8
120	Pr	128	51.8
121	Ph	129	76.7
122	4-MeOPh	130	18.2
123	4-NO_2Ph	131	79.6

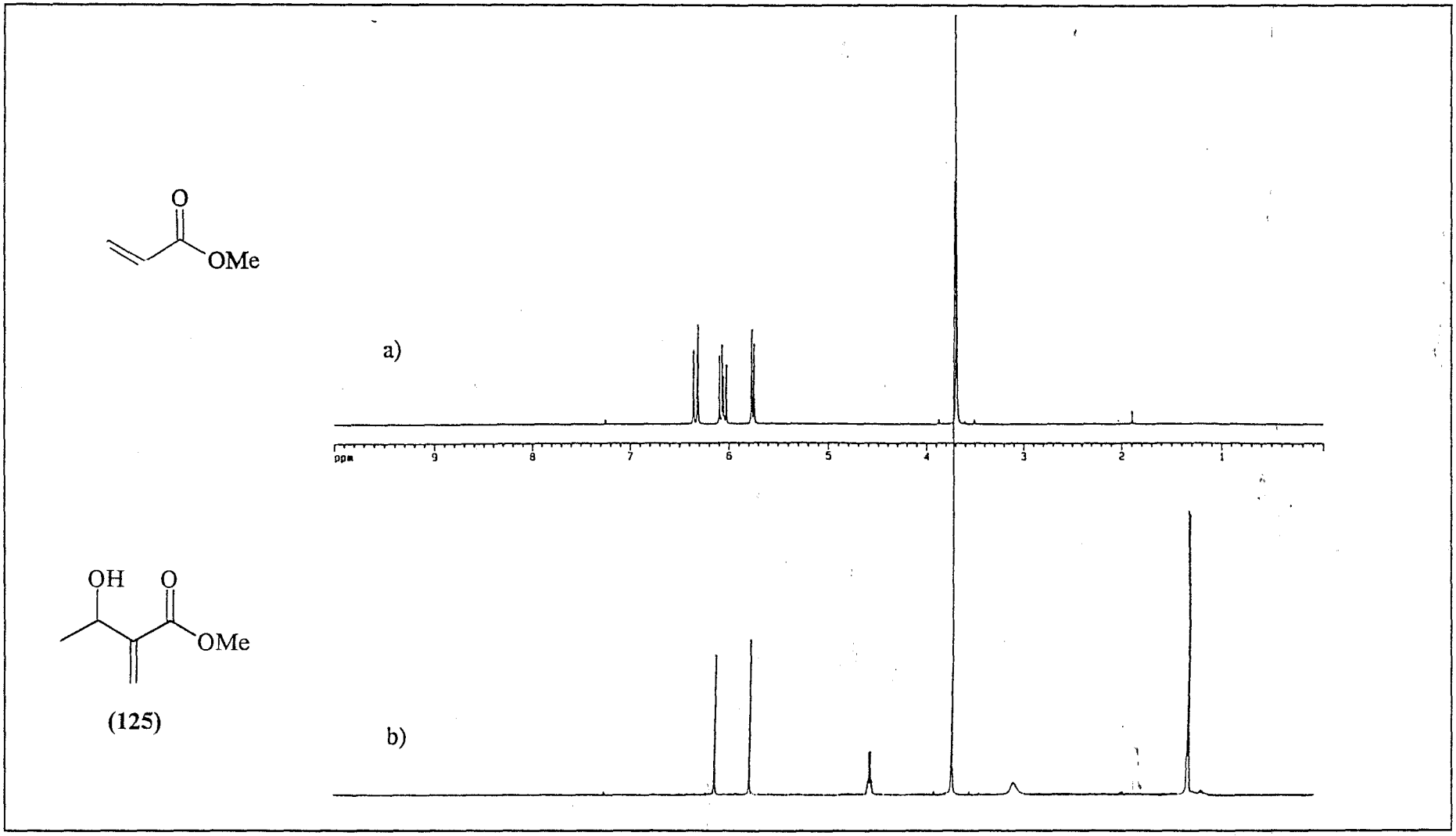
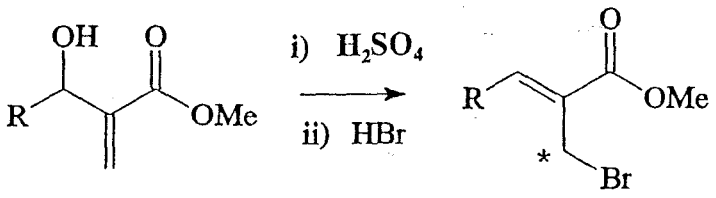


Figure 4. 400 MHz ^{1}H NMR spectra of a) methyl acrylate and b) methyl 3-hydroxy-2-methylenebutanoate (**125**)

2.3 Bromination of Selected Baylis-Hillman Products

Drewes *et. al.* have reported the use of allylic bromo esters in necic acid synthesis.[58] These compounds were obtained by brominating Baylis-Hillman products *via* two different procedures, *viz.* using NBS/Me_2S or H_2SO_4/HBr. In the present study, the H_2SO_4/HBr method was used to afford the products detailed in Table 3.

Table 3 Results of the bromination of selected Baylis-Hillman products



Substrate	R	Product	Yield %	^{13}C NMR values for methylene *C / ppm
124	H	133	70.1	29.1
125	Me	134	60.0	23.8
129	Ph	135	77.9	26.1

The hydroxy functionality is not a good leaving group but, under the acidic conditions used, protonation facilitates its displacement *via* an S_N' process (Scheme 20) to afford the rearranged products **(133-135)**. The structural changes accompaning bromination are clearly evident in the ^{1}H NMR spectra shown in Figure 5; thus, the vinyl methylene signals of the precursor at *ca.* 6 ppm are replaced by a methylene singlet at *ca.* 4.4 ppm.

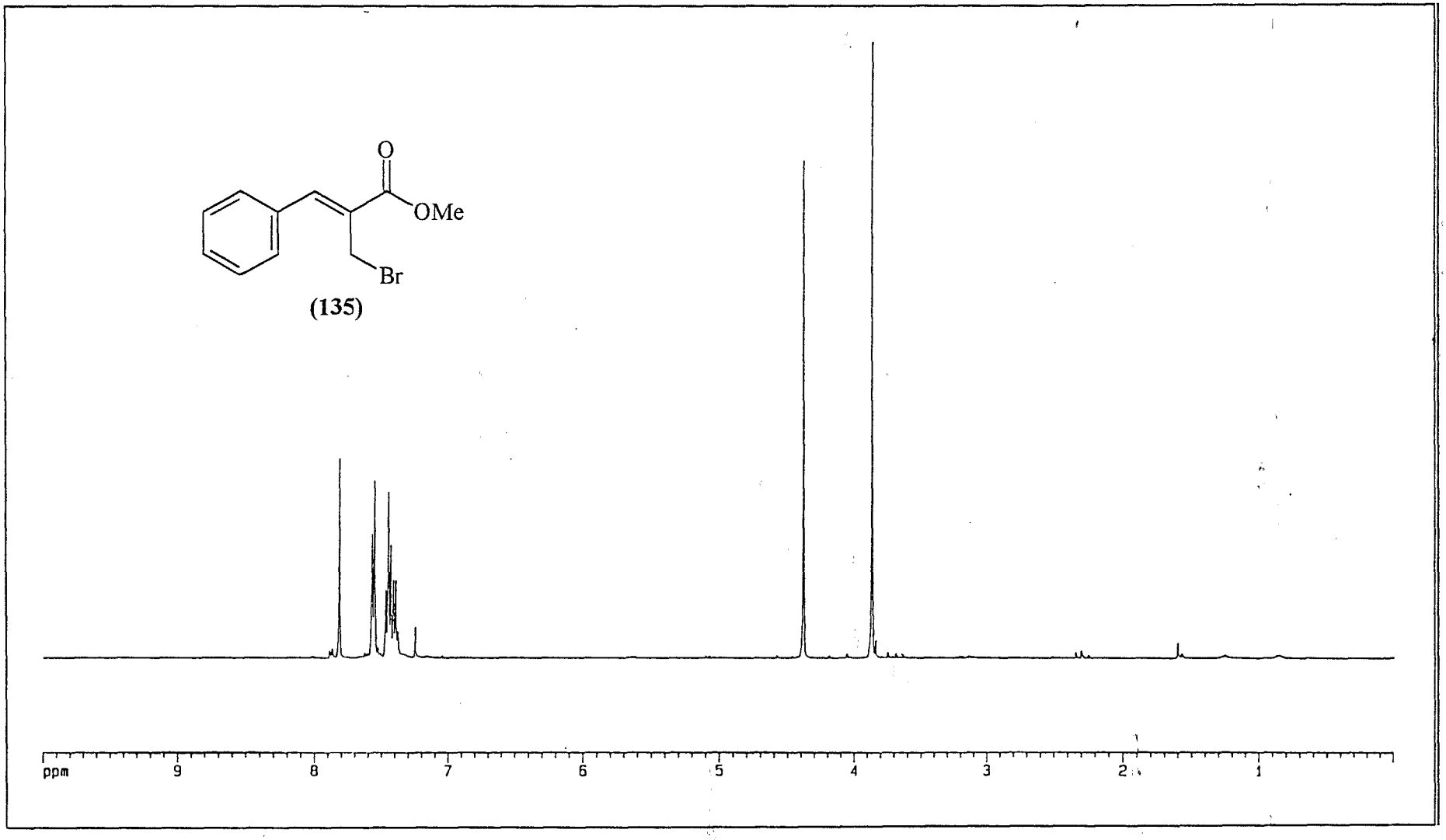
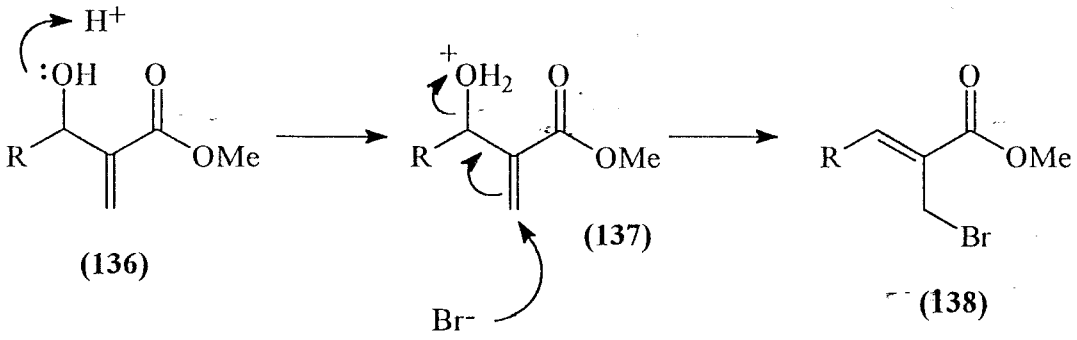


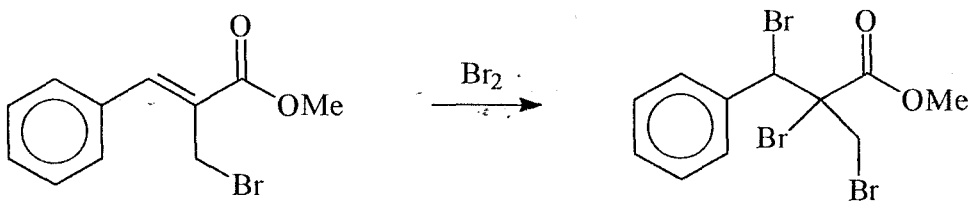
Figure 5. 400 MHz ^{1}H NMR spectrum of methyl (*Z*)-2-(bromomethyl)-3-phenyl-2-propenoate (135)



Scheme 20

A study of necic acid synthons by Kaye *et. al.*[62] investigated the formation of (*E*)- and (*Z*)-2-bromomethyl-2-butenoate esters using X-ray crystallographic and ^{13}C NMR techniques. This study revealed ^{13}C NMR spectroscopy to be an effective method for distinguishing between (*E*)- and (*Z*)-isomers. The shift for the allylic carbon bearing the Br was found to vary between 23.4 and 26.6 for selected (*Z*)-acids and esters and from 36.2 to 36.8 for equivalent (*E*)-acids and esters. Shift values obtained (Table 3) suggest that the rearranged bromo esters, **(134)** and **(135)** both exist as the (*Z*)-geometric isomers.

The bromination of compound **(129)** gave, in addition to the expected product **(135)**, an impurity which was identified as the tribromo compound **(139)** using NMR and mass spectroscopy. This product may arise from the electrophilic addition of bromine (Br_2) across the double bond of the initial product **(135)** (Scheme 21), the bromine being generated *in situ* by the oxidation of HBr by the H_2SO_4.



(135) **(139)**

Scheme 21

2.4 Thiomethylation of Selected α,ß-Unsaturated Alkenoate Esters

Previous studies have shown that unsaturated hydroxy esters are useful intermediates in necic acid synthesis. Acetylation of the hydroxy function, as well as bromination at the allylic position, has also resulted in interesting substrates, susceptible to nucleophilic attack.[58-64] The mode of nucleophilic attack depends, most importantly, on the solvent and the nature of the leaving group and the entering nucleophile. Because mercaptans (thiolates) are good nucleophiles it was decided to study the thiomethylation of selected substrates in order to determine what mode of attack was preferred. Five possible modes of nucleophilic attack are indicated in Figure 6 and detailed below.

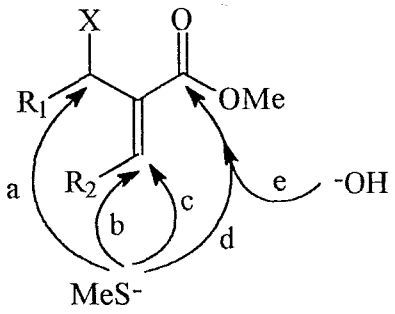


Figure 6 Possible modes for nucleophilic attack

a). Nucleophilic substitution (S_N) by the mercapto species - racemic substrates affording racemic products.

b). Nucleophilic substitution at the vinylic carbon (S_N') with migration of the double bond to give an achiral rearranged product (for R_2=H).

c). Conjugate addition resulting in a diastereomeric mixture of products with two chiral centres (except when R^1 = H).

