Studies in Marine Natural Products: *Onchidoris bilamellata*, Nanaimoal and Capnellene

by

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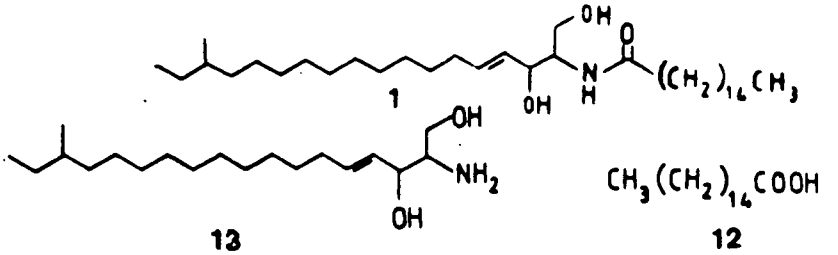
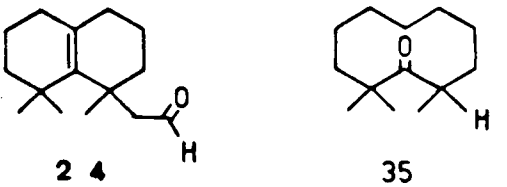
Abstract

The following thesis is divided into three chapters. The first describes the isolation and identification of a sphingolipid 1 from the methanolic skin extract of the British Columbia nudibranch Onchidoris bilamellata. The long chain base has been identified as (E)-1,3-dihydroxy-2-amino-16-methyl-4-octadecene (13) and the fatty acid moiety as palmitic acid (12). This ceramide possesses antibacterial activity towards the microorganisms Bacillus subtilis and Staphylococcus aureus.



1 13 12

The second chapter presents our attempt to synthesize a hypothetical structure of nanaimoal (24), a marine sesquiterpenoid, isolated from the British Columbia nudibranch Acanthadoris nanaimoensis. The proposed route envisaged photolysis of a 2,2,10,10-tetrasubstituted cyclodecanone. This work lend to a study of the solution photochemistry of 2,2,10-trimethyl-cyclodecanone (35).



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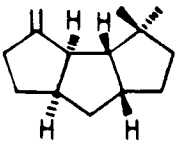

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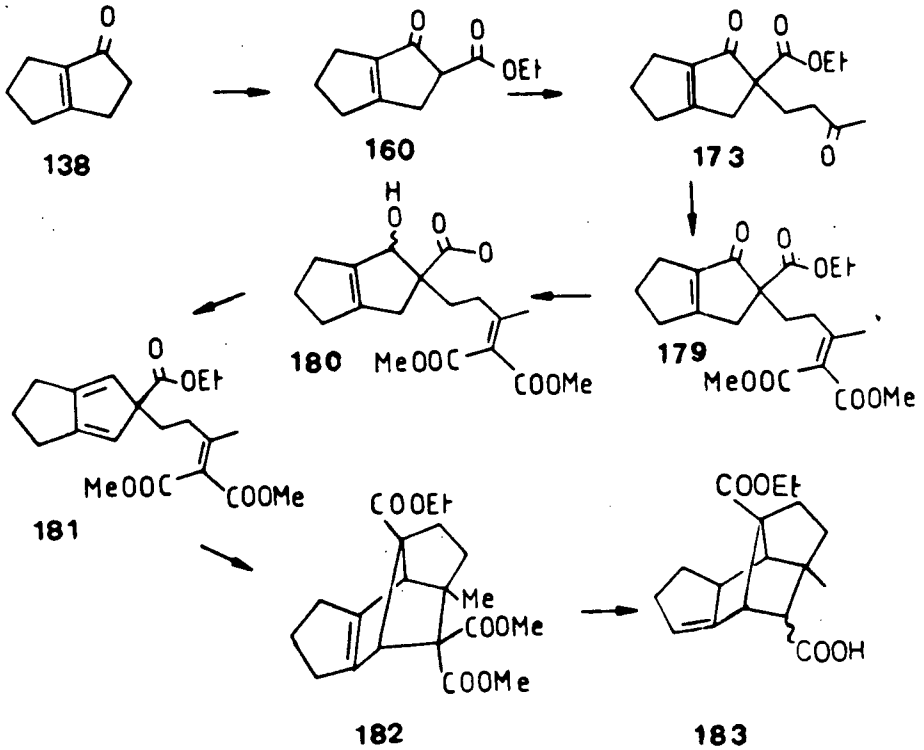
The last chapter outlines studies directed toward the synthesis of capnellene (51), a tricyclopentanoid obtained by Djerassi and co-workers

from the soft coral Capnella imbricata. Starting with an improved synthesis of the known ketone $\Delta^{1,5}$-bicyclo[3.3.0] octen-2-one (138), an acylation method was developed for the preparation of $\Delta^{1,5}$-3-carboethoxybicyclo-[3.3.0] octen-2-one (160). The procedure is of general utility and has been extended to related ketones. This unsaturated keto-ester underwent a Michael addition with methyl vinyl ketone to give 178. Selective Knoevenagal condensation of the methyl ketone produced $\Delta^{1,5}$-3-carboethoxy-3-(dimethyl-3-methyl-3-butenyl-4,4-dicarboxylate)-bicyclo[3.3.0] octen-2-one (179). Reduction of the unsaturated ketone and dehydration of the allylic alcohol produced a 1,1,3,4-tetrasubstituted cyclopentadiene derivative 181. Intramolecular Diels-Alder cyclization of the latter afforded the tetracyclic tricarboxylic ester 182. Selective hydrolysis of the malonic ester functionality of 182 followed by decarboxylation led to 183, a key intermediate for the ultimate construction of the capnellane ring system.



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List of Abbreviations

mCPBA:	meta-chloroperbenzoic acid
DEPC:	diethyl pyrocarbonate
DMAP:	4-dimethylaminopyridine
DME:	dimethoxyethane
DMF:	N,N-dimethylformamide
DMSO:	dimethyl sulfoxide
DNPH:	2,4-dinitrophenylhydrazine
Et:	ethyl
$Eu(fod)_3$:	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctanedionatoeuropium (III)
GLC:	gas-liquid chromatography
HMPA:	hexamethylphosphoramide
HPLC:	high pressure liquid chromatography
IR:	infrared
LDA:	lithium diisopropylamine
Me:	methyl
MP:	melting point
MS:	mass spectrum
MsCl:	methane sulfonyl chloride
NMR:	nuclear magnetic resonance
PTLC:	preparative thin layer chromatography
RT:	room temperature
SFORD:	single frequency off resonance decoupling
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMS:	tetramethylsilane
pTsOH:	para-toluenesulfonic acid
UV:	ultraviolet

Acknowledgements

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I would especially like to thank my two supervisors, Dr. R.J. Andersen at UBC, and Dr. A.G. Fallis at MUN, who allowed such an inconvenient arrangement to take place, for their understanding, advice and help throughout this work.

Without the support of my husband who knew how to put problems back into perspective, this research would not have taken place.

Last and certainly not least, Miss Teresa Barker for her continuous help with typing this thesis over and over again!

Chapter 1

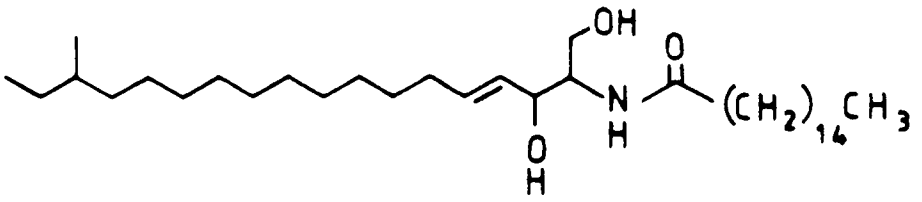
Onchidoris bilamellata

I.1. Introduction[1]

This chapter describes the isolation and identification of a sphingolipid 1 from Onchidoris bilamellata, a nudibranch collected in British Columbia.

A short introduction to the biology of nudibranchs, preceeds an outline of the chemical aspects in the study of opisthobranch molluscs. Some examples of metabolites isolated from opisthobranch molluscs with novel structures and interesting biological properties are included.

The work related to the identification of sphingolipid 1 obtained from methanolic skin extracts of O. bilamellata is then presented. This is followed by a discussion of the chemistry, biochemistry and biology of molecules related to 1.



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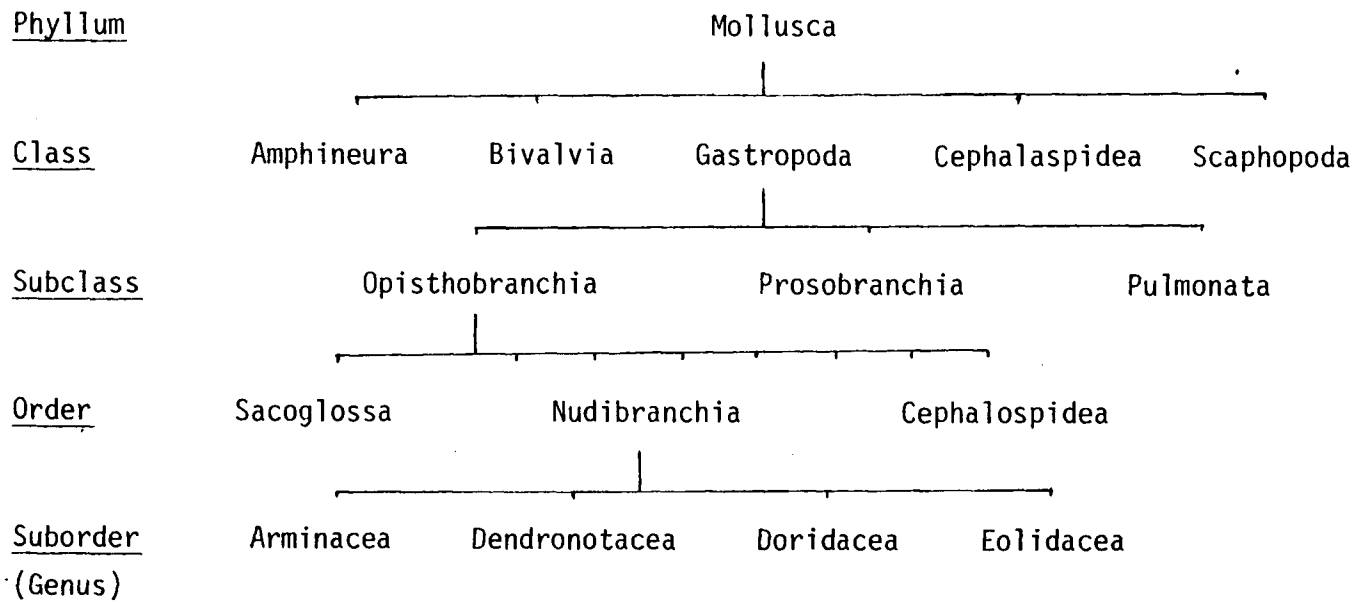
The phyllum Mollusca contains the second largest number of invertebrate species. Gastropoda represents its major class (see Scheme 1), with specimens found in a large variety of marine and terrestrial habitats. Members of this class have an asymmetric body and only one shell (univalve).

Scheme 1

Classification of the Phyllum Mollusca



N.B. Organisms are classified according to Kozloff[4].

One of the three subclasses of gastropods is the Opisthobranchia, with mainly marine members characterized by a shell and mantle cavity reduced in size or absent. The Opisthobranchia can be further subdivided into eight orders,. including: Sacoglossa, Nudibranchia and Cephalospidea. In the order Nudibranchia (nudibranchs are also known as sea slugs or naked shellfish) the animals have no shell or mantle cavity and as indicated by their name, do not have internal gills. Their body assumes an elongated form with a bilateral symmetry. Among the Nudibranchia, members of the suborder Doridaceae are characterized by the presence of a secondary gill ring encircling the dorsal anus[2].

Figure 1 shows a dorsal view of a dorid nudibranch. Members of this suborder vary from 1 to 12 cm in length and from 0.5 to 3 cm in thickness. Their color ranges from white to numerous shades of yellow and orange, often with some particular color pattern ("spots") on their mantle. They are found on rocky surfaces from the shore line up to depths of more than 18 m.

A special morphological feature worth mentioning is the two rhinophores, which represent modified tentacles used as sense organs. Experiments have shown that rhinophores are the most likely site for chemoreception in nudibranchs[3].

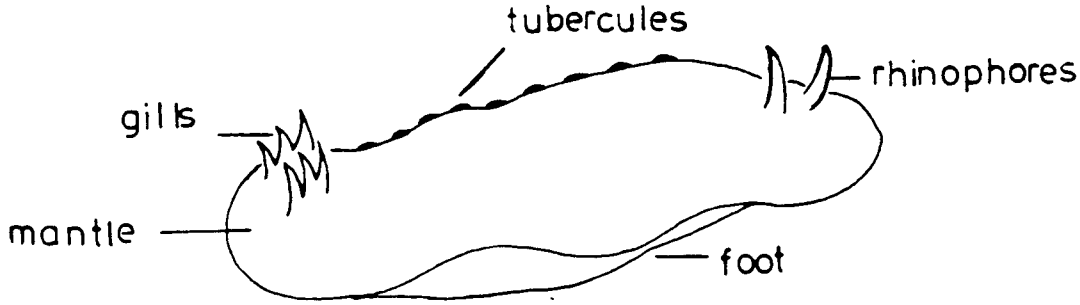


Figure 1

Dorsal View of a Dorid Nudibranch

Nudibranchs are slow-moving organisms without an exterior shell and with no other obvious protective feature. Four groups of animals have been suggested as possible predators[5]: other opisthobranchs, crustaceans, sea stars and fish. The fact that nudibranchs avoid direct predation has raised interest among biologists.

L.G. Harris[5] has reviewed the results of several studies concerning nudibranch defensive mechanisms. He grouped them into five categories, as follows:

1) Behavioral response
2) Spicules
3) Nematocysts
4) Color camouflage
5) Chemical secretions

Experiments have shown that upon disturbance, the behavior of nudibranchs is altered. Immediate retraction of rhinophores and gills and sometimes swimming can be observed[6]. Although this is a response to being attacked, it does not explain the ability of nudibranchs to survive since their escape is usually slow in comparison to the predator's speed.

Spicules of a calcareous nature are present in the mantle of some dorid species. Paine[7] postulated that these give the nudibranchs a rather rigid shape and make them difficult for other opisthobranchs to swallow.

Nematocysts are cells containing stinging structures originating from ingested coelenterates. Stored by some nudibranchs, they can be released when the animal is disturbed[8]. Different types of nematocyst exist and some nudibranchs appear to select the type they store. It is believed that some types of nematocyst are more effective against certain predators. Of the

four nudibranch suborders, only three are known to feed on coelenterates; the Eolidacea, Dendronotacea and Arminacea. Dorid nudibranchs feed predominantly on sponges, bryozoans and colonial tunicates[5] and do not utilize nematocysts for defense.

Coloration may be interpreted as a camouflage in some cases (white nudibranchs on white coral), or as a warning in the case of brightly colored nudibranchs. Often, the pigmentation of the nudibranch varies with its diet. The ability of fish to perceive color is still uncertain[9] and information on other predators is lacking. Hence, aspects of this defensive mechanism remain to be investigated.

The final and most interesting means of protection from a chemist's point of view are the secretions emanating from epidermal glands. These secretions are designated as defensive because they are usually emitted when the animal is disturbed. It was reported in the early literature that the secretions from eolid nudibranchs might be strong acids such as HCl and H_2SO_4[10]. Recently, it has been shown that organic molecules with interesting structures are secreted by some species[8,11]. In some cases the defensive molecules are related to a dietary source[8].

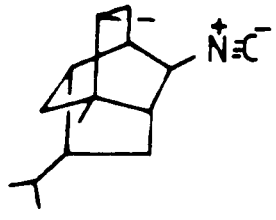
A critical study of the relative importance of the different defensive mechanisms in nudibranchs is difficult due to the limited amount of information available concerning predator-prey interactions. However, it seems very likely that chemical secretions may play an important defensive role.

It must be stated that such defensive substances have not been unequivocally proven to exist in nudibranchs. However, on the basis of studies involving other organisms such as arthropods[12], it would be logical to hypothesize that defensive secretions are also operative in nudibranchs.

Research in marine natural products chemistry has made significant advances in the last ten years. The first book to appear in this field was edited by P.J. Scheuer[13] in 1973, while one of the first review papers was written in 1974 by D.J. Faulkner and R.J. Andersen[14]. Since then, many other review papers, symposia proceedings and structural papers have been published. Among these, two reviews deal with the chemistry of the molluscs in general[15,16], and with the opisthobranch molluscs in particular[17].

The following examples illustrate the variety of novel structures and biological properties that have been assigned to compounds isolated from opisthobranch molluscs.

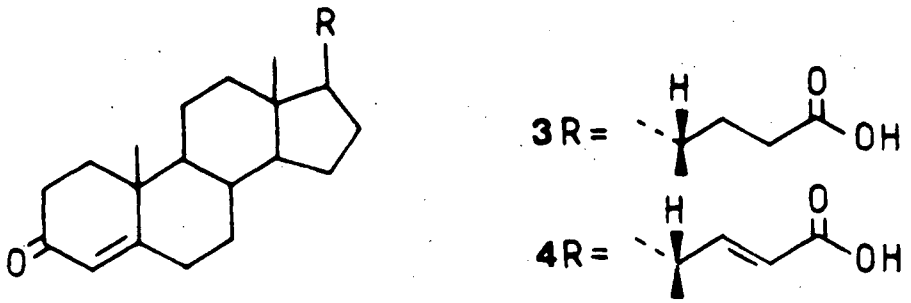
The rearranged terpenoid 9-isocyanopupukeanane (2) was isolated from both the nudibranch Phyllidia varicosa and its prey, a sponge from the Hymeniacidon sp.[8]. The nudibranch was known to produce a smelly substance lethal to small fish and crustaceans. Allomone 2 was shown to have a certain specificity in killing small crustaceans[18].



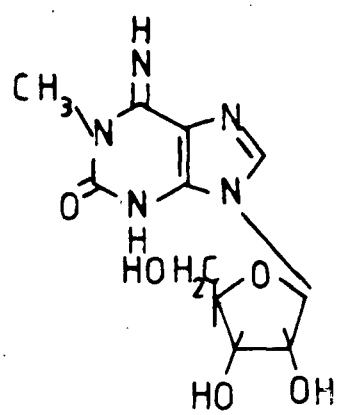
2

A novel steroidal ketone 3 isolated from Aldisa sanguina cooperi shows antifeedant activity in a standard goldfish bioassay[19]. It is believed that the dorid nudibranch obtains an inactive metabolite from its

prey, the sponge Anthoarcurata gracea, and modifies it to produce the two steroidal ketones 3 and 4.



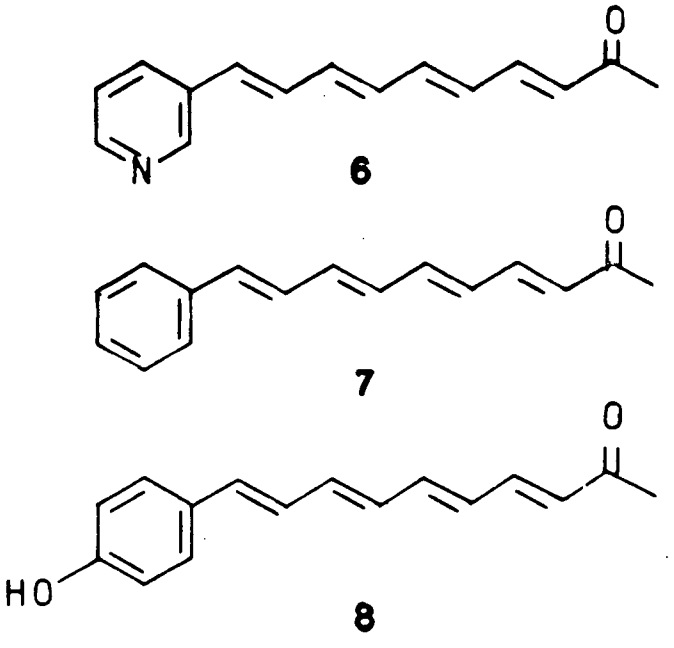
Doridosine[20] (5), the first purine base isolated from a nudibranch, produces hypotension, bradycardia, coronary dilation and relaxation of smooth muscle in mammals for many hours. (Other analogs act for only a few minutes.) This new hypotensive N-methyl purine riboside 5 has been isolated from the aqueous extract of the digestive glands of Anisodoris nobilis.



5

Navanax inermis of the order Cephalospidea is known to be a voracious predator on other opisthobranch molluscs[21]. It locates its prey by contact chemoreception. N. inermis recognizes the mucus trail of an acceptable prey

and follows it to its source. N. inermis also produces a "trail-breaking pheromone". When secreted by an individual, this pheromone causes an individual of the same species to turn away from the mucus trail it is following at an angle greater than 90°. Navenones A (6), B (7) and C (8) have been extracted from the colored secretion emitted when the animals are irritated. When present in a 4:2:1 mixture (ratio found in the extract) they elicit the trail-breaking response.



Many other structurally interesting molecules have been isolated from the skin extracts or the digestive gland extracts of the opisthobranch molluscs.

I.2. Results

As part of a program aimed at studying the chemistry of British Columbia nudibranchs, we have examined Onchidoris bilamellata. Interest in this organism arose when we noticed that the methanolic extract of this species possesses antibacterial activity towards the microorganisms Bacillus subtilis and Staphylococcus aureus.

There are only two studies directly related to O. bilamellata in the biological or chemical literature. The first[22] is concerned with the population ecology of O. bilamellata in Robin Hood's Bay, England. The second study[23] is related to the "effects of aromatic petroleum hydrocarbons on the chemosensory behavior of O. bilamellata", and it was done at the University of Washington, Seattle.

Onchidoris bilamellata is classified as follows[4]:

Phyllum: Mollusca

Class: Gastropoda

Subclass: Opisthobranchia

Order: Nudibranchia

Suborder: Doridacea

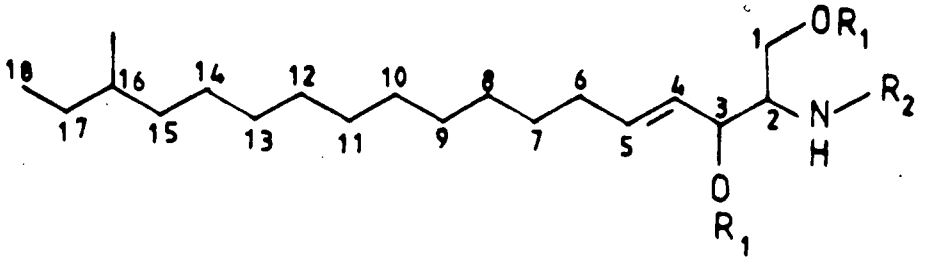
Specimens of O. bilamellata were collected by hand, from the south shore of English Bay, Vancouver, at low tide during the periods November 1979 to May 1980 and February 1981 to May 1981. These abundant intertidal organisms were usually found on the undersides of rocks, especially where the barnacles upon which they feed are present.

The nudibranchs, which vary in colour from beige-tan to brown (present in bands), have an average size of 1 cm and an average dry weight of 75 mg.

Following collection, the nudibranchs were stored in methanol at -35°C for several weeks. After thawing, the supernatant was filtered, evaporated

to one half of the original volume and partitioned between brine and ethyl acetate. After drying the organic extract and evaporation of the solvent, the oily residue was purified by silica column chromatography. Elution of the active fraction from the column was facilitated by a gradient of increasing solvent polarity. The fractions obtained were screened for antibacterial activity. The fractions which gave a positive result were further purified by preparative thin layer chromatography (PTLC).

Ceramide 1, with a free primary alcohol has been isolated from O. bilamellata and is responsible for the antibacterial activity. By means of spectral analysis and chemical correlations, the long chain base has been characterized as (E)-1,3-dihydroxy-2-amino-16-methyl-4-octadecene (13) and the fatty acid moiety as palmitic acid (12).



	R_1	R_2
1	H	$CO(CH_2)_{14}CH_3$
9	$COCH_3$	$CO(CH_2)_{14}CH_3$
13	H	H

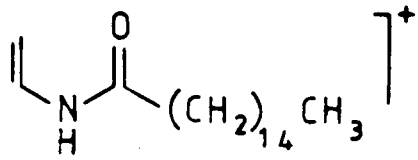
12 $CH_3(CH_2)_{14}COOH$

Appromixately 20 mg of 1 was obtained from 1200 to 1500 nudibranchs (yield ≃ 0.02% of dry weight of animals).

The MS (Figure 4) of 1 gives a parent ion of weak intensity at m/z = 533.5173 (Exact Mass calculated 533.5155) corresponding to the molecular formula $C_{35}H_{67}NO_2$. A fragment resulting from the loss of H_2O at m/z 515 is observed.

The MS of the diacetylated derivative 9 (Figure 7) displays a molecular ion at m/z = 635.5481 (Exact Mass calculated 635.5470) corresponding to $C_{39}H_{73}NO_5$ and fragments resulting from the loss of two residues of acetic acid at m/z = 575 and 515. The latter result indicated that the molecular formula of the parent compound 1 was therefore $C_{35}H_{69}NO_3$ and that the molecular ion was not actually observed in the MS. Hence, the isolated molecule has two sites of unsaturation and two alcohol functionalities.

A major ion observed in the MS of both 1 and 9 (Figures 4 and 7) at m/z = 280 ($C_{18}H_{34}NO$) results from an allylic cleavage between C(2) - C(3) followed by elimination of H_2O, to give 10. A fragment at m/z 298 resulting from this allylic cleavage before the loss of H_2O is also present.



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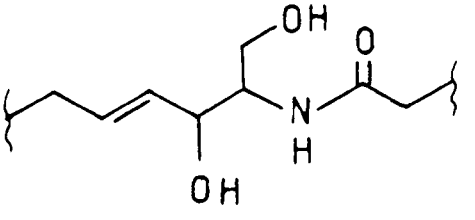
The IR spectra of ceramide 1 and its diacetylated derivative 9 (Figures 3 and 6) show absorptions at 3400 and 1660 cm^{-1}, corresponding to an amide functionality, which accounts for one degree of unsaturation.

The upfield region of the ^1H NMR spectrum of 1 (Figure 2, Table 1) indicated the presence of: two primary methyl groups (at δ = 0.86, 0.89 ppm, two triplets, J = 7 Hz); a secondary methyl group (at δ = 0.85 ppm, doublet, J = 7 Hz) and a straight chain hydrocarbon. Proton-proton spin decoupling experiments (Table 2) performed by irradiating the signals resonating between δ = 3.5 and 6.0 ppm and integrating for seven protons, suggested the presence of partial structure 11 in the molecule. Therefore partial structure 11 accounts for the second degree of unsaturation (a trans double bond) and for the relative position of the two alcohol functionalities.



11

A SFORD ^{13}C NMR spectrum (Table 3) of 1 confirmed the presence of an amide, a 1,2-disubstituted double bond and of two carbons attached to oxygen atoms. Comparison of the chemical shift values of the three methyl carbons (13.7 ppm for C-16, 10.8 ppm for C-18, 18.8 ppm for C-19) with those in the literature[24] for n-decane (13.9 ppm) and 3-methylheptane (11.3 ppm for C-1, 19.3 ppm for C-8) showed that one end of the molecule consisted of an unbranched chain, while the other had a methyl at the anteiso position ($-CH(CH_3)CH_2CH_3$).

Table 1

400 MHz 'H NMR Spectral Data

H on C#	Ceramide 1	diacetylated derivative 9	triacetylated derivative 13
2H-1	3.93 (m)	4.05 (dd,4.5,12)	4.05 (dd,4.5,12)
		4.32 (dd,6,12)	4.31 (dd,6,12)
1H-2	3.71 (m)	4.49 (m)	4.44 (m)
1H-3	4.33 (m)	5.30 (t,7)	5.28 (t,7)
1H-4	5.53 (dd,15,7)	5.40 (dd,15,7)	5.39 (dd,15,7)
1H-5	5.79 (dt,15,7)	5.82 (dt,15,7)	5.80 (dt,15,7)
2H-6	2.06 (q,7)	2.06 (q,7)	
$(CH_2)_n$	1.26 (s)	1.26 (s)	1.26 (s)
2'	2.23 (t,8)	2.12 (t,8)	
16*	0.86 (t,7)	0.86 (t,7)	
18*	0.89 (t,7)	0.88 (t,7)	0.88 (t,7)
19	0.85 (d,7)	0.85 (d,7)	0.85 (d,7)
NH	6.24 (bd,9)	5.63 (bd,9)	5.66 (bd,9)
$NHCOCH_3$*			2.00 (s)
$OCOCH_3$*			2.06 (s)
			2.07 (s)

* interchangeable

Numbers represent the chemical shifts δ (ppm). Multiplicities and coupling constants (Hz) are in parantheses.

Table 2

Proton-Proton Spin Decoupling Experiment Performed on Diacetylated Derivative 9

δ^a	5.82	5.63	5.40	5.30	4.49	4.32	4.05	2.06
J^b	(dt,15,7)	(bd,9)	(dd,15,7)	(t,7)	(m)	(dd,6,12)	(dd,4.5,12)	(q,7)
	I^c	D^d	(d,7)					D
DECOUPLING EXPERIMENTS	D	I	D		dm			
	(t,7)	D	I	D				
			D	I	D			
	T	(s)		(d,7)	I	D	(d,12)	
	S				D	I	D	
					(bdd, 8,6)	D	I	

a. chemical shift of original spectrum (in ppm)

b. original multiplicity observed, coupling constants in Hertz

c. irradiated signal

d. indicates distorted signal due to proximity to the irradiated signal on the chemical shift scale or due to a real coupling

Table 3

100.1 MHz ^{13}C NMR Spectral Data for Ceramide 1

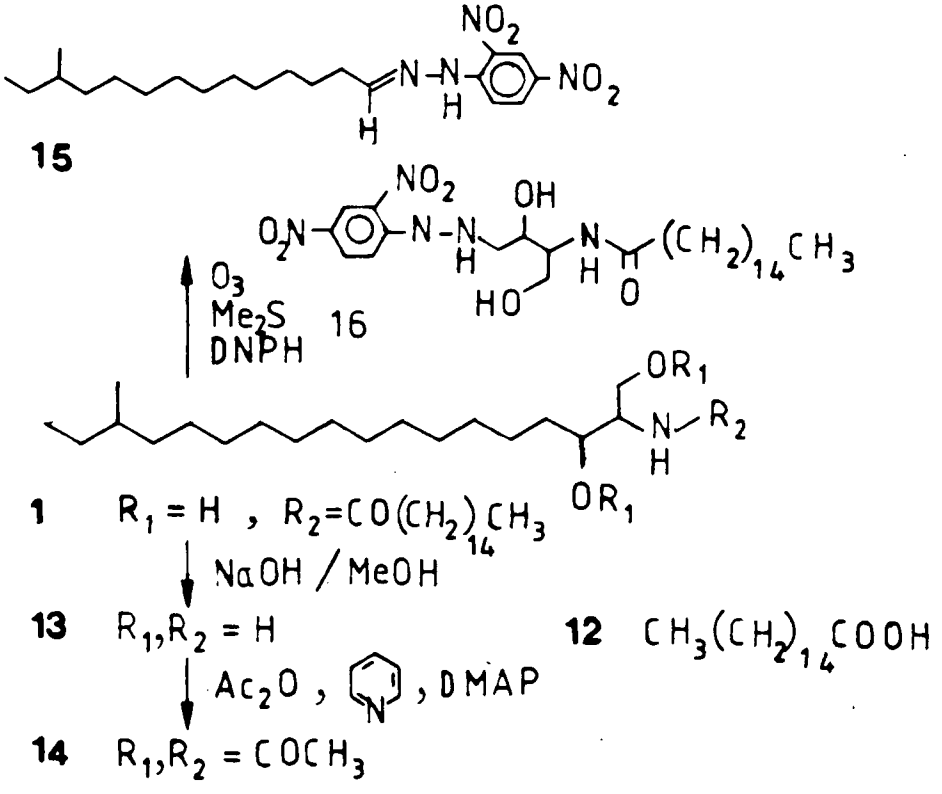
C #	δ (multiplicity)
1	61.9 (t)
2	53.8 (d)
3	74.0 (d)
4*	133.5 (d)
5*	128.8 (d)
6†	31.6 (t)
1'	172.3 (s)
2',†	36.3 (t)
16'	13.7 (q)
16	33.8 (d)
18	10.8 (q)
19	18.8 (q)

* † : interchangeable

In order to determine the number of carbon atoms on each side of the amide function and the location of the secondary methyl, a hydrolysis reaction and ozonolysis reaction were performed. The hydrolysis carried out under basic conditions cleaved the molecule into a C-16 straight chain fatty acid, 12 and a C-19 long chain unit possessing the anteiso methyl, 13. The long chain base was acetylated and the triacetyl derivative 14 characterized (MS, IR, 'H NMR). The products of the reductive ozonolysis reaction were isolated as their 2,4-dinitrophenylhydrazone derivatives, with molecular formulas of $C_{21}H_{34}N_4O_4$ for 15 and $C_{26}H_{43}N_5O_7$ for 16. This experiment confirmed the position of the double bond, by showing the presence of a C-15 unit on one side and a C-20 unit and remaining hetero-atoms on the other side.

Scheme 2

Reactions Performed on Ceramide 1



To ascertain whether the primary alcohol of ceramide 1 was an artifact of the isolation procedure, the extraction of one hundred and fifty nudibranchs was performed within ten minutes of their collection (see Experimental). After acetylation and purification of the crude extract, 2 mg of a diacetylated compound identical to 9 (Co-TLC and ^{1}H NMR) was isolated. This yield (0.015% of dry weight) is very similar to the one obtained when the nudibranchs were stored in methanol at -35°C for several weeks before extraction (0.02% of dry weight).

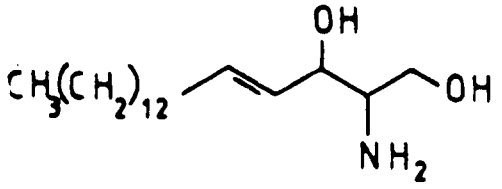
It is known from the literature[25,29] that 12 h is needed to hydrolyze cerebrosides and glycolipids under acidic conditions: 1M HCl/MeOH/100°C; and 2 h to hydrolyze sphingomyelins under acidic conditions: 2M HCl/100°C, or 20 min under basic conditions: 1M NaOH/MeOH/37°C. It seems safe to assume that ceramide 1 obtained from the skin extracts of *O. bilamellata*, exists with a free primary alcohol.

In order to learn more about the bioligical role of ceramide 1, we performed an antifeedant activity test[38]. The response of the fish to food pellets covered with 1 does not encourage us to believe that sphingolipid 1 is used for chemical defense purposes towards fish. However, this result is maybe not so surprising since *O. bilamellata* is an intertidal organism, living under the surface of rocks, where mainly crustaceans are present. Unfortunately, not enough sample of 1 was available to perform tests on small crabs and crustaceans found in the natural environment of *Onchidoris bilamellata*.

I.3. Discussion

The molecule responsible for the antibacterial activity of the organic skin extract of the nudibranch Onchidoris bilamellata belongs to a class of molecules called sphingolipids.

Terrestrial animals and plants have been the source of a wide variety of sphingolipids[25,26]. In animals, these lipids derive mainly from sphingosine (17), while in plants, derivatives of phytosphingosine (18) predominate. The isolated ceramides are N-acyl derivatives of 17 and 18 or related molecules. Often, a monosaccharide (cerebroside), a complex glycoside (ganglioside) or a phosphate ester (sphingomyelin) is attached to the primary alcohol.



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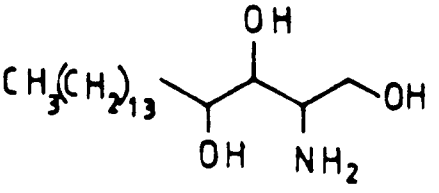
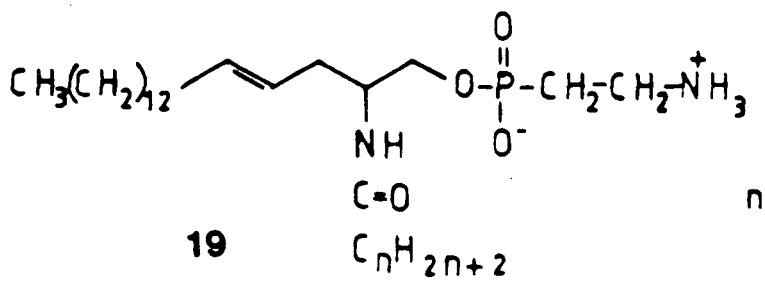
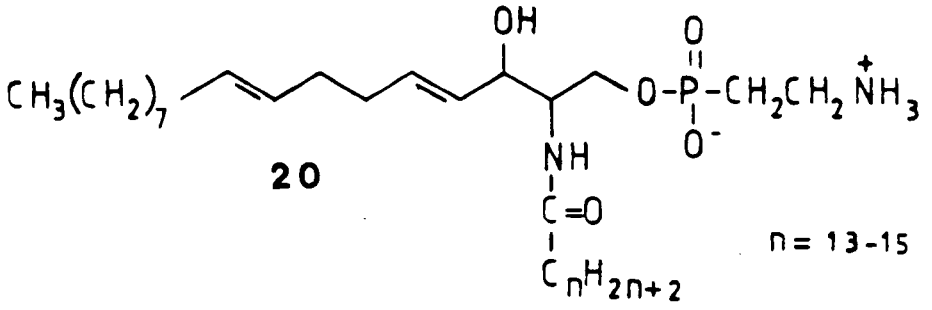


18

There have been few investigations of sphingolipids from marine organisms. Nevertheless, a variety of structures have been found as illustrated by the following examples. The ceramide aminoethylphosphonates 19 and 20 have been isolated from the sea anemones Anthopleura elegantissima[27] and Metridium senile[28] respectively. Various cerebrosides with twenty two carbon bases were obtained from the sea star Asteria rubens[29].

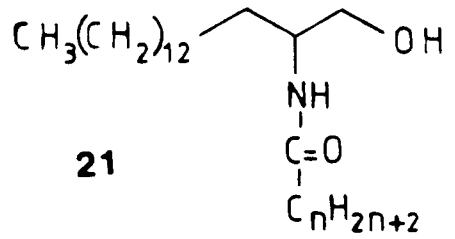


19 n = 13 to 18

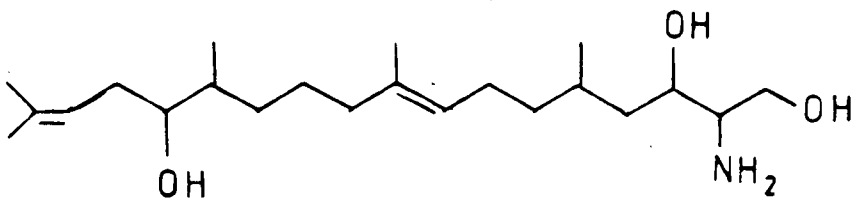


20 n = 13-15

Caulerpicin (21) is a toxic constituent of the marine algae Caulerpa sp.[30] and aplidiasphingosine (22) is an antimicrobial and anti-tumor terpenoid derivative of sphingosine isolated from a marine tunicate of the Aplidium sp.[31].



21 n = 24-26



22

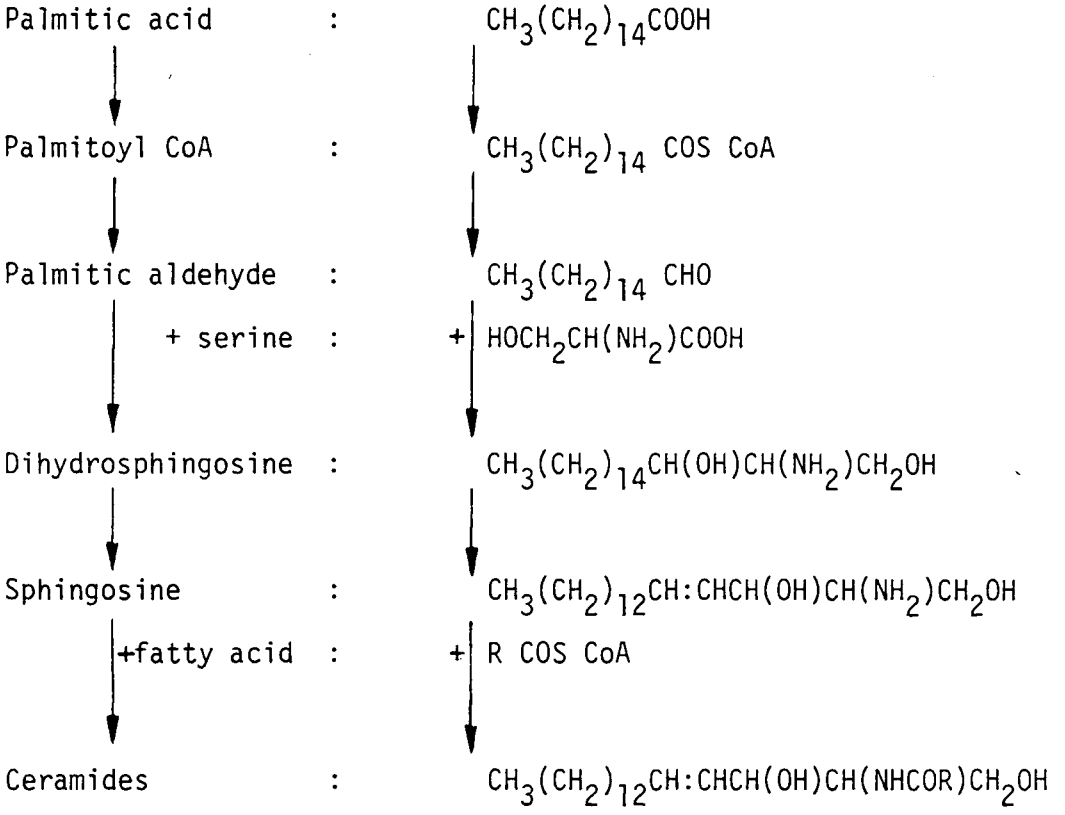
The long chain base 13 of the sphingolipid isolated from Onchidoris bilamellata has been previously identified as being one of 31 long chain bases obtained from bovine milk[32]. In that experiment sphingomyelins, phosphorous and choline containing sphingolipids of the general formula 23, were extracted from buttermilk powder. These were hydrolyzed to the corresponding ceramides, which were in turn hydrogenated and the latter product rehydrolyzed into fatty acids and bases. These bases underwent a sodium periodate oxidation and the resulting aldehydes were analyzed by GLC. These aldehydes were reduced and the alcohols also analyzed by GLC.

The biosynthesis of the long chain fatty base, sphingosine (17), is believed to occur as shown in Scheme 3 through the condensation of palmitaldehyde with the amino acid serine[33].

The stereochemistry of sphingosine has also been established. Carbon 2 has the D configuration, carbon 3 has an erythro relationship to carbon 2, while the double bond is the E isomer.

Scheme 3

Biosynthesis of Sphingolipids



Sphingolipids are known to be located mainly in the upper half of the lipid bilayer of the surface membranes of cells[34]. It has been suggested that the presence of sphingolipids in the membrane makes it more dense, more permeable to both polar and non-polar substances.

Several biological properties have been reported in the literature. For example, sphingolipids with polar head groups composed of carbohydrates have been associated with Na^+ transport in cells[34]. Sphingosine was found to inhibit blood clotting[35], while N-acetyl sphingosine and sphingomyelins have effects similar to cortisone in guinea pigs[36], and glycosphingolipids have immunological activity[37].

It has also been postulated[29] that the difference in the complexity of sphingolipids extracted from different sources might indicate their origin. Obtaining a complex mixture, as in the case of sea star cerebrosides for example, would indicate their origin from a functionally disparate organ or organism. A simpler mixture, however, as in the present study, would indicate their origin from a simpler structure.