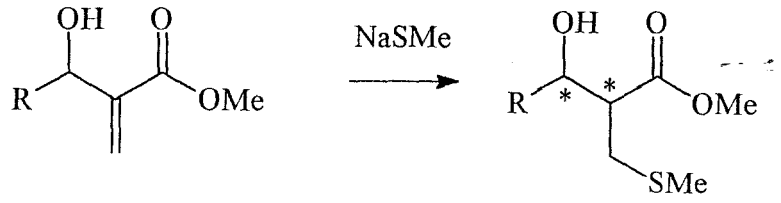
d). Nucleophilic acyl substitution at the ester carbonyl group by the mercapto species to give a thioester.

e). Simple base-catalysed hydrolysis (nucleophilic acyl substitution) of the ester due to the presence of strong base (NaOH) in the reactant mixture.

Previous studies of thiomethylation of α,ß-unsaturated Baylis-Hillman esters showed that hydrolysis of the ester occurred readily under the basic conditions used, while the corresponding α,ß-unsaturated nitriles gave a mixture of S_N' and conjugate addition products.[89] In the present investigation, a range of substrates was subjected to thiomethylation under controlled conditions in order to explore substituent and leaving group effects on a) the regioselectivity of nucleophilic attack and b) the diastereoselectivity in conjugate addition.

Selected substrates **(125-131)** were treated with a 21% sodium methyl mercaptan (SMM) solution in aqueous sodium hydroxide at room temperature for *ca.* 30 min. Under these conditions hydrolysis of the ester moiety could be suppressed and the hydroxy esters typically underwent conjugate addition, the results of which are summarised in Table 4. The diastereoselectivity was determined from ^{1}H NMR spectra of both crude and purified product mixtures.

Table 4 Results of the thiomethylation of selected substrates which gave conjugate addition



Substrate	R	Product	Pure Yield %	% d.e. (Crude)	% d.e. (Pure)
125	Me	140	47.0	66	52
126	Et	141	20.1	§	§
127	Pr^i	142	20.6	15	10
128	Pr	143	52.8	15	10
129	Ph	144	37.0	18	19
130	4-MeOPh	145	62.2	7	2
131	4-NO_2Ph	146	54.8	20	6

The diastereoselectivities shown in Table 4 do not reflect the expectation that the stereoselectivity should increase with increasing steric bulk of the R group. The results obtained are, in fact, opposite to what was expected and as the steric bulk of the R group increases so the diastereoselectivity decreases. This may be explained by considering the intermediate enolate in which hydrogen bonding is expected to fix its conformation as shown in Figure 7. When the R group is small, steric approach control (I) accounts for preferential

§The ^{1}H NMR peaks were not sufficiently resolved to calculate d.e.

approach of the electrophilic species (H^+) at the less hindered face. In the resulting product, the R group and the thiomethyl function will be *syn* to one another. As the steric bulk of the R group increases so do the unfavourable steric interactions in the product and, thus, product development control (II) is expected to become increasingly important with a consequent decrease in selectivity.[90]

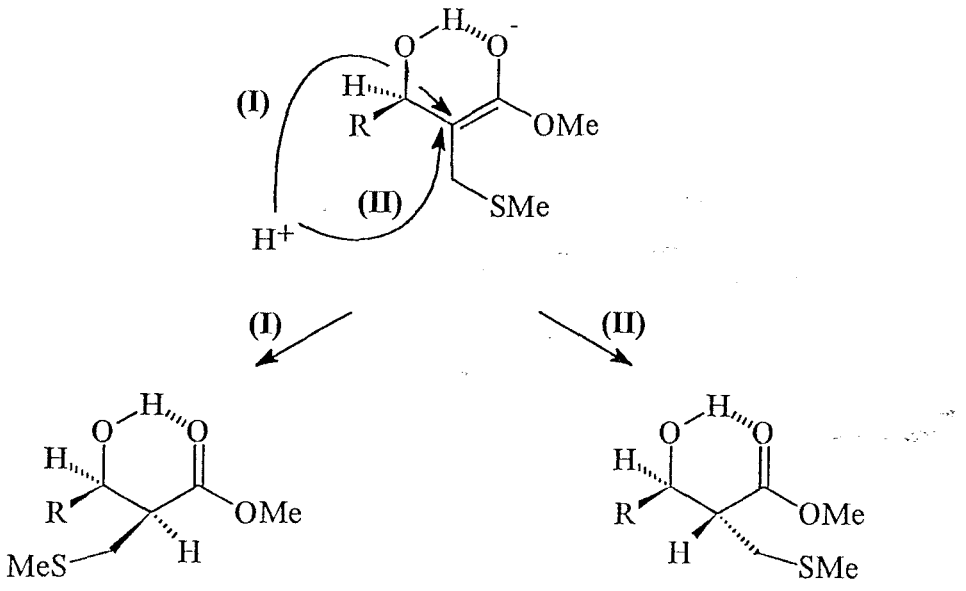
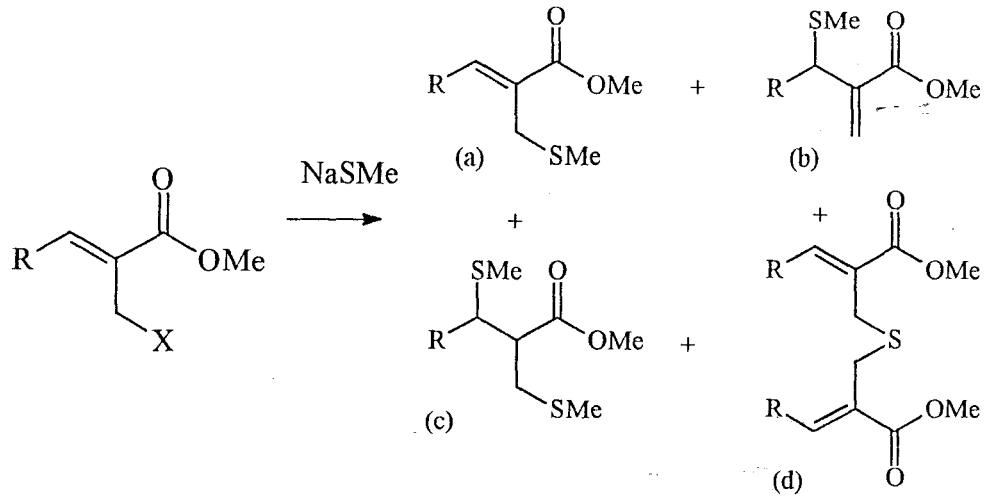


Figure 7 Diastereoselective protonation illustrated for one enantiomeric system

The hydroxy group is not a good leaving group and, consequently, substitution does not normally occur. In a cognate study, acetylation of the hydroxy function prior to thiomethylation has been shown to give rise to substitution and rearrangement reactions, rather than addition.[91] Acetate, being a better leaving group than hydroxy, clearly facilitates such substitution. In the case of methyl 3-hydroxy-2-methylenepropanoate **(124)** and the bromo

esters(**133-135**), nucleophilic substitution also occurs; the bromide ion, of course, being a much better leaving group than hydroxide (Table 5). ^{1}H NMR Spectra of the different products clearly indicates whether the nucleophilic reaction involves an S_N or S_N' or conjugate addition process (see Figure 8). Thus, products of type *(a)* arise from the normal (S_N) displacement and products of type *(b)* from allylic displacement (S_N'). Products of type *(b)* were not isolated (identified using ^{1}H NMR spectra of the reaction mixture) as they rearranged during work-up to the more stable type *(a)* products. The formation of products of type *(c)* involve addition of the nucleophile to products, **(147a)** and **(148a)**, obtained from displacement reactions. The presence of sodium hydrogen sulfide (NaSH) as an impurity in the SMM reactant solution gives rise to a further series of products of type *(d)* where the hydrosulfide sulfur acts as a nucleophile in two displacement reactions.

Table 5 Results of the thiomethylation of selected substrates which gave rise to displacement products



Comp. no.	X	R	Comp. no.	a % Crude Yield	b[§] % Crude Yield	c % Crude Yield	d % Crude Yield
124	OH	H	147	16.2	a=b	26.9	-
133	Br	H	147	62.6	a=b	8.1	3.4
134	Br	Me	148	40.8	30.6	-	6.4
135	Br	Ph	149	6.6	13.2	-	6.4

[§]Products of type (b) were not isolated as they rearranged at r.t. to products of type (a).

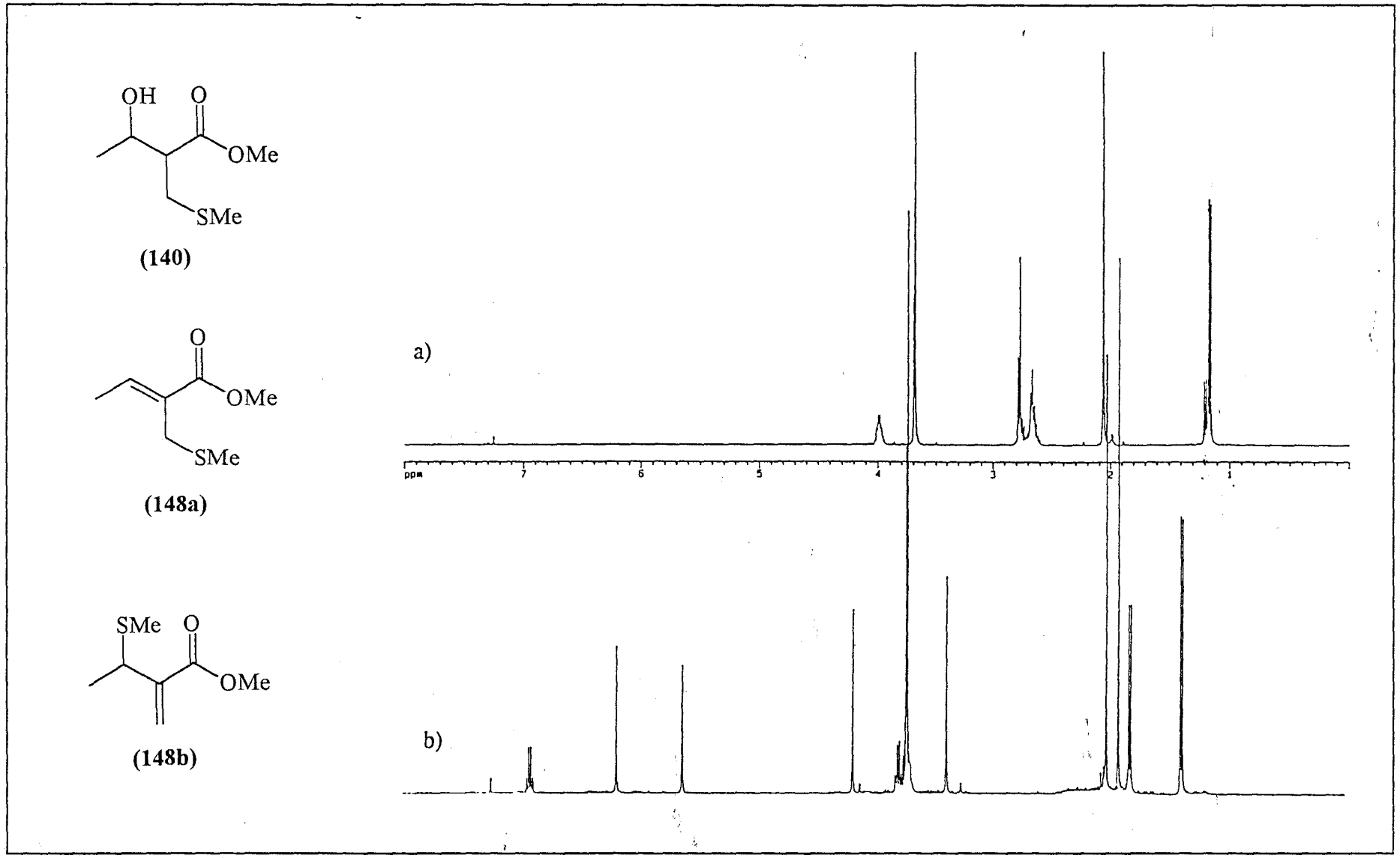
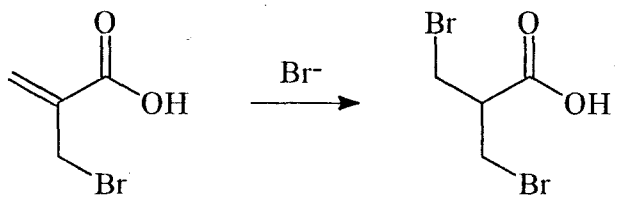


Figure 8 400 MHz ^{1}H NMR spectra of a) conjugate addition product (**140**) and b) S_N products (**148 a,b**)

2.5 Synthesis of 2-Alkenoic Acids as possible Necic Acid Precursors.

The bromo esters **(133-135)** were subjected to acid-catalysed hydrolysis by refluxing in 48% hydrobromic acid. The reaction proceeded with some charring and the required acids products **(150-152)** were obtained, after recrystallisation, in low overall yields (Table 6). In one case, the initial product **(150)** underwent subsequent Michael-type addition of bromide ion to afford the symmetrical dibromo saturated acid **(150a)** as the major product (Scheme 22). The results shown in Tables 5 and 6 indicate that the 2-propenoate systems are highly susceptible to nucleophilic attack, compounds **(124)**, **(133)** and **(150)** all producing side products *via* Michael-type addition reactions.

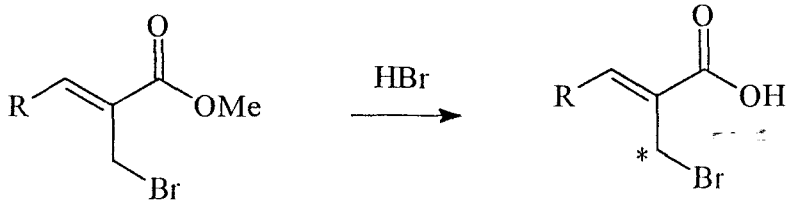
The bromo acids **(151)** and **(152)** obtained by hydrolysis of the corresponding esters appear to retain their (*Z*)-geometric configuration as evidenced by the ^{13}C NMR shift values for the methylene carbon (Table 6), which correspond to the expected values[62] for (*Z*)-systems.