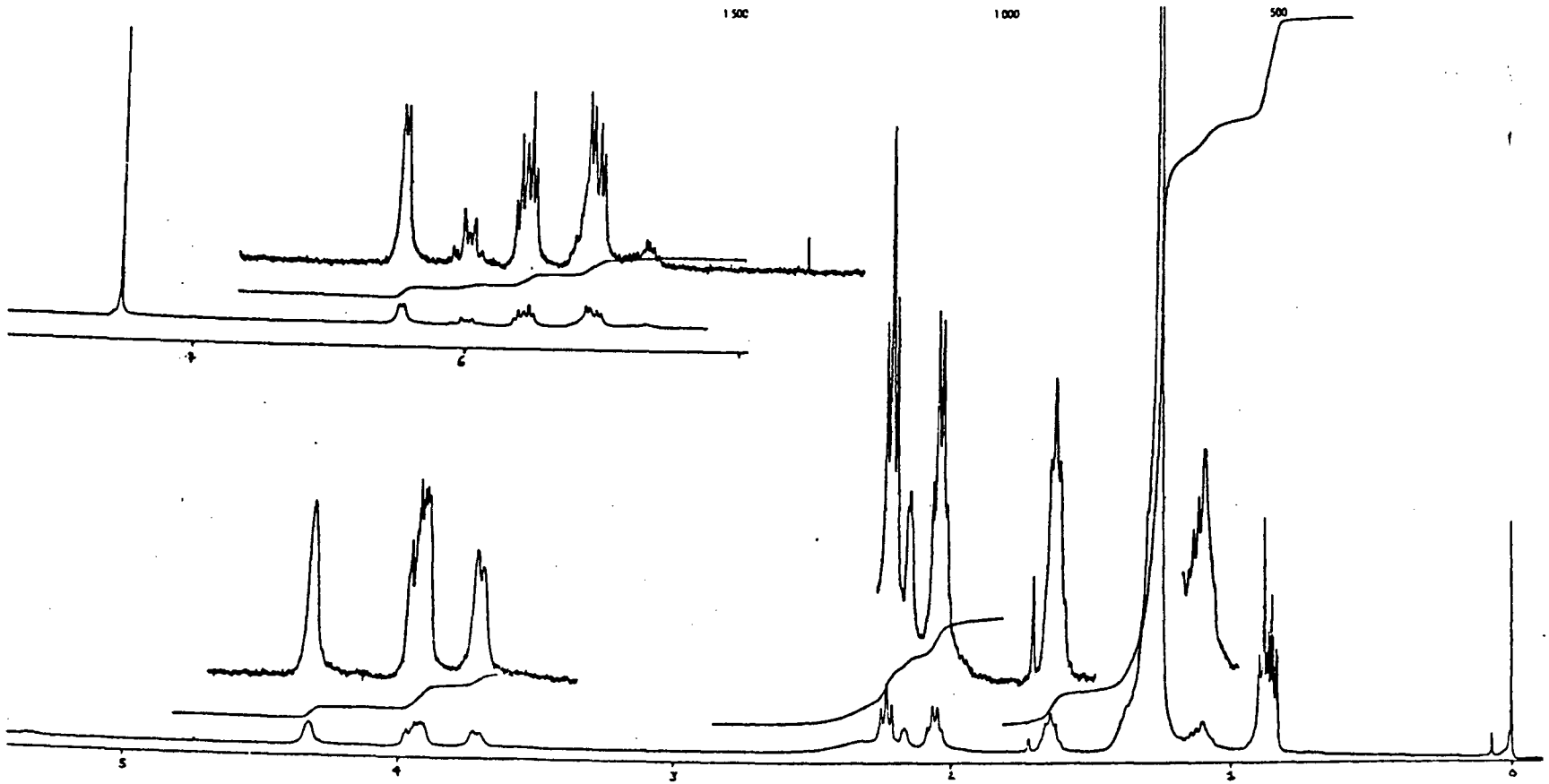


Figure 2

400 MHz ^{1}H NMR Spectrum of Ceramide 1 ($CDCl_3$)

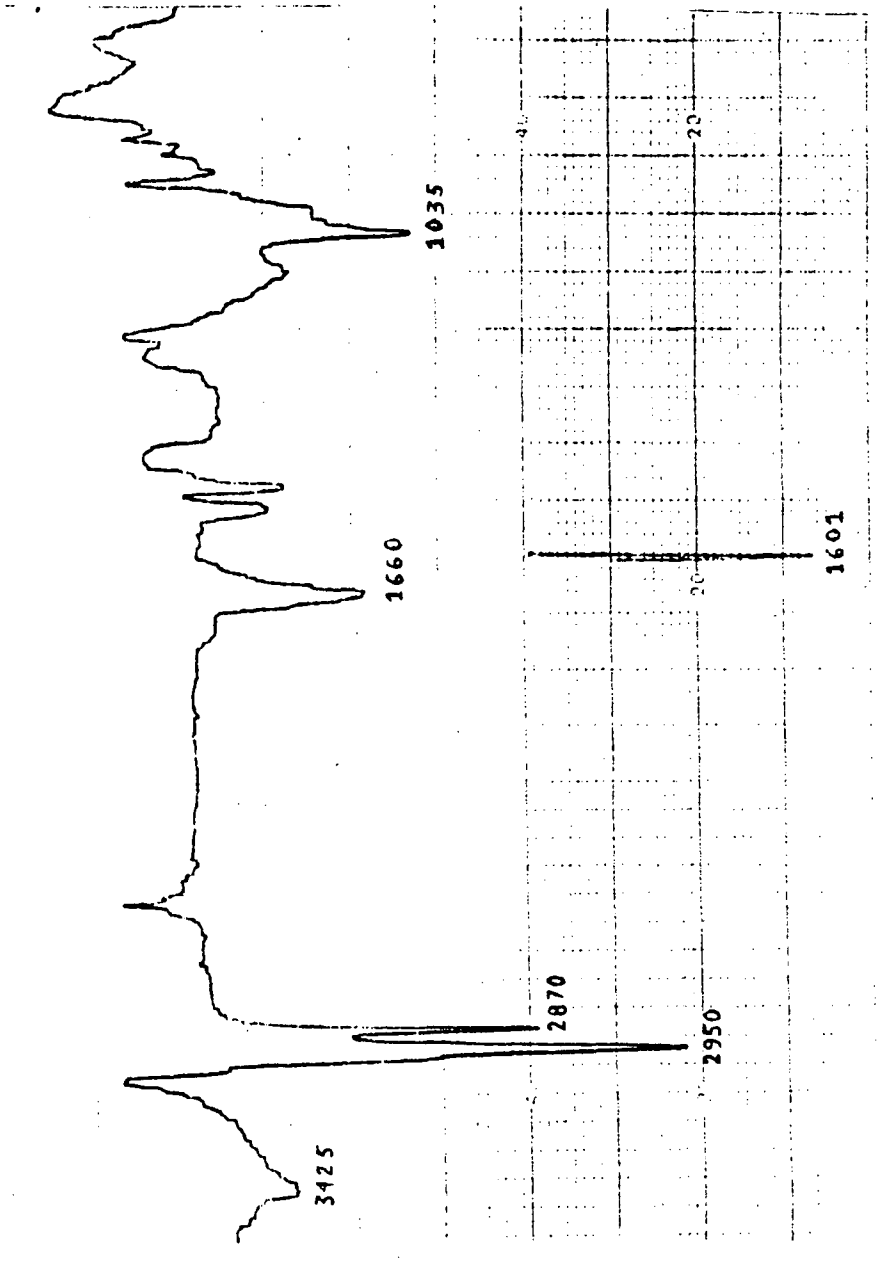


Figure 3

IR Spectrum of Ceramide 1 ($CHCl_3$)

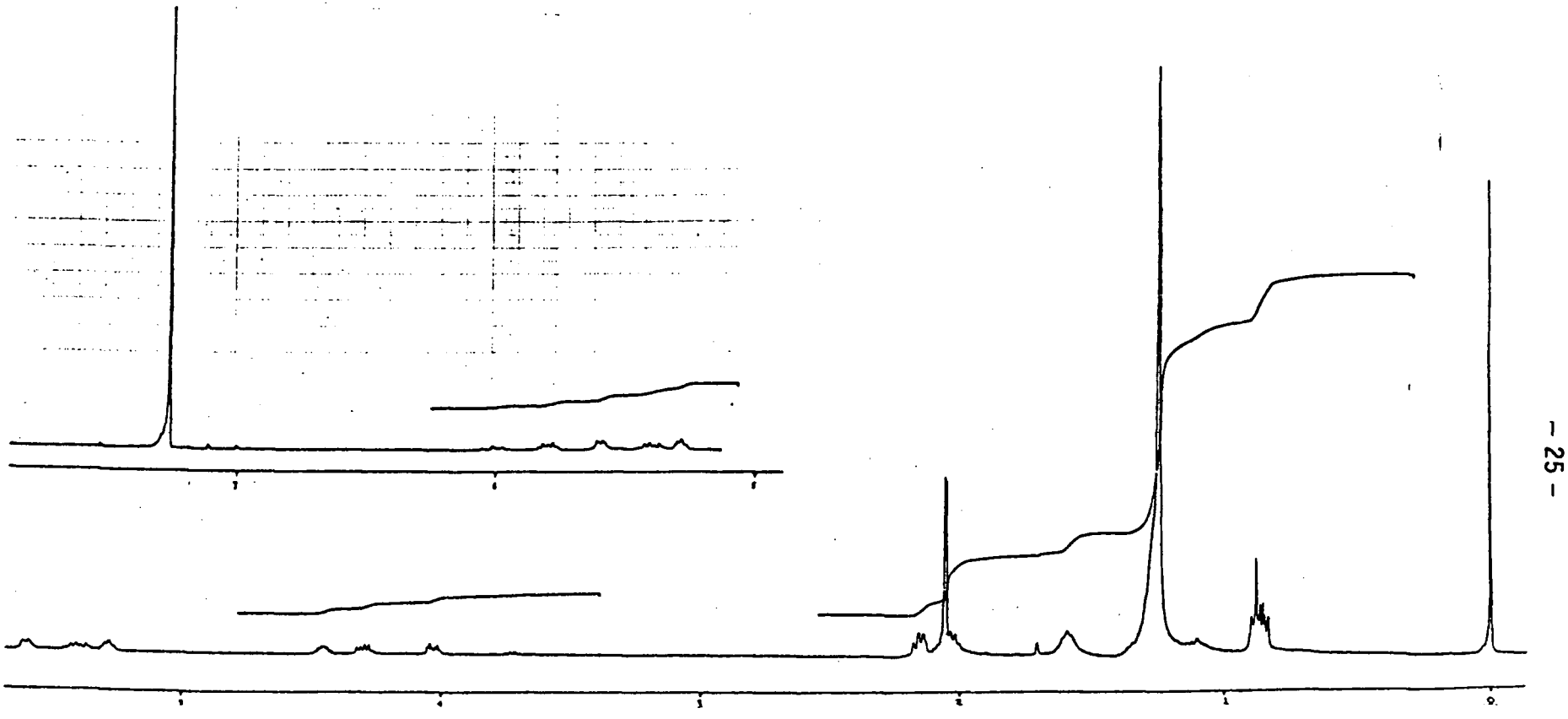


Figure 4

400 MHz 'H NMR Spectrum of Diacetylated Derivative 9 ($CDCl_3$)

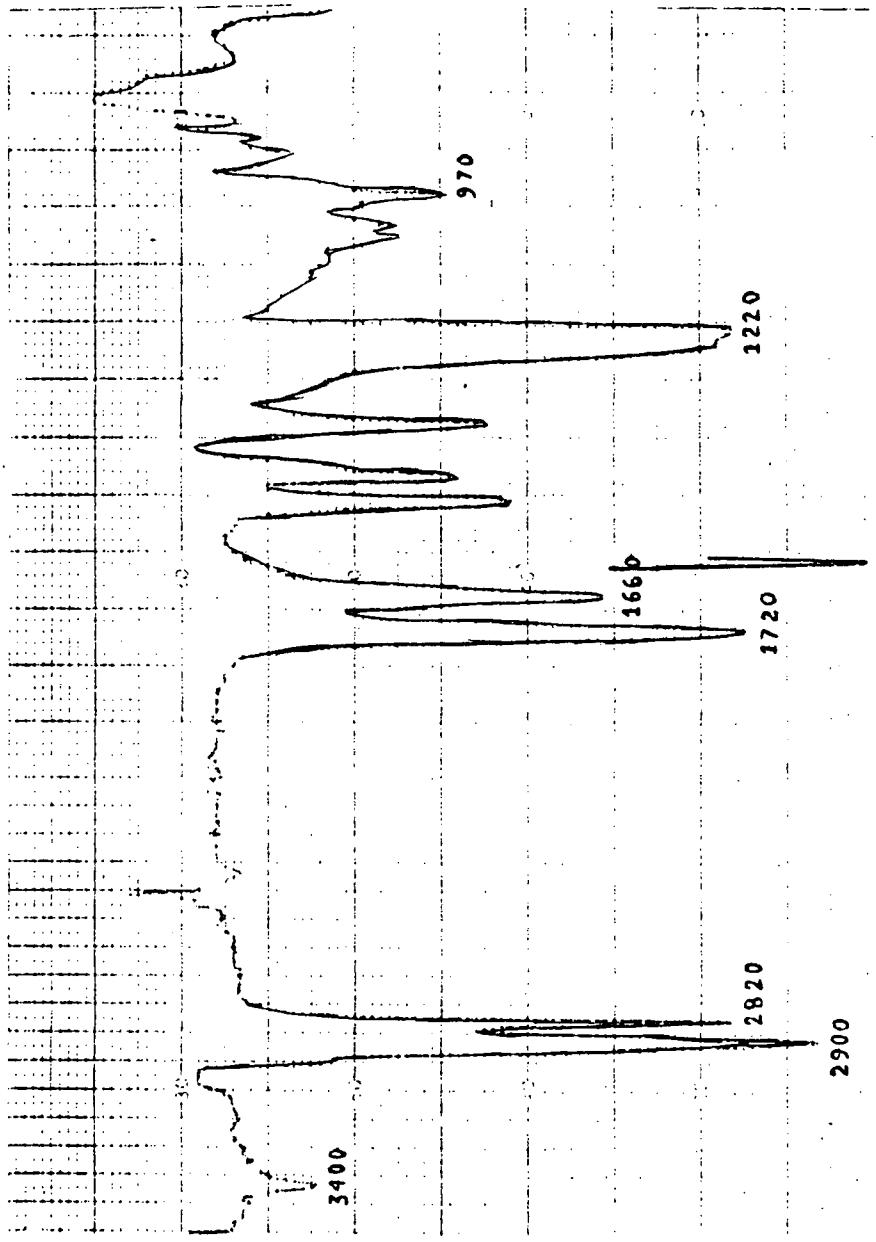


Figure 5

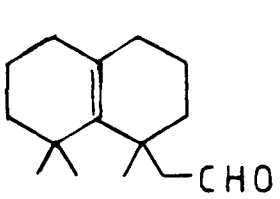
IR Spectrum of Diacetylated Derivative 9 ($CHCl_3$)

Chapter 2

Nanaimoal

II.1. Introduction

The synthetic studies outlined in this section arose as a logical sequel to my M.Sc. thesis[1] research. This partly concerned the identification of the marine natural product nanaimoal (24), (25) or (26), isolated from a British Columbia nudibranch. A straightforward synthetic approach to one of the hypothetical structures 24 of nanaimoal is proposed. This is followed by the results obtained from pursuing that synthetic route and a discussion of the chemistry of medium ring molecules. The work that enabled the structural elucidation of nanaimoal (26) by colleagues[39] at the University of British Columbia is then briefly reported.



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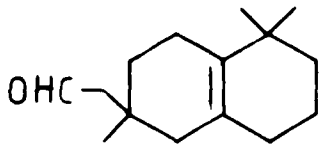

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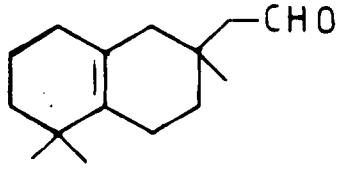


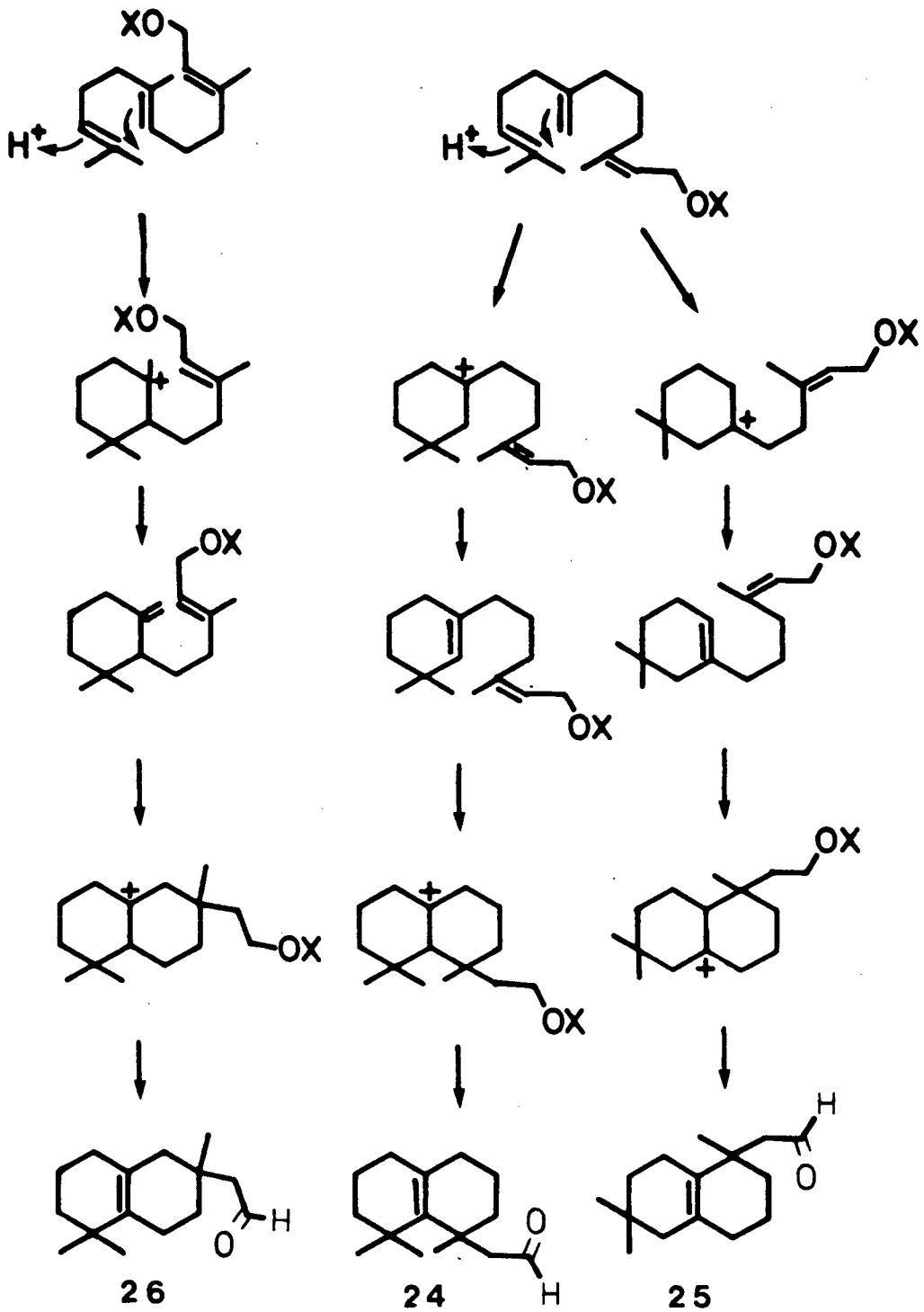
26

As part of a program aimed at studying the chemistry of British Columbia nudibranchs, we examined the skin extract of Acanthadoris nanaimoensis. Interest in that organism arose when we noticed its sweet fragrance while sorting specimens after a diving expedition.

The 'H NMR of the major constituent(s) of the extract of A. nanaimoensis indicated the presence of two closely related sesquiterpenoid aldehydes, present in a 4:1 ratio. The MS of this mixture of compounds, its reduction product and DNPH derivative pointed to a molecular formula for nanaimoal of $C_{15}H_{20}O$. From the spectral data available (IR, MS, 'H, and ^{13}C NMR) several features of this molecule could be discerned:

Scheme 4

Possible Biosynthesis of the Nanaimoane C Skeleton



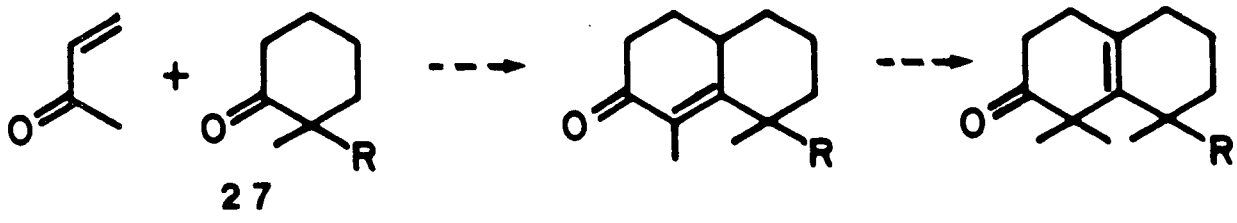
1. four sites of unsaturation: a carbonyl (aldehyde), a tetrasubstituted double bond, and two rings.
2. a sesquiterpenoid framework
3. fragment -C-CH_2-CHO
4. three methyl groups attached to quaternary carbons.

Biosynthetic reasoning (Scheme 4) suggested three hypothetical structures 24, 25 and 26. As attempts to prepare a suitable derivative for X-ray diffraction analysis were unsuccessful and other spectral measurements did not permit an unambiguous structural assignment, a synthesis of one of the proposed structures 24 was undertaken.

Two conventional approaches have been used to prepare bicyclo[4.4.0] decanes (decalins); either Robinson annulations or Diels-Alder reactions. As illustrated in Scheme 5 (for structure 24) these two approaches could start with an appropriate six membered ring, such as 27 or 28, and subsequently attach the required second six membered ring.

Scheme 5

Possible Robinson Annulation and Diels-Alder Approach to 24



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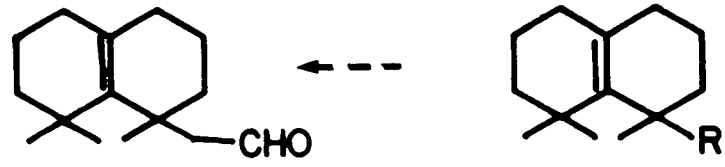

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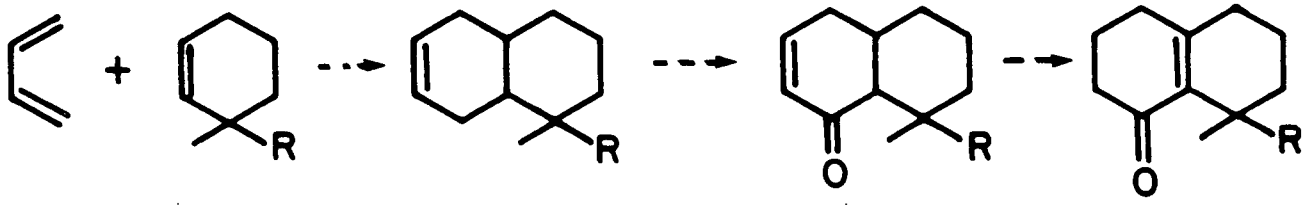


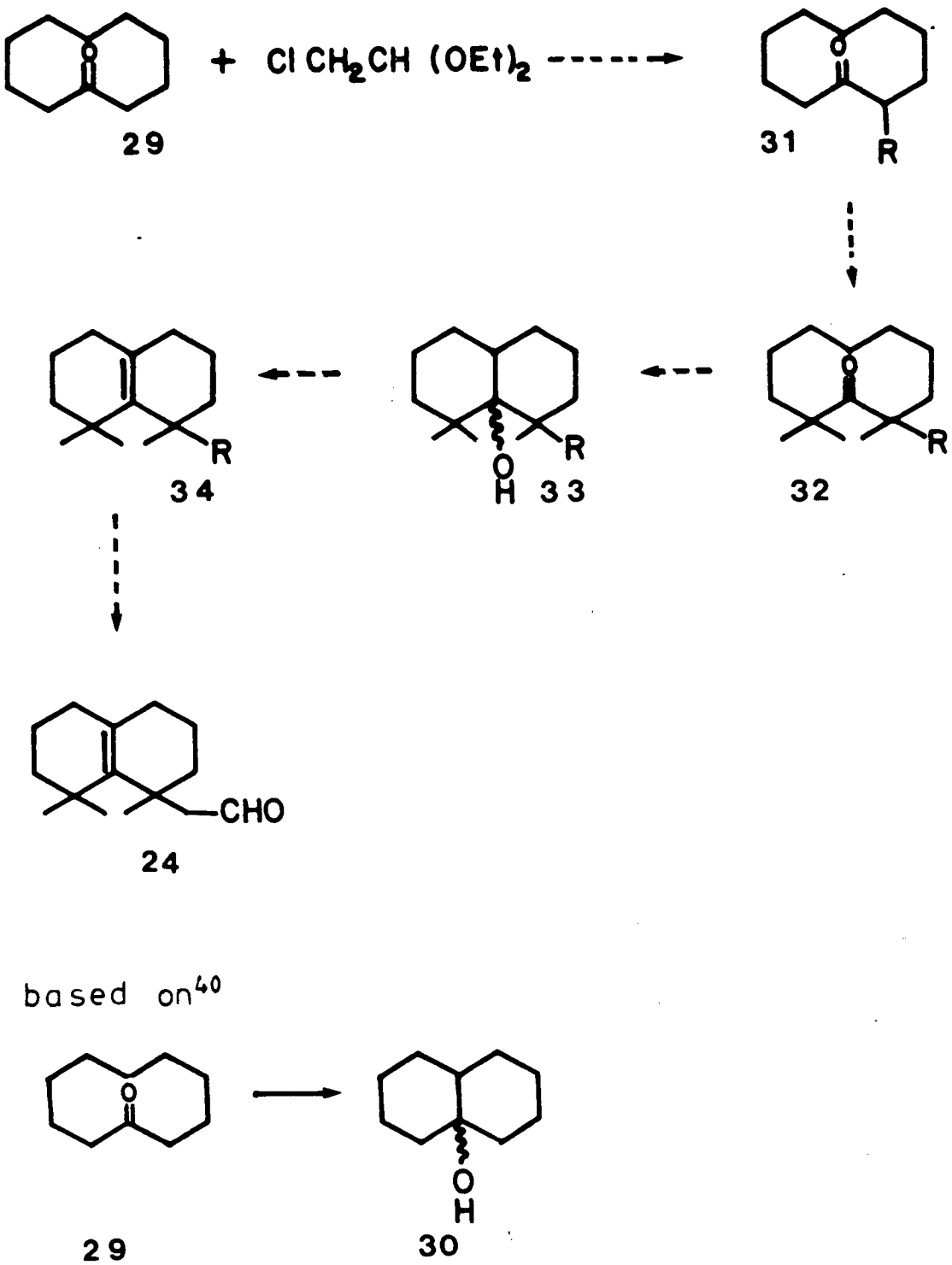
28

R: $CH_2CH(OEt)_2$

The photochemical behaviour of cyclodecanone (29) was studied in 1959 by Barnard and Yang[40]. They found that irradiation of 29 in cyclohexane for 132 hours afforded the alcohol 30 (Scheme 6) in 52% yield (42% cis, 10% trans). No subsequent study of substituted cyclodecanones has appeared. Our synthetic route (Scheme 6) was based on the expectation that sequential cyclodecanone alkylations would introduce a two carbon chain (such as $-CH_2CH(OEt)_2$), followed by the requisite methyl substituents, to give 32. Provided the photolysis paralleled that of cyclodecanone (29), dehydration of the alcohol product 33 and deprotection of the aldehyde would give the target molecule 24.

Scheme 6

Proposed Photochemical Approach to Nanaimoal (24)



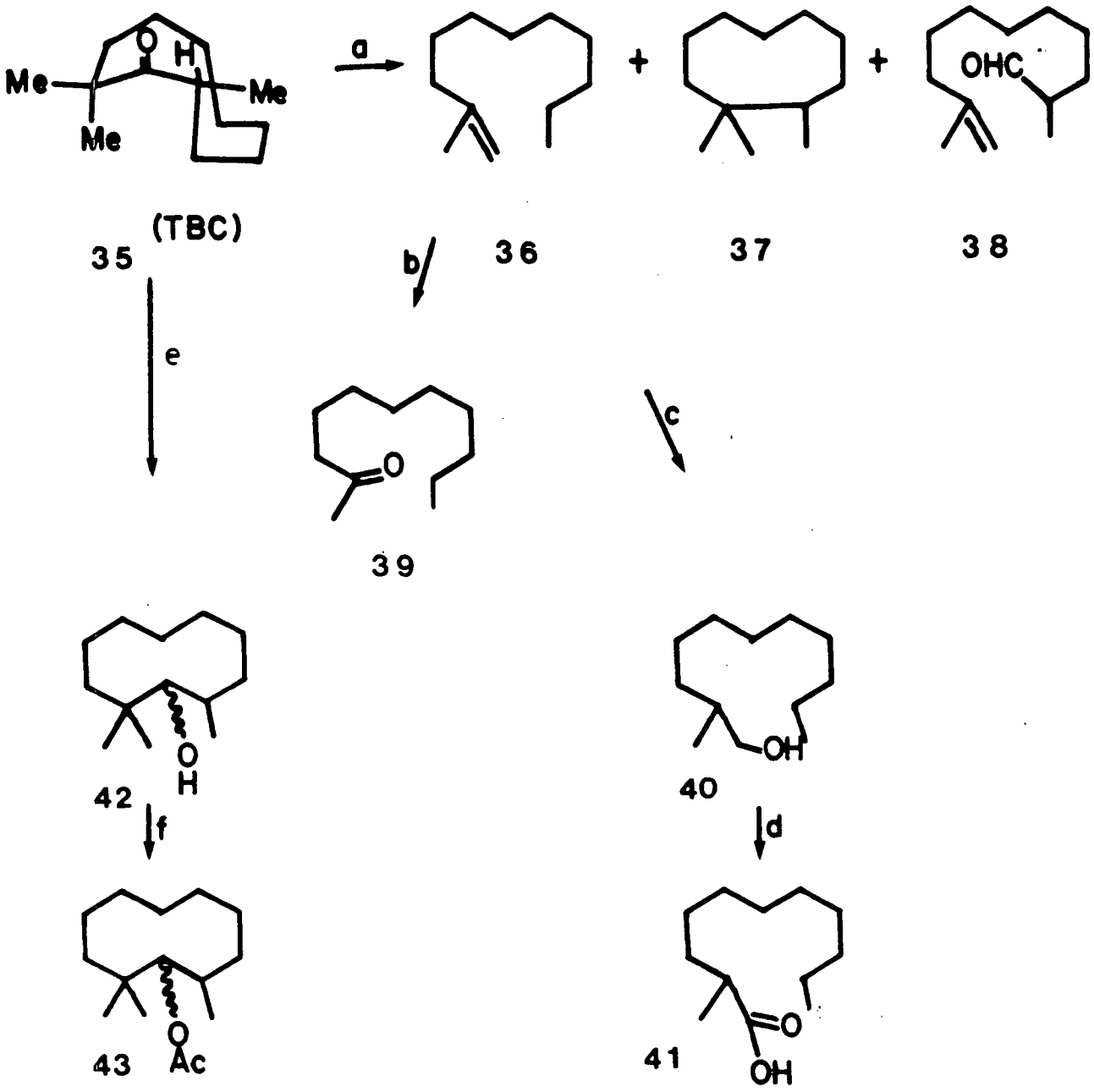
based on[40]

II.2. Results

The preparation of 2,2,10,10-tetramethylcyclodecanone was undertaken in order to ascertain its photochemical behaviour. Treatment of cyclodecanone (29) with sodium hydride in THF in the presence of excess methyl iodide afforded, after refluxing for 5 h, a single new product. This reaction was easily monitored by GLC. Although the tetramethyl derivative of cyclodecanone was expected, the MS (Figure 10) indicated a parent ion at m/z = 198 corresponding to a molecular formula of $C_{13}H_{26}O$, which represents the trisubstituted derivative 35. Lanthanide shift ($Eu(fod)_3$) ^1H NMR experiments confirmed the 2,2,10-trimethylcyclodecanone (35) structure Additional evidence was provided by acetate 43 (obtained by lithium aluminum hydride reduction and acetylation of 35, Scheme 7), which displayed in the ^1H NMR spectrum, a doublet J = 1.5 Hz at δ = 4.60 ppm for the major isomer and J = 2.5 Hz at δ = 5.10 ppm for the minor isomer[41] (6:1). These signals would not have appeared as doublets from the tetrasubstituted ketone 32, and there would have been only one isomer. The ^1H NMR spectrum (Figure 12) of 35, also displayed a signal at 3.31 ppm (m). Upon irradiation of this multiplet, the methyl doublet at 1.04 ppm collapsed to a singlet. The SFORD ^{13}C NMR spectrum of 35 showed eleven signals between δ = 22 and 40 ppm, the signal due to the CO group at 220.85 ppm being detected only in a concentrated solution. The band ascribed to a CO group appeared at 292 nm (log ε = 1.77) in the uv spectrum.

Scheme 7

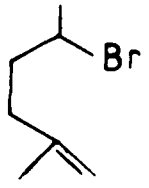
Reactions Performed on 2,2,10-trimethylcyclodecanone (35)



a:hν; b:O_3, MeOH or $KMnO_4$, benzene; c: BH_3, H_2O_2;

d:Jones oxidation; e:$LiAlH_4$, ether; f:Ac_2O, pyridine, DMAP

The photochemical behaviour of 35 was investigated in the absence of 32. Photolysis of 35 in cyclohexane for 5 h resulted in the complete disappearance of the starting ketone. Although "homogeneous" by GLC (one peak) and TLC (one spot) analysis, the major photolysis product was not a single olefin as implied by the ^{1}H NMR spectrum. Olefinic signals appeared in the ^{1}H NMR between δ = 4.6 and 6.0 ppm. A broad singlet at 4.64 ppm represented about 70% of the combined integrated intensity of these signals. The presence of a vinyl methyl at 1.70 ppm (s) and of a methylene (2.0 ppm, triplet, J = 7 Hz) alpha to the double bond was also indicated. These three signals were identical to those displayed by 5-bromo-2-methyl-hexene (44) and together with the MS (Exact Mass calculated for $C_{12}H_{24}$: 168.1872, observed: 168.1860) permitted the identification of this major olefin as 2-methyl-1-undecene[42] (36). The presence of a 1,1-disubstituted double bond was also revealed in the IR at 880 cm^{-1}.



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The structure of this major olefin 36 was proved by performing the following series of reactions (Scheme 7). Oxidation of the olefinic fraction with potassium permanganate in benzene in the presence of crown ether[42], gave a single ketone 39. This same methyl ketone product was obtained in better yield when ozonolysis was performed, followed by a dimethyl sulfide reductive work-up. The ^{1}H NMR indicated the presence of a methyl ketone (2.07 ppm, singlet) the IR confirmed the presence of a carbonyl group (1715 cm^{-1}) and the MS (Exact Mass calculated for $C_{11}H_{22}O$: 170.1665,

observed: 170.1622) and b.p. (228-230° observed, literature 231-232[43]) proved that 2-undecanone (39) was the product.

Hydroboration[44] of the olefinic fraction followed by treatment with basic hydrogen peroxide afforded a primary alcohol 40. The 'H NMR spectrum of alcohol 40 displayed a doublet (J = 6 Hz) at 3.31 ppm, and the IR spectrum had a band at 3300-3400 cm^{-1}. The MS of 2-methyl-1-undecanol (40) was almost identical to that of 2-methyl-1-undecene (36) indicating that H_2O is readily lost from the expected parent ion. The primary nature of the alcohol was further proved by Jones oxidation[44] to the corresponding carboxylic acid 41.

A non-polar fraction having the same R_f as the starting material was isolated in about 20% yield from the hydroboration and ozonolysis reactions. The 'H NMR spectrum of this fraction showed no deshielded signals, the IR showed no bands corresponding to a carbonyl or a hydroxyl group, and the MS still displayed a molecular ion at m/z = 164 ($C_{12}H_{24}$). Structure 37 is tentatively assigned to this minor product of the photolysis reaction.

On one occasion when bubbling of nitrogen was omitted before the photochemical reaction, a more polar product having the right spectral properties (IR, 'H NMR, MS) for 2,10-dimethyl-10-undecene-1-al (38) was isolated.

While the photochemical reaction was under study, we attempted to synthesize a tetrasubstituted cyclodecanone. The tetrahydropyranyl (THP) derivative of 2-chloro-1-ethanol was prepared under catalytic acidic conditions[44]. Since the alkylation of cyclodecanone did not take place with the chlorine as the leaving group, the iodine conterpart was prepared. In both cases (Cl, I), it seems that elimination of HCl or HI takes place at a higher rate than alkylation. This is deduced from the presence of three

new olefinic signals in the 'H NMR spectrum (typical vinyl group, ABX pattern) of the tetrahydropyranyl derivative and the recovery of cyclodecanone. Various cyclodecanone alkylations with electrophiles such as alkyl iodide, cinnamyl iodide and benzyl bromide, followed by methyl iodide, using bases such as NaH, KH, LDA, KCH_2SOCH_3, KNH_2, KOR, and a variety of solvents such as THF, DMSO, HMPA, DME, DMF, NH_3, ROH, were investigated under various temperature conditions, including sealed tubes. Unfortunately none of these experiments gave a tetrasubstituted product. Subsequent attempts to prepare enol ethers and acetates of 2,2,10-trimethyl-cyclodecanone also met with no success, while a D_2O quenching experiment was inconclusive. Thus this photochemical approach to nanaimoal (24) was abandoned.

II.3. Discussion

In spite of important contributions[45,46,47] to the conformation and reactivity of medium-ring C_8 to C_{11} cycloalkanes, cycloalkanones and related molecules made in the last twenty years detailed understanding is still lacking. Clearly, two significant aspects of this study are the failure of the photochemical reaction to follow the anticipated path, and the difficulty in preparing a tetrasubstituted cyclodecanone. The course of these reactions is largely a consequence of the conformational preferences of the molecule. The preferred conformation of 2,2,10-trimethylcyclodecanone (35) can be tentatively deduced based on the present work and earlier studies of ten membered ring molecules.

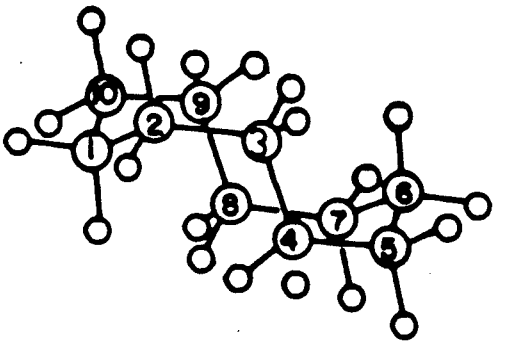
Although the cyclodecane molecule is capable of existing in a number of conformations (Figure 6), the BCB[48] conformation having all staggered linkages[47] is preferred. In the case of cyclodecanone, there are three possible BCB ("diamond-lattice") conformations[49] (Figure 7). Only BCB-3, with the carbonyl in an endocyclic position, has no steric hindrance with the hydrogen atoms on the opposite side of the ring. It is significantly more stable according to strain energy calculations[50] and 'H NMR measurements[51]. This conformation relieves a particularly serious "transannular non-bonded repulsion". This is also consistent with the photochemical results of Barnard and Yang[40]. The carbonyl group is partially located inside the ring and participates readily in the observed transannular reaction. The BCB-1 conformation has been proposed as being more in accordance with C-13[52] measurements, while dipole moment calculations favor an endocyclic carbonyl as in BBC-1[45].

Other more stable conformations have been found or proposed for substituted cyclodecanes, and some examples follow. The TBC conformation

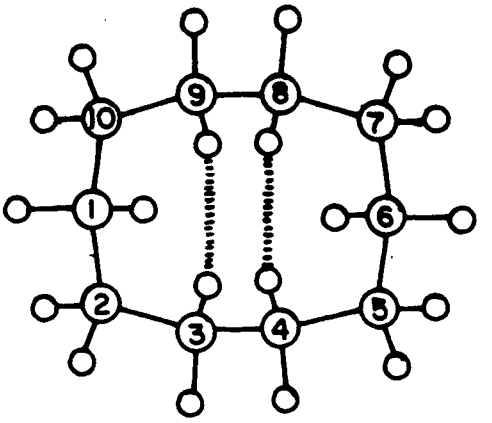
Figure 6

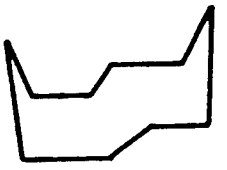
Some Conformations of Cyclodecane

B: boat
C: chair
L: long
T: twisted

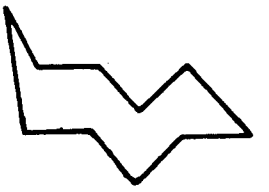


BCB





BCC



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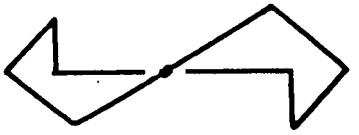
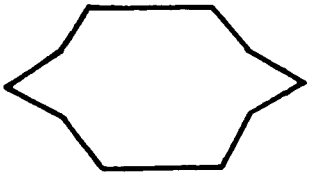


TBC

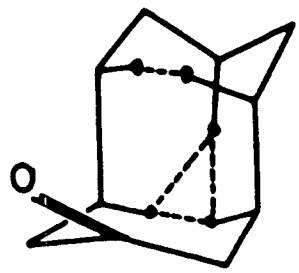
TBCC



LC

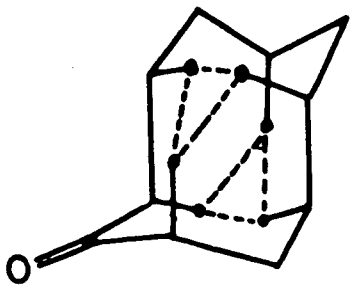
Figure 7

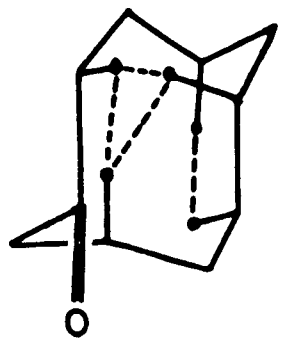
Some Conformations of Cyclodecanone



exocyclic

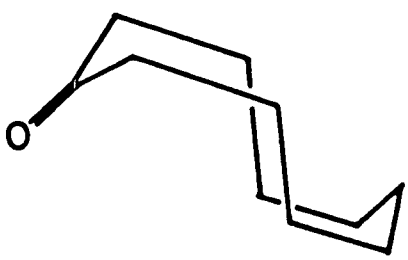
CO



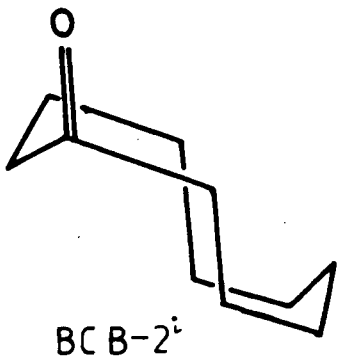


endocyclic

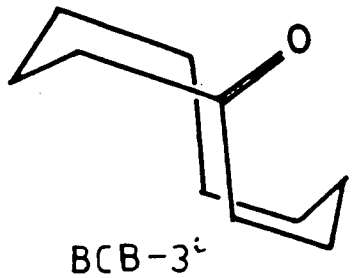
CO



BCB-1[i]



BCB-2[i]



BCB-3[i]

[i]: Refers to numbering used for cyclodecane, Figure 6

has been suggested as more stable in the case of 4,4,8,8-tetramethylcyclodecanone[53]. Through X-ray analysis[54,55] of 4,4,7,7-tetramethylcyclodecane-1-carboxylic acid, the two conformations TBC and TBCC were assigned to this molecule in the solid state. Cyclodecane-1,6-dione has been the subject of several studies[47,56] which indicate a difference between the conformation of the molecule in the liquid state (IR, UV, ^{1}H and ^{13}C NMR) and the same molecule in the solid state (IR, X-ray). The major conformer in solution seems to be a distorted "decalin-like" or TCCC molecule. This latter study indicated that trying to obtain a solid derivative (such as 2,4-dinitrophenylhydrazone) of 35 probably would not be warranted.

The reactivity of molecules also depends on their ring size[46,57]. For example, reaction rates vary when oxidations or reductions are performed[i]. The products obtained from transannular reactions going through a carbanion or carbonium ion intermediate also change with the size of a ring. In addition, as has been observed previously[40,59,60] and in the present study, the products of a photolysis reaction vary with the size and the substitution of the ring.

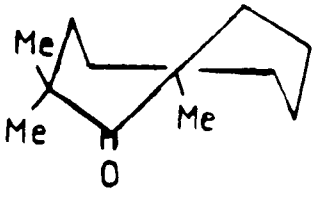
Three different studies, and especially X-ray diffraction analysis[61], indicate that "the structures of medium-ring molecules are very different from what is suggested by the floppy necklaces of atoms produced by conventional molecular models".[62,63]

In view of the conformational studies outlined above, it appears that 2,2,10-trimethylcyclodecanone (35) in solution adopts a conformation in which abstraction of a proton from carbon-10 is extremely difficult.

[i] Comparison of the alkylation[58] of cyclohexanone and cyclodecanone using benzyl bromide/NaH/THF. After 5 h reflux, cyclohexanone gave: 62% monoalkylated product, 10% dialkylated product and no starting material. After 48 h reflux, cyclodecanone gave: 70% monoalkylated product, < 1% dialkylated product, 15% starting material.

A recent paper[62], published after this work was finished, deals with the effect of a methyl substituent on the "stereoselective formation of a new asymmetric centre". A table gives the energy (molecular mechanics . calculations) needed to introduce a methyl into the three non-equivalent pseudoaxial positions of cyclodecane existing in the BCB conformation: 6.6 kcal/mole at C-1, 0 kcal/mole at C-2 and 9.2 kcal/mole at C-3. This means that for sites 2, 5, 7 and 10 (Figure 8) at the four corners of the BCB, there is no energetic penalty associated with the introduction of an axial methyl substituent. However, for the remaining six positions, the energy required is so large that the introduction of an axial substituent is actually forbidden.

Therefore if we consider 2,2,10-trimethylcyclodecanone (35) in a TBC conformation, "tub shaped" like the cyclooctanes, (based on the arguments above), the introduction of the fourth group must be taking place at a position equivalent to C-4[64] and is effectively energetically forbidden. In our opinion a twisted-boat-chair conformation is best suited to the photochemical and spectral data obtained for 35, where:



TBC

1. The photochemical reaction indicated that abstraction of a transannular proton by the CO group is not preferred.
2. The chemical shift of the C-10 proton, δ = 3.31 ppm (similar to that of a methylene α to the CO of a six membered ring lactone, δ = 3.31 ppm[41a]) indicated that, in the average conformation adopted in solution by 35, H-10 is in the deshielding cone of the carbonyl group. This requirement

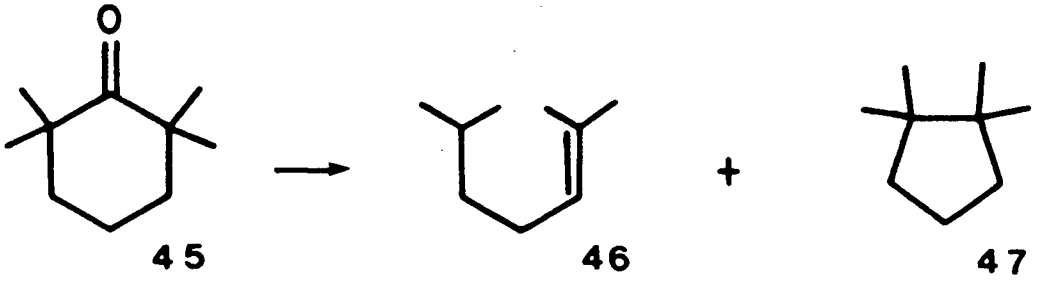
implies that the substituted side of the molecule is partly flat. To obtain an angle close to 0° between the CO at C-1 and the methine proton at C-10, a TB conformation is necessary.

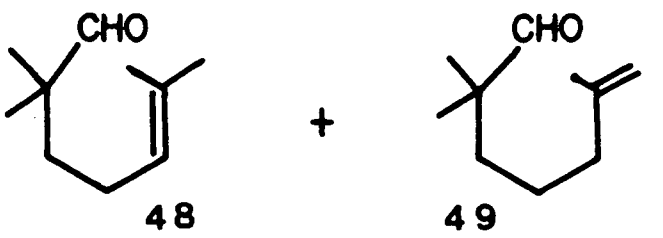
3. The eleven alkyl signals obtained in the SFORD ^{13}C NMR ($C_{13}H_{22}O$:1 CO and 12 alkyl C) indicate an absence of symmetry in the average conformation adopted by 35[65].

The results of the photolysis reaction can be explained by comparison to the behaviour of small ring ketones such as cyclohexanone[67,68], rather than related medium ring ketones[40,59,60]. For example, when 2,2,6,6-tetramethylcyclohexanone (45) was photolysed[69], four products, 46 to 49, were identified (Scheme 8). The stability of the acyl alkyl diradical intermediate is increased by the substituents in the α and α' positions. Therefore, the loss of carbon monoxide with subsequent intramolecular reactions (disproportionation and combination) was promoted in 45.

Scheme 8

Photochemical Behaviour of 2,2,6,6-tetracyclohexanone (45)[69]

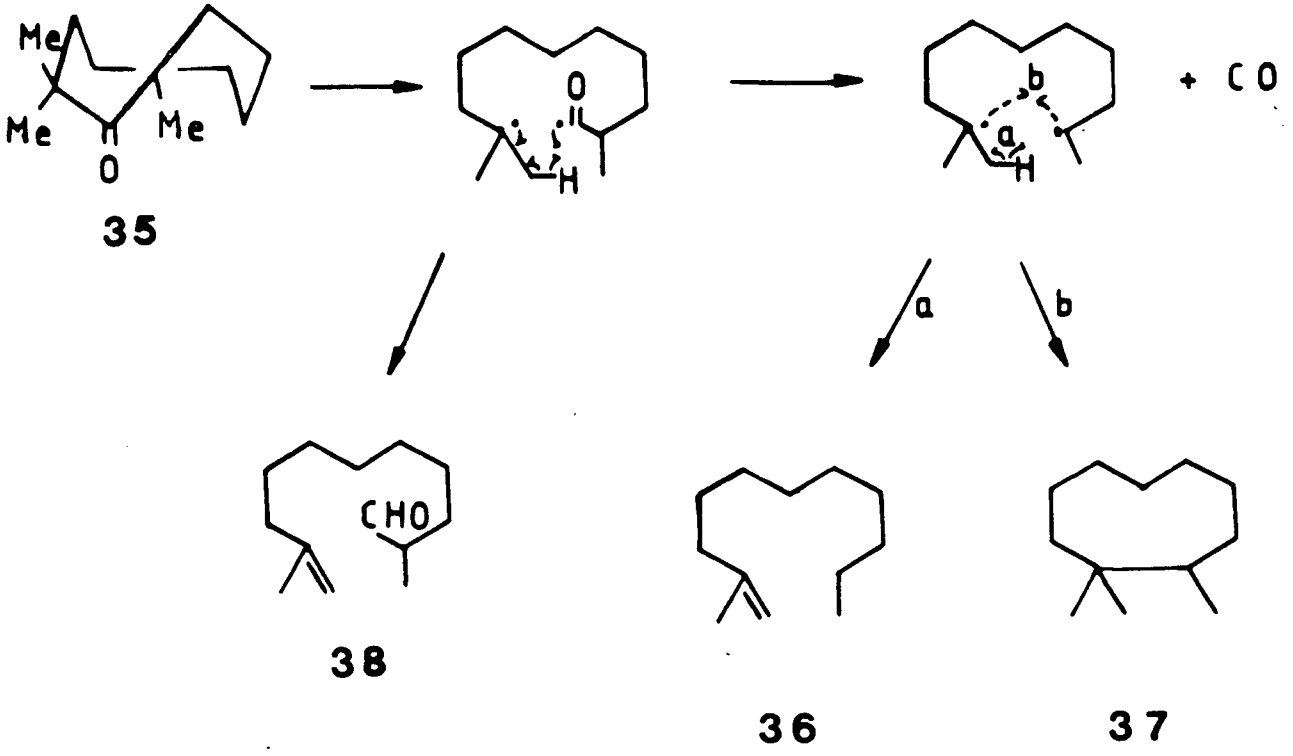




In the case of 35, minor product 37 resulted from a Norrish type I cleavage (on the more substituted side of the CO group) followed by a decarbonylation and cyclization (Scheme 9). Product 38 resulted from a Norrish type I cleavage followed by a proton abstraction from one of the gem dimethyls. The major product 36 is obtained from a Norrish type I cleavage, a decarbonylation and a proton abstraction. The Norrish type II cleavage anticipated is not favored due to the geometrical requirements of 35. Therefore, no decalin product was obtained.

Scheme 9

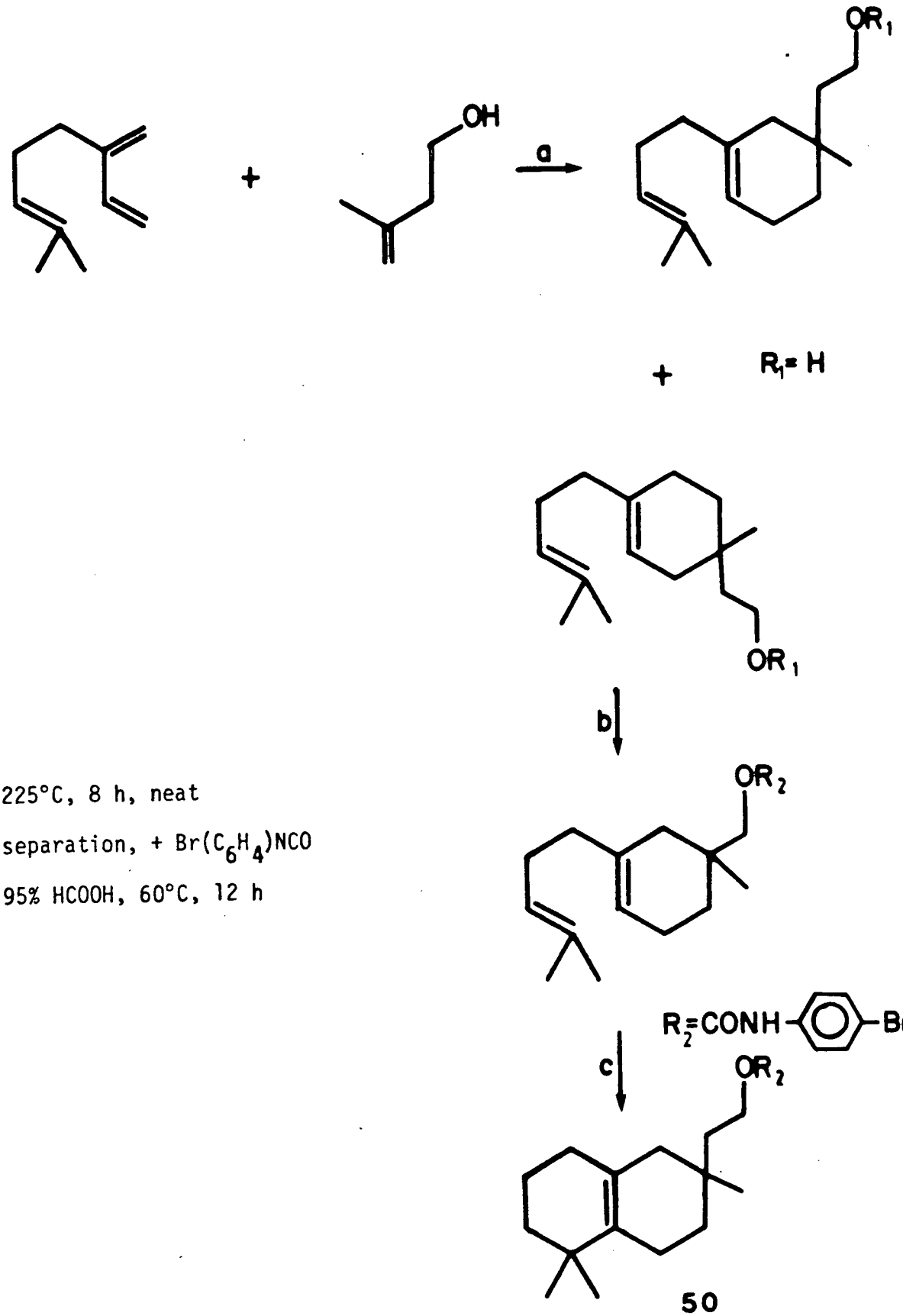
Photochemical behaviour of 2,2,10-trimethylcyclodecanone 35



As mentioned in the introduction, the present study was directed at the synthesis of 24, one of the three (24, 25 or 26) hypothetical structures proposed for nanaimoal. Subsequent to this study, the elucidation of the structure of nanaimoal (26) was successfully accomplished by Andersen and collaborators[39], at the University of British Columbia. The Diels-Alder synthesis of 50, the p-bromophenylisocyanate derivative of nanaimoal is outlined in Scheme 10.