(150) **(150a)**

Scheme 22

Table 6 Results of the hydrolysis of bromo esters (133-135) using 48% HBr

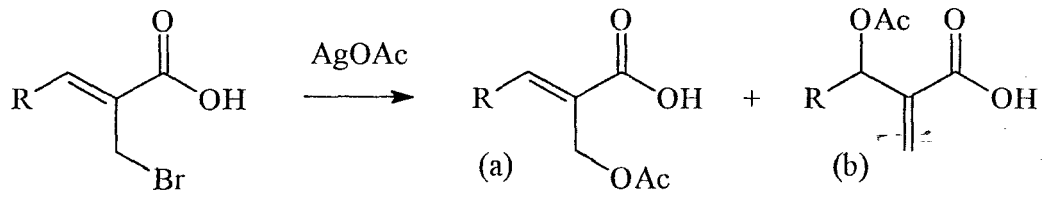


Substrate	R	Product	Yield/ %	^{13}C NMR values for methylene *C / ppm
133	H	150	1.1[§]	28.4
134	Me	151	50.0	23.3
135	Ph	152	50.2	26.1

The similarity between compound **(151)** and the necic acid, sarracinic acid **(10)**, prompted the acetylation of compounds **(151)** and **(152)**. Silver acetate was used in the acetylation[92] to give mixtures of products **(153a,b)** and **(154a,b)** (Table 7). ^{1}H NMR spectroscopy of the crude products indicates that the acetylation afforded both S_N and S_N' products together with a silver-grey precipitate of silver bromide as illustrated for compounds **(153a,b)** in (Figure 10). The product spread (*ca* 70:30) obtained from the acetylation of **(151)** and **(152)** corresponds to expectations for a unimolecular pathway (Figure 9) in which the S_N product is favoured.[80]

[§]The dibromo derivative (**150a**) was obtained as the major product.

Table 7 Results of the acetylation of bromo acids using AgOAc



Substrate	R	Product	Yield (a)/ %	Yield (b)/ %
151	Me	153	41.6	15.9
152	Ph	154	56.9	28.2

Sarracinic acid occurs naturally as the (*Z*)-isomer in the *Senecio* alkaloid, sarracine, but acetylation of the (*Z*)-bromo acids, **(151)** and **(152)**, gave rise to the acetylated (*E*)-analogues of sarracinic acid. It should be noted that substitution of the acetoxy group for bromine alters the relative priorities of the alkene substituents but that the actual configuration does not change.

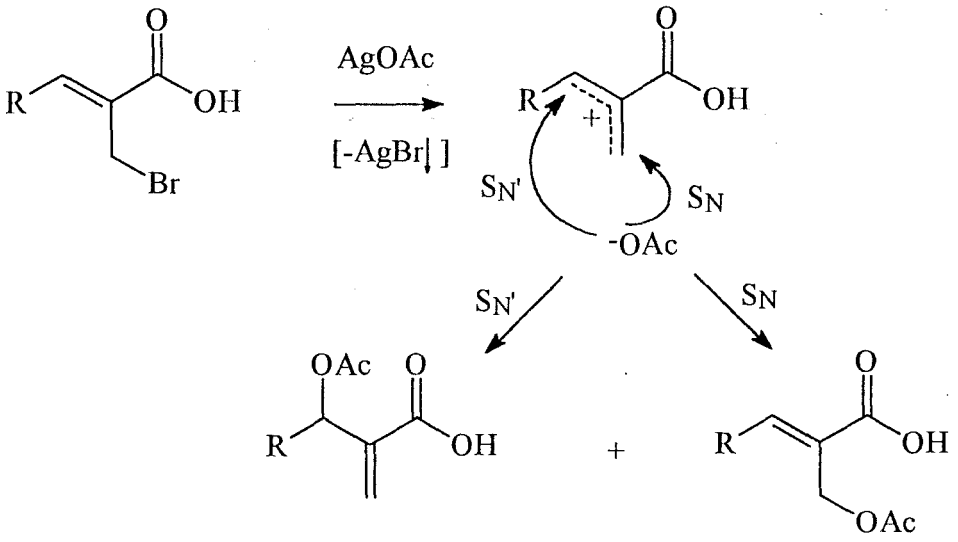


Figure 9 Proposed unimolecular pathway in the acetylation of bromo compounds **(151)** and **(152)** using AgOAc

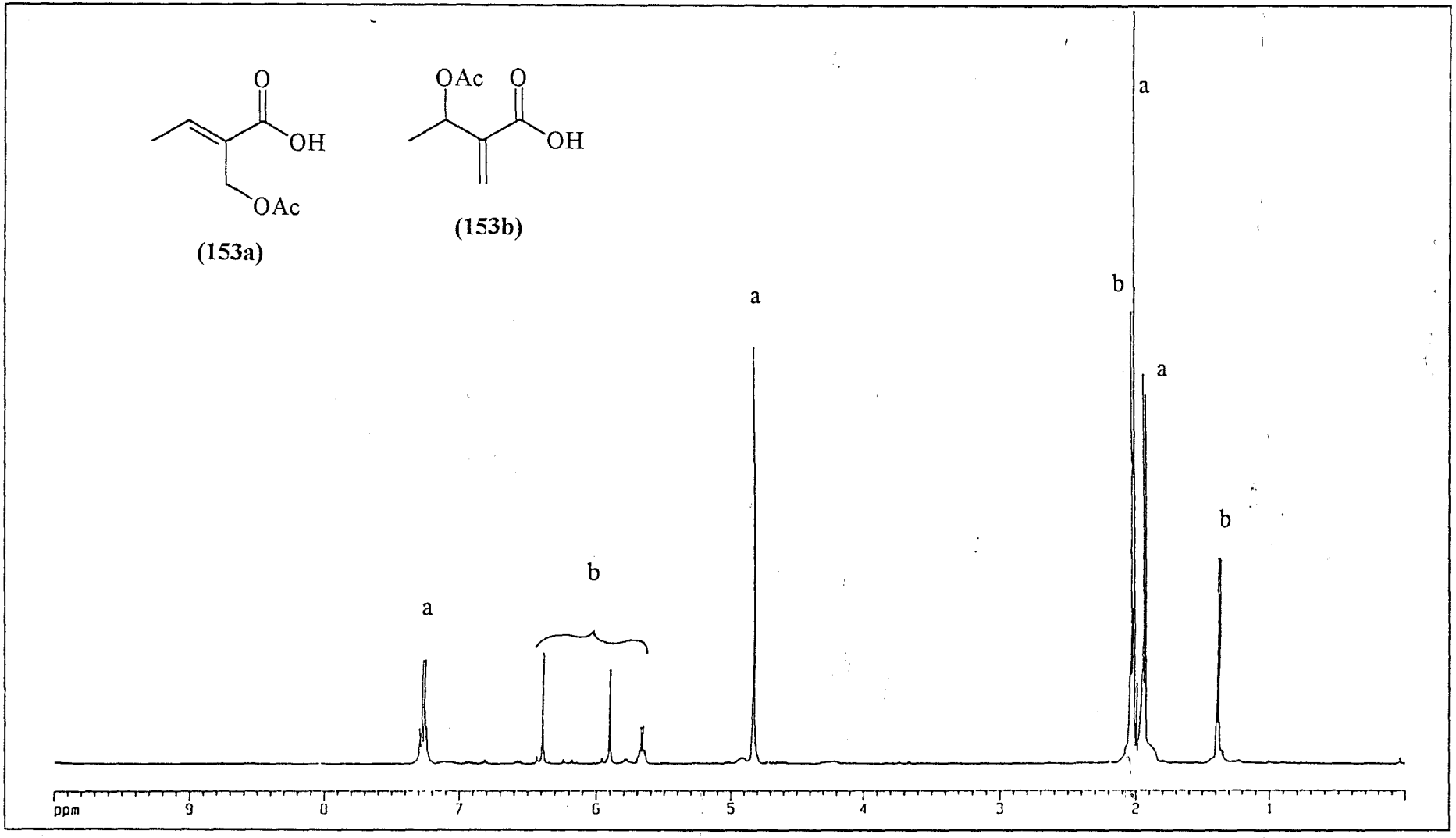


Figure 10 400 MHz ^{1}H NMR spectrum of acetylated products (**153a**) and (**153b**)

2.6 Synthesis of (*E*)-2-Isopropylcrotonic Acid as a Precursor to the Necic Acids, Viridifloric and Trachelanthic Acid.

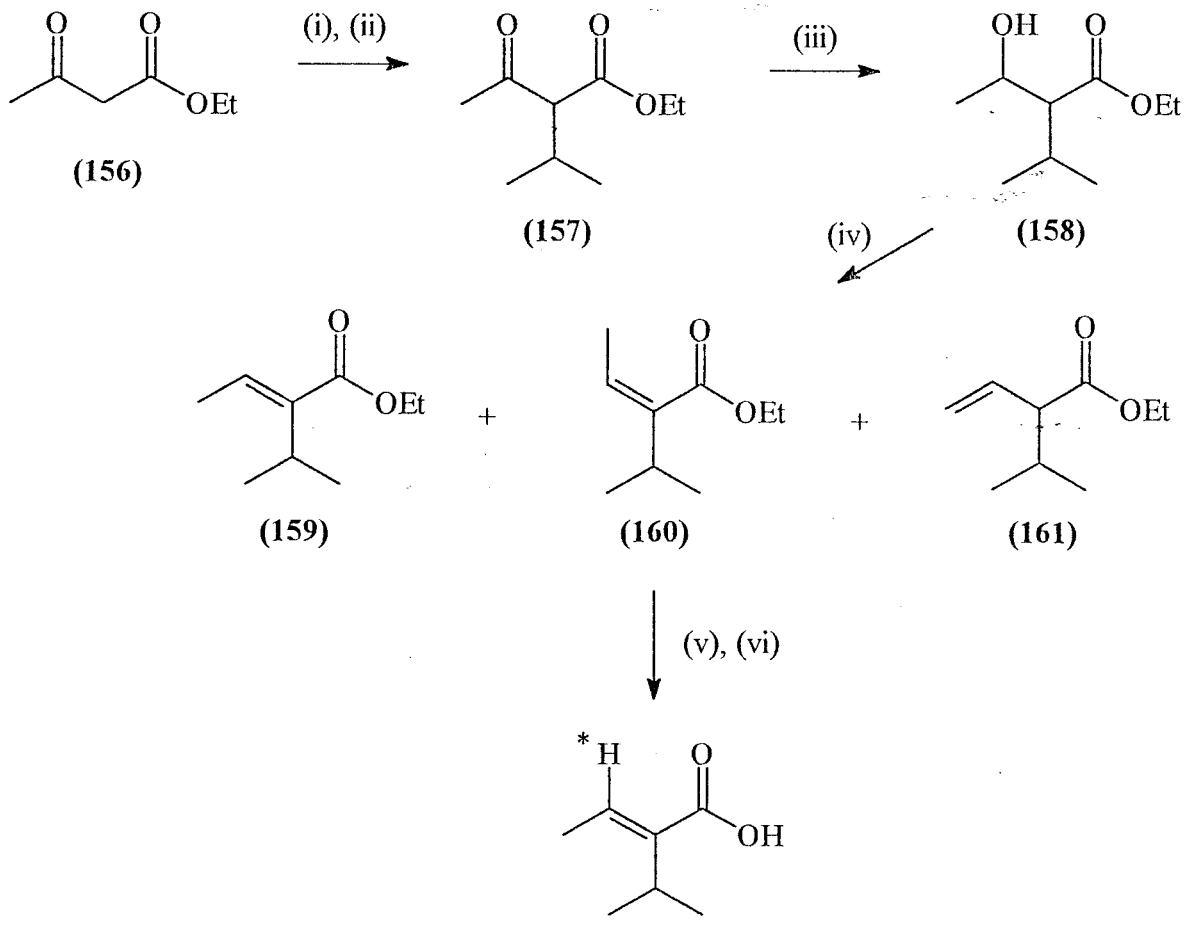
Viridifloric **(29)** and trachelanthic acid **(5)** are C-7 necic acids which are found esterified to a number of different necine bases. The *Senecio* alkaloids of interest containing these systems are lycopsamine **(155)**, and its derivatives, and indicine **(3)**, the *N*-oxide of which has proved successful in antitumour investigations.[93]

The very close similarities in structure between the alkaloids in question prompted a closer chemical investigation. The diasteromers, viridifloric **(29)** and trachelanthic acid **(5)** have been synthesised previously[28-31] but, in order to obtain all four diasteromers, an older approach was utilised, requiring the selective dihydroxylation of 2-isopropylcrotonic acid.[27]

In the current investigation (Scheme 23), ethyl acetoacetate **(156)** was treated with sodium ethoxide (prepared *in situ*) to form the enolate, which was then alkylated with isopropyl bromide to give compound **(157)** in 74.3% yield. The 3-keto ester **(157)** was then selectively reduced with sodium borohydride in a clean and efficient reaction to afford the 3-hydroxy derivative **(158)** in 78.7% yield. The reaction time was optimised in a trial run.

When the 3-hydroxy ester **(158)** was dehydrated using phosphorus oxychloride, rather than the more commonly used phosphorus pentoxide, a cleaner, purer product was obtained. The crude material was distilled and subjected to flash chromatography but the isomeric products **(159)**,

(160) and **(161)** could not be separated and therefore had to be identified using 2D NMR spectroscopy. Fortunately, the products are easily distinguished from one another. In any event, the subsequent step rendered purification of the unsaturated esters **(159-161)** unnecessary as the base catalysed hydrolysis of the crude mixture using potassium hydroxide yielded, in 35.0 % yield, a single crystalline isomer identified as (*E*)-2-isopropylcrotonic acid **(162)** using ^{1}H NMR spectroscopy (See Figure 11 and Table 8). Dihydroxylation was attempted using a variety of reagent systems. However, isolation of the water-soluble products proved problematic and, due to time constraints, this aspect of the project could not be developed further.



Scheme 23

Reagents: i). NaOEt; ii). Pr^{i}Br; iii). $NaBH_4$, MeOH; iv). $POCl_3$, pyridine, HCl; v). KOH; vi). HCl.

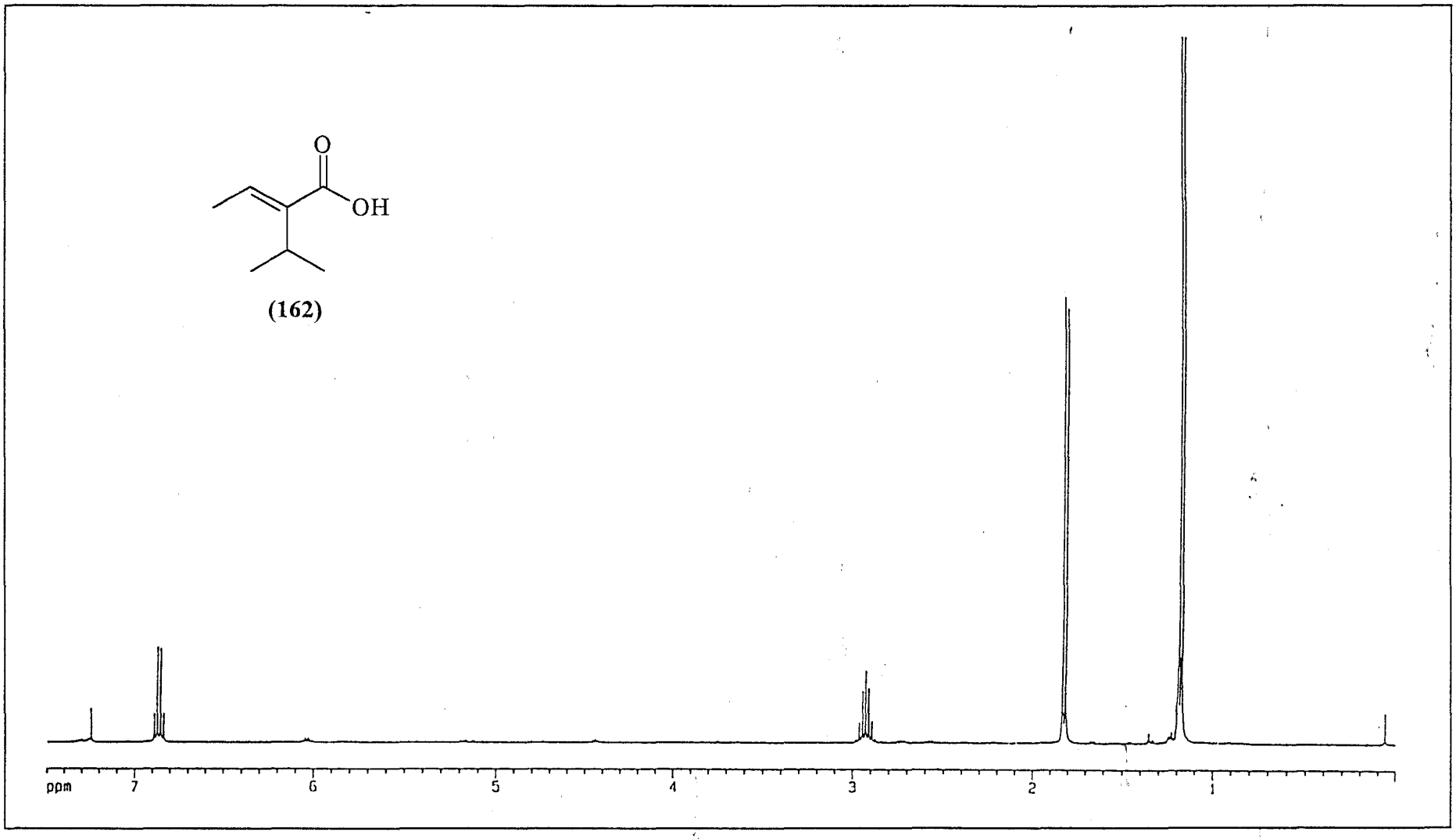


Figure 11 400 MHz ^{1}H NMR spectrum of (*E*)-2-isopropylcrotonic acid (**162**)

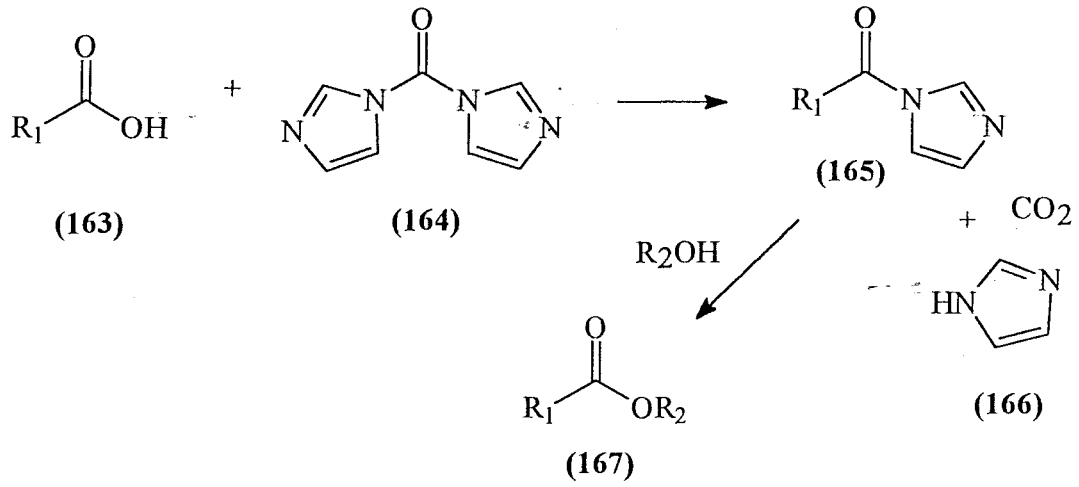
Table 8 Calculated and found ^{1}H NMR shift values (ppm) for the vinylic proton of compound (162)

Calc. (*E*)	Calc. (*Z*)	Found
6.68	6.13	6.87

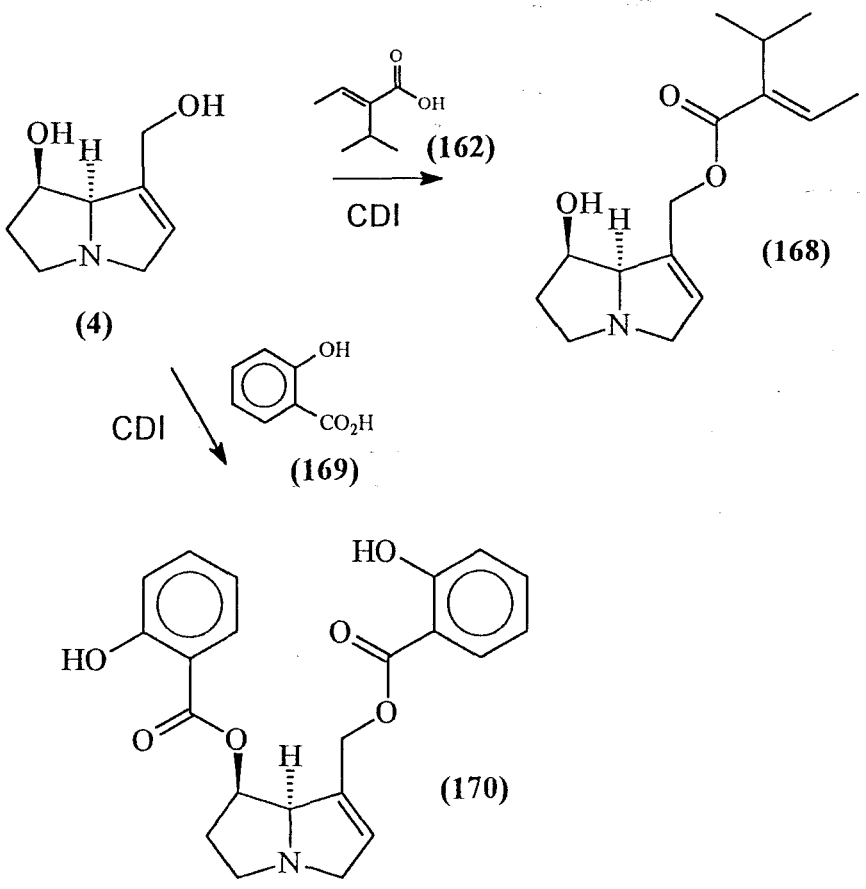
2.7 Synthesis of *Senecio* alkaloid analogues.

The esterification of necic acids with appropriate necine bases has received considerable attention. The preparation of macrocyclic diesters requires very different coupling techniques compared to those used for monoesters and acyclic diesters. The regioselectivity of the coupling reagents is a crucial factor too when there is more than one hydroxy group in the necine base, as is the case with retronecine **(4)**.

1,1-Carbonyldiimidazole (CDI) **(164)** has been used previously[5,6] to effect preferential esterification at C-9 rather than C-7. The alkaloids of the lycopsamine-type are all esterified at C-9 and thus CDI **(164)** has been used as a coupling agent in the synthesis of such compounds (Scheme 24).[94] In the present investigation, retronecine **(4)** was added to a stirred mixture of the acid **(162)** and CDI **(164)** to give a C-9 esterified alkaloid **(168)** (Scheme 25; Figure 12). A similar reaction with salicylic acid **(169)** gave, unexpectedly, the diester **(170)** (Scheme 25; Figure 13), the esterification occuring at both the primary (C-9) and secondary (C-7) positions. It is thus apparent, that retronecine **(4)** with CDI **(164)** does not always direct esterification to the C-9 position only.



Scheme 24



Scheme 25

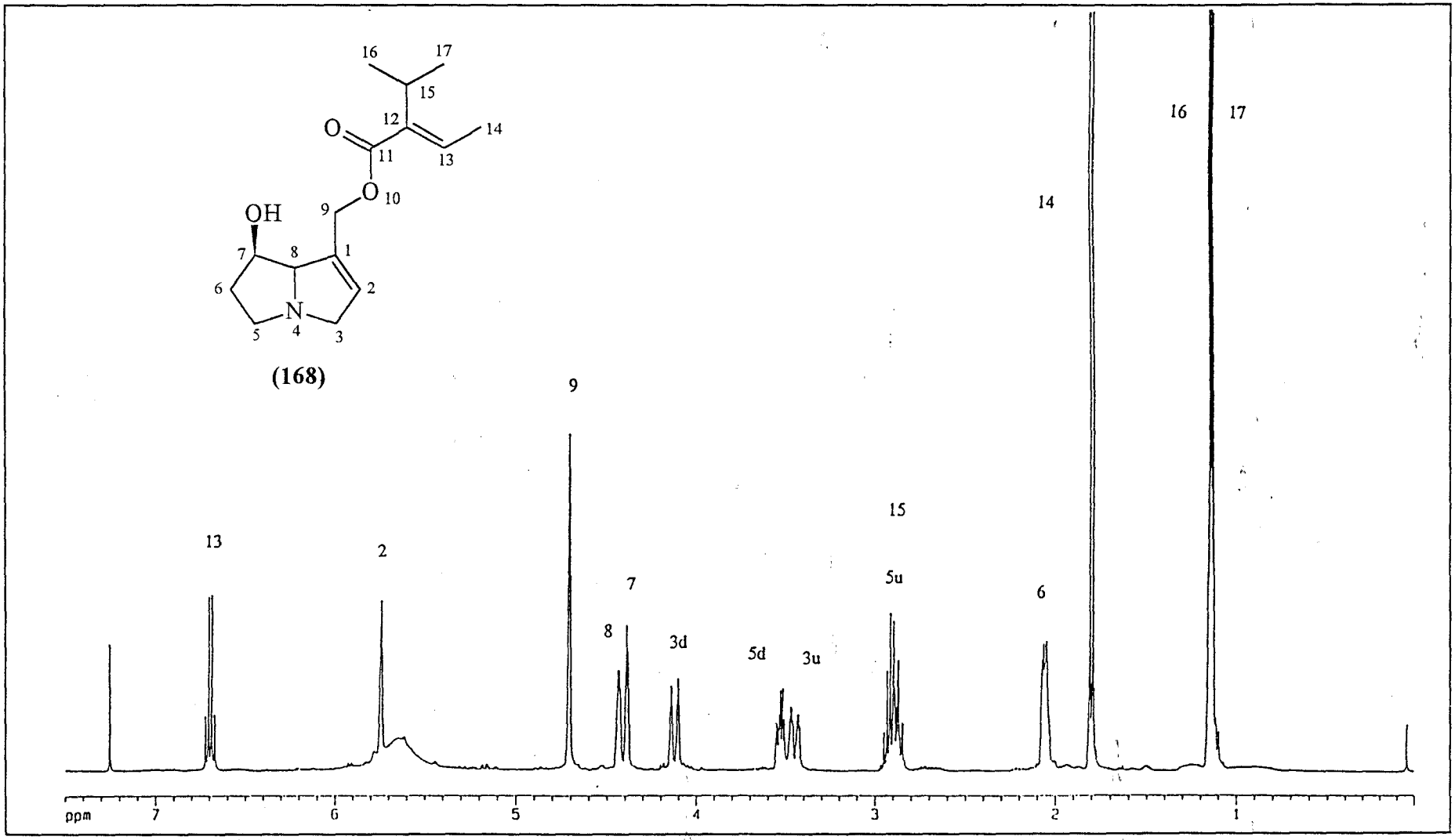


Figure 12 400 MHz ^{1}H NMR spectrum of 9-retronecine (*E*)-2-isopropylcrotonate (**168**). The notation (d=downfield; u=upfield) refers to relative shifts of geminal protons

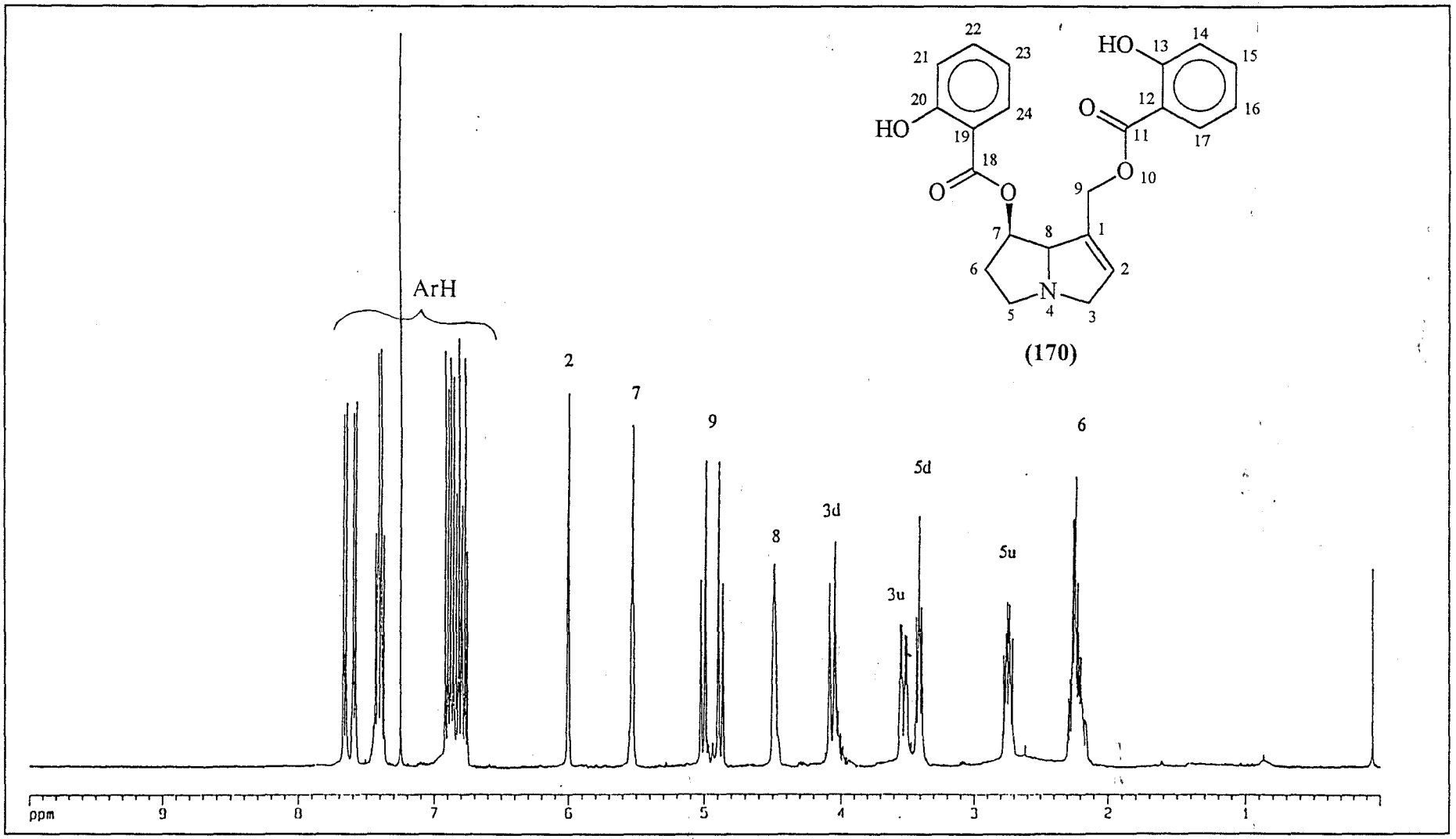


Figure 13 400 MHz ^{1}H NMR spectrum of retronecine disalicylate (**170**). See note for Figure 12, p. 59.