Scheme 10

Synthesis of 50, a Derivative of Nanaimoal (26) [39]



a: 225°C, 8 h, neat

b: separation, + $Br(C_6H_4)NCO$

c: 95% HCOOH, 60°C, 12 h

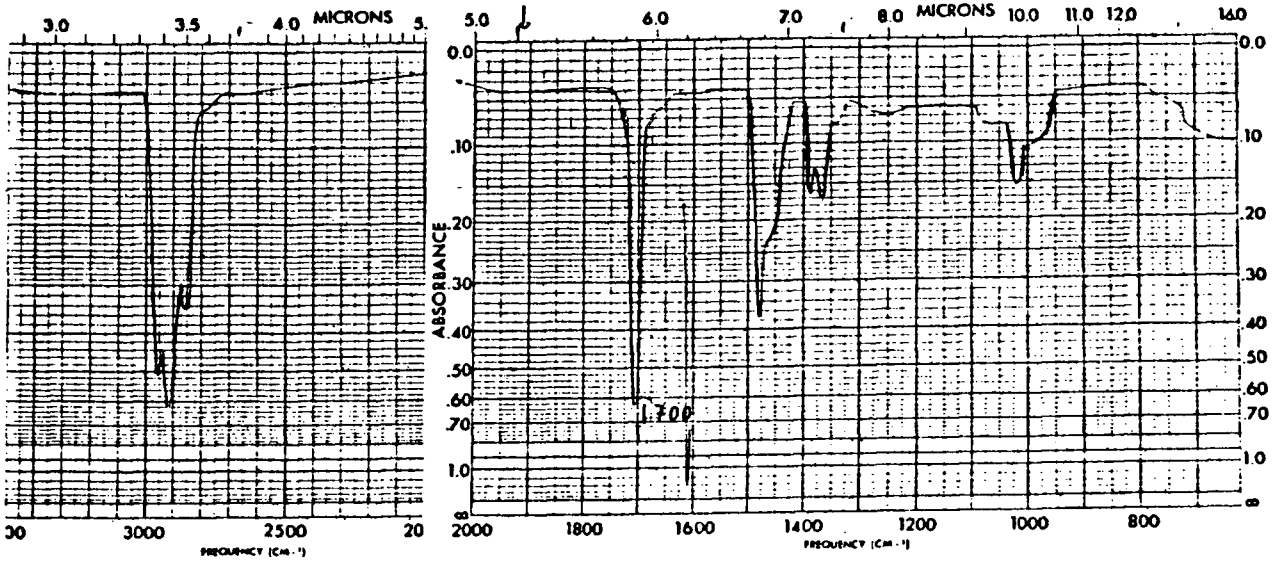


Figure 8

IR spectrum of 2,2,10-trimethylcyclodecanone (35, neat)

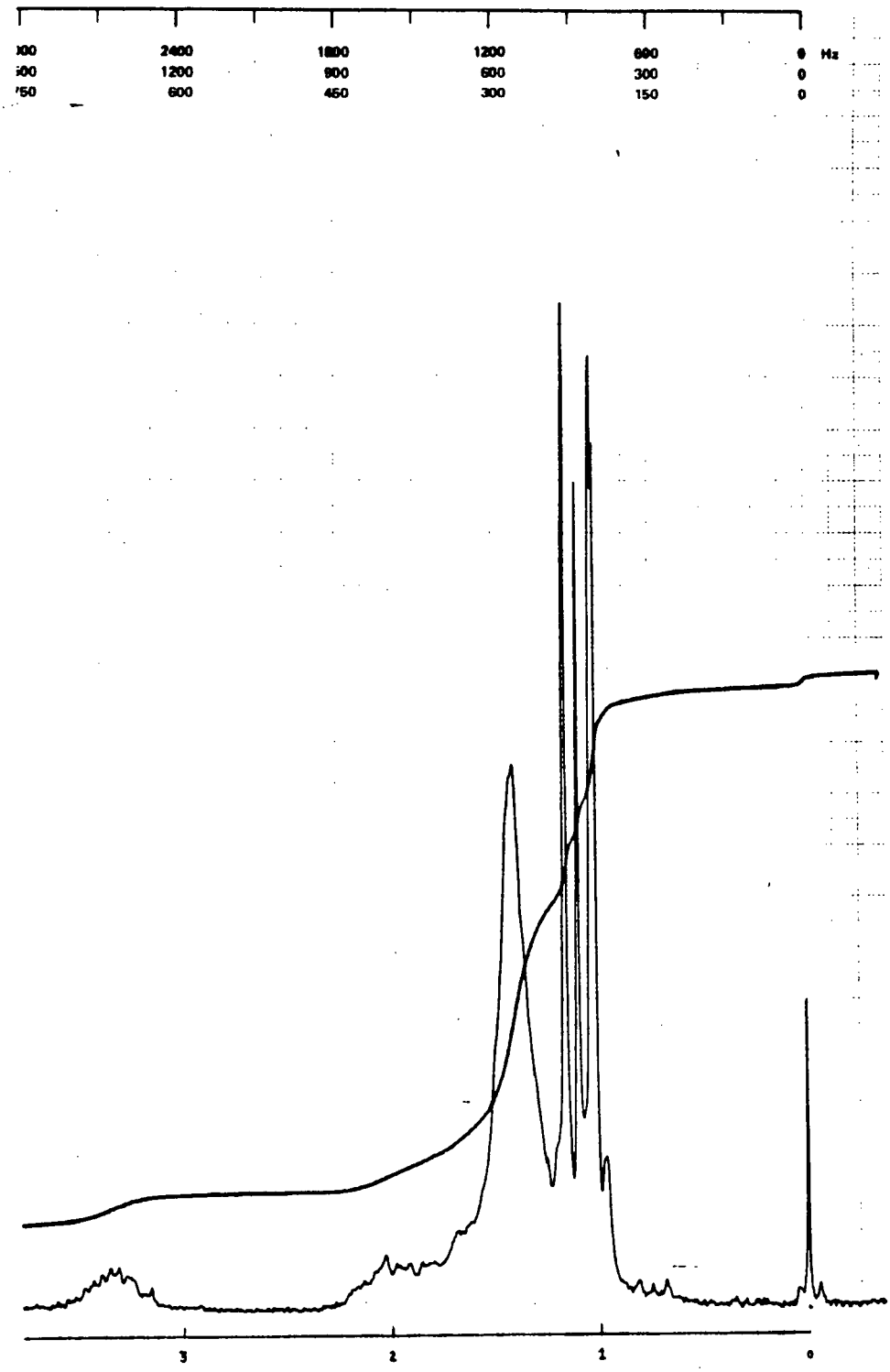


Figure 9

80 MHz ^{1}H NMR Spectrum of 2,2,10-trimethylcyclodecanone (35 $CDCl_3$)

Chapter 3

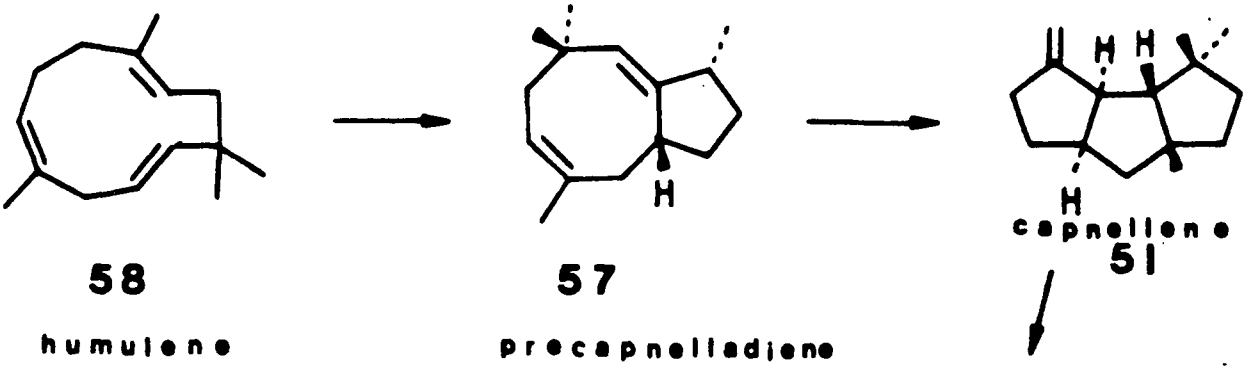
Capnellene

III.1. Introduction

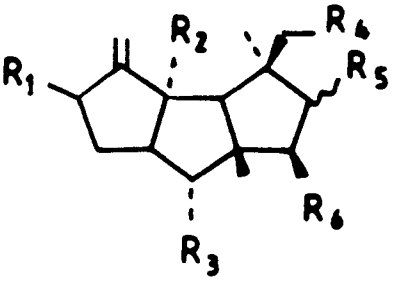
$\Delta^{9,12}$ Capnellene (51) is a member of a family of seven sesquiterpenoids isolated from the soft coral Capnella imbricata, collected in Indonesia and New Guinea. The most abundant alcohol 52 was first isolated in 1974[70], followed by the structure determination of our other alcohol representatives 53 to 56, in 1976 and 1977[71-73]. The tricyclic hydrocarbon capnellene (51) was identified in 1978[74] and the unstable and volatile bicyclic hydrocarbon precapnelladiene (57) in 1979[75].

Scheme 11

Biogenetic Relationship of the Capnellanes



	OH	H
52	$R_{1,2,6}$	$R_{3,4,5}$
53	$R_{1,2}$	$R_{3,4,5,6}$
54	$R_{1,2,3}$	$R_{4,5,6}$
55	$R_{1,2,5}$	$R_{3,4,6}$
56	$R_{1,2,4,6}$	$R_{3,5}$

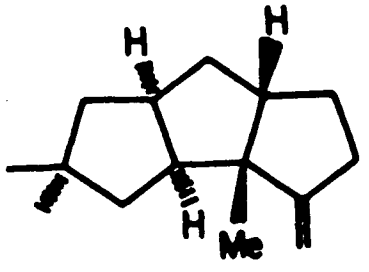


capnellols

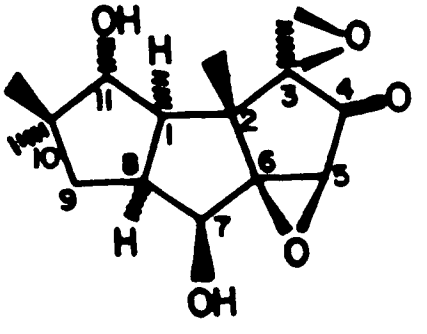
It has been suggested[76] that compounds 51 to 57 could serve in a chemical defense mechanism, "to ward off algal and microbial growth and prevent the settlement of larvae"[71] on the soft coral.

The biogenetic relationship outlined in Scheme 11 has been proposed for the capnellane family[71,74,75,77].

The capnellanes and hirsutanes (which comprise for example hirsutene (59) and coriolin (60)) are two tricyclopentanoid families fused in a cis-trans-cis arrangement. These triquinanes have received considerable attention from synthetic chemists in the last few years.



59



60

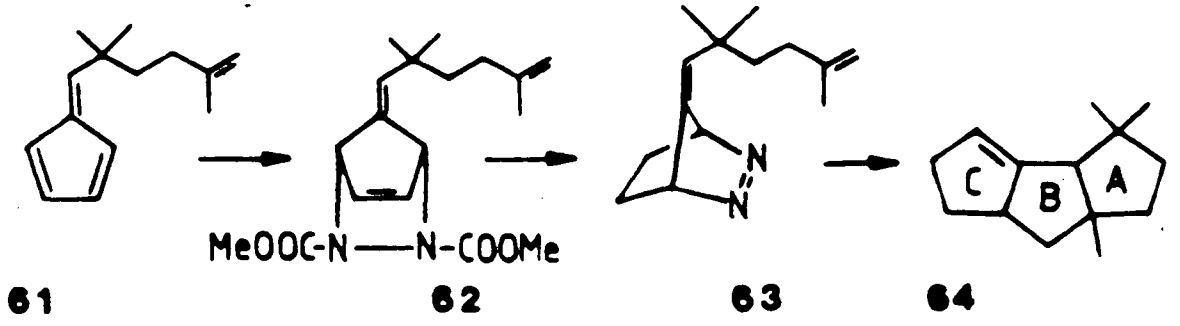
When we decided to synthetize capnellene (51) only one communication[78] dealing with the synthesis of epi-precapnelladiene had appeared in the literature. Since then, 51 has been the subject of several total syntheses[79-86], the carbon skeleton has been prepared[87] and diol 53 has also been synthesized[88]. In the next few pages, these syntheses are outlined briefly.

The key steps in these syntheses are shown in Schemes 12 to 21. The first total synthesis of 51 by Little's group[79] involved a Diels-Alder reaction (0°, 3 h, >91% yield of 62) between the fulvene 61 and dimethyl-azodicarboxylate. This was followed by a novel 1,3-diyl trapping reaction

(dropwise addition of 63, 66 h, refluxing THF, >56% yield of 64) of the related azo compound 63, with elimination of nitrogen, to produce 64 (and 2 isomers) a tricyclic precursor of 51.

Scheme 12

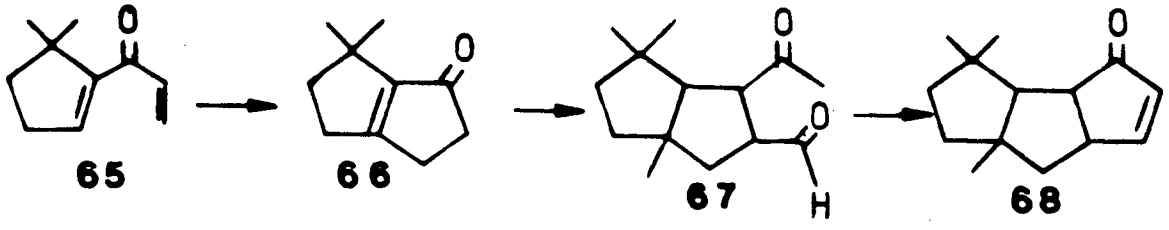
Synthesis of 51, by R.D. Little and G.L. Carroll[79]



Paquette's synthesis is shown in Scheme 13. Initially the sensitive dienone 65 underwent a Nazarov cyclization (8% P_2O_5, CH_3SO_3H, 20°, 2 min, 68% yield) to bicyclic ketone 66. Further alkylation and cyclization of the resulting γ-keto-aldehyde 67 under basic conditions (5% KOH, ether, THF, 79% yield) led to 68, a different precursor of 51.

Scheme 13

Synthesis of 51, by L.A. Paquette and K.E. Stevens[80]

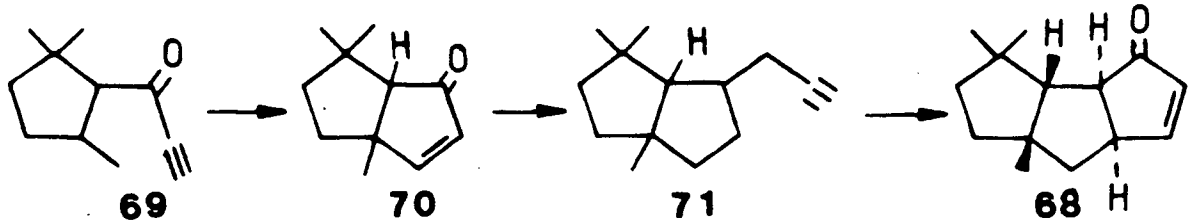


In Drieding's synthesis[81], the α-alkynone 69 was prepared from methyl 2-oxocyclopentanecarboxylate. Thermolysis (620°, 78% yield) of 69 afforded the unsaturated ketone 70, which was converted to a second α-alkynone 71.

Thermolysis (620°, 33% yield) of 71 gave 68 (and one isomer).

Scheme 14

Synthesis of 51, by L. Huguet, M. Karpf and A.S. Drieding[81]

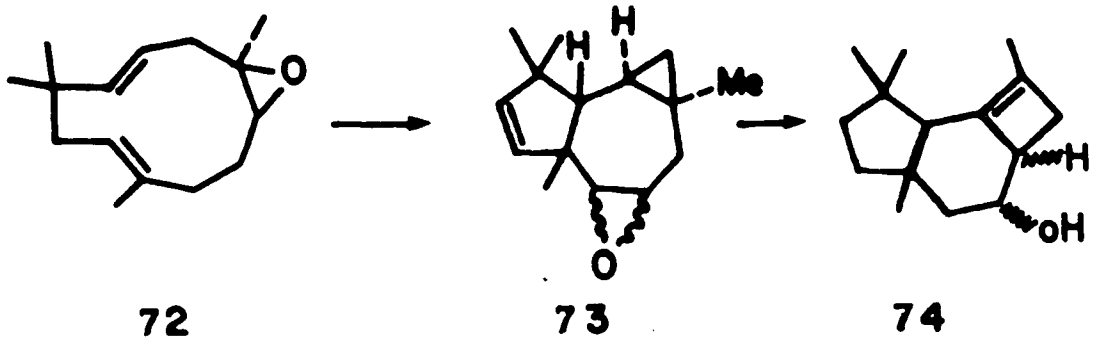


Fujita et al's synthesis[82] started with the preparation of a humulene derivative 72, which after several transformations led to tricyclic epoxide 73. The key steps in this synthesis involved an initial rearrangement (TMSOTf, toluene, RT; 1N HCl; 54% yield of 73) with migration of a methyl, followed by solvolytic rearrangement (MsCl, CH_2Cl_2, DMAP, 0° to RT, 20 min; NaOAc, AcOH, 70°, 6 h; 93% yield of 74, plus 1 isomer). Another series of steps afforded capnellene (and an isomer).

Scheme 15

Synthesis of 51, by

T. Fujita, T. Ohtsuka, H. Shirahama and T. Matsumoto[82]

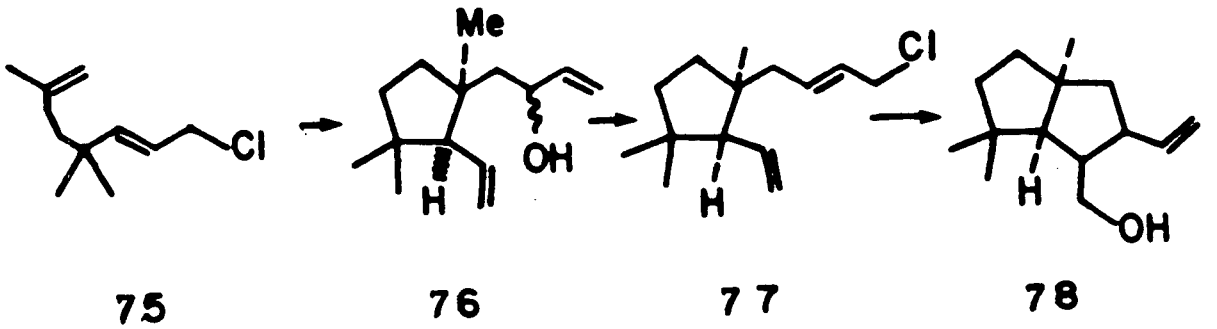


In Oppolzer's synthesis[83] rings A and B were formed through two "magnesium-ene" reactions. The linear allylic chloride 75, and the monocyclic

allylic chloride 77 were cyclized under mild conditions (Mg powder, ether; 60°, 23 h; acrolein; 57% yield) to 76 and (Mg powder, ether; RT, 2 h; O_2; 70% yield) to 78. Subsequent transformation of 78 afforded γ-keto-aldehyde 67 which underwent an aldol condensation to give 51.

Scheme 16

Synthesis of 51, by W. Oppolzer and K. Battig[83]

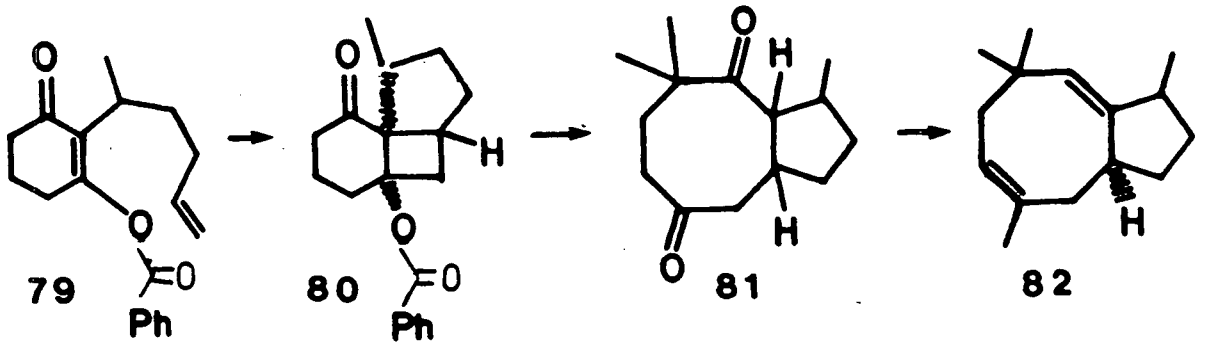


75 76 77 78

The first biogenetic type synthesis was undertaken by Pattenden[84] (Scheme 17). In this case, the starting material was 1,3-dimethoxybenzene. This aromatic molecule was converted to 79. Photochemical cyclization (6 h, 450 w, hexane, >90% yield) of 79 to 80, followed by fragmentation in base (KOH, EtOH, 48 h, 25°, 36% yield) gave diketone 81. Further reaction of 81 led to epiprecapnelladiene (82 and one isomer), the biosynthetic precursor of 51. The transannular cyclization was accomplished using boron trifluoride etherate (benzene, reflux, 1 h, 50% yield, plus two isomers).

Scheme 17

Synthesis of 51, by A.M. Birch and G. Pattenden[84]

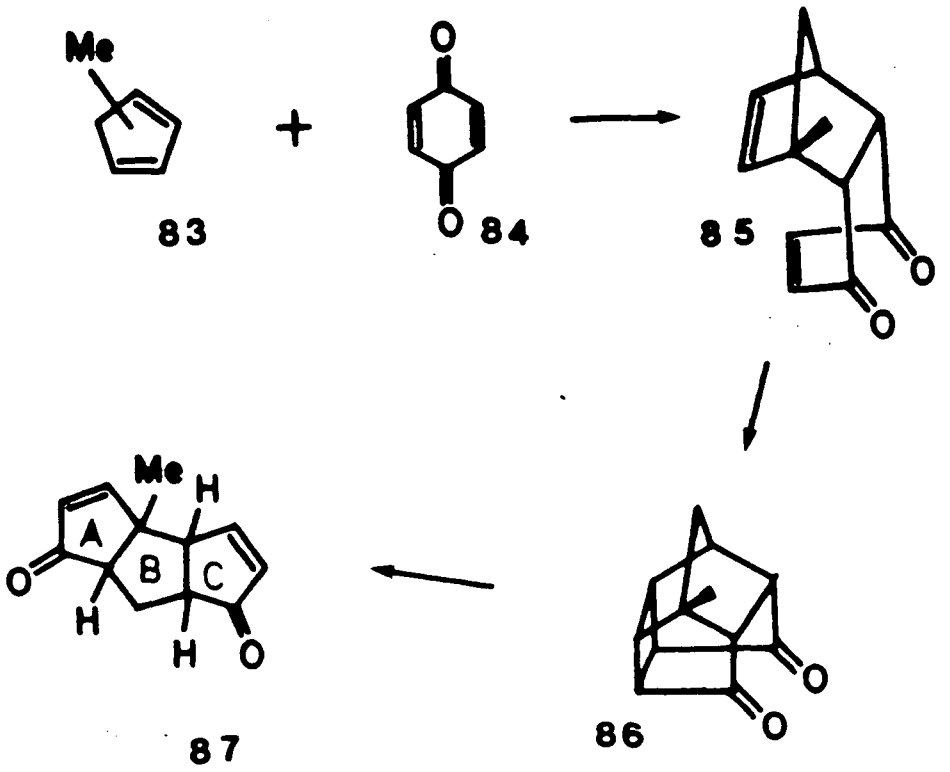


79 80 81 82

Mehta's synthesis[85] started with a Diels-Alder reaction (THF, RT) between methyl cyclopentadiene and p-benzoquinone. An intramolecular photochemical cycloaddition (EtOAc, 450 w, 75% yield) of 85 afforded the pentacyclic dione 86. Flash column pyrolysis (530°, 0.1 mm Hg, 60% yield) of 86 led to the tricyclopentanoid 87 with cis-cisoid-cis fused rings. Isomerization of the double bond in ring C of 87 and reduction of the double bond in ring A gave 68, a known precursor of 51.

Scheme 18

Synthesis of 51, by G. Mehta, D.R. Reddy and A.N. Murty[85]

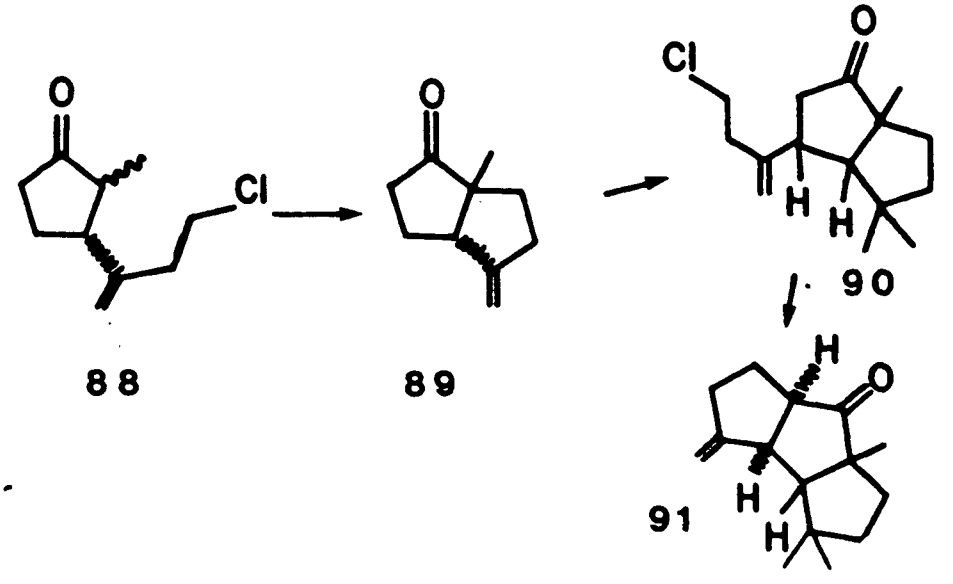


A very recent synthesis[86] by Piers is outlined in Scheme 19. Conjugate addition of a vinylic Grignard reagent afforded chloroketone 88. Intramolecular alkylation (KH, THF, RT, 75% yield) of 88 gave 89. After

further preparation of chloroketone 90, the second key step was achieved by performing a second methylene cyclopentane annulation (KH, THF, RT, 69% yield), and deoxygenation to afford 91.

Scheme 19

Synthesis of 51, by E. Piers and V. Karumaratne[86]

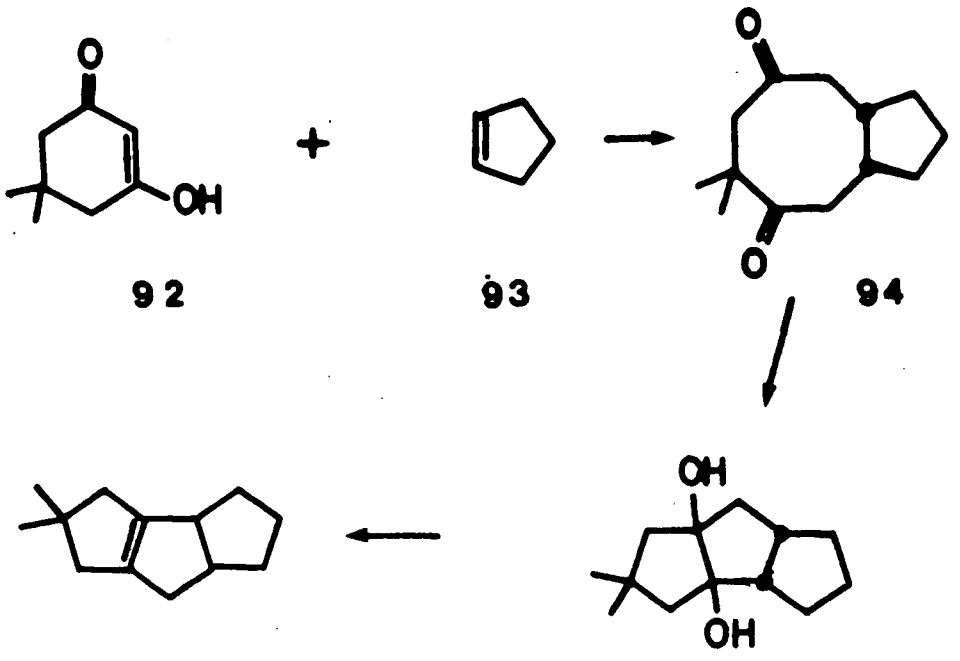


Two other syntheses related to 51 should be mentioned. The first[87] shown in Scheme 20 consists of the synthesis of a tricycloundecane skeleton 96 that could be adapted to a synthesis of the capnellanes or hirsutanes. A photochemical addition (MeOH, uv light of 254 nm, 90% yield) involving cyclohexane-1,3-dione 92 and cyclopentene (93) afforded bicyclic diketone 94. Coupling of 94 using a low valence titanium species ($TiCl_3$, K, THF, 5 min, only product) gave olefin 96.

Scheme 20

Synthesis of a C skeleton related to 51,

by J.E. Paw and A.C. Weedon[87]

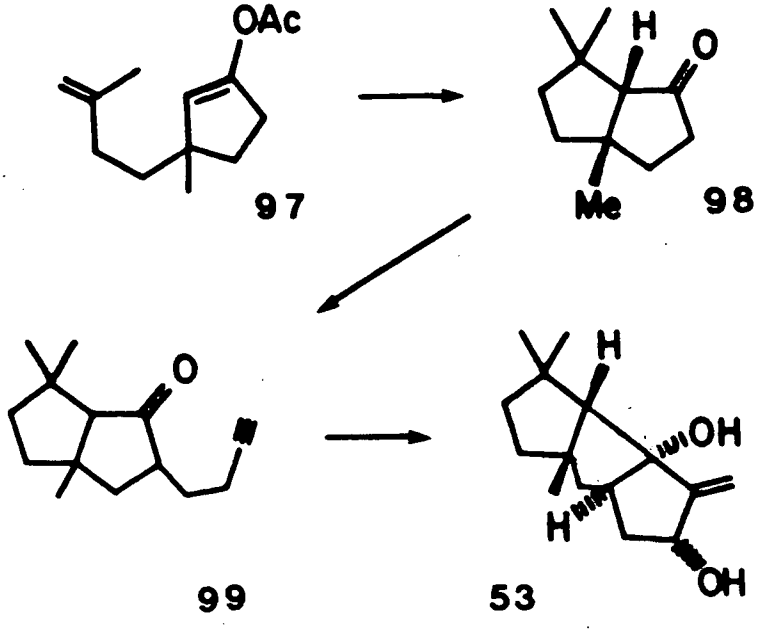


92 93 94 95 96

Finally, another synthesis by Pattenden[88] has diol 53 for its target (Scheme 21). A stannic chloride (moist CH_2Cl_2, 63% yield) induced cyclization of enol acetate 97 produced bicyclooctanone 98. Further reactions led to the keto acetylene 99. The last cyclization was accomplished with sodium naphthalene radical anion (THF, 25°, 26% yield) and afforded after an oxidation step, diol 53.

Scheme 21

Synthesis of 53, by G. Pattenden and S.J. Teaque[88]



In summary, the ten syntheses presented in Schemes 12 to 21 can be divided into 3 categories. In the first, the rings were assembled one at a time. For example, in Schemes 13, 14 and 16, ring B was attached to ring A; then ring C added; in Schemes 12, 19 and 21, rings A and C were joined to ring B.

The second group consists of the biogenetic type syntheses. In one case, Scheme 15, the "starting material" was a medium ring molecule (humulene) possessing the 15 carbons necessary for 51. After several transformations via tricyclo[6.3.$0^{1,8}.0^{2,4}$] and tricyclo[6.3.$0^{1,4}.0^{7,11}$]-undecanes, the triquinane system was obtained. In Schemes 17 and 20, the key intermediate was a bicyclo[6.3.0]undecane molecule (related to precapnelladiene). The required tricyclopentanoid was then obtained through an intramolecular cyclization.

Scheme 18 represents another special approach. Starting with a 5 and a 6 membered ring, a tricyclic intermediate was formed, followed by a pentacyclic ring system and finally the tricyclic target.

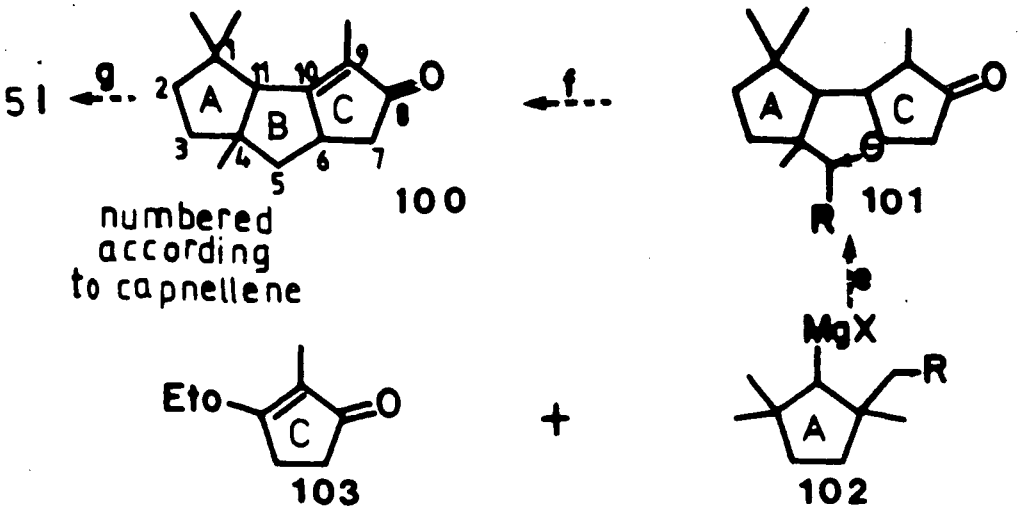
III.2. Results and Discussion

This section describes studies aimed at the total synthesis of the tricyclopentanoid marine natural product, capnellene (51). The results are discussed chronologically in order to show the logical development of the present work.

Our first retrosynthetic analysis (Scheme 22) of 51 envisaged the disconnection of the C-5, C-6 bond of ring B, preceded by the disconnection of the C-10, C-11 bond. Therefore, the synthesis begins with the preparation of the appropriate ring A, which would later be joined to ring C[89].

Scheme 22

Enol ether approach to 51

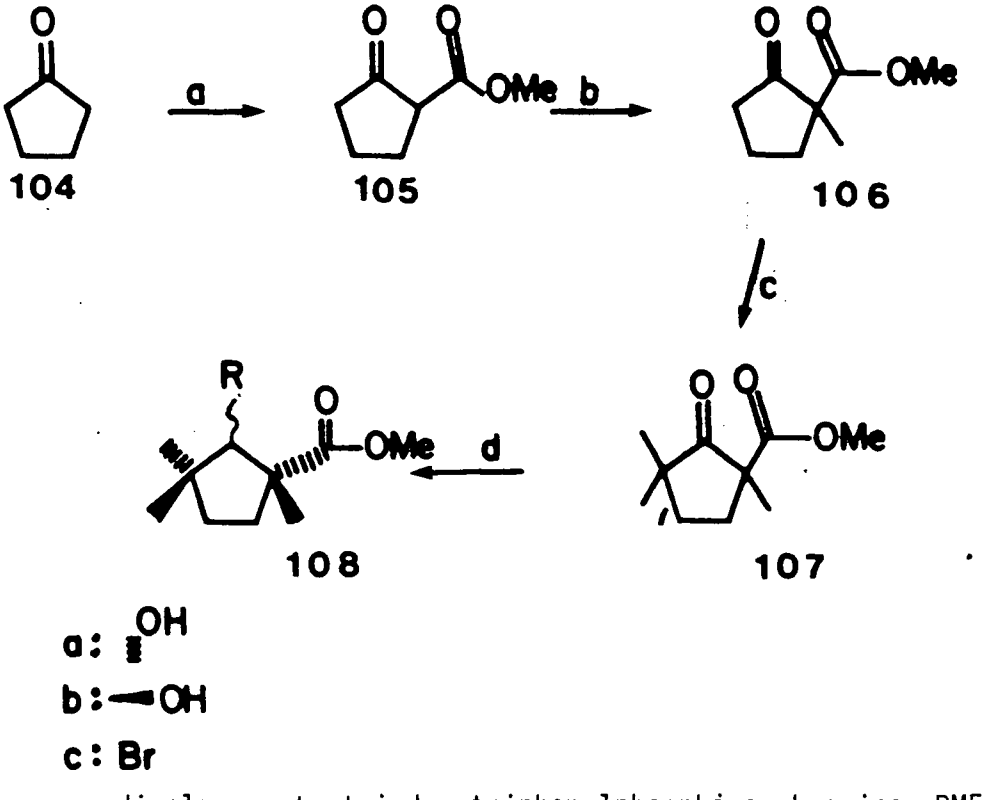


As illustrated in Scheme 23, our first approach to ring A started with cyclopentanone (104). After formation of methyl 2-oxocyclopentanecarboxylate (105), trimethylation of the β-keto-ester and reduction of ketone 107[90], alcohol 108 was obtained with a very good overall yield (30% from 104, or 56% from 105). The ^{1}H NMR of alcohol 108 displays a singlet at 4.05 ppm, which is assigned to the methine proton. The presence of only one new singlet,

indicates that probably only one alcohol isomer is formed. The orientation is uncertain but if the reagent coordinates with the ester[91], then isomer 108b would be obtained. All attempts to displace the alcohol by a bromine or chlorine seemed to be unsuccessful[i]. A space-filling model of 108 showed that the difficulty encountered in displacing the alcohol is due to steric hindrance, regardless of the alcohol isomer considered. It was appreciated that the resulting Grignard (or lithium) reagent would be quite hindered, however t-butyl groups were successfully added to 103 in related experiments[ii].

Scheme 23

Synthesis of 108



a:

b:

c: Br

[i] Hydroxyl group displacements tried: triphenylphosphine, bromine, DMF; phosphorus tribromide, ether; p-toluenesulfonyl chloride, pyridine; hydrobromic acid (g), THF; phosphorus dibromide, pyridine, sodium bromide; thionyl chloride, pyridine, reflux, or sodium chloride in benzene; aluminum trichloride, ether; methanesulfonyl chloride, pyridine; phosphorus pentachloride, calcium carbonate, chloroform. No MS was available at the time.

[ii] S.J. Alward, unpublished results, reaction between t-butyl lithium and 3-ethoxy-2-methyl-2-cyclopentenone (103).

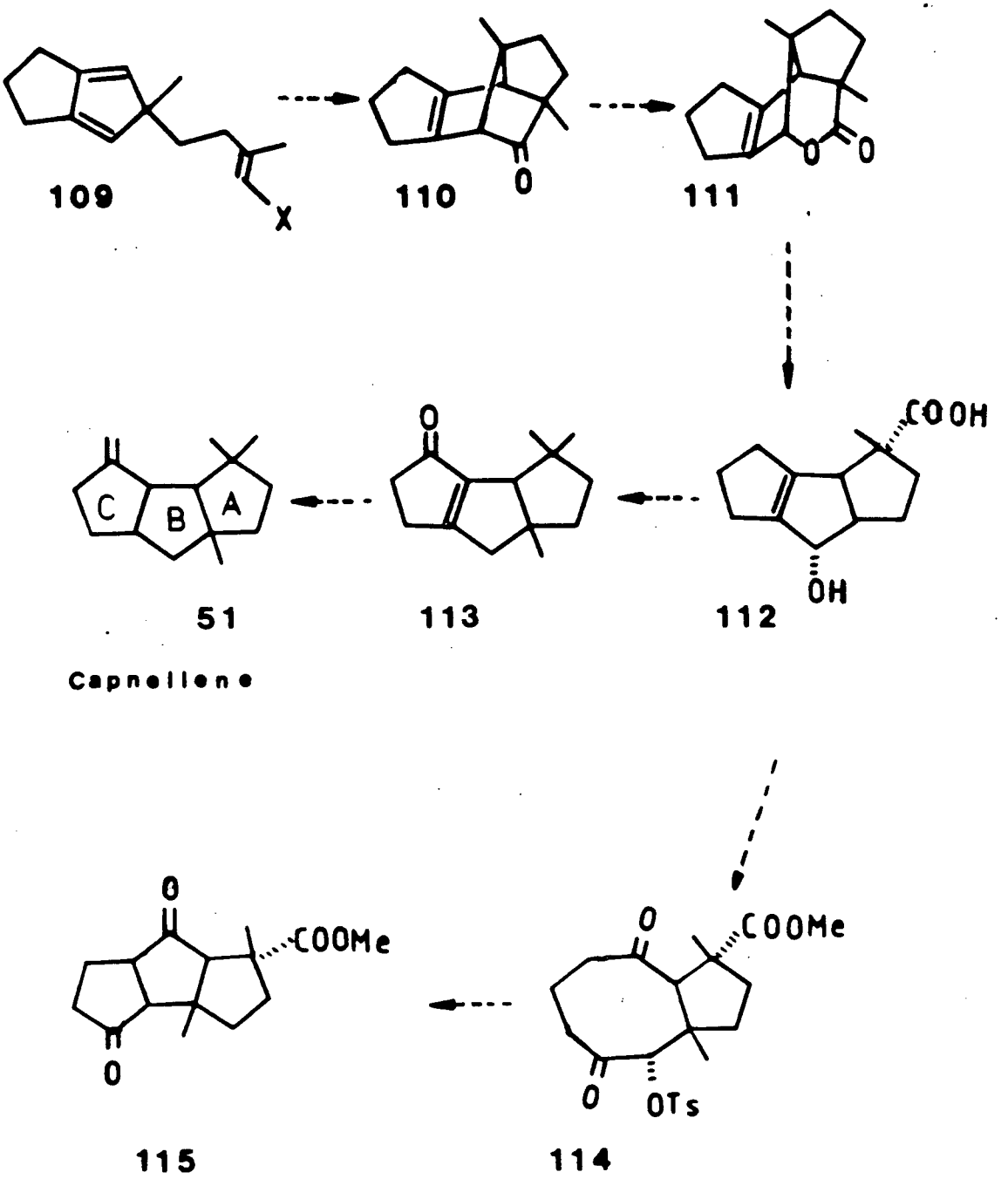
While these experiments were in progress cyclopentenone annulation results became available[93]. The work undertaken by colleagues in our laboratory indicated that step "f" (Scheme 22) would not be straightforward. Thus, it was decided that another route towards the synthesis of 51 might prove more rewarding.

The second approach selected (Scheme 24) was based on an intramolecular Diels-Alder reaction of 109. It was anticipated that Baeyer-Villiger oxidation of tetracyclic ketone 110 would be directed by the presence of the allylic double bond. Ring opening of lactone 111 followed by hydrogenation would lead to capnellene 51. The introduction of a ketone (later a double bond) to ring C could be accomplished by allylic oxidation at several potential points. The proposed route would provide access to oxygenated capnellanes. It was hoped that intermediate 112 could eventually be used to prepare related triquinanes via ozonolysis and base catalyzed ring closure. This approach (Scheme 24) was selected since it allows good stereocontrol and versatility.

As will be outlined below, the preparation of a cyclopentadiene derivative related to 109 has proved particularly challenging. In spite of several possible starting materials and routes to 109, establishing the double bonds in the required position represented a major task.

Scheme 24

Cyclopentadiene Approach to Capnellene



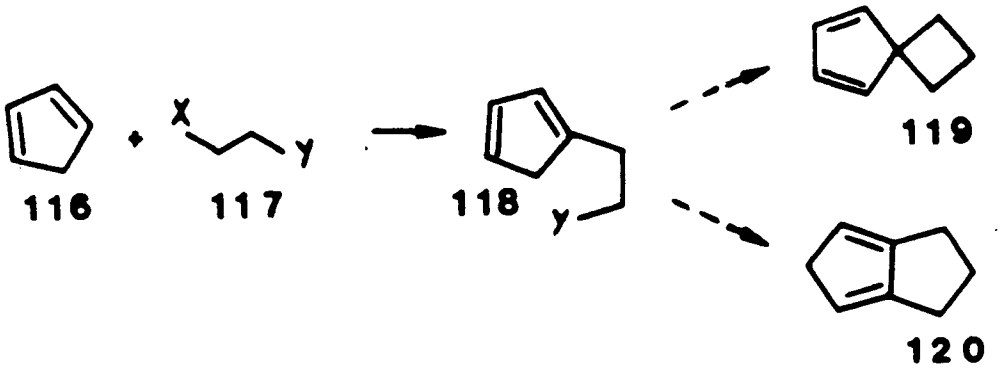
Our first approach to 109 appeared to be direct, and offered the opportunity to increase our understanding of the behaviour and reactivity of fused bicyclopentadiene systems.

Alkylation of cyclopentadiene (116, Scheme 25) with a suitable three carbon chain, followed by an intramolecular alkylation, was expected to give bicyclo[3.3.0]octadiene 120. This second step could produce either structural isomer 119 or 120. (Only one positional isomer of 120 is illustrated in Scheme 25).

The spiro system 119 is known to be unstable[i], and thus 120 should be preferred. Also, if Y in structure 118 (Scheme 25) represents a species possessing a carbonyl group, a product such as 120 should be even more favoured.[ii]

Scheme 25

Alkylation of cyclopentadiene 116



[i] Spiro molecule 119 was reported over thirty years ago[94], and some controversy surrounds its first synthesis[95-97].

[ii] According to Baldwin's rules, 5-exo-tet and 4-exo-tet processes are favoured, however "five and six membered ring compounds are formed more easily than their analogues with smaller or larger rings".[98]

Table 4

Conditions for the alkylation of 116

	117 X	117 Y	Temperature (°C)	Time (h)	Yield (%) of 118
a)	Cl	$COOCH_3$	0	4	75
b)	COCl	Cl	-78	1	i
			0	1	ii
c)	CHO	Cl	20	2	iii
d)	Cl	$CH(OCH_2)_2$	0	16	82
e)	Cl	$CH(OCH_3)_2$	20	4	89
f)	Br	CH_2OCOCH_3	0	4	90
g)	Br	CH_2Cl	-78	6	65
h)	Br	CH_2Br	-45	1	88
i)	I	CH_2I	0	.5	91

i: ~40%, yield of possibly 1,3:1,1 diacetylated cyclopentadiene (1:4)

ii: ~40%, yield of possibly 1,3:1,1 diacetylated cyclopentadiene (1:1)

iii: ~5%, possibly product with alcohol α to the cyclopentadiene

As expected, the first alkylation of cyclopentadiene (116) proved straightforward in a number of cases (Scheme 25 and Table 4). However, when 3-chloropropionyl chloride (117b) was used, two diacylated products were obtained. Also, reaction of cyclopentadiene with 3-chloropropanal proceeded in poor yield (unstable product if not kept in solution).

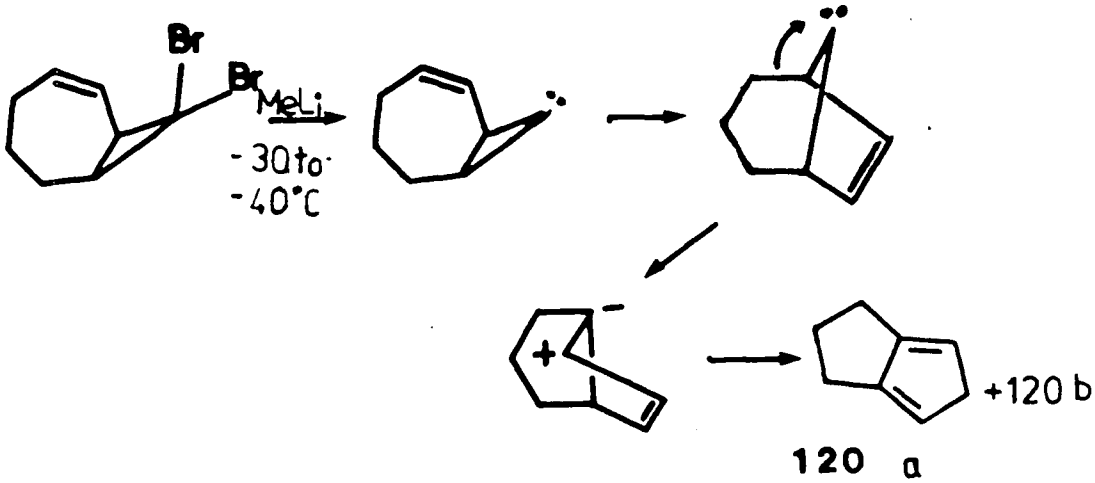
Products 118 were best purified by column chromatography on neutral alumina. When standard flash chromatography was used, more decomposition occurred. It was also possible to distill some of these products (in vacuo), but the yields were reduced to 20% from 65 to 90%. Most products could be readily identified. Only the products of the reaction of cyclopentadiene with 3-chloropropionyl chloride and 3-chloropropanal are tentative, as indicated in Table 4.

In order to cyclize products 118d and 118e (acetals) it was necessary to deprotect the aldehyde. This step could not be achieved cleanly under a variety of conditions[i]. Cyclopentane annulations of 118a (Y = $COOCH_3$), 118f (Y converted to CH_2OTs, CHO), 118g (Y = CH_2Cl), 118h (Y = CH_2Br), 118i (Y = CH_2I) were attempted using NaH or KH (1 or 2 equivalents), in different solvents, (ether, THF, DME, DMF, DMSO) and at different temperatures (from -78°C to 100°C). No product was detected from any of these reactions. Usually the starting material (mild conditions) or some insoluble product was recovered. There is a precedent[99] for alkylating cyclopentadiene with ethyl acetate and a catalytic amount of base (NaOEt). This mild procedure was tried on 118a and other modifications. All these reactions were unsuccessful, which is probably partly due to the high sensitivity of 120, to heat and base.

[i] Deprotections tried: 1% hydrochloric acid; oxalic acid and acetone; aluminum trichloride, dichloromethane; boron trifluoride etherate, ether; trimethylsilyl chloride, sodium iodide, acetonitrile; trimethylsilyl chloride, sodium iodide, acetonitrile and butadiene.

Scheme 26

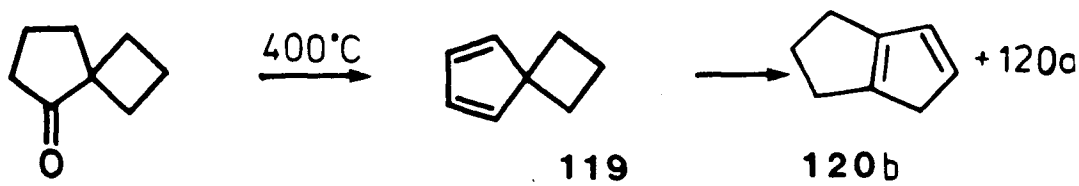
Synthesis of 120, by M.S. Baird and C.B. Reese[96]



Compound 120 has been previously synthesized as shown in Schemes 26 and 27. However these procedures are not of preparative value.