3 CONCLUSIONS

The Baylis-Hillman reaction has been successfully utilised to synthesise a series of α,ß-unsaturated esters as synthetic precursors. Bromination of selected Baylis-Hillman products using HBr has afforded a series of allylic bromo esters in good yields. The bromo esters have been hydrolysed and subsequently acetylated using silver acetate to obtain precursors for the synthesis of necic acid analogues; however, acetylation proceeded without the desired regioselectivity and the reactions afforded a mixture of rearranged products *via* S_N and S_N' pathways.

The Baylis-Hillman products and brominated ester derivatives were treated with SMM in order to investigate the diastereo- and regioselectivity of the reaction. The allylic hydroxy Baylis-Hillman substrates have been shown to undergo conjugate addition, due to the poor leaving ability of the hydroxy group, with the generation of an additional chiral centre. Diastereoselectivity was exhibited with up to 66% d.e., but trends seem to indicate that product development control is responsible for a decrease in diastereoselectivity with increasing steric bulk. The allylic bromo esters, however, were shown to favour nucleophilic displacement reactions (S_N and S_N') when treated with SMM under the same conditions. Surprisingly the S_N' products appeared to rearrange to S_N products at room temperature and were thus not isolated but identified in the reaction mixtures using ^{1}H NMR spectroscopy.

The synthesis of (*E*)-2-isopropylcrotonic acid has been achieved *via* a four-step pathway with

an overall yield of 6.1%. The CDI coupling of the necine base, retronecine, to (*E*)-2-isopropylcrotonic acid and salicylic acid proved successful, although with salicylic acid an interesting diester was obtained, rather than the expected monoester.

Thus, various objectives identified during the course of this research have been achieved while certain aspects require further investigation. These include:-

i). A detailed investigation of the influence of substituents on product development control in conjugate addition reactions of Baylis-Hillman products.

ii). Optimisation of the efficiency of successive steps in the synthesis of (*E*)-2-isopropylcrotonic acid.

iii). Extension of diastereo- and regioselective reactions to the synthesis of known necic acids or precursors thereof.

4 EXPERIMENTAL

4.1 General Methods

All ^{1}H and ^{13}C NMR spectra for solutions in $CDCl_3$ were run on a Bruker AMX 400 spectrometer using reference peaks (δ_H 7.25 and δ_C 77.0 ppm). Melting points were obtained using a Kofler micro heating stage and infrared spectra using a Perkin-Elmer 180 spectrophotometer. Low resolution MS spectra were run on a Hewlett-Packard 5988A mass spectrometer and a Kratos double focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit) was used for high resolution MS spectra.

4.2 Extraction of *Senecio orthonnoflorus*[4]

Retrorsine (6)

Flowering plant material was collected in February 1993 from One Oak Farm in the Bedford/Adelaide district in the Eastern Cape. The air-dried plant material (1.67 kg) was chopped and then soaked in hexane for 3d. to remove plant fats. The hexane was decanted and replaced with methanol. After 6d. the methanol was removed, filtered and concentrated to about 1/15 of its original volume. The resulting sludge was then dissolved in 2**M**-H_2SO_4 (400 ml) and the solution filtered. The solid material was washed with more 2**M**-H_2SO_4 (100 ml) and the aqueous acid washings were extracted with $CHCl_3$ until the washings were relatively

opaque.

Zn dust (3 g) was added to the acid layer and the mixture left to stir overnight to reduce the *N*-oxides. The aqueous phase was then basified using 2M-NH_4OH to pH 9-10. The aqueous layer was extracted using CH_2Cl_2 (8x200 ml) and the combined extracts were concentrated to yield yellow-brown granules of retrorsine[§] (23.8 g, 1.4%) which decomposes without melting at 210°C (lit.[95] 214-215°C); δ_H 0.85 (3H, d, 19-H), 1.68-1.78 (2H, overlapping m, 13-H and 14u-H), 1.83 (3H, d, 21-H), 2.15 (1H, m, 6u-H), 2.20 (1H, d, 14d-H), 2.38 (1H, dd, 6d-H), 2.53 (1H, m, 5u-H), 3.25 (1H, t, 5d-H), 3.38 (1H, dd, 3u-H), 3.68 (2H, dd, 18-H), 3.93 (1H, d, 3d-H), 4.09 (1H, d, 9u-H), 4.26 (1H, s, 8-H), 5.00 (1H, t, 7-H), 5.50 (1H, d, 9d-H), 5.71 (1H, q, 20-H) and 6.20 (1H, s, 2-H); δ_C 11.7 (C-19), 15.0 (C-17), 34.8 (C-6), 35.7 (C-13), 37.9 (C-14), 53.0 (C-5), 61.2 (C-3), 62.9 (C-9), 66.9 (C-18), 75.1 (C-7), 77.5 (C-8), 81.3 (C-12), 131.3 (C-1), 132.5 (C-15), 134.6 (C-16), 136.9 (C-2), 167.4 (C-20) and 175.7 (C-11).

4.3 Hydrolysis of Retrorsine (6)[4,5]

***Retronecine* (4)**

A mixture of retrorsine **(6)** (5.0 g, 14 mmol) and $Ba(OH)_2.8H_2O$ (18 g, 57 mmol) in water (200 ml) was boiled under reflux for 18h. The solution was cooled and then saturated with

[§]See Figure 3 on page 34 for the numbering of structure (**6**). The "d" and "u" merely differentiate NMR shift values for the protons on the same carbon being downfield or upfield of one another.

CO_2 by adding excess dry ice and stirring. The insoluble $BaCO_3$ was filtered off and the solvent removed from the filtrate under vacuum. Methanol (150 ml) was added to the residue and the resulting mixture was stirred for 1d. after which it was filtered. The methanol was evaporated from the filtrate *in vacuo* and $CHCl_3$ (100 ml) was added to the residue and the mixture then stirred for 2d. The solution was decanted off and concentrated to afford retronecine **(4)** as a creamy-yellow solid (1.6 g). A fresh aliqot of $CHCl_3$ (50 ml) was added to the methanol residue and after 1d. a further quantity of retronecine[§] **(4)** was obtained (0.30 g) to give an overall yield of 84.6%, m.p. 118-120°C (lit.,[96] 121-122°C); δ_H 1.89-1.99 (2H, m, 6-H), 2.72 (1H, m, 5u-H), 3.24 (1H, t, 5d-H), 3.41 (1H, dd, 3u-H), 3.86 (1H, d, 3d-H), 4.14 (1H, d, 9u-H), 4.18 (1H, s, 8-H), 4.31 (1H, s, 7-H), 4.35 (1H, d, 9d-H) and 5.73 (1H, s, 2-H); δ_C 35.4 (C-6), 54.1 (C-5), 59.1 (C-9), 61.9 (C-3), 71.2 (C-7), 79.5 (C-8), 127.3 (C-2) and 137.3 (C-1).

4.4 Synthesis of 3-Hydroxy-2-methylenealkanoate Esters[97]

Methyl 3-hydroxy-2-methylenepropanoate (124)[98]

A mixture of methyl acrylate (18 ml, 0.15 mol), paraformaldehyde **(116)** (9.1 g, 0.30 mol) and DABCO (1.2 g, 11mmol) was stirred in an autoclave at 95°C for 5h. The resulting mixture was washed sequentially with 2**M**-HCl (2x40 ml), 2**M**-NaOH (2x40 ml) and finally with satd. brine (1x50 ml) to give the crude methyl 3-hydroxy-2-methylenepropanoate

---

[§]See Figure 3 on page 34 for numbering of structure (**4**).

(124)(24 g); ν_{max}/cm^{-1} 3520 (OH), 1720 (C=O) and 1635 (C=C); δ_H 3.72 (3H, s, CH_3), 4.20 (2H, s, CH_2OH) and 5.86 and 6.27 (2H, 2xs, CH_2=C); δ_C 51.7 (CH_3), 68.8 (CH_2OH), 125.9 (CH_2=C), 136.9 (C=CH_2) and 166.1 (C=O). In order to minimise polymerisation, the crude product was not purified any further.

***Methyl 3-hydroxy-2-methylenebutanoate* (125)**

A homogeneous mixture of acetaldehyde **(117)** (28 ml, 0.50 mol), methyl acrylate (29 ml, 0.33 mol) and DABCO (1.8 g, 16 mmol) was kept under N_2 in a stoppered flask at r.t. for 7d. with occasional agitation. The solution was then diluted with Et_2O (150 ml), washed with 2**M**-HCl (2x40 ml), 2**M**-NaOH (2x40 ml) and then with satd. brine (1x50 ml). The Et_2O layer was dried (anhydr. $MgSO_4$), concentrated *in vacuo* and the residue distilled to afford methyl 3-hydroxy-2-methylenebutanoate **(125)** (9.5 g, 22.4%), b.p. 32-34°C/ 0.3mmHg;[§99] ν_{max}/cm^{-1} 3430 (OH), 1715 (CO) and 1630 (C=C); δ_H 1.30 (3H, d, CH_3CH), 3.05 (1H, br s, OH), 3.71 (3H, s, CH_3O), 4.55 (1H, q, CH) and 5.78 and 6.14 (2H, 2xs, CH_2=C); δ_C 22.1 (CH_3CH), 51.8 (CH_3O), 66.9 (CH), 124.0 (CH_2), 143.6 (C=CH_2) and 167.0 (C=O).

***Methyl 3-hydroxy-2-methylenepentanoate* (126)**

The procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate **(125)** was followed using propionaldehyde **(118)** (20 ml, 0.28 mol), methyl acrylate (23 ml, 0.26

[§]Reported without physical data.

mol) and DABCO (0.62 g, 5.5 mmol). After 12d. the mixture was worked up and the crude product distilled to afford methyl 3-hydroxy-2-methylenepentanoate **(126)** (16 g, 42.7%), b.p. 56-58°C/1.0 mmHg (lit.,[100] 65°C/1.5 mmHg); ν_{max}/cm^{-1} 3440 (OH), 1720 (C=O) and 1630 (C=C); δ_H 0.91 (3H, t, CH_3CH_2), 1.64 (2H, m, CH_2CH_3), 2.69 (1H, br s, OH), 3.74 (3H, s, CH_3O) and 5.77 and 6.20 (2H, 2xs, CH_2C); δ_C 10.2 (CH_3CH_2), 29.0 (CH_2CH_3), 51.8 (CH_3O), 72.8 (CH), 125.0 (CH_2=C), 142.2 (C=CH_2) and 167.0 (C=O).

***Methyl 3-hydroxy-4-methyl-2-methylenepentanoate* (127)**

The procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate **(125)** was followed using isobutyraldehyde **(119)** (20 ml, 0.22 mol), methyl acrylate (17 ml, 0.19 mol) and DABCO (0.60 g, 5.3 mmol). After 17d. the reaction mixture was worked up and the crude product distilled to give methyl 3-hydroxy-4-methyl-2-methylenepentanoate **(127)** (8.3 g, 27.8%), b.p. 46-52°C/0.05 mmHg;[§99] ν_{max}/cm^{-1} 3480 (OH), 1715 (C=O) and 1630 (C=C); δ_H 0.85 and 0.91 (6H, 2xd, $(CH_3)_2CH$), 1.62 (1H, m, $CH(CH_3)_2$), 2.56 (1H, br s, OH), 3.74 (3H, s, CH_3O), 4.06 (1H, d, CHOH) and 5.73 and 6.22 (2H, 2xs, CH_2=C); δ_C 17.5 and 19.5 (2xCH_3CH), 32.6 ($CHCH_3$), 51.8 (CH_3O), 77.6 (CHOH), 126.0 (CH_2=C), 141.4 (C=CH_2) and 167.2 (C=O).

[§]Reported without physical data

***Methyl 3-hydroxy-2-methylenehexanoate* (128)**

The procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate **(125)** was followed using butyraldehyde **(120)** (20 ml, 0.22 mol), methyl acrylate (18 ml, 0.17 mol) and DABCO (0.58 g, 5.2 mmol). After 14d. the reaction mixture was worked up and the crude product distilled to yield methyl 3-hydroxy-2-methylenehexanoate **(128)** (14 g, 51.8%), b.p. 56-59°C/0.1 mmHg;[§101] ν_{max}/cm^{-1} 3440 (OH), 1715 (C=O) and 1630 (C=C); δ_H 0.89 (3H, t, CH_3CH_2), 1.31-1.44 (2H, m, CH_2CH_3), 1.56 (2H, m, CH_2CH), 2.67 (1H, br s, OH), 3.73 (3H, s, CH_3O), 4.37 (1H, brs, CHOH) and 5.76 and 6.17 (2H, 2xs, CH_2=C); δ_C 13.6 (CH_3CH_2), 18.9 (CH_2CH_3), 38.3 (CH_2CH), 51.7 (CH_3O), 71.2 (CHOH), 124.7 (CH_2=C), 142.7 (C=CH_2) and 167.0 (C=O).

***Methyl 3-hydroxy-2-methylene-3-phenylpropanoate* (129)**

The procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate **(125)** was followed using purified benzaldehyde **(121)**[102] (15 ml, 0.15 mol), methyl acrylate (13 ml, 0.14 mol) and DABCO (0.59 g, 5.3 mmol). After 27d. the reaction mixture was worked up and the crude product distilled to afford methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(129)** (21 g, 76.7%), b.p. 106-109°C/0.2 mmHg;[§103] ν_{max}/cm^{-1} 3450 (OH), 1715 (C=O) and 1625 (C=C); δ_H 3.16 (1H, br s, OH), 3.71 (3H, s, CH_3O), 5.82 (1H, s, CHOH), 5.82 and 6.33 (2H, 2xs, CH_2=C) and 7.29-7.38 (5H, m, ArH); δ_C 51.9 (CH_3O), 73.2 (CHOH), 126.0,

[§]Reported without physical data.

126.6, 127.8, 128.4, 141.3 and 142.1 (ArC, C=CH_2 and CH_2=C) and 166.8 (C=O).

***Methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate* (130)**

The procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate **(125)** was followed using anisaldehyde **(122)** (10 ml, 82mmol), methyl acrylate (7.0 ml, 78 mmol) and DABCO (0.40 g, 3.6 mmol). After 30d. the reaction mixture was worked up and the starting material was removed *via* distillation to yield crystalline *methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate* **(130)** (3.1 g, 18.2%), m.p. 61-62°C (Found: M^+, 222.0894. $C_{12}H_{14}O_4$ requires: M 222.0888); ν_{max} /cm^{-1} 3480 (OH), 1710 (C=O) and 1620 (C=C); δ_H 3.00 (1H, br s, OH), 3.69 (3H, s, CH_3OC), 3.77 (3H, s, CH_3OAr), 5.49 (1H, s, C*H*OH), 5.84 and 6.29 (2H, 2xs, CH_2=C) and 6.85 and 7.26 (4H, 2xd, ArH); δ_C 51.8 and 55.2 (CH_3O), 72.7 (CHOH), 113.8, 125.5, 127.9, 133.5, 142.2 and 159.2 (ArC, C=CH_2 and CH_2=C) and 166.8 (C=O).

***Methyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate* (131)**

The procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate **(125)** was followed using 4-nitrobenzaldehyde **(123)** (3.4 g, 22 mmol), methyl acrylate (3.0 ml, 33 mmol) and DABCO (1.0 g, 9.0 mmol). After 33d. the reaction mixture was worked up to yield methyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate **(131)** (4.23g, 79.6%);[§104]

[§]Reported without physical data.

ν_{max}/cm^{-1} 3495 (OH), 1710 (C=O) and 1630 (C=C); δ_H 3.70 (3H, s, CH_3O), 5.60 (1H, s, C*H*OH), 5.86 and 6.38 (2H, 2xs, CH_2=C) and 7.53 and 8.14 (4H, 2xd, ArH); δ_C 52.1 (CH_3O), 72.4 (CHOH), 123.5, 127.0, 127.3, 141.1, 147.4 and 148.7 (ArC, *C*=CH_2 and *C*H_2=C) and 166.3 (C=O).

4.5 Synthesis of 2-(Bromomethyl)-2-alkenoate Esters[97]

Methyl 2-(bromomethyl)-2-propenoate (133)

Conc. H_2SO_4 (40 ml) was added dropwise to an ice-cooled, stirred solution of the hydroxy ester **(124)** (24 g, 0.21 mol) in conc. HBr (45% in acetic acid, 44 ml). The temperature was then allowed to rise and the reaction mixture was stirred for 16h. at r.t. The upper organic layer was then separated, taken up in Et_2O (100 ml), washed with satd. aq. $NaHCO_3$ (3x100 ml), dried (anhydr. $MgSO_4$), concentrated *in vacuo* and distilled to afford methyl 2-(bromomethyl)-2-propenoate **(133)** (29 g, 78.6%), b.p. 69-71°C (lit.,[105] 35-37°C, 1.3mmHg); ν_{max}/cm^{-1} 1720 (C=O) and 1630 (C=C); δ_H 3.77 (3H, s, CH_3O), 4.14 (2H, s, CH_2Br) and 5.92 and 6.29 (2H, 2xs, CH_2=C); δ_C 29.1 (CH_2Br), 52.1 (CH_3O), 129.0 (*C*H_2=C), 137.1 (*C*=CH_2) and 165.2 (C=O); *m/z* 178 (M^+, 38%) and 99 (100).

Methyl (Z)-*2-(bromomethyl)-2-butenoate* (134)

The procedure described for the preparation of methyl 3-bromo-2-methylenepropanoate **(133)**

was followed using conc. H_2SO_4 (20 ml), hydroxy ester **(125)** (9.5 g, 73 mmol) and conc. HBr (45% in acetic acid, 22 ml). After 16h., the work-up gave methyl (*Z*)-2-(bromomethyl)-2-butenoate **(134)** (8.4 g, 60.0%);[§61] ν_{max}/cm^{-1} 1715 (C=O) and 1640 (C=C); δ_H 1.87 (3H, d, CH_3CH), 3.75 (3H, s, CH_3O), 4.13 (2H, s, CH_2Br) and 7.03 (1H, q, $CHCH_3$); δ_C 14.3 (CH_3CH), 23.8 (CH_2Br), 51.9 (CH_3O), 130.1 (CCH_2Br), 143.1 ($CHCH_3$) and 165.7 (C=O).

***Methyl (Z)-2-(bromomethyl)-3-phenyl-2-propenoate* (135)**[101]

The procedure described for the preparation of methyl 3-bromo-2-methylenepropanoate **(133)** was followed using conc. H_2SO_4 (10 ml), hydroxy ester **(129)** (8.3 g, 43 mmol) and conc. HBr (45% in acetic acid, 21 ml). The temperature was allowed to rise and the mixture was stirred for 10h. at r.t. Only one layer was evident and therefore satd. aq. $NaHCO_3$ (50 ml) was added carefully. The upper organic layer was then separated, taken up in Et_2O (100 ml), washed with sat. aq. $NaHCO_3$, dried (anhydr. $MgSO_4$) and concentrated *in vacuo* to give methyl (*Z*)-2-(bromomethyl)-3-phenyl-2-propenoate **(135)**[§106] (10 g, 92.2%)[§§]; ν_{max}/cm^{-1} 1715 (C=O) and 1640 (C=C); δ_H 3.87 (3H, s, CH_3O), 4.38 (2H, s, CH_2Br), 7.37-7.53 (5H, m, Ar) and 7.81 (1H, s, CHBr); δ_C 26.7 (CH_2Br), 52.4 (CH_3O), 128.7, 128.9, 129.6, 129.7, 134.3

[§]Reported without physical data.

[§§]An impurity obtained from the addition of Br_2 (formed *in situ*) to **(135)** was also isolated and identified as *methyl 2,3-dibromo-2-(bromomethyl)-3-phenylpropanoate* **(139)** (0.19 g, 1.1%), (Found: M^+, 411.8320. $C_{11}H_{11}Br_3O_2$ requires: *M*, 411.8310); δ_H 3.75 (3H, s, CH_3O), 4.16 (2H, dd, CH_2Br), 5.65 (1H, s, CHBr) and 7.32-7.61 (5H, m, ArH); δ_C 37.9 (CH_2Br), 53.8 (CH_3O), 56.2 (CHBr), 68.6 (CC=O), 128.0, 129.3, 130.3 and 136.3 (ArC) and 166.4 (C=O).

(ArC and CCH_2Br), 142.9 (CHAr) and 166.6 (C=O).

4.6 Synthesis of 2-(Methylthiomethyl)alkanoate Esters[89]

Thiomethylation of Methyl 3-hydroxy-2-methylenepropanoate (124)

An aqueous solution of sodium methylmercaptan (SMM) (20 %;1.8 g, 26 mmol) was added slowly to a stirred mixture of the hydroxy ester **(124)** (3.0 g, 26 mmol) in THF (10 ml) over a period of 10 min. The temperature of the resulting mixture rose from 18 to 30°C and the reaction was left to stir for 30 min. The reaction was monitored using TLC and quenched using satd. brine (10 ml). The organic material was extracted using ethyl acetate (3x10 ml) and the combined extracts were dried (anhydr. $MgSO_4$) and concentrated *in vacuo* to yield a crude mixture of products **(147a)** (16.2%) and **(147c)** (26.9%). Purification using preparative layer chromatography (PLC) [on silica; elution with ethyl acetate-benzene-hexane (1:3:6)] afforded two products: i) *methyl 2-(methylthiomethyl)-2-propenoate* **(147a)** (0.83 g, 21.9%) [(Found: M^+, 146.0413. $C_6H_{10}O_2S$ requires: *M*, 146.0401); δ_H 2.02 (3H, s, CH_3S), 3.34 (2H, s, CH_2S), 3.78 (3H, s, CH_3O) and 5.62 and 6.21 (2H, 2xs, CH_2=C); δ_C 15.1 (CH_3S), 35.0 (CH_2S), 52.1 (CH_3O), 125.8 (CH_2=C), 136.4 (*C*=CH_2) and 166.7 (C=O)]; and ii) *methyl 2-(methylthiomethyl)-3-(methylthio)propanoate* **(147c)** (0.91 g, 18.0%) [(Found: M^+, 194.0444. $C_7H_{14}O_2S_2$ requires: *M*, 194.0435); δ_H 2.11 (6H, s, 2xCH_3S), 2.74-2.89 (5H, series of multiplets, 2xCH_2CH and C*H*$(CH_2)_2$) and 3.78 (3H, s, CH_3O); δ_C 16.0 (2xCH_3S), 35.4 (2xCH_2S), 45.6 (*C*H$(CH_2)_2$), 52.0 (CH_3O) and 173.7 (C=O)].

***Methyl 3-hydroxy-2-(methylthiomethyl)butanoate* (140)**

The procedure described for the synthesis of methyl 2-(methylthiomethyl)-2-propenoate **(147a)** was followed using the hydroxy ester **(125)** (1.5 g, 12 mmol) and SMM (0.84 g, 12 mmol). The solution turned pale yellow and the temperature rose slightly from 17 to 20°C. After 35 min, work-up afforded the crude product which was purified using flash column chromatography on silica gel, with ethyl acetate-benzene-chloroform (2:4:4), to give *methyl 3-hydroxy-2-(methylthiomethyl)butanoate* **(140)** (0.98 g, 47.0%), (Found: M^+, 178.0660. $C_7H_{14}O_3S$ requires: *M*, 178.0664); δ_H 1.16/1.19[§] (3H, d, CH_3CH), 2.06 (3H, s, CH_3S), 2.60-2.77 (3H, series of multiplets, CH_2CH and $CHCH_2$), 3.68/3.69 (3H, s, CH_3O) and 3.98 (1H, br q, CHOH); δ_C 15.7/15.8 (CH_3S), 20.6/21.3 (CH_3CH), 32.1/33.1 (CH_2S), 51.8 (CH_3O), 52.2/52.5 (*C*HC=O), 67.6/68.0 (CHOH) and 173.9/174.1 (C=O); *m/z* 178 (M^+, 14%) and 87 (100).

***Methyl 3-hydroxy-2-(methylthiomethyl)pentanoate* (141)**

The procedure described for the synthesis of methyl 3-hydroxy-2-(methylthiomethyl)butanoate **(140)** was followed using the hydroxy ester **(126)** (2.1 g, 15 mmol) and SMM (1.0 g, 15 mmol). The solution immediately turned bright yellow and the temperature rose from 17 to 24°C. After 25min, work-up and purification afforded *methyl 3-hydroxy-2-(methylthiomethyl)pentanoate* **(141)** (0.55 g, 20.1%) (Found: M^+, 192.0806. $C_8H_{16}O_3S$

[§]This notation, used here and elsewhere, represents the presence of diastereomers.

requires: *M*, 192.0820); δ_H 0.95 (3H, t, CH_3CH_2), 1.46 (2H, m, CH_2CH_3), 2.08 (3H, s, CH_3S), 2.71-2.82 (3H, series of multiplets, $CHCH_2S$), 3.70 (3H, s, CH_3O) and 3.74 (1H, m, CHOH); δ_C 10.0/10.1 (CH_3CH_2), 15.9 (CH_3S), 27.5/28.6 (CH_2CH_3),31.8/33.6 (CH_2S), 50.2/51.0 (CHC=O), 51.8/51.9 (CH_3O), 73.0/73.3 (CHOH) and 174.2/174.3 (C=O).

***Methyl 3-hydroxy-4-methyl-2-(methylthiomethyl)pentanoate* (142)**

The procedure described for the synthesis of methyl 3-hydroxy-2-(methylthiomethyl)butanoate **(140)** was followed using the hydroxy ester **(127)** (1.1 g, 6.9 mmol) and SMM (0.48 g, 6.9 mmol). The solution turned yellow upon addition of SMM and the temperature rose from 18 to 23°C. After 30min, work-up and purification afforded *methyl 3-hydroxy-4-methyl-2-(methylthiomethyl)pentanoate* **(142)** (0.29 g, 20.6%) (Found: M^+, 206.0964. $C_9H_{18}O_3S$ requires: *M*, 206.0976); δ_H 0.94 (6H, 4xd, $(CH_3)_2CH$), 1.61 (1H, m, $CH(CH_3)_2$), 2.09 (CH_3S), 2.26 (1H, brs, OH), 2.73-2.88 (3H, series of multiplets, CHC=O and CH_2S), 3.49 (1H, m, CHOH) and 3.71 (CH_3O); δ_C 15.8 (CH_3S), 16.8/17.9 and 19.3/19.4 ($(CH_3)_2CH$), 31.2/31.9 (CH_2S), 32.4/34.0 ($CH(CH_3)_2$), 47.7/49.1 (CHC=O), 51.8 (CH_3O), 76.7 (CHOH) and 174.4/174.6 (C=O); *m/z* 206 (M^+, 19%) and 87 (100).