Scheme 27

Synthesis of 120, by A. De Meijere and L. Meyer[97]



Since molecule 120 was elusive, a modified approach to 126 (Scheme 28), which bears a methyl substituent was examined. The enol ether 103 formed from 2-methyl-1,3-cyclopentanedione (121) has been converted by Koreeda, Liang and Akagi[100] into bicyclic enol ether 122. This sequence was repeated, followed by hydrolysis and reduction of 122. Several dehydrations[i] of allylic alcohol 124 were attempted, but no dehydrated product of type 126

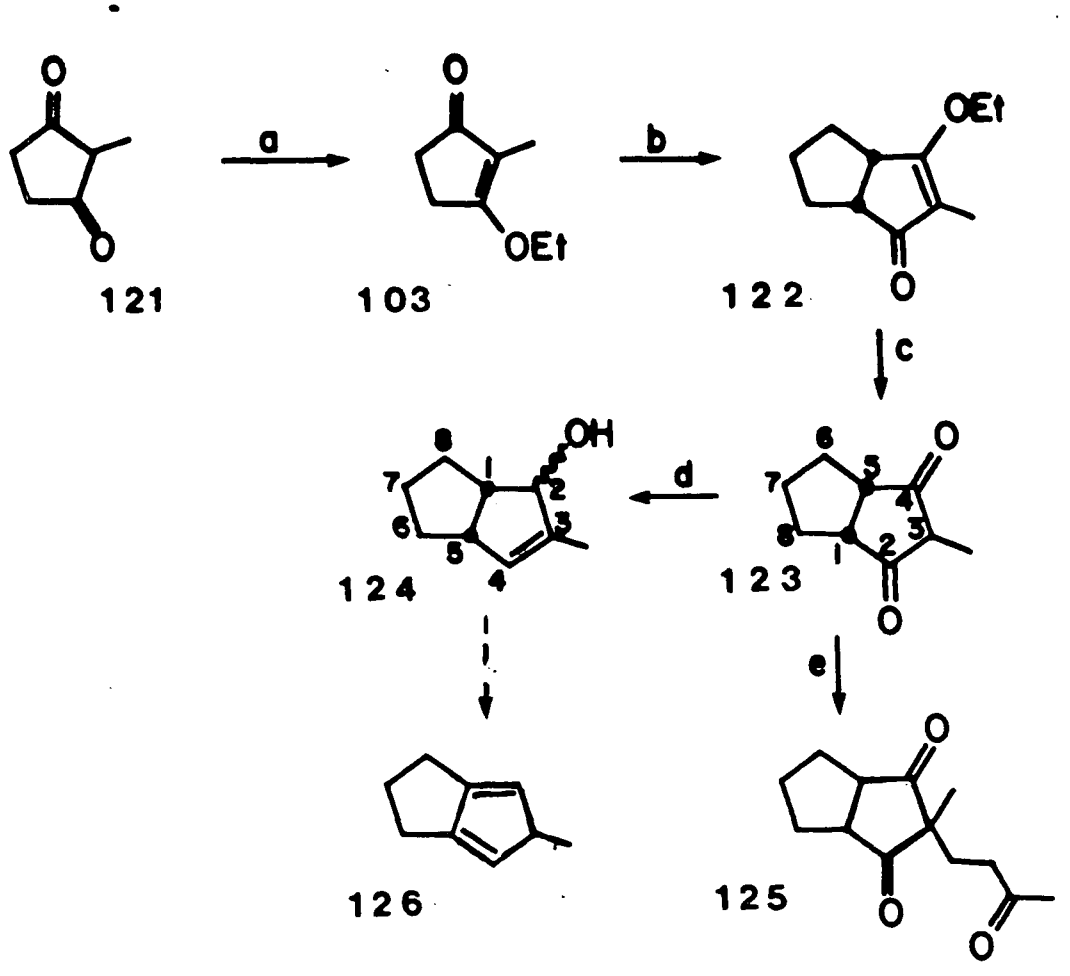
[i] Dehydrations tried: hydrogen chloride (g), chloroform; phosphorus oxychloride; thionyl chloride; N-phenylselenophthalimide, n-tributylphosphine; phosphorus pentachloride, chloroform; trifluoroacetic anhydride, dimethylaminopyridine, 1,5-diazabicyclo[5.4.0]undec-5-ene; p-toluenesulfonyl chloride, pyridine, dichloromethane. In retrospect, the Burgess reagent or methanesulfonyl chloride and the sulfur dioxide dehydrations (see experimental) might have given a better result.

could be isolated. Thus, alternative step "e" (Scheme 28) which would introduce a second substituent in ring B before dehydration was explored.

It is known[101] that β-diketones such as 121 can be alkylated using methyl vinyl ketone. The product of this Michael addition depends on the reaction conditions (Scheme 29). Under neutral conditions (reaction in water), 121 afforded 128. Under catalytic basic conditions (chromatography of 128 on alumina, or standing of 128 at 20°C for a few days), ketol 130 was produced. In contrast, when 128 was submitted to acidic conditions, 129 was obtained.

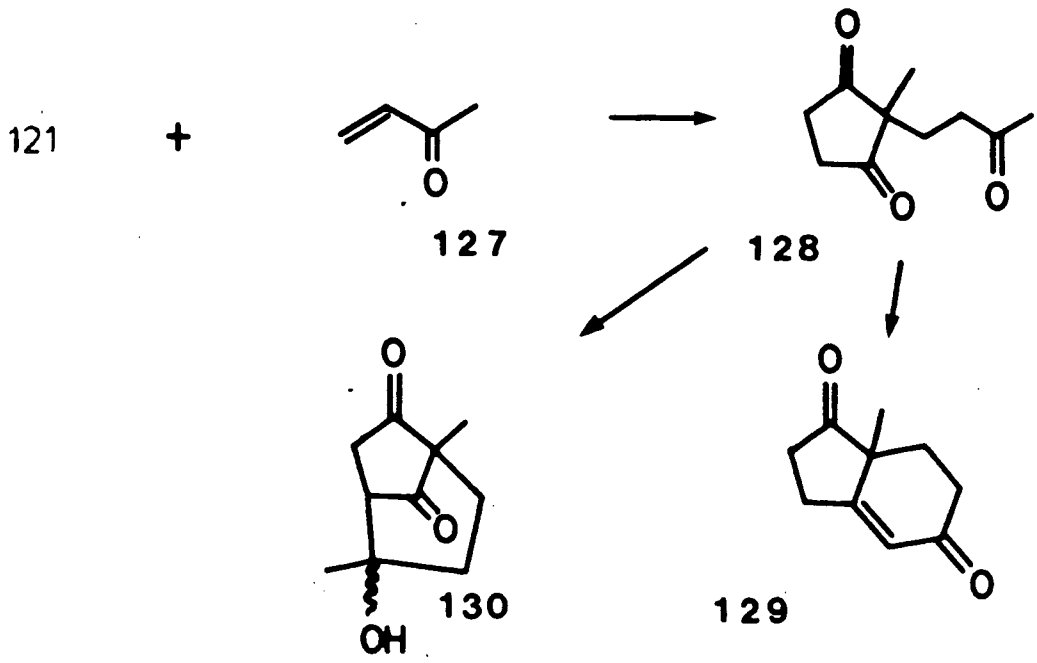
Scheme 28

Reactions of β-diketone 121

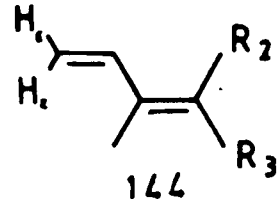


Scheme 29

Known alkylation of 121



A Michael addition between 123 and methyl vinyl ketone proceeded satisfactorily to give 125, as indicated by the IR spectrum (no OH) and ^{1}H NMR spectrum (CH_3, s, 0.94 and 2.02 ppm), characteristic of a non-cyclized product. Selective functionalization[i] of the methyl ketone in 125 did not proceed as expected. Therefore a 1,6-addition between 2-methyl-1,3-cyclopentanedione 121 or bicyclic ketone 123 and 144b was attempted. The latter reaction did not afford the required product even though literature precedent exists[102]. Since these attempts were unsuccessful a different approach to the bicyclic skeleton was adopted.



144

a R_2, R_3 = H, COOEt

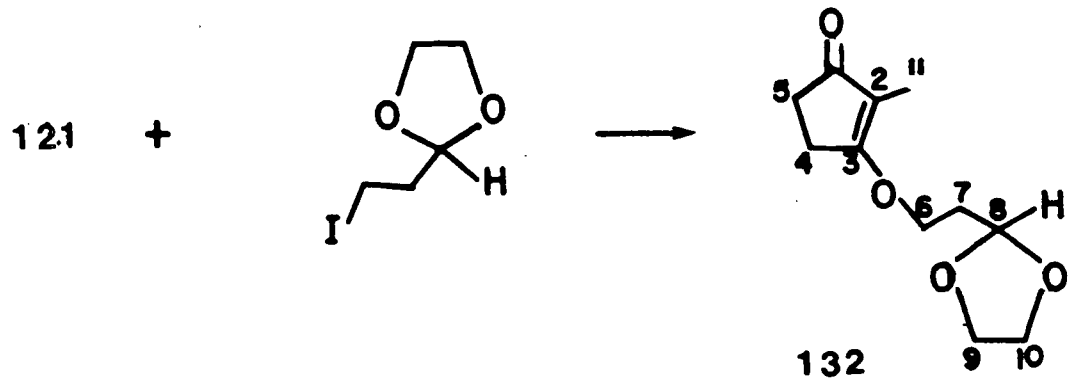
b $R_2 = R_3$ = COOMe

[i] Reactions attempted: Wittig, Horner-Emmonds and Knoevenagal condensations, as well as Grignard additions.

One of the results obtained while investigating the alkylation of β-diketone 121 is presented in Scheme 30. In keeping with literature precedent[103], O rather than C-alkylation occurred when 121 was treated with an alkyliodide in an aprotic polar solvent (DMF or HMPA) and a mild base (K_2CO_3).

Scheme 30

O-alkylation of 121



The IR and 'H NMR spectra of the O-alkylated product enabled its identification. Two bands appeared in the IR spectrum at 1700 and 1640 cm^{-1}, and these were assigned to a carbonyl and a conjugated double bond. The 'H NMR spectrum displayed the following signals at: δ = 5.00 ppm (1H, t, J = 7 Hz); 4.30 ppm (2H, t, J = 7Hz); 3.92 ppm (4H, bs) and 1.58 ppm (3H, bs). The remaining six protons appeared as a multiplet between 2.1 and 2.8 ppm. The MS of 132 displayed a very weak (3%) parent ion at m/z = 212.

A paper by Coates and Hobbs[104] which appeared in early 1984, offers a variant to the Michael reaction. It involves the reaction of readily enolizable carbonyl compounds with α,β-enols or ethoxyallenes. It was observed that the reaction between 2-methyl-1,3-cyclopentanedione (121) and acrolein acetal ($CH_2CHCH(OEt)_2$) takes place neat in a sealed tube, at 200°C

in 33 h (82%) or in refluxing 1,2-dichloroethane, 85°, in 0.25 h (67%). This reaction may present another possible approach.

Approach to 138

The results described above influenced the next route examined which starts with $\Delta^{1,5}$bicyclo[3.3.0]octen-2-one (138), a ketone previously prepared by several groups[105,106]. Another approach to this ketone which has a precedent (for and against it!!) in the literature[107,108] is outlined in Scheme 31. Diol 133 was prepared from Grignard addition of propargyl alcohol ($ClMgCCCH_2OMgCl$) to cyclopentanone (100). Although the (Meyer rearrangement) acid-catalyzed rearrangement of the tertiary α-acetylenic alcohol 133 took place (since 134, 135 and traces of 136 were partially identified through ^1H NMR and IR spectra, see Experimental), the sensitive dienone 136 did not undergo the Nazarov cyclization. Instead, ketone 137 (self-condensation of 104), formed by decomposition of the Grignard product was isolated. Although the IR and ^1H NMR spectra of bicyclopentyliden-2-one (137) were similar to those of $\Delta^{1,5}$-bicyclo[3.3.0]octen-2-one 138, the MS of the DNPH derivative of 137 (M^+ = 330 $C_{16}H_{18}N_4O_5$, therefore the molecular formula of the ketone is $C_{10}H_{14}O$) and the ^{13}C NMR spectrum (10 signals observed at: 20.09, 25.23, 26.94, 29.52, 32,55, 34.30, 39.79, 128.69, 158.66 and 207.39 ppm) left no doubt as to the dimeric nature of this product. Therefore, 138 was synthesized according to the known route shown in Scheme 31[105].

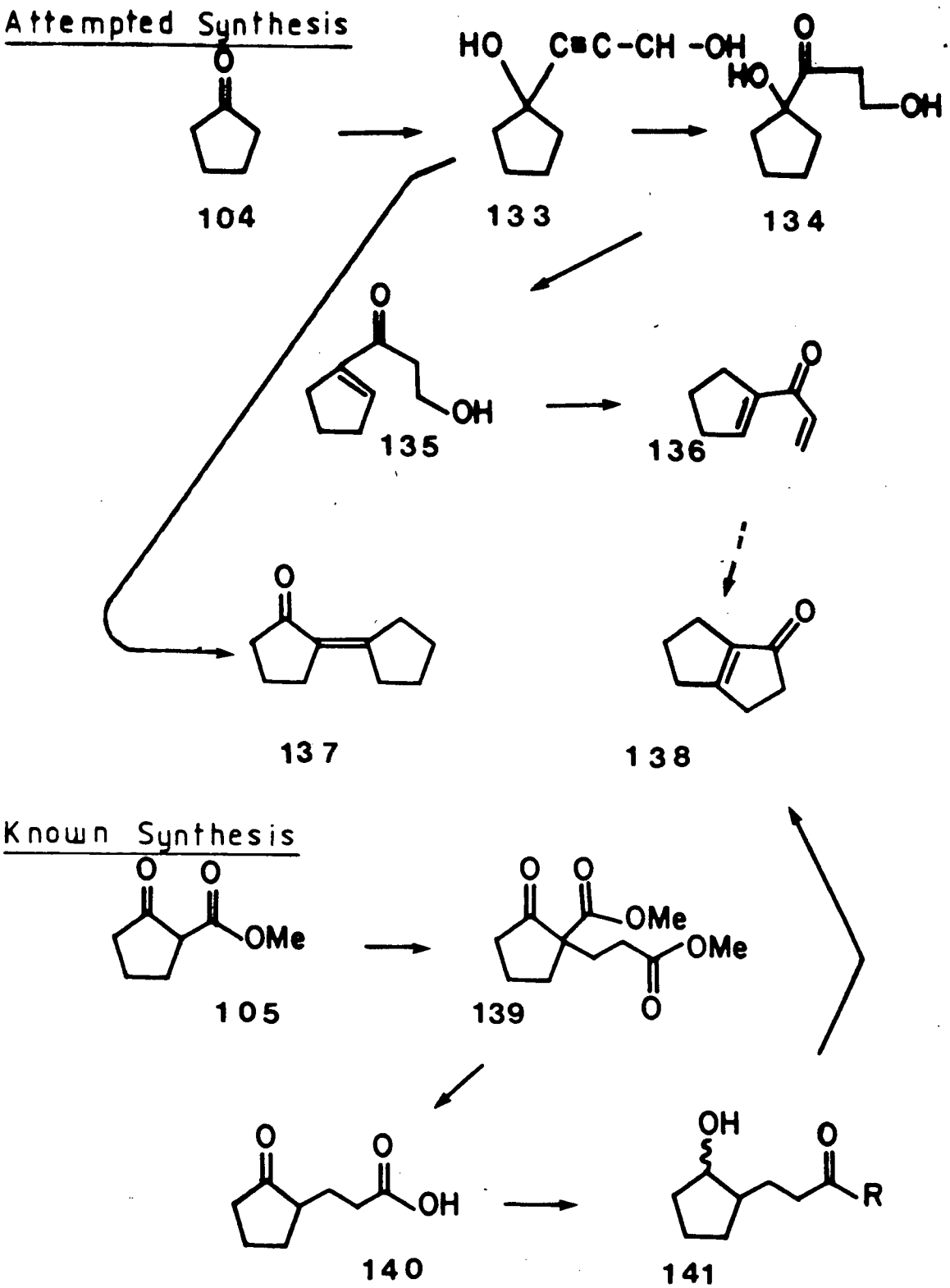
The approach illustrated in Scheme 31, consists of alkylating β-keto-ester 105 with methyl acrylate; decarboxylating the β-keto-ester and hydrolyzing the primary ester of 139 in one step. Reducing the ketone of 140 and finally performing a Meyer rearrangement. The four steps of this synthesis were reported to give 92, 90, 97 and 77% yield, respectively. The first three steps

could be reproduced in the same quantitative way (73% overall yield), however the cyclization step proceeded in 30-40% yield.[i] Therefore, instead of using polyphosphoric acid (P_2O_5, H_3PO_4) as in Kulkarni and Dev's synthesis[105]; Easton, Carlson and Lee's improved alternative[110] (P_2O_5, CH_3SO_3H) was followed. This mixture was easier to handle and did not require a continuous extraction in the work-up procedure. When this modified cyclization procedure was used, the yields increased to 60%.

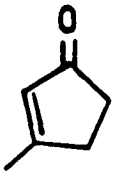
[i] According to the IUPAC Nomenclature of Organic Chemistry $\Delta^{1,5}$bicyclo[3.3.0]octen-2-one (138) can also be named bicyclo[3.3.0]-oct-1(5)-en-2-one or 1(5)-bicyclo[3.3.0]octen-2-one. These two variations apply to the molecules where the delta nomenclature has been used.

Scheme 31

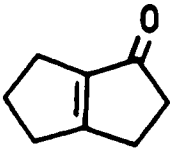
Synthesis of ^{1,5}-bicyclo 3.3.0 octenone (138)



The next steps in the synthesis require sequential α' alkylations of 138. However, due to its ready availability, 3-methyl-2-cyclopentenone 142 was chosen as a model for most of the next reactions. The selective formation and reaction of an anion from these cyclopentenones was experimentally troublesome. Model compound 142 was even more sensitive than 138. In order to minimize the self-condensation of these ketones, it was necessary to perform the reactions (involving a carbanion) at low temperatures (< 20°C), using relatively reactive electrophiles (reacting in a few minutes). Therefore, an activating group was needed as the first α' substituent to facilitate the introduction of the side chain. This activating group could later be converted into a methyl group. A number of reagents were examined: dimethyl carbonate ($CO(OMe)_2$) was not sufficiently reactive, methyl chloroformate (ClCOOMe) was too reactive, but diethyl pyrocarbonate (DEPC, $O(COOEt)_2$) diethyl oxalate ($(COOEt)_2$) and ethyl formate (HCOOEt) could be used as described in the next pages.



142



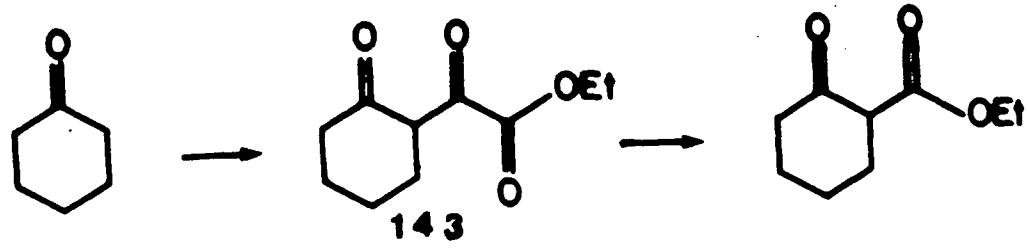
138

Approach Using 138 and Diethyl Oxalate

It has been reported in the literature[111], that upon reaction of cyclohexanone with diethyl oxalate, 143 is obtained in 65% yield (Scheme 32). Decarbonylation of 143, using powdered glass and iron powder, at 165-175°C produces the related β-keto-ester (65%). The same reactions were expected with 138 and 142, and thus the acylation was conducted according to the literature (95% and 65% yield). Decarbonylation of the cyclopentenone derivatives, under the reported conditions and higher temperatures (including sealed tubes) proved impossible. Therefore, the reduction and alkylation of 145 was studied (Scheme 33).

Scheme 32

A known reaction of cyclohexanone



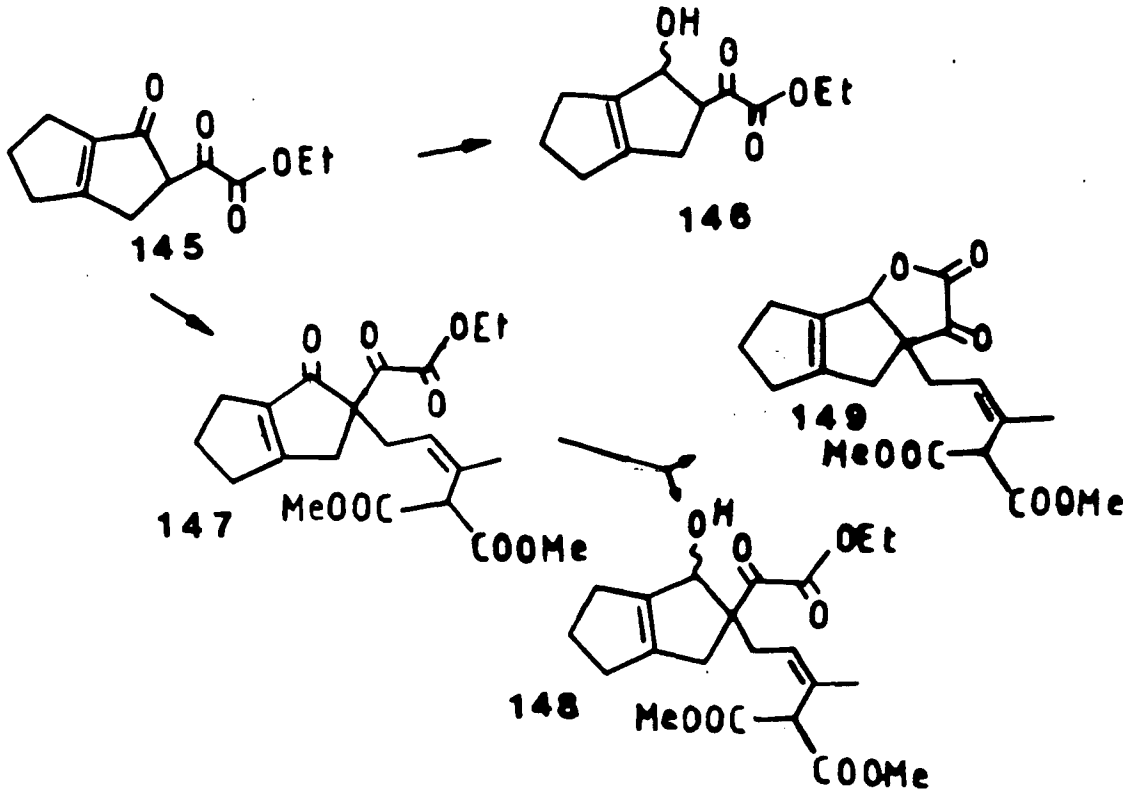
143

Reduction of 145 (with $NaBH_4$ in MeOH), cleanly reduced the unsaturated carbonyl (76%). The trifluoroester of this alcohol 146 was formed quantitatively (98%, upon addition of TFAA, DMAP in CH_2Cl_2 at 20°C). The proposed structure for 146 was supported by its ^1H NMR and IR spectra. A deshielded signal appeared in the ^1H NMR spectrum at 5.40 ppm (d, J = 3 Hz). The chemical shift of this methine corresponded to the reduction of the unsaturated carbonyl[41] (δ expected: ~5.6 ppm), rather than to the side chain carbonyl[41] (δ expected: ~6.1 ppm). The small coupling observed represented a vicinal coupling between H-1 and H-8 (J_{8-9} expected to be

7 Hz). The IR spectrum of this ester displayed bands at 1800, 1750, 1700 and 1630 cm^{-1}. The first band was assigned to the trifluoroester, the second to the ethyl ester, the third to the ketone and the last possibly to a double bond. Another observation that supported this interpretation, that the reduction took place at the unsaturated carbonyl, comes from TLC analysis. A DNPH spray was used to visualize the spots on TLC. In the case of compound 145, a red colour was observed while for 146, an orange colour was produced. Since DNPH derivatives of unsaturated carbonyls are known[112] to be coloured red rather than orange (qualitative test, not quantitative), this result would tend to support the spectral data.

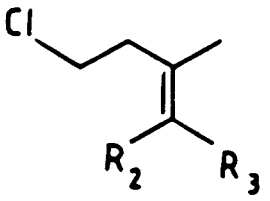
Scheme 33

Reactions performed on 145



The trifluoroester of 146 could not be readily eliminated (using DBU) to give the diene. Since alcohol 146 does not represent a very good model for alcohol 148 (which has a tetrasubstituted α carbon, Scheme 33), the dehydration of 146 was not extensively studied.

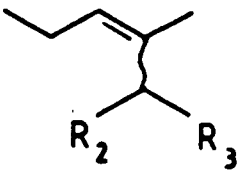
In view of the encouraging results of the reduction study, our attention was turned to the alkylation of 145. A method was developed for the alkylation of 5-carboxy-2-cyclopentenones with a chloro ester such as 131 (a or b). This alkylating reagent can react in two competing manners. In the present case, displacement of the chlorine was anticipated, however abstraction of the γ proton (γ to the ester) followed by elimination may compete. Conditions were found which favored the alkylation and reduced the side reaction. These consisted of using sodium ethoxide to generate an insoluble anion of the 5-carboxy-2-cyclopentenone in ether at 20°C, adding DMSO and the alkyl halide, and stirring the reaction mixture in a pre-warmed (75-80°C) bath, for two hours (see Experimental, Table 7, for several examples). When reagent 131a (1:1, E;Z) was used, the E isomer (trans) reacted at a higher rate than the Z isomer. Therefore, two equivalents of the alkyl chloride 131a were used and the Z isomer (cis) recovered after work-up. When reagent 131b was used, the dehydrohalogenated diester was recovered. In this case, 1.1 equivalents of 131b were used.



131

a: R_3, R_2 = H, COOEt

b: R_3 = R_2 = COOMe



The bicyclic molecule 145 was alkylated with diester 131b (90% yield). During this alkylation, the double bond in the side chain isomerized out of conjugation (as in 147, Scheme 33). The isomerization was easily identified from the ^{1}H NMR spectrum. The chemical shift of the signal assigned to the

vinyl methyl changed from 2.01 ppm (s) in 131b to 1.68 ppm (bs) in 147, while a new olefinic signal appeared at 5.04 ppm (t, J = 7 Hz)[i]. The presence of base in the solution appeared to promote the formation of the more stable double bond isomer (non-conjugated!). This behaviour has also been observed by Danishefsky, Koppel and Levine[113].

After alkylation of 145 and reduction of 147, a product with no ethoxy group was isolated together with the expected alcohol (Scheme 33). The reduction was performed with sodium borohydride or sodium cyanoborohydride in methanol or water in the presence of ammonium chloride or at pH 4. However the formation of the side product 149 could not be eliminated. Structure 149 (Scheme 33) has been tentitatively assigned to this major reduction product (alcohol:lactone, 1:4), based on the lack of OEt group in the ^{1}H NMR spectrum and the IR spectrum which showed no band corresponding to an OH.

Treatment of alcohol 148 with trifluoroacetic anhydride, dimethylaminopyridine, and then 1,5-diazabicyclo[5.4.0]undec-5-ene, achieved partial isomerization of the side chain double bond (back into conjugation as in structure 131b), and the isolation of the trifluoroester of 148. The presence of the trifluoroester was mainly deduced from its IR spectrum. The 3300-3500 cm^{-1} band assigned to an OH group had disappeared and a new band characteristic of $OCOCF_3$ appeared at 1800 cm^{-1}. A signal due to $\underline{H}C(OCOCF_3)$ was observed in the isomerized derivative at 5.06 ppm (s). When a stronger base was used to eliminate $HOCOCF_3$, only hydrolysis of the ester was observed upon work-up (no elimination). Other dehydration procedures performed on alcohol 148 did not lead to a cyclopentadiene derivative.

[i] Ethyl 3-methyl-2,4-pentadienoate 144a has also been used in later alkylation experiments (Michael addition, see Table 7 in experimental for model reactions which will not be discussed). An isomerization of the side chain double bond was also observed. The chemical shift of the vinyl methyl and olefinic proton are different for 144a (2.18 ppm, CH_3, s for E isomer; 5.71 ppm, 1H, bs) and for the product (1.71 ppm, CH_3, bs; 5.06 ppm, 1H, t, J = 7 Hz).

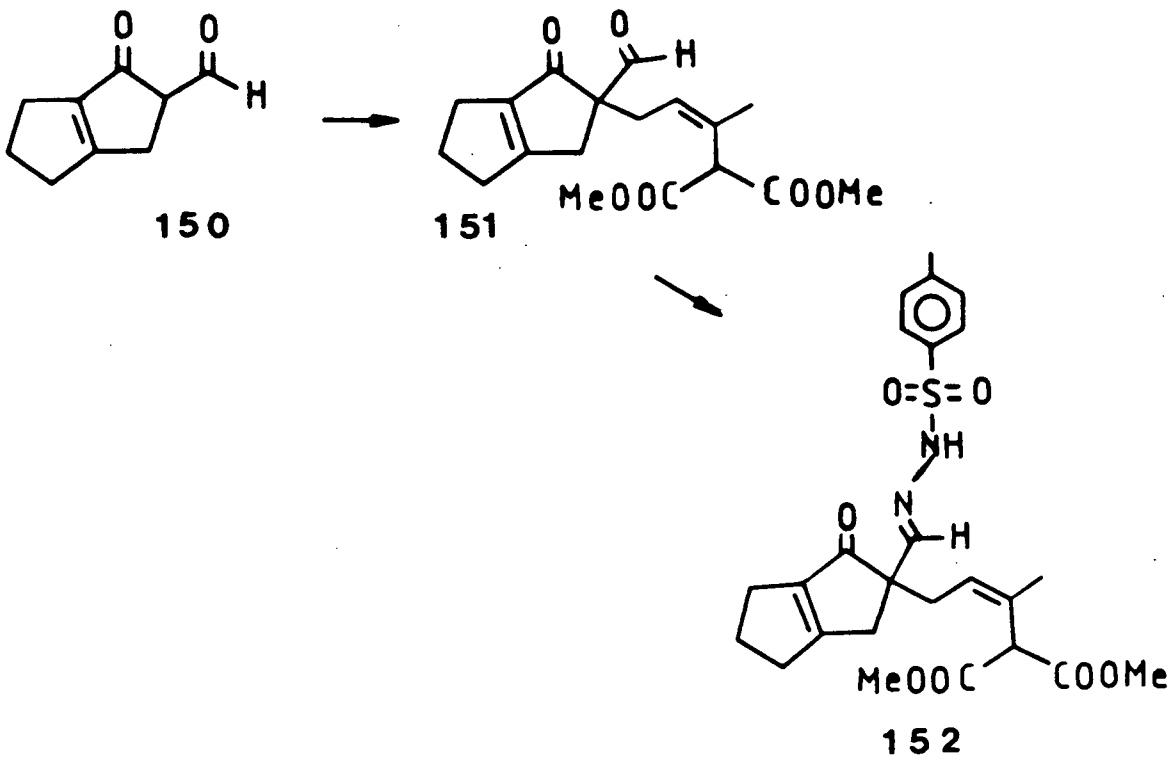
Approach Using 138 and Ethyl Chloroformate

Due to the complications encountered with the first activating group (COCOOEt), another known activating group (CHO) was chosen. Reaction of ethyl chloroformate with ketones[114] produces β-keto-aldehydes. It was anticipated that oxidation of the unsaturated β-keto-aldehyde 150 (Scheme 34) and esterification of the resulting carboxylic acid would give a stable β-keto-ester. In practice, the acylation of the cyclopentenones took place (45 and 60% yield, reaction of 142 and 138), but the aldehyde could not be converted into a β-keto-ester[i]. Therefore, the alkylation of 150 with 131b was performed as described in the previous section (58%) and the tosylhydrazone derivative 152 of the aldehyde was prepared. Simultaneous reduction of the carbonyl and hydrazone leading to an unsaturated alcohol and methyl group was expected[115]. Sodium borohydride and catecholborane reductions were tried at several temperatures. The alcohol was obtained, but the tosylhydrazone did not afford a methyl group. These observations are based on the ^{1}H NMR and IR spectral data. No methyl derivative was isolated. Reduction of the β-keto-aldehyde to a diol, tosylation of the primary alcohol and subsequent reduction to a methyl group also did not give encouraging results.

[i] Oxidations tried: Jones reagent; manganese dioxide, sodium cyanide, acetic acid; silver oxide, THF, water.

Scheme 34

Reactions performed on 150



The Use of Diethyl Pyrocarbonate (DEPC)[116]:

At this point of our investigations, it seemed desirable to construct unsaturated β-keto-esters 159 and 160 (Table 6) directly from the requisite unsaturated ketone.

As indicated in Table 5 several reagents have been employed in the literature to encourage C acylation of various cyclic ketones but many of these require additional steps after the base catalyzed condensation. Acid chlorides display a tendency to yield enol derivatives although this may be suppressed by employing a 2-3 fold excess of ketone[117], an impractical solution in the middle of a total synthesis.

Table 5

Acylation Reagents

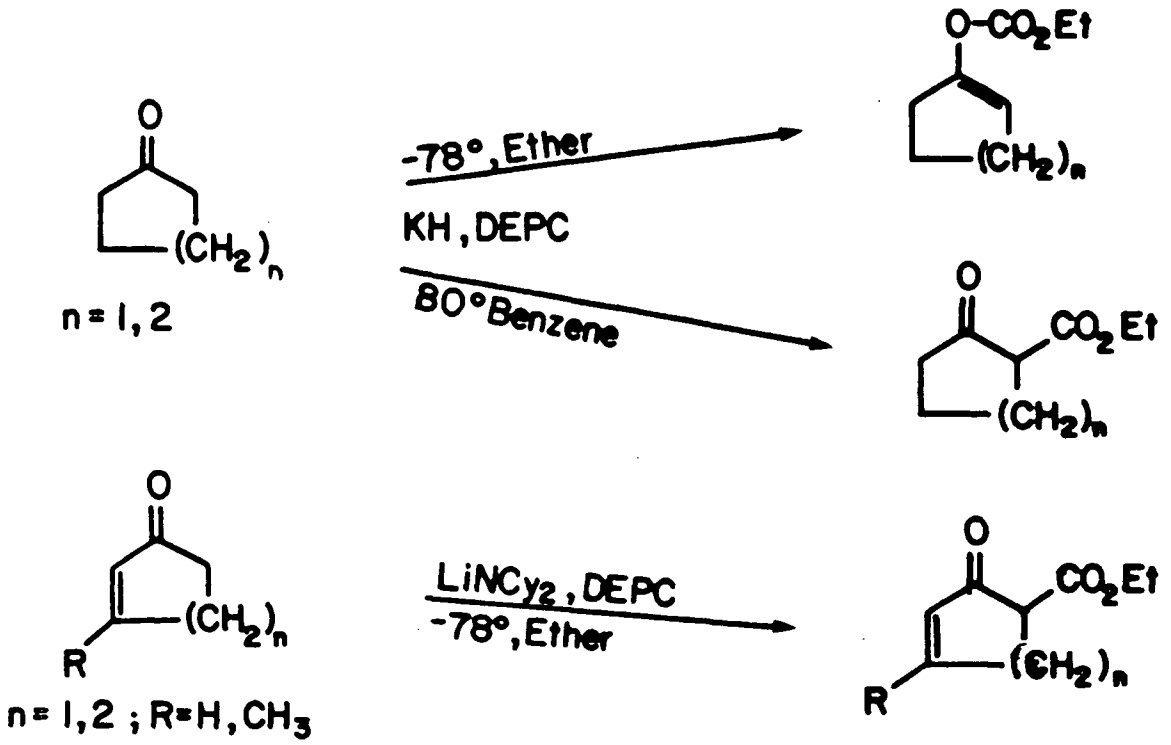
	RCOOET	Reaction conditions	Base	Yield	Reference
1	R=H	Ether, 0-22°C	NaOEt	70-80%	114
2	R=Cl	DME, 23°C	Ph_3K	29% (enol)	118
3	R=OEt	Benzene, 80°C	NaH	92%	119-122
4	R=COOEt	EtOH, 10°C	NaOEt	65%	123
5	$R=PO(OEt)_2$	n-Bu_2O, 30-60°C	NaH	80%	124
6	$Mg(OCOOMe)_2$	Me_2NCHO, 130°C	Mg	45%	125

In unsymmetrical ketones an additional complication often arises due to the generation of both kinetic and thermodynamic enolate anions which may react at different rates and afford complex product mixtures. α, β-Unsaturated ketones are particularly challenging since double bond migration may also occur[126]. Selective introduction of a carboethoxy group at the α' position usually requires a strong nonnucleophilic base, an aprotic solvent,

and a reactive acylation reagent in order that the reaction may be conducted at low temperature. Our investigations revealed that diethyl pyrocarbonate (DEPC) fulfills these requirements providing a convenient route to both saturated and unsaturated β-keto-esters as illustrated in the general scheme below.

Scheme 35

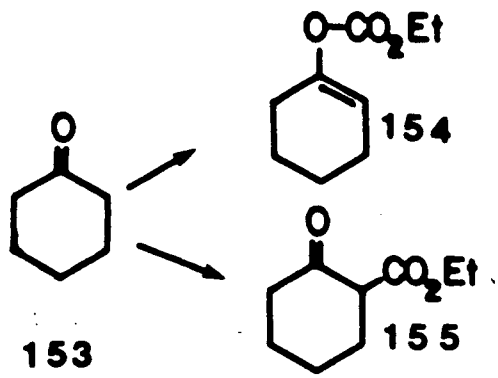
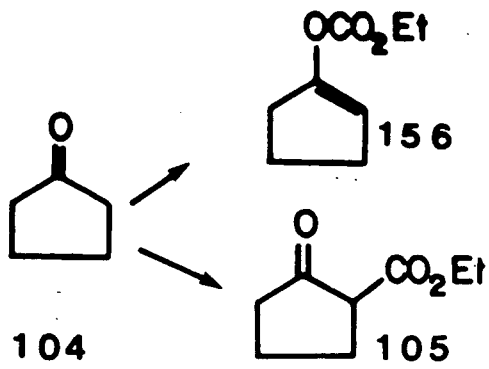
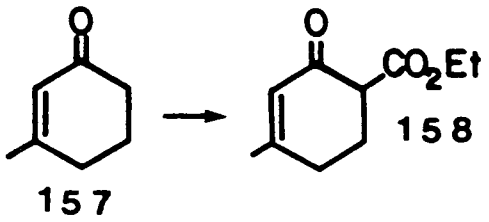
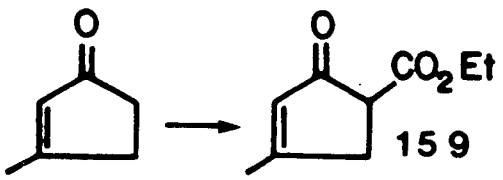
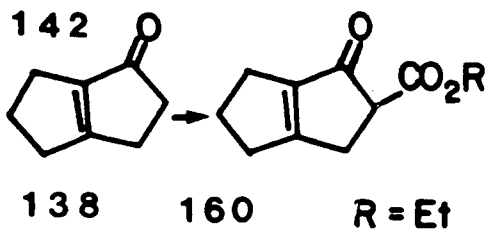
The Use of DEPC



The results of this study are summarized in Table 6. For the saturated cyclic ketones 153 and 104 the reaction was controlled by varying the conditions to give either the O acylation (-78°C, diethyl ether) or C acylation (80°C, benzene) products 154 and 156 or 155 and 105 as desired (entries a-h). Of the bases examined lithium dicyclohexylamide ($LiNCy_2$) with diethyl ether as the solvent was preferred, particularly for the unsaturated ketones in which self condensation could be a problem. The nucleophilic attack of the base on DEPC was minimized by adding a mixture of DEPC and the ketone to the base and conducting the acylation at -78°C. The conditions

Table 6

Preparation of Cyclic β-Keto-Esters

Product	Entry	Base	Procedure (see experimental)	Yield
	a	KH	A	98%
	b	KOtBu	A	50%
	c	$LiNCy_2$	A	47%
	d	KH	B	72%
	e	KOtBu	A	52%
	f	KOtBu	B	62%
	g	$LiNCy_2$	B	60%
	h	KH	B	61%
	i	KOtBu	A	0% (50%)
	j	$LiNCy_2$	A	58%(25%)
	k	$LiNCy_2$	B	64%(14%)
	l	LDA		60%
	m	$LiNCy_2$	A	64%(15%)
	n	$LiNCy_2$	B	71%(8%)
	o	LDA		35%
	p	$LiNCy_2$	A	37%
	q	$LiNCy_2$	B	78%(15%)
	r	$LiNCy_2$	B	46%(22%)

employed were mild and were especially useful with sensitive compounds. Isolated yields are indicated followed by the amount of recovered starting material in parentheses. The procedures (A or B) used are described in detail in the experimental section.

Diethyl pyrocarbonate has been used previously for N acylation in enzyme studies[127,128] and its reactivity with nitrogen, oxygen, and sulphur nucleophiles compared[129] but its use for carbon acylations appears not to have been examined. Recently dimethyl pyrocarbonate became commercially available[130] and as anticipated, (entry r) it behaved in analogous fashion although the yields were lower. These reagents are useful additions to the arsenal of the synthetic organic chemist for the preparation of β-keto-esters under mild reaction conditions.

A paper dealing[131] with an alternative procedure for the introduction of an activating group (using methyl cyanoformate) at the α' position of an unsaturated ketone appeared after the work described above was completed.

Approach using DEPC:

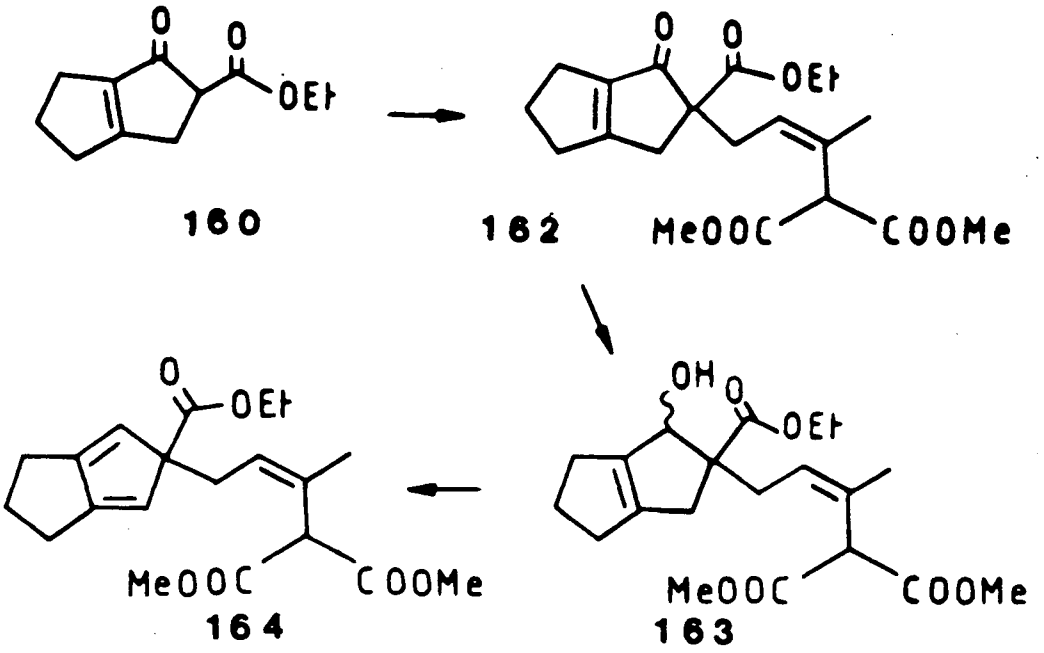
Our next approach started with unsaturated keto-ester 160 (Scheme 36) prepared by the method described in the previous section. Then, an alkylation was performed between bicyclic molecule 160 and chloro ester 131b (76%, Scheme 36, as described for the alkylation of 150).

Next, reduction of the ketone in 162 was considered. The reduction was accomplished most effectively using sodium borohydride and cerous chloride[132]. The addition of cerous chloride minimizes 1,4-proton addition which is often observed with cyclopentenones, including this case. Gemal and Luche have shown that the presence of lanthanoid chlorides with the sodium borohydride in methanol, facilitates a complexation of the solvent by Ln^{+3}. This combination increases the acidity of the medium. The reducing species in this case is not

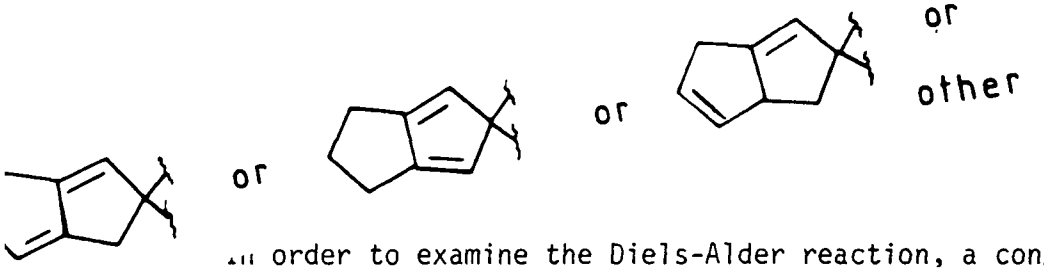
BH_4^- but the derived alkoxyborohydrides $NaBH_{4-n}(OR)_n$. These species are more reactive than BH_4^-, consistent with the enhancement of the reaction rate. Also, the substitution of hydrides in BH_4^- by alkoxy groups increases the hardness of the reagent (hard and soft acid-base theory)[132], this explains the higher selectivity (1,2-reduction) observed with this system. The attack of the cyclopentenones (and conjugate enones in general) is enhanced at the hard site, which is the carbonyl.

Scheme 36

Some reactions performed on 160

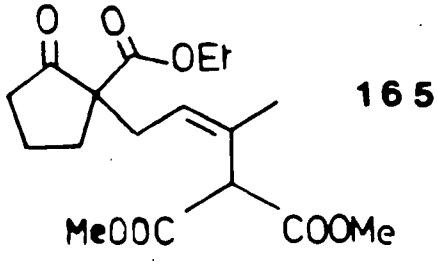


The dehydration step was performed using several procedures ($MsCl.SO_2$, DMAP, pyridine in CH_2Cl_2, 1 h, 20°C[133], 70%; or $CHCl_3$, HCl (g), 2 h, 20°C[134], 60%). These different procedures gave different dehydration products (shown below), as deduced from 'H NMR spectral analysis of 164. The product obtained from the second dehydration (HCl) displayed three signals in the olefinic region at δ = 5.21 (m), 5.77 (bs), 6.22 ppm (bs), present in a 11:4:2 ratio, integrating for three protons. The product of the methanesulfonyl chloride dehydration displayed olefinic signals at δ = 5.36 (bm) and 5.77 ppm (bs), 4:1, integrating for three protons. The Burgess reagent[135] could also be used (30%). All these 'H NMR spectra also displayed a one proton singlet at ~4.00 ppm, characteristic of $(MeOOC)_2\underline{CH}$, which indicates that the double bond of the side chain is [illegible] conjugation.



In order to examine the Diels-Alder reaction, a conjugated double bond is required in the side chain, as well as a diene in ring B of 164 (Scheme 36). Although it had previously been possible to isomerize the side chain double bond (of the trifluoro ester of 148) with base, reaction of 162, 163 or 164 with pyridine or other bases, higher temperatures, longer reaction times did not give the required product. For example, on one occasion, (DBU, THF reflux, 18 h, 80%) three double bond isomers of 162 were obtained in a 3:2:5 ratio. The presence of three olefinic signals (m) was observed in the 'H NMR spectrum at 4.52, 5.00 and 5.52 ppm. Also, three possible methyl signals (bs) appeared at 1.65, 1.87 and 2.06 ppm. Earlier in our synthetic studies, the isomerization of 165 did not take place under acidic conditions

(using $(COOH)_2$, pTsOH or CH_3COOH in refluxing ethanol). Therefore, the Diels-Alder reaction (on a mixture of 164 isomers) was tried, while hoping for a favorable thermal isomerization to take place[136]. The Diels-Alder was also tried using a Lewis acid ($BF_3.Et_2O$) or a catalytic amount of base at various temperatures, but mainly decomposition was observed. In one case, where N,N,N',N'-tetramethylethylenediamine was used as a catalyst, a decarboxylation (-COOMe from 164,Scheme 36 sealed tube reaction, in toluene 110° to 190°, 4 days, 25%) was observed, according to MS and 'H NMR spectral analysis.



165

A recent paper[137] which appeared after these attempts were undertaken, uses polyphosphoric acid (1 eq) in refluxing dichloromethane, containing silica gel, for 24 h to convert 166 to 167 (Scheme 37). These unusual conditions reveal the difficulty in accomplishing such a transformation (isomerization into conjugation), even in a "simple" system such as 166.

Scheme 37

Isomerization of 166

166 167

Successful Diels-Alder approach

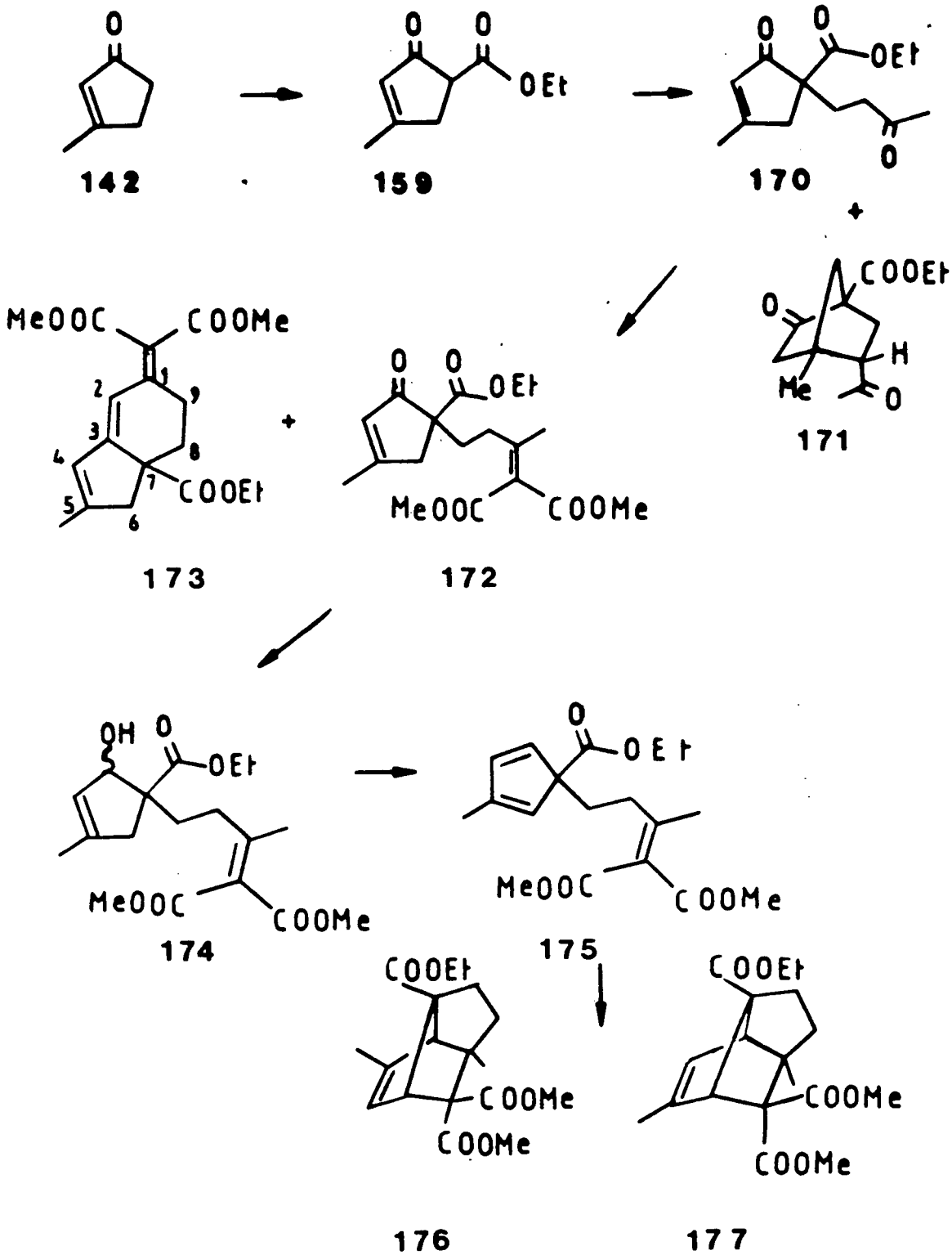
In the next few pages, the model study performed on compound 142 will be discussed first, then the work performed on bicyclooctenone 138.