***Methyl 3-hydroxy-2-(methylthiomethyl)hexanoate* (143)**

The procedure described for the synthesis of methyl 3-hydroxy-2-(methylthiomethyl)butanoate **(140)** was followed using the hydroxy ester **(128)** (2.1 g, 13 mmol) and SMM (0.91 g, 13 mmol). No colour change was observed but the the temperature rose from 18 to 23°C. After 25min, work-up and purification afforded *methyl 3-hydroxy-2-(methylthiomethyl)hexanoate* **(143)** (1.42 g, 52.8%) (Found: M^+, 206.0968. $C_9H_{18}O_3S$ requires: *M*, 206.0976); δ_H 0.89 (3H, t, CH_3CH_2), 1.42 (4H, 2xm, $CH_2CH_2CH_3$), 2.08 (3H, s, CH_3S), 2.67-2.82 (3H, series of multiplets, CHC=O and CH_2S), 3.70 (3H, s, CH_3O) and 3.77/3.84 (1H, m, CHOH); δ_C 13.8 (CH_3CH_2), 15.9 (CH_3S), 18.9 (CH_2CH_3), 31.8/33.5 (CH_2S), 36.7/37.7 (CH_2CHOH), 50.6/51.3 (CHC=O), 51.8 (CH_3O), 71.3/71.6 (CHOH) and 174.2/174.3 (C=O); *m/z* 206 (M^+, 31%) and 87 (100).

***Methyl 3-hydroxy-2-(methylthiomethyl)-3-phenylpropanoate* (144)**

The procedure described for the synthesis of methyl 3-hydroxy-2-(methylthiomethyl)butanoate **(140)** was followed using the hydroxy ester **(129)** (2.3 g, 12 mmol) and SMM (0.84 g, 12 mmol). The reaction mixture turned pale yellow on the addition of SMM and the temperature rose from 17 to 25°C. After 25min, work-up and purification afforded *methyl 3-hydroxy-2-(methylthiomethyl)-3-phenylpropanoate* **(144)** (1.1 g, 37.0%) (Found: M^+, 240.0821. $C_{12}H_{16}O_3S$ requires: *M*, 240.0822); δ_H 2.02 (3H, s, CH_3S), 2.52-3.02 (3H, series of multiplets, CH_2S and CHC=O), 3.58/3.69 (3H, s, CH_3O), 4.89/4.97 (1H, d, CHOH) and

7.30 (5H, m, ArH); δ_C 15.8 (CH_3S), 31.7/33.3 (CH_2S), 51.8/51.9 (CH_3O), 52.9/53.3 (*C*HC=O), 74.1/74.4 (CHOH), 126.0/126.2, 128.1/128.3, 128.4/128.6 and 141.0/141.3 (ArC) and 173.6/174.1 (C=O); *m/z* 240 (M^+, 17%) and 87 (100).

***Methyl 3-hydroxy-3-(4-methoxyphenyl)-2-(methylthiomethyl)propanoate* (145)**

The procedure described for the synthesis of methyl 3-hydroxy-2-(methylthiomethyl)butanoate **(140)** was followed using the hydroxy ester **(130)** (1.0 g, 4.5 mmol) and SMM (0.32 g, 4.5 mmol). The reaction mixture turned pale yellow on the addition of SMM and the temperature rose from 17 to 22°C. After 25min, work-up and purification afforded *methyl 3-hydroxy-3-(4-methoxyphenyl)-2-(methylthiomethyl)propanoate* **(145)** (0.76 g, 62.2%) (Found: M^+, 270.0934. $C_{13}H_{18}O_4S$ requires: *M*, 270.0925); δ_H 2.00/2.03 (CH_3S), 2.42-2.98 (3H, series of multiplets, C*H*C*H*$_2$S), 3.56/3.70 and 3.77/3.78 (6H, 2xs, 2xCH_3O), 4.81/4.88 (1H , d, C*H*OH) and 6.87 and 7.23 (4H, dd, ArH); δ_C 15.7 (CH_3S), 32.0/33.2 (CH_2S), 51.7/51.8 (CH_3OC=O), 53.0/53.5 (*C*HC=O), 55.1 (CH_3OAr), 73.8/74.1 (CHOH), 113.7/113.9, 127.2/127.4, 133.2/133.3 and 159.2/159.4 (ArC) and 173.4/174.1 (C=O); *m/z* 270 (M^+, 15%) and 137 (100).

***Methyl 3-hydroxy-2-(methylthiomethyl)-3-(4-nitrophenyl)propanoate* (146)**

The procedure described for the synthesis of methyl 3-hydroxy-2-(methylthiomethyl)butanoate **(140)** was followed using the hydroxy ester **(131)** (1.5 g, 6.5 mmol) and SMM (0.46 g, 6.5

mmol). The reaction mixture turned a green-brown colour upon the addition of the SMM and the temperature rose from 18 to 22°C. After 20min, work-up and purification afforded *methyl 3-hydroxy-2-(methylthiomethyl)-3-(4-nitrophenyl)propanoate* **(146)** (0.97 g, 54.8%) (Found: M^+, 285.0663. $C_{12}H_{15}NO_5S$ requires: *M*, 285.0670); δ_H 2.03/2.10 (3H, s, CH_3S), 2.65-3.03 (3H, series of multiplets, CH_2S and CHC=O), 3.28/3.53 (1H, d, OH), 3.65 (3H, s, CH_3O), 5.12/5.15 (1H, t, CHOH) and 7.53 and 8.21 (4H, 2xdd, ArC); δ_C 15.9/16.1 (CH_3S), 31.4/33.5 (CH_2S), 52.0 (CH_3O), 52.2/52.4 (CHC=O), 72.8/73.0 (CHOH), 123.6/123.7, 126.9/127.0, 147.6/148.1 and 148.9 (ArC) and 173.4/173.5 (C=O); *m/z* 285 (M^+, 1%) and 87 (100).

***Thiomethylation of Methyl 2-(bromomethyl)-2-propenoate* (133)**

The procedure described for the synthesis of methyl 2-(methylthiomethyl)-2-propenoate **(147a)** from methyl 3-hydroxy-2-methylenepropanoate **(124)** was followed using methyl 2-(bromomethyl)-2-propenoate **(133)** (2.0 g, 11 mmol) and SMM (0.80g, 11 mmol). The temperature of the reaction mixture rose from 18 to 26°C on the addition of the SMM. After 30min, work-up yielded a crude mixture **(147a)** (62.6%), **(147c)** (8.1%) and **(147d)** (3.4%). Purification afforded three products: i) *methyl 2-(methylthiomethyl)-2-propenoate* **(147a)** (0.73 g, 43.9%); ii) *methyl 2-(methylthiomethyl)-3-(thiomethyl)propanoate* **(147c)** (0.10 g, 4.7%); and iii) *di(2-carbomethoxy-2-propenyl) sulphide* **(147d)** (73 mg, 5.8%) (Found: M^+, 230.0610. $C_{10}H_{14}O_2S$ requires: *M*, 230.0611); δ_H 3.33 (4H, s, 2xCH_2S), 3.78 (6H, s, 2xCH_3O) and 5.68 and 6.23 (4H, 2xs, 2xCH_2=C); δ_C 32.2 (CH_2S), 52.1 (CH_3O), 126.3

(CH_2=C), 136.7 (C=CH_2) and 166.6 (C=O).

***Thiomethylation of Methyl* (Z)-*2-(bromomethyl)-2-butenoate* (134)**

The procedure described for the synthesis of methyl 2-(methylthiomethyl)-2-propenoate **(147a)** from methyl 3-hydroxy-2-methylenepropanoate **(124)** was followed using the bromo ester **(134)** (1.1 g, 5.5 mmol) and SMM (0.30 g, 5.5 mmol). The temperature of the reaction mixture rose from 18 to 25°C. After 55min, work-up yielded three products identified *via* ^{1}H NMR spectoscopy as **(148a)** (40.8%), **(148b)** (30.6%) and **(148d)** (6.4%). Purification afforded two products:[§] i) *methyl 2-(methylthiomethyl)-2-butenoate* **(148a)** (0.33 g, 37.1%), [(Found: M^+, 160.0548. $C_7H_{12}O_2S$ requires: M, 160.0557); δ_H 1.85 (3H, d, CH_3CH), 2.05 (3H, s, CH_3S), 3.42 (2H, s, CH_2S), 3.74 (3H, s, CH_3O) and 6.95 (1H, q, CHCH); δ_C 14.5 (CH_3S), 15.3 (CH_3CH), 35.0 (CH_2S), 51.8 (CH_3O), 129.9 (C=CH), 139.3 (CH=C) and 167.3 (C=O)] and ii) *di(2-carbomethoxy-2-butenyl) sulphide* **(148d)** (63 mg, 8.8%) [(Found: M^+, 258.0926. $C_{12}H_{18}O_4S$ requires: M, 258.0925); δ_H 1.86 (6H, d, 2xCH_3CH), 3.50 (4H, s, 2xCH_2S), 3.75 (6H, s, 2xCH_3O) and 6.94 (2H, q, 2xCHCH$_3$); δ_C 14.6 (CH_3CH), 27.9 (CH_2S), 51.9 (CH_3O), 130.0 (C=CH), 140.0 (CH=C) and 167.3 (C=O); *m/z* 258 (M^+, 11%) and 113 (100)].

[§]The third product, which was not isolated, was identified by ^{1}H NMR spectroscopy of the crude product as *methyl 2-methylene-3-(thiomethyl)butanoate* **(148b)** (30.6%); δ_H 1.38 (3H, d, CH_3CH), 1.92 (3H, s, CH_3S), 3.73 (3H, s, CH_3O), 3.80 (1H, q, CHCH) and 5.63 and 6.12 (2H, 2xs, CH_2=C).

***Thiomethylation of Methyl* (Z)-*2-(bromomethyl)-3-phenyl-2-propenoate* (135)**

The procedure described for the synthesis of methyl 2-(methylthiomethyl)-2-propenoate **(147a)** from methyl 3-hydroxy-2-methylenepropanoate **(124)** was followed using the bromo ester **(135)** (2.1 g, 8.1 mmol) and SMM (0.56 g, 8.1 mmol). The reaction mixture turned pale yellow on the addition of SMM and the temperature rose from 22 to 28°C. After 25min, work-up yielded three products identified *via* ^{1}H NMR spectroscopy as **(149a)** (6.6%), **(149b)** (13.2%) and **(149d)** (6.4%). Purification afforded two products:[§] i) *methyl 2-(methylthiomethyl)-3-phenyl-2-propenoate* **(149a)** (1.0 g, 56.1%) [(Found: M^+, 222.0722. $C_{12}H_{14}O_2S$ requires: *M*, 222.0711); δ_H 2.09 (3H, s, CH_3S), 3.63 (3H, s, CH_3O), 7.34-7.48 (5H, m, ArH) and 7.75 (1H, s, CHAr); δ_C 16.2 (CH_3S), 30.5 (CH_2S), 52.2 (CH_3O), 128.6, 128.9, 129.5, 129.6, 135.0 and 140.6 (ArC, *C*=CH and *C*H=C) and 168.0 (C=O)]; and ii) *di(2-carbomethoxy-3-phenyl-2-propenyl) sulphide* **(149d)** (98 mg, 5.8%) [(Found: M^+, 382.1239. $C_{22}H_{22}O_4S$ requires: *M*, 382.1238); δ_H 3.73 (4H, s, 2xCH_2S), 3.83 (6H, s, 2xCH_3O), 7.32-7.50 (10H, m, 2xArH) and 7.74 (2H, s, 2xCHAr); δ_C 30.1 (CH_2S), 52.2 (CH_3O), 128.6, 128.9, 129.0, 129.7, 134.9 and 141.1 (ArC, *C*=CH and *C*H=C) and 167.8 (C=O)].

[§]The third product, which was not isolated, was identified by ^{1}H NMR spectroscopy of the crude product as *methyl 2-methylene-3-phenyl-3-(thiomethyl)propanoate* **(149b)** (13.2%); δ_H 1.97 (3H, s, CH_3S), 3.68 (3H, s, CH_3O), 4.96 (1H, s, CHS), 6.02 and 6.44 (2H, 2 x s, CH_2=C) and 7.18 to 7.56 (5H, m, ArH).

4.7 Synthesis of 2-Alkenoic Acids as Possible Necic Acid Precursors

4.7.1 Synthesis of 2-(Bromomethyl)-2-alkenoic Acids[97]

2-(Bromomethyl)-2-propenoic Acid **(150)**

A mixture of methyl 2-(bromomethyl)-2-propenoate **(133)** (29 g, 0.16 mol) and HBr (48% in H_2O, 150 ml) was boiled under reflux for 4h. After cooling the solution in ice the crude crystalline acid was separated *via* filtration and washed with ice-water (2x20 ml), hexane (2x10 ml) and dried *in vacuo*. The crude crystalline material was sublimed[§] *in vacuo* (0.05 mmHg) to give 2-(bromomethyl)-2-propenoic acid **(150)** (0.3 g, 1.1%) (collected at bath temp. *ca.* 35-37°C) m.p. 69-72°C (lit.,[107] 70-73°C); δ_H 4.17 (2H, s, CH_2Br) and 6.09 and 6.49 (2H, 2xs, CH_2C); δ_C 28.4 (CH_2Br), 131.5 (CH_2=C), 136.8 (*C*=CH_2) and 169.6 (C=O).

2-(Bromomethyl)-2-butenoic Acid **(151)**

The procedure described for the synthesis of 2-(bromomethyl)-propenoic acid **(150)** was followed using the bromo ester **(134)** (7.2 g, 38 mmol) and HBr (48% in H_2O, 100 ml). The crude product was washed with ice-water (2x20 ml), hexane (2x10 ml) and dried *in vacuo* to

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[§]Sublimation also gave 3-bromo-2-(bromomethyl)propanoic acid [§§][108] **(150a)**, (7.9 g, 20.3%) m.p. 97-99°C, (Collected at bath temp. *ca.* 105 - 110°C) [(Found: M^+, 243.8722. Calc. for $C_4H_6Br_2O_2$: *M*, 243.8734); δ_H 3.24 (1H, quintet, C*H*$(CH_2)_2$) and 3.76 (4H, 2 x dd $(CH_2)_2$CH); δ_C 29.8 (CH_2CH), 48.4 (*C*H$(CH_2)_2$) and 175.6 (C=O); *m/z* 244 (M^+, 3%) and 167 (100)].

give 2-(bromomethyl)-2-butenoic acid **(151)** (3.4 g, 50.0%), m.p. ($CHCl_3$) 104-106°C;[§] δ_H 1.96 (3H, d, CH_3CH), 4.22 (2H, s, CH_2Br) and 7.22 (1H, q, $CHCH_3$); δ_C 14.8 (CH_3CH), 23.27 (CH_2Br), 129.8 (C=CH), 145.9 ($CHCH_3$) and 170.3 (C=O).