The new route (Scheme 38) starts with the alkylation of β-keto-ester 159 with methyl vinyl ketone. This Michael addition had to be performed under "very controlled" catalytic conditions. If the amount of base was not kept to a minimum, and/or the reaction time was too long, side product 171 was obtained in varying amounts. Bicyclo[2.2.1]heptan-2-one (171) results from a base catalyzed 1,4-intramolecular-addition between the enolized methyl ketone and the unsaturated ketone of 170 (Scheme 39).

Structure 171 was deduced from 400 MHz 'H NMR, IR and MS spectra. Although some impurity or decomposition was present (Figure 34, signals at δ = 5.92 (bs) and 6.12 (bs) ppm), the two singlets appearing at 1.45 ($-C-CH_3$) and 2.22 ($COCH_3$) ppm in the 'H NMR spectrum, could definitely be assigned to methyl groups. The signals at 4.22 ppm (q, J = 7 Hz, OCH_2) and 1.30 ppm (t, J = 7 Hz, CH_3) are easily assigned to the ethyl ester. Another set of signals integrating for one proton appeared at 3.02 ppm (ddd, J = 2,6, 12 Hz). Because the coupling constants (vicinal and long-range) in norbornane systems have been well studied[41], interpretation of this coupling was possible.

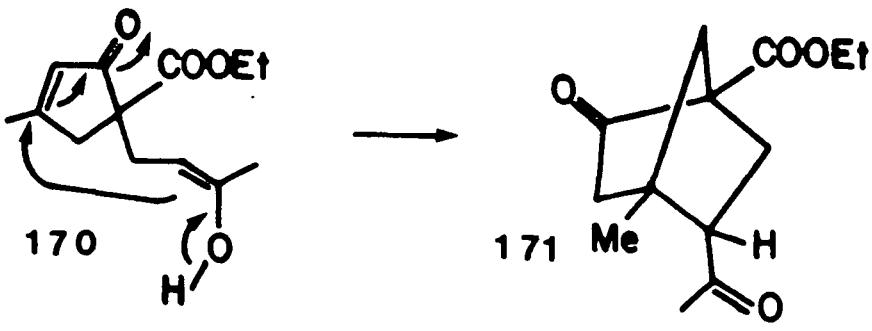
Scheme 38

Diels-Alder Approach to 176, 177

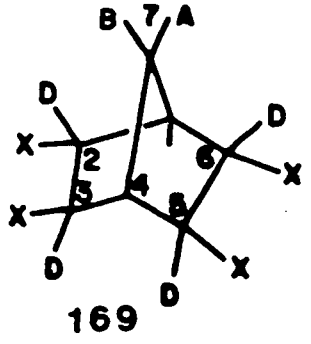


Scheme 39

Formation of Side Product 171



It is known that in molecules such as 169, the coupling constants are as follows: J_{2D-3D} = 6-7 Hz; J_{2X-3X} = 9-10 Hz; $J_{2X\leftrightarrow 3D}$ = 2.5 Hz; J_{1-2X} = 3-4 Hz; J_{1-2D} = 0-2 Hz; J_{3X-5X} = 1-2 Hz; J_{5D-7B} = 1.5-5 Hz. Therefore, the 2 Hz coupling in 171 was due to a W long-range coupling (H-5, H-7), the 6 Hz coupling to an endo-exo coupling (H-5, H-6), and the 12 Hz coupling to an exo-exo coupling (H-5, H-6). Interpretation of this coupling allows us to place proton 5 in the exo position as shown for 171 in Scheme 39; and the methyl ketone substituent in the endo position. The IR of 171 indicated that a strained ketone (CO band at 1765 cm^{-1}) was present in addition to other carbonyls (broad CO band at 1715 cm^{-1}, $COCH_3$ and COOEt). The MS displayed a molecular ion at m/z = 238 ($C_{13}H_{18}O_4$).

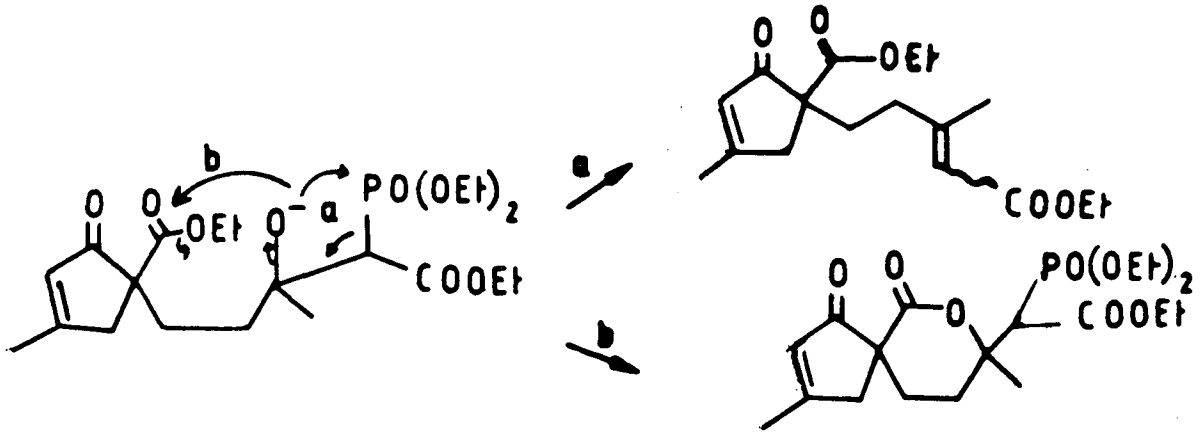


D = Endo
X = Exo

The desired product 170 of the Michael addition was easily identified from the 'H NMR, IR and MS. In the next step of the synthesis, the methyl ketone in 170 was reacted selectively. Although the dithioketal of the methyl ketone was selectively formed ($BF_3.Et_2O$, 20°, 1 h, 70%) when the reaction was performed in acetic acid[138], the deprotection could not be accomplished[i] on this derivative, the corresponding alcohol, or diol. A Horner-Emmonds[139] reaction of 170 proceeded selectively in very low yield (10%). The 'H NMR spectrum of the major product indicated the presence of three ethoxy groups and a methine proton (2.82 ppm, d, J = 20 Hz) coupled to phosphorus. Probably an internal reaction, giving a 6-membered-ring lactone predominated over the usual rearrangement of the phosphonate. Also, a Wittig reaction of 170 was not selective (30% of the direacted product, according to MS and 'H NMR analysis).

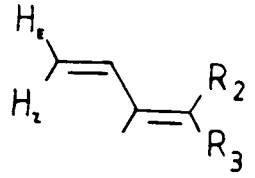
Scheme 40

Possible Rearrangement Reaction



A Knoevenagel reaction[92] using titanium tetrachloride and dimethyl malonate ($CH_2(COOMe)_2$ at 20°, 12 h), gave 172. Side product 173 was formed when the reaction time exceeded 12 h. (Scheme 41).

[i] Deprotections tried: mercury(II) chloride, potassium carbonate, 80% acetonitrile, water, reflux; silver nitrate, acetonitrile, water; thallic trifluoroacetate, tetrahydrofuran.



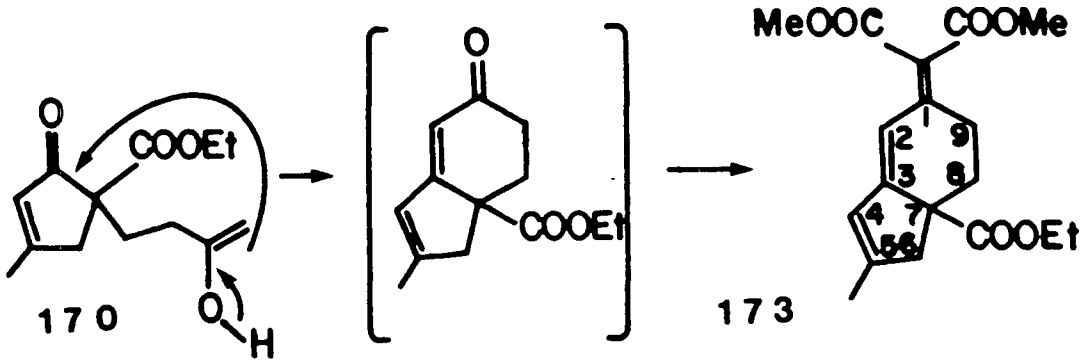
a: $R_2, R_3 = H, COOEt$

b: $R_2, R_3 = COOMe$

Triunsaturated triester 173 (Scheme 41) could result from an acid catalyzed intramolecular addition (taking place between the enolized methyl ketone and the unsaturated carbonyl of 170), followed by a Knoevenagel condensation. Compound 173 was sensitive to silica chromatography, especially PTLC, and decomposed rapidly. The unsaturated ketone precursor would also be expected to be unstable. Product 173 displayed in its ^1H NMR spectrum, two olefinic protons at 6.58 (s) and 6.02 (bs) ppm. These were tentatively assigned to H-2 and H-4, by comparison of the chemical shift values to 144b (H-4, 7.00 ppm; H_E-5, 5.43 ppm; H_Z-5, 5.68 ppm); 144a (R_2 = COOEt; R_3 = H at 5.79 ppm; H-4, 6.70 ppm; $H_{E,Z}$-5, 5.28 ppm) and the literature[41]. Also, the signal at 6.02 ppm appeared as a broad singlet, which is characteristic of long-range coupling between this proton and the vinylic methyl. The vinylic methyl signal appeared at 1.91 (bs) ppm; two singlets at 3.70 and 3.73 ppm were due to the methyl esters; while signals assigned to the ethoxy group appeared at 4.10 (CH_2, q, J = 7 Hz) and 1.21 (CH_3, t, J = 7 Hz) ppm. The parent ion observed in the MS at m/z = 334, confirmed that the molecular formula of 173 was $C_{18}H_{22}O_6$, and differed from 172 by the loss of H_2O.

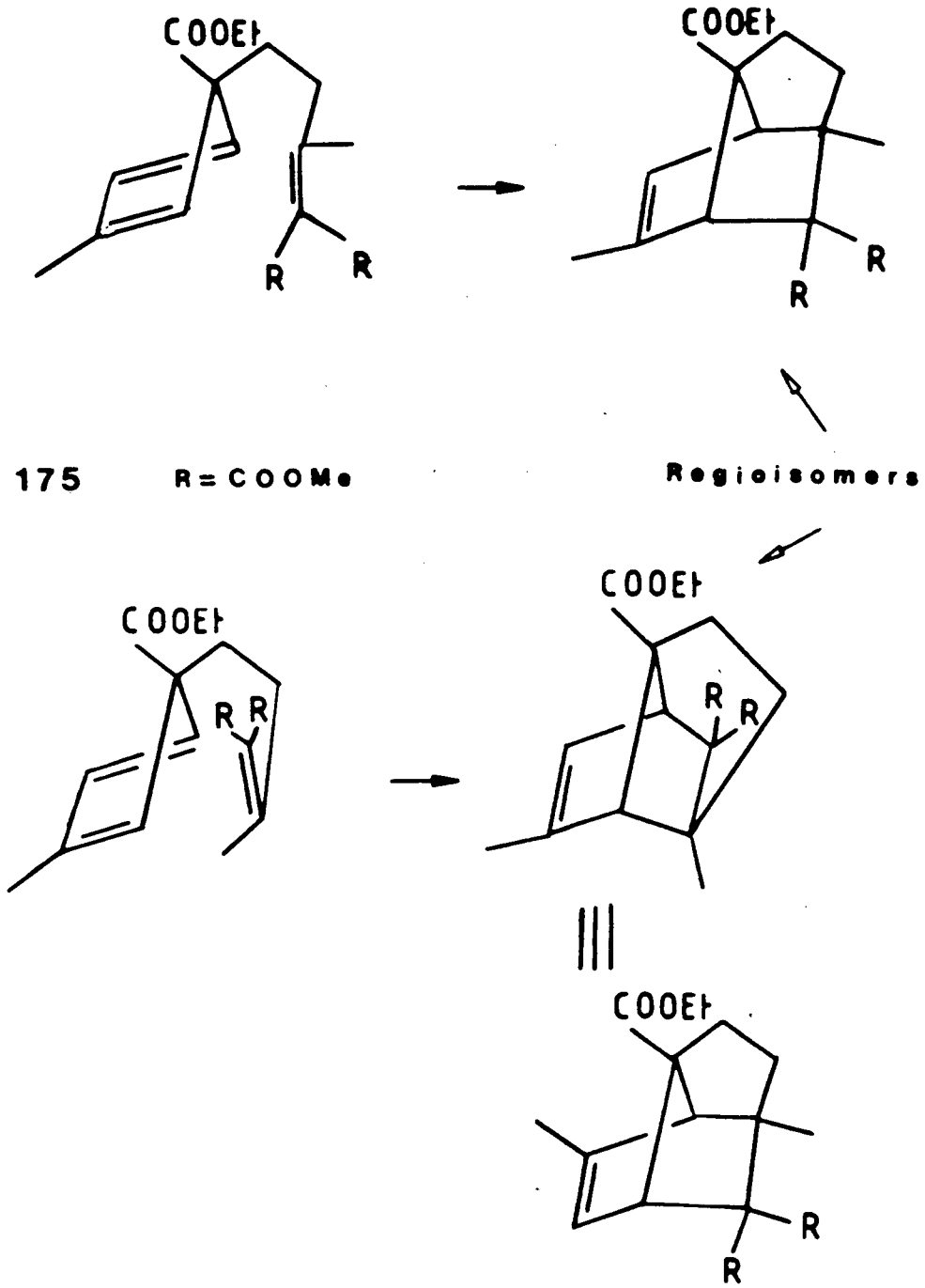
Scheme 41

Formation of Side Product 173



Scheme 42

Diels-Alder Reaction of 175

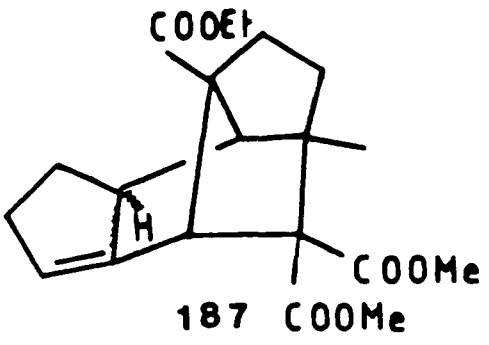


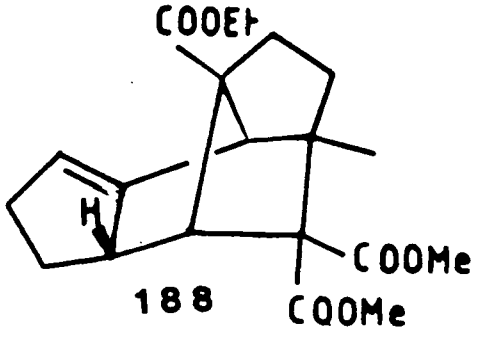
The product 172 from the Knoevenagel condensation was characterized through its ^{1}H NMR, MS and IR spectral data. Compound 172 was then reduced using zinc borohydride[140]. This reduction procedure resulted in better yields when the reaction was performed on a large scale. After dehydration of 174 (MsCl.SO_2 or MsCl, no SO_2) the Diels-Alder was attempted. A related intermolecular example to our intramolecular Diels-Alder (diactivated diene, cyclopentadiene as dienophile) has been described by Levina and Godovikov, in 1955[141]. It takes place between cyclopentadiene and diethyl methylene malonate (CH_2=HC(COOEt)$_2$) in refluxing benzene for 6 h (60%). The Diels-Alder reaction of 175 took place in toluene, at 140° (sealed tube) during 10 h (40%).

As indicated in Scheme 42, two regioisomers can be formed during the Diels-Alder step. The ^{1}H NMR spectrum obtained on the purified reaction product would tend to indicate the presence of two adducts. The signals assigned to the vinyl methyl (2.02 and 2.04 ppm) and olefinic proton are doubled (6.20 and 7.10 ppm) and present in a 5:4 ratio.

The series of reactions described above was next performed on bicyclic β-keto-ester 160 (Scheme 43). The Michael addition performed between 160 and methyl vinyl ketone produced 178, and no side product was detected. Knoevenagel condensation of 178 with dimethyl malonate (20°C, 20 to 24 h) afforded triester 179. In this case, only traces (< 1%) of a side product similar to 173 were obtained on one occasion. Reduction of the ketone in 179 ($Zn(BH_4)_2$) and dehydration of alcohol 180 (MsCl.SO_2 or MsCl, no SO_2) produced diene 181 (more than one double bond isomer, as mentioned earlier for the dehydration of alcohol 163, p. 85). The intramolecular Diels-Alder took place in toluene, at 140°C (sealed tube) during 10 h.

In the present case, the Diels-Alder cyclization can only give one product (two enantiomers, Scheme 44). This is due to the presence of a plane of symmetry in the ring moiety of 181. However, an isomerization of the newly formed double bond in 182 is observed. A 4:1:3 mixture of tri:tri:tetra-substituted double bond is present, according to the 'H NMR spectrum. The major olefinic signal appears at 5.45 ppm (m), and the minor one at 5.76 ppm (m).





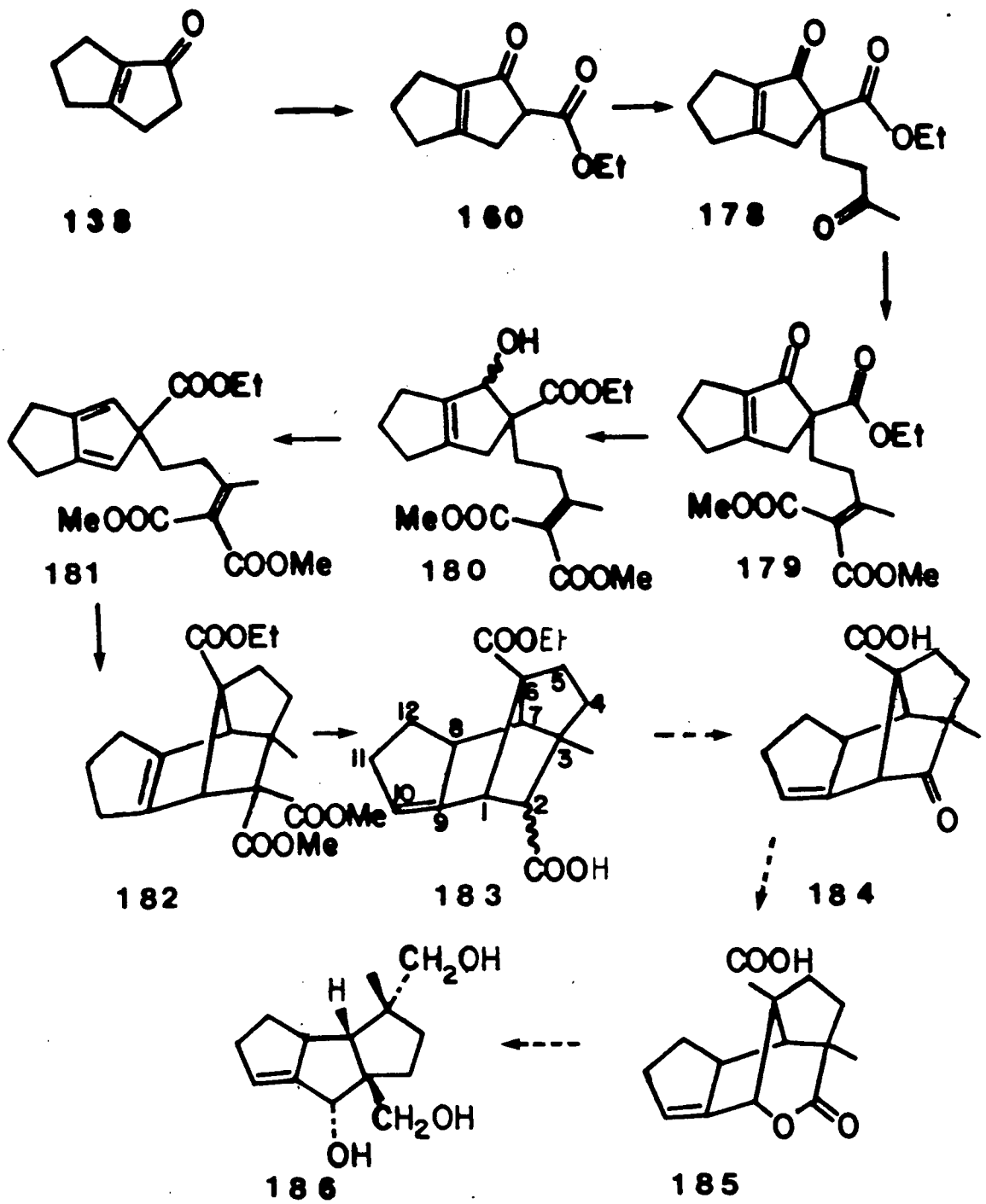
Two structures (187 and 188) can be drawn for the isomerized Diels-Alder adduct. Molecular mechanics calculations performed at the Université de Sherbrooke indicate that structure 187 with the double bond at C-9 and the ring exo is slightly more stable (~ 1.5 kcal) than adduct 182, and that structure 188 is less stable (~ 5.5 kcal) than 182.[i] In order to establish the accuracy of structure 187, an X-ray diffraction analysis is required. Unfortunately none of the derivatives prepared to date[ii] have proved satisfactory for X-ray analysis.

[i] We are grateful to C. Bayly and P. Deslongchamps for the calculations. The two olefinic signals observed in the 'H NMR spectrum could be due to exo 187 and endo 187.

[ii] Derivatives of 183 prepared: dicarboxylic acid, diol, di-p-bromobenzoate, the dianilide derivative.

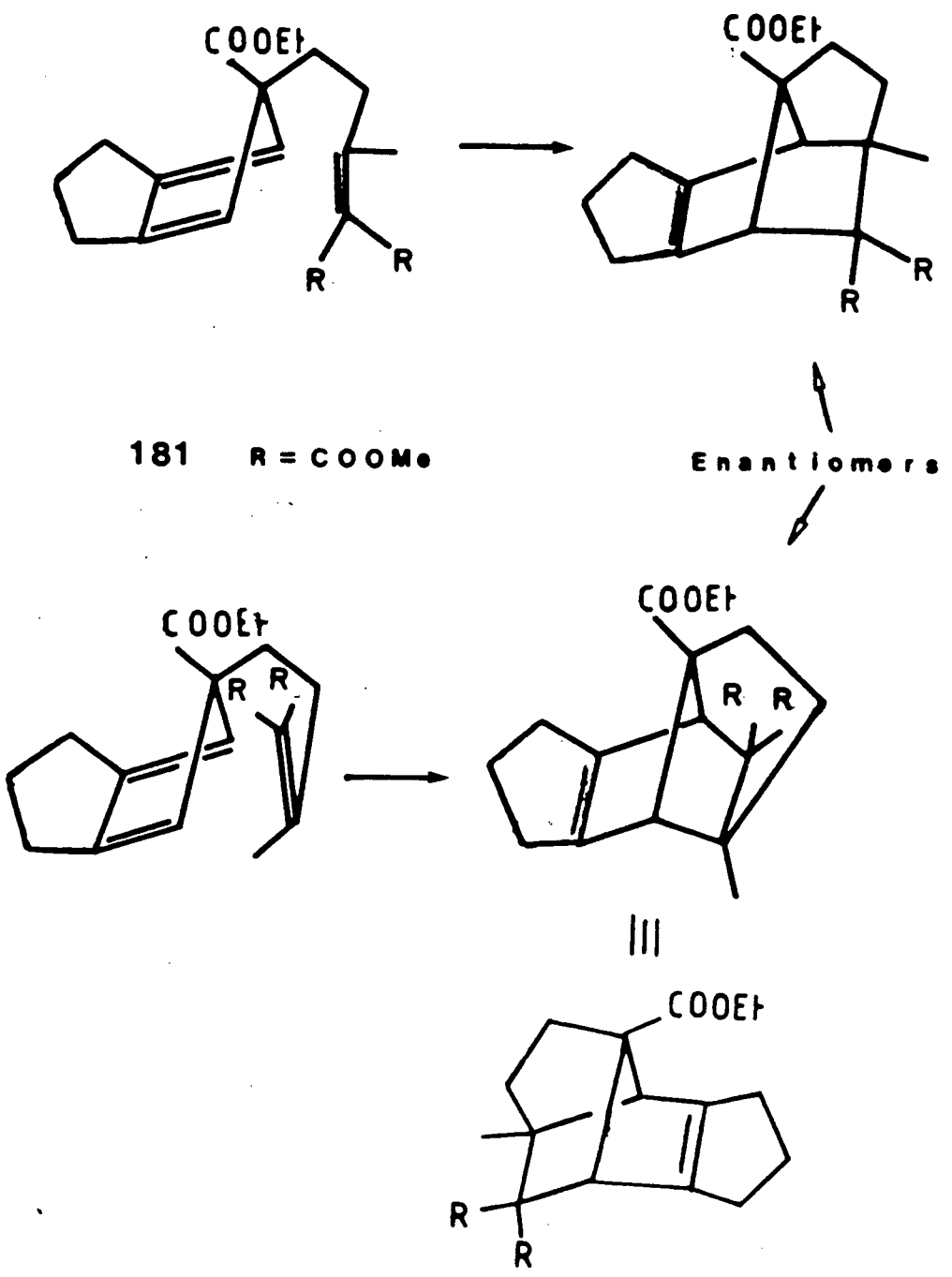
Scheme 43

Diels-Alder Approach to 182



Scheme 44

Diels-Alder Reaction of 181



Several routes can be envisaged to convert the malonic ester functionality in key molecule 182 to the required ketone functionality (as in 184, Scheme 43). A conventional method[142] applied in the 1960's to perform this transformation consists of the following six step procedure: hydrolysis of a malonic ester, decarboxylation of a malonic acid, treatment of the carboxylic acid with methyl lithium, conversion of the methyl ketone to an acetate, hydrolysis of the acetate and finally oxidation of the alcohol. Although this sequence of reactions would convert a malonic acid into a ketone, in our case the ethyl ester and double bond would also be affected.

Another possibility which has been applied in several cases[143], but unfortunately gives rise to different side products in the case of the norbornane system[144], involves the use of lead tetraacetate. This oxidative decarboxylation leads directly from a malonic acid to a ketone. A different approach would consist of the decarboxylation of the malonic ester (NaCN in HMPA[145] or LiCl in H_2O-DMSO[146]), followed by hydrolysis of the methyl ester ($AlCl_3$ in EtSH[147]) and oxidative decarboxylation (see below).

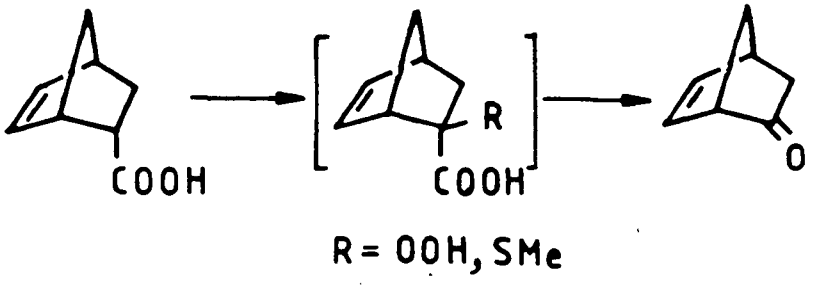
Decarboxylation of the malonic ester using sodium cyanide or lithium chloride was unsuccessful in our case. However treatment of 182 with aluminum trichloride in ethanethiol hydrolyzed the methyl esters in the presence of the ethyl ester, in acceptable yields (> 40%). The 'H NMR of this crude product displayed only one singlet in the olefinic region at 5.85 ppm. The presence of the Lewis acid apparently isomerized the double bond mixture of the Diels-Alder adducts, to the C-9 double bond. Decarboxylation was accomplished by refluxing the malonic acid in toluene for two hours. The 'H NMR spectrum of 183 showed an upfield shift for the methyl singlet, from 1.23 to 1.10 ppm. This result would tend to indicate that the exo carboxylic acid has been eliminated, therefore the effect due

to this substituent has disappeared. Endo substituted norbornanes have been reported to be more stable than the exo isomers[146].

Wasserman and Lipshutz's[148] oxidative decarboxylation (LDA, O_2; DMF-acetal) as well as Trost and Tamaru's[149] procedure (LDA, Me_2S_2; $NaHCO_3$, N-Cl-succinimide) were attempted, however no product 184 could be isolated in either case (reaction in THF and in THF-HMPA). Therefore, model reactions were performed on 4-carboxybicyclo[2.2.1]heptene (Scheme 45). These studies indicated that the carboxylic acid dianion could only be generated at 0° to 20°C, and that the methyl disulfide procedure was more reliable, since the intermediate sulfenylated acid could be isolated and characterized before treatment with N-chlorosuccinimide. These results also showed that a temperature of 20°C was needed for the sulfenylation to take place and that in the presence of an ester, this reaction did not proceed as expected. Since our earlier attempts to sulfenylate 183 showed that the ethyl ester did not survive the reaction conditions, the ester was hydrolyzed. The trianion of this dicarboxylic acid was then generated, however the sulfenylation did not proceed.

Scheme 45

Model Studies of the Oxidative Decarboxylation



Conclusion:

These studies revealed that a Diels-Alder approach to capnellene (51) may be feasible. They have resulted in a useful new acylation procedure for cyclic ketones and enones. In addition, the types of intermediates and reactions which will permit further development of this strategy have been delineated.

It is anticipated that upon generation of ketone 184, the Baeyer-Villiger oxidation (mCPBA) would be directed by the double bond to afford lactone 185 preferentially. Reduction ($LiAlH_4$) of this lactone would give triol 186 with the capnellane carbon skeleton, except for one carbon. This missing carbon represents the exocyclic double bond which could be introduced at an earlier step in the synthesis, possibly by allylic oxidation (SeO_2) followed by Wittig condensation. Other modifications of this route are also possible.

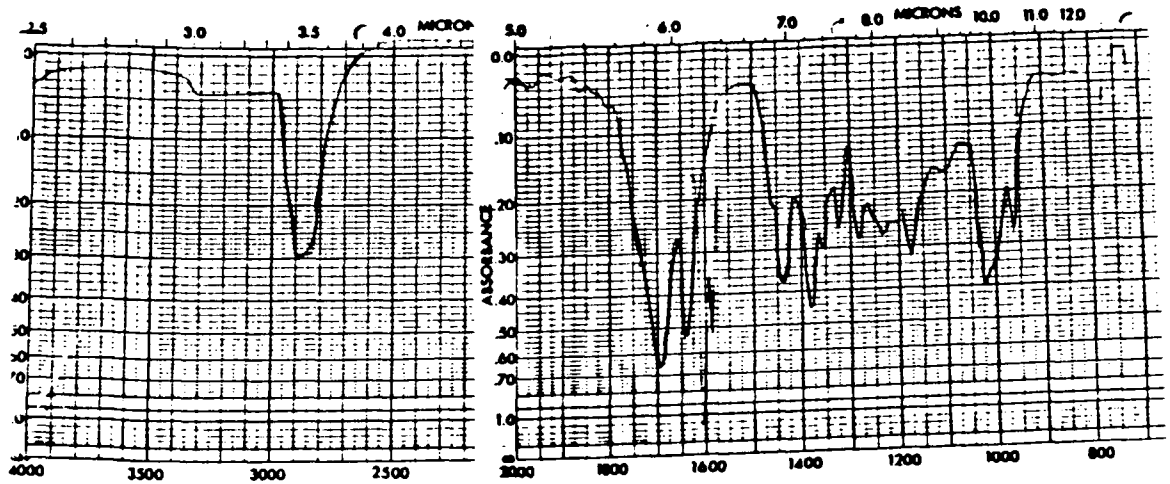


Figure 10

IR Spectrum of $\Delta^{1,5}$-bicyclo[3.3.0]octen-2-one (138, neat)

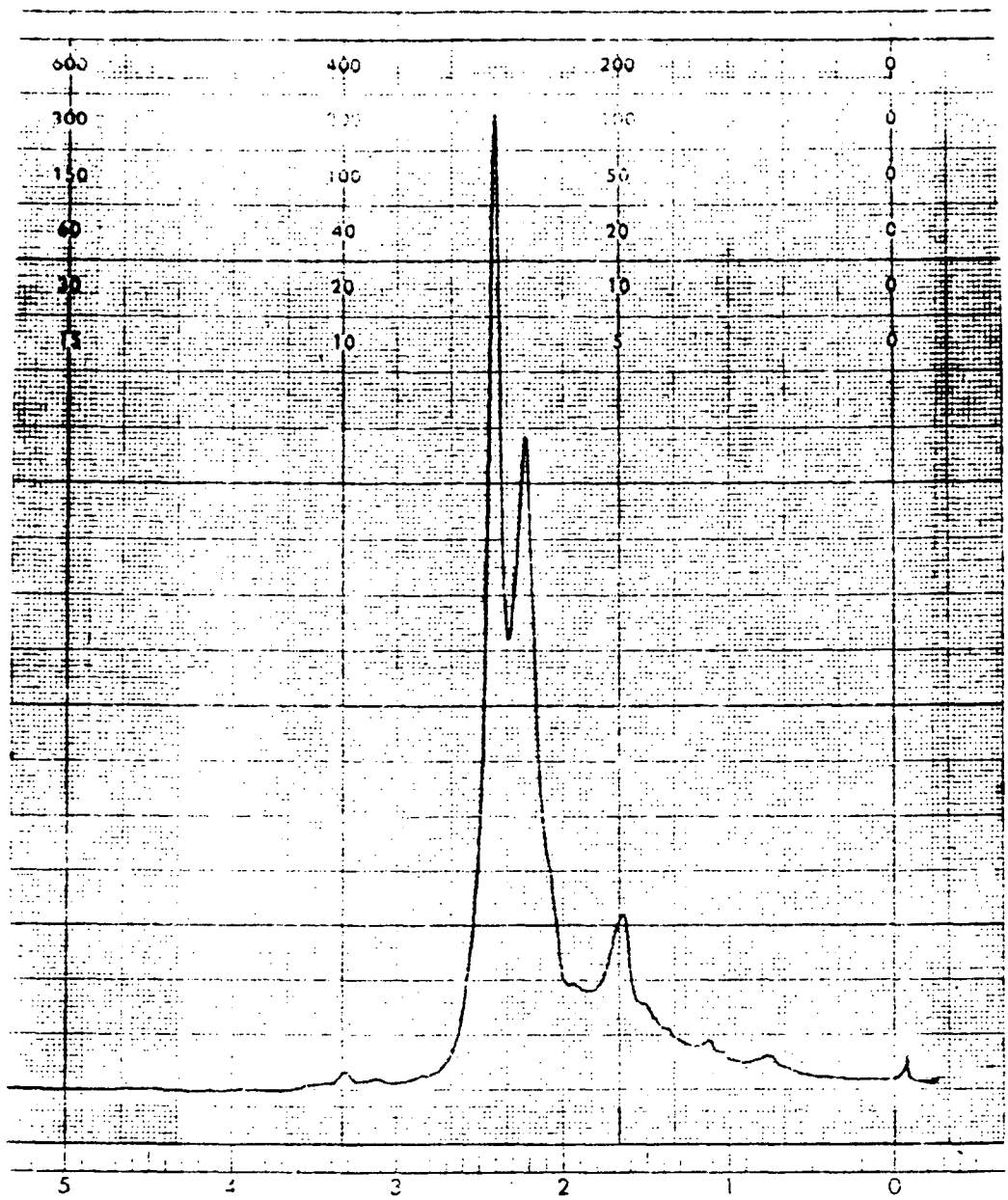


Figure 11

60 MHz ^{1}H NMR Spectrum of $\Delta^{1,5}$-bicyclo[3.3.0]octen-2-one (138, CCl_4)

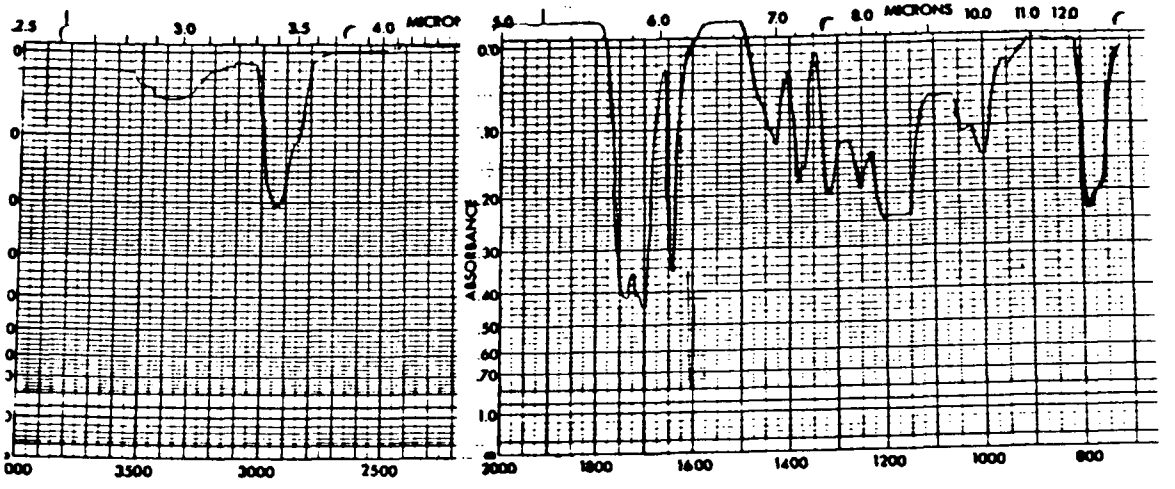


Figure 12

IR Spectrum of $\Delta^{1,5}$3-carboethoxybicyclo[3.3.0]octen-2-one (160, neat)

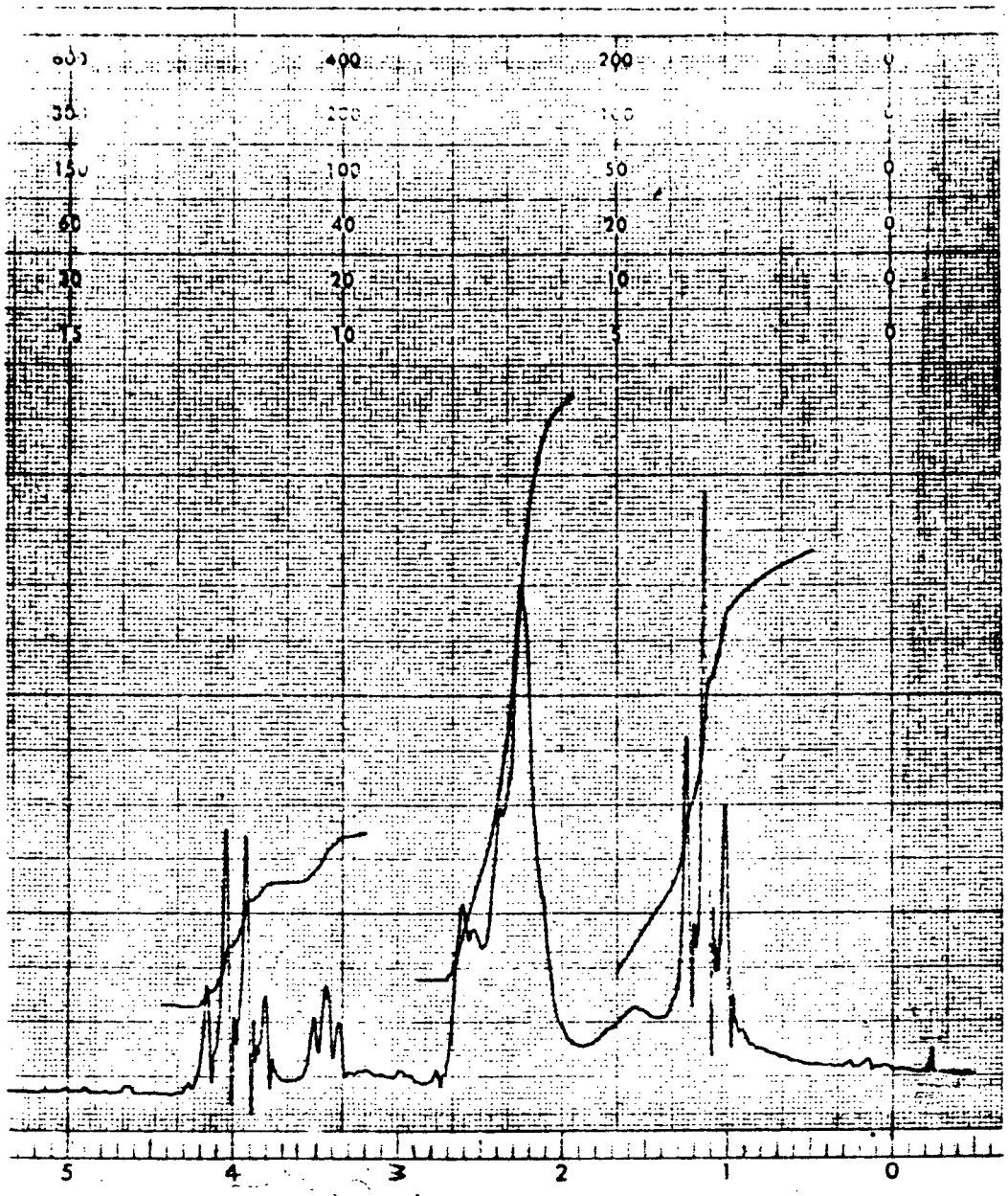


Figure 13

60 MHz ^{1}H NMR Spectrum of $\Delta^{1,5}$3-carboethoxybicyclo[3.3.0]octen-2-one (160, CCl_4)

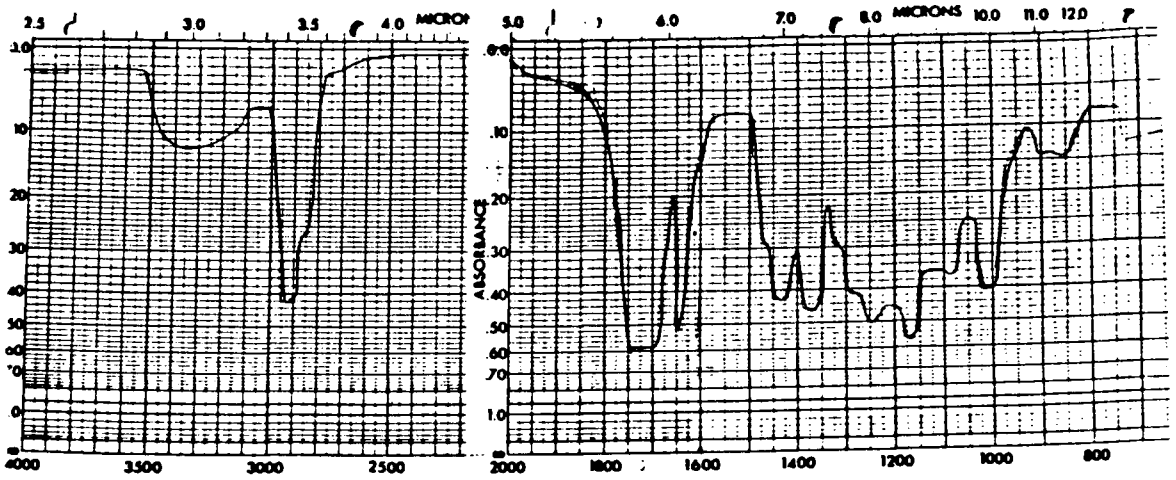


Figure 14

IR Spectrum of $\Delta^{1,5}$-3-(butan-3-one)-3-carboethoxybicyclo[3.3.0]octen-2-one (178, neat)

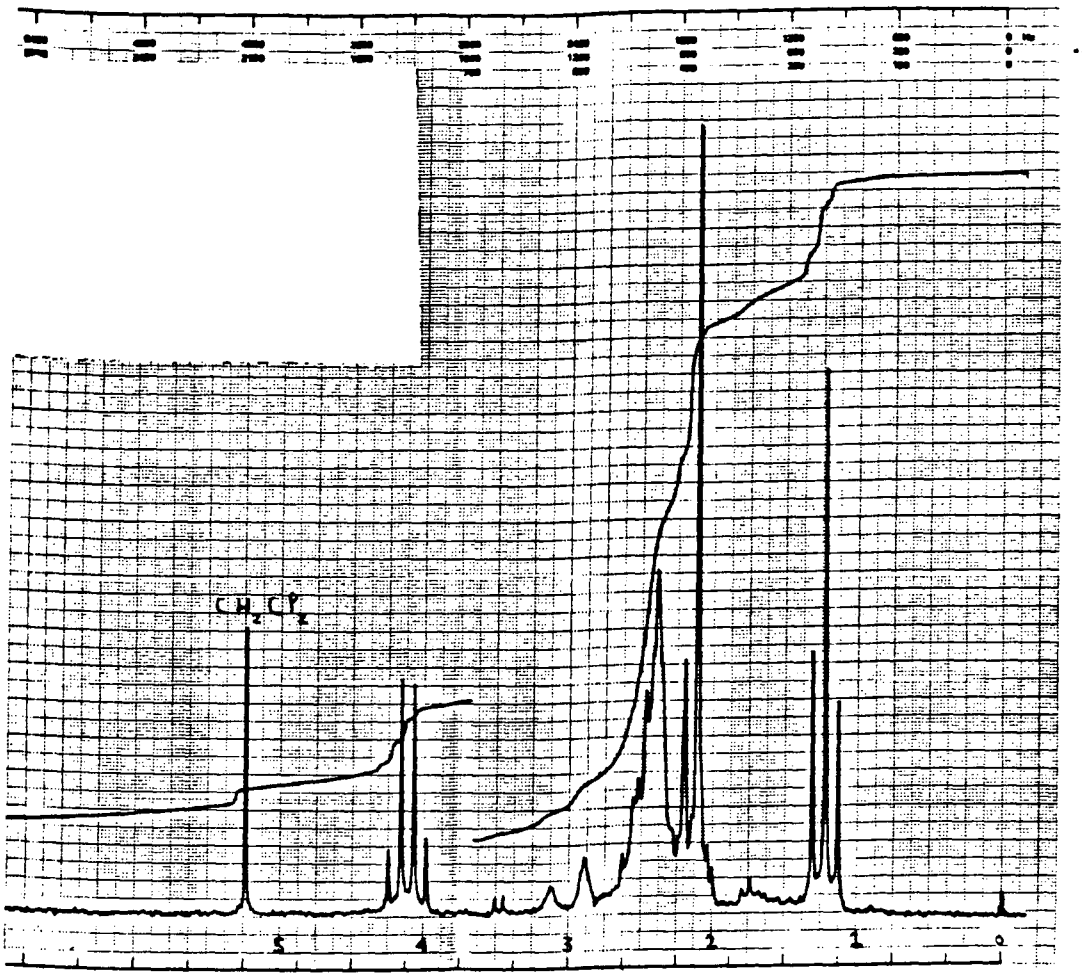


Figure 15

80 MHz ^1H NMR Spectrum of

$\Delta^{1,5}$-3-(butan-3-one)-3-carboethoxybicyclo[3.3.0]octen-2-one (178, $CDCl_3$)

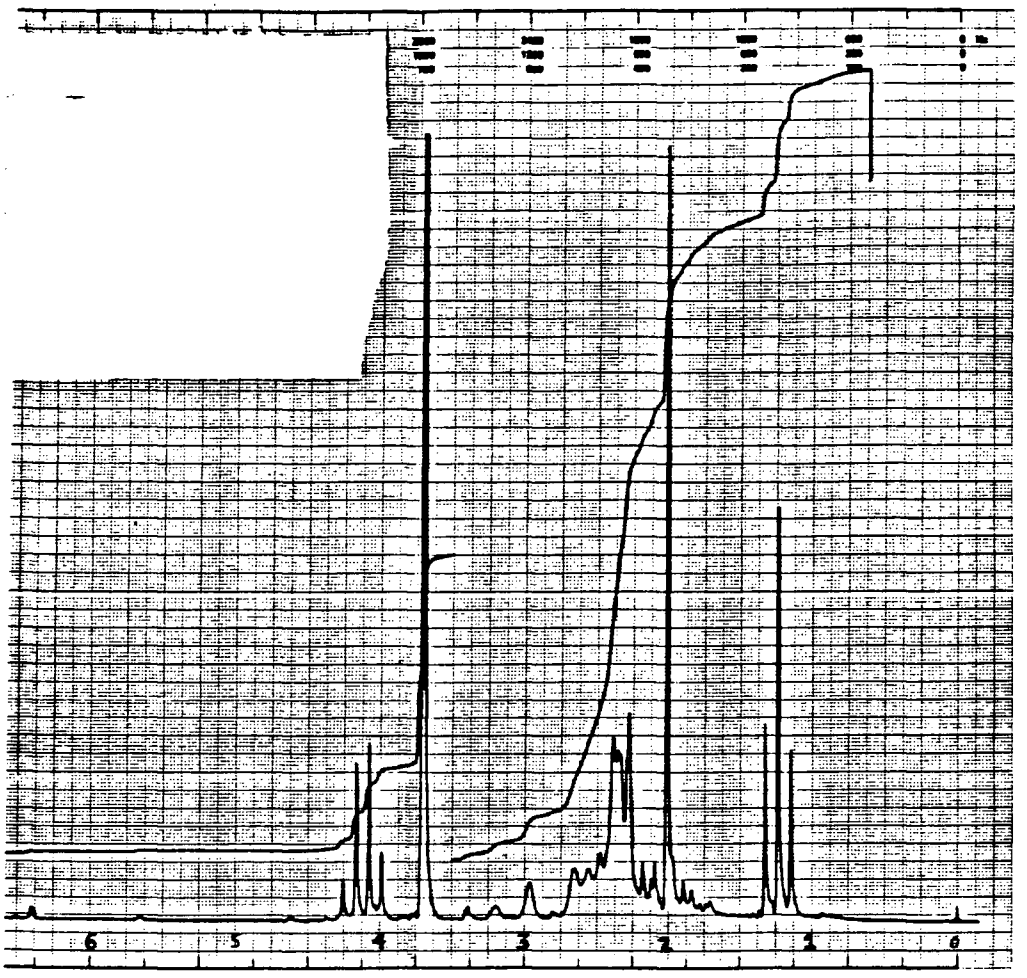


Figure 16

80 MHz ^{1}H NMR Spectrum of $\Delta^{1,5}$-3-carboethoxy-3-(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate)bicyclo[3.3.0]octen-2-one (179, $CDCl_3$)

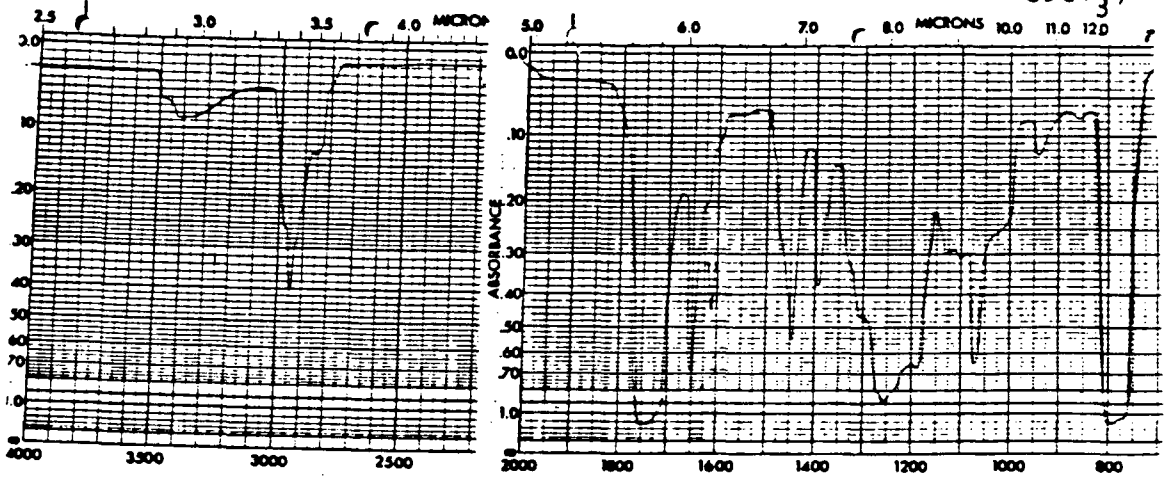


Figure 17

IR Spectrum of $\Delta^{1,5}$-3-carboethoxy-3-(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate)bicyclo[3.3.0]octen-2-one (179, neat)

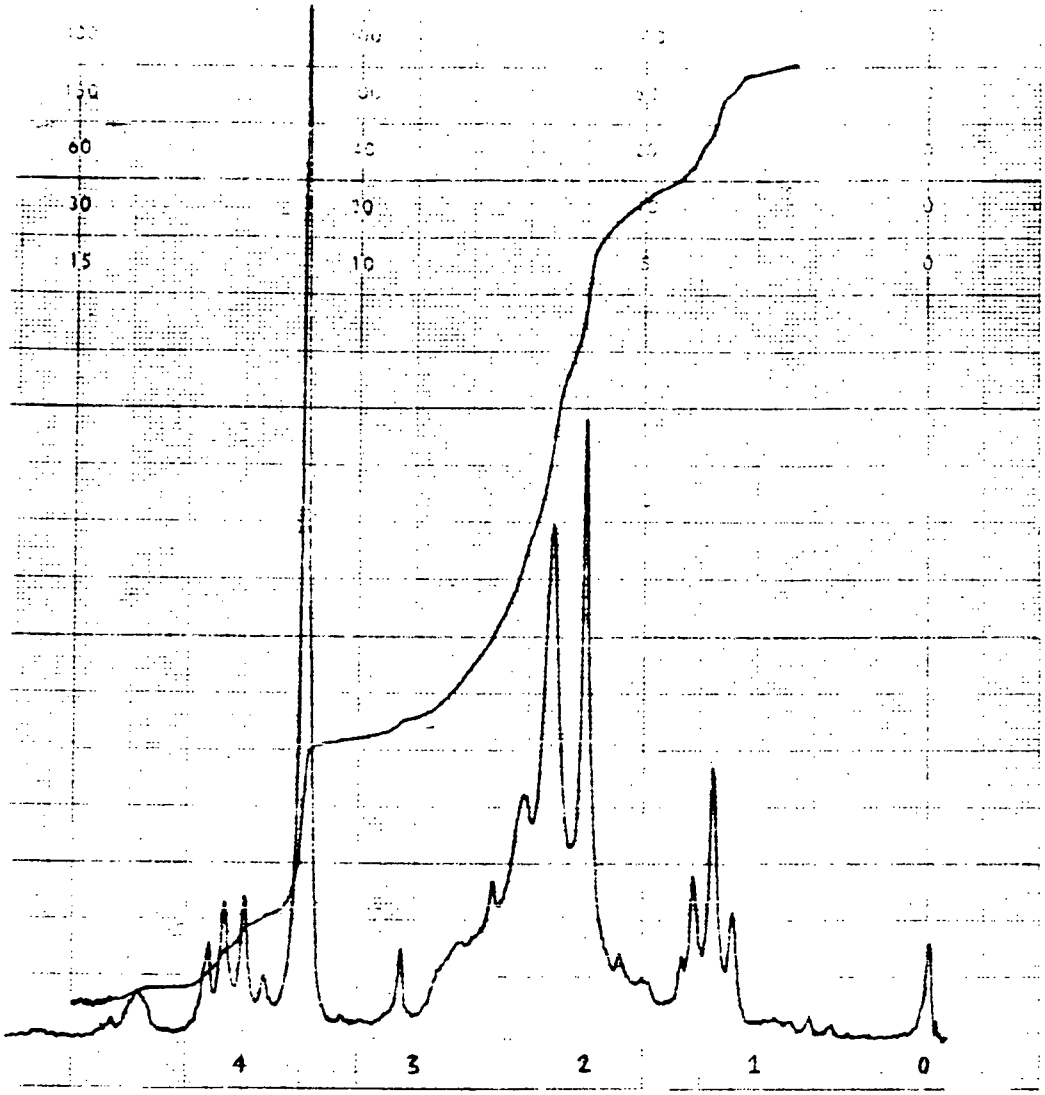


Figure 18

60 MHz ^{1}H NMR Spectrum of $\Delta^{1,5}$-3-carboethoxy-3-(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate)bicyclo[3.3.0]octen-2-ol (180, CCl_4)

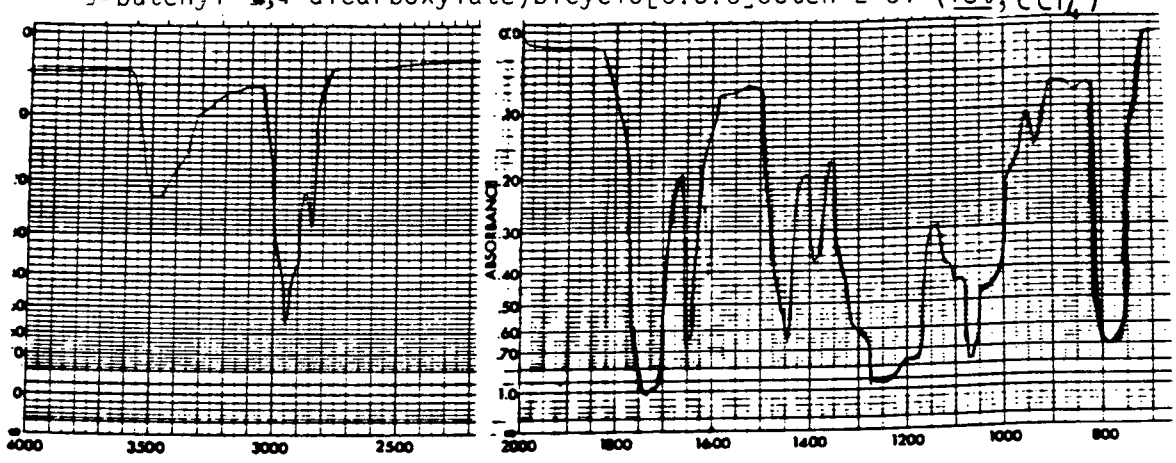


Figure 19

IR Spectrum of $\Delta^{1,5}$-3-carboethoxy-3-(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate)bicyclo[3.3.0]octen-2-ol (180, neat)

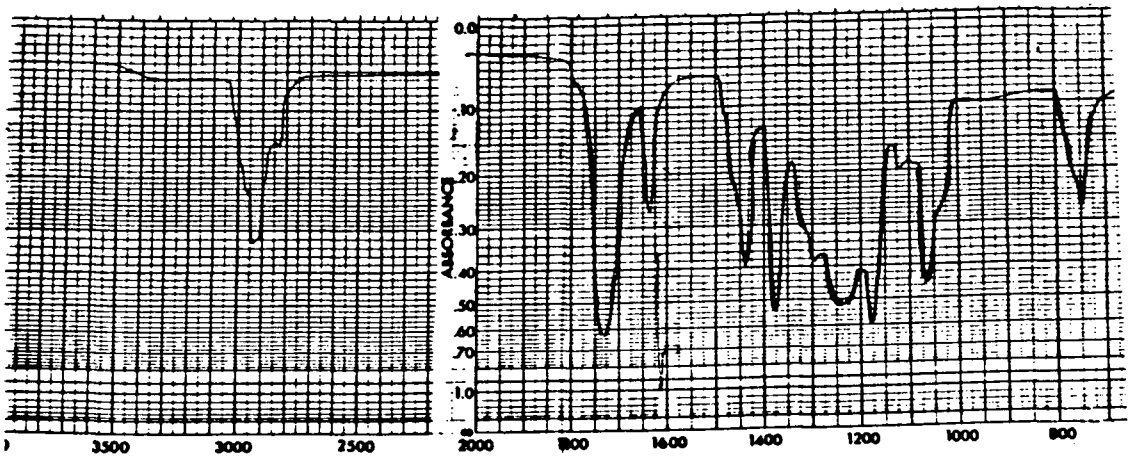


Figure 20

IR Spectrum of 3-carboethoxy-3-(dimethyl 2-methyl-1-butenyl-1, 1-dicarboxylate)bicyclo[3.3.0]octa-1,4-diene (181, neat)

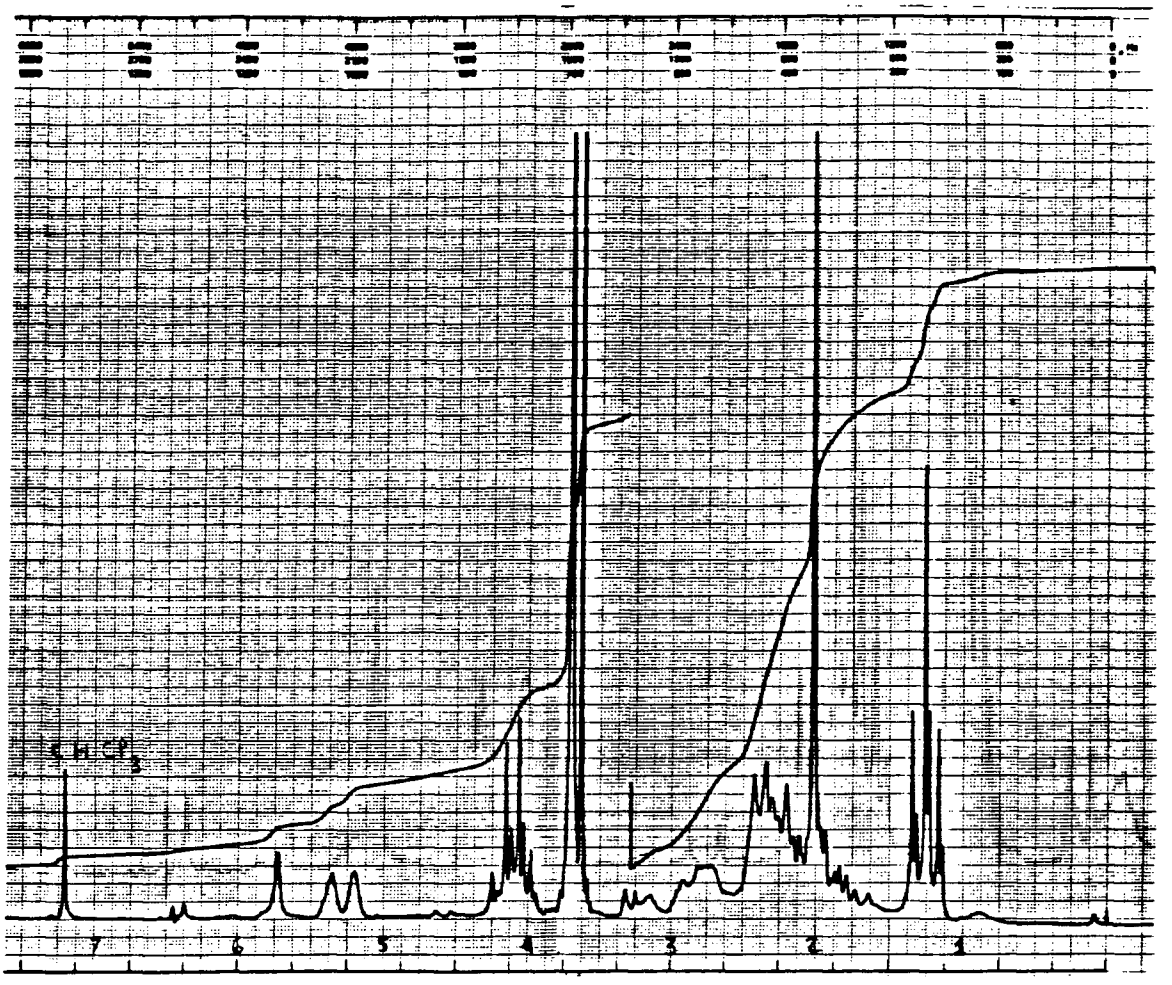


Figure 21

80 MHz ^{1}H NMR Spectrum of 3-carboethoxy-3-(dimethyl-2-methyl-1-butenyl-1,1-dicarboxylate)bicyclo[3.3.0]octa-1,4-diene (181, $CDCl_3$)

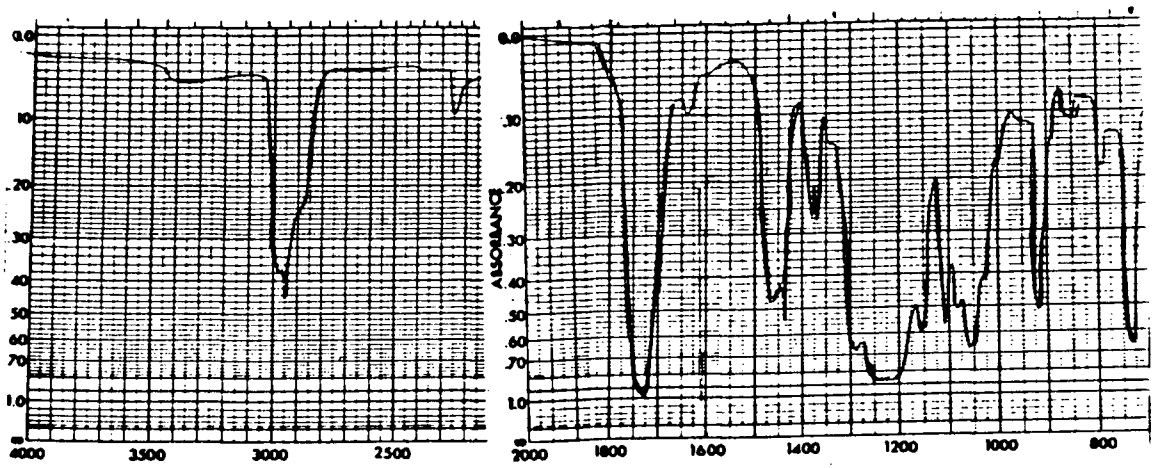


Figure 22

IR Spectrum of $\Delta^{8,12}$-6-carboethoxy-2-dicarbomethoxy-3-methyl-tetracyclo[6.4.$0^{1,6}$.$0^{3,7}$.$0^{8,12}$]-dodecene (182, neat)

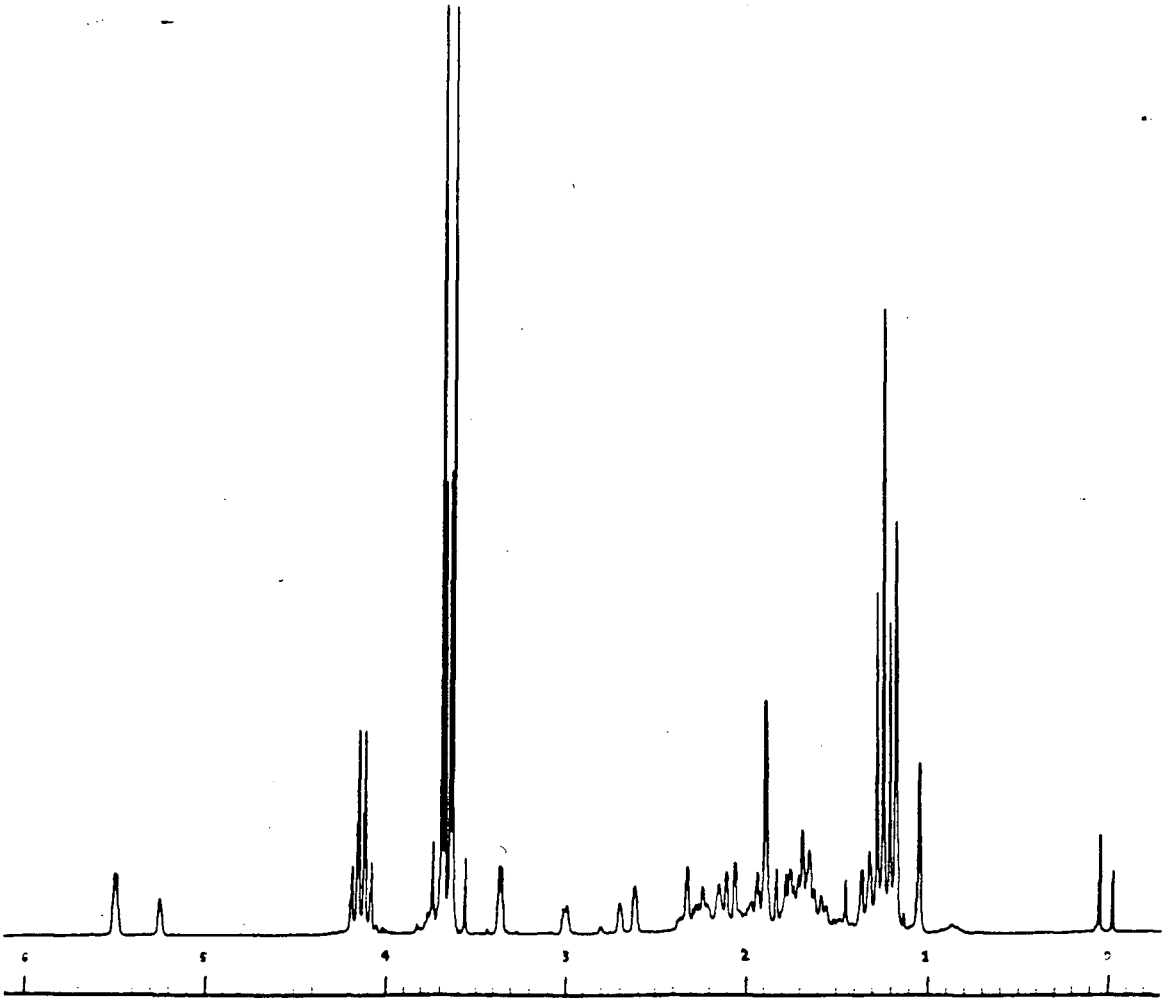


Figure 23

400 MHz ^{1}H NMR Spectrum of $\Delta^{8,12}$-6-carboethoxy-2-dicarbomethoxy-3-methyltetracyclo[6.4.0^{1,6}.0^{3,7}.0^{8,12}]-dodecene (182, $CDCl_3$)

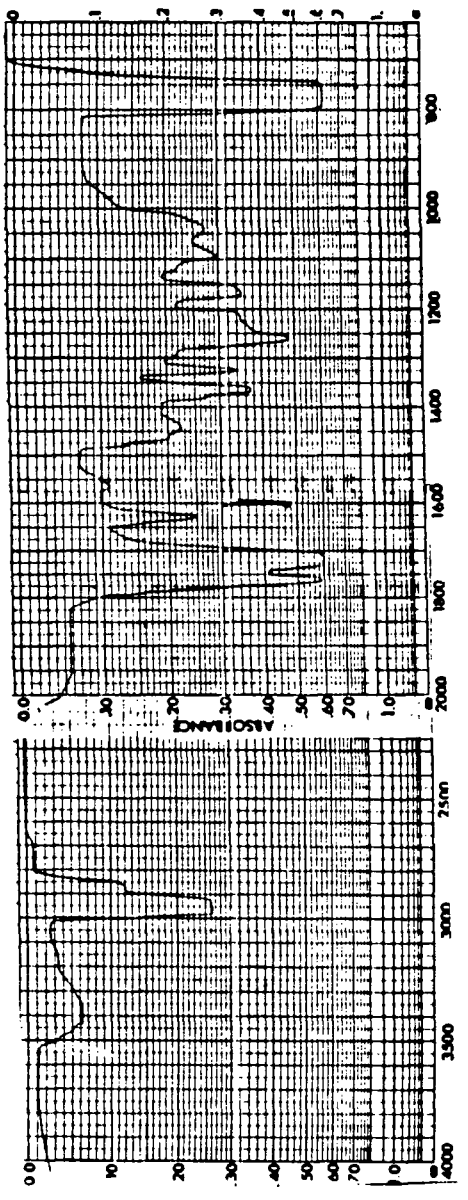


Figure 24

IR Spectrum of endo-1-carboethoxy-4-methyl-5-acetylbicyclo[2.2.1]heptan-2-one (171, neat)

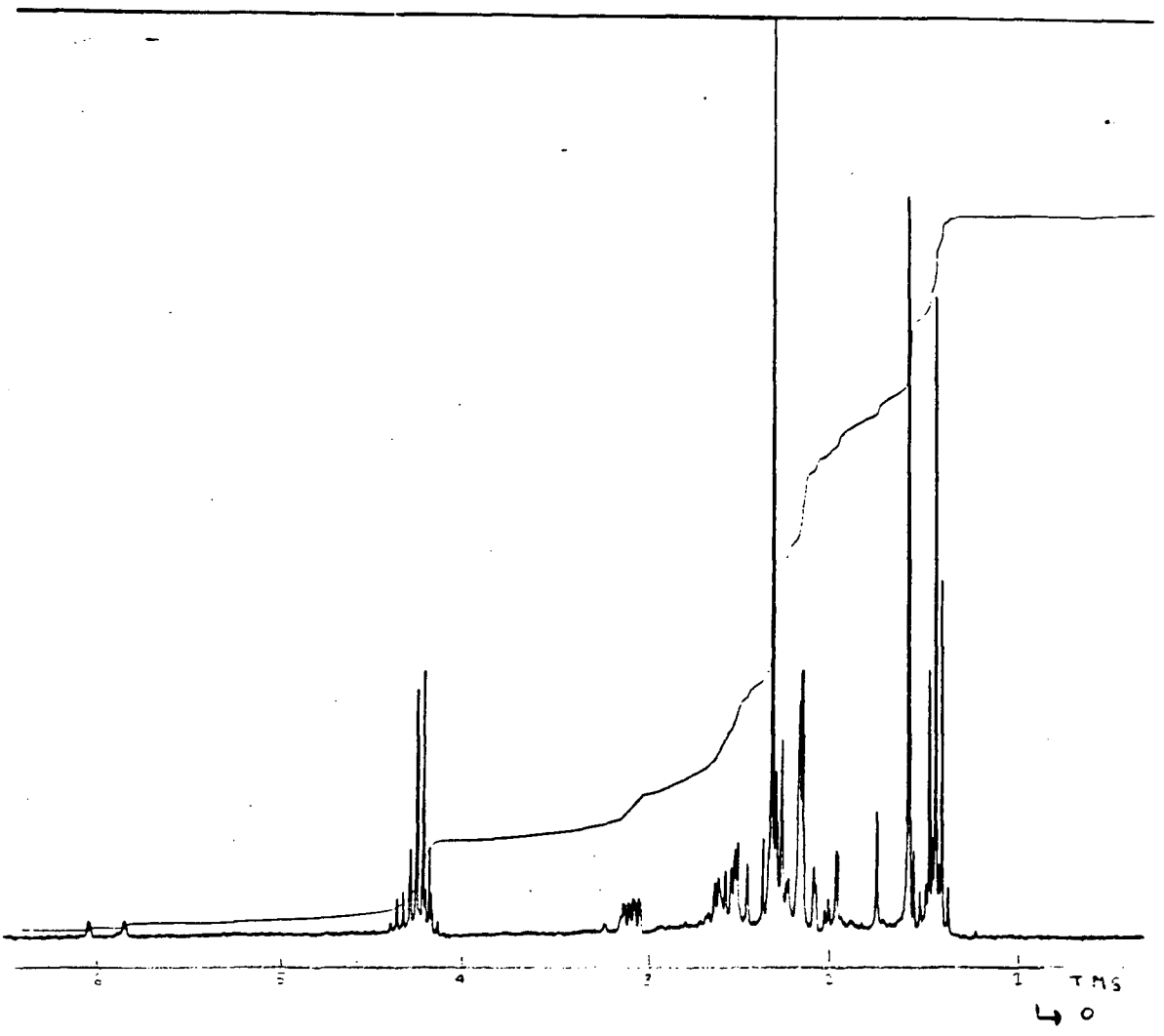


Figure 25

400 MHz ^{1}H NMR Spectrum of endo-1-carboethoxy-4-methyl-5-acetylbicyclo[2.2.1]heptan-2-one (171, $CDCl_3$)

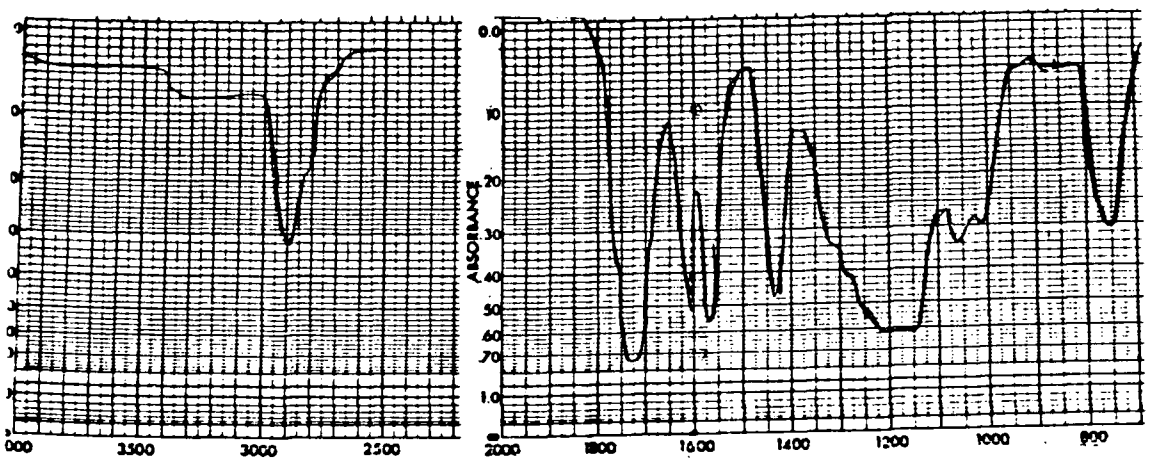


Figure 26

IR Spectrum of 6-carboethoxy-8-methyl-3-dimethyl methylenedicarboxylatebicyclo[4.3.0^{1,6}]nona-1,8-diene (173, neat)

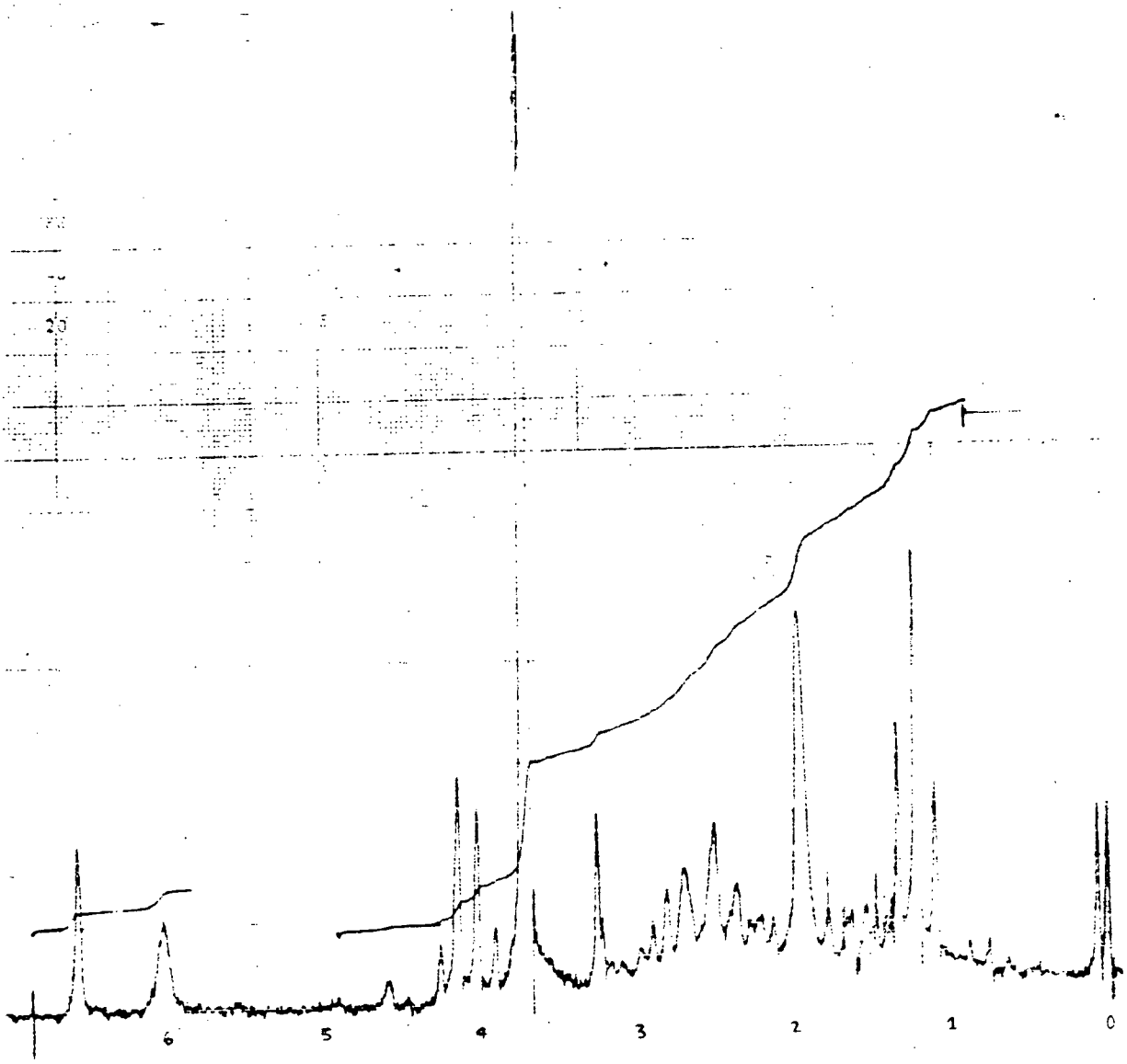


Figure 27

60 MHz 'H NMR Spectrum of 6-carboethoxy-8-methyl-3-dimethylmethylenedicarboxylatebicyclo[4.3.0]nona-1,8-diene (173, CCl_4)

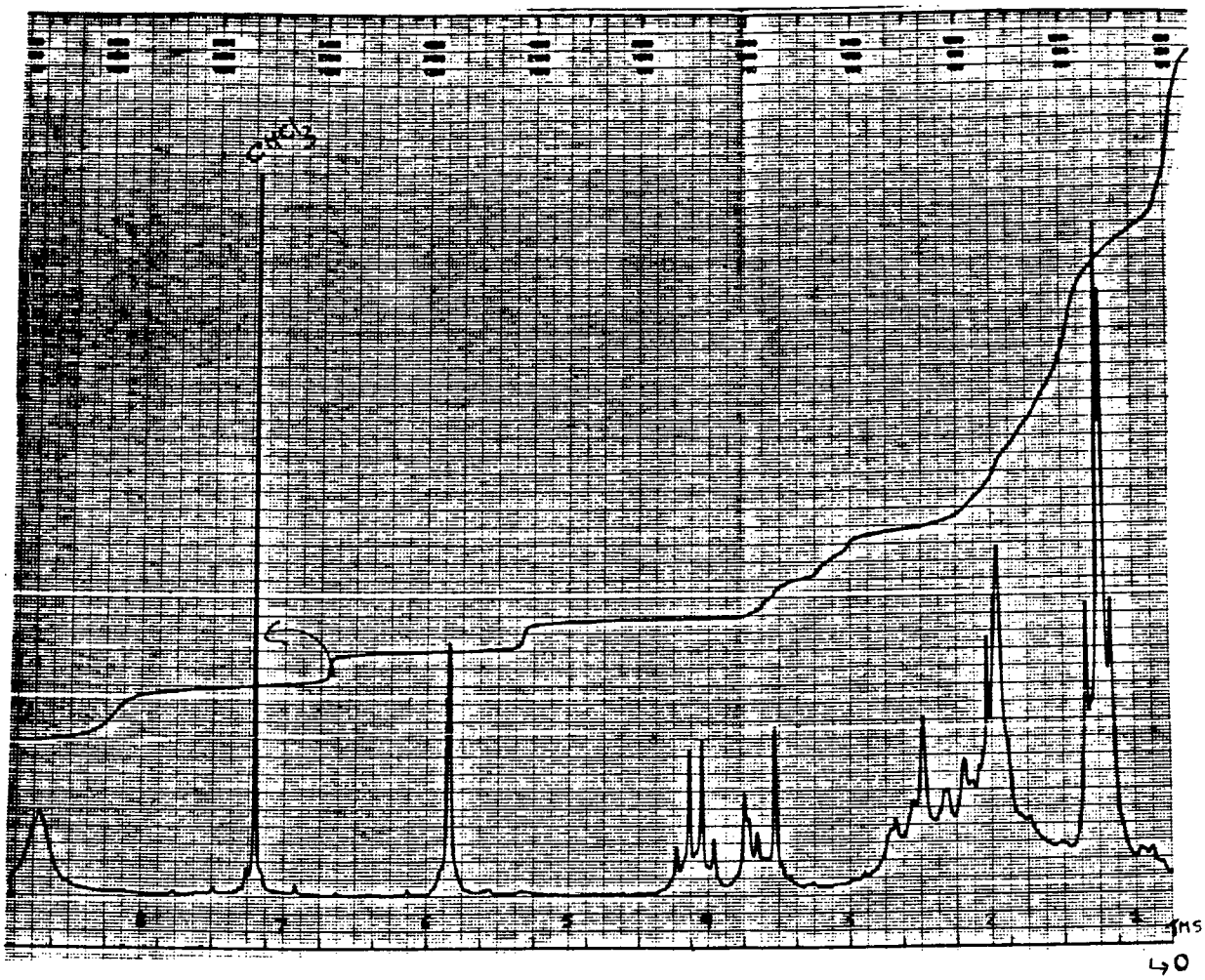


Figure 28

80 MHz ^{1}H NMR Spectrum of $\Delta^{11,12}$-6-carboethoxy-2-dicarboxylic acid 3-methyltetracyclo]6.4.0^{1,6}.0^{3,7}.0^{8,12}]-dodecene ($CDCl_3$)

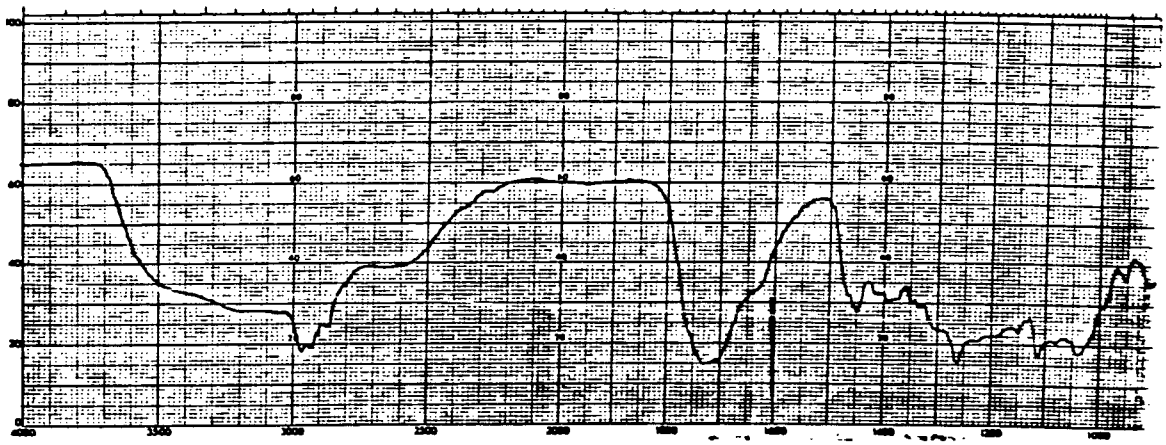


Figure 29

IR Spectrum of $\Delta^{11,12}$-6-carboethoxy-2-dicarboxylic acid 3-methyltetracyclo]6.4.0^{1,6}.0^{3,7}.0^{8,12}]-dodecene (neat)

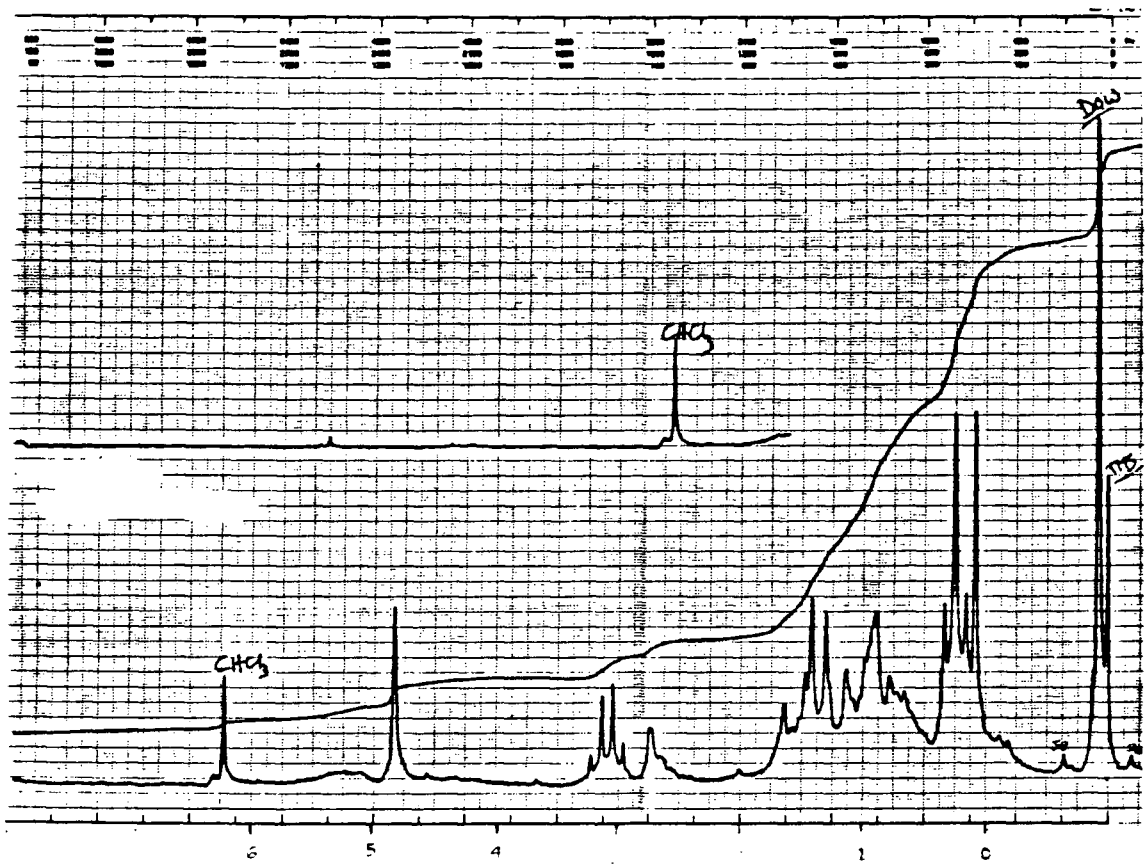


Figure 30

80 MHz ^{1}H NMR Spectrum of $\Delta^{9,10}$-6-carboethoxy-2-carboxylic acid 3-methyltetracyclo[6.4.0^{1,6}.0^{3,7}.0^{8,12}]dodecene (183, $CDCl_3$)

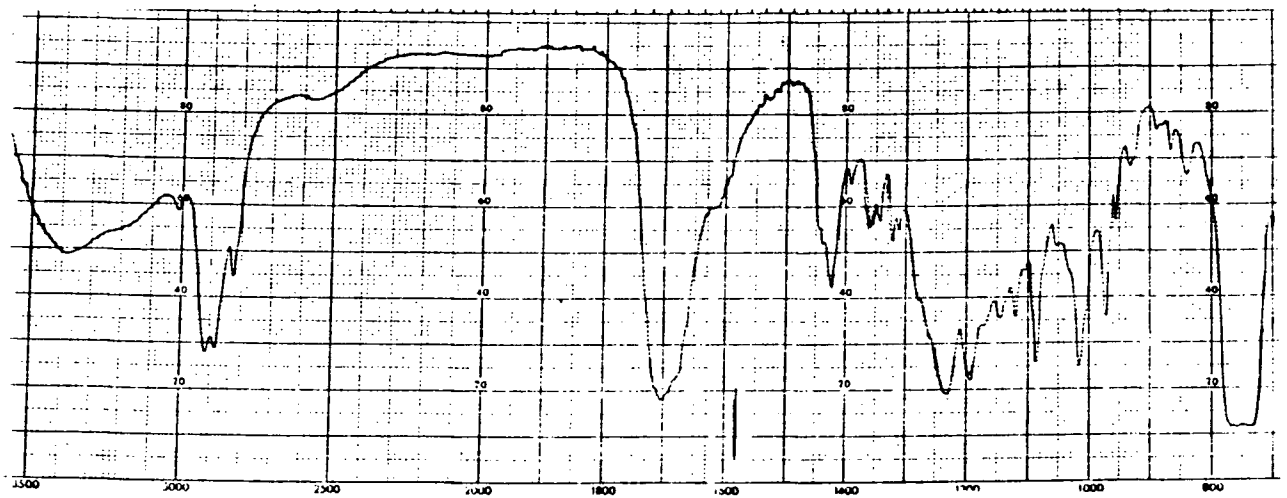


Figure 31

IR Spectrum of $\Delta^{9,10}$-6-carboethoxy-2-carboxylic acid 3-methyltetracyclo[6.4.0^{1,6}.0^{3,7}.0^{8,12}]dodecene (183, neat)

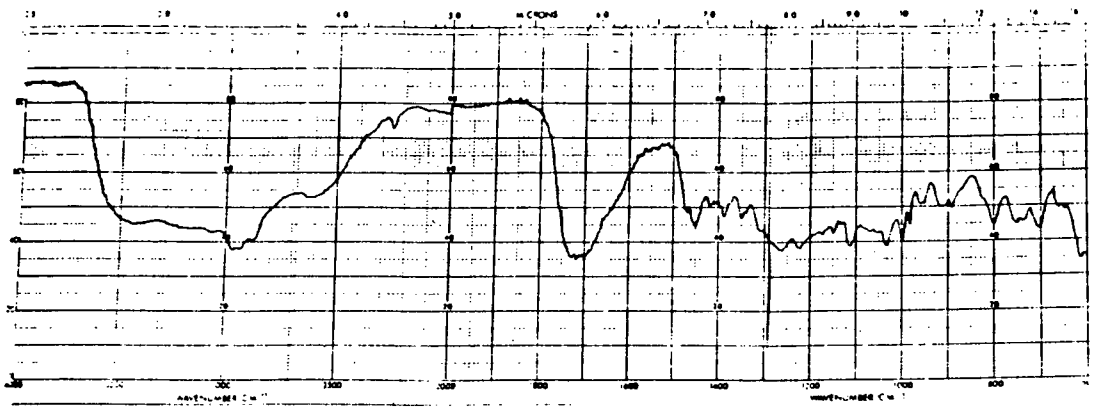


Figure 32

IR Spectrum of $\Delta^{9,10}$ 2,6-dicarboxylic acid

3-methyltetracyclo[6.4.$0^{1,6}$.$0^{3,7}$.$0^{8,12}$]dodecene ($CHCl_3$)

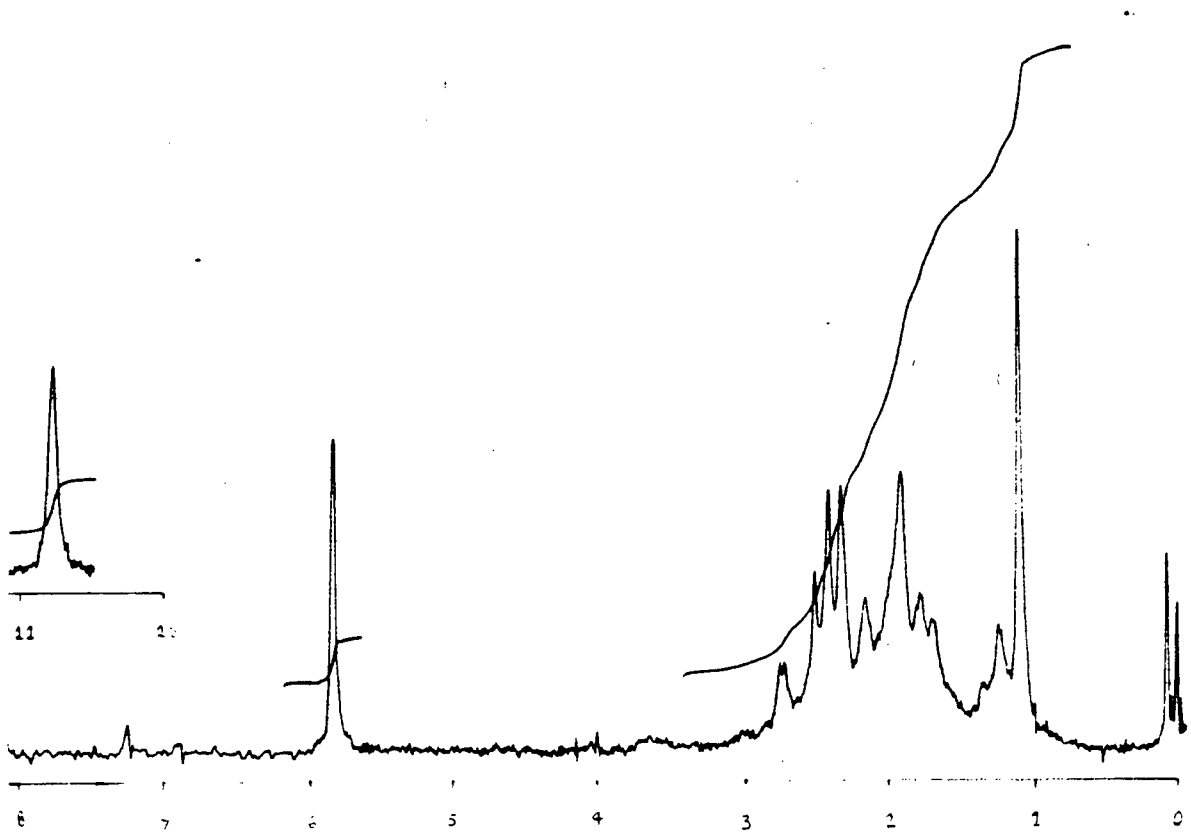


Figure 33

60 MHz ^{1}H NMR Spectrum of $\Delta^{9,10}$ 2,6-dicarboxylic acid 3-methyltetracyclo[6.4.0^{1,6}.0^{3,7}.0^{8,12}]dodecene ($CDCl_3$)

Experimental

Infrared spectra were recorded on Perkin Elmer 70B (compounds 1, 9, 12 and 13), 237B (compounds 35 to 43), 451 or 1320 (other compounds) spectrophotometers. Spectra were calibrated with the 1601 cm^{-1} band of polystyrene film. Bands were assigned when possible or the intensities were indicated (s: strong, m: medium, w: weak). Ultraviolet spectra were recorded on a Perkin-Elmer 202 uv-visible spectrophotometer and were calibrated with the 279.4 nm band of a Holmium oxide filter.

Proton magnetic resonance spectra were recorded on Nicolet-Oxford H-270 or Brucker WH 400 (compounds 1, 9, 12 and 13 at UBC; 171 and 182 at U. of Alberta), or Brucker WP-80 or Varian EM-360 (other compounds at MUN). Signal positions are reported in ppm downfield from tetramethylsilane (delta scale) used as an internal standard. The number of protons, multiplicity, coupling constants (Hz) and proton assignment are indicated in parentheses.

Low resolution mass spectra were obtained on a A.E.I. MS-902 spectrometer and high resolution mass spectra on A.E.I. MS-50 (compounds 1, 9, 12, 13, 15 and 16). The intensities for the plotted mass spectra were calculated from the low resolution spectra. Plotting starts with the peak at m/z = 32 and peaks of 3% intensity and higher are indicated. The other low and high resolution mass spectra were determined on a V.G. Micromass 7070-HS instrument using an ionization energy of 70 electron volts. (In some cases, the fragment lost from M^+ is indicated.)

Optical rotations were measured on a Perkin-Elmer 141 polarimeter, using a 1 dm cell. Melting points were obtained on a Fisher-Johns apparatus and values are uncorrected. Gas liquid chromatographic analyses were conducted on a Hewlett Packard 402B gas chromatograph equipped with a column (3m x 6mm i.d.) containing 1.5% OV-17 supported on Gas Chrome Q (noe)

using helium as the carrier gas. Photochemical experiments were conducted in stoppered quartz containers using a water-cooled Hanovian 450W medium pressure mercury arc lamp.

Thin layer chromatographic analyses were carried out on precoated silica gel plates with fluorescent indicator (Eastman Kodak silica gel 13181). Preparative thin layer chromatography was conducted on 20 x 20 cm glass plates coated with silica gel $PF_{254 + 366}$ type 60 (Merck). Merck silica gel 60, particle size 0.063-0.200 mm (70-230 mesh ASTM) was used for columns (compounds 1, 9, 12 and 13), while flash chromatography using BDH silica gel 60, 230-400 mesh was used for all other columns.

Solvents used were HPLC grade or distilled reagent grades. Petroleum ether refers to a fraction with boiling range 30-60°C. Anhydrous diethyl ether (ether), tetrahydrofuran, dimethoxyethane and dioxane were obtained by distillation from lithium aluminum hydride or potassium/benzophenone. Absolute ethanol and methanol were dried by distillation from magnesium. Dry hexamethylphosphoramide, dimethylformamide, dimethyl sulfoxide and diisopropylamine were prepared by distillation from calcium hydride. Solutions in organic solvents were dried over anhydrous magnesium sulfate and the solvent was removed using a Büchi rotary evaporator connected to a water aspirator. Sodium bicarbonate and ammonium chloride refer to aqueous saturated solutions, while 5 and 10% HCl refers to aqueous solutions. Unless otherwise indicated all reactions were conducted under an atmosphere of dry nitrogen.