2-(Bromomethyl)-3-phenyl-2-propenoic Acid **(152)**[109]

The procedure used for the synthesis of 2-(bromomethyl)-2-butenoic acid **(151)** was followed using the bromo ester **(135)** (6.7 g, 26 mmol) and HBr (48% in H_2O, 75 ml) to afford light brown crystals of 2-(bromomethyl)-3-phenyl-2-propenoic acid **(152)** (3.2 g, 50.2%), m.p. 162-164 ($CHCl_3$); δ_H, 4.41 (CH_2Br), 7.41-7.51 (5H, m, ArH) and 7.95 (1H, s, CHAr); δ_C 26.1 (CH_2Br), 127.9, 129.0, 129.9, 130.0, 134.0 and 145.0 (ArC, CHAr and C=CH) and 170.7 (C=O).

4.7.2 Synthesis of Acetylated Derivatives[92]

Acetylation of (Z)-2-(Bromomethyl)-2-butenoic Acid **(151)**

The bromo acid **(151)** (1.0 g, 5.6 mmol) was boiled under reflux in AcOH (30 ml) with AgOAc (0.93 g, 5.6 mmol) for 45 min. The mixture was filtered to remove the AgBr

[§]Reported without physical data.

precipitate and then concentrated *in vacuo* to give a mixture of two products:[§] i) (*Z*)-2-(acetoxymethyl)-2-butenoic acid **(153a)** (0.37 g, 41.6%) [δ_H 1.94 (3H, d, C*H*$_3$CH=C), 2.03 (3H, s, CH$_3$C=O), 4.83 (2H, s, CH$_2$O) and 7.27 (1H, q, C*H*CH$_3$)]; and ii) 3-acetoxy-2-methylenebutanoic acid **(153b)** (0.14 g, 15.9%) [δ_H 1.39 (3H, d, C*H*$_3$CHOAc), 2.05 (3H, s, CH$_3$C=O), 5.68 (1H, q, CHOAc) and 5.90 and 6.39 (2H, 2xs, CH$_2$=C)].

***Acetylation of (Z)-2-(Bromomethyl)-3-phenyl-2-propenoic Acid* (152)**

The bromo acid **(152)** (0.44 g, 1.7 mmol) was boiled under reflux in AcOH (20 ml) with AgOAc (0.28 g, 1.7 mmol) for 45 min. The mixture was filtered to remove the AgBr precipitate and then concentrated *in vacuo* to give a mixture of two products:[§] i) (*Z*)-2-(acetoxymethyl)-3-phenyl-2-propenoic acid **(153a)** (0.21 g, 56.9%) [δ_H 2.10 (3H, s, CH$_3$C=O), 4.95 (2H, s, CH$_2$OAc), 7.36 (5H, s, ArH) and 8.02 (CHAr)]; and ii) 3-acetoxy-2-methylene-3-phenylpropanoic acid **(153b)** (0.11 g, 28.2%) [δ_H 2.08 (3H, s, CH$_3$C=O), 5.95 and 6.51 (2H, 2xs, CH$_2$=C), 6.66 (1H, s, ArC*H*OAc) and 7.30-7.31 (5H, m, ArH)].

4.8 Synthesis of (*E*)-2-Isopropylcrotonic Acid (162)

***Ethyl 2-isopropylacetoacetate* (157)**[110]

Sodium metal (10 g, 0.44 mol) was added carefully, over a period of 1h., to dry ethanol (100

[§]The products were not isolated, but identified using ^{1}H NMR spectroscopy.

ml) in a 3-necked r.b. flask fitted with condenser, thermometer and a dropping funnel. A further quantity of dry ethanol (200 ml) was added and the mixture was heated to reflux. Ethyl acetoacetate **(156)** (52 g, 0.40 mol) was added dropwise over 40 min. and the resulting mixture then boiled under reflux for 30min. Isopropyl bromide (82 g, 0.67 mol) was added over 1h. with refluxing and the mixture was boiled under reflux for 24h. A white precipitate was produced and the supernatant solution turned yellow. The solution was decanted and the precipitate was washed with a small quantity of Et_2O which was then combined with the decanted solution. Water (200 ml) was added to the solution after which the mixture was acidified (pH 4) and extracted using Et_2O (3x200 ml) and then chloroform (100 ml) respectively. The combined organic extracts were washed with satd. brine (2x50 ml), dried (anhydr. $MgSO_4$), concentrated and then distilled to afford ethyl 2-isopropylacetoacetate **(157)** (48 g, 71.0%), b.p. 95-97°C/20 mmHg (lit.,[27] 93-94°C/18 mmHg); δ_H 0.83 and 0.87 (6H, 2xd, $(CH_3)_2CH$), 1.16 (3H, t, CH_3CH_2), 2.10 (3H, s, $CH_3C{=}O$), 2.30 (1H, m, $CH(CH_3)_2$), 3.08 (1H, d, $CHC{=}O$) and 4.08 (2H, q, CH_2O), δ_C 13.9 (CH_3CH_2), 20.2 and 20.3 ($(CH_3)_2CH$), 28.4 ($CH_3C{=}O$), 28.9 ($CH(CH_3)_2$), 60.9 (CH_2CH_3), 67.5 ($O{=}CCHC{=}O$), 169.0 (CO_2CH_2) and 202.9 ($CH_3C{=}O$).

***Ethyl 3-hydroxy-2-isopropylbutanoate* (158)**[111]

A solution of ethyl 2-isopropylacetoacetate **(157)** (158 g, 0.78 mol) in ethanol (200 ml) was stirred in an ice/salt bath at 0°C. A similarly cooled solution of $NaBH_4$ (37 g, 0.97 mol) in ethanol (600 ml) and water (200 ml) was added over 90min. The reaction was monitored

using TLC and after 2h. quenched with dil. HCl (50 ml). The organic material was extracted using Et_2O (3x100 ml) followed by chloroform (100 ml), and the combined extracts were dried (anhydr. $MgSO_4$), concentrated *in vacuo* and distilled to afford ethyl 3-hydroxy-2-isopropylbutanoate **(158)** (73 g, 54.1%), b.p. 54-55°C/ 0.1mmHg (lit.,[27] 69-72/1 mmHg); δ_H 0.94 and 0.98 (6H, 2xd, $(CH_3)_2CH$), 1.15 (3H, d, CH_3CH), 1.22 (3H, t, CH_3CH_2), 2.10 (1H, m, $CH(CH_3)_2$), 2.25 (1H, t, CHC=O), 4.02 (1H, brq, CHOH) and 4.12 (2H, q, CH_2O); δ_C 13.9 (CH_3CH_2), 18.8/19.6 (CH_3CHOH), 20.3/20.5 and 20.9/21.6 ($(CH_3)_2CH$), 26.8/27.4 ($CH(CH_3)_2$), 58.7/58.9 ($CHCO_2$), 59.7/59.9 (CH_2CH_3), 65.9/66.1 (CHOH) and 173.4/174.8 (C=O).

***Ethyl* (E/Z)-*2-isopropylcrotonate* (159-160)**[112]

A solution of ethyl 3-hydroxy-2-isopropylbutanoate **(158)** (16 g, 89 mmol) in pyridine (32 ml) was cooled to 2°C in an ice/salt bath. $POCl_3$ (8.4 ml, 90 mmol) was added slowly with vigorous stirring after which the solution was stirred for 2d at r.t. After boiling under reflux for 4h., the mixture was decanted into a separating funnel containing crushed ice (100 g) and the reaction flask was also rinsed with a small mass of ice followed by hexane (50 ml). The mixture was extracted using hexane (3x100 ml) and the combined extracts were washed with dil. HCl (2x50 ml) and then satd. brine (2x50 ml). The organic phase was dried (anhydr. $MgSO_4$), concentrated *in vacuo* and distilled to yield an inseparable mixture (2.9 g, 45.3%),

b.p. 66-68°C/ 14mmHg, of two products:[§] i) ethyl (*E*)-2-isopropyl crotonate **(159)** [δ_H 1.14 (6H, d, $(CH_3)_2CH$), 1.26 (3H, t, CH_3CH_2), 1.79 (3H, d, $CH_3CH=C$), 2.92 (1H, septet, $CH(CH_3)_2$), 4.15 (2H, q, CH_2O) and 6.65 (1H, q, $C=CHCH_3$)]; and ii) ethyl (*Z*)-2-isopropylcrotonate **(160)** [δ_H 1.02 (6H, d, $(CH_3)_2CH$), 1.30 (3H, t, CH_3CH_2), 1.87 (3H, d, $CH_3CH=C$), 2.65 (1H, m, $CH(CH_3)_2$), 4.21 (2H, q, CH_2O) and 5.80 ($C=CHCH_3$)].

(E)-*2-Isopropylcrotonic Acid* (162)[27]

The *E/Z* mixture of ethyl 2-isopropylcrotonate (5.0 g, 32 mmol) was added to a 3.5M solution (60ml) of KOH in ethanol-water (5:1) and the resulting mixture boiled under reflux for 4h. The solution was concentrated *in vacuo* to a volume of *ca.* 10ml and then acidified with dil. HCl (20 ml). The product mixture was placed in ice overnight to yield a white crystalline product. The crystals were washed with ice-water (3x5 ml) to afford (*E*)-2-isopropylcrotonic acid **(162)** (1.3 g, 35.0%), m.p. 53-54°C (lit.,[27] 54°C); δ_H 1.18 (6H, d, $(CH_3)_2CH$), 2.83 (3H, d, $CH_3CH=C$), 2.94 (1H, hept, $CH(CH_3)_2$), 6.87 (1H, q, $C=CHCH_3$); δ_C 13.97 (CH_3CH), 20.52 (($CH_3)_2CH$), 26.73 ($CH(CH_3)_3$), 138.0 ($C=CH$), 138.5 ($CHCH_3$) and 173.6 ($C=O$).

[§]The products were not isolated, but identified using 2D NMR spectroscopy. A third compound was identified in the crude mixture as ethyl 2-isopropyl-3-butenoate **(161)**. δ_H 0.86 (6H, 2xd, $(CH_3)_2CH$), 1.28 (3H, t, CH_3CH_2), 1.96 (1H, m, $CH(CH_3)_2$), 2.62 (1H, t, $CHCH=CH_2$), 4.10 (2H, q, CH_2CH_3), 5.05 (2H, 2xd, $CH_2=CH$), 5.78 (1H, m, $CH=CH_2$).

4.9 Synthesis of *Senecio* Alkaloid Analogues[9]

9-Retronecine (E)-*2-isopropylcrotonate* (168)

1,1-Carbonyldiimidazole (CDI) **(164)** (0.15 g, 0.91 mmol) and (*E*)-2-isopropylcrotonic acid **(162)** (0.11 g, 0.86 mmol) were stirred under N_2 in dry, ethanol-free chloroform[113] for 45 min. The evolution of CO_2 gas was evident during this period. Retronecine **(4)** (0.14 g, 0.87 mmol) was added and the reaction stirred under N_2 for 48h. The crude product was washed with 10% $NaHCO_3$ (2x5 ml) and purified using PLC [on silica; elution with $CHCl_3$-CH_3OH-NH_3OH (85:14:1)] to afford *9-retronecine (E)-2-isopropylcrotonate* **(168)**[§] (22 mg, 9.6%), (Found: M^+, 265.1672. $C_{15}H_{23}NO_3$ requires: *M*, 265.1677), δ_H 1.14 (6H, dd, $(CH_3)_2CH$), 1.80 (3H, d, $CH_3CH{=}C$), 2.07 (2H, m, CH_2CHO), 2.88 (1H, m) and 3.53 (1H, m) [CH_2CH_2N], 2.92 (1H, heptet, $CH(CH_3)_2$), 3.45 (1H, 2xdd) and 4.11 (1H, d) [$CHCH_2N$], 4.38 (1H, s, *CH*OH), 4.43 (1H, s, *CH*C=CH), 4.69 (2H, s, CCH_2O), 5.74 (1H, s, C=*CH*CH_2) and 6.68 (1H, q, C=*CH*CH_3); δ_C 14.0 (*C*H_3CH=C), 20.6 ((*C*H_3)$_2$CH), 27.0 (*C*H$(CH_3)_2$), 35.6 (*C*H_2CHOH), 53.5 (CH_2CH_2N), 60.5 (CCH_2O), 61.8 ($CHCH_2N$), 70.7 (CHOH), 77.9 (*C*HC=CH), 126.4 (C=*C*HCH_2N), 133.5 (*C*=CHCH_2N), 137.0 (C=*C*HCH_3), 138.2 (*C*=CHCH_3) and 167.4 (C=O).

[§]See Figure 12 on page 59 for numbering of compound **(168)**.

***Retronecine disalicylate* (170)**

1,1-Carbonyldiimidazole (CDI) **(164)** (0.44 g, 2.7 mmol) and salicylic acid **(169)** (0.36 g, 2.6 mmol) were stirred under N_2 in dry, ethanol-free chloroform[113] for 45min. Retronecine **(4)** (0.40 g, 2.6 mmol) was added and the reaction was stirred under N_2 for 48h. The crude product was washed with 10% $NaHCO_3$ (2x5 ml) and purified using PLC [on silica; elution with $CHCl_3$-CH_3OH-NH_3OH (85:14:1)] to yield *retronecine disalicylate* **(170)**[§] (53 mg, 5.3%), (Found: M^+, 395.1362. $C_{22}H_{21}NO_6$ requires: *M*, 395.1369); δ_H 2.24-2.26 (2H, m, CH_2CHO), 2.75 (1H, m) and 3.44 (1H, t) [CH_2CH_2N], 3.55 (1H, dd) and 4.86 (1H, d) [CHCH_2N], 4.52 (1H, s, C*H*C=CH), 4.95 (2H, dd, CCH_2O), 5.54 (1H, s, CHO), 6.00 (1H, s, CH_2CH=C) and 6.77-7.65 (8H, series of multiplets, 2xArH); δ_C 34.6 (CH_2CH_2CHO), 53.6 (CH_2CH_2N), 61.3 (CH=CCH_2O), 62.9 (C=CHCH_2N), 75.2 (CH_2CHO), 76.1 (*C*HC=CH), 111.9, 112.3, 117.6, 117.7, 119.1, 119.3, 129.4, 129.6, 135.9 and 161.7 (2xArC), 129.3 (CHC=*C*HCH_2), 132.9 (CH*C*=CHCH_2), 169.0 (CH_2CHOC=O) and 169.6 (CH=CCH_2OC=O).

[§]See Figure 13 on page 60 for numbering of compound **(170)**.

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