Extraction and Crude Separation (Onchidoris bilamellata)

Following collection, the nudibranchs were immersed in methanol and soaked at -35°C for several weeks. The supernatant was then filtered through Whatman #1 filter paper and evaporated to about one half of the original volume. The concentrated extract was then partitioned between brine and ethyl acetate. This extraction procedure was repeated three times. The organic phase was dried over sodium sulfate, filtered and evaporated to give an oily residue.

The crude extract was purified by silica column chromatography. Elution of the active fraction from the column was facilitated by a gradient of increasing solvent polarity (dichloromethane-ethyl acetate). The fractions obtained were screened for antibacterial activity. The fraction eluting with ethyl acetate gave a positive result and was further purified by preparative thin layer chromatography (PTLC). The band having an R_f of 0.05 in ethyl acetate:chloroform (1:1) corresponded to ceramide 1. This compound was subsequently shown to inhibit the growth of the microorganisms Bacillus subtilis and Staphylococcus aureus.

Ceramide 1

Approximately 20 mg of ceramide 1 were obtained from 1200 to 1500 nudibranchs (yield = 0.02% of dry weight).

IR (Figure 4): 3420 (NH), 1660 (CO) cm^{-1}

^1H NMR: (Figure 2, Table 1)

^{13}C NMR: (Table 2)

MS (m/z, relative % intensity, Figure 4): 533(3), 515(3), 298(10), 280(12)

Exact Mass calculated for $C_{35}H_{67}NO_2$: 533.5155, obtained: 533.5173.

MP = 77-78°C

$[\alpha]_D$ = -11°(c 1.0, $CHCl_3$)

Acetylation of 1

A sample of ceramide 1 (10 mg, 1.8 x 10^{-2} mmole) was added to a solution containing acetic anhydride (0.2 mL), pyridine (0.2 mL) and dimethylaminopyridine (2 mg). The reaction mixture was stirred for 18 h at 20°C. Removal of the solvents in vacuo and purification by PTLC (R_f = 0.58, chloroform:ethyl acetate, 1:1) gave diacetylated derivative 9, 10 mg (1.5 x 10^{-2} mmole, 87%).

IR (Figure 6): 3400 (NH), 1720 (CO), 1660 (CO) cm^{-1}.

'H NMR: (Figure 5, Table 1)

MS (m/z, relative % intensity, Figure 7): 635(3), 575(3), 515(5), 280(85), 43(100).

Exact Mass calculated for $C_{39}H_{73}NO_5$: 635.5470, obtained: 635.5481.

MP: 88 - 90°C

$[\alpha]_D$ = -40°(c 1.5, $CHCl_3$)

Hydrolysis of 1

A solution of 1 (10 mg, 1.8 x 10^{-2} mmoles), dioxane (0.2 mL), sodium hydroxide in methanol (1 mL, 1 N) was refluxed for 48 hrs. The reaction mixture was partitioned between water and ether, and the aqueous layer acidified and reextracted with ether. The two organic extracts were neutralized and reextracted, the organic layers dried over sodium sulfate and the solvents evaporated in vacuo to give the long chain base 13 and the fatty acid 12.

The fraction containing 13 was acetylated as described for 1 and purified by PTLC (R_f = 0.53, ethyl acetate:chloroform, 1:1) to give triacetylated derivative 14, 2 mg (4.5×10^{-3} mmole, 25%) and starting material 1, 6 mg (1.1×10^{-2} mmoles, 60%).

IR: 3400 (NH), 1720 (CO), 1660 (CO) cm^{-1}

^1H NMR: (Table 1)

MS (m/z, relative % intensity): 439(3), 397(3), 380(5), 278(5), 144(85), 43(100).

Exact Mass calculated for $C_{25}H_{45}NO_5$: 439.3287, observed: 439.3304

Ozonolysis of 1

Ozone was passed for ten minutes through a solution containing 1 (2 mg, 3.6×10^{-6} moles) and methanol (1 mL) maintained at -78°C. Oxygen was then bubbled through the reaction mixture to flush the remaining ozone and dimethylsulfide was added in excess. After the solvent was evaporated, the residue was reacted with a 2,4-dinitrophenylhydrazine solution (5 mg in 1 mL methanol and 1 drop of concentrated HCl). The products of this reaction were purified by PTLC and two compounds 15 and 16 having R_f values of 0.20 and 0.72 in chloroform were collected.

15, MS (m/z, relative % intensity): 537(1), 429(1), 335(2), 280(3), 250(3). Decomposed before a high resolution MS could be obtained.

16, MS (m/z, relative % intensity): 406(5), 308(5), 235(6), 206(50), 181(12).

Exact Mass calculated for $C_{21}H_{34}N_4O_4$: 406.2572, observed: 406.2571.

2,2,10-trimethylcyclodecanone (35)

Cyclodecanone (2.0 g, 13 mmol, Aldrich) was added to a magnetically stirred suspension of dry THF (80 mL) containing sodium hydride (3.6 g,

60% in oil, 93 mmol). After 15 min, methyl iodide (15 g, 105 mmol) was added dropwise and stirring continued for 4 h with GLC monitoring until the reaction was complete. The reaction flask was cooled to 0° and methanol added dropwise to destroy excess sodium hydride followed by water, and the aqueous solution extracted with ether (5 x 30 ml). The combined organic extracts were dried, filtered, concentrated and purified by chromatography (dichloromethane) to give 35, 2.56 g (99% yield) as a viscous oil.

UV (λmax (log E)): 290(1.3)

IR (neat, Figure 2): 1700 cm^{-1} (CO)

^1H NMR ($CDCl_3$, Figure 3): 1.03 ppm (s, 3H, CH_3), 1.04 ppm (D, J = 7 Hz, 3H, CH_3), 1.17 ppm (s, 3H, CH_3), 3.31 ppm (m, 1H)

MS (m/z, relative % intensity, Figure 1): 196(30), 178(5), 163(3), 69(72), 56(100)

Exact Mass calculated for $C_{13}H_{24}O$: 196.1821, observed: 196.1835

SFORD ^{13}C NMR ($CDCl_3$): 22.24, 22.58, 23.11, 25.54, 26.41, 27.23, 27.82, 29.76, 35.30, 38.55, 38.69 (t, each) and 220.85 (s) ppm for the CO.

Photolysis of 35

2,2,10-trimethylcyclodecanone (35) (0.90 g, 4.6 mmol) was dissolved in cyclohexane (180 mL) placed in a quartz container flushed with nitrogen and stoppered. This solution was irradiated (450 w, medium pressure Hanovia) for 5 h (followed by GLC, until cyclodecanone (29) was no longer present) the solvent evaporated and the residue purified by chromatography (100% petroleum ether to 15% ethyl acetate-petroleum ether) to give an "olefinic mixture" (40%).

36, IR (neat): 1640, 1470, 1460, 1450, 880 cm^{-1} (all m intensity peaks)

^1H NMR ($CDCl_3$): 4.64 ppm (bs, 2H, $=CH_2$), 2.0 ppm (t, J = 7 Hz, 2H, CH_2-CO), 1.70 ppm (s, 3H, CH_3CO)

MS (m/z, relative % intensity): 168(5), 70(72), 56(100)

Exact Mass calculated for $C_{12}H_{24}$: 168.1872, observed: 168.1860.

37, IR (neat): 1460, 1455, 1445, 1375, 1260, 1240 cm^{-1} (all m intensity peaks)

'H NMR (CCl_4): 0.8-2.0 ppm (m)

MS (m/z, relative % intensity): 168(10), 166(6), 69(75), 57(100), 55(96), 43(100), 41(100)

When the bubbling of N_2 was omitted, the products consisted of the olefinic mixture (25%) and 38 (40%).

38, IR (neat): 1725(CO)

'H NMR (CCl_4): 9.54 ppm (d, J = 2Hz, 1H, CHO), 4.54 ppm (bs, 2H, $=CH_2$), 1.96 (t, J = 6 Hz, 2H, CH_2), 1.66 (s, 3H, CH_3)

MS (m/z, relative % intensity): 196(20), 178(3), 69(68), 56(100).

2,2,10-trimethylacetoxycyclodecane (43)

2,2,10-trimethylcyclodecanone (35) (0.215 g, 1.1 mmol) was added to a stirred ether (5 mL) suspension of lithium aluminum hydride (0.042 g, 1.1 mmol) at 22°C and stirring continued for 0.85 h. After dropwise addition of water, the solution was extracted with ether (3 x 25 ml), the combined organic extracts dried, filtered and concentrated to give 2,2,10-trimethylcyclodecanol (42), 0.190 g (82%).

42, IR (neat): 3300-3500 cm^{-1} (OH)

'H NMR ($CDCl_3$): 0.80-1.15 ppm (m, 9H, $3CH_3$), 1.20-2.00 ppm (m, 16H), 3.14 ppm (m, 1H).

The alcohol 42 was dissolved in CCl_4 (2 mL), acetic anhydride (0.2 mL), and pyridine (0.1 mL) added and the solution stirred at 22° for 15 h. Ether (30 mL) was added and the solution washed with 5% aqueous HCl, brine, the

organic layer dried and concentrated to give the acetate 43, 0.185 g (85%).

43: IR (neat): 1725 cm^{-1} (CO)

'H NMR ($CDCl_3$): 0.83 ppm (s, 3H, CH_3), 0.93 ppm (s, 3H, CH_3), 0.97 ppm (d, J = 7 Hz, 3H, CH_3), 2.07 ppm (s, 3H, CH_3), 4.56 and 5.10 ppm (d, J = 1.5 and 2.5 Hz, 1H, CH(OAc)

MS (m/z, relative % intensity): 239(55), 225(28), 181(72), 43(100).

Potassium Permanganate Oxidation of Olefins (obtained from photolysis of 35)

18-Crown-6-ether (30 mg, 0.08 mmol) and potassium permanganate (252 mg, 1.6 mmol) were added to a benzene solution (15 mL) of the olefinic mixture (100 mg, 5.6 mmol) and the reaction stirred for 120 h at 23°. Water was added, the reaction mixture extracted with ether (3 x 25 mL), dried, filtered, concentrated and the neutral material purified by PTLC (5% ethyl acetate:dichloromethane) to give ketone 39, 10 mg (9%).

IR (neat): 1715 cm^{-1} (CO)

'H NMR (CCl_4): 2.07 (s, 3H, CH_3, CO), 2.10 (t, J = 7 Hz, 2H, CH_2CO)

MS (m/z, relative % intensity): 170(11), 58(100), 43(83)

Exact Mass calculated for $C_{11}H_{22}O$: 170.1665, observed: 170.1682.

Hydroboration of Olefins (obtained from photolysis of 35)

The THF solution (4 ml) containing the olefinic mixture (100 mg, 0.56 mmol) was cooled to 0° and BH_3-THF (0.64 mL, 0.6 mmol, Aldrich) added dropwise. After 5 min the ice bath was removed and the solution stirred at 23° for 2 h. A 3N aqueous solution of sodium hydroxide (0.08 mL) and 30% hydrogen peroxide (0.08 mL) were added and stirring continued for an additional 2 h. Water was added, the reaction mixture extracted with ether (3 x 20 ml), the combined organic extracts dried, filtered, concentrated and

the resulting oil purified by PTLC (dichloromethane) to give hydrocarbon 15, 20 mg (20%) and primary alcohol 40, 60 mg (60%)

40: IR (neat): 3600-3300 cm^{-1} (OH)

'H NMR (CCl_4): 3.30 ppm (d, J = 5 Hz, 2H, CH_2-OH), .8-1.4 (m, 22H)

MS (m/z, relative % intensity): 168(5%), 57(100%), 43(95)

Exact Mass calculated for $C_{12}H_{24}$: ($M^+ - H_2O$) 168.1878, observed: 168.1875.

Jones Oxidation of 40

To an acetone solution (2 mL) containing alcohol 40 (15 mg, 0.08 mmol), Jones reagent[7] was added dropwise until a green precipitate was obtained. This mixture was stirred for an additional 15 min and 2-propanol (2 mL) was added to destroy any excess Jones reagent. The reaction mixture was then filtered, dried, filtered again and the solvent concentrated to give the carboxylic acid 41, 15 mg (93%).

IR (neat): 3400-2800 (OH), 1700 (CO) cm^{-1}

'H NMR ($CDCl_3$): 10.2 ppm (bs, 1H), .8-2.0 ppm (m, ~23H)

MS (m/z, relative % intensity): 200(10), 140(12), 74(100).

Ozonolysis of Olefinic Mixture (obtained from photolysis of 35)

Ozone was passed during 5 min through a solution containing the olefinic mixture (100 mg, 5.6 mmol) in methanol (2 mL), at -78°C. Oxygen was then bubbled through the solution to flush any remaining ozone and dimethyl sulfide (0.5 mL) was added. After stirring for 1 h at 20°, the solution was concentrated and the residue purified by PTLC (5% ethyl acetate:dichloromethane) to afford hydrocarbon 37, 20 mg (20%) and ketone 39, 60 mg (54%).

Spectral data reported in previous experimental sections.

Methyl-2-oxocyclopentanecarboxylate (105)

Sodium hydride (2.46 g, 60% oil dispersion, 63 mmol, BDH) and dimethylcarbonate (20 g, 220 mmol, Eastman) were added to benzene (50 mL) and the solution refluxed. Cyclopentanone (2.47 g, 29 mmol, Aldrich) was added dropwise and stirring continued for 2 h. The cold reaction (0°C) was acidified (5% HCl) and extracted with ether. The combined extracts were washed with sodium bicarbonate, brine, dried, filtered and concentrated, to afford 105 after distillation, 2.1 g (55%).

bp 97-100°C/12 Torr

IR (CCl_4): 1750 (s), 1660 (m) cm^{-1}

'H NMR (CCl_4): δ = 7.50 ppm (1H, s, enol), 3.78 ppm (3H, s, CH_3OCO), 1.5-2.5 ppm (6H, m).

Methyl 1-methyl-2-oxocyclopentanecarboxylate (106)

A solution containing β-keto-ester 105 (1.8 g, 13 mmol) and potassium carbonate (7.3 g, 53 mmol, BDH) in acetone (25 mL) was heated to 40°C. Iodomethane (3.8 g, 26 mmol, Aldrich) added dropwise, and the mixture stirred for 1 h. The reaction was cooled, filtered, water added and extracted with ether. The combined extracts were dried, filtered and concentrated to give 106, 1.8 g (98%).

IR (CCl_4): 1725 (s), 1675 (m), 1625 (w) cm^{-1}

'H NMR (CCl_4): δ = 3.50 ppm (3H, s, CH_3OCO), 1.5-2.5 ppm (6H, m), 1.18 ppm (3H, s, CH_3)

MS (m/z, relative % intensity): 142(38), 110(52) - MeOH.

Methyl 1,3,3-trimethyl-2-oxocyclopentanecarboxylate (107)

A potassium-t-amyloxide solution was prepared by refluxing DME (200 mL),

t-amyl alcohol (22.52 g, 0.256 mol, Fisher) and potassium (11.9 g, 0.306 mol, BDH) for 2 days. Titration of an aliquot (2 mL) containing phenolphthalein, with HCl, determined the concentration of the solution (1.2 M). Ketone 106 (210 mg, 1.3 mmol) was added to DMF (3 mL) containing potassium-t-amyloxide (2.2 mL, 2.6 mmol) and stirred at -20°C. Iodomethane (0.93 g, 6.5 mmol, Aldrich) was added to the orange solution, and stirring continued for 10 min. Excess ammonium chloride was added, and the solution extracted with ether. The combined extracts dried, filtered, concentrated and purified by chromatography (5% ethyl acetate-petroleum ether) to afford 107, 155 mg (70%).

IR (CCl_4): 1750 (w), 1730 (w) cm^{-1}

'H NMR (CCl_4): δ = 3.69 ppm (3H, s, CH_3OCO), 1.5-2.5 ppm 4H, m), 1.23, 1.10 and 1.02 ppm (each, 3H, s, CH_3).

Methyl 1,3,3-trimethyl-2-hydroxy cyclopentanecarboxylate (108)

Sodium borohydride (0.90 g, 24 mmol, BDH) was added to a methanol (10 mL) solution of ketone 107 (3.1 g, 17 mmol). After stirring for 1 h, the solution was acidified (5% HCL) and extracted with ether. The combined extracts dried, filtered, concentrated and purified by chromatography (10% ethyl acetate-petroleum ether), to afford 108, 2.4 g (83%).

IR (CCl_4): 3500 (OH), 1725 (CO) cm^{-1}

'H NMR (CCl_4): δ = 4.05 ppm (1H, s, CH(OH)), 3.83 ppm (3H, s, CH_3OCO), 3.20 ppm (1H, bs, OH), 1.18, 1.02 and 0.92 ppm (each, 3H, s, CH_3).

Methyl 3-chloropropanoate (117a)

Prepared from 3-chloropropionyl chloride, based on the procedure of Carpino et al[150] (97%).

IR (CCl_4): 1740 (CO) cm^{-1}

'H NMR (CCl_4): δ = 2.78 ppm (2H, t, J = 7 Hz, CH_2COO), 3.69 ppm (3H, s, COOMe), 3.73 ppm (2H, t, J = 7 Hz, CH_2Cl)

MS (m/z, relative % intensity): 123(22), 87(85) - HCl, 63(100) - CH_2CH_2Cl.

3-Chloropropanal (117c)

Prepared as 117d, neat, no solvent (85%). The product was obtained as a trimer:monomer (10:1), according to 'H NMR analysis.

IR (CCl_4): 1725 (CO) cm^{-1}

'H NMR (CCl_4): δ = 8.42 and 5.07 ppm (1H, bs:t, J = 4 Hz, CH = CHOH), 3.56 ppm (2H, t, J = 7 Hz, CH_2Cl), 2.10 ppm (2H, dt, J = 4, 7 Hz, CH_2CHO).

3-Chloropropanal ethylene acetal (117d)

Ethylene glycol (30 g, 0.49 mol, Fisher) was placed in a flask equipped with a mechanical stirrer, condenser and drying tube, at 0°C. Gaseous hydrochloric acid (16 g, 0.42 mol, Fisher) was bubbled into the flask,. followed by the dropwise addition of acrolein (23.8 mL, 0.4 mol, Aldrich). The ice bath was then removed and the reaction stirred for 4 h and extracted with petroleum ether. The combined extracts washed with sodium bicarbonate, water, dried, filtered and concentrated to afford 117d, 55.6 g (83%).

bp 40-42°C/0.07 Torr

IR (CCl_4): 2950, 2850 (CH) cm^{-1}

'H NMR (CCl_4): δ = 4.86 ppm (1H, t, J = 4 Hz, $\underline{H}C(OCH_2)_2$), 3.84 ppm (4H, s, CH_2O), 3.47 ppm (2H, t, J = 7 Hz, CH_2Cl), 2.02 ppm (2H, dt, J = 4, 7 Hz, $C\underline{H}_2CH(OCH_2)_2$

MS (m/z, relative % intensity): 137(8), 73(100) - $HC(OCH_2)_2$.

3-Chloro-1,1-dimethoxy propane (117e)

Prepared as above, using methanol (1.25 mol) instead of ethylene glycol (75%).

IR (CCl_4): 2975, 2940, 2810 (CH) cm^{-1}

'H NMR (CCl_4): δ = 4.75 ppm (1H, t, J = 4 Hz, $\underline{H}C(OMe)_2$), 3.54 ppm (2H, t, J = 7 Hz, CH_2Cl), 3.28 ppm (6H, s, CH_3O), 1.9 ppm (2H, dt, J = 4, 7 Hz, $C\underline{H}_2CH(OMe)_2$)

MS (m/z, relative % intensity): 107(100) M^+-OMe, 103(15) - Cl

Exact Mass calculated for $C_5H_{11}O_2Cl$: 138.0444, observed: 138.0380.

3-Bromopropanol acetate (117f)

Prepared from the related alcohol (14 g, 0.1 mol), stirred at 20°C with acetic anhydride (11 g, 0.11 mol, Fisher), pyridine (8.8 g, 0.12 mol) in CCl_4 (10 mL), for 16 h. Cold water and chloroform were then added to the solution. The chloroform extracts were washed with 10% HCl, dried, filtered, and concentrated, to afford 117f, 14.3 g (83%).

IR (CCl_4): 1740 (CO) cm^{-1}

'H NMR (CCl_4): δ = 4.11 ppm (2H, t, J = 7 Hz, CH_2Br), 3.43 ppm (2H, t, J = 7 Hz, CH_2O), 2.28 ppm (2H, quint., J = 7 Hz, $CH_2C\underline{H}_2CH_2$), 2.20 ppm (3H, s, CH_3CO).

Typical Alkylation of Cyclopentadiene using 117

Freshly distilled cyclopentadiene (5 mmol, Aldrich, bp 38-40°C) in THF (2 mL) was added dropwise to sodium hydride (5.5 mmol, 60% oil dispersion, Aldrich) in THF (15 mL), stirring at 0°C. The solution stopped bubbling after 5-10 min, and the alkylating reagent 117 (5 mmol) was added. The reaction was stirred at the appropriate temperature, for the requisite time (Table 4).

The solution was cooled, acidified (5% HCl, dropwise) and extracted with ether. The combined ether extracts washed with brine, dried, filtered, concentrated and the product purified by chromatography (neutral alumina, ether-petroleum ether). The reaction of 117b was performed using 4 equiv. of cyclopentadiene, while reaction of 117i was done in THF:DME, 1:1.

Typical spectral data for products 118, in this case, 118e.

IR (CCl_4): 300-2810, 1615, 1605 (CH) cm^{-1}

'H NMR (CCl_4): δ = 6.3-5.8 ppm (m, 3H, olefinic cyclopentadiene protons), 4.27 ppm (1H, t, J = 4 Hz, $C\underline{H}(OMe)_2$), 3.23 ppm (6H, s, CH_3O), 2.85 ppm (2H, bs, CH_2 in cyclopentadiene), 2.35 and 1.84 ppm (each, CH_2, m, $C\underline{H}_2CH(OMe)_2$ or CH_2-cyclopentadiene)

MS (m/z, relative % intensity): 168(13), 136(74) - MeOH, 104(62) - 2MeOH,

Exact Mass calculated for $C_{10}H_{16}O_2$: 168.1146, observed: 168.1135.

1,1-diacylated product "118b", 'H NMR: (CCl_4) δ = 6.3 ppm (4H, bs, olefins), 3.68 ppm (4H, m, CH_2Cl), 3.0 ppm (4H, m, CH_2CO)

1,3-diacylated product "118b", 'H NMR: (CCl_4) δ = 7.30 ppm (2H, d, J = 4 Hz), 6.32 ppm (1H, t, J = 4 Hz), 3.82 ppm (4H, t, J = 7 Hz), 3.30 ppm (4H, t, J = 7 Hz), 2.70 ppm (1H, t, J = 4 Hz).

3-Ethoxy-2-methyl-2-cyclopentenone (103)

Prepared from 2-methylcyclopentane-1,3-dione, based on the procedure of House et al[91] (90%).

IR (CCl_4): 1680 (CO), 1620 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 4.23 ppm (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 2.8-2.3 ppm (4H, m, CH_2CH_2), 1.56 ppm (3H, bs, CH_3C=C), 1.40 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$).

4-Ethoxy-3-methylbicyclo[3.3.0]oct-3-en-2-one (122)

Prepared from enol ether 103 by the method of Koreeda et al[110] (68%).

bp 90-93°C/0.5 Torr

IR (CCl_4): 1700 (CO), 1645 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 4.28 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.20 ppm (1H, m, $CHC{=}C$), 2.73 ppm (1H, m, CHCO), 1.58 ppm (9H, bs), 1.36 ppm (3H, 5, J = 7 Hz, $C\underline{H}_3CH_2$)

MS (m/z, relative % intensity): 181(30)M^+ + 1, 180(100), 152(48) -Et, 124(83) $-CH_2CH_2CO$

Exact Mass calculated for $C_{11}H_{26}O_2$: 180.1146, observed: 180.1158.

2-Methyl-2,4-bicyclo[3.3.0]octadione (123)

Enol ether 122 (1.8 g, 10 mmol) was hydrolyzed using sulfuric acid (conc. 3.5 mL, 70 mmol) and water (7 mL, 70 mmol) at 100°C, for 18 h. The reaction was cooled to 20°C, and extracted with hot ethyl acetate and hot dichloromethane. The combined organic extracts were washed with sodium bicarbonate, brine, dried, filtered and concentrated to afford 123, 0.6-1.2 g (40-80%), recrystallized in hot dichloromethane.

mp 158-160°C

IR ($CHCl_3$): 1700 (CO), 1645 (C=C) cm^{-1}

'H NMR ($CDCl_3$): δ = 7.10 and 4.18 ppm (1H, bs, OH), 2.60 ppm (1H, s, CH-C=C), 2.20 ppm (1H, s, CHCO), 1.26 ppm (3H, s, CH_3)

MS (m/z, relative & intensity): 152(54), 124(63) -CO, 28(100) -CO

Exact Mass calculated for $C_9H_{12}O_2$: 152.0834, observed: 152.0833.

3-Methylbicyclo[3.3.0]-3-octen-2-ol (124)

Lithium aluminum hydride (42 mg, 1.1 mmol or 4.4 equiv., Aldrich) was

added to enol ether 122 (180 mg, 1 mmol) dissolved in ether (10 mL) and the reaction stirred at 20°C. After 2 h, water (0.1 mL, 5.6 mmol) was added to the cold (0°C) reaction. The mixture was then filtered, and the residue washed with ether. The combined extracts dried, filtered, concentrated and the products purified by chromatography (8% ethyl acetate-dichloromethane).

124a, least polar product, 70 mg (40%),

IR (CCl_4): 3600 (w, OH) cm^{-1}

'H NMR (CCl_4): δ = 5.20 ppm (1H, bs), 4.0 ppm (1H, bs), 3.10 ppm (1H, bs)

MS (m/z, relative % intensity): 138(57), 120(38) $-H_2O$, 123(38) $-CH_3$, 109(100)

124b, more polar product, 88 mg (49%),

IR (CCl_4): 3600 (s, OH), 3450 (m) cm^{-1}

'H NMR (CCl_4): δ = 5.10 ppm (1H, bs), 4.36 ppm (1H, bd, J = 7 Hz), 2.80 ppm (2H, m)

MS (m/z, relative % intensity): 138(60), 123(30) $-CH_3$, 120(20) $-H_2O$, 109(100).

3-Methyl-3-(3-oxobutyl)-2,4-bicyclo[3.3.0]octadione (125)

Prepared from 3-methyl-2,4-bicyclo[3.3.0]octadione, based on the procedure of Hajos and Parrish[101a] (85%).

IR (neat): 1760 (m), 1725 (s) cm^{-1}

'H NMR ($CDCl_3$): δ = 3.68 ppm (2H, t, J = 7 Hz, CH_2CH_2CO), 3.30 ppm (2H, m), 2.57 ppm (2H, t, J = 7 Hz, CH_2CO), 2.05 ppm (3H, s, $COCH_3$), 0.96 ppm (3H, s, CH_3)

MS (m/z, relative % intensity): 222(20), 152(77) - C_4H_7O, 124(100) - C_4H_6O, CO

Exact Mass calculated for $C_{13}H_{18}O_3$: 22.1251, observed: 222.1249.

3-(Propyloxy-3-al ethylene acetal)-2-methyl-2-cyclopentenone (132)

3-iodopropanal ethylene acetal (2 equiv., Aldrich), 18-crown-6 (catalytic, Aldrich), and sodium carbonate (2 equiv., BDH) were added to diketone 121 (1 equiv.) present in solvent system a, b. The reaction mixture was refluxed for 18 h and water added to quench the reaction (20°), this was followed by extraction with ethyl acetate. The combined extracts were washed, dried, filtered and concentrated. Purification by chromatography (ether) afforded 132.

Solvents used, a: THF, 0%; b: HMPA at 150°C, 35%.

IR (CCl_4): 1700(CO), 1640(C=C) cm^{-1}

'H NMR ($CDCl_3$): 5.0 ppm (1H, t, J = 4 Hz, $C\underline{H}(OCH_2)_2$), 4.30 ppm (2H, t, J = 7 Hz, $C\underline{H}_2CH_2(CH_2O)_2$), 3.90 ppm (4H, bs, CH_2O), 1.62 ppm (3H, bs, CH_3)

MS (m/z, relative % intensity): 212(2), 168(34) $-CH_3CO$, 124(36).

Ethyl 3-methyl-2,4-pentadienoate (131a)

Prepared as for 144a, except 4-chlorobutanone was replaced by methyl vinyl ketone. The product obtained after extraction (90%) was pure enough for further use. However, it could be distilled.

bp 80-82°C/15 Torr (19%)

IR (neat): 1715 (CO), 1635, 1610, 1605 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 7.62 ppm and 6.17 ppm (1H, dd, J = 12, 18 Hz and HC=C and J = 10, 18 Hz, 1:1, $C\underline{H}=CH_2$), 5.49 ppm (2H, bs, 1 of $C\underline{H}_2=C$), 5.15 ppm (1H, m, 1 of $CH_2=C$), 3.86 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 2.00 and 1.72 ppm (3H, s:s, 1:1, $CH_3C=C$), 1.00 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$)

MS (m/z, relative % intensity): 140(3), 111(18) -Et, 95(63) -OEt, 43(100)

Exact Mass calculated for $C_8H_{12}O_2$: 140.0834, observed 140.0843.

3-Methyl-4,4-dicarbomethoxy-1,3-butadiene (131b)

Alkyl chloride 144b (3 g, 17 mmol) was added dropwise to a stirred solution of sodium (0.4 g, 17 mmol, BDH) in methanol (50 mL).

After stirring for 1 h at 0°C, the solution was neutralized (10% HCl), and the aqueous layer extracted with ethyl acetate. The combined extracts were dried, filtered and concentrated to afford 131b, 2.1 g (90%) pure enough for further use.

IR (neat): 1710 CO), 1610, 1575 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 7.00 ppm (1H, dd, J = 10, 16 Hz, HC=C), 5.68 ppm (1H, bd, J = 16 Hz, CH=CH, E), 5.43 ppm (1H, bd, J = 10 Hz, CH=CH, Z), 3.70 ppm (6H, s, CH_3COO), 2.10 ppm (3H, s, CH_3C=C).

1-(prop-1-yn-3-ol)-1-cyclopentanol (133)

Methyl magnesium chloride (13.1 mL, 39 mmol, 2.99 M solution, Aldrich) was added slowly to freshly distilled propargyl alcohol (1 g, 18 mmol, bp 28-30°C/10 Torr, Aldrich) in THF (25 mL). The solution was stirred for 10 min at 0°C, then 30 min at 20°C. Cyclopentanone (1.5 g, 18 mmol, Aldrich) in THF (2 mL) was added to the cold (0°C) solution. The mixture was filtered through celite, extracted with ethyl acetate, dried, filtered and concentrated to afford 133, 2.2 g (87%).

IR (neat): 3500-3400 (OH) cm^{-1}

'H NMR ($CDCl_3$): δ = 4.27 ppm (2H, s, CH_2OH), 4 ppm (2H, bs, OH), 1.88 ppm (8H, bs)

MS (m/z, relative % intensity): 140(2), 79(100)

Exact Mass calculated for $C_8H_{12}O_2$: 140.0834, observed: 140.0832.

"Intermediates" 134 to 136 and product 137

Diol 133 or acetylated 133 (prepared as described previously for 117f), was treated with sulfuric acid:methanol, 1:1, at various temperatures (0°.to 20°C), for different lengths of time (5 min to 2 h). Intermediates 134 to 137 were isolated (from 5 to 30%) and product 137 (~30-40%).

134, IR (neat): 3500 (OH), 1730 (CO) cm^{-1}

'H NMR (CCl_4): δ = 4.18 ppm (2H, s, CH_2OH), 3.20 ppm (2H, s, OH), 1.8 ppm (8H, m)

135, IR (neat): 3500 (OH) 1700 (CO) cm^{-1}

'H NMR (CCl_4): δ = 5.92 ppm (1H, s, HC=C), 4.20 ppm (2H, s, CH_2OH), 1.5-2.5 ppm (8H, m)

136, 'H NMR (CCl_4): 6.50 ppm (2H, m), 6.10 ppm (1H, m), 5.80 (1H, dd, J = 2, 10 Hz)

137, IR (neat): 1700 (CO), 1630 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 1.5-2.8 ppm (m)

MS (m/z, relative % intensity): 150(18), 149(100), M^+-1

Exact Mass calculated for $C_{10}H_{14}O$: 150.1041, observed: 150.1041.

^{13}C NMR ($CDCl_3$): δ = 20.09, 25.23, 26.94, 29.52, 32.55, 34.30, 39.79, 128.69, 158.66 and 207.39 ppm.

2,4-Dinitrophenylhydrazone derivative of 137

Ketone 137 (300 mg, 2 mmol) was added to a solution of 2,4-dinitrophenylhydrazine (500 mg, 2.5 mmol, Aldrich) in methanol (5 mL) and HCl (conc. 2 drops). A precipitate formed instantaneously, it was then filtered off and recrystallized in chloroform:methanol, to afford the DNPH derivative of 137, 650 mg (98%).

mp 226-228°C

IR ($CHCl_3$): 1650, 1600, 1520 cm^{-1}

'H NMR ($CDCl_3$): 9.10 ppm (1H, d, J = 2 Hz), 8.30 (1H, dd, J = 2, 10 Hz), 7.80 ppm (H, d, J = 10 Hz), 1.7-3.0 ppm (10H, m)

MS (m/z, relative % intensity): 330(8), 149(100) - $C_6H_3N_3O_4$

Exact Mass calculated for $C_{16}H_{18}N_4O_5$: 330.1328, observed: 330.1372.

$\Delta^{1,5}$-bicyclo[3.3.0]octen-2-one (138)

Prepared from methyl-2-oxocyclopentanecarboxylate by the method of Kulkarni and Dev[115] (30-40%). Also prepared from 83, based on the procedure of Easton Carlson and Lee[120] (~60%). The largest scale on which this reaction could be performed is 0.11 mole of hydroxy-acid using five equivalents of phosphorus pentoxide and methanesulfonic acid, instead of ten equivalents recommended in the literature (58%).

IR (neat): 1700 (CO), 1640 (C=C) cm^{-1}

'H NMR (CCl_4): 2.2 to 2.8 ppm (m)

MS (m/z, relative % intensity): 122(100), 107(5), 93(20), 79(95)

Exact Mass calculated for $C_8H_{10}O$: 122.0729, observed: 122.0713.

UV (λ max (log ε)): 241 (3.5)

5-Ethoxalyl-3-methyl-2-cyclopentenone (189) and

$\Delta^{1,5}$-ethoxalylbicyclo[3.3.0]octen-2-one (145)

A sodium ethoxide solution (prepared from sodium, 0.115 g, 5 mmol BDH, and dry ethanol, 1.8 mL, 30 mmol) was dissolved in ether (10 mL) and cooled to 0° with an external ice bath. Diethyl oxalate (0.73 g, 5 mmol, Aldrich) was added, followed after 5 min by ketone 138 or 142 (5 mmol), resulting in an immediate precipitate. After a further 10 min, the solution was acidified (10% HCl), extracted with ethyl acetate, the combined extracts dried,

filtered, concentrated and the product purified by chromatography (15% ethyl acetate petroleum ether) to afford 145, 1 g (90%), mp 65-67°C; or 189, 600 mg (62%), mp 60-62°C.

145 IR ($CHCl_3$): 1760 (m), 1725 (s), 1700 (w), 1660 (s), 1625 (w), 1600 (w) cm^{-1}

'H NMR ($CDCl_3$): δ = 11.80 ppm (1H, bs, enol), 4.33 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.38 ppm (2H, bs, $(C=C)_2-CH_2$), 2.48 ppm (6H, m), 1.38 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 223(12) $M^+ + 1$, 222(13), 194(4) - Et, 149(100) - COOEt, 121(31) - COCOOEt.

189 IR ($CHCl_3$): 1740 (m), 1720 (s), 1660 (s), 1610 (w) cm^{-1}

'H NMR ($CDCl_3$): δ = 12.32 ppm (1H, bs, enol), 6.06 ppm (1H, bs, HC=C), 4.28 ppm (2H, q, J = 7 Hz, CH_2CH_3), 3.37 ppm (2H, bs, $(C=C)_2-CH$), 2.20 mmp (3H, s, CH_3CO), 1.37 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 197(9) $M^+ + 1$, 196(10), 168(3) - CO, 123(100) - COOEt, 95(55) - COCOOEt.

5-Formyl-3-methyl-2-cyclopentenone (189) and $\Delta^{1,5}$-3-formyl bicyclo[3.3.0]octen-2-one (150)

A sodium ethoxide solution (prepared from sodium, 0.35 g, 15 mmol BDH, and dry ethanol, 5.1 mL, 90 mmol) was dissolved in ether (20 mL), and cooled to 0°C with an external ice bath. A mixture of ethyl formate (1.3 mL, 16.5 mmol, Aldrich) and ketone 138 or 142 (15 mmol) in ether (5 mL) was added, resulting in an immediate precipitate. After stirring for 30 min, the solution was acidified (10% HCl), extracted with ethyl acetate, the combined extracts dried, filtered, concentrated and purified by chromatography (20% ethyl acetate - petroleum ether) to afford 150, 1.3 g (58%), mp 120°-122°C;

or 189, 830 mg (45%), mp 70-80°C.

150, IR (Nujol): 2800-2600 (w, enol), 1705 (s), 1700 (m) 1615 (s), 1560 (m) cm^{-1}

'H NMR ($CDCl_3$): δ = 7.70, 7.22, 7.0 ppm (1H, bs:s:s, enol), 2.98 ppm (2H, bs, $(C=C)_1-CH_2$), 2.40 ppm (6H, bs)

MS (m/z, relative % intensity): 151(12) $M^+ + 1$, 150(100), 122(59) - CO, 94(90), 93(40) - COCHO

Exact Mass calculated for $C_9H_{10}O_2$: 150.0680, observed: 150.0680.

189, IR (Nujol): 3300-3500 (enol), 1700 (s), 1695 (s), 1620 (m) cm^{-1}

'H NMR ($CDCl_3$): δ = 9.72, 8.80, 7.10, 6.02, 5.84 ppm (3H, s, bs, s, bs, bs, representing aldehyde, enol, olefinic protons, 1:3:3:2:2), 3.03 ppm (2H, bs, $(C=C)_2CH_2$), 2.12 ppm (3H, bs, $CH_3-C=C$)

MS (m/z, relative % intensity): 125(22) $M^+ + 1$, 124(55), 96(100) - CO, 95(68) - CHO, 67(59) - COCH).

Exact Mass calculated for $C_7H_8O_2$: 124.0522, observed 124.0526.

General Acylation Procedures

(1) Potassium Hydride (KH), Procedure A: Cyclohexanone (153) (0.490 g, 5 mmol, Aldrich) in diethyl ether (10 mL) was added dropwise over 20 min to a stirred mixture of potassium hydride (1.25 g, 11 mmol, 35% oil dispersion, Aldrich) in refluxing ether (15 mL) under nitrogen. After an additional 0.5 h the reaction mixture was cooled to -78°C and diethyl pyrocarbonate (DEPC, 0.890 g, 5.5 mmol, Aldrich) in ether (2 mL) added in one aliquot. After 1 h at -78°C aqueous 10% HCl (30 mL) was added, the reaction was allowed to warm to 22°C, extracted with ether, the combined ether extracts washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography on silica gel (400-230 mesh, 5% ether-petroleum ether) afforded 1-cyclo-

hexenyl ethyl carbonate (154) 9.820 g (98%).

IR (neat): γ = 1753, 1695 cm^{-1}

'H NMR (CCl_4): δ = 1.30 (t, 3H, CH_2CH_3, J = 7 Hz), 1.70 (m, 4H, CH_2CH_2), 2.10 (m, 4H, CH_2CH_2), 4.20 (q, 2H, $-OCH_2CH_3$, J = 7 Hz), 5.38 (br s, 1H, HC=C-O).

(2) Potassium t-Butoxide (KOtBu), Procedure A: Cyclopentanone (104) (0.420 g, 5 mmol, Aldrich) was added dropwise over 20 min to a stirred mixture of potassium t-butoxide (0.615 g, 5.5 mmol) in ether at -78°C under nitrogen. After an additional 0.5 h at -78°C aqueous 10% HCl (30 mL) was added and the reaction worked up as above to give 1-cyclopentenyl ethyl carbonate (156) 0.410 g (52%).

IR (neat): γ = 1758, 1688 cm^{-1}

'H NMR (CCl_4): δ = 1.27 (t, 3H, CH_2CH_3, J = 7 Hz); 1.6-2.6 (m, 6H, $CH_2CH_2CH_2$); 4.13 (q, 2H, OCH_2CH_3, J = 7 Hz); 5.32 (br s, 1H, HC=C-O).

(3) Potassium t-Butoxide (KOtBu), Procedure B: Cyclopentanone (104) (0.420 g, 5 mmol) and DEPC (1.20 g, 7.5 mmol) was dissolved in ether (2 mL) and added dropwise over 5 min to a stirred mixture of potassium t-butoxide (0.615 g, 5.5 mmol) in ether at -78°C under nitrogen. After 1 h at -78°C aqueous 10% HCl (30 mL) was added and the reaction worked up as above to give 1-cyclopentenyl ethyl carbonate (156) 0.480 g (62%).

(4) Potassium Hydride (KH), Procedure B: Cyclohexanone (153) (0.490 g, 5 mmol, Aldrich) in benzene (2 mL) containing DEPC (1.22 g, 7.5 mmol) was added rapidly (1 min) to a stirred mixture of potassium hydride (1.25 g, 11 mmol, 35% oil dispersion, Aldrich) in refluxing benzene (15 mL) under nitrogen. After an additional 0.5 h the reaction mixture was cooled in an ice bath, aqueous 10% HCl (30 mL) added and the reaction allowed to warm to 22°C to give after work up as above and flash chromatography (5% ether-

petroleum ether) 2-carboethoxycyclohexanone (155) 0.602 g (72%).

IR (neat): γ = 1740, 1722, 1660, 1620 cm^{-1}

'H NMR (CCl_4): δ = 1.31 (t, 3H, CH_2CH_3, J = 7 Hz); 1.61 (m, 4H, CH_2CH_2); 2.10 (m, 4H, CH_2CH_2); 4.20 (q, 2H, $-OCH_2CH_3$, J = 7 Hz); 12.12 (s, 1H, HO-C=CCO).

(5) Potassium Hydride (KH), Procedure B: Cyclopentanone (104) (0.420 g, 5 mmol, Aldrich) in benzene (2 mL) containing DEPC (1.22 g, 7.5 mmol) was added rapidly (1 min) to a stirred mixture of potassium hydride (1.25 g, 11 mmol, 35% oil dispersion, Aldrich) in refluxing benzene (15 mL) under nitrogen. After an additional 0.5 h the reaction mixture was cooled in an ice bath, aqueous 10% HCl (30 mL) added and the reaction allowed to warm to 22°C to give after work up as above and flash chromatography (5% ether-petroleum ether) 2-carboethoxycyclopentanone (105) 0.472 g (61%)

IR (neat): γ = 1765, 1735, 1660 (w), 1620 (w) cm^{-1}

'H NMR (CCl_4): δ = 1.23 (t, 3H, CH_2CH_3, J = 7 Hz); 2.22 (m, 6H, CH_2); 3.02 (br t, 1H, CO-CH-CO); 4.14 (q, 2H, $-OCH_2CH_3$, J = 7 Hz).

(6) Lithium Dicyclohexylamide ($LiNCy_2$), Procedure A: 3-Methyl-2-cyclohexenone (157) (0.550 g, 5 mmol, Aldrich) in ether (10 mL) was added dropwise over 20 min to a stirred solution of lithium dicyclohexylamide ($LiNCy_2$, prepared from 4.2 mL of n-butyllithium (2.5 M, 10.5 mmol, Aldrich), dicyclohexylamine (2.15 mL, 11 mmol)) in ether (15 mL) at -78°C under nitrogen. After an additional 0.5 h DEPC (0.890 g, 5.5 mmol) in ether (2 mL) was added in one aliquot. After 1 h at -78°C the reaction was quenched with aqueous 10% citric acid (10 mL) allowed to warm to 22°C to give after work up as above and flash chromatography (15% ether-petroleum ether) 6-carboethoxy-3-methyl-2-cyclohexenone (158) 0.530 g (58%).

IR (neat): γ = 1740, 1670, 1630 cm^{-1}

'H NMR (CCl_4): δ = 1.21 (t, 3H, CH_2CH_3, J = 7 Hz): 1.90 (s, 3H, $=CCH_3$); 2-2.4 (m, 4H); 3.21 (m, 1H, CO-CH-CO); 4.10 (q, 2H, OCH_2CH_3, J = 7 Hz); 5.70 (br s, 1H, =CH).

(7) Lithium Dicyclohexylamide ($LiNCy_2$), Procedure B: 3-Methyl-2-cyclohexenone (157) (0.550 g, 5 mmol) in ether (10 mL) containing DEPC (1.2 g, 7.5 mmol) was added rapidly (5 min maximum) to a stirred solution of lithium dicyclohexylamide ($LiNCy_2$, prepared from 4.2 mL of n-butyllithium (2.5 M, 10.5 mmol, Aldrich), dicylcohexylamine (2.15 mL, 11 mmol)) in ether (15 mL) at -78°C under nitrogen. After 1 h at -78°C the reaction was quenched with aqueous 10% citric acid (10 mL) allowed to warm to 22°C to give after workup as above and flash chromatography (15% ether-petroleum ether) 6-carboethoxy-3-methyl-2-cyclohexenone (158) 0.580 g (64%).

(8) Lithium Dicyclohexylamide ($LiNCy_2$), Procedure B: 3-Methyl-2-cyclopentenone (142) (0.480 g, 5 mmol) in ether (10 mL) containing DEPC (1.2 g, 7.5 mmol) was added rapidly (5 min maximum) to a stirred solution of lithium dicyclohexylamide ($LiNCy_2$, prepared from 4.2 mL of n-butyllithium (2.5 M, 10.5 mmol, Aldrich), dicyclohexylamine (2.15 mL, 11 mmol)) in ether (15 mL) at -78°C under nitrogen. After 1 h at -78°C the reaction was quenched with aqueous 10% citric acid (10 mL) allowed to warm to 22°C to give after work up as above and flash chromatography (15% ether-petroleum ether) 5-carboethoxy-3-methyl-2-cyclopentenone (159) 0.590 g (71%).

IR (neat): γ = 1730, 1690, 1615 cm^{-1}

'H NMR (CCl_4): δ = 1.27 (t, 3H, CH_2CH_3, J = 7 Hz); 2.19 (br s, 3H, $=CCH_3$); 2.80 (m, 2H, CH_2-C=); 3.31 (m, 1H, CO-CH-CO); 4.12 (q, 2H, OCH_2CH_3, J = 7 Hz); 5.80 (br s, 1H, =CH).

MS (m/z, relative % intensity): 169(28) M^+ + 1, 123(64) - OEt, 96(100) - HCOOEt.

Exact Mass calculated for $C_9H_{12}O_3$: 168.0783, observed: 168.0787.

(9) Lithium Dicyclohexylamide ($LiNCy_2$), Procedure B: 3-Methyl-2-cyclopentenone (142) (9.60 g, 100 mmol) in ether (50 mL) containing DEPC (24.3 g, 150 mmol) was added rapidly (5 min maximum) to a mechanically stirred solution of lithium dicyclohexylamide ($LiNCy_2$), prepared from 21 mL of n-butyllithium (2.5 M, 200 mmol, Aldrich), dicyclohexylamine (41.8 mL, 210 mmol) in ether (200 mL) at -78°C under nitrogen. After 1 h at -78°C the reaction was quenched with aqueous 20% citric acid (100 mL) allowed to warm to 22°C, extracted with ether, the combined ether extracts washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Distillation of the residual DEPC and keto-ester (40-60°C/0.1 Torr) followed by flash chromatography (15% ether-petroleum ether) gave 5-carboethoxy-3-methyl-2-cyclopentenone (159) 7.56 g (45%).

(10) Lithium Dicyclohexylamine ($LiNCy_2$), Procedure B: $\Delta^{1,5}$-Bicyclo[3.3.0]oct-en-2-one (138) (0.610 g, 5 mmol) in ether (10 mL) containing DEPC (1.2 g, 7.5 mmol) was added rapidly (5 min maximum) to a stirred solution of lithium dicyclohexylamide ($LiNCy_2$, prepared from 4.2 mL of n-butyllithium (2.5 M, 10.5 mmol, Aldrich), dicyclohexylamine (2.15 mL, 11 mmol)) in ether (15 mL) at -78°C under nitrogen. After 1 h at -78°C the reaction was quenched with aqueous 10% citric acid (10 mL) allowed to warm to 22°C to give after work up as above and flash chromatography (15% ether-petroleum ether) $\Delta^{1,5}$-3-carboethoxybicyclo-[3.3.0]octen-2-one (160) 0.760 g (78%).

IR (neat): γ = 1735, 1700, 1640 cm^{-1}

'H NMR (CCl_4): δ = 1.28 (t, 3H, CH_2CH_3, J = 7 Hz); 2.1-2.9 (m, 8H); 3.61 (br t, 1H, J = 5 Hz, CO-CH-CO); 4.18 (q, 2H, OCH_2CH_3, J = 7 Hz).

MS (m/z, relative % intensity): 195(100) M^+ + 1, 194(39), 149(73) - OEt, 120(86) - HCOOEt.

Exact Mass calculated for $C_{11}H_{14}O_3$: 194.0939, observed: 194.0931.

UV (λ max (log ε)): 245 (3.6).

The same procedure employing dimethyl pyrocarbonate in place of DEPC afforded $\Delta^{1,5}$-3-carbomethoxybicyclo[3.3.0]octen-2-one (161) in 46% yield.

IR (neat): γ = 1745, 1710, 1640 cm^{-1}

^1H NMR (CCl_4): δ = 2.1-2.9 (m, 8H); 3.59 (m, 1H, CO-CH-CO); 3.63 (s, 3H, OCH_3).

(11) Lithium Dicyclohexylamide ($LiNCy_2$), Procedure B: $\Delta^{1,5}$Bicyclo[3.3.0]-octen-2-one (138) (4.88 g, 40 mmol) in ether (20 mL) containing DEPC (9.7 g, 60 mmol) was added rapidly (5 min maximum to a mechanically stirred solution of lithium dicyclohexylamide ($LiNCy_2$, prepared from 8.6 mL of n-butyllithium (9.5 M, 80 mmol, Aldrich), dicyclohexylamine (18 mL, 88 mmol)) in ether (70 mL) at -78°C under nitrogen. After 1 h at -78°C the reaction was quenched with aqueous 20% citric acid (100 mL) allowed to warm to 22°C, extracted with ether, the combined ether extracts washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Distillation of the residual DEPC and the keto-ester (40-60°C/0.1 Torr) followed by flash chromatography (15% ether-petroleum ether) gave $\Delta^{1,5}$-3-carboethoxybicyclo-[3.3.0]octen-2-one (160) 5.58 g (72%).

Alkylation of the 5-carboxy-2-cyclopentenone derivatives 189 and 190, Method A

5-Carboxy-2-cyclopentenone (5 mmol) was added to a sodium ethoxide solution (prepared from sodium, 5 mmol, BDH and dry ethanol, 30 mmol) in ether (4 mL), at 20°C, resulting in an immediate precipitate. The reaction mixture was lowered into an oil bath (75-80°C), dimethyl sulfoxide (10 mL) added, followed by the alkyl halide (6 mmol of 131a or 10 mmol of 131b), and stirring continued for 2 h. The solution was then cooled (0°), acidified

(10% HCl) and extracted with ethyl acetate. The combined extracts washed with brine, dried, filtered, concentrated and the product purified by chromatography (ether-petroleum ether).

Yields of various reactions are reported in Table 7, 'H NMR spectral data in Tables 8 and 11, IR data in Tables 9 and 12, and MS results in Tables 10 and 13.

Alkylation of the 5-carboxy-2-cyclopentenone derivatives 189 and 190, Method B

5-Carboxy-2-cyclopentenone (5 mmol) in t-butyl alcohol (2 mL) was added to a potassium-t-butoxide solution (prepared from potassium, 0.01 mmol, BDH and t-butyl alcohol 4 mL, in ether, 2 mL, Fisher), at 20°C. The activated diene 144b (10 mmol) in t-butyl alcohol (2 mL) was added at a rate that kept the temperature of the reaction constant (20°C). After stirring for 16 h, the reaction was cooled (0°) and acidified (1% HCl). After extraction of the aqueous layer with ethyl acetate, the combined extracts were washed with brine, dried, filtered, concentrated and the product purified by chromatography (ether-petroleum ether).

Yields are reported in Table 7, 'H, NMR, IR and MS data are reported in Tables 8 to 13.

$\Delta^{1,5}$-3-Carboethoxy-3-methylbicyclo[3.3.0]octen-2-one

Prepared by alkylation of 160 (R_1 = OEt, R_4 = Me) by the previously described Method A (82%).

IR: 1740 (CO), 1705 (CO), 1640 C=C) cm^{-1}

'H NMR (CCl_4): δ = 4.13 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 2.45 ppm (8H, bs), 1.33 ppm (3H, s, CH_3), 1.23 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 208(28), 180(59) - CO, 135(92) - COOEt,

Table 7

Yields Obtained in Various Alkylations of 189 and 190

Starting material	R_1 R_4 = H	Method	Product	R_2	R_3	% Yield
190	COOEt	A	192	COOMe	COOMe	90
189	COOEt	A	191	COOMe	COOMe	62
189	H	A	191	COOMe	COOMe	58
189	H	A	192	COOMe	COOMe	45
189	OEt	A	192	H	COOEt	76
190	OEt	A	192	COOMe	COOMe	65
190	OMe	A	192	H	COOEt	45
190	OEt	B	192	H	COOEt	86
189	OEt	B	191	H	COOEt	90
190	OEt	C	190	R_4 = Me		82
190	OEt	D	190	R_4 =		75-95[a]
190	OEt	D	190	R_4 =		40-95[a]

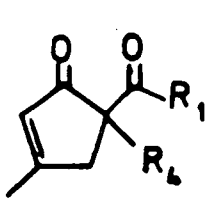
a: See text (Chapter 3) for variation in yield.

Method A: alkylation using 131

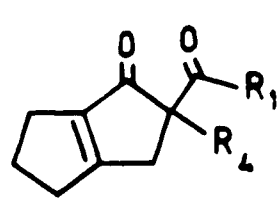
Method B: alkylation using 144

Method C: alkylation using methyl iodide (MeI)

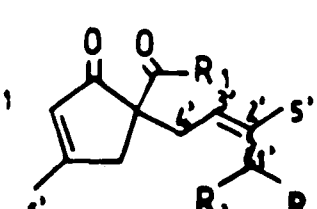
Method D: alkylation using methyl vinyl ketone (CH_2=$CHCOCH_3$)



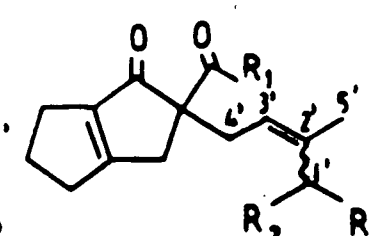
189



190



191



192

Table 8

60 MHz 'H NMR Spectral Data Related to 192

	R_1	R_2	R_3	H-2'	3H-5'	H-4'	R_1	R_2	R_3
1)	H	COOMe	COOMe	5.22 (t, 7)	1.80 (s)	4.04 (s)	9.50 (s)	3.72 (s)	3.72 (s)
2)	OEt	COOMe	COOMe	5.18 (t, 7)	1.78 (bs)	3.93 (s)	1.27 (t, 7) 4.14 (q, 7)	3.70 (s)	3.70 (s)
3)	COOEt	COOMe	COOMe	5.04 (t, 7)	1.68 (bs)	3.83 (s)	1.27 (t, 7) 4.15 (q, 7)	3.70 (s)	3.70 (s)
4)	OEt	H	COOEt	5.06 (t, 7)	1.72 (bs)		1.14 (t, 7) 4.06* (q, 7)		1.14 (t, 7) 4.11* (q, 7)
5)	OMe	H	COOEt	5.01 (t, 7)	1.73 (bs)		3.66 (s) 3.68 (s)		1.18 (t, 7) 4.04 (q, 7)

- Numbers in Table represent the chemical shift (δ in ppm).
- Parentheses indicate the multiplicity and the coupling constants (in Hz).

* Values are interchangeable.

Table 9

IR Spectral Data Related to 192

	R_1	R_2	R_3	bands (cm^{-1})
1)	H	COOMe	COOMe	1745 (s), 1700 (s), 1630 (m)
2)	OEt	COOMe	COOMe	1745 (s), 1700 (s), 1640 (m)
3)	COOEt	COOMe	COOMe	1740 (s), 1700 (s), 1640 (m)
4)	OEt	H	COOEt	1745 (s), 1705 (s), 1645 (m)
5)	OMe	H	COOEt	1745 (s), 1700 (s), 1635 (m)

Table 10

MS Results Related to 192

	R_1	R_2	R_3	m/z (relative % intensity)
1)	H	COOMe	COOMe	335(4) $M^+ + 1$, 334(5), 305 (12) - CHO, 150(100)[a]
2)	OEt	COOMe	COOMe	378(2), 316(3) - COOMe, 305(7) - COOEt, 194(112)[a]
3)	OEt	H	COOEt	335(11) $M^+ + 1$, 334(4), 288(7) - EtOH, 261(48) - COOEt, 215(50) - COOEt - EtOH, 194 (100)[b]
4)	OMe	H	COOEt	321(3) $M^+ + 1$, 288(6) - MeOH, 261(20) - COOMe, 215(33) - COOMe - MeOH, 180(100)[b]

a - $C_9H_{14}O_4$, -186 (rearrangement with loss of side chain).

b - $C_8H_{12}O_2$, - 140 (rearrangement with loss of side chain).

151, entry 1: Exact Mass calculated for $C_{18}H_{22}O_6$: 334.1410, observed: 334.1407.

162, entry 2: Exact Mass calculated for $C_{20}H_{26}O_7$: 378.1671, observed: 378.1725.

entry 3: Exact Mass calculated for $C_{19}H_{26}O_5$: 334.1694, observed: 334.1792.

Table 11

60 MHz 'H NMR Spectral Data Related to 191

	R_1	R_2	R_3	H-2	3H-6'	H-2'	3H-5'	H-4'	R_1	R_2	R_3
1)[a]	COOEt	COOMe	COOMe	5.73 (bs)	2.00 (bs)	5.08 (t, 7)	1.58 (bs)	3.73 (s)	1.08 (t, 7) 4.06 (q, 7)	3.67 (s)	3.62 (s)
2)	H	COOMe	COOMe	5.68 (bs)	2.12 (bs)	5.06 (t, 7)	1.68 (bs)	3.80 (s)	9.60 (s)	3.68 (s)	3.68 (s)
3)	OEt	H	COOEt	5.72 (bs)	2.12 (bs)	5.00 (t, 7)	1.70 (bs)	2.86 (bs)	1.22[b] (t, 7) 4.02 (q, 7)		1.26[b] (t, 7) 4.05 (q, 7)

- Numbers in Table represent the chemical shift (δ in ppm).
- Parentheses indicate the multiplicity and the coupling constants (in Hz).

a tosylhydrazone derivative

b values are interchangeable.

Table 12

IR Spectral Data Related to 191

	R_1	R_2	R_3	bands (cm^{-1})
1)[a]	COOEt	COOMe	COOME	1740 (s), 1700 (s), 1625 (m), 1600 (w)
2)	H	COOMe	COOMe	1740 (s), 1705 (s) 1620 (m)
3)	OEt	H	COOEt	1740 (s), 1710 (s), 1630 (m)

a tosylhydrazone derivative

Table 13

MS Results Related to 191

	R_1	R_2	R_3	m/z (relative % intensity)
1)[a]	COOEt	COOMe	COOMe	549(12) $M^+ + 1$, 531(8) - CH_3, 489(5) - COOMe, 393(30) - $C_6H_6SO_2$ - CH_3
2)	OEt	COOMe	COOMe	352(3), 321(6) - OMe, 288(10) - 2MeOH, 168(100) - side chain, $C_9H_{12}O_4$
3)	OEt	H	COOEt	309(3) $M^+ + 1$, 262(5) - EtOH, 235(50) - COOEt

a tosylhydrazone derivative

Exact Mass for 188, entry 2: no parent ion, but base peak for $C_9H_{12}O_3$,
calculated: 168.0786, observed: 168.0811.

134(100) - HCOOEt

Exact Mass calculated for $C_{12}H_{16}O_3$: 208.1094, observed: 208.1091.

$\Delta^{1,5}$-3-Methylbicyclo[3.3.0]octen-2-one

Ketone 160 (350 mg, 1.68 mmol) was added to a solution of HCl (conc. 1 mL), water (1 mL) and methanol (1 mL). This reaction mixture was refluxed for 24 h. It was then cooled (0°C) and extracted with ether, the combined extracts dried, filtered and concentrated to afford $\Delta^{1,5}$-3-methylbicyclo-[3.3.0]octen-2-one, 160 mg (70%).

IR (heat): 1700 (CO), 1635 (C=C) cm^{-1}

'H NMR (CCl_4): δ 2.32 ppm (9H, bs), 1.11 ppm (3H, d, J = 7 Hz, CH_3CH)

MS (m/z, relative % intensity): 136(86), 121(100) - CH_3, 93(69) - CH_3 - CO.

Exact Mass calculated for $C_9H_{12}O$: 136.0885, observed: 136.0868.

Tosylhydrazone derivative of 151

p-Toluenesulfonylhydrazide (360 mg, 2 mmol, Aldrich) dissolved in methanol:water (5 mL, 7:3) was added to 151 (640 mg, 2 mmol) and stirred at 20° for 4 h. This solution was then extracted with ether, the combined extracts dried, filtered, and concentrated to afford the hydrazone derivative, 1 g (96%).

IR (neat): 3200 (NH), 1750 (s), 1700 (s), 1640 (m), 1605 (m) cm^{-1}

'H NMR ($CDCl_3$): δ = 9.0 ppm (1H, bs, NH), 7.80 ppm (2H, d, J = 8 Hz, aromatic), 7.30 ppm (2H, d, J = 8 Hz, aromatic), 5.10 ppm (1H, t, J = 7 Hz, HC=C), 3.92 ppm (1H, s, $CH(COOMe)_2$), 3.75 ppm (6H, s, COOMe), 1.70 ppm (3H, bs, CH_3C=C)

MS (m/z, relative % intensity): 503(8) $M^+ + 1$, 443(6) - COOMe, 318(10) - side chain, $C_9H_{13}O_4$, 91(100).

Exact Mass calculated for $C_{25}H_{30}O_7N_2S$: 502.1765, observed: 502.1745.

Alcohols 146:

Sodium borohydride (1 mole - eq, BDH) was added to ketone (1 eq) in methanol, at 20°C. After stirring for 16 h, the solution was acidified (5% HCl) and extracted with ethyl acetate. The combined extracts dried, filtered and concentrated. In the case of ketone 145, sodium cyanoborohydride (1 eq, BDH) was used, and ammonium chloride (2 eq), in methanol or in aqueous acid (0.1 HCl) for hydrolysis. On one occasion the different alcohol isomers were separated by chromatography (ethylacetate - petroleum ether) before attempting the dehydrations. Later, the mixture was used (yields between 40 and 70%).

$\Delta^{1,5}$-3-ethoxalylbicyclo[3.3.0]octen-2-ol (146)

Same procedure as for previous alcohols (70%).

IR (neat): 3500 (OH), 1750 (CO), 1710 (CO), 1635 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 4.20 ppm (3H, m, OCH_2, CH(OH)), 3.30 ppm (2H, m, CH_2), 1.32 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 225(7) M^+ + 1, 224(5), 151(25) - COOEt, 123(10) - COCOOEt

Exact Mass calculated for $C_{12}H_{16}O_4$: 224.1044, observed: 224.1050.

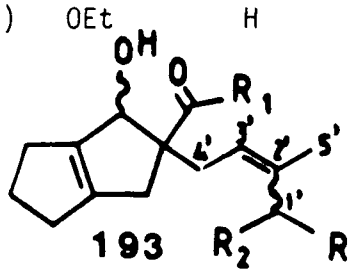
Trifluoroacetate of 146

1,5-diazabicyclo[5.4.0]undec-5-ene (0.04 mL, 0.27 mmol, 96%, Aldrich) was added to alcohol 146 (50 mg, 0.25 mmol), N,N-dimethyl aminopyridine (2 mg, Aldrich) and trifluoroacetic anhydride (0.04 mL, 0.27 mmol, Aldrich) in dichloromethane (5 mL), stirred at -78°C. The reaction was warmed to 0°C,

Table 14

60 MHz 'H NMR Spectral Data Related to 193[a]

	R_1	R_2	R_3	H-2'	H-1	3H-5'	H-4'	R_1	$R_{2,3}$
1)	COOEt	COOMe	COOMe	4.37 (s)	4.98 (m)	1.70 (bs)	3.88 (s)	1.30 (t, 7) 4.20 (m)	3.62 (s)
2)	H[b]	COOMe	COOMe	4.50 (m)	5.00 (t, 7)	1.70 (bs)	3.90 (s)	-	3.77 (s)
3)	OEt	COOMe	COOMe	4.70 (m)	5.36 (m)	1.76 (bs)	3.98 (s)	1.28 (t, 7) 4.12 (q, 7)	3.70 (s)
4)	OEt[c]	COOMe	COOMe		5.35 (t, 7)	1.75 (bs)	3.92 (s)	1.17 (t, 7) 4.07 (q, 7)	3.70 (s)
5)	OMe	H	COOEt	4.70 (m)	5.18 (m)	1.68 (bs)	2.87 (bs)	3.62 3.64 (s:s)	1.25 (t, 7) 4.08 (q, 7)
6)	OEt	H	COOEt	4.70 (m)	5.20 (m)	1.70 (bs)	2.90 (bs)	1.27 (t, 7) 4.08 (q, 7)	1.27 (t, 7) 4.08 (q, 7)



193

- Numbers in Table represent the chemical shift (δ in ppm).
- Parentheses indicate the multiplicity and the coupling constants (in Hz).

a Spectral data in Tables 14, 15, 16 for major isomer.

b Tosylhydrazone derivative.

c Tosylate derivative.

Table 15

IR Spectral Data Related to 193

	R_1	R_2	R_3	bands (cm^{-1})
1)	COOEt	COOMe	COOMe	3500 (w), 1750 (s), 1700 (s), 1640 (m)
2)	H[b]			3500 (m), 1750 (s), 1725 (s), 1670 (m), 1625 (m)
3)	OEt	COOMe	COOMe	3500 (m), 1760-1725 (s), 1630 (w)
4)	OEt[c]	COOMe	COOMe	3500 (m), 1750-1720 (s), 1630 (m)
5)	OMe	H	COOEt	3500 (m), 1750-1725 (s), 1640 (m)
6)	OEt	H	COOEt	3500 (m), 1730 (s)

Table 16

MS Results Related to 193

	R_1	R_2	R_3	m/z (relative % intensity)
1)	OEt	COOMe	COOMe	380(2), 362(2) - H_2O, 318(10) - 2OMe, 177(32) - sidechain, $C_9H_{13}O_4$
2)	OEt[c]	COOMe	COOMe	533(12) $M^+ + 1$, 474(5) - HCOOMe, 362(60) - HOTs, 316(80) - HOTs - EtOH
3)	OMe	H	COOEt	322(3), 288(8) - HOMe, 261(19) - COOMe, 180(100) - sidechain, $C_8H_{12}O_2$
4)	OEt	H	COOEt	264(14) - COOEt, 195(32) - sidechain, $C_8H_{13}O_2$

190, entry 3: Exact Mass calculated for $C_{18}H_{26}O_5$: 322.1695, observed: 322.1636.

in ~ 2 h, and ammonium chloride was added. The aqueous layer was separated and extracted with dichloromethane. The combined extracts were dried, filtered and concentrated to afford the product, 78 mg (98%).
IR (neat): 1800 ($CDCF_3$), 1750 (CO), 1700 (CO), 1630 (C=C) cm^{-1}
'H NMR (CCl_4): δ = 5.40 ppm (1H, d, J = 3 Hz, $CHCOCF_3$), 4.12 ppm (2H, q, J = 7 Hz, CH_2CH_3), 3.30 ppm (2H, bs, CH_2), 2.35 ppm (6H, bs), 1.20 ppm (3H, t, J = 7 Hz, CH_3CH_2).

$\Delta^{1,5}$-7-(3-methyl-4,4-dicarbomethoxy-2-butenyl)-10-oxatricyclo [6.3.0^{1,5}.0^{7,11}]undecen-8,9-dione (149)

Lactone 149 was separated from ketone 147 as the DNPH derivative after alkylation of 145. The lactone:ketone ratio was found to be ~ 1:4. The lactone 149 also separated from alcohol 148 upon reduction of ketone 147. The alcohol:lactone ratio in this case was found to be ~ 4:1.
149, IR (neat): 1750 (CO), 1700 (CO), 1640 (C=C) cm^{-1}
'H NMR (CCl_4): δ = 5.20 ppm (1H, t, J = 7 Hz, $CH(COOMe)_2$), 3.83 ppm (1H, s, CHO), 3.70 ppm (6H, s, CH_3OCO), 2.30 ppm (10H, bs), 1.68 ppm (3H, bs, CH_3C=C) no MS could be obtained on 149.

2,4-Dinitrophenylhydrazone derivative of 147

Ketone 147 (100 mg, 0.25 mmol) in methanol (1 mL) was added to a solution of 2,4-dinitrophenylhydrazine (55 mg, 0.27 mmol, Aldrich) in methanol (2 mL) and HCl (1 drop). A precipitate was instantaneously formed. It was filtered and purified by chromatography (25% petroleum ether - ether) to afford the hydrazone derivative 147, 90 mg (64%); and of 149, 40 mg (30%).
mp 146-148°C for the DNPH derivative of 147 and 158-160°C for 149

DNPH derivative of 147, IR (Nujol): 1760 (m), 1740 (s), 1700 (s), 1645 (m), 1620 (m), 1595 (m) cm^{-1}

'H NMR ($CDCl_3$): δ = 9.00 ppm (1H, d, J = 2 Hz), 8.40 ppm (1H, dd, J = 2,.10 Hz), 8.00 ppm (H, d, J = 10 Hz), 5.40 ppm (1H, t, J = 7 Hz, HC=C), 4.27 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 4.02 ppm (1H, s, $CH(COOMe)_2$), 3.73, 3.70 ppm (each, 3H, s, CH_3COO), 1.83 ppm (3H, bs, $CH_3C=C$), 1.27 ppm (3H, t, J = 7 Hz, CH_3CH_2)

no MS could be obtained (FAB or EI)

DNPH derivative of 149, IR (Nujol): 1755 (m), 1740 (m), 1600 (s), 1590 (m) cm^{-1}

'H NMR ($CDCl_3$): δ = 11.25 ppm (1H, bs, NH), 8.95 ppm (1H, d, J = 2 Hz), 8.23 ppm (1H, dd, J = 2, 10 Hz), 7.90 ppm (1H, d, J = 10 Hz), 5.48 ppm (1H, t, J = 7 Hz, HC=C), 4.08 ppm (1H, s, $CH(COOMe)_2$), 3.76 ppm (6H, s, CH_3OCO), 1.85 ppm (3H, bs, $CH_3C=C$)

no MS could be obtained (FAB or EI).

Tosylhydrazone derivative of "monocyclic" 147 (142 as starting material)

Ketone 142 (90 mg, 0.24 mmol) in methanol (1 mL) was added to a solution of p-toluenesulfonylhydrazide (45 mg, 0.24 mmol, Aldrich) in methanol (2 mL) and stirred at 15°C for 6 h. After concentration of the solution, the product was purified by chromatography (20% petroleum ether - ether) to afford the "monocyclic" hydrazone derivative 147, 100 mg (79%) and 149, 20 mg (18%). Tosylhydrazone of 147, IR ($CHCl_3$): 1740 (s), 1700 (s), 1630 (m), 1600 (w) cm^{-1}

'H NMR (CCl_4): δ = 7.74 ppm (2H, d, J = 8 Hz), 7.22 ppm (2H, d, J = 8 Hz), 7.02 ppm (1H, s), 5.73 ppm (1H, bs, HC=C), 5.08 ppm (1H, m, HC=C), 4.06 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.73 ppm (1H, s, $CH(COOMe)_2$), 3.62 ppm (6H, s,

COOMe), 2.00, 1.58 ppm (each, 3H, bs, $CH_3C=C$), 1.08 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 549(3) $M^+ + 1$, 447(2) - COCOOEt, 91(100).

Tosylhydrazone of 149 IR ($CHCl_3$): 1750-1680 (s), 1630 (m), 1605 (m) cm^{-1}

'H NMR (CCl_4): δ = 7.79 ppm (2H, d, J = 8 Hz), 7.24 ppm (2H, d, J = 8 Hz), 7.10 ppm (1H, s), 5.82 ppm (1H, bs, HC=C), 5.18 ppm (1H, m, HC=C), 3.89 ppm (1H, s, $CH(COOMe)_2$), 3.70 ppm (6H, s, COOMe)

MS (m/z, relative % intensity): 449(12) M^+ - 55, 417(5) - HOMe from 449, 389(8) - HCOOMe from 449, 293(28) - $C_7H_8SO_2$ from 449, 91(100).

$\Delta^{1,5}$-3-Hydroxymethyl-3-(3-methyl-4,4-dicarbomethoxy-2-butenyl) bicyclo[3.3.0]octen-2-ol

This alcohol was prepared by reduction of 151, using sodium borohydride in methanol as described previously.

IR (neat): 3500-3400 (OH), 1735 (CO) cm^{-1}

'H NMR ($CDCl_3$): 5.22 ppm (2H, m, CH-(OH) and CHC=C), 4.92 ppm (1H, s, $CH(COOMe)_2$), 3.68 ppm (6H, s, CH_3OCO), 3.35 ppm (2H, bs, CH_2OH), 1.70 ppm (3H, bs, $CH_3C=C$)

MS (m/z, relative % intensity): 338(5), 302(12) - $2H_2O$, 185(20) side chain, $C_9H_{13}O_4$.

3-Carboethoxy-3-(3-methyl-4,4-dicarbomethoxy-2-butenyl) bicyclo[3.3.0]octadiene (164) or (194)

Alcohol 163 was dehydrated using several methods.

a) Tosylation method

Alcohol 163 (760 mg, 2 mmol) was added to THF (2 mL) containing p-toluenesulfonyl chloride (380 mg, 2 mmol, Aldrich), pyridine (0.4 mL,

5 mmol) and N,N-dimethylaminopyridine (10 mg, Aldrich). The solution was stirred at ~ 20°C for 16 h, acidified (10% HCl) and extracted with ether. The combined extracts were dried, filtered, concentrated and the products purified by chromatography (ether - petroleum ether), to afford the tosylate derivative, 685 mg (68%) and a dehydrated product 164 (or diene isomer), 40 mg (5%).

b) Hydrochloric acid method

Alcohol 163 (100 mg, 0.26 mmol) was added to a chloroform (5 mL) solution into which hydrogen chloride (Fisher) had been bubbled for 10 min. This mixture was stirred at 20°C for 2 h. It was then poured into a cold sodium bicarbonate solution, and the aqueous layer extracted with chloroform. The combined extracts dried, filtered, concentrated and purified by chromatography (10% ether - petroleum ether) to afford product 164 (or diene isomer), 55 mg (60%).

c) Burgess reagent method

Alcohol 163 (190 mg, 0.5 mmol) in benzene (1 mL) was added to methyl (carboxysulfamoyl)triethylammonium hydroxide inner salt ($Et_3N^+SO_2^-NCOOMe$, preparation based on the procedure of Burgess and Penton[146c], 150 mg, 0.55 mmol) in benzene (1 mL). The reaction mixture was heated to 50°C for 1 h. It was then cooled and added to water. The aqueous layer was extracted with ether, the combined extracts dried, filtered, concentrated and purified by chromatography (10% ether - petroleum ether), to afford product 164 (or diene isomer), 50 mg (30%)

d) Methanesulfonylchloride method

Gaseous sulfur dioxide (Fisher) was bubbled into a dichloromethane (1 mL) solution containing methanesulfonyl chloride (0.48 mL, 6 mmol, Aldrich) for 10 min, and added to alcohol 163 (200 mg, 0.6 mmol), pyridine

(0.56 mL, 7.2 mmol), N,N-dimethylaminopyridine (2 mg, Aldrich) dissolved in dichloromethane (3 mL). The solution was stirred at 20°C for 1 h, cooled to 0°C and water added. It was then extracted with dichloromethane, and the combined extracts were dried, filtered, concentrated and purified by chromatography (8 to 30% ether - petroleum ether) to afford 164 (or diene isomer), 130 mg (70%). This procedure was also used omitting the sulfur dioxide.

Decarboxylation of 164

A solution of 164, (80 mg, 0.24 mmol) in toluene (2.0 mL), was heated in a sealed tube with tetramethylethylenediamine (80 mg, 0.69 mmol, Aldrich) to 180-190°C, for 96 h. The solution was then concentrated and the product purified by chromatography (12% ether - petroleum ether), to afford 164, 20 mg (25%).

IR (neat): 1730-1725 (CO) cm^{-1}

^1H NMR (CCl_4): δ = 5.30 ppm (2H, m, olefinic signals), 4.11 ppm (2H, q, 7 Hz, OCH_2CH_3), 3.62 ppm (3H, s, CH_3OCO), 1.68 ppm (3H, bs, $CH_3C{=}C$), 1.26 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 304(9), 258(7) - HOEt, 231(42) - COOEt, 177(100) - sidechain, $C_8H_{13}O_2$.

Exact Mass calculated for $C_{18}H_{24}O_4$: 304.1668, observed: 304.1672.

UV (λ max (log ε)): 215 (3.4), 250 (3.2)

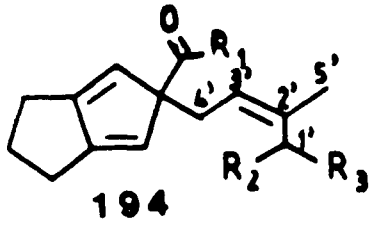
Ethyl 5-chloro-3-methyl-2-pentenoate (144a)

a) Ethynyl ether (18.5 g, 0.26 mmol, Farchan, freshly distilled, bp 49-50°C) in THF (50 mL) was added to methylmagnesium chloride (8.3 mL, 0.24 mol, 2.99 M, Aldrich) dissolved in THF (250 mL) at 22°C. The resulting mixture

Table 17

H' NMR Spectral Data Related to 194 (isomers) or 164

Dehydration Method	R_1	R_2	R_3	3 olefins ratio:δ	3H-5'	H-4'	R_1	R_2, R_3
(a)	OEt	COOMe	COOMe	1:5.77 (bs) 4:5.36 (m)	2.02 (s) 1.75 (bs)	4.27 (s)	1.24 (t, 7) 4.46 (q, 7)	3.70 (s)
(b)	OEt	COOMe	COOMe	2:6.22 (bs) 4:5.77 (bs) 11:5.21 (m)	1.68 (bs)	3.85 (s)	1.22 (t, 7) 4.02 (q, 7)	3.66 (s)
(b)	OEt	H	COOEt	1:6.20 (s) 2:5.72 (bs) 4:5.18 (m)	1.64 (bs) 1.69 (bs)	3.50 (s)	1.18 (t, 7) 4.03* (q, 7)	1.18 (t, 7) 3.98* (q, 7)
(c)	OEt	COOMe	COOMe	1:5.69 (bs) 8:5.18 (m)	1.67 (bs)	3.68 (s)	1.18 (t, 7) 4.06 (q, 7)	3.65 (s)
(d)	OEt	H	COOEt	1:5.62 (bs) 3:5.22 (m)	1.64 (bs)	-	1.20 (t, 7) 4.02 (q, 7)	1.20 (t, 7) 4.02 (q, 7)



194

- Numbers in Table represent the chemical shift (δ in ppm)
- Parentheses indicate the multiplicity and the coupling constants (in Hz).

* values are interchangeable

Table 18

IR Spectral Data Related to 194

R_1	R_2	R_3	bands (cm^{-1})
OEt	COOMe	COOMe	1755-1730 (COO)
OEt	H	COOEt	1725 (COO)

Table 19

MS Results Related to 194

	R_1	R_2	R_3	m/z (relative % intensity)
1)	OEt	COOMe	COOMe	362(3), 289(8) - COOEt, 177(100) - side chain, $C_9H_{13}O_4$
2)	OEt	H	COOEt	318(6), 244(13) - HCOOEt, 177(100) - side chain, $C_8H_{13}O_2$

was stirred for 0.5 h, 4-chlorobutanone (14 g, 0.13 mol) in THF (10 mL) was added over 5 min and stirring continued for a further 20 h at 22°C. The reaction mixture was cooled to 0°C and water was added dropwise, until gas evolution ceased. Then, the mixture was filtered through Celite. The organic layer was separated and the aqueous layer extracted with ether. The combined extracts dried, filtered, concentrated and the product purified by chromatography (5% ether - petroleum ether), to give 168 as an orange oil, 20 g (88%).

IR (neat): 33-3500 (OH), 2250 (C≡C) cm^{-1}.

'H NMR (CCl_4): δ = 4.08 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.60 ppm (2H, m, CH_2Cl), 3.04 ppm (1H, s, OH), 1.96 ppm (2H, m, $CH_2C(OH)$), 1.48 ppm (3H, s, $CH_3C(OH)$), 1.38 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 176(6), 113(45) - OEt - H_2O, 85(100)

Exact Mass calculated for $C_8H_{13}O_2Cl$: 176.06005, observed: 176.0604.

b) 4-chloro-2-ethynyl ether 2-butanol (20 g, 0.11 mol) in ethanol (20 mL) was added dropwise to 5% sulfuric acid - ethanol (20 mL), kept at 0°C. After addition was complete, the reaction mixture was stirred for 20 h at 0 to 10°C. Water was then added to the solution, and the product extracted with ether. The combined ether extracts were washed with sodium bicarbonate, dried, filtered, concentrated and the product purified by chromatography (as above) to afford 144a, 15 g (75%) which could be further purified by distillation.

bp 65-68°C/0.5 Torr

IR (neat): 1710 (CO), 1655 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 5.70 ppm (1H, bs, HC=C), 4.10 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.63 ppm (2H, t, J = 7 Hz, CH_2Cl), 3.02 and 2.67 ppm (2H, t:t, 1:1, J = 7 Hz, 2:E, CH_2-C=), 2.18 and 1.99 ppm (3H, s:s, 1:1, $CH_3C=C$), 1.27 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 177(17) M^+ + 1, 176(17), 141(83) - Cl, 131(100) - OEt, 113(91) - OEt - H_2O.

4-Chloro-2-methyl-1,1-dicarbomethoxy-1-butene 131b

Titanium tetrachloride (11 mL, 0.10 mol, BDH) and CCl_4 (25 mL) were slowly added (45 min) to a 1 L three neck flask equipped with a mechanical stirrer, condenser and dropping funnel. After addition was complete, a yellow precipitate was present. Then, 4-chlorobutanone (5.3 g, 0.05 mol) and dimethyl malonate (6.6 g, 0.05 mol, Eastman) were added dropwise over 15 min, followed by pyridine (16 g, Eastman, 0.2 mol) in THF (40 mL) over 30 min. The resulting dark orange solution was stirred at 20°C for 24 h. The reaction mixture was added to cold water, the organic layer separated and the aqueous layer extracted with ethyl acetate. The combined extracts were dried, filtered, and concentrated to afford 144b, 6.6 g (60%). This product was pure enough for further use. It could also be distilled, bp 96-98°C/0.3 Torr, 5.5 g (50%).

IR (neat): 1725 (CO), 1640 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 3.63 ppm (6H, s, COOMe), 3.58 ppm (2H, t, J = 7 Hz, CH_2Cl), 2.76 ppm (2H, t, J = 7 Hz, CH_2C=), 1.98 ppm (3H, s, CH_3C=)

MS (m/z, relative % intensity): 221(2), 188(5) - MeOH, 153(28) - MeOH - HCl, 121(12) - 2MeOH - HCl.

Exact Mass calculated for $C_9H_{13}O_4Cl$ (M^+-MeOH): 188.0237, observed: 188.0223.

5-Carboethoxy-5(3-oxobutylethylenethioketal)-3-methyl-2-cyclopentenone

Ethanedithiol (50 mg, 0.55 mmol, Aldrich) and boron trifluoride etherate (2 drops, Aldrich) were added to 170 (100 mg, Aldrich, 0.42 mmol) dissolved in acetic acid (2 mL) at 20°C. The solution was stirred for 1 h, poured into cold water and the aqueous layer extracted with ethyl acetate. The combined extracts were washed with sodium bicarbonate, dried, filtered, concentrated and purified by chromatography (12% ethyl acetate-hexane) to afford the thioketal, 120 mg (70%).

IR (neat): 1750 (s), 1705 (s), 1630 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 5.75 ppm (1H, bs, CH=C), 4.12 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.22 ppm (4H, s, CH_2S), 2.18 ppm (3H, bs, CH_3C=C), 1.70 ppm (3H, s, CH_3-C($5CH_2$)$_2$), 1.22 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$)

MS (m/z, relative % intensity): 314(2), 168(28) - $C_6H_{10}S_2$, side chain, 119(100) - $C_6H_{10}S_2$, side chain, - CO.

5-Carboethoxy-5(3-oxobutylethylenethioketal)-3-methyl-2-cyclopentenol

Sodium borohydride (180 mg, 4.77 mmol, BDH) was added to the above product (1.5 g, 4.77 mmol) and cerous chloride ($CeCl_3.7H_2O$, 1.3 g, 4.77 mmol, BDH) dissolved in methanol (25 mL). The solution was stirred at 20°C for 30 min. It was then acidified (5% HCl) and extracted with ethyl acetate. The combined extracts washed, dried, filtered, concentrated and purified by chromatography (25% ethyl acetate-hexane) to afford the corresponding alcohol, 110 mg (76%).

IR (neat): 3500-3400 (OH), 1730 (CO), 1625 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 5.82 ppm (1H, bs, HC=C), 5.38, 4.78 ppm (1H, bs:bs, 1:1, CH(OH)), 4.13 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.27 ppm (4H, s, CH_2S), 2.20 ppm (3H, bs, CH_3C=C), 1.73 (3H, s, CH_3CO), 1.27 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 316(3), 298(8), 168(25), 119(100).

5-Hydroxymethyl-5(3-oxobutylethylenethioketal)-3-methyl-2-cyclopentenol

Prepared by lithium aluminum hydride reduction of the corresponding β-keto-ester, as described above (50%).

IR (neat): 3300-3500 (OH) cm^{-1}

'H NMR ($CDCl_3$): δ = 6.20 ppm (1H, m, HC=C), 4.8 ppm (1H, m, CH(OH)), 3.42 ppm (2H, bs, CH_2OH), 3.30 ppm (4H, s, CH_2S)

MS (m/z, relative % intensity): 256(13) M^+ - H_2O, 119 (100).

1-(3-Oxobutylethylenethioketal)-1-carboethoxy-4-methylcyclopentadiene

Prepared by the methanesulfonyl chloride dehydration method, of the corresponding alcohol (68%) as described above.

IR (neat): 1725 (CO), 1625 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 6.10 ppm (2H, m, olefins), 4.80 ppm (1H, m, olefin), 4.10, 4.06 ppm (2H, q:q, 1:1, J = 7 Hz, OCH_2CH_3), 3.75 ppm (4H, s, CH_2S), 3.27 ppm (3H, bs, CH_3C=C), 1.73 ppm (3H, s, $CH_3C(SCH_2)_2$), 1.25, 1.23 ppm (3H, t:t, 1:1, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 298(18), 225(6) - COOEt, 119(100).

Exact Mass calculated for $C_{15}H_{22}S_2O_2$: 298.1060, observed: 298.1038.

5-(3-Oxobutyl)-5-carboethoxy-3-methyl-2-cyclopentenone (170)

Prepared by alkylation of 142 as described previously, Method B. The amount of potassium-t-butoxide used was kept to a minimum catalytic amount (for example, for 20 mmol of ketone, 0.2 mmol of potassium). The yield of 170 depended on the catalytic amount of base (40 to 95%).

IR (neat): 1730 (s), 1700 (s), 1625 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 5.87 ppm (1H, bs, HC=C), 4.11 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 2.19 ppm (3H, bs, CH_3C=C), 2.10 ppm (3H, s, CH_3CO), 1.22 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 239(2) $M^+ + 1$, 238(1), 192(4) - HOEt, 168(46) - C_4H_6O, side chain, 43(100) - CH_3CO.

Product 171 endo-1-carboethoxy-4-methyl-5-acetylbicyclo[2.2.1]heptan-2-one was also obtained in varying amounts (0 to 50%).

IR (neat): 1775 (CO strained), 1725 (CO), 1625 (C=C) cm^{-1}

'H NMR ($CDCl_3$): δ = 4.21 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.03 ppm (1H, ddd, J = 2, 6, 12 Hz, H-5 exo), 2.21 ppm (3H, s, CH_3CO), 1.45 ppm (3H, s, CH_3-C-), 1.30 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 239(3) $M^+ + 1$, 238(3), 193(9) - OEt, 125(100) $C_7H_{10}O$.

Exact Mass calculated for $C_{13}H_{18}O_4$: 238.1200, observed: 238.1211.

UV (λ max (log ε)): 224 (3.3)

5-Carboethoxy-5-(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate) 3-methyl-2-cyclopentenone (172)

Prepared by Knoevenagal condensation (using 170) as described for 144b, except the reaction time was reduced to 12 h. Purification of the products by chromatography (20% to 50% ethyl acetate - petroleum ether) afforded 173 (7%), 172 (53%), 170 (12%).

172, IR (neat): 1750-1700 (CO), 1630 (C=C) cm^{-1}

^1H NMR (CCl_4): δ = 5.78 ppm (1H, bs, HC=C), 4.11 ppm (2H, q, 7 Hz, OCH_2CH_3), 3.72 ppm (6H, s, CH_3OCO), 2.22 ppm (3H, bs, $CH_3C=CH$), 2.03 ppm (3H, s, $CH_3C=C$), 1.23 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 352(2), 321(6) - OMe, 288(12) - HCOOMe, 168(100) $C_9H_{12}O_3$.

173, 6-carboethoxy-8-methyl-3-(dimethyl methylenedicarboxylate) bicyclo[4.3.0] nona-1,8-diene

IR (neat): 1740-1710 (CO), 1610, 1570 (C=C) cm^{-1}

^1H NMR (CCl_4): δ = 6.57 ppm (1H, s, HC=C), 6.03 ppm (1H, bs, HC=C), 4.07 ppm (2H, q, J = 7 Hz, OCH_2CH_3), 3.68 ppm (6H, s, CH_3OCO), 1.91 ppm (3H, bs, $CH_3C=C$), 1.23 ppm (3H, t, J = 7 Hz, CH_3CH_2)

MS (m/z, relative % intensity): 334(8), 302(18) - HOMe, 119(100), 117(100).

Exact Mass calculated for $C_{18}H_{22}O_6$: 334.1414, observed: 334.1196.

UV (λ max (log ε)): 226 (4.2)

5-Carboethoxy-5(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate) 3-methyl-2-cyclopentenol (174)

Sodium borohydride (12 mg, 0.31 mmol, BDH) was added to a methanol (10 mL) solution containing ketone 172 (100 mg, 0.28 mmol) and cerous chloride ($CeCl_3.7H_2O$, 115 mg, 0.31 mmol, BDH), and stirred at 20° for 1 h. The reaction mixture was then acidified (5% HCl), and extracted with ethyl-acetate. The combined extracts were washed, dried, filtered, concentrated, and the product purified by chromatography (25% ethyl acetate-hexane) to afford 174 65 mg (62% best yield).

IR (neat): 3300-3500 (OH), 1725 (CO), 1625 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 5.87 ppm (1H, bs, HC=C), 5.35, 4.90 ppm (1H, m, 1:1, CH(OH)), 4.20 ppm (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 3.78 ppm (6H, s, CH_3OCO), 2.27 ppm (3H, bs, $CH_3C{=}CH$), 2.08 ppm (3H, s, $CH_3C{=}C$), 1.29 ppm (3H, t, J = 7 Hz, $\underline{CH_3}CH_2$).

1-Carboethoxy-1(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate) 4-methyl cyclopentadiene (175)

Prepared by dehydration of 174 using the methanesulfonyl chloride method described above. The reaction was purified by chromatography (the mesylate derivative dehydrated on the column, 30% ether-petroleum ether) to afford 175 (53%).

IR (neat): 1725 (CO), 1635 (C=C) cm^{-1}

'H NMR ($CDCl_3$): δ = 6.10 ppm (2H, m, olefins), 4.80 ppm (1H, m, olefin), 4.07, 4.12 ppm (2H, q:q, 1:1, J = 7 Hz, $O\underline{CH_2}CH_3$), 3.65 ppm (6H, s, CH_3OCO), 2.01 ppm (3H, s, $CH_3C{=}C$), 1.82 ppm (3H, bs, $CH_3C{=}CH$), 1.23, 1.26 ppm (3H, t:t, 1:1, $\underline{CH_3}CH_2$)

MS (m/z, relative % intensity): 336(3), 304(5) - HOMe, 19 [(60), 91(100).

$\Delta^{2,3}$-5-Carboethoxy-9-dicarbomethoxy-2,8-dimethyl-tricyclo[4.3.0^{1,5}.0^{4,8}] nonene (176)

A solution of 175 (30 mg, 0.089 mmol) in toluene (1 mL) was placed in a sealed tube and heated (oil bath) to 140°C for 10 h. The solution was then concentrated and purified by chromatography (6% ether-petroleum ether) to afford 176 and 177, 14 mg (40%).

IR (neat): 1730 (CO) cm^{-1}

'H NMR ($CDCl_3$): δ = 7.10 and 6.20 ppm (1H, bs, HC=C, 5:4), 4.11 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.70 ppm (6H, s, CH_3OCO), 2.02 and 2.04 ppm (3H, bs, CH_3C=C, 5:4)

MS (m/z, relative % intensity): 336(7), 209(23) - HOEt, 258(43) - HOEt, HOMe, 226(75) - EtOH, 2HOMe, 29(100).

Exact Mass calculated for $C_{18}H_{24}O_6$: 336.1572, observed: 336.1561.

$\Delta^{1,5}$-3-(3-oxobutyl)-3-carboethoxybicyclo[3.3.0]octen-2-one (178)

Prepared by alkylation of 160, as described previously, Method B (95%).

IR (neat): 1750-1700 (CO), 1645 (C=C) cm^{-1}

'H NMR ($CDCl_3$): δ = 4.11 ppm (CH_2, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 2.11 ppm (3H, s, CH_3CO), 1.23 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$)

MS (m/z, relative % intensity): 264(3), 194(9) - C_4H_6O, 43(100) CH_3CO.

Exact Mass calculated for $C_{16}H_{22}O_5$: 264.1360, observed: 264.1331.

$\Delta^{1,5}$-3-Carboethoxy-3-(dimethyl 3-methyl-3-butenyl-4,4-dicarboxylate) bicyclo[3.3.0]octen-2-one (179)

Prepared by Knoevenagal condensation (using 178), as described above for 151b, except that the reaction time was 20 to 24 h. Purification of the reaction by chromatography (20% to 30% ether-petroleum ether) afforded 179 (60%) and 178 (30%).

IR (neat): 1755-1725 (CO), 1650 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 4.12 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.73, 3.70 ppm (6H, s:s, 1:1, CH_3OCO), 2.02 ppm (3H, s, $CH_3C{=}C$), 1.24 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$)

MS (m/z, relative % intensity): 240(3) M^+ - 138, 194(16) M^+ - side chain, $C_9H_{12}O_4$.

On one occasion a cyclized product of type 173 was isolated (< 1%).

IR (neat): 1730 (CO), 1620, 1575 (C=C) cm^{-1}

'H NMR ($CDCl_3$): δ = 6.52 ppm (1H, s, HC=C), 4.11 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.74 and 3.77 ppm (3H each, s, CH_3COO), 1.22 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2O$).

MS (m/z, relative % intensity): 360(6), 328(13) -MeOH, 255(28) -MeOH, COOEt.

$\Delta^{1,5}$-3-Carboethoxy-3-(dimethyl-3-methyl-3-butenyl-4,4-dicarboxylate) bicyclo[3.3.0]octen-2-ol (180)

Prepared by reduction of 179 as described previously for 172 (67%: best yield).

IR (neat): 3500 (OH), 1750-1705 (CO), 1650 (C=C) cm^{-1}

'H NMR (CCl_4): δ = 4.60 ppm (1H, bs, CH(OH)), 4.05 ppm (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.64 ppm (6H, s, CH_3OCO), 1.27 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$).

This reduction was accomplished also using zinc borohydride[151]. A zinc borohydride solution (60 mL, ~0.16 M in ether, 8.8 mmol) was added to an ether (40 mL) solution containing ketone 179 (3 g, 7.9 mmol) at 0°C. After stirring for 30 min at 0°C, and 30 min at 20°C, a saturated solution of sodium tartrate was added dropwise (~1.5 mL) until bubbling ceased. This solution was then dried, filtered, concentrated and the product purified by chromatography (30% ether-petroleum ether) to afford 180, 1.6 g (58%).

3-Carboethoxy-3-(dimethyl-3-methyl-3-butenyl-4,4-dicarboxylate) bicyclo[3.3.0]octa-1,4-diene (181)

Prepared by dehydration of 180 using the methanesulfonyl chloride method described above (60%).

IR (neat): 1730 (CO), 1635 (C=C) cm^{-1}

'H NMR ($CDCl_3$): δ = 5.73, 5.35, 5.20 ppm (2H, bs:bs:bs, olefins), 4.10, 4.06 ppm (2H, q:q, ~2:1, $OC\underline{H}_2CH_3$), 3.72, 3.64 ppm (6H, s:s, ~2:1, CH_3OCO), 2.01 ppm (3H, s, CH_3C=C), 1.51, 1.48 ppm (3H, t:t, ~2:1, $C\underline{H}_3CH_2$)

MS (m/z, relative % intensity): 362(4), 257(5) - HOMe, COOEt or HCOOEt, OMe, 117(38).

$\Delta^{8,9}$-6-Carboethoxy-2-dicarbomethoxy-3-methyltetracyclo[6.4.$0^{1,6}$.$0^{3,7}$.$0^{8,12}$]-dodecene (181) (also $\Delta^{8,12}$ and $\Delta^{9,10}$)

Prepared using 181 (30 mg, 0.081 mmol) in toluene (1 mL) as described above for the Diels-Alder reaction of 175 (50%).

IR (neat): 1735 (CO) cm^{-1}

'H NMR ($CDCl_3$): 5.45, 5.26 ppm (4:1, 5/8 of the integration of 1H; bs:bs, olefin), 4.14 and 4.15 ppm (2H, 4:1, q:q, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.71, 3.65 and 3.69, 3.66 ppm (6H, s:s:s:s, 4:4:1:1, CH_3OCO), 1.25 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$), 1.17 ppm (3H, s, CH_3-C-)

MS (m/z, relative % intensity): 363(15) M^+ + 1, 362(15), 302(19) - HCOOMe, 288(17) - HCOOEt, 228(19) - HCOOEt, HCOOMe, 153(59), 117(100).

Exact Mass calculated for $C_{20}H_{26}O_6$: 362.1727, observed: 362.1720.

$\Delta^{11,12}$-6-Carboethoxy-3-methyltetracyclo[6.4.$0^{1,6}$.$0^{3,7}$. dodecene-2-dicarboxylic acid

Triester 182 (200 mg, 0.55 mmol) was added to a solution containing aluminum trichloride (140 mg, 1.1 mmol, Fisher) in ethanethiol (2 mL,

Eastman). Immediately a very viscous precipitate was formed and stirring continued at 20°C for 20 h. The reaction mixture was then poured into cold acid (1% HCl) and extracted with ether and chloroform. The combined extracts were dried, filtered, concentrated and the crude product, 170 mg (94%) used in the next reaction.

IR (neat): 3700-2800 (OH), 1725 (CO) cm^{-1}

'H NMR ($CDCl_3$): δ = 8.80 ppm (2H, bs, COOH), 5.85 ppm (1H, s, HC=C), 4.08 ppm (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 1.25 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$), 1.23 ppm (3H, s, CH_3).

$\underline{\Delta^{9,10}\text{-6-Carboethoxy-3-methyltetracyclo[6.4.0}^{1,6}\text{.0}^{3,7}\text{.dodecene-2-carboxylic acid (183)}}$

The above dicarboxylic acid (170 mg, 0.50 mmol) was dissolved in toluene (2 mL) and the solution refluxed for 2 h. The solvent was evaporated and the product purified by chromatography (20% ether-petroleum ether) to obtain the monocarboxylic acid product 183, 65 mg (38% for two steps).

IR (neat): 3700-2800 (OH), 1720 (CO) cm^{-1}

'H NMR ($CDCl_3$): δ = 5.85 ppm (1H, bs, COOH), 5.82 ppm (1H, s, HC=C), 4.09 ppm (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 1.25 ppm (3H, t, J = 7 Hz, $C\underline{H}_3CH_2$), 1.10 ppm (3H, s, CH_3).

MS (m/z, relative % intensity): 291(13) M^+ + 1, 290(6), 246(45)-OEt, 217(45)-COOEt, 172(98)-COOEt, COOH and dicarboxylic acid 183, 60 mg (35% for two steps).

Spectral data in next paragraph.

$\Delta^{9,10}$-3-Methyltetracyclo[6.4.$0^{1,6}$.$0^{3,7}$.$0^{8,12}$]dodecene-2,6-dicarboxylic acid

Ester 183 (110 mg, 0.38 mmol) was added to a sodium hydroxide solution (10% aqueous NaOH, 1 mL, ~2.5 mmol) and this mixture refluxed for 2 h. After cooling the solution, it was acidified (10% HCl) and extracted with ethyl acetate. The combined extracts were dried, filtered and concentrated to afford ~100 mg (99%).

IR ($CHCl_3$): 3500-300 (COOH), 1720 (CO) cm^{-1}

'H NMR ($CDCl_3$): δ = 10.80 ppm (1H, bs, COOH), 5.85 ppm (1H, s, HC=C), 1.10 ppm (3H, s, CH_3).

MS (m/z, relative % intensity): 262(5), 217(18)-COOH, 172(28)-2COOH.

MP: 206-208°C.

